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The Antiphospholipid Syndrome and Warfarin: How Much is Enough?

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Pharmacotherapy Rounds
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Objectives:

1. Review the background, epidemiology, and diagnostic criteria for the antiphospholipid syndrome
2. List clinical manifestations associated with antiphospholipid syndrome
3. Describe the pathophysiology of thrombosis in the antiphospholipid syndrome
4. Evaluate the evidence for the different intensities of oral anticoagulation in the antiphospholipid syndrome

I. Introduction

1. Background[1-3]
    i. Antiphospholipid syndrome (APS) is an autoimmune disease characterized by the presence of antiphospholipid antibodies (aPL), vascular thrombosis, and/or recurrent fetal loss
        1. Primary APS
            a. Presence of antibodies in patients with vascular thrombosis or pregnancy morbidity
        2. Secondary APS
            a. APS occurs with other conditions such as systemic lupus erythematosus (SLE)
        3. Catastrophic APS
            a. Accelerated form of APS
            b. Specific classification criteria available which includes multi- system organ failure
            c. Associated with a 50% mortality rate

2. History[1-2,4-5]
    i. Antiphospholipid antibody was first detected in patients with syphilis in 1906
    ii. Syphilis screening led to the finding that many patients with SLE had a positive Venereal Disease Research Laboratory (VDRL) test with no clinical manifestations of syphilis
    iii. An anticoagulant associated with SLE was later discovered in 1952
    iv. In 1963, a relationship between circulating anticoagulants in SLE and thrombosis was established
    v. The circulating anticoagulants were termed “lupus anticoagulants” (LA) and associated with thrombosis and spontaneous abortions
    vi. An immunoassay that was more sensitive than VDRL to detect anticardiolipin antibodies (aCL) was later created in 1983

II. Epidemiology[1,5-6]
    i. APS is the most common cause of hypercoagulability in the general population
    ii. Antiphospholipid antibodies (LA and aCL) are found in 1 to 5% of young, healthy adults
    iii. aCL and LA are present together in approximately 38% of patients with aPL
    iv. More common in young to middle-aged adults
    v. More common in females, especially secondary APS
    vi. No defined racial predominance
    vii. Prevalence of antiphospholipid antibodies is higher in SLE
        1. Approximately 12 to 30% for aCL
        2. Approximately 15 to 34% for LA
    viii. Associated with a higher incidence of thrombosis

Abbreviations
APS=Antiphospholipid syndrome aPL=Antiphospholipid antibodies SLE=Systemic Lupus Erythematosus VDRL= Venereal Disease Research Laboratory LA=Lupus Anticoagulant aCL=anticardiolipin

III. Table 1: Clinical Manifestations [1,5-7]

Peripheral venous system	• Venous thrombosis is the most common clinical manifestation • 29-55% of cases manifest as deep venous thrombosis o Half of these cases also present with pulmonary embolism (PE)
Central nervous system	• Approximately 50% of arterial thrombosis cases manifest as cerebral ischemia.
Cardiac	• Associated with increased risk of atherosclerosis and coronary artery disease • Approximately 4% of patients with primary or secondary APS have mitral or aortic vegetations
Dermatologic	• Livedo reticularis is a red or blue, reticular or mottled pattern on the trunk, arms, or legs • Occurs in 11-22% of patients and is more prevalent in those patients with SLE and females
Renal	• Involves lesions of renal small-artery and chronic renal ischemia
Obstetric	• Manifests as pregnancy loss and eclampsia
Hematologic	• Hemolytic anemia occurs in 14-23% of patients • Thrombocytopenia occurs in 40-50% of patients and is more common in patients with both APS and SLE • Also is associated with idiopathic thrombocytopenic purpura (ITP)

IV. Antiphospholipid antibodies (aPL) [2,5-10]

1. Anticardiolipin antibodies
    i. Antibodies target a protein, cardiolipin and promote a prothrombotic endothelial surface
    ii. IgG, IgM, and IgA are the three main isotypes
        1. IgG isotype is most strongly associated with thrombosis
    iii. Method of detection is anticardiolipin enzyme-linked immunosorbent assay (ELISA)
    iv. Occurs more often than LA and is associated with venous and arterial thrombosis
2. Lupus Anticoagulants (LA)
    i. Non-specific inhibitor of coagulation factors
    ii. LA isotypes include IgG, IgM, IgA, or a combination
    iii. Prolongs phospholipid-dependent tests of coagulation
        1. Prothrombin time (PT)
        2. Activated partial thromboplastin time (APTT)
        3. Kaolin clotting time (KCT)
        4. Dilute Russell's viper venom time [dRVVT]
    iv. Method of detection is coagulation assays
    v. LA is a strong risk factor for thrombosis and is more commonly associated with thrombosis and pregnancy morbidity
    vi. Associated with thrombosis in SLE patients

Abbreviations
APS=Antiphospholipid syndrome SLE=Systemic Lupus Erythematosus ITP= idiopathic thrombocytopenia purpura aPL=Antiphospholipid antibodies ELISA=Enzyme-linked immunosorbent assay aCL=Anticardiolipin antibodies LA= Lupus anticoagulant PT= Prothrombin Time APTT= Activated partial thromboplastin time KCT= Kaolin clotting time dRVVT= Diulte Russell's viper venom time

