Bleeding and Recurrent Thrombosis in Definite Antiphospholipid Syndrome

Analysis of a Series of 66 Patients Treated With Oral Anticoagulation to a Target International Normalized Ratio of 3.5

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Background: Prolonged anticoagulation is the treatment of choice for patients with thrombosis and the antiphospholipid syndrome. However, there is still debate about the optimum intensity of anticoagulation.

Methods: The study included 66 patients with antiphospholipid syndrome (Sapporo criteria) and previous thrombosis. All were receiving oral anticoagulation to a target international normalized ratio of 3.5. Every patient was individually interviewed to recall major bleeding and thrombotic episodes during the previous 12 months.

Results: Patients were mainly women and white. The rate of major bleeding was 6 cases per 100 patient-years (95% confidence interval [CI] 1.6-15.0). The rate of intracranial bleed was 1.5 per 100 patient-years (95% CI, 0.04-8.4). None of the bleeding episodes was fatal. The rate of thrombotic recurrences was 9.1 cases per 100 patient-years (95% CI, 3.3-19.6). Most recurrences took place in the same vascular bed as the original thrombosis. Age, time receiving anticoagulant therapy, primary vs secondary antiphospholipid syndrome, positivity for anticardiolipin antibodies, positivity for lupus anticoagulant, previous arterial thrombosis, previous stroke, previous venous thrombosis, and previous thrombocytopenia were not predictive of bleeding events. However, the risk of thrombotic recurrences was independently higher in patients who were receiving anticoagulation for longer periods.

Conclusions: The risk of intracranial and fatal bleeding in patients with definite antiphospholipid syndrome and previous thrombosis treated with oral anticoagulation to a target international normalized ratio of 3.5 is similar than in groups of patients treated to lower target ratios. The risk of thrombotic recurrences, even during anticoagulation, was high. Most recurrences took place in the same territory as original thromboses.

Arch Intern Med. 2002;162:1164-1169

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Soon after the description of Hughes (antiphospholipid) syndrome, it became clear that anticoagulant therapy was more effective than treatment with antiaggregant drugs for prevention of recurrent thrombosis in patients with antiphospholipid antibodies (aPLs).\(^1\)\(^-\)\(^4\) However, the optimum intensity of oral anticoagulation has since been a matter of debate. Two retrospective series including 70\(^1\) and 147\(^2\) patients with the antiphospholipid syndrome (APS) and thrombosis showed a lower rate of recurrences when international normalized ratios (INRs) were higher than 3.0. In contrast, 2 small observational prospective studies of patients with histories of venous thromboembolism and aPL\(^3\)\(^,\)\(^6\) reported no thrombotic recurrences in patients at INRs between 2.0 and 3.0. As a result, definite conclusions are difficult to draw, and even recent guidelines for the treatment of patients with APS and previous thrombosis do not agree, recommending target INRs of 3.5\(^7\) or 2.5\(^8\).

The heterogeneity of the different cohorts could explain in part these divergent results. For instance, patients included in the prospective studies\(^3\)\(^,\)\(^6\) had no history of arterial thromboses, a high prevalence of low-titer anticardiolipin antibodies (aCLs), and a lower risk of recurrences after warfarin sodium withdrawal compared with those of retrospective series.\(^1\)\(^,\)\(^2\) An additional major concern has been the increased risk of bleeding with high-intensity (INR, 3.0-4.0) oral anticoagulation. This study was an attempt to clarify the risks and benefits of oral anticoagulation to a target INR of 3.5 in patients with definite APS and previous thrombosis.

Results: The clinical profile of our cohort is summarized in Table 1. Our study popula-
PATIENTS AND METHODS

STUDY DESIGN

This was a retrospective cohort study in which every patient included was individually interviewed by one of us (G.R.-I., A.E., or M.J.C.). The interview included specific questions to recall bleeding episodes and thrombotic recurrences as well as the audit of anticoagulant therapy, all within the previous 12 months (see "Patients" subsection). Every major bleeding episode or thrombosis was documented by checking the clinical notes of the patient or by medical letters if they attended other centers. We limited the study to the 12 months before the interview to reduce heterogeneity in treatments and anticoagulation surveillance and also to ensure a good recall of clinical episodes by the patients.

