MANIFESTAZIONI CARDIOVASCOLARI E METABOLICHE IN REUMATOLOGIA

TORINO, 4-5 aprile 2014

Sindrome Antifosfolipidi

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I. E. nata 20-8-65

Dicembre 1983 (18 a)
Poliartralgie con artrite alle mani
Segno di vasculite a mani e piedi
Corticosteridi x 7 gg con beneficio

Aprile 1984 (19 a)
Diagnosi di RAA
Borsite poplitea Dx
Tromboflebite Sin
Corticosteroidi x 7 gg con beneficio

Luglio 84 dopo esposizione al sole
Eritema malare, lesioni mucocutanee estese
Febbre e astenia
Nausea, vomito
Mialgie con CPK 1120, LDH 1170
Creatinina 1.5, azotemia 59, proteinuria 500mg/24h
GB 2000, Hb 10, PP 117000
ANA, anti ds-DNA positivi alto titolo
CH50 indosabile
Anti ENA pos (PCNA)
Anticardiolipina negativi

3 boli 800 mg metiprednisolone seguito da prednisone 60 mg /die (in progressiva riduzione dopo 3 mesi) e azatioprina.

I. E. nata 20-8-65

1987 sospende azatioprina x gastralgie
Viene introdotta idrossiclorochina
(con prednisone attorno a 7.5 mg/die)

1989 sospede Idrossiclorochina x scarsa compliance
1990 viene sospeso definitivamente il prednisone

1994 ripresa di lesioni mucocutanee e di poliartralgie
Anti ds-DNA positivi
CH50 C3 e C4 ridotti
Anti ENA PCNA
aCL negativi
GB 3130 PP 125000
Creatinina 0.8

Prednisone 15 mg/dì, Azatioprina, Plaquenil, Carioaspirin

1996 sospende il prednisone

tra gli esami di controllo
LA positivo
aCL e anti Beta2GPI negativi

1998 sospende idrossiclorochina
(CV apparentemente alterato)

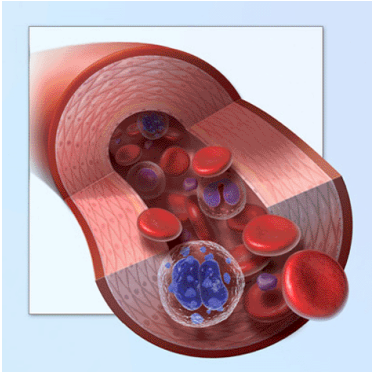
Riduce e sospende progressivamente i trattamenti
Da 2010 nessun farmaco

Nel Gennaio 2012:
IgG aCL pos
IgG anti Beta2 pos
LAC pos

I. E. nata 20-8-65

Nel Gennaio 2012
IgG aCL pos
IgG anti Beta2 pos
LAC pos

Novembre 2012
Asportazione mioma uterino in laparoscopia
Dopo 2 settimane comparsa di dolore toracico con febbricola e profonda astenia.
Varie terapie antibiotiche senza successo



Gennaio 2013 ritorna presso il nostro centro:

- Trombosi venosa profonda arto inf. Dx (v. femorale sup., v. poplitea, vv tibiali posteriori, v femorale comune, v. femorale profonda);
- trombosi vena giugulare int.sin;
- embolia polmonare segmentaria e subsegmentaria (lingula e segmento basale laterale lobo inf. Dx);
- infarto polmonare del segmento basale laterale del lobo inferiore dx.

R.I. nata 21-9-64

1995 ci consulta dopo una gravidanza complicata da preeclampsia a 28 settimane esitata nella nascita di un bimbo di 850 g morto in seconda giornata.

Riferisce disturbi visivi nei giorni che precedono il ciclo mestruale e spiccata fotosensibilità; nulla di oggettivo PAO normalizzata.
ANA pos (basso titolo)
IgG aCL pos
IgG anti Beta2 pos
LAC pos

1996 prima gravidanza in LDA e basse dosi di corticosteroidi, non complicata.
TC a 38.3 settimane per PROM. Bimbo di 3100.

1998 accusa qualche giramento di testa e rari episodi di diplopia.
Idrossiclorochina e LDA.

Nel 1999 seconda gravidanza in LDA, basse dosi di corticosteroidi e idrossiclorochina (sospesa a 17 settimane per prurito). A 36settimane (**28-1-2000**) TC per rialzo pressorio. Bimba 2510, senza problemi.

