Hypertensions pulmonaires associées aux sclérodermies: Prise en charge thérapeutique

Athénaïs Boucly

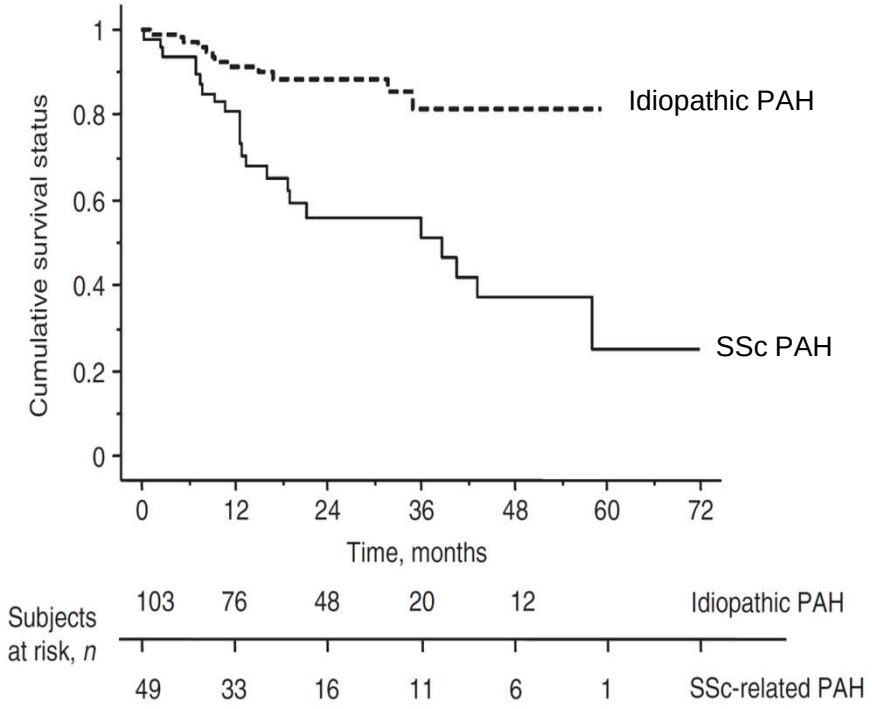
Centre de Référence de l'Hypertension Pulmonaire Sévère
Hôpital Universitaire de Bicêtre – INSERM U999
Université Paris-Sud – Le Kremlin-Bicêtre – France

DHU Thorax Innovation

HTAP-SSc : un pronostic sombre…

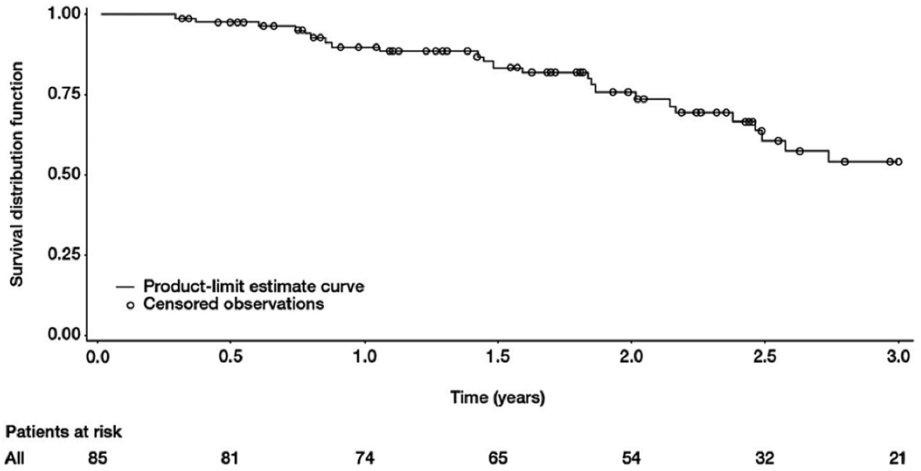
Long-term outcome of systemic sclerosis-associated pulmonary arterial hypertension treated with bosentan as first-line monotherapy followed or not by the addition of prostanoids or sildenafil

David Launay[1,2,3,4], Olivier Sitbon[1,2,3], Jérôme Le Pavec[1,2,3], Laurent Savale[1,2,3], Colas Tchérakian[1,2,3], Azzedine Yaïci[1,2,3], Lara Achouh[1,2,3], Florence Parent[1,2,3], Xavier Jais[1,2,3], Gérald Simonneau[1,2,3] and Marc Humbert[1,2,3]



Survival in systemic sclerosis-associated pulmonary arterial hypertension in the modern management era

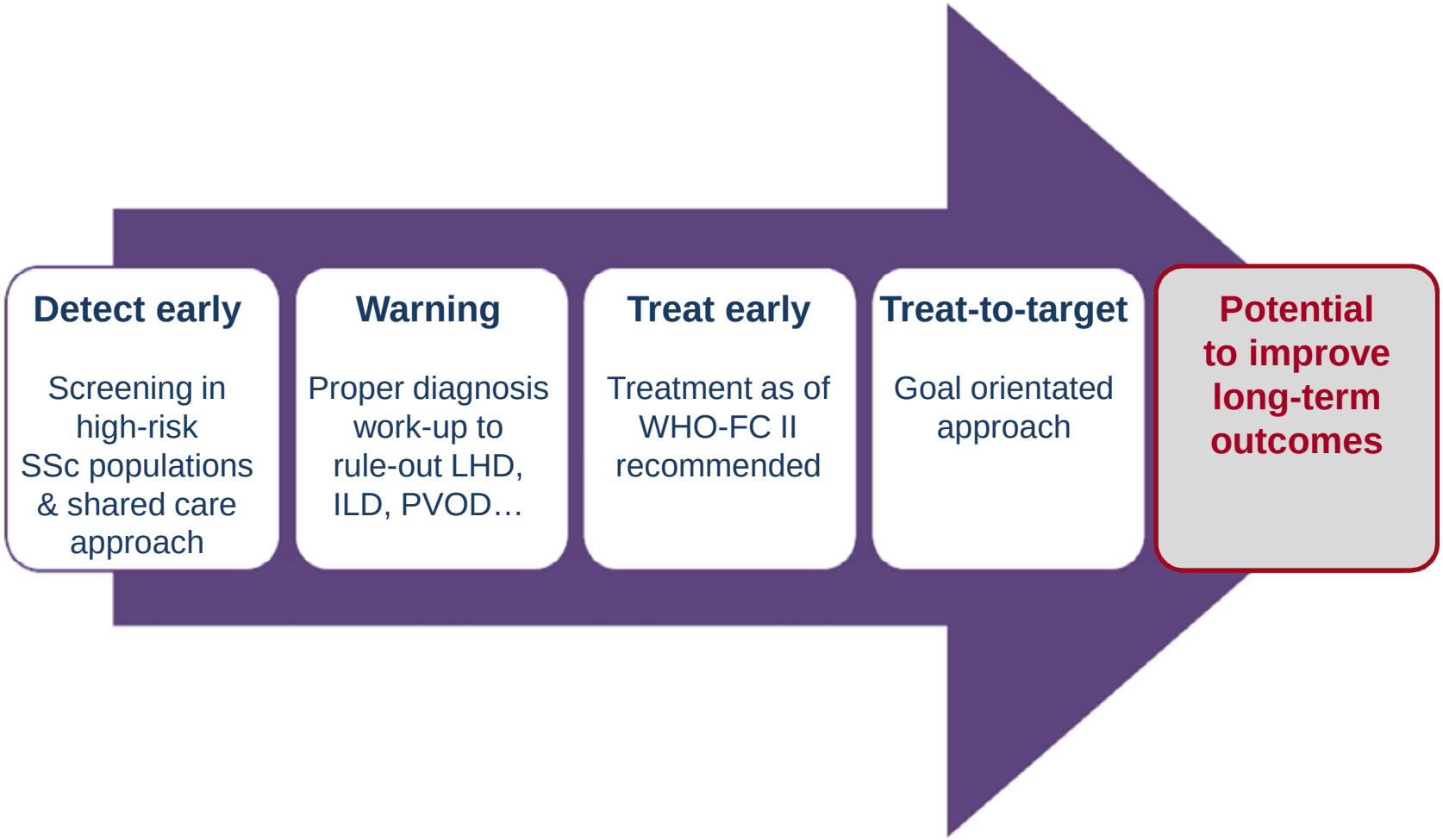
David Launay,[1,2] Olivier Sitbon,[3,4,5] Eric Hachulla,[1,2] Luc Mouthon,[6] Virginie Gressin,[7] Laurence Rottat,[3,4,5] Pierre Clerson,[8] Jean-François Cordier,[9] Gerald Simonneau,[3,4,5] Marc Humbert[3,4,5]



Survival **90%** **78%** **56%**

Launay D, *et al*. *Rheumatology* 2010;49:490-500.
Launay D. *et al. Ann Rheum Dis* 2013;72:1940-6.

Improving PAH-SSc patients' care priorities:



Adapted from Humbert M et al. Eur Respir Rev 2012; 21: 126, 306–312

2015 ESC/ERS Guidelines

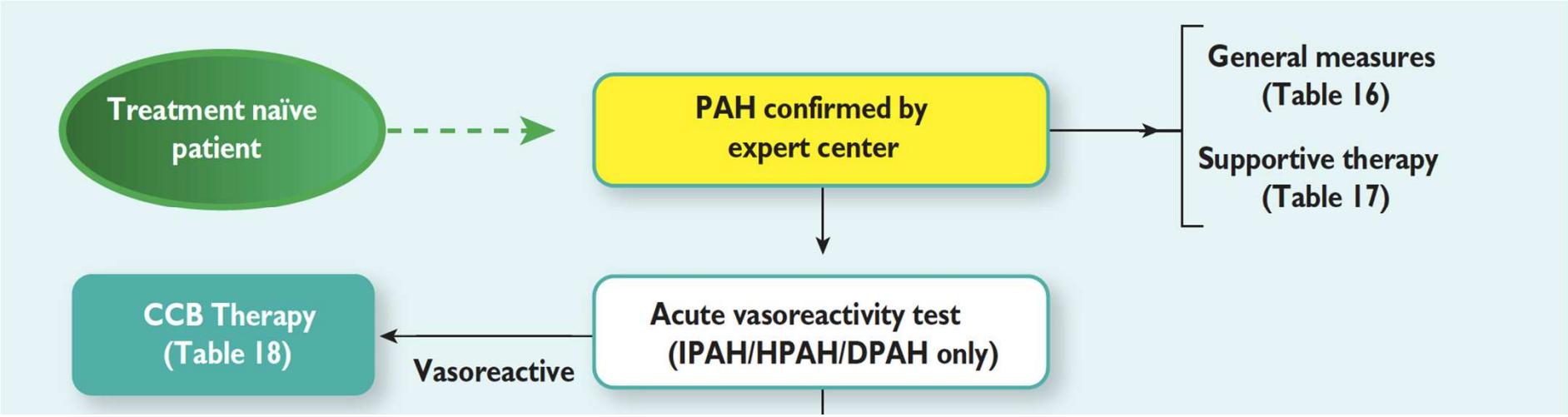
Table 26 Recommendations for pulmonary arterial hypertension associated with connective tissue disease

Recommendations	Class[a]	Level[b]	Ref.[c]
In patients with PAH associated with CTD, the same treatment algorithm as for patients with IPAH is recommended	I	C	46
Oral anticoagulation may be considered on an individual basis and in the presence of thrombophilic predisposition	IIb	C	175,339

[a] Class of recommendation
[b] Level of evidence

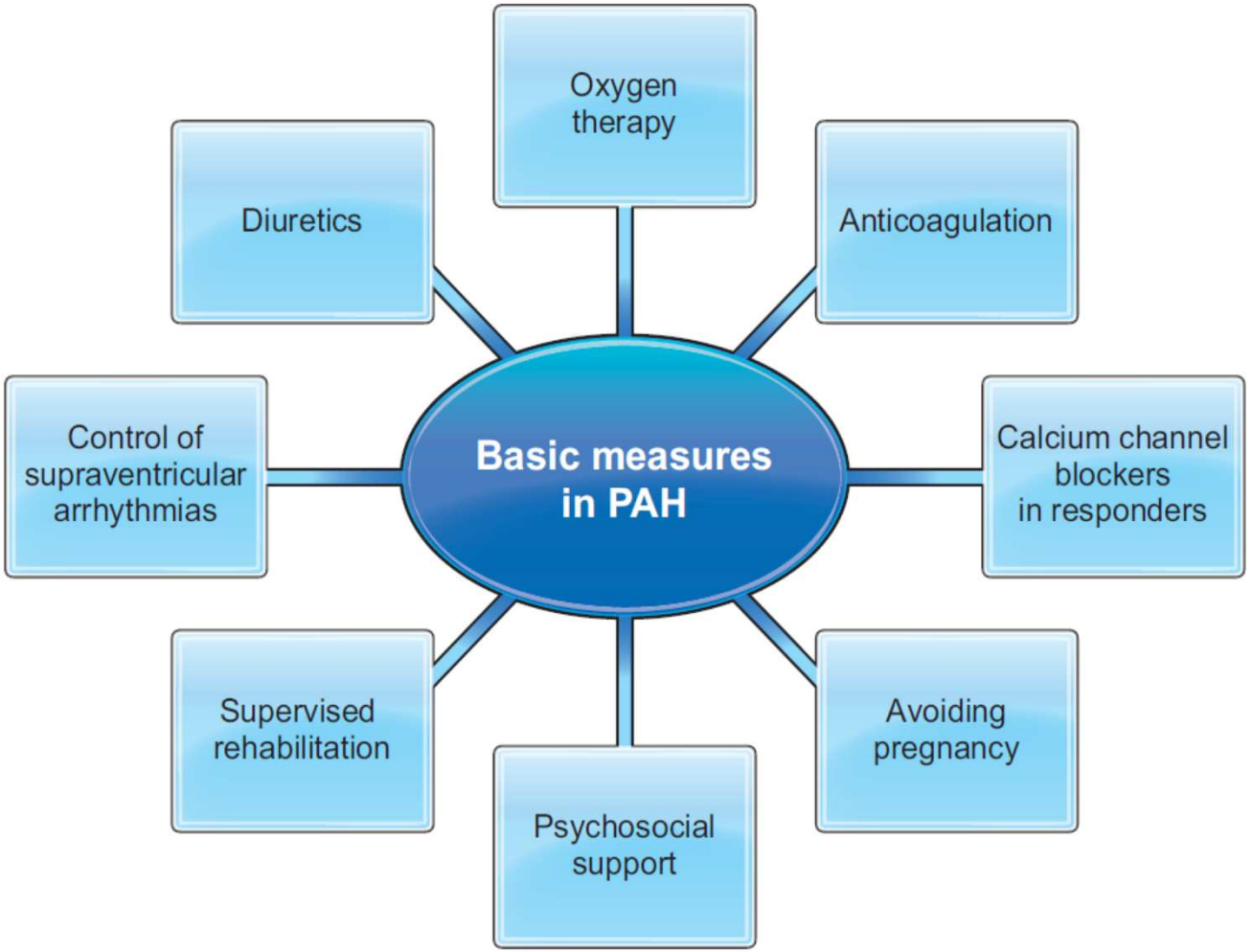
Galiè N, Humbert M, *et al*. ESC/ERS Guidelines. *Eur Respir J* 2015 & *Eur Heart J* 2016.

