Treatment algorithm in pulmonary arterial hypertesion

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European Reference Network
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Conflict of interest disclosure

Affiliation / Financial interest	Commercial Company
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A story of treatment algorithms in PAH

WPHS 2003

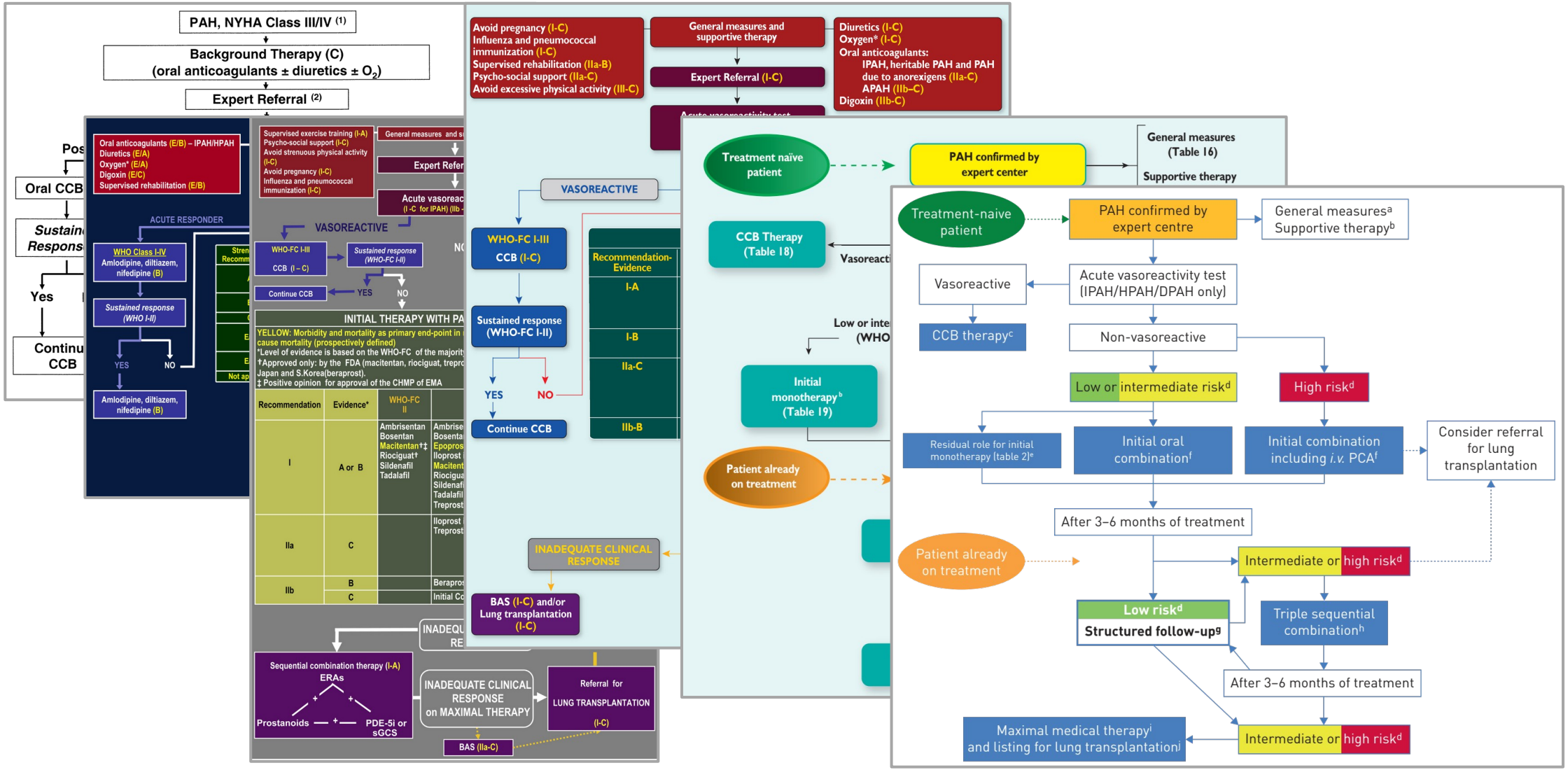
WPHS 2008

WPHS 2013

ESC-ERS Guidelines 2009

ESC-ERS Guidelines 2015

WPHS 2018



Galiè N, *et al. J Am Coll Cardiol* 2004;43:81S–88S; Barst RJ, *et al. J Am Coll Cardiol* 2009;54:S78–84. Galiè N, *et al. J Am Coll Cardiol* 2013;62:D60–72.. Galiè N, *et al. Eur Heart J* 2009; 30: 2493–2537.

Treatment algorithm for patients with idiopathic, heritable, drug-associated, and CTD-associated PAH

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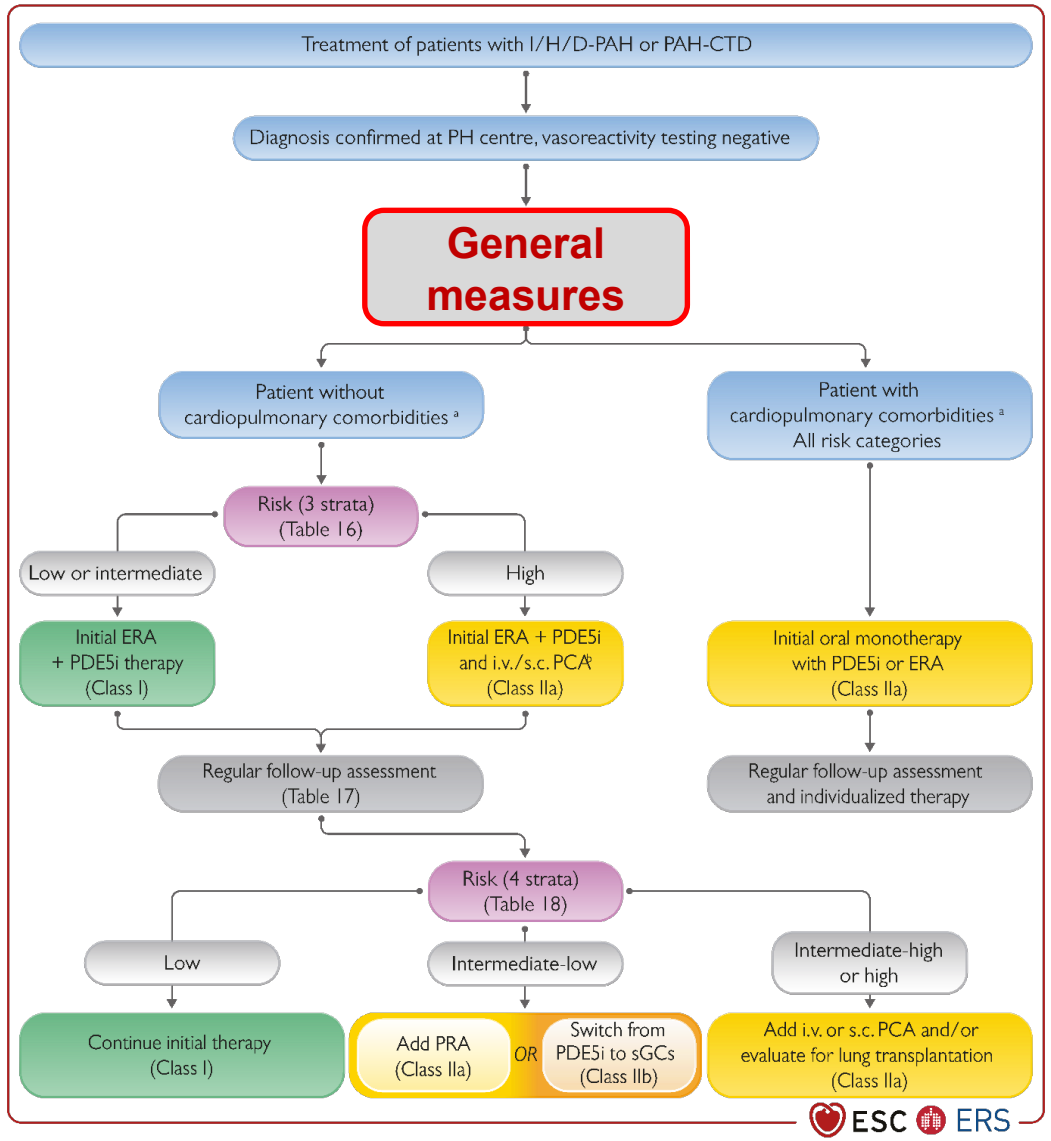
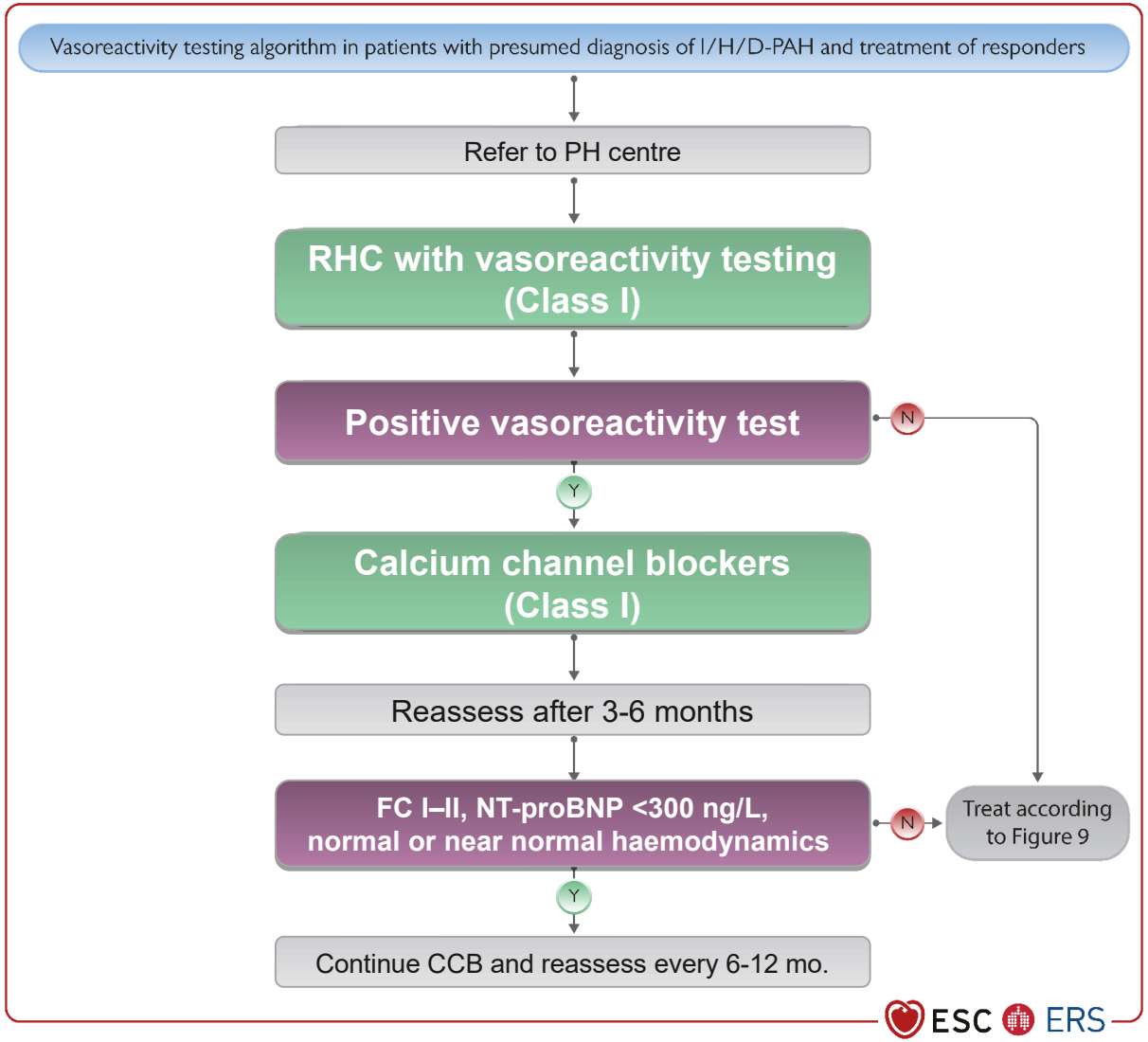


