Pulmonary Arterial Hypertension RELATED TO CONNECTIVE TISSUE DISORDER

The strategy of INITIAL COMBINATION THERAPY

Eftychia Demerouti MD, MSc, PhD
Cardiologist
Onassis Cardiac Surgery Center

CONFLICT OF INTERESTS

None related to this presentation

NAME OF COMPANIES WITH WICH RELATIONSHIP EXISTS

Actelion Pharmaceuticals Ltd, Bayer Schering, Galenica, GlaxoSmithKline, Lilly, MSD, Pfizer Ltd

NAME OF RELATIONSHIP

Consultant, Honoraria, Advisory Board Member

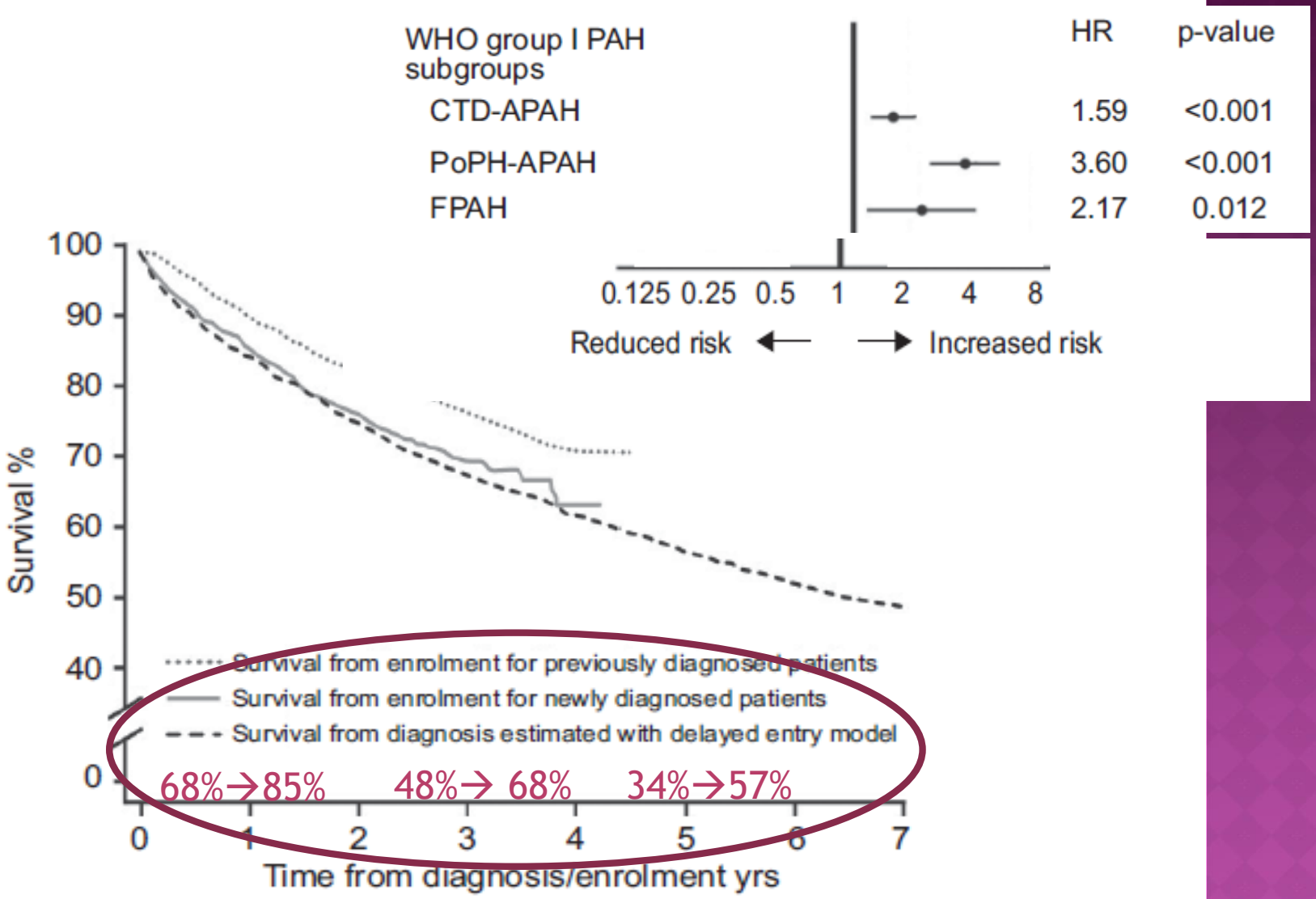
EVOLVING THERAPIES FOR PAH

- **1976-1992** : single case report or cases series of the effects of vasodilators : *Isoproterenol, Hydralazine, Diazoxide,Calcium-Channel Blockers*

- **1996- 2013** :Short-term RCTs of drugs targeting *Prostacyclin, Endothelin and Nitric oxyde pathways* (6'WD as primary E-P)

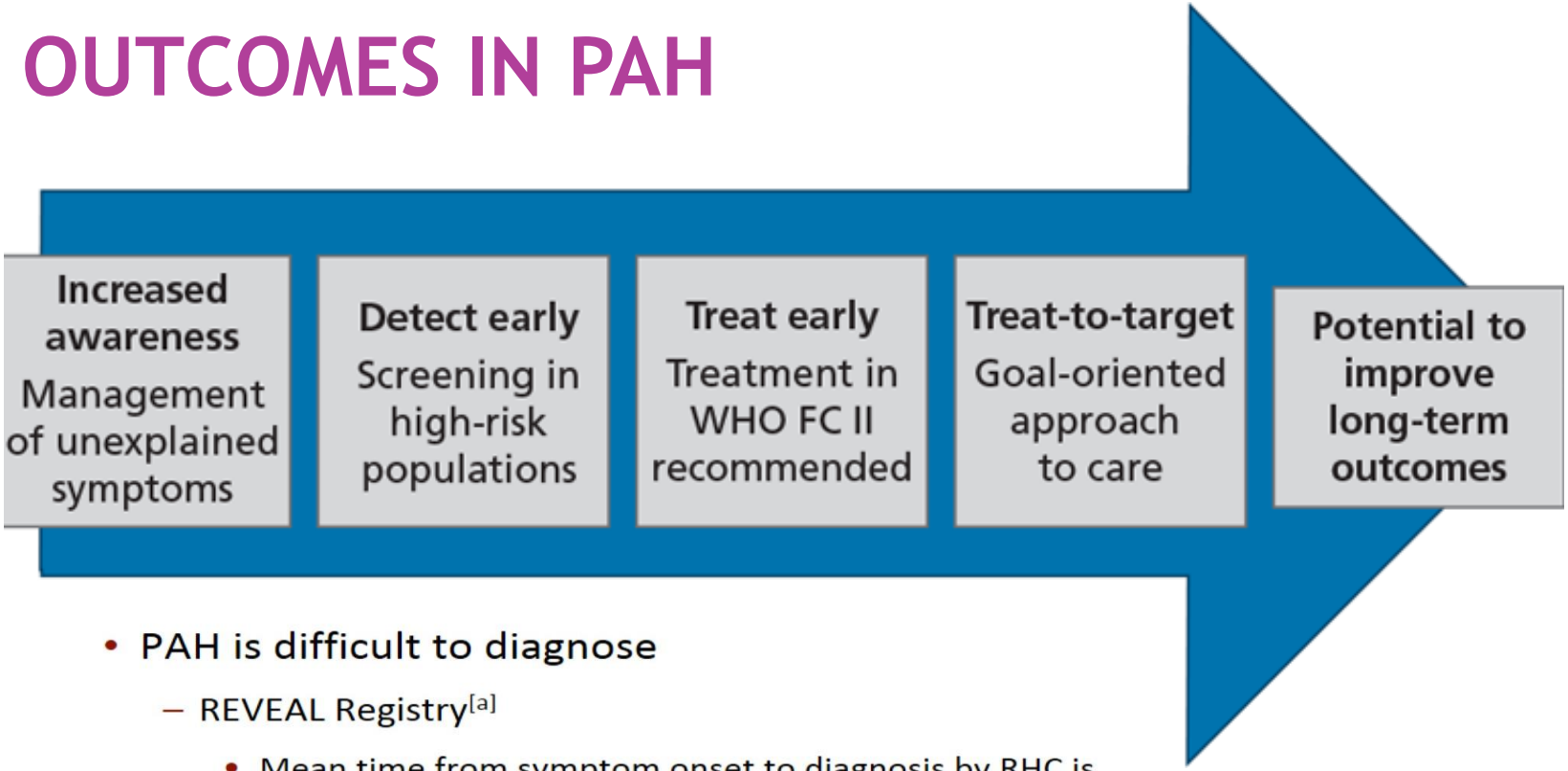
- **2013-2016** : Long-term RCTs of dugs targeting same pathways but combined (morbidity and mortality as primary E-P)

REVEAL REGISTRY



Eur Respir Rev 2012; 21:123,8-18

PATHWAY TO IMPROVING LONG-TERM OUTCOMES IN PAH



- PAH is difficult to diagnose
  - REVEAL Registry[a]
    - Mean time from symptom onset to diagnosis by RHC is ~2.8 years
    - 73.6% of patients diagnosed at advanced stages of disease
- Delayed diagnosis one of the biggest barriers to better patient outcomes[b]
- Collaboration between PH specialty centers and referring physicians is essential

a. Brown LM, et al. *Chest*. 2011;140:19-26.
b. Galiè N, et al. *Eur Respir Rev*. 2015;24:550-551.

A 54-YEAR-OLD-MAN

Scleroderma limited cutaneous

Emphysema

Arterial Hypertension

BMI 28 Kg/m2

Methotrexate
Antihypertensive treatment
O2

Dyspnea

Echocardiogram 2 years ago, PASP 40 mmHg

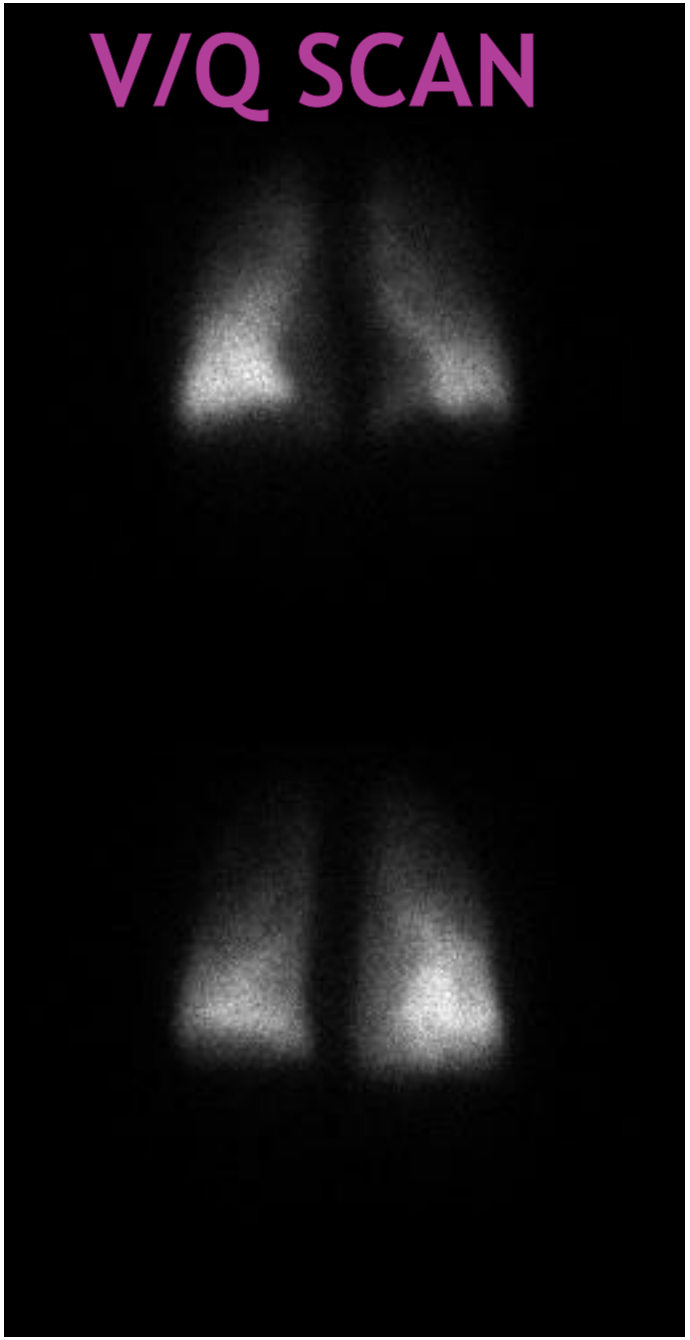
SPIROMETRY

pO2 (room air) 61 mmHg,
PaCO2 36 mmHg
P(A-a)O2 25
FiO2 0,21

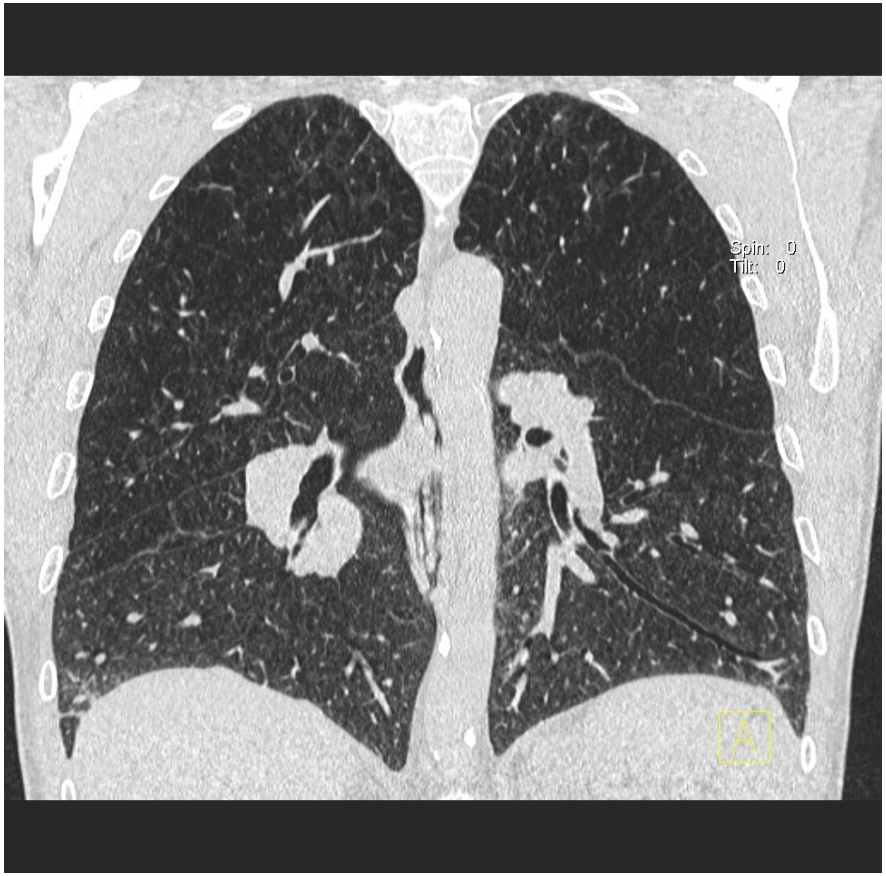
FVC 80%
FEV1 48%
FEV1/FVC 59.5%

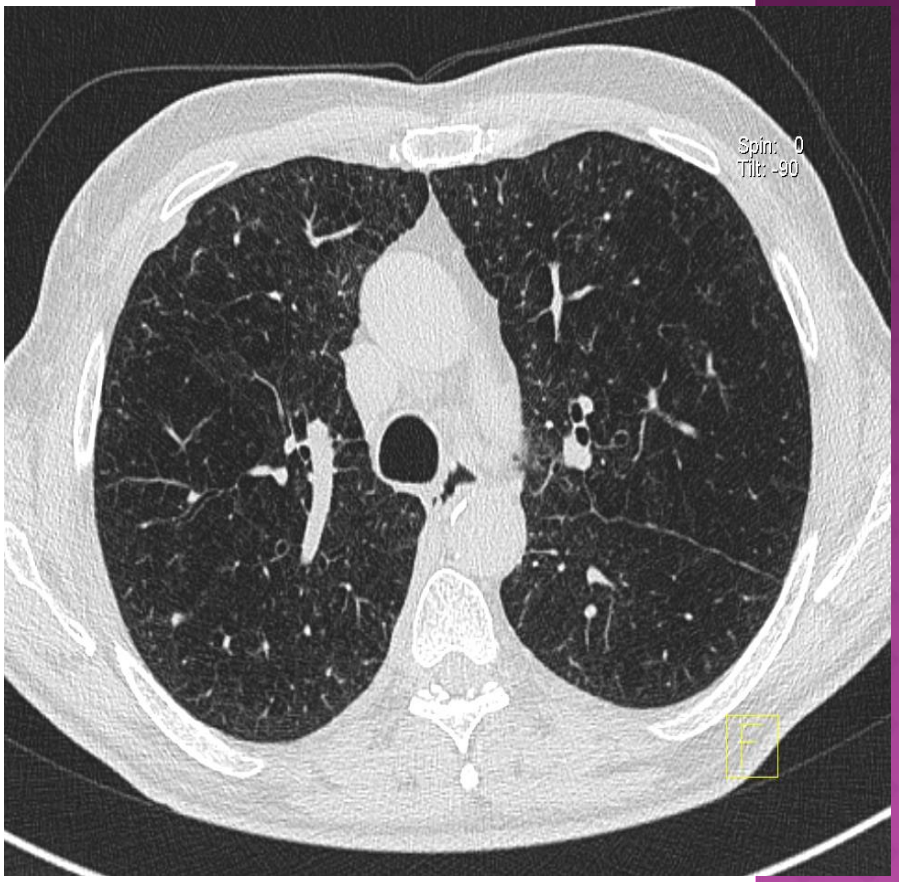
TLC 138,2% (9,23L)
DLCO: 43%

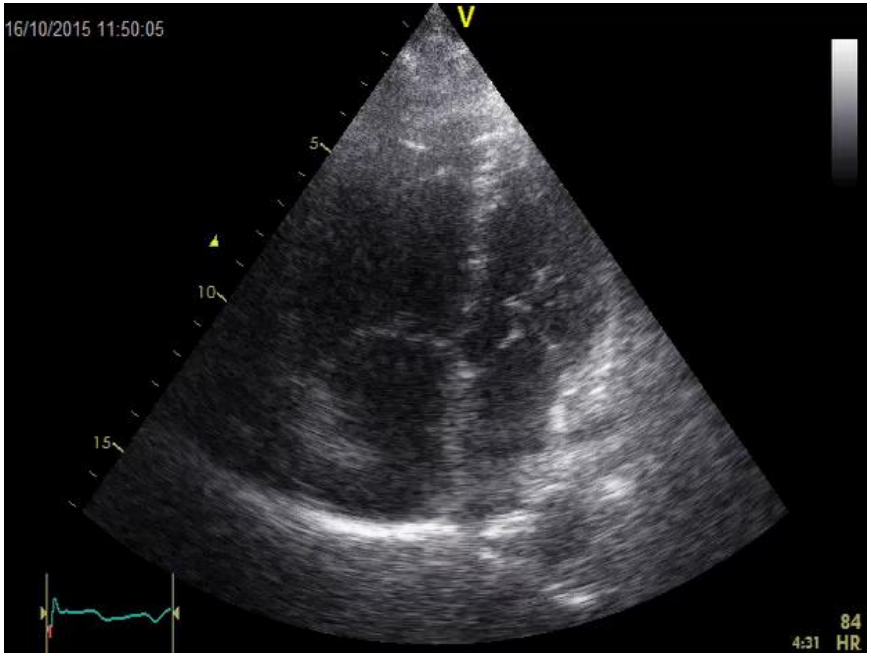
HIGH PROBABILITY OF PE
IN LEFT UPER LOBE AND RIGHT APEX

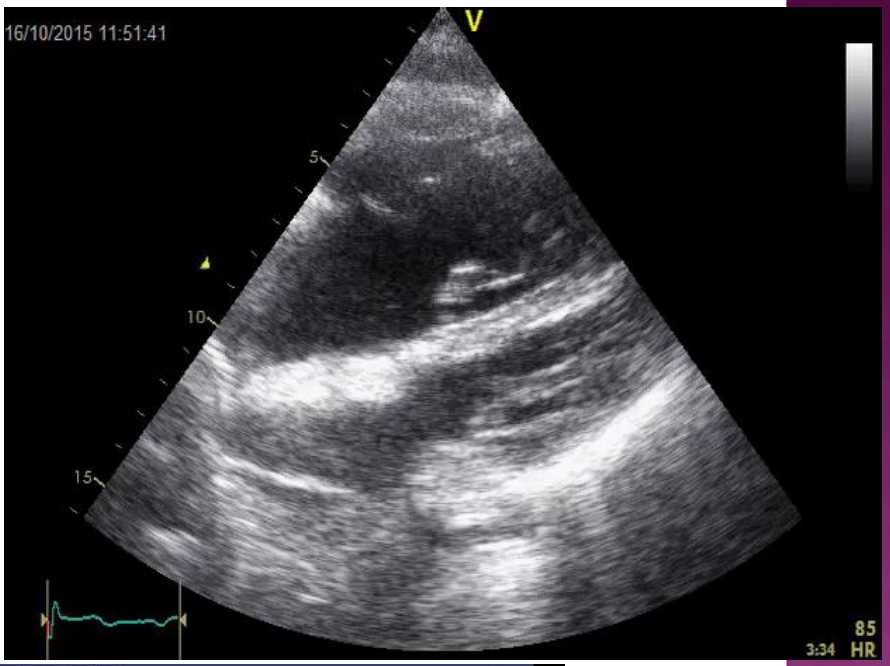


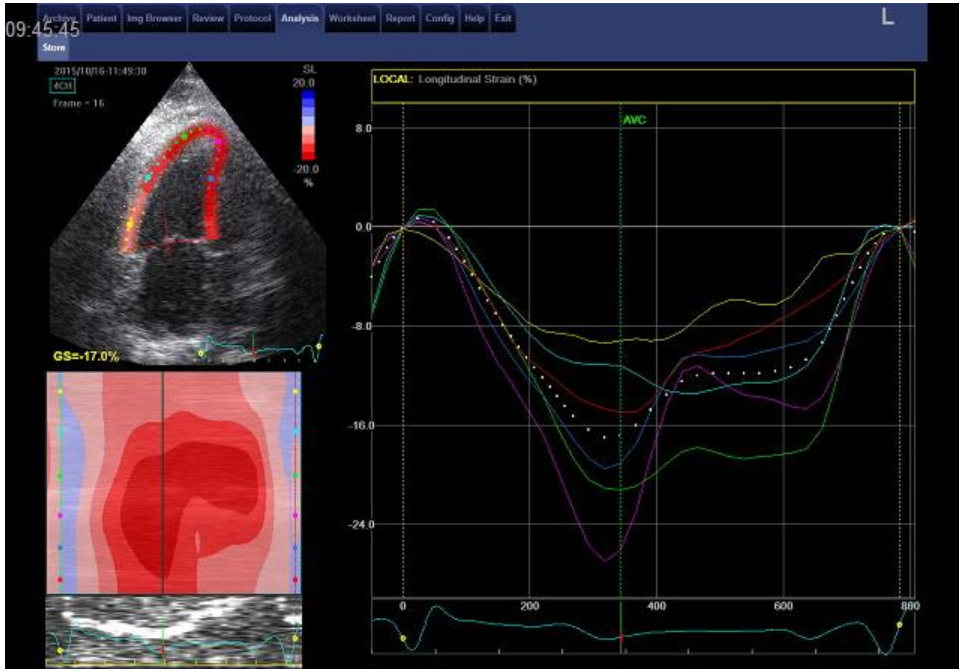
LUNG CT



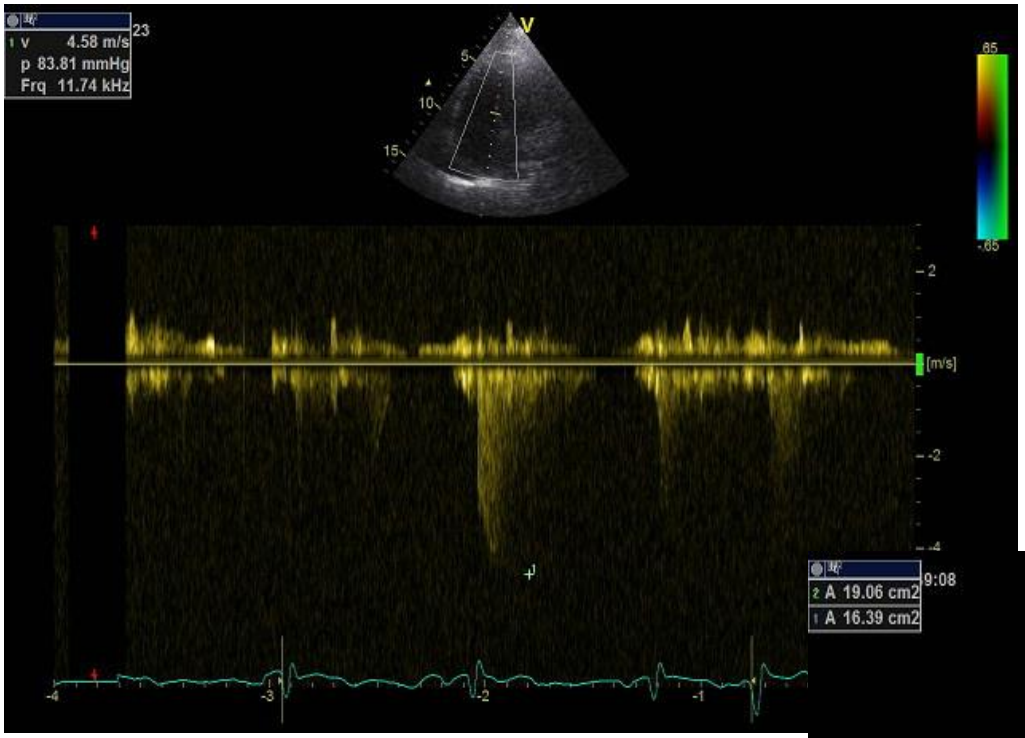


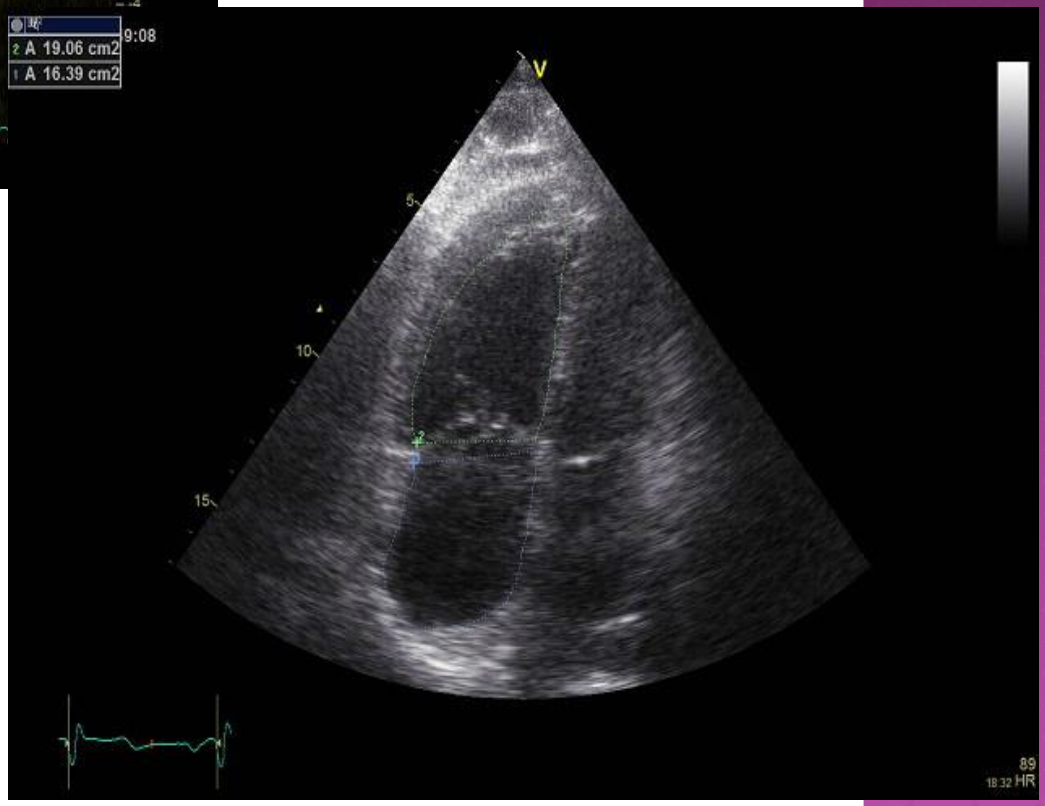

16/10/2015 11:50:05
V
5
10
15
84
4:31 HR


16/10/2015 11:51:41
V
5
10
15
85
3:34 HR


09:45:45
Archive
Patient
Img Browser
Review
Protocol
Analysis
Worksheet
Report
Config
Help
Exit
Store
L
2015/10/16-11:49:38
4CH
Frame = 16
SL
20.0
-20.0
%
GS=-17.0%
LOCAL: Longitudinal Strain (%)
AVC
8.0
0.0
-8.0
-16.0
-24.0
0
200
400
600
800

ECHO



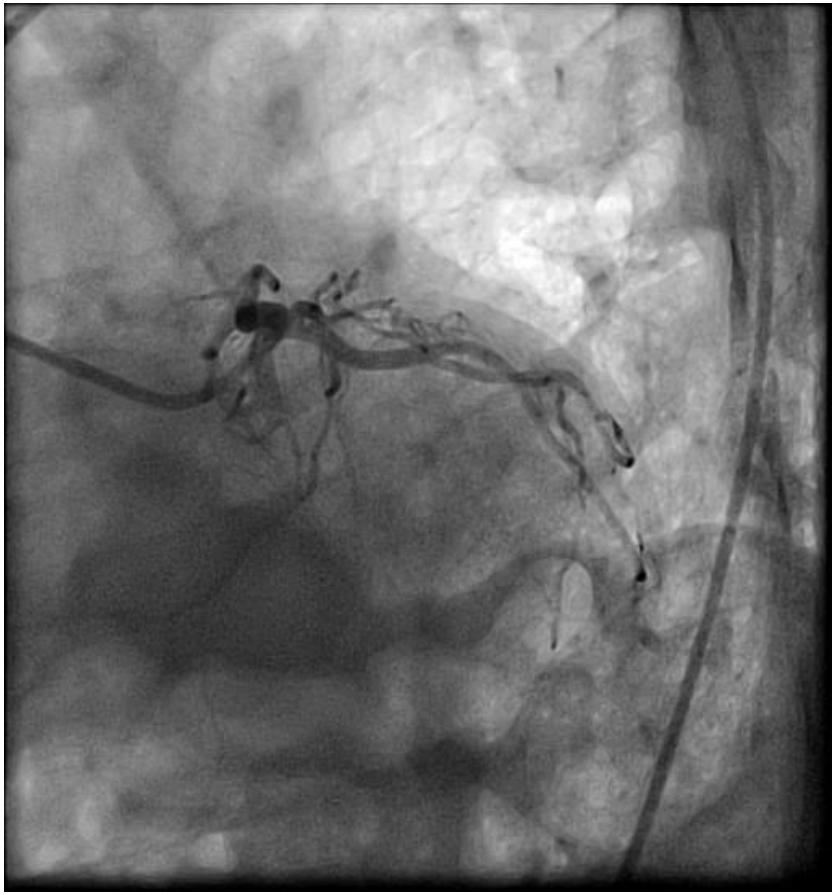


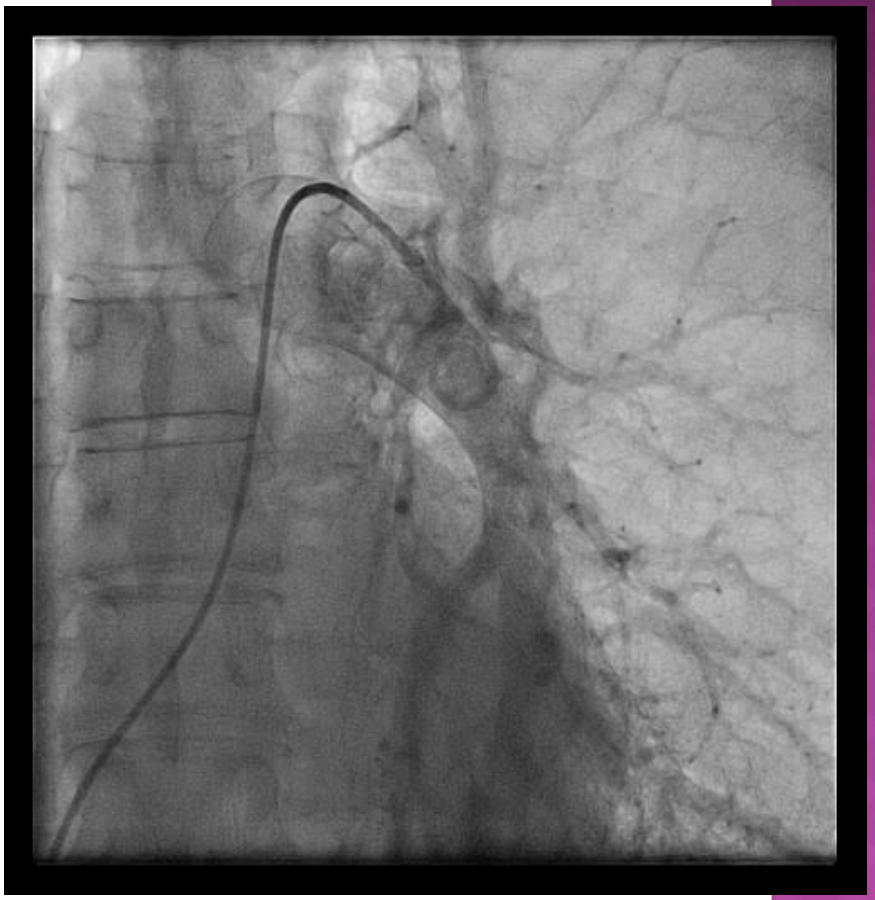
RHC 11/2015

RA (mmHg)	13
PA (mmHg)	104/55/73
PAP (mmHg)	18
Oxymetry	
PA (O2%)	71.4
LV (O2)	96%
CI (l/min/m2)	1,7
PVR (WU)	22