PATIENTS

Patients attending our antiphospholipid clinic were enrolled consecutively from March 1 to August 31, 2000. To be included in the study, patients had to fulfill all of the following criteria:

1. Definite APS according to Sapporo criteria. Thus, only patients who tested positive—twice at least 6 weeks apart—for aCLs at medium or high titers and/or lupus anticoagulant (LA) entered the study.
2. History of thrombosis. Deep vein thrombosis was documented by appropriate imaging (ultrasonography and/or venography); pulmonary embolism, by high-probability lung scan, spiral computed tomographic scanning, or pulmonary arteriography; stroke, by computed tomographic scanning or magnetic resonance imaging; and peripheral and visceral arterial thrombosis, by arteriography or surgery. Cerebral transient ischemic attacks were diagnosed in the setting of acute local neurologic symptoms or signs lasting less than 24 hours. Myocardial infarction was defined as typical chest pain with characteristic electrocardiographic features and elevated creatine kinase (MB fraction) levels.
3. Treatment with oral anticoagulants to a target INR of 3.5 (INR range, 3.0-4.0) during the previous 12 months.

ANTIPHOSPHOLIPID ANTIBODY DETERMINATIONS

All the determinations were performed at the laboratories of the Lupus Research Unit (aCL assays) and the coagulation laboratories (LA assays) of St Thomas’ Hospital, London, England.

The IgG and IgM aCLs were measured by β2-glycoprotein I–dependent standardized enzyme-linked immunosorbent assay, as described elsewhere. Results are expressed in a semiquantitative fashion as follows: negative (IgG, <5 G phospholipid [GPL] units; IgM, <3.2 M phospholipid [MPL] units); low positive (IgG, 5-15 GPL units; IgM, 3.2-6 MPL units); medium positive (IgG, 16-80 GPL units; IgM, 7-50 MPL units); and high positive (IgG, >80 GPL units; IgM, >50 MPL units).

The LA was detected according to the guidelines of the International Society on Thrombosis and Hemostasis, Scientific Subcommittee on Lupus Anticoagulant/Phospholipid-Dependent Antibodies, using activated partial thromboplastin time and diluted Russell viper venom time as screening tests.

Determinations of IgA aCLs or antibodies directed against other phospholipids or phospholipid-binding proteins (eg, β2-glycoprotein I–specific enzyme-linked immunosorbent assay, antiprothrombin antibodies, Continued on next page

AUDIT OF ANTICOAGULANT THERAPY

Data on anticoagulation surveillance were available for 59 patients (89%). One thousand fifty INR determinations were performed in a total of 638 patient-months, thus resulting in 1.65 determinations per patient-month. The range of determinations per patient during the study period was 5 to 43. The cumulative number of INR determinations within each predefined range is shown in the Figure. Of the INRs, 391 (37%) were between 3.0 and 4.0, 323 (31%) between 2.0 and 2.9, and 137 (13%) between 4.0 and 4.9. At the extremes, 123 (12%) were lower than 2.0 and 77 (7%) were higher than 5.0.

BLEEDING

Bleeding rates are given in Table 3, and details regarding bleeding episodes are given in Table 4.

Major bleeding was observed in 4 patients (2 retroperitoneal, 1 intracranial, and 1 rectal), resulting in a rate of 6 cases per 100 patient-years (95% CI, 1.6-15.0). The rate of intracranial bleeding was 1.5 per 100 patient-years (95% CI, 0.04-8.4). None of the bleeding episodes was fatal. In a population of 66 patients, this results in a 95% CI of 0 to 3.7 deaths due to bleeding per 100 patient-years.