Recommendations	Class	Level
Supervised exercise training is recommended in patients with PAH under medical therapy	I	A
Psychosocial support is recommended in patients with PAH	I	C
Immunization of patients with PAH against SARS-CoV2, influenza, and *Streptococcus pneumoniae* is recommended	I	C
Diuretic treatment is recommended in patients with PAH with signs of RV failure and fluid retention	I	C
Long-term oxygen therapy is recommended in patients with PAH whose arterial blood oxygen pressure is <8 kPa (60 mmHg)	I	C
In the presence of iron-deficiency anaemia, **correction of iron status** is recommended in patients with PAH	I	C
Anticoagulation is not generally recommended in patients with PAH but may be considered on an individual basis	IIb	C

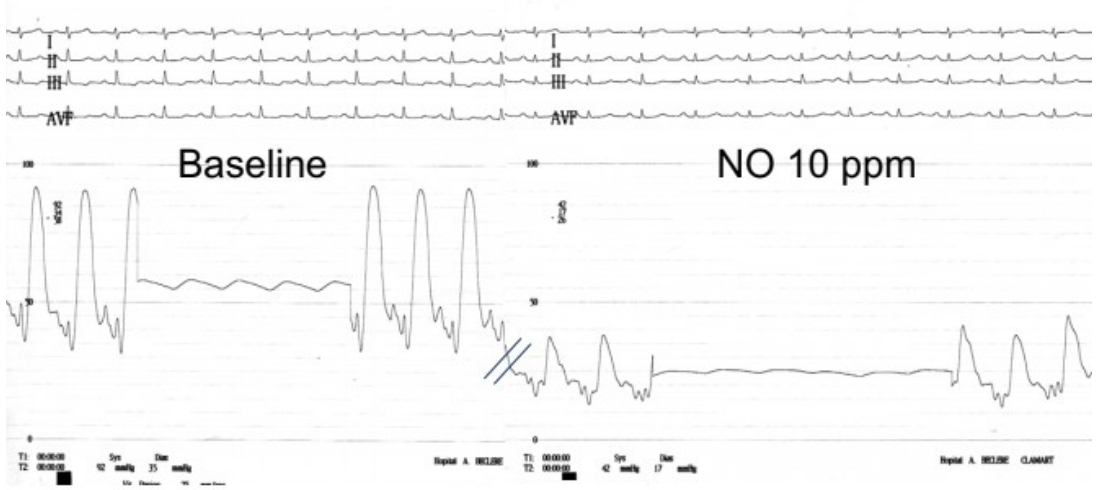
Humbert M *et al. Eur Respir J* 2022; *in press*: 2200879; Humbert M, *et al. Eur Heart J* 2022; 43: 3618-3731.

Vasoreactivity testing algorithm of patients with presumed diagnosis of idiopathic, heritable, or drug-associated PAH



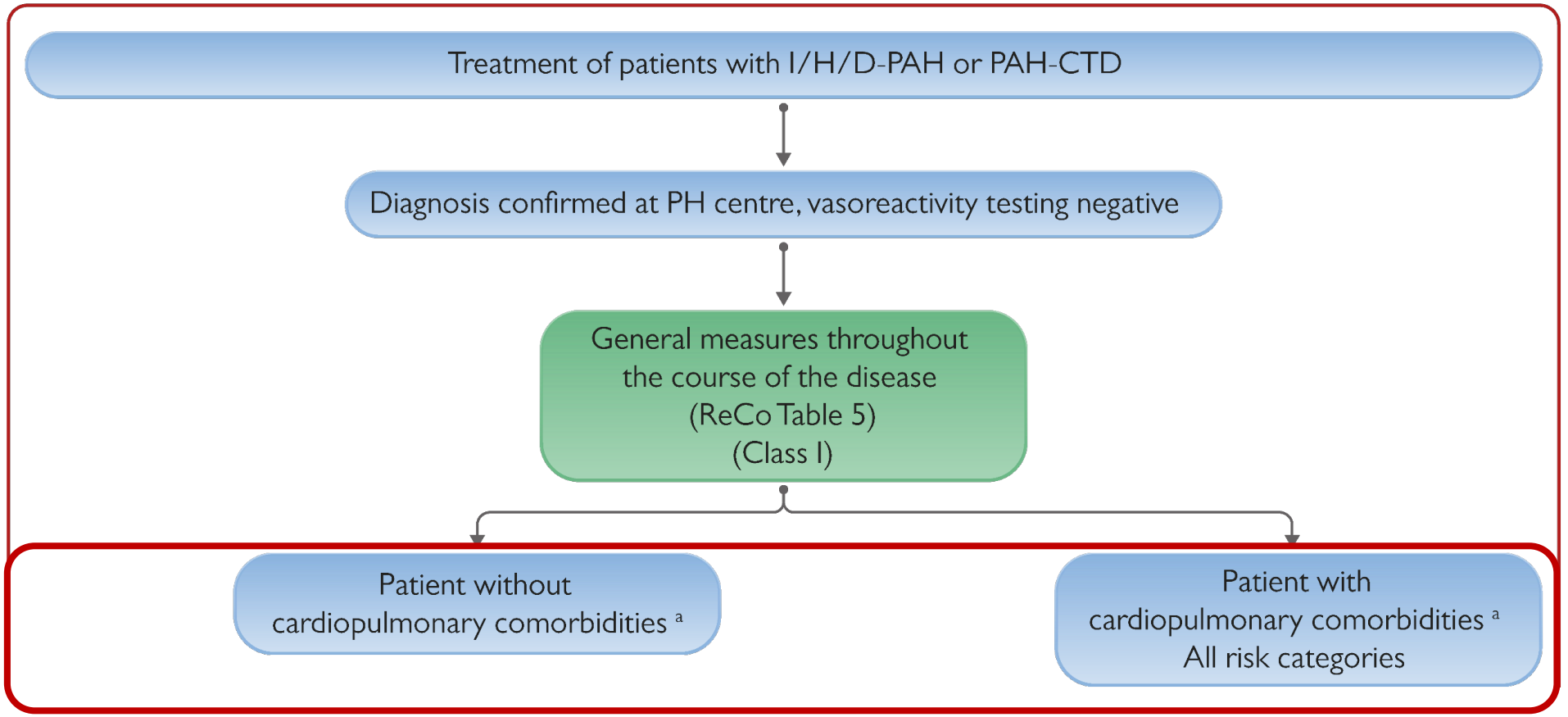
Compound	Route	Half-life	Dosage	Duration
Nitric oxide	inh	15–30 s	10–20 p.p.m.	5–10 min
Iloprost	inh	30 min	5–10 µg	10–15 min
Epoprostenol	i.v.	3 min	2–12 ng/kg/min	10 min

Positive vasoareactivity test
≥ 10 mmHg mPAP drop from baseline to ≤ 40 mmHg,
Without decrease in CO/CI



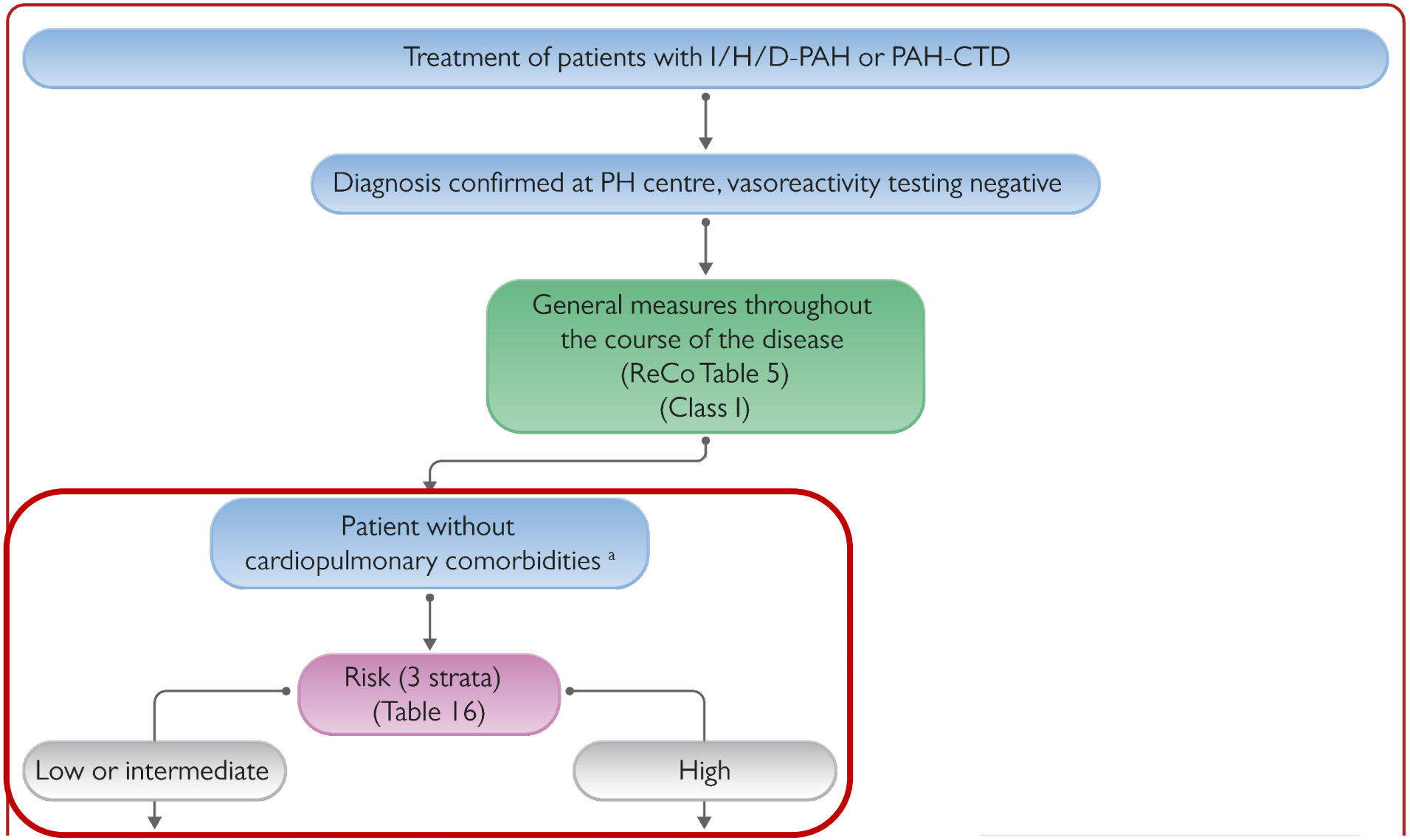
Humbert M *et al. Eur Respir J* 2022; *in press*: 2200879; Humbert M, *et al. Eur Heart J* 2022; 43: 3618-3731.

