PNEUMOLOGIA 2016

Milano, 16 – 18 giugno 2016 · Centro Congressi Palazzo delle Stelline

Dalla monoterapia alla terapia di associazioni, ai nuovi farmaci, come trattare il paziente con ipertensione polmonare?

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Conflict of interests disclosures

Actelion

Boehringer Ingelheim

InterMune

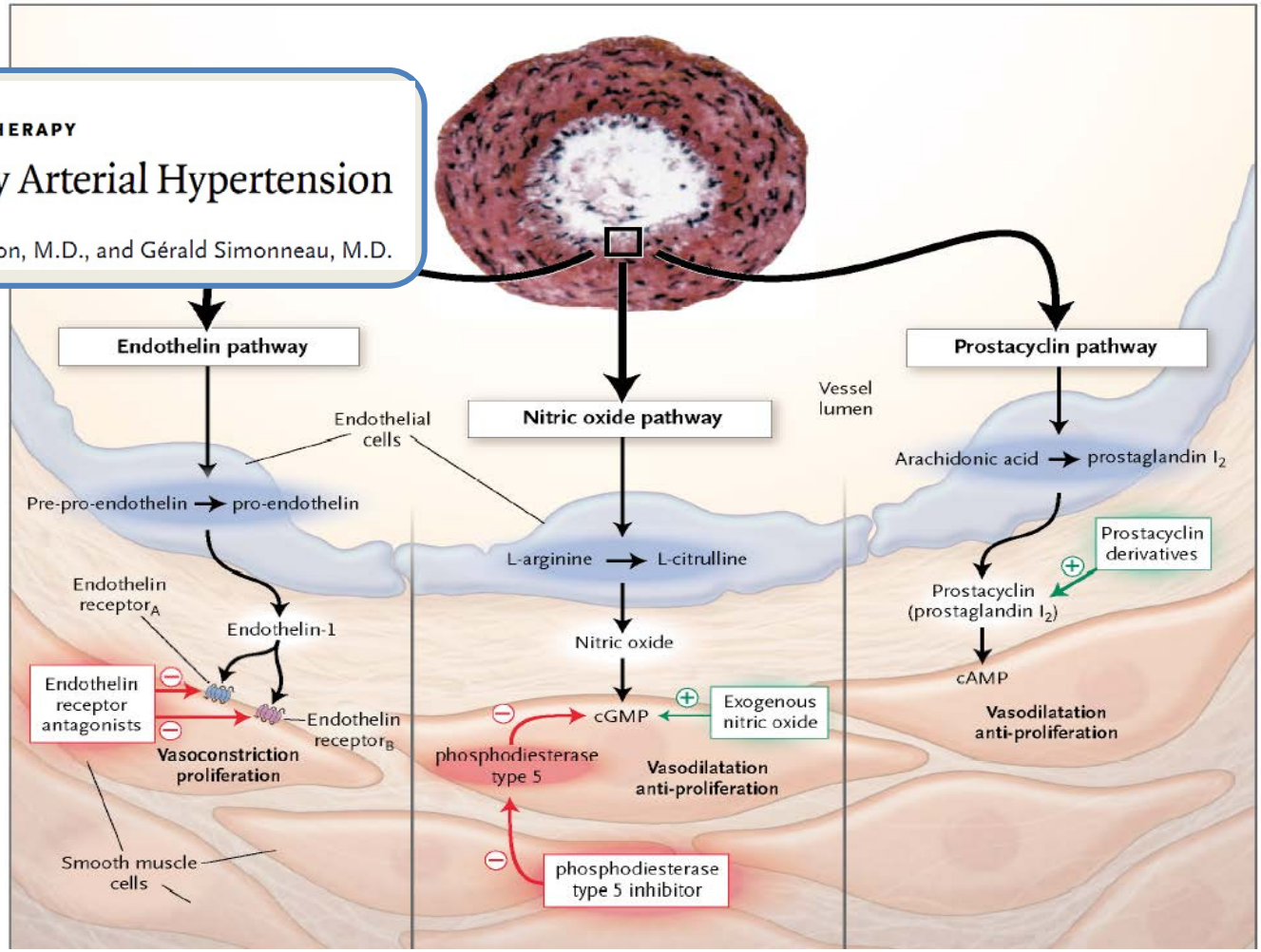
Roche

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.

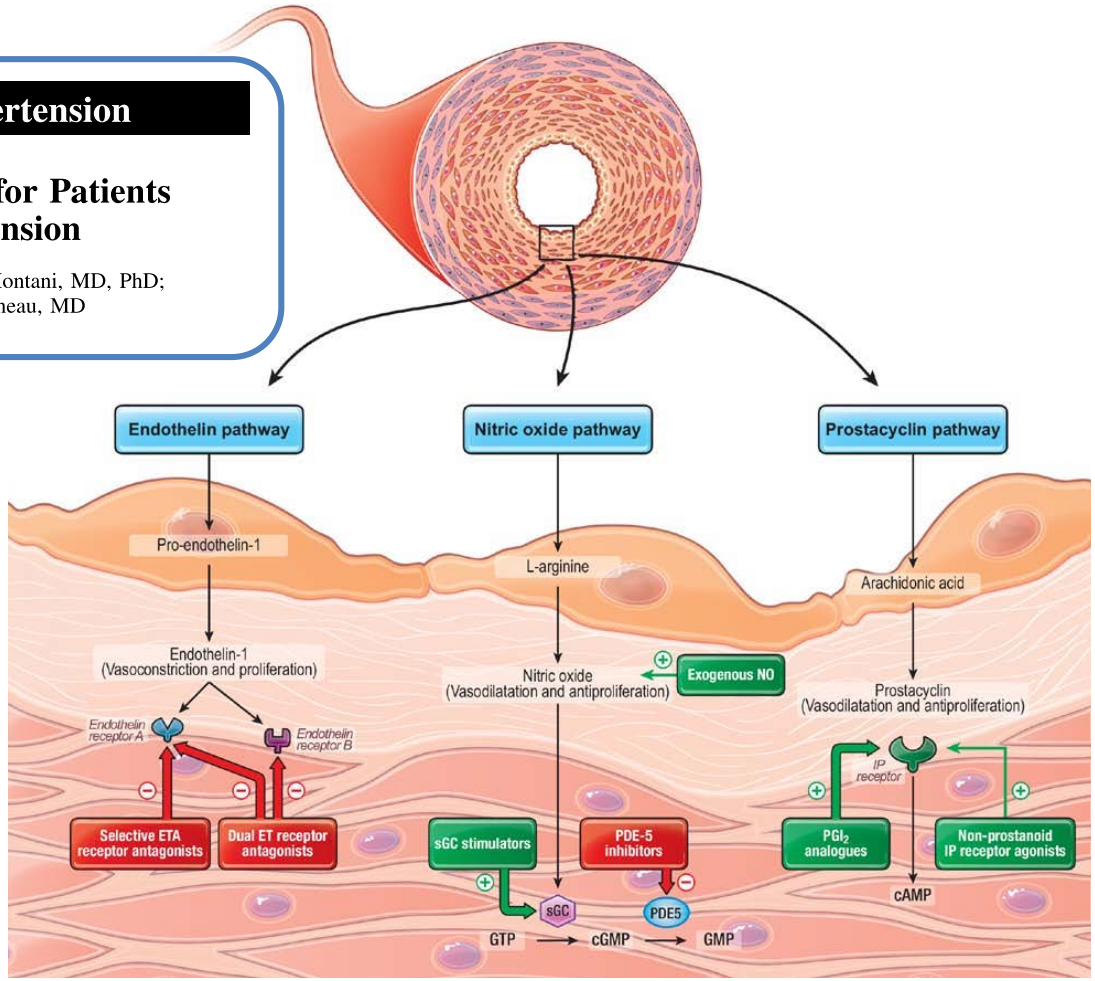
Humbert M *et al. N Engl J Med* 2004;351:1425–36.

Targeting 3 major dysfunctional pathways in PAH (2014)

Recent Advances in Pulmonary Hypertension

Advances in Therapeutic Interventions for Patients With Pulmonary Arterial Hypertension

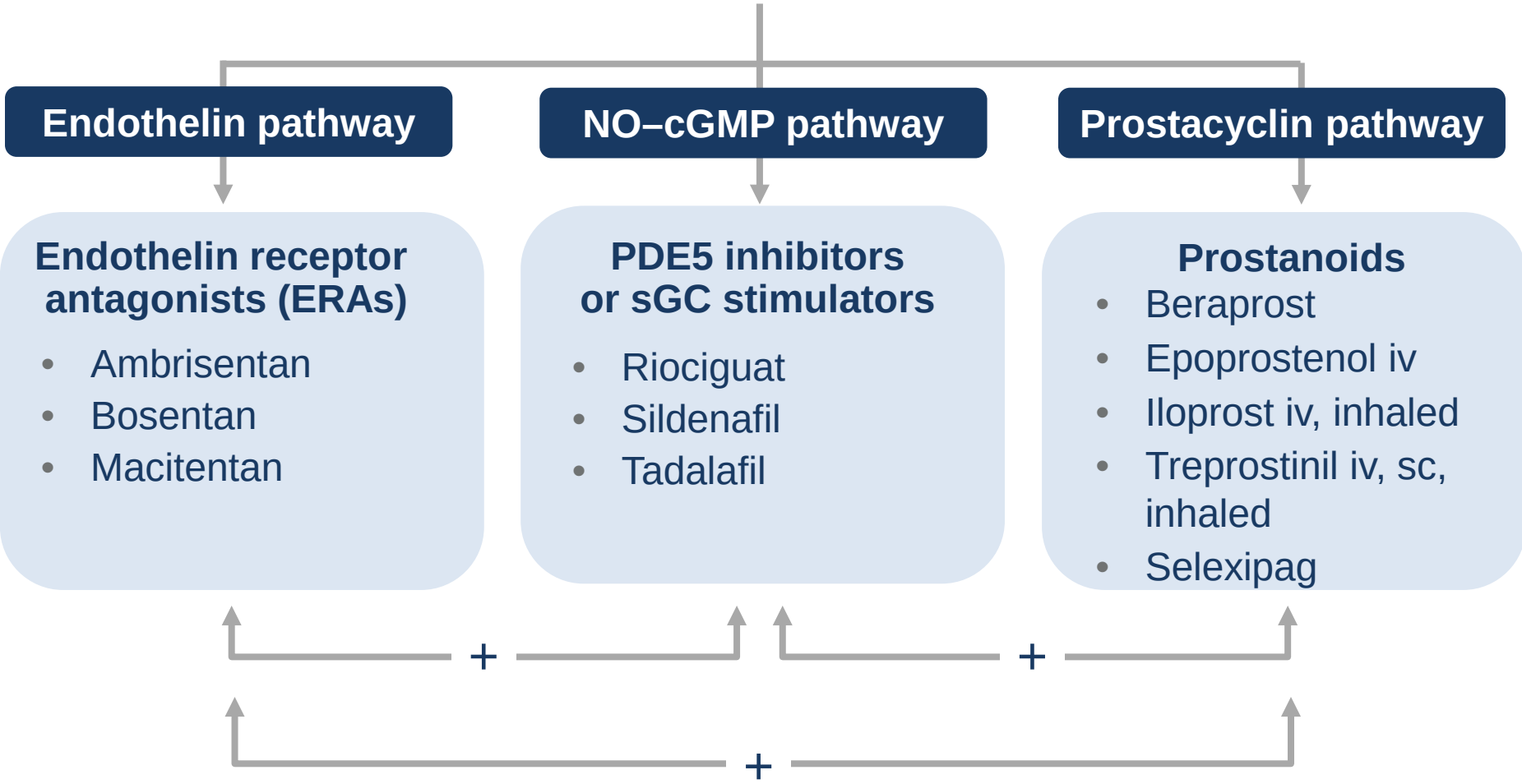
Marc Humbert, MD, PhD; Edmund M.T. Lau, MD, PhD; David Montani, MD, PhD; Xavier Jaïs, MD; Oliver Sitbon, MD, PhD; Gérald Simonneau, MD



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.

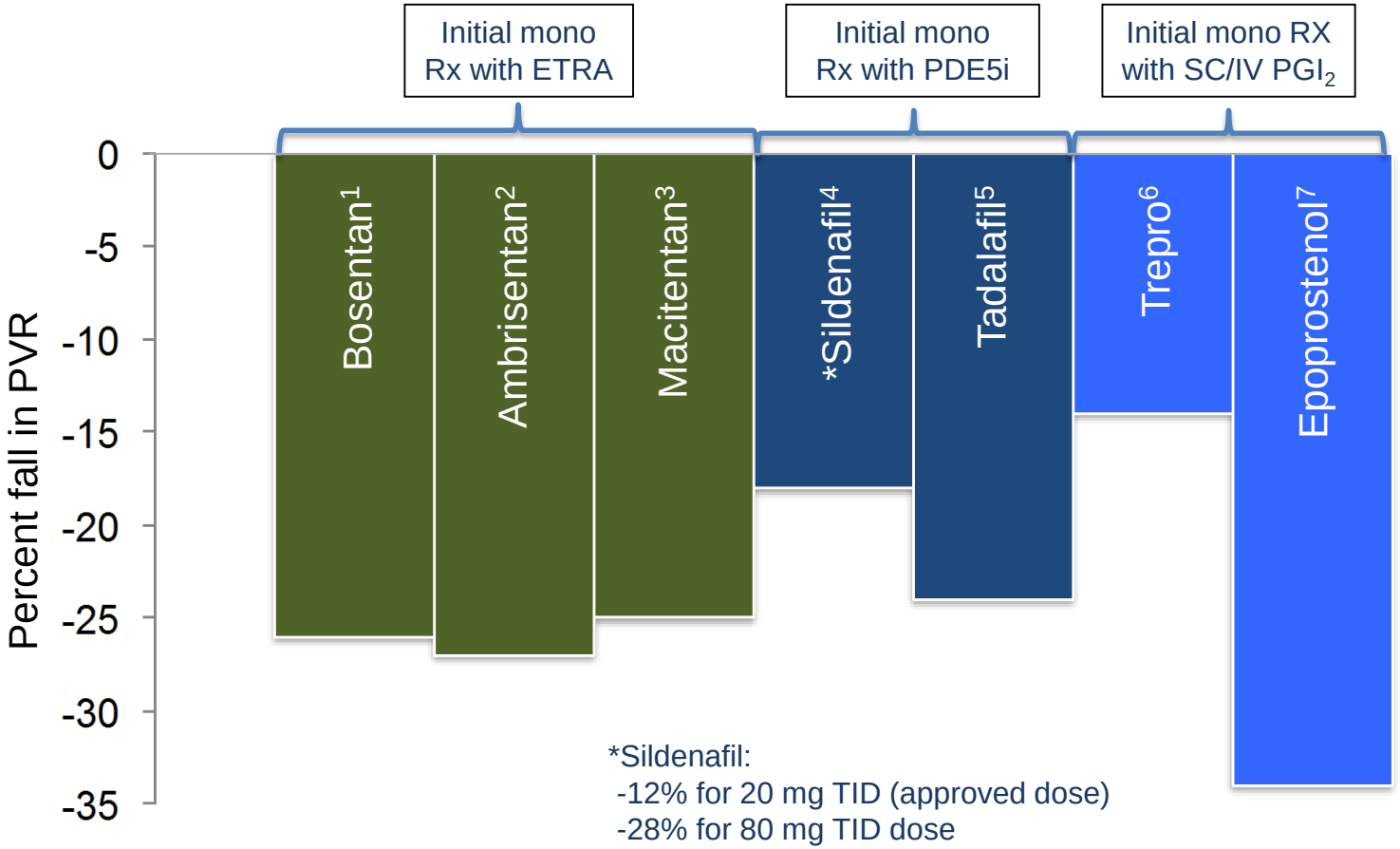
Humbert M *et al. Circulation* 2014;130:2189–208.

