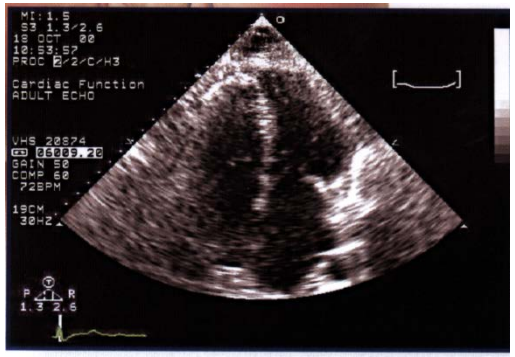
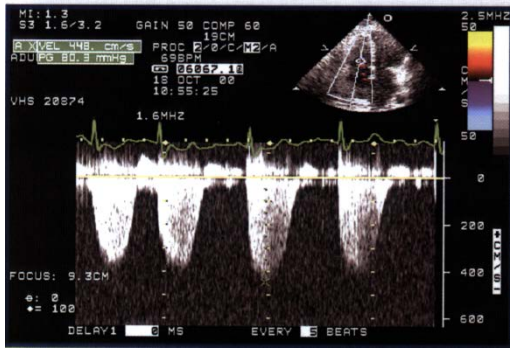
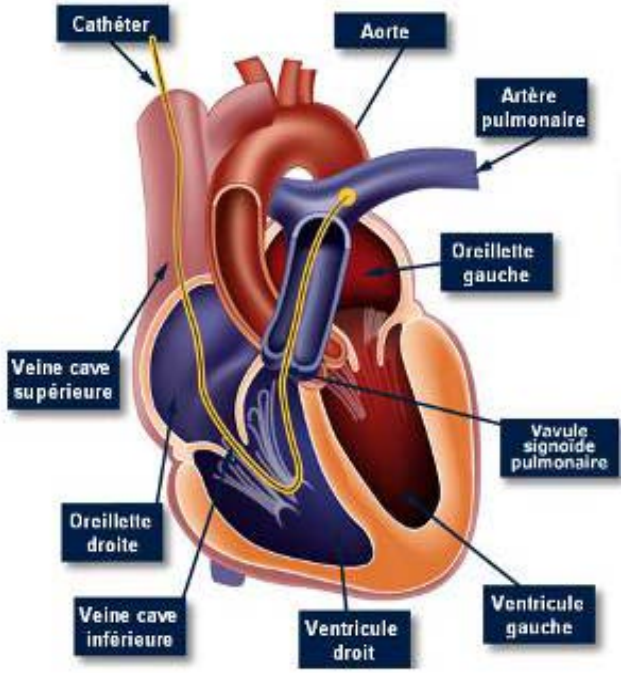
Hemodynamic classification of pulmonary hypertension (PH)

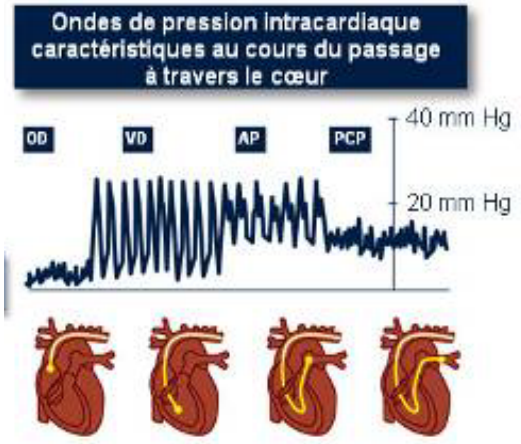
Screening
Transthoracic echo
(TRJV > 2.8 m/s)





Diagnosis
Right Heart Catheterisation
(Mean PAP > 25 mmHg)





- Precapillary PH : PAWP ≤ 15 mmHg (PAH: PVR > 3 Wood units)
- Post-capillary PH : PAWP > 15 mmHg (isolated if dPAP-PAWP < 7 mmHg)

Galiè N. et al. ESC/ERS Guidelines. Eur Heart J & Eur Respir J 2015.

Hemodynamic classification of pulmonary hypertension (PH)

Definition	Characteristics[a]
PH	PAPm ≥25 mmHg
Pre-capillary PH	PAPm ≥25 mmHg PAWP ≤15 mmHg
Post-capillary PH	PAPm ≥25 mmHg PAWP >15 mmHg
Isolated post-capillary PH (Ipc-PH)	DPG <7 mmHg and/or PVR ≤3 WU[c]
Combined post-capillary and pre-capillary PH (Cpc-PH)	DPG ≥7 mmHg and/or PVR >3 WU[c]

Vachiéry JL, et al. J Am Coll Cardiol 2013.
Galiè N. et al. ESC/ERS Guidelines. Eur Heart J & Eur Respir J 2015.

Clinical classification of pulmonary hypertension (PH)

1. Pulmonary arterial hypertension

1.1 Idiopathic
1.2 Heritable
  1.2.1 BMPR2 mutation
  1.2.2 Other mutations
1.3 Drugs and toxins induced
1.4 Associated with:
  1.4.1 Connective tissue disease
  1.4.2 Human immunodeficiency virus (HIV) infection
  1.4.3 Portal hypertension
  1.4.4 Congenital heart disease (Table 6)
  1.4.5 Schistosomiasis

1'. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis

1'.1 Idiopathic
1'.2 Heritable
  1'.2.1 EIF2AK4 mutation
  1'.2.2 Other mutations
1'.3 Drugs, toxins and radiation induced
1'.4 Associated with:
  1'.4.1 Connective tissue disease
  1'.4.2 HIV infection

1''. Persistent pulmonary hypertension of the newborn

2. Pulmonary hypertension due to left heart disease

2.1 Left ventricular systolic dysfunction
2.2 Left ventricular diastolic dysfunction
2.3 Valvular disease
2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
2.5 Congenital/acquired pulmonary veins stenosis

3. Pulmonary hypertension due to lung diseases and/or hypoxia

3.1 Chronic obstructive pulmonary disease
3.2 Interstitial lung disease
3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4 Sleep-disordered breathing
3.5 Alveolar hypoventilation disorders
3.6 Chronic exposure to high altitude
3.7 Developmental lung diseases (Web Table III)

4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions

4.1 Chronic thromboembolic pulmonary hypertension
4.2 Other pulmonary artery obstructions
  4.2.1 Angiosarcoma
  4.2.2 Other intravascular tumors
  4.2.3 Arteritis
  4.2.4 Congenital pulmonary arteries stenoses
  4.2.5 Parasites (hydatidosis)

5. Pulmonary hypertension with unclear and/or multifactorial mechanisms

5.1 Haematological disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy
5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis, neurofibromatosis
5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4 Others: pulmonary tumoral thrombotic microangiopathy, fibrosing mediastinitis, chronic renal failure (with/without dialysis), segmental pulmonary hypertension

Galiè N. et al. ESC/ERS Guidelines. Eur Heart J & Eur Respir J 2015.

Hemodynamic classification of pulmonary hypertension (PH) – Group 2

PH associated with left heart diseases

Post-capillary PH	PAPm ≥25 mmHg PAWP >15 mmHg
Isolated post-capillary PH (Ipc-PH)	DPG <7 mmHg and/or PVR ≤3 WU[c]
Combined post-capillary and pre-capillary PH (Cpc-PH)	DPG ≥7 mmHg and/or PVR >3 WU[c]

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

Galiè N. et al. ESC/ERS Guidelines. Eur Heart J & Eur Respir J 2015.

Hemodynamic classification of pulmonary hypertension (PH) – Group 3

PH associated with chronic lung diseases

Terminology	Haemodynamics (right heart catheterization)
COPD/IPF/CPFE without PH	PAPm <25 mmHg
COPD/IPF/CPFE with PH	PAPm ⩾25 mmHg
COPD/IPF/CPFE with severe PH	PAPm >35 mmHg, or PAPm ⩾25 mmHg in the presence of a low cardiac output (CI <2.5 L/min, not explained by other causes)

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

Galiè N. et al. ESC/ERS Guidelines. Eur Heart J & Eur Respir J 2015.

