Risk Stratification and Current Management of Pulmonary Hypertension

Olivier SITBON

Centre de Référence de l'Hypertension Pulmonaire Sévère – Hôpital Universitaire de Bicêtre – INSERM UMR S_999 – Université Paris-Sud – Le Kremlin-Bicêtre – France

Conflict of interest disclosure

I have the following real or perceived conflicts of interest that relate to this presentation:

Affiliation / Financial interest	Commercial Company
Grants/research support:	Actelion Pharmaceuticals, Bayer HealthCare, GlaxoSmithKline, Merck
Honoraria or consultation fees:	Actelion Pharmaceuticals, Acceleron Pharmaceuticals, Arena Pharmaceuticals, Bayer HealthCare, GlaxoSmithKline, Gossamer Bio, Merck
Participation in a company sponsored bureau:	No
Stock shareholder:	No
Spouse / partner:	No
Other support / potential conflict of interest:	No

PAH & PH: What are we talking about?

1 PAH

- 1.1 Idiopathic PAH
- 1.2 Heritable PAH
- 1.3 Drug- and toxin-induced PAH
- 1.4 PAH associated with:
  - 1.4.1 Connective tissue disease
  - 1.4.2 HIV infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease
  - 1.4.5 Schistosomiasis
- 1.5 PAH long-term responders to CCBs
- 1.6 PAH with overt features of venous/capillaries (PVOD/PCH) involvement
- 1.7 Persistent PH of the newborn syndrome

2 PH due to left heart disease

- 2.1 PH due to heart failure with preserved LVEF
- 2.2 PH due to heart failure with reduced LVEF
- 2.3 Valvular heart disease
- 2.4 Congenital/acquired cardiovascular conditions leading to post-capillary PH

3 PH due to lung diseases and/or hypoxia

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

4 PH due to pulmonary artery obstructions

- 4.1 Chronic thromboembolic PH
- 4.2 Other pulmonary artery obstructions

5 PH with unclear and/or multifactorial mechanisms

- 5.1 Haematological disorders
- 5.2 Systemic and metabolic disorders
- 5.3 Others
- 5.4 Complex congenital heart disease

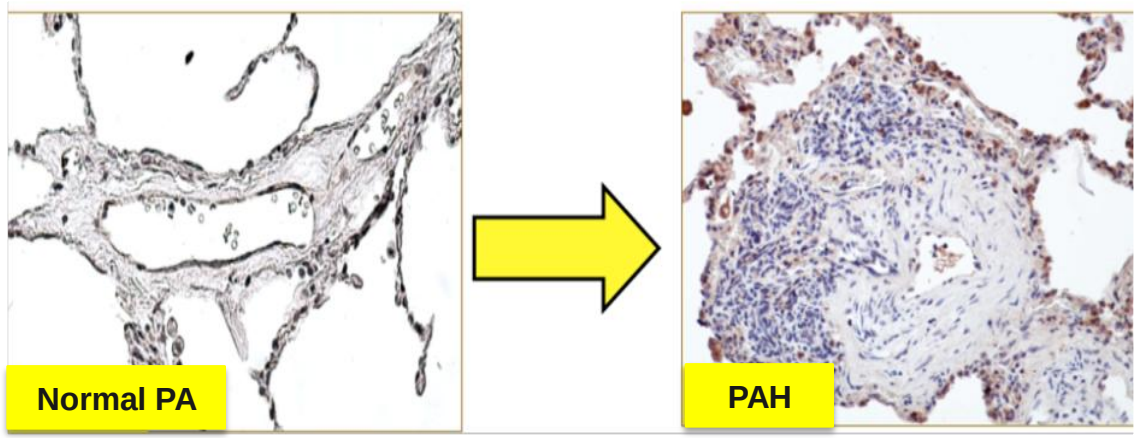
Simonneau G, *et al. Eur Respir J* 2019; 53: 1801913.

PAH: What are we talking about?

1 PAH

- 1.1 Idiopathic PAH
- 1.2 Heritable PAH
- 1.3 Drug- and toxin-induced PAH
- 1.4 PAH associated with:
  - 1.4.1 Connective tissue disease
  - 1.4.2 HIV infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease
  - 1.4.5 Schistosomiasis
- 1.5 PAH long-term responders to CCBs
- 1.6 PAH with overt features of venous/capillaries (PVOD/PCH) involvement
- 1.7 Persistent PH of the newborn syndrome

- Rare disease(s)
- Severe precapillary pulmonary hypertension
- Intense pulmonary artery remodelling with proliferation of endothelial and smooth muscle cells
- Endothelial dysfunction = main target of current available therapies



Simonneau G, *et al. Eur Respir J* 2019; 53: 1801913.

PH: What are we talking about?

2 PH due to left heart disease

- 2.1 PH due to heart failure with preserved LVEF
- 2.2 PH due to heart failure with reduced LVEF
- 2.3 Valvular heart disease
- 2.4 Congenital/acquired CV conditions leading to post-capillary PH

The use of PAH-approved therapies is not recommended in PH-LHD	III	C

3 PH due to lung diseases and/or hypoxia

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

The use of drugs approved for PAH is not recommended in patients with PH due to lung diseases	III	C

4 PH due to pulmonary artery obstructions

- 4.1 Chronic thromboembolic PH
- 4.2 Other pulmonary artery obstructions

Group 4 (CTEPH)	Surgery (PEA) Interventional (BPA) Medical (riociguat)

5 PH with unclear and/or multifactorial mechanisms

- 5.1 Haematological disorders
- 5.2 Systemic and metabolic disorders
- 5.3 Others
- 5.4 Complex congenital heart disease

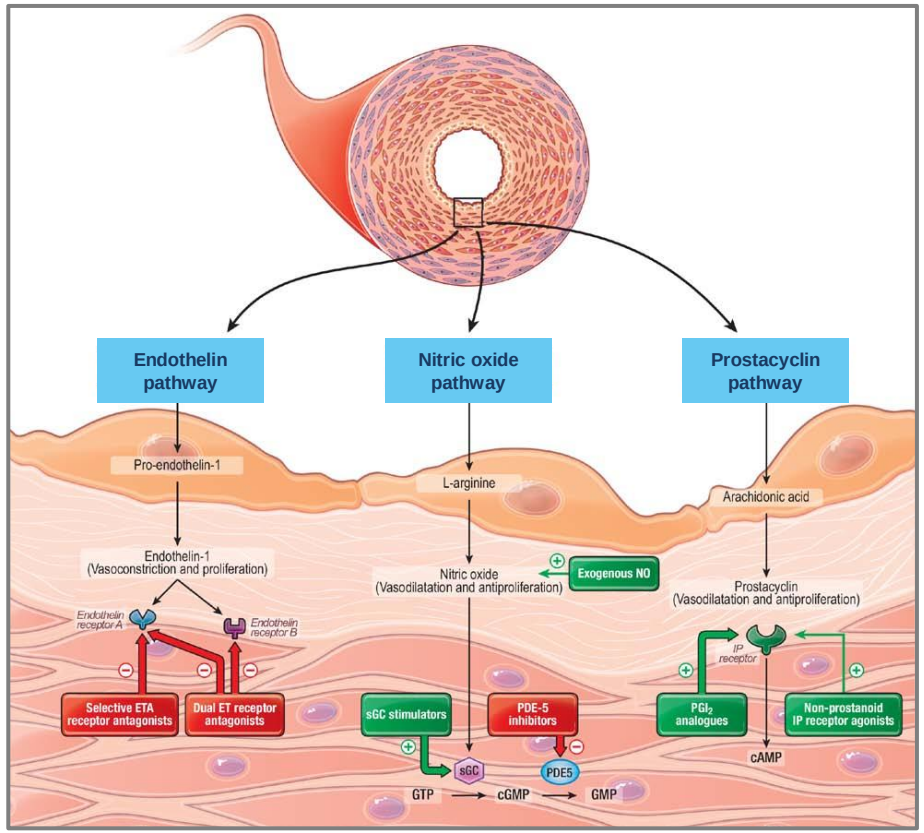
Group 5: No clear-cut treatment recommendations)

Simonneau G, *et al. Eur Respir J* 2019; 53: 1801913.

At least 10 available PAH medications targeting the three dysfunctional signalling pathways involved in PAH…

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



Circulation. 2014;130:2189-2208.

Endothelin pathway

Endothelin receptor antagonists (ERAs)

- Ambrisentan
- Bosentan
- Macitentan

NO–cGMP pathway

PDE5 inhibitors

- Sildenafil
- Tadalafil

sGC stimulators
Riociguat

Prostacyclin pathway

Prostanoids

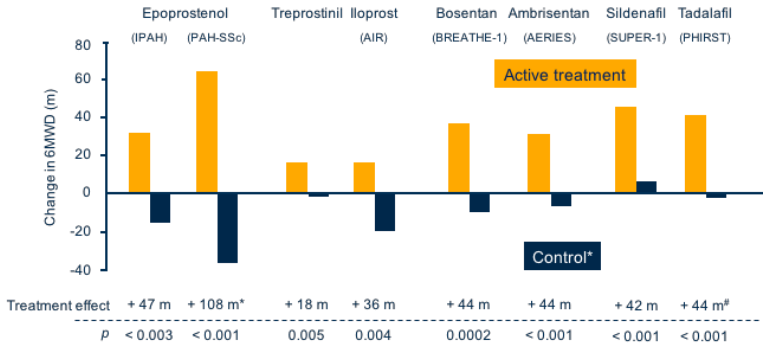
- Epoprostenol iv
- Iloprost inhaled, iv
- Treprostinil sc, iv, (inhaled, oral)*
- (Beraprost)**

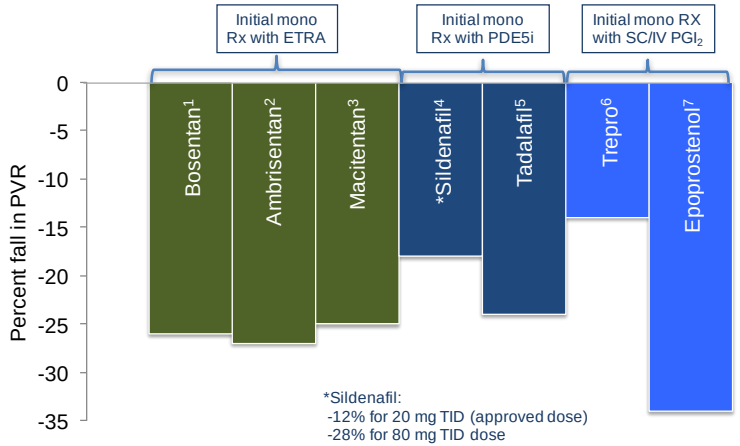
Non prostanoids IP receptor agonist
Selexipag (oral)

*Only approved in the US; **Only approved in Japan and South Korea

Initial monotherapy in PAH

- Many RCTs with all drugs targeting the 3 dysfunctional pathways (PGI_2, ERA, PDE-5 inhibitors)
  - Improvement in exercise capacity (35-45 m) after 3-6 months[1-7]
  - Modest improvement in haemodynamics[1-7]
    - 25-35% decrease in PVR;
    - almost no change in PAP
  - 43% reduction in mortality in a metaanalysis[8]: 23 RCTs, 14.3 weeks, 3140 patients
- Huge experience worldwide



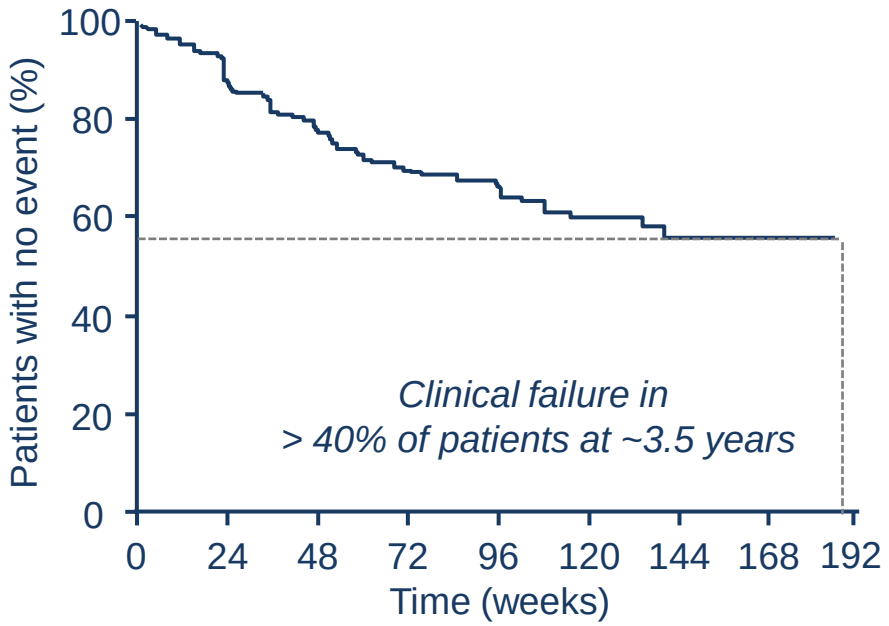


1. Channick RN. *Lancet* 2001; 2. Galiè N. *J Am Coll Cardiol* 2005; 3.Pulido T. *N Engl J Med* 2013; 4. Galiè N. *N Engl J Med* 2005; 5. Galiè N. *Circulation* 2009; 6. Simonneau G. *Am J Respir Crit Care Med* 2002; 7. Barst RJ. *N Engl J Med* 1996. 8. Galiè N. *Eur Heart J* 2009.

PAH progresses rapidly in patients on monotherapy

Pooled monotherapy arm from AMBITION

Time to first event of clinical failure* (primary endpoint)



Number at risk:

Pooled monotherapy	247	209	155	108	77	49	25	5

*Clinical failure: the first occurrence of a composite endpoint of death, hospitalization for PAH worsening, disease progression, or unsatisfactory long-term clinical response.

AMBITION, AMBrisentan and Tadalafil in patients with pulmonary arterial HypertensION.

