Pitfalls in the organization of an APS multicentre study:
Lessons from the “Euro-Phospholipid”, the “CAPS Registry” and the PRECISESADS project

Ricard Cervera
Department of Autoimmune Diseases
Hospital Clínic
Barcelona
Lupus anticoagulant
Lupus anticoagulant
Lupus anticoagulant

Positive serological tests for syphilis
Lupus anticoagulant

Positive serological tests for syphilis
Lupus anticoagulant

Positive serological tests for syphilis

Anti-cardiolipin antibodies
Lupus anticoagulant

Positive serological tests for syphilis

Anti-cardiolipin antibodies
Lupus anticoagulant

Positive serological tests for syphilis

Anti-cardiolipin antibodies

APS without aPL
Lupus anticoagulant
Positive serological tests for syphilis
Anti-cardiolipin antibodies
APS without aPL
Lupus anticoagulant

Positive serological tests for syphilis

Anti-cardiolipin antibodies

APS without aPL

Thrombosis marker
Lupus anticoagulant

Positive serological tests for syphilis

Anti-cardiolipin antibodies

APS without aPL

Thrombosis marker
European Forum on aPL
New Orleans, USA
1996
European Forum on aPL

New Orleans, USA

1996

PROMOTERS:
Marie-Claire Boffa
Jean-Charles Piette
(Paris, France)
1997

Paris

1st Meeting of the European Forum on aPL

PROMOTERS: Marie-Claire Boffa Jean-Charles Piette (Paris, France)
EDITORIAL

European Working Party on Systemic Lupus Erythematosus and European Forum on antiphospholipid antibodies: two networks promoting European research on autoimmunity

R Cervera, MD, PhD, FRCP1 and A Tincani2

1Department of Autoimmune Diseases, Institut Clínic de Medicina i Dermatologia (ICMiD), Hospital Clinic, Barcelona, Catalonia, Spain; and
2Rheumatology and Clinical Immunology, Spedali Civili e Università di Brescia, Brescia, Italy
EUROPEAN FORUM ON ANTIPHOSPHOLIPID ANTIBODIES

OBJECTIVES

1. To move forward in standardization workshops
2. To initiate new biological, clinical and therapeutic projects
3. To find a consensus on controversial issues

Web content: EFAFL Info Desk.
Last updated: 23 April 1999
Marie-Claire Boffa
Paris, France
1997-2004

Angela Tincani
Brescia, Italy
2004-2009
EUROPEAN FORUM ON ANTIPHOSPHOLIPID ANTIBODIES

GENERAL COORDINATOR

Ricard Cervera
Barcelona, Catalonia

Denis Wahl
Nancy, France

2009-2017

2017- now
MULTICENTRE STUDIES

- Euro-Phospholipid project
- The CAPS Registry
- APLS Babies Register
- Familial Antiphospholipid Syndrome
- Warfarin in the Antiphospholipid Syndrome (WAPS)
- Pulmonary Hypertension and Antiphospholipid Antibodies
- Standardization of the Antiphospholipid Antibodies
- Cerebral Ischaemia in the Primary Antiphospholipid Syndrome: Source of Thrombi European Study (STEP)
- FcgRIIa polymorphism in the Antiphospholipid Syndrome
- CRP and ischemic cerebral manifestations
New kit according to the Forum proposals
Quantitative LA tests
β-2-GPI specific LAC assay
Factors that influence the anti-β-2-GPI ELISA
Avidity of anti-β-2-GPI antibodies
Binding of β-2-GPI to phospholipids
Standardization of ELISA anti-PE antibodies
Soluble CD40 ligand in APS
TACT and TACIT Projects
aPL tissue targeting
FcγRIIA in SLE, APS and CAPS
Genetics of APS: FcγRIIA polymorphisms and beyond
Annexin V in APS
APS in women presenting with recurrent miscarriage
PedAPS Registry
European Registry of Obstetric Antiphospholipid Syndrome
MULTICENTRE STUDIES

- Registry of infants with thrombosis born to mothers having aPL
- Brain neurosonography in infants born to mothers having aPL
- ALIWAPAS trial
- Infections and aPL
- Atherosclerosis in APS
- Multiple positivity of aPL
- Future projects
Catastrophic Antiphospholipid Syndrome

Clues to the Pathogenesis From a Series of 50 Patients

R. A. Asherson, R. Ekan, G. Espinosa, R. Cervera, J. A. Gómez-Puerto, J. Ramon-Casals, M. Ingelmo, J. C. Reverter, J. Font, and A. Aschner for the CAPS Registry Group

