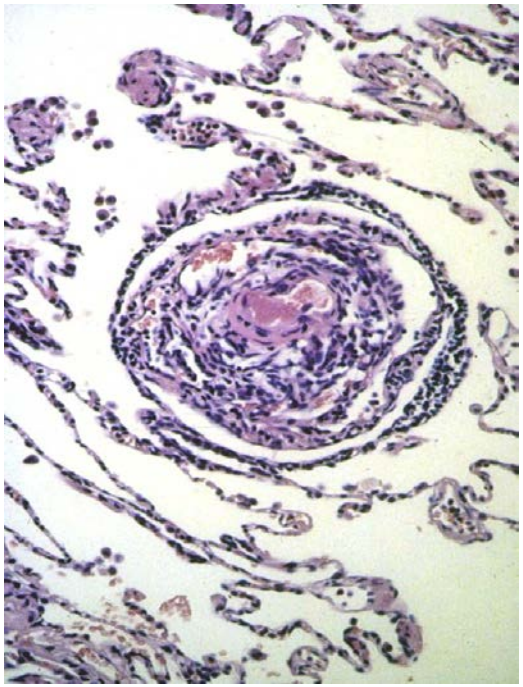
Ipertensione arteriosa polmonare: nuove terapie



Sergio Harari
U.O. di Pneumologia e UTIR
Servizio di Emodinamica e
Fisiopatologia Respiratoria
Ospedale San Giuseppe - Milano

Conflict of interests disclosures

Actelion

Boehringer Ingelheim

InterMune

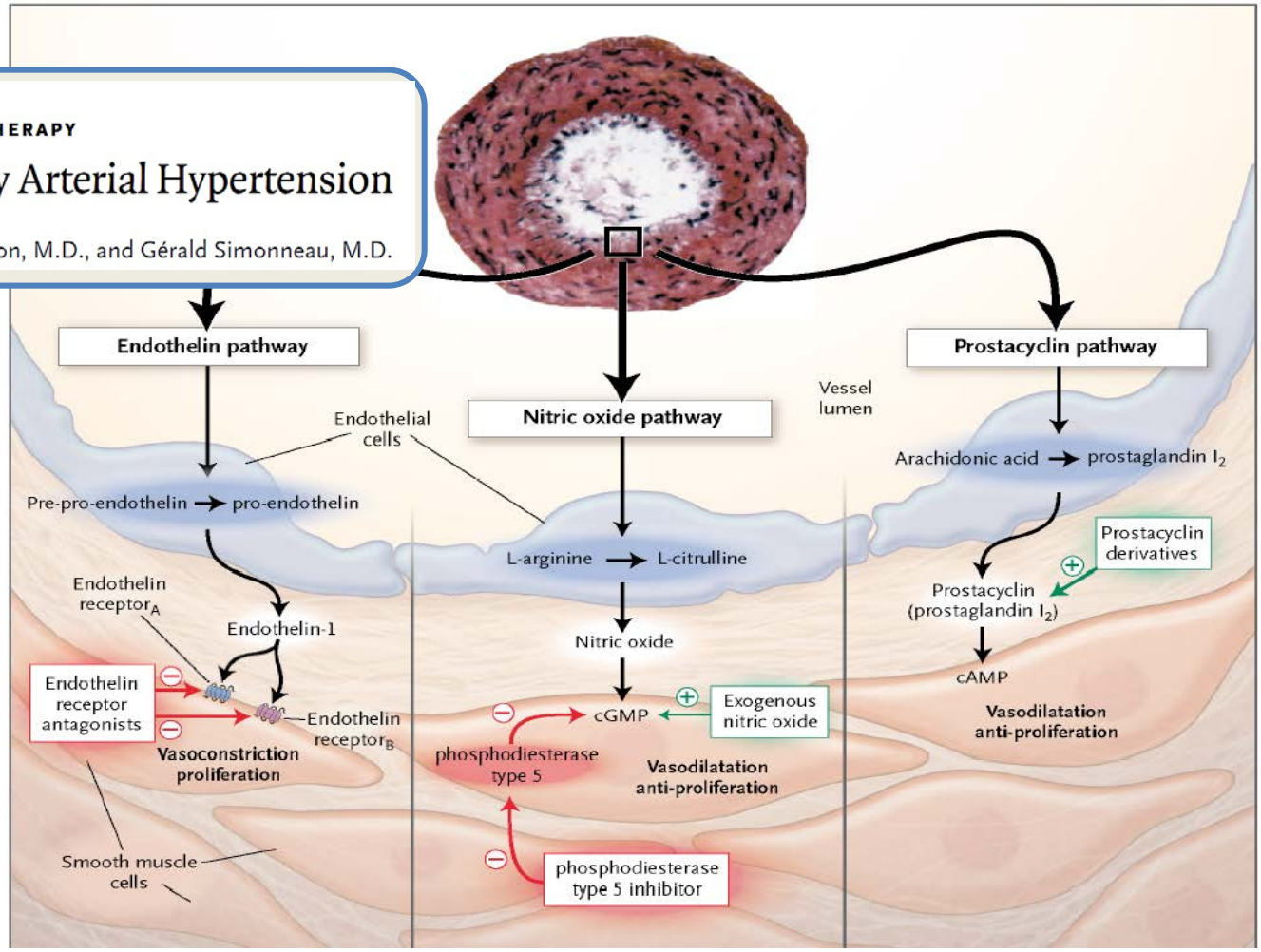
Roche

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.

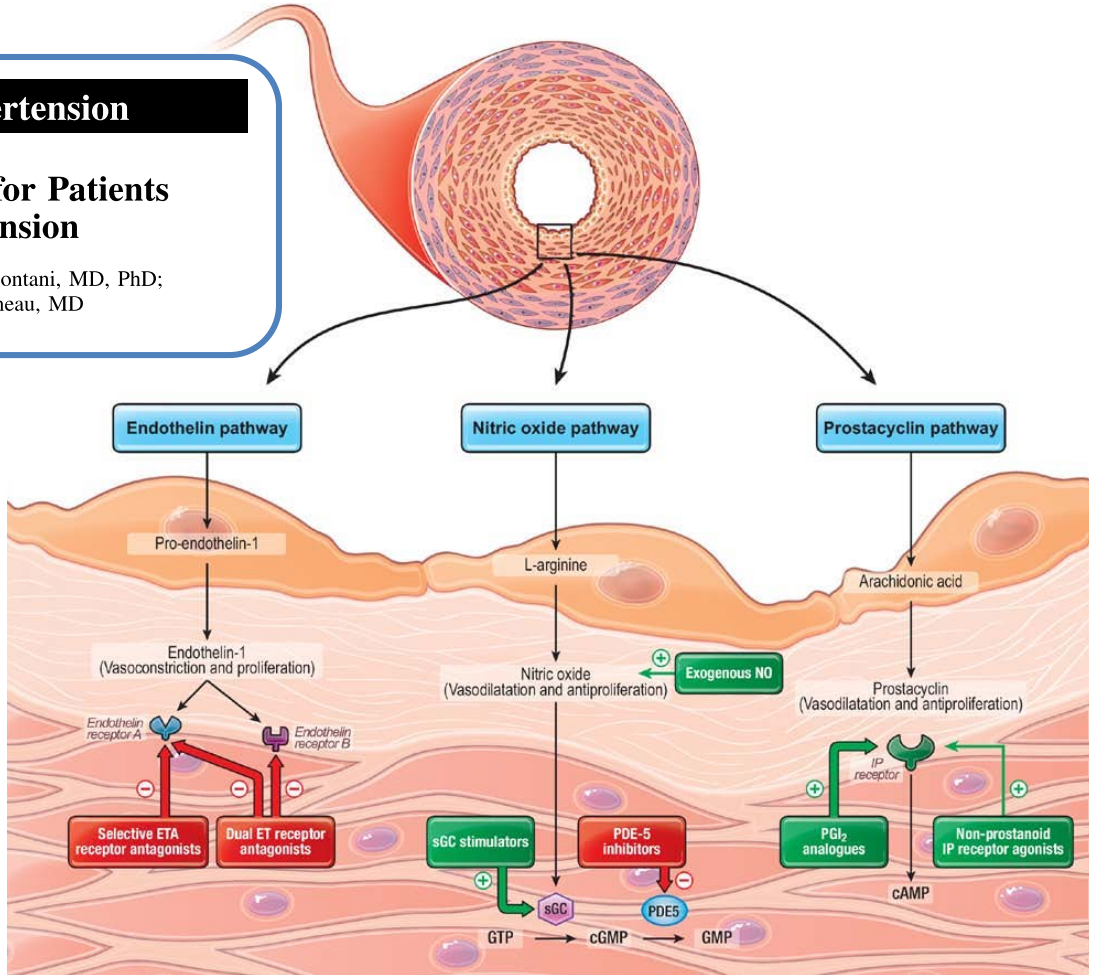
Humbert M *et al. N Engl J Med* 2004;351:1425–36.

Targeting 3 major dysfunctional pathways in PAH (2014)

Recent Advances in Pulmonary Hypertension

Advances in Therapeutic Interventions for Patients With Pulmonary Arterial Hypertension

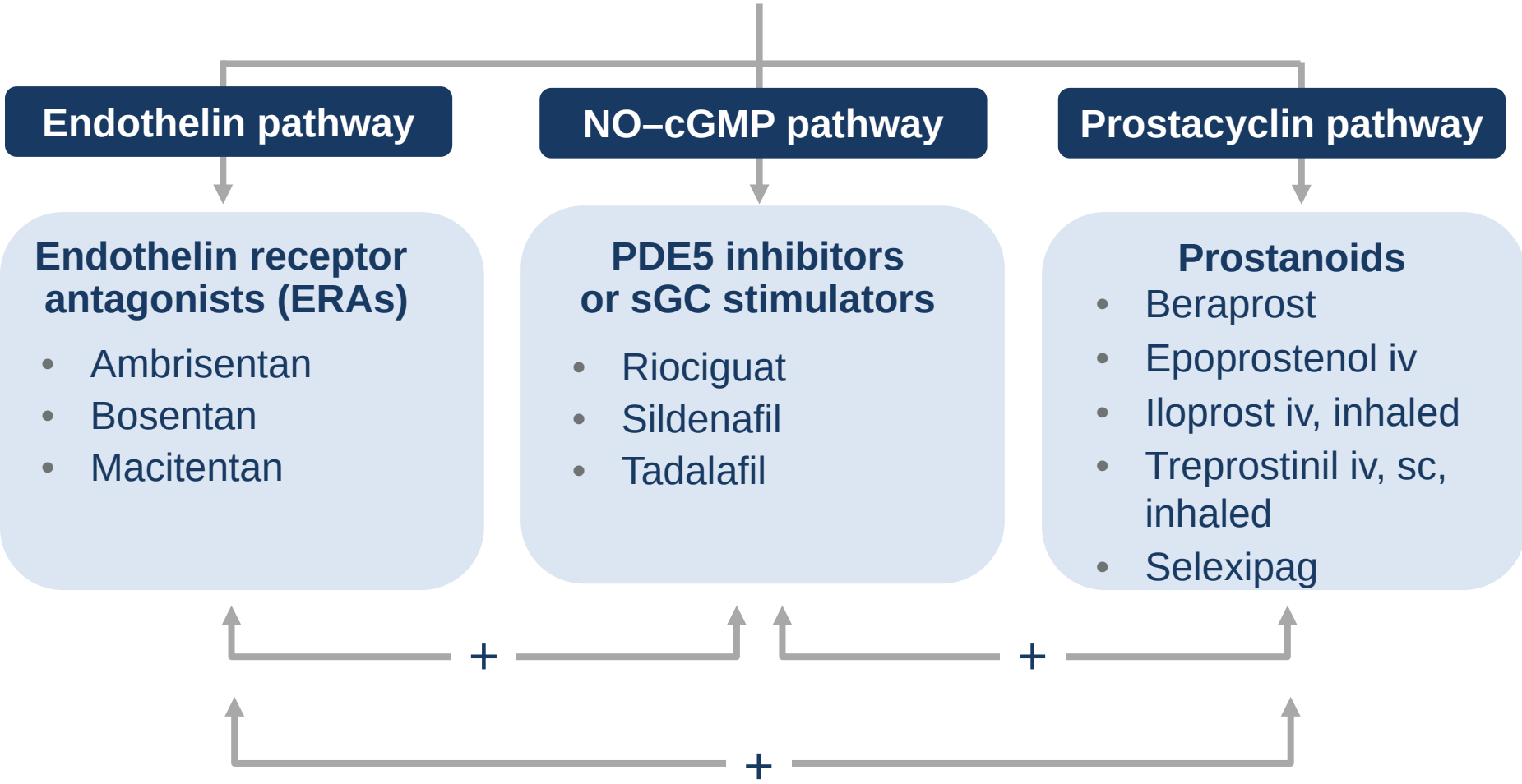
Marc Humbert, MD, PhD; Edmund M.T. Lau, MD, PhD; David Montani, MD, PhD; Xavier Jaïs, MD; Oliver Sitbon, MD, PhD; Gérald Simonneau, MD



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.

