Overview of randomized controlled trials in pulmonary arterial hypertension

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TORINO DHU Thorax Innovation

Hôpitaux universitaires Paris-Sud Antoine-Béclère Bicêtre Paul-Brousse

Disclosures

–**Actelion:** consultancy (current), board or advisory committee (current), speaker (current)
–**Bayer:** consultancy (current), board or advisory committee (current), speaker (current)
–**GSK:** consultancy (current), board or advisory committee (current), speaker (current), research support (current)
–**Novartis:** consultancy (current), board or advisory committee (current), speaker (current), research support (current)
–**Pfizer:** consultancy (current), board or advisory committee (current), speaker (current), research support (past)

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

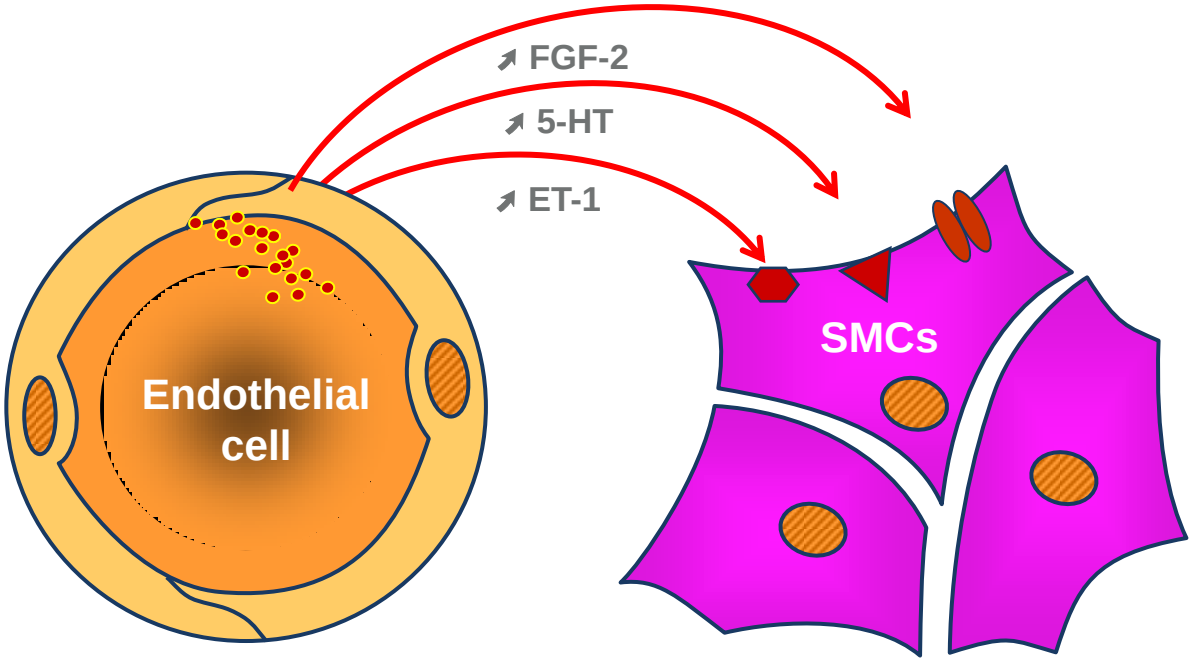
2.1 Left ventricular systolic dysfunction
2.2 Left ventricular diastolic dysfunction
2.3 Valvular disease
2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
2.5 Congenital/acquired pulmonary veins stenosis

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.

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.

PAH treatment: Targeting 3 major dysfunctional pathways (2004 – 2014)

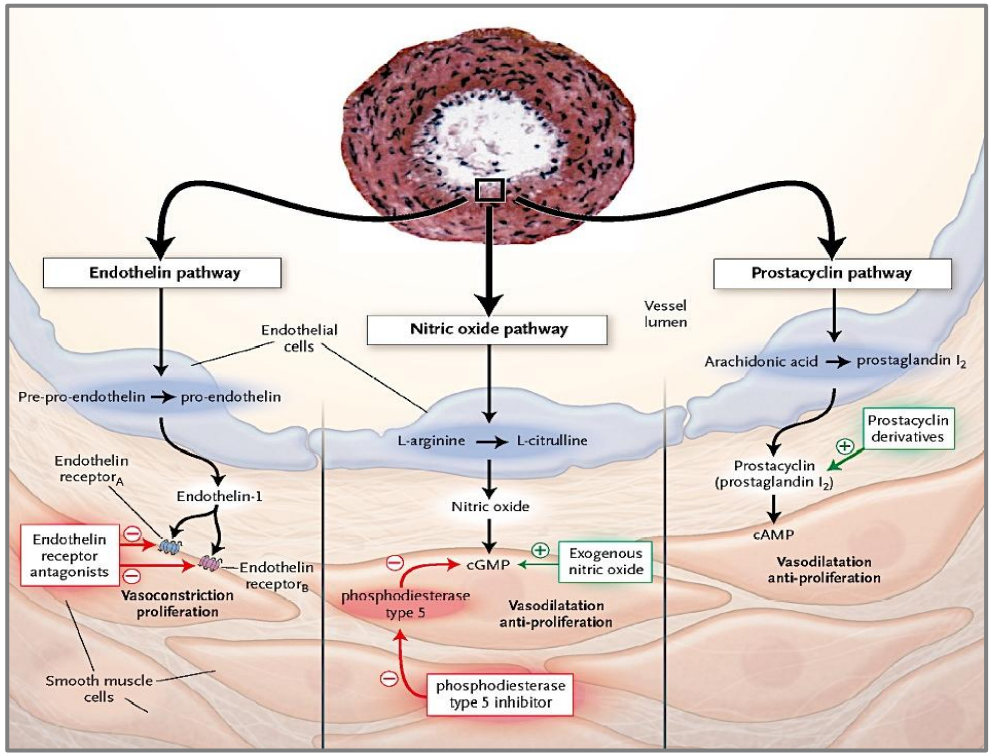
DRUG THERAPY

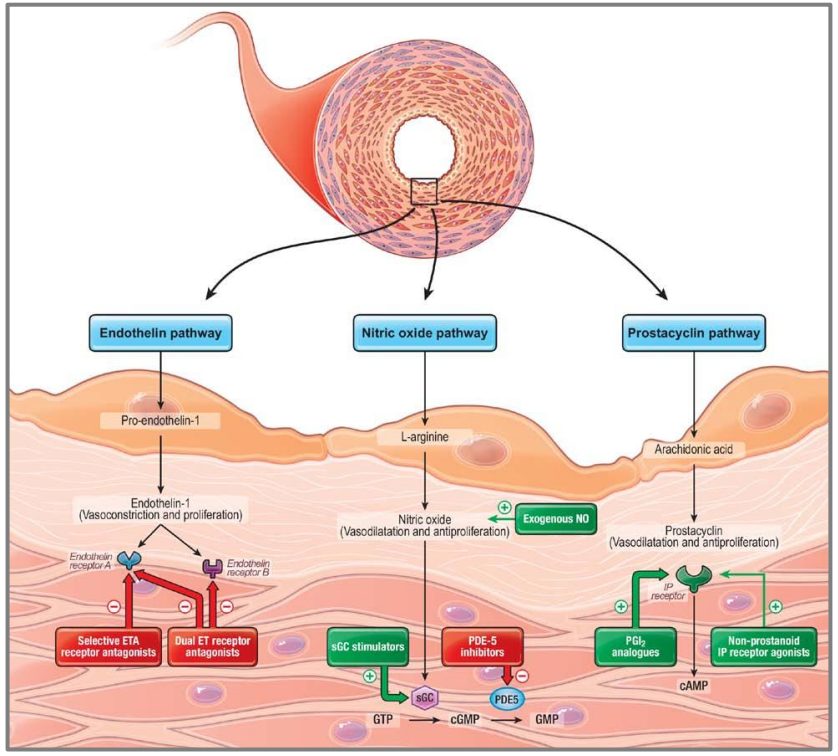
Treatment of Pulmonary Arterial Hypertension

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

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

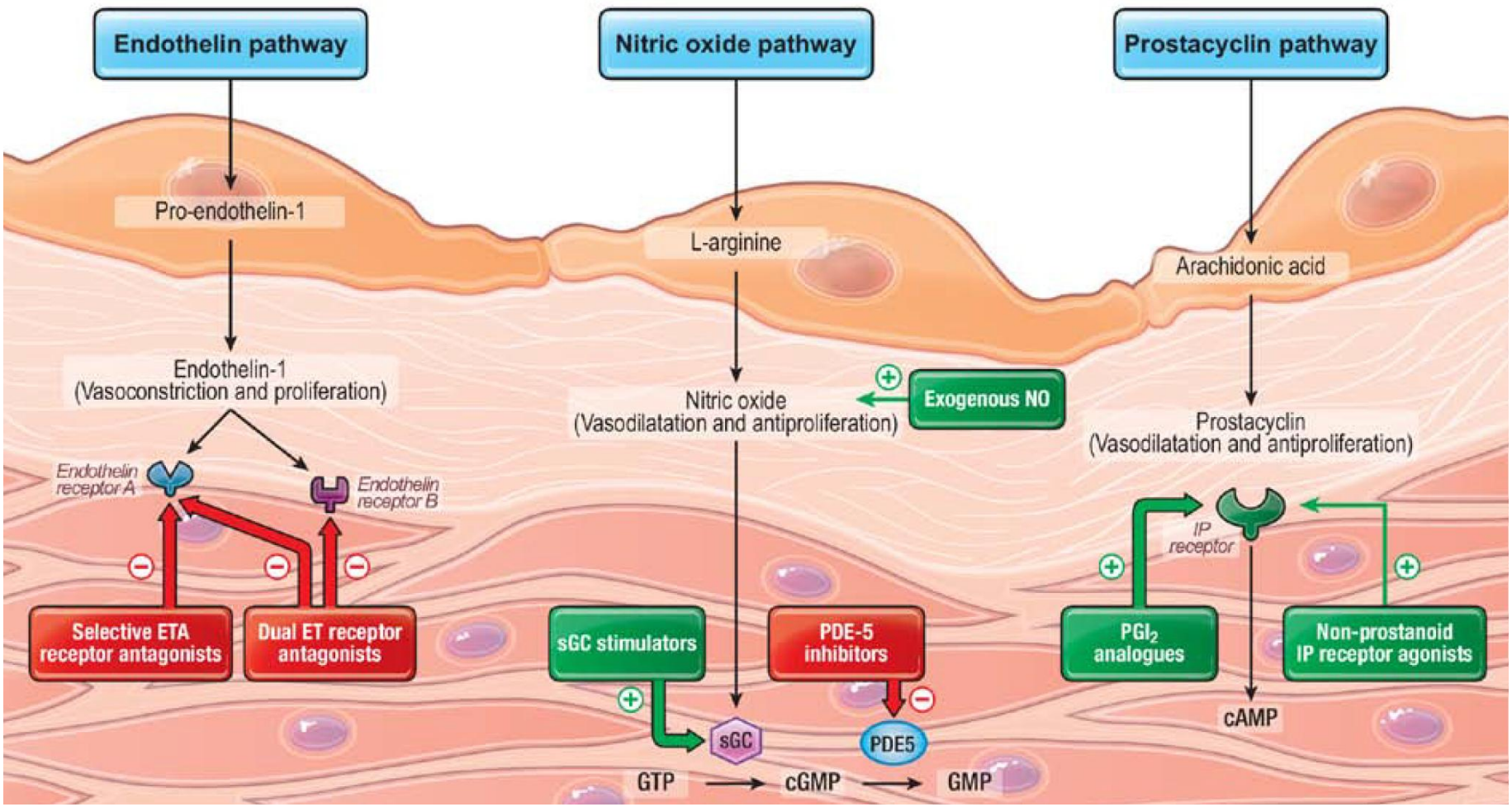




N Engl J Med 2004;351:1425–36.

