Hemorrhagic Complications of Long-term Anticoagulant Therapy

Mark N. Levine, M.D., M.Sc.
Gary Raskob, M.Sc.
Jack Hirsh, M.D., F.C.C.P.

The main complication of anticoagulation therapy is bleeding. We have conducted a literature review to determine: (a) the rate of bleeding during long-term anticoagulant therapy in various clinical disorders, and (b) the clinical and laboratory risk factors that predispose patients to bleeding. For the purposes of this review, we defined long-term therapy as lasting greater than 4 weeks. Hemorrhagic complications were also described for 2 other indications, myocardial infarction and hip surgery, where oral anticoagulant therapy was used for a shorter duration (approximately 4 weeks). The analysis was performed in patients with: (1) ischemic cerebrovascular disease (completed stroke, stroke-in-evolution, and transient ischemic attacks); (2) prosthetic cardiac valves; (3) chronic atrial fibrillation with and without associated rheumatic valvular disease; (4) ischemic heart disease (angina, myocardial infarction); and (5) in the prevention and treatment of venous thromboembolic disease.

We reviewed each report seeking the following information:

1. A clear 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 was 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 (human, North American, or bovine).
6. The results of the prothrombin time immediately before the hemorrhagic episode in patients who bled as well as the results 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 cotherapeutic features such as hypertension, malignancy, ulcer disease, and other drug therapy in patients who bled and those who did not bleed.

The primary objective of the majority of these reports was to evaluate the efficacy of treatment, not its safety. Nevertheless, it was possible to achieve 2 of our objectives, ie, valid estimates of bleeding rates for each of the disorders of interest, and for some of the disorders, the contribution of specific risk factors for both the occurrence of bleeding and its severity. Very few studies reported their success in maintaining patients within the stated therapeutic range, an important limitation of the analysis.

METHODS

We analyzed the results for each of the clinical indications separately. Potentially useful articles were identified through a computerized literature search (Medline) and through relevant review articles. The reports were classified into 1 of 4 categories using the criteria for strength of study design which is outlined by Sackett. In addition, we reviewed nonrandomized studies (case series with or without historical control) and classified them as level V studies. Case reports were not included in our analysis, since they do not provide a valid estimate of bleeding rates or risk factors.

The major analysis for each of the indications was derived from studies in the highest category. For example, there were a number of level I studies available for ischemic cerebrovascular disease, myocardial infarction, and venous thromboembolism, whereas only level IV studies were available for patients with prosthetic cardiac valves and only level V studies for atrial fibrillation.

The definition of major and minor bleeding differed between studies. For the purposes of our review, we classified bleeds as major if they were intracranial or retroperitoneal or if they led directly to death, hospitalization, or transfusion. All other bleeds (including some GI bleeds and most epistaxis, hematuria, ecchymosis, and hemoptysis) were classified as minor bleeds.

For the purpose of comparison between studies, we have converted the reported prothrombin time or thrombostest into the International Normalized Ratio (INR). (See report on Therapeutic Range for the Control of Oral Anticoagulant Therapy).

RESULTS

Ischemic Cerebrovascular Disease—Randomized Controlled Trials: Level I Evidence

There were 6 studies which were classified as level I (Table 1), and in only 3 was the duration of anticoagulant therapy clearly described.1,2,4 In all 6, the rate of bleeding was greater in the treatment group than in the nontreatment group, low-dose anticoagulant group, or antiplatelet group. The difference was statistically significant in 5 of 6 studies and there was a strong trend in the sixth in which warfarin was compared with ASA and dipyridamole.3 The risk of bleeding was impressive and varied between 11.8% and 39.7%. The risk of major bleeding was also high, 7% or more in 4 of 6 studies.1,4,5,6 Fatal hemorrhage occurred in more than 5% of patients in 4 studies1,4,5,7 and in more than 2% of patients in the other 2 studies.3,8

In the study by Olsson et al,3 all patients received

*Results are reported for only highest levels of evidence. Details of hemorrhage for other level studies can be obtained on request from authors.
anticoagulants for 2 months before they were randomized to either continuation of oral anticoagulant therapy or replacement with antiplatelet agents. The lower bleeding rates in this study might be explained by a selection bias, since patients who bled before randomization would not have been included in the study.

There was no obvious relationship between the anticoagulant effect (measured by either the prothrombin time, PT, or thrombostest, TT) and rate of bleeding, but none of the studies was designed to examine this question. It is clear, however, that bleeding, even major bleeding, occurred with relatively moderate prolongation of the PT. For example, in the study by Hill et al.,7,8 a therapeutic range of 2.0-2.5 times control with human brain thromboplastin (estimated INR 2.0-2.5) was used. This is equivalent to a prothrombin time of 1.3-1.5 times control using North American thromboplastins; yet the rate of bleeding in the Hill group’s study was substantial and greater than that in the study reported by McDowell et al.,2 in which the therapeutic range was 2.0-2.5 times control using North American thromboplastin (INR 4.4-7.5).

As a group, patients with cerebrovascular disease have a high risk for bleeding. Hypertension was identified as a possible risk factor for cerebral bleeds (which were usually fatal) in 4 of the 6 studies.1,4,5,7 In 1 study, 75% of the bleeders were hypertensive compared with 55% of the nonbleeders, which produces a relative risk of 2.4.5

The risk of bleeding was fairly evenly distributed throughout the duration of anticoagulant therapy, with no obvious clustering within the first few weeks or months.

Major bleeding in this group was dominated by cerebral hemorrhage. It is unlikely that this complication resulted from the unintentional inclusion of patients who had a hemorrhagic stroke at presentation, because similar high rates of cerebral hemorrhage were reported in patients who had TIA at presentation.34 Therefore, within the limitations of the available information (which is considerable), we conclude that the high risk of bleeding in cerebrovascular disease is unlikely to be due to the inadvertent inclusion of patients with cerebral hemorrhage and more likely to be related to a true risk of cerebral bleeding during anticoagulant therapy in patients with ischemic cerebrovascular disease.