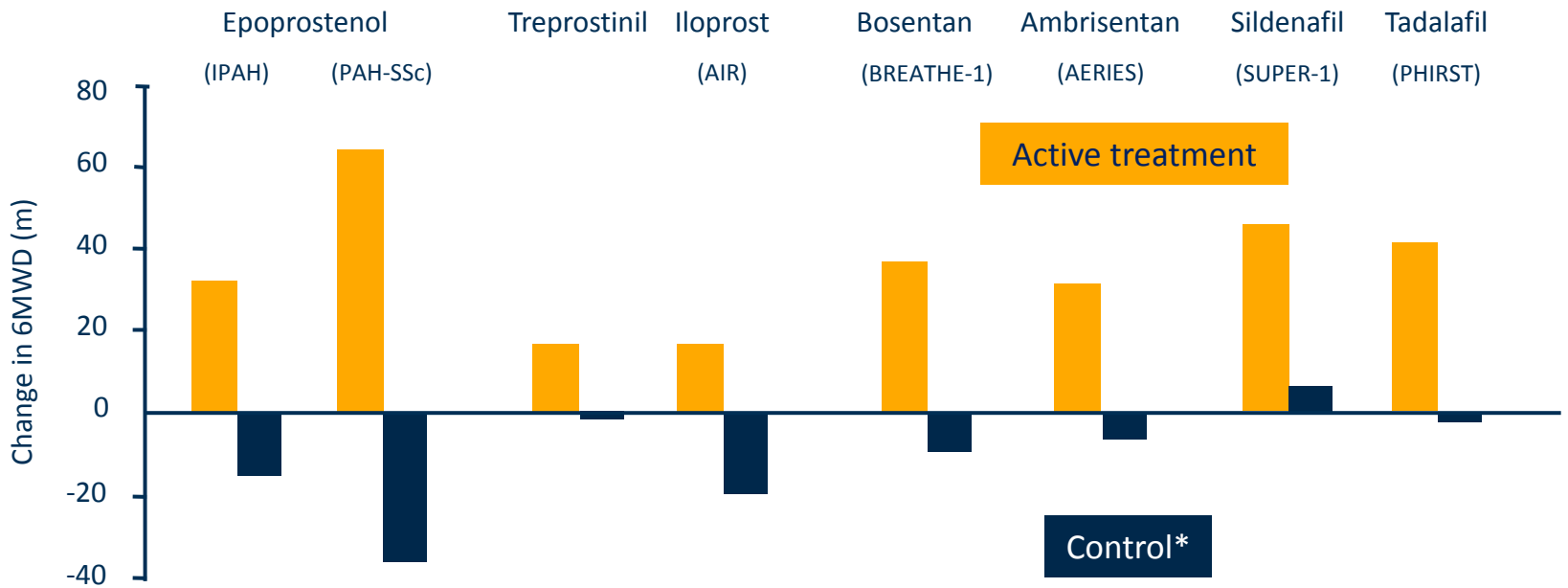
PAH-specific therapies target the 3 signaling pathways involved in PAH



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

RCTs with monotherapy in PAH

Improvement in exercise capacity (3-4 months)



* Control = placebo except for epoprostenol trials ('Conventional therapy')

#: monotherapy only

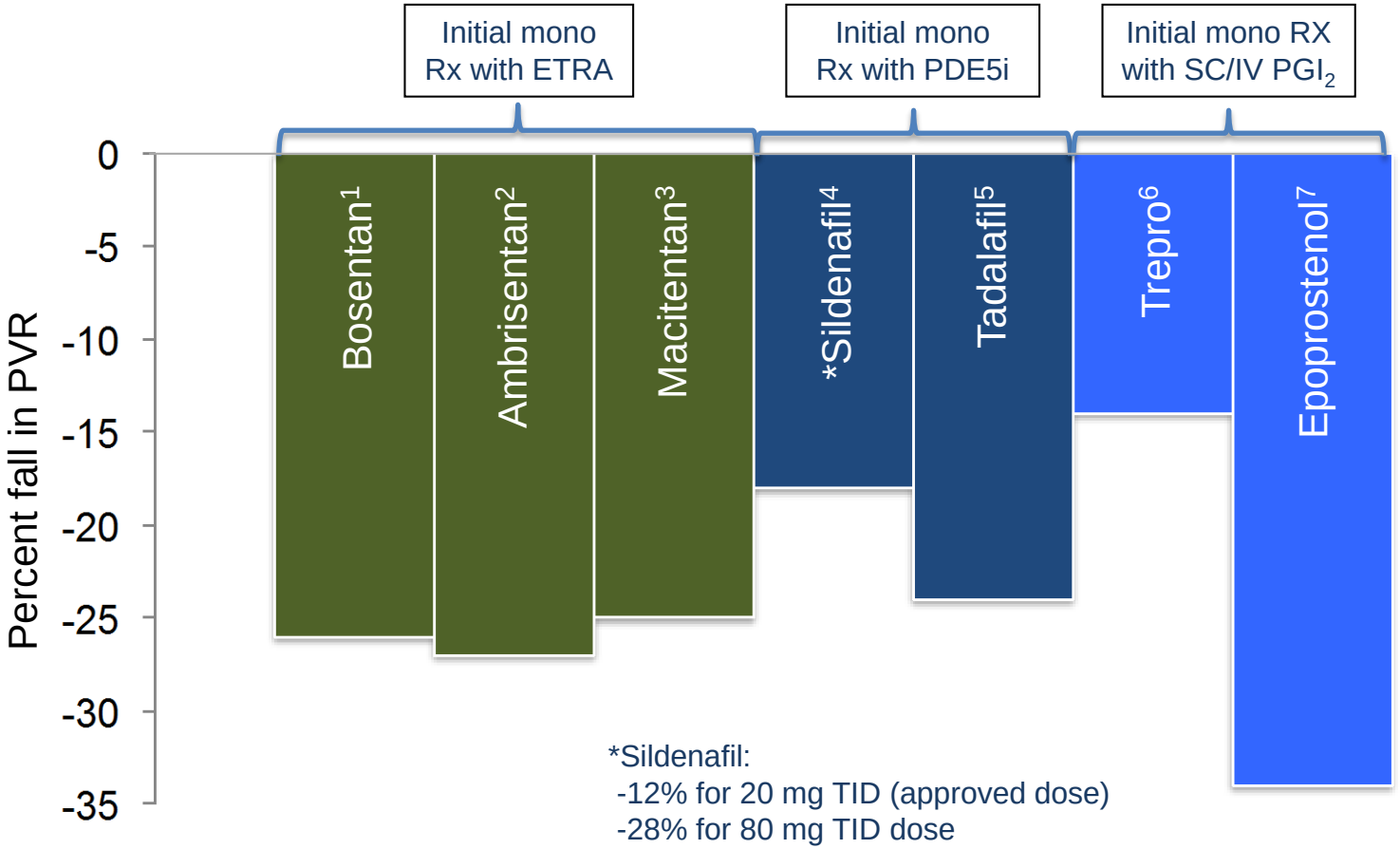
Barst, NEJM 1996.
Badesch, Ann Int Med 2000.

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



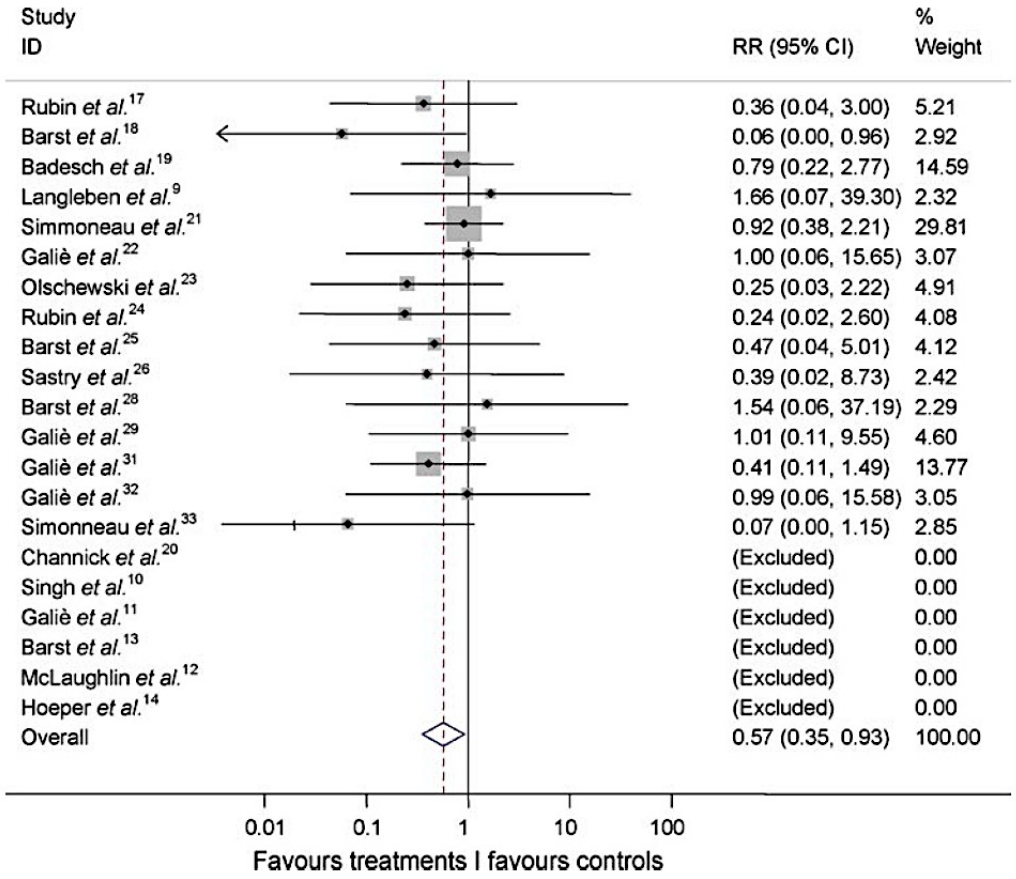
*Sildenafil:
-12% for 20 mg TID (approved dose)
-28% for 80 mg TID dose

