Reassessment of Anticoagulant Therapy in Various Types of Occlusive Cerebrovascular Disease

BY CLARK H. MILLIKAN, M.D.

Abstract: Reassessment of Anticoagulant Therapy in Various Types of Occlusive Cerebrovascular Disease

- Precise use of categorical terms and definitions is mandatory in discussing the use of anticoagulants in treating occlusive cerebrovascular disease. The components of the temporal profile of the disease are described.

Six reports have appeared which describe the results of anticoagulant therapy in transient cerebral ischemic attacks. From these six studies it is concluded that anticoagulant therapy significantly decreased the risk of cerebral infarction in patients who had attacks of transient focal cerebral ischemia.

In the few carefully performed investigations of the use of anticoagulant for acute progressing stroke the evidence points to the lack of progression in patients receiving treatment when compared to individuals not getting such drugs.

There continues to be a definite difference of opinion about the results of anticoagulant therapy in completed stroke. If anticoagulant is to be administered on a long-term basis, it must be considered dangerous and every effort made to control the level of anticoagulant action precisely. Hypertension must be effectively controlled.

ADDITIONAL KEY WORDS: transient ischemic attacks, progressing stroke, cerebral infarction, completed stroke, hypertension

- Precise use of categorical terms and definitions is mandatory in discussing as complex a subject as the use of anticoagulants in treating occlusive cerebrovascular disease. It is incorrect to group all patients with occlusive cerebrovascular disease together. The temporal profile of the disease with which one is dealing must be carefully delineated. I will discuss transient ischemic attacks, progressing infarction (stroke-in-evolution), and complete stroke.

Transient ischemic attacks are defined as episodes commonly of a few minutes' duration (maximum 24 hours) which come on swiftly (in a few seconds) and consist of a focal neurological deficit. The attacks are usually spoken of as being in the carotid system or in the vertebral-basilar system; these adjectives designate the part of the brain which is clinically ischemic and which is normally supplied by the named arterial system, even though, due to arterial disease, all or a portion of the blood to the transiently ischemic area may be provided through some collateral channel or channels.

A progressing stroke or stroke-in-evolution is that category in which there has been progression (increased severity of the neurological signs) within recent minutes—this value judgment may be made from analysis of the history or by repeated examination of the patient. It may be difficult to be certain from minute to minute or even from hour to hour whether further progression will occur. However, if there has been worsening of the neurological deficit in the few minutes antecedent to making a judgment about a particular patient's status, the situation should be categorized as a progressing cerebral infarction or
stroke-in-evolution. If the site of the lesion is in the carotid system, 18 hours to 24 hours without progression is ordinarily sufficient to mean that further progression is unlikely and that the patient's status should no longer be categorized as "progressing stroke." If the lesion is in brain supplied by the vertebral-basilar system, a longer period of time (up to 72 hours) should probably elapse before the patient is removed from the progressing-stroke category and designated as a "completed stroke," since there is a tendency for aliquots of progression to be separated by many hours when the impaired circulation is in the vertebral-basilar system.

Completed stroke is the instance where the focal neurological deficit is stable; the number of hours suggested for making this decision has just been discussed under progressing stroke. The word "completed" does not imply that a particular neurological sign has become maximal in quantity—that is, hemiplegia as distinguished from hemiparesis. A cerebral infarct may be judged to be completed when the neurological deficit is minor or when it is severe.

The primary objective of anticoagulant therapy is to impede or prevent thrombosis and thus maintain the integrity of arterial flow patterns and, in certain instances, to prevent the formation of emboli which consist of fragments of thrombus. The practical objectives of such treatment are (1) to stop or ameliorate focal transient ischemic attacks, (2) to prevent cerebral infarction (and the attendant persistent neurological deficit) in patients having transient ischemic attacks, (3) to stop the progression in patients with stroke-in-evolution, (4) to prevent the formation of emboli arising from a cardiac source, and (5) to prevent or decrease the number and severity of all types of thromboembolic complications, including recurrent cerebral infarction in the same arterial system as a previous event or in a different arterial system. Obviously, the objectives fall into the general category of "prevention."

