Screening of PAH in systemic sclerosis and in *BMPR2* mutation carriers

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Disclosures – Marc Humbert, MD, PhD

- Relevant financial relationships with a commercial interest:
  - **Actelion/J&J:** consultancy (current), board or advisory committee (current), speaker (current)
  - **Bayer/Merck:** consultancy (current), board or advisory committee (current), speaker (current)
  - **GSK:** consultancy (current), board or advisory committee (current), speaker (current), research support (current)
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CLINICAL CLASSIFICATION OF PH

1. Pulmonary Arterial Hypertension

1.1 Idiopathic PAH
1.2 Heritable PAH
1.3 Drugs and toxins induced
1.4 Associated with:
- 1.5.1 Connective tissue disease
- 1.5.2 HIV infection
- 1.5.3 Portal hypertension
- 1.5.4 Congenital heart disease
- 1.5.5 Schistosomiasis

1.5 PAH long-term responders to CCB)
1.6 PAH with overt signs of venous/capillaries (PVOD/PCH) involvement
1.7 Persistent PH of the Newborn syndrome

5. PH with unclear mechanisms

5.1 Haematologic disorders
5.2 Systemic disorders
5.3 Others
5.4 Complex congenital heart disease

3. PH due to lung diseases and/or hypoxia

3.1 Obstructive lung disease
3.2 Restrictive lung disease
3.3 Other lung disease with mixed restrictive/obstructive pattern
3.4 Hypoxia without lung disease
3.5 Developmental lung disorders (Table P3)

4. PH due to pulmonary artery obstruction

4.1 Chronic thromboembolic PH
4.2 Other pulmonary artery obstructions

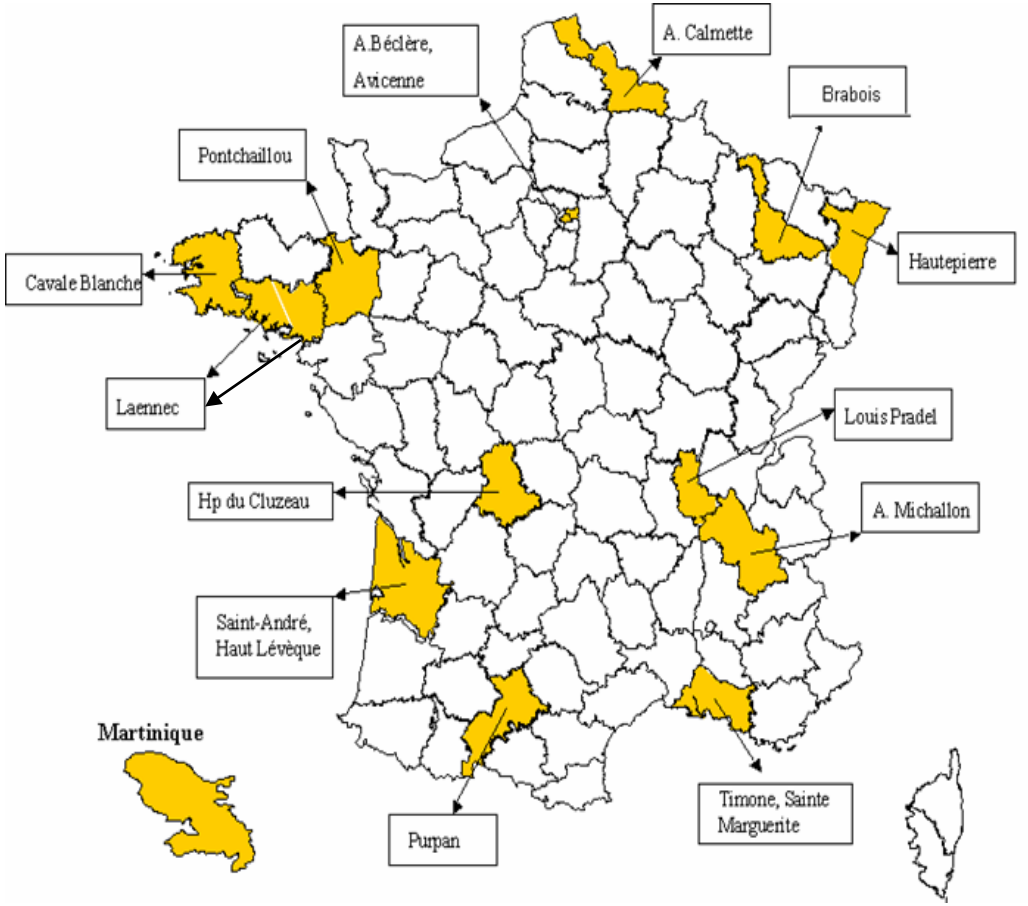
5. PH with unclear mechanisms

5.1 Haematologic disorders
5.2 Systemic disorders
5.3 Others
5.4 Complex congenital heart disease (Table P4)

Simonneau et al. Eur Respir J 2019

THE FRENCH PAH REGISTRY

- National registry: 674 patients, 17 medical centres (respiratory medicine, cardiology and internal medicine) spread across France
- Adult patients (>18 years) suffering from PAH (idiopathic, familial or associated conditions)
- Prospective cohort monitored and on-site audits



Humbert M, et al. Am J Respir Crit Care Med 2006

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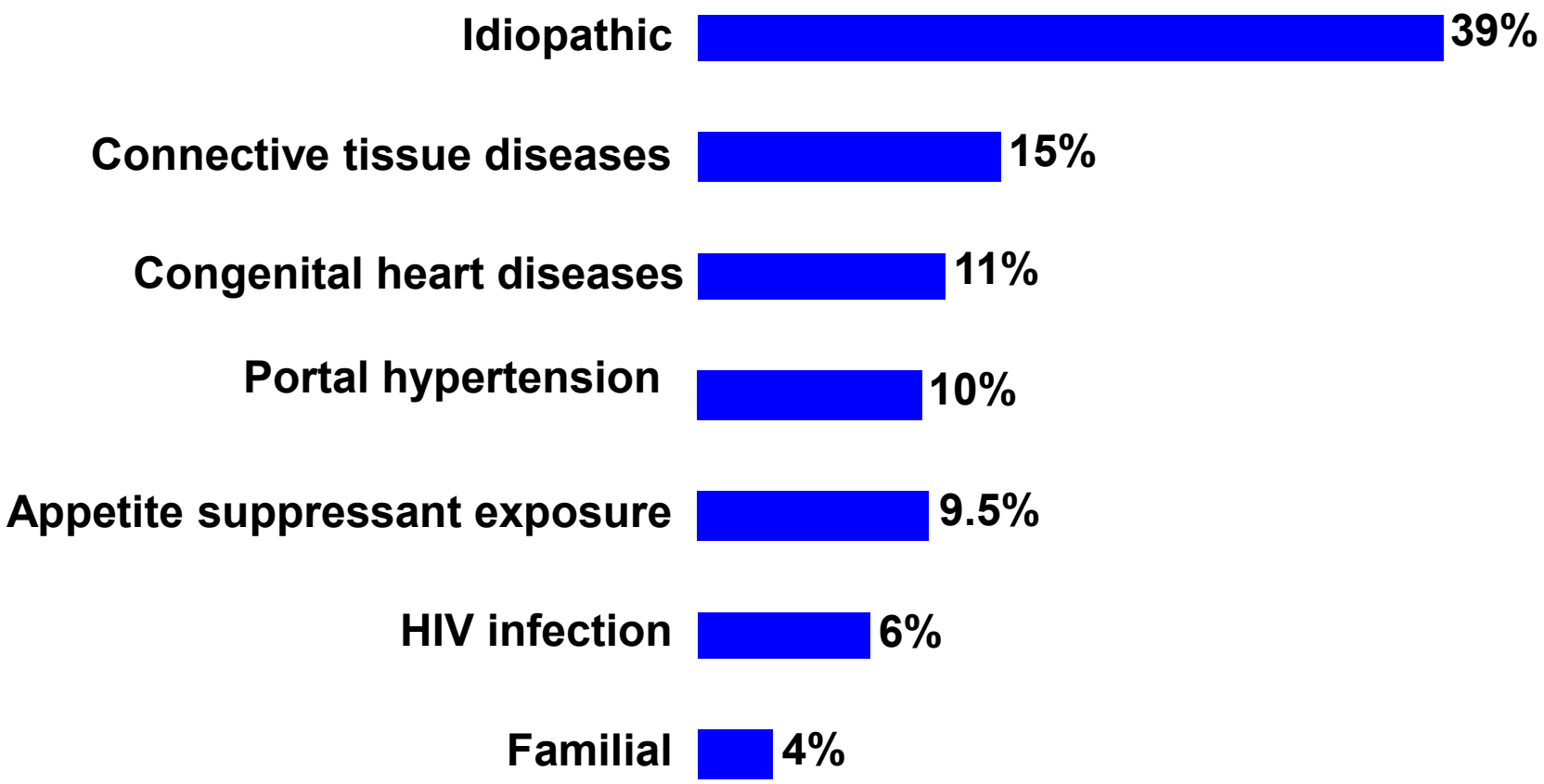

