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Long term anticoagulant therapy after acute myocardial infarction : a review of the literature

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ACUTE MYOCARDIAL INFARCTION

·A Review of the Literature

By: Brent E. Krantz
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INTRODUCTION

The purpose of this review is threefold: (1) to present the views
and studies; (2) to elucidate the results of the studies; and (3) to
present the difficulties in performing the investigations. Many dif-
ferent aspects can be discussed, and certainly separate dissertations
on some of these aspects could be written. This paper will avoid
detailed tangential discussions.

In 1947, Nichol and Fasset (1) described the favorable use of Dicum-
arol for long term anticoagulant therapy in five patients following acute
myocardial infarction. They could not know at that time the great con-
troversy they began. Since this initial paper, a multitude of views have
been presented in the world's literature and conferences. Long term
anticoagulation after acute myocardial infarction has been a difficult
treatment to evaluate adequately and accurately. Even after twenty-one
years of research and discussion, no agreement as to the use of the long
term therapy has evolved.

Few of the many investigations have been well controlled for the
reason that there is an inherent difficulty in selection of patients and
controls, and further, because of a prevailing attitude during the first
decade of this research that non-use of long term anticoagulants after
myocardial infarction might constitute malpractice. During the past
eleven years, however, evaluation has improved with several well exe-
cuted prospective studies such as those by Bjerkelund (2), Aspenstrom
and Korsan-Bengsten (3), Manchester (4), The British Medical Research

Council Report (5), Borchgrevink (6), Seaman (7), MacMillan, et. al. (8), Harvald, et. al. (9), Lovell, et. al. (10), Veteran's Administration Hospital Cooperative Study (11), and most recently, Loeliger (12). While other less satisfactory studies and opinions are discussed in this paper, the above mentioned investigations will be considered in the most detail.

COMMONLY USED AGENTS IN LONG TERM ANTICOAGULATION

To discuss in detail the pros and cons of the various anticoagulant agents is beyond the scope of this paper. However, the pharmacology, according to Drill (13) and Goth (14), of the commonly used agents is briefly described.

Heparin is the only parenteral anticoagulant that has been used clinically in long term post-myocardial infarction therapy. Heparin has essentially three effects on the blood clotting mechanism:

1. Inhibition of conversion of prothrombin to thrombin.

2. Antithrombin effect with the presence of a yet to be identified plasma cofactor.

3. Depression of the agglutination of platelets.

Heparin apparently facilitates clot resolution by preventing extension of an existing intravascular clot. No evidence of fibrinolytic activities has been reported.

Heparin is not absorbed from the gastrointestinal tract and reports of sublingual absorption have not been confirmed. Intramuscular injection in ten milligrams per milliliter concentration has been observed to be painful locally, while one hundred milligrams per milliliter concentrations have not. Subcutaneous administration is frequently used in dosages similar to intramuscular injections. A gelatin dextrose preparation is used for repository injections, which is important to long term anticoagulant therapy. Intravenous administration is generally used in a hospitalized patient because of better maintenance of therapeutic clotting times.

Overdosages of heparin frequently result in hemorrhage. Long term use is frequently associated with osteoporosis. If an antidote for the

former reaction is needed, toluidine blue and protamine sulfate are the drugs of choice.

Twenty to twenty-five per cent of the drug given in a single dose is excreted in the urine. The remainder is metabolized by liver heparinase and possibly a yet to be identified blood heparinase and is taken up by mast cells. More will be said about the use of heparin in long term anticoagulant therapy after myocardial infarction.

Coumarin compounds apparently act as depressors of liver formation of Factors VII, IX, X, and prothrombin. This is possibly due to enzymatic competition with vitamin K_1. Bishydroxycoumarin (Dicumarol) is the oldest of the coumarin derivatives and has been used in many studies of long term anticoagulation. Newer drugs with different efficacies are: biscoumacetate (Tromexan), sodium warfarin (Coumadin), and cyclocumarol (Cumopyran). Since the dosages of these drugs must be regulated by laboratory control, no definite dosages can be described here. The slow action, the variable absorption from the gastrointestinal tract, and the variable metabolism among individuals who use Dicumarol, are the reasons why so many substitutes have been synthesized.

Coumarin drugs are all administered orally. Coumadin, however, may be used parenterally although it is not frequently done . Following the administration of coumarin drugs, a latent period results because of the necessity of clearing Factors VII, IX, X, and prothrombin from the blood. Following discontinuance of the drug, the drug is cleared from the body in one to eight days. Metabolism of the coumarin compounds in the liver is believed to be fairly complete since very little is observed in the liver unchanged.

The main toxicity of the coumarin drugs is hemorrhage which can be

treated with vitamin K_1. The effect of this vitamin occurs within one-half hour.

Inandione compounds have been used in several long term therapy studies. Their action is believed the same as coumarin compounds. The principle preparations are phenindione (Hedulin; Danilone) and diphenadione (Dipaxin). Phenylindandione has been used and is now available. As with the coumarin drugs, the dosages must be regulated by laboratory control.

Although there have been case reports of granulocytopenia and jaundice-producing liver disease with the inandiones, this probably represents hypersensitivity rather than toxicity. Polydipsia, polyuria, and tachycardia as well as overdosage and subsequent hemorrhage are the toxicities of these drugs. Vitamin K_1 can be used as an antidote for the hemorrhage, but higher dosages must be used than for coumarin compounds.

In summary, the inandiones and coumarin compounds have similar mechanisms of action, while heparin has a different one. In theory, the end result should be the same, both preventing clot formation or at least extension of an existing clot. Results of studies using these drugs will be presented.

THE FIRST DECADE (1947-1957):   OPTIMISM WITHOUT CONFIRMATION

Nichol and Fasset (1) reported five patients who were followed for six to thirty-two months on long term Dicumarol therapy after an acute recurrent myocardial infarction. One of the patients died while he was "inadequately anticoagulated", but the other four patients suffered no ill effects. This study, done in 1947, began the era of long term anti-coagulant therapy after myocardial infarction.

