

# Manifestazioni cardiovascolari: Lupus eritematoso sistemico

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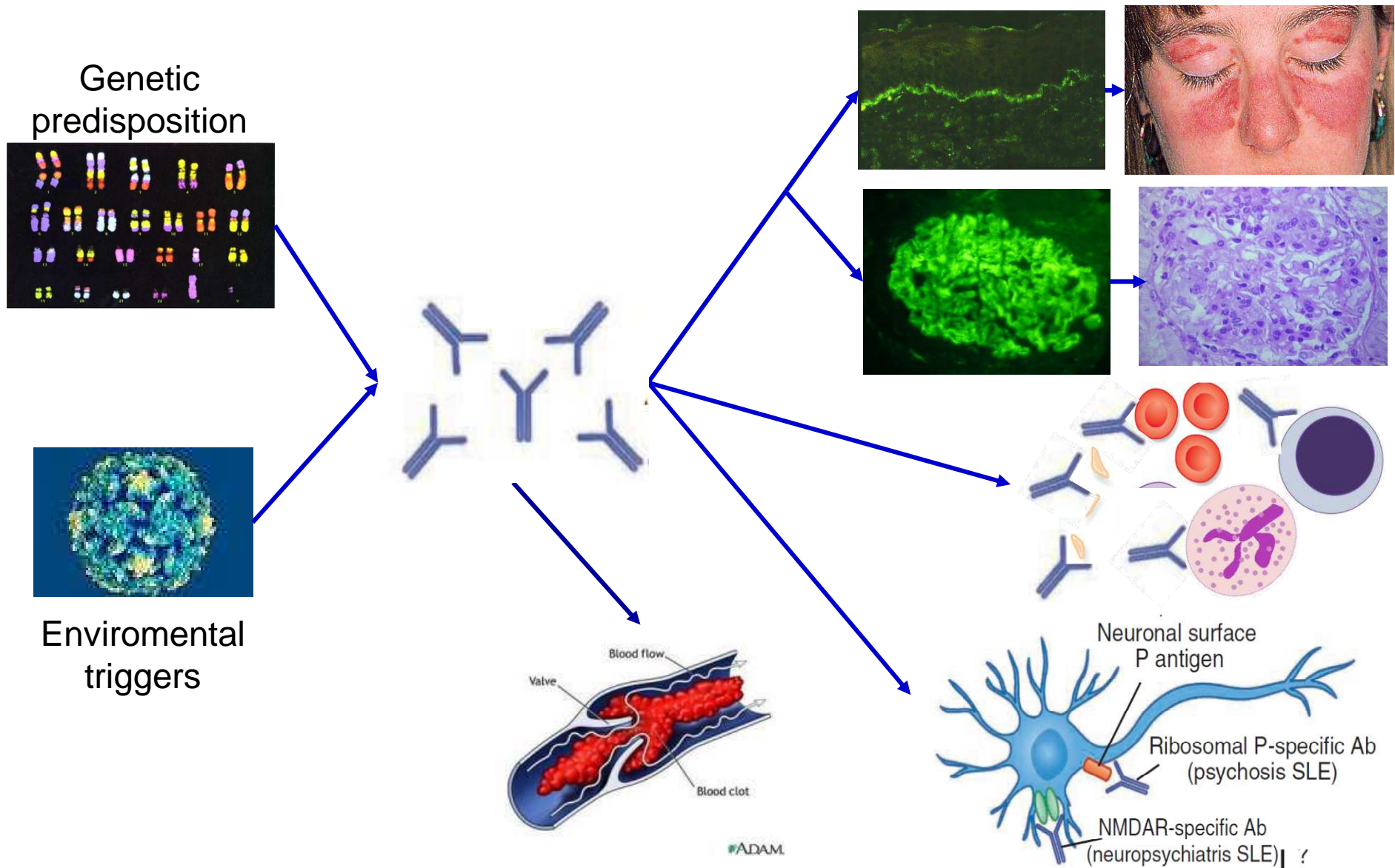
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Manifestazioni cardiovascolari e Metaboliche

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# Natural history of SLE



“Heart lesions develop in nearly all patients at some time during the course of their disease when life is prolonged by modern . . . therapy”