Recommendations for initial therapy



Humbert M *et al. Eur Respir J* 2022; *in press*: 2200879; Humbert M, *et al. Eur Heart J* 2022; 43: 3618-3731.

Recommendations for patients without comorbidities



Humbert M *et al. Eur Respir J* 2022; *in press*: 2200879; Humbert M, *et al. Eur Heart J* 2022; 43: 3618-3731.

Updated risk stratification table

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Recommendations	Class	Level
For risk stratification **at the time of diagnosis**, the use of a **three-strata model** (low, intermediate, and high risk) is recommended, taking into account all available data including haemodynamics	I	B

Determinants of prognosis (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–20%	High risk >20%
Signs of right heart failure	Absent	Absent	Present
Progression of symptoms and clinical manifestations	No	Slow	Rapid
Syncope	No	Occasional syncope	Repeated syncope
WHO-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	Peak VO_2 <11 mL/min/kg (<35% pred.) VE/VCO_2 slope >44
BNP or NT-proBNP	BNP <50 ng/L NT-proBNP <300 ng/L	BNP 50–800 ng/L NT-proBNP 300–1100 ng/L	BNP >800 ng/L NT-proBNP >1100 ng/L
Echocardiography	RA area <18 cm^2 TAPSE/sPAP >0.32 mm/mmHg No pericardial effusion	RA area 18–26 cm^2 TAPSE/sPAP 0.19–0.32 mm/mmHg Minimal pericardial effusion	RA area >26 cm^2 TAPSE/sPAP <0.19 mm/mmHg Moderate or large pericardial effusion
cMRI	RVEF >54% SVI >40 mL/m^2 RVESVI <42 mL/m^2	RVEF 37–54% SVI 26–40 mL/m^2 RVESVI 42–54 mL/m^2	RVEF <37% SVI <26 mL/m^2 RVESVI >54 mL/m^2
Haemodynamics	RAP <8 mmHg CI ≥2.5 $L/min/m^2$ SVI >38 mL/m^2 SvO_2 >65%	RAP 8–14 mmHg CI 2.0–2.4 $L/min/m^2$ SVI 31–38 mL/m^2 SvO_2 60–65%	RAP >14 mmHg CI <2.0 $L/min/m^2$ SVI <31 mL/m^2 SvO_2 <60%

Humbert M *et al. Eur Respir J* 2022; *in press*: 2200879; Humbert M, *et al. Eur Heart J* 2022; 43: 3618-3731.

Risk assessment (3-strata model) - changes

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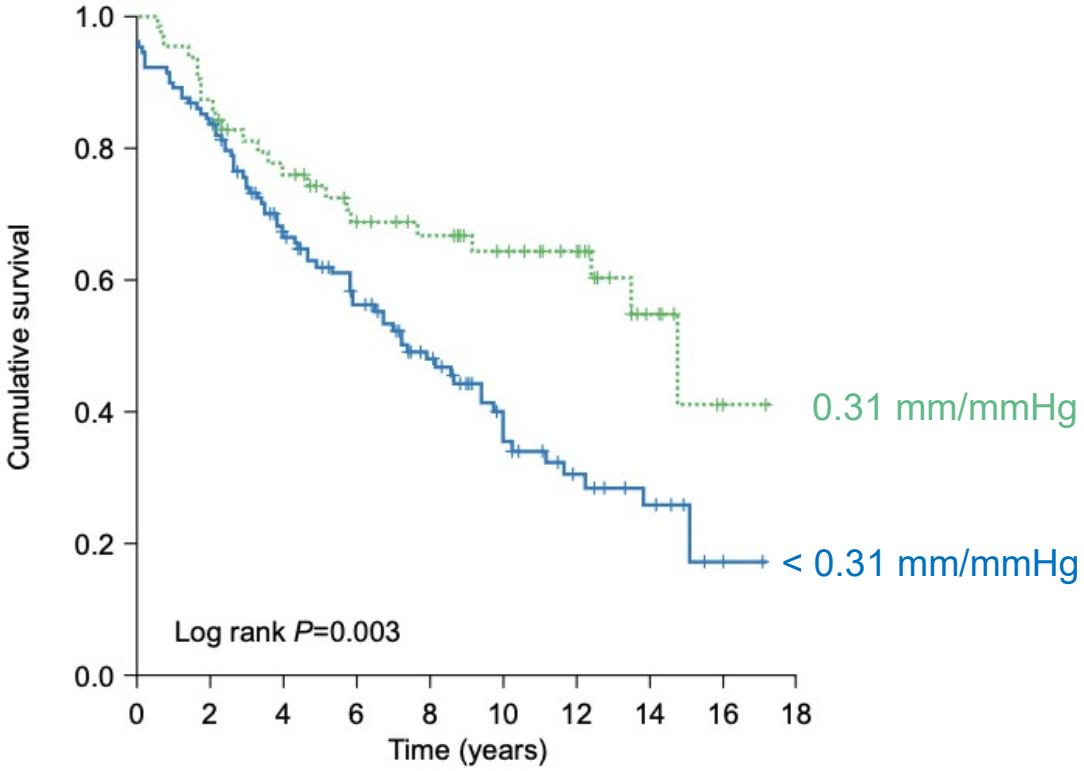
Determinants of prognosis	Low risk <5%	Intermediate risk 5–20%	High risk >20%
Biomarkers: BNP or NT-proBNP	BNP <50 ng/L NT-proBNP <300 ng/L	BNP 50–**800** ng/L NT-proBNP 300–**1100** ng/L	BNP >**800** ng/L NT-proBNP >**1100** ng/L
Echocardiography	RA area <18 cm2 **TAPSE/sPAP** **>0.32 mm/mmHg** No pericardial effusion	RA area 18–26 cm2 **TAPSE/sPAP** **0.19–0.32 mm/mmHg** Minimal pericardial effusion	RA area >26 cm2 **TAPSE/sPAP** **<0.19 mm/mmHg** Moderate or large pericardial effusion
cMRI	**RVEF >54%** **SVI >40 mL/m²** **RVESVI <42 mL/m²**	**RVEF 37–54%** **SVI 26–40 mL/m²** **RVESVI 42–54 mL/m²**	**RVEF <37%** **SVI <26 mL/m²** **RVESVI >54 mL/m²**
Haemodynamics	RAP <8 mmHg CI ≥2.5 L/min/m2 **SVI >38 mL/m²** SvO_2 >65%	RAP 8–14 mmHg CI 2.0–2.4 L/min/m2 **SVI 31–38 mL/m²** SvO_2 60–65%	RAP >14 mmHg CI <2.0 L/min/m2 **SVI <31 mL/m²** SvO_2 <60%

Humbert M *et al. Eur Respir J* 2022; *in press*: 2200879; Humbert M, *et al. Eur Heart J* 2022; 43: 3618-3731.

Advanced risk stratification using TAPSE/sPAP (RV-PA coupling) as a prognostic marker

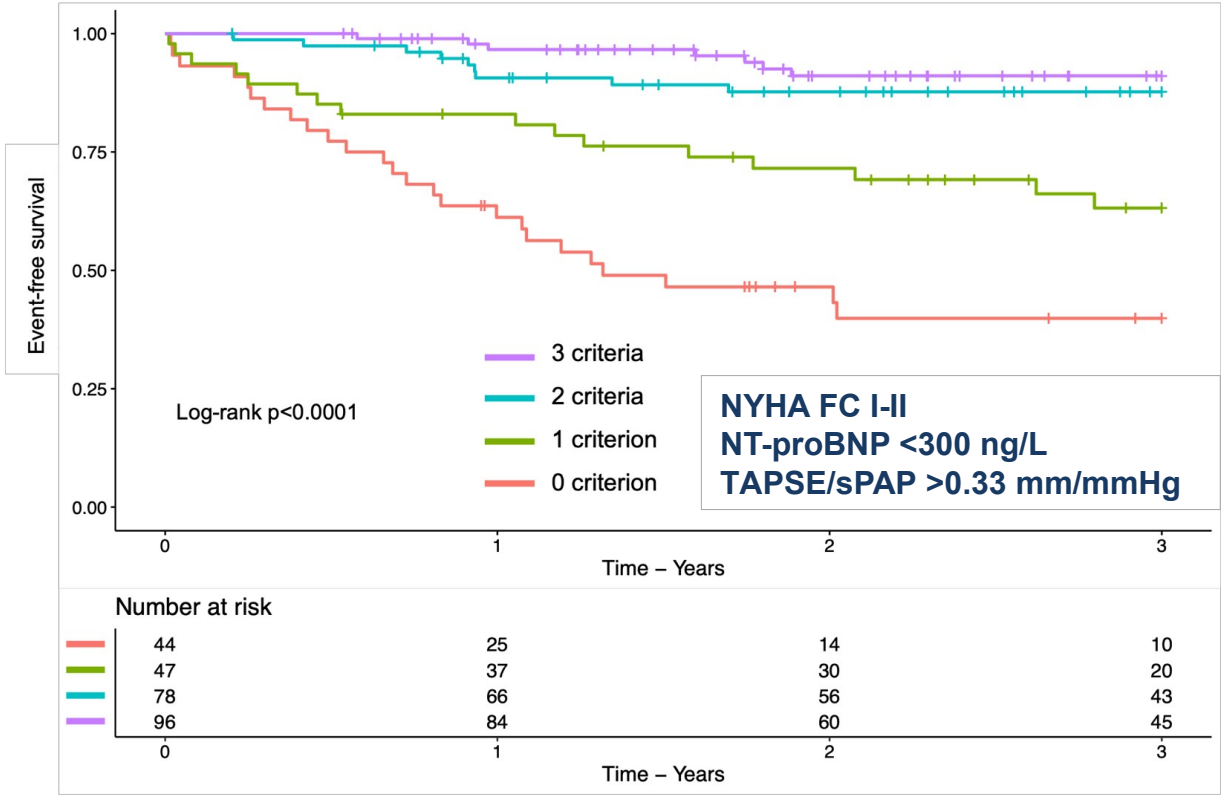
Survival according to TAPSE/sPAP cut-off



Number at risk	1 year	3 years	5 years
<0.31 mm/mm Hg	115	92	68
≥0.31 mm/mm Hg	61	49	41

Tello K, *et al. Circ Cardiovasc Imaging*. 2019; 12: e009047.

Survival according to the number of non-invasive low-risk criteria achieved at first re-evaluation



Fauvel C, *et al. J Heart Lung Transplant* 2022; *in press*.