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



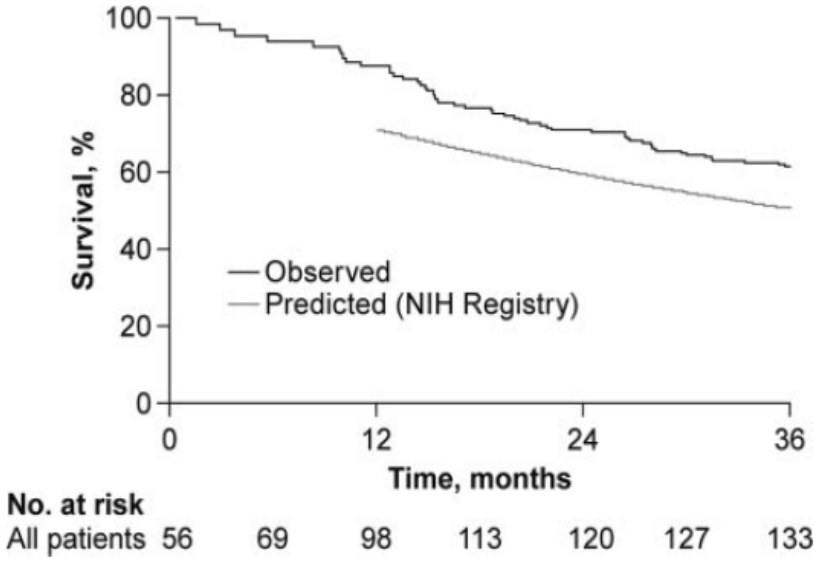
- 23 RCTs
- Average duration 14.3 wks
- 3140 patients
- All-cause mortality rate in the control group = 3.8%
- Active treatments:
  - 43% reduction in mortality
  - RR 0.57 (95%CI 0.35–0.92)
  - P = 0.023

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

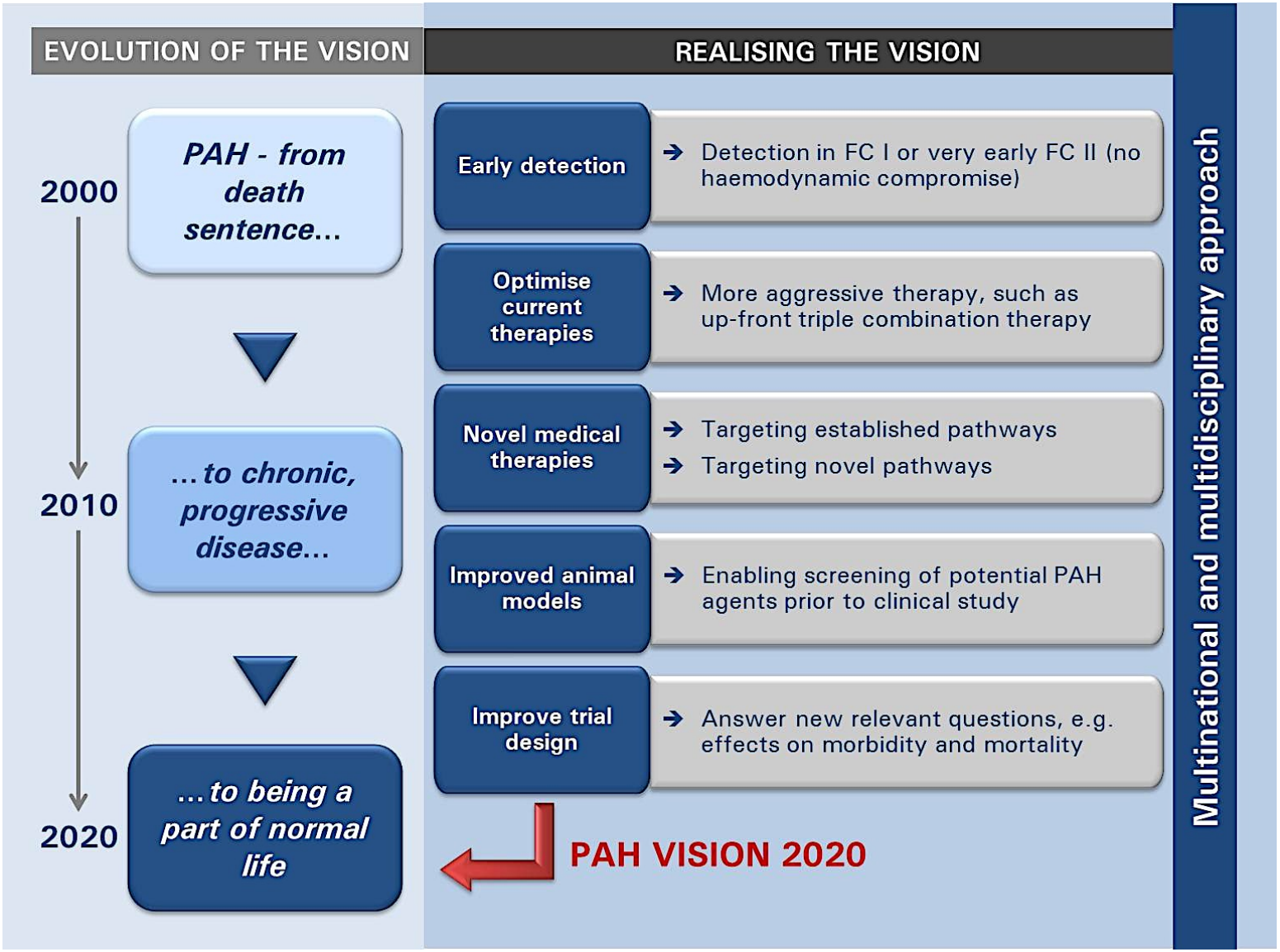
Marc Humbert, MD, PhD; Olivier Sitbon, MD, PhD; Ari Chaouat, MD, PhD; Michèle Bertocchi, MD; Gilbert Habib, MD; Virginie Gressin, MD; Azzedine Yaïci, MD; Emmanuel Weitzenblum, MD; Jean-François Cordier, MD; François Chabot, MD, PhD; Claire Dromer, MD; Christophe Pison, MD, PhD; Martine Reynaud-Gaubert,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



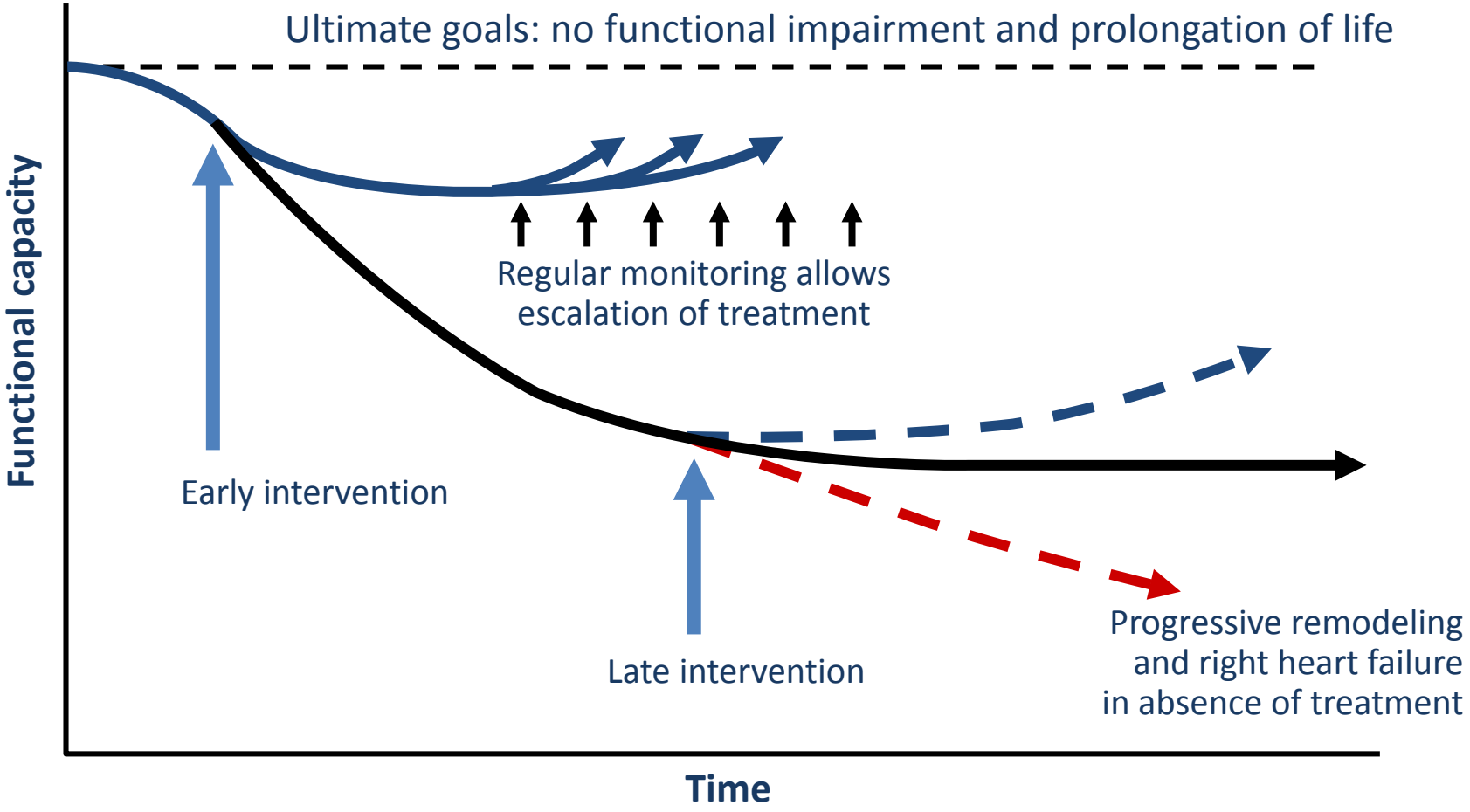
NIH, National Institutes of Health.

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.

