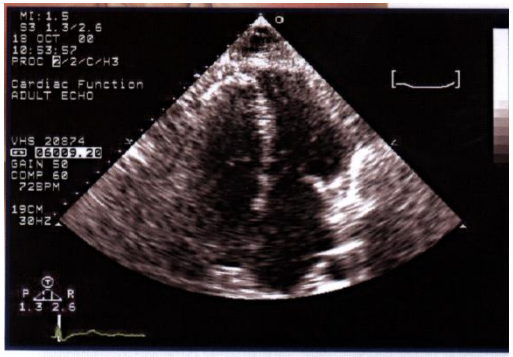
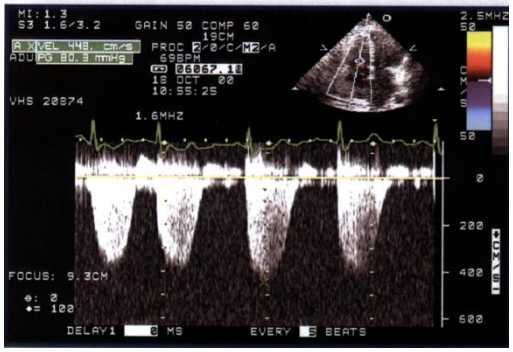
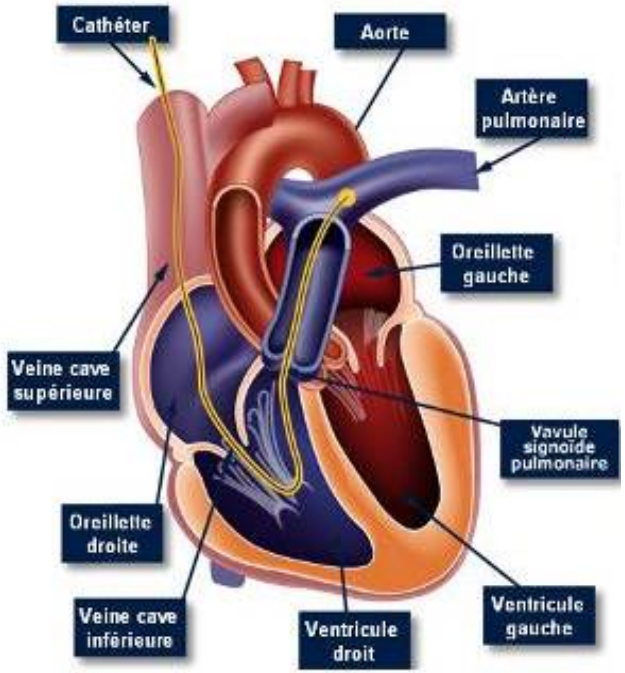
# Hemodynamic classification of pulmonary hypertension (PH)

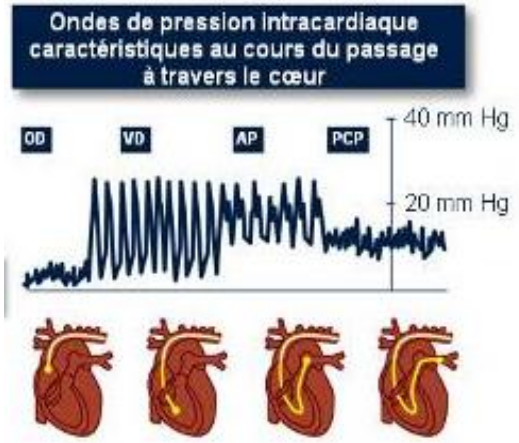
**Screening**
Transthoracic echo
(TRJV > 2.8 m/s)





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

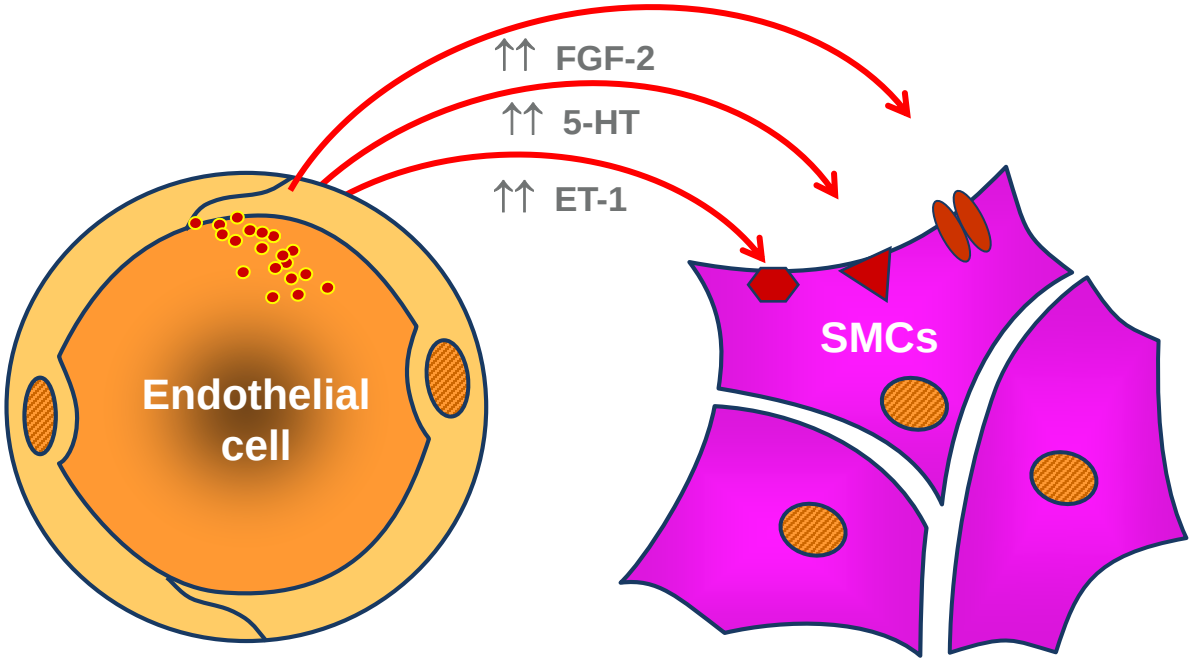
# Clinical classification of pulmonary hypertension (PH) – Group 1 : PAH

