PAH Treatment Algorithm
Comments and proposals

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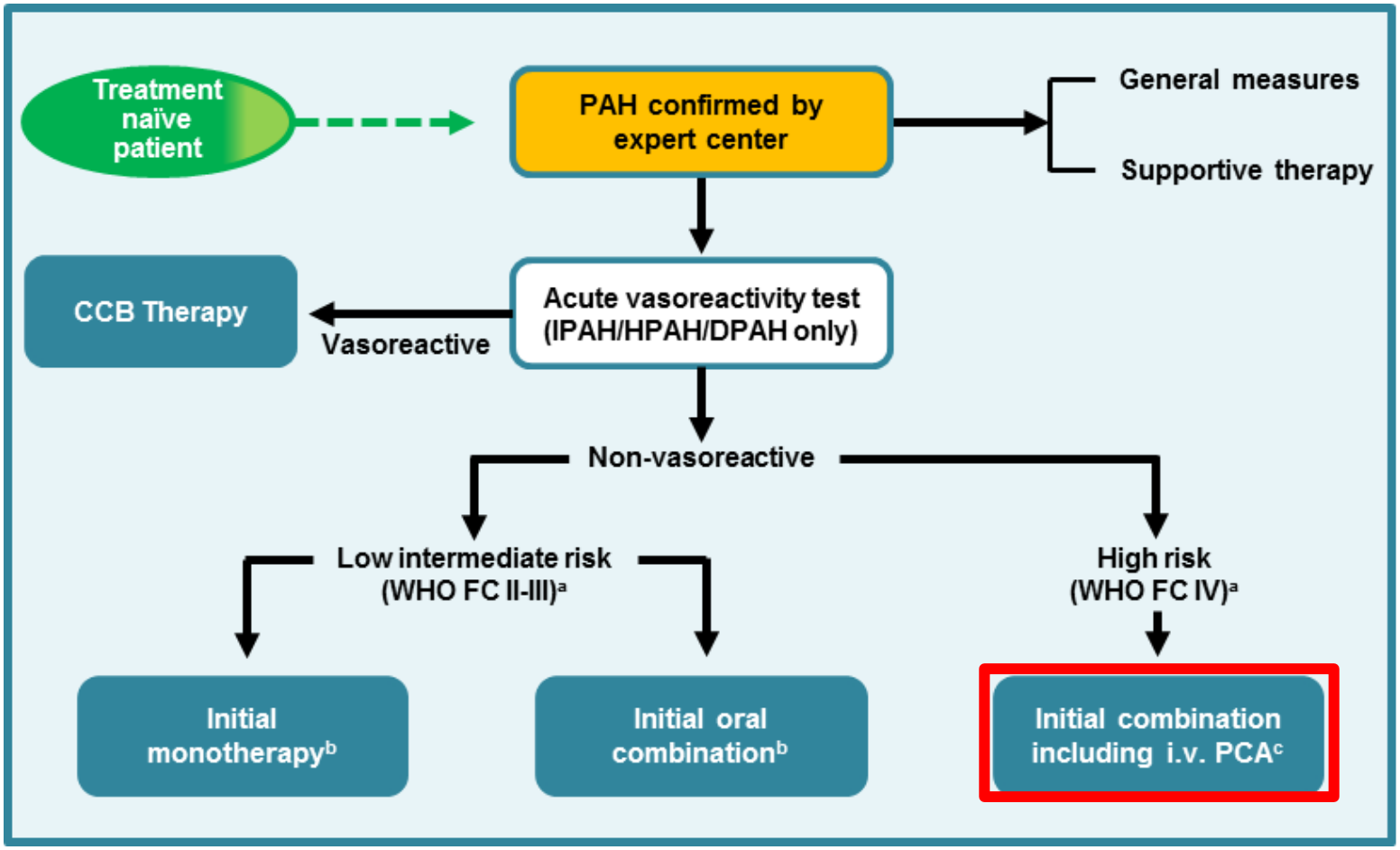
2015 ESC/ERS guidelines treatment algorithm



Eur Heart J 2016 & *Eur Respir J* 2015

Recommendations for initial combination therapy in NYHA functional class IV (high risk patients)

Measure/ treatment	WHO-FC IV	
Ambrisentan + tadalafil[d]	IIb	C
Other ERA + PDE-5i	IIb	C
Bosentan + sildenafil + i.v. epoprostenol	IIa	C
Bosentan + i.v. epoprostenol	IIa	C
Other ERA or PDE-5i + s.c. treprostinil	IIb	C
Other ERA or PDE-5i + other i.v. prostacyclin analogues	IIb	C

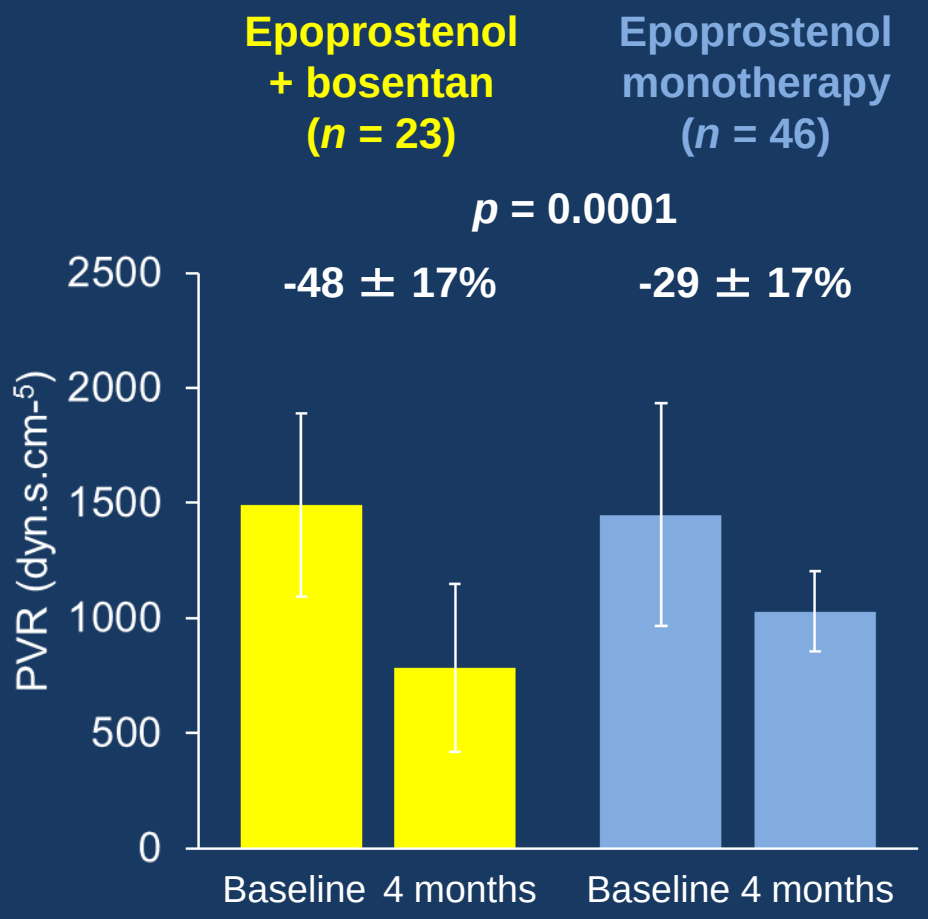
Usefulness of first-line combination therapy with epoprostenol and bosentan in pulmonary arterial hypertension.

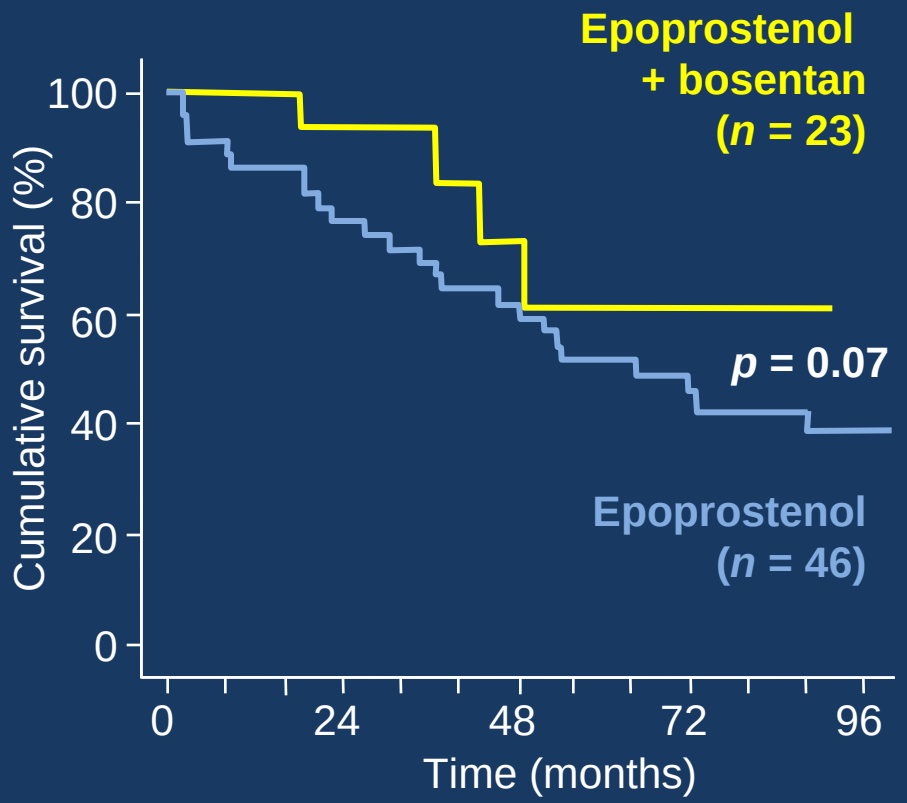
K Kemp, L Savale, D O'Callaghan, X Jaïs, D Montani, M Humbert, G Simonneau, O Sitbon

	Combination Tx bosentan+ Flolan cohort n = 23)	Matched-cohort on Flolan only (n = 46)	p value
Age at treatment start, y	43 ± 15	43 ± 15	0.94
Baseline NYHA III : IV, n	(70% : 30%)	(74% : 26%)	> 0.5
Baseline 6MWD, m	287 ± 133	250 ± 144	0.30
Baseline haemodynamics			
RAP, mmHg	11 ± 7	12 ± 6	0.29
mPAP, mmHg	65 ± 13	68 ± 13	0.33
CI, $L.min^{-1}.m^{-2}$	1.8 ± 0.3	1.9 ± 0.5	0.28
PVR, $d.s.cm^{-5}$	1493 ± 398	1515 ± 559	0.77
SvO_2, %	55 ± 7	55 ± 10	0.85

Kemp K, *et al. J Heart Lung Transpl*

First-line combination therapy with epoprostenol and bosentan in pulmonary arterial hypertension.





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

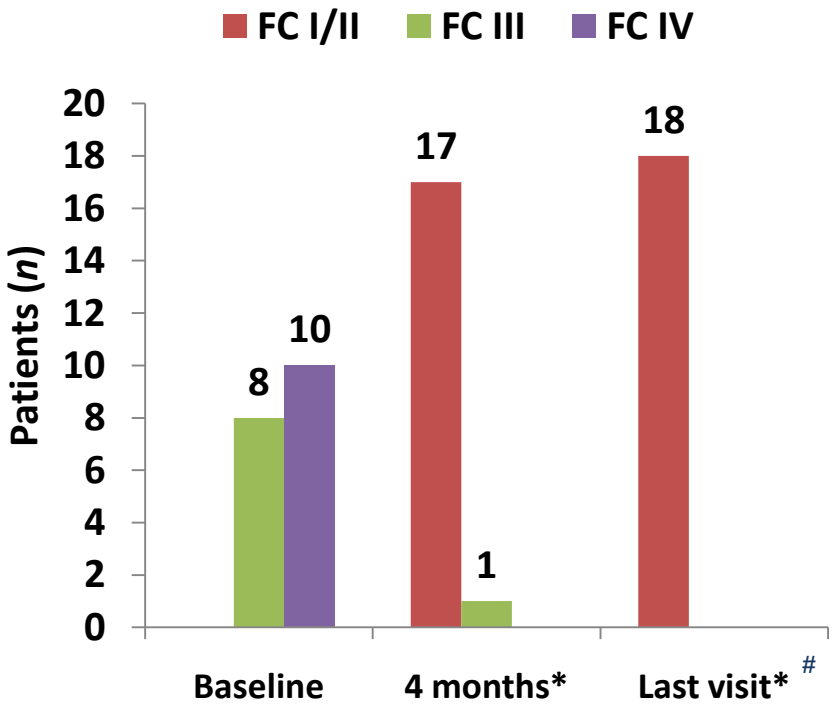
Upfront triple combination therapy in pulmonary arterial hypertension: a pilot study