One patient had bilateral subdural hematomas in South America, when she omitted anticoagulation monitoring for more than 1 month. At the time of bleeding, she had experienced a recent head trauma and her INR was more than 20. After surgical intervention, she had full recovery. Two patients had retroperitoneal bleeding when they restarted warfarin treatment after a transient withdrawal for a renal biopsy. The INRs at the time of the events were 5.2 and 1.9. Finally, 1 patient suffered continuous rectal bleeding at INRs below 3 until sur...
antiphosphatidylserine, and phosphatidylcholine) were not considered for the purposes of this study.

**AUDIT OF ANTICOAGULANT THERAPY**

Although the target INR for every individual patient is recommended by our unit, anticoagulant monitoring is provided by their local anticoagulation clinic or general practitioner. The periodicity of INR controls was determined by the physicians responsible for anticoagulation monitoring according to their own judgment.

During the interview, every patient’s personal anticoagulation book was checked, when available. The audit consisted of counting the number of times during the previous 12 months that the INR lay within predefined limits: less than 2.0, 2.0 to 2.9, 3.0 to 4.0, 4.1 to 4.9, 5.0 to 6.0, and more than 6.0. The proportion of measurements in each range was then calculated for the entire population. Patients who did not provide their anticoagulation book were included in the study for clinical end points (see “Clinical End Points” subsection), although they could not be included in the audit.

**CLINICAL END POINTS**

The clinical end points were documented major bleeding and recurrent thrombosis. Only episodes of major bleeding, defined as intracranial, intraocular, gastrointestinal, retroperitoneal, or requiring transfusion or admission to a hospital, were considered for the purposes of this study. Minor bleeding was not an end point because of its clinical irrelevance and patients’ difficulty in recalling such episodes. Recurrent thromboses were diagnosed by the same criteria as for original thromboses. Patients having bleeding or thrombosis were investigated for specific risk factors at the time of the event.

During the interview, every patient with recurrent thrombosis (yes/no) used as dependent variables. Recurrent thromboses were diagnosed by the same criteria as for original thromboses. Patients having bleeding or thrombosis were investigated for specific risk factors at the time of the event.

Details of thrombotic episodes are summarized in Table 4. Six patients had thrombotic recurrences during the follow-up, a rate of 9.1 per 100 patient-years (95% CI, 3.3-19.6). Four episodes were arterial and 2 were venous thromboses. Three patients with arterial events had additional risk factors such as high blood pressure and cigarette smoking. The woman who suffered subdural hema-
tomas had a subsequent venous thrombosis when deprived of thromboprophylaxis postoperatively. Two patients had no other risk factors for thrombosis. The INRs at the time of thrombosis were between 2.1 and 2.6 (it was not determined in 1 case). No patient died of thrombosis (95% CI, 0-3.7). Five of 6 patients experienced a recurrence in the same vascular bed as the original thrombosis.

**PREDICTORS OF EVENTS**

The following clinical variables were included in 2 logistic regression models to determine which could pre-
dict bleeding or thrombosis: age, time receiving anticoagulant therapy, primary vs secondary APS, aCL positive, LA positive, previous arterial thrombosis, previous stroke, previous venous thrombosis, and previous thrombocytopenia. Sex and race were not included in the model, since more than 90% of the cohort were women and white.

One of the potential problems of the study was that patients who missed the scheduled clinic could have been admitted somewhere else—or even died—because of bleeding or thrombosis, thus underestimating the rate of severe complications. However, it is usual practice for local hos-
itals or general practitioners looking after our patients to inform us of any complications arising. Any patients who failed to attend clinic in the study period were contacted by staff nurses to ensure they had not had any major bleeding or thrombotic events. No patient missed a clinic appointment during the study period because of major bleeding, thrombosis, or death from any cause.

**STATISTICAL ANALYSIS**

Data filing and processing and statistical calculations were performed with StatView software (version 5.0.1 for Power Macintosh; SAS Institute Inc, Cary, NC). The results were expressed as rates of events per 100 patient-years, which were calculated as

$$(\text{Total No. of Events} \times 100)/\text{Total Person-Years}.$$  

In this case, the total person-years was equal to the total number of patients, as the study period was 12 months in all cases. Confidence intervals (CIs) were calculated assuming a Poisson distribution, since the results were expressed as rates, the events were random and independent, and the number of events was small, thus not allowing a normal approximation.

