# Sclerosi Sistemica e PAH


**Dott. Grosso Marra Walter**

**Citta' della Salute e della Scienza**

**Dipartimento Cardiovascolare**

# Il Reumatologo

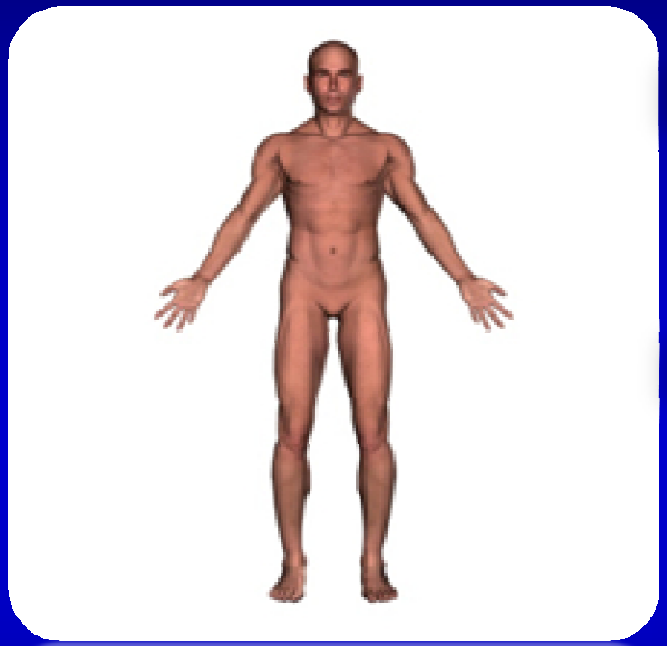

HOUSE M.D.
TUE 9/8c FOX

# IL CARDIOLOGO

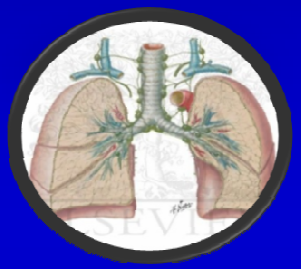
La Sclerosi Sistemica (SSc) è un disordine autoimmune caratterizzato da una progressiva fibrosi che coinvolge la cute e organi interni, causata da una vasculopatia periferica.

American College of Rheumatology (www.rheumatology.org)

# SSc:una patologia multiorgano

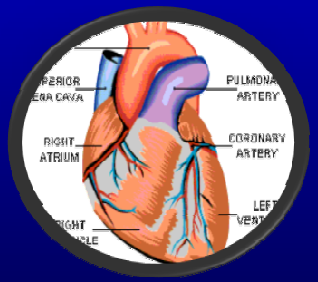


**Ulcere digitali**



**Fibrosi Polmonare Interstiziale**
**Ipertensione Arteriosa Polmonare**

**Crisi renale**



**Interessamento cardiaco**

Mayes, Systemic Sclerosis A clinical features. In: JH Klippel et al., Primer on the Rheumatic Diseases. Springer-Verlag, Berlin, 2007.

Il **coinvolgimento cardiaco** è spesso clinicamente occulto, ma è riconosciuto come un **fattore prognostico negativo** e essendo una delle **principali cause di mortalità** nei pazienti con SSc..


Kahan A. Primary myocardial involvement in systemic sclerosis. Rheumatology (Oxford) 2006

Ferri C. Systemic sclerosis: demographic, clinical, and serologic features and survival in 1,012 Italian patients. Medicine (Baltimore) 2002

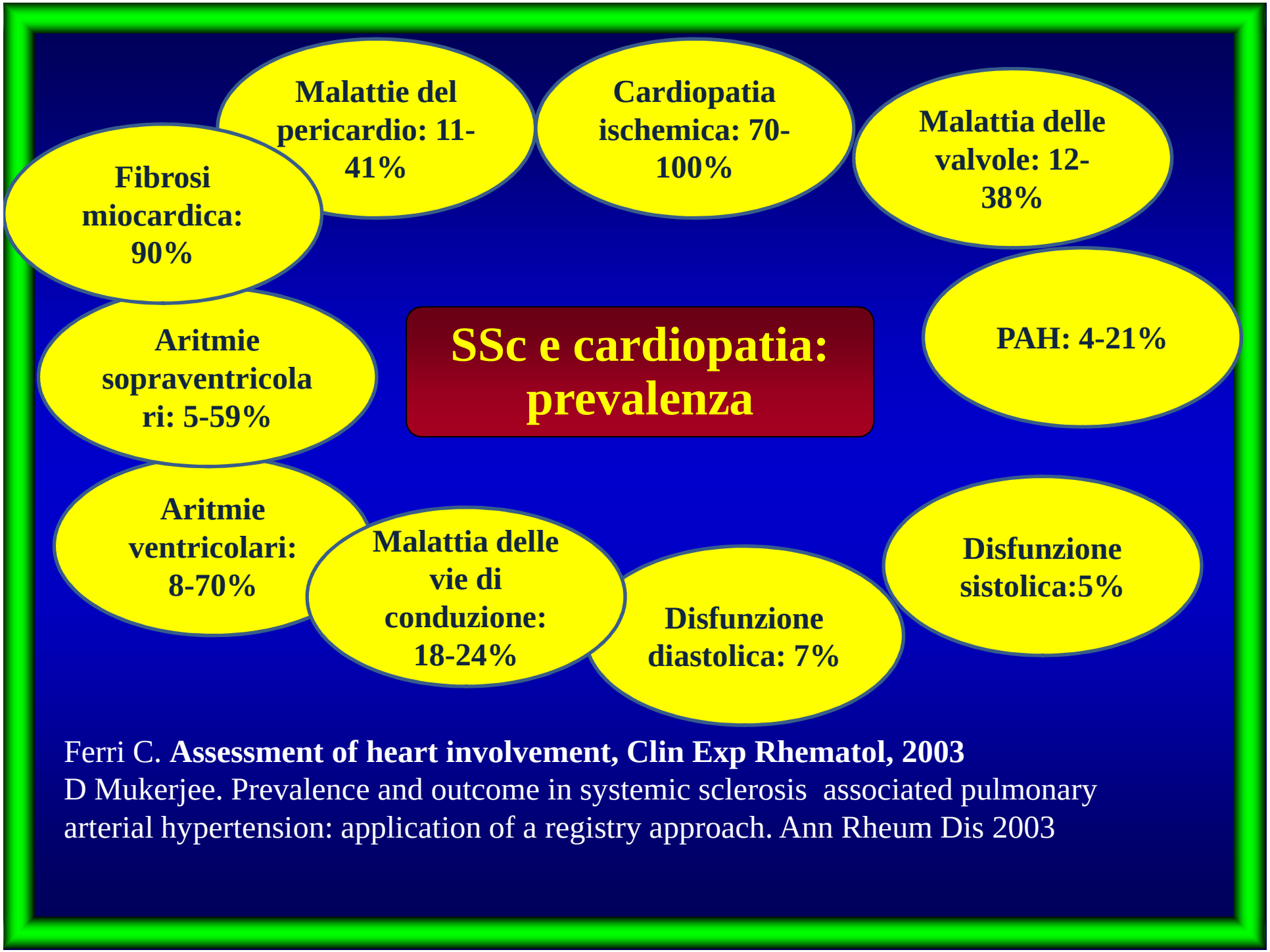
Ferri C. **Assessment of heart involvement, Clin Exp Rhematol, 2003**

# Dimensioni del problema

**La prevalenza del coinvolgimento cardiaco è:**

- **Forma limitata: 23%**
- **Forma diffusa : 32%**

Ferri C. Systemic sclerosis: demographic, clinical, and serologic features and survival in 1,012 Italian patients. Medicine (Baltimore) 2002




Ferri C. **Assessment of heart involvement, Clin Exp Rhematol, 2003**
D Mukerjee. Prevalence and outcome in systemic sclerosis associated pulmonary arterial hypertension: application of a registry approach. Ann Rheum Dis 2003

# Sclerosi Sistemica e PAH

European Heart Journal (2009) **30**, 2493–2537
doi:10.1093/eurheartj/ehp297

ESC/ERS GUIDELINES

## Guidelines for the diagnosis and treatment of pulmonary hypertension

# Sclerosi Sistemica e PAH

**Table 4** Updated clinical classification of pulmonary hypertension (Dana Point, 2008[1])

**1 Pulmonary arterial hypertension (PAH)**
- 1.1 Idiopathic
- 1.2 Heritable
  - 1.2.1 BMPR2
  - 1.2.2 ALK1, endoglin (with or without hereditary haemorrhagic telangiectasia)
  - 1.2.3 Unknown
- 1.3 Drugs and toxins induced
- 1.4 Associated with (APAH)
  - 1.4.1 Connective tissue diseases
  - 1.4.2 HIV infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease
  - 1.4.5 Schistosomiasis
  - 1.4.6 Chronic haemolytic anaemia
- 1.5 Persistent pulmonary hypertension of the newborn

**1′ Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis**

**2 Pulmonary hypertension due to left heart disease**
- 2.1 Systolic dysfunction
- 2.2 Diastolic dysfunction
- 2.3 Valvular disease

**3 Pulmonary hypertension due to lung diseases and/or hypoxia**
- 3.1 Chronic obstructive pulmonary disease
- 3.2 Interstitial lung disease
- 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
- 3.4 Sleep-disordered breathing
- 3.5 Alveolar hypoventilation disorders
- 3.6 Chronic exposure to high altitude
- 3.7 Developmental abnormalities

**4 Chronic thromboembolic pulmonary hypertension**

**5 PH with unclear and/or multifactorial mechanisms**
- 5.1 Haematological disorders: myeloproliferative disorders, splenectomy.
- 5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
- 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
- 5.4 Others: tumoural obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

# Sclerosi Sistemica e PAH

**Table 26** Recommendations for PAH associated with connective tissue disease

| Statement | Class[a] | Level[b] |
|---|---|---|
| In patients with PAH associated with CTD the same treatment algorithm as in patients with IPAH is recommended | I | A |
| Echocardiographic screening for the detection of PH is recommended in symptomatic patients with scleroderma spectrum of diseases | I | B |
| Echocardiographic screening for the detection of PH is recommended in symptomatic patients with all other CTDs | I | C |
| RHC is indicated in all cases of suspected PAH associated with CTD, in particular if specific drug therapy is considered | I | C |
| Oral anticoagulation should be considered on an individual basis | IIa | C |
| Echocardiographic screening for the detection of PH may be considered in asymptomatic patients with the scleroderma spectrum of disease | IIb | C |

**?**

**Entità nosologica differnte?**

- **PAH causa 30% dei decessi nei pz con SS**
- **Sopravvivenza media di 1 anno dopo diagnosi di PAH associata a SS (differente da IPAH)**

Ann Rheum Dis. 2007 Jul;66(7):940-4.
Eur Respir J. 2010 Sep;36(3):549-5.
Chest. 2003 Feb;123(2):344-50.