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.

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



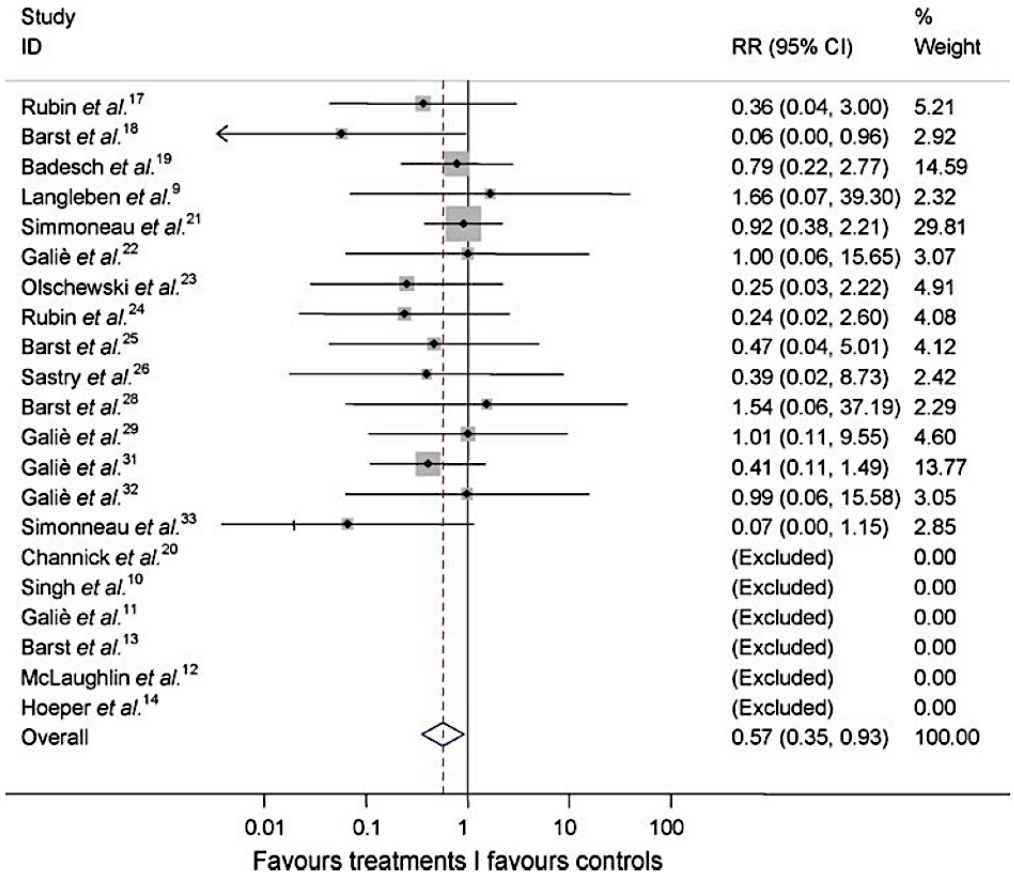
*Sildenafil:
-12% for 20 mg TID (approved dose)
-28% for 80 mg TID dose

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



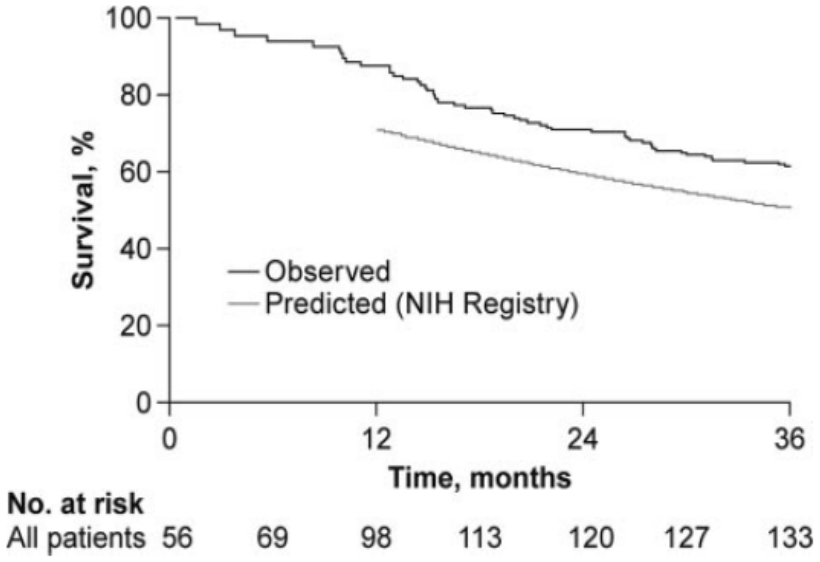
- 23 RCTs
- Average duration 14.3 wks
- 3140 patients
- All-cause mortality rate in the control group = 3.8%
- Active treatments:
  - 43% reduction in mortality
  - RR 0.57 (95%CI 0.35–0.92)
  - P = 0.023

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

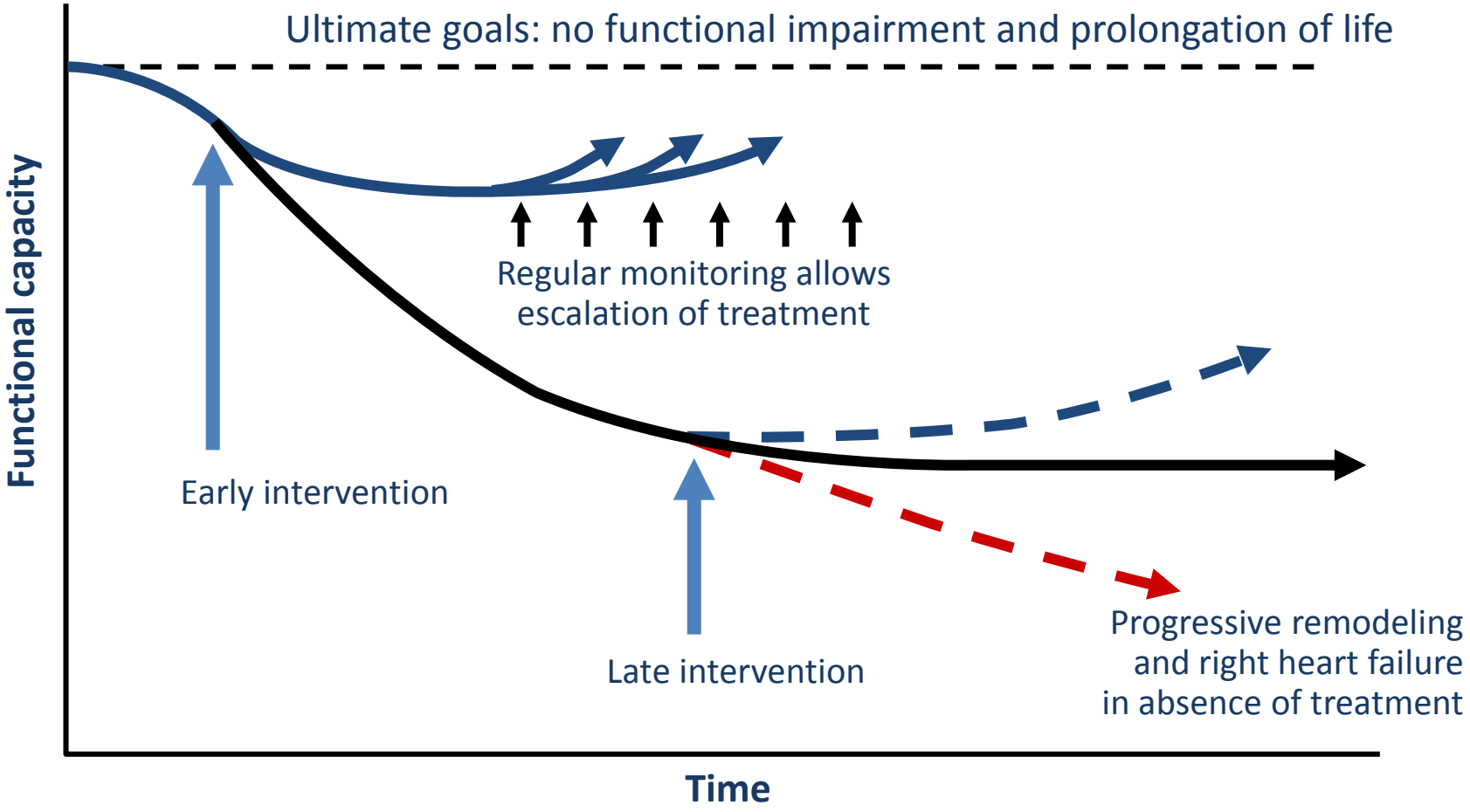
Marc Humbert, MD, PhD; Olivier Sitbon, MD, PhD; Ari Chaouat, MD, PhD; Michèle Bertocchi, MD; Gilbert Habib, MD; Virginie Gressin, MD; Azzedine Yaïci, MD; Emmanuel Weitzenblum, MD; Jean-François Cordier, MD; François Chabot, MD, PhD; Claire Dromer, MD; Christophe Pison, MD, PhD; Martine Reynaud-Gaubert,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

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.

Goal-oriented therapy (risk assessment)

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 Respir J & Eur Heart J*. 2015.

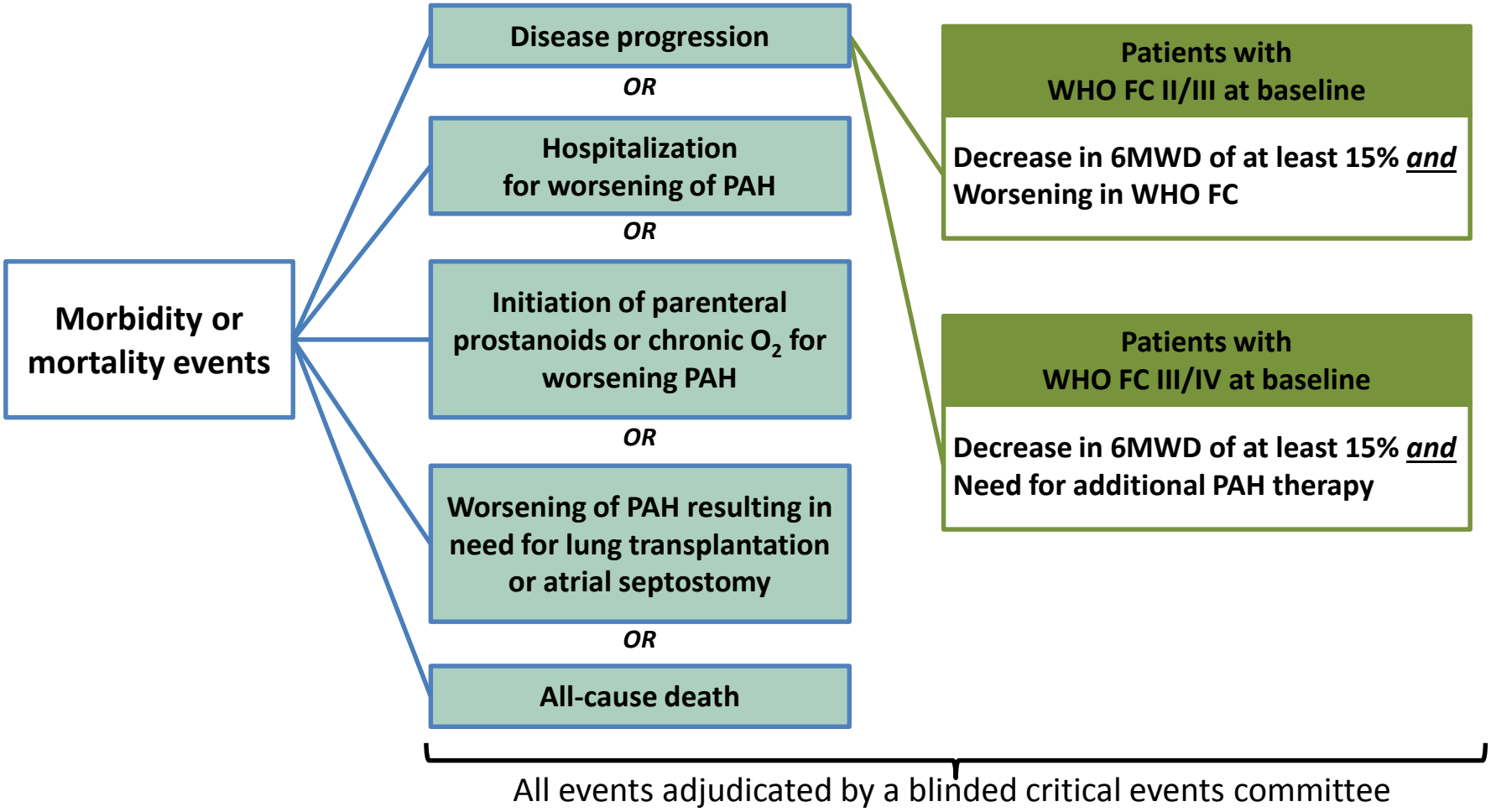
Sequential combination therapy: results are not uniform…

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 +

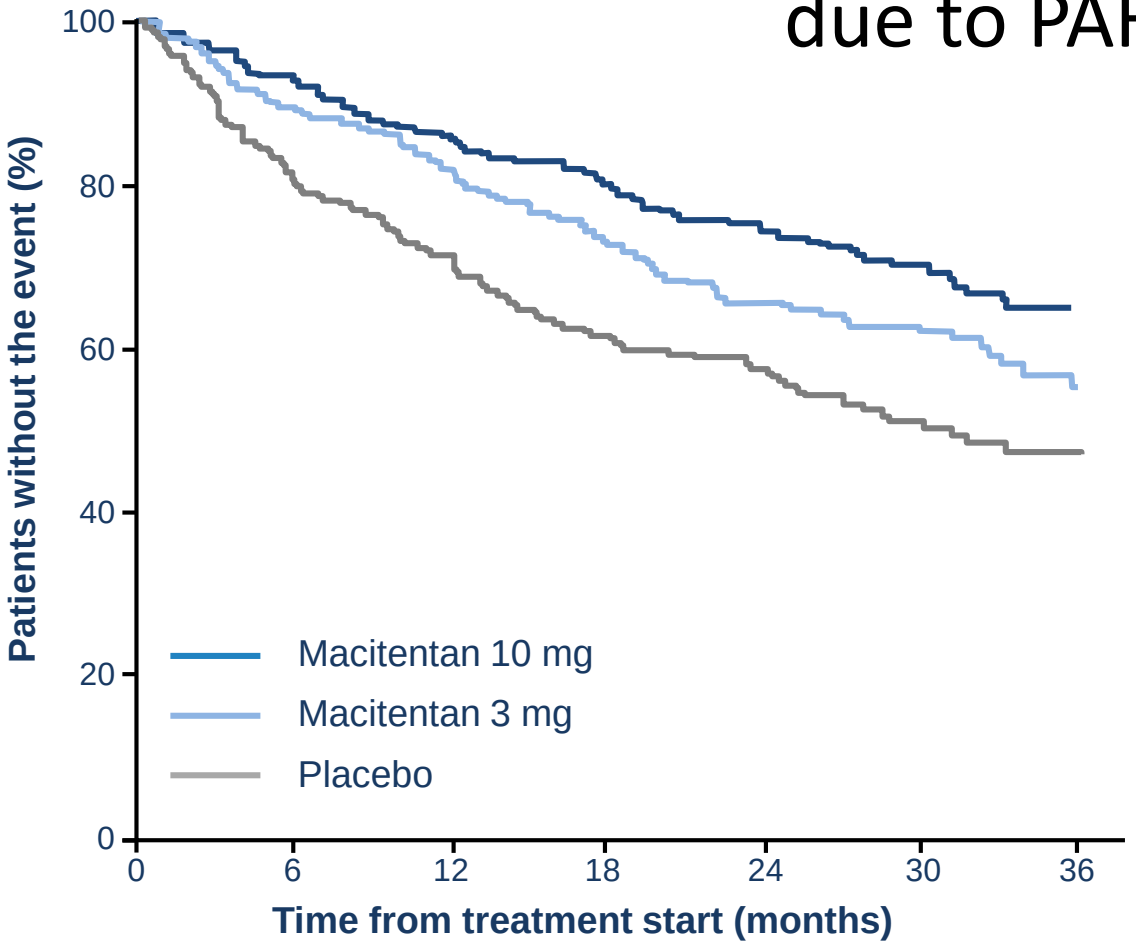
Seraphin: primary endpoint: Time to first occurrence of death or morbidity due to PH up to EOT



