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OMICS Group has organized 500 conferences, workshops and national symposiums across the major cities including San Francisco, Las Vegas, San Antonio, Omaha, Orlando, Raleigh, Santa Clara, Chicago, Philadelphia, Baltimore, United Kingdom, Valencia, Dubai, Beijing, Hyderabad, Bengaluru and Mumbai.

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Cardiac Involvement in the Antiphospholipid Syndrome

Ljudmila Stojanovich
Aleksandra Djokovic

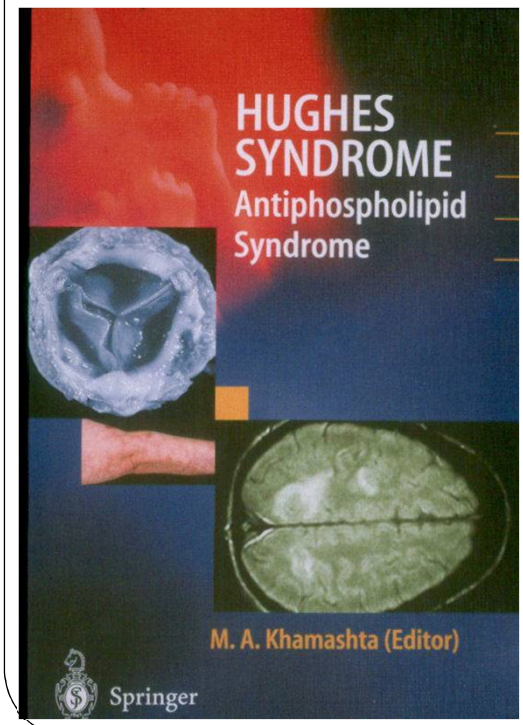
Bezanijska Kosa",
University Medical Center, Belgrade, Serbia

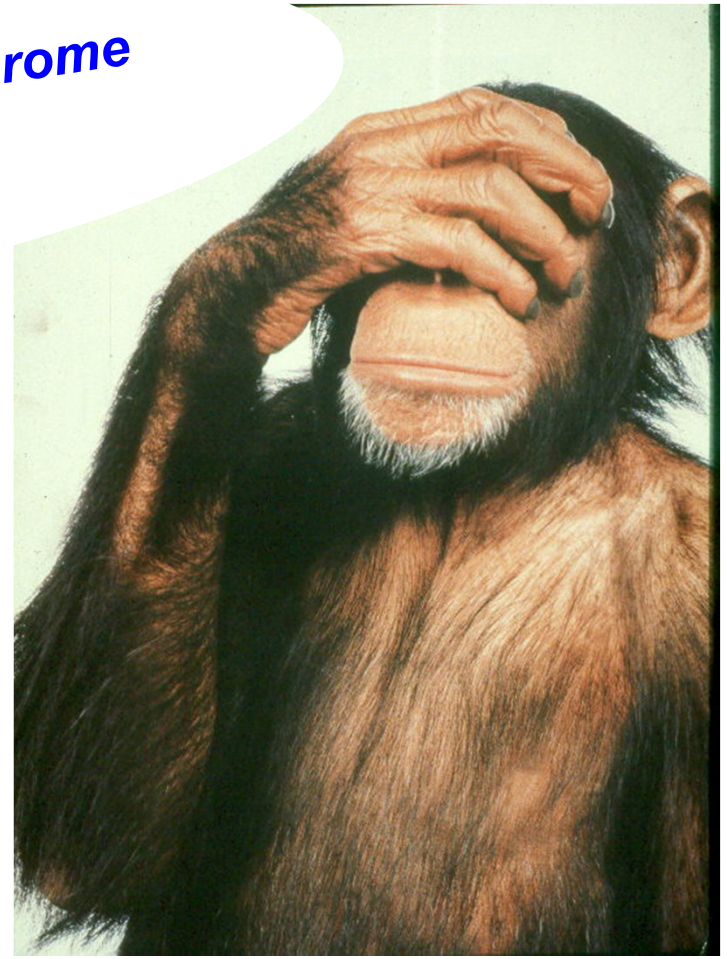




Antiphospholipid Syndrome Towards The Third Decade

The full Antiphospholipid Syndrome was not recognized until 1983





Stojanovich L, MD, PhD



ANTIPHOSPHOLIPID SYNDROME 1983

Thrombosis, abortion, cerebral disease, and the lupus anticoagulant

GRAHAM R V HUGHES

Consultant Physician,
Hammersmith Hospital,
London W12 0HS

BRITISH MEDICAL JOURNAL VOLUME 287 15 OCTOBER 1983

15 October 1983, 287, 1088 - 1089

Thrombosis, abortion, cerebral disease, and the lupus anticoagulant

What is Antiphospholipid Antibody Syndrome?

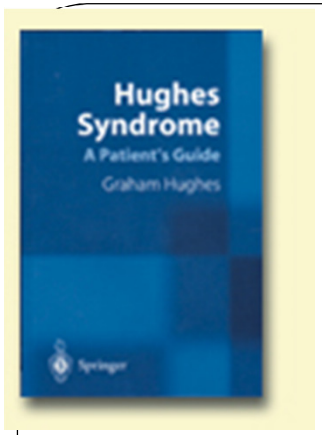


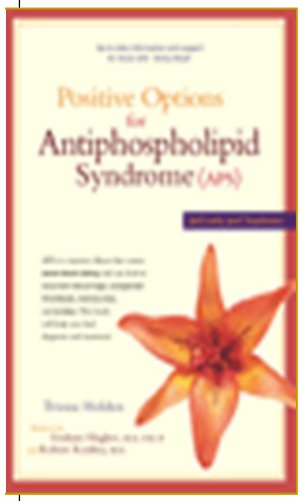
Auto-Immune Disorders

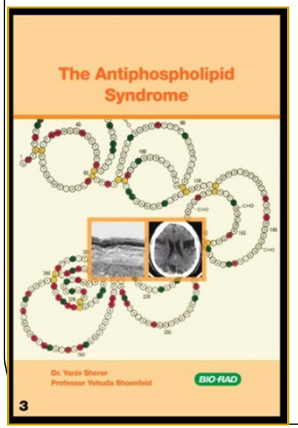


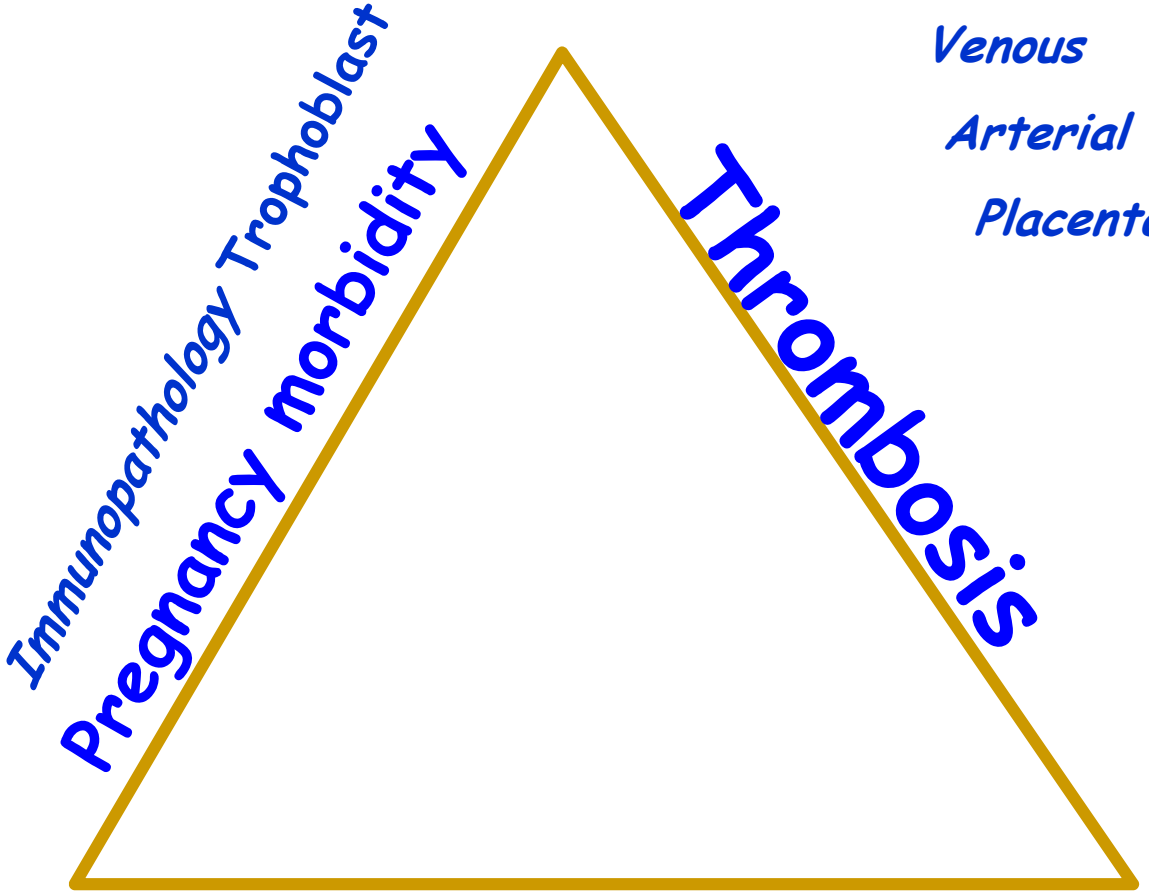
IT'S NOT LUPUS

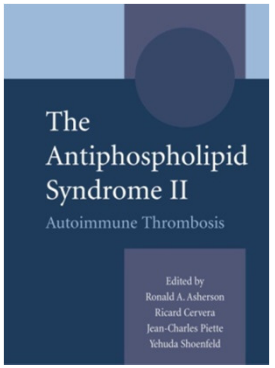
Antiphospholipid Syndrome

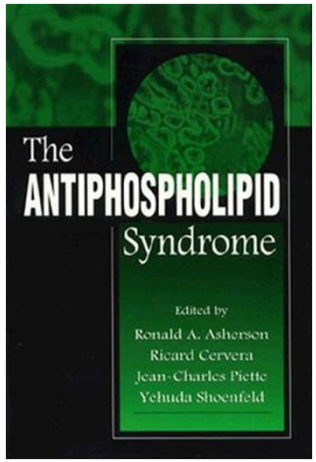












Stojanovich L, MD, PhD

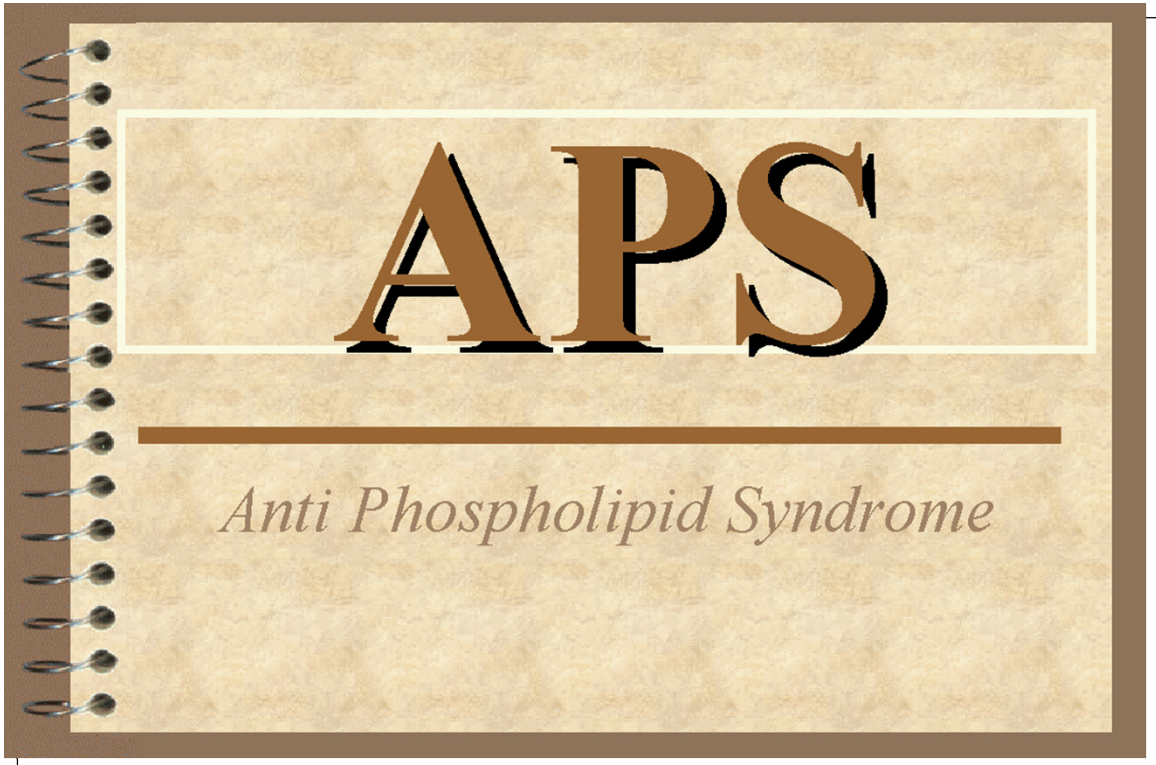


Antiphospholipid Syndrome

Very frequent Sy:

