PH IN CTD

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NEW DELHI

Pulmonary Hypertension

- **Pulmonary hypertension (PH) is defined as a resting mean pulmonary artery pressure (mPAP) of ≥25 mmHg measured during right heart catheterization (RHC)**

MAYO CLINIC

Although the prognosis of PAH has improved with targeted therapies, the outcome is dependent on early detection and an accurate diagnosis

Respiratory Medicine 143 (2018) 139–146
Mayo Clin Proc.2020;95(9):1978-1988.
JAMA Intern Med. 2013 May 27;173(10):887-93.

European Heart Journal Supplements (2019) **21** (Supplement K), K4–K8
The Heart of the Matter
doi:10.1093/eurheartj/suz211

ESC
European Society
of Cardiology

The revised definition of pulmonary hypertension: exploring the impact on patient management

Gérald Simonneau[1]* and Marius M. Hoeper[2]

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[2]*Department of Respiratory Medicine, Hannover Medical School and German Center for Lung Research, 30625 Hannover, Germany*

Table 1 Haemodynamic definitions of PH

	Clinical groups[a]	Definition at rest	
		Previous[2,3]	Revised[1]
Pre-capillary PH	1, 3, 4 and 5	mPAP ≥25 mmHg PAWP ≤15 mmHg[b]	mPAP >20 mmHg PAWP ≤15 mmHg PVR ≥3 WU
Isolated post-capillary PH (IpcPH)	2 and 5	mPAP ≥25 mmHg PAWP >15 mmHg DPG <7 mmHg and/or PVR ≤3 WU	mPAP >20 mmHg PAWP >15 mmHg PVR <3 WU
Combined post-capillary and pre-capillary PH (CpcPH)	2 and 5	mPAP ≥25 mmHg PAWP >15 mmHg DPG ≥7 mmHg and/or PVR >3 WU	mPAP >20 mmHg PAWP >15 mmHg PVR ≥3 WU

VENICE 2003 CLASSIFICATION

1. Pulmonary arterial hypertension

- **Idiopathic PAH**
  - **Heritable**
    - **BMPR2**
    - **ALK1, endoglin**
    - **unknown**
  - **Drugs and toxins induced**
  - **Associated with:**

– Connective tissue diseases
– HIV infection
– Portal hypertension
– systemic to pulmonary shunts
– Schistosomiasis
– Chronic haemolytic anaemia

1'Pulm. veno- occlusive disease (PVO) and/or pulmonary capillary haemangiomatosis (PCH)

2. Pulmonary hypertension due to left heart disease

- **Systolic dysfunction**
- **Diastolic dysfunction**
- **Valvular disease**

3. Pulmonary hypertension due to lung diseases and/or hypoxia

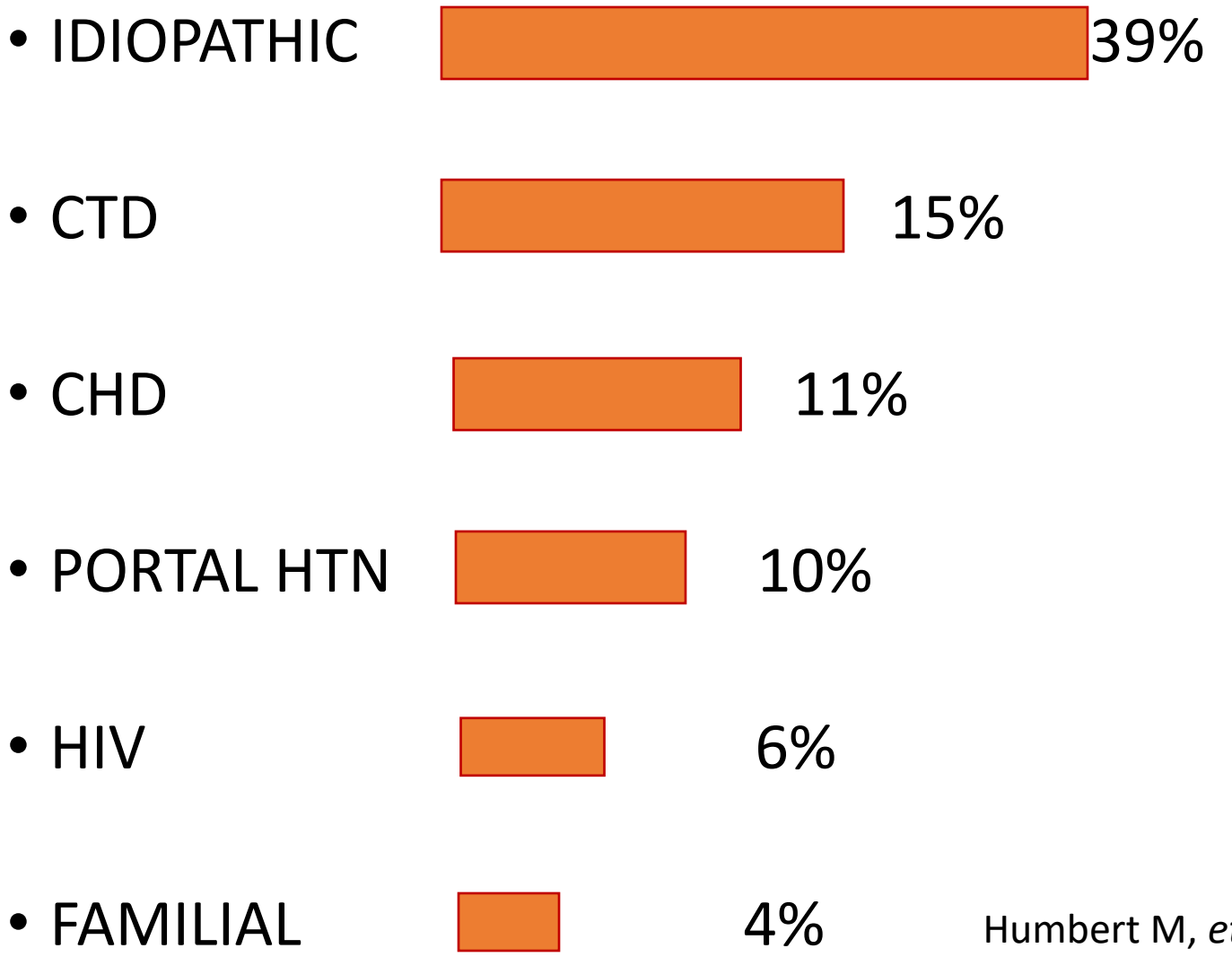
- **Chronic obstructive pulmonary disease**
- **Interstitial lung disease**
- **Sleep-disordered breathing**
- **Chronic exposure to high altitude**
- **Broncho pulmonary dysplasia (BPD)**
- **Developmental abnormalities**

4. Chronic thromboembolic pulmonary hypertension (CTEPH)

5. Pulmonary Hypertension with unclear and/or mulifactorial mechanisms

- **Haematologic disorders**
  myeloproliferative disorders; splenectomy
- **Systemic disorders**
  Vasculitis sarcoidosis, pulmonary Langerhans cell histiocytosis LAM, neurofibromatosis.
- **Metabolic disorders**
  Glycogen storage disease, Gaucher disease, thyroid disorders
- **Congenital heart disease**
  other than systemic to pulmonary shunt
- **Others**: *obstruction by tumours, fibrosingmediastinitis,*

CTD LEADING CAUSE OF PAH

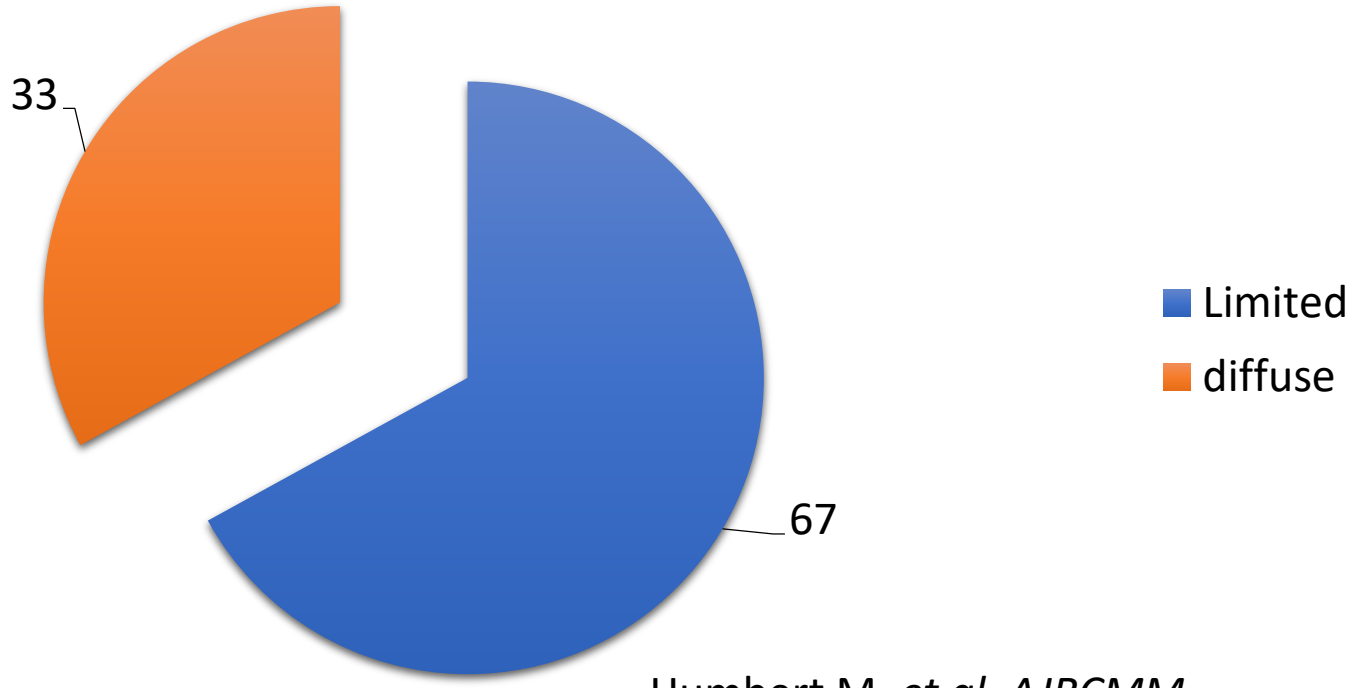


Humbert M, *et al. AJRCMM 2006;173:1023–30*

- SSc is the leading cause of death from PAH amongst the CTD.
- SLE-15%
- SSc- 76%

Humbert M, *et al. AJRCMM 2006;173:1023–30*

PAH in SSC



Humbert M, *et al. AJRCMM 2006;173:1023–30*

PAH in SSc worse than SLE

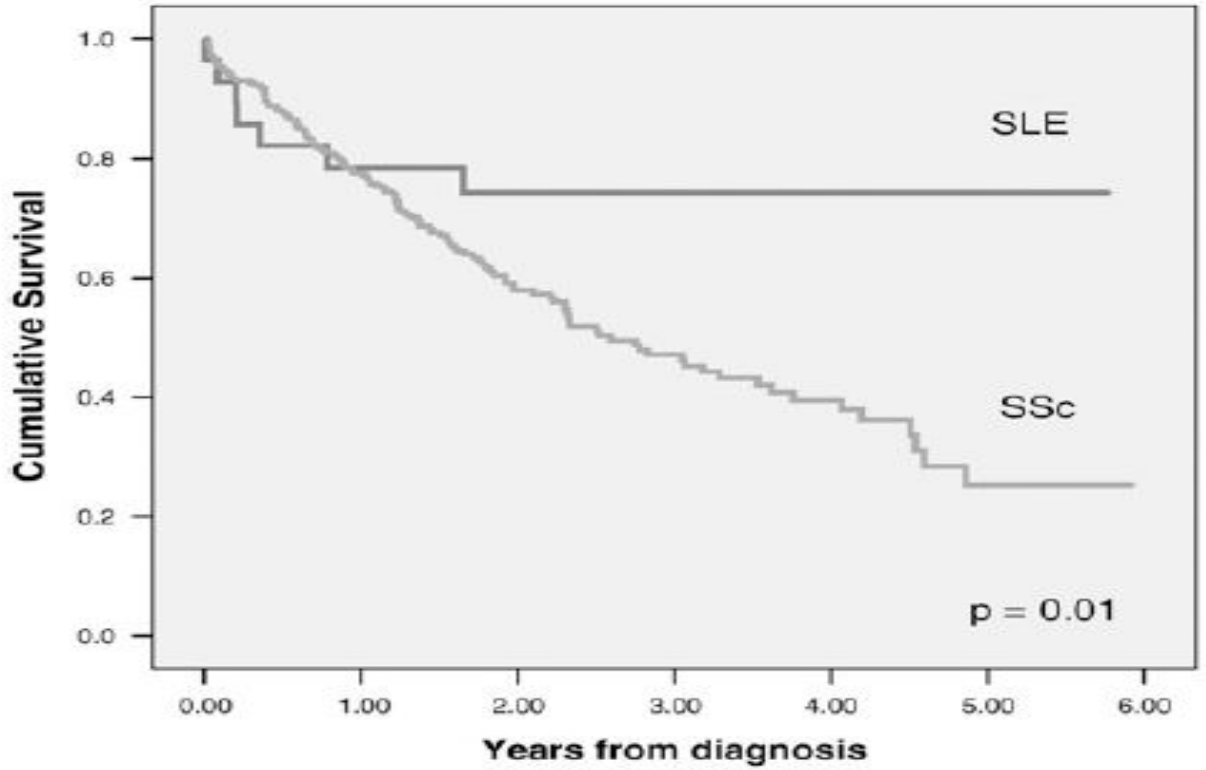


Figure 5. Survival from diagnosis of patients with isolated systemic sclerosis–associated pulmonary arterial hypertension and systemic lupus erythematosus–pulmonary arterial hypertension.

PH in SSC causes

Table 2. 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.

Venice 2003 classification of PH

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- **Metabolic disorders**
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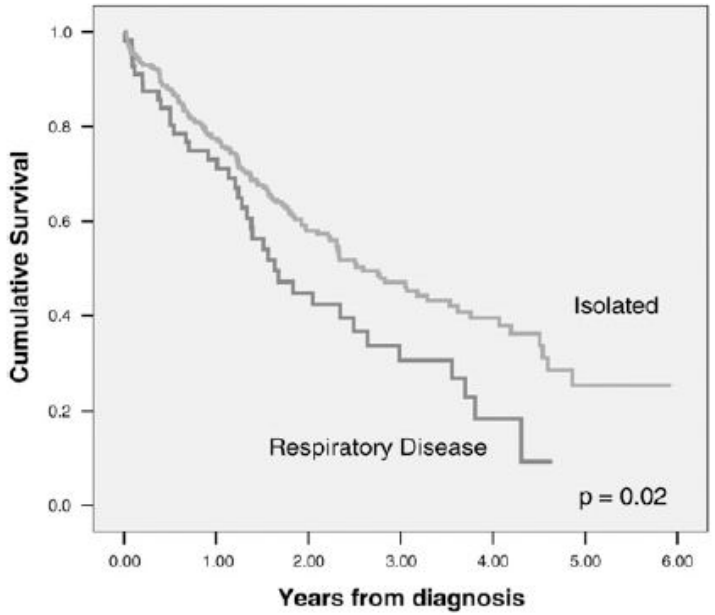
- **Congenital heart disease**
  other than systemic to pulmonary shunt
- **Others**: *obstruction by tumours, fibrosingmediastinitis, chronic renal failure on dialysis*

PH-ILD worse than isolated PH

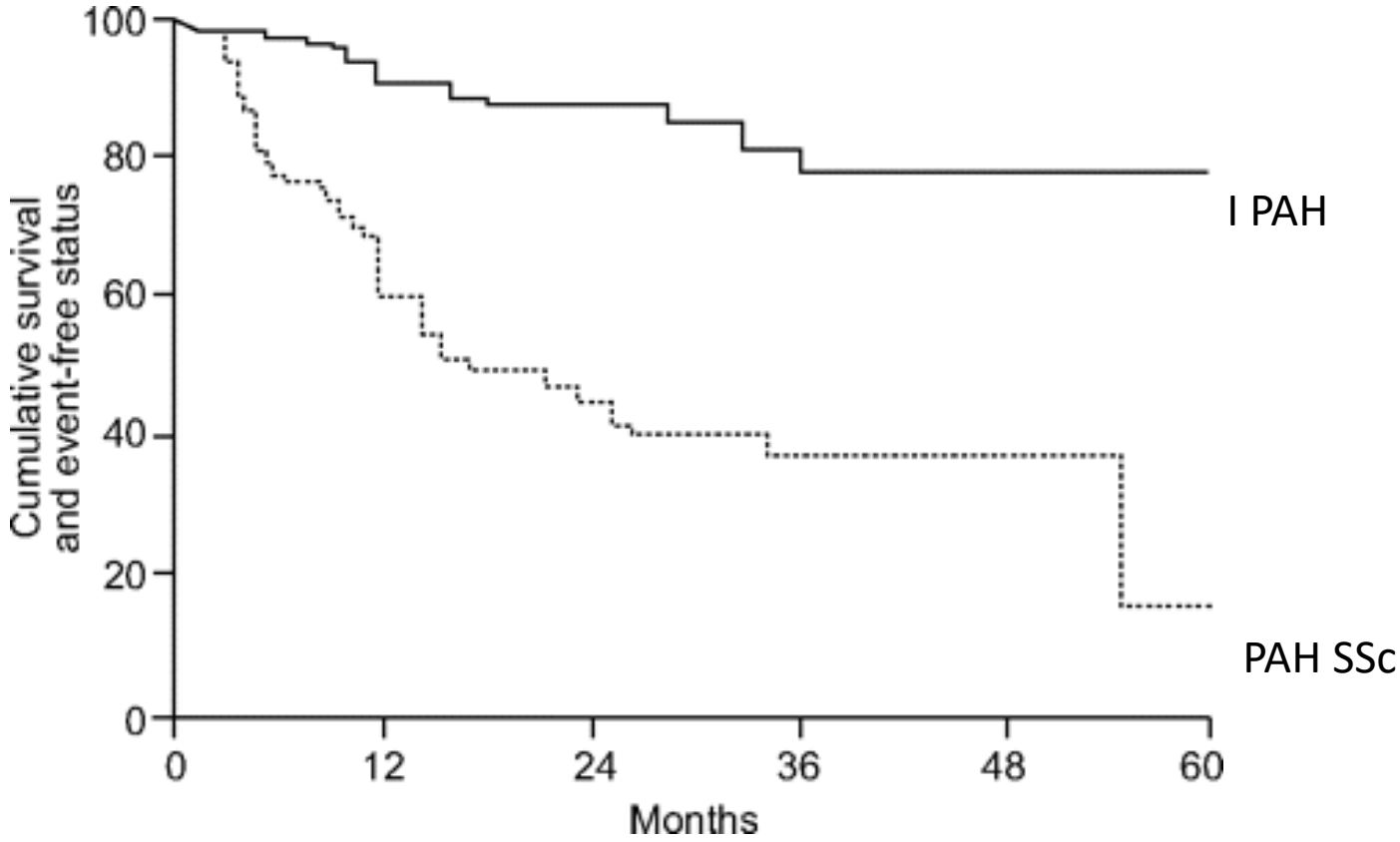


Patients at risk

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.

I PAH vs PAH SSc



Kawut et al. chest 2003

PHAROS STUDY

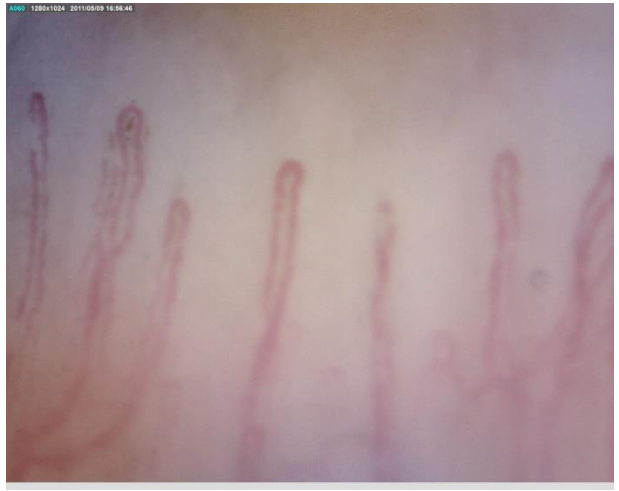
- 2 YR OUTCOME FOR PRE-PAH IN SSc
- ENTRY CRITERIA- DLCO <55%
- ECHO PASP- >40MMHG
- 205 PATIENTS ENROLLED SCREENED ANNUALY
- AFRICAN AMERICAN, AND NUCLEOLAR U3 RNP AB,DLCO
- CONCLUSION- AT 2YRS 22% CUMULATIVE DEV OF PAH IN PATIENTS AT HIGH RISK
- VERY LOW DLCO(40%) WAS THE BEST PREDICTOR
- ECHO PASP VARIABLE OVER TIME DID NOT CORRELATE WITH SPAP ON RHC.

OTHER risk factors for PAH in SSC

- Nt pro-BNP

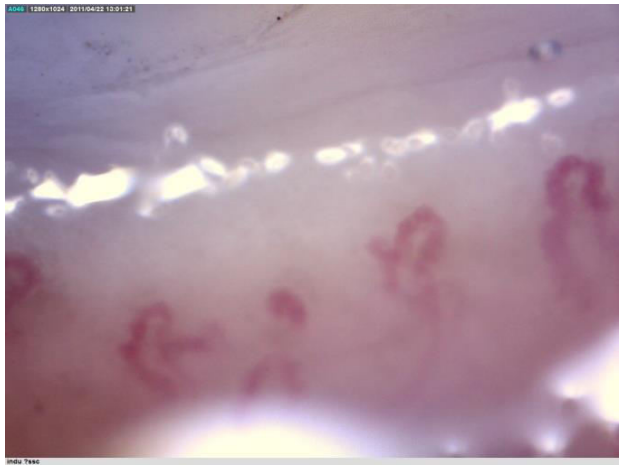
- Telengectasias >10

Nail fold Capillaroscopy

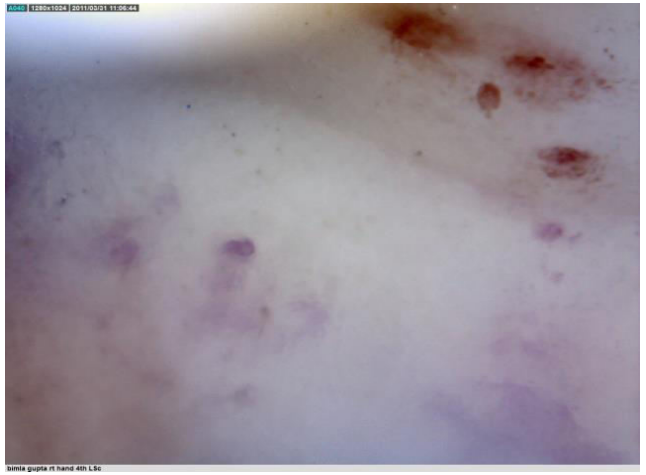


NORMAL

EARLY SSc



ACTIVE SSc



LATE SSc

Not associated with risk of developing PAH

- Digital ulcers
- Digital gangrene
- Renal crisis

S.12.5 CLINICAL SUBTYPE AND AUTOANTIBODIES BOTH HELP PREDICT PULMONARY ARTERIAL HYPERTENSION, BUT AUTOANTIBODIES ARE STRONGER PREDICTORS OF DEVELOPING SECONDARY PULMONARY HYPERTENSION

M. Mohile , M. Lucas , T. Medsger , R. Domsic

University of Pittsburgh, Pittsburgh, USA

Table 1: Multivariable Predictors of PAH

	Odds Ratio (95% Confidence Interval)	p-value
Age (years) at initial visit		< 0.0001
< 35	----	
35-44	0.88 (0.37 – 2.10)	
45-54	1.07 (0.48 – 2.42)	
55-64	2.11 (0.94 – 4.73)	
>65	3.64 (1.64 – 8.07)	
Limited cutaneous involvement	2.74 (1.67 – 4.48)	< 0.0001
Th/To or U3RNP positive (nucleolar ANA)	2.66 (1.61 – 4.41)	< 0.0001

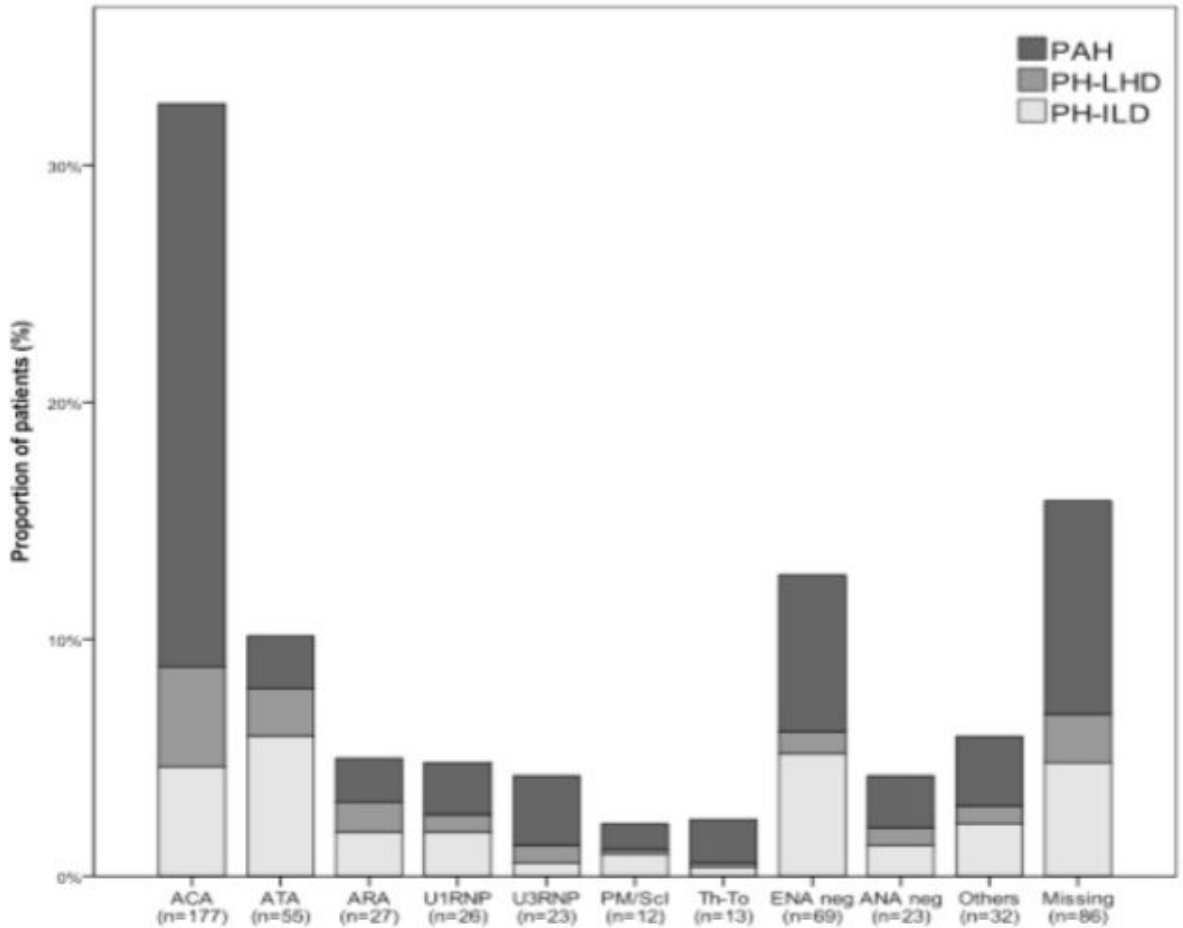
Table 2: Multivariable Predictors of Secondary PH