EOT: End of double-blind treatment

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

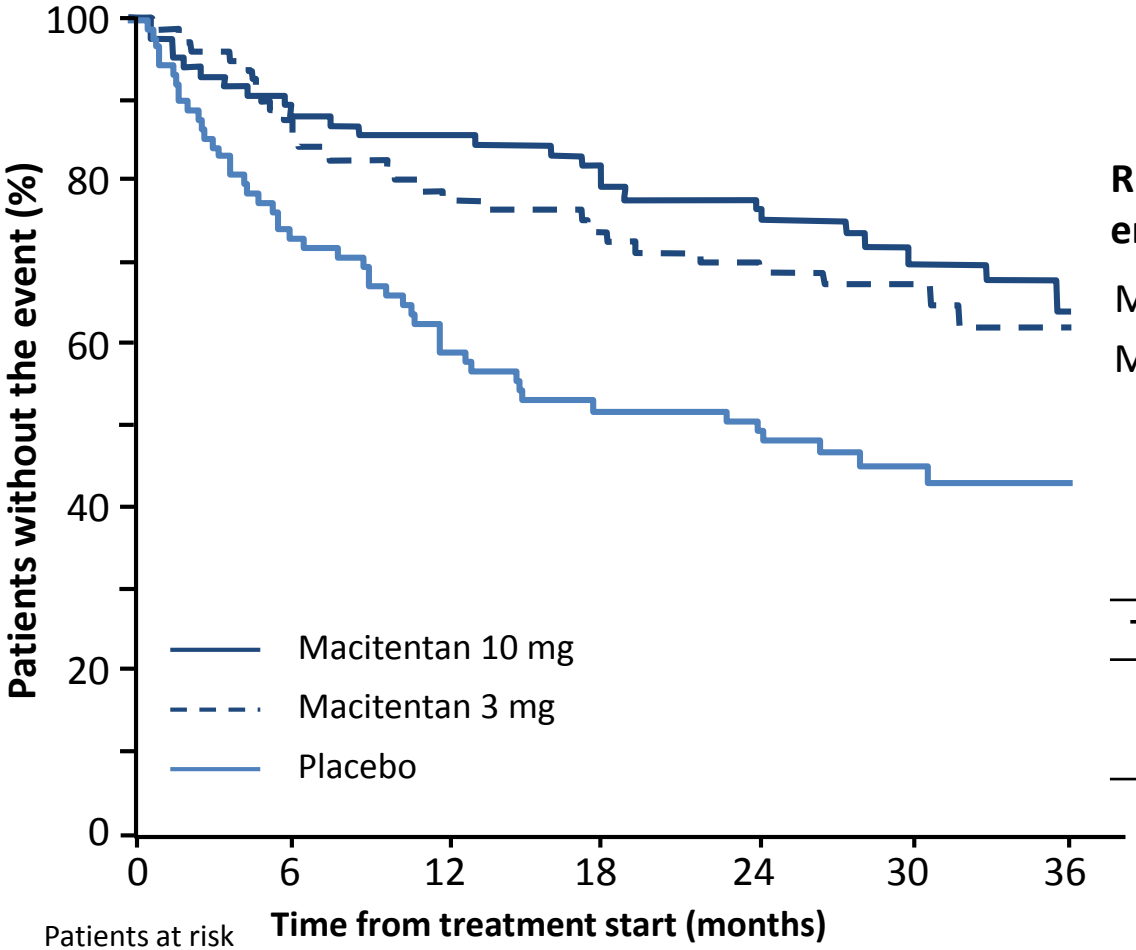
Risk reduction of primary endpoint event vs placebo
Macitentan 10 mg: 45%
Macitentan 3 mg: 30%

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.

Morbidity and mortality in patients not on background PAH therapy



Risk reduction of primary endpoint event vs placebo

Macitentan 10 mg: 55%

Macitentan 3 mg: 47%

Treatment difference	3 mg	10 mg
Hazard ratio (HR)	0.53	0.45
Log-rank *p*-value	0.007	<0.001

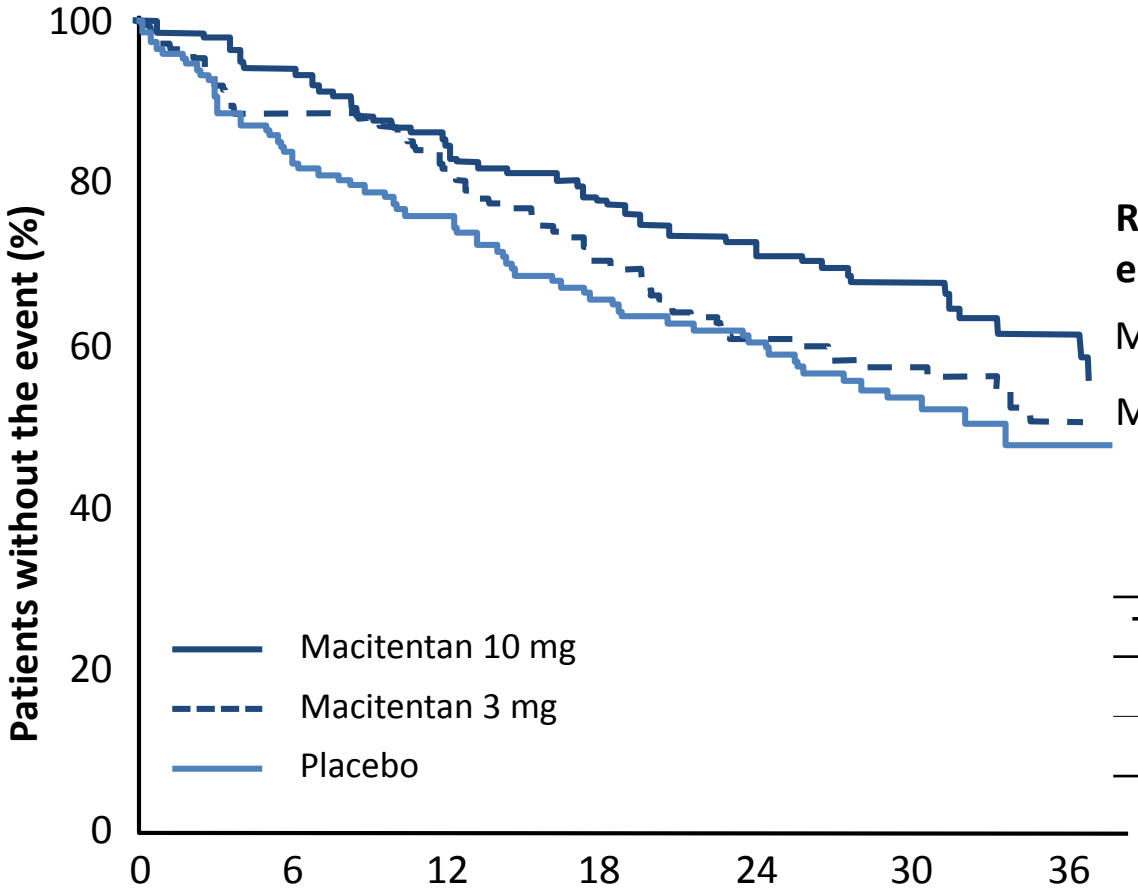
Patients at risk

88	74	68	64	58	38	17
86	74	63	59	56	29	13
96	66	54	45	42	24	13

Macitentan 10 mg
Macitentan 3 mg
Placebo

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

Morbidity and mortality in patients on background PAH therapy



Risk reduction of primary endpoint event vs placebo

Macitentan 10 mg: 38%

Macitentan 3 mg: 17%

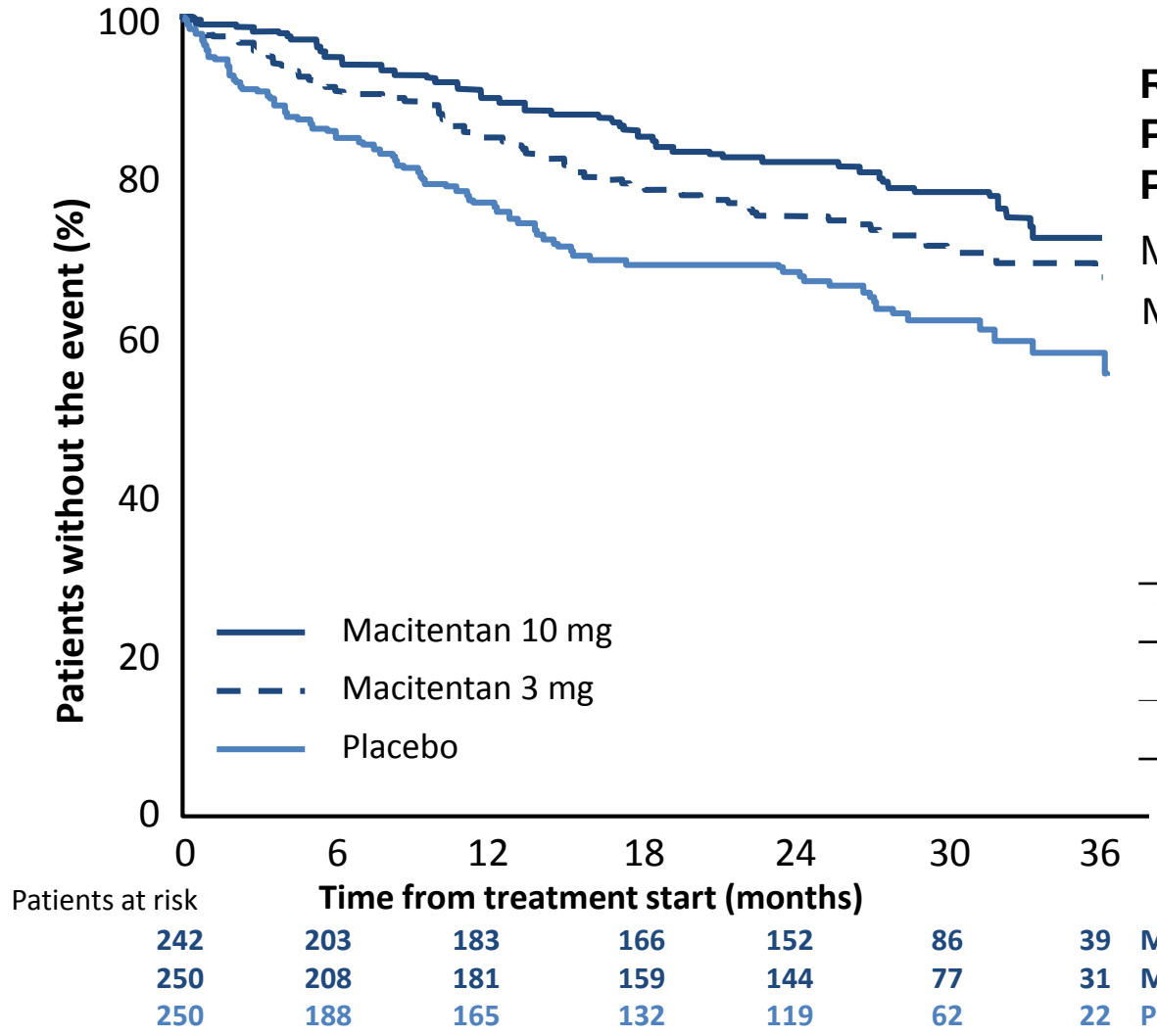
Treatment difference	3 mg	10 mg
Hazard ratio (HR)	0.83	0.62
Log-rank *p*-value	0.27	0.009

Patients at risk

154	134	119	107	97	53	24	Macitentan 10 mg
164	139	125	107	91	51	19	Macitentan 3 mg
154	122	106	90	80	40	10	Placebo

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

Secondary endpoint: Death due to PAH or hospitalisation for PAH



Risk reduction of death due to PAH or hospitalisation for PAH event *vs* placebo

Macitentan 10 mg: 50%

Macitentan 3 mg: 33%

Treatment difference	3 mg	10 mg
Hazard ratio (HR)	0.67	0.50
Log-rank *p*-value	0.01	< 0.001

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

Selexipag in Pulmonary Arterial Hypertension – GRIPHON trial

- GRIPHON: ProstaGlandin I_2 Receptor agonist In Pulmonary arterial HypertensiON
- Large, international, multicenter, long-term phase 3 study
- Double-blind, placebo-controlled study assessing the safety and efficacy of selexipag on morbidity and mortality in patients with PAH
- Event-driven study
- Primary outcome measure: Time to first adjudicated morbidity or mortality event (up to 7 days after last study-drug intake)