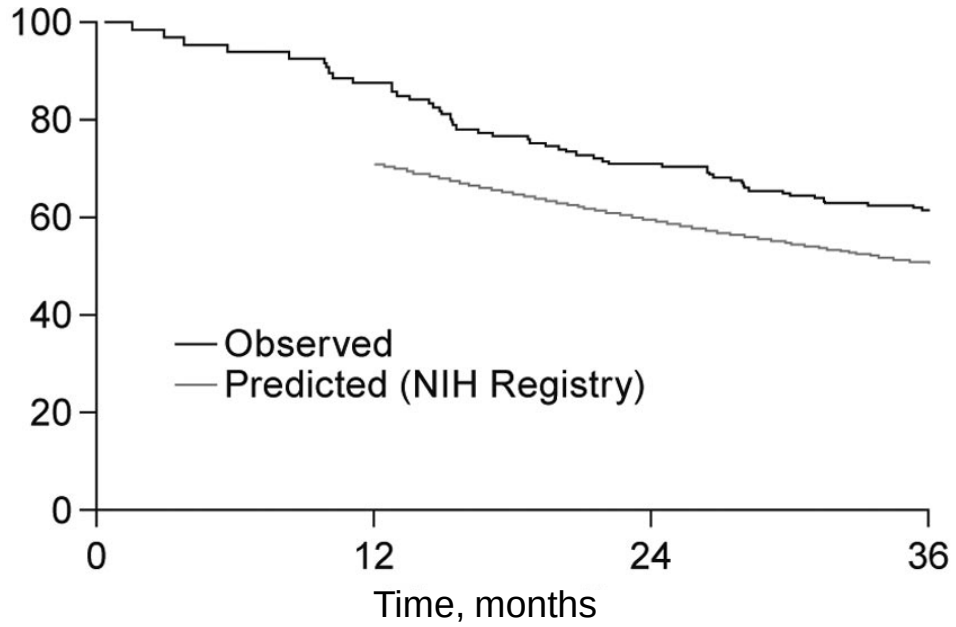
Adapted from Galiè N *et al*. *N Engl J Med* 2015;373:834–44.

PAH: Long-term survival is unsatisfactory…

French cohort: Idiopathic, heritable and drug-induced PAH

2002-2003

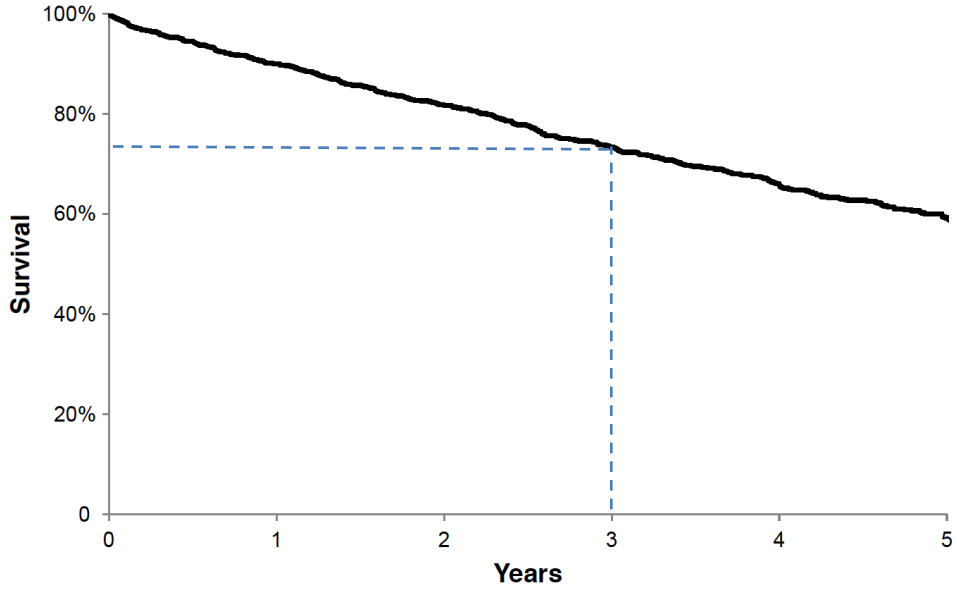
N=190 (incident)



3-year survival
58%

2006-2016

N=1592 (incident)



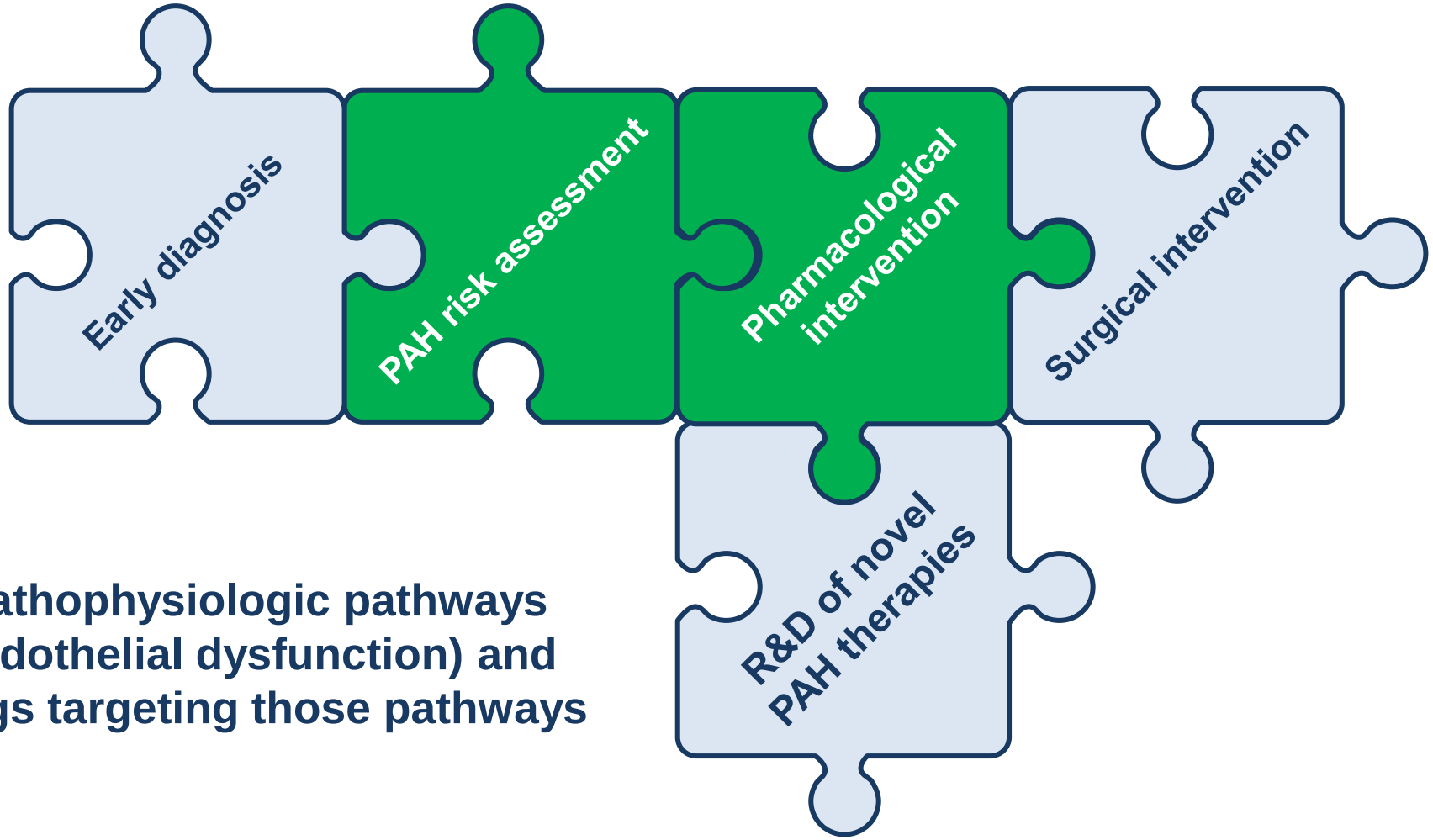
Patients at risk, n	1591	1063	823	605	417	285
Overall survival		90%				59%

3-year survival
73%

1. Humbert M, *et al. Circulation*. 2010;122:156-63.
2. Boucly A, *et al. Eur Respir J* 2017;50:1700889.

PAH survival: How to do better?
Optimal treatment strategies to improve long-term outcomes

- Do better with what we have today



- Consider other pathophysiologic pathways (different from endothelial dysfunction) and develop new drugs targeting those pathways

ESC/ERS Guidelines recommend achieving a low-risk profile

	Recommendations for evaluation of PAH severity and response to therapy	Class	Level
Risk stratification	It is recommended to evaluate the severity of PAH patients with a panel of data derived from clinical assessment, exercise tests, biochemical markers and echocardiographic and hemodynamic evaluations	I	C
	It is recommended to perform regular follow-up assessments every 3-6 months in stable patients	I	C
Treatment goal	Achievement / maintenance of a low-risk profile is recommended as an adequate treatment response for patients with PAH	I	C
	Achievement / maintenance of an intermediate-risk profile should be considered an inadequate treatment response for most patients with PAH	IIa	C

Galiè N, *et al. Eur Respir J* 2015; 46:903-75; Galiè N, *et al. Eur Heart J* 2016; 37:67-119.

Multiple risk equations / models are available to predict outcomes and guide management in PAH

1. NIH registry equation[1]
2. French network equation[2,3]
3. PH Connection (PHC) equation[4,5]
4. Scottish composite score[6]
5. REVEAL equation[7] and risk score[8]
6. ESC/ERS risk stratification table[9,10]

1. D'Alonzo GE, *et al. Ann Intern Med* 1991; 115:343-9; 2. Humbert M, *et al. Circulation* 2010; 122:156-63; 3. Humbert M, *et al. Eur Respir J* 2010; 36:549-55; 4. Thenappan T, *et al. Eur Respir J* 2010; 35:1079-87; 5. Thenappan T, *et al. Chest J* 2012; 141:642-65; 6. Lee WT, *et al. Eur Respir J* 2012; 40:604-11; 7. Benza R, *et al. Circulation* 2010; 122:164-72; 8. Benza R, *et al. Chest* 2012; 141:354-62; 9. Galiè N, *et al. Eur Respir J* 2015; 46:903-75; 10. Galiè N, *et al. Eur Heart J* 2016; 37:67-119.

2015 ESC/ERS Guidelines recommend regular multiparameter risk assessments, both at diagnosis and follow-up appointments

	Determinants of prognosis	Estimated 1-year mortality		
		Low risk < 5%	Intermediate risk 5-10%	High risk > 10%
Clinical Evaluation	Clinical signs of right heart failure	Absent	Absent	Present
	Progression of symptoms	No	Slow	Rapid
	Syncope	No	Occasional syncope	Repeated syncope
	FC	I, II	III	IV
Exercise Capacity	6MWD	> 440 m	165-440 m	< 165 m
	CPET	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 < 11ml/min/kg (< 35% pred.) VE/VCO_2 slope ≥ 45
Right Ventricular Function	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 (echo, CMR)	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
	Hemodynamics	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%

BNP: brain natriuretic peptide; CI: cardiac index; CPET: cardio-pulmonary exercise test; FC: functional class; NT-proBNP: N-terminal proBNP; RA: right atrial; RAP: RA pressure; 6MWD: 6-minute walk distance; SvO2: mixed venous oxygen saturation

Galiè N, *et al. Eur Respir J* 2015; 46:903-75; Galiè N, *et al. Eur Heart J* 2016; 37:67-119.

Two recent registry studies validated the risk stratification table for determination of prognosis in PAH

ESC European Society of Cardiology
European Heart Journal (2018) 39, 4175–4181
doi:10.1093/eurheartj/ehx257

CLINICAL RESEARCH
Pulmonary arterial hypertension

A comprehensive risk stratification at early follow-up determines prognosis in pulmonary arterial hypertension

David Kylhammar[1]*, Barbro Kjellström[2], Clara Hjalmarsson[3], Kjell Jansson[4], Magnus Nisell[5], Stefan Söderberg[6], Gerhard Wikström[7], and Göran Rådegran[1], on behalf of SveFPH and SPAHR

[1]Department of Clinical Sciences Lund, Cardiology, Lund University, and The Section for Heart Failure and Valvular Disease, VO Heart and Lung Medicine, Skåne University Hospital, 221 85 Lund, Sweden; [2]Cardiology Unit, Department of Medicine Solna, Karolinska Institute, 171 76 Stockholm, Sweden; [3]Department of Cardiology, Sahlgrenska Academy, University of Gothenburg, and Sahlgrenska University Hospital, 413 45 Gothenburg, Sweden; [4]Departments of Cardiology and Clinical Physiology, Institution of Medicine and Health Sciences, Linköping University, 581 85 Linköping, Sweden; [5]Department of Medicine Solna, Karolinska Institute, and The Department of Respiratory Medicine and Allergy, Karolinska University Hospital, 176 77 Stockholm, Sweden; [6]Department of Public Health and Clinical Medicine, Heart Centre, Umeå University, 901 87 Umeå, Sweden; and [7]Department of Medical Sciences, Cardiology, Uppsala University, and Uppsala Academic Hospital, 751 85 Uppsala, Sweden

Received 5 December 2016; revised 25 February 2017; editorial decision 26 April 2017; accepted 27 April 2017; online publish-ahead-of-print 1 June 2017

SPAHR[1]

Mortality in pulmonary arterial hypertension: prediction by the 2015 European pulmonary hypertension guidelines risk stratification model

Marius M. Hoeper[1,2], Tilmann Kramer[3,4], Zixuan Pan[5], Christina A. Eichstaedt[5], Jens Spiesshoefer[6], Nicola Benjamin[5], Karen M. Olsson[1,2], Katrin Meyer[1], Carmine Dario Vizza[7], Anton Vonk-Noordegraaf[8], Oliver Distler[9], Christian Opitz[10], J. Simon R. Gibbs[11], Marion Delcroix[12], H. Ardeschir Ghofrani[13], Doerte Huscher[14], David Pittrow[15], Stephan Rosenkranz[3,4] and Ekkehard Grünig[2,5]