R.I. nata 21-9-64

4-2-2000

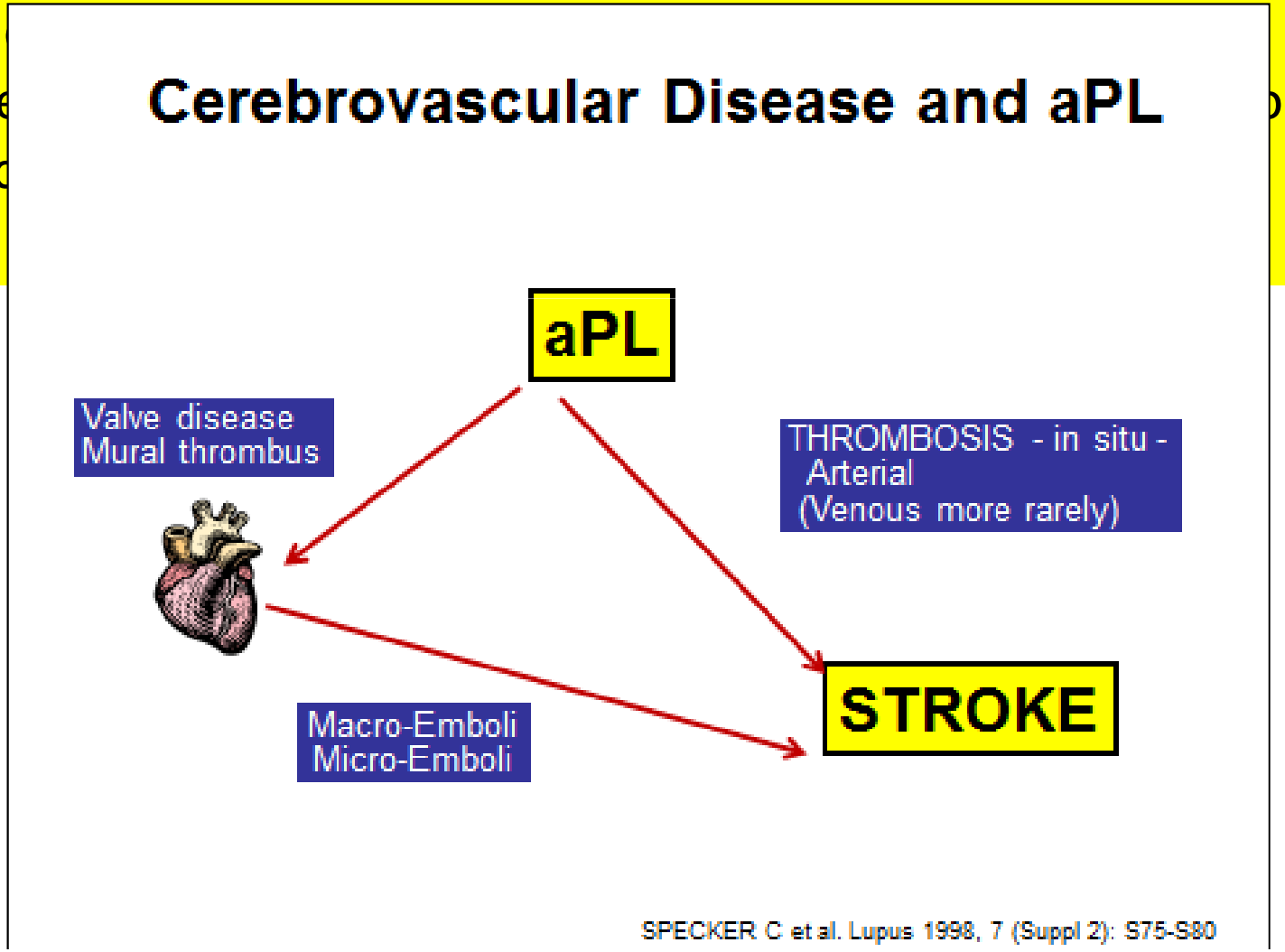
Disartria, alessia, emiparesi dx. PAO 140-100.

Al mom

TAC cere o del

nucleo c

sinistra.



ESTIMATED OVERALL PREVALENCE OF aPL IN PATIENTS WITH THROMBOEMBOLIC DISORDERS AND PREGNANCY LOSS

	aPL Confirmation (-) (Mean, Median, Range)	aPL Confirmation (+) (Mean, Median, Range)	Average (Median)
PREGNANCY LOSS (n=59)	12, 9 (0-48) (n=50)	14, 14 (0-25) (n=9)	12%
STROKE/TIA (n=48)	23, 21 (0-49) (n=38)	10, 6 (0-53) (n=10)	14%
MYOCARDIAL INFARCTION/ANGINA (n=20)	14, 8 (3-39) (n=16)	17, 17 (14-21) (n=4)	13%
DEEP VENOUS THROMBOSIS & THROMBOEMBOLISM (n=27)	14, 11 (0-35) (n=20)	10, 9 (5-19) (n=7)	10%

APS | ACTION
ANTIPHOSPHOLIPID SYNDROME
ALLIANCE FOR CLINICAL TRIALS
& INTERNATIONAL NETWORKING

Andreoli L. Chighizola C et alArthritis Care & Research
Vol. 65, No. 11, November 2013, pp 1869–1873