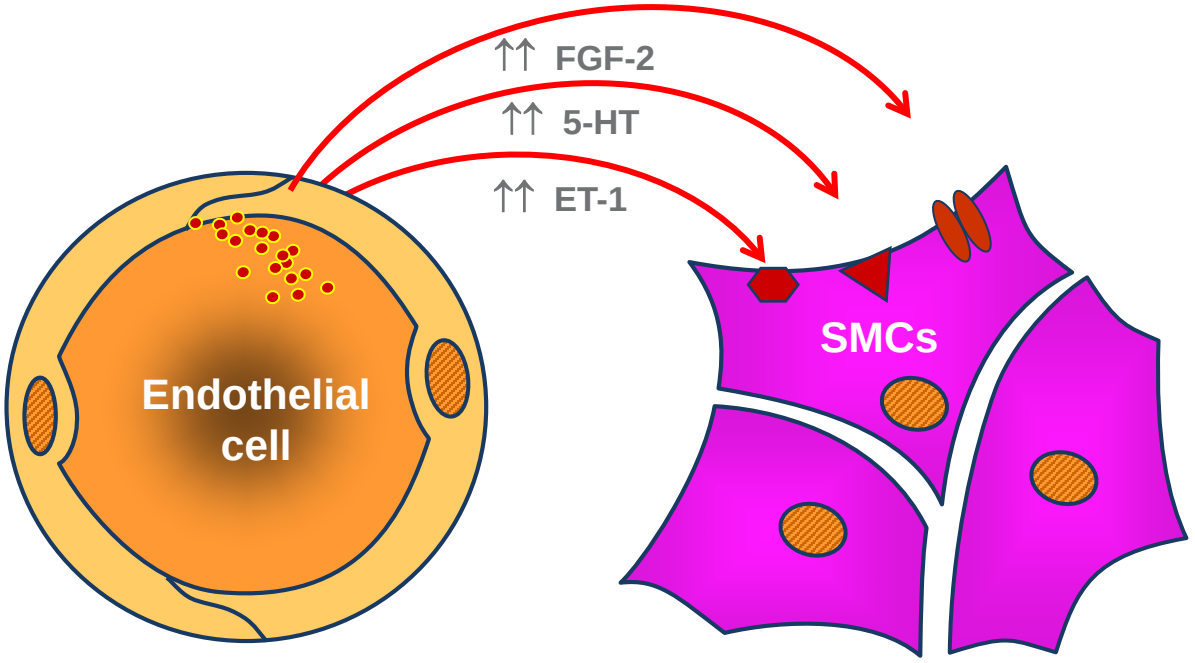
Clinical classification of pulmonary hypertension (PH) – Group 1 : PAH

1. Pulmonary arterial hypertension
1.1 Idiopathic
1.2 Heritable
1.2.1 BMPR2 mutation
1.2.2 Other mutations
1.3 Drugs and toxins induced
1.4 Associated with:
1.4.1 Connective tissue disease
1.4.2 Human immunodeficiency virus (HIV) infection
1.4.3 Portal hypertension
1.4.4 Congenital heart disease (Table 6)
1.4.5 Schistosomiasis

Galiè N. et al. ESC/ERS Guidelines. Eur Heart J & Eur Respir J 2015.

PAH: A rare, but not an orphan disease

- Rare: prevalence 15–50/million (incidence 6/million/year)
- Pathophysiology: pulmonary artery endothelial cell dysfunction…
- Drugs: 10 agents approved in the last 15 years (orphan drug status)
- Lung/heart–lung transplantation: if refractory to medical therapy



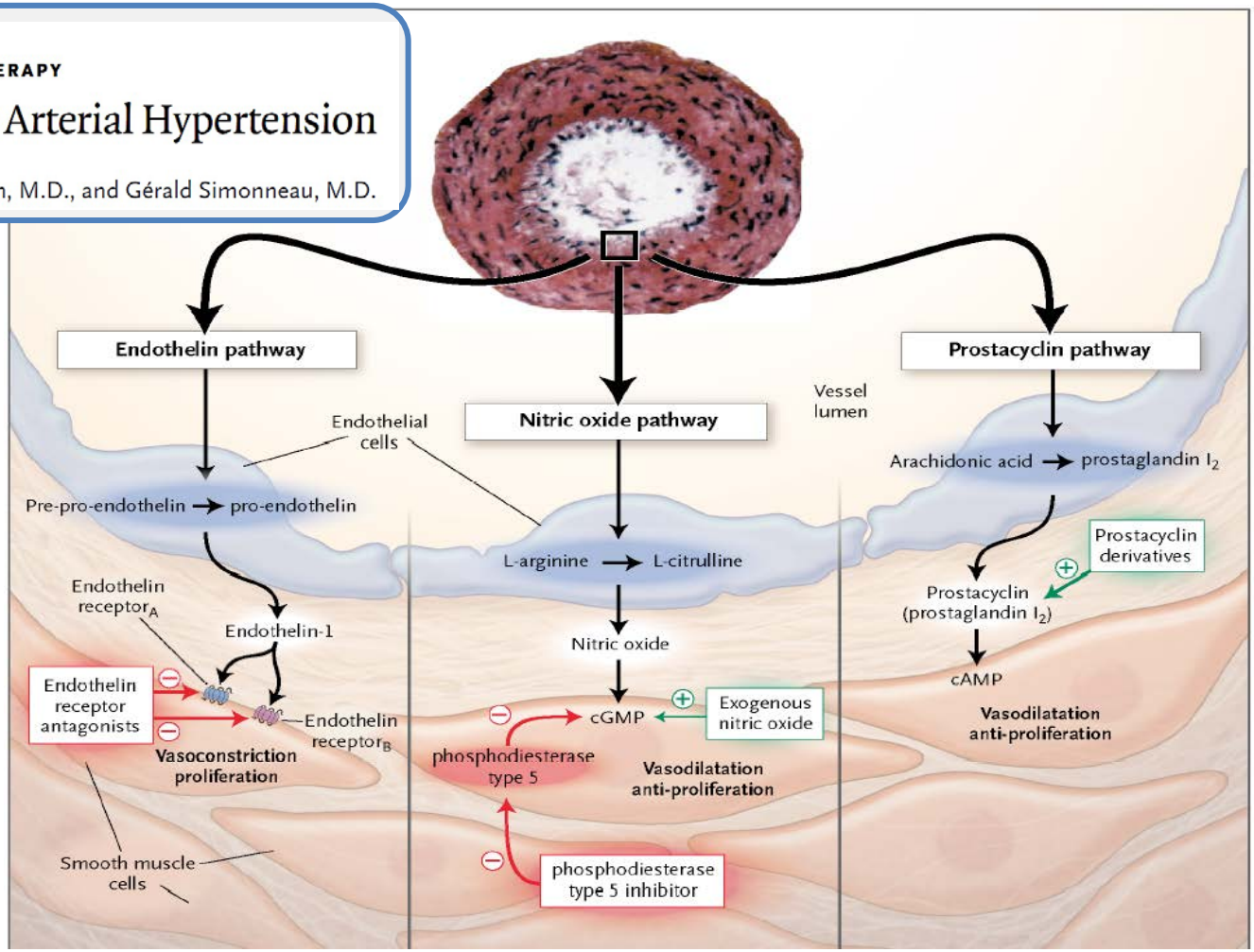
5-HT, 5-hydroxytryptamine; ET-1, endothelin 1 ; FGF-2, fibroblast growth factor 2; SMC, smooth muscle cell.

Treatment: Targeting 3 major dysfunctional pathways in PAH (2004)

DRUG THERAPY

Treatment of Pulmonary Arterial Hypertension

Marc Humbert, M.D., Ph.D., Olivier Sitbon, M.D., and Gérald Simonneau, M.D.



cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate.

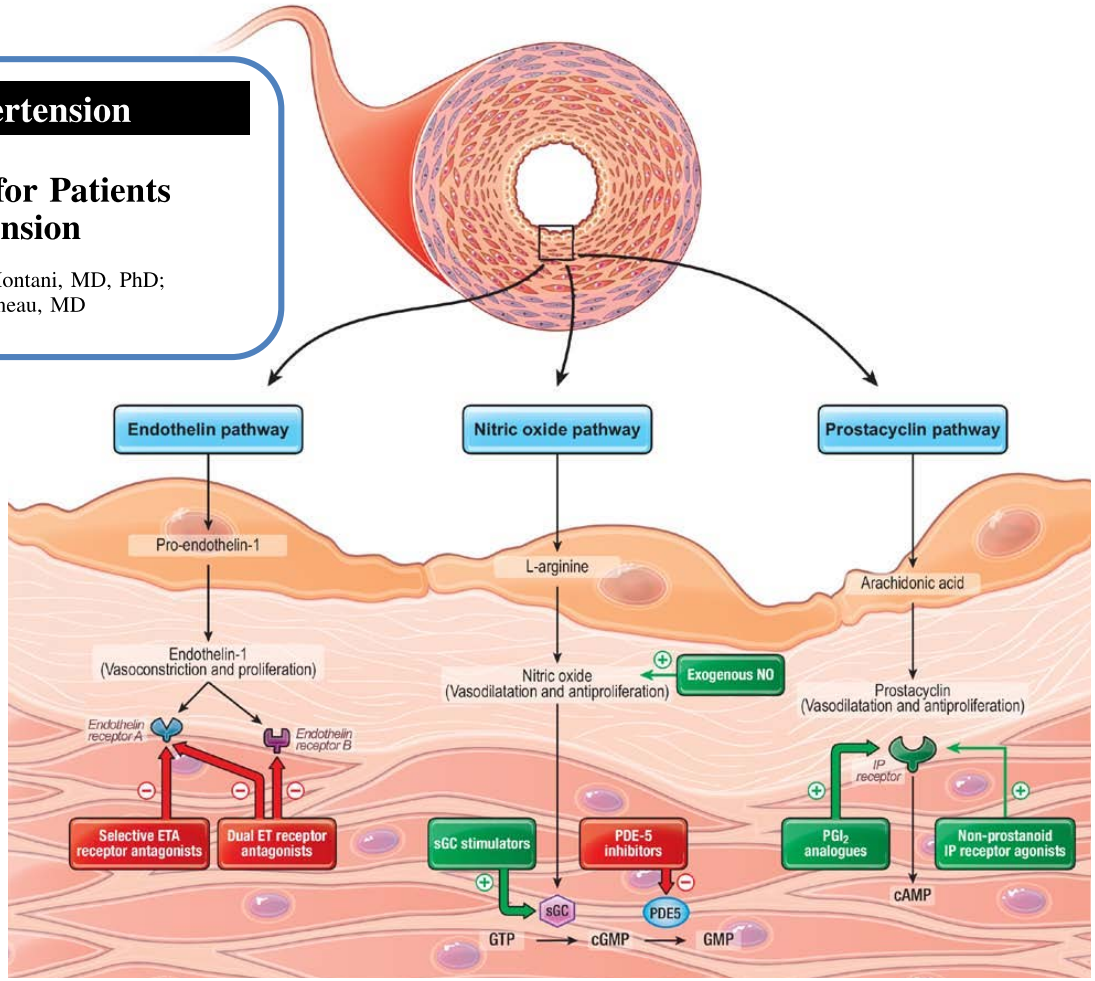
Humbert M *et al. N Engl J Med* 2004;351:1425–36.