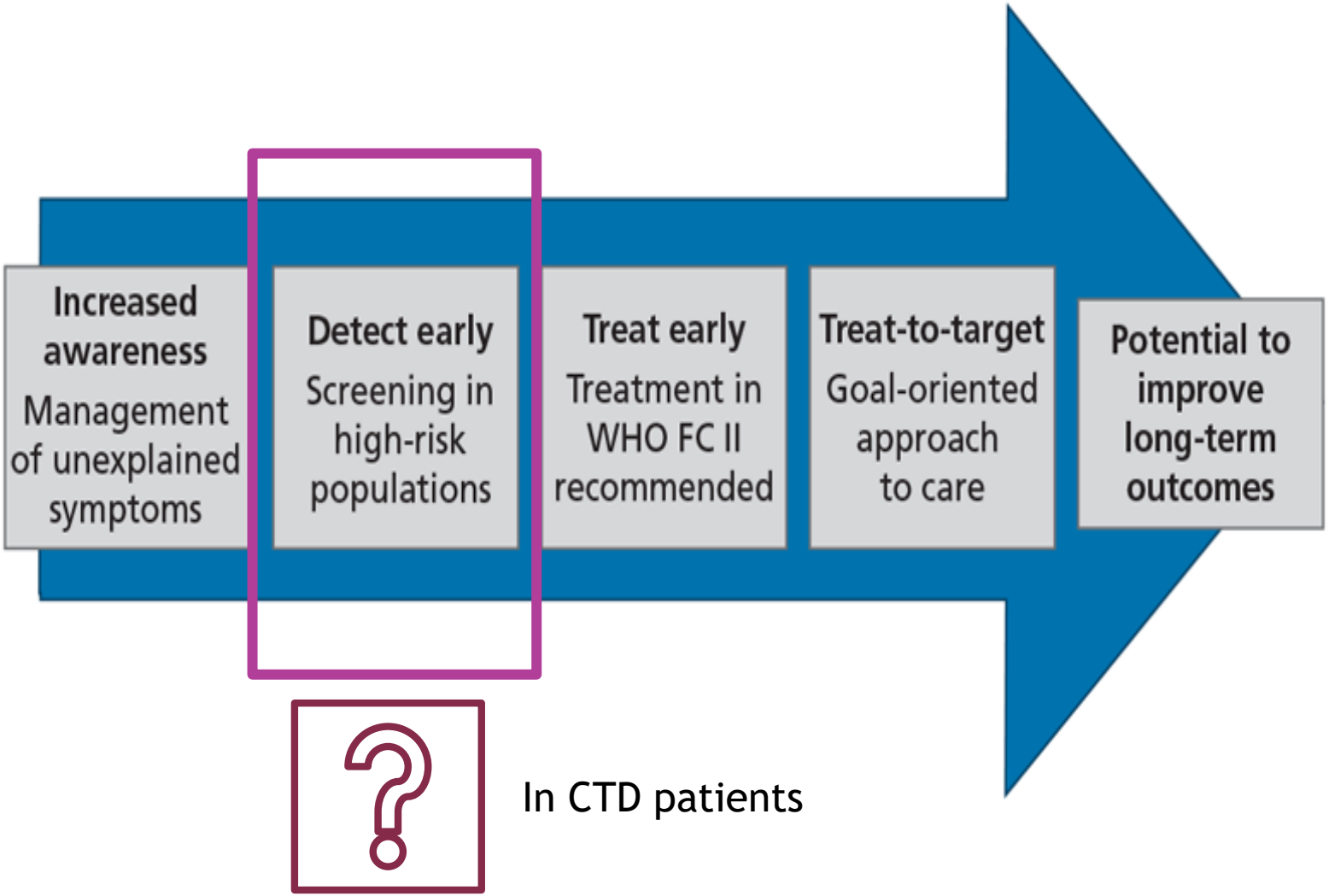
WHO III
NT-pro BNP 1400 pg/ml
6MWT 320 m

CORONARY AND PULMONARY ANGIOGRAPHY





PATHWAY TO IMPROVING LONG-TERM OUTCOMES IN PAH



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.

DETECT ALGORITHM – PH IN SSC

Annual screening

WITH DLCO <60% AND DISEASE DURATION>3YEARS

WITH SIGNS AND SYMPTOMS → RHC

Without clinical signs or symptoms

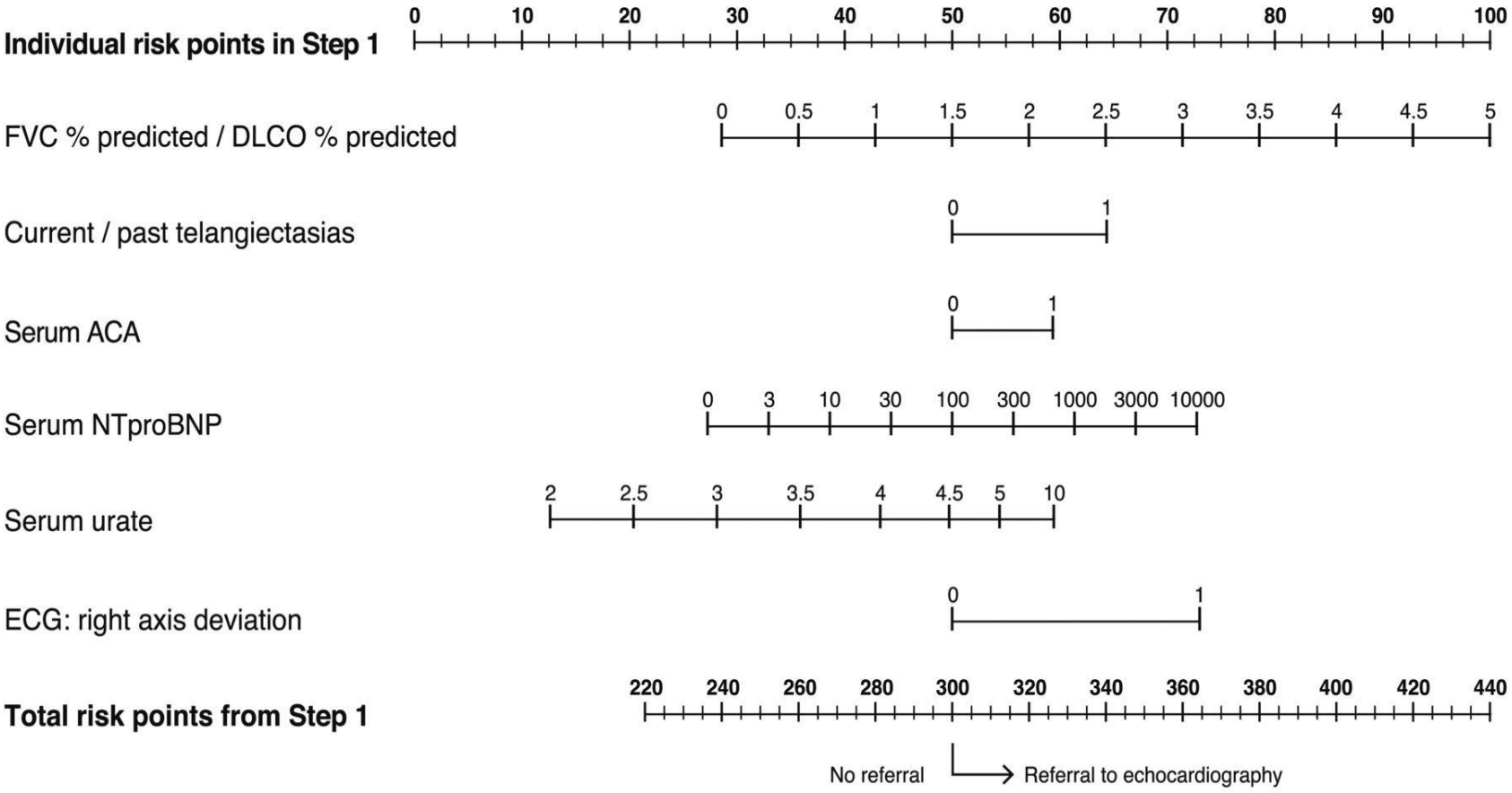
1st STEP: Assessment for telangiectasia, anticentromere antibodies, PFT, DLCO ECG, biomarkers (uric acid, NT-proBNP)

IF ABNORMAL FINDINGS

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

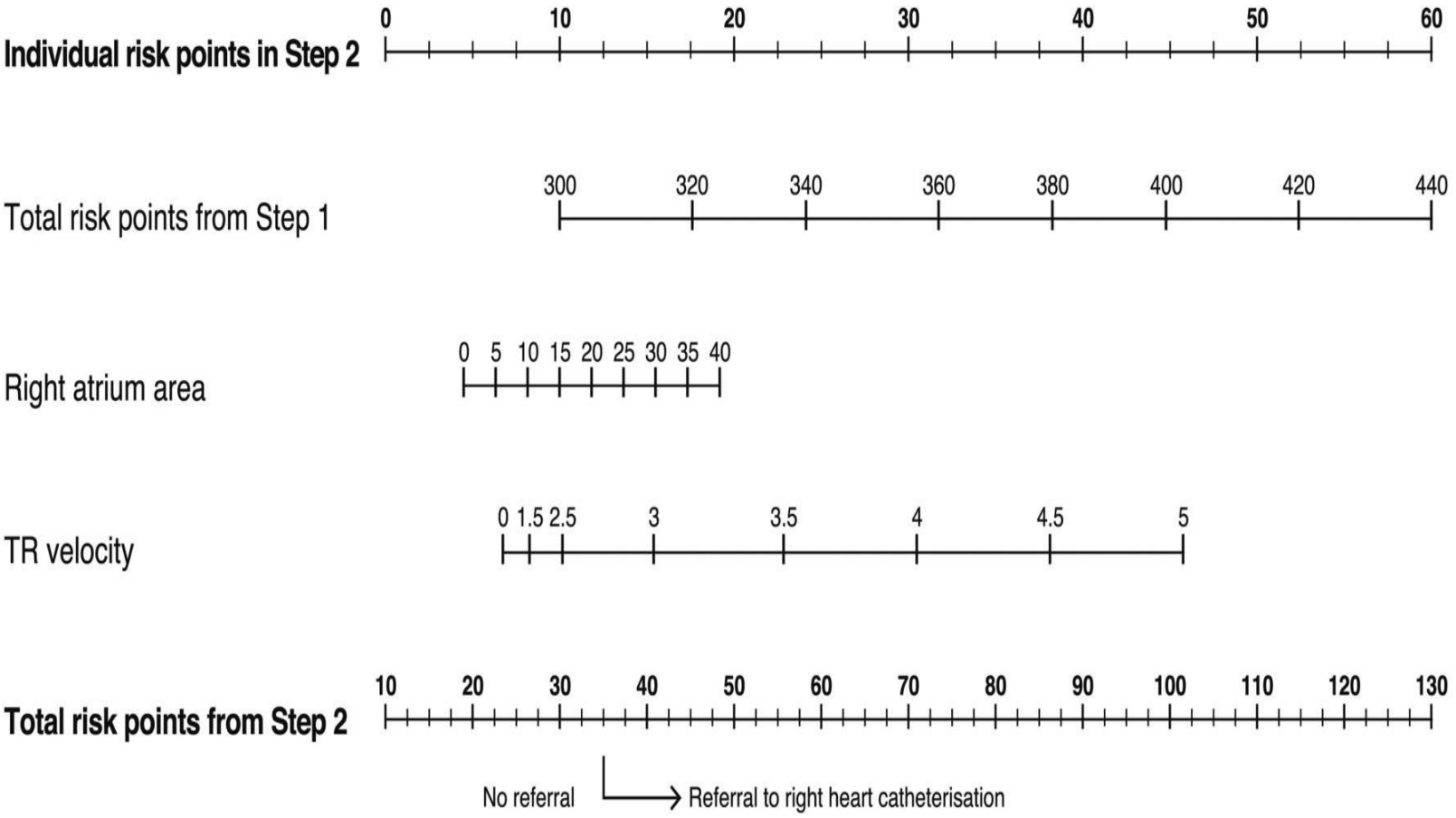
Ann Rheum Dis 2014; 73: 1340-1349

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

In patients with SSc spectrum of diseases (defined as patients with systemic sclerosis, mixed connective tissue disease, or other CTDs with prominent scleroderma features such as sclerodactyly, nail fold capillary abnormalities, SSc-specific autoantibodies).

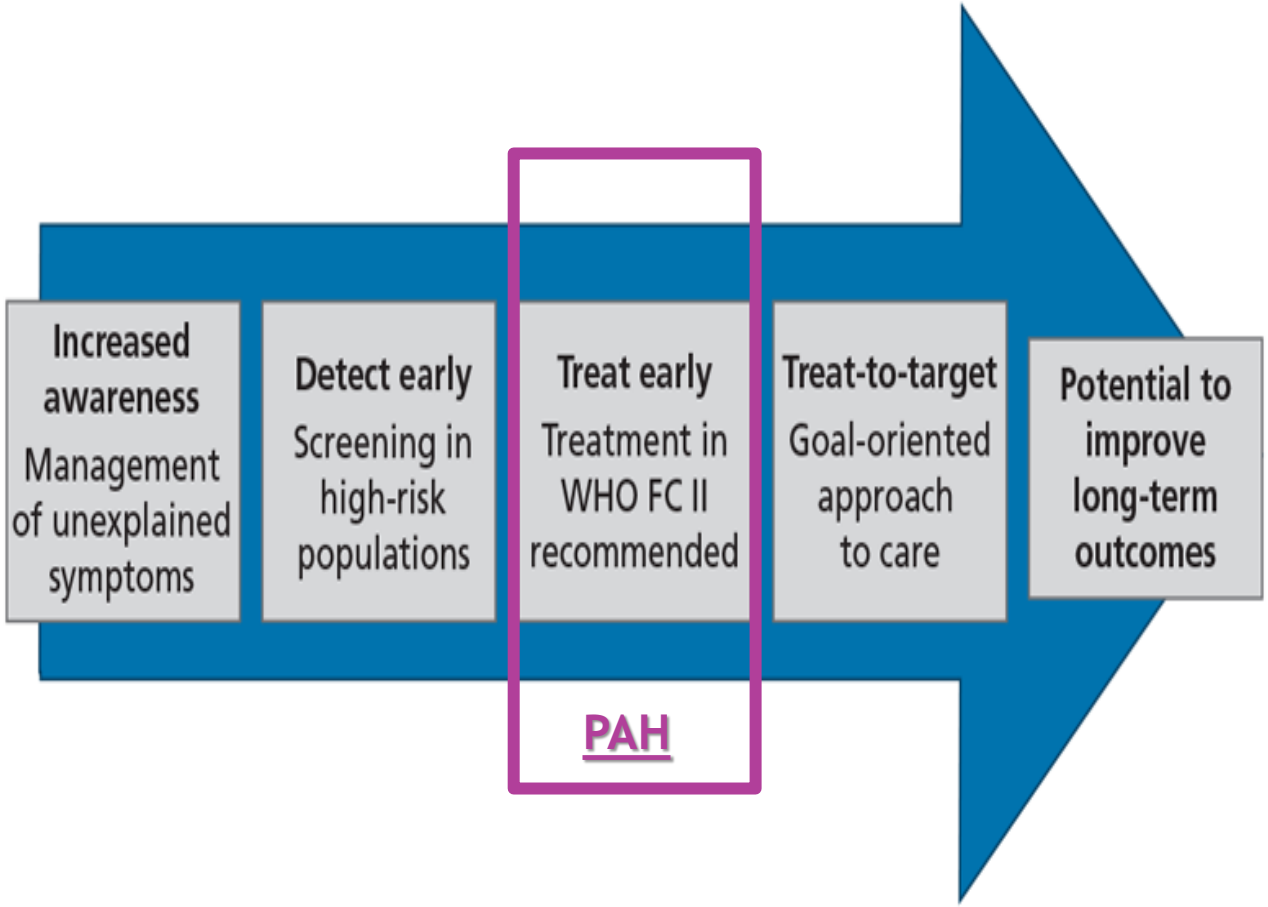
No such guidelines exist for other CTDs.

ECHOCARDIOGRAPHIC PROBABILITY & DIAGNOSTIC STRATEGY

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	

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

PATHWAY TO IMPROVING LONG-TERM OUTCOMES IN PAH



SPECIFIC PAH DRUG THERAPY

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

THE PATIENT

PH classification

RA (mmHg)	13
PA (mmHg)	104/55/73
PAP (mmHg)	18
Oxymetry	
PA (O2%)	71.4
LV (O2)	96%
CI (l/min/m2)	1,7
PVR (WU)	22

1. PAH
2. PH due to Left Heart Disease
3. PH due to Lung Diseases
4. Chronic Thromboembolic Pulmonary Hypertension
5. PH due to unclear or multifactorial mechanisms

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

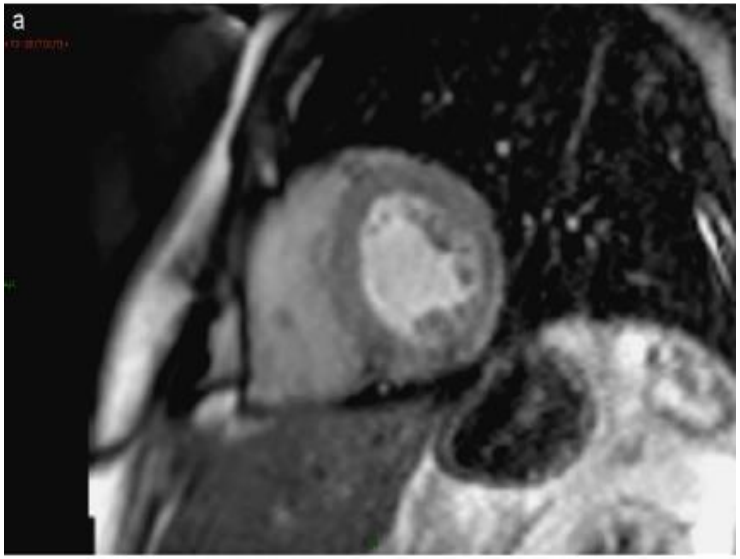
JACC 2013; 62: D42-50

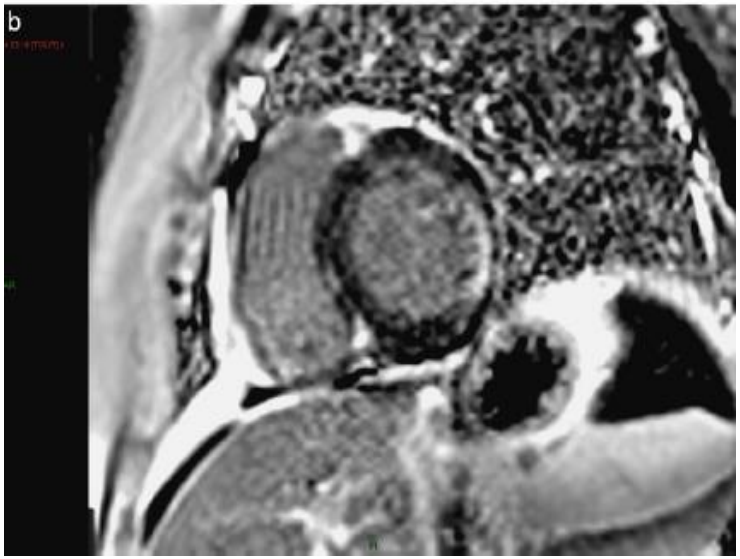
ECHOCARDIOGRAPHY IN PAH-SSC

	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

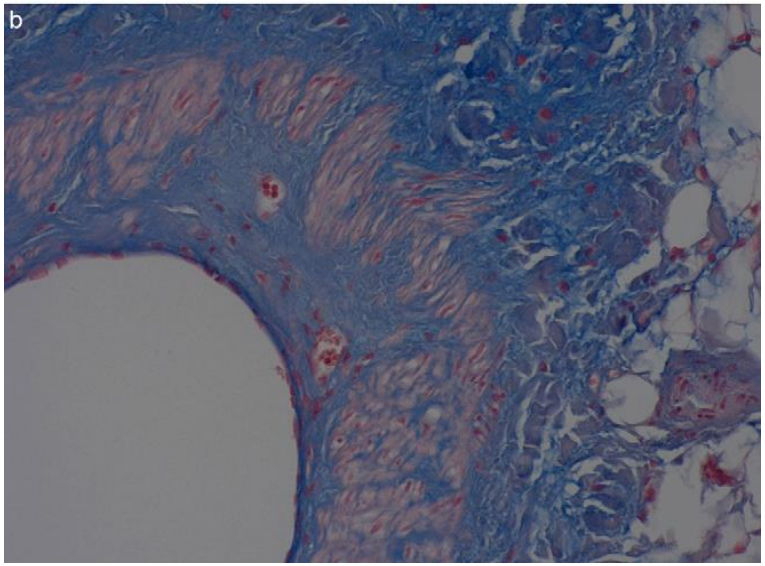
Fisher MR et al. *Arthritis Rheum*. 2006;54:3043-3050.

MYOCARDIAL FIBROSIS





Myocardial fibrosis is thought to occur after repeated focal ischaemia



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

PA (mmHg)

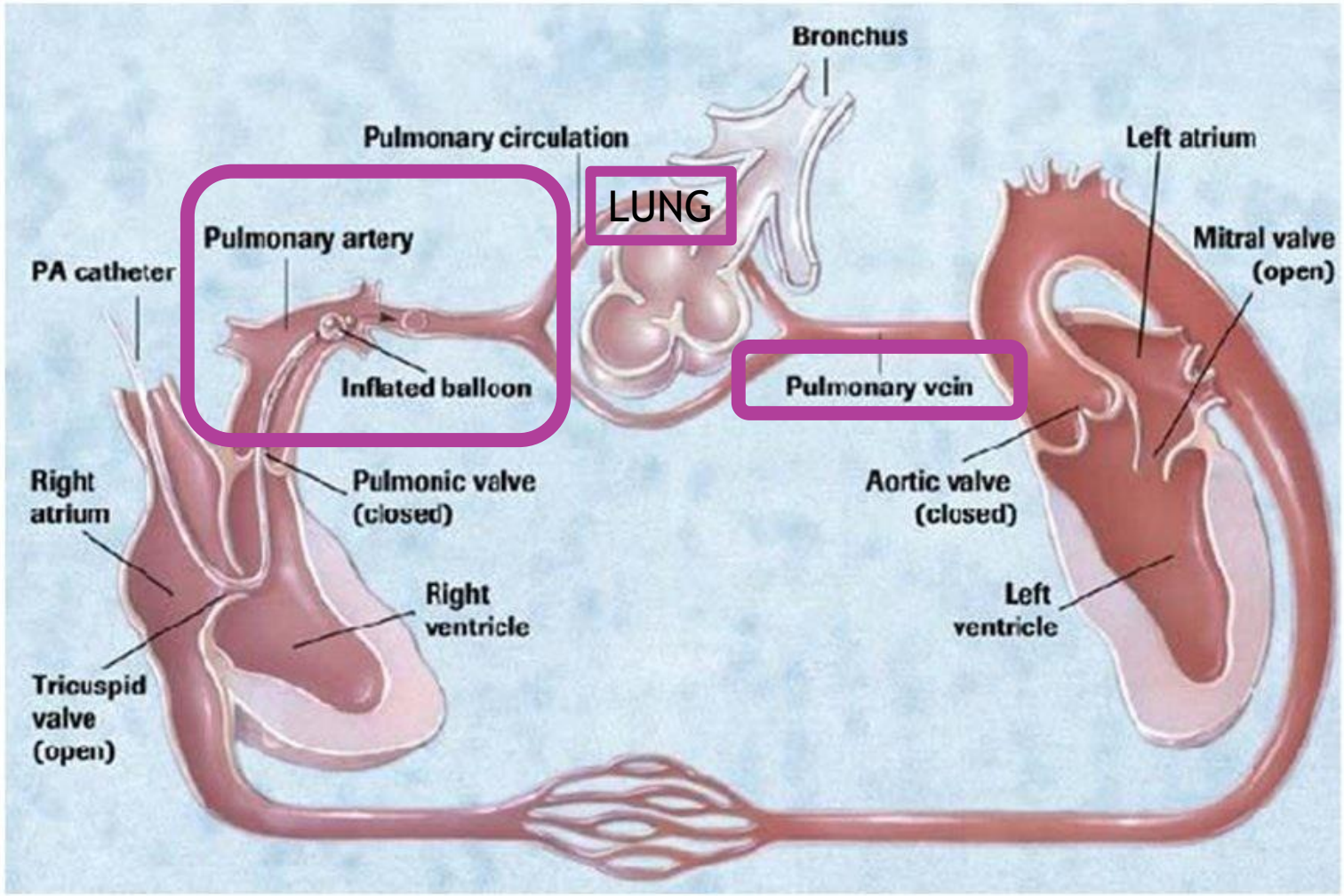
104/55/73

PAP (mmHg) 18

DPG: 37 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

HAEMODYNAMIC ASSESSMENT



RHC: PAPmean>25mmHg, PVR>3WU

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

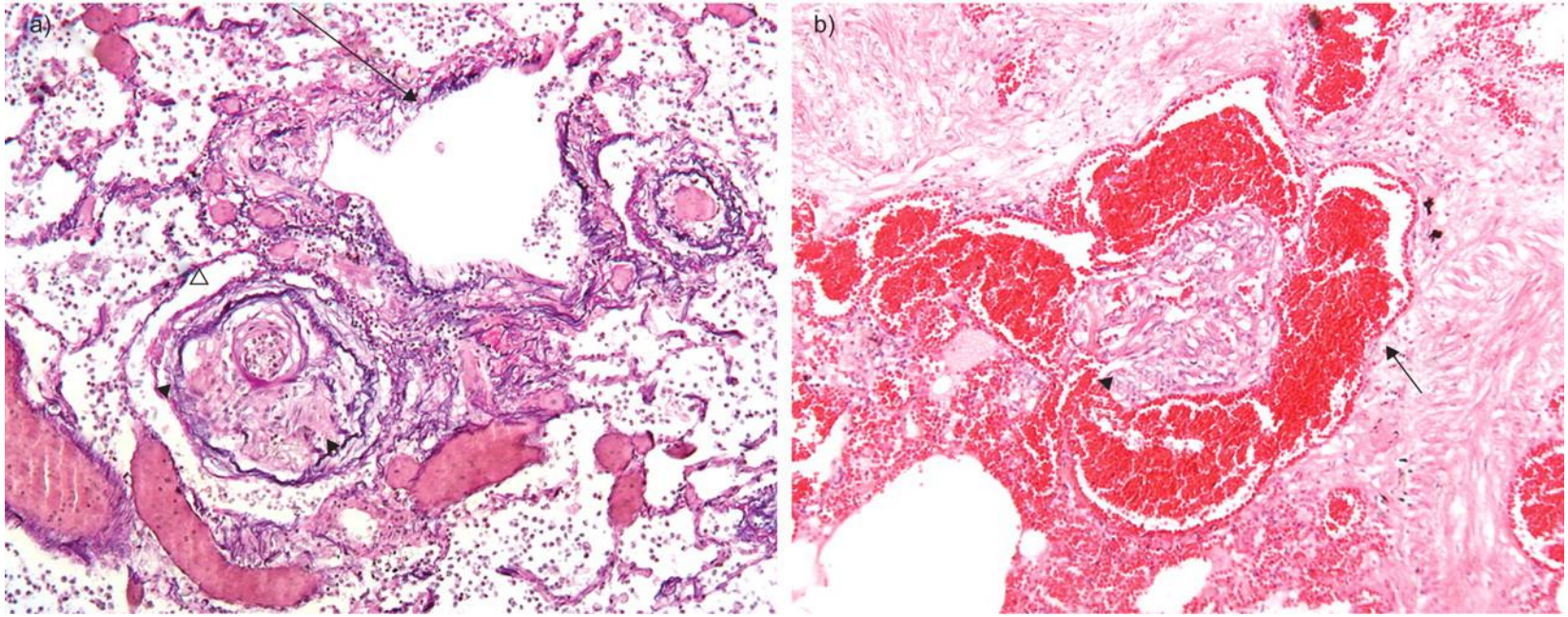
RA (mmHg)	13
PA (mmHg)	104/55/73
PAP (mmHg)	18
Oxymetry	
PA (O2%)	71.4
LV (O2)	96%
CI (l/min/m2)	1,7
PVR (WU)	22

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

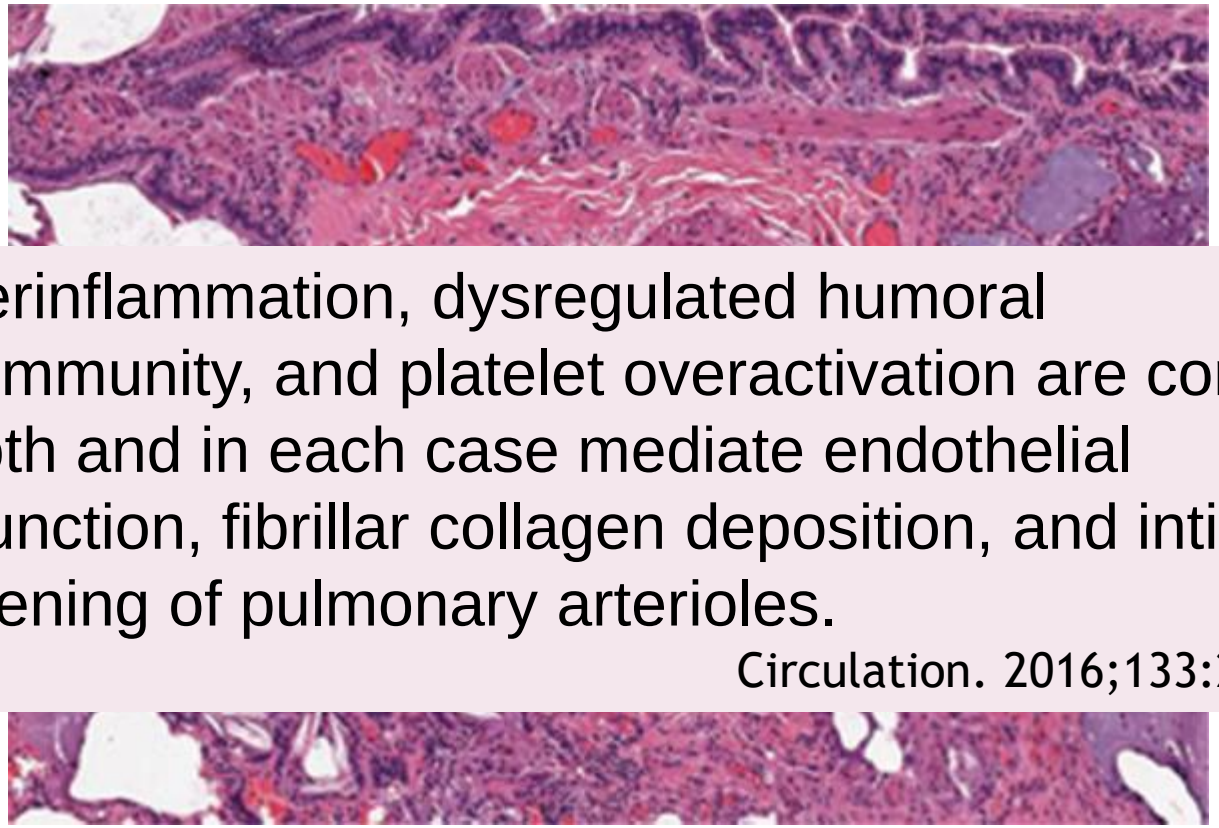
a) Single lesion in the systemic sclerosis-associated pulmonary arterial hypertension (PAH) group mostly resembling a plexiform lesion : localisation adjacent to a bronchiolus (arrow); intimal fibrosis with recanalisation (black arrowheads)...



