Clinical features of Antiphospholipid syndrome (APS)

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Antiphospholipid Syndrome: Definition

- Recurrent arterial and/or venous thrombotic events and/or
- Pregnancy morbidity plus
- aCL (β2GPI dependent) antibodies and/or
- Lupus Anticoagulant (LA).

*Definite diagnosis: 1 clinical and 1 laboratory criterion*

APS: Definitions

• Detection of thrombosis:
  – With any imaging technique
  – With biopsy (fibrin microthrombi).

• Definition of pregnancy morbidity:
  – One or more of unexplained fetal deaths (10\textsuperscript{th} week) morphologically normal fetus
  – One or more premature childbirths (preeclampsia or placental insufficiency)
  – Three or more abortions unexplained otherwise

APS: The discovery of a new antigen

McNeil HP et al, PNAS (USA) 1990;87:4120-24
Anti-cardiolipin (aCL) ELISA: What does a positive value mean?

aCL-β2GPI independent antibodies

aCL (β2GPI dependent) antibodies

Anti-β2 (CL independent) antibodies
APS/anti-phospholipid antibodies: epidemiology

• aCL in normal individuals: 0.2 - 9 %

• Anti-β2GPI in normal individuals: 3 – 13 %

• SLE: positive for aCL: 30 – 50 %
  – 1/3 of SLE aCL positive will develop APS

• SLE: positive for LA: 11-15 %

APS: alone or in association with underlying conditions.

<table>
<thead>
<tr>
<th>Underlying condition</th>
<th>No</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary antiphospholipid syndrome</td>
<td>531</td>
<td>(53)</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>362</td>
<td>(36)</td>
</tr>
<tr>
<td>Lupus-like syndrome</td>
<td>50</td>
<td>(5)</td>
</tr>
<tr>
<td>Primary Sjogren’s syndrome</td>
<td>22</td>
<td>(2)</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>18</td>
<td>(2)</td>
</tr>
<tr>
<td>Systemic sclerosis</td>
<td>7</td>
<td>(0.7)</td>
</tr>
<tr>
<td>Systemic vasculitis</td>
<td>7</td>
<td>(0.7)</td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>5</td>
<td>(0.5)</td>
</tr>
</tbody>
</table>

Clinical features at disease onset in 1000 patients with antiphospholipid syndrome

<table>
<thead>
<tr>
<th>Manifestations</th>
<th>No</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deep vein thrombosis</td>
<td>317</td>
<td>(32)</td>
</tr>
<tr>
<td>Thrombocytopenia (&lt;100,000/μL)</td>
<td>219</td>
<td>(22)</td>
</tr>
<tr>
<td>Livedo reticularis</td>
<td>204</td>
<td>(20)</td>
</tr>
<tr>
<td>Stroke</td>
<td>131</td>
<td>(13)</td>
</tr>
<tr>
<td>Superficial thrombophlebitis</td>
<td>91</td>
<td>(9)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>90</td>
<td>(9)</td>
</tr>
<tr>
<td>Fetal loss</td>
<td>83</td>
<td>(8)</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>70</td>
<td>(7)</td>
</tr>
<tr>
<td>Hemolytic anemia</td>
<td>66</td>
<td>(7)</td>
</tr>
<tr>
<td>Skin ulcers</td>
<td>39</td>
<td>(4)</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>34</td>
<td>(3)</td>
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<tr>
<td>Pseudovasculitic skin lesions</td>
<td>26</td>
<td>(3)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>28</td>
<td>(3)</td>
</tr>
<tr>
<td>Amavrosis fugax</td>
<td>28</td>
<td>(3)</td>
</tr>
<tr>
<td>Digital gangrene</td>
<td>19</td>
<td>(2)</td>
</tr>
</tbody>
</table>

APS: Differential Diagnosis

• Inherited:
  – Defective inhibition of coagulation factors
    • Factor V Leiden
    • Antithrombin III deficiency
    • Protein C/S deficiency
  – Impaired clot lysis
    • Dysfibrinogemia
    • Plasminogen deficiency
    • tPA deficiency
    • PAI-1 excess

• Uncertain
  – Homocystinouria

• Acquired:
  – Diseases or Syndromes
    • SLE
    • Malignancy
    • Myeloproliferative disorder
    • TTP
    • Estrogens
    • Hyperlipidemia
    • Diabetes mellitus
    • Hyperviscosity
    • Nephrotic syndrome
    • PNH
  – Physiologic states

*R.I. Handin, Harrison’s*
Clinical features of venous thrombosis (1)