# Sclerosi Sistemica e PAH

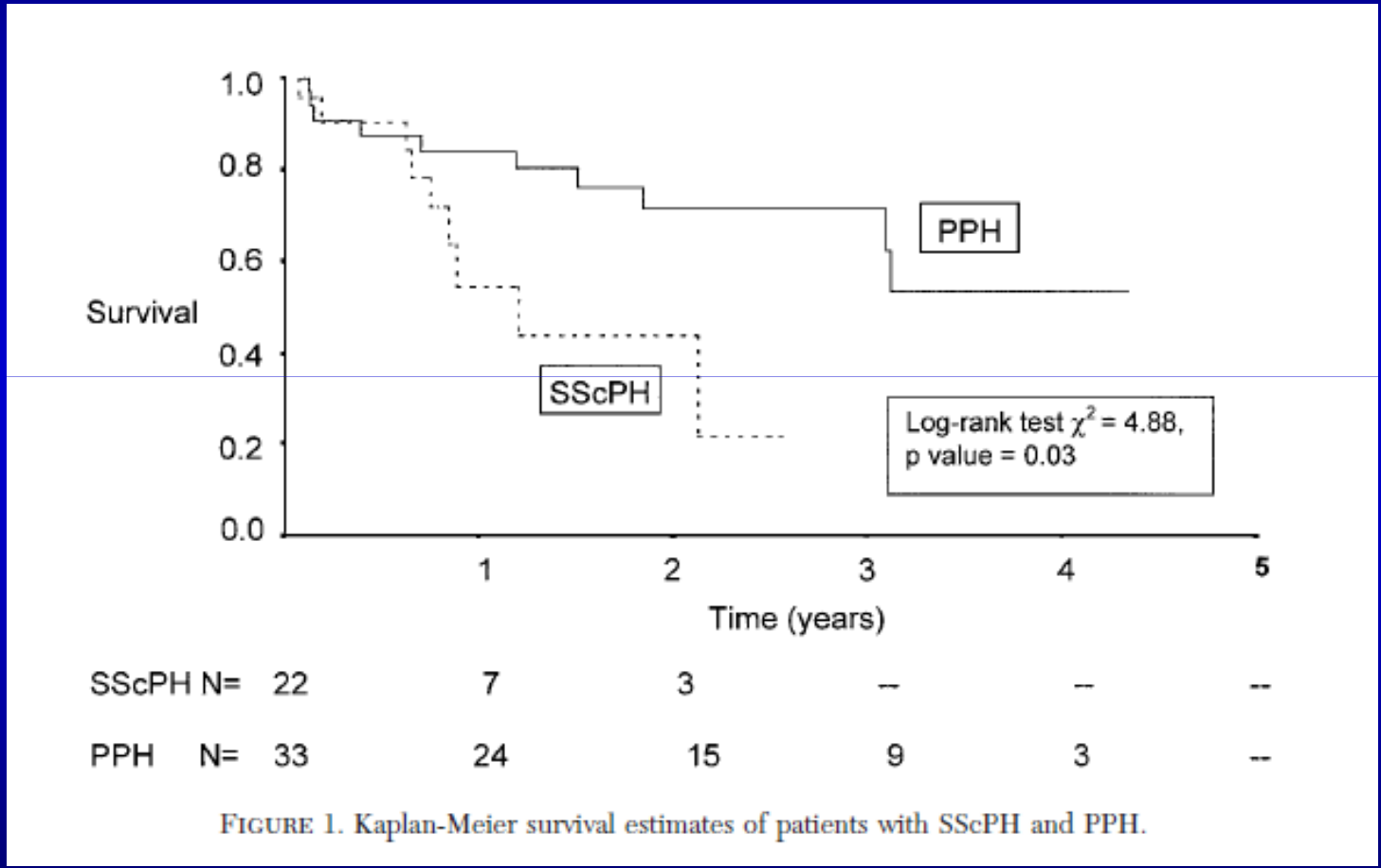
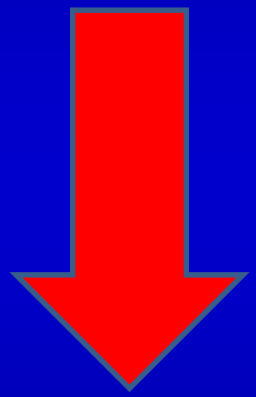



FIGURE 1. Kaplan-Meier survival estimates of patients with SScPH and PPH.

Chest. 2003 Feb;123(2):344-50.

**La scarsa prognosi dei pazienti con PAH associata a SS può spiegata da:**

1. **Ritardo nella diagnosi**
2. **Aggressività della malattia di base**

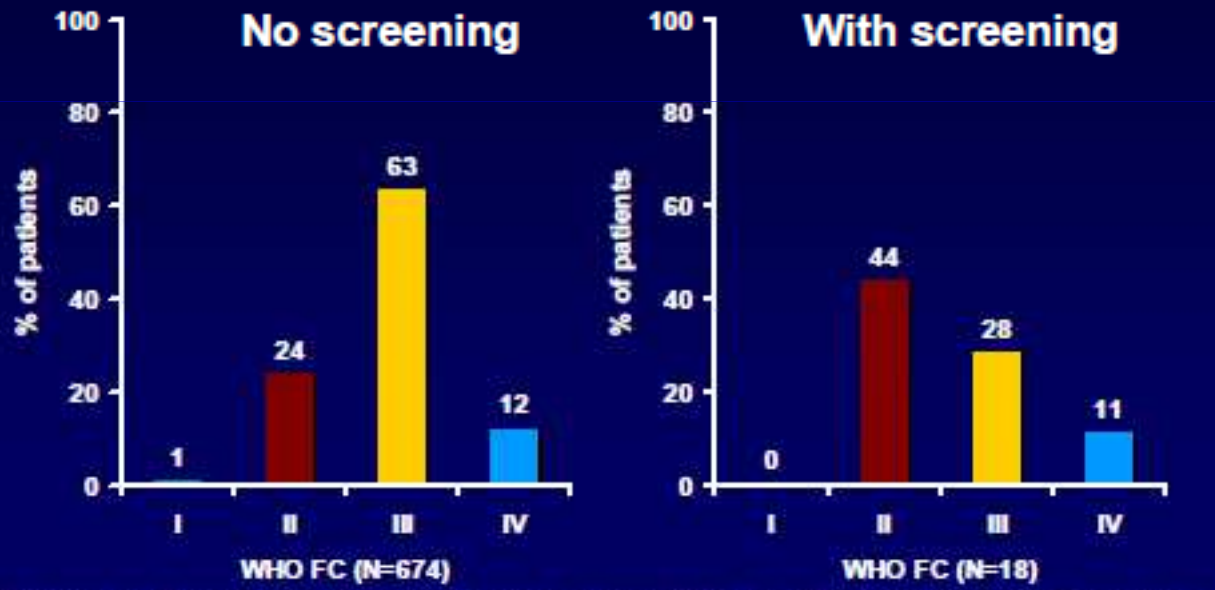


**Necessità di**

1. **Sottoporre a screening i pazienti con SS per fare diagnosi precoce di PAH**
2. **Trattare la malattia di base aggressivamente**

# Sclerosi Sistemica e PAH
# 1- screening e diagnosi precoce

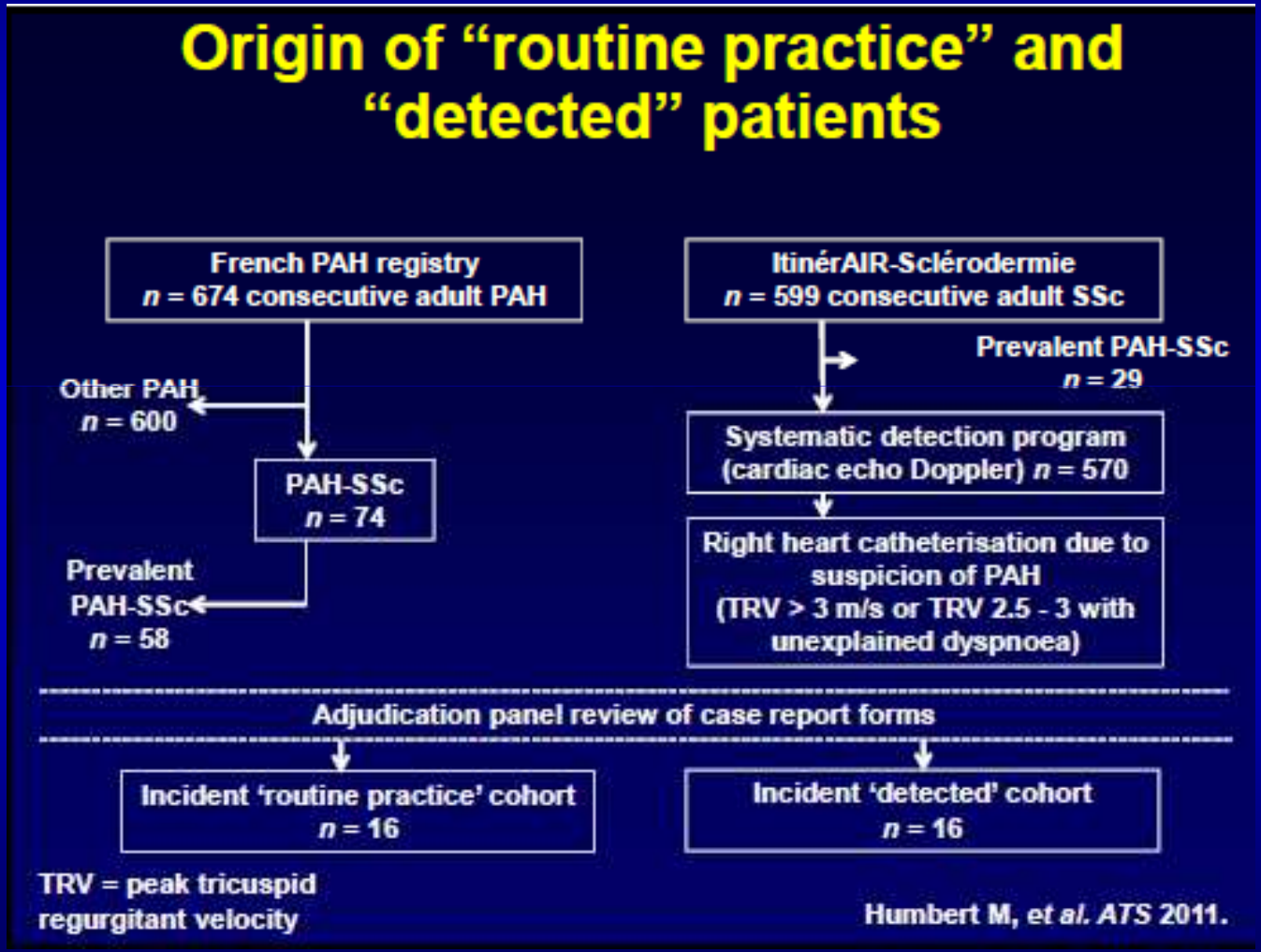
## Screening Can Help in Diagnosing the Disease in an Early Stage




Without screening, the majority of patients were diagnosed in WHO FC III or FC IV, and only 24% of patients were in WHO FC II at diagnosis.[1]

[1]Humbert M *et al. Am.J.Respir.Crit Care Med* 2006;173:1023-1030. [2]Hachulla E *et al. Arthritis Rheum* 2005; 52:3792-3800.