Three years after his initial report, Nichol teamed with Borg (15) and added seventy-three patients to the original five. This report was also favorable to the use of long term anticoagulant therapy and indicated its feasibility in spite of the variability of the Dicumarol require-ments, as determined by the Quick one-stage prothrombin test. The fact that the therapy was feasible did not deter the authors' opinion "that the therapy was much trouble for both the patient and the physician".

The third report, in 1954, by Nichol and his associates (16) included two hundred ninety-five patients between the ages of thirty-three and eighty-three years. One hundred twenty-nine patients continued therapy while the remainder dropped out for various reasons including death, hemorrhage, and loss of interest and willingness to co-operate. Of the patients who discontinued the study, thirty-seven deaths occurred from ten days to three years after therapy was stopped.

Hemorrhage was frequent, seventy-three patients having developed hemorrhagic complications. The results of this study prompted Nichol to conclude, "Hemorrhage must be accepted as a calculated risk when embark-ing on long term anticoagulant therapy and weighed against the results to be derived." This statement holds true today, if one accepts long term anticoagulant therapy as beneficial after myocardial infarction. However,

at the time of this statement, no one had conducted a prospective study with controls; this made such a statement in 1954 premature. Perhaps this opinion reflected the consensus at that time that long term therapy was sound treatment and that its omission bordered on malpractice.

Foley and Wright (17) and Scott (18) wrote in separate small studies about the feasibility of long term anticoagulant therapy after myocardial infarction. The former emphasized the necessity of one-stage Quick prothrombin determinations every seven to fourteen days, while the latter recommended determinations each week. Hemorrhages were frequent complications in both studies, but no deaths were attributed to hemorrhage.

Owren (19), Lund (20), and Muri (21) reported separate studies using long term Dicumarol therapy in small groups of thirty-seven, fourteen, and sixty-seven patients, respectively, who were followed with the PP prothrombin-proconvertin determination. Results indicated that when the PP values were within the ten to thirty per cent therapeutic range, the treatment was valuable prophylactically. Fortunately, the treatment was feasible with good physician, laboratory, and patient co-operation. These studies were uncontrolled and too small to make valid conclusions. Indeed, for want of controls, Muri compared the results of his study favorably with other studies which investigated prognosis following myocardial infarction in other countries during a different time period.

Olwin (22) reported on the control of long term anticoagulant therapy with Dicumarol using a two-stage prothrombin determination. Bleeding occurred in "only fifteen per cent" of his small series and this was treated with vitamin K administration and discontinuance of therapy. He felt that the two-stage method allowed more accurate follow-up of therapy compared with the one-stage Quick method. Many different tests for the

determination of prothrombin levels have been developed, each with its proponents. The Quick one-stage method has been used mostly in the United States, whereas, PP determinations and thrombotests have been used principally in Scandinavia and other European countries during the past fifteen years.

In 1953, Keyes, et. al. (23) published their first report on a restrospective study with "two comparable groups with myocardial infarction". Long term therapy was defined as that continuing beyond six weeks. The majority of the patients were followed from one to two years. The patients were treated with long term Dicumarol for the following reasons: (1) continuation of refractory angina pectoris after recovery from myocardial infarction; (2) survival of a recurrent myocardial infarction; and (3) development of coronary insufficiency suggesting impending coronary occlusion following an asymptomatic post-infarction period. The therapy was regulated with the use of the one-stage Quick prothrombin determination. The treated group of sixty-three patients was much smaller than the one hundred forty-seven patients who served as controls. The controls were selected from patients treated for myocardial infarction prior to the era of long term anticoagulant therapy. The results were markedly in favor of long term anticoagulant therapy as to reinfarction and mortality. Hemorrhage occurred in ten per cent of the patients treated and one death was attributed to the anticoagulation. The authors emphasized the recurrence of myocardial infarction in seven patients who stopped therapy shortly before the episodes. As can be seen, this study is open for bias because of the inequity in the size of the control and treated groups, as well as the bias inherent in retrospective studies.

In 1956, Keyes and his associates (24) divided the patients into single and multiple infarction groups. Each of these was subdivided into treated and control groups. The single infarction group of two hundred fifty-seven patients was divided into the treated group of seventy-one patients with recurrent coronary pain or failure, and the control group of one hundred eighty-six patients who were without recurrent symptoms. In the recurrent infarction group, the controls (forty-eight patients) were those who had been treated prior to 1946 and the advent of long term anticoagulant thereapy; the treated group (fifty patients) were those who had their myocardial infarctions after 1946. The results were very favorable for long term anticoagulant therapy, since only nine per cent of all treated patients died as opposed to forty-one per cent of the control patients who succumbed. Hemorrhage occurred frequently in spite of the therapy controlled by the one-stage Quick method. In fifty-one patients, there were fifty-four episodes of hemorrhage, but no deaths occurred. However, the authors felt that the benefits of therapy outweighed the disadvantages. The same criticism which was made for the 1953 study by Keyes holds true.

In 1956, Tulloch and Wright (25) studied the use of Dicumarol in treating many types of thromboembolic disorders including thirty-five myocardial infarctions in thirty-two patients. The one-stage Quick method was used to keep prothrombin times between twenty-five and thirty seconds. Five thromboembolic episodes occurred during treatment with two deaths. There were seventy hemorrhages in forty-three patients in the entire series. When prothrombin times were available, they were found to be frequently less than twenty seconds with the thromboembolic episodes and greater than forty seconds with the majority of the hemorrhages. This study also emphasized the feasibility of long term anticoagulant

therapy with adequate control of prothrombin levels. The conclusion is similar to previous investigations which have been favorable to long term anticoagulant therapy. However, since no controls were described, the study is invalidated from the viewpoint of effect of therapy on recurrence of thromboembolic phenomena.