3. Anti-ß2-Glycoprotein I antibodies
    i. ß2-Glycoprotein I is also known as apolipoprotein H and is a naturally occurring anticoagulant
    ii. ß2-Glycoprotein I is the predominant target of aPL
    iii. Antibodies bind and inhibit activation of the intrinsic coagulation pathway, platelet prothrombinase activity, and also induce platelet aggregation
    iv. Anti-ß2-Glycoprotein I antibody isotypes include IgG and IgM
    v. Method of detection is ELISA
    vi. Presence of Anti- ß2-Glycoprotein I Antibodies is an independent risk factor for thrombosis

V. Pathophysiology

Table 2: Several proposed mechanisms[1,4-7,10-11]

Activation of endothelial cells	• aPL bind to ß2-Glycoprotein I and prothrombin which activates endothelial cells • Leads to upregulation of expression of adhesion molecules and secretion of cytokines, and metabolism of prostacyclines resulting in hypercoagulability
Oxidant-mediated injury of the endothelium	• Antibodies may develop to oxidized low density lipoprotein (LDL) • Macrophage uptake of oxidized LDL and aPL causes macrophage activation and endothelial damage
Stimulation of platelet function	• Anti-ß2-Glycoprotein I antibodies bind to platelets, endothelial cells, and monocytes • Leads to the expression of tissue factor and platelet aggregation
Other proteins important in the coagulation cascade may be targeted by aPL including prothrombin, protein C and S, and annexin V	• aPL antibodies bind and cause decreased protein C activation, decreased antithrombin III activity, decreased Annexin V binding, decreased fibrinolysis, and increased tissue factor activity
"Second hit"	• Other factors may play a role in whether patients develop clinical manifestations of APS • These include vascular injury, nonimmunologic procoagulant factors, or infection subsequently causing endothelial cell activation and thrombosis

Abbreviations
aPL=Antiphospholipid antibodies ELISA=Enzyme-linked immunosorbent assay APS=Antiphospholipid syndrome

VI. Diagnostic Criteria/Sapporo Criteria[7,12-13]

1. Original Sapporo criteria 1999
    i. Clinical criteria
        1. Vascular thrombosis
        2. Pregnancy morbidity
    ii. Laboratory criteria
        1. aCL on 2 or more occasions at least 6 weeks apart
        2. LA on 2 or more occasions at least 6 weeks apart
2. Sapporo criteria revised in 2006
    i. Include specific definitions for clinical manifestations and laboratory titers
    ii. Include anti- ß2-glycoprotein I antibody as a laboratory item
    iii. Laboratory time requirement extended from 6 weeks to 12 weeks
    iv. Specify time interval between laboratory results and clinical manifestations
    v. Recommend classifying patients in clinical trials into different categories
        1. >1 laboratory criteria present
        2. LA present alone
        3. aCL antibody present alone
        4. Anti- ß2-glycoprotein I antibody present alone
    vi. Addresses the issue of patients who (i) meet the laboratory criteria but do meet the clinical criteria and (ii) meet the clinical criteria but do not meet the laboratory criteria
        1. These patients are classified as “probable APS”, “features associated with APS”, or “non-criteria features of APS” and should clearly be distinguished from patients with definite APS in clinical trials

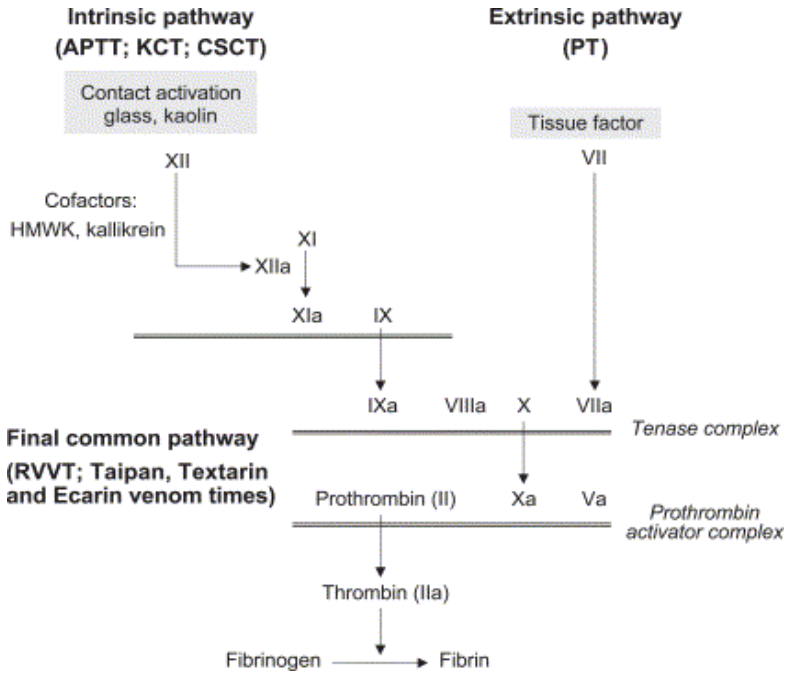
Abbreviations
aCL=Anticardiolipin antibodies LA= Lupus anticoagulant APS=Antiphospholipid syndrome

Table 3: Revised classification criteria for the antiphospholipid syndrome[7]
APS is present if at least one of the clinical criteria and one of the laboratory criteria are met*