	Odds Ratio (95% Confidence Interval)	p-value
Age (years) at initial visit		0.03
< 35	-----	
35-44	1.23 (0.43 – 3.59)	
45-54	1.95 (0.72 – 5.29)	
55-64	2.70 (0.98 – 7.43)	
>65	3.53 (1.25 – 9.97)	
Male	2.18 (1.32 – 3.59)	< 0.002
Anti-U11/U12 RNP positive	1.51 (0.93 – 2.45)	0.02
ACA	0.27 (0.11 – 0.67)	0.004
Limited cutaneous involvement	3.12 (1.17 – 8.34)	0.09

PS21 AUTOANTIBODY PROFILE IN SYSTEMIC SCLEROSIS ASSOCIATED PULMONARY HYPERTENSION

V. Sobanski [1], S. Nihtyanova [1], B. Lynch [1], B. Schreiber [2], J. Harvey [3], C. Handler [2], C. Denton [1], G. Coghlan [2]

[1] Centre For Rheumatology and Connective Tissue Diseases - Royal Free Hospital - University College London, London, UNITED KINGDOM,[2] National Pulmonary Hypertension Unit - Royal Free Hospital - University College London, London, UNITED KINGDOM,[3] Department of Clinical Immunology - Royal Free Hospital - University College London, London, UNITED KINGDOM

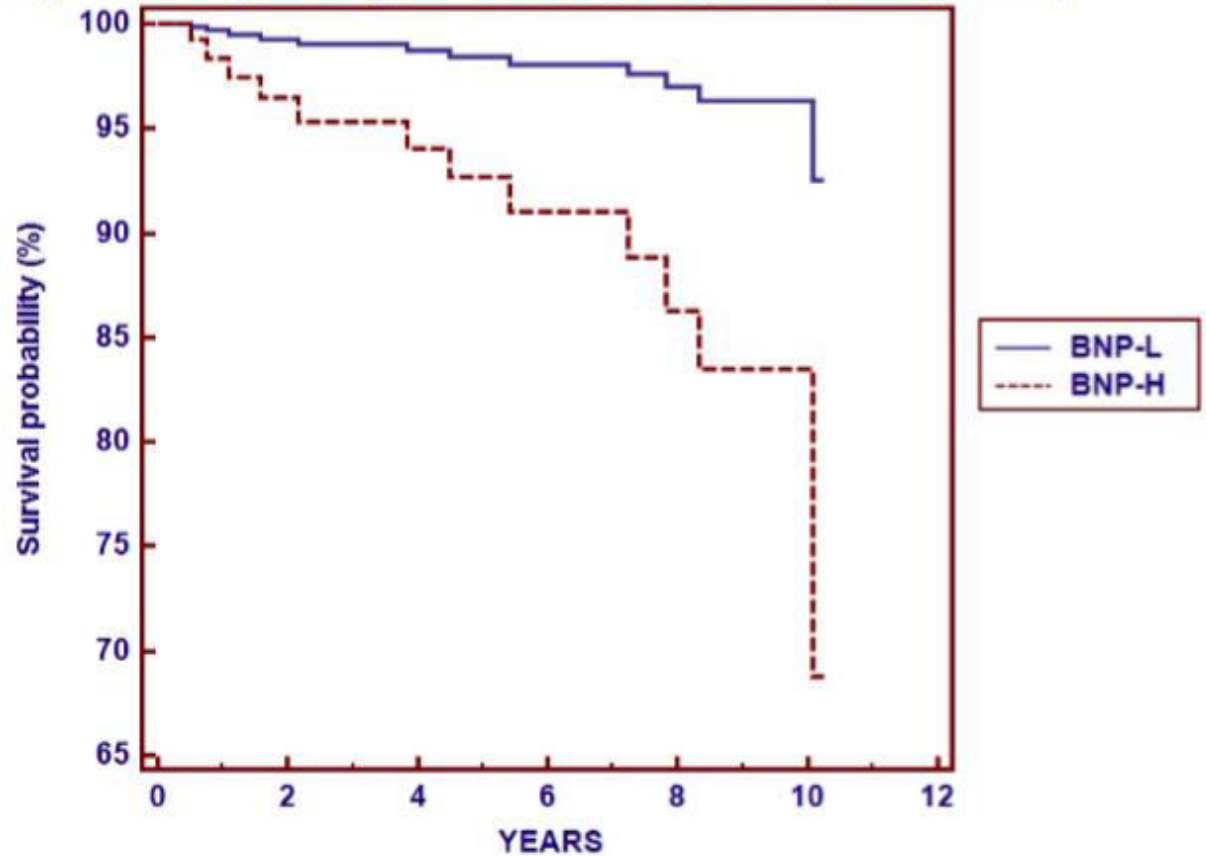


S.12.6 PROGNOSTIC VALUE OF NT-PROBNP IN SYSTEMIC SCLEROSIS PATIENTS WITHOUT PULMONARY HYPERTENSION

M. Antivalle, M. Battellino, M.C. Ditto, M. Chevallard, A. Mutti, A. Batticciotto, V. Varisco, F. Rigamonti, F. Atzeni, P. Sarzi-Puttini

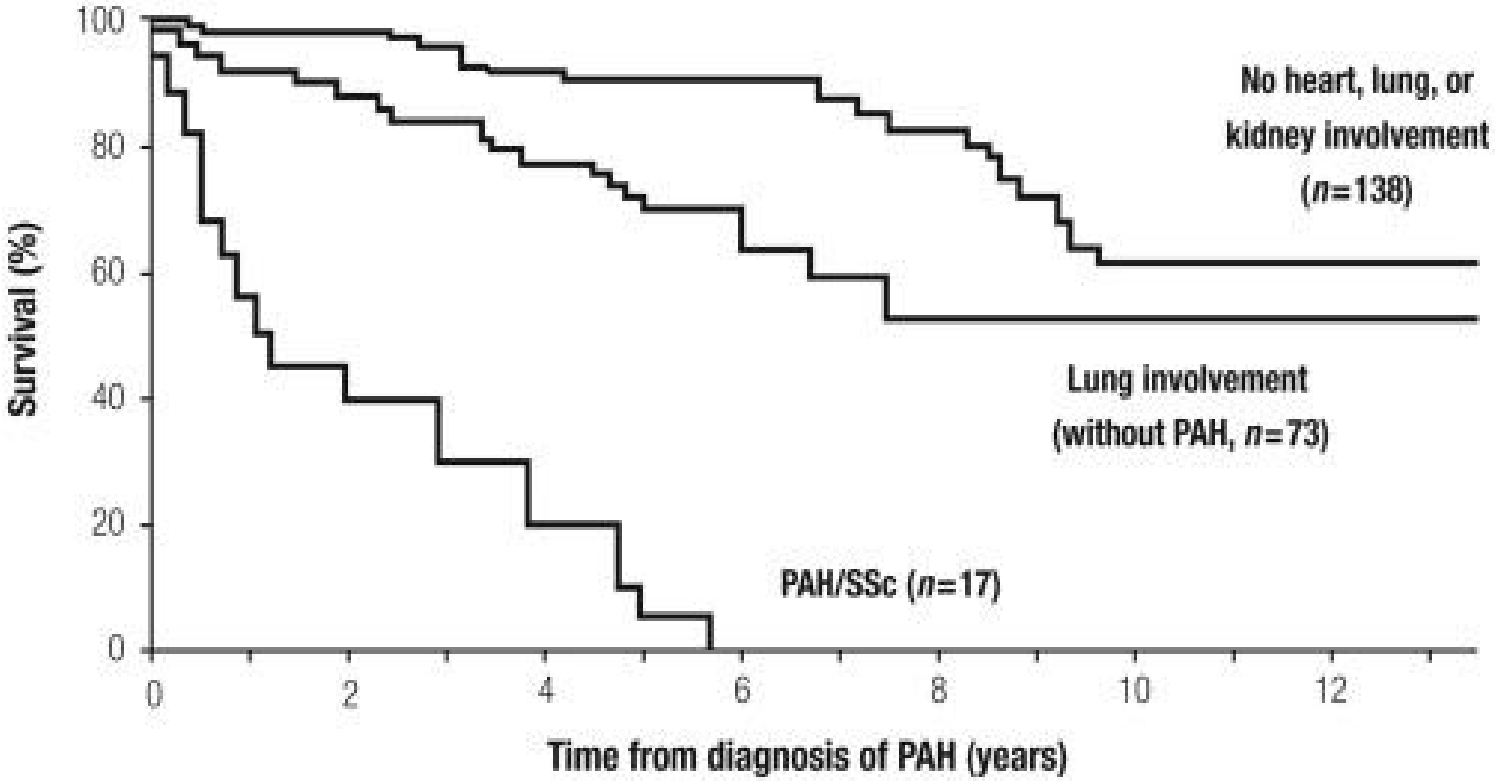
Rheumatology - L.Sacco University Hospital, Milano, ITALY

Fig. 1 - Survival probability in BNP-L and BNP-H patients (Cox regression)



SCREENING FOR PAH

Why screening



Koh ET, et al Pulmonary hypertension in systemic sclerosis: an analysis of 17 patients. Br J Rheumatol 1996;35:989–93

ECS

Positive screen on echocardiography (referral to RHC recommended)

- TRV >3.4 m/s
- or TRV >2.8-≤3.4 m/s and symptoms (current dyspnoea, current syncope/near syncope, presence of peripheral oedema)
- or TRV ≤2.8 m/s and symptoms and additional suggestive echo variable (e.g. RA area >18 cm^2)

Itine´rAIR-Scle´rodermie study

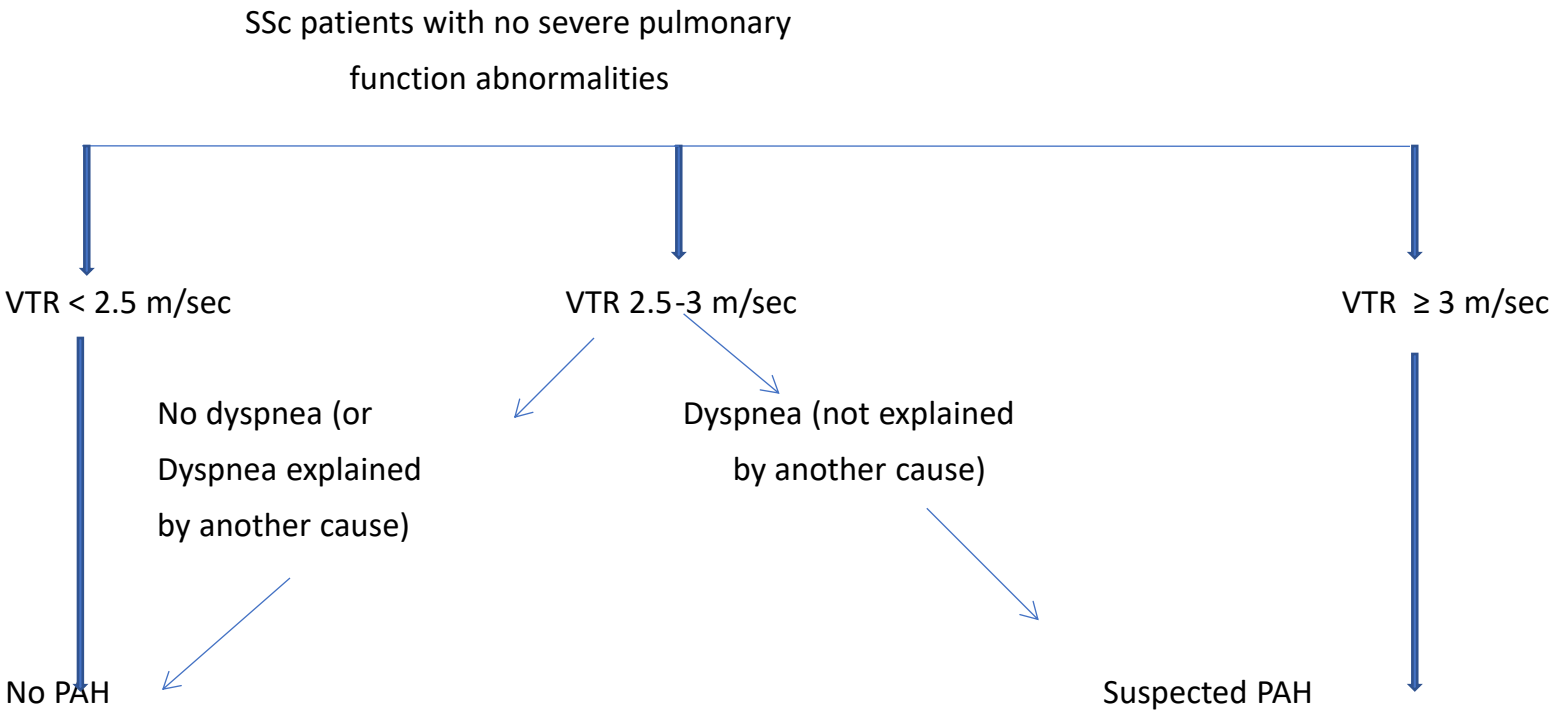
- 559 pts without severe Pulmonary function abnormalities underwent Doppler echocardiography.

- Patients with a peak velocity of tricuspid regurgitation (VTR) of >3 m/s or 2.5–3 m/s accompanied by unexplained dyspnoea then underwent right heart catheterization (RHC) to confirm PAH according to international guidelines

- Based on Doppler echocardiography-
  33 of the 559 patients had suspected PAH.

Hachulla E et al. ArthritisRheum 2005;52:3792–800.

Doppler echocardiography

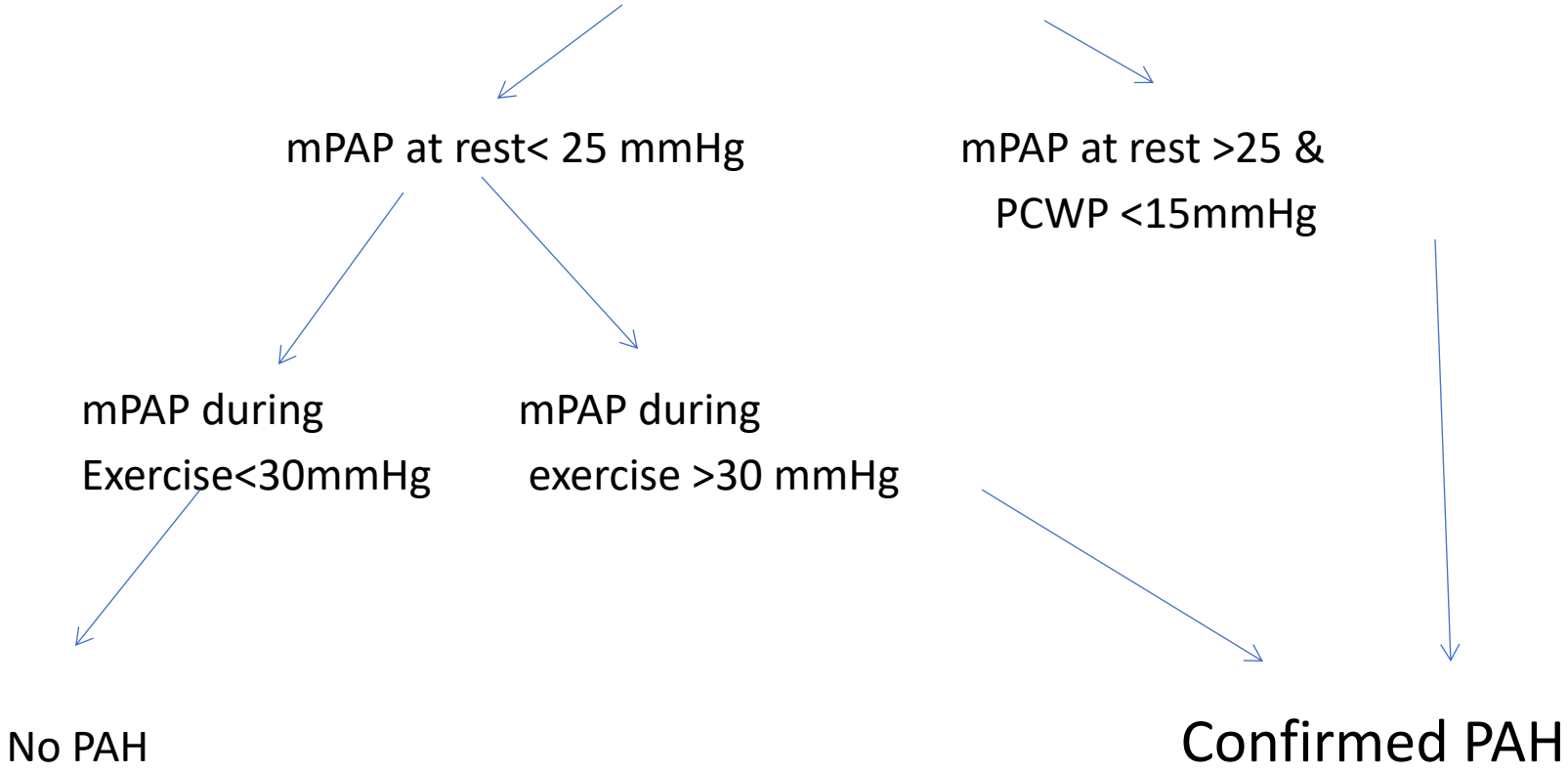


VTR : Peak velocity of pulmonary regurgitation

Hachulla E. Arthritis Rheum 2005; 52 (12): 3792-3800

Right heart catheterization

- Suspected PAH on Doppler echocardiography



Hachulla E. Arthritis Rheum 2005; 52 (12): 3792-3800

RHC

PAH: 18

- 14 had a mPAP ≥ 25 mmHg at rest
- ≥ 25-35 mmHg : 9
- ≥ 35-45 mmHg : 4
- ≥ 45 mmHg : 1
- 4 had a mPAP < 25 mmHg at rest but ≥ 30 mmHg at exercise

No PAH : 12/33

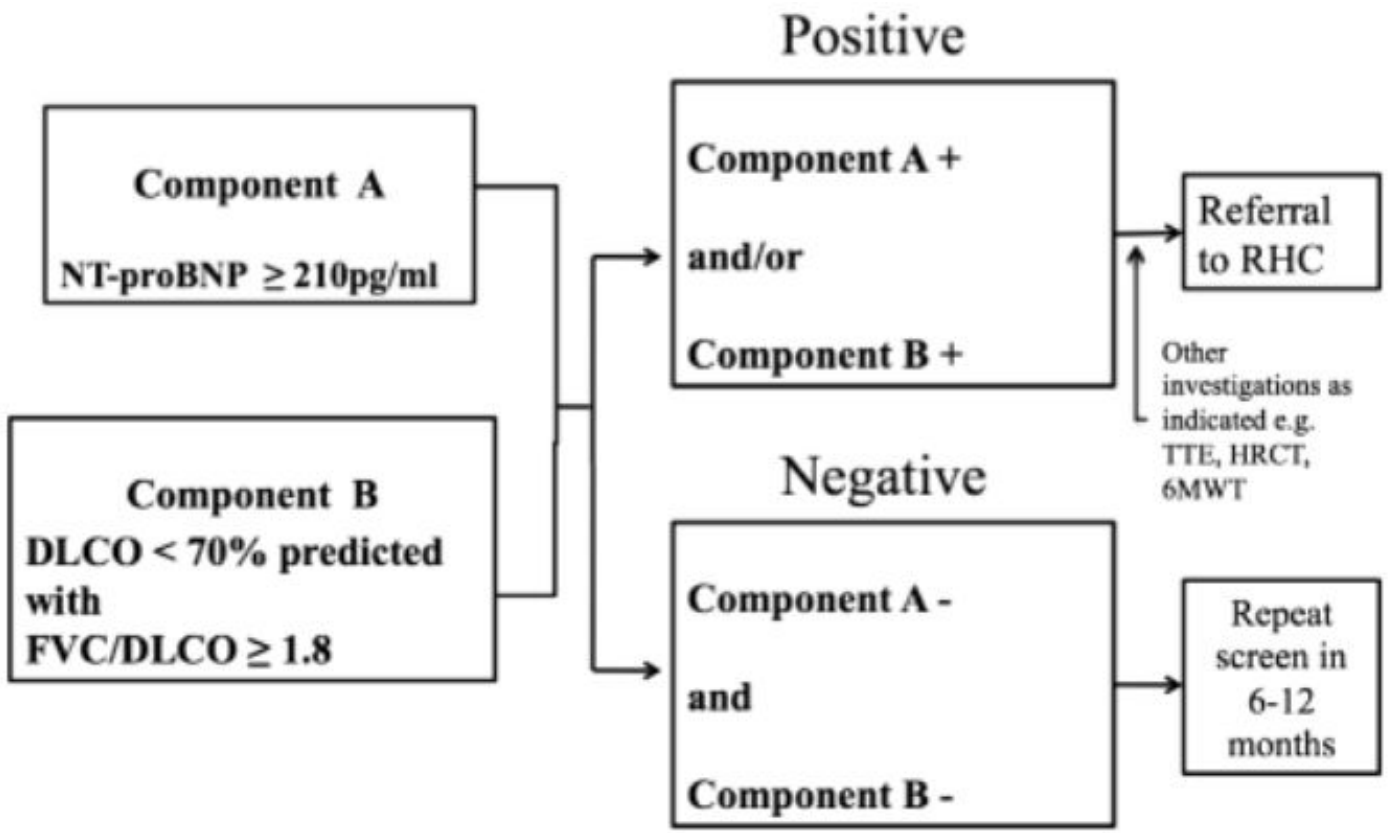
- 5 had no exercise RHC
- 6 had a mPAP > 20 mmHg

Post capillary PH : 3/33

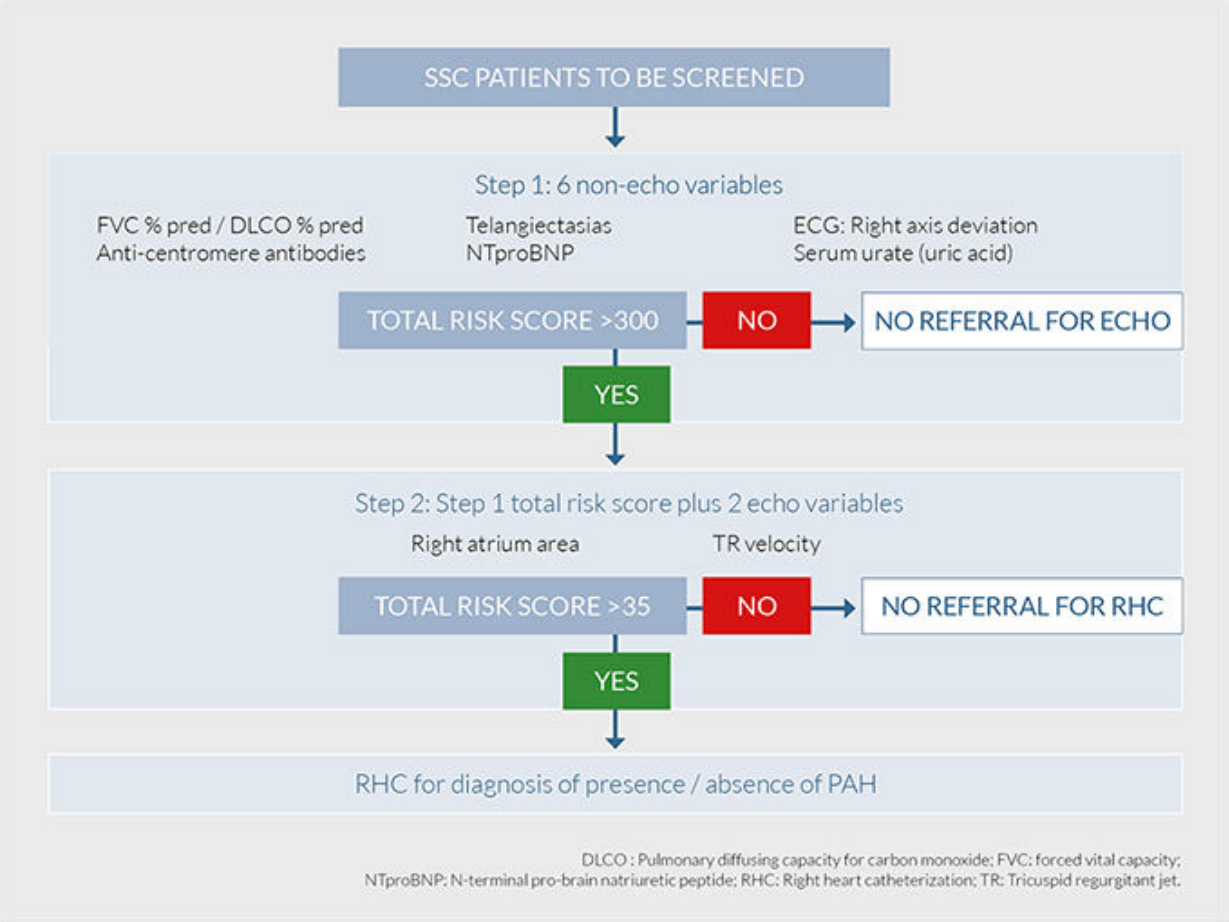
Key take home points

- Echo cardiography is a good screening tool.
- Echo cardiography tends to overestimate PAH as compared to RHC.
- Left heart disease is a major differential diagnosis and may be missed a on Echo.

ASIG


Positive
Component A
NT-proBNP ≥ 210pg/ml
Component B
DLCO < 70% predicted with
FVC/DLCO ≥ 1.8
Component A +
and/or
Component B +
Referral to RHC
Other investigations as indicated e.g. TTE, HRCT, 6MWT
Negative
Component A -
and
Component B -
Repeat screen in 6-12 months

DETECT


SSC PATIENTS TO BE SCREENED
Step 1: 6 non-echo variables
FVC % pred / DLCO % pred
Anti-centromere antibodies
Telangiectasias
NTproBNP
ECG: Right axis deviation
Serum urate (uric acid)
TOTAL RISK SCORE >300
NO
NO REFERRAL FOR ECHO
YES
Step 2: Step 1 total risk score plus 2 echo variables
Right atrium area
TR velocity
TOTAL RISK SCORE >35
NO
NO REFERRAL FOR RHC
YES
RHC for diagnosis of presence / absence of PAH
DLCO : Pulmonary diffusing capacity for carbon monoxide; FVC: forced vital capacity;
NTproBNP: N-terminal pro-brain natriuretic peptide; RHC: Right heart catheterization; TR: Tricuspid regurgitant jet.