- ✓ 1 / 5 Young strokes (under 45)
- ✓ 1 / 5 Young heart attacks (under 45)
- ✓ 1 / 5 DVT
- ✓ 1 / 5 Pregnancy loss
- ✓ 1 / 5 SLE

G.Hughes in "Clinical Case Studies", London. 2015:39

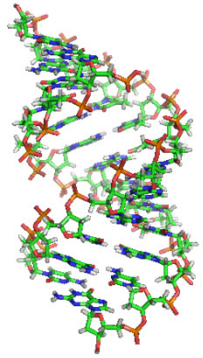


There are two major "new" diseases of the late 20th century- AIDS and APS"

Dr. Vilardell
Barselona, 2002

Stojanovich L, MD, PhD

The Sapporo APS classification criteria (1998, published in 1999) were replaced by the Sydney criteria in 2006



Clinical criteria

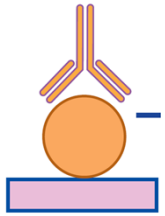
- ✓ Vascular thrombosis
- ✓ Pregnancy morbidity

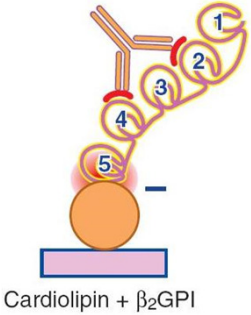
Laboratory criteria

- ✓ Lupus anticoagulant
- ✓ Anticardiolipin antibody

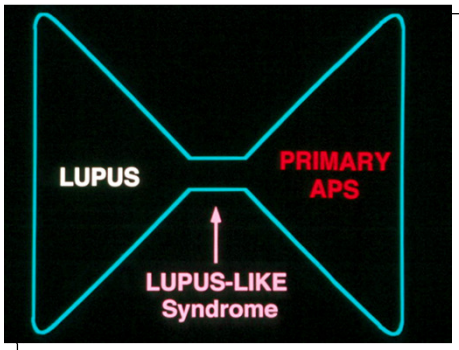
dependent of β_2-GPI

aPL profile in patients with APS





Stojanovich L, MD, PhD



Evolution of APS

7-10% PAPS
may go on to develop SLE

>1 % APS may go on to develop CAPS

CAPS

aPL
Thrombosis

SLE

PAPS

Seronegative
Syndromes

Stojanovich L, MD, PhD

Evidence for increased risk of coronary heart disease in SLE and APS

Urowitz et al: *The bimodal mortality pattern of systemic lupus erythematosus.*

Am J Med 60: 21-5, 1976.

- Pts with SLE have 5-10 times the risk of CHD-related events compared with the background population.

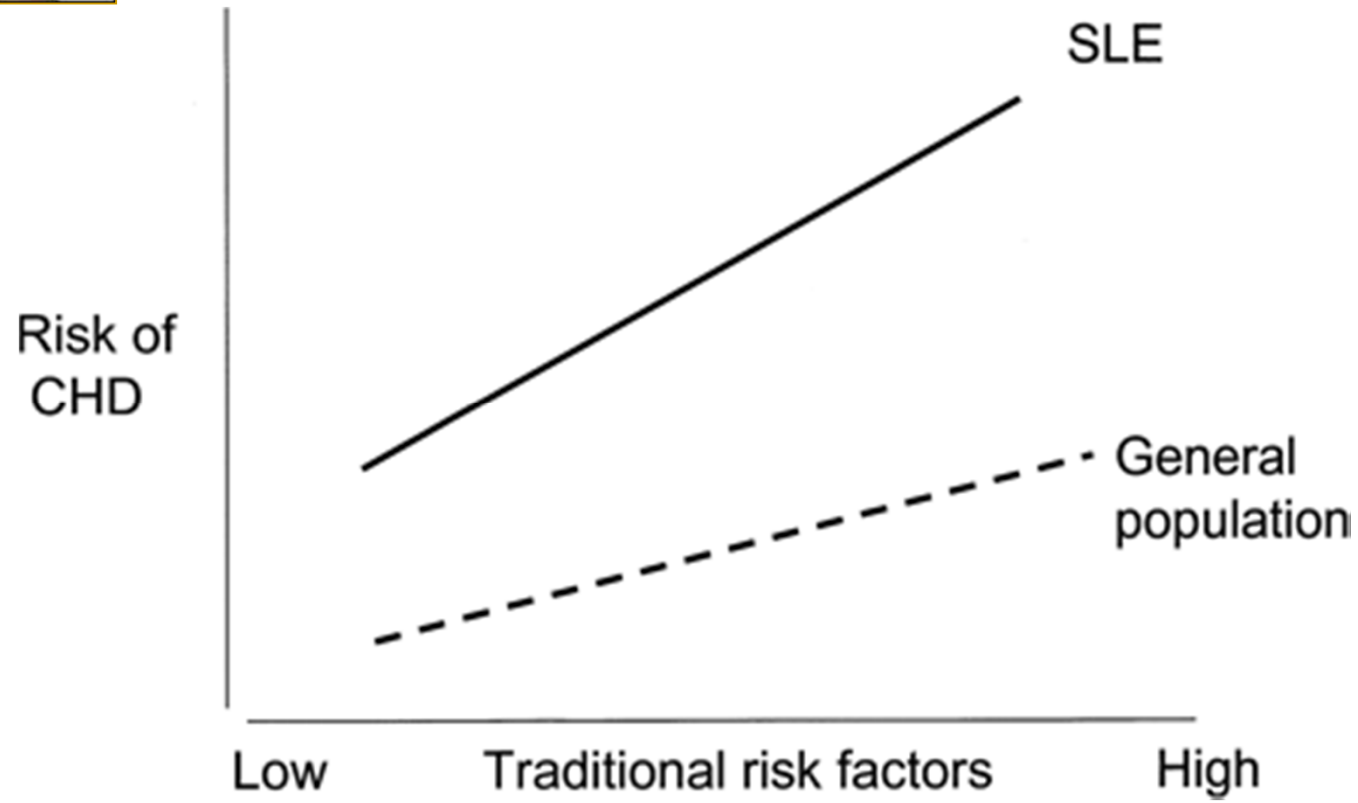
- SLE women aged 35-44yr have 50-times (!!!) greater risk of IM relative to healthy (Framingham Study cohort).

Bruce IN et al: Premature atherosclerosis in SLE. Rheum Dis Clin North Am 26:257-8, 2000.

Ljudmila Stojanovich, MD,
PhD, Belgrade, Serbia



Summary of the probable influence of classic risk factors on CHD risk in SLE

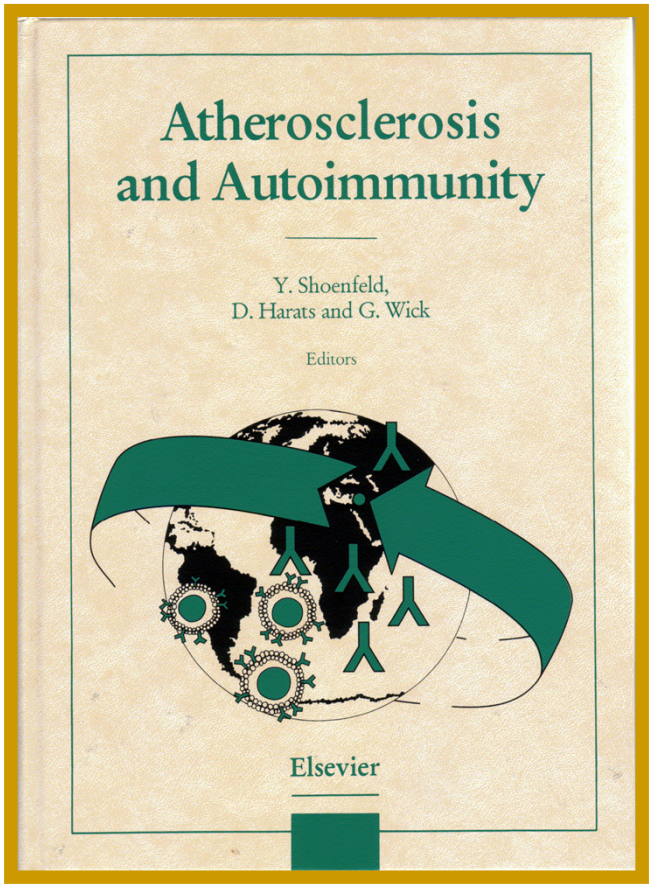


Patients with SLE may be more susceptible to the effects of risk factors than the general population

Ljudmila Stojanovich, MD, PhD, Belgrade, Serbia



Atherosclerosis and Autoimmunity



"Everything is autoimmune until proven otherwise even atherosclerosis"

Y. Shoenfeld

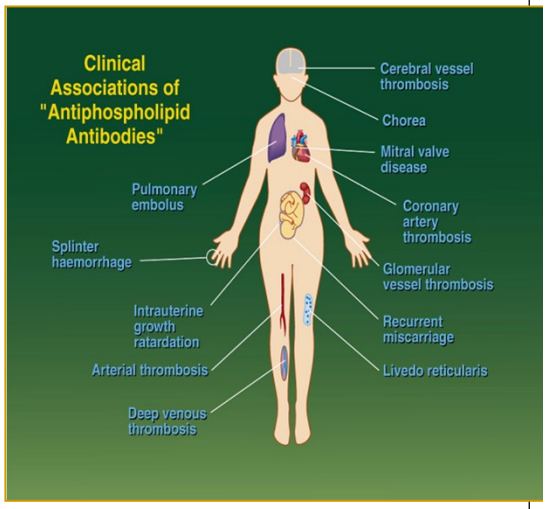
Ljudmila Stojanovich, MD,
PhD, Belgrade, Serbia



Systemic APS by Shoenfeld Y
Lupus. 2003



1) Skin (livedo reticularis)
2) Heart (non-verrucal endocarditis)
3) Kidneys (renal artery stenosis)
4) Circulation (hypertension, atherosclerosis)
5) Lung (pulmonary hypertension)
6) Brain (cognitive impairment)
7) Brain Vasculature (migraine)
8) Blood elements (AIHA, thrombocytopenia)
9) Bones (osteonecrosis)
10) Adrenals (apoplexy)
11) Placenta (insuficiency, fetal death)
12) Pregnancy (eclampsia, pregnansy loss)
13) Coagulation (hypercoagulable state)
14) Blood vessels (accelerated atherosclerosis)
15) Eyes (amaurasis fugox, optic neuritis)
16) Ears (acute hearing loss)
17) GI involvement (spleen, Budd Chiari)



Stojanovich L, MD, PhD



LE - Microsoft Internet Explorer prop

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p://www.med.ub.es/MIMMUN/FORUM/INDEX.HTM Ir a Vínculos

Euro-Phospholipid on Line

Official Web-site of the "European Forum on Antiphospholipid Antibodies"

- Organization
- Membership Directory
- Workshops and Meetings
- Multicentre Studies

Internet

Inicio | Bandeja de entrada - Micr... | Home EWPSLE - Mic... | Microsoft PowerPoint - [Fo... | 1:22



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- Euro-Phospholipid project
- 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
- The CAPS Registry
- Future projects