- Deep vein thrombosis ........39%
- Pulmonary embolism ...........14%
- Superficial vein thrombosis ...12%
- Pulmonary hypertension .......2%
- Budd-Chiari syndrome ..........1%
- Retinal vein thrombosis .......1%
- Cerebral venous thrombosis ...1%

Clinical features of venous thrombosis (2)

• **Budd- Chiari syndrome**
  – Striking hepatomegaly
  – Abdominal pain
  – Ascites
  – Mild jaundice

• **Consider also:**
  – *Polycythemia roubra vera*
  – *PNH*
  – *Myelofibrosis*
  – *Trauma, infection*
  – *Other coagulopathies*
Clinical features of venous thrombosis (3)

Hemorrhage and congestion in all centrilobular areas

Loss of virtually all zone 3 hepatocytes

Sublobular vein filled with organizing thrombotic material

Striking dissection of red blood cells into the space of Disse. Loss of hepatocytes

Budd-Chiari syndrome, Figures by F.A. Mitros MD
Clinical features of venous thrombosis (4)

- Cerebral venous thrombosis:
  - Headaches
  - Nausea
  - Vomiting
  - Seizures (possibly)
  - Papilledema
  - Forehead skin and eyelid edema, proptosis
  - Cranial nerve III, IV, VI compromise
  - Focal neurologic symptoms

MR venography: absent flow in the right transverse sinous, sigmoid sinous and internal jugular vein

Hypodense left temporal lobe venous infarct
Clinical features of venous thrombosis (5)

Pulmonary emboli
Clinical features of arterial thrombosis (1)

- Migraine .............................................................. 20%
- Stroke ................................................................. 19%
- Cardiac valve thickening/dysfunction .................. 12%
- Transient ischemic attack ................................. 11%
- Myocardial infarction .......................................... 6%
- Arterial thrombosis in the legs ......................... 4%
- Arterial thrombosis in the arms ....................... 3%
- Angina ................................................................. 3%
- Vegetations .......................................................... 3%
- Avascular necrosis of the bone ......................... 2%
- Renal artery stenosis and glomerular lesions ...... 2%
- Infarcts of spleen, pancreas, adrenals, peritoneum.. 2%

Clinical features of arterial thrombosis (2)

Libman-Sacks endocarditis

Vegetations in U/S, autopsy and histopathologic examination

Linear splinter hemorrhages
Clinical features of arterial thrombosis (2)

*Brain microinfarcts*

*Peripheral arterial thrombosis*
APS: Arterial are followed by arterial and venous by venous thrombotic events. Results from a cohort of 85 patients (Tektonidou et al QJ Med 2000;93:523)

<table>
<thead>
<tr>
<th>Clinical manifestations</th>
<th>Presenting events</th>
<th>Subsequent events</th>
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<tbody>
<tr>
<td>Venous thrombosis</td>
<td>18 (20.7)</td>
<td>50 (32.7)</td>
</tr>
<tr>
<td>Arterial thrombosis</td>
<td>4 (4.6)</td>
<td>8 (5.3)</td>
</tr>
<tr>
<td>Recurrent abortions</td>
<td>16 (18.4)</td>
<td>15 (9.8)</td>
</tr>
<tr>
<td>Autoimmune hemolytic anemia</td>
<td>12 (13.8)</td>
<td>19 (12.4)</td>
</tr>
<tr>
<td>Central venous system events</td>
<td>15 (17.3)</td>
<td>43 (28.1)</td>
</tr>
</tbody>
</table>
### APS: Neurologic manifestations

<table>
<thead>
<tr>
<th>Condition</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine</td>
<td>202 (20.2)</td>
</tr>
<tr>
<td>Stroke</td>
<td>198 (19.8)</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>111 (11.1)</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>70 (7.0)</td>
</tr>
<tr>
<td>Multiinfarct dementia</td>
<td>25 (2.5)</td>
</tr>
<tr>
<td>Chorea</td>
<td>13 (1.3)</td>
</tr>
<tr>
<td>Acute encephalopathy</td>
<td>11 (1.1)</td>
</tr>
<tr>
<td>Transient amnesia</td>
<td>7 (0.7)</td>
</tr>
<tr>
<td>Cerebral venous thrombosis</td>
<td>7 (0.7)</td>
</tr>
<tr>
<td>Cerebellar ataxia</td>
<td>7 (0.7)</td>
</tr>
<tr>
<td>Transverse myelopathy</td>
<td>4 (0.4)</td>
</tr>
<tr>
<td>Hemiballismus</td>
<td>3 (0.3)</td>
</tr>
</tbody>
</table>