Disseminated intravascular coagulation in catastrophic antiphospholipid syndrome: clinical and haematological characteristics of 23 patients

R. A. Asherson, G. Espinosa, R. Cervera, J. A. Gómez-Puerto, J. Ramon-Casals, M. Ingelmo, J. C. Reverter, J. Font, and A. Aschner for the CAPS Registry Group

Thrombotic microangiopathic haemolytic anaemia and antiphospholipid antibodies


The role of malignancies in patients with catastrophic anti-phospholipid (Asherson’s) syndrome

W. Bucher, C. Faes, E. J. de Groot, J. Garcia-Garces, Y. Silvestri, A. Van den Berghe, A. Van den Berghe, and Members of the CAPS Registry Group

The acute respiratory distress syndrome in catastrophic antiphospholipid syndrome: analysis of a series of 47 patients

S. Buccionirri, G. Espinosa, R. A. Asherson, R. Cervera, G. Claver, J. A. Gómez-Puerto, M. Ramon-Casals, M. Ingelmo, J. Font for the Catastrophic Antiphospholipid Syndrome Registry Group

Intestinal involvement secondary to the Antiphospholipid Syndrome (APS): Clinical and Immunologic Characteristics of 97 Patients: Comparison of Classic and Catastrophic APS

R. Cervera, MD, PhD, FRCPath, R. Ekan, MD, G. Espinosa, MD, PhD, J. Font, MD, P. A. Massie, MD, L. A. Montserrat, MD, G. de la Red, MD, J. C. Reverter, MD, J. M. Dhal, MD, M. Gratacos, MD, J. Font, MD, J. A. Gómez-Puerto, MD, M. Ingelmo, MD, R. A. Aschner, MD, J. Ramon-Casals, MD, A. Aschner, MD, F. Cervera, MD, J. Font, MD, P. A. Massie, MD, J. A. Gómez-Puerto, MD, M. Ingelmo, MD, A. Aschner, MD, Cervera, MD, and for the Catastrophic Antiphospholipid Syndrome (CAPS) Registry Group

Mortality in the Catastrophic Antiphospholipid Syndrome

Causes of Death and Prognostic Factors in a Series of 250 Patients

Silvia Buccionirri, Gerard Espinosa, R. A. Asherson, J. A. Gómez-Puerto, Manuel Ramon-Casals, J. Font, and Ronald A. Asherson for the CAPS Registry Group

The Clinical Spectrum of Catastrophic Antiphospholipid Syndrome in the Absence and Presence of Lupus

ULAS D. BAYRAKTAR, DORUK EKAN, SILVIA BUCCHIARELLI, GERARD ESPINOSA, and RONALD ASHERSON, for the Catastrophic Antiphospholipid Syndrome Project Group

(J. Rheumatol 2007;34:346-52)
MULTICENTRE STUDIES

- Euro-Phospholipid project
- The CAPS Registry
- APLS Babies Register
- Familial Antiphospholipid Syndrome
- Warfarin in the Antiphospholipid Syndrome (WAPS)
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- Standardization of the Antiphospholipid Antibodies
- Cerebral Ischaemia in the Primary Antiphospholipid Syndrome: Source of Thrombi European Study (STEP)
- FcgRIIa polymorphism in the Antiphospholipid Syndrome
- CRP and ischemic cerebral manifestations
“EURO-PHOSPHOLIPID” PROJECT

Coordinators:
Ricard Cervera, Josep Font (Barcelona)*,
Jean-Charles Piette, Marie-Claire Boffa (Paris),
Munther A. Khamashta and Graham R.V. Hughes (London)

*deceased
“EURO-LUPUS” PROJECT: Morbidity and mortality in 1,000 European SLE patients during a 10-year follow-up period

“EURO-PHOSPHOLIPID” PROJECT: Morbidity and mortality in 1,000 European APS patients during a 10-year follow-up period
“EURO-PHOSPHOLIPID” PROJECT

AIM:

To evaluate prospectively the clinical and serological manifestations and the long-term evolution of the APS in Europe by means of a 10-year-follow-up study of 1000 patients attending 20 university centres.
“EURO-PHOSPHOLIPID” PROJECT

- **PART I: Cross-sectional Study (2000)**
  - Epidemiological features
  - Clinical and immunological patterns

- **PART II: 5-yr follow-up study (2005)**
  - Assessment of morbidity and mortality
  - Risk factors with prognostic value