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

EULAR Scl trials and EUSTAR group.

Is PAH really a late complication of systemic sclerosis?



Hyperinflammation, dysregulated humoral autoimmunity, and platelet overactivation are common to both and in each case mediate endothelial dysfunction, fibrillar collagen deposition, and intimal thickening of pulmonary arterioles.

Circulation. 2016;133:2345-2347

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

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

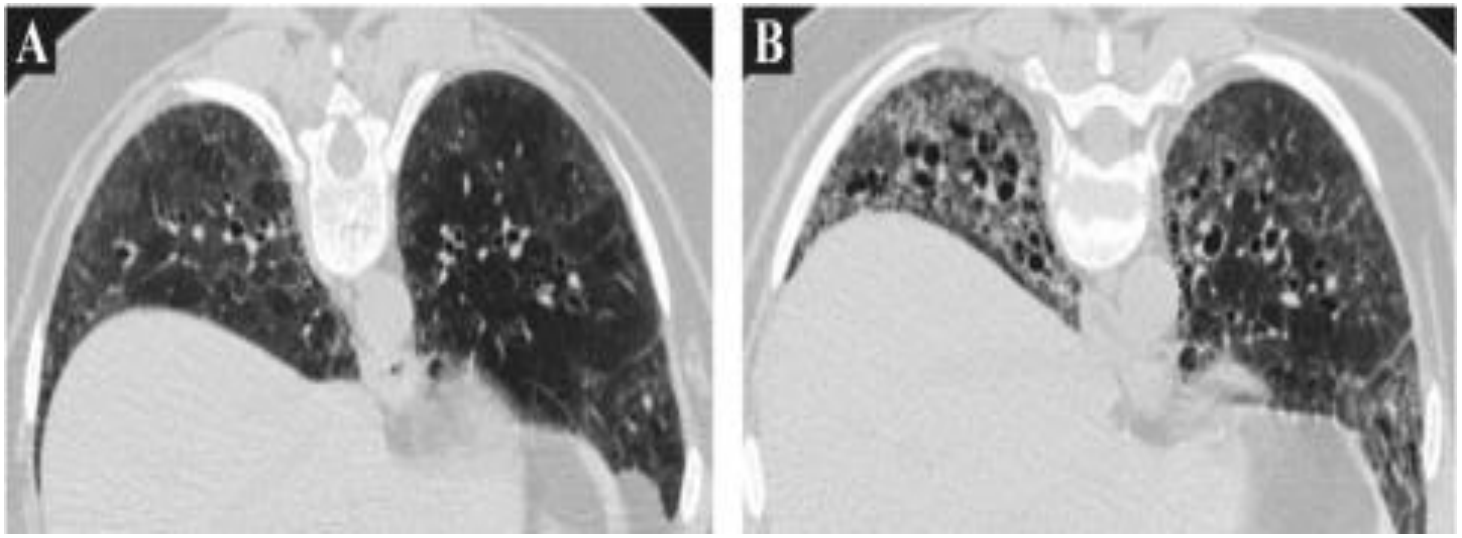
GROUP 3 PH

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

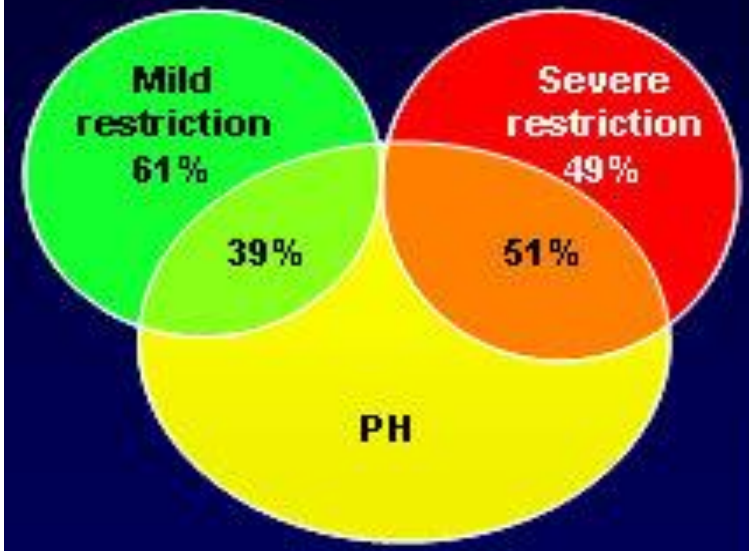


In the Scleroderma Lung Study, there were no significant differences in the frequency of alveolitis on HRCT scan between lcSSc and dcSSc, suggesting that all patients with SSc are at risk for ILD

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

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

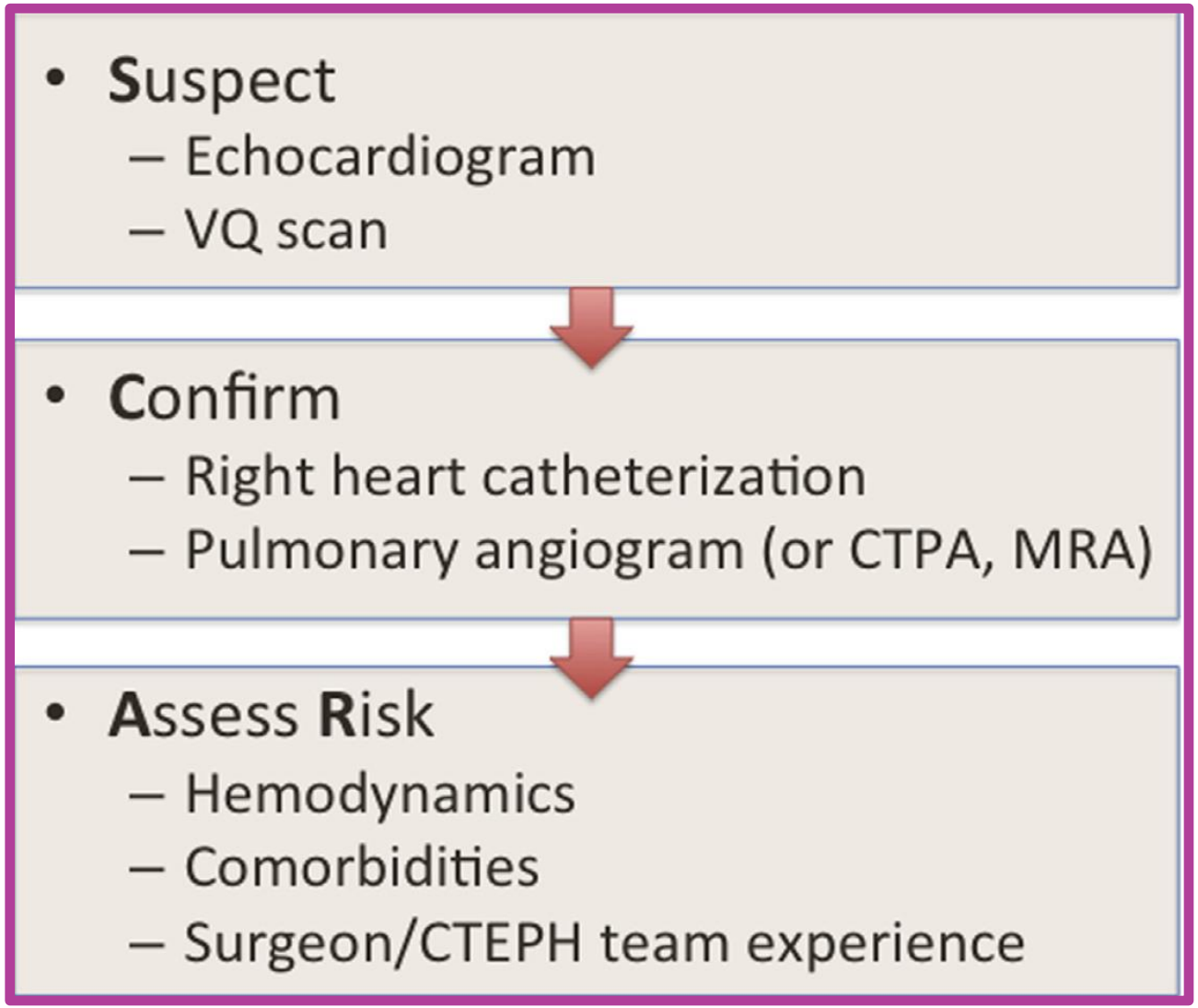
Chang B et al. *J Rheumatol*. 2003;30:2398.

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 Nucl Med 2007; 48:680-684



J Am Coll Cardiol 2013; 62:D92-9

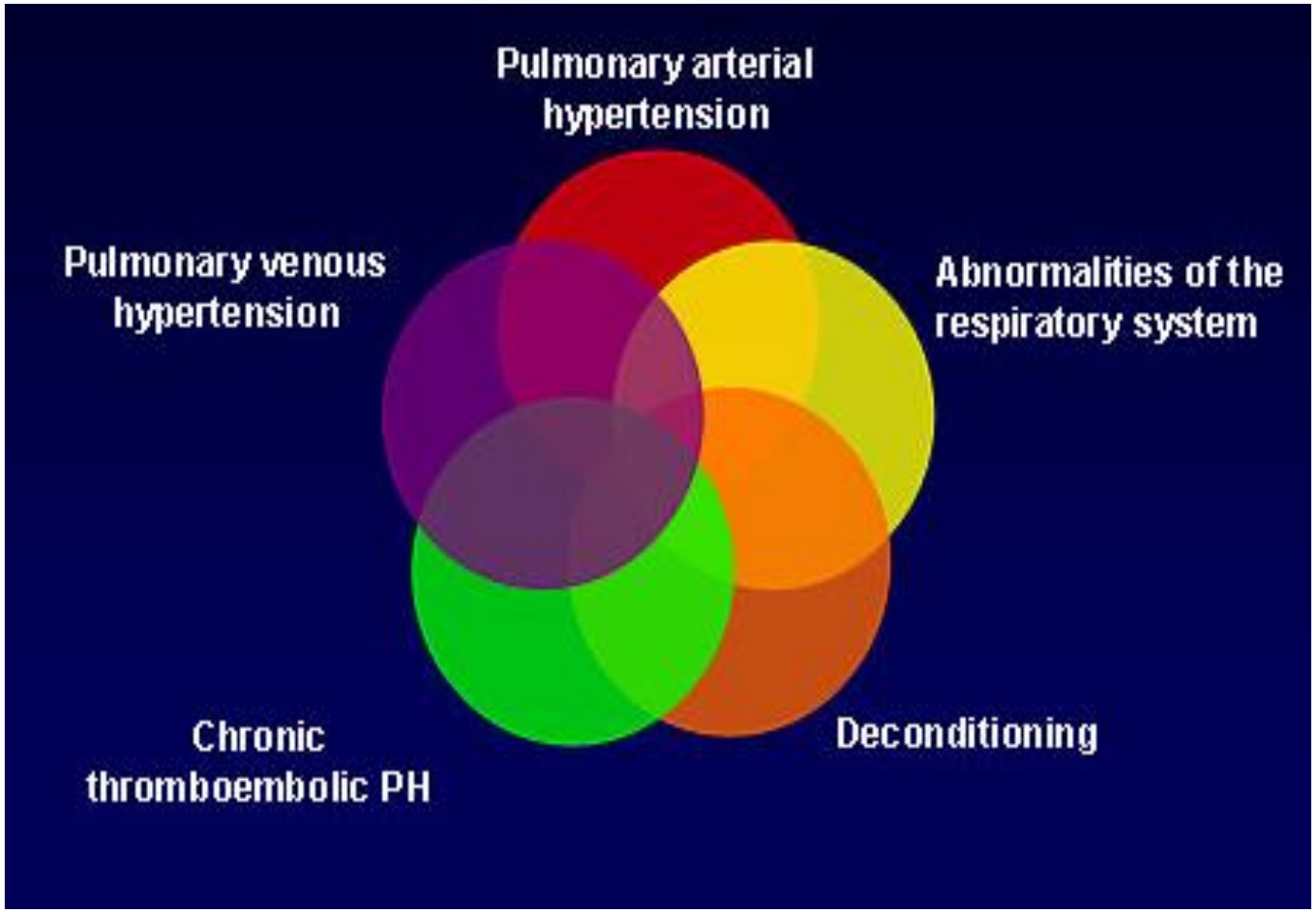
ANTIPHOSPHOLIPID ANTIBODIES IN SSC

- 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]

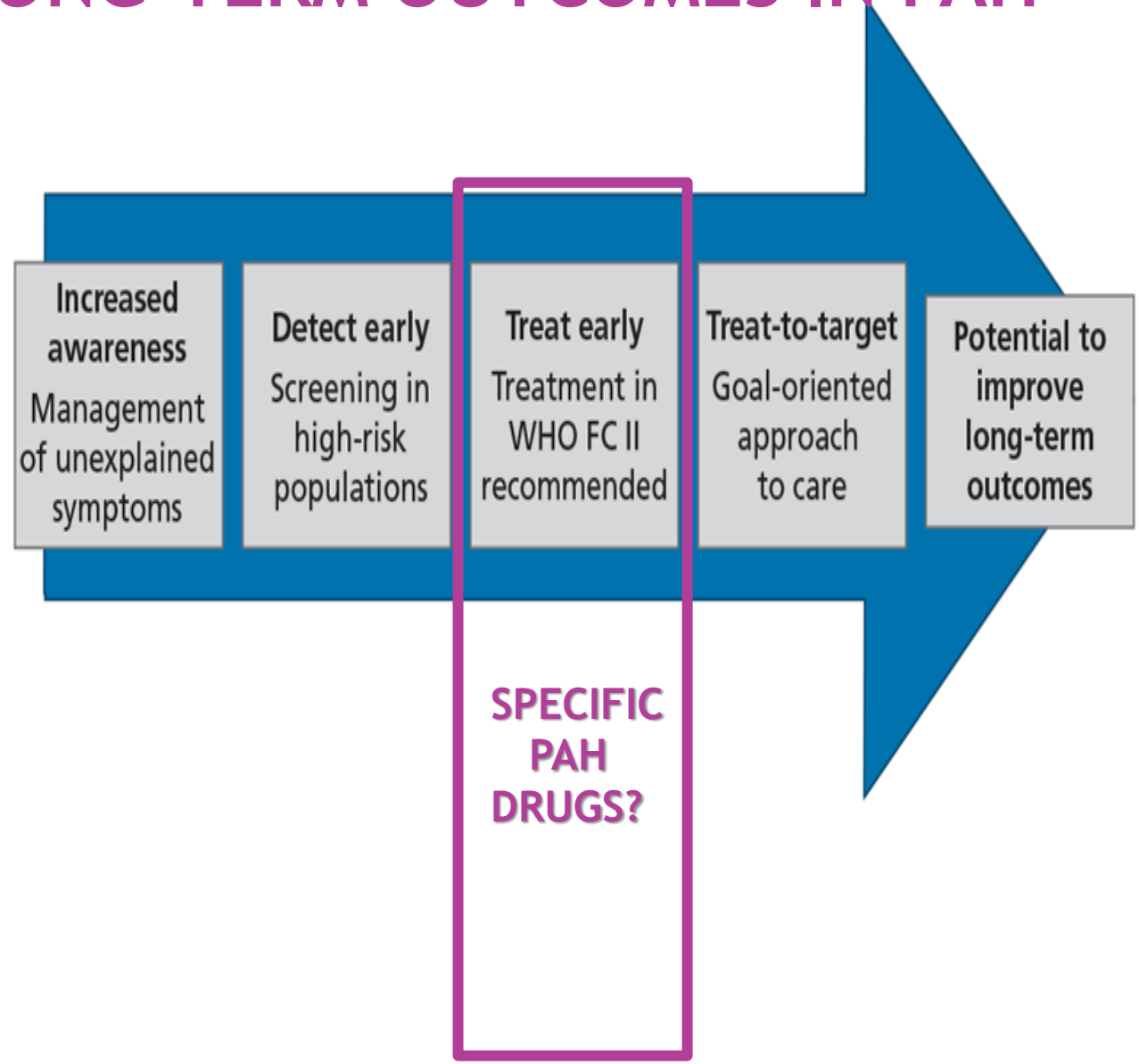
1. Assous N et al. *Clin Exp Rheumatol*. 2005;23:199-204.
2. Swadzba J et al. *Pol Merkur Lekarski*. 1996;1:310-312.
3. Finazzi G et al. *Am J Med*. 1996;100(5):530-536.
4. Cervera R et al. *Medicine*. (Baltimore) 1999;78(3):167-175.

REALITY IN SCLERODERMA

OUR PATIENT : GROUP 1, 2, 3



PATHWAY TO IMPROVING LONG-TERM OUTCOMES IN PAH



PAH DRUGS: POTENTIAL BENEFITS

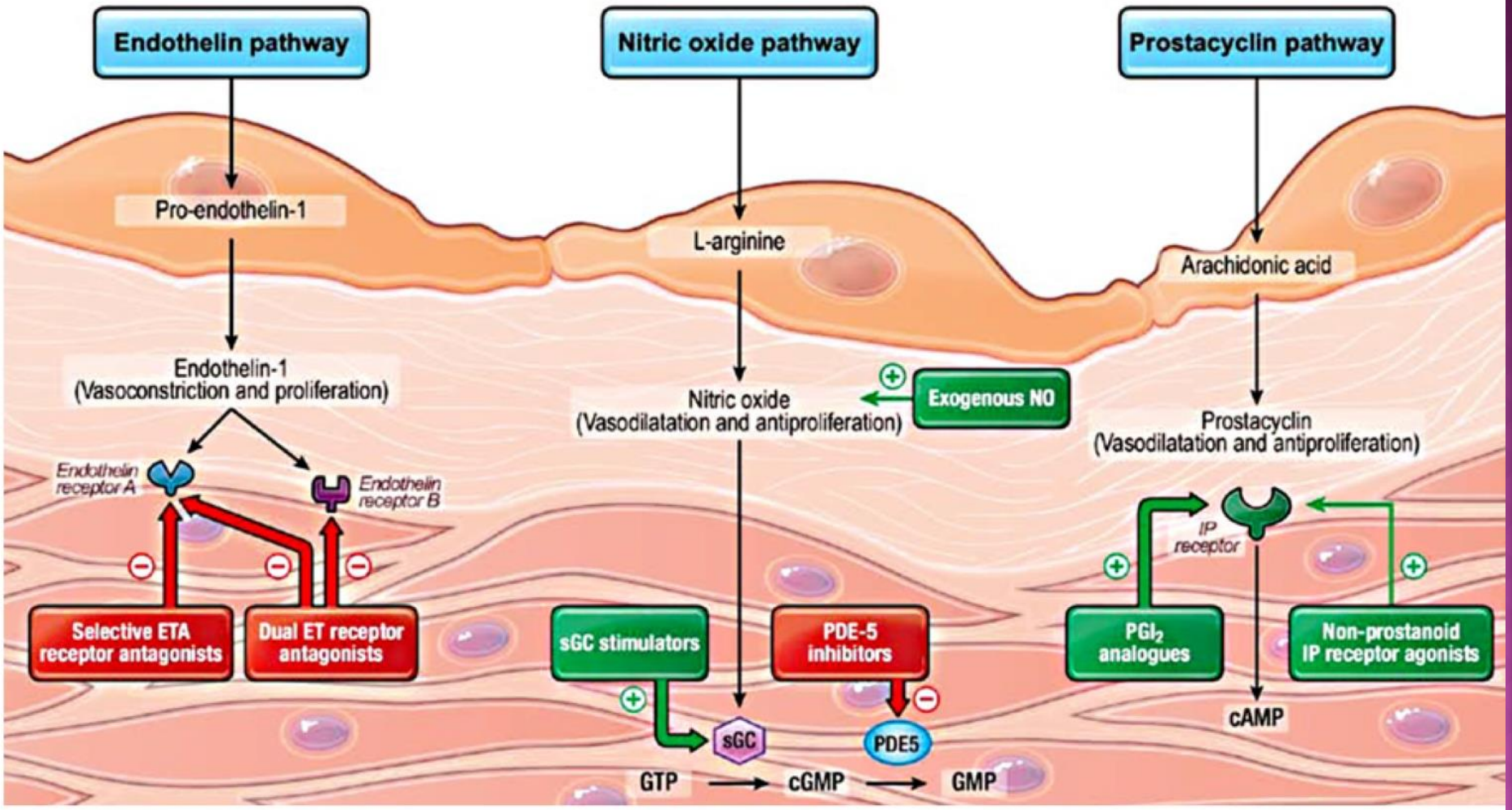
GROUP 2 PH

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

GROUP 3 PH

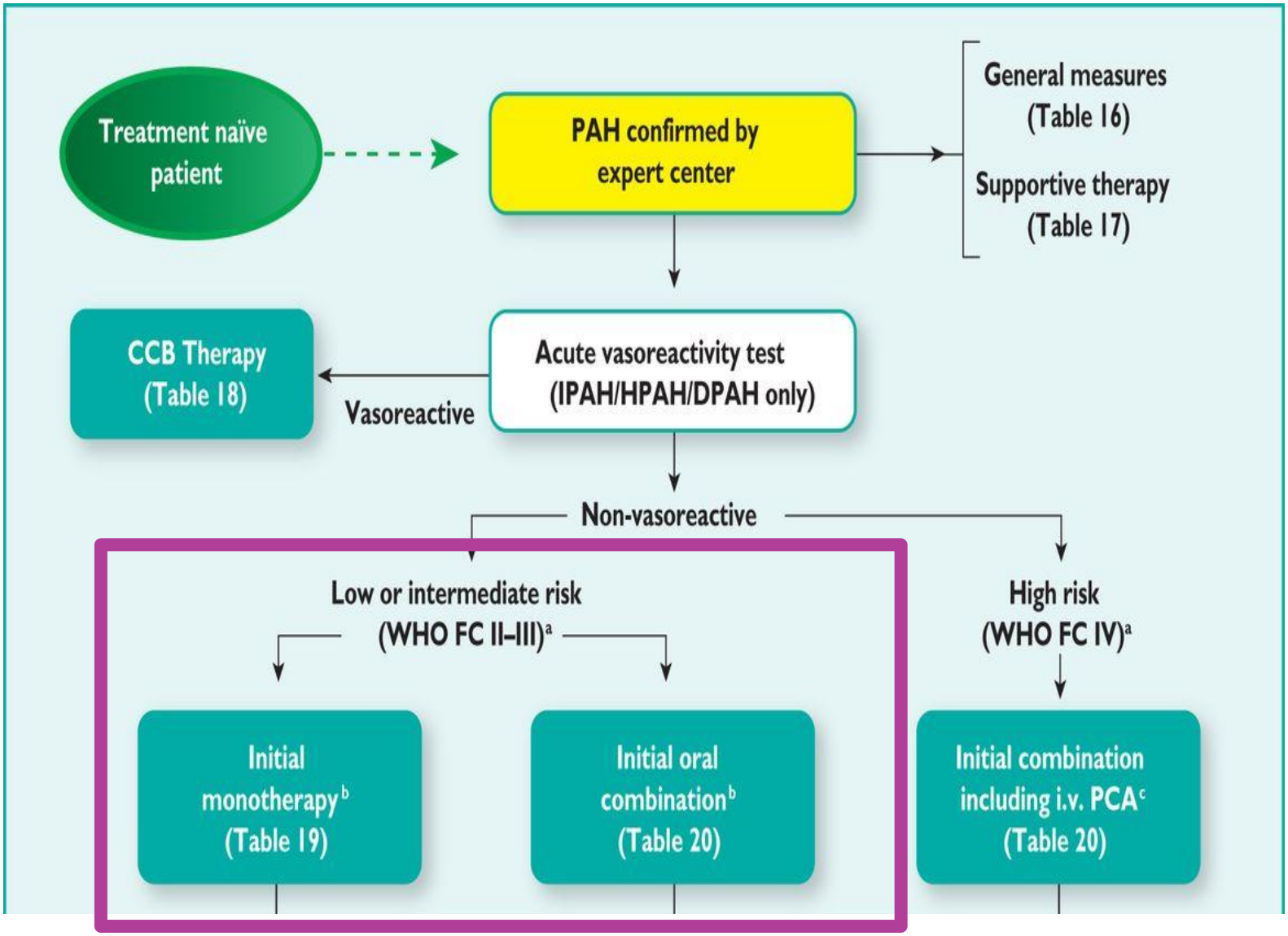
Underlying Lung Disease	mPAP ≥35 mm Hg at Rest*
COPD with FEV1 ≥60% of predicted IPF with FVC ≥70% of predicted CT: absence of or only very modest airway or parenchymal abnormalities	PH classification uncertain: discrimination between PAH (group 1) with concomitant lung disease or PH caused by lung disease (group 3) Refer to a center with expertise in both PH and chronic lung disease
COPD with FEV1 <60% of predicted IPF with FVC <70% of predicted Combined pulmonary fibrosis and emphysema on CT	Severe PH-COPD, severe PH-IPF, severe PH-CPFE Refer to a center with expertise in both PH and chronic lung disease for individualized patient care because of poor prognosis; randomized controlled trials required

ENDOTHELIAL DYSFUNCTION IN PULMONARY ARTERIAL HYPERTENSION



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

EVIDENCED BASED TREATMENT ALGORITHM

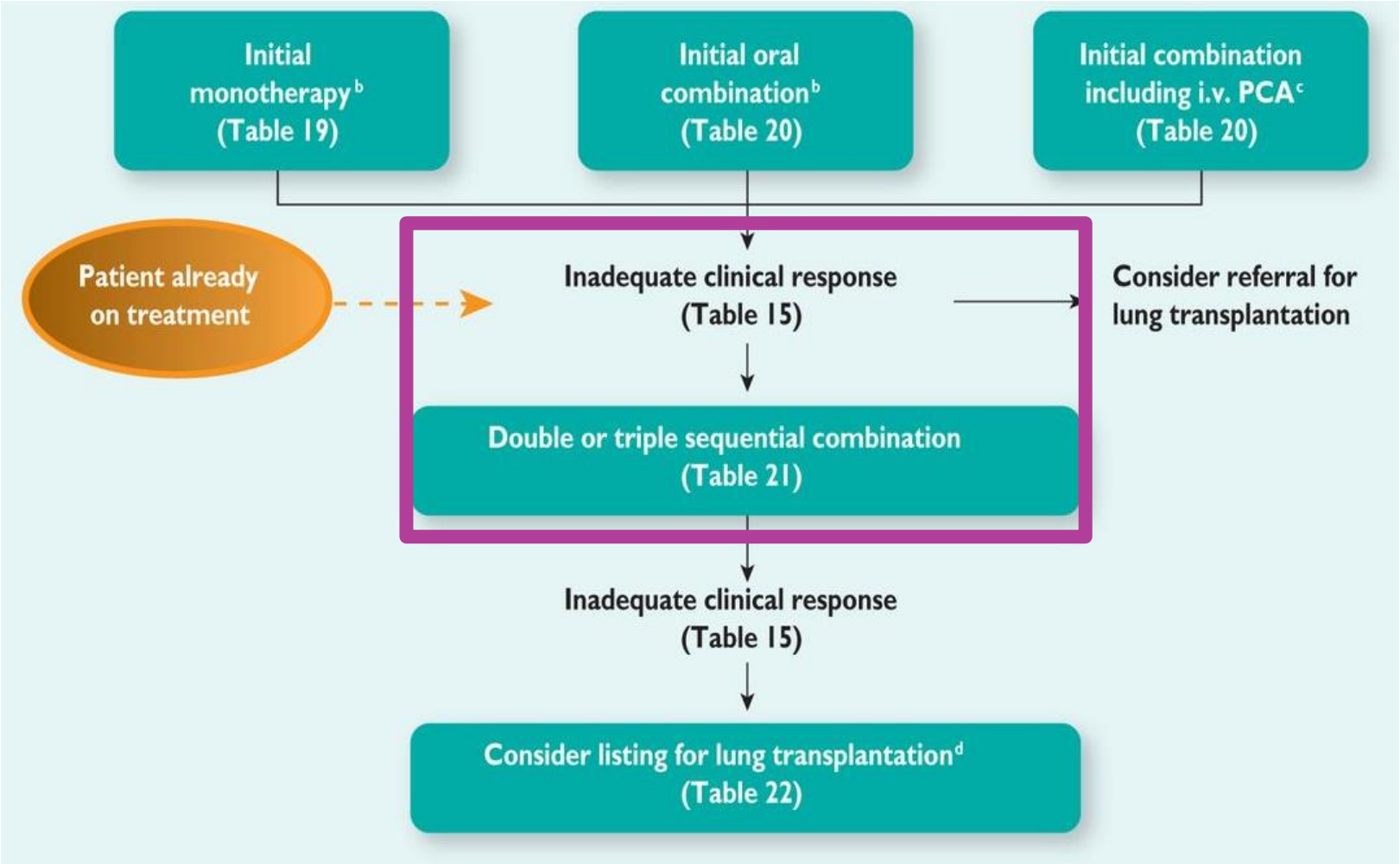


RISK ASSESSMENT IN PAH

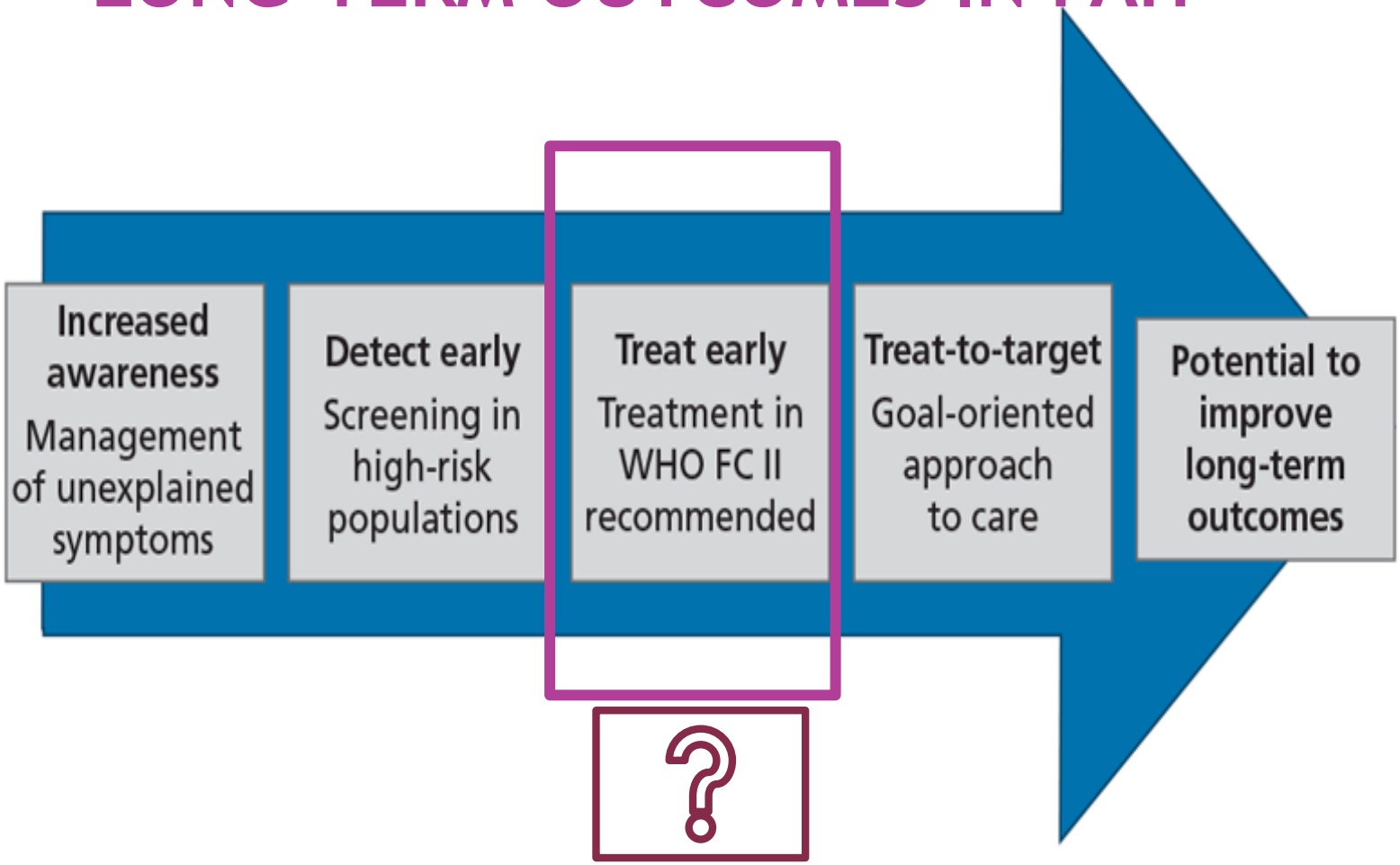
Determinants of prognosis[a] (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope[b]	Repeated syncope[c]
WHO functional class	I, II	III	IV
6MWD	>440 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



