Prise en charge actuelle de l'HTAP

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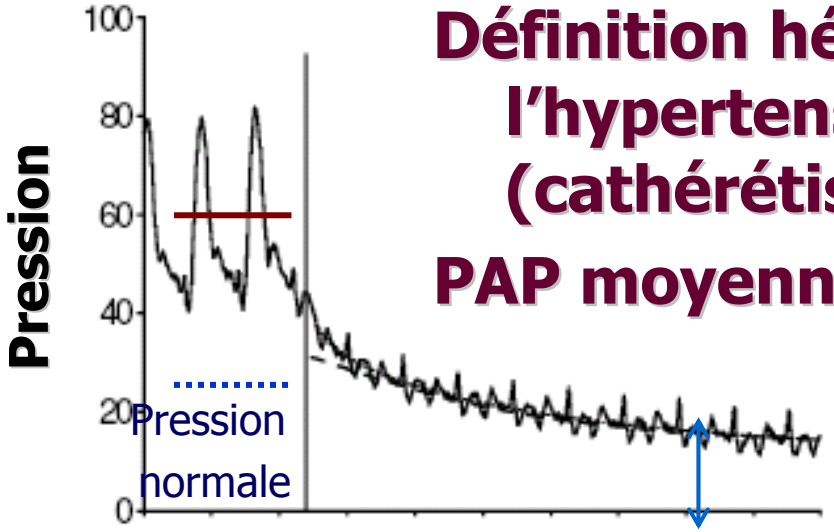
Laguiole, 21 juin 2014

Conflicts of interest

- **Consultant**: Actelion, CSL Behring, LFB Biotechnologies, Lilly, Pfizer, Octapharma
  - Financial support to ARMIIC
- **Investigator**: Actelion, CSL Behring, Pfizer
- **Financial support (grants to ARMIIC)**: Actelion, CSL Behring, GSK, LFB Biotechnologies, Pfizer
- **Invited conference**: SOBI, Roche, Actelion, CSL Behring, Octapharma, GSK, LFB Biotechnologies, Pfizer, Lilly, UCB pharma

HTAP: définition



Définition hémodynamique de l'hypertension pulmonaire (cathérétisme droit)

PAP moyenne > 25 mmHg au repos

Définition hémodynamique de l'hypertension artérielle pulmonaire (cathérétisme droit):

- PAP moyenne > 25 mmHg au repos

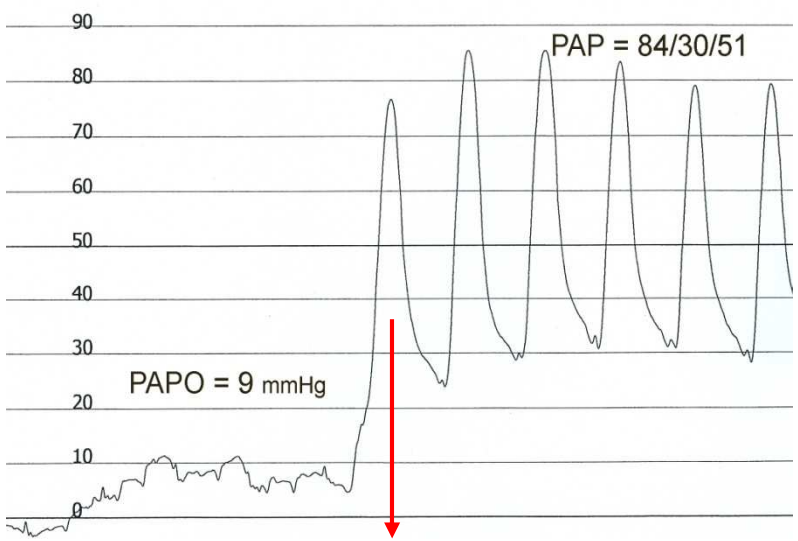
Et

- Pression capillaire pulmonaire < 15 mmHg au repos

Galiè N et coll. Eur Heart J. 2009 & Eur Resp J 2009

ᑭ pré et post capillaire
inition

HTP pré capillaire

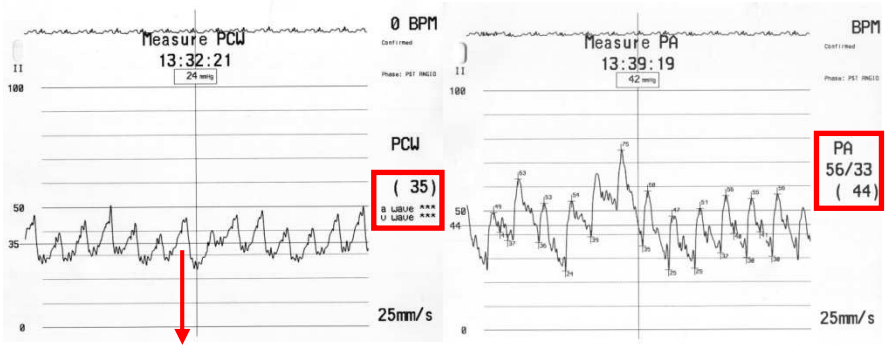


PAPm ≥ 25 mmHg[1]

PAPO ≤ 15 mmHg[1]

PAPd – PAPO > 10 mmHg[2]

HTP post capillaire passive



PAPm ≥ 25 mmHg[1]

PAPO > 15 mmHg[1]

GTP ≤ 12 mmHg[1]

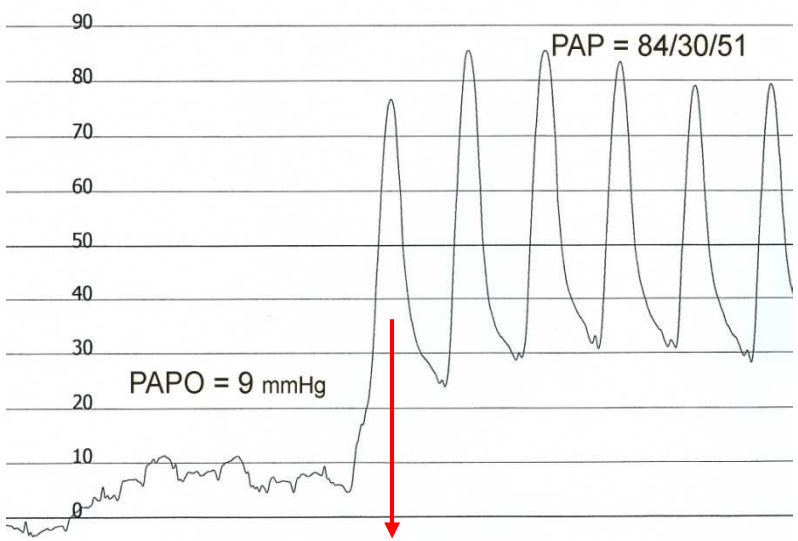
PAPd – PAPO ≤ 10 mmHg[2]

1. *Galiè N et al. Eur Respir J 2009*
2. *Chemla D et al. Eur Respir J 2002*

Courtesy X Jais

ᑭ pré et post capillaire
inition

HTP pré capillaire



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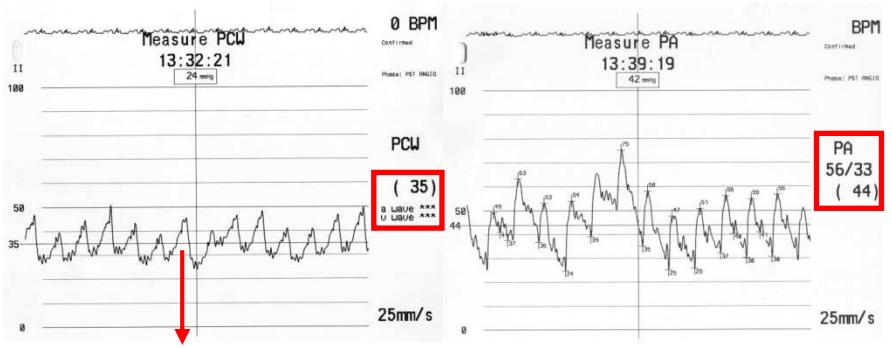
HTP post capillaire passive



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Courtesy X Jais

Updated clinical classification of pulmonary hypertension

(4th PH World Conference – Dana Point, CA – Feb 2008)

1. Pulmonary Arterial Hypertension

- 1.1. Idiopathic PAH
- 1.2. Heritable
  - 1.2.1. BMPR2
  - 1.2.2. ALK1, endoglin (with or w/o HHT)
  - 1.2.3. Unknown
- 1.3. Drugs and toxins induced
- 1.4. Associated with:
  - 1.4.1. Connective tissue diseases
  - 1.4.2. HIV infection
  - 1.4.3. Portal hypertension
  - 1.4.4. Congenital heart diseases
  - 1.4.5. Schistosomiasis
  - 1.4.6. Chronic haemolytic anemia
- 1.5. Persistent PH of the newborn

1'. PVOD and PCH

2. PH due to left heart diseases

- 2.1. Systolic dysfunction
- 2.2. Diastolic dysfunction
- 2.3. Valvular disease

3. PH due to lung diseases and/or hypoxia

- 3.1. COPD
- 3.2. Interstitial lung diseases
- 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 PH (CTEPH)

5. PH with unclear and/or mulifactorial mechanisms

- 5.1. Haematological disorders : myeloproliferative disorders splenectomy.
- 5.2. Systemic disorders, Sarcoidosis, pulmonary Langerhans cell histiocytosis, LAM, neurofibromatosis, vasculitis
- 5.3. Metabolic disorders : Glycogen storage disease, Gaucher disease, Thyroid disorders
- 5.4. Others : tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis.

Simonneau G, et al. J Am Coll Cardiol 2009.

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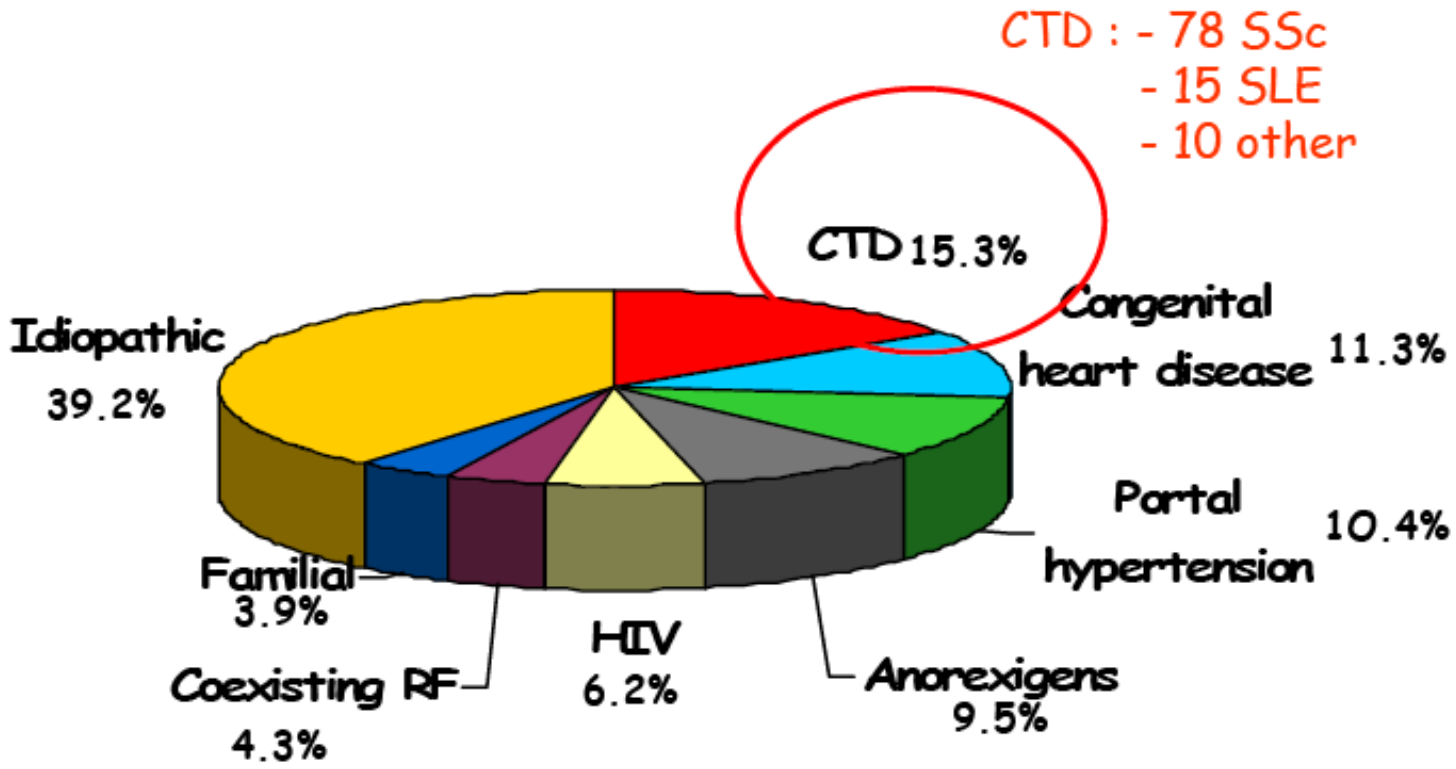
Simonneau G, et al. J Am Coll Cardiol 2009.