2 RISK FACTORS 4%

Humbert M, et al. Am J Respir Crit Care Med 2006

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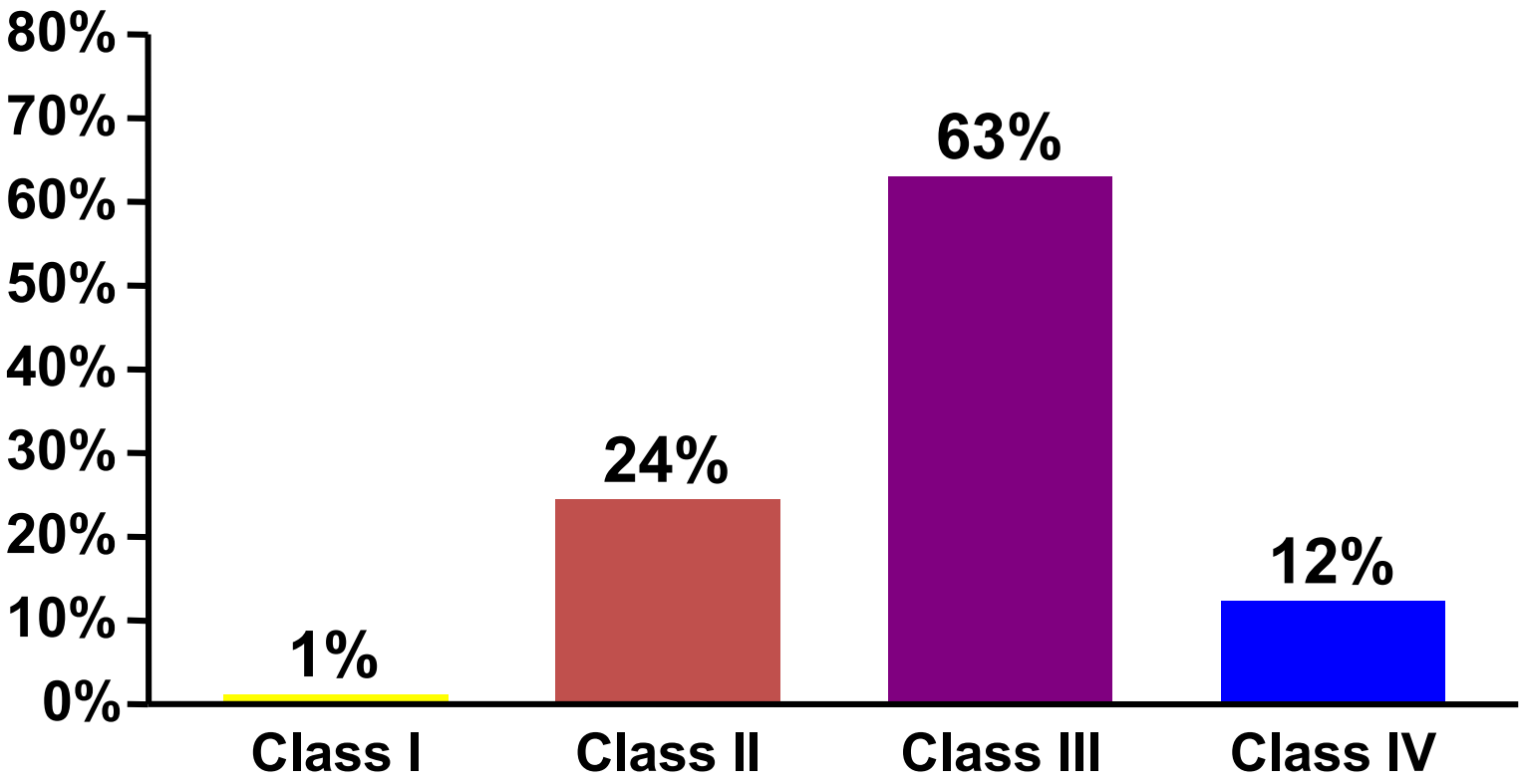
NYHA FUNCTIONAL CLASSES AT DIAGNOSIS

→ Delay between onset of symptoms and diagnosis: 27 months



Humbert M, et al. Am J Respir Crit Care Med 2006

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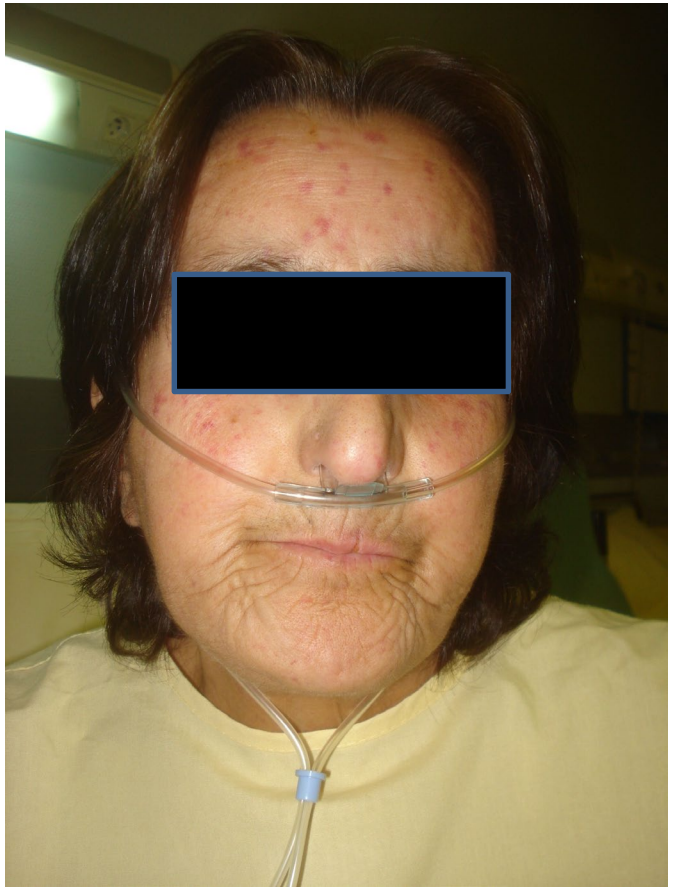
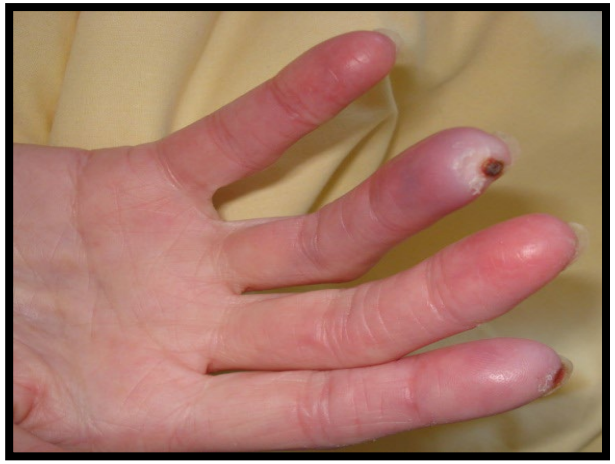
SCLERODERMA





Simonneau et al. Eur Respir J 2019

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PREVALENCE OF PAH IN SSc

Reference	Methodology	Patients (N)	SSc profile	PAH definition	PAH prevalence
Ungerer 1983 USA	Prospective Monocentric 1973 to 1979	49	Proximal SSc and CREST	Mean PAP $\geq$ 20 mmHg and mean PCWP $\leq$ 12 mmHg (right heart catheterization)	16%
Murata 1992 Japan	Prospective Monocentric 1988 to 1991	71	SSc and MCTD	$V_{IT} \geq 2.5$ m/s Doppler Echo	17%
Battle 1996 USA	Prospective Monocentric	34	**Diffuse or limited c SSc**	sPAP $\geq$ 30 mmHg Doppler Echo	35%
Koh 1996 Canada	Prospective Monocentric 1978 to 1994	344	**Diffuse or limited cutaneous SSc**	RHC: PAPm $\geq$ 25 and PCWP $\leq$ 12 mmHg , OR Echo: PsVD > 35 mmHg or RV dilatation, P or T insufficiency, or paradoxical septum motion	4.9%
MacGregor 2001 UK	Prospective Monocentric 1992 to 1997	152	**Diffuse or limited c SSc**	PAPs > 30 mmHg Doppler Echo	13%
Mukerjee 2003 UK	**Prospective Monocentric 1998 to 2002**	**722**	**Diffuse or limited c SSc**	**RHC: mPAP > 25 mmHg at rest or > 30 on exercise, PCWP < 15 mmHg**	**12 %**
Hachulla 2005 France	**Prospective Multicentric 2002-3**	**599**	**Diffuse or limited c SSc**	**RHC: mPAP > 25 mmHg at rest or > 30 on exercise, PCWP < 15 mmHg**	**7.85%**

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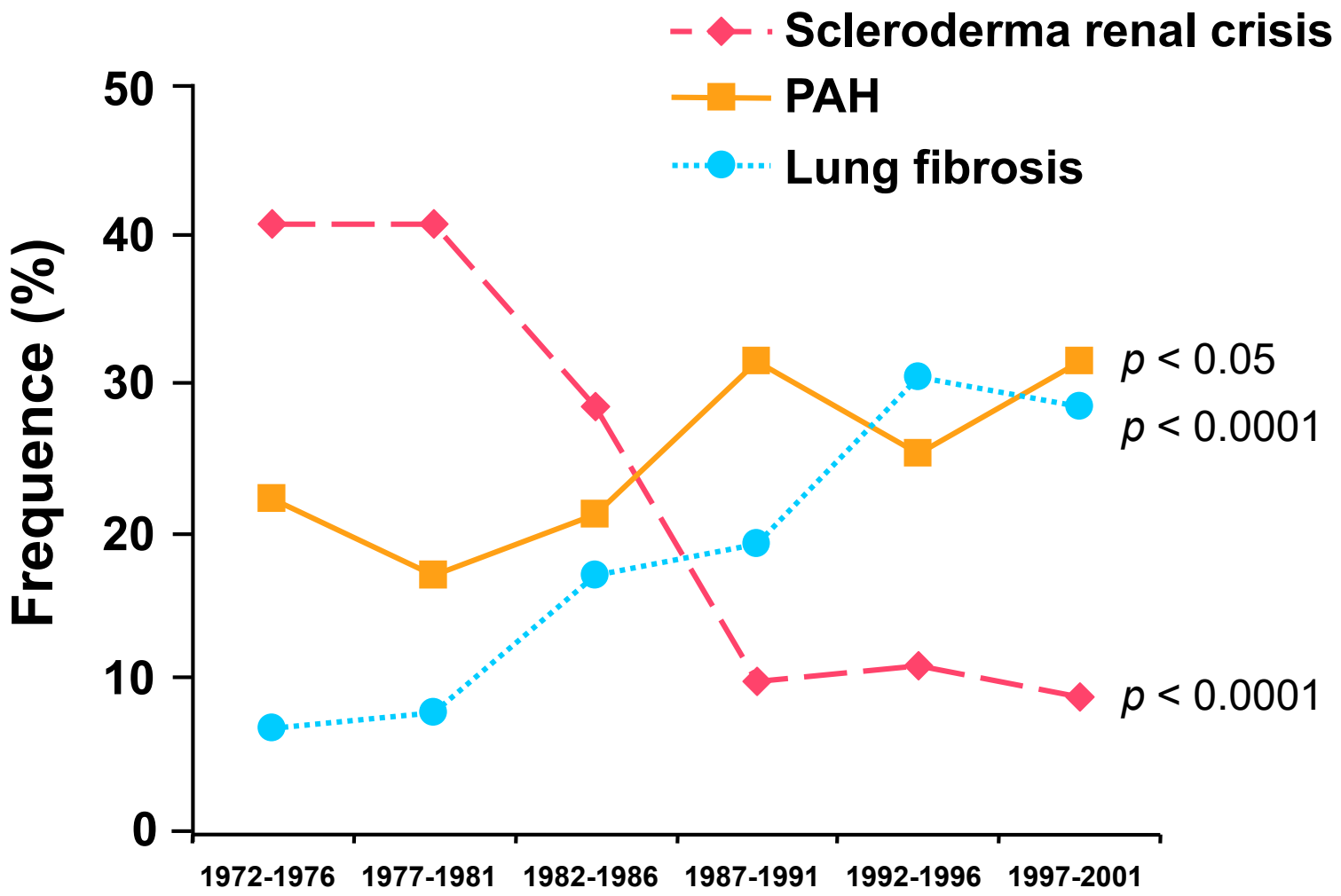
SSc LUNG INVOLVEMENT IS THE FIRST CAUSE OF DEATH