Treatment Algorithm for PAH



Galiè N, Humbert M, *et al*. ESC/ERS Guidelines. *Eur Respir J* 2015 & *Eur Heart J* 2016.

General measures and Supportive therapy



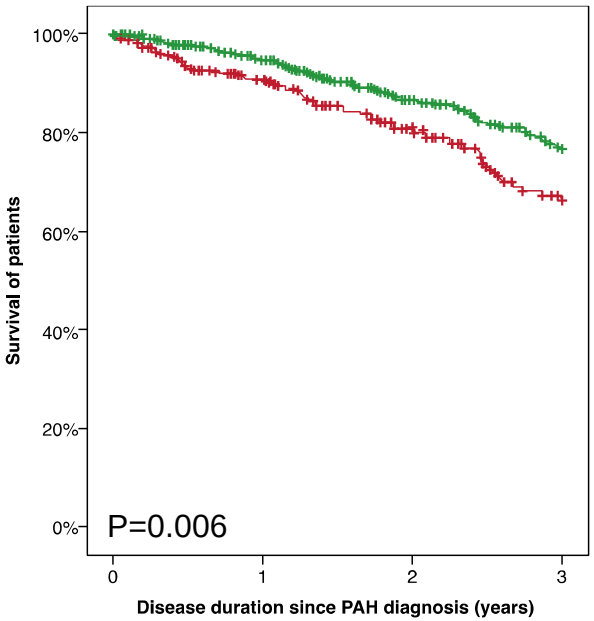
Humbert M, *et al. Circulation* 130:2189–208.
Galiè N, Humbert M, *et al*. ESC/ERS Guidelines. *Eur Respir J* 2015 & *Eur Heart J* 2016.

Quelle place pour les anticoagulants?

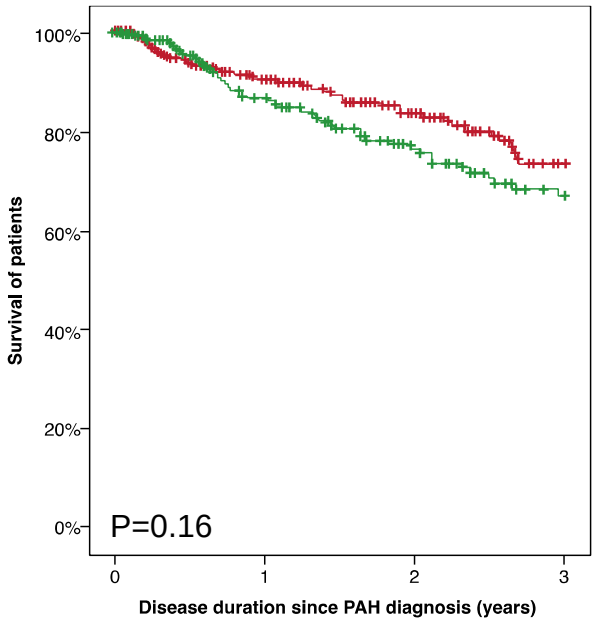
Quelle place pour les anticoagulants ?

EU COMPERA Registry: 2414 PAH, incl. 1283 incident cases
800 idiopathic PAH: Oral anticoagulation in 66%
483 other forms of PAH (incl. 208 PAH-SSc): Oral AC in 43%

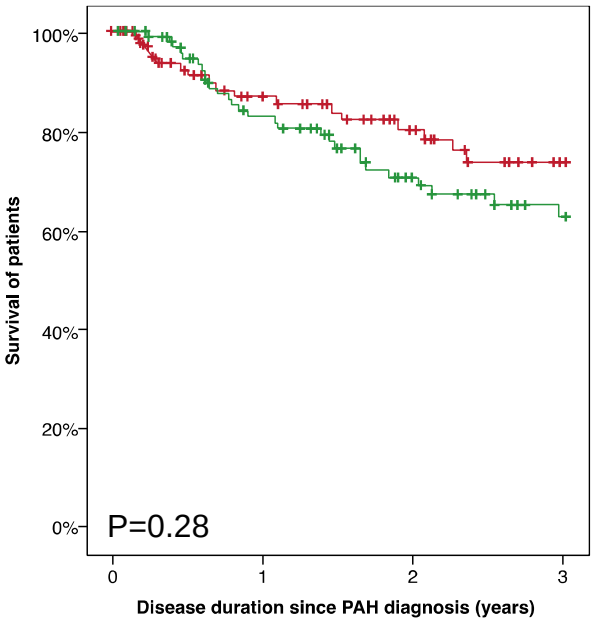
Idiopathic PAH



Non-idiopathic PAH



PAH-SSc



no anticoagulation

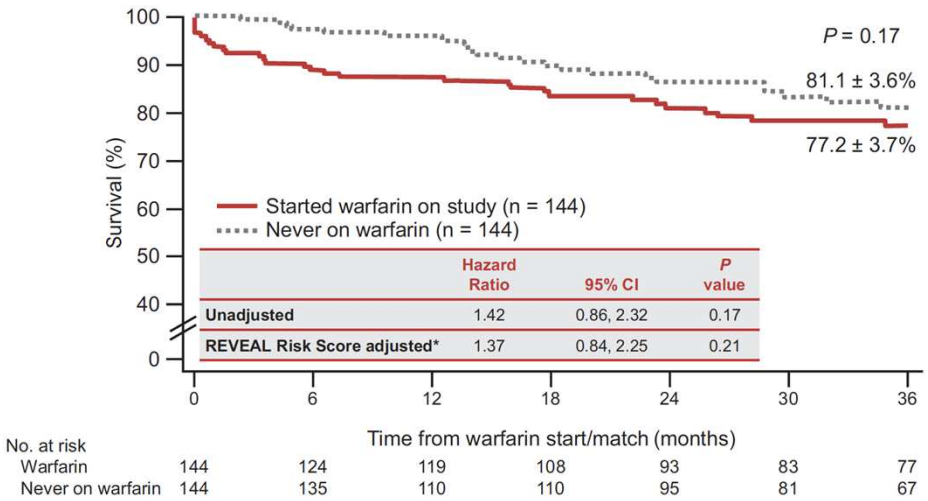
anticoagulation

Olsson KM, *et al. Circulation*. 2014;129:57-65.

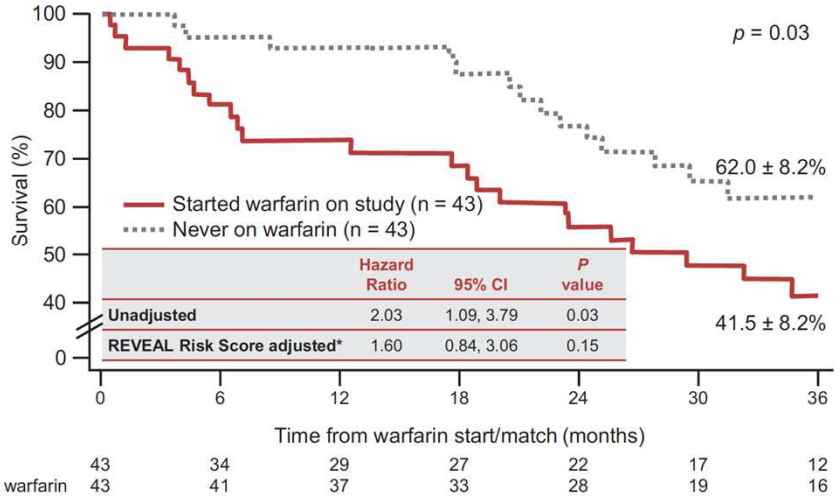
Quelle place pour les anticoagulants ?

US REVEAL Registry

Idiopathic PAH



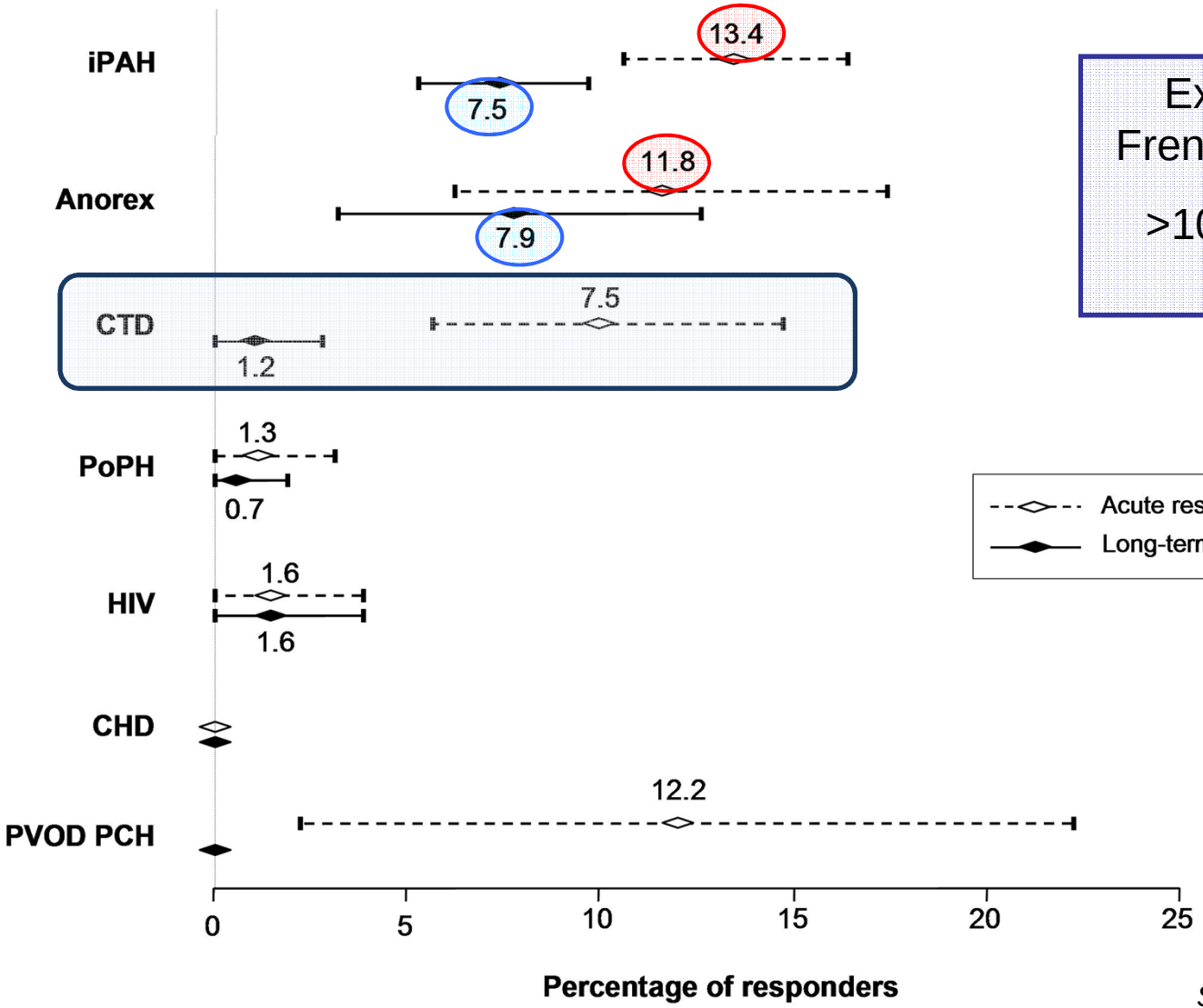
PAH-SSc



Preston IR, *et al. Circulation*. 2015;132:2403-11.

Faut-il rechercher et traiter une vasoréactivité au NO?