*Cervera R et al Arthritis Rheum 2002; 46:1019-1027*
APS: Pulmonary manifestations

- Pulmonary embolism 141 (14.1)
- Pulmonary hypertension 22 (2.2)
- Pulmonary microthrombosis 15 (1.5)
- Fibrosing alveolitis 12 (1.2)
- Other (adult respiratory distress syndrome, 7 (0.7) pulmonary hemorrhage, pulmonary artery thrombosis)

### APS: Cardiac manifestations

- Valve thickening/dysfunction: 116 (11.6)
- Myocardial infarction: 55 (5.5)
- Angina: 27 (2.7)
- Myocardiopathy: 29 (2.9)
- Vegetations: 27 (2.7)
- Coronary bypass rethrombosis: 11 (1.1)
- Intracardiac thrombus: 4 (0.4)

*Cervera R et al Arthritis Rheum 2002; 46:1019-1027*
APS: Obstetric & Fetal manifestations

Obstetric manifestations (n 590 pregnant women)
- Preeclampsia 56 (9.5)
- Eclampsia 26 (4.4)
- Abruptio placentae 12 (2.0)
- Postpartum cardiopulmonary syndrome 3 (0.5)

Fetal manifestations (n 1,580 pregnancies)
- Early fetal loss (10 weeks) 560 (35.4)
- Late fetal loss (10 weeks) 267 (16.9)
- Live birth 753 (47.7)
- Premature birth, no. premature/no. live births 80/753

Livedo reticularis: a sign of APS
(24% of the patients, Cervera R et al A&R, 2002;86:1019)
Catastrophic APS: Definition

- Life threatening form of APS characterized by high titers of anti-phospholipid antibodies accompanied by concurrent insufficiency of at least two major organs due to diffuse thromboembolic occlusion of small vessels.

Catastrophic APS: Lessons from a case

• Male 36 year old in 1994

• 1993: Tibia ulcers
• 1994: Seizures, Proteinuria, Anemia, ESR↑
• Brain MRI negative
• ANA 1/320 fine speckled
• Anti-DNA negative
• aCL/IgG 922 units (normal<100)
• LA positive
Catastrophic APS: Lessons from a case

- 12/7/94 Kidney biopsy:
  - 4 out of 9 glomeruli were fibrotic.
  - Rare inflammatory infiltrates of the interstitial space
  - Tubular atrophy
  - Fibrous intimal hyperplasia of the vessels within the kidney

- Presolon. Warfarin, anti-epileptics Azathiprine

- Divorce, poor compliance with therapy.
- Vomiting with azathioprine → discontinued.
Catastrophic APS: Lessons from a case

- 9/1997 → Tibia ulcer
  - Coombs positive hemolytic anemia
  - Pulmonary edema
  - Pulmonary hypertension
  - Loss of vision developed suddenly
  - High 24 hour urine protein

- Cyclophosphamide IV pulses, Medrol, anti-epileptics, warfarin
Catastrophic APS: Lessons from a case

- 1/1998: warfarin was discontinued with the responsibility of the patient.
- Paresis of the left arm
- Brain MRI: infarct in the right internal capsule
- Multiple pulmonary emboli
- Deterioration of renal function
- Heart failure
Catastrophic APS: Lessons from a case

• 7/1998: Pulmonary edema
  – Renal failure → dialysis
  – Fever
  – New brain infarcts
  – Liver failure (INR=20)
  – Pulmonary hypertention (>100 mmHg)
  – Plasmapheresis/ Corticosteroids IV/ transfusions.

• ICU:
  – Ventricular fibrillation → Death
Catastrophic APS: Lessons from a case

- Always high titer of aCL antibodies
- Usually LA positive
- Triggering factor (for instance withdrawal of warfarin)
- Intensive immunotherapy does not seem to help
- In general the results of therapy are very poor.
Catastrophic APS

Ischemic infarct of the occipital lobe in a patient with SLE, after the course of typhoid fever. Rapidly progressive glomerulonephritis followed this event.

Hayem G et al Arthritis & Rheum, 1999;42: 1056-1061
Catastrophic APS: multiple ischemic infarcts of the bone marrow

Ischemic necrosis of the bone marrow is usually associated with the HELLP syndrome (Hemolysis Elevated liver enzymes, Low platelets).

