PAH treatment updates. Guidelines and Beyond

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Objectives

- ECS ERS 2022 guidelines-
  - New approach to therapy
  - Compare and contrast major recommendations with 2015
  - Recent literature to support decision making

- New drug in a new family .

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).

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Marc H, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2022;00:1-114

RECOMMENDATIONS

Table 3 **Classes of recommendations**

Classes of recommendations	Definition	Wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended or is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy.	Should be considered
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

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Table 4 **Levels of evidence**

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

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Definition

Table 5 Haemodynamic definitions of pulmonary hypertension

Definition	Haemodynamic characteristics
PH	mPAP >20 mmHg
Pre-capillary PH	mPAP >20 mmHg PAWP ≤15 mmHg PVR >2 WU
IpcPH	mPAP >20 mmHg PAWP >15 mmHg PVR ≤2 WU
CpcPH	mPAP >20 mmHg PAWP >15 mmHg PVR >2 WU
Exercise PH	mPAP/CO slope between rest and exercise >3 mmHg/L/min

CO, cardiac output; CpcPH, combined post- and pre-capillary pulmonary hyperte
IpcPH, isolated post-capillary pulmonary hypertension; mPAP, mean pulmonary a
pressure; PAWP, pulmonary arterial wedge pressure; PH, pulmonary hyperte
PVR, pulmonary vascular resistance; WU, Wood units.
Some patients present with elevated mPAP (>20 mmHg) but low PVR (≤2 WU
low PAWP (≤15 mmHg); this haemodynamic condition may be described by the
'unclassified PH' (see text for further details).

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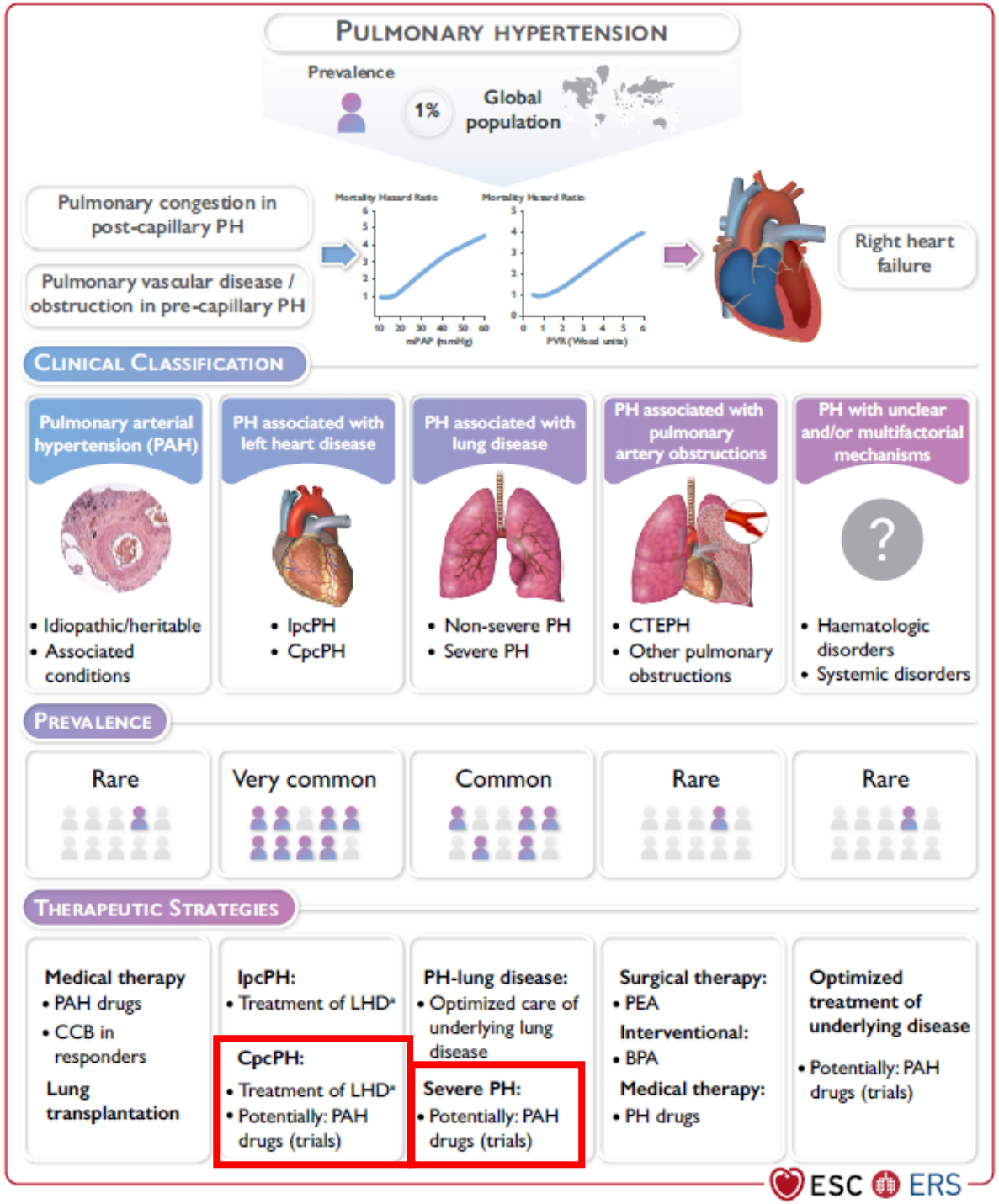
PAH with comorbidities



Risk assessment in PAH (three-strata model)

Table 16 Comprehensive risk assessment in pulmonary arterial hypertension (three-strata model)

Determinants of prognosis (estimated 1-year mortality)	Low risk (<5%)	Intermediate risk (5–20%)	High risk (>20%)
Clinical observations and modifiable variables			
Signs of right HF	Absent	Absent	Present
Progression of symptoms and clinical manifestations	No	Slow	Rapid
Syncope	No	Occasional syncope[a]	Repeated syncope[b]
WHO-FC	I, II	III	IV
6MWD[c]	>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
Biomarkers: BNP or NT-proBNP[d]	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[e]	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%

6MWD, 6-minute walking distance; BNP, brain natriuretic peptide; CI, cardiac index; cMRI, cardiac magnetic resonance imaging; CPET, cardiopulmonary exercise testing; HF, heart failure; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; pred., predicted; RA, right atrium; RAP, right atrial pressure; sPAP, systolic pulmonary arterial pressure; SvO_2, mixed venous oxygen saturation; RVESVI, right ventricular end-systolic volume index; RVEF, right ventricular ejection fraction; SVI, stroke volume index; TAPSE, tricuspid annular plane systolic excursion; VE/VCO_2, ventilatory equivalents for carbon dioxide; VO_2, oxygen uptake; WHO-FC, World Health Organization functional class.

[a]Occasional syncope during heavy exercise or occasional orthostatic syncope in a stable patient.

[b]Repeated episodes of syncope even with little or regular physical activity.

[c]Observe that 6MWD is dependent upon age, height, and burden of comorbidities.

[d]To harmonize with the four-strata model shown in *Table 18*, the BNP and NT-proBNP cut-off levels have been updated from the 2015 version based on data from the REVEAL registry, acknowledging that the European validation studies have used the original cut-off levels.[274,292,293,295,296,302]

[e]cMRI parameters adapted from Section 6.2.2.2.

Based on registry data, **higher risk of death** at 1-year acknowledged

Reinforces the need for **proactive management** of PAH

ECHO, cMRI, HD criteria added

NT-proBNP and BNP high risk thresholds adjusted

Simplified four-strata risk-assessment tool (table 18)

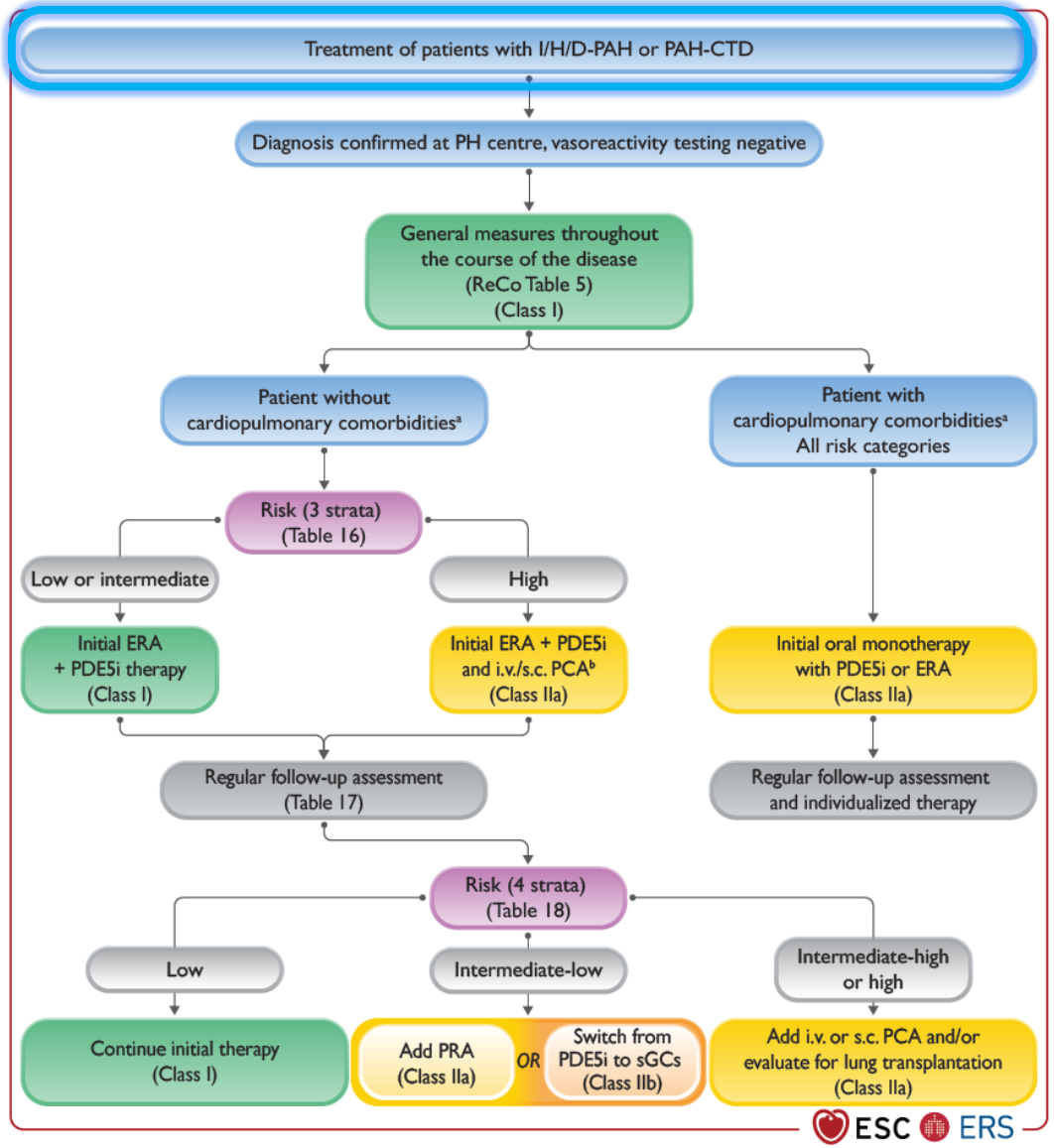
Determinants of prognosis	Low risk	Intermediate–low risk	Intermediate–high risk	High risk
Points assigned	1	2	3	4
WHO-FC	I or II[a]	-	III	IV
6MWD, m	>440	320–440	165–319	<165
BNP or NT-proBNP,[a] ng/L	<50 <300	50–199 300–649	200–800 650–1100	>800 >1100

Risk is calculated by dividing the sum of all grades by the number of variables and rounding to the next integer.

