



Up date sul trattamento dell'Ipertensione polmonare

**Congresso Sezione
Regionale AIPO Toscana**

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Conflict of interests disclosures

Actelion

Boehringer Ingelheim

InterMune

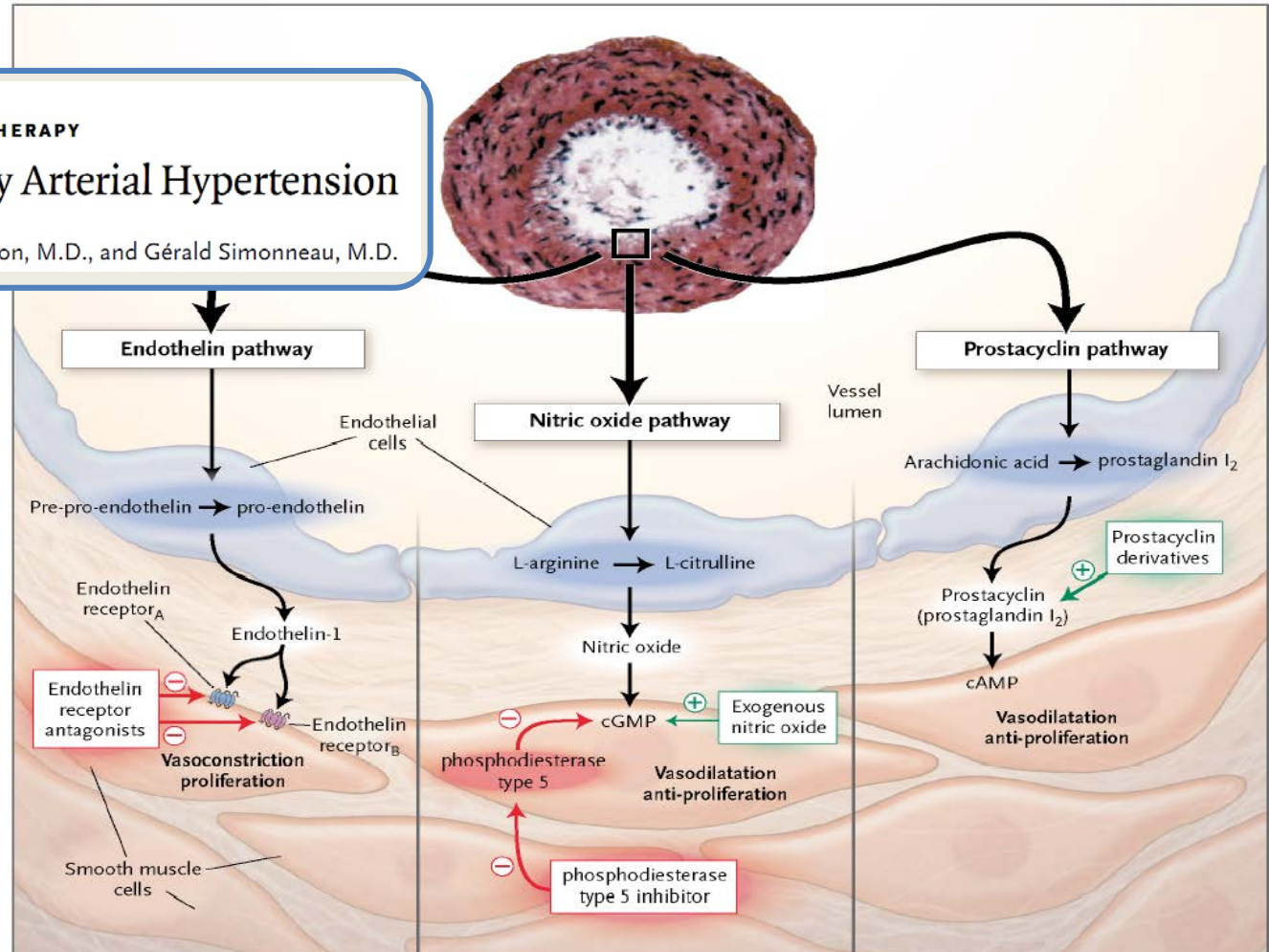
Roche

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 G rard Simonneau, M.D.



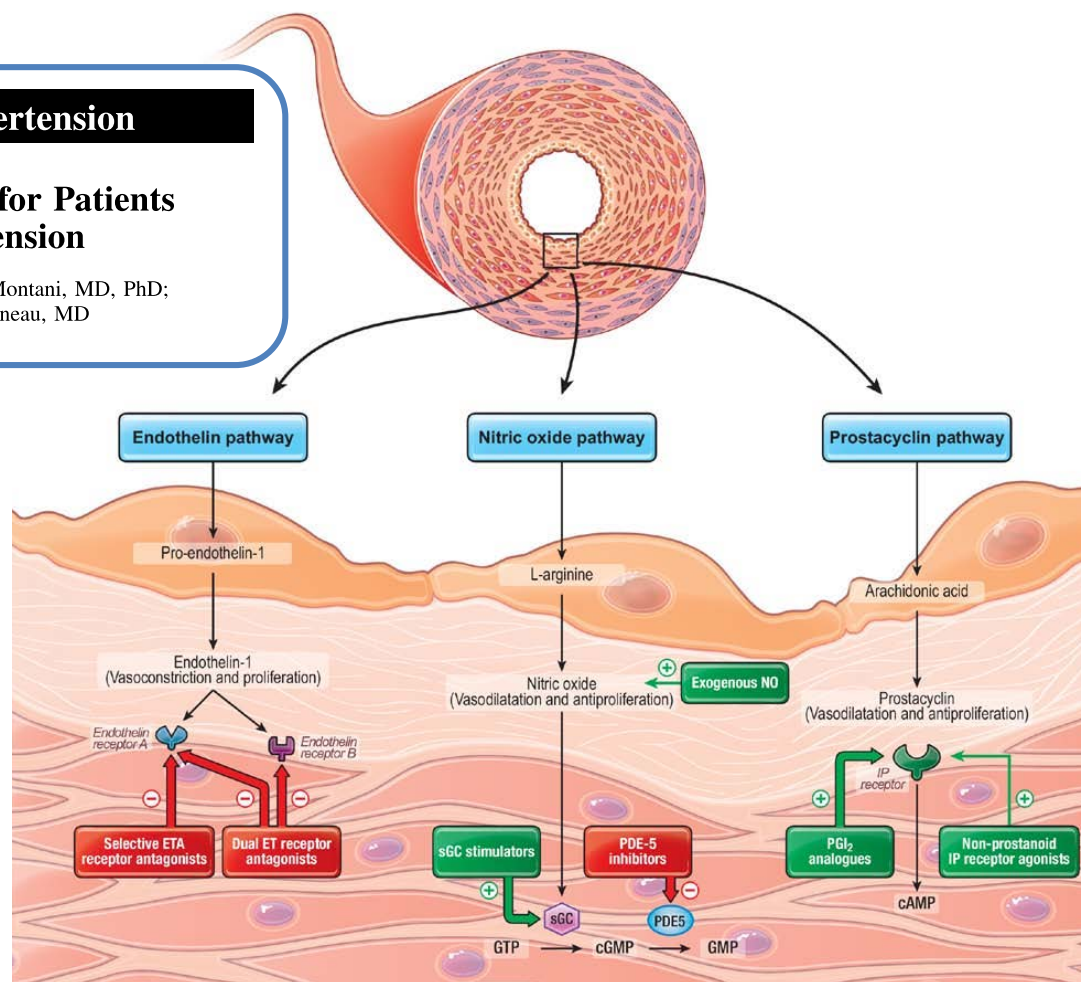
cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate.

Targeting 3 major dysfunctional pathways in PAH (2014)

Recent Advances in Pulmonary Hypertension

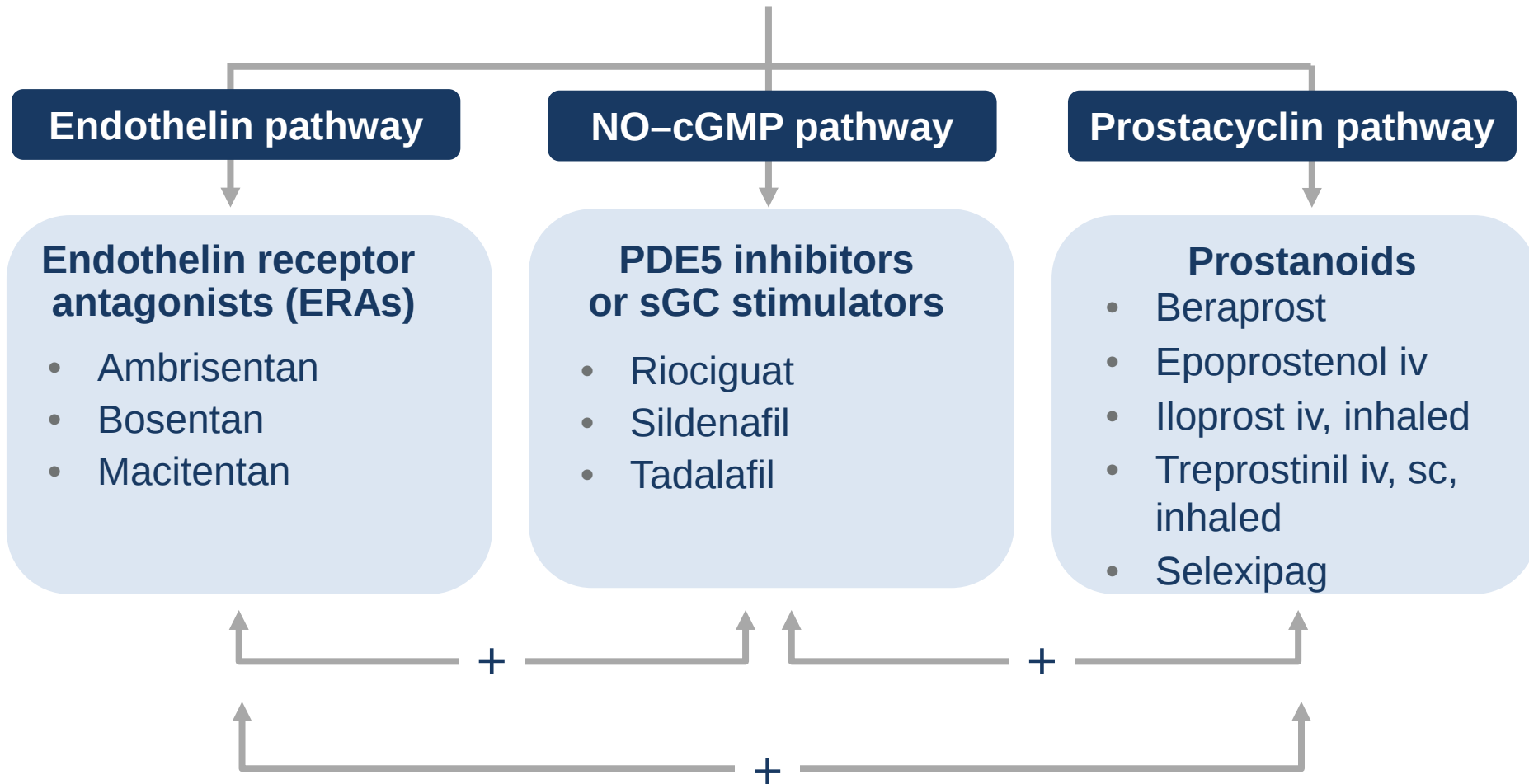
Advances in Therapeutic Interventions for Patients With Pulmonary Arterial Hypertension

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



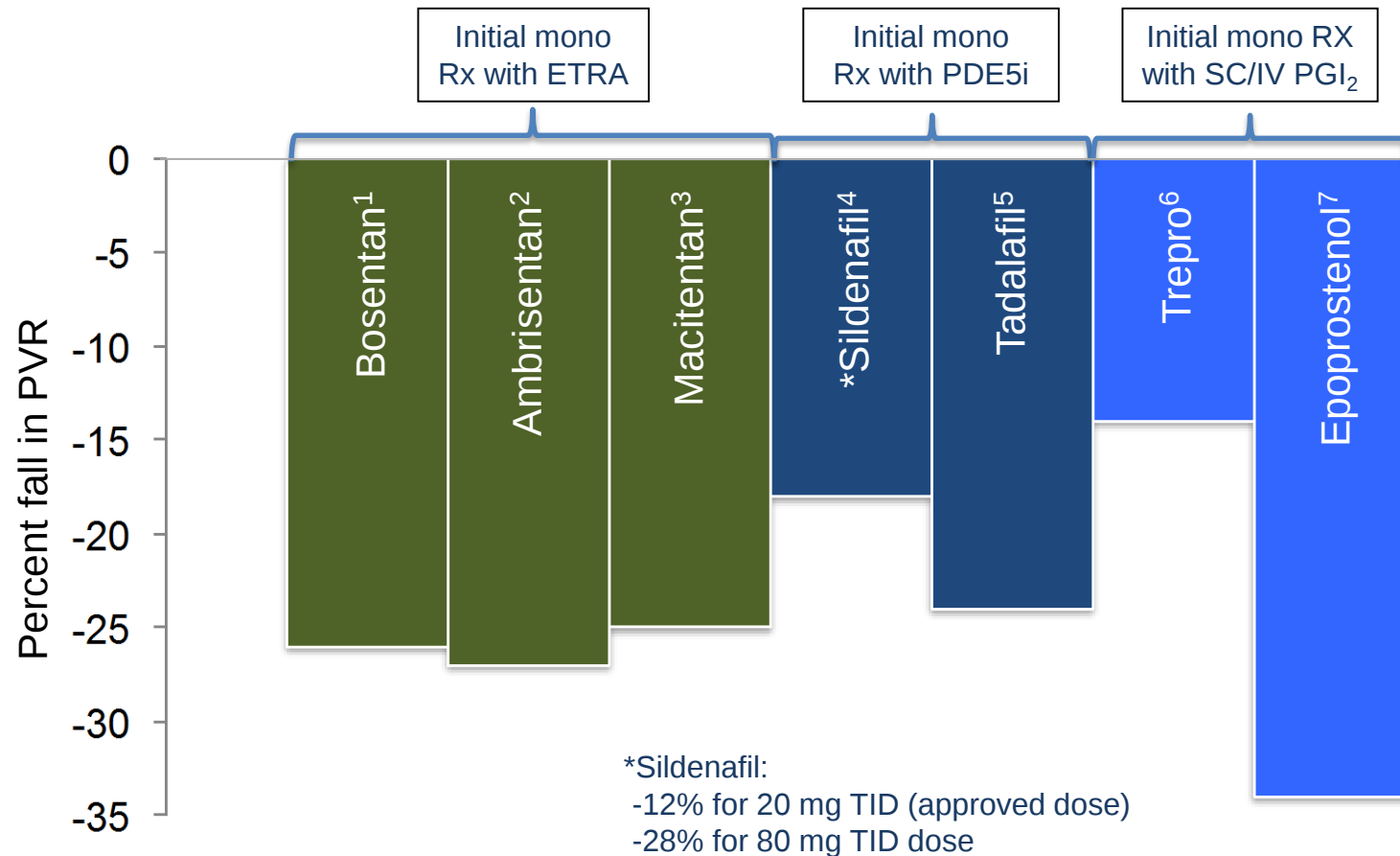
cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; ET, endothelin; ETA, endothelin receptor A; GTP, guanosine triphosphate; NO, nitric oxide; PGI₂, prostaglandin I₂; sGC, soluble guanylate cyclase.