Hayem G et al Arthritis & rheum, 1999;42: 1056-1061
Catastrophic APS: Acute pulmonary failure

Transesophageal U/S indicating vegetations of the mitral valve

Widermann et al, J Int Medicine 2000;247:723
Catastrophic APS: Acute pulmonary failure

ARDS

Widermann et al, J Int Medicine 2000;247:723
Catastrophic APS: Acute respiratory failure

ARDS

Widermann et al, J Int Medicine 2000;247:723
Catastrophic APS: Acute respiratory failure

ARDS in remission after instituting plasmapheresis and cyclophosphamide therapy

Widermann et al, J Int Medicine 2000;247:723
Preliminary criteria for the classification of Catastrophic APS

1. Evidence of involvement of three or more organ systems/tissues
2. Development of manifestations simultaneously or in less than one week.
3. Confirmation by histopathology of small vessel occlusion at least in one organ or tissue.
4. Laboratory confirmation of the presence of antiphospholipid antibodies (LA and/or aCL)

Definite CAPS: all four criteria
Probable CAPS: involvement of 2 organs/tissues or criteria 1,2,4 or 1,3,4

Asherson RA et al, Lupus 2003;12: 530-4
Catastrophic APS: Demographic and epidemiological characteristics

- Male ........................................... 30%
- Female ........................................ 70%
- Mean age (years), (+/- SD) ......... 38 (14)
- Primary APS .................................. 48%
- SLE ............................................. 40%
- Lupus like syndrome .................... 5%
- Others ......................................... 7%

Cervera R et al, Ann Rheum Dis 2005; 64: 1205-1209
Precipitating factors of the catastrophic APS

- Infections ........................................ 20%
- Surgical procedures ..................... 14%
- Neoplasms ........................................ 9%
- Anticoagulation withdrawal .......... 7%
- Obstetric complications ............. 5%
- Lupus flaires ................................. 4%
- Oral contraceptives ...................... 3%

Cervera R et al, Ann Rheum Dis 2005; 64: 1205-1209
Renal manifestations of APS: A diagnostic and therapeutic challenge

• Problems in studying APS Nephropathy:
  – Renal involvement in primary APS (PAPS) occurs rarely
  – Renal involvement in secondary APS can be attributed to the underlying disease, mainly SLE
  – The clinical characteristics of APS nephropathy represent a continuum from PAPS to SLE
FREQUENCY OF RENAL MANIFESTATIONS OF PATIENTS WITH PRIMARY ANTIPHOSPHOLIPID SYNDROME (PAPS)

Retrospective evaluation of 16 patients with PAPS & renal manifestations

Clinical Manifestations associated with kidney pathology

- Systemic Hypertension .................................................. 15 (93)
- Renal Insufficiency .......................................................... 14 (87)
- Proteinuria (0.2 to 7 g/d) ................................................... 12 (75)
- Haematuria .................................................................... 9 (56)
- Microangiopathic anemia .................................................. 1 (6)
- Nephrotic Syndrome ......................................................... 1 (6)

RENAL MANIFESTATIONS OF APS:
THE SPECTRUM OF RENAL HISTOPATHOLOGIC LESIONS

A. VASCULAR LESIONS

1. Arteriosclerosis: 75% of biopsies in PAPS Nephropathy

- Definition: Fibrous intimal thickening with luminal reduction in the arcuate and interlobular arteries, associated with arterial hyaline and arteriosclerosis.

Cellular proliferation of the fibrous intima and irregular contours of the markedly retracted lumen. (Masson’s trichrome stain)
RENAL MANIFESTATIONS OF APS: THE SPECTRUM OF RENAL HISTOPATHOLOGIC LESIONS

A. VASCULAR LESIONS

2. Fibrous Intimal Hyperplasia (FIH) 75% of biopsies of PAPS Nephropathy

Definition: The interlobular arteries and their branches are tortuous, with their intima thickened by an intense thyofibroblastic intimal cellular proliferation


Tektonidou et al A&R 2004; 50:2569
RENAL MANIFESTATIONS OF APS:
THE SPECTRUM OF RENAL HISTOPATHOLOGIC LESIONS

• **Definition:**
  Fibrous intimal projections or cushions bulging into the lumen.

• The cells of the cellular proliferation of the intima are positive for alpha- and gamma-smooth muscle actin (anti-human muscle actin antibody HHF35).