S.12.4 A COMPARISON OF THE PREDICTIVE ACCURACY OF THREE SCREENING MODELS (DETECT V. ESC/ERS V. ASIG) FOR PULMONARY ARTERIAL HYPERTENSION IN SYSTEMIC SCLEROSIS

Y.J. Hao [1,2], V. Thakkar [1,2], W. Stevens [1], D. Prior [2], C. Rabusa [1,2], P. Youssef [3], E. Gabbay [4], J. Roddy [4], J.G. Walker [5], J. Zochling [6], J. Sahhar [7], P. Nash [8], S. Lester [9], C. Hill [9], M. Rischmueller [9], S.M. Proudman [10], M. Nikpour [1,2]

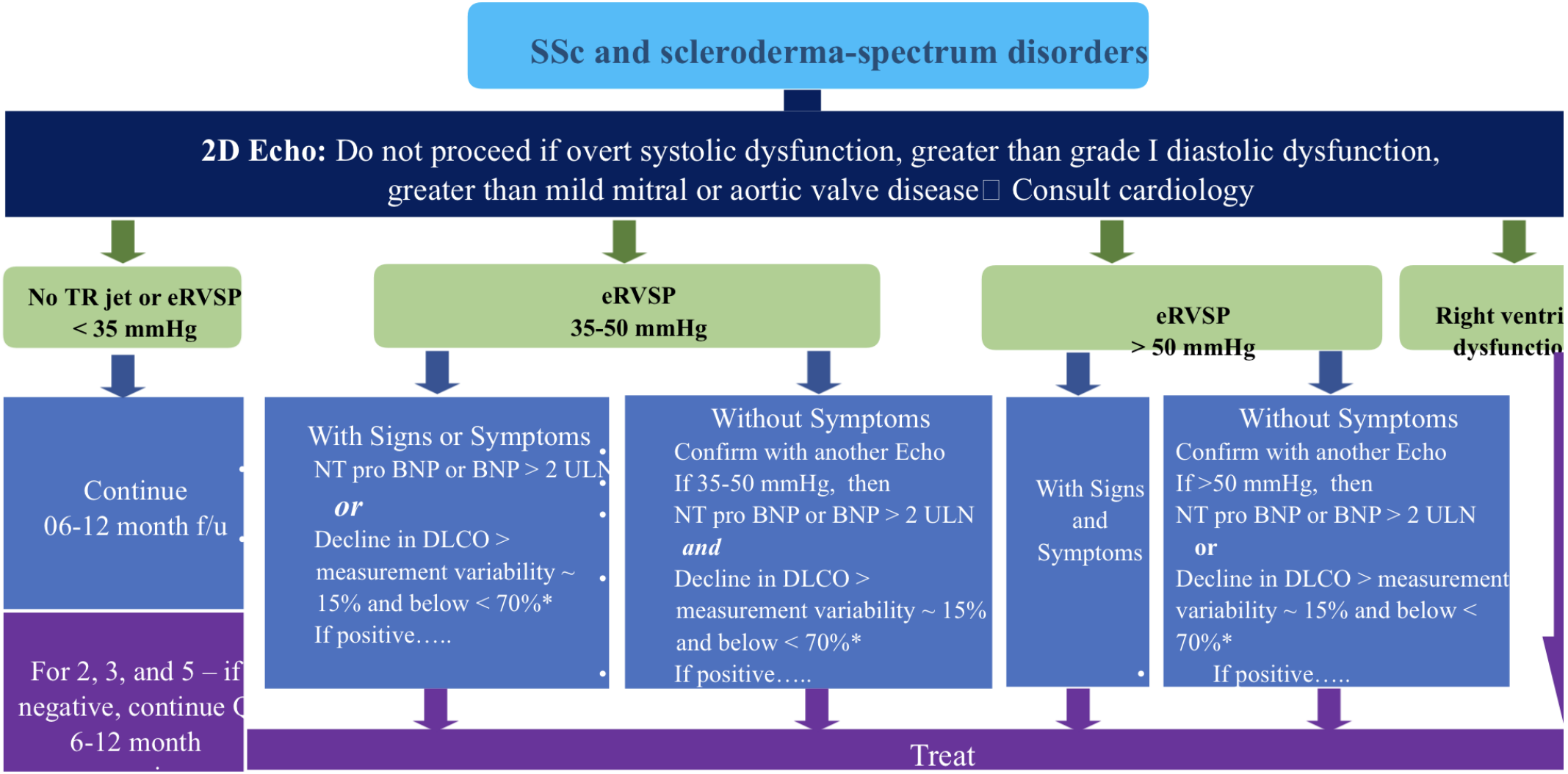
[1] Department of Rheumatology, St Vincent's Hospital Melbourne, Melbourne, AUSTRALIA,[2] The University of Melbourne Department of Medicine at St Vincent's Hospital Melbourne, Melbourne, AUSTRALIA,[3] Institute of Rheumatology and Orthopaedics, Royal Prince Alfred Hospital, Sydney, AUSTRALIA,[4] Pulmonary Hypertension Service and Department of Rheumatology, Royal Perth Hospital, Perth, AUSTRALIA, [5] Department of Rheumatology, Flinders Medical Centre, Adelaide, AUSTRALIA,[6] The Menzies Research Institute Tasmania, Tasmania, AUSTRALIA,[7] Department of Rheumatology, Monash Medical Centre, Melbourne, AUSTRALIA,[8] Sunshine Coast Rheumatology, Sunshine Coast, AUSTRALIA,[9] Rheumatology Department, The Queen Elizabeth Hospital, Adelaide, AUSTRALIA,[10] Department of Rheumatology, Royal Adelaide Hospital, Adelaide, AUSTRALIA

Table 1. Comparison of the performance of DETECT v. ESC/ERS v. ASIG screening models for SSc-PAH

				PAH prevalence set at 10%		
	DETECT n=61	**ESC/ERS** n=58	**ASIG** n=61	**DETECT** n=61	**ESC/ERS** n=58	**ASIG** n=61
Sensitivity (95% CI)	100% (87.2-100)	96.3% (81-99.9)	100% (87.2-100)	100% (54.1-100)	96.3% (54.1-100)	100% (54.1-100)
Specificity (95% CI)	35.3% (19.7-53.5)	29.0% (19.7-53.5)	47.1% (29.8-64.9)	35.3% (23.8-50.4)	29.0% (12.5-36.8)	47.1% (35.4-62.9)
PPV (95% CI)	55.1% (40.2-69.3)	54.2% (39.2-68.6)	60% (44.3-74.3)	14.7% (5.6-29.2)	13.1% (4.9-26.3)	17.4% (6.8-34.5)
NPV (95% CI)	100% (63.1-100)	90.0% (55.5-99.7)	100% (79.4-100)	100% (83.2-100)	99.7% (73.5-100)	100% (87.2-100)

BUT…… IS IT PRACTICALLY POSSIBLE TO DO RHC IN OUR COUNTRY TO DIAGNOSE PAH?

Recommendations— Treatment based on non-invasive tests



Symptoms: dyspnea on rest or exercise, fatigue, pre-syncope/ syncope, chest pain, palpitations, dizziness, lightheadedness.
Signs: Loud pulmonic sound, peripheral edema-- *without progression in ILD (if present) , ** right ventricular enlargement or failure or evidence of flattening of intraventricular

TREATMENT FOR PAH

?Role of immunosuppresive therapy in CTD PAH

Immunosuppressive Therapy in Connective Tissue Diseases-Associated Pulmonary Arterial Hypertension

- Eight of 28 patients [29%] were responders
- [SLE], n = 5
- [MCTD] n = 3
- No patients with systemic sclerosis responded,

Sanchez et al CHEST 2006

Rheumatology Advance Access published April 29, 2015

RHEUMATOLOGY

54

Original article

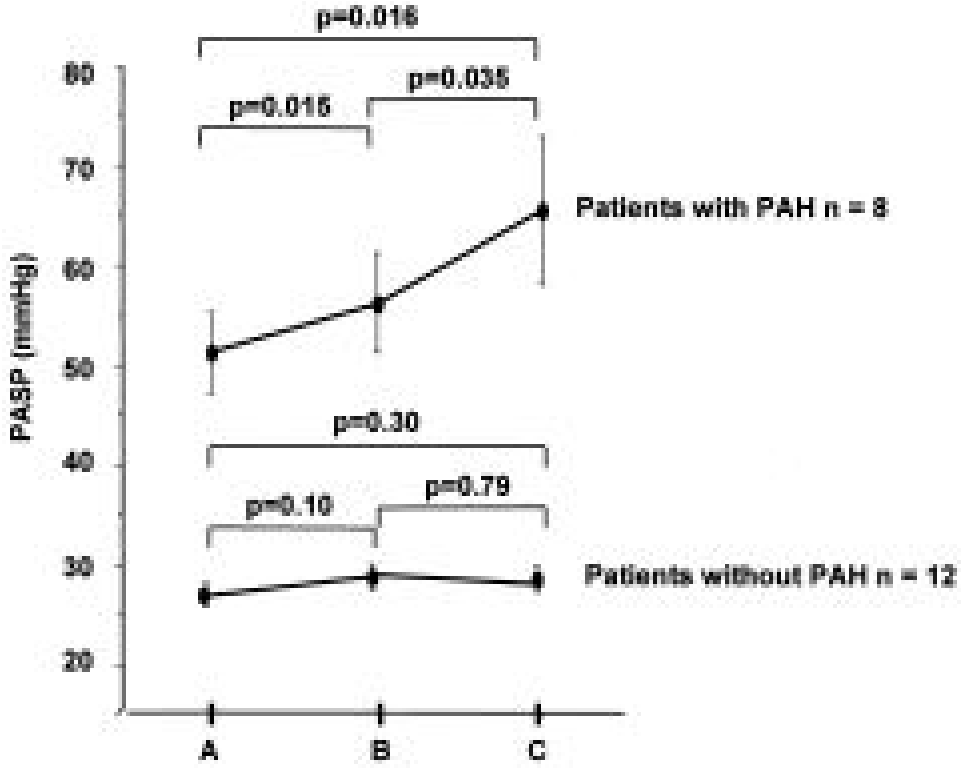
doi:10.1093/rheumatology/kev097

Pulmonary arterial hypertension in systemic lupus erythematosus may benefit by addition of immunosuppression to vasodilator therapy: an observational study

Sirisha Kommireddy[1], Srinivas Bhyravavajhala[2], Kishorebabu Kurimeti[1], Srinivasa Chennareddy[1], Suresh Kanchinadham[1], Irlapati Rajendra Vara Prasad[1] and Liza Rajasekhar[1]

?Role of immunosuppresive therapy in SSc PAH

CYC IN SSc-PAH



Effect of intravenous pulse cyclophosphamide (CYC) treatment on pulmonary artery systolic pressure (PASP) in 20 patients with ILD. A = before CYC treatment; B = at the end of CYC treatment; C = ≥6 months after completion of CYC treatment. Values are the mean ± SD.

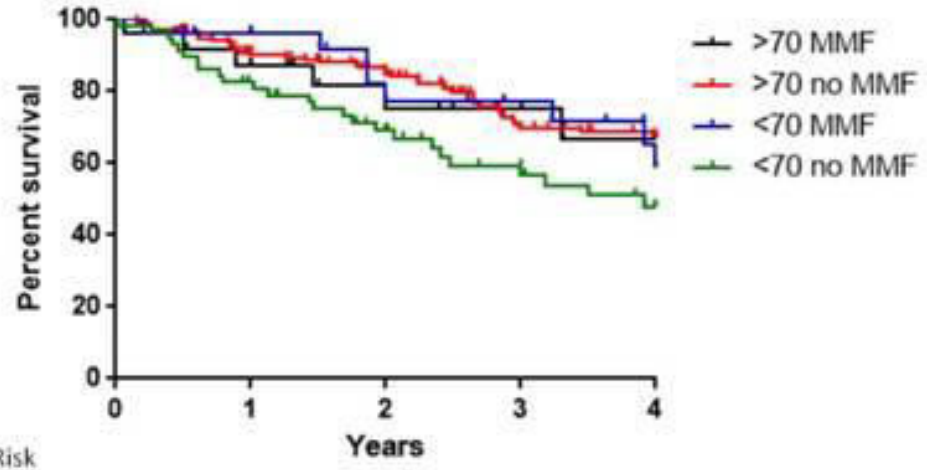
TRAD ET AL A&R 2006

Mycophenolate Mofetil (MMF) Use in Scleroderma Patients with Pulmonary Hypertension: Observations from the Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma Cohort

Lesley Ann Saketkoo[1], Matthew R. Lammi[2], Aryeh Fischer[3], Jerry A. Molitor[4] and Virginia D. Steen[5], [1]Scleroderma and Sarcoidosis Patient Care and Research Center, Rheumatology and Pulmonary Medicine, Louisiana State University Health Sciences Center, New Orleans, LA, [2]Louisiana State University Health Sciences Center, Pulmonary and Critical Medicine, New Orleans, LA, [3]Rheumatology / ILD Program, National Jewish Health, Denver, CO, [4]Rheumatology, University of Minnesota, Minneapolis, MN, [5]Department of Rheumatology, Georgetown University Medical Center, Washington, DC

Meeting: 2014 ACR/ARHP Annual Meeting

Diagram 1. Survival across groups partitioned by FVC and MMF use.



No. At Risk					
FVC >70% +MMF	25	20	13	11	7
FVC >70% - MMF	158	135	109	71	50
FVC <70% +MMF	28	23	17	15	10
FVC <70% - MMF	52	45	34	23	14

The trend for improved survival in patients with PH with FVC <70 who were treated with MMF even in the absence of improvement of FVC is intriguing. Whether it has an effect on pulmonary artery remodeling should be considered. These findings warrant prospective controlled investigations of MMF in SSc PH particularly in those with restrictive lung disease.

Does Mycophenolate Mofetil (mmf) Have An Effect On Pulmonary Hemodynamics? Observations From The Pulmonary Hypertension Assessment And Recognition Of Outcomes In Scleroderma (pharos) Cohort

L. Saketkoo[1, 2], M. R. Lammi[1], J. Gordon[3], P. Lauto[1], V. Steen[4], PHAROS Investigators

[1]Louisiana State University Health Sciences Center, New Orleans, LA, [2, 3]Hospital for Special Surgery, New York, NY, [4]Georgetown University Medical Center, Washington, DC

Table 1. Comparison between SSc patients on No IS medications and MMF at time of first RHC. Continuous variables are reported as median, interquartile range; categorical values are proportional.

	No IS	MMF	p Value
n	203	39	
Age	60 (52,68)	54 (47,63)	*0.0143
Sex (% female)	84%	65%	0.6491
N (%) Limited SSc	144 (71%)	14 (35%)	*< 0.0001
Time from 1st SSc Symptom (years)	11.2 (5.3,21.0)	6.9 (3.0,10.3)	*0.0004
mPAP	33 (28,44)	29 (25,35)	*0.0016
PVR	355 (242,692)	222 (162,344)	*0.0006
PCWP	11 (8,14)	11 (9,15)	0.7036
FVC	78.1 (64,88)	68.9 (48,84)	*0.0298
TLC	76.5 (66,93)	62.8 (47,80)	*0.0002
FEV/FVC	81 (75,87)	87 (81,93)	*0.0048
DLCO	37.5 (30,50)	34.3 (28,39)	0.0929
FVC:DLCO	1.94 (1.6,2.4)	1.85 (1.4,2.5)	0.6908
6MWD	338.3 (238,428)	396.2 (343,475)	*0.0298

Am J Respir Crit Care Med 189;2014:A4744

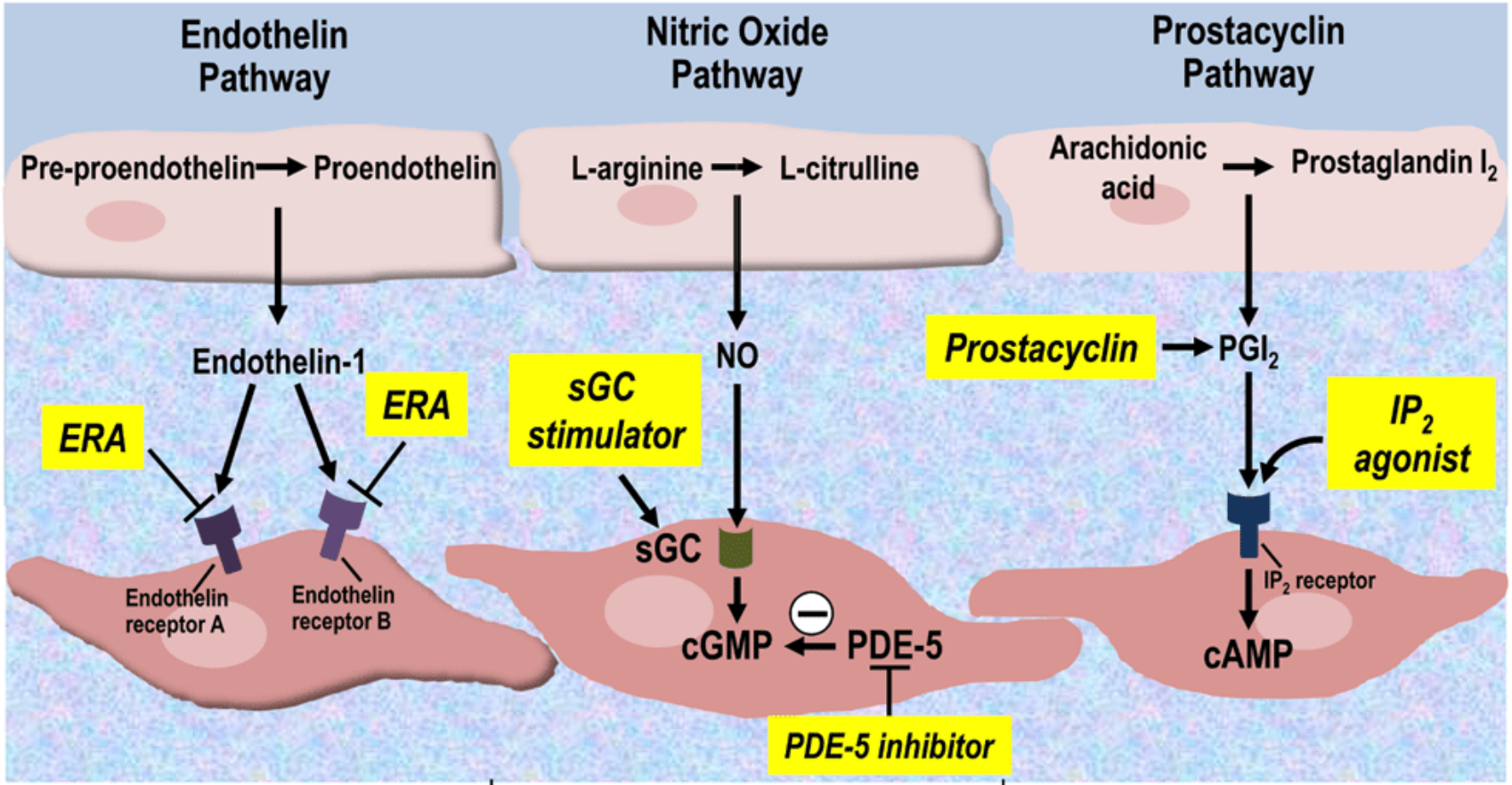
POOR LONG TERM RESPONSE TO CCB'S IN CTD PAH

	N0. OF TESTED PATIENTS*	ACUTE RESPONDERS#	LONG TERM RESPONDERS
IDOPATHIC PAH	523	13.5%	7.5%
APPETITE SUPRESS.	127	11.8%	7.9%
CTD-PAH	168	10.1%	1.2%
PVOD	34	12.2%	0
HIV ASSOC. PAH	124	1.6%	1.6%
CHD PAH	50	0	NA
FAMILIAL PAH	34	0	NA
POTROPULM. PAH	153	1.3%	0.7%

* With NO and/or PgI2 ; # fall in mPAP and PVR > 20%

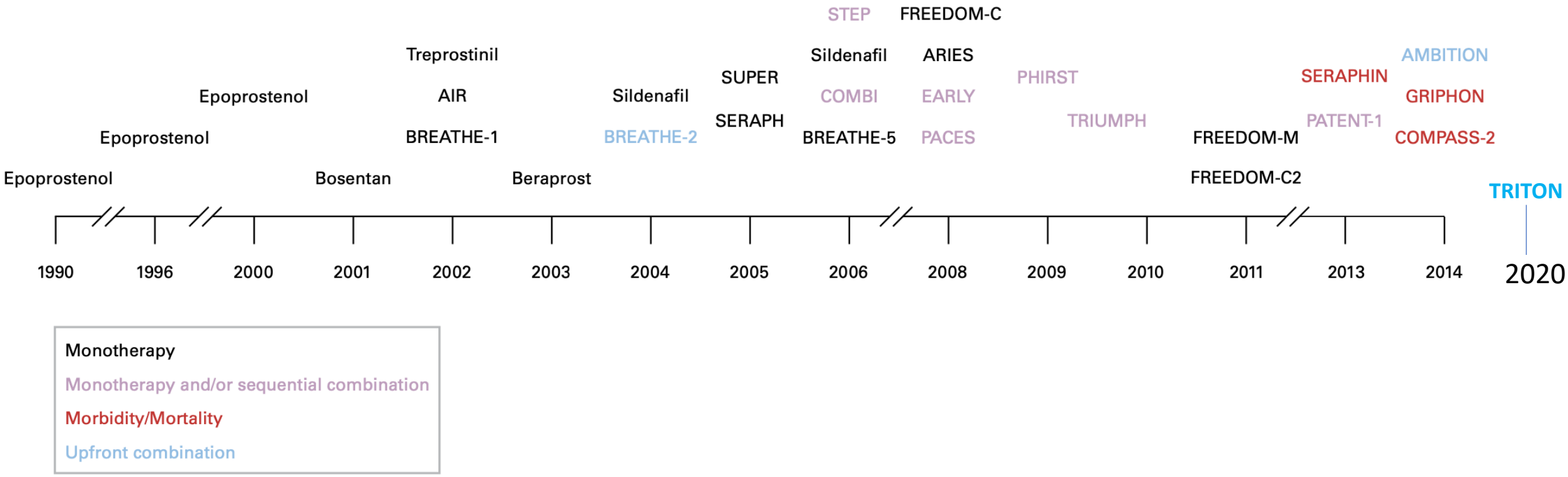
O. Sitbon et al ATS 2003

THREE MAIN PATHWAYS IN PATHOPHYSIOLOGY OF PAH



FDA Approved PAH Drugs	ERA	PDE-5i	sGC stimulator	Prostacyclins	IP_2 agonist
	bosentan ambrisentan macitentan	sildenafil tadalafil	riociguat	epoprostenol (IV) iloprost (INH) treprostinil (IV, SQ, INH, oral)	selexipag

TIMELINE OF TREATMENT OF PAH

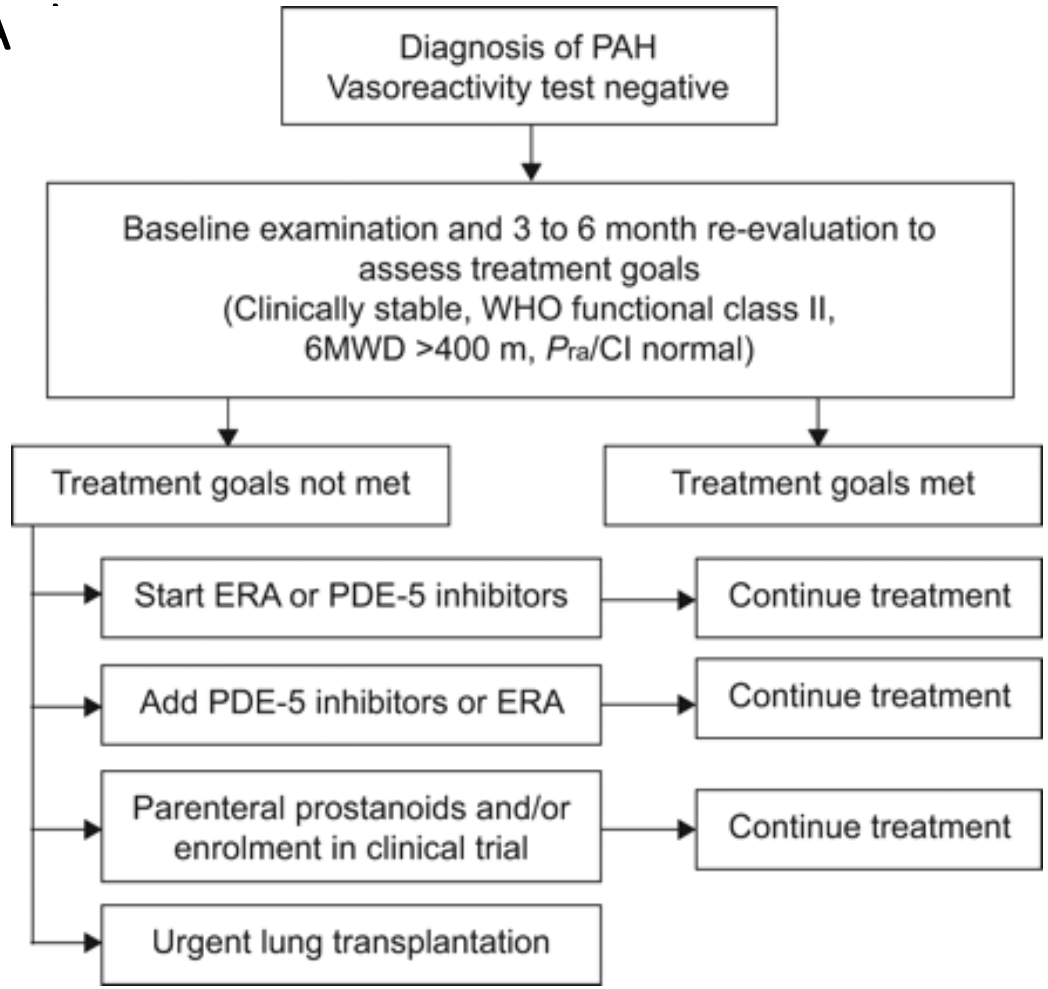


TREAT TO TARGET

- Close monitoring of patients for early identification of inadequate response, so that treatment can be escalated promptly and before the patient‘s condition deteriorates further.