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

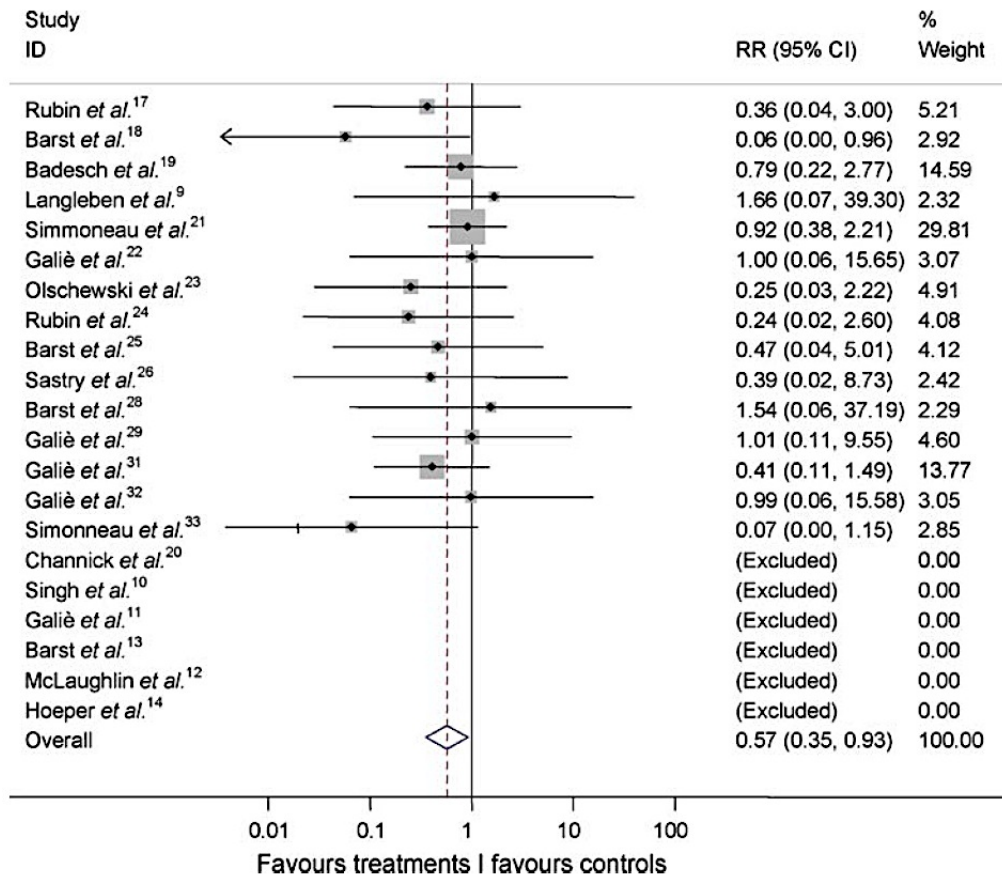


1. Channick RN. *Lancet* 2001; 2. Galie N. *J Am Coll Cardiol* 2005; 3. Pulido T. *N Engl J Med* 2013; 4. Galie N. *N Engl J Med* 2005; 5. Galie N. *Circulation* 2009; 6. Simonneau G. *Am J Respir Crit Care Med* 2002; 7. Barst RJ. *N Engl J Med* 1996.

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



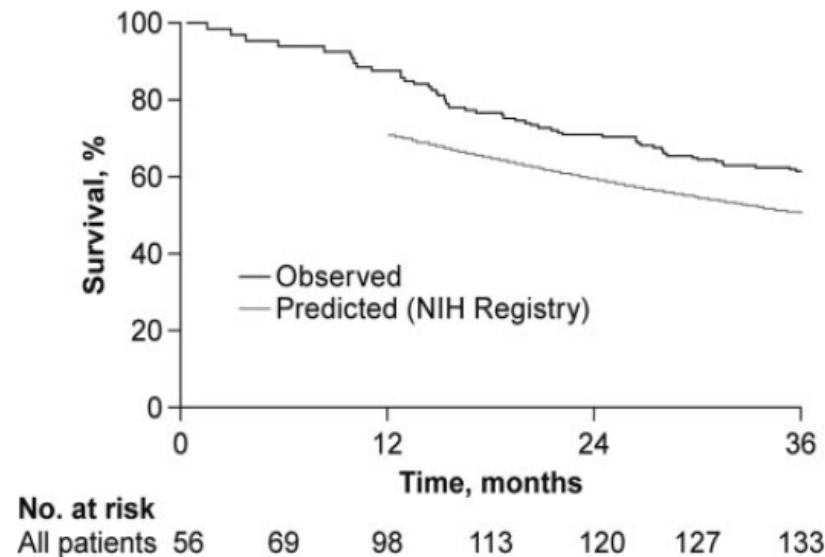
- 23 RCTs
- Average duration 14.3 wks
- 3140 patients
- All-cause mortality rate in the control group = 3.8%
- Active treatments:
 - 43% reduction in mortality
 - RR 0.57 (95%CI 0.35–0.92)
 - P = 0.023

Unmet need in the modern management era

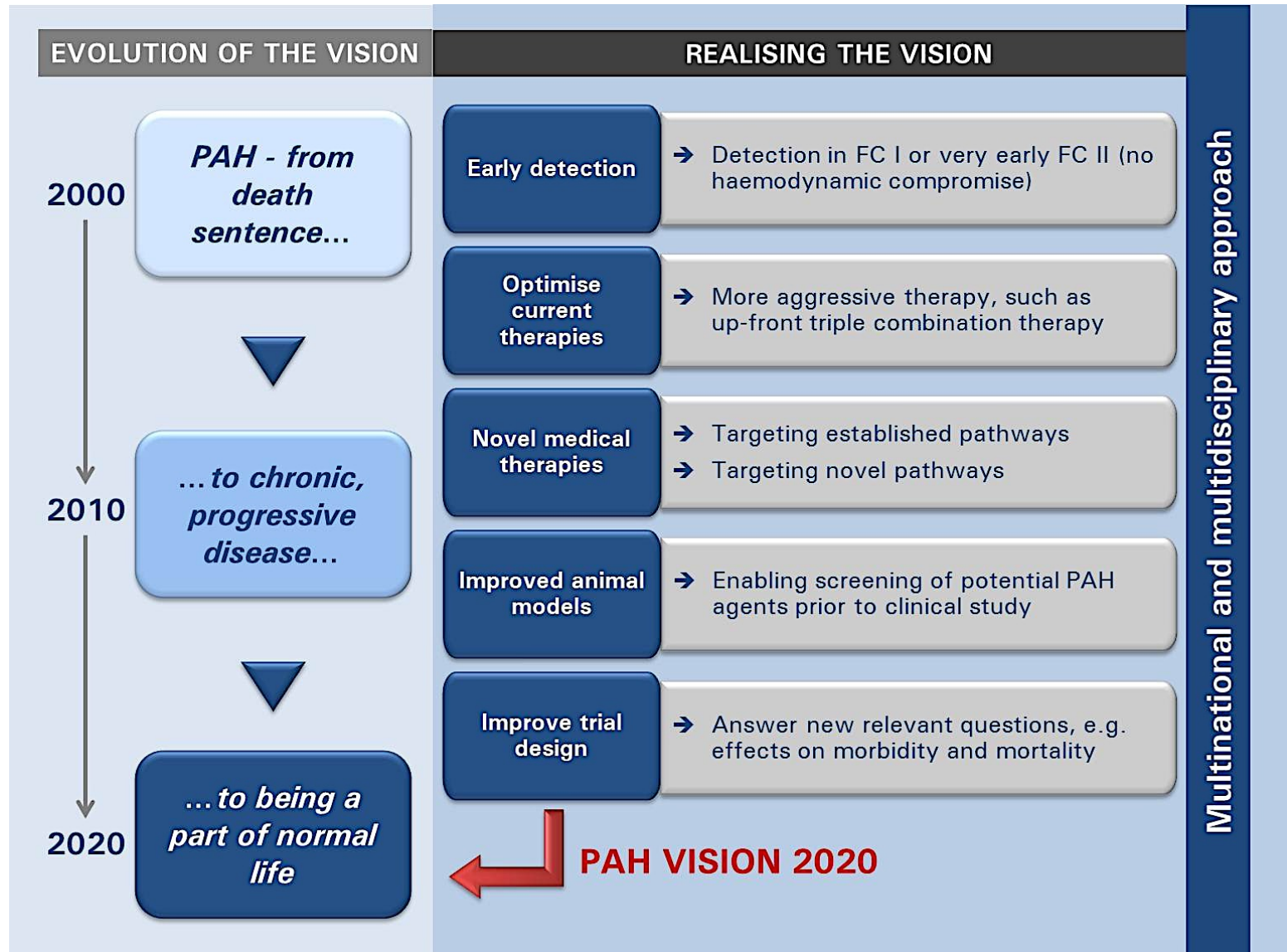
Despite drug discovery and development PAH remains a devastating condition

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

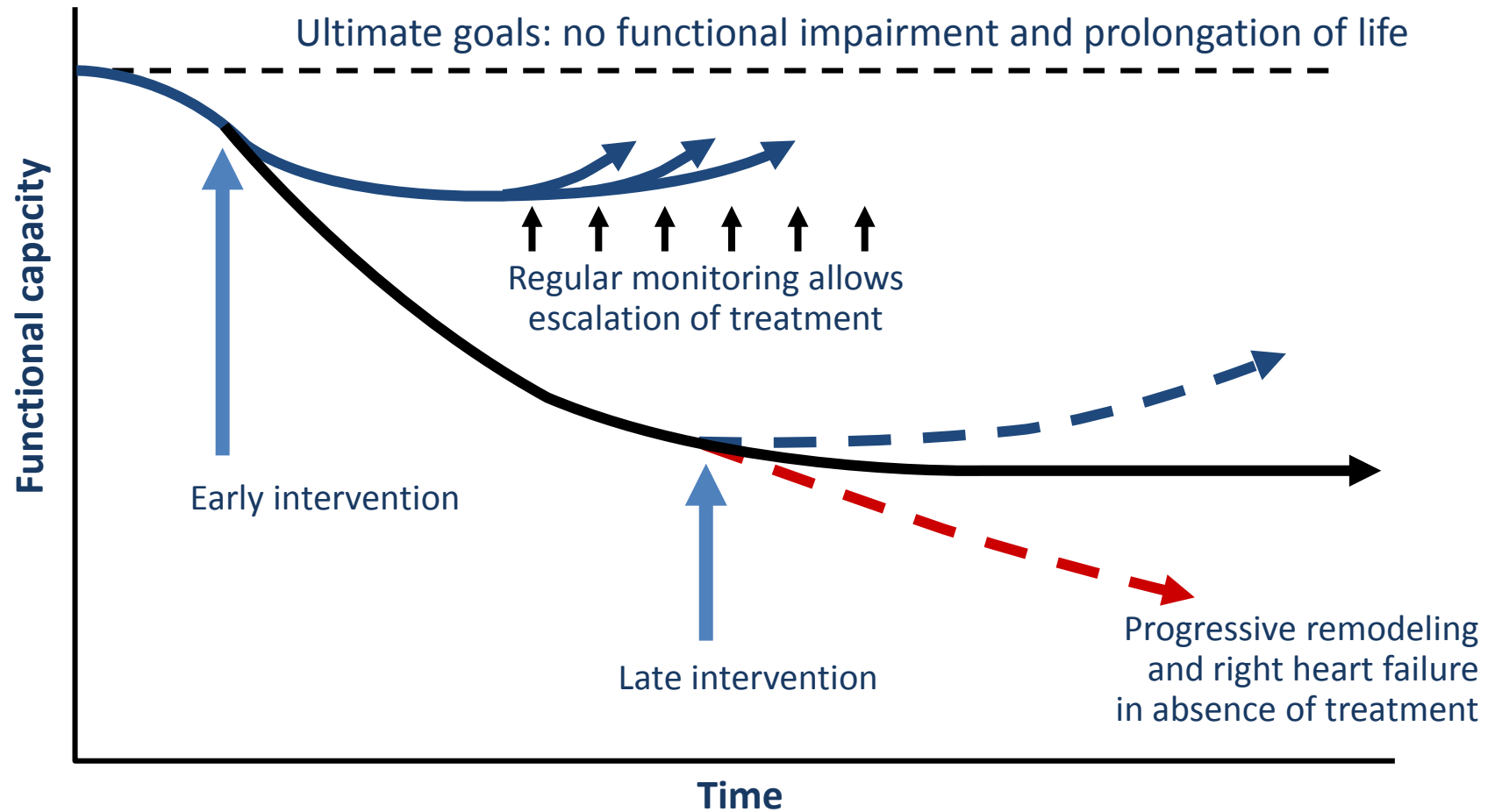
Marc Humbert, MD, PhD; Olivier Sitbon, MD, PhD; Ari Chaouat, MD, PhD; Michèle Bertocchi, MD; Gilbert Habib, MD; Virginie Gressin, MD; Azzedine Yaïci, MD; Emmanuel Weitzenblum, MD; Jean-François Cordier, MD; François Chabot, MD, PhD; Claire Dromer, MD; Christophe Pison, MD, PhD; Martine Reynaud-Gaubert,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



PAH management: How to do better?