- Prognostic assessment at FU is based on assessment of WHO-FC, 6MWD and NT-proBNP/BNP
- **Follow-up risk score calculated** based on ≥2 parameters to give
  - 1 (low) 1-year risk of death <3%
  - 2 (intermediate-low) 1-year risk of death <2-7%
  - 3 (intermediate-high) 1-year risk of death <9-19%
  - 4 (high) 1-year risk of death >20%
- Additional variables can be considered as needed, however no thresholds are proposed
- The authors expect that the "simplified" approach with foster greater adoption of risk assessment

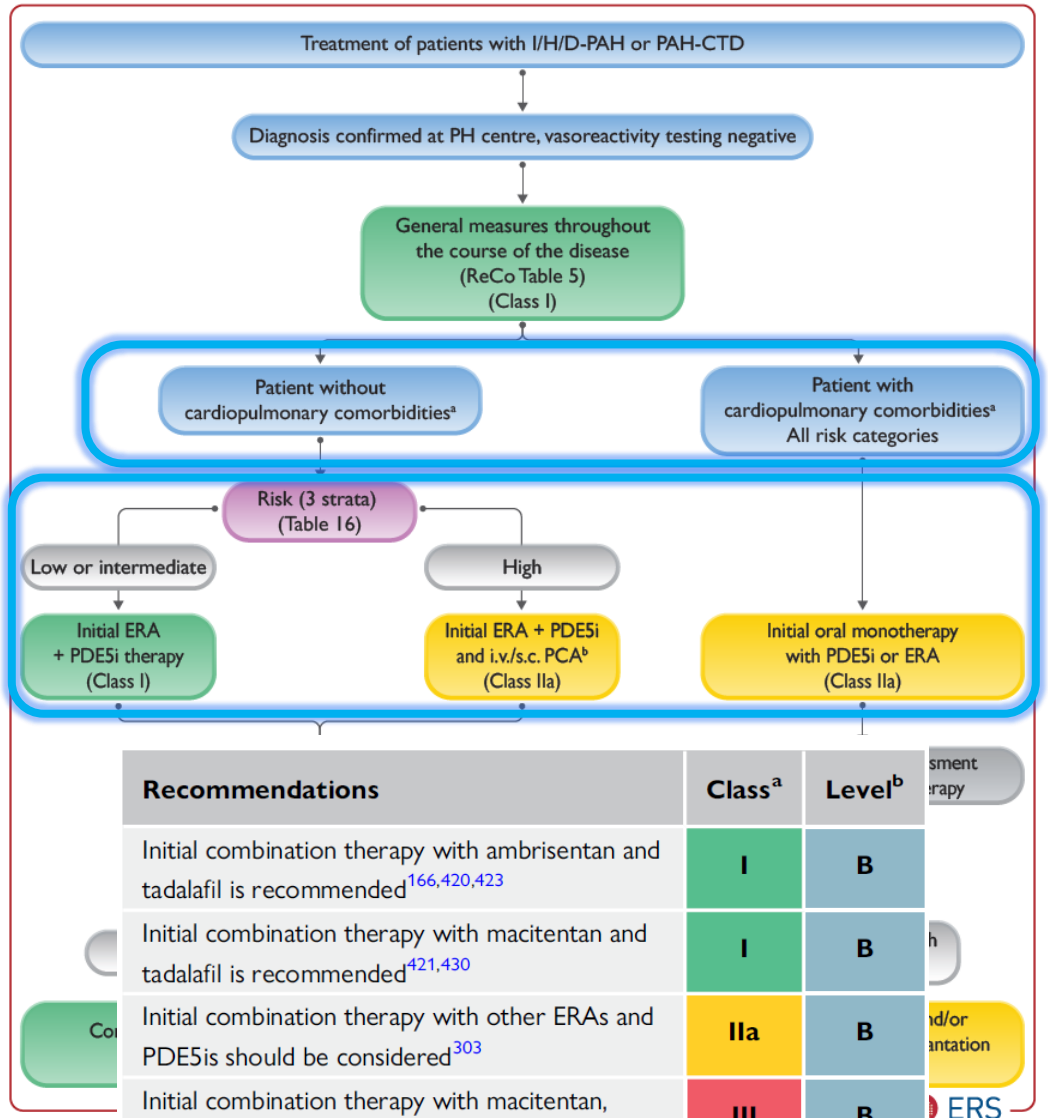
Table 18, p.42

PAH treatment algorithm



- Algorithm calls out **I/H/D-PAH and PAH-CTD**
- For PAH-CHD -patients who should be treated:
  - PAH-CHD patient with small/coincidental defects
  - PAH-CHD patients with corrected defect

Treatment initiation



Recommendations	Class[a]	Level[b]
Initial combination therapy with ambrisentan and tadalafil is recommended[166,420,423]	I	B
Initial combination therapy with macitentan and tadalafil is recommended[421,430]	I	B
Initial combination therapy with other ERAs and PDE5is should be considered[303]	IIa	B
Initial combination therapy with macitentan, tadalafil, and selexipag is not recommended[421]	III	B

- The treatment algorithm calls out patients with and without **cardiopulmonary comorbidities**
- In **non-comorbid** patients
  - **Strong recommendation of initial dual** (ERA & PDE5i) in low & intermediate
  - **Recommendation for initial triple incl. parenteral** PCA in high risk
  - **No recommendation for initial triple oral** based on TRITON (short term endpoints)
- In **comorbid patients initial monotherapy** (ERA / PDE5i) is recommended

Triple therapy

2015

Table 20 Recommendations for efficacy of initial drug combination therapy for pulmonary arterial hypertension (group 1) according to World Health Organization functional class. Sequence is by rating

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

2022

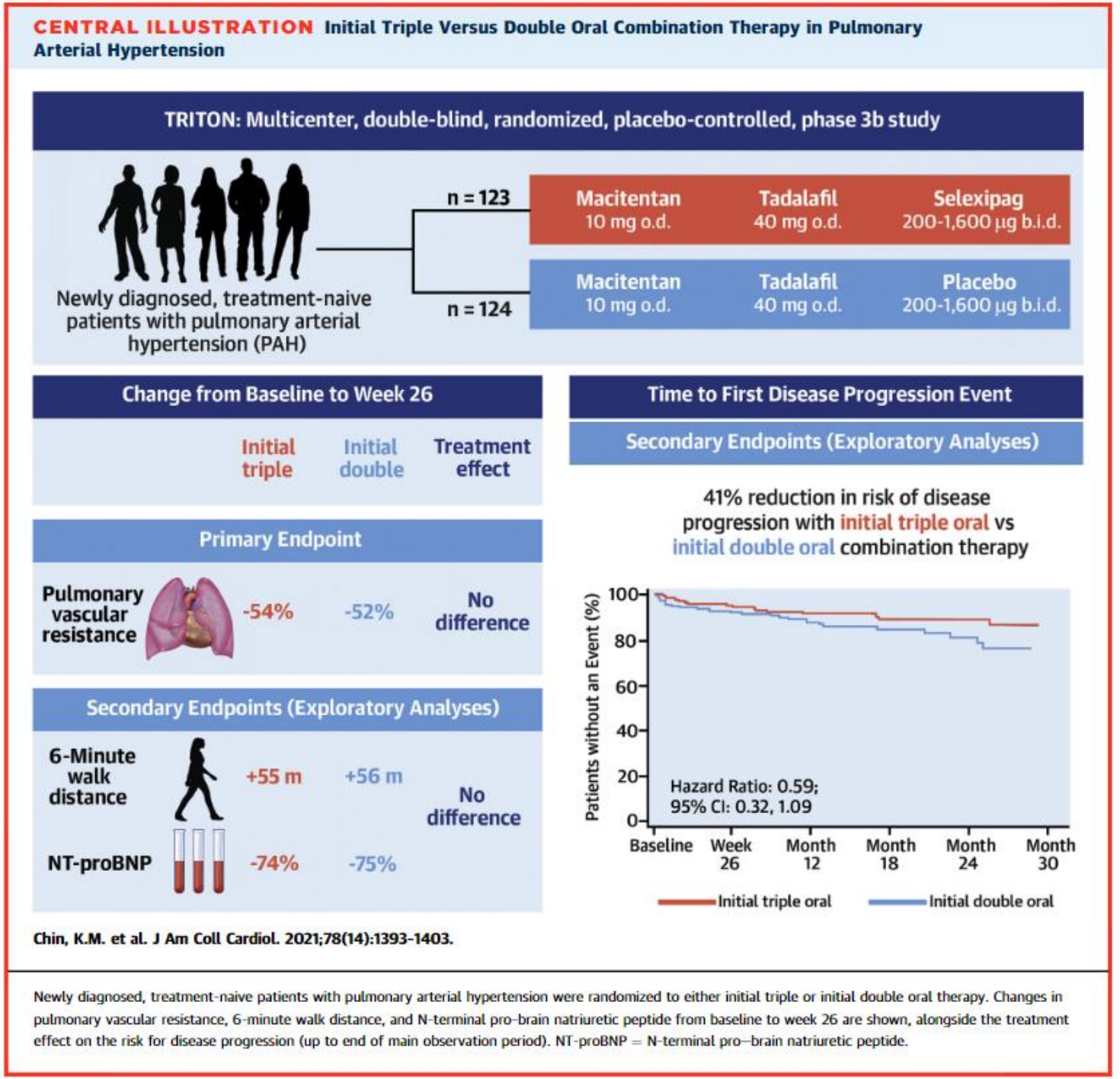
Recommendation Table 9 — Recommendations for initial oral drug combination therapy for patients with idiopathic, heritable, or drug-associated pulmonary arterial hypertension without cardiopulmonary comorbidities

Recommendations	Class[a]	Level[b]
Initial combination therapy with ambrisentan and tadalafil is recommended[166,420,423]	I	B
Initial combination therapy with macitentan and tadalafil is recommended[421,430]	I	B
Initial combination therapy with other ERAs and PDE5is should be considered[303]	IIa	B
Initial combination therapy with macitentan, tadalafil, and selexipag is not recommended[421]	III	B

Galiè N, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. European Heart Journal 2015

Marc H, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2022;00:1-114

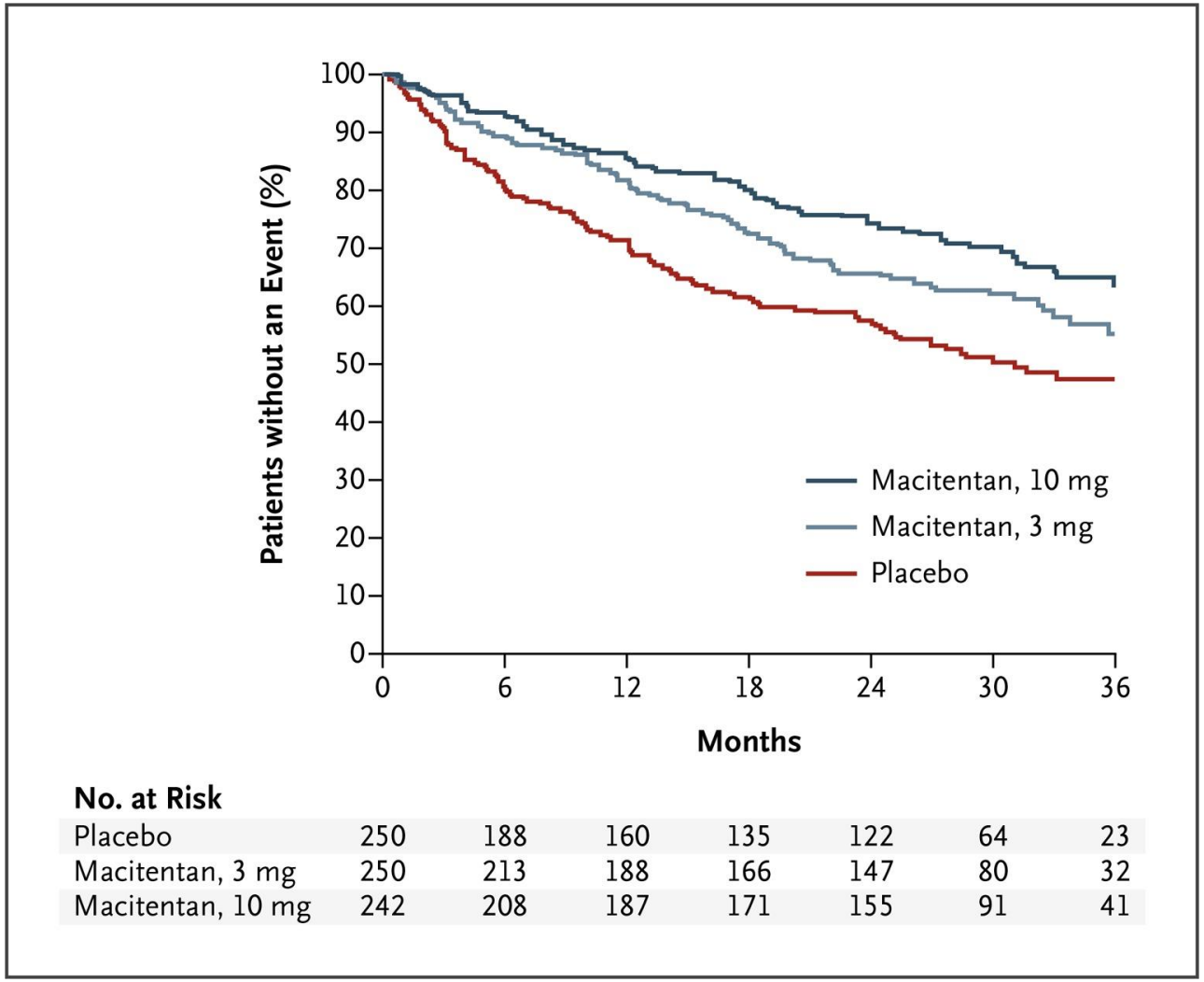
Triton study



SERAPHIN Trial 2013

- In an event-driven trial, macitentan (an endothelin-receptor antagonist) at a dose of 3 or 10 mg was compared with placebo in patients with symptomatic pulmonary arterial hypertension.
- At a median of 115 weeks, both macitentan doses were associated with reduced morbidity and mortality.

Composite Primary End Point of a First Event Related to Pulmonary Arterial Hypertension or Death from Any Cause.