COMPERA[2]

n = 530 PAH (2008-2016)	*n* = 1588 PAH (2009-2016)
WHO FC / 6MWD / BNP or NT-proBNP RAP / CI / SvO_2 RA area / Pericardial effusion	WHO FC / 6MWD / BNP or NT-proBNP RAP / CI / SvO_2
Sum of grades (1 low-3 high) / number available variables	

COMPERA: Comparative Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension
SPAHR: Swedish Pulmonary Arterial Hypertension Register

1. Kylhammar D, *et al. Eur Heart J* 2018; 39:4175-81;
2. Hoeper MM, *et al. Eur Respir J* 2017; 50:1700740.

SPAHR and COMPERA: Methodology

Determinants of prognosis	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	Repeated syncope
FC	I, II	III	IV
6MWD	> 440 m	165-440 m	< 165 m
CPET	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 < 11ml/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 (echo, CMR)	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
Hemodynamics	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%

1
2
2
3
1
2

Score = 1 + 1 + 2 + 2 + 3 = 9

Score divided by the number of available variables (5):
9 / 5 = 1.8

Rounded to nearest integer = 2

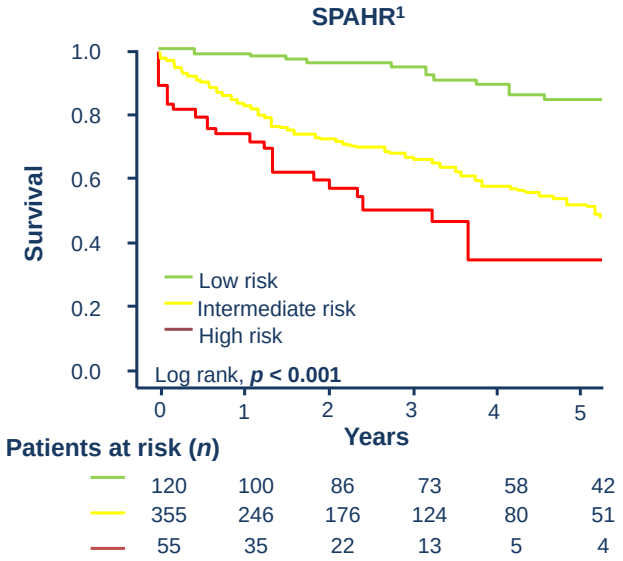
→ **Intermediate risk**

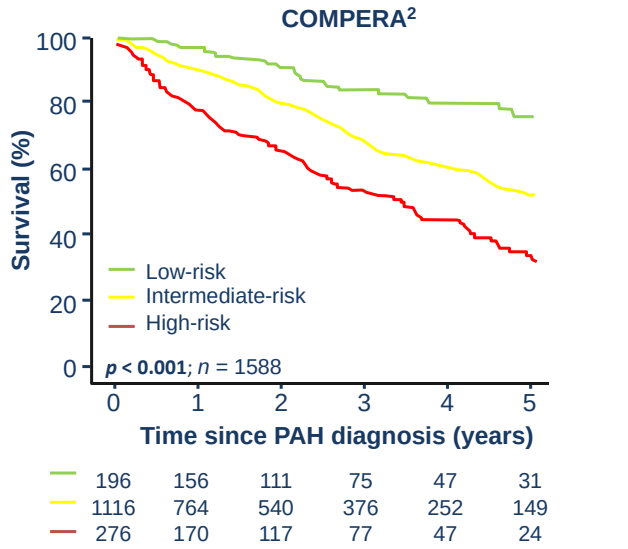
COMPERA: Comparative Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension;
SPAHR: Swedish Pulmonary Arterial Hypertension Register

1. Kylhammar D, *et al. Eur Heart J* 2018; 39:4175-81;
2. Hoeper MM, *et al. Eur Respir J* 2017; 50:1700740.

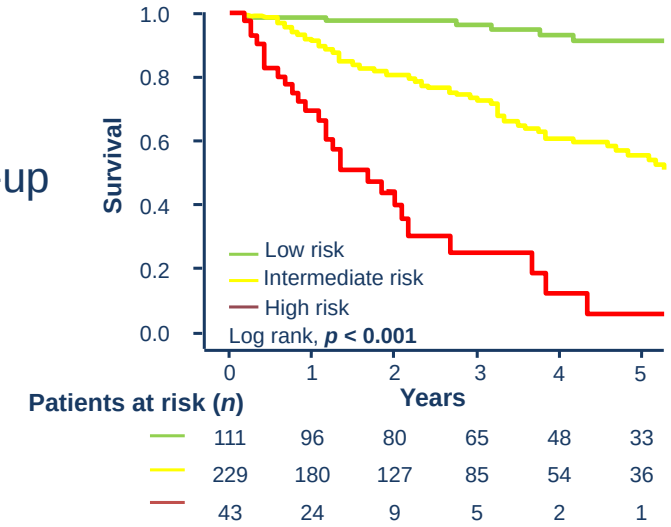
Validation of ESC/ERS risk stratification in large registries

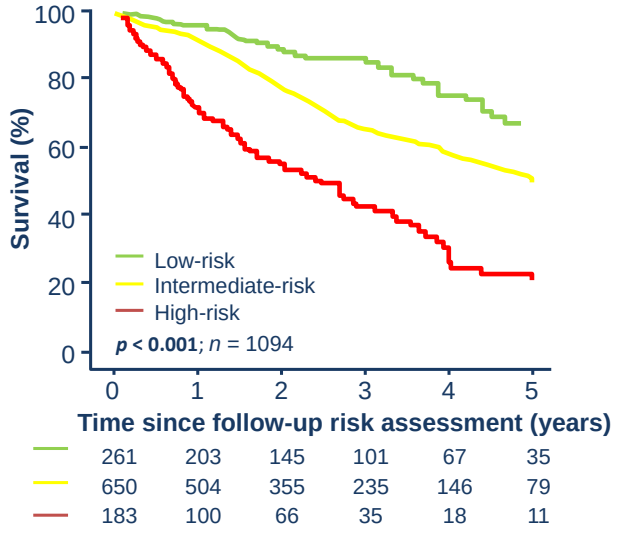
Baseline

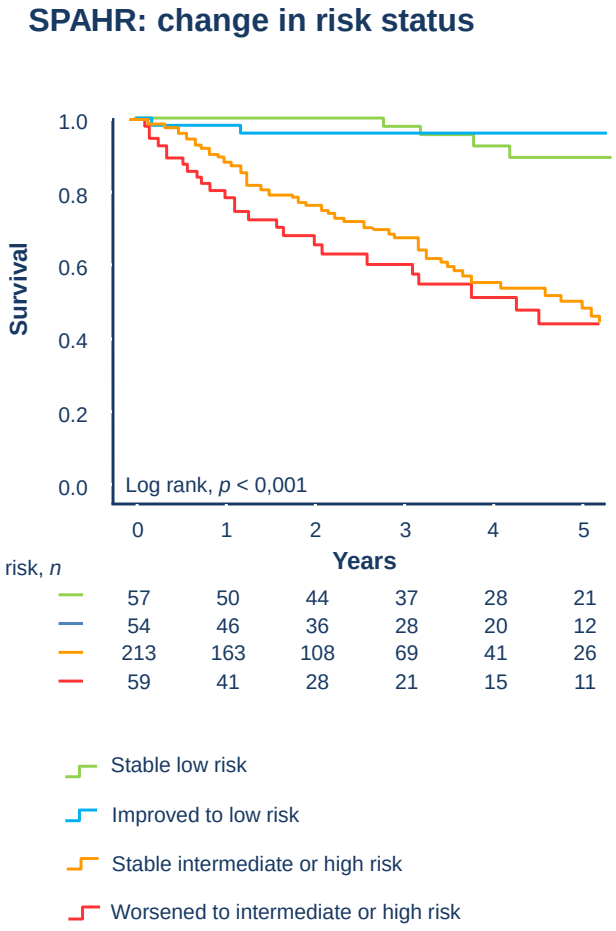




Follow-up







1. Kylhammar D, *et al. Eur Heart J* 2018; 39:4175-8.
Hoeper MM, *et al. Eur Respir J* 2017; 50:1700740.

A low-risk profile can be determined by the number of low-risk criteria present or achieved (treatment goals)

Risk assessment, prognosis and guideline implementation in pulmonary arterial hypertension

Athénaïs Boucly[1,2,3], Jason Weatherald[2,3,4], Laurent Savale[1,2,3], Xavier Jaïs[1,2,3], Vincent Cottin[5], Grégoire Prevot[6], François Picard[7], Pascal de Groote[8], Mitja Jevnikar[1,2,3], Emmanuel Bergot[9], Ari Chaouat[10,11], Céline Chabanne[12], Arnaud Bourdin[13], Florence Parent[1,2,3], David Montani[1,2,3], Gérald Simonneau[1,2,3], Marc Humbert[1,2,3] and Olivier Sitbon[1,2,3]

FPHN

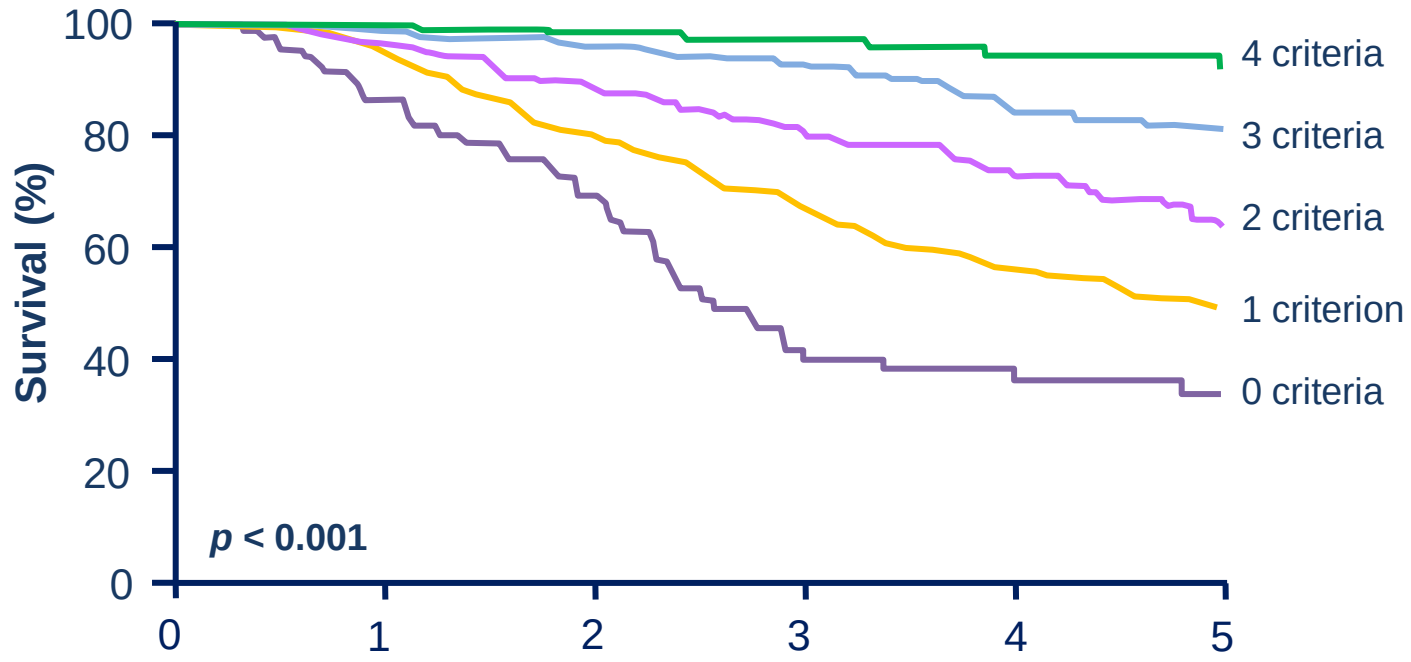
- 2006-2016
- 1017 incident idiopathic/heritable PAH and D&T-induced PAH
- All patients having all variables available at baseline and first follow-up visit
- 602 patients with BNP/NT-proBNP also available

Determinants of prognosis	Low risk < 5%
Clinical signs of right heart failure	Absent
Progression of symptoms	No
Syncope	No
FC	I, II
6MWD	> 440 m
CPET	Peak VO_2 > 15 ml/min/kg (> 65% pred.) VE/VCO_2 slope < 36
NT-proBNP plasma levels	BNP < 50 ng/l NT-proBNP < 300 ng/l
Imaging (echo, CMR)	RA area < 18 cm^2 No pericardial effusion
Hemodynamics	RAP < 8 mmHg CI ≥ 2.5 l/min/m^2 SvO_2 > 65%

FPHN: French Pulmonary Hypertension Network

Boucly A, *et al. Eur Respir J* 2017; 50:1700889.