Steen VD & Medsger TA. Ann Rheum Dis 2007

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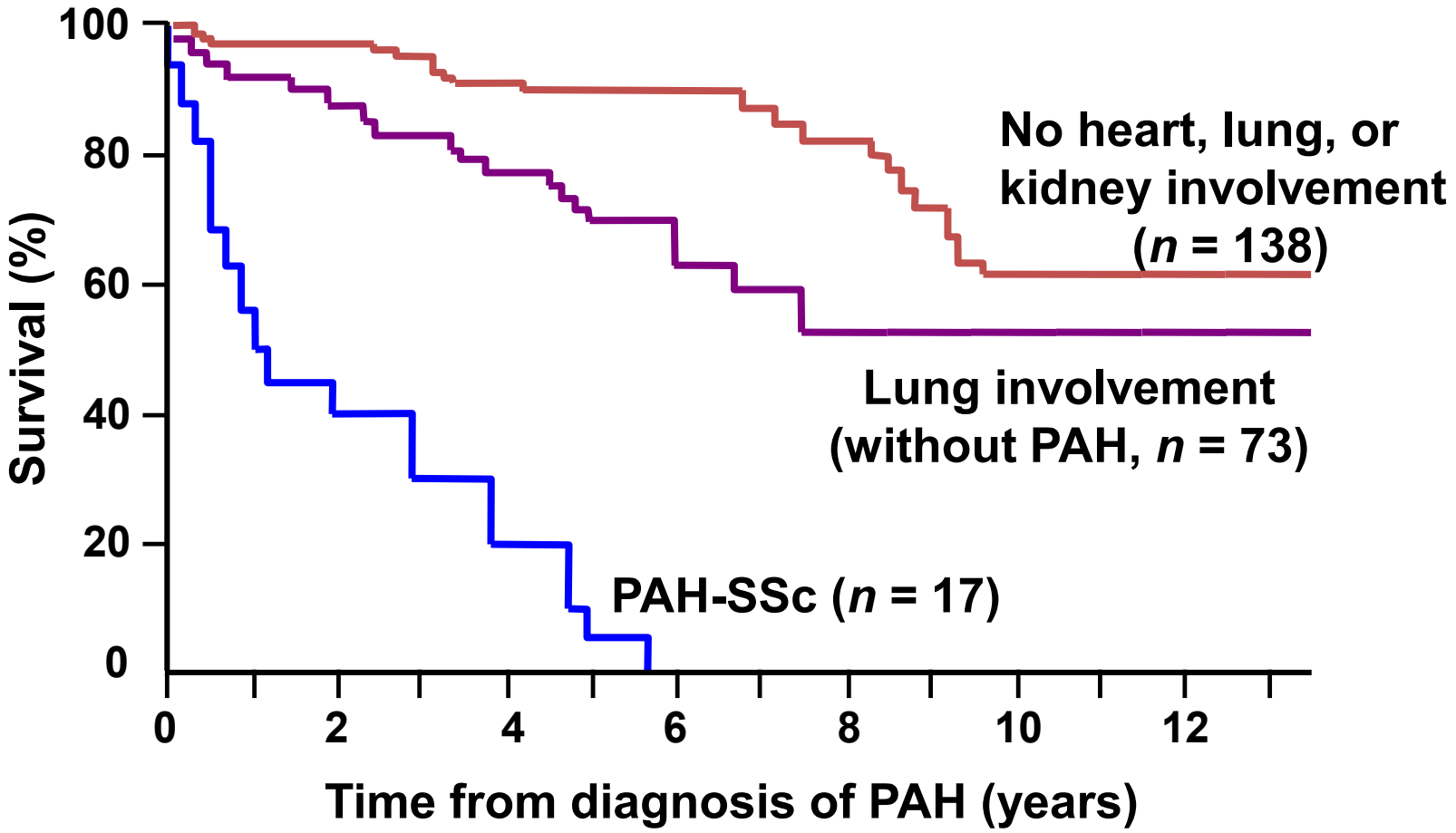

Koh ET, et al. Br J Rheumatol 1996

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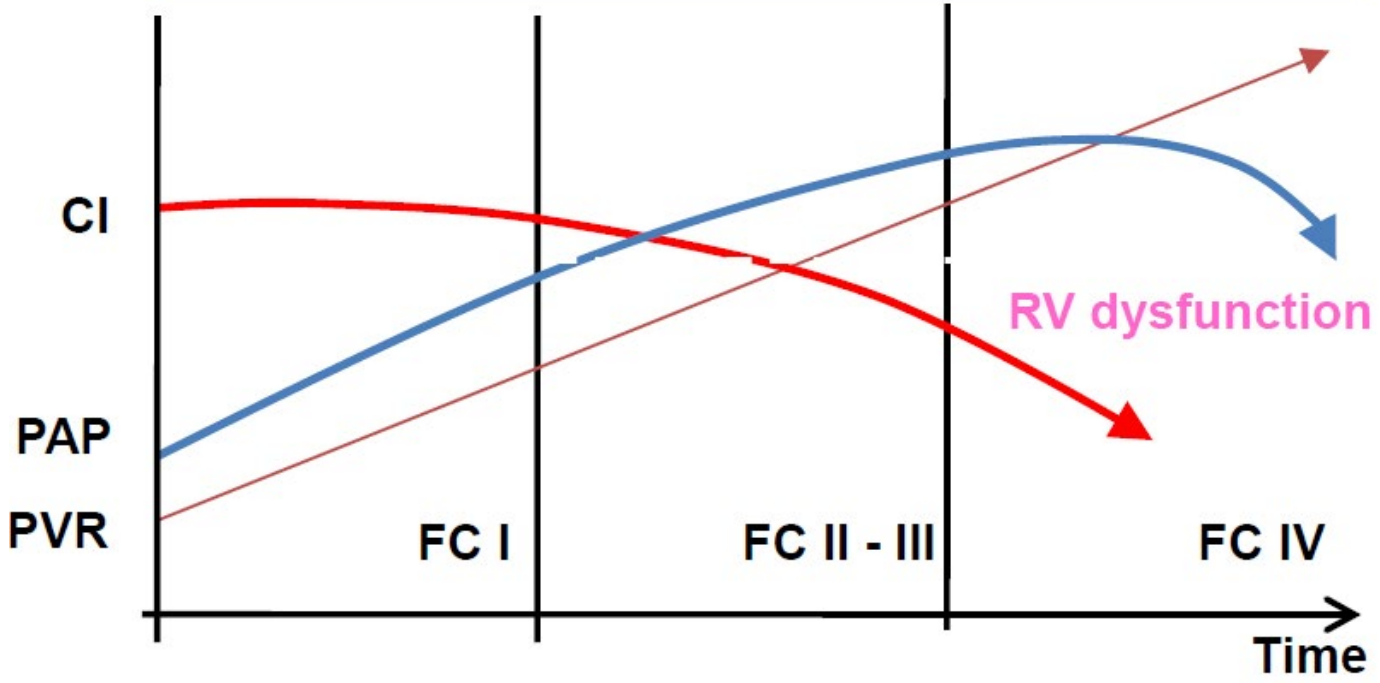
When possible, a PAH screening programme may allow early intervention and improve outcomes



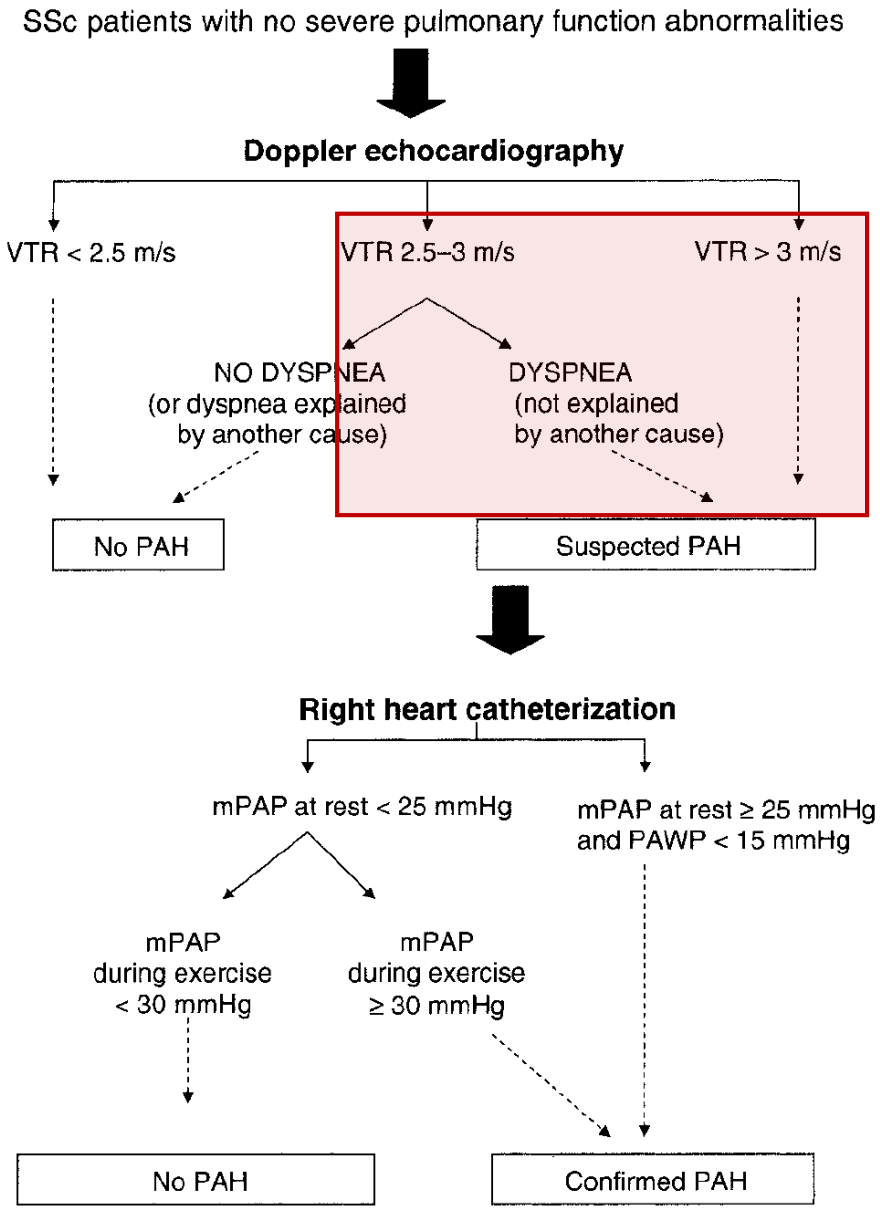
Braunwald E, et al., eds. Harrison's Principles of Internal Medicine. New York: McGraw-Hill; 2001:1506

