Anticoagulation in Antiphospholipid Antibody Syndrome

Pharmacotherapy Rounds
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OBJECTIVES:

1. Define antiphospholipid antibody syndrome (APS)
2. Understand the pathogenesis of thrombosis
3. Identify central issues regarding prevention and treatment of thrombotic events
4. Review clinical evidence regarding anticoagulation intensity
5. Discuss future treatment options

I. Introduction

A. Definition

- Antiphospholipid antibody syndrome is an autoimmune disease characterized by the of presence of antiphospholipid antibodies in the plasma together with clinical manifestations of thrombosis or pregnancy complications[1]
- Antiphospholipid antibody syndrome is one of the most common acquired thrombophilias in which thrombosis can occur at both the venous and arterial level[2]
- When present in patients without clinical evidence of another autoimmune disease, the term primary APS is used, whereas in patients with an underlying autoimmune disease (most commonly systemic lupus erythematosus or SLE), it is termed secondary APS[3]
- Antiphospholipid antibodies are divided into two groups, the anticardiolipin antibodies and lupus anticoagulant antibodies, based on the method of detection

B. Epidemiology

- Antiphospholipid antibodies are present in the general population at a prevalence of 1-5% for both lupus anticoagulant and anticardiolipin antibodies[4]
- In patients with SLE, the prevalence of anticardiolipin antibodies is 12-30% and 15-34% for lupus anticoagulant[5]
- An estimated 50% of patients with stroke less than 50 years old[6] and up to 20% of patients with idiopathic deep vein thrombosis[7] test positive for antiphospholipid antibodies
- In SLE patients, there is a 50% risk of developing thrombosis in the next 20 years for those testing positive for lupus anticoagulant[8]
- After a first episode of thrombosis, patients testing positive for antiphospholipid antibodies have a higher risk of recurrent thrombosis than patients without the antibodies[7]

II. Background

A. Historical Background

- In 1906, the first recognized antiphospholipid antibodies were detected in patients with a false-positive test for syphilis[5]
- The antigen to these antibodies was identified as cardiolipin, a type of phospholipid mixed with syphilis antigen in the Venereal Disease Research Laboratory (VDRL) test
- Patients with anticardiolipin antibodies in their plasma therefore tested positive to this phospholipid-dependent test
- Through mass screenings for syphilis, it was observed that many patients with SLE had a false-positive VDRL test
- The VDRL test could not be used to screen for antiphospholipid antibodies because of its low specificity and sensitivity, so in 1983, a solid-phase immunoassay was developed to detect anticardiolipin antibodies[9]

- Lupus anticoagulants, a group of antibodies which can prolong the partial thromboplastin time, were first observed in 1952 in two patients with SLE and a bleeding disorder[10]
- In 1963, an association between lupus anticoagulants and thrombosis was observed[10]
- In the early 1990s it was discovered that some anticardiolipin antibodies require the presence of a plasma phospholipid-binding protein, ß2-glycoprotein I, in order to bind to cardiolipin[11,12]
- This discovery changed the focus of study regarding the target of the antibodies from phospholipids to phospholipid-binding proteins[5]

B. Pathogenesis

- Recent research suggests antiphospholipid antibodies are directed against phospholipid-binding proteins, rather than the antiphospholipid itself[13]
- The most significant phospholipid-binding protein is ß2-glycoprotein I
- Other potential target proteins which are currently being investigated include prothrombin, protein S, protein C, and annexin V[14]

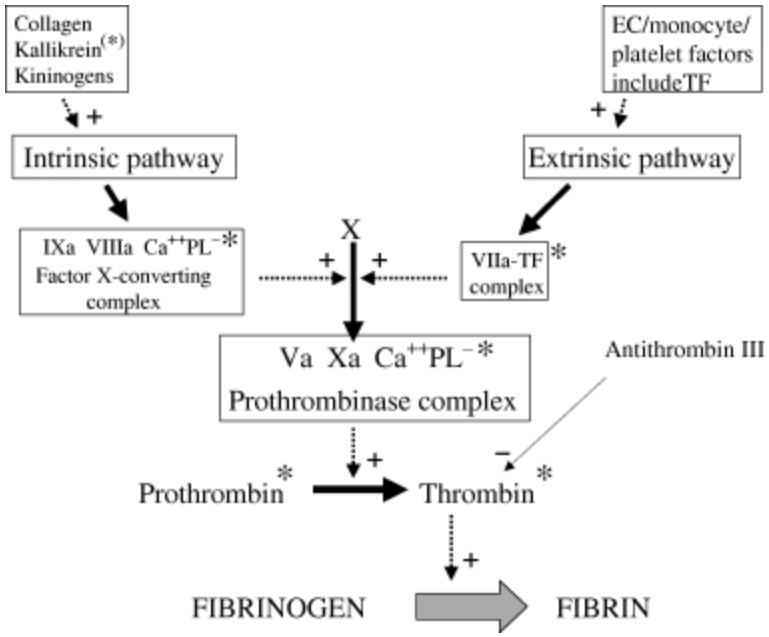


Figure 1: A summary of the coagulation pathways. Asterisks indicate potential sites of action of antibodies in APS.[13]