Brigden et al, 1960

# Pericarditis: 11-54%

- IC mediated
- Common at the disease onset or during SLE relapses
- Patients with pericardial effusion are more likely to have active lupus elsewhere
- Echocardiography shows effusion (usually mild) and/or thickening
- Co-existent pleurisy is also common

# Myocarditis: 7-10%

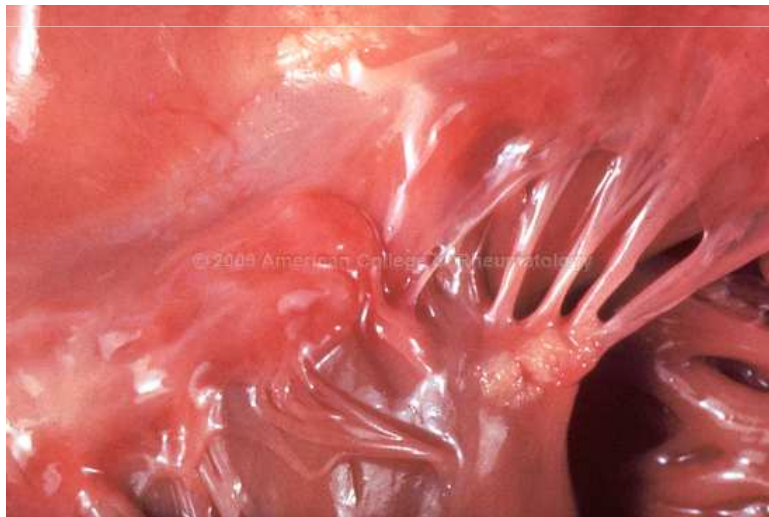
- IC mediated
- Pathology is arteritis or arteriopathy, not myositis
- Subclinical: 20% using echos (global hypokinesis) or MRI
- It can lead to ventricular dysfunction, dilated cardiomyopathy, heart failure

# Valvular Disease

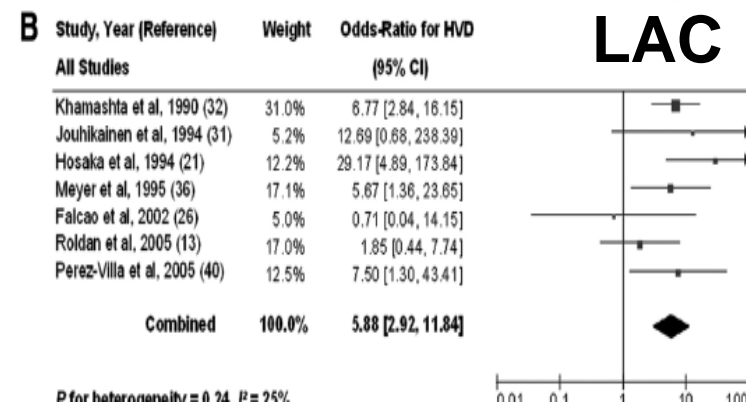
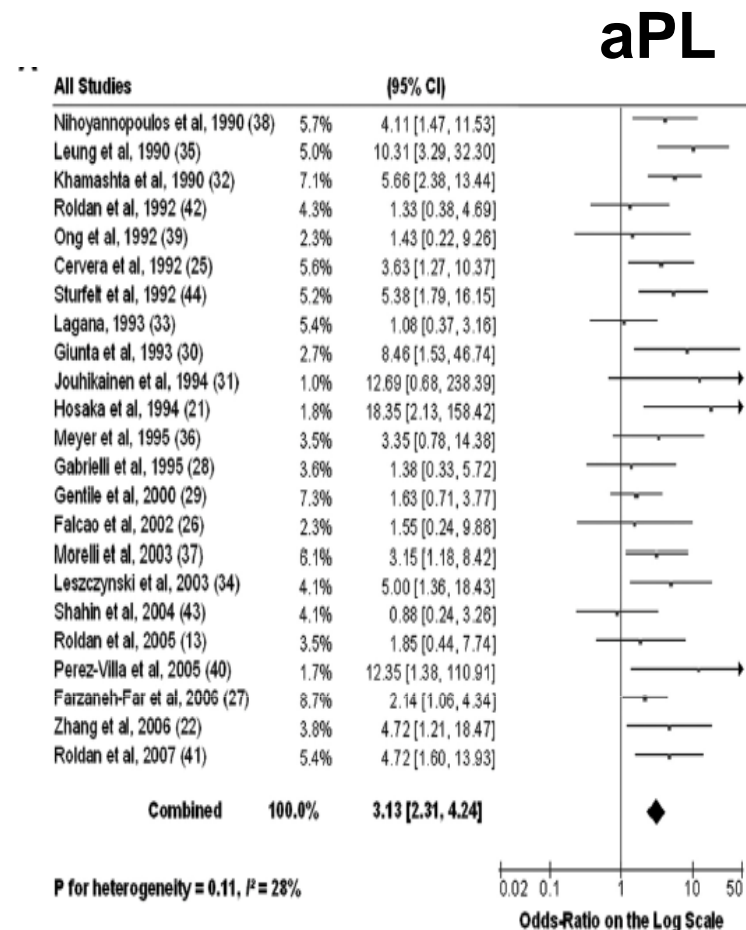
- Valvular thickening or regurgitation is common
- Libman-Saks verrucous endocarditis is characteristic
- aPL and/or IC mediated
- Prevalence anatomical lesions: 15-75% by necroscopy studies; 40-50% by TTE, 50-60% by TEE
- No correlation between verrucous endocarditis and cardiac murmurs
- Clinically important in only 3-4%
- Infectious endocarditis in 7%; stroke or peripheral embolism in 13%