In assessing how well these objectives are accomplished, the beneficial results must be weighed against the complications and other problems associated with the therapy. Because of the inherent danger in producing hypoprothrombinemia, the following criteria must be present before short-term anticoagulant therapy is instituted in the hospital: (1) accurate diagnosis of cerebrovascular disease, (2) physician knowledgeable in the use of anticoagulants, (3) availability of accurate clotting tests, and (4) no significant contraindications to the treatment. In the hospital, active bleeding is the primary or absolute contraindication to the treatment. If there is a bleeding tendency, hepatic disease, renal disease, or extraordinarily severe hypertension, anticoagulants should be used only with extreme caution, and the high blood pressure should be prudently reduced. Out of the hospital, if anticoagulant is to be administered for a longer period of time, additional qualifications must be met. These include absolute cooperation of patient and relatives in following instructions accurately, and optimum control of arterial hypertension. If these criteria are met, the serious complication rate is acceptably low.

In the study of focal transient cerebral ischemic attacks reported by Baker and co-workers in 1966, there were no serious complications of anticoagulant therapy. In experience at the Mayo Clinic, it has been interesting to note that, if one uses a period of follow-up as long as five years, 5% of patients treated for transient focal cerebral ischemia will develop intracerebral hemorrhage; however, 4% of patients not receiving anticoagulant therapy also die of intracerebral bleeding. This suggests that the patient population being studied is one in which there are significant cerebrovascular disease and weakening of arteries, and, therefore, a significant incidence of intracerebral hemorrhage.

To evaluate how well the objectives of anticoagulant therapy have been accomplished it is necessary to understand fully the variable natural history of occlusive cerebrovascular disease and to compare the results of treatment with observations of a similar group of patients not undergoing anticoagulant therapy. The natural history of focal transient cerebral ischemic attacks and of progressing stroke is so variable that no significant judgment can be made about the efficacy of a therapy from simple observation of an occasional patient.

This assessment of the status of the use of anticoagulant therapy in occlusive cerebrovascular disease will, therefore, be limited to those reported studies which have carefully designat-
ed the temporal category of cerebrovascular disease being treated and have compared observations of an anticoagulant-treated group with observations of a similar group of patients not receiving anticoagulant. However, there are some studies of the natural history of focal transient cerebral ischemic attacks which do not include a study of any method of treatment. Therefore, table 1 is included so that a direct comparison can be made of the latter observations. Particular attention should be directed to the length of the follow-up period and the percentage of patients developing cerebral infarction during that follow-up period. The basic or underlying pathological process, atherosclerosis, is one which develops over considerable time, and focal defects in various organs also appear over many months or several years.

Only two studies of the natural history of transient ischemic attacks (that of Pearce and associates and Marshall) describe a percentage of patients developing cerebral infarction which is significantly different from the other six studies. In the instance of Pearce and associates, the follow-up period was less than a year. This means, in effect, that had these same patients been observed for as long as 50 or 60 months, there would probably have been more of them with cerebral infarction than in any of the other studies reported. This leaves the experience noted by Marshall as the only one which is entirely different from any other reported in the literature. One can only speculate on the reasons for this strange observation. Although the title of the paper is "The natural history of transient ischemic cerebrovascular attacks," and group 2 in the article contains 61 patients having transient ischemic attacks and followed for about 45 months, there is almost nothing in the paper about this group of patients! The descriptive material almost completely relates to group 1—68 patients seen because of "completed stroke" who gave a retrospective history of having had transient ischemic attacks before cerebral infarction. The inspection of this latter group of patients, of course, gives the reader no information about what we ordinarily refer to as the natural history of transient ischemic attacks. If one then attempts to find out about the group 2 patients, one cannot even determine the nature of the attacks and can only note that there was a high incidence of vertigo among these patients; one of the case reports describes an individual who had episodes of vertigo lasting only ten seconds. Obviously the inclusion of patients such as this one will skew the natural history toward benignity, as it has been known for many years that attacks of this nature are not a forewarning of cerebral infarction.