No. 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

N Engl J Med
Volume 369(9):809-818

SERAPHIN OL 2022

Open label extension of SERAPHIN to study the safety, tolerability and survival of patients with PAH on Macitentan

Of the 742 patients randomized in SERAPHIN 550 were enrolled

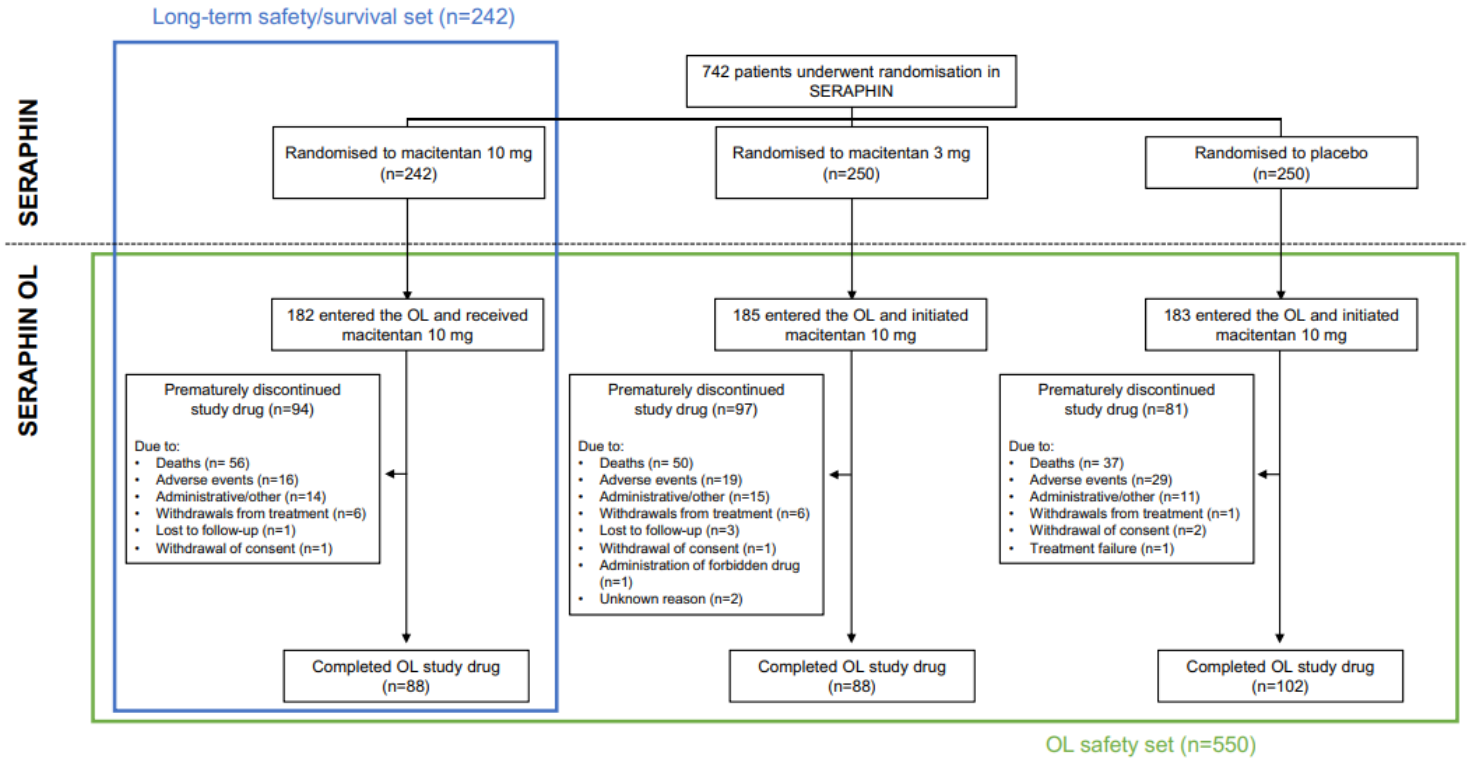


Fig. 1 Patient disposition in SERAPHIN and SERAPHIN OL. *OL* open-label

Table 1 Treatment disposition at end of SERAPHIN OL

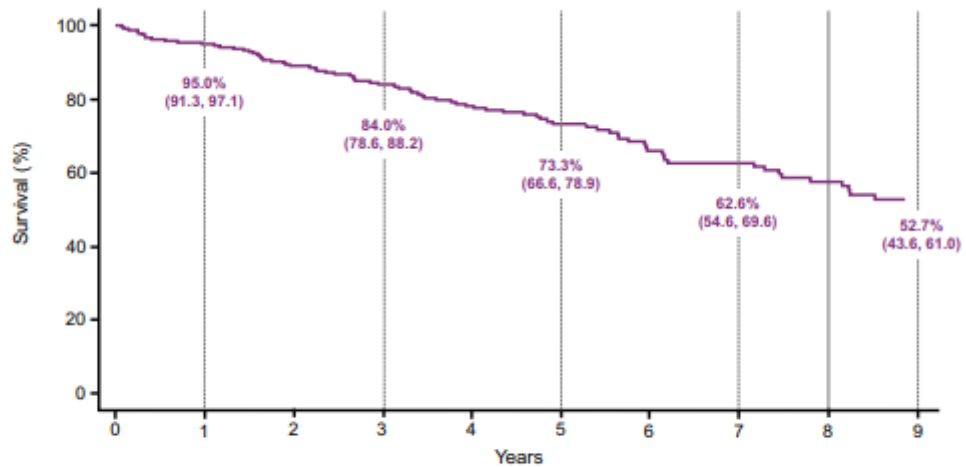
	OL safety set (N = 550)	Long-term safety/survival set (N = 242)
Completed study treatment[a], *n* (%)	278 (50.5)	95 (39.3)
Discontinued study treatment, *n* (%)	272[b] (49.5)	147 (60.7)
Reason for discontinuation, *n* (%)[c]		
Death	143 (26.0)	66 (27.3)
Adverse event	64 (11.6)	38 (15.7)
Administrative/ other	40 (7.3)	19 (7.9)
Withdrawal from treatment	13 (2.4)	18 (7.4)
Lost to follow-up	4 (0.7)	1 (0.4)
Other[d]	6 (1.1)	5 (2.1)

OL open-label

[a]Completed study treatment in SERAPHIN or SERAPHIN OL: Patients who received study treatment as per protocol and did not prematurely discontinue study treatment

[b]Includes two patients who discontinued but did not have a reason for discontinuation recorded; these two patients and their time on treatment are excluded from the premature study drug discontinua-

Most frequent[c] adverse events	*n* (%)	Incidence rate per 100 patient-years[a]	*n* (%)	Incidence rate per 100 patient-years[a]
PAH worsening	157 (28.5)	8.7	86 (35.5)	9.4
Upper respiratory tract infection	127 (23.1)	7.6	62 (25.6)	6.8
Peripheral oedema	107 (19.5)	5.8	63 (26.0)	6.7
Nasopharyngitis	105 (19.1)	6.2	52 (21.5)	5.7
Anaemia	97 (17.6)	5.4	47 (19.4)	4.7
Bronchitis	86 (15.6)	4.7	45 (18.6)	4.6
Right ventricular failure	86 (15.6)	4.4	47 (19.4)	4.5
Cough	74 (13.5)	3.9	33 (13.6)	3.1
Dyspnoea	67 (12.2)	3.5	40 (16.5)	3.8
Headache	65 (11.8)	3.5	47 (19.4)	4.8
Pneumonia	61 (11.1)	3.1	28 (11.6)	2.6
Diarrhoea	60 (10.9)	3.1	39 (16.1)	3.8
Dizziness	56 (10.2)	2.9	39 (16.1)	3.9
Urinary tract infection	48 (8.7)	2.5	29 (12.0)	2.8
Chest pain	44 (8.0)	2.3	30 (12.4)	2.8



Patients at risk	242	225	210	171	145	105	79	69	49	22
Number of events	0	12	26	37	48	56	65	69	74	78

Treatment follow-up (no comorbidities)

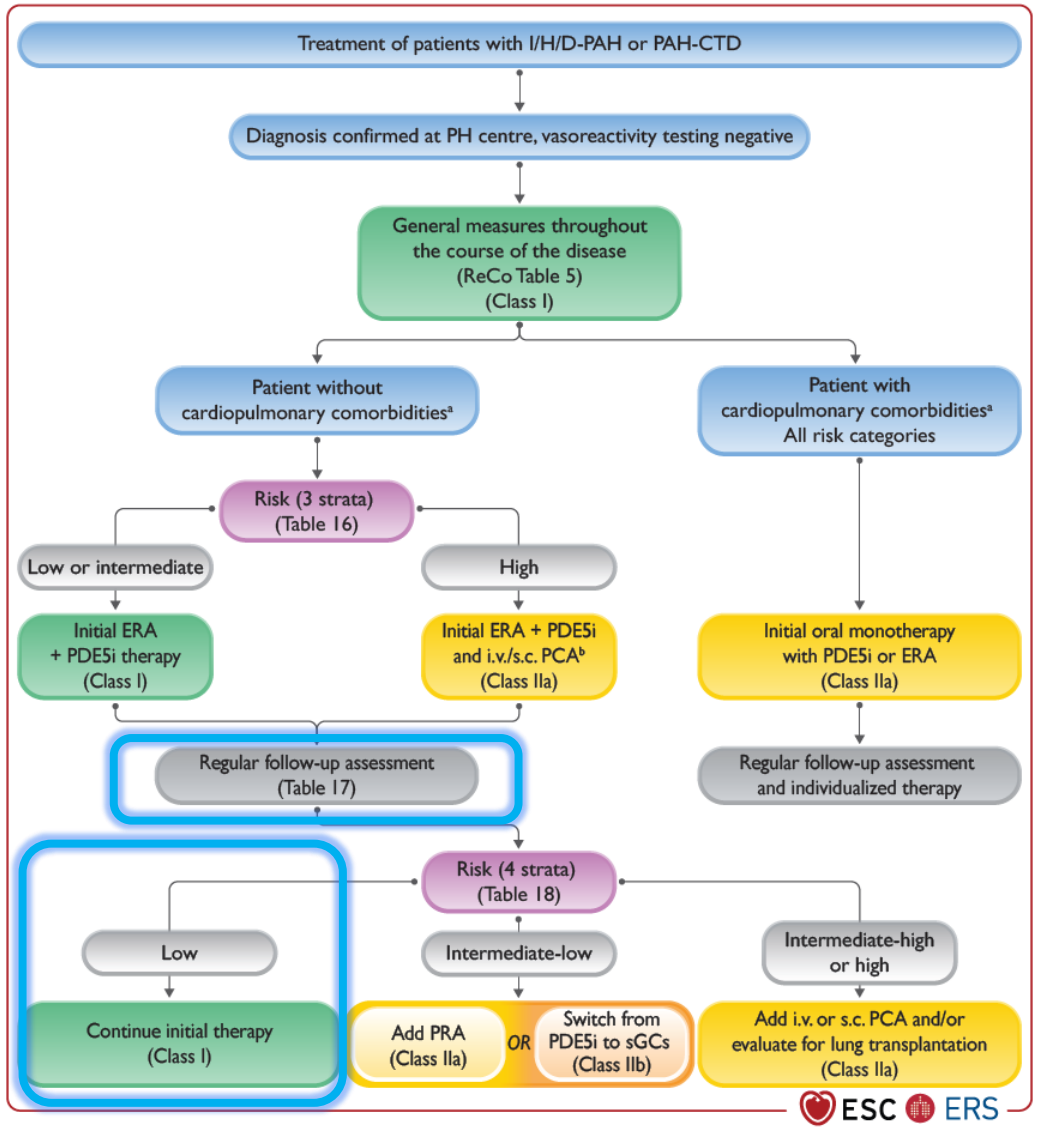


Figure 9, p.49

- Following regular follow-up assessment, patients at low risk should continue on double combination therapy

- Distribution of patients by risk at follow up:
  - **Low:** **17.0%**
  - Intermediate-low: 27.9%
  - Intermediate-high: 37.8%
  - High: 17.3%

Treatment follow-up (no comorbidities)

