A randomized clinical trial of high-intensity warfarin vs. conventional antithrombotic therapy for the prevention of recurrent thrombosis in patients with the antiphospholipid syndrome (WAPS)

G. Finazzi,* R. Marchioli,† V. Brancaccio,§ P. Schinco,¶ F. Wisloff,** J. Musial,*** F. Baudo,†† M. Berrettini,§§ S. Testa, §§ A. D’Angeolo,¶¶ G. Tognoni† and T. Barbui*

*The Ospedali Riuniti, Bergamo, Italy; †Consorzio Mario Negri Sud, Santa Maria Imbaro, Italy; ‡Ospedale Cardarelli, Napoli, Italy; §Ospedale Molinette, Torino, Italy; ¶Ullevaal Hospital, Oslo, Norway; **Jagiellonian University, Crakow, Poland; ††Ospedale Niguarda, Milano, Italy; §§Università di Perugia, Italy; §§§Ospedale di Cremona, Italy; and ¶¶Ospedale S. Raffaele, Milano, Italy


See also Anderson DR. Oral anticoagulation for the antiphospholipid antibody syndrome: can we now say less is more? This issue, pp 846–7; Scully M-F. Moderate dose oral anticoagulant therapy in patients with the antiphospholipid syndrome? Yes. This issue, pp 840–1; Rickles FR, Marder VJ. Moderate dose oral anticoagulant therapy in patients with the antiphospholipid syndrome? No. This issue, pp 842–3; Khamashta MA, Hunt BJ. Moderate dose oral anticoagulant therapy in patients with the antiphospholipid syndrome? No. This issue, pp 844–5.

Summary. Background: The optimal intensity of oral anticoagulation for the prevention of recurrent thrombosis in patients with antiphospholipid antibody syndrome is uncertain. Retrospective studies show that only high-intensity oral anticoagulation [target international normalized ratio (INR) > 3.0] is effective but a recent randomized clinical trial comparing high (INR range 3.0–4.0) vs. moderate (INR 2.0–3.0) intensities of anticoagulation failed to confirm this assumption. Methods: We conducted a randomized trial in which 109 patients with antiphospholipid syndrome (APS) and previous thrombosis were given either high-intensity warfarin (INR range 3.0–4.5) or standard antithrombotic therapy (warfarin, INR range 2.0–3.0 in 52 patients or aspirin alone, 100 mg day−1 in three patients) to determine whether intensive anticoagulation is superior to standard treatment in preventing symptomatic thromboembolism without increasing the bleeding risk. Results: The 109 patients enrolled in the trial were followed up for a median time of 3.6 years. Mean INR during follow-up was 3.2 (SD 0.6) in the high-intensity warfarin group and 2.5 (SD 0.3) (P < 0.0001) in the conventional treatment patients given warfarin. Recurrent thrombosis was observed in six of 54 patients (11.1%) assigned to receive high-intensity warfarin and in three of 55 patients (5.5%) assigned to receive conventional treatment [hazard ratio for the high intensity group, 1.97; 95% confidence interval (CI) 0.49–7.89]. Major and minor bleeding occurred in 15 patients (two major) (27.8%) assigned to receive high-intensity warfarin and eight (three major) (14.6%) assigned to receive conventional treatment (hazard ratio 2.18; 95% CI 0.92–5.15). Conclusions: High-intensity warfarin was not superior to standard treatment in preventing recurrent thrombosis in patients with APS and was associated with an increased rate of minor hemorrhagic complications.

Keywords: antiphospholipid syndrome, oral anticoagulation, thrombosis.

Introduction

Antiphospholipid antibody syndrome (APS) is an uncommon autoimmune disease in which venous and arterial thrombosis frequently occur [1,2]. Retrospective studies have reported that only high-intensity oral anticoagulation [to achieve an international normalized ratio (INR) above 3.0] was effective in preventing thrombotic recurrences [3–5]. However, concerns were raised about the hemorrhagic risk of such intensive anticoagulation treatments [6,7]. A recent randomized clinical trial comparing high vs. moderate intensities of warfarin failed to show a superiority of the more intense regimen for the
secondary thromboprophylaxis in APS patients [8]. As it is often the case for rare diseases with severe prognosis, the small size of the study population and the limited number of events on which the negative findings are based do confirm the difficulty of providing univocal answers for this type of clinical conditions.