# aPL & heart valve disease (HVD)

- Metaanalysis SLE
- 23 studies
- 508 +HVD/ 988 -HVD



Zuily S, et al. *Circulation*. 2011;124(2):215-24.



# Arrhythmias

- Sinus tachycardia most common: 6 – 100%  
(due to fever, anemia, pericarditis, myocarditis, hyperthyroidism , autonomic dysfunction)
- Possibly a manifestation of active disease
- Other rhythm and conduction abnormalities are rare



# Coronary artery disease

## Coronary arteritis

- Child or young adult, active disease, short history of corticosteroid exposure
- Coronary aneurysms, smooth focal lesions, rapidly developing stenoses

## Coronary artery thrombosis

- aPL

## Coronary atherosclerosis

- Older patients
- Longer disease duration
- Long history of corticosteroid exposure

## Relative risks for CVD in patients with SLE

Outcomes	Relative risk
CV events	17.0
Stroke	7.9
MI	5-6
MI in women aged 35-44 years	50

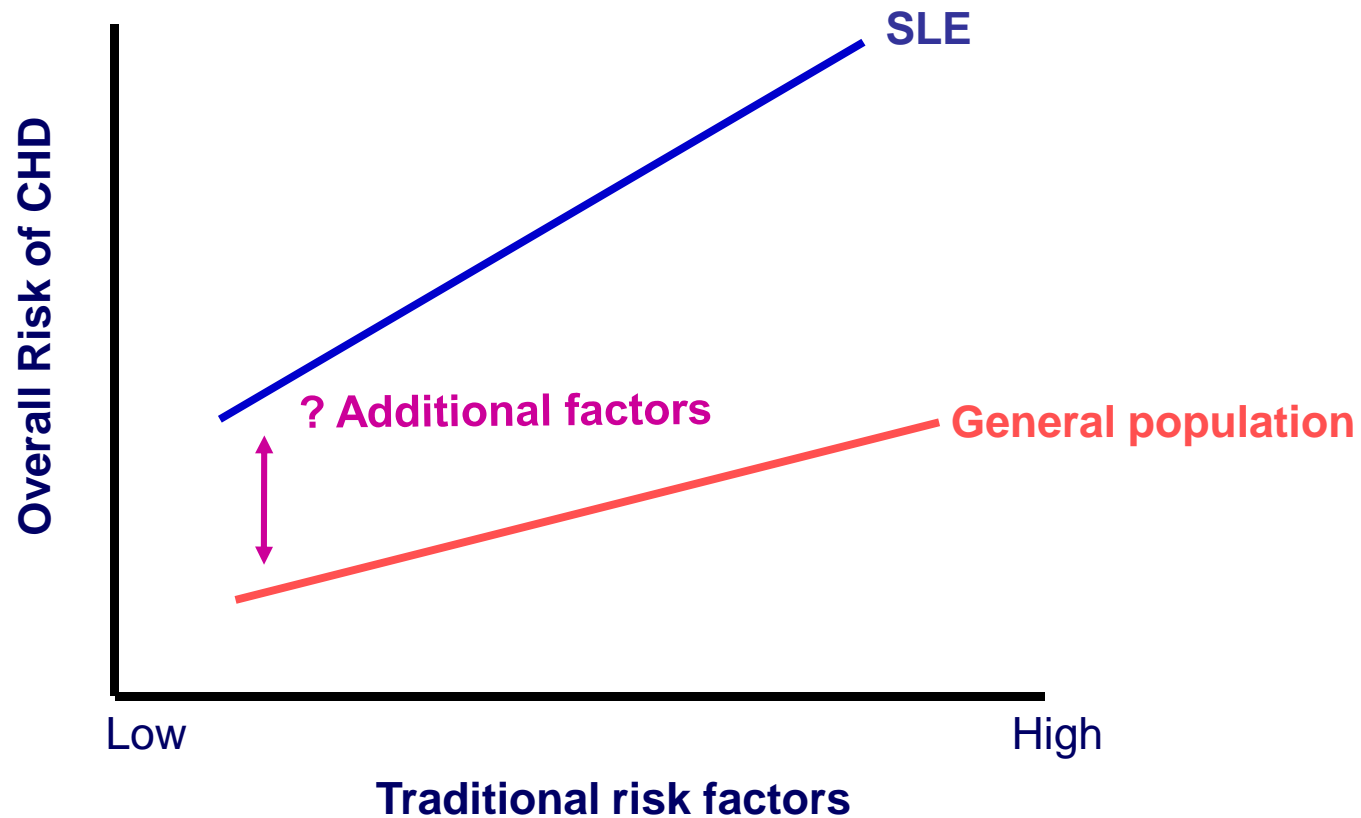
Manzi S. Am J Epidemiol 1997; 145: 408-15