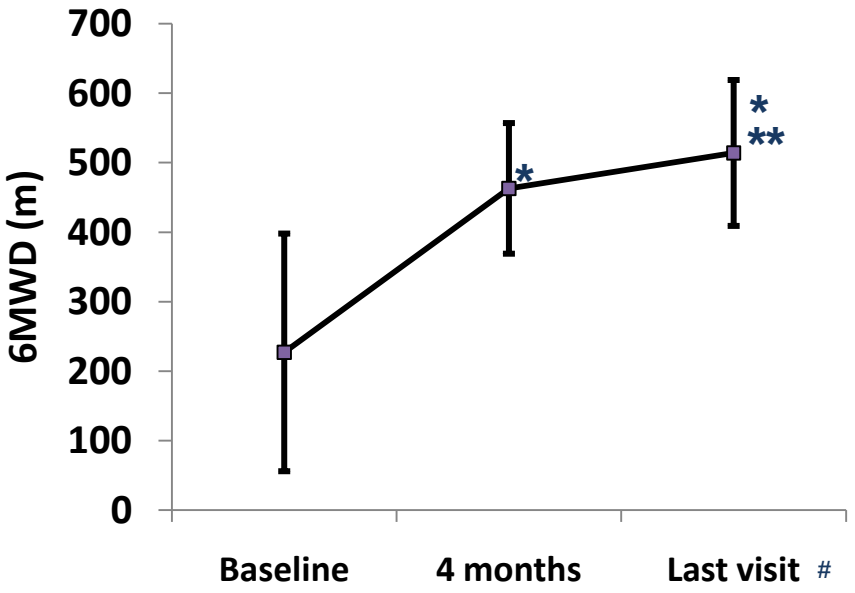
Olivier Sitbon[1,2,3], Xavier Jaïs[1,2,3], Laurent Savale[1,2,3], Vincent Cottin[4], Emmanuel Bergot[5], Elise Artaud Macari[1,2,3], Hélène Bouvaist[6], Claire Dauphin[7], François Picard[8], Sophie Bulifon[1,2,3], David Montani[1,2,3], Marc Humbert[1,2,3] and Gérald Simonneau[1,2,3]

- Upfront triple combination therapy:
  i.v. epoprostenol + bosentan + sildenafil
- 19 incident patients with PAH
  (*n* = 10) idiopathic or heritable (*n* = 9)
- Mean age 39 ± 14 years (18 – 63)
- NYHA FC III (*n* = 8) or IV (*n* = 11)
- Severe haemodynamics:
  CI <1.7 L/min/m^2 and PVR > 1700 dyn.s.cm^{-5}

Upfront triple combination therapy: Effect on FC and 6MWD

Prospective, observational analysis of idiopathic or heritable PAH patients (*n* = 19) treated with upfront combination therapy (epoprostenol, bosentan and sildenafil)

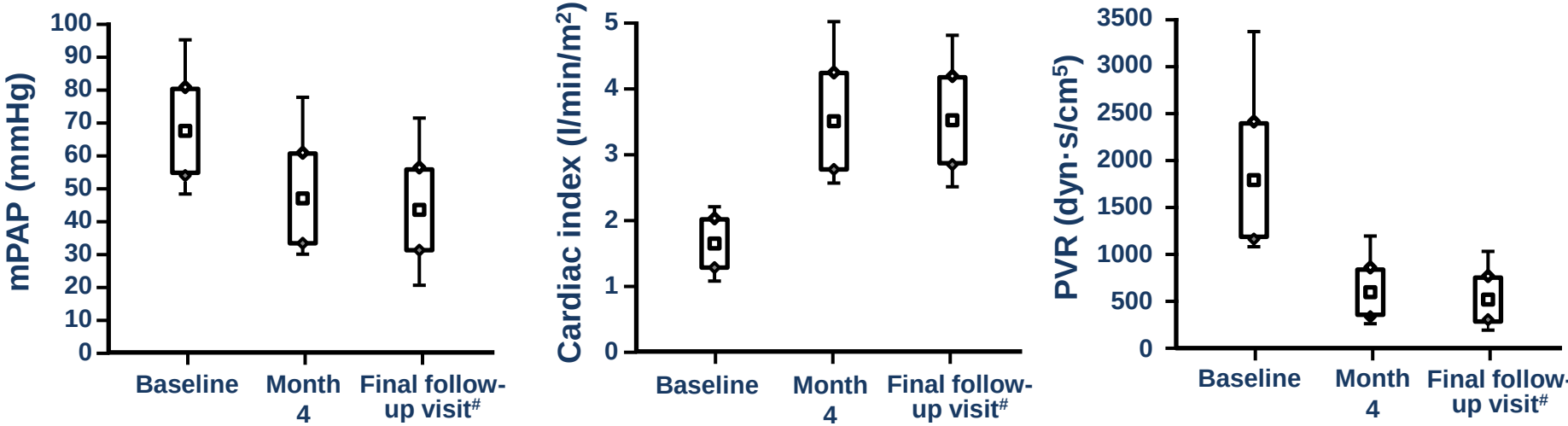




#32 ± 19 months
**p* < 0.01 versus baseline; ** p < 0.01 versus 4 months

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

Upfront triple combination therapy: Effect on haemodynamics



	Baseline	Month 4	Final follow-up#
RAP (mmHg)	11.9 ± 5.2	4.9 ± 4.9*	5.2 ± 3.5*
mPAP (mmHg)	65.8 ± 13.7	45.7 ± 14.0*	44.4 ± 13.4*
CI (l/min/m^2)	1.66 ± 0.35	3.49 ± 0.69*	3.64 ± 0.65*
PVR (d.s.cm^{-5})	1718 ± 627	564 ± 260*	492 ± 209*

#32 ± 19 months *p < 0.01 versus baseline

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

Upfront triple combination therapy in severe PAH

19 Patients with a Median follow-up: 39months

- 1 patients undergone urgent H-L transplantations.

  Others are still receiving triple therapy
- All patients well and alive in NYHA FC I-II

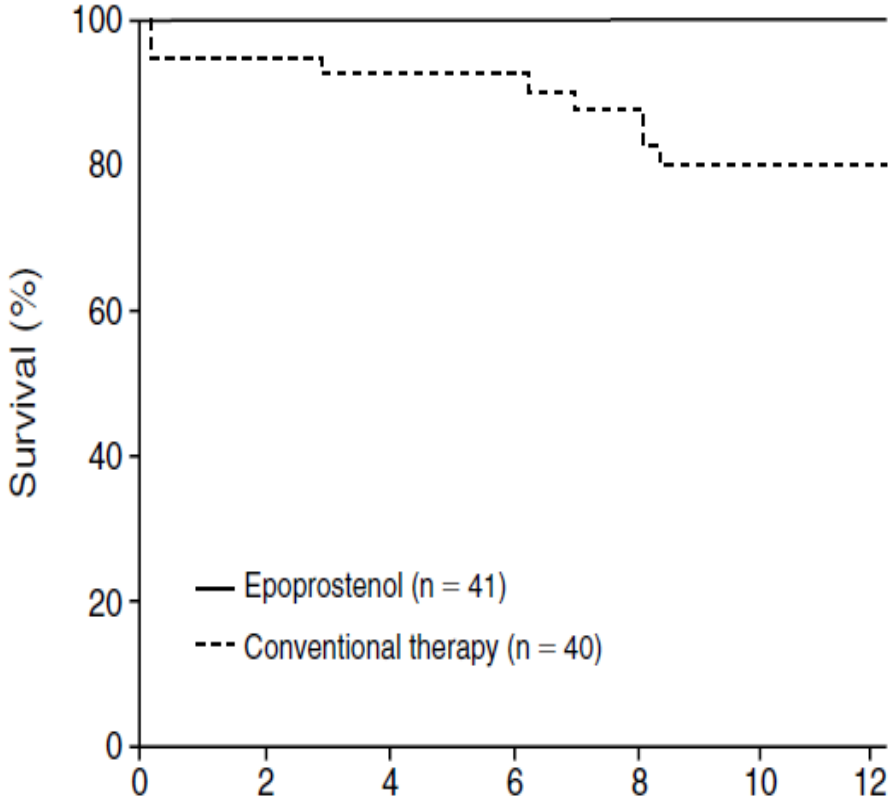
  6/18 patients with mPAP < 30 mmHg

Survival	1-year	2-year	3-year
Actual survival	100%	100%	100%
Transplant free survival	94%	94%	94%
Expected* survival [95% CI]	75% [68%-82%]	60% [50%-70%]	49% [38%-60%]

1. Sitbon O, *et al. Eur Respir J* 2014. 2.Humbert M, *et al. Eur Respir J* 2010

A COMPARISON OF CONTINUOUS INTRAVENOUS EPOPROSTENOL (PROSTACYCLIN) WITH CONVENTIONAL THERAPY FOR PRIMARY PULMONARY HYPERTENSION

ROBYN J. BARST, M.D., LEWIS J. RUBIN, M.D., WALKER A. LONG, M.D., MICHAEL D. MCGOON, M.D., STUART RICH, M.D., DAVID B. BADESCH, M.D., BERTRON M. GROVES, M.D., VICTOR F. TAPSON, M.D., ROBERT C. BOURGE, M.D., BRUCE H. BRUNDAGE, M.D., SPENCER K. KOERNER, M.D., DAVID LANGLEBEN, M.D., CESAR A. KELLER, M.D., SRINIVAS MURALI, M.D., BARRY F. URETSKY, M.D., LINDA M. CLAYTON, PHARM.D., MARIA M. JÖBSIS, B.A., SHELMER D. BLACKBURN, JR., B.A., DENISE SHORTINO, M.S., JAMES W. CROW, PH.D., FOR THE PRIMARY PULMONARY HYPERTENSION STUDY GROUP*



- 8 patients died during the 12-Week study

- All in the conventional therapy group

-Comparison of baseline charecteristics between survivors and those who died;

- Equal distribution in FC III and IV
- No differences in Hemodynamics
- Significant difference for the 6MWD (mean 6MWD:195 m in 8 patients who died mean 6WD :305 m in 73 survivors (P<0.003)