Acute vasodilator testing and long-term response to CCB

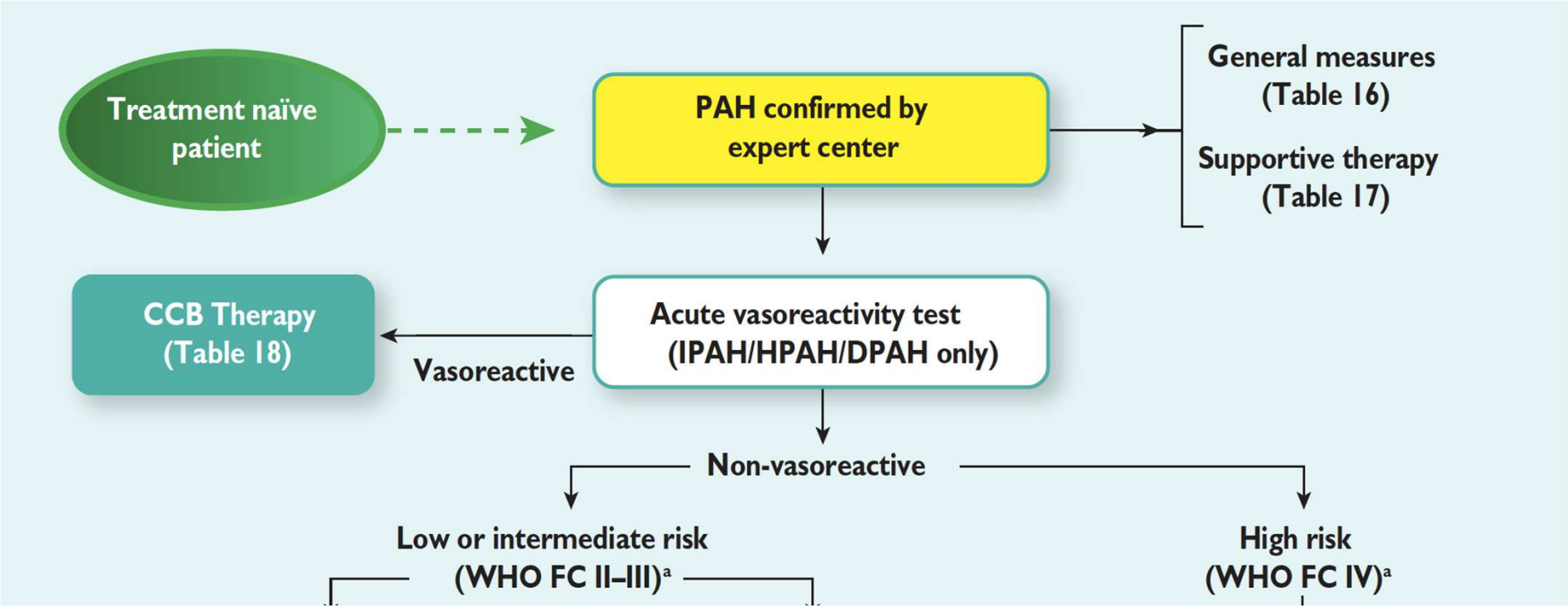


Experience of the French Referral centre

>1000 patients with acute testing

Sitbon O, et al. Circulation 2005.
Montani D, et al. Eur Heart J 2010.

Treatment Algorithm for PAH



Galiè N, Humbert M, *et al*. ESC/ERS Guidelines. *Eur Respir J* 2015 & *Eur Heart J* 2016.

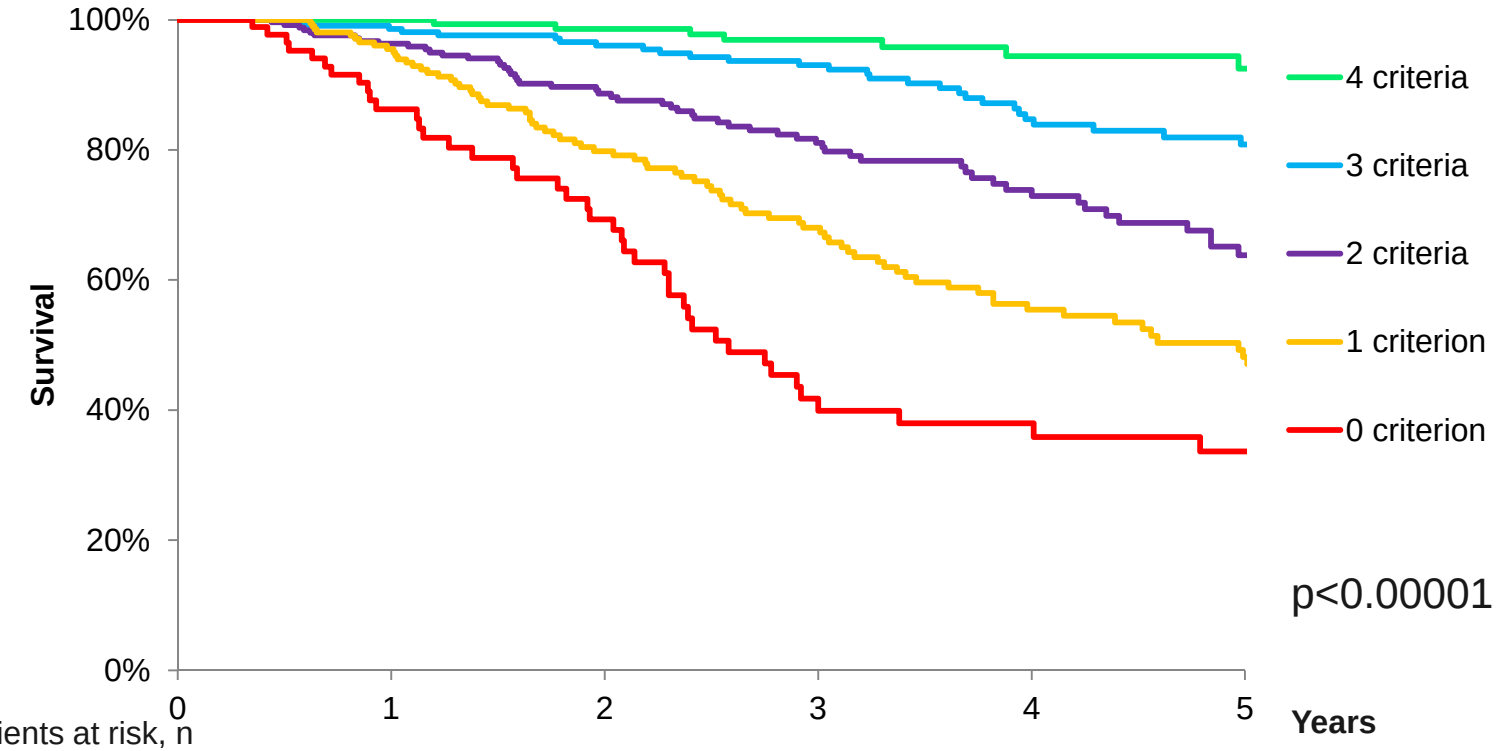
Traitements spécifiques de l’HTAP

Treatment Algorithm for 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 slope ≥45
NT-proBNP plasma levels	BNP <50 ng/l NT-proBNP <300 ng/l	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%

Galiè N, Humbert M, *et al*. ESC/ERS Guidelines. *Eur Respir J* 2015 & *Eur Heart J* 2016.

Transplant-free survival according to the number of “low-risk” criteria achieved at first re-evaluation

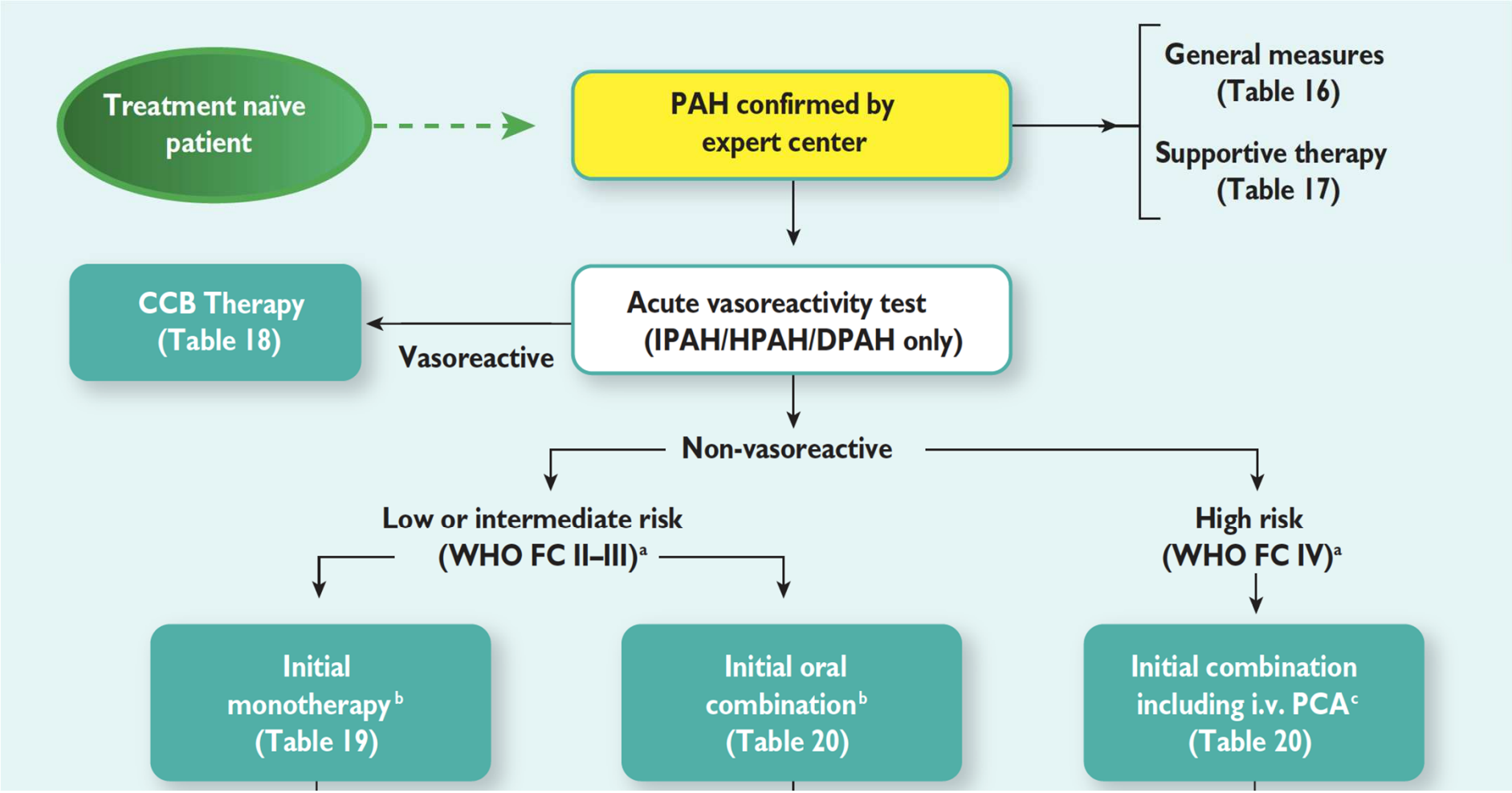


Patients at risk, n

4 criteria	175	153	128	102	63	48
3 criteria	247	204	175	140	102	72
2 criteria	275	219	171	122	78	49
1 criterion	225	183	128	91	62	45
0 criterion	95	61	44	22	18	14

Boucly-A et al. *Eur Respir J* 2017

Treatment Algorithm for PAH

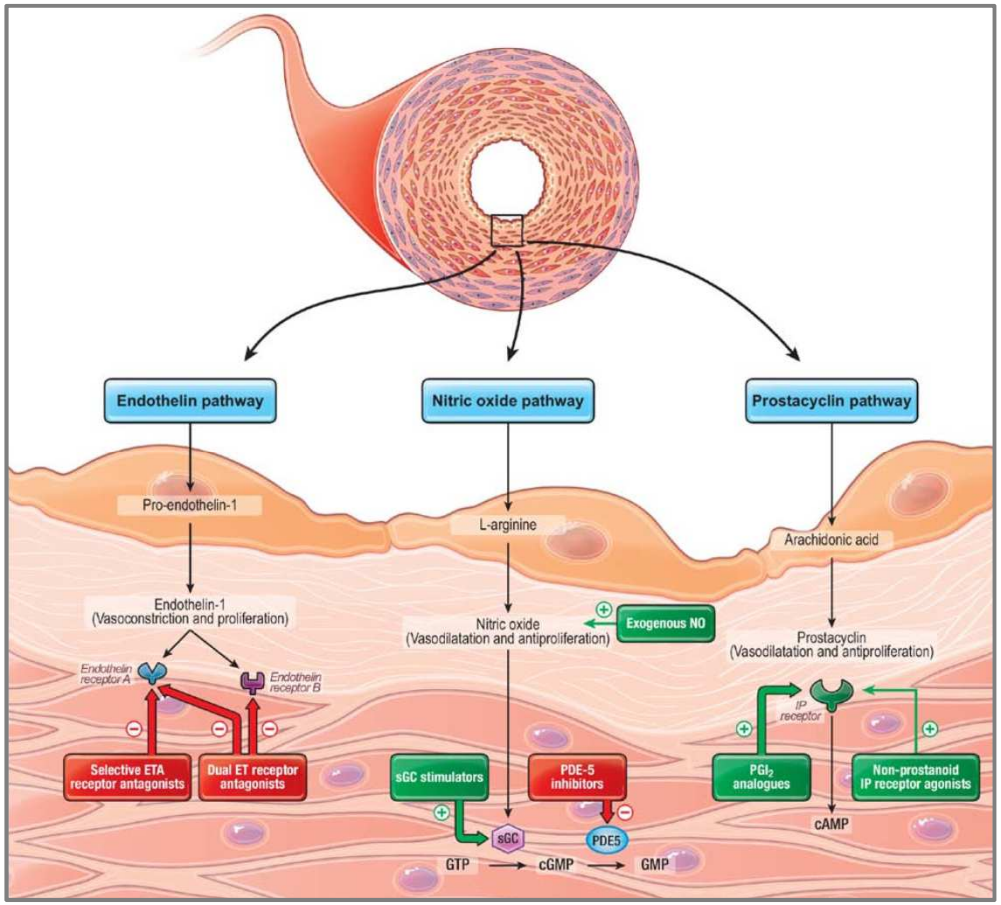


Galiè N, Humbert M, *et al*. ESC/ERS Guidelines. *Eur Respir J* 2015 & *Eur Heart J* 2016.