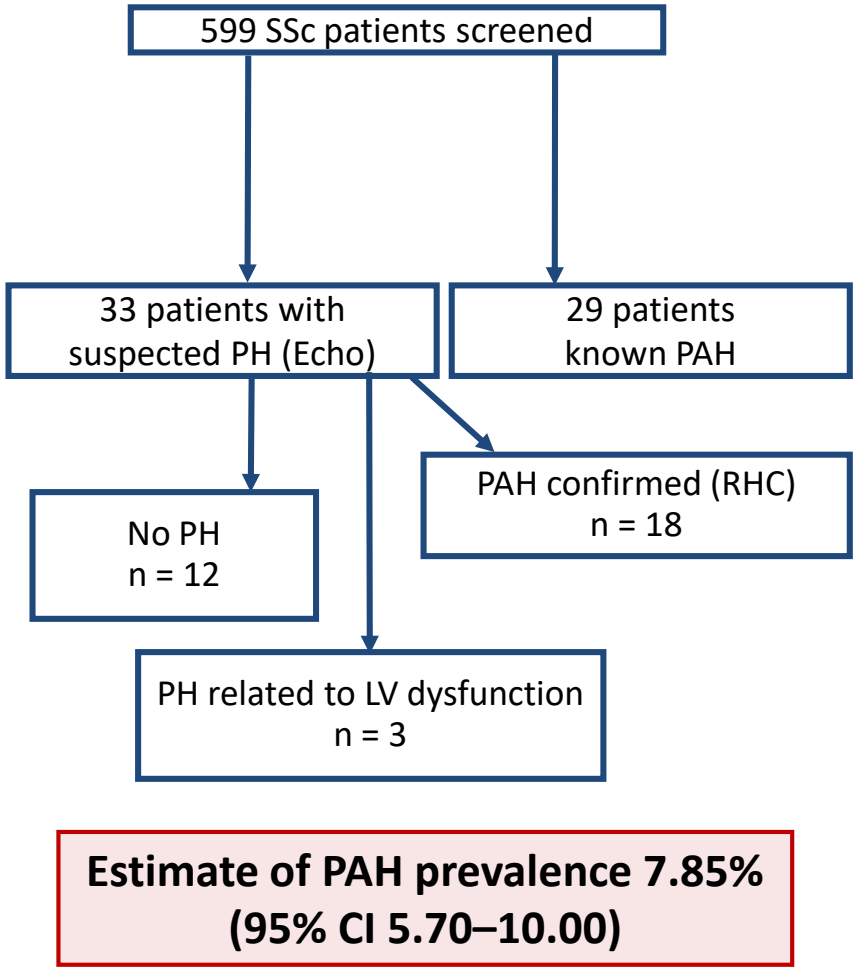
PAH screening in SSc patients

- **Echocardiography** remains central to pulmonary hypertension detection (ItinérAIR study)
- The **DETECT** study and derived algorithm have been developed to better screen for PAH in SSc (> 3-year duration & DLCO<60%)
- Using DETECT approach, screening of patients with the SSc spectrum of diseases without clinical signs and symptoms of PH would include a 2-step approach:
  - Clinical assessment for the presence of telangiectasia, anti-centromere antibodies, PFT and DLCO measurements, electrocardiogram and biomarkers (NT-proBNP and uric acid)
  - Echocardiography and consideration of RHC in patients with abnormal findings, although there is a lack of data with DLCO > 60%

Hoeper MM, et al. J Am Coll Cardiol 2013; 62:D42-50.

Early detection of PAH in SSc





Estimate of PAH prevalence 7.85%
(95% CI 5.70–10.00)

Hachulla E, et al. Arthritis Rheum 2005

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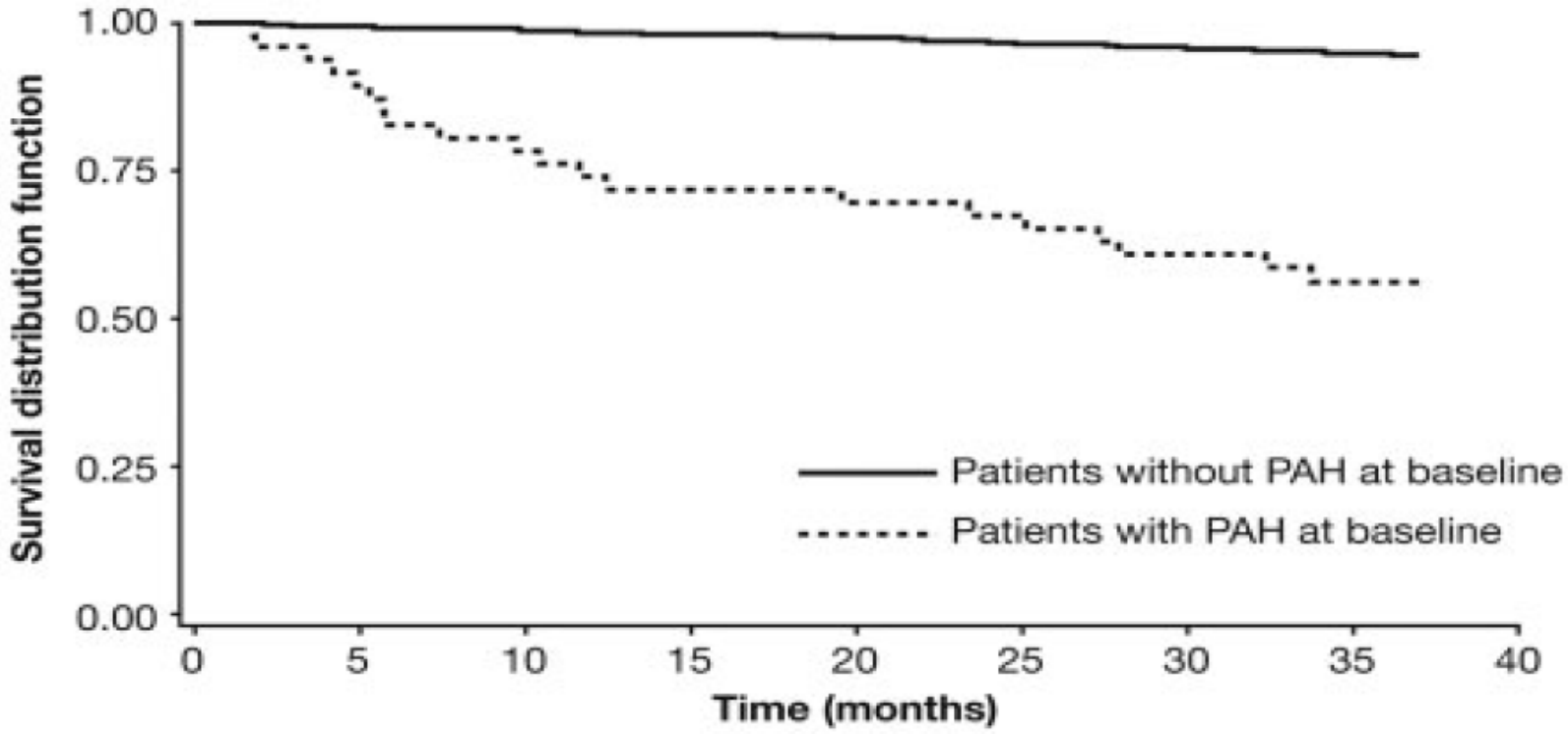
PAH IS A MAJOR CAUSE OF MORTALITY IN SSc

Risk factors for death and the 3-year survival of patients with systemic sclerosis: the French ItinérAIR-Sclérodermie study

Eric Hachulla[1], Patrick Carpentier[2], Virginie Gressin[3], Elisabeth Diot[4], Yannick Allanore[5], Jean Sibilia[6], David Launay[1], Luc Mouthon[7], Patrick Jego[8], Jean Cabane[9], Pascal de Groote[10], Amélie Chabrol[11], Isabelle Lazareth[12], Loïc Guillevin[7], Pierre Clerson[13], Marc Humbert[14] and the ItinérAIR-Sclérodermie Study Investigators