Esdaile JM. Arthritis Rheum 2001; 44: 2331-2337

Ward MM. Arthritis Rheum 1999; 42: 338-46

Fischer LM. Am J Cardiol 2004; 93: 198-200

# Cardiovascular risk in SLE



Wajed et al. Rheumatol 2004; 43: 7

# Risk factors for clinical CHD in UK SLE patients

Risk factor	Age and gender adjusted	
	OR	95% CI
Hypertension	2.56	1.05, 6.25
Hyperlipidaemia	3.06	0.99, 9.52
Smoker – ever	1.54	0.52, 2.56
Family history	3.62	1.15, 11.34
Body mass index	1.05	0.91, 1.21

# Risk factors for clinical CHD in UK SLE patients

Risk factor	Unadjusted		Age and gender adjusted	
	OR	95% CI	OR	95% CI
Renal disease	0.79	0.37, 1.67	1.26	0.50, 3.20
Damage Index (SDI)	2.20	1.09, 4.44	1.73	0.73, 4.11
APL antibody or lupus anticoagulant	0.95	0.44, 2.03	2.57	0.93, 7.09
Corticosteroids	2.46	1.03, 5.88	2.63	0.97, 7.16
Azathioprine	2.33	1.16, 4.67	3.18	1.33, 7.59
Cyclophosphamide	0.92	0.30, 2.87	1.25	0.32, 4.91
Hydroxychloroquine	1.13	0.54, 2.39	1.11	0.46, 2.66