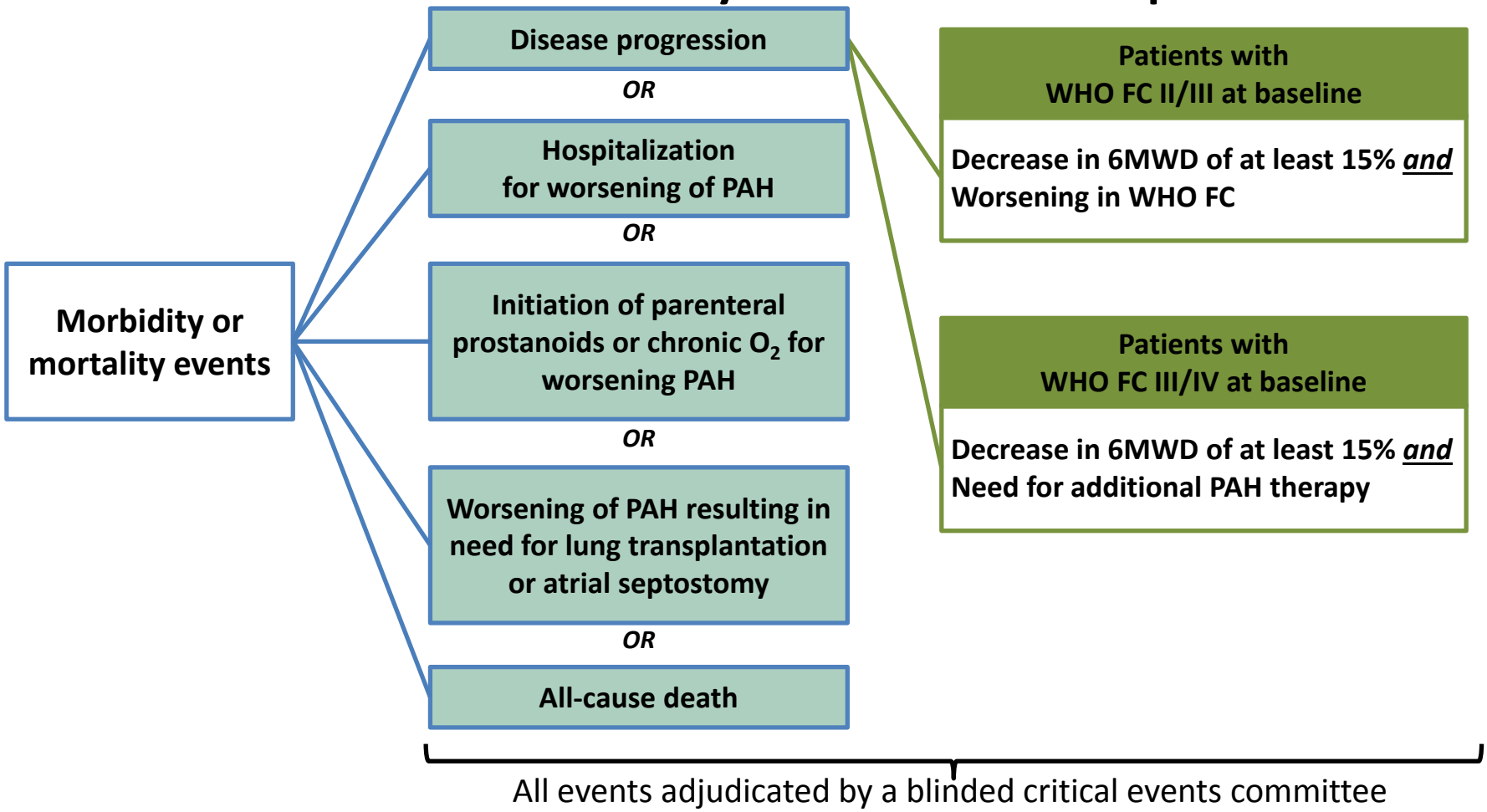
Sequential combination therapy: results are not uniform…

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

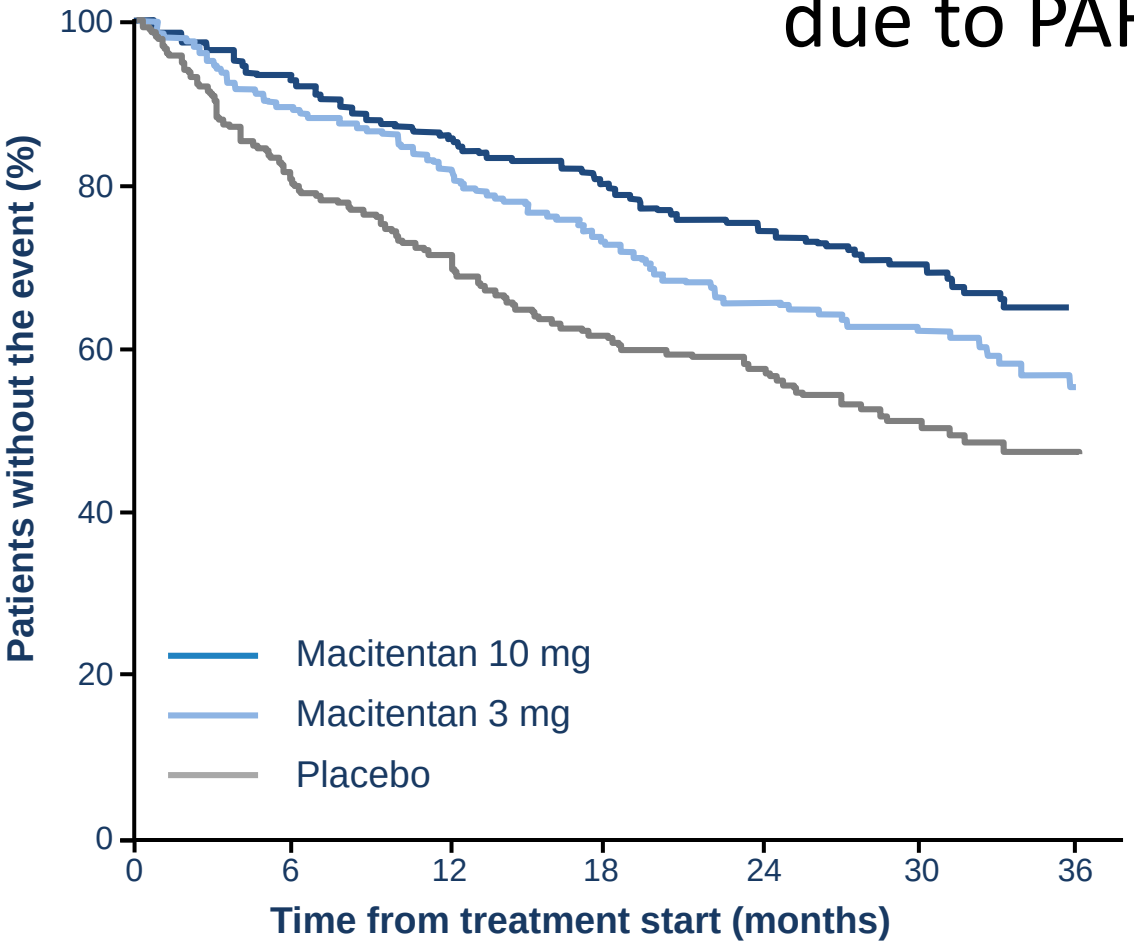
Drug tested	Study	Background	N	Duration (weeks)	Primary endpoint
Riociguat	PATENT	None (50%), bosentan or prostanoids	443	12	Δ6MWD +
Macitentan	SERAPHIN	None (36%), PDE5i (61%) or oral/inhaled prostanoids	742	≈ 100	Time to first event of death or morbidity +
Selexipag	GRIPHON	None (21%), ERA (13%), PDE5i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

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



EOT: End of double-blind treatment

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%

Patients at risk

242	203	187	171	155	91	41	Macitentan 10 mg
250	213	188	166	147	80	32	Macitentan 3 mg
250	188	160	135	122	64	23	Placebo

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

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

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

Death (all cause)

All events were adjudicated

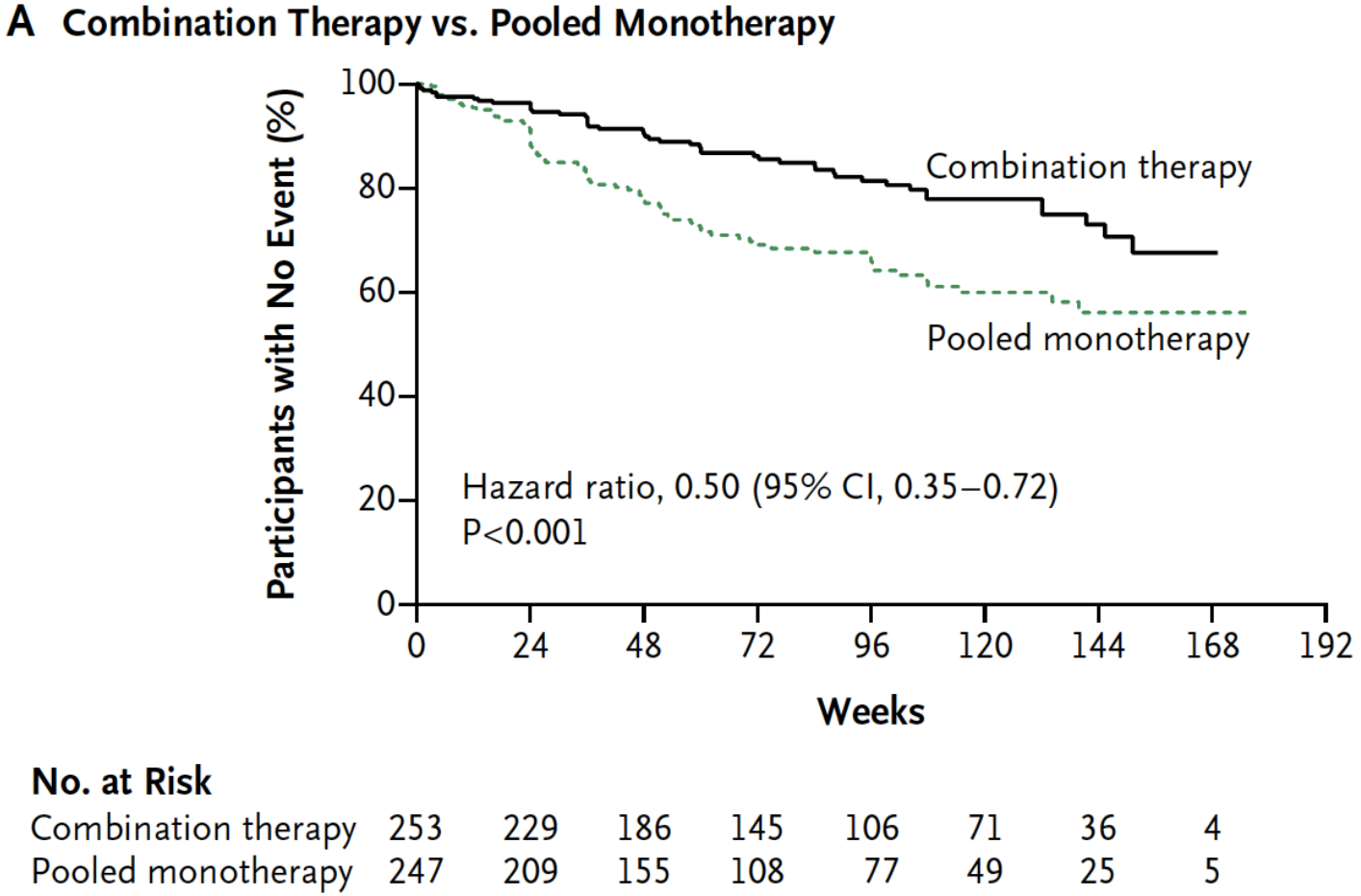
Hospitalization for worsening PAH → Any hospitalization for worsening PAH; Lung transplantation; Atrial septostomy; Initiation of parenteral prostanoid therapy

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

The AMBITION trial: main result

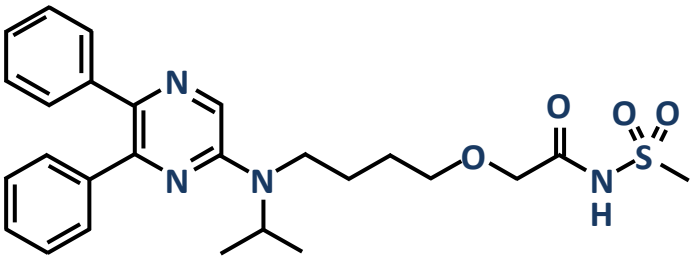
Galiè N, et al. N Engl J Med 2015;273:834:44.



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

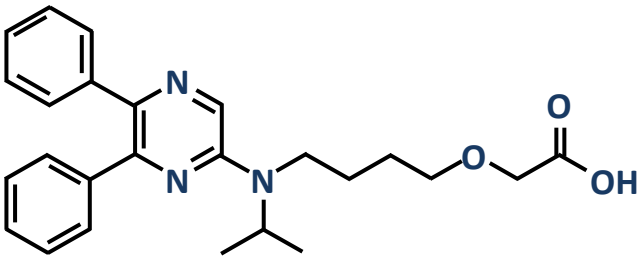
Selexipag: First in class oral non-prostanoid IP receptor agonist

ACT987 (drug)



Hydrolysis

MRE-269 (major metabolite)



- ACT987
  - Orally available diphenylpyrazine derivative
- MRE-269
  - Potent and highly selective prostacyclin receptor agonist

Kuwano K, *et al*. *J Pharmacol Exp Ther* 2007; 326:1181-8.

