The Prevention of Thromboembolic Complications in Myocardial Infarction by Anticoagulant Therapy
A Clinical-Pathologic Study

By Helen I. Glueck, M.D., Henry W. Ryder, M.D., and Philip Wasserman, M.D.

Autopsy records of 151 patients dying of acute myocardial infarction, in a large private hospital, were reviewed. Half of the patients received anticoagulant therapy. Hemorrhage was not a significant cause of death in Dicumarol-treated patients. Embolic complications, often undiagnosed clinically, were of common occurrence. Adequate anticoagulant therapy effectively reduced, not only the total number of emboli, but also the number of serious or fatal emboli. In this role, anticoagulants serve a useful purpose in the treatment of myocardial infarction.

EARLY optimism regarding the effectiveness of anticoagulant therapy in patients with myocardial infarction has been tempered by changing concepts of the mortality in this disease, by the risk of hemorrhage attending their use, and by the difficulty in clinical appraisal of any therapeutic agent in a disease characterized by great variability.1-5 Although thousands of cases are included in the clinical data, with few exceptions autopsy material has not been utilized to study the effects of these drugs.1-8 It is known that death in myocardial infarction may result from shock, congestive failure, arrhythmia, embolization, or ventricular rupture. These multiple factors influence the prognosis of the patient in diverse ways so that a clinical appraisal of one factor, thromboembolism, and its role in mortality and morbidity has been difficult to assess. With reliance solely on clinical data, it is even more difficult to determine the efficacy of anticoagulant therapy in preventing these complications of myocardial infarction. The present series of autopsied cases demonstrates the importance of thromboembolic complications as a cause of death in myocardial infarction, gives quantitative evidence of the value of anticoagulant therapy in preventing these complications and indicates how slight is the risk of hemorrhage subsequent to their utilization.

Material and Methods
The present series of 151 autopsied cases was collected from a private general hospital with an active service in cardiovascular disease. All records were obtained from patients admitted between January 1, 1946, and December 31, 1953, inclusive. This eight-year period was selected for 2 reasons: first, records classified by the “unit” system were easily obtained, and second, during this interval a standard anticoagulant data sheet had been utilized for all patients receiving the drugs. The daily dosage, the prothrombin response, and the complications of therapy were thus clearly indicated on all records.

The clinical diagnosis of myocardial infarction was made in 960 instances during this period. This figure included, not only those dying shortly after admission, but also those dead on arrival to the hospital in whom the diagnosis was often presumptive. Of the patients admitted with this diagnosis 316 (32 per cent) died and 193 autopsy records (61 per cent) were available. Forty-two records were discarded because the patient had survived in the hospital less than 24 hours and the data were therefore incomplete. One hundred fifty-one suitable records otherwise unselected were thus available for study.

Medical care was largely directed by private physicians, among whom internists predominated.

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This study was supported by a grant to the May Institute for Medical Research from the Max Thurnauer Fund.
CHARACTER OF THE SAMPLE—CLINICAL ANALYSIS

The final clinical discharge diagnoses at death are summarized in table 1. Seventy-six patients receiving any form of anticoagulant therapy were included in the “treated” group. The “untreated” consisted of 75 in whom no such drugs were administered.† A discrepancy existed between the clinical and pathologic diagnosis in 26 of the “untreated” and 4 of the “treated” patients. Since the diagnoses were often more obscure in the “untreated” group, it is clear that the two groups were not selected completely at random ($P = <.001$). Nevertheless, it is possible to compare the groups in a number of their clinical and pathologic attributes, once these differences in the samples are recognized.

The clinical features of the two groups are presented in table 2. The two groups were similar in regard to age, race, sex, obesity, the presence of failure, arrhythmia, history of previous occlusion, and the finding of shock. The mean age of the “treated” group was 62.2 years, of the “untreated” 64.9. Figure 1 shows the similar age distribution of the two groups by three-year intervals. A high incidence of failure characterized both groups (table 2). Serious arrhythmias were likewise of common occurrence in both groups (table 2). These included atrial fibrillation or flutter, frequent atrial or ventricular extrasystoles, various degrees of heart block, and ventricular tachycardia or fibrillation.

The duration of illness from onset of symptoms to death is plotted in figure 2. Twenty-two patients in whom emboli were a primary cause of death, or a major contributing cause of death (as determined by pathologic study) have been plotted separately. Six of these deaths occurred in “treated” patients, 16 in “untreated” patients. The time-mortality curves for the three groups are similar. By the tenth day of hospitalization half of all the

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† The similarity in numbers of the 2 groups is fortuitous. The study was terminated in 1953, since anticoagulant therapy is at present almost routinely used, thus limiting the number of “untreated” patients.