L'HTAP en France: données du registre national

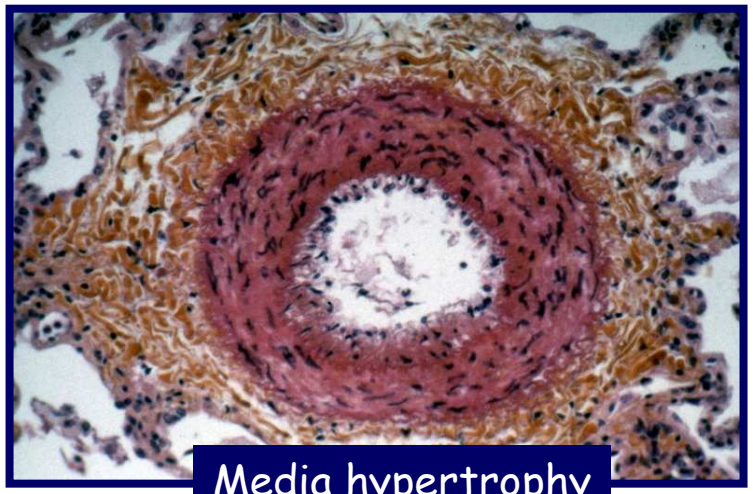


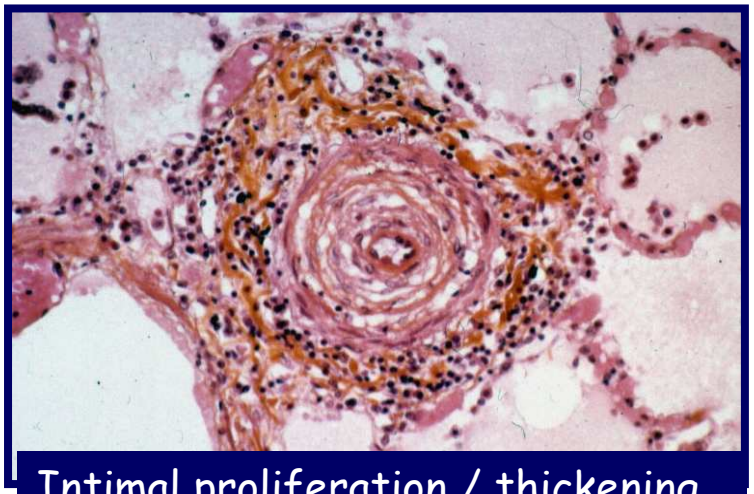
N = 674

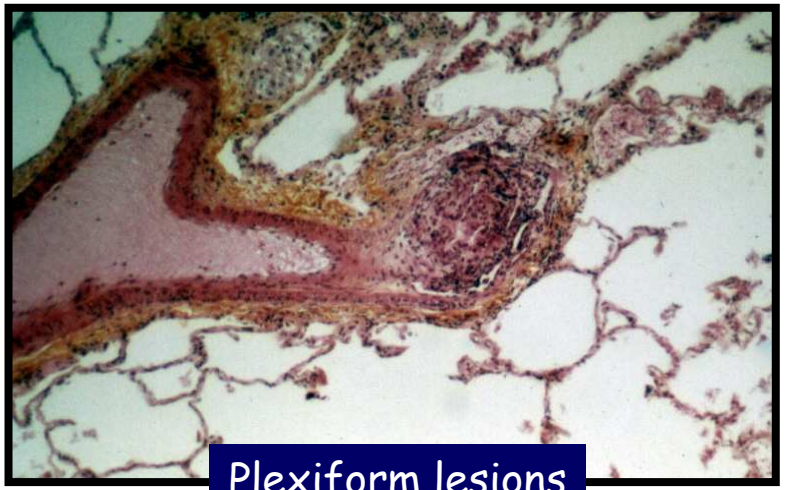
Humbert M et al. Am J Respir Crit Care Med 2006;173:1023

HYPERTENSION ARTERIELLE PULMONAIRE
Anatomopathologie

- Prolifération des cellules musculaires lisses et des cellules endothéliales

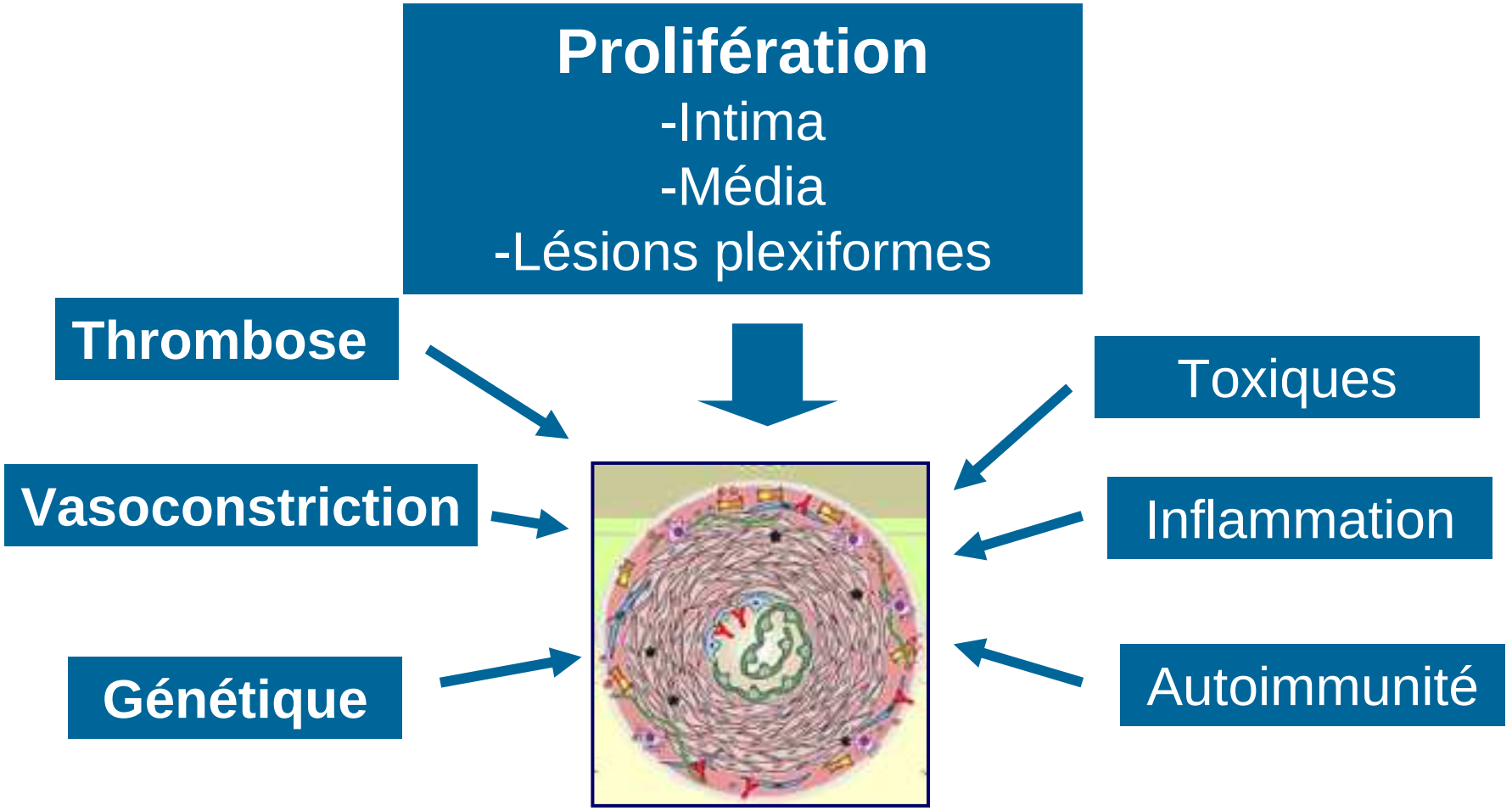

Media hypertrophy


Intimal proliferation / thickening


Plexiform lesions

Courtesy of Marc Humbert

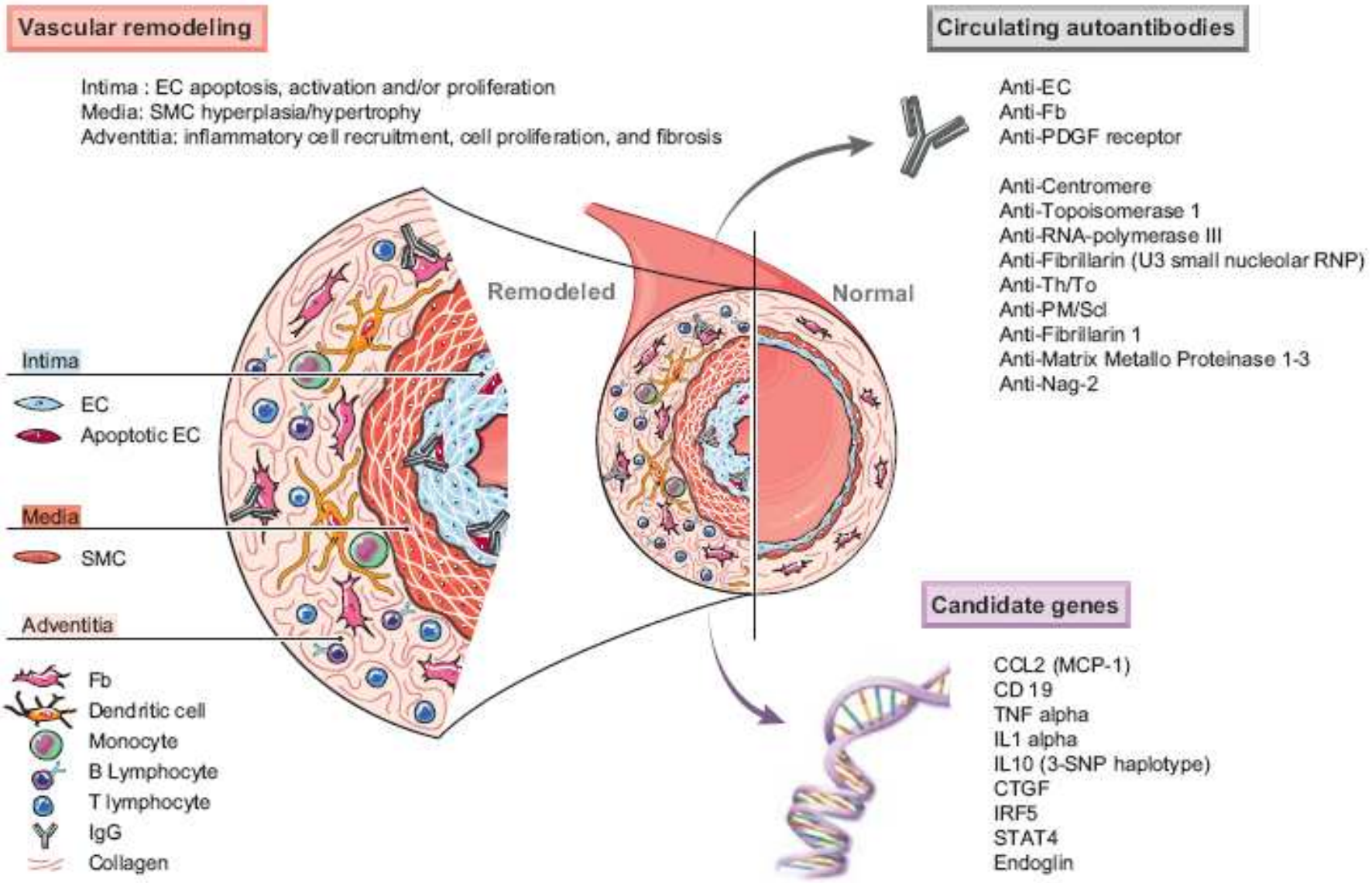
HTAP: principaux mécanismes en cause



Réduction de la lumière artériolaire pulmonaire

Remodelage vasculaire

Pulmonary vascular remodeling in SSc-PAH



Le Pavec J et al Am J Resp Crit Care Med 2010

Heritable forms of PAH

- Germline mutation BMPR2
- Endoglin
- ALK1
- SMAD9
- CAV1
- KCNK3 (gene encoding potassium channel subfamily K, member 3)

- Autosomal dominant
- Reduced penetrance

Austin ED Semin Resp Crit Care Med 2013

Risk factors for and associated conditions of PAH

Definite	Possible
Aminorex	Cocaine
Fenfluramine	Phenylpropanolamine
Dexfenfluramine	St John's Wort
Toxic rapeseed oil	Chemotherapeutic agents
Benfluorex	Selective serotonin reuptake inhibitors
Dasatinib	Pergolide
Likely	**Unlikely**
Amphetamines	Oral contraceptives
L-Tryptophan	Oestrogen
Methamphetamines	Cigarette smoking

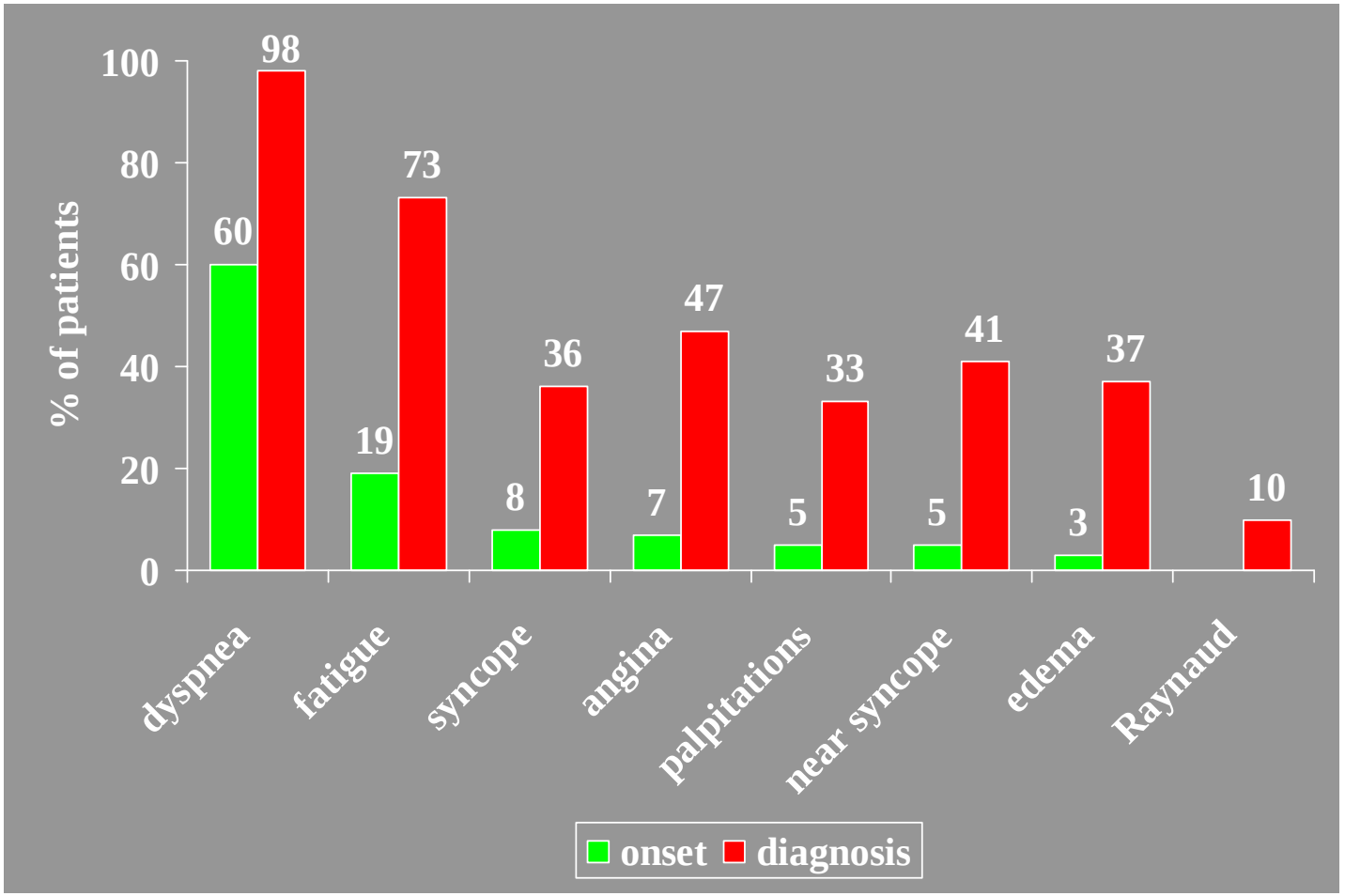
Montani et al. Eur Respir Rev 2013; 22: 244–250