One can, therefore, only conclude that the series mentioned by Marshall as group 2 patients is entirely different from those reported by other authors and does not represent the natural history of transient ischemic attacks. From the available data, it appears realistic to judge that 25 to 40% of patients who have more than one transient ischemic attack will have cerebral infarction if followed as long as five years.

**Transient Ischemic Attacks**

Table 2 shows some data from five reports of direct attempts to compare untreated patients
TABLE 2  

Anticoagulant Therapy and Transient Ischemic Attacks

| Study            | Control | Treated | Control | Treated | Control | Treated | Control | Treated | Control | Treated |
|------------------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
| Siekert et al.   | 160     | 60      | 83 (52%)|         | 51 (32%)| 18 (11%)| 7 (4%)  |
| Baker et al.     | 175     | 60      | 131 (75%)|        | 7 (4%)  | 3 (2%)  | 13 (7%) |
| Fisher*          | 20      | 18      | ?       |         | 5 (25%) | 1 (5%)  | 0       |
| Pearce et al.    | 20      | 10.6    | 11 (55%)|         | 2 (10%) | ?       | ?       |
| Friedman et al.  | 30      | 40.6    | ?       |         | 7* (23%)| ?       | ?       |
|      | 30      | 37.9    | ?       |         | 2 (7%)  | ?       | 0       |

Patients (no.)  Follow-up (mo)  Normal  Cerebral Infarct (total)  Cerebral Infarct (kthal)  Cerebral hemorrhage

- Three patients randomized as treated had CVA after anticoagulation stopped.
- One cerebral hemorrhage in treated group but while off anticoagulant
- One patient had been on anticoagulant but this was discontinued before the cerebral infarction.

who had transient ischemic attacks with those receiving anticoagulant drugs. It is recognized that variations occur in the individual patient responses to the effect of an anticoagulant. In each of the studies, the anticoagulant was administered by personnel expert in controlling such treatment; one must realize that there must have been an unknown number of times when each patient had too much anticoagulant action or too little anticoagulant action. The problem is somewhat analogous to the precision with which it is possible to control diabetes or hypertension. It is important to note the number of months of follow-up in each study, to recall the long-term nature of the problem of observing the complications of atherosclerosis, and to reflect on the significance of follow-up of less than a year, as in the study of Pearce and associates. The actual numbers of patients in each of four of the studies were so small as to make comparison between treated and untreated groups of only relative statistical significance. Nevertheless, the percentage of individuals developing cerebral infarction was similar (spread of from 3% to 7%) in all of the treated groups of each study. While there was more variation in the percentage of individuals developing cerebral infarction in the control groups, only Pearce and associates reported a figure of less than 23% and their follow-up was less than a year.

Cerebral hemorrhage was the complication most feared, and occurred in 7% of the Mayo patients receiving anticoagulant. During observation of similar untreated patients over five years, the Mayo investigators reported that 4% had cerebral hemorrhage. These observations suggest that one is dealing with a cerebrovascular disease population at high risk for cerebral hemorrhage, and some of the problems observed in those individuals receiving anticoagulant might well have occurred had the individuals not been taking such a drug. In table 2 no record is made of the number of transient ischemic attacks reported by treated and untreated patients. All authors mention that transient ischemic attacks stop while the patient is receiving anticoagulant, while the untreated patients continue to have such transient episodes in many instances.

From these observations—the cessation of transient ischemic attacks in patients receiving anticoagulant, and particularly the
lowered incidence of cerebral infarction while taking the drug—it is concluded that anticoagulant therapy significantly decreased the risk of cerebral infarction in patients who had attacks of transient ischemia, and in this carefully selected group of patients it is worthwhile therapy if the anticoagulant program is managed so as to keep complications minimal.