Clinical Criteria	
1	Vascular thrombosis • One or more clinical episodes of arterial, venous, or small vessel thrombosis¶, in any tissue or organ confirmed by objective validated criteria (i.e. imaging studies, Doppler studies)
2.	Pregnancy morbidity • One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation with normal fetal morphology documented by ultrasound or by direct examination of the fetus **or** • One or more premature births of a morphologically normal neonate before the 34th week of gestation because of: (i) eclampsia or severe pre-eclampsia or (ii) recognized features of placental insufficiency **or** • Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded
Laboratory Criteria	
1.	Lupus anticoagulant (LA) present in plasma, on two or more occasions at least **12 weeks** apart detected according to the guidelines of the International Society on Thrombosis and Haemostasis§
2.	Anticardiolipin (aCL) antibody of **IgG and/or IgM** isotype in serum or plasma, present in medium or high titer **(>40 GPL or MPL, or >99th percentile),** on two or more occasions, at least **12 weeks** apart, measured by a standardized ELISA
3.	**Anti- ß2-glycoprotein I antibody** of IgG and/or IgM isotype in serum or plasma (in titer > 99th percentile) present on two or more occasions, at least 12 weeks apart, measured by standardized ELISA

*Classification of APS should be avoided if less than 12 weeks or more than 5 years separate the positive aPL test and clinical manifestations ¶superficial venous thrombosis is not included § Laboratory detection of LA[14] should include prolongation of a PL-dependent clotting assay, evidence of inhibition demonstrated by mixing studies, evidence of PL dependence, lack of specific inhibition of any one coagulation factor

Figure 1: A Schematic Representation of In Vitro Coagulation[15]



Source: Derksen RHWM, de Groot PG. Tests for lupus anticoagulant revisited. *Thromb Res.* 2004: 114; 521-526.

Abbreviations
APS=Antiphospholipid syndrome LA= Lupus anticoagulant aCL=Anticardiolipin antibodies ELISA=Enzyme-linked immunosorbent assay aPL=Antiphospholipid antibodies PT= Prothrombin Time APTT= Activated partial thromboplastin time KCT= Kaolin clotting time CSCT=Colloidal silica clotting time HMWK=High molecular weight kininogen RVVT= Russell's viper venom time

VIII. Thrombophilia screening[16-21]

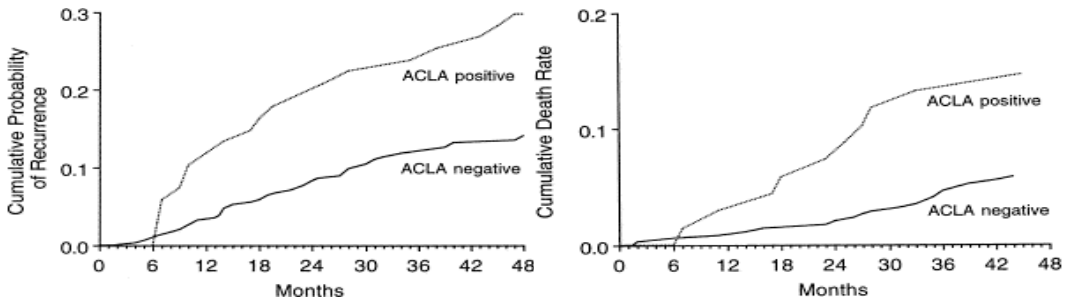
i. Primary Prevention of thrombosis
   1. Consideration for women who are considering oral contraceptive use and/or family history of thrombophilia

ii. Secondary Prevention of thrombosis
   1. Thrombophilic work up is not usually recommended for the first thrombotic episode
   2. APS is the exception
   3. Rates of recurrence
      a. aPL positive patients with a history of thrombosis are at a high rate of recurrence
      b. Schulman et al. reported a recurrence rate of 29% in patients with aCL vs. 14% in those without over a 4 year follow up period (RR=2.1, 95% CI 1.3-3.3, p=0.0013)
      c. Four year mortality rate was 15% in those with antibodies vs. 6% in those without antibodies (RR=1.8, 95% CI 0.9-3.6, p=0.01)
      d. Patients with clinical manifestations associated with APS should receive thrombophilia screening

Figure 1: Cumulative Probability of Recurrence and Cumulative Death Rate Among Patients with Venous Thromboembolism following Anticoagulant Therapy in Patients with Anticardiolipin Antibodies [21]

Panel 1. Cumulative probability of recurrent venous thromboembolism in patients after a first episode, anticoagulated for 6 months

Panel 2. Mortality in patients with a first episode of venous thromboembolism, anticoagulated for 6 months



ACLA= Anticardiolipin Antibody
Source: Schulman S, Svenungsson E, Granqvist S. Anticardiolipin Antibodies Predict Early Recurrence of Thromboembolism and Death Among Patients with Venous Thromboembolism following Anticoagulant Therapy. *Am J Med.*1998;104:332-38.