Although a number of studies reported that major bleeding was associated with an excessive anticoagulant effect, major bleeding (including fatal bleeding) frequently occurred when the result of the PT or TT was within the targeted therapeutic range.

### Prosthetic Heart Valves—Randomized Controlled Trials: Level IV Evidence

There were 5 level IV studies of long-term anticoagulant therapy in patients with prosthetic heart valves (Table 2). In 4 of these studies oral anticoagulant therapy was compared with a combination of oral anticoagulants and antiplatelet agents, and in the fifth
trial standard intensity warfarin was compared with a less intense warfarin regimen.8-14 Since none of these studies compared an oral anticoagulant with placebo or an antiplatelet agent alone, they were designated as level IV studies (cohort), even though they were randomized trials. In 3 of the studies the duration of anticoagulant therapy was clearly documented. The frequency of bleeding varied between 1.2% and 13.9% in the patients treated with anticoagulant alone, and the frequency of major bleeding varied from 0 to 6.8%. Fatal bleeding was 0 in two studies19 and was as high as 4.1% in another,11 most fatal bleeds being cerebral in origin.

The targeted therapeutic range was described in 3 of the 5 studies, and the intensity of anticoagulant therapy was similar.11-13 The relationship between intensity of anticoagulant therapy and bleeding was described in only 1 study. In a trial reported recently by Turpie et al14 in patients with tissue heart valves, the rate of clinically important bleeding was reduced from 14% in the standard intensity group to 6% in the low intensity group without loss of antithrombotic efficacy. In 2 of the 4 studies, there was a significantly greater frequency of bleeding when ASA was added to warfarin sodium (Coumadin), but this was not evident in the 2 studies comparing dipyridamole plus Coumadin with Coumadin alone.10,13 Most of the bleeding episodes during combined treatment with anticoagulant and ASA were GI in origin.

Prosthetic Heart Valves—Level V Evidence

Of the 53 descriptive studies* evaluating long-term anticoagulant therapy in patients with prosthetic cardiac valves, only 28* mentioned bleeding complications. The reliability of the reported rates was low because there was no clear description of an inception cohort (clearly defined group of patients commencing therapy), the duration of anticoagulant therapy was not described, and bleeding outcomes were not defined.

The study by Forfar15 provided some evidence for a relationship between bleeding and the intensity of anticoagulant therapy. Although this study included patients with a variety of disorders, the majority of patients received anticoagulant therapy because they had prosthetic heart valves. Forfar reported an 8% risk of bleeding, with a 2% risk of major bleeding and a 0.4% risk of fatal bleeding, and the probability of hemorrhage remained fairly constant throughout the duration of therapy. The intensity of anticoagulant treatment was mild compared with North American standards. A human brain thromboplastin ratio of 1.8-2.6 times control (INR 1.8-2.6) was used, which is equivalent to a North American thromboplastin ratio

*Details provided on request from authors.

Table 2—Prosthetic Heart Valves Randomized Controlled Trials—Level IV

<table>
<thead>
<tr>
<th>Study</th>
<th>Anticoagulant</th>
<th>Patient No.</th>
<th>Anticoagulant Duration (Patient Yr)</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>Altman et al, 1976</td>
<td>Acenocoumarin + ASA (500 mg) vs Acenocoumarin</td>
<td>57</td>
<td>121.8</td>
<td>7 (12.3)</td>
<td>1 (1.7)</td>
<td>1 (1.7)</td>
<td>Human</td>
<td>1.8-2.3x</td>
<td>1.8-2.3</td>
</tr>
<tr>
<td>Chesebro et al, 1983</td>
<td>Warfarin + ASA (250 mg bid) vs Warfarin + DIP (100 mg qid)</td>
<td>170</td>
<td>166.7</td>
<td>23 (13.5)</td>
<td>20 (11.8)</td>
<td>3 (1.8)</td>
<td>North American</td>
<td>1.5-2.5x</td>
<td>2.6-7.5</td>
</tr>
<tr>
<td>Dale et al, 1977; 1980</td>
<td>Warfarin + ASA (500 mg bid) vs Warfarin</td>
<td>183</td>
<td>§</td>
<td>9 (4.9)†</td>
<td>4 (2.2)</td>
<td>0</td>
<td>Bovine</td>
<td>10-12%</td>
<td>2.0-2.2</td>
</tr>
<tr>
<td>Sullivan et al, 1971</td>
<td>Warfarin + DIP (400 mg) vs Warfarin</td>
<td>75</td>
<td>§</td>
<td>6 (8.2)†</td>
<td>5 (6.8)</td>
<td>3 (4.1)</td>
<td>North American</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Turpie et al, 1988</td>
<td>Warfarin vs Warfarin (less intense)</td>
<td>102</td>
<td>25.5</td>
<td>6 (5.9)†</td>
<td>0</td>
<td>0</td>
<td>Human</td>
<td>2.0-2.5</td>
<td>2.0-2.25</td>
</tr>
</tbody>
</table>

*All fatal bleeds cerebral in origin.
†p<0.05.
‡Nonrandomized concurrent control.
§Reported to be receiving long-term anticoagulants.
of 1.2-1.6 times control. The PT was prolonged beyond the therapeutic range in 23 of 24 episodes of life-threatening hemorrhage. In contrast, the PT was prolonged beyond the therapeutic range in only one of the 27 occasions with less serious hemorrhage.

In general, the rate of bleeding was lower in patients with prosthetic heart valves than in those with cerebrovascular disease.