Barst RJ, *et al. N Engl J Med* 1996

Eur Respir J 2004; 24: 353–359
DOI: 10.1183/09031936.04.00028404

European Respiratory Journal
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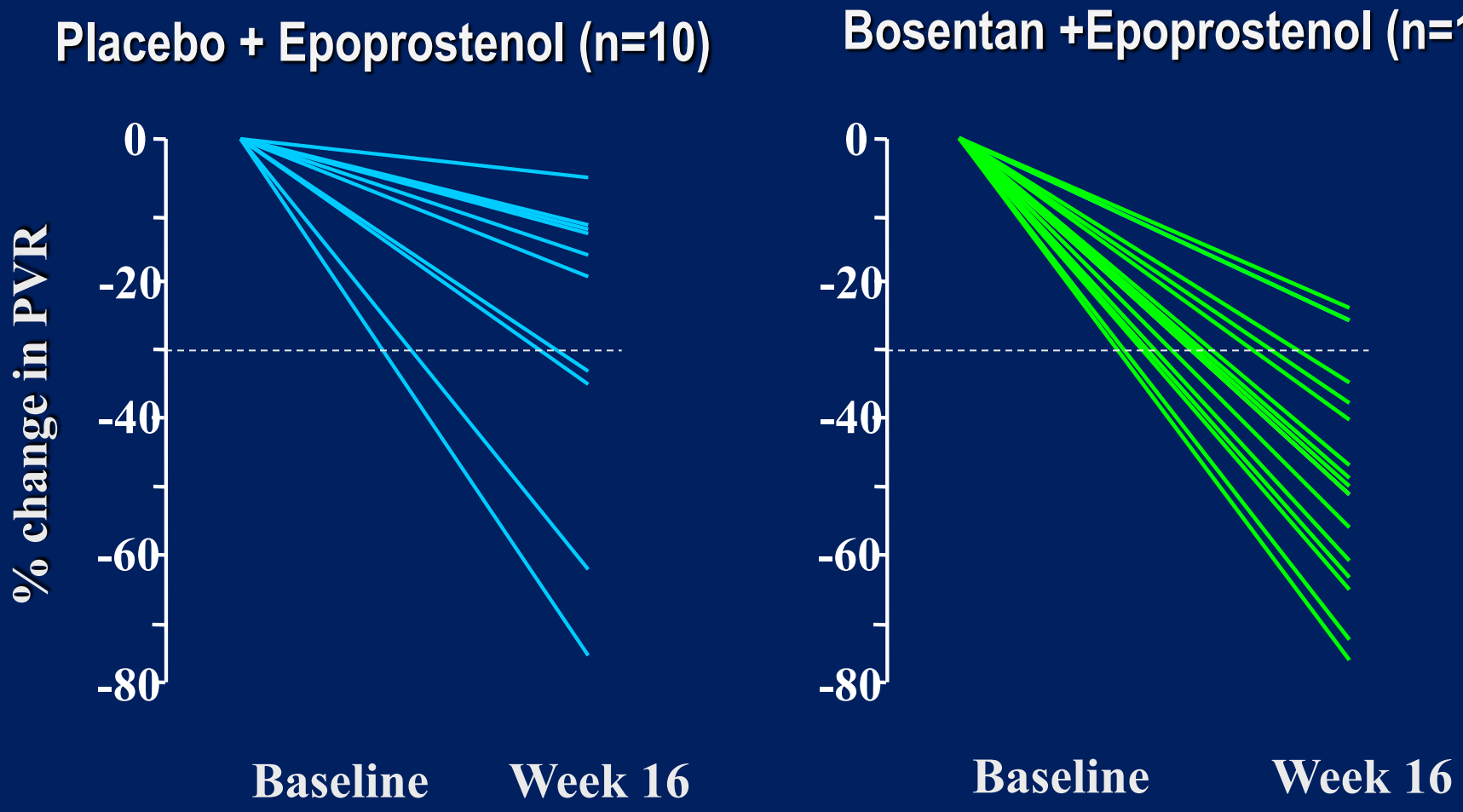
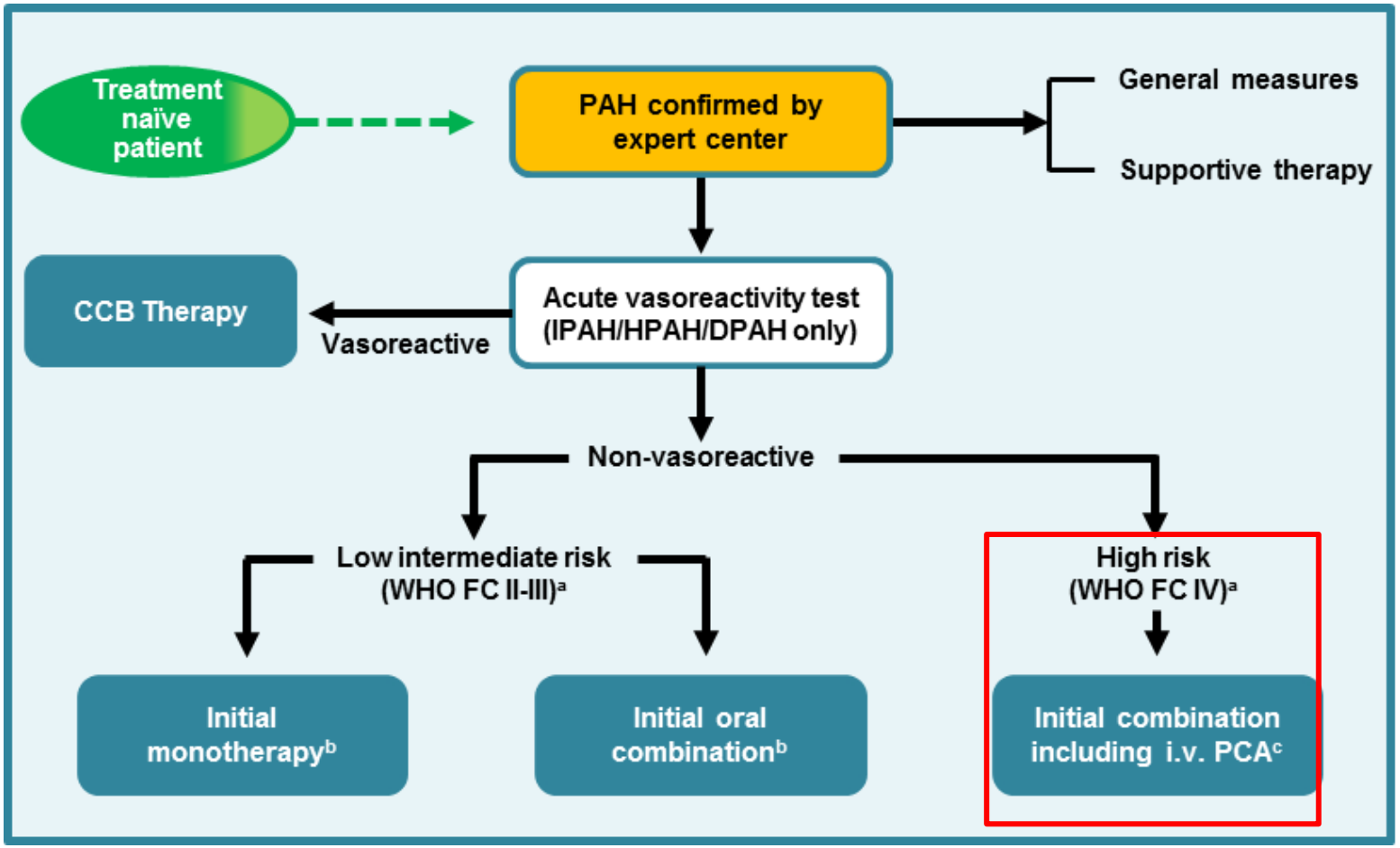
Combination of bosentan with epoprostenol in pulmonary arterial hypertension: BREATHE-2

M. Humbert*, R.J. Barst#, I.M. Robbins¶, R.N. Channick+, N. Galiè§, A. Boonstraƒ, L.J. Rubin+, E.M. Hom#, A. Manes§, G. Simonneau*

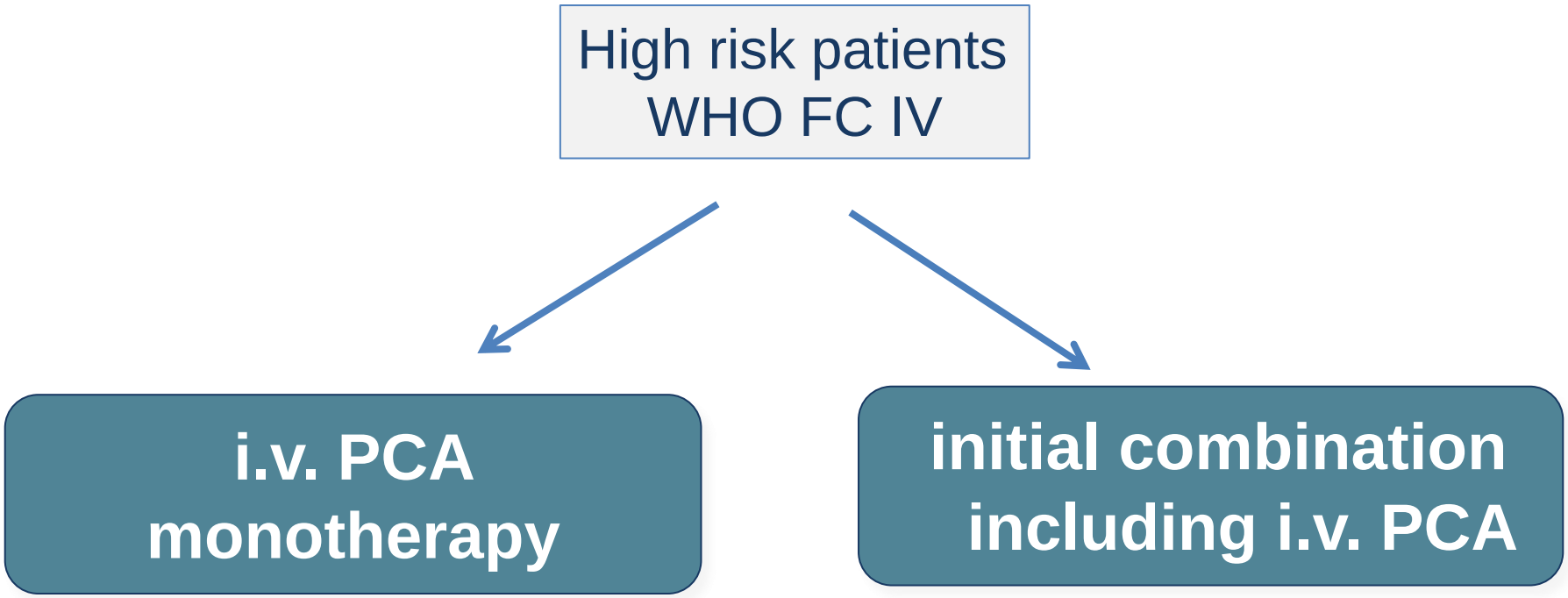


2015 ESC/ERS guidelines treatment algorithm

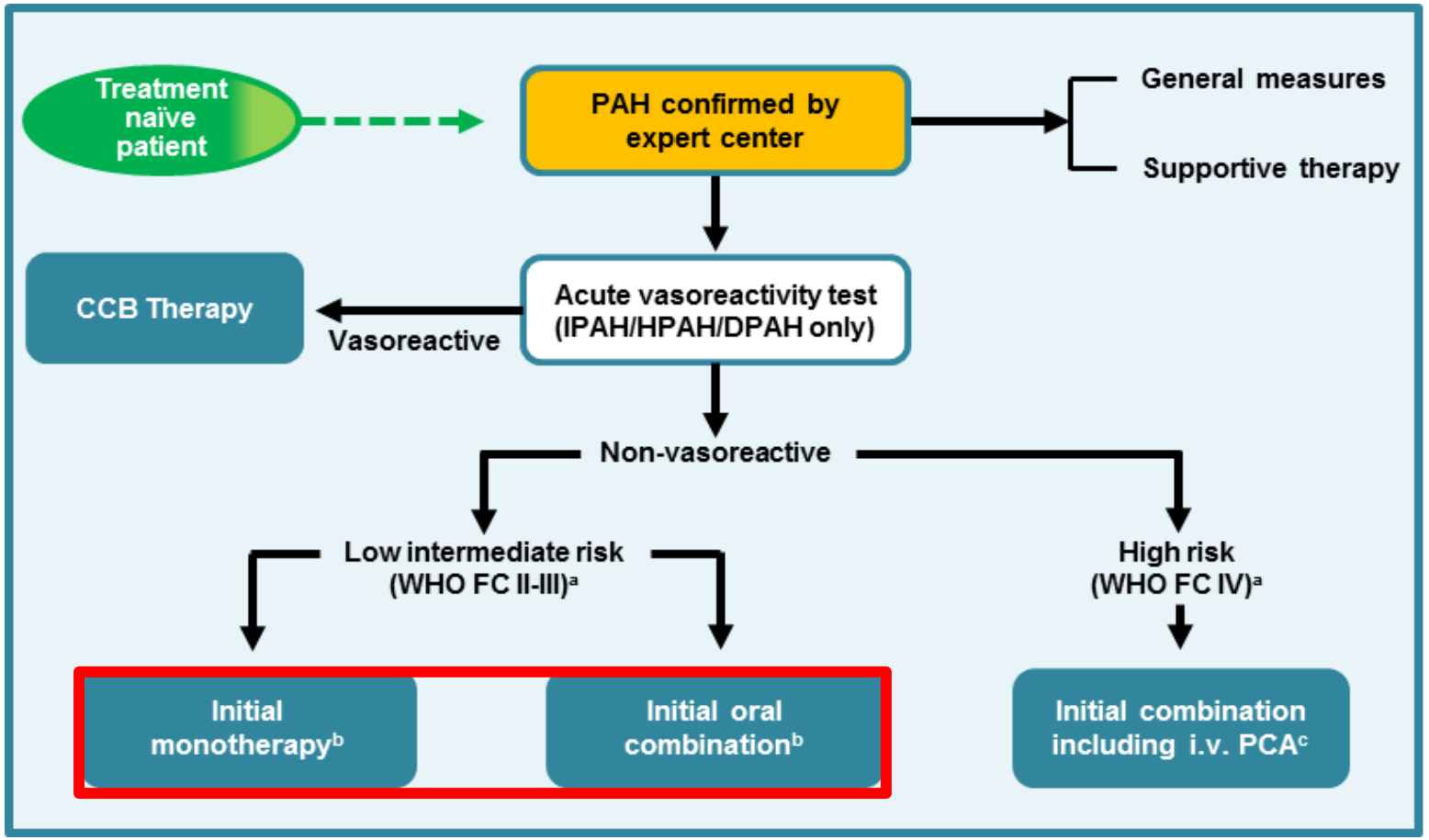


Eur Heart J 2016 & *Eur Respir J* 2015.

Proposal : High risk Patients

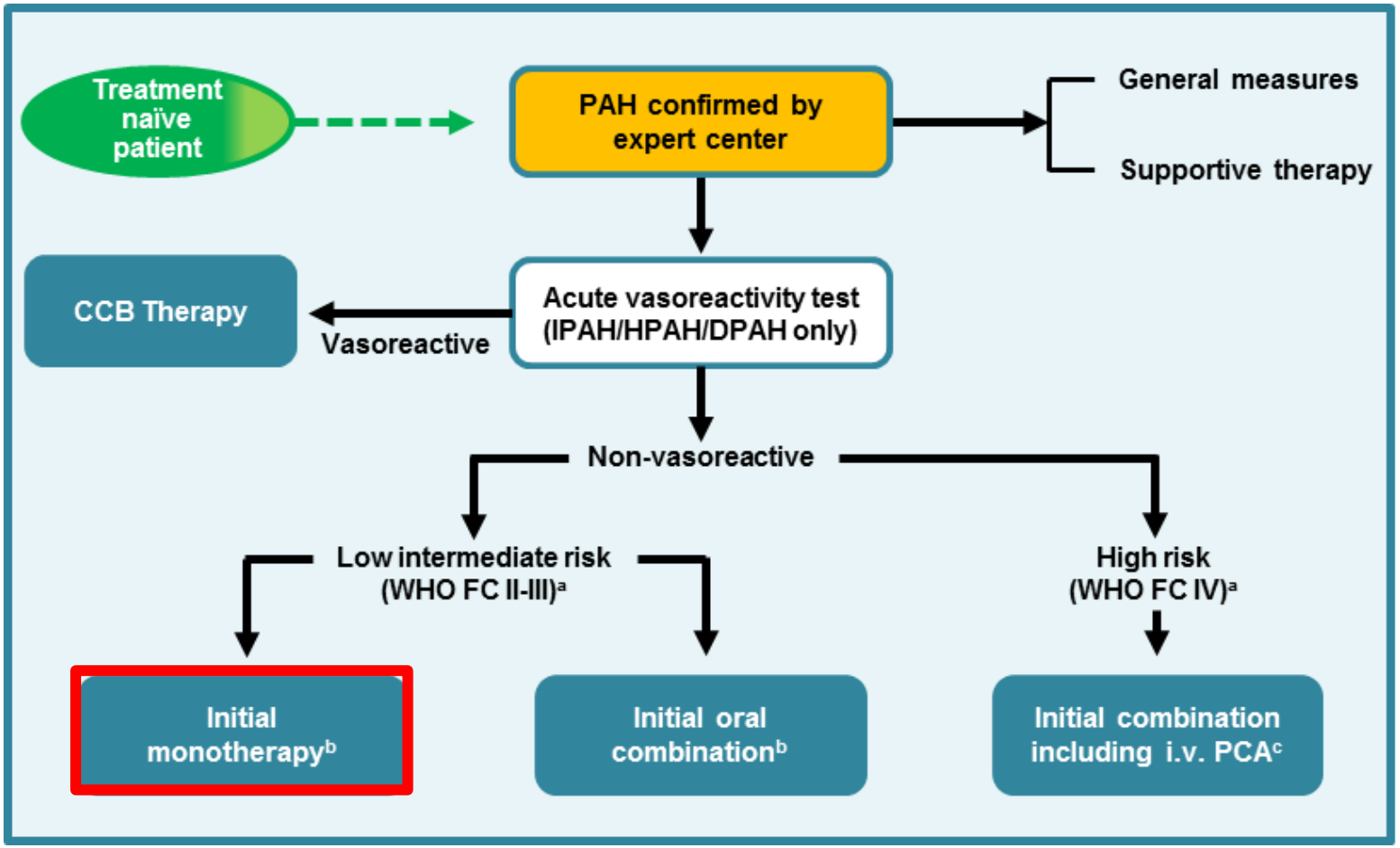


2015 ESC/ERS guidelines treatment algorithm



Eur Heart J 2016 & *Eur Respir J* 2015.