Benfluorex

- Benzoate ester, structural and pharmacological characteristics similar to fenfluramine derivatives (active and common metabolite: norfenfluramine).
- 1976: treatment for diabetes and metabolic syndrome
- Prescribed mainly in France (5 million patients exposed).
- 2009 - case series: possible cardiotoxic effects
- Case-control study: benfluorex is associated with valvular heart diseases and premature deaths.
- French PAH Network: 85 cases of PH associated with benfluorex exposure including 70 patients with PAH.
- 33% of patients were also exposed to fenfluramine derivatives
- Additional risk factor for PAH identified in 20/70 PAH patients.
- It is highly probable that benfluorex triggers PAH.

Frachon I et al. Plos One 2010
Savale L et al. Eur Respir J 2012

Symptoms (IPAH)



NIH registry: Rich, Ann Intern Med 1987

Work-Up Pulmonary hypertension (I)

- NYHA Functional Class
- Blood tests
- 6-MWD
- Chest Radiography
- ECG
- Echocardiography
- Abdominal ultrasound
- HRCT of the chest
- V/Q lung scan (± pulmonary angiography)
- Right heart catheterization

WHO/NYHA Functional Classification

Class I

Are without resulting limitation of physical activity
ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain or near syncope

Class II

Have slight limitation of physical activity
they are comfortable at rest
ordinary physical activity causes undue dyspnoea or fatigue, chest pain or near syncope

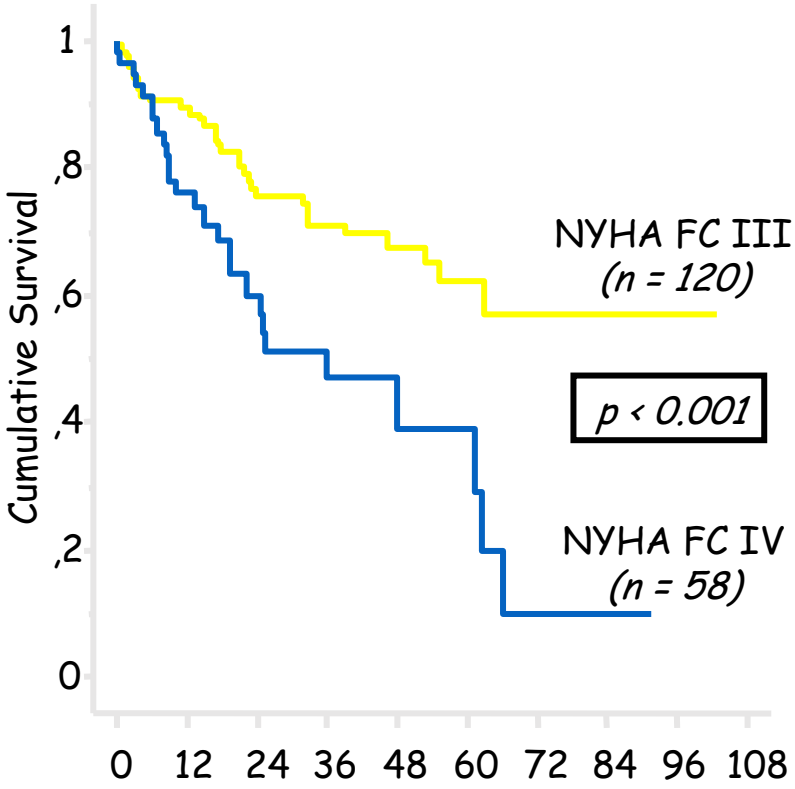
Class III

Have a pronounced limitation of physical activity
they are comfortable at rest
less than ordinary activity causes undue dyspnoea or fatigue, chest pain or near syncope

Class IV

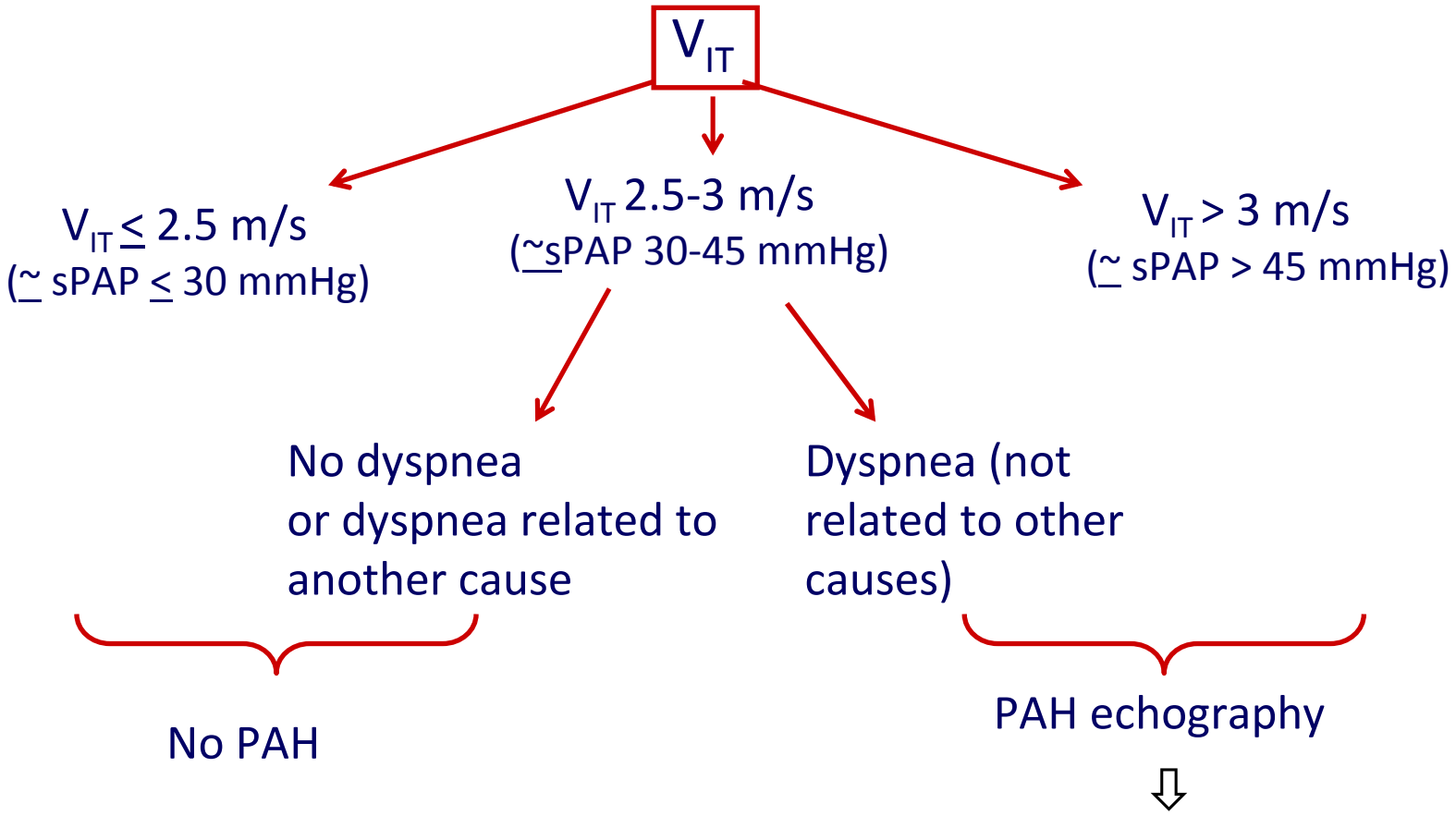
Show inability to carry out any physical activity without symptoms
these patients manifest signs of right heart failure
dyspnoea and/or fatigue may even be present at rest
discomfort is increased by any physical activity

Survival in IPAH patients according to baseline NYHA functional class



Sitbon, J Am Coll Cardiol 2002

Cardiac EchoDoppler
PAH definition



Hachulla et al. Arthritis Rheum 2005

Cardiac catheterisation (n=33)

- PAH : 18
- [mPAP > 25 mmHg at rest or > 30 mmHg at exercise with PAwP < 15 mmHg]
  - 25-35 mmHg: 14
  - 35-45 mmHg: 3
  - 45 mmHg: 1
- Post-capillary “venous”pulmonary hypertension: 3 (10%)
- No PAH : 12 => 6 with mPAP > 20 mmHg

Hachulla et al. Arthritis Rheum 2005

Estimated incidence of pulmonary hypertension during the 3-year followup period*

	Estimated incidence (no. of cases per 100 patient-years)	95% CI
All forms of pulmonary hypertension	1.37	0.74–2.00
Pulmonary arterial hypertension	0.61	0.26–1.20
Among patients with lcSSc	0.40	0.11–1.03
Among patients with dcSSc	1.25	0.34–3.20
Postcapillary pulmonary hypertension	0.61	0.26–1.20
Pulmonary hypertension secondary to pulmonary fibrosis	0.15	0.02–0.55

* 95% CI = 95% confidence interval; lcSSc = limited cutaneous systemic sclerosis; dcSSc = diffuse cutaneous systemic sclerosis.

Hachulla et al. Arthritis Rheum 2009

Work-Up Pulmonary hypertension (II)

- **Doppler Echocardiography is a good tool to detect PH**
- **Diagnostic workup for PAH includes …**
  - **Blood tests for HIV, ANA etc. …**
  - **NYHA functional class, 6-MWD , PFT, ECG**
  - **Imaging**

    - HRCT of the chest
    - V/Q lung scan (± pulmonary angiography)
    - Echo for liver

Cave: Additional investigations of associated disease

Work-Up Pulmonary hypertension (III)

- Accurate exploration at baseline is important to estimate

a) Prognosis of patients
b) Discuss PAH specific treatment

Right Heart Catheterization

RHC must be performed in all cases:

- To confirm diagnosis (pre-capillary PH)
- To assess severity
- To perform acute vasodilator testing
- To make decision on therapy
- To assess response to therapy

Rationale for DETECT

- PAH is a leading cause of death in SSc patients[1,2]
- Screening may lead to early diagnosis and beneficial early intervention
- Current screening is based on consensus rather than robust evidence
- TR velocity forms the basis of ESC / ERS screening recommendations, but it…
  - …does not accurately reflect invasive pressures
  - …is not present in all patients[3,4]

/ ERS: European Society of Cardiology / European
piratory Society; TR: tricuspid regurgitant jet
20 October 2013