Owren (26) reported a second series of 700 patients of which two hundred thirty-four were post-myocardial infarction patients who were treated with long term (eight weeks or more) Dicumarol therapy and continually evaluated with the prothrombin-proconvertin test at levels of ten to thirty per cent determined at one to three week intervals. Both daily maintenance and intermittent dosages were used and evaluated with the former proving to maintain PP values in the therapeutic range more effectively. This study also indicated decreased mortality and decreased reinfarction rates, but without controls. The principle value, like the previous studies mentioned, was the indication of feasibility of long term therapy.

In a retrospective study, Bay (27) also investigated a small number of patients (sixty-eight) treated with long term anticoagulant therapy after myocardial infarction. He found a mortality rate of three and one-half per cent and hemorrhagic complications in ten and one-half per cent of the patients. Bay concluded from his study that the value of anticoagulation ceased to improve the reinfarction rate after two to three years and that it might be advantageous to stop therapy at that time. This was the first study to suggest the discontinuance of therapy after a certain period of time. However, lack of a control again deterred from the study. Many authors have emphasized the discontinuing of therapy after variable periods of therapy and these will be discussed later.

Foley, et. al., (28) described two groups of eleven and twelve

patients who were treated for a total of five hundred ninety-seven

months and five hundred fifty-four months, respectively, with long term

post-myocardial infarction Dicumarol therapy controlled by Quick's one-

stage method. The first group were patients with more than one previous

infarction and the second group with just one infarction. The results

indicated that therapy should be instituted in recurrent infarctions,

in prominent episodes of congestive heart failure, and when multiple

embolic episodes have occurred. Hemorrhage did not seem to be a problem

since there were only thirty-one episodes in eight years. Unfortunately,

this study, like many others, was without controls.

Engelberg (29) introduced long term intermittent subcutaneous

heparin therapy in two hundred patients with myocardial infarction.

Efforts to control the study included a treated and control group of fair

comparability as to age and sex, but without other comparisons. Therapy

was extremely successful in terms of difference in mortality with twenty-

one per cent in the control group and four per cent in the treated

group. This optimistic report with at least a token control group was

the only study done with long term heparin in the 1947-1957 decade of

therapy. This study marks the first one in the literature that was

carried out in a prospective manner. Further discussion of long term

heparin therapy will follow in the section which discusses the period,

1958 to the present.

Returning to oral therapy with Dicumarol, Suzman, et. al. (30)

divided two hundred eight patients into three groups: eighty-eight in

the "short term" control group treated three months or less; eighty-two

in the "long term" group treated from three to seventy-six months; and

thirty-eight in the group of dropouts who had been under therapy for three to thirty months. As usual for the American studies, the Quick one-stage prothrombin time determination was used for regulation of therapy. The comparability of the two principle groups, "short term" and "long term", was fairly good; however, the main drawback of the study was that "the decision for the patients' participation was left entirely up to the patient". Selection by this method allows economic considerations to be important and thereby produces bias. The differences in mortality and reinfarction rates seem statistically significant in favor of long term anticoagulant therapy—twenty-nine deaths and twenty-four reinfarctions in the "short term" group and six deaths and seven reinfarctions in the "long term" group. Other differences in the two groups were not significant. They did consider the history of previous infarction and concluded that from their investigations that mild and uncomplicated cases, whether treated or not, had a favorable prognosis in contrast to the substantial mortality rate found in severe or complicated cases. However, in contrast, the patients most likely to benefit from long term anticoagulant therapy were those in whom the presenting attack was severe and there had been a previous myocardial infarction. In a later article, Suzman (31) acknowledged the need for further well-controlled prospective studies for establishing or disestablishing the treatment.

Manchester (32) studied seven hundred twelve patients who were divided into a treated group taking Dicumarol and ascorbic acid and a placebo group taking ascorbic acid only. Four hundred four patients remained in the study after ten years and one hundred fifty-seven patients who were taking no medication were followed. This group was called the

untreated or "control" group. The inclusion of the "control" group
destroyed any comparability that the three groups may have had in addi-
tion to disallowing random selection. Upon finding eight times greater
mortality in the untreated and placebo groups, Manchester acknowledged
the advantages of the Dicumarol treatment. He also suggested that
ascorbic acid may decrease the fragility of the vessels and aid in the
therapy. He emphasized that in spite of the many favorable studies on
the long term anticoagulant therapy, including his own, the therapy must
be individualized to meet the demands of the patient.

In 1957, both Tanzi and Van Ness (33) and Owren (34) presented uncon-
trolled studies on the use of long term Dicumarol and phenindandione,
respectively. Typically, the American investigation was controlled by
the Quick one-stage prothrombin time and the Scandinavian study with the
PP determination. Both studies compared their series with other studies'
done at different times and places, and the results were typically favor-
able.

A preliminary report on the long term use of Dicumarol with PP value
control after myocardial infarction was presented by Aspenstrom and
Korsan-Bengsten (35). Fifty-seven patients were followed, including
twenty-eight "good risk" and twenty-nine "poor risk" patients using the
criteria by Brofman, et. al. (36) for classification. Seven patients,
two in the former and five in the latter group, died. No fatalities were
ascribed to the therapy. Although few patients had been studied, the
investigators believed that patients who were stress hyperreactors (persons
so classified in regard to their blood coagulability) would achieve the
most benefit from the drug. They conceded the need for much more study
to prove their hypothesis.

Finally, ten years after the initial report on long term anti-coagulant therapy after myocardial infarction, an excellent prospective study with random selection of the patients was reported by C. J. Bjerkelund (2). Bjerkelund believed that most of the studies previously done were concerned more with feasibility and practicality of long term therapy and not with the results of the treatment. In the previous studies discussed in this paper, this is true with the notable exceptions of the Suzman and Manchester studies. Bjerkelund was the first to emphasize the factors of pathogenesis of coronary occlusion. He stated that thrombosis had been commonly known to occur in only fifty per cent of the myocardial infarctions. He believed that this fact established theoretical limitations to long term anticoagulant therapy.