Early treatment of PAH



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,¶
Massimiliano 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/m²)

6-min walk distance

>380 to 440 m; may not be aggressive enough in young individuals

Cardiopulmonary exercise testing

Peak VO₂ >15 ml/min/kg and EqCO₂ <45 l/min/l/min

B-type natriuretic peptide level

Normal

CI, cardiac index; CMR, cardiovascular magnetic resonance; EqCO₂, breathing equivalent for CO₂;
RAP, right atrial pressure; RV, right ventricle; VO₂, 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...

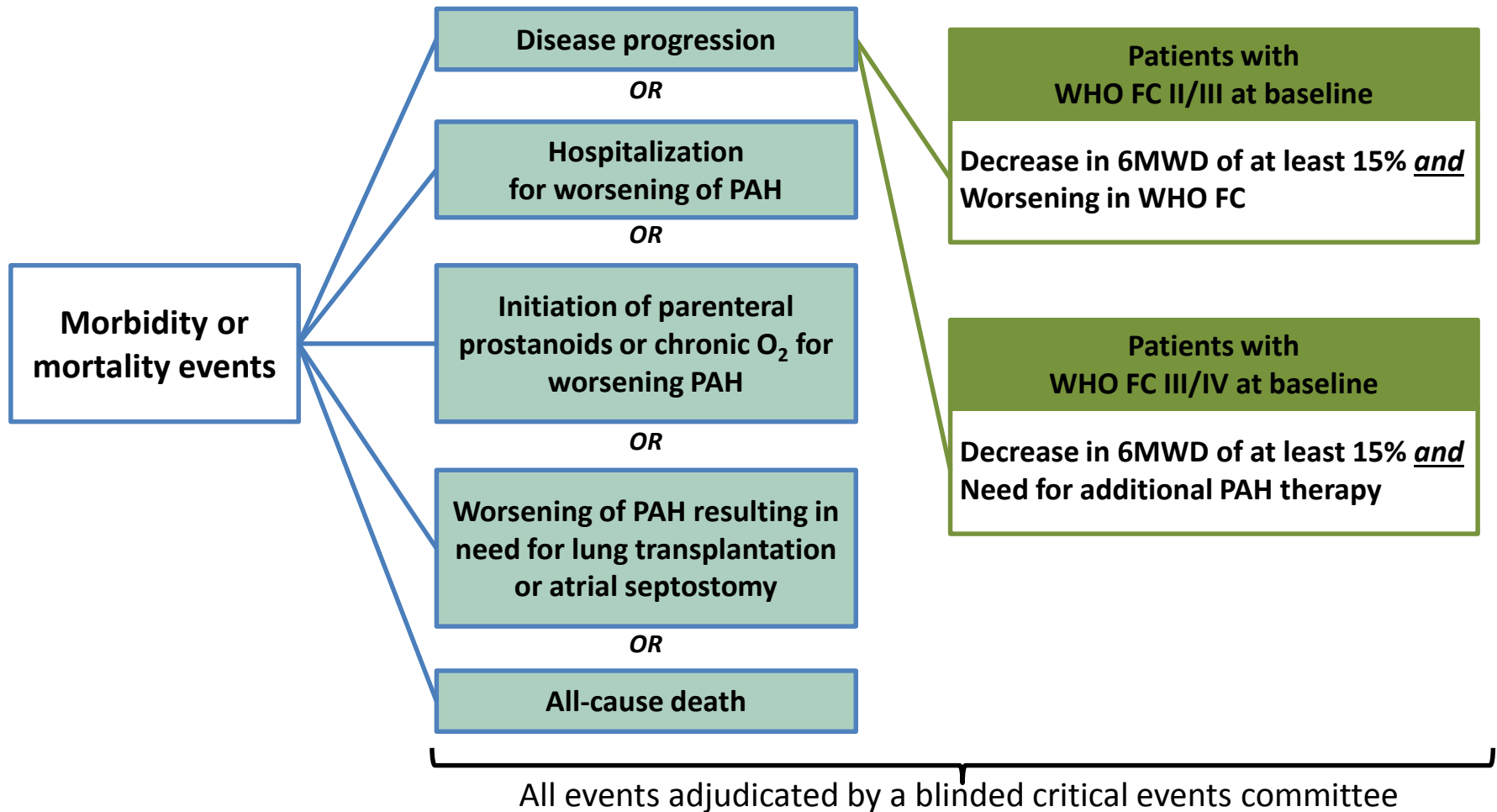
Drug tested	Study	Background	N	Duration (weeks)	Primary endpoint
Bosentan	EARLY	None or sildenafil (16%)	185	24	PVR +, Δ 6MWD (NS)
Bosentan	COMPASS-2	Sildenafil	334	92	Morbi-mortality (NS)
Iloprost	STEP	Bosentan	67	12	Δ 6MWD (NS)
Iloprost	COMBI	Bosentan	40	12	Δ 6MWD (NS)
Imatinib	Phase II	Bosentan &/or sildenafil &/or prostanoids	59	24	Δ 6MWD (NS)
Imatinib	IMPRES	Bosentan &/or sildenafil &/or prostanoids	202	24	Δ 6MWD +
Selexipag	Phase II	Bosentan &/or sildenafil	43	17	PVR +
Sildenafil	PACES	Epoprostenol	264	16	Δ 6MWD +
Sildenafil	NCT00323297	Bosentan	104	12	Δ 6MWD (NS)
Tadalafil	PHIRST	None or bosentan (54%)	405	16	Δ 6MWD (NS)
Trepstinil	Inhaled- TRIUMPH	Bosentan or sildenafil	235	12	Δ 6MWD +
Trepstinil	Oral- FREEDOM C1	Bosentan &/or sildenafil	354	16	Δ 6MWD (NS)
Trepstinil	Oral- FREEDOM C2	Bosentan &/or sildenafil	310	16	Δ 6MWD (NS)

Sequential combination therapy:

Recent studies

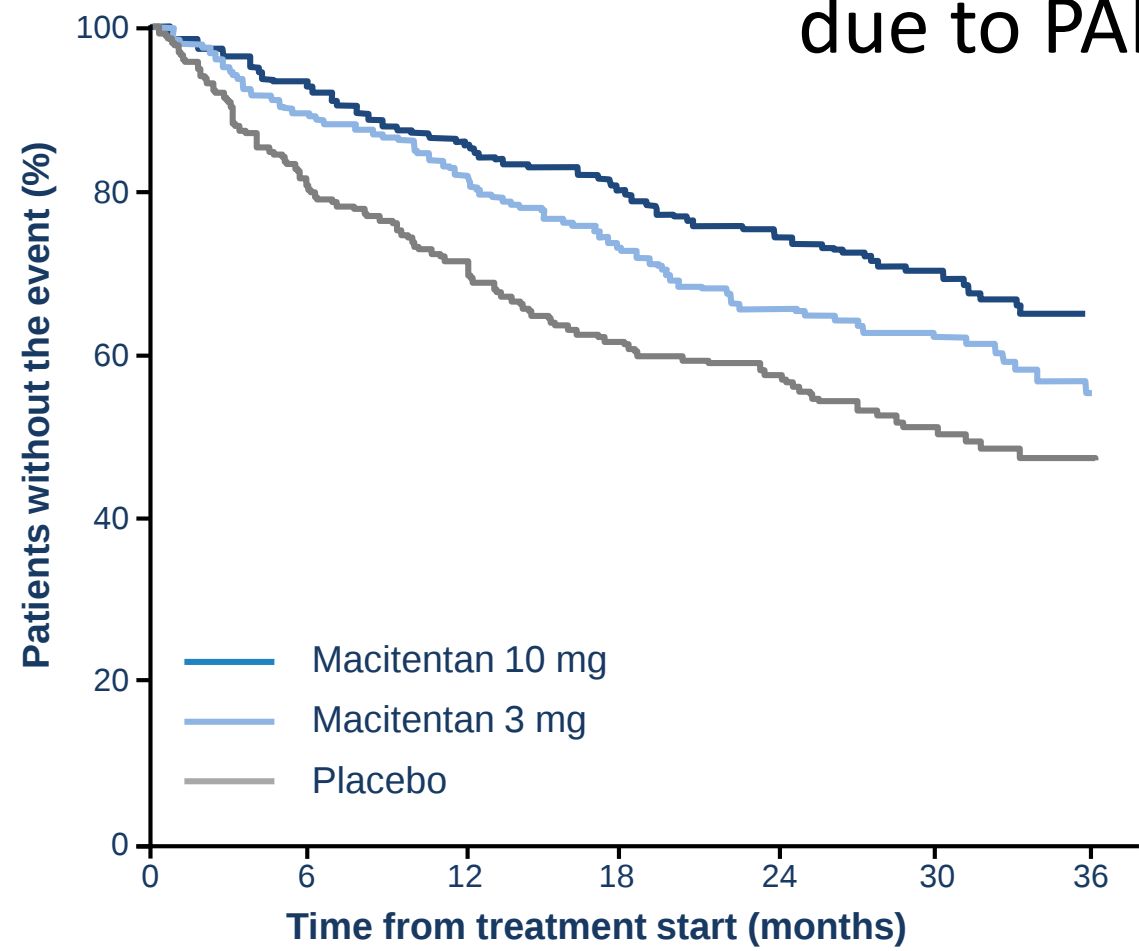
Drug tested	Study	Background	N	Duration (weeks)	Primary endpoint
Riociguat	PATENT	None (50%), bosentan or prostanoids	443	12	Δ 6MWD +
Macitentan	SERAPHIN	None (36%), PDE5i (61%) or oral/inhaled prostanoids	742	$\approx$ 100	Time to first event of death or morbidity +
Selexipag	GRIPHON	None (21%), ERA (13%), PDE5i (32%) or both (34%)	1156	$\approx$ 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

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

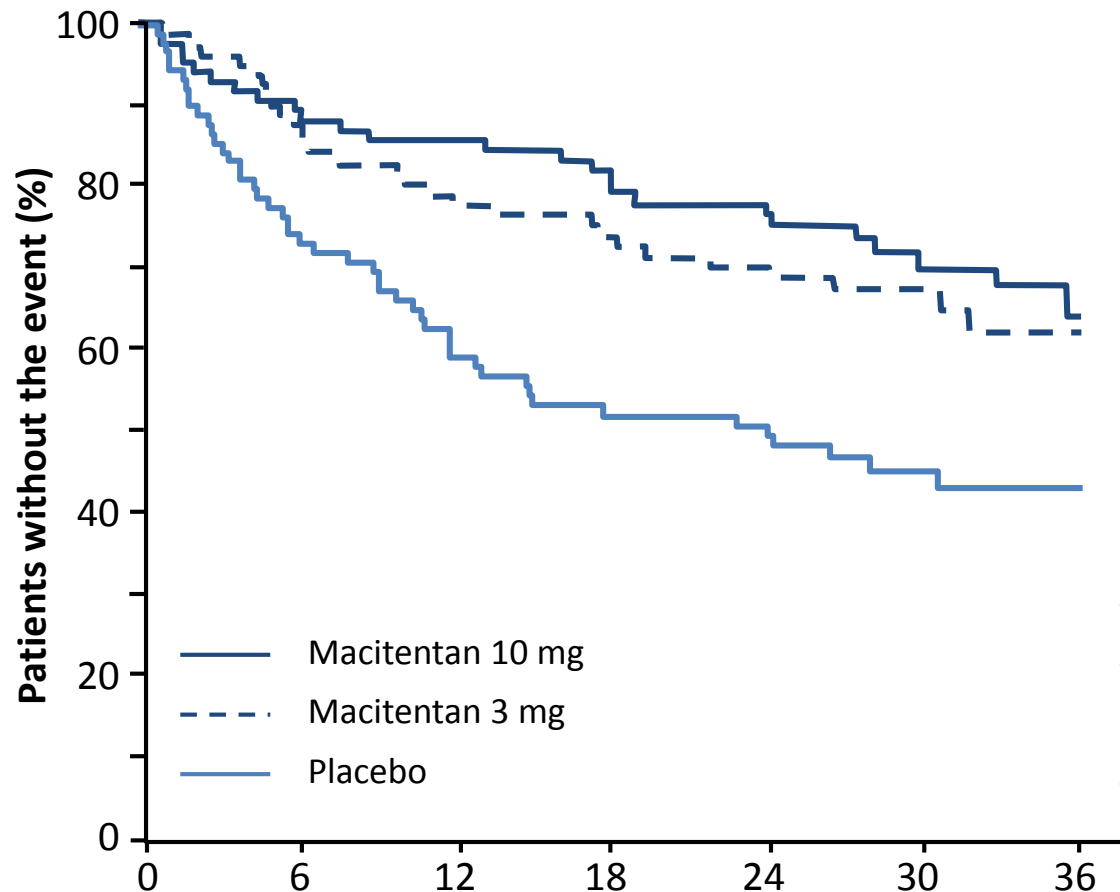


Treatment difference	3 mg	10 mg
Hazard ratio	0.70	0.55
Log-rank <i>p</i> -value	0.01	< 0.001

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

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 <i>p</i> -value	0.007	<0.001

Patients at risk Time from treatment start (months)