FPHN: The more low-risk criteria at follow-up, the better the patient's outcome



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 criteria	95	61	44	22	18	14

- Patients achieving 3-4 low-risk criteria have a good prognosis
- Achieving 3-4 low-risk criteria may be considered as treatment goals

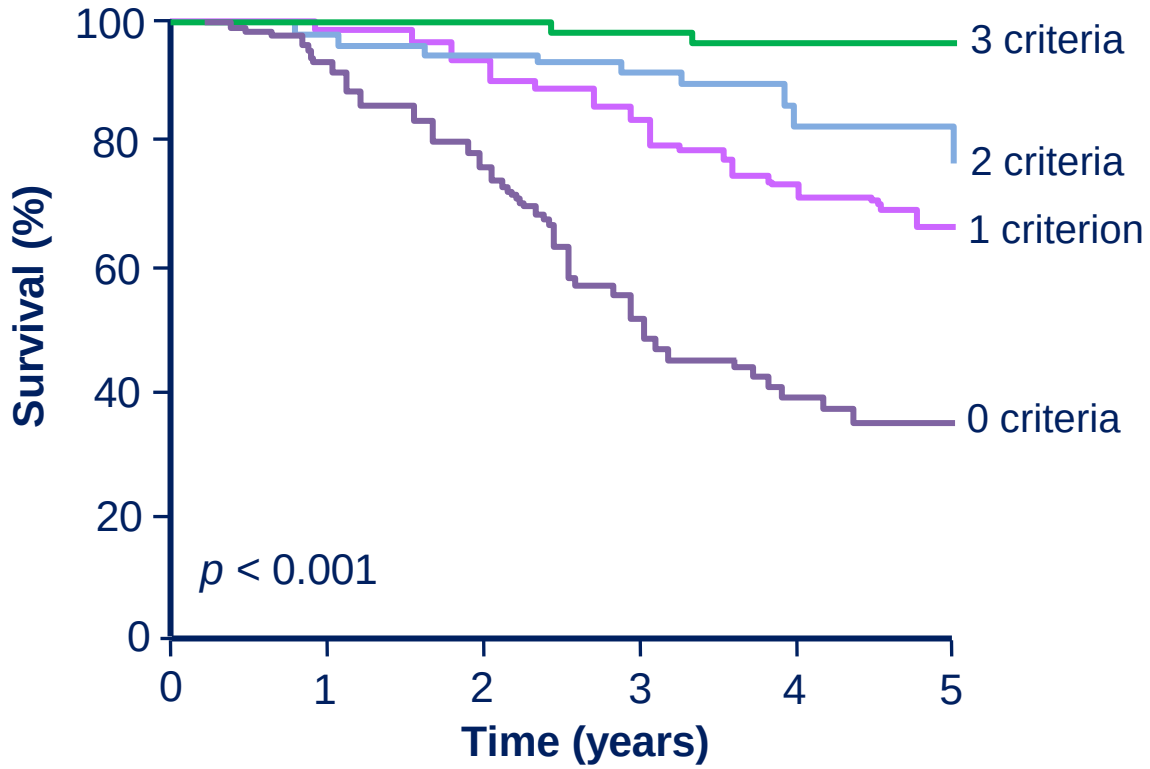
Low-risk criteria:

- **FC I or II**
- **CI ≥ 2.5 L/min/m²**
- **RAP < 8 mmHg**
- **6MWD > 440 m**

Incident patients enrolled in the French registry.

Boucly A, *et al. Eur Respir J* 2017; 50:1700889.

FPHN: Excellent survival in patients with three non-invasive low-risk criteria achieved at first follow-up



Patients at risk, *n* (*n* = 603)

3 criteria	115	97	81	63	38	26
2 criteria	145	116	95	72	36	21
1 criterion	175	136	101	62	38	24
0 criteria	168	117	76	39	23	11

- Routine hemodynamic follow-up may not be necessary for all patients, those who attain and maintain all 3 non-invasive low-risk criteria

➔ However, invasive hemodynamic risk assessment provides important prognostic information in patients who do not achieve non-invasive low-risk criteria

Low-risk criteria:

- **FC I or II**
- **6MWD > 440 m**
- **BNP < 50 ng/L**

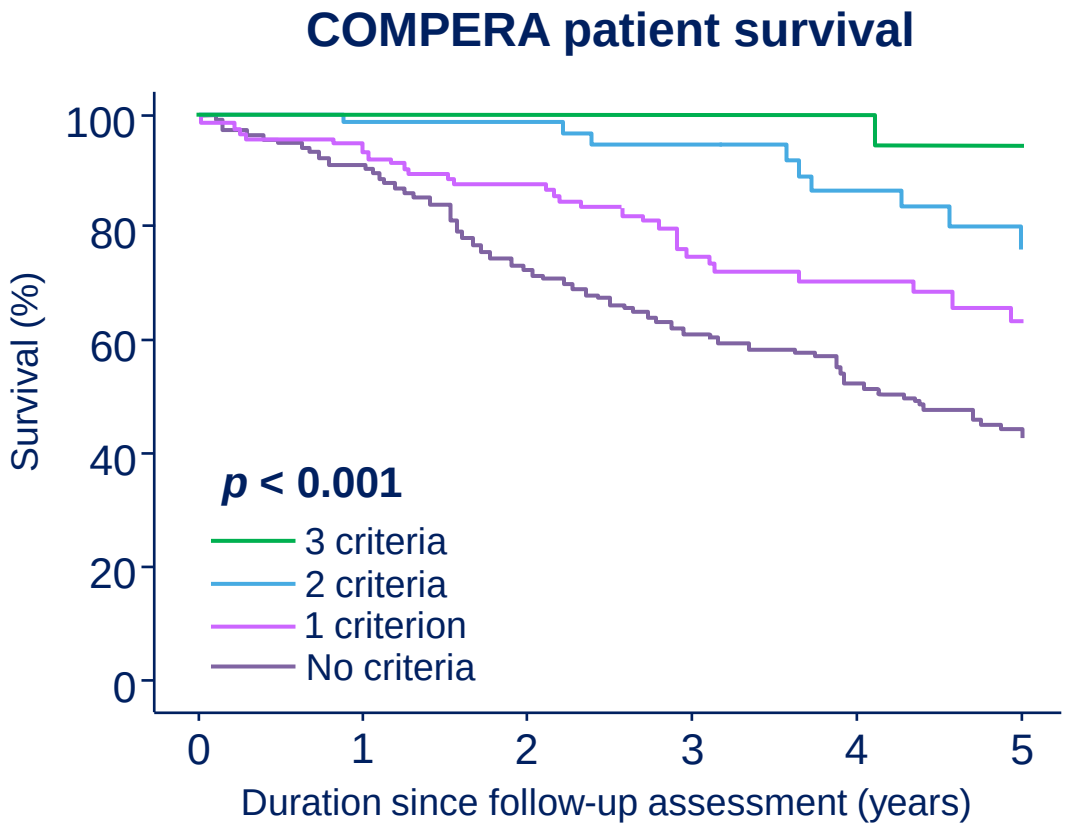
  OR

  NT-proBNP < 300 ng/L

Boucly A, *et al. Eur Respir J* 2017; 50:1700889.

When the French registry risk score was applied to the COMPERA population…

…Comparable survival rates for COMPERA and French Registry patients were observed

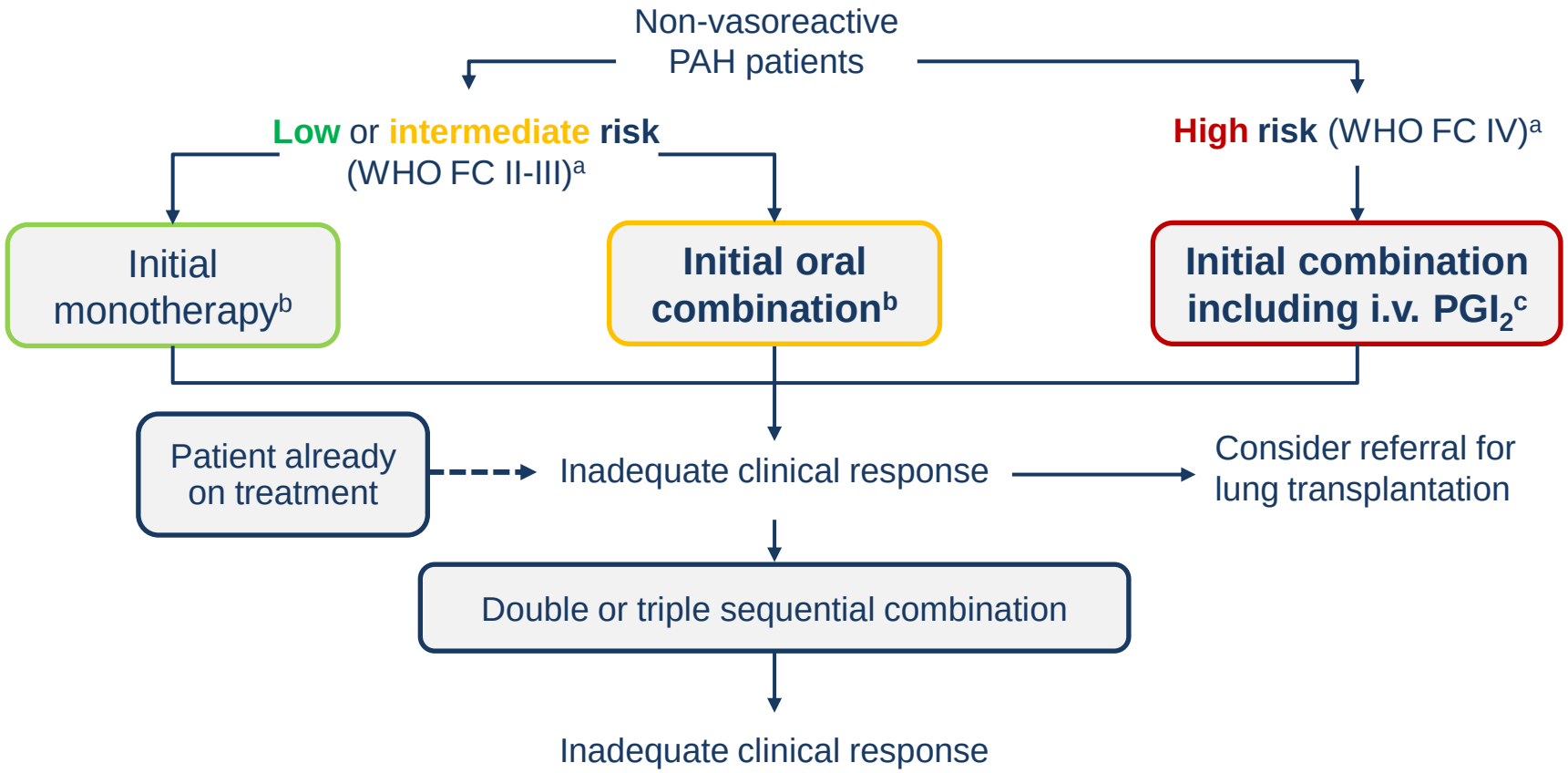


	Number of low-risk criteria at follow up	1 Year survival estimate	3 Year survival estimate	5 Year survival estimate
COMPERA	3 low-risk criteria	100%	100%	95%
	2 low-risk criteria	99%	95%	76%
	1 low-risk criterion	93%	75%	64%
	0 low-risk criteria	90%	61%	43%
French registry	3 low-risk criteria	100%	97%	96%
	2 low-risk criteria	98%	90%	77%
	1 low-risk criterion	98%	83%	66%
	0 low-risk criteria	94%	52%	35%

n = 579; IPAH patients for whom complete data sets of FC, 6MWD and BNP/NT-proBNP were available at first follow-up (median 4.6 months, interquartile range 3.1-9.5 months) after treatment initiation.

Hoeper MM, *et al. Eur Respir J* 2018; 51:1702606.

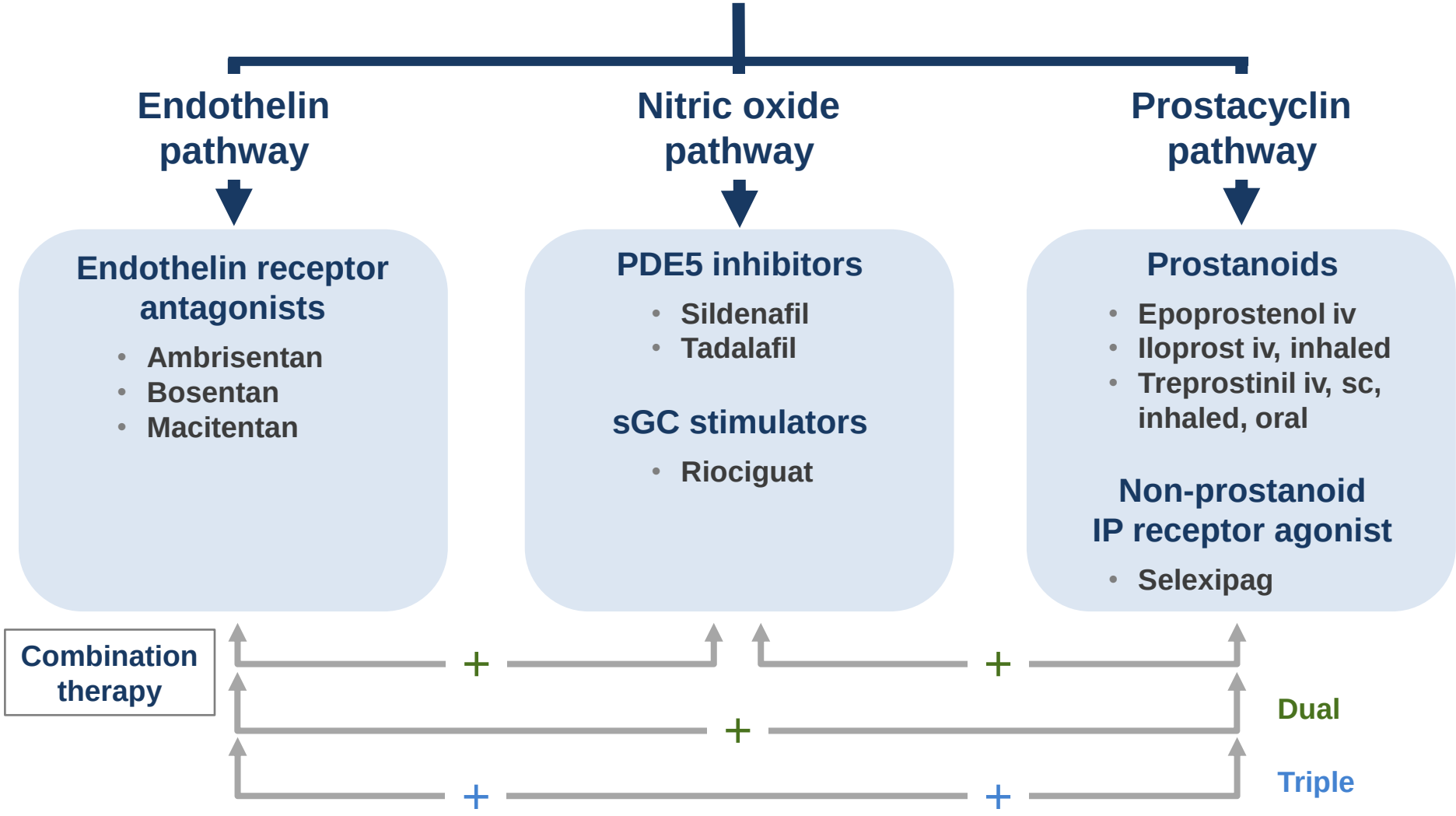
Risk assessment has a central place in the PAH treatment algorithm



[a] Some WHO-FC III patients may be considered high-risk;
[b] Initial combination with ambrisentan plus tadalafil has proven to be superior to initial monotherapy with ambrisentan or tadalafil in delaying clinical failure;
[c] Intravenous epoprostenol should be prioritized as it has reduced the 3 month rate for mortality in high-risk PAH patients also as monotherapy.