PAH therapy:
Targeting 3 major dysfunctional pathways

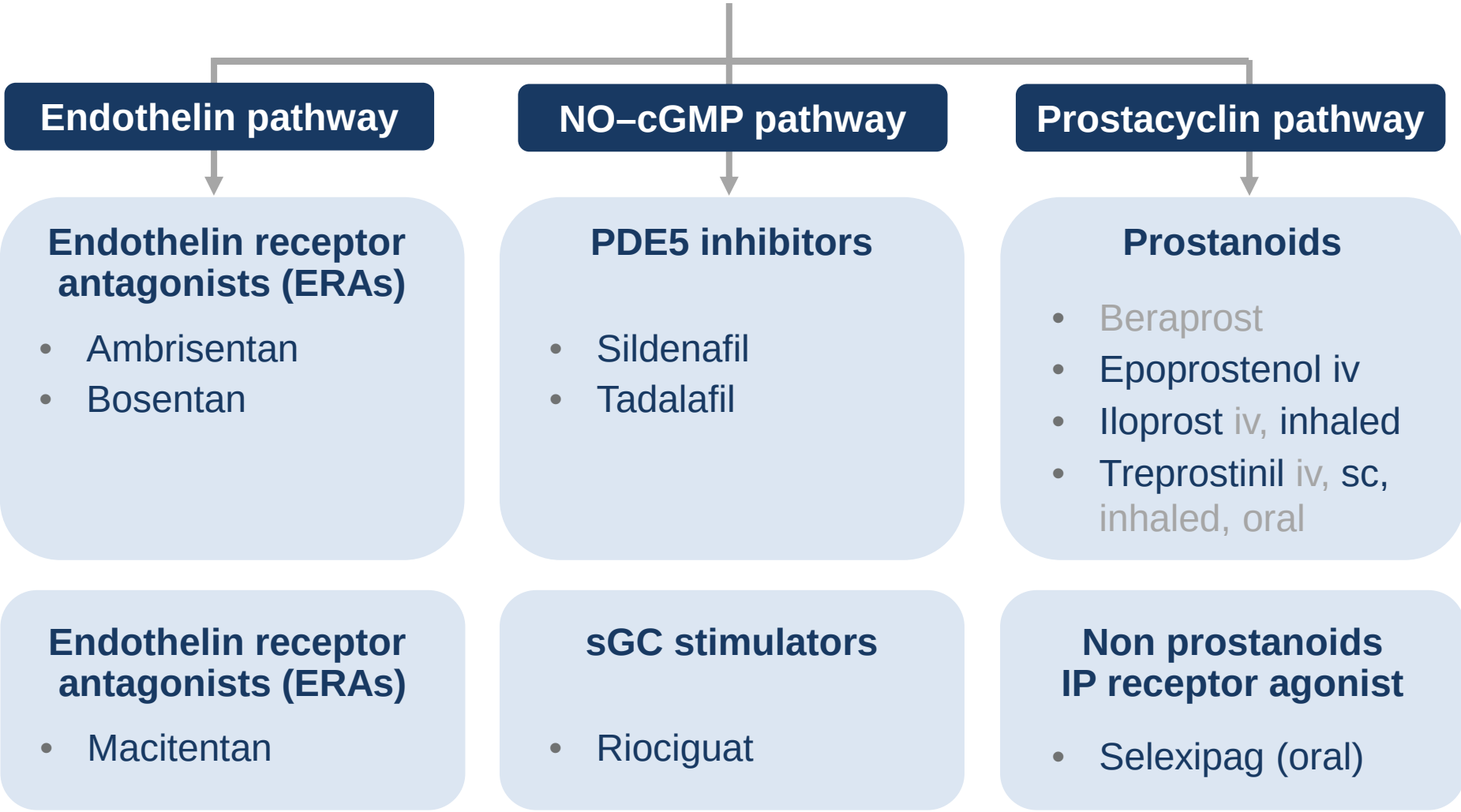
Advances in Therapeutic Interventions for Patients With Pulmonary Arterial Hypertension

Marc Humbert, MD, PhD; Edmund M.T. Lau, MD, PhD; David Montani, MD, PhD; Xavier Jaïs, MD; Oliver Sitbon, MD, PhD; Gérald Simonneau, MD



Humbert M, *et al*. *Circulation* 2014;130:2189–208.

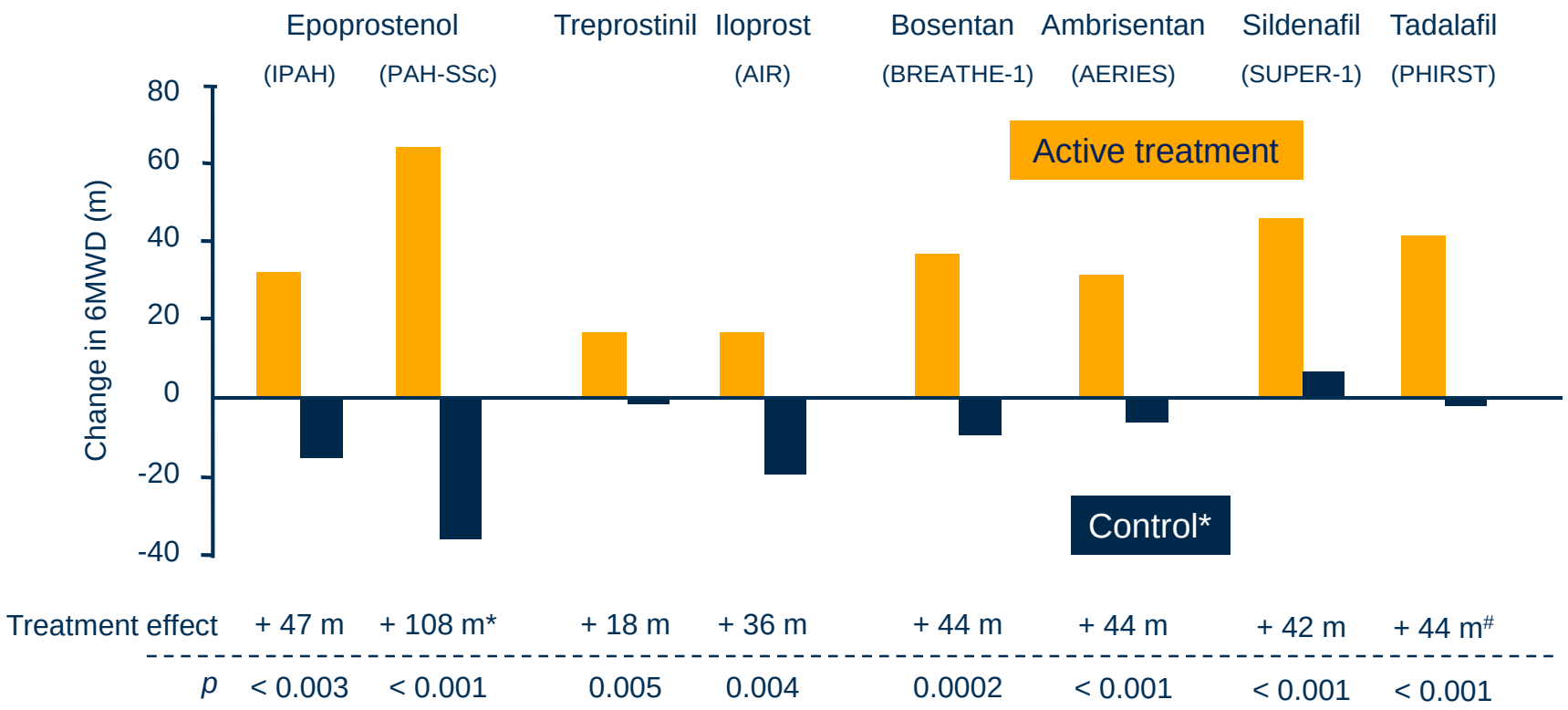
PAH-specific therapies target the 3 signaling pathways involved in PAH



Adapted from Galiè N et al. J Am Coll Cardiol 2013;62:D60–72.

RCTs with monotherapy in PAH

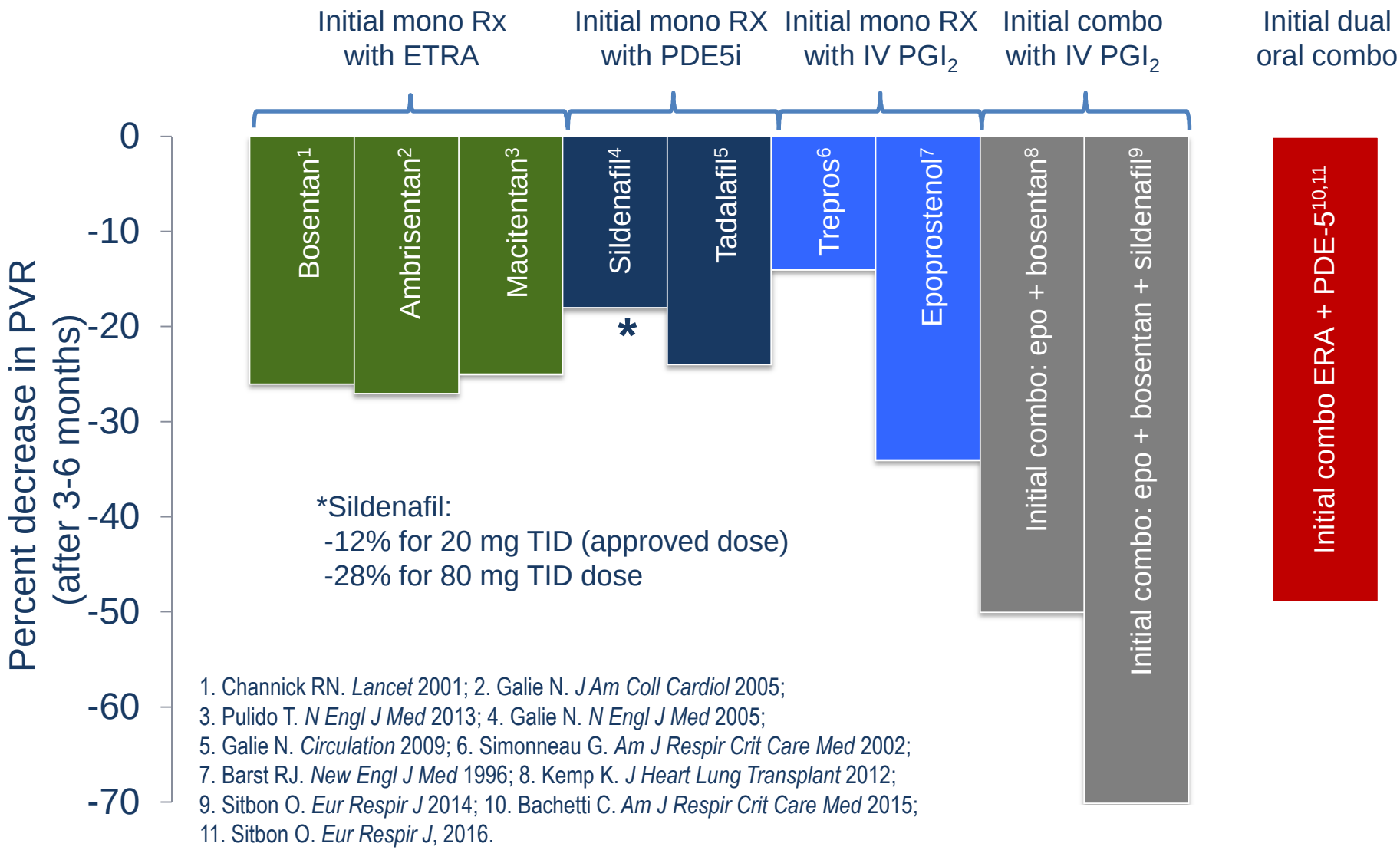
Improvement in exercise capacity (3-4 months)



* Control = placebo except for epoprostenol trials ('Conventional therapy') #: monotherapy only

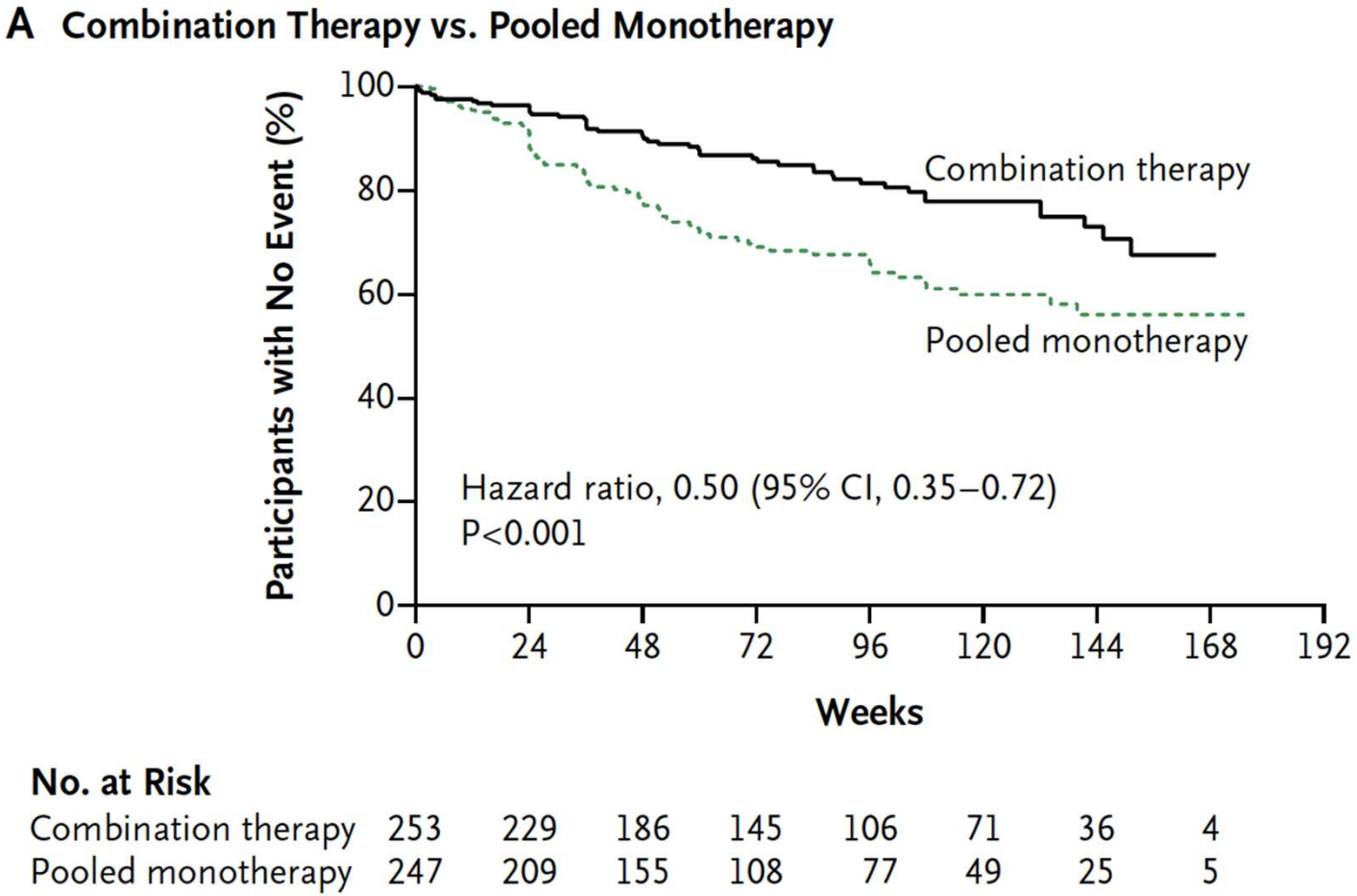
Barst, NEJM 1996.
Badesch, Ann Int Med 2000.
Simonneau, AJRCCM 2002.
Olschewski, NEJM 2002.
Rubin, NEJM 2002.
Galiè, Circulation 2008.
Galiè, NEJM 2005.
Galiè, Circulation 2009.