- **PART III: 10-yr follow-up study (2010)**
  - Assessment of morbidity and mortality after a long-term follow-up period
“EURO-PHOSPHOLIPID” PROJECT
Participating Centres (I)

• Hospital Clínic, Barcelona, Catalonia, Spain
• Hospital Clínico, Málaga, Spain
• Hospital Regional del SAS, Málaga, Spain
• St. Thomas’ Hospital, London, England, UK
• Chaim Sheba Medical Center, Tel-Hashomer, Israel
• CHU Pitié-Salpetrière, Paris, France
• CHRU de Nîmes, Nîmes, France
• Hôpital Claude Huriez, Lille, France
• Hvidovre Hospital, Hvidovre, Denmark
• Univ. Medical School, Debrecen, Hungary
“EURO-PHOSPHOLIPID” PROJECT
Participating Centres (II)

- Spedali Civili, Brescia, Italy
- Policlinico Le Scotte, Siena, Italy
- Università di Pisa, Pisa, Italy
- IRCCS Policlinico, Milano, Italy
- Hippocration Hospital, Athens, Greece
- University Hospital, Utrecht, The Netherlands
- Medical University, Sofia, Bulgaria
- Cliniques Univer. Saint-Luc, Brussels, Belgium
- Hospital S. António, Porto, Portugal
- Technische Univer Dresden, Dresden, Germany
- Rheumaklinik Berlin-Buch, Berlin, Germany
Antiphospholipid Syndrome
Clinical and Immunological Manifestations and Patterns of Disease in the Euro-Phospholipid Cohort of 1,000 Patients

Ricard Cervera,1 Jean-Charles Piette,2 Josep Font,1 Munth Yehuda Shoenfeld,4 María Teresa Camps,5 Soren Jacobsen,6 Gabriela Irene Kentopoulou-Griva,7 Mauro Galeazzi,10 Pier La Ronald H W M Derksen,12 Philip G de Groot,12 Erika Grooje Marta Mosca,15 Stefano Bombardieri,16 Frédéric Houssiau,16 J Isabelle Quéré,17 Eric Hachulla,17 Carlos Vasconcelos,21 Antonio Fernández-Nebro,21 Marie-Claire Buffa,2 Graham Miguel Ingelmo,1 for the Euro-Phospholipid Project

EXTENDED REPORT
Morbidity and mortality in the antiphospholipid syndrome during a 10-year period: a multicentre prospective study of 1000 patients

R Cervera,1 R Serrano,1 G J Pons-Estel,1 L Ceberiego-Hualde,2 Y Shoenfeld,3 E de Ramón,4 V Buonauro,4 S Jacobsen,5 M M Zeher,6 T Tar,6 A Tincani,7 M Taglietti,7 G Theodossiades,8 E Nomikou,8 M Galeazzi,9 F Bellisai,9 P L Meroni,10 R H M Derksen,11 P G de Groot,12 M Baleva,13 M Mosca,14 S Bombardieri,14 F Houssiau,15 A Gris,16 I Quéré,16 E Hachulla,17 C Vasconcelos,18 A Fernández-Nebro,21 J-C Piette,22 G Espinosa,1 S Bucciarelli,1 C N Pisoni,2 Bertolaccini,2 M-C Boffa,22 G R V Hughes,22 on behalf of the Euro-Phospholipid Project Group (European Forum on Antiphospholipid Antibodies)
“CAPS REGISTRY”
(European-Extended Project)

Coordinators:
Ricard Cervera, Ronald A. Asherson*,
Gerard Espinosa (Barcelona),
Doruk Erkan (New York),
Yehuda Shoenfeld (Tel-Hashomer)

*deceased
"CAPS REGISTRY"

**AIM:**

To put together all the published case reports as well as the newly diagnosed cases of catastrophic APS from all over the world in a web-site based registry in order to increase our knowledge of this “rare” disease.
THE "CAPS" REGISTRY

REGISTRY OF THE "EUROPEAN FORUM ON ANTIPHOSPHOLIPID ANTIBODIES" FOR PATIENTS WITH THE "CATASTROPHIC" ANTIPHOSPHOLIPID SYNDROME

COORDINATORS

Ricard Cervera, Jean Charles Piette, Yehuda Shoenfeld, Josep Font, and Ronald A. Asherson on behalf of the European Forum on Antiphospholipid Antibodies.

AIM

To establish an International Registry of all diagnosed patients with the "catastrophic" antiphospholipid syndrome, considered as a "rare disease".