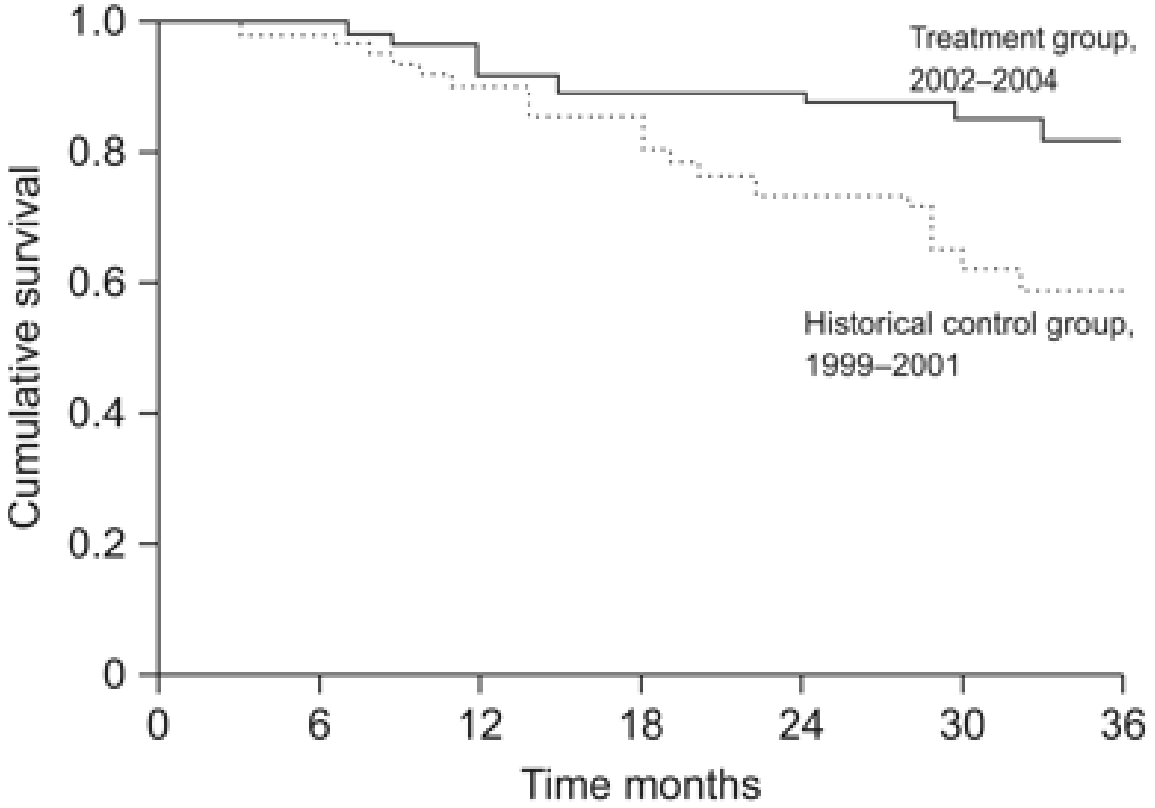
- Goal-oriented therapy determines the timing of treatment escalation by inadequate Response to known prognostic indicators

An algorithm for goal-oriented therapy in pulmonary arterial hypertension (PA



WHO: World Health Organization; 6MWD: 6-min walk distance; P_{ra}: right atrial pressure; CI: cardiac index; ERA: endothelin receptor antagonist; PDE: phosphodiesterase

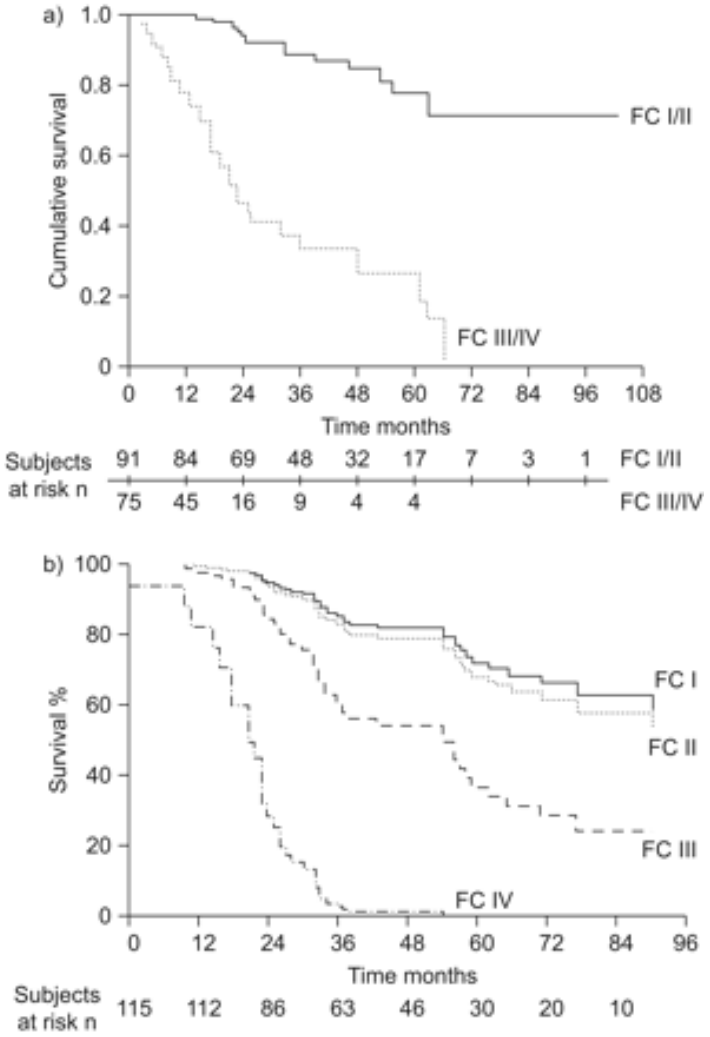
Hoeper MM, et al. *Eur Respir J 2005; 26:858-63.*



Subjects at risk n							
Treatment group	89	83	69	61	46	43	37
Historical control group	67	64	47	38	31	23	20

O Sitbon ,ERS 2010

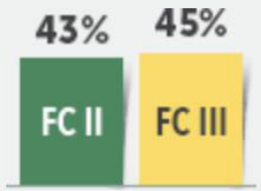
6MWD & NYHA- FC STRONGLY CORRELATES WITH SURVIVAL



O Sitbon ,ERS 2010

FINDINGS FROM THE REVEAL REGISTRY*

FC II



FC II PAH patients were as likely to clinically worsen within 1 year as those in FC III
(43% [401/925] vs 45% [625/1399], respectively)[1†]

Almost 1 in 4 (24% [58/244]) of PAH-related hospitalizations occurred in newly diagnosed **FC II** patients[2‡]

https://uptravihcp.com/ctd-subgroup/

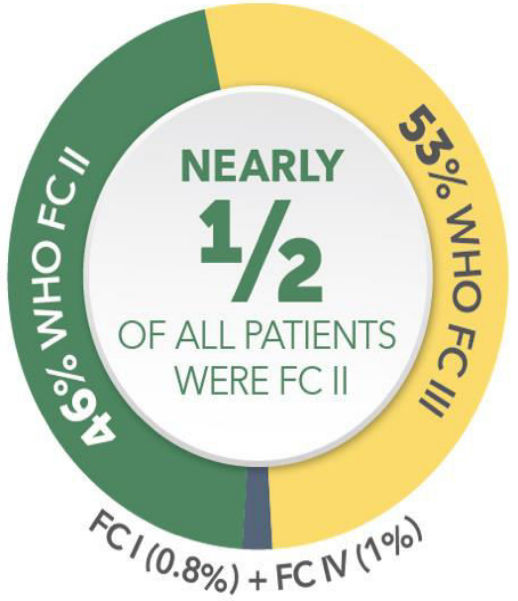
FINDINGS FROM THE DETECT STUDY[§]

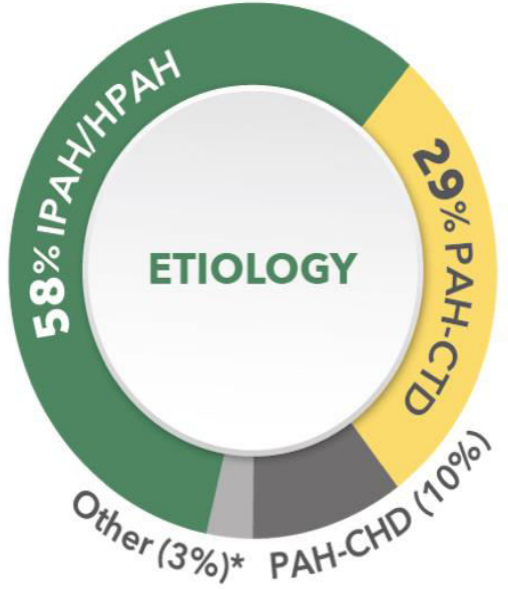
https://uptravihcp.com/ctd-subgroup/

GRIPHON—The Largest PAH-CTD Subpopulation in a Randomized Controlled PAH Trial (n=334)

Baseline patient characteristics

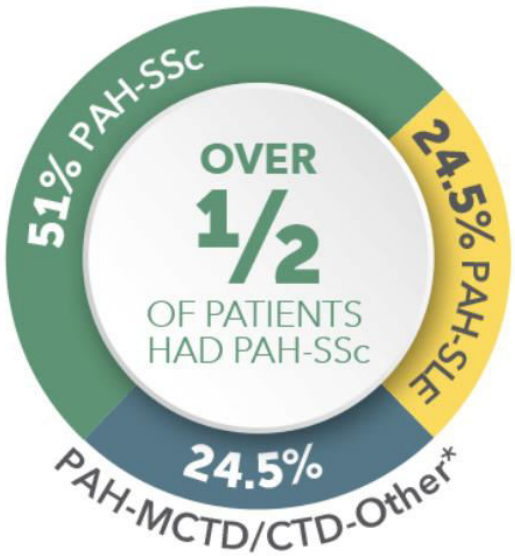
- Mean age: 48 years
- Female: 80%

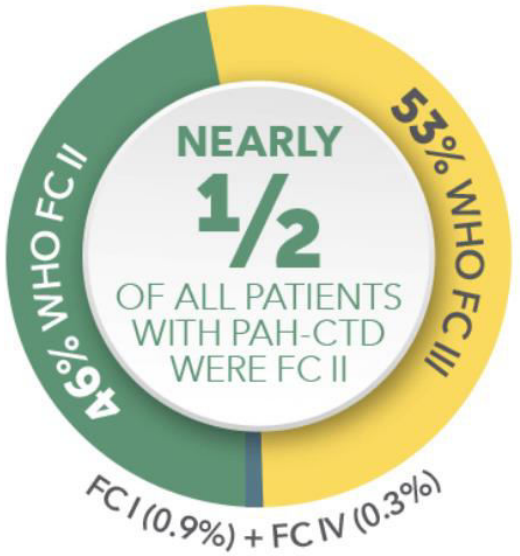




https://uptravihcp.com/ctd-subgroup/

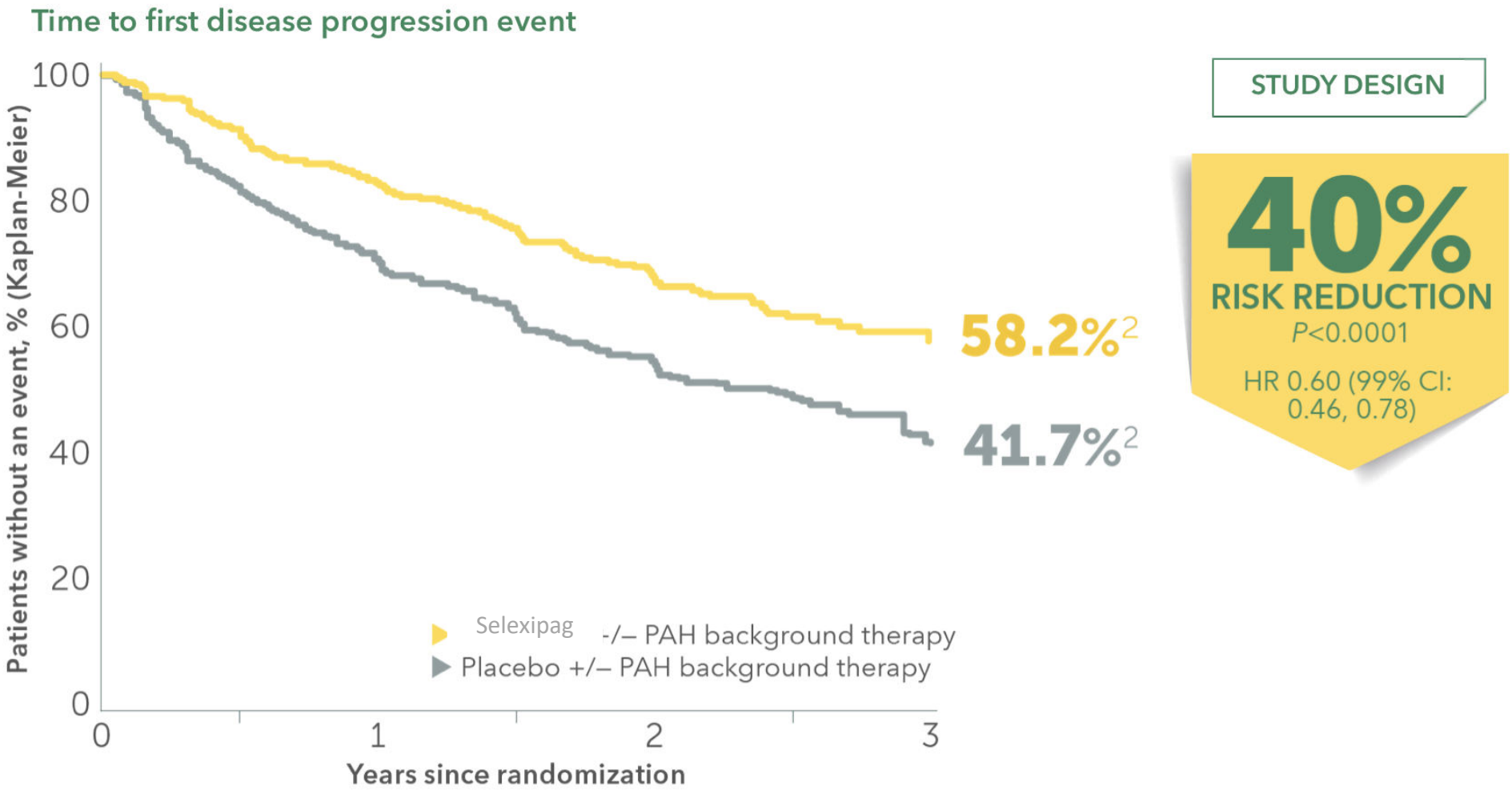
PAH-CTD was a prespecified subgroup of the GRIPHON phase 3 trial (Selexipag: n=167, placebo: n=167)





https://uptravihcp.com/ctd-subgroup/

Prevents Disease Progression



https://uptravihcp.com/ctd-subgroup/

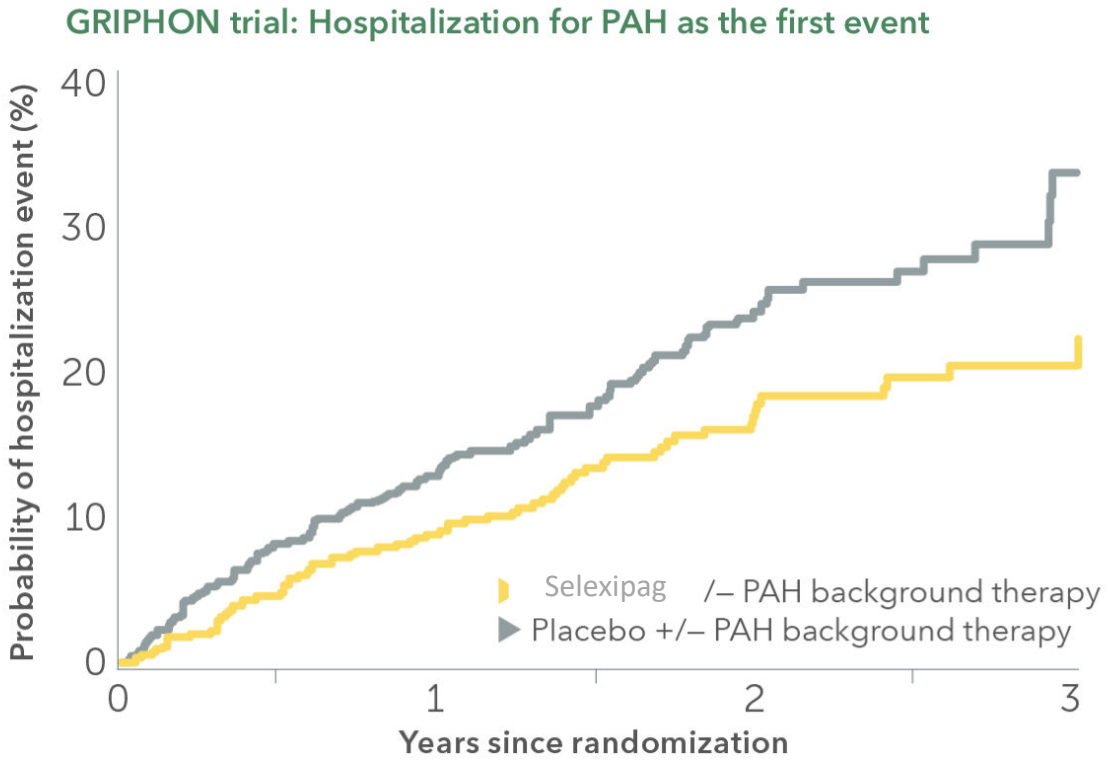
Excellent Efficacy

Summary of primary endpoint events

	Selexipag n=574 % (n)	Placebo n=582 % (n)
All primary endpoint events	27.0% (155)	41.6% (242)
FIRST EVENT WAS:		
Hospitalization for PAH	**13.6% (78)**	**18.7% (109)**
Other disease progression (decrease in 6MWD plus worsening FC or need for other therapy)	**6.6% (38)**	**17.2% (100)**
Death	4.9% (28)	3.1% (18)
Parenteral prostanoid or chronic oxygen therapy	1.7% (10)	2.2% (13)
Need for lung transplantation or balloon atrial septostomy for worsening of PAH	0.2% (1)	0.3% (2)

https://uptravihcp.com/ctd-subgroup/

Reduces Hospitalizations



STUDY DESIGN

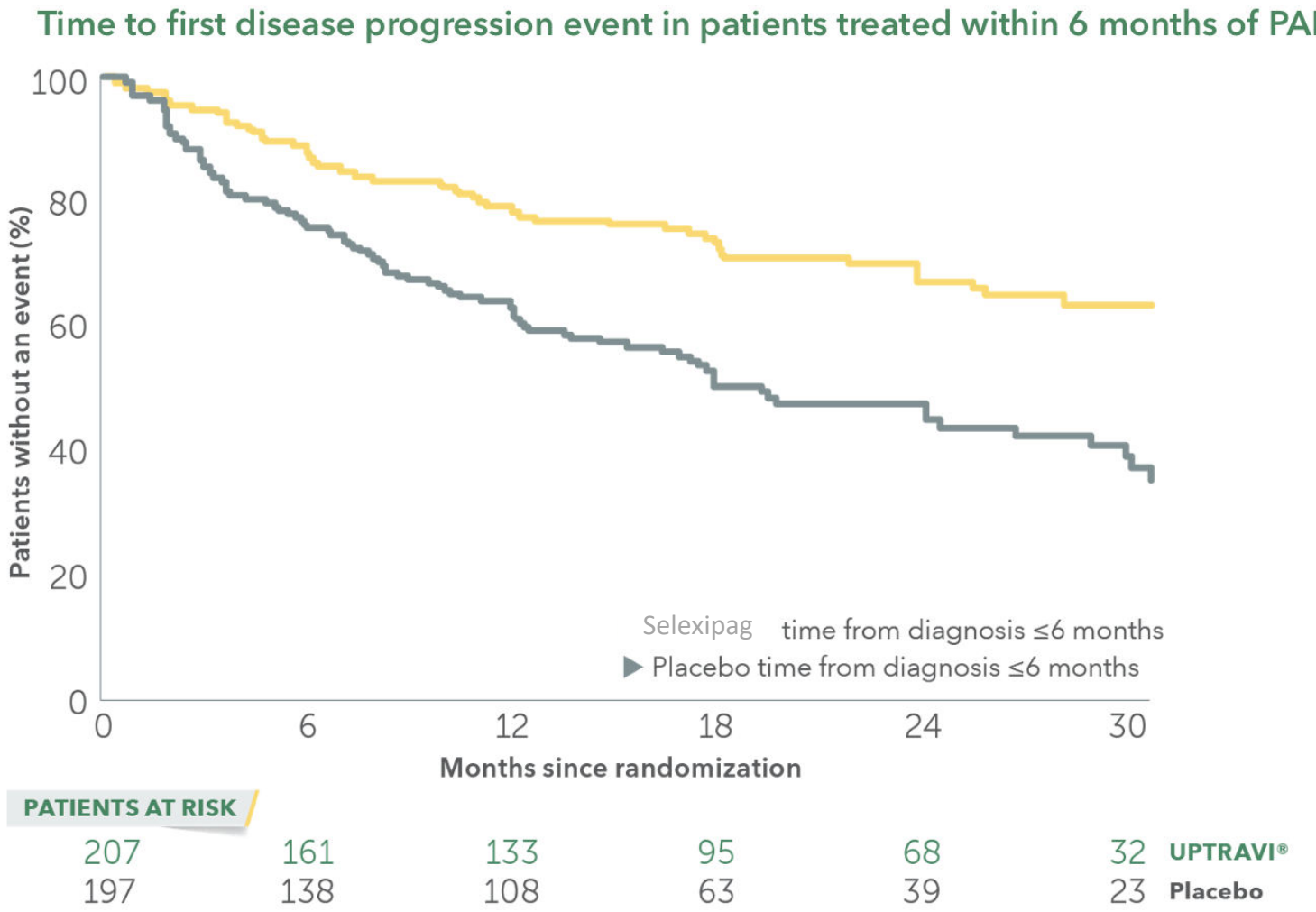
Hospitalization as first event up to end of treatment:

UPTRAVI®
13.6%
(n=78)

Placebo
18.7%
(n=109)

https://uptravihcp.com/ctd-subgroup/

Initiation before 6 months

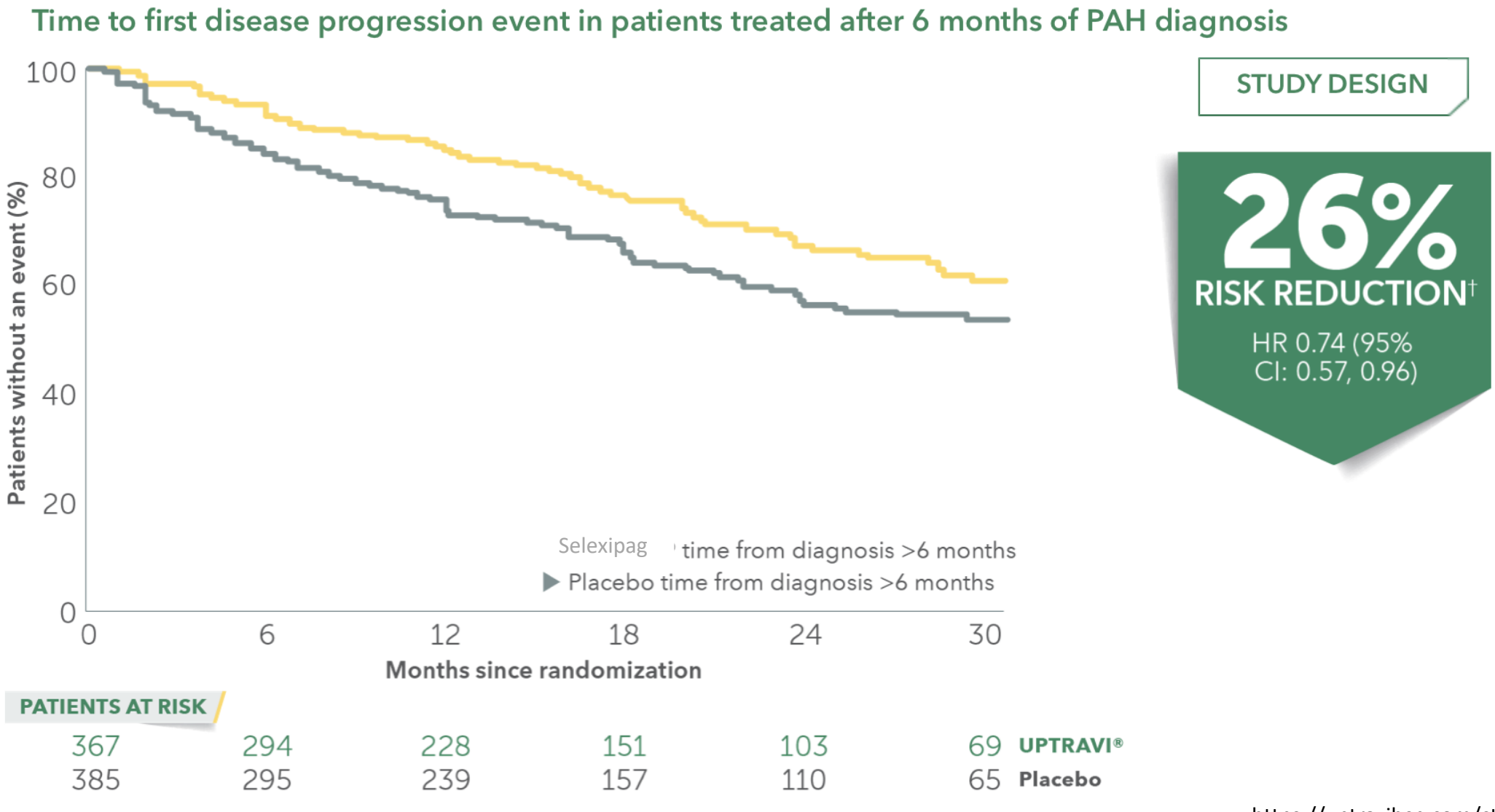


STUDY DESIGN

55%
RISK REDUCTION†
HR 0.45 (95% CI: 0.33, 0.63)

https://uptravihcp.com/ctd-subgroup/

Initiation after 6 months



https://uptravihcp.com/ctd-subgroup/

Triple combination subgroup

Baseline patient characteristics

- 33% (n=376) of all patients in GRIPHON were receiving an ERA and a PDE-5i at baseline (31% FC II and 68% FC III)*
- Etiology in triple-combination subgroup: IPAH/HPAH (64%), PAH-CTD (26%), PAH-CHD (5%), other (5%)