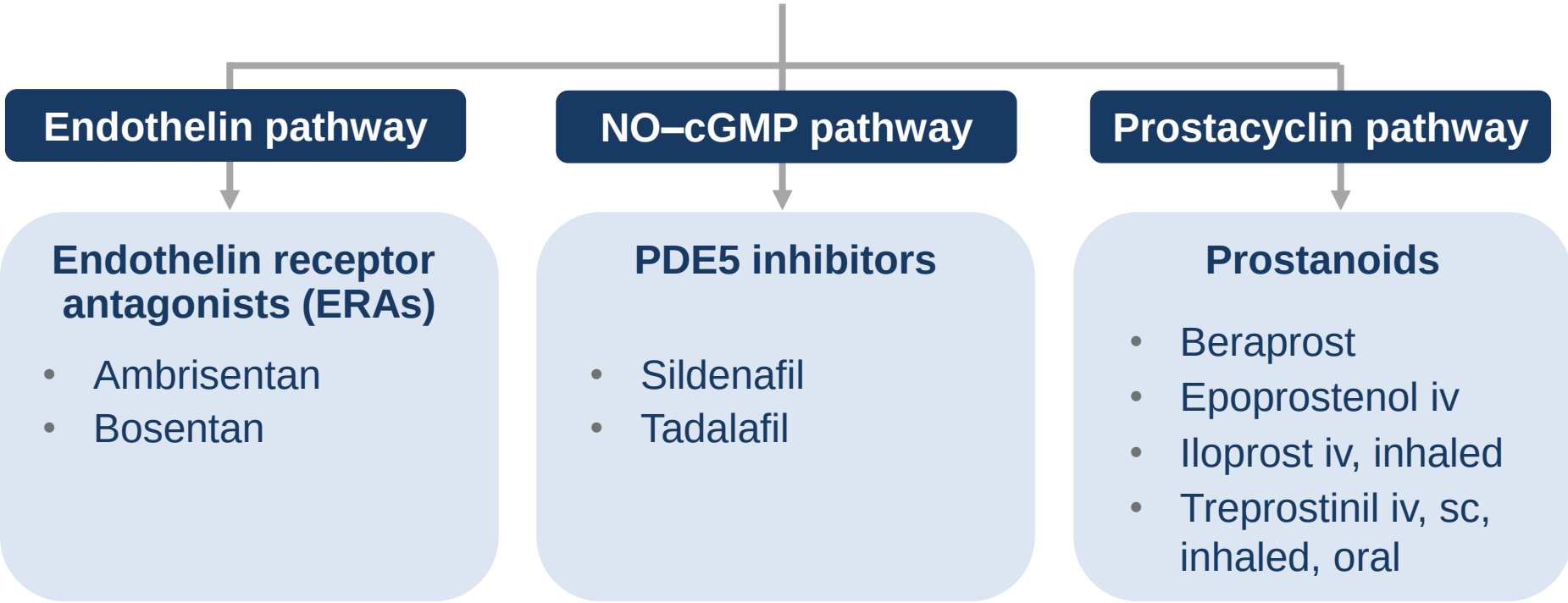
Circulation 2014;130:2189–208.

Endothelial dysfunction in PAH



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

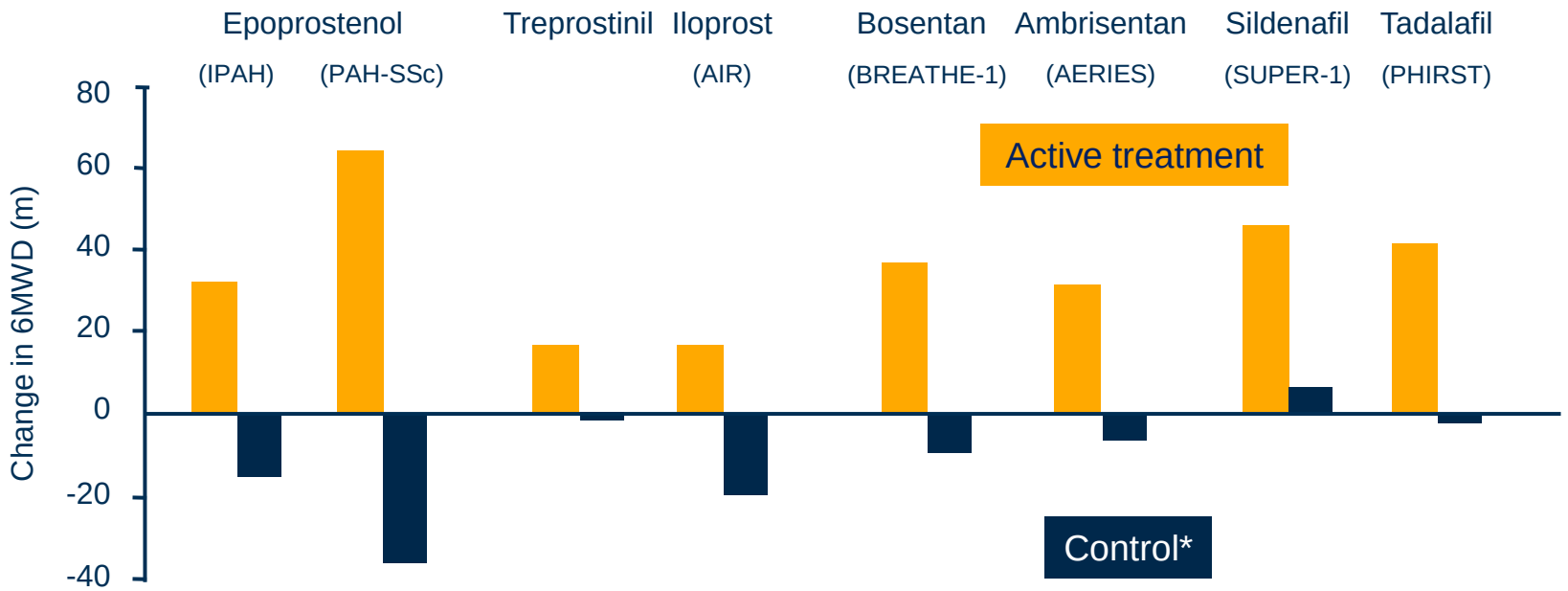
PAH-specific therapies target the 3 signaling pathways involved in PAH: “Drugs used in early trials”



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

RCTs with monotherapy in PAH

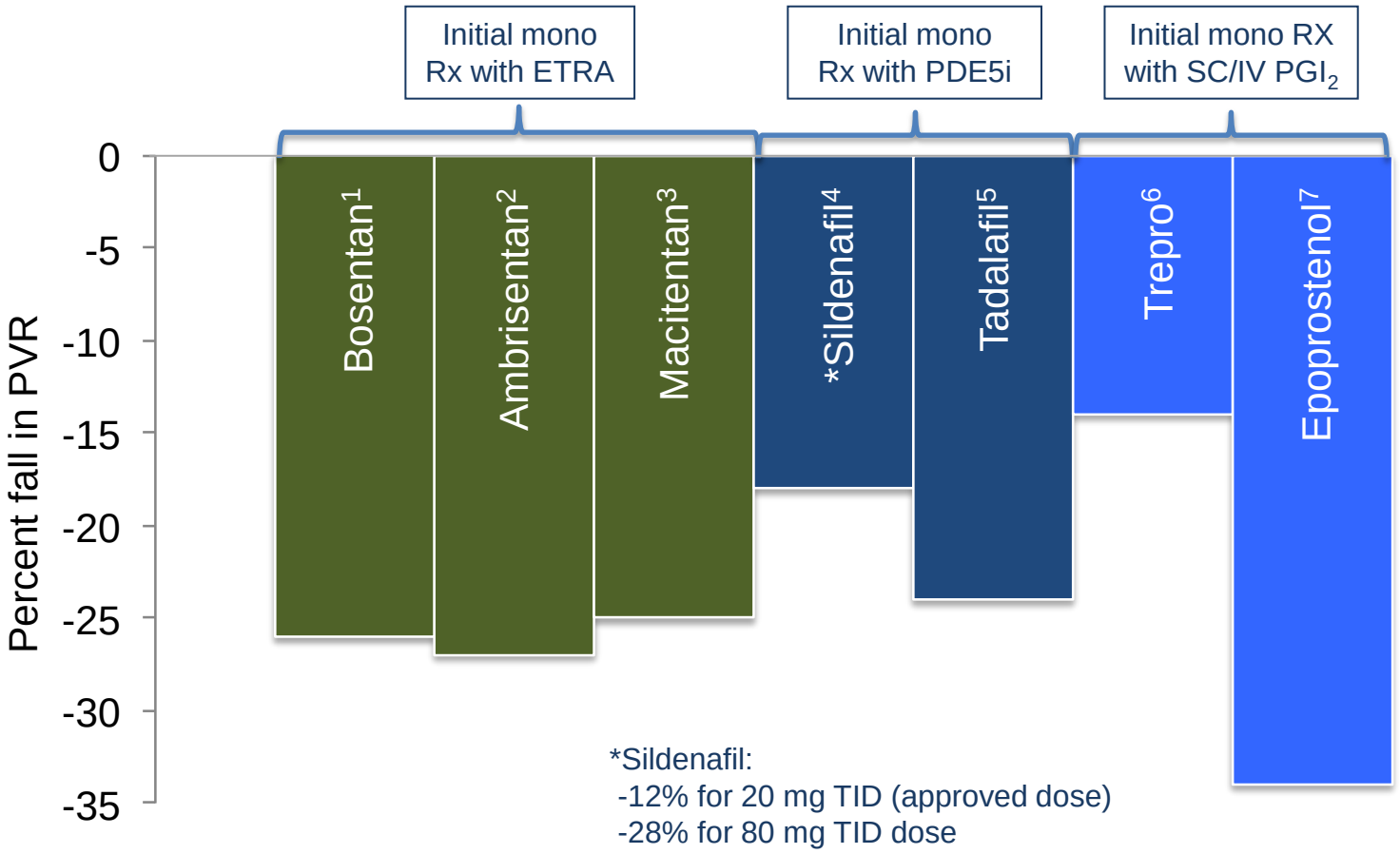
Improvement in exercise capacity (3-4 months)