1. Galiè N, *et al. Eur Respir J* 2015; 46:903-75;
2. Galiè N, *et al. Eur Heart J* 2016; 37:67-119.

Can we improve current survival with the 10 available therapies?



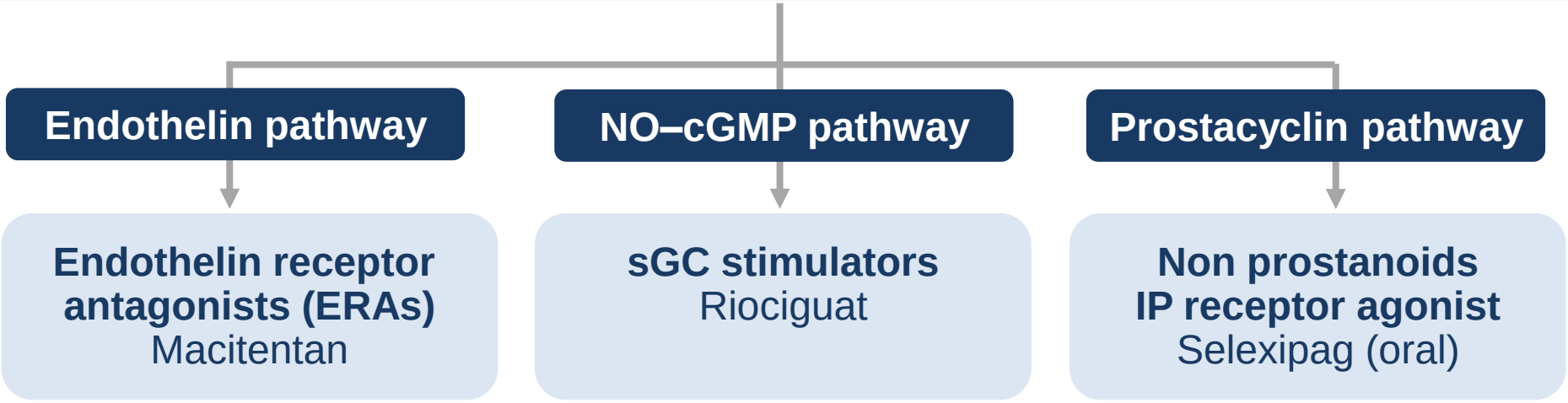
iv, intravenous; PDE5, phosphodiesterase type 5; sc, subcutaneous; sGC, soluble guanylate cyclase.
Adapted from Galiè N *et al. Eur Respir J* 2015;46:903–75; *Eur Heart J* 2016;37:67–119.

Sequential combination therapy with change in 6MWD as primary endpoint: results are not uniform…

Drug tested	Study	Background	N	Duration (weeks)	Primary endpoint
Bosentan[1]	COMPASS-2	Sildenafil	334	92	Morbi-mortality **(NEG)**
Iloprost[2]	STEP	Bosentan	67	12	Δ6MWD **(NEG)**
Iloprost[3]	COMBI	Bosentan	40	12	Δ6MWD **(NEG)**
Riociguat[4]	PATENT-1	None or bosentan (44%) or prostanoid (6%)	443	12	Δ6MWD **(POS)**
Sildenafil[5]	PACES	Epoprostenol	264	16	Δ6MWD **(POS)**
Sildenafil	NCT00323297	Bosentan	104	12	Δ6MWD **(NEG)**
Tadalafil[6]	PHIRST	None or bosentan (54%)	405	16	Δ6MWD **(NEG)**
Treprostinil[7]	Inhaled- TRIUMPH	Bosentan or sildenafil	235	12	Δ6MWD **(POS)**
Treprostinil[8]	Oral- FREEDOM C1	Bosentan &/or sildenafil	354	16	Δ6MWD **(NEG)**
Treprostinil[9]	Oral- FREEDOM C2	Bosentan &/or sildenafil	310	16	Δ6MWD **(NEG)**

1. McLaughlin V. *Eur Respir J* 2015. 2. McLaughlin V. *AmJ Respir Crit Care Med* 2006. 3. Hoeper M. *Eur Respir J* 2006. 4. Ghofrani HA. *N Engl J Med* 2013. 5. Simonneau. *Ann Intern Med* 2008. 6.Galiè N. *Circulation* 2009. 7. McLaughlin V. *J Am Coll Cardiol* 2010. 8. Tapson V. *Chest* 2012. 9. Tapson V. *Chest* 2013.

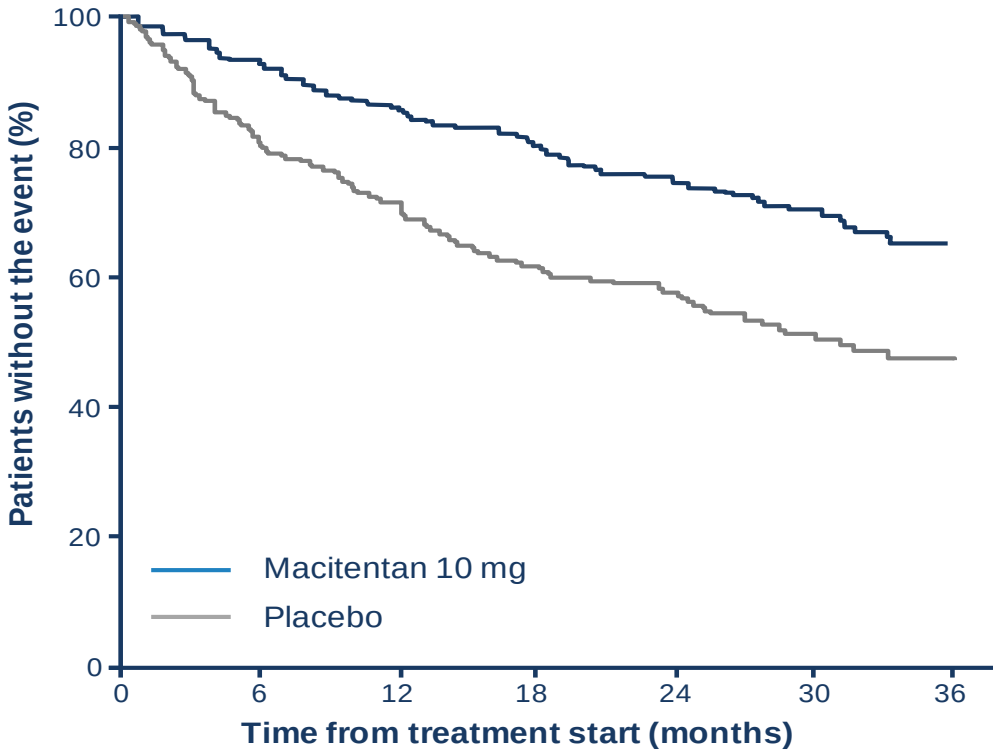
Combination therapy in PAH: New endpoints/ New strategies



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

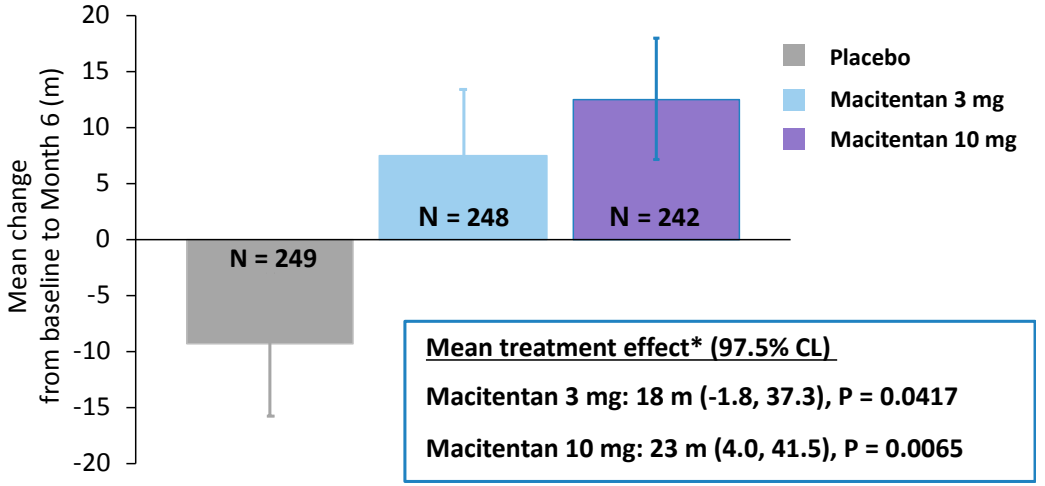
1. McLaughlin VV, *et al*. *Eur Respir J* 2015. 2. Pulido T, et al. *N Engl J Med* 2013. 3. Sitbon O, et al. *N Engl J Med* 2015. 4. Galié N, et al. *N Engl J Med* 2015.

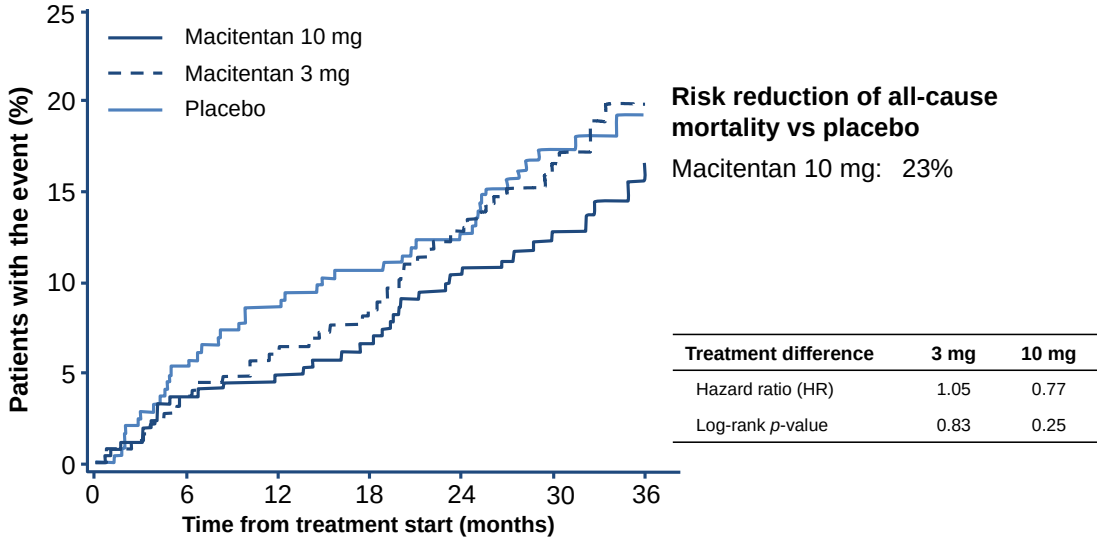
SERAPHIN: macitentan reduced the risk of the primary outcome composite of death or morbidity due to PAH



Risk reduction of primary endpoint event vs placebo
Macitentan 10 mg: 45% (< 0.001)