PATHWAY TO IMPROVING LONG-TERM OUTCOMES IN PAH



WHICH STRATEGY

INITIAL COMBINATION THERAPY

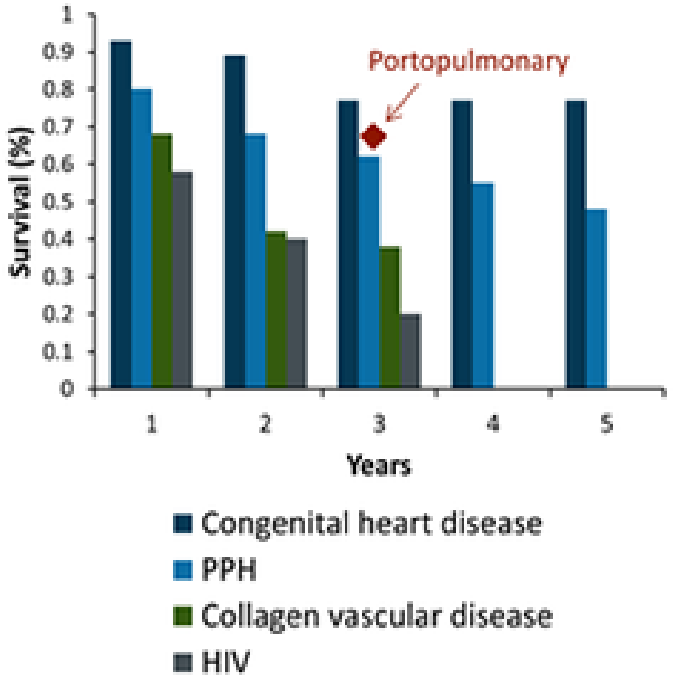
SEVERE HAEMODYNAMIC IMPAIRMENT
SCLERODERMA DISEASE

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)

Survival in Patients With Various Origins of PAH



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

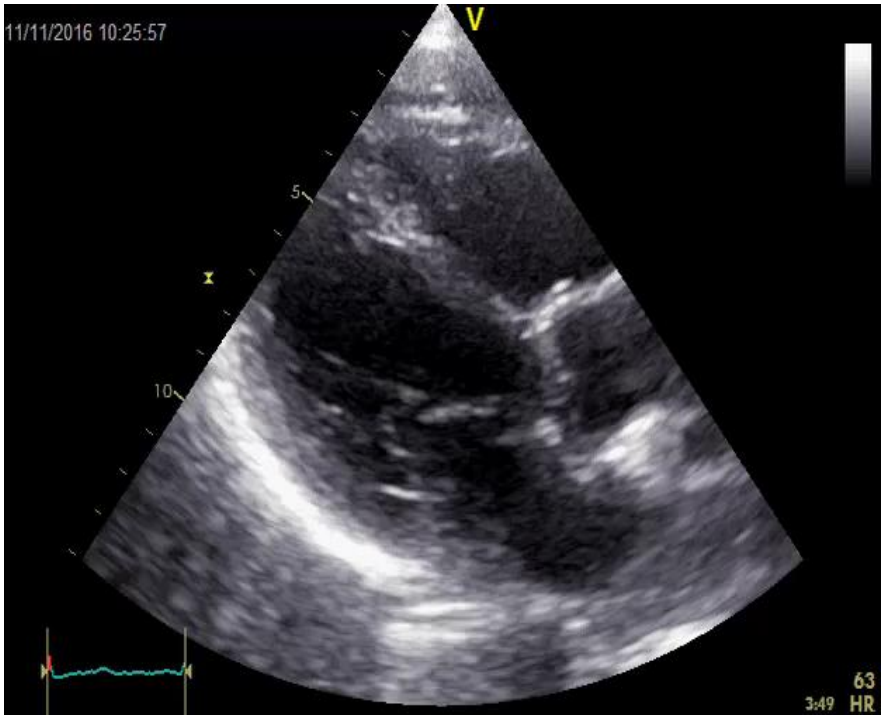
6. Eur Respir J 2012; 40: 604-11
19. Eur Respir J 2010; 35: 1079-87
27. Circulation 2010; 122: 164-72
34. Eur Respir J 2012; 40:596-603
37. Chest 2011; 140:301-9
40. Chest 2012; 141:354-62

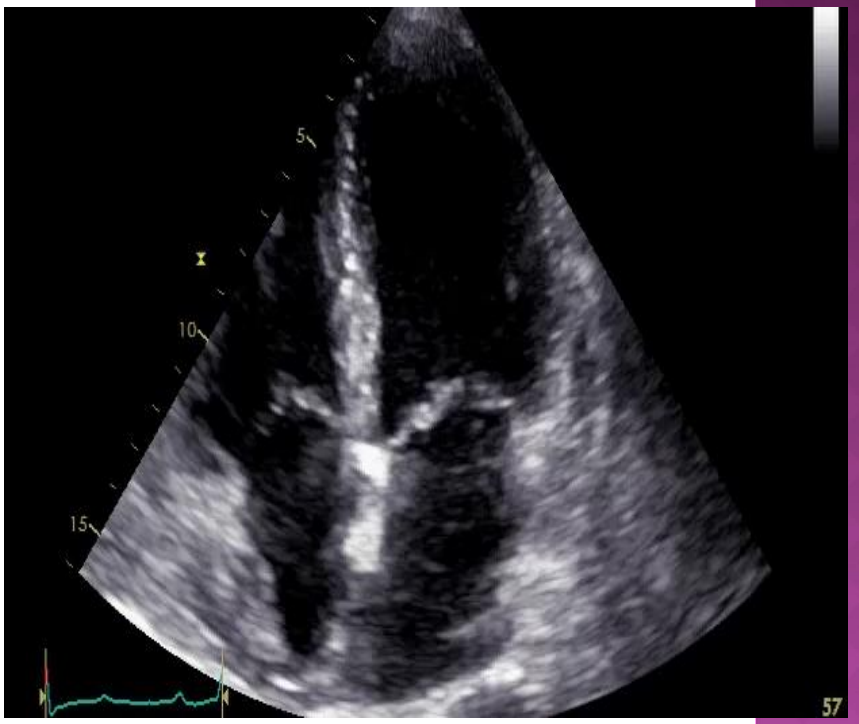
JACC 2013; 62:25

INITIAL COMBINATION THERAPY WITH AMBRISENTAN AND TADALAFIL

	11/2015	03/2016	11/2016
RA (mmHg)	13	9	8
PA (mmHg)	104/55/73	87/19/58	84/16/53
PAP (mmHg)	18	13	12
Oxymetry			
PA (O2%)	71.4	71.3	74.1
LV (O2 %)	96	94	95
CI (l/min)	1,7	2.1	2.6
PVR (WU)	22	15.1	10.5

INITIAL COMBINATION THERAPY WITH AMBRISENTAN AND TADALAFIL





11/2016: WHO II, 6MWT: 410m, NT-proBNP 280 pg/ml

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

2015 ESC/ERS GUIDELINES INITIAL COMBINATION THERAPY

Recommendations for Efficacy of Initial Drug Combination Therapy for PAH

Treatment (Sequenced By Rating)	Class / Level of Evidence		
	WHO FC I /	WHO FC III	WHO FC IV
Ambrisentan + tadalafil	I / B	I / B	IIb / C
Other ERA + PDE-5i	IIa / C	IIa / C	IIb / C
Bosentan + sildenafil + IV epoprostenol		IIa / C	IIb / C
Bosentan + IV epoprostenol		IIa / C	IIb / C
Other ERA or PDE-5i + SC treprostinil		IIb / C	IIb / C
Other ERA or PDE-5i + other IV prostacyclin analogues		IIb / C	IIb / C

PRIMARY ENDPOINT: TIME TO CLINICAL FAILURE

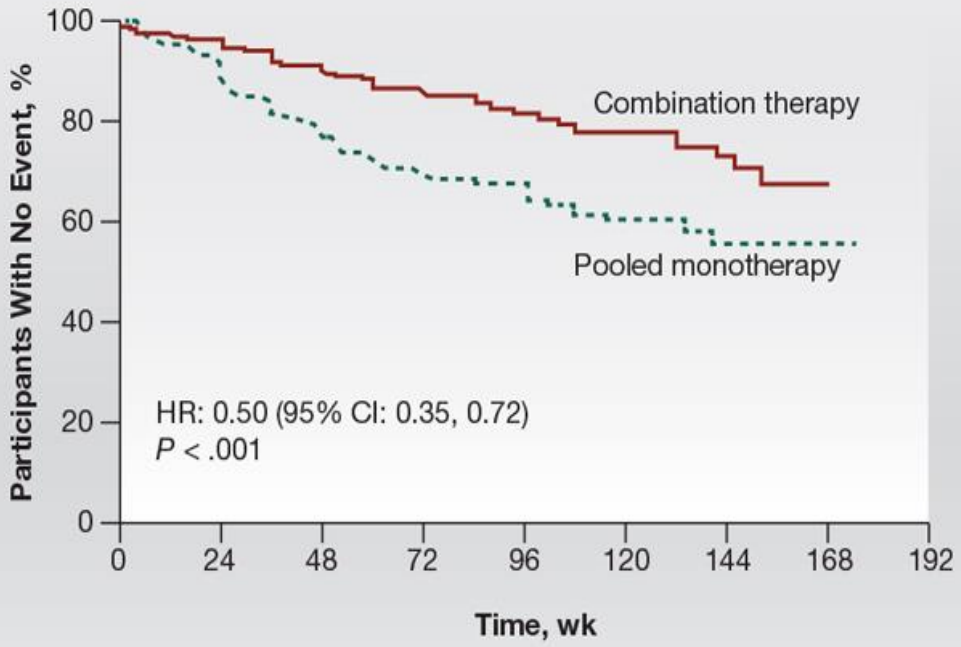
AMBITION[1]

Time to clinical failure

Time to first occurrence of

- Death
- Disease progression
  - Decrease of >15% from BL in the 6MWD + WHO FC III or IV symptoms at 2 consecutive visits (separated by ≥14 d)
- **Hospitalisation for worsening PAH**
- Unsatisfactory long-term clinical response
  - ↓ BL in 6MWD at 2 consecutive visits (14 d apart); WHO FC III at 2 clinic visits (6 mo apart)

Combination therapy reduced the risk of clinical failure events vs the pooled monotherapy arms by 50%



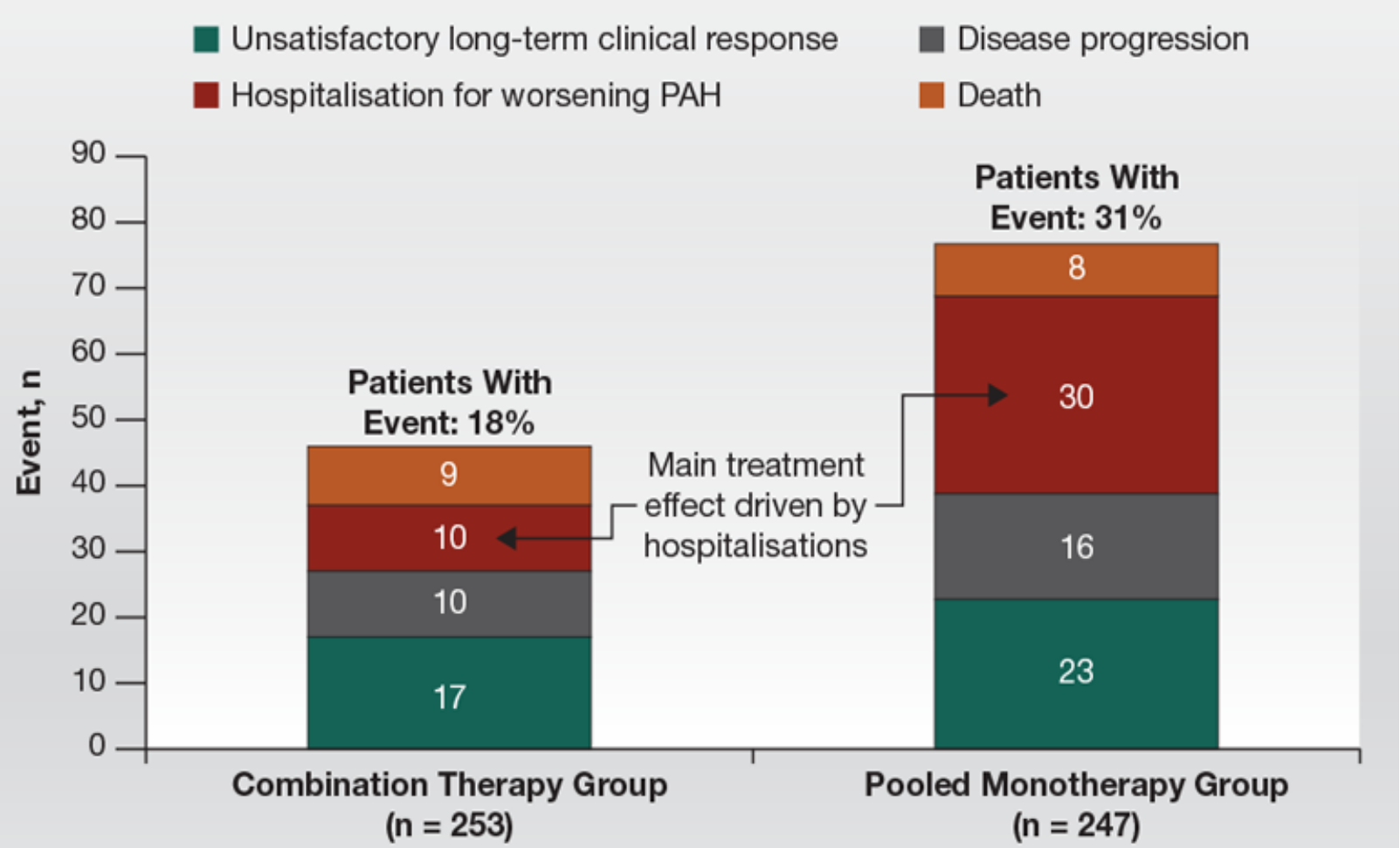
N Engl J Med. 2015;373:834-844.

Baseline Characteristics

Characteristic	Combination Therapy (n=253)	Pooled Monotherapy (n=247)	Ambrisentan monotherapy (n=126)	Tadalafil Monotherapy (n=121)
Baseline Who Functional Class				
II	76 (30%)	79 (32%)	38 (30%)	41 (34%)
III	177 (70%)	168 (68%)	88 (70%)	80 (66%)
Baseline 6MWD (m) ± SD	353.5 (87.9)	351.7 (91.8)	354.2 (92.3)	349.2 (91.6)
Hemodynamic variables				
RAP, mm Hg, mean ± SD	7.7 ± 4.5	7.9 ± 4.7	7.4 ± 4.6	8.4 ± 4.8
PAP, mm Hg, mean ± SD	48.1 ± 12.4	49.3 ± 12.6	50.4 ± 12.5	48.1 ± 12.6
PCWP, mm Hg, mean ± SD	8.4 ± 3.1	8.9 ± 3.4	8.6 ± 3.3	9.3 ± 3.5
CI, L/min/m^2, mean ± SD	2.41 ± 0.64	2.43 ± 0.71	2.41 ± 0.66	2.45 ± 0.77
PVR, dyne.sec/cm^5, mean ± SD	824.1 ± 467.0	825.7 ± 402.1	852.4 ± 394.7	798.0 ± 409.4
Time on study medication to FAV, days, mean ± SD	550.0 ± 340.8	NA	466.5 ± 341.4	501.2 ± 328.7

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

AMBITION TRIAL
PRIMARY ENDPOINT BY CLINICAL FAILURE EVENT

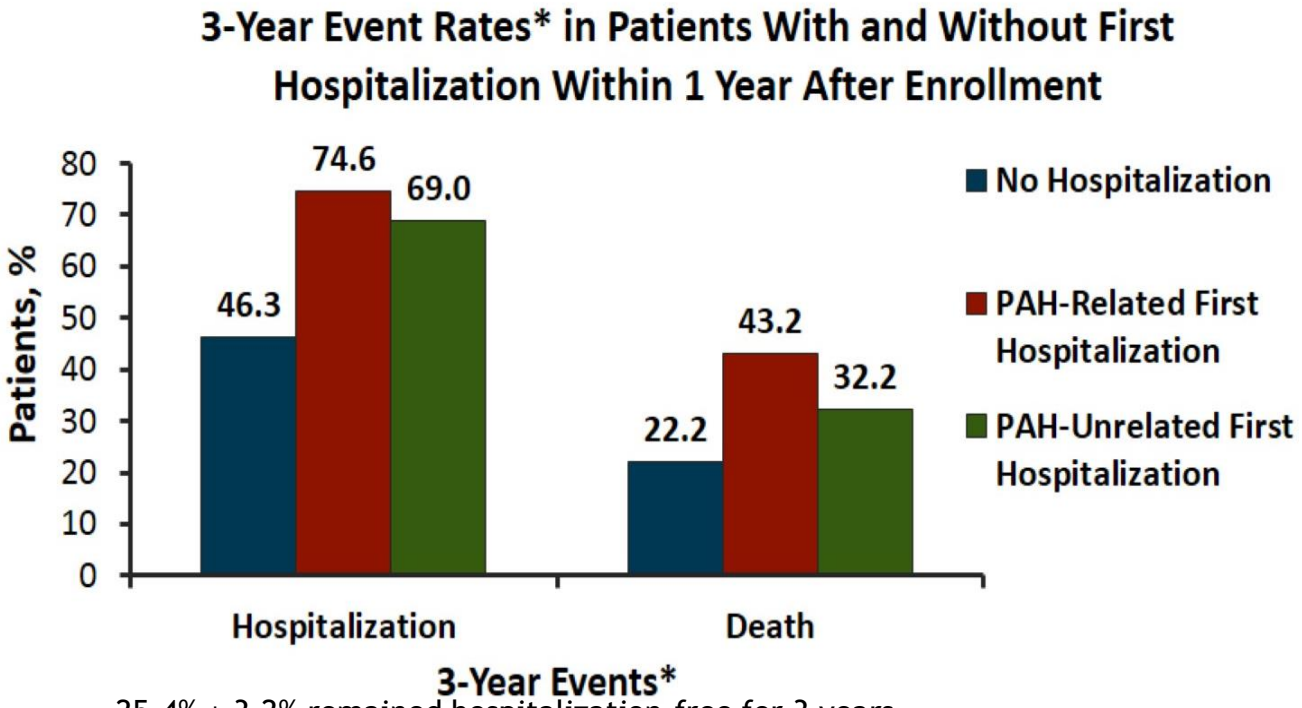


- Combination therapy was also superior to each individual monotherapy arm ($P < .01$)

N Engl J Med. 2015;373:834-844

REVEAL REGISTRY

HOSPITALISATION WORSENS LONG-TERM OUTCOMES



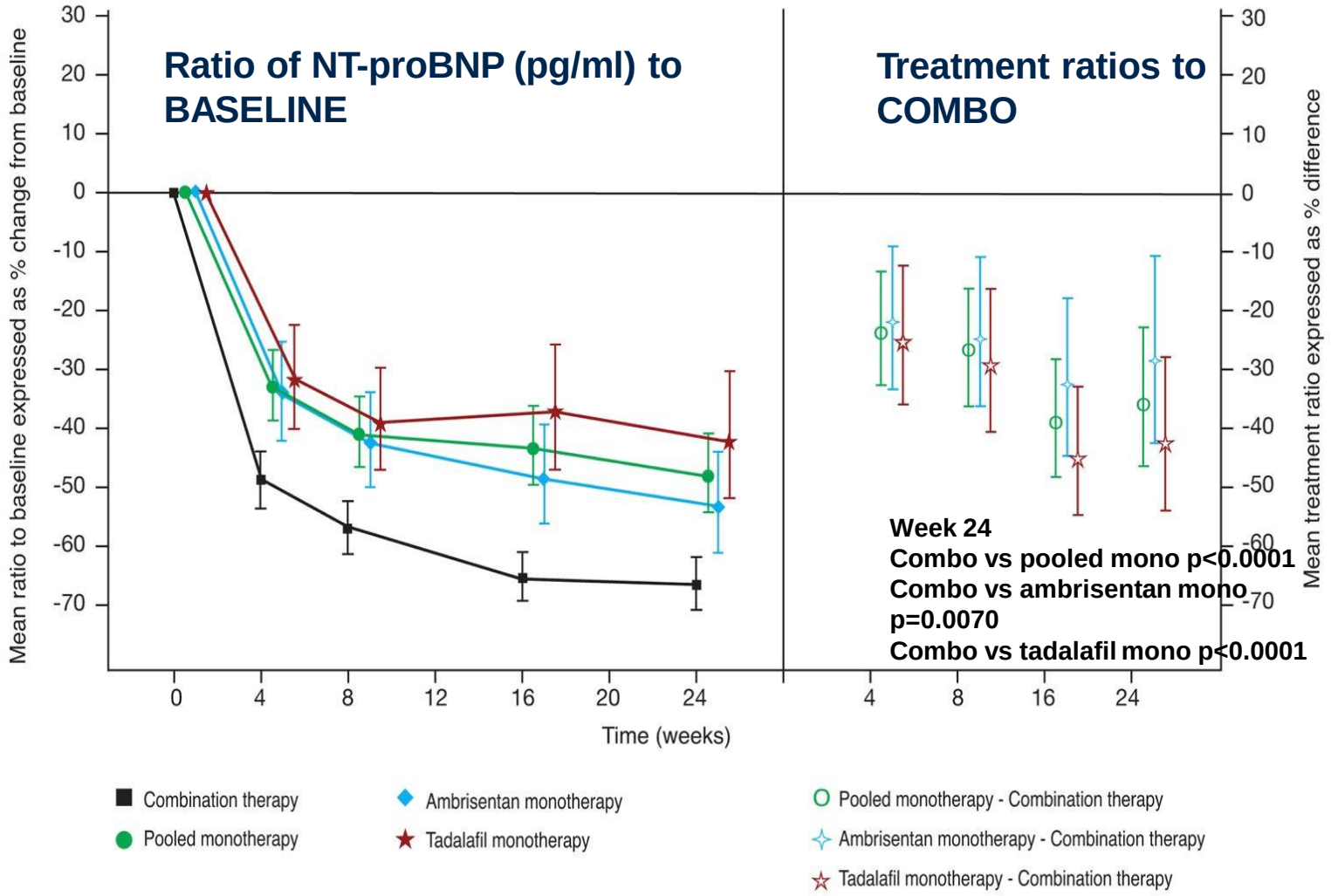
25.4% ± 3.2% remained hospitalization-free for 3 years

*3 years from discharge in patients with first hospitalization; 3 years from 1-year follow-up in patients without hospitalization.

Survival estimates at 3 years post-discharge were 56.8% ± 3.5% and 67.8% ± 3.6% (P = .037) for patients with PAH-related and PAH-unrelated hospitalization, respectively.

Chest 2014 Nov;146(5):1263-73

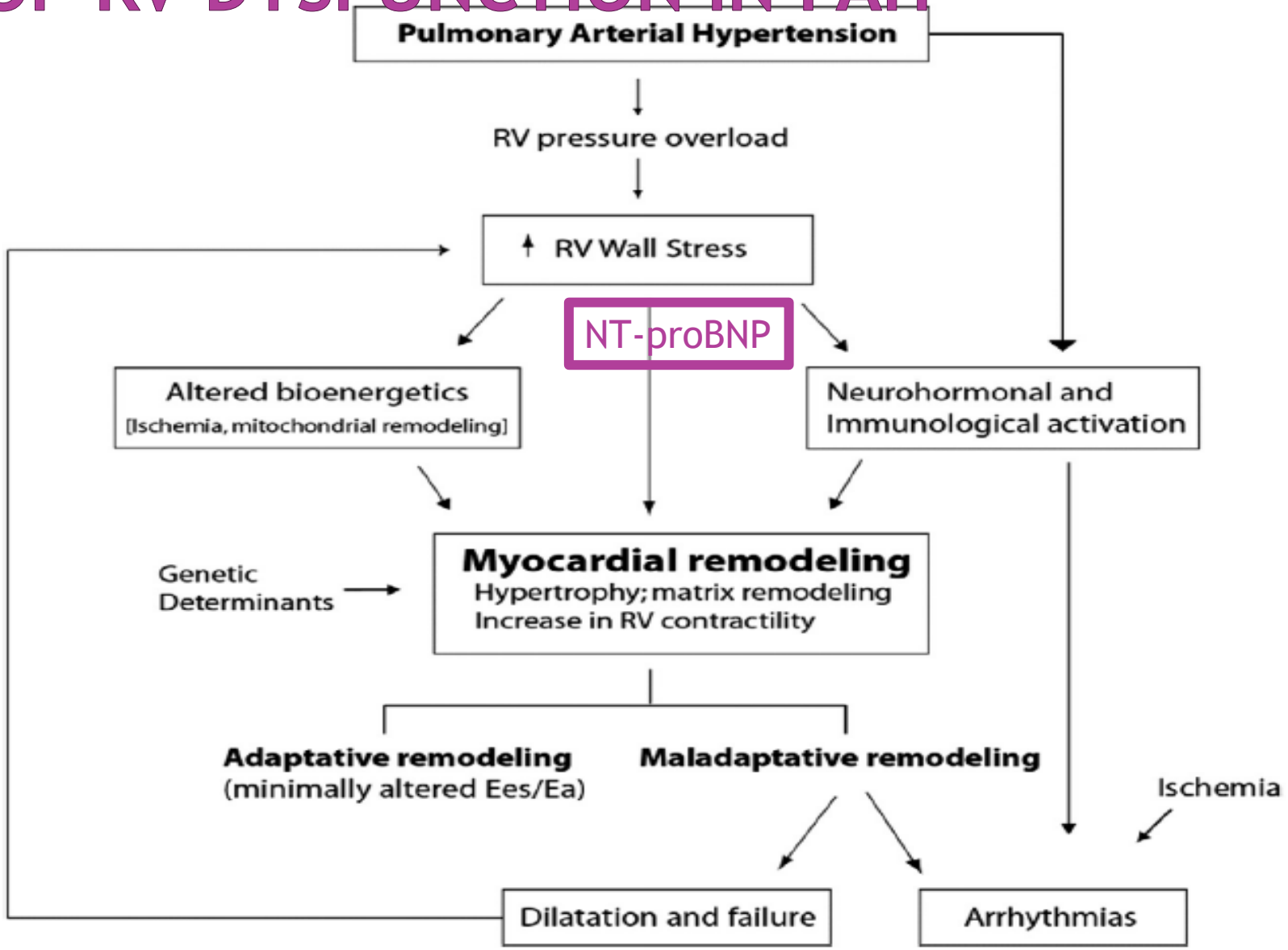
NT-proBNP: change from baseline to week 24 and treatment differences



Vertical bars represent 95% CIs. Graph is a mixed models repeated measures (MMRM) analysis adjusted for baseline aetiology of PAH (IPAH/HPAH vs non-IPAH), WHO FC (II vs III) and baseline, with no imputation for missing data.