**Progressing Stroke**

 Apparently there is considerable variation in the type of patient accepted into this category. This variation evolves from different uses of the term "progressing stroke" and from different methods of deciding, at the bedside, when a patient should be further categorized as "completed stroke." Ordinarily, patients should be placed in the "progressing stroke" category when there is a pre-hospital history, in the preceding minutes to hours, of progressing symptoms and signs, or when there has been an increase in severity or distribution of the neurological deficit after admission to the hospital. If patients are included whose neurological deficit reached its maximum 24 hours prior to admission (or 48 or 72 hours prior to admission), one will find the "progressing stroke" category contaminated with many individuals in whom the dynamic pathophysiological process has stopped its progression. Inclusion of such patients can only accrue to the relative disadvantage of any scheme of treatment, since in such patients there is no progression to treat. That is, the absence of progression indicates that the pathophysiological process has reached its maximum degree and from that point the natural history of such patients is usually one of improvement, sometimes at a fairly rapid rate.

In most instances in the literature, little distinction is made between progressing stroke in the vertebral-basilar system and in the carotid system. Whisnant reported a mortality of 8.5% with anticoagulant treatment of patients having progressing stroke in the vertebral-basilar system, whereas 58.9% of a similar untreated group died. Whisnant went on to comment that:

There has been a point of confusion in the literature regarding the mortality of vertebral-basilar thrombosis. The confusion has arisen, I believe, from the inclusion in this category of limited brain stem infarcts, that is, well-localized infarcts in the distribution of a single arterial branch. Since these limited lesions in the stem have a fairly good prognosis, the inclusion of these obviously lowers the mortality rate.

Thus, Whisnant found that of 140 patients treated with anticoagulant where there had been progression with fluctuation or stepwise accumulation of the neurological deficit related to the territory of more than a single arterial branch of the vertebral artery or vertebral-basilar system, 12 patients died, whereas of 39 not receiving anticoagulant, 23 died.

Unfortunately, there are few reports where the term "progressing stroke" is used in relatively uniform fashion and in which a comparison is made between a group of patients treated with anticoagulant medication and a group not receiving such treatment. Because of the acute, often emergent, nature of the disorder, anticoagulant treatment usually is initiated by intravenous administration of heparin, and it is common practice to then continue with an oral anticoagulant, at least during the period of hospitalization. The extraordinary variability in the natural history of acute progressing stroke makes it mandatory that comparison be made by the individual investigator or group of investigators of treated and untreated patients of similar type. It is obvious that the quality of the observations made at the bedside of such patients must be of high order or valid inferences cannot be made from either group or from a comparison.

Table 3 summarizes those studies in the literature which in general fulfill the above qualifications. In each investigation, a primary determination was made of the state of the patient at the time of his admission to the study: progression of the neurological deficit had taken place in the preceding few minutes. There was frequent reevaluation of the neurological deficit, and subsequently a comparison was made between the maximum neurological defect developed and the neurological defect present at the time of entry into the study. The percentage of patients showing progression of neurological deficit (after primary assessment) in the control and treated groups of each report is in the right-hand column of the table. In each instance, the treated group fared considerably better than those not receiving anticoagulant—for example, in the Mayo study, 20% of those treated showed evidence of neurological progression after entry into the study.
TABLE 3

