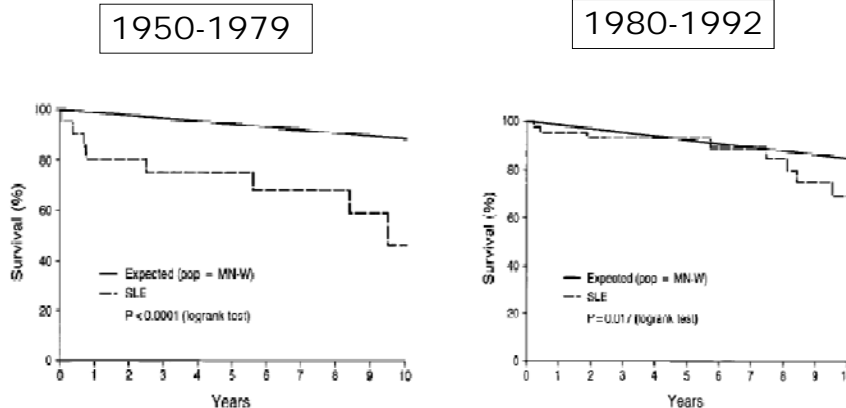


LUPUS AND HEART WHAT DO YOU NEED TO KNOW ?

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Overall Survival in Lupus has Improved



Gabriel, S. et al., *Arthritis Rheum* 1999;42:46-50.

Common Forms of Heart Disease in Systemic Lupus Erythematosus

- ▣ 1. Pericarditis
- ▣ 2. Myocarditis
- ▣ 3. Nonbacterial, endocarditis
- ▣ 4. Cardiac arrhythmias and conduction disturbances
- ▣ 5. Coronary artery disease
 - Coronary arteritis
 - Premature coronary atherosclerosis
- ▣ 6. Systemic hypertension
 - and
- ▣ 7. Pulmonary Arterial Hypertension

PERICARDITIS

- ▣ Acute lupus pericarditis is the most prevalent form of heart disease, occurring in 30 to 40% of SLE patients clinically and up to 75% when studied by echocardiography
- ▣ The pericardial fluid is usually an exudate that is high in protein content and low in complement levels
- ▣ About 15 to 25% of patients with acute lupus pericarditis may show atrial arrhythmias(irregular heart rhtym)

SYMPTOMS OF PERICARDITIS

Sharp, left sided chest, neck or shoulder pain, which may be aggravated by deep breathing, coughing, or supine posture, and is relieved by sitting up and leaning forward

DIAGNOSIS

- ▣ Characteristic chest pain
- ▣ Physical exam
- ▣ Electrocardiogram
- ▣ Echocardiogram

MANAGEMENT

- ▣ NSAIDs, small doses of prednisone, 10 to 20 mg/day.
- ▣ Higher doses of prednisone, 40 to 60 mg/day, may be needed, particularly when there is large pericardial effusion or concurrent evidence of myocarditis
- ▣ Pericardiocentesis
- ▣ Intrapericardial instillation of corticosteroids
- ▣ Pericardiectomy