- Several hypotheses have emerged to explain the correlation between antiphospholipid antibodies and thrombosis:
  1. **Activation of endothelial cells**
     - Normally endothelial cells help maintain homeostasis and blood fluidity through mediators that inhibit coagulation[13]
     - Some findings suggest antiphospholipid antibodies recognize ß2-glycoprotein I that is bound to resting endothelial cells[15]
     - The antibodies then bind to ß2-glycoprotein I which induces activation of the endothelial cells, leading to up-regulation of adhesion molecules, secretion of cytokines, expression of tissue factor, and metabolism of prostacyclins[16]
     - These procoagulant effects on endothelial cells potentially result in a hypercoagulable state[13]
  2. **Oxidant-mediated injury of vascular endothelium**
     - Antiphospholipid antibodies may promote atherogenesis by acting against oxidized low-density lipoprotein (LDL)[17]
     - In this potential mechanism, the antibodies bind to ß2-glycoprotein I, which is also known as apolipoprotein H and is present in oxidized LDL[13]
     - Uptake of oxidized LDL by macrophages leads to macrophage activation, damage to endothelial cells, and subsequent promotion of thrombosis[5]
  3. **Interference with phospholipid-binding proteins involved in regulation of coagulation**
     - ß2-glycoprotein I plays a regulatory role within the coagulation pathways and may act as a natural anticoagulant[18]
     - The binding of antiphospholipid antibodies to ß2-glycoprotein I may inhibit its anticoagulant activity[5]
     - Other phospholipid-binding proteins, such as tissue factor-factor VIIa complex and prekallikrein which are components of the extrinsic and intrinsic coagulation pathways respectively, may be targets of antiphospholipid antibodies[13]
  4. **Effect on platelets**
     - Antiphospholipid antibodies may promote activation of platelets, facilitating adherence to the endothelium[19]
     - One model suggests that the binding of antibodies to ß2-glycoprotein I increases adhesion of platelets to collagen, as well as platelet aggregation[14]
  5. **Potential action on protein C in the coagulation pathway**[13]
     - Activated protein C combines with protein S in the presence of phospholipid to catalyze the degradation of factors Va and VIIIa
     - Antiphospholipid antibodies may have an inhibitory effect on the protein C/protein S complex, resulting in impairment of the degradation of factor V by protein C

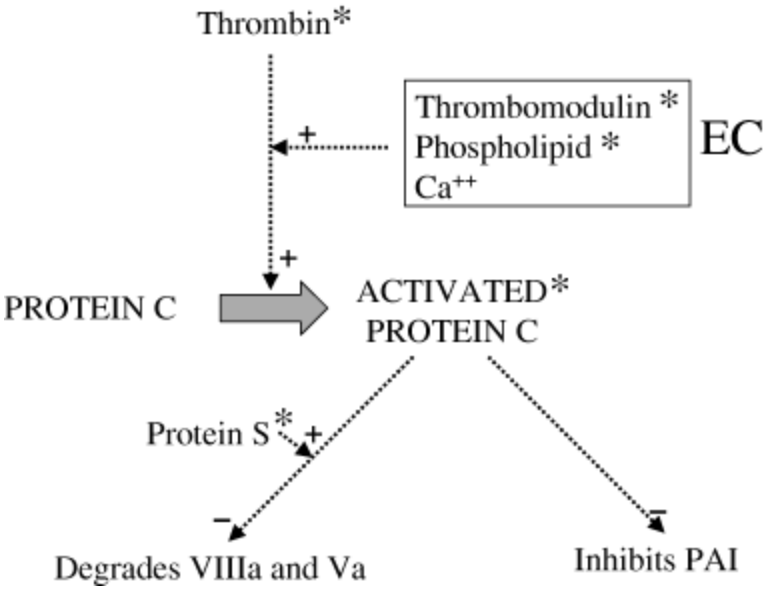


Figure 2: A summary of the protein C pathway. Asterisks indicate potential sites of action of antibodies in APS.[13]

- "Second hit" hypothesis
  - Many patients with antiphospholipid antibodies do not develop clinical features of antiphospholipid antibody syndrome[13]
  - For many patients, additional factors may be required for thrombosis to occur, such as vascular injury, pregnancy, or presence of factor V Leiden[3]
- Proposed link to infection
  - The presence of anticardiolipin antibodies has been noted in patients with chronic infections such as syphilis, HIV, and hepatitis C[20,21]
  - Infection-induced antiphospholipid antibodies are not commonly associated with thrombosis, possibly due to the fact that they are not dependent on ß2-glycoprotein-I for binding to phospholipids[3]
- Drug-induced antiphospholipid antibodies
  - Certain drugs may induce antiphospholipid antibodies, such as chlorpromazine, procainamide, phenytoin, hydralazine, and quinidine[22]
  - These antibodies are typically reversible when the drug is discontinued and are not generally linked to thrombotic complications[3]

C. Clinical Manifestations

- **Venous or arterial thrombosis**
  - DVT is the most common manifestation overall, occurring in 29 to 55% of patients with APS during an average follow-up of less than six years[5]
  - Pulmonary embolism accompanies DVT in up to 50% of patients.[5]
  - Other potential venous sites for thrombus are ophthalmic, renal, splenic, hepatic, portal, or mesenteric veins[3]
  - Stroke and transient ischemic attack are the most common presentation of arterial occlusion, making up 23% of the overall thrombotic events in APS[3]