Prognostic value of Cardiac MRI: RVESVi and RVEF

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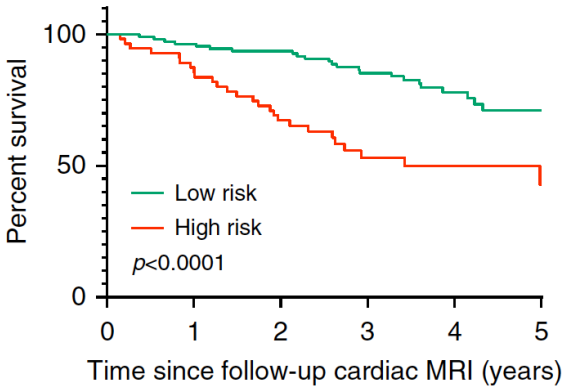
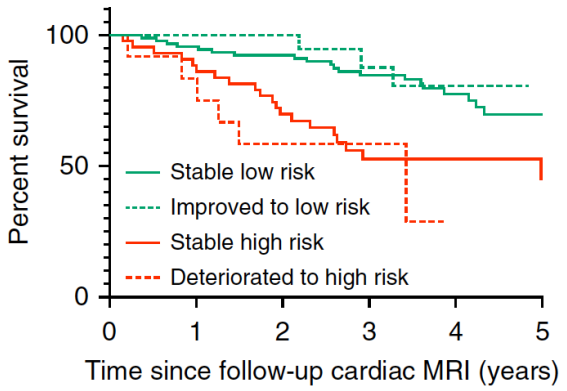
Determinants of prognosis	Low risk <5%	Intermediate risk 5–20%	High risk >20%
cMRI	**RVEF >54%** SVI >40 mL/m² **RVESVI <42 mL/m²**	**RVEF 37–54%** SVI 26–40 mL/m² **RVESVI 42–54 mL/m²**	**RVEF <37%** SVI <26 mL/m² **RVESVI >54 mL/m²**

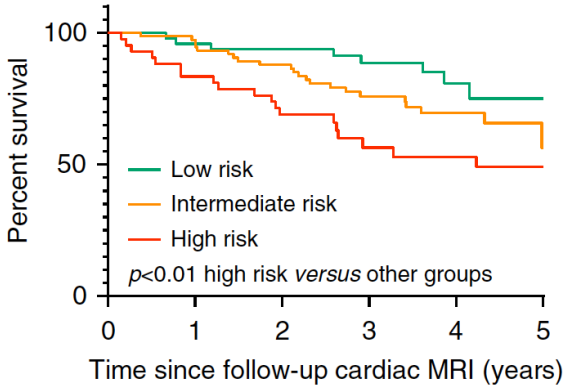
RVESVi at follow-up



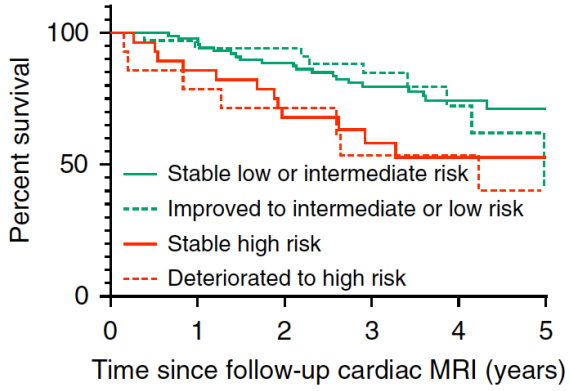
Change in RVESVi



RVEF at follow-up



Change in RVEF



Lewis RA, *et al. Am J Respir Crit Care Med* 2020; 201: 458-68; Humbert M *et al. Eur Respir J* 2022; *in press*: 2200879; Humbert M, *et al. Eur Heart J* 2022; 43: 3618-3731.

Stroke Volume Index is an important prognostic marker

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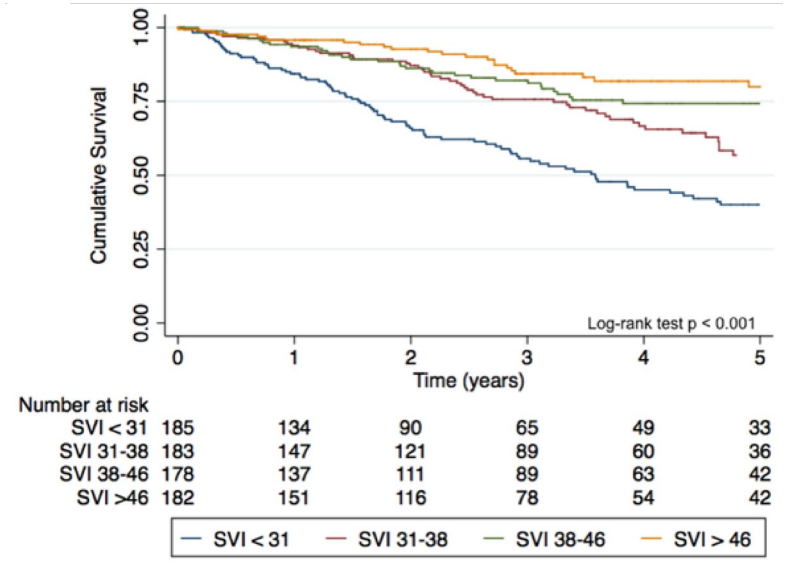
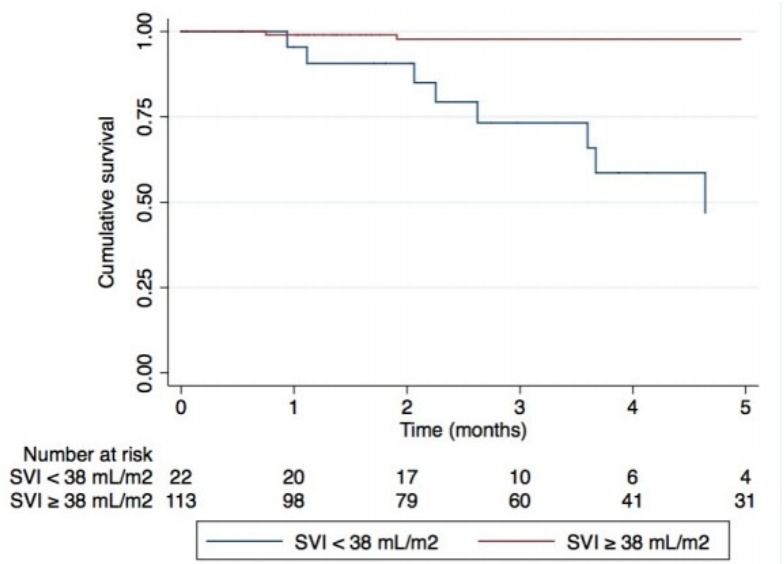
Determinants of prognosis (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–20%	High risk >20%
Haemodynamics	RAP <8 mmHg CI ≥2.5 L/min/m2 **SVI >38 mL/m²** SvO2 >65%	RAP 8–14 mmHg CI 2.0–2.4 L/min/m2 **SVI 31–38 mL/m²** SvO2 60–65%	RAP >14 mmHg CI <2.0 L/min/m2 **SVI <31 mL/m²** SvO2 <60%





Weatherald J, *et al. Circulation* 2018;137:693–704; Humbert M *et al. Eur Respir J* 2022; *in press*: 2200879; Humbert M, *et al. Eur Heart J* 2022; 43: 3618-3731.

Current therapeutic targets of PAH

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Endothelin-receptor antagonists