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

PATHOPHYSIOLOGY OF RV DYSFUNCTION IN PAH



AMBITION
SELECTED BASELINE CHARACTERISTICS

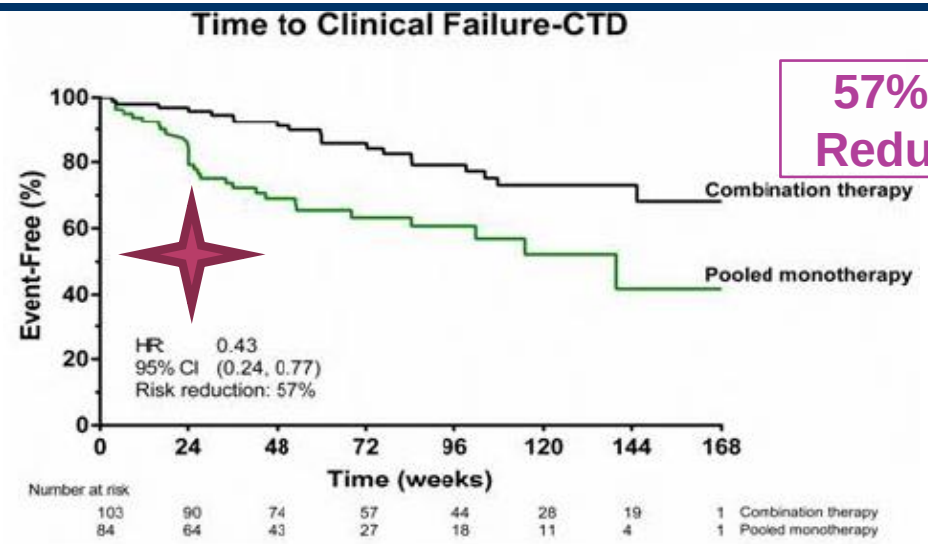
- 74% to 83% of patients were female, with a mean BMI ~28

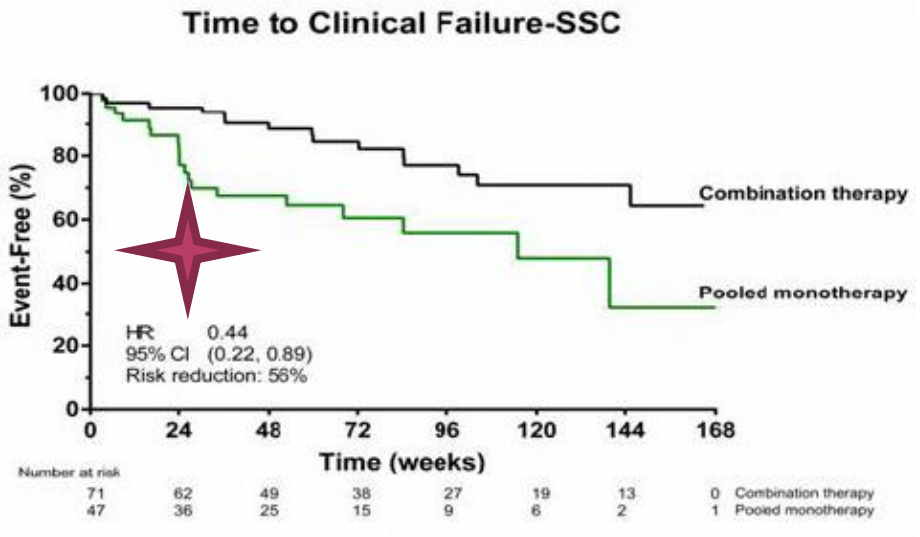
Characteristics	Combination Therapy (n = 253)	Pooled Monotherapy (n = 247)	ABS Monotherapy (n = 126)	TAD Monotherapy (n = 121)
Age, y	54.5 ± 14.3	54.2 ± 14.9	53.9 ± 14.7	54.5 ± 15.2
Region, %				
North America	46	45	40	50
Europe	51	52	57	46
Coexisting Conditions, %				
Hypertension	41	38	41	36
Diabetes	8	12	10	14
CAD	6	2	2	2
Classification of PAH, %				
Idiopathic	50	56	57	55
Associated with CTD	41	34	35	33
No PAH therapy history, %	96	96	95	95

[a] Other reported characteristics not listed include sex; race; further classifications of PAH, including heritable, associated with CHD, HIV, drug use or toxin exposure; prior medications; and median time for diagnosis to first administration of study drug.

CTD-PAH SUBGROUP ANALYSIS

57% Risk Reduction



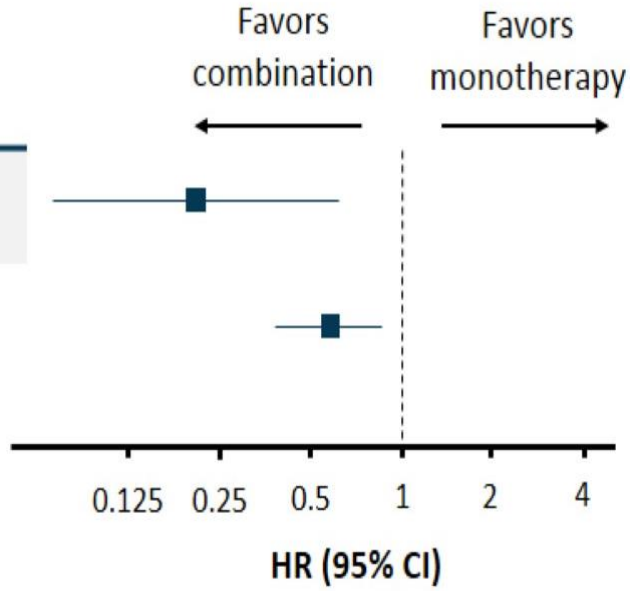


Coghlan et al. Ann Rheum Dis 2015;74:Suppl 2.173

AMBITION: FIRST ADJUDICATED CLINICAL FAILURE BY BASELINE FC

Subgroup	n	Events*	HR (95% CI)
WHO FC II	155	17 (22%)	0.21 (0.07-0.63)
WHO FC III	345	60 (36%)	0.58 (0.39-0.86)

*Monotherapy pooled group

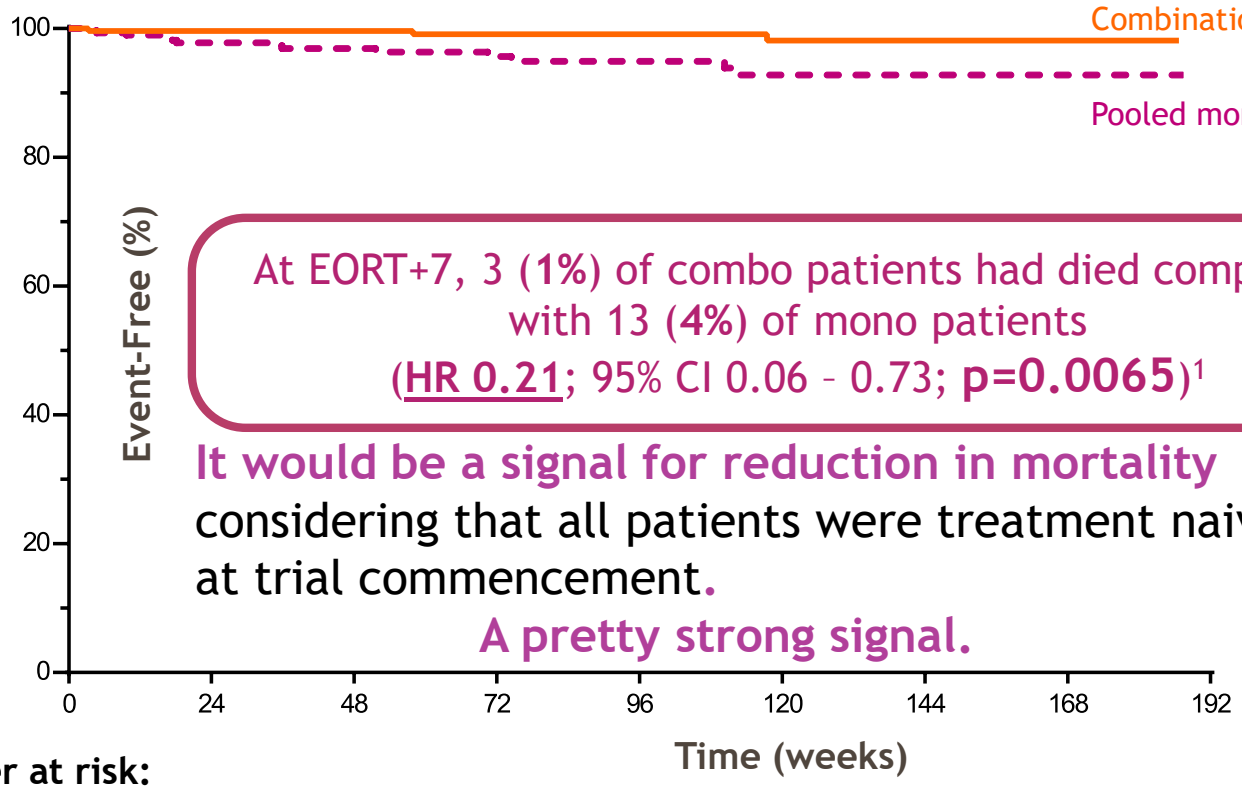


- Data support treatment of patients with PAH as early as possible and, in the AMBITION study, with initial combination therapy to improve patient outcomes

Galiè N, et al. *N Engl J Med*. 2015;373:834-844.

KAPLAN-MEIER SURVIVAL ESTIMATE FROM BASELINE TO END OF RANDOMISED TREATMENT (POST HOC)[1]

79% mortality risk reduction



At EORT+7, 3 (1%) of combo patients had died compared with 13 (4%) of mono patients (HR 0.21; 95% CI 0.06 – 0.73; **p=0.0065**)[1]

It would be a signal for reduction in mortality considering that all patients were treatment naive at trial commencement.

A pretty strong signal.

Number at risk:

Combination	302	257	218	178	137	94	59	23
Pooled Mono	303	245	185	136	109	75	44	14

1.Hoeper et al. Lancet Respir Med 2016;4:894-901

INSIGHTS OF THIS STUDY

People are dying on monotherapies before physicians have the opportunity to step-up treatments?

"Patients on monotherapy who have treatment failure can be rescued by addition of further drugs?"

"A radically different therapeutic approach (upfront combination therapy) might improve the only meaningful endpoint (death) in this disease"

"AMBITION used ambrisentan and tadalafil. It is not known if these findings can be extrapolated to other combinations"

1.Hoeper et al. Lancet Respir Med 2016;4:894–901

MORTALITY DATA IN SERAPHIN STUDY

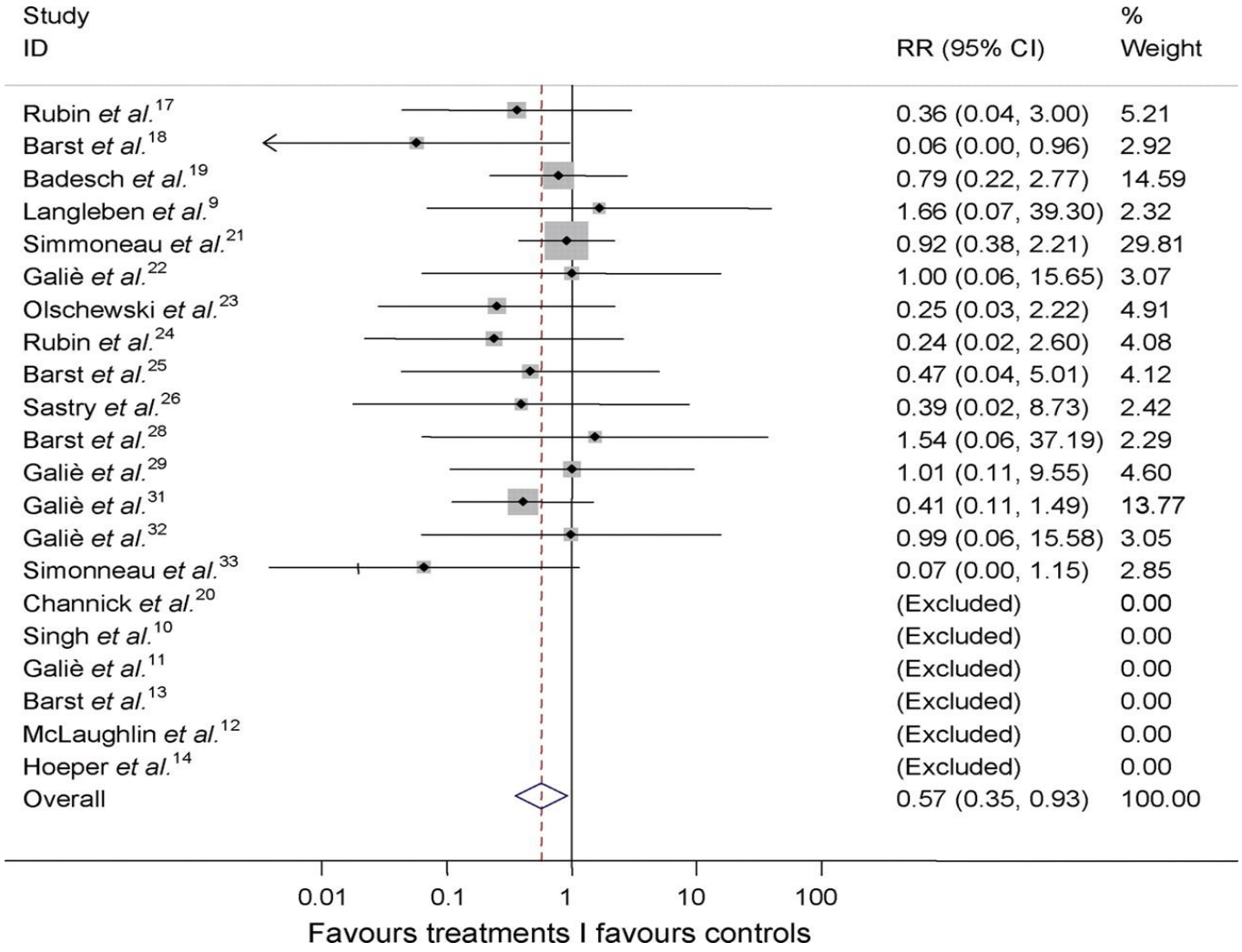
- "Mortality at 7 days after the end of assigned treatment was reduced by active therapy compared with placebo, **but the difference was not significant**

  (HR 0.64, p=0.20)"

- "Similar results were obtained with the end-of-study analysis **(HR 0.77, p=0.25)**"

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

Cumulative RR estimate of death in active treatment groups when compared with control groups (RR [95% CI]).



In various meta-analyses of subsequent trials (12–16 weeks in duration), **survival was not shown convincingly to be improved with monotherapy or combined therapy**

Eur Heart J 2009;30:394-403

2015 ESC/ERS GUIDELINES INITIAL COMBINATION THERAPY

Recommendations for Efficacy of Initial Drug Combination Therapy for PAH

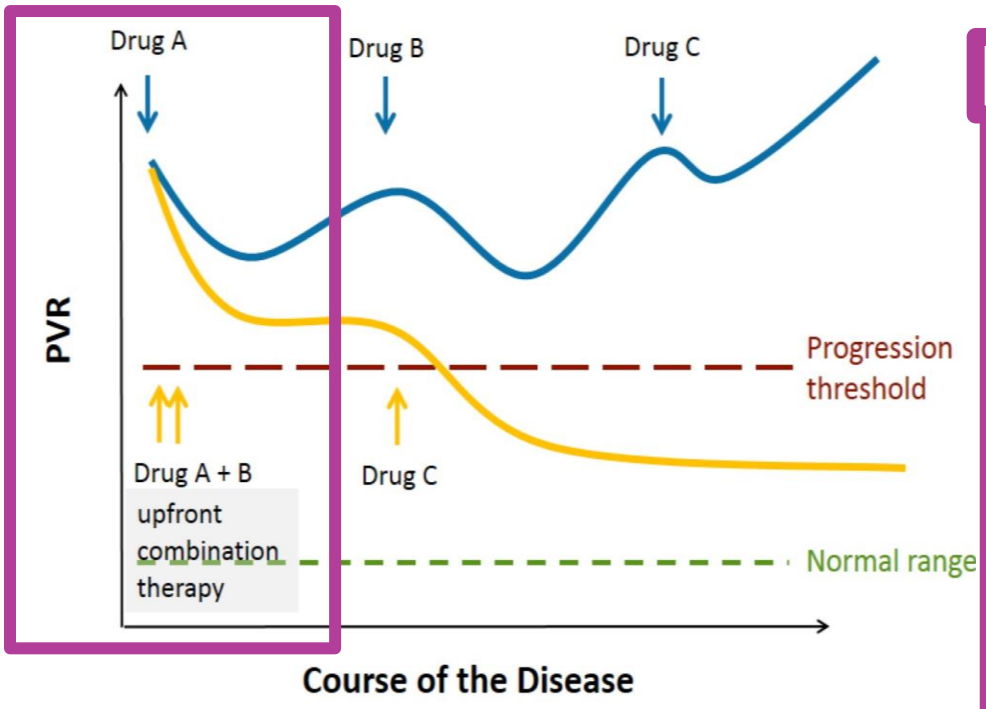
Treatment (Sequenced By Rating)	Class / Level of Evidence		
	WHO FC I	WHO FC III	WHO FC IV
Ambrisentan + tadalafil	I / B	I / B	IIb / C
Other ERA + PDE-5i	IIa / C	IIa / C	IIb / C
Bosentan + sildenafil + IV epoprostenol		IIa / C	IIb / C
Bosentan + IV epoprostenol		IIa / C	IIb / C
Other ERA or PDE-5i + SC treprostinil		IIb / C	IIb / C
Other ERA or PDE-5i + other IV prostacyclin analogues		IIb / C	IIb / C

It strongly raises the possibility that a radically different therapeutic approach might improve the only meaningful endpoint (ie, death) in this disease.

IN TREATMENT NAÏVE PATIENTS, THE MOST APPROPRIATE APPROACH.

TREAT PAH AS AGGRESSIVELY AS POSSIBLE

This is a fundamental approach and probably a shift from a goal-oriented treatment strategy to an outcome-oriented treatment strategy



Slide courtesy of H. Ardeschir Ghofrani, MD.

TREATMENT GOALS

IMPROVE LONG TERM OUTCOME

- Prevent disease progression
- Improve survival
- Improve quality of life
- Improve functional class to I or II
- Maintain good right ventricular function

INITIAL COMBINATION THERAPY CHALLENGES

How to apply combination therapy?

- Data are available for certain combinations of drugs, but not all
  - Is the combination of drugs that I want to use effective?

How to monitor combination therapy?

- Is the combination of drugs that I want to use safe?
  - Adverse safety signals not observed in recent, large PAH studies of combination therapy (eg, SERAPHIN, GRIPHON, AMBITION)
- Should 2 drugs be started together (initial combination therapy) vs sequentially?
  - AEs can be easier to monitor when drugs started sequentially

Treatment decisions must be individualized based on patient condition and needs/desires

ADVERSE EVENTS

- Similar rates of SAEs and AEs leading to study drug discontinuation between arms
- No new safety signals for either drug as monotherapy or combination therapy

AEs, %[a]	Combination Therapy (n = 253)	ABS Monotherapy (n = 126)	TAD Monotherapy (n = 121)
AEs Occurring More Frequently in Combination Arm			
Peripheral oedema	45	33	28
Headache	42	33	35
Nasal congestion	21	15	12
Anaemia	15	6	12
Other AEs of Clinical Interest			
Hypotension	8	7	7
Syncope	5	6	8

N Engl J Med. 2015;373:834-844

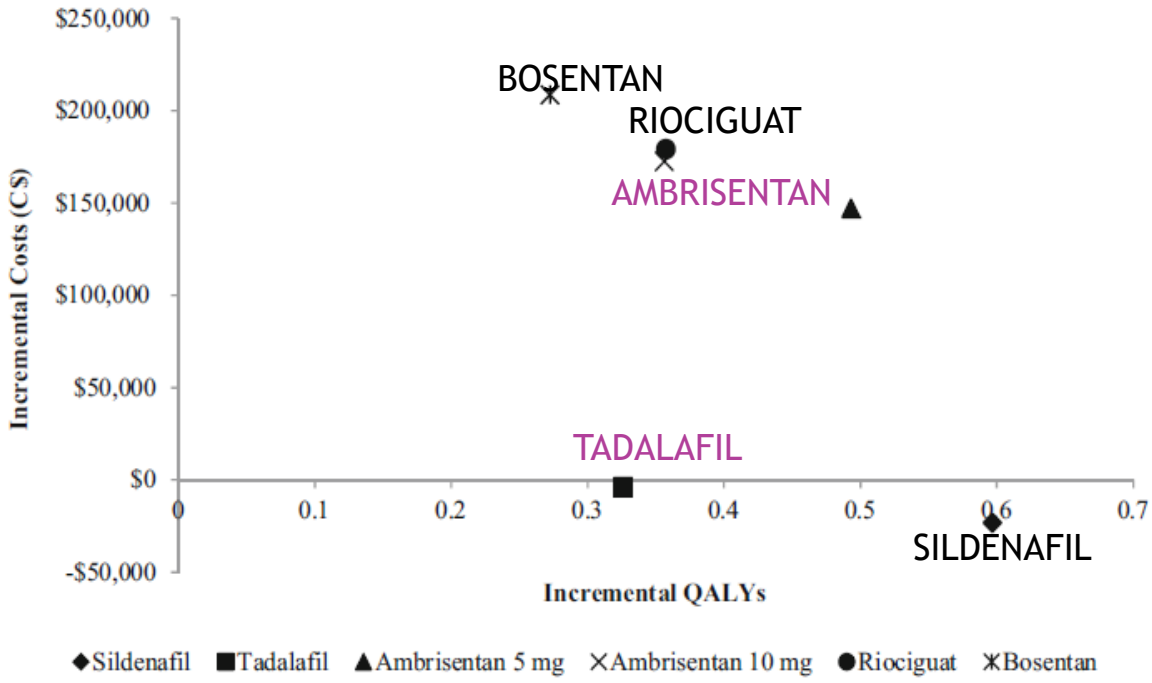
COST EFFECTIVENESS

Specific PAH oral drugs

PRICES Euro/month

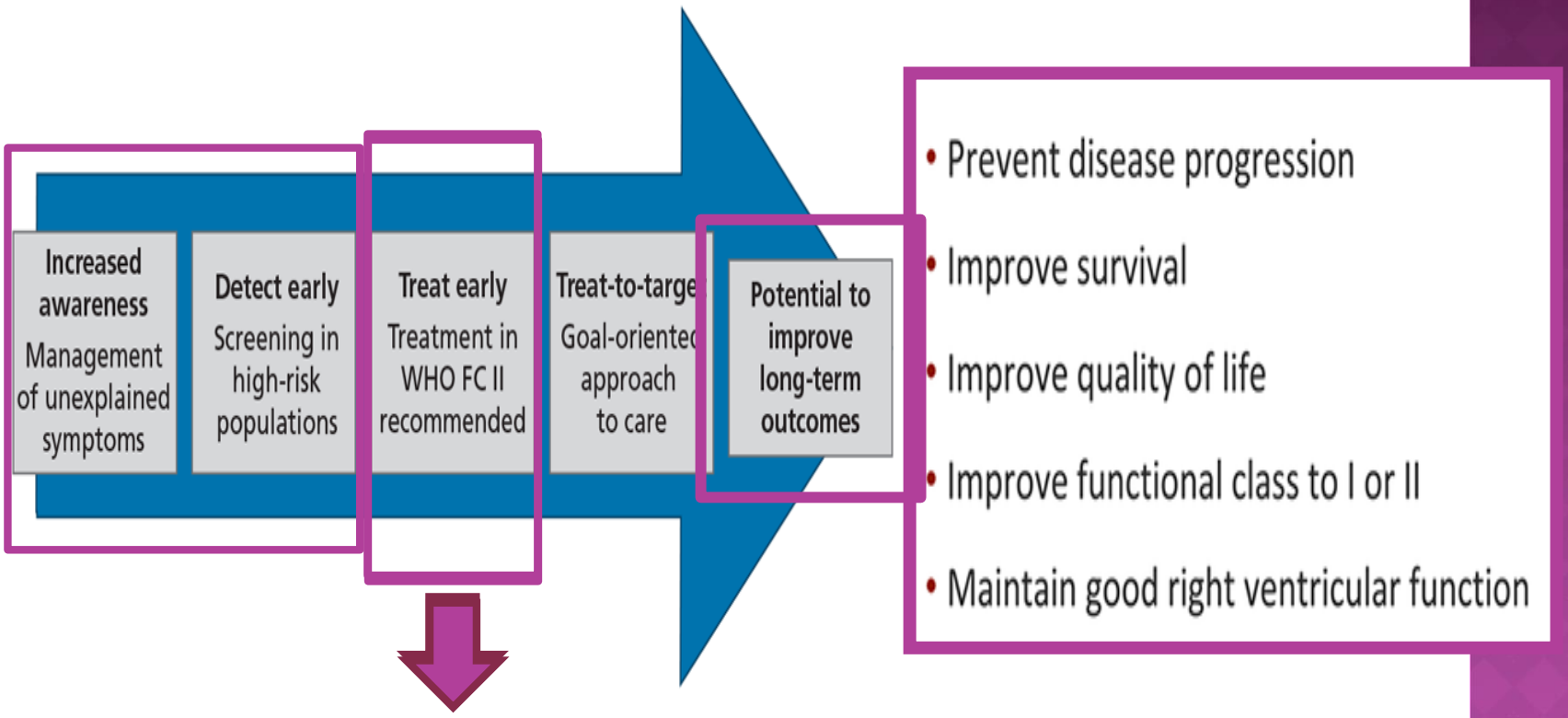
Revatio	450,19
Adcirca	544,30
Riociguat	*2600*
Klimurtan	1350,60
Tracleer	2043,21
Volibris	2115,94
Opsumit	*2762,18*

Greece, November 2016



Pharmaco-Economics (2016) 34:509–520

PATHWAY TO IMPROVING LONG-TERM OUTCOMES IN PAH

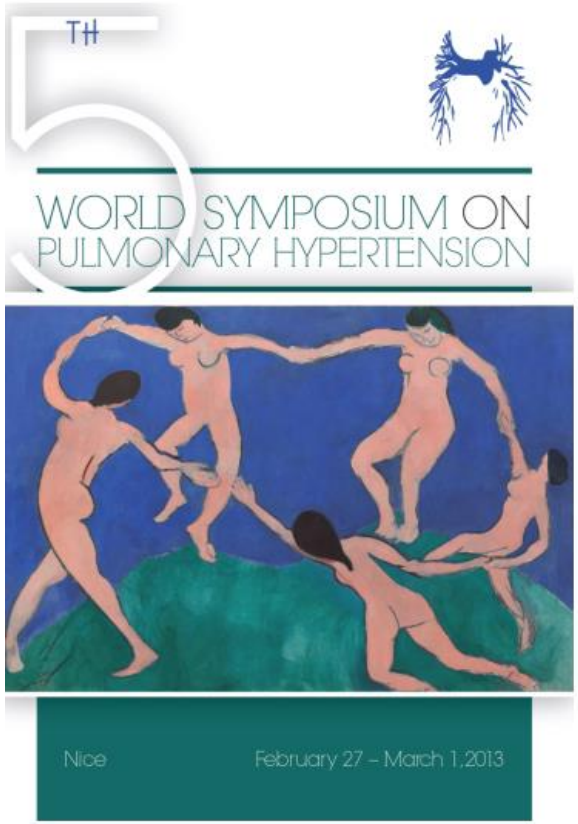


We cannot cure PAH in most cases today,
but at least we can control the disease so it is no longer progressive

Initial Combination Therapy

THANK YOU

PRIMARY ENDPOINT IN PAH FROM 6MWT TO A COMPOSITE ENDPOINT OF MORBIDITY AND MORTALITY



New Trial Designs and Potential Therapies for Pulmonary Artery Hypertension

Mardi Gomberg-Maitland, MD, MSc[*], Todd M. Bull, MD[†], Rajeev Saggar, MD[‡], Robyn J. Barst, MD[§], Amany Elgazayerly, MD, PhD[‖], Thomas R. Fleming, PhD[¶], Friedrich Grimminger, MD, PhD[#], Maurizio Rainisio, PhD[**], Duncan J. Stewart, MD[††], Norman Stockbridge, MD, PhD[‡‡], Carlo Ventura, MD, PhD[§§], Ardeschir H. Ghofrani, MD[#], and Lewis J. Rubin, MD[‖‖]

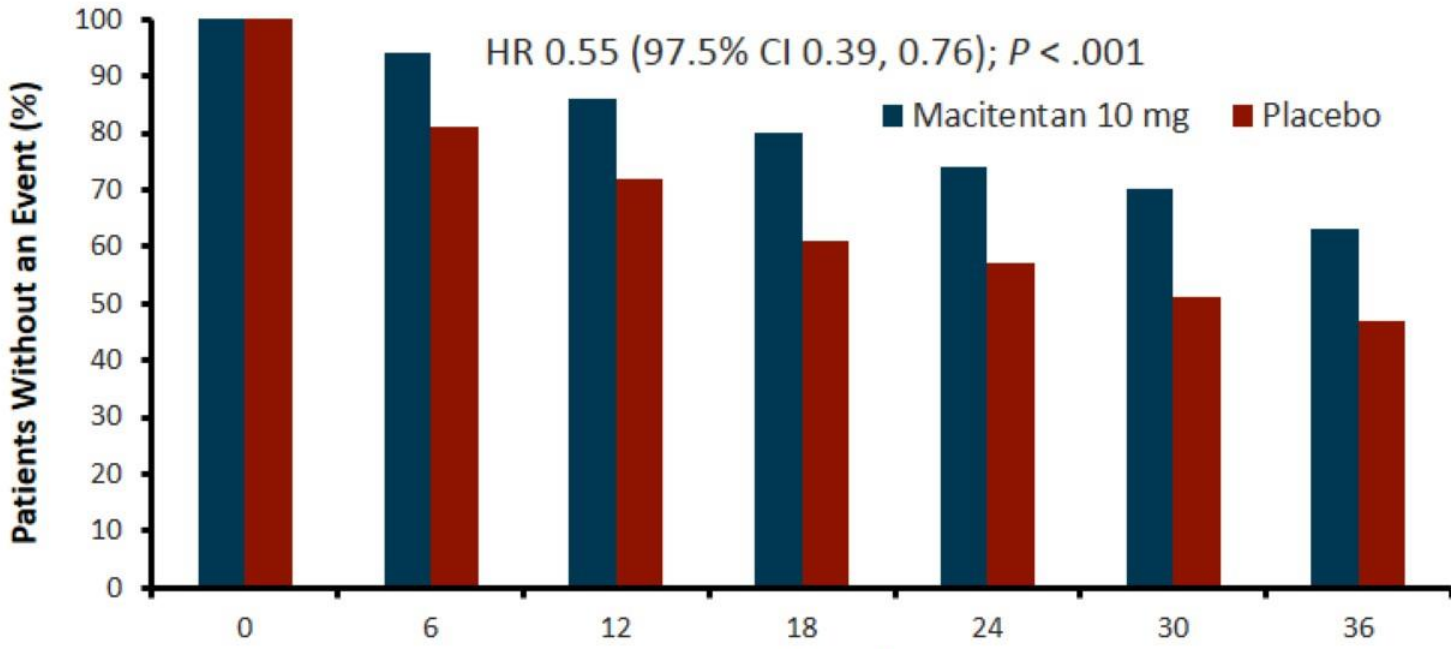
« As defined at the 4th World Symposium… the composite endpoint of morbidity and mortality could include: death, lung transplantation, initiation of iv Pgl2, worsening of the function (6'WD and FC)…This composite endpoint may be more suitable and meaningful than 6'WD, particurlarly as new trials will be assessing patients on background therapies and for longer periods of observation. »

SEQUENTIAL COMBINATION THERAPY

The efficacy and safety of sequential combination therapy has been evaluated in long-term trials using morbidity and mortality as a primary endpoint

SERAPHIN TRIAL & GRIPHON TRIAL

SERAPHIN TRIAL



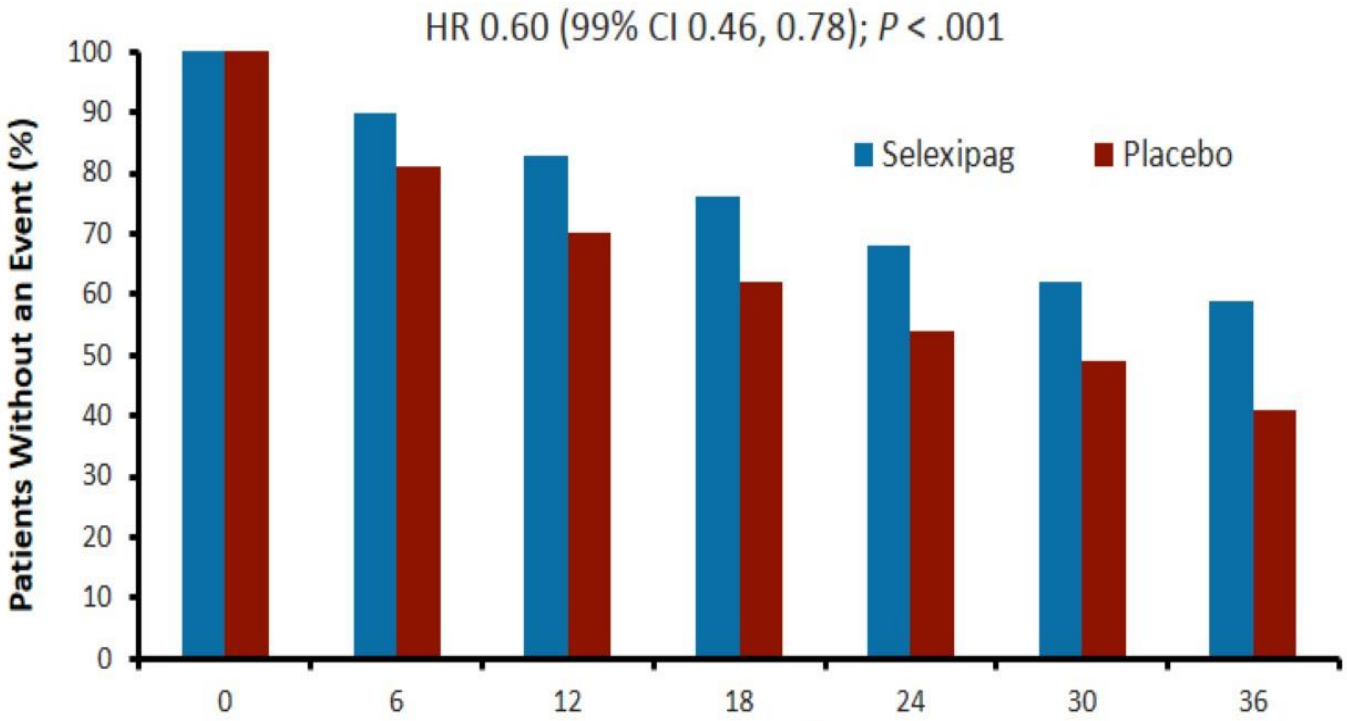
No at Risk							
Placebo	250	188	160	135	122	54	23
Macitentan 10 mg	242	208	187	171	155	91	41

The safety and efficacy of macitentan vs placebo was evaluated in symptomatic PAH patients on stable background therapy.