- Arterial thrombosis can also occur in coronary vessels, including aortic occlusion, as well as mesenteric and peripheral arteries[23]
- In APS thrombosis can occur in vascular sites that are infrequently affected in other hypercoagulable states[5]

Table 1: Other Clinical Manifestations of Antiphospholipid Antibody Syndrome[3,5,22]

Obstetric complications	Women with APS have a high rate of miscarriage in the fetal period (≥ 10 weeks of gestation), in contrast to the general population in which pre-embryonic and embryonic loss (< 10 weeks of gestation) is more common Early delivery due to pre-eclampsia, intrauterine growth restriction, and HELLP syndrome (hemolytic anemia, elevated liver enzymes, and low platelet counts)
Thrombocytopenia	Occurs in 40-50% of patients with antiphospholipid antibody syndrome
Cardiac manifestations	Patients with antiphospholipid antibodies commonly have valvular heart disease, including valvular thickening and development of nonbacterial vegetations
Livedo reticularis	A purplish lattice-like pattern of dilated skin veins is the most common cutaneous manifestation of antiphospholipid antibody syndrome
Renal manifestations	Thrombosis may occur in the renal vein, the renal artery, or glomerular capillaries
Catastrophic antiphospholipid antibody syndrome	Rarely, antiphospholipid antibody syndrome presents as acute multiorgan failure due to multiple vascular occlusions throughout the body The mortality rate of this severe complication is 50%

D. Classification criteria of the antiphospholipid syndrome (Sapporo criteria)[1]

- Clinical criteria:
  1. Vascular thrombosis
     - One or more clinical episodes of arterial, venous, or small vessel thrombosis in any tissue or organ
  2. Pregnancy morbidity
     - One or more unexplained deaths of morphologically normal fetuses at or beyond the 10th week of gestation, or
     - One or more premature births of morphologically normal neonates at or before the 34th week of gestation, or
     - Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation
- Laboratory criteria:
  1. Anticardiolipin antibodies
     - Anticardiolipin IgG and/or IgM isotype present in the blood in medium or high titer

- Positive on two or more occasions at least 6 weeks apart
- Measured by a standardized enzyme-linked immunosorbent assay for ß2-glycoprotein I-dependent anticardiolipin antibodies

2. Lupus anticoagulant
   - Lupus anticoagulant present in the blood on 2 or more occasions at least 6 weeks apart
   - Detected according to the guidelines of the International Society on Thrombosis and Hemostasis in the following steps:
     - Prolonged phospholipid-dependent coagulation test (activated partial thromboplastin time, dilute Russell's viper venom time, kaolin clotting time)
     - Failure to correct on mixing with normal platelet-poor plasma
     - Correction on prolonged coagulation time by the addition of excess phospholipids
     - Exclusion of other coagulopathies

- Definite antiphospholipid antibody syndrome is considered to be present if at least one of the clinical criteria and at least one of the laboratory criteria are met

III. Central issue of treatment: What is the appropriate target INR range for warfarin therapy in the secondary prevention of thrombosis in patients with antiphospholipid antibody syndrome?

A. CHEST Guidelines 2004[24,25]
- For patients with a first episode of DVT or pulmonary embolism and documented antiphospholipid antibodies, the recommended treatment is a oral vitamin K antagonist adjusted to maintain a target INR of 2.5 (INR range 2.0 to 3.0)
- CHEST recommends against high-intensity warfarin therapy (INR range 3.1 to 4.0)
- The recommended treatment duration is 12 months, and indefinite anticoagulation therapy is suggested
- In patients who have recurrent thromboembolic events with a therapeutic INR or other additional risk factors for thrombosis, a target INR of 3.0 (INR range, 2.5 to 3.5) is suggested

B. International Consensus Committee Guidelines 2002
- For venous thromboembolism secondary prophylaxis, warfarin intensity should be based on individual patients' risk factors, including clinical severity of venous thromboembolic event, whether event occurred while on anticoagulation, risk of major bleeding, and other concomitant risk factors[26]
- Warfarin therapy targeting an INR > 3.0 is recommended for patients with recurrent thrombotic events[26]
- In patients with antiphospholipid antibody syndrome and previous stroke, the data is not strong enough to support one form of antithrombotic therapy over another, so an optimal therapy cannot be recommended[27]

IV. Clinical Evidence

A. Retrospective Studies

1. The management of thrombosis in the antiphospholipid antibody syndrome. Khamashta et al[28]

- **Objective**: Evaluate the efficacy of warfarin, low-dose aspirin, or both in the prevention of recurrent thrombosis in patients with antiphospholipid antibody syndrome
- **Study Design**: Retrospective
- **Duration**: Median follow-up 6.0 years
- **Subjects**: 147 subjects, 66 patients with SLE, 19 patients with lupus-like syndrome, 62 patients with primary antiphospholipid antibody syndrome
- **Inclusion Criteria**:
  - Positive test for lupus anticoagulant, anticardiolipin antibodies, or both
  - History of thrombosis (venous, arterial, or both)
- **Primary Outcome Measures**: Thrombotic events and bleeding complications
- **Treatment**:
  - No treatment
  - Low-dose aspirin (75 mg/day)
  - Low-intensity warfarin (target INR < 3.0) +/- aspirin
  - High-intensity warfarin (target INR ≥ 3.0) +/- aspirin
- **Results**:

Table 2: Comparison of Antithrombotic Treatments and Recurrent Thrombotic Events

Treatment	Number of Patients	Number of Recurrent Events	Recurrence Rate per Patient-Year	Relative Risk (95% CI)	P Value
None	84	80	0.29	1.00	-
Aspirin	70	43	0.18	0.63 (0.43-0.92)	0.013
Warfarin Any Treatment	104	42	0.10	0.36 (0.24-0.53)	<0.001
INR < 3	67	32	0.23	0.79 (0.51-1.21)	0.270
With aspirin	14	7	0.22	0.78 (0.30-1.69)	0.531
INR ≥ 3	64	3	0.015	0.05 (0.01-0.16)	<0.001
With aspirin	17	0	0	0.00 (0.00-0.33)	<0.001

  - 101 patients (69%) experienced recurrent thrombotic events
  - High-intensity warfarin with or without low-dose aspirin was significantly more effective ($p<0.001$ by the log-rank test) than low-intensity warfarin with or without aspirin or low-dose aspirin alone in preventing recurrent thrombosis

    - The recurrence rates per patient-year for high-intensity warfarin, low-intensity warfarin, and aspirin alone were 0.015, 0.23, and 0.18, respectively
    - In patients treated with high-intensity warfarin plus low-dose aspirin, there were no recurrences of thrombosis, a significantly lower rate than with no treatment (recurrence rate 0.29, $p<0.001$)
    - The highest rate of thrombosis recurrence (1.30 thrombotic events per year) occurred during the first 6 months after cessation of warfarin therapy
    - Bleeding complications occurred in 29 patients during warfarin treatment (0.071 occurrences per patient-year, 95% CI 0.047-0.102), and the INR was $\geq$ 3.0 in all of these patients at the time of the bleeding episode
    - Severe bleeding occurred in 7 of the 29 patients (0.017 occurrences per patient-year, 95% CI 0.007-0.035)
- **Conclusions**:
    - High-intensity warfarin therapy targeting an INR $\geq$ 3.0 with or without low-dose aspirin is more effective than low-intensity warfarin or aspirin alone in preventing recurrent venous or arterial thrombosis in patients with antiphospholipid antibody syndrome
    - Patients with APS have a high risk of recurrent thrombosis
    - The high rate of events during the first 6 months after cessation of warfarin supports long-term warfarin therapy in patients with APS and a history of thrombosis

2. Antiphospholipid thrombosis: clinical course after the first thrombotic event in 70 patients. Rosove and Brewer[29]

- **Objective**: Determine the clinical course and influence of antithrombotic therapy in patients with lupus anticoagulant, anticardiolipin antibodies, or both after the first thromboembolic event
- **Study Design**: Retrospective
- **Duration**: Total follow-up 361.0 patient-years
- **Subjects**: 70 patients with antiphospholipid antibodies and one prior thrombotic event
- **Treatment**:
    - No treatment
    - Aspirin 81-325 mg/day
    - Low-intensity warfarin (target INR $\leq$ 1.9)
    - Intermediate-intensity warfarin (target INR 2.0-2.9)
    - High-intensity warfarin (target INR $\geq$ 3.0)
- **Measurements**: Site of initial and recurrent thrombotic event (venous or arterial), type of therapy, and intensity of anticoagulation

- **Results**:

Table 3: Comparison of Antithrombotic Treatments and Recurrent Event Rates

Treatment	Patient-Years of Follow-up	Number of Events	Events per Year of Follow-up
None	161.2	31	0.19
Aspirin	37.8	12	0.32
Aspirin alone	27.5	10	0.36
Aspirin plus intermediate-intensity warfarin	5.3	2	0.38
Aspirin plus high-intensity warfarin	5.0	0	0
Heparin	7.5	4	0.53
Warfarin	164.8	9	0.05
Low-intensity warfarin	11.3	6	0.57
Intermediate-intensity warfarin	40.9	3	0.07*
High-intensity warfarin	110.2	0	0±

*P = 0.12
±P < 0.001

  - 37 patients (53%) experienced recurrence of thrombosis
  - Patients treated with high-intensity warfarin experienced no thrombotic recurrences during 110.2 patient-years of follow-up ($p<0.001$), in comparison to patients receiving no treatment who had 31 recurrent thromboses in 161.2 patient-years (0.19 recurrences per patient-year)
  - The recurrence rate in patients receiving intermediate-intensity warfarin therapy was relatively low at 0.07 recurrences per patient-year but did not achieve statistical significance ($p=0.12$) in comparison to no treatment
  - Neither low-intensity warfarin nor aspirin alone offered protection against thrombosis with recurrence rates of 0.57 and 0.32 per patient-year, respectively
  - The highest INR at the time of thrombosis was 2.6
  - Three major bleeding episodes occurred in which two of the patients were receiving high-intensity warfarin and the other's anticoagulation intensity was unknown
  - There were 5 bleeding complications overall during warfarin treatment (0.031 complications per patient-year)
- **Conclusions**:
  - Intermediate- to high-intensity warfarin appears to be more effective than low- to intermediate-intensity warfarin or aspirin in protecting patients with APS from recurrent thrombotic events
- **Important Considerations**:
  - Both this study and Khamashta's study have limitations intrinsic to retrospective studies, including non-randomization and potential for missing information and patient recall bias[2]
  - In both of these studies, patients were classified according to target INR rather than INR actually achieved and recurrent thrombosis was not confirmed by independent adjudication[30]