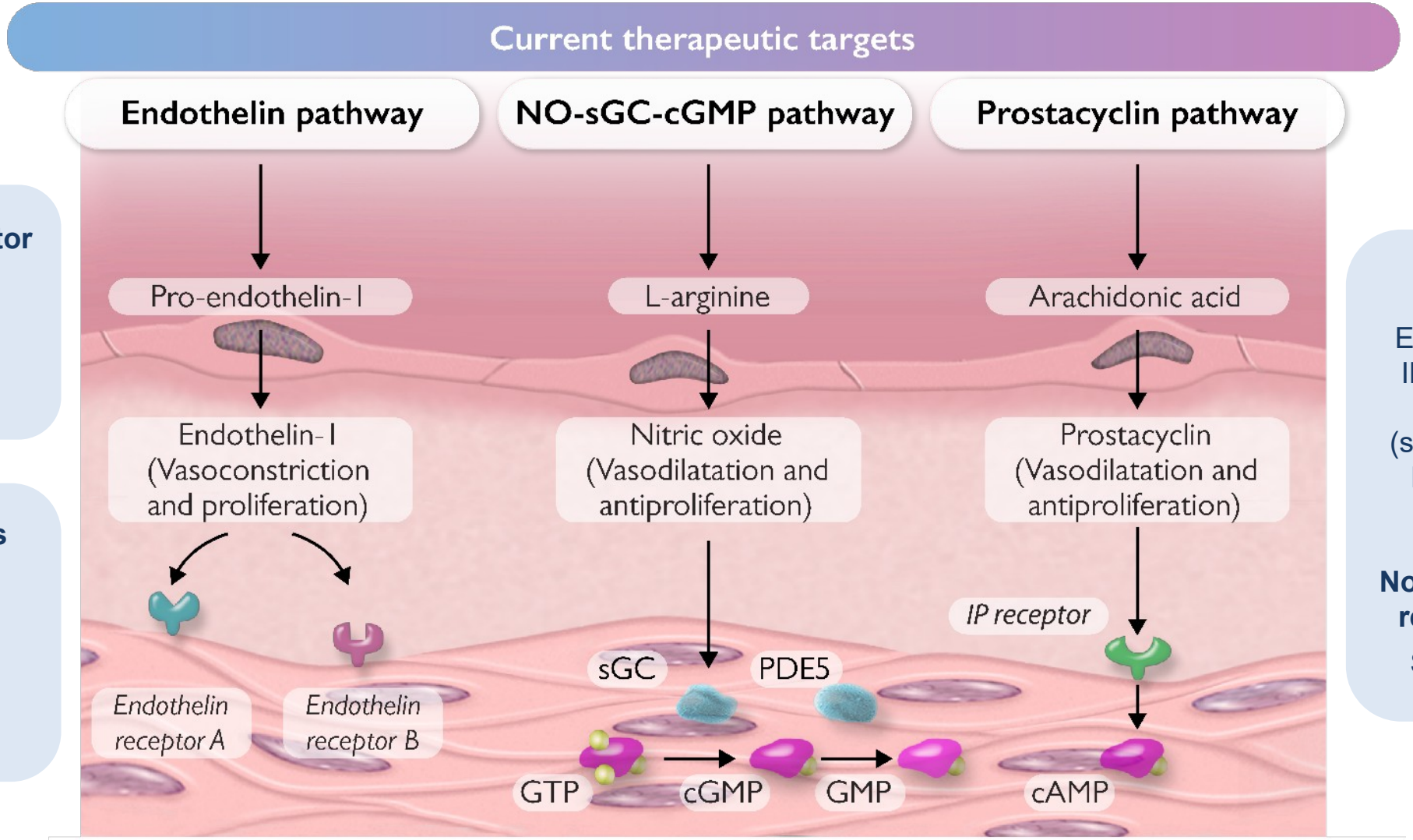
Ambrisentan
Bosentan
Macitentan

PDE-5 inhibitors

Sildenafil
Tadalafil

sGC stimulator

Riociguat



Prostanoids

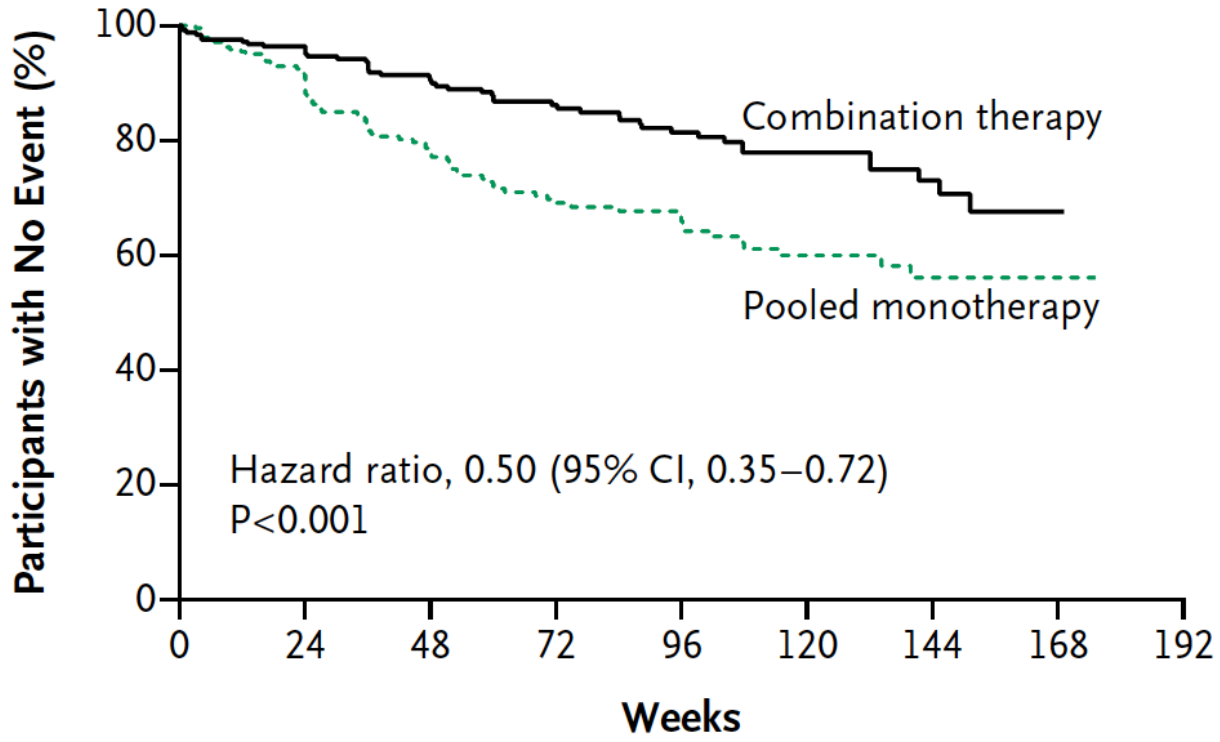
Epoprostenol (i.v.)
Iloprost (inh., i.v.)
Treprostinil (s.c., i.v., inh., oral)
Beraprost (oral)

Non prostanoids IP receptor agonist

Selexipag (oral)

Humbert M *et al. Eur Respir J* 2022; *in press*: 2200879; Humbert M, *et al. Eur Heart J* 2022; 43: 3618-3731.

INITIAL THERAPY: Initial combination of ambrisentan AND tadalafil is superior to monotherapy with ambrisentan OR tadalafil



No. at Risk

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

- **AMBITION study**
- 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

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

Initial dual oral combination in PAH:
A matter of strategy, not a matter of drugs…

	AMBITION–BONSAI* Ambri + tada (n=19)[1]	Ambrisentan + Tadalafil in PAH-SSc (n = 24)[2]	Joint–INTENTION# Bos + sil (n=23)[3]	French PH Network ERA + PDE-5i (n=97)[4]	OPTIMA Macitentan + tadalafil (n=46)[5]	TRITON Macitentan + tadalafil (n=124)[6]
Δ RAP (%)	- 17	- 28	- 36	- 29	- 4	- 17
Δ mPAP (%)	- 33	- 29 *(-12 mmHg)*	- 21	- 16 *(-10 mmHg)*	- 16 *(-8 mmHg)*	- 23 *(-12 mmHg)*
Δ CI (%)	+ 56	+ 27 *(+0.7 L/min/m²)*	+ 63	+ 46 *(+1 L/min/m²)*	+ 41 *(+0.9 L/min/m²)*	+ 43 *(+0.8 L/min/m²)*
Δ PVR (%)	- 61	- 51	- 60	- 43	- 47	- 52
Δ 6MWD (%)	+ 25	+ 15 *(+52 m)*	+ 42	+ 22 *(+71 m)*	+ 10 *(+36 m)*	+ 17 *(+56 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.Hassoun P, *et al. Am J Respir Crit Care Med* 2015; 192:1102-10; 3. Palazzini M *et al. Am J Respir Crit Care Med* 2016;193:A6317; 4. Sitbon O *et al. Eur Respir J* 2016;47:1727–36; 5. Sitbon O, *et al. Eur Respir J* 2020;56:2000673; 6. Chin K, *et al. J Am Coll Cardiol* 2021;78:1393-1403.

Recommendations for initial therapy in patients with PAH without comorbidities

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Recommendations for initial therapy	Class	Level

Recommendations	Class	Level
Initial combination therapy with ambrisentan and tadalafil is recommended	I	B
Initial combination therapy with macitentan and tadalafil is recommended	I	B

	GRADE			
Recommendations	Quality of evidence	Strength of recommendation	Class	Level
In patients with IPAH/HPAH/DPAH who present at low or intermediate risk of death, initial combination therapy with a PDE5i and an ERA is recommended	Low	Conditional	I	B

Humbert M *et al. Eur Respir J* 2022; *in press*: 2200879; Humbert M, *et al. Eur Heart J* 2022; 43: 3618-3731.

INITIAL THERAPY: Recommendations in patients with PAH without comorbidities

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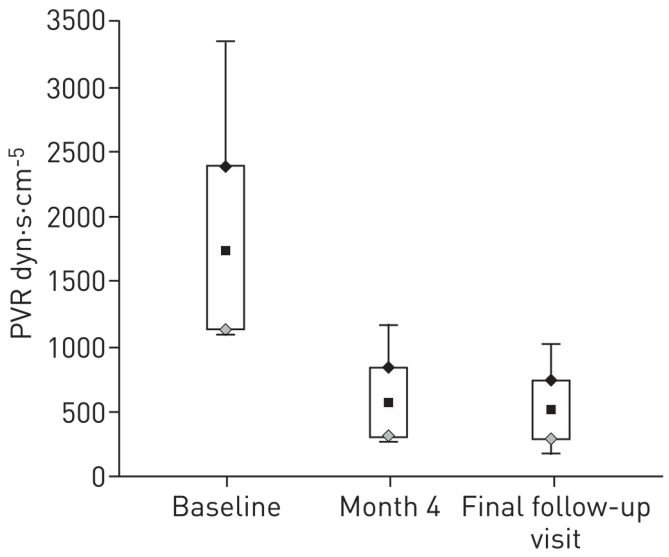
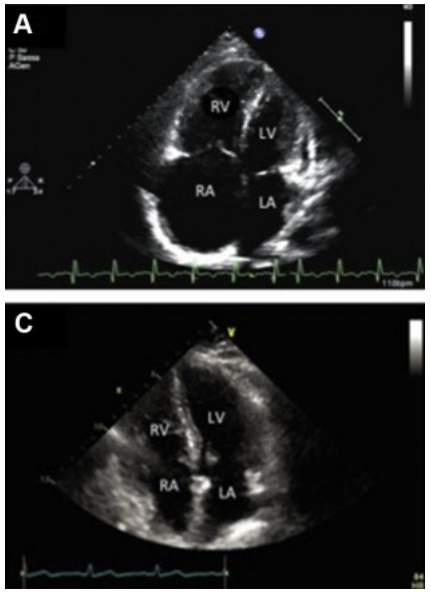
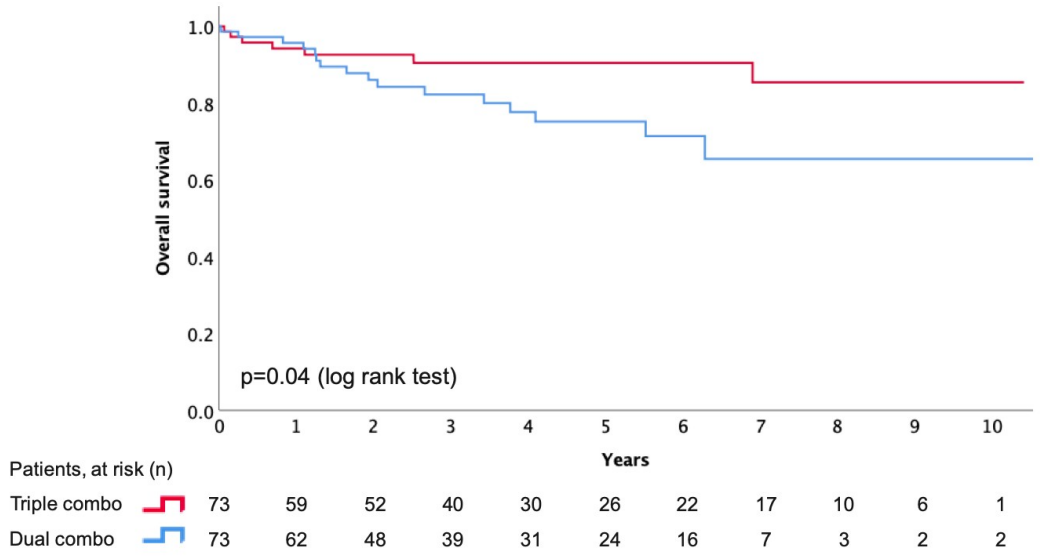
Recommendations for initial therapy	Class	Level
Patients at high risk of death		
In patients with IPAH/HPAH/DPAH who present at high risk of death, initial combination therapy with a PDE5i, an ERA, and i.v./s.c. prostacyclin analogues should be considered	IIa	C







Sitbon O, *et al. Eur Respir J* 2014; 43: 1691-1697; D'Alto M, *et al. CHEST* 2020; 157: 376-383. Boucly A, *et al. Am J Respir Crit Care Med* 2021; 204: 842-854. Humbert M *et al. Eur Respir J* 2022; *in press*: 2200879; Humbert M, *et al. Eur Heart J* 2022; 43: 3618-3731.