88

74

68

64

58

38

17

Macitentan 10 mg

86

74

63

59

56

29

13

Macitentan 3 mg

96

66

54

45

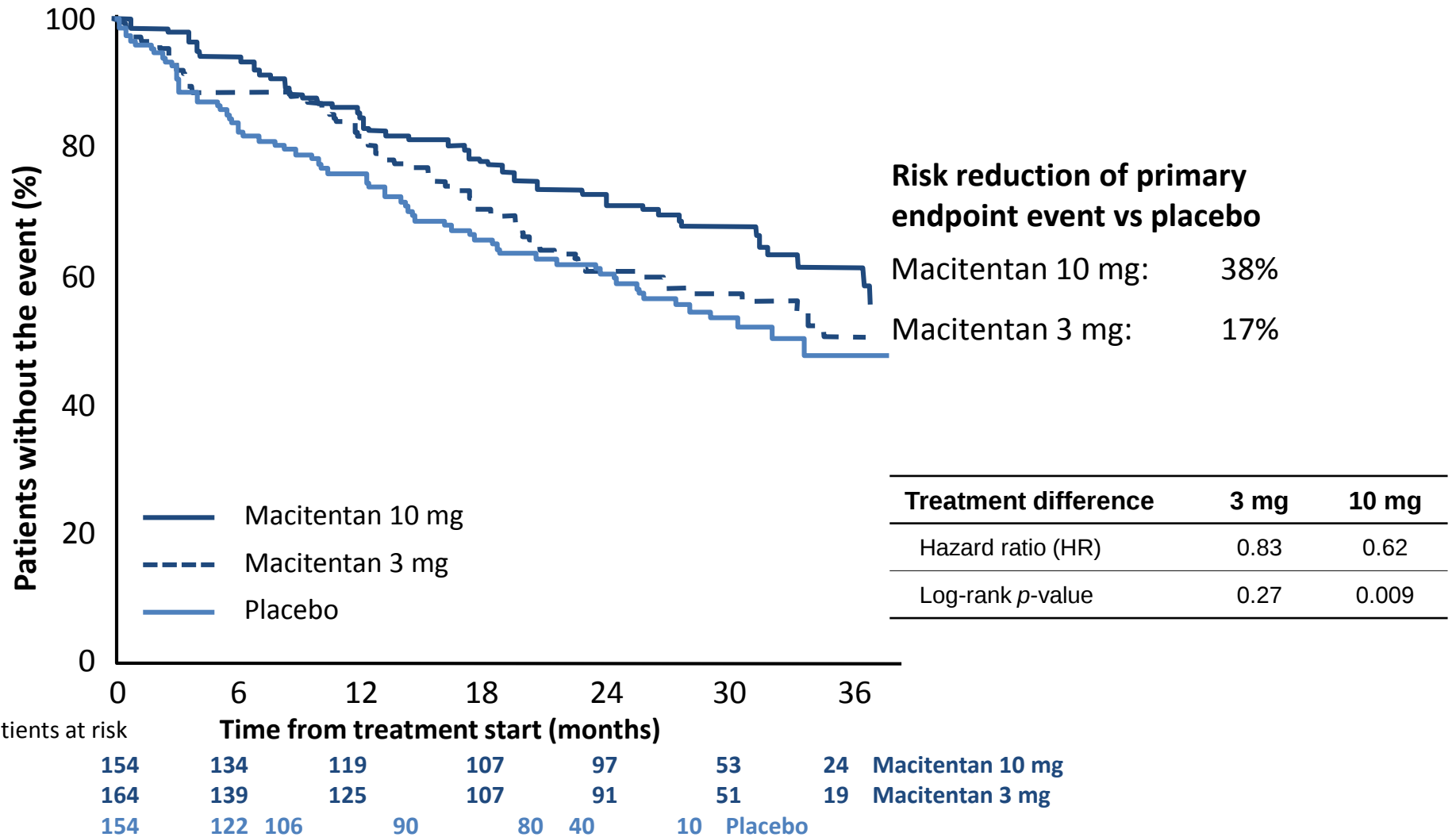
42

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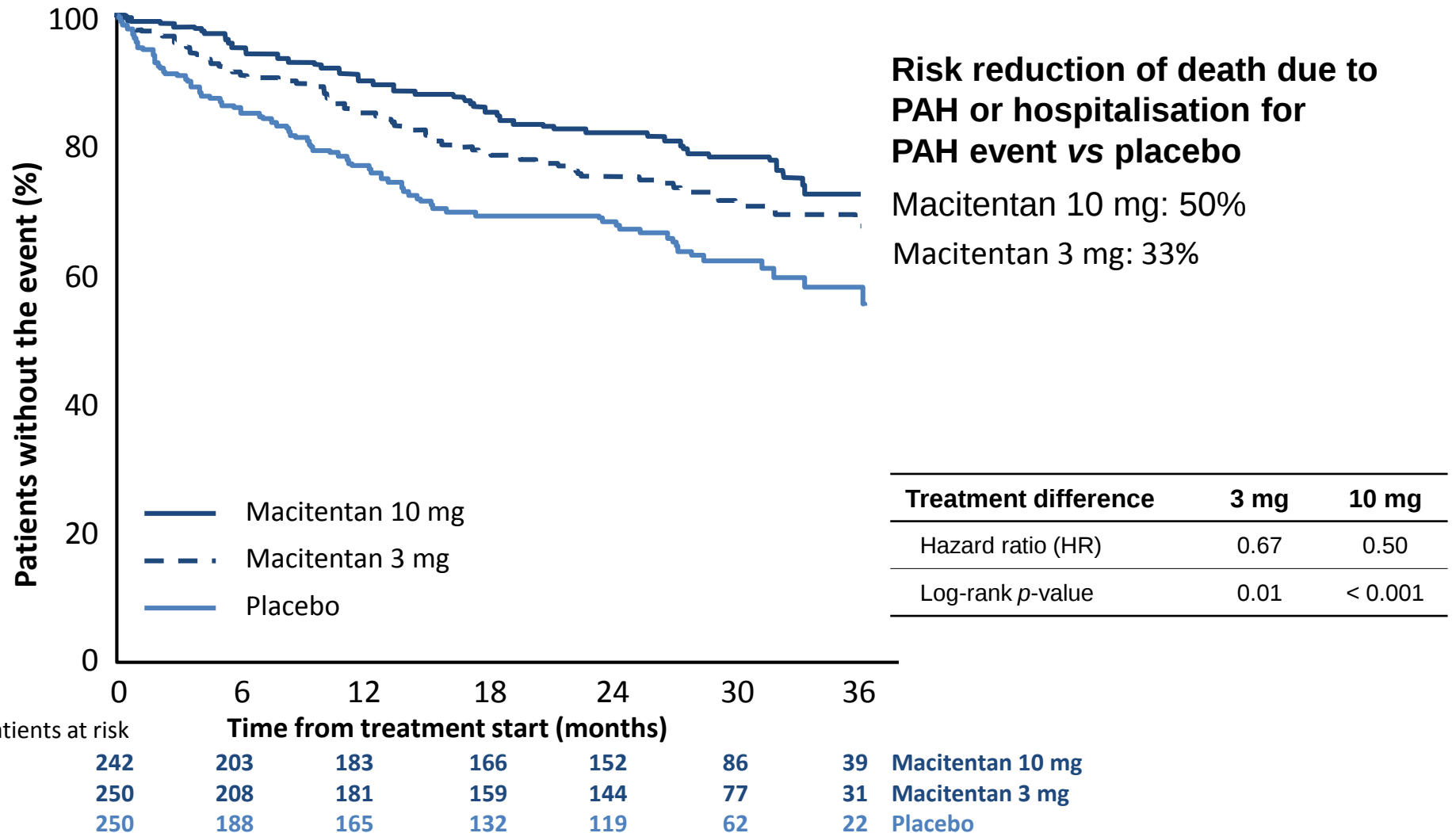
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Placebo

Morbidity and mortality in patients on background PAH therapy



Secondary endpoint: Death due to PAH or hospitalisation for PAH



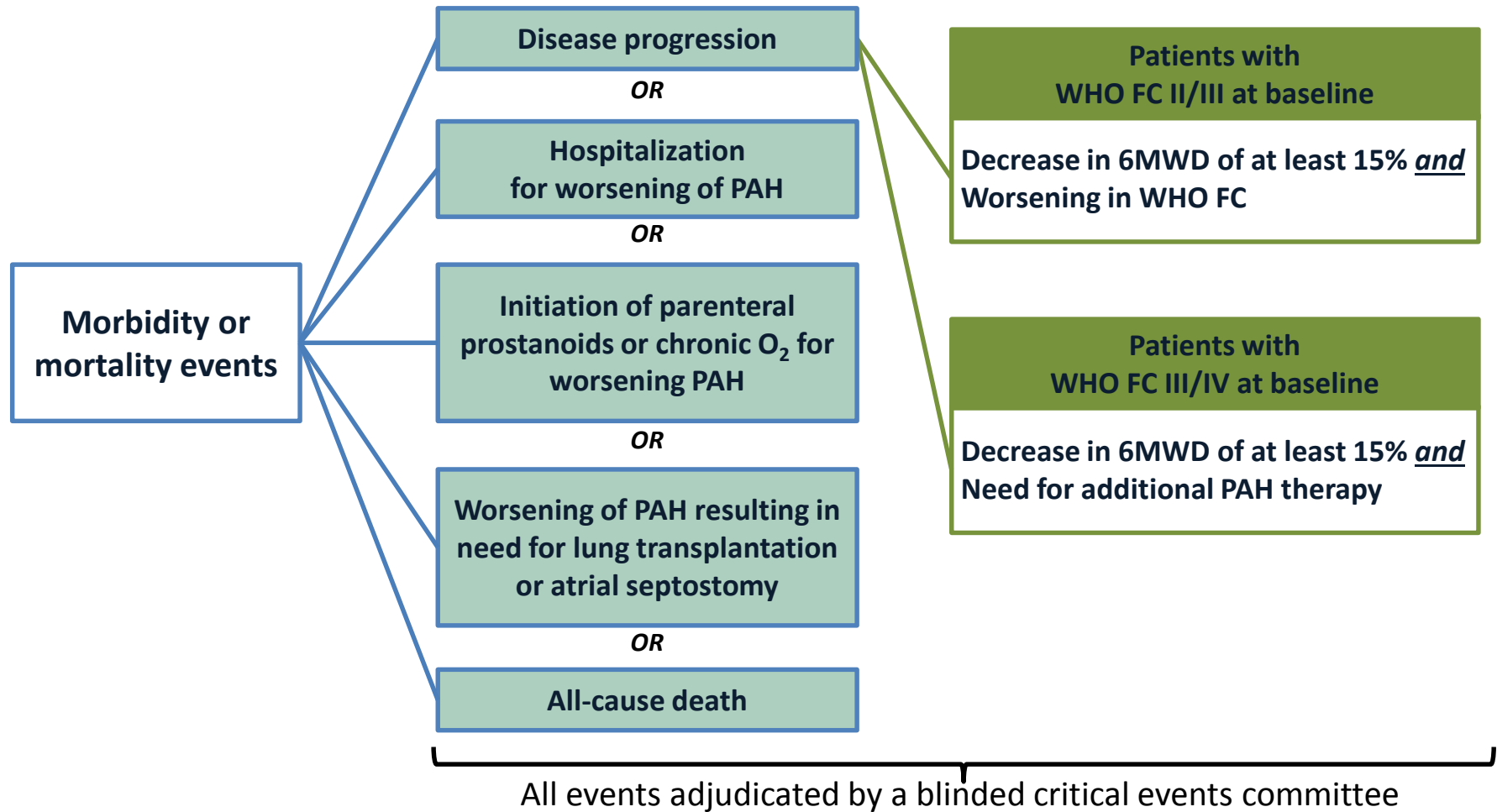
Selexipag in Pulmonary Arterial Hypertension – GRIPHON trial

- GRIPHON: ProstaGlandin I₂ 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)

GRIPHON trial – results

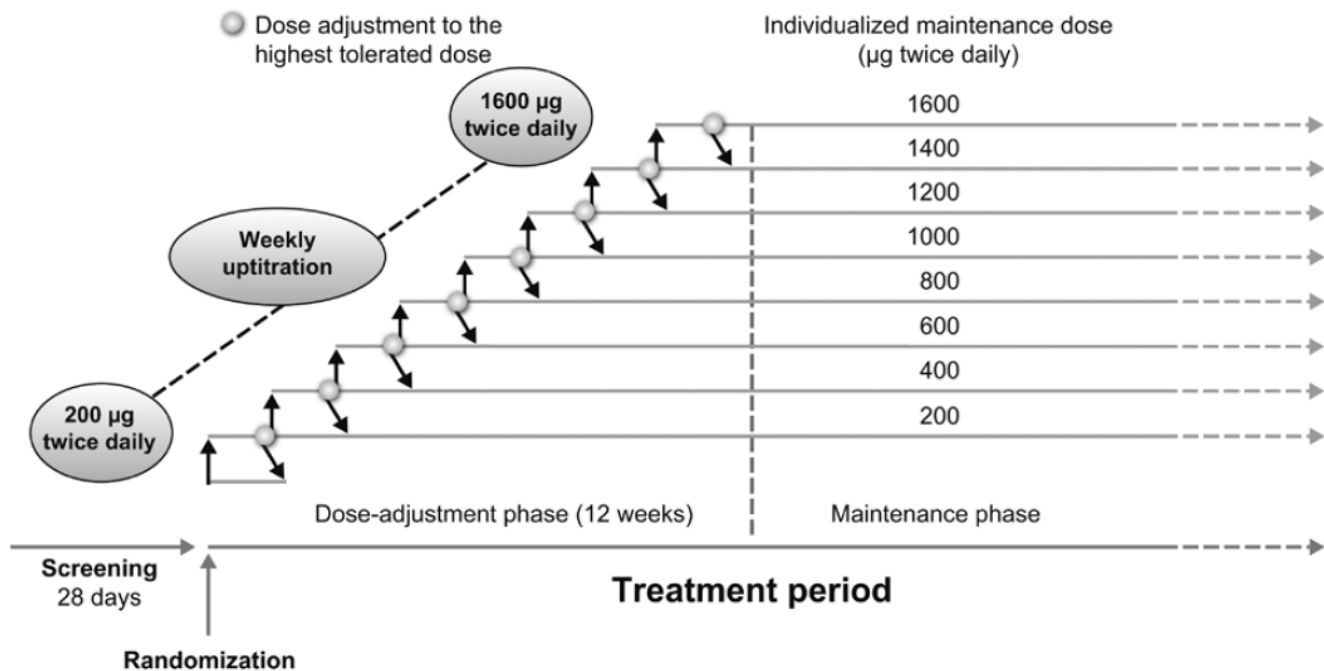
- 1156 PAH adult patients included and treated for up to 4.3 years.
- 80% on background treatment with ERA and/or PDE-5i
- Uptitration of selexipag allows each patient's maintenance dose to be individualized based on tolerability (to a maximum of 1600 mcg bid)