# Sclerosi Sistemica e PAH
# 1- screening e diagnosi precoce



# Sclerosi Sistemica e PAH
# 1- screenin e diagnosi precoce

## Haemodynamics at PAH-SSc diagnosis: "Routine practice" and "detected" patients

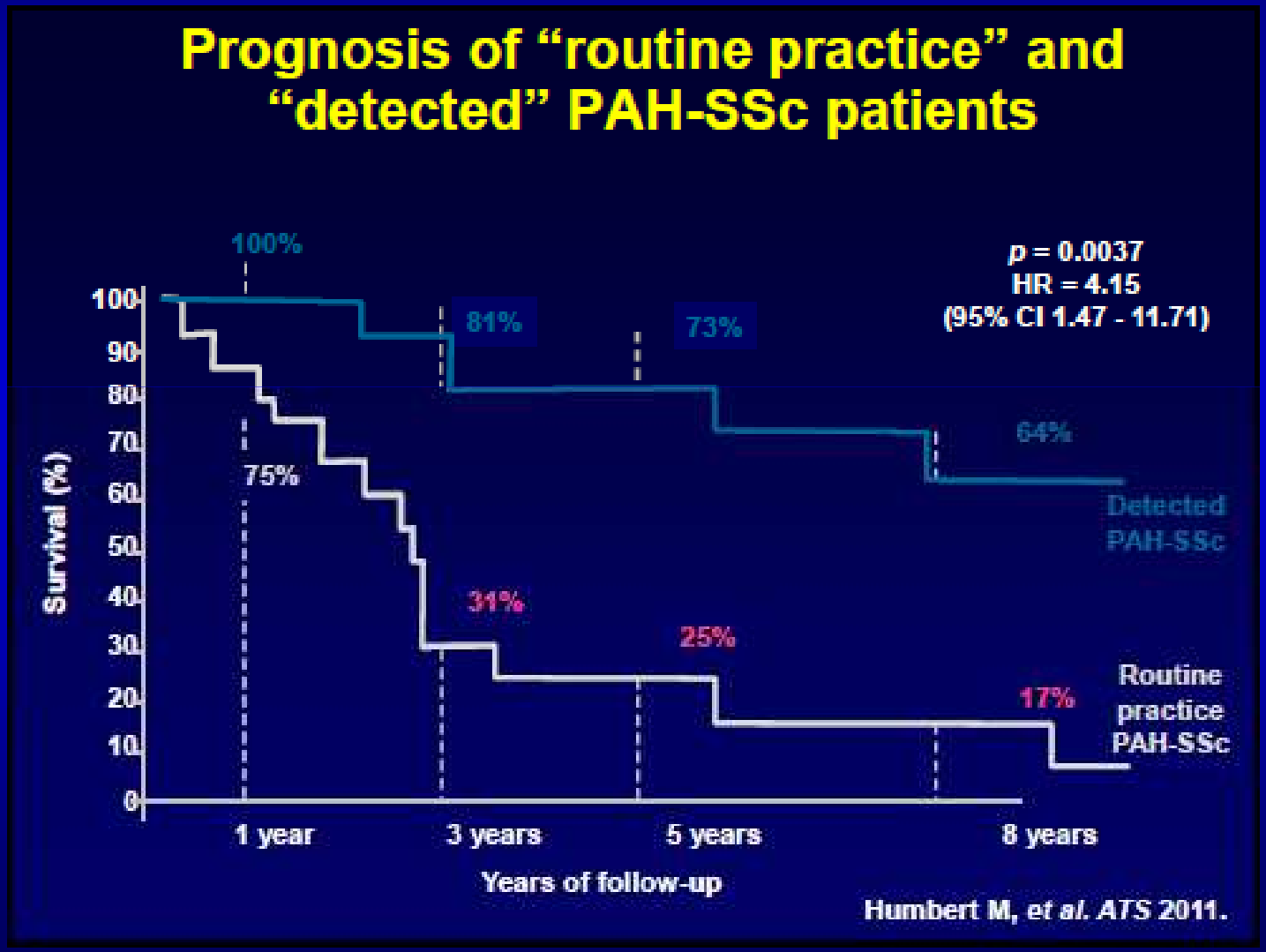
| | Routine practice ($n$ = 16) | Detected ($n$ = 16) | $p$ |
|---|---|---|---|
| RAP (mmHg) | 10 ± 5 | 6 ± 3 | 0.020 |
| mPAP (mmHg) | 49 ± 11 | 34 ± 10 | 0.0004 |
| mPAWP (mmHg) | 9 ± 4 | 10 ± 3 | 0.28 |
| Cardiac output (l/min) | 3.59 ± 1.10 | 5.96 ± 1.51 | < 0.0001 |
| Cardiac index (l/min/m²) | 2.37 ± 0.81 | 3.42 ± 0.92 | 0.0028 |
| PVRi (dynes·s·cm⁻⁵) | 1500 ± 602 | 613 ± 400 | < 0.0001 |

RAP = right atrial pressure; mPAP= mean pulmonary artery pressure;
mPAWP = mean pulmonary artery wedge pressure;
PVRi = pulmonary vascular resistance indexed;

Values are mean ± SD

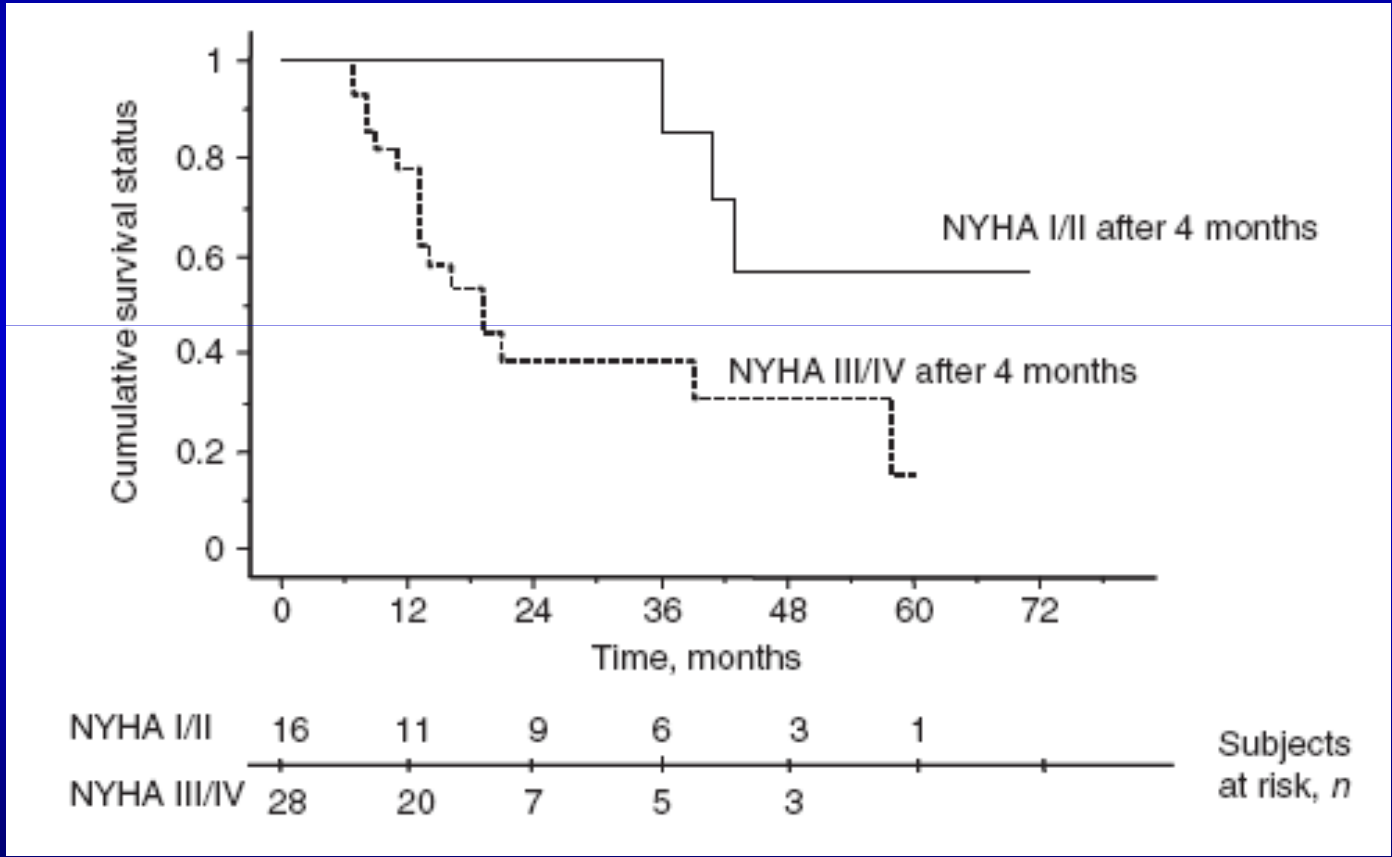
Humbert M, *et al. ATS* 2011.

# Sclerosi Sistemica e PAH
# 1- screenin e diagnosi precoce



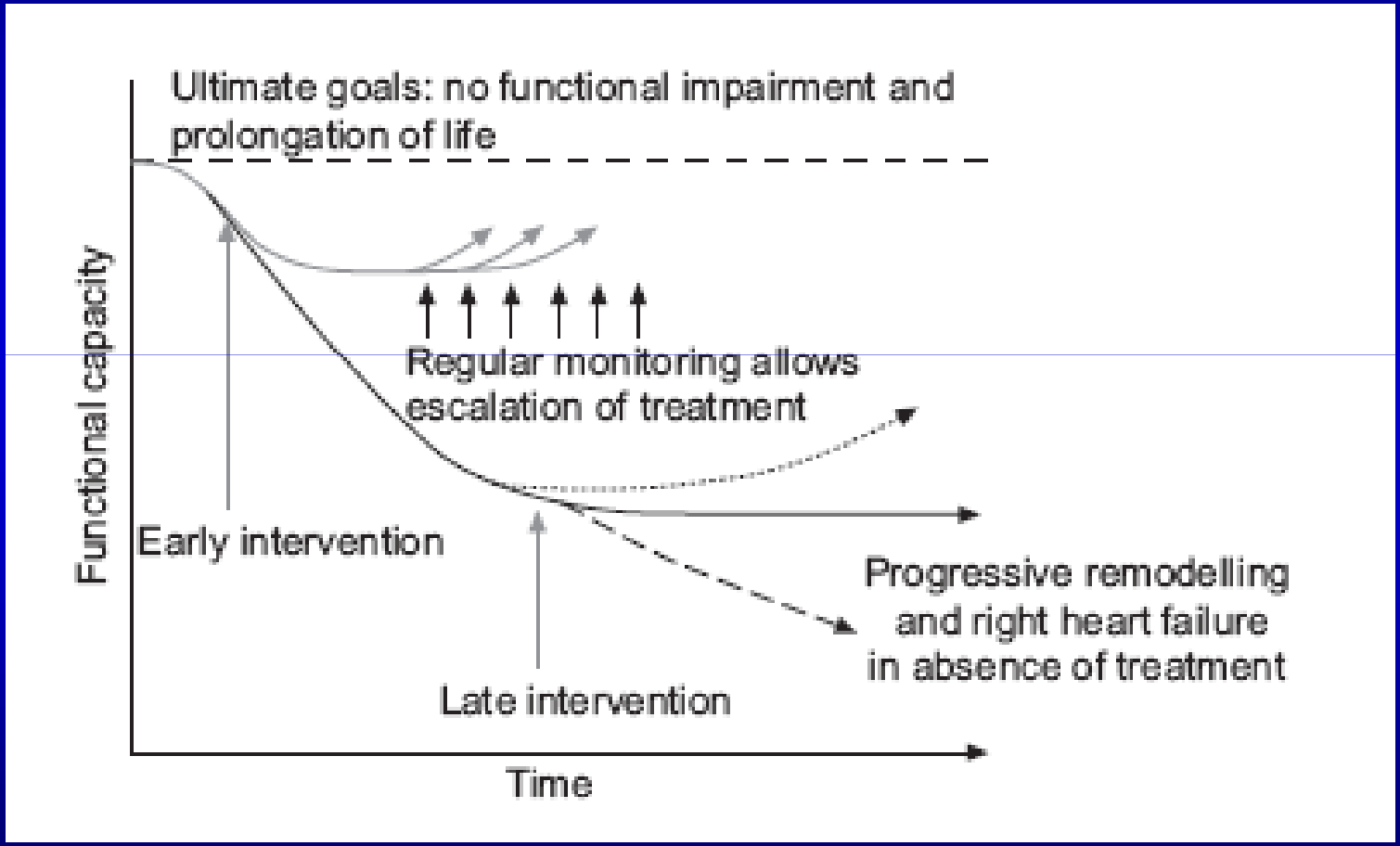
# Diagnosi precoce = prognosi migliore

systemic sclerosis-associated pulmonary arterial hypertension treated with bosentan




Launay D, et al. Rheumatology 2010; 49: 490-500.

# INTERVENIRE PRECOCEMENTE: AGIRE QUANDO È ANCORA POSSIBILE UN EFFETTO IMPORTANTE SULL'EVOLUZIONE DELLA MALATTIA.




Sitbon O and Galiè N. Eur Respir Rev 2010; 19: 118, 272-278

# Sclerosi Sistemica e PAH
# 1- screening e diagnosi precoce

## Quali a maggior rischio?

Arthritis Care & Research
Vol. 64, No. 3, March 2012, pp 303–310

**Table 2. Features associated with presence of PAH in scleroderma***

| | |
|---|---|
| Symptoms | Exertional dyspnea |
| Physical examination findings | Evidence of right-heart compromise; e.g., lower extremity edema, the murmur of TR, jugular venous distension, hepatomegaly, right ventricular heave, increased intensity of pulmonic component of second heart sound, diastolic pulmonic regurgitation murmur, or a prominent A wave in jugular venous pulse |
| Echocardiographic findings | RVSP >40 mm Hg<br>TR jet >3.0 meters/second<br>Right ventricular dilation/hypokinesis<br>RA dilation<br>Pericardial effusion |
| PFT parameters | DLCO <60% predicted in absence of extensive ILD<br>FVC%/DLCO% >1.6 |
| Other features | Elevated BNP or NT-proBNP<br>Oxygen desaturation with exercise |

* PAH = pulmonary arterial hypertension; TR = tricuspid regurgitation; RVSP = right ventricular systolic pressure; RA = right arterial; PFT = pulmonary function testing; DLCO = diffusing capacity for carbon monoxide; ILD = interstitial lung disease; FVC = forced vital capacity; BNP = B-type natriuretic peptide; NT-proBNP = N-terminal pro–brain natriuretic peptide.