The cardiac involvement in APS

- Heart valve lesions
- Coronary heart disease
- Cardiac thromboembolism

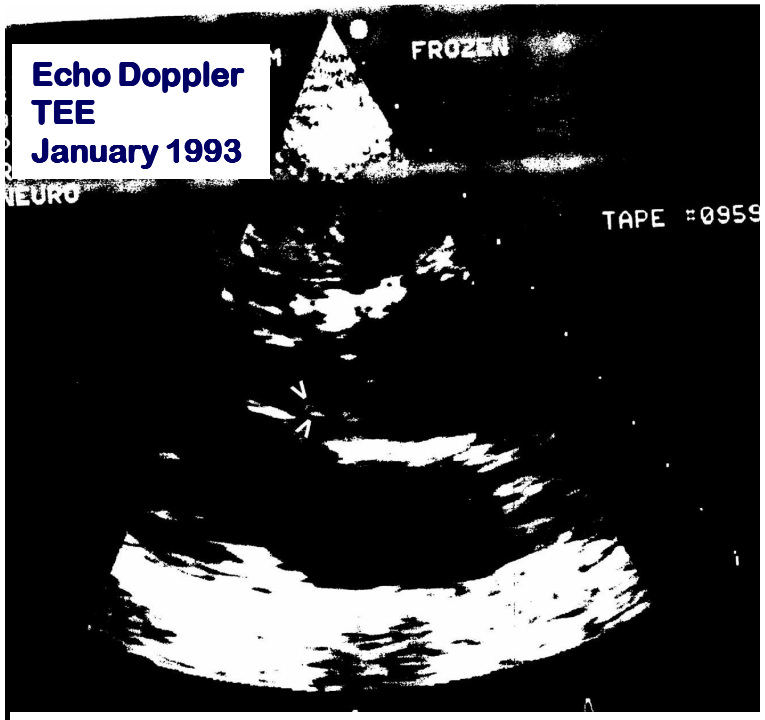
LF N, 30 years old housewife in 1992

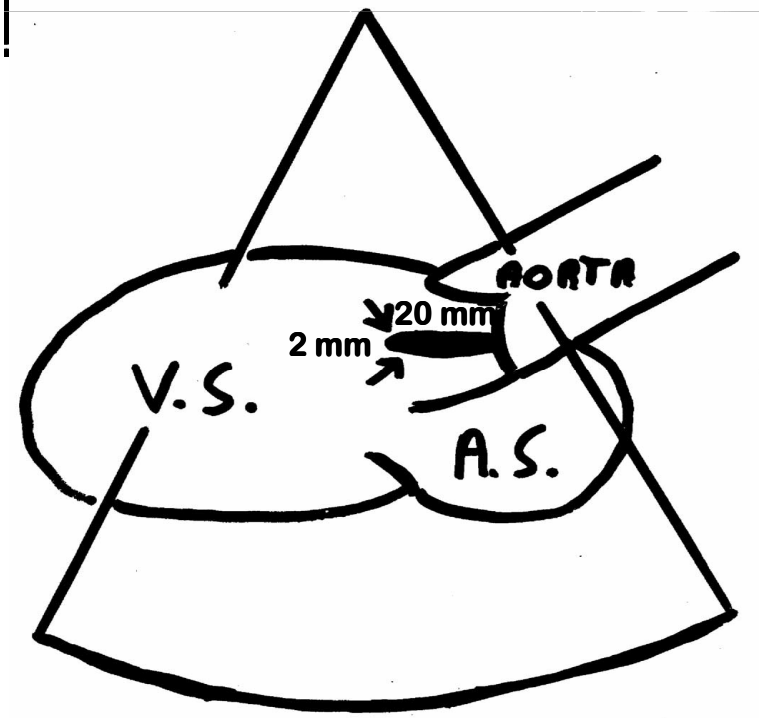
Referred because of persistent headache, dizziness, transient amaurosis episode and paresthesias, in the presence of aPL (LA and IgG aCL).

In her recent hystory, a cesarean section at 30 weeks of gestation, because of severe preeclampsia. The baby died (7th day) because of important IUGR.

No particular problems in the past.
In 1986 an uncomplicated pregnancy.
No symptoms or serological signs of SLE.

The patient was started with coumadin. The vegetation was found first reduced and than (May 1993) completely absent.



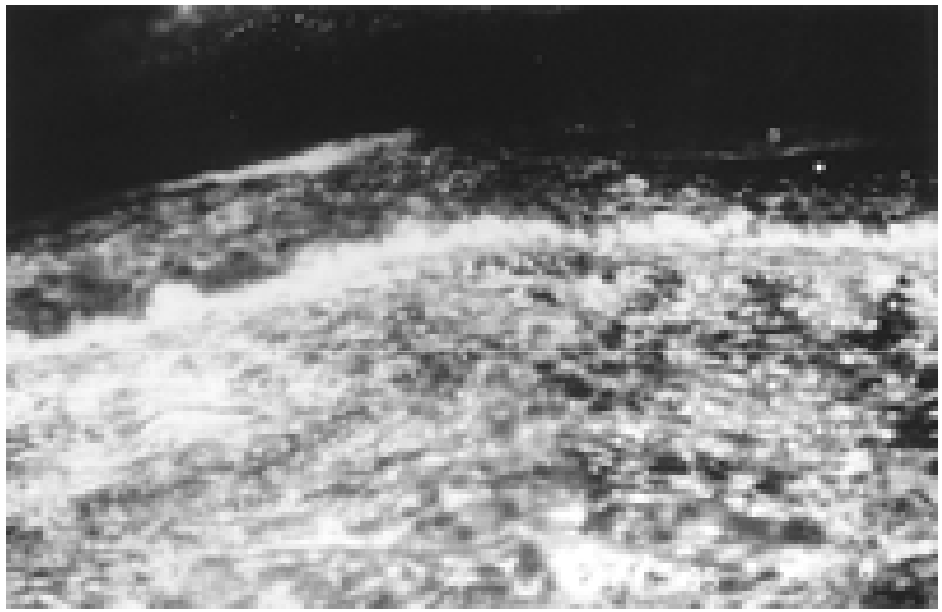


Pathogenesis of valves abnormalities in APS

Histopathology

Superficial or intravalvular fibrin deposition and subsequent organization: vascular proliferation, fibroblast influx, fibrosis and calcification

..inflammatory changes..



From Hojnik M et al,
Circulation 1996;93:1579-1587

Immunofluorescence or immunohistochemistry

Linear deposition of IgG (identified as aCL) at subendothelial level along the surphace of leaflets and cuspis.
C1q, C3c, and C4 are shown in the same shape but more granular suggesting immunecomplexes deposition (probably "planted" antigens).

→ **Thickening, fusion, rigidity** → **Loss of function**

Valves abnormalities in APS

Definition

Thickening of the leaflets with irregular nodular excrescences on the atrial face of the mitral valve and/or the vascular face of the aortic valve, often producing regurgitation, and varying from minimal thickening to severe valve distortion and dysfunction requiring surgical replacement.

Ziporen L, et al Lupus 1996;5: 196-205.

Clinical association

Arterial thombotic events.
Atherosclerosis risk factors
Livaedo
Migrain

Pardos-Gea J, et al, Lupus 2010, 19: 575-582

Prevalence of valvular involvements in Primary APS

1000 pts with APS

Not really different in primary or secondanry APS.

- ✓11.6 % as clinical record
- ✓6.6 % appered in 10 years follow-up

Cervera R, et al ARD 2014

89 pts with primary APS investigated by TTE
(not hemodynamically significant; no surgical indication)

69% as prevalence study

BS-Spedali Civili 1984-2002

Valves abnormalities in APS
long term evolution

53 patients (1986-2007); transthoracic echocardiogram.

Initial echo	*Patients, n (%)* n = *53*
Valvulopathy[b]	29 (54)
Regurgitation	11 (20)
Mitral	6 (11)
Aortic	2 (3)
Tricuspid	1 (2)
Mitral + Aortic	2 (3)
Mild	9 (17)
Moderate	1 (2)
Severe	1 (2)
Stenosis	—
Thickening	25 (47)
Vegetation	4 (7)
No valvulopathy	24 (45)

No valvulopathy	2 (3)
Valvulopathy	27 (51)
Regurgitation	18 (34)[c]
Mitral	9 (17)
Aortic	3 (5)
Tricuspid	2 (3)
Mitral + Aortic	4 (7)
Mild	6 (11)
Moderate	10 (18)[d]
Severe	2 (3)
Stenosis	2 (3)
Thickening	24 (45)
Vegetation	3 (5)

No valvulopathy	22 (41)
Valvulopathy	2 (3)
Regurgitation	2 (3)
Mitral	2 (3)
Aortic	—
Tricuspid	—
Mitral + Aortic	—
Mild	2 (3)
Moderate	—
Severe	—
Stenosis	—
Thickening	2 (3)
Vegetations	—

Pardos-Gea J, et al, Lupus 2010, 19: 575-582

The cardiac involvement in APS

- Heart valve lesions
- Coronary heart disease
- Cardiac thromboembolism

International consensus statement on an update of the preliminary classification criteria of the antiphospholipid syndrome

Clinical criteria

1. Vascular thrombosis

One or more clinical episodes of arterial, venous, or small vessel thrombosis, in any tissue or organ. Thrombosis must be confirmed by imaging or Doppler studies or hystopathology, with the exception of superficial venous thrombosis. For hystopathologic confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall.