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



Dose adjustment

Tritation scheme



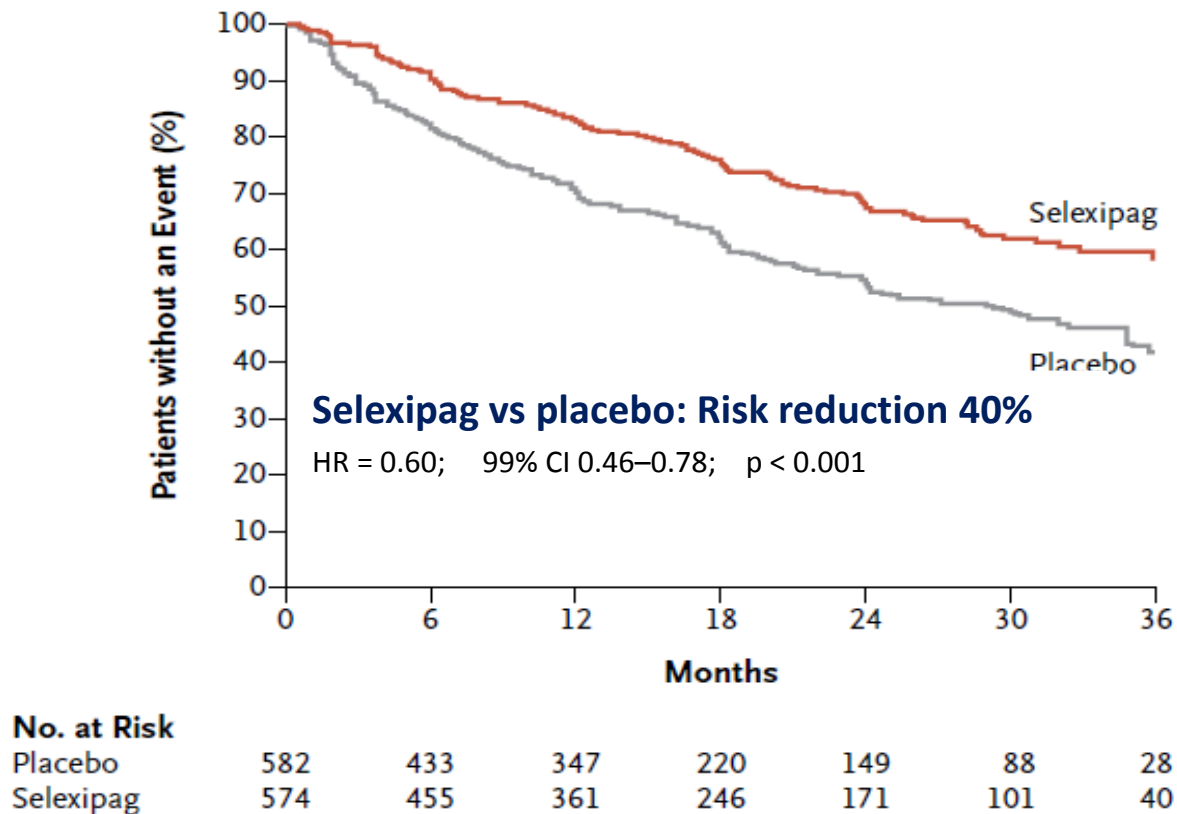
GRIPHON trial – results

- 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

GRIPHON trial – results

Primary composite end point

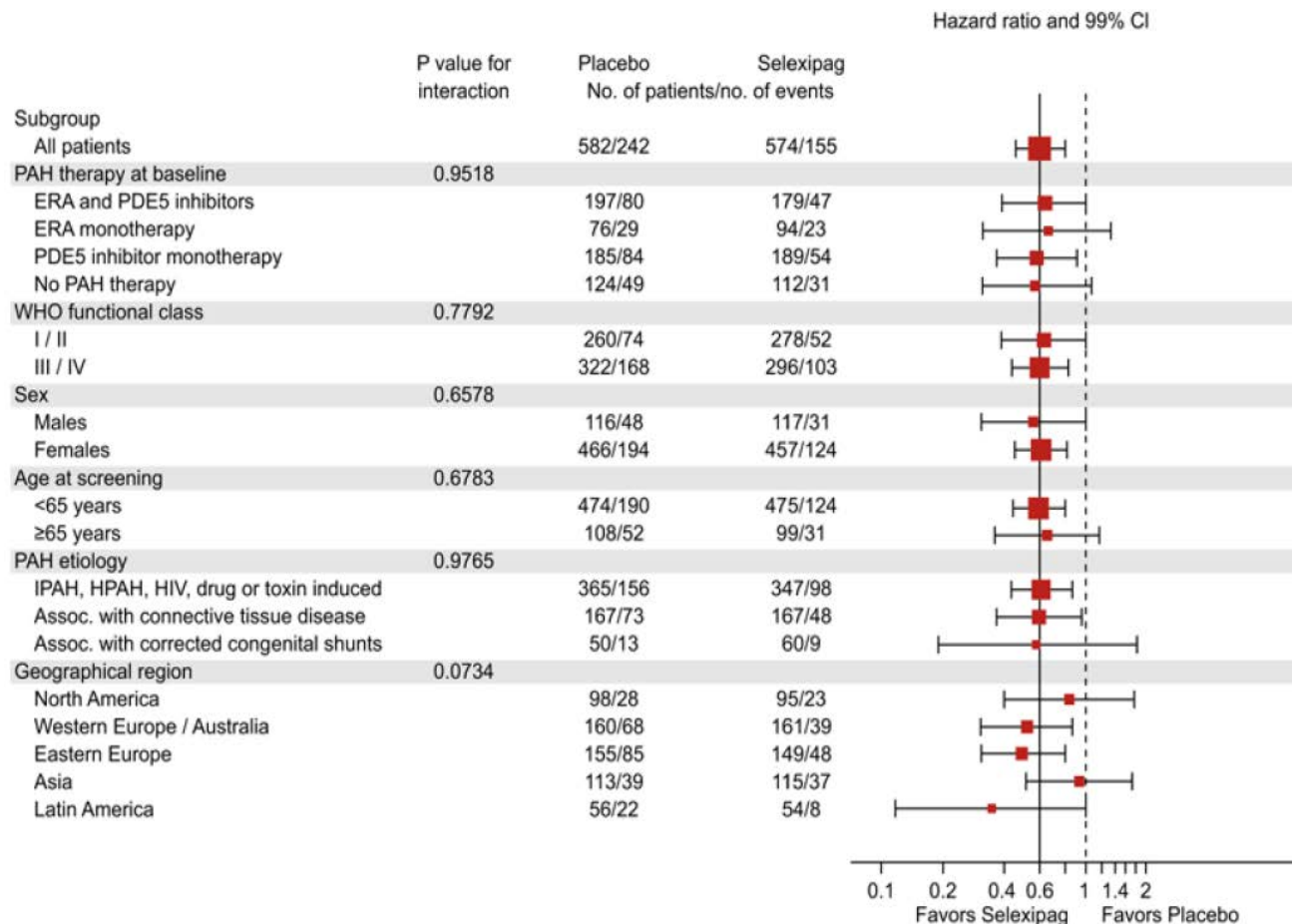
A significant treatment effect in favor of selexipag



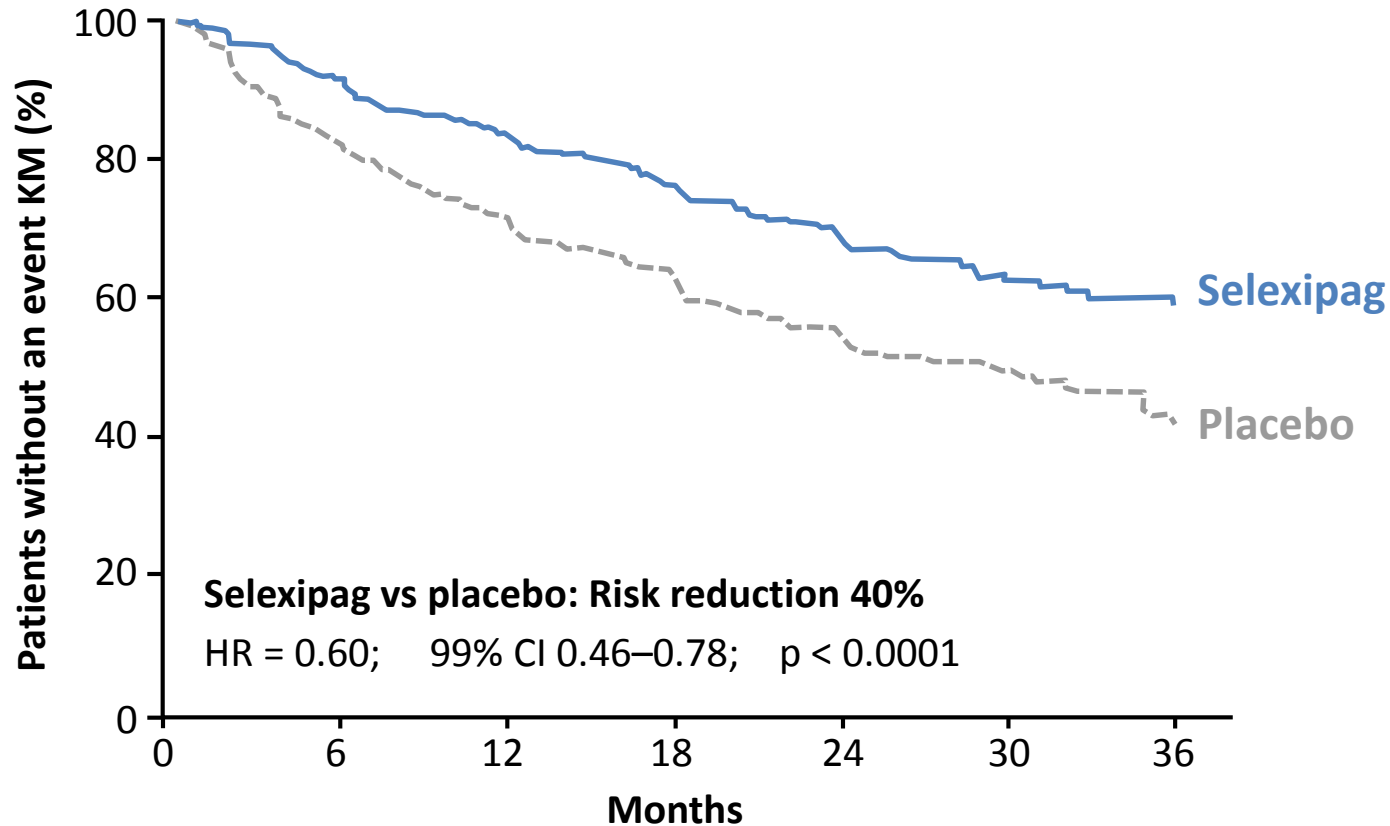
GRIPHON trial – results

Primary composite end point

Effect of selexipag across subgroups



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

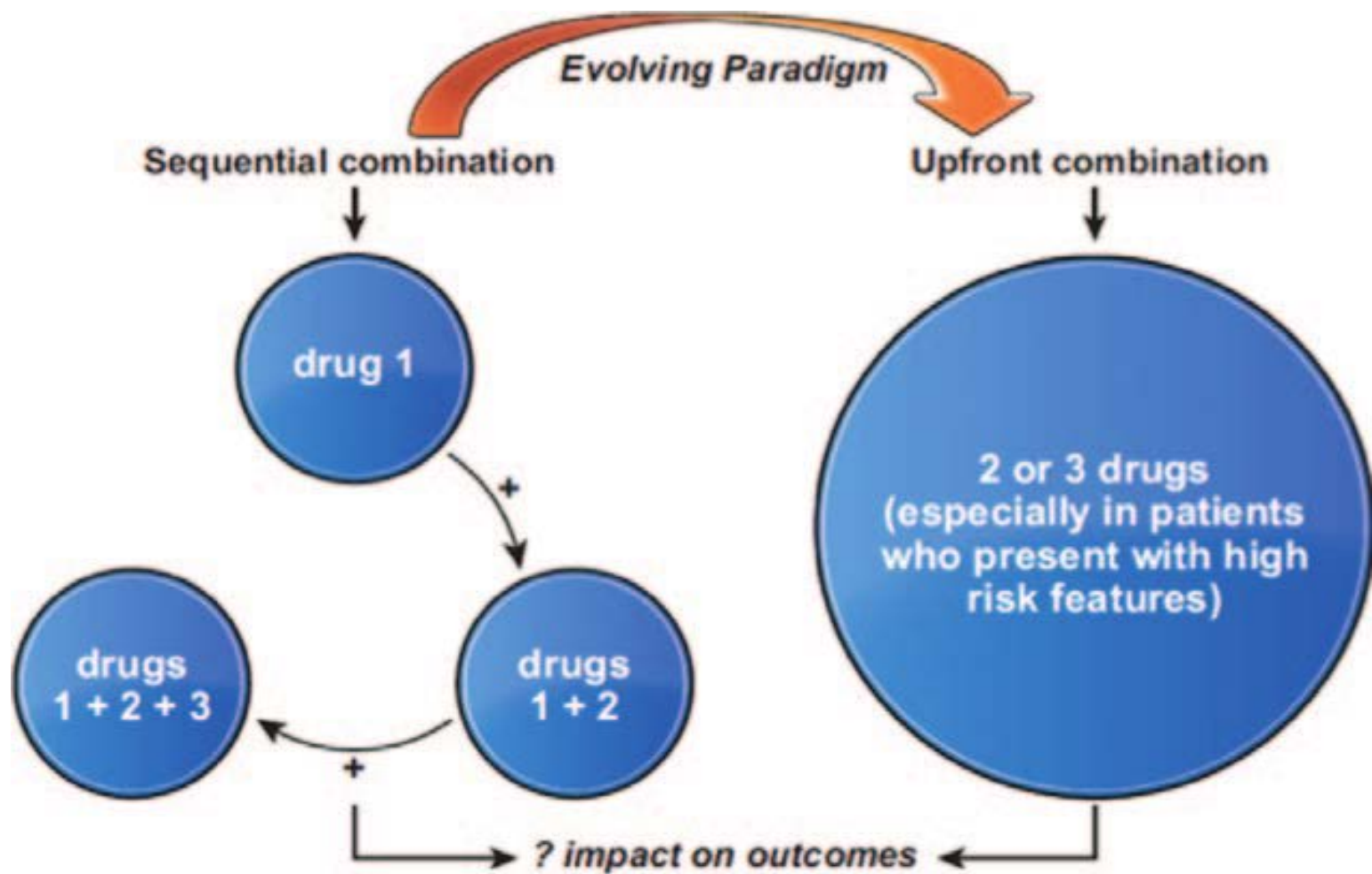


No. at Risk

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.