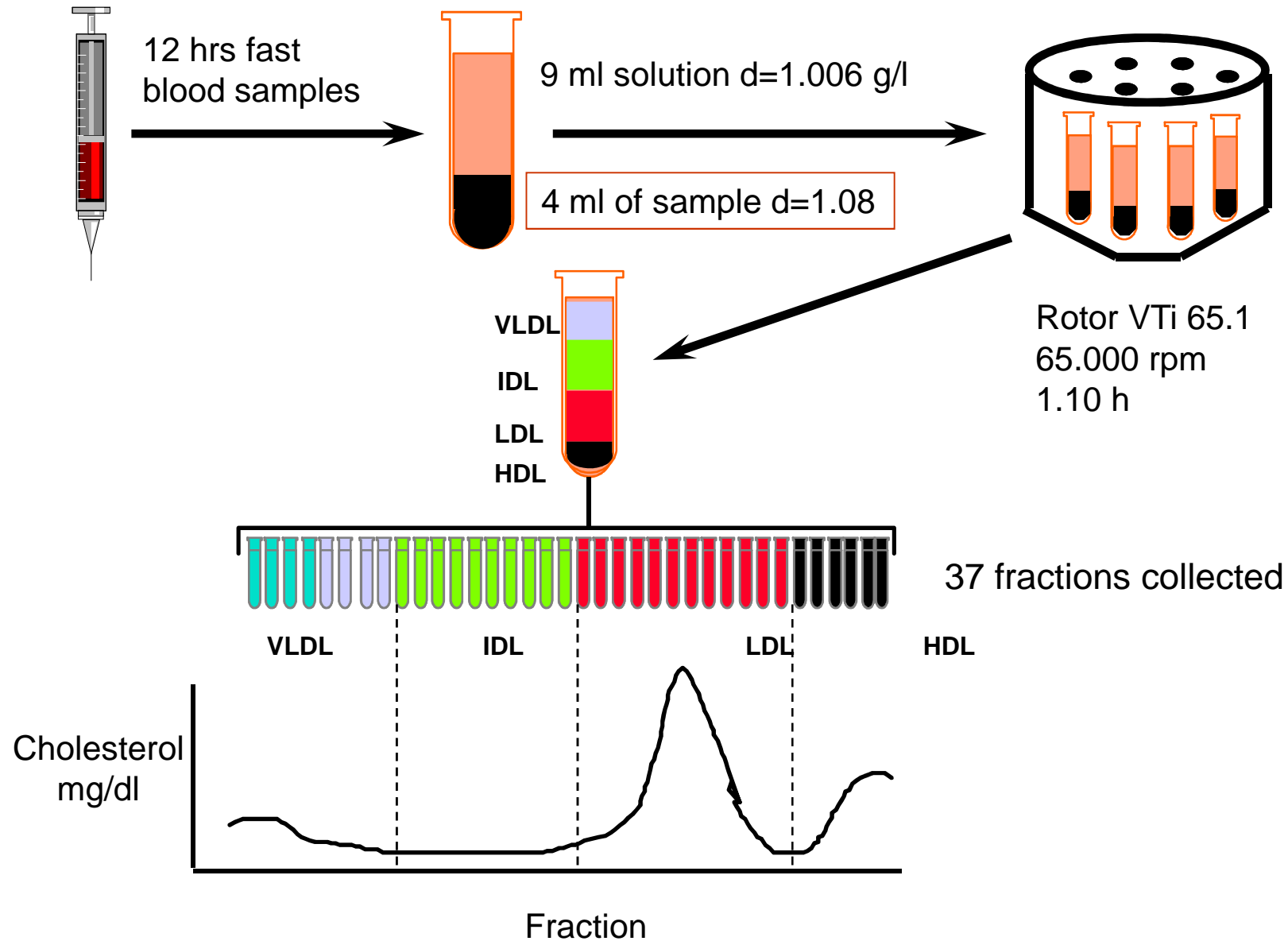
# Traditional risk factors for ATS in 78 SLE patients subdivided according to cumulative PDN intake