Hachulla E, et al. Arthritis Rheum 2009

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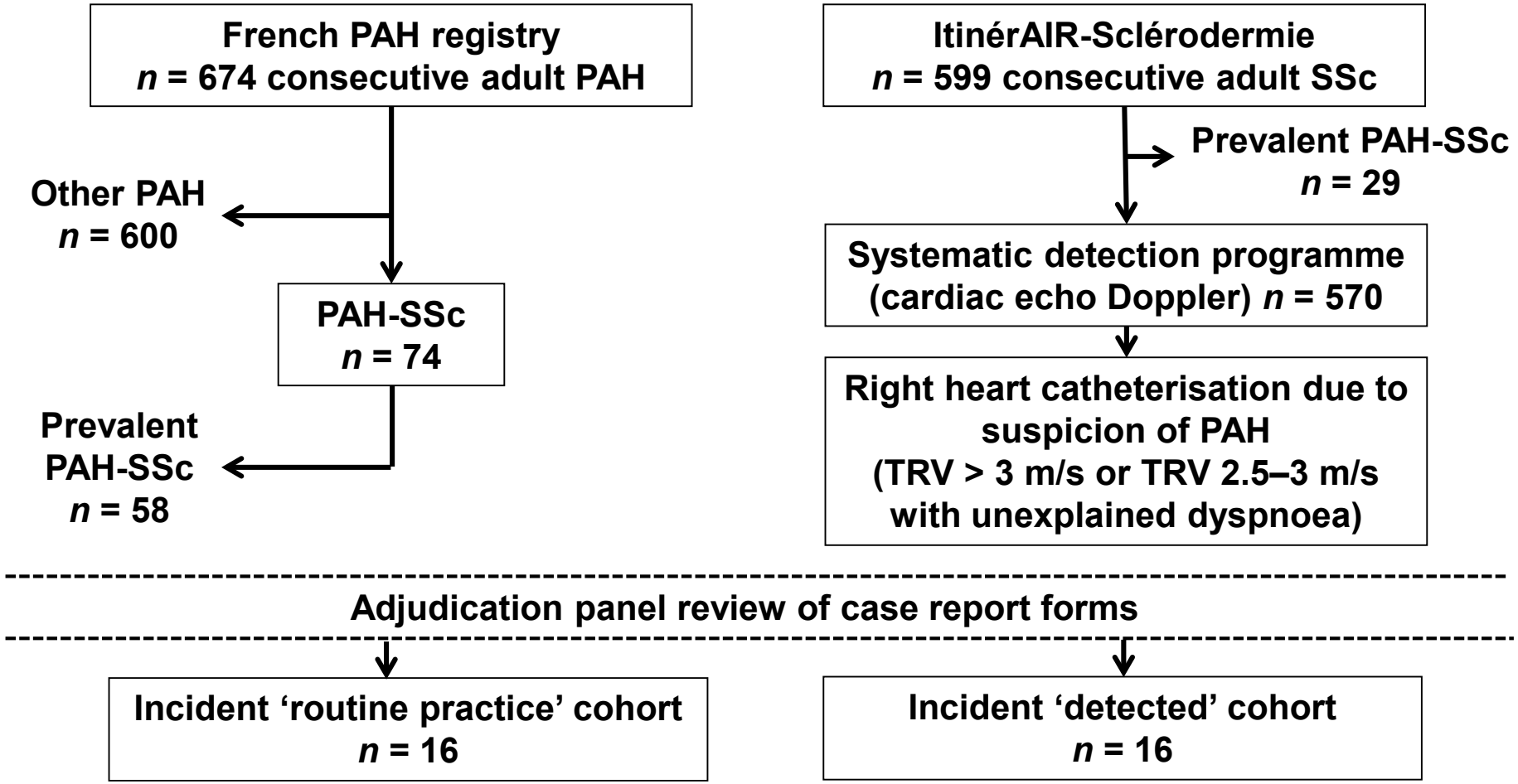
The value of early detection: “Routine practice” and “detected” PAH-SSc patients



Humbert M, et al. Arthritis Rheum 2011

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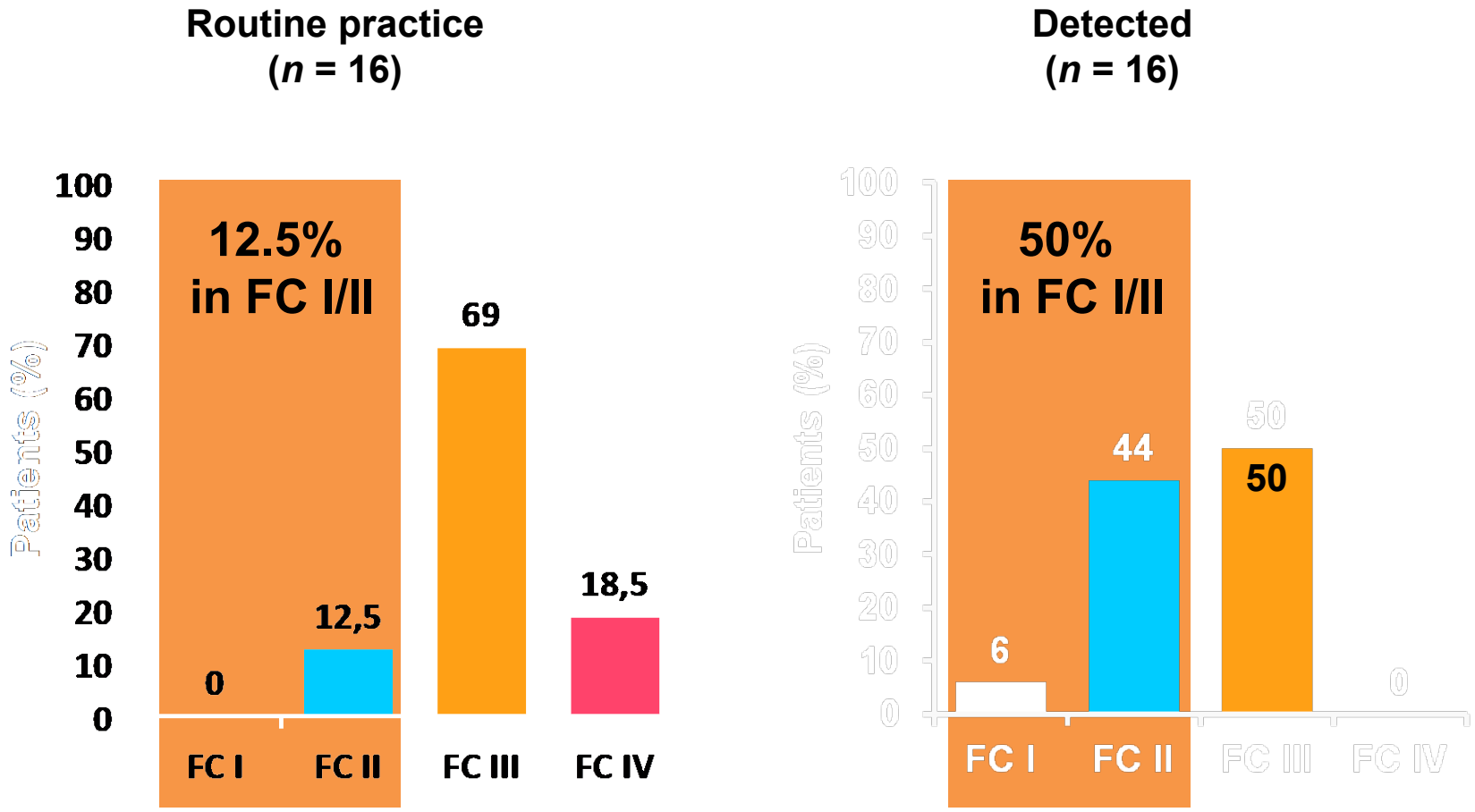
FC at PAH-SSc diagnosis: “Routine practice” and “detected” patients



p = 0.036; routine versus detected patients

FC = WHO functional class

Humbert M, et al. Arthritis Rheum 2011

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

	Routine practice (*n* = 16)	Screened (*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/m^2)	2.37 ± 0.81	3.42 ± 0.92	0.0028
PVRi (dynes·s·cm^{-5}.m^2)	1500 ± 602	613 ± 400	< 0.0001

mPAWP = mean pulmonary artery wedge pressure
PVRi = pulmonary vascular resistance indexed

Humbert M, et al. Arthritis Rheum 2011

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PAH therapies prescribed at PAH-SSc diagnosis: "Routine practice" and "detected" patients

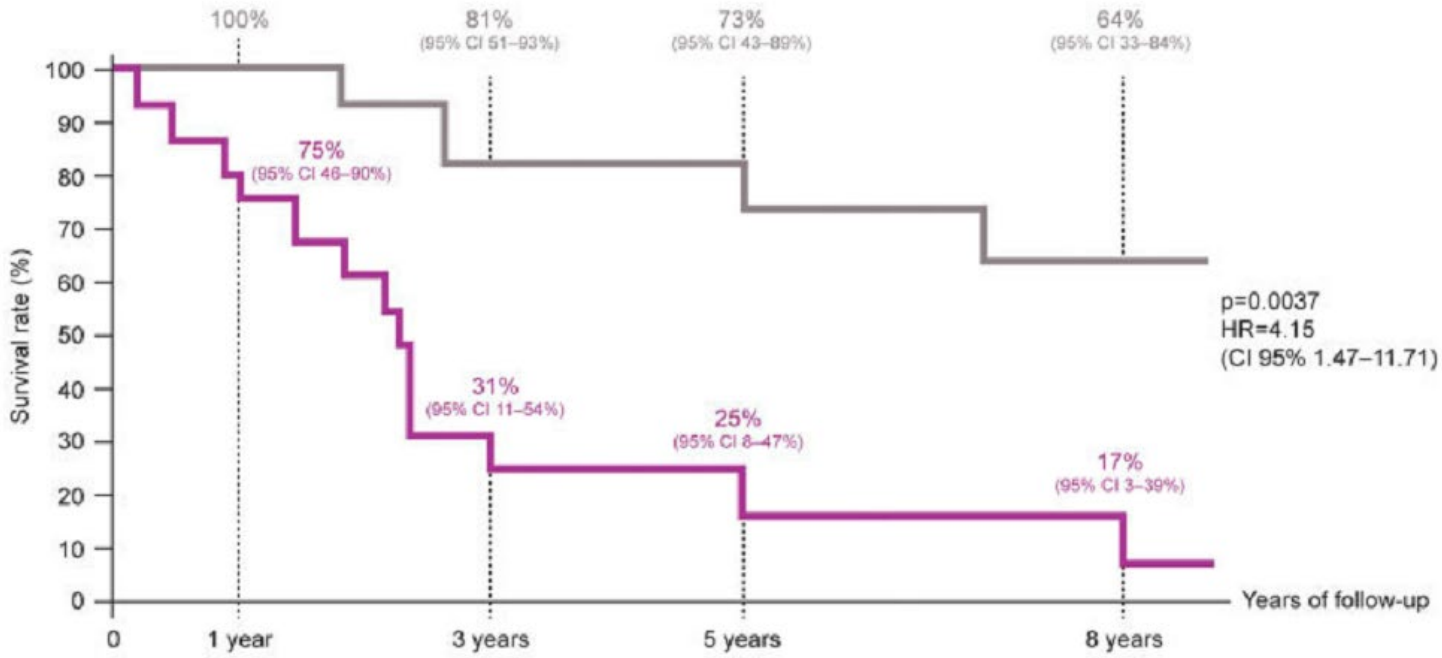
	Routine practice (*n* = 16)	Detected (*n* = 16)	*p*
Conventional therapy			
Warfarin, *n* (%)	12 (75)	4 (25)	0.005
Diuretics, *n* (%)	13 (81)	3 (19)	0.0004
Digoxin, *n* (%)	1 (6)	0 (0)	1
Oxygen, *n* (%)	2 (12.5)	4 (25)	0.65
CCB, *n* (%)	2 (12.5)	2 (12.5)	1
PAH-specific therapy			
ERA, *n* (%)	13 (81)	13 (81)	1
PDE-5i, *n* (%)	6 (37.5)	3 (19)	0.43
Prostacyclin, *n* (%)	2 (12.5)	2 (12.5)	1
None, *n* (%)	2 (12.5)	3 (18)	1
Combination therapy, *n* (%)	6 (37.5)	4 (25)	1
Time from PAH-SSc diagnosis to initiation of PAH therapy (months), median (interquartile range)	0 (3)	1 (5)	0.23