2. Pregnancy morbidity

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 Hemostasis (Scientific Subcommittee on LAs/phospholipid-dependent antibodies) .
2. Anticardiolipin (aCL) antibody of IgG and/or IgM isotype in serum or plasma, present in medium or high titer (i.e. >40 GPL or MPL, or >the 99th percentile), on

CAD fulfills the thrombosis criterion for APS.

Because hypertension, smoking, dyslipidemia, diabetes, and obesity are more prevalent than aPL (Cooper et al, 2000) and account for more than 90% of the overall risk for MI worldwide (Yusuf et al the Inter heart Study, 2004), the committee advises that patient populations be stratified according to known risk factors and aPL.

Myakis et al *J Thromb Haemost* 2006;4:295-306

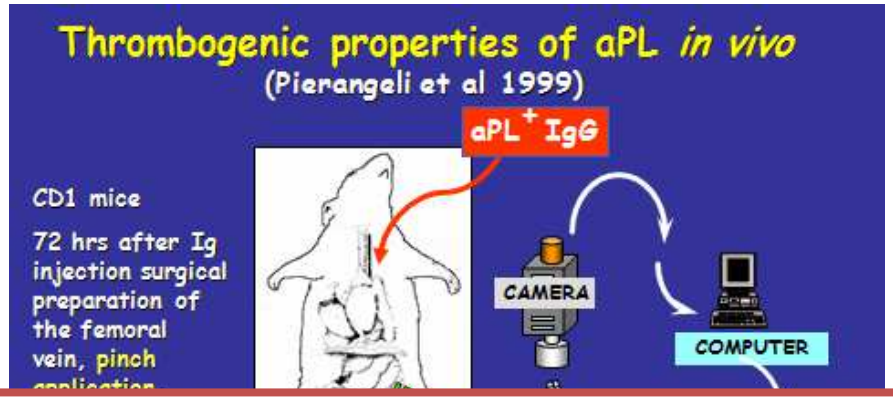
aPL = fattori di rischio

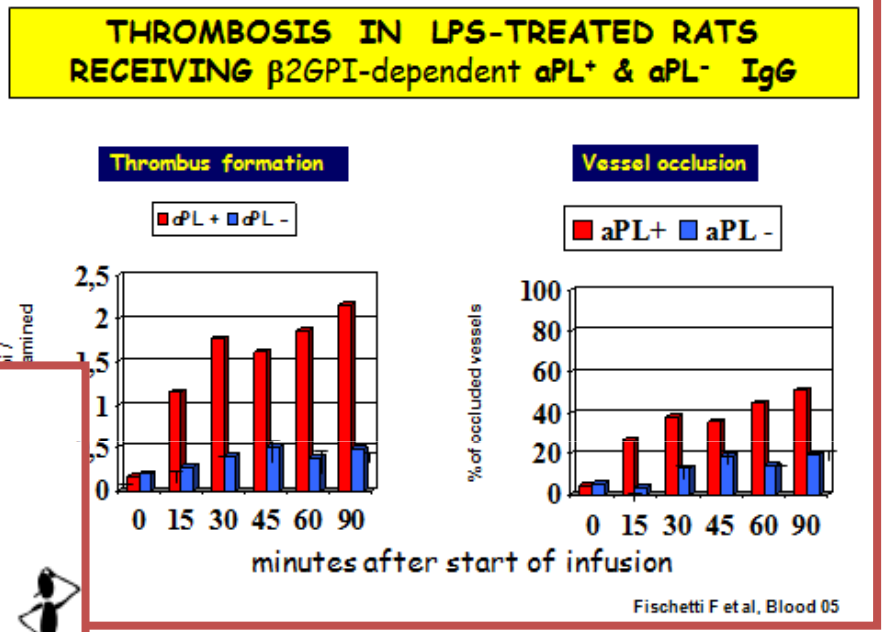
Non tutti i pazienti con aPL hanno CVD

Molti soggetti con DVD non hanno aPL

Andreoli L, Tincani A. Beyond the “Syndrome”: Antiphospholipid antibodies as risk factors. Arthritis Rheum 2012; 64:342-5.

ANIIMAL MODELS of THROMBOSIS





ANTIPHOSPHOLIPID SYNDROME:
thrombophilic condition:
the "*second hit*" hypothesis

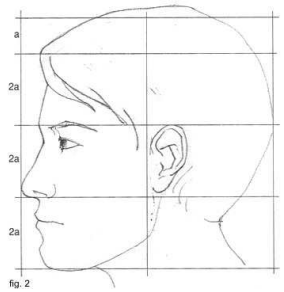
MICE and **MEN**

- Pinch on the femoral vein
- Lipopolysaccharide

- pregnancy
- puerperium
- Infections
- oral contraceptives
- hormone therapy
- hypertension
- smoke

Come si fa a sapere il peso degli aPL nel danno CV ???????????

ANTIPHOSPHOLIPID ANTIBODY PROFILE



	Anti-cardiolipin antibody	Anti-B2GPI Antibody	Lupus Anticoagulant
Isotype	IgG, IgM (IgA)	IgG, IgM (IgA)	/
Titre	>40 GPL/MPL	low, medium, high	?+/-
Iterpretation of isolated positivity	+	++	+++