Treatment: Targeting 3 major dysfunctional pathways in PAH (2014)

Recent Advances in Pulmonary Hypertension

Advances in Therapeutic Interventions for Patients With Pulmonary Arterial Hypertension

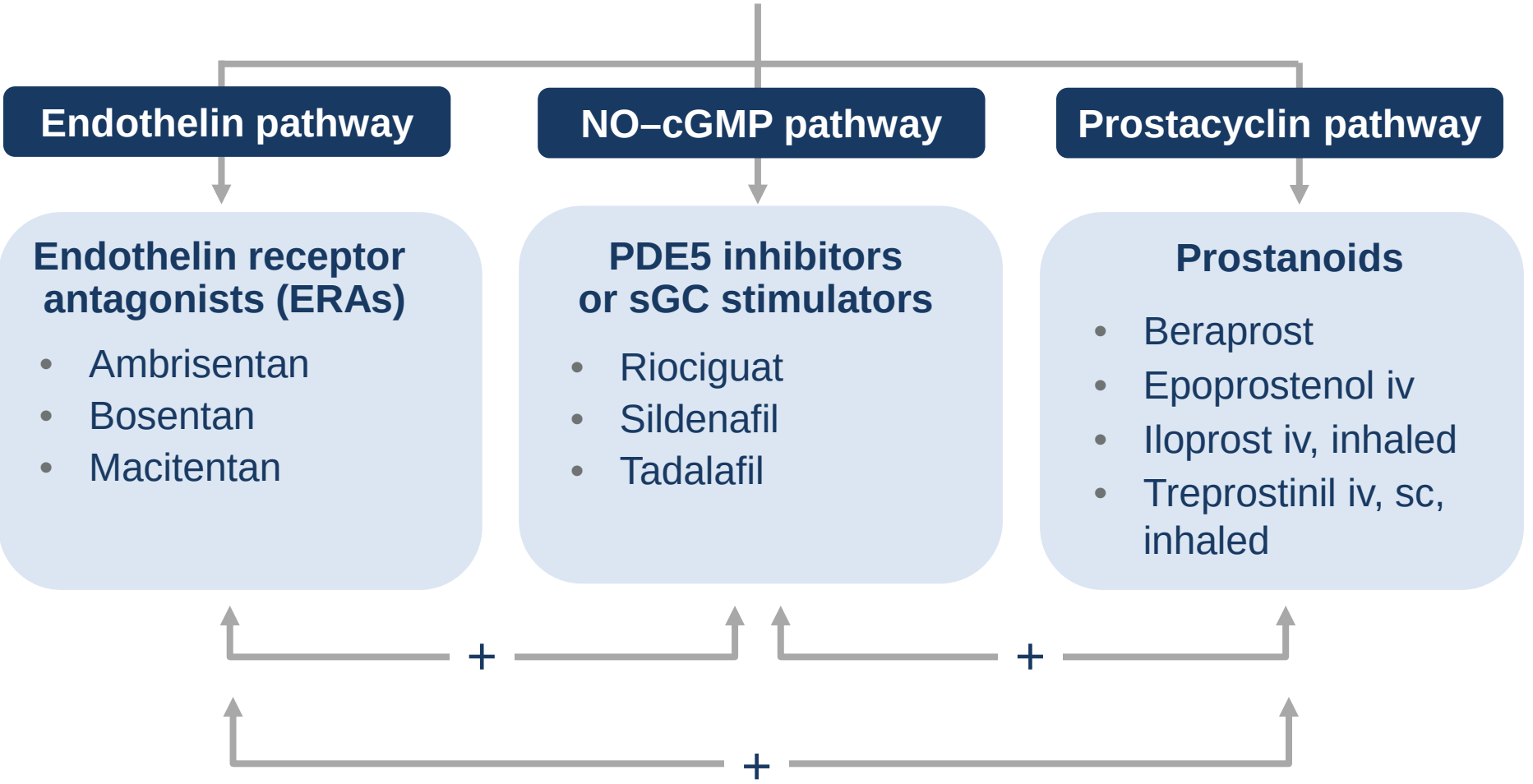
Marc Humbert, MD, PhD; Edmund M.T. Lau, MD, PhD; David Montani, MD, PhD; Xavier Jaïs, MD; Oliver Sitbon, MD, PhD; Gérald Simonneau, MD



cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; ET, endothelin; ETA, endothelin receptor A; GTP, guanosine triphosphate; NO, nitric oxide; PGI_2, prostaglandin I_2; sGC, soluble guanylate cyclase.

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

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

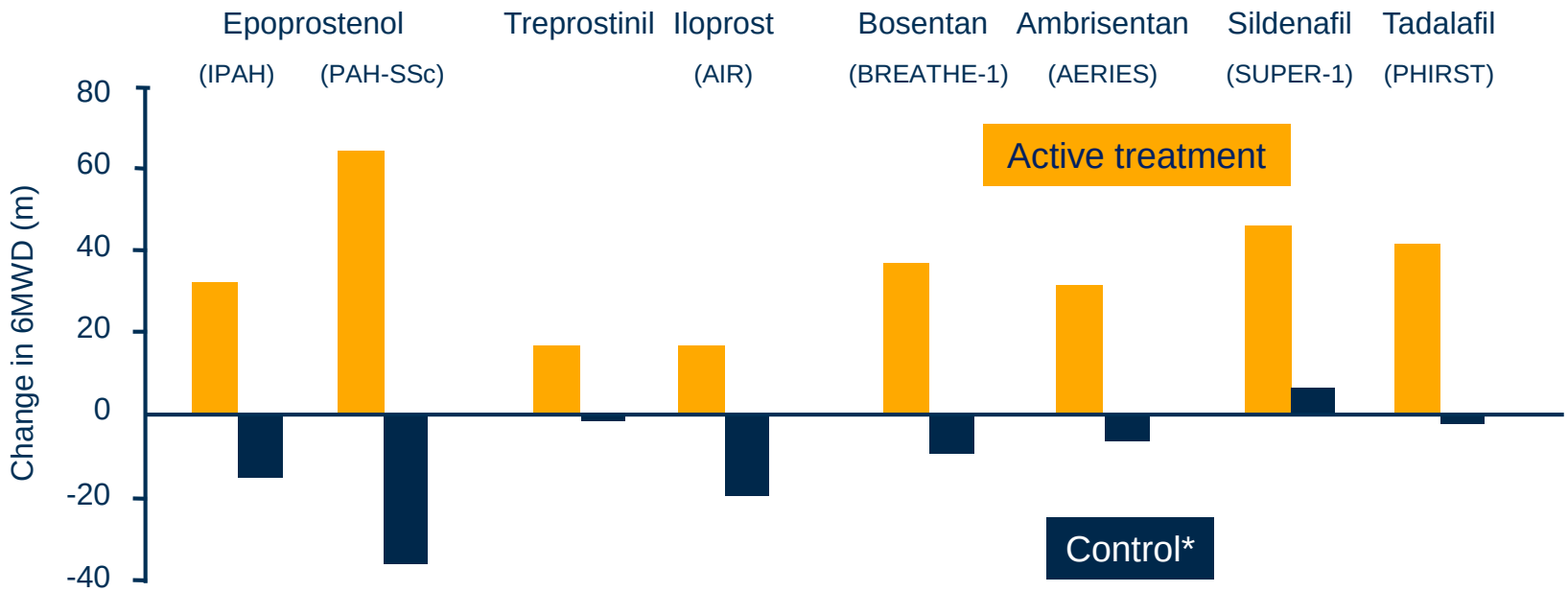


cGMP, cyclic guanosine monophosphate; iv, intravenous; NO, nitric oxide; PDE5, phosphodiesterase type 5; sc, subcutaneous; sGC, soluble guanylate cyclase.