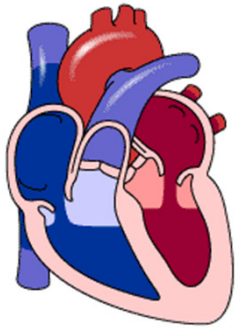
Internet

Programas

Inicio STUDIES... Bandeja de ... Microsoft W... SMS Europa... Microsoft Po... 18:23

CARDIOLOGICAL MANIFESTATIONS

- ✓ Prevalence: 40 %
- ✓ Morbidity: 4-6%



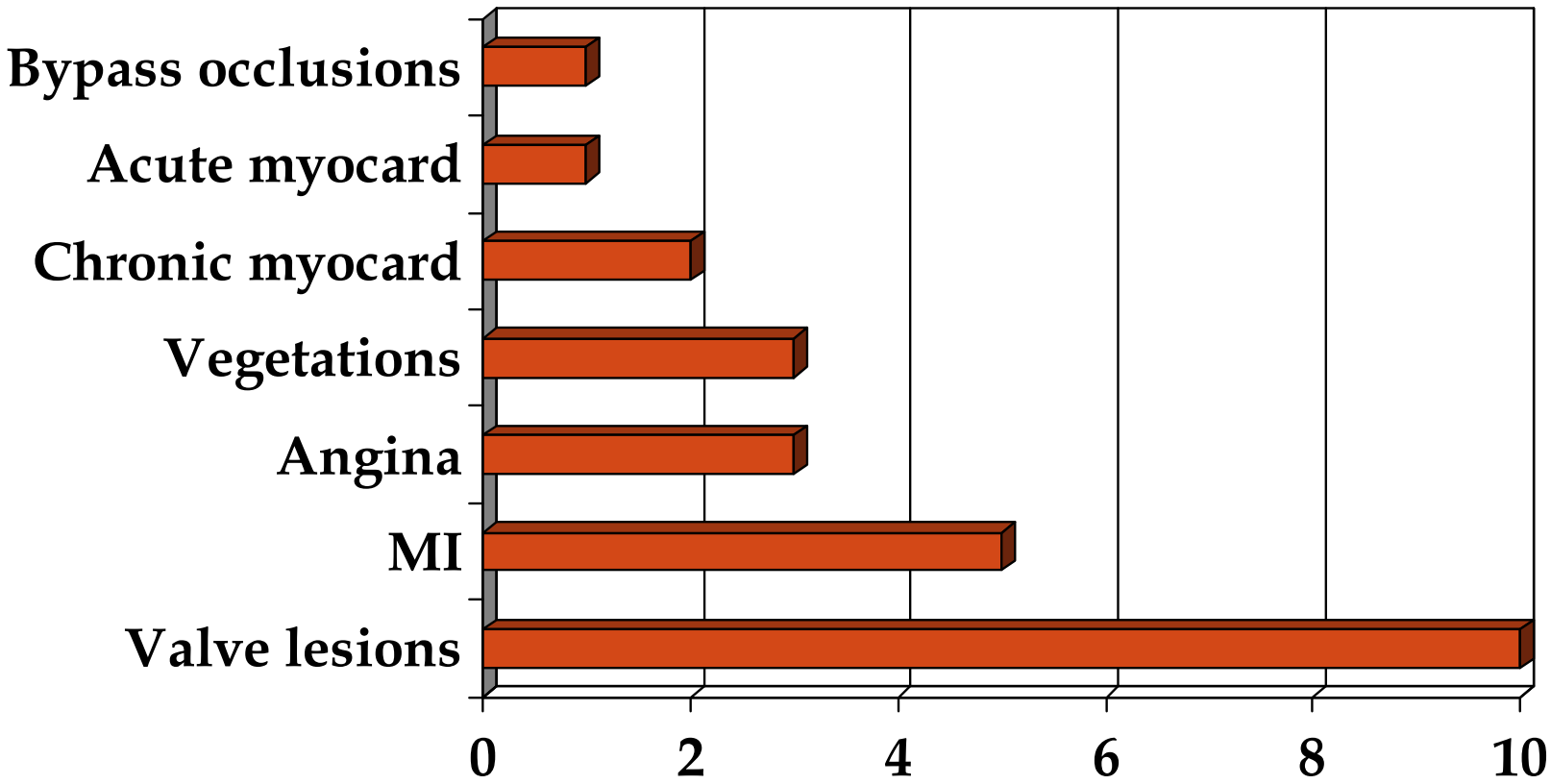
ARTHRITIS & RHEUMATISM
Vol. 46, No. 4, April 2002, pp 1019–1027
DOI 10.1002/art.10187
© 2002, American College of Rheumatology

Antiphospholipid Syndrome

Clinical and Immunologic Manifestations and Patterns of Disease Expression in a Cohort of 1,000 Patients

Ricard Cervera,[1] Jean-Charles Piette,[2] Josep Font,[1] Munther A. Khamashta,[3] Yehuda Shoenfeld,[4] María Teresa Camps,[5] Soren Jacobsen,[6] Gabriella Lakos,[7] Angela Tincani,[8] Irene Kontopoulou-Griva,[9] Mauro Galeazzi,[10] Pier Luigi Meroni,[11] Ronald H. W. M. Derksen,[12] Philip G. de Groot,[12] Erika Gromnica-Ihle,[13] Marta Baleva,[14] Marta Mosca,[15] Stefano Bombardieri,[15] Frédéric Houssiau,[16] Jean-Christophe Gris,[17] Isabelle Quéré,[17] Eric Hachulla,[18] Carlos Vasconcelos,[19] Beate Roch,[20] Antonio Fernández-Nebro,[21] Marie-Claire Boffa,[2] Graham R. V. Hughes,[3] and Miguel Ingelmo,[1] for the Euro-Phospholipid Project Group

EURO-PHOSPHOLIPID PROJECT
Cardiac manifestations





Project Issued by the Ministry of Science of the Republic of Serbia

- *Grant number 145020 for 2005-2010:*

Multidisciplinary Study of Risk Factors for the Development of Thrombosis in APS

- *Grant number 175041 for 2011-2015:*

Multidisciplinary study of genetic and acquired abnormalities of the immune response for the occurrence of systemic antiphospholipid syndrome manifestations.

Stojanovich L, MD, PhD



Research Goal

1. To determine prevalence and types of aPL titer (LA, ACL, β2GPI) in patients with thrombotic and non-thrombotic manifestations of the disease.
2. Analisys of gene polymorphisms that are important for the T (H) 17 and regulatory T cells differentiation in APS patients, and their corellation with the disease.
3. Determination of aPL association with the innate Thrombophilia (defficiency of AT, PC, PS, FXII, polymorphisms FV Leiden, prothrombin 20210 and MTHFR) and clinical expression.
4. Determination of aPL role in the development of induced atherosclerosis, including subclinical forms of the disease using the latest technology methods such as multi sliced computed tomography (64 MSCT), which would present the extent and location of changes in blood vessels.
5. To determine the importance of oxidative stress, markers of inflammation, endothelial adhesion receptor molecules induction and activation, as additional factors in the complicated pathophysiology and multifactorial etiology of APS thrombosis.
6. To continue in obtaining the national APS patients registry with the possibilities of its participating in international studies.
7. To overview the patient outcomes with various APS therapeutic protocols.

Stojanovich L, MD, PhD



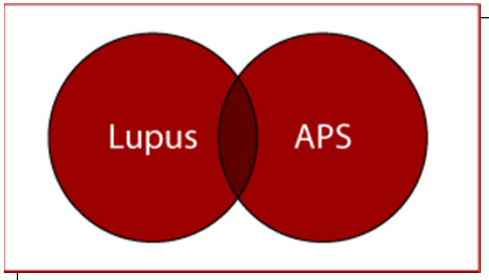
Goals





✓Aim of this study was to observe and investigate cardiac manifestations in our prospective study of APS patients.

✓Differences between patients with primary and secondary APS were also analyzed.



Patient Group Description

from 514 APS registry
389patients:

260 PAPS patients:

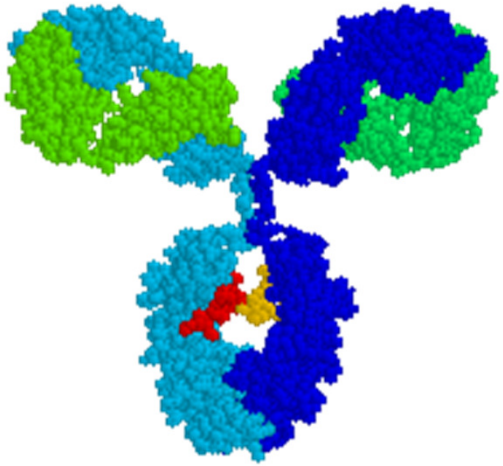
- 201 female and 59 male
- mean age 45.2 + 13.7 years

114 SLE patients with secondary APS

- 106 female and 9 male
- mean age 46.9 + 15.9 years

15 (2.9%) patients with CAPS: 7 SLE+ 8 PAPS

Methodology

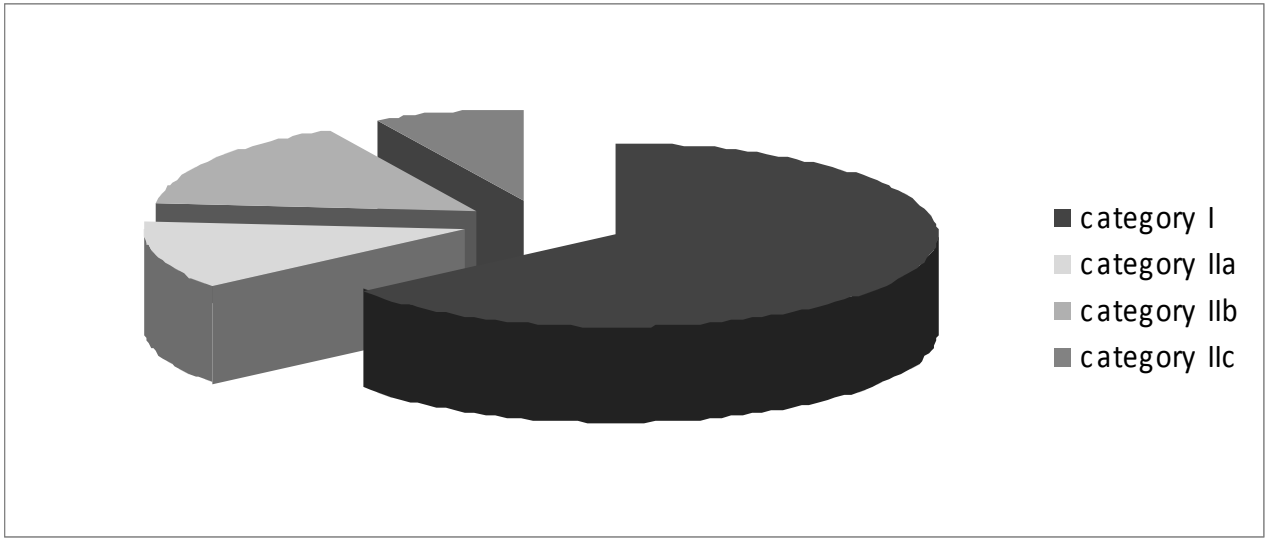


- ✓ LA
- ✓ aCL (IgG/IgM) and
- ✓ ß$_2$GPI (IgG/IgM)

by positive levels:

- ✓ *low (10–30)*
- ✓ *medium (31–99)*
- ✓ *high (>100PLU/ml)*

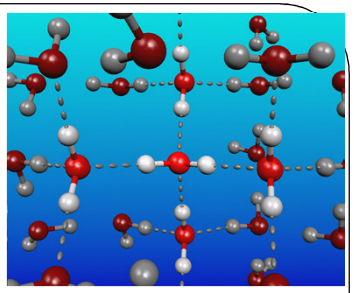
Distribution of patients according to antibody category