MYOCARDITIS

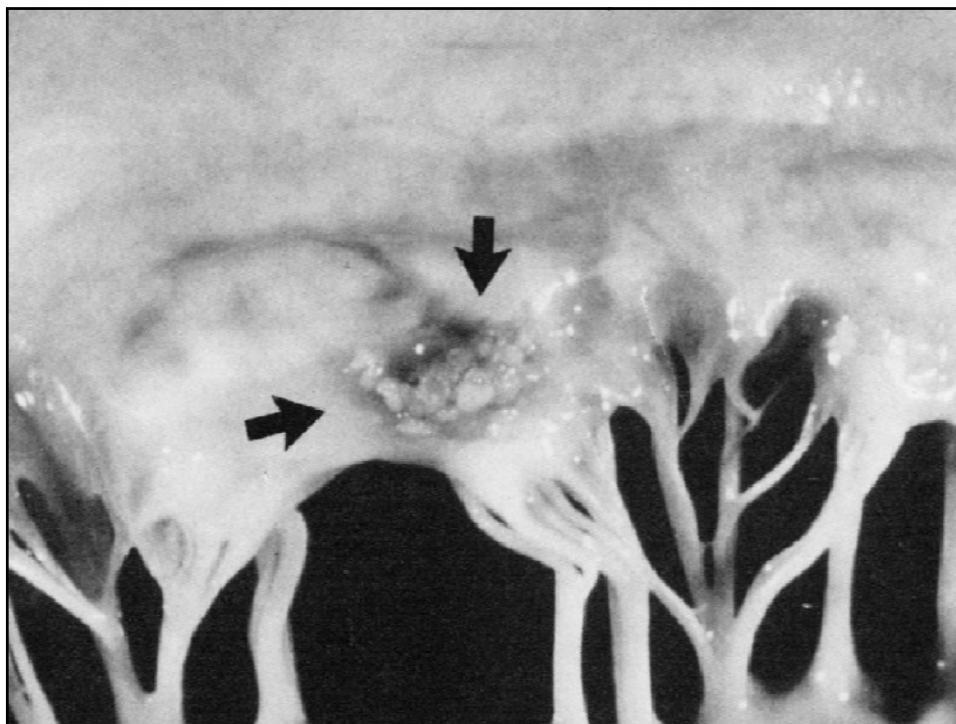
- ▣ Rarer in steroid era
- ▣ May be clinically silent or insidious (symptoms may range from dyspnea on exertion only to full blown congestive heart failure and / or cardiac arrhythmias)
- ▣ First degree AV block and widespread ST-T wave changes in the electrocardiogram
- ▣ Occasionally, skeletal myositis may be concurrently present

ENDOCARDITIS

Should be suspected when there is a new significant heart murmur or valvular dysfunction (stenosis or leakage)

ENDOCARDITIS

- ▣ Similar to lupus myocarditis, the clinical recognition of Libman-Sacks endocarditis may be difficult
- ▣ Valvular distortion is usually minimal, most common location of vegetations is atrial surface of posterior mitral leaflet
- ▣ Rarely, these vegetations embolize and may produce cerebrovascular accident or myocardial infarction.
- ▣ Transesophageal echocardiography may be necessary for diagnosis



- ▣ Frequently associated with anticardiolipin antibodies.

- ▣ Because Libman-Sacks endocarditis predisposes to secondary infective endocarditis("double-decker" endocarditis), prophylaxis before dental,genitourinary or gastrointestinal surgery is needed.

CARDIAC ARRHYTHMIAS AND CONDUCTION DEFECTS

SYMPTOMS OF CARDIAC ARRHYTHMIAS AND CONDUCTION DEFECTS

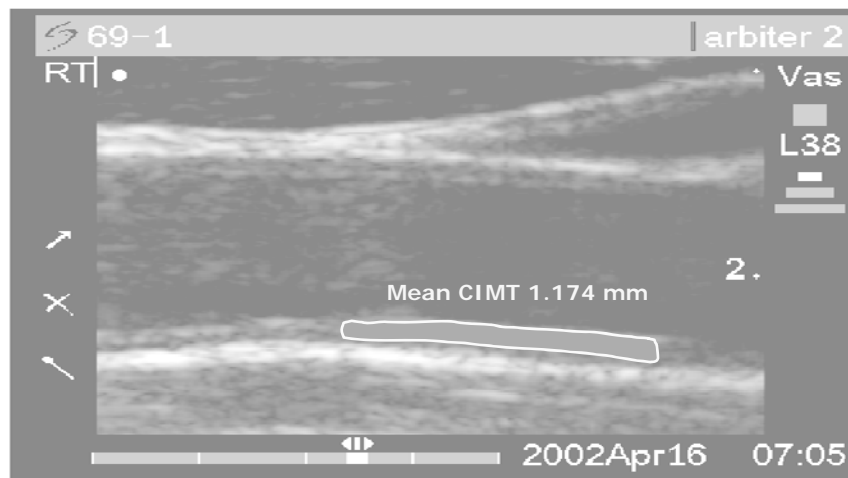
- ▣ Palpitations
- ▣ Weakness
- ▣ Dizziness, lightheadedness
- ▣ Faintness
- ▣ Syncope(black-out spells)

- ▣ Atrial fibrillation and atrial flutter may accompany acute lupus pericarditis
- ▣ Ventricular arrhythmias and first degree AV block may appear during the course of acute myocarditis
- ▣ Acquired complete heart block is a rare event