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**Table 1.**—Final Clinical Diagnosis on 151 Autopsied Patients with Myocardial Infarction Classified with Regard to the Use of Anticoagulant Therapy

<table>
<thead>
<tr>
<th>Category</th>
<th>No. of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Anticoagulant therapy</td>
<td></td>
</tr>
<tr>
<td>(“treated”)</td>
<td>(76)*</td>
</tr>
<tr>
<td>A. Infarct diagnosed clinically</td>
<td>(72)</td>
</tr>
<tr>
<td>B. Infarct not diagnosed clinically</td>
<td>(4)</td>
</tr>
<tr>
<td>Final clinical diagnosis:</td>
<td></td>
</tr>
<tr>
<td>Congestive failure</td>
<td>1</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>3</td>
</tr>
<tr>
<td>2. No anticoagulant therapy (“untreated”)</td>
<td>(75)</td>
</tr>
<tr>
<td>A. Infarct diagnosed clinically</td>
<td>(49)</td>
</tr>
<tr>
<td>Reasons for omission of drug:</td>
<td></td>
</tr>
<tr>
<td>Years before general use of drug</td>
<td>16</td>
</tr>
<tr>
<td>Diagnosis late or uncertain</td>
<td>14</td>
</tr>
<tr>
<td>No stated reason</td>
<td>5</td>
</tr>
<tr>
<td>Associated cerebral symptoms</td>
<td>3</td>
</tr>
<tr>
<td>Recent ulcer</td>
<td>3</td>
</tr>
<tr>
<td>Doctor or patient refusal</td>
<td>3</td>
</tr>
<tr>
<td>Surgery contemplated</td>
<td>3</td>
</tr>
<tr>
<td>Renal disease, uremia</td>
<td>2</td>
</tr>
<tr>
<td>B. Infarct not diagnosed clinically</td>
<td>(26)</td>
</tr>
<tr>
<td>Final clinical diagnosis:</td>
<td></td>
</tr>
<tr>
<td>Congestive failure</td>
<td>8</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>8</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>3</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>7†</td>
</tr>
</tbody>
</table>

* In parenthesis, total number in that category.
† Generalized vascular sclerosis, gastric hemorrhage, ruptured ventricle, ruptured aneurysm, diabetes, uremia, pulmonary embolism.

Seventy-six per cent of patients receiving the drugs, as well as 76 per cent of those not given anticoagulant therapy, were attended by internists. The remainder of the patients in both groups were seen either by general practitioners or on the service wards of the hospital. Consultation was widely used in the latter two categories.

Autopsies were performed by or under the direction of two senior pathologists,* thus insuring uniform interpretation of pathologic material. For the most part, the autopsies were completed independent of the present investigation, so that the pathologic findings were unbiased by the present study.

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* Dr. Philip Wasserman, Director, Department of Pathology, Jewish Hospital Association, and Dr. Jan Schwartz, Associate Director, Department of Pathology, Jewish Hospital Association.
deaths had occurred. Patients who survived were usually hospitalized for 4 to 6 weeks. This period of observation was sufficiently long for serious late complications to be included in the pathologic material.

Significant differences were noted in the “treated” and “untreated” groups in regard to sex, diabetes, hypertension, and angina (table 2). Their confirmation by pathologic data and their role in the patients’ deaths are considered.

**Adequacy of Anticoagulant Therapy**

It was observed early in the study that certain of the “treated” patients had received only “token” anticoagulant therapy. An occasional patient had received only 1 or 2 doses of the drugs during 10 or more days. Others had received small, inadequate dosage. In order to define therapy as “adequate,” certain arbitrary criteria were established. In general, they correspond to those of Wright and the group of the American Heart Association. These criteria for adequacy are as follows:

1. Initiation of anticoagulant therapy not later than six days after the onset of symptoms suggesting myocardial infarction.
2. At least 21 days of therapy.