Study Design

A multicenter, double blind, randomized, parallel-group, placebo-controlled, event-driven, phase 3 study.

The Prostacyclin (PGI2) Receptor Agonist In Pulmonary Arterial Hypertension (GRIPHON) study, to investigate the safety and efficacy of selexipag

Sitbon O et al., N Engl J Med 2015; 373(26):2522-3

Study Design

Inclusion criteria (eligible for enrollment)

- Male and female patients (18-75 years old)
- Patients with PAH characterized as:
  Idiopathic PAH (IPAH)
  Heritable PAH (HPAH)
  Associated with
    - Connective tissue disease (PAH-CTD)
    - Repaired congenital simple systemic-to-pulmonary shunt (PAH-CHD)
    - HIV infection (PAH-HIV)

- A hemodynamic diagnosis of PAH by right heart catheterization (RHC) (PVR ≥ 400 dyn·s·cm^{-5})
- 6MWD between 50 and 450 m at screening within two weeks prior to the baseline visit
- Patients "naïve"- treated with ERAs, PDE5i or both (a dose that had been stable for at least 3 months)

Exclusion criteria

Patients who were receiving prostacyclin analogues

Sitbon O et al., N Engl J Med 2015; 373(26):2522-3

Study Design

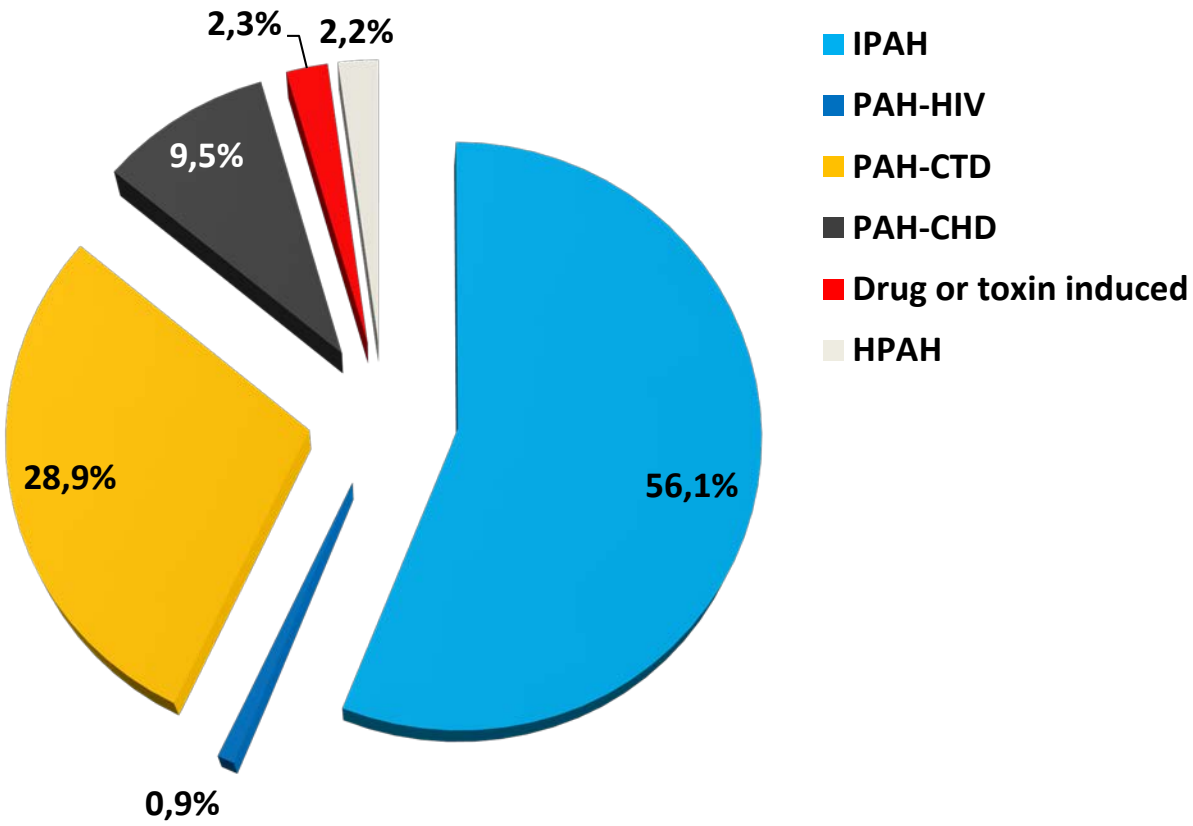
Demographics and baseline characteristics

Characteristic	Placebo (N = 582)	Selexipag (N = 574)	All Patients (N = 1156)
WHO functional class — no. (%)‡			
I	5 (0.9)	4 (0.7)	9 (0.8)
II	255 (43.8)	274 (47.7)	529 (45.8)
III	314 (54.0)	293 (51.0)	607 (52.5)
IV	8 (1.4)	3 (0.5)	11 (1.0)
6-Minute walk distance — m	348.0±83.23	358.5±76.31	353.2±80.01
Use of medications for PAH — no. (%)			
None	124 (21.3)	112 (19.5)	236 (20.4)
Endothelin-receptor antagonists	76 (13.1)	94 (16.4)	170 (14.7)
Phosphodiesterase type 5 inhibitors	185 (31.8)	189 (32.9)	374 (32.4)
Endothelin-receptor antagonists plus phosphodiesterase type 5 inhibitors	197 (33.8)	179 (31.2)	376 (32.5)

Sitbon O et al., N Engl J Med 2015; 373(26):2522-3

Study Design

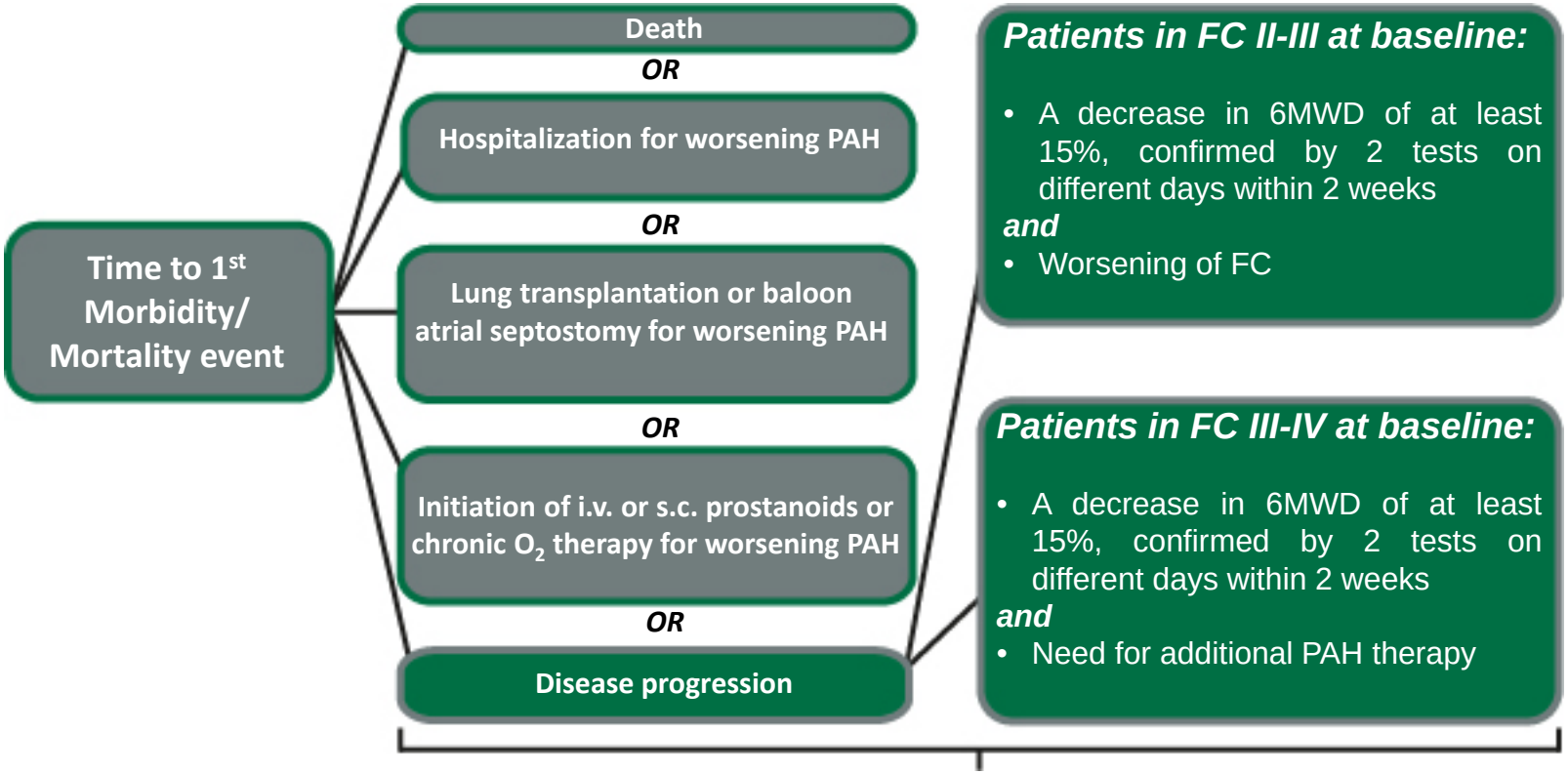
PAH etiology



Sitbon O et al., N Engl J Med 2015; 373(26):2522-3

Study Design

Primary endpoint: Time to first morbidity or mortality event



All events adjudicated by a blinded Critical Events Committee (CEC)

Sitbon O et al., N Engl J Med 2015; 373(26):2522-3

Study Design

Secondary endpoints

6MWD	Absolute change from baseline to week 26 in 6MWD
FC	Absence of worsening from baseline to week 26 in FC
Time to death	Time to death from randomization up to study closure
Hospitalization for worsening of PAH or death due to PAH	Up to the end of treatment period
NT -proBNP	Change in N-terminal pro–brain natriuretic peptide (NT -proBNP) level from baseline to week 26 was analyzed as an **exploratory** end point

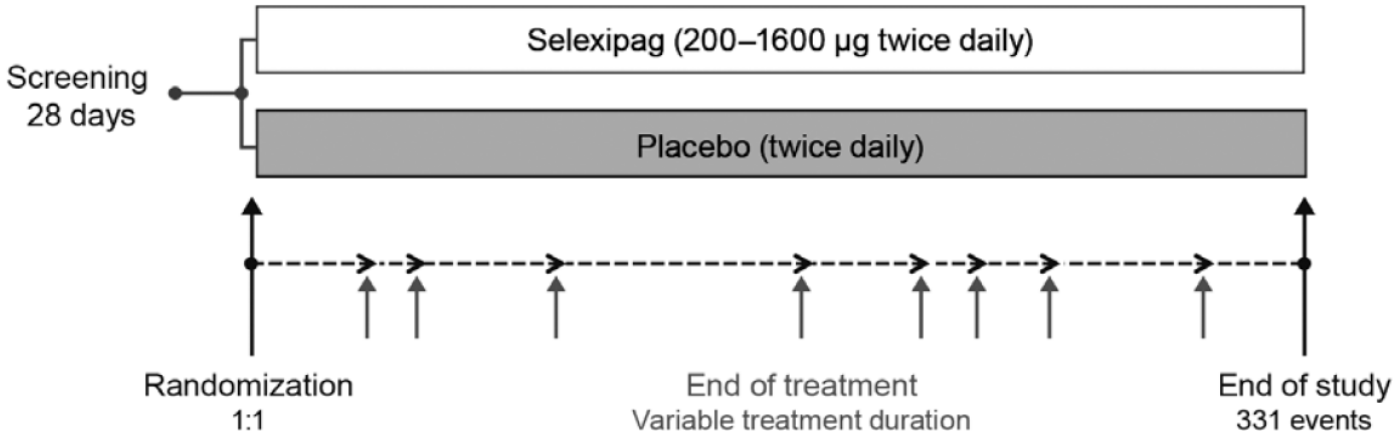
Sitbon O et al., N Engl J Med 2015; 373(26):2522-3

Study Design

Patients were randomly assigned, in a 1:1 ratio to placebo or selexipag

- The end of the study was declared when the prespecified number of primary end-point events was reached

- The end of treatment differed for each patient and was defined as the last intake of double-blind treatment (placebo or selexipag) plus 7 days.