Two hundred seventy-seven consecutive patients under seventy-six years of age who survived thirty days following an acute myocardial infarction were randomly appointed to a treated group and control group in Bjerkelund's study. Forty patients were excluded from therapy for similar reasons in both groups. Finally, one hundred nineteen patients were treated with anticoagulant therapy, while one hundred eighteen patients were in the control group. Detailed statistical analyses were applied to the control and treated groups and no significant differences at the five per cent level of statistical significance were found in any of the compared factors, including the treatment during the acute phase of the myocardial infarction. Anticoagulation was controlled with PP determinations and values less than thirty per cent were found in eighty-two and one-half per cent of the determinations, and less than forty per cent in ninety-two and three tenths per cent of the PP values for the treatment period. Generally, PP values of ten to thirty per cent were considered to be in the therapeutic range. According to Bjerkelund, an

analysis of PP values near the time of reinfarction and death in thirty-one patients revealed that a relative reduction in the intensity of treatment could not have played an important part in causing these episodes.

The mortality rate of patients under sixty years of age who had been treated with anticoagulants for the first twelve months of therapy was less than the control group, and this difference was statistically significant at the five per cent level. Although the trend of the study was in favor of the use of anticoagulants, this result was the only one that assumed statistical significance at the five per cent level. However, when the patients of all ages were compared as to modes of life, ability to work, and morbidity, the study revealed that morbidity was greater in the control patients who were admitted to the hospital more often and stayed longer than the treated patients.

Hemorrhage occurred once in every seven and nine-tenths patient-years of treatment. If only the moderate and major hemorrhages are included, occurrence was once in every thirteen and one-tenth patient years of treatment. Four of these hemorrhages were fatal cerebrovascular accidents.

In previous studies treatment had been especially indicated for patients with recurrent infarction and in those myocardial infarction cases with a tendency to heart failure and thromboembolic episodes. Bjerkelund's study presented evidence that showed that the major benefit was primarily in the younger patients who had had only one infarction. This seems reasonable when one remembers that the treatment is primarily prophylactic and not curative. Therefore, according to this study, long term therapy seems to be indicated primarily for the "good risk" cases.

Thus, with the exception of Bjerkelund's study (2), investigations during the first ten years of treatment for myocardial infarction by long term anticoagulant drugs demonstrated the feasibility of the treatment much more than they proved the scientific significance of the treatment itself.

THE SECOND DECADE (1958 to the present):   IMPROVED INVESTIGATION WITHOUT
GENERAL AGREEMENT

The second decade, like the first, has been marked with studies
which have continued to emphasize feasibility rather than effectiveness
of therapy. Most of these studies were early in the decade.

Eisenstadt (37), Wrage and his associates (38), Loughridge (39),
Nora (40), Swan (41), and Pollard with his associates (42) described the
care of small numbers of patients for varying periods on oral anticoag-
ulants in each of their papers. Even in 1965, Reinberg and Lipson (43)
reported a series of one hundred eighteen patients followed for eight
years with thrombotest and PP determinations. Though the conditions
of the studies were different, the conclusions were the same: that long
term oral anticoagulant therapy is feasible, practical, and effective in
preventing thromboembolic episodes. One cannot argue that the long term
therapy is not feasible and practical, but the conclusion in regard to
effectiveness of the therapy must be reserved for more detailed and well-
controlled studies.

Seaman (44) has described three factors that govern feasibility.
First, the therapist must be experienced and thoroughly familiar with the
particular anticoagulant selected. Second, a dependable laboratory method
of assessing control must be available. Finally, the patient must be
reliable, fully informed of the necessity of his co-operation and aware
of the risks, both of his disease and of the therapy. The first two
factors must be available before anticoagulant therapy can even be pre-
sented to the patient. If they are, there is less chance of complication
and perhaps increased value in the therapy.

Fewer retrospective studies appeared during the second decade.
Odegaard (45), Connel and Mayer (46), Lund-Johansen (47), and Roysten (48)

reported studies done in retrospect. As had been true of previous,
similar studies, success with long term anticoagulant treatment after
myocardial infarction was noted. Roysten emphasized that a case should
be in the therapeutic anticoagulation range at least eighty-five per cent
of the time in order to render treatment effective. He felt that the
effectiveness of the therapy had been proven by his study and others,
and believed that future investigation should concentrate on the degree
of control of prothrombin levels.

Toohey (49) undertook a careful retrospective study, but took
control patients from the period preceding long term anticoagulant
therapy as well as patients who were more severely ill. The decrease
in mortality and reinfarction rates were striking compared to the control
group, and because the patients who were treated were more severely ill,
Toohey believed that this strengthened the case for the use of anti-
coagulants.

Nichol, et. al. (50) reported a composite study compiled by many
investigators from many different areas consisting of 1091 patients.
"Controls" were those patients who discontinued therapy after three to
eighty months of therapy. Dicumarol and Cumopyran were used, and the
one-stage Quick test was employed to evaluate the prothrombin levels.
Marked differences between control and treated groups suggested not only
the value of the therapy, but the presence of a "rebound phenomenon".
The patients who discontinued therapy abruptly seemed to be more sus-
ceptible to reinfarction than patients who continued therapy. There
were twenty deaths in the first month after having stopped therapy.
Hemorrhage occurred in twenty per cent of the patients who were treated.

Ensor and Peters (51) presented a study of two hundred sixty-eight

patients who had been treated prophylactically after myocardial infarc-
tion. Patients who had discontinued therapy were called "pseudocontrols".
After five years, the mortality rate of the treated group was twenty-one
per cent as compared to twenty-nine and three-tenths per cent of the
"pseudocontrols", and forty-four and two-tenths per cent of a control
group taken from the literature. Both the Nichol study (49) and the
Ensor and Peters study used withdrawals from therapy and called them
"controls" and "pseudocontrols", respectively, using the quotation marks
in recognition of the low control value these groups represented.