3. A retrospective review of 61 patients with antiphospholipid syndrome. Krnic-Barrie et al[31]

- **Objective**: To gain insight regarding the predisposing factors and the prevention of thrombotic recurrence in antiphosholipid antibody syndrome
- **Study Design**: Retrospective cohort
- **Duration**: Median follow-up time of 77 months
- **Subjects**: 61 patients who received one of the following treatments: aspirin, warfarin, warfarin plus aspirin, or prednisone (includes prednisone alone or in combination with warfarin or aspirin)
- **Inclusion Criteria**:
  - History of venous or arterial thrombosis, pregnancy loss, or thrombocytopenia
  - Presence of IgG or IgM anticardiolipin antibodies or positive lupus anticoagulant test
- **Primary Outcome Measures**: Thrombosis, death, or end of study
- **Results**:
  - The prothrombin ratios for 19 of the warfarin-treated patients were analyzed to assess the effect of anticoagulation intensity on recurrence
  - Recurrent thrombosis occurred in 5 patients taking warfarin; in 3 of these events the prothrombin ratios ranged from 1.2 to 1.5 and in the other 2 the ratios were 1.57 and 2.21
  - Bleeding occurred in 4 patients, 2 of whom had prothrombin ratios higher than 2.0 at the time

Table 4: Comparison of No Treatment with Various Regimens (Recurrent Arterial Events Only)

Treatment at recurrence	Patient-years of follow-up	Recurrent events	Events per year of follow-up	Relative risk (95% CI)	P*
None	124.9	24	0.192	1.00	***
Warfarin plus aspirin	30.6	0	0.00	0.00 (0.00-0.64)	0.03
Warfarin only	63.0	3	0.048	0.25 (0.08-0.75)	0.01
Aspirin only	36.6	3	0.082	0.43 (0.13-1.37)	0.15
Any prednisone	34.3	7	0.204	1.06 (0.46-2.46)	0.89
Any warfarin	99.0	5	0.051	0.26 (0.11-0.64)	0.003

*Bonferroni-adjusted cutoff of P=0.02 used for statistical significance

Table 5: Comparison of No Treatment with Various Regimens (Recurrent Venous Events Only)

Treatment at recurrence	Patient-years of follow-up	Recurrent events	Events per year of follow-up	Relative risk (95% CI)	P*
None	127.5	14	0.110	1.00	***
Warfarin plus aspirin	30.6	0	0.00	0.00 (0.00-1.38)	0.07
Warfarin only	64.2	0	0.00	0.00 (0.00-0.30)	0.008
Aspirin only	36.6	1	0.027	0.25 (0.04-1.62)	0.15
Any prednisone	33.1	8	0.242	2.20 (0.94-5.13)	0.07
Any warfarin	100.0	2	0.020	0.18 (0.05-0.68)	0.01

*Bonferroni-adjusted cutoff of P=0.02 used for statistical significance

- **Conclusions**:
    - Treatment with warfarin was most effective in preventing recurrent arterial and venous thrombosis
    - Thrombotic recurrences were infrequent in patients with prothrombin ratios of 1.5 to 2.0, suggesting a target INR of 2.5 to 3.0 is appropriate
- **Important Considerations**:
    - A strength of this study is the separate analysis of arterial and venous events
    - The intensity of anticoagulation was measured in a minority of patients, thus sufficient data regarding the efficacy of one level of intensity over another is lacking[2]

4. Bleeding and recurrent thrombosis in definite antiphospholipid syndrome. Ruiz-Irastorza et al[31]

- **Objective**: Clarify risk and benefits of oral anticoagulation with warfarin targeting an INR of 3.5 in patients with definite antiphospholipid antibody syndrome and previous thrombosis
- **Study Design**: Retrospective cohort
- **Duration**: Patients interviewed regarding events within the previous 12-month period
- **Subjects:** 66 patients attending an antiphospholipid clinic
- **Inclusion Criteria**:
    - Definite antiphospholipid antibody syndrome according to Sapporo criteria
    - History of thrombosis (DVT, PE, stroke, peripheral and visceral arterial thrombosis, transient ischemic attack, myocardial infarction)
    - Received treatment with oral anticoagulation targeting an INR range of 3.0 to 4.0 during the previous 12-month period
- **Primary Outcome Measures**: Major bleeding and recurrent thrombosis
- **Results**:
    - Major bleeding occurred in 4 patients, resulting in a bleeding rate of 6 cases per 100 patient-years (95% CI, 1.6 to 15.0)
    - The rate of intracranial bleeding was 1.5 per 100 patient-years (95% CI, 0.04 to 8.4)
    - None of the bleeding events were fatal, and all the patients with a major bleeding episode had a clear precipitating factor
    - 6 patients experienced recurrent thrombosis, a rate of 9.1 events per 100 patient-years (95% CI, 3.3 to 19.6)
    - The INR values at the time of thrombosis were between 2.1 and 2.6 (unknown in one case)
- **Conclusions**:
    - Treating patients with antiphospholipid antibody syndrome and prior thrombosis with oral anticoagulation to a target INR of 3.5 does not result in a high incidence of intracranial or fatal bleeding

    - The increased risk of thrombotic recurrence over time seen in this study supports indefinite anticoagulation for patients with antiphospholipid antibody syndrome and previous thrombosis
    - Patients with define APS and prior thrombosis should be treated with warfarin to a target INR of 3.5, except for possibly patients with only venous events and those with a high risk of bleeding, for whom lower intensity anticoagulation could be considered
- **Important Considerations**:
    - Limited by retrospective design and heavy reliance on patient recall
    - Patients' INR values were in the target range of 3.0 to 4.0 only 37% of the time

B. Prospective Studies

1. A comparison of 2 intensities of warfarin for prevention of recurrent thrombosis in patients with the antiphospholipid antibody syndrome.