Recommendations for initial therapy in patients with PAH without comorbidities

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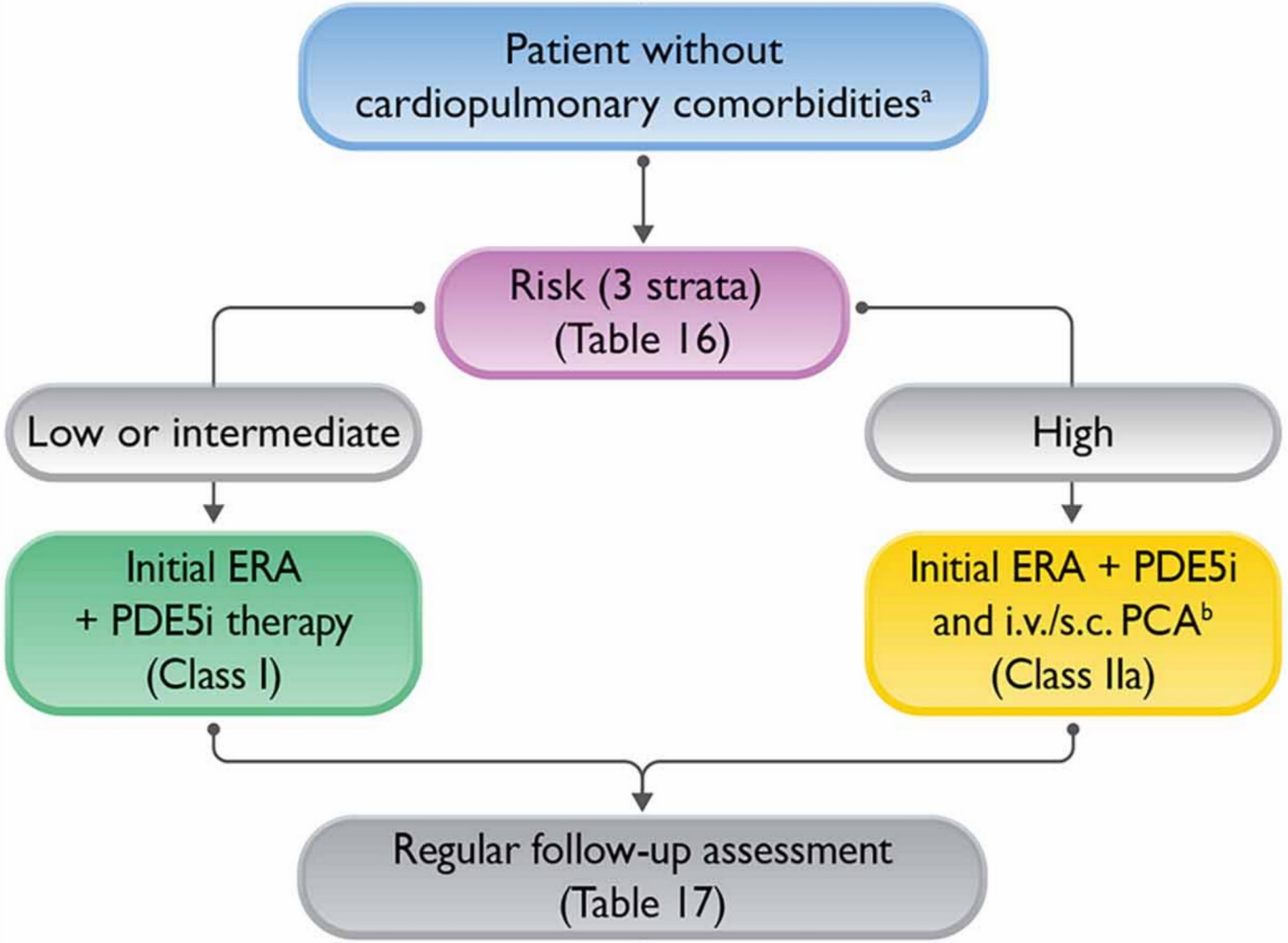
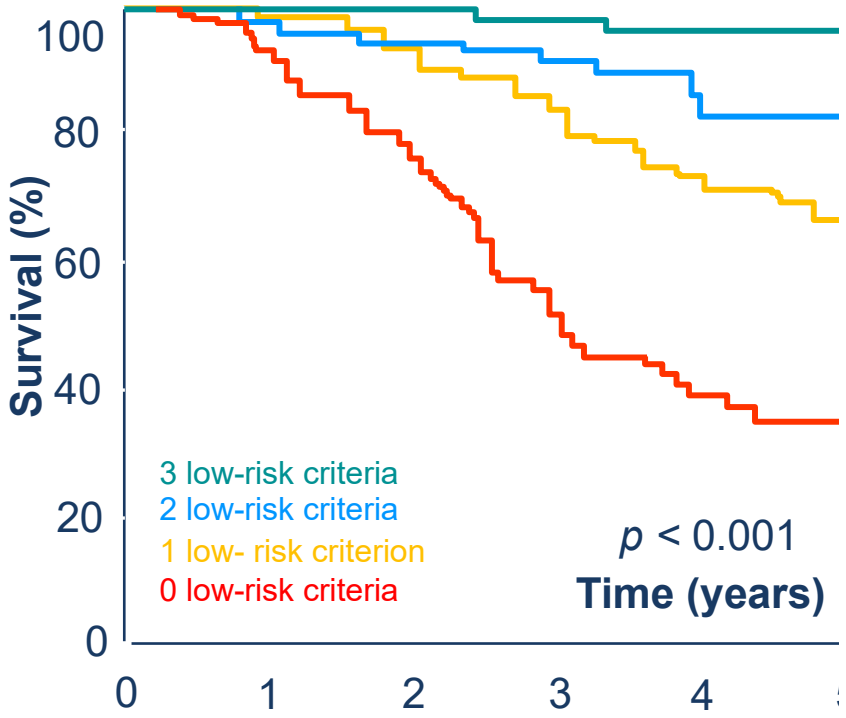


Humbert M *et al. Eur Respir J* 2022; *in press*: 2200879; Humbert M, *et al. Eur Heart J* 2022; 43: 3618-3731.

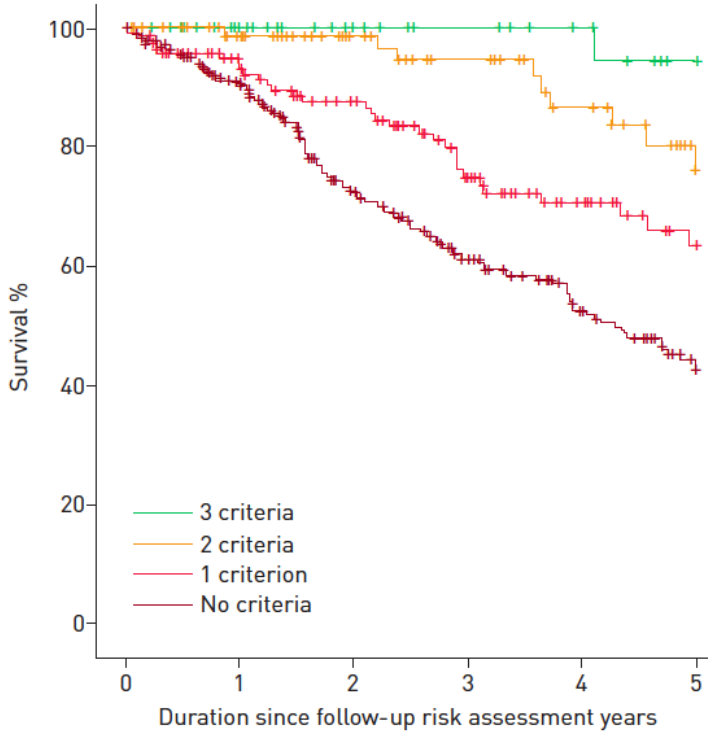
Non invasive assessment (NYHA FC, 6MWD, BNP) is possible

French cohort



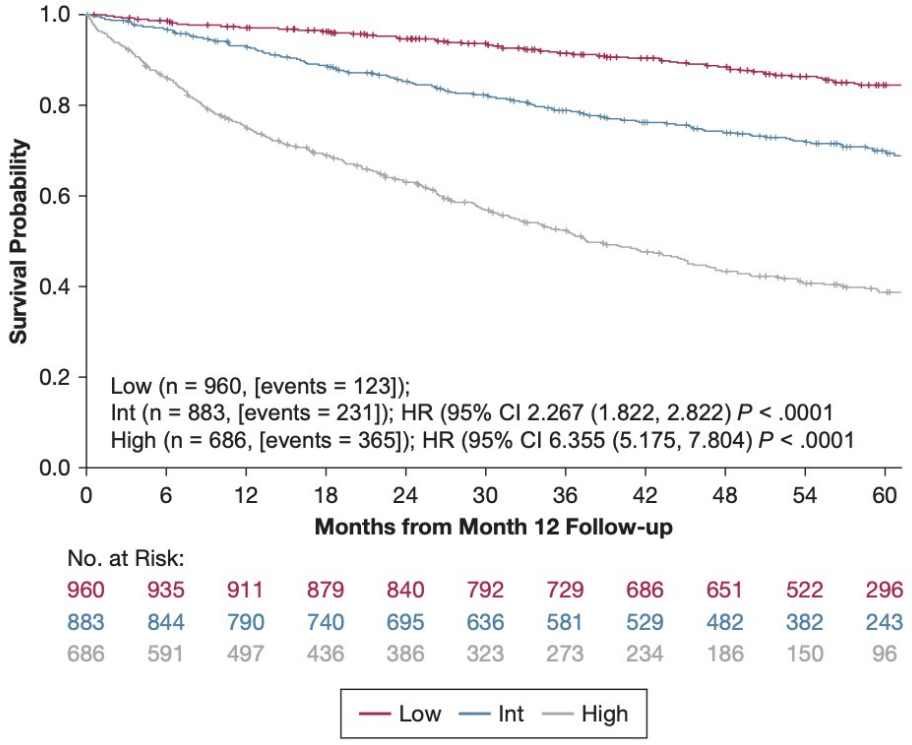
Boucly A, *et al. Eur Respir J* 2017; 50: 1700889.

COMPERA



Hoeper, et al, *Eur Respir J* 2018;51(3):1702606.

REVEAL Lite 2



Benza et al. *Chest.* 2021;159(1):337-346.

New simplified 4-strata risk-assessment tool

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Recommendation	Class	Level
For risk stratification **during follow-up**, the use of a **four-strata model** (low, intermediate-low, intermediate-high, and high risk) based on WHO-FC, 6MWD, and BNP/NT-proBNP is recommended, with additional variables taken into account as necessary	I	B

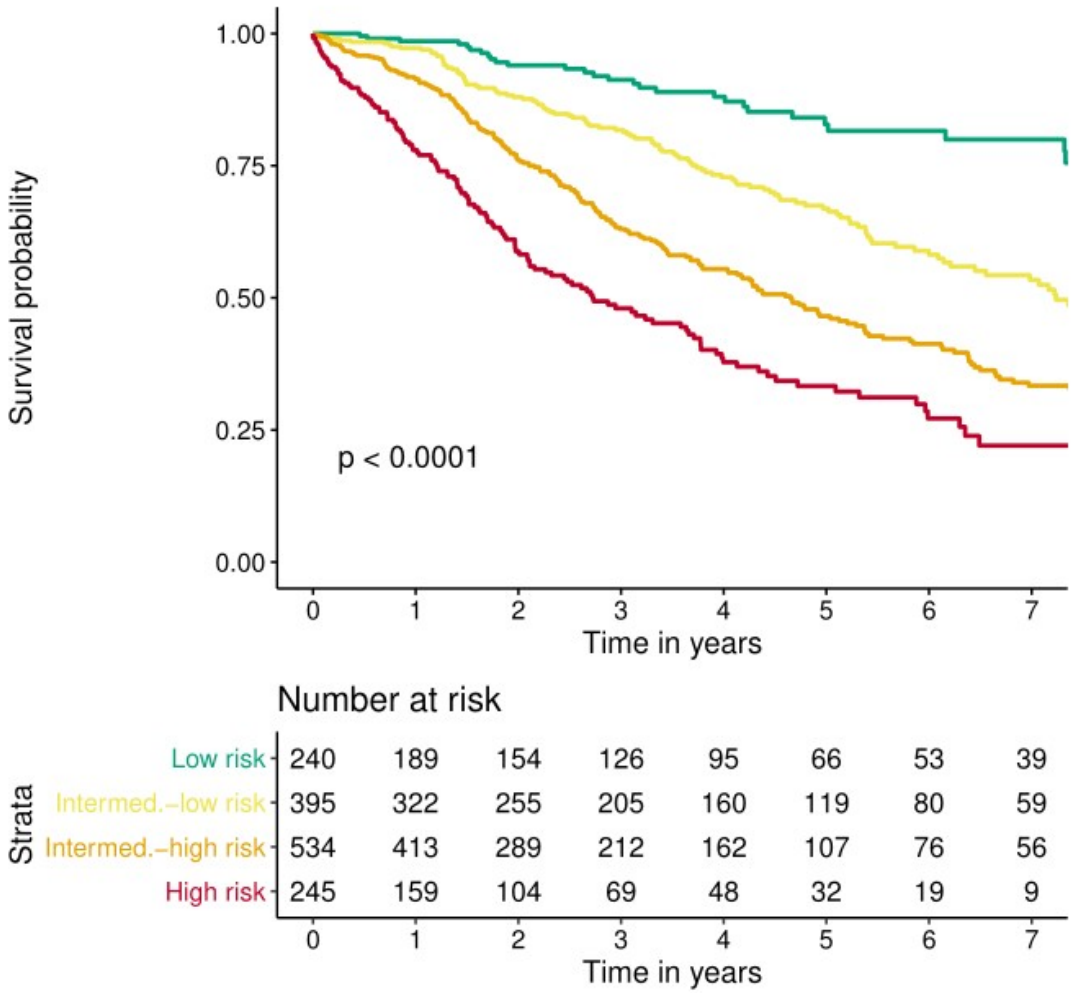
Determinants of prognosis	Low risk	Intermediate-low risk	Intermediate-high risk	High risk
Points assigned	1	2	3	4
WHO-FC	I or II	-	III	IV
6MWD, m	>440	320–440	165–319	<165
BNP or NT-proBNP, ng/L	<50 <300	50–199 300–649	200–800 650–1100	>800 >1100