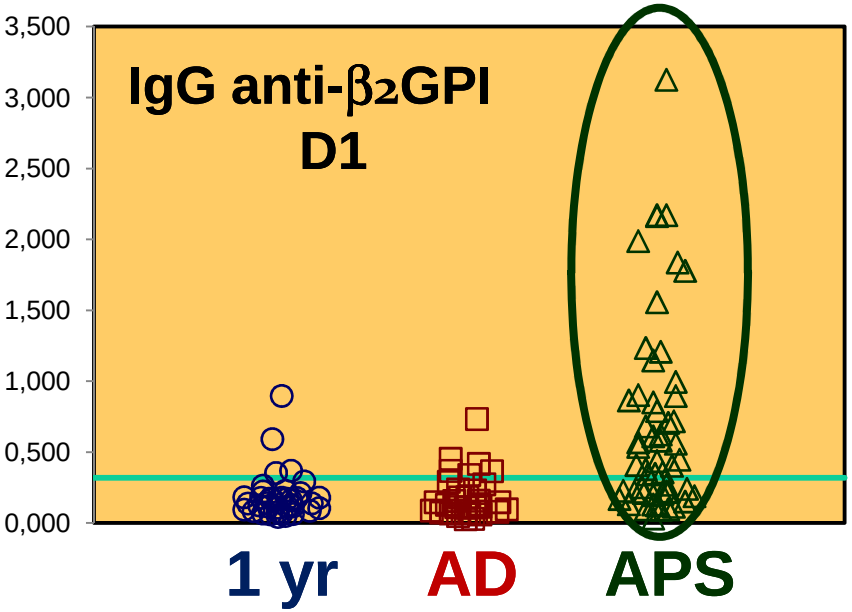
Le caratteristiche del ***profilo ad alto rischio*** sono state definite come:

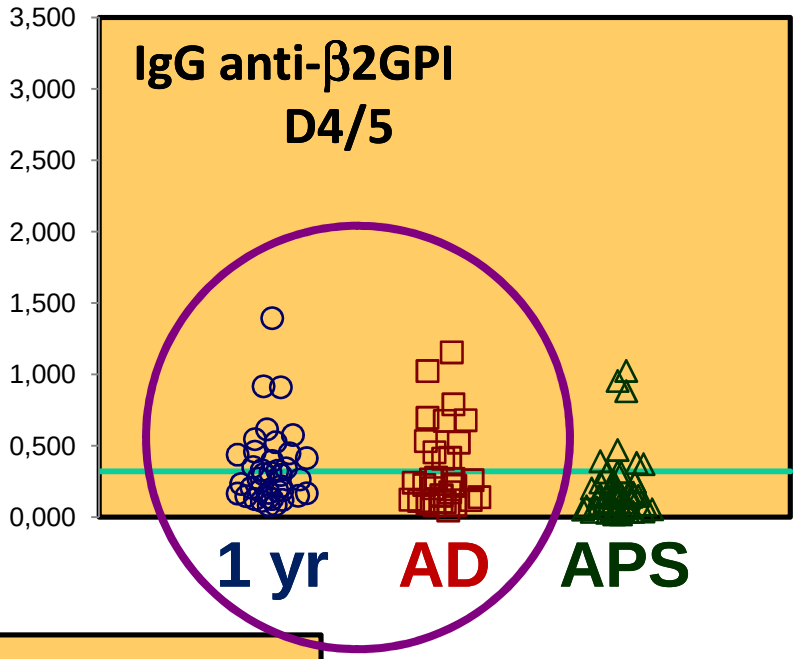
1) positività del LA considerato il maggior predittore indipendente delle manifestazioni cliniche di APS;

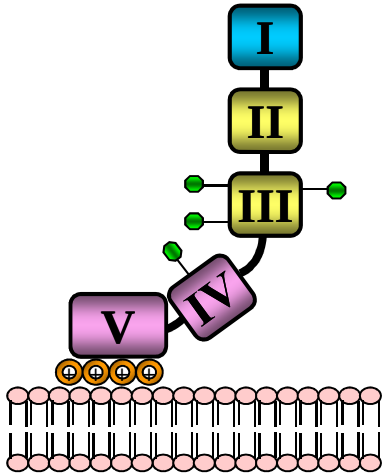
2) nell'ambito del test immunometrici (aCL e anti-B2GPI), titoli elevati e isotipo IgG sono associati a un rischio maggiore rispetto a bassi titoli e a isotipo IgM;

3) la triplice positività è associata ad un rischio maggiore rispetto alla positività singola o a quella di due test soltanto;

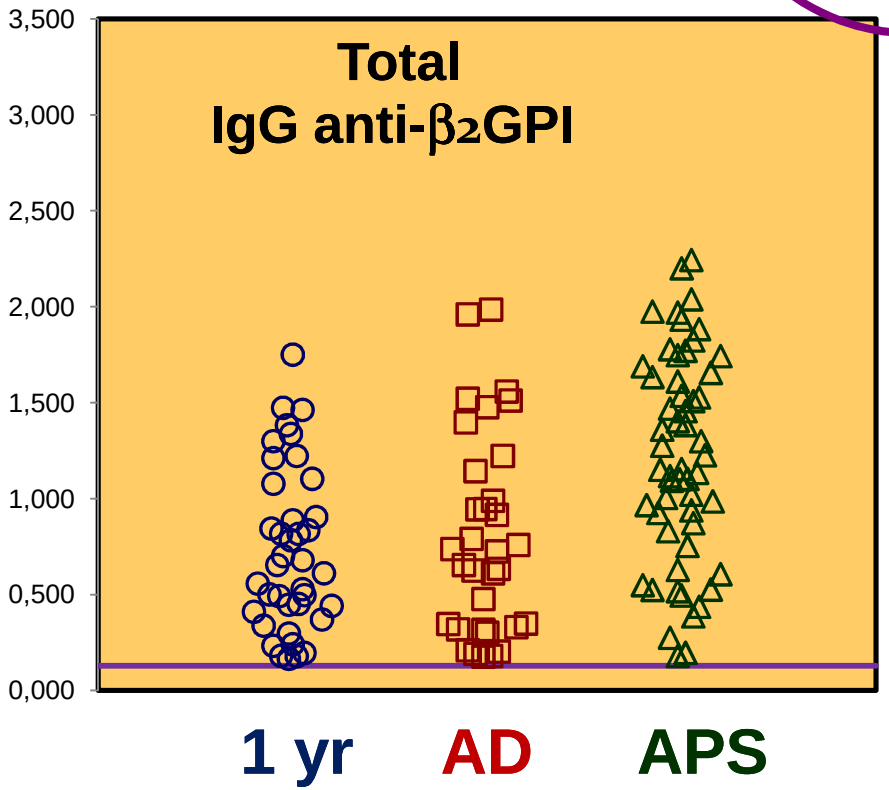
4) la persistenza è una caratteristica fondamentale degli aPL "autoimmuni" legati allo sviluppo di patologia, mentre valori positivi transitori sono comuni durante le infezioni.