For additional information and inclusion of patients, please e-mail cervera@medicina.ub.es

For review of the already collected data, please click: CAPS registry
# Table 1. General clinical manifestations of patients with catastrophic APS.

<table>
<thead>
<tr>
<th>PATIENT No.</th>
<th>SEX</th>
<th>AGE</th>
<th>DIAGNOSIS</th>
<th>PREVIOUS APS MANIFESTATIONS</th>
<th>PRECIPITATING FACTOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>32</td>
<td></td>
<td>Subclavian vein thrombosis, fetal losses, thrombocytopenia, skin ulcers</td>
<td>Post-fetal loss</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>43</td>
<td>Lupus-like</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>22</td>
<td>Lupus-like</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>22</td>
<td>SLE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>40</td>
<td>PAPS</td>
<td>Myocardial infarction, epilepsy</td>
<td></td>
</tr>
</tbody>
</table>
Table 2. Thrombotic clinical manifestations of patients at the time of catastrophic APS.

<table>
<thead>
<tr>
<th>N.</th>
<th>PERIPHERAL</th>
<th>CEREBRAL</th>
<th>CARDIAC</th>
<th>PULMONARY</th>
<th>INTRAABDOMINAL</th>
<th>SKIN</th>
<th>OTHER</th>
<th>TREATMENT</th>
<th>OUTCOME</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sub clavian</td>
<td>Infarcta</td>
<td>Failure</td>
<td>ARDS</td>
<td>Ranal</td>
<td>LR,</td>
<td>Retinal artery</td>
<td>Ancrod, cyclo</td>
<td>Recovery</td>
</tr>
<tr>
<td>2</td>
<td>DVT</td>
<td>Infarcta</td>
<td></td>
<td>ARDS</td>
<td>Ranal</td>
<td>LR,</td>
<td></td>
<td>8, P, cyclo, AC</td>
<td>Recovery</td>
</tr>
<tr>
<td>3</td>
<td>Infarcta</td>
<td></td>
<td></td>
<td>ARDS</td>
<td>Ranal, hepatic, pancreatic</td>
<td>LR,</td>
<td>Retinal artery</td>
<td>8, P, cyclo, AC</td>
<td>Recovery</td>
</tr>
<tr>
<td>4</td>
<td>Infarcta</td>
<td>MI, VL</td>
<td></td>
<td>Microthrombi</td>
<td>Digital ischemia</td>
<td>LR,</td>
<td></td>
<td>8, cyclo</td>
<td>Death</td>
</tr>
<tr>
<td>5</td>
<td>Infarcta</td>
<td>MI, VL</td>
<td></td>
<td>ARDS</td>
<td>Ranal, adrenal, gastrointestinal</td>
<td>LR</td>
<td>Myomatium</td>
<td>8, AC</td>
<td>Death</td>
</tr>
<tr>
<td>6</td>
<td>Infarcta</td>
<td>MI</td>
<td></td>
<td>ARDS</td>
<td>Ranal, adrenal, gastrointestinal</td>
<td>LR</td>
<td>Myomatium</td>
<td>8, AC</td>
<td>Death</td>
</tr>
<tr>
<td>7</td>
<td>Infarcta</td>
<td></td>
<td></td>
<td></td>
<td>Hepatic, renal, mesenteric</td>
<td>LR</td>
<td>Mononuaria</td>
<td>8</td>
<td>Death</td>
</tr>
<tr>
<td>8</td>
<td>Infarcta</td>
<td>MI</td>
<td></td>
<td></td>
<td>Ranal</td>
<td>LR,</td>
<td></td>
<td>8, P, HD</td>
<td>Recovery</td>
</tr>
<tr>
<td>9</td>
<td>Infarcta</td>
<td>MI</td>
<td></td>
<td></td>
<td>Hepatic, renal, portal vein</td>
<td>LR</td>
<td></td>
<td>8, AC</td>
<td>Recovery</td>
</tr>
<tr>
<td>10</td>
<td>Infarcta</td>
<td></td>
<td></td>
<td></td>
<td>Hepatic, renal, adrenal</td>
<td>LR</td>
<td></td>
<td>8, AC</td>
<td>Recovery</td>
</tr>
</tbody>
</table>
### Table 3. Laboratory findings of patients with catastrophic APS.