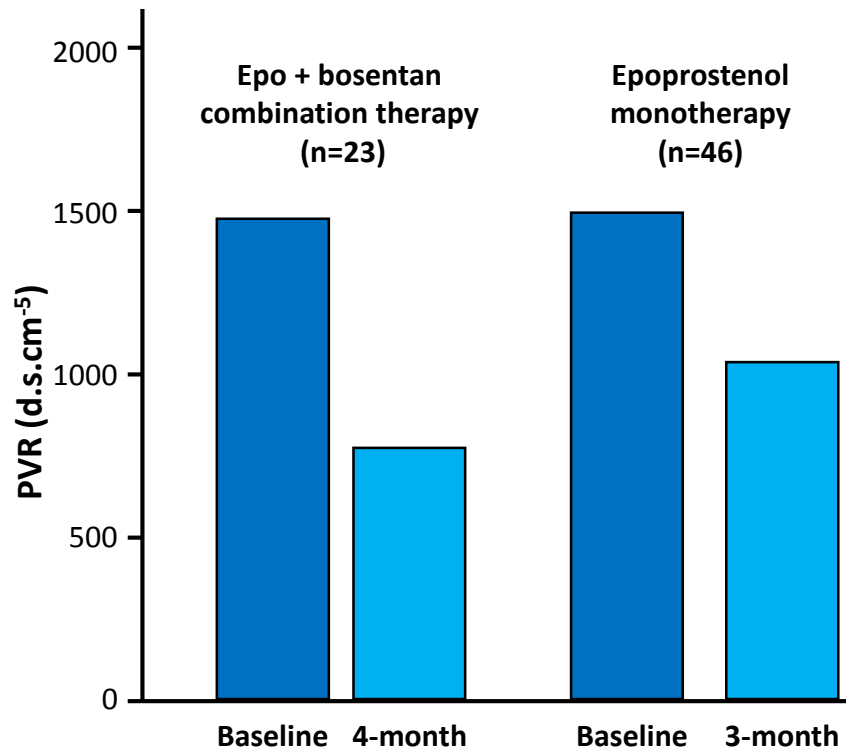
Evolving paradigm: From sequential to initial combination therapy



Humbert M, et al. *Circulation* 2014.

Up-front double combination therapy with epoprostenol and bosentan

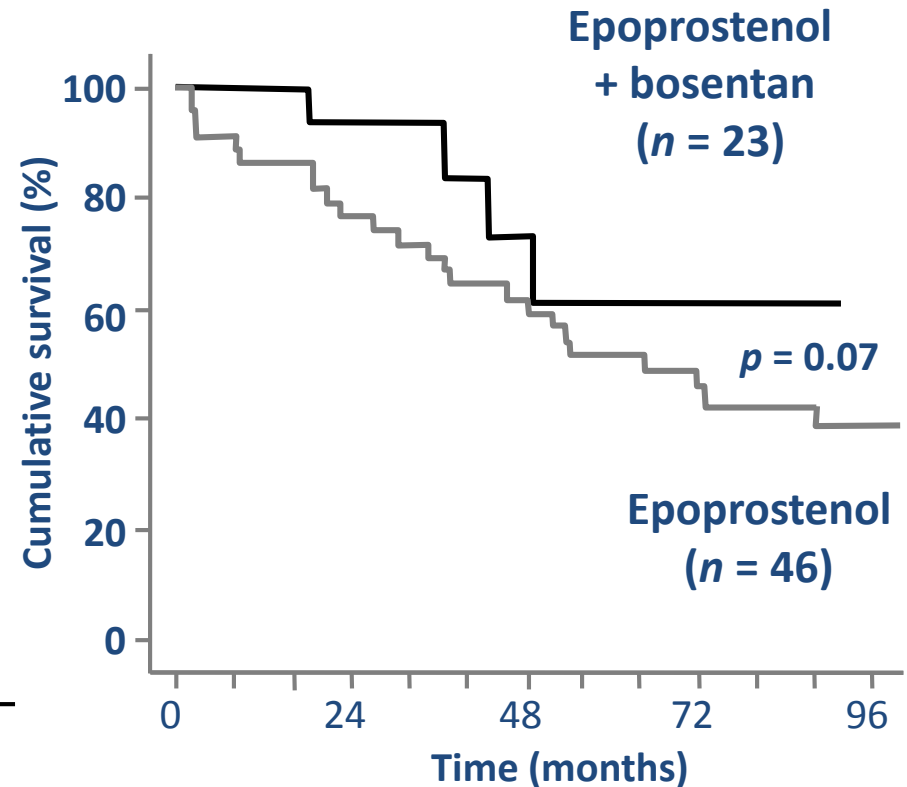
Percent change in PVR from baseline to 1st f-up evaluation (3–6 months)



-48 ± 17%

-29 ± 17%

P=0.0001

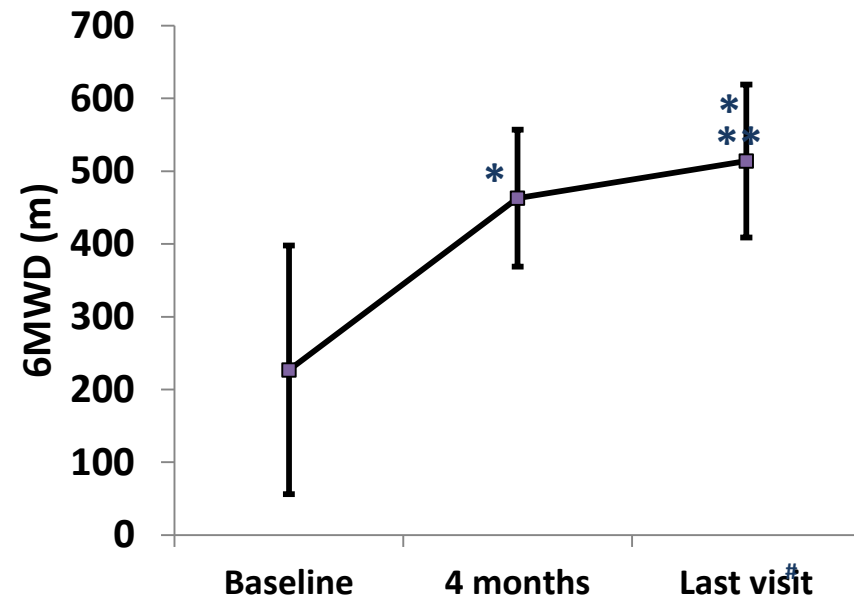
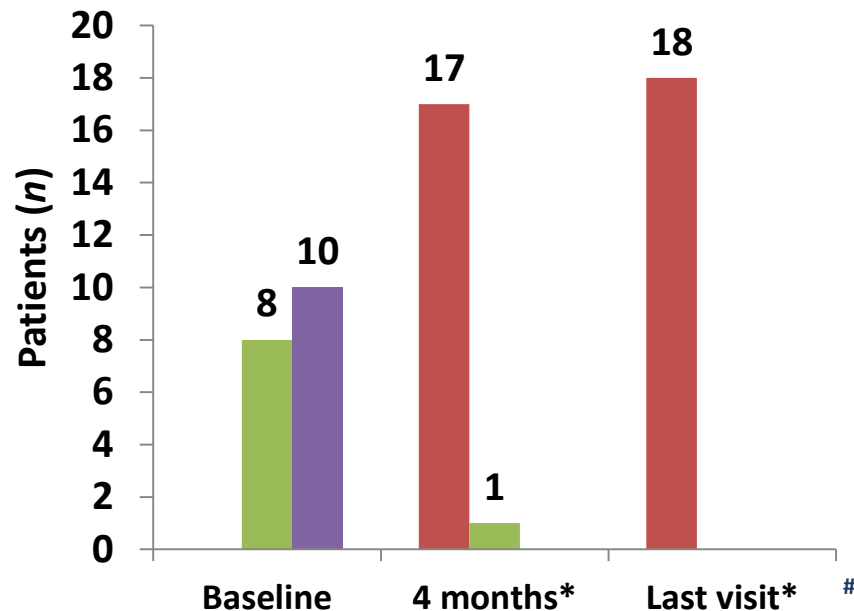


Kemp K, et al. J Heart Lung Transplant 2012;31:150–8.

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)

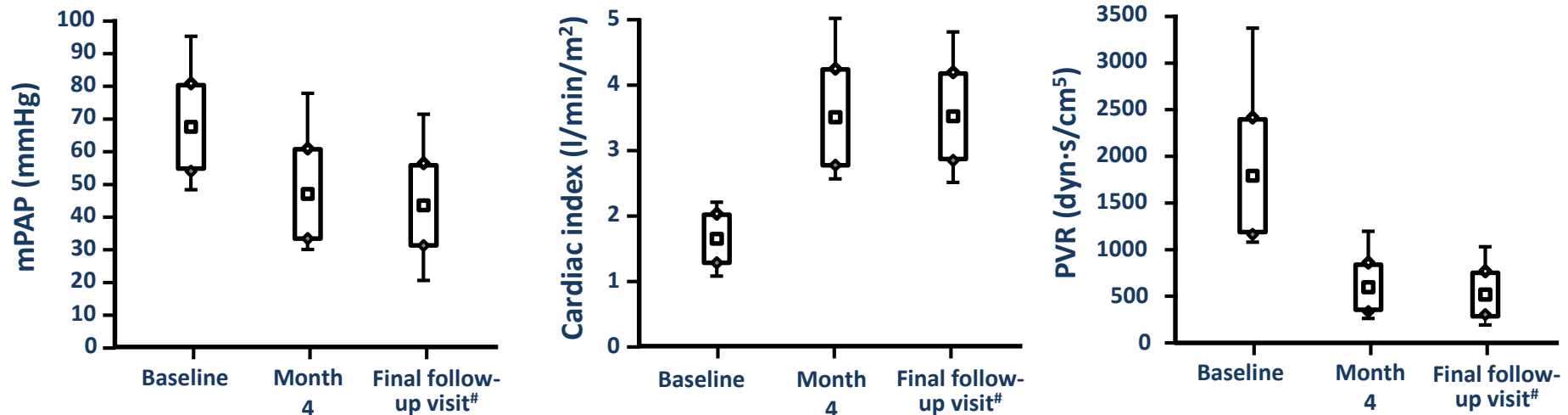
■ FC I/II ■ FC III ■ FC IV



#32 ± 19 months

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

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)

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)

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)

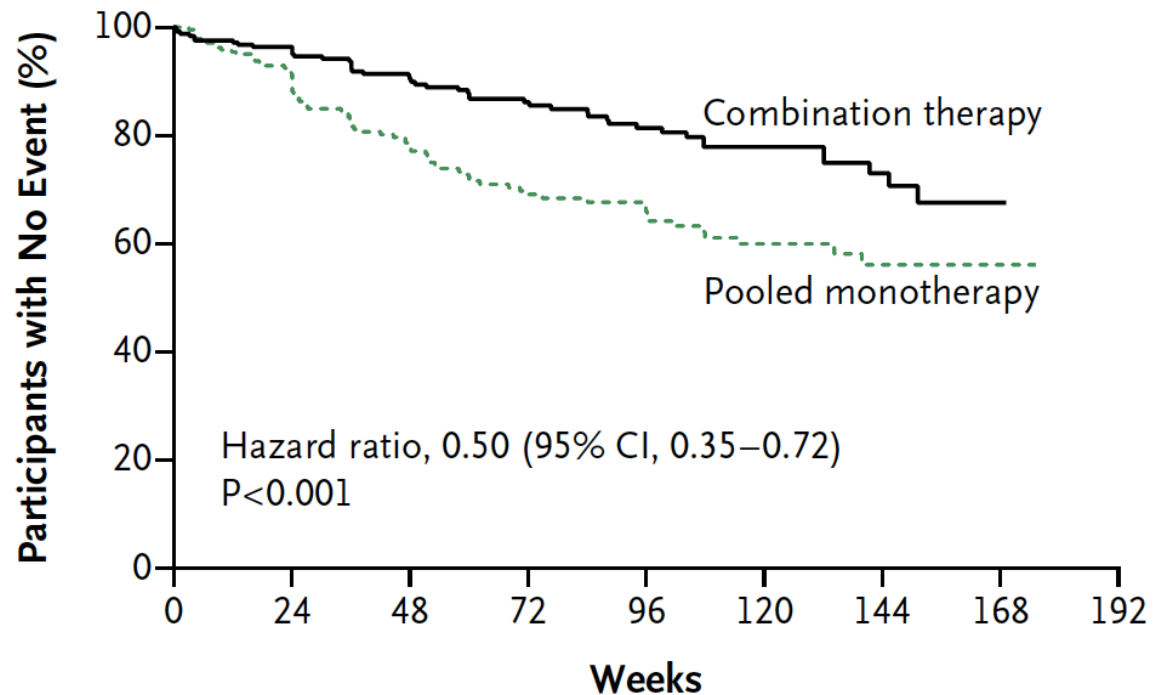
**Unsatisfactory
long-term response**

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

A Combination Therapy vs. Pooled Monotherapy



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

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 Cottin⁶, Xavier Jaïs^{1,2,3}, Pascal De Groote⁷, Ari Chaouat^{8,9}, Céline Chabannes¹⁰, Emmanuel Bergot¹¹, Hélène Bouvaist¹², Claire Dauphin¹³, Arnaud Bourdin¹⁴, Fabrice Bauer¹⁵, David Montani^{1,2,3}, Marc Humbert^{1,2,3} and Gérald Simonneau^{1,2,3}