**Atrial Fibrillation Level V Evidence**

There are 7 studies, all level V, describing bleeding in patients with atrial fibrillation, and in only 2 was the frequency of bleeding adequately described, with rates of 7% and 36%, respectively. However, several randomized trials are in progress evaluating long-term, less intense warfarin therapy in patients with atrial fibrillation that should provide more information on the hemorrhagic risks.

**Ischemic Heart Disease (Therapy Longer than 4 Weeks); Level I Evidence**

There were 7 studies that were classified as level I (Table 3). In 5, anticoagulant therapy was compared with placebo or control, in the sixth anticoagulant was compared with ASA, and in the seventh anticoagulant therapy was compared with ASA and placebo. The difference in total bleeding between the anticoagulant group and the control or aspirin groups was statistically significant in all of the studies. In 3 studies, patients were treated with anticoagulants for variable periods before randomization. The risk of total bleeding was impressive, varying between 3.8% and 36.5%. The rates of major bleeding were variable; in 1 study there were no major bleeding episodes, in 4 studies major bleeding episodes occurred in fewer than 5% of patients, and in 2 studies major bleeding occurred in greater than 10%,. Fatal hemorrhages occurred less frequently in patients treated than for stroke and prosthetic heart valves and ranged from 0.7% to 2.9% in 3 studies there were no fatal bleeds. Fatal bleeding was usually due to intracranial bleeding.

In none of these studies was the time of the bleeding event specified. Two of the studies included a group who received ASA alone at a dose of 1.5 g daily. In the EPSM study there was significantly more bleeding in the anticoagulant group than the ASA

**Table 3—Ischemic Heart Disease: Level I**

<table>
<thead>
<tr>
<th>Study</th>
<th>Anticoagulant</th>
<th>No. of Patients</th>
<th>Anticoagulant Duration (Patient Yr)</th>
<th>Bleeding</th>
<th>Targeted Therapeutic Range</th>
<th>INR Equivalent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sixty-Plus Reinfarction Trial, 1980, 1982</td>
<td>Acenocoumarin/Phenprocoumon vs Placebo</td>
<td>439</td>
<td>684.9</td>
<td>74 (17) 18 (4.1) 6 (1.4)</td>
<td>Bovine</td>
<td>5-10%</td>
</tr>
<tr>
<td>EPSIM Group, 1982</td>
<td>Acenocoumarol (422) vs Fluindione (140) Ethylbiscoumarinacetate (70) Phenindione (8) Tioclamarol (3)</td>
<td>652</td>
<td>$104 (16.0) 21 (3.2) 8 (1.2)</td>
<td>?</td>
<td>25-35%</td>
<td></td>
</tr>
<tr>
<td>Breddin et al, 1980</td>
<td>Acenocoumarol (500 mg tid) vs ASA (500 mg tid) Phenprocoumon vs Placebo</td>
<td>651</td>
<td>109.8</td>
<td>35 (5.4) 5 (0.8) 4 (0.6)</td>
<td>ASA</td>
<td>5-15%</td>
</tr>
<tr>
<td>Meuwissen et al, 1969</td>
<td>Acenocoumarol (500 mg tid) vs ASA (500 mg tid) Phenprocoumon vs Placebo</td>
<td>317</td>
<td>122.9</td>
<td>10</td>
<td>Bovine</td>
<td>5-13%</td>
</tr>
<tr>
<td>Loeliger et al, 1967</td>
<td>Phenprocoumon vs Placebo</td>
<td>70</td>
<td>168.0</td>
<td>17 (13.3) 1 (0.8) 0</td>
<td>Bovine</td>
<td>5-15%</td>
</tr>
<tr>
<td>Bjerkelund, 1957, Dicumarol 1963</td>
<td>Phenprocoumon vs Placebo</td>
<td>122</td>
<td>138.0</td>
<td>17 (5.7) 1 (0.8) 1 (0.8)</td>
<td>Human</td>
<td>10-30%</td>
</tr>
<tr>
<td>Harvald et al, 1962</td>
<td>Dicumarol vs Placebo</td>
<td>145</td>
<td>362.5</td>
<td>19 (6.5) 5 (3.6) 1 (0.7)</td>
<td>Human</td>
<td>10-25%</td>
</tr>
</tbody>
</table>

*All fatal hemorrhages cerebral in origin, except EPSIM study where not specified.
†p<0.01.
‡Long-term anticoagulants, but duration uncertain.
§Coagulation test used was P-P (prothrombin-proconvertin).
group, but there was significantly more gastritis and peptic ulcer disease in the ASA group. In the second study, by Breddin et al., no difference was detected in the rate of bleeding between the anticoagulant and ASA groups. There were, however, more GI “complaints” in the ASA group. In 2 studies, underlying risk factors for bleeding were described. In the Sixty-Plus trial, 4 patients with malignancies bled, and in the study by Bjerke- lund, 2 patients bled from malignant lesions. In Bjerke- lund’s study, 4 of 5 cerebral bleeds occurred in hypertensive patients, 3 patients bled from duodenal ulcers, 2 had hematuria due to underlying urolithiasis, and 1 bled from an occult gastric carcinoma.

It is not possible from these reports to assess the relationship between bleeding and the level of anticoagulant therapy. Although several studies noted that major bleeding occurred when the PT was outside the therapeutic range, bleeding often occurred when the PT or TT was within the therapeutic range.

Ischemic Heart Disease (Treatment for 4 Weeks or Less): Level 1 Evidence

There were 3 level I studies of short-term anticoagulant therapy in patients with myocardial infarction (Table 4). Oral anticoagulant therapy was compared with placebo in 2 of the studies and with low-dose anticoagulant therapy in the third. Treatment duration was 28 days in 2 trials and in the third lasted for the period of hospitalization. In all 3 studies patients received an initial additional 24-36 hours of heparin therapy following randomization.