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

RCTs with monotherapy in PAH

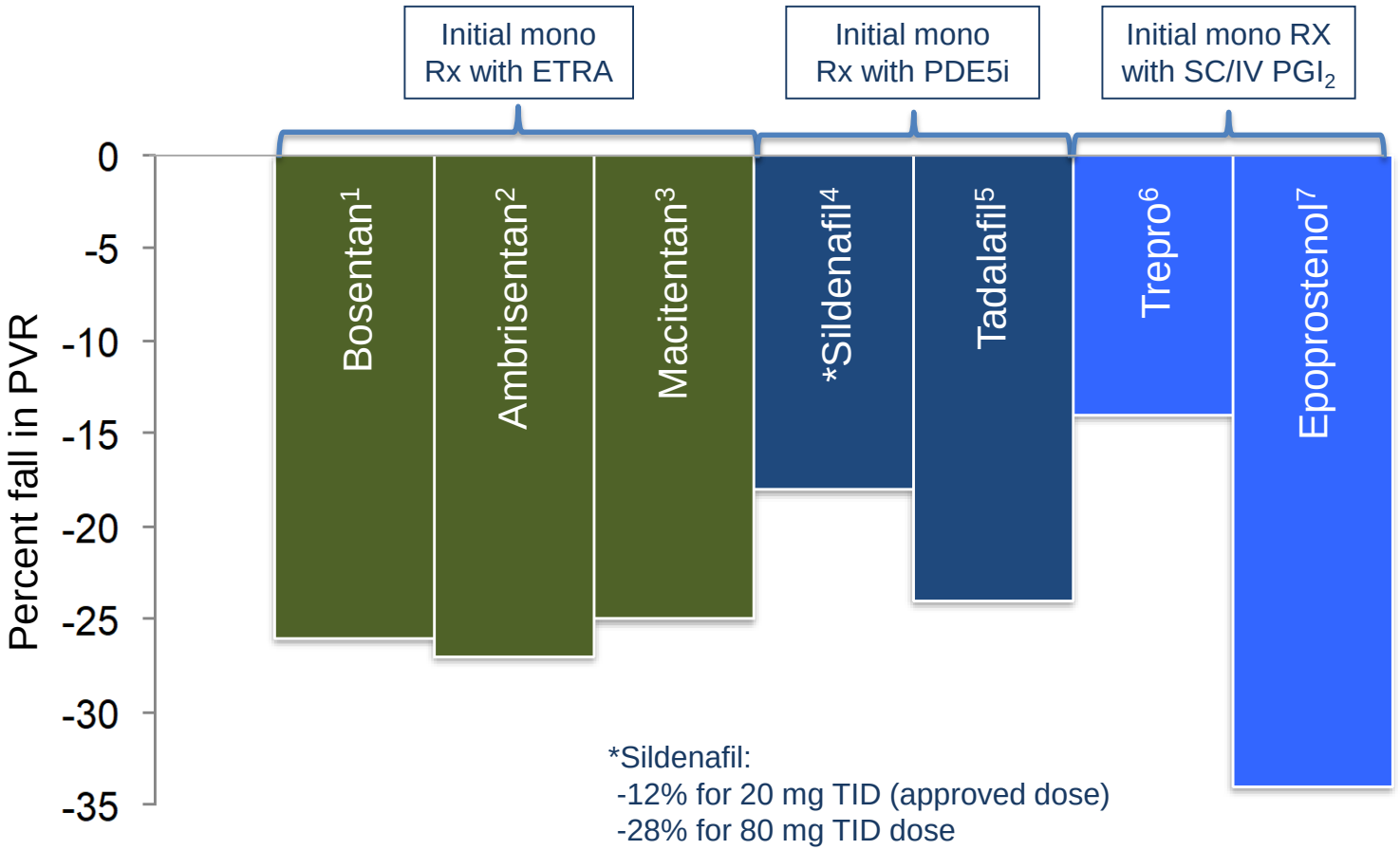
Improvement in exercise capacity (3-4 months)



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

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

Effect of PAH-specific therapies on PVR after 3-6 months



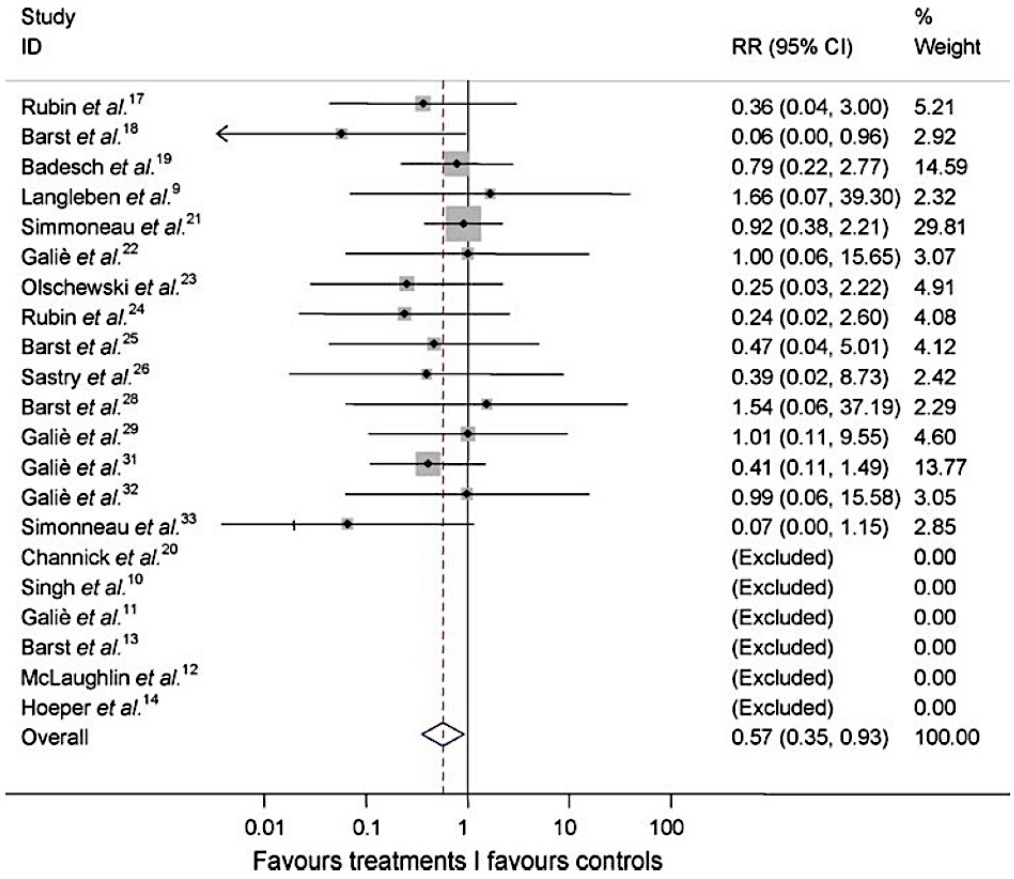
*Sildenafil:
-12% for 20 mg TID (approved dose)
-28% for 80 mg TID dose

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

A meta-analysis of randomized controlled trials in pulmonary arterial hypertension

Nazzareno Galiè*, Alessandra Manes, Luca Negro, Massimiliano Palazzini, Maria Letizia Bacchi-Reggiani, and Angelo Branzi

European Heart Journal (2009) **30**, 394–403



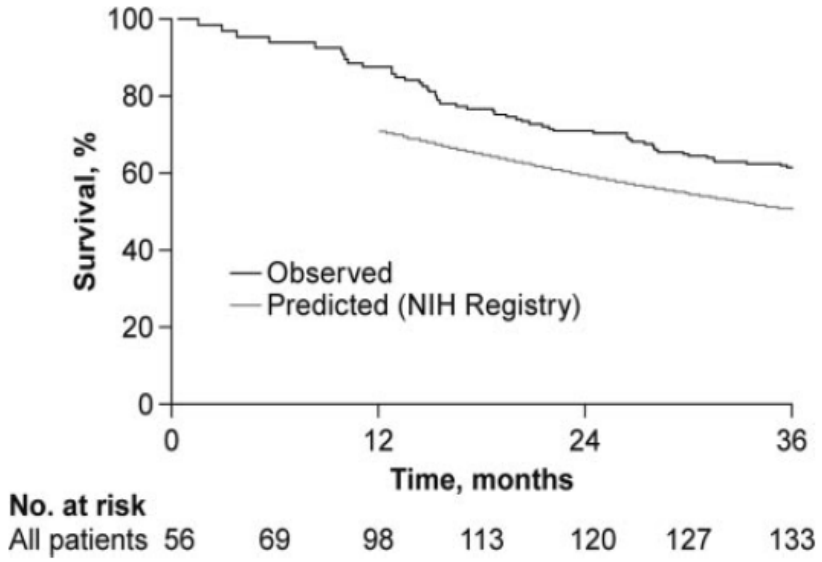
- 23 RCTs
- Average duration 14.3 wks
- 3140 patients
- All-cause mortality rate in the control group = 3.8%
- Active treatments:
  - 43% reduction in mortality
  - RR 0.57 (95%CI 0.35–0.92)
  - P = 0.023

Unmet need in the modern management era

Despite drug discovery and development PAH remains a devastating condition

Survival in Patients With Idiopathic, Familial, and Anorexigen-Associated Pulmonary Arterial Hypertension in the Modern Management Era