Humbert M, et al. Arthritis Rheum 2011

Screening for Pulmonary Arterial Hypertension in Patients With Systemic Sclerosis

Clinical Characteristics at Diagnosis and Long-Term Survival

Marc Humbert,[1] Azzedine Yaici,[1] Pascal de Groote,[2] David Montani,[1] Olivier Sitbon,[1] David Launay,[3] Virginie Gressin,[4] Loïc Guillevin,[5] Pierre Clerson,[6] Gérald Simonneau,[1] and Eric Hachulla[3]



Humbert M, et al. Arthritis Rheum 2011

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Limitations

- **Over-diagnosis**
- **Non-randomised, open-label, pragmatic study**
- **Length-time bias**
- **Lead-time bias**

Humbert M, et al. Arthritis Rheum 2011

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2015 Recommendations ESC/ERS

Web Table X Recommendations for pulmonary arterial hypertension screening

Recommendations	Class[a]	Level[b]
Resting echocardiography is recommended as a screening test in asymptomatic patients with systemic sclerosis.	I	B
A combined approach (including biomarkers, PFTs and echocardiography) should be considered to predict PH in systemic sclerosis.	IIa	B
Systemic sclerosis patients with a mean PAP ranging from 21 to 24 mmHg should be closely monitored, because of a higher risk of PAH.	IIa	B
Initial screening using the stepwise DETECT algorithm may be considered in adult systemic sclerosis patients with >3 years' disease duration and a DLCO <60% predicted.	IIb	B
Annual screening with echocardiography, PFTs and biomarkers may be considered in patients with systemic sclerosis.	IIb	B

Galiè et al. Eur Respir J 2015

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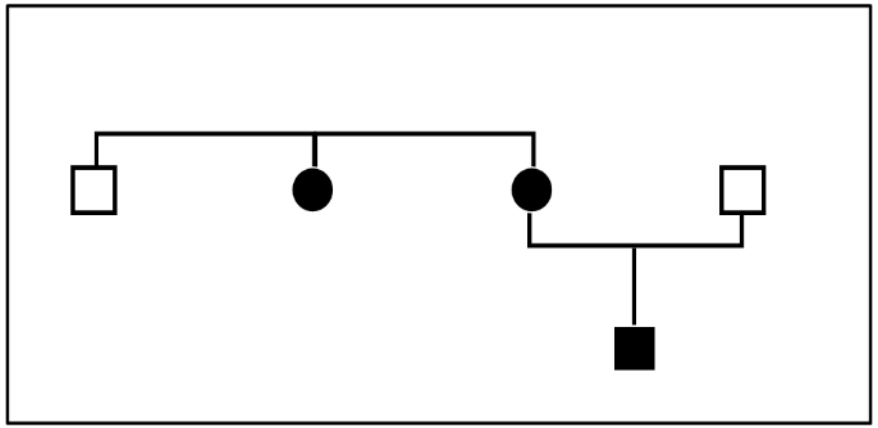
1st familial cases of PAH reported in 1954



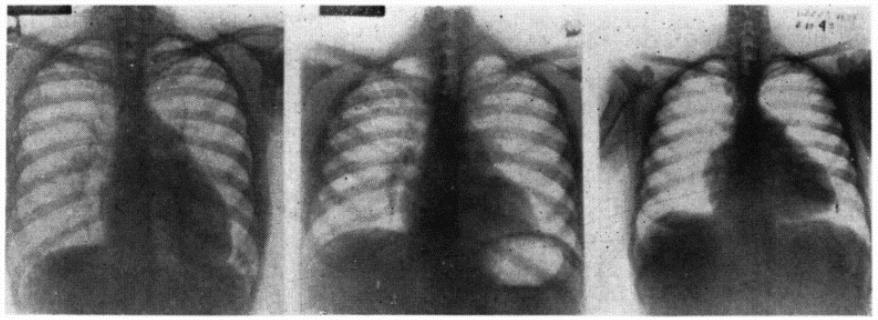


Fig. 3—Chest x-rays of three members of the same family showing prominent pulmonary artery segments, prominent hilar vessels and normal or decreased pulmonary vascular markings.

Dresdale DT, Bull NY Acad Med 1954

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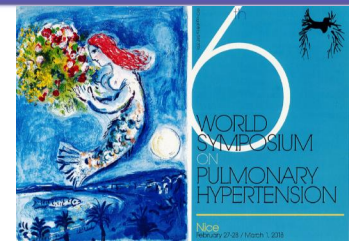
HERITABLE PAH



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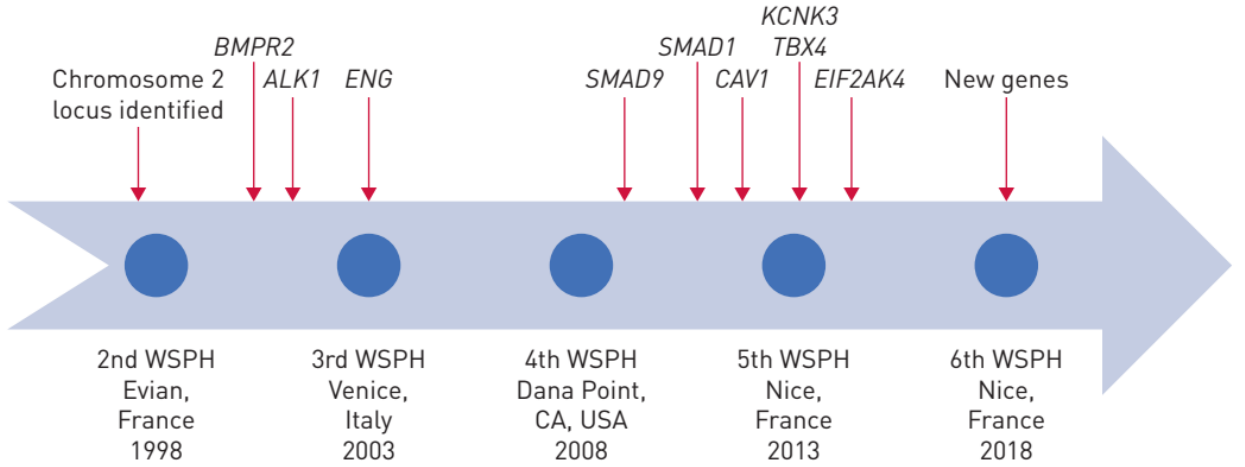

Simonneau et al. Eur Respir J 2019
Morrell NJ, Eur Respir J 2019

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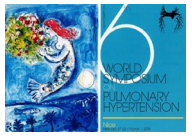

TASKFORCE 2: Genetics & Genomics

Higher level of evidence
BMPR2 *EIF2AK4*; *TBX4*; *ATP13A3*; *GDF2*; *SOX17*; *AQP1*; *ACVRL1*; *SMAD9*; *ENG*; *KCNK3*; *CAV1*
Lower
SMAD4; *SMAD1*; *KLF2*; *BMPR1B*; *KCNA5*