Sitbon O et al., N Engl J Med 2015; 373(26):2522-3

Dose adjustment

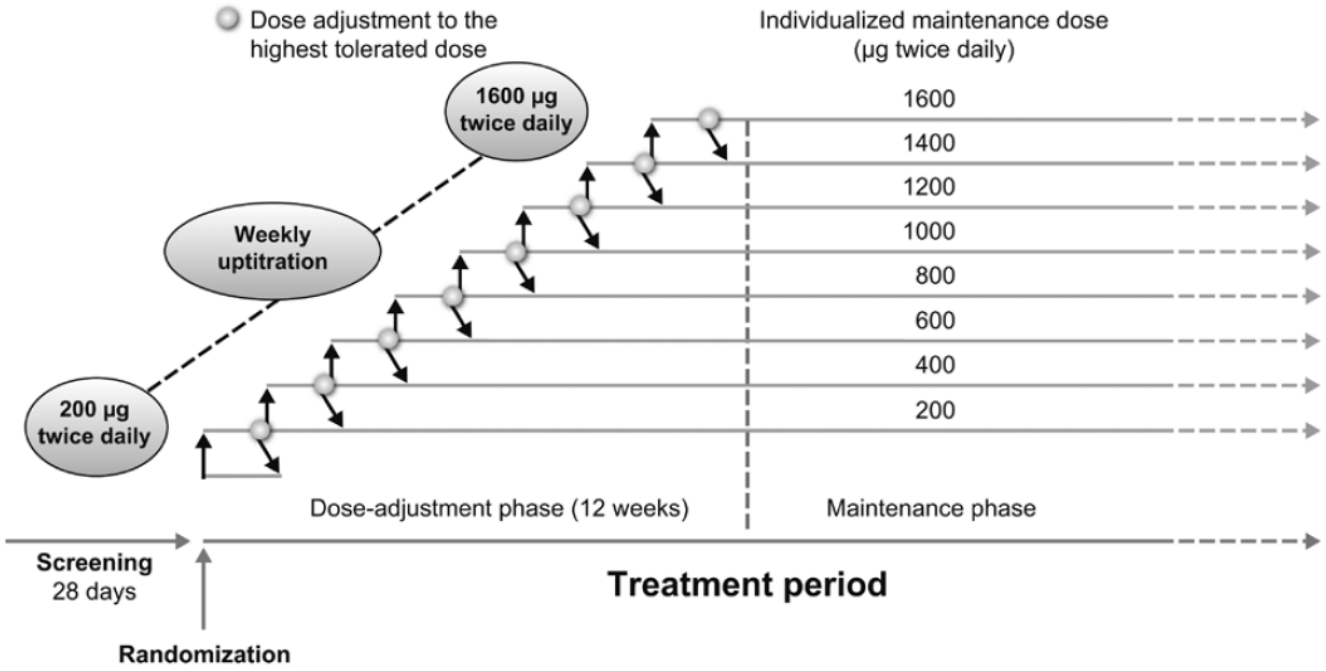
- During the 12-week dose-adjustment phase, study drug was initiated at 200 µg twice daily and titrated weekly in 200 µg twice-daily increments until prostacyclin-associated adverse were unmanageable.
- The dose was then decreased by 200 µg in both daily doses, giving the highest tolerated dose.
- The maximum dose allowed was 1600 µg twice daily.
- After 12 weeks, patients entered the maintenance phase of the study.

Dose reductions were allowed at any time

Sitbon O et al., N Engl J Med 2015; 373(26):2522-3

Dose adjustment

Tritation scheme



Sitbon O et al., N Engl J Med 2015; 373(26):2522-3

Results

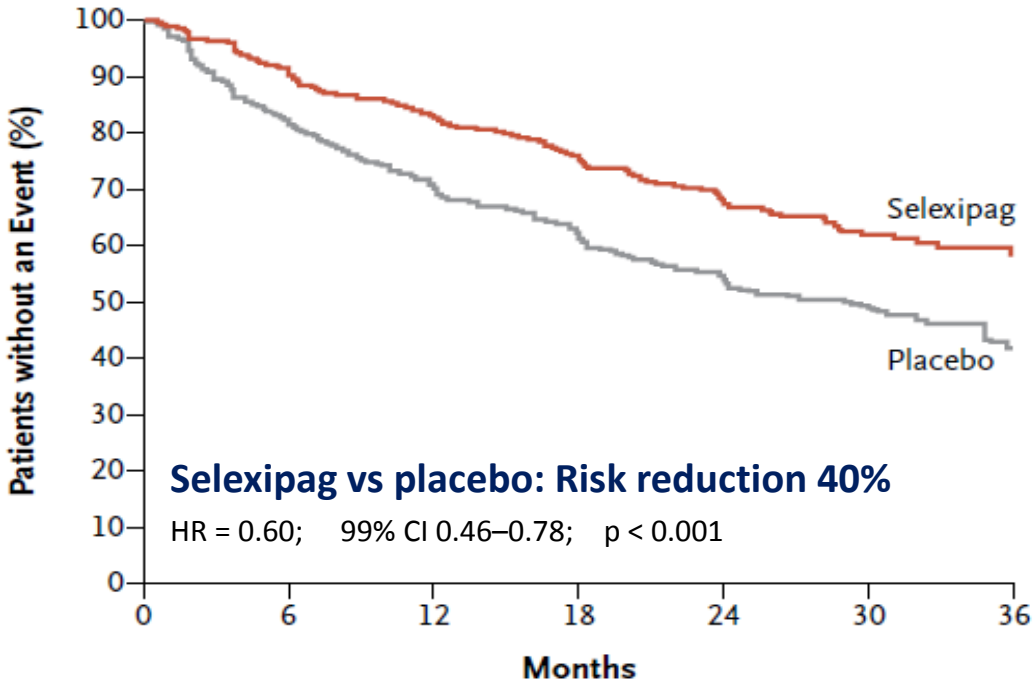
- The GRIPHON study with selexipag met its primary objective in patients with PAH
- Selexipag reduced the risk of a morbidity/mortality event (primary endpoint) by 40% compared with placebo
- The efficacy of selexipag was consistent across subgroups: Age, gender, FC, PAH etiology, and background PAH therapy
- The overall tolerability profile of selexipag in GRIPHON was consistent with prostacyclin therapies
- The patients in the selexipag group received selexipag for a median duration of 70.7 weeks

Sitbon O et al., N Engl J Med 2015; 373(26):2522-3

Results

Primary composite end point

A significant treatment effect in favor of selexipag



No. at Risk							
Placebo	582	433	347	220	149	88	28
Selexipag	574	455	361	246	171	101	40

Sitbon O et al., N Engl J Med 2015; 373(26):2522-3

Events contributing to the primary endpoint up to EOT

Primary endpoint events, n (%)	Placebo n = 582	Selexipag n = 574
All primary endpoint events	242 (41.6)	155 (27.0)
Hospitalization for PAH	109 (18.7)	78 (13.6)
Disease progression	100 (17.2)	38 (6.6)
Death (all causes)	18 (3.1)	28 (4.9)
Parenteral prostanoid or chronic O_2 therapy	13 (2.2)	10 (1.7)
PAH worsening resulting in need for lung transplantation or balloon atrial septostomy	2 (0.3)	1 (0.2)

McLaughlin V, *et al.* Presented at *ACC Annual Congress* 2015.

Study Design

A consistent treatment effect

Primary composite end point

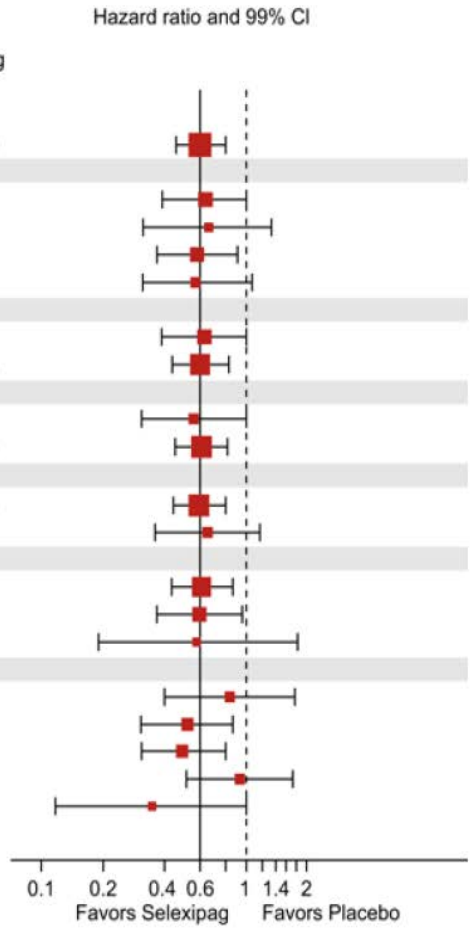
Effect of selexipag across subgroups

Efficacia confermata in monoterapia ed in combinazione con 1 o 2 farmaci

Efficacia nelle diverse FC

Efficacia confermata in tutte le eziologie di PAH

Subgroup	P value for interaction	Placebo No. of patients/no. of events	Selexipag No. of patients/no. of events
All patients		582/242	574/155
PAH therapy at baseline	0.9518		
ERA and PDE5 inhibitors		197/80	179/47
ERA monotherapy		76/29	94/23
PDE5 inhibitor monotherapy		185/84	189/54
No PAH therapy		124/49	112/31
WHO functional class	0.7792		
I / II		260/74	278/52
III / IV		322/168	296/103
Sex	0.6578		
Males		116/48	117/31
Females		466/194	457/124
Age at screening	0.6783		
<65 years		474/190	475/124
≥65 years		108/52	99/31
PAH etiology	0.9765		
IPAH, HPAH, HIV, drug or toxin induced		365/156	347/98
Assoc. with connective tissue disease		167/73	167/48
Assoc. with corrected congenital shunts		50/13	60/9
Geographical region	0.0734		
North America		98/28	95/23
Western Europe / Australia		160/68	161/39
Eastern Europe		155/85	149/48
Asia		113/39	115/37
Latin America		56/22	54/8



Sitbon O et al., N Engl J Med 2015; 373(26):2522-3

Study Design

Primary composite end point

Patients Grouped by Prespecified Selexipag Individual Maintenance Dose

The effect of selexipag was consistent in the all dose strata:

- **low** (200, 400 µg twice daily) (HR 0.60)
- **medium** (600, 800, 1000 µg twice daily) (HR 0.53)
- **high** (1200, 1400, 1600 µg twice daily) (HR 0.64)