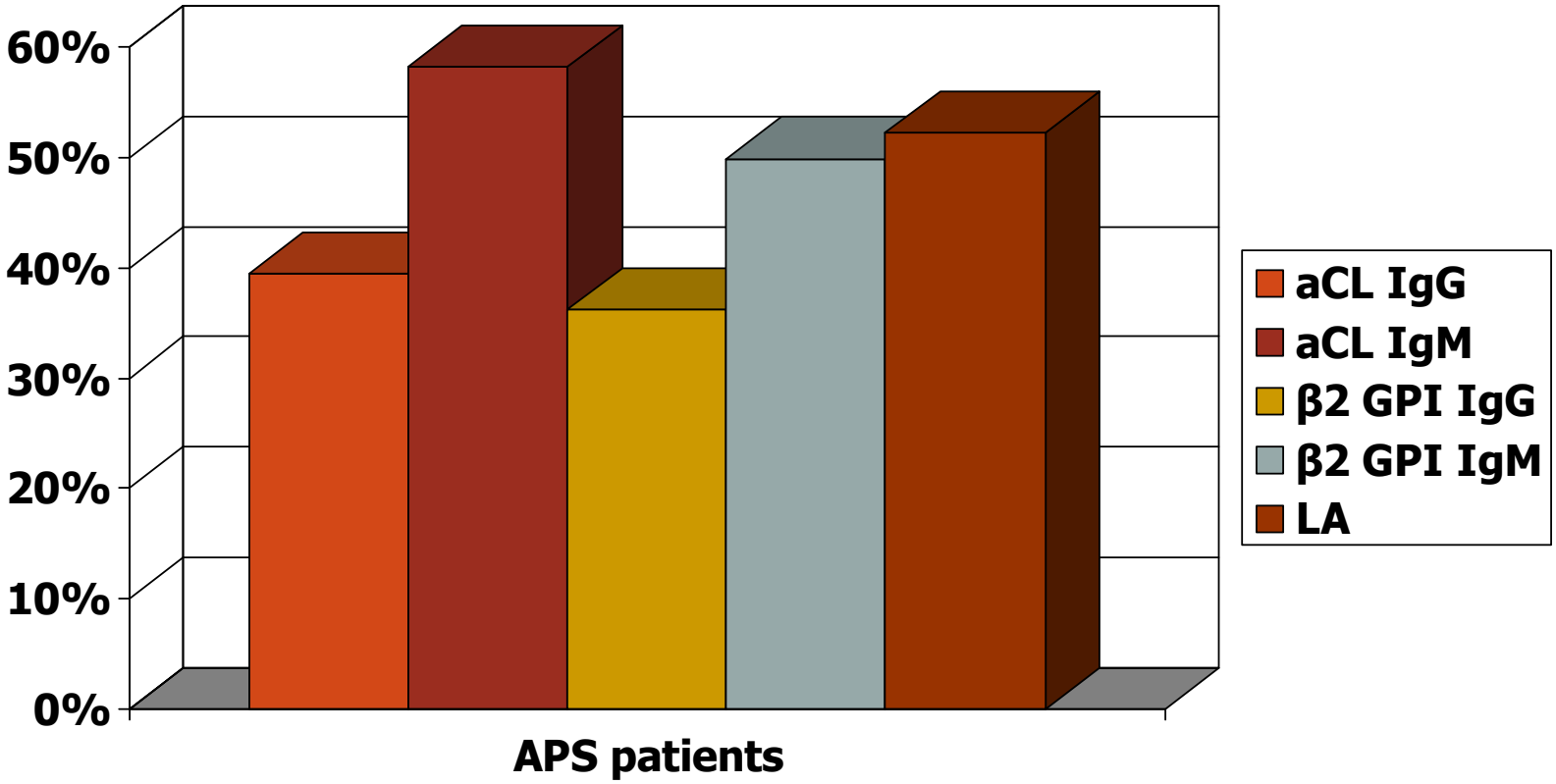


- More than one type of antibodies (category I) was present in 64.5%
- Lupus anticoagulant was present alone in 12.1% patients (category IIa)
- aCL antibodies were present alone in 16% patients (category IIb)
- anti-β2GPI antibodies were present alone in 7.4% patients (category IIc)

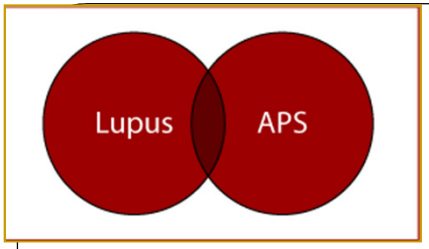
PengoV et al.
Antibody profiles for the diagnosis of APS.
Thromb Haemost 2005

Break-down of Patients According to the Type of aPL





Stojanovich L, MD, PhD

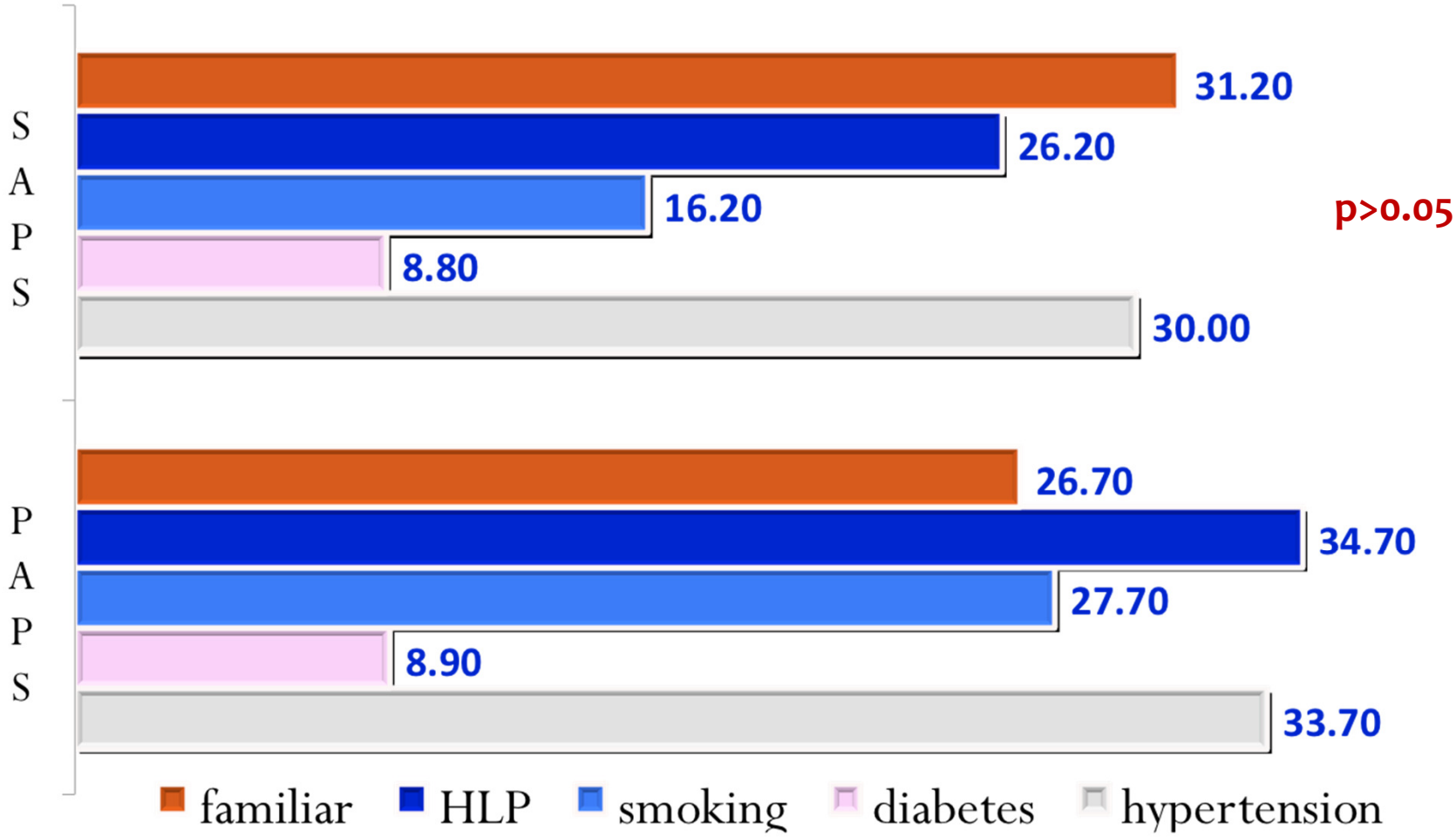


Distribution of aPL in PAPS and SAPS

	PAPS %	SAPS %	p
aCL IgG	35.8	53.9	0.001*
aCL IgM	54.1	65.2	0.096
ß$_2$GPI IgG	34.9	45.2	0.239
ß$_2$GPI IgM	34.4	46.6	0.092
LA	51.4	45.2	0.002*

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Standard atherosclerotic risk factors prevalence in APS patients (%)



Stojanovich L, MD, PhD

Lupus (2011) 0, 1–8
http://lup.sagepub.com

LUPUS AROUND THE WORLD

Influence of antiphospholipid antibody levels and type on thrombotic manifestations: results from the Serbian National Cohort Study

L Stojanovich[1], O Markovic[1], D Marisavljevic[1,2], I Elezovic[3,2], N Ilijevski[4,2] and N Stanisavljevic[1]
[1]Internal medicine, "Bezanijska Kosa", University Medical Center, Belgrade, Serbia; [2]University of Belgrade, Faculty of Medicine, Belgrade, Serbia; [3]Hematology Clinics, Clinical Center of Serbia, Belgrade, Serbia; [4]Institute of Cardiovascular Disease "Dedinje", Belgrade, Serbia



- ✓ Pregnancy loss: 41% pts
- ✓ Arterial thrombosis: 51% pts
- ✓ Venous thrombosis: 28% pts

Case Communications



Treatment of Antiphospholipid Syndrome in Pregnancy with Low Doses of Intravenous Immunoglobulin

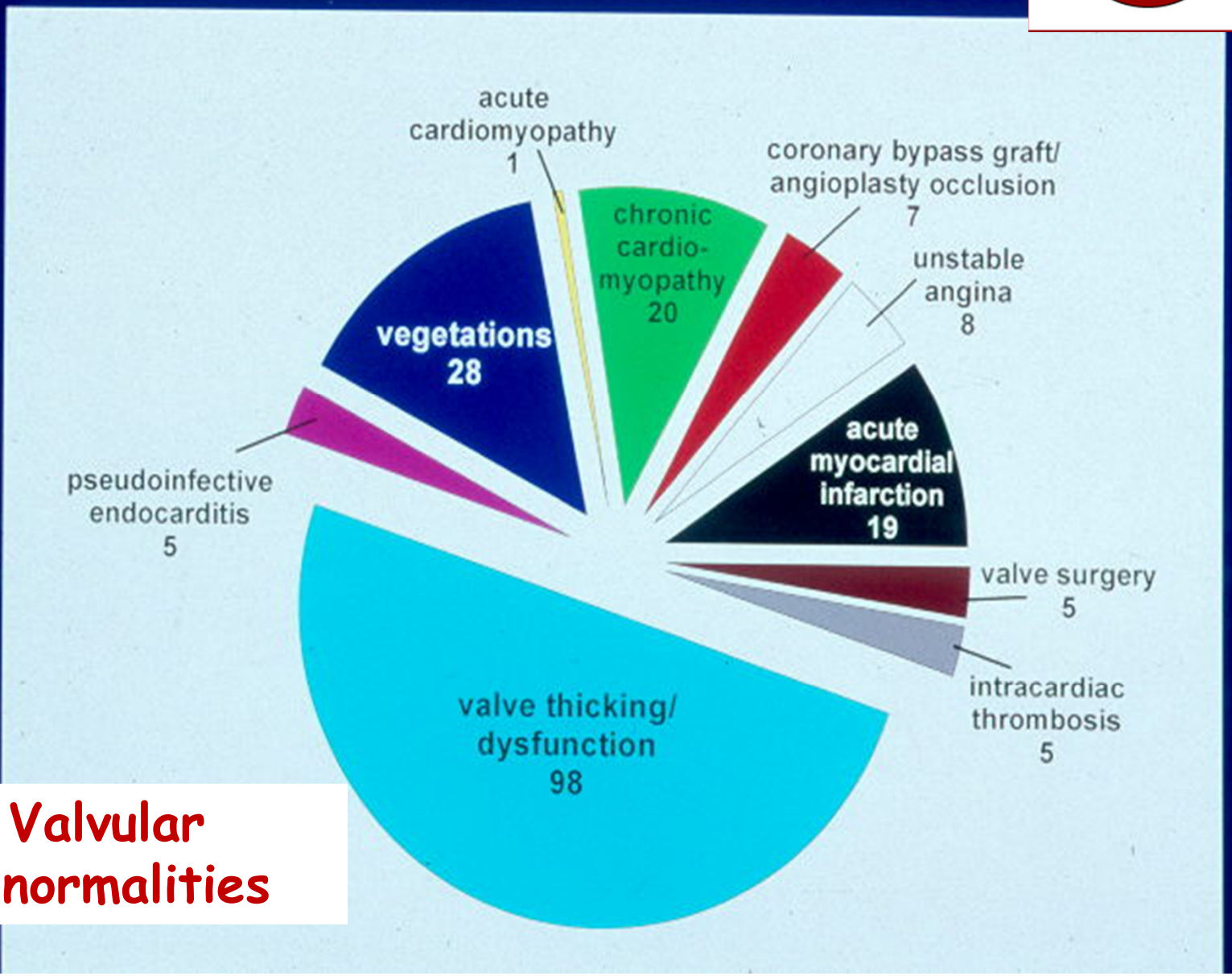
Ljudmila Stojanovich MD PhD[1], Željko Mikovic MD PhD[2], Vesna Mandic MD PhD[2] and Dragana Popovich-Kuzmanovich MD[1]