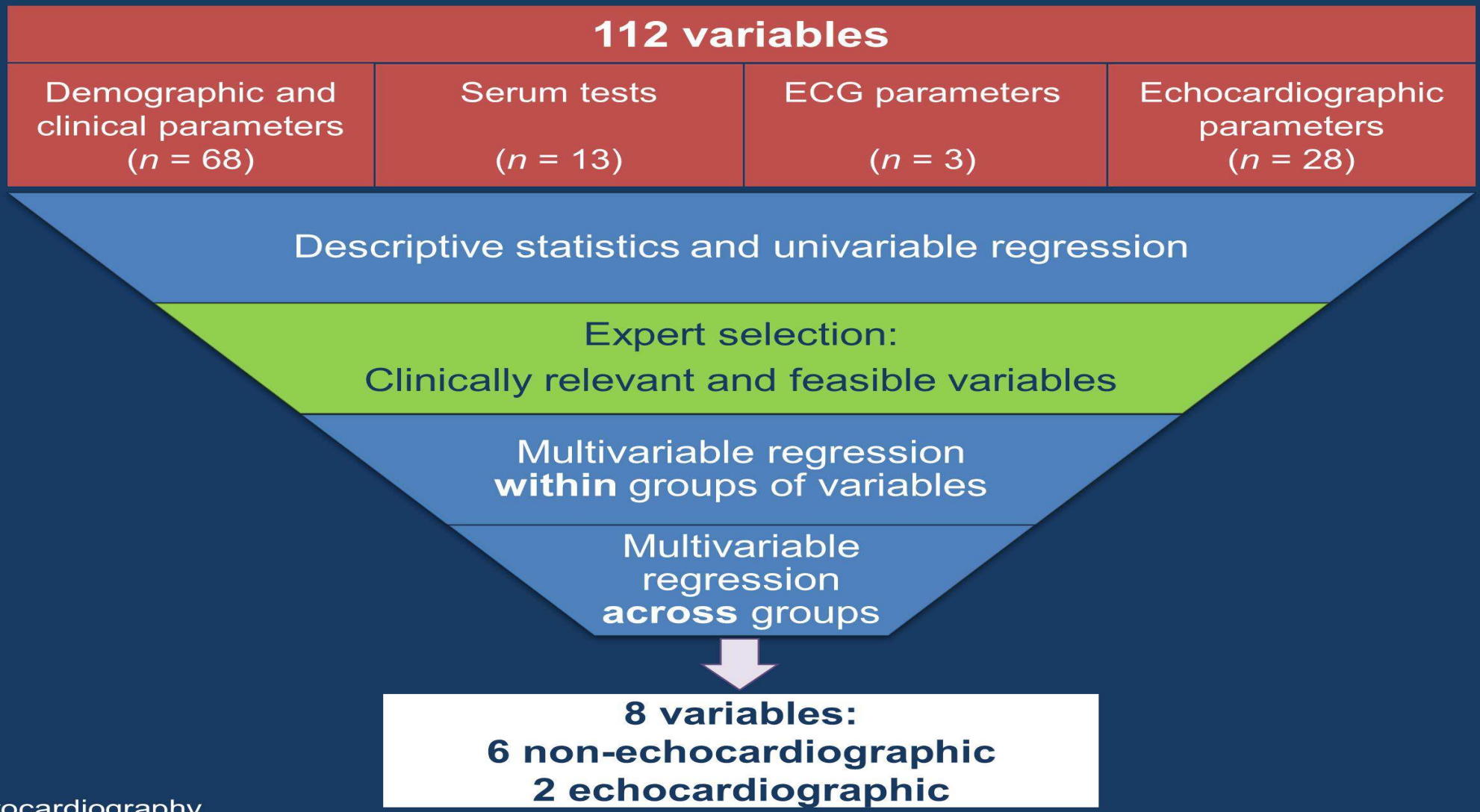
1. Steen VD and Medsger TA. *Ann Rheum Dis* 2007; 66:94
2. Tyndall AJ, *et al. Ann Rheum Dis* 2010; 69:180
3. Fisher MR, *et al. Am J Respir Crit Care Med* 2009; 179:61
4. Parent F, *et al. N Engl J Med* 2011; 365:44

DETECT study: Main objective

- Prospectively develop an evidence-based screening algorithm for PAH in SSc patients that would
  - Minimise the number of missed PAH diagnoses
  - Optimise the use of diagnostic right heart catheterisation

Coghlan JG, *et al. Ann Rheum Dis* 2013; Epub ahead of p

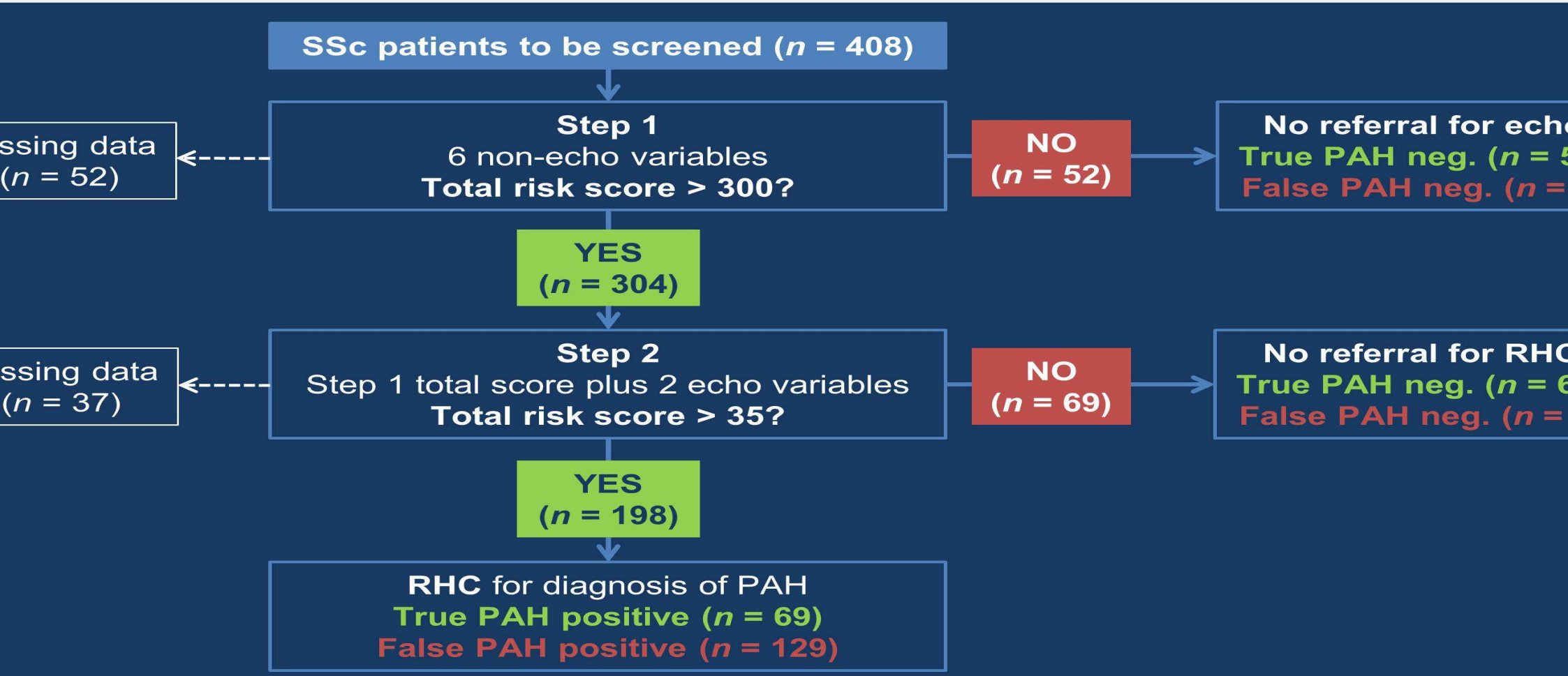
Selection of screening variables in the DETECT study



G: electrocardiography
20 October 2013

Coghlan JG, *et al. Ann Rheum Dis* 2013; Epub ahead of p

DETECT: Two-step decision tree performance



step 1: ROC AUC = 0.844 (95% CI, 0.795, 0.898)
step 2: ROC AUC = 0.881 (95% CI, 0.824, 0.923)

C: receiver operating characteristic; AUC: area under the curve

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Coghlan JG, *et al. Ann Rheum Dis* 2013; Epub ahead of p

Detect: results

- Six simple assessments in Step 1 of the algorithm determined referral to echocardiography.
  - FVC % predicted/DLCO %predicted
  - Current/past telangiectasia
  - Anti-centromere Abs
  - Serum NT-pro-BNP
  - Serum urate
  - ECG: right axis deviation
- In Step 2, the Step 1 prediction score and two echocardiographic variables determined referral to RHC.
  - Right atrium area
  - TR velocity

Coghlan G, ARD, 2013

DETECT online PAH risk calculator

DETECT
DETECTion of PAH in SSc

HOME | WHAT IS DETECT? | PAH RISK CALCULATOR | ABOUT SSC AND PAH | SUPPORTING INFORMATION

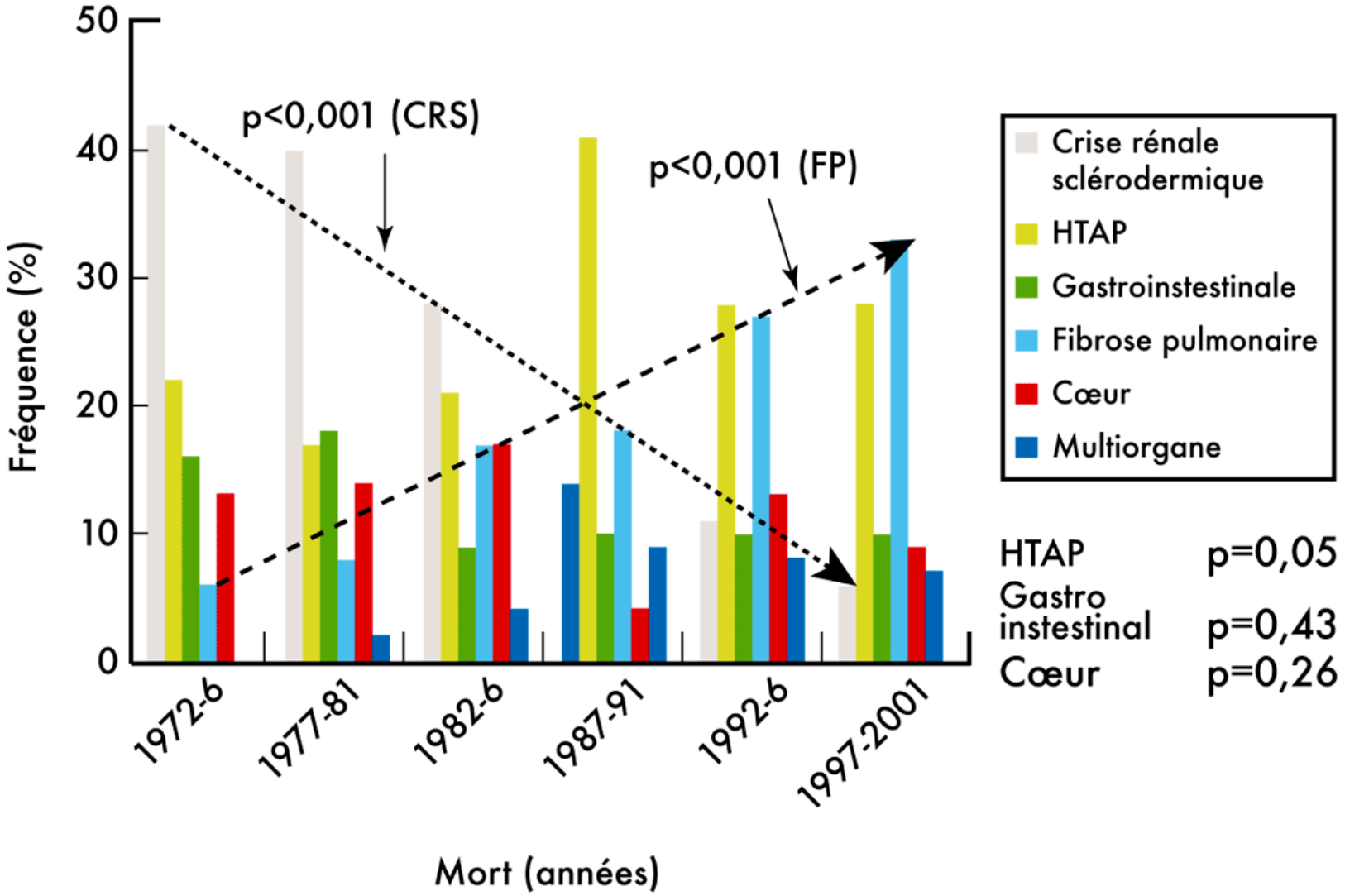
WELCOME TO THE PAH RISK CALCULATOR

The PAH risk calculator is a tool for all physicians dealing with systemic sclerosis (SSc). The calculator was developed and validated in the DETECT study. The DETECT study was designed and carried out by a group of experts, all of whom are physicians practising in different countries, and was supported by Actelion Pharmaceuticals Ltd.

The calculator was developed for your daily clinical practise. It will help you to identify and diagnose SSc patients with pulmonary arterial hypertension (PAH), which is a serious condition that develops in 8-13% of SSc patients and is the leading cause of death in patients with this disease. The calculator is based on an algorithm with a high sensitivity and specificity and can help you to decide which of your SSc patients should be evaluated using echocardiography, and of those patients who should be referred for right heart catheterization.

START CALCULATOR

Changes in causes of Systemic Sclerosis related deaths between 1972 and 2001



Steen et Medsger. Ann Rheum Dis 2007

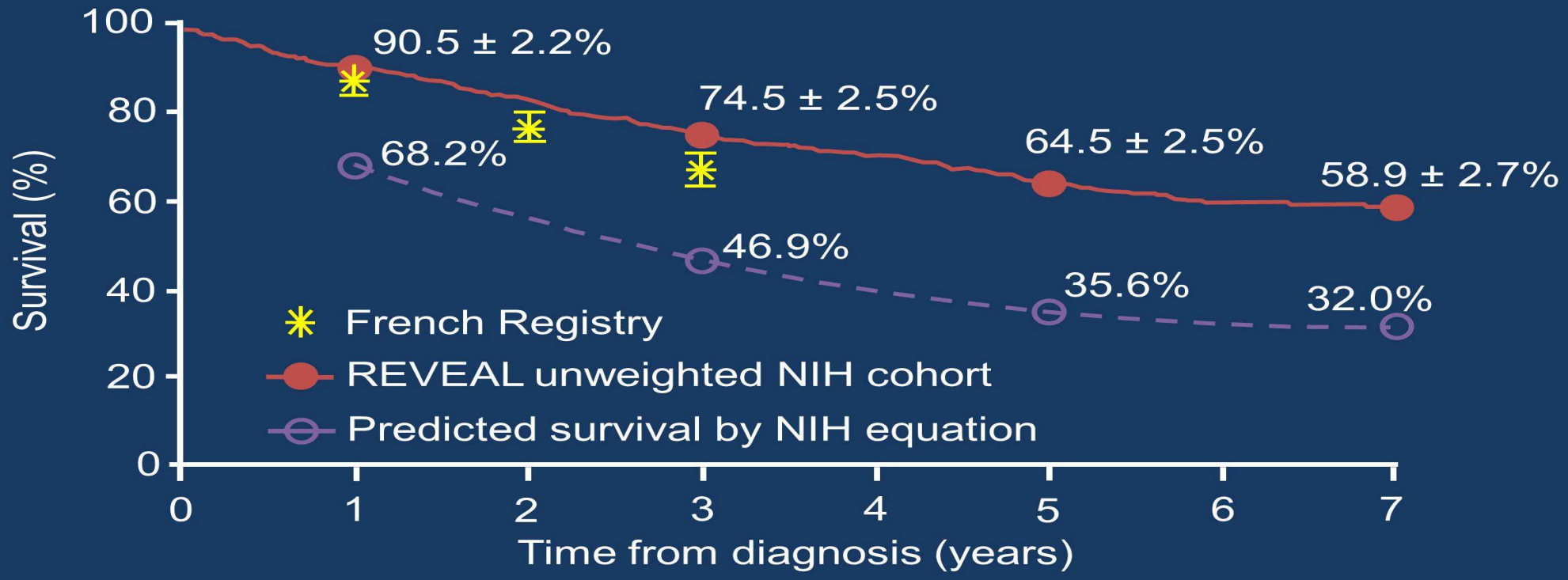
Causes of death in SSc patients

TABLE 2. Causes of death observed in the total population

Causes of death, *n* (%)	All patients (*n* = 546)
Total number of deaths	47 (8.6)
Scleroderma-related causes of death	24 (4.4)
PAH	17
Pulmonary fibrosis	2
Gastrointestinal	2
Renal crisis	3
Non-scleroderma-related causes of death	23 (4.2)
Cancer	8
Infection	4
Cardiovascular or cerebrovascular atherosclerosis	2
Other cause	2
Unknown cause	7