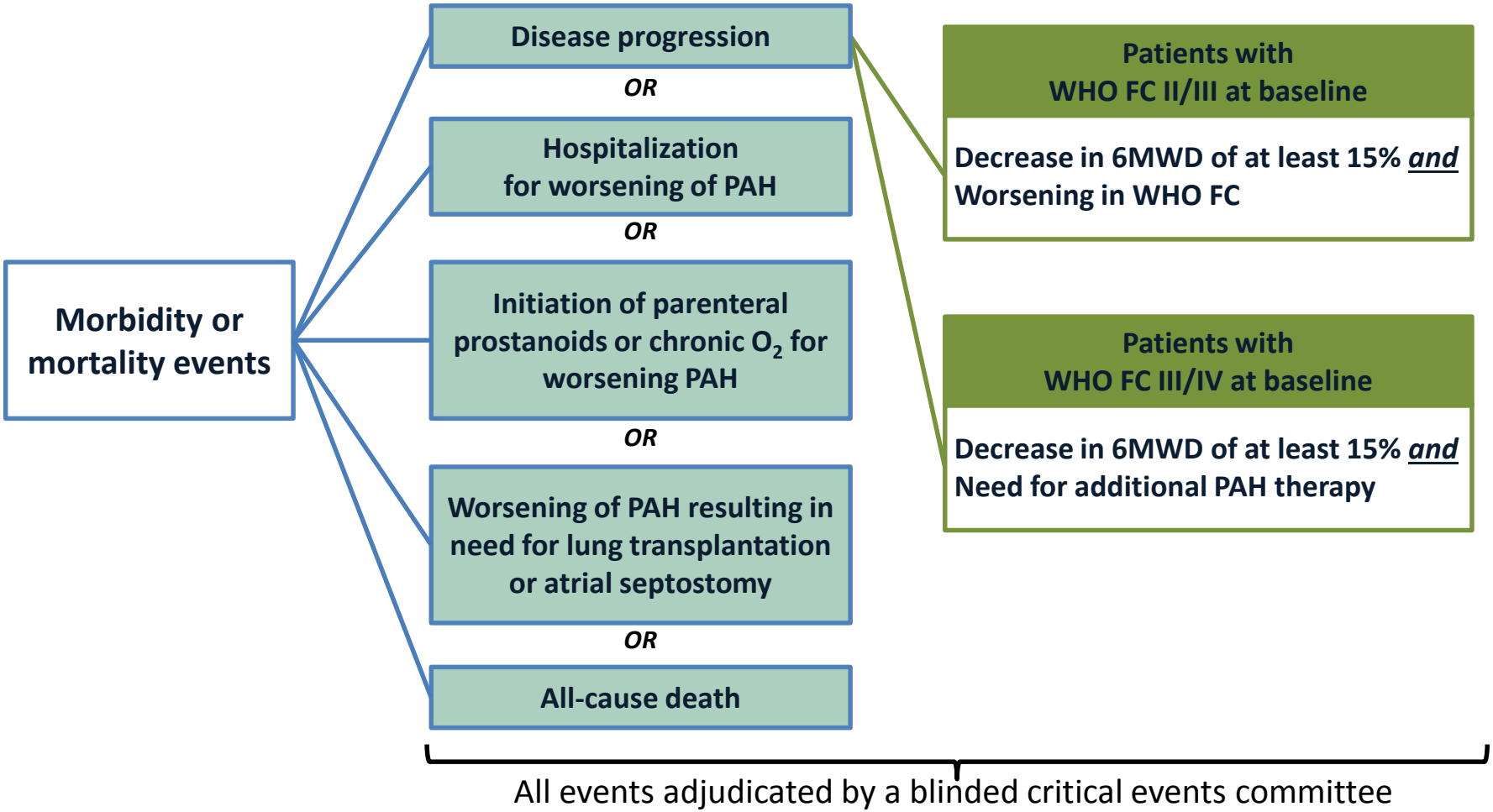
Sitbon O et al., N Engl J Med 2015; 373(26):2522-3

GRIPHON trial – results

- 1156 PAH adult patients included and treated for up to 4.3 years.
- 80% on background treatment with ERA and/or PDE-5i
- Uptitration of selexipag allows each patient's maintenance dose to be individualized based on tolerability (to a maximum of 1600 mcg bid)

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

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

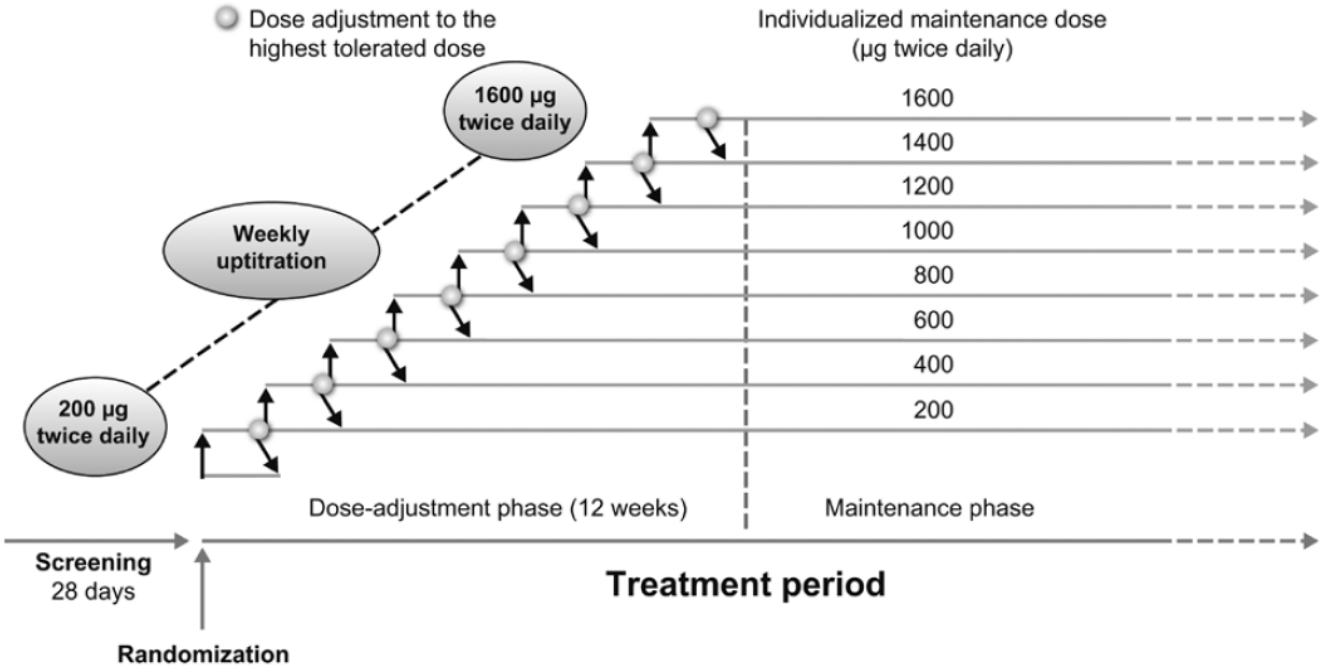


EOT: End of double-blind treatment

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

GRIPHON trial – results

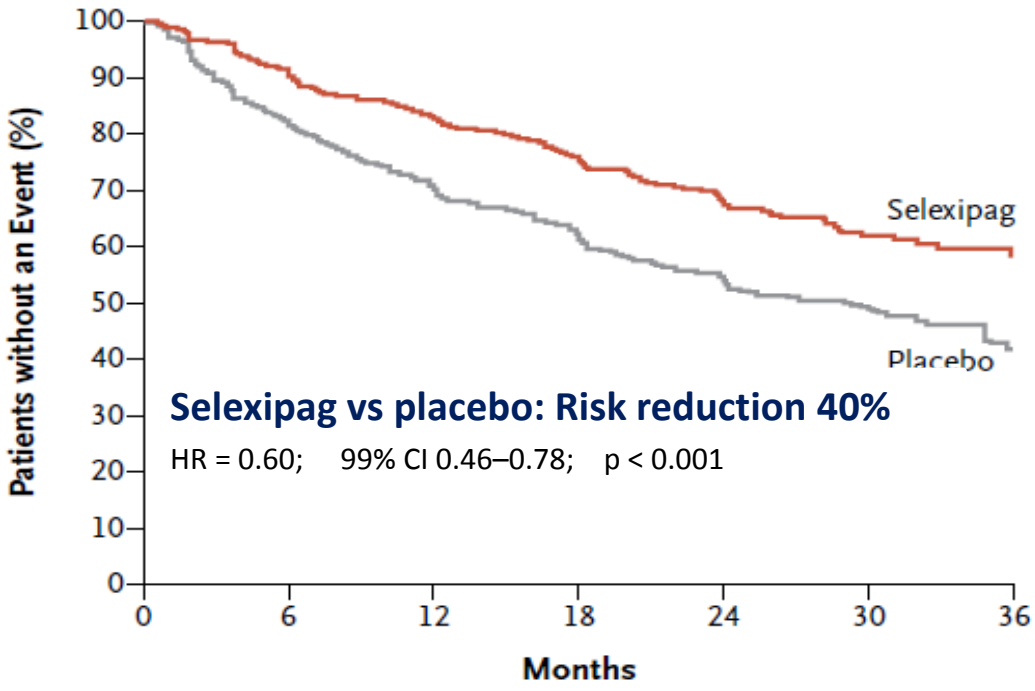
- The GRIPHON study with selexipag met its primary objective in patients with PAH
- Selexipag reduced the risk of a morbidity/mortality event (primary endpoint) by 40% compared with placebo
- The efficacy of selexipag was consistent across subgroups: Age, gender, FC, PAH etiology, and background PAH 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

GRIPHON trial – 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

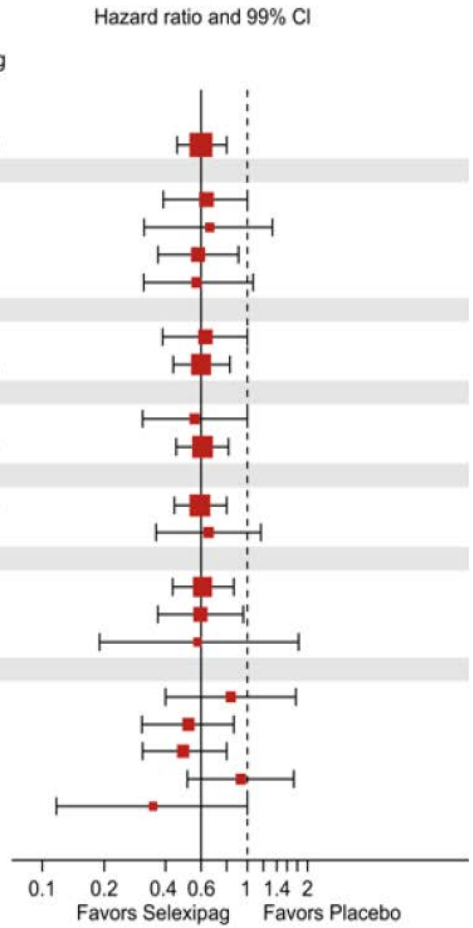
Sitbon O et al., N Engl J Med 2015; 373(26):2522-3

GRIPHON trial – results

Primary composite end point

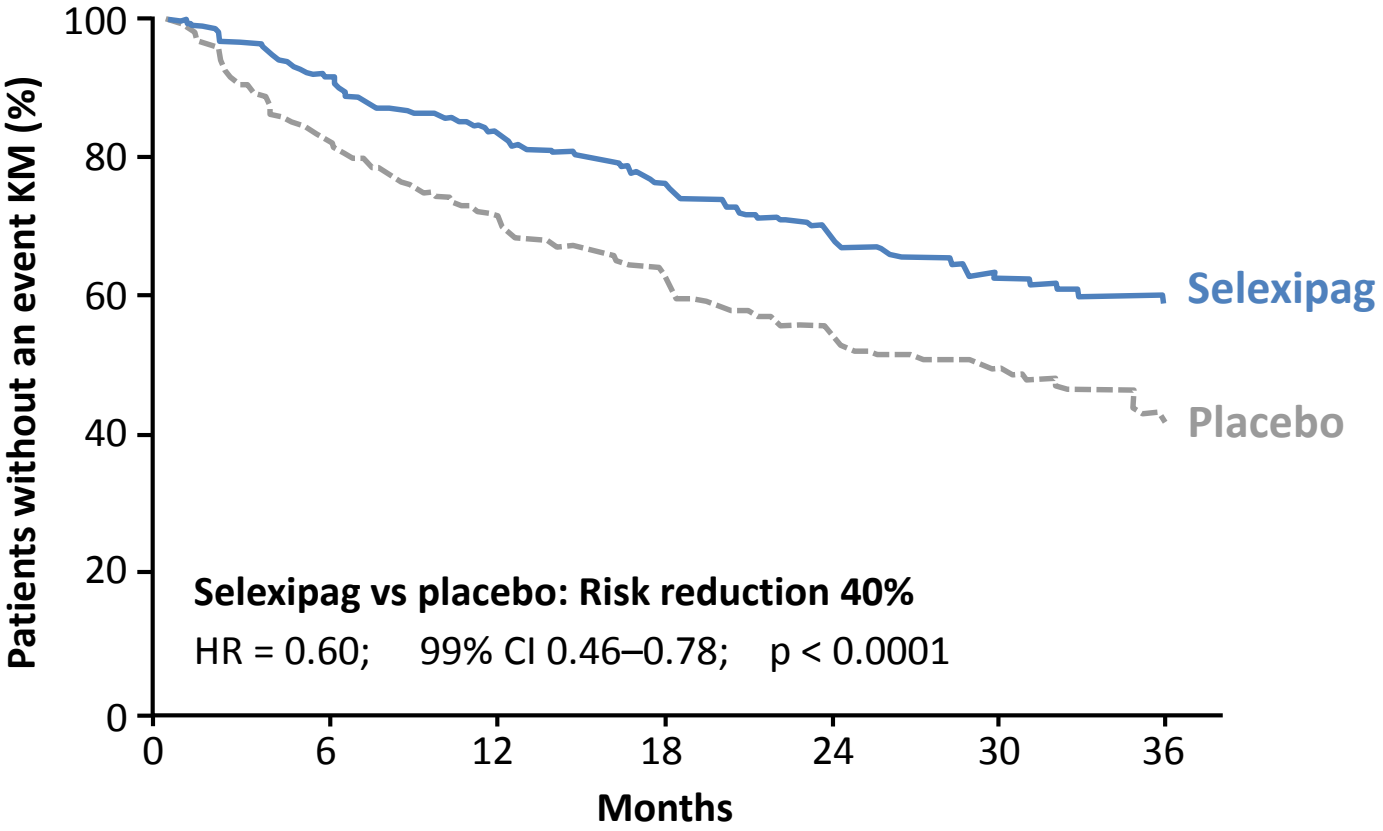
Effect of selexipag across subgroups

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

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

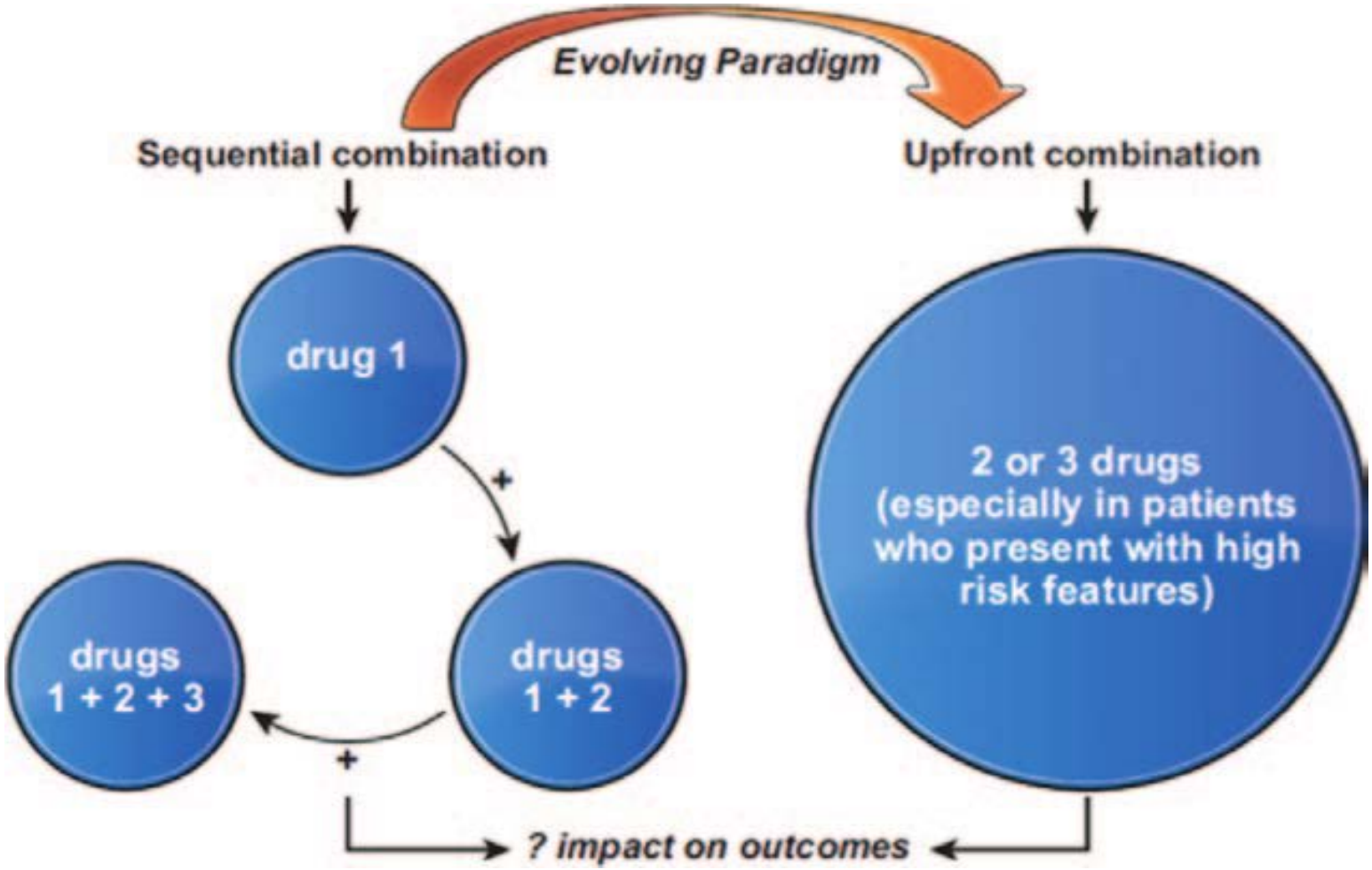


No. at Risk							
Placebo	582	433	347	220	149	88	28
Selexipag	574	455	361	246	171	101	40