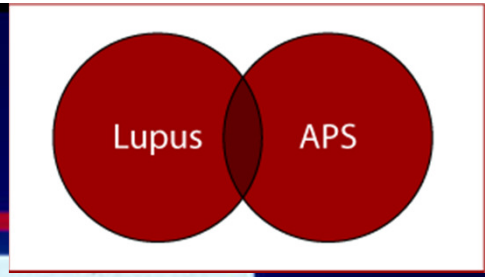
[1]Internal Medicine Department, University Medical Center Bezanijska Kosa, and [2]High Risk Pregnancy Department, Obstetrics/Gynecology University Clinic Narodni Front, Belgrade, Serbia

Key words: antiphospholipid syndrome, neonatal lupus, pregnancy, intravenous immunoglobulin

IMAI 2007;9:555–556

Cardiac Manifestations

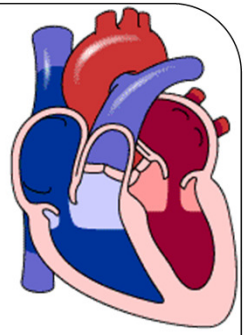




Valvular abnormalities



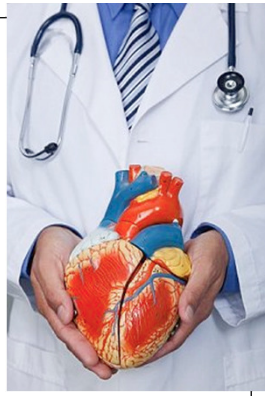
Data considering



- acute myocardial infarction,
- unstable angina,
- coronary artery bypass grafting (CABG)
- percutaneus coronary artery angioplasty (PTCA)
- manifestations of chronic or acute heart failure

Stojanovich L, MD, PhD

Results

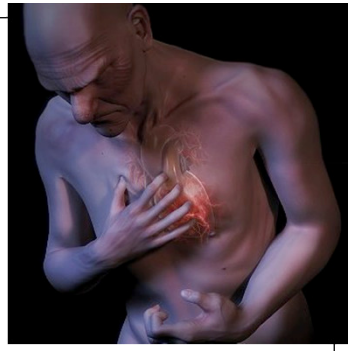


There was no correlation between cardiologycal manifestations and:

- ✓ others clinical manifestations of SLE
- ✓ cardiovascular risk factors (including diabetes)
- ✓ SLE activity (SLEDAI) and other parameters

(p> 0.05)

Results



There was a correlation between:

Patients with aCL – IgM and:

- ***CABG/PTCA (p=0.026)***

coronary artery bypass grafting/ percutaneus coronary artery angioplasty

- **Pseudoinfective endocarditis *(p=0.037)***

- **Pseudoinfective endocarditis *and* Patients without LA *(p=0.014)***

Distribution of pts with PAPS according to aCL-IgG levels

	Negative %	*Low %*	*Medium %*	*High %*	p
Pseudoinfective endocarditis	40.0	60.0	0	0	0.547
Non stable angina	61.9	28.6	9.5	0	0.588
Coronary bypass occlusion	50.0	50.0	0	0	0.312

P> 05

Stojanovich L, MD, PhD



Autoimmunity Reviews 10 (2011) 235–237

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journal homepage: www.elsevier.com/locate/autrev



Review

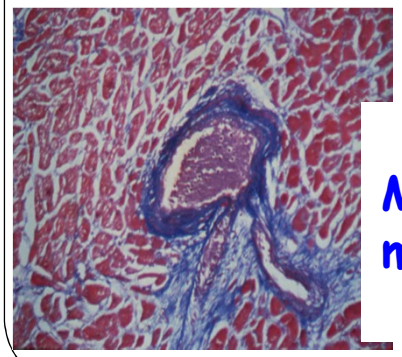
Systemic vascular diseases in the antiphospholipid syndrome. What is the best diagnostic choice?

Jovica Saponjski *,1, Ljudmila Stojanovich 1, A. Djokovic, M. Petkovic, D. Mrda

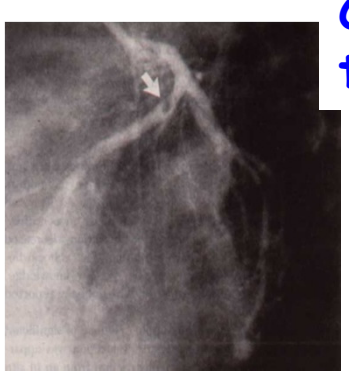
Internal medicine, "Bezanijska Kosa", University Medical Center, Belgrade, Serbia

Diagnostic of vascular manifestations in APS

- Physical examination
- X-ray diagnosis of chest
- Vascular ultrasonography (Doppler)
- Peripheral angiography
- Vascular magnetic resonance imaging/ MRA angiography
- Computed tomographic angiography (CTA) 64-multi slice CT - *whole body angiography can allow us excellent visualization of all major and minor blood vessels*



Myocardial microtrombosis



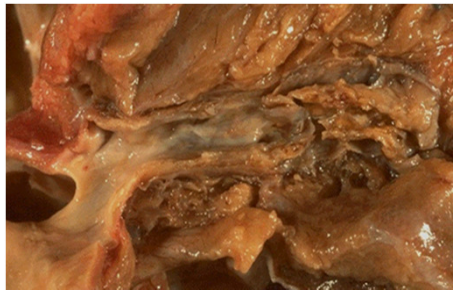
Coronary thrombosis

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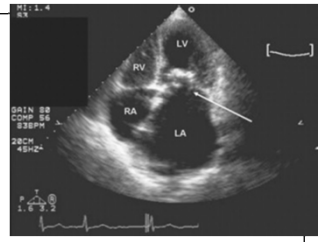
Methodology

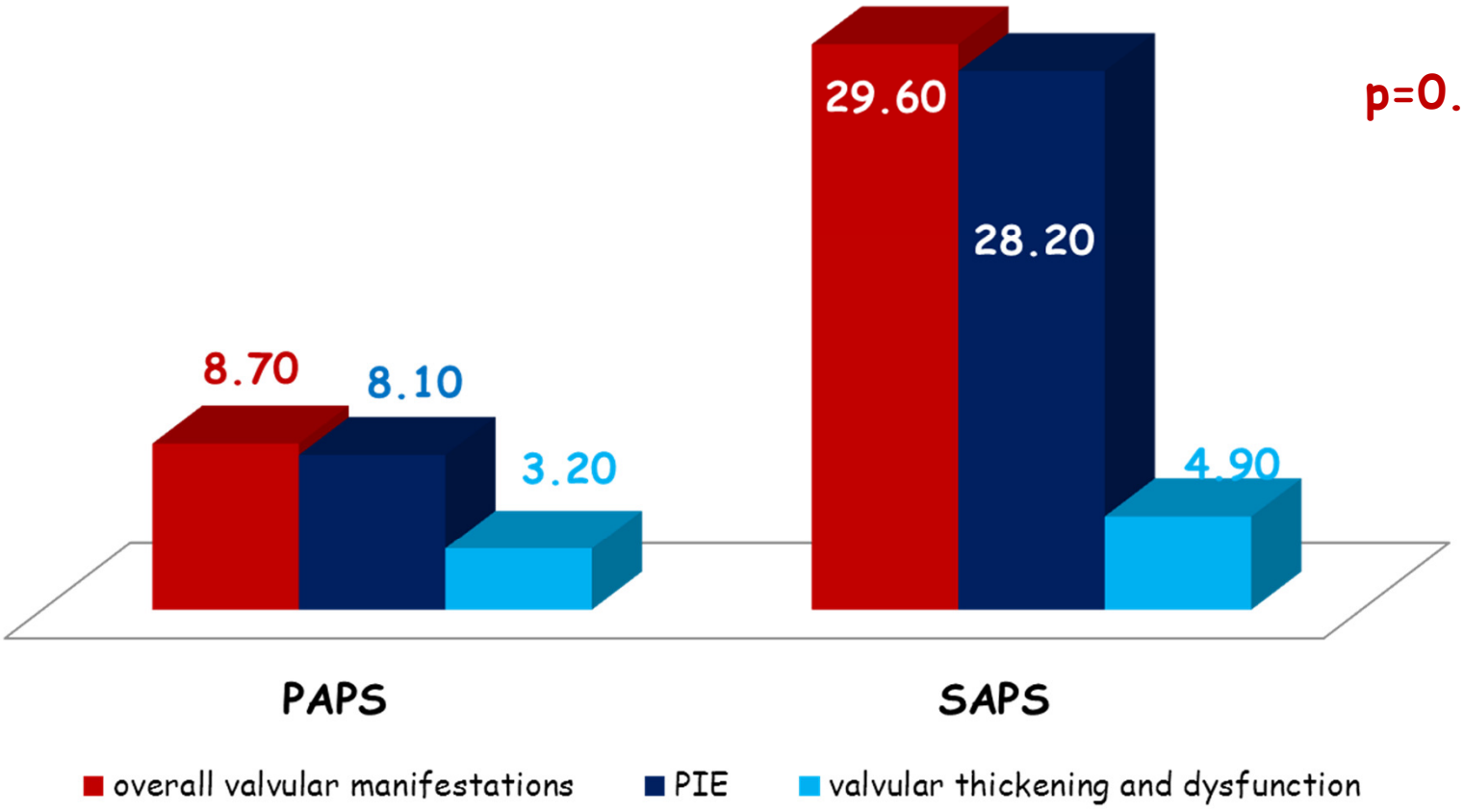
Echocardiography study was performed to reveal the presence of:

- vegetations,
- pseudoinfective endocarditis,
- intracardiac thrombus,
- valve thickening or dysfunction



Prevalence of Valvular Manifestations in %



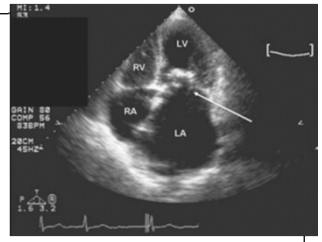


p=0.0001

*PIE – pseudoinfective endocarditis

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Valvular manifestations and aPL type



aCL IgG	Positive	Negative	p
PIE	19.5%	10.1%	0.004
Valvular dysfunction	6.5%	2.0%	0.013
aCL IgM			
PIE	9.1%	2.6%	0.002

*PIE – pseudoinfective endocarditis

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Methodology

Doppler ultrasonography was performed to reveal the evidence on:

- **common carotid artery (CCA), its bifurcation (CCAbiff),**
- **internal carotid artery (ICA) on both sides.**

We defined cIMT values 1.1mm and higher as plaque presence.