RENAL MANIFESTATIONS OF APS: THE SPECTRUM OF RENAL HISTOPATHOLOGIC LESIONS

• A. VASCULAR LESIONS

• 3. Arterial and arteriolar fibrous and fibrocellular occlusions (68% of biopsies of APS nephropathy)

• Definition: occlusions of the interlobular arteries by fibrous material.
A. VASCULAR LESIONS

4. Thrombotic microangiopathy (TMA)
(31% of biopsies)

Definition:
Presence of fibrin thrombi in arterials and glomeruli.
Co-occurs with FIH
Commonly affected:
preglomerular arterioles, small interlobular arteries, glomerular capillaries.

Nochy et al
RENAL MANIFESTATIONS OF APS: THE SPECTRUM OF RENAL HISTOPATHOLOGIC LESIONS

B. OTHER LESIONS:
   1. Focal Cortical Atrophy (FCA) (62% of biopsies)

**Definition:** Subcapsular lesions as foci or triangles
Dense interstitial fibrosis, ischemic wrinkled glomeruli, massive tubular atrophy.

_Focal Cortical Atrophy_
# Renal involvement in aCL positive patients with and without APS: Clinical and histopathologic characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>PAPS (n=78)</th>
<th>APS \ SLE (n=40)</th>
<th>SLE (n=82)</th>
<th>Inc. SLE (n=48)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male n, (%)</td>
<td>19 (24)</td>
<td>8 (20)</td>
<td>4 (5)</td>
<td>7 (15)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>44 (56)</td>
<td>26 (64)</td>
<td>31 (38)</td>
<td>0 (0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Criteria for Renal biopsy n, (%)</td>
<td>8 (10)</td>
<td>24 (60)</td>
<td>43 (52)</td>
<td>4 (8)</td>
<td></td>
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<tr>
<td>WHO-I or-II n, (%)</td>
<td>1 (12)</td>
<td>3 (12)</td>
<td>6 (14)</td>
<td>2 (50)</td>
<td>NS</td>
</tr>
<tr>
<td>WHO-III or-IV n, (%)</td>
<td>1 (12)</td>
<td>11 (46)</td>
<td>26 (60)</td>
<td>2 (50)</td>
<td>NS</td>
</tr>
<tr>
<td>WHO V n, (%)</td>
<td>2 (24)</td>
<td>6 (25)</td>
<td>7 (16)</td>
<td>0 (0)</td>
<td>NS</td>
</tr>
<tr>
<td>Thrombi n, (%)</td>
<td>1 (12)</td>
<td>6 (25)</td>
<td>9 (21)</td>
<td>0 (0)</td>
<td>NS</td>
</tr>
<tr>
<td>FIH n, (%)</td>
<td>3 (37)</td>
<td>15 (62)</td>
<td>11 (26)</td>
<td>0 (0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>FCA n, (%)</td>
<td>1 (12)</td>
<td>4 (17)</td>
<td>5 (12)</td>
<td>0 (0)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Vlachoyiannopoulos et al Nephrol Dial Transplant 2001;16:56-62*
Antiphospholipid syndrome nephropathy in patients with SLE and antiphospholipid antibodies

Tektonidou et al, Arthritis & Rheum 2004;50:2569-79

APS nephropathy (APSN) was arbitrarily chosen as the presence of at least one of the following:

**Acute**
1. Thrombotic microangiopathy

**Chronic**
2. Fibrous intimal hyperplasia
3. Organized thrombi
4. Fibrous arterial/arteriolar occlusions
5. Focal cortical atrophy
Antiphospholipid syndrome nephropathy in patients with SLE and antiphospholipid antibodies

Tektonidou et al, Arthritis & Rheum 2004;50:2569-79
Clinical and laboratory associations with APS nephropathy in patients with SLE

<table>
<thead>
<tr>
<th></th>
<th>Patients without APS</th>
<th>Patients with APS</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=116 (%)</td>
<td>n=35 (%)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>APS</td>
<td>6 (5.2)</td>
<td>12 (34.3)</td>
<td>Not selected</td>
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<tr>
<td>LA</td>
<td>4 (3.4)</td>
<td>16 (45.7)</td>
<td>11.46 (3.1-41.7)</td>
</tr>
<tr>
<td>aCL</td>
<td>51 (44)</td>
<td>30 (85.7)</td>
<td>5.7 (1.8-17.8)</td>
</tr>
<tr>
<td>Livedo</td>
<td>29 (25)</td>
<td>20 (57.1)</td>
<td>Not selected</td>
</tr>
<tr>
<td>Hypertension</td>
<td>42 (36.2)</td>
<td>27 (77.1)</td>
<td>4 (1.5-8.6)</td>
</tr>
<tr>
<td>Increased serum creatinine</td>
<td>19 (16.3)</td>
<td>17 (48.5)</td>
<td>Not selected</td>
</tr>
</tbody>
</table>