| 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



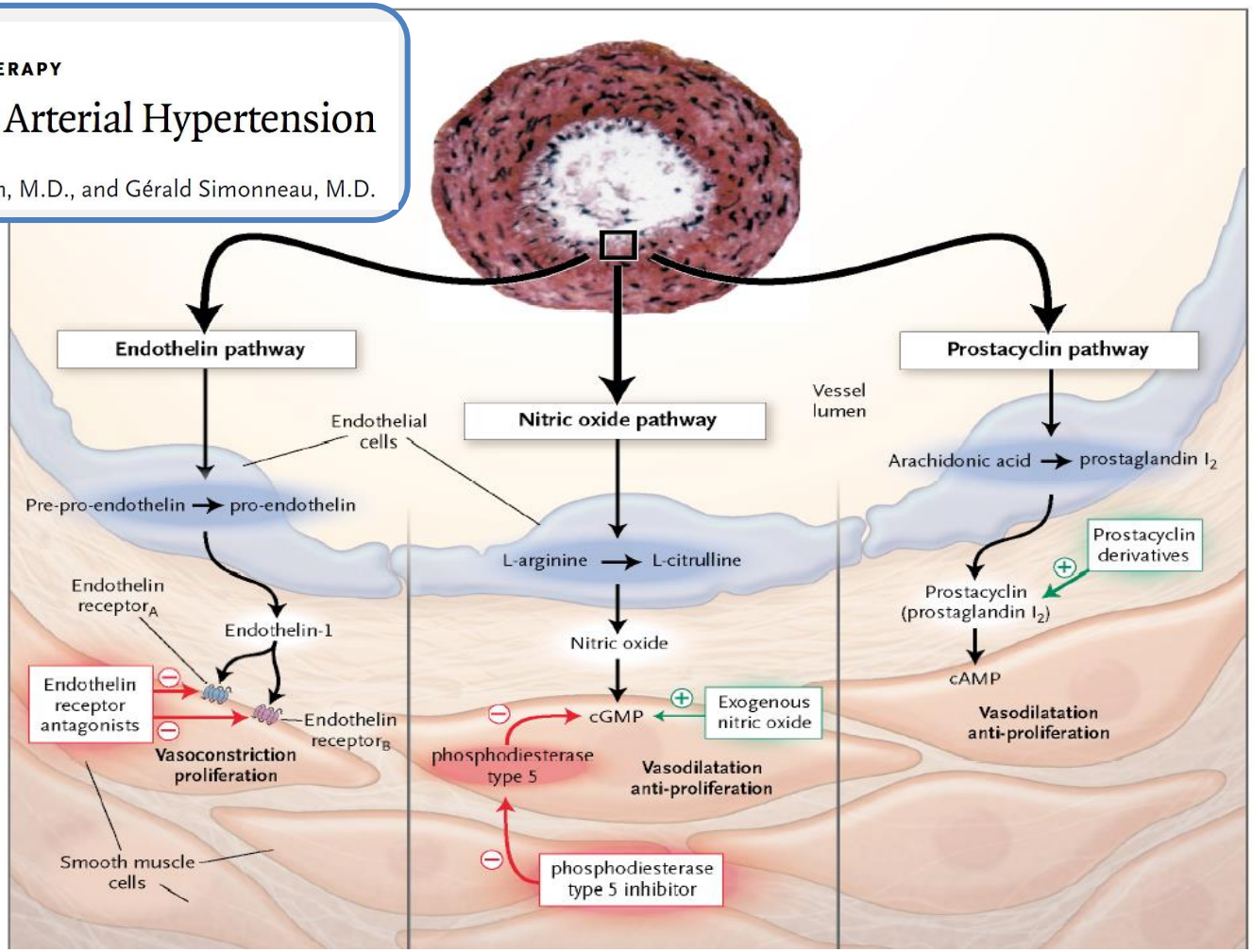

5-HT, 5-hydroxytryptamine; ET-1, endothelin 1 ; FGF-2, fibroblast growth factor 2; SMC, smooth muscle cell.

# 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.

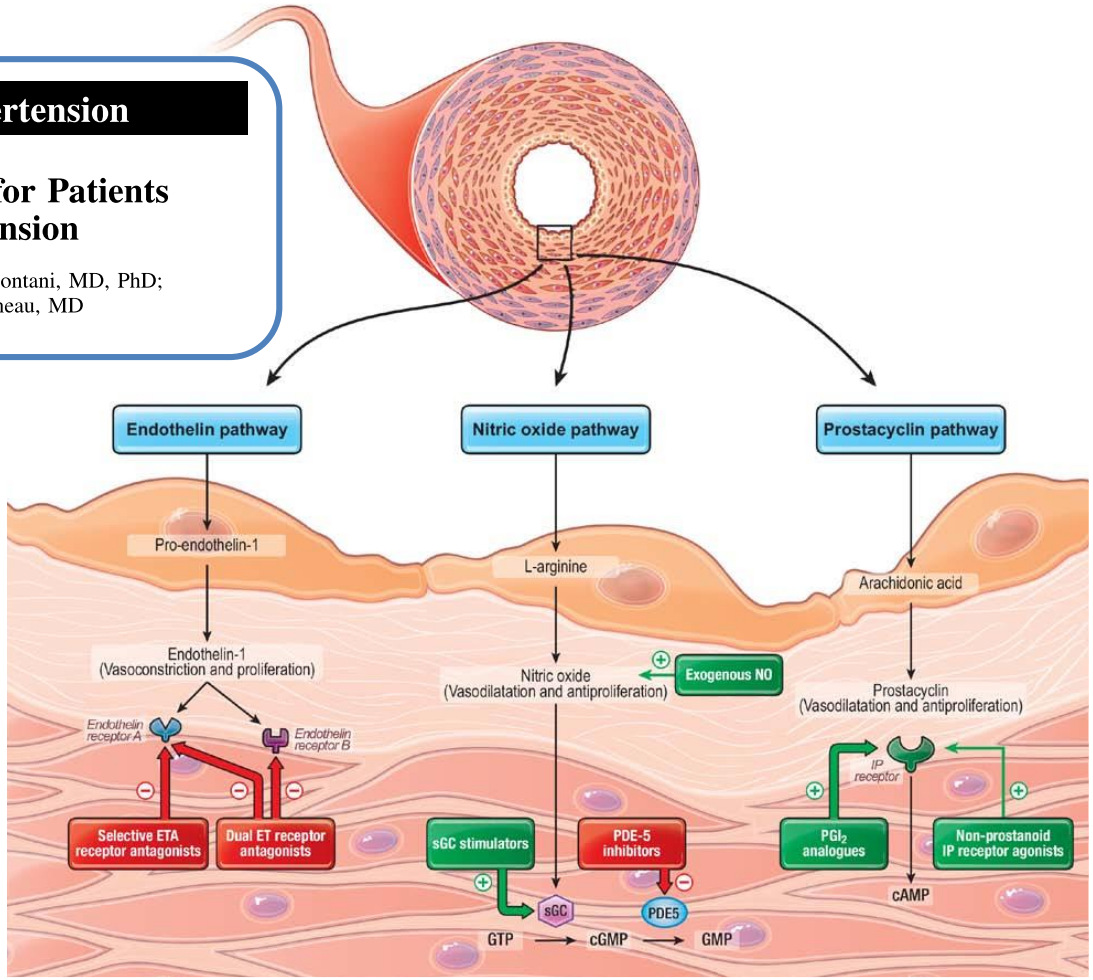
Humbert M *et al. N Engl J Med* 2004;351:1425–36.