2015 ESC/ERS guidelines treatment algorithm

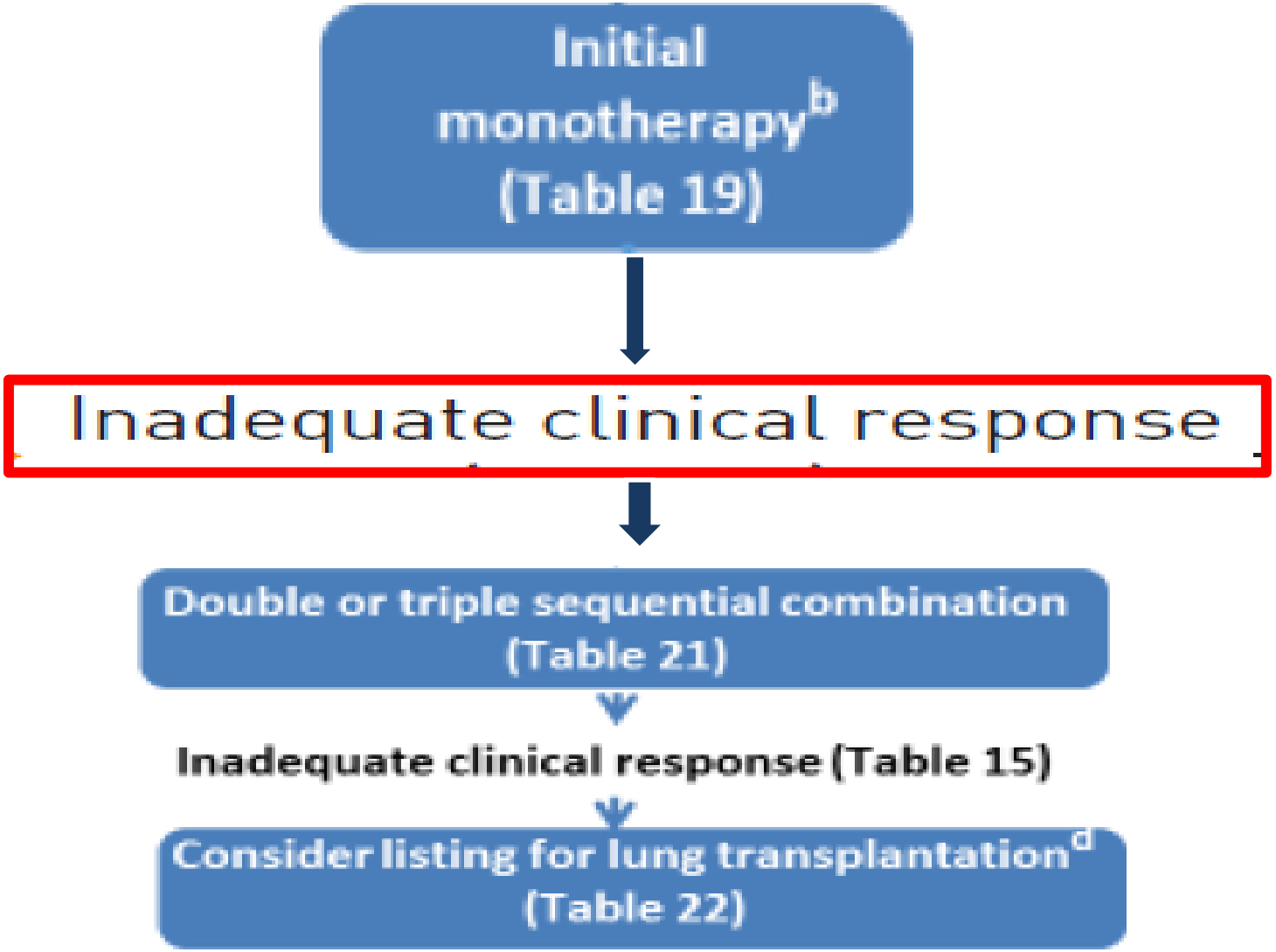


Eur Heart J 2016.& Eur Respir J 2015.

Recommandations for initial monotherapy in low/intermediate risk patients (NYHA FC II &III)

▪ ERA dual (ET_A & ET_B) ▪ ERA selective (ET_A)	▪ Prostanoids	▪ PDE-5 inhibitor ▪ sGC stimulators
Bosentan **(I A)**	**IV Epoprostenol** **(I A)**	**Sildenafil** **(I A)**
Ambrisentan **(I A)**	**Inh Iloprost** **(I B)**	**Tadalafil** **(I B)**
Macitentan **(I B)**	**SC treprostinil** **(I B)**	**Riociguat** **(I B)**
	Oral selexipag **(I B)**	

2015 ESC/ERS guidelines treatment algorithm



Recommendations for evaluation of the severity of PAH **and clinical response to therapy**

Recommendations	Class[a]	Level[b]
It is recommended to evaluate the severity of PAH patients with a panel of data derived from clinical assessment, exercise tests, biochemical markers and echocardiographic and haemodynamic evaluations (*Tables 13* and *14*)	I	C
It is recommended to perform regular follow-up assessments every 3—6 months in stable patients (*Table 14*)	I	C
Achievement/maintenance of a low-risk profile (*Table 13*) is recommended as an adequate treatment response for patients with PAH	I	C
Achievement/maintenance of an intermediate-risk profile (*Table 13*) should be considered an inadequate treatment response for most patients with PAH	IIa	C

Sequential combination therapy in PAH: RCTs with ERA and PDE-5 inh. or SGC

	Background therapy	Added therapy	Patients (n)	Primary endpoint	Primary-EP met
PHIRST	Naïve or bosentan	Tadalafil	405 (206)	6MWD	NO
PFIZER Study	Bosentan	Sildenafil	103	6MWD	NO
COMPASS-2	Sildenafil	Bosentan	334	Morbi-mortality	NO
PATENT	Naïve or ERA	Riociguat	443	6MWD	**Yes**
SERAPHIN	Naïve or sildenafil	Macitentan	742	Morbi-mortality	**Yes**

Sequential combination therapy in PAH: RCTs with Prostanoids and ERA or PDE-5 inh.

Study	Background therapy	Drug added	*n*	Primary endpoint	Primary EP met
STEP	Bosentan	Inh. iloprost	67	Δ6MWD	NO
COMBI	Bosentan	Inh. iloprost	40	Δ6MWD	NO
PACES	i.v. epoprostenol	Sildenafil	264	Δ6MWD	YES
TRIUMPH	Bosentan or sildenafil	Inh. treprostinil	235	Δ6MWD	YES
FREEDOM-C	Bosentan and/or sildenafil	Oral trepostinil	354	Δ6MWD	NO
FREEDOM-C2	Bosentan and/or sildenafil	Oral trepostinil	310	Δ6MWD	NO
GRIPHON	None, PDE-5i and/or ERA	Selexipag	1156	Morbidity-mortality	YES

Sequential combination therapy

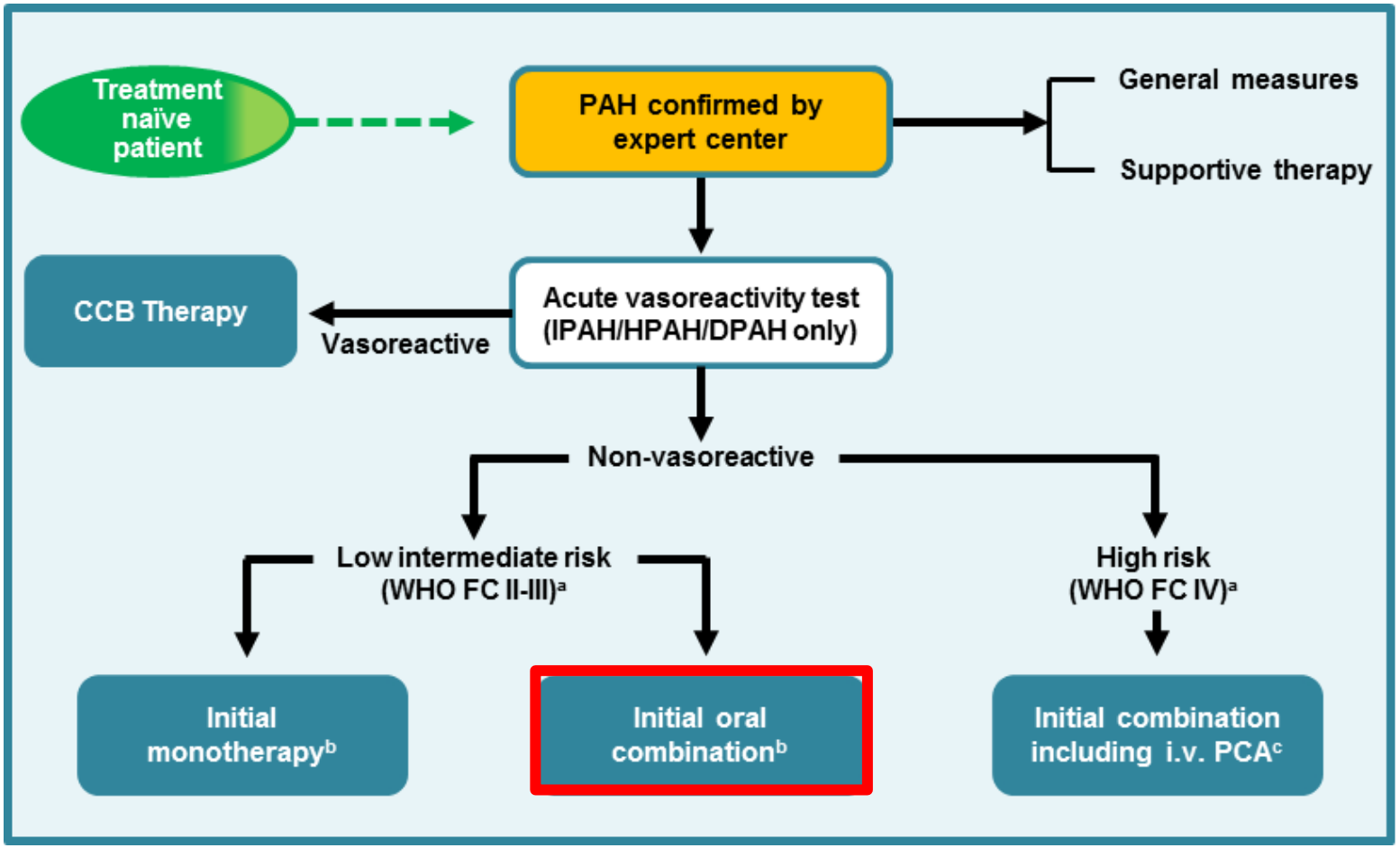
Table 20 Recommendations for efficacy of sequential drug combination therapy for pulmonary arterial hypertension (group 1), according to World Health Organization functional class. Sequence is by rating and by alphabetical order

Measure/treatment	Class[a] – Level[b]					
	WHO-FC II		WHO-FC III		WHO-FC IV	
Macitentan added to sildenafil[c]	I	B	I	B	IIa	C
Riociguat added to bosentan	I	B	I	B	IIa	C
Selexipag[d] added to ERA and/or PDE-5i[c]	I	B	I	B	IIa	C
Sildenafil added to epoprostenol	-	-	I	B	IIa	B
Treprostinil inhaled added to sildenafil or bosentan	IIa	B	IIa	B	IIa	C
Iloprost inhaled added to bosentan	IIb	B	IIb	B	IIb	C
Tadalafil added to bosentan	IIa	C	IIa	C	IIa	C
Bosentan added to epoprostenol	-	-	IIb	C	IIb	C
Bosentan added to sildenafil	IIb	C	IIb	C	IIb	C
Sildenafil added to bosentan	IIb	C	IIb	C	IIb	C
Other double combinations	IIb	C	IIb	C	IIb	C
Other triple combinations	IIb	C	IIb	C	IIb	C
Riociguat added to sildenafil or other PDE-5i	III	B	III	B	III	B

European Respiratory Society

***Eur Heart J* 2016 & *Eur Respir J* 2015**

2015 ESC/ERS guidelines treatment algorithm



Eur Heart J 2016. & *Eur Respir J* 2015.