# Sclerosi Sistemica e PAH
# 1- screening e diagnosi precoce

**Quale screening?**

## Metodica ideale

**Semplice**

**Poco costosa**

**Facilmente applicabile**

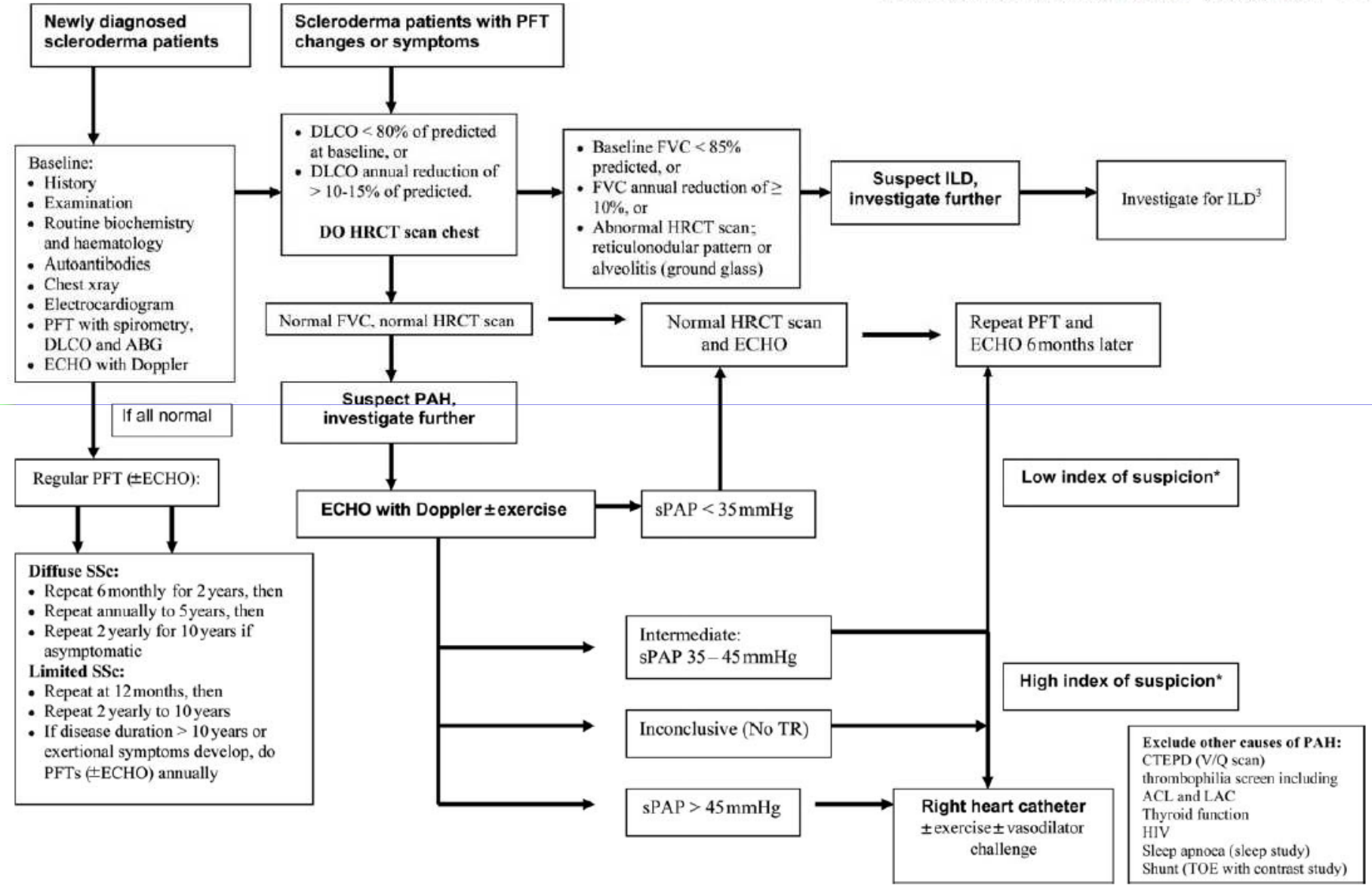
**Alta sensibilità**

**Alta specificità**

## Diverse proposte

# Proposed assessment pathway for detecting lung disease in patients with systemic sclerosis

*Internal Medicine Journal* **37** (2007) 485–494



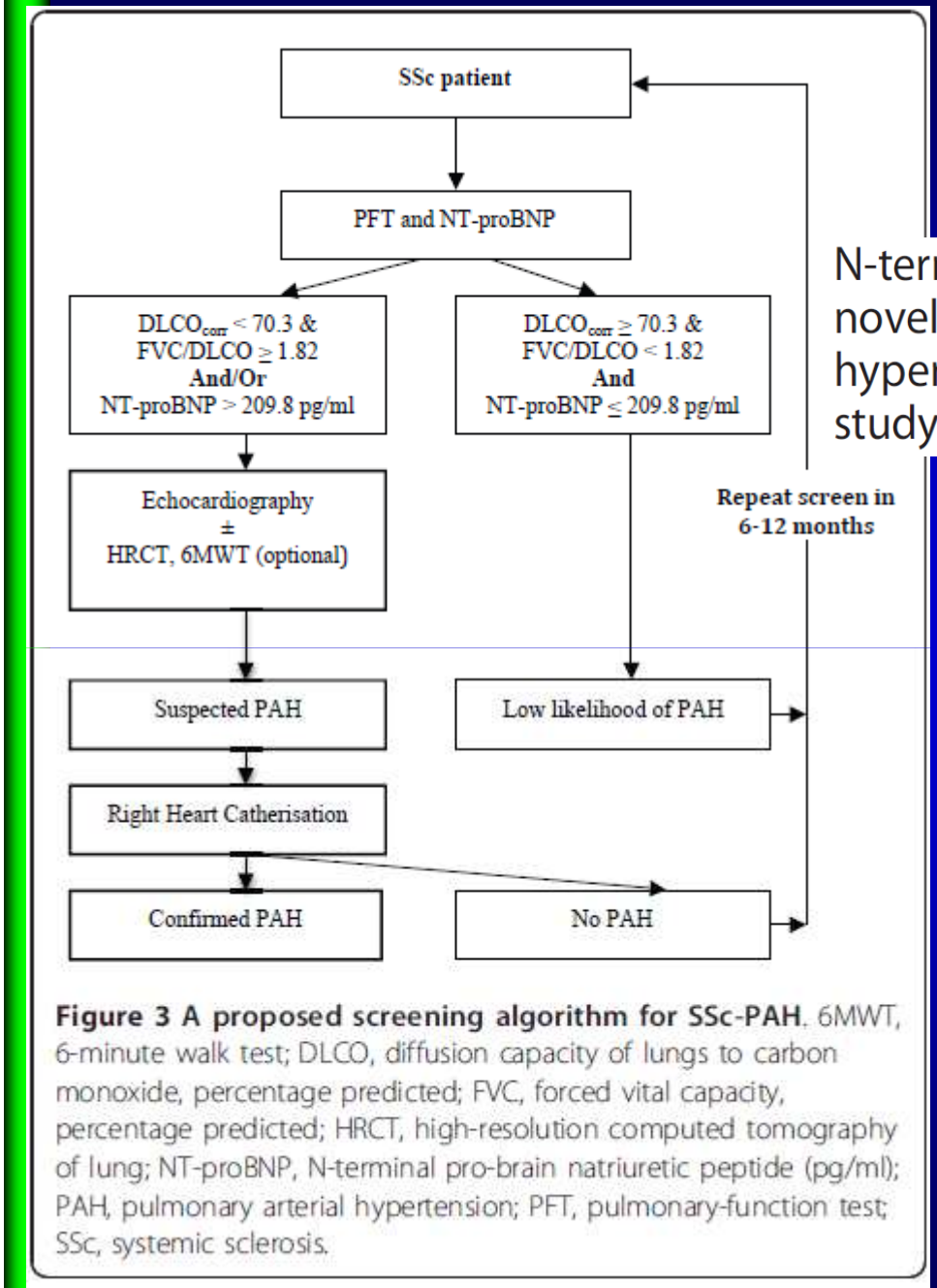



**Figure 3 A proposed screening algorithm for SSc-PAH**. 6MWT, 6-minute walk test; DLCO, diffusion capacity of lungs to carbon monoxide, percentage predicted; FVC, forced vital capacity, percentage predicted; HRCT, high-resolution computed tomography of lung; NT-proBNP, N-terminal pro-brain natriuretic peptide (pg/ml); PAH, pulmonary arterial hypertension; PFT, pulmonary-function test; SSc, systemic sclerosis.

N-terminal pro-brain natriuretic peptide in a novel screening algorithm for pulmonary arterial hypertension in systemic sclerosis: a case-control study

Thakkar *et al. Arthritis Research & Therapy* 2012, **14**:R143
http://arthritis-research.com/content/14/3/R143

# Sclerosi Sistemica e PAH
# 1- screening e diagnosi precoce

## Quale screening?

Table 3. Decision algorithm for screening and performing RHC in scleroderma*

| | Low risk | Mild risk | Moderate risk | High risk |
|---|---|---|---|---|
| Dyspnea, or Raynaud's phenomenon duration >8 years, or positive for anticentromere, or positive for isolated nucleolar-ANAs | No | Yes | Yes | Yes |
| DLco% (without extensive emphysema or ILD) | >70 | >70 | <70 | <60 |
| FVC%/DLco% | <1.6 | <1.6 | >1.6 | >1.6 |
| RVSP, mm Hg | <35 | <35 | >35 | >40 |
| Next step | Repeat PFTs annually Repeat echocardiogram in 2–3 years | Repeat PFTs and echocardiogram annually | Consider repeat echocardiogram in 3–6 months or proceed to RHC | Proceed to RHC |

* The presence of echocardiographic features of right ventricular hypokinesis or dilatation or an increased B-type natriuretic peptide (BNP) and N-terminal proBNP in a dyspneic scleroderma patient should lead to right-sided heart catheterization (RHC) irrespective of the estimated right ventricular systolic pressure (RSVP). ANAs = antinuclear antibodies; DLco = diffusing capacity for carbon monoxide; ILD = interstitial lung disease; FVC = forced vital capacity; PFT = pulmonary function testing.