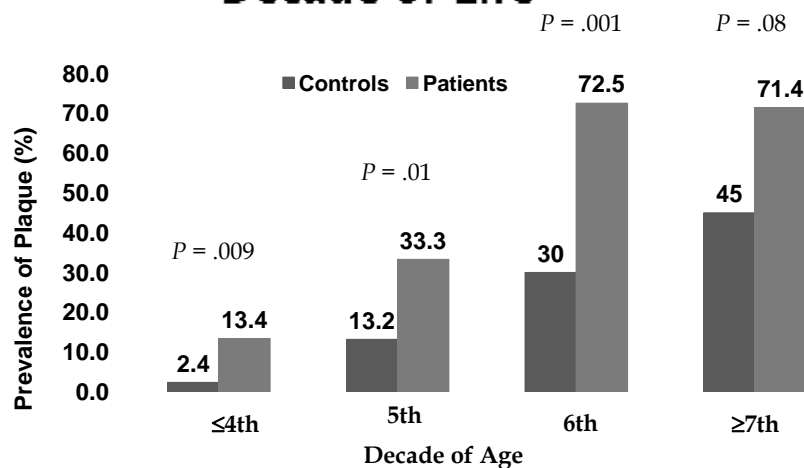
Complete congenital heart block in infants born to mothers with SLE is associated with antibody to soluble tissue ribonucleic protein antigen called RO(SS-A) which crosses the placenta in the early gestation period and causes destruction of the developing conduction system of fetal heart

LUPUS AND ATHEROSCLEROSIS

DETECTION OF ATHEROSCLEROSIS



Prevalence of atherosclerotic Plaque Among Control Subjects and Patients With SLE, According to Decade of Life



Roman MJ, et al. *N Engl J Med.* 2003;349:2399-2406. [Evidence Level B]

Risk Factors of Carotid Plaque in SLE

Independent predictors of increased atherosclerosis in SLE using multivariate analysis

- Higher amount of damage (SLICC damage index)
- Longer disease duration
- Cumulative steroid used
- Post menopause status
- Less use of cyclophosphamide (Cytosan)

Roman, et al., *NEJM* 2003;349:25.

LUPUS AND CORONARY HEART DISEASE

- ▣ In the Johns Hopkins SLE cohort, CHD (defined as angina, MI, or sudden death) occurred in 8.3 percent of 229 patients and was responsible for 3 of 10 deaths in three years
- ▣ In the Toronto cohort of over 1000 patients, 11 percent developed an atherosclerotic event (MI, angina, transient ischemic attack, stroke, atherosclerotic peripheral artery disease, and sudden death) during a mean follow-up of eight years
- ▣ In a case controlled study in Pittsburgh, 498 patients were matched by age and sex to people followed in the Framingham Offspring Cohort Study , **A >50 fold elevated risk of myocardial infarction was found among young women with SLE, ages 35 to 44**
- ▣ In the Nurses' Health Study of 119,332 female nurses, 148 women were diagnosed with SLE after enrollment and were prospectively followed for a mean of 6.6 years The mean age at diagnosis of SLE in this group was 54 years. The age-adjusted relative risk of CHD was 2.25 (95% CI 1.77-4.27). **After adjustment for other risk factors, the hazard ratio remained greater than 2 for this group of older women with SLE.**

- ▣ 35% of SLE patients without clinically evident atherosclerosis have evidence of subclinical disease on **stress myocardial perfusion imaging studies**
- ▣ Subclinical disease detected by this method has also been found to correlate with abnormalities in the anatomy of coronary vessels, and with future significant cardiovascular events.