Crowther et al[30]

- **Objective**: Demonstrate that high-intensity warfarin is more effective than moderate-intensity warfarin in preventing recurrent thrombosis in patients with antiphospholipid antibodies
- **Study Design**: Prospective, randomized, double-blind trial
- **Duration**: Mean follow-up of 2.7 years
- **Subjects**: 114 subjects randomized to receive high-intensity warfarin with a target INR range of 3.1 – 4.0 or moderate-intensity warfarin targeting an INR range of 2.0 – 3.0
- **Inclusion Criteria**:
    - Previous arterial or venous thrombus
    - Presence of lupus anticoagulant, moderate or high titer of IgG anticardiolipin antibodies, or both, measured on 2 occasions at least three months apart
- **Exclusion Criteria**:
    - Presence of only IgM anticardiolipin antibodies
    - History of recurrent thrombosis while on warfarin therapy targeting an INR $\geq$ 2.0
    - History of stroke, intracranial hemorrhage, or GI bleeding within the last three months
- **Primary Outcomes**: Recurrent thrombotic event (stroke, TIA, MI, peripheral arterial thrombosis, cerebral-vein thrombosis, DVT, or PE) and bleeding events
- **Results:**
    - 6 of 56 (10.7%) patients randomized to high-intensity warfarin and 2 out of 58 (3.4%) patients assigned to moderate-intensity warfarin experienced recurrent thrombosis (hazard ratio 3.1, 95% CI 0.6 to 15.0, p value = 0.15)

    - The annual risk of major bleeding was 3.6% (3 patients) with the high-intensity warfarin group and 2.2% (4 patients) with the moderate-intensity group
- **Conclusions**:
    - High-intensity warfarin therapy is not more effective than moderate-intensity warfarin in prevention of recurrent thrombosis in patients with antiphospholipid antibodies
    - When warfarin therapy is used with a target INR range of 2.0 – 3.0, the rate of recurrent thrombosis is low
    - Moderate-intensity warfarin is appropriate for patients with antiphospholipid antibody syndrome
- **Important Considerations**:
    - 4 out of 6 patients in high-intensity warfarin group had an INR of less than 2.0 at the time of the recurrent thrombosis
    - The high-intensity warfarin group was subtherapeutic (INR less than 3.0) 43% of the time
    - 80% of the patients had venous and not arterial thrombosis, so this data may not be generalizable to patients with arterial thrombosis[3]
    - The fact that the risk of major bleeding was not higher in the high-intensity warfarin group may suggest that the statistical power of the study was possibly insufficient to demonstrate a difference between groups for both bleeding and preventing thrombosis[33,34]

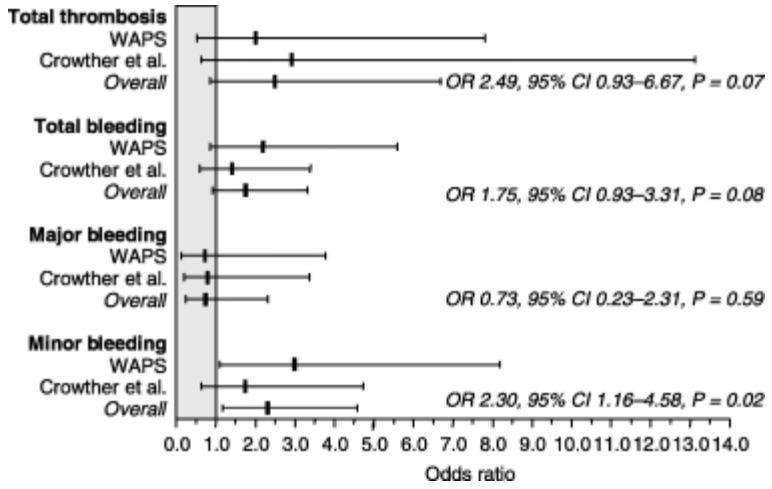
2. Warfarin in the AntiPhospholipid Syndrome Study (WAPS).
Finazzi et al[35]

- **Objective**: To determine whether high-intensity anticoagulation is superior to standard treatment in preventing recurrent thromboembolism without increasing bleeding risk in antiphospholipid antibody syndrome
- **Study Design**: Prospective, randomized, open-label clinical trial
- **Subjects**: 109 patients randomized to receive high-intensity warfarin (INR 3.0 – 4.5, 54 patients) or standard antithrombotic treatment (warfarin with INR 2.0 – 3.0, 52 patients) or aspirin 100 mg/day in 3 patients
- **Inclusion Criteria**:
    - Presence of lupus anticoagulant and/or moderate-high titer anticardiolipin antibodies
    - History of arterial or venous thrombosis
    - Clinically confirmed antiphospholipid antibody syndrome within last five years
- **Exclusion Criteria**:
    - History of recurrent thrombosis while on anticoagulant prophylaxis
    - Active bleeding disorders with a contraindication to warfarin
- **Primary Outcome Measures**: Vascular death, major arterial and venous events (MI, stroke, PE, DVT, TIA) and major bleeding

