PULMONARY HYPERTENSION

DIAGNOSTIC STRATEGY AND MANAGEMENT

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CONFLICT OF INTERESTS

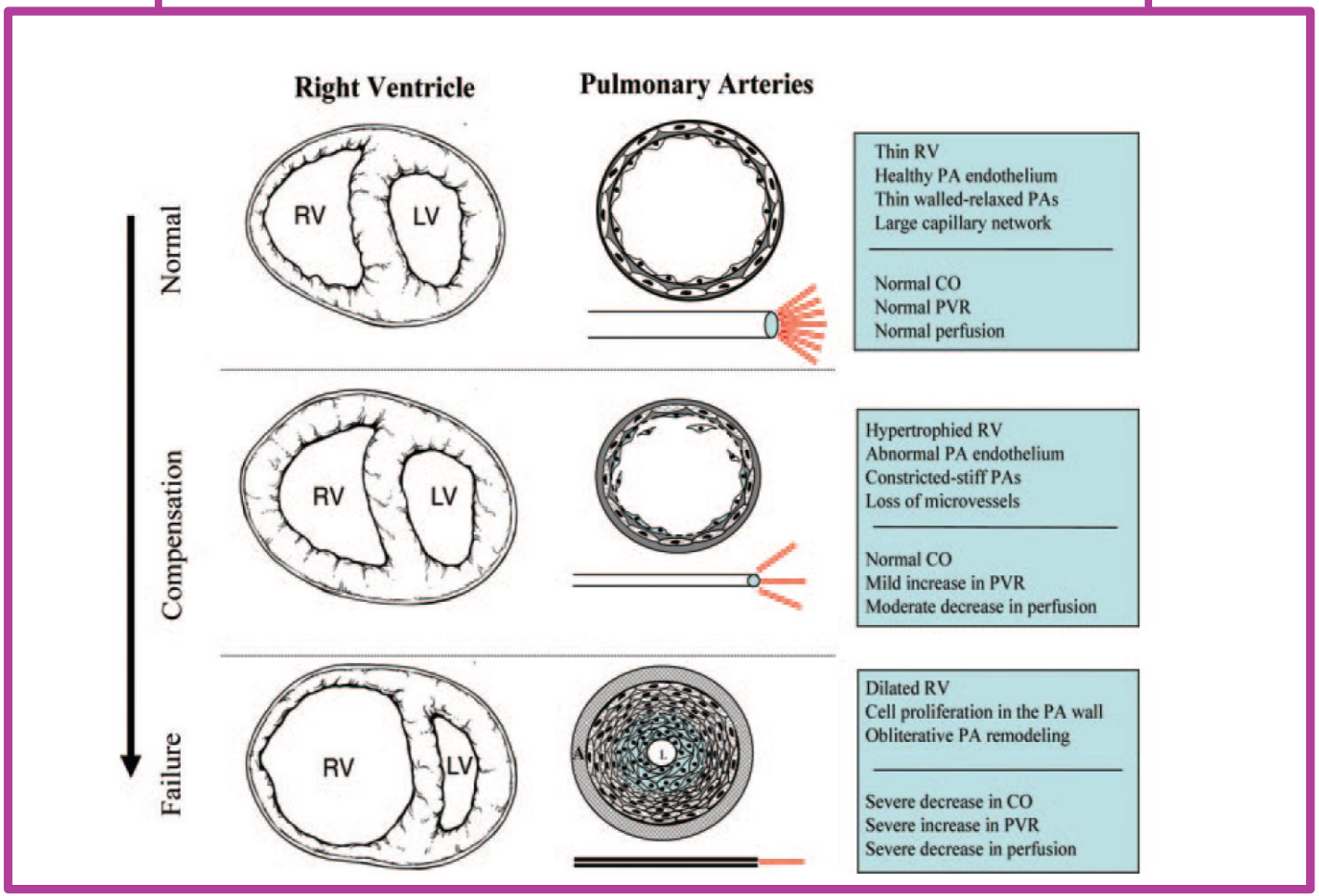
- Advisory Board Member for Actelion Pharmaceuticals, Bayer-Schering, Galenica, Lilly and MSD.
- Consultant fees from Actelion Pharmaceuticals, Bayer-Schering, GlaxoSmithKline and Galenica.
- Honorarium and Speaker fees from Actelion Pharmaceuticals, Bayer-Schering and GlaxoSmithKline.

PULMONARY HYPERTENSION

Haemodynamic & Pathophysiologic Condition

mPAP ≥ 25 mmHg

ESC GUIDELINES 2015



UPDATED CLASSIFICATION OF P.H.

1. Pulmonary ARTERIAL Hypertension

Idiopathic
Heritable (1. BMPR2, 2. ALK-1, ENG, SMAD9, CAV1, KCNK3, 3. Unknown)
Drug and toxin induced
Associated with Connective Tissue Disorder, HIV infection
Portal Hypertension Congenital Heart Diseases
Schistosomiasis

2. P.H. due to Left Heart Disease

3. P.H. due to Lung diseases +/- hypoxia

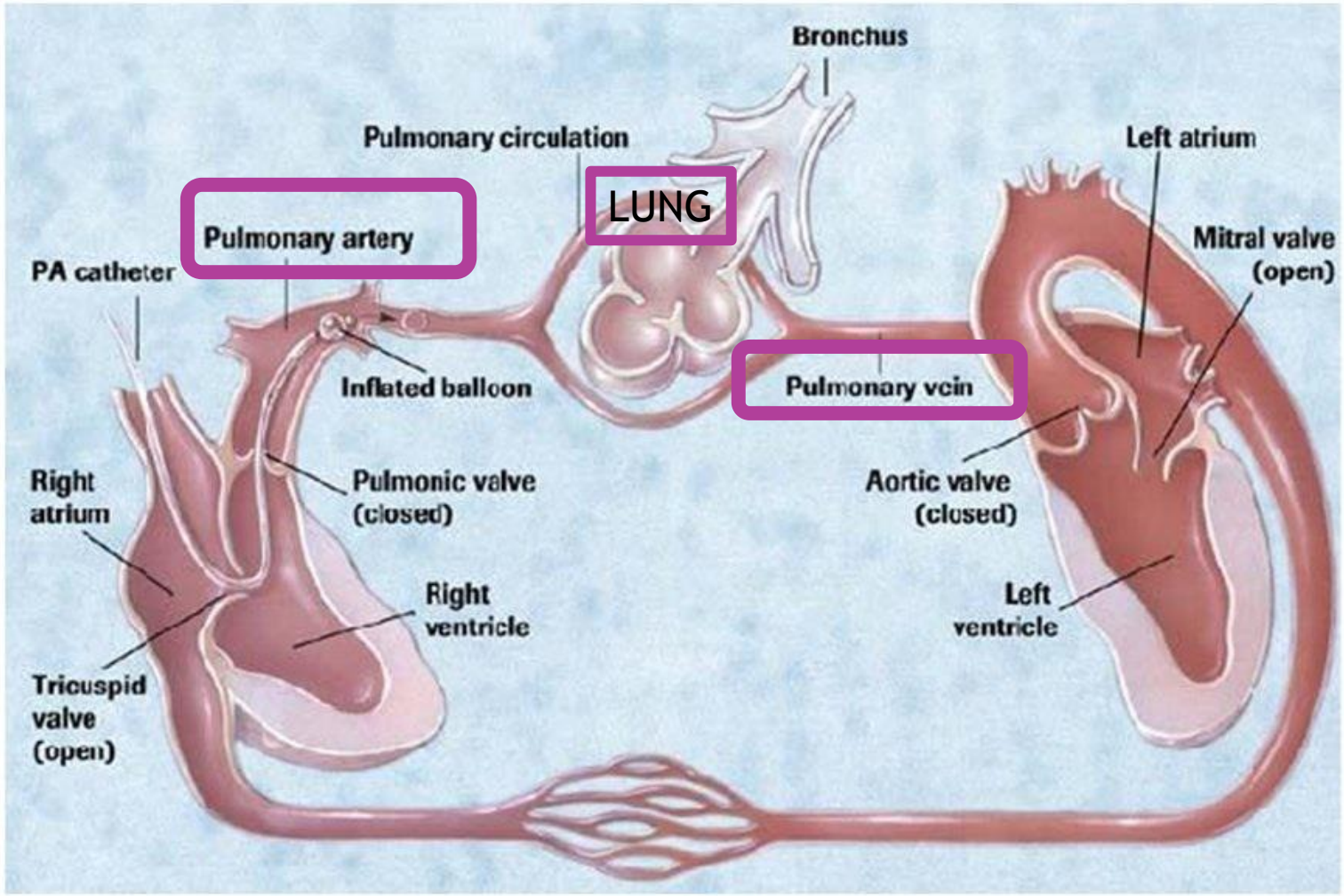
4. Chronic Thromboembolic Pulmonary Hypertension

5. P.H. with unclear multifactorial mechanisms

1. Hematologic disorders: CHA, MPD, Splenectomy
2. Systemic Disorders: sarcoidosis,P histiocytosis, lympangioleiomyomatosis
3. Metabolic disorders: GGD, Gaucher, Thyroid disorders
4. Others: tumoral obstruction, fibrosing mediastinitis, CRF, segmental PH

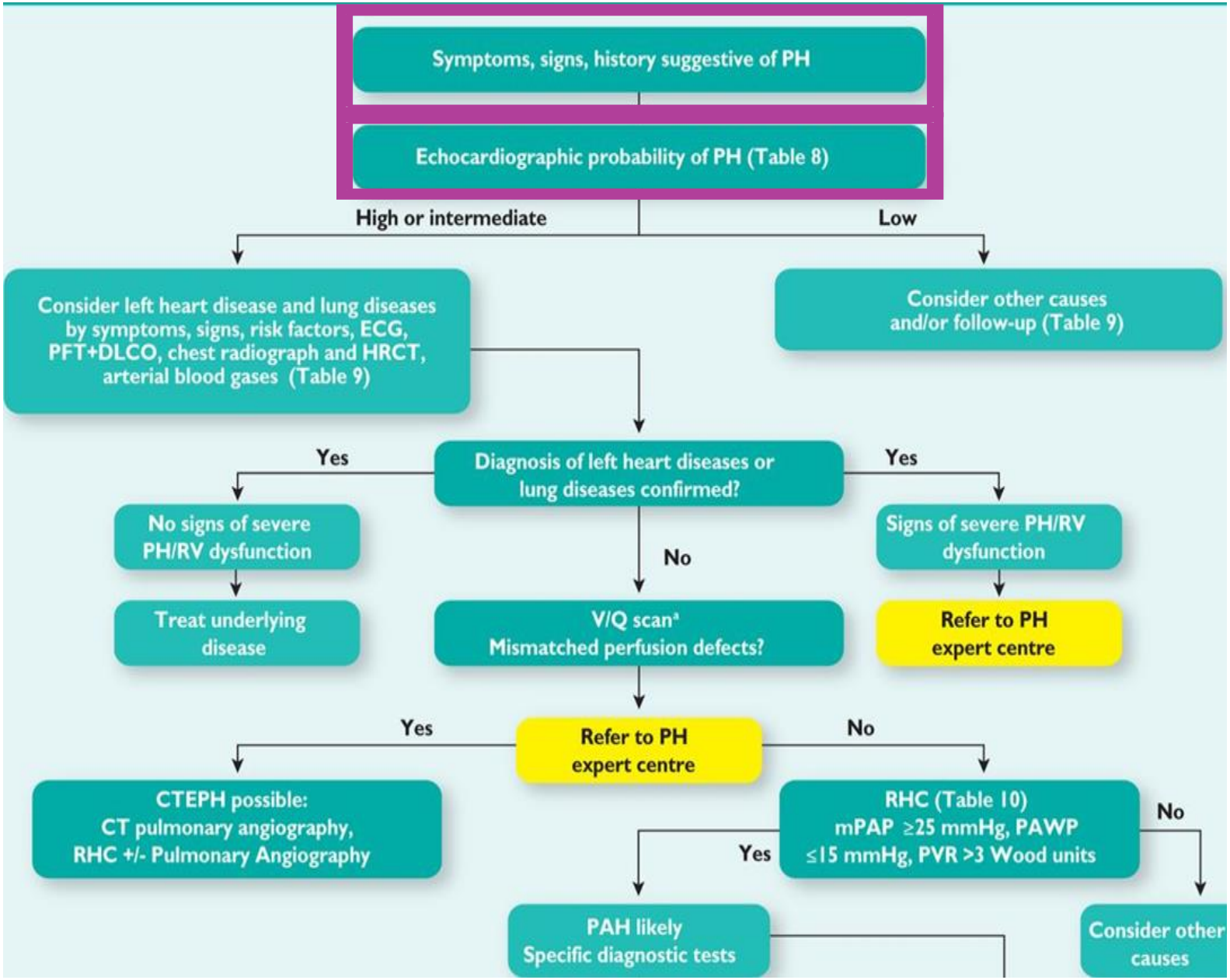
JACC 2013; 62: D42-50

HAEMODYNAMIC ASSESSMENT



mPAP >25mmHg

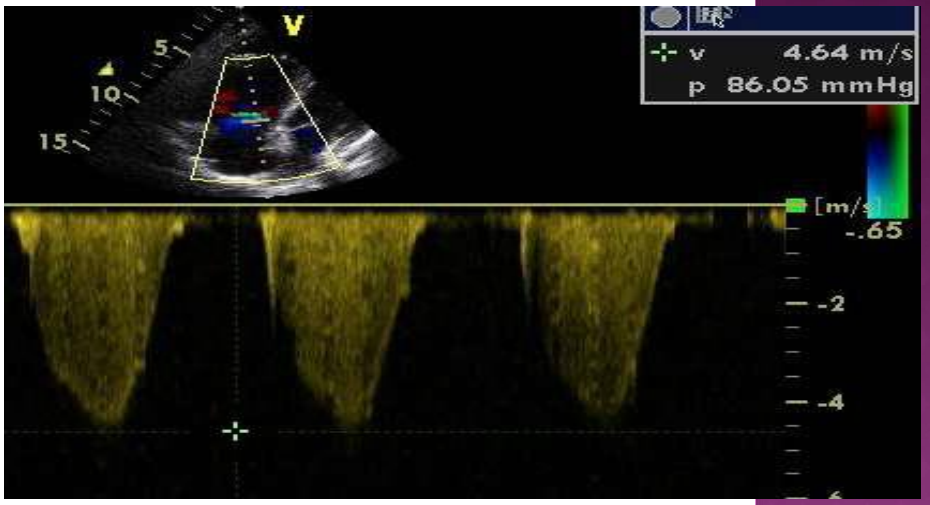
DIAGNOSTIC STRATEGY



Echocardiographic evaluation

Bernoulli equation

PASP: 4 V^2 + RAP



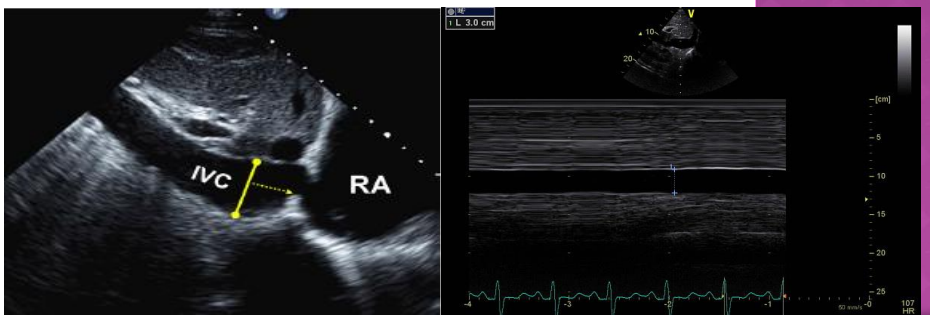
Right atrial pressure

SUBCOSTAL VIEW: IVC in its long axis, end-expiration, 0.5-3.0 cm proximal to the ostium of the RA

IVC < 2.1 cm with > 50% respiratory excursion: 0- 5 mm Hg

Dilated IVC (>2.1cm) with < 50% respiratory excursion: 10 - 20 mm Hg

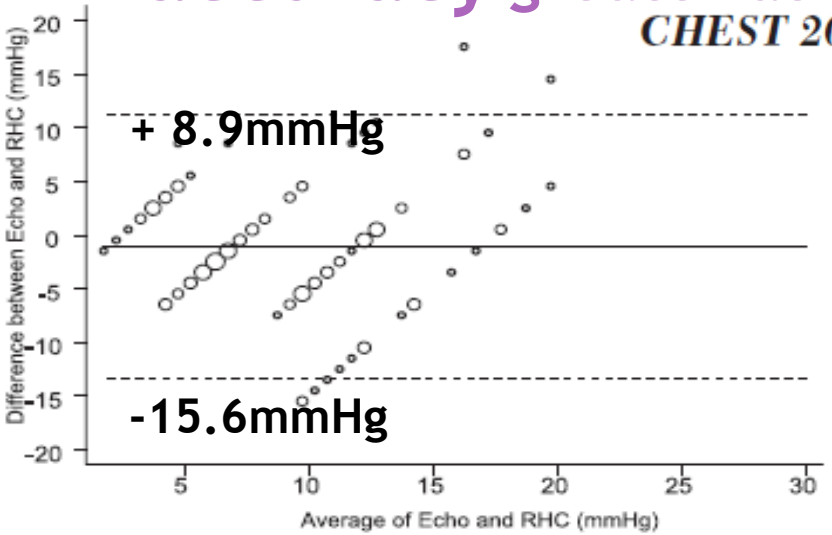
IN OTHER SCENARIOS: RAP: 8 mmHg

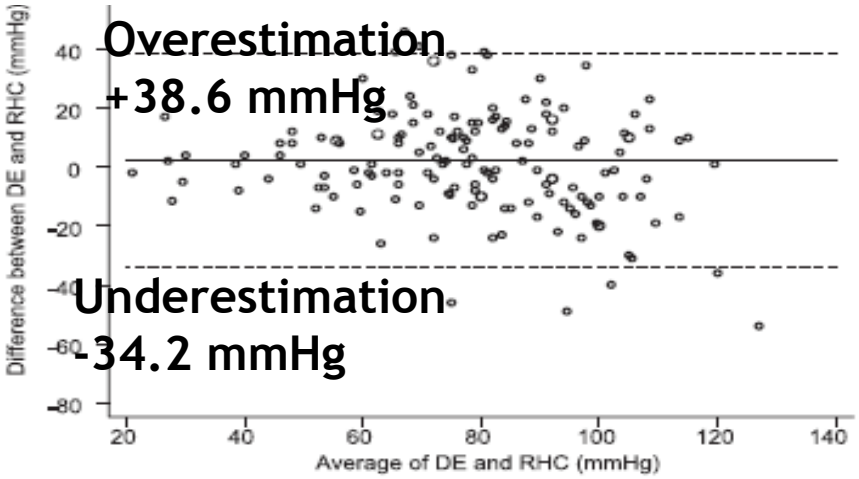


Accuracy of Doppler Echocardiography in the Hemodynamic Assessment of Pulmonary Hypertension