A closely comparable and totally unrelated protocol – Warfarin in the AntiPhospholipid Syndrome (WAPS) trial – running concurrently in Europe had similar difficulties in enrolling a high enough number of patients to provide reliable estimates on the efficacy and safety of high- vs. standard-intensity oral anticoagulation. The results of the WAPS trial are reported here, and their chronological coincidence with those of Crowther et al. [8] provides a unique opportunity to verify, with a test of consistency, the reliability of the statistically weak power of both studies.

**Methods**

**Study design**

Twenty-six centers from Italy, Norway, Poland, Argentina, and Czechoslovakia screened and enrolled, in a prospective registry, 462 patients with lupus anticoagulant and/or moderate to high positive anticardiolipin antibodies. Of 316 patients (68%) with a confirmed history of major arterial or venous thrombosis, 109 patients with clinically confirmed APS within the last 5 years were enrolled according to the Prospective Randomized Open Blinded Endpoint adjudication design (PROBE) [9–10] in an open-label randomized clinical trial with ascertainment of prospectively defined end-points by a blinded Endpoint Validation Committee.

Fifty-four patients were randomly allocated to high-intensity warfarin therapy (INR range 3.0–4.5, target 3.5) and 55 to the standard antithrombotic prophylaxis recommended for patients without antiphospholipid antibodies: (i) warfarin at doses adjusted to an INR range of 2.0–3.0 (target 2.5) if they had had a previous episode of venous thromboembolism, cardioembolic cerebral or peripheral ischemia, or in the presence of atrial fibrillation or rheumatic valve disease; or (ii) low-dose aspirin (100 mg day⁻¹), in case of non-embolic arterial thrombosis. Patients were excluded from randomization if they were of age <18 years (n = 8), history of recurrent thrombosis during anticoagulant prophylaxis (n = 57), active bleeding or hemorrhagic disorders contraindicating oral anticoagulant therapy (n = 25), pregnancy, other co-morbidities contraindicating oral anticoagulants or any serious illness with a life expectancy <3 years (n = 28), inability to give informed consent or to attend regular follow-up visits (n = 97) or more than one reason (n = 39). Thirty-one patients were excluded from the trial for unknown reasons.

Patients were stratified according to center and history of recurrent thrombosis occurred off therapy. Randomization was centralized at Consorzio Mario Negri Sud (Italy). Experimental treatments were randomly allocated by a program based on the ‘biased-coin’ algorithm, automatically assigned to sequential patient numbers, and communicated to the centers by telephone.

All the patients were examined at baseline, 3, 6 months and then every 12 months until the end of the study. All the patients were instructed to report to the clinical center any new symptom suggestive of thrombosis or bleeding.

The frequency of INR testing and warfarin dose adjustments were left to the responsibility of the physician in charge of the patient and were verified by the investigators during the follow-up visits scheduled for the study. INR test results, and type of thromboplastin used to perform the tests were recorded from the time of randomization to the end-of-study visit.

The study protocol conformed to good clinical practice for trials and to the Declaration of Helsinki on medical research in humans. We obtained the approval of the local ethics committees of the participating centers before the start of the trial. All patients were required to give informed written consent. The study was independently conceived, conducted, and analyzed under the responsibility of the Steering Committee.

**Laboratory methods**

Sample collection and processing, which complied with national guidelines, was performed as previously described [11]. Diagnosis of lupus anticoagulant was established according to currently recommended criteria [12]: (i) prolongation of at least one phospholipid-dependent clotting test, (ii) persistent abnormality after 1 : 1 mixing of patient’s plasma with normal pooled plasma; and (iii) correction of the abnormality after increasing the phospholipid concentration in the abnormal test(s).