The AMBITION trial

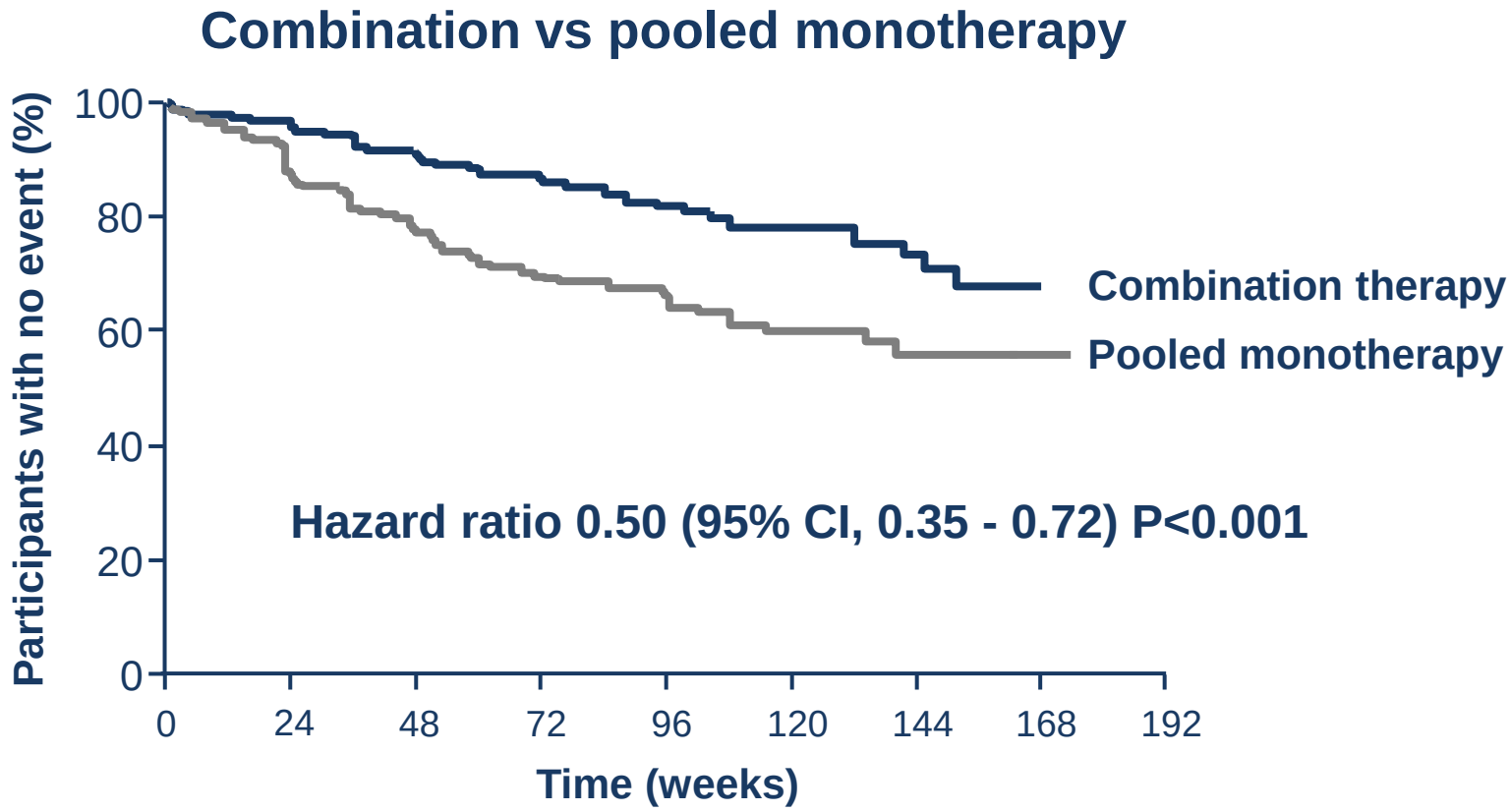
Initial Use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension

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

Galiè N, et al. N Engl J Med 2015

Ambition: Initial combination is better than monotherapy



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

Galiè N, *et al. N Engl J Med* 2015.

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]

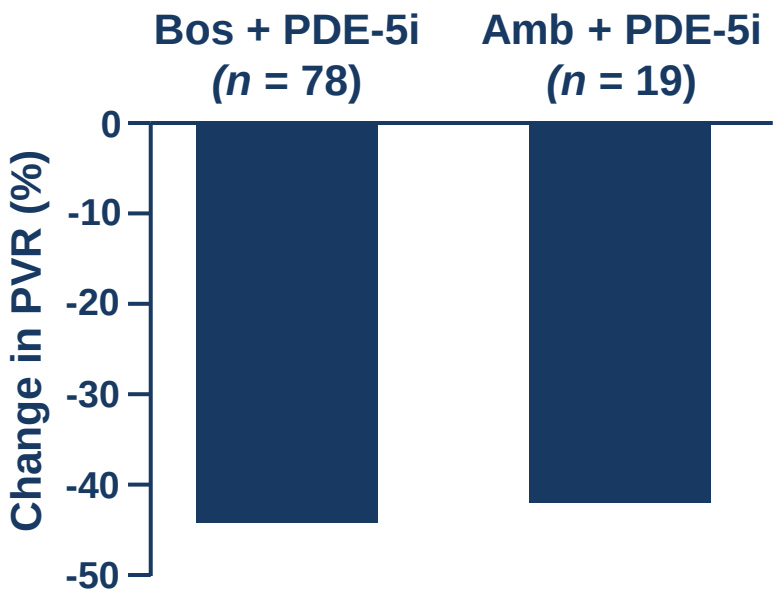
Sitbon O, *et al. Eur Respir J* 2016

Initial dual oral combination therapy
Effect on exercise capacity and haemodynamics

n=97	Baseline	*Median 4.1 months*	P-value[#]
NYHA FC (I : II : III : IV), *n*	0 : 15 : 70 : 12	4 : 57 : 31 : 5	<.001
6MWD, *m*	324 ± 132	395 ± 114	<.00001
BNP level, *ng/L* (n=42, median)	372	62	<.00001
Haemodynamics			
RAP, *mmHg*	9.5 ± 5.7	6.7 ± 4.5	<.00001
mPAP, *mmHg*	53.9 ± 10.4	45.1 ± 10.9	<.00001
CI, *L/min/m²*	2.14 ± 0.51	3.13 ± 0.79	<.00001
PVR, *dyn.s.cm⁻⁵*	1021 ± 357	565 ± 252	<.00001
Mean BP, *mmHg*	97.5 ± 17.7	87.2 ± 12.6	<.00001

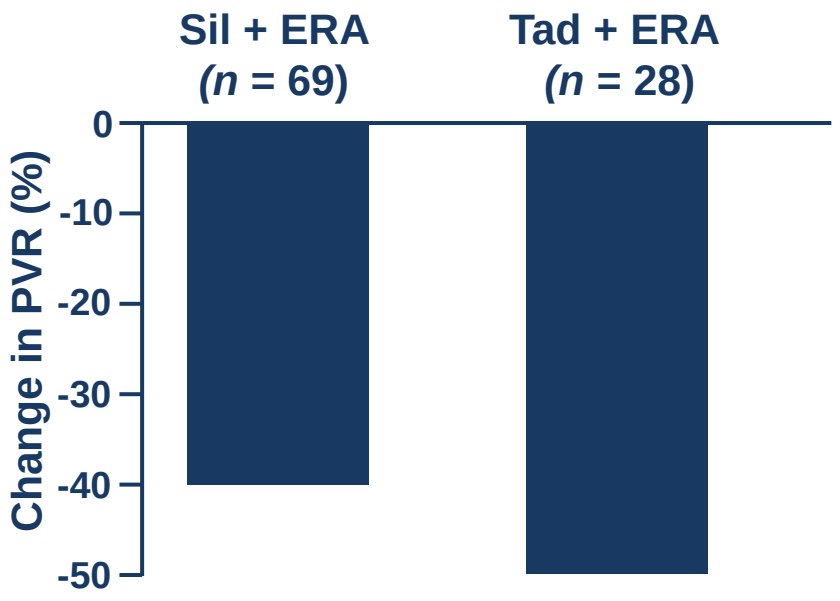
Sitbon O, *et al. Eur Respir J* 2016

The strategy works with different combinations



p = 0.74

Mean ± SD	-44% ± 20%	-42% ± 21%
95%CI	[-48%; -39%]	[-51%; -32%]

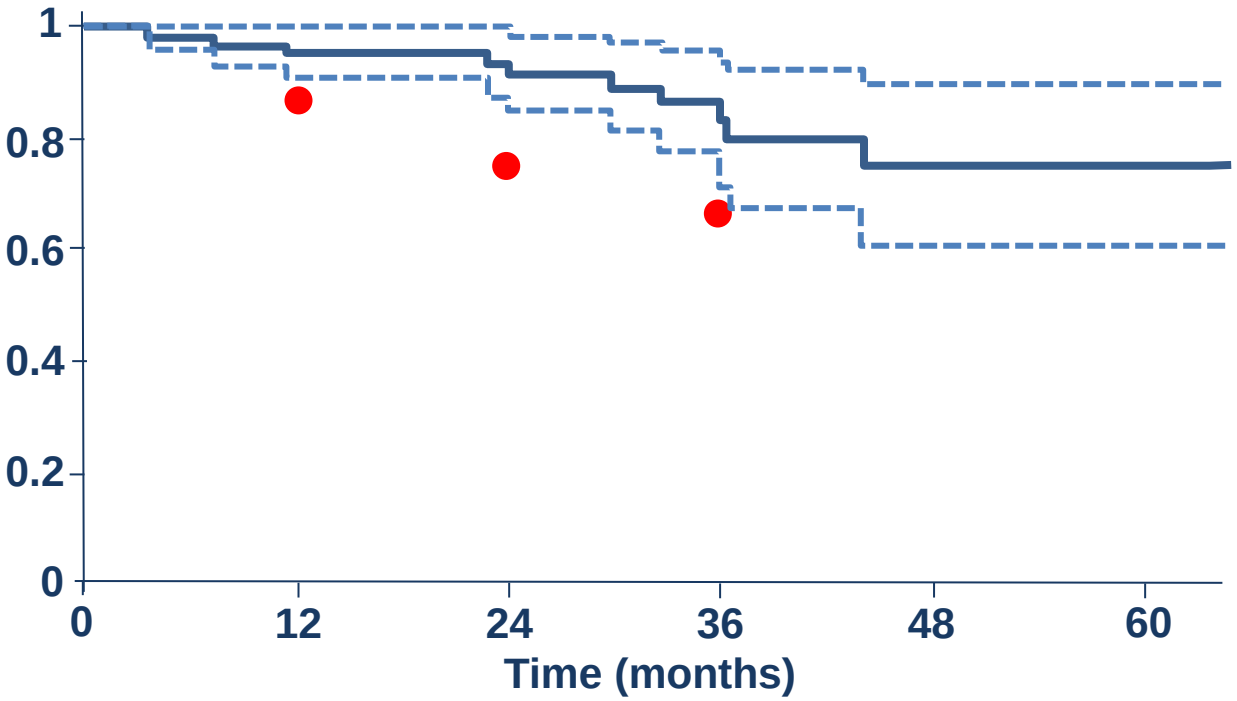


p = 0.03

-41% ± 20%	-49% ± 19%
[-45% ;-36%]	[-56%; -42%]

Sitbon O, *et al. Eur Respir J* 2016.

Long-term outcome



At risk, *n*	74	66	51	27	14	6
Actual survival [CI 95%]		96 [91-100]	94 [88-99]	84 [72-95]	75 [61-90]	
Expected survival [CI 95%]		86 [83-88]	75 [71-79]	66 [62-71]		

Humbert M, *et al. Eur Respir J* 201;Sitbon O, *et al. Eur Respir J* 2016.