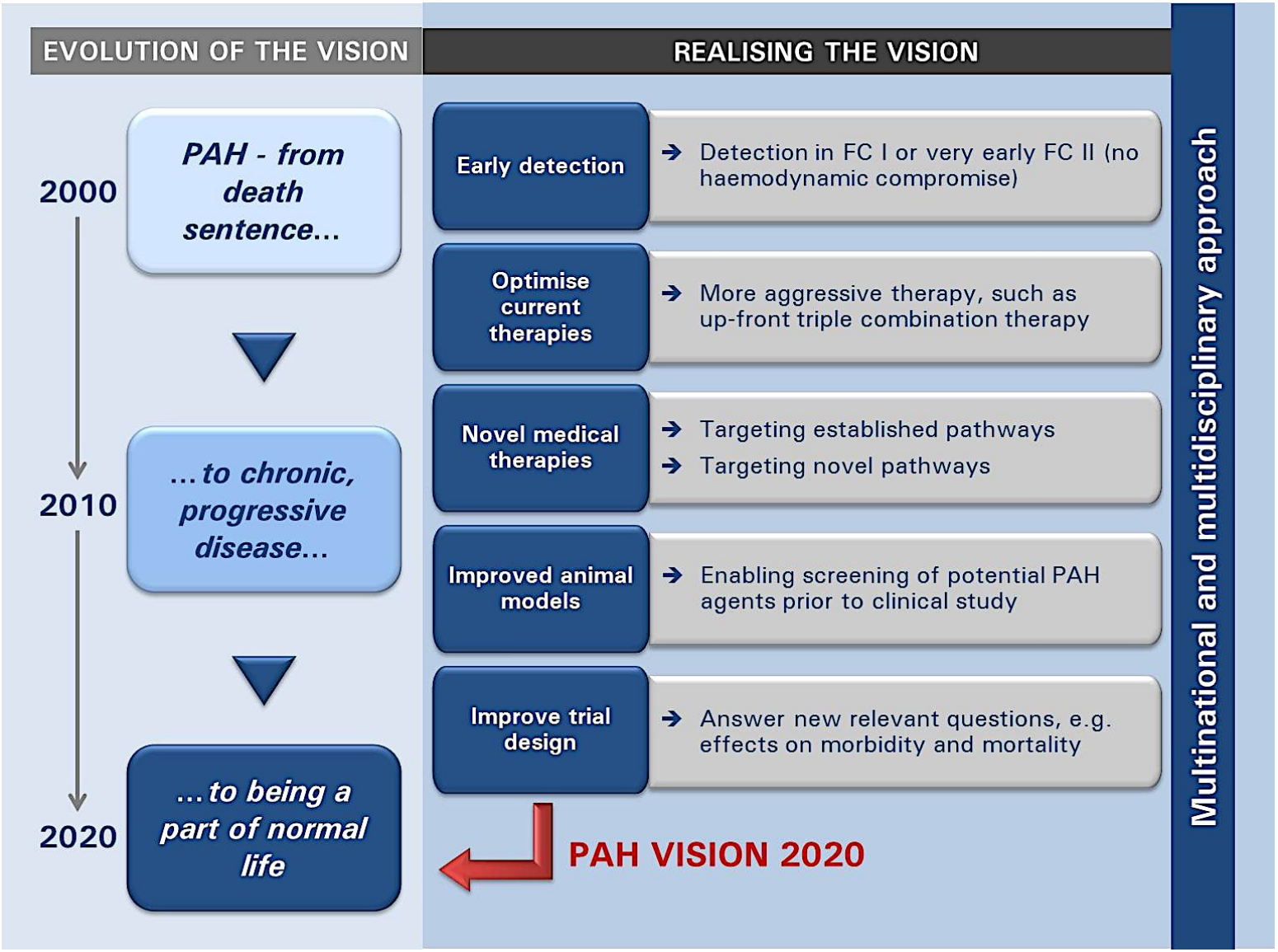
Marc Humbert, MD, PhD; Olivier Sitbon, MD, PhD; Ari Chaouat, MD, PhD; Michèle Bertocchi, MD; Gilbert Habib, MD; Virginie Gressin, MD; Azzedine Yaïci, MD; Emmanuel Weitzenblum, MD; Jean-François Cordier, MD; François Chabot, MD, PhD; Claire Dromer, MD; Christophe Pison, MD, PhD; Martine Reynaud-Gaubert, MD, PhD; Alain Haloun, MD; Marcel Laurent, MD; Eric Hachulla, MD, PhD; Vincent Cottin, MD, PhD; Bruno Degano, MD, PhD; Xavier Jaïs, MD; David Montani, MD, PhD; Rogério Souza, MD, PhD; Gérald Simonneau, MD



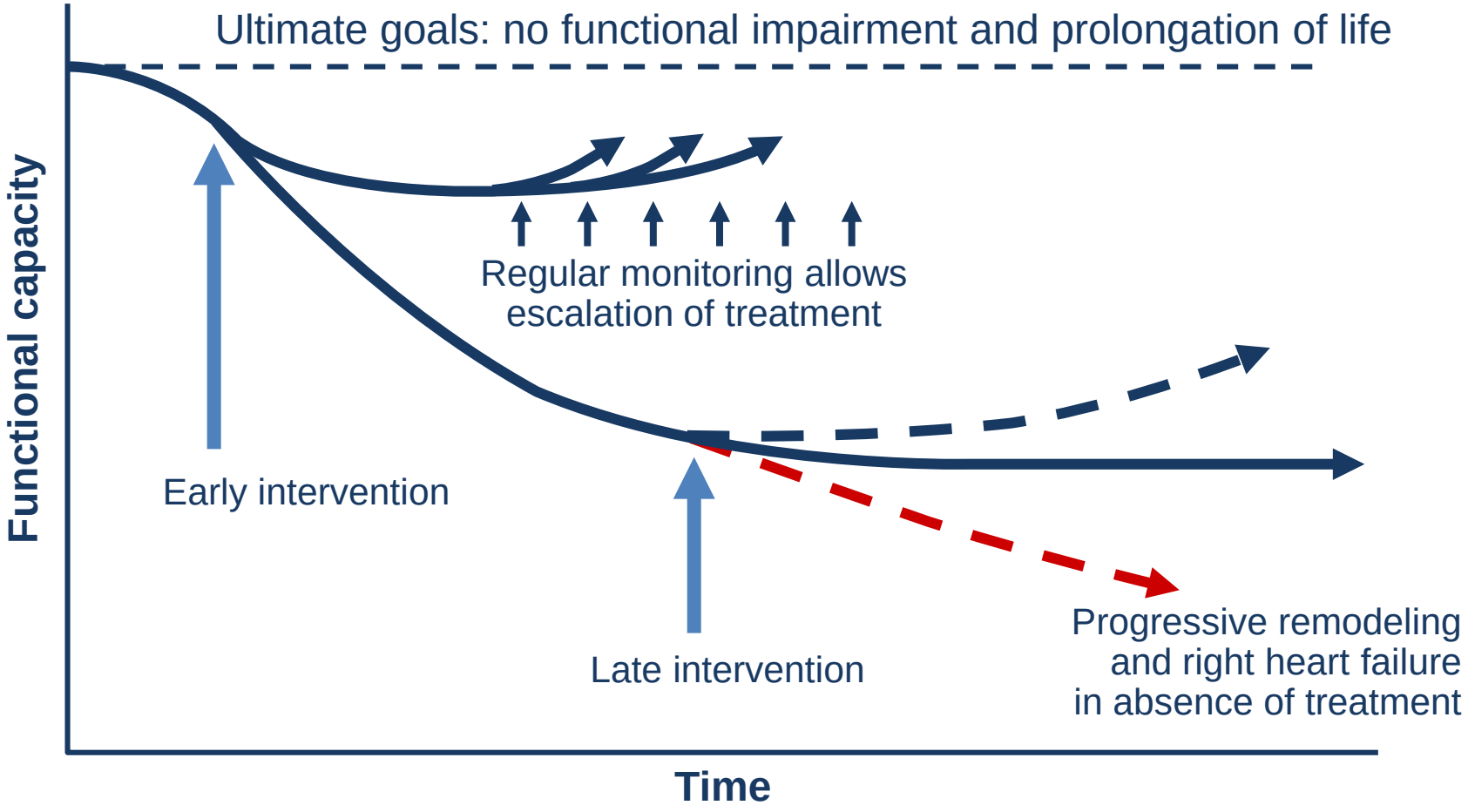
NIH, National Institutes of Health.

Humbert M *et al. Circulation* 2010;122:156–63.

PAH management: How to do better?



Early treatment of PAH



Sitbon O, Galiè N. *Eur Respir Rev* 2010;19:272–8.

Goal-oriented therapy (risk assessment)

Treatment Goals of Pulmonary Hypertension

Vallerie V. McLaughlin, MD,* Sean Patrick Gaine, MD, PHD,† Luke S. Howard, DPHIL,‡ Hanno H. Leuchte, MD,§ Michael A. Mathier, MD,|| Sanjay Mehta, MD,¶ Massimillano Palazzini, MD,# Myung H. Park, MD,** Victor F. Tapson, MD,†† Olivier Sitbon, MD, PHD‡‡

Functional class
I or II
Echocardiography/CMR
Normal/near-normal RV size and function
Hemodynamics
Normalization of RV function (RAP $<$8 mm Hg and CI $>$2.5 to 3.0 l/min/m^2)
6-min walk distance
$>$380 to 440 m; may not be aggressive enough in young individuals
Cardiopulmonary exercise testing
Peak VO_2 $>$15 ml/min/kg and $EqCO_2$ $<$45 l/min/l/min
B-type natriuretic peptide level
Normal

CI, cardiac index; CMR, cardiovascular magnetic resonance; $EqCO_2$, breathing equivalent for CO_2; RAP, right atrial pressure; RV, right ventricle; VO_2, oxygen consumption.