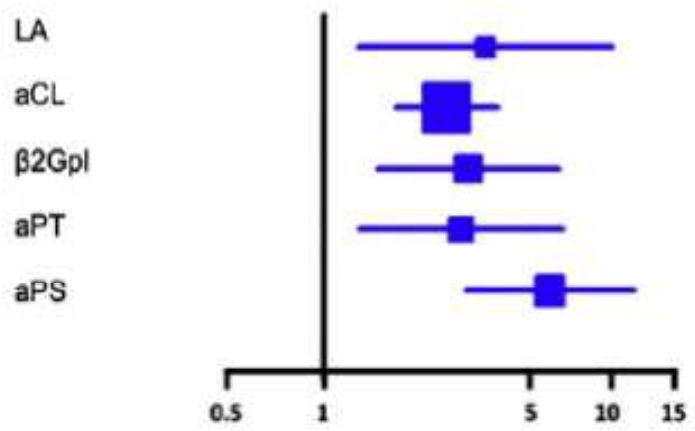


Modified from Miyakis S, Thromb Res 2004; 114:335-46



Andreoli L et al., Ann Rheum Dis. 2011 Feb;70(2):380-3.

Risk of arterial thrombosis according to type of antiphospholipid antibodies in adults without systemic lupus erythematosus: A systematic review and meta-analysis



	OR [95%CI]	No. studies	No. patients	p ass.	p het.
LA	3.58 [1.29; 9.92]	8	3760	0.01	Random
aCL	2.65 [1.75; 4.00]	17	8289	<0.001	Random
β2GpI	3.12 [1.51; 6.44]	3	1671	0.002	0.44
aPT	2.95 [1.31; 6.66]	2	1327	0.009	0.27
aPS	6.00 [3.07; 11.7]	2	1331	<0.001	0.47

aCL: anti-cardiolipin, aPE: anti-phosphatidyl ethanolamine, aPS: anti-phosphatidyl serine, aPT: anti-prothrombin, LA: lupus anticoagulant, No.: number of, OR (95%CI): odds ratio and 95% confidence interval, p ass: p-value for association, p het: p-value for heterogeneity, β2GpI: anti-β2 Glycoprotein I

Q. Reynaud et al. / Autoimmunity Reviews 13 (2014) 595–608

Contrasting data have been reported on the association between the presence of anti-phospholipid antibodies and arterial thrombotic events, particularly those in coronary arteries.

This discrepancy is perhaps related to the confounding effect of traditional risk factors.

APL and arterial events.

The confounding role of comorbidities

Anti-beta 2 glycoprotein I antibodies and the risk of myocardial infarction in young premenopausal women

172 cases hospitalized for … 45 years and
172 controls individually … ex and geographical origin.
50 unselected patients with … men; mean age + SD, 53 + 11 years)

Adjusted for smoking and hypertension

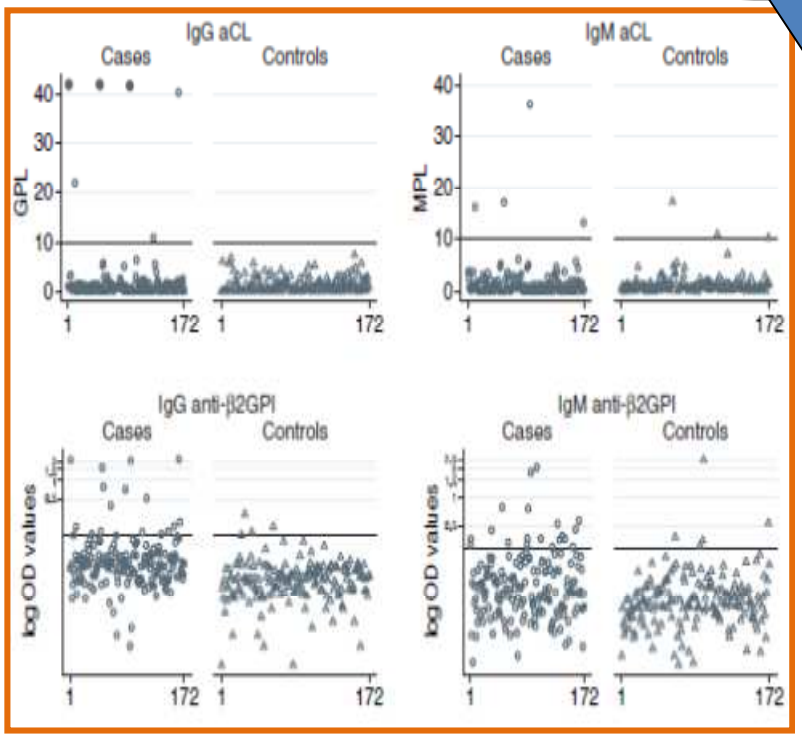


Table 3 Association of ANA and anti-β2GPI antibodies with MI

	Unadjusted OR (95% CI)	*P*	Adjusted OR* (95% CI)	*P*
ANA – Antiβ2GPI				
ANA 1:40	0.94 (0.59–1.51)	0.811	1.31 (0.74–2.31)	0.357
ANA 1:160	0.6 (0.26–1.37)	0.236	0.58 (0.23–1.47)	0.252
Anti-β2GPI – IgG†	2.36 (1.81–3.07)	<0.0001	2.47 (1.81–3.38)	<0.0001
Anti-β2GPI – IgM OD				
<0.0595	1.0 (ref)		1.0 (ref)	
0 .0595–0.087	0.66 (0.33–1.32)	0.243	0.64 (0.29–1.42)	0.27
0.087–0 .1395	1.46 (0.76–2.79)	0.253	1.40 (0.67–2.95)	0.37
>0 .1395	3.96 (1.93–8.14)	<0.0001	3.68 (1.69–8.02)	0.001

ANA, anti-nuclear antibodies; MI, myocardial infarction; anti-β2GPI, anti-beta2 glycoprotein I.
*ORs adjusted for smoking and hypertension.
†Quartile of anti-β2GPI antibodies treated as a continuous variable.