Arthritis Care & Research
Vol. 64, No. 3, March 2012, pp 303–310

# Sclerosi Sistemica e PAH
# 1- screenin e diagnosi precoce

**Quale screening?**

Echo Doppler Predictors of Pulmonary Artery Hypertension in Patients with Systemic Sclerosis

Simone Frea, M.D.,* Michele Capriolo, M.D.,* Walter Grosso Marra, M.D.,* Margherita Cannillo, M.D.,* Enrico Fusaro, M.D.,† Daniela Libertucci, M.D.,‡ Mara Morello, M.D.,* and Fiorenzo Gaita, M.D.*

**Individuati predittori di sviluppo di PAH nella popolazione esaminata:**

- **TRV/TVI > 0.16**
- **TRV/AcT ≥ 0.022**

Echocardiography 2011; 28: 860-869

# Clinical and exercise-in systemic sc

Luna Gargani, MD,[a] Al
Eugenia Capati, MD,[e] I
Marco Fabio Costantin
Denisa Muraru, MD,[f] C
Federico Perfetto, MD,
Stefano Bombardieri, M
Eduardo Bossone, MD,
*Padua, Potenza, and S*

MD,[g]

*osseto,*

**Background** Patie
associated with a poor pr
in pulmonary artery syst

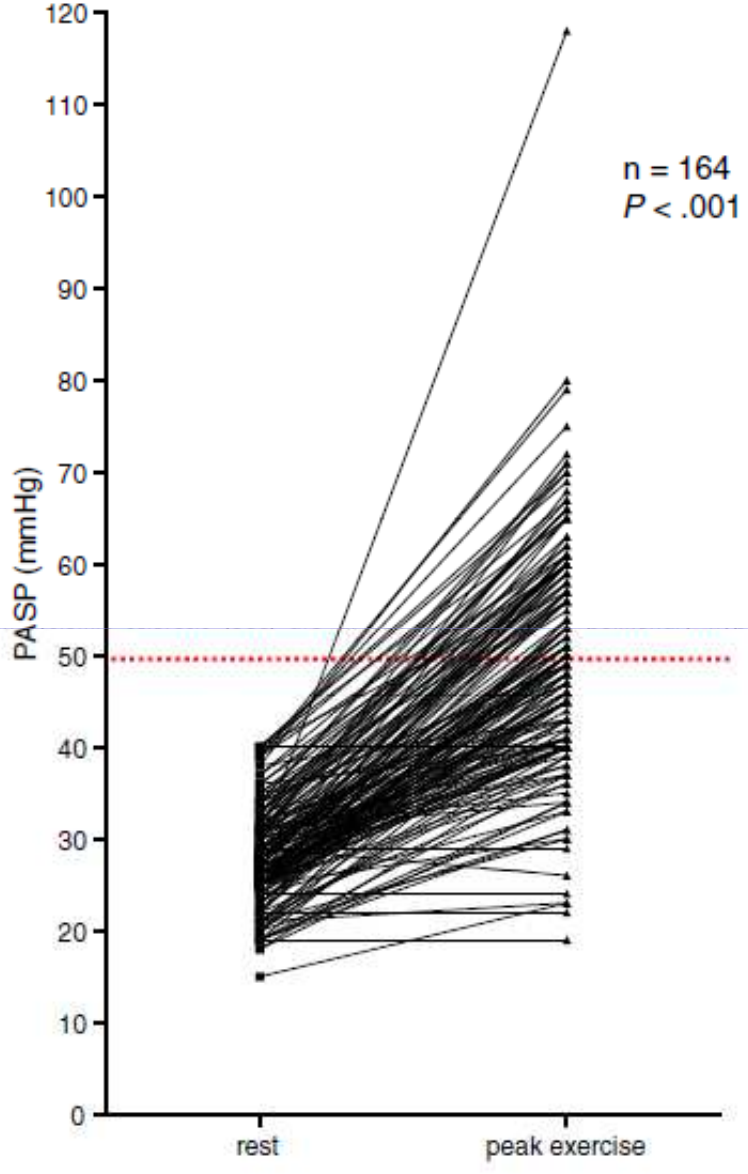
**Aim** The aim of this stu
PASP in a large populatic

**Methods** We selecte
who underwent a compr
Doppler echocardiograph
estimated noninvasively.
significant exercise-induce

**Results** Sixty-nine (42
Wood Units was present
presence of interstitial lun
none of these parameters

**Conclusions** Exerci
Peak exercise PASP is affe
5% of the patients, is as
underlying exercise-induc

on, which is
ced increase
n.
d increase in
<40 mm Hg)
bine exercise
e (PVR) were
considered a
peak PVR ≥3
ed that age,
) mm Hg, but
resting PASP.
and, only in
mechanisms



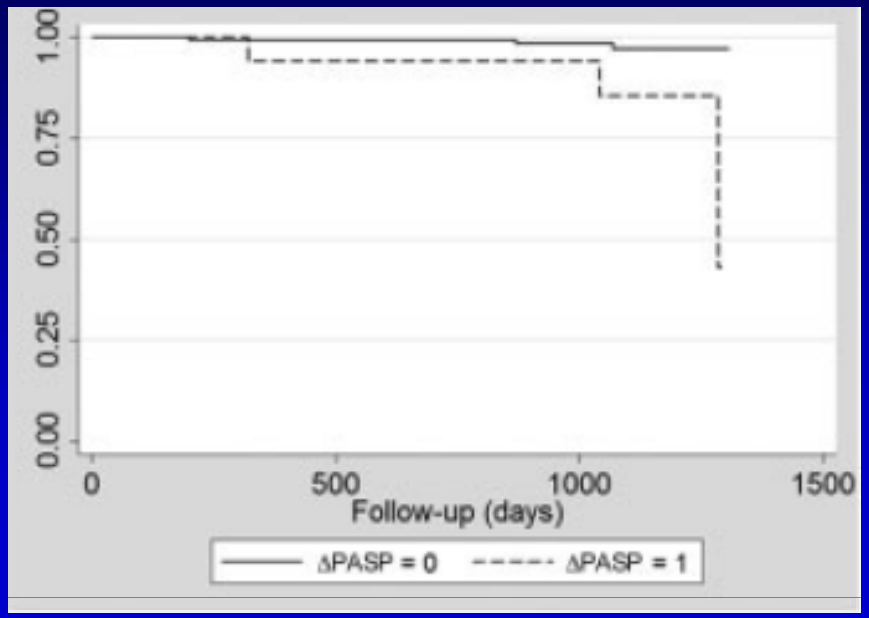

Changes in PASP values from rest to peak exercise for each individual patient.

ARTHRITIS & RHEUMATISM
Vol. 65, No. 9, September 2013, pp 2403–2411
DOI 10.1002/art.38043


# Stress Doppler Echocardiography in Systemic Sclerosis

## Evidence for a Role in the Prediction of Pulmonary Hypertension

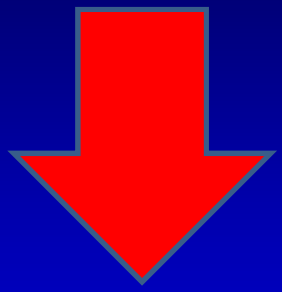
Veronica Codullo,[1] Roberto Caporali,[1] Giovanna Cuomo,[2] Stefano Ghio,[1] Michele D'Alto,[3] Chiara Fusetti,[1] Elena Borgogno,[1] Carlomaurizio Montecucco,[1] and Gabriele Valentini[2]




Curve di sopravvivenza libera da PAH in accordo con il deltaPAPS tra eco basale ed ecostress 0 ≤ 18 mmHg, 1 > 18 mmHg

*Conclusion.* An inappropriate response to exercise among patients with SSC is detectable by stress Doppler echocardiography. Independently of other clinical associations, increased Δpulmonary artery systolic pressure heralds PH. Stress Doppler echocardiography may represent an additional screening tool for this severe complication.

# Sceening applicando nuovi score di rischio

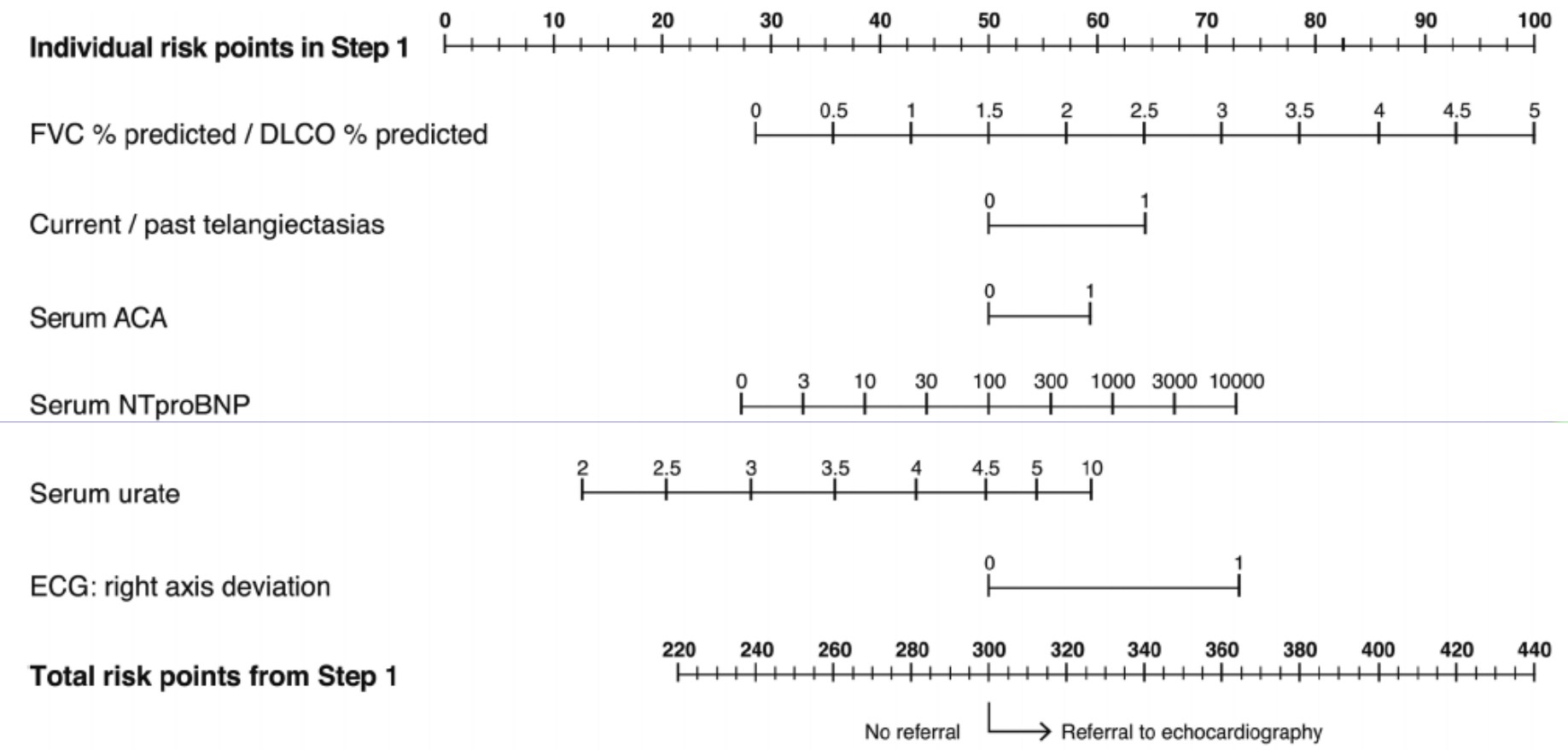


# The DETECT study

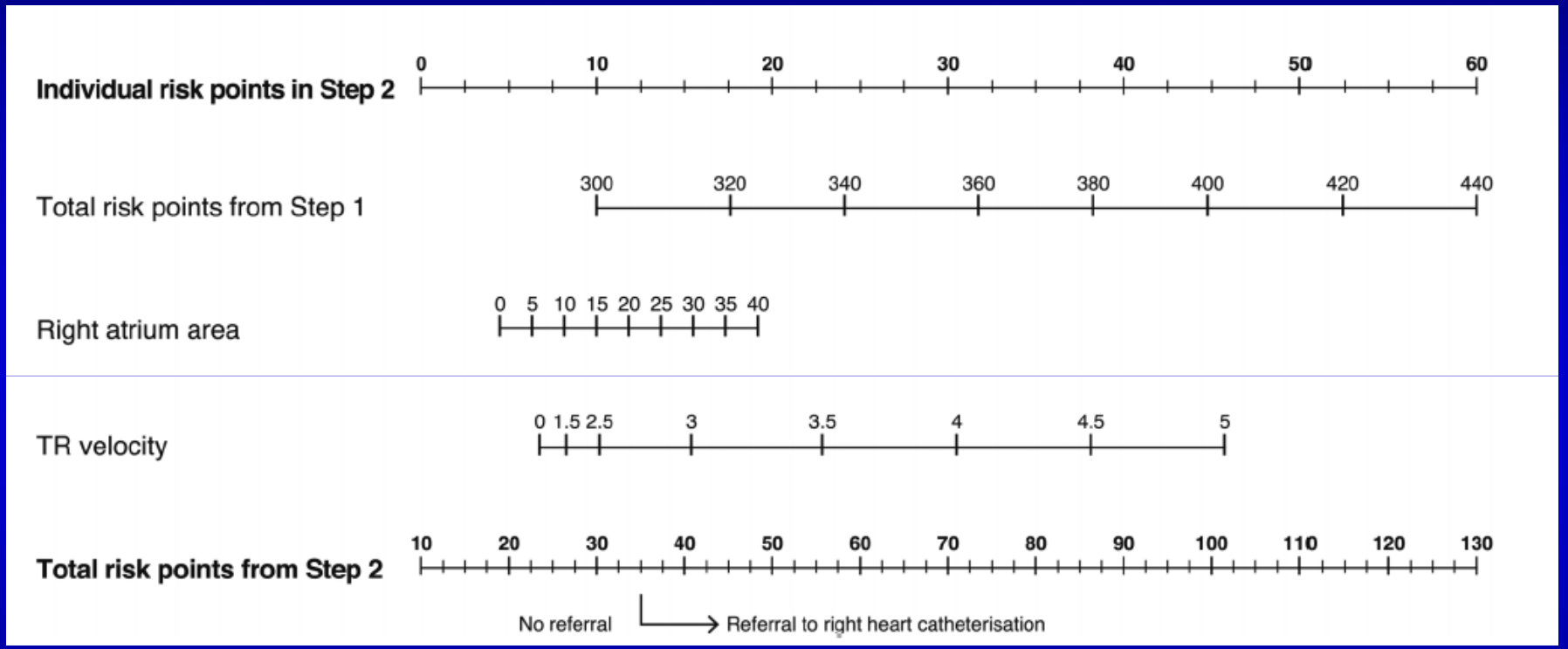
## Evidence-based detection of pulmonary arterial hypertension in systemic sclerosis: the DETECT study