* 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

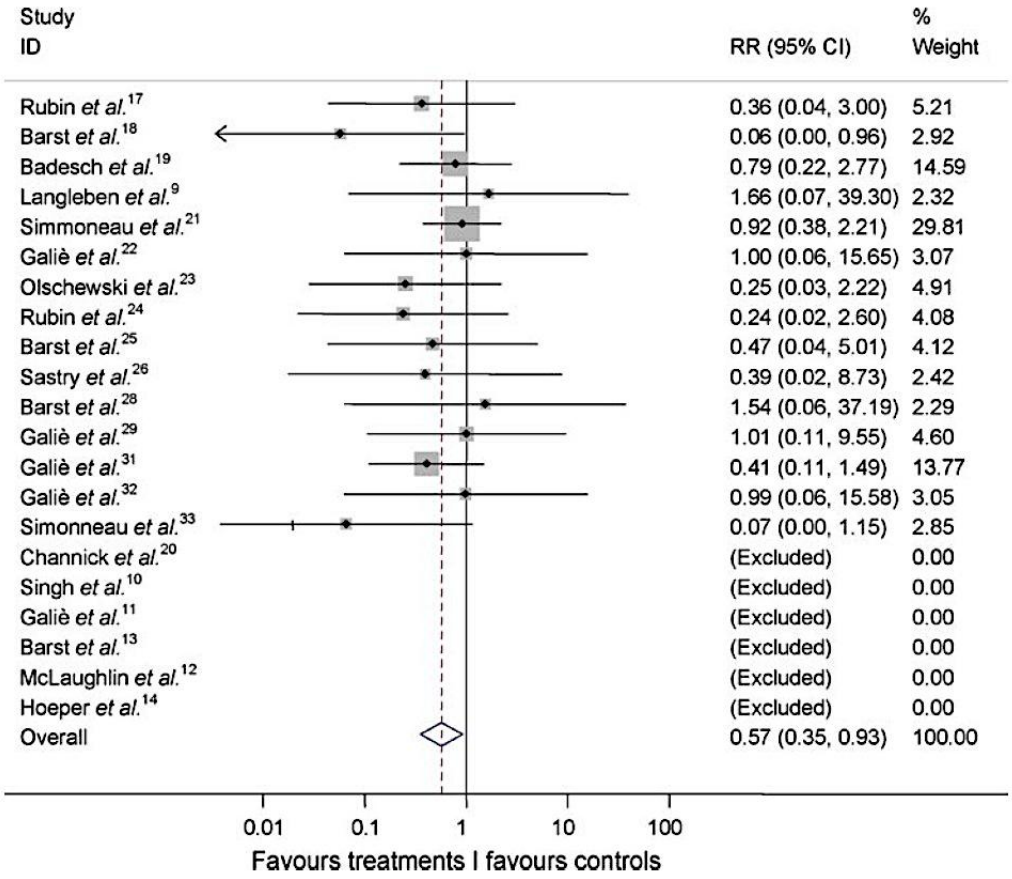


1. Channick RN. *Lancet* 2001; 2. Galie N. *J Am Coll Cardiol* 2005; 3.Pulido T. *N Engl J Med* 2013; 4. Galie N. *N Engl J Med* 2005; 5. Galie N. *Circulation* 2009; 6. Simonneau G. *Am J Respir Crit Care Med* 2002; 7. Barst RJ. *N Engl J Med* 1996.

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

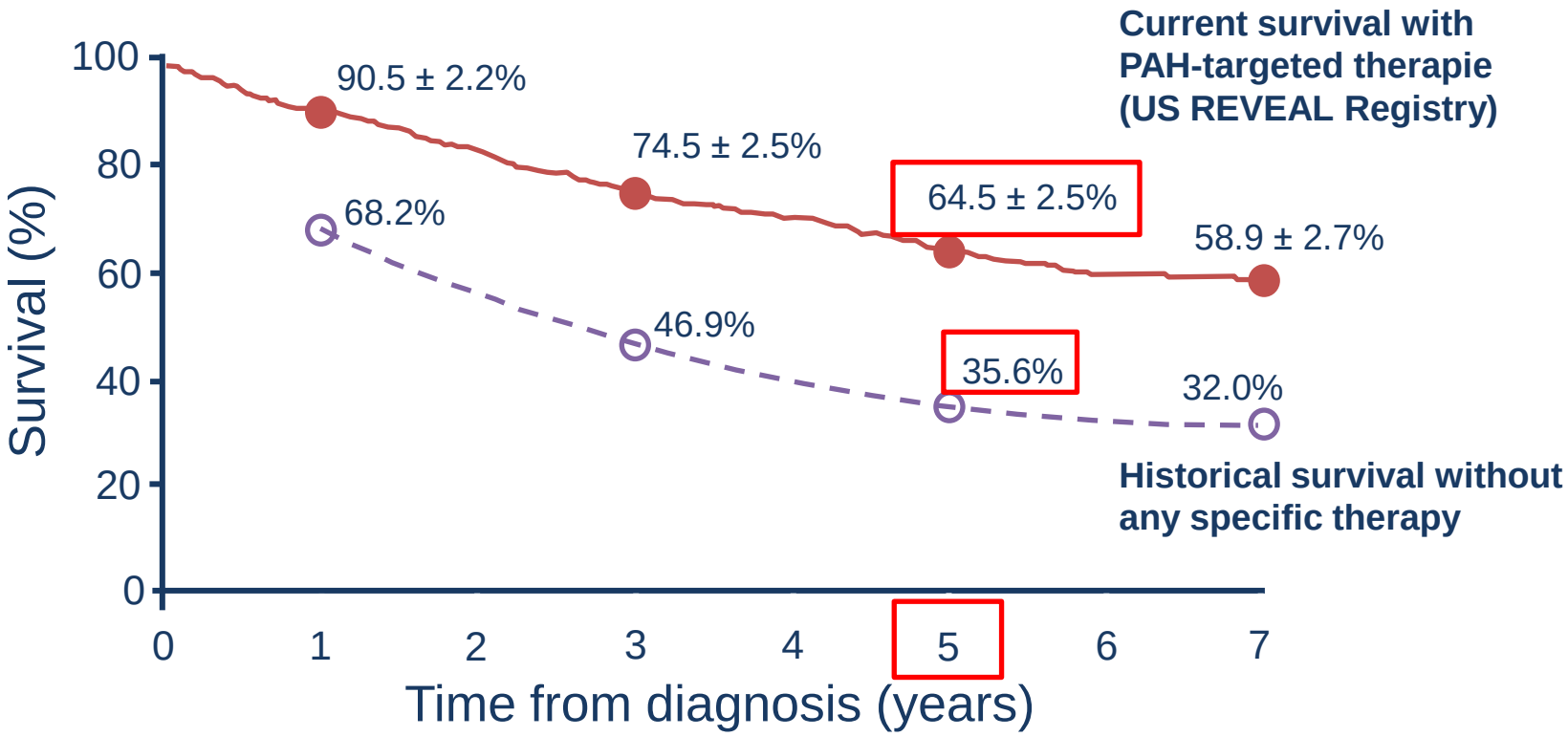
Nazzareno Galiè*, Alessandra Manes, Luca Negro, Massimiliano Palazzini, Maria Letizia Bacchi-Reggiani, and Angelo Branzi

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

Despite drug discovery and development PAH remains a devastating condition



Benza RL, et al. Chest. 2012;142:448–56.

How to do better?

- **Do better with what we have**
  - **Prevention: Detect and treat "early"**
  - **Treat more aggressively and be ambitious!**
    - **Goal-oriented treatment strategy and sequential combination therapy**
    - **Changing strategy: Initial combination therapy**
- **Consider new drugs targeting novel pathways (TKIs? Statins? 5-HT? Oxidative stress?…)**

Strategies for combination therapy in PAH

1. **Sequential combination after clinical deterioration**
   - Slow sequential combo
   - Add drug B sometimes months/years after drug A
   - Likely the worst strategy…
2. **Sequential combination if treatment goals are not met (goal-oriented treatment strategy)**
   - Rapid (“aggressive”) sequential combo
   - Add drug B rapidly (3-6 months) after drug A
3. **Initial (“upfront”) combination therapy**
   - Treatment initiation with 2 or 3 drugs
   - Really different than option 2?
   - Some physicians are reluctant
     - “I prefer to keep a drug with me if my patient deteriorates…”
     - “I’m affraid by side effects...”

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

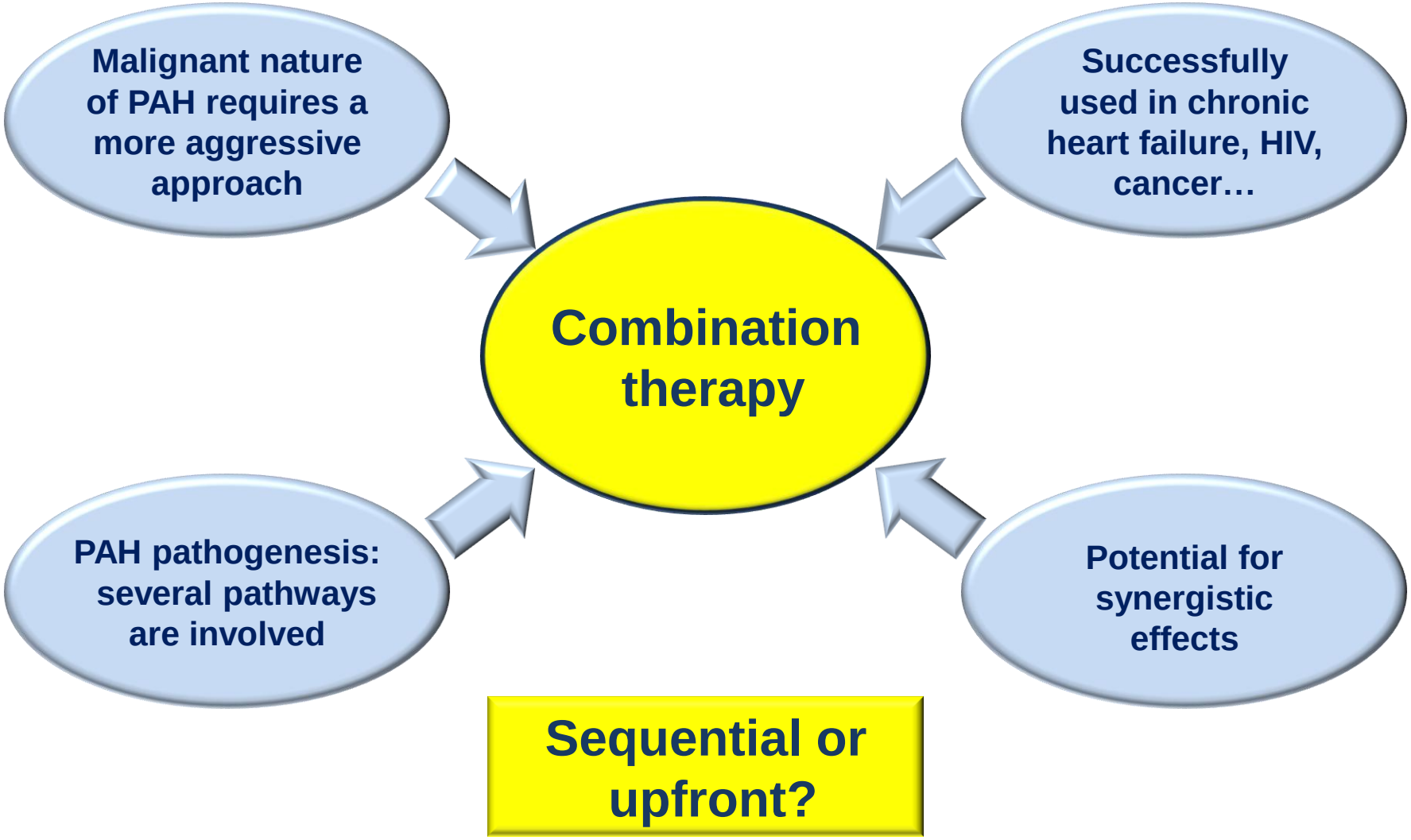
	At baseline	Every 3–6 months[a]	Every 6–12 months[a]	3–6 months after changes in therapy[a]	In case of clinical worsening
Medical assessment and determination of functional class	+	+	+	+	+
ECG	+	+	+	+	+
6MWT/Borg dyspnoea score	+	+	+	+	+
CPET	+		+		+[e]
Echo	+		+	+	+
Basic lab[b]	+	+	+	+	+
Extended lab[c]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