In all studies the rate of total bleeding was greater in the treatment group than in the control group. Total bleeding ranged from 2.6% to 12.8%, but most, if not all, of these bleeding episodes were minor. There were no fatal bleeding events. In the Veterans Administration study, anticoagulant therapy was discontinued in 5 patients, but it was not possible from the information provided to ascertain whether any of the 13 hemorrhagic episodes were major according to our criteria.

In the other 2 studies there were no major bleeding events. The time of the bleeding event was not specified in any of the studies.

The targeted therapeutic range was described in all studies and was mild by North American standards: INR 2-2.5 in two studies and 1.7-2.1 in the third. The relationship between the intensity of anticoagulant therapy and bleeding was not described in any of the studies.

In summary, when short-term oral anticoagulant therapy was used in patients with myocardial infarction, major bleeding was rare, and fatal bleeding did not occur.

Venous Thromboembolism—Level 1 Evidence

There were 4 level I studies that evaluated bleeding during anticoagulant therapy in patients with venous thromboembolism (Table 5). In all of these, patients who received warfarin monitored to maintain the PT (North American thromboplastin) at approximately twice control (INR ~4.5) were compared with a less intensely anticoagulated group. In two of the studies, the less intense group was low-dose subcutaneous heparin (5,000 units subcutaneously twice daily) in the third it was adjusted-dose subcutaneous heparin; and in the fourth it was less intense warfarin, which was monitored to maintain the standardized human brain prothrombin time at approximately twice control (INR ~2), (which is approximately equivalent to 1.2-1.3 times control using a rabbit brain thromboplastin). In all 4 studies total bleeding was significantly greater in the more intensely anticoagulated

<table>
<thead>
<tr>
<th>Study</th>
<th>Anticoagulant*†</th>
<th>No. of Patients</th>
<th>Total (%)</th>
<th>Major (%)</th>
<th>Fatal</th>
<th>Thromboplastin†</th>
<th>Targeted Therapeutic Range (INR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drapkin and Merskey</td>
<td>Phenindione</td>
<td>745</td>
<td>$96 (12.8)</td>
<td>0</td>
<td>0</td>
<td>Human</td>
<td>2.0-2.5 (2.0-2.5)</td>
</tr>
<tr>
<td>vs Placebo</td>
<td></td>
<td>391</td>
<td>$51 (5.3)</td>
<td>0</td>
<td>0</td>
<td>Human</td>
<td>2.0-2.5 (2.0-2.5)</td>
</tr>
<tr>
<td>Veterans Administration</td>
<td>Coumadin</td>
<td>500</td>
<td>13 (2.6)</td>
<td>—</td>
<td>0</td>
<td>Human</td>
<td>2.0-2.5 (2.0-2.5)</td>
</tr>
<tr>
<td>vs Placebo</td>
<td></td>
<td>499</td>
<td>6 (1.2)</td>
<td>0</td>
<td>0</td>
<td>Bovine</td>
<td>10-20% (1.7-2.1)</td>
</tr>
<tr>
<td>MRC</td>
<td>Phenindione</td>
<td>712</td>
<td>36 (5.0)</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>vs Phenindione (low dose)</td>
<td></td>
<td>715</td>
<td>$9 (1.2)</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Anticoagulant duration: Drapkin and Merskey hospitalization period; VA and MRC, 28 days.
†In all studies heparin was used in addition to oral anticoagulant therapy for first 24-36 h.
‡Test is prothrombin time when North American or human brain used, and thrombotest when bovine thromboplastin.
§p<0.05.
‖Of 13 patients with bleeding episodes, 5 had anticoagulant discontinued because of hemorrhage, but it was not possible to ascertain whether any of the bleeds were major.

308
2nd ACCP Conference on Antithrombotic Therapy
Table 5—Venous Thromboembolism Randomized Controlled Trials—Level I

<table>
<thead>
<tr>
<th>Study</th>
<th>Anticoagulant</th>
<th>No. of Patients</th>
<th>Anticoagulant Duration (Patient Years)</th>
<th>Bleeding</th>
<th>Targeted Therapeutic Range</th>
<th>INR Equivalent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bynum and Wilson, 1979</td>
<td>Heparin (low dose sc)</td>
<td>24</td>
<td>6 mo</td>
<td>1 (4.2)*</td>
<td>Rabbit</td>
<td>1.5-2x</td>
</tr>
<tr>
<td></td>
<td>Warfarin</td>
<td>24</td>
<td>3 mo</td>
<td>9 (37.5)†</td>
<td>4 (16.7)</td>
<td>1.5-2x</td>
</tr>
<tr>
<td>Hull et al, 1979</td>
<td>Warfarin</td>
<td>33</td>
<td>3 mo</td>
<td>7 (21.2)</td>
<td>Rabbit</td>
<td>1.5-2x</td>
</tr>
<tr>
<td>Hull et al, 1982</td>
<td>Heparin (low dose sc)</td>
<td>35</td>
<td>6 mo</td>
<td>0*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hull et al, 1982</td>
<td>Warfarin</td>
<td>53</td>
<td>3 mo</td>
<td>9 (17.0)</td>
<td>Rabbit</td>
<td>1.5-2x</td>
</tr>
<tr>
<td>Hull et al, 1982</td>
<td>Heparin (adjusted sc)</td>
<td>53</td>
<td>3 mo</td>
<td>1 (1.9)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hull et al, 1982</td>
<td>Warfarin</td>
<td>49</td>
<td>3 mo</td>
<td>11 (22.4)</td>
<td>2 (4.1)</td>
<td>1.5-2x</td>
</tr>
<tr>
<td></td>
<td>Warfarin (less intense)</td>
<td>47</td>
<td>3 mo</td>
<td>2 (4.3)*</td>
<td>2 (4.3)</td>
<td>Human</td>
</tr>
</tbody>
</table>

*p<0.01.
†No fatal hemorrhages.