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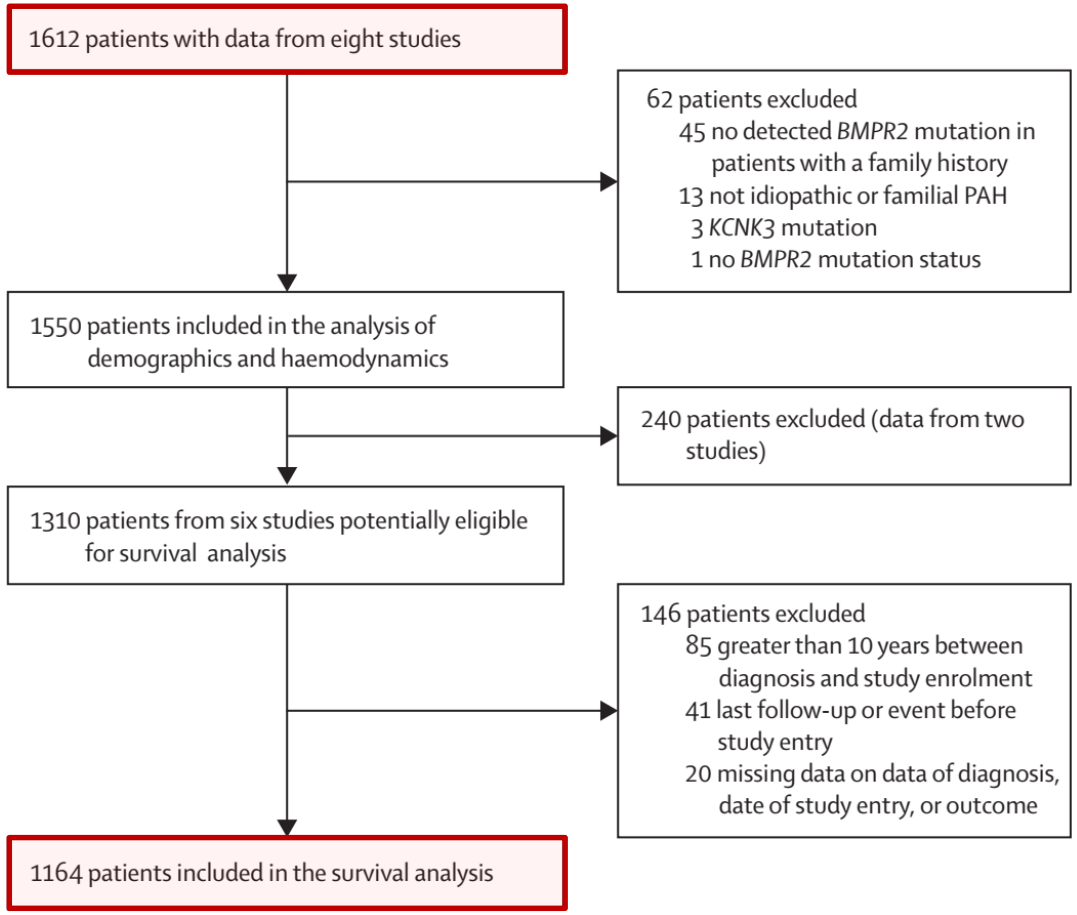
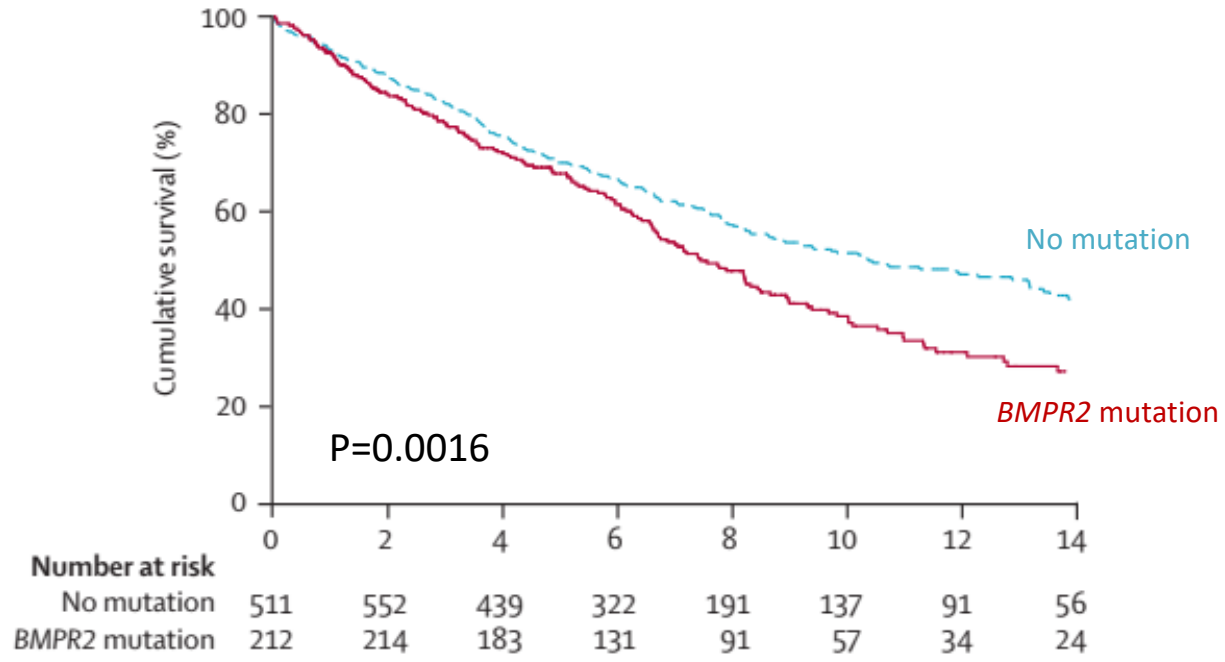
HERITABLE PAH DUE TO *BMPR2* MUTATION

BMPR2 mutations and survival in pulmonary arterial hypertension: an individual participant data meta-analysis

Jonathan D W Evans, Barbara Girerd, David Montani, Xiao-Jian Wang, Nazzareno Galiè, Eric D Austin, Greg Elliott, Koichiro Asano, Ekkehard Grünig, Yi Yan, Zhi-Cheng Jing, Alessandra Manes, Massimiliano Palazzini, Lisa A Wheeler, Ikue Nakayama, Toru Satoh, Christina Eichstaedt, Katrin Hinderhofer, Matthias Wolf, Erika B Rosenzweig, Wendy K Chung, Florent Soubrier, Gérald Simonneau, Olivier Sitbon, Stefan Gräf, Stephen Kaptoge, Emanuele Di Angelantonio, Marc Humbert*, Nicholas W Morrell**



Transplant-free Survival



Evans JDW, *Lancet Respir Med 2016*

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6th World Symposium on PH

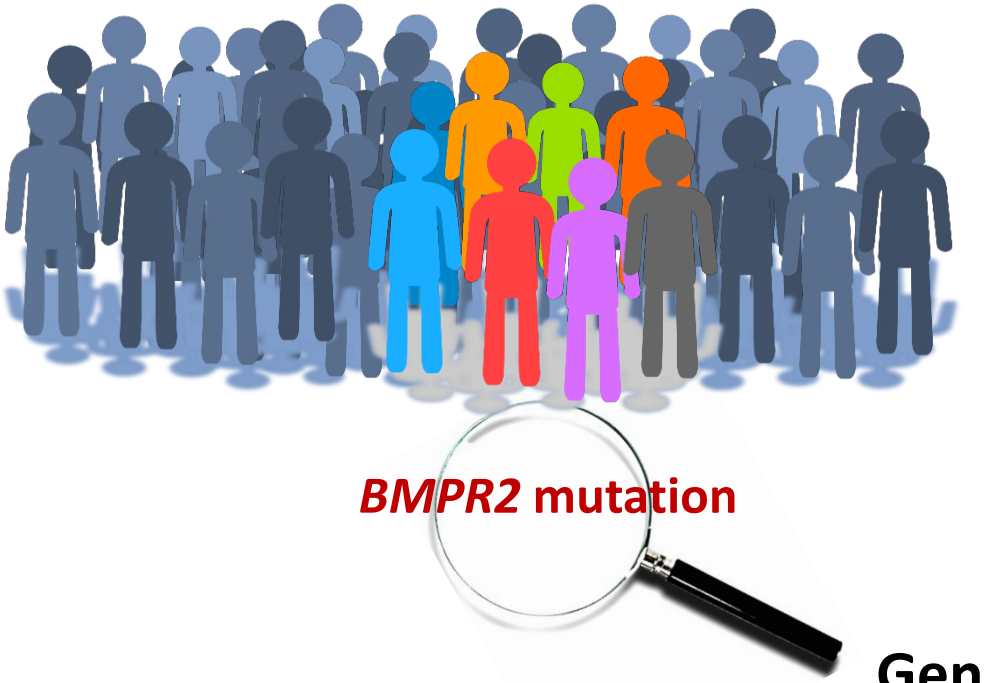
Genetic education and counselling should be performed prior to genetic testing for PAH to address the complex issues of incomplete penetrance, questions of surveillance for genetically at-risk family members, reproductive questions, concerns about genetic discrimination, as well as psychosocial issues of guilt and blame that can accompany genetically based diseases.

In France, genetic testing for PAH:

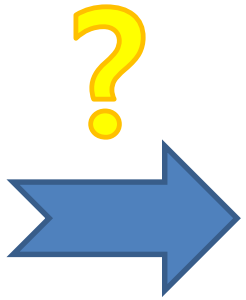
- is restricted to adults (>18 y-o) in asymptomatic relatives of PAH patients
- can be proposed in children with unexplained symptom that could be related to PAH

PAH patients

1st degree relatives



Genetic counseling



PAH

***BMPR2* mutation**

50% of *BMPR2* mutation

Genetic testing

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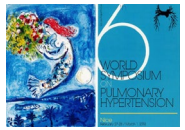
Recommendations in mutation carriers

2015 ESC/ERS Guidelines

Recommendations	Class[a]	Level[b]
Resting echocardiography is recommended as a screening test in *BMPR2* mutation carriers or first-degree relatives of patients with HPAH	I	C
In individuals who test positive for PAH-causing mutations and first-degree relatives of HPAH cases may be considered to have an annual screening echocardiogram.	IIb	C
Exercise echocardiography is not recommended to predict PH in high risk population.	III	C



6th World Symposium on PH

Recommendations

- Genetic counselling of all idiopathic, anorexiant and familial PAH patients and first-generation asymptomatic family members of patients with known genetic mutations.
- Subsequent evaluations for PAH should be offered (*e.g.* CPET and TTE), in mutation-positive individuals.