Normal cIMT values (carotid intima-media thickness):

Age (years)	*<30*	*30 to 50*	*>50*
Women	<0,50mm	<0,65mm	<0,70mm
Men	<0,55mm	<0,70mm	<0,80mm

cIMT values in PAPS and SAPS patients

	PAPS	SAPS	Overall
CCA right (mm)	0.79±0.24	0.77±0.17	0.79±0.21
CCA left (mm)	0.77±0.18	0.77±0.17	0.77±0.17
CCA biff right (mm)	0.95±0.33	1.03±0.40	0.99±0.36
CCA biff left (mm)	0.95±0.29	1.039±0.51	0.99±0.40
ICA right (mm)	0.85±0.25	0.86±0.24	0.85±0.24
ICA left (mm)	0.84±0.24	0.86±0.33	0.85±0.28

cIMT – carotid intima-media thickness

CCA – common carotid artery

ICA – internal carotid artery

$p>0.05$

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Significance of specific aPL presence in PAPS and SAPS considering MI

Type of APL	PAPS with IM %			SAPS with IM %		
	Negative	Positive	p	Negative	Positive	p
aCL IgG	5.6	13.0	0.094	2.1	4.3	0.500
aCL IgM	10.4	5.9	0.222	2.3	4.7	0.311
$ß_2$GPI IgG	8.2	7.7	0.592	3.8	2.4	0.598
$ß_2$GPI IgM	6.7	9.7	0.335	4.3	2.1	0.484
LA	6.7	9.2	0.385	2.1	4.3	0.500

P> 05

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Significance of specific aPL presence in PAPS and SAPS considering UAP

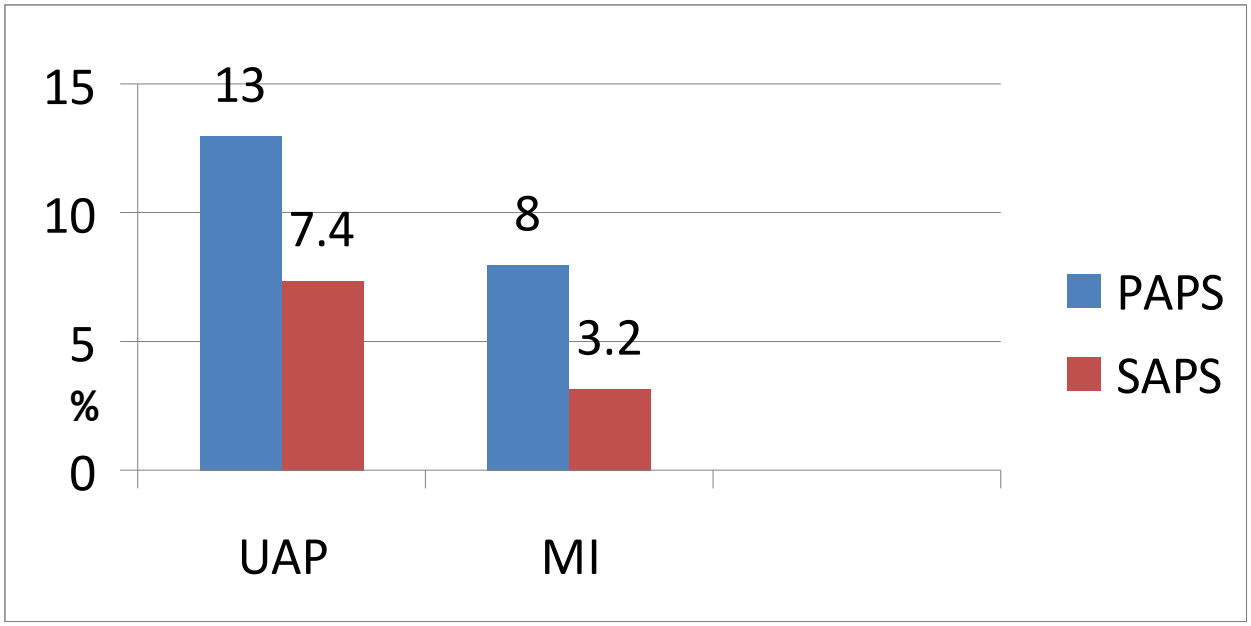
Type of aPL	PAPS with UAP %			SAPS with UAP %		
	Negative	Positive	p	Negative	Positive	p
aCL IgG	12.0	14.8	0.395	6.4	8.5	0.500
aCL IgM	11.7	12.9	0.238	10.0	6.3	0.396
$ß_2$GPI IgG	14.5	9.6	0.272	11.3	0.0	0.107
$ß_2$GPI IgM	13.3	12.5	0.534	10.9	4.2	0.200
LA	14.7	11.5	0.357	8.5	6.4	0.500

P> 05

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Results





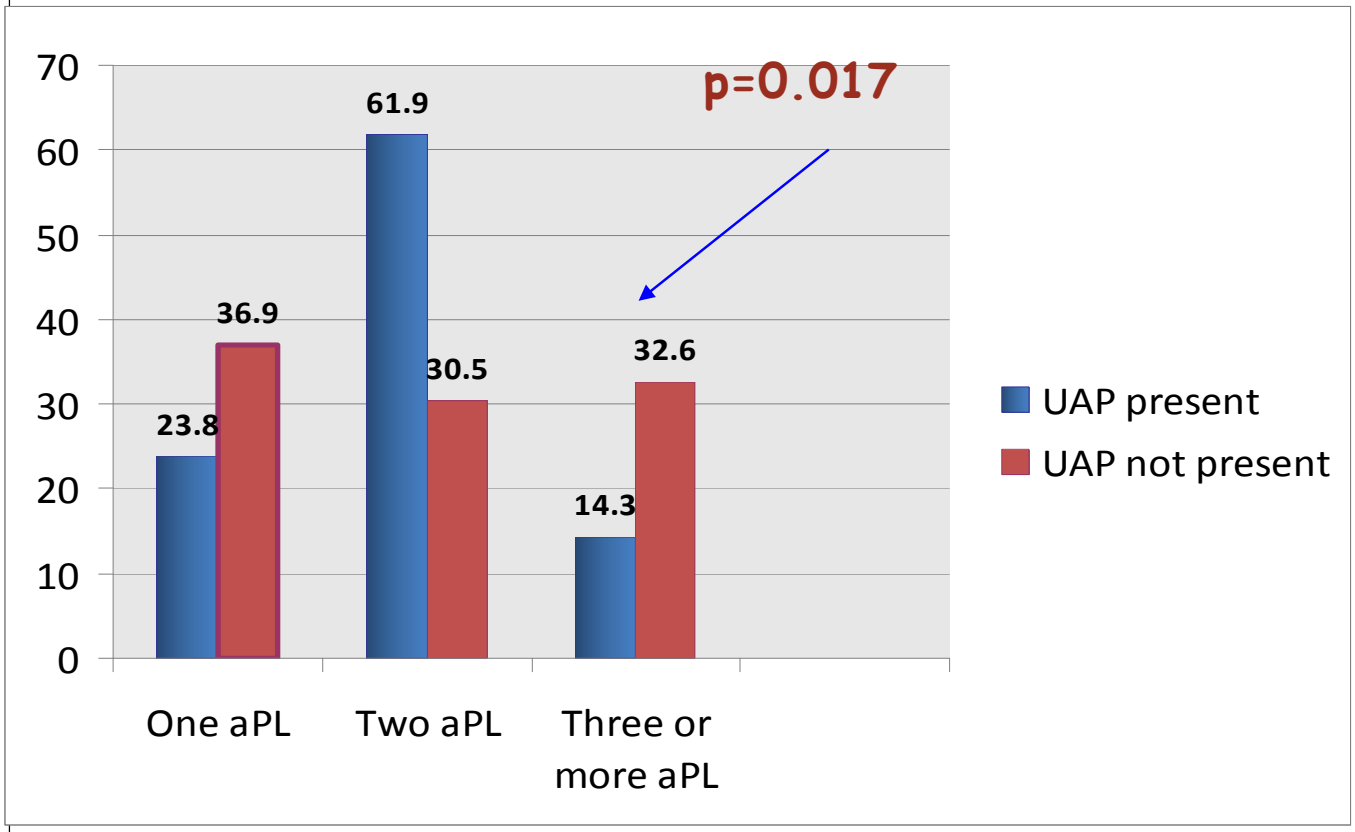
PAPS and SLE patients did not differ among themselves with regard to the occurrence of MI (p = 0,102) and UAP (p = 0.123)

unstable angina pectoris (UAP)

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Distribution of UAP according to number of aPL

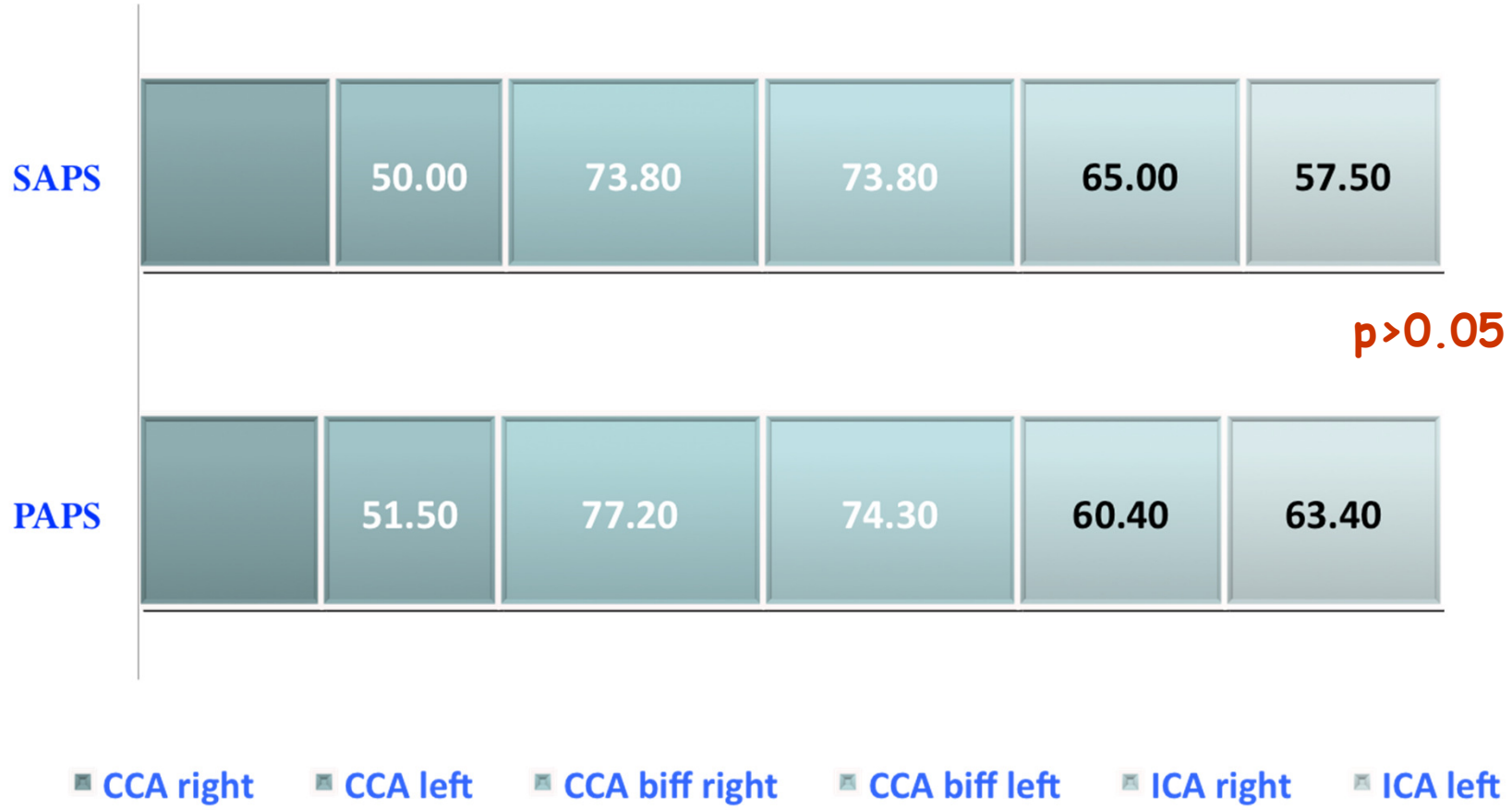




Unstable Angina Pectoris (UAP)