J Gerry Coghlan,[1] Christopher P Denton,[2] Ekkehard Grünig,[3] Diana Bonderman,[4] Oliver Distler,[5] Dinesh Khanna,[6] Ulf Müller-Ladner,[7] Janet E Pope,[8] Madelon C Vonk,[9] Martin Doelberg,[10] Harbajan Chadha-Boreham,[11] Harald Heinzl,[12] Daniel M Rosenberg,[11] Vallerie V McLaughlin,[6] James R Seibold,[13] on behalf of the DETECT study group

Coghlan JG, *et al*. *Ann Rheum Dis* 2013;**00**:1–10. doi:10.1136/annrheumdis-2013-203301




Coghlan JG, *et al*. *Ann Rheum Dis* 2013;**00**:1–10. doi:10.1136/annrheumdis-2013-203301




Coghlan JG, *et al*. *Ann Rheum Dis* 2013;**00**:1–10. doi:10.1136/annrheumdis-2013-203301

# The DETECT study: superare le linee guida

Table 3 Model performance: comparison of PAH detection approaches

| Approach | RHC referral rate, % (positive detection assessments/all patients) | Overall missed PAH diagnoses, % (false negatives) | Overall sensitivity, % | Overall specificity, % | Overall PPV, % | Overall NPV, % |
|---|---|---|---|---|---|---|
| Primary analysis | | | | | | |
| DETECT algorithm N=319 | 62 | 4 | 96 | 48 | 35 | 98 |
| Other analyses | | | | | | |
| DETECT algorithm with 65% specificity at Step 2 N=319 | 41 | 15 | 85 | 72 | 47 | 94 |
| ESC/ERS guidelines*[1] N=371 | 40 | 29 | 71 | 69 | 40 | 89 |

*Evaluated on a subset of patients (N=371) with available data for the variables defined in the guideline, using the following criteria for RHC referral[1]: (a) Tricuspid regurgitant jet velocity >3.4 m/s; or (b) Tricuspid regurgitant jet velocity >2.8–≤3.4 m/s AND symptomatic (defined as at least one of the following DETECT parameters: current anginal pain, current syncope/near syncope, current dyspnoea, presence of peripheral oedema); or (c) Tricuspid regurgitant jet velocity ≤2.8 m/s AND symptomatic (defined as above) AND presence of additional echocardiography variables suggestive of pulmonary hypertension (defined as right atrium area >16 $cm^2$ and/or ratio of right ventricular diameter/left ventricular end diastolic diameter >0.8).

ESC/ERS, European Society of Cardiology/European Respiratory Society; NPV, negative predictive value; PAH, pulmonary arterial hypertension; PPV, positive predictive value (confirmed PAH out of all RHC referrals); RHC, right heart catheterisation.

Coghlan JG, *et al*. *Ann Rheum Dis* 2013;**00**:1–10. doi:10.1136/annrheumdis-2013-203301

## Sclerosi Sistemica e PAH
## 2- Trattare la malattia di base

**Trattare la malattia di base aggressivamente perchè i meccanismi fisiopatologici della PAH sono gli stessi della malattia di base (fibrosi, vasculite, disfunzione endoteliale).**
**Pazienti con forme aggressive di SS hanno PAH con cattiva prognosi.**

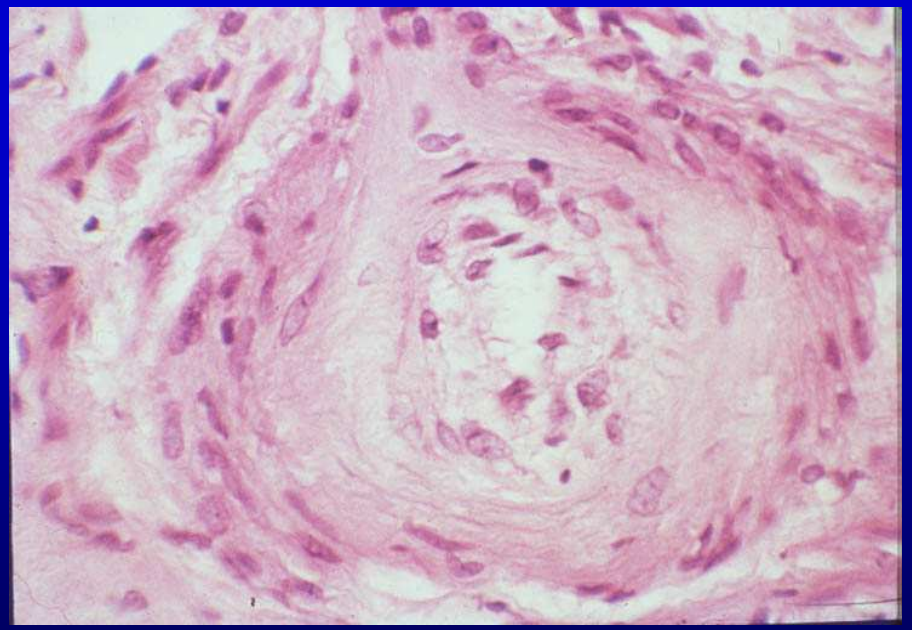
# Fisiopatologia dell' ipertensione arteriosa polmonare nella SSc:

Autoimmunità: -ACA

-ANA: U3-RNP,anti-dsDNA, anti-RO,U1-RNP

Angiogenesi

Infiammazione



Dorfmuller P  Hum Pathol 2007;38:893–902.

# Associazione con interstiziopatia polmonare

## Connective Tissue Disease–associated Pulmonary Arterial Hypertension in the Modern Treatment Era

Robin Condliffe[1,2], David G. Kiely[1], Andrew J. Peacock[3], Paul A. Corris[4,5], J. Simon R. Gibbs[6], Florenc Vrapi[7], Clare Das[7], Charlie A. Elliot[1], Martin Johnson[3], Julia DeSoyza[4], Chantal Torpy[6], Kim Goldsmith[2], Denise Hodgkins[2], Rodney J. Hughes[2], Joanna Pepke-Zaba[2], and J. Gerry Coghlan[7]

*Rationale*: Pulmonary arterial hypertension in association with connective tissue disease (CTD-PAH) has historically had a poor prognosis, with a 1-year survival rate among patients with systemic sclerosis–associated pulmonary arterial hypertension (SSc-PAH) of 45%. However, more therapies have become available.

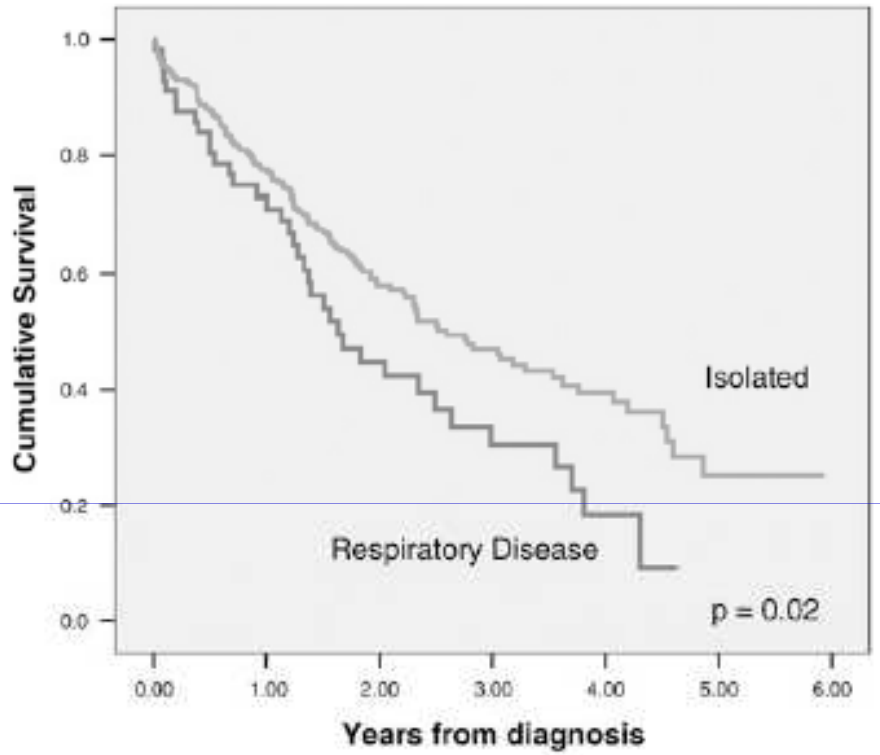
*Objectives*: To investigate the survival and characteristics of all patients diagnosed with CTD-PAH in the U.K. pulmonary hypertension service.

*Methods*: National registry of all incident cases of CTD-PAH diagnosed consecutively between January 2001 and June 2006.

*Measurements and Main Results*: Patients with CTD-PAH (429; 73% SSc-PAH) were diagnosed by a catheter-based approach. One- and 3-year survival rates were 78 and 47% for patients with isolated SSc-PAH. Survival was worse for those with respiratory disease–associated SSc-PAH (3-yr survival, 28%; $P = 0.005$) whereas survival among patients with exercise-induced SSc-PAH was superior (3-yr survival, 86%; $P = < 0.001$). Age, sex, mixed venous oxygen saturation, and World Health Organization functional class were independent predictors of survival in isolated SSc-PAH. Nineteen percent of patients with exercise-induced SSc-PAH and 39% of patients with isolated SSc-PAH who were in functional classes I and II had evidence of disease progression. The prevalence of diagnosed SSc-PAH is 2.93 per 1 million. The 3-year survival rate of 75% for those with pulmonary arterial hypertension associated with systemic lupus erythematosus (SLE-PAH) was significantly better than that for patients with SSc-PAH ($P = 0.01$).

*Conclusions*: Survival of patients with SSc-PAH in the modern treatment era is better than in historical series. A significant proportion of patients with mild functional impairment or exercise-induced SSc-PAH have evidence of disease progression. Survival of patients with respiratory disease–associated pulmonary hypertension is inferior. SLE-PAH has a better prognosis than SSc-PAH.

# Associazione con interstiziopatia polmonare




**Patients at risk**

| | | | | | | |
|---|---|---|---|---|---|---|
| 259 | 179 | 94 | 53 | 27 | 6 | Isolated |
| 56 | 38 | 18 | 10 | 3 | | Respiratory disease |

***Figure 2.*** Survival from diagnosis of patients with systemic sclerosis and isolated or respiratory disease–associated pulmonary hypertension.