Anticardiolipin antibodies titers of IgG and IgM class were measured with in-house or commercial enzyme-linked immunosorbent assay (ELISA) procedure in use at each center and expressed as GPL or MPL units [13].

Both lupus anticoagulant and anticardiolipin antibodies titers were confirmed in at least another determination 6–8 weeks apart to exclude transient antibodies. Patients with persistent lupus anticoagulant and/or moderate or high positive anticardiolipin antibodies values (> 40 U GPL or MPL) were enrolled.

**Outcome measures**

Two cumulative, co-primary end-points were established: (i) vascular death, non-fatal major arterial and venous thrombotic events (i.e. myocardial infarction, stroke, pulmonary embolism, deep vein thrombosis, transient ischemic attack), and (ii) all the above plus major hemorrhage.

The secondary end-points were: total, minor (superficial thrombophlebitis), and major thrombotic events, and fatal and non-fatal cerebrovascular and cardiac events. Additional analyses for each component of the primary end-points and for the main causes of death were performed.

The safety of the experimental treatments was assessed by analyzing: (i) fatal and non-fatal major hemorrhage, (ii) minor hemorrhage, and (iii) any adverse event leading to treatment
withdrawal. Adherence to protocol and the rate of drug discontinuation were also evaluated.

The principal events were defined and classified according to the International Classification of Diseases, 9th Edition. The category of cardiovascular death included: documented diagnosis of myocardial infarction or stroke in the absence of any other evident cause, sudden death, death from heart failure, and all deaths classified as being cardiovascular in nature. Myocardial infarction was accepted as a confirmed event if the investigator had identified this complication on a standard form or if a death certificate or hospital records described it as a fatal myocardial infarction. Non-fatal acute myocardial infarction was defined as at least two of the following: chest pain of typical intensity and duration, ST segment elevation or depression of ≥1 mm in any limb lead of the electrocardiogram, of ≥2 mm in any precordial lead, or both, or at least a doubling in cardiac enzymes. Abrupt onset of a neurological deficit that resolved completely in <24 h was diagnosed as transient ischemic attack. Patients with new neurological deficits persisting for >24 h underwent cerebral computerized tomography (CT) scan or magnetic resonance imaging to discriminate hemorrhagic and ischemic strokes. Diagnosis of a new or recurrent venous thromboembolic event (e.g. deep vein thrombosis and/or pulmonary embolism) underwent leg ultrasound, lung scanning, computed tomography (CT) scan or angiography as indicated. Acute peripheral arterial thrombosis was diagnosed in the presence of a typical clinical picture (pain, absence of peripheral pulse) with positive arteriography or surgery. Bleeding was defined as major if it was fatal, intracranial, retroperitoneal or associated with need for blood transfusion or surgery. All other overt hemorrhages were considered as minor hemorrhagic events.

The validation of the clinical events included in the primary end-points was ensured by an ad hoc committee of expert clinicians blinded to patients’ treatment assignment. Each event was validated independently by two evaluators and disagreement between the evaluators was assessed by the chairman of the study.

**Planned sample size and early termination of the trial**

Based on available information, the rate of vascular death and non-fatal major thrombotic events had been estimated in the protocol to be 10% over a 3-year follow-up. As treatment with high-dose warfarin was expected to reduce such incidence rate by 50%, a sample size of 500 patients per arm in a 3-year study was calculated ($\beta = 0.80$, $\alpha = 0.05$ two-tailed). The aforementioned sample size was a conservative expectation of efficacy of high-intensity anticoagulation as retrospective studies [3,4] suggested a definitively higher reduction of thrombosis with the absolute rate of thrombosis ranging from 7%–32% to 0%–1.3% per year in patients treated without or with high-intensity warfarin therapy, respectively.