Hachulla et al. Rheumatology 2009

Outcomes have improved significantly in PAH, but are still suboptimal



No. at risk*: 279 377 390 388 328 240 153 88

/EAL cohort
20 October 2013

Benza RL, *et al. Chest* 2012; 142:448

PAH in SSc: prognosis

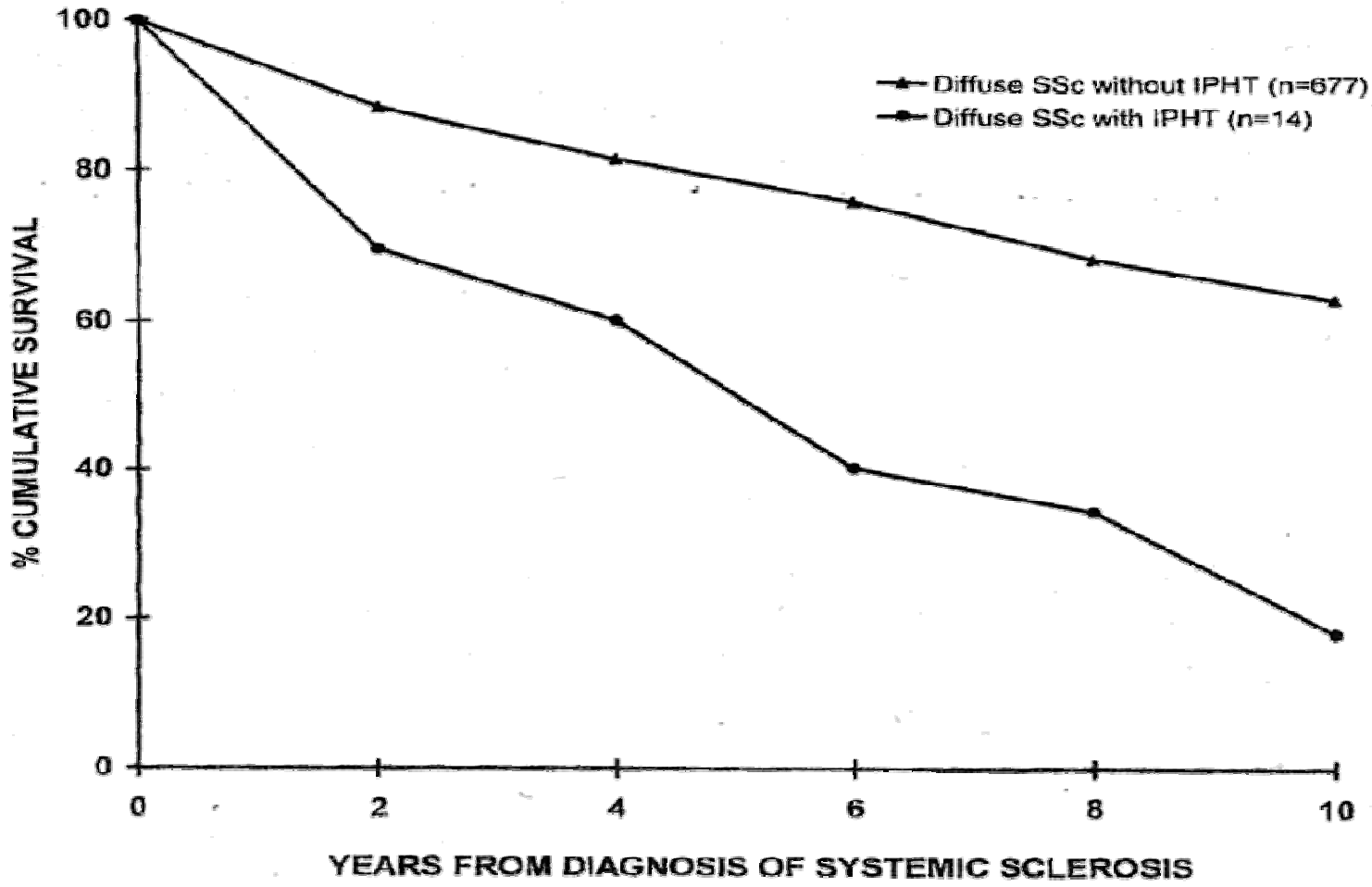
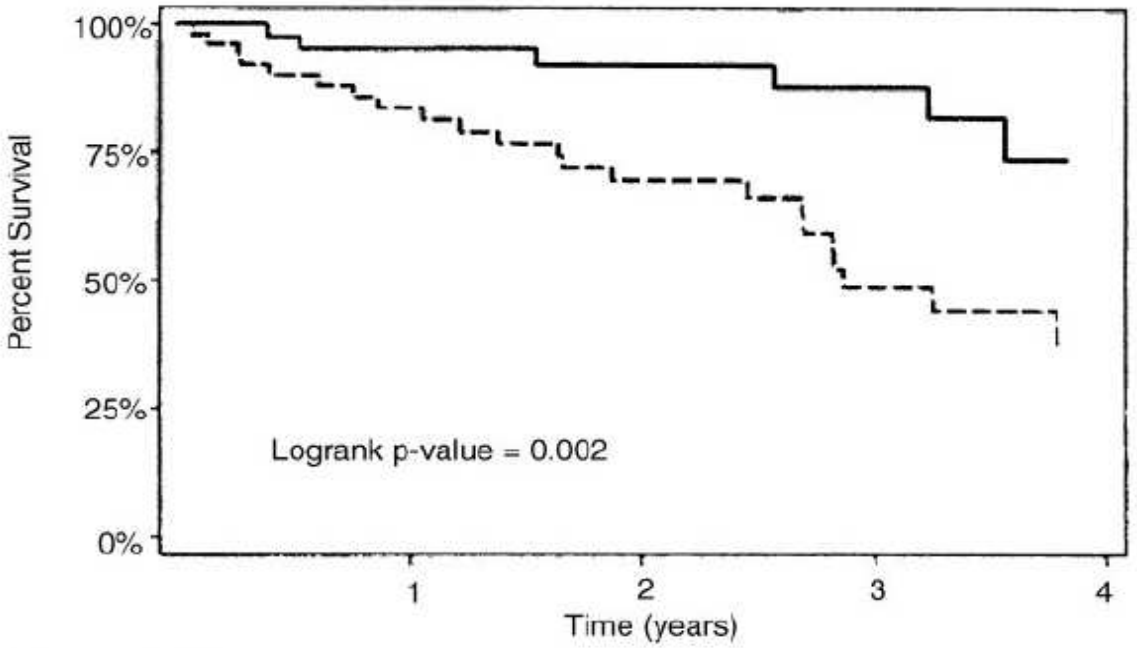


Figure 1. Cumulative survival from diagnosis of SSc in patients with dcSSc with (n = 15) or without (n = 677) IPHT . Patients with IPHT have significantly decreased survival ($p < 0.001$) compared to others with dcSSc.

Medsger *et al.* J Rheum 1996

PAH complicating Connective Tissue Diseases

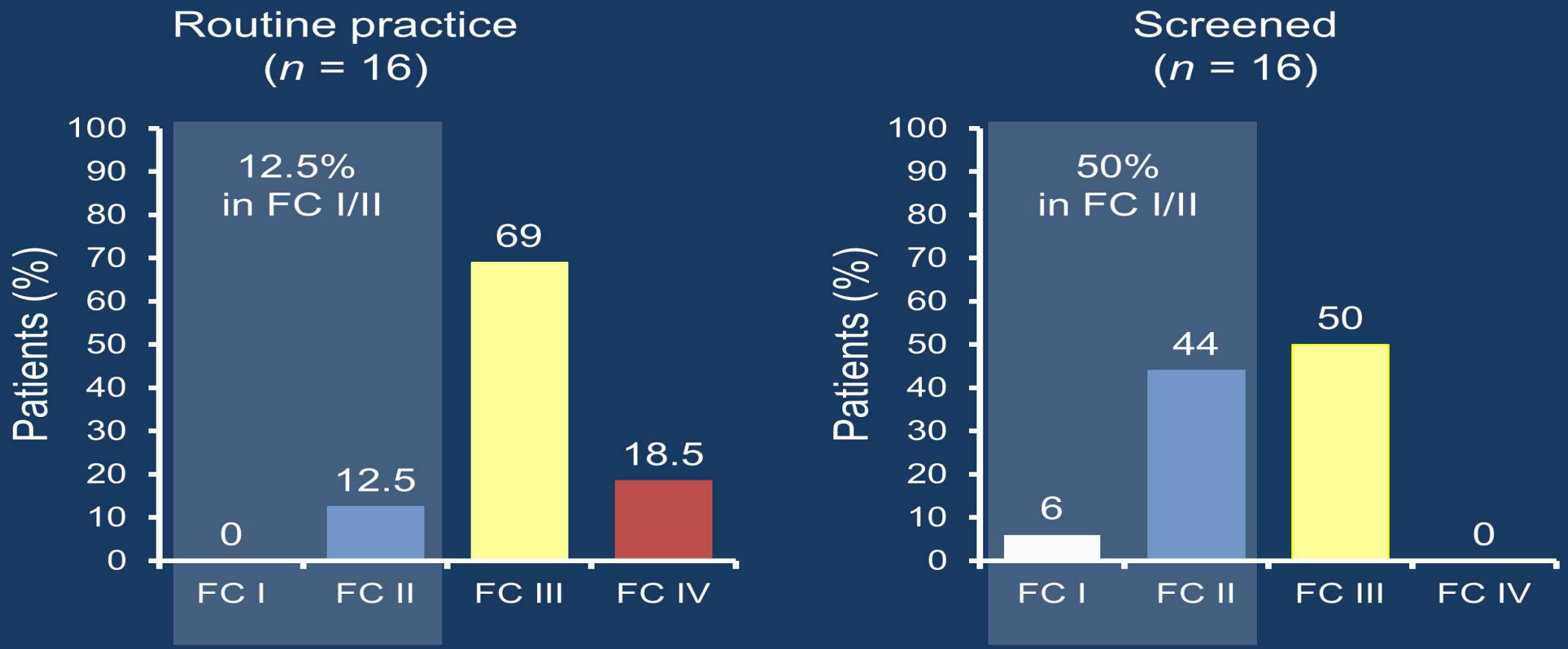


iPAH

SSc-PAH

Hassoun *et al.* Semin Respir Crit Care Med 2009

Screening allows earlier detection of PAH in SSc patients

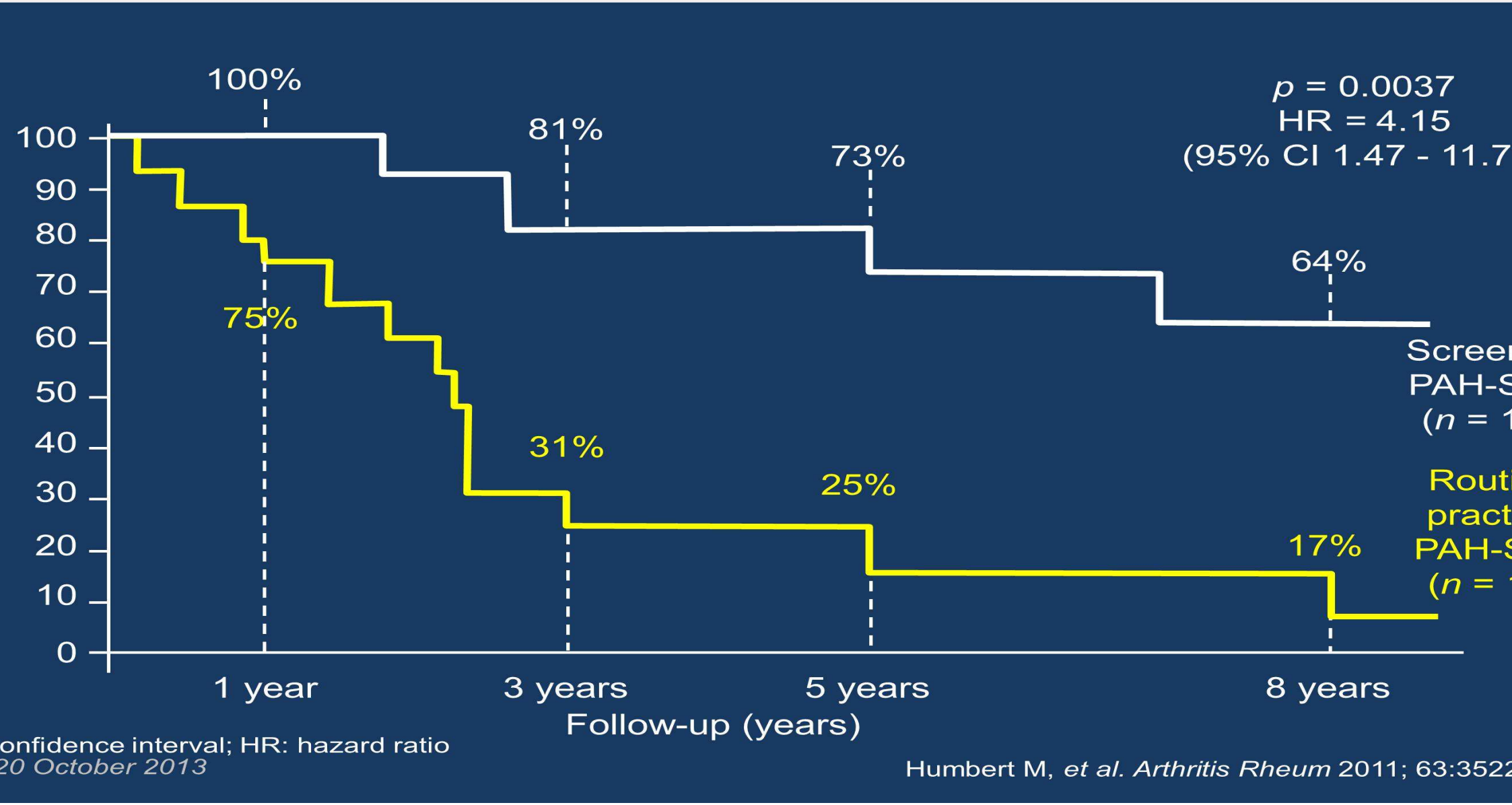


$p = 0.036$; routine versus screened patients

World Health Organisation functional class

Humbert M, *et al. Arthritis Rheum* 2011; 63:3522

Impact of screening in PAH-SSc: Improved long-term outcomes



onfidence interval; HR: hazard ratio

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Humbert M, *et al. Arthritis Rheum* 2011; 63:3522

Sclérodermie systémique: Impact des comorbidités

- Age
- Atteinte myocardique
- Atteinte musculo-squelettique
- Fibrose pulmonaire
- Maladie veino-occlusive pulmonaire

Le Pavec et al. AJRCCM 2009

SSc-PAH: why a so bad prognosis?