Primary endpoint = first event related to PAH or death from any cause

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

GRIPHON TRIAL



No at Risk							
Placebo	582	433	347	220	149	88	28
Selexipag	574	455	361	246	171	101	40

The safety and efficacy of selexipag vs placebo were evaluated in patients with PAH who were not receiving therapy at baseline or who were already receiving 1 or 2 PAH therapies at baseline.

Primary endpoint = death from any cause or a complication related to PAH

Sitbon O, et al. *N Engl J Med*. 2015;373:2522-2533.

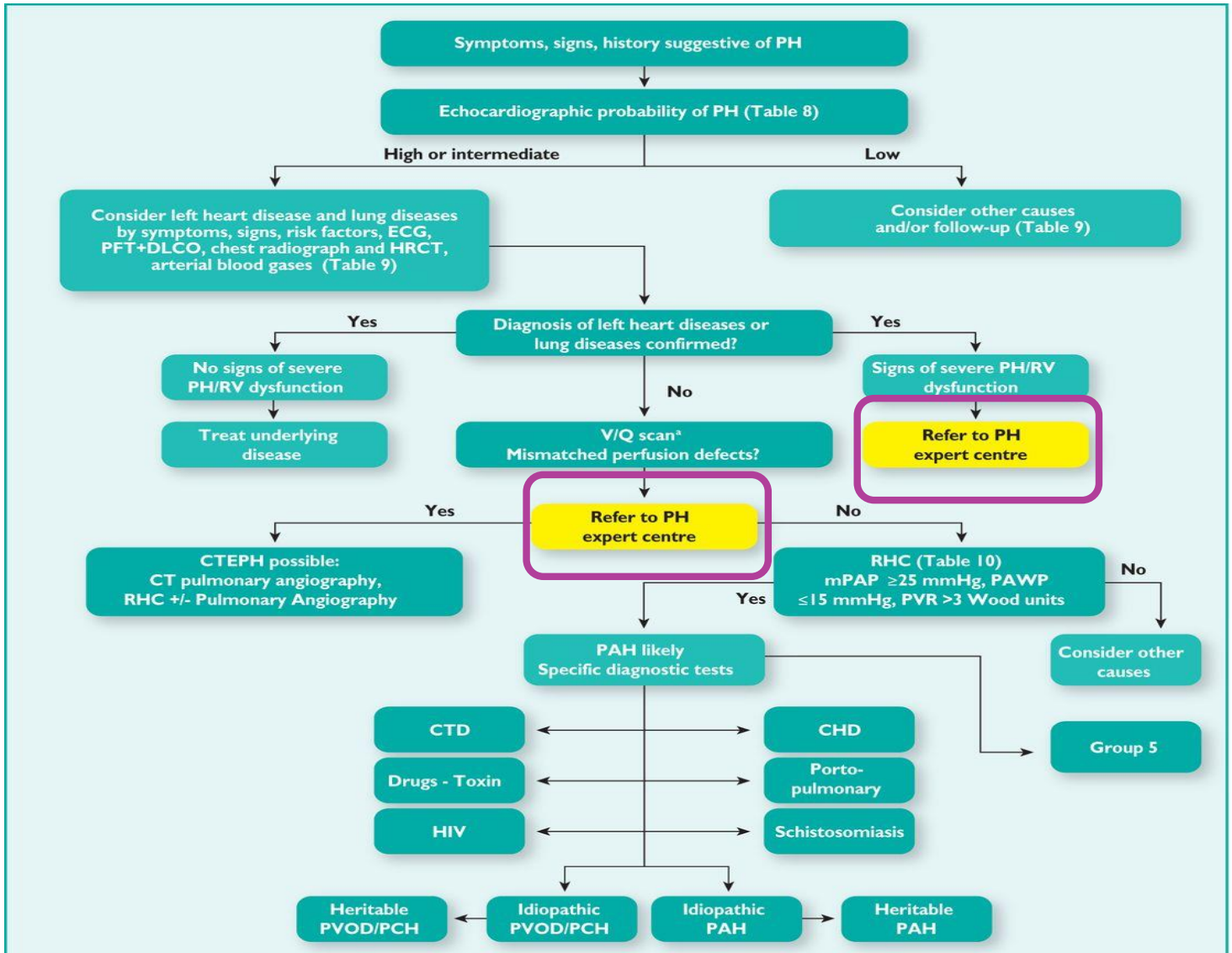
Selexipag
Prolongs the Time to Morbidity/Mortality Events in Key Subgroup Populations:
Results from GRIPHON, a Randomized Controlled Study in PAH

The patients with SSc-PAH had a 54.8% risk reduction in the primary end point, a treatment effect that exceeded the 41% risk
reduction in the entire study population

Could it be that the
6-minute-walk test has limitations as a primary end point in patients with SSc-PAH?

Could it be that PAH-specific therapies really do
benefit patients with SSc-PAH if studied in adequate numbers with
“hard” and clinically relevant end points?

DIAGNOSTIC ALGORITHM



CHD = congenital heart diseases; CT = computed tomography; CTD = connective tissue disease; CTEPH = chronic thromboembolic pulmonary hypertension; DLCO = carbon monoxide diffusing capacity; ECG = electrocardiogram; HIV = Human immunodeficiency virus; HR-CT = high resolution CT; mPAP = mean pulmonary arterial pressure; PA = pulmonary angiography; PAH = pulmonary arterial hypertension; PAWP = pulmonary artery wedge pressure; PFT = pulmonary function tests; PH = pulmonary hypertension; PVOD/PCH = pulmonary veno-occlusive disease or pulmonary capillary hemangiomathosis; PVR = pulmonary vascular resistance; RHC = right heart catheterisation; RV = right ventricular; V/Q = ventilation/perfusion.

[a]CT pulmonary angiography alone may miss diagnosis of chronic thromboembolic pulmonary hypertension.

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

Immunosuppresive therapy alone

Pulmonary vasodilators +/- Immunosuppresive 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

META-ANALYSIS OF MONOTHERAPY VERSUS COMBINATION THERAPY FOR PAH

Six randomized controlled trials including 729 patients met inclusion criteria

Compared to MT, CT resulted in a modest increase in 6-minute walk distance at the end of follow-up (weighted mean difference 25.2 m, 95% confidence interval [CI] 13.3 to 37.2). CT did not decrease mortality (risk ratio [RR] 0.42, 95% CI 0.08 to 2.25), admissions for worsening PAH (RR 0.72, 95% CI 0.36 to 1.44), or escalation of therapy (RR 0.36, 95% CI 0.09 to 1.39) and did not improve New York Heart Association functional class (RR 1.32, 95% CI 0.38 to 4.5) compared to MT

Combined therapy did not decrease the composite endpoint of

mortality, hospital admission for worsening PAH, lung transplantation, or escalation of therapy.

Am J Cardiol. 2011 Oct 15;108(8):1177-82

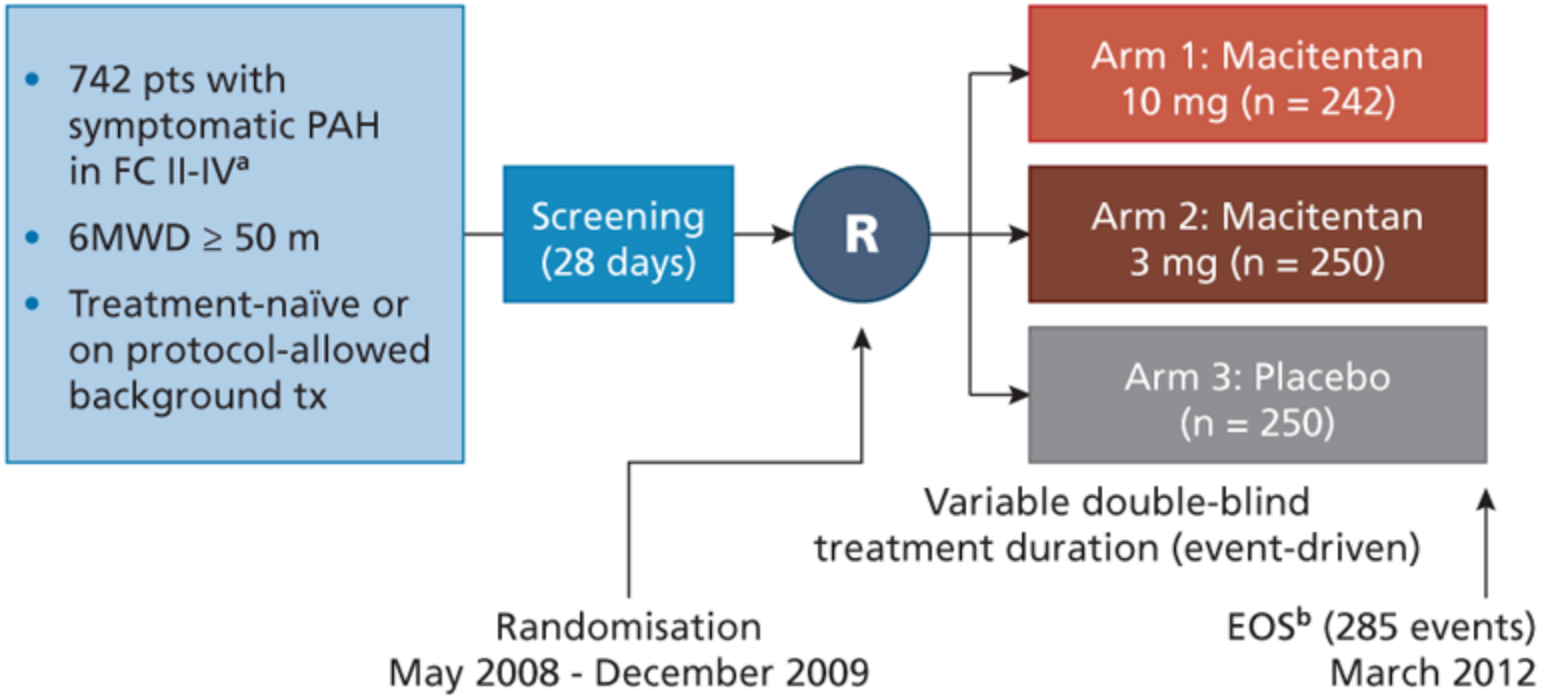
COMBINATION THERAPY VERSUS MONOTHERAPY FOR PAH: A META-ANALYSIS

Improvement in functional status and a reduction in risk of clinical worsening with combination therapy, but the
reduction in mortality was non-significant

Lancet Respir Med 2016 Apr;4(4):291-305

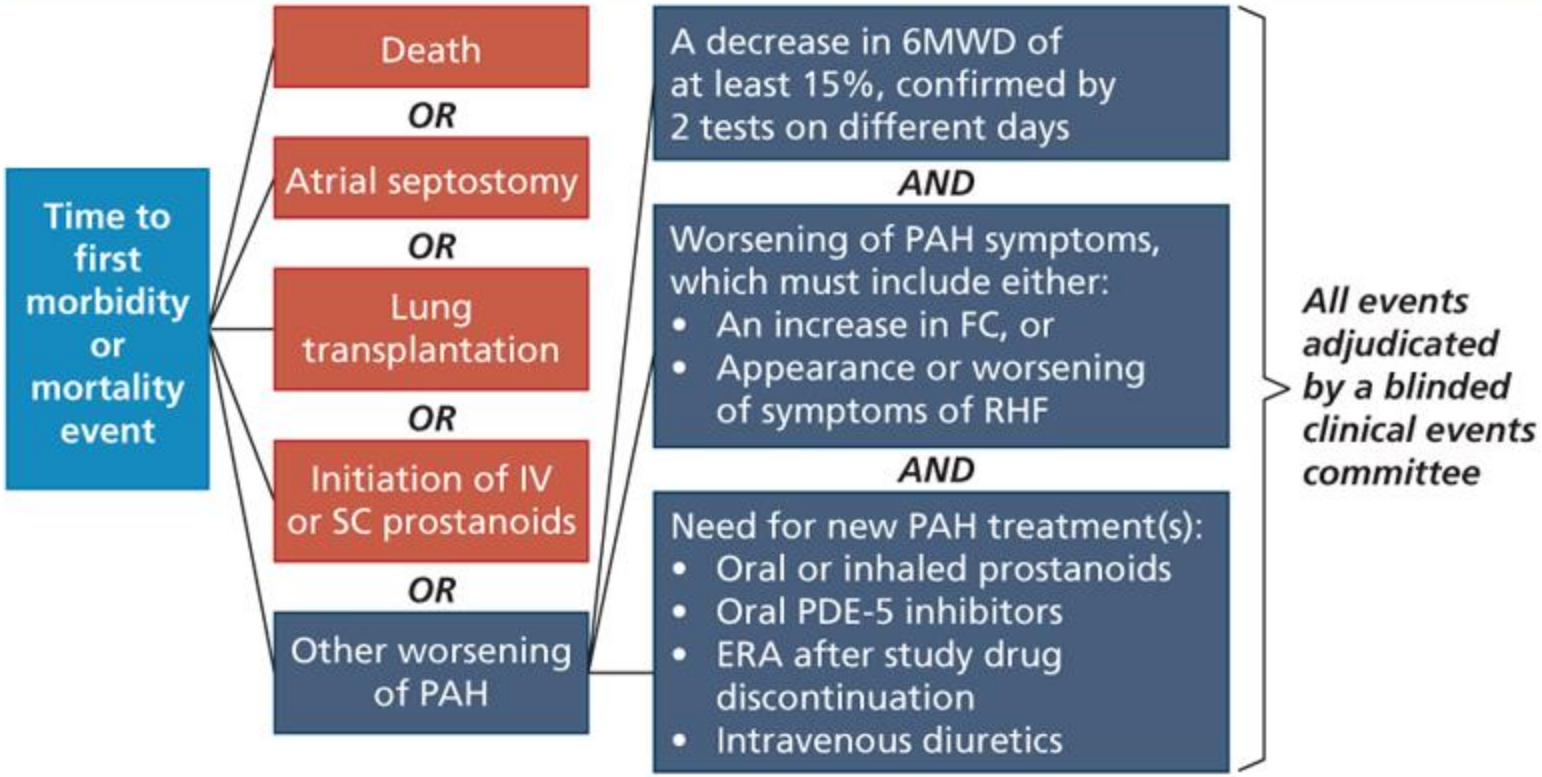
SERAPHIN Study Design

- Global (39 countries) multicentre, double-blind, randomised, placebo-controlled, parallel-group, event-driven, phase 3 clinical trial



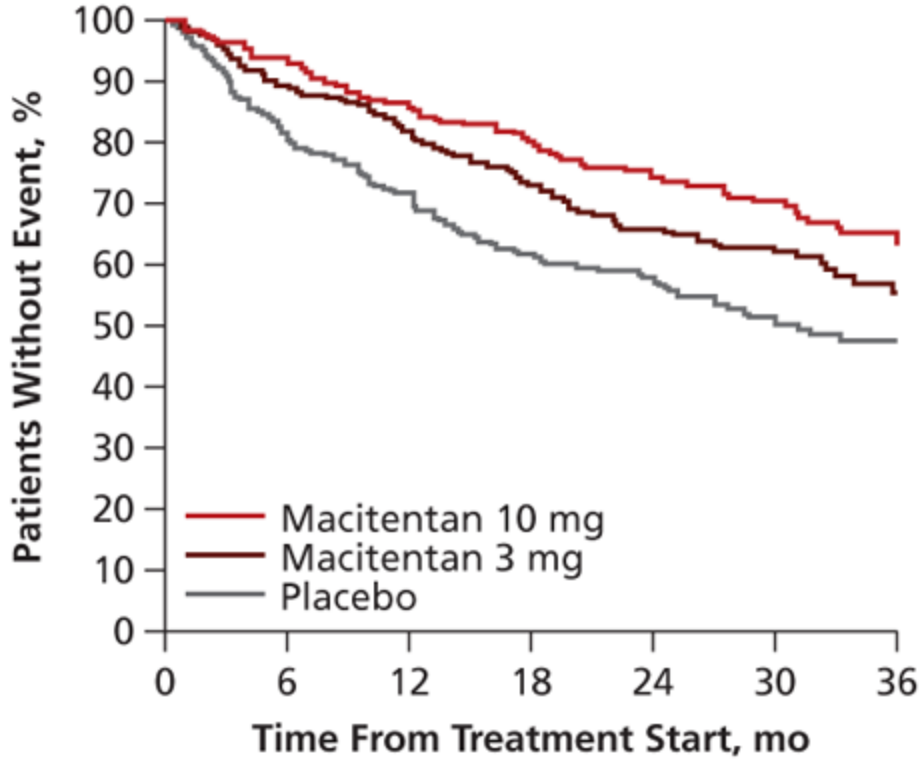
[a] Idiopathic, heritable, or related to connective tissue disease, repaired congenital systemic-to-pulmonary shunts, HIV infection, or drugs and toxins; confirmed by RHC.
[b] Patients were censored at end of double-blind treatment.

SERAPHIN's Primary Endpoint: Time to First Morbidity or Mortality Event



- **Secondary endpoints** were: change in 6MWD at month 6, change in WHO functional class at month 6, time to death due to PAH or hospitalisation for PAH, all-cause mortality, and safety/tolerability

Primary Endpoint: Significant 45% Reduction in Morbidity and Mortality Events With Macitentan 10 mg



N at risk

Placebo	250	188	160	135	122	64	23
Macitentan 3 mg	250	213	188	166	147	80	32
Macitentan 10 mg	242	208	187	171	155	91	41

Risk reduction vs placebo

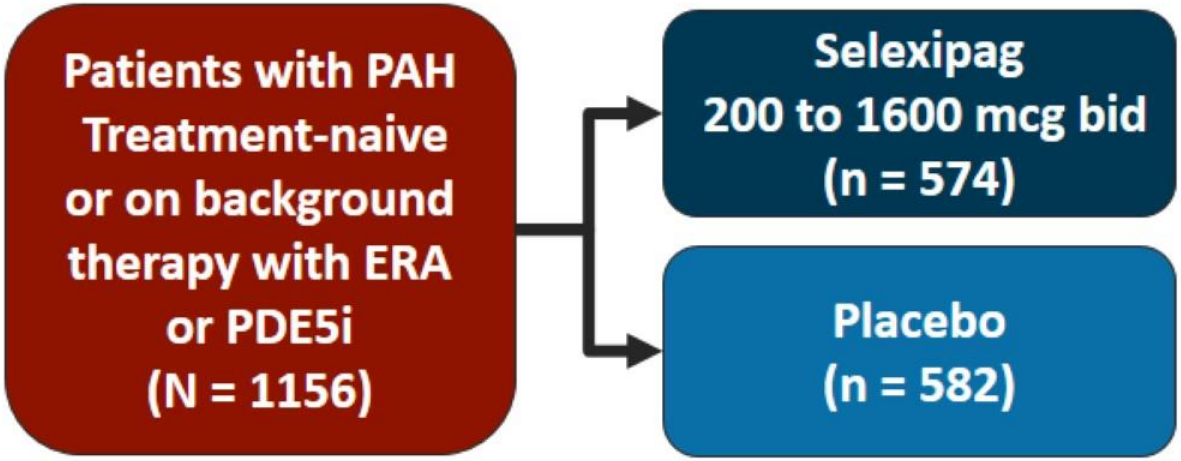
Macitentan 10 mg: 45%

Macitentan 3 mg: 30%

Treatment difference

	10 mg	3 mg
HR	0.55	0.70
P	< .001	.01

GRIPHON



- Primary endpoint:
  - Time to first morbidity/ mortality event
    - Disease progression
    - Hospitalization for PAH worsening
    - Worsening PAH
    - All-cause death

- Dosage: was not prespecified
  - Dosing was initiated at 200 mcg orally twice daily
  - Up-titrated in steps of 200 mcg twice daily, based on patient tolerability, to a maximum of 1600 mcg orally twice daily

Sitbon O, et al. *N Engl J Med*. 2015;373:2522-2533.

GRIPHON

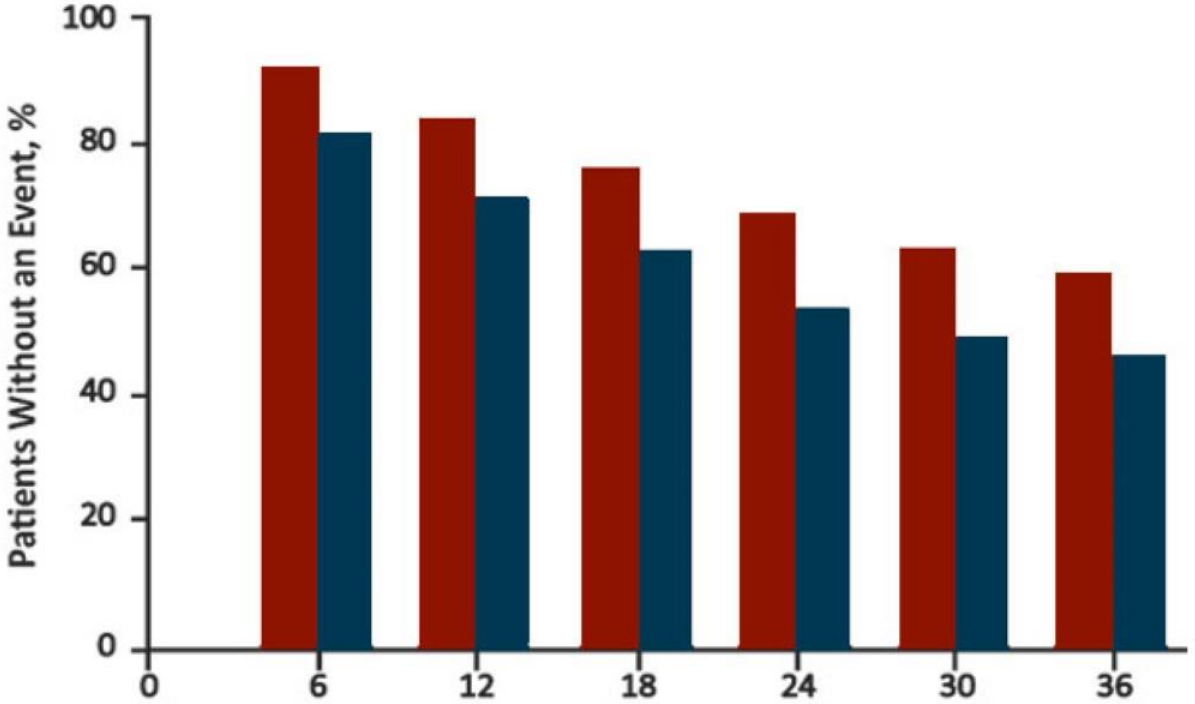
Baseline Characteristics

- Mean age = 48; 80% women
- Nearly 30% had CTD
- 10% had repaired congenital heart disease
- Background therapy:
  - 20% of patients were treatment-naive
  - Remainder (80%) background treatment with a PDE-5i and/or ERA
  - One-third were on background combination therapy; patients randomized to the active arm were then on triple therapy

Sitbon O, et al. *N Engl J Med*. 2015;373:2522-2533.

GRIPHON
Primary Endpoint

- Time to first morbidity or mortality event up to the end of the double-blind treatment phase



ITT population

No. at Risk							
Placebo	582	433	347	220	149	88	28
Selexipag	574	455	361	246	171	101	40

Sitbon O, et al. *N Engl J Med*. 2015;373:2522-2533.

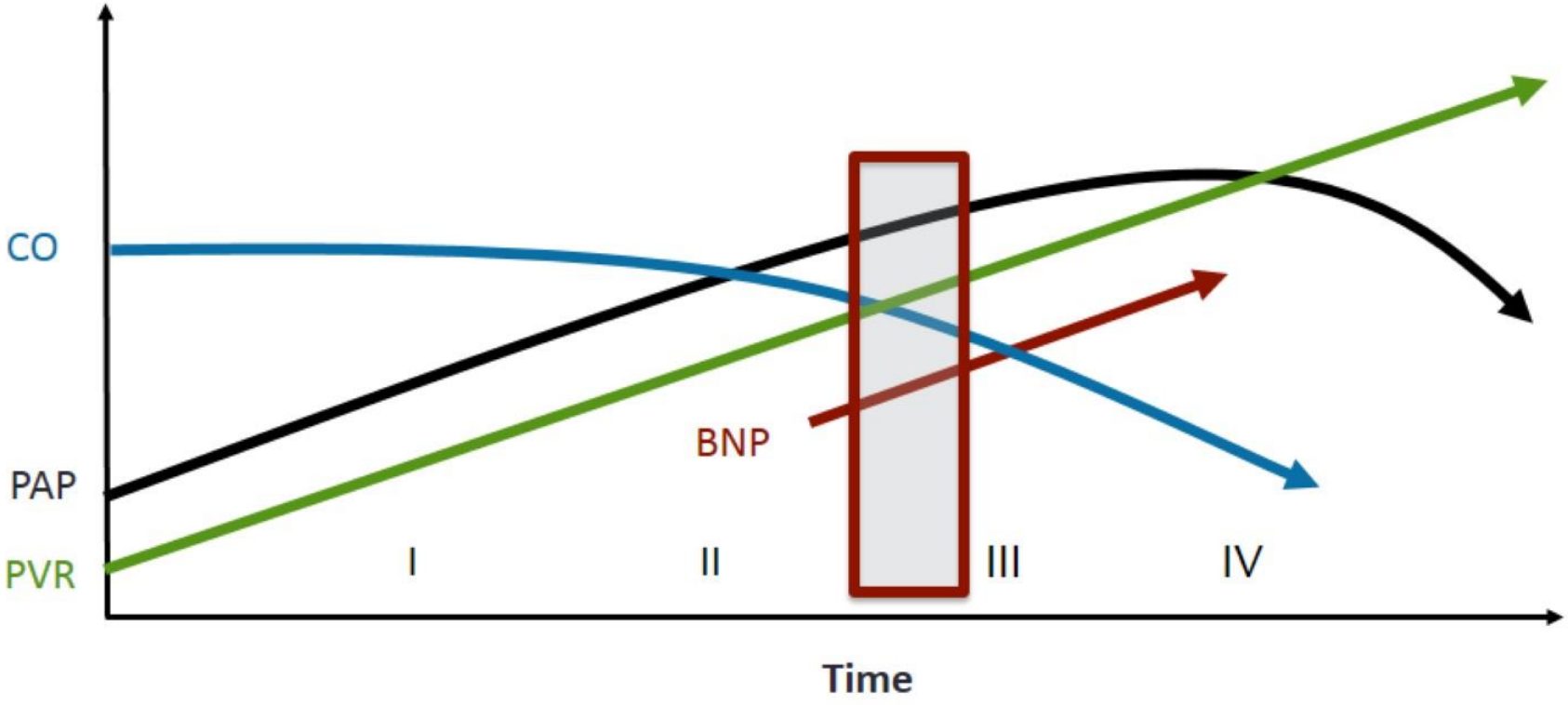
Initial vs Sequential Combination Therapy: How to Choose?

High-Risk Patients	Low/Intermediate-Risk Patients

• Clear rationale for initial combination therapy
• Include use of IV prostanoid
	• Either initial or sequential combination therapy can be used
	  • ESC/ERS guidelines allow for individual patient needs/desires
	  • Reimbursement situations different in various countries

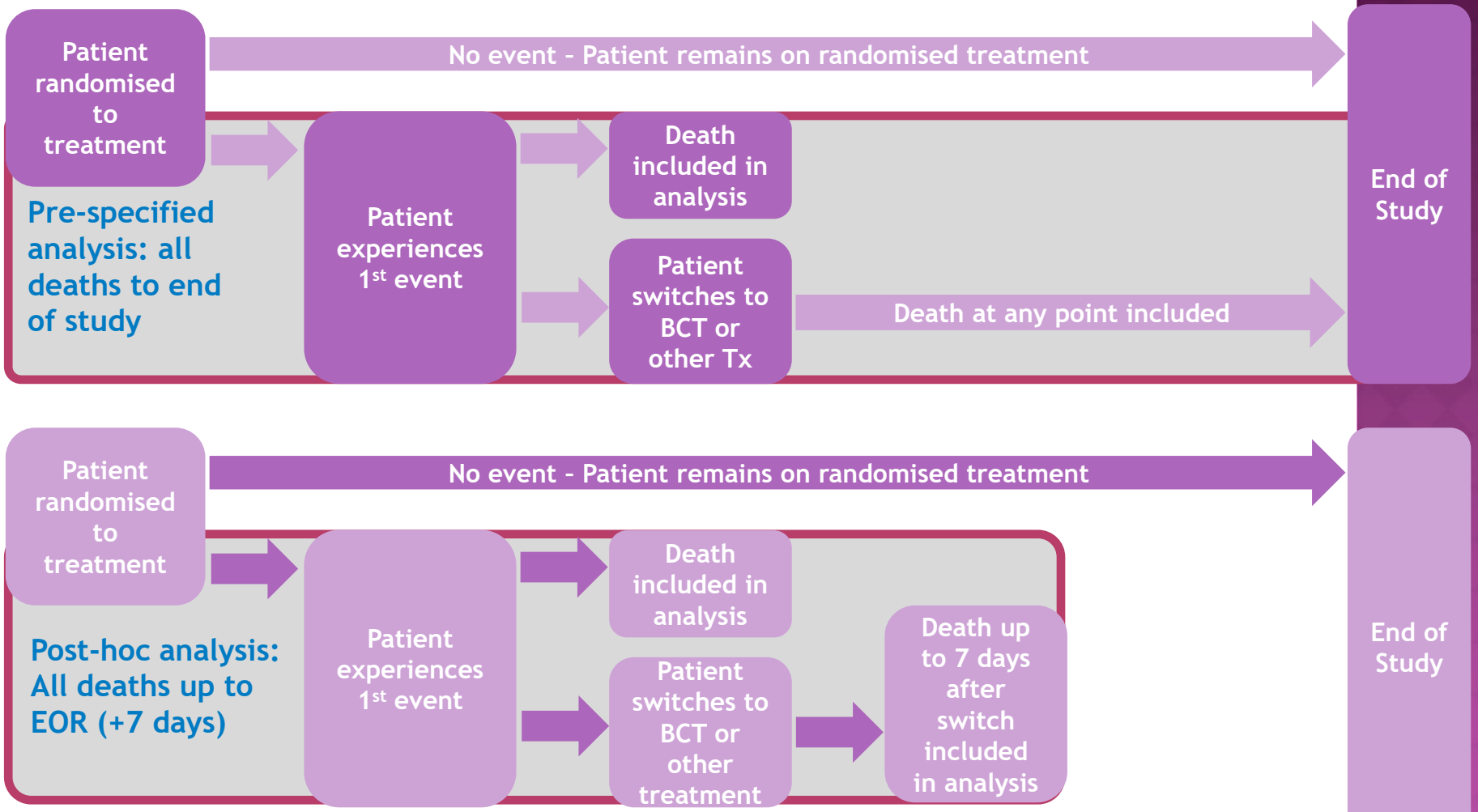
Galiè N, et al. *Eur Heart J.* 2016;37:67-119.