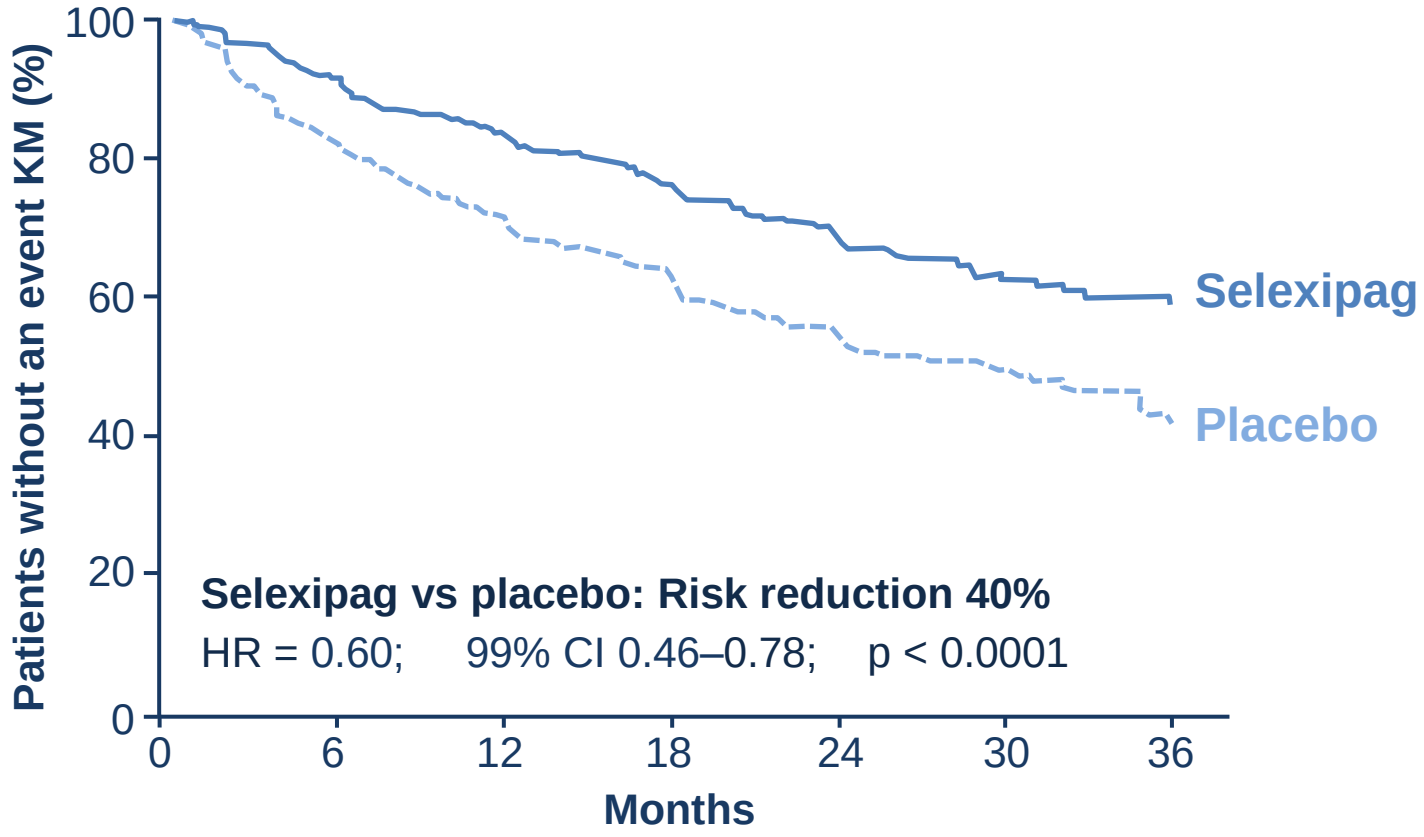
Disease progression was the main component of the primary composite endpoint





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

GRIPHON: Selexipag reduced the risk of the primary outcome composite of death or morbidity due to PAH

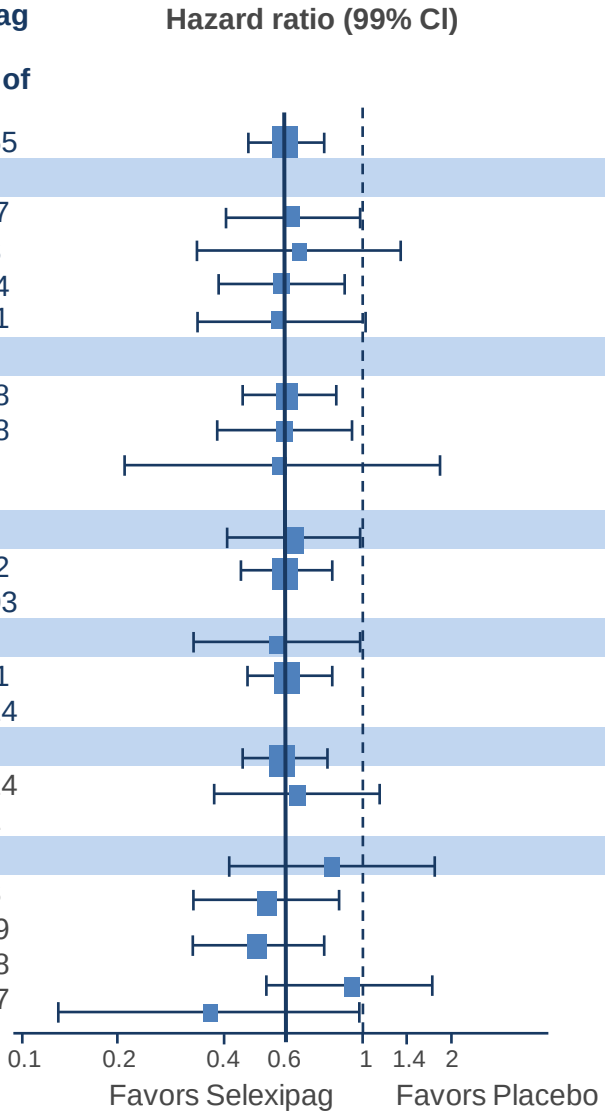


Hospitalisation for PAH and disease progression were the main components of the primary composite endpoint

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

GRIPHON Primary endpoint: Consistent treatment effect across pre-specified subgroups

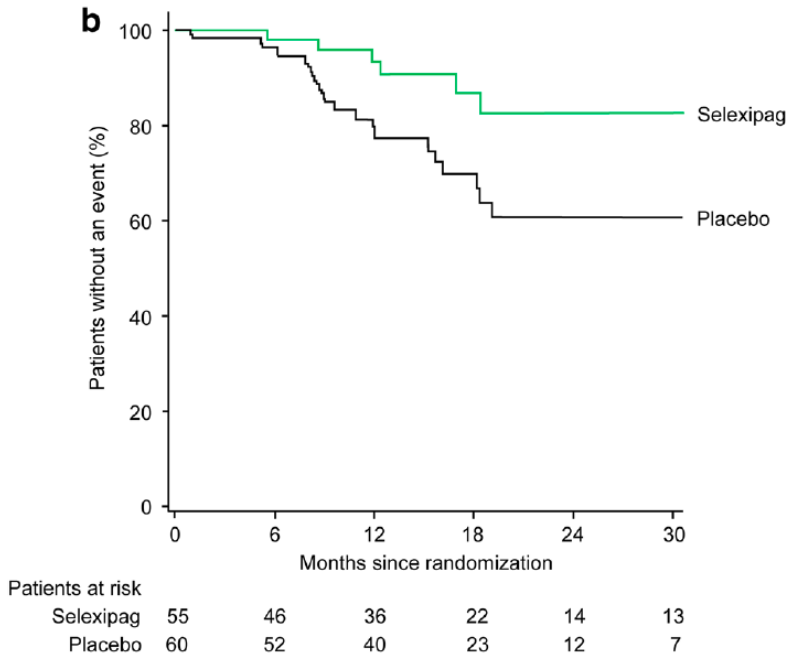
Subgroup	p-value for interaction	Placebo	Selexipag
		No. of patients/no. of events	
All patients		582/242	574/155
PAH therapy at baseline	**0.95**		
ERA and PDE5 inhibitor		197/80	179/47
ERA monotherapy		76/29	94/23
PDE5 inhibitor monotherapy		185/84	189/54
No PAH therapy		124/49	112/31
PAH etiology	**0.98**		
IPAH, HPAH, HIV, drug/toxin-induced		365/156	347/98
Assoc. with connective tissue disease		167/73	167/48
Assoc. with corrected congenital shunts		50/13	60/9
WHO functional class at baseline	**0.78**		
I/II		260/74	278/52
III/IV		322/168	296/103
Sex	**0.66**		
Males		116/48	117/31
Females		466/194	457/124
Age at screening	**0.68**		
<65 years		474/190	475/124
≥65 years		108/52	99/31
Geographical region	**0.07**		
North America		98/28	95/23
Western Europe/Australia		160/68	161/39
Eastern Europe		155/85	149/48
Asia		113/39	115/37
Latin America		56/22	54/8



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

Effect of selexipag on primary composite endpoint in patients receiving dual combination therapy (ERA and PDE-5i)

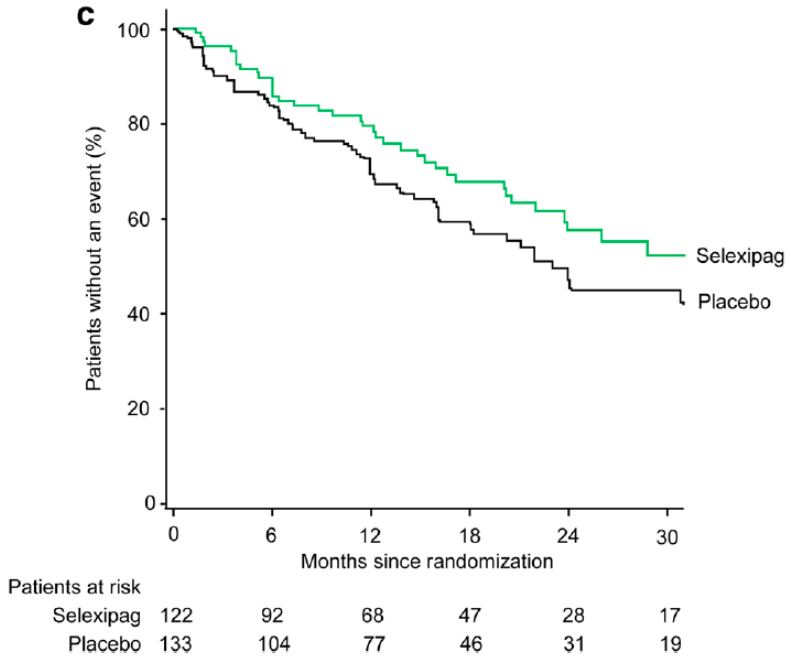
FC II symptoms



HR 0.36
(95% CI 0.14 – 0.91)

Risk reduction
FC II patients 63%
FC III patients 26%

FC III symptoms

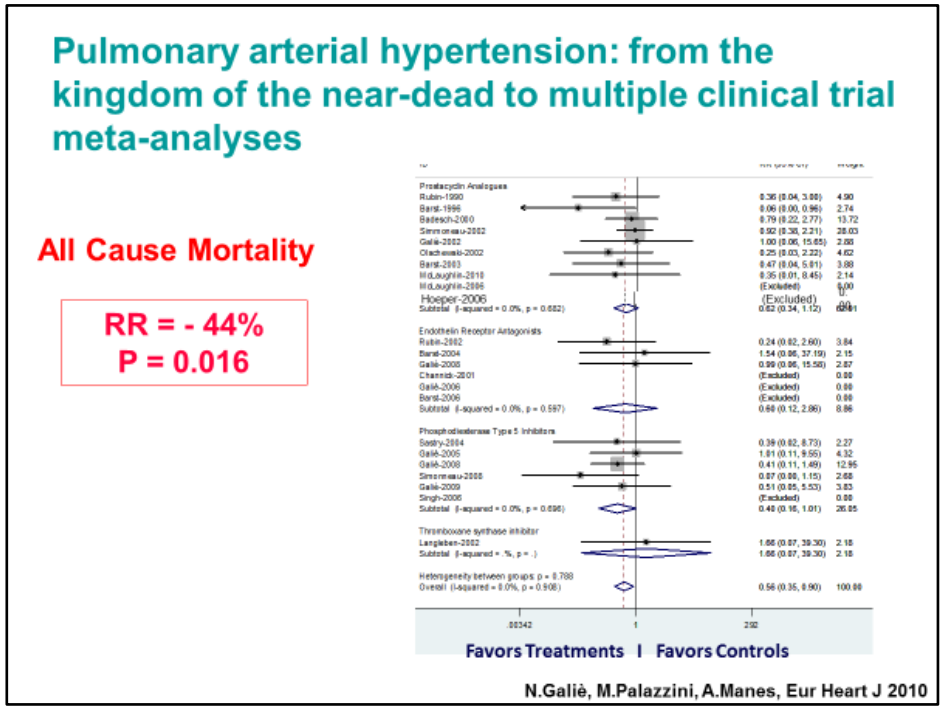


HR 0.74
(95% CI 0.50 – 1.10)

Coghlan JG, *et al. Am J Cardiovasc Drugs* 2018;18:37–47.

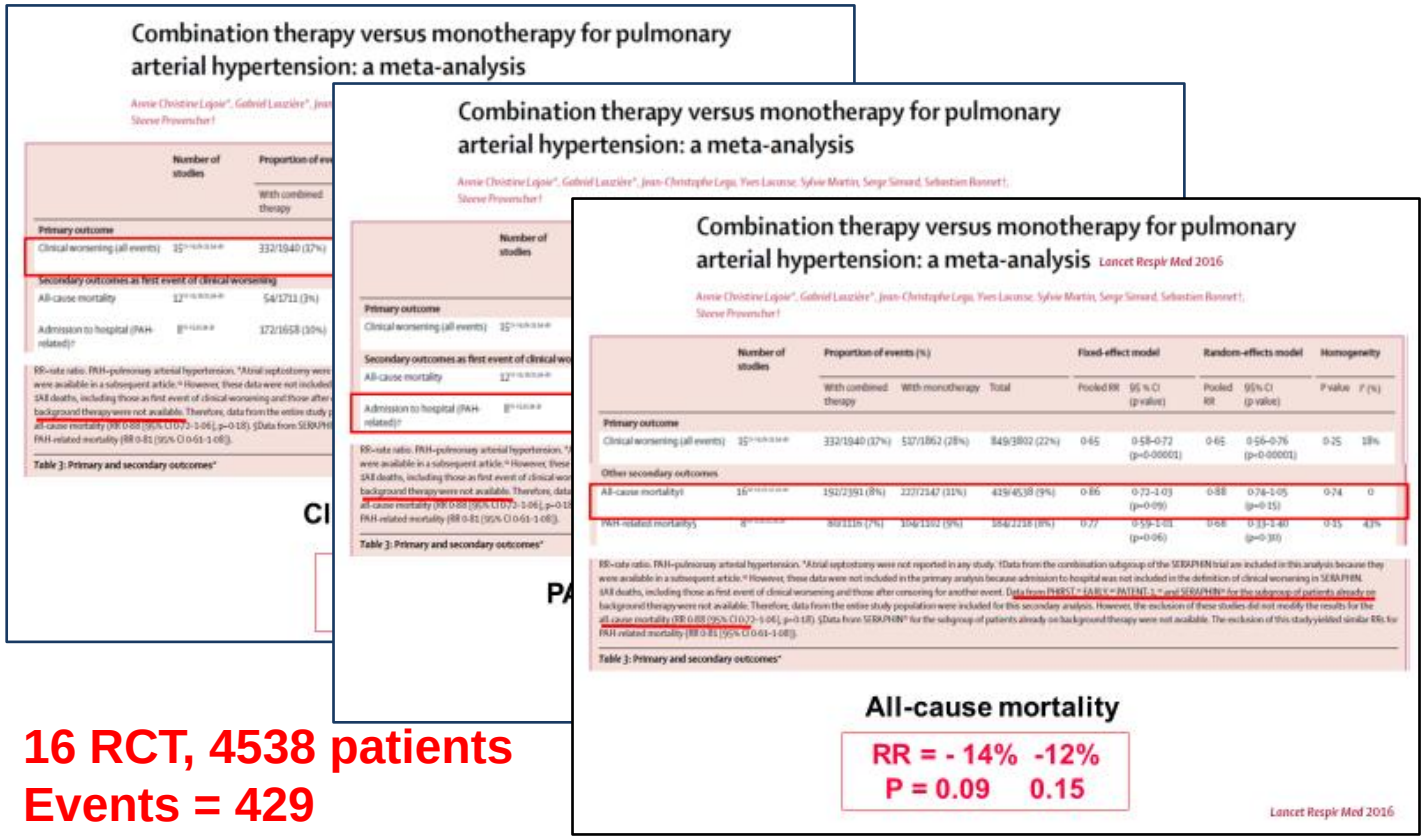
Meta-analyses comparison on all-cause mortality

MONOTHERAPY



25 RCTs, 3839 patients
Events = 86
Average Mortality = 2.5%
Average Exposure Period = 14.2 weeks

SEQUENTIAL COMBINATION



16 RCT, 4538 patients
Events = 429
Average Mortality = 9%
Average Exposure Period = 36.9 weeks

Slide courtesy of Nazzareno Galiè

Initial combination therapy: What is the evidence?