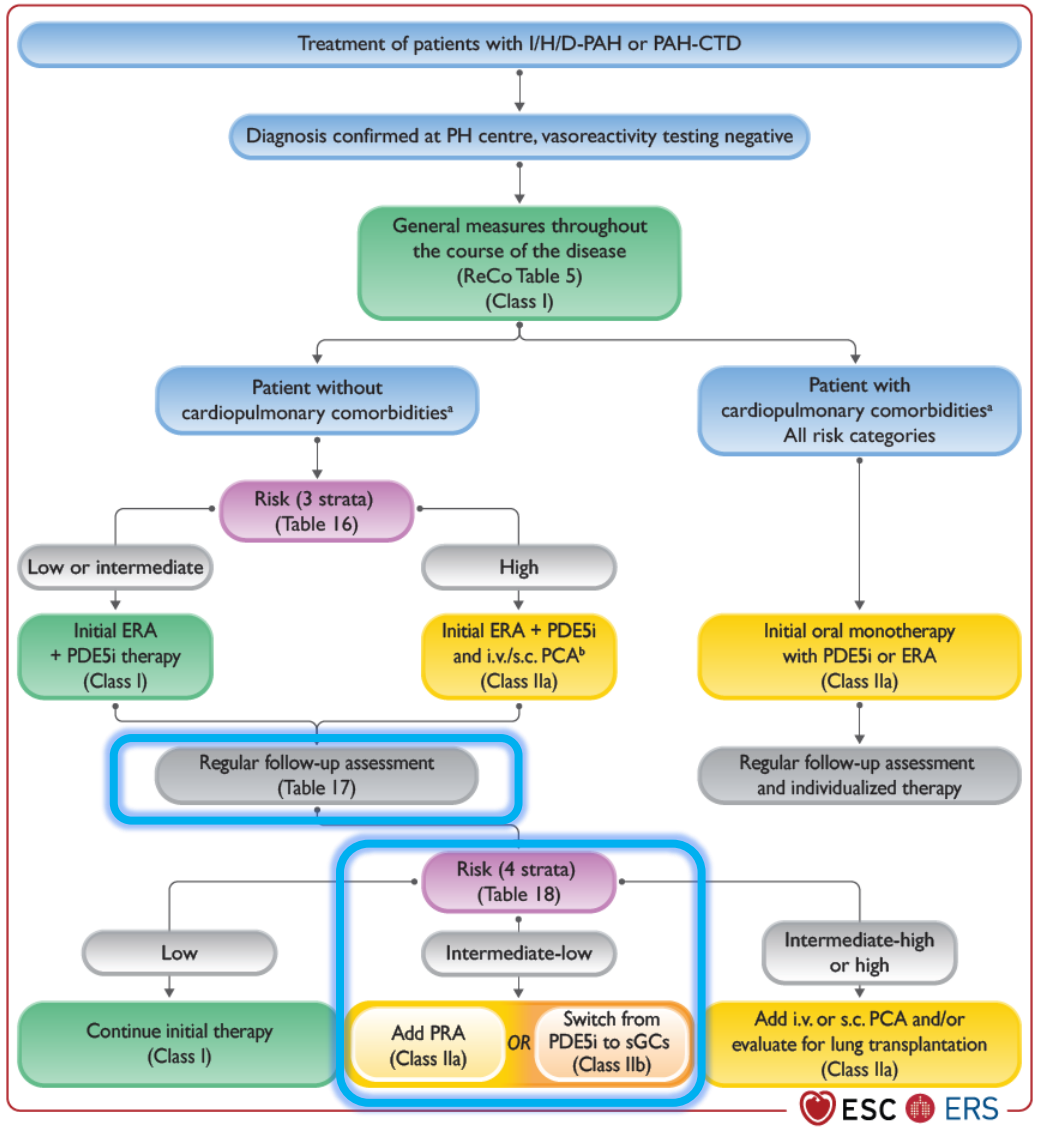


Figure 9, p.49

- Intermediate-low at FU (ca. 28% in COMPERA) **add selexipag** or **switch PDE5i to riociguat** recommended
- **Level of recommendation is stronger for selexipag** GRIPHON large long-term RCT) compared with riociguat (REPLACE short-term open label study)
  - **Escalation is more consistent with the guidelines** overall approach

Treatment follow-up (no comorbidities)

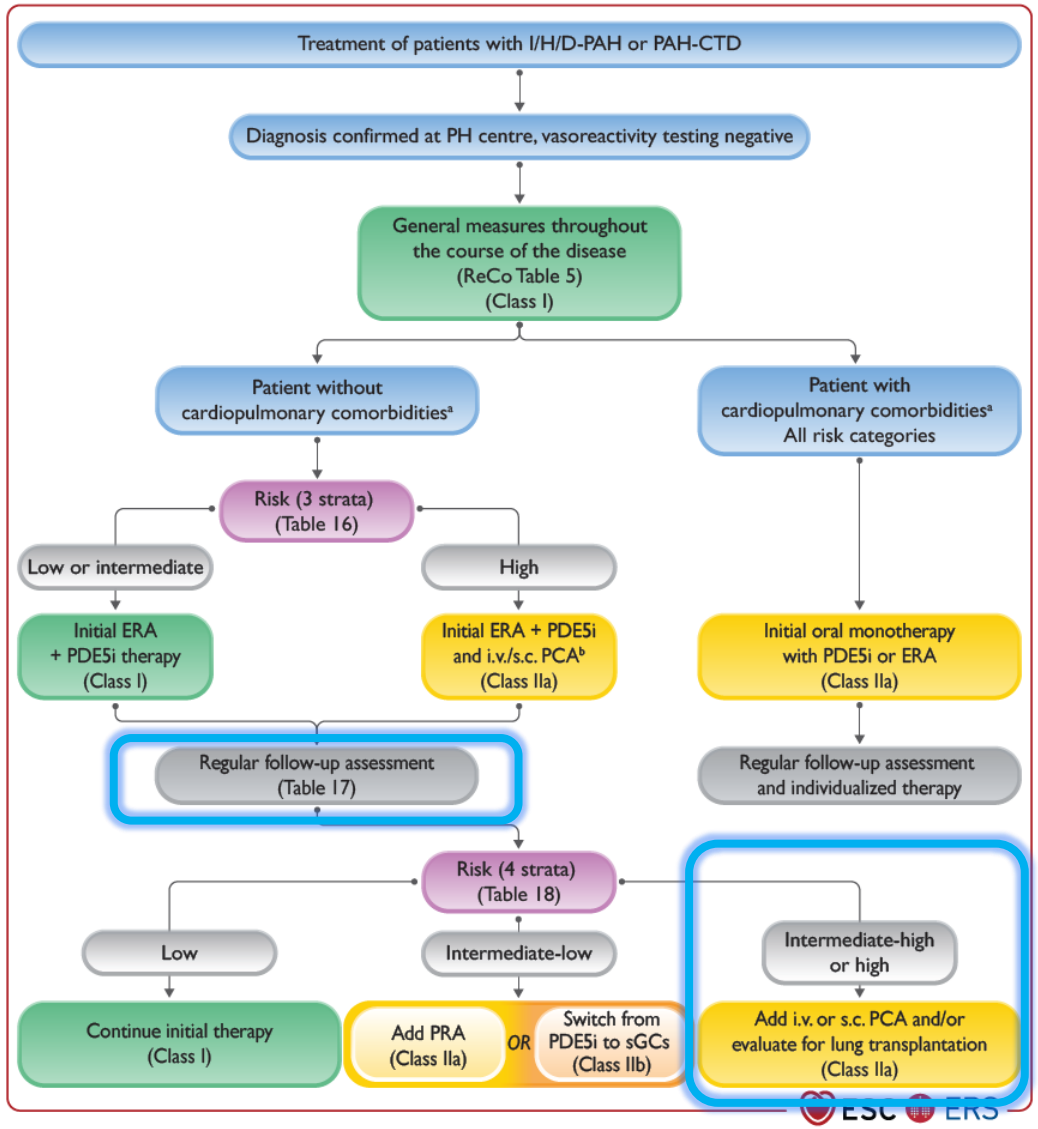


Figure 9, p.49

- Intermediate-high (~38% in COMPERA) and high (~17% in COMPERA) at follow-up; add parenteral PCA and evaluate for lung Tx recommended
- Note: text outlines **addition of selexipag** or **switch from PDE5i to riociguat** if adding i.v./s.c. prostacyclin analogues is unfeasible
    - **Stronger rationale to escalate** and target the prostacyclin pathway with selexipag adding

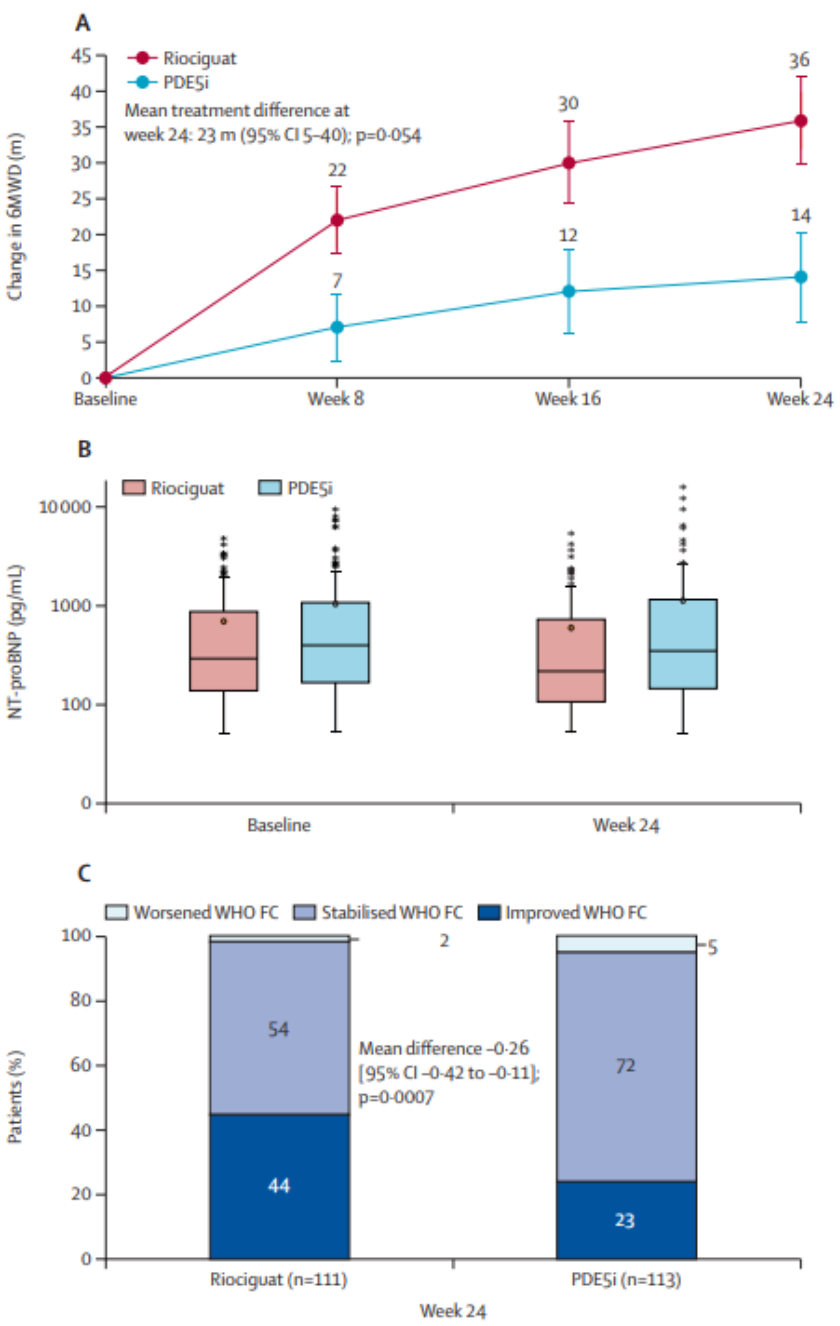
Replace study 2021

Prospective open label

PAH type I, H, D, CTD, and CHD

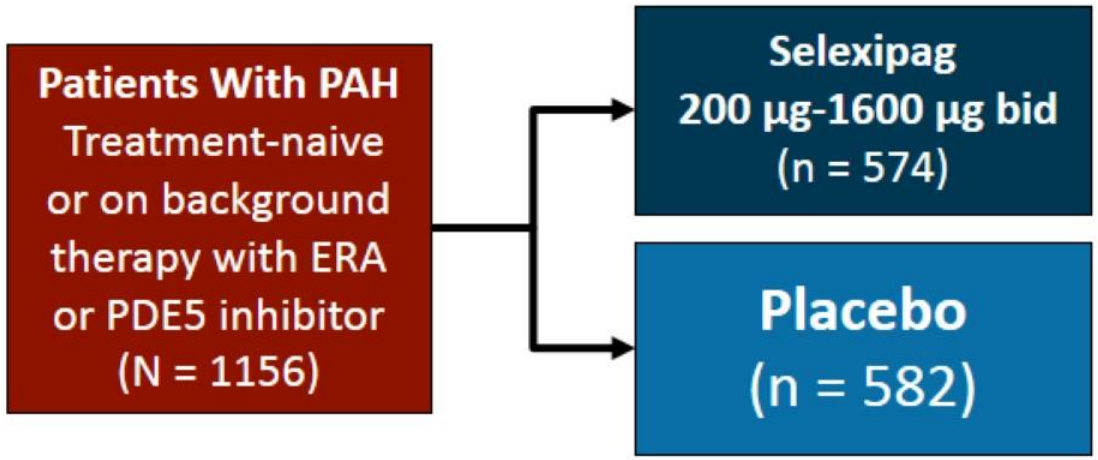
Patients on ERA with PDE5i or PDE5i alone were randomized to shift from PDE5i to Riociguat to stay the same.

Composite end point of 6 minutes walk, ProBNP, and Functional Class improvement .