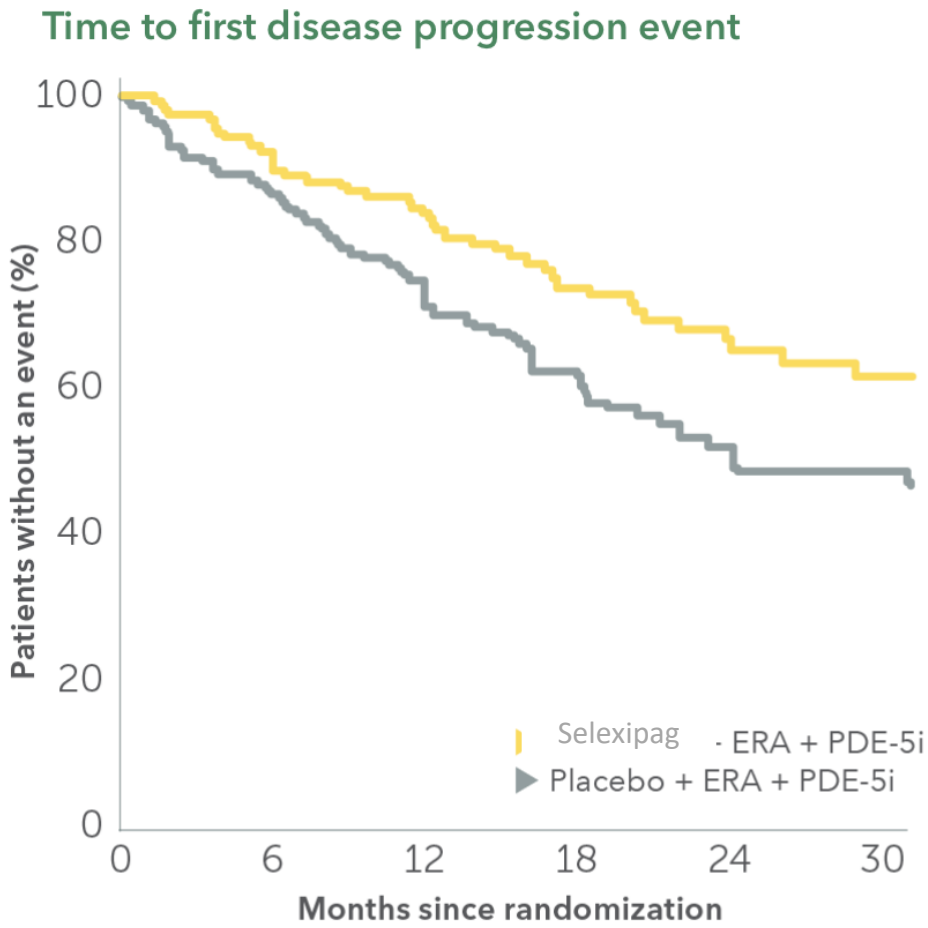
Notable differences from overall population

The triple-combination subgroup had:

- Longer time from diagnosis (3.8 years vs 2.4 years in the overall population)
- Larger percentage from Western Europe/Australia (53% vs 28%)
- Larger percentage from North America (29% vs 17%)

https://uptravihcp.com/ctd-subgroup/

Prevents Disease Progression



PATIENTS AT RISK						
179	140	105	70	43	31	UPTRAVI®
197	158	119	70	44	27	Placebo

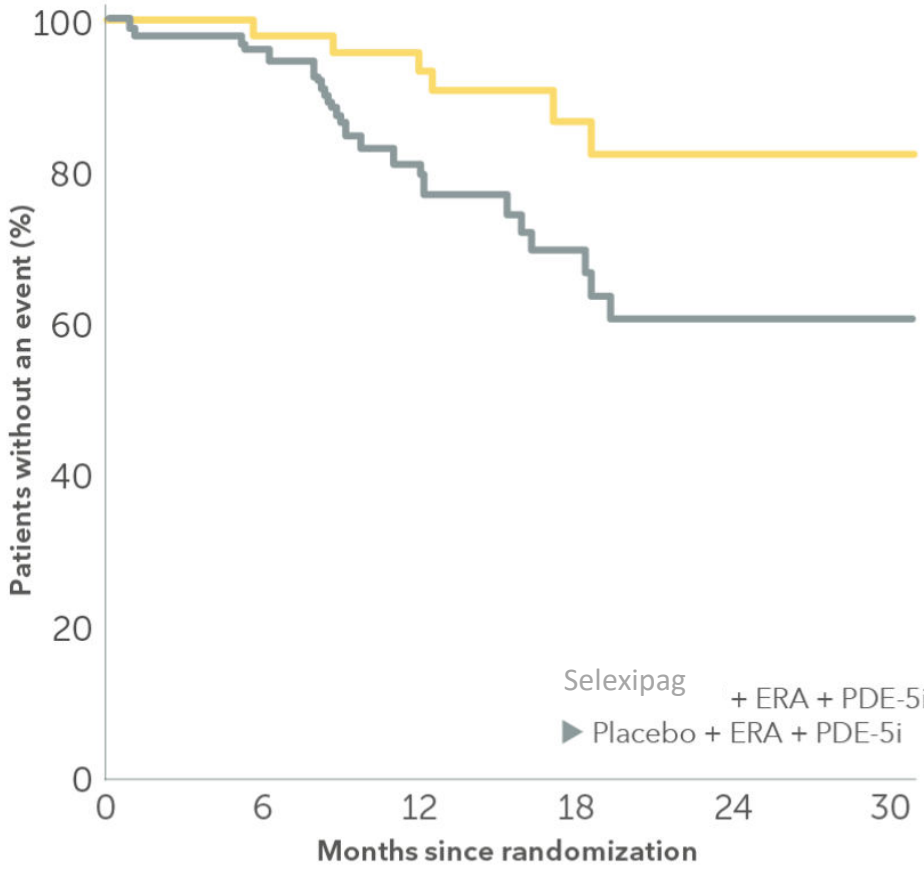
STUDY DESIGN

37%
RISK REDUCTION
HR 0.63 (95% CI: 0.44, 0.90)

https://uptravihcp.com/ctd-subgroup/

FC II SUBGROUP

Time to first disease progression event in FC II patients receiving ERA + PDE-5i at baseline



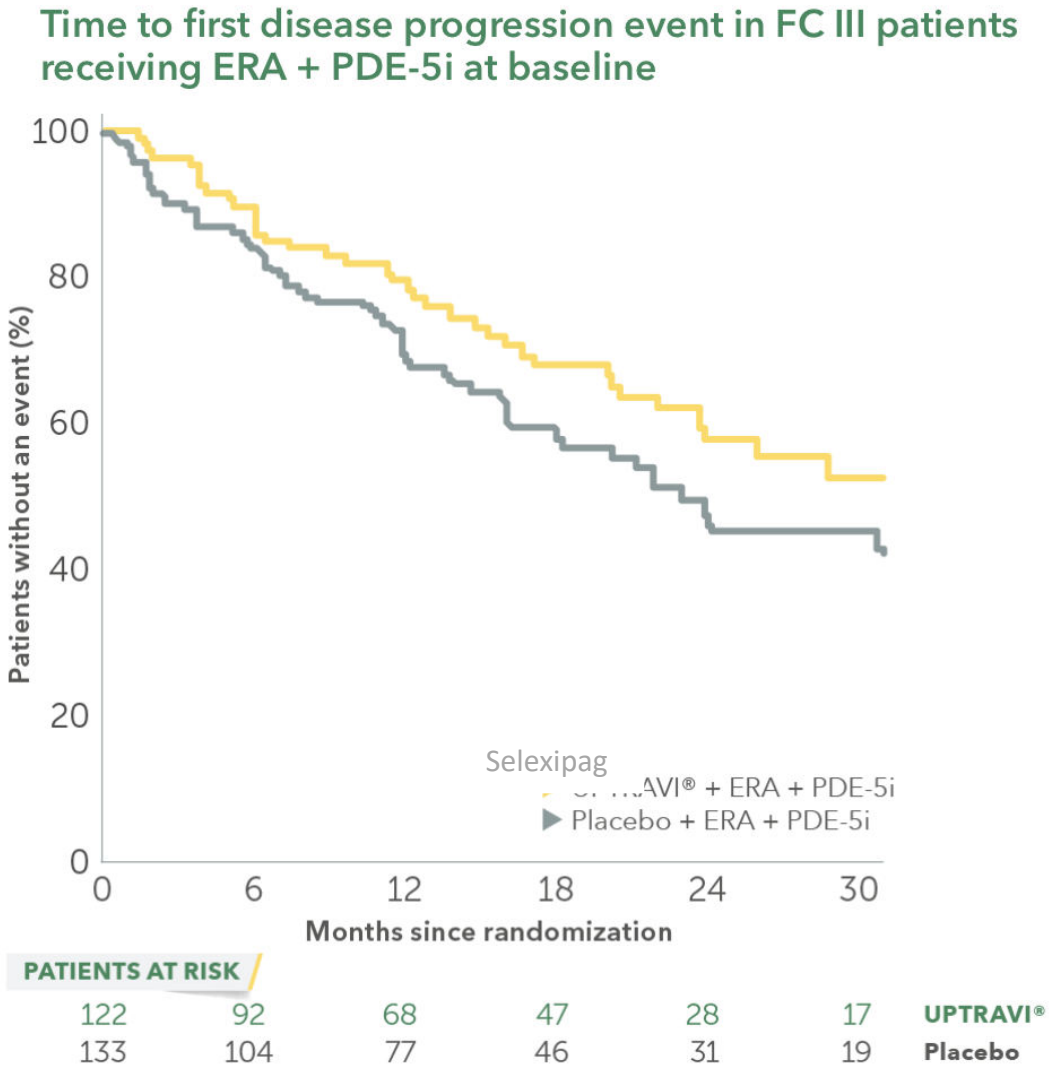
PATIENTS AT RISK						
55	46	36	22	14	13	UPTRAVI®
60	52	40	23	12	7	Placebo

STUDY DESIGN

64%
RISK REDUCTION
HR 0.36 (95% CI: 0.14, 0.91)

https://uptravihcp.com/ctd-subgroup/

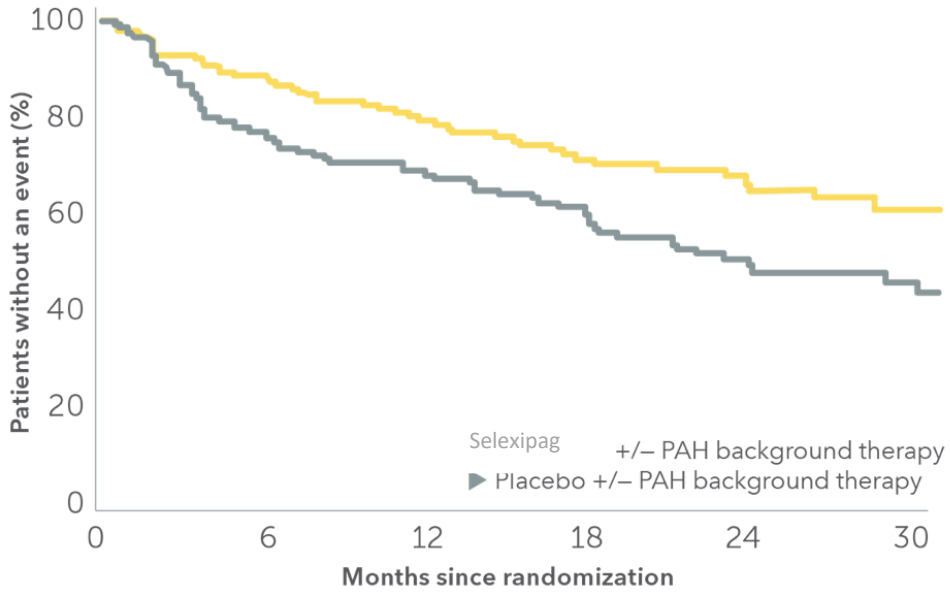
FC III SUBGROUP



https://uptravihcp.com/ctd-subgroup/

POST HOC ANALYSIS: 41% RISK REDUCTION OF DISEASE PROGRESSION IN PAH-CTD PATIENTS TREATED WITH UPTRAVI®

Time to first disease progression event in patients with PAH-CTD



STUDY DESIGN

41%
RISK REDUCTION
HR 0.59 (95% CI: 0.41, 0.85)

PATIENTS AT RISK

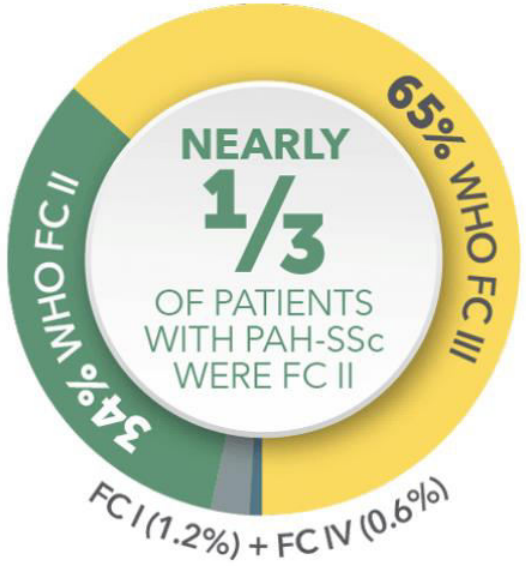
167	129	102	70	44	21	**UPTRAVI®**
167	114	92	57	38	21	**Placebo**

https://uptravihcp.com/ctd-subgroup/

SSC SUBGROUP

PAH-SSc baseline patient characteristics

Of the 334 patients with PAH-CTD in GRIPHON, **51% (n=170) had PAH-SSc.**



https://uptravihcp.com/ctd-subgroup/

The risk reduction of selexipag versus placebo was 44% in patients with PAH-SSc and 34%in patients with PAH-SLE

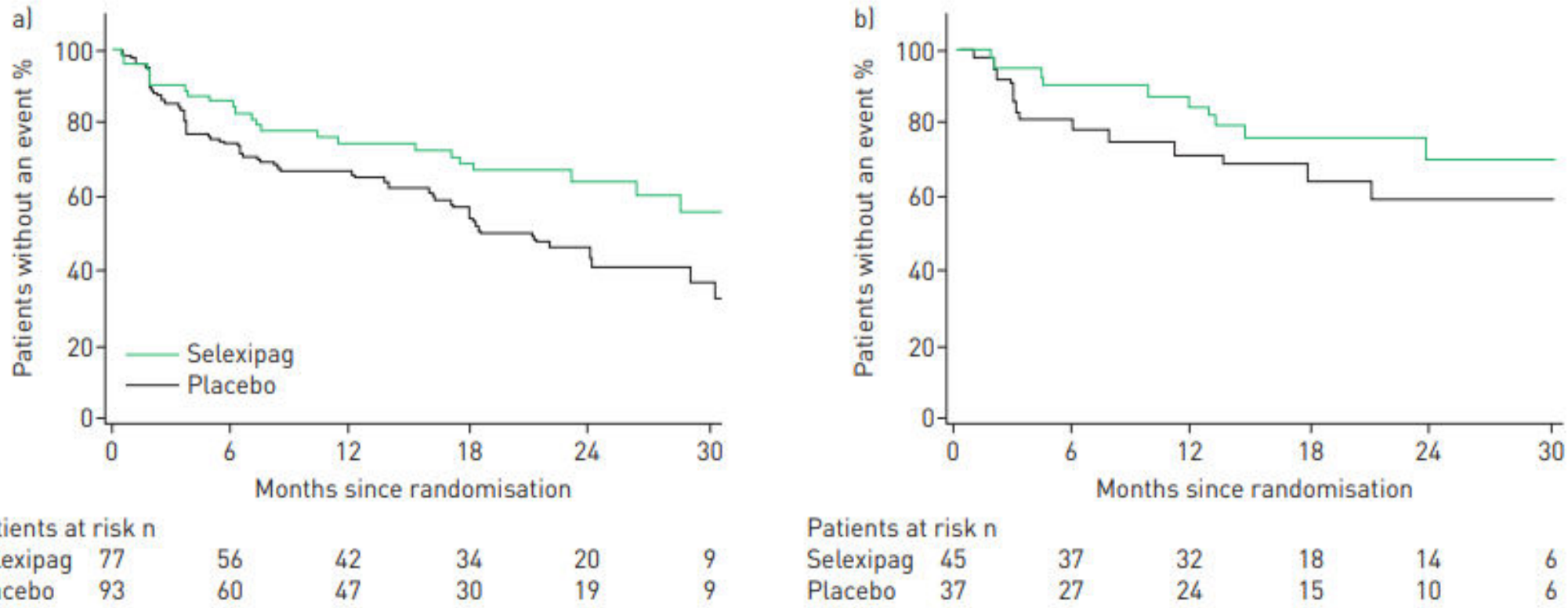


FIGURE 2 Effect of selexipag on the primary composite endpoint of morbidity/mortality in patients with a) pulmonary arterial hypertension associated with systemic sclerosis and b) pulmonary arterial hypertension associated with systemic lupus erythematosus.

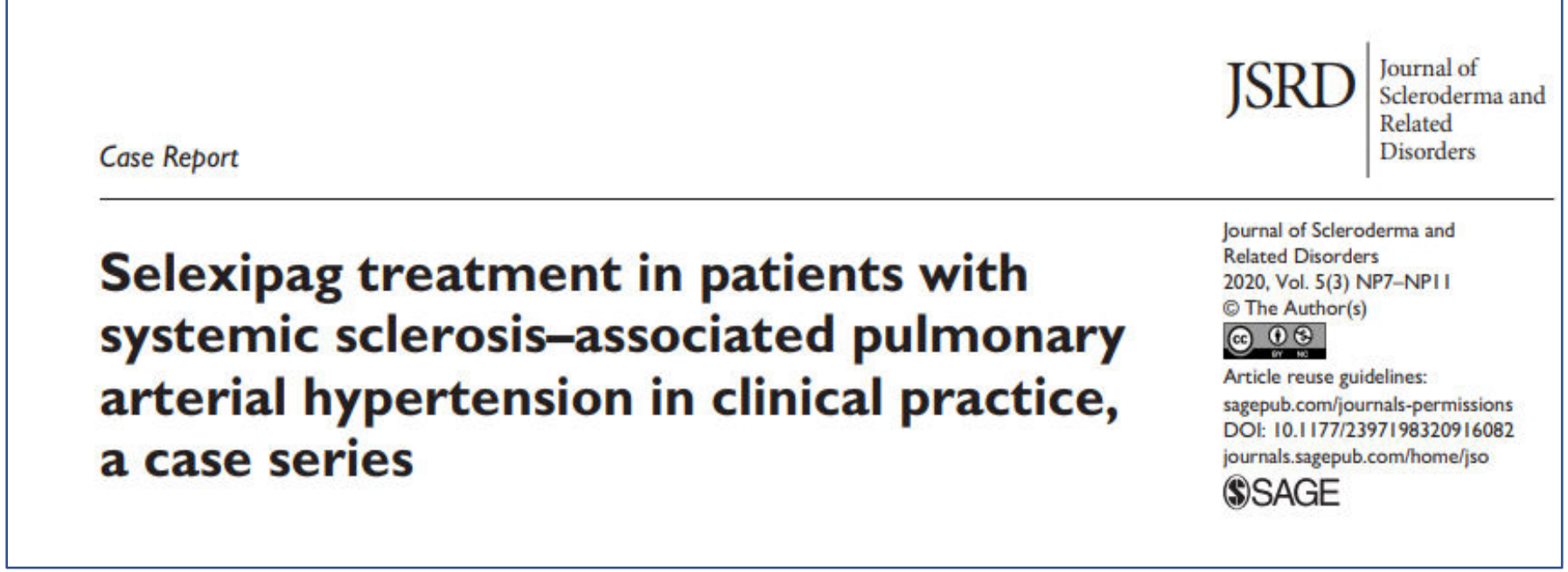
Eur Respir J 2017; 50: 1602493

Most frequent adverse events among patients with PAH associated with connective tissue

	Placebo	Selexipag
Subjects n	165[#]	167
Adverse events n	1301	1499
Patients with at least one adverse event	160 (97.0)	164 (98.2)
Patients with at least one serious adverse event	85 (51.5)	80 (47.9)
Patients with adverse event leading to discontinuation of study drug	15 (9.1)	32 (19.2)
Adverse event[¶]		
Headache	60 (36.4)	104 (62.3)
Diarrhoea	42 (25.5)	67 (40.1)
Nausea	41 (24.8)	62 (37.1)
Worsening of PAH	62 (37.6)	39 (23.4)
Dizziness	30 (18.2)	35 (21.0)
Vomiting	10 (6.1)	34 (20.4)
Upper respiratory tract infection	31 (18.8)	33 (19.8)
Peripheral oedema	31 (18.8)	32 (19.2)
Pain in extremity	8 (4.8)	31 (18.6)
Dyspnoea	37 (22.4)	30 (18.0)
Pain in jaw	11 (6.7)	24 (14.4)
Myalgia	10 (6.1)	21 (12.6)
Arthralgia	12 (7.3)	19 (11.4)
Nasopharyngitis	12 (7.3)	19 (11.4)
Flushing	8 (4.8)	19 (11.4)
Cough	23 (13.9)	17 (10.2)
Chest pain	15 (9.1)	17 (10.2)
Decreased appetite	9 (5.5)	17 (10.2)
Anaemia	17 (10.3)	16 (9.6)

Data are presented as n (%), unless otherwise stated. [#]: among the patients randomly assigned to the placebo group, two did not receive study treatment and were not included in the safety analysis set; [¶]: adverse events are listed for those that occurred in more than 10% of the patients in any study group during the double-blind period and up to 7 days after placebo or selexipag was discontinued.

Eur Respir J 2017; 50: 1602493



Case Report

JSRD Journal of Scleroderma and Related Disorders

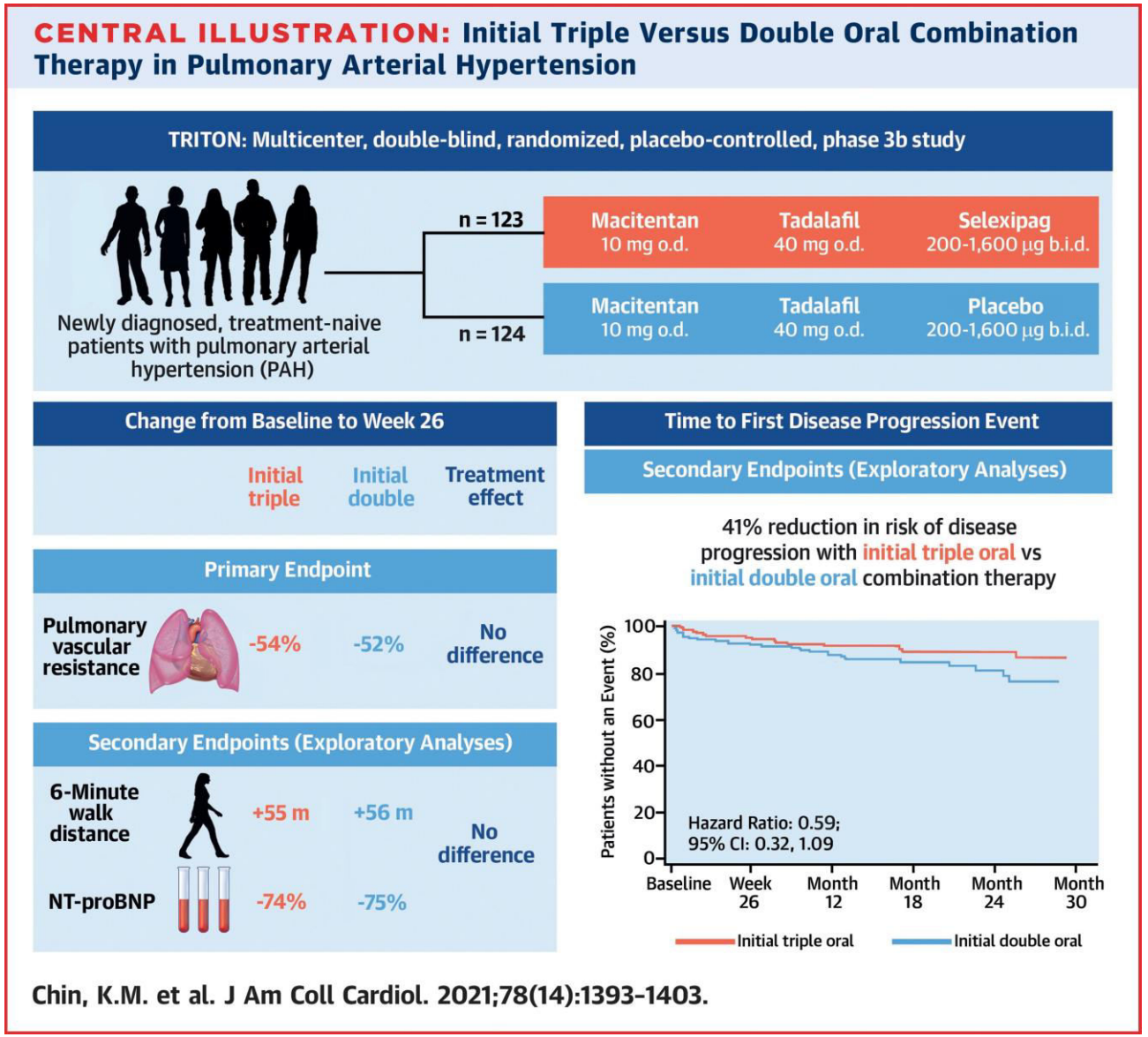
Selexipag treatment in patients with systemic sclerosis–associated pulmonary arterial hypertension in clinical practice, a case series

Journal of Scleroderma and Related Disorders
2020, Vol. 5(3) NP7–NP11

DOI: 10.1177/2397198320916082
journals.sagepub.com/home/jso
SAGE

- Study included 13 systemic sclerosis–associated pulmonary arterial hypertension patients, 10 patients were female, median age (interquartile range) of 68 (58–75) years, median systemic sclerosis disease duration of 7.4 (4.7–13.5) years, and median pulmonary arterial hypertension duration of 4 (2.5–7.5) years
- Adding selexipag to background therapy in a high-risk cohort of systemic sclerosis–associated pulmonary arterial hypertension patients provided sustained stabilization of symptoms with an acceptable safety profile

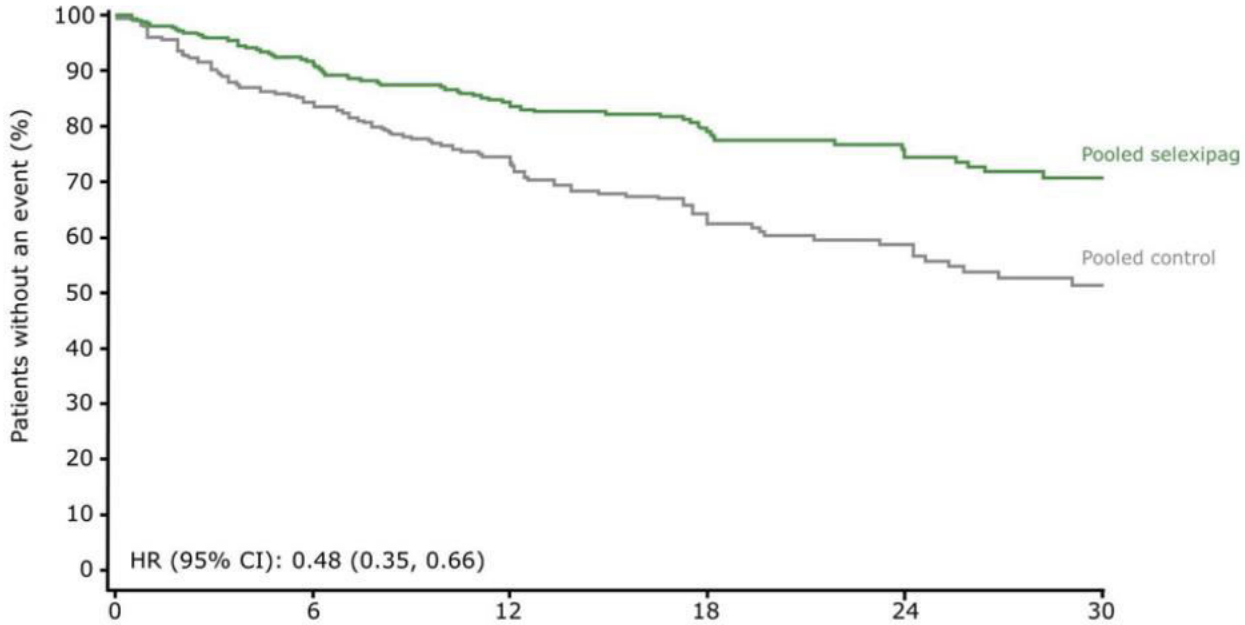
TRITON TRIAL



Chin, K.M. et al. J Am Coll Cardiol. 2021;78(14):1393-1403.