Measure/ treatment	Class[a]-Level[b]					
	WHO-FC II		WHO-FC III		WHO-FC IV	
Ambrisentan + tadalafil[d]	I	B	I	B	IIb	C
Other ERA + PDE-5i	IIa	C	IIa	C	IIb	C
Bosentan + sildenafil + i.v. epoprostenol	-	-	IIa	C	IIa	C
Bosentan + i.v. epoprostenol	-	-	IIa	C	IIa	C
Other ERA or PDE-5i + s.c. treprostinil			IIb	C	IIb	C
Other ERA or PDE-5i + other i.v. prostacyclin analogues			IIb	C	IIb	C

- 2 **RCTs** + 1 ongoing

- 2 open-label studies
- Small observational studies

AMBITION: Galiè N, *et al. N Engl J Med* 2015.

Hassoun P, *et al. Am J Respir Crit Care Med* 2015.

Sitbon O, *et al. Eur Respir J* 2016.
Joint-INTENTION; OPTIMA

Sitbon O, *et al. Eur Respir J.* 2014.

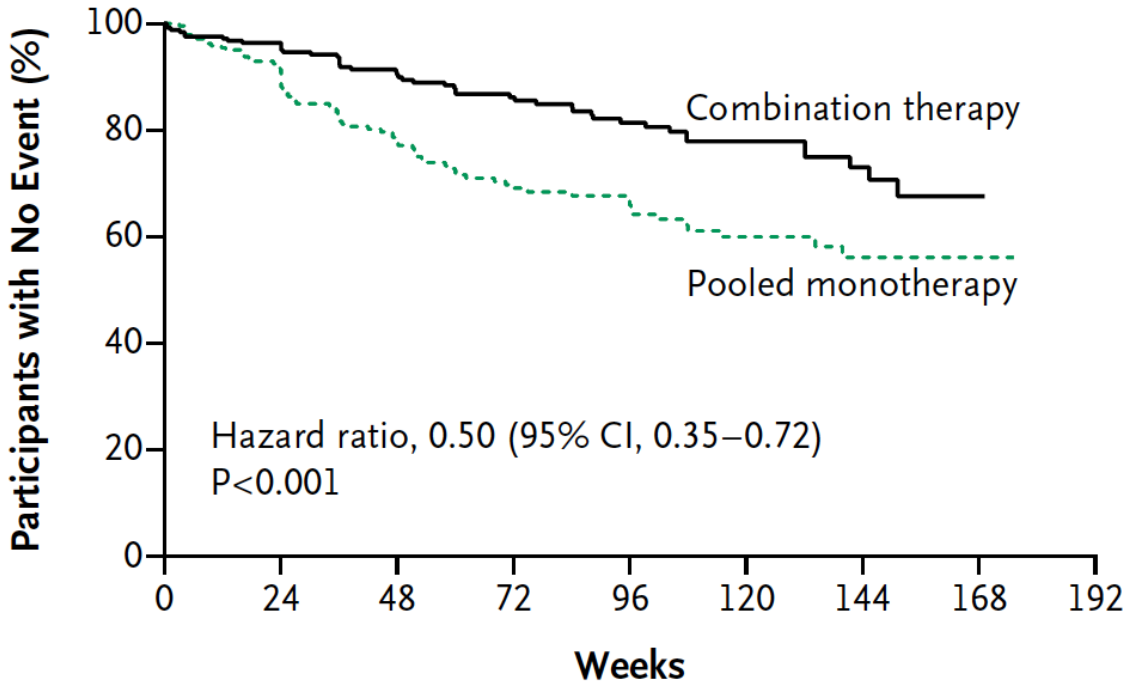
BREATHE-2: Humbert M, *et al. Eur Respir J.* 2004.
Kemp K, *et al*. *J Heart Lung Transplant* 2012.

TRITON study (macitentan, tadalafil, ± selexipag) ongoing

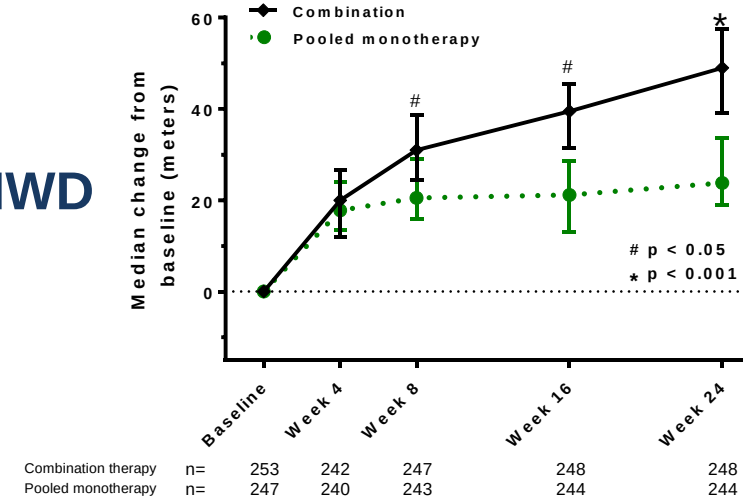
Galiè N, Humbert M, *et al. Eur Respir J* 2015;46:903–75; *Eur Heart J* 2016;37:67–119.

AMBITION: Initial combo of ambrisentan AND tadalafil is superior to monotherapy with ambrisentan OR tadalafil

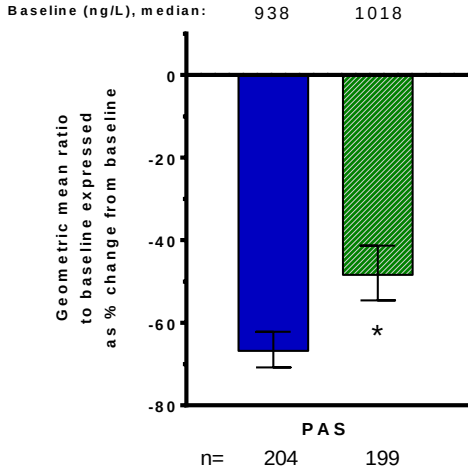
- N=500 treatment-naïve patients with PAH (31% FC II)
- **Primary endpoint**: Time to the first occurrence of a composite endpoint of death, hospitalization for PAH worsening, disease progression, or unsatisfactory long-term clinical response



6MWD



NT-ProBNP



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 of ambrisentan and tadalafil in SSc-associated 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.

Initial dual oral combination in PAH: *A matter of drugs or strategy?*

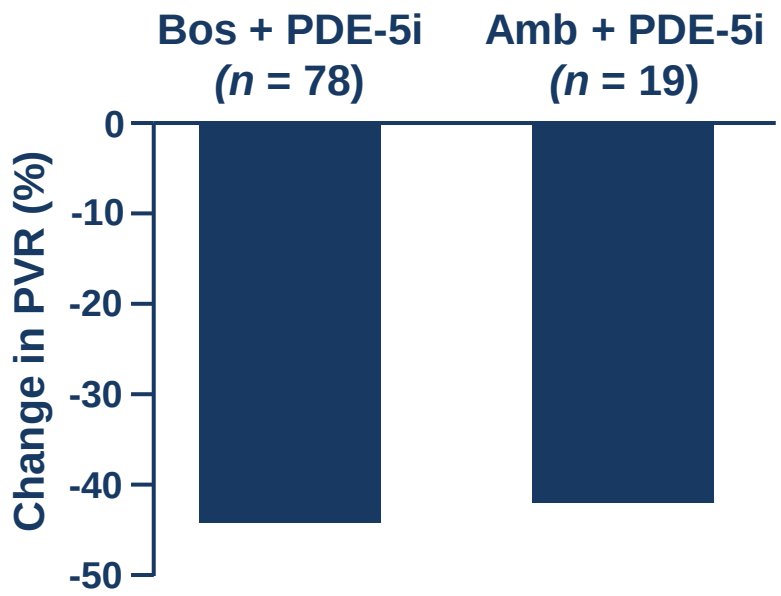
	AMBITION–BONSAI* Ambrisentan + tadalafil (n=19)[1]	Joint–INTENTION# Bosentan + sildenafil (n=23)[2]	French Network Cohort ERA + PDE5i (n=97)[3]	OPTIMA Macitentan + tadalafil (n=46)
Δ RAP (%)	-17	- 36	-29	-4
Δ mPAP (%)	-33	- 21	-16 (-10 mmHg)	-16 (-8 mmHg)
Δ CI (%)	+56	+63	+46 (+1 L/min/m^2)	+41 (+0.9 L/min/m^2)
Δ PVR (%)	-61	-60	-43 (from 12.7 WU)	-47 (from 11.7 WU)
Δ 6MWD (%)	+25	+ 42	+22 (+71 m)	+10 (+36 m)

*BONSAI: BOlogNa Sub-study on hAemodynamIcs

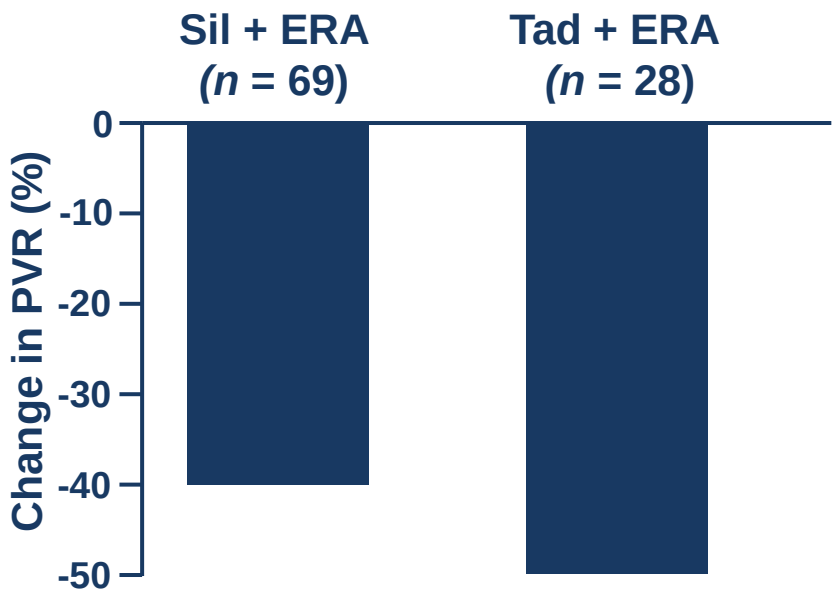
#Joint Bologna and Calgary study on INiTial bosENTan plus sIldenafil in pulmonary arterial hypertension.

1. Bachetti C *et al. Am J Respir Crit Care Med* 2015;191:A479.
2. Palazzini M *et al. Am J Respir Crit Care Med* 2016;193:A6317.
3. Sitbon O *et al. Eur Respir J* 2016;47:1727–36.

The strategy works with different combinations



p = 0.74



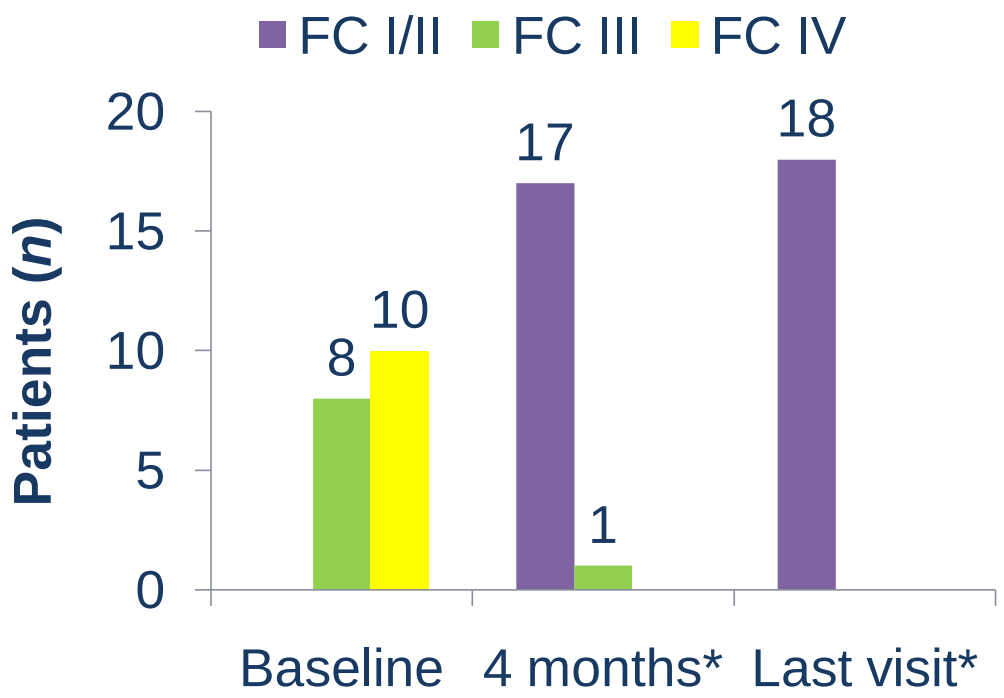
p = 0.03

Mean ± SD	-44% ± 20%	-42% ± 21%
95%CI	[-48%; -39%]	[-51%; -32%]

Sitbon O, *et al. Eur Respir J* 2016; 47: 1727–1736.