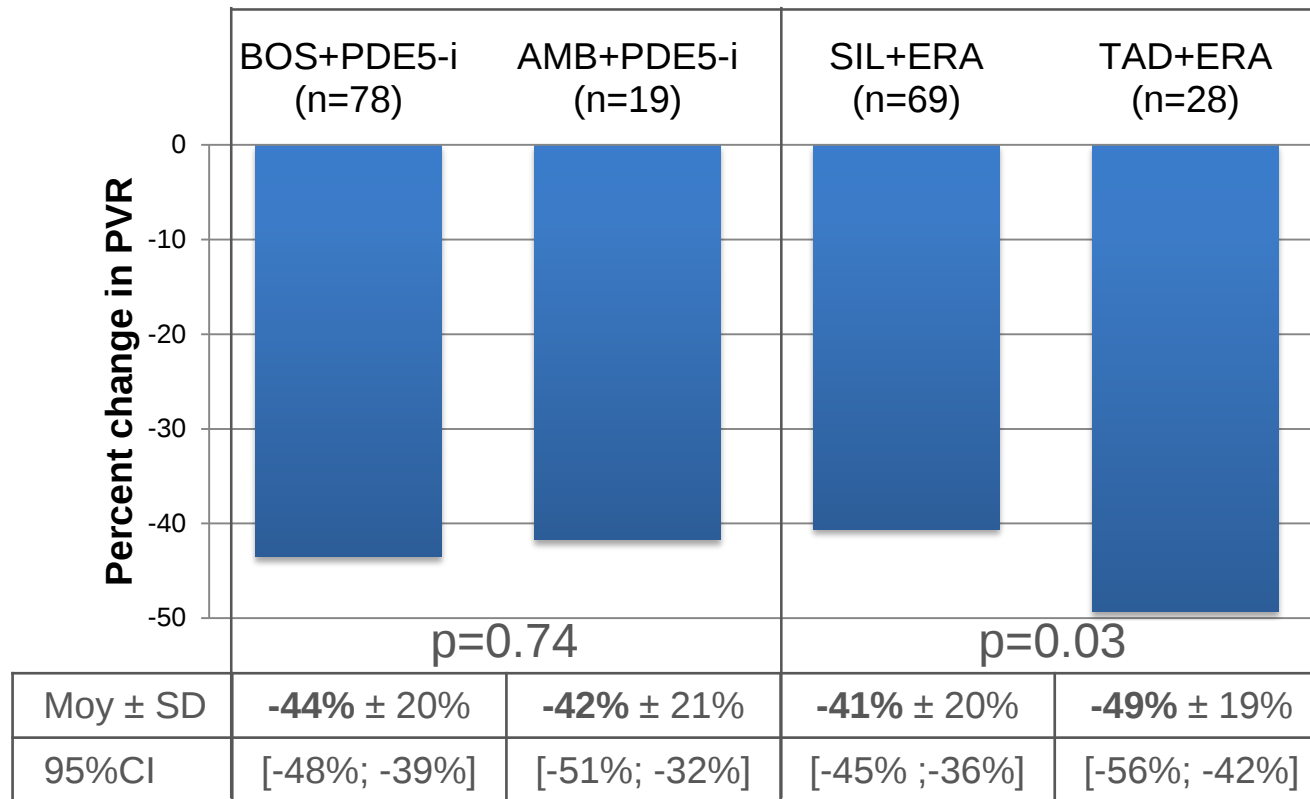


- 2007 – 2013
- 97 incident patients with PAH
 - Mean age 54
 - NYHA FC II-III (88%) & IV (12%)
- Initial dual oral combination therapy with ERA and PDE5i
 - BOS-SIL (n=61)
 - BOS-TAD (n=17)
 - AMB-SIL (n=8)
 - AMB-TAD (n=11)
- Median follow-up: 30 months [20 – 43]

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

	Baseline	4 months	<i>p</i> -value
NYHA FC (I : II : III : IV), <i>n</i>	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

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

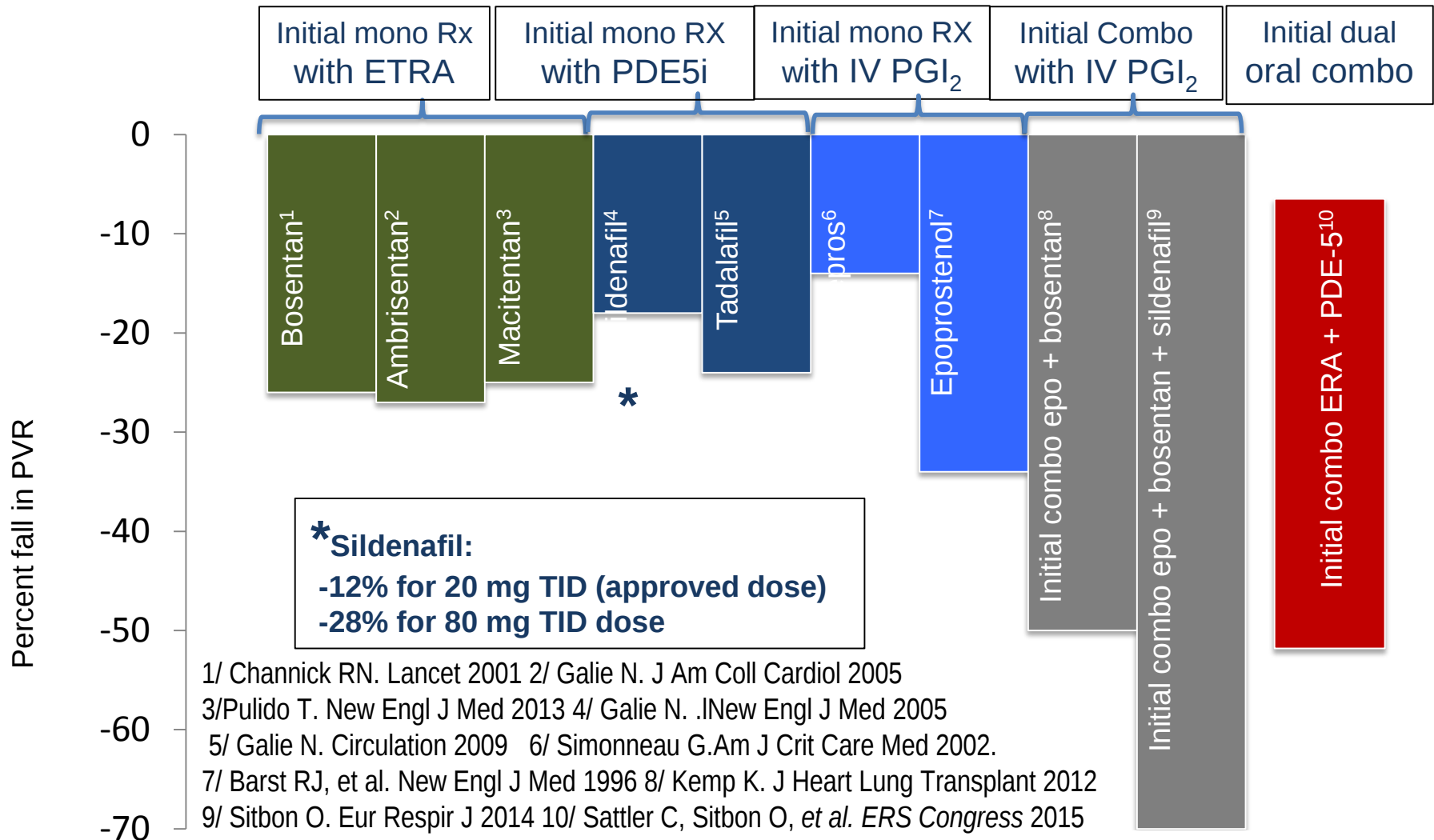


**median 4.1 months [IQR: 3.5 – 4.9]*

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



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.

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.

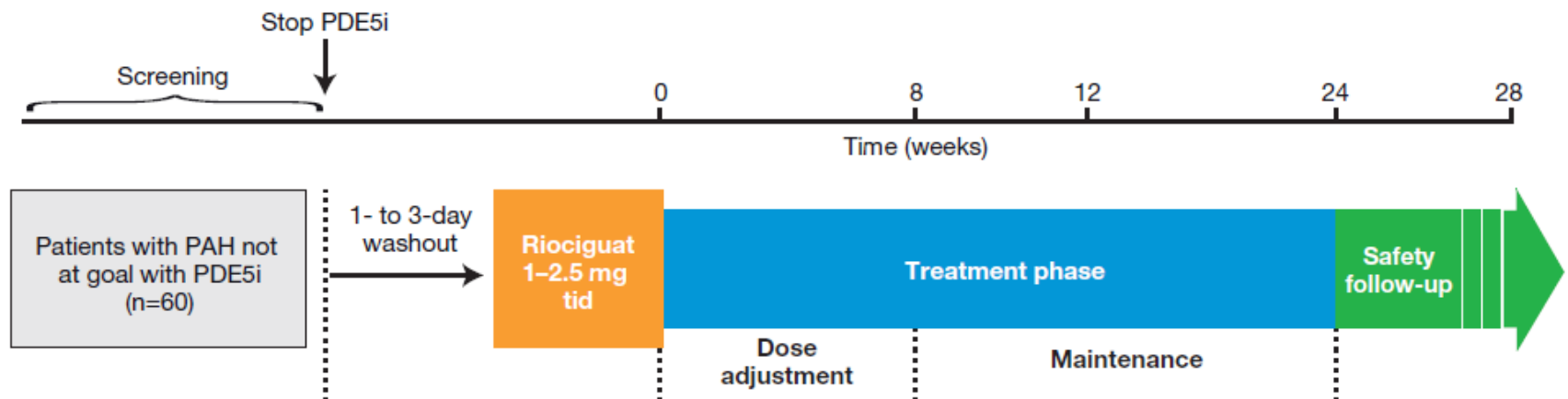
Hoeper MM, et al. Am J Respir Crit Care Med 2016;193:A6315.

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.

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 $<3.0 \text{ L/min/m}^2$
- mPAP $>30 \text{ mmHg}$
- PVR $>400 \text{ dyn}\cdot\text{s}\cdot\text{cm}^{-5}$

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	27 (90)
1.3 Toxin induced	1 (3)
1.4 APAH congenital heart disease	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)

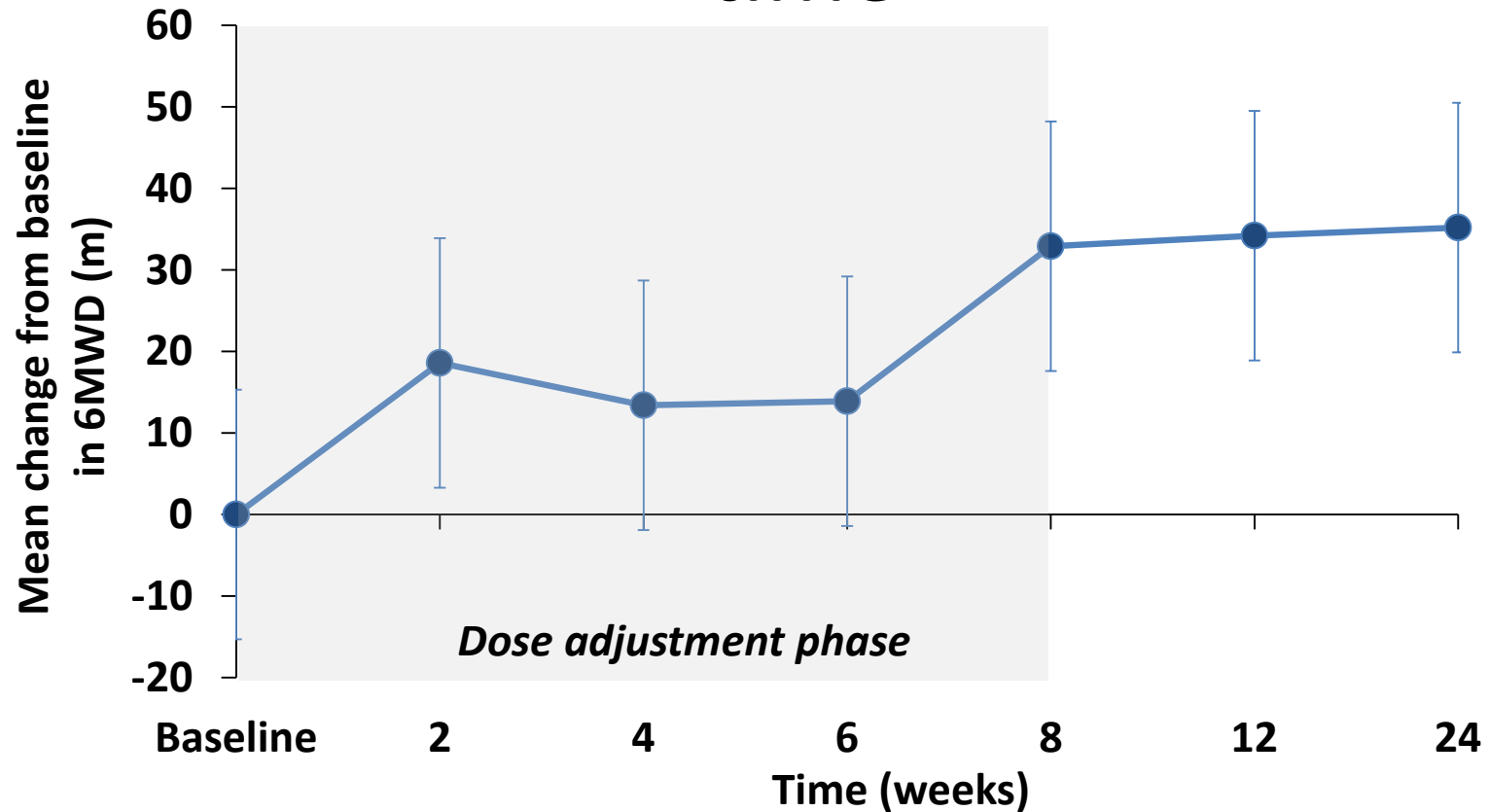
*n=29; Baseline = the last documented value before start of riociguat treatment (from screening or Week 0; hemodynamics from screening only).

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.