Summary (1)

To combine drugs targeting different pathophysiologic PAH pathways is an appealing strategy to improve outcome

Effectiveness of sequential combination therapy is now well established. However results differ according to the study design and the nature of the combination tested and the level of recommendation should be individualized

Several recent RCTs have shown that the addition of a second drug is superior to monotherapy

The Griphon study has demonstrated for the 1st time that the sequential combination of 3 drugs is superior to 2 drugs

Summary (2)

Regarding upfront combination therapy data are still scarce. However there is growing evidence that this strategy could be highly effective and safe

In moderate risk patients (FC II and stable FC III) initial dual combination therapy with ERA and PD-E inhibitors seems effective and safe. Ambition study has clearly demonstrated that initial combination therapy is superior to monotherpy

Today, there is no direct comparison of efficacy and safety of initial combination therapy vs optimized sequential combination therapy

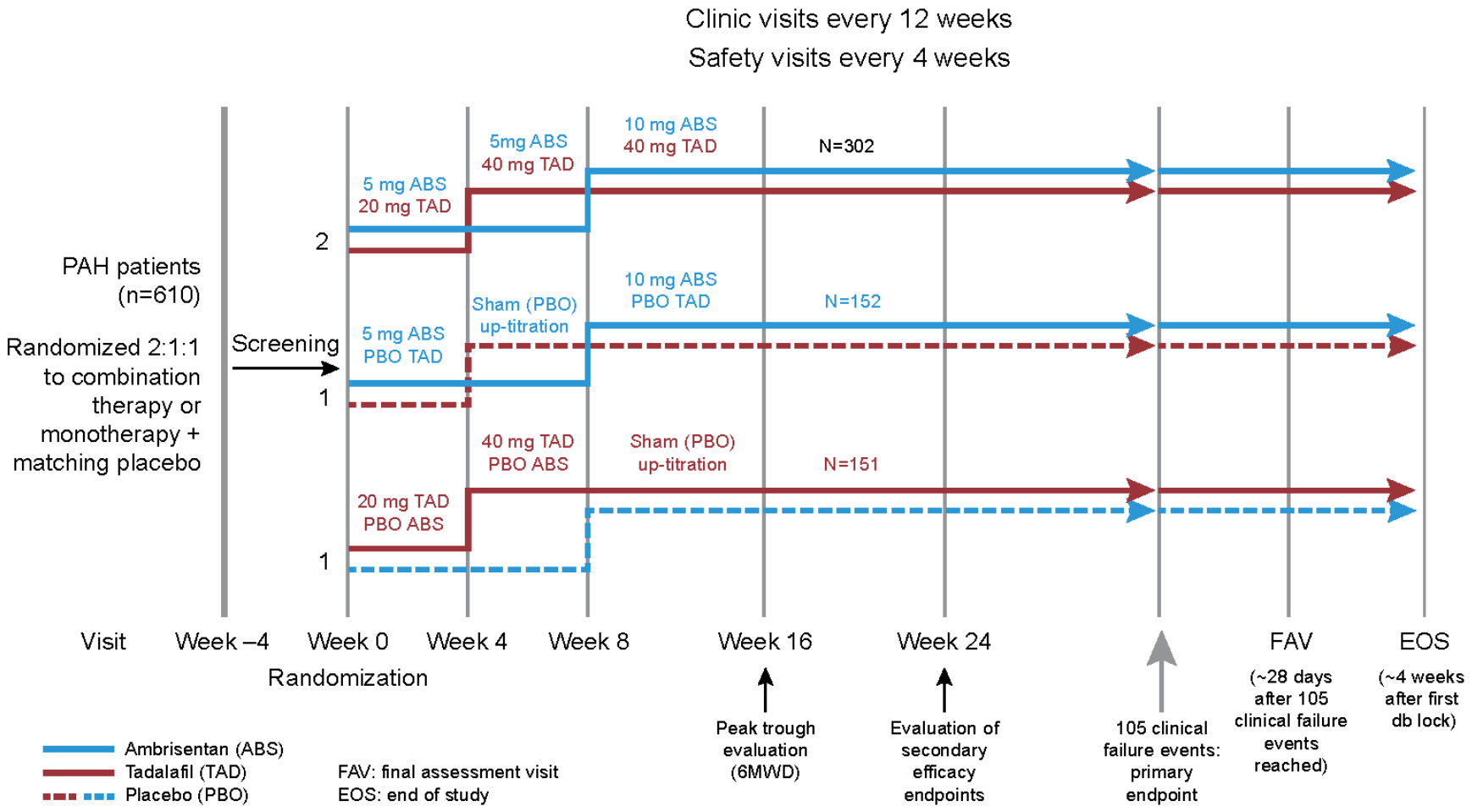
Combination therapy in PAH

Combination therapy In PAH:

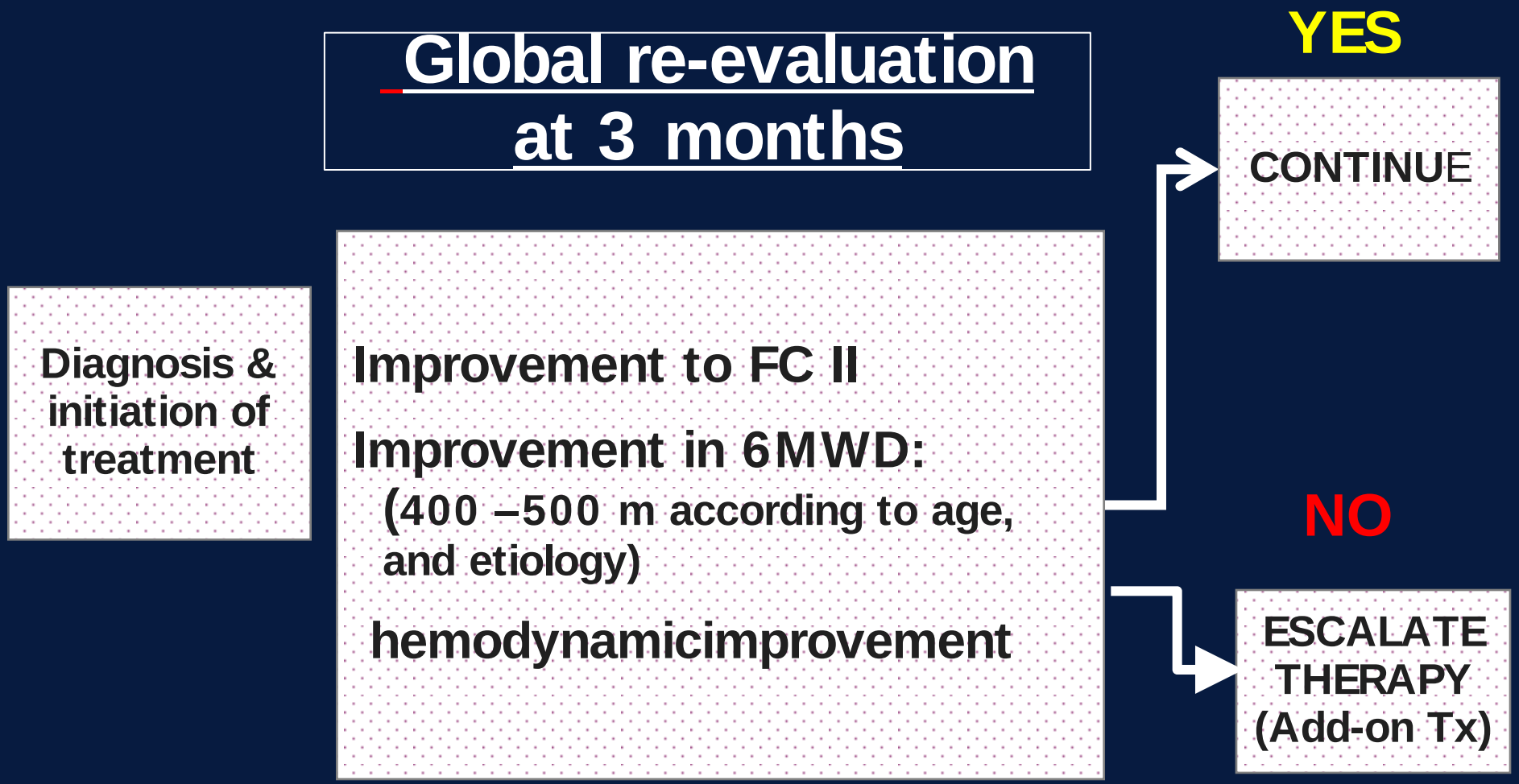
What is the best strategy?

Sequential (add-on)
or
up-front (first line)?

Ambition Sudy : Drugs titration

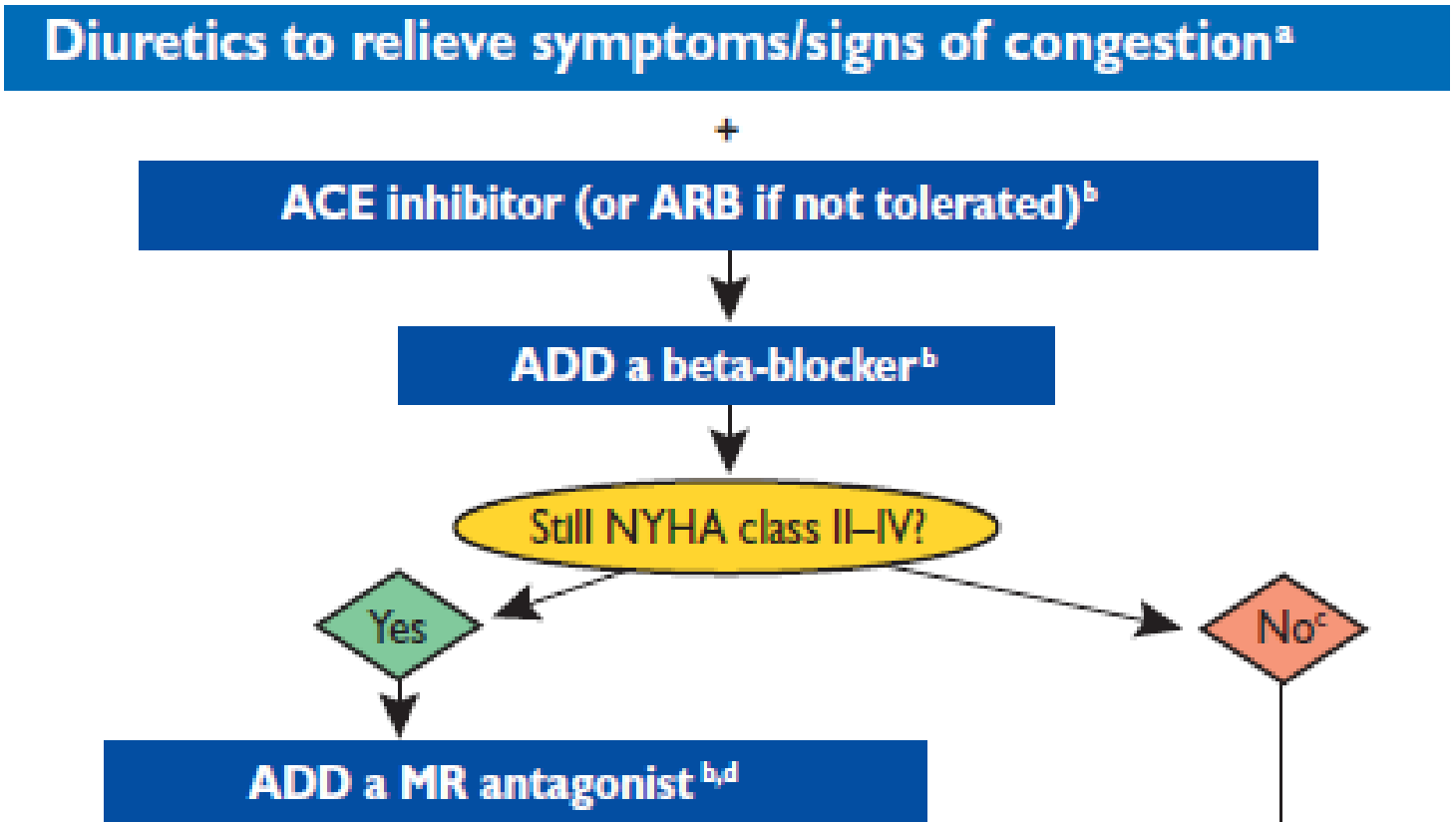


Paris-Sud University : Goal orientated strategy for sequential combination therapy (intermediate risk)



ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012

7. Pharmacological treatment of heart failure with reduced ejection fraction (systolic heart failure)



ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012

7. Pharmacological treatment of heart failure with reduced ejection fraction (systolic heart failure)

7.2 Treatments recommended in potentially all patients with systolic heart failure

7.2.1 Angiotensin-converting enzyme inhibitors and beta-blockers

The pivotal trials with beta-blockers were conducted in patients with continuing symptoms and a persistently low EF, despite treatment with an ACE inhibitor and, in most cases, a diuretic. Despite this, there is consensus that these treatments are complementary and that a beta-blocker and an ACE inhibitor should both be started as soon as possible after diagnosis of HF-REF.