Rationale for combination therapy



Combination therapy: *What's the evidence?*

- Sequential combination therapy
  - A lot of studies (RCTs) available
  - Results are not uniform
- Initial combination therapy
  - Only two RCTs: one negative (BREATHE-2), one positive (AMBITION)
  - Expanded experience in clinical practice (dual, triple)
- Recent meta-analysis[1]: Combination therapy (all strategies, sequential and initial) is associated with significant risk reduction for clinical worsening compared with monotherapy:
  risk ratio [RR] 0.65 [95% CI 0.58–0.72], p<0.00001

→ No comparison between sequential and initial combination therapy

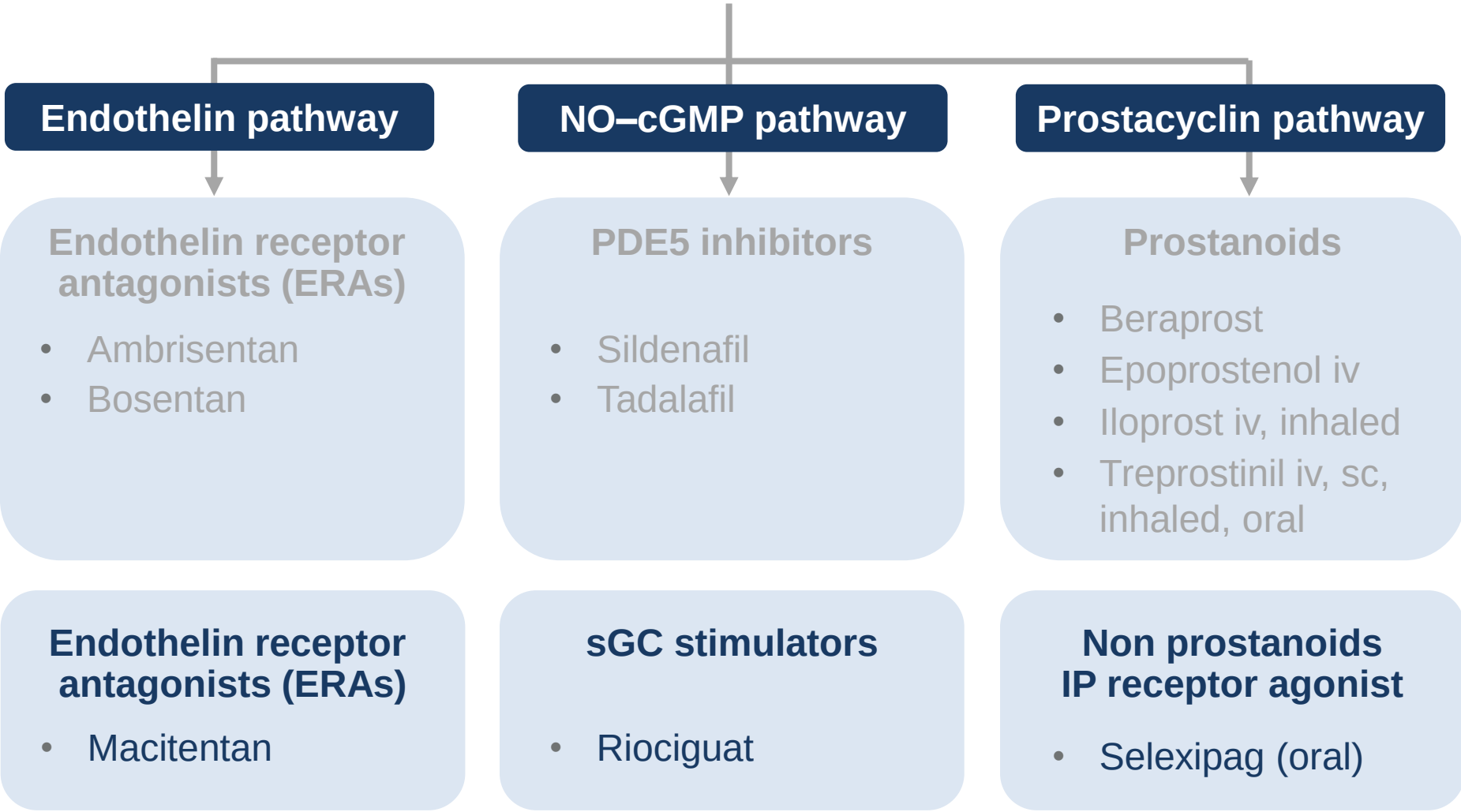
1. Lajoie AC, *et al.* Lancet Respir Med 2016. Published Online February 26, 2016.

Sequential combination therapy with “drugs used in early trials”: results are not uniform…

Drug tested	Study	Background	N	Duration (weeks)	Primary endpoint
Bosentan[1]	EARLY	None or sildenafil (16%)	185	24	PVR +, Δ6MWD **(NS)**
Bosentan[2]	COMPASS-2	Sildenafil	334	92	Morbi-mortality **(NS)**
Iloprost[3]	STEP	Bosentan	67	12	Δ6MWD **(NS)**
Iloprost[4]	COMBI	Bosentan	40	12	Δ6MWD **(NS)**
Sildenafil[5]	PACES	Epoprostenol	264	16	Δ6MWD **(POS)**
Sildenafil	NCT00323297	Bosentan	104	12	Δ6MWD **(NS)**
Tadalafil[6]	PHIRST	None or bosentan (54%)	405	16	Δ6MWD **(NS)**
Treprostinil[7]	Inhaled- TRIUMPH	Bosentan or sildenafil	235	12	Δ6MWD **(POS)**
Treprostinil[8]	Oral- FREEDOM C1	Bosentan &/or sildenafil	354	16	Δ6MWD **(NS)**
Treprostinil[9]	Oral- FREEDOM C2	Bosentan &/or sildenafil	310	16	Δ6MWD **(NS)**

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

PAH-specific therapies target the 3 signaling pathways involved in PAH: drugs used in recent trials



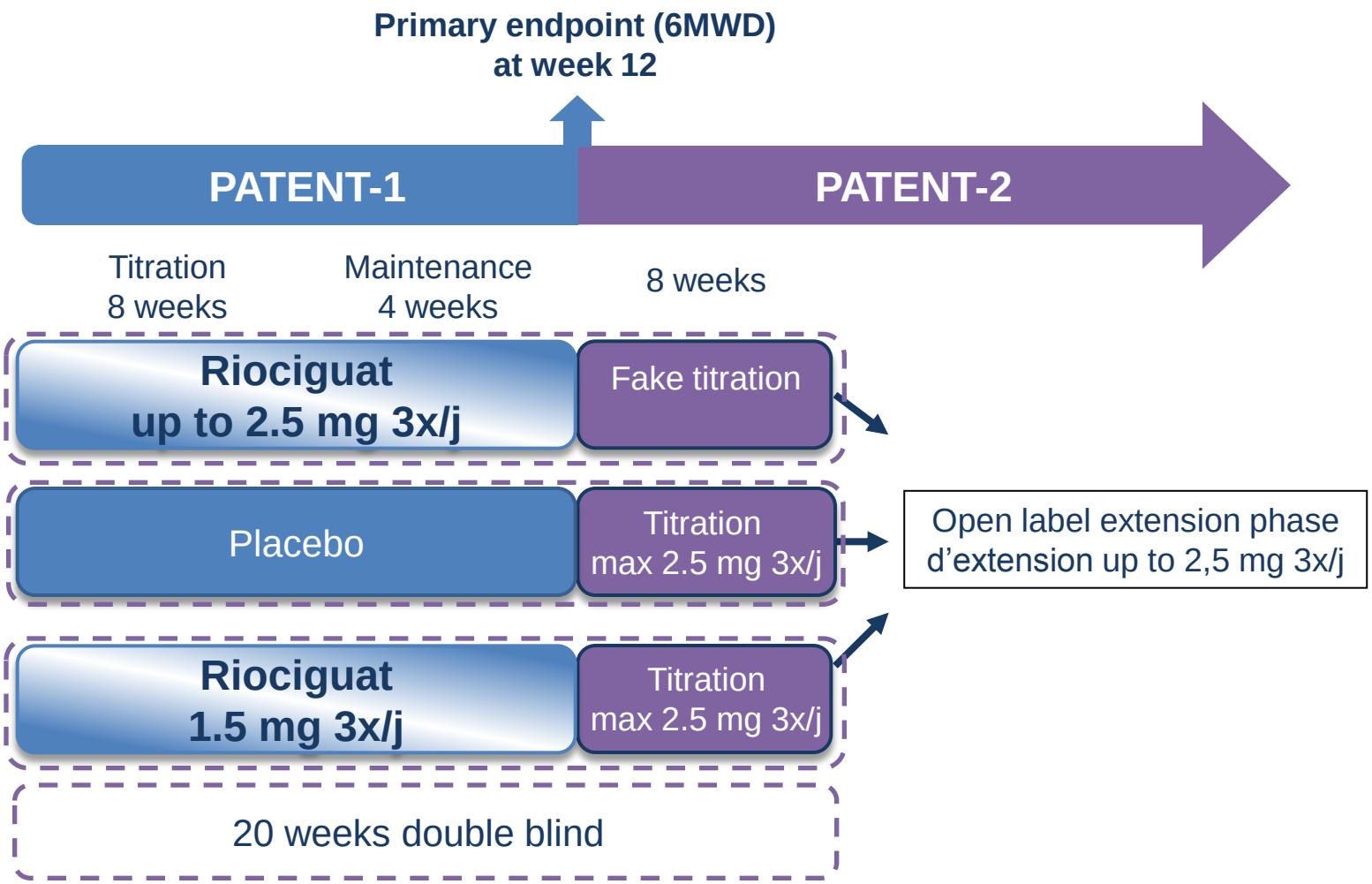
Adapted from Galiè N et al. J Am Coll Cardiol 2013;62:D60–72.

Sequential combination therapy: Recent studies

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

1. Ghofrani HA, *et al*. *Eur Respir J* 2015.
2. Pulido T, et al. *N Engl J Med* 2013; 369:809-18.
3. Sitbon O, et al. *N Engl J Med* 2015;373:2522-33.

PATENT : *Study Design*

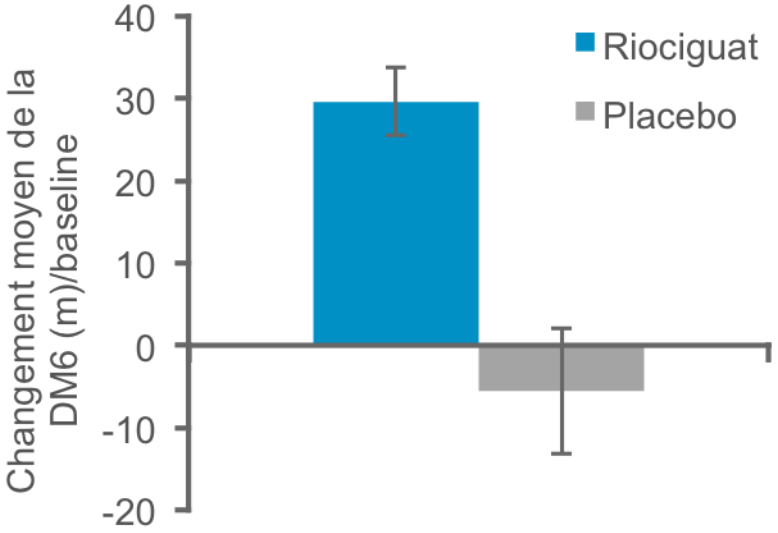


Ghofrani HA, *et al. N Engl J Med* 2013.