P. L . MERONI, F . PEYVANDI, L . FOCO, L . BERNARDINELLI, R. FETIVEAU, P . M. MANNUCCI and A. TINCANI, ON BEHALF OF THE ATHEROSCLEROSIS, THROMBOSIS AND VASCULAR BIOLOGY ITALIAN STUDY GROUP

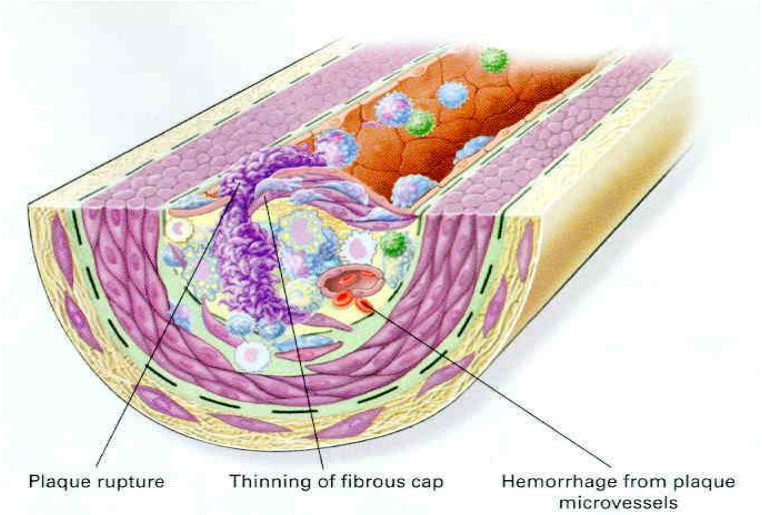
aPL & Atherothrombosis: more thrombosis than athero…?

Association of anti-b2GPI antibodies with MI was confirmed in pts without significant coronary stenosis

(anti-b2GPI IgG crude OR = 2.60, 95% CI 1.59–4.23, P < 0.0001;
adjusted OR 2.52 95%, CI 1.54–4.11, P < 0.0001;
anti-b2GPI IgM crude OR = 1.97, 95% CI 1.30–3.00, P = 0.001;
adjusted OR = 2.24, 95% CI 1.33–3.75, P = 0.002)

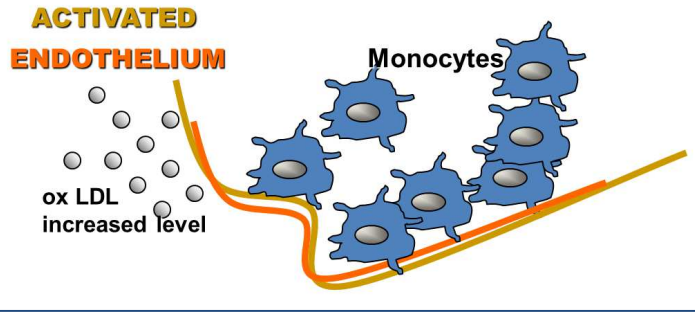
and in those with significant stenosis

(anti-b2GPI IgG crude OR = 2.25,95%CI 1.59–3.18, P < 0.0001;
adjusted OR 2.29 95%, CI 1.43–3.68, P = 0.001;
anti-b2GPI IgM crude OR = 1.38, 95%CI 1.04–1.85, P = 0.027;
adjusted OR = 1.88, 95% CI 1.18–3.01, P = 0.008).

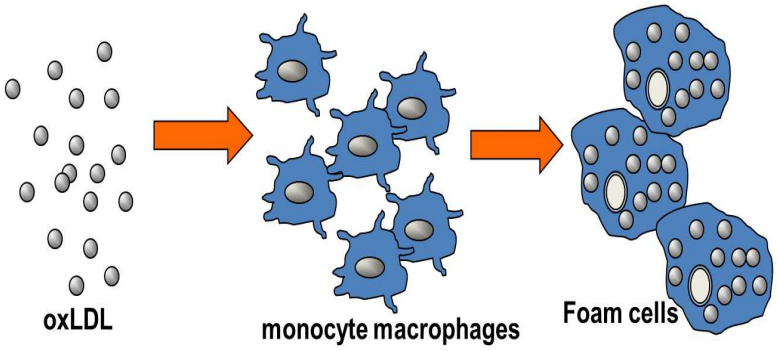


b2GPI dependent aPL are independently associated with MI in premenopausal women, despite the absence, or small degree, of the atherosclerotic burden in coronary arteries.

The role of anti-beta 2GPI in atherosclerosis



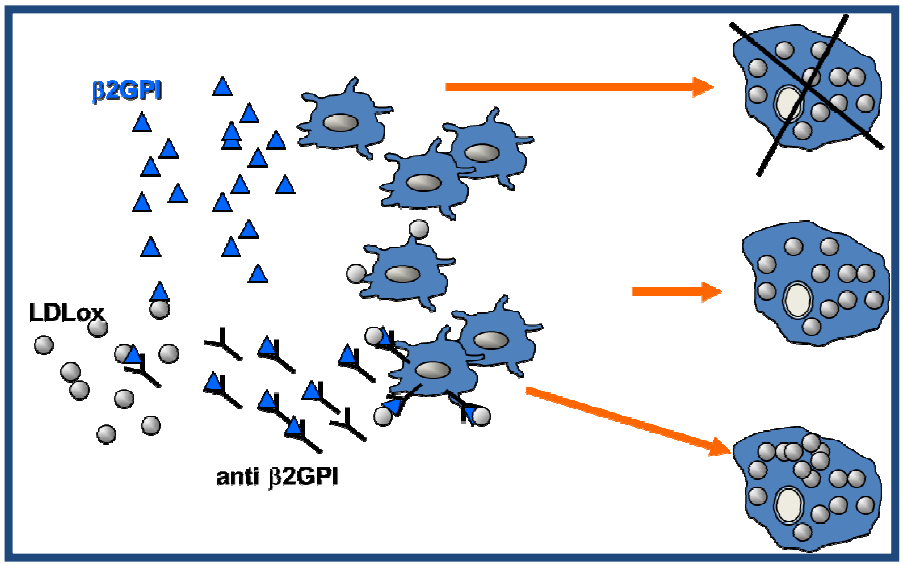
The plaque initiating process is the binding of circulating monocytes to arterial endothelial cells mediated by vascular cell adhesion molecul-1 (VCAM-1) and intracellular adhesion molecul-1(ICAM-1).