Inaccuracy greater at higher values

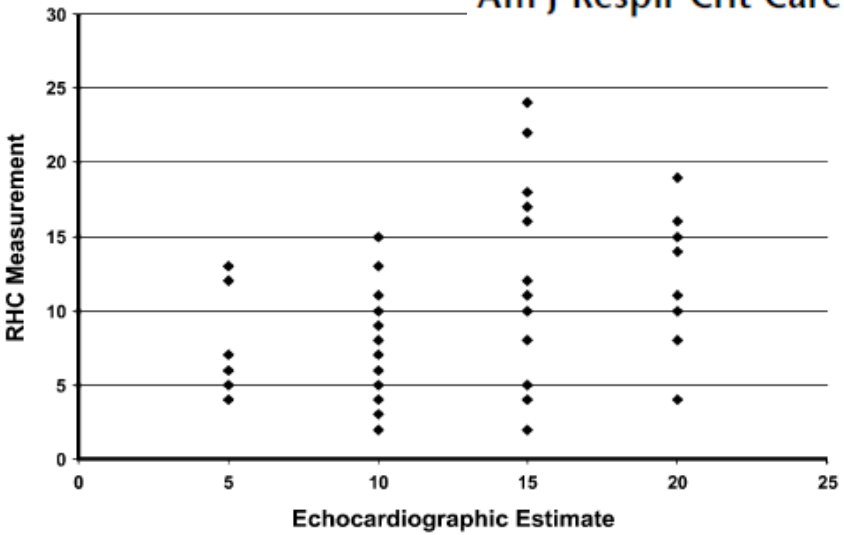
CHEST 2011; 139(5):988–993

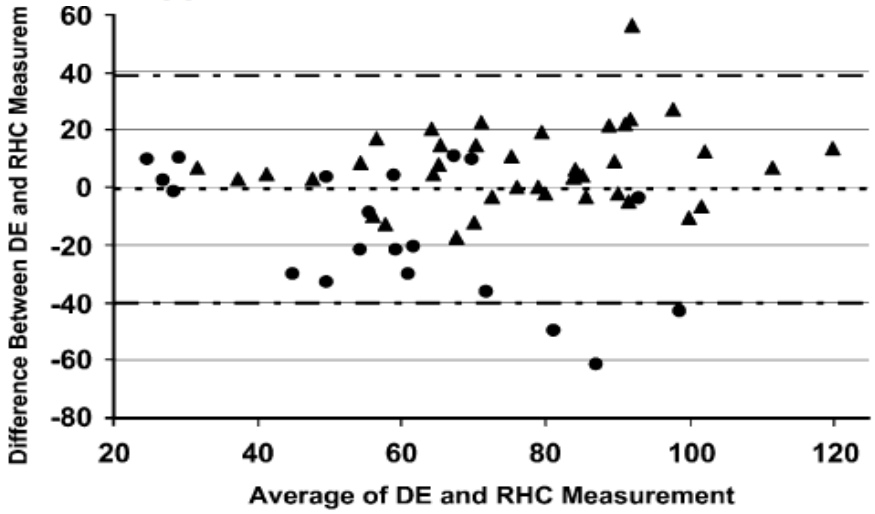




OF THE 6 OF PTS WITH NO TR, 4 OF THESE HAD PH BY RHC

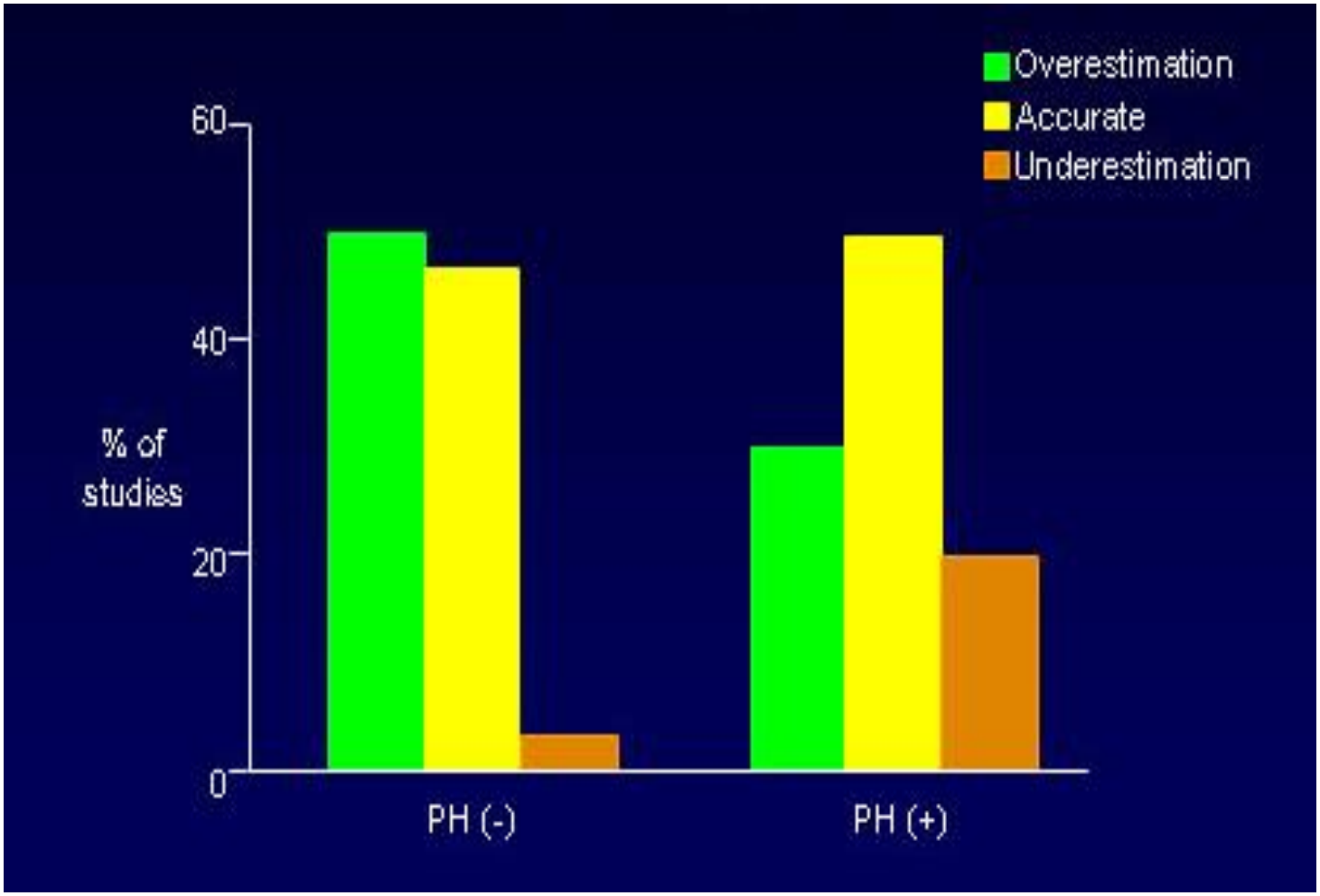
Am J Respir Crit Care Med Vol 179. pp 615–621, 2009





INACCURACY OF PH DIAGNOSIS BY ECHO IN ADVANCED LUNG DISEASE

The echocardiogram was accurate only about 50% of the time



Am J Respir Crit Care Med 2003; 167: 735-740

ECHOCARDIOGRAPHIC PROBABILITY SYMPTOMATIC PATIENT WITH SUSPICION OF PH

Peak tricuspid regurgitation velocity (m/s)	Presence of other echo 'PH signs'[a]	Echocardiographic probability of pulmonary hypertension
≤2.8 or not measurable	No	Low
≤2.8 or not measurable	Yes	Intermediate
2.9–3.4	No	
2.9–3.4	Yes	High
>3.4	Not required	

Eur Heart J. **2015** Aug 29. pii: ehv317. Epub ahead of print

ECHOCARDIOGRAPHIC PROBABILITY & DIAGNOSTIC STRATEGY

Echocardiographic probability of PH	Without risk factors or associated condition for PAH or CTEPH[d]	Class[a]	Level[b]	With risk factors or associated conditions for PAH or CTEPH[c]	Class[a]	Level[b]
Low	Alternative diagnosis should be considered	IIa	C	Echo follow-up should be considered	IIa	C
Intermediate	Alternative diagnosis, echo follow-up, should be considered	IIa	C	Further assessment of PH including RHC should be considered[e]	IIa	B
	Further investigation of PH may be considered[e]	IIb				
High	Further investigation of PH (including RHC[e]) is recommended	I	C	Further investigation of PH[e] including RHC is recommended	I	C

DIAGNOSTIC APPROACH TO PH

SYMPTOMS, SIGNS, HISTORY suggestive of PH

1 ECHOCARDIOGRAM COMPATIBLE WITH PH

2 LEFT HEART OR

3 LUNG DISEASE ?

- → UNDERLYING DISEASE
- → IF SIGNS OF SEVERE PH DISEASE→ EXPERT CENTER

4 V/Q SCINTIGRAPHY → CTEPH → EXPERT CENTER

RHC +/- ANGIO

PAH LIKELY →

- CTD
- PORTOPULMONARY
- SCHISTOSOMIASIS
- HIV
- PVOD, PCH
- DRUGS, TOXINS

JACC 2013; 62: D42-50

PULMONARY HYPERTENSION GROUP 2

2. Pulmonary hypertension due to left heart disease

2.1 Left ventricular systolic dysfunction
2.2 Left ventricular diastolic dysfunction
2.3 Valvular disease
2.4 Congenital / acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
2.5 Congenital /acquired pulmonary veins stenosis

SSc vascular lesions result in general impairment of the microcirculation

The **EUSTAR registry** collected data from 7073 consecutive patients (mean age 56±14 years) and demonstrated an overall **5.4% prevalence of reduced LVEF**

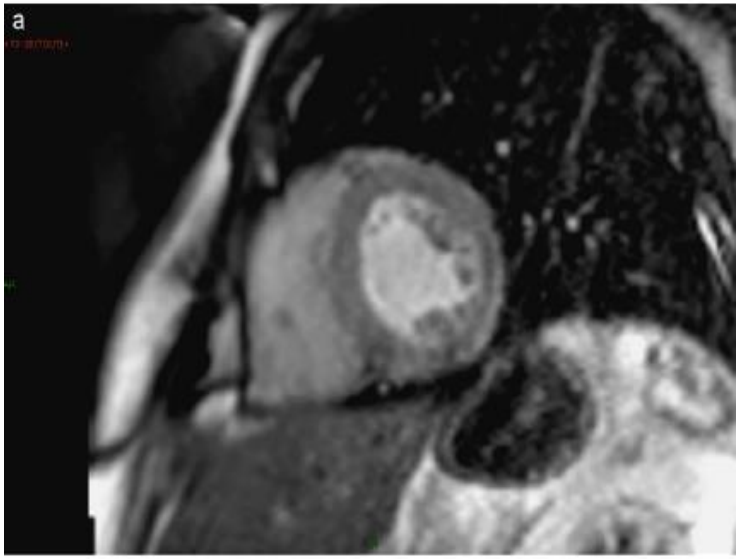
The prevalence of **diastolic dysfunction** was increased compared with age and sex-matched controls [9], and **ranged from 17 to 30%**

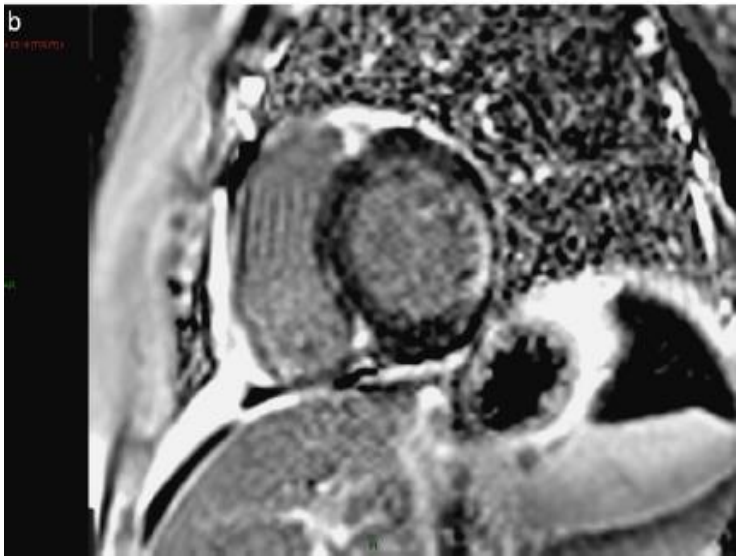
ECHOCARDIOGRAPHY IN PAH-SSC

	IPAH (n=38)	PAH-SSc (n=49)	*p* Value
RA dilation (%)	81.6	73.5	0.37
RV dilation (%)	89.5	79.6	0.21
RVH (%)	18.4	10.2	0.27
LAD (mean ± SEM)	3.3 ± 0.2	3.8 ± 0.1	0.004
LVH (%)	13.2	34.7	0.039
LVEF (mean ± SEM)	57.3 ± 1.6	55.7 ± 1.4	0.44
Diastolic dysfunction	13.2	32.7	0.035
Pericardial effusion	13.2	34.7	0.022

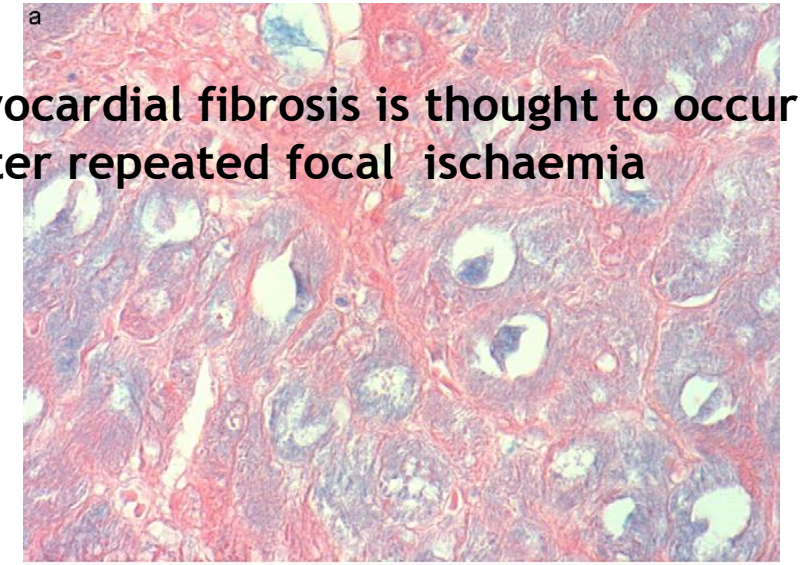
Fisher MR et al. *Arthritis Rheum*. 2006;54:3043-3050.

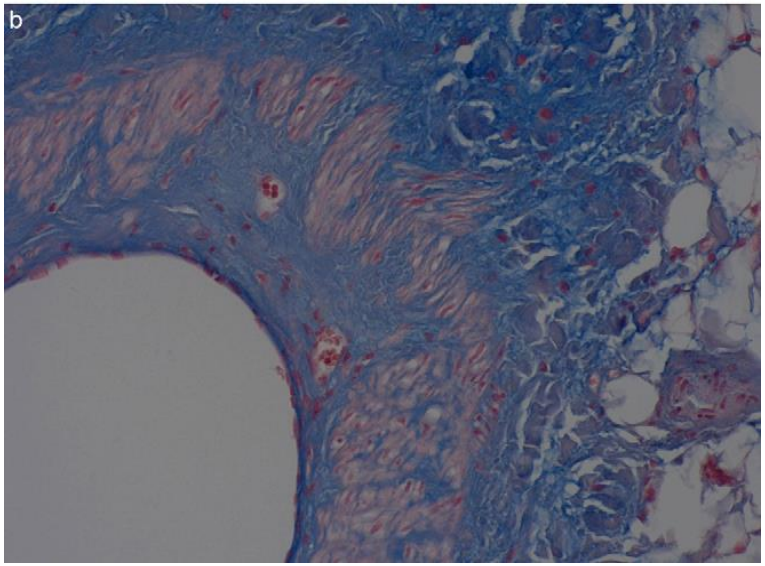
MYOCARDIAL FIBROSIS





Myocardial fibrosis is thought to occur after repeated focal ischaemia





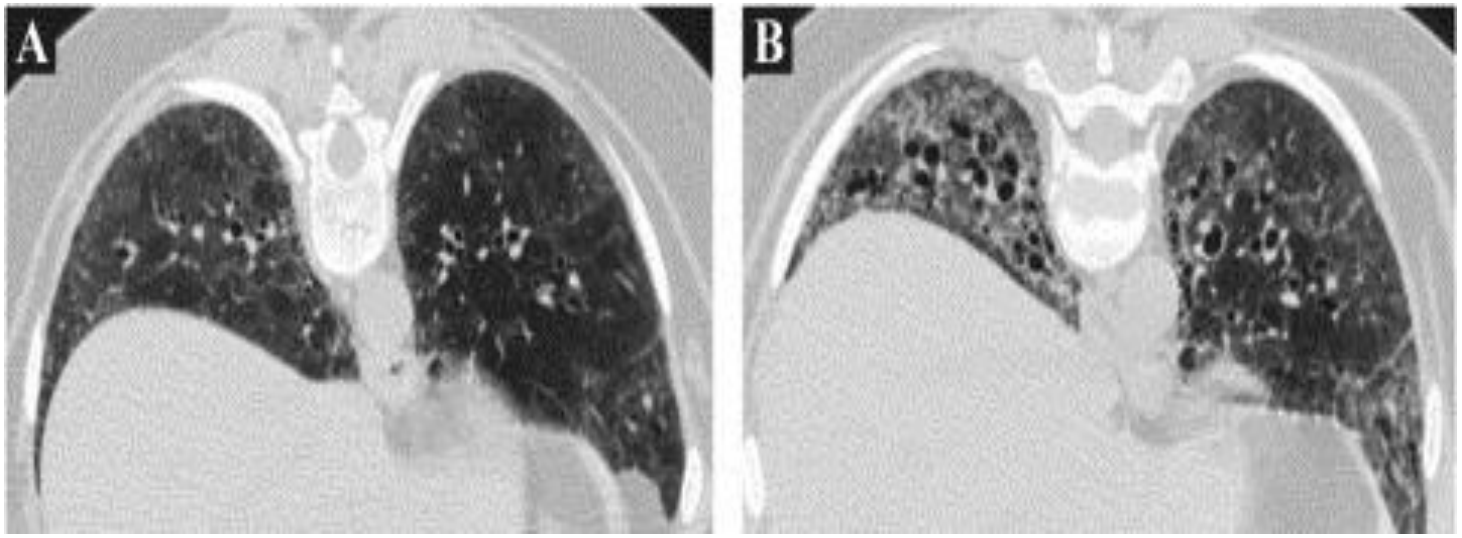
GROUP 3 PH

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

- 3.1 Chronic obstructive pulmonary disease
- 3.2 Interstitial lung disease
- 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
- 3.4 Sleep-disordered breathing
- 3.5 Alveolar hypoventilation disorders
- 3.6 Chronic exposure to high altitude
- 3.7 Developmental lung diseases (Web Table III)

CTD-associated ILD, with a focus on systemic sclerosis (SSc),
rheumatoid arthritis (RA), and
idiopathic inflammatory myopathy (IIM)

PULMONARY FIBROSIS



In the Scleroderma Lung Study, there were no significant differences in the frequency of alveolitis on HRCT scan between lcSSc and dcSSc, suggesting that all patients with SSc are at risk for ILD

More pulmonary fibrosis was seen in the dcSSc group (53% v 30%)
EULAR Scl trials and EUSTAR group

GROUP 3. HAEMODYNAMIC CLASSIFICATION

COPD/IPF/CPFE

WITH PH: mPAP>25mmHg

WITH SEVERE PH: mPAP > 25mmHg with low C.I.
mPAP > 35mmHg

WITHOUT PH mPAP<25mmHg

CPFE	+	+ mPAP	> 25 mmHg
COPD	+ FEV1 < 60%	+ mPAP	> 25mmHg
IPF	+ FVC < 70%	+ mPAP	> 25mmHg

