Hemorrhagic Complications of Long-Term Anticoagulant Therapy for Ischemic Cerebral Vascular Disease

MARK LEVINE, M.D.,*† AND JACK HIRSH, M.D.*

SUMMARY The main complication of anticoagulant therapy is bleeding. Although the use of long-term oral anticoagulants in patients with transient cerebral ischemia and/or minor stroke is controversial, anticoagulants are still used in some instances. We have carried out a literature review of the risk of hemorrhage during long-term oral anticoagulant therapy in patients with cerebrovascular disease to determine the rate of bleeding and the clinical and laboratory risk factors which predispose patients to bleeding. The risk of bleeding was substantial with major bleeding episodes ranging from 2% to 22% per year and fatal bleeds from 2% to 9% per year. Only hypertension emerged as an identifiable risk factor and its presence increased the relative risk of bleeding to more than two fold. Major bleeding was almost always intracranial, possibly because of associated hypertension or because of cerebrovascular disease per se. We could not detect a relationship between bleeding and the intensity of anticoagulant therapy, although major bleeding occurred frequently even with only moderately intense anticoagulant therapy. The net gain or loss in efficacy rate of treating patients with minor stroke with long-term oral anticoagulant therapy was examined and it was concluded that in order for such treatment to be beneficial, a risk reduction of more than 50% in stroke rate, and a major bleeding rate of less than 2% per year are required. Since the risk reduction for stroke and death with anticoagulant therapy is unlikely to be 50% and the risk of major bleeding likely to be more than 2%, the present evidence does not support the use of anticoagulant therapy in minor stroke.

CONSIDERABLE PROGRESS has been made in the management of patients with cerebrovascular disease. A number of studies have demonstrated that aspirin is effective in patients with transient cerebral ischemia and minor strokes and there is a strong impression that carotid endarterectomy is useful in selected patients. The role of long-term anticoagulants in patients with transient cerebral ischemia and/or minor strokes is controversial. Some neurologists use anticoagulant therapy in patients who fail to respond to aspirin or who do not have surgically correctable lesions; others consider anticoagulants the treatment of choice, while some neurologists feel that anticoagulants have no place in the long-term management of patients with non-embolic cerebral vascular disease. The reluctance to use oral anticoagulants in patients with minor strokes stems from lack of definitive evidence that anticoagulants prevent morbidity and mortality in these patients and on the strong clinical impressions that anticoagulants produce serious bleeding in patients with cerebral vascular disease. We have carried out a literature review of the risk of bleeding during long-term oral anticoagulant therapy in patients with cerebral vascular disease to determine the rate of bleeding and the clinical and laboratory risk factors which predispose patients to bleeding. The reported bleeding rates have been used to construct a simple risk/benefit ratio table for various levels of benefit. It was necessary to assume levels of benefit because none of the trials of long-term anticoagulant therapy in minor stroke provided reliable estimates of risk reduction.

Before reviewing the potential risks and benefits of long-term anticoagulant therapy in ischemic cerebral vascular disease, it is important to appreciate that there were differences in the intensity of anticoagulant therapy used in the different trials (based on different therapeutic ranges and differences in the responsiveness of the laboratory tests used to monitor therapy) and to consider the risks of bleeding associated with the different intensities of anticoagulant effect.

The Laboratory Control of Anticoagulant Therapy

Oral anticoagulant therapy (with the vitamin K antagonists) is usually monitored by the 1-stage prothrombin time (PT) (Quick-time), or less commonly, the thrombotest (TT). The aim of anticoagulant therapy is to reduce the coagulability of blood into a therapeutic range within which the patient is protected against thrombosis, while being exposed to a minimal risk of bleeding. The PT result can be expressed as time in seconds, as a ratio (patient time in seconds/control time in seconds), or as an index (which is control

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Received April 25, 1985; accepted April 30, 1985.
time/patient time multiplied by 100), or as a percent of normal control plasma using a saline dilution curve.