On the occasion of a planned interim safety analysis after 3 years of enrolment, the following information was submitted to the attention of the Steering Committee: (i) because of important logistic and administrative difficulties, the recruiting centers across Europe were much fewer than expected and the rate of new randomizations was practically reduced to zero; and (ii) the transmission of data from the investigators to the Coordinating Centre was delayed, thus suggesting that the adherence of the investigators to the planned schedule of follow-up visits was starting to fade. According to the aforementioned points, the decision to stop the study and to ask for the completion of follow-up of randomized patients was taken up. Up to 94.5% of the randomized patients, for a median follow-up duration of 3.6 years (interquartile range 2.7–4.5 years) and a total follow-up of 369.7 person-years, were traced by the investigators.

**Statistical analysis**

Analysis was performed by intention-to-treat. Hazard ratios along with 95% confidence intervals (CI) were calculated by fitting a Cox proportional hazards model. Events included in composite end-points were managed hierarchically, i.e. we first looked at information on vital status and, if the patient was alive at the end of the study, assessed whether a non-fatal event had occurred. We used the Kruskal–Wallis test for continuous variables.

Petos method was used for the pooling of our data with those published by Crowther et al. [8] where 114 patients with APS were randomly allocated to standard-intensity (INR 2.0–3.0) or high-intensity (INR 3.1–4.0) oral anticoagulant regimen and were followed up for an average of 2.7 years. All $P$-values were two-sided. All analyses were carried out using the SAS statistical package.

**Results**

The demographic and clinical characteristics of the two randomized arms are comparable, as documented in Table 1.

**Table 1** Baseline characteristics of the patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>High-intensity anticoagulation</th>
<th>Conventional treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>54</td>
<td>55</td>
</tr>
<tr>
<td>Follow-up duration (years)</td>
<td>3.5 (1.2)</td>
<td>3.3 (1.2)</td>
</tr>
<tr>
<td>Person-years</td>
<td>188.86</td>
<td>180.85</td>
</tr>
<tr>
<td>Males</td>
<td>21 (38.9)</td>
<td>20 (36.4)</td>
</tr>
<tr>
<td>Age at recruitment (years)</td>
<td>41.1 (±12.1)</td>
<td>41.0 (±12.3)</td>
</tr>
<tr>
<td>Prior arterial thrombosis, n (%)</td>
<td>21 (38.9)</td>
<td>23 (41.8)</td>
</tr>
<tr>
<td>Prior venous thrombosis, n (%)</td>
<td>37 (68.5)</td>
<td>38 (69.1)</td>
</tr>
<tr>
<td>Systemic lupus erythematosus, n (%)</td>
<td>5 (9.3)</td>
<td>9 (16.4)</td>
</tr>
<tr>
<td>Other autoimmune disease, n (%)</td>
<td>9 (17.2)</td>
<td>9 (16.4)</td>
</tr>
<tr>
<td>Congenital thrombophilia, n (%)</td>
<td>7 (13.0)</td>
<td>10 (18.2)</td>
</tr>
<tr>
<td>Antiphospholipid antibodies [n (%)]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticardiolipin antibody alone</td>
<td>9 (16.7)</td>
<td>10 (19.2)</td>
</tr>
<tr>
<td>Lupus anticoagulant alone</td>
<td>14 (26.9)</td>
<td>13 (25.0)</td>
</tr>
<tr>
<td>Anticardiolipin antibody and lupus anticoagulant</td>
<td>29 (55.8)</td>
<td>29 (55.8)</td>
</tr>
<tr>
<td>Aspirin therapy at enrolment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin + anticoagulants</td>
<td>4 (7.4%)</td>
<td>3 (5.5%)</td>
</tr>
<tr>
<td>Only aspirin</td>
<td>3 (5.5%)</td>
<td></td>
</tr>
</tbody>
</table>

© 2005 International Society on Thrombosis and Haemostasis
which describes a relatively young population (47% of patients were aged ≤40 years) with a severe history of thrombotic events. About 50% of patients were diagnosed with APS in the year preceding enrolment in the study.

Mean INR during follow-up was 3.2 (SD 0.6) in the high-intensity anticoagulation arm and 2.5 (SD 0.3) (P < 0.0001) in the patients treated with warfarin in the conventional therapy arm.