Grading system for Classes of Recommendation & Level of Evidence used in ESC/ERS Guidelines

Classes of Recommendations	Definition	Suggested wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended/is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness /efficacy of the given treatment or procedure.	
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy.	Should be considered
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/ effective, and in some cases may be harmful.	Is not recommended

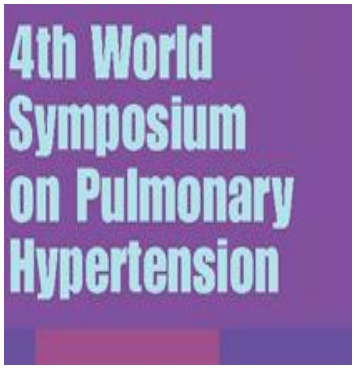
Level of Evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of Evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of Evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

This grading system presents some limitations for evaluation of drugs in rare diseases

In PAH, characteristics and designs of trials are non homogeneous

- Primary end point : 6' WD, 6' WD+FC, morbidity mortality, treatment failure
- Duration : from 12 weeks to 3 years
- Sample size : from 32 to 1156 patients
- Difference with regard secondary end points results

Recommended primary endpoint in phase III PAH studies



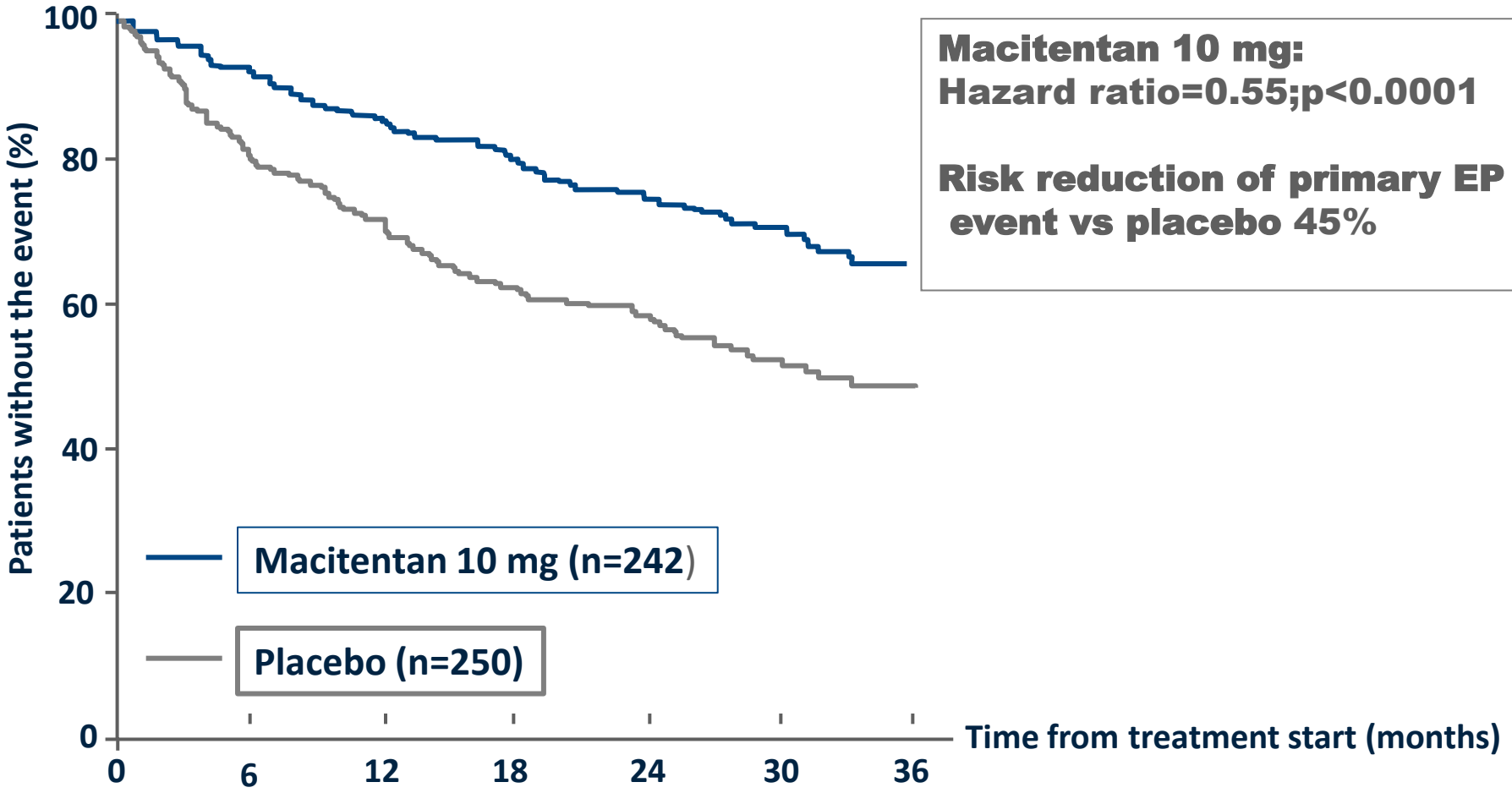
It was recommended :

- A composite clinical outcome endpoint that includes mortality should be used as the primary endpoint in future phase III trials in PAH
- A uniform definition of PAH worsening should be employed
- Events should be adjudicated by blinded independent committee

Interpretation of morbidity-mortality trials in PAH

TRIAL	Inclusion Period	Maximum Follow-up
Seraphin (n=742) : Primary end-point met Macitentan vs placebo 64% pre- treated with PDE5-inh or Prostanoids	1.5 year	3 years
Griphon (n=1156) : Primary end-point met Selexipag vs placebo 80% treated with PDE5-in and or ERA	3.5 years	3 years
Ambition (n=605) : Primary end-point met Ambrisentan+Tadalafil vs monotherapy	3.8 years	3 years

Seraphin :Primary endpoint: morbidity and mortality



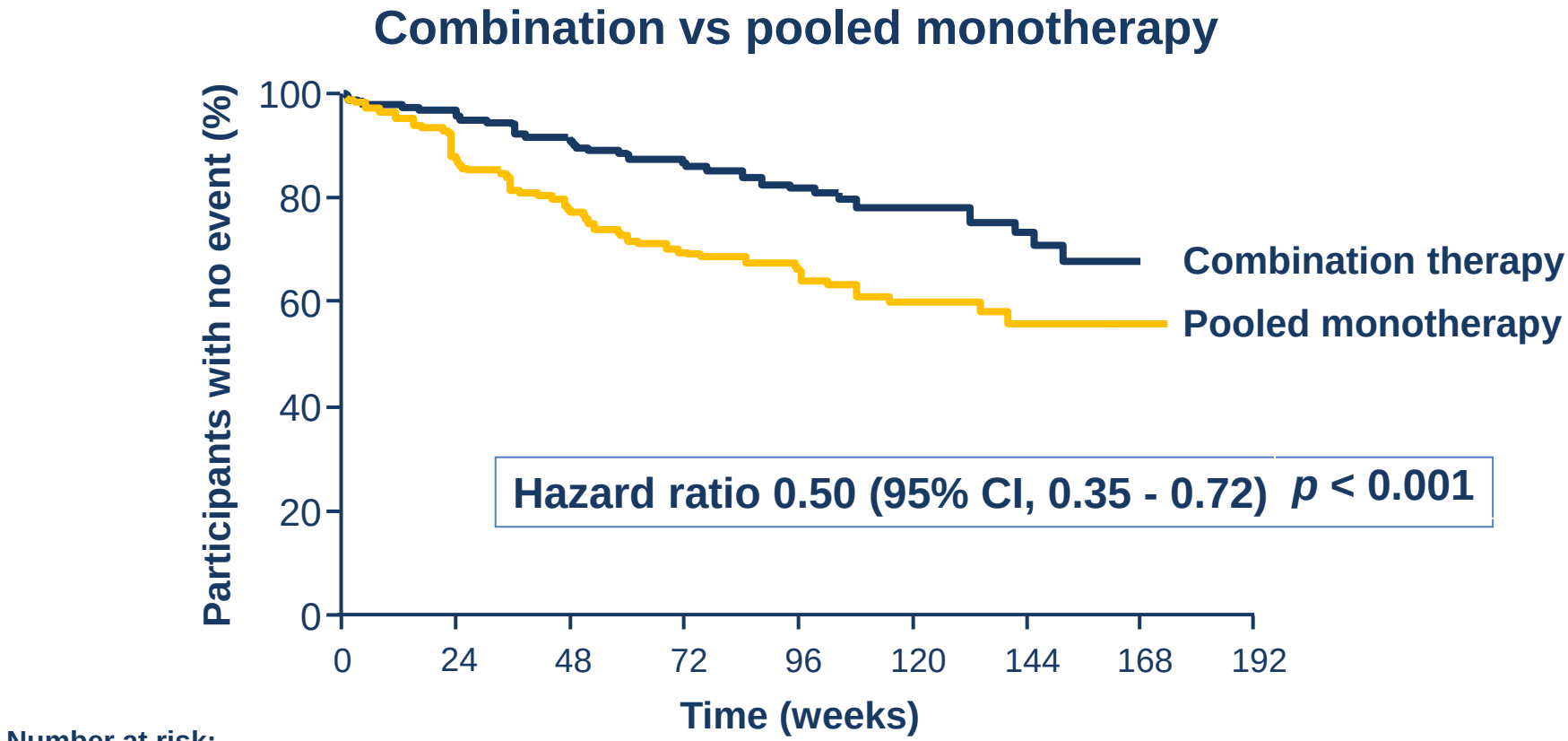
Pulido T, *et al. N Engl J Med* 2013

SERAPHIN :Different components of the morbidity-mortality primary endpoint

	Placebo *n* = 250	Macitentan 10 mg *n* = 242
Patients with an event n (%)	**116 (46.4)**	**76 (31.4)**
Type of the 1st event, n (%)		
PAH worsening	**93 (37.2)**	**59 (24.4)**
Initiation of Prostanoids	**6 (2.4)**	**1 (0.4)**
Deaths All causes	**17 (6.8)**	**16 (6.6)**

Pulido T, *et al. N Engl J Med* 2013

Ambition: Primary endpoint: morbidity and mortality



Number at risk:

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

Galiè N, *et al. N Engl J Med* 2015.

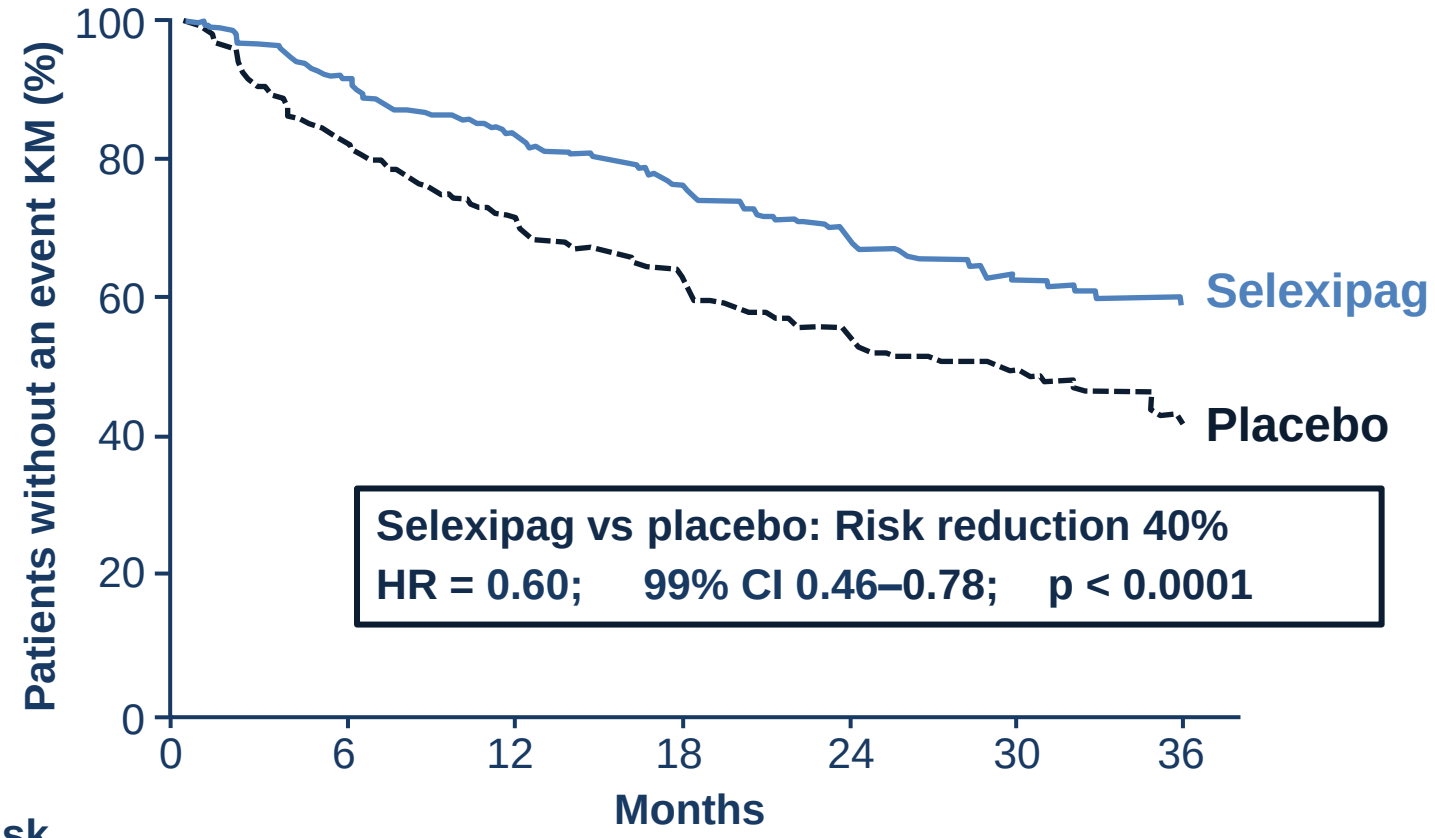
Ambition:Different components of the morbidity-mortality primary endpoint