The thromboplastins used for the PT in North America are derived from rabbit brain or a mixture of rabbit brain and lung, those used in the United Kingdom are usually derived from human brain, while the thromboplastin used for the TT (a test commonly used in Scandinavia) is derived from bovine brain.

In general, the human brain thromboplastins are more sensitive to deficiencies in the vitamin K dependent clotting factors than the rabbit brain thromboplastins in current use; although it is possible to prepare rabbit brain thromboplastins of approximately similar sensitivity to human brain thromboplastin. In order to standardize the laboratory control of oral anticoagulant therapy the WHO has prepared an international reference standard of thromboplastin from human brain, and based on this, international committees have made joint recommendations for the adoption of a uniform calibration system whereby the prothrombin time ratio is expressed in terms of the International Normalized Ratio (INR*). 8, 9

The optimal therapeutic range for laboratory control of oral anticoagulant therapy has been debated for over 30 years10-12 and has remained unresolved because it had never been assessed in properly designed studies. Resolution of this important question can best be achieved by randomizing patients prospectively into groups which have their PT monitored to obtain different intensities of anticoagulant effect and by measuring clinically relevant outcomes. Until recently no such studies had been performed and the recommended guidelines have been based on informed opinions which have differed widely between experts. 9, 11

In the early 1950's, Wright and associates12 suggested that the optimal therapeutic range (using commercially available rabbit brain thromboplastin) is obtained with a PT ratio of 2 to 2.5 times the normal control value (INR equivalent 4.4-7.5). By and large this recommendation was accepted and has been adhered to in North America for the last 30 years. Although it was not based on what we would now consider as solid evidence.

In 1982, Poller10 stated that most British hospitals consider that the optimal therapeutic ratio using the standardized human brain thromboplastin is 2 to 4.5 (INR 2-4.5) times the control (which is equivalent to a prothrombin time ratio using commercially available rabbit brain thromboplastin of 1.3 to 2.0 times the normal control).

If the therapeutic ratio used by most British hospitals is correct, then patients in North America monitored by rabbit brain thromboplastin at a ratio of 2 to 2.5 times control (equivalent to a ratio using human brain thromboplastin of 4.4-7.5 times control) are being treated with unnecessarily high doses of anticoagulants and are being exposed to an unnecessary risk of bleeding. Conversely, if the recommendations made by Wright and associates are correct, a rabbit brain prothrombin time ratio of 2 to 2.5 times control (INR equivalent 4.4-7.5)) then it could be argued that patients in the United Kingdom who are treated to achieve a less intense anticoagulant effect (INR 2-2.5) are receiving suboptimal anticoagulant therapy.

The optimal therapeutic range for oral anticoagulant therapy in patients with cerebral vascular disease has never been established by adequately designed clinical trials. Indeed the optimal therapeutic range for oral anticoagulant therapy in patients with ischemic heart disease, prosthetic heart valve replacement, arterial thromboembolism, and atrial fibrillation has never been established by adequately designed clinical trials. 13 Recently, however, clinical trials have been performed evaluating the optimal therapeutic range for oral anticoagulants for the continued treatment of venous thrombosis and for the prevention of venous thrombosis in high risk surgical patients. These studies have demonstrated that patients with venous thrombosis can be treated effectively and more safely by using an INR of 2 which is equivalent to a rabbit brain thromboplastin time of 1.2 to 1.4 times the control value rather than the recommended range of 2 to 2.5 times control.14

It is uncertain whether this less intense anticoagulant regimen would be effective in patients with other forms of thrombotic or vascular disease but there is evidence (discussed below) that even the less intense anticoagulant treatment regimen is associated with a high risk of major bleeding in patients with cerebral vascular disease.