**Table 2.** Clinical Comparison of “Treated” and “Untreated” Groups, Classified with Regard to Clinical Characteristics and Statistical Significance

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Treated</th>
<th>Untreated</th>
<th>$p^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, mean</td>
<td>62.2</td>
<td>64.9</td>
<td></td>
</tr>
<tr>
<td>Race (Jewish)</td>
<td>25</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>15</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Congestive failure</td>
<td>46</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>Major arrhythmia</td>
<td>16</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Shock</td>
<td>20</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Previous occlusion</td>
<td>22</td>
<td>17</td>
<td></td>
</tr>
</tbody>
</table>

A. Differences Not Statistically Significant

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Treated</th>
<th>Untreated</th>
<th>$p^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male)</td>
<td>54</td>
<td>35</td>
<td>.01-.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>10</td>
<td>23</td>
<td>~.01</td>
</tr>
<tr>
<td>Hypertension (history or finding on admission)</td>
<td>35</td>
<td>53</td>
<td>.01-.001</td>
</tr>
<tr>
<td>Angina</td>
<td>36</td>
<td>18</td>
<td>.01-.001</td>
</tr>
</tbody>
</table>

$^*$ $P$ = probability of the chance occurrence of such distributions, calculated from $x^2$.
3. Prothrombin concentration of 30 per cent or less (Quick assay) at least 70 per cent of the time dicumarol was administered, excluding the first 5 days of therapy.

All but 2 of the patients in this series received heparin by various routes at the onset of treatment, along with dicumarol. Heparin was continued until the prothrombin concentration had fallen to 30 per cent or less of the normal concentration. One patient received phenindione (Hedulin). Of the 76 patients receiving anticoagulants, 56 had adequate therapy when classified by the above criteria.

**Character of the Sample—Pathologic Analysis**

The primary cause of death as classified by the pathologist is noted in table 3. All 151 patients died with myocardial infarction, although secondary causes, for example, failure or shock, were often immediately responsible for the patient’s death. On pathologic examination, many of the clinical differences between the 2 groups could not be confirmed. Congestive failure occurred in 66 of the “treated” and 48 of the “untreated” group (table 4). Although a portion of the failure might be ascribed to terminal pulmonary edema, the incidence of failure was higher in both groups than the clinical data had suggested.

Clinically, hypertension was commoner in the “treated” group. Cardiac hypertrophy, however, one objective reflection of sustained hypertension, was of equal distribution in both groups (fig. 3). Likewise the incidence of a previous occlusion was greater in both groups than the history had indicated, since it was found at autopsy in 30 of the “treated” and 27 of the “untreated” patients.

Aneurysmal dilatation of the left ventricle resulting from a previous infarct was found in 5 of the “untreated” and in 12 of the “treated” patients ($P = .1-.05$). Old mural thrombi in association with the aneurysm were found in 3 of the former and 7 of the latter categories, which confirm the findings of Schlichter, Hellerstein, and Katz regarding the frequency of this complication in patients with myocardial infarction.10

A definite thrombotic coronary occlusion was found on gross examination in 61 patients in the “untreated” and 64 of the “treated” group. Myocardial infarction without thrombosis was noted in 14 of the “untreated” and 12 of the “treated” patients. The left coronary artery was thrombosed in 27 of the “treated” and 25 of the “untreated” patients, the right artery in 8 of the “untreated” and 9 of the “treated” patients. Thrombosis was noted in the circumflex artery in 8 “untreated” and 4

### Table 3.—Pathologic Diagnosis of the Primary Cause of Death in 151 Patients Dying with Acute Myocardial Infarction

<table>
<thead>
<tr>
<th>Condition</th>
<th>“Treated” Patients</th>
<th>“Untreated” Patients</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction*</td>
<td>53</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>Ruptured ventricle</td>
<td>6</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>1</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Congestive failure</td>
<td>6</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Pyelonephritis (chronic)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perforated duodenal ulcer</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Multiple hemorrhages</td>
<td></td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

**A. Differences Not Statistically Significant**

**B. Differences Statistically Significant**

<table>
<thead>
<tr>
<th>Emboli</th>
<th>7†</th>
<th>16</th>
<th>.02-.01</th>
</tr>
</thead>
</table>

* In the cases listed as myocardial infarction the pathologist could find no other immediate cause of death. In the remainder of the cases, the causes listed were considered the primary factor precipitating death, even though often consequent to the infarct.

† Of these 7 patients in the “treated” category, 5 received inadequate anticoagulant therapy. Excluding these patients, $P = .0025$.