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

**Recent Advances in Pulmonary Hypertension**

**Advances in Therapeutic Interventions for Patients With Pulmonary Arterial Hypertension**

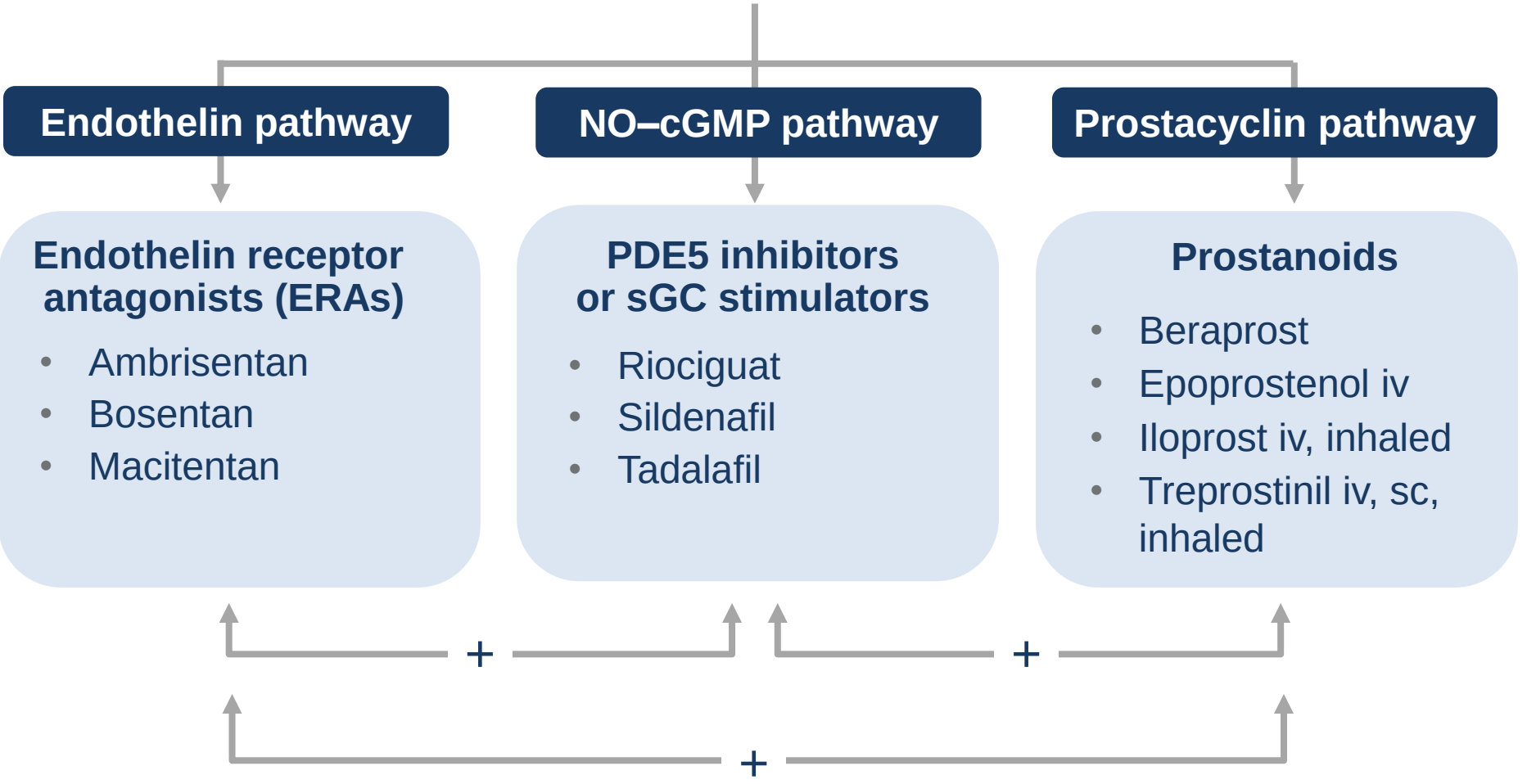
Marc Humbert, MD, PhD; Edmund M.T. Lau, MD, PhD; David Montani, MD, PhD; Xavier Jaïs, MD; Oliver Sitbon, MD, PhD; Gérald Simonneau, MD




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

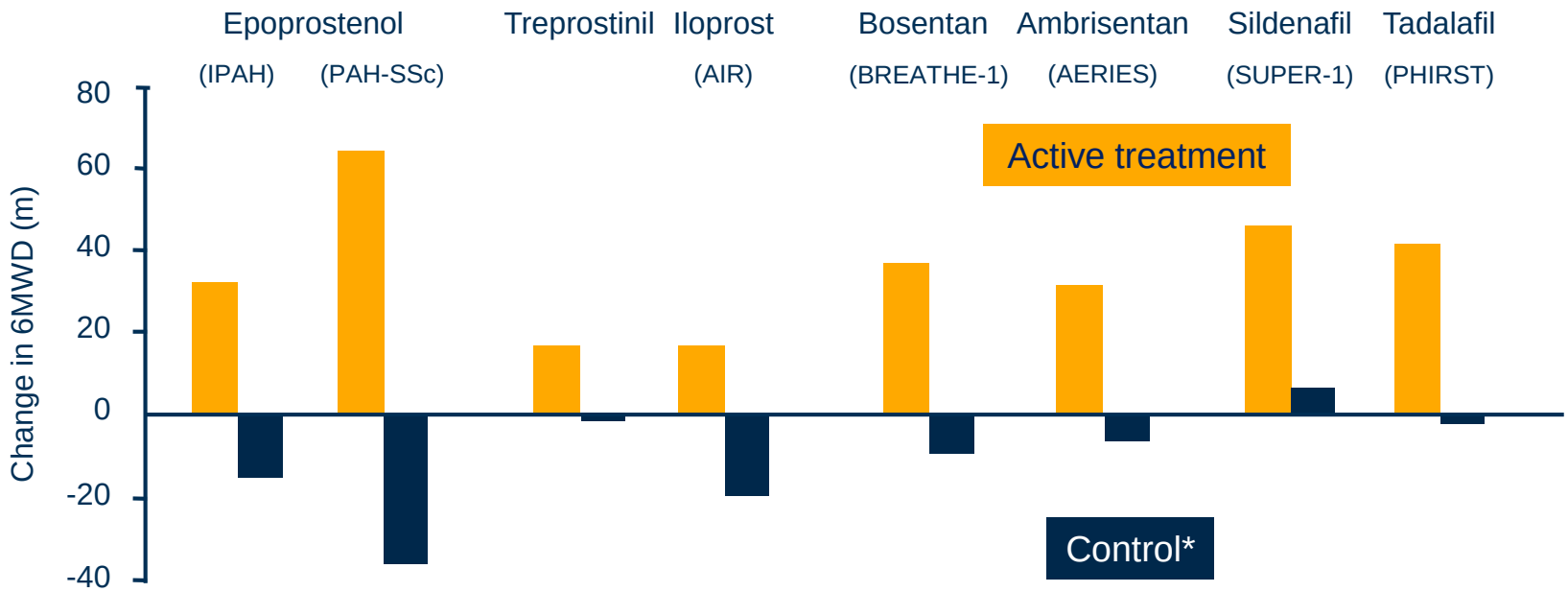



cGMP, cyclic guanosine monophosphate; iv, intravenous; NO, nitric oxide; PDE5, phosphodiesterase type 5; sc, subcutaneous; sGC, soluble guanylate cyclase.