Group: A <18 g, B 18-38 g, C >38 g

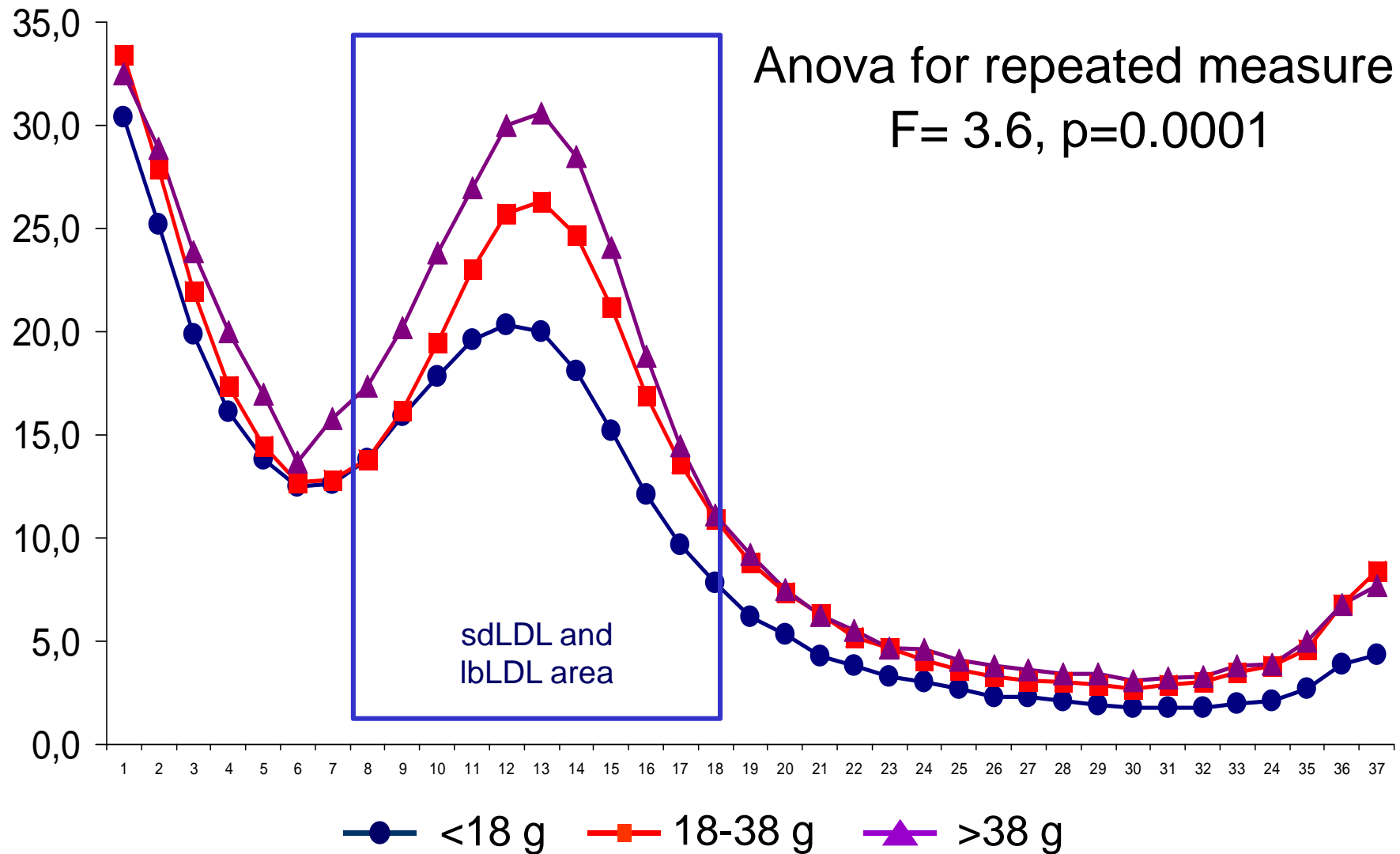
	Group A	Group B	Group C	
	Mean±SD	Mean±SD	Mean±SD	P=
SBP (mmHg)	120±12	127±10	131±16	0.007
DBP (mmHg)	75±7	83±9	84±8	0.000
Total cholesterol (mmol/l)	4.7±0.86	5.27±1.18	5.66±1.17	0.008
HDL (mg/dl)	118.2±20.1	128.3±25.8	136.9±38.9	0.082
LDL totali (mg/dl)	183.5±48.4	225.2±74.4	260.7±70.8	<0.001
• sdLDL (mg/dl)	60.2±14.8	62.4±18.2	77±27.2	0.009
• lbLDL (mg/dl)	123.3±41.5	162.7±59.7	183.7±50	<0.001
IDL (mg/dl)	35.6±17.1	49.8±24.4	53.5±19.9	0.007
VLDL (mg/dl)	22.6±19.2	38.1±32.2	42.2±29.9	0.030