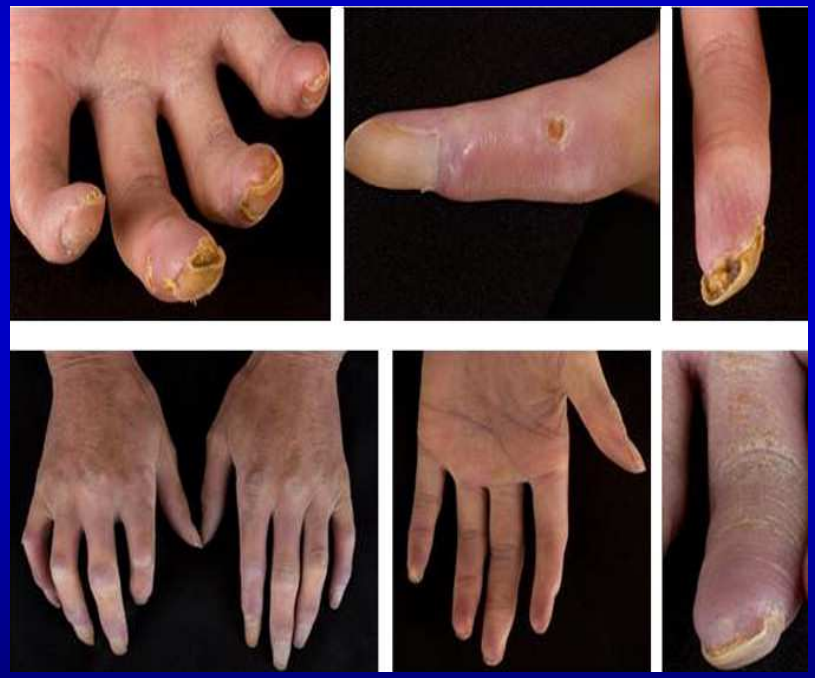
AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE VOL 179 2009

# Associazione con ulcere digitali

Le ulcere digitali (DUs) rappresentano una delle caratteristiche tipiche della vasculopatia della SSc.

Sono caratterizzate da:

- Dolore
- Perdita di tessuto
- Perdita di funzionalità manuale
- Diminuita Quality Of Life



# Associazione con ulcere digitali

## Farmaci efficaci nel trattamento di PAH e di ulcere digitali

Rheumatology 2014;53:570–571
doi:1(
Advar

In sy
and (

**Combination therapy with an endothelin-1 receptor antagonist (bosentan) and a phosphodiesterase V inhibitor (sildenafil) for the management of severe digital ulcerations in systemic sclerosis**

Clin Rheumatol. 2013 May;32(5):679-83. doi: 10.1007/s10067-013-2172-z. Epub 2013 Jan 24.

**Low occurrence of digital ulcers in scleroderma patients treated with bosentan for pulmonary arterial hypertension: a retrospective case-control study.**

Cozzi Rheumatol Int. 2013 Apr;33(4):1047-52. doi: 10.1007/s00296-012-2466-5. Epub 2012 Jul 26.

**Prospective, open-label, uncontrolled pilot study to study safety and efficacy of sildenafil in systemic sclerosis-related pulmonary artery hypertension and cutaneous vascular complications**

Ann Rheum Dis. 2011 Jan;70(1):32-8. doi: 10.1136/ard.2010.130658. Epub 2010 Aug 30.

**Bosentan treatment of digital ulcers related to systemic sclerosis: results from the RAPIDS-2 randomised, double blind, placebo-controlled trial.**

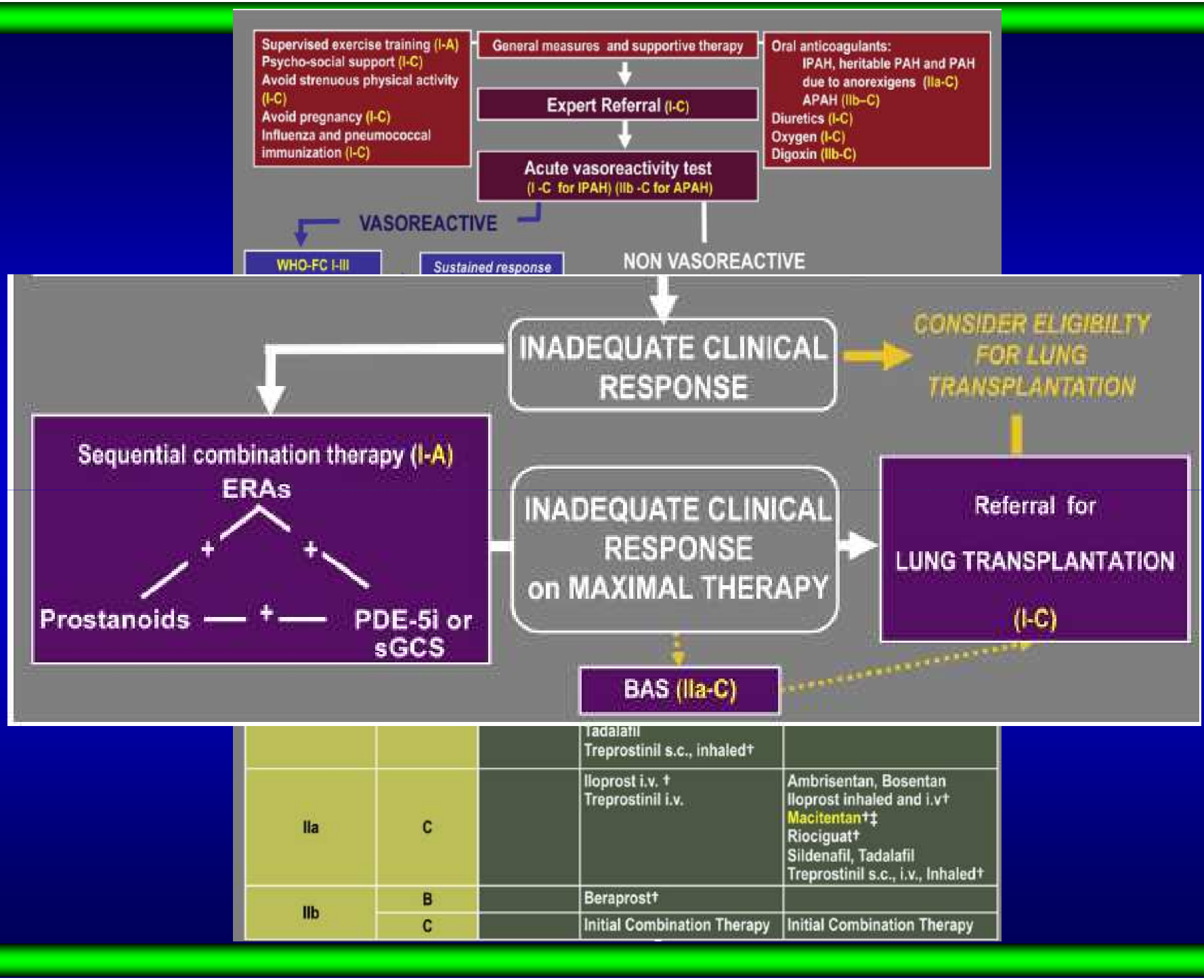
Matucci-Cerinic M[1], Denton CP, Furst DE, Mayes MD, Hsu VM, Carpentier P, Wigley FM, Black CM, Fessler BJ, Merkel PA, Pope JE, Sweiss NJ, Doyle MK, Hellmich B, Medsger TA Jr, Morganti A, Kramer F, Korn JH, Seibold JR.

# Sclerosi Sistemica e PAH

## TERAPIA PRECOCE E GOAL ORIENTED

| Determinants of prognosis | Worse prognosis | Better prognosis |
|---|---|---|
| Clinical evidence of RV failure | Yes | No |
| te of progression of symptoms | Rapid | Slow |
| Syncope | Yes | No |
| WHO-FC | IV | I, II |
| 6MWT | Shorter (<300 m) | Longer (>500 m)[a] |
| rdio-pulmonary exercise testing | Peak $O_2$ consumption <12 mL/min/kg | Peak $O_2$ consumption >15 mL/min/kg |
| NP/NT-proBNP plasma levels | Very elevated and rising | Normal or near-normal |
| Echocardiographic findings[b] | Pericardial effusion<br>TAPSE[b] <1.5 cm | No pericardial effusion<br>TAPSE[b] >2.0 cm |
| Haemodynamics | RAP >15 mmHg<br>or CI ≤2.0 L/min/m$^2$ | RAP <8 mmHg<br>and CI ≥2.5 L/min/m$^2$ |

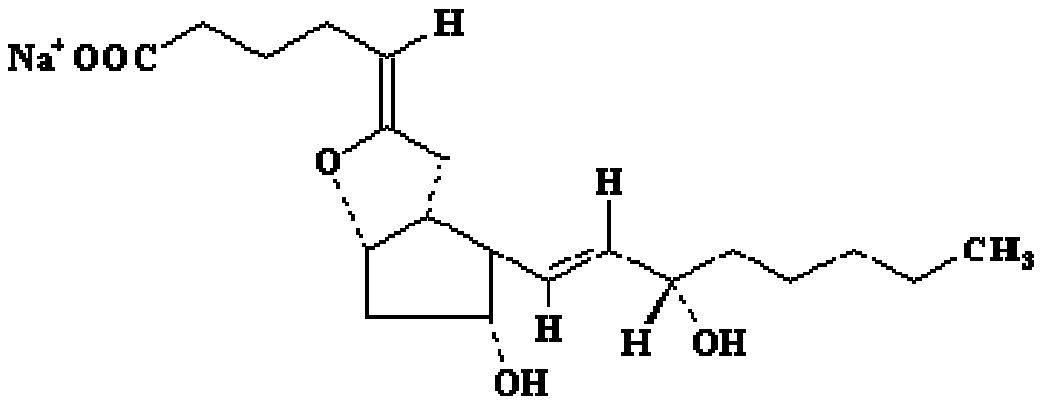
*Table 15*, patients with better or worse prognosis are separated by an intermediate group for which prognostication is more difficult. In these cases, additional factors not included in *Table 15*




| | | | | |
|---|---|---|---|---|
| | | | Tadalafil<br>Treprostinil s.c., inhaled† | |
| IIa | C | | Iloprost i.v. †<br>Treprostinil i.v. | Ambrisentan, Bosentan<br>Iloprost inhaled and i.v†<br>Macitentan†‡<br>Riociguat†<br>Sildenafil, Tadalafil<br>Treprostinil s.c., i.v., Inhaled† |
| IIb | B | | Beraprost† | |
| | C | | Initial Combination Therapy | Initial Combination Therapy |


**Epoprostenol**

$C_{20}H_{31}NaO_5$



**Survival in patients with primary pulmonary hypertension. Results from a national prospective registry.**

D'Alonzo GE1, Barst RJ, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, Fishman AP, Goldring RM, Groves BM, Kernis JT, et al.

Ann Intern Med. 1991 Sep 1;115(5):343-9.

[(P(t) = e((-A(x,y,z)t)), A(x,y,z) = e((-1.270-0.0148x + 0.0402y - 0.361z)), where P(t) is the probability of survival, t the time interval in years, x the mean pulmonary artery pressure, y the mean right atrial pressure, and z the cardiac index] and the French equation in patients with idiopathic, heritable, and anorexigen-associated PAH (n = 449).

# PAH: le novità

## 3- TERAPIA

**2. FARMACI SPECIFICI: a PDE5-i, ERA e prostanoidi si aggiungono….**

**MACITETAN E RIOCIGUAT**

**(+ farmaci non ancora approvati:Imatinib, Selexipag)**

## BACKGROUND

Current therapies for pulmonary arterial hypertension have been adopted on the basis of short-term trials with exercise capacity as the primary end point. We assessed the efficacy of macitentan, a new dual endothelin-receptor antagonist, using a primary end point of morbidity and mortality in a long-term trial.