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

EOT: End of double-blind treatment

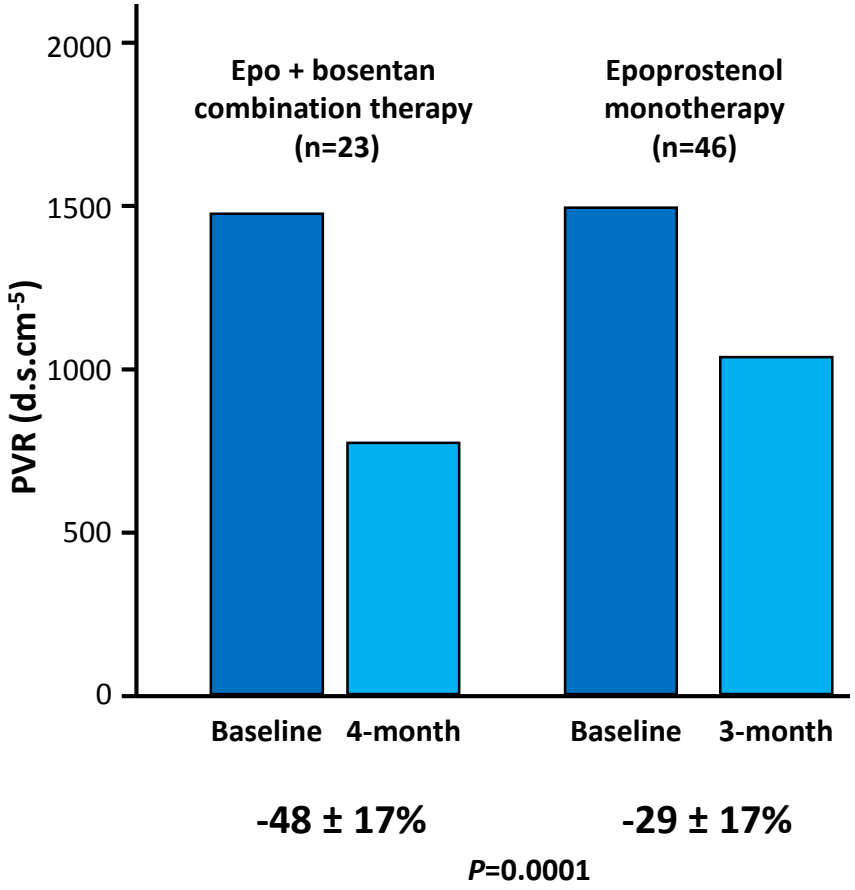
Evolving paradigm: From sequential to initial combination therapy

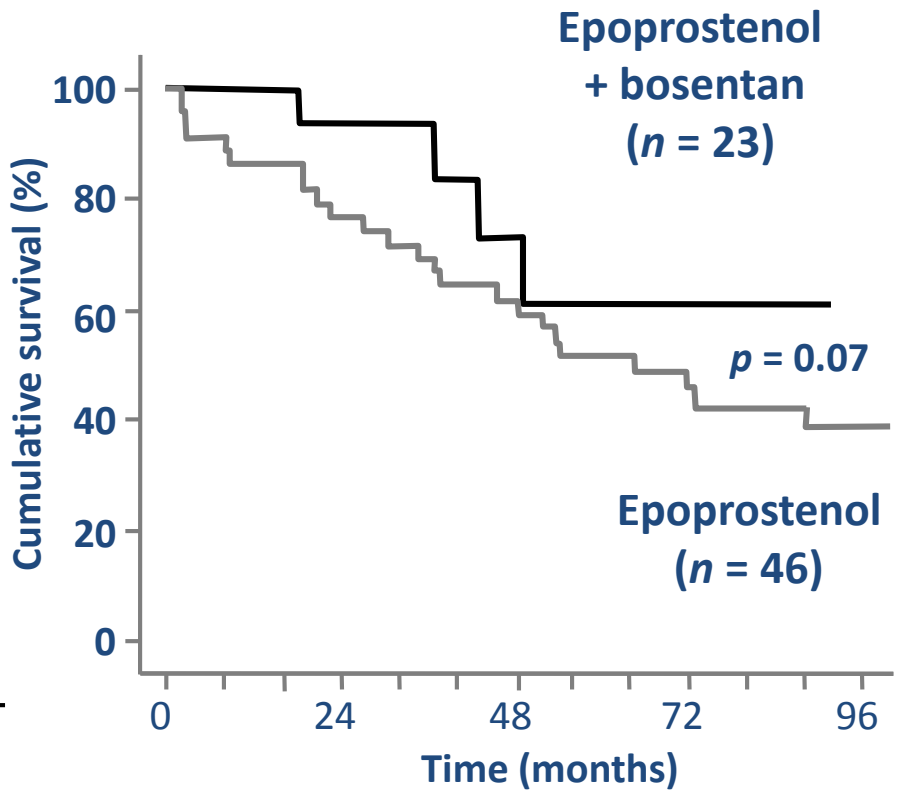


Humbert M, *et al*. *Circulation* 2014.

Up-front double combination therapy with epoprostenol and bosentan

Percent change in PVR from baseline to 1st f-up evaluation (3–6 months)

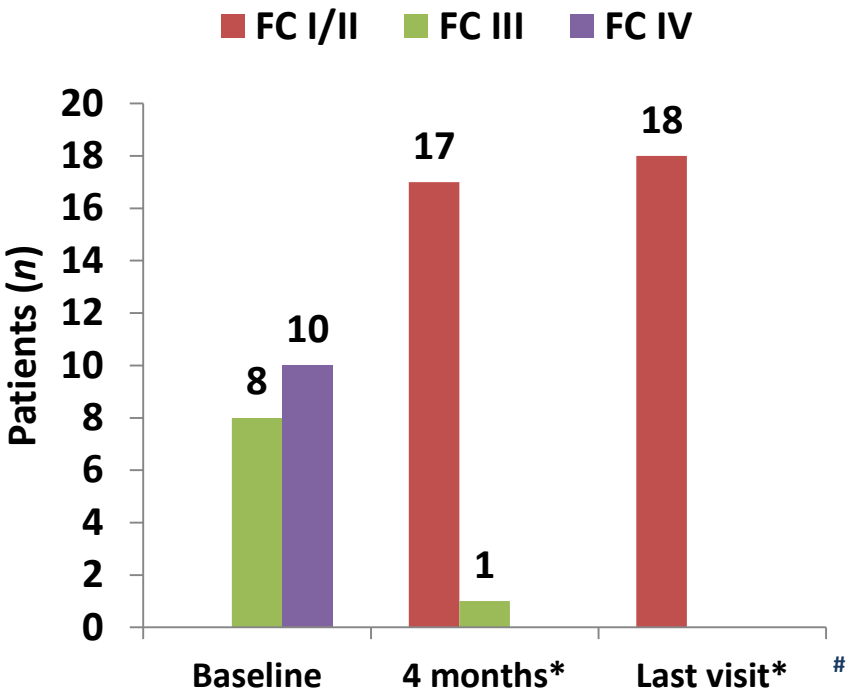


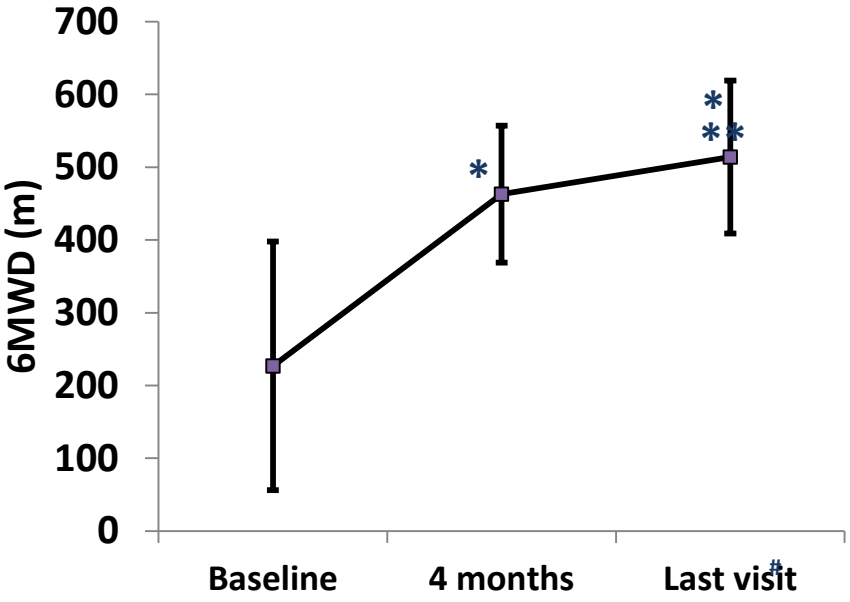


Kemp K, *et al*. J Heart Lung Transplant 2012;31:150–8.

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)



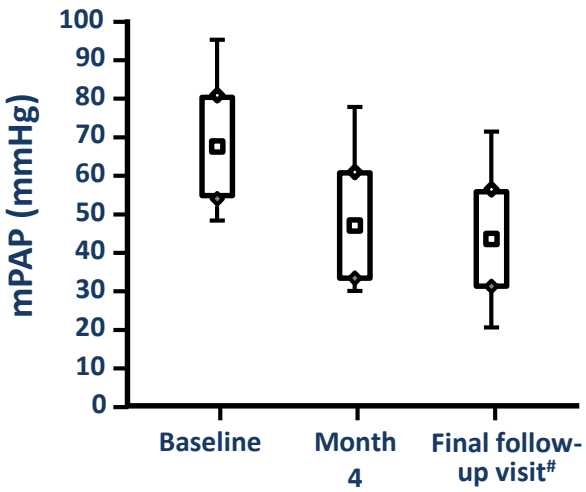


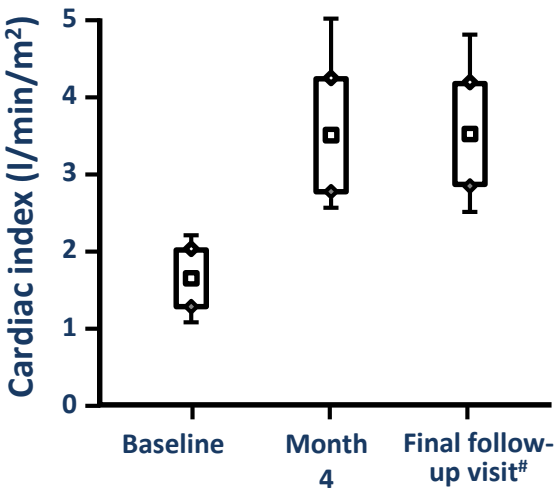
#32 ± 19 months

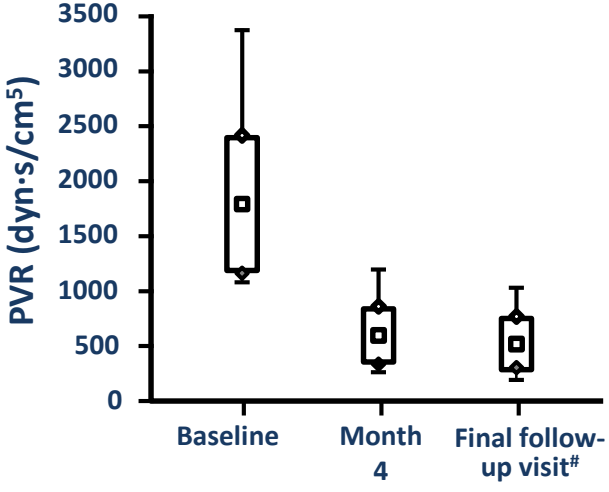
*p < 0.01 versus baseline; ** p < 0.01 versus 4 months

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%

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

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

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)

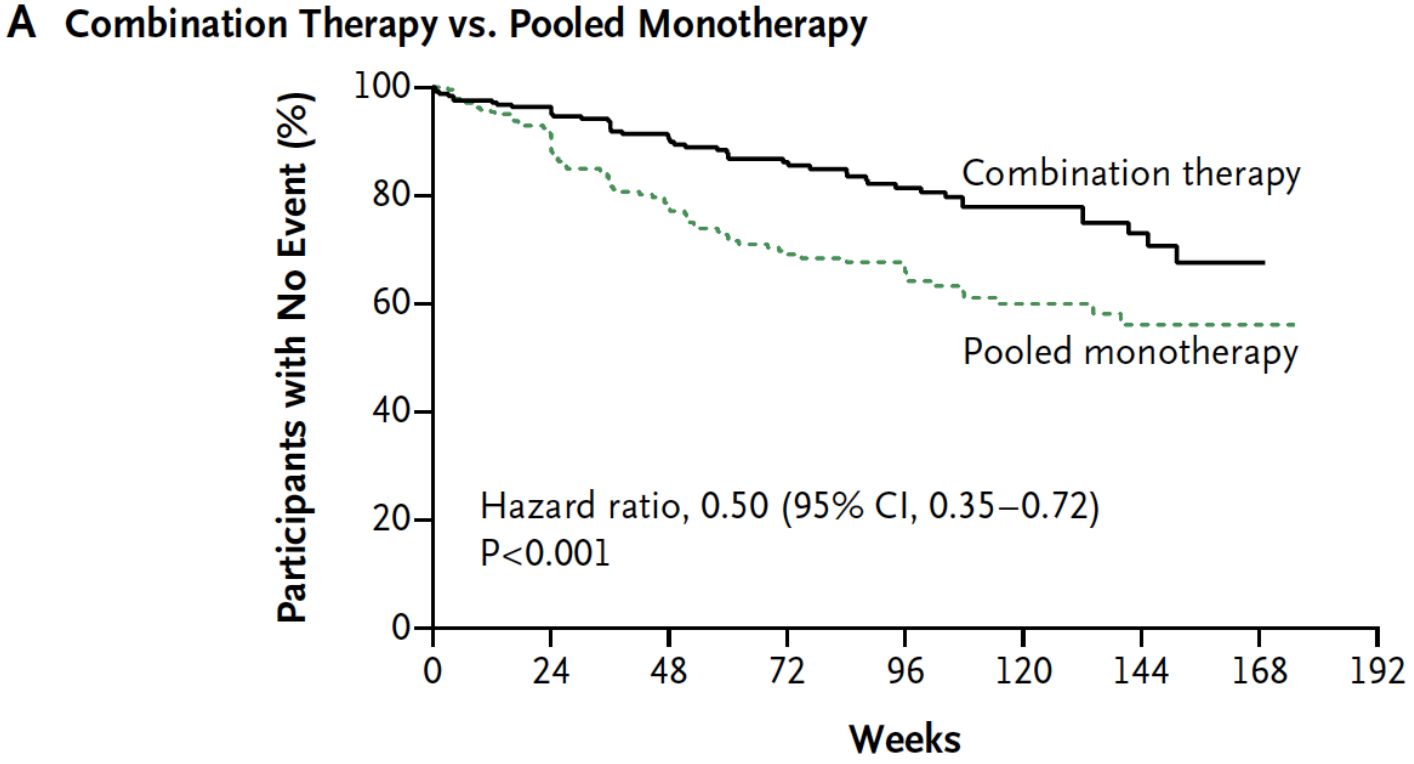
All events were adjudicated

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



No. at Risk

Combination therapy	253	229	186	145	106	71	36	4
Pooled monotherapy	247	209	155	108	77	49	25	5