6MWD: Change from baseline over time

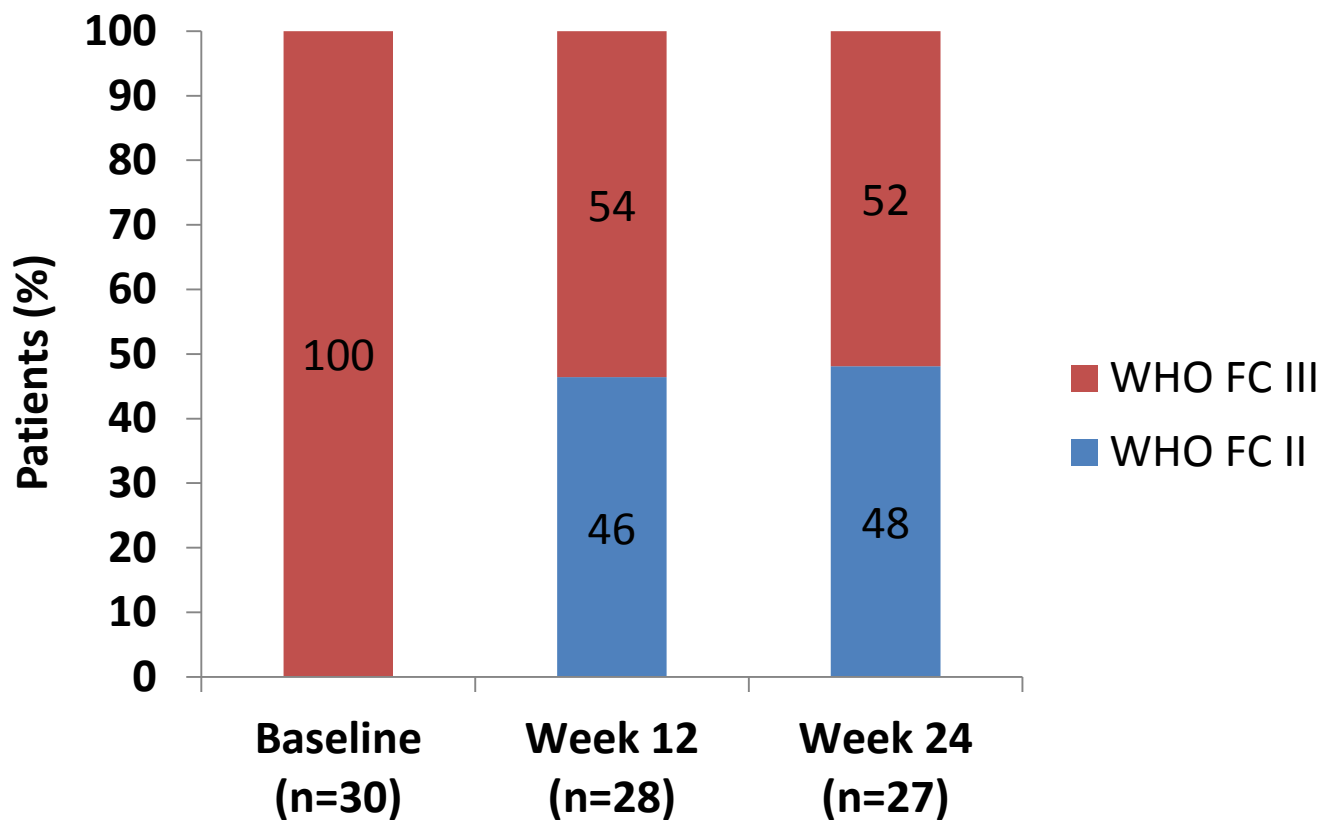


No. of patients	30	20	25	17	27	26	26
Mean absolute values (m)	353	386	377	373	385	386	386

Data are mean $\pm$ 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.

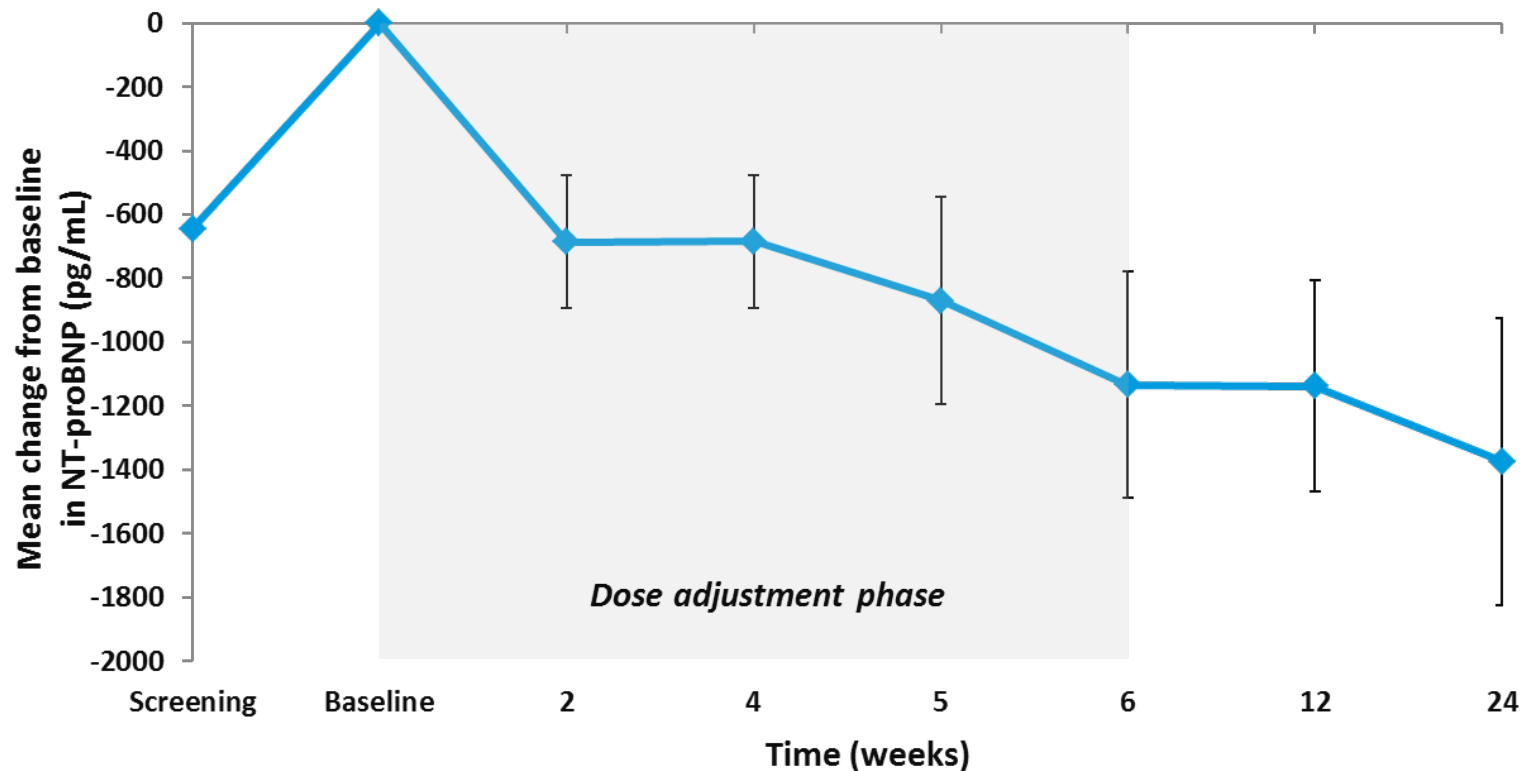
WHO FC: Change from baseline at Weeks 12 and 24



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



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.

Study drug-related and serious adverse events

AE, n (%)	Riociguat up to 2.5 mg tid (n=30)
<i>Study drug-related^a AEs in ≥10% of patients</i>	
Headache	5 (17)
Dyspepsia	4 (13)
Epistaxis	4 (13)
Dizziness	3 (10)
<i>SAEs</i>	
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)
<i>Deaths (main study phase – 24 weeks)</i>	
Any ^c	2 (7)
Pneumonia	1 (3)
Subdural hematoma	1 (3)

^aAs judged by the investigator. ^bEvents occurred in the same patient. ^cOne additional death occurred during the long-term extension.

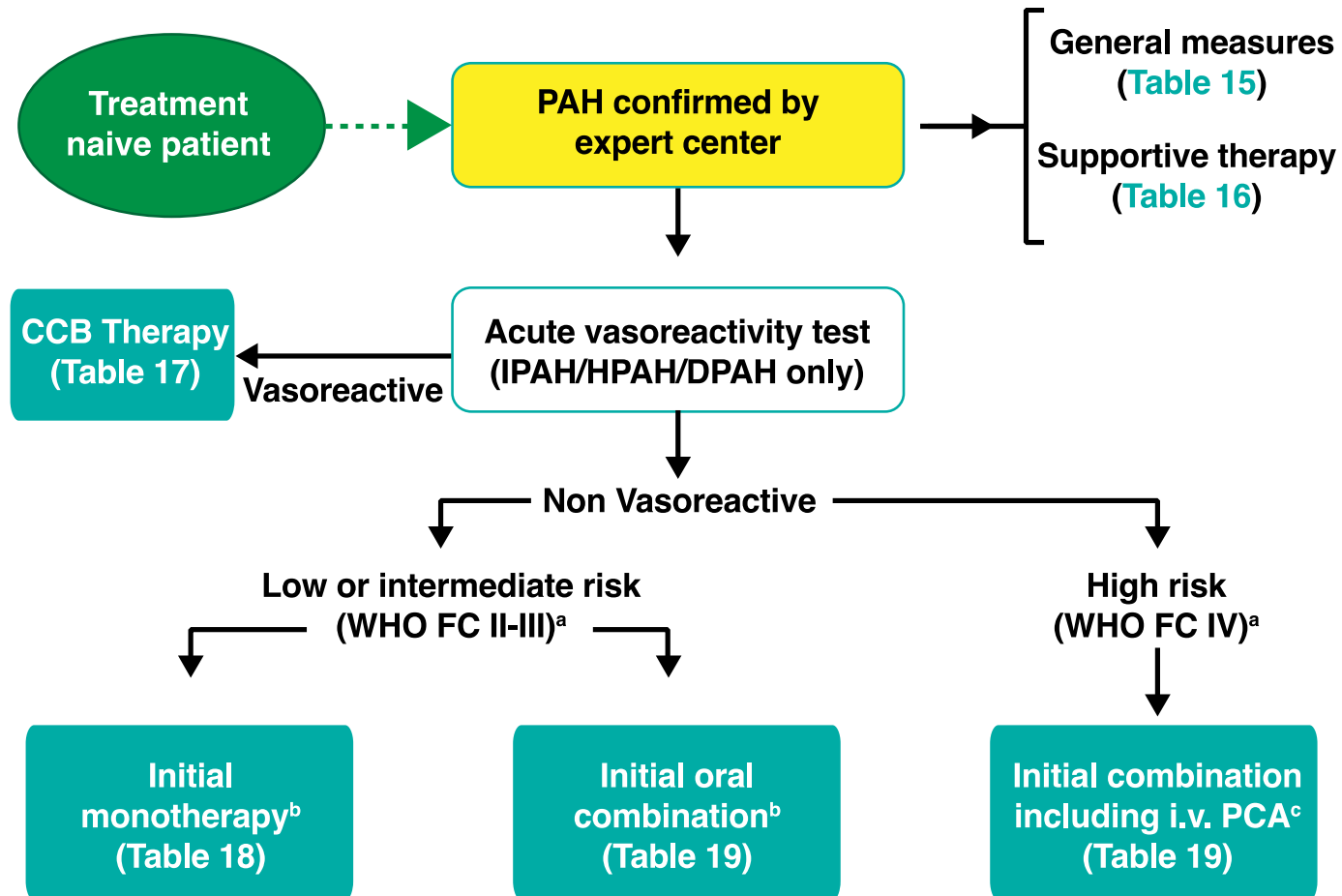
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Hoeper MM, et al. Am J Respir Crit Care Med 2016;193:A6315.

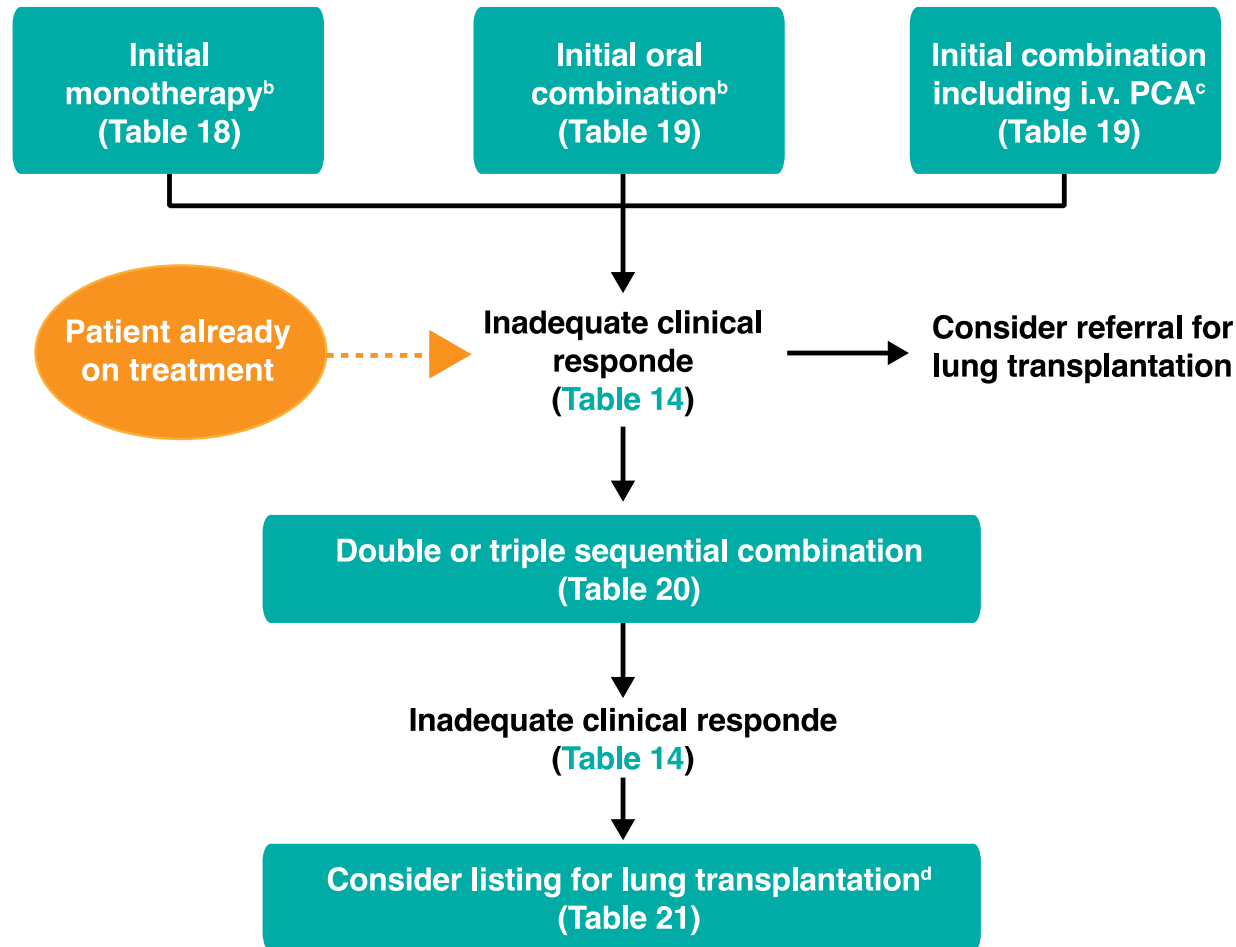
Conclusions

- 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

2015 ESC/ERS guidelines treatment algorithm



2015 ESC/ERS guidelines treatment algorithm



Quali novità nelle strategie terapeutiche dell'Iipertensione 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 (Trepstinil) nei pazienti più gravi (IV NYHA 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.