Recommendation	Class	Level
Achieving and maintaining a **low-risk profile** on optimized medical therapy is recommended as a **treatment goal** in patients with PAH	I	B

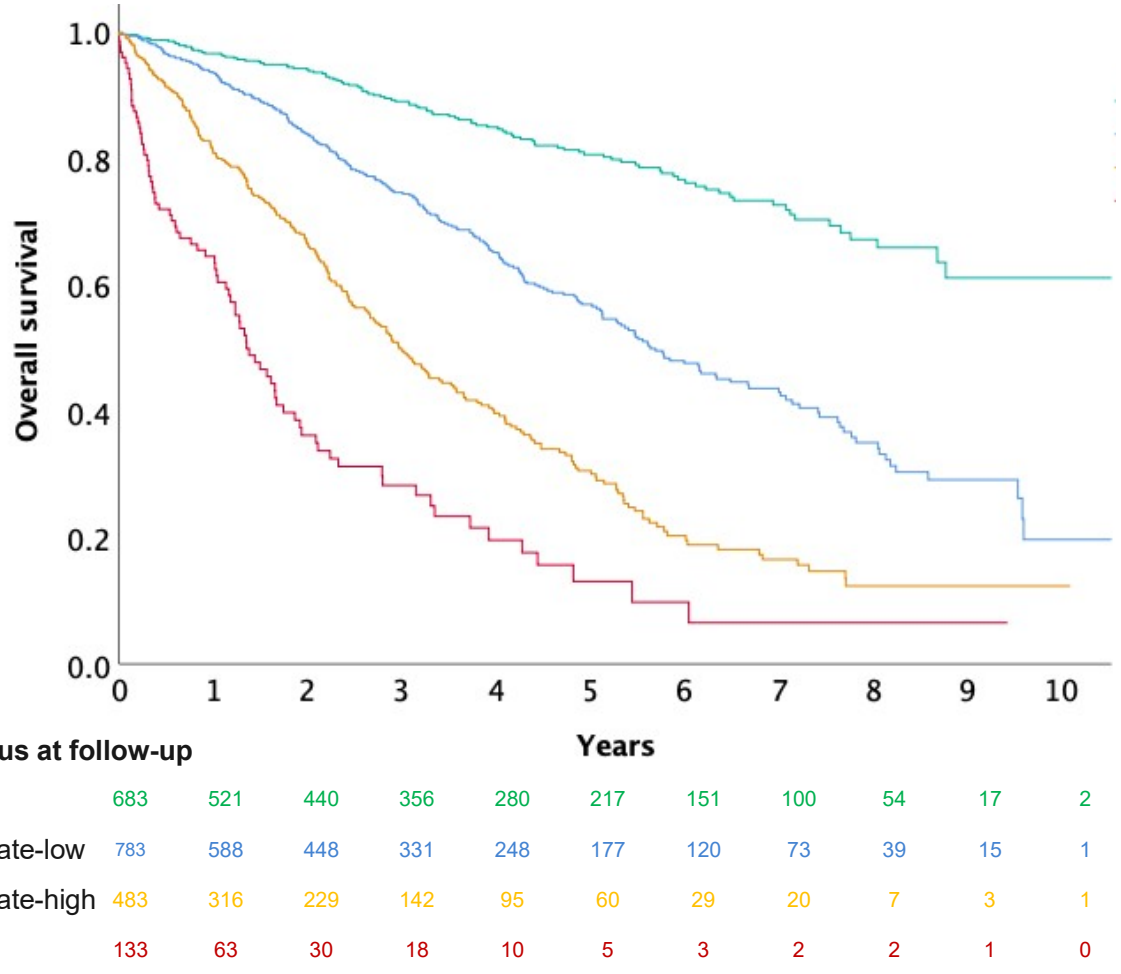
Humbert M *et al. Eur Respir J* 2022; *in press*: 2200879; Humbert M, *et al. Eur Heart J* 2022; 43: 3618-3731.

4-strata risk assessment validated in two large European cohorts

COMPERA[1] **:** 1655 incident PAH

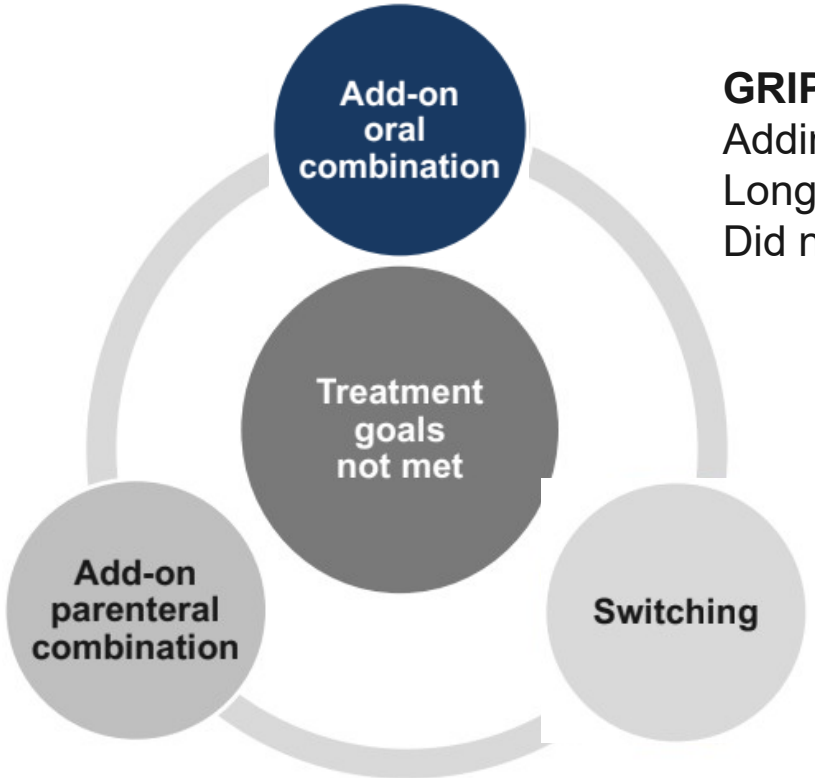


French Registry[2] **:** 2879 incident PAH

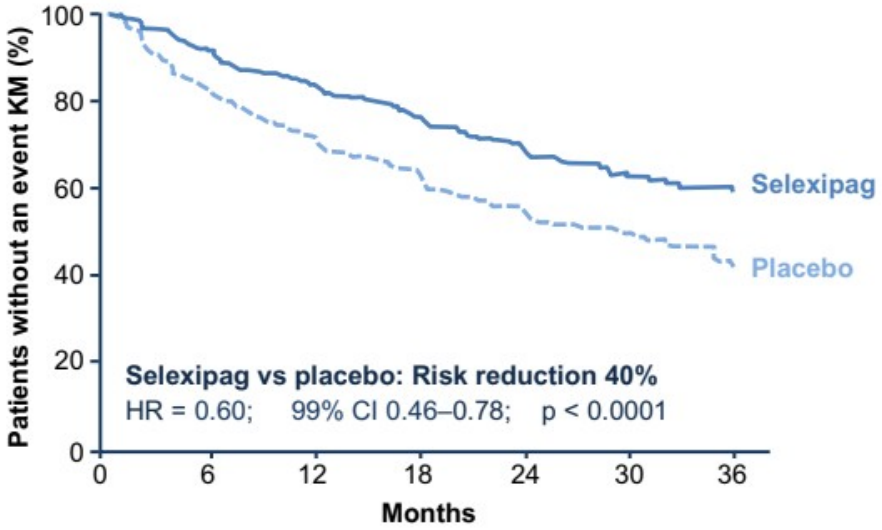


1. Hoeper, *et al*, *Eur Respir J*. 2022; 60: 2102311; 2. Boucly, Weatherald, *et al*, *Eur Respir J*. 2022; 59: 2102419.

Sequential combination therapy: Combining or switching for treatment escalation?



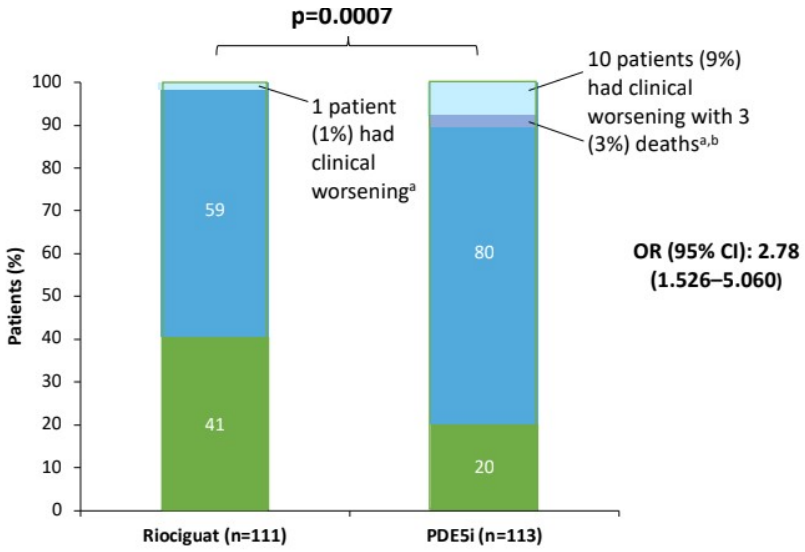
GRIPHON
Adding selexipag on top of background Rx
Long-term event-driven study
Did not capture clinical improvement



REPLACE
Switching from PDE-5i to riociguat
Multicomponent clinical improvement endpoint
Non-blinded study

Meeting at least 2 criteria + absence of clinical worsening

1. **WHO FC:** Improvement from FC III to FC I or II
2. **NT-proBNP:** ≥30% improvement
3. **6MWD:** ≥10% or ≥30 m improvement