The 3 studies carried out by Hull and associates were performed sequentially and provided an opportunity to examine the risk factors associated with bleeding during warfarin therapy. There were 135 patients treated with more intense warfarin therapy over a 3-year period. Twenty-seven patients bled, and 9 patients (6.7%) experienced major bleeding. Every major bleed was associated with an underlying, predisposing cause. Two patients with major thigh hematomas were paraplegic and bled following trauma to an anesthetic limb. One hemarthrosis occurred 1 week after knee surgery, and 3 GI bleeds occurred in association with occult carcinoma of the colon (1 patient) and unsuspected duodenal ulcers (2 patients). Three major bleeds occurred in patients who had undergone recent surgery. Two of these 9 major bleeds occurred with the PT more than 4 times control (INR >10) and 2 with the PT excessively prolonged but less than 3 times control (INR <10). In this cohort of patients, there were 18 minor bleeds with essentially no underlying cause, except 2 soft tissue bleeds associated with trauma. Of these 18 minor bleeds, 9 occurred within the therapeutic range of 1.5-2 times control (INR 2.6-4.4), 6 bleeds with the PT 2-3 times control (INR 4.4-10), and 3 bleeds with the PT greater than 3 times control (INR >10). Thus, all the major bleeds were associated with underlying risk factors, some of which are also risk factors for venous thrombosis (ie, hip surgery, malignancy, and paraplegia).

More recently 2 studies were published in which patients received oral anticoagulant therapy for deep vein thrombosis. Although both reported on the incidence of bleeding, it is uncertain whether minor bleeding was sought in a prospective manner. Langerstedt et al in a level II study randomized 51 patients with calf vein thrombosis who had received 5 days of heparin therapy to either warfarin (INR 2.5-4.2) for 3 months or no further treatment. There were no bleeds in either patient group. In a trial examining the optimal duration of oral anticoagulant therapy, Holmgren et al randomized patients to either 1 month of warfarin (69 patients) or 6 months of warfarin (66 patients). The targeted therapeutic range for both groups was a thrombotest of 5-14% (INR 2.0-5.0). There was 1 retroperitoneal hemorrhage (1.4%) in a patient randomized into the 1-month group.

**Short-term Oral Anticoagulant Therapy for Hip Surgery**

Although the thromboembolic risk following hip surgery is substantial, there has been general reluctance to use prophylactic oral anticoagulant therapy because of the common belief that the use of these drugs is complicated by clinically important hemorrhage, especially from the operative site. To assess reliably the risk of hemorrhage (especially local hemorrhage) following hip surgery, 2 important criteria should be satisfied to eliminate potential bias: (1) there should be a concurrent placebo control group; and (2) objective outcome criteria should be used to assess bleeding.
There have been no placebo-controlled, randomized trials of oral anticoagulant therapy in patients undergoing hip surgery in which bleeding has been assessed blindly. However, several studies have used objective criteria to assess the risk of hemorrhage (Table 6). There have been 2 level I studies, 37,38 3 level II studies, 39-41 and 2 level III studies 36,40 in which coumadin or phenindione was compared to a no-treatment control group in patients who were operated on for fractured hips. The duration of therapy ranged from 2 weeks in 1 study 40 to as long as 3 months in another. 43

The rate of total bleeding varied from 0 to 47%. In most instances, however, major bleeding events were far less frequent and ranged from 0 to 10%. There were no major bleeds in 2 studies, 36,41 fewer than 5% major bleeds in 3 studies 36,40,42 and 2 studies had a major bleeding rate of greater than 5%. 37,43 In only 1 study was there a statistically significant difference in major bleeding events between the treatment and control groups. 37 The study by Salzman et al 42 demonstrates the importance of having a control group to assess the hemorrhagic risk of oral anticoagulant therapy and to differentiate this from the role of surgery alone in inducing bleeding. In this study there were 6 major bleeds in the anticoagulant group (4 wound hematomas and 2 GI bleeds) and 4 major bleeds in the control group (2 wound hematomas and 2 GI); not a statistically significant difference. In several studies, no difference was detected in the operative blood loss or transfusion requirements between patients receiving anticoagulant therapy and no treatment. 36,40 In all of the studies combined, there was 1 fatal hemorrhagic event in the anticoagulant group and 1 in the control group. In a recently reported trial, 44 194 patients undergoing surgery for fractured hips were randomized to either postoperative warfarin (INR 2.0-2.7), ASA, or placebo. There were 6 clinically important bleeds in the warfarin group, 3 in the ASA group, and 6 in the placebo group.

We were unable to detect (but the design of the studies did not allow us to exclude) a relationship between the intensity of anticoagulant therapy and the bleeding risk, nor was it possible to determine whether a relationship existed between the time of initiation of oral anticoagulant therapy (preoperatively or postoperatively) and the risk of hemorrhage.

In summary, the hemorrhagic risk in patients undergoing hip surgery who receive oral anticoagulant therapy is likely to be lower than was believed previously. Given the significant thromboembolic risk following hip surgery, 36 the demonstrated efficacy of prophylactic oral anticoagulant therapy, 36 and the uncommon risk of major or fatal bleeding, the potential benefit of oral anticoagulation therapy is likely to outweigh the hemorrhagic risk.