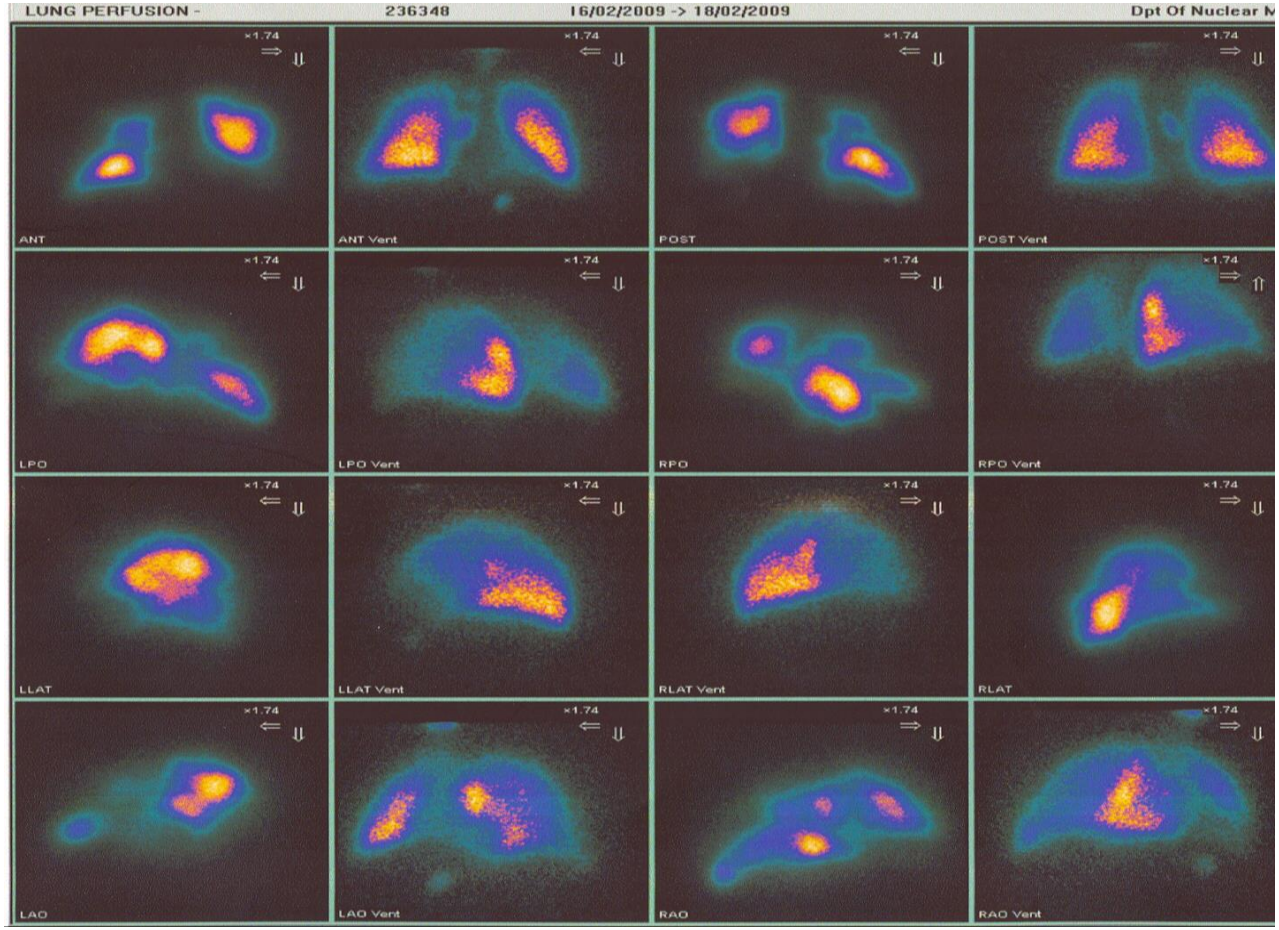
→ PH GROUP 3

RHC is indicated : Clinical worsening and progressive exercise limitation disproportionate to ventilator impairment
(alternative diagnosis-PAH,CTEPH,LV dysfunction)

V/Q SCAN FOR SCREENING (INITIAL STEP)

Sensitivity > 96% (CTPA: sensitivity 51%)

less radiation exposure, no complications related to i.v. contrast, cost benefit, less likelihood for detection of incidental findings, less training



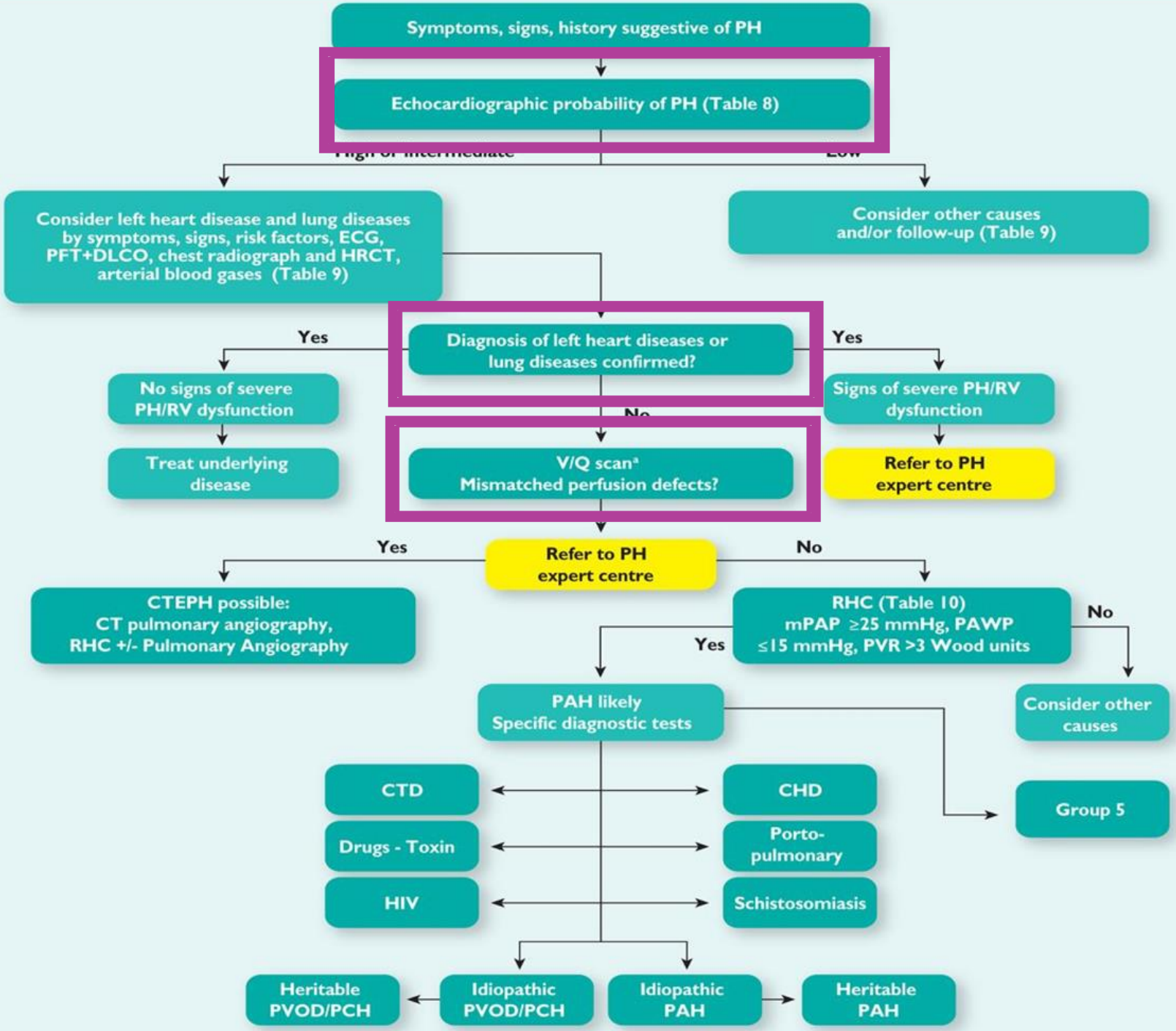
J Am Coll Cardiol 2013; 62:D92-9

J Nucl Med 2007; 48:680–684

ANTIPHOSPHOLIPID ANTIBODIES IN SSC

- N=108
- 14% anticardiolipin and/or β2-glycoprotein I
- Presence of antibodies associated with PAH (p=0.009) and endothelial injury[1]
- Historical risk: 52%
- Prospective risk: 3-7%/year/APL[2,3,4]

1. Assous N et al. *Clin Exp Rheumatol*. 2005;23:199-204.
2. Swadzba J et al. *Pol Merkur Lekarski*. 1996;1:310-312.
3. Finazzi G et al. *Am J Med*. 1996;100(5):530-536.
4. Cervera R et al. *Medicine*. (Baltimore) 1999;78(3):167-175.


Symptoms, signs, history suggestive of PH
Echocardiographic probability of PH (Table 8)
Consider left heart disease and lung diseases by symptoms, signs, risk factors, ECG, PFT+DLCO, chest radiograph and HRCT, arterial blood gases (Table 9)
Consider other causes and/or follow-up (Table 9)
Diagnosis of left heart diseases or lung diseases confirmed?
Yes
No signs of severe PH/RV dysfunction
Treat underlying disease
Yes
Signs of severe PH/RV dysfunction
Refer to PH expert centre
No
V/Q scan[a] Mismatched perfusion defects?
Yes
Refer to PH expert centre
No
CTEPH possible: CT pulmonary angiography, RHC +/- Pulmonary Angiography
RHC (Table 10) mPAP ≥25 mmHg, PAWP ≤15 mmHg, PVR >3 Wood units
Yes
No
PAH likely Specific diagnostic tests
Consider other causes
CTD
CHD
Drugs - Toxin
Porto-pulmonary
HIV
Schistosomiasis
Group 5
Heritable PVOD/PCH
Idiopathic PVOD/PCH
Idiopathic PAH
Heritable PAH

RIGHT HEART CATHETERIZATION IS MANDATORY

BEFORE P.A.H. SPECIFIC DRUG INITIATION

PULMONARY ARTERIAL HYPERTENSION

clinical condition
pathophysiologic condition
HAEMODYNAMIC CONDITION

mPAP ≥25 mmHg, **PAWP≤ 15 mmHg,** PVR > 3 WU

PULMONARY ARTERIAL HYPERTENSION

Idiopathic

Heritable 1. BMPR2,
2. ALK1, ENG, SMAD9, CAV1, KCNK3
3.Unknown

Drug and toxin induced

Associated with

CONNECTIVE TISSUE DISORDER
CHD
HIV
Portal Hypertension
Schistosomiasis

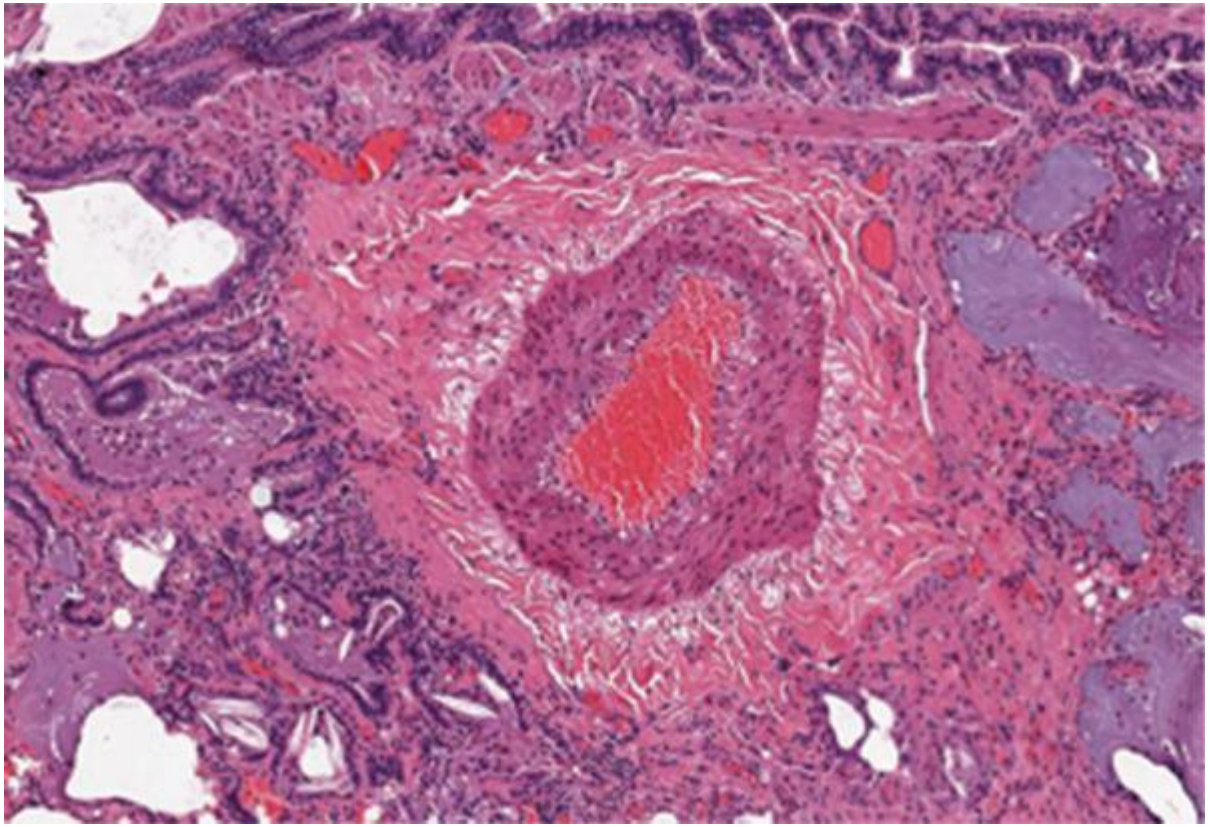
EPIDEMIOLOGY AND BURDEN OF DISEASE

- PAH is rare
  - Estimated prevalence of 15-50 cases per million[a]
- Idiopathic PAH[b,c]
  - Annual incidence is approximately 1-2 cases per million people in Europe and the United States
  - 2-4 times more common in women vs men
- Prevalence is higher in at-risk groups[d-g]
  - Systemic sclerosis (~7%-12%)
  - HIV infection (0.5%)
  - Schistosomiasis (~5%)

a. Peacock AJ, et al. *Eur Respir J.* 2007;30:104-109; b. Gaine SP, et al. *Lancet.* 1998;352:719-725; c. Badesch DB, et al. *Chest.* 2010;137:376-387; d. Hachulla E, et al. *Arthritis Rheum.* 2005;52:3792-3800; e. Mukerjee D, et al. *Ann Rheum Dis.* 2003;62:1088-1093; f. Sitbon O, et al. *Am J Respir Crit Care Med.* 2008;177:108-113; g. Lapa M, et al. *Circulation.* 2009;119:1518-1523.

Is PAH really a late complication of systemic sclerosis?

Chest 2009 Nov;136(5):1211-9



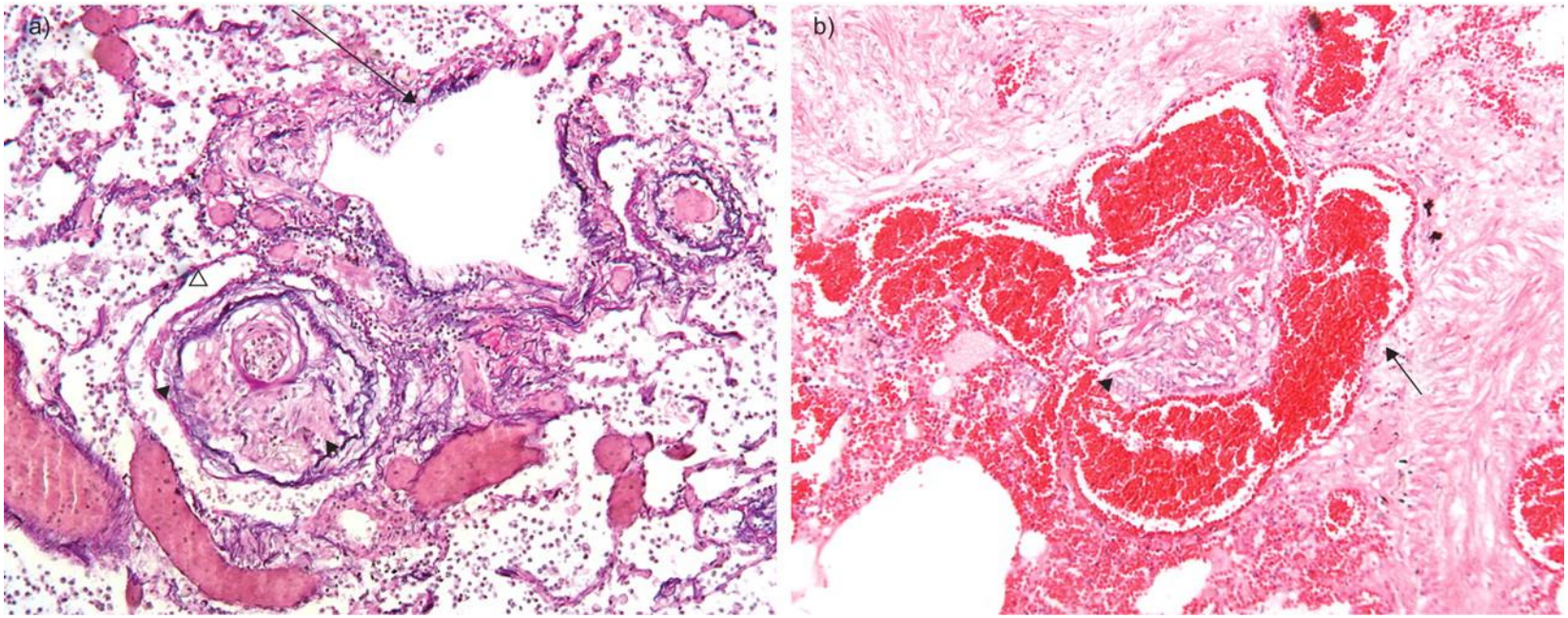
A pulmonary arteriole from a patient with systemic sclerosis-associated pulmonary artery hypertension showing significant medial hypertrophy

PAH in limited cutaneous systemic sclerosis: a distinctive vasculopathy

Eur Respir J 2009;34:371-379

Early-onset PAH is as frequent among patients with diffuse SSc as those with limited SSc

a) Single lesion in the systemic sclerosis-associated pulmonary arterial hypertension (PAH) group mostly resembling a plexiform lesion : localisation adjacent to a bronchiolus (arrow); intimal fibrosis with recanalisation (black arrowheads)...



PAH was almost equal (19% v 17%) in dSc and LSc

EULAR Scl trials and EUSTAR group.