The similarity of the two regimens with respect to primary and secondary end-points is presented in Table 2. No significant difference was observed between the two groups for the efficacy and safety end-points with the exception of minor bleedings which were significantly more frequent in the high-intensity warfarin group (hazard ratio 2.92, 95% CI 1.13–7.52, P = 0.0269).

Five patients allocated to high-intensity oral anticoagulation and four to standard therapy discontinued the treatment prior to the end of the study, permanently. Reasons for withdrawing drug therapy were as follows: patient’s refusal in three, essential thrombocytopenia in one, headache in one, physician’s decision in three, and unknown reason in one. Four and three patients assigned to high-intensity anticoagulation and standard therapy, respectively, were given anticoagulation plus aspirin based on the treating physician’s decision. Three patients with non-embolic arterial thrombosis allocated to standard therapy were given aspirin only according to the study protocol. These three patients did not experience major bleeding or thrombotic events during the follow-up. There was no difference in the main results of the trial if patients treated with aspirin were excluded from the analysis.

The cumulative evidence of our and Crowther’s trial [8] is shown in Fig. 1 and confirms a significant excess of minor bleeding (hazard ratio 2.30, 95% CI 1.16–4.58, P = 0.02) as well as a borderline significant estimate of an excess thrombotic risk with high-intensity anticoagulation (hazard ratio 2.49, 95% CI 0.93–6.67, P = 0.07).

Discussion

Although previous retrospective analyses suggested a beneficial effect of high-intensity anticoagulation on the thrombotic risk in APS [3–5], two independently and concomitantly run randomized trials did not confirm this finding [8 and this study]. Both studies have limited statistical power, because of the well-known difficulties in conducting adequately sized trials in uncommon diseases. The remarkable coincidence of the two protocols, however, translates into a perfect overlapping of the direction of the results with respect to both efficacy (i.e. thrombosis) and safety (i.e. hemorrhage) outcome measures. The consistency of the findings against the experimental hypothesis support the adoption of moderate-intensity anticoagulation with an INR targeted at 2.5 (range 2.0–3.0) as the best evidence-based recommendation available for secondary

### Table 2 Major study end-points according to treatment group

<table>
<thead>
<tr>
<th>Outcome</th>
<th>High-intensity anticoagulation (n = 54)</th>
<th>Conventional treatment (n = 55)</th>
<th>Hazards ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular death, major thrombosis*</td>
<td>5 (9.3%)</td>
<td>3 (5.5%)</td>
<td>1.63 (0.39–6.83)</td>
<td>0.5043</td>
</tr>
<tr>
<td>Vascular death, major thrombosis or major hemorrhage</td>
<td>6 (11.1)</td>
<td>5 (9.1)</td>
<td>1.17 (0.36–3.83)</td>
<td>0.7979</td>
</tr>
<tr>
<td>Death</td>
<td>3 (5.6%)</td>
<td>2 (3.6%)</td>
<td>1.41 (0.23–8.47)</td>
<td>0.7078</td>
</tr>
<tr>
<td>Total thrombosis</td>
<td>6 (11.1%)</td>
<td>3 (5.5%)</td>
<td>1.97 (0.49–7.89)</td>
<td>0.3383</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transient ischemic attacks</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deep venous thrombosis</td>
<td>2</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superficial thrombophlebitis</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total hemorrhage</td>
<td>15 (27.8%)</td>
<td>8 (14.6%)</td>
<td>2.18 (0.92–5.15)</td>
<td>0.0755</td>
</tr>
<tr>
<td>Major hemorrhage</td>
<td>2 (3.7%)</td>
<td>3 (5.5%)</td>
<td>0.66 (0.11–3.96)</td>
<td>0.6518</td>
</tr>
<tr>
<td>Minor hemorrhage</td>
<td>15 (27.8%)</td>
<td>6 (10.9%)</td>
<td>2.92 (1.13–7.52)</td>
<td>0.027</td>
</tr>
</tbody>
</table>

Hazards ratios for high-intensity warfarin when compared with conventional treatment. CI denotes confidence interval. Patients with two or more events of different types appear more than once in columns but only once in rows.