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

# RCTs with monotherapy in PAH

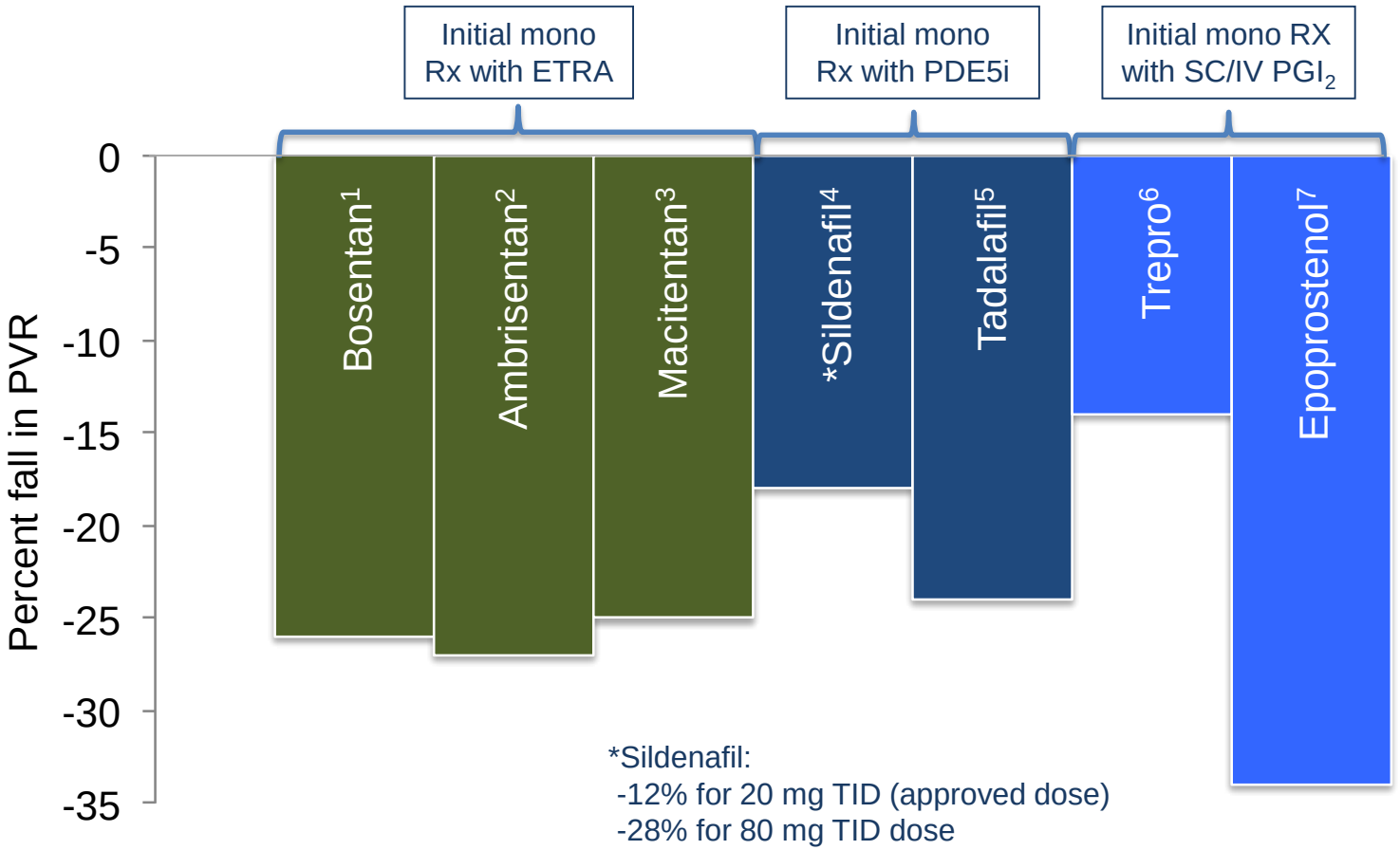
## *Improvement in exercise capacity (3-4 months)*




* 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

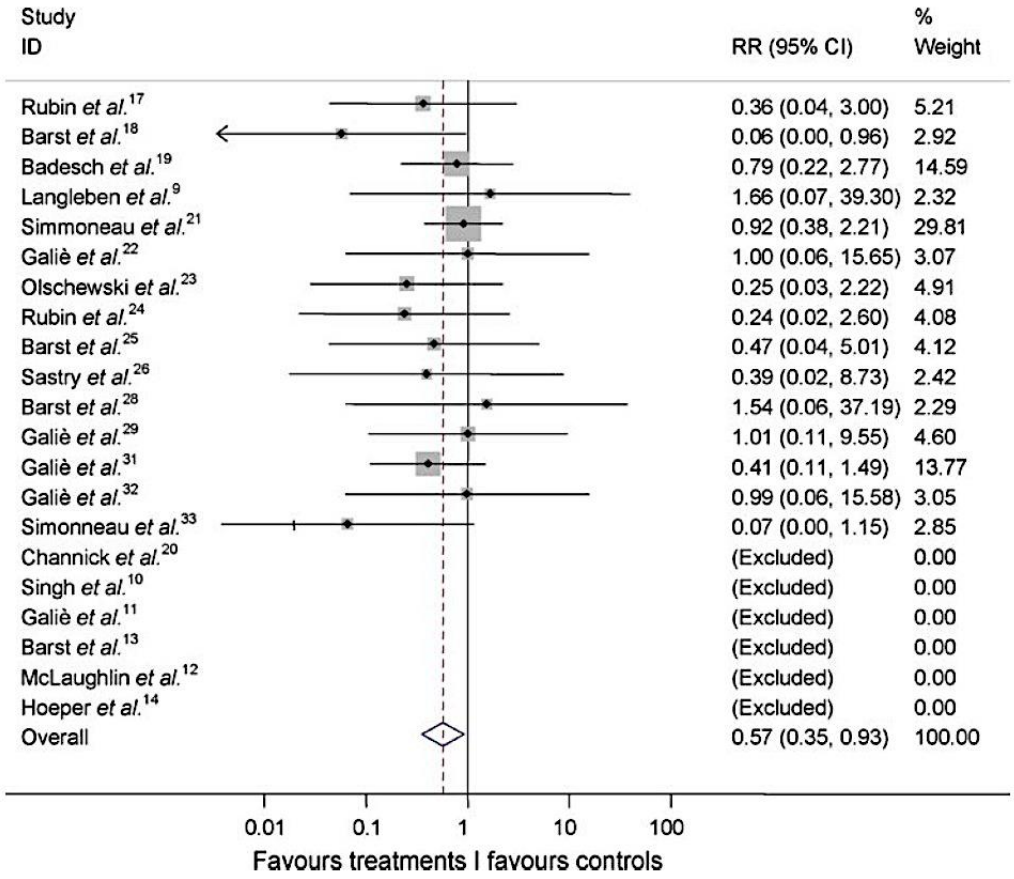



1. Channick RN. *Lancet* 2001; 2. Galie N. *J Am Coll Cardiol* 2005; 3.Pulido T. *N Engl J Med* 2013; 4. Galie N. *N Engl J Med* 2005; 5. Galie N. *Circulation* 2009; 6. Simonneau G. *Am J Respir Crit Care Med* 2002; 7. Barst RJ. *N Engl J Med* 1996.

# 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



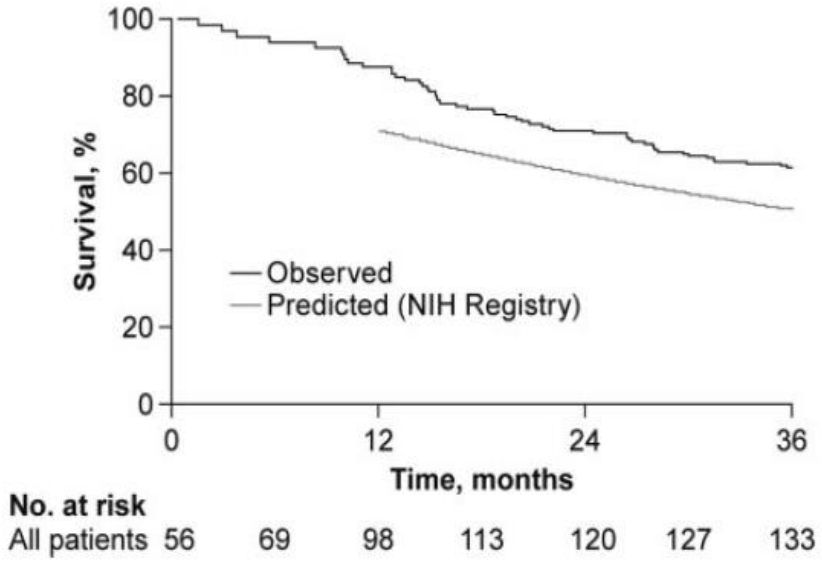

- 23 RCTs
- Average duration 14.3 wks
- 3140 patients
- All-cause mortality rate in the control group = 3.8%
- Active treatments:
  - 43% reduction in mortality
  - RR 0.57 (95%CI 0.35–0.92)
  - P = 0.023