### Table 4.—Pathologic Observations on Congestive Failure in 151 Autopsied Patients with Myocardial Infarction

<table>
<thead>
<tr>
<th>Condition</th>
<th>“Treated”</th>
<th>“Untreated”</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary congestion</td>
<td>38</td>
<td>34</td>
<td>72</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>10</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>Right-sided failure</td>
<td>3</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Combined—right and left</td>
<td>15</td>
<td>24</td>
<td>39</td>
</tr>
<tr>
<td>No failure</td>
<td>10</td>
<td>7</td>
<td>17</td>
</tr>
</tbody>
</table>

Differences are not statistically significant.
TABLE 5.—Chamber Involvement by Mural Thrombi in 151 Patients with Myocardial Infarction, Classified by Treatment Categories and Number of Chambers Involved

<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>One</th>
<th>More Than 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Treated&quot; adequately...</td>
<td>(56)</td>
<td>43</td>
<td>10</td>
</tr>
<tr>
<td>&quot;Treated&quot; inadequately.</td>
<td>(20)</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>&quot;Untreated&quot;</td>
<td>(75)</td>
<td>44</td>
<td>19</td>
</tr>
</tbody>
</table>

In parentheses are the number of patients in that category. When only the presence or absence of mural thrombosis is considered, the probability is between .01-.001 that the differences in the three groups are due to chance alone.

TABLE 6.—Embolization in 151 Patients with Myocardial Infarction, Classified by Treatment Categories, Number of Emboli Per Patient, and Significance of the Emboli

<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>One</th>
<th>More than one</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Treated&quot; adequately...</td>
<td>(56)</td>
<td>51</td>
<td>4</td>
</tr>
<tr>
<td>&quot;Treated&quot; inadequately.</td>
<td>(20)</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>&quot;Untreated&quot;</td>
<td>(75)</td>
<td>44</td>
<td>14</td>
</tr>
</tbody>
</table>

In parentheses are the number of patients in that treatment category.

When only the presence or absence of embolization is considered, the probability is less than .001 that the differences in the three groups are due to chance alone.

* "Primary"—emboli as a primary cause of death or major contributing cause of death. (See text.) The probability is between .01 and .001 that the differences in the 3 groups are due to chance alone.

"treated" patients. The remainder of the coronary thrombi were found in various combinations.

THROMBOEMBOLIC COMPLICATIONS AS AFFECTED BY ANTICOAGULANT THERAPY

Mural Thrombi

Mural thrombi, visible grossly, were significantly reduced by adequate therapy. They were present in 13 of the “adequately treated” group, while 31 in the “untreated” group showed this complication. Inadequate therapy, however, was of no advantage, since mural thrombi were found in 12 of 20 “inadequately treated” patients (table 5). In the “adequately treated” group, more than 1 chamber was involved in 3 cases, whereas there were 19 such instances in the “untreated” group (table 5).

The early appearance of mural thrombi is noteworthy, occurring in a number of patients whose clinical history was brief. Twenty-two patients receiving adequate anticoagulant therapy died on or before the fifth day of illness (fig. 2); mural thrombi were present in 5 of them. Nineteen of the “untreated” group died in the same interval; mural thrombi were present in 7. Mural thrombi were present in 2 of 6 “inadequately treated” patients dying during this same period.

Emboli

A striking reduction in emboli was observed in the present series of patients receiving anticoagulant drugs. In the “untreated” group, 31 instances of such complications were noted (41 per cent); among “adequately treated” patients, 5 were found (9 per cent) (table 6). Inadequate therapy was of no noticeable advantage when compared with the “untreated” group, since 9 such patients (45 per cent) were found with emboli.

Adequate anticoagulant therapy not only prevented emboli, but if emboli were present, they occurred in fewer numbers. In the “adequately treated” group, only 1 patient had emboli in more than 1 site, while 17 such in-
stances were found in the “untreated” group. Again inadequate therapy offered no advantage (table 6), 83 embolic sites being found in the “untreated” group, whereas only 6 were observed in “adequately treated” patients. The diminution in the number of emboli is important, since widely scattered, multiple emboli have a serious prognosis.

Emboli as a Major Contributing Cause of Death

The significance of the emboli in relation to the death of the patient was studied. Cases were selected in which the pathologist classified the emboli at the time of autopsy, as “primary cause of death” or “major contributing cause of death.” Sixteen such patients were found in the “untreated” group (21 per cent), whereas only 2 were observed in the “adequately treated” patients (3 per cent) (table 6). Considered as an important cause of death were massive, repeated or multiple pulmonary infarcts, venous thrombosis associated with massive pulmonary infarction, extensive cerebral thrombosis or infarction, peripheral arterial or mesenteric occlusion, and multiple emboli in scattered areas. As was previously observed in regard to the number of patients affected with emboli, inadequate therapy offered no protection against this complication.

