Curr Rheumatol Rep (2010) 12:64–69
DOI 10.1007/s11926-009-0070-9

Intensity of Warfarin Coagulation in the Antiphospholipid Syndrome

Mark Crowther · Mark A. Crowther

Published online: 8 January 2010
© Springer Science+Business Media, LLC 2010

Abstract Antiphospholipid syndrome is a condition with an increased propensity for both arterial and venous thrombosis. Compared with the normal population there is also a higher rate of recurrence. Most evidence exists for the use of warfarin in the secondary prevention of thromboembolism, aiming for an international normalized ratio between 2.0 and 3.0. Care must be taken with all anticoagulants because of the increased risk of bleeding. Several other strategies are available if warfarin fails, including the addition of aspirin, increasing the warfarin target range, and use of heparin.

Keywords Warfarin · Anticoagulation · Antiphospholipid syndrome · Lupus anticoagulant

Introduction

Antiphospholipid syndrome (APS) causes considerable morbidity and mortality [1]. Many patients with APS are treated with warfarin. This review briefly discusses the indications for warfarin and the target range in which warfarin is therapeutic in APS.

APS Definition

The most recent international consensus classification (modified Sapporo) [2] defines APS as the presence of either vascular thrombosis (arterial, venous, or small vessel) or adverse pregnancy outcome (one or more unexplained deaths in a normal foetus beyond 10 weeks; one or more premature births of morphologically normal neonates before 34 weeks caused by eclampsia, severe preeclampsia, or placental insufficiency; or three or more unexplained deaths before 10 weeks gestation) with specific laboratory outcomes (one of a positive lupus anticoagulant [LA]; a medium-to-high titer of anticardiolipin antibodies [ACL; IgM or IgG] or anti-β_2-glycoprotein-1 [IgM or IgG in a titer greater than the 99th percentile], all of which must be persistent for more than 12 weeks).

M. Crowther (✉) · M. A. Crowther
Division of Hematology and Thromboembolism, McMaster University, St Joseph's Hospital, 50 Charlton Ave, East Hamilton, Ontario, Canada
e-mail: mark.crowther@nhs.net

M. A. Crowther
e-mail: crowthrm@mcmaster.ca

APS and Thrombosis

The antibodies in APS were originally thought to cause bleeding because of their ability to prolong clotting times but now it is known that they cause thrombosis [3]. The exact mechanism is unclear but it is thought to be caused by a complex interaction between antibodies to anionic phospholipids and the cell wall, platelets, and pro- and anticoagulants. This leads to a procoagulant state [4].

Anticoagulation Therapy

Patients Without Thrombosis or Adverse Pregnancy Outcomes

Antiphospholipid antibodies (aPL) may be present in patients who have had neither thrombosis nor adverse pregnancy outcomes. These antibodies are commonly discovered during the investigation of a prolonged in vitro clotting time—patients with asymptomatic aPL do not have

the APS. Cross-sectional studies of blood donors have demonstrated a high prevalence of both LA and ACL. Depending on the assay used, as many as 8% of unselected people will have a positive LA, 9.4% an IgM ACL, and 6.5% an IgG ACL [5, 6]. In many cases, these antibodies are not persistent and do not appear to predispose to thrombosis.

A large systematic review found that patients with aPL without prior clinical events had an increased risk of thrombosis [7]. Many of the studies included in this systematic review were small case series and did not use widely accepted laboratory criteria to establish the presence of an aPL [2]. Overall, LA presence most significantly increased thrombosis risk, with no increased risk seen with IgM ACL alone but an increased risk with higher titer IgG ACL. The Framingham Cohort also suggested an increased risk of stroke in women with a positive ACL antibody [8].

In asymptomatic patients without prior thrombosis, no studies have clearly demonstrated that primary prophylaxis with warfarin or aspirin reduces the rate of subsequent thrombosis. Given the low overall incidence of thrombotic events in this group, it is likely that the side effects of anticoagulant therapy would outweigh any benefits. Studies have examined the benefit of aspirin; the only randomized controlled trial (RCT) [9] performed to date provided no evidence for efficacy compared with other nonrandomized studies [10, 11].