Thomes and his associates (52, 53) presented two papers indicating
favorable results using anticoagulant treatment on patients with thrombo-
emoblic phenomena, but did not describe their results with myocardial
infarction patients. However, they felt that it was important to remember
that if long term anticoagulants did improve prognosis and prolong life,
controlled studies would be difficult after a short period of time because
of the accumulation of "poor risk" patients in the treated groups.

Kuhn, et. al. (54) carried out an investigation for nine years of
long term Dicumarol therapy following myocardial infarction with the one-
stage Quick prothrombin test used to evaluate prothrombin levels. As
with other retrospective studies on this subject, there was no randomi-
zation. However, withdrawal patients were not placed in a "control"
group as in the previous studies by Nichol (50) and Ensor and Peters (51).
The study indicated a favorable decrease in reinfarction and mortality
rates, comparing well with other studies. Kuhn felt that the occurrence
of hemorrhage in only eleven per cent was well within the limits of toler-
ation when compared with the effectiveness of therapy.

In the first decade, 1947-1957, few papers were written about the
control of therapy and the true therapeutic clotting factor levels that

would produce fewer hemorrhages and fewer thromboembolic episodes. Most authors have commented about the type of laboratory study used and the factor levels which were believed to be therapeutic. Following are several studies on control of therapy which are appropriate because of the increasing number of well-controlled prospective studies.

Hjoit and Molne (55) studied forty-five patients who had an average thrombotest value of twenty-three and nine-tenths per cent before reinfarction and upon admission to the hospital, after reinfarction, the average values were twenty-nine and four-tenths per cent. Although the difference between these two values seems statistically significant, the difference is too small to justify conclusions that recurrent infarction is usually caused by "escape" from anticoagulant therapy. However, Molne and her associates (56) later related the level of anticoagulation with autopsy findings after death. On final admission to the hospital, PP value or the thrombotest was determined. The group of patients with coronary thrombosis and myocardial infarction had a mean prothrombin content of thirty-two and three-tenths per cent while those with only myocardial infarction had a mean prothrombin content of twenty-four and seven-tenths per cent. They concluded that adequate anticoagulant therapy may afford some protection against coronary thrombosis.

Bjerkelund (57) concurred and stated that episodes of reinfarction and sudden death occurred with PP values that were statistically in agreement with the PP level during the total period of treatment in his study. He concluded that rises in the PP values above the therapeutic range were not responsible for these episodes. It must be remembered, however, that many factors including stress, reinfarction, concurrent illness, drugs, and changes in emotion may vary the PP value or thrombotest value.

Therefore, one cannot prove by either of these studies that infarction occurred when the prothrombin ranges were in "therapeutic ranges".

Owren (58) described the importance of Factor X in regulating anticoagulant therapy. He stated that the thrombotest was the only one of the commonly used tests that measured this factor, and, therefore, was the best test for anticoagulant therapy control. The bleeding complications produced by "too intensive" therapy were all associated with a Factor X level below five per cent.

Moschos and his associates (59) derived an investigation to determine prothrombin concentrations in which there were the fewest hemorrhages and thromboembolic complications. Four types of laboratory tests were used, the one-stage method of Quick, the one-stage method of Owren, and near the end of the study, the PP determination and the thrombotest. One hundred seventy-eight patients were divided into the intensive (ten per cent to twenty-five per cent of normal), moderate (thirty per cent to fifty per cent of normal), and control (greater than sixty per cent of normal) groups. In this study, moderate therapy was the best because the sum of the risk of complication and the risk of hemorrhage were least.

Two years later, Moschos (60) presented a follow-up of the original patients and concluded that moderate anticoagulation remained the best therapy even though this was not proven conclusively by the study.

Borchgrevink (6) preceded the Moschos study, but had two groups with high degree of comparability. His study included patients with myocardial infarction, angina pectoris, or both. He divided his patients randomly into the intensively treated (twenty per cent PP value), and moderately treated (fifty per cent PP value). He declined the use of a control group because he felt there was a previous indication of therapeutic necessity. Phenindandione was used as the anticoagulant agent. The

differences between the two groups were significant as to mortality and reinfarction with the intensive group showing better results than the later study by Moschos (59, 60). Both studies were without control groups which detracted from their conclusions.

Since the Borchgrevink study supported intensive treatment and the Moschos study supported moderate treatment, another study was needed. Loeliger, et. al. (12) used the thrombotest and found intensive therapy (five per cent to twelve per cent of normal) to be effective, whereas, moderate hypocoagulability (twelve per cent to twenty-five per cent of normal) was of limited or no value. Loeliger's study is one of the most recent well-controlled, double blind, randomized trials in the literature on long term anticoagulant therapy after myocardial infarction. Phenprocoumon was the agent used. The difference in the rate of cardiovascular deaths was not significant between the treated group (four and eight-tenths per cent), and the placebo group (seven and two-tenths per cent). The difference in the two groups as to reinfarction was much more obvious (treated, one and two-tenths per cent to the placebo, eight and seven-tenths per cent) and of high statistical significance. The main fear of therapy with this intensity is hemorrhage. In Loeliger's study, hemorrhage occurred once in every ten patient-years of treatment. Thus, we have cited three good studies which have investigated, specifically, the intensity of treatment. The most convincing papers suggest that high intensity therapy is the most valuable.

The achievement of therapeutic levels described in these studies are easily taken for granted upon reading them in the literature. However, are therapeutic levels easily obtained in practice? Hutton (61) reported a study in which less than fifty per cent of the patients who had been

treated with oral anticoagulants by a hospital house physician, were well-controlled in their therapeutic levels.