Bleeding During Anticoagulant Therapy in Cerebral Vascular Disease

Methods

Potentially useful articles were identified through a computerized literature search (Medline) and through relevant review articles. Each report was reviewed seeking the following information:

1) Description of the cohort of patients being treated, including age, sex, indication for anticoagulant therapy and duration of anticoagulant therapy (patient-years of exposure).
2) Evidence that bias was avoided by having a concurrent randomized placebo treated control group.
3) A clear description of the criteria used for assessing bleeding and evaluating the severity of bleeding.
4) Evidence that a sufficient number of patients were treated to provide acceptable confidence limits for the reported rate of bleeding.
5) The defined therapeutic range used for anticoagulant control and the type of thromboplastin used (whether human, rabbit, or bovine in origin).
6) The results of the prothrombin time immediately before the hemorrhagic episode in patients who bled as well as the result of the prothrombin time obtained at regular intervals throughout the period of treatment in patients who both did and did not bleed.
7) The interval between commencing anticoagulant therapy and the occurrence of bleeding, in addition to the number of patients exposed to anticoagulant therapy at each reported time of bleeding.
8) A description of comorbid and co-therapeutic features such as hypertension, malignancy, ulcer disease and other drug therapy in both patients who bled and those who did not bleed. The reports were classified into one of 4 categories based on the strength of the study design; level I representing studies which provided the most reliable information and level IV the least reliable.

Level I studies were randomized controlled trials with sufficient numbers to provide a reliable index of bleeding, or in which a clinically and statistically significant difference in bleeding was detected. Studies classified as Level II, III and IV provided less reliable information either because they contained too few patients or because they lacked a concurrent control group.

Case reports were not included in the analysis since they do not provide a valid estimate of bleeding rates or risk factors.

The definition of major and minor bleeding differed between studies. For the purposes of our analysis, we classified episodes of hemorrhage as major if they lead directly to death, hospitalization or transfusion. All other bleeding episodes (including some gastrointestinal bleeds, most cases of epistaxis, hematuria, ecchymosis, and hemoptysis) were classified as being minor.

For the purpose of comparison between studies, we have converted the reported test results for monitoring anticoagulant therapy into the International Normalized Ratio (INR)* (fig. 1).

Results and Discussion
Randomized Controlled Trials — Level I Evidence

There were 6 studies which were classified as Level I (see table 1). In only three of these was the duration of anticoagulant therapy clearly described. In all 6, the rate of bleeding was greater in the treatment group than in the groups receiving no treatment or either low doses of anticoagulants or anti-platelet agents. The difference was statistically significant in 5 of 6 studies and there was a strong trend in the sixth in which coumadin was compared to ASA and dipyridamole. The risk of bleeding was impressive and varied between 11.8% and 39.7%. The risk of major bleeding was also high, being 7% or more in 4 of 6 studies. Fatal hemorrhage occurred in more than 5% of patients in 4 studies and in more than 1% in the two other studies. The lowest bleeding rates were reported by Olsson et al. In this study, all patients were treated with anticoagulants for two months and were then randomized to either continue oral anticoagulants or to stop anticoagulants and receive antiplatelet agents. The low bleeding rates in this study might be explained by a selection bias since as stated by the author, patients who bled before randomization were not included in the analysis. One of the highest bleeding rates was reported in the study by Baker et al. Twenty-two bleeding episodes occurred within the first month of therapy. These high bleeding rates might be explained by the initial use of heparin plus oral anticoagulants in some patients. It was only possible to calculate bleeding per 100 patient years of therapy for the studies which provided information on exposure time to anticoagulants (table 2).

The high rate of bleeding occurred irrespectively of the anticoagulant effect (as judged by the targeted therapeutic range). There was a very considerable risk of bleeding even with low intensity anticoagulant regimens. For example, in the studies by Hill a therapeutic range of 2-2.5 times control with human brain thromboplastin (estimated INR 2-2.5) was used. This anticoagulant intensity is equivalent to a prothrombin time of 1.2-1.4 times control using the currently available commercial rabbit brain thromboplastin; yet the rate of bleeding in Hill's study was 21% for all bleeding episodes, and 7% for major and fatal bleeding episodes respectively.