Doria A, et al. Arthritis Rheum 2004; 50: S191-S192

# Ultracentrifuga a gradiente di densità (DGUC)



## Sub-fraction profile in 78 SLE patients according to the cumulative prednisone equivalent dose uptake



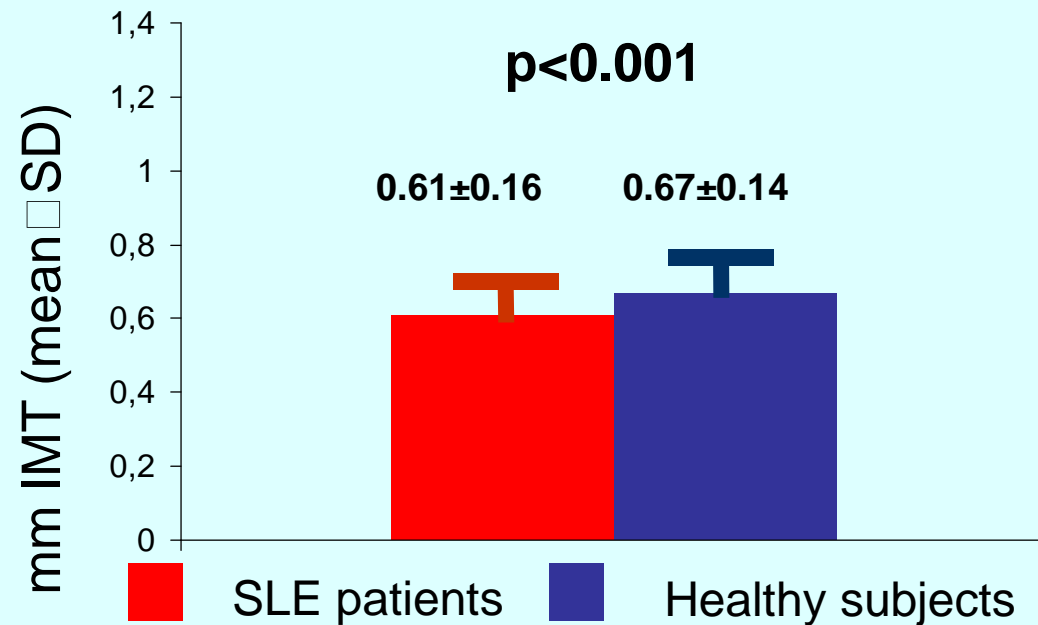


# Non-invasive techniques for the detection of subclinical atherosclerosis

- [
- [ ATS abnormalities in 10-40% of
- ( cases
- Electron Beam Computed Tomography (CT)
- Are these abnormalities in SLE
- patients predictive of CV events as they are in general populations?
  - Thallium-201
  - Dual Isotope Myocardial Perfusion Imaging (DIMPI)

# Carotid ultrasound studies in SLE

Roman MJ, et al. N Eng J Med 2003; 349: 2399-406



Thompson  
(2008)

217

45

100

89

12

>50% than  
surrounding  
area

Patients n.						
Mean age (years)						
Female %						
White %						
Previous CVD %						
Plaque definition	> 50% than surrounding area					
Plaque %	40	38	37	17	32	31
Mean IMT (mm)	0.71±0.14	0.60±0.14	0.61±0.16	0.55±0.15	0.71±0.1	0.63±0.1
Risk factor evaluation	Cross sectional	Cross sectional	Cross sectional	Longitudinal	Cross sectional	Longitudinal

# Novel risk factors for atherosclerosis

<b>Markers of inflammation</b> <ul style="list-style-type: none"><li>• Acute-phase proteins<ul style="list-style-type: none"><li>• CRP</li><li>• PTX3</li><li>• Serum amyloid A</li></ul></li><li>• Adesion molecules<ul style="list-style-type: none"><li>• ICAM-1</li><li>• VCAM</li><li>• Selectins</li></ul></li><li>• Proteases<ul style="list-style-type: none"><li>• MMP</li></ul></li><li>• Cytokines<ul style="list-style-type: none"><li>• IL-1</li><li>• IL-6</li><li>• TNF<math>\alpha</math></li></ul></li></ul>	<b>Immunological factors</b> <ul style="list-style-type: none"><li>• Innate immunity<ul style="list-style-type: none"><li>–Toll-like receptor (TLRs)<ul style="list-style-type: none"><li>–TLR4</li></ul></li><li>–Scavenger receptors (SR)<ul style="list-style-type: none"><li>–SR-A</li><li>–CD36</li></ul></li></ul></li><li>• Adaptive immunity<ul style="list-style-type: none"><li>–Immune cells<ul style="list-style-type: none"><li>–CD4+ TCRab+</li><li>–CD4+ CD28null</li></ul></li><li>–Autoantibodies<ul style="list-style-type: none"><li>–Anti-<math>\beta</math>2GPI</li><li>–Anti-oxLDL</li><li>–Anti-HSP-65</li></ul></li></ul></li></ul>	<b>Lipoproteins and modified lipids</b> <ul style="list-style-type: none"><li>• Lipoprotein (a)</li><li>• Oxidized LDL</li><li>• Small, dense, LDL</li></ul> <b>Coagulation factors</b> <ul style="list-style-type: none"><li>• Tissue Factor</li><li>• Fibrinogen</li><li>• PAI-1</li><li>• Homocysteine</li></ul> <b>Hormones</b> <ul style="list-style-type: none"><li>• Leptin</li><li>• Resistin</li></ul>
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## Frequency of oxLDL/ $\beta_2$ GPI complex and autoantibodies in SLE patients and controls