Age of Patient and Occurrence of Emboli

The relationship of age and the incidence of embolization is seen in figure 4. There was a higher incidence of emboli in patients 60 years of age and over, particularly in the “untreated” group. The diagram illustrates the marked diminution in embolic phenomena in this age group when anticoagulants were used. There were, however, 47 patients under 60 years of age in the entire group of patients studied. In these 47 patients, 10 showed emboli (21 per cent). Only 1 of the 10 patients of this combined group had received adequate anticoagulant therapy.

The Clinical Diagnosis of Embolism

The present study emphasizes the difficulty in the clinical diagnosis of emboli as recently shown by Towbin11 and others.5 The clinical diagnosis of embolism was made only 7 times in the “untreated” group, whereas 31 patients were found with this complication. In the “treated” group the diagnosis was correctly made in 5 of the 15 patients in whom emboli were found at autopsy. The diagnosis was usually correct when cerebrovascular or peripheral arterial occlusion occurred. Pulmonary emboli, however, were often overlooked clinically, even when obvious on gross dissection. The diagnosis was even more difficult in the presence of multiple emboli.

Cerebrovascular Accidents and Myocardial Infarction

In 8 of the “untreated” and 3 of the “treated” patients (table 1) cerebrovascular accidents obscured the diagnosis of myocardial infarction. The common association of these 2 disorders as emphasized by Bean12 adds further difficulty in the diagnosis of myocardial infarction.

Thromboembolic Complications as Influenced by the Characteristic of the Sample

The greater incidence of emboli observed in the “untreated” group could not be ascribed to differences in the 2 groups in regard to sex, clinical history of hypertension, and diabetes (Appendix A, B, C, table 1). Emboli were less
common in the “untreated” group with a history of angina (Appendix D, table 1). No association of age, sex, diabetes, or mural thrombi in these “untreated” patients with a history of angina could explain this difference (Appendix, table 2). It is possible that the subjective history of angina in this group of acutely ill patients was unreliable.

Extension of Infarct or New Infarct

Four patients in the “untreated” group showed either extension of a fresh infarct upon an older infarct or a completely new infarct in association with an older one, in either case suggesting a recent extension of the coronary thrombosis with further vascular occlusion. Five of the “treated” group (4 on adequate dicumarol therapy) showed similar extension. In every instance, whether or not the patient received anticoagulant drugs, extension was always associated with profound calcification of the arteries, the lumina often being so narrowed as to be imperceptible on dissection.

Thrombophlebitis

The venous channels of the legs are a well-known focus of emboli in patients with myocardial infarction. Although dissection of the calf veins was not carried out in the present study, 6 of the patients in the “untreated” group (8 per cent) had thrombosis of the inferior vena cava or the iliac veins. No instance of thrombosis of these vessels was found in the “treated” group \( (P = .01–.001).^{14} \) In 5 of the 6 patients with venous thrombosis, multiple or massive pulmonary emboli were found at autopsy. Anticoagulants seemed highly effective in preventing thrombophlebitis and subsequent disastrous emboli.

Complications of Therapy: Hemorrhage, Ruptured Ventricle, and Hemorrhagic Pericarditis

Table 7 summarizes the data in regard to hemorrhage. Of interest was the occurrence of hemorrhage in the “untreated” group. At autopsy, 5 (6.6 per cent) of the “untreated” group showed gross evidence of hemorrhage, while a sixth had severe nosebleeds when alive. Serious significance was ascribed to hemorrhage from duodenal ulcer in 1 of the “untreated” patients, and to a cerebral hemorrhage in a second. Seven of the patients receiving dicumarol (9.2 per cent) showed evidence of gross hemorrhage. In 1 patient with gastric bleeding and a second with gross hematuria, the diagnosis was made clinically, and the drugs were discontinued. Microscopic hematuria often occurred with adequate anticoagulant therapy and was not regarded as a contraindication to the drug. Death was ascribed to hemorrhage in 1 “treated” patient. Massive bleeding was noted in the medulla, the large and small bowel, and the bladder. These hemorrhages were not detected clinically, nor was the prothrombin concentration excessively low during life. There is no statistical significance between the occurrence of hemorrhage in the “untreated” and “treated” group.