IX. Antithrombotic Treatment – How much warfarin is enough?

1. Uncertain in those patients who have recurrent thrombotic events
2. Minimal evidence is available to support the use of additional antiplatelet agents in addition to warfarin
3. Guidelines for treatment recommend various target INRs[22-27]

Abbreviations
APS=Antiphospholipid syndrome aPL=Antiphospholipid antibodies aCL=Anticardiolipin antibodies

Table 4: Treatment Intensity for First Thrombotic Event

Guidelines	CHEST 2008[23]	British Committee for Standards in Hematology 2005[25]	International Consensus Committee Guidelines 2002[27]
Target INR	2.5	2.5	-
Recommendation	In patients who have a lupus inhibitor and who have no additional risk factors and no lack of response to therapy, a target INR of 2.5 (INR range 2-3) is appropriate	A target INR of 2.5 is recommended for patient with DVT or PE associated with antiphospholipid syndrome **Stroke due to cerebral infarction in APS should be treated with long term anticoagulant therapy with a target INR of 2.5	Intensity should be based on individual risk stratification (severity, risk of bleeding)
Grade of Recommendation	1A: Consistent evidence from RCTs without important limitations or exceptionally strong evidence from observational studies	A: Requires at least one randomized controlled trial as part of a body of literature of overall good quality and consistency addressing specific recommendation **B: Requires the availability of well conducted clinical studies but no randomized clinical trials on the topic of recommendation	N/A

Table 5: Treatment Intensity for Second Thrombotic Event

Guidelines	CHEST 2008[23]	British Committee for Standards in Hematology 2005[25,26]	International Consensus Committee Guidelines 2002[27]
Target INR	3.0	3.5	>3.0
Recommendation	In patients who have recurrent thromboembolic events with a therapeutic INR, a target INR of 3.0 (INR range of 2.5-3.5) is suggested	A target INR of 3.5 is recommended for patients who suffer recurrence of VTE while on warfarin with an INR between 2-3	A high intensity regimen (INR >3) is recommended in patients with recurrent thrombotic events
Grade of Recommendation	2C:Evidence for at least one critical outcome, from observational studies, case series, or RCT* but with serious flaws; other alternatives may be equally reasonable	C: Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities Indicates an absence of directly applicable clinical studies of good quality	N/A

Table 6: Treatment Duration for Initial and Recurrent Events

Guidelines	CHEST 2008[24]	British Committee for Standards in Hematology 2005[25,26]	International Consensus Committee Guidelines 2002[27]
Recommended Duration	Initial: After 3months of anticoagulant therapy, all patients with unprovoked VTE should be evaluated for the risk-to-benefit ratio of long-term therapy	Initial: At least 6 months after an initial venous thrombotic event Recurrent venous thrombosis should be treated long term	Long-term warfarin treatment in APS patients with DVT and/ or PE is preferred
Grade of Recommendation	1C: Evidence for at least one critical outcome from observational studies, case series,or from RCTs with serious flaws or indirect evidence	A: Requires at least one randomized controlled trial as part of a body of literature of overall good quality and consistency addressing specific recommendation	N/A

RCT=Randomized Controlled Trials N/A= Not Available APS=Antiphospholipid syndrome INR=International Normalized Ratio
VTE=Venous thromboembolism DVT=Deep venous thrombosis PE= Pulmonary Embolism

X. Clinical Trials

1. Randomized trials

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. 349:1133-8.

Study Design	Prospective, randomized, double blind trial
Objective	Evaluate whether high-intensity warfarin therapy (INR of 3.1-4) is more effective than moderate intensity (INR 2-3) in preventing recurrent thrombosis
Number of Patients	114 patients at 13 clinical centers • High intensity: 56 • Moderate intensity: 58
Inclusion Criteria	Confirmed arterial or venous thrombosis Positive test for antiphospholipid antibodies on two occasions at least three months apart • Presence of lupus anticoagulant, moderate or high titer of IgG anticardiolipin antibody, or both
Exclusion Criteria	Presence of IgM anticardiolipin antibodies alone Clinically significant bleeding (e.g., refractory thrombocytopenia) History of intracranial hemorrhage, stroke, or gastrointestinal bleeding within the previous 3 months History of objectively confirmed recurrent thrombosis while receiving warfarin targeted to an INR ≥ 2 Pregnancy or planned pregnancy
Methods	Patients were stratified according to the presence or absence of previous arterial thromboembolism Unscheduled INR measurements performed during an episode of recurrent thrombosis were obtained; if not obtained, the previous INR reported was recorded Follow up data obtained at 3 month intervals; Patients seen twice yearly Enrollment extended for an additional 18 months to increase recruitment
Endpoints	Efficacy outcome: recurrent thrombosis Safety outcome: bleeding
Statistical Analysis	Two-sided alpha error of 5% and power of 80% for sample size (76 patients total:38 per group) Intention-to- treat analysis Time to first recurrent thrombotic event compared using log-rank test Hazard ratios for recurrent thrombosis were calculated using Cox proportional-hazards model
Baseline Characteristics	Mean age: 43 (high intensity) vs. 41 (low intensity) Female (%): 48 vs.71 (p value=0.01) Venous thrombosis (%): 75 vs. 78 Systemic lupus erythematosus (%): 18 vs. 10 IgG anticardiolipin antibody alone (No.): 22 vs. 22 Lupus anticoagulant alone (No.): 24 vs. 25 IgG anticardiolipin antibody and lupus anticoagulant (No.): 10 vs. 11 Thromboembolism within 6 months before randomization (%): 29 vs. 36 Aspirin therapy at enrollment and throughout the study (%): 14 vs. 10
Results	Recurrent Thrombosis • 8 patients (7%) had recurrent thrombosis o 6/56 (10.7%) patients in the high intensity group (0.032/pt-yr) o 2/58 (3.4%) patients in the moderate intensity group (0.013/pt-yr) o Hazard Ratio 3.1, 95% CI 0.6-15.0, p value=0.15