Primary endpoint: 6MWD

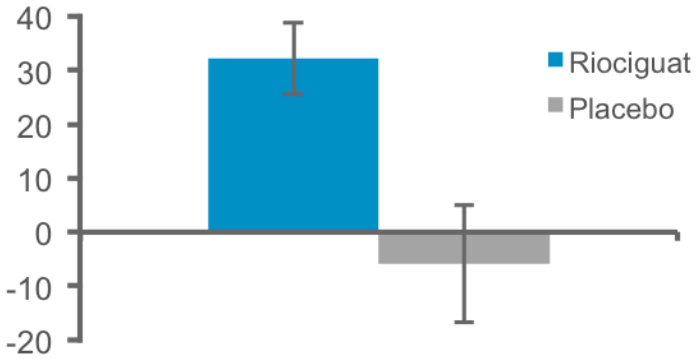
Total population (n=254/126)

+36 m
p<0.0001
(95% CI: 20–52 m)



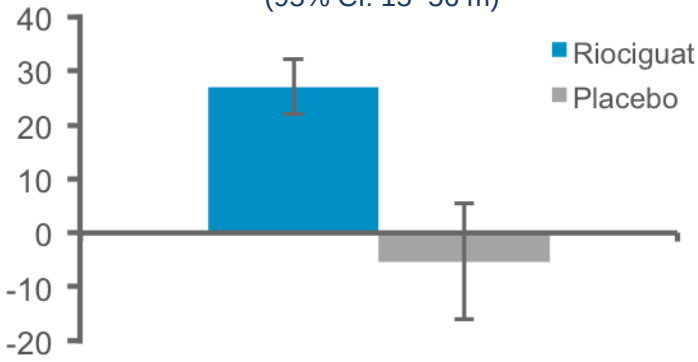
Naïve population naïve (n=123/66)

+38 m
(95% CI: 15–62 m)



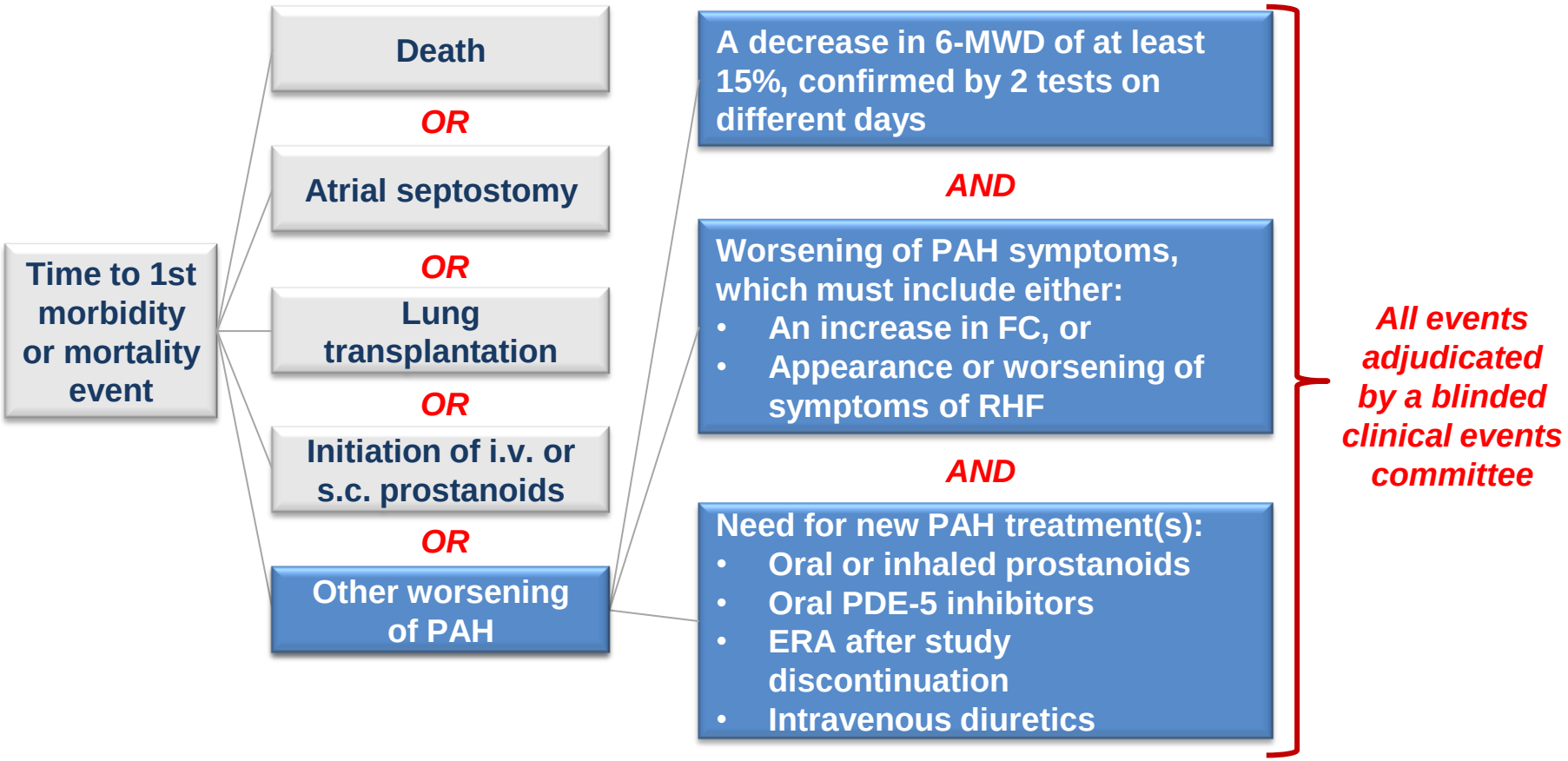
Pre-treated population (n=131/60)

+36 m
(95% CI: 15–56 m)



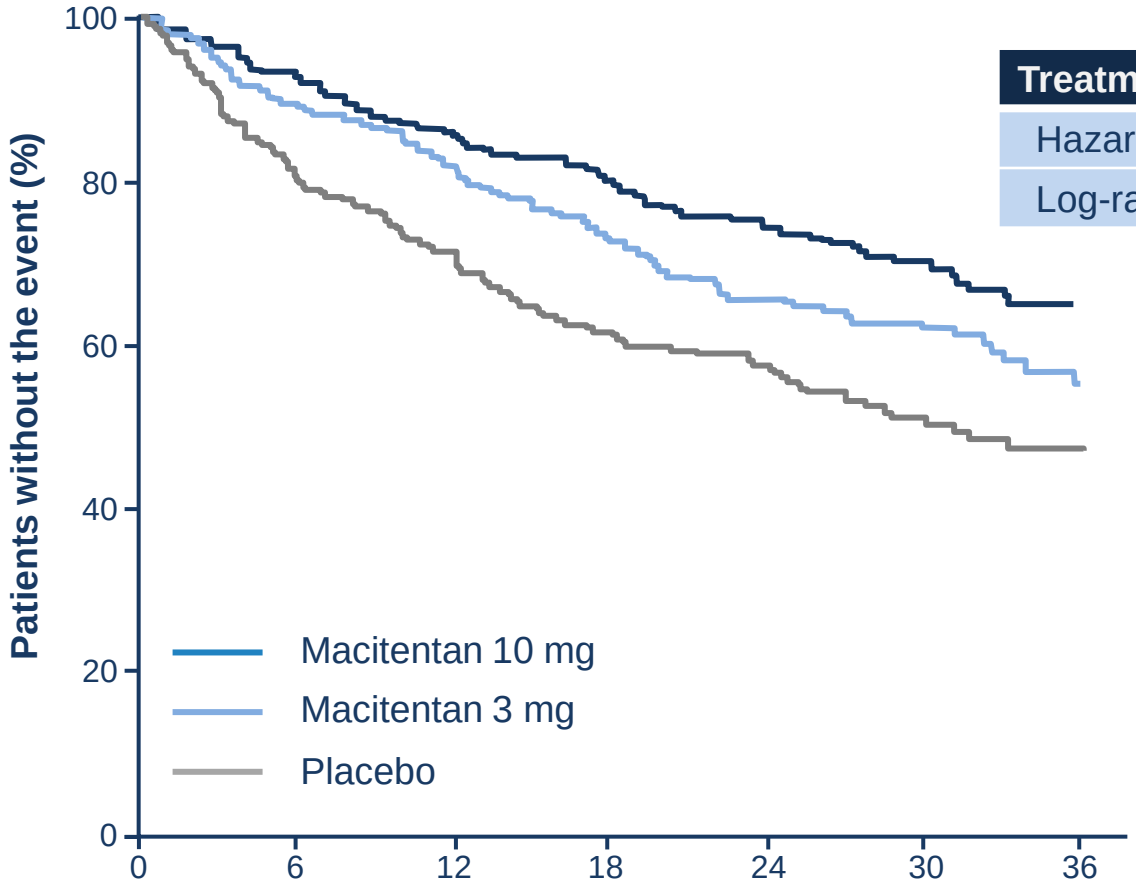
Ghofrani HA, *et al. N Engl J Med* 2013.

SERAPHIN : Primary endpoint



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

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



Treatment difference	3 mg	10 mg
Hazard ratio	0.70	0.55
Log-rank *p*-value	0.01	< 0.001

Risk reduction of primary endpoint event vs placebo
Macitentan 10 mg: 45%
Macitentan 3 mg: 30%

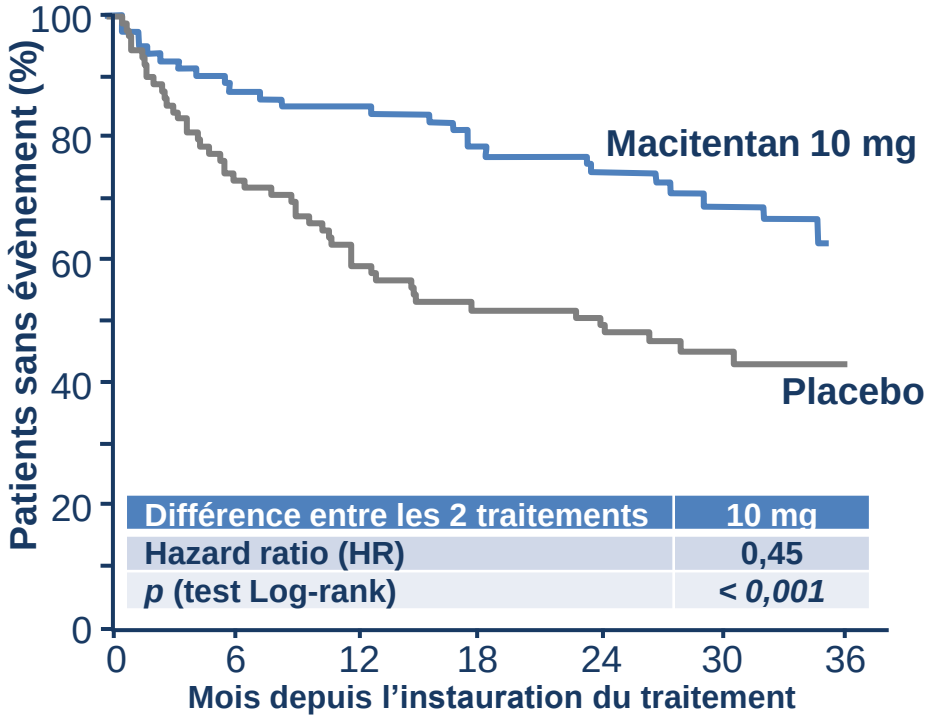
PAH worsening was the main component of the primary endpoint