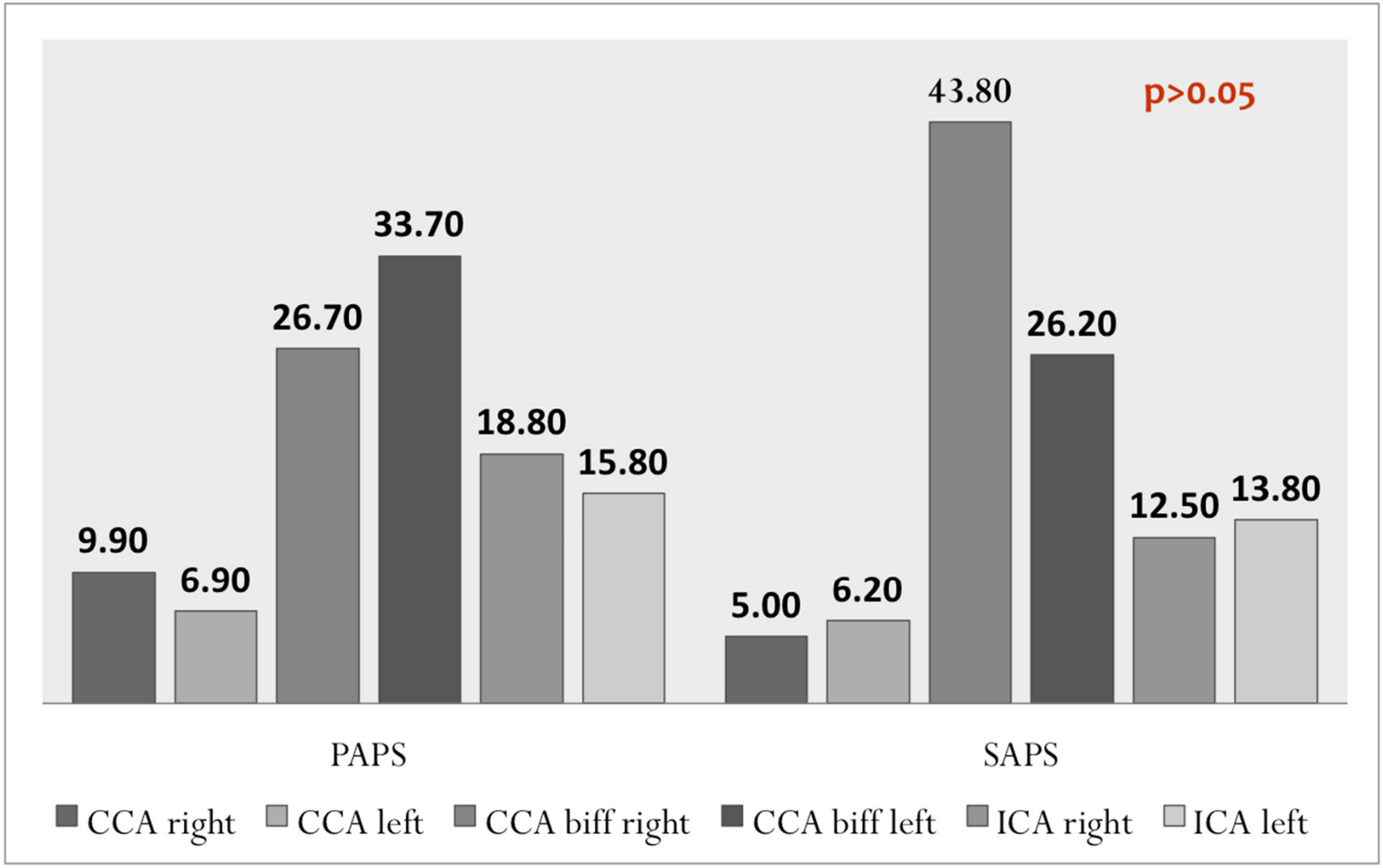
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Prevalence of elevated carotid intima-media thickness (cIMT) values in PAPS and SAPS patients (%)



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Carotid arteries plaque presence in PAPS and SAPS patients (%)



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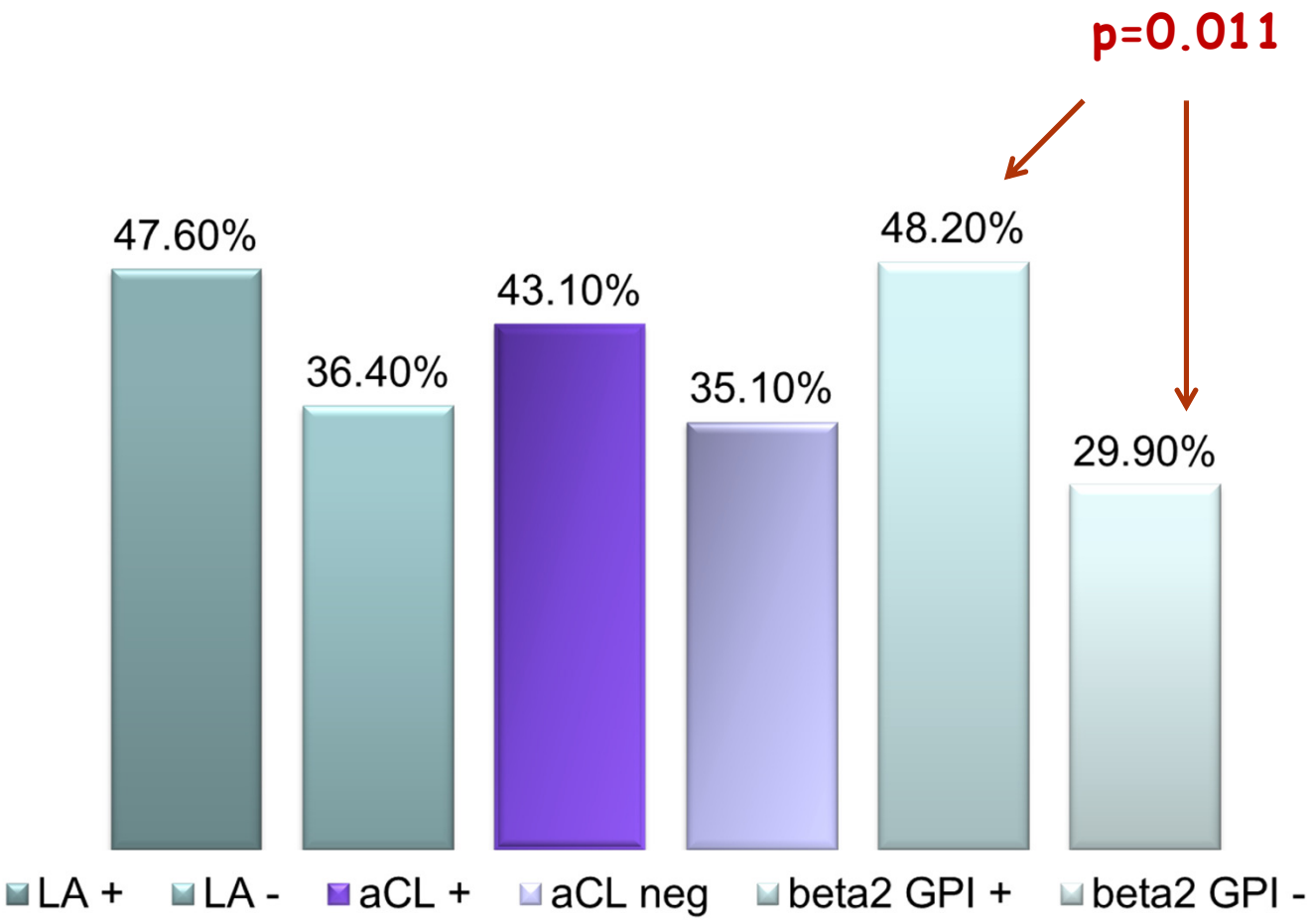
Overall prevalence of elevated carotid intima-media thickness (cIMT) values and carotid arteries plaque presence in PAPS and SAPS patients

	PAPS (%)	SAPS (%)	Overall (%)
Elevated values of cIMT	71.3	68.8	81.8
Carotid arteries plaque presence	37.6	46.2	41.4

$p>0.05$

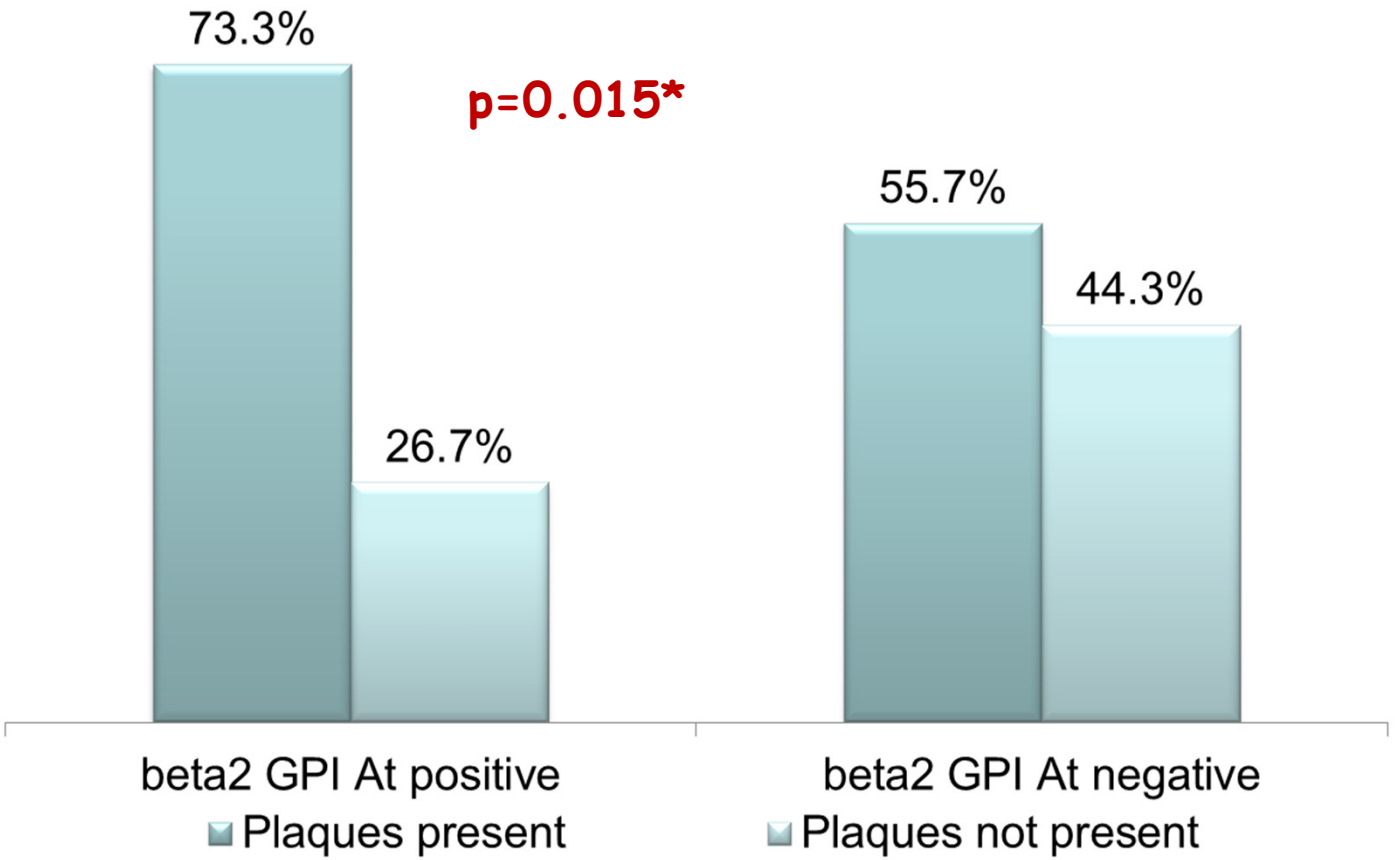
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aPL types and carotid arteries plaque presence