## METHODS

We randomly assigned patients with symptomatic pulmonary arterial hypertension to receive placebo once daily, macitentan at a once-daily dose of 3 mg, or macitentan at a once-daily dose of 10 mg. Stable use of oral or inhaled therapy for pulmonary arterial hypertension, other than endothelin-receptor antagonists, was allowed at study entry. The primary end point was the time from the initiation of treatment to the first occurrence of a composite end point of death, atrial septostomy, lung transplantation, initiation of treatment with intravenous or subcutaneous prostanoids, or worsening of pulmonary arterial hypertension.

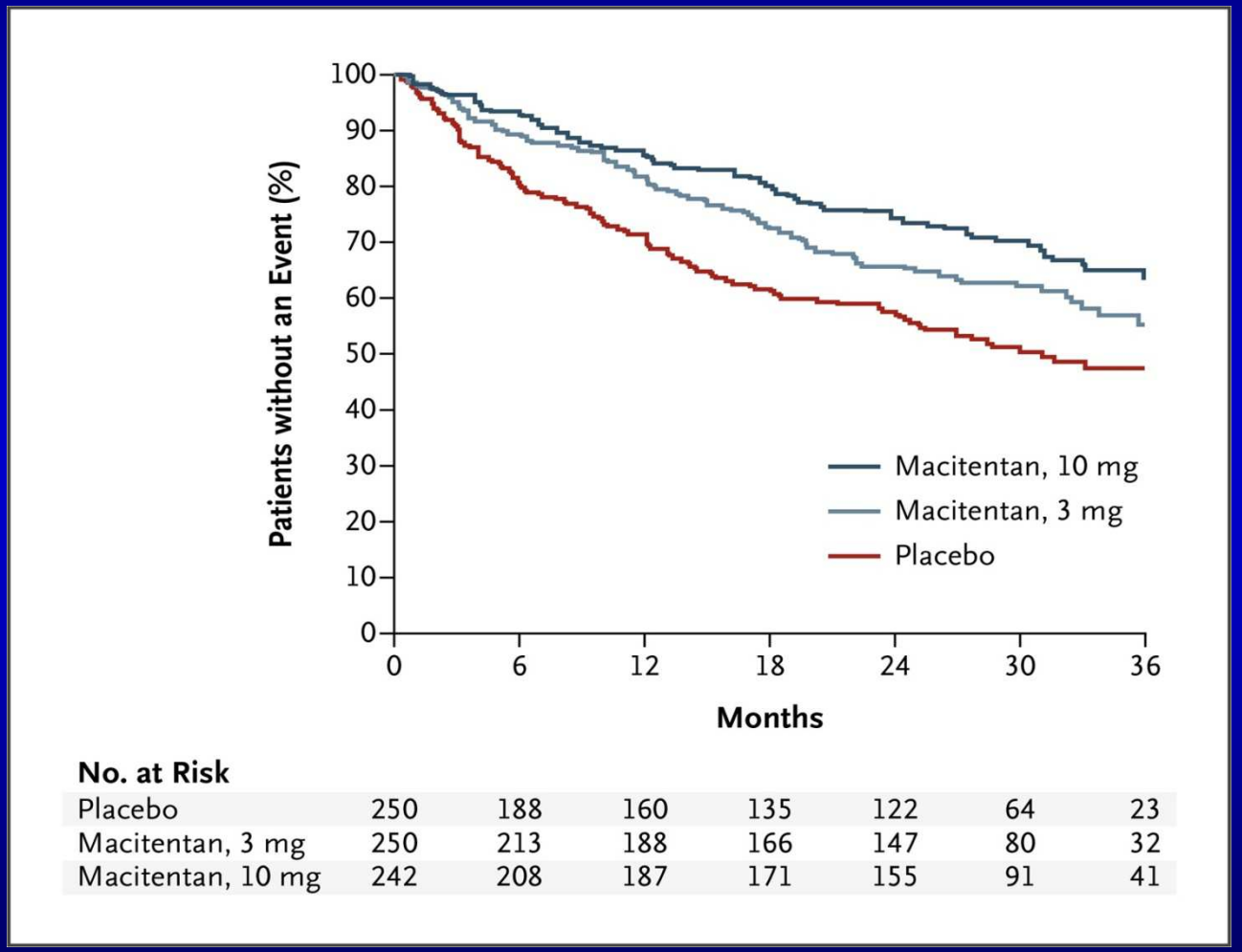
## RESULTS

A total of 250 patients were randomly assigned to placebo, 250 to the 3-mg macitentan dose, and 242 to the 10-mg macitentan dose. The primary end point occurred in 46.4%, 38.0%, and 31.4% of the patients in these groups, respectively. The hazard ratio for the 3-mg macitentan dose as compared with placebo was 0.70 (97.5% confidence interval [CI], 0.52 to 0.96; P=0.01), and the hazard ratio for the 10-mg macitentan dose as compared with placebo was 0.55 (97.5% CI, 0.39 to 0.76; P<0.001). Worsening of pulmonary arterial hypertension was the most frequent primary end-point event. The effect of macitentan on this end point was observed regardless of whether the patient was receiving therapy for pulmonary arterial hypertension at baseline. Adverse events more frequently associated with macitentan than with placebo were headache, nasopharyngitis, and anemia.

## CONCLUSIONS

Macitentan significantly reduced morbidity and mortality among patients with pulmonary arterial hypertension in this event-driven study. (Funded by Actelion Pharmaceuticals; SERAPHIN ClinicalTrials.gov number, NCT00660179.)

# Effect of Macitentan on the Composite Primary End Point of a First Event Related to Pulmonary Arterial Hypertension or Death from Any Cause.




| No. at Risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Placebo | 250 | 188 | 160 | 135 | 122 | 64 | 23 |
| Macitentan, 3 mg | 250 | 213 | 188 | 166 | 147 | 80 | 32 |
| Macitentan, 10 mg | 242 | 208 | 187 | 171 | 155 | 91 | 41 |

Pulido T et al. N Engl J Med 2013;369:809-818

The NEW ENGLAND JOURNAL of MEDICINE

# PAH: le novità

## 3- TERAPIA

**2. FARMACI SPECIFICI: nuovi e “vecchi” farmaci**

**Ma con quale e con quanti iniziare????**

# Choosing the best first line oral drug agent in patients with pulmonary hypertension: Evidence from a network meta-analysis

Giuseppe Biondi-Zoccai [b,e], Fabrizio D'Ascenzo [a,e,*], Margherita Cannillo [a], Nicky J. Welton [f], Walter Grosso Marra [a], Pierluigi Omedè [a], Daniela Libertucci [c], Enrico Fusaro [d], Michele Capriolo [a], Jacopo Perversi [a], Francesco Fedele [b], Giacomo Frati [b], Massimo Mancone [b], James J. DiNicolantonio [g], Carmine Dario Vizza [b], Claudio Moretti [a,e], Fiorenzo Gaita [a]

**Table 1**
Results from the Bayesian meta-analysis. Odds ratios (95% credible intervals) are reported for all treatment comparisons and outcomes where there was data available for estimation.

| Odds ratio (95% credible interval) Treatment comparison | Death | Clinical improvement | Clinical worsening |
|---|---|---|---|
| *Assuming each drug has its own independent effect relative to placebo* | | | |
| Bosentan vs. placebo | 0.64 (0.04, 2.71) | **1.81 (1.17, 2.71)** | **0.25 (0.11, 0.48)** |
| Sildenafil vs. placebo | 7.34 (0.14, 37.82) | **9.64 (3.31, 25.22)** | 0.54 (0.17, 1.33) |
| Beraprost vs. placebo | 0.96 (0.07, 4.09) | 1.06 (0.54, 1.89) | 0.74 (0.31, 1.48) |
| Ambrisentan vs. placebo | 0.50 (0.09, 1.58) | | **0.28 (0.12, 0.56)** |
| Sildenafil vs. bosentan | 37.97 (0.17, 174.90) | **5.57 (1.70, 15.20)** | 2.47 (0.56, 7.23) |
| Beraprost vs. bosentan | 4.70 (0.09, 26.90) | 0.61 (0.27, 1.20) | **3.40 (1.01, 8.53)** |
| Ambrisentan vs. bosentan | 2.38 (0.09, 12.60) | | 1.31 (0.39, 3.29) |
| Beraprost vs. Sildenafil | 1.45 (0.01, 9.01) | 0.14 (0.03, 0.38) | 1.82 (0.40, 5.33) |
| Ambrisentan vs. sildenafil | 0.74 (0.01, 4.09) | | 0.70 (0.15, 2.02) |
| Ambrisentan vs. beraprost | 1.58 (0.06, 8.51) | | 0.45 (0.13, 1.15) |
| *Assuming each PAH treatment effect relative to placebo is "similar" and come from a random effect distribution with a class effect mean and between drug, within class, variation.* | | | |
| Bosentan vs. placebo | 0.61 (0.11, 1.86) | **1.82 (1.19, 2.68)** | **0.30 (0.14, 0.52)** |
| Sildenafil vs. placebo | 1.06 (0.17, 4.48) | **7.76 (2.83, 19.14)** | **0.45 (0.19, 0.98)** |
| Beraprost vs. placebo | 0.71 (0.14, 2.28) | 1.12 (0.57, 1.98) | 0.56 (0.26, 1.17) |
| Ambrisentan vs. placebo | 0.54 (0.13, 1.39) | | **0.32 (0.15, 0.56)** |
| Sildenafil vs. bosentan | 2.95 (0.29, 15.25) | **4.44 (1.44, 11.36)** | 1.69 (0.63, 4.64) |
| Beraprost vs. bosentan | 1.84 (0.22, 7.87) | 0.64 (0.29, 1.24) | 2.17 (0.83, 5.85) |
| Ambrisentan vs. bosentan | 1.31 (0.19, 4.66) | | 1.18 (0.48, 2.61) |
| Beraprost vs. sildenafil | 1.20 (0.09, 4.41) | **0.19 (0.05, 0.48)** | 1.45 (0.51, 3.75) |
| Ambrisentan vs. sildenafil | 0.93 (0.07, 2.92) | | 0.83 (0.24, 1.79) |
| Ambrisentan vs. beraprost | 1.10 (0.14, 3.65) | | 0.66 (0.19, 1.28) |
| Mean effect PAH vs. placebo | 0.89 (0.12, 2.68) | 10.21 (0.15, 36.31) | 0.44 (0.13, 1.07) |
| Between drug, within class SD | 0.88 (0.03, 3.42) | 1.88 (0.44, 4.59) | 0.72 (0.03, 2.77) |

# Choosing the best first line oral drug agent in patients with pulmonary hypertension: Evidence from a network meta-analysis

Giuseppe Biondi-Zoccai [b,e], Fabrizio D'Ascenzo [a,e,*], Margherita Cannillo [a], Nicky J. Welton [f], Walter Grosso Marra [a], Pierluigi Omedè [a], Daniela Libertucci [c], Enrico Fusaro [d], Michele Capriolo [a], Jacopo Perversi [a], Francesco Fedele [b], Giacomo Frati [b], Massimo Mancone [b], James J. DiNicolantonio [g], Carmine Dario Vizza [b], Claudio Moretti [a,e], Fiorenzo Gaita [a]

The main results of the present work are: a) all drugs, except for beraprost, improved clinical outcomes; b) sildenafil offered higher rates of clinical improvement when compared to bosentan; and c) beraprost was inferior to sildenafil.

worsening, that sildenafil should be appraised as first choice for patients being treated for the first time. Moreover beraprost

# Monoterapia o terapia combinata?

**Terapia combinata sequenziale, non ancora evidenze a favore di terapia combinata di prima linea**

# Monoterapia o terapia combinata?

## Per avere risposte certe, sono necessari nuovi studi

## AMBITION study: trial in corso

**first line monotherapy with Tadalafil VS first line monotherapy with Ambrisentan VS first line combined therapihy with Tadalafil +Ambrisentan**

# IL TRAPIANTO POLMONE ?????

# Sclerosi Sistemica e PAH

## CONCLUSIONI

- PAH associata a SS: prognosi infausta
- Necessità di screening e diagnosi precoce
- Oltre a terapia PAH, non dimenticare la patologia di base

# Sclerosi Sistemica e PAH

**GRAZIE**