Natural Course of Pulmonary Hypertension



Gaine S. *JAMA.* 2000;284:3160-3168.

PRE-SPECIFIED & POST-HOC MORTALITY ANALYSIS[1]



including those who discontinued medication but remained in the study

BCT = blinded combination therapy

1.Hoeper et al. Lancet Respir Med 2016;4:894-901

Lancet Respir Med. 2016 Nov;4(11):894-901.

Initial combination therapy with ambrisentan and tadalafil and mortality in patients with pulmonaryarterial hypertension: a secondary analysis of the results from the randomised, controlled AMBITIONstudy.

We analysed survival data from the modified intention-to-treat population of the Ambrisentan and Tadalafil in Patients with Pulmonary Arterial Hypertension (AMBITION) trial.

The study population consisted of 605 patients with pulmonary arterial hypertension who were randomly assigned and received combination therapy (n=302) or monotherapy (n=303; 152 patients assigned to ambrisentan monotherapy and 151 patients to tadalafil monotherapy). At the end of the study, 29 (10%) of 302 patients in the combination therapy group had died compared with 41 (14%) of 303 patients in the monotherapy group (hazard ratio 0·67, 95% CI 0·42-1·08; stratified log-rank p=0·10). At 7 days after the end of randomised treatment, fewer patients had died in the combination therapy group (3 [1%] of 302 patients) compared with the monotherapy group (13 [4%] of 303 patients; hazard ratio 0·21, 95% CI 0·06-0·73).

EXPLORATORY ANALYSIS RESULTS

The following baseline factors were found to be predictive of better survival[1]

6MWD
≥ 357m
(median)

NT-proBNP
< 870 ng/l
(median)

Haemodynamics
CI < 2.37 L/min/m^2
(median)

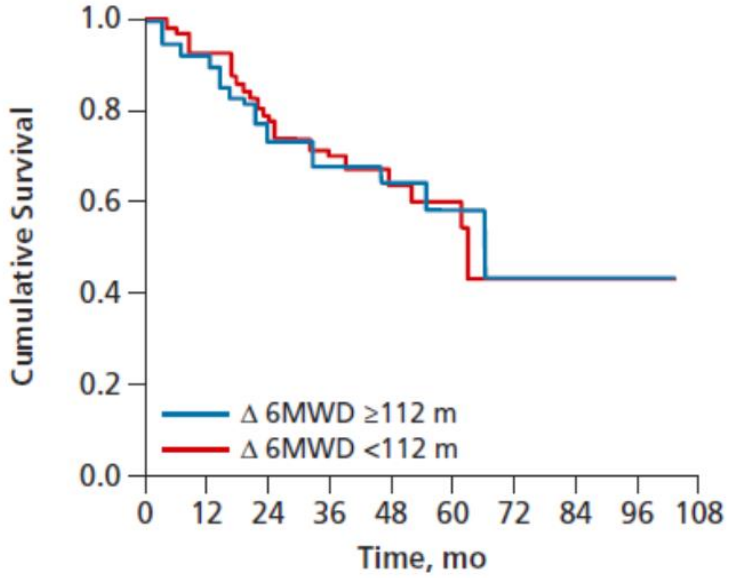
Population
PAS

1.Hoeper et al. Lancet Respir Med 2016;4:894-901

Survival in IPAH patients after 3 months on epoprostenol

An improvement of 112 m (median) in 6MWD

- Significant improvement in exercise capacity
- No effect on survival



IPAH: idiopathic PAH.

Sitbon O et al. *J Am Coll Cardiol.* 2002;40:780-788.

The AMBITION and GRIPHON subgroup analyses demonstrate a treatment benefit in patients with CTD-PAH

Whether up-front combination therapy is superior to goal-directed sequential therapy in all patient populations remains a topic of debate.

However, given the poor prognosis of CTD-PAH, up-front combination therapy is a reasonable approach, particularly in symptomatic patients with similar clinical characteristics to those in the study of Hassoun and colleagues (New York Heart Association functional class II [35%] and III [65%], with a mean pulmonary artery pressure of 42 mm Hg).

However, it is unclear whether patients with mild PAH (mean pulmonary artery pressure, 25–30 mm Hg), especially functional class II, which is more typical of those identified via aggressive screening programs, should also be treated with up-front combination therapy. Further trials are needed in this patient population to advocate up-front combination therapies. Until then, the rheumatology, cardiology, and pulmonary communities should work together to be proactive in screening, early detection, and treatment of PAH in patients with CTDs, especially

Ambrisentan and Tadalafil Up-front Combination Therapy in Scleroderma-associated Pulmonary Arterial Hypertension

Am J Respir Crit Care Med Vol 192, Iss 9, pp 1102–1110, Nov 1, 2015

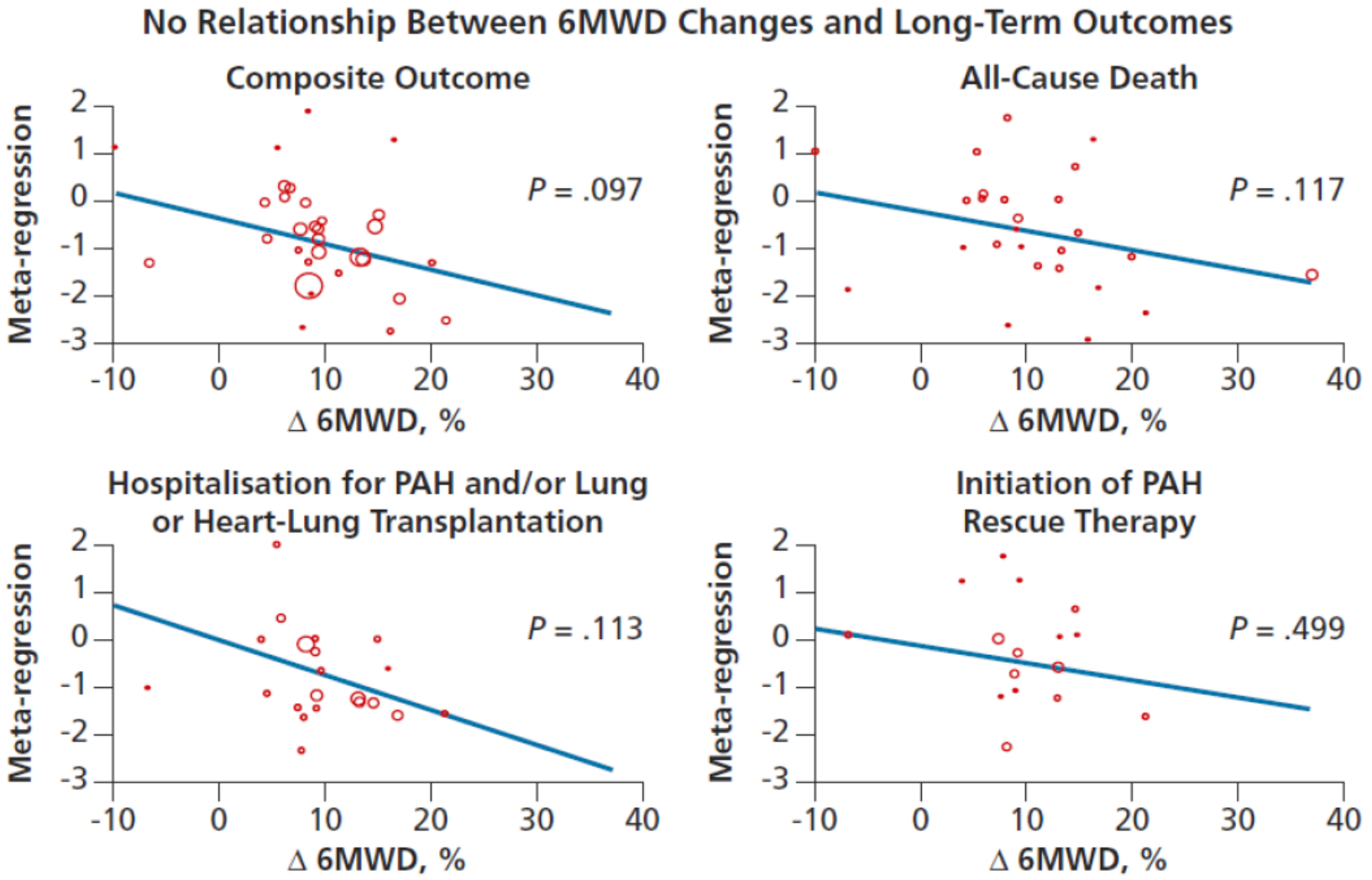
	Baseline	36 wk	*P* Value
Hemodynamics			
Heart rate, beats/min	77 ± 15	73 ± 10	NS
RAP, mm Hg	7 ± 5	5 ± 3	<0.05
mPAP, mm Hg	42 ± 12	30 ± 7	<0.01
PCWP, mm Hg	9 ± 3	11 ± 4	NS
CO, L/min	4.8 ± 1.6	5.7 ± 1.7	<0.05
CI, L/min/m^2	2.6 ± 0.7	3.3 ± 1.2	<0.01
SV, ml	63.4 ± 20.0	78.4 ± 19.7	<0.01
SVI, ml/m^2	34 ± 9	45 ± 14	<0.01
PVR, Wood units	8.4 ± 5.1	4.1 ± 3	<0.01
PP, mm Hg	44 ± 16	32 ± 10	<0.01
SV/PP, ml/mm Hg	1.8 ± 1.1	3.0 ± 1.3	<0.001
Pulmonary arterial oxygen saturation, %	65 ± 6	71 ± 4	<0.001
Functional status			
6MWD, m	343 ± 131	395 ± 99	<0.001
Borg dyspnea score	4 ± 2.5	2.8 ± 1.7	<0.02
WHO functional class I/II/III/IV, %	0/35/65/0	4/57/39/0	<0.05

Ambrisentan and Tadalafil Up-front Combination Therapy in Scleroderma-associated Pulmonary Arterial Hypertension

Am J Respir Crit Care Med Vol 192, Iss 9, pp 1102–1110, Nov 1, 2015

Variable	Baseline	36 wk	*P* Value
RVED mass, g	32.5 (23.2–41.4)	28.0 (20.6–32.9)	0.02
RV mass index, g/m^2	17.2 (13.4–27.3)	15.4 (11.7–20.3)	0.02
RVED volume, ml	151.2 (138.4–177.4)	146.4 (120.5–165.4)	0.3
RVES volume, ml	82.1 (65.6–97.7)	55.8 (49.4–79.2)	0.001
LVED volume, ml	114.0 (84.8–130.2)	135.3 (112.4–160.1)	<0.0001
LVES volume, ml	37.7 (30.1–50.2)	49.8 (41.4–60.6)	0.01
LV mass, g	88.3 (71.3–102.6)	97.2 (75.0–107.8)	0.1
LV mass/BSA, g/m^2	46.5 (42.8–58.1)	51.1 (41.7–65.9)	0.1
VMI	0.32 (0.29–0.45)	0.27 (0.23–0.33)	0.02

Meta-Analysis: 6MWD's Relationship to Long-Term Outcomes in PAH



Savarese G et al. *J Am Coll Cardiol.* 2012;60:1192-1201.

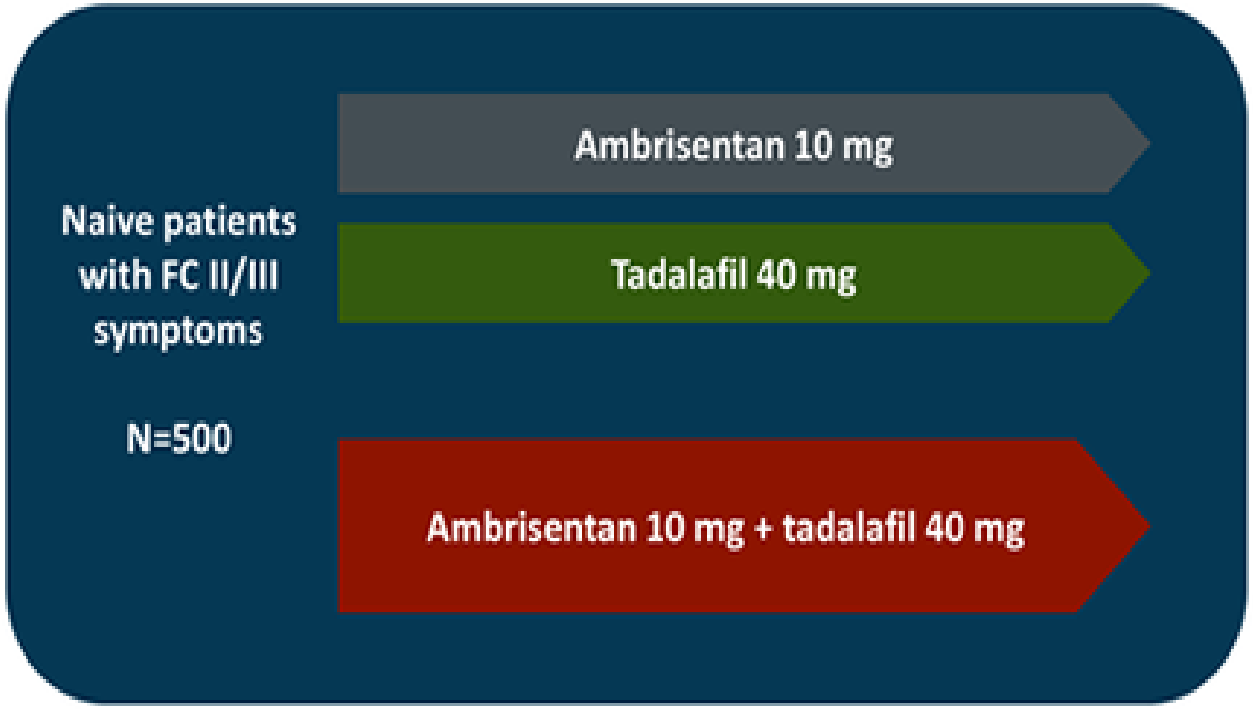
A Disconnect Between 6MWD and TTCW

Study	6MWD, m	TTCW
Study 351[1]	*P* = .021	*P* = .033
BREATHE-1[2]	*P* < .001	*P* = .002
EARLY[3]	NS	*P* < .001
SUPER-1[4]	*P* < .001	NS
ARIES-1[5]	*P* < .01	NS
ARIES-2[6]	*P* < .05	*P* < .05

Evolution of PAH Treatment

Anderson JA, et al. *J Thorac Dis.* 2016;8:S562-S565.
Humbert M, et al. *Thorax*. 2016;71:73-83.

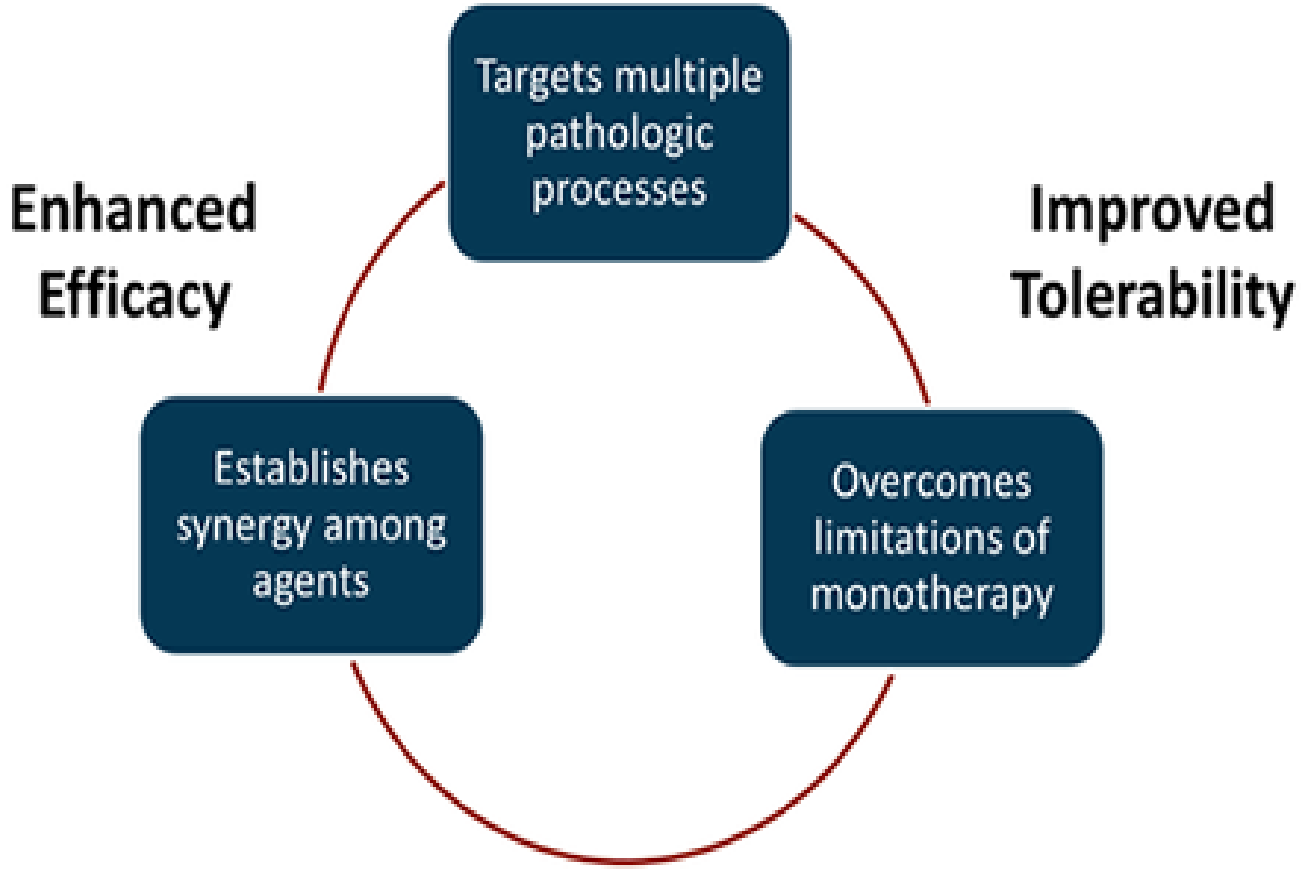
Initial Use of Ambrisentan Plus Tadalafil in PAH: The AMBITION Trial



- 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.

Combination Pharmacotherapy in PAH: Rationale and Potential Clinical Benefits



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

PHAROS REGISTRY

We defined
a classification listing of “Pre-PAH” based on the presence of **any one** of these three criteria on study entry:

1. Diffusing capacity for carbon monoxide (DLCO) < 55% predicted without severe ILD (as defined by forced vital capacity (FVC) < 65% predicted and/or a thoracic high resolution computed tomography (HRCT) scan that showed moderate to severe ILD according to the local radiologist)(7) or
2. FVC %predicted / DLCO %predicted ratio ≥1.6 or
3. Estimated right ventricular systolic pressure (RVSP) > 35 mmHg on Doppler echocardiography.

At baseline, 16 subjects (10%) of the Pre-PAH group had symptoms, an elevated RVSP (mean +/− SD 38 +/− 10, range 19–62), or PFT abnormalities that led individual investigators to do a RHC that revealed a normal mPAP. Four of these had an estimated RVSP on echocardiogram > 40mm Hg, the mean +/− SD DLCO% predicted in this group was markedly reduced (38% +/− 16) and the mean PCWP was 8 mm Hg. Ten RHC-negative subjects had undergone a thoracic HRCT that revealed no (n=5), mild (n=3), moderate (n=1), or severe (n=1) fibrosis.

PHAROS

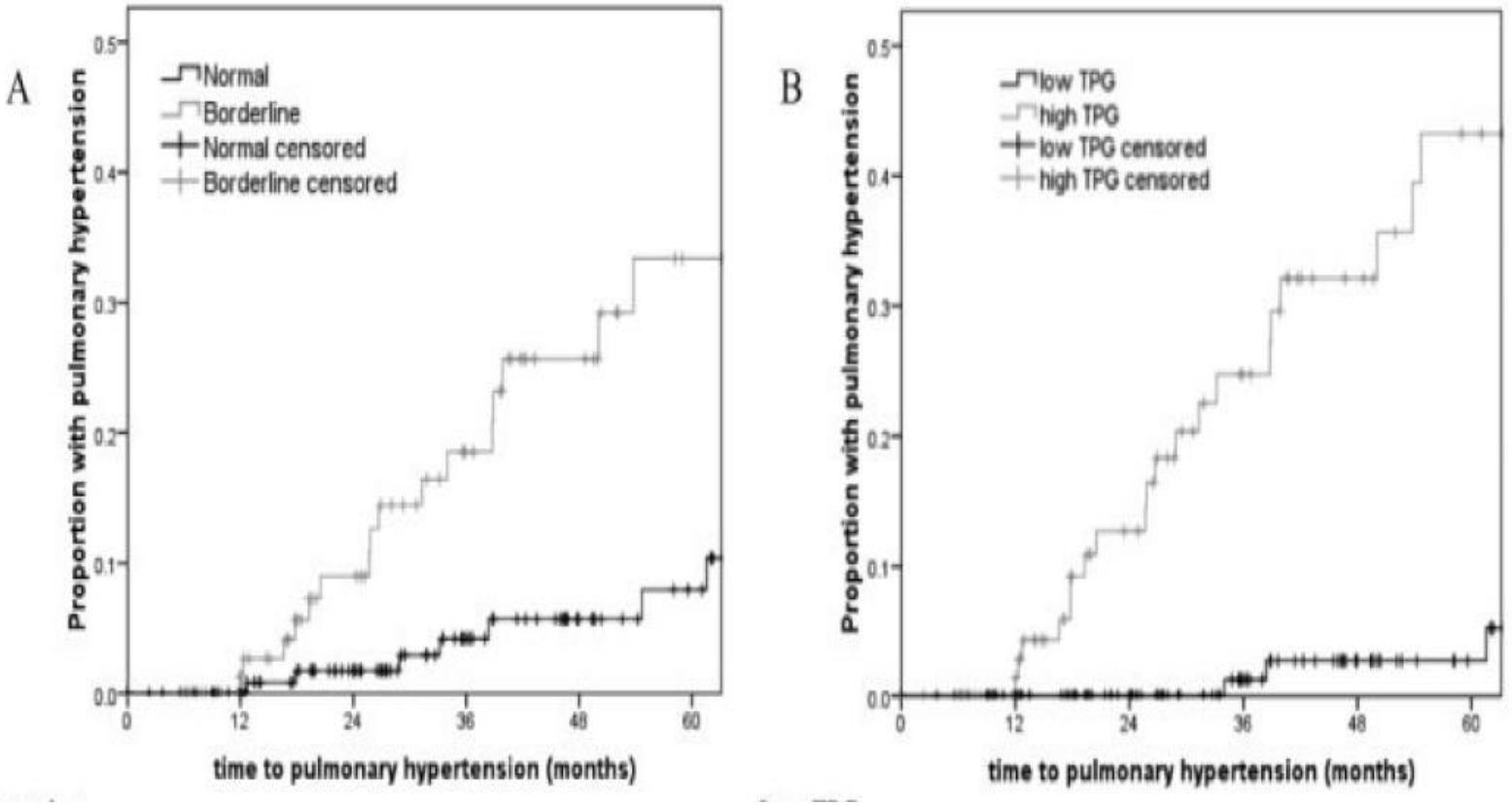
We found that one-third (22/71) of subjects
thought to be at high-risk for PAH according to our three criteria were found to have PVH or
PH-ILD. Thus, it is imperative that clinicians treating patients with SSc realize that a right
heart catheterization is necessary to accurately establish the diagnosis of PAH

Only 14% of those with PH had a DLCO that
was > 55% predicted. Interestingly, the mean DLCO was lowest in Groups 2 and 3 showing that a low DLCO itself does not necessarily predict PAH compared to PVH and PH-ILD. However, the mean FVC% predicted was significantly lower in the non-PAH groups, and importantly the mean FVC%/DLCO% ratio was highest in those with PAH. Eighty-two percent of those with PAH, 70% with PVH and only 25% with PH-ILD had a FVC/DLCO ratio >1.6. Thus, the high ratio may be a useful parameter to use as part of the determination of whether an SSc-PH patient has PAH compared to other causes of PH.

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



ENDOTHELIAL DYSFUNCTION IN CTD

DECREASED NO production in PAH and SSc

DECREASED eNOS expression in IPAH lung

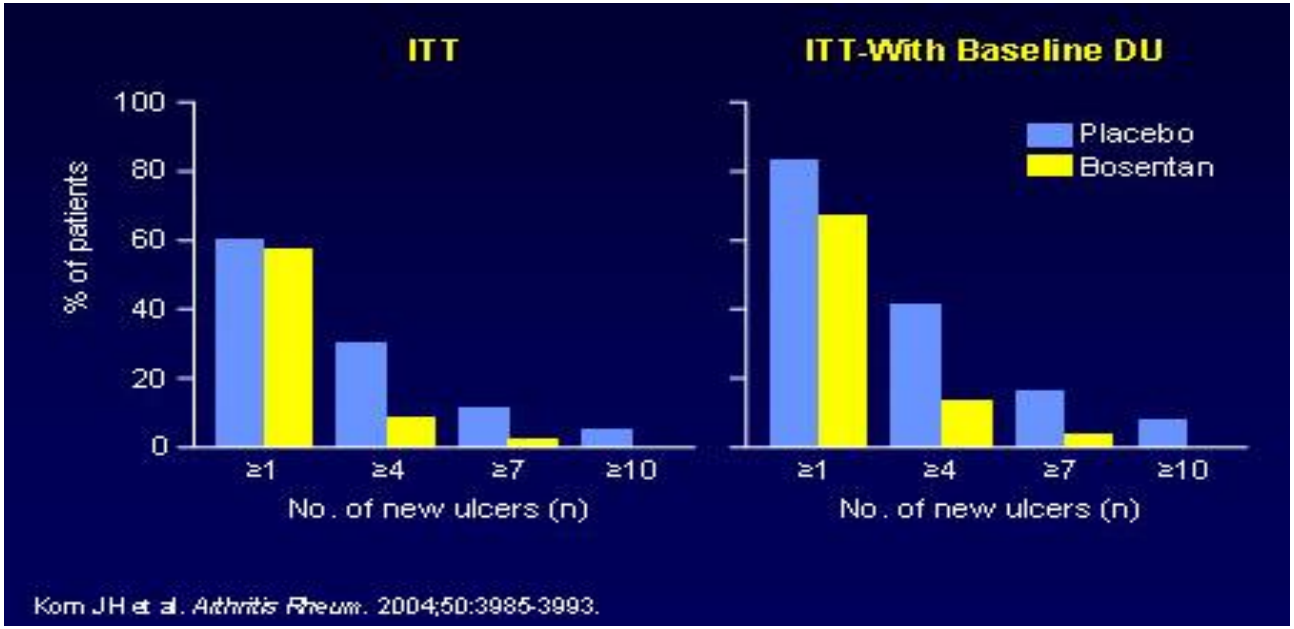
DECREASED eNOS expression in SSc dermal microvasculature

ROLE OF ENDOTHELIN

ET-1 increased in SSc serum

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

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

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

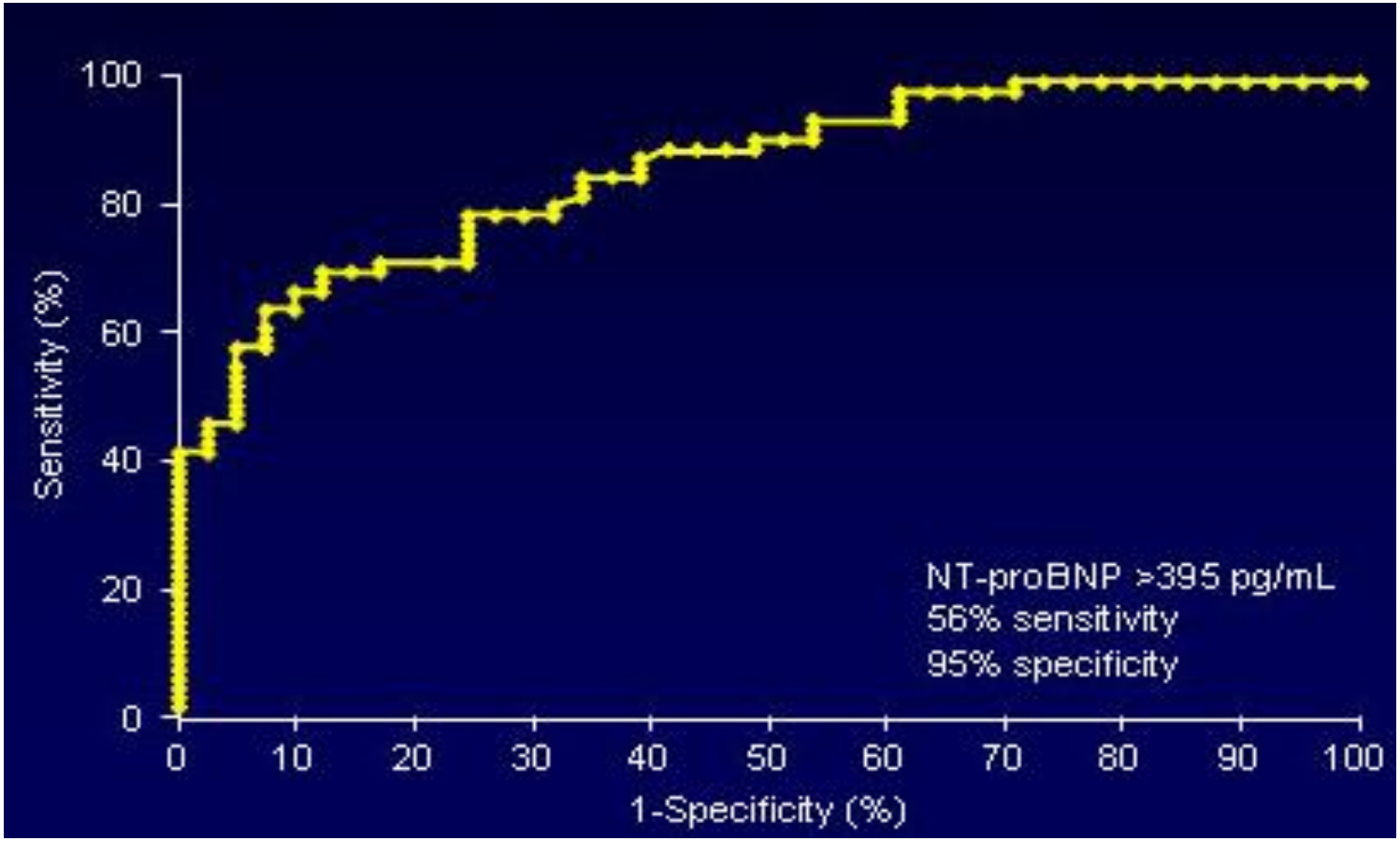
Correlation: BAL vs HRCT

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%

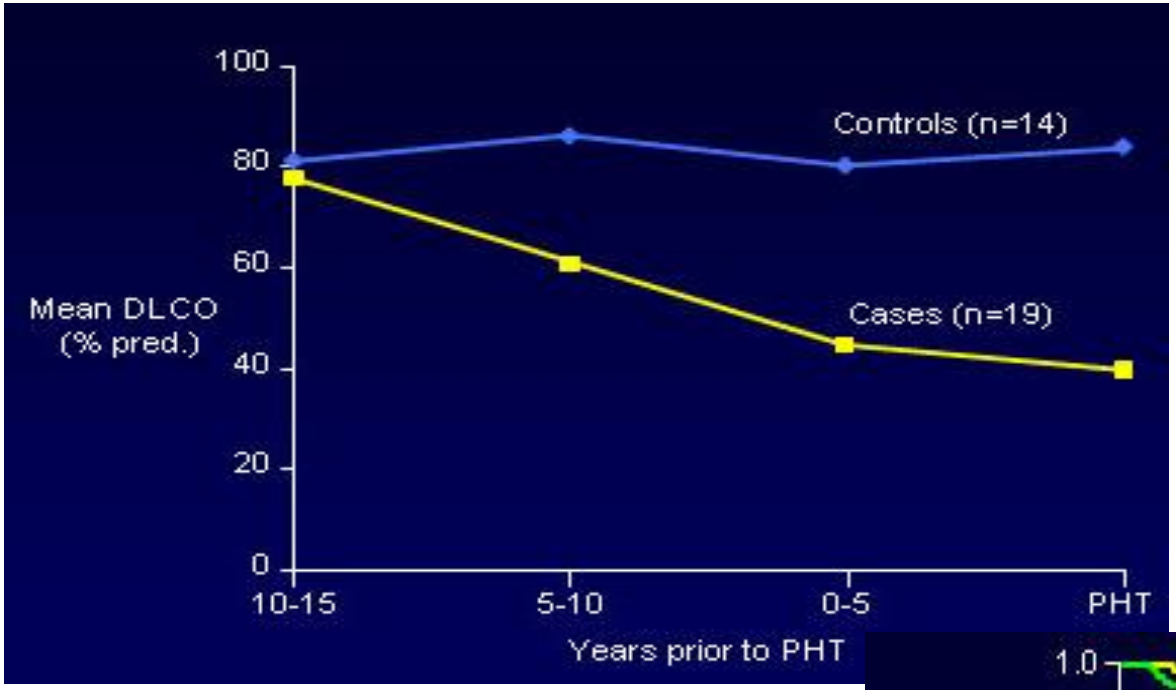
Silver R et al. *Am J Respir Crit Care Med.* 2004;169:A227.