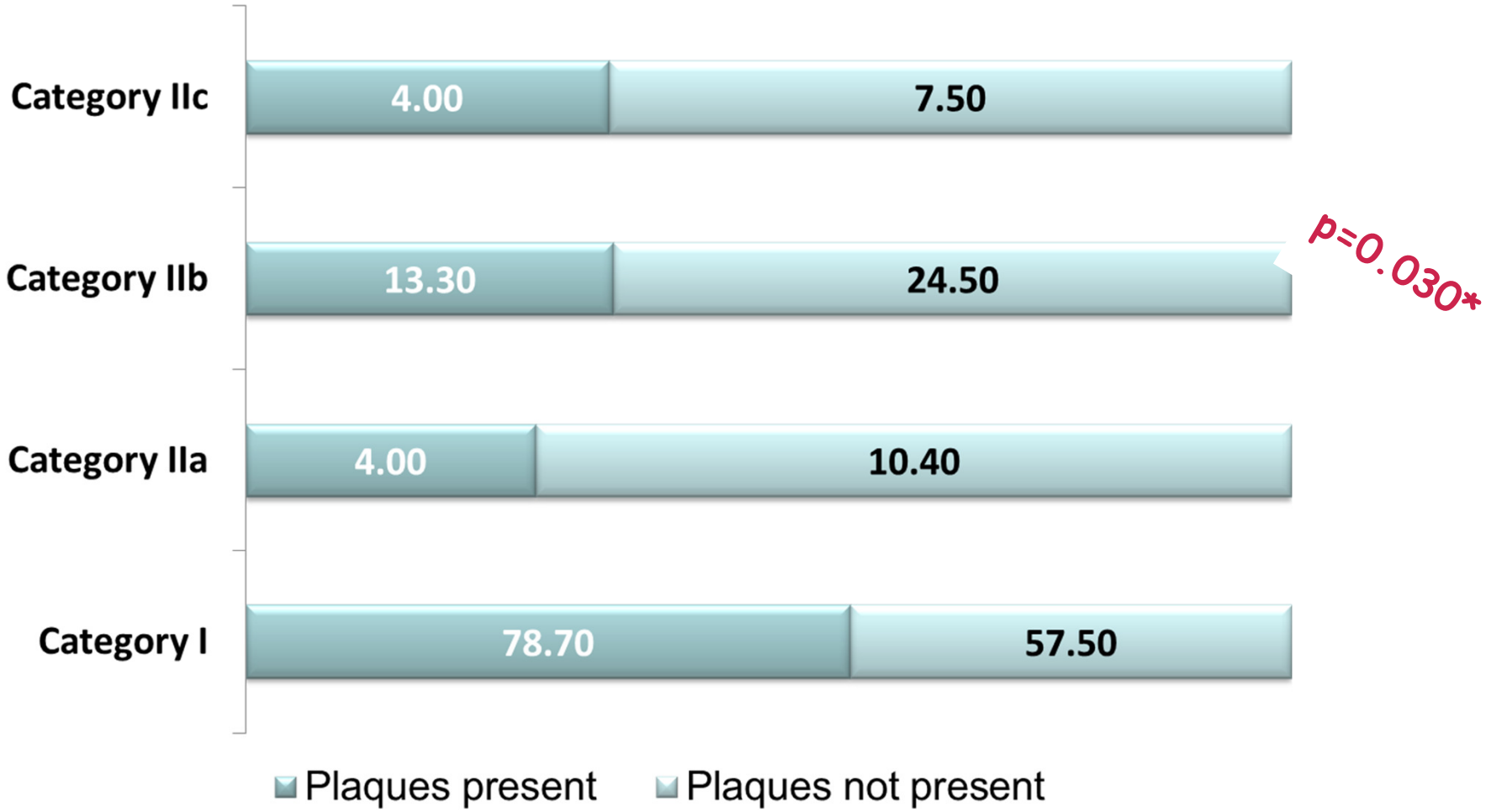
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Overall positivity of aß$_2$GPI and carotid arteries plaque presence in APS patients



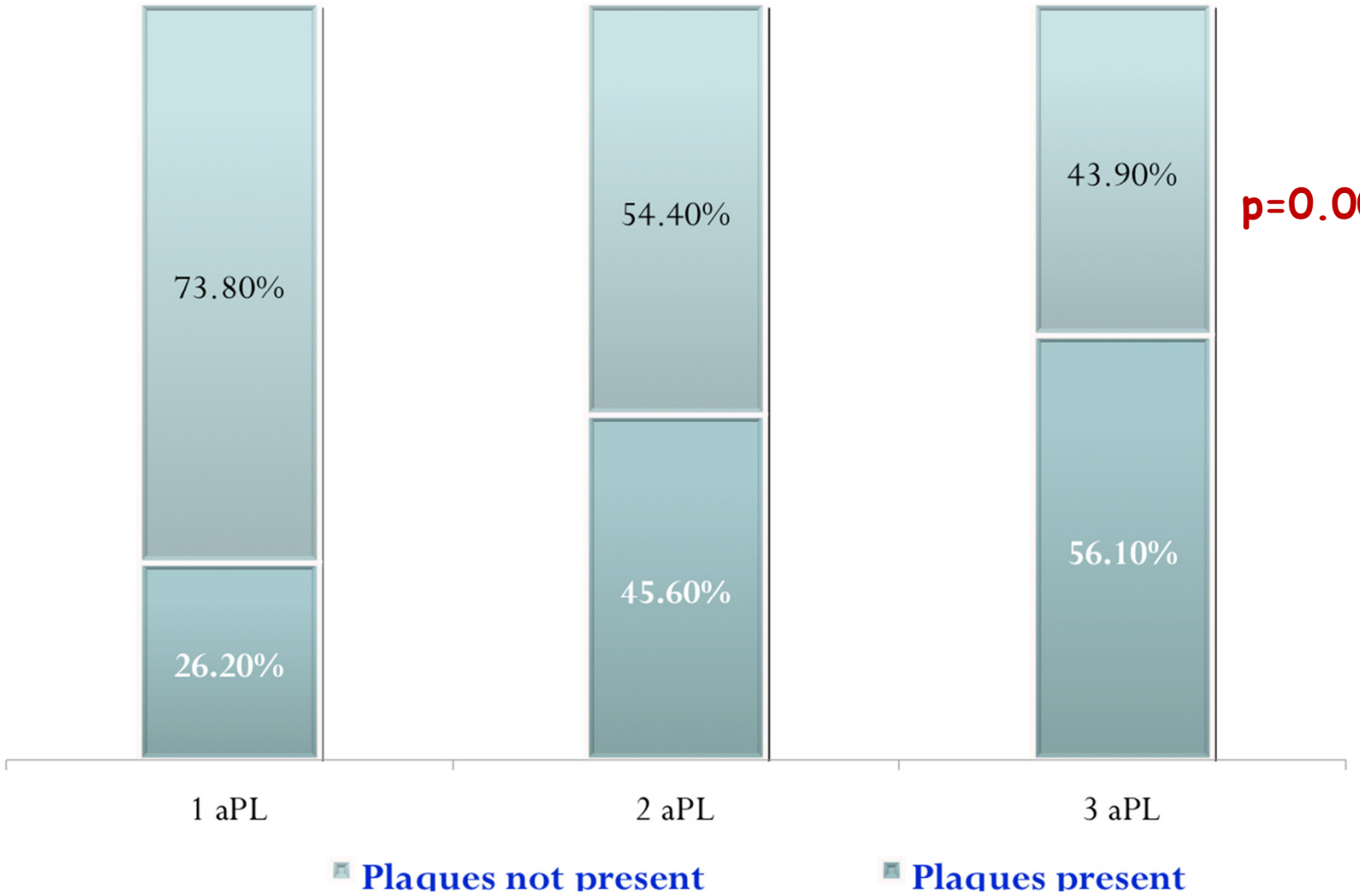
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aPL category and carotid arteries plaque presence in APS patients (%)



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Number of aPL types and carotid arteries plaque presence in APS patients



p=0.007**

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Close association between valvar heart disease and central nervous system manifestations in the antiphospholipid syndrome

I Krause[1], S Lev[2], A Fraser[2], M Blank[1], M Lorber[3], L Stojanovich[4], J Rovensky[5], J Chapman[6] and Y Shoenfeld[1]

[1] Research Centre for Autoimmune Diseases, Sheba Medical Centre, Tel-Hashomer and Sackler Faculty of Medicine, Tel-Aviv University, Israel
[2] Department of Medicine "E", Rabin Medical Centre, Sackler Faculty of Medicine, Tel-Aviv University, Israel
[3] Institute of Allergy, Clinical Immunology and AIDS, Rambam Medical Centre and Rappaport Faculty of Medicine, Technion, Israel
[4] Institute of Rheumatology, University Hospital, Belgrade, Yugoslavia
[5] National Institute of Rheumatic Diseases, Bratislava, Slovak Republic
[6] Department of Neurology, Sheba Medical Centre

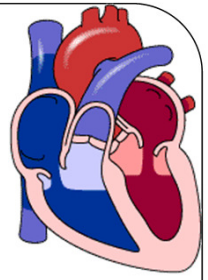
Valvular abnormalities 65%:

- ✓ **Leaflet thickening, regurgitation, stenosis**
- ✓ **Vegetations**

Intracardiac thrombi, pericardial effusion, cardiomyopathy



Association between neurological and cardiac manifestations in PAPS group

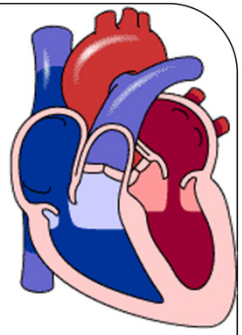


PAPS patients		Transient ischemic attack /N			Epilepsy N			Transient global amnesia /N			Depression N		
		-	+	p	-	+	p	-	+	p	-	+	p
Non stable angina pectoris	-	158	36	0.002*	187	7	0.006*	193	1	0.002*	187	6	0.217
	+	13	11		20	4		22	2		22	2	
Valve vegetations	-	160	40	0.064	193	7	0.001*	198	2	0.285	15	3	0.002*
	+	11	7		14	4		17	1		194	5	

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Association between neurological and cardiac manifestations in SAPS group

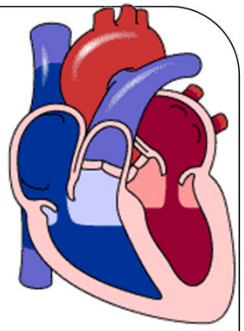


SAPS patients		Transient ischemic attack (N)			Acute ischemic encephalopathy (N)		
		not present	present	p	not present	present	p
Non stable angina pectoris (N)	not present	80	24	0.004	102	2	0.000
	present	4	7		8	3	

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Analysis of localization of thrombosis and age



Age was a significant risk factor for:

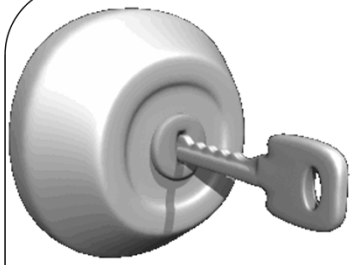
- CVI: 51.92 and 41.97 years, respectively p=0.001
- MI: 56.6 and 43.6 years, respectively p=0.0001

Take-home messages



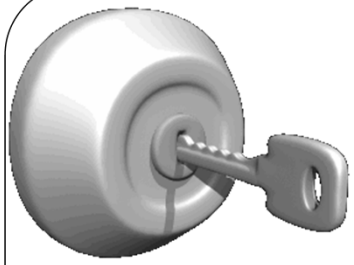
- ✓ APS patients can be presented with a wide variety of cardiac manifestations.
- ✓ The certain aPL type and level correlated with cardiac APS manifestations, suggesting their predictive or protective role.
- ✓ Our study confirmed that presence of cardiac manifestations may be a risk factor for several types of CNS involvement in APS.

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Take-home messages

- ✓ The Serbian National APS Registry allowed us to ascertain a significantly increased incidence of endocarditis development in APS patients with aCL-IgM.
- ✓ Presence of LA was significantly connected to lower incidence of pseudoinfective endocarditis.
- • Presence of aβ_2GPI positivity brought higher atherosclerotic risk in our study group.



Take-home messages

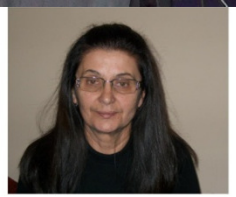
- Presence of more than one aPL in APS patients additionally accelerate atherosclerotic continuum.
- Besides glucocorticoid therapy in SLE pts there was no significant difference between SAPS and PAPS patients regarding the extent of atherosclerosis.
- In this subgroup of APS patients more aggressive approach towards prevention and control of standard atherosclerotic risk factors is crucial.

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Acknowledgements

With grateful thanks to my colleagues





















PreHT, HT & CMS 2016

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www.prehypertension.org





With love and respect, and hoping to welcome you in Belgrade very soon



Thanks' for your kind attention!!!!!!



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