Initial therapy: The more the better



1. Channick RN. *Lancet* 2001; 2. Galie N. *J Am Coll Cardiol* 2005;
3. Pulido T. *N Engl J Med* 2013; 4. Galie N. *N Engl J Med* 2005;
5. Galie N. *Circulation* 2009; 6. Simonneau G. *Am J Respir Crit Care Med* 2002;
7. Barst RJ. *New Engl J Med* 1996; 8. Kemp K. *J Heart Lung Transplant* 2012;
9. Sitbon O. *Eur Respir J* 2014; 10. Bachetti C. *Am J Respir Crit Care Med* 2015;
11. Sitbon O. *Eur Respir J*, 2016.

Initial combination therapy: The AMBITION trial



Hospitalisation for PAH worsening was the main component of the primary endpoint

Galiè N, et al. N Engl J Med 2015;273:834:44.

Initial combination is efficacious in SSc-PAH

- 36 week prospective multicentre open-label uncontrolled study
- Initial combination of ambrisentan & tadalafil
  - 24 treatment-naïve patients with PAH-SSc
  - FC II / III: 35% / 65%

	Baseline	36 weeks	*p*
mPAP (mmHg)	42 ± 12	30 ± 7	< 0.01
CI (L/min/m^2)	2.6 ± 0.7	3.3 ± 1.2	< 0.01
PVR (Wood units)	8.4 ± 5.1	4.1 ± 3	< 0.01

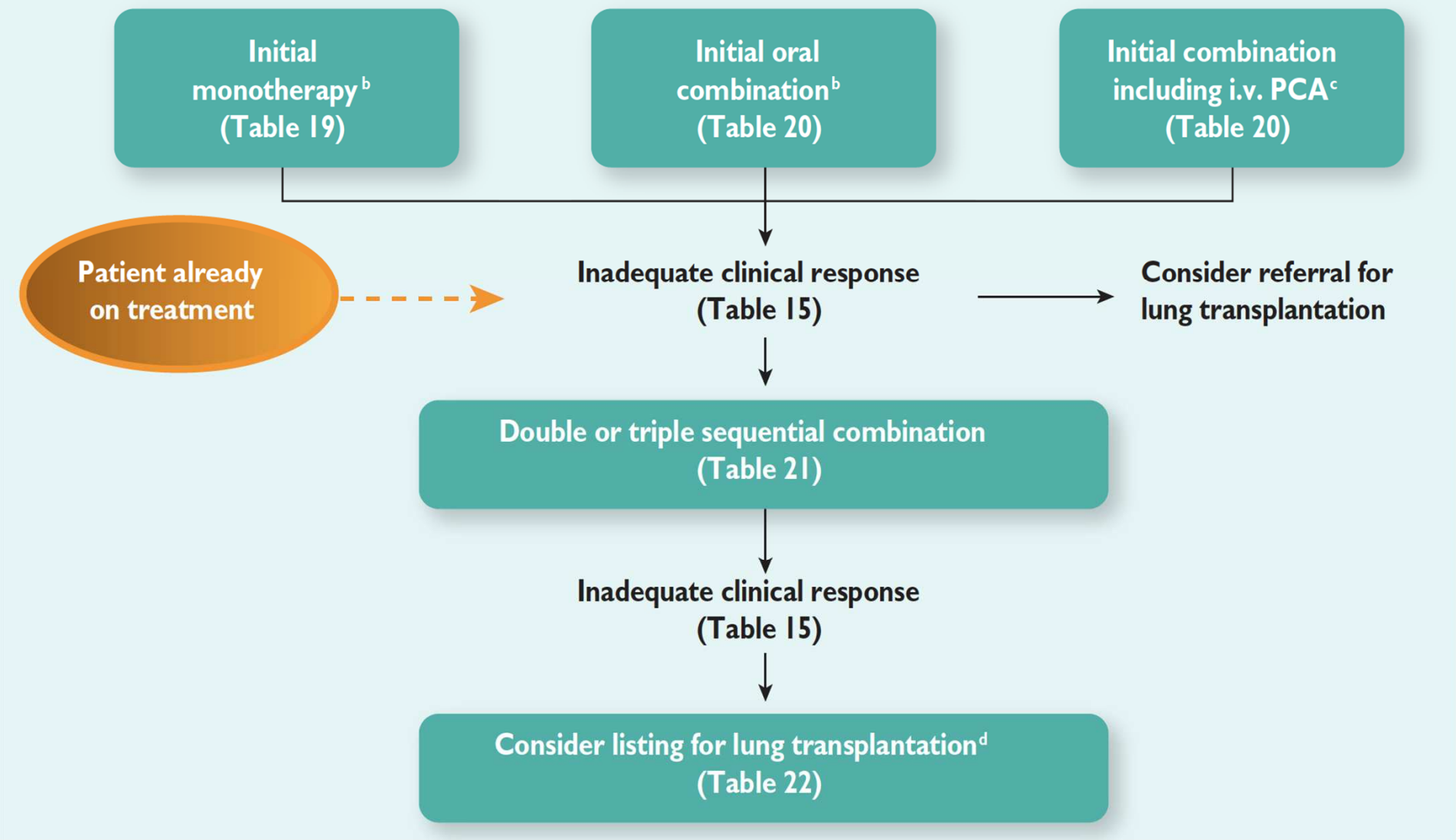
Hassoun P, *et al. Am J Respir Crit Care Med* 2015; 192:1102-10.

Treatment Algorithm for PAH

	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]

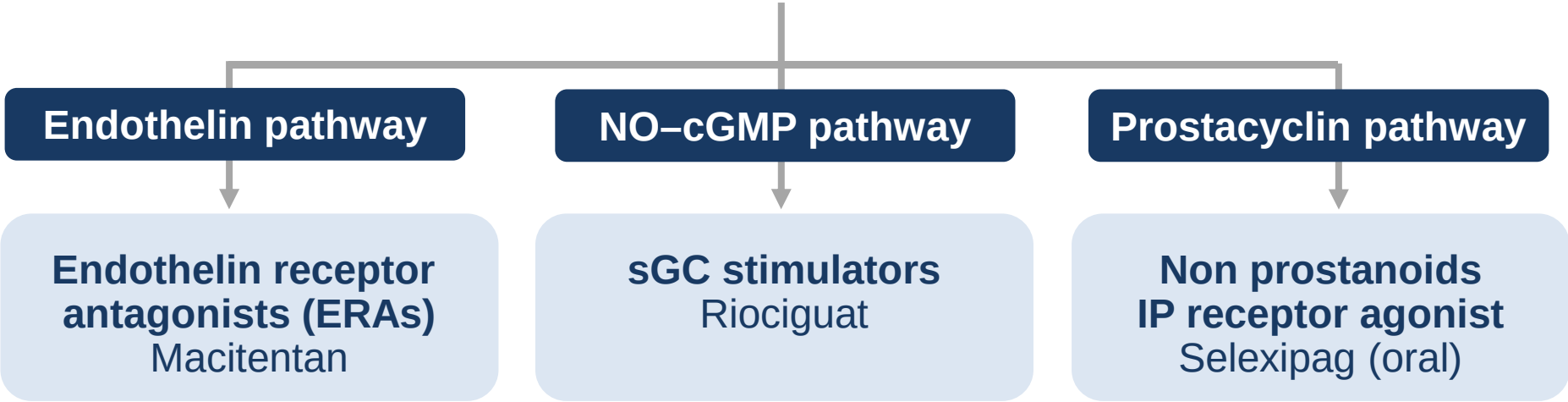
Galiè N, Humbert M, *et al*. ESC/ERS Guidelines. *Eur Respir J* 2015 & *Eur Heart J* 2016.

Treatment Algorithm for PAH



Galiè N, Humbert M, *et al*. ESC/ERS Guidelines. *Eur Respir J* 2015 & *Eur Heart J* 2016.

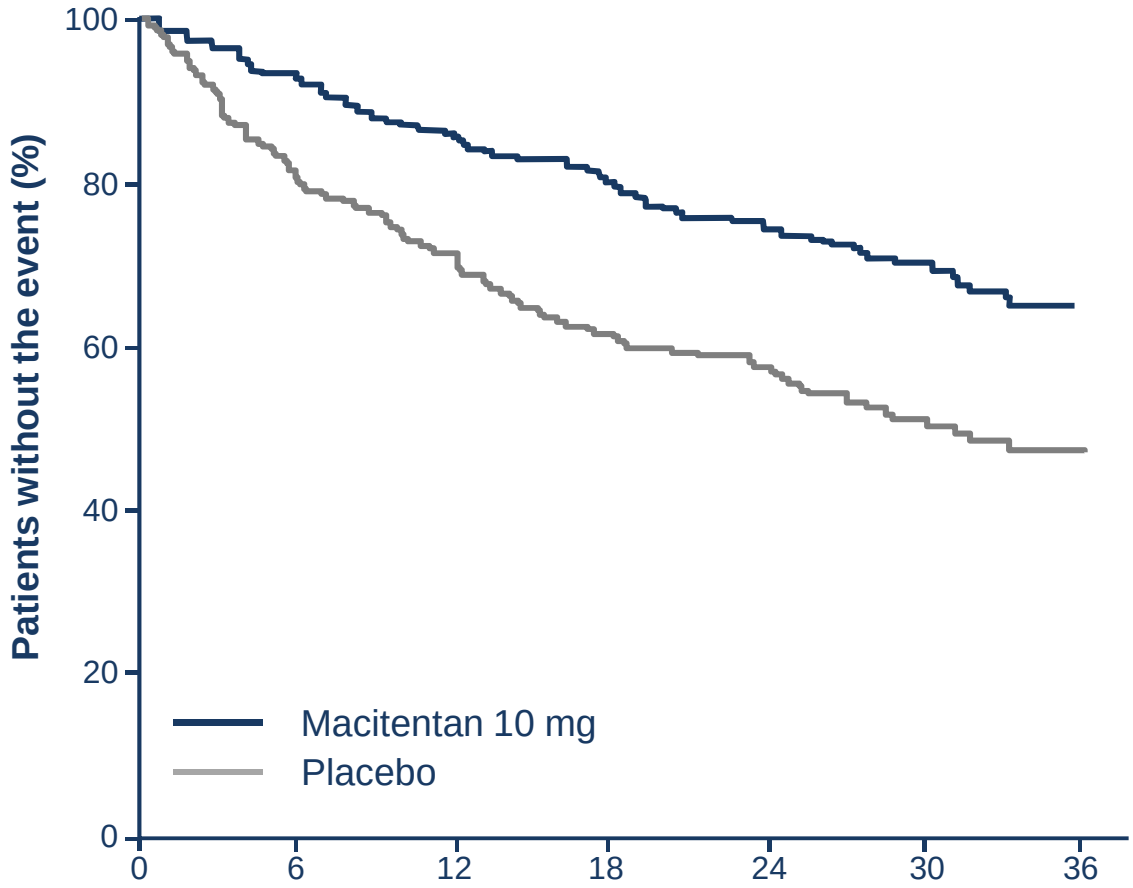
Combination therapy in PAH: New drugs / New strategies



Drug tested	Study	Background	N	Duration (weeks)	Primary endpoint
Bosentan	COMPASS-2[1]	Sildenafil	334	92	Time to first event of death or morbidity **(NS)**
Macitentan	SERAPHIN[2]	None (36%), PDE5i (61%) or oral/inhaled prostanoids	742	≈ 100	Time to first event of death or morbidity **(POS)**
Selexipag	GRIPHON[3]	None (21%), ERA (13%), PDE5i (32%) or both (34%)	1156	≈ 70	Time to first event of death or morbidity **(POS)**
Ambrisentan + tadalafil	AMBITION[4]	None (incident cases)	500	≈ 74	Time to clinical failure event **(POS)**

1. McLaughlin VV, *et al*. *Eur Respir J* 2015. 2. Pulido T, et al. *N Engl J Med* 2013.
3. Sitbon O, et al. *N Engl J Med* 2015. 4. Galié N, et al. *N Engl J Med* 2015.