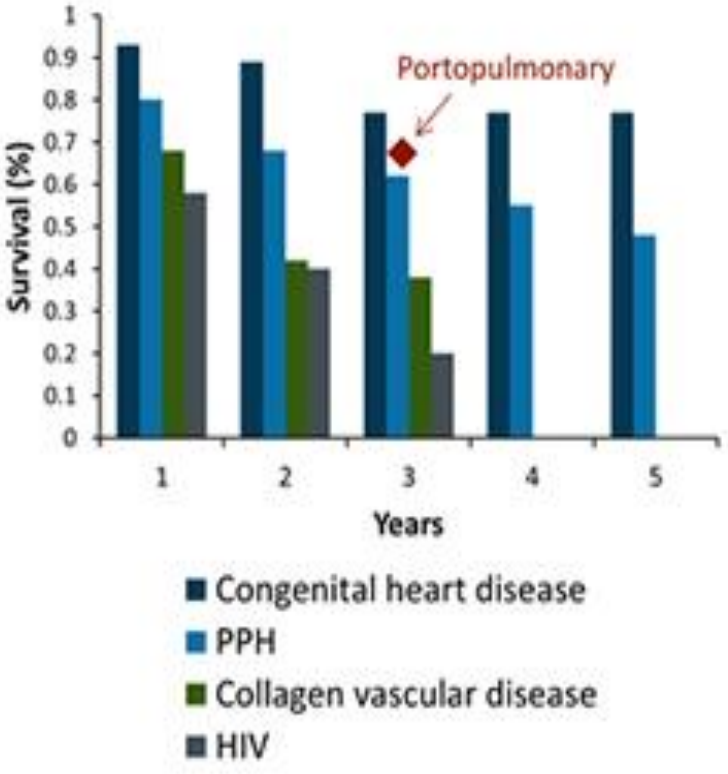
PAH REGISTRIES

Registry (Ref. #)	Study Cohort	Predominant Etiologies of PAH
U.S. NIH (17,18)	IPAH	NA
U.S. PHC (19)	Group 1 PH, age >18 yrs	IPAH, 48%; CTD-PAH, 30%; CHD-PAH, 11%
Scottish-SMR (20)	Group 1 PH (IPAH, CHD-PAH, and CTD-PAH), age 16–65 yrs	IPAH, 47%; CTD-PAH, 30%; CHD-PAH, 23%
French (9,21,22)	Group 1 PH, age >18 yrs	IPAH, 39%; CTD-PAH, 15% (SSc, 76%); CHD-PAH, 11%
Chinese (23)	IPAH and HPAH	NA
U.S. REVEAL (8,24–33)	Group 1 PH	IPAH, 46%; CTD-PAH, 25% (SSc, 62%); CHD-PAH, 10%
Spanish (34)	Group 1 PH and CTEPH, age >14 yrs	IPAH, 30%; CTD-PAH, 15% (SSc 61%); CHD-PAH, 16%
UK (6,35)	IPAH, HPAH, and anorexigen-associated PAH	NA
New Chinese Registry (36,37)	Group 1 PH, age >18 yrs	CHD-PAH, 43%; IPAH, 35%; CTD-PAH, 19% (SLE, 51%; SSc, 9%)
Mayo (38)	Group 1 PH	IPAH, HPAH 56%; CTD-PAH, 24%, other, 20%
Compera (39)	IPAH, age >18 yrs	IPAH, 100%

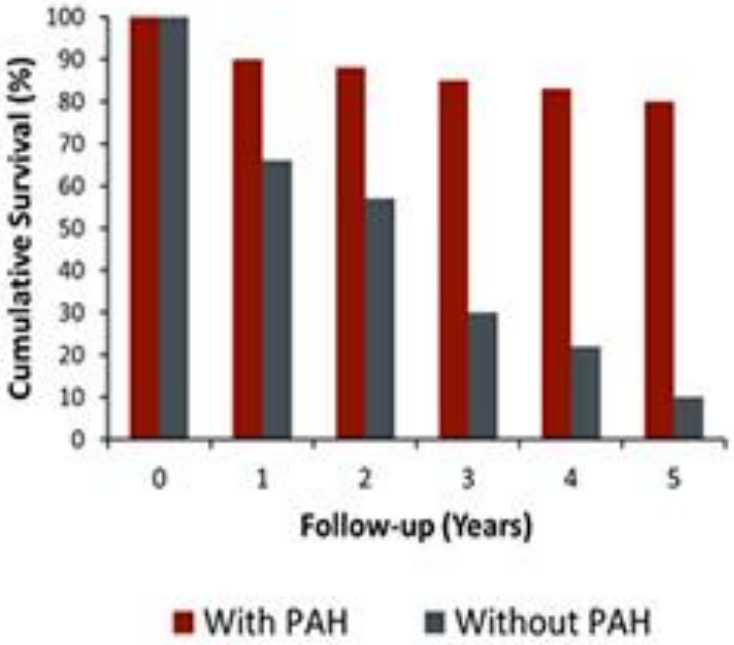
PAH Europe: Prevalence 15-60 subjects / million population
Incidence 5-10 cases / million / year

OUTCOMES IN PAH

Survival in Patients With Various Origins of PAH



Survival of Scleroderma Patients With and Without PAH



McLaughlin VV, et al. *Circulation*. 2006;114:1417-1431.

PAH: PREDICTORS OF SURVIVAL

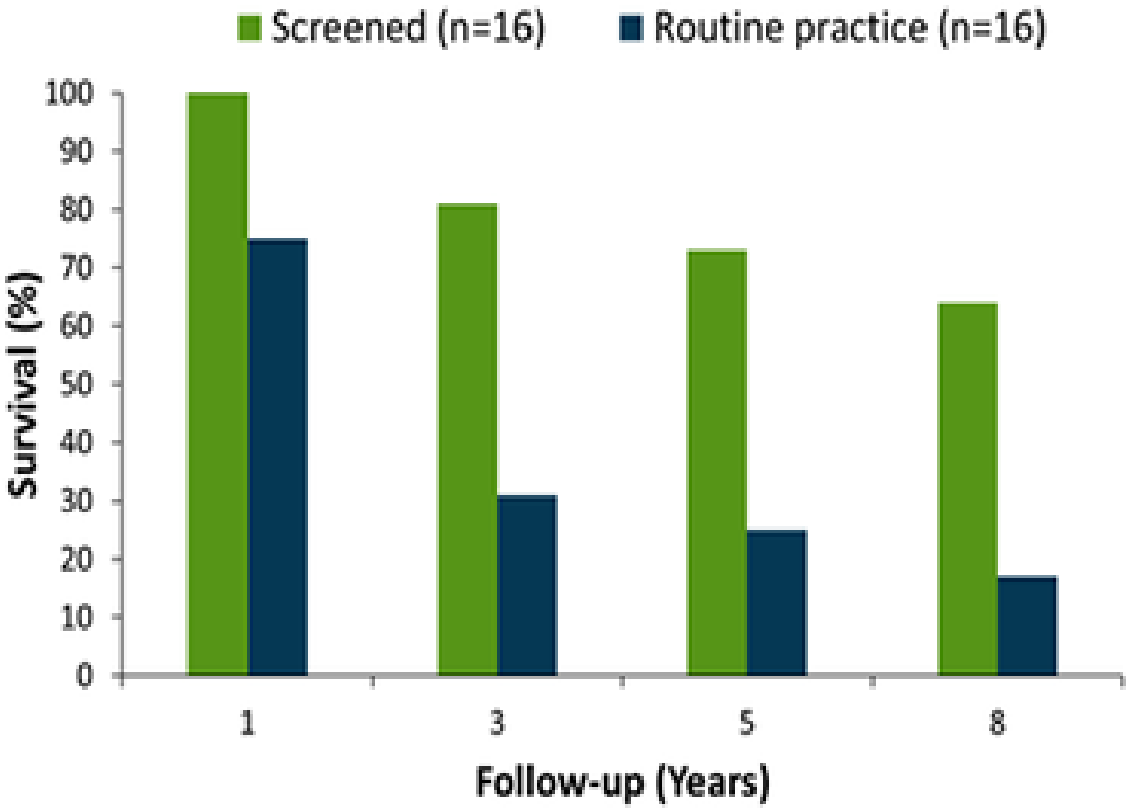
Table 4 Multivariate Predictors of Survival

Category	Increase Risk
Demographics	Sex (male) and age interaction (>65 yrs) (9,27,33,40)
	Age (6,19)
	Male (6,9,27,34)
	Etiology: CTD, (6,19,27,34,37,40)
	PoPH, (6,34,40); HPAH, (27,40); PVOD (6,34)

JACC 2013; 62:25

6. Eur Respir J 2012; 40: 604-11
19. Eur Respir J 2010; 35: 1079-87
27. Circulation 2010; 122: 164-72
34. Eur Respir J 2012; 40:596-603
37. Chest 2011; 140:301-9
40. Chest 2012; 141:354-62

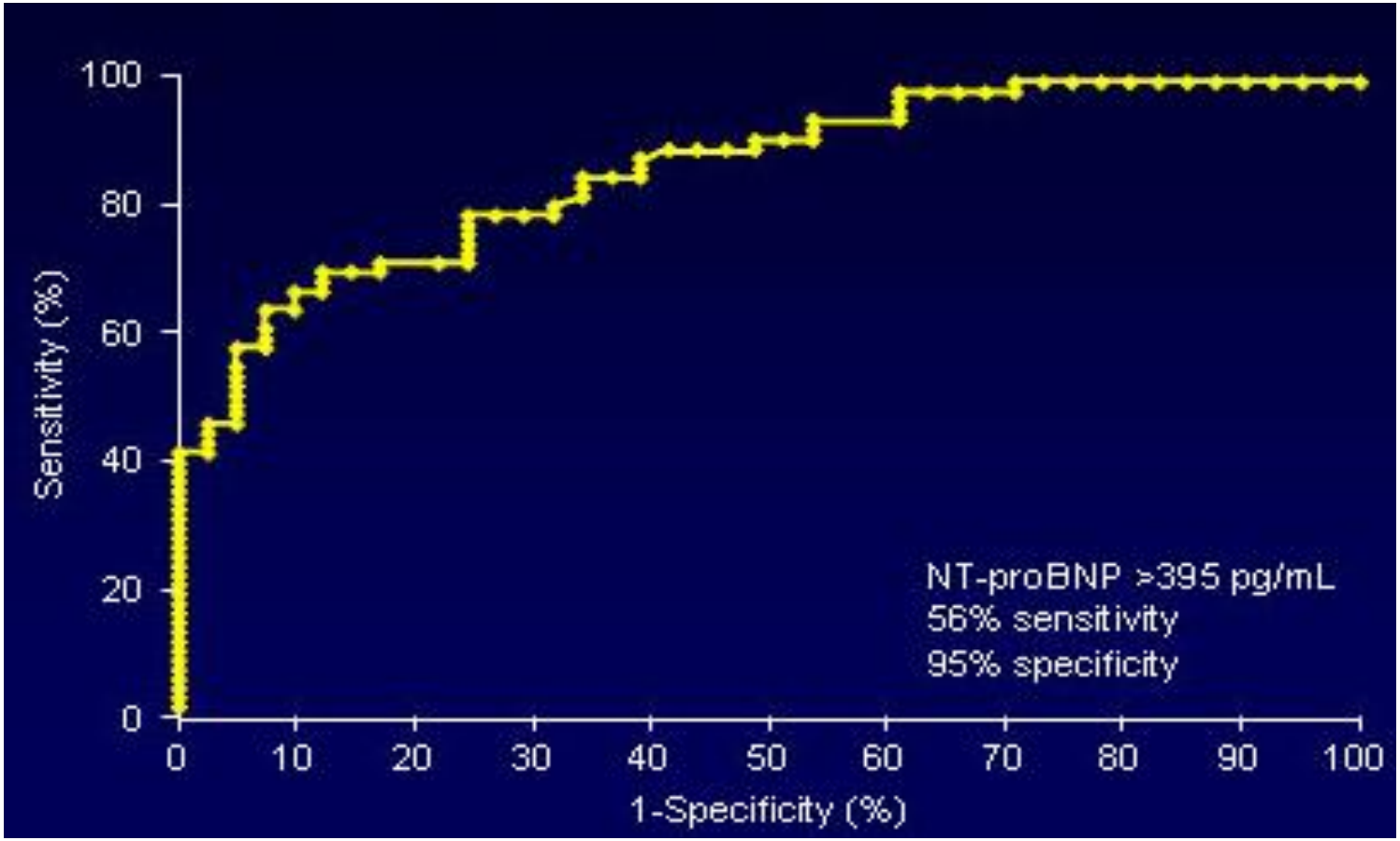
Screening in Patients With SSc-PAH: Results of a Disease Registry in France



- Better prognosis for SSc-PAH patients detected via screening program vs routine practice, *P*=.0037; HR, 4.15 (95% CI: 1.47-11.71)

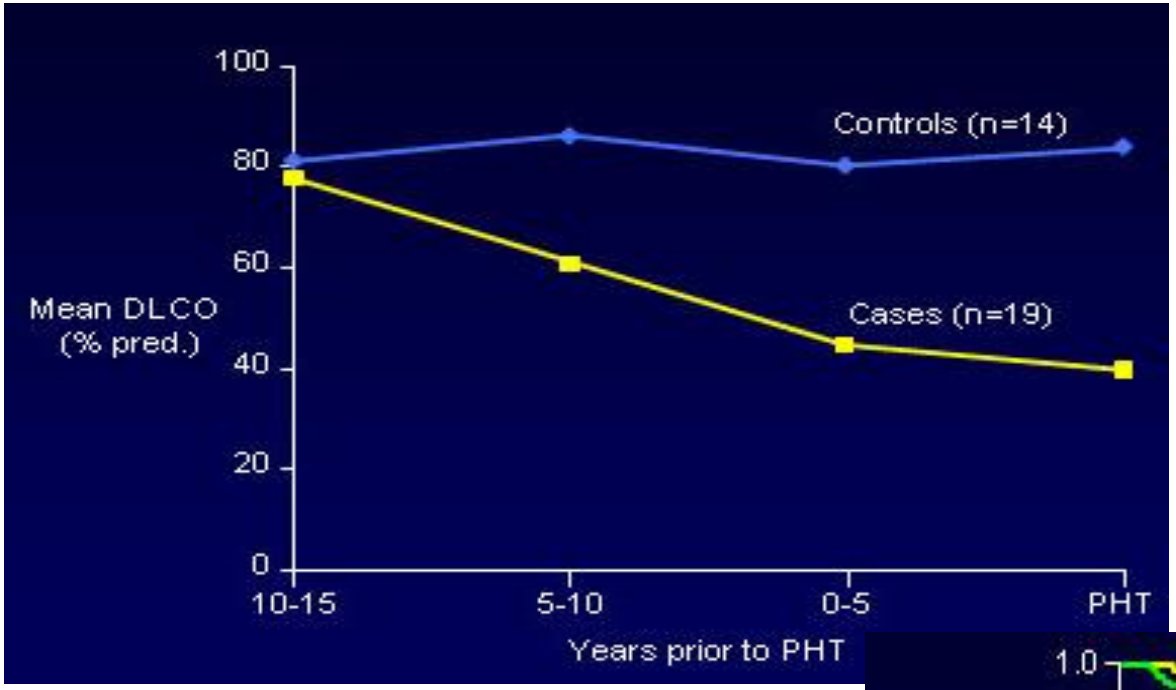
Humbert M, et al. *Arthritis Rheum*. 2011;63:3522-3530.

NT-PROBNP SSC – PAH PREDICTION
ROC CURVES



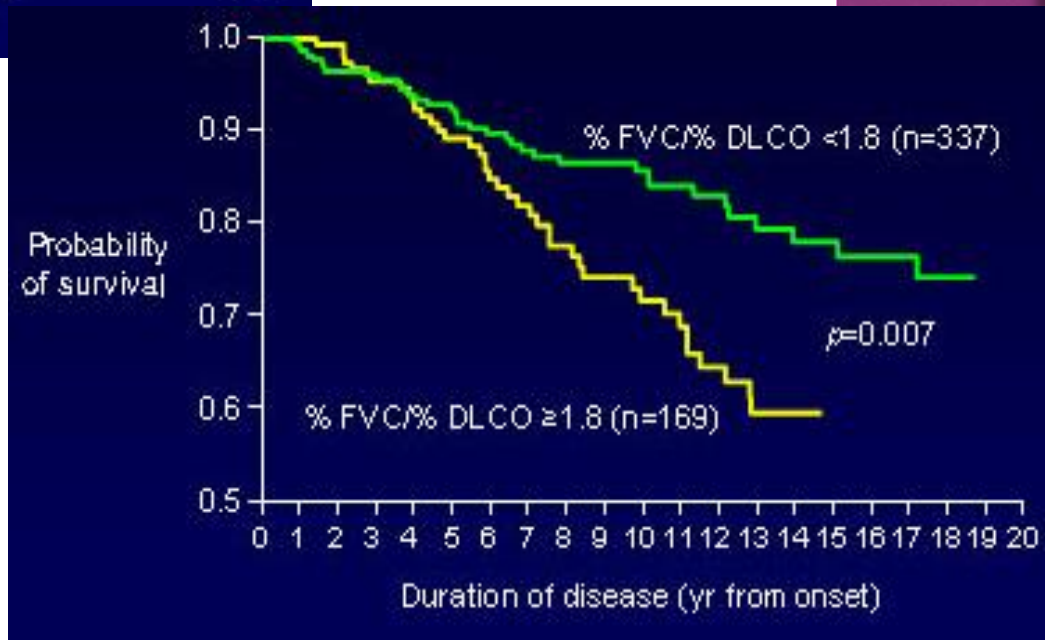
Eur Heart J 2006; 27: 1485-1494

SSC – PREDICTORS OF PAH



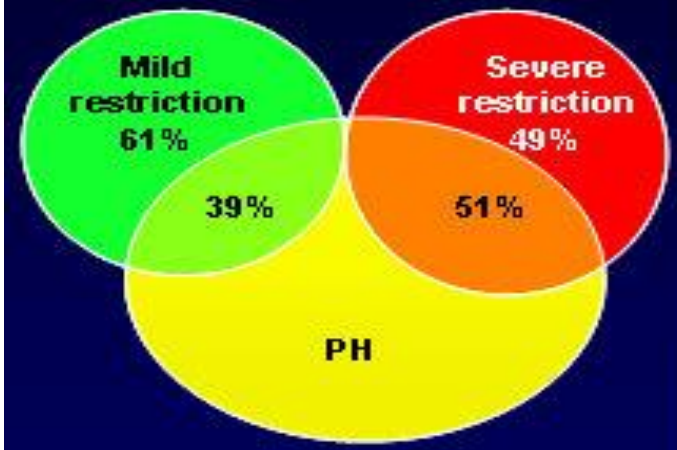
Courtesy of James Seibdd

Arthritis Rheum 2003; 43:516-522



COMBINED PAH AND ILD IN SSC

Combined PH and ILD in SSc



Patients With SSc (N=619)	n (%)	Mortality Risk
No ILD or PAH	249 (41)	1.0
Isolated restriction	139 (22)	1.6
Isolated PAH	119 (19)	2.9
Both ILD and PH	118 (18)	2.4

Chang B et al. *J Rheumatol*. 2003;30:2398.