Treatment effect of selexipag on time to disease progression when initiated early in pulmonary arterial hypertension (PAH) patients: GRIPHON and TRITON pooled analysis

G.J. Coghlan[1], S. Gaine[2], R.N. Channick[3], K.M. Chin[4], C. Du Roure[5], J.S.R. Gibbs[6], M.M. Hoeper[7], I.M. Lang[8], S.C. Mathai[9], V.V. McLaughlin[10],



Patients at risk						
Pooled selexipag	329	264	205	144	95	43
Pooled control	320	245	177	104	61	34

Number of events						
Pooled selexipag	0	25	46	55	63	67
Pooled control	0	48	78	98	104	111

ESC Congress 2021 – 27–30 August 2021

SUMMARY

- CTD PAH ARE ONE OF THE MAJOR GROUPS OF PAH
- SCLERODERMA FOLLOWED BY LUPUS ACCOUNT FOR MOST OF THE CASES
- SCREENING PROTOCOLS ARE VERY USEFUL FOR EARLY DETECTION
- IMMUNOSUPRESSIVE THERAPY IS DEFINITELY USEFUL IN SLE AND PROBABLY USEFUL IN SCLERODERMA
- WE SHOULD TREAT TO TARGET(FC-1)
- COMBINATION THERAPIES (TRIPLE WITH SELEXIPAG) IS PROBABLY THE FUTURE

THANK YOU

- PAH definition
- PAH classification
- PAH screening
- PAH pathophysiology
- PAH management
- PAH follow up

Medication	Monotherapy	Sequential Dual Combination	Sequential Triple Combination
Selexipag			
Riociguat			*
Inhaled Treprostinil	**		
Oral Treprostinil			

Green: Positive event-driven trial. Yellow: Positive 6-minute walk-driven trial. Orange: Clinical experience, nonrandomized data, or trends in randomized data suggest possible benefit.

*Cannot utilize with phosphodiesterase type 5 inhibitor; experience with prostanoids is thus far limited. **Rarely used as monotherapy.

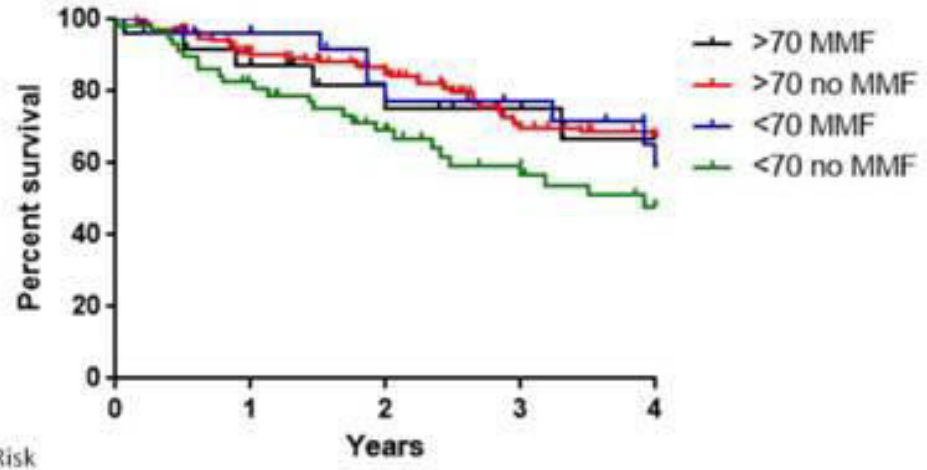
	Efficacy	Tolerability	Convenience	Safety
+ Intravenous Epoprostenol	+++++	+++	++	+++
+ Intravenous Treprostinil	+++++	+++	++	+++
+ Subcutaneous Treprostinil	+++++	+++	++	++++
+ Selexipag	++++	++++	++++	+++++
+ Inhaled Treprostinil	+++	++++	+++	+++++
ERA + Riociguat*	+++	+++++	+++++	+++++
Oral Treprostinil**	++	+++	++++	+++++
*Cannot combine riociguat with PDE5 inhibitor. **Oral treprostinil has not met endpoints in randomized combination use.				

Mycophenolate Mofetil (MMF) Use in Scleroderma Patients with Pulmonary Hypertension: Observations from the Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma Cohort

Lesley Ann Saketkoo[1], Matthew R. Lammi[2], Aryeh Fischer[3], Jerry A. Molitor[4] and Virginia D. Steen[5], [1]Scleroderma and Sarcoidosis Patient Care and Research Center, Rheumatology and Pulmonary Medicine, Louisiana State University Health Sciences Center, New Orleans, LA, [2]Louisiana State University Health Sciences Center, Pulmonary and Critical Medicine, New Orleans, LA, [3]Rheumatology / ILD Program, National Jewish Health, Denver, CO, [4]Rheumatology, University of Minnesota, Minneapolis, MN, [5]Department of Rheumatology, Georgetown University Medical Center, Washington, DC

Meeting: 2014 ACR/ARHP Annual Meeting

Diagram 1. Survival across groups partitioned by FVC and MMF use.



No. At Risk					
FVC >70% +MMF	25	20	13	11	7
FVC >70% - MMF	158	135	109	71	50
FVC <70% +MMF	28	23	17	15	10
FVC <70% - MMF	52	45	34	23	14

The trend for improved survival in patients with PH with FVC <70 who were treated with MMF even in the absence of improvement of FVC is intriguing. Whether it has an effect on pulmonary artery remodeling should be considered. These findings warrant prospective controlled investigations of MMF in SSc PH particularly in those with restrictive lung disease.

Does Mycophenolate Mofetil (mmf) Have An Effect On Pulmonary Hemodynamics? Observations From The Pulmonary Hypertension Assessment And Recognition Of Outcomes In Scleroderma (pharos) Cohort

L. Saketkoo[1, 2], M. R. Lammi[1], J. Gordon[3], P. Lauto[1], V. Steen[4], PHAROS Investigators

[1]Louisiana State University Health Sciences Center, New Orleans, LA, [2, 3]Hospital for Special Surgery, New York, NY, [4]Georgetown University Medical Center, Washington, DC

Table 1. Comparison between SSc patients on No IS medications and MMF at time of first RHC. Continuous variables are reported as median, interquartile range; categorical values are proportional.

	No IS	MMF	p Value
n	203	39	
Age	60 (52,68)	54 (47,63)	*0.0143
Sex (% female)	84%	65%	0.6491
N (%) Limited SSc	144 (71%)	14 (35%)	*< 0.0001
Time from 1st SSc Symptom (years)	11.2 (5.3,21.0)	6.9 (3.0,10.3)	*0.0004
mPAP	33 (28,44)	29 (25,35)	*0.0016
PVR	355 (242,692)	222 (162,344)	*0.0006
PCWP	11 (8,14)	11 (9,15)	0.7036
FVC	78.1 (64,88)	68.9 (48,84)	*0.0298
TLC	76.5 (66,93)	62.8 (47,80)	*0.0002
FEV/FVC	81 (75,87)	87 (81,93)	*0.0048
DLCO	37.5 (30,50)	34.3 (28,39)	0.0929
FVC:DLCO	1.94 (1.6,2.4)	1.85 (1.4,2.5)	0.6908
6MWD	338.3 (238,428)	396.2 (343,475)	*0.0298

Am J Respir Crit Care Med 189;2014:A4744

S.12.4 A COMPARISON OF THE PREDICTIVE ACCURACY OF THREE SCREENING MODELS (DETECT V. ESC/ERS V. ASIG) FOR PULMONARY ARTERIAL HYPERTENSION IN SYSTEMIC SCLEROSIS

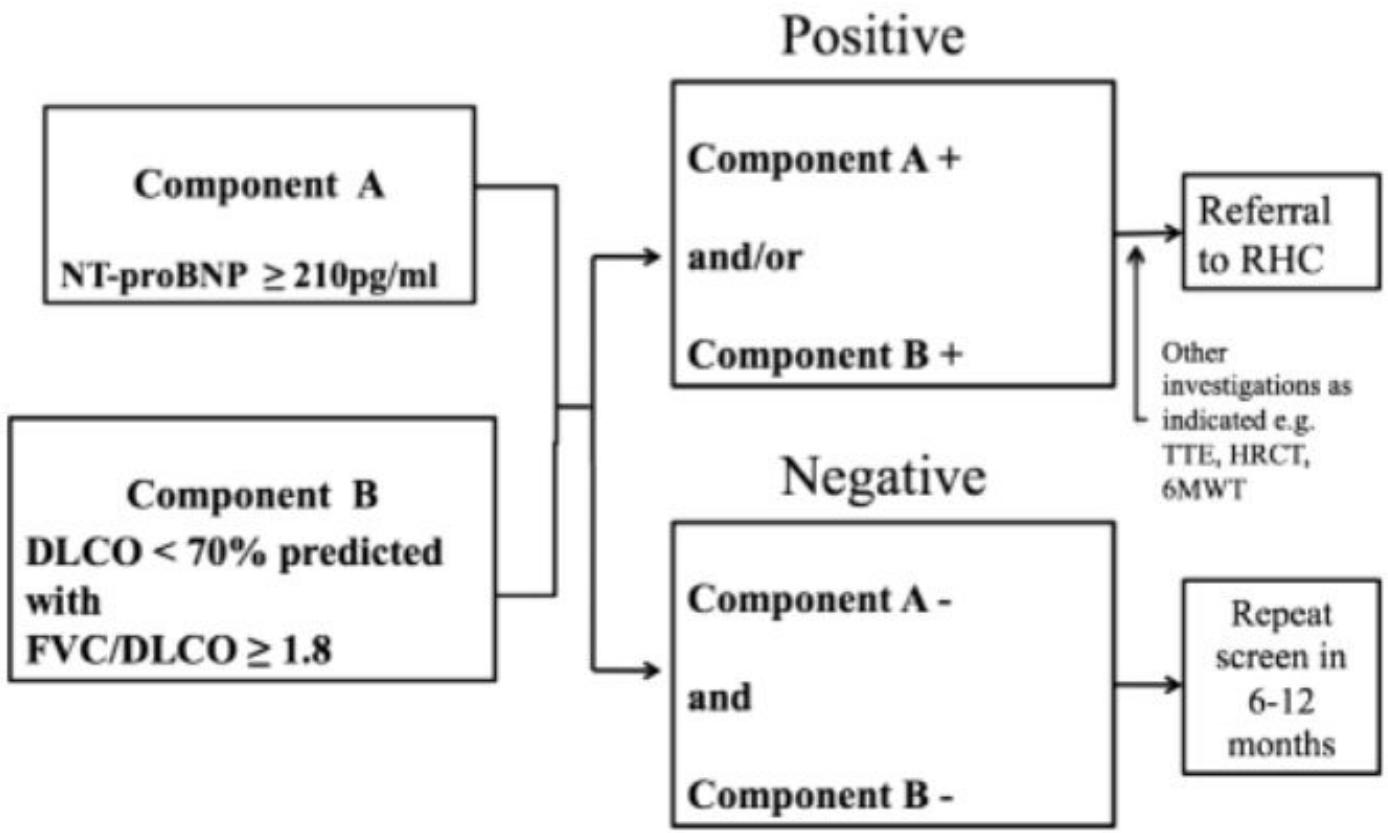
Y.J. Hao [1,2], V. Thakkar [1,2], W. Stevens [1], D. Prior [2], C. Rabusa [1,2], P. Youssef [3], E. Gabbay [4], J. Roddy [4], J.G. Walker [5], J. Zochling [6], J. Sahhar [7], P. Nash [8], S. Lester [9], C. Hill [9], M. Rischmueller [9], S.M. Proudman [10], M. Nikpour [1,2]

[1] Department of Rheumatology, St Vincent's Hospital Melbourne, Melbourne, AUSTRALIA,[2] The University of Melbourne Department of Medicine at St Vincent's Hospital Melbourne, Melbourne, AUSTRALIA,[3] Institute of Rheumatology and Orthopaedics, Royal Prince Alfred Hospital, Sydney, AUSTRALIA,[4] Pulmonary Hypertension Service and Department of Rheumatology, Royal Perth Hospital, Perth, AUSTRALIA, [5] Department of Rheumatology, Flinders Medical Centre, Adelaide, AUSTRALIA,[6] The Menzies Research Institute Tasmania, Tasmania, AUSTRALIA,[7] Department of Rheumatology, Monash Medical Centre, Melbourne, AUSTRALIA,[8] Sunshine Coast Rheumatology, Sunshine Coast, AUSTRALIA,[9] Rheumatology Department, The Queen Elizabeth Hospital, Adelaide, AUSTRALIA,[10] Department of Rheumatology, Royal Adelaide Hospital, Adelaide, AUSTRALIA

Table 1. Comparison of the performance of DETECT v. ESC/ERS v. ASIG screening models for SSc-PAH

				PAH prevalence set at 10%		
	DETECT n=61	**ESC/ERS** n=58	**ASIG** n=61	**DETECT** n=61	**ESC/ERS** n=58	**ASIG** n=61
Sensitivity (95% CI)	100% (87.2-100)	96.3% (81-99.9)	100% (87.2-100)	100% (54.1-100)	96.3% (54.1-100)	100% (54.1-100)
Specificity (95% CI)	35.3% (19.7-53.5)	29.0% (19.7-53.5)	47.1% (29.8-64.9)	35.3% (23.8-50.4)	29.0% (12.5-36.8)	47.1% (35.4-62.9)
PPV (95% CI)	55.1% (40.2-69.3)	54.2% (39.2-68.6)	60% (44.3-74.3)	14.7% (5.6-29.2)	13.1% (4.9-26.3)	17.4% (6.8-34.5)
NPV (95% CI)	100% (63.1-100)	90.0% (55.5-99.7)	100% (79.4-100)	100% (83.2-100)	99.7% (73.5-100)	100% (87.2-100)

ASIG

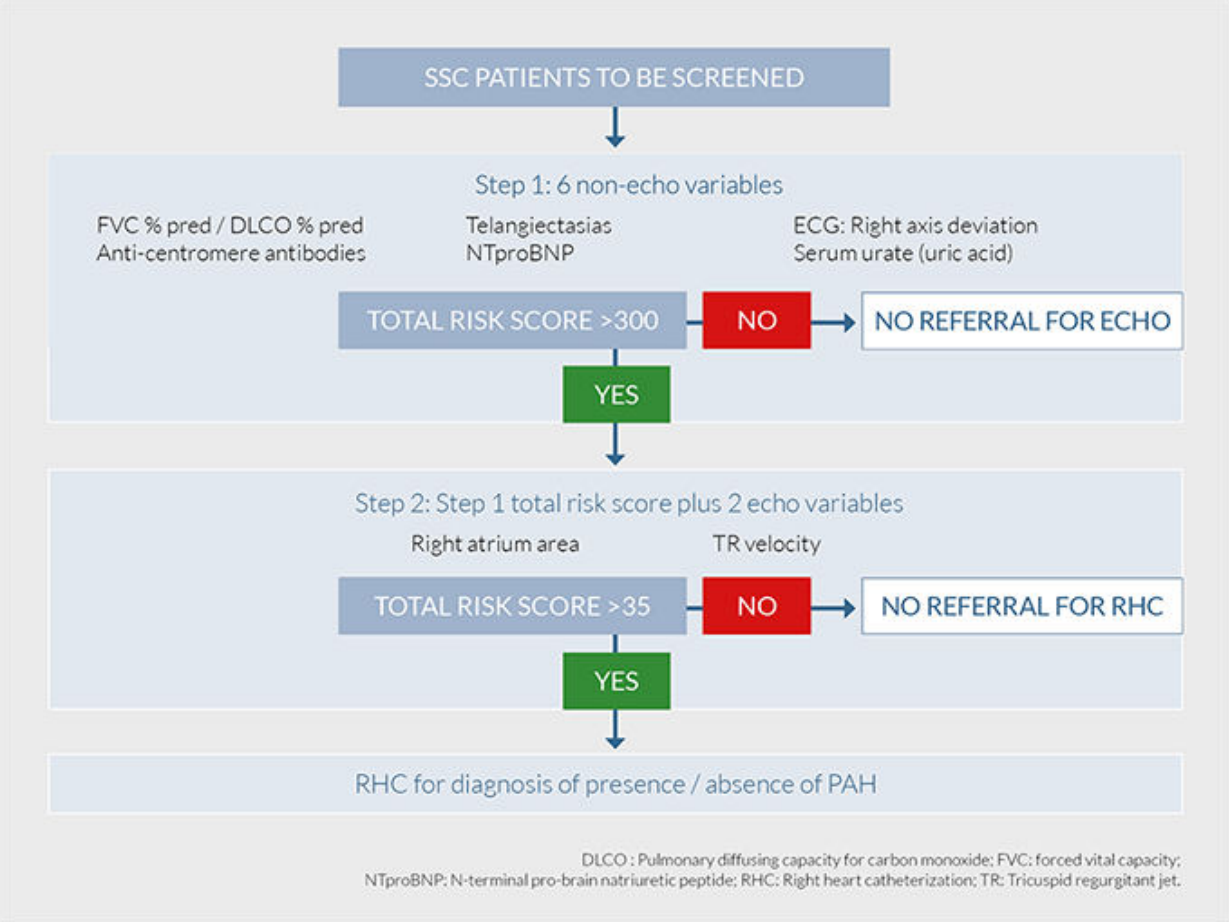

Positive
Component A
NT-proBNP ≥ 210pg/ml
Component B
DLCO < 70% predicted with
FVC/DLCO ≥ 1.8
Component A +
and/or
Component B +
Referral to RHC
Other investigations as indicated e.g. TTE, HRCT, 6MWT
Negative
Component A -
and
Component B -
Repeat screen in 6-12 months

ECS

Positive screen on echocardiography (referral to RHC recommended)

- TRV >3.4 m/s
- or TRV >2.8-≤3.4 m/s and symptoms (current dyspnoea, current syncope/near syncope, presence of peripheral oedema)
- or TRV ≤2.8 m/s and symptoms and additional suggestive echo variable (e.g. RA area >18 cm^2)

DETECT


SSC PATIENTS TO BE SCREENED
Step 1: 6 non-echo variables
FVC % pred / DLCO % pred
Anti-centromere antibodies
Telangiectasias
NTproBNP
ECG: Right axis deviation
Serum urate (uric acid)
TOTAL RISK SCORE >300
NO
NO REFERRAL FOR ECHO
YES
Step 2: Step 1 total risk score plus 2 echo variables
Right atrium area
TR velocity
TOTAL RISK SCORE >35
NO
NO REFERRAL FOR RHC
YES
RHC for diagnosis of presence / absence of PAH
DLCO : Pulmonary diffusing capacity for carbon monoxide; FVC: forced vital capacity;
NTproBNP: N-terminal pro-brain natriuretic peptide; RHC: Right heart catheterization; TR: Tricuspid regurgitant jet.

S.12.5 CLINICAL SUBTYPE AND AUTOANTIBODIES BOTH HELP PREDICT PULMONARY ARTERIAL HYPERTENSION, BUT AUTOANTIBODIES ARE STRONGER PREDICTORS OF DEVELOPING SECONDARY PULMONARY HYPERTENSION

M. Mohile , M. Lucas , T. Medsger , R. Domsic

University of Pittsburgh, Pittsburgh, USA

Table 1: Multivariable Predictors of PAH

	Odds Ratio (95% Confidence Interval)	p-value
Age (years) at initial visit		< 0.0001
< 35	----	
35-44	0.88 (0.37 – 2.10)	
45-54	1.07 (0.48 – 2.42)	
55-64	2.11 (0.94 – 4.73)	
>65	3.64 (1.64 – 8.07)	
Limited cutaneous involvement	2.74 (1.67 – 4.48)	< 0.0001
Th/To or U3RNP positive (nucleolar ANA)	2.66 (1.61 – 4.41)	< 0.0001

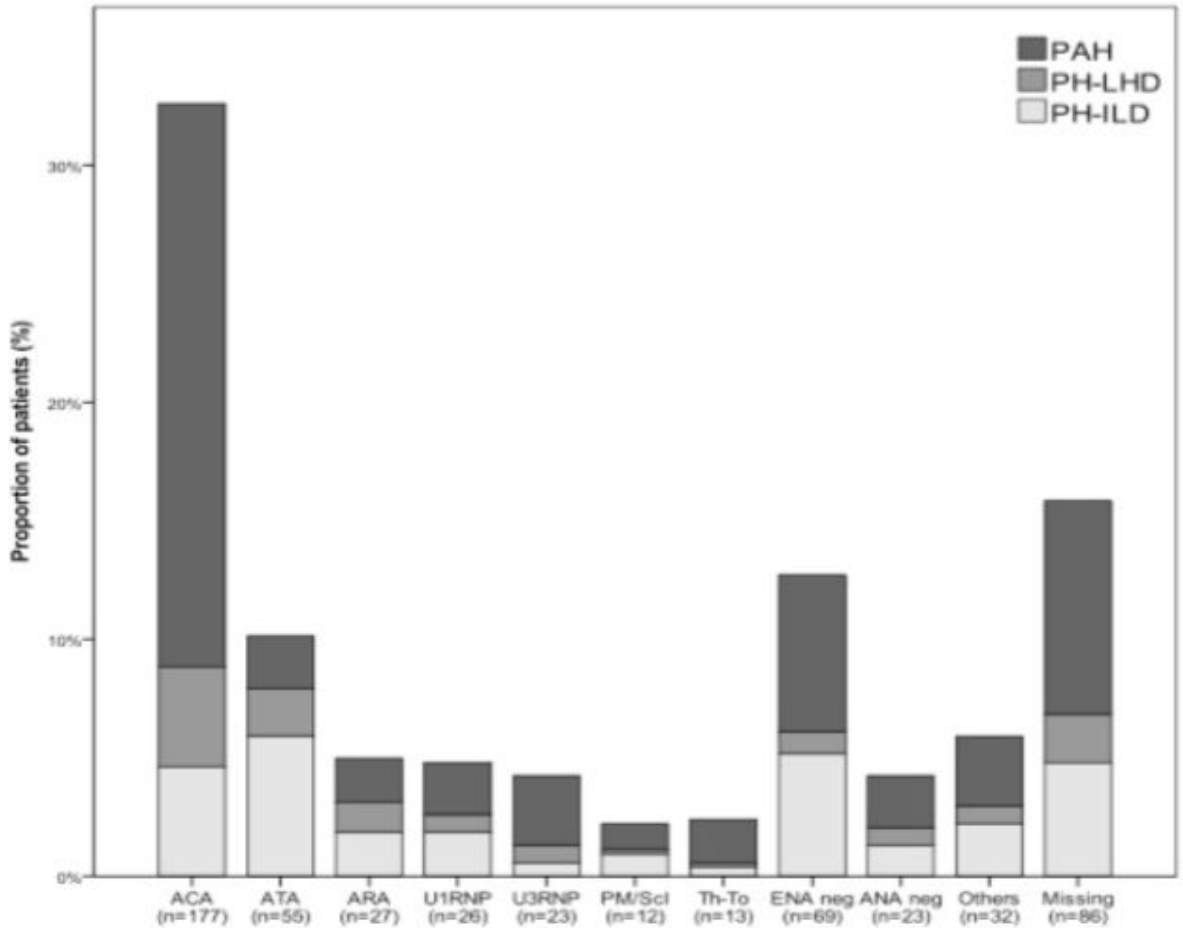
Table 2: Multivariable Predictors of Secondary PH

	Odds Ratio (95% Confidence Interval)	p-value
Age (years) at initial visit		0.03
< 35	-----	
35-44	1.23 (0.43 – 3.59)	
45-54	1.95 (0.72 – 5.29)	
55-64	2.70 (0.98 – 7.43)	
>65	3.53 (1.25 – 9.97)	
Male	2.18 (1.32 – 3.59)	< 0.002
Anti-U11/U12 RNP positive	1.51 (0.93 – 2.45)	0.02
ACA	0.27 (0.11 – 0.67)	0.004
Limited cutaneous involvement	3.12 (1.17 – 8.34)	0.09

PS21 AUTOANTIBODY PROFILE IN SYSTEMIC SCLEROSIS ASSOCIATED PULMONARY HYPERTENSION

V. Sobanski [1], S. Nihtyanova [1], B. Lynch [1], B. Schreiber [2], J. Harvey [3], C. Handler [2], C. Denton [1], G. Coghlan [2]

[1] Centre For Rheumatology and Connective Tissue Diseases - Royal Free Hospital - University College London, London, UNITED KINGDOM,[2] National Pulmonary Hypertension Unit - Royal Free Hospital - University College London, London, UNITED KINGDOM,[3] Department of Clinical Immunology - Royal Free Hospital - University College London, London, UNITED KINGDOM