Five patients in the “untreated” group (6.6 per cent) and 6 receiving dicumarol (7.9 per cent) died with rupture of the left ventricle. One patient in each group was found to have hemorrhagic pericarditis without obvious rupture. A higher incidence of fibrinous pericarditis without gross hemorrhage or rupture, however, was found in the “treated” group, 7 such instances being found in the “treated” group, while 2 were found in the “untreated” \( (P = .1–.05). \)

Discussion

The 2 groups were similar in regard to age, heart weight, and duration of illness. There
were likewise no significant differences in regard to race, obesity, congestive failure, major arrhythmia, shock, previous infarction, extension of infarction, aneurysmal dilatation of the ventricles, or hemorrhage. Excluding emboli, the primary causes of death were similar in the 2 groups. Furthermore, even though there were observed differences in regard to sex, diabetes, and history of hypertension, the effectiveness of anticoagulant therapy in reducing embolic complications was not modified by these differences. We assume that the association between angina and diminution in emboli was fortuitous.

The incidence of thromboembolic complications in the 2 groups stands in sharp contrast to these fundamental similarities. The total number of emboli, the incidence of emboli as a primary cause of death, and the incidence of mural thrombosis were all reduced by adequate specific therapy until they were no longer major factors in the over-all mortality.

The present series of autopsied patients emphasizes the observation that patients seriously ill with myocardial infarction are prone to thromboembolic complications. These data confirm the observations of Hellerstein and Martin,\textsuperscript{15} who studied a group of autopsied patients not receiving dicumarol. They found an incidence of 26 per cent serious or fatal emboli. Miller and co-authors,\textsuperscript{16} studied a similar group and found fatal thromboembolic complications in 14 per cent of their cases. In the collected autopsy series of Wright, Marple, and Beck\textsuperscript{8} the extra cardiac complications of myocardial infarction were reduced from 125 per 100 cases in the “untreated” to 45 per 100 patients given anticoagulants. Burton\textsuperscript{8} noted a reduction in emboli from 62 per cent of the “untreated” to 10 per cent of the “treated” cases. Gilchrist and Tulloch\textsuperscript{8} found thromboembolic complications 23.4 more frequent in the “untreated” than the “treated” group. In the present series, not only were the total number of patients affected by emboli reduced with anticoagulants, but also the incidence of fatal or serious emboli was markedly diminished.

The present study indicates that anticoagulant therapy must be started early and used adequately in order to be effective. Inadequate, poorly planned therapy is no more effective in preventing emboli than no therapy whatsoever. The time-mortality curve of fatal embolization, the findings of fresh mural thrombi by the fifth day of symptoms, and the occurrence of aneurysms containing old mural thrombi forming a nidus for propagation of a new thrombosis, emphasize the urgency of early anticoagulant therapy. These observations theoretically justify the concomitant use of heparin and dicumarol on the initiation of therapy, since dicumarol is ineffective during the first few days of its use.

There is an undue risk in waiting to make a definitive diagnosis of myocardial infarction in doubtful or dubious cases. It is necessary only to recognize that the patient has a condition in which thromboembolic complications are a real hazard.\textsuperscript{17-19} Without question, anticoagulant therapy diminishes the disability and death associated with embolic complications, not only in patients with myocardial infarction, but also those without infarction whose clinical status is otherwise similar.

Russek and co-authors\textsuperscript{20, 21} have recommended that patients on admission to the hospital be classified according to “good” or “bad risk” categories, reserving anticoagulant therapy only for the latter group. Schnur\textsuperscript{2} has shown that the response to any type of therapy in myocardial infarction, insofar as reduction in mortality is concerned, varies with the severity of the clinical status of the patient rather than the effect of any specific drugs. It is being recognized, however, that the prognosis of the patient cannot be made definitely, especially on admission to the hospital, particularly for the first 48 hours.\textsuperscript{22} In the present series many patients shifted from “good risk” to “bad risk” categories (table 2). The pathologic data revealed the difficulties in such rigid clinical classification as well as the difficulty in diagnosing the atypical infarct or myocardial infarction associated with cerebrovascular accidents.

The important condition for the clinician to consider is that the patient has a real risk of developing thromboembolism because of failure, shock, arrhythmia, or prolonged inac-
tivity. A definitive diagnosis of myocardial infarction is not of great moment at this early stage. Yet early treatment is life-saving, since half of the patients with embolic complications die within 10 days of the onset of the symptoms of myocardial infarction.

The difficulty in accurate clinical diagnosis of emboli observed in the present series of cases has been noted by Hellerstein and Martin,15 Wright and associates,8 and others. This difficulty must be considered when it is stated that clinically emboli are uncommon in patients with myocardial infarction.1

Emboli were more frequent in the present series in patients of older age (fig. 4). Nevertheless emboli were present in every age category, a finding confirmed by others. It is not unexpected, therefore, that the reduction in emboli in the present series and that of Wright and associates8 was the most striking in patients past 60 years of age. Nevertheless, thromboembolic disease, a hazard at all ages, is largely preventable; youth per se therefore should not be a contraindication to the use of the drugs.