# 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**

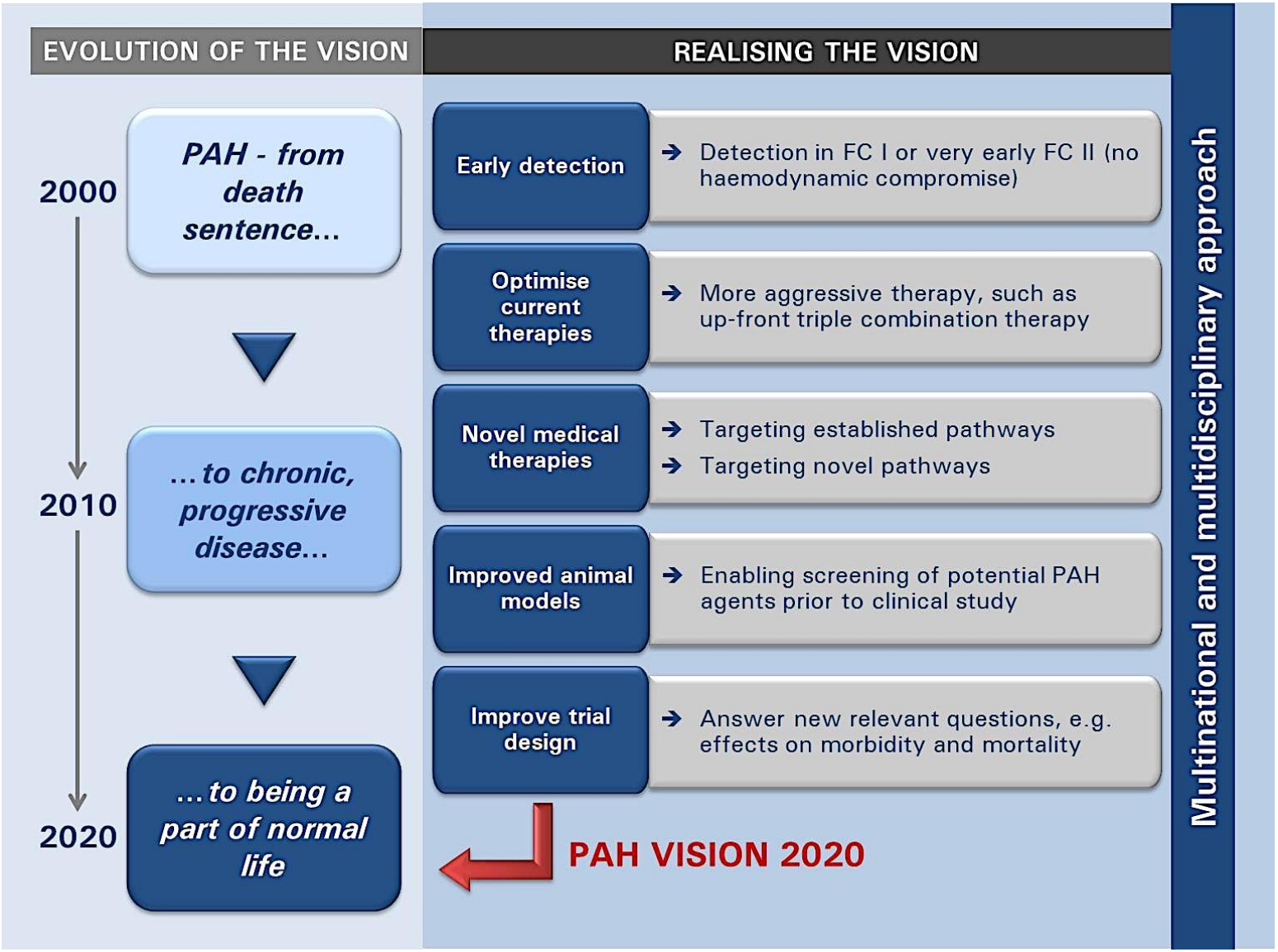
Marc Humbert, MD, PhD; Olivier Sitbon, MD, PhD; Ari Chaouat, MD, PhD; Michèle Bertocchi, MD; Gilbert Habib, MD; Virginie Gressin, MD; Azzedine Yaïci, MD; Emmanuel Weitzenblum, MD; Jean-François Cordier, MD; François Chabot, MD, PhD; Claire Dromer, MD; Christophe Pison, MD, PhD; Martine Reynaud-Gaubert, 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



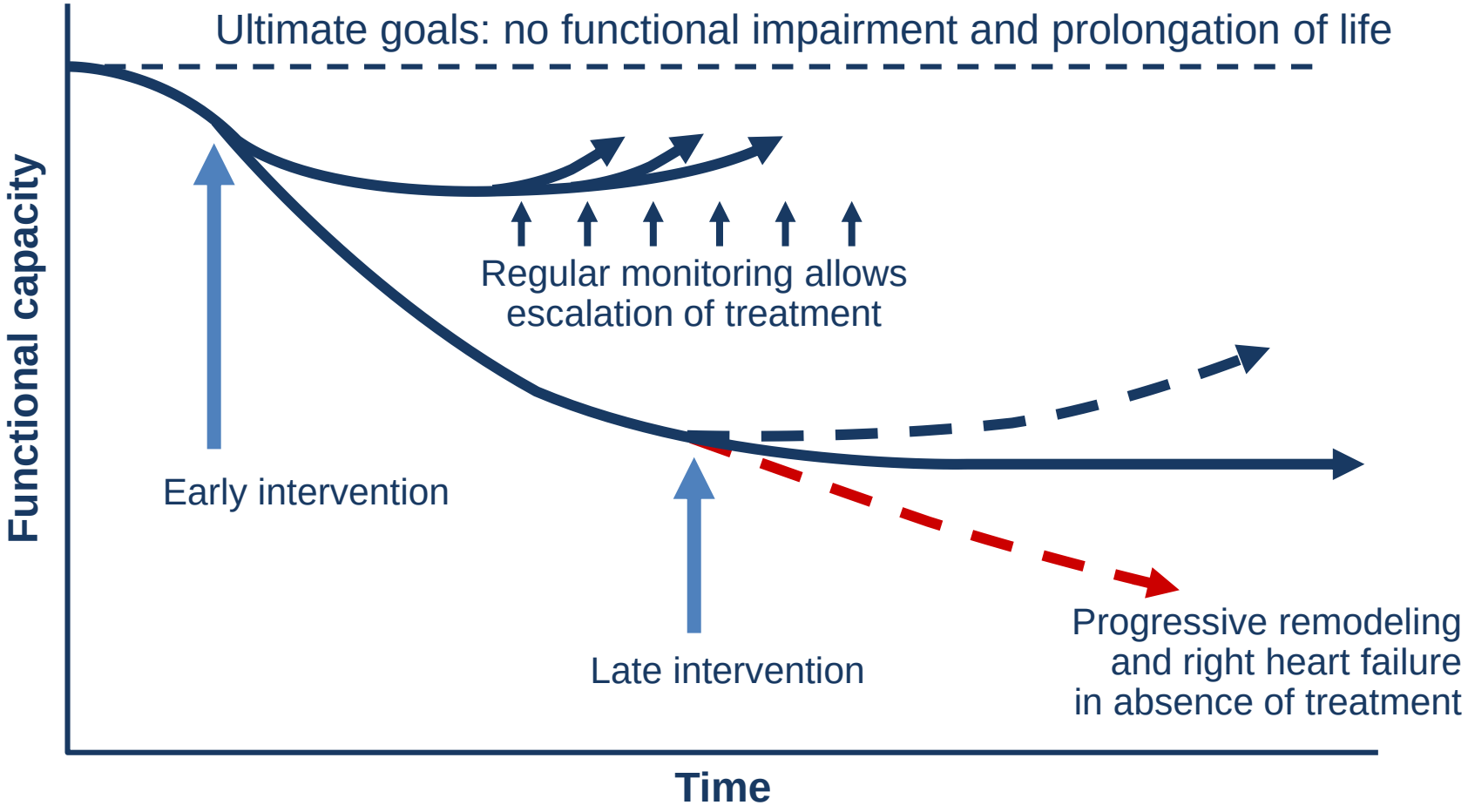

NIH, National Institutes of Health.