Table 3. Baseline echocardiographic findings*

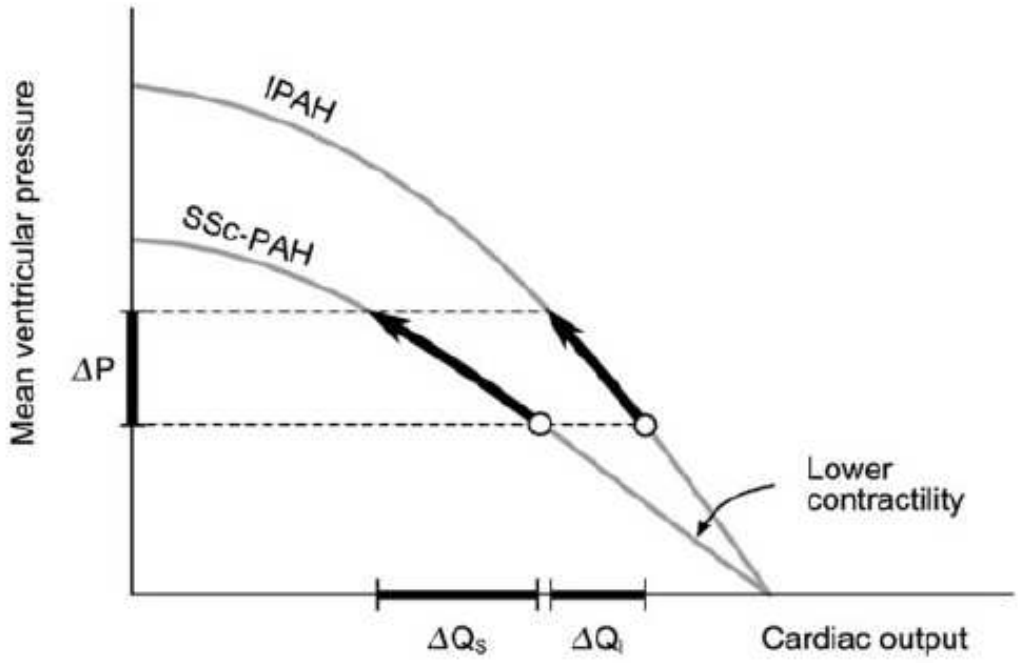
	IPAH (n = 38)	PAH-Scl (n = 49)	*P*
Right atrial dilation	31 (81.6)	36 (73.5)	0.37
Right ventricular dilation	34 (89.5)	39 (79.6)	0.21
Right ventricular hypertrophy	7 (18.4)	5 (10.2)	0.27
Left atrial diameter, mean ± SEM cm	3.3 ± 0.2	3.8 ± 0.1	0.004
Left atrial dilation	4 (10.5)	14 (28.6)	0.039
Left ventricular hypertrophy	5 (13.2)	17 (34.7)	0.022
Left ventricular ejection fraction, mean ± SEM	57.3 ± 1.6	55.7 ± 1.4	0.44
Diastolic dysfunction	5 (13.2)	16 (32.7)	0.035
Pericardial effusion	5 (13.2)	17 (34.7)	0.022

* Except where indicated otherwise, values are the number (%). See Table 1 for definitions.

- Multivariate analysis, factors associated with increased death:
  - Left ventricular dysfunction
  - Pericardial effusion

Fisher *et al.* Arthritis Rheum 2006

Right ventricular function in SSc-PAH



- SSc-PAH has a poorer exercise capacity and worse prognosis than those reported in other types of PAH.
- This appears related to a relative RV failure, explained by altered contractility and maybe also decreased pulmonary arterial compliance.

Overbeek *et al.* ERJ 2008

PAH complicating Pulmonary fibrosis

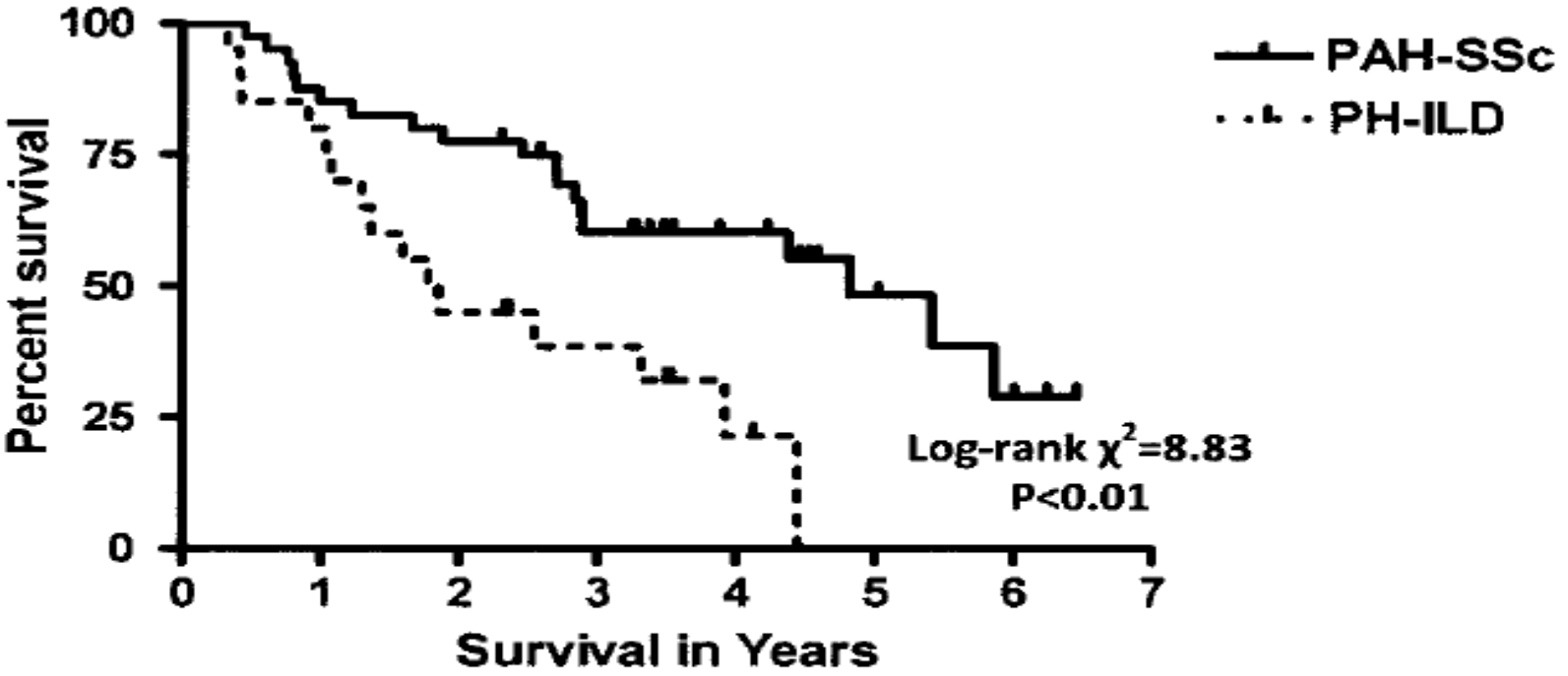
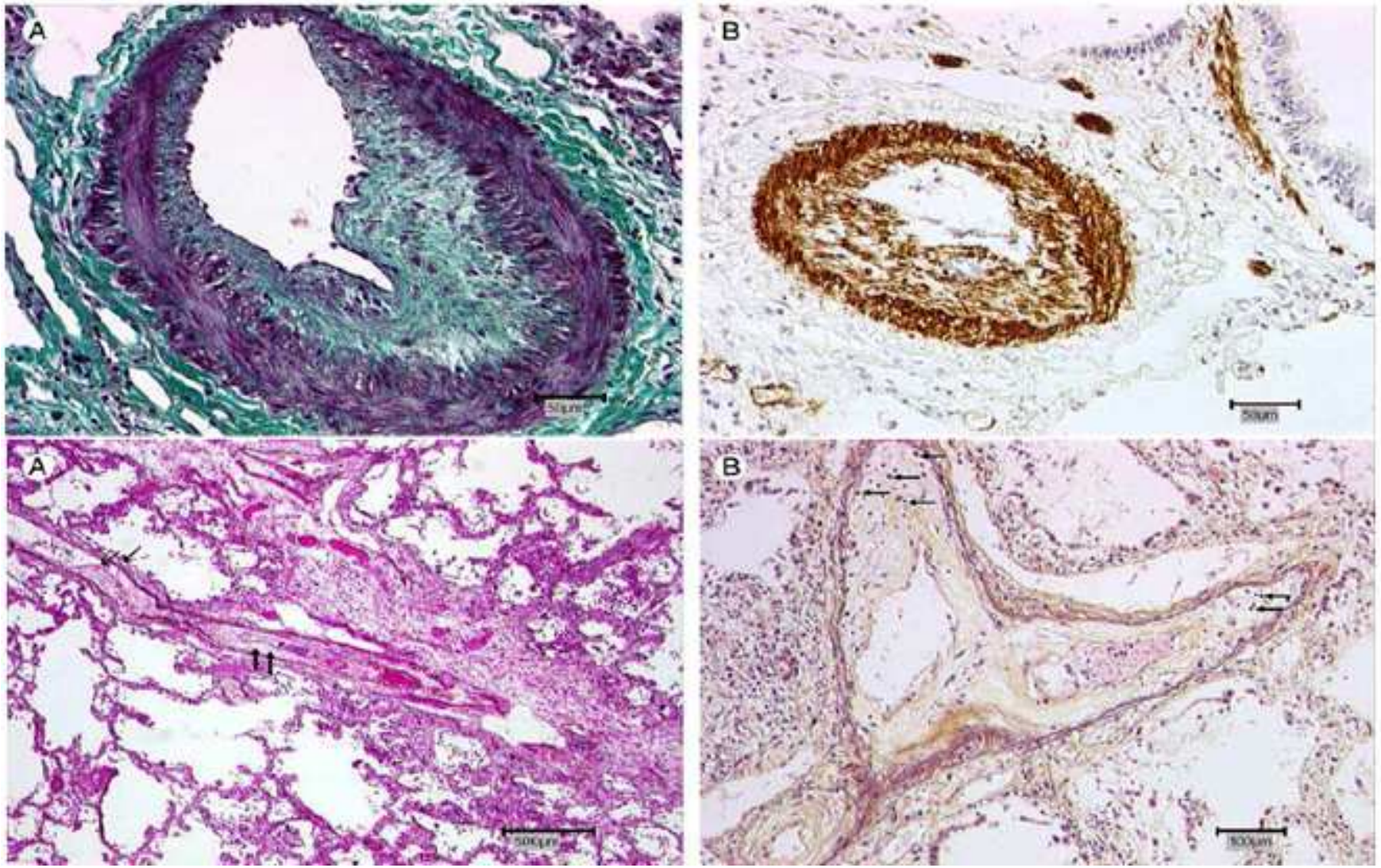


Figure 1. Kaplan-Meier survival graph comparing patients with systemic sclerosis (SSc) and pulmonary arterial hypertension (PAH) with those with SSc and interstitial lung disease (ILD)–associated pulmonary hypertension (PH). The x-axis shows years from diagnosis of PH by right heart catheterization.