In the present series intracardiac mural thrombi were definitely diminished by adequate anticoagulant therapy. Hellerstein and Martin15 noted mural thrombi in 41 per cent of 160 patients not receiving dicumarol. Jordan et al.23 found mural thrombi in the left ventricle in 33 per cent of 327 patients. In Bean's series12 of 300 autopsied patients the incidence was 47 per cent.

The few large series comparing the incidence of mural thrombi in "untreated" patients and those receiving dicumarol, have all shown a reduction in the number of mural thrombi under adequate anticoagulant therapy. Wright and associates8 found mural thrombi present in 63 per cent of the "untreated" and 33 per cent of the "treated" cases. Burton's series,4 collected from a single source, showed mural thrombi in 69 per cent of the "untreated" cases and 43 per cent of patients receiving anticoagulant therapy. Howell and Kyser,7 and Gilchrist and Tullock8 noted reduction in mural thrombi and subsequent emboli in patients on anticoagulant therapy.

In the present series adequate anticoagulant therapy failed to prevent the extension of the infarct or a new thrombosis in the coronary circulation. In the entire group with this complication, sclerosis was of such intensity that the drug appeared ineffectual. The failure of adequate anticoagulant therapy to prevent extension of infarction in the presence of severe atherosclerosis has been confirmed by the autopsy studies of Wright, Marple, and Beck.5

Thrombophlebitis of the venous channels in the extremities was diminished with anticoagulant therapy, no single instance being noted in the "treated" group. Five of the 6 patients with this complication in the "untreated" group had emboli. One of the chief contributions of anticoagulant drugs may well be their effect on venous thromboses, which are so commonly associated with cardiac disease.

The incidence of hemopericardium and rupture was higher in Wright's series of patients receiving dicumarol than in his "untreated" group.5 Similar observations were made by Waldron and co-authors.24 Goldstein and Wolff25 found hemopericardium associated with fibrinous pericarditis in patients receiving dicumarol for myocardial infarction. Anderson and co-workers,26 however, reported similar findings in 1 patient not receiving dicumarol. Dicumarol has produced hemopericardium when given after myocardial trauma,27 and in patients with nonspecific pericarditis.28, 29 In the present series, small areas of focal hemorrhage were usually observed with exudative fibrinous pericarditis. In the 2 cases of frank hemorrhagic pericarditis, however (table 7), the area of fibrinous pericarditis was localized and well circumscribed.

The incidence of hemorrhagic complications is low, in most series.5–6 In our opinion the increased risk of hemorrhage, of hemorrhagic pericarditis, and of rupture of the ventricle is less than the benefit to be obtained with the judicious use of these drugs, provided there is adequate laboratory control and clinical awareness of the risk their use entails.

The present communication indicates that the chief purpose of anticoagulant therapy in acute myocardial infarction is the prevention of the thromboembolic disease that often accompanies the infarct. In this role, anti-
coagulant drugs serve a useful purpose largely in controlling this serious complication. Their use should not divert the clinician from the problems of shock, failure, and arrhythmia, which together play a more decisive role in the final outcome of the patient.

Summary

Autopsy records of 151 patients dying of myocardial infarction in a large private hospital were reviewed. Seventy-six patients received anticoagulant therapy, and 75 patients did not. Embolic phenomena were of common occurrence in patients dying with myocardial infarction. Clinically, these were often overlooked. The utilization of anticoagulant drugs reduced strikingly the incidence of embolic complications from 41 per cent in the "untreated" series to 9 per cent in the "adequately treated" group. Emboli responsible for the death of the patient, as judged by the pathologist, were reduced from 21 per cent in the "untreated" group to 4 per cent in patients receiving adequate therapy. Inadequate, delayed or poorly planned therapy afforded the patients no protection from this complication. Thrombophlebitis was markedly diminished in "treated" patients, and fewer mural thrombi were found in patients who received adequate therapy. Extension of the infarct or a new infarct was uninfluenced by anticoagulant drugs.

Hemorrhage in the present series was not a significant cause of death. Rupture of the ventricle was noted to occur in both groups regardless of therapy.

The patients could not be rigidly classified on admission to the hospital in regard to their eventual prognosis. This observation, plus the difficulty of diagnosis and the unpredictability of the disease, confirmed the inference that the decision to use anticoagulant therapy should not be dependent upon rigid diagnostic criteria for infarction. The benefit to be obtained from these drugs during the acute phase of illness can be ascribed to the prevention of thromboembolic complications. The indication for their use is a clinical condition in which thromboembolism is a real hazard. In this role they are a useful adjunct in the treatment of myocardial infarction.