Univariate comparison between continuous variables was performed by 2-tailed t test. To disclose clinical variables that could be risk factors for the specific outcomes (bleeding or thrombosis), we performed backward stepwise logistic regression, with bleeding (yes/no) and thrombosis (yes/no) used as dependent variables.

Since 1995, we have adopted oral anticoagulation to a target INR of 3.5 (range, 3.0-4.0) as the standard therapy for patients with aPLs and previous thromboses. In this study, we found that this practice does not result in a high incidence of intracranial or fatal bleeding in patients with definite APS who are at a high risk of recurrent thrombosis.
The actual risk of thrombosis in patients with aPLs is not well established, particularly for patients without previous events. We know that the presence of LA or aCLs at medium to high titers increases that risk, especially in the setting of a history of thrombosis. In retrospective series the rates of thrombotic recurrences in untreated subjects were between 19 and 29 events per 100 patient-years.

The risk of bleeding during oral anticoagulant treatment is not well defined in the general population. Table 5 summarizes the results of 5 relevant studies that cover this issue: a meta-analysis on the efficacy of anticoagulation in atrial fibrillation; a randomized controlled trial of anticoagulation vs aspirin after a transient ischemic attack; a prospective cohort of anticoagulation in clinical practice; a prospective inception cohort to study bleeding complications of oral anticoagulant therapy; and a randomized controlled trial of long vs short anticoagulation in venous thromboembolism.

In the meta-analysis by Hart et al, the risk per year of major extracranial bleeding and intracranial hemorrhage was 0.9% and 0.3%, respectively. These figures are in keeping with the results of the Italian prospective inception cohort and the prospective series of Kalra et al. However, other authors have found higher rates of bleeding. The results of the Stroke Prevention in Reversible Ischemia Trial (SPIRIT) were particularly striking. In that study, patients with a recent transient ischemic attack allocated to receive oral anticoagulants to an INR of between 3.0 and 4.5 suffered major and intracranial bleeding at very high rates of 7 and 3.7 per 100 patient-years, respectively.

Factors that may increase the risk of hemorrhage during oral anticoagulant therapy include age greater than 65 to 75 years, receiving multiple medications, history of gastrointestinal tract bleeding, arterial thrombosis or stroke, and INRs higher than 4.5 to 5.0. If one focuses specifically on intracerebral bleeding, the presence of leukoariosis (diffuse white matter hypodensity on magnetic resonance imaging or computed tomographic scanning) has been recognized as the most important risk factor for bleeding in the SPIRIT cohort. In the same study, the intensity of anticoagulation was not an independent predictor of bleeding in the multivariate model.

In our group, anticoagulation control was not as strict as we wished. The INRs within the "therapeutic" range between 3.0 and 4.0 were accomplished in only 37% of determinations. Although the sort of audit we used implied a bias toward an increase in “out of range” determinations, the actual risk of thrombosis in patients with aPLs is not well established, particularly for patients without previous events. We know that the presence of LA or aCLs at medium to high titers increases that risk, especially in the setting of a history of thrombosis. In retrospective series the rates of thrombotic recurrences in untreated subjects were between 19 and 29 events per 100 patient-years.
presence of LA.16,17 The tendency of patients with APS different risk of recurrences depending on aCL titers and than 3.0 from retrospective series,1,2 thus highlighting the that in patients receiving anticoagulation at INRs higher than the risk observed in the studies not including pa-
tients with APS (Table 5). This rate was also higher than the risk in all patients who bled in our series.

In fact, our population was at a particularly high risk—our results may also reflect the fears of many an-
ticoagulation clinics of long-term high-intensity antico-
agulation in routine clinical practice. In the United King-
dom, the majority of patients attending anticoagulant clinics are receiving warfarin because they have atrial fibrillation and are aiming for a target INR of 2.0 to 3.0. Our policy did, however, maintain INRs above 2.0 in all patients who bled in our series.