Sella EM et al. (2003) Coronary artery angiography in systemic lupus erythematosus patients with abnormal myocardial perfusion scintigraphy. Arthritis Rheum 48 : 3168-3175

**SLE and Traditional Cardiac Risk
Factors,
Baltimore Lupus Cohort**

RISK FACTOR	
High Blood Pressure	41%
Family History Heart Disease	41%
Smoking	35%
Increased Cholesterol	56%
Diabetes	7%
Sedentary Lifestyle	70%

Petri et al. Medicine 1992

BLOOD LIPID PROFILE

**TOTAL CHOLESTEROL = TRIGLYCERIDES / 5 + HDL-
CHOLESTEROL (GOOD CHOLESTEROL) + LDL-
CHOLESTEROL (BAD CHOLESTEROL)**

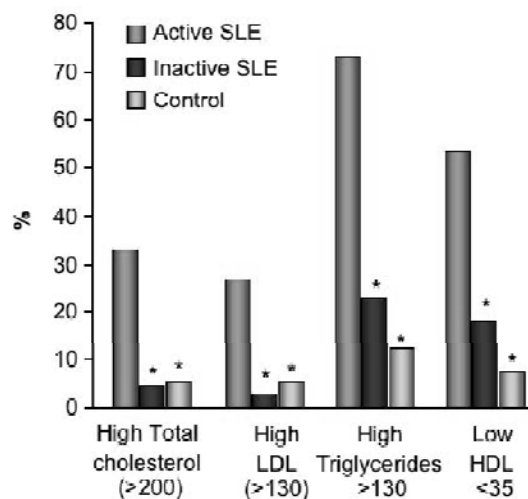
**ORDINARILY ONE FOURTH OF TOTAL BLOOD
CHOLESTEROL SHOULD BE GOOD CHOLESTEROL,
HDL-CHOLESTEROL**

Traditional Framingham Risk Factors Do Not Fully Explain Risk of CHD in SLE

- ▣ Canadian cohort
 - 296 Patients
 - Even after controlling for age, sex, cholesterol, HTN, DM, tobacco use
 - 10 x Increased risk for nonfatal MI
 - 17 x Increased risk for death due to CAD
 - 8 x Increased risk for stroke

Esdale JM, et al. *Arthritis Rheum.* 2001;44:2331-2337. [Evidence Level B]

SLE Disease Activity Influences Standard Lipid Levels



Posadas-Romero et al. *Arthritis Rheum.* 2004;50:160-165

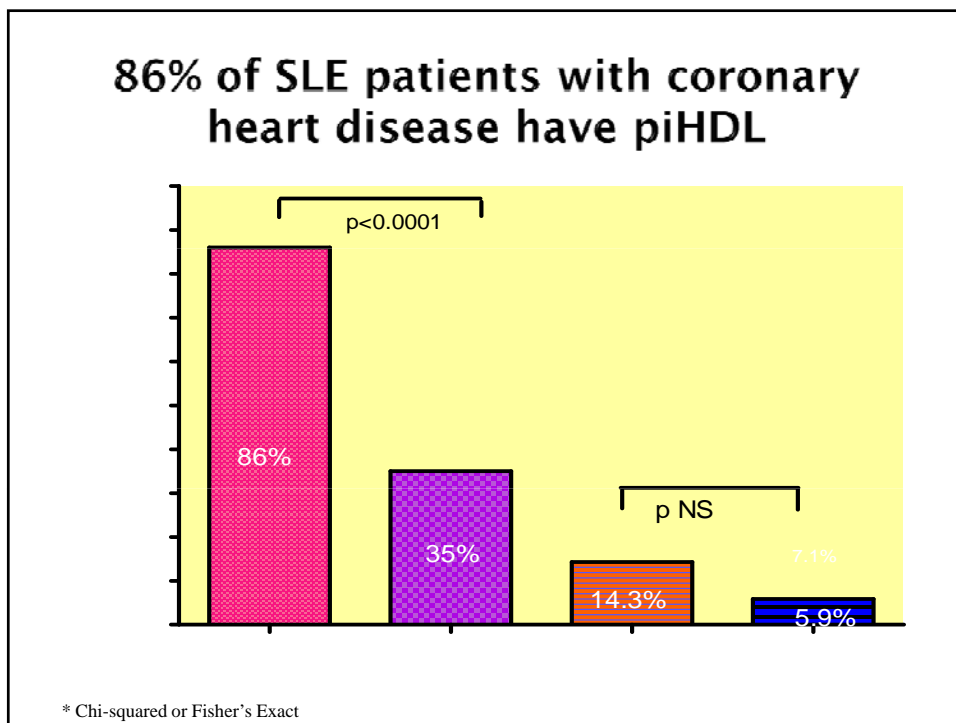
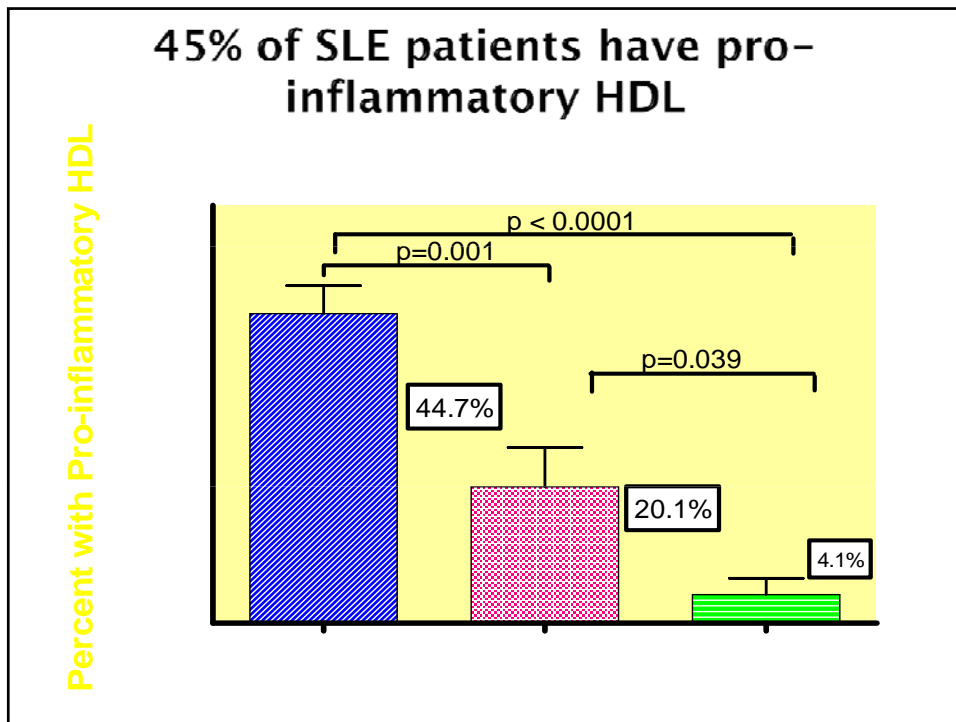
LUPUS SPECIFIC RISK FACTORS