Patients with Previous Adverse Pregnancy Outcomes But No Thrombosis

One study suggested a high risk of first thrombosis in patients who had suffered fetal loss (59% in 8 years) and a possible benefit from aspirin (reduction to 10%) [12]. However, another study demonstrated a low rate of thrombosis in the postpartum period, arguably the highest-risk time for a thrombosis. There are no randomized studies in this area [13].

In patients with persistent LA or IgG ACL antibodies who have not had a prior thrombosis, good practice would require informing them and their families of the symptoms and signs of thrombosis and what to do if they appear. As they are probably at higher risk than the general population, consideration should be given to effective thromboprophylaxis during high risk periods (eg, postoperatively, during periods of immobility).

Patients with Previous Thrombosis

After initial treatment of venous thromboembolism with heparin and warfarin, patients with aPL have a higher rate of recurrence after stopping warfarin compared with aPL-negative patients; this finding has been reviewed systematically [14]. Compared with aPL-negative patients, the RR of recurrence by 4 years is 2.1 (95% CI, 1.3–3.3) [15] for patients with ACL antibodies and the HR for LA-positive patients is 6.8 (95% CI, 1.5–31). Based on these studies, the American College of Chest Physicians (ACCP) recommends 12 months of anticoagulation therapy (grade 1C+) but suggests indefinite anticoagulation therapy for patients with prior venous thrombosis and an aPL (grade 2C), although they neither discussed how the antibody should be detected nor did they discuss arterial thrombosis in APS [16•]. In the Short-term Oral Anticoagulation for a First Acute Secondary Thrombosis (SOFAST) study, patients were randomly assigned to receive either 1 or 3 months of anticoagulation if they had a thrombosis associated with a transient risk factor (eg, those occurring in the postoperative setting, during pregnancy, or with the use of exogenous estrogens) [17]. On follow-up, the presence of either ACL or LA did not predict recurrence; therefore, they may not require prolonged anticoagulation.

The Antiphospholipid and Stroke Study (APASS) [18] randomly allocated patients with nonembolic cryptogenic stroke to either aspirin (325 mg) or warfarin (international normalized ratio [INR], 1.4–2.8) and demonstrated no difference in risk of recurrence. Patients enrolled in this study did not meet the criteria for APS as there was only a single measure of aPL presence. If these findings were replicated in APS patients, aspirin would be recommended over warfarin as it offers a lower bleeding risk and increased ease for the patient.

In summary, patients who have had a venous thromboembolism or an embolic arterial thrombosis should receive warfarin, at least for 12 months but ideally for longer. The decisions as to the actual duration depends on the bleeding risk of the individual patient.

The Target INR

Early studies suggested that an increased INR reduced the rate of recurrent thrombosis in patients with APS [1, 19]. These studies were not randomized, had variable follow-up, and did not use the modified Sapporo classification to ensure uniformity of enrolled patients. As RCTs tend to be less prone to bias than nonrandomized studies [20], two independent RCTs were conducted to determine if an INR in excess of 3.0 is necessary to prevent recurrent thrombosis [21, 22]. Table 1 summarizes the results of these two studies.

The first published trial, Crowther et al. [21], was conducted in 13 centers. Patients were enrolled if they had had an arterial embolus or venous thromboembolism and were either positive for LA or had moderate-to-high levels of ACL IgG antibody (that were persistently positive), hence fulfilling the modified Sapporo criteria. They were excluded if their platelets were under 50×10^6/L, if they had a contraindication to warfarin, a target INR greater than 3.0, were pregnant, or had previous bleeding problems.