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

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

Treatment-naïve patients

Risk reduction 55 %



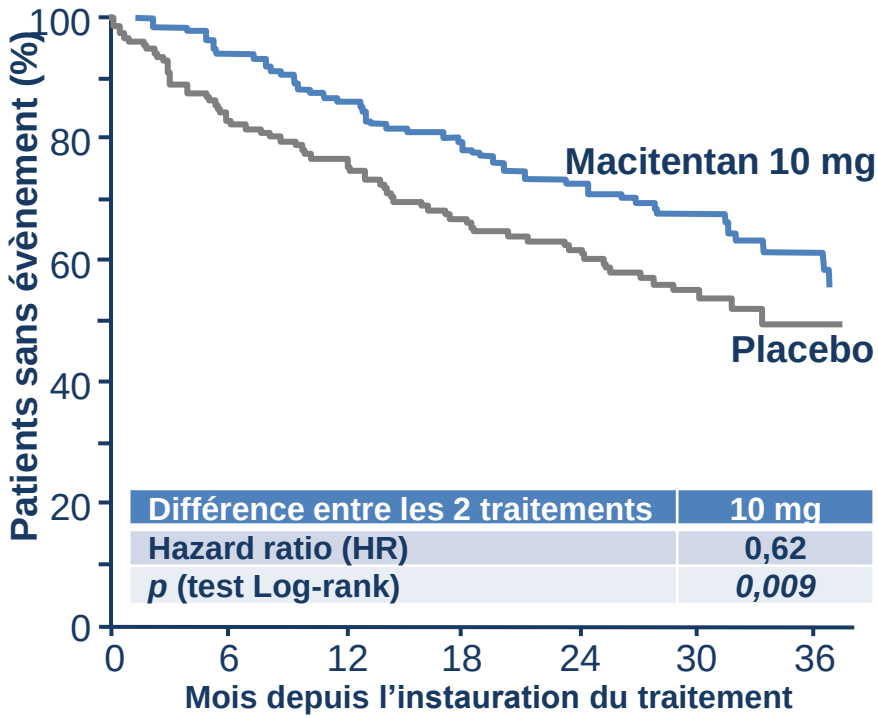
Différence entre les 2 traitements	10 mg
Hazard ratio (HR)	0,45
p (test Log-rank)	*< 0,001*

Patients à risque

Macitentan 10 mg	88	74	68	64	58	38	17
Placebo	96	66	13	54	45	42	24

Patients on background therapy

Risk reduction 38 %



Différence entre les 2 traitements	10 mg
Hazard ratio (HR)	0,62
p (test Log-rank)	*0,009*

Patients à risque

Macitentan 10 mg	154	134	119	107	97	53	24
Placebo	154	122	106	90	80	40	10

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

GRIPHON study (phase III): ProstaGlandin I_2 Receptor agonist In Pulmonary arterial HypertensiON

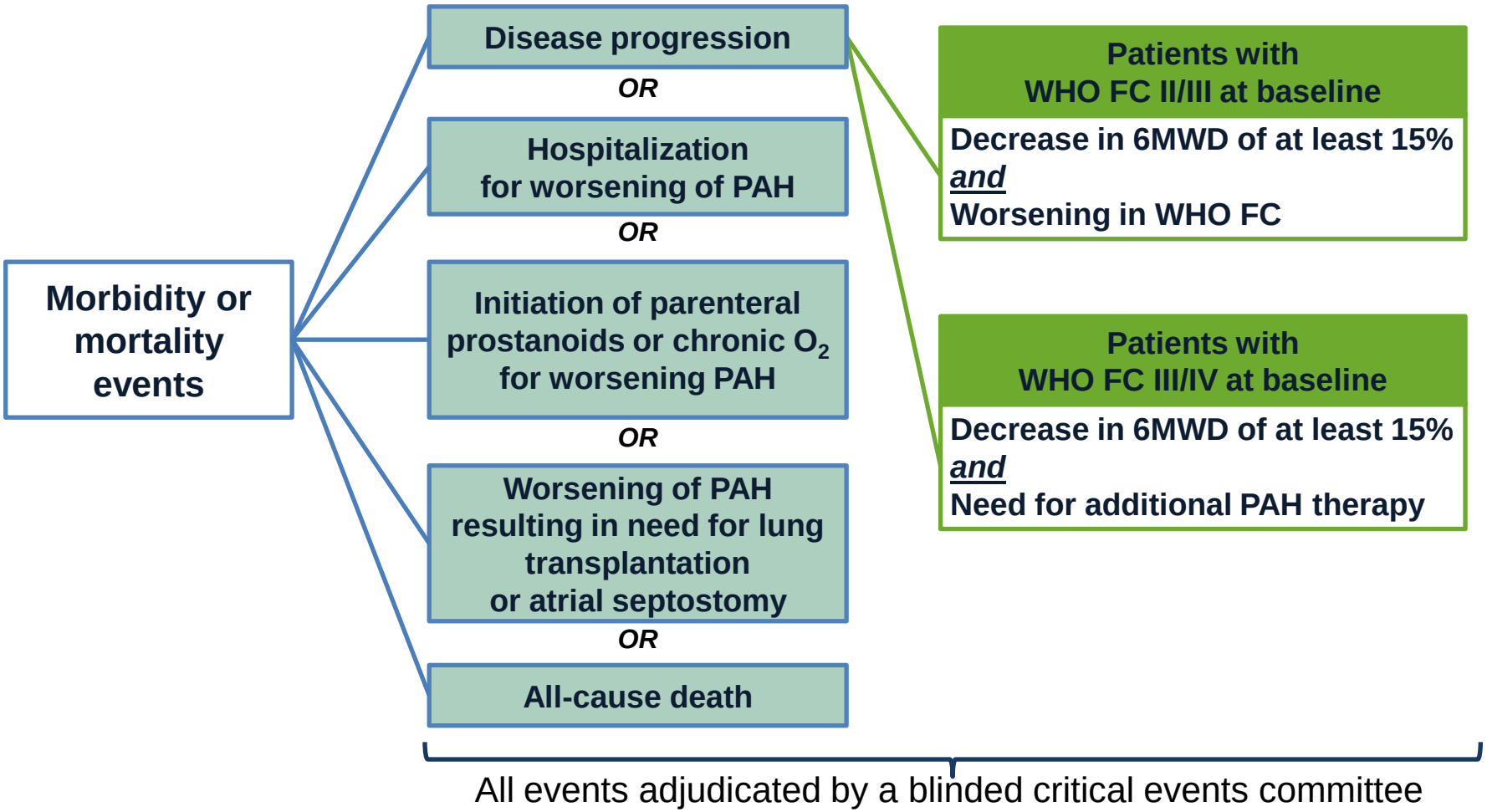
- Multicenter, double-blind, placebo-controlled event-driven study
- 1156 PAH adult patients
- 80% on background treatment with ERA and/or PDE-5i
- Composite primary outcome measure: time to the first occurrence of death or morbidity event

GRIPHON
Prostacyclin (PGI_2) Receptor agonist In Pulmonary arterial HypertensiON

NCT01106014: www.clinicaltrials.gov

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

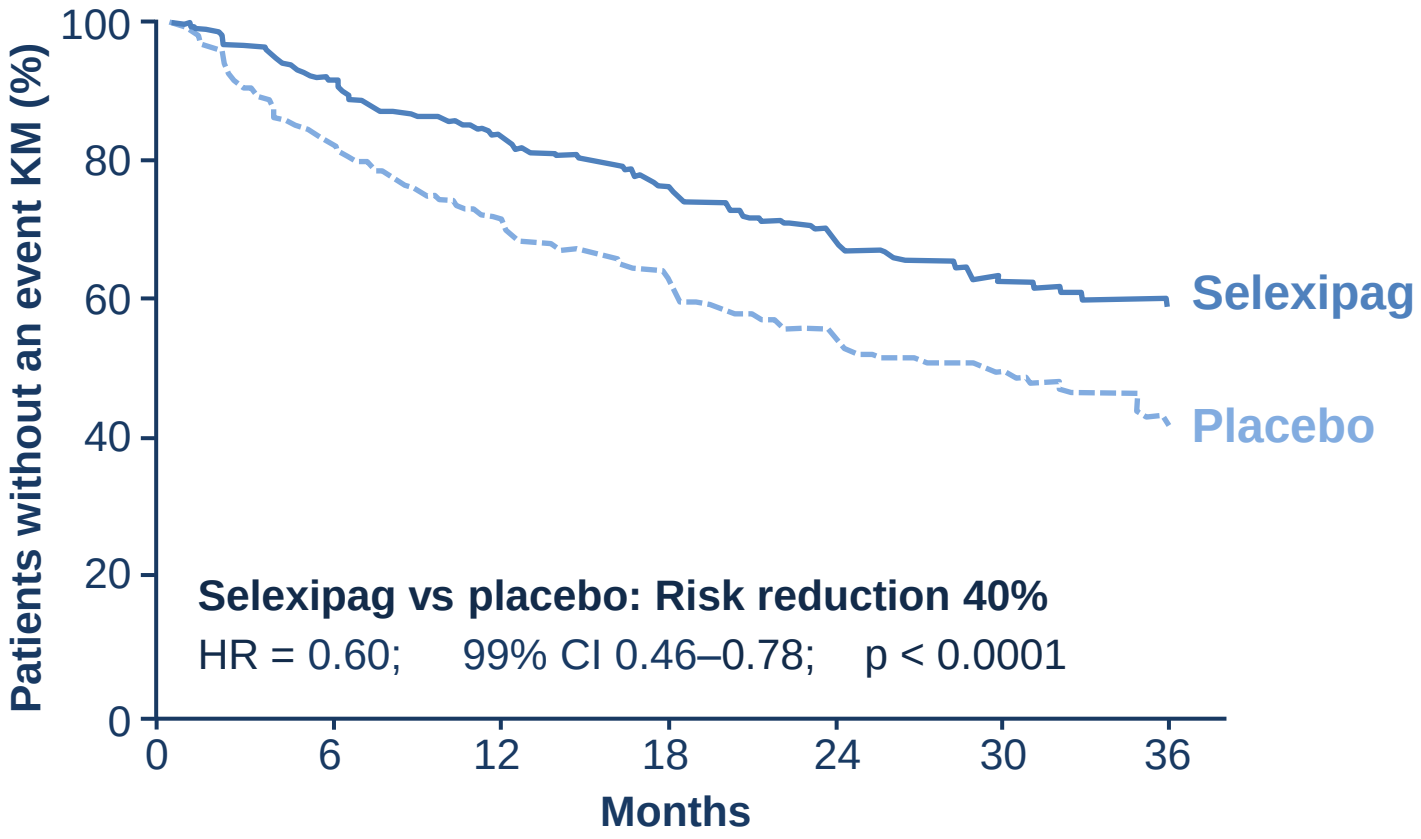
GRIPHON Primary endpoint: Time to first occurrence of death or morbidity due to PH up to EOT