<table>
<thead>
<tr>
<th></th>
<th>Pet lent! (no.)</th>
<th>Follow-up (mo)</th>
<th>Death, cerebral into net</th>
<th>Death, cerebral hemorrhage</th>
<th>Progressive infarct</th>
<th>Progression (total %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Millikan</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>60</td>
<td>12</td>
<td>25 (40%)</td>
<td>0</td>
<td>8 (13%)</td>
<td>52</td>
</tr>
<tr>
<td>Treated</td>
<td>181</td>
<td>12</td>
<td>12 (7%)</td>
<td>0</td>
<td>25 (14%)</td>
<td>20</td>
</tr>
<tr>
<td>Carter</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>38</td>
<td>6</td>
<td>7 (17%)</td>
<td>0</td>
<td>12 (33%)</td>
<td>50</td>
</tr>
<tr>
<td>Treated</td>
<td>38</td>
<td>6</td>
<td>3 (7%)</td>
<td>0</td>
<td>9 (24%)</td>
<td>32</td>
</tr>
<tr>
<td>Baker et al.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>67</td>
<td>15</td>
<td>10 (15%)</td>
<td>0</td>
<td>21 (31%)</td>
<td>46</td>
</tr>
<tr>
<td>Treated</td>
<td>61</td>
<td>12</td>
<td>5 (8%)</td>
<td>1 (2%)</td>
<td>8 (13%)</td>
<td>23</td>
</tr>
<tr>
<td>Fisher</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>14</td>
<td>?</td>
<td>0</td>
<td>0</td>
<td>9</td>
<td>64</td>
</tr>
<tr>
<td>Treated</td>
<td>14</td>
<td>?</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>21</td>
</tr>
<tr>
<td>Fisher</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>49</td>
<td>7.4</td>
<td>7</td>
<td></td>
<td>14 (29%)</td>
<td>40</td>
</tr>
<tr>
<td>Treated</td>
<td>51</td>
<td>5.7</td>
<td>4</td>
<td>1</td>
<td>7 (14%)</td>
<td>14</td>
</tr>
</tbody>
</table>

whereas 52% of patients not receiving anticoagulant showed progression after initial evaluation. The figures from Fisher (National Study) are difficult to interpret but are included since the patients were said to be randomized. Fisher said:

In regard to progression of the infarction the number of patients was 14 in the control and seven in the treated. Now if we analyze the number of episodes of progression and classify them as early (within two weeks of randomization) and late (after two weeks) there were in the control 11 early and nine late and in the treated six early and one late. If one adds these together, one gets 20 episodes in the control group and seven episodes in the treated group; this suggests that anticoagulants were having a beneficial effect on the process of thrombosis and infarction.

In Fisher's personally observed patients, the total number of subjects is too small to provide a statistically significant result. However, the trend was definite, with only 21% of the treated patients showing progression compared with 64% of those not receiving anticoagulant. The observations of the cooperative group, in 1962, confirm this trend; twice as many nontreated patients had progression after entry into the study as did individuals receiving anticoagulant. Thus, in the few carefully performed investigations of the use of anticoagulant for acute progressing stroke, the evidence points to the lack of progression in patients receiving anticoagulant when compared to individuals not getting such drugs.

**Completed Stroke**

Once again, in the literature, the lack of uniform terminology is apparent. The objective of anticoagulant treatment in this category is to prevent recurrent thrombosis or embolism in all parts of the body including the brain. Students of the pathology and pathophysiology of cerebral infarction generally have believed that when a lesion was so severe that a total motor deficit (hemiplegia) persisted for many hours, it was highly unlikely that anticoagulant would produce any change which would significantly benefit the infarcted tissue. Might such infarcts be the site of increased risk of hemorrhage if anticoagulants were administered? This was the experience of Wood and associates in laboratory animals. However, Marshall and Shaw studied this question with their stated primary aim "... to assess the influence of anticoagulant therapy on the immediate mortality—i.e., within 6 weeks of the cerebrovascular accident, ..." The criterion for admission to the study in either the group treated with anticoagulant or those individuals not treated was that within 72 hours before admission the patient had sustained a severe focal neurological deficit thought to be due to cerebral infarction. By using the paired patient technique, the authors observed that the
REASSESSMENT OF ANTICOAGULANT THERAPY