NT-PROBNP SSC – PAH PREDICTION
ROC CURVES



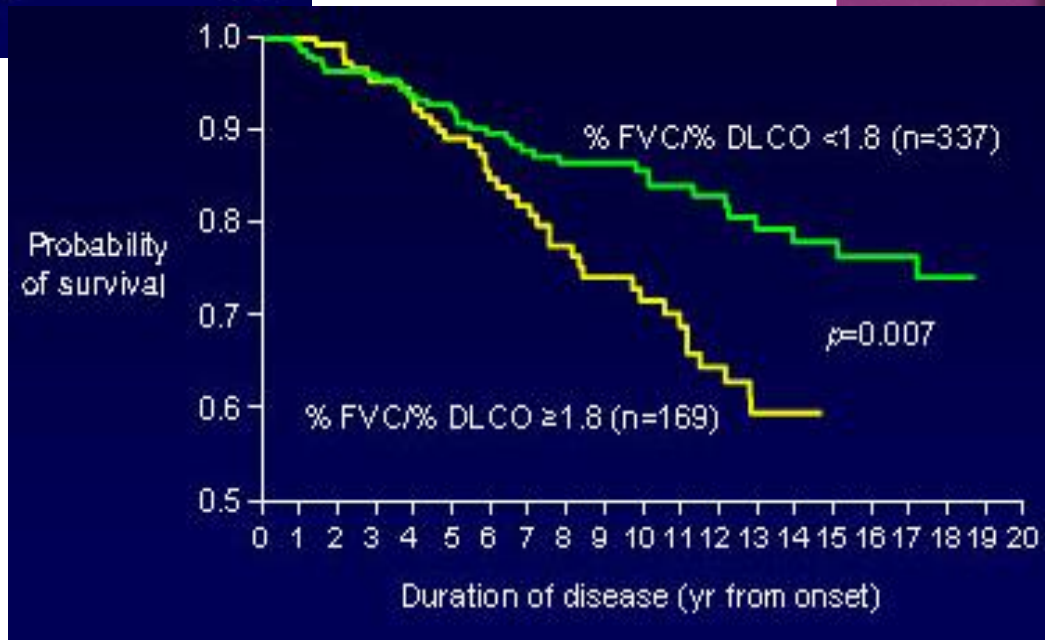
Eur Heart J 2006; 27: 1485-1494

SSC – PREDICTORS OF PAH



Courtesy of James Seibdd

Arthritis Rheum 2003; 43:516-522



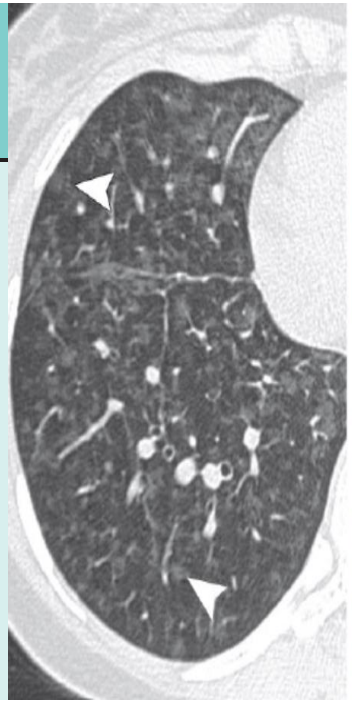
DD PAH - GROUP 3

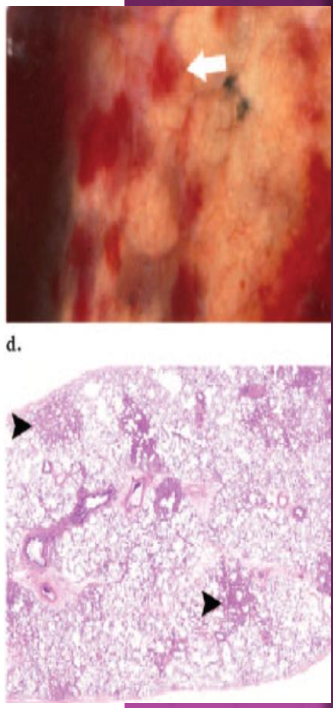
Criteria Favoring Group 1 (PAH)	Criteria Favoring Group 3 (PH Due to Lung Disease)
Normal or mildly impaired	Moderate to very severe impairment
FEV1 >60% predicted (COPD)	FEV1 <60% predicted (COPD)
FVC >70% predicted (IPF)	FVC <70% predicted (IPF)
Absence of or only modest airway or parenchymal abnormalities	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

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





PAH Challenges
High-Risk Populations (cont)

- DETECT study[a]
  - 446 patients w/SSc at increased risk for PAH (SSc >3 years, predicted DLCO < 60%)
    - Noninvasive assessments (standard clinical parameters, serum analysis, ECG, echocardiography) followed by diagnostic RHC
  - Results
    - RHC-confirmed PAH: 19%
    - WHO FC I and II: 64%
    - RHC referral rate
    - DETECT algorithm: 64%
    - ERS guidelines: 40%
  - Missed diagnoses
    - DETECT algorithm: 4%
    - ERS guidelines: 29%

- French Nationwide Study[b]
  - 599 patients without severe PF abnormalities from 21 SSc centers; 2002-2003
  - Echo criteria to undergo confirmatory RHC
  - VTR >3 m/s or 2.5-3 m/sec with unexplained dyspnea
  - Results
  - 29 patients with known PAH
    - Hemodynamics → mPAP: 49 ± 17 mm Hg; TPR: 1007 ± 615 dynes x sec/cm^5
  - 33 patients with suspected PAH
    - 54.5% confirmed PAH
    - Mild severity → mPAP: 30 ± 9 mm Hg; mTPR:524 ± 382 dynes x second/cm^5
  - Estimated PAH prevalence in SSc: 7.85%

a. Coghlan JG, et al. *Ann Rheum Dis*. 2014;73:1340-1349[8]; b. Hachulla E, et al. *Arthritis Rheum*. 2005;52:3792-3800.[9]

GRIPHON: Primary Endpoint

Composite of Death or a Complication Related to PAH Up to the End of the Treatment Period

Endpoint	Placebo N = 582	Selexipag N = 574	HR (99% CI)	*P* Value
All events, %	41.6	27.0	0.60 (0.46, 0.78)	< .001
Hospitalization for worsening of PAH, %	18.7	13.6		
Disease progression, %	17.2	6.6		
Death from any cause, %	3.1	4.9		
Initiation of parenteral prostanoid therapy or long-term oxygen therapy for worsening of PAH, %	2.2	1.7		
Need for lung transplantation of balloon atrial septostomy for worsening of PAH, %	0.3	0.2		

Sitbon O, et al. *N Engl J Med*. 2015;373:2522-2533.

GRIPHON

Treatment Effect by Subgroup

HR for Selexipag vs Placebo by Subgroup

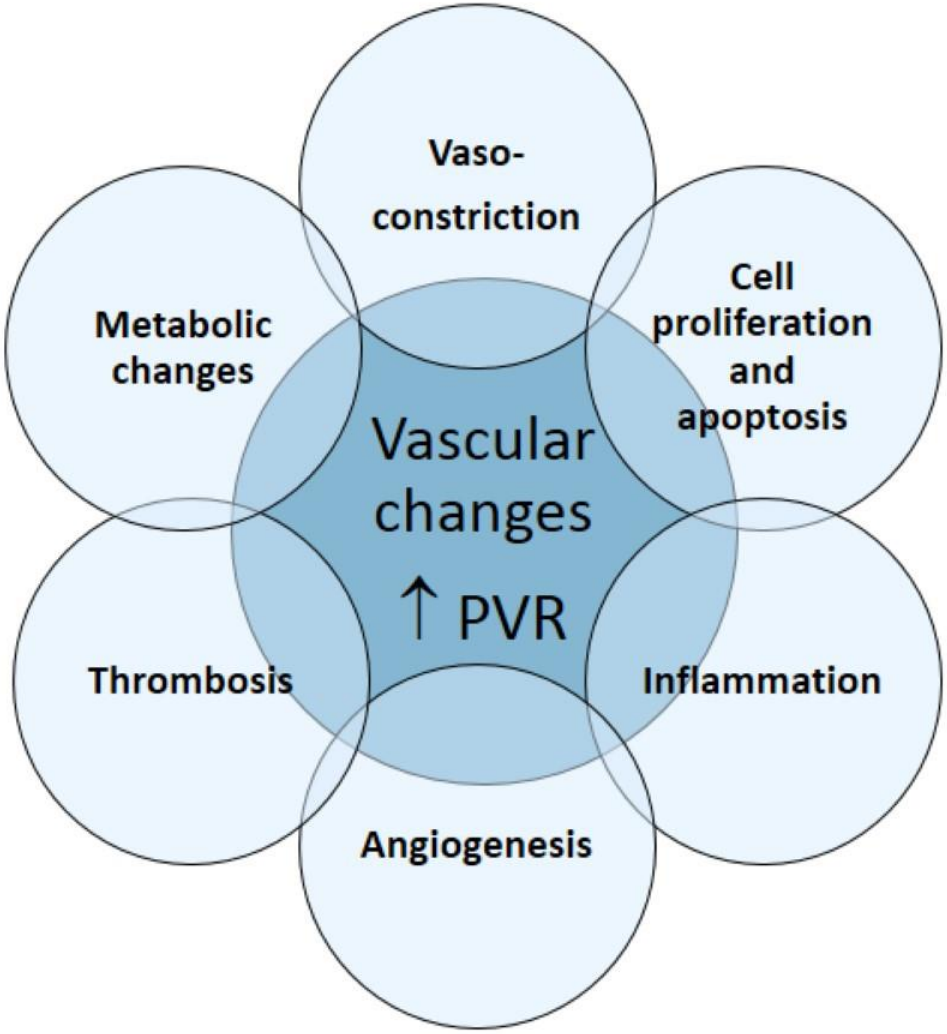
	%	HR (99% CI) M/M for Selexipag vs Placebo
Etiology		
IPAH/other*	61.6	0.61 (0.44, 0.86)
PAH-CTD	28.9	0.59 (0.37, 0.96)
PAH-CHD	9.5	0.58 (0.19, 1.79)
Age		
< 65 years	82.1	0.59 (0.44, 0.80)
≥ 65 years	17.9	0.65 (0.36, 1.17)

	%	HR (99% CI) M/M for Selexipag vs Placebo
Geographical Region		
Western Europe/Australia	27.8	0.52 (0.31, 0.87)
Eastern Europe	26.3	0.49 (0.31, 0.79)
Asia	19.7	0.94 (0.52, 1.70)
North America	16.7	0.83 (0.40, 1.72)
Latin America	9.5	0.35 (0.12, 1.00)

*IPAH/other, idiopathic, heritable, HIV- or drug-induced.

Sitbon O, et al. *N Engl J Med*. 2015;373:2522-2533.

Pathological Mechanisms Underlying Vascular Changes in PH



Wilkins MR. *Eur Respir Rev*. 2012;21:19-26.

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

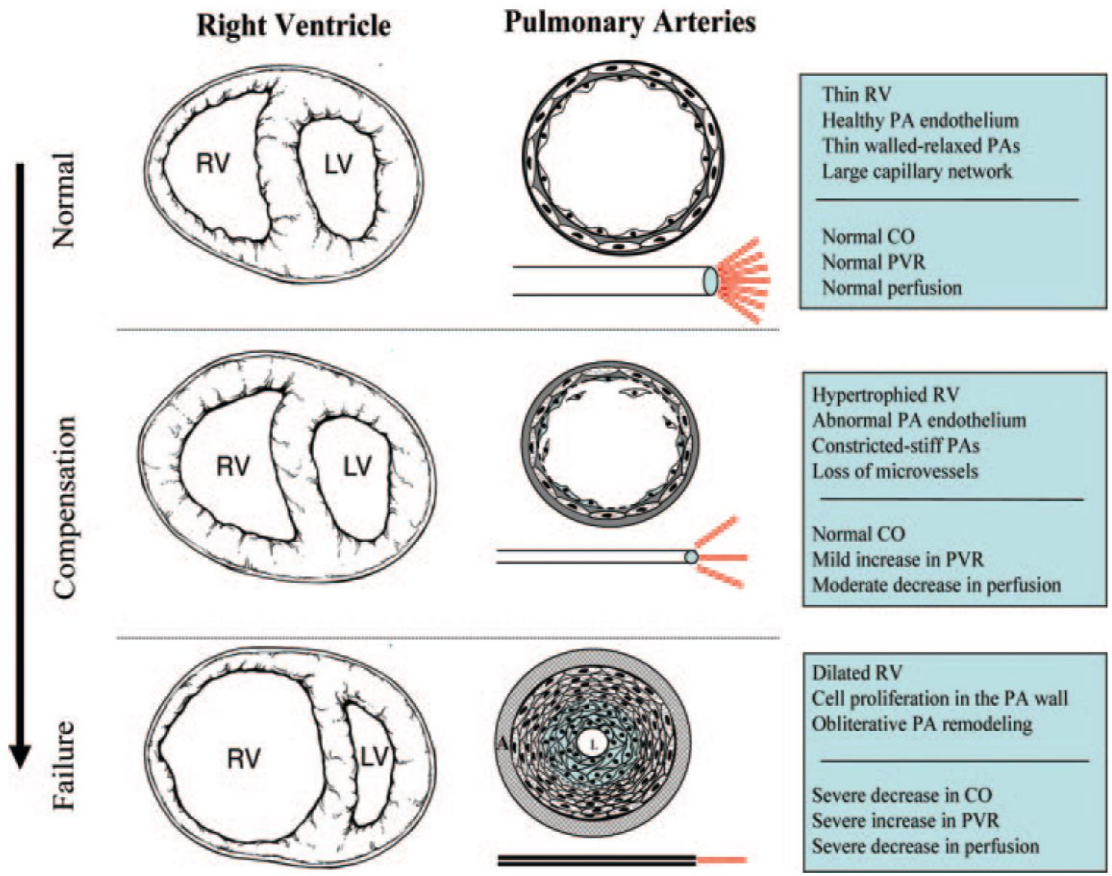
RHC is indicated : Clinical worsening and progressive exercise limitation disproportionate to ventilator impairment
(alternative diagnosis-PAH,CTEPH,LV dysfunction)

PULMONARY HYPERTENSION

Haemodynamic & Pathophysiologic Condition

mPAP ≥ 25 mmHg

ESC GUIDELINES 2015



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

ECHO SIGNS SUGGESTING PH

[a]Echocardiographic signs from at least two different categories (A/B/C) from the list should be present to alter the level of echocardiographic probability of pulmonary hypertension.

A: The ventricles[a]	B: Pulmonary artery[a]	C: Inferior vena cava and right atrium[a]
Right ventricle/ left ventricle basal diameter ratio >1.0	Right ventricular outflow Doppler acceleration time <105 msec and/or midsystolic notching	Inferior cava diameter >21 mm with decreased inspiratory collapse (<50 % with a sniff or <20 % with quiet inspiration)
Flattening of the interventricular septum (left ventricular eccentricity index >1.1 in systole and/or diastole)	Early diastolic pulmonary regurgitation velocity >2.2 m/sec	Right atrial area (end-systole) >18 cm^2
	PA diameter >25 mm.	

ESC Guidelines 2015

WHO FC change at week 24

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

	Combination therapy (n=253)	Pooled monotherapy (n=247)	Ambrisentan monotherapy (n=126)	Tadalafil monotherapy (n=121)
Baseline WHO FC, observed, n	**253**	**247**	**126**	**121**
II	76 (30%)	79 (32%)	38 (30%)	41 (34%)
III	177 (70%)	168 (68%)	88 (70%)	80 (66%)
Week 24 WHO FC, observed, n	**233**	**220**	**109**	**111**
Improved	89 (38%)	80 (36%)	41 (38%)	39 (35%)
No change	138 (59%)	133 (60%)	63 (58%)	70 (63%)
Deteriorated				2 (2%)
Week 24 WHO FC, impu				**120**
Improved				39 (33%)
No change				74 (62%)
Deteriorated	12 (5%)	16 (7%)	9 (7%)	7 (6%)
p value		0.2375	0.3011	0.3641

It is possible that the FC assessment is not sensitive enough to pick up differences in improvements in FC between two active treatment groups

*Worst case imputation (0) was used for missing data following death or adjudicated hospitalisation; otherwise, LOCF imputation was used. Baseline data have not been used for imputation. p value from CMH tests stratified by baseline aetiology of PAH (IPAH/HPAH vs non-IPAH) and WHO FC (II vs III).

SECONDARY ENDPOINTS: SELECTED RESULTS AT WEEK 24

Endpoint	Combination Therapy (n = 253)	Pooled Monotherapy (n = 257)
NT-proBNP level, % change in mean from BL	-67.2	-50.4 (*P* < .001)
Satisfactory clinical response[b], n of participants/total n (%)	91/234 (39)	66/226 (29)
6MWD, median (IQR) change from BL	48.98 (4.63 to 85.75)	23.80 (-12.25 to 64.53) (*P* < .001)

N Engl J Med. 2015;373:834-844

ADVERSE EVENTS (≥15% IN COMB)

AE Term n, (%)	COMB (n=253)	AMB Mono (n=126)	TAD Mono (n=121)
Any AE	**247 (98%)**	**120 (95%)**	**114 (94%)**
Oedema peripheral	115 (45%)	41 (33%)	34 (28%)
Headache	107 (42%)	41 (33%)	42 (35%)
Nasal congestion	54 (21%)	19 (15%)	15 (12%)
Diarrhoea	50 (20%)	29 (23%)	23 (19%)
Dizziness	50 (20%)	24 (19%)	14 (12%)
Dyspnoea	44 (17%)	22 (17%)	20 (17%)
Nausea	43 (17%)	18 (14%)	20 (17%)
Cough	40 (16%)	14 (11%)	21 (17%)
Flushing	38 (15%)	18 (14%)	11 (9%)
Anemia	37 (15%)	8 (6%)	14 (12%)
Nasopharyngitis	37 (15%)	26 (21%)	18 (15%)
Pain in extremity	37 (15%)	14 (11%)	18 (15%)
Syncope	13 (5%)	7 (6%)	10 (8%)

Only adverse events on randomised treatment, with onset between first dose of study drug and last dose+30 days are shown

DISCONTINUATIONS DUE TO AES

AE leading to discontinuation n, (%)	Combination (n=253)	AMB Mono (n=126)	TAD Mono (n=121)
Any event	**31 (12%)**	**14 (11%)**	**14 (12%)**
Dyspnoea	5 (2%)	0	1 (<1%)
Oedema, peripheral	4 (2%)	3 (2%)	1 (<1%)
Headache	4 (2%)	0	1 (<1%)
Pulmonary Hypertension	1 (<1%)	2 (2%)	1 (<1%)
Anaemia	1 (<1%)	2 (2%)	0
Myalgia	0	0	3 (2%)
Cardiac Failure	0	2 (2%)	0

Only adverse events on randomised treatment, with onset between first dose of study drug and last dose+30 days are shown

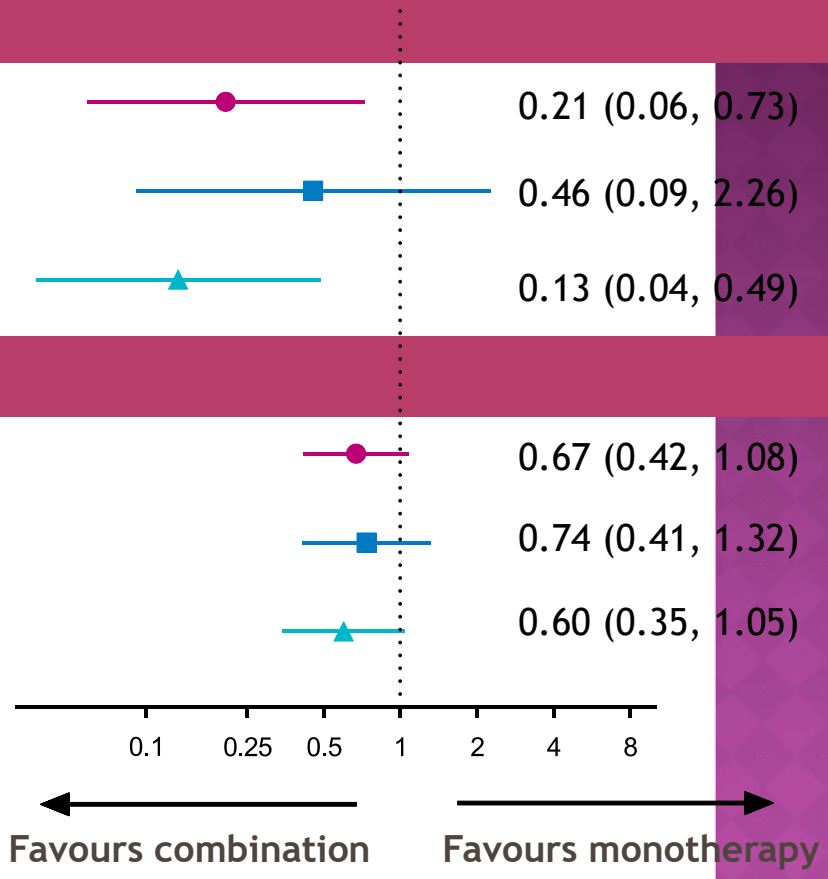
Liver Events – AST/ALT >3xULN

	On Randomized Treatment		
	Combination Therapy N = 253	Ambrisentan Monotherapy N = 126	Tadalafil Monotherapy N = 121
Subjects with ALT/AST >3xULN	5 (2%)	0	2 (2%)

Data on file

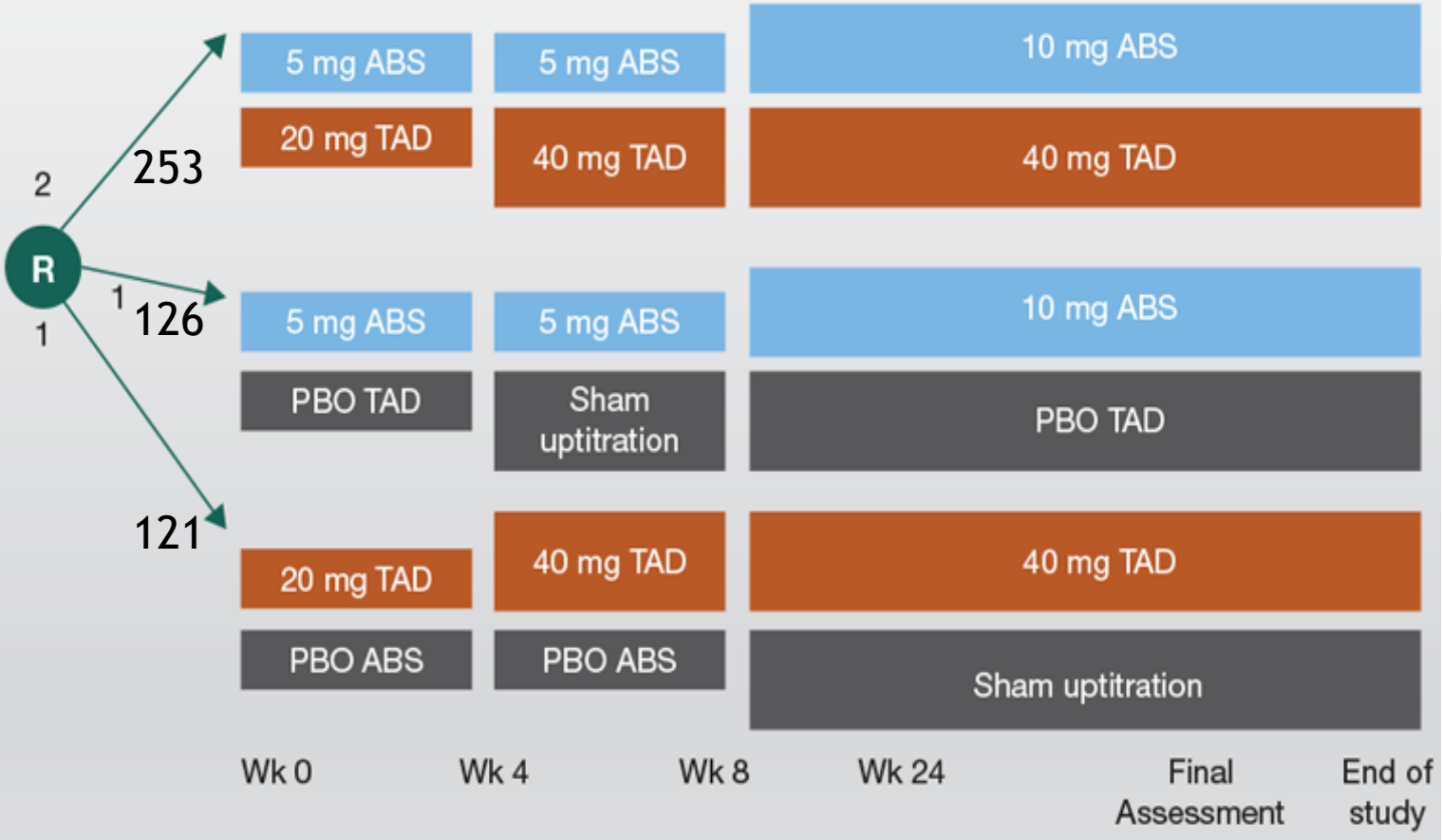
SURVIVAL FOREST PLOT[1]

	Group	Events Patients with events/ total patients (%)	Hazard Ratio (95% CI)
EoT+7	Combination therapy	3/302 (<1)	
	Pooled monotherapy	13/303 (4)	0.21 (0.06, 0.73)
	AMB monotherapy	3/152 (2)	0.46 (0.09, 2.26)
	TAD monotherapy	10/151 (7)	0.13 (0.04, 0.49)
Final EoS	Combination therapy	29/302 (10)	
	Pooled monotherapy	41/303 (14)	0.67 (0.42, 1.08)
	AMB monotherapy	19/152 (13)	0.74 (0.41, 1.32)
	TAD monotherapy	22/151 (15)	0.60 (0.35, 1.05)



Hoeper et al. Lancet Respir Med 2016;4:894-901

AMBITION:
TITRATING THE DOSES OF COMBINATION THERAPY



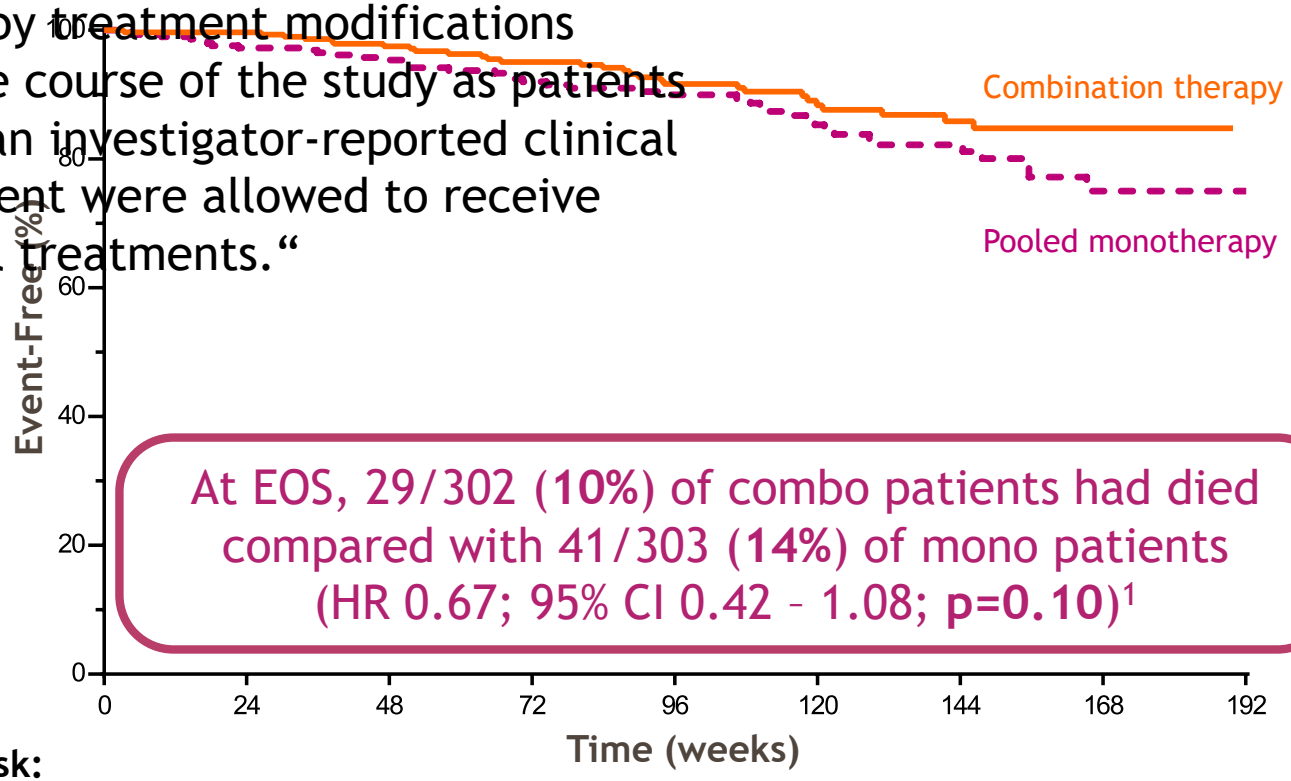
Evaluation of secondary efficacy endpoints

~28 d after 105 clinical failure events reached

517days→609 days

KAPLAN-MEIER SURVIVAL ESTIMATE FROM BASELINE TO END OF STUDY (MITT)[1]

"long-term survival might have been affected by treatment modifications during the course of the study as patients who had an investigator-reported clinical failure event were allowed to receive additional treatments."



33% mortality risk reduction

At EOS, 29/302 (**10%**) of combo patients had died compared with 41/303 (**14%**) of mono patients (HR 0.67; 95% CI 0.42 – 1.08; **p=0.10**)[1]

Number at risk:

Combination	302	287	256	218	179	125	81	33
Pooled Mono	303	275	243	200	162	117	80	30

1.Hoeper et al. Lancet Respir Med 2016;4:894-901