Lancet Respir Med 2021; 9: 573–84

GRIPHON



Primary endpoint:
Time to first morbidity/mortality event

- Disease progression
- Hospitalization for PAH worsening
- Worsening PAH
- All-cause death

- 47% patients on monotherapy; 33% on combination therapy
- 40% risk reduction for morbidity/mortality events vs placebo (HR = 0.60; 99% CI: 0.46, 0.78, *P* <.0001)
- Treatment effect consistent across multiple subgroups, including type of background therapy
- Safety profile consistent with prostacyclin effects

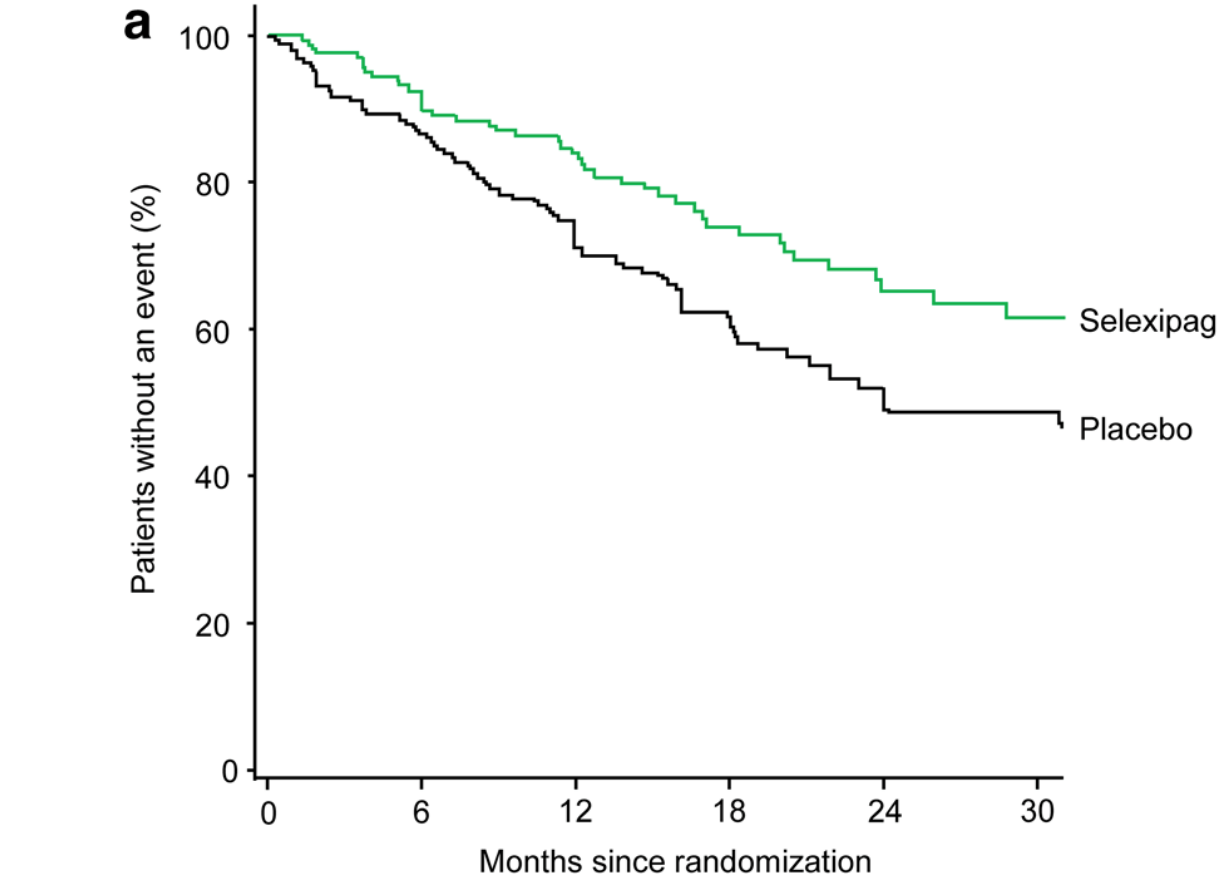
Sitbon O, et al. *N Engl J Med*. 2015;373:2522-2533.

Adding Selexipag to double combination therapy

- 376 PAH patients in GRIPHON study were already receiving double combination therapy of Endothelin Receptor Antagonist (ERA) and Phosphodiesterase-5 Inhibitor (PDE-5i)
  - 115 WHO FC II symptoms
  - 255 WHO FC III symptoms
- Post Hoc analysis of these patients can shed light on the efficacy, and safety of Selexipag as a third agent
    - Coghlan, AM J Cardiovasc Drugs -2018

Effect of selexipag on the primary composite endpoint of morbidity/mortality when added to Dual therapy

- Overall
- 37% reduction

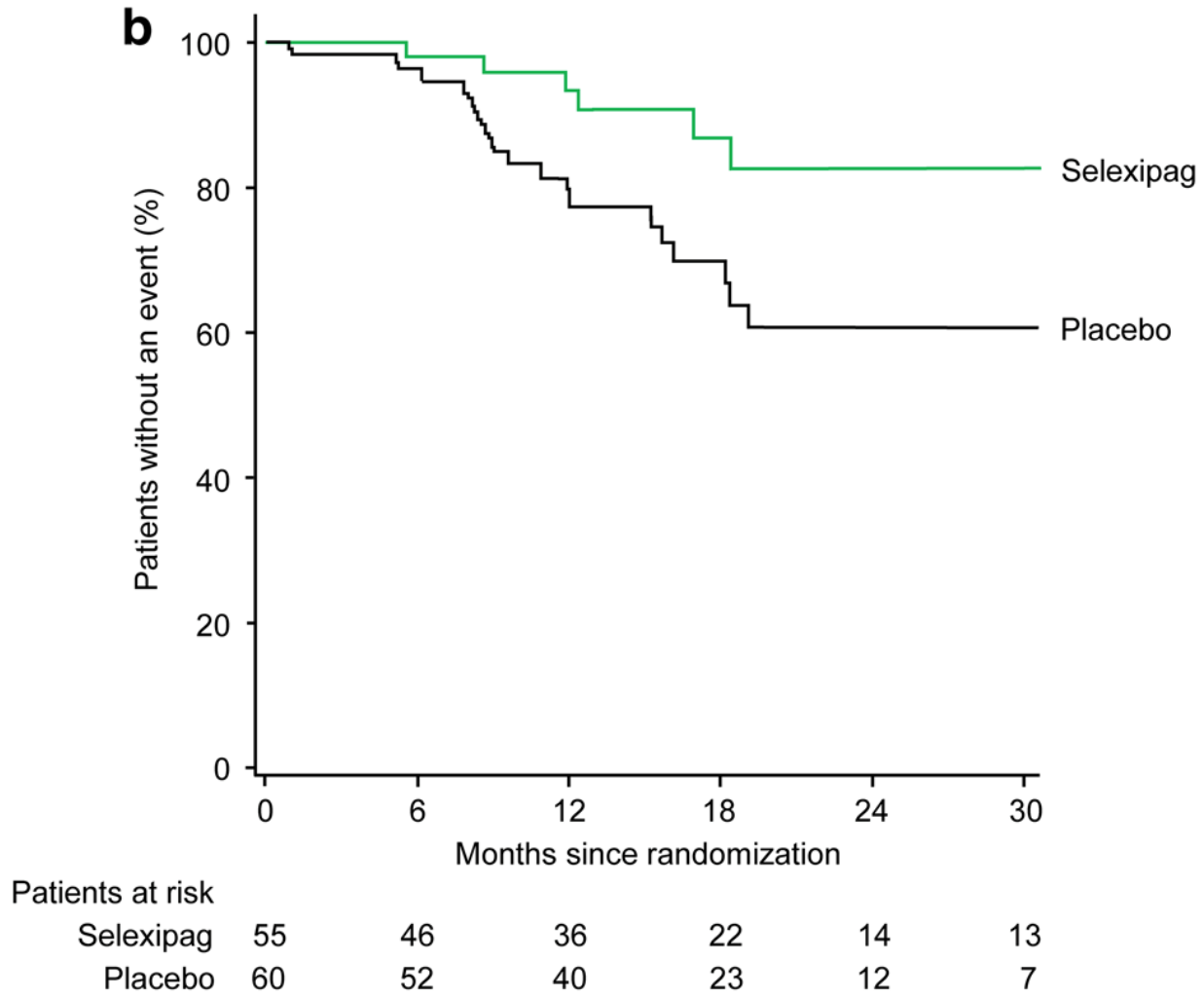


Effect of selexipag on the primary composite endpoint of morbidity/mortality when added to Dual therapy

- WHO

FC II symptoms

64% reduction

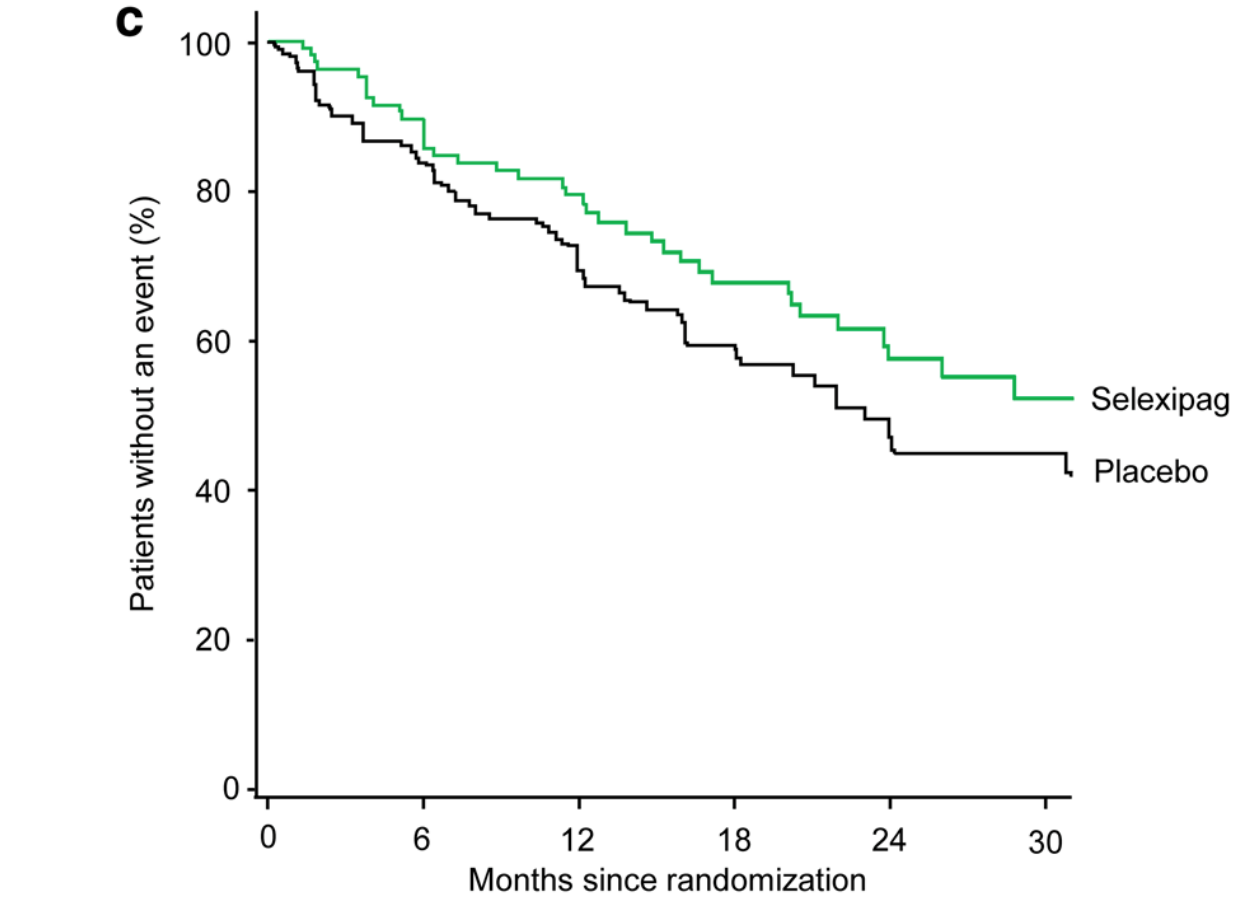


Effect of selexipag on the primary composite endpoint of morbidity/mortality when added to Dual therapy