**Comparison Between Indications**

Bleeding rates (pooled rates) during long-term an-

### Table 6—Short-term Oral Anticoagulant Therapy for Hip Surgery

<table>
<thead>
<tr>
<th>Study*</th>
<th>Treatment</th>
<th>No. of Patients</th>
<th>Anticoagulant Duration (Days)</th>
<th>Total (%)</th>
<th>Major (%)</th>
<th>Fatal (%)</th>
<th>Thromboplastin Targeted Therapeutic Range</th>
<th>INR Equivalent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morris and Mitchell (Level I)</td>
<td>Coumadin vs Control</td>
<td>90</td>
<td>25</td>
<td>16 (10.0)</td>
<td>8 (10.0)</td>
<td>1 (1.2)</td>
<td>Bovine</td>
<td>10%</td>
</tr>
<tr>
<td>Eskeland et al (Level I)</td>
<td>Phenindione vs Control</td>
<td>100</td>
<td>18</td>
<td>77 (8.5)</td>
<td>2 (3.0)</td>
<td>0</td>
<td>Human†</td>
<td>&lt;30%</td>
</tr>
<tr>
<td>Hamilton et al (Level II)</td>
<td>Phenindione vs Control</td>
<td>38</td>
<td>—</td>
<td>18 (47.0)</td>
<td>0</td>
<td>0</td>
<td>North American</td>
<td>2.0-2.5</td>
</tr>
<tr>
<td>Pinto (Level II)</td>
<td>Coumadin vs Control</td>
<td>25</td>
<td>14</td>
<td>7 (16.0)</td>
<td>0</td>
<td>0</td>
<td>Bovine</td>
<td>5-15%</td>
</tr>
<tr>
<td>Borgstrom et al (Level II)</td>
<td>Dicoumarol vs Control</td>
<td>29</td>
<td>—</td>
<td>1 (4.0)</td>
<td>0</td>
<td>0</td>
<td>Prothrombin Index</td>
<td>~40</td>
</tr>
<tr>
<td>Sevitt and Gallagher (Level III)</td>
<td>Phenindione vs Control</td>
<td>150</td>
<td>35</td>
<td>30 (20.0)</td>
<td>5 (3.3)</td>
<td>0</td>
<td>Human</td>
<td>2.0-3.0</td>
</tr>
<tr>
<td>Salzman et al (Level III)</td>
<td>Coumadin vs Control</td>
<td>83</td>
<td>—</td>
<td>12 (8.0)</td>
<td>2 (1.3)</td>
<td>0</td>
<td>North American</td>
<td>1.7-2.5</td>
</tr>
</tbody>
</table>

*Indicates anticoagulant prophylaxis: fractured hips in all studies except Pinto et al, which included some patients with elective hip surgery.

†Anticoagulation test used, P-F (prothrombin-proconvertin).

‡Anticoagulation duration uncertain, but usually short-term until patient ambulatory.

Downloaded From: http://journal.publications.chestnet.org/pdffaccess.ashx?url=/data/journals/chest/21589/ on 04/01/2017
Table 7—Hemorrhage during Long-term Anticoagulant Therapy

<table>
<thead>
<tr>
<th>Indication</th>
<th>No. of Patients</th>
<th>Total (%)</th>
<th>Minor (%)</th>
<th>Major (%)</th>
<th>Fatal (%)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic cerebrovascular (Level I)</td>
<td>588</td>
<td>169 (28.7)</td>
<td>128 (21.8)</td>
<td>41 (7.0)</td>
<td>28 (4.8)</td>
</tr>
<tr>
<td>Prosthetic heart valves (Level IV)</td>
<td>405</td>
<td>23 (5.7)</td>
<td>13 (3.2)</td>
<td>10 (2.4)</td>
<td>7 (1.7)</td>
</tr>
<tr>
<td>Atrial fibrillation (Level V)</td>
<td>302</td>
<td>46 (15.2)</td>
<td>43 (14.2)</td>
<td>3 (0.01)</td>
<td>1 (0.003)</td>
</tr>
<tr>
<td>Ischemic heart (Level I)</td>
<td>1890</td>
<td>299 (19.1)</td>
<td>199 (10.5)</td>
<td>88 (4.7)</td>
<td>19 (1.0)</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>159</td>
<td>36 (22.6)</td>
<td>23 (14.4)</td>
<td>13 (8.1)</td>
<td>0</td>
</tr>
</tbody>
</table>

*Results of individual studies pooled.

Anticoagulant therapy are substantial. For total bleeding, the rates ranged from 5.7% to 28.7%, for major bleeding 1.4% to 8.1%, and for fatal bleeding 0 to 4.8% (Table 7). There were differences in the rate of bleeding among the 5 subgroups studied. The highest rates were seen in patients with cerebrovascular disease and venous thromboembolism. Bleeding for most studies was expressed in terms of absolute rates, i.e., the proportion of patients who bled. We have also determined bleeding per 100 patient-years of therapy for those studies where exposure time was available (Table 8).

In ischemic cerebrovascular disease, total bleeding ranged from 10 to 68 bleeds per 100 patient-years, major bleeding from 2 to 22/100 patient-years, and fatal bleeding from 2 to 9/100 patient years. In prosthetic heart valves (2 studies) major bleeding was only 0.8/100 patient-years. In myocardial infarction, bleeding rates were substantial; total bleeds ranged between 6.4 and 14.6/100 patient-years, major bleeds 0 to 7.7/100 patient-years, and fatal bleeds 0 to 1.0/100 patient years.

Relationship between Intensity of Anticoagulant Therapy and Hemorrhage

It was possible to seek a relationship between intensity of anticoagulant therapy and risk of bleeding from only 4 of the studies. Hull et al.4,14,15,33 showed a strong relationship in venous thrombosis, with the incidence of bleeding in patients who were randomized to receive a less intense warfarin regimen (targeted INR 2.0) being significantly lower (4% vs 22%) than in those receiving more intense therapy (targeted INR 2.5-4.5). All 13 patients in this study who bled did so when the Manchester Comparative Time (which is identical to the INR) was prolonged to more than three times the control value. Similarly, Turpie et al.4 reported a 50% reduction in bleeding in those patients receiving less intense warfarin therapy (targeted INR 2.0-2.5) compared with more intense therapy (INR 2.5-4.5).