SERAPHIN: macitentan reduces the risk of the primary outcome composite of death or morbidity due to PAH



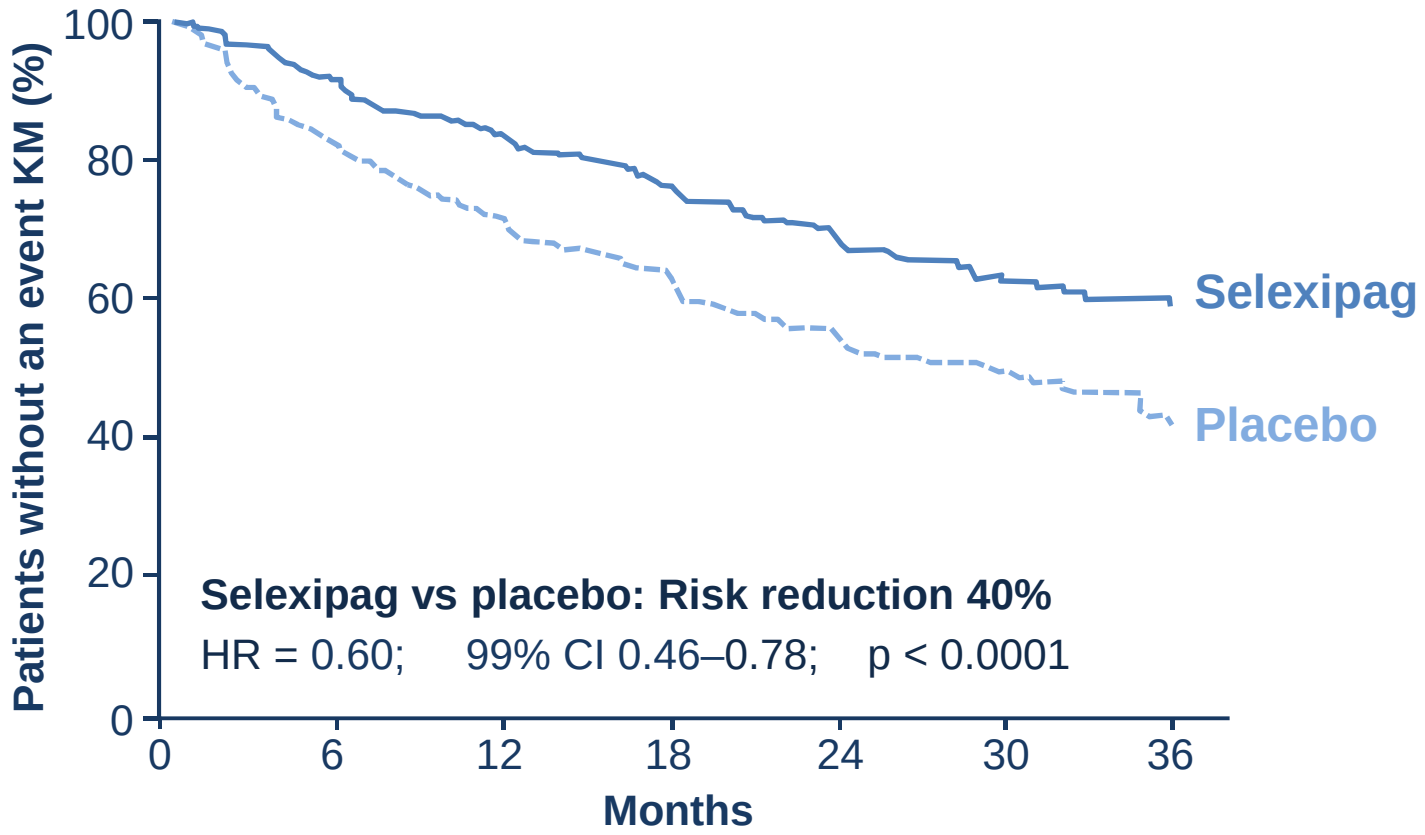
Treatment difference	10 mg
Hazard ratio	0.55
Log-rank *p*-value	< 0.001

Risk reduction of primary endpoint event vs placebo
Macitentan 10 mg: 45%

PAH worsening was the main component of the primary endpoint

Pulido T, *et al. N Engl J Med* 2013; 369:809-18.

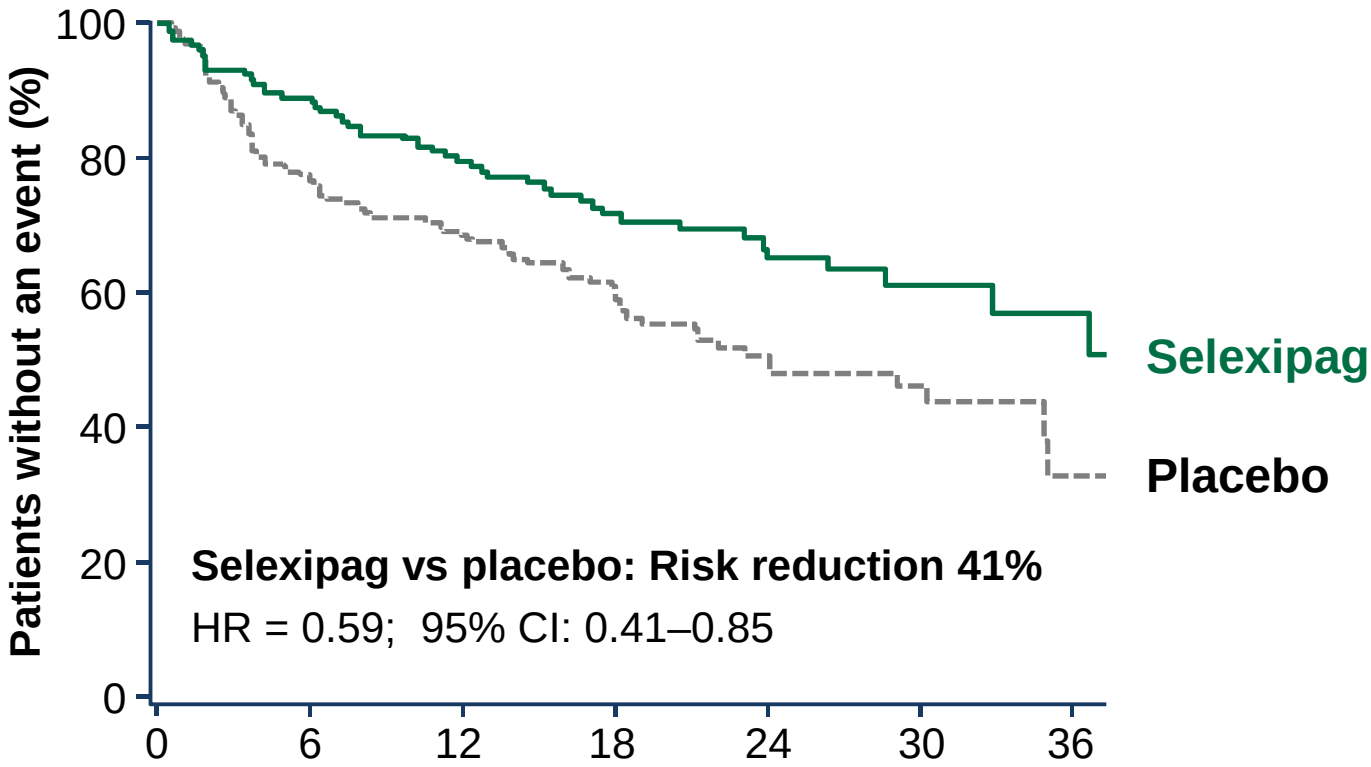
GRIPHON: selexipag reduces the risk of the primary outcome composite of death or morbidity due to PAH



Hospitalisation for PAH worsening and disease progression were the main components of the primary endpoint

Sitbon O, et al. *N Engl J Med* 2015;373:2522-33.

Selexipag reduces the risk of the primary outcome composite of death or morbidity event in PAH-CTD patients



No. at Risk							
Placebo	167	114	92	57	38	21	3
Selexipag	167	129	102	70	44	21	10

Gaine S, *et al*. *Eur Respir J* 2017; *in press*.

Faut-il traiter toutes les HTAP associées à une sclérodermie?

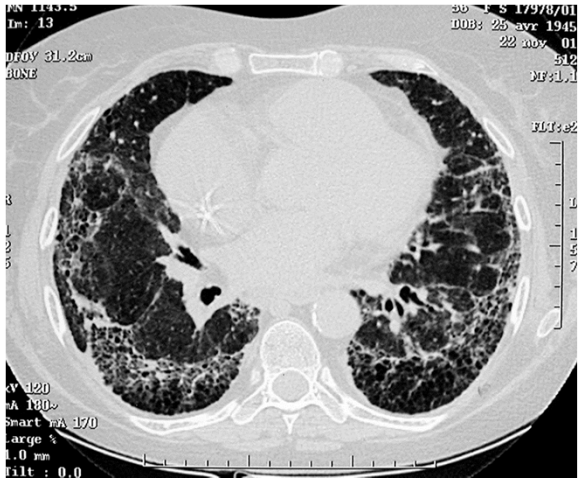
PH in SSc with ILD

Differential diagnosis between Group 1 (PAH) and Group 3 (PH-ILD)

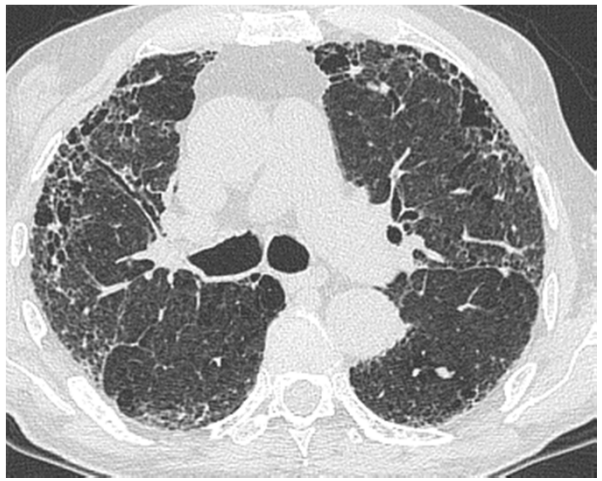
Criteria Favouring Group 1	Criteria Favouring Group 3

• Normal or mildly impaired
  • FEV1 > 60% predicted
  • FVC > 70% predicted
• Absence of or only modest airway or parenchymal abnormalities on high-resolution CT scan
	• Moderate to very severe impairment
	  • FEV1 < 60% predicted
	  • FVC < 70% predicted
	• Characteristic airway and / or parenchymal abnormalities on high-resolution CT scan

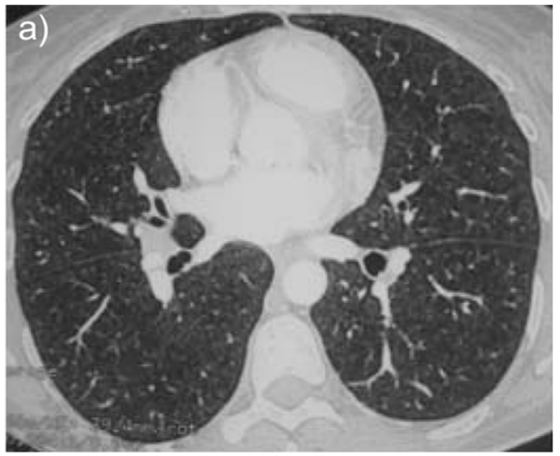
Severe ILD



Moderate ILD

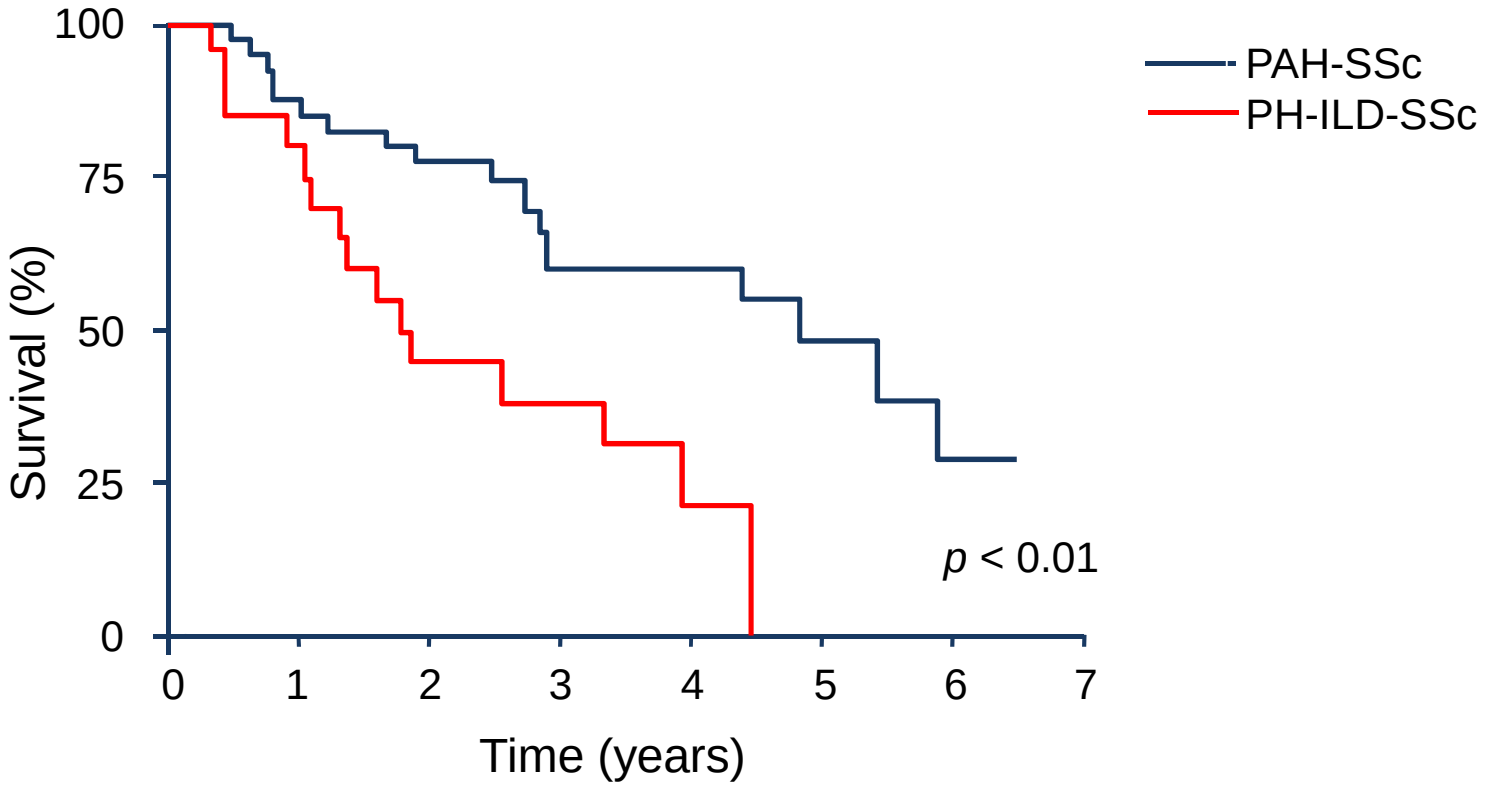


Mild/no ILD



Seeger W, *et al. J Am Coll Cardiol* 2013; 62:D109-16.