We observed a risk of major bleeding that was in-
termediate between those of the SPIRIT study and groups of patients with atrial fibrillation (Table 5). In particular, our frequency of intracerebral bleeding was within the 95% CI of the “clinical practice” cohort of Kalra et al20 and was not substantially higher than in other series (Table 5). The increased risk of using a high target INR may have been compensated for by the fact that patients with APS are generally young, since advanced age is a consistent risk factor for cerebral bleeding in patients receiving anticoagulation.21,23-26 Moreover, the differences seen in the frequency of intracranial bleeding between our series and that of Gorter26 may also suggest that the nature of the presumed small vessel damage may not be the same in patients with cerebral thrombosis caused by APS and that caused by long-standing arterial hypertension and/or diabetes. Of note, in a recent article from our unit that describes 15 cases of major bleeding in patients with APS between 1989 and 1999, we did not find any episode of intracerebral bleeding.28 Finally, concurrent risk factors, including renal biopsies in 2 patients, were present in all patients who bled in our series.

Table 4. Bleeding and Thrombotic Complications*

<table>
<thead>
<tr>
<th>Patient No./ Sex/Age, y</th>
<th>Previous Thrombosis</th>
<th>Event</th>
<th>Site/ Type of Event</th>
<th>INR at Event</th>
<th>Risk Factors for the Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/54</td>
<td>Venous</td>
<td>Bleeding</td>
<td>Retroperitoneal</td>
<td>5.2</td>
<td>Renal biopsy, aspirin</td>
</tr>
<tr>
<td>2/M/28</td>
<td>Venous</td>
<td>Bleeding</td>
<td>Retroperitoneal</td>
<td>1.9</td>
<td>Renal biopsy</td>
</tr>
<tr>
<td>3/M/35</td>
<td>Arterial + venous</td>
<td>Bleeding</td>
<td>Rectal</td>
<td>2.5</td>
<td>Internal hemorrhoids, aspirin</td>
</tr>
<tr>
<td>4/F/36</td>
<td>Arterial + venous</td>
<td>Bleeding</td>
<td>Intracranial</td>
<td>&gt;20</td>
<td>Head trauma</td>
</tr>
<tr>
<td>5/F/28</td>
<td>Arterial</td>
<td>Thrombosis</td>
<td>Venous</td>
<td>2.1</td>
<td>Transient warfarin withdrawal</td>
</tr>
<tr>
<td>6/F/24</td>
<td>Arterial</td>
<td>Thrombosis</td>
<td>Stroke</td>
<td>2.5</td>
<td>Hypertension</td>
</tr>
<tr>
<td>7/M/39</td>
<td>Venous</td>
<td>Thrombosis</td>
<td>Venous</td>
<td>2.5</td>
<td>None</td>
</tr>
<tr>
<td>8/F/34</td>
<td>Arterial</td>
<td>Thrombosis</td>
<td>TIA</td>
<td>2.3</td>
<td>None</td>
</tr>
<tr>
<td>9/M/44</td>
<td>Venous</td>
<td>Thrombosis</td>
<td>MI</td>
<td>2.6</td>
<td>Smoking, hypertension, hypercholesterolemia</td>
</tr>
</tbody>
</table>

*INR indicates international normalized ratio; TIA, transient ischemic attack; and MI, myocardial infarction.