- ▣ Proinflammatory HDL-C
- ▣ Cumulative steroid therapy ?
- ▣ Inflammation burden, prior pericarditis
- ▣ Antiphospholipid syndrome ?
- ▣ Renal disease ?
- ▣ Homocysteinemia ?

Pro-inflammatory HDL Good cholesterol turning into bad cholesterol

- ▣ One study in non-SLE patients with coronary heart disease but no cardiac risk factors found that 90% had “Pro-Inflammatory HDL”, HDL with abnormal protective function

Ansell et al. Circulation 2003



Presence of piHDL Greatly Increases Risk for Carotid Plaque in SLE

- ▣ After taking traditional risk factors (age, high blood pressure, diabetes, high cholesterol and current smoking) into account, there is still increased ODDS FOR PLAQUE IN piHDL POSITIVE SLE = **8.8**

Summary

HDL are abnormal and “Pro-Inflammatory” in a substantial proportion of patients with SLE and RA.

Pro-Inflammatory HDL are significantly associated with plaque on carotid ultrasound in women with SLE but not in healthy controls.

Currently not routinely available as a laboratory test

WHAT CAN LUPUS PATIENTS DO TO DECREASE THEIR RISK OF HEART DISEASE?

Ways to Improve Coronary Heart Disease Risk Factors Without Medications

- ▣ Reduced intakes of saturated fat and cholesterol
- ▣ Minimize salt intake if hypertensive
- ▣ Increased physical activity
- ▣ Weight control
- ▣ Stop smoking

***HP2010.NHLBIHIN.NET/AT
PIII/CALCULATOR.ASP***

www.onlinelipidologist.com
www.pulmonaryhypertensionexpert.com

Control High Blood Pressure and hyperlipidemia

- ▣ Blood Pressure Targets should be
 - <130 mm/Hg systolic blood pressure
 - <80 mm/Hg diastolic blood pressure

- ▣ Lipids Targets should be determined per National Cholesterol Education Program guidelines as in the general population, LDL - Cholesterol < 100