A Comparison of Two Intensities of Warfarin for the prevention of Recurrent Thrombosis in Patients with the Antiphospholipid Antibody Syndrome (continued) [28]

Results	Bleeding • 7 patients (6%) had major bleeding o 3/56 (5.4%) in the high intensity group (0.027/pt-yr) o 4/58 (6.9%) in the moderate intensity group (0.03/pt-yr) o Hazard Ratio 1.9, 95% CI 0.8-4.2, p value=0.13 o Annual risk of major bleeding was 2.2% with moderate intensity warfarin and 3.6% with high intensity warfarin Average INR values • High intensity = 3.3 o Above range 17% of the time o Below range 43% of the time o Within range 40% of the time • Moderate intensity= 2.3 o Above range 11% of the time o Below range 19% of the time o Within range 71% of the time Mean follow up=2.7 years
Author's Conclusions	High intensity warfarin therapy is not more effective than moderate intensity for the prevention of recurrent thrombosis Absolute risk for recurrent thrombosis was low with moderate intensity Unable to comment on management in patients with a high risk of bleeding No conclusion drawn in regards to concomitant aspirin therapy
Critique	Did not examine effectiveness of warfarin in the initial 3 months following a first episode of thrombosis Excluded patients with a high risk of bleeding Excluded patients who had previous thrombosis on warfarin Excluded patients with a history of stroke within the previous 3 months Most patients had a history of venous thrombosis No conclusion drawn in regards to concomitant aspirin therapy High intensity group out of range 43% of the time Small sample size Due to exclusion criteria, difficult to apply results to all APS patients

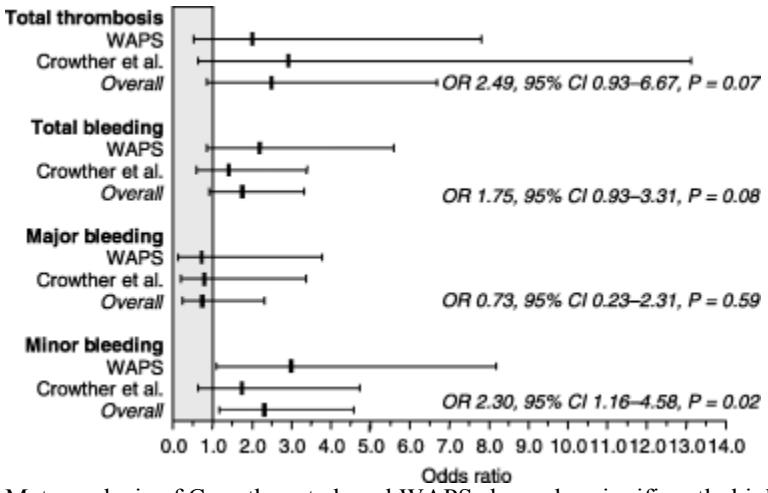
Finazzi G, Marchioli R, Brancaccio V, et al. **A randomized clinical trial of high-intensity warfarin vs. conventional antithrombotic therapy for the prevention of recurrent thrombosis in patients with the antiphospholipid syndrome (WAPS)** . *J Thromb Haemost.* 2005;3:848-53.

Study Design	Prospective, randomized open label design
Objective	Assess if high intensity oral anticoagulation (INR>3) is more effective than moderate intensity (INR 2-3) in preventing thrombosis
Number of Patients	109 patients with clinically confirmed APS • 54 patients assigned to high intensity warfarin (INR 3-4.5, target 3.5) • 55 patients assigned to moderate intensity warfarin (INR 2-3, target 2.5) • 3 patients assigned to aspirin 100mg/day
Inclusion Criteria	Lupus anticoagulant and/or moderate to high anticardiolipin antibodies measured 6-8 weeks apart and confirmed history of major arterial or venous thrombosis
Exclusion Criteria	Age <18 years History of recurrent thrombosis during anticoagulant prophylaxis Co-morbidities contraindicating oral anticoagulants or any serious illness with a life expectancy <3 years Pregnancy

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) (continued) [29]