Sitbon O et al., N Engl J Med 2015; 373(26):2522-3

Safety

Most frequent AEs and abnormal laboratory results

Variable	Placebo (N = 577)	Selexipag (N = 575)	P Value
Adverse events — no.	3937	4607	
Patients with ≥1 adverse event — no. (%)	559 (96.9)	565 (98.3)	0.18
Patients with ≥1 serious adverse event — no. (%)†	272 (47.1)	252 (43.8)	0.26
Patients with adverse events leading to discontinuation of study agent — no. (%)	41 (7.1)	82 (14.3)	<0.001
Adverse event — no. of patients (%)‡			
Headache	189 (32.8)	375 (65.2)	<0.001
Diarrhea	110 (19.1)	244 (42.4)	<0.001
Nausea	107 (18.5)	193 (33.6)	<0.001
Pain in jaw	36 (6.2)	148 (25.7)	<0.001
Worsening of PAH	206 (35.7)	126 (21.9)	<0.001
Vomiting	49 (8.5)	104 (18.1)	<0.001
Pain in extremity	46 (8.0)	97 (16.9)	<0.001
Dyspnea	121 (21.0)	92 (16.0)	0.03
Myalgia	34 (5.9)	92 (16.0)	<0.001
Dizziness	85 (14.7)	86 (15.0)	0.93
Peripheral edema	104 (18.0)	80 (13.9)	0.06
Upper respiratory tract infection	80 (13.9)	75 (13.0)	0.73
Nasopharyngitis	63 (10.9)	75 (13.0)	0.28
Flushing	29 (5.0)	70 (12.2)	<0.001
Arthralgia	44 (7.6)	62 (10.8)	0.07
Cough	67 (11.6)	56 (9.7)	0.34
Fatigue	59 (10.2)	46 (8.0)	0.22
Right ventricular failure	58 (10.1)	46 (8.0)	0.26
Other adverse events and laboratory findings of interest — no. of patients (%)§			
Hyperthyroidism	0	8 (1.4)	0.004
Hypotension	18 (3.1)	29 (5.0)	0.10
Anemia	31 (5.4)	48 (8.3)	0.05
Syncope	51 (8.8)	37 (6.4)	0.15
Major bleeding event¶	12 (2.1)	14 (2.4)	0.70
Hemoglobin <8 g/dl‖	4 (0.7)	7 (1.3)	0.38

Sitbon O et al., N Engl J Med 2015; 373(26):2522-3

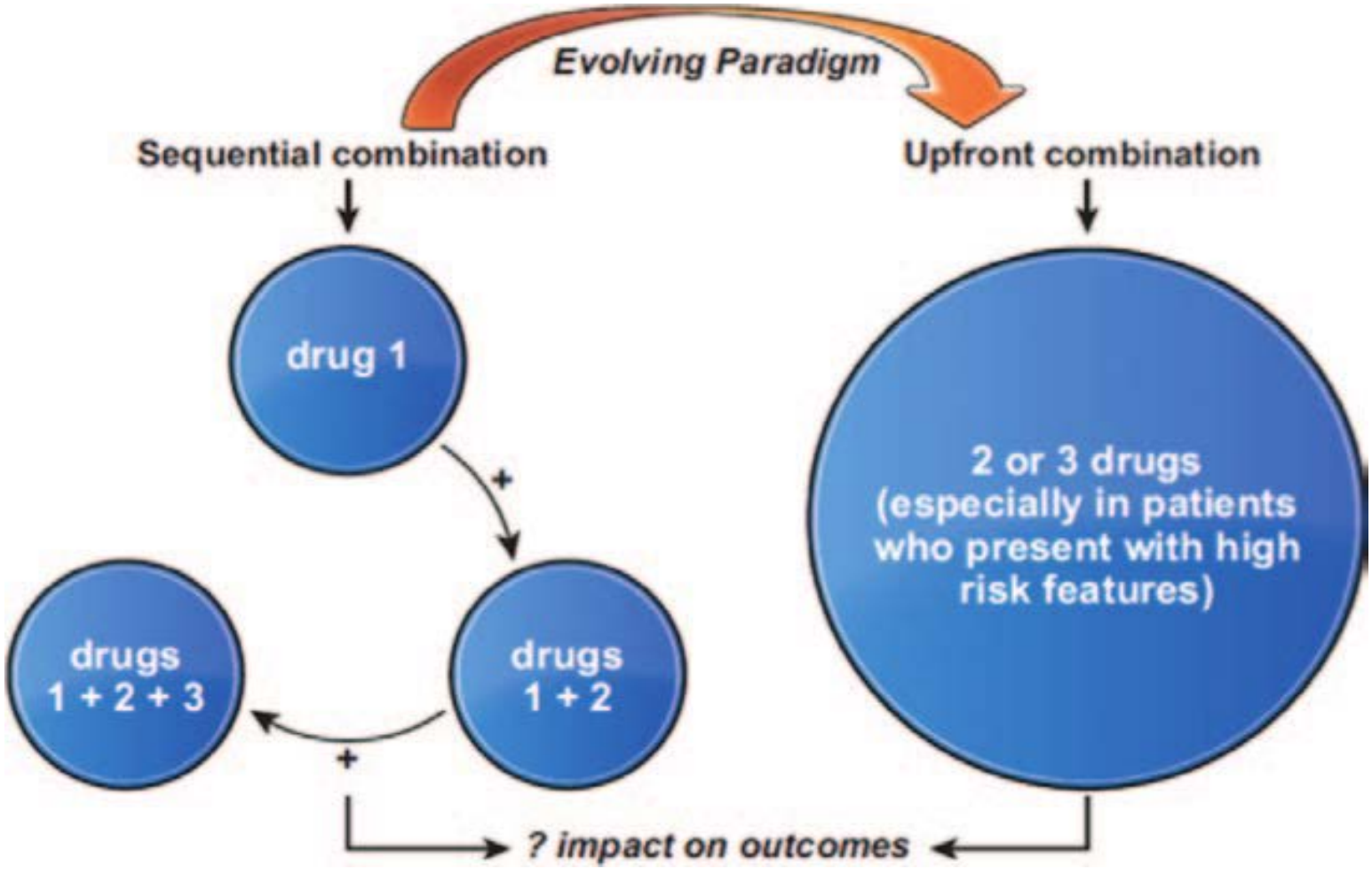
Conclusion

Among patients with pulmonary arterial hypertension, the risk of the primary composite end point of death or a complication related to pulmonary arterial hypertension was significantly lower among patients who received selexipag than among those who received placebo.

A consistent treatment effect was observed across prespecified subgroups: pulmonary arterial hypertension therapy at baseline, WHO functional class at baseline, sex, age at screening, pulmonary arterial hypertension etiology and geographical region.

Sitbon O et al., N Engl J Med 2015; 373(26):2522-3

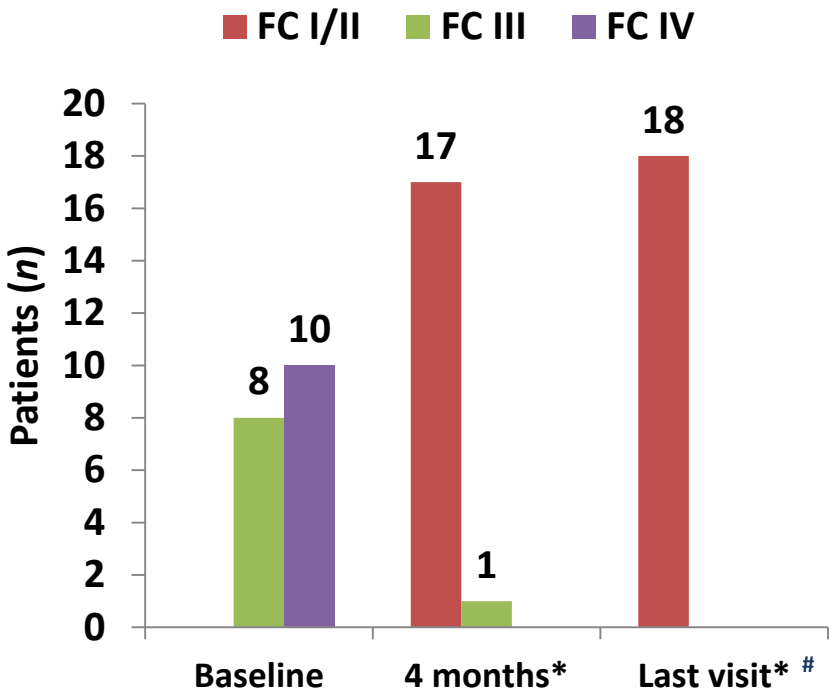
Evolving paradigm: From sequential to initial combination therapy

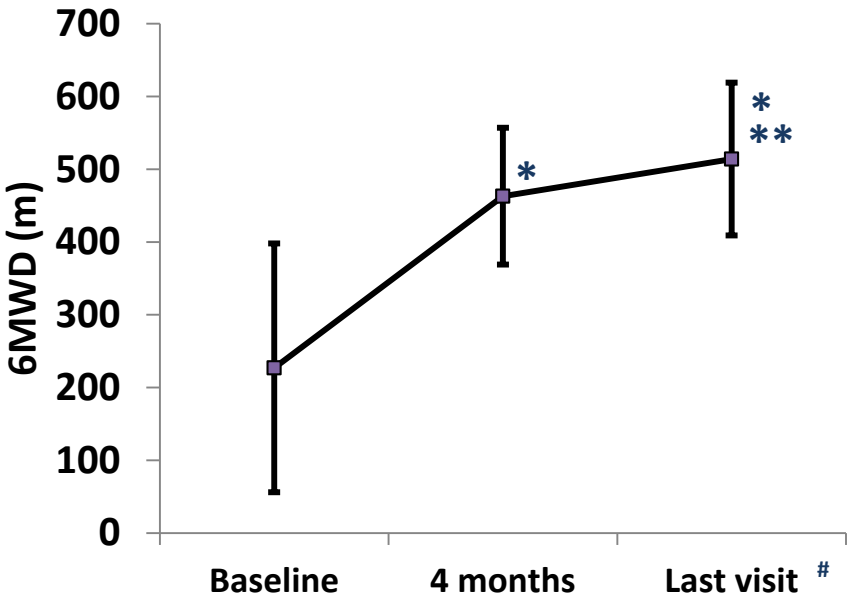


Humbert M, *et al*. *Circulation* 2014.