- **Results**:
  - 6 out of 54 patients (11.1%) assigned to high-intensity warfarin and 3 out of 55 patients (5.5%) assigned to the conventional treatment group experienced recurrent thrombosis (hazard ratio for high-intensity 1.97, 95% CI 0.49 – 7.89, p = 0.3383)
  - Minor bleeding was significantly more frequent in the high-intensity warfarin group (hazard ratio 2.92, 95% CI 1.13 – 7.52, p = 0.0269), but the two groups did not differ significantly in frequency of major bleeding (p=0.6518)
  - A meta-analysis of the WAPS and Crowther's study also showed a significantly higher occurrence of minor bleeding in the high-intensity warfarin group (hazard ratio 2.30, 95% CI 1.16-4.58, p=0.02)
  - The meta-analysis demonstrated a trend toward significance of a higher risk of thrombosis in the group with high-intensity anticoagulation (hazard ratio 2.49, 95% 0.93-6.67, p=0.07)

- **Conclusions**:
  - High-intensity warfarin (INR 3.0-4.5) is not superior to conventional anticoagulation treatment in preventing recurrent thrombosis in patients with antiphospholipid antibody syndrome
  - High-intensity warfarin was associated with an increase in minor bleeding but not major bleeding complications
- **Important Considerations**:
  - Difficulty recruiting patients led to early termination of the study and limited statistical power due to small sample size
  - Patients with venous thromboembolism represented nearly 70% of the cases

Figure 3: Odds ratios for high-intensity anticoagulation vs. conventional treatment in the WAPS and Crowther's studies



V. Potential Confounding Factors

1. **Titer and transiency of anticardiolipin antibodies**
    - **Antiphospholipid Antibodies and Stroke Study (APASS).** Levine et al[36]
    - **Objective**: Evaluate the effect of antiphospholipid antibody positivity on subsequent thrombotic events, including recurrent stroke
    - **Study Design**: Prospective cohort study within the Warfarin vs Aspirin Recurrent Stroke Study (WARSS)
    - **Duration**: 2 years or until a primary end point
    - **Subjects**: 1770 patients who had been randomized in the WARSS to receive warfarin (INR target 1.4-2.8) or aspirin 325 mg/day
    - **Inclusion Criteria**:
        - Enrolled in WARSS
        - Antiphospholipid antibody status determined within 90 days of enrollment in the WARSS based on blood samples obtained at baseline
        - Ischemic stroke within 30 days of WARSS enrollment
    - **Exclusion Criteria**:
        - Baseline INR > 1.4
        - Stroke due to procedure, carotid stenosis, or cardiac source of embolism
    - **Primary Outcome Measures**: Death from any cause or any thrombo-occlusive event (ischemic stroke, MI, TIA, DVT, PE, or peripheral arterial embolism)
    - **Results**:
        - There was no increased risk of death or thrombo-occlusive event associated with positive antiphospholipid antibody status observed in either the warfarin-treated group (RR 0.99, 95% CI 0.75-1.31, p=0.94) or the aspirin group (RR 0.94, 95% CI 0.70-1.28, p=0.71)
        - The overall thrombo-occlusive event rate for the combined warfarin and aspirin treatment groups was 24.2% in antiphospholipid antibody positive patients and 24.0% in antiphospholipid antibody negative patients (p=0.83)
        - Warfarin was not associated with fewer thrombo-occlusive events than aspirin treatment (p=0.91)
        - Patients testing positive for both lupus anticoagulant and anticardiolipin antibodies tended to have a greater risk for death or thrombotic event than those antiphospholipid antibody negative patients (31.7% vs 24.0%, RR 1.36, 95% CI 0.97-1.92, p=0.07)
    - **Conclusions**:
        - The presence of lupus anticoagulant or anticardiolipin antibodies in patients with ischemic stroke did not confer increased risk of recurrent thrombotic events over 2 years or a differential response to warfarin or aspirin treatment

- **Important Considerations**:
    - High rate of antiphospholipid antibody positivity (41%).
    - Antiphospholipid antibody status based on single determination[37]
    - Included many patients with low-titer anticardiolipin antibodies and IgA isotype anticardiolipin antibodies.[2]
    - Lupus anticoagulant assays were not performed according to international recommendations[38]
    - The mean age of the patient population in this study was higher than that of the typical antiphospholipid antibody syndrome population[37]

2. Treatment duration

- **Anticardiolipin antibodies predict early recurrence of thromboembolism and death among patients with venous thromboembolism following anticoagulant therapy.** Schulman et al[7]
- **Objective**: To compare the risk of recurrent venous thromboembolism in patients with and without antiphospholipid antibodies
- **Study Design**: Prospective 4-year follow-up
- **Subjects**: 412 patients with anticardiolipin antibodies and a first episode of venous thromboembolism who received oral anticoagulation targeting an INR of 2.0 to 2.85 for 6 months
- **Primary Outcome Measures**: Recurrent venous thromboembolism, death, or hemorrhage requiring hospitalization, infusion with blood products, or treatment with vitamin K
- **Results**:
    - The risk of thromboembolic recurrence was 29% in patients with anticardiolipin antibodies and 14% in those without ($p = 0.0013$)
    - In those with antibodies, there was an increased risk during the first 6 months after discontinuation of anticoagulation
- **Conclusions**:
    - The presence of elevated titers of anticardiolipin antibodies 6 months after an episode of venous thromboembolism is a predictor for an increased risk of recurrence
    - Patients with anticardiolipin antibodies and venous thromboembolism seem to benefit from prolonged oral anticoagulation