EOT: End of double-blind treatment

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

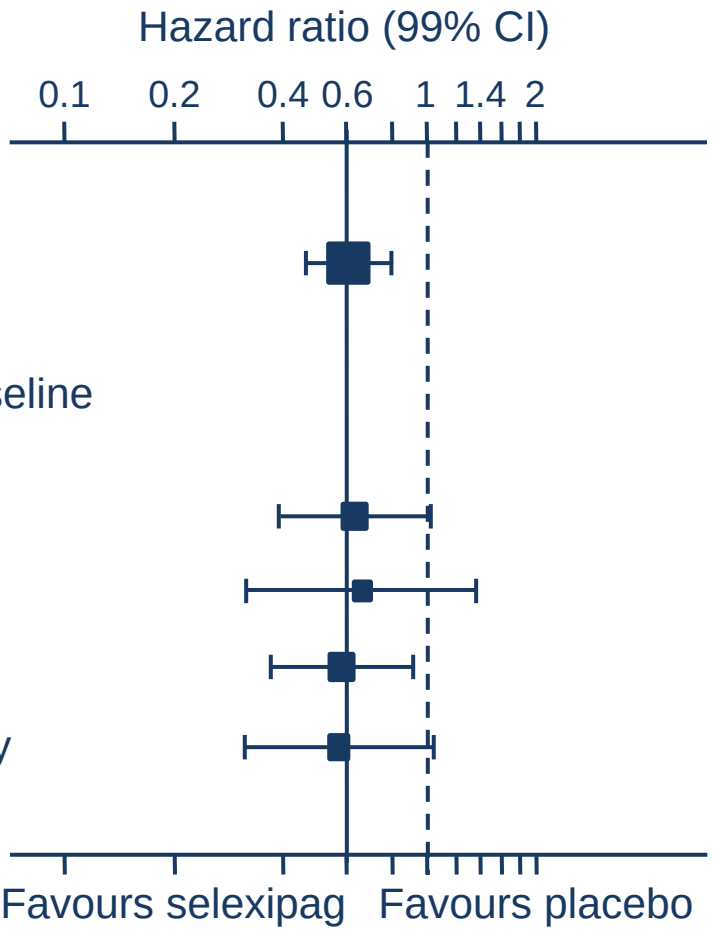
Selexipag reduced the risk of the primary outcome composite of death or morbidity due to PH



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

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

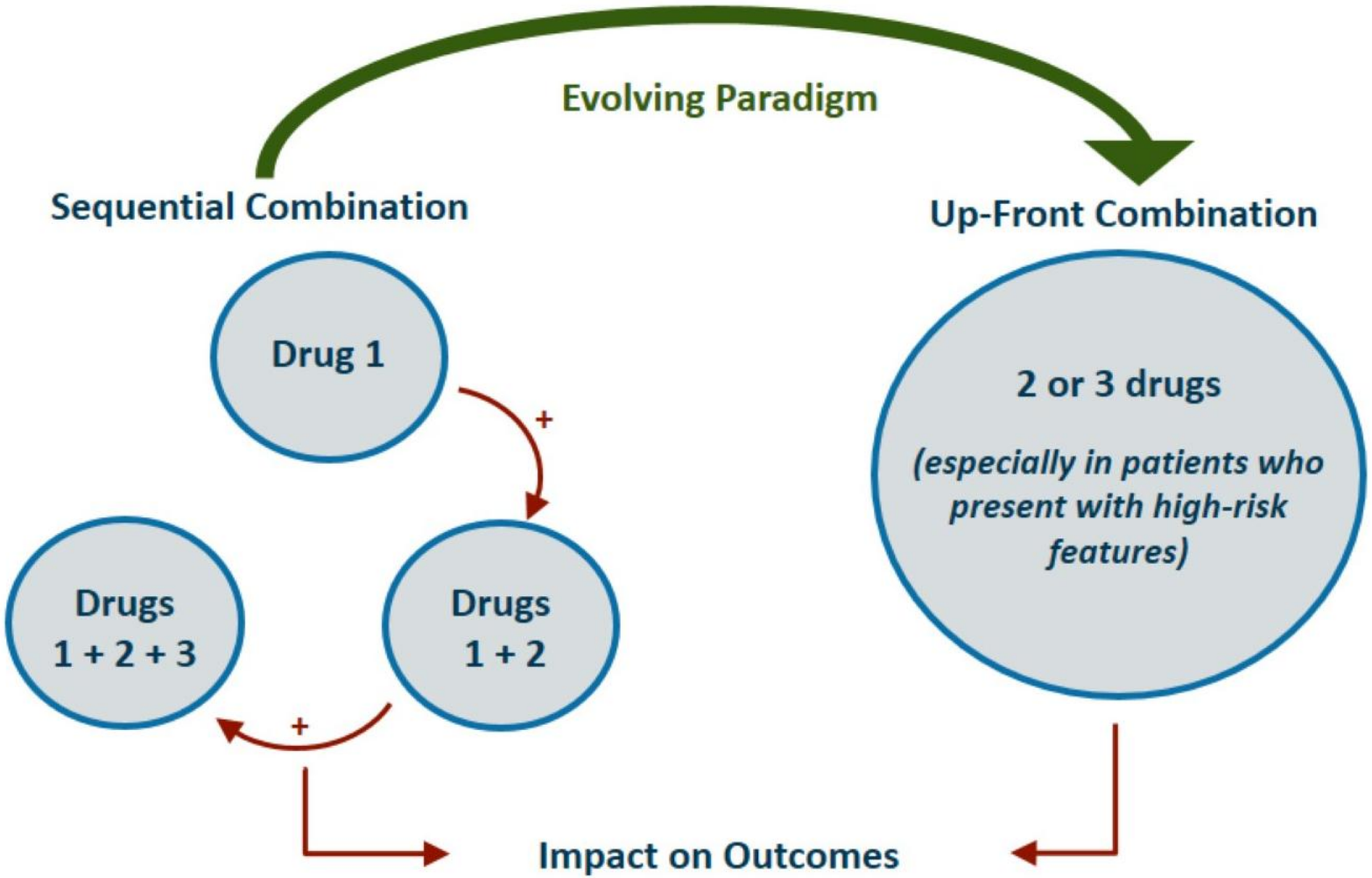
Consistent treatment effect of selexipag on primary composite endpoint according to background therapy



	Selexipag	Placebo
Selexipag vs placebo	No. of patients/ no. of events	
All patients	574/155	582/242
PAH specific therapy at baseline (interaction *p* value = 0.95)		
ERA + PDE-5i	179/47	197/80
ERA monotherapy	94/23	76/29
PDE-5i monotherapy	189/54	185/84
No PAH-specific therapy	112/31	124/49

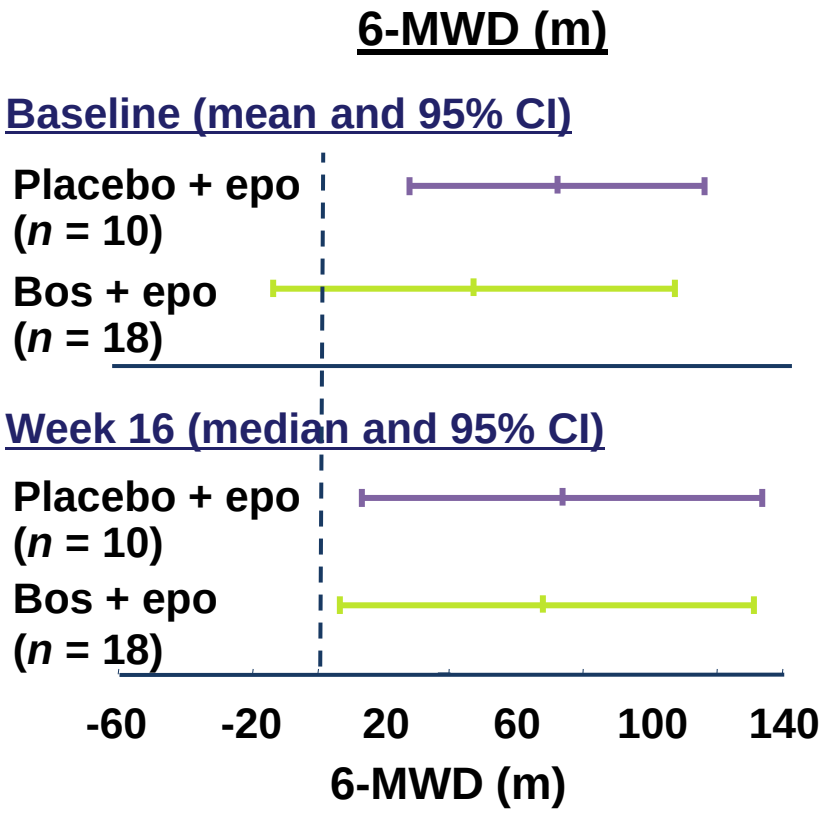
1. Sitbon O, et al. *N Engl J Med* 2015;373:2522-33.

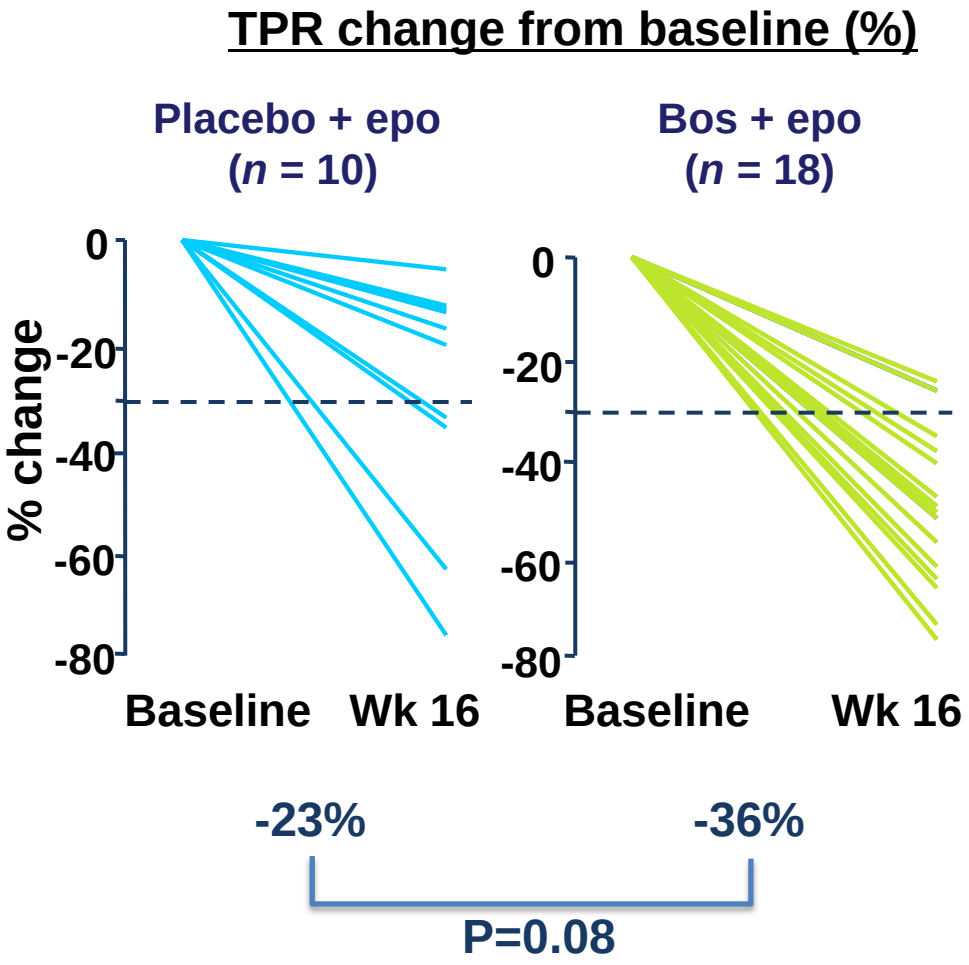
Evolving paradigm: From sequential to initial combination therapy



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

BREATHE-2: Initial dual combination therapy with epoprostenol and bosentan





Humbert M, *et al. Eur Respir J.* 2004;24:353-9.