<table>
<tr><td>Methods</td><td>Patients were stratified according to history of recurrent thrombosis
Patients examined at baseline, 3 and 6 months, and then every 12 months
Frequency of INR and dose adjustments dependent on provider</td></tr>
<tr><td>Endpoints</td><td>Primary end points
1.) Vascular death, non fatal major arterial and venous thromboembolic events (e.g.,. myocardial infarction, stroke, pulmonary embolism, deep vein thrombosis, transient ischemic attack) plus major hemorrhage
Secondary end points
1.) Total, minor, and major thrombotic events, and fatal and non-fatal cerebrovascular and cardiac events</td></tr>
<tr><td>Statistical Analysis</td><td>Intention-to-treat analysis
Two-tailed alpha error of 5% and power of 80% for sample size (500 patients per study arm in a 3-year follow up)
Cox proportional hazards model utilized for hazard ratios with 95% confidence intervals
Kruskal-Wallis test utilized for continuous variables
Peto’s method used for pooling of data with results of Crowther et al.
2 sided p values</td></tr>
<tr><td>Baseline Characteristics</td><td>Mean age at recruitment: 41
Systemic lupus erythematosus (SLE: 9.3% in high intensity group vs. 16.4% in moderate intensity
Aspirin therapy: 0 vs. 5.5%
Aspirin+anticoagulants: 7.4% vs. 5.5%
<table>
<tr><th>Characteristic n (%)</th><th>High-Intensity Anticoagulation</th><th>Conventional Treatment</th></tr>
<tr><td>Prior arterial thrombosis</td><td>21 (38.9)</td><td>23 (41.8)</td></tr>
<tr><td>Prior venous thrombosis</td><td>37 (68.5)</td><td>38 (69.1)</td></tr>
<tr><td colspan="3">Antiphospholipid antibodies</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>
</table></td></tr>
<tr><td>Results</td><td>Recurrent thrombosis
• 9 patients (8%) had recurrent thrombosis
o 6/54 patients (11.1%) in the high intensity group (0.031/pt-yr)
o 3/55 patients (5.5%) in the moderate intensity group (0.016/pt-yr)
o Hazard Ratio 1.97, 95% CI 0.49-7.89, p=0.3383
Bleeding
• 5 patients (6%) experienced major bleeding
o 2/54 patients (3.7%) in the high intensity group (0.010/pt-yr)
o 3/55 patients (5.5%) in the moderate intensity group (0.016/pt-yr)
o Hazard Ratio 0.66, 95% CI 0.11-3.96, p=0.6518
• 21 patients (19%) experienced minor bleeding
o 15/54 patients (27.8%) in the high intensity group
o 6/55 patients (10.9%) in the moderate intensity group
o Hazard Ratio 2.92, 95% CI 1.13-7.52, p=0.0269
Mean INR during follow up was 3.2 in the high intensity group vs. 2.5 moderate intensity
Median follow up= 3.6 years</td></tr>
</table>

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) (continued) [29]

Results	Odds ratios for high intensity anticoagulation vs. conventional treatment in Crowther et al. and WAPS  Meta analysis of Crowther et al. and WAPS showed a significantly higher occurrence of minor bleeding and a borderline higher risk of thrombosis with high intensity anticoagulation
Author's Conclusions	Supported moderate intensity warfarin (INR 2-3, target 2.5) High intensity oral anticoagulation is difficult to manage and associated with an increase in minor bleeding
Critique	Excluded those with recurrent thrombosis while receiving oral anticoagulant therapy Most patients had a history of venous thrombosis Mean INR in high intensity group was 3.2, did not report time in therapeutic range Non-blinded treatment allocation Trial terminated early

2. Retrospective studies

Khamashta MA, Cuadrado MJ, Mujic F et al. **The Management of Thrombosis in the Antiphospholipid-Antibody Syndrome.** *N Engl J Med.* 1995;332:993-7.

Study Design	Retrospective study
Objective	To assess the efficacy of warfarin, low-dose aspirin, or both in preventing recurrent thrombosis
Number of Patients	147 patients • APS with SLE=66 patients • APS with lupus-like syndrome=19 patients • Primary APS=62 patients
Inclusion Criteria	Positive tests for lupus anticoagulants, anticardiolipin antibodies, or both History of thrombosis (venous, arterial, or both)
Exclusion Criteria	History of thrombosis with follow up of less than 1 year or those loss to follow up Antiphospholipid antibody syndrome manifested only by recurrent fetal loss with no history of thrombosis Thrombocytopenia but no history of vascular occlusion Antiphospholipid antibodies and thrombosis undocumented by objective tests

The Management of Thrombosis in the Antiphospholipid-Antibody Syndrome (continued)[19]

<table>
<tr><td>Methods</td><td>Treated according to physician
Three page questionnaire used to obtain patient history
Categorized into 4 groups
• No treatment
• Aspirin 75mg
• Warfarin low intensity (INR<3) with or without aspirin
• Warfarin (INR ≥3) with or without aspirin</td></tr>
<tr><td>Endpoint</td><td>Recurrent thrombosis
Bleeding complications</td></tr>
<tr><td>Statistical Analysis</td><td>Poisson heterogenecity test with 95% CI used to measure follow up rates
Thrombosis free survival rates were calculated with the Kaplan-Meier method
Log rank test was used to compare individual periods of treatment throughout follow up
Proportional hazards regression analysis with the Wald significance test was used to examine combined effect of treatments
Hazard ratios with 95% confidence intervals and p values used to present results
Bonferroni's adjustment for multiple comparisons</td></tr>
<tr><td>Baseline Characteristics</td><td>Median age=32
84% female, 16% male
Initial thrombosis: Venous=76%; Arterial=46%
Positive anticardiolipin antibody test=83%
Positive lupus anticoagulant test=76%</td></tr>
<tr><td>Results</td><td>Comparison of Antithrombotic Treatments Used