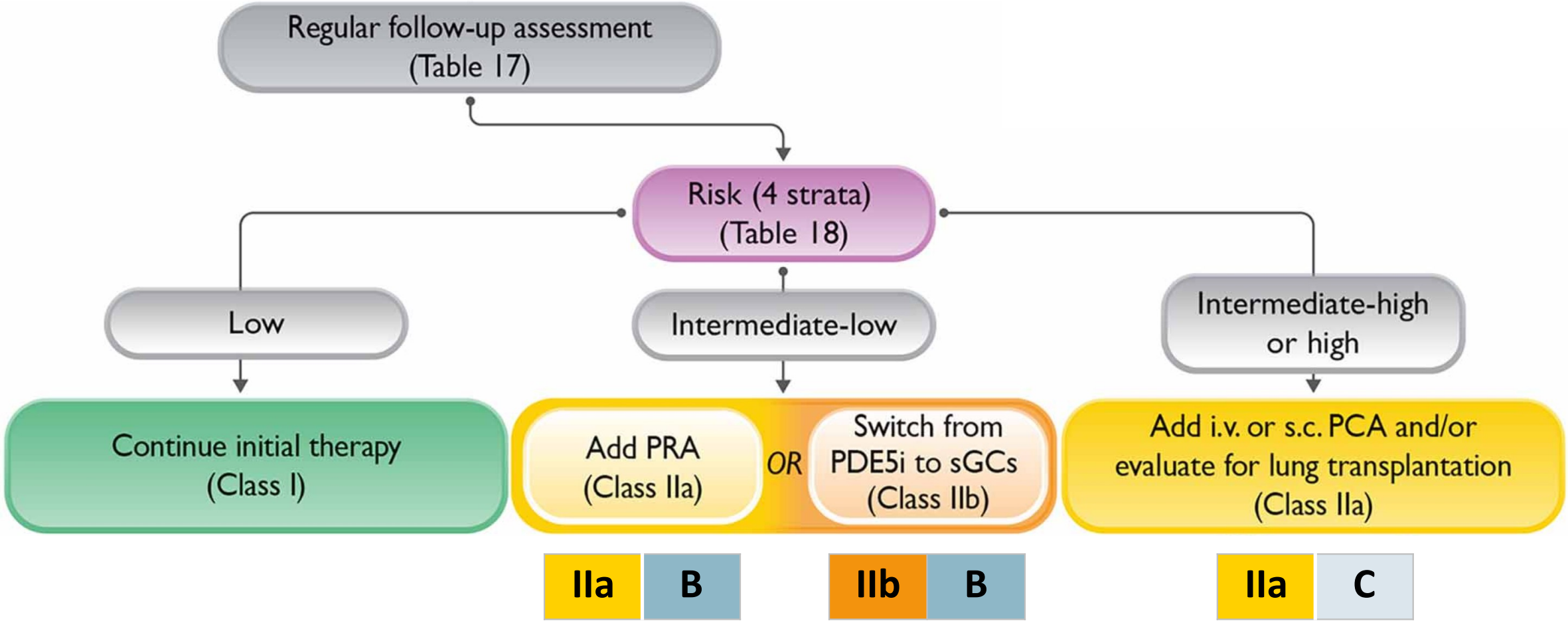


Sitbon O, *et al. N Engl J Med* 2(

Recommendations for therapy during follow-up in patients with PAH without comorbidities

Guidelines 2022

ESC ERS



Humbert M *et al. Eur Respir J* 2022; *in press*: 2200879; Humbert M, *et al. Eur Heart J* 2022; 43: 3618-3731.

Recommendations for patients with comorbidities

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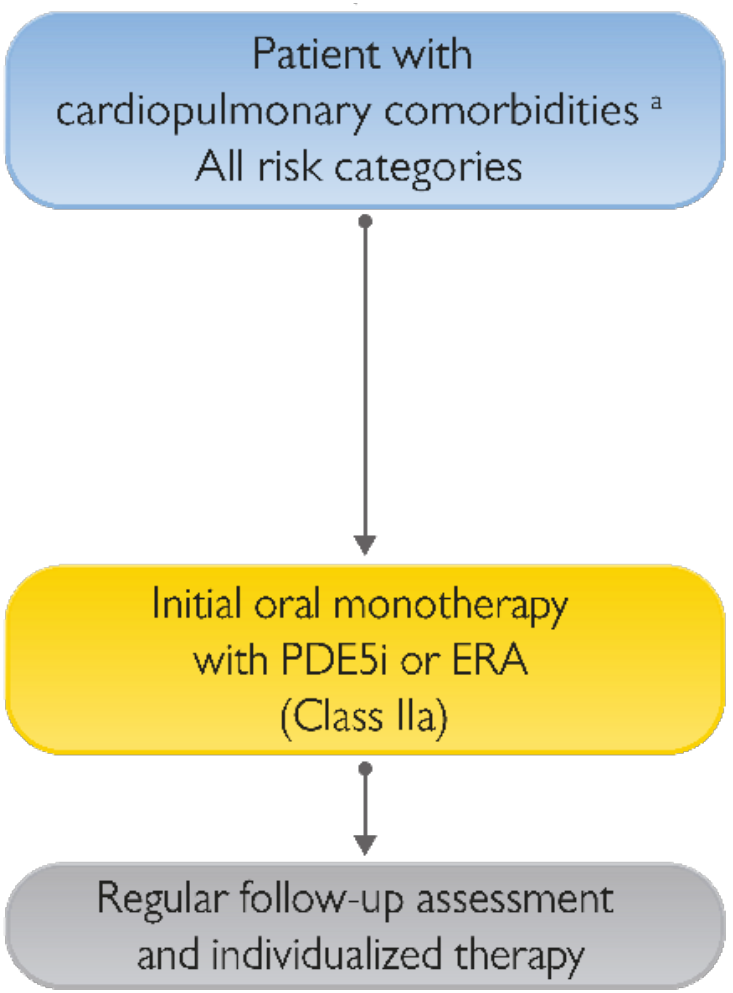
Cardiopulmonary comorbidities are conditions associated with an **increased risk of LV diastolic dysfunction**, and include obesity, hypertension, diabetes mellitus, and coronary heart disease;

Pulmonary comorbidities may include signs of **mild parenchymal lung disease** and are often associated with a **low DLCO** (<45% of the predicted value)

Recommendations	Class	Level
For initial therapy		
In patients with IPAH/HPAH/DPAH and cardiopulmonary **comorbidities**, **initial monotherapy** with a PDE5i or an ERA should be considered	**IIa**	**C**
During follow-up		
In patients with IPAH/HPAH/DPAH with cardiopulmonary comorbidities who present at intermediate or high risk of death while receiving PDE5i or ERA monotherapy, **additional PAH medications** may be considered on an **individual basis**	**IIb**	**C**



Humbert M *et al. Eur Respir J* 2022; *in press*: 2200879; Humbert M, *et al. Eur Heart J* 2022; 43: 3618-3731.

Unresolved questions…

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EUROPEAN RESPIRATORY JOURNAL
ERS OFFICIAL DOCUMENTS
M. HUMBERT ET AL.

2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

Developed by the task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS)

Endorsed by the International Society for Heart and Lung Transplantation (ISHLT) and the European Reference Network on rare respiratory diseases (ERN-LUNG)

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ESC European Society of Cardiology
European Heart Journal (2022) **43**, 3618–3731
https://doi.org/10.1093/eurheartj/ehac237

ESC/ERS GUIDELINES

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Authors/Task Force Members: Marc Humbert (France), Gabor Kovacs (Austria), Marius M. Hoeper (Germany), Roberto Badagliacca (Italy), Rolf M.F. Berger (Netherlands), Margarita Brida (Croatia), Jørn Carlsen (Denmark), Andrew J.S. Coats (United Kingdom), Pilar Escribano-Subias (Spain), Pisana Ferrari (Italy), Diogenes S. Ferreira (Brazil), Hossein Ardeschir Ghofrani (Germany), George Giannakoulas (Greece), David G. Kiely (United Kingdom), Eckhard Mayer (Germany), Gergely Meszaros (Hungary), Blin Nagavci (Germany), Karen M. Olsson (Germany), Joanna Pepke-Zaba (United Kingdom), Jennifer K. Quint (United Kingdom), Göran Rådegran (Sweden), Gerald Simonneau (France), Olivier Sitbon (France), Thomy Tonia (Switzerland), Mark Toshner (United Kingdom), Jean-Luc Vachiery (Belgium), Anton Vonk Noordegraaf (Netherlands), Marion Delcroix *† (ERS Chairperson) (Belgium), Stephan Rosenkranz *† (ESC Chairperson) (Germany), and ESC/ERS Scientific Document Group

Humbert M *et al. Eur Respir J* 2022; *in press*: 2200879; Humbert M, *et al. Eur Heart J* 2022; 43: 3618-3731.

Why two different scores at diagnosis and during follow-up?

The main advantage of **the four-strata model** over the three-strata model is **better discrimination within the intermediate-risk group**, which helps guide therapeutic decision-making.

However, **the three-strata model** **is maintained for initial assessment**, which **should** be comprehensive and **include echocardiographic and haemodynamic variables**, for which cut-off values for the four-strata model have yet to be established

Humbert M *et al. Eur Respir J* 2022; *in press*: 2200879; Humbert M, *et al. Eur Heart J* 2022; 43: 3618-3731.

Which place for invasive haemodynamic evaluation at follow-up?

Suggested assessment and timing for the follow-up of patients with PAH

	At baseline	3–6 months after changes in therapy	Every 3–6 months in stable patients	In case of clinical worsening
Medical assessment (including WHO-FC)				
6MWT				
Blood test (including NT-proBNP)				
ECG				
Echocardiography or cMRI				
ABG or pulse oximetry				
Disease-specific HR-QoL				
CPET				
RHC				

Class I :
« is recommended »

Class IIa :
« should be considered »

Class IIb :
« may be considered »

At follow-up, the four-strata model (based on WHO-FC, 6MWT and NT-proBNP) is recommended as a basic risk-stratification tool, but **additional variables should be considered as needed**, especially right heart imaging and **haemodynamics**.

Humbert M *et al. Eur Respir J* 2022; *in press*: 2200879; Humbert M, *et al. Eur Heart J* 2022; 43: 3618-3731.

Which place for other risk scores?

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Recommendations	Class	Level
For risk stratification **at the time of diagnosis**, the use of a **three-strata model** (low, intermediate, and high risk) is recommended, taking into account all available data including haemodynamics	I	B
For risk stratification **during follow-up**, the use of a **four-strata model** (low, intermediate-low, intermediate-high, and high risk) based on WHO-FC, 6MWD, and BNP/NT-proBNP is recommended, with additional variables taken into account as necessary	I	B

Recommendations	Class	Level
It is recommended that potentially eligible candidates are **referred for LTx evaluation** when they have an inadequate response to oral combination therapy, indicated by an intermediate-high or high risk or by a **REVEAL risk score >7**	I	C
It is recommended **to list patients for LTx** who present with a high risk of death or with a **REVEAL risk score ≥10** despite receiving optimized medical therapy including s.c. or i.v. prostacyclin analogues	I	C

Humbert M *et al. Eur Respir J* 2022; *in press*: 2200879; Humbert M, *et al. Eur Heart J* 2022; 43: 3618-3731.

Last but not least… The issue of **comorbidities**

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- **Cardiopulmonary comorbidities** are conditions associated with an **increased risk of LV diastolic dysfunction**, and include obesity, hypertension, diabetes mellitus, and coronary heart disease
  - **Number** of comorbidities should be considered
  - **Control** of comorbidities should be considered
  - Relationship between **PVR level** and comorbidities (group 1 *vs*. group 2)

- **Pulmonary comorbidities** may include signs of **mild parenchymal lung disease** and are often associated with a **low DLCO** (<45% of the predicted value)
  - Do we have to call this phenotype **group 3 PH**? **PVOD**?

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Treatment algorithm in PAH: Take-Home Messages

The **treatment algorithm** for PAH has been simplified, with a clear focus on risk assessment, cardiopulmonary comorbidities, and treatment goals.

Initial combination therapy and treatment escalation at follow-up when appropriate are current standards.

The importance of PAH **patient phenotypes** and the relevance of **comorbidities** on treatment goals and outcomes must be further evaluated

Grazie per l'attenzione