*Tektonidou et al. Arthritis & Rheum 2004;50:2569-79*
A real case of a patient with APS and premature atherosclerosis

- Woman 35 y old, secretary
- Admitted for right hemiparesis
- Brain MRI: thromboembolic event of the left internal capsule
- Heart ultrasound negative
- Carotid doppler: atheroma at the bifurcation of the left carotid artery (90% stenosis)
- Endarterectomy: atherosclerotic lesion type 6 (atheroma + thrombus)
- Lipid profile normal
- Thrombophilia work up: MTHFR, FV Leyden, FII mutations negative
- aCL: IgG 700 u/L, IgM (-) NR 0-100 u/L
- aβ2GPI IgG: 1758, IgM (-) NR 0-100 u/L
- Lupus anticoagulant positive
• 33 premenopausal women with APS
  – Age-matched controls: SLE with/without aCL, RA, healthy subjects
• Outcome: Ultrasonography of carotid and femoral arteries for IMT and atherosclerotic plaques
• APS pts had more affected vessels than RA and healthy controls but not than SLE pts
• No evidence that aCL or aβ2GPI were associated with the presence of atherosclerotic lesions in the carotid or femoral arteries
APS pts had more affected vessels than RA and healthy controls but not than SLE pts

<table>
<thead>
<tr>
<th>Subject group</th>
<th>No. of subjects (%)</th>
<th>No. of vessels (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>APS</td>
<td>5 (15)</td>
<td>8 (6)</td>
</tr>
<tr>
<td>SLE/aCL-positive</td>
<td>2 (6)</td>
<td>6 (5)</td>
</tr>
<tr>
<td>SLE/aCL-negative</td>
<td>4 (12)</td>
<td>8 (6)</td>
</tr>
<tr>
<td>RA</td>
<td>1 (3)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Healthy</td>
<td>1 (3)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>All</td>
<td>13 (8)</td>
<td>25 (4)</td>
</tr>
<tr>
<td><em>P</em></td>
<td>0.33</td>
<td>0.042</td>
</tr>
</tbody>
</table>

*Fisher’s exact test for the comparison between the five groups.
### Predictors of atherosclerosis in the carotid or femoral arteries

#### Table 4. Predictors of atherosclerotic lesions in the carotid or femoral arteries

<table>
<thead>
<tr>
<th>Candidate predictor</th>
<th>Odds ratio (95% CI)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per yr)</td>
<td>1.135 (1.046–1.231)</td>
<td>0.002</td>
</tr>
<tr>
<td>BMI (per kg/m²)</td>
<td>1.073 (0.959–1.200)</td>
<td>0.22</td>
</tr>
<tr>
<td>Total cholesterol (per mg/dl)</td>
<td>1.016 (1.004–1.028)</td>
<td>0.010</td>
</tr>
<tr>
<td>LDL (per mg/dl)</td>
<td>1.019 (1.005–1.033)</td>
<td>0.009</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.58 (0.50–13.3)</td>
<td>0.26</td>
</tr>
<tr>
<td>Smoking (per 1 pack-year)</td>
<td>1.032 (0.991–1.076)</td>
<td>0.13</td>
</tr>
<tr>
<td>Cumulative steroid dose (per g methylprednisolone)</td>
<td>1.040 (1.010–1.071)</td>
<td>0.008</td>
</tr>
<tr>
<td>Disease duration (per yr)</td>
<td>NP</td>
<td>NP</td>
</tr>
<tr>
<td>aCL IgG</td>
<td>NP</td>
<td>NP</td>
</tr>
<tr>
<td>aCL IgM</td>
<td>NP</td>
<td>NP</td>
</tr>
<tr>
<td>Anti-( \beta_2 )GPI IgG</td>
<td>NP</td>
<td>NP</td>
</tr>
<tr>
<td>APS or SLE</td>
<td>4.00 (0.86–18.7)</td>
<td>0.078</td>
</tr>
</tbody>
</table>
APS: Concluding remarks

- Occurs in 1/3 of SLE patients positive for aCL antibodies
- 50% of patients have primary APS.
- Arterial are usually followed by arterial and venous by venous thrombotic events.
- Wide range of clinical features and outcomes.
- Precipitating factors for catastrophic APS should be always evaluated.
- Vascular events contribute to the pathogenesis of APS nephropathy
- Premature atherosclerosis may be part of the syndrome