The AMBITION trial

Initial Use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension

N. Galiè, J.A. Barberà, A.E. Frost, H.-A. Ghofrani, M.M. Hoeper, V.V. McLaughlin, A.J. Peacock, G. Simonneau, J.-L. Vachiery, E. Grünig, R.J. Oudiz, A. Vonk-Noordegraaf, R.J. White, C. Blair, H. Gillies, K.L. Miller, J.H.N. Harris, J. Langley, and L.J. Rubin, for the AMBITION Investigators*

- Event-driven study
- Initial combo AMB+TADA vs monotherapy AMB or TADA
- N=500 treatment-naïve patients with PAH (31% FC II)

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

The AMBITION trial: Primary endpoint

Time to first clinical failure event

Death (all cause)

Hospitalization for worsening PAH → Any hospitalization for worsening PAH; Lung transplantation; Atrial septostomy; Initiation of parenteral prostanoid therapy

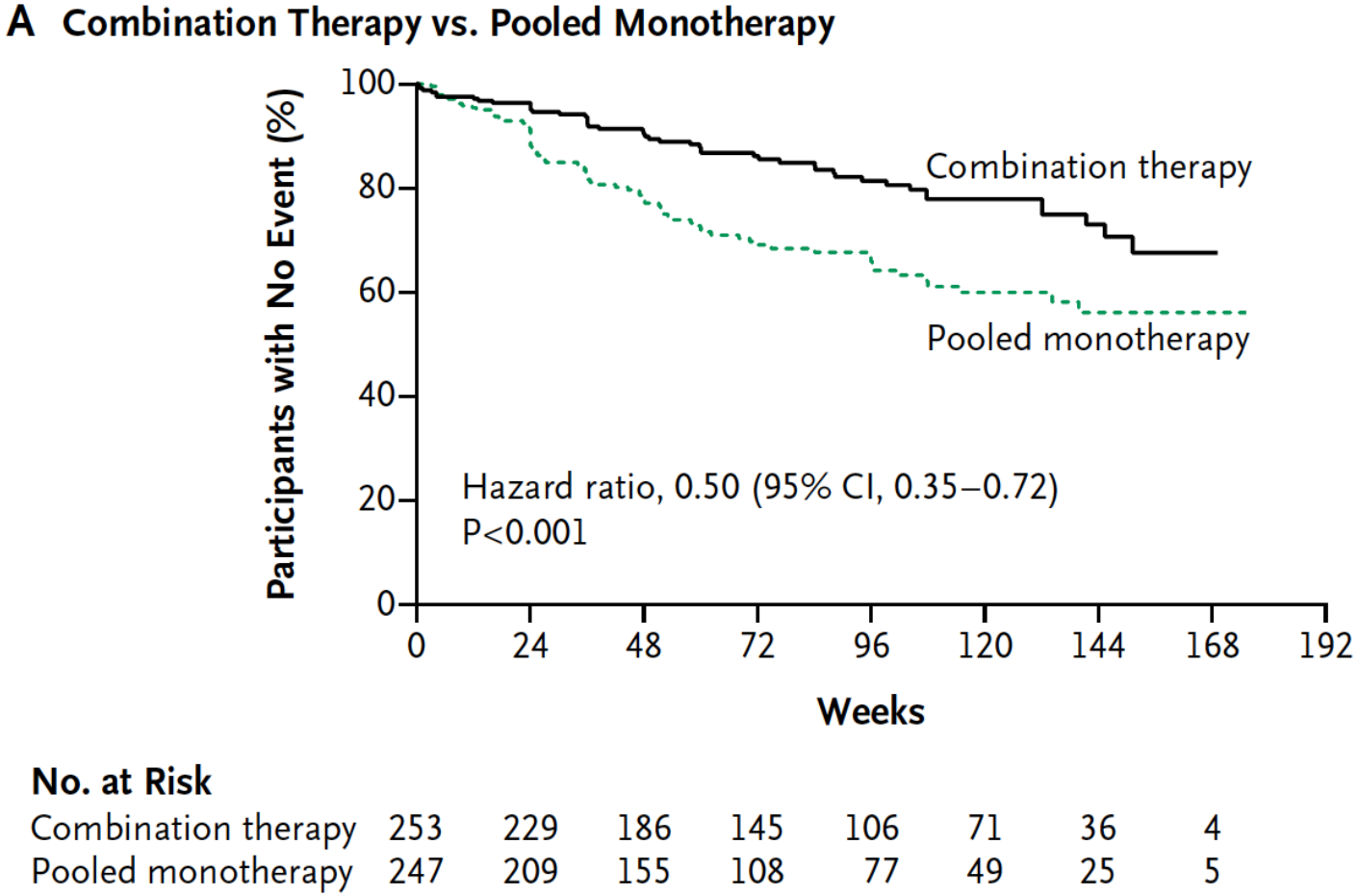
Disease progression → Decrease in 6MWD > 15% vs baseline with FC III-IV (2 visits > 14 days)

Unsatisfactory long-term response → ALL → 1 dose of IP and > 6 months in study; Decrease in 6MWD (any amount); FC III at 2 visits separated by 6 months

All events were adjudicated

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

The AMBITION trial: main result



Hospitalisation for PAH worsening was the main component of the primary endpoint

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

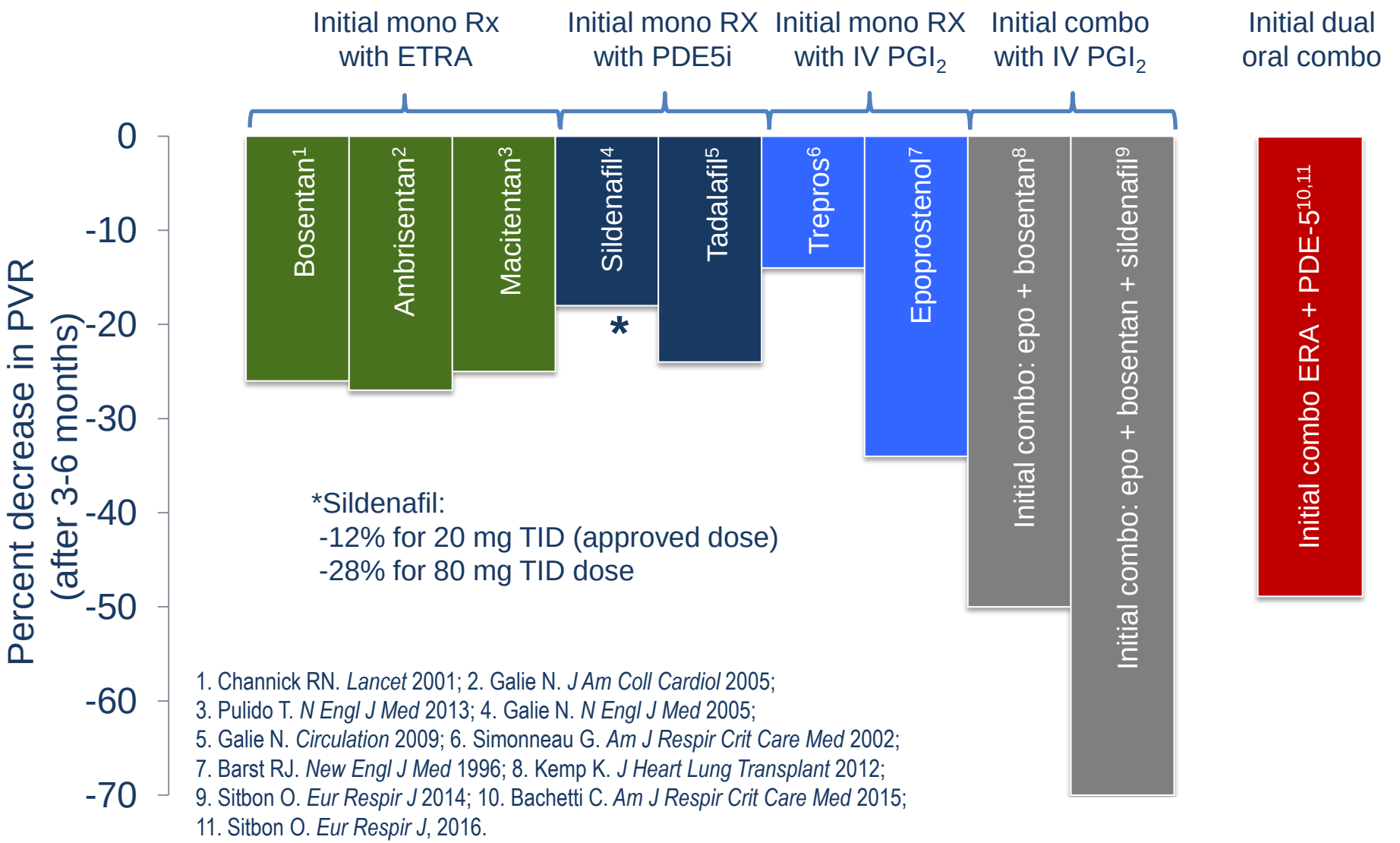
Initial combination is also efficacious in SSc-PAH

- 36 week prospective multicentre open-label uncontrolled study
- Initial combination of ambrisentan & tadalafil
  - 24 treatment-naïve patients with PAH-SSc
  - FC II / III: 35% / 65%

	Baseline	36 weeks	*p*
mPAP (mmHg)	42 ± 12	30 ± 7	< 0.01
CI (L/min/m^2)	2.6 ± 0.7	3.3 ± 1.2	< 0.01
PVR (Wood units)	8.4 ± 5.1	4.1 ± 3	< 0.01

Hassoun P, *et al. Am J Respir Crit Care Med* 2015; 192:1102-10.

Initial therapy: effects on PVR



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7. Barst RJ. *New Engl J Med* 1996; 8. Kemp K. *J Heart Lung Transplant* 2012;
9. Sitbon O. *Eur Respir J* 2014; 10. Bachetti C. *Am J Respir Crit Care Med* 2015;
11. Sitbon O. *Eur Respir J*, 2016.

Take-home messages

- Many PAH drugs are now available
- Strategy of sequential combination therapy with available medications has a positive impact on disease progression
- Sequential combination therapy may be more effective if part of a goal-oriented strategy
- Initial combination therapy is an appealing strategy:
  - Initial double/triple combination therapy incl. parenteral PGI_2 is notably effective in most severe patients (FC IV and some III)
  - Initial dual oral combination therapy with ERA and PDE5i is superior to monotherapy in FC II-III patients (AMBITION)

NICE

6TH

February 27-28
March 1, 2018

WORLD SYMPOSIUM ON PULMONARY HYPERTENSION