Table 5. Summary of Studies Including Cohorts of Warfarin-Treated Patients*

<table>
<thead>
<tr>
<th>Type of study</th>
<th>Indication for therapy</th>
<th>Type of prevention</th>
<th>Type of study</th>
<th>Group size</th>
<th>Mean age, y</th>
<th>Female sex, %</th>
<th>Target INR</th>
<th>Major bleeding</th>
<th>Intracranial bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hart et al.18 1999</td>
<td>Meta-analysis</td>
<td>Atrial fibrillation</td>
<td>Primary and secondary</td>
<td>1450</td>
<td>69</td>
<td>58</td>
<td>1.4-4.5 (range)§</td>
<td>0.9</td>
<td>0.3</td>
</tr>
<tr>
<td>SPIRIT, 1997</td>
<td>RCT</td>
<td>Atrial fibrillation</td>
<td>Secondary</td>
<td>651</td>
<td>47% &gt;67</td>
<td>59</td>
<td>2.5</td>
<td>7</td>
<td>3.7</td>
</tr>
<tr>
<td>Kalra et al.20 2000</td>
<td>Prospective cohort</td>
<td>Atrial fibrillation</td>
<td>Primary</td>
<td>167</td>
<td>77</td>
<td>58</td>
<td>2.0-4.5 (range)§</td>
<td>3</td>
<td>0.3</td>
</tr>
<tr>
<td>Pialareti et al.21 1996</td>
<td>Prospective cohort</td>
<td>Venous</td>
<td>Mostly secondary</td>
<td>2745</td>
<td>&gt;60</td>
<td>42</td>
<td>2.5</td>
<td>1.1</td>
<td>0.45</td>
</tr>
<tr>
<td>Kearon et al.22 1999</td>
<td>RCT</td>
<td>VTE</td>
<td>Secondary</td>
<td>79</td>
<td>59</td>
<td>40</td>
<td>3.5</td>
<td>1</td>
<td>1.5</td>
</tr>
<tr>
<td>This Study</td>
<td>Retrospective cohort</td>
<td>APS</td>
<td>Secondary</td>
<td>66</td>
<td>66</td>
<td>41</td>
<td>3.5</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>

*SPIRIT indicates Stroke Prevention in Reversible Ischemia Trial; RCT, randomized controlled trial; VTE, venous thromboembolism; APS, antiphospholipid syndrome; and INR, international normalized ratio.
†Including VTE (32%), heart disease (38.8%), arterial thrombosis (10%), and valve prosthesis (10.8%).
‡Varied among different studies reviewed in the meta-analysis.
§Varied depending on the indication.
||Rates per 100 patient-years.
Probably in part because of sample size restrictions, we could not define factors that predict bleeding or recurrent thromboses in patients with APS. The only relevant finding in the multivariate analysis was that the risk of thrombotic recurrences does not decrease—it actually increases—with time. Therefore, this study supports the belief that indefinite anticoagulation is indicated for this group.1,2,4,22

Our study has obvious limitations. The main one is its retrospective design. This was partially compensated for by personally interviewing every patient, which allowed recognition of major bleeding and thrombotic episodes even if treated at other hospitals. The audit of anticoagulant therapy did not calculate the actual time at each range of INRs, the most accurate method of monitoring.20 Our audit does, however, offer an indication of the quality of anticoagulation in our patients in the United Kingdom. Finally, the relatively small sample size widened CIs.

On the other hand, to our knowledge, this is the first study of anticoagulation including patients who fulfilled Sapporo criteria. Thus, our population had definite APS (ie, low-titer aCLs were not included) and was at high risk of thrombotic recurrences, as our own re-
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When the indication for and intensity of anticoagulant therapy are determined in an individual patient, bleeding risk is clearly not the only factor to consider. It must be weighed against the possibility of recurrent serious thrombosis.23,28 On the basis of a cautious analysis of our results and those of previous studies,1,3 we believe that most patients with definite APS and previous thrombo-
sis should be treated to a target INR of 3.5. The exception could be individuals with only venous events and those at high risk of bleeding (aged or with previous life-
threatening bleeding episodes), who could be consid-
ered for lower intensities of anticoagulation.22 Every ef-
f ort must be made to limit concomitant medications and invasive procedures in this group. Furthermore, the ade-
quate control of additional risk factors for thrombosis, such as smoking, hypertension, and hyperlipidemia, must be considered an integral part of therapy in patients with definite APS.

Accepted for publication September 25, 2001.

This study was supported by grant 99/5007 of Fondo de Investigacion Sanitaria, Spain; the Department of Health of the Basque Government, Vitoria-Gasteiz, the Basque Coun-
try, Spain; and Lupus UK, Essex, England.

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