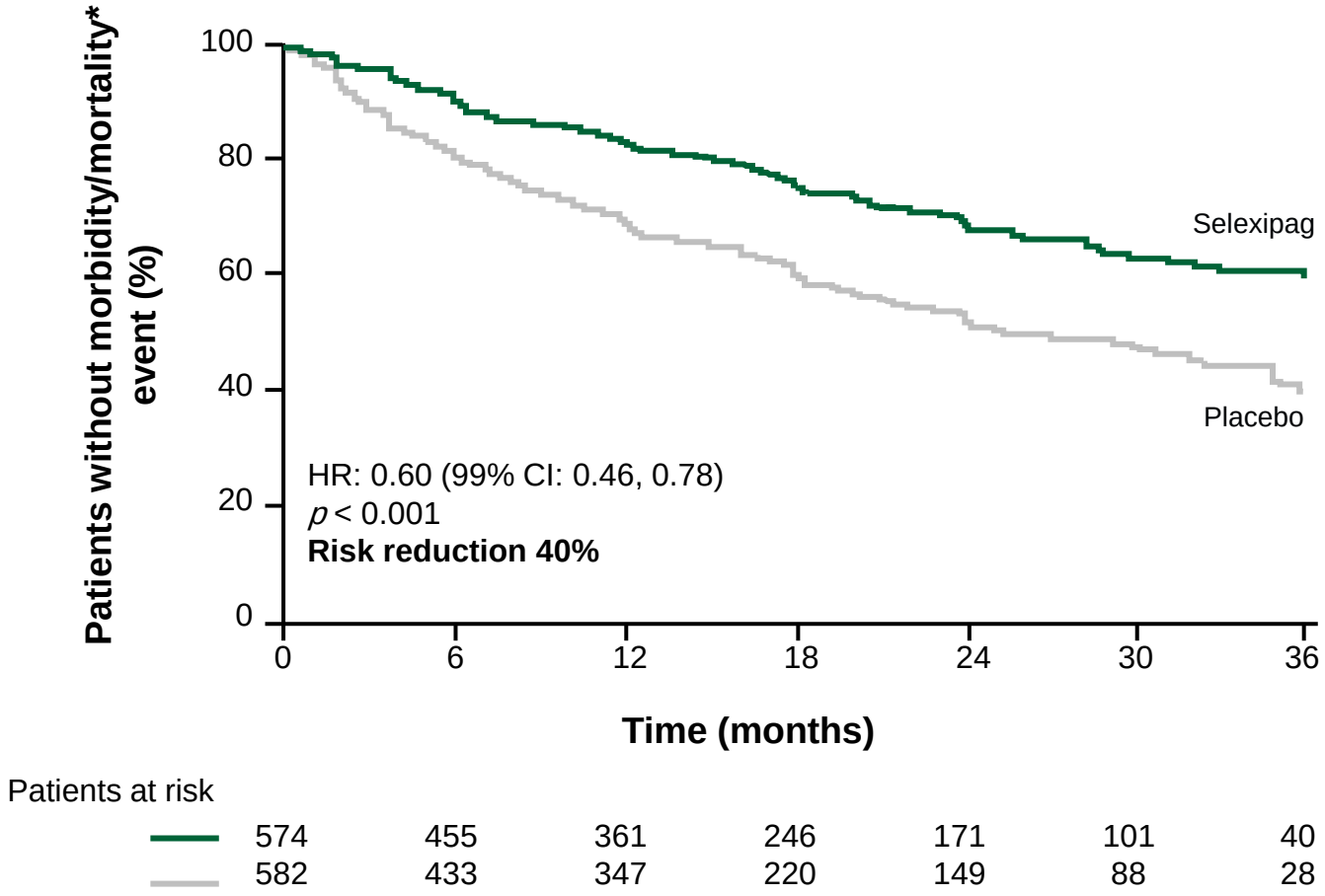
- WHO

FC III symptoms

26% reduction



Primary composite endpoint of morbidity/mortality in GRIPHON



Griphon OL

- Open label extension study in 2021
- Data on long term safety, tolerability, and survival of PAH patients
- Longest follow up period of PAH patients to date

Adv Ther
https://doi.org/10.1007/s12325-021-01898-1

Griphon OL

Table 1 Treatment disposition at the cut-off date (1 Sep 2019)

	Selexipag treated patients, (n = 953)
Ongoing in study, n (%)	216 (22.7)
Completed study treatment, n (%)	163 (17.1)
Discontinued study treatment, n (%)	574 (60.2)
Reason for discontinuation[a], n (%)	
Adverse event	251 (26.3)
Death	152 (15.9)
Withdrawal by patient	107 (11.2)
Progression of PAH	24 (2.5)
Physician decision	18 (1.9)
Lost to follow-up	10 (1.0)
Other	12 (1.3)

Data presented for the safety/tolerability set
PAH pulmonary arterial hypertension
[a]A patient may have discontinued selexipag for multiple reasons, but only the primary reason for discontinuation is reported here

Most frequent[b] adverse events	**n (%)**	**Incidence rate per year per 100 treated patients**
Headache	647 (67.9)	66.3
Diarrhoea	425 (44.6)	23.0
Nausea	313 (32.8)	14.3
PAH worsening	311 (32.6)	11.9
Pain in jaw	268 (28.1)	12.0
Pain in extremity	175 (18.4)	6.7
Vomiting	174 (18.3)	6.8
Dyspnoea	172 (18.0)	6.4
Oedema peripheral	159 (16.7)	5.8
Myalgia	157 (16.5)	6.1
Dizziness	156 (16.4)	5.9
Nasopharyngitis	149 (15.6)	5.6
Right ventricular failure	147 (15.4)	5.1
Upper respiratory tract infection	136 (14.3)	5.1
Cough	130 (13.6)	4.8
Arthralgia	119 (12.5)	4.4
Flushing	117 (12.3)	4.4
Anaemia	108 (11.3)	3.9
Bronchitis	100 (10.5)	3.6

Data presented for the safety/tolerability set
PAH pulmonary arterial hypertension
[a]All adverse events leading to discontinuation of selexipag are reported here and not only those considered the primary reason for discontinuation as presented in Table 1
[b]Occurring in ≥ 10% of patients

Adv Ther
https://doi.org/10.1007/s12325-021-01898-1

Griphon OL

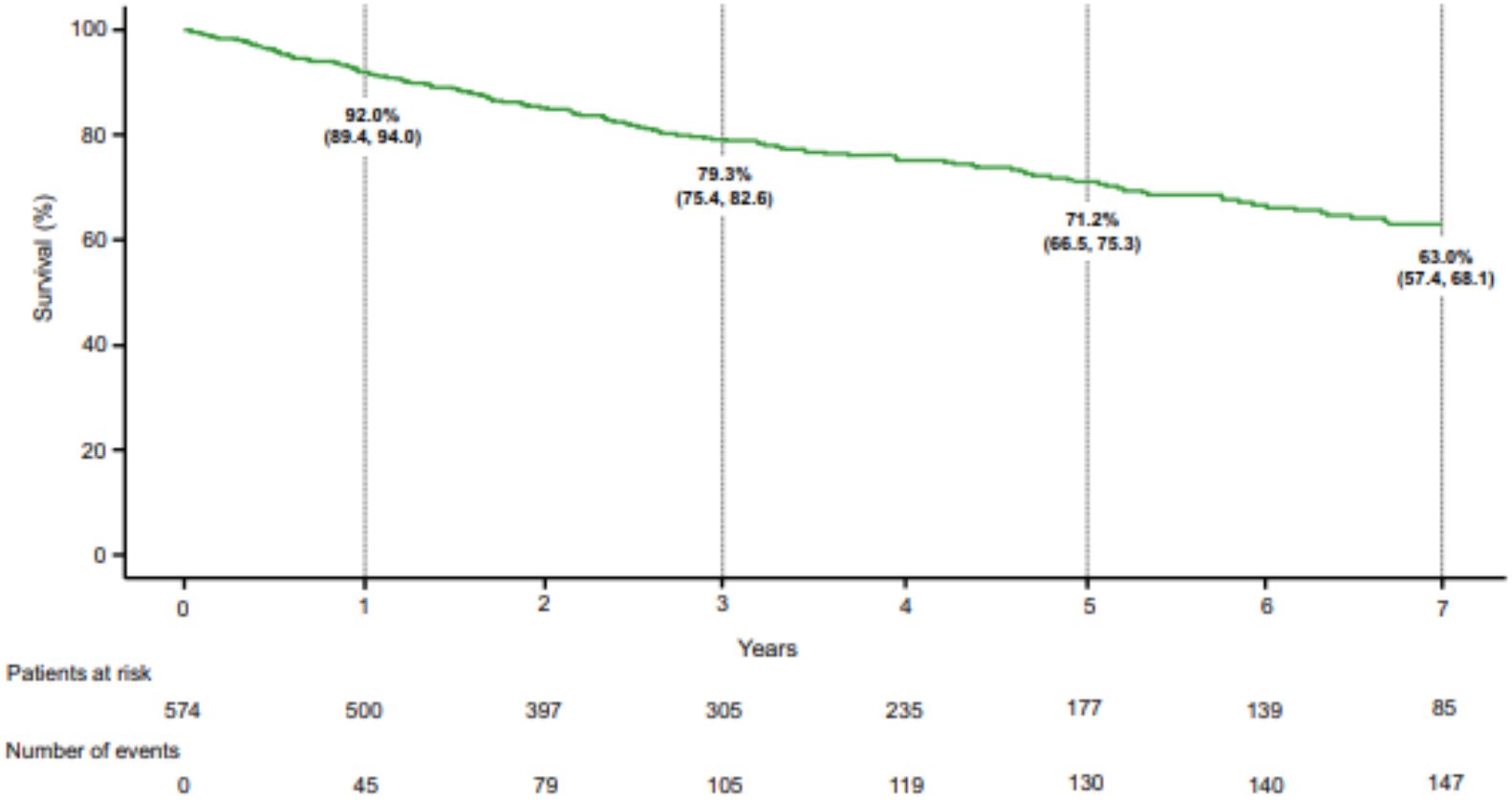


Fig. 2 Survival in selexipag treated patients. Analyses performed in the survival analysis set. Kaplan–Meier curve for time from selexipag initiation to death up to data cut-off (1 September 2019). Kaplan–Meier estimates (95% CI) are shown at 1, 3, 5 and 7 years

Adv Ther
https://doi.org/10.1007/s12325-021-01898-1

Treatment follow-up (with comorbidities)

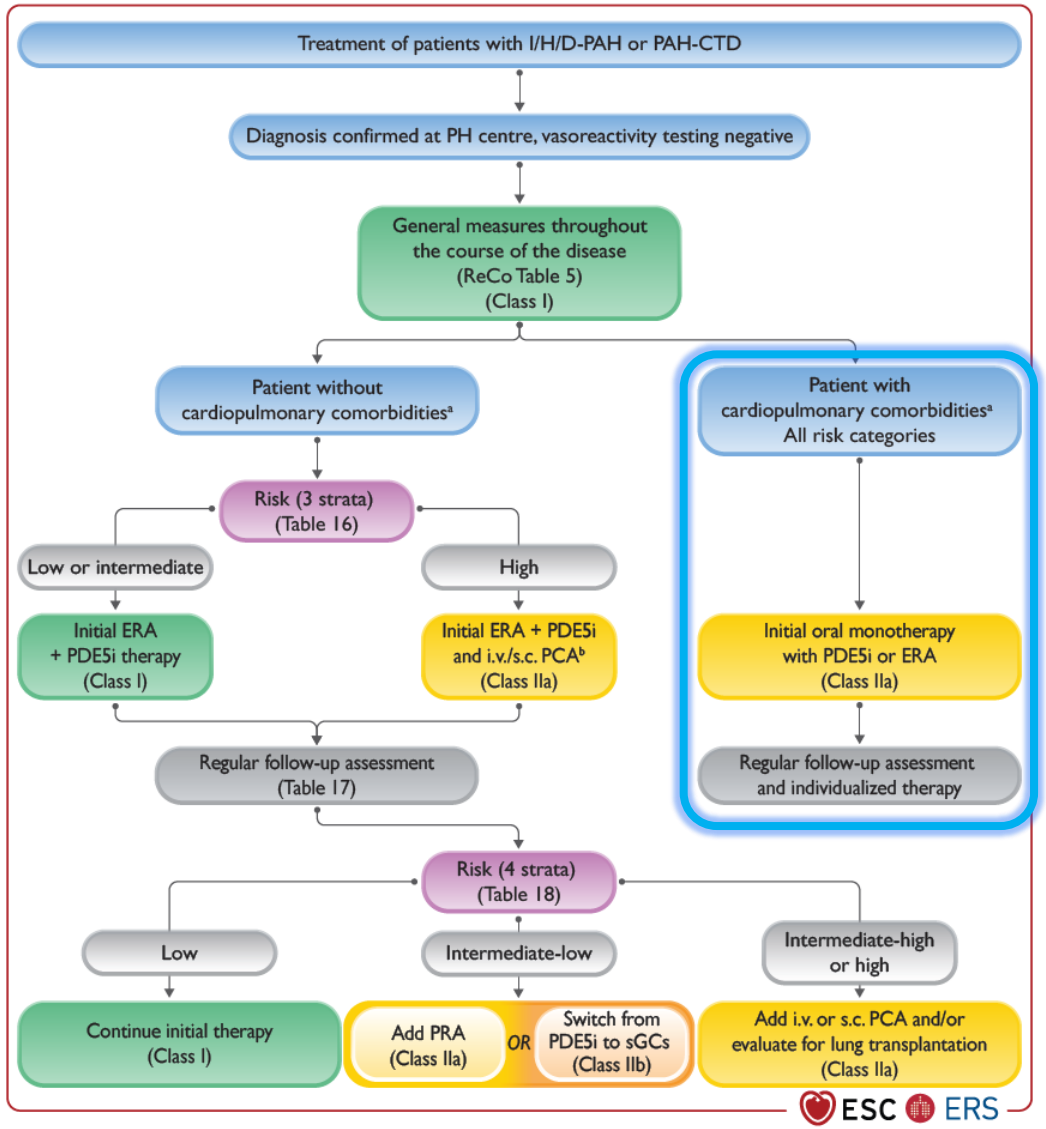


Figure 9, p.49

- Comorbid patients have **no specific treatment recommendation** at follow-up beyond decisioning on an individual basis in the figure
- Text outlines that for patients with cardiopulmonary comorbidities who present at intermediate or high risk of death while receiving monotherapy, **additional PAH medication may be considered** on an individual basis (Class IIb)

PHENOTYPING TYPE 2 OR TYPE 2.