Beyond double oral combination therapy: Initial triple combination therapy in severe PAH

Prospective, observational analysis of idiopathic or heritable PAH patients (*n* = 18) treated with triple initial combination therapy (epoprostenol, bosentan and sildenafil)



	Baseline	4-month	Last visit (32 ± 19 months)
RAP (mmHg)	11.9 ± 5.2	4.9 ± 4.9*	5.2 ± 3.5*
mPAP (mmHg)	65.8 ± 13.7	45.7 ± 14.0*	44.4 ± 13.4*
CI (l/min/m^2)	1.66 ± 0.35	3.49 ± 0.69*	3.64 ± 0.65*
PVR (d.s.cm^{-5})	1718 ± 627	564 ± 260*	492 ± 209*
SvO_2 (%)	51.0 ± 8.5	69.7 ± 5.2*	72.2 ± 4.0*

*p < 0.01 versus baseline

Median follow-up: 6.8 years [*Q1–Q3: 6.4 – 8.0*]
One death (30 months) & Two lung transplantations (4 & 41 months)
Transplant-free survival= 84% @ 5 years

Sitbon O, *et al. Eur Respir J.* 2014;43:1691–7.

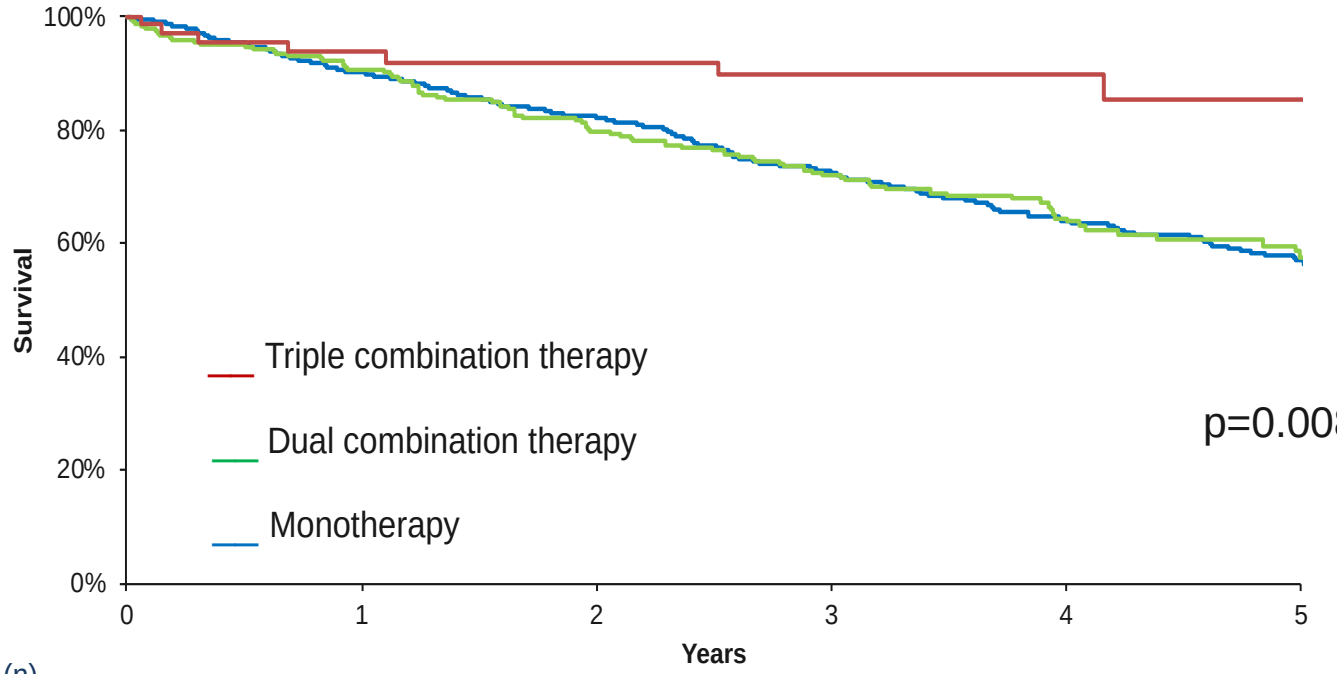
Impact of initial treatment strategy on survival

French Registry (2006-2016)

1295 / 1591 patients initiated with PAH-targeted therapy

46% of patients initiated with monotherapy have been escalated to double or triple combination within the first 2 years of follow-up

27% of patients on initial double combination escalated to triple combination within the first 2 years



Patients, at risk (n)						
Monotherapy	814	577	462	343	244	175
Dual combo.	410	274	202	148	91	54
Triple combo.	71	54	41	34	23	15

Boucly A, *et al. Presented at ATS Conference 2019*.

Impact of initial treatment strategy on survival

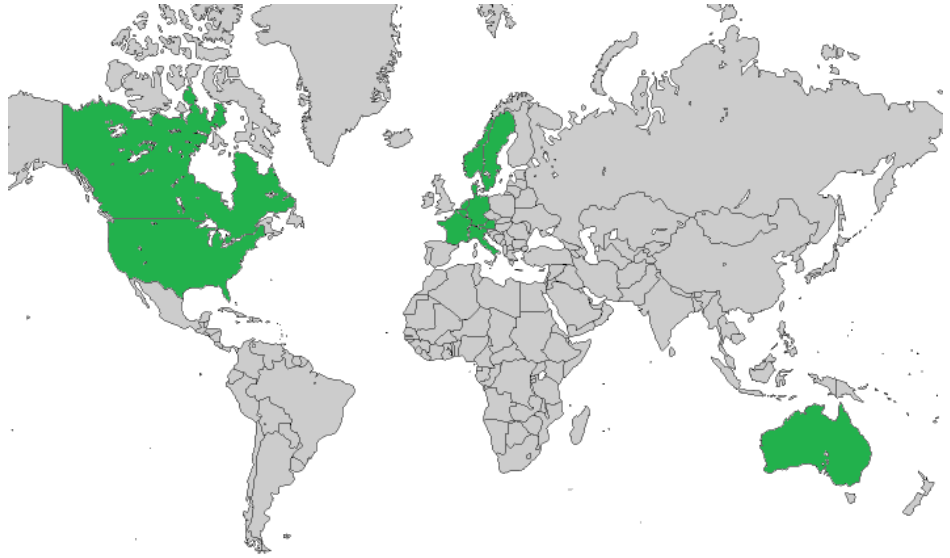
n= 1295	Monotherapy n=814	Dual combo n=410	Triple combo n=71	P-value
Age, *years*	64 ± 15	57 ± 18	41 ± 16	<0.001
NYHA FC II : III : IV, *%*	26 : 63 : 11	15 : 64 : 21	3 : 53 : 44	<0.001
mPAP, *mmHg* **CI**, *L/min/m²* **PVR**, *WU*	46 ± 11 2.5 ± 0.7 9 ± 5	53 ± 12 2.2 ± 0.6 12 ± 6	62 ± 16 1.8 ± 0.5 19 ± 8	<0.001 <0.001 <0.001

Multivariate analysis	HR	95% CI	P-value
Age	1.040	1.030 – 1.050	0.001
Sex (female)	0.470	0.370 – 0.600	0.001
NYHA functional class IV	2.090	1.320 – 3.310	0.007
6MWD	0.996	0.995 – 0.998	0.001
Initial triple combination incl. parenteral PGI_2	0.320	0.120 – 0.900	0.030

Boucly A, *et al. Presented at ATS Conference 2019*.

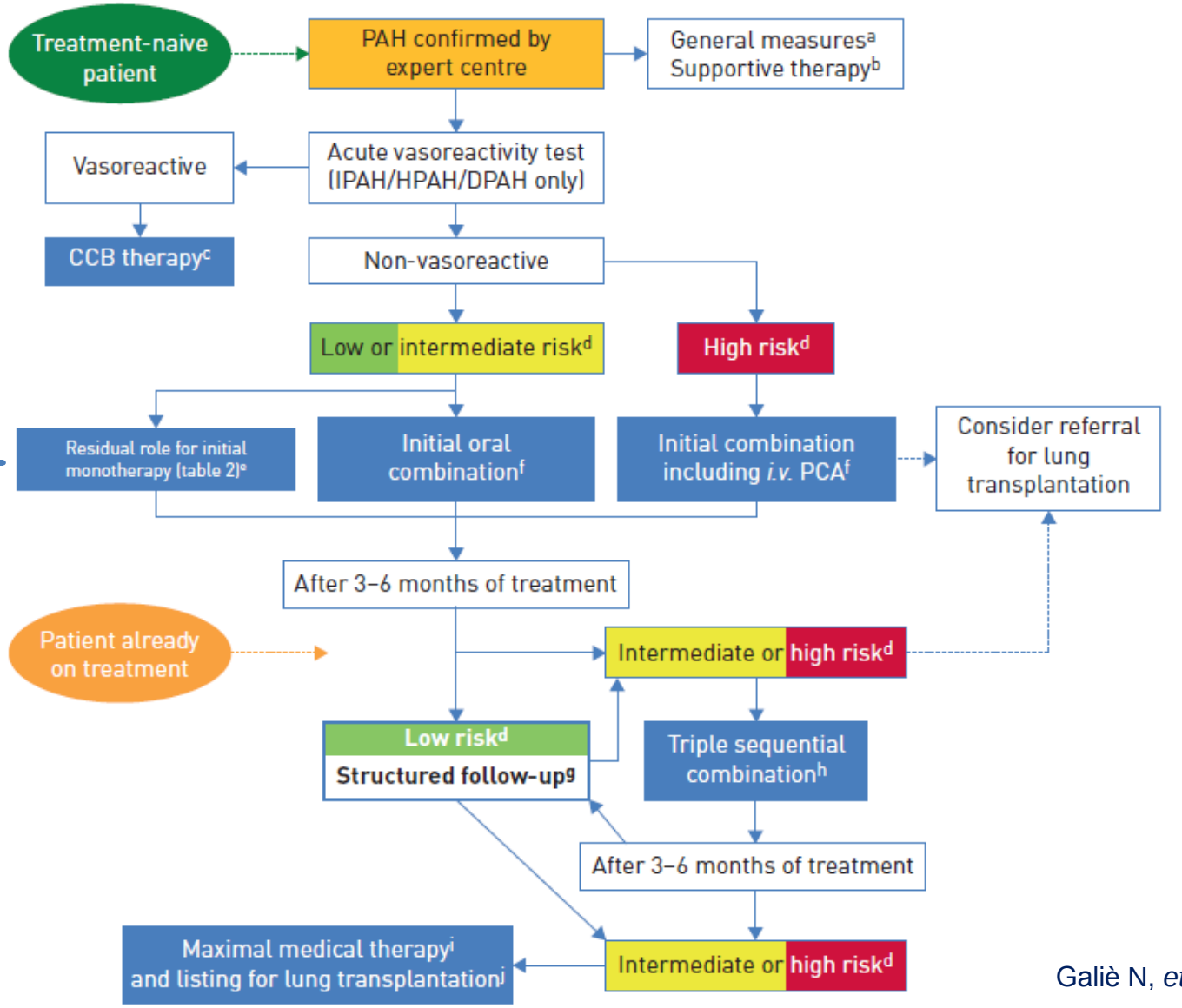
Initial triple oral combination therapy

- Prospective, multicenter, double-blind, randomized, placebo-controlled, parallel-group Phase IIIb study
- To assess the efficacy and safety of initial triple *vs* initial dual oral combination therapy in patients with newly diagnosed treatment-naïve PAH
- 238 patients randomized
  - macitentan + tadalafil + selexipag
  - *vs* macitentan + tadalafil + *placebo*
- 57 sites in 13 countries
- Key results expected in Q4 2019



Risk assessment plays a prominent role in the newly proposed treatment algorithm from WSPH

- **PAH > 75 yo with multiple risk factors for HFpEF**
- High probability of **PVOD/PCH**
- **HIV, PoPH, uncorrected CHD**
- **Very mild disease**
- **Combination therapy unavailable** or contraindicated



Galiè N, *et al*. *Eur Respir J* 2019; 53: 1801889.

With many strategies available it is important to identify the best approach for each individual patient

Comorbidities

Age

Lifestyle

Cognitive functioning

Motivation

Concomitant medications

Family support

Health literacy

Take-home messages

- Risk stratification
  - The “low-risk” designation requires a precise definition (Multi-parameter risk assessment) and is an appropriate goal for therapy that should be to achieve at any time
- Treatment strategies
  - Many drugs available… but strategies are more important than drugs
  - Strategy of sequential combination therapy with available medications has a positive impact on disease progression
  - Initial dual oral combination therapy with ERA and PDE5i is superior to monotherapy in FC II-III patients and is becoming the “gold standard”
  - Initial double/triple combination therapy including parenteral PGI_2 is notably effective in severe PAH patients (FC IV and some III with high risk profile) and improves survival