*Major thrombosis included myocardial infarction, stroke, pulmonary embolism, deep vein thrombosis and transient ischemic attacks.

†Total thrombosis included major thrombosis plus superficial thrombophlebitis.

![Fig. 1. Odds ratios for high-intensity anticoagulation vs. conventional treatment in the WAPS and Crowther et al. [8] trials. The meta-analysis of the main outcome measures was carried out according to Peto's method. A significant excess of minor bleeding (hazard ratio 2.30, 95% CI 1.16–4.58, P = 0.02) as well as a borderline significant estimate of an excess thrombotic risk with high-intensity anticoagulation (hazard ratio 2.49, 95% CI 0.93–6.67, P = 0.07) is observed.](image-url)
prevention of thrombosis in patients with antiphospholipid antibodies.

This recommendation applies particularly to patients with venous thromboembolism who represented nearly 70% of the cases enrolled in the two trials. Caution should be exerted to extend this recommendation to patients with arterial thrombosis because of the limited number of randomized cases. In addition, a recent randomized clinical trial in patients with antiphospholipid antibodies and ischemic stroke showed similar antithrombotic benefit using aspirin (325 mg day⁻¹) or warfarin (target INR 1.4–2.8) [14]. Nevertheless, no evidence is currently available form randomized clinical trials to support the use of high-dose warfarin therapy (i.e. INR >3.0) in patients with arterial thrombosis. Whether a high therapeutic range might be useful for selected patients at extremely high thrombotic risk, such as those with recurrent vascular events during conventional antithrombotic prophylaxis, remains to be established as such patients have been excluded from randomization both in the Crowther’s study [8] and in this trial.

Bleeding is a major concern with intensive anticoagulation. Most bleeding complications were minor in our study, but intracranial hemorrhages have been reported in other studies in which patients with antiphospholipid antibodies were given warfarin to a target INR >3.0 [5,6]. In addition, high-intensity oral anticoagulation is more difficult to be managed by physicians and accepted by patients, because of frequent hemmorhages as well as the need for a strict and cumbersome anticoagulation control.

Some limitations of this study should be acknowledged. Firstly, the trial was not double-blind. To control for this potential bias, an objective documentation of all major thrombotic and hemorrhagic complications was obtained and the outcome events were validated by an ad hoc committee blinded to patients’ treatment assignment. Secondly, the trial was stopped for futility when the study population was much smaller than expected on the basis of the sample size estimated in the trial protocol. Since the rate of thrombosis in the high-intensity anticoagulation arm was higher than in the control arm in both Crowther’s [8] and our trial, the prolongation of enrolment or follow-up was unlikely to reverse such unfavorable trend.

Finally, these findings may be seen as a further confirmation of the absolute need of testing prospectively any biologically plausible hypotheses generated by retrospective series of cases. The activation of large-scale international networks capable of enrolling sufficiently large populations in prospective trials should be considered a research priority for clinicians and institutions who care for rare diseases such as the APS.

Addendum

The role of each author in this study is as follows: TB was the principal investigator. TB and GF drafted the protocol and developed the original manuscript. RM and GT contributed to the concept and design of the study, supervised the study, coordinated the data management and analysis and critically reviewed the manuscript preparation. FW and JM were the national coordinators of the study in their respective countries. VB, PS, FB, MB, ST and A d’A contributed to the study design, followed the patients generating laboratory and clinical data and critically reviewed the analysis and interpretation of the data.

Acknowledgements

We are indebted to Douglas Triplett, Jos Vermelyn, Marie-Claire Boffa, Luis Carreras, Sam Machin, Takao Koike, Jasome Monasterio and Inge Scharrer for their help in establishing the study and drafting the protocol. We thank Elena Oldani for assistance with the data management.

References

10. Hansson L, Zanchetti A, Carruthers SG, Dahlo¨fB ,E l m f e l tD ,J u l i u s
Appendix


Event adjudicating committee – G. Finazzi, M. Galli, T. Barbui (Chair).