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.)<br>$VE/VCO_2$ slope <36 | Peak $VO_2$<br>11–15 ml/min/kg (35–65% pred.)<br>$VE/VCO_2$ slope 36–44.9 | Peak $VO_2$ <11 ml/min/kg (<35% pred.)<br>$VE/VCO_2$ slope ≥45 |
| NT-proBNP plasma levels | BNP <50 ng/l<br>NT-proBNP <300 ng/l | BNP 50–300 ng/l<br>NT-proBNP 300–1400 ng/l | BNP >300 ng/l<br>NT-proBNP >1400 ng/l |
| Imaging (echocardiography, CMR imaging) | RA area <18 $cm^2$<br>No pericardial effusion | RA area 18–26 $cm^2$<br>No or minimal, pericardial effusion | RA area >26 $cm^2$<br>Pericardial effusion |
| Haemodynamics | RAP <8 mmHg<br>CI ≥2.5 l/min/$m^2$<br>$SvO_2$ >65% | RAP 8–14 mmHg<br>CI 2.0–2.4 l/min/$m^2$<br>$SvO_2$ 60–65% | RAP >14 mmHg<br>CI <2.0 l/min/$m^2$<br>$SvO_2$ <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.*

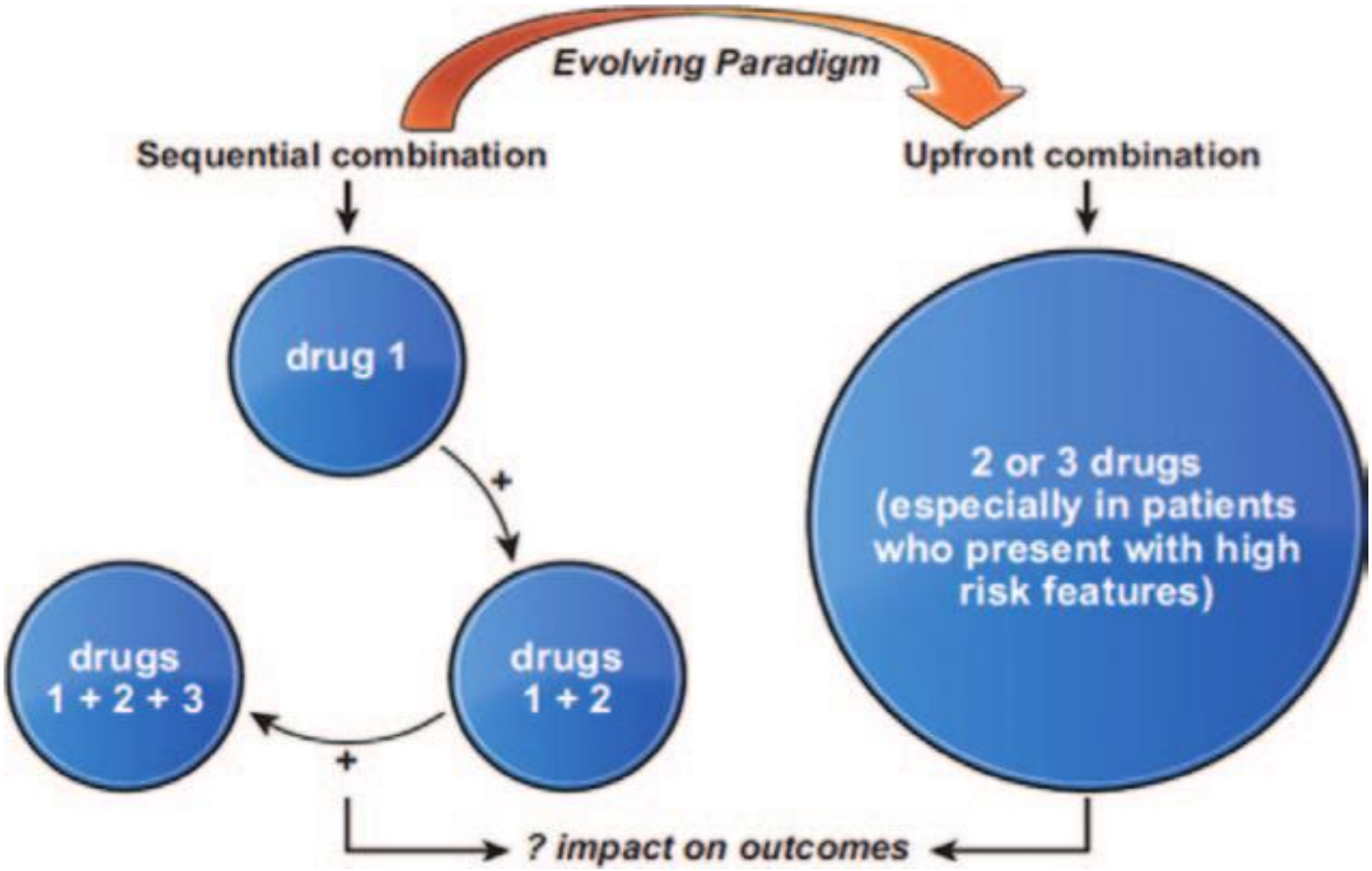
# Sequential combination therapy: results are not uniform…

| 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 + |

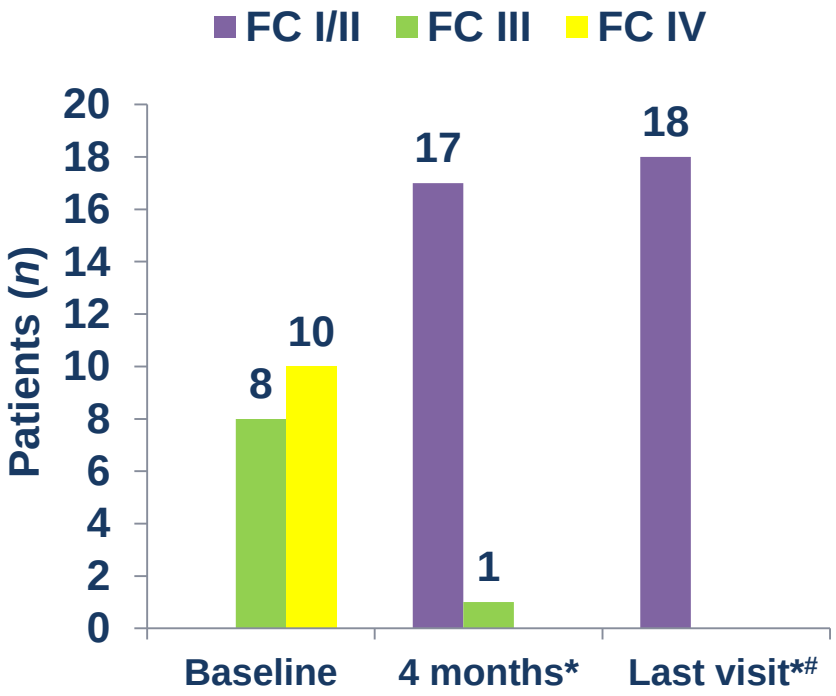
# Evolving paradigm: From sequential to initial combination therapy