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 dual oral combination therapy in pulmonary arterial hypertension

Olivier Sitbon[1,2,3], Caroline Sattler[1,2,3], Laurent Bertoletti[4,5], Laurent Savale[1,2,3], Vincent Cottin[6], Xavier Jaïs[1,2,3], Pascal De Groote[7], Ari Chaouat[8,9], Céline Chabannes[10], Emmanuel Bergot[11], Hélène Bouvaist[12], Claire Dauphin[13], Arnaud Bourdin[14], Fabrice Bauer[15], David Montani[1,2,3], Marc Humbert[1,2,3] and Gérald Simonneau[1,2,3]

- 2007 – 2013
- 97 incident patients with PAH
  - Mean age 54
  - NYHA FC II-III (88%) & IV (12%)
- Initial dual oral combination therapy with ERA and PDE5i
  - BOS-SIL (n=61)
  - BOS-TAD (n=17)
  - AMB-SIL (n=8)
  - AMB-TAD (n=11)
- Median follow-up: 30 months [20 – 43]

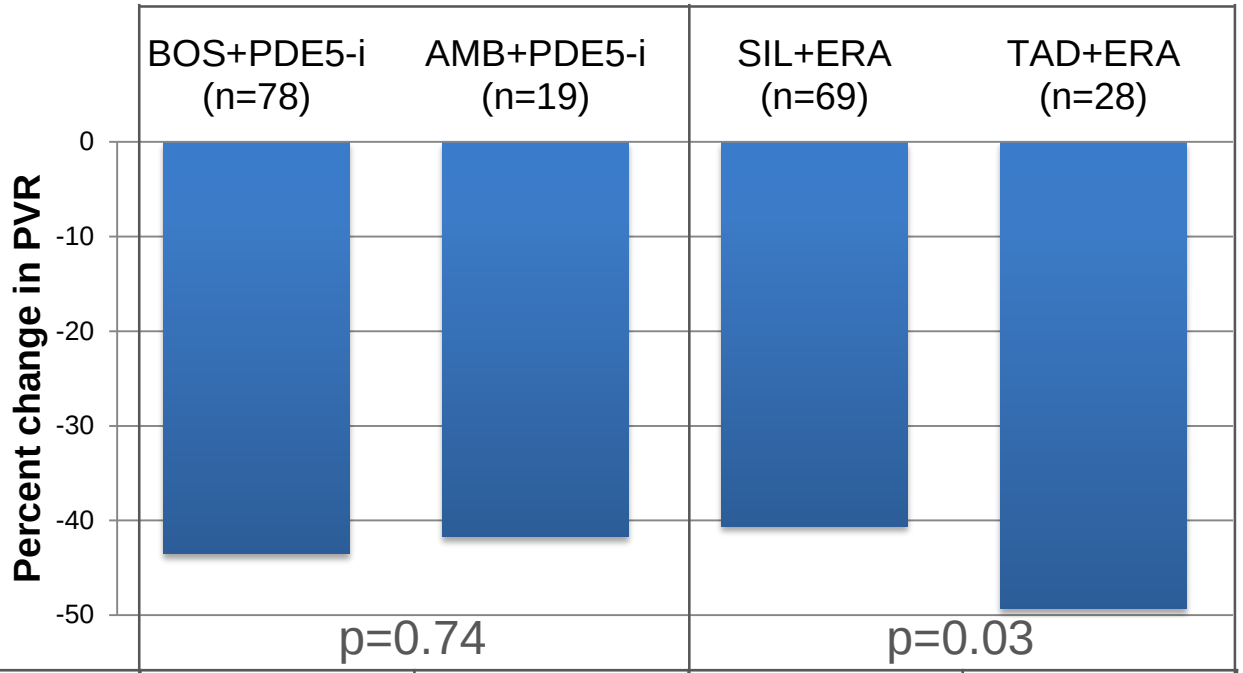
Sitbon O, *et al. Eur Respir J* 2016; Epub on 17 March.

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

Sitbon O, *et al. Eur Respir J* 2016; Epub on 17 March.

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



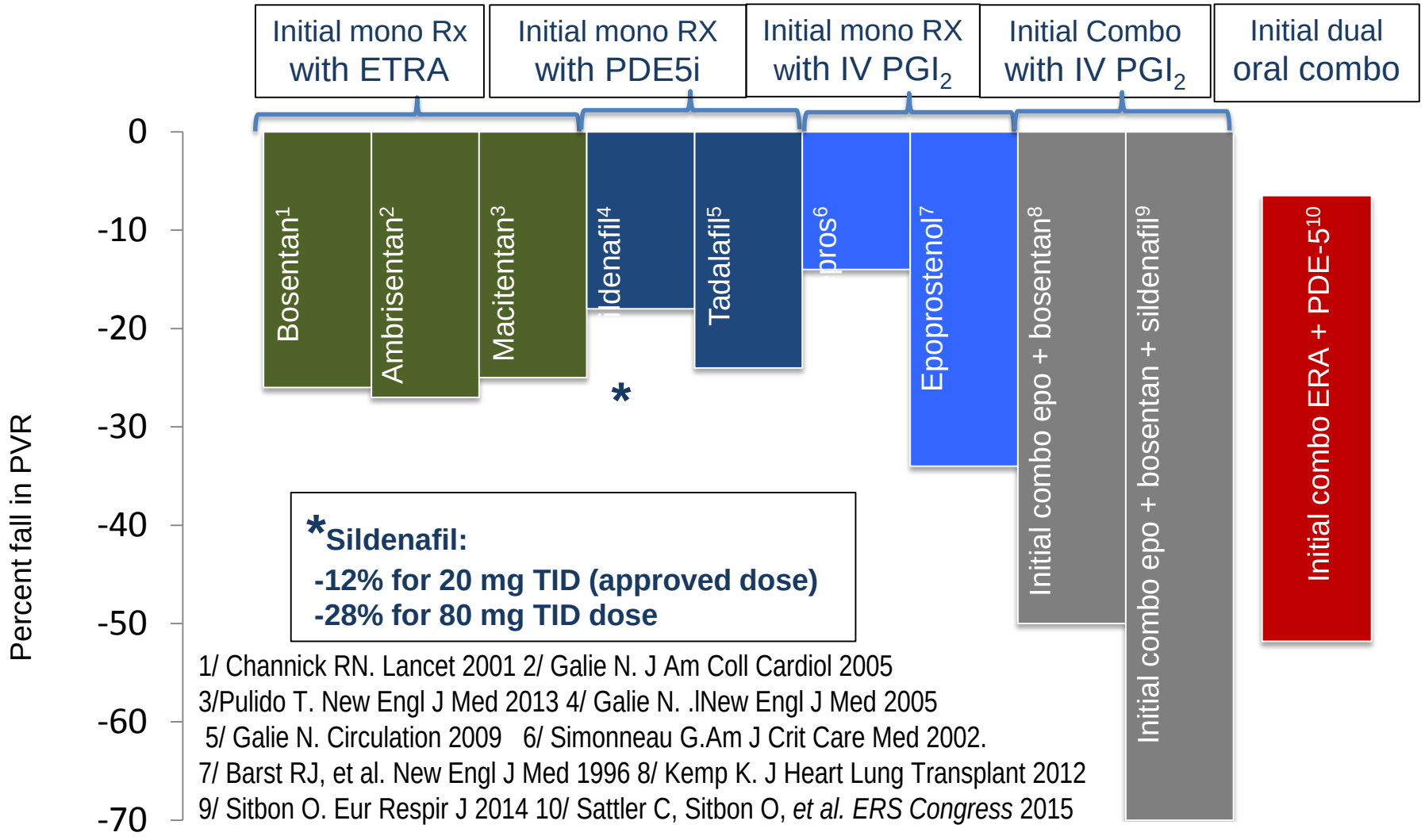
	BOS+PDE5-i (n=78)	AMB+PDE5-i (n=19)	SIL+ERA (n=69)	TAD+ERA (n=28)
Moy ± SD	**-44%** ± 20%	**-42%** ± 21%	**-41%** ± 20%	**-49%** ± 19%
95%CI	[-48%; -39%]	[-51%; -32%]	[-45% ;-36%]	[-56%; -42%]

**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)

Sitbon O, *et al. Eur Respir J* 2016; Epub on 17 March.

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

RESPITE study: Riociguat in patients with PAH and an inadequate response to PDE5i

Interim analysis (ATS presentation in May 2016)

Marius M Hoeper, Paul A Corris, James R Klinger, David Langleben, Robert Naeije, Gérald Simonneau, Christian Meier, Dennis Busse, Pablo Colorado, Raymond L Benza.

Hoeper MM, et al. Poster presented at ATS 2016, San Francisco, CA, USA.

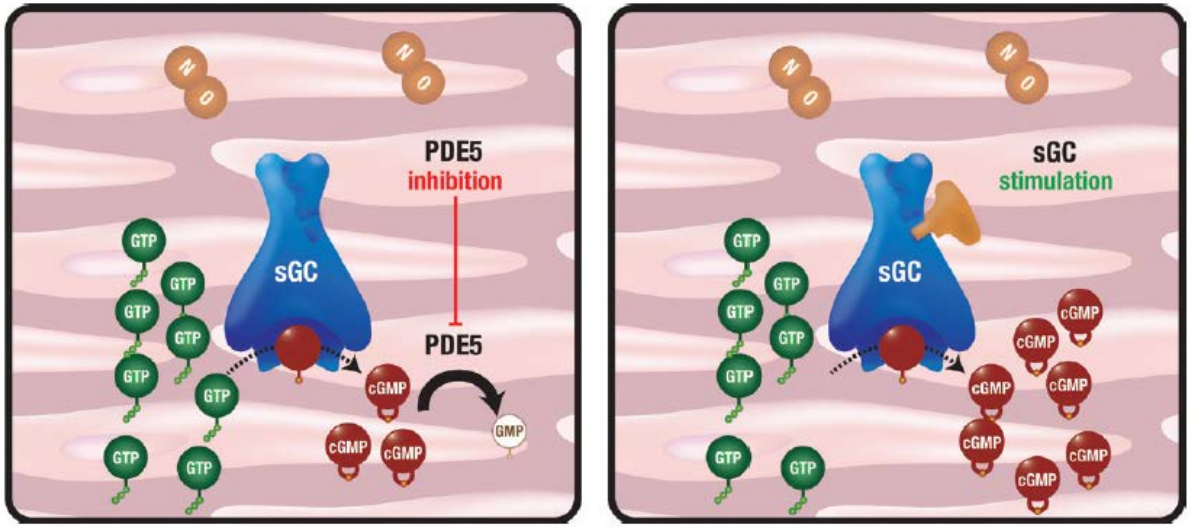
RESPITE study: Clinical implications

- Preliminary data from the interim analysis of RESPITE (n=30) support the hypothesis that patients with PAH who have an insufficient response to PDE5i therapy may benefit from a transition to riociguat
- Transition to riociguat is an option that could be favourable to both PAH patients who have an insufficient response to PDE5i therapy and physicians, rather than increasing treatment burden with combination therapy
- The efficacy of riociguat treatment in patients who have previously failed to respond to PDE5i therapy supports preclinical data that suggest that riociguat has a different mode of action to PDE5is

Hoeper MM, et al. Poster presented at ATS 2016, San Francisco, CA, USA.
Hoeper MM, et al. Am J Respir Crit Care Med 2016;193:A6315.
6MWD: 6-minute walking distance; NT-proBNP: NT-proBNP, *N*-terminal prohormone of brain natriuretic peptide; PAH: pulmonary arterial hypertension; PDE5i: phosphodiesterase type 5 inhibitors; WHO FC: World Health Organization functional class.

RESPITE study: Background and objectives

- A significant proportion (20–60%) of patients with PAH do not reach treatment goals with PDE5is[1,2]



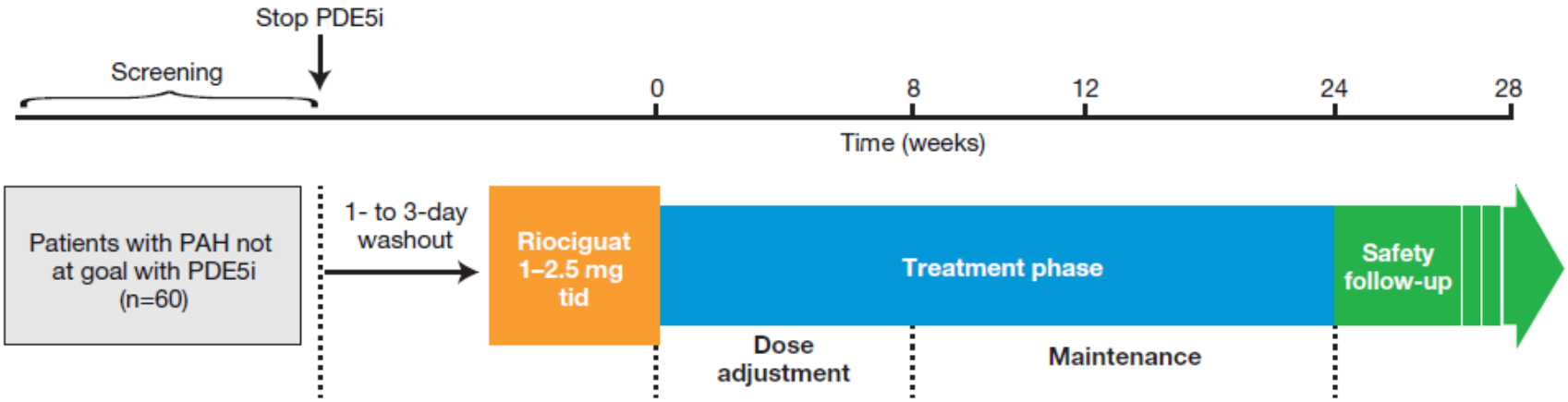
- The RESPITE study was designed to investigate whether it is safe, feasible, and beneficial to replace PDE5i therapies with riociguat in patients with PAH who have an inadequate response to PDE5i[3,4]

1. Chockalingam A, et al. Int J Cardiol 2005;99:91–95.
2. Leuchte HH, et al. Chest 2004;125:580–586.
3. Hoeper MM, et al. Poster presented at ATS 2016, San Francisco, CA, USA.
4. Hoeper MM, et al. Am JH Respir Crit Care Med 2016;193:A6315.

cGMP: cyclic guanosine monophosphate; GTP: guanosine triphosphate; NO: nitric oxide; PAH: pulmonary arterial hypertension; PDE5: phosphodiesterase type 5; sGC: soluble guanylate cyclase.