In a study by Enger and Boyesen who reported an even less intense anticoagulant regimen than Hill, (INR equivalent 1.5-2.1 which is equivalent to a rabbit brain thromboplastin of 1.2-1.3), the bleeding rates...
were 10% per year for all bleeds, 4% per year for major bleeds, and 3% per year for fatal bleeds.17

Hypertension was identified as a possible risk factor for cerebral hemorrhage (which was usually fatal), and in the one study where it was possible to calculate a relative risk of bleeding in hypertensives, it was 2.4.19

A relationship between bleeding and age was sought with the intensity of anticoagulant therapy in patients with ischemic cerebrovascular disease. It was similar to that reported in patients with completed stroke. Therefore, within the limitations of available information it appears that the high risk of bleeding in cerebrovascular disease is unlikely to be due to inappropriate anticoagulant treatment of unrecognized cerebral hemorrhage and more likely to be related to a true risk of cerebral bleeding during anticoagulant therapy in patients with ischemic cerebrovascular disease.

It was not possible to demonstrate a relationship between bleeding and the intensity of anticoagulant therapy at the time of bleeding. Although a number of studies documented major bleeding in association with excess hypocoagulability, major bleeding (including fatal bleeding) also occurred when the result of the PT or TT was within the targeted therapeutic range. Of 30 major hemorrhagic episodes, 18 occurred at a PT (or TT) above the targeted therapeutic range, while 12 bleeds occurred within a therapeutic range equivalent to that reported in patients with completed stroke.

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<table>
<thead>
<tr>
<th>Study</th>
<th>Anticoagulant</th>
<th>Patient No.</th>
<th>Anticoagulant duration (patient years)</th>
<th>Total (%)</th>
<th>Major (%)</th>
<th>Fatal (%)</th>
<th>Thromboplatin</th>
<th>Targeted therapeutic range</th>
<th>INR equivalent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baker (VA)</td>
<td>Warfarin/Dicumarol vs. No Rx control</td>
<td>78</td>
<td>45.3</td>
<td>31 (39.7)</td>
<td>10 (12.8)</td>
<td>4 (5.1)</td>
<td>Rabbit</td>
<td>20% 5.6</td>
<td></td>
</tr>
<tr>
<td>Baker et al</td>
<td>Dicumarol vs. Placebo</td>
<td>224</td>
<td>96.8</td>
<td>88 (39.3)</td>
<td>18 (8.0)</td>
<td>12 (5.4)</td>
<td>Rabbit</td>
<td>15-25% 4.5-7.2</td>
<td></td>
</tr>
<tr>
<td>Enger and Boyesen</td>
<td>Phenylindandione vs. Placebo</td>
<td>52</td>
<td>96.8</td>
<td>10 (19.2)</td>
<td>4 (7.7)</td>
<td>3 (5.8)</td>
<td>Bovine</td>
<td>10-25% 1.5-2.1</td>
<td></td>
</tr>
<tr>
<td>Hill et al</td>
<td>Phenindione (high) vs. Phenindione (low)</td>
<td>71</td>
<td>71</td>
<td>15 (21.1)</td>
<td>5 (7.0)</td>
<td>5 (7.0)</td>
<td>Human</td>
<td>2-2.5x 2-2.5</td>
<td></td>
</tr>
<tr>
<td>McDowell et al</td>
<td>Warfarin vs. No Rx control</td>
<td>37</td>
<td>93.4</td>
<td>17 (17.9)</td>
<td>2 (2.1)</td>
<td>2 (2.1)</td>
<td>Rabbit</td>
<td>2-2.5x 4.4-7.5</td>
<td></td>
</tr>
<tr>
<td>Olsson et al</td>
<td>Warfarin vs. ASA + Dipyridamole</td>
<td>67</td>
<td>3 (4.5)</td>
<td>8 (11.8)</td>
<td>2 (2.9)</td>
<td>1 (1.5)</td>
<td>Bovine</td>
<td>7-15% 1.9-3.7</td>
<td></td>
</tr>
</tbody>
</table>

* Sufficient patient number (>50) and bleeding described adequately.
† p < 0.001
‡ Long-term anticoagulation, but duration uncertain.
§ In anticoagulant groups, of 27 fatal bleeds 19 cerebral in origin.
| Test is prothrombin time when rabbit brain or human brain used, and thrombotest when bovine thromboplastin.