Status of Statins in Rheumatic Diseases

- ▣ RA: 116 patients treated 6 months with atorvastatin 40 mg qd
 - Disease activity score was significantly lower in statin group, $P=.004$ but small change (-0.5)
 - Markers of inflammation (ESR, CRP) lower in patients taking statins

McCarey et al. *Lancet*. 2004;363:2015-2021

Statins in SLE

- **LAPS trial: RCT of Atorvastatin 40 mg vs. placebo in 200 SLE patients, followed for 2 years**
 - No effect on coronary calcium progression
 - No significant improvement in disease activity
 - No significant difference in mean artery thickness (IMT) change, although there was a significant difference in the proportion of patients in whom IMT stayed the same, or got worse, favoring atorvastatin
- **Further long-term studies need to be performed; for now, treat according to NCEP guidelines**

Petri et al., *Arthritis Rheum* 2006; 54: suppl 1246

Summary of Statin role in Rheumatology

- ▣ Statins have the expected effects on lipid levels
- ▣ They lower markers of inflammation (ESR and CRP)
- ▣ Effects on disease activity in RA and SLE and atherosclerotic plaque build up are not large in doses and preparation studied to date.
- ▣ They lower piHDL but not to normal

Antimalarial Drugs and Heart disease in SLE

- ▣ Antimalarial drugs may have a beneficial effect on lipid profiles in SLE
 - Compare 160 patients on stable dosage prednisone (mean, 9.7 mg/d) with 180 patients on stable prednisone dosage (mean, 10.2 mg/d) and antimalarial
 - Antimalarial patients had 11% reduction in TC when compared with patients on prednisone alone ($P < .01$)

Rahman P, et al. *J Rheum.* 1999;26:325-330. [Evidence Level B]

Hydroxychloroquine in SLE

- ▣ Patients treated with hydroxychloroquine were nearly half as likely to increase overall damage from lupus compared to patients not taking the drug.
- ▣ Decrease in risk of thrombosis likely contribute to decreased risk of coronary heart disease
- ▣ Patients treated with hydroxychloroquine were less likely to have plaque on carotid US

Fessler BJ et al., *Arth Rheum* 05; Ho KT et al., *Rheumatol* 2005; Rahman et al., *J Rheum* 1999; Roman et al *NEJM* 2003

DAILY ASA ?

- ▣ Definitely yes if antiphospholipid antibodies positive
- ▣ Probably yes if antiphospholipid antibodies negative or unknown

Leung MH et al. (2002) Mortality and malignancy in the multi-ethnic Birmingham Lupus Cohort - aspirin use is beneficial and non-Caucasian origin is not associated with a poor outcome. *Rheumatol* 41 (Suppl 1): S17

Conclusions

- ▣ Risk of atherosclerotic disease is increased in SLE
 - Likely multifactorial
 - Combination of traditional, disease-related risk factors
- ▣ Low threshold to get screened for CHD
- ▣ Minimize Traditional risk factors
 - BP control
 - Diet
 - Exercise
 - Control High Cholesterol

LUPUS AND PULMONARY ARTERIAL HYPERTENSION

What is PAH?

PAH is a syndrome characterised by a progressive increase in resistance (PVR) of the arteries and arterioles of the lungs.

- leads to right heart overload
- eventually leads to right heart failure and premature death¹
- If untreated, the median survival is 2.8 years² which is comparable with some malignancies

1. Sitbon O et al. *Circulation* 2005
2. D'Alonzo GE et al. *Ann Intern Med* 1991

FACTS ABOUT PAH ASSOCIATED WITH SLE

- ▣ Prevalence of PAH range from 0.5% to 43%
- ▣ In one study prevalence increased from 14% to 43% with 5 years of follow-up
- ▣ Symptoms include insidious onset of shortness of breath, fatigue, and chest pain
- ▣ The disease process is usually far advanced with irreversible changes of the pulmonary vasculature by the time symptoms or signs develop

SCREENING FOR PAH

- ▣ Properly done and interpreted echocardiogram

- ▣ If any question right heart catheterization

Possible Risk Factors for the Development of Pulmonary Hypertension in Systemic Lupus Erythematosus