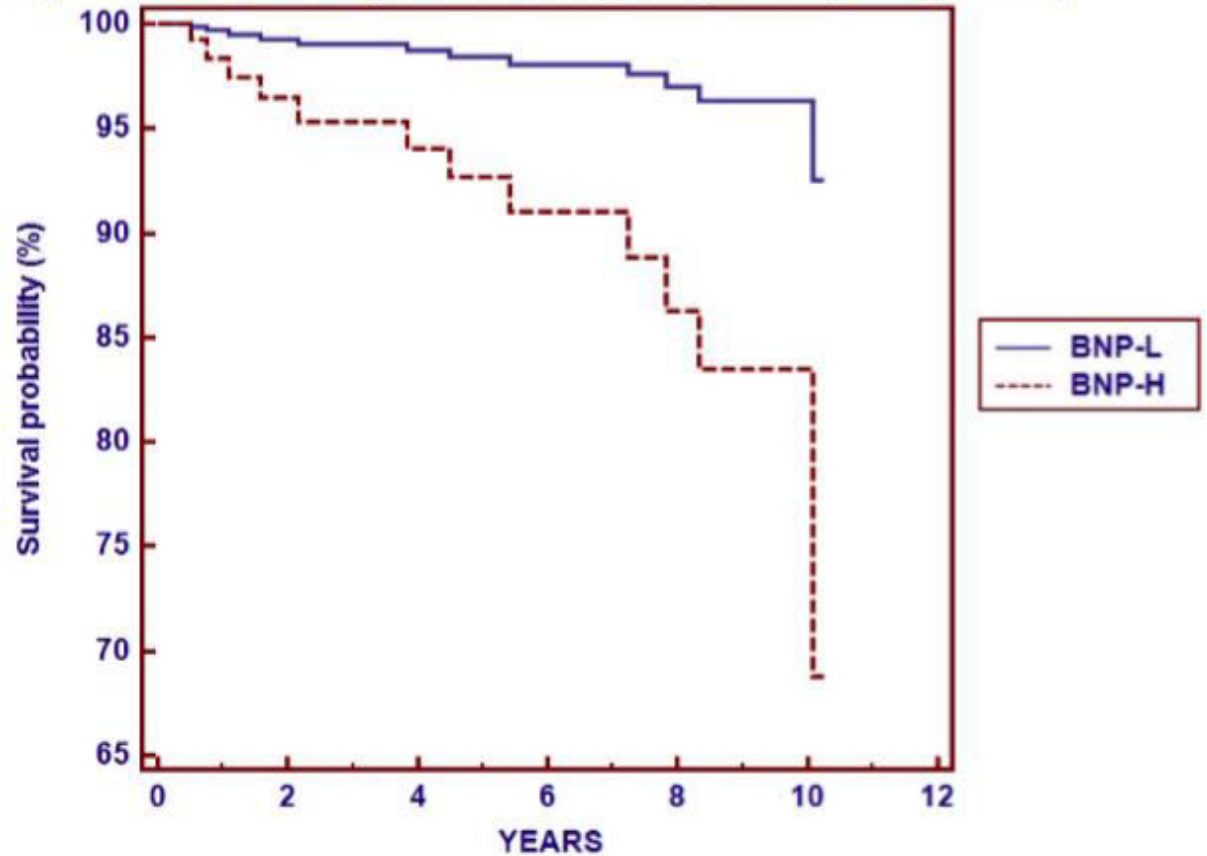


S.12.6 PROGNOSTIC VALUE OF NT-PROBNP IN SYSTEMIC SCLEROSIS PATIENTS WITHOUT PULMONARY HYPERTENSION

M. Antivalle, M. Battellino, M.C. Ditto, M. Chevallard, A. Mutti, A. Batticciotto, V. Varisco, F. Rigamonti, F. Atzeni, P. Sarzi-Puttini

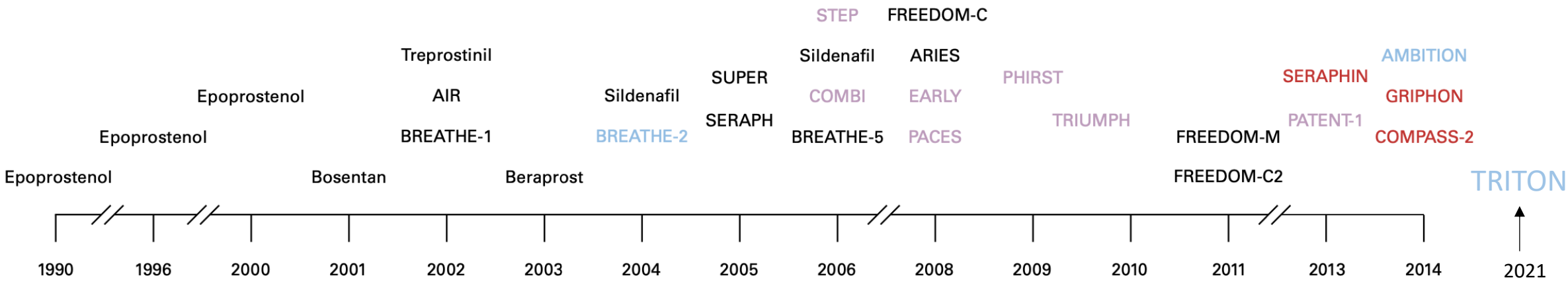
Rheumatology - L.Sacco University Hospital, Milano, ITALY

Fig. 1 - Survival probability in BNP-L and BNP-H patients (Cox regression)



TREATMENT

TIMELINE OF PAH THERAPIES



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PS23 COST SAVINGS WITH A BIOMARKER-BASED SCREENING ALGORITHM FOR PULMONARY ARTERIAL HYPERTENSION IN SYSTEMIC SCLEROSIS

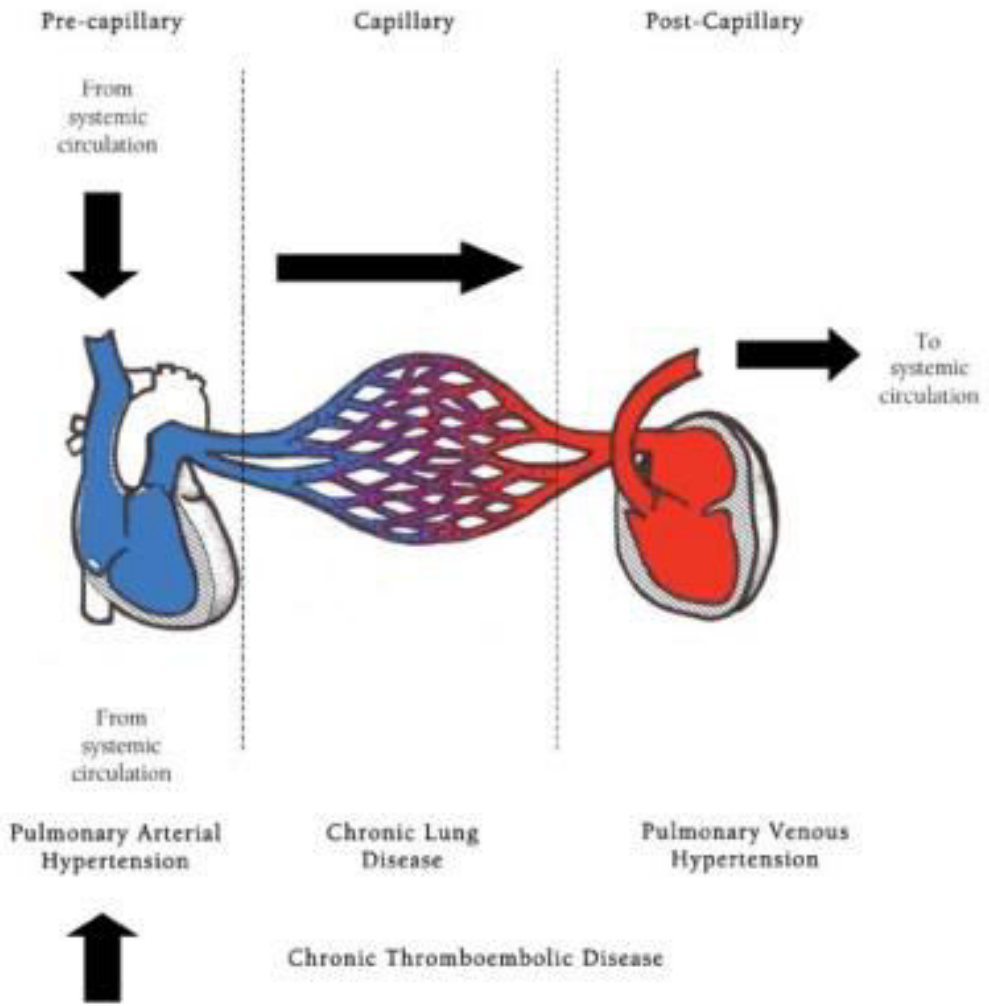
A. Quinlivan [1,2], V. Thakkar [1,2], W. Stevens [1], D. Prior [2], C. Rabusa [1], P. Youssef [3], E. Gabbay [4], J. Roddy [4], J. Walker [5], J. Zochling [6], J. Sahhar [7], P. Nash [8], S. Lester [9], C. Hill [9], M. Rischmueller [9], S. Proudman [10], M. Nikpour [1,2]

[1] St. Vincent's Hospital, Melbourne, AUSTRALIA,[2] The University of Melbourne, Melbourne, AUSTRALIA,[3] Royal Prince Alfred Hospital, Sydney, AUSTRALIA,[4] Royal Perth Hospital, Perth, AUSTRALIA,[5] Flinders Medical Centre, Adelaide, AUSTRALIA,[6] Menzies Reseach Institute Tasmania, Hobart, AUSTRALIA,[7] Monash Medical Centre, Melbourne, AUSTRALIA,[8] Sunshine Coast Rheumatology, Sunshine Coast, AUSTRALIA,[9] The Queen Elizabeth Hospital, Adelaide, AUSTRALIA,[10] Royal Adelaide Hospital, Adelaide, AUSTRALIA

	$ASIG_{OLD}$	$ASIG_{NEW}$
Total number of patients	643	643
Number (%) screen+	256 (40%)	231 (36%)
% screen+ with PAH on RHC	45%	50%
TTE required	643	231
RHC required	256	231
NNS to get one screen+	2.50	2.78
Number of RHC to diagnose one case PAH	2.20	2.00
NNS to diagnose one case of PAH	5.50	5.56
Total cost of screening and diagnosis	$851,917	$727,833
Cost of diagnosis of one case of PAH	$7,311.70	$6,300.20

Table 1. $ASIG_{OLD}$ and $ASIG_{NEW}$ algorithms applied to 643 consecutive patients with SSc. NNS=number needed to screen. All costs are in Australian Dollars.

Pulmonary vasculature



nomenclatures

- PH – pulmonary hypertension
- PAH- Pulm. Arterial hypertension
- mPAP- Mean Pulm. Arterial pressure
- PCWP- Pulm. Capillary wedge pressure.
- VTR – Velocity of Tricusp. Regur.
- PFT- Pulm. Function test
- 6MWD- 6 min walk distance
- BNP- B-type natriuretic peptide

Definition &Classification of PH

PH DEFINITION

Table 3 Haemodynamic definitions of pulmonary hypertension[a]

Definition	Characteristics	Clinical group(s)[b]
Pulmonary hypertension (PH)	Mean PAP ≥25 mmHg	All
Pre-capillary PH	Mean PAP ≥25 mmHg PWP ≤15 mmHg CO normal or reduced[c]	1. Pulmonary arterial hypertension 3. PH due to lung diseases 4. Chronic thromboembolic PH 5. PH with unclear and/or multifactorial mechanisms
Post-capillary PH	Mean PAP ≥25 mmHg PWP >15 mmHg CO normal or reduced[c]	2. PH due to left heart disease
Passive	TPG ≤12 mmHg	
Reactive (out of proportion)	TPG >12 mmHg	

[a]All values measured at rest.
[b]According to *Table 4*.
[c]High CO can be present in cases of hyperkinetic conditions such as systemic-to-pulmonary shunts (only in the pulmonary circulation), anaemia, hyperthyroidism, etc.
CO = cardiac output; PAP = pulmonary arterial pressure; PH = pulmonary hypertension; PWP = pulmonary wedge pressure; TPG = transpulmonary pressure gradient (mean PAP − mean PWP).

mPAP >30mmhg
after exercise
NOT VALID

ECHO definitions for PH

- PH unlikely- vTR < 2.8m/s,PA syst pressure<36mHg
- PH possible- vTR 2.9- 3.4m/s,PA syst pressure 37- 50mmHg
- PH likely – vTR - >3.4m/s, PA syst pressure >50mmHg

ECHO CAN NEVER DIAGNOSE PAH

Venice 2003 classification of PH

1. Pulmonary arterial hypertension

- **Idiopathic PAH**
- **Heritable**
  - **BMPR2**
  - **ALK1, endoglin**
  - **unknown**
- **Drugs and toxins induced**
- **Associated with:**
  - Connective tissue diseases
  - HIV infection
  - Portal hypertension
  - systemic to pulmonary shunts
  - Schistosomiasis
  - Chronic haemolytic anaemia

1'Pulm. veno- occlusive disease (PVO) and/or pulmonary capillary haemangiomatosis (PCH)

2. Pulmonary hypertension due to left heart disease

- **Systolic dysfunction**
- **Diastolic dysfunction**
- **Valvular disease**

3. Pulmonary hypertension due to lung diseases and/or hypoxia

- **Chronic obstructive pulmonary disease**
- **Interstitial lung disease**
- **Sleep-disordered breathing**
- **Chronic exposure to high altitude**
- **Broncho pulmonary dysplasia (BPD)**
- **Developmental abnormalities**

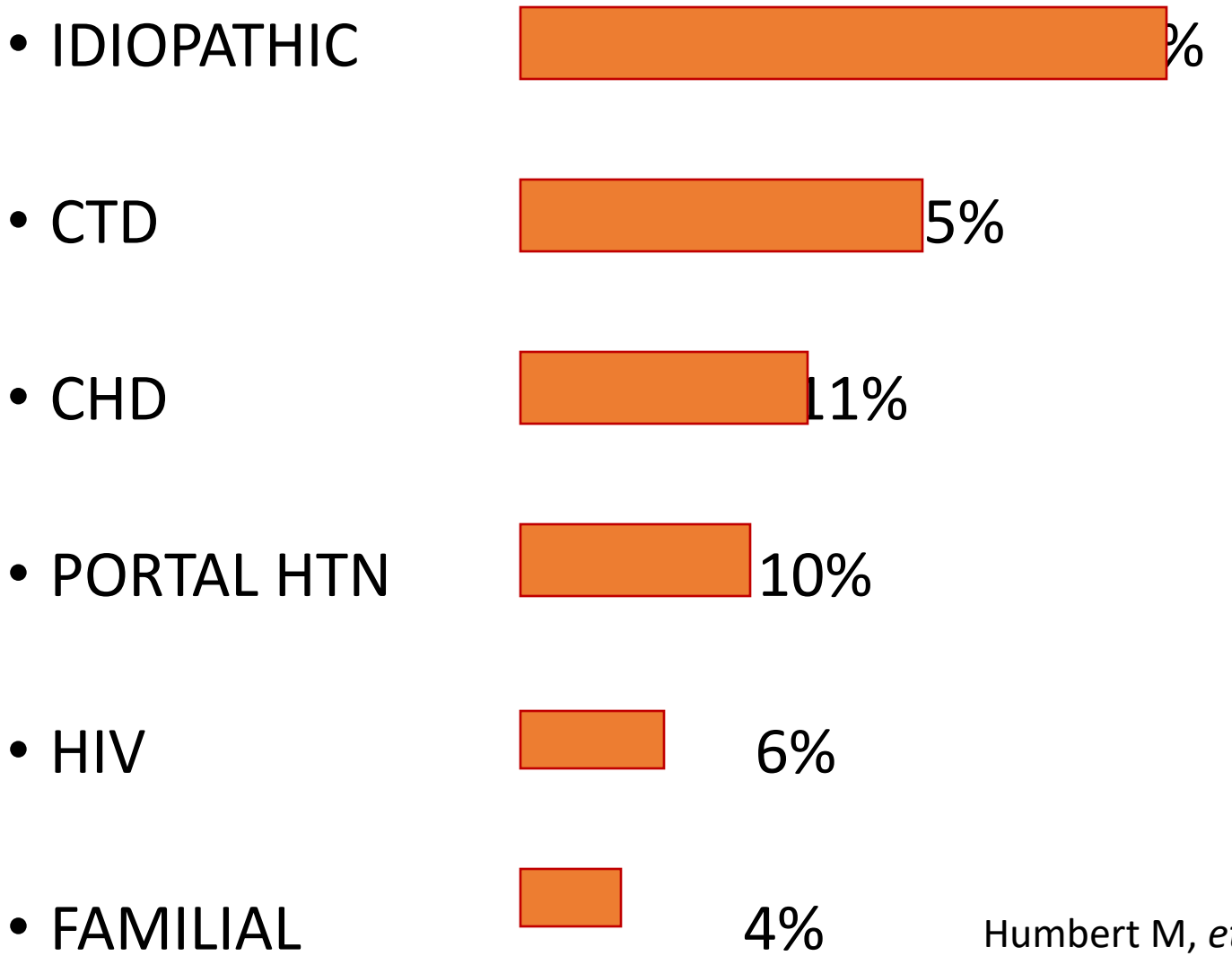
4. Chronic thromboembolic pulmonary hypertension (CTEPH)

5. Pulmonary Hypertension with unclear and/or mulifactorial mechanisms

- **Haematologic disorders**
  myeloproliferative disorders; splenectomy
- **Systemic disorders**
  Vasculitis sarcoidosis, pulmonary Langerhans cell histiocytosis LAM, neurofibromatosis.
- **Metabolic disorders**
  Glycogen storage disease, Gaucher disease, thyroid disorders
- **Congenital heart disease**
  other than systemic to pulmonary shunt
- **Others**: *obstruction by tumours, fibrosingmediastinitis, chronic renal failure on dialysis*

PH in CTD & Systemic Sclerosis

CTD LEADING CAUSE OF PAH



Humbert M, *et al. AJRCMM 2006;173:1023–30*

J Respir Crit Care Med Am Vol 179. pp 151–157, 2009

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]

[1]Pulmonary Vascular Disease Unit, Royal Hallamshire Hospital, Sheffield; [2]Pulmonary Vascular Disease Unit, Papworth Hospital, Cambridge; [3]Scottish Pulmonary Vascular Disease Unit, Western Infirmary, Glasgow; [4]Northern Vascular Unit, Freeman Hospital, Newcastle-upon-Tyne; [5]Institute of Cellular Medicine, Newcastle University, Newcastle-upon-Tyne; [6]Department of Cardiology, Hammersmith Hospital, London; and [7]Department of Cardiology, Royal Free Hospital, London, United Kingdom

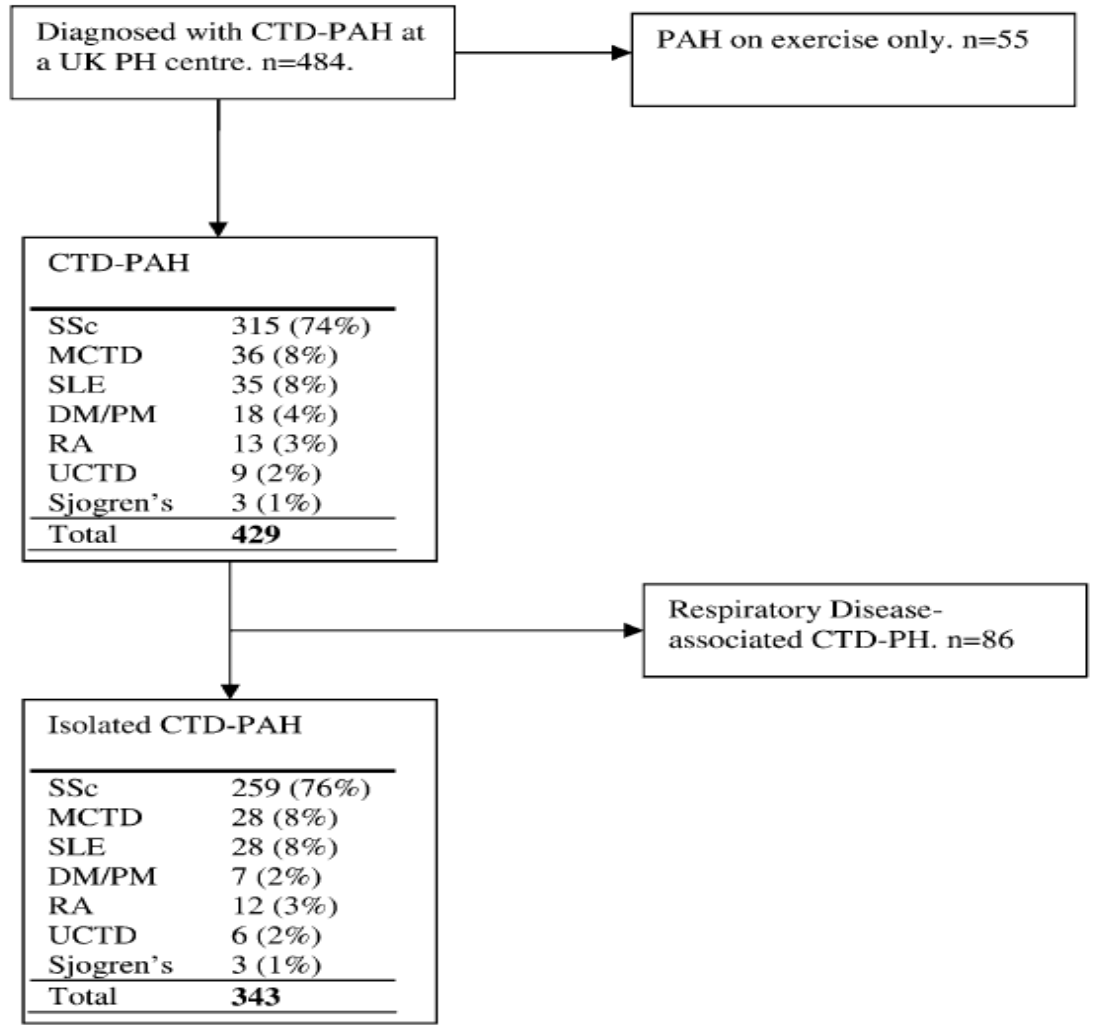
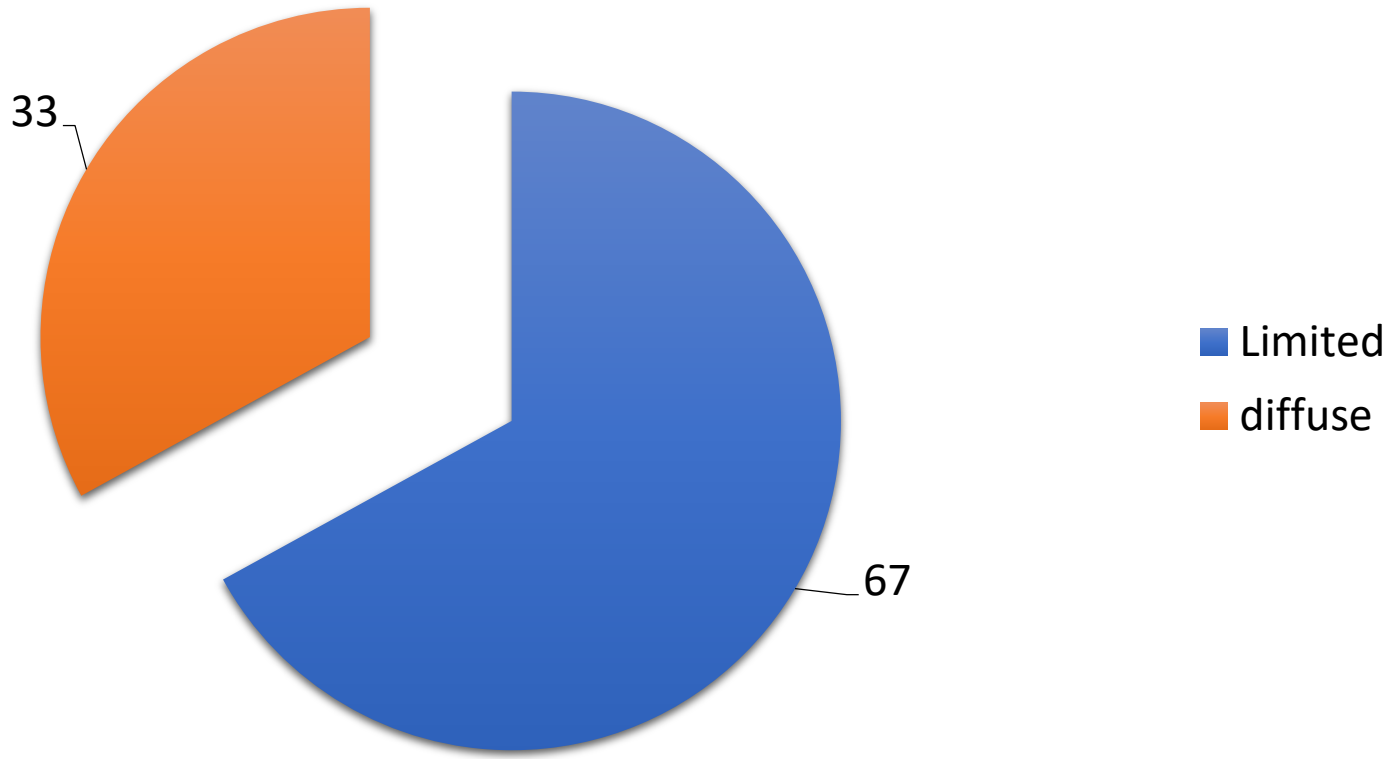


Figure 1. Study cohort. CTD-PH/PAH = connective tissue disease–associated pulmonary hypertension/pulmonary arterial hypertension; DM/PM = dermatomyositis/polymyositis; MCTD = mixed connective tissue disease; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; SSc = systemic sclerosis; UCTD = undifferentiated connective tissue disease; UK-PH = U.K. pulmonary hypertension center.