<table>
<thead>
<tr>
<th>No</th>
<th>PLATELET COUNT</th>
<th>HEMOLYSIS</th>
<th>DIC</th>
<th>SCHISTOCYTE</th>
<th>IgG-aCL</th>
<th>IgM-aCL</th>
<th>LA</th>
<th>ANA</th>
<th>DNA</th>
<th>ENA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Normal</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>NR</td>
<td>NR</td>
<td>+</td>
<td>1:320</td>
<td>+</td>
<td>NR</td>
</tr>
<tr>
<td>2</td>
<td>Low</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>1:320</td>
<td>+</td>
<td>Ro</td>
</tr>
<tr>
<td>3</td>
<td>Low</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>1:120</td>
<td>+</td>
<td>Ro, La, RNP</td>
</tr>
<tr>
<td>4</td>
<td>Low</td>
<td>-</td>
<td>-</td>
<td>High +</td>
<td>-</td>
<td>NR</td>
<td>1:640</td>
<td>+</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Low</td>
<td>-</td>
<td>+</td>
<td>High +</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>NR</td>
</tr>
<tr>
<td>6</td>
<td>Low</td>
<td>+</td>
<td>+</td>
<td>High +</td>
<td>-</td>
<td>NR</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>Normal</td>
<td>-</td>
<td>-</td>
<td>High +</td>
<td>NR</td>
<td>+</td>
<td>1:30</td>
<td>+</td>
<td>NR</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>Normal</td>
<td>-</td>
<td>-</td>
<td>High +</td>
<td>Moderate</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>
145. Jacek Musia, M.D. Professor of Medicine, Jagiellonian University School of Medicine, Skawińska 8, 31-066 Krakow, Poland. Tel and fax: (+48-12) 430-53-14, Fax: (+48-12) 430-52-03; E-mail: mmmusia@kinga.cyf.kr.edu.pl

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151-152-153. Maria Tektonidou, Haralampos M. Moutsopoulos, Department of Pathophysiology, Medical School, National University of Athens, 75 Mikras Asias st. 114 27 Athens, Greece. Phone: 30.10.7771163; Fax: 30 10 7462664; e-mail: balts@otenet.gr
CAPS REGISTRY

REGISTRY OF THE "EUROPEAN FORUM ON ANTIPHOSPHOLIPID ANTIBODIES” FOR PATIENTS WITH THE "CATASTROPHIC" ANTIPHOSPHOLIPID SYNDROME

COORDINATORS

Ricard Cervera, Gerard Espinosa, Doruk Erkan, and Yehuda Shoenfeld on behalf of the European Forum on Antiphospholipid Antibodies.

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For additional information and inclusion of patients, please e-mail rcervera@clinic.ub.es
For review of the already collected data, please go to Public CAPS Registry

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EUROPEAN FORUM ON ANTIPHOSPHOLIPID ANTIBODIES

Click any of the images to enlarge it.
Catastrophic Antiphospholipid Syndrome

Clinical and Laboratory Features of 50 Patients

RONALD A. ASHERSON, RICARD CERVERA, JEAN-CHARLES PYTET, JOSEP FONT, J. T. LIE*, AINSINUR BURCOGLU, KEN LIM, FRANCISCO J. MUÑOZ-RODRIGUEZ, ROGER A. LEVY, FRANÇOIS BOUÉ, JÉRÔME ROSSERT, AND MIGUEL INGELMO


Molecular reclassification to find clinically useful biomarkers for systemic autoimmune diseases.
Collaboration between the public academy and pharmaceuticals

Supported by the Innovative Medicines Initiative (IMI)
Expected Impact

By means of state-of-the-art high-throughput technologies and the application of integrative bioinformatics strategies we expect to yield major impacts at multiple levels.

The following outcomes will directly result from the activity of the PRECISESADS consortium:

→ Identification of biomarkers for clinical use (diagnosis, prognosis, response to drugs) for SAD patients.
→ Identification of clusters of biomarkers that characterize groups of SADs patients.
→ Reclassification of SADs based on meaningful clinical biomarkers.
→ Crucial scientific insights on the interplay between different clinical features among SADs.
→ Development of a protocol for patient management.
WP Structure of PRECISESADS

WP1 - Coordination

WP3 – Clinical Data Management

Cross-Sectional Study

WP2 – Samples & Biobanking

WP4 – Genomics
WP5 – Cellular & Cytometry
WP6 – Proteome & Metabolome
WP8 – Bioinformatics & Biostatistics

Preclinical Study
WP7 – Tissue Taxonomy

Candidate Disease Clusters
Validation Inception cohort
Validated Disease Clusters

WP9 – Knowledge dissemination & training

2,500 patients
European Forum on Antiphospholipid Antibodies