Acknowledgment

We are indebted to Miss Caroline J. Watkins, Record Librarian, for her help in obtaining records; Ruth Slutz gave valuable aid.

Summary in Interlingua

Es revidite le protocollas autoptic de 151 patientes morte ab infarcimento myocardiac in un grande hospital private. Septanta-sex patientes recipiva therapia anticoagulant; 75 non. Phenomenos embolic esseva de occurrentia commun in patientes moriente ab infarcimento myocardiac. Illos escapava frequentemente al observation clinic. Le utilisation de drogas anticoagulante reduceva le frequentia de complicationes embolic frappantemente ab 41 pro cento in le serie "non tractate" a 9 pro cento in le serie "a tractamento adequate." Embolos considerate per le pathologo como responsabile pro le morte del paciente esseva reducita ab 21 pro cento in le grupo "non tractate" a 4 pro cento in le grupo "a tractamento adequate." Cursos de therapia inadequate, retardate, o mal planate non protegeva le paciente contra iste complication. Thrombophlebitis esseva marcatemente reducita in patientes "tractate," e minus thrombos mural esseva trovate in patientes qui recipiva therapias adequate. Extension del infarcimento o disveloppamento de un nove infarcimento non esseva influentiate per drogas anticoagulante.

In le presente serie hemorrhagia non esseva un significativo causa de morte. Ruptura del ventriculo occurreva in ambe gruppous sin reguardo al uso o non-uso del therapia.

Le patientes non poteva esser classificate strictemente secundo lor ultime prognose al tempore de lor admission al hospital. Iste observation, insimul con le difficoltate del diagnose e le inprediciabilitate del morbo, supportava le conclusione che le decision de usar drogas anticoagulante non debe depender de strict crietrios diagnostic pro infarcimento. Le beneficio obtenibile ab iste drogas durante le phase acute del morbo pote esser ascrizite al prevention de complicationes thrombo-embolic. Lor uso es indicate si le condition clinic
es de natura a render le disveloppamento de thrombo-embolismo un ver hasardo. In tal casos illos es un utile adjuncto al tractamento de infarcimento myocardiac.

REFERENCES

TABLE 1.—Association of Thromboembolism, Treatment Category, and Clinical Characteristics of the Sample

<table>
<thead>
<tr>
<th>Thromboembolism</th>
<th>Present</th>
<th>Absent</th>
<th>Present</th>
<th>Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
</tr>
</tbody>
</table>
| A. Sex
  "Treated" adequately | 4       | 37     | 1       | 14     |
  "Treated" inadequately | 7       | 8      | 2       | 3      |
  "Untreated" | 11      | 24     | 20      | 20     |
| B. Diabetes
  "Treated" adequately | 2       | 6      | 3       | 45     |
  "Treated" inadequately | 1       | 1      | 8       | 10     |
  "Untreated" | 9       | 14     | 22      | 30     |
| C. Hypertension (History or Finding)
  "Treated" adequately | 2       | 23     | 3       | 28     |
  "Treated" inadequately | 5       | 4      | 4       | 7      |
  "Untreated" | 22      | 31     | 9       | 13     |
| D. Angina
  "Treated" adequately | 4       | 23     | 1       | 28     |
  "Treated" inadequately | 2       | 7      | 7       | 4      |
  "Untreated" | 2       | 16     | 29      | 28     |

TABLE 2.—Association of Diagnostic Categories, Sex, and Presence or Absence of Angina

<table>
<thead>
<tr>
<th>Diagnostic Category</th>
<th>&quot;Treated&quot; Diagnosis Made</th>
<th>&quot;Treated&quot; Diagnosis Missed</th>
<th>&quot;Untreated&quot; Diagnosis Made</th>
<th>&quot;Untreated&quot; Diagnosis Missed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>F</td>
</tr>
</tbody>
</table>
| Angina
  Present........... | 25 | 11 | 9 | 7 | 2 | 0 |
  Absent............. | 30 | 10 | 13 | 20 | 10 | 14 |
The Prevention of Thromboembolic Complications in Myocardial Infarction by Anticoagulant Therapy: A Clinical-Pathologic Study
HELEN I. GLUECK, HENRY W. RYDER and PHILIP WASSERMAN

_Circulation_. 1956;13:884-895
doi: 10.1161/01.CIR.13.6.884
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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