3. Effect of lupus anticoagulant on INR

- **Monitoring warfarin therapy in patients with lupus anticoagulants.** Moll and Ortel[39]
- **Objective**: Determine the validity of the INR as a monitoring parameter for warfarin therapy in patients with lupus anticoagulant
- **Study Design**: Prospective case series
- **Subjects**: 34 patients testing positive for lupus anticoagulant

- **Primary Outcome Measures**: Prothrombin times using several thromboplastins and calculated INRs
- **Results**:
    - In patients with lupus anticoagulant who were not receiving warfarin, prothrombin times were often elevated and varied significantly with different thromboplastins
    - For patients receiving warfarin, INRs obtained using different thromboplastins greatly varied and often overestimated the extent of anticoagulation
- **Conclusions**: Lupus anticoagulant can influence prothrombin times and result in INR values that do not accurately reflect the true level of anticoagulation

4. Presence of lupus anticoagulant vs. anticardiolipin antibodies and the risk of thrombosis

- **Lupus anticoagulants are stronger risk factors for thrombosis than anticardiolipin antibodies in the antiphospholipid antibody syndrome: a systematic review of the literature.** Galli et al[40]
- **Objective:** Establish the risk of lupus anticoagulants and anticardiolipin antibodies for arterial and venous thromboembolism
- **Study Design**: Medline search of the literature
- **Selection of studies**: Prospective, cross-sectional, case-control studies that investigated lupus anticoagulants and/or anticardiolipin antibodies and thrombosis
- **Results**:
    - 5 studies comparing lupus anticoagulants with anticardiolipin antibodies reported a significant odds ratio with 95% CI between lupus anticoagulants and thrombosis, with the odds ratio ranging from 5.71 to 9.4
    - Anticardiolipin antibodies were not significantly associated with venous or arterial thrombosis in any of the 5 studies
    - In 4 studies analyzing only lupus anticoagulants, all associations between lupus anticoagulants and thrombosis showed a significant 95% CI, and the odds ratio ranged form 4.09 to 16.2
    - 16 studies were used to evaluate 28 associations between anticardiolipin antibodies and thrombosis, and the odds ratio was significant with a 95% CI in 15 of the cases
- **Conclusions**:
    - Lupus anticoagulants are strong risk factors for thrombosis, regardless of the site and type of thrombosis
    - Anticardiolipin antibodies are not as strong of risk factors for thrombosis as lupus anticoagulants
    - Anticardiolipin titer correlated with the odds ratio of thrombosis

VI. Conclusions and Recommendations

A. Summary

- Patients with antiphospholipid antibody syndrome have a high risk of recurrent thrombotic events
- Retrospective studies and more recent prospective studies present conflicting data on the optimal treatment strategy for preventing recurrent thrombosis in this patient population
- Although oral anticoagulation has been established as the treatment of choice for secondary prevention of thrombosis, the most appropriate intensity of warfarin therapy remains unclear
- Confounding factors such a low-titer or transient antibodies and the effect of the antibodies on anticoagulation monitoring parameters may play a role

B. Conclusions

- Patients with venous thrombosis and those with arterial events may require different intensities of oral anticoagulation therapy
- Current evidence suggests that anticoagulation with warfarin targeting an INR of 2.5 (INR range 2.0 to 3.0) is acceptable for secondary prevention of venous thrombotic events, but not necessarily arterial events
- Due to the high risk of recurrence, patients with antiphospholipid antibody syndrome and thrombosis benefit from long-term anticoagulation
- The role of aspirin in combination with warfarin in preventing thrombotic events remains uncertain
- Risk stratification may be needed to determine optimal antithrombotic therapy based on individual patients' risk factors
- More prospective controlled trials are needed comparing different intensities of warfarin for secondary prevention of arterial and venous thrombosis

C. Future Directions

- Therapeutic agents
- New monitoring and detection assays

Table 6: Potential Therapeutic Agents for Thrombosis Prevention in Antiphospholipid Antibody Syndrome[41]

Agent	Proposed mechanism
Statins	Inhibit endothelial cell activation; reduce the isoprenylation of signaling molecules and exert pleiotropic effect of vasculature
ACE Inhibitors	Inhibit monocyte tissue factor expression
Dilazep, dipyridamole	Antiplatelet effects; inhibit monocyte tissue factor expression
Hydroxychloroquine	Inhibits platelet activation; immunomodulatory effects
LJP 1082	β2GPI-specific B cell toleragen; binds β2GPI-specific B cells and reduce anti-β2GPI antibody titers
Ximelagatran	Oral direct thrombin inhibitor

*Adapted from Roubey RAS. New approaches to prevention of thrombosis in the antiphospholipid syndrome: hopes, trials, and tribulations. *Arth Rheum* 2003; 48(11): 3004-3008.

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