In Forfar's cohort study,15 the targeted therapeutic range was a PT of 1.8-2.6 (INR 1.8-2.6) times control using human brain thromboplastin. In 23 of 24 episodes of life-threatening hemorrhage, the PT was prolonged beyond the therapeutic range. In contrast, the PT was prolonged beyond the therapeutic range on only 1 of 27 occasions of less serious hemorrhage, a relative risk of 40 in favor of a prolonged PT producing severe life-threatening hemorrhage. A PT ratio greater than 3.4 to 1.0 was recorded overall in 2.5% of patients who did not bleed; an observation that supports an association between intensity of anticoagulant effect and excess bleeding.

Table 8—Bleeding Rates during Long-term Anticoagulant Therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Indication</th>
<th>Patient No.</th>
<th>Total Exposure Time (Patient Years)</th>
<th>Number of Bleeds per 100 Patient-Yr of Anticoagulant Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enger, 1965</td>
<td>Cerebrovascular</td>
<td>52</td>
<td>96.8</td>
<td>10.0  4.0  3.0</td>
</tr>
<tr>
<td>McDowell, 1963</td>
<td>Cerebrovascular</td>
<td>95</td>
<td>93.4</td>
<td>18.0  2.0  2.0</td>
</tr>
<tr>
<td>Baker, 1961</td>
<td>Cerebrovascular</td>
<td>78</td>
<td>45.3</td>
<td>68.0  22.0  9.0</td>
</tr>
<tr>
<td>Altman, 1978</td>
<td>Heart valve</td>
<td>57</td>
<td>121.8</td>
<td>6.0   0.8  0.8</td>
</tr>
<tr>
<td>Chessbro, 1983</td>
<td>Heart valve</td>
<td>153</td>
<td>166.7</td>
<td>1.8   0.8  0.6</td>
</tr>
<tr>
<td>Forfar, 1979</td>
<td>Heart valve</td>
<td>506</td>
<td>99.9</td>
<td>3.4   0.7  0.2</td>
</tr>
<tr>
<td>Sisty-Plus, 1982</td>
<td>Myocardial infarction</td>
<td>439</td>
<td>684.8</td>
<td>10.8  2.6  0.9</td>
</tr>
<tr>
<td>Meuwissen, 1989</td>
<td>Myocardial infarction</td>
<td>68</td>
<td>109.8</td>
<td>6.4   0.0  0</td>
</tr>
<tr>
<td>Loeliger, 1967</td>
<td>Myocardial infarction</td>
<td>128</td>
<td>168.0</td>
<td>10.0  0.6  0</td>
</tr>
<tr>
<td>Bjerkelund, 1963</td>
<td>Myocardial infarction</td>
<td>119</td>
<td>418.3</td>
<td>7.6   4.8  1.0</td>
</tr>
<tr>
<td>Harvald, 1962</td>
<td>Myocardial infarction</td>
<td>145</td>
<td>362.5</td>
<td>14.6  7.7  0.2</td>
</tr>
</tbody>
</table>
Finally, Moschos et al\textsuperscript{22} randomized patients with ischemic heart disease to 3 different intensities of warfarin therapy, with targeted therapeutic ranges for PT expressed in INR of 5.0-10.0 (high dose), 1.6-3.8 (moderate dose), and 1.2 (low dose). Although bleeding episodes were not well documented, the highest bleeding rate occurred in the high-dose group, which is suggestive of a relationship between intensity of anticoagulation and bleeding.

The PT (or TT) was recorded at the time of the bleeding episode in several studies. Interstudy comparisons of the relationship between intensity of the anticoagulant effect and bleeding were not possible because the targeted therapeutic ranges varied among studies. Of 25 major hemorrhagic episodes in patients treated with anticoagulants for cerebrovascular disease, 18 occurred at a PT (or TT) above the desired therapeutic range, while 12 episodes occurred within a therapeutic range equivalent to 1.5-2.0 times control using a North American thromboplastin (INR 2.5-4.4), a range that is commonly used in North America. In the 2 studies of patients with prosthetic heart valves, where information on level of intensity of the anticoagulant effect was available, 9 of 15 hemorrhagic episodes occurred when PT was beyond the desired range. Similarly, of 113 bleeding events in patients treated with anticoagulants for ischemic heart disease, 37 occurred at a PT (TT) above the therapeutic range. Finally, in venous thrombosis, 14 bleeding episodes occurred at a level of coagulation within the defined therapeutic range (INR 2.5-4.4).

\textbf{Discussion}

We reviewed the literature on long-term oral anticoagulant therapy to determine: (1) the rates of bleeding occurring during long-term anticoagulant therapy; (2) the clinical risk factors responsible for bleeding; (3) the time of the bleeding in relationship to commencing anticoagulant therapy; and (4) the relationship between bleeding and the prothrombin time.

\textbf{The Rate of Bleeding during Long-term Anticoagulant Therapy}

Reliable estimates of bleeding rates were obtained for ischemic cerebrovascular disease, ischemic heart disease, prosthetic heart valves, and venous thromboembolism. The frequency of bleeding was expressed in terms of absolute rates (i.e., the proportion of patients who bled) and, when possible, in terms of the annual incidence of bleeding. Most of the reports did not provide information on the total time of patient exposure to anticoagulant therapy and, therefore, it was often not possible to calculate annual incidence of bleeding. The risk of bleeding was substantial and most marked in patients with ischemic cerebrovascular disease, ischemic heart disease, and venous thromboembolism. Major bleeding was particularly evident in patients with ischemic cerebrovascular disease and venous thromboembolism, possibly due to a higher prevalence of underlying risk factors in these 2 conditions.