Oxidized LDL and other lipoproteins can be actively taken up by scavenger receptor mediated endocitosis, transforming macrophages into the so called foam cells.

Anti-beta2 GPI can be responsible of the LDL oxidation.

- IgG anti-HDL and IgG anti-b2GPI are associated with reduced paraxonase activity in SLE and APS.
- The physiological role of paraxonase is to prevent the oxidation of LDL.



Da Koike T, 1998

Atherosclerosis & b2GPI:

Clinical & Experimental Evidences

Beta 2 glycoprotein I and atherosclerotic plaque

studied in human carotid samples

Immunolocalization of β2-glycoprotein I (apolipoprotein H) to human atherosclerotic plaques: Potential implications for lesion progression.

β2GPI co-localized with T CD4+ lymphocytes

George et al; Circulation, 99: 2227-2230; 1999

IMMUNIZATION WITH HUMAN β2 GLYCOPROTEIN I

In LDL-receptor-deficient mice or Apo-E knock-out, immunization with β2GPI enhances atherosclerotic lesions (including CD4+ lymphocytes)

George J et al Circulation 1998;
Afek A et al, Pathobiology 1999

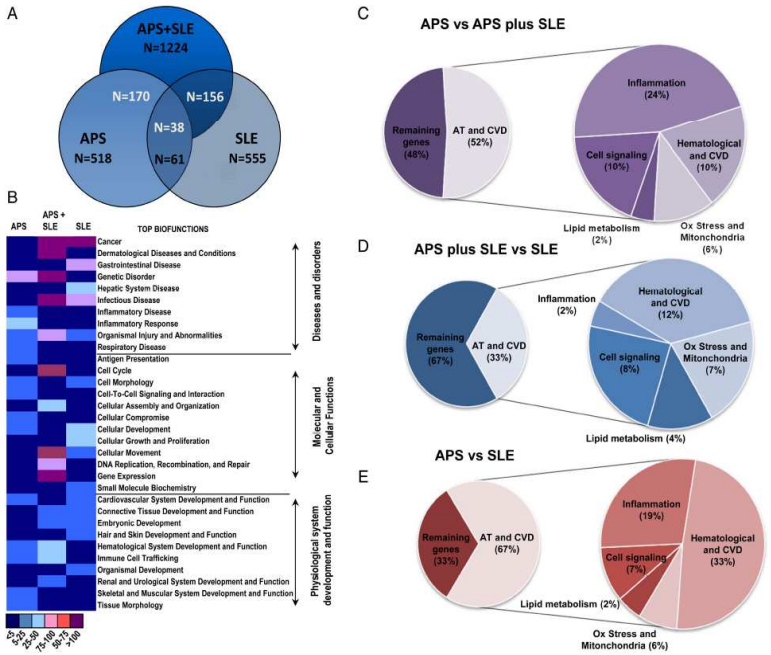
T cells depletion impairs the experimental model reproduction !!

The transfer of lymphocytes from mice immunized with β2GPI to mice of similar genetic background, increases atherosclerotic lesions compared to those occurring in animals tranferred with lymphocytes from mice immunized with ovalbumin.

Gene profiling specific molecular pathways in the pathogenesis of atherosclerosis and cardiovascular disease in APS, APS+SLE and SLE

126 patients, 41 with APS, 31 with APS plus SLE and 54 with SLE, 61 healthy donors

555 (SLE), 1224 (APS + SLE)and 518(APS) genes were differentially expressed;
25–30% of differentially expressed genes were related to AT and CVD



Microarray expression profiling was performed in monocytes.

APS + SLE patients not only display a significantly different gene profile but also appear to be at greater risk of developing certain pathological features compared with those SLE patients who do not have aPL.
Our results indicate that aPL-positive lupus patients have an increase in both markers of <u>early atherosclerosis</u> development and <u>thrombotic events</u>.

Carlos Perez-Sanchez et al. ARD March 2014

Atherosclerosis
Cause of death in APS

Table 4 Causes of death during the 10 year follow-up (1999–2009) of the total cohort of 1000 patients

Causes of death*	0–5 year (n=53) No. (%)†	5–10 year (n=40) No. (%)†	0–10 year (n=93) No. (%)†
Bacterial infection	11 (20.8)	9 (22.5)	20 (21.5)
Myocardial infarction	10 (18.9)	3 (7.5)	13 (13.9)
Stroke	7 (13.2)	4 (10)	11 (11.8)
Haemorrhage	6 (11.3)	4 (10)	10 (10.7)
Malignancy	6 (11.3)	7 (17.4)	13 (13.9)
Catastrophic APS	5 (9.4)	0	5 (5.4)
Pulmonary embolism	5 (9.4)	0	5 (5.4)
SLE pulmonary involvement	3 (5.7)	0	3 (3.2)
SLE renal involvement	2 (3.8)	1 (2.5)	2 (2.5)
SLE central nervous system involvement	1 (1.9)	0	1 (1.1)
SLE haematological involvement	0	1 (2.5)	1 (1.1)
Chronic renal failure	0	2 (5)	2 (2.5)
Viral infection	0	4 (10)	4 (4.3)
Fungal infection	1 (1.9)	0	1 (1.1)
Trauma/accident	0	3 (7.5)	3 (3.2)
Unknown	0	3 (7.5)	3 (3.2)

*Several patients had more than one cause of death.
†Percentage of death.
APS, antiphospholipid syndrome; SLE, systemic lupus erythematosus.

93 (9.3%) patients
(72 female and 21 male)
died.
Mean (SD) age at death was
59 (14) years (range 19–94).

The mortality rate was
similar in both periods:
5.3% in the initial 5-year
follow-up period and 4% in
the ensuing 5 years.

Cervera R, et al ARD 2014

The cardiac involvement in APS

- Heart valve lesions
- **Coronary heart disease**
  - Significant aPL profile
  - Low concomitant morbities (i.e.young age)
  - With and without atherosclerosis
  - High mortality rate
- Cardiac thromboembolism

Greetings from Brescia Rheumatology Unit

Thank you for your attention !