Table 23 Patient phenotyping and likelihood for left heart disease as cause of pulmonary hypertension

Feature	PH-LHD unlikely	Intermediate probability	PH-LHD likely
Age	<60 years	60–70 years	>70 years
Obesity, hypertension, dyslipidaemia, glucose intolerance/ diabetes	No factors	1–2 factors	>2 factors
Presence of known LHD	No	Yes	Yes
Previous cardiac intervention	No	No	Yes
Atrial fibrillation	No	Paroxysmal	Permanent/persistent
Structural LHD	No	No	Present
ECG	Normal or signs of RV strain	Mild LVH	LBBB or LVH
Echocardiography	No LA dilation E/e′ <13	No LA dilation Grade <2 mitral flow	LA dilation (LAVI >34 mL/ m^2) LVH Grade >2 mitral flow
CPET	High VE/VCO_2 slope No EOV	Elevated VE/VCO_2 slope EOV	Mildly elevated VE/VCO_2 slope EOV
cMRI	No left heart abnormalities		LVH LA dilation (strain or LA/RA >1)

cMRI, cardiac magnetic resonance imaging; CPET, cardiopulmonary exercise testing; E/e', ratio between early mitral inflow velocity and mitral annular early diastolic velocity; ECG, electrocardiogram; EOV, exercise oscillatory ventilation; LA, left atrial; LAVI, left atrial volume index; LBBB, left bundle branch block; LHD, left heart disease; LVH, left ventricular hypertrophy; PH, pulmonary hypertension; PH-LHD, left heart disease associated with pulmonary hypertension; RA, right atrium; RV, right ventricle; $VE/VECO_2$, ventilatory equivalents for carbon dioxide.

Assigning the likelihood of LHD as a cause of PH. This assessment may help to decide which patients should undergo a full work-up, including invasive haemodynamic assessment (see *Figure 11* and *Figure S2*).

Recommendation Table 22A

Recommendations			Class[a]	Level[b]
In patients with LHD, optimizing treatment of the underlying condition is recommended before considering assessment of suspected PH[27,28]			I	A
RHC is recommended for suspected PH in patients with LHD, if it aids management decisions			I	C
RHC is recommended in patients with severe tricuspid regurgitation with or without LHD prior to surgical or interventional valve repair			I	C
For patients with LHD and suspected PH with features of a severe pre-capillary component and/or markers of RV dysfunction, referral to a PH centre for a complete diagnostic work-up is recommended[29,47,142]			I	C
In patients with LHD and CpcPH with a severe pre-capillary component (e.g. PVR >5 WU), an individualized approach to treatment is recommended			I	C
When patients with PH and multiple risk factors for LHD, who have a normal PAWP at rest but an abnormal response to exercise or fluid challenge, are treated with PAH drugs, close monitoring is recommended			I	C
In patients with PH at RHC, a borderline PAWP (13–15 mmHg) and features of HFpEF, additional testing with exercise or fluid challenge may be considered to uncover post-capillary PH[133,143]			IIb	C
Drugs approved for PAH are not recommended in PH-LHD[c] [631,678,683,684,701,706]			III	A
The use of PDE5is in patients with HFpEF and isolated post-capillary PH is not recommended	Low	Conditional	III	C

PHENOTYPING TYPE 3 OR TYPE 3.

Recommendations	Class[a]	Level[b]
If PH is suspected in patients with lung disease, it is recommended that echocardiography[c] be performed and the results interpreted in conjunction with ABG, PFTs including DLCO, and CT imaging	I	C
In patients with lung disease and suspected PH, it is recommended to optimize treatment of the underlying lung disease and, where indicated, hypoxaemia, sleep-disordered breathing, and/or alveolar hypoventilation	I	C
In patients with lung disease and suspected severe PH, or where there is uncertainty regarding the treatment of PH, referral to a PH centre is recommended[d]	I	C
In patients with lung disease and severe PH, an individualized approach to treatment is recommended	I	C
It is recommended to refer eligible patients with lung disease and PH for LTx evaluation	I	C
In patients with lung disease and suspected PH, RHC is recommended if the results are expected to aid management decisions	I	C
Inhaled treprostinil may be considered in patients with PH associated with ILD[734]	IIb	B
The use of ambrisentan is not recommended in patients with PH associated with IPF[740]	III	B
The use of riociguat is not recommended in patients with PH associated with IIP[181]	III	B
The use of PAH medication is not recommended in patients with lung disease and non-severe PH[e]	III	C

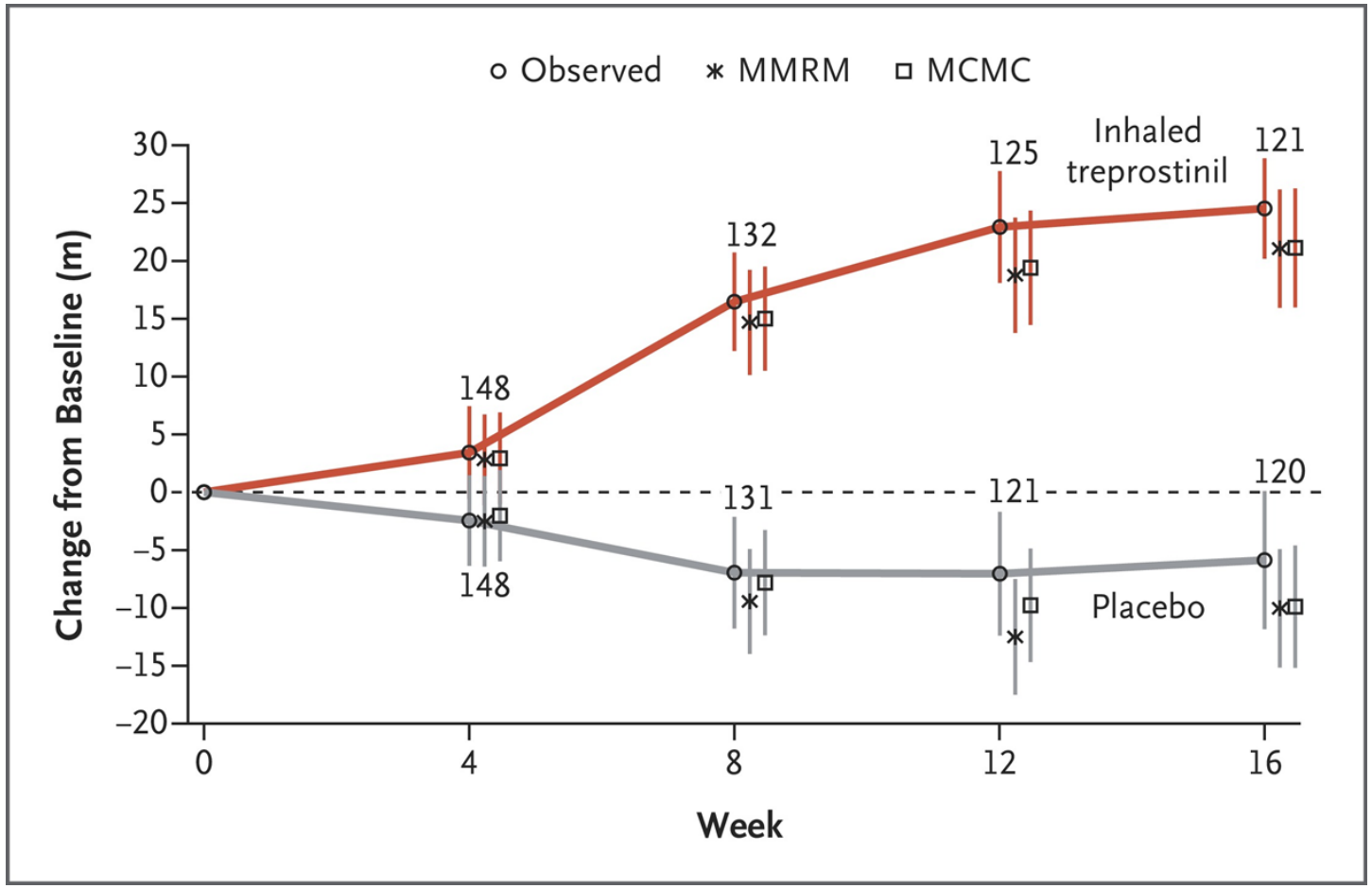
PHENOTYPING TYPE 3 OR TYPE 3.

Recommendations			Class[a]	Level[b]
If PH is suspected in patients with lung disease, it is recommended that echocardiography[c] be performed and the results interpreted in conjunction with ABG, PFTs including DLCO, and CT imaging			I	C
In patients with lung disease and suspected PH, it is recommended to optimize treatment of the underlying lung disease and, where indicated, hypoxaemia, sleep-disordered breathing, and/or alveolar hypoventilation			I	C
In patients with lung disease and suspected severe PH, or where there is uncertainty regarding the treatment of PH, referral to a PH centre is recommended[d]			I	C
In patients with lung disease and severe PH, an individualized approach to treatment is recommended			I	C
It is recommended to refer eligible patients with lung disease and PH for LTx evaluation			I	C
In patients with lung disease and suspected PH, RHC is recommended if the results are expected to aid management decisions			I	C
Inhaled treprostinil may be considered in patients with PH associated with ILD[734]			IIb	B
The use of ambrisentan is not recommended in patients with PH associated with IPF[740]			III	B
The use of riociguat is not recommended in patients with PH associated with IIP[181]			III	B
The use of PAH medication is not recommended in patients with lung disease and non-severe PH[e]			III	C
PDE5is may be considered in patients with severe PH associated with ILD (individual decision-making in PH centres)	Very low	Conditional	IIb	C
The use of PDE5is in patients with ILD and non-severe PH is not recommended	Very low	Conditional	III	C

Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease-2021

- Patients with pulmonary hypertension due to interstitial lung disease were randomly assigned to inhaled treprostinil or placebo.
- At 16 weeks, there was a significant improvement in exercise capacity with inhaled treprostinil as compared with placebo as assessed by a 6-minute walk test.

Mean Change from Baseline in Peak 6-Minute Walk Distance through Week 16.

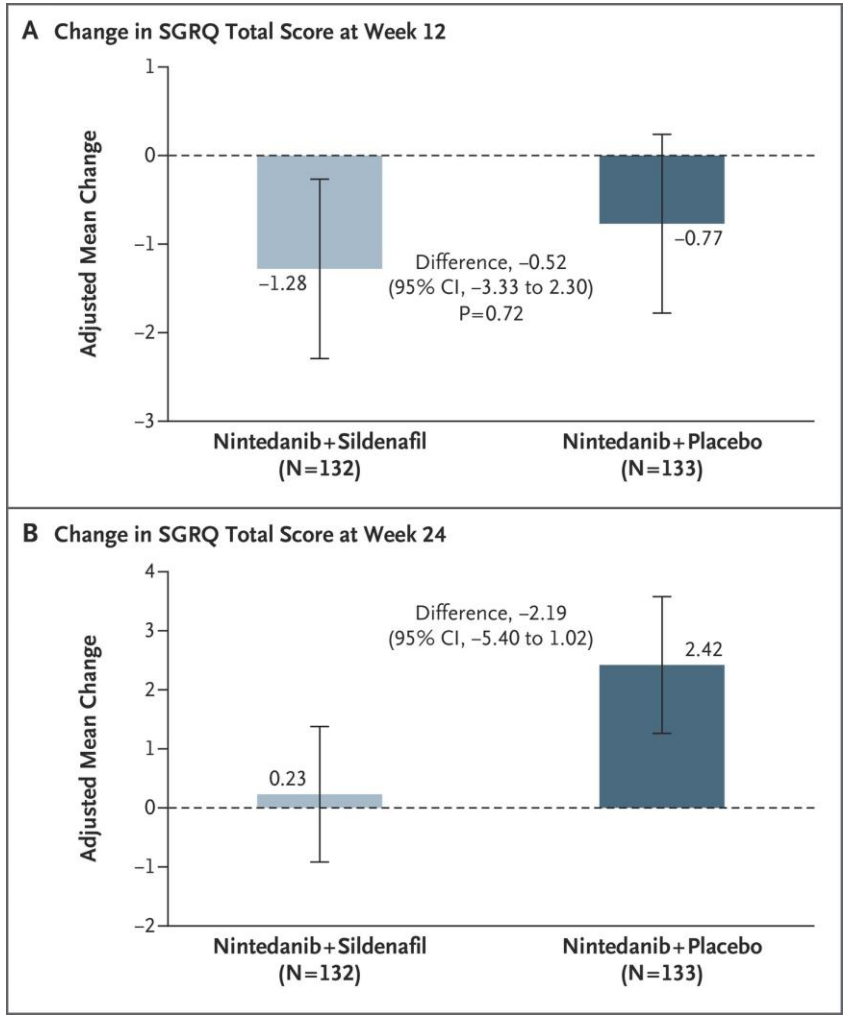


N Engl J Med
Volume 384(4):325-334
January 28, 2021

Nintedanib plus Sildenafil in Patients with Idiopathic Pulmonary Fibrosis

- In a trial, patients with moderate to severely advanced idiopathic pulmonary fibrosis were treated with nintedanib plus sildenafil or nintedanib alone, with the goal of decreasing IPF symptoms.
- There were no between-group differences in any of three symptom measures.