\textbf{Clinical Risk Factors Responsible for Bleeding}

Documentation of clinical risk factors was lacking in most reports, but hypertension emerged as an important risk factor in patients with ischemic cerebrovascular disease, and major bleeding in venous thrombosis was frequently associated with recognized underlying risk factors (ulcer, cancer, recent surgery). These comorbid conditions (cancer, recent surgery, and paraplegia) are also predisposing factors for thrombosis. In cerebrovascular disease, major bleeding was almost always intracerebral, possibly because of associated hypertension or the cerebrovascular disease per se.

The addition of ASA to warfarin increased the risk of bleeding, but the addition of dipyridamole did not appear to add to the risk of bleeding with anticoagu- lants. A relationship between bleeding and age was sought but could not be detected, since the reports lacked the necessary information.

\textbf{Time of Bleed}

To determine the distribution of bleeding in relationship to the time of commencing anticoagulant therapy, knowledge of both the time of the bleeding event and the number of patients at risk at the time in question is necessary. Although the time of bleeding was documented in several reports, information on the number of patients at risk at the time of bleeding was not available; therefore, it was not possible to determine whether bleeding events were concentrated soon after commencing anticoagulant therapy.

\textbf{Intensity of Anticoagulant Therapy}

To assess reliably the relationship between the intensity of anticoagulant therapy and bleeding, the following information is required: (1) a clear definition of the therapeutic range and of the thromboplastin used, and (2) the laboratory test (prothrombin time) results in all patients who bled and who did not bleed. It was possible to seek a relationship between intensity of anticoagulant therapy and risk of bleeding from only 4 of the studies.\textsuperscript{14,15,33,48} The relationship between bleeding and the level of anticoagulant therapy was most clearly demonstrated in the studies by Hull et al\textsuperscript{14} and Turpie et al.\textsuperscript{48} These reports, on patients with proximal vein thrombosis and tissue prosthetic heart valves, demonstrated that the risk of bleeding was markedly reduced by using a less intense anticoagulant regimen monitored to maintain the PT (human brain thromboplastin) at 2 times control (INR = 2.0), which is equivalent to a North American thromboplastin of
bleeding. valves, embolism. received ischemic and ease, therapy (ischemic therapy to ischemic disease, and thrombosis), probably due to associated risk factors in both conditions.

4. There is a strong association between major bleeding and underlying risk factors. 

5. Bleeding frequently occurs during anticoagulant therapy when the PT is within the more intense therapeutic range (INR 3.0-4.5). Bleeding occurs less frequently when the PT is within the less intense therapeutic range (INR 2.0-3.0).

**SUMMARY and Recommendations**

The main complication of anticoagulant therapy is bleeding. We have conducted a literature review to determine the following: (1) the rate of bleeding (major, minor, and fatal) during long-term oral anticoagulant therapy (greater than four weeks) in various disorders (ischemic cerebrovascular disease, prosthetic cardiac valves, chronic atrial fibrillation, ischemic heart disease, and venous thrombosis), and (2) the clinical and laboratory risk factors that predispose patients to bleeding. Using strictly defined methodologic criteria, 171 studies were evaluated and classified into one of five categories based on the strength of the study design, with level I (randomized trials) representing studies that provided the most reliable information and level V (case series) the least reliable.

The risk of bleeding (pooled rates) was substantial and most marked in patients with ischemic cerebrovascular disease (29%) and venous thromboembolism (23%), while the rates for ischemic heart disease, prosthetic heart valves, and atrial fibrillation were 23%, 6%, and 15%, respectively. Major bleeding ranged from 2.4% to 8.1%, with ischemic cerebrovascular disease 7%, venous thromboembolism 8.1%, ischemic heart disease 4.7%, and prosthetic heart valves 2.4%. The incidence of fatal bleeding was highest in cerebrovascular disease at 4.8%, while fatal bleeding rates were 1.0% and 1.7%, respectively, for ischemic heart disease and prosthetic heart valves. There were no fatal bleeding episodes in patients who received anticoagulant therapy for venous thromboembolism. Reliable estimates of major and fatal bleeding rates for atrial fibrillation were not available.

It was possible to calculate bleeding per 100 patient years of therapy for several studies that provided information on the duration of anticoagulant therapy. For ischemic cerebrovascular disease, major bleeding rates ranged from 2 to 7/100 patient years and fatal bleeding from 2 to 9/100 patient years. In patients with prosthetic heart valves, anticoagulation was 0.6/100 patient years in two studies. In myocardial infarction, major bleeding rates ranged from 0 to 7.7/100 patient years, and fatal bleeding from 0 to 1.0/100 patient years.

Major bleeding in venous thrombosis and cerebrovascular disease was frequently associated with an underlying risk factor. In venous thromboembolism, these comorbid conditions (cancer, congestive heart failure, paraplegia) were also pre-existing for ischemic thrombosis. In cerebrovascular disease, major bleeding was almost always intracerebral, possibly because of associated hypertension or the cerebrovascular disease per se. We were unable to determine whether bleeding events were clustered soon after commencing anticoagulant therapy and whether they predispose to hemorrhage.

Two studies that evaluated the importance of anticoagulant therapy demonstrated that the risk of bleeding was reduced by using less intense anticoagulant regimens.

**REFERENCES**


Drapkin A, Merskey C. Anticoagulant therapy after acute myocardial infarction. JAMA 1972; 222:541-48

Veterans Administration. Anticoagulants in acute myocardial infarction. JAMA 1973; 225:724-29


Moschos CB, Wong PCY, Sise HS. Controlled study of the effective level of long-term anticoagulation. JAMA 1964; 190:799-805