McLaughlin VV *et al. J Am Coll Cardiol* 2013;62:D73–81.

ESC/ERS 2015 Guidelines for risk assessment in PAH

Determinants of prognosis[a] (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope[b]	Repeated syncope[c]
WHO functional class	I, II	III	IV
6MWD	>440 m	165–440 m	<165 m
Cardiopulmonary exercise testing	Peak VO_2 >15 ml/min/kg (>65% pred.) VE/VCO_2 slope <36	Peak VO_2 11–15 ml/min/kg (35–65% pred.) VE/VCO_2 slope 36–44.9	Peak VO_2 <11 ml/min/kg (<35% pred.) VE/VCO_2 slope ≥45
NT-proBNP plasma levels	BNP <50 ng/l NT-proBNP <300 ng/l	BNP 50–300 ng/l NT-proBNP 300–1400 ng/l	BNP >300 ng/l NT-proBNP >1400 ng/l
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2 No pericardial effusion	RA area 18–26 cm^2 No or minimal, pericardial effusion	RA area >26 cm^2 Pericardial effusion
Haemodynamics	RAP <8 mmHg CI ≥2.5 l/min/m^2 SvO_2 >65%	RAP 8–14 mmHg CI 2.0–2.4 l/min/m^2 SvO_2 60–65%	RAP >14 mmHg CI <2.0 l/min/m^2 SvO_2 <60%

Galiè N. et al. ESC/ERS Guidelines. Eur Heart J & Eur Respir J 2015.

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

	At baseline	Every 3–6 months[a]	Every 6–12 months[a]	3–6 months after changes in therapy[a]	In case of clinical worsening
Medical assessment and determination of functional class	+	+	+	+	+
ECG	+	+	+	+	+
6MWT/Borg dyspnoea score	+	+	+	+	+
CPET	+		+		+[e]
Echo	+		+	+	+
Basic lab[b]	+	+	+	+	+
Extended lab[c]	+		+		+
Blood gas analysis[d]	+		+	+	+
Right heart catheterization	+		+[f]	+[e]	+[e]

Should be considered

Some centres perform RHCs at regular intervals during follow-up

Galiè N. et al. ESC/ERS Guidelines. Eur Heart J & Eur Respir J 2015.

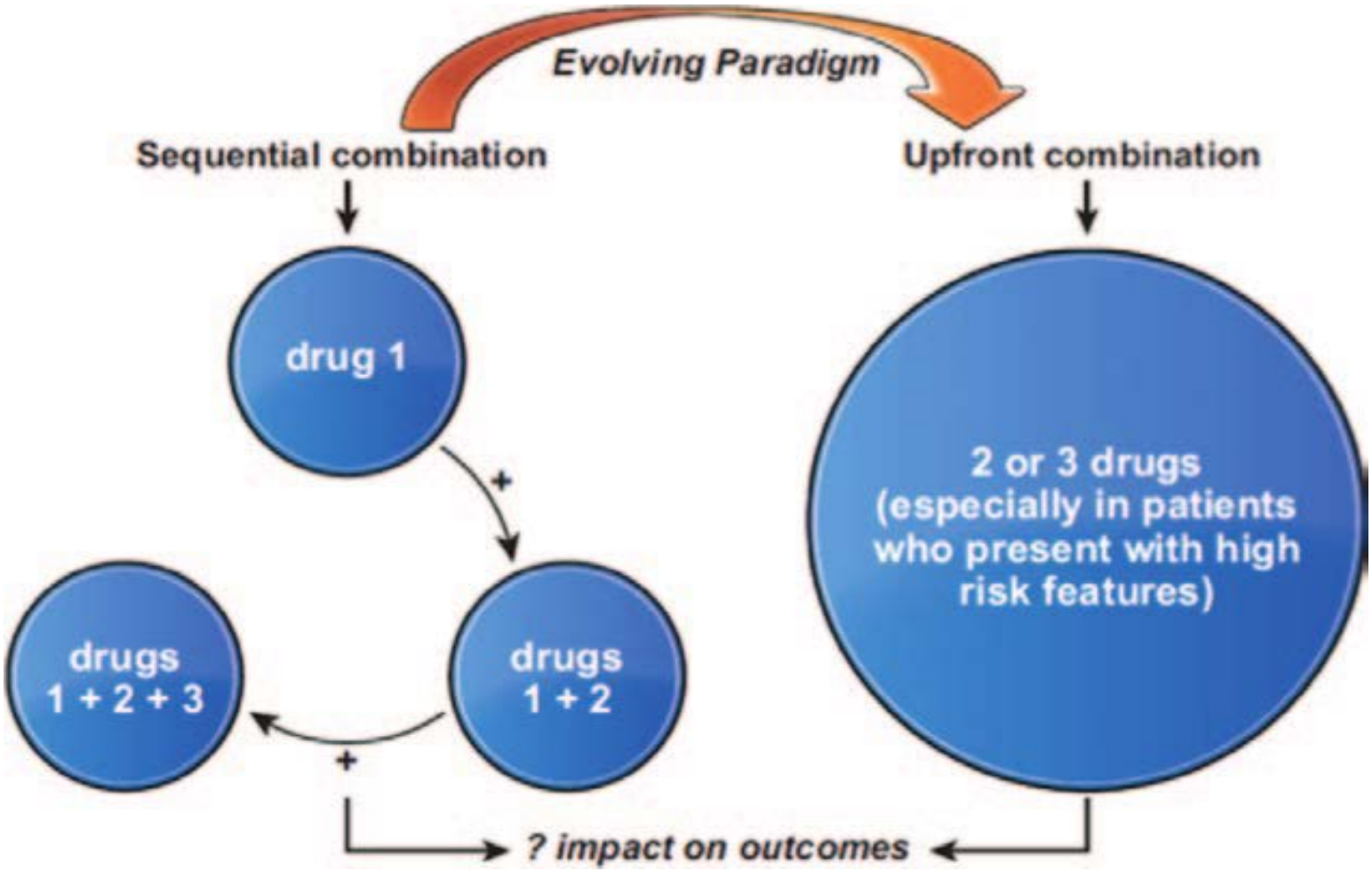
Sequential combination therapy: results are not uniform…

Drug tested	Study	Background	N	Duration (weeks)	Primary endpoint
Bosentan	EARLY	None or sildenafil (16%)	185	24	PVR +, Δ6MWD **(NS)**
Bosentan	COMPASS-2	Sildenafil	334	92	Morbi-mortality **(NS)**
Iloprost	STEP	Bosentan	67	12	Δ6MWD **(NS)**
Iloprost	COMBI	Bosentan	40	12	Δ6MWD **(NS)**
Imatinib	Phase II	Bosentan &/or sildenafil &/or prostanoids	59	24	Δ6MWD **(NS)**
Imatinib	IMPRES	Bosentan &/or sildenafil &/or prostanoids	202	24	Δ6MWD +
Selexipag	Phase II	Bosentan &/or sildenafil	43	17	PVR +
Sildenafil	PACES	Epoprostenol	264	16	Δ6MWD +
Sildenafil	NCT00323297	Bosentan	104	12	Δ6MWD **(NS)**
Tadalafil	PHIRST	None or bosentan (54%)	405	16	Δ6MWD **(NS)**
Trepostinil	Inhaled- TRIUMPH	Bosentan or sildenafil	235	12	Δ6MWD +
Trepostinil	Oral- FREEDOM C1	Bosentan &/or sildenafil	354	16	Δ6MWD **(NS)**
Trepostinil	Oral- FREEDOM C2	Bosentan &/or sildenafil	310	16	Δ6MWD **(NS)**

Sequential combination therapy: Recent studies

Drug tested	Study	Background	N	Duration (weeks)	Primary endpoint
Riociguat	PATENT	None (50%), bosentan or prostanoids	443	12	Δ6MWD +
Macitentan	SERAPHIN	None (36%), PDE5i (61%) or oral/inhaled prostanoids	742	≈ 100	Time to first event of death or morbidity +
Selexipag	GRIPHON	None (21%), ERA (13%), PDE5i (32%) or both (34%)	1156	≈ 70	Time to first event of death or morbidity +