<table>
<thead>
<tr>
<th>Study</th>
<th>Indication</th>
<th>Patient No.</th>
<th>Total exposure time (patient years)</th>
<th>No of bleeds per 100 patient years of anticoagulant therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enger</td>
<td>Cerebrovascular</td>
<td>52</td>
<td>96.8</td>
<td>10.0 4.0 3.0</td>
</tr>
<tr>
<td>McDowell</td>
<td>Cerebrovascular</td>
<td>95</td>
<td>93.4</td>
<td>18.0 2.0 2.0</td>
</tr>
<tr>
<td>Baker</td>
<td>Cerebrovascular</td>
<td>78</td>
<td>45.3</td>
<td>68.0 22.0 9.0</td>
</tr>
</tbody>
</table>
to 1.5 to 2 times using a rabbit brain thromboplastin (INR 2.6 to 4.4), a range which is commonly used in North America.

Level II-IV Evidence

In general, the rate of bleeding was consistent with that found in Level I studies, although the range of bleeding rates was wider; total bleeding rates ranged from 0–63%, major bleeding ranged from 0–11.5% and fatal bleeding from 0–11.5%.23-34 The most common cause of fatal bleeding was cerebral hemorrhage (tables 3 and 4).

The time of the hemorrhagic event was equally distributed over the period of observation and bleeding was no more frequent in the first several months. In two of the studies, some of the bleeding episodes occurred in patients with hypertension,32,33 but the frequency of hypertension in the non-bleeders was not specified. Major bleeding was reported both in association with an excessive anticoagulant effect and with anticoagulant effects which were within the therapeutic range.

**Table 3 Ischemic Cerebrovascular Disease. Randomized Controlled Trials* — Level II**

<table>
<thead>
<tr>
<th>Study</th>
<th>Anticoagulant</th>
<th>Patient No.</th>
<th>Anticoagulant duration (patient years)</th>
<th>Total (%)</th>
<th>Major (%)</th>
<th>Fatal (%)</th>
<th>Thromboplastin</th>
<th>Targeted therapeutic range</th>
<th>INR equivalent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baker et al23‡</td>
<td>Coumadin/Dicumarol vs. no Rx control</td>
<td>30</td>
<td>$3 (10.0) 2 (6.7)</td>
<td>0 0</td>
<td>Rabbit</td>
<td>2–2.5x</td>
<td>4.4–7.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buren, Ygge24‡</td>
<td>Uncertain vs. ASA + Dipyridamole</td>
<td>60</td>
<td>$4 (6.7) 3 (4.6)</td>
<td>0 2 (3.0)</td>
<td>Bovine</td>
<td>10–20% 1.7–2.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carter25</td>
<td>Phenindione vs. no Rx control</td>
<td>38 38</td>
<td>4 weeks 4 weeks</td>
<td>15 (39.5) 12 (12.0)</td>
<td>Human</td>
<td>2–3x 2–3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marshall, Shaw36, 27</td>
<td>Phenindione vs. no Rx control</td>
<td>26 25</td>
<td>6 weeks 6 weeks</td>
<td>3 (11.5) 3 (12.0)</td>
<td>Human</td>
<td>2–3x 2–3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pearce et al38‡</td>
<td>Phenindione (high) vs. Phenindione (low)</td>
<td>17 20</td>
<td>$0 0</td>
<td>0 0</td>
<td>Human</td>
<td>10–25% 4.5–9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wallace39</td>
<td>Phenindione/Coumadin vs. no Rx control</td>
<td>27 25</td>
<td>$17 (63.0) 6 (24.0)</td>
<td>2 (7.4) 1 (4.0)</td>
<td>?  ?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Insufficient patient numbers and/or bleeding inadequately described.
†All fatal bleeds cerebral in origin.
‡Anticoagulant indication transient ischemic attack.
§Long-term anticoagulation, but duration uncertain.