<table>
<tr><th>Treatment</th><th>No. of patients</th><th>Patient-Years of Follow-Up</th><th>Recurrent Events</th><th>Events Per year of follow up</th><th>Relative Risk (95% CI)</th><th>P value</th></tr>
<tr><td>None</td><td>84</td><td>280.6</td><td>80 (34/46)</td><td>0.29</td><td>1.00</td><td></td></tr>
<tr><td>Aspirin</td><td>70</td><td>240.3</td><td>43 (5/38)</td><td>0.18</td><td>063 (0.43-0.92)</td><td>0.013</td></tr>
<tr><td>Warfarin Any Treatment</td><td>104</td><td>409.8</td><td>42 (16/26)</td><td>0.10</td><td>0.36 (0.24-0.53)</td><td><0.001</td></tr>
<tr><td>INR<3</td><td>67</td><td>141.3</td><td>32 (14/18)</td><td>0.23</td><td>0.78 (0.30-1.69)</td><td>0.531</td></tr>
<tr><td>With Aspirin</td><td>14</td><td>31.4</td><td>7 (0/7)</td><td>0.22</td><td>0.78 (0.30-1.69)</td><td>0.531</td></tr>
<tr><td>INR≥3</td><td>64</td><td>197.3</td><td>3 (2/1)</td><td>0.015</td><td>0.05 (0.01-0.16)</td><td><0.0001</td></tr>
<tr><td>With Aspirin</td><td>17</td><td>39.8</td><td>0 (0/0)</td><td>0</td><td>0.00 (0.00-0.33)</td><td><0.001</td></tr>
<tr><td>During 6 months after cessation of any warfarin treatment</td><td>39</td><td>16.2</td><td>21 (20/1)</td><td>1.30</td><td>4.55 (2.67-7.43)</td><td><0.001</td></tr>
<tr><td>All</td><td>147</td><td>946.9</td><td>186 (75/111)</td><td>0.20</td><td>-</td><td><0.001</td></tr>
</table>
Recurrent Thrombosis
• 101 patients (69%) had 186 recurrences of thrombosis
o Arterial: 52%, venous:40%, both: 8%
• Highest rate of thrombosis occurred during the first 6 months after cessation of warfarin therapy: Recurrence rate 1.30/year
Bleeding
• Occurred in 29 patients (all treated with high intensity warfarin): 7 were also receiving aspirin
• Minor bleeding: 22/29 patients; 0.071/patient year, 95% CI 0.047 -0.102
• Major bleeding: 7/29 patients; 0.017/patient year, 95% CI 0.007-0.035</td></tr>
</table>

The Management of Thrombosis in the Antiphospholipid-Antibody Syndrome (continued) [19]

Results	Treatment with high intensity warfarin (INR≥3) with or without low-dose aspirin was significantly more effective than treatment with low intensity warfarin with or without aspirin or aspirin alone (p value < 0.001) Median follow-up=6 years
Author's Conclusions	High intensity (INR ≥3) warfarin therapy with or without low-dose aspirin is effective prophylaxis against venous and arterial thrombosis Cessation of warfarin therapy is associated with a high risk of recurrent thrombosis Highest risk of recurrence was during the first 6 months after the discontinuation of warfarin No evidence that low dose aspirin prevented recurrences of thrombosis Appropriate to maintain an INR ≥3
Critique	Retrospective design Non-blinded treatment allocation Did not report time within INR range or average INR values Considered cardiovascular risk factors

Ruiz-Irastorza G, Khamashta MA, Hunt BJ, et al. **Bleeding and Recurrent Thrombosis in Definite Antiphospholipid Syndrome.** *Arch Intern Med.* 2002; 162: 1164-1169.

Design	Retrospective cohort study
Objective	Clarify risks and benefits of oral anticoagulation to a target INR of 3.5 in patients with definite APS and previous thrombosis
Number of patients	66 patients all receiving oral anticoagulation to target INR of 3.5
Inclusion Criteria	Definite APS according to Sapporo criteria History of thrombosis Treatment with oral anticoagulation to a target INR of 3.5 (INR range 3-4) during the previous 12 months
Methods	Anticoagulant monitoring provided by local anticoagulation clinic or general practitioner Performed audit of anticoagulation therapy for each patient Calculated proportion of measurements of INR within range in the previous 12 months
Endpoints	Recurrent thrombosis Major bleeding
Statistical Analysis	Results expressed as rates of events per 100 patient-years calculated as: (Total No. of Events X 100)/Total Person-Years CI calculated assuming Poisson distribution 2-tailed t test utilized to for univariate comparison between continuous variables Stepwise logistic regression utilized for clinical variables (e.g., bleeding or thrombosis)
Baseline Characteristics	91% female, 9% male 94% white, 3% black, 3% Indian 48% primary APS, 48% SLE, 3% other Median age= 40 Median time receiving anticoagulants=5 years Previous manifestations; 77% arterial thrombosis; 58% stroke;48% VTE; 52% obstetric
Results	Thrombosis • Total of 6 patients (9%) had thrombotic recurrences o 9.1/100 patient-years, 95% CI 3.3-19.6 o 4 episodes=arterial; 3 patients had additional risk factors (hypertension, cigarette smoking) o 2 episodes=venous

Bleeding and Recurrent Thrombosis in Definite Antiphospholipid Syndrome (continued)[30]

<table>
<tr><td>Results</td><td>Bleeding
4 patients experienced major bleeding
Bleeding Rates<table><tr><td>Type of Bleeding</td><td>Events per 100 patient years (95% CI)</td></tr><tr><td>Major</td><td>6 (1.6-15)</td></tr><tr><td>Intracranial</td><td>1.5 (0.04-8.4)</td></tr><tr><td>Fatal</td><td>0 (0-3.7)</td></tr></table>Percentage of INR determinations within the predefined range
INR 3-4: 37%
INR 2-2.9: 31%
INR 4-4.9: 13%
INR <2: 12%
INR >5: 7%</td></tr>
<tr><td>Author's Conclusions</td><td>Most patients with definite APS and previous thrombosis should be treated to a target INR of 3.5
A higher target INR does not result in a high incidence of intracranial or fatal bleeding
Consider low intensity for those patients at higher risk of bleeding (e.g., elderly, history of bleeding episodes)
Risk of recurrence increases and patients should be treated with oral anticoagulation indefinitely</td></tr>
<tr><td>Critique</td><td>Retrospective design
Small sample size
Relied on patient interviews</td></tr>
</table>