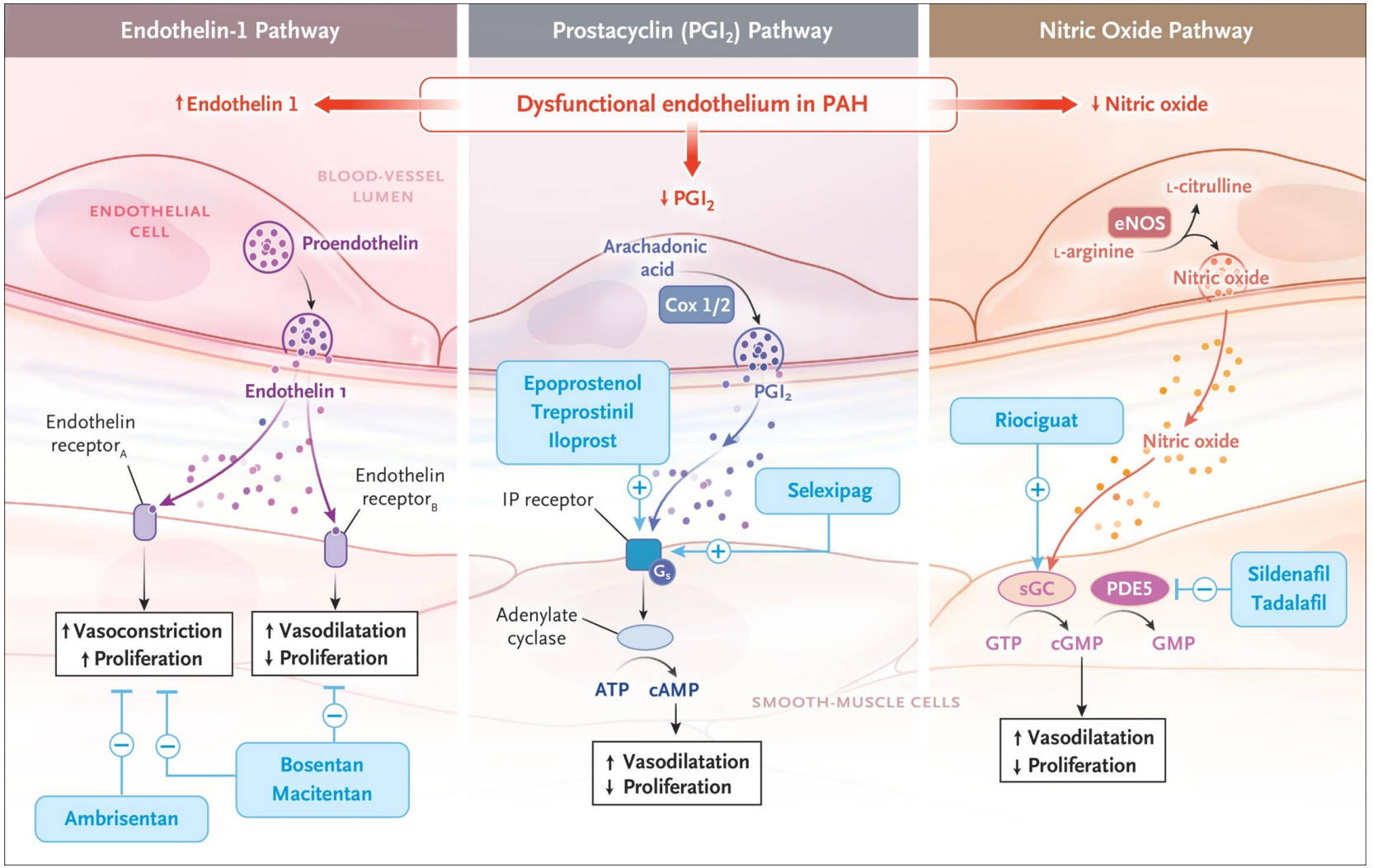
Change from Baseline in the SGRQ Total Score at Week 12 and Week 24.



N Engl J Med
Volume 379(18):1722-1731
November 1, 2018

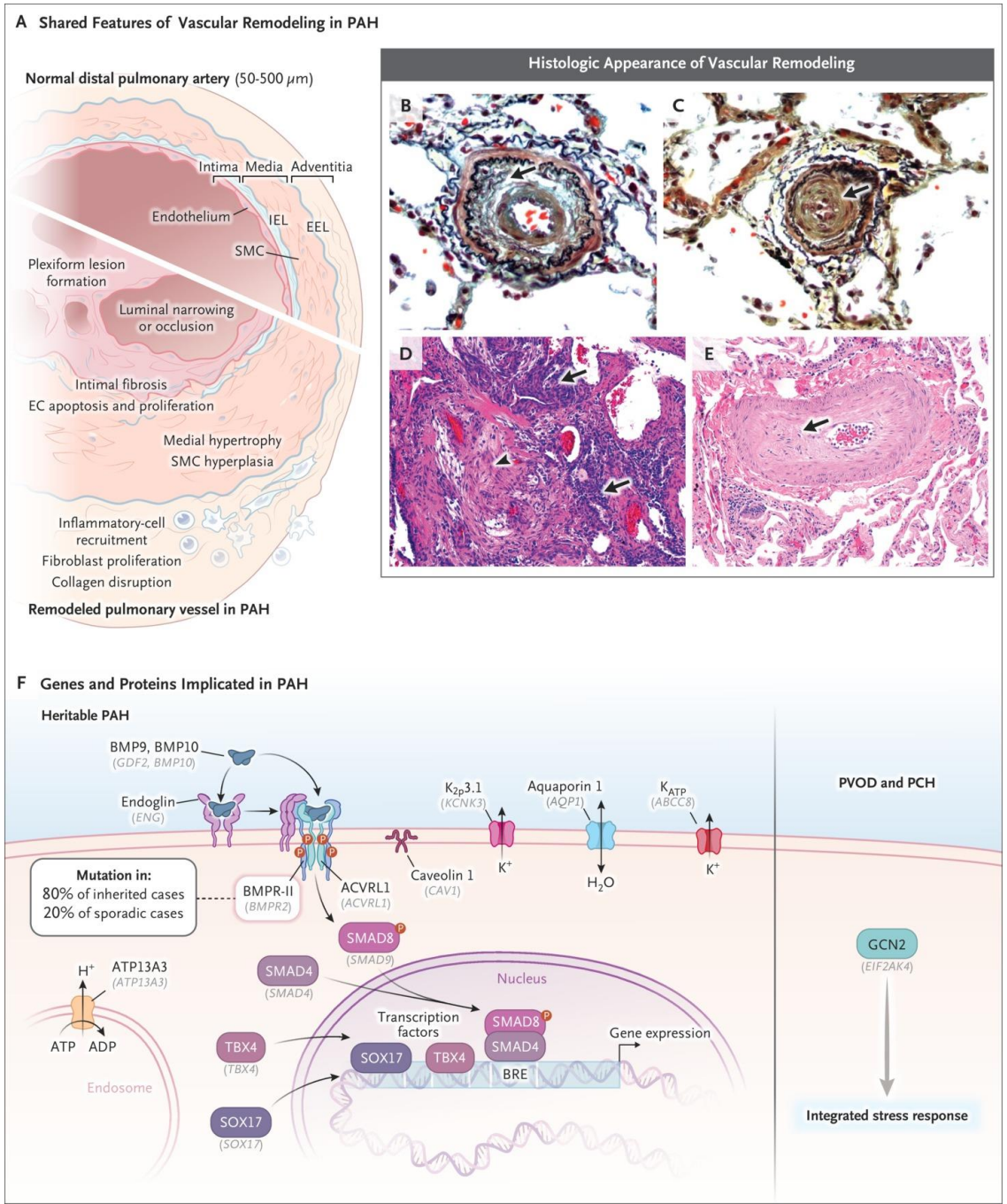
New Kid in town ???

Three Classic Pathways of Targeted Therapy for PAH.



Hassoun PM. N Engl J Med 2021;385:2361-2376

Pathobiologic Features of Pulmonary Arterial Hypertension.



Hassoun PM. N Engl J Med 2021;385:2361-2376

Phase 3 Trial of Sotatercept for Treatment of Pulmonary Arterial Hypertension

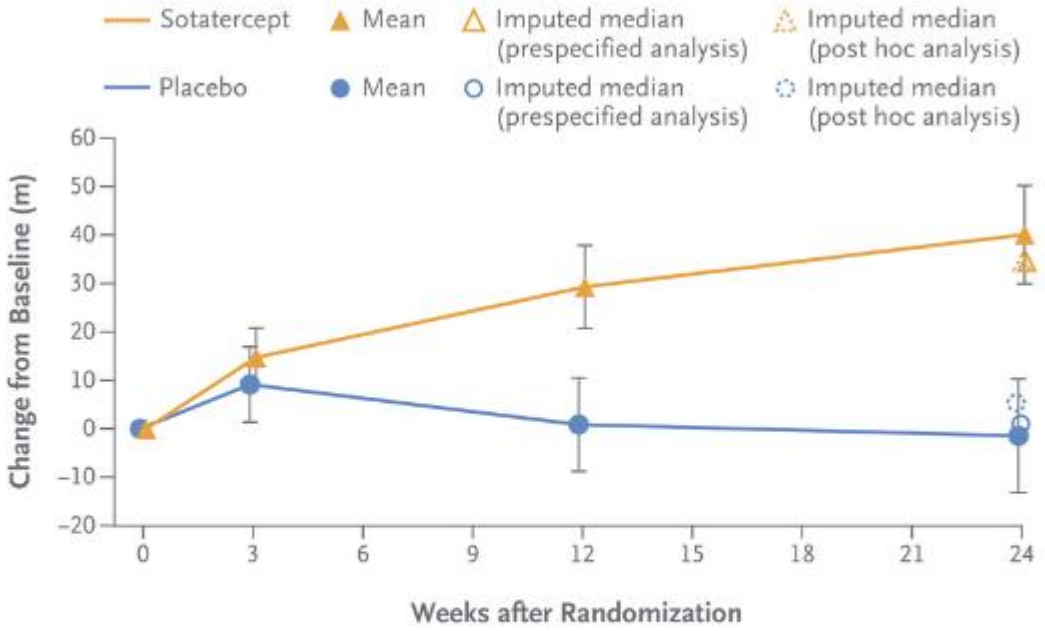
Sotatercept is a first-in-class fusion protein consisting of the Fc domain of human IgG linked to the extracellular domain of human ActRIIA, which acts as a ligand trap for selected **TGF-β superfamily members**. Inhibition of these ligands by sotatercept is proposed to rebalance pulmonary vascular homeostasis toward growth-inhibiting

RCT 262- Subcutaneous q 3 weeks. Over 24 weeks

In patients with pulmonary arterial hypertension who were receiving stable background therapy, sotatercept resulted in a greater improvement in exercise capacity (as assessed by the 6-minute walk test) than placebo.

N Engl J Med
Volume 388(16):1478-1490
April 20, 2023

Change in 6-Minute Walk Distance through Week 24



	Sotatercept	Placebo
Median change in 6-minute walk distance	34.4 m (95% CI, 33.0 to 35.5)	1.0 m (95% CI, −0.3 to 3.5)
Hodges–Lehmann estimate of the difference in change from baseline	40.8 m (95% CI, 27.5 to 54.1); P<0.001	

Adverse Events of Interest or Special Interest

	Sotatercept (N=163)	Placebo (N=160)
	no. of patients (%)	
Increased hemoglobin	9 (5.5)	0
Thrombocytopenia	10 (6.1)	4 (2.5)
Bleeding events	35 (21.5)	20 (12.5)
Increased blood pressure	6 (3.7)	1 (0.6)
Telangiectasia	17 (10.4)	5 (3.1)

Take home message

- It is now clear that PAH type 1 treatment start with dual therapy.
- Long term data is now available and encouraging
- Escalate early based on a simplified risk assessment to triple therapy.
- Monotherapy is now reserved for patients with PH with phenotypes from class 2 or 3 pulmonary hypertension
- A new class of medication is being investigated with short term encouraging results.