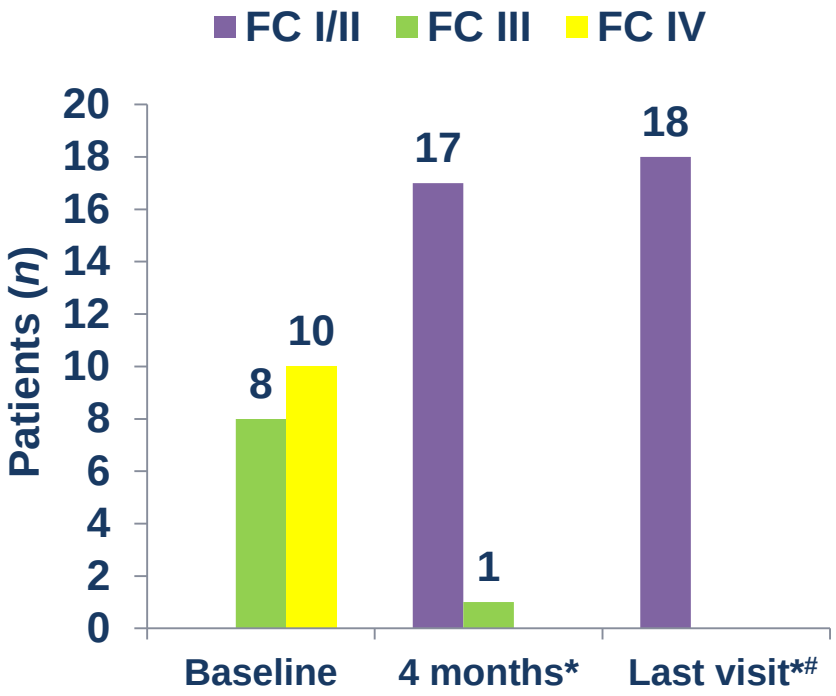
Evolving paradigm: From sequential to initial combination therapy

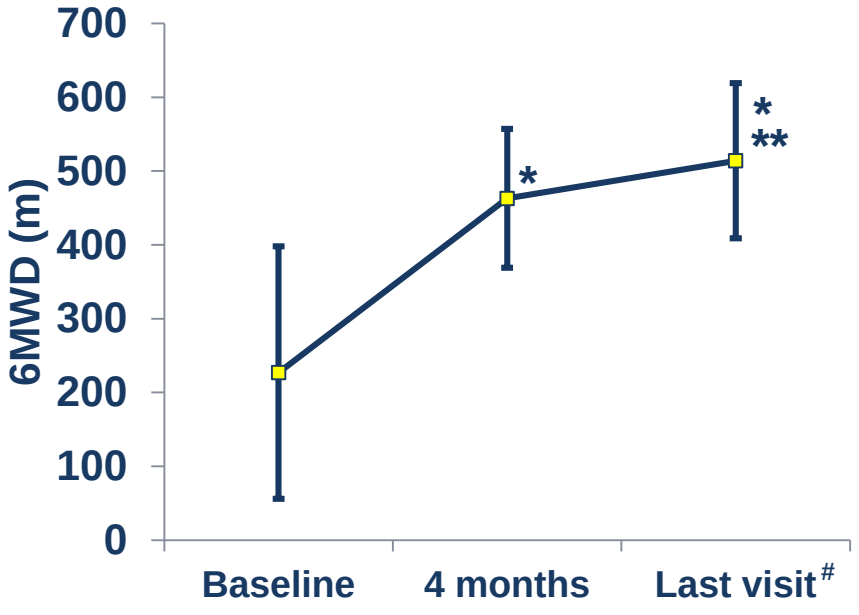


Humbert M, *et al*. *Circulation* 2014.

Upfront triple combination therapy: Effect on FC and 6MWD

Prospective, observational analysis of idiopathic or heritable PAH patients (*n* = 19) treated with upfront combination therapy (epoprostenol, bosentan and sildenafil)



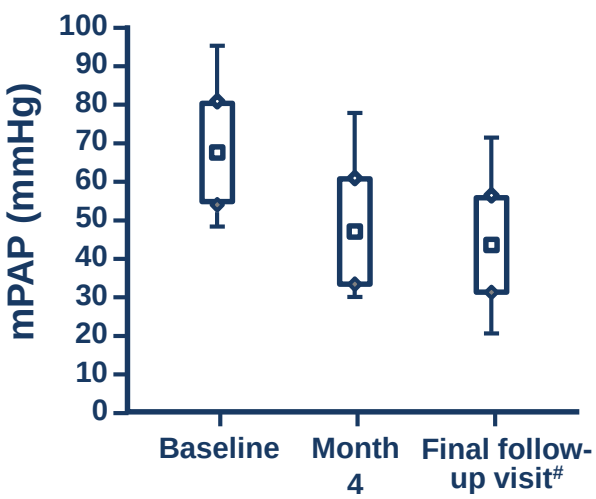


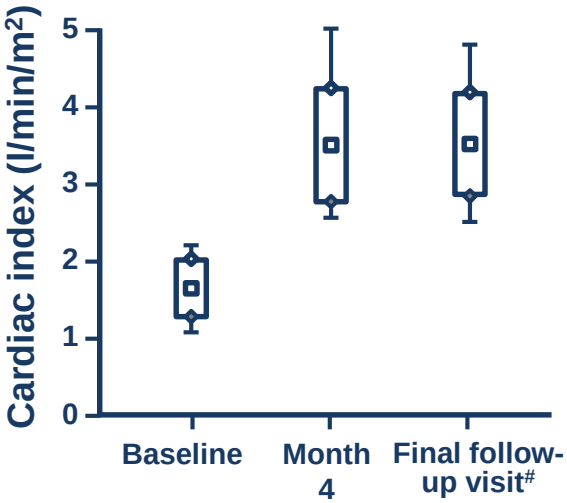
#32 ± 19 months

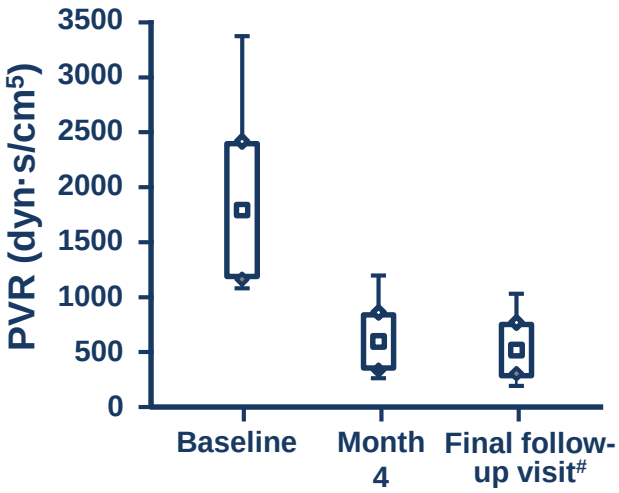
**p* < 0.01 versus baseline; ** p < 0.01 versus 4 months

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

Upfront triple combination therapy: Effect on haemodynamics







	Baseline	Month 4	Final follow-up[#]
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*

[#]32 ± 19 months *$p < 0.01$ versus baseline

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

Upfront triple combination therapy: Long-term outcome / survival

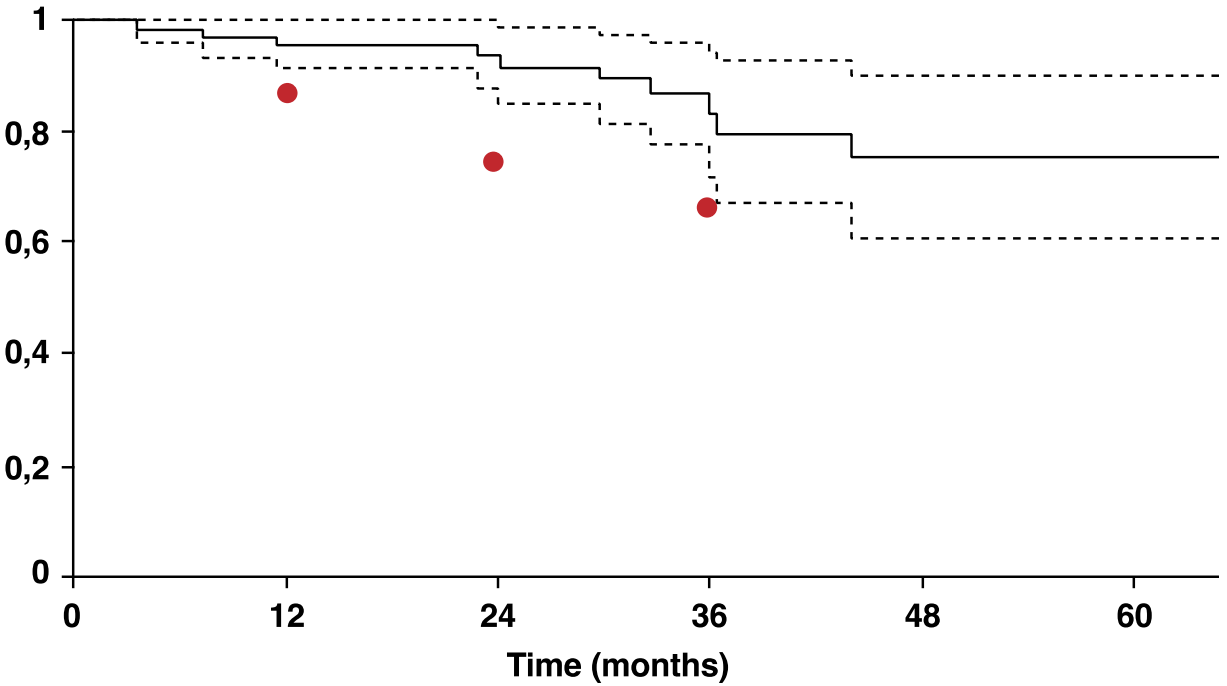
- Long-term follow-up *(n=19)*
  - Median follow-up: 58.7 months (IQR: 52.5 – 70.0 months)
  - Two patients underwent LT (after 3.8 and 41.4 months)
  - 17 patients well and alive in NYHA FC I-II
  - 7 patients with mPAP < 35 mmHg (incl. one < 20 mmHg)
- Survival *(n=19)*