The study of the Working Party on Anticoagulant Therapy in Coronary Thrombosis of the British Medical Research Council (5) in 1959 was the first major investigation published in the second decade. It was conducted because there had been few good studies prior to that time. The patients were divided into groups according to their number of infarctions, and then these groups were randomly divided into "high and low dosage" sub-groups. Phenindione was given in therapeutic dosages to the high dosage group to keep the one-stage method of Quick at two and one-half times normal. The "low dosage" group was given one milligram of phenindione which was not enough to affect the prothrombin time. The death rates showed the "high dosage" group to be better than the "low dosage" group but not with statistical significance. However, in patients under fifty-five years of age, the reinfarction rates in the "high dosage" group were one-fifth that of the "low dosage" group which is statistically significant. Although the risk of reinfarction was more improved by high dosage regime in patients with previous history of myocardial infarction, there was no statistically significant difference. It was apparent to the investigators that the patients on the high dosage returned to work during the treatment years more frequently than patients on the low dosage. Both Arnott (62) and an article in the British Medical Journal (63) reviewed and summarized the BMRC study favorably.

A follow-up of the BMRC report (64), published in 1964, showed no significant changes from the earlier report. However, the report pointed out that the use of anticoagulant therapy reduced the reinfarction and mortality rates decreasingly for up to two years post-infarction, compared

to Bjerkelund's report (2) that after twelve months, little benefit resulted.

McMichael (65) reviewed the BMRC report and took issue with its conclusions and defined the following flaws in the method. Instead of the BMRC's concept that long term therapy began after twenty-nine to forty-three days, he proposed three months as the upper limit of short-term therapy because in his opinion, studies have shown that after three months, little improvement in mortality or morbidity rates is gained. Since reinfarctions are so difficult to diagnose and many of the rein-farctions were so benign, he questioned the validity of the diagnosis and, therefore, the conclusion that anticoagulant therapy aided the treated patients in this respect. He attacked the division of the patients as to age and sex after the study was completed instead of prospectively. The risk of hemorrhage in the study was ten per cent, which in McMichael's opinion did not counterbalance the small value of therapy. McMichael suggested the following paragraph as the concluding one of the study instead of the favorable one that actually ended the study.

"If one hundred patients were treated for two years after the acute phase (three months) was over, there would probably be no difference in mortality from a control untreated series. The untreated patients may have more disquieting episodes of chest pain, but these will neither increase the mortality nor the disabling consequences of myocardial necrosis. On the other hand, the treatment even in first class centers is difficult to control and supervise. Serious, or even fatal bleeding may occur in ten per cent of the cases: death and disability from cere-bral hemorrhage are real risks. Further, those who die of the treatment are not necessarily those who would have died without it. The regime thus involves human sacrifice for a very dubious gain. An effective prophylactic regime against thrombosis should continue to work and not suddenly cease to be effective at the end of two years: any other con-clusion is not logical. Therefore, the long term use of our present anticoagulants for coronary disease should be abandoned."

McMichael's arguments are valid and convincing. Equally as much caution, however, should be observed in the acceptance of negative con-

clusions as have been in the acceptance of the positive conclusions.
Further, it is important to remember that no perfect study has ever been
devised. There are most certainly "loopholes" in all investigations and
one wonders if such an astute critic as McMichael could not rewrite favor-
able concluding paragraphs to many other studies as negative as he has
done this one.

In 1961, Manchester (66, 67) reiterated his first study and reported
a follow-up in 1964. In his follow-up he concluded that the long term
therapy was more effective in patients under sixty years of age than
over. He stated that the present results of continuous anticoagulant
therapy for five to fifteen years offers more for the individual who has
recovered from a myocardial infarction against the hazards and probability
of reinfarction than any currently employed medical regime that is avail-
able. The younger the patient, the more imperative is the need for such
therapy. The critique of the original study applies to this one. The
further conclusions drawn from the second report are acceptable only if
one realizes that the follow-up was carried out over a long period of time.
The many changes in the control and treated groups caused by death and
withdrawals for many reasons allowed even more variables to enter the study
to produce bias.

In 1961, Bjerkelund (68) summarized his previous study as well as his
follow-up of his original patients. He still believed that treatment is
primarily indicated in the younger age groups, that it is perhaps not
worthwhile to continue this therapy more than twelve months after the
acute attack, and that the effect achieved during the first twelve months
is not lost after gradual cessation of therapy.

In 1960, Brown, MacMillan and Watt (8) presented their first report
on a small group of fifty-eight patients invited to participate in a

study of long term Dicumarol therapy after myocardial infarction.
Therapeutic values were considered to be between twenty to thirty seconds
with the one-stage Quick method of determination. Only fifty patients
participated in the study because eight patients did not return for follow-
up. They were divided into high and low dosage therapy by chance. The
results were in opposition to all previous studies. The high dosage group
had greater mortality and reinfarction rates than the low dosage group.
Their conclusion was that the establishment or disestablishment of the
therapy had not yet been denied or upheld. A year later, they followed
their first report with a follow-up which was published in two journals
(69, 70). They added twenty-one patients to the study and the conclusions
were unchanged. The main criticisms of this study were the small size of
the group, the invitation for participation to the patients, and twenty to
thirty second prothrombin times being considered therapeutic. The first
two criticisms were acknowledged by the authors. The latter criticism is
considered in view of the previous presentation of Loeliger's (12) work,
even though different tests for evaluation were used. The negative results
of the therapy have been explained by proponents of long term anticoagula-
tion on the basis of the "likelihood" of inadequate therapy.

In 1961, Conrad, et. al. (71) reported a study of twenty-five patients
treated with phenprocoumon and twenty-five patients treated with place-
bos. Both groups had been selected randomly and began treatment on the
twenty-eighth day of post-infarction. The treated patients were controlled
by the one-stage Quick method. Few of the patients in either group had pre-
vious complications. At the time of the study, no difference could be
found between the two groups as far as mortality and reinfarction rates
were concerned.