Design of the RESPITE study

- Open-label, multicenter, uncontrolled Phase IIIb pilot study



Not at goal on PDE5i defined as:

- WHO FC III
- 6MWD 165–440 m
- Cardiac index <3.0 L/min/m^2
- mPAP >30 mmHg
- PVR >400 dyn·s·cm^{-5}

Hoeper MM, et al. Poster presented at ATS 2016, San Francisco, CA, USA.
Hoeper MM, et al. Am J Respir Crit Care Med 2016;193:A6315.
mPAP: mean pulmonary arterial pressure; PVR: pulmonary vascular resistance; tid: three times daily.

Demographics at baseline

Parameter	Riociguat up to 2.5 mg tid (n=30)
Female, n (%)	22 (73)
Caucasian, n (%)	28 (93)
Mean age, years (SD)	58 (13)
Mean BMI, kg/m^2 (SD)	28.0 (5)
Dana Point classification of PH, n (%) 1.1 idiopathic PAH 1.3 Toxin induced 1.4 APAH congenital heart disease	 27 (90) 1 (3) 2 (7)
Pretreated with ERA, n (%)	22 (73)
Pretreated with sildenafil, n (%)	21 (70)
Pretreated with tadalafil, n (%)	9 (30)
Mean time since first PH diagnosis, years (SD)	4 (4)
Mean 6MWD, m (SD)	353 (78)
WHO FC III, n (%)	30 (100)
NT-proBNP, pg/mL [screening NT-proBNP, pg/mL]*	2208 (2961) [1564 (2179)]
eGFR, mL/min/1.73 m^2	71 (20)

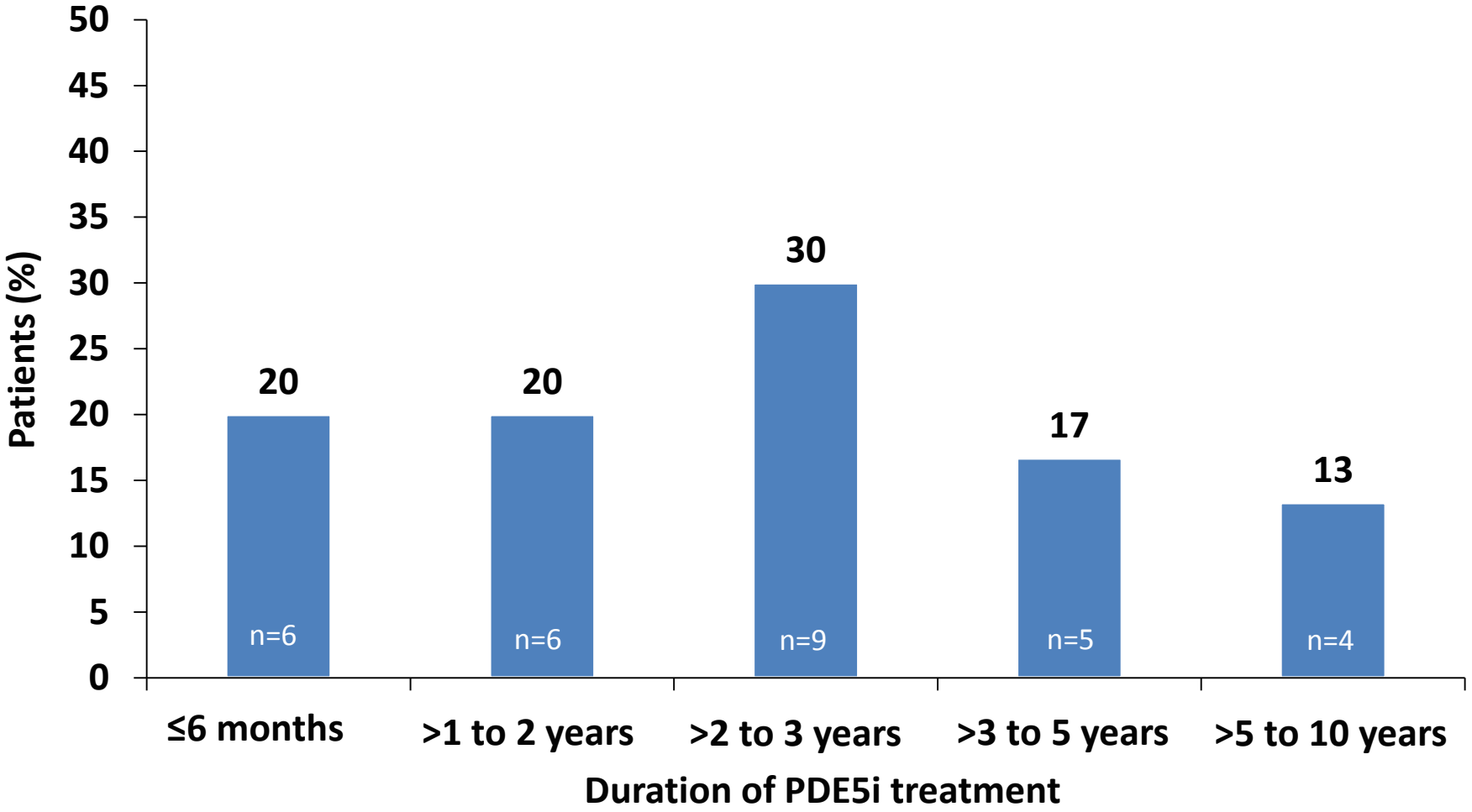
*n=29; Baseline = the last documented value before start of riociguat treatment (from screening or Week 0; hemodynamics from screening only).

Hoeper MM, et al. Poster presented at ATS 2016, San Francisco, CA, USA.

Hoeper MM, et al. Am J Respir Crit Care Med 2016;193:A6315.

BMI: body mass index; eGFR: estimated glomerular filtration rate; ERA: endothelin receptor antagonist; PH: pulmonary hypertension; SD: standard deviation.

Duration of prior PDE5i treatment



Hoeper MM, et al. Poster presented at ATS 2016, San Francisco, CA, USA.

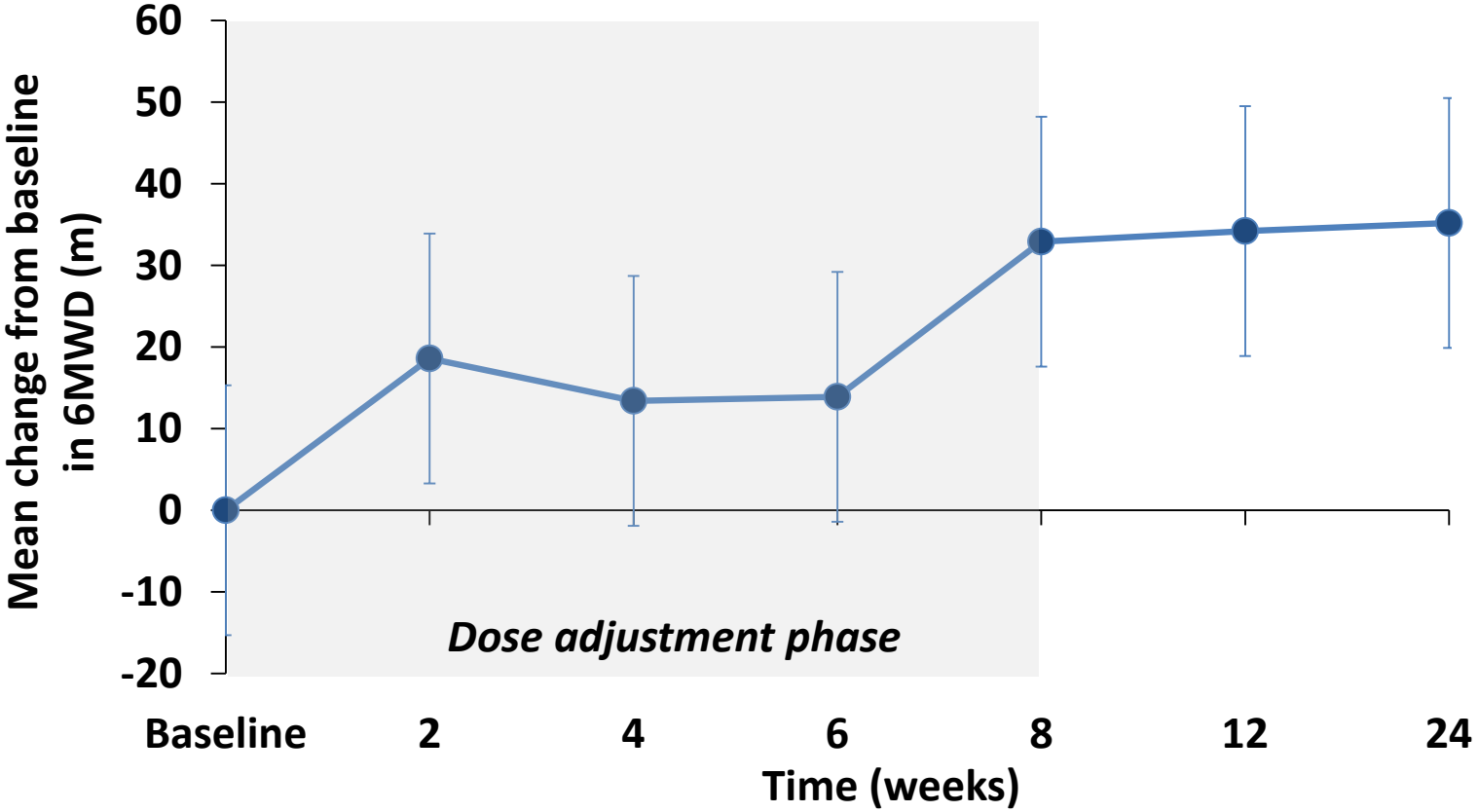
Clinical worsening

	Study day	Event, n (%)
Patients with clinical worsening[a]		**4 (13)**
Death	Days 27 and 49	2 (7)[b]
Persistent worsening in 6MWD due to PH[c]	Day 31	1 (3)
Start of new PAH-specific treatment	Days 59 and 170	2 (7)

[a]Patients could experience more than one event.
[b]An additional death occurred in the extended drug supply phase.
[c]Persistent decrease of 15% from baseline or 30% compared with the last study-related measurement.
One of the two patients who started a new PAH-specific treatment also experienced persistent worsening of 6MWD due to PAH. Clinical worsening is defined as death (all-cause mortality), atrial septostomy, lung transplantation, non-planned PAH-related hospitalization, start of new PAH-specific treatment (ERA, inhaled or oral prostanoid) or modification of pre-existing treatment, initiation of intravenous or subcutaneous prostanoids, persistent decrease of >15% from baseline or >30% from last measurement in 6MWD, persistent worsening of FC, or appearance or worsening of signs/symptoms of right heart failure that do not respond to optimized oral diuretic therapy.

Hoeper MM, et al. Poster presented at ATS 2016, San Francisco, CA, USA.
Hoeper MM, et al. Am J Respir Crit Care Med 2016;193:A6315.

6MWD: Change from baseline over time

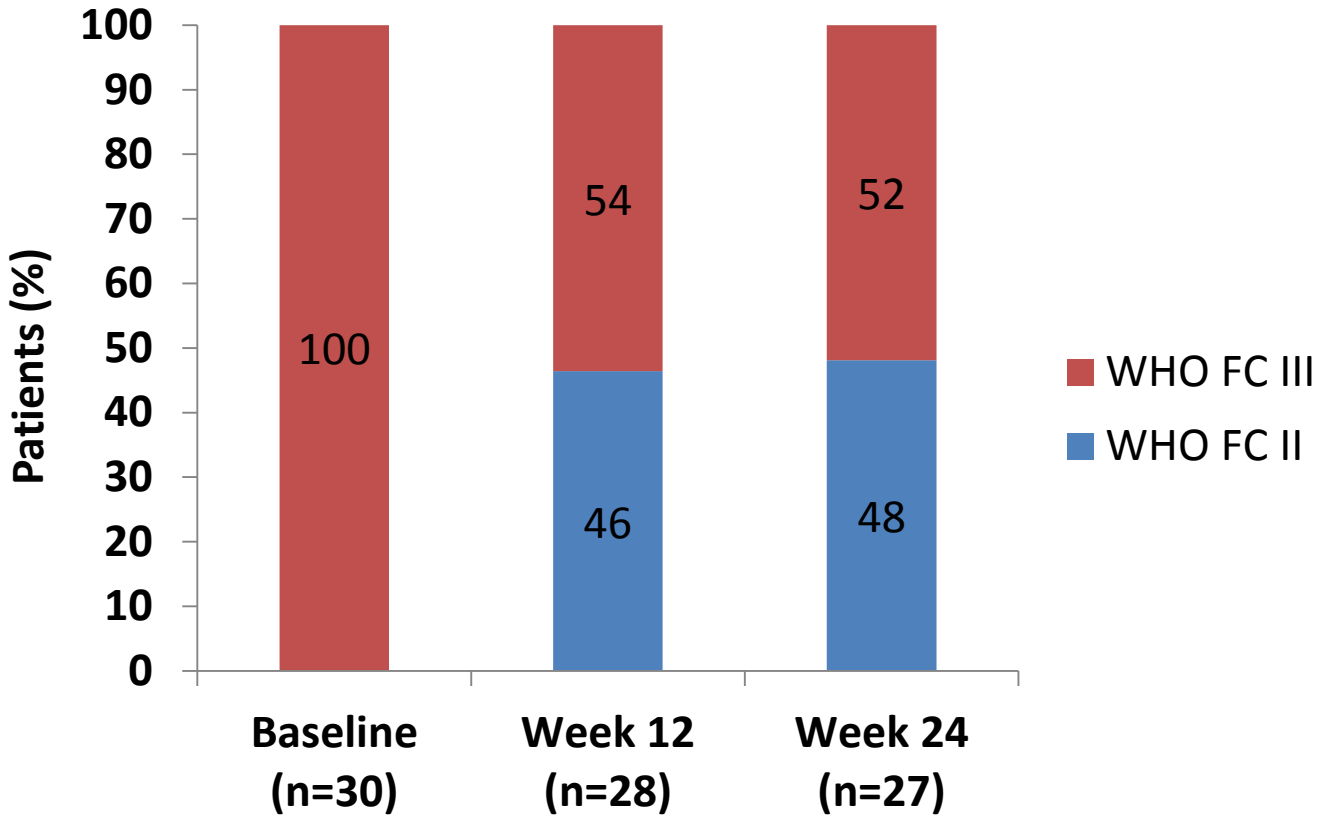


	Baseline	2	4	6	8	12	24
No. of patients	30	20	25	17	27	26	26
Mean absolute values (m)	353	386	377	373	385	386	386

Data are mean ± standard error of the mean. Baseline = the last documented value before start of riociguat treatment (Week 0 [post-washout] values; in cases where Week 0 values were not available, the screening value was used).