### TABLE 4

<table>
<thead>
<tr>
<th>Anticoagulant Therapy for Completed Stroke</th>
<th>Patient (no.)</th>
<th>Follow-up (mo)</th>
<th>Cerebral Infarct</th>
<th>Cerebral Infarct (died)</th>
<th>Hemorrhage, severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baker et al.15</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>60</td>
<td>16</td>
<td>16(27%)</td>
<td>5(8%)</td>
<td>0</td>
</tr>
<tr>
<td>Treated</td>
<td>72</td>
<td>10</td>
<td>30(42%)</td>
<td>6(8%)</td>
<td>7(10%)</td>
</tr>
<tr>
<td>Hill et al.16</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>65</td>
<td>31</td>
<td>19(29%)</td>
<td>1(2%)</td>
<td>0</td>
</tr>
<tr>
<td>Treated</td>
<td>66</td>
<td>28</td>
<td>22(33%)</td>
<td>5(8%)</td>
<td>7(11%)</td>
</tr>
<tr>
<td>McDowell &amp; McDevitt18</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>99</td>
<td>33.5</td>
<td>22(22%)</td>
<td>7(7%)</td>
<td>2(2%)</td>
</tr>
<tr>
<td>Treated</td>
<td>92</td>
<td>42.2</td>
<td>1(1%)</td>
<td>1</td>
<td>7(7.6%)</td>
</tr>
<tr>
<td>Enger &amp; Bøyesen17</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>49</td>
<td>39.2</td>
<td>8(16%)</td>
<td>3(6%)</td>
<td>0</td>
</tr>
<tr>
<td>Treated</td>
<td>51</td>
<td>22.8</td>
<td>4(8%)</td>
<td>1(2%)</td>
<td>3*(6%)</td>
</tr>
<tr>
<td>Howell et al.18</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>92</td>
<td>36</td>
<td>28(30%)</td>
<td>?</td>
<td>0</td>
</tr>
<tr>
<td>Treated</td>
<td>103</td>
<td>16</td>
<td>7(7%)</td>
<td>?</td>
<td>4(4%)</td>
</tr>
</tbody>
</table>

* Patients hypertensive, not treated.

The treatment could not possibly be effective, so the study was stopped while results were inconclusive in that there was no statistical evidence that the treatment was dangerous.

Table 415-18 is a summary of those investigations where there is evidence that the authors used the standard definition of "completed stroke" and compared control with treated patients. If one looks only at the percentage of patients developing repeated cerebral infarction, three investigations display percentages slightly in favor of treatment. However, this does not take into account the complications which occurred. Also, it is important to notice the variable time period of follow-up, since atherosclerosis and stroke as a complication of atherosclerosis is a long-duration issue. In the Howell and co-workers18 study, the treated patients were followed for only 16 months while the control patients had a follow-up of 36 months and, therefore, over twice as long a time period during which to have repeated cerebral infarcts. The authors note, in the manuscript, that they did count the number of strokes occurring in the first 16 months in both series—in the control group there were 12 and in the treated group there was one such event. Thus, there continued to be a suggestion of beneficial preventative effect of the medication. However, in the report of the cooperative group,3 the treated patients were followed for only ten months and yet had a recurrence of cerebral infarct in 42% of the patients, while only 27% of the control group followed for 16 months had the same events. In this investigation, the treated patients had a 10% incidence of severe hemorrhage. This combination of results would suggest that anticoagulant therapy is actually contraindicated under the definitions of the authors. The same conclusion must be reached from looking at the data accumulated by Hill and associates.16

Therefore, there continues to be a definite difference of opinion about the results of the use of anticoagulant in this category of cerebrovascular disease. It is obvious that if anticoagulant is to be administered on a long-term basis, it must be considered somewhat dangerous, and every effort should be made to control the level of the anticoagulant action precisely. Hypertension must be effectively controlled and certain relative contraindications to the use of the medicine are impaired liver, renal, or gastroenterological function.

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207

Addenda

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