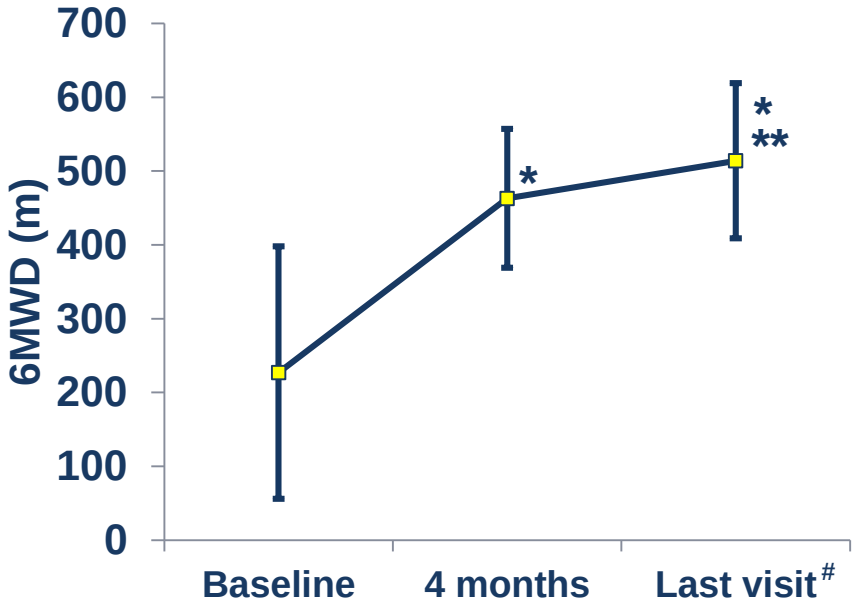



Humbert M, *et al*. *Circulation* 2014.

# 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)**

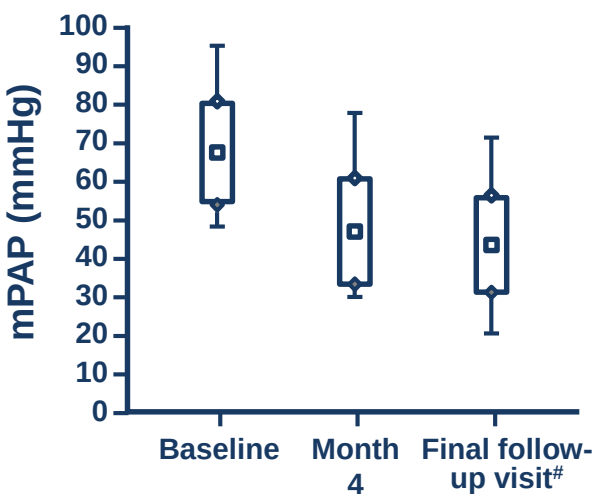


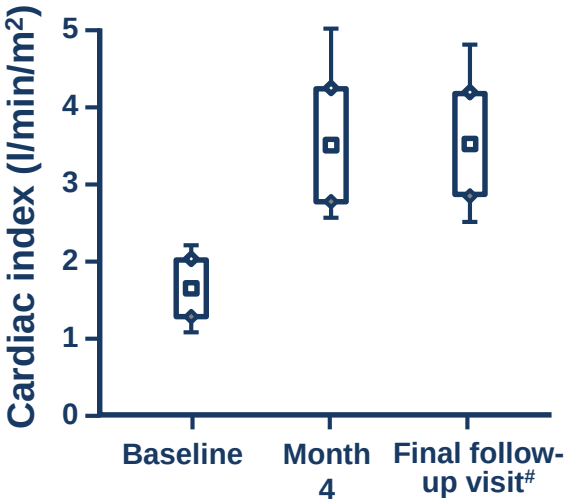



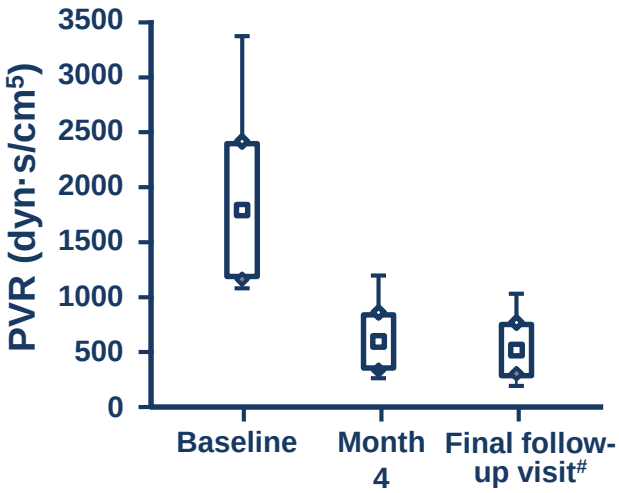

#32 ± 19 months
**p* < 0.01 versus baseline; ** p < 0.01 versus 4 months

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

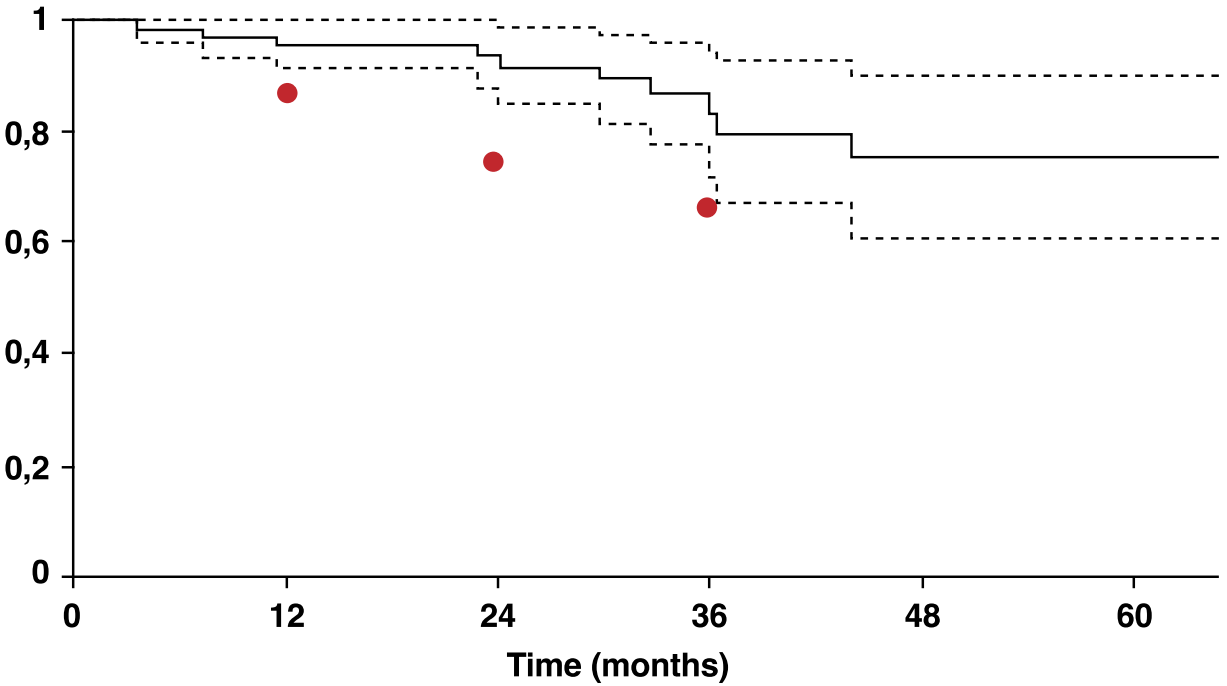
- Long-term follow-up *(n=19)*
  - Median follow-up: 58.7 months (IQR: 52.5 – 70.0 months)
  - Two patients underwent LT (after 3.8 and 41.4 months)
  - 17 patients well and alive in NYHA FC I-II
  - 7 patients with mPAP < 35 mmHg (incl. one < 20 mmHg)
- Survival *(n=19)*

| | 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.