**Table 4 Ischemic Cerebrovascular Disease. Level III-IV**

<table>
<thead>
<tr>
<th>Study</th>
<th>Anticoagulant</th>
<th>Patient No.</th>
<th>Anticoagulant duration (patient years)</th>
<th>Total (%)</th>
<th>Major (%)</th>
<th>Fatal (%)</th>
<th>Thromboplastin</th>
<th>Targeted therapeutic range</th>
<th>INR equivalent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eriksson, Link30*</td>
<td>Coumadin</td>
<td>137</td>
<td>$38 (27.7) 31 (17.4)</td>
<td>8 (5.8) 9 (5.0)</td>
<td>Bovine</td>
<td>5–15% 1.9–5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olsson et al31†</td>
<td>Dicumarol</td>
<td>178</td>
<td>$31 (17.4) 42 (22.1)</td>
<td>9 (5.0) 10 (5.2)</td>
<td>Bovine</td>
<td>10–20% 1.7–2.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Siekert et al32‡</td>
<td>Coumadin or Bishydroxycoumarin</td>
<td>190</td>
<td>$42 (22.1) 42 (22.1)</td>
<td>10 (5.2) 10 (5.2)</td>
<td>Rabbit</td>
<td>2–2.5x 4.4–7.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Terent, Anderson33*†</td>
<td>Coumadin</td>
<td>74</td>
<td>$15 (20.2) 6 (8.7)</td>
<td>3 (4.0) 6 (8.7)</td>
<td>Bovine</td>
<td>5–15% 1.9–5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whisnant et al34‡</td>
<td>Coumadin</td>
<td>69</td>
<td>$6 (8.7) 15 (20.2)</td>
<td>6 (8.7) 7 (4.6)</td>
<td>Rabbit</td>
<td>1.5–2.5x 2.6–7.5</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Anticoagulant indication completed stroke.
†Anticoagulant indication transient ischemic attack.
‡Long-term anticoagulation, but duration uncertain.

**Risks and Benefits for Anticoagulant Therapy**

We have constructed a simple risk/benefit table in order to examine the net gain or loss in efficacy rate (doing more good than harm) of treating patients with TIA and minor stroke with long-term anticoagulant therapy (table 5). The calculations for risk/benefit were made using the following assumptions:

1) That the stroke rate for untreated patients with TIA or minor stroke is 8% per year. This assumption is based on the recorded rates of stroke and death from natural history studies and from the placebo arm of randomized controlled studies of antiplatelet agents in these disorders.1,2,13,35 Natural history studies and randomized trials have demonstrated that patients with TIA and minor stroke who are untreated have a risk of stroke and death of between 5 and 10% per year.

2) That for patients treated with anticoagulants, a stroke and an anticoagulant-related major bleeding episode results in similar morbidity and mortality. This assumption is supported by the findings from randomized studies in patients with cerebral vascular...
lalar disease during anticoagulant therapy in which major bleeding rates ranged from 2–22% per year and were almost always intracranial and often fatal.

From table 5 it is clear that the benefit from anticoagulants would have to be substantial in order to neutralize the associated risk of major bleeding. For example, if anticoagulants cause a 20% risk reduction, the stroke rate would fall from 8% to 6.4% per year and the absolute change in stroke rate would be 1.6% per year. Even with the lowest reported rate of major bleeding of 2%, the rate of major bleeding would exceed the rate of stroke reduction and therefore treatment would result in a net loss of efficacy of 0.4% per year. If the major bleeding rate was 4%, then oral anticoagulants would have to be more than 50% effective (at a stroke rate of 8% per year) to warrant their use in patients with transient cerebral ischemia or minor stroke. Since it is unlikely that the true benefit of anticoagulant therapy in preventing stroke or death in patients with transient cerebral ischemia is 50% and much more likely that it is no greater than 20 to 30%, the present evidence does not support the use of long-term anticoagulant therapy in patients with transient cerebral ischemia or minor strokes.

**References**


Hemorrhagic complications of long-term anticoagulant therapy for ischemic cerebral vascular disease.
M Levine and J Hirsh