Mathai et al,Arthritis Rheum. 2009;60:569---77

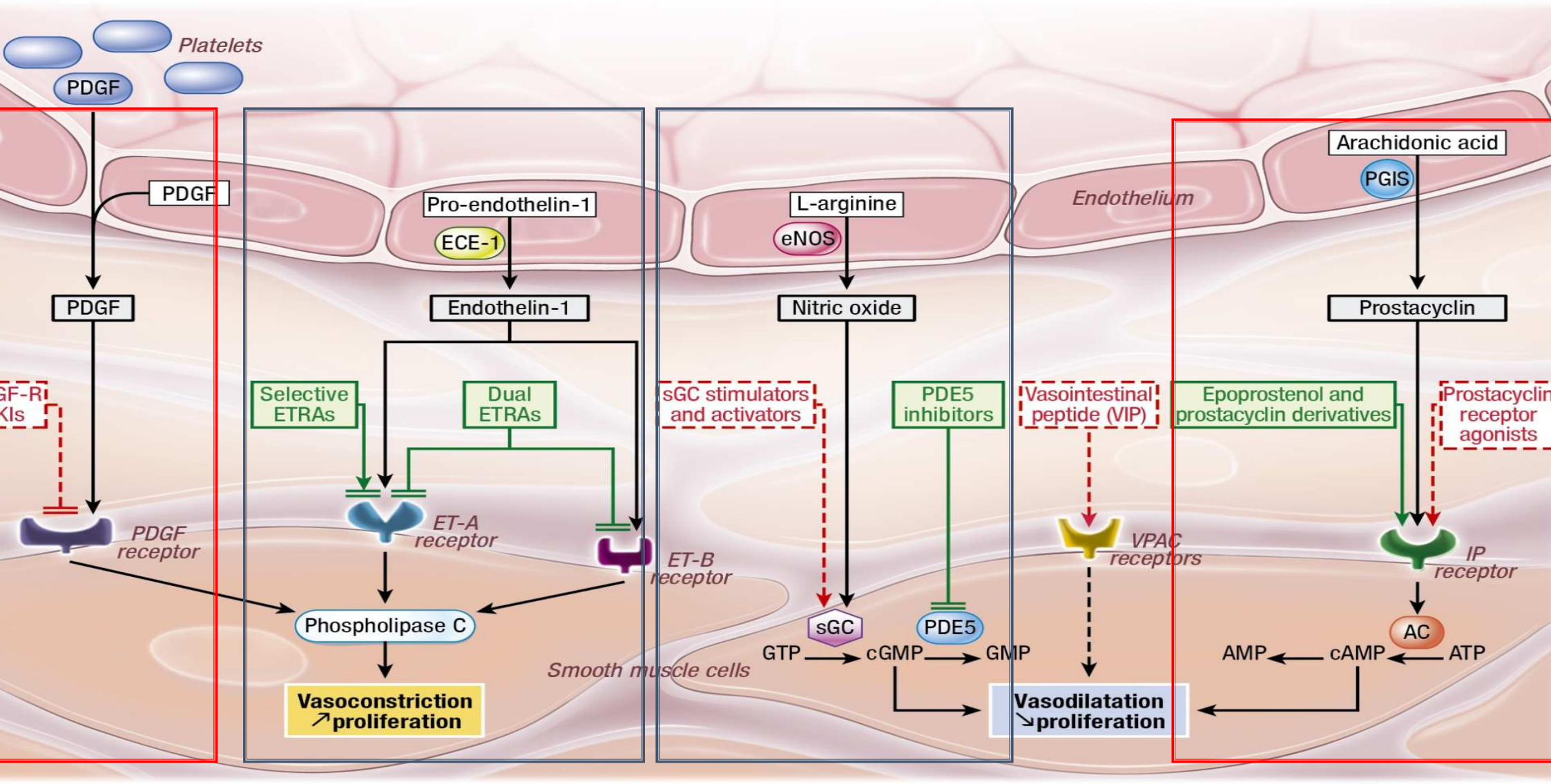
Fibrous remodeling of the pulmonary venous system in PAH associated with CTD



Bon pronostic [1]	Déterminants du pronostic [1]	Mauvais pronostic [1]
Non	Signes cliniques d'insuffisance ventriculaire droite	Oui
Lente	Progression	Rapide
Non	Syncope	Oui
I, II	Classe fonctionnelle (OMS)	IV
> 500 m (fonction de l'âge)	Test de marche de 6 minutes	< 300 m
VO_2max > 15 ml/min/kg	Épreuve d'effort cardiopulmonaire	VO_2max < 12 ml/min/kg
Normal ou quasi-normal	BNP/NT-proBNP (taux plasmatiques)	Très élevé et croissant
Pas d'épanchement péricardique TAPSE > 2,0 cm	Echocardiographie	Épanchement péricardique TAPSE < 1,5 cm
PAD < 8 mmHg et IC ≥ 2,5L/min/m^2	Hémodynamique	PAD > 15 mmHg ou IC ≤ 2,0 L/min/m^2

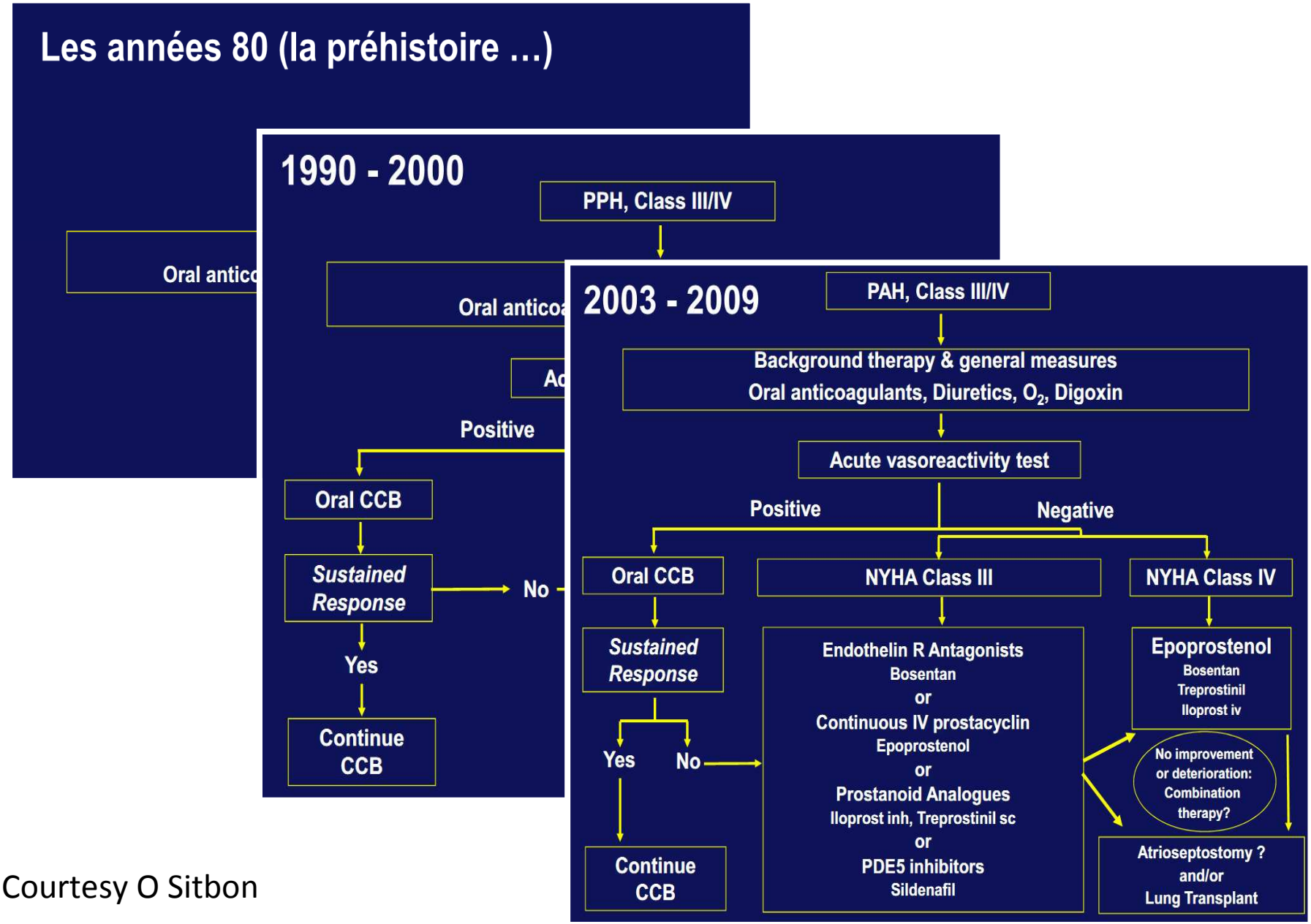
1. Galiè N et coll. Guidelines for the diagnosis and treatment of pulmonary hypertension: The Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). Eur Heart J. 2009;30:2493-537.

urrent and Emerging Targets and Therapies in PAH



DS, Savale L, Montani D, Jaïs X, Sitbon O, Simonneau G & Humbert M. Nat Clin Practice Cardiol 2011; 19:526-538

Les algorithmes thérapeutiques dans l'HTAP



Courtesy O Sitbon

Grossesse contre-indiquée (I-C)
Vaccination antigrippale et antipneumococcique (I-C)
Réhabilitation (IIa-B)
Soutien psychologique (IIa-C)
Éviter les efforts excessifs (III-C)

Mesures générales

Avis d'experts (I-C)

Test de vasoréactivité
HTAPi (I-C) – HTAP associées (IIb-C)

Diurétiques (I-C)
Oxygène (I-C)
Anticoagulants oraux
- *HTAPi, héritable ou associée à des anorexigènes (IIa-C)*
- *HTAP associées (IIb-C)*

Digoxine (IIb-C)

POSITIF

NEGATIF

Classe fonctionnelle I-III
ICs (I-C)

Réponse maintenue (CF I-II)

OUI

NON

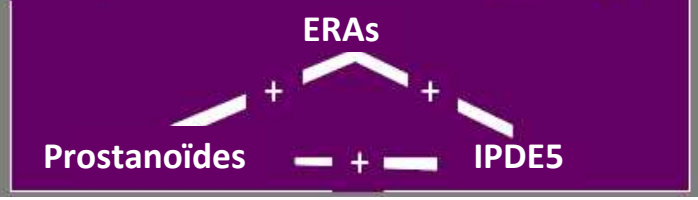
Maintien des ICs

TRAITEMENT INITIAL

Recommandation Preuve	Classe fonctionnelle II	Classe fonctionnelle III	Classe fonctionnelle IV
I-A	Ambrisentan Bosentan Sildenafil	Ambrisentan, Bosentan Sitaxentan, Sildenafil Epoprosténol i.v. Iloprost inhalé	Epoprosténol i.v.
I-B	Tadalafil*	Tadalafil* Téprostinil s.c, inhalé*	
IIa-C	Sitaxentan	Iloprost i.v.* Téprostinil i.v.*	Ambrisentan, Bosentan Sitaxentan, Sildenafil, Tadalafil* Iloprost inhalé, i.v.* Téprostinil s.c, inhalé* Traitements combinés
IIb-B		Béraprost*	

REPONSE CLINIQUE INADEQUATE

Combinaison thérapeutique séquencée (IIa-B)

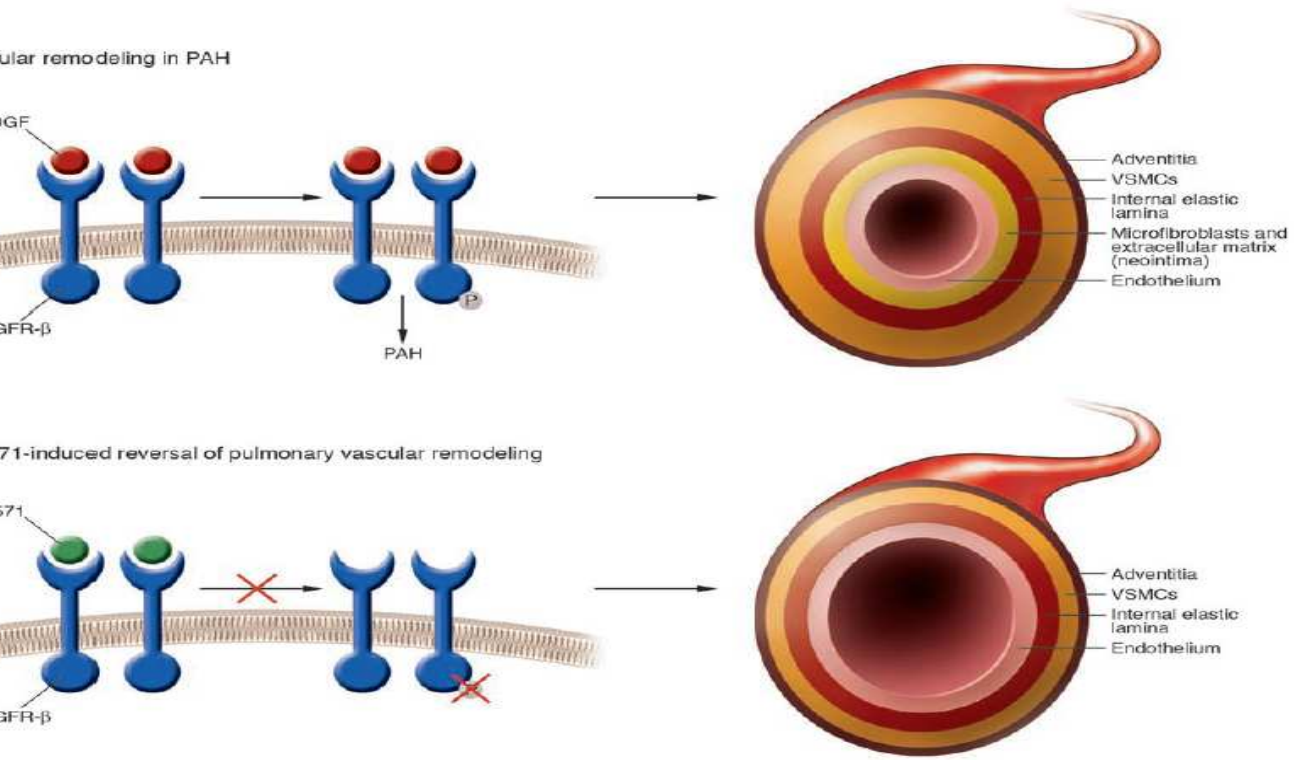


REPONSE CLINIQUE INADEQUATE

Atrioseptostomie (I-C) et/ou Transplantation pulmonaire (I-C)