DETECT ALGORITHM – PH IN SSC

Annual screening

WITH DLCO <60% AND DISEASE DURATION>3YEARS

WITH SIGNS AND SYMPTOMS → RHC

Without clinical signs or symptoms

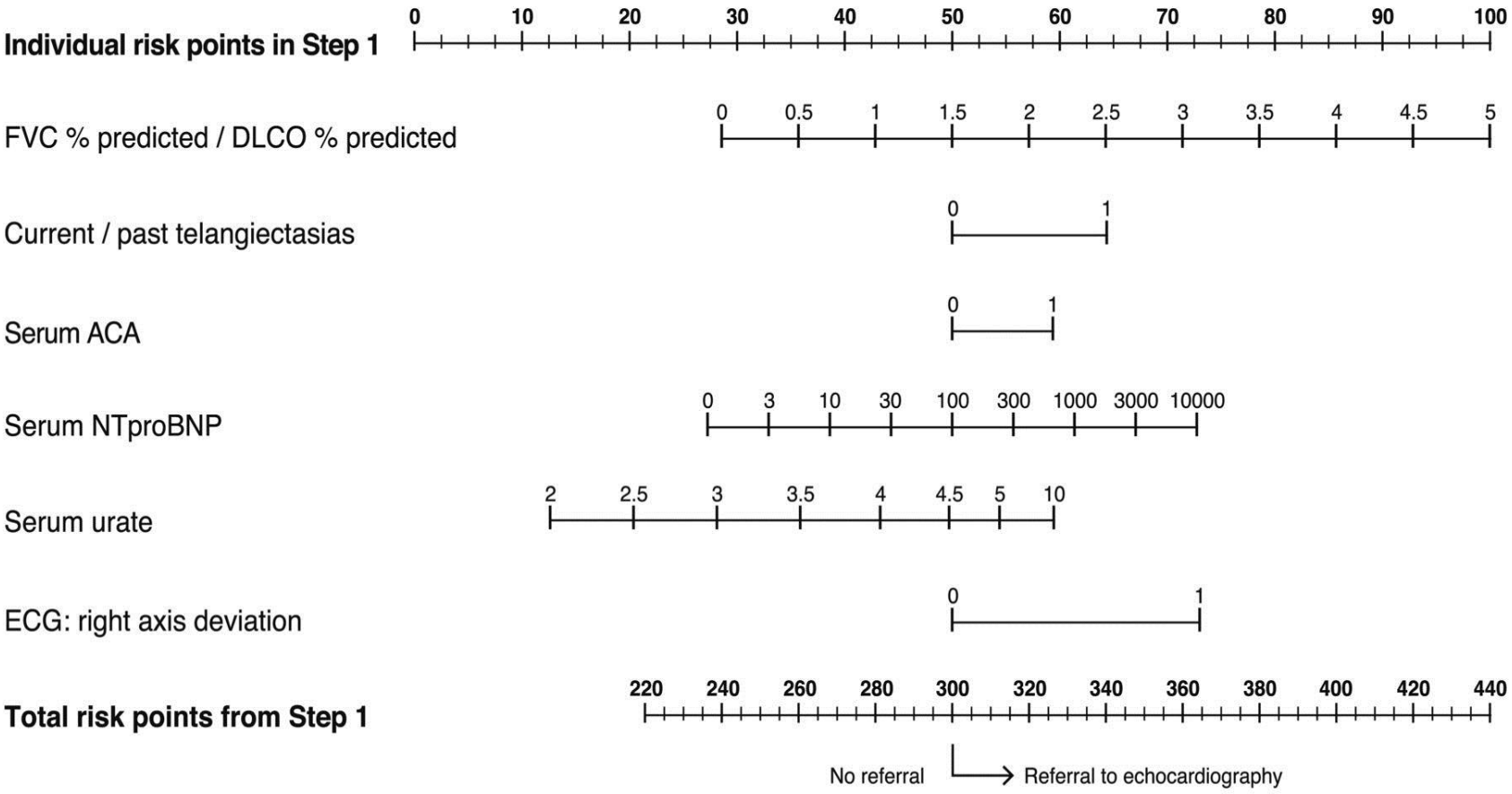
1st STEP: Assessment for telangiectasia, anticentromere antibodies, PFT, DLCO ECG, biomarkers (uric acid, NT-proBNP)

IF ABNORMAL FINDINGS

2nd STEP: Echocardiography (TR jet and RA area) and RHC

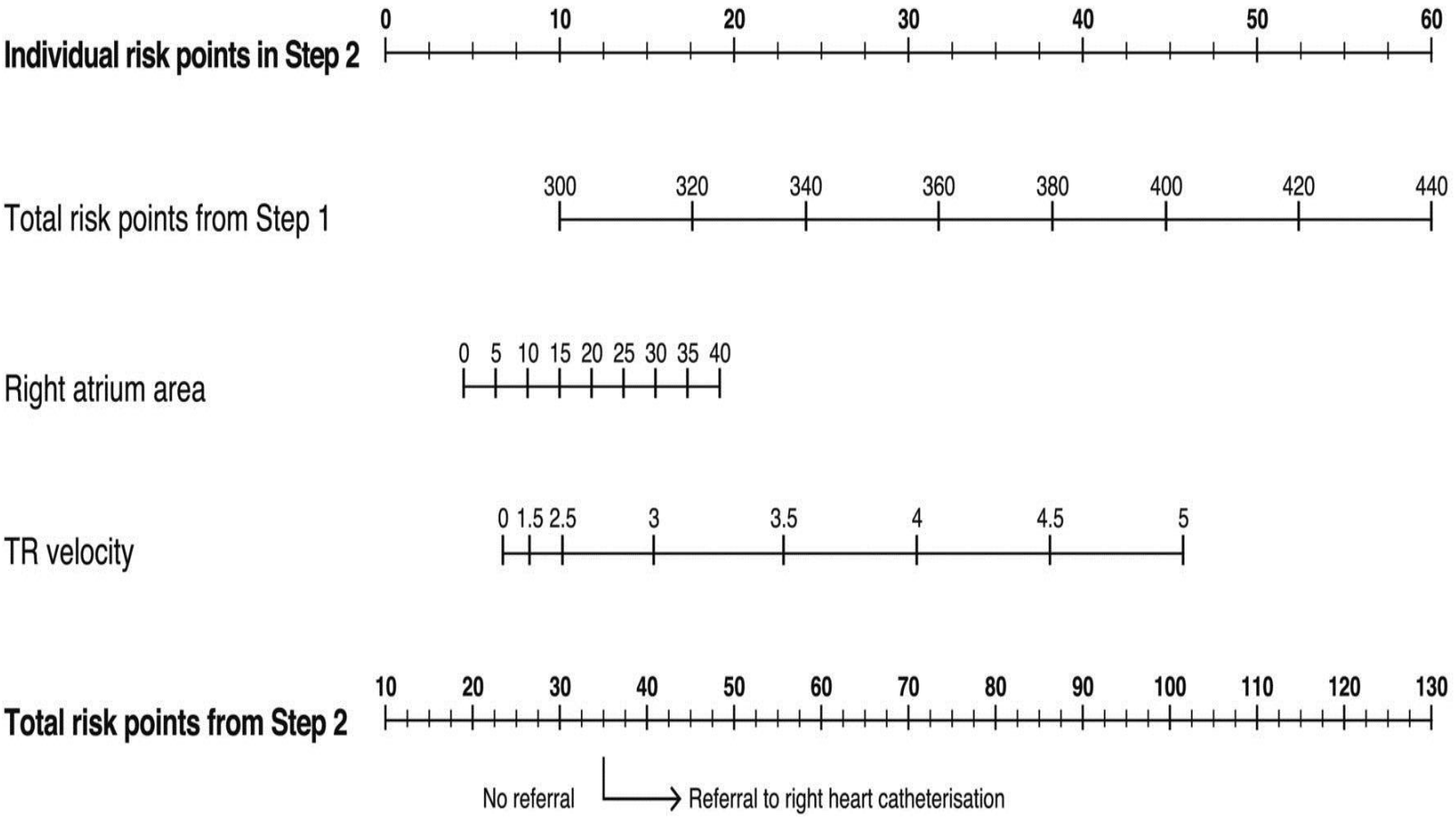
Ann Rheum Dis 2014; 73: 1340-1349

DETECT ALGORITHM NOMOGRAM STEP 1



J Gerry Coghlan et al. Ann Rheum Dis 2014;73:1340-1349

DETECT ALGORITHM NOMOGRAM STEP 2



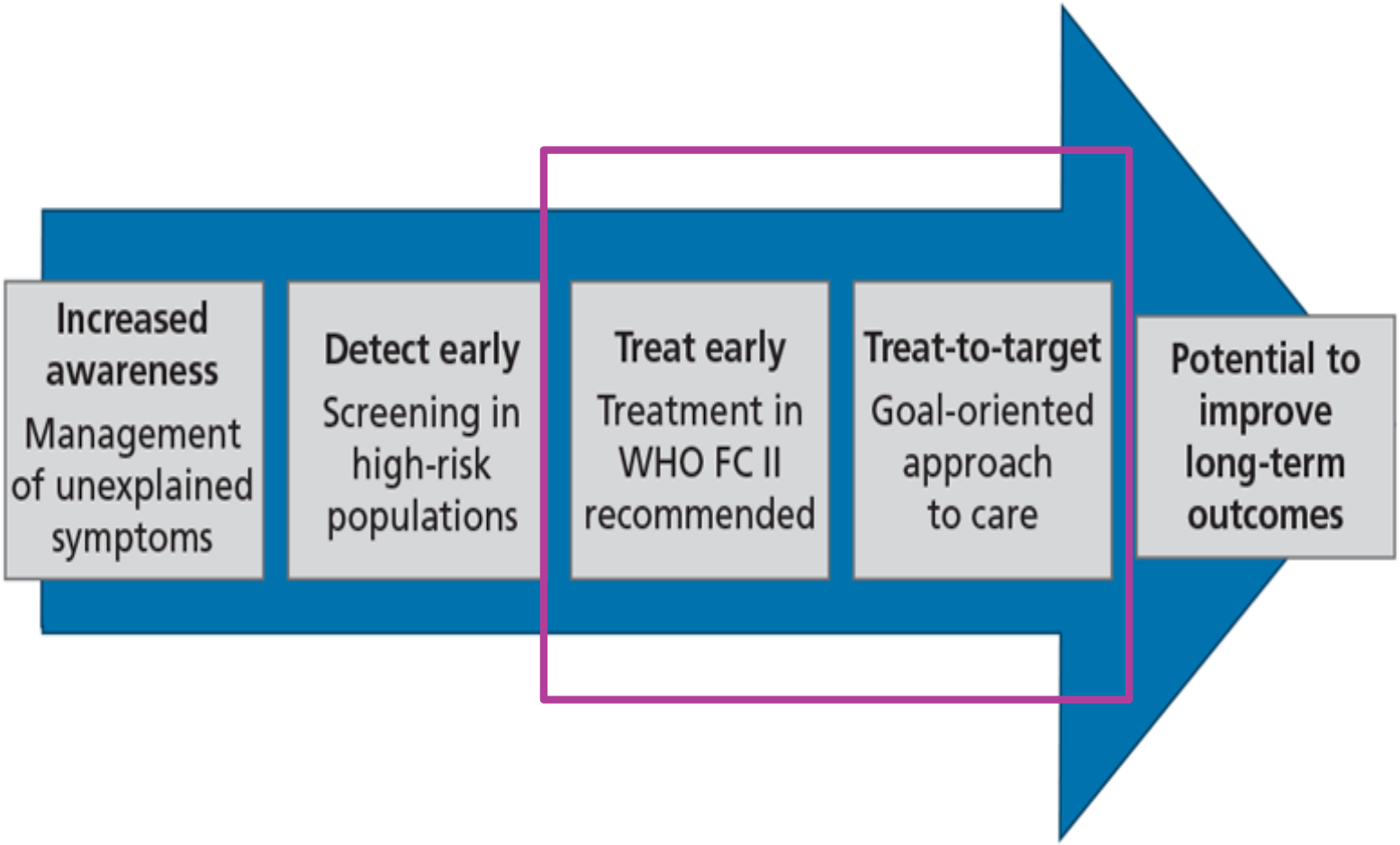
J Gerry Coghlan et al. Ann Rheum Dis 2014;73:1340-1349

CTD-PH

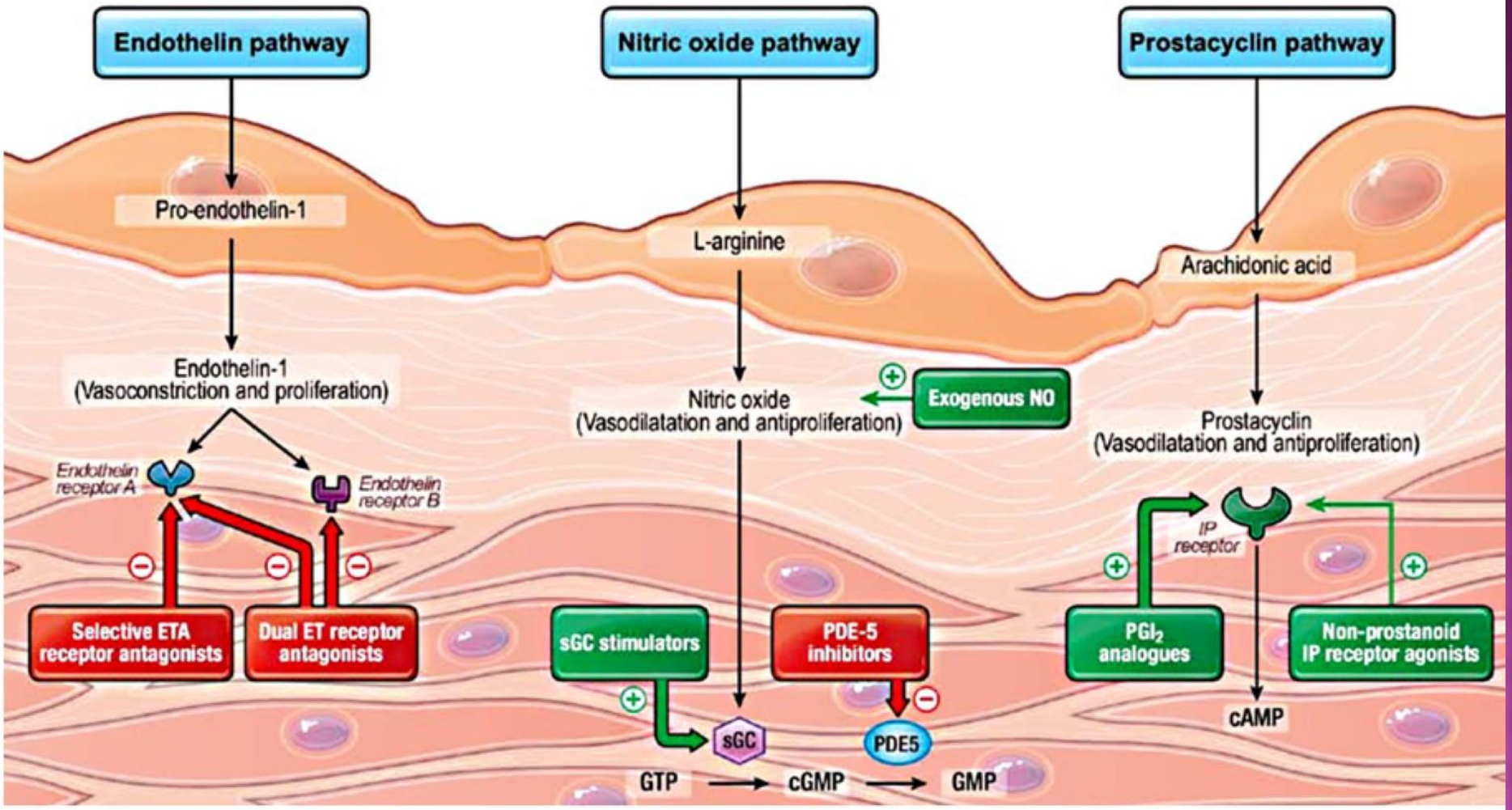
Resting echocardiography is recommended as a screening test in asymptomatic patients with SSc, followed by annual screening with echocardiography, DLCO and biomarkers	I	C
RHC is recommended in all cases of suspected PAH associated with CTD	I	C

ESC/ERS GUIDELINES, 2015

PATHWAY TO IMPROVING LONG-TERM OUTCOMES IN PAH

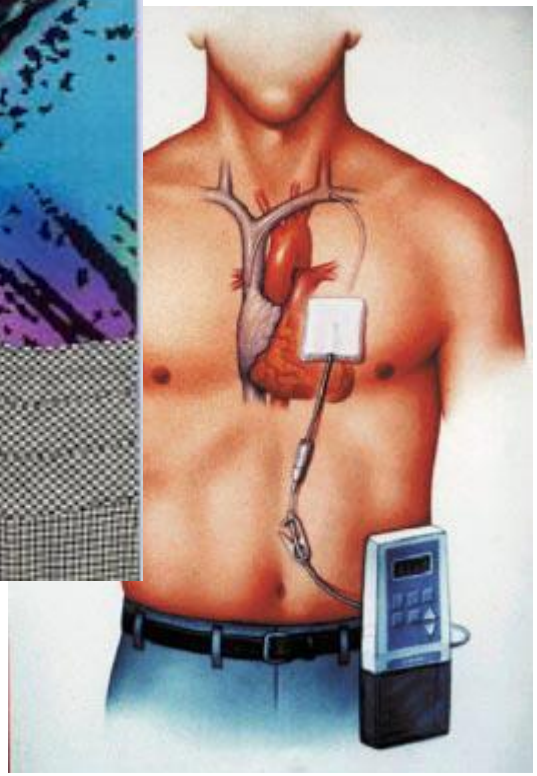


ENDOTHELIAL DYSFUNCTION IN PULMONARY ARTERIAL HYPERTENSION

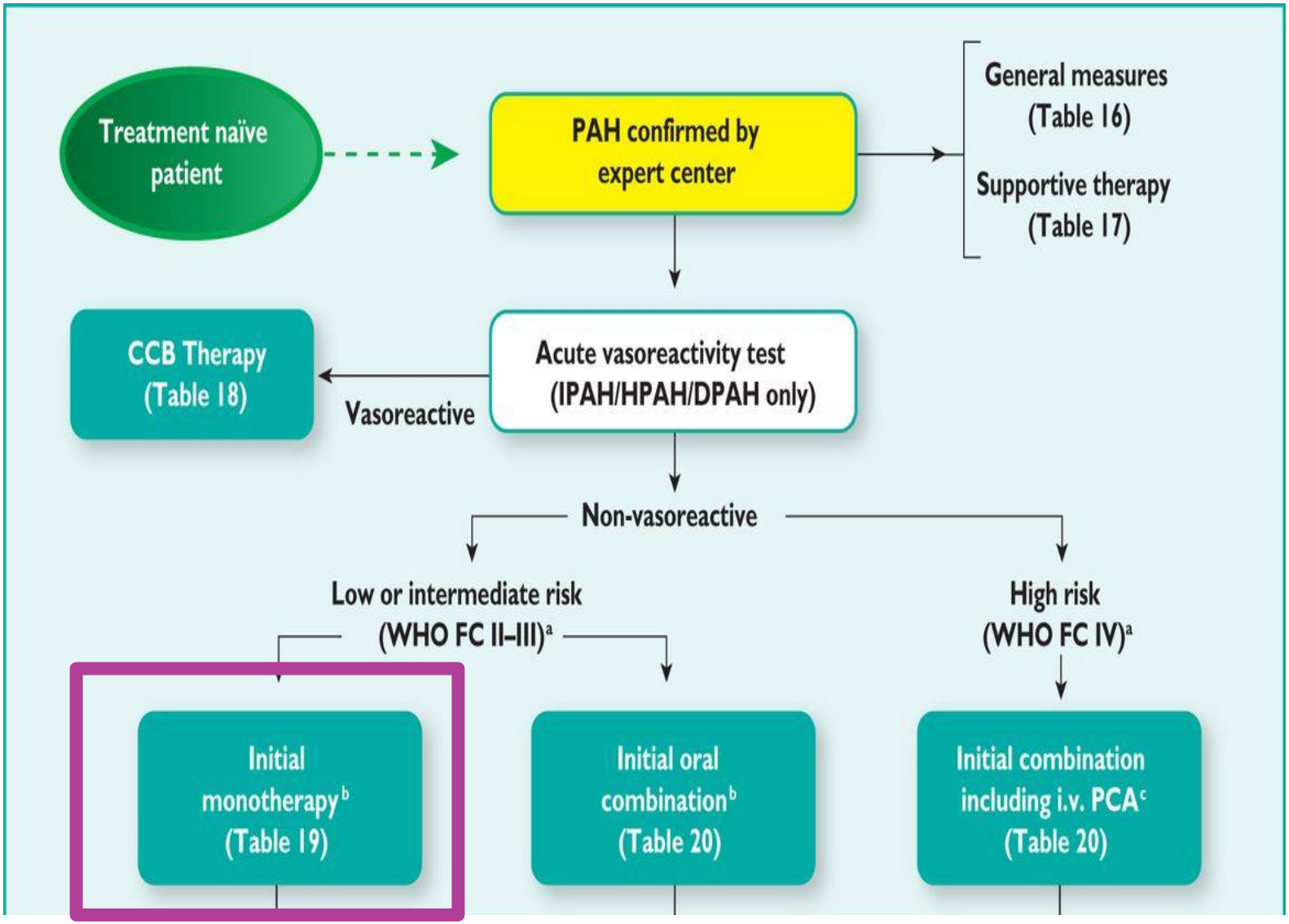


Humbert M, et al. *Circulation* 2014;130:2189-2208.