Hoeper MM, et al. Poster presented at ATS 2016, San Francisco, CA, USA.

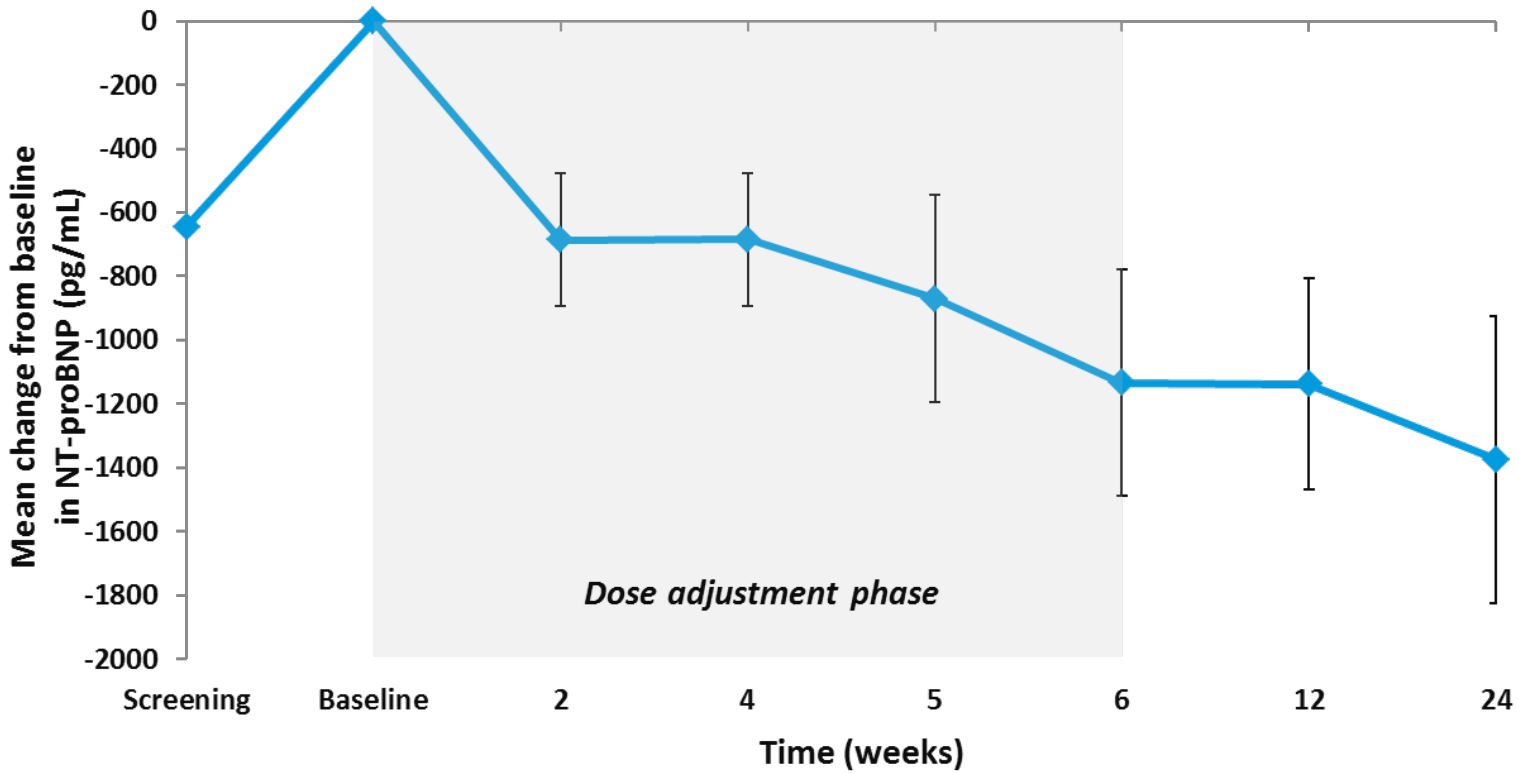
WHO FC: Change from baseline at Weeks 12 and 24



Baseline = the last documented value before start of riociguat treatment (Week 0 [post-washout] values; in cases where Week 0 values were not available, the screening value was used).

Hoeper MM, et al. Poster presented at ATS 2016, San Francisco, CA, USA.

NT-proBNP: Change from baseline over time



	Screening	Baseline	2	4	5	6	12	24
No. of patients	29	30	30	29	29	28	28	27
Mean absolute values (pg/mL)	1564	2208	1523	1456	1270	1067	1063	803

Screening = patients still receiving PDE5is. Baseline = the last documented value before start of riociguat treatment (Week 0 [post-washout] values; in cases where Week 0 values were not available, the screening value was used).

Hoeper MM, et al. Poster presented at ATS 2016, San Francisco, CA, USA.

Change from baseline to Week 24 in hemodynamics and clinical efficacy endpoints in RESPITE

Parameter	n	Baseline	n	Week 24	Change from baseline to Week 24
PVR, dyn·s·cm^{-5}	27	858 (276)	26	770 (456)	–93 (336)
Cardiac output, L/min	27	4.0 (0.7)	26	4.7 (1.1)	+0.6 (1.0)
Cardiac index, L/min/m^2	27	2.2 (0.3)	26	2.6 (0.6)	+0.4 (0.6)
mPAP, mmHg	27	52 (11)	26	50 (14)	–2.7 (8.9)
RAP, mmHg	27	9.9 (4.9)	26	8.2 (5.3)	–1.9 (4.1)
SvO_2	24	62.7 (6.6)	25	64.4 (8.2)	+2.1 (7.0)
NT-proBNP	30	2208 (2961)	27	803 (1048)	–1375 (2344)
6MWD	30	353 (78)	26	386 (114)	+35 (78)

Baseline = the last documented value before start of riociguat treatment (from screening or Week 0; hemodynamics from screening only).
Hoeper MM, et al. Poster presented at ATS 2016, San Francisco, CA, USA.
RAP: right atrial pressure; SvO_2: mixed venous oxygen saturation.

Adverse events

AE, n (%)	Riociguat up to 2.5 mg tid (n=30)
Most frequently reported AEs (>10% of patients)	
Dyspepsia	7 (23)
Right ventricular failure	5 (17)
Nasopharyngitis	5 (17)
Headache	5 (17)
Diarrhea	4 (13)
Vomiting	4 (13)
Dizziness	4 (13)
Epistaxis	4 (13)
Hypotension	4 (13)
AEs of special interest	
Hypotension	4 (13)
Hemoptysis	0 (0)

- Overall incidence of treatment-emergent adverse events: 93%

Hoeper MM, et al. Poster presented at ATS 2016, San Francisco, CA, USA.
AE: adverse event.

Study drug-related and serious adverse events

AE, n (%)	Riociguat up to 2.5 mg tid (n=30)
Study drug-related[a] AEs in ≥10% of patients	
Headache	5 (17)
Dyspepsia	4 (13)
Epistaxis	4 (13)
Dizziness	3 (10)
SAEs	
Any	5 (17)
Right ventricular failure[b]	1 (3)
Dyspepsia	1 (3)
Pneumonia	1 (3)
Subdural hematoma	1 (3)
Depression	1 (3)
Hypotension[b]	1 (3)
Deaths (main study phase – 24 weeks)	
Any[c]	2 (7)
Pneumonia	1 (3)
Subdural hematoma	1 (3)

[a]As judged by the investigator. [b]Events occurred in the same patient. [c]One additional death occurred during the long-term extension.

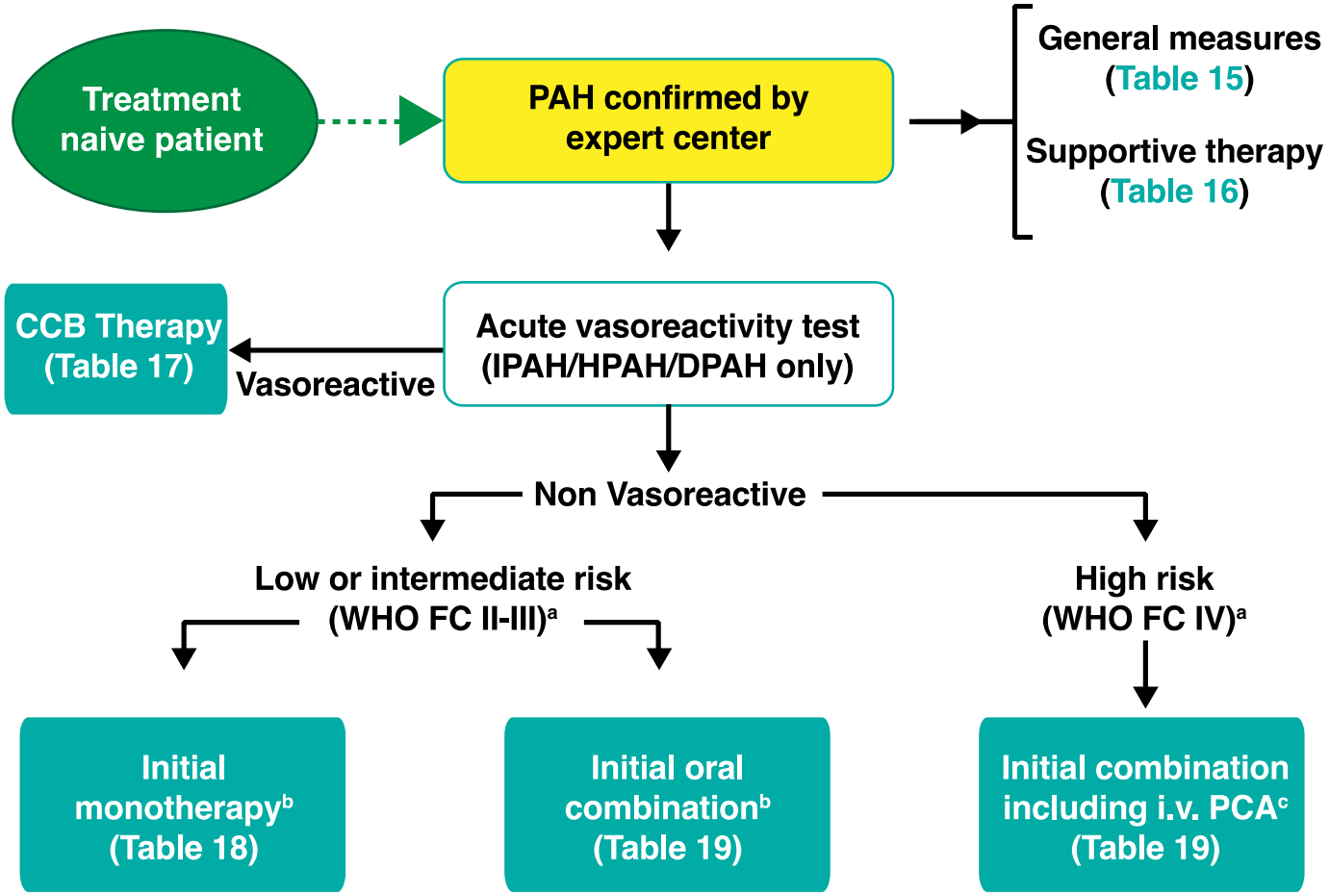
Hoeper MM, et al. Poster presented at ATS 2016, San Francisco, CA, USA.
Hoeper MM, et al. Am J Respir Crit Care Med 2016;193:A6315.

Conclusions

- In this interim analysis of RESPITE, riociguat improved 6MWD, hemodynamics, NT-proBNP, and WHO FC in patients, who had an insufficient response to PDE5is
- Transition to riociguat was well tolerated with no new safety signals observed
- Randomized controlled trials are required to investigate this approach further

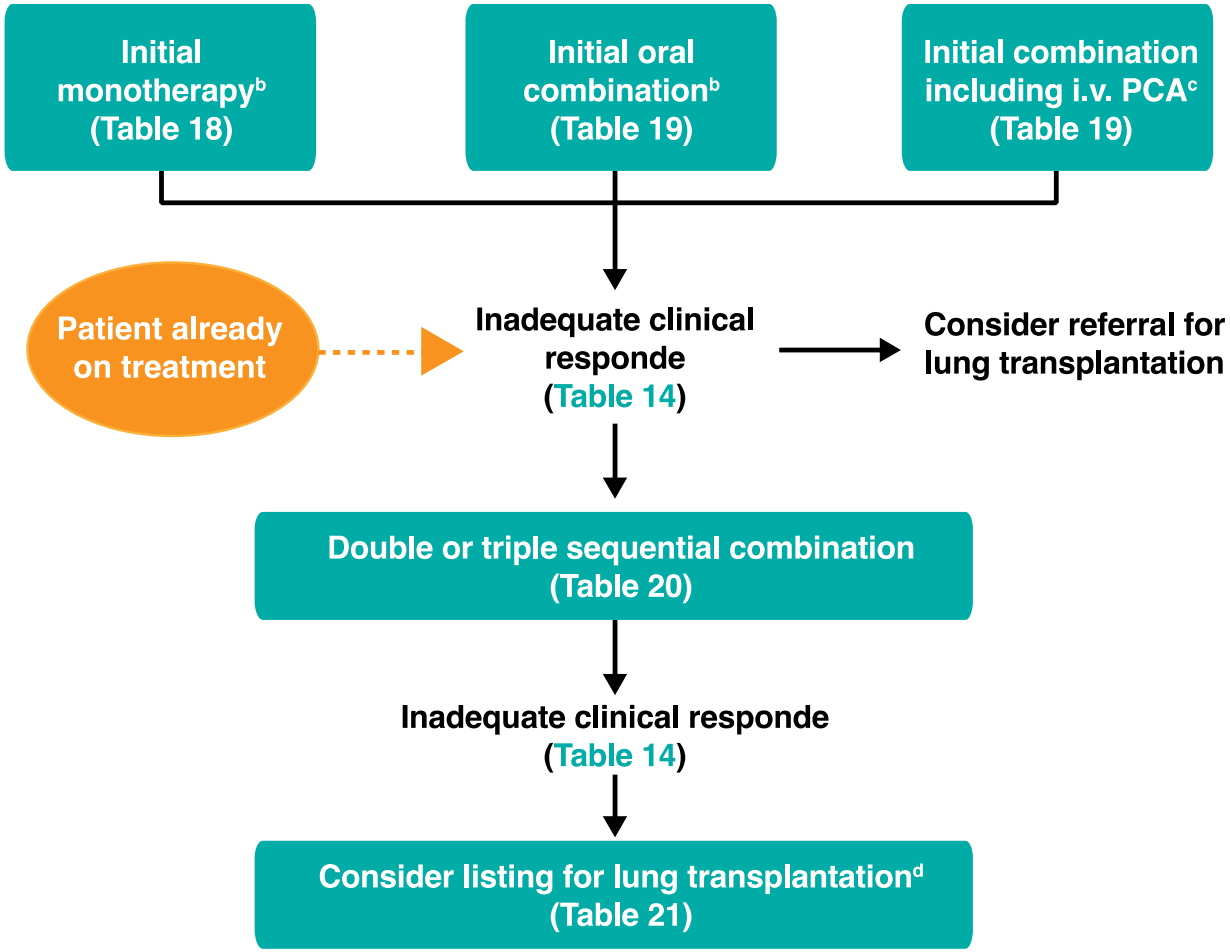
Hoeper MM, et al. Poster presented at ATS 2016, San Francisco, CA, USA.
Hoeper MM, et al. Am J Respir Crit Care Med 2016;193:A6315.

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.