Markers	Frequency (%)		P
	SLE (n=78)	Healthy subjects (n=72 )	
oxLDL/ $\beta_2$ GPI	58	11	<0.001
IgG anti-oxLDL/ $\beta_2$ GPI	74	18	<0.001
IgM anti-oxLDL/ $\beta_2$ GPI	69	15	<0.001
anti-MBL	32	nd	-
anti-CRP	22	nd	-

Bassi N, Doria A. Autoimmunity 2009; 42(4): 289-91

## Relationship between oxLDL/ $\beta_2$ GPI, autoantibodies and subclinical atherosclerosis

Mean-IMT			Plaques			
	r	p		Yes (n=13)	No (n=65)	p
oxLDL/ $\beta_2$ GPI	0.245	0.031	oxLDL/ $\beta_2$ GPI	43	29	n.s.
IgG anti-oxLDL/ $\beta_2$ GPI	0.275	0.015	IgG anti-oxLDL/ $\beta_2$ GPI	61	39	n.s.
IgM anti-oxLDL/ $\beta_2$ GPI	0.036	n.s.	IgM anti-oxLDL/ $\beta_2$ GPI	16	21	n.s.
anti-CRP	0.011	n.s.	anti-CRP	0.29	0.27	n.s.
anti-MBL	0.099	n.s.	anti-MBL	3.4	5.03	n.s.

Bassi N, Doria A. Autoimmunity 2009; 42(4): 289-91

# Ideal targets to prevent atherosclerosis in SLE patients

## 1) Potentially modifiable classic risk factors:

Cholesterol:	total <4.52 mmol/l* ; LDL <2.6 mmol/l*;
Triglycerides	<150 mg/dl*
Blood pressure	<130 mmHg systolic and <80 diastolic*
Smoking	stop smoking
Diabetes	fasting glucose <110 mg/dl*
Obesity	Body mass index <25*
Sedentary lifestyle	Aerobic physical activity at least 30 min three times per week
Vitamin D	>75 nmol/l

## 2) Management of disease activity/severity using the lowest effective dosage of corticosteroids

## 3) Additional interventions:

Aspirin	in case of positive of antiphospholipid antibodies, hypertension, cigarette smoking, diabetes
ACE-inhibitors	left ventricular hypertrophy, heart failure, hypertension, glomerulonephritis, diabetes
Statins	dyslipidemia, subclinical atherosclerosis by carotid ultrasound or cardiac CT
HCQ	in all patients
MMF	in patients with active or severe disease

\* Italian Ministry of Health recommendations for the prevention of atherosclerosis in type 2 Diabetes (September 2004).

# Management of dyslipidemia in SLE patients

LDL value*	Other CV risk factors	Non pharmacologic interventions	Pharmacologic interventions
<2.6 mmol/l	No	Annual assessment	None
	Yes	Annual assessment of current CV risk factors and others; aerobic exercise at least 3 times a week for half an hour	Only if requested to manage others CV risk factors
2.6 – 3.4 mmol/l	No	Weight loss, dietary modifications, aerobic exercise at least 3 times a week for half an hour	Antimalarials; decrease of corticosteroid dosage
	Yes	Weight loss, dietary modifications, management others CV risk factors, aerobic exercise at least three times a week for half an hour	Antimalarials, ↓ corticosteroid dosage, additional drugs (eg ACE inhibitors, aspirin) if requested
>3.4 mmol/l	No	Weight loss, dietary modifications, aerobic exercise at least 3 times a week for half an hour	Statins, antimalarials decrease dosage or withdrawn corticosteroids, if possible
	Yes	Weight loss, dietary modifications, management of others CV risk factors, aerobic exercise at least 3 times a week for half an hour	Statins, antimalarials; ↓ or withdrawn corticosteroids, and use additional drugs (eg ACE inhibitors, aspirin).









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Aula Magna, Bo'  
Palace

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Galileo's  
Chair

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