Table 1 Two randomized controlled trials comparing different intensities of anticoagulation, describing patient demographics and important outcomes

	INR, 2.0–3.0		INR > 3	
	Crowther et al. [21]	Finazzi et al. [22]	Crowther et al. [21]	Finazzi et al. [22]
Patients, *n*	58	55	56	54
Men	17 (29%)	20 (36%)	29 (52%)	21 (39%)
Arterial thrombosis	13 (22%)	23 (42%)	14 (25%)	21 (39%)
Venous thrombosis	45 (78%)	38 (69%)	42 (75%)	37 (69%)
SLE	6 (10%)	9 (16%)	10 (18%)	5 (9%)
aCL positive	22 (38%)	10 (19%)	22 (39%)	9 (17%)
LA positive	25 (43%)	13 (25%)	24 (43%)	14 (27%)
LA and aCL positive	11 (19%)	29 (56%)	10 (18%)	29 (56%)
Outcomes				
Recurrent thrombosis	2 (3%)	3 (6%)	6 (11%)	6 (11%)
Death	0 (0%)	2 (4%)	0 (0%)	3 (6%)
Major bleeds	4 (7%)	3 (6%)	3 (5%)	2 (4%)
Minor bleeds	7 (13%)	6 (11%)	11 (20%)	15 (28%)

aCL anticardiolipin, *INR* international normalized ratio, *LA* lupus anticoagulant, *SLE* systemic lupus erythematosus

Upon written informed consent, patients were randomly allocated (centrally with stratification to center and to type of previous thrombosis, either arterial or venous) to receive either moderate-intensity anticoagulation (INR, 2–3) or high-intensity anticoagulation (INR, 3–4). Patients and local investigators were blinded to the treatment decision and INRs were performed centrally to maintain blinding. Clinicians were discouraged from checking INRs that would break blinding, unless the clinical situation demanded it.

Patients were followed-up initially every 3 months then every 6 months for the duration of the trial. They were encouraged to report new symptoms of either thrombosis or bleeding. The primary efficacy outcome was episodes of thrombosis, whereas the primary safety outcome was bleeding events. Prespecified criteria for thrombosis and bleeding were used by two independent blinded adjudicators.

Between February 1998 and May 2001, 325 patients were screened and 114 enrolled. The trial had been powered, assuming 15% thrombosis rate in the moderate-intensity arm and 2.5% in the high-intensity arm. However, a lower than expected thrombosis rate led the study to be extended by the data monitoring committee. Mean follow-up was 2.7 years and 2.6 years in the moderate- and high-intensity groups, respectively.

Eight patients had recurrent thrombosis during the period of the trial, two (3.4%) patients in the moderate-intensity arm and six (10.7%) patients in the high-intensity arm. This suggests no difference in terms of recurrent thrombosis between the two regimens (HR, 3.1; 95% CI, 0.6–15; P= 0.15). Recurrences in the moderate-intensity arm happened at an INR of 1.6 and 2.8 and in the high-intensity arm at 3.1, 1.0, 0.9, 1.9, 3.9, and when a patient had stopped warfarin. There was no difference in the rate of major bleeding (4 [2.2%] vs 3 [3.6%]) or any bleeding (11 [19%] vs 14 [25%]) in the moderate-intensity and high-intensity arms, respectively. There were no deaths in either arm.

Finazzi et al. [22], published 2 years later, was a multicenter trial with 26 centers in Europe. Patients were sourced from a registry of APS patients (who fulfilled the Sapporo criteria with a positive LA or moderate-to-high titers of ACL antibody). Exclusion criteria were under 18 years; previous thrombosis on warfarin; bleeding disorders; pregnancy; and life-expectancy less than 3 years. Those who met the inclusion criteria and had been diagnosed in the previous 5 years were randomly assigned to standard care (moderate-intensity warfarin with an INR of 2.0–3.0 or 100 mg of aspirin if the thrombotic event was a nonembolic arterial event) or high-intensity anticoagulation (INR, 3.0–4.5). There was central randomization but patients and care providers were not blinded. Warfarin management was determined by the individual clinics.

Patients were examined at 3, 6, and 12 months, then yearly. They were encouraged to report bleeding and new thrombosis. Primary outcomes were 1) vascular death and new thrombosis and 2) major hemorrhage. Secondary outcomes were total thrombotic events and cerebrovascular/cardiac events. Safety outcomes were major hemorrhage, minor hemorrhage, and adverse drug reactions.