XI. Summary

1. Patients with APS have a high risk of recurrent thrombotic events, however guidelines for treatment with oral anticoagulation treatment recommend varying durations of therapy
2. Guidelines for treatment with oral anticoagulant treatment in this patient population recommend different target INRs
3. Retrospective studies and prospective trials report conflicting data on the optimal target INR for preventing recurrent thrombosis in patients with definite antiphospholipid syndrome according to the 1999 diagnostic criteria

XII. Conclusions

1. Patients may benefit from long-term warfarin therapy due to the risk of recurrent thrombotic events
    i. Assessment of individual patient risk for recurrent thrombotic events and major bleeding should be completed
2. The intensity of warfarin treatment in this patient population remains unclear
3. The role of aspirin in combination with warfarin in preventing recurrent thrombotic events remains unclear
4. Optimal treatment for arterial thromboembolic events remains controversial
5. Randomized clinical trials are needed to assess the safety and efficacy of high intensity oral anticoagulation in patients with definite APS according to the 2006 revised diagnostic criteria

XIII. Practical considerations[31]

1. A comprehensive work up that includes chronic disease states, concomitant medications, assessment of cardiovascular risk factors, and bleeding risk should be completed
2. Patients may have a prolonged aPTT which can make monitoring patients on heparin challenging
    i. Monitoring anti-factor Xa levels is an alternative
    ii. Patients could be switched to low molecular weight heparin (LMWH)
3. Lupus anticoagulants may affect the prothrombin time and prolong the INR complicating warfarin monitoring
    i. Monitoring chromogenic factor X assay is an alternative

XIV. References

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Appendix 1: Other Trials Evaluating Secondary Prophylaxis in Patients with APS according to 1999 Sapporo criteria[38]

Author, Year [Reference]	No. of Patients	Study Design	Thrombotic events at diagnosis, arterial/venous	Treatment	Follow Up	Thrombosis Rates	Bleeding Rates (Major)
Ames, 2005 [32]	67	Prospective cohort	17/50	Warfarin INR <2 Warfarin INR 2-3 Warfarin INR 3.1-4 Warfarin INR >4	Median 9 weeks Median 122 weeks Median 9 weeks Median 5 weeks	0 0.04/pt-yr 0.1/pt-yr 0	0 0.0057/pt-yr 0.10/pt-yr 0
Derksen, 1993 [20]	19	Retrospective cohort	0/19	None Warfarin INR 2.5-4.0	16-248 months	NA	2 patients
Giron-Gonzalez, 2004 [33]	158	Prospective cohort	70/106*	Warfarin INR 2.5-3.5	624 pt-yrs	0.005/pt-yr	0.006/pt-yr
Munoz-Rodriguez, 1999 [34]	47	Retrospective cohort	19/28	None Low-dose aspirin Warfarin INR 2.5-3.5	Median 49 months	91% 41% 19%	4 patients
Wittkowsky 2006 [35]	36	Retrospective cohort	14/16§	Warfarin INR 2-3 Warfarin INR >3	62.5 pt-yrs	0.096/pt-yr	0.032/pt-yr

*Patients who died (n=18) were excluded §Six events not specified

Appendix 2: Other Trials Evaluating Secondary Prophylaxis in Patients with antiphospholipid antibodies[38]

Author, Year [Reference]	No. of Patients	Study Design	Thrombotic events at diagnosis, arterial/venous	Treatment	Follow Up	Thrombosis Rates	Bleeding Rates (Major)
Rosove, 1992 [17]	70	Retrospective cohort	31/39	None Low-dose aspirin Warfarin INR <2 Warfarin INR 2-2.9 Warfarin INR ≥ 3	161.2 pt-yrs 37.8 pt-yrs 11.3 pt-yrs 40.9 pt-yrs 110.2 pt-yrs	0.19/pt-yr 0.32/pt-yr 0.57/pt-yr 0.07/pt-yr 0	0 0 0.031/pt-yr (all warfarin groups)
Krnic-Barrie 1997 [35]	61	Retrospective cohort	38/23	None Low-dose aspirin Warfarin Warfarin+low-dose aspirin	124.9 pt-yrs 36.6 pt-yrs 63.0 pt-yrs 30.6 pt-yrs	0.192 (a) 0.11(v) 0.082 (a) 0.027(v) 0.048(a) 0 (v) 0 (a) 0 (v)	4 patients
Levine 2004 [37]	720	RCT subgroup analysis	720/0	Low-dose aspirin Warfarin INR 1.4-2.8	2 yrs	22.2% 26.2%	NA

RCT=Randomized Controlled Trials N/A= Not Available APS=Antiphospholipid syndrome INR=International Normalized Ratio VTE=Venous thromboembolism
M=Major m=minor a=arterial v=venous pt-yrs=patients years