** Molécules ne disposant pas à ce jour d'une AMM en France dans le traitement de l'HTAP*

Imatinib inhibits PDGF signaling in PAH



st, J Clin Invest, 2005

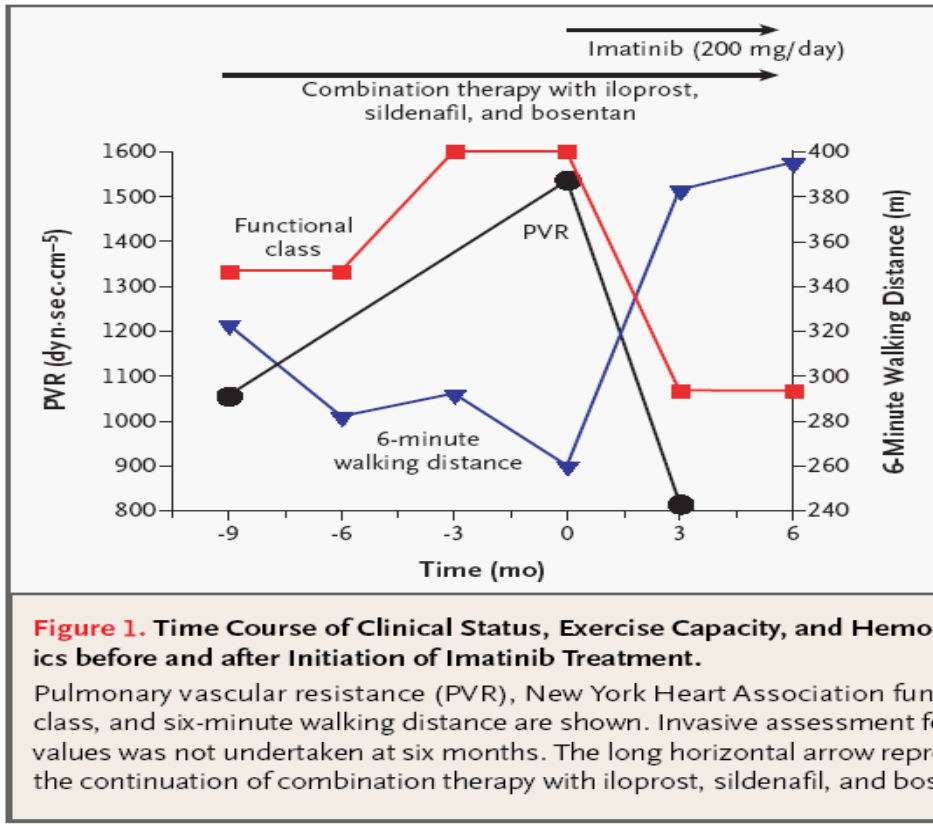


Figure 1. Time Course of Clinical Status, Exercise Capacity, and Hemo ics before and after Initiation of Imatinib Treatment.

Pulmonary vascular resistance (PVR), New York Heart Association fun class, and six-minute walking distance are shown. Invasive assessment f values was not undertaken at six months. The long horizontal arrow repr the continuation of combination therapy with iloprost, sildenafil, and bos

***Ghofrani et al, N Engl J Med* 2005**
Farber et al, Ann Int Med 2006
Souza et al, Thorax 2006

Prospective randomized trail in PAH patients: negative on the primary end point

Ghofrani et al, ERS 2008

Nouveaux traitements évalués depuis 2009

	SERAPHIN[1]	PATENT[2]	IMPRES[3]
Molécule	Macitentan	Riociguat	Imatinib
Classe thérapeutique	ERA à forte affinité tissulaire	Stimulateur GC soluble	Inhibiteur de tyrosine kinase
Critère principal de jugement	Morbi-mortalité	TM6	TM6
Durée	~ 96 semaines	12 semaines	24 semaines
Patients, n	742	443	202
Traitement antérieur	Naïf ou monothérapie (PDE5i)	Naïf ou monothérapie (ERA)	Association (≥ bithérapie)
Résultat principal	Réduction de 45 % des évènements de morbi-mortalité (10 mg)	TM6 +36 m	TM6 +32 m, mais > 30 % sorties d'essai groupe imatinib
Tolérance	Elévation enzymes hépatiques : pas de différence avec placebo. Diminution Hb	Vasodilatation systémique, hypotension (Hémoptysies)	Effets secondaires ++, Hématomes sous-duraux, Rapport bénéfice/risque discutable

1. Rubin LJ, *et al*. Presented at CHEST 2012. 2. Ghofrani HA, *et al*. Presented at CHEST 2012. 3. Hoeper MM, *et al*. Presented at CHEST 2011.

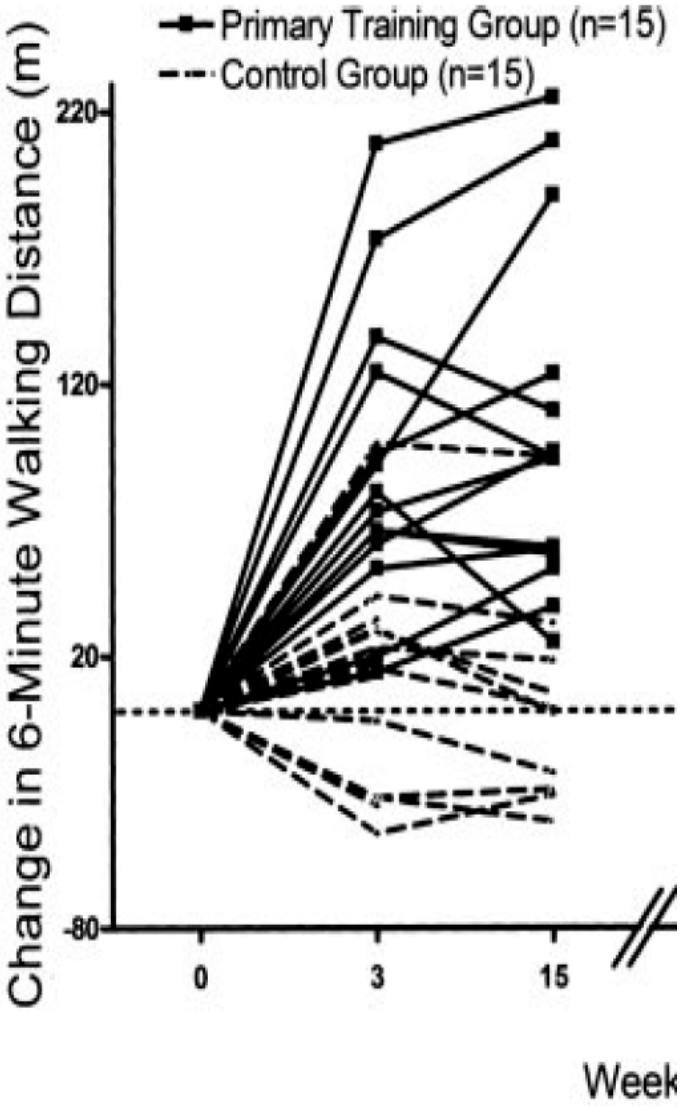
Traitement initial par médicaments approuvés dans l'HTAP						
	Amélioration des capacités à l'exercice			Diminution de la morbi-mortalité		
Recommandation - Evidence	CF II	CF III	CF IV	CF II	CF III	CF IV
I - A	Ambrisentan, Bosentan, Sildenafil	Ambrisentan, Bosentan, Sildenafil, Iloprost inhalé, Epoprostenol iv	Epoprostenol iv			
I - B	Tadalafil, Riociguat	Tadalafil, Treprostinil sc, inhalé, Riociguat		Macitentan	Epoprostenol iv (HTAPi), Macitentan	Epoprostenol iv (HTAPi)
II a - C		Iloprost iv, Treprostinil iv	Ambrisentan, Bosentan, Sildenafil, Tadalafil, Iloprost inhalé et iv, Treprostinil sc, iv, inhalé, Traitement combiné d'emblée			
II b - B		Beraprost				
II b - C		Traitement combiné d'emblée				

Quelles pistes pour améliorer l'algorithme de traitement actuel ?

- Quelle place pour les nouvelles molécules (macitentan, riociguat, imatinib) ?
- Traitement combiné d'emblée ?
- Anticoagulants : est-ce indispensable ?
- Comment gérer les complications aiguës ?
- Comment intégrer les thérapeutiques non médicamenteuses ?
  - Réhabilitation à l'exercice
  - Indications de l'assistance ventriculaire droite ?
  - Timing optimal de la transplantation pulmonaire ?
  - Quelle place pour l'atrioseptostomie ?

Quelle place pour la réhabilitation à l'effort dans l'HTAP ?

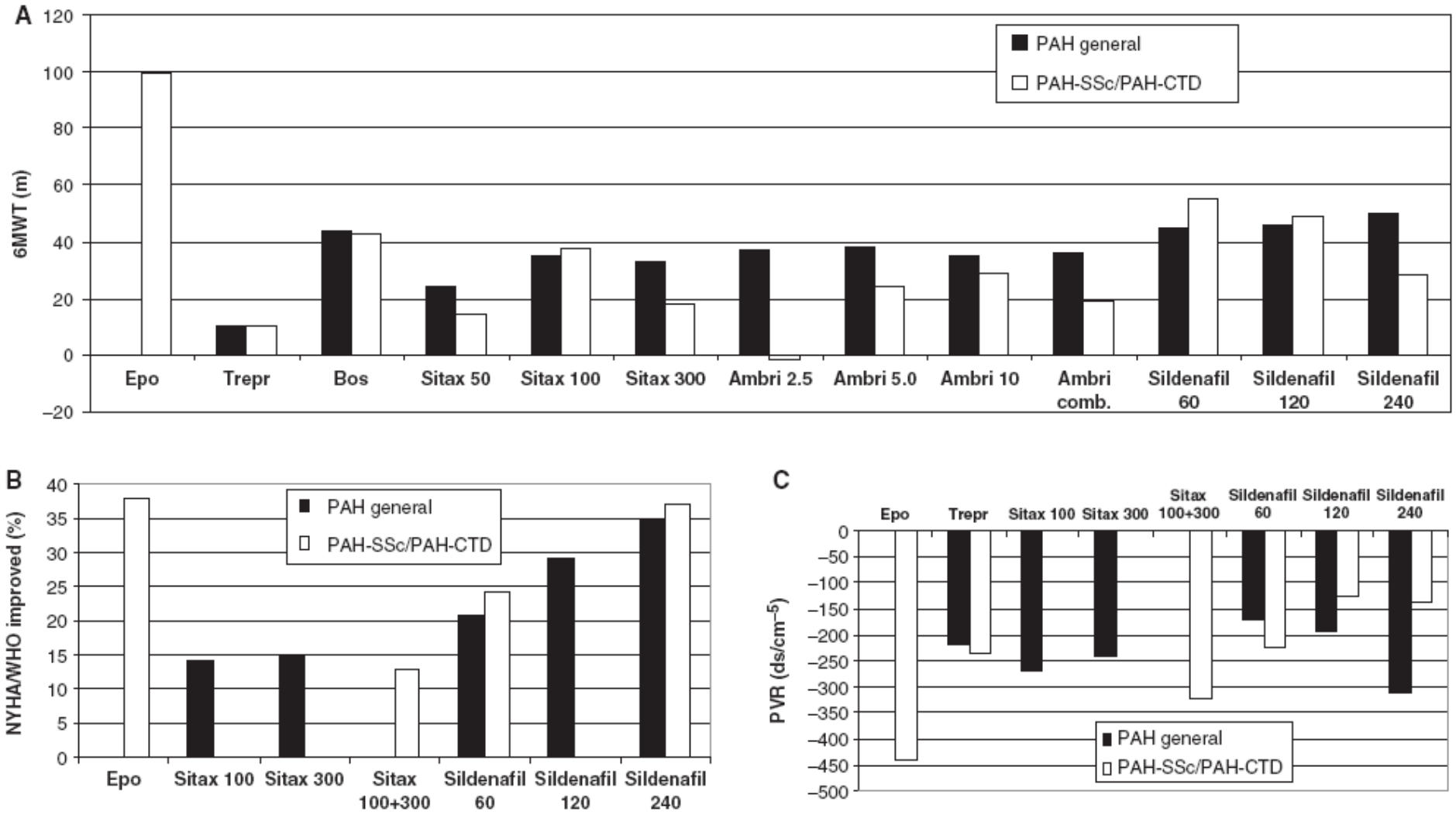
- 30 stable PH patients (23 PAH, 7 CTEPH)
- Supervised exercise training program for 15 weeks, in the hospital for the initial 3 weeks
- Mean difference between the control and the primary training group = 111 m (95 % CI, 65 - 139 m; *p < 0.001*)
- Improvement in QOL, FC, peak VO_2, VO_2 @ AT and achieved workload
- No change in echocardiographic parameters
- Exercise training was well tolerated



Mereles D *et al*. Circulation 2006.

Outcome measures in pulmonary arterial hypertension associated with systemic sclerosis

O. Kowal-Bielecka et al Rheumatology 2008



Mean/median effects of PAH therapies on the 6MWD (A), NYHA/WHO functional class (B) and PVR (C) in the pivotal randomized trials for which data on SSc or CTD subgroups could be retrieved.

A number of patients with PAH improved with anti-inflammatory agents

- Immunosuppressive therapy in connective tissue disease associated PAH (Sanchez O et al Chest 2006)
- Immunotherapy in SLE and MCDT associated PAH (Jaïs X et al Arthritis Rheum 2008)
- Reversibility of PAH in HIV/HHV8-associated Castlemann disease (Montani et al Eur Respir J 2005)
- PAH: a rare complication of primary Sjogren's syndrome (Launay D et al, (Baltimore) 2007)

Conclusions (I)

- La physiopathologie de l'HTAP est complexe et varie probablement en fonction de la pathologie associée
- Nouvelles mutations en plus des mutations de BMPRII
- Nouveaux médicaments inducteurs: benfluorex et dasatinib
- Echo coeur dépistage, cathétérisme droit diagnostic et suivi évolutif

Conclusions (II)

- **Nouvelles thérapeutiques disponibles: macitentan, riociguat et imatinib**
- **Effet du macitentan sur la morbimortalité**
- **Intérêt des traitements combinés**
- **Place des traitements non pharmacologiques en cours d'évaluation (réhabilitation à l'effort)**

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GFRS

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