- ▣
 - Female sex
 - Isolated reduction in lung diffusion capacity
 - Raynaud phenomenon, up to 75%
 - Renal disease
 - Digital gangrene
 - Cutaneous vasculitis/livedo reticularis
 - Rheumatoid factor, 50-80%
 - Antiribonuclear protein, (RNP)
 - Antiphospholipid antibodies, (aPL) , 83%
 - Antiendothelial antibodies,(aECA)

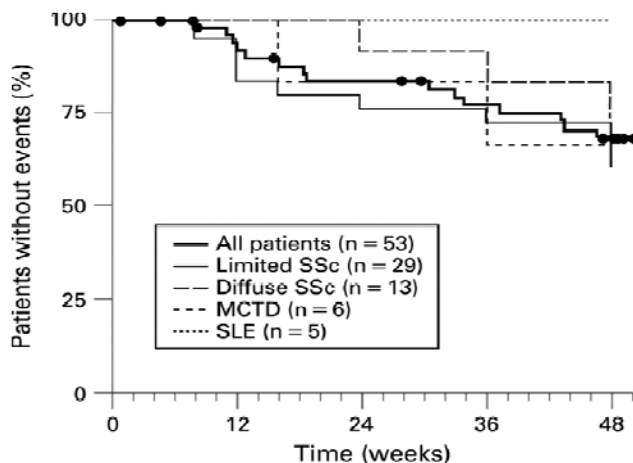
PAH MANAGEMENT IN THE PRESENCE OF CONNECTIVE TISSUE DISEASE

- ▣ Endothelin receptor antagonists
Bosentan,Ambrisentan*
- ▣ Prostanoid therapy
*Epoprostenol**
- ▣ Phosphodiesterase type-5 inhibitors
- ▣ Immunosuppressive therapy ?
- ▣ Heart-lung and lung transplantation

Epoprostenol for Treatment of Pulmonary Hypertension in Patients With Systemic Lupus

- ▣ Clinically, all patients improved from New York Heart Association class III or IV to class I or II
 - ▣ Longest duration of therapy has been 2.5 years
 - ▣ Side effects from epoprostenol have not differed from those seen in patients with primary pulmonary hypertension
- ▣ Ivan M. Robbins, MD, Sean P. Gaine, MD, Robert Schilz, DO, PhD, Victor F. Tapson, MD, FCCP, Lewis J. Rubin, MD, FCCP and James E. Loyd, MD
CHEST January 2000 vol. 117 no. 1 14-18

Kaplan–Meier estimates for time to clinical worsening, defined as the combined endpoint of death, hospitalisation due to pulmonary arterial hypertension (PAH) complications, use of epoprostenol or prostacyclin analogues for worsening of PAH, lung transplantation, or discontinuation due to worsening of PAH on bosentan monotherapy.



Denton C P et al. Ann Rheum Dis 2008;67:1222-1228

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ROLE OF IMMUNOSUPPRESSIVE THERAPY IN PAH

- ▣ May be considered as monotherapy for patients in WHO functional class I or II and/or with a cardiac index greater than 3.1 L/m/m² at baseline and a pulmonary vascular resistance less than 6.6 mmHg/L/min
- ▣ Relapse rate is high necessitating maintenance regimen
- ▣ Additional benefit in combination with PAH specific therapy not known

CONCLUSIONS

- ▣ Cardiac and Pulmonary manifestations are common in SLE
- ▣ Onset of cardiopulmonary disease in SLE patients can be insidious, initially symptoms can be nonspecific and attributed to SLE itself
- ▣ Periodic screening especially in the presence of symptoms should be considered using stress MPI and echocardiography
- ▣ Screening is especially important for SLE patients with Raynaud phenomenon, positive aPL, RNP, RF, aECA, or those considering pregnancy

CONCLUSIONS

- ▣ Cardiovascular risk modification should be adopted as per NCEP guidelines.
- ▣ Regular exercise , at least 30 minutes a day , is best way to improve blood lipoprotein abnormalities
- ▣ Approach to PAH should be evidence based keeping in mind the usually advanced stage at the time of diagnosis and worse prognosis than idiopathic PAH if not treated but better prognosis if treated
- ▣ In patients with SLE-PH, experts suggest that the underlying SLE should be aggressively treated with immunosuppressive therapy in addition to PAH-specific therapies.