PAH - PROSTANOID USE



EVIDENCED BASED TREATMENT ALGORITHM



PAH- TIMING FOR THE FOLLOW UP

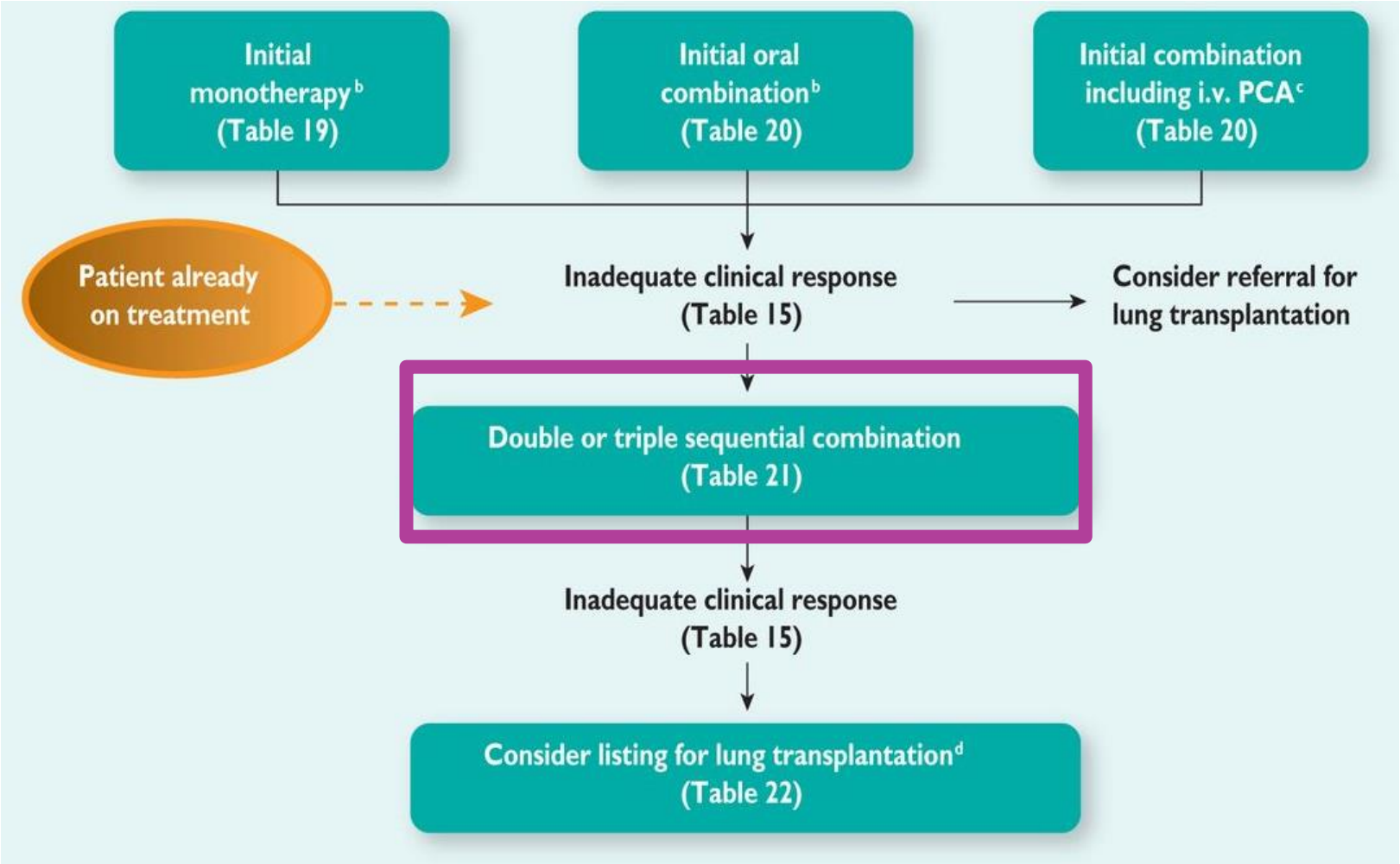
	At baseline	Every 3–6 months[a]	Every 6–12 months[a]	3–6 months after changes in therapy[a]	In case of clinical worsening
Medical assessment and determination of functional class	+	+	+	+	+
ECG	+	+	+	+	+
6MWT/Borg dyspnoea score	+	+	+	+	+
CPET	+		+		+[e]
Echo	+		+	+	+
Basic lab[b]	+	+	+	+	+
Extended lab[c]	+		+		+
Blood gas analysis[d]	+		+	+	+
Right heart catheterization	+		+[f]	+[e]	+[e]

RISK ASSESSMENT IN PAH

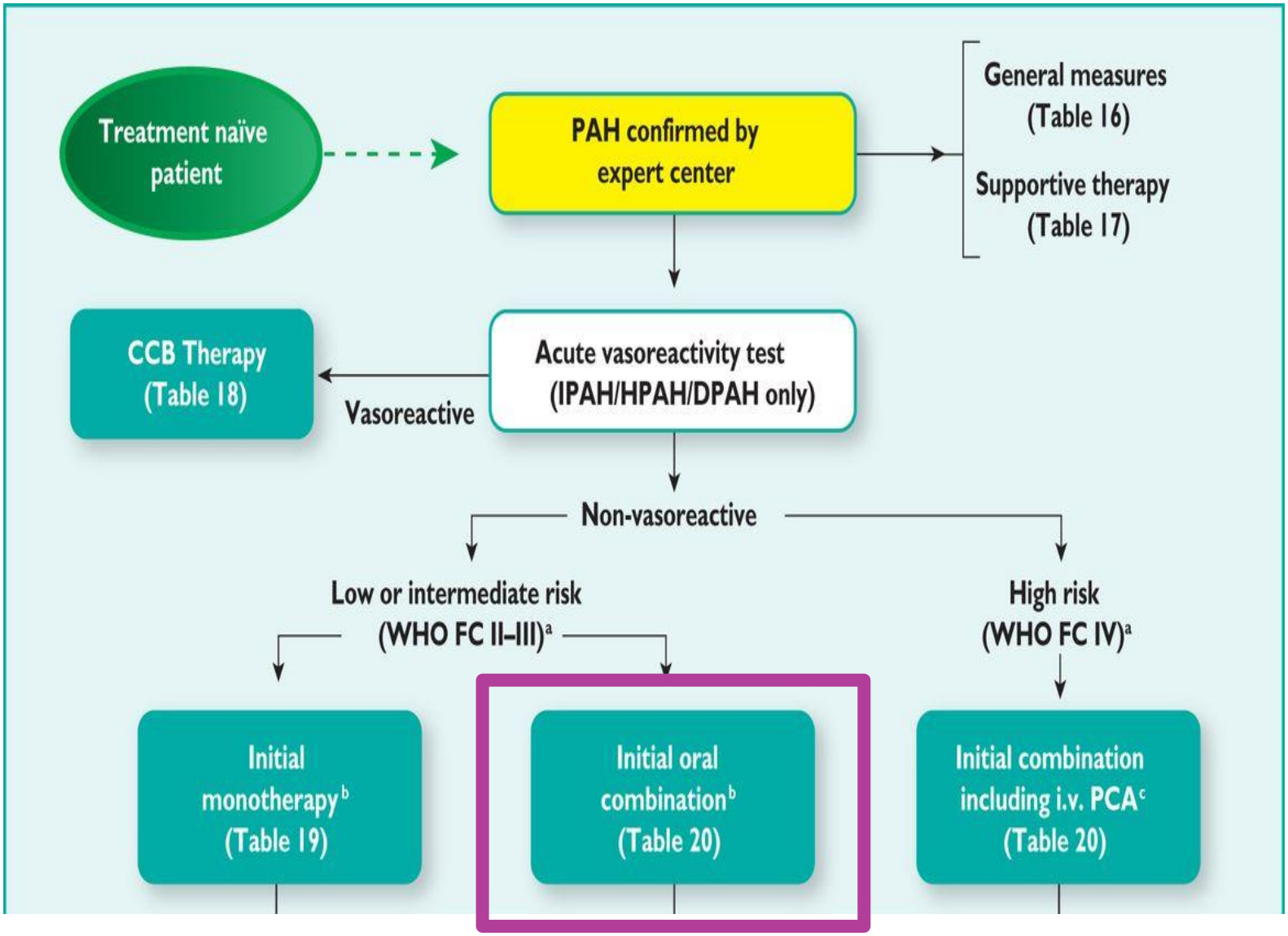
Determinants of prognosis[a] (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope[b]	Repeated syncope[c]
WHO functional class	I, II	III	IV
6MWD	>440 m	165–440 m	<165 m
Cardiopulmonary exercise testing	Peak VO_2 >15 ml/min/kg (>65% pred.) VE/VCO_2 slope <36	Peak VO_2 11–15 ml/min/kg (35–65% pred.) VE/VCO_2 slope 36–44.9	Peak VO_2 <11 ml/min/kg (<35% pred.) VE/VCO_2 ≥45
NT-proBNP plasma levels	BNP <50 ng/l NT-proBNP <300 ng/ml	BNP 50–300 ng/l NT-proBNP 300–1400 ng/l	BNP >300 ng/l NT-proBNP >1400 ng/l
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2 No pericardial effusion	RA area 18–26 cm^2 No or minimal, pericardial effusion	RA area >26 cm^2 Pericardial effusion
Haemodynamics	RAP <8 mmHg CI ≥2.5 l/min/m^2 SvO_2 >65%	RAP 8–14 mmHg CI 2.0–2.4 l/min/m^2 SvO_2 60–65%	RAP >14 mmHg CI <2.0 l/min/m^2 SvO_2 <60%

2015 ESC GUIDELINES

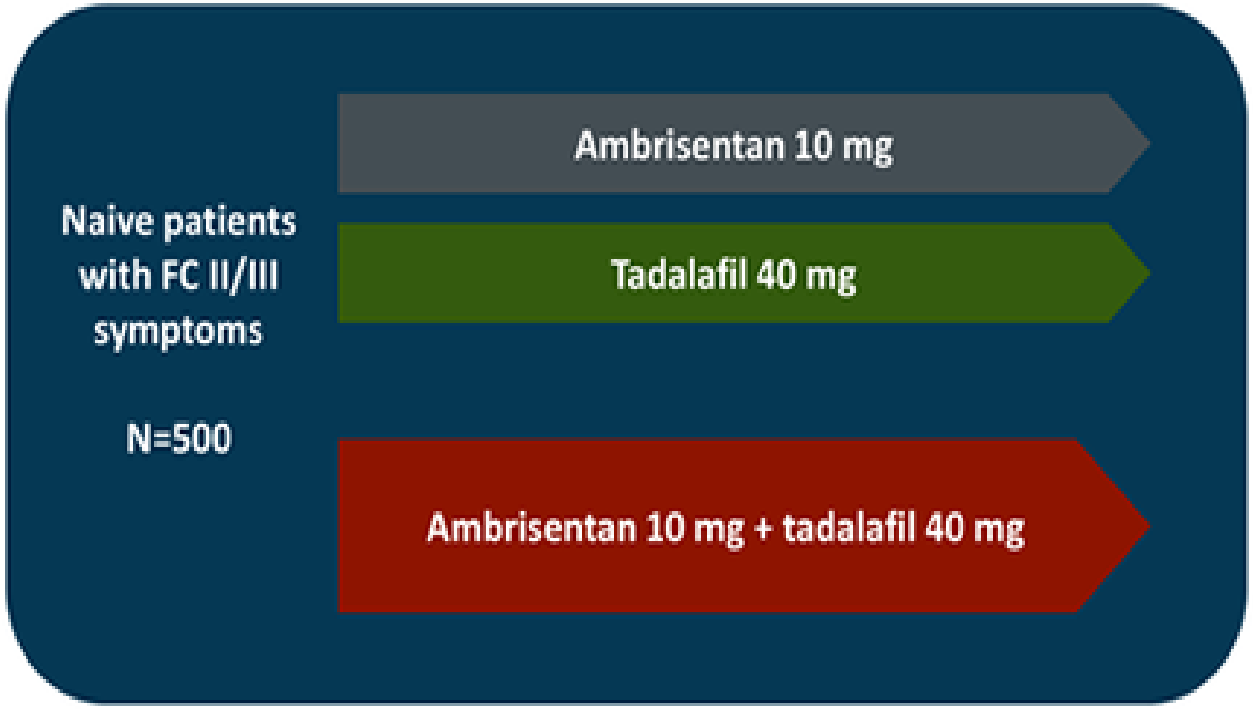
EVIDENCED BASED TREATMENT ALGORITHM



EVIDENCED BASED TREATMENT ALGORITHM



Initial Use of Ambrisentan Plus Tadalafil in PAH: The AMBITION Trial

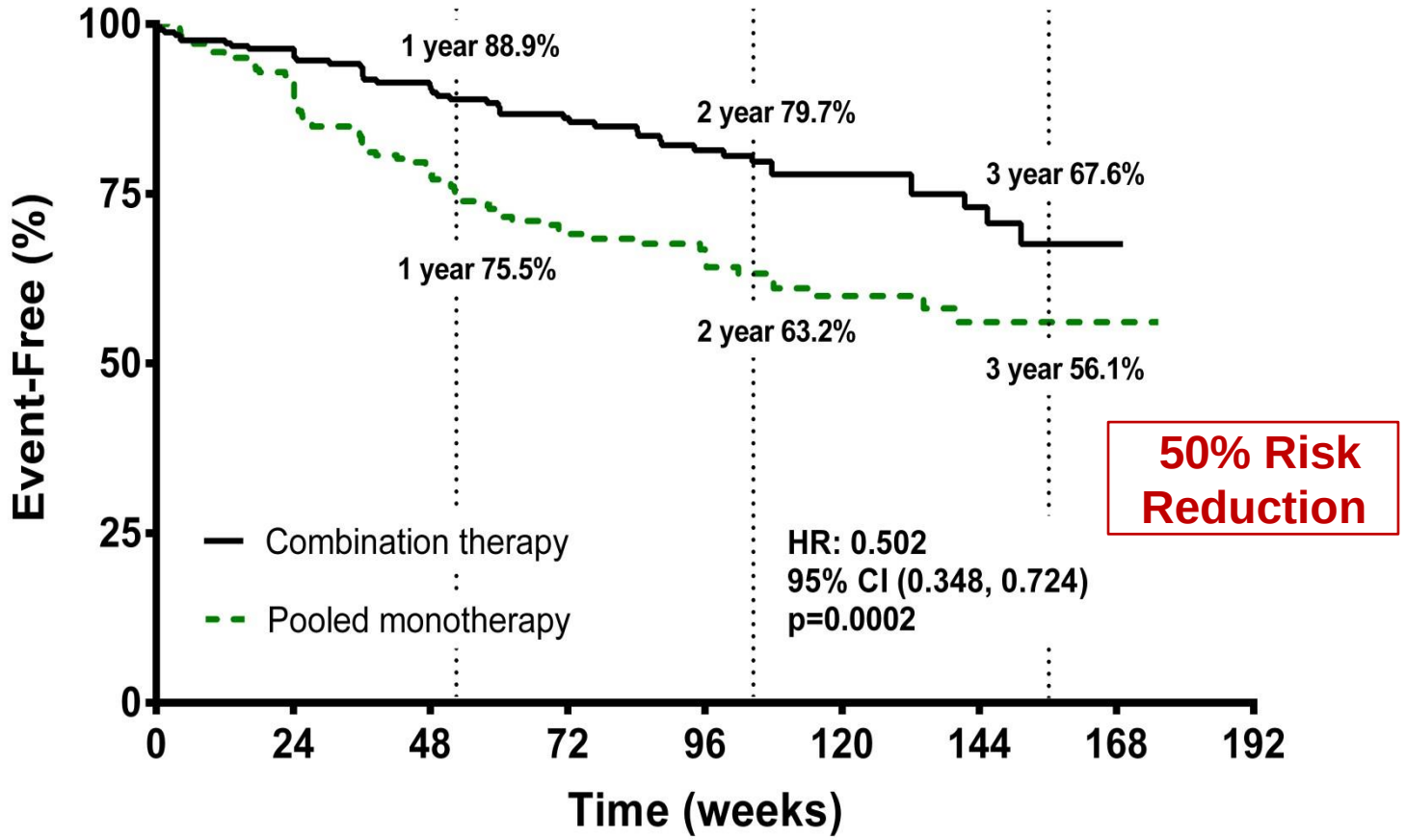


- Primary endpoint: time to clinical failure (death, hospitalization, disease progression, unsatisfactory clinical response)

Galie N, et al. *N Engl J Med*. 2015;379:834-844.

Upfront combination therapy with ambrisentan/tadalafil reduced the risk of morbidity/mortality

Primary Endpoint: Time to First Clinical Failure Event (Primary Analysis Set)



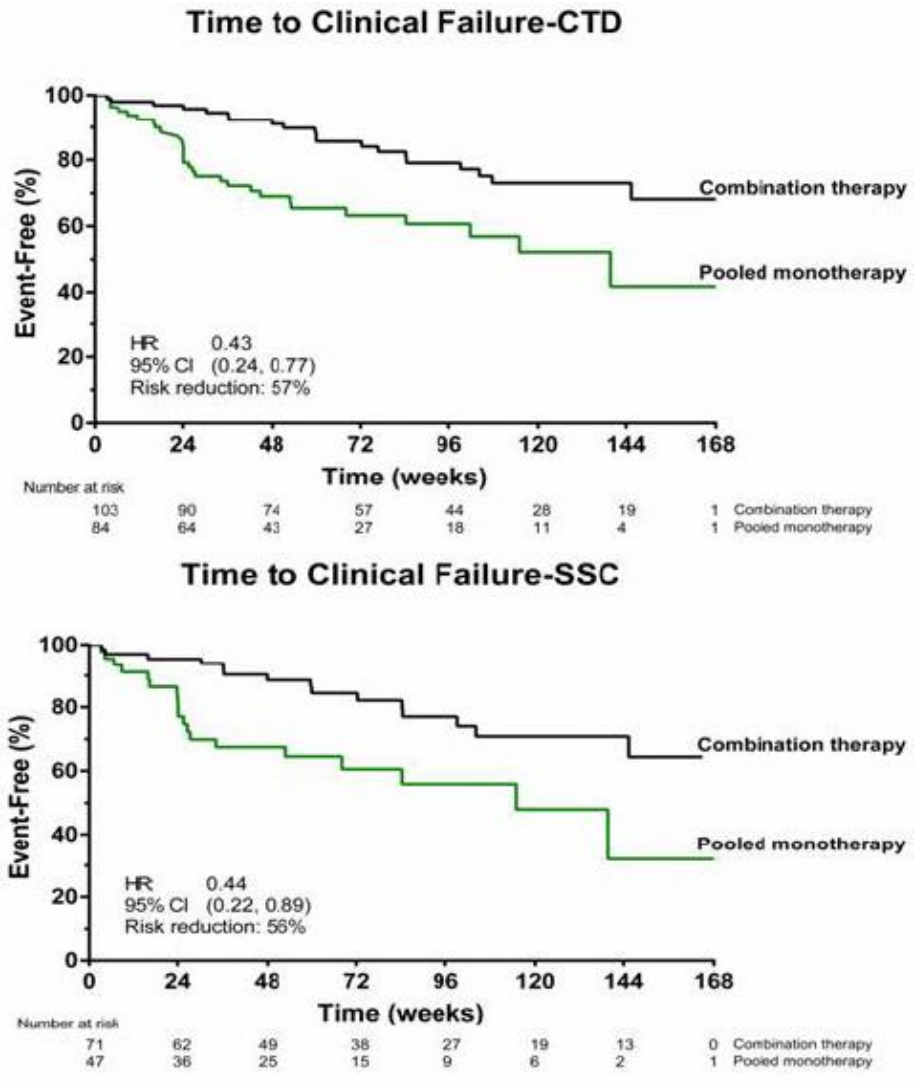
Number at risk:

Combination:	253	229	186	145	106	71	36	4
Pooled monotherapy:	247	209	155	108	77	49	25	5

95% CIs (using log-log transform method) are presented for each treatment group at weeks 4, 8, 16, 24, and then every 12 weeks up to week 96.