	1-year	2-year	3-year	5-year
Actual	100%	100%	100%	100%
*Expected** *[95% CI]*	*75%* *[68%-82%]*	*60%* *[50%-70%]*	*49%* *[38%-60%]*	-
Transplant-free	94%	94%	94%	89%

** according to the French equation (Humbert M, et al. Eur Respir J 2010)*

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

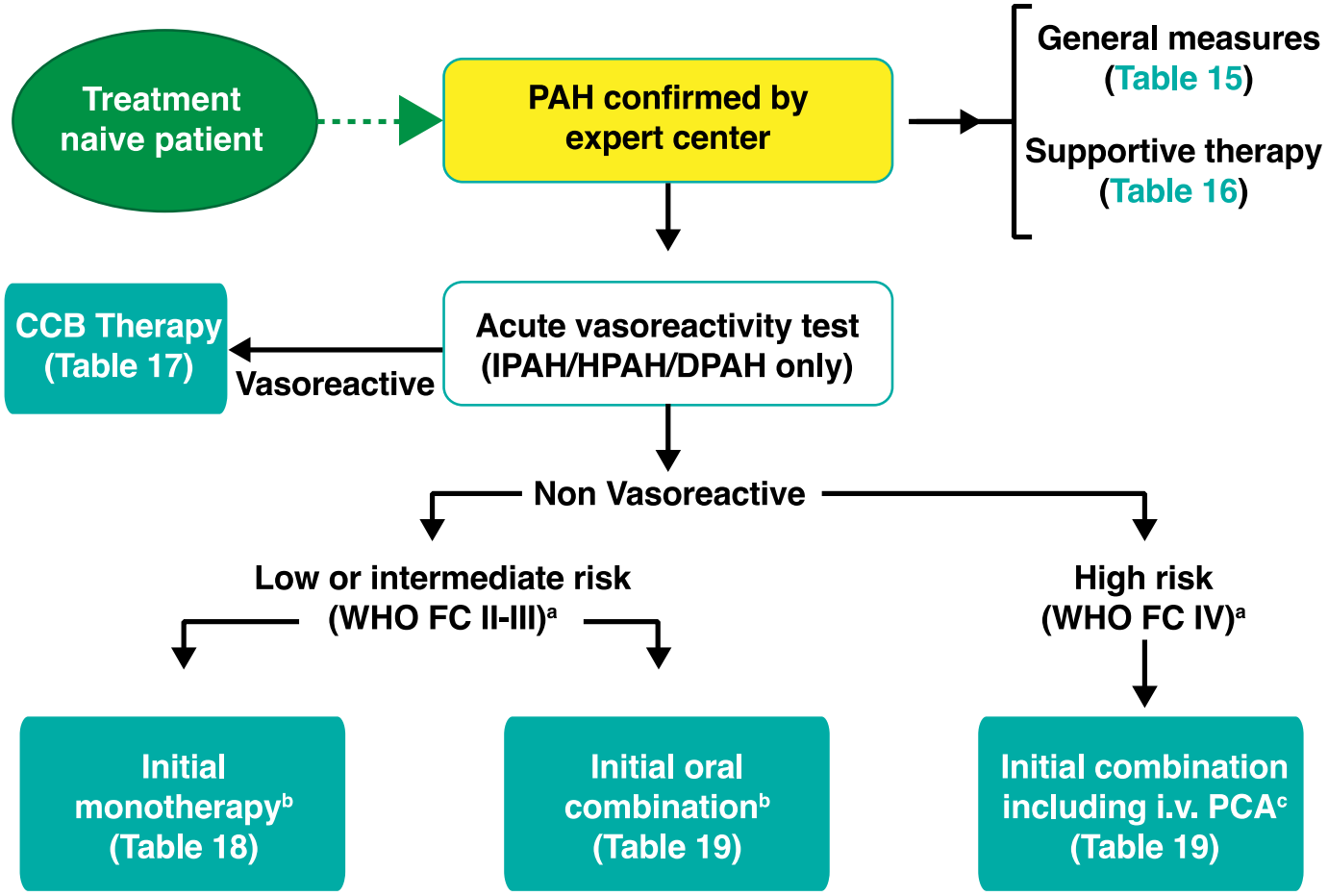
Survival of patients with idiopathic, heritable and anorexigen-associated PAH (n=74)



At risk, n	74	66	51	27	14	6
Actual survival [IC 95%]		96 [91-100]	94 [88-99]	84 [72-95]	75 [61-90]	
Expected survival [IC 95%]		86 [83-88]	75 [71-79]	66 [62-71]		

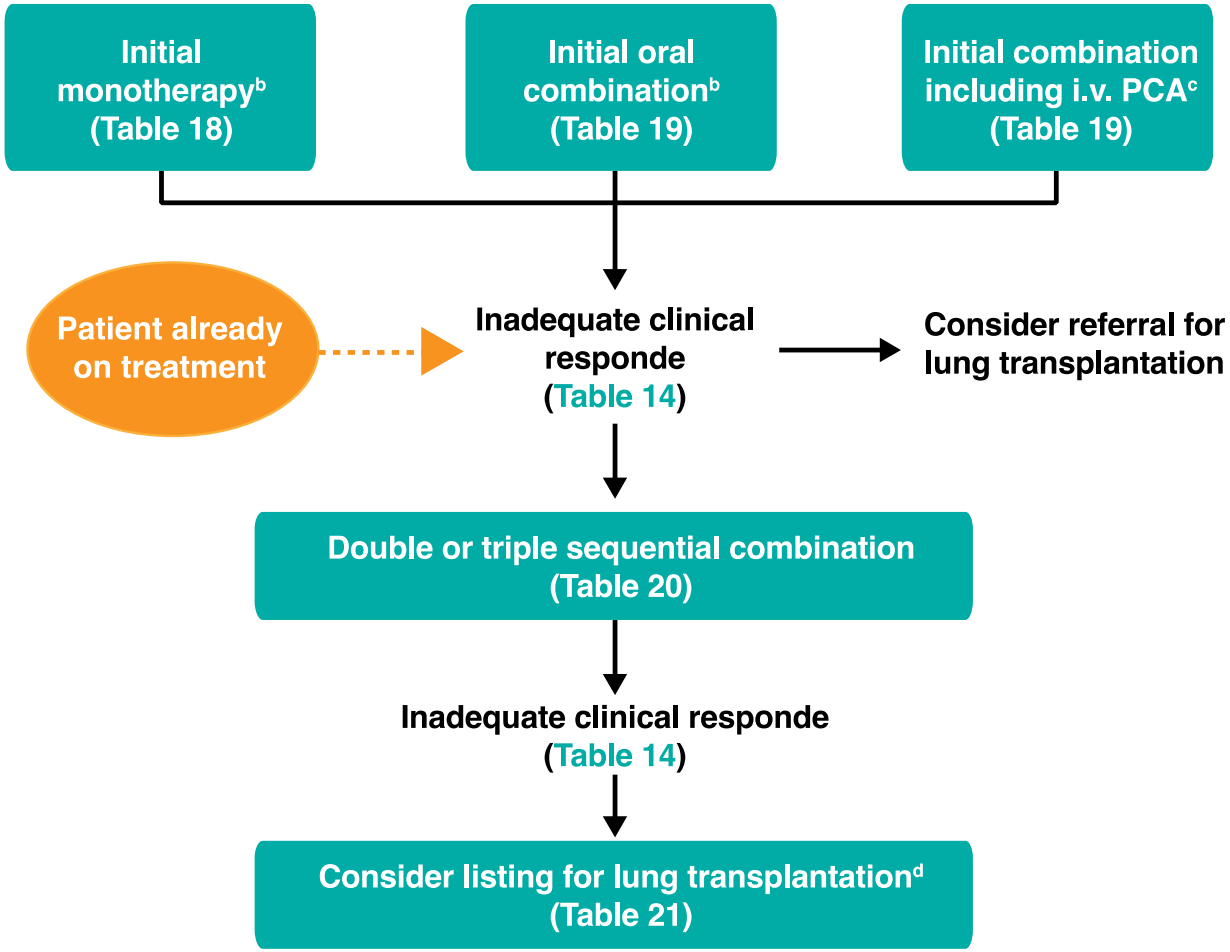
Humbert M, et al. Eur Respir J 2010; 36:549-55.
Sattler C, Sitbon O, *et al. ERS Congress* 2015.

2015 ESC/ERS guidelines treatment algorithm



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

2015 ESC/ERS guidelines treatment algorithm



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

Current PAH management: Summary

- Many progresses have been made in treatment strategies
  - Sequential combinations delay time to clinical worsening
  - More aggressive sequential combination in a goal-oriented approach likely more efficacious (no proof)
- Initial combination therapy is likely the way forward
  - Including a parenteral prostacyclin in the most severe patients (high risk and/or FC IV)
  - Initial dual oral combination therapy with ERA and PDE-5 inhibitor is superior to monotherapy in patients with low/intermediate risk (FC II-III)
- No direct comparison neither in between different combinations of drugs nor in between sequential and initial combination strategies