Conrad's second study (72), using the same criteria but with an increased number of patients, concluded that patients over sixty who had a previous history of atherosclerotic heart disease benefitted from the prophylaxis afforded by long term anticoagulation. There were thirty-nine bleeding episodes in twenty-three patients. The investigators attributed the increased reinfarction rate among the good risk patients under fifty-five years of age to the increased number of patients who stopped therapy because of hemorrhage. The high association with reinfarction shortly after stopping therapy has been referred to as "rebound phenomena".

Although many investigators had mentioned an increased incidence of thromboembolism shortly after stopping therapy, Carter and his associates (73) were the first to study this aspect specifically. They found a definite increase in the number of thromboembolic episodes within six weeks after the discontinuance of therapy. They suggested tapering off the therapy over a period of several days or weeks.

Sise (74) did a retrospective study of two hundred thirty-nine patients and found that the greatest risk was when the patient discontinued anticoagulant therapy because of bleeding. He postulated that the transfusions may cause hypercoagulability because of the clotting factors in the transfused blood, that bleeding may accelerate the formation of clotting factors, that vitamin K_1 therapy may "overshoot", and, finally, that the stasis that results from bedrest in the hospital may cause this increased number of episodes. Sise's second report with his associates (75) arrived at much the same conclusion, although it included more patients. The authors felt that interruption of treatment for reasons other than bleeding was not associated with early thromboembolic complications.

Dinon and Vander Veer (76), Sivertssen and his associates (77), and an article in the British Medical Journal (78) discussed the "rebound phenomena", the former two presenting limited investigations. Dinon and Vander Veer both ascribed to the gradual tapering off of therapy because of the "rebound", but Sivertssen found no evidence of "rebound phenomena". The British Medical Journal discussion commented on the advisability of resuming anticoagulant therapy after stopping for hemorrhage and then discontinuing the therapy over a lengthy period of time.

Van Cleve (79, 80) has presented two good articles on his study of "rebound phenomena". Two groups were selected, but not randomly. The first discontinued their Coumadin therapy over a six week period; the second group stopped anticoagulant therapy abruptly. The results suggested that clinically recognized "rebound thrombosis" does not occur after long term Coumadin treatment. However, the long held opinion that patients who stop therapy because of bleeding are more susceptible to "rebound thrombosis" was a possible exception to the negative findings. In the second study, his results were the same and his conclusion was that among the patients selected to stop therapy (all had been treated at least three years) the results of the study suggested that "rebound" was not a significant problem.

To continue with the prospective studies on long term anticoagulation after myocardial infarction, Harvald, Hilden, and Lund (9) reported a series of three hundred fifteen patients who were observed from five to seven years in a well-controlled study. The one hundred forty-five patients who were treated were given Dicumarol or phenprocoumon and controlled by the PP determination. The one hundred seventy patients in

the control group were given placebos. The PP values were in the therapeutic range in eighty-five per cent of the determinations. The groups were comparable as to age, sex, and risks. Although the results showed a trend toward decreased mortality and reinfarction rates in the first year among the treated patients, the only statistical difference was in the reinfarction rate of patients over sixty years of age. This is similar to the findings of Conrad (71, 72). No "rebound phenomena" were discovered in this study. Harvald stated that as matters stand today, it does not seem justifiable to advise anticoagulation as a routine after myocardial infarction. It is at this time impossible to describe which patients should get the drug, let alone the duration of the treatment. The need for anticoagulants cannot be ruled out after myocardial infarction, but the present study has shown no great benefits to the prophylaxis of the disease.

Seaman, et. al. (81) presented a preliminary report of a double-blind study with three groups of patients allocated randomly: those with phenindione, those with placebo, and controls. The former two groups were treated alike and seen at least every four weeks, while the controls were seen every six months. PP determinations were used to evaluate the therapy using twenty per cent levels as therapeutic. At the time of the first report, no advantages were found in anticoagulant therapy in regard to mortality or reinfarction rates.

The second report (7) a year later indicated no statistical signi-ficant differences between the three groups, but stated that the anti-coagulated group spent more time in the hospital than the other two. No "rebound phenomena" were recognized in this study. The investigation was well conducted with three comparable groups. The double-blind method and its inherent ability to decrease bias is an aid to most studies which

are otherwise well conducted. Loeliger (12) would argue that the twenty

per cent PP level is not within the best therapeutic range and, therefore,

the positive effects of the treatment are lost.

Aspenstrom and Korsan-Bengsten (3) conducted a double-blind study

of Dicumarol prophylaxis after myocardial infarction. They found no

significant differences in the over-all mortality rate, but they did find

significant differences in the number of fatal reinfarctions, the anti-

coagulated group having fewer. The striking difference in this study was

between good and poor risk patients. The poor risk patients were class-

ified under Russek's criteria (82) as listed here:

1. Previous infarction
2. Intractable pain
3. Extreme degree or persistence of shock
4. Significant cardiac enlargement
5. Gallop rhythm
6. Congestive heart failure
7. Atrial fibrillation or flutter, ventricular
   tachycardia, or intraventricular block
8. Diabetic acidosis, marked obesity, previous
   pulmonary emboli, varicosities of the lower
   extremity, thrombophlebitis, or other states
   predisposing to thrombophlebitis.

Aspenstrom and Korsan-Bengsten judged five year survival rates in good

risk patients on Dicumarol and placebo treatment. The groups had eighty-

four one hundredths and ninety-one one hundredths deaths per year,

respectively, while the poor risk patients had rates of forty-seven one

hundredths deaths per year in the Dicumarol group and thirty-four one

hundredths deaths per year in the placebo group. The investigators felt

that the patients in the poor risk group had decreased mortality in the

second through the fifth year of the study. They concluded that good

risk patients had little benefit from long term anticoagulant prophylaxis

while high risk patients may be provided with protection in regard to

thromboemboli.