Survival is worse for SSc patients with PH-ILD than for SSc patients with PAH alone



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

PAH therapies showed no clear benefits in SSc-PH-ILD patients

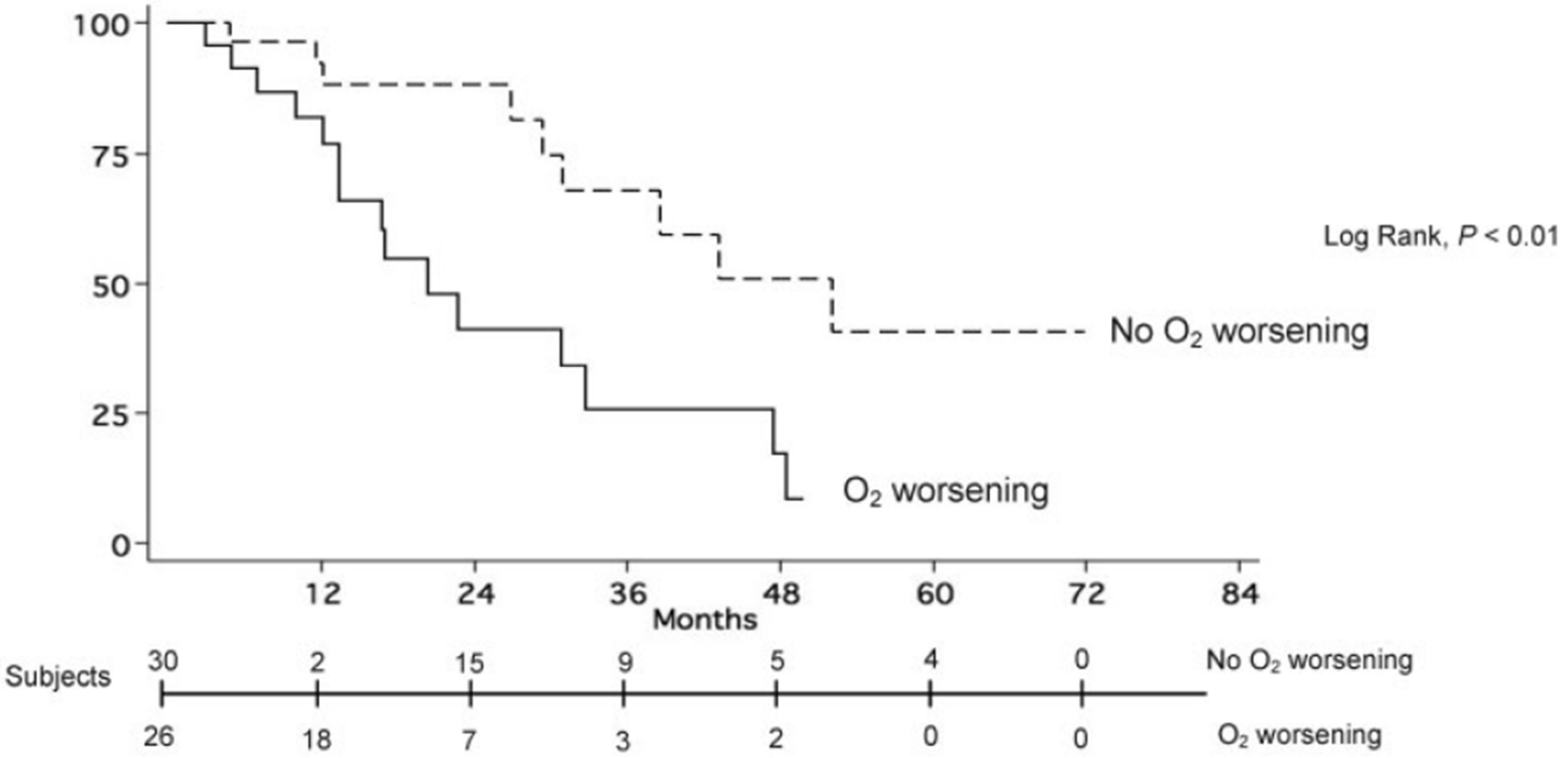
Table 2. Response to therapy for pulmonary arterial hypertension at followup evaluation*

	Baseline	Followup	*P*
No. in WHO functional class I–II/III–IV (n = 67)	12/55	16/51	0.52
6-minute walk distance, mean ± SD meters (n = 34)	293 ± 105	298 ± 106	0.77
Hemodynamics, mean ± SD (n = 34)			
Heart rate, bpm	84 ± 16	84 ± 15	0.88
Mean systemic blood pressure, mm Hg	92 ± 16	83 ± 14	0.003
Right atrial pressure, mm Hg	6 ± 4	7 ± 5	0.66
Pulmonary capillary wedge pressure, mm Hg	8 ± 4	9 ± 5	0.57
Mean pulmonary artery pressure, mm Hg	45 ± 11	44 ± 10	0.63
Cardiac output, liters/minute	4.3 ± 1.5	4.6 ± 1.1	0.19
Cardiac index, liters/minute/m^2	2.6 ± 1.0	2.7 ± 0.6	0.27
Pulmonary vascular resistance, dynes × seconds/cm^5	752 ± 442	616 ± 210	0.08
Oxygen requirement, mean ± SD liters/minute			
Entire population (n = 56)	0.4 ± 0.05	1.4 ± 0.3	<0.001
Patients using oxygen at baseline (n = 26)	2.4 ± 2.0	3.8 ± 1.6	<0.001
Arterial oxygen saturation, mean ± SD %			
Entire population (n = 56)	95 ± 4	93 ± 5	0.01
Patients using oxygen at baseline (n = 26)	94 ± 5	92 ± 5	0.03

* Followup evaluation was performed a mean ± SD of 7.7 ± 6.2 months after baseline. In patients requiring oxygen, arterial oxygen saturation was measured while they were receiving supplemental oxygen. *P* values were determined by Fisher's exact test or paired *t*-test, as appropriate. WHO = World Health Organization.

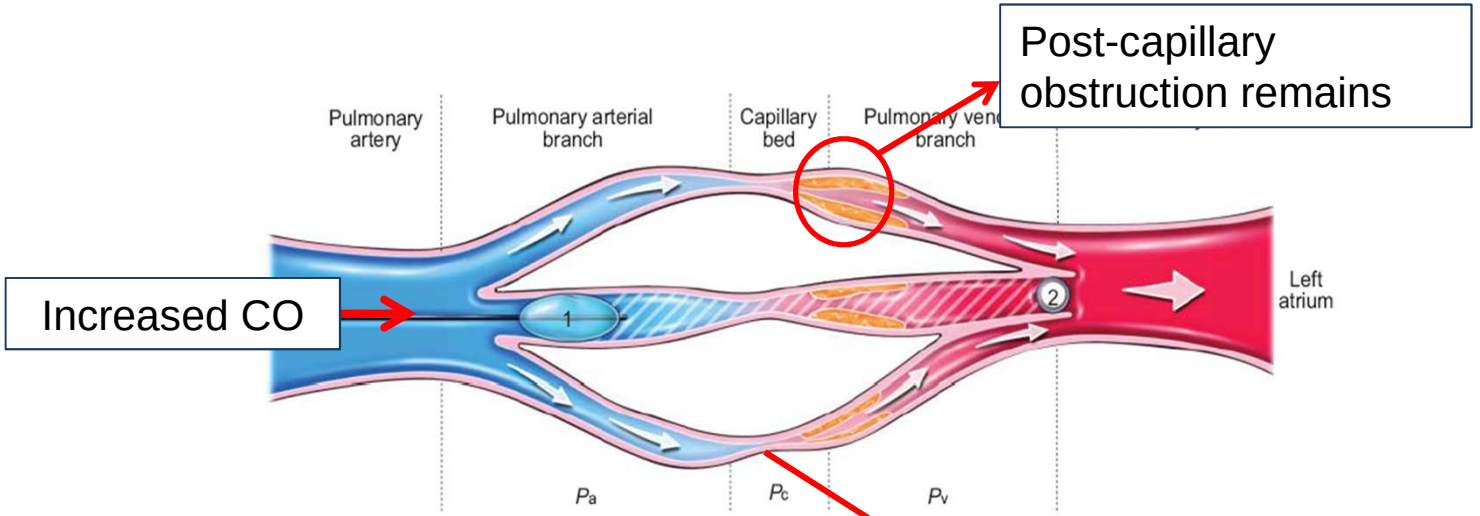
Le Pavec J, *et al. Arthritis Rheum* 2011; 63:2456-64.

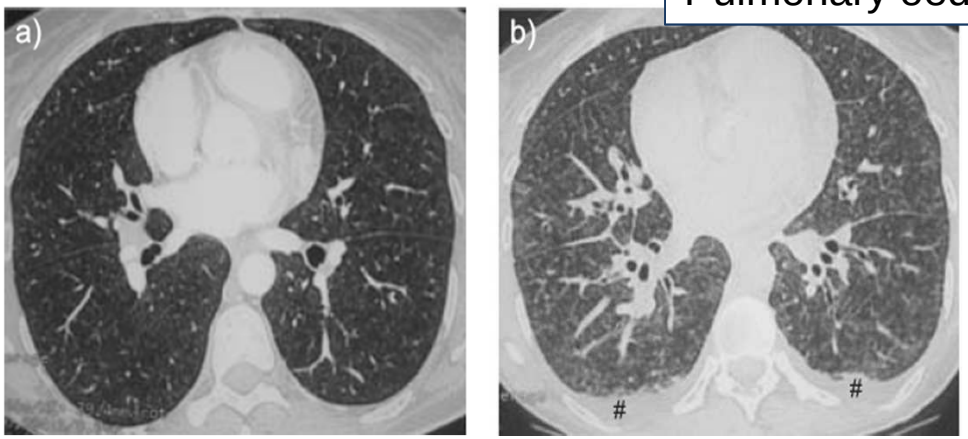
Oxygenation deterioration was an important determinant of long-term survival in SSc-PH-ILD



Le Pavec J, *et al. Arthritis Rheum* 2011; 63:2456-64.

Pulmonary veno-occlusive disease (PVOD) is not uncommon in SSc





Pre-PAH therapy initiation

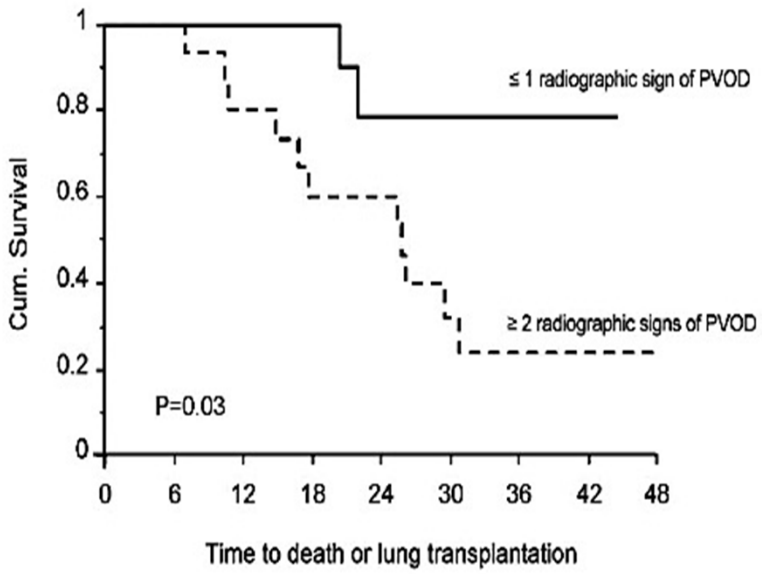
Post-PAH therapy

Günther S, *et al. Arthritis Rheum* 2012; 64:2995-3005.
Montani D, *et al. Eur Respir J* 2009; 33:189-200.