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)



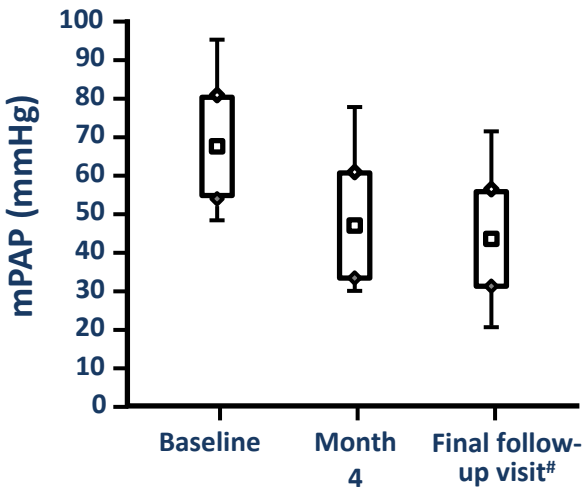


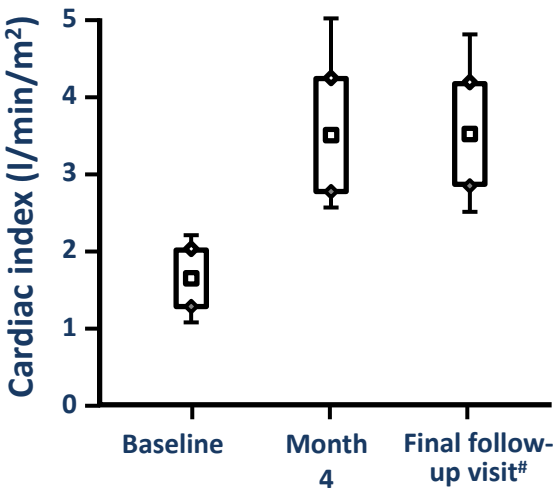
#32 ± 19 months

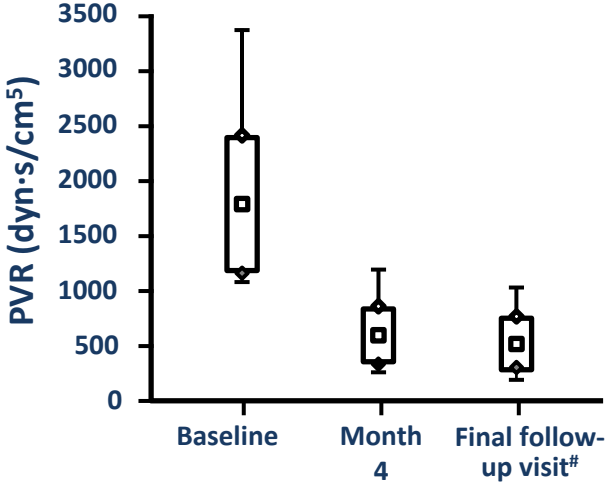
*$p < 0.01$ versus baseline; ** $p < 0.01$ versus 4 months

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*

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

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

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%

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

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

Initial dual oral combination therapy for PAH: Experience of the French network

- From January 2007 to December 2013
- 97 incident patients with PAH (75% IHA), mean age 54
  - 88% NYHA FC II & III
  - 12% NYHA FC IV
- Initial dual combination therapy with
  - ERA: bosentan (*n* = 78) or ambrisentan (*n* = 19), and
  - PDE-5i: sildenafil (*n* = 69) or tadalafil (*n* = 28)
- Systematic haemodynamic evaluation at 4 months
- Median observational follow-up: 30 months [20 – 43]

Sattler C, Sitbon O, *et al. ERS Congress* 2015.

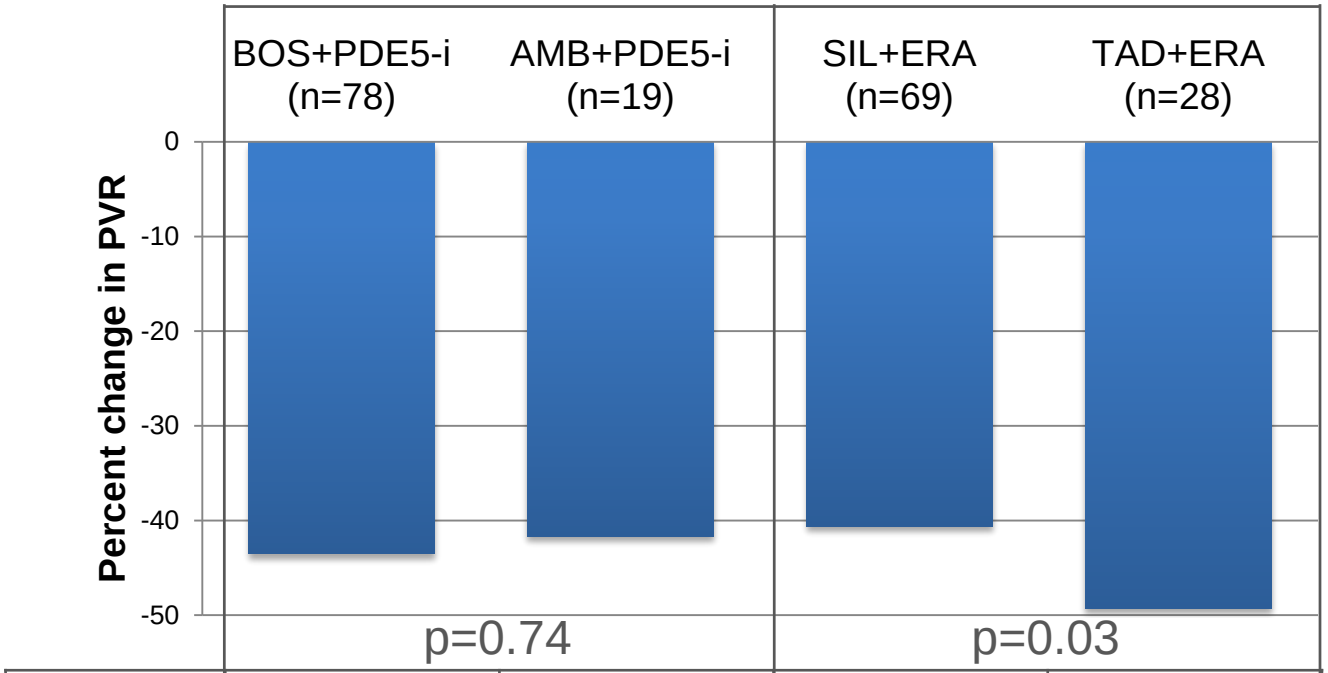
Initial dual oral combination therapy for PAH: Experience of the French network

	Baseline	4 months	*p*-value
NYHA FC (I : II : III : IV), *n*	0 : 18 : 70 : 12	4 : 57 : 31 : 5	< 0.001
6MWD, m	324 ± 132	395 ± 114	< 0.00001
Haemodynamics			
RAP, *mmHg*	9.5 ± 5.7	6.7 ± 4.5	<.00001
mPAP, mmHg	53.9 ± 10.4	45.1 ± 10.9	< 0.00001
CI, L/min/m^2	2.14 ± 0.51	3.13 ± 0.79	< 0.00001
PVR, dyn.s.cm^{-5}	1021 ± 357	565 ± 252 (-43%)	< 0.00001
Mean BP, *mmHg*	97.5 ± 17.7	87.2 ± 12.6	<.00001

Sattler C, Sitbon O, *et al. ERS Congress* 2015.

Initial dual oral combination therapy in PAH:
Change in PVR from baseline to first reassessment

Sattler C, Sitbon O, *et al. ERS Congress* 2015.

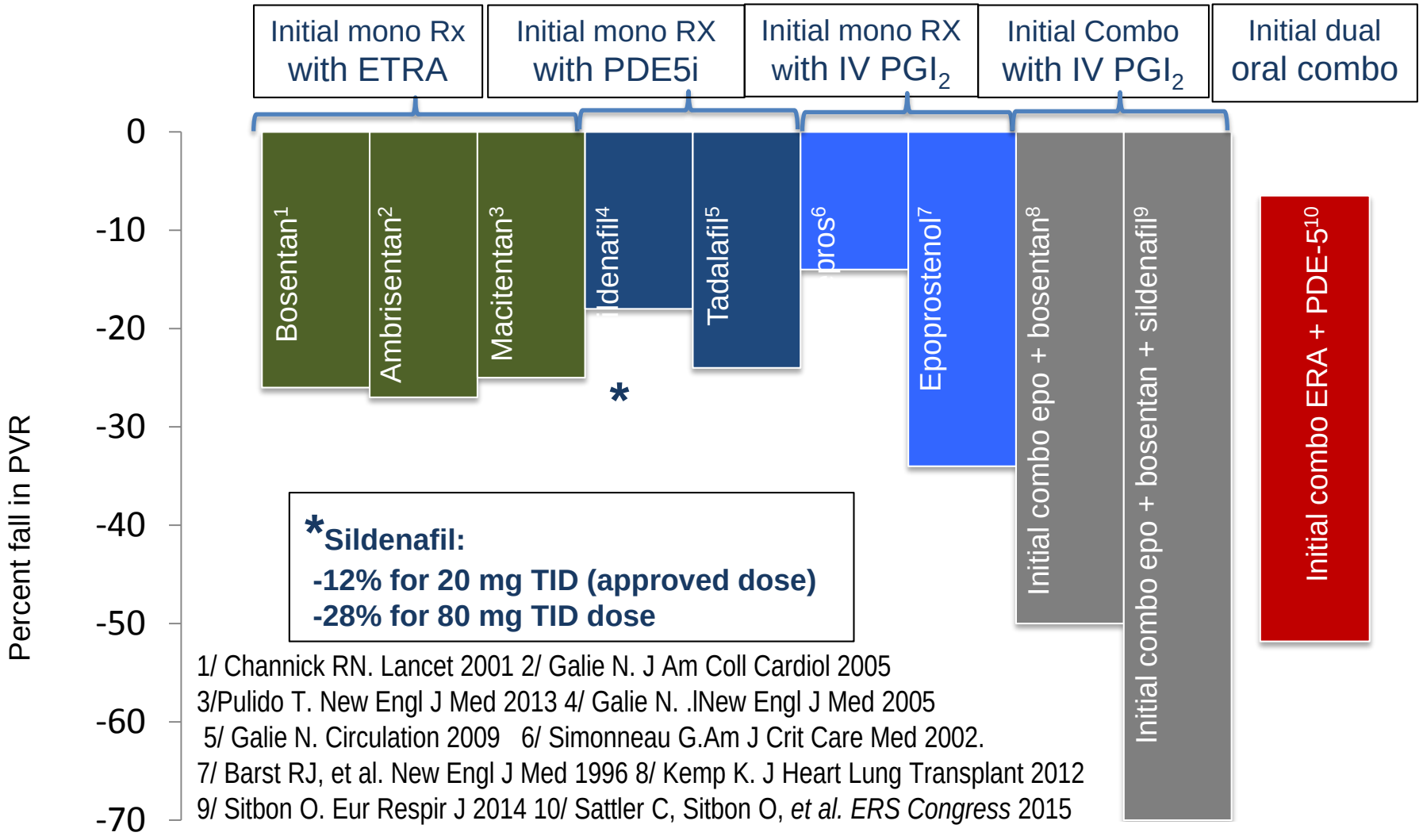


	BOS+PDE5-i (n=78)	AMB+PDE5-i (n=19)	SIL+ERA (n=69)	TAD+ERA (n=28)
Moy ± SD	**-44%** ± 20%	**-42%** ± 21%	**-41%** ± 20%	**-49%** ± 19%
95%CI	[-48%; -39%]	[-51%; -32%]	[-45% ;-36%]	[-56%; -42%]

**median 4.1 months [IQR: 3.5 – 4.9]*

BOS-SIL (n=61), BOS-TAD (n=17), AMB-SIL(n=8), AMB-TAD (n=11)

Hemodynamic effect of different PAH therapies: %Changes in PVR after 3-6 months



1/ Channick RN. Lancet 2001 2/ Galie N. J Am Coll Cardiol 2005
3/Pulido T. New Engl J Med 2013 4/ Galie N. .lNew Engl J Med 2005
5/ Galie N. Circulation 2009 6/ Simonneau G.Am J Crit Care Med 2002.
7/ Barst RJ, et al. New Engl J Med 1996 8/ Kemp K. J Heart Lung Transplant 2012
9/ Sitbon O. Eur Respir J 2014 10/ Sattler C, Sitbon O, *et al. ERS Congress* 2015

Quali novità nelle strategie terapeutiche dell'Ipertensione arteriosa polmonare nel 2016?

- Miglior utilizzo dei farmaci attualmente disponibili
- La terapia sequenziale rallenta l'evoluzione di malattia
- L'approccio sequenziale è verosimilmente più efficace se precoce (goal oriented) ma non abbiamo forti evidenze scientifiche.
- Abbiamo solidi argomenti per un terapia d'attacco combinata:
- Con una PC parenterale (epoprostenol) o sc (Trepostinil) nei pazienti più gravi (IV NHYA e III avanzata) – Ruolo Selexipag ?
- Superiorità della doppia terapia orale rispetto alla mono nei pazienti in classe NYHA 2 e 3
- Non disponiamo di studi comparativi fra le diverse terapie di associazione e tra associazione d'emble e sequenziale combinata.