- SSc is the leading cause of death from PAH amongst the CTD.
- SLE-8%
- SSc- 74%

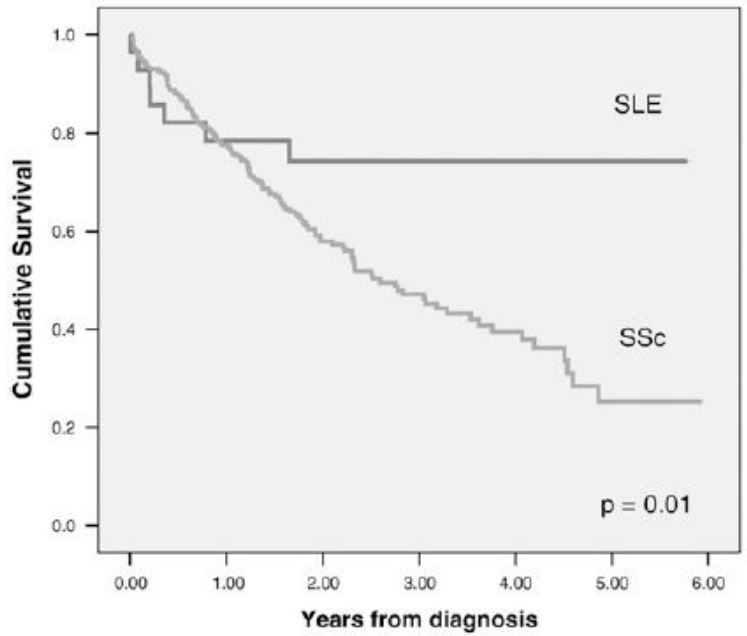
Humbert M, *et al. AJRCMM 2006;173:1023–30*

PAH in SSC



Humbert M, *et al. AJRCMM 2006;173:1023–30*

PAH in SSc worse than SLE

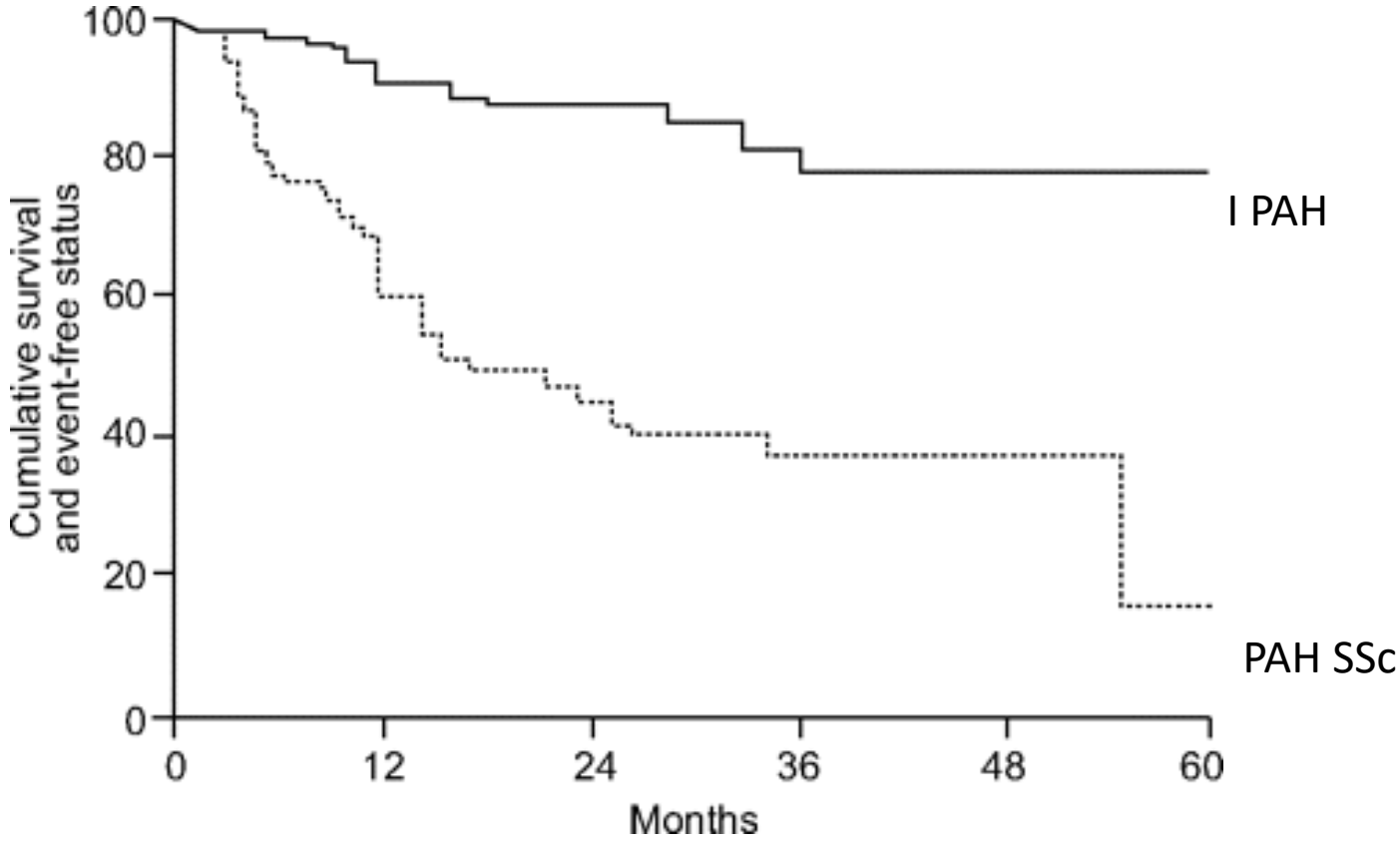


Patients at risk

28	21	15	12	9	2	SLE
259	179	94	53	27	6	SSc

Figure 5. Survival from diagnosis of patients with isolated systemic sclerosis–associated pulmonary arterial hypertension and systemic lupus erythematosus–pulmonary arterial hypertension.

I PAH vs PAH SSc



Kawut et al. chest 2003

PH in SSC causes

Table 2. 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.

Venice 2003 classification of PH

1. Pulmonary arterial hypertension

- **Idiopathic PAH**
- **Heritable**
  - **BMPR2**
  - **ALK1, endoglin**
  - **unknown**
- **Drugs and toxins induced**
- **Associated with:**
  - Connective tissue diseases
  - HIV infection
  - Portal hypertension
  - systemic to pulmonary shunts
  - Schistosomiasis
  - Chronic haemolytic anaemia

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4. Chronic thromboembolic pulmonary hypertension (CTEPH)

5. Pulmonary Hypertension with unclear and/or mulifactorial mechanisms

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  Vasculitis sarcoidosis, pulmonary Langerhans cell histiocytosis LAM, neurofibromatosis.
- **Metabolic disorders**
  Glycogen storage disease, Gaucher disease, thyroid disorders
- **Congenital heart disease**
  other than systemic to pulmonary shunt
- **Others**: *obstruction by tumours, fibrosingmediastinitis, chronic renal failure on dialysis*

PH in Scleroderma can be multifactorial and difficult to asses.

- PVOD- characterised by intimal proliferation and fibrosis of the intrapulm veins and venules.

  Dorfmuller p et al Hum pathol 2007

- PVOD is an under recognised cause of PH in SSc patients.
  Montani D et al Eur Respir J 2009;33:189-200

- SSc-PAH may be charcterised by more frequent coexistent PVOD.
  Dorfmuller p et al Hum pathol 2007

PH in SSc due to left heart failure

ARTHRITIS & RHEUMATISM
Vol. 58, No. 6, June 2008, pp 1803–1809
DOI 10.1002/art.23463

Cardiac Involvement in Systemic Sclerosis Assessed by Tissue-Doppler Echocardiography During Routine Care

A Controlled Study of 100 Consecutive Patients

Christophe Meune, Jérôme Avouac, Karim Wahbi, Laure Cabanes, Julien Wipff, Luc Mouthon, Loïc Guillevin, André Kahan, and Yannick Allanore

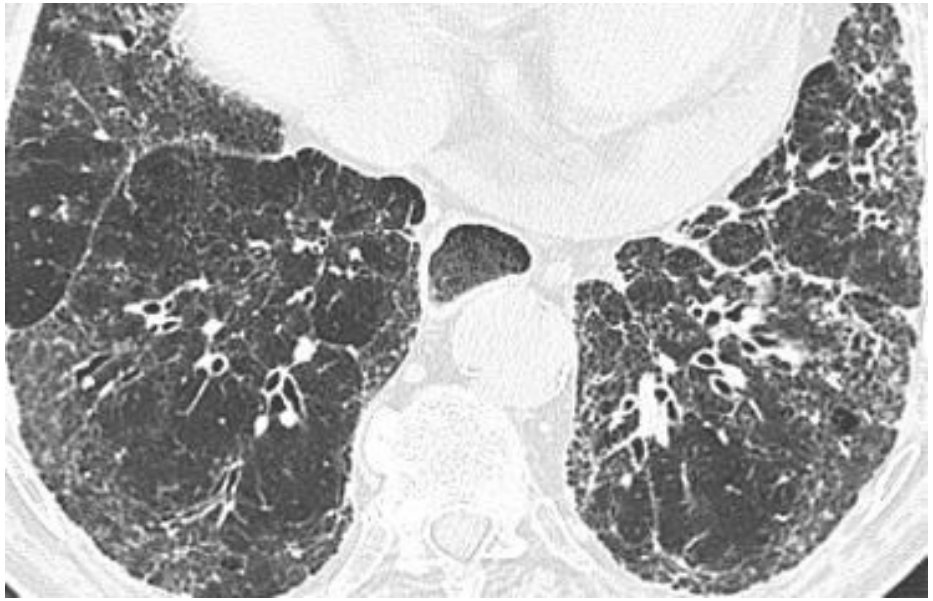
Table 2. Echocardiographic findings in the 100 SSc patients and 26 age- and sex-matched controls*

	SSc patients (n = 100)	Controls (n = 26)	P†
Left ventricular end-diastolic diameter, mm	46.1 ± 0.5	47.1 ± 1.4	0.394
Interventricular septum thickness, mm	9.2 ± 0.2	9.7 ± 0.3	0.198
Posterior wall thickness, mm	8.5 ± 0.2	8.8 ± 0.2	0.330
Left ventricular ejection fraction, %	64.9 ± 0.6	67.2 ± 0.7	0.069
No. with left ventricular ejection fraction <55%	7	0	0.343
Left atrial diameter, mm	34.0 ± 0.5	31.1 ± 1.1	0.020
Transmitral Doppler E/A ratio	1.0 ± 0.3	1.2 ± 0.6	0.038
No. with pericardial effusion	15	1	0.189
Pulmonary arterial pressure, mm Hg	33.3 ± 0.6	30.8 ± 1.0	0.053
No. with pulmonary arterial pressure >40 mm Hg	11	0	0.118
Mitral valve findings, no. of patients			
Regurgitation	48	8	NS
Grade I	45	7	–
Grade II	3	1	–
Stenosis	2	0	NS
Prolapse	2	0	NS
Aortic valve findings, no. of patients			
Insufficiency	18	0	0.023
Grade I	15	0	–
Grade II	3	0	–
Stenosis	3	0	NS
S_M, cm/second	11.0 ± 0.3	12.2 ± 0.5	0.090
No. with S_M <7.5 cm/second	14	0	0.040
No. with E_A <10 cm/second	30	2	0.022
E/E_A ratio	5.9 ± 0.2	5.2 ± 0.3	0.177
No. with S_T <11.5 cm/second	15	0	0.039

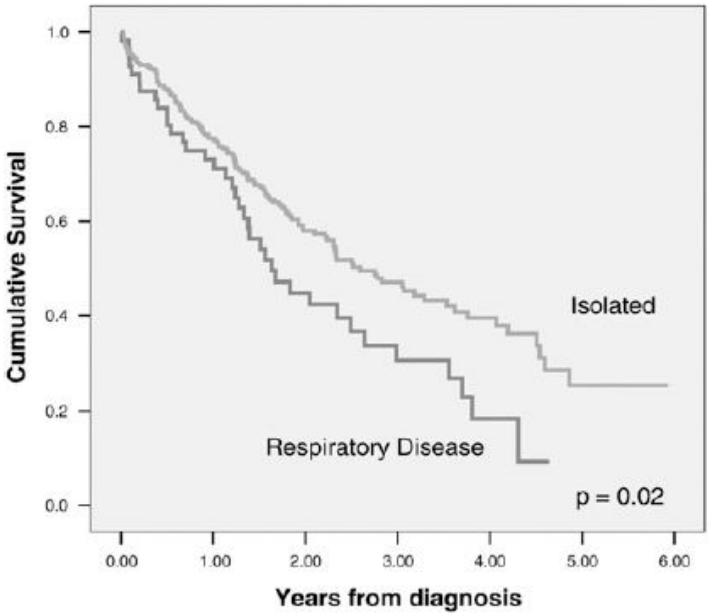
* Except where indicated otherwise, values are the mean ± SD. SSc = systemic sclerosis; S_M = systolic mitral annular velocity; E_A = lateral annulus early diastolic velocity; S_T = systolic tricuspid annular velocity.

† By Student's *t*-test for continuous variables or by chi-square or Fisher's exact test for categorical variables, as appropriate. NS = not significant.

PH due to pulmonary fibrosis



PH-ILD worse than isolated PH

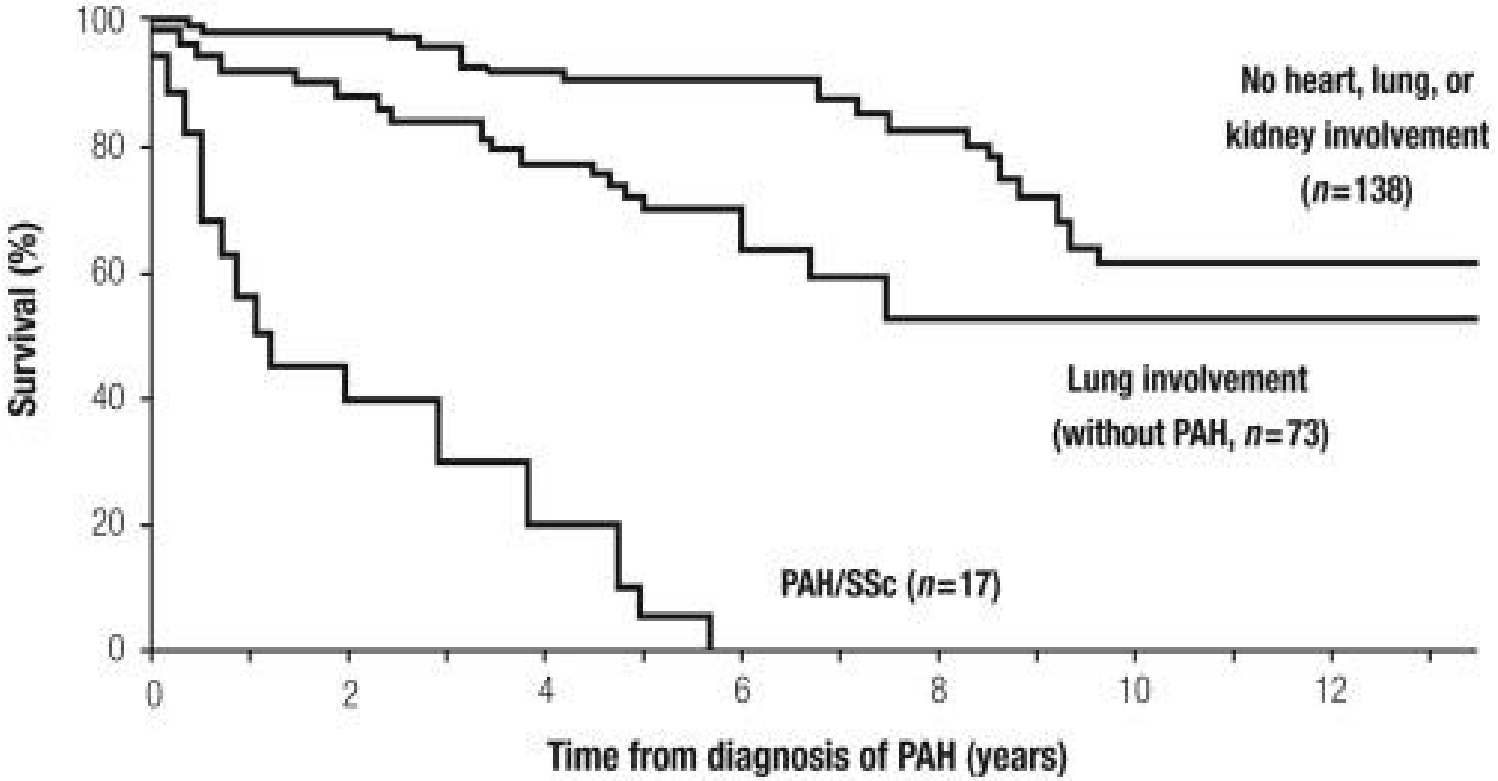


Patients at risk

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.

Why screening



Koh ET, et al Pulmonary hypertension in systemic sclerosis: an analysis of 17 patients. Br J Rheumatol 1996;35:989–93

Methods of screening

Itine´rAIR-Scle´rodermie study

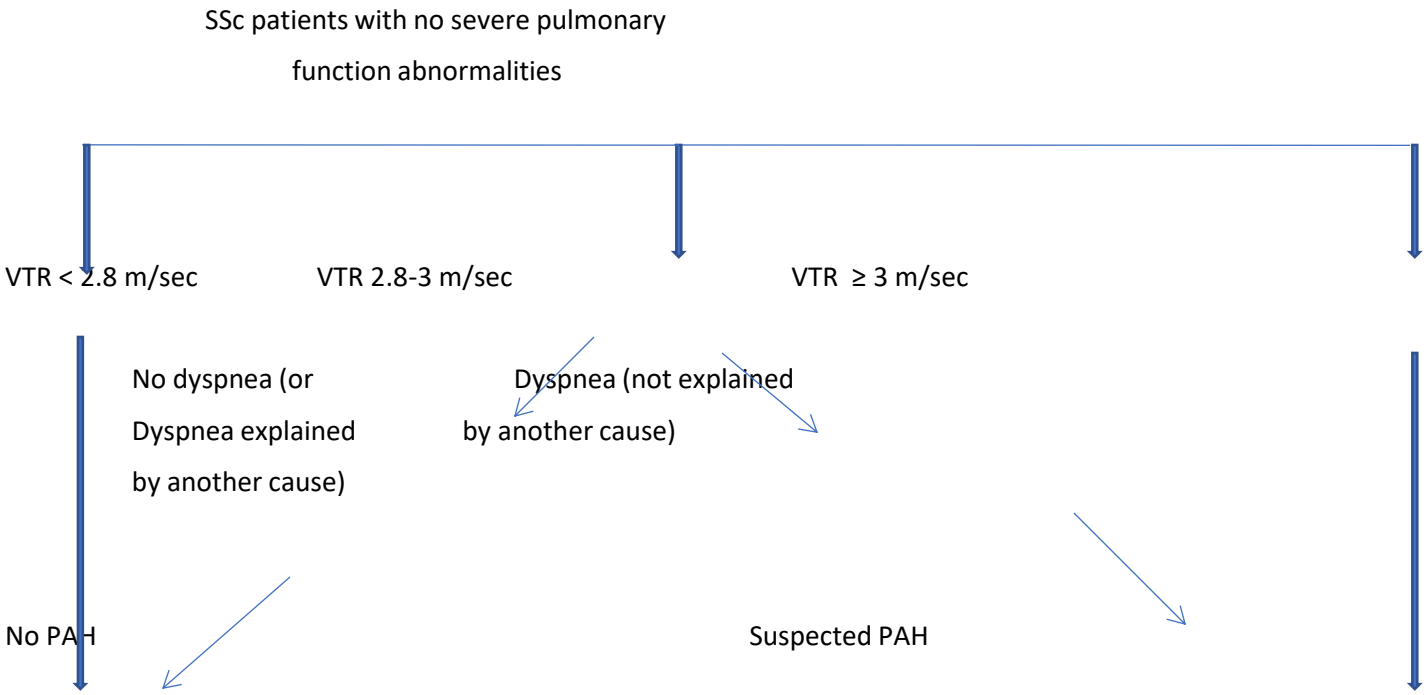
- 559 pts without severe Pulmonary function abnormalities

  underwent Doppler echocardiography.

- Patients with a peak velocity of tricuspid regurgitation (VTR) of >3 m/s or 2.8–3 m/s accompanied by unexplained dyspnoea then underwent right heart catheterization (RHC) to confirm PAH according to international guidelines

Hachulla E et al. ArthritisRheum 2005;52:3792–800.

Doppler echocardiography



VTR : Peak velocity of pulmonary regurgitation

Hachulla E. Arthritis Rheum 2005; 52 (12): 3792-3800

Based on Doppler echocardiography-

33 of the 559 patients had suspected PAH.

RHC

PAH: 18

- 14 had a mPAP ≥ 25 mmHg at rest
- ≥ 25-35 mmHg : 9
- ≥ 35-45 mmHg : 4
- ≥ 45 mmHg : 1
- 4 had a mPAP < 25 mmHg at rest but ≥ 30 mmHg at exercise

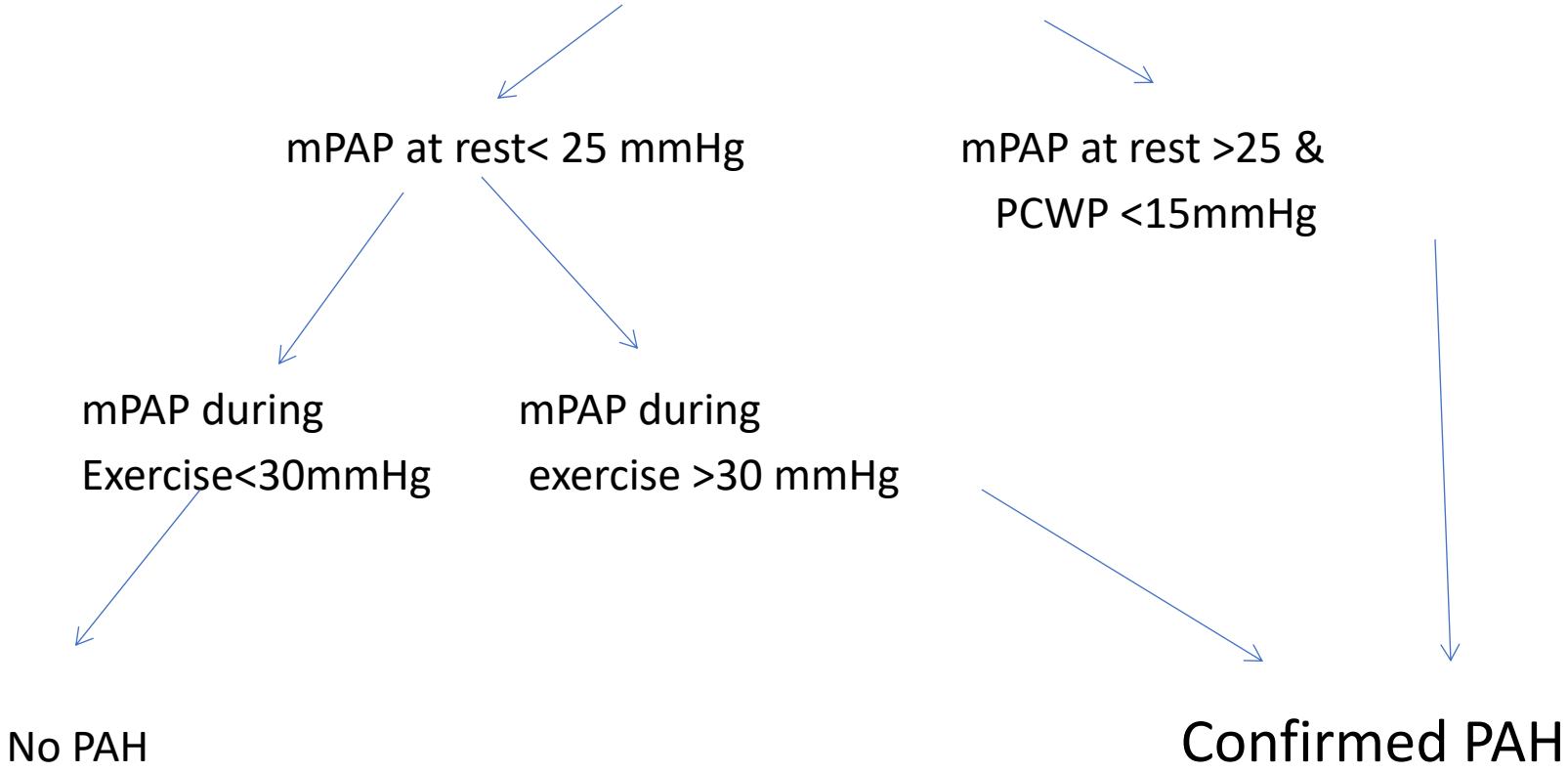
No PAH : 12/33

- 5 had no exercise RHC
- 6 had a mPAP > 20 mmHg

Post capillary PH : 3/33

Right heart catheterization

- Suspected PAH on Doppler echocardiography



Hachulla E. Arthritis Rheum 2005; 52 (12): 3792-3800

Key take home points

- Echo cardiography is a good screening tool.
- Echo cardiography tends to overestimate PAH as compared to RHC.
- PAH can never be diagnosed on ECHO.

Other methods of screening

PHAROS STUDY

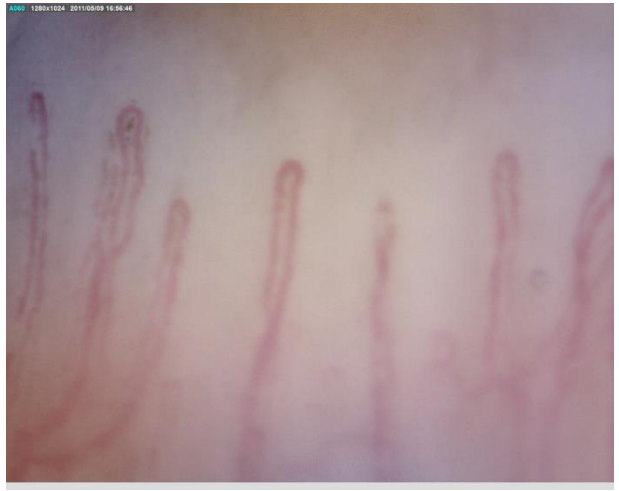
- 2 YR OUTCOME FOR PRE-PAH IN SSc
- ENTRY CRITERIA- DLCO <55%
- ECHO PASP- >40MMHG
- 205 PATIENTS ENROLLED SCREENED ANNUALY
- AFRICAN AMERICAN, AND NUCLEOLAR U3 RNP AB,DLCO
- CONCLUSION- AT 2YRS 22% CUMULATIVE DEV OF PAH IN PATIENTS AT HIGH RISK
- VERY LOW DLCO(40%) WAS THE BEST PREDICTOR
- ECHO PASP VARIABLE OVER TIME DID NOT CORRELATE WITH SPAP ON RHC.

OTHER risk factors for PAH in SSC

- Nt pro-BNP

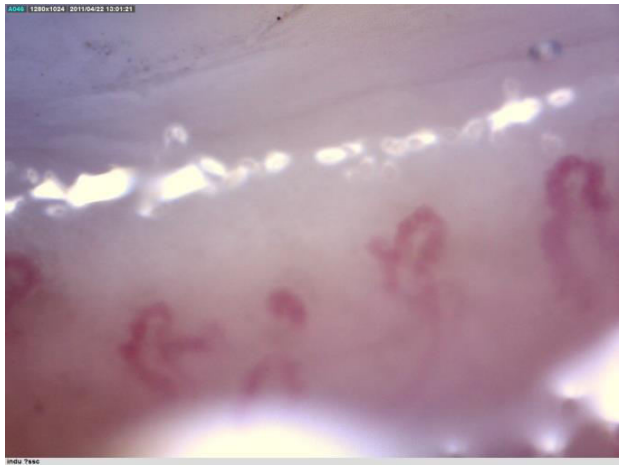
- Telengectasias >10

Nail fold Capillaroscopy

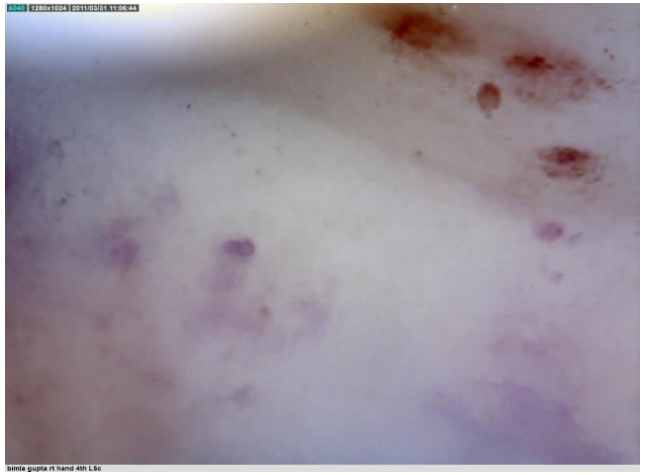


NORMAL

EARLY SSc



ACTIVE SSc



LATE SSc

Not associated with risk of developing PAH

- Digital ulcers
- Digital gangrene
- Renal crisis