N. Galiè, et al. N Engl J Med 2015;373:834-44

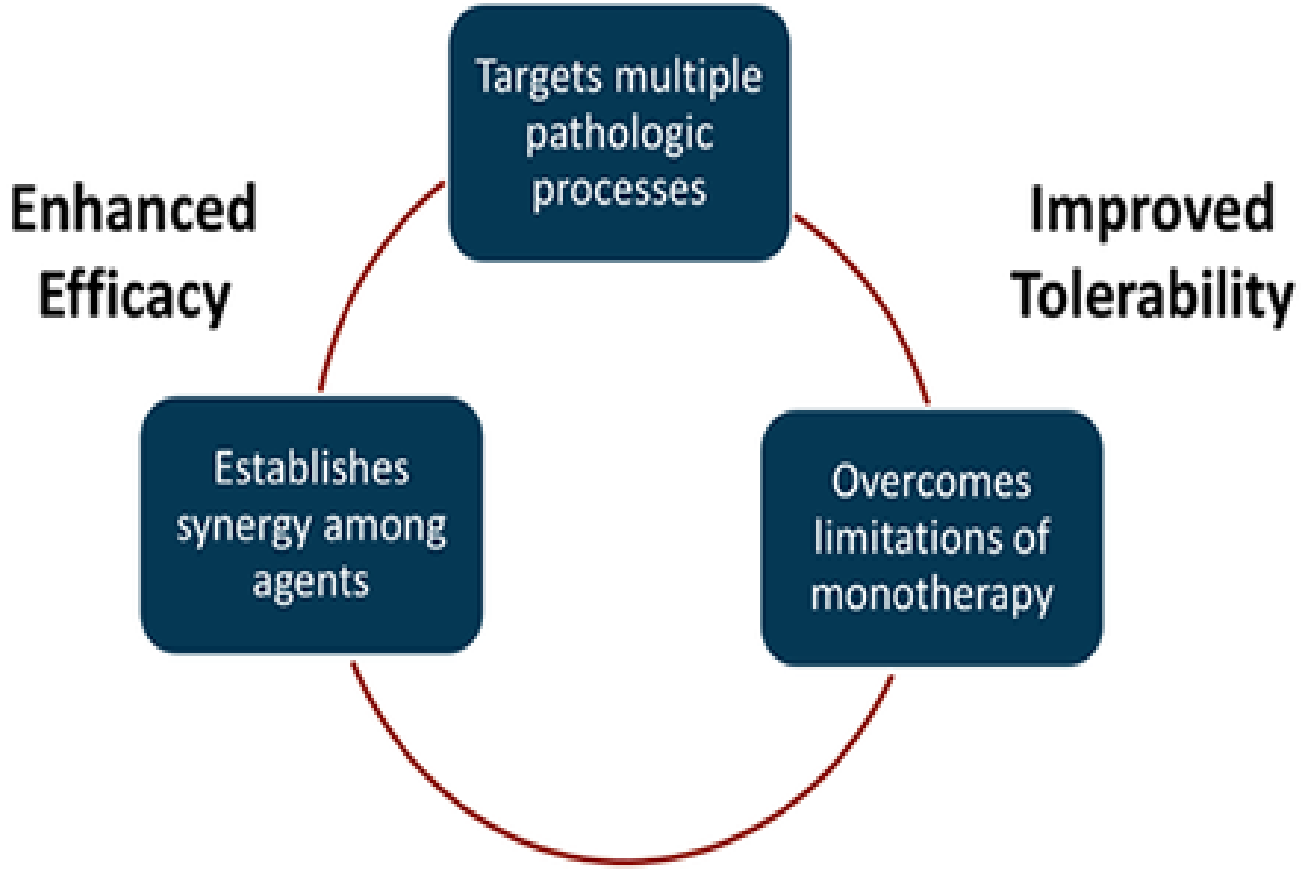
CTD-PAH SUBGROUP ANALYSIS



57% Risk Reduction

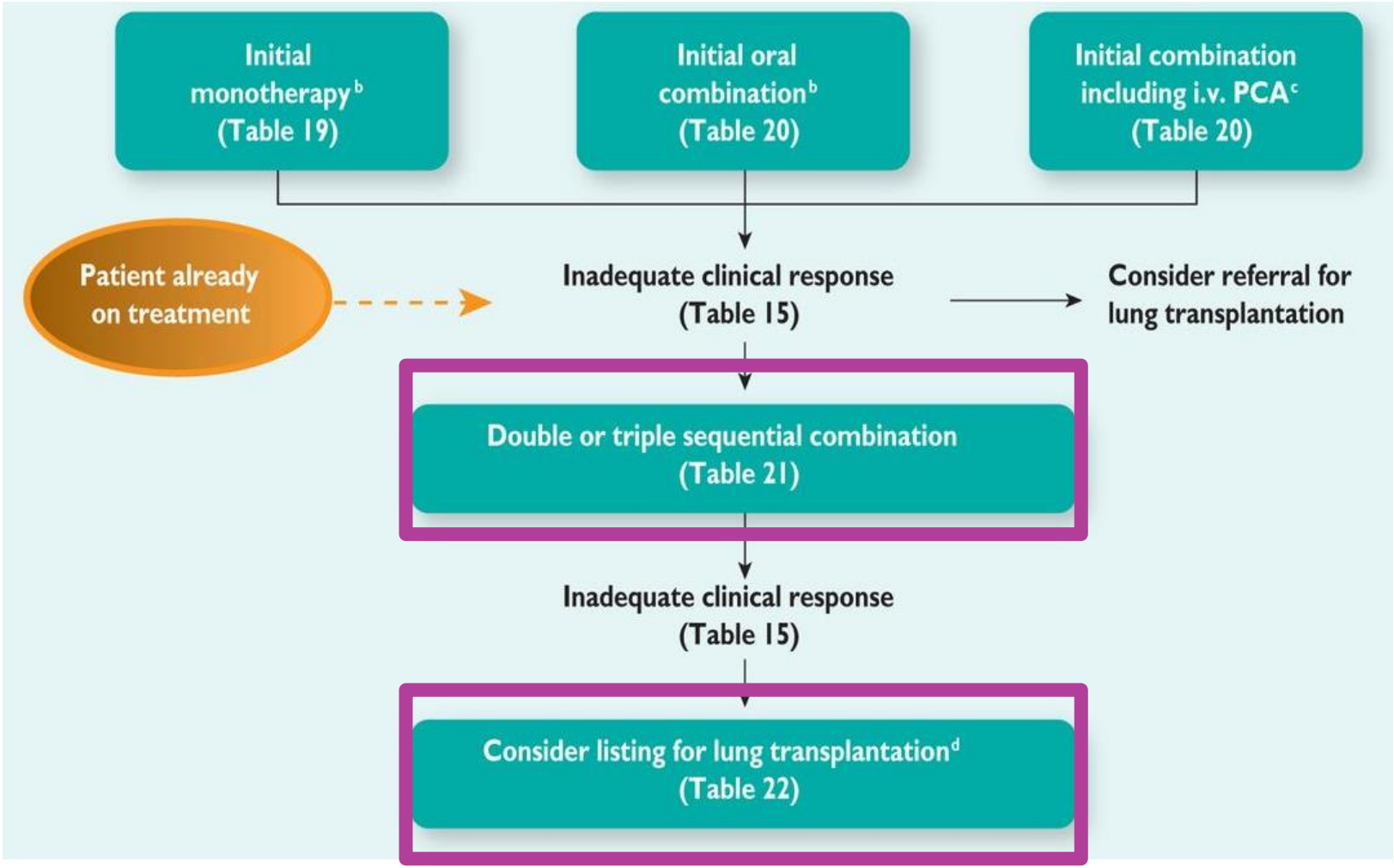
Coghlan et al. Ann Rheum Dis 2015;74:Suppl 2.173

Combination Pharmacotherapy in PAH: Rationale and Potential Clinical Benefits



Ghofrani HA, et al. *Eur Respir Rev*. 2014;23:469-475.

EVIDENCED BASED TREATMENT ALGORITHM



PULMONARY HYPERTENSION - TREATMENT

1. Pulmonary ARTERIAL Hypertension

Idiopathic
Heritable (1. BMPR2, 2. ALK-1, ENG, SMAD9, CAV1, KCNK3, 3. Unknown)
Drug and toxin induced
Associated with **Connective Tissue Disorder**, HIV infection
Portal Hypertension Congenital Heart Diseases
Schistosomiasis

2. P.H. due to Left Heart Disease

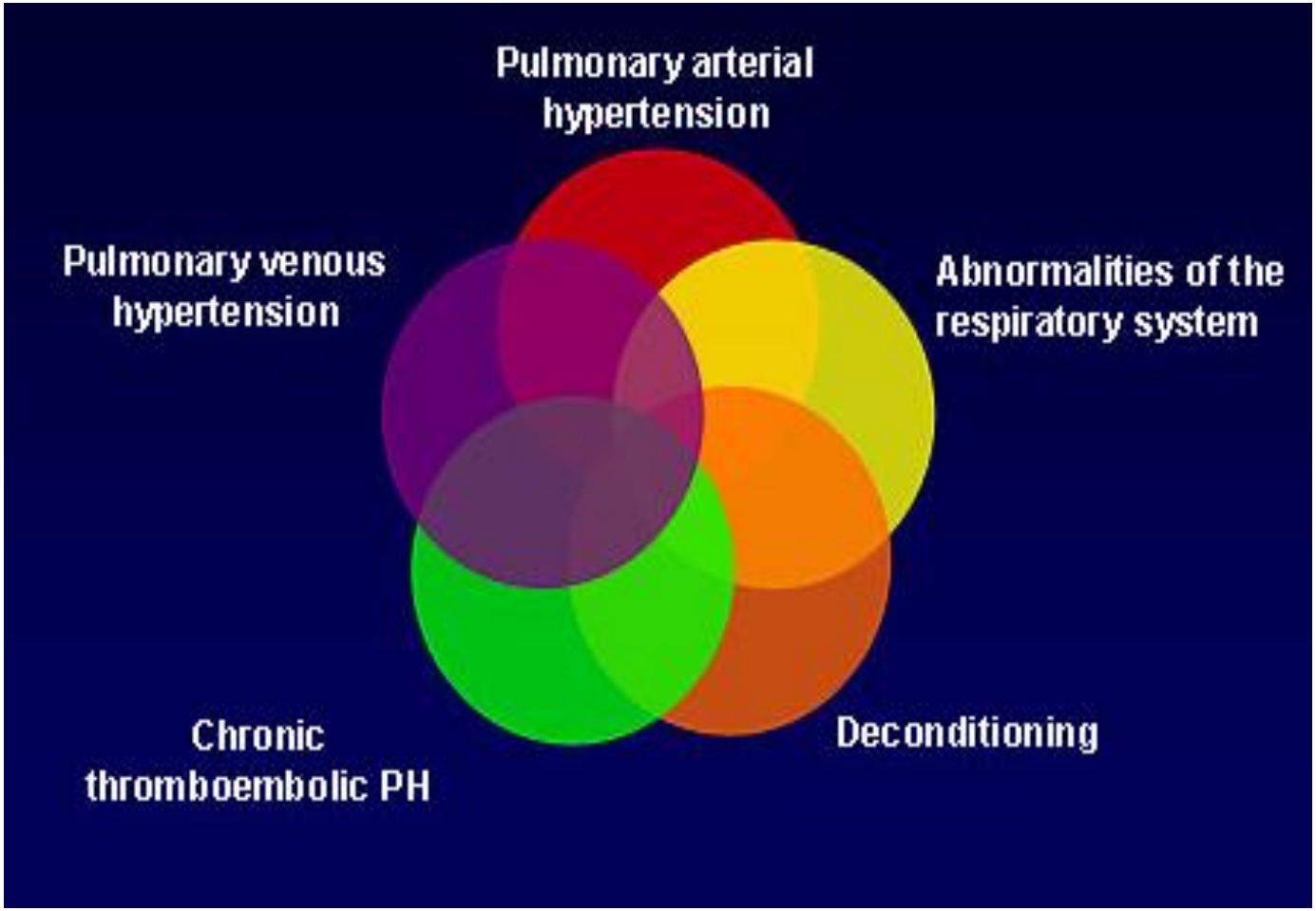
3. P.H. due to Lung diseases +/- hypoxia

4. Chronic Thromboembolic Pulmonary Hypertension

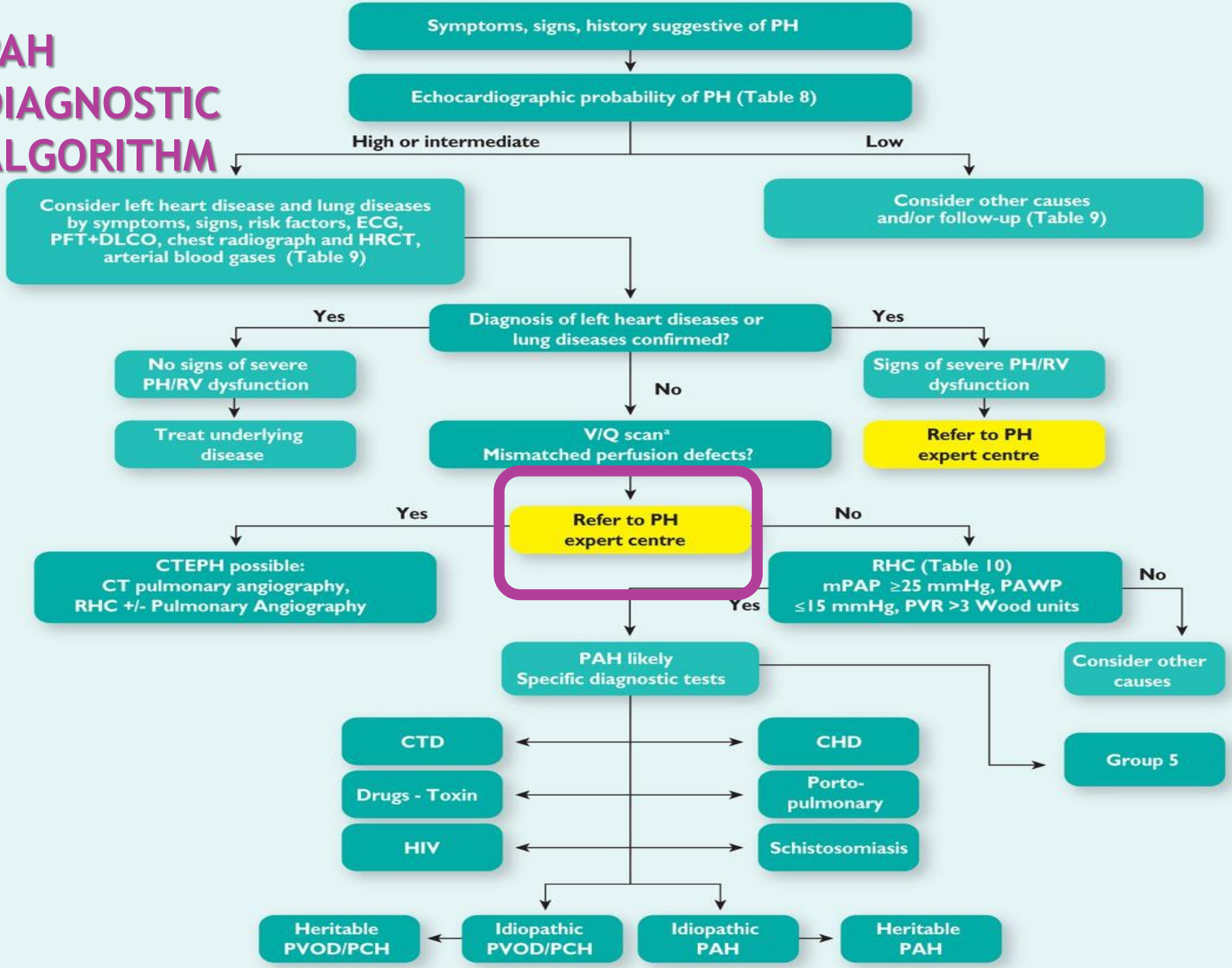
5. P.H. with unclear multifactorial mechanisms