Fifty-five and 54 patients were randomly assigned to the moderate-intensity and high-intensity arms, respectively. The study was stopped early because of poor recruitment and a low number of events. This resulted in a median follow-up of 3.6 years (range, 2.7–4.5 y) and a total of 369.7 patient years.

As in Crowther et al. [21], this trial showed no statistically significant difference in the rates of thrombosis, three (5.5%) patients in the moderate-intensity arm compared with six (11.1%) patients in the high-intensity arm (HR, 0.7; 95% CI, 0.15–2.56; P=0.34). There was, however, an increased incidence of minor hemorrhage (15 vs 6 episodes; HR, 2.92; 95% CI, 1.13–7.52; P=0.027) but not major hemorrhage (2 vs 3 episodes; HR, 0.66; 95% CI, 0.11–3.96; P=0.65) in the high-intensity arm compared with the moderate-intensity arm. Two deaths occurred in those allocated to moderate-intensity warfarin, and three deaths in those allocated to high-intensity warfarin.

Finazzi et al. [22] also combined their data with that of Crowther et al. [21]. Their combined data suggested a trend toward less thrombosis in the moderate-intensity arm compared with the high-intensity arm (OR, 2.49; 95% CI, 0.93–6.67; P=0.07) with the advantage of less minor bleeding (OR, 2.30; 95% CI, 1.16–4.58; P=0.02) but no difference in major hemorrhage (OR, 0.73; 95% CI, 0.23–2.31; P=0.59).

Limitations

The studies were not designed as equivalence studies and are therefore underpowered. However, given the observation that both studies favored moderate-intensity warfarin, it is very unlikely that larger studies will find moderate-intensity warfarin inferior to high-intensity warfarin. Although one trial was well-blinded [21], the other was open-label [22], which may have led to bias, although the similarity in results suggest this bias was minimal. Because only a small number of patients had arterial thrombosis, the evidence in these patients was weaker. Excluding patients with a history of thrombosis while receiving warfarin means that these conclusions only apply to patients with one previous thrombotic event who had not previously failed warfarin. Because patients were studied in a trial may lead to better INR control as the patients were more closely monitored than in the "real world." However, because patients were encouraged to report bleeding or thrombosis to investigators, this may mean the reporting of normal, nonclinically significant events that are recorded as significant. Both trials had extensive exclusion criteria and, as such, the results of this study cannot be extrapolated to those who were excluded.

In conclusion, current evidence suggests that for the secondary prevention of venous thrombosis (and perhaps arterial thrombosis), a target INR of between 2.0 and 3.0 is as effective as an INR of greater than 3.0. This lower INR is also likely to be safer with the reduction of hemorrhage [23]. Such a reduction was not detected in the contributing studies as a result of small sample sizes. The INR needs to be tightly controlled as five of the eight thromboses reported in Crowther et al. [21] occurred when the INR was lower than 2.0.

Thrombosis on Warfarin

In Crowther et al. [21], one patient with an INR within the target range of 2.0 to 3.0 suffered an objectively confirmed thrombosis. When a patient is reported to have suffered "warfarin failure," the first task is to determine if the INR was in the desired reference interval at the time of the clot. In most cases, warfarin "failure" was in fact recurrent thrombosis occurring while the INR was subtherapeutic [21]. If the patient was subtherapeutic when the thrombosis occurred, this does not require a change to the target INR but improvement in the warfarin control.

It must be remembered that in some patients with an LA, some prothrombin reagents are sensitive to the effects of the LA, leading to a falsely prolonged prothrombin time and INR. Ideally, lupus insensitive reagents should be used to monitor the INR of patients with aPL. The impact of the antibody on the reagents used for point-of-care devices should also be considered. Before commencing warfarin, a baseline INR should be determined, as prolongation at this stage suggests that the reagents are lupus-sensitive. Several methods of INR measurement may need to be tried before a lupus-insensitive method is found. On changing reagents/analyzers, it should be ensured that there is concordance with the previous results. Prolongation caused by an LA can be differentiated from prolongation caused by warfarin by in vitro mixing tests. The addition of normal plasma should correct the effect of warfarin but have little or no effect on prolongation caused by an LA.