Pulmonary vein involvement (“PVOD”) is not uncommon in SSc and prognosis is poor

Suggests PVOD in patients with severe PH & SSc

- Clinical
  - More severe (NYHA III-IV)
  - History of pulmonary oedema (on PAH therapy +++)
- HRCT
  - Lymph node enlargement
  - Centrilobular ground-glass opacities
  - Septal lines
- PFTs & ABG
  - Lower DLCO
  - Lower PaO_2
- BAL
  - Hemosiderin-laden macrophages

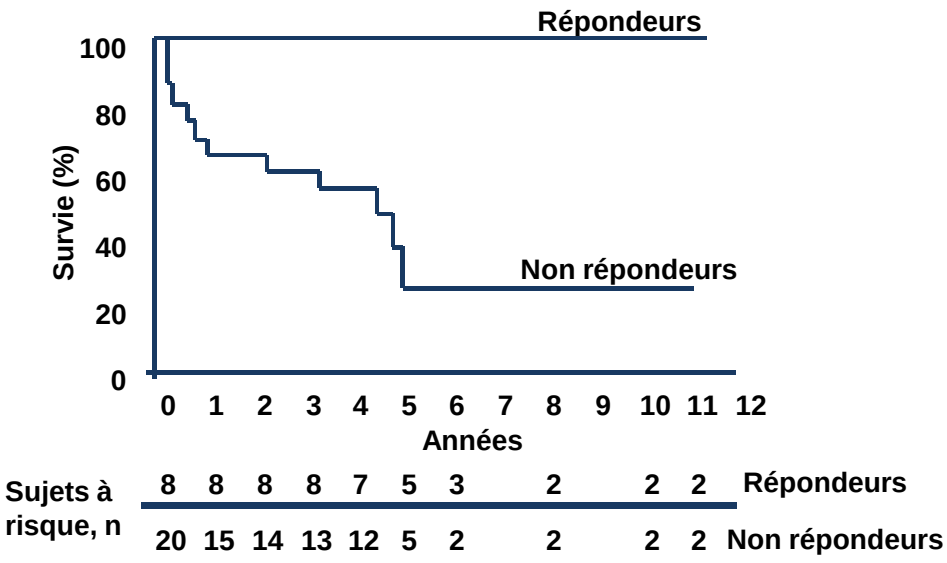


Günther S, *et al. Arthritis Rheum* 2012; 64:2995-3005.

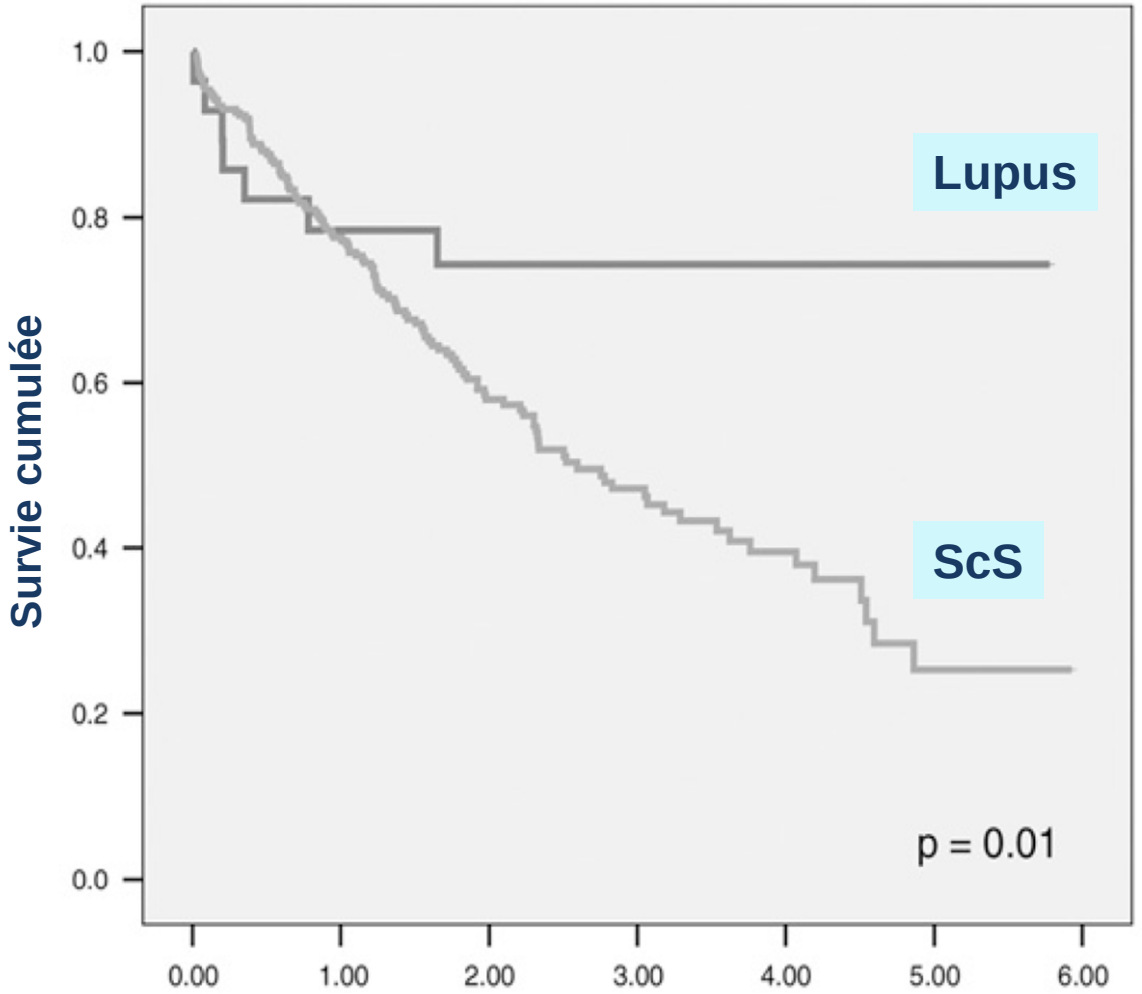
Place des immunosuppresseurs?

IMMUNOSUPPRESSIVE THERAPY IN CTD-PAH

- First line immunosuppressive therapy
  - Monthly IV cyclophosphamide pulses (600 mg/m^2)
  - Steroids (prednisone 0.5 - 1 mg/kg/j)
- Eight out of 28 patients (32%) were “responders” (NYHA I-II after 1 yr)
- No patient with systemic sclerosis responded
- 38% of SLE and MCTD patients responded after 7 ± 6 CYC pulses
  - SLE n = 5 / 13
  - MCTD n = 3 / 8
  - SSc n = 0 / 6



Sanchez O, *et al*. *CHEST* 2006;130;182-9.



Patients à risque, n

28	21	15	12	9	2	**Lupus**
259	179	94	53	27	6	**ScS**

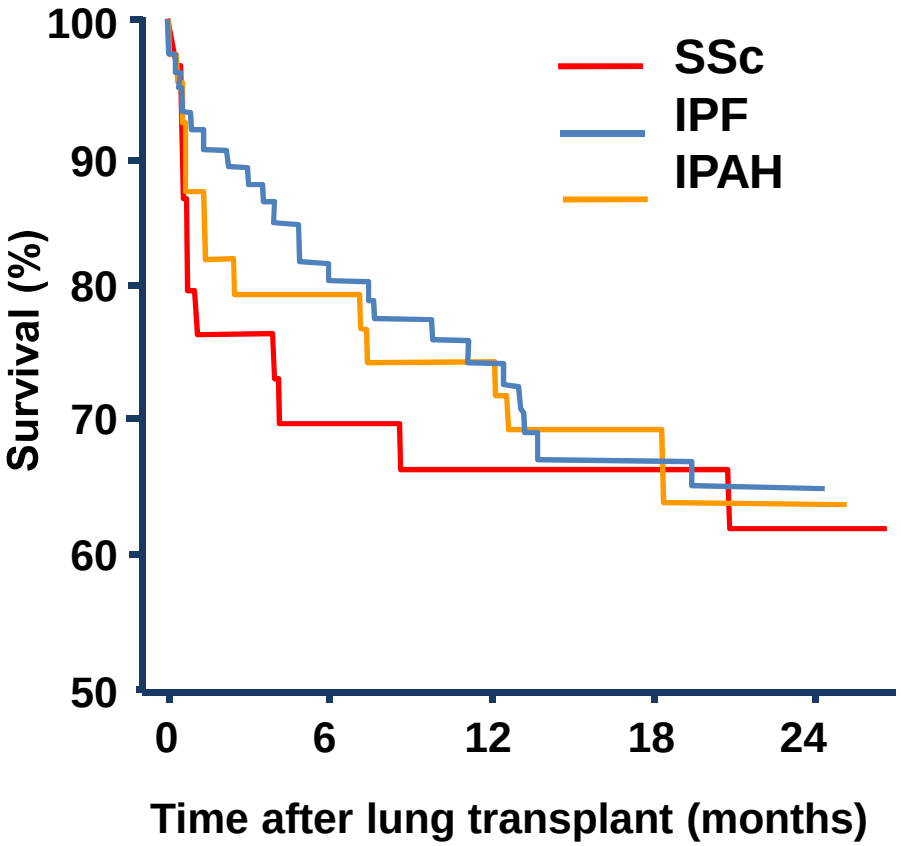
Condliffe et al. Am J Respir Crit Care Med 2009;17:151–7.

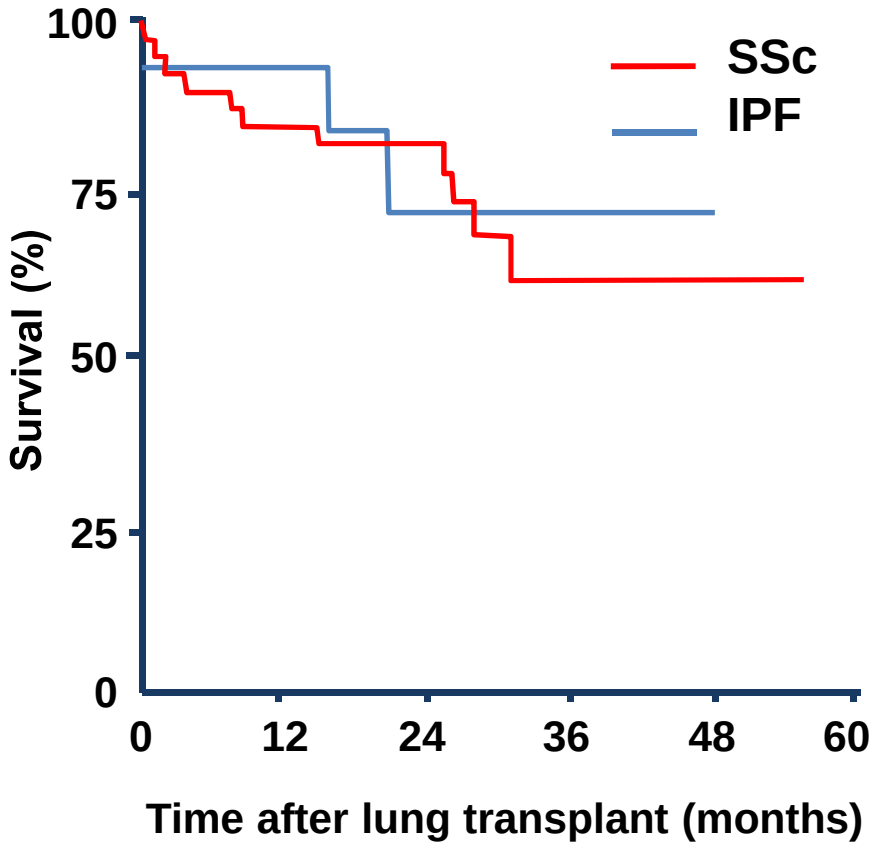
Quelle place pour la transplantation pulmonaire?

HTAP-SSc: quelle place pour la transplantion pulmonaire ?

Transplantation pulmonaire dans la SSc : réticence des chirurgiens

(Maladie systémique, Raynaud, Ulcères digitaux, RGO…)





Schachna L, *et al. Arthritis Rheum* 2006; 54:3954-61.
Saggar R, *et al. Eur Respir J* 2010; 36:893-900.

SSc-PAH: Any place for lung transplantation?

Lung and heart-lung transplantation for systemic sclerosis patients. A monocentric experience of 13 patients, review of the literature and position paper of a multidisciplinary Working Group

David Launay[1,2,3], Laurent Savale[4,5,6], Alice Berezne[7,17], Jérôme Le Pavec[4,6,8,17], Eric Hachulla[1,2,3], Luc Mouthon[7], Olivier Sitbon[4,5,6], Benoit Lambert[9], Marianne Gaudric[10], Xavier Jais[4,5,6], Francois Stephan[11], Pierre-Yves Hatron[1,2], Nicolas Lamblin[1,12], Olivier Vignaux[13], Vincent Cottin[14], Dominique Farge[15], Benoît Wallaert[1,16], Loic Guillevin[7], Gerald Simonneau[4,5,6], Olaf Mercier[4,6,8], Elie Fadel[4,6,8], Philippe Dartevelle[4,6,8], Marc Humbert[4,5,6], Sacha Mussot[4,6,8], On behalf of the Working Group on Heart/Lung transplantation in systemic sclerosis of the French Network on Pulmonary Hypertension

Launay D, *et al. Presse Med* 2014; 43:e345-e363.

SSc-PAH: Any place for lung transplantation?

Proposed SSc specific contraindications

- Muscles
  - Uncontrolled active inflammatory myopathy
  - Myopathy with diaphragm involvement
- DU: 1 severe episode of DU per year despite optimal treatment
- Gastrointestinal
  - Oesophageal stricture
  - Active and and severe GI ulcerations despite optimal treatment
  - High grade dysplasia in a Barett's oesophagus
  - Gastroparesis
- Heart
  - Conduction abnormalities and/or rhythm disturbances (not a CI if HLT is considered)
- Kidneys

Launay D, *et al. Presse Med* 2014; 43:e345-e363.

PH-SSc: *Take home messages*

- Pas d’anticoagulation
- Traitements spécifiques de l’HTAP
  - Moins efficaces que dans l’HTAP idiopathique : comorbidités, atteinte interstitielle, atteinte veinulaire, dysfonction VG
  - Risque d’aggravation sous traitement en cas d’atteinte interstitielle ou veinulaire (inégalités ventilation/perfusion, risque d’oedèmes pulmonaires)
  - Pas d’indication aux traitements spécifiques en cas d’atteinte interstitielle sévère
- Pas d’effet des immunosuppresseurs
- La transplantation pulmonaire doit être considérée