JACC 2013; 62: D42-50

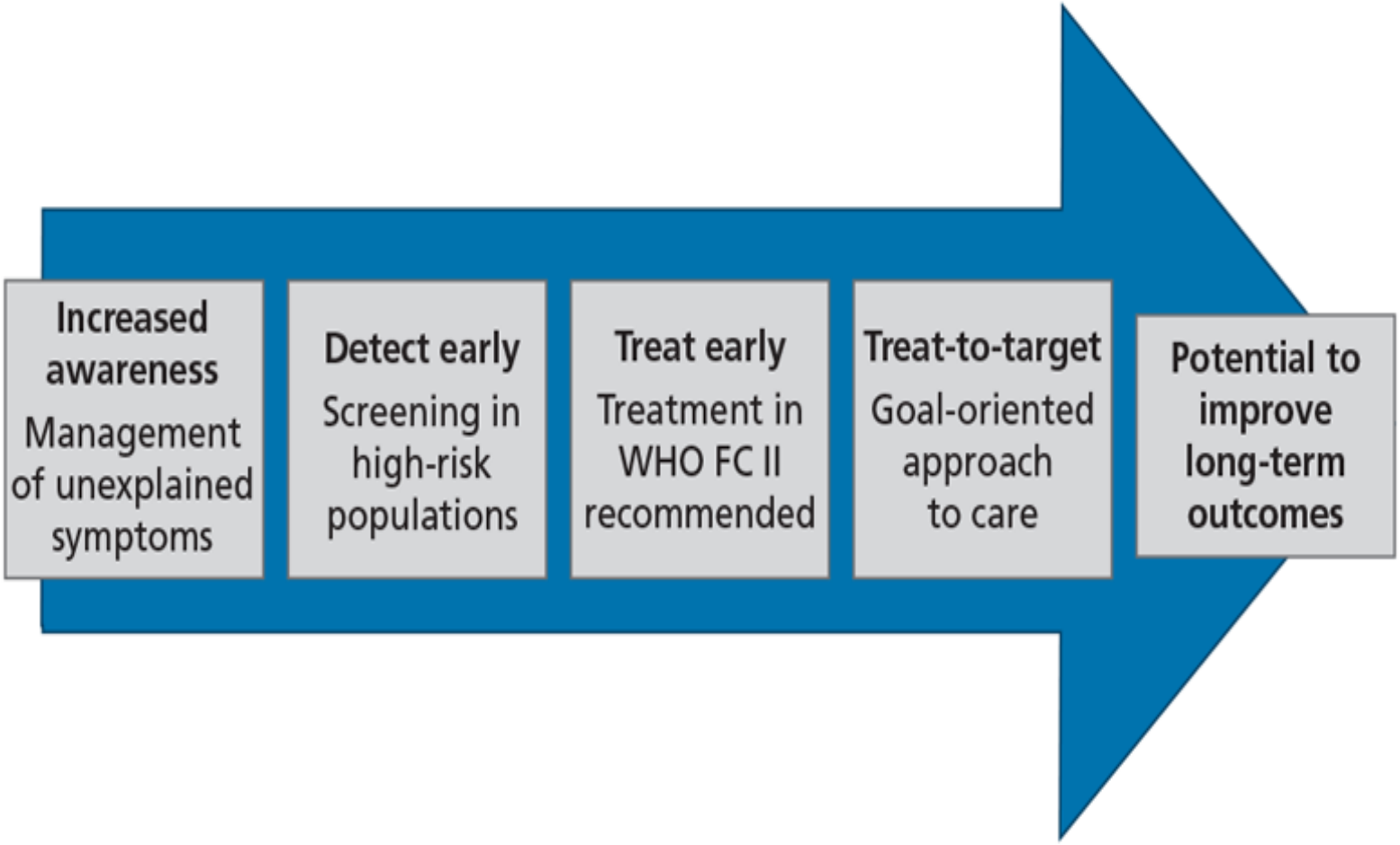
REALITY IN SCLERODERMA



PAH DIAGNOSTIC ALGORITHM



PATHWAY TO IMPROVING LONG-TERM OUTCOMES IN PAH

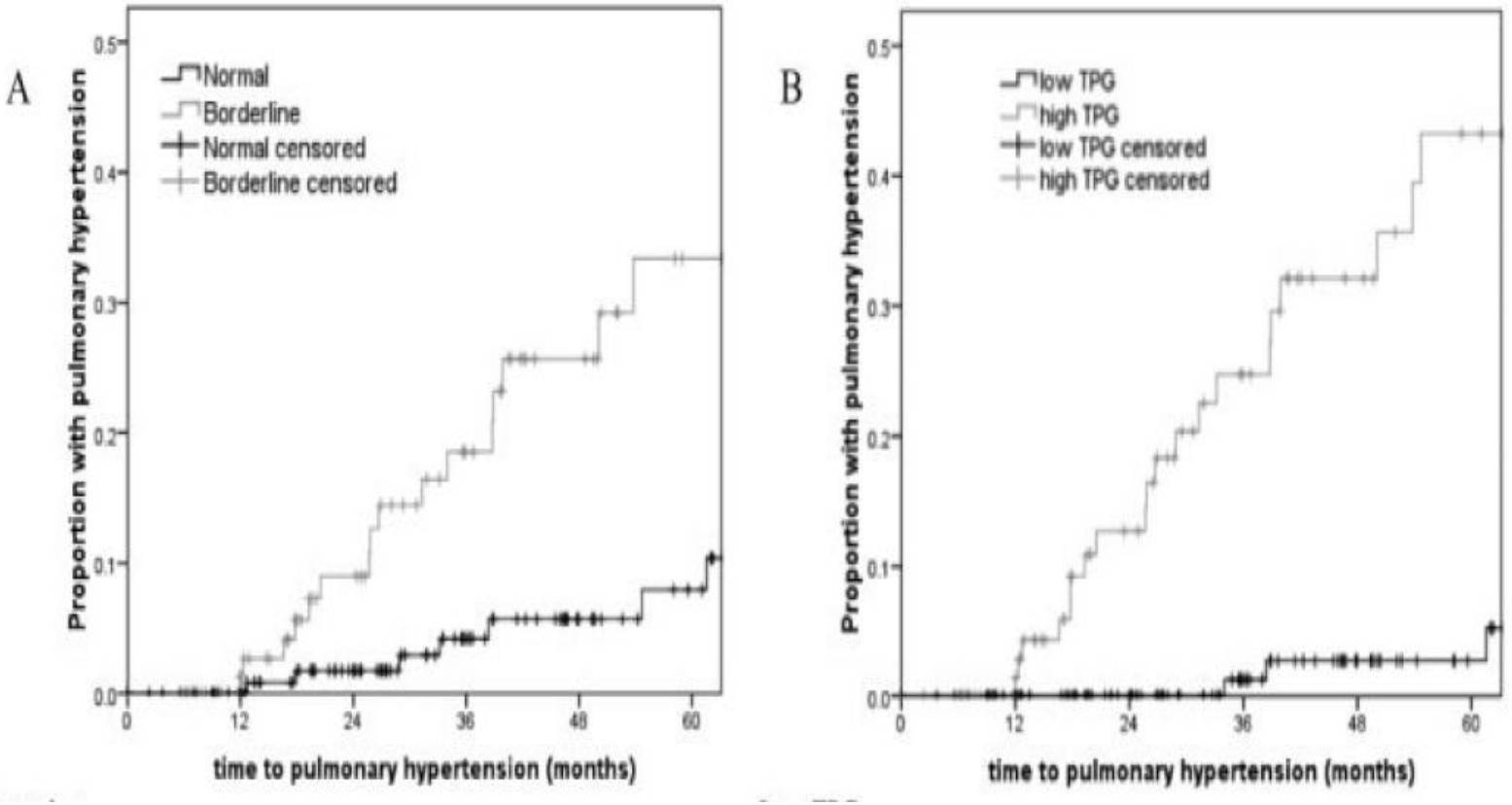


THANK YOU

Borderline Mean Pulmonary Artery Pressure in Patients With Systemic Sclerosis

Transpulmonary Gradient Predicts Risk of Developing Pulmonary Hypertension

ARTHRITIS & RHEUMATISM
Vol. 65, No. 4, April 2013, pp 1074–1084



ECHOCARDIOGRAPHIC PROBABILITY SYMPTOMATIC PATIENT WITH SUSPICION OF PH

Peak tricuspid regurgitation velocity (m/s)	Presence of other echo 'PH signs'[a]	Echocardiographic probability of pulmonary hypertension
≤2.8 or not measurable	No	Low
≤2.8 or not measurable	Yes	Intermediate
2.9–3.4	No	
2.9–3.4	Yes	High
>3.4	Not required	

Eur Heart J. **2015** Aug 29. pii: ehv317. Epub ahead of print

Immunosuppressive Therapy in Lupus- and Mixed Connective Tissue Disease–Associated Pulmonary Arterial Hypertension

A Retrospective Analysis of Twenty-Three Cases

Xavier Jais,[1] David Launay,[2] Azzedine Yaici,[1] Jérôme Le Pavec,[1] Colas Tchérakian,[1] Olivier Sitbon,[1] Gérald Simonneau,[1] and Marc Humbert[1]

SLE- or MCTD-associated PAH

Conventional therapy

WHO II OR III with C.I.>3.1 l/min/m2

WHO III WITH C.I.<3.1 or WHO IV

Immunosupresive therapy alone

Pulmonary vasodilators +/- Immunosupresive therapy ?

Evaluation 4-6months after

response

Start maintenance regimen
Azathioprine, mycophenolate, mofetil

No response

Stop immunosuppressive
Pulmonary vasodilators

Arthritis & Rheumatism 2008; 58: 521-531

Patients who could benefit from this immunosuppressive therapy could be those who have less severe disease at baseline

ENDOTHELIAL DYSFUNCTION IN CTD

DECREASED NO production in PAH and SSc

DECREASED eNOS expression in IPAH lung

DECREASED eNOS expression in SSc dermal microvasculature

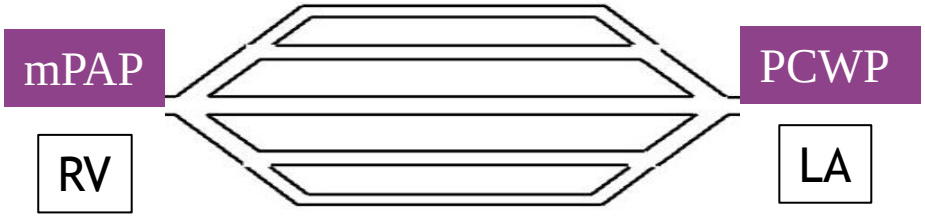
ROLE OF ENDOTHELIN

ET-1 increased in SSc serum

Vasc Med 2000; 5:147-158
N Engl J Med 1995; 333:214-221

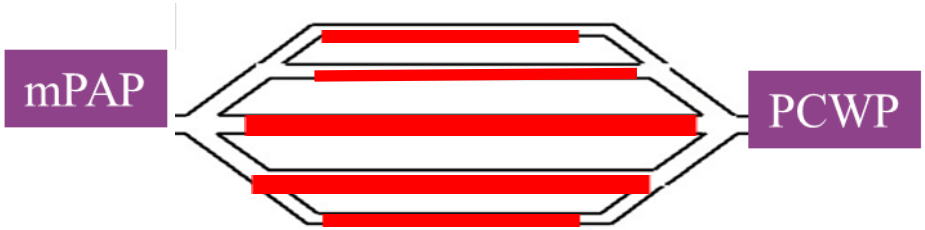
HAEMODYNAMIC DEFINITIONS

PASSIVE



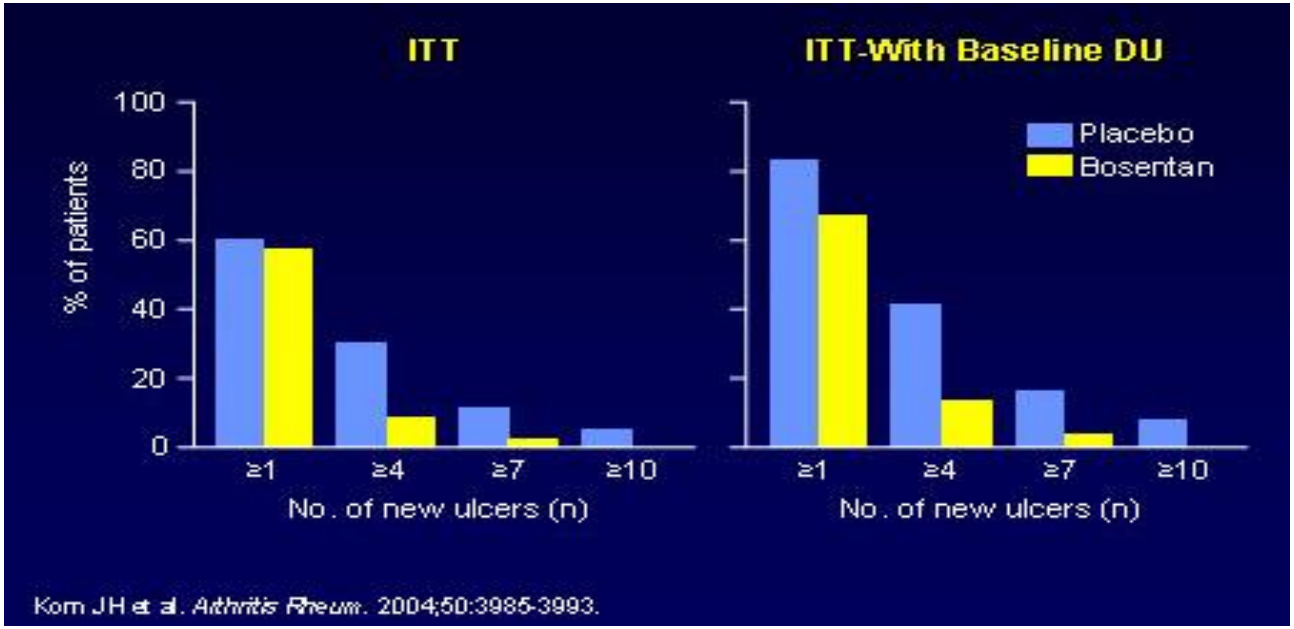
TPG < 15 mmHg
Or
PVR < 3 WU

MIXED



TPG > 15mmHg
Or
PVR > 3 WU

RAPIDS-1 STUDY



EPOPROSTENOL FOR DIGITAL ISCHEMIA

- Consider for persistent ischemic symptoms (hrs) or gangrene
- IV infusion via central line: 3-10 ng/kg/min for 5 days, then wean and transition to PDE-5 inhibitor

SCREENING HIGH-RISK GROUPS FOR PAH

Substrate	Further Assessment
BMPR2 mutation	Echo yearly; RHC if echo is compatible with pulmonary hypertension
First-degree relative with *BMPR2* mutation or within pedigree of 2+ pts with diagnosis of PAH	Genetic counselling and recommendation for *BMPR2* genotyping; proceed as above if positive
Systemic sclerosis	Echo yearly; RHC if echo is compatible with pulmonary hypertension
HIV infection	Echo if symptoms/signs suggestive of PAH; RHC if echo is compatible with pulmonary hypertension
Portal hypertension	Echo if OLT considered or if symptoms/signs suggestive of PAH; RHC if echo is compatible with pulmonary hypertension
Prior use of PAH-causing drugs	Echo only if symptomatic
Congenital heart disease with shunt	Echo and RHC at time of diagnosis; consider repair of defect

PH GROUP II

2. Pulmonary hypertension due to left heart disease

2.1 Left ventricular systolic dysfunction
2.2 Left ventricular diastolic dysfunction
2.3 Valvular disease
2.4 Congenital / acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
2.5 Congenital /acquired pulmonary veins stenosis

Post-capillary PH	Mean PAP ≥25 mmHg PWP >15 mmHg CO normal or reduced[c]
Passive	TPG ≤12 mmHg
Reactive (out of proportion)	TPG >12 mmHg

Terminology	PAWP	Diastolic PAP – PAWP
Isolated post-capillary PH	>15 mm Hg	<7 mm Hg
Combined post-capillary and pre-capillary PH	>15 mm Hg	≥7 mm Hg

PAH DRUGS- COST EFFECTIVENESS

Table 1: PAH Drug Costs per Cycle Within the Economic Model

Drug/Comparator	Dosing Used in the Model	Drug Cost per Three-Month Cycle[a]
Stimulators of sGC		
Riociguat (Adempas)	1 mg three times daily increased to 2.5 mg three times daily	$12,639[b]
ERA		
Macitentan (Opsumit)	10 mg once daily	$12,656[b]
Ambrisentan (Volibris)	5 mg for two weeks, then 10 mg once daily	$12,074
Bosentan (Tracleer)	62.5 mg twice daily increased to 125 mg twice daily after four weeks	$12,650[c]
PDE-5 inhibitors		
Sildenafil (Revatio)	20 mg three times daily	$3,288
Tadalafil (Adcirca)	40 mg once daily	$2,634
Parenteral prostanoids		
Epoprostenol (Flolan)	First cycle: 2 ng/kg/min increased to 4 ng/kg/min by day 7, and then increased at a rate of 2.5 ng/kg/min every 21 days Subsequent cycles: 27 ng/kg/min, with increases of 5 ng/kg/min every two years until a ceiling of 50 ng/kg/min is reached	First cycle: $5,274[d,e] Subsequent cycles: $11,247[d,e]

Canadian Agency for Drugs And Technology in Health, March 2015

DD PAH - GROUP 3

Criteria Favoring Group 1 (PAH)	Criteria Favoring Group 3 (PH Due to Lung Disease)
Normal or mildly impaired	Moderate to very severe impairment
FEV1 >60% predicted (COPD)	FEV1 <60% predicted (COPD)
FVC >70% predicted (IPF)	FVC <70% predicted (IPF)
Absence of or only modest airway or parenchymal abnormalities	Characteristic airway and/or parenchymal abnormalities
Features of exhausted circulatory reserve	Features of exhausted ventilator reserve
Preserved breathing reserve	Reduced breathing reserve
Reduced oxygen pulse	Normal oxygen pulse
Low Co/Vo_2 slope	Normal Co/Vo_2 slope
Mixed venous oxygen saturation at lower limit	Mixed venous oxygen saturation above lower limit
No change or decrease in $PaCo_2$ during exercise	Increase in $PaCo_2$ during exercise

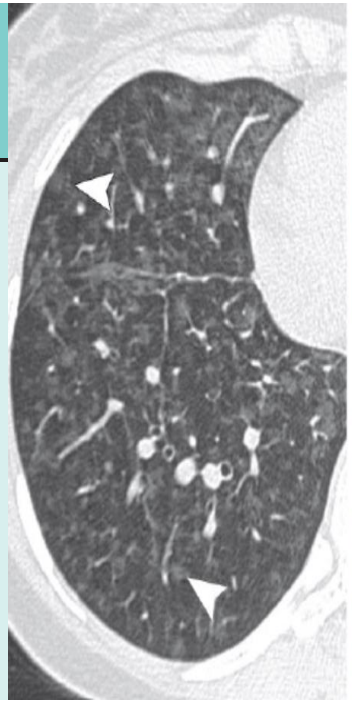
RISK LEVEL OF DRUG AND TOXINS INDUCED PAH

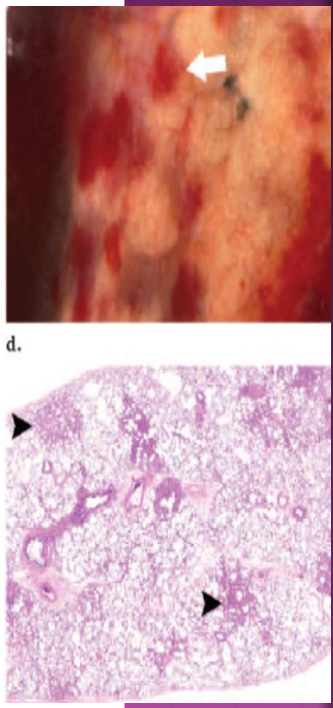
Definite	Likely	Possible
• Aminorex • Fenfluramine • Dexfenfluramine • Toxic rapeseed oil • Benfluorex • Selective serotonin reuptake inhibitors[a]	• Amphetamines • Dasatinib • L-tryptophan • Methamphetamines	• Cocaine • Phenylpropanolamine • St John's Wort • Amphetamine-like drugs • Interferon α and β • Some chemotherapeutic agents such as alkylating agents (mytomycine C, cyclophosphamide)[b]

PVOD

1'. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis

- 1'.1 Idiopathic
- 1'.2 Heritable
  - 1'.2.1 EIF2AK4 mutation
  - 1'.2.2 Other mutations
- 1'.3 Drugs, toxins and radiation induced
- 1'.4 Associated with:
  - 1'.4.1 Connective tissue disease
  - 1'.4.2 HIV infection





PULMONARY FUNCTION TESTING

Prevalence abnormal physiology 45-100%
Restrictive ventilator pattern 25-41%
Isolated reduction in DLCO 18-47%
- early sign of SSc – ILD
- also suggestive of PAH

Exercise desaturation: earliest abnormality

Correlation: BAL vs HRCT

Test	HRCT +	HRCT –	Total
BAL +	89 (49%)	17 (9%)	106 (58%)
BAL –	48 (27%)	27 (15%)	75 (42%)
Total	137 (76%)	44 (24%)	181

- HRCT: sensitivity 90.6%
- BAL: sensitivity 70%
- Concordance: 65%

Silver R et al. *Am J Respir Crit Care Med.* 2004;169:A227.