If the thrombosis recurred when the INR was in excess of 2.0 then there are four options, none of which are evidence based:

1) Increase the INR target range to 3.0 to 4.0. Although this is recommended by the British Committee for Standards in Haematology [24], based on the two RCTs [21, 22], this may increase the hemorrhage risk without an impact on thrombosis risk.
2) Add aspirin to warfarin. As discussed, aspirin may have a role in both primary and secondary prophylaxis in APS.
3) Subcutaneous unfractionated heparin could be used, but this has been superseded by low-molecular-weight heparin.
4) Long-term low-molecular-weight heparin, a more intense therapy, has been used successfully in patients with malignancy-associated thrombosis [25] and in pregnancy [26]. There are also reports of its use in APS [27]. Side effects include heparin-induced thrombocytopenia, bleeding, allergy, and osteoporosis. Because of

its renal excretion, it is relatively contraindicated in patients with renal dysfunction.

New Anticoagulants

Several new antithrombotics have been recently licensed or are undergoing clinical trials. These aim to be as effective as the current antithrombotics and have lower side-effect profiles or better ease of use. So far, there are no high-quality studies of these drugs in patients with aPL. However, several large ongoing studies examining the use of these agents for the prevention and treatment of both arterial and venous thrombosis will include patients with aPL, from which subgroup analysis may be possible.

Conclusions

Current evidence suggests that warfarin should be used for the secondary prophylaxis of venous thromboembolism and arterial embolism in APS. The length of treatment should ideally be lifelong but depend on the individual bleeding risk. The optimum INR for most indications appears to be between 2.0 and 3.0. Due to the risk of thrombosis when the INR is subtherapeutic, care should be taken to ensure maximum time in range. There is little evidence for the most effective treatment if there is recurrent thrombosis with an INR in excess of 2.0.

Disclosure Dr. Mark A. Crowther has received research support from Pfizer, Leo Laboratories, Sanofi Aventis, and Octaphrama; he has been a consultant for Pfizer, Bayer, Artisan Pharma, Boehringer Ingelheim, and Sanofi Aventis; he has been on the speakers bureau for Pfizer, Leo Laboratories, Bayer, Boehringer Ingelheim; he has received honoraria from Pfizer, Leo Laboratories, Bayer, Organon, and Artisan; he has been on the scientific advisory board of Bayer and Alexion; and he receives substantial income from current anticoagulant treatment regimens.

No further potential conflict of interest relevant to this article was reported.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance