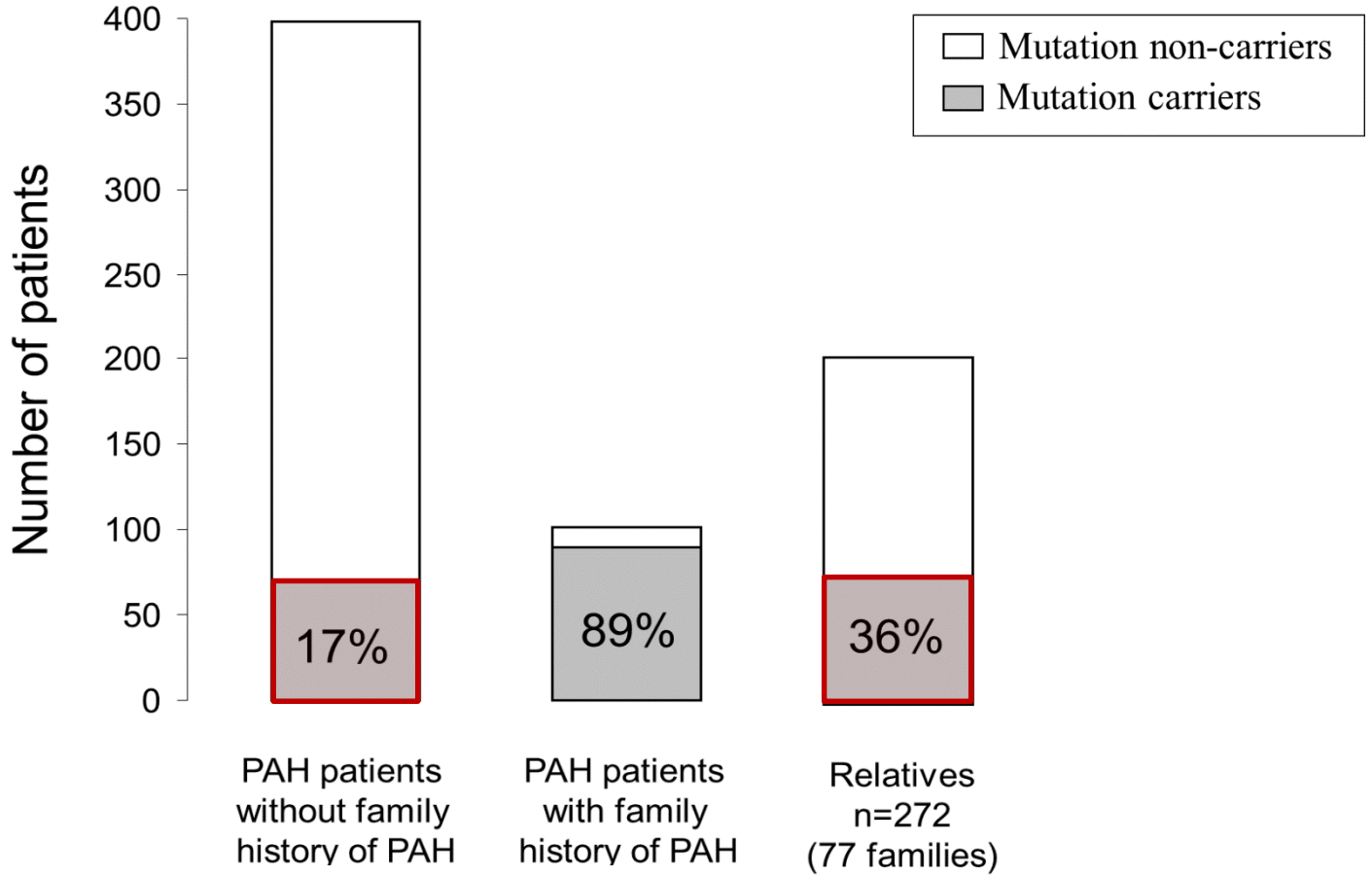
DELPHI-2
Dépistage et ÉvaLuation des facteurs Prédictifs de la survenue d'une Hypertension artérIelle pulmonaire chez les sujets asymptomatiques, porteurs de mutation du gène BMPR2

NCT01600898

HTaPFrance

French PAH patients association

French National Program for PAH screening in asymptomatic *BMPR2* mutation carriers



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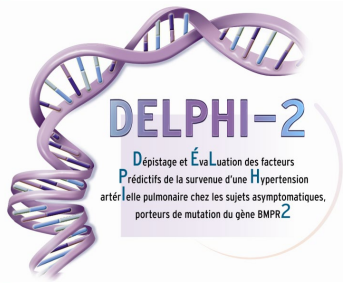
PAH SCREENING: DELPHI2



Asymptomatic *BMPR2* mutation carriers (adults)

Optional at inclusion
Right heart cath
Rest / exercise

Every 12 months or symptoms

Visit
- . NYHA
- . NT-pro BNP
- . ECG
- . Chest Rx

Functional tests
- . 6MWT
- . CPET
- . PFTs
- . DLCO/DLNO……

Echocardio
- . TRJ
- . TAPSE
- . RV, RA

Biobank
- . Plasma
- . serum

Dyspnea or unexplained syncopa

or

Decrease in VO_2 max > 20 %

or

TRJ > 2.8 m/s

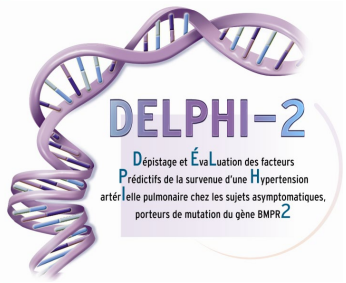
Right Heart Cath
Rest / exercise

Confirmed PAH

Withdrawal from the study

Management according to ERS / ESC guidelines

PAH SCREENING: DELPHI2



Relatives of PAH patients carrying a *BMPR2* mutation

n=274 *(77 families)*

↓

Relatives carrying a *BMPR2* mutation

n=94 (45 families)

→ *3 relatives developped PAH before the beginning of the study*

↓

Asymptomatic carrying *BMPR2* mutations potentially incluable in DELPHI-2

n=91 *(44 families)*

→ *36 patients denied to participate*

↓

Asymptomatic *BMPR2* mutations carriers included in DELPHI-2

n=55 *(31 families)*

2 year follow-up
Long-term extension study

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PAH SCREENING: DELPHI2

DELPHI-2
Dépistage et ÉvaLuation des facteurs Prédictifs de la survenue d'une Hypertension artérielle pulmonaire chez les sujets asymptomatiques, porteurs de mutation du gène BMPR2

Asymptomatic *BMPR2* mutations carriers

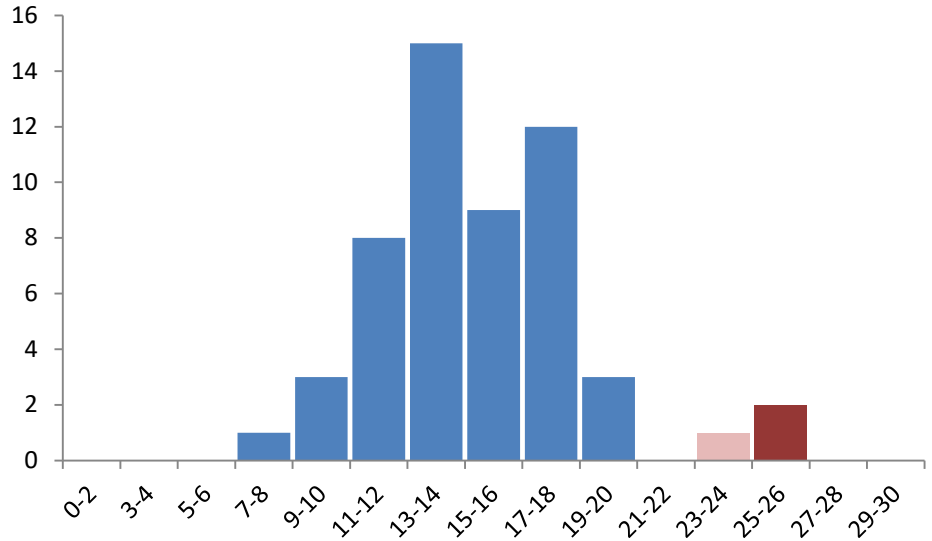
n=55

RHC at rest at inclusion

No PAH
n=53

PAH
n=2

Distribution mPAP



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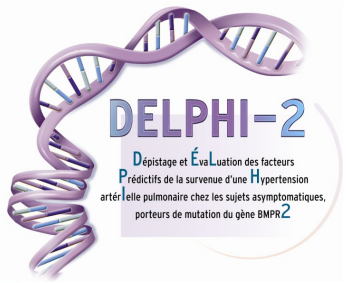
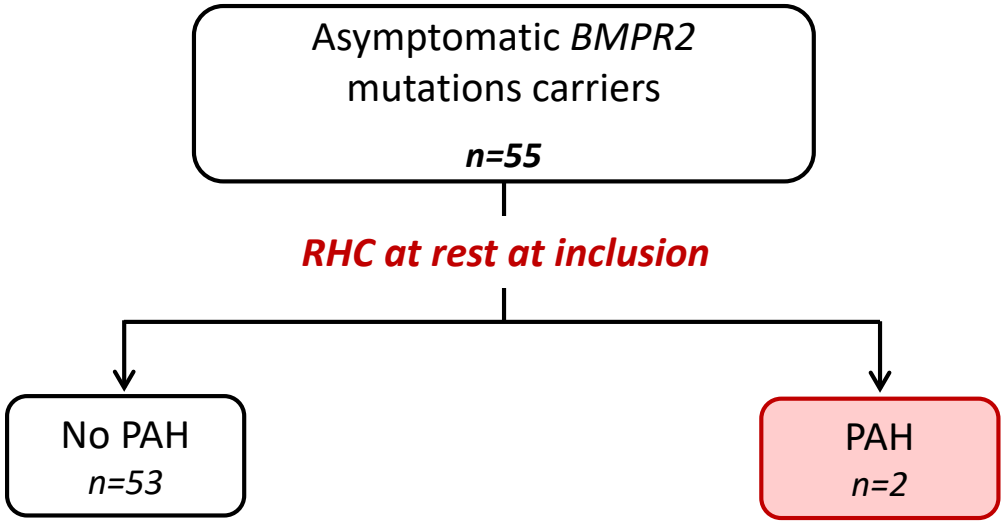
PAH SCREENING: DELPHI2





	No PAH (n=53)	Patient 1	Patient 2
Age, years	37.1 (18 – 67.5)	25.5	78.1
Sex ratio, M/F	26/27	F	F
Tobacco exposure >5p.y	28 (52%)	Yes	No
BMI	22.5 (16.8 – 32.2)	22.0	25.2
Arterial hypertension, n(%)	10 (19%)	No	Yes
Diabetes, n(%)	3 (6%)	No	Yes
Dyslipidemia, n(%)	3 (6%)	No	No

Patient 1

	At Screening
NYHA FC	I
6-MWD, m	533
mPAP, mmHg	**26**
PcwP, mmHg	8
Cardiac output, $L.min^{-1}$	7.27
Cardiac index, $L.min^{-1}.m^2$	**4.38**
PVR, WU	**2.5**
BNP, (normal < 80)	9
PAH therapy	-

Female 25 year-old
3 months **post-partum**

TTE : **TRV 2 m/s**
TAPSE 25 mm
considered as « normal »

CPET: VO2 sp 72% theo
VD/VT normal
PaO2 at exercise normal

BNP : normal

CONCLUSIONS

- Genetic counseling should be proposed to all first degree relatives of patients with heritable PAH due to *BMPR2* mutations to identify asymptomatic mutation carriers at risk to develop PAH

- No preventive therapy but **potential benefits**:
  - Reproductive informations and options (adoption, donor gametes, pre-implantation diagnosis)
  - Early diagnosis

- ESC/ERS guidelines recommended **annual echocardiogram** based on experts consensus

- Preliminary data from DELPHI2 program suggest that non single invasive exams may be **unable to screen PAH in asymptomatic patients**

  $\Rightarrow$ Further analysis may bring additional informations.

- Another strategy could be to **identify a subgroup with high penetrance** (female, post-partum, mutation type, biomarkers….) and to propose right heart catheterization for this high-risk population.

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