Hensen (83), a co-author in the later Loeliger study, reported a
double-blind study in a series of patients (only malignancies and atrial
fibrillation patients were omitted from the study). The patients were
randomly placed in phenprocoumon and control groups. Among patients
with some contraindication to anticoagulant therapy, the thrombotest
values were kept from seven to thirteen per cent. Among the other
patients, five to ten per cent thrombotest levels were used as
therapeutic. Only six per cent of the thrombotest values done in the
study were less than fifteen per cent. The differences in reinfarction
rates were of high statistical significance in favor of the anticoagu-
lated group, while the mortality rate differences were not significant.
Although Hensen concluded that the study demonstrated the benefit that
can be expected from intensive long term anticoagulation therapy, and
that negative or less impressive results most probably originate in the
less intensive therapy, the fact that mortality is not appreciably altered
and that reinfarction is such a difficult diagnosis allows us to question
the impressiveness of this study. However, if his hypothesis is accepted,
then a long acting drug, together with a thrombosis service in a medical
center hospital, and close co-operation between the staff of this service
with the attending physicians is absolutely necessary.

Menwissen (84) reported the protocol and early results of his first
year of a double-blind randomized study on the use of long term anti-
coagulant therapy after myocardial infarction. The long term period
began three months after the myocardial infarction. One hundred forty
patients were studied and no significant differences in the two groups
were found. However, the trend was definitely toward prophylactic
benefits with Marcoumar.

The Veteran's Administration Hospital co-operative study (11) which has been reiterated by Schnaper (85) was done in the VA Hospitals throughout the country with central controls and carried out for seven years. Dicumarol and Coumadin were the agents used with evaluation of therapy by the one-stage Quick method at ten to twenty per cent of prothrombin activity on a plasma dilution curve (twenty-six to thirty seconds). Eighty-one and six-tenths per cent of the values were in the therapeutic range of twenty-per cent or less, while eighty-nine and one-tenth per cent were in the range of twenty-five per cent or less. This large study of seven hundred forty-seven patients was divided into comparable groups by the sealed envelope technique. The difference in mortality rates were statistically significant in patients below the age of fifty-five years. Protection was afforded to all age groups to recurrent myocardial infarction with high statistical significance. Bleeding occurred in over fifty per cent of the treated group at some time during the therapy. There were three fatalities.

The fact that the study was not double-blind is a deterrent, and in spite of the favorable results, the incidence of bleeding, even in minor episodes, was extremely high. The results are more favorable than many similar studies. However, since the investigations were carried out in many different hospitals, even though the protocol was the same, the many different observers may cause inconsistencies and possible bias.

The study by Lovell and his associates was reported on three occasions (10, 86, 87). The patients were divided randomly into three groups: the intermittent heparin group, the oral therapy group, and the group on inadequate dosages of oral anticoagulants. After one year of therapy, there was no indication that the heparin therapy would prove more beneficial than phenprocoumon therapy in terms of mortality. In the

second report, there was no significant difference in the non-fatal re-
current infarction rate in the three groups.

In the final report of the study, the number of patients had in-
creased to four hundred twelve, randomly allocated to one of the three
groups. The range of therapy was fifteen per cent to thirty per cent
of normal prothrombin activity. The survival rates revealed no differ-
ences between the groups treated with low dosage phenprocoumon and
heparin regimens. For men aged fifty-five years and under, but not for
older men, the survival rate of the high dosage group was better than
that of the low dosage group for the first two years. The authors
acknowledged the difficulties in the conduction of these studies on the
basis of insufficient numbers of patients. Lovell was very dogmatic in
his belief that the value of the study should be based on improvements
in mortality rates, since this is the important end factor, rather than
upon improvement of reinfarction and other cardiovascular complication
rates. It must be remembered that anticoagulation, if of value, is a
prophylactic measure and not a cure.

One other observation may be inferred from Lovell's study. If
anticoagulant drugs are administered at all, oral administration is as
effective and much less inconvenient than the parenteral drug.

In addition to the Lovell study, only two other studies have been
reviewed with heparin being used intermittently for myocardial infarctions
for long periods of time. In the study by Hughes and his associates (88),
heparin was injected in one hundred to two hundred milligram dosages sub-
cutaneously every three days in fifty-three patients while Coumadin was
used in fifty-one patients. In comparing the results, the heparin group
did better in both mortality and reinfarction rates. The study also

confirmed the feasibility and practicability of long term heparin therapy. Griffth (89) used heparin with favorable results, but no control group was used.

CONCLUSION

Many studies which are in general disagreement have been re-
viewed. No physician has discovered the ideal treatment for myocardial
infarction, although some feel that long term anticoagulant therapy ap-
proaches it. Each investigator recommends the use of anticoagulants for
a certain patient. Unfortunately, no two studies seem to agree on which
patient.

The evaluation of long term anticoagulation after myocardial in-
farction has been, and will be, extremely difficult because of the
multitude of variables in each patient. There seems to be no hope for
a study done so well that there would or could be a definite conclusion.
However, the studies have shown a trend toward better results with the
use of long term anticoagulant treatment. Whether this is the result of
bias is not definitely known.

If one intends to anticoagulate his patients on a long term basis
following myocardial infarction, then it is imperative that the patient
be reliable and co-operative. A physician must adopt the use of one
drug and learn its actions well. The laboratory control is apparently
very important; therefore, the laboratory performing the studies must be
able to produce consistent results with one of the tests. Thrombotest
and the prothrombin proconvertin determinations seem to be the most
reliable; however, in this country, the one-stage Quick test has been
used almost exclusively.

The treatment of the post-myocardial infarction patient may center
about his anticoagulant therapy, but it is more imperative to treat com-
plications such as congestive heart failure with the appropriate measures
than to do a Stat. prothrombin time.

There seems to be no excuse for a physician to use long term anti-
coagulant therapy if he does not have the facilities to control the
therapy. Good medical center control would be ideal, and if this is not
available, the patient would have less over-all risk by withholding the
long term therapy.

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