1. Rosove MH, Brewer PM: Antiphospholipid thrombosis: clinical course after the first thrombotic event in 70 patients. Ann Intern Med 1992, 117:303–308.
2. Miyakis S, Lockshin MD, Atsumi T, et al.: International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost 2006, 4:295–306.
3. Conley CL, Hartmann RC: A haemorrhage disorder caused by circulating anticoagulant in patients with disseminated lupus erythematosus. J Lab Clin Invest 1952, 31:621–622.
4. Giannakopoulos B, Passam F, Rahgozar S, Krilis SA: Current concepts on the pathogenesis of the antiphospholipid syndrome. Blood 2007, 109:422–430.
5. Shi W, Krilis SA, Chong BH, et al.: Prevalence of lupus anticoagulant and anticardiolipin antibodies in a healthy population. Aust NZ J Med 1990, 20:231–236.
6. Vila P, Hernandez MC, Lopez-Fernandez MF, Batlle J: Prevalence, follow-up and clinical significance of the anticardiolipin antibodies in normal subjects. Thromb Haemost 1994, 72:209–213.
7. Galli M, Luciani D, Bertolini G, Barbui T: Lupus anticoagulants are stronger risk factors for thrombosis than anticardiolipin antibodies in the antiphospholipid syndrome: a systematic review of the literature. Blood 2003, 101:1827–1832.
8. Janardhan V, Wolf PA, Kase CS, et al.: Anticardiolipin antibodies and risk of ischemic stroke and transient ischemic attack: the Framingham cohort and offspring study. Stroke 2004, 35:736–741.
9. Erkan D, Harrison MJ, Levy R, et al.: Aspirin for primary thrombosis prevention in the antiphospholipid syndrome: a randomized, double-blind, placebo-controlled trial in asymptomatic antiphospholipid antibody-positive individuals. Arthritis Rheum 2007, 56:2382–2391.
10. Ruffatti A, Del Ross T, Ciprian M, et al.: Risk factors for a first thrombotic event in antiphospholipid antibody carriers: a multicentre, retrospective follow-up study. Ann Rheum Dis 2009, 68:397–399.
11. Hereng T, Lambert M, Hachulla E, et al.: Influence of aspirin on the clinical outcomes of 103 anti-phospholipid antibodies-positive patients. Lupus 2008, 17:11–15.
12. Erkan D, Merrill JT, Yazici Y, et al.: High thrombosis rate after fetal loss in antiphospholipid syndrome: effective prophylaxis with aspirin. Arthritis Rheum 2001, 44:1466–1467.
13. Clark CA, Spitzer KA, Crowther MA, et al.: Incidence of postpartum thrombosis and preterm delivery in women with antiphospholipid antibodies and recurrent pregnancy loss. J Rheumatol 2007, 34:992–996.
14. Lim W, Crowther MA, Eikelboom JW: Management of antiphospholipid antibody syndrome: a systematic review. JAMA 2006, 295:1050–1057.
15. Schulman S, Svenungsson E, Granqvist S: Anticardiolipin antibodies predict early recurrence of thromboembolism and death among patients with venous thromboembolism following anticoagulant therapy. Duration of Anticoagulation Study Group. Am J Med 1998, 104:332–338.
16. • Kearon C, Kahn SR, Agnelli G, et al.: Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008, 133:454S–545S. (Published erratum appears in Chest 2008, 134:892.). *This paper provides an up-to-date evidence guideline covering most aspects of the management of thromboembolism*.
17. Kearon C, Ginsberg JS, Anderson DR, et al.: Comparison of 1 month with 3 months of anticoagulation for a first episode of venous thromboembolism associated with a transient risk factor. J Thromb Haemost 2004, 2:743–749.
18. Levine SR, Brey RL, Tilley BC, et al.: Antiphospholipid antibodies and subsequent thrombo-occlusive events in patients with ischemic stroke. JAMA 2004, 291:576–584.
19. Khamashta MA, Cuadrado MJ, Mujic F, et al.: The management of thrombosis in the antiphospholipid-antibody syndrome. N Engl J Med 1995, 332:993–997.

20. Kunz R, Oxman AD: The unpredictability paradox: review of empirical comparisons of randomised and non-randomised clinical trials. BMJ 1998, 317:1185–1190.
21. Crowther MA, Ginsberg JS, Julian J, et al.: A comparison of two intensities of warfarin for the prevention of recurrent thrombosis in patients with the antiphospholipid antibody syndrome. N Engl J Med 2003, 349:1133–1138. (Published erratum appears in N Engl J Med 2003, 349:2577; N Engl J Med 2004, 351:200.)
22. Finazzi G, Marchioli R, Brancaccio V, et al.: 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). J Thromb Haemost 2005, 3:848–853.
23. Oden A, Fahlen M: Oral anticoagulation and risk of death: a medical record linkage study. BMJ 2002, 325:1073–1075.
24. Baglin TP, Keeling DM, Watson HG, British Committee for Standards in Haemotology: Guidelines on oral anticoagulation (warfarin): third edition—2005 update. Br J Haematol 2006, 132:277–285.
25. Lee AYY, Levine MN, Baker RI, et al.: Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med 2003, 349:146–153.
26. Greer IA, Nelson-Piercy C: Low-molecular-weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: a systematic review of safety and efficacy. Blood 2005, 106:401–407.
27. Dentali F, Manfredi E, Crowther M, Ageno W: Long-duration therapy with low molecular weight heparin in patients with antiphospholipid antibody syndrome resistant to warfarin therapy. J Thromb Haemost 2005, 3:21–23.