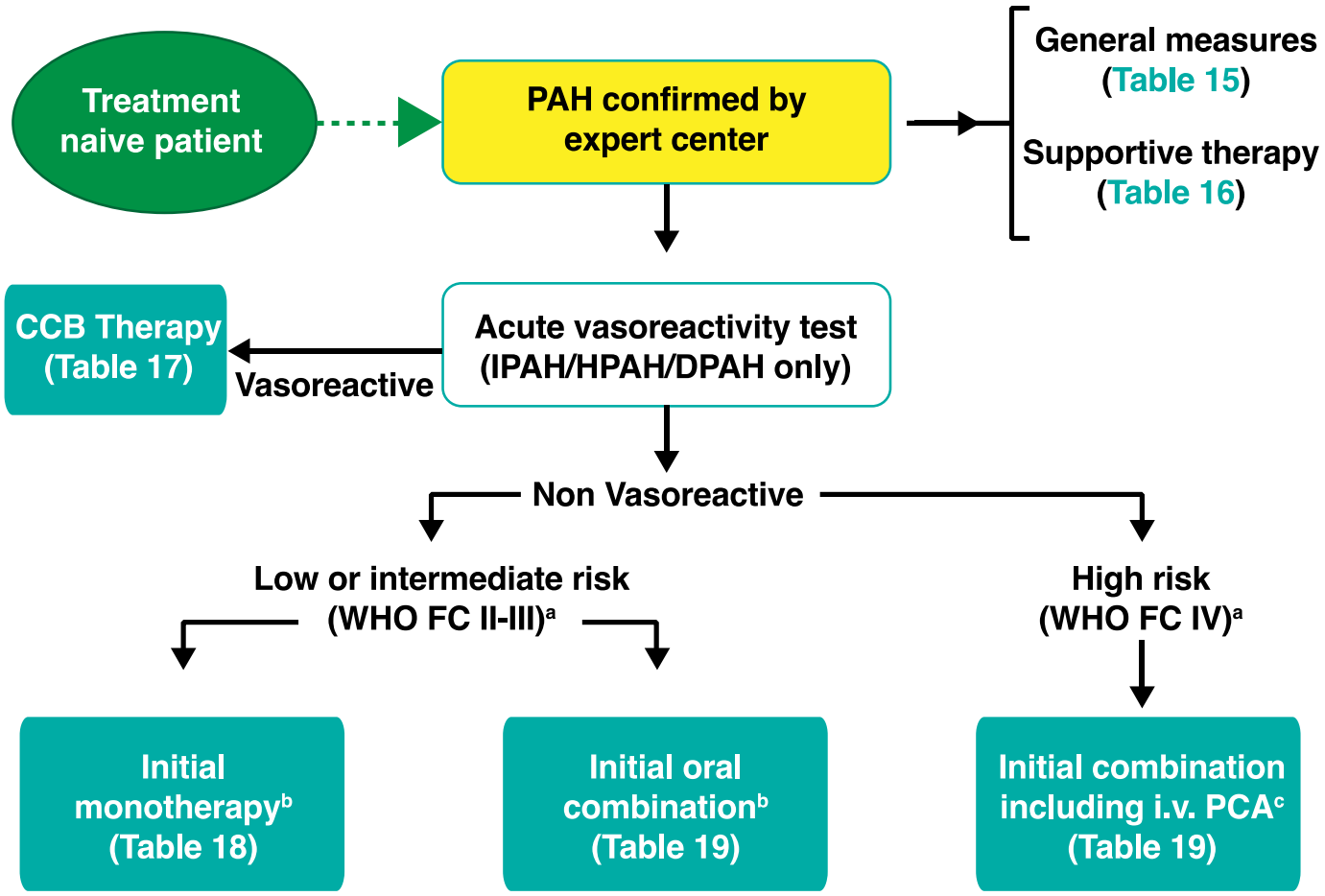
# Survival of patients with idiopathic, heritable and anorexigen-associated PAH (n=74)




| | | | | | | |
|---|---|---|---|---|---|---|
| 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] | | |

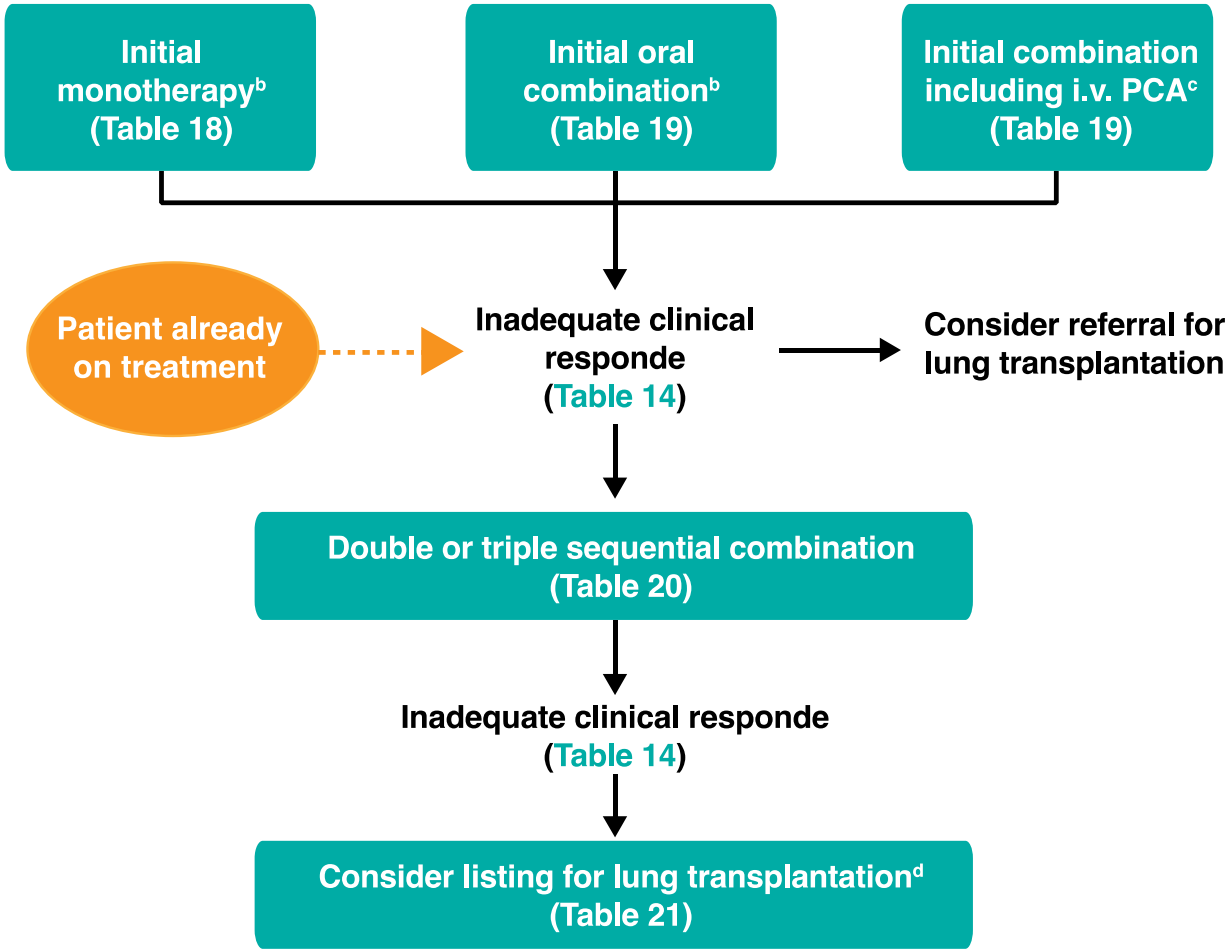
Humbert M, et al. Eur Respir J 2010; 36:549-55.
Sattler C, Sitbon O, *et al. ERS Congress* 2015.

# 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