	Combination therapy (n=253)	Pooled monotherapy (n=247)	Ambrisentan monotherapy (n=126)	Tadalafil monotherapy (n=121)	Total (n=500)
Number of subjects with first event, n (%)	46 (18%)	77 (31%)	43 (34%)	34 (28%)	123 (25%)
Death	9 (3.6%)	8 (3.2%)	2 (2%)	6 (5%)	17 (3%)
Hospitalisation for worsening PAH	10 (4%)	30 (12%)	18 (14%)	12 (10%)	40 (8%)
Disease progression	10 (4%)	16 (6%)	12 (10%)	4 (3%)	26 (5%)
Unsatisfactory long-term clinical response	17 (7%)	23 (9%)	11 (9%)	12 (10%)	40 (8%)

Based on subject's first event

Galie N et al New Engl J Med 2015

Griphon: Primary endpoint: morbidity and mortality



No. at Risk

Placebo	582	433	347	220	149	88	28
Selexipag	574	455	361	246	171	101	40

O Sitbon et al N Engl J Med 2015

Griphon: Primary endpoint: morbidity and mortality

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)

O Sitbon et al N Engl J Med 2015

Death as first event in morbidity-mortality trials

- PAH is a progressive disease and death is generally preceded by a clinical deterioration

- Sudden death is rare, especially in Functional Class II or III patients. It is more frequent in Class IV unstable patients, but this population is excluded from current RCTs

- In a patient with a 1st event of clinical deterioration then receiving iv PGI and finally dying the 1st event taken in account for the primary endpoint in this patient is not « death » but « clinical deterioration «

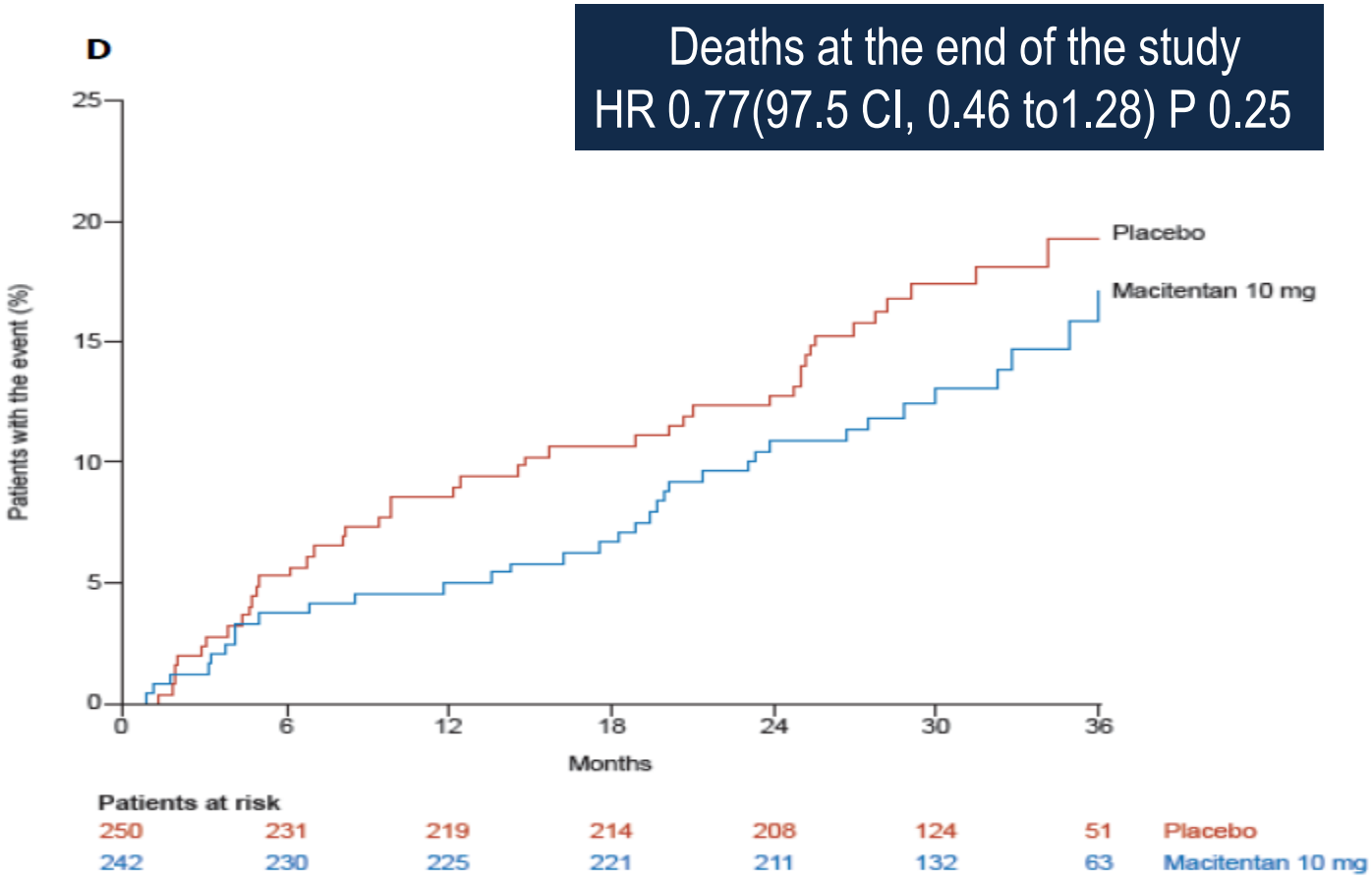
Mortality: Other analysis

- Mortality as first event

- Mortality at the end of the treatment (EOT)
  end of double-blind period (including deaths occuring within 4 weeks after an adjudicated worsening event)

- Mortality at the end of the study (EOS)
  EOS when the pre-specified number of events of the primary E-P is reached. Vital status should be analyzed in all patients at this time point. Nethertheless, the risk of death is limited at the EOS, because patients are allowed after an adjudicated worsening event to receive other PAH drugs (iv PGI2) and/or open label study drug.

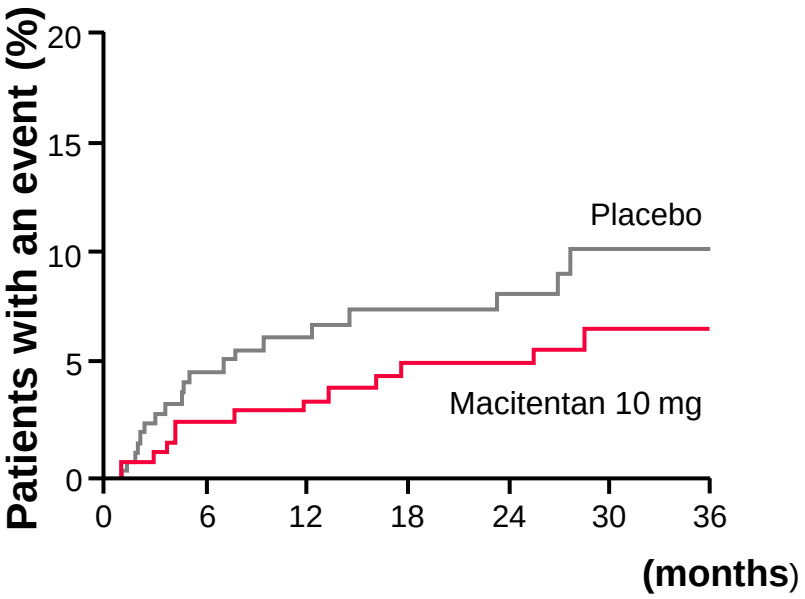
Seraphin deaths at the end of the study



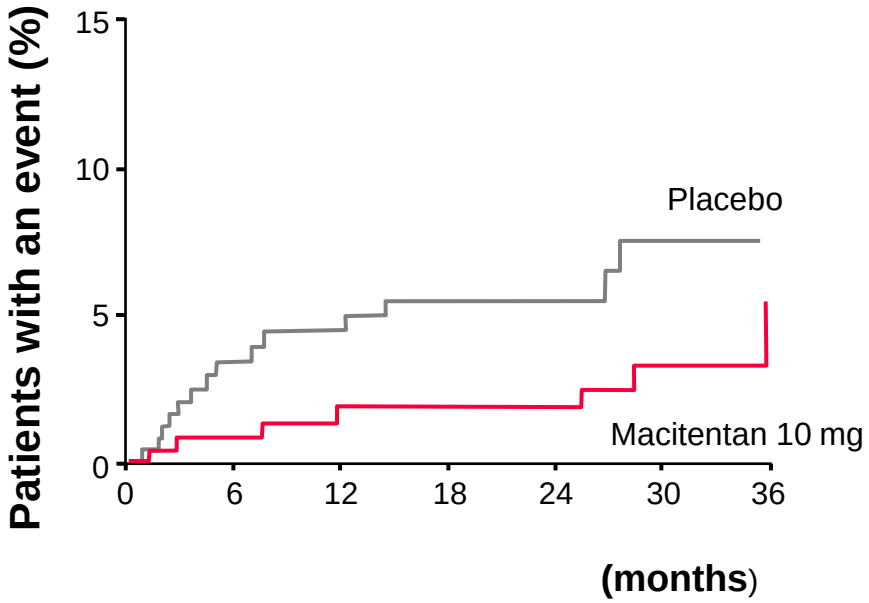
Pulido T, *et al. N Engl J Med* 2013; Suppl

Seraphin deaths at the end of randomized treatment

All causes of deaths
HR 0.64 (97.5% CI 0.29 to 1.42) p = 0.20



Deaths due to PAH
HR 0.44 (97.5% CI 0.22 to 1.12) p = 0.07



Pulido T, *et al. N Engl J Med* 2013; Suppl

Ambition: deaths at the end of the study

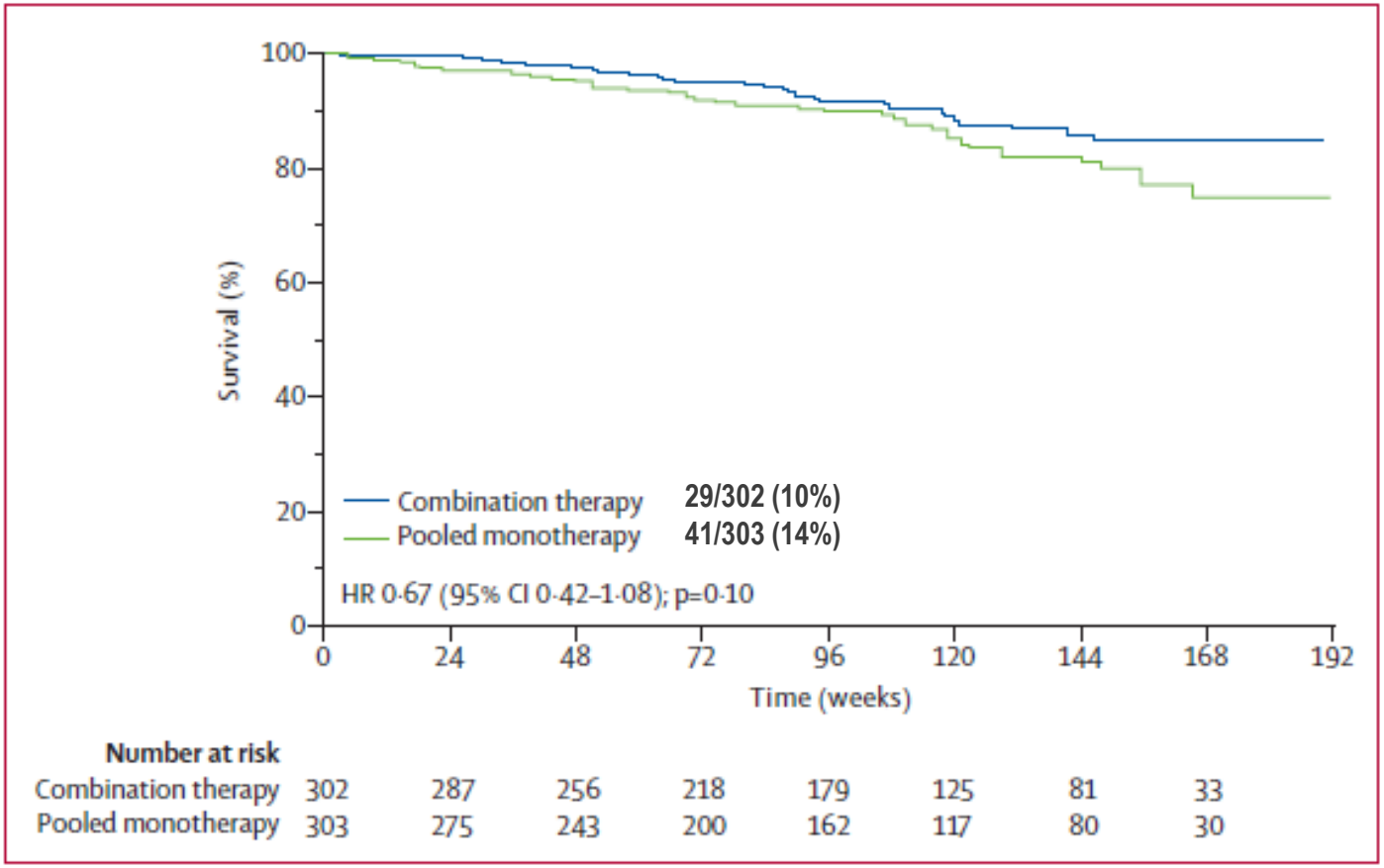


Figure 1: **Kaplan-Meier estimates of survival from baseline to end of study**

M Hoeper et al Lancet Respir Med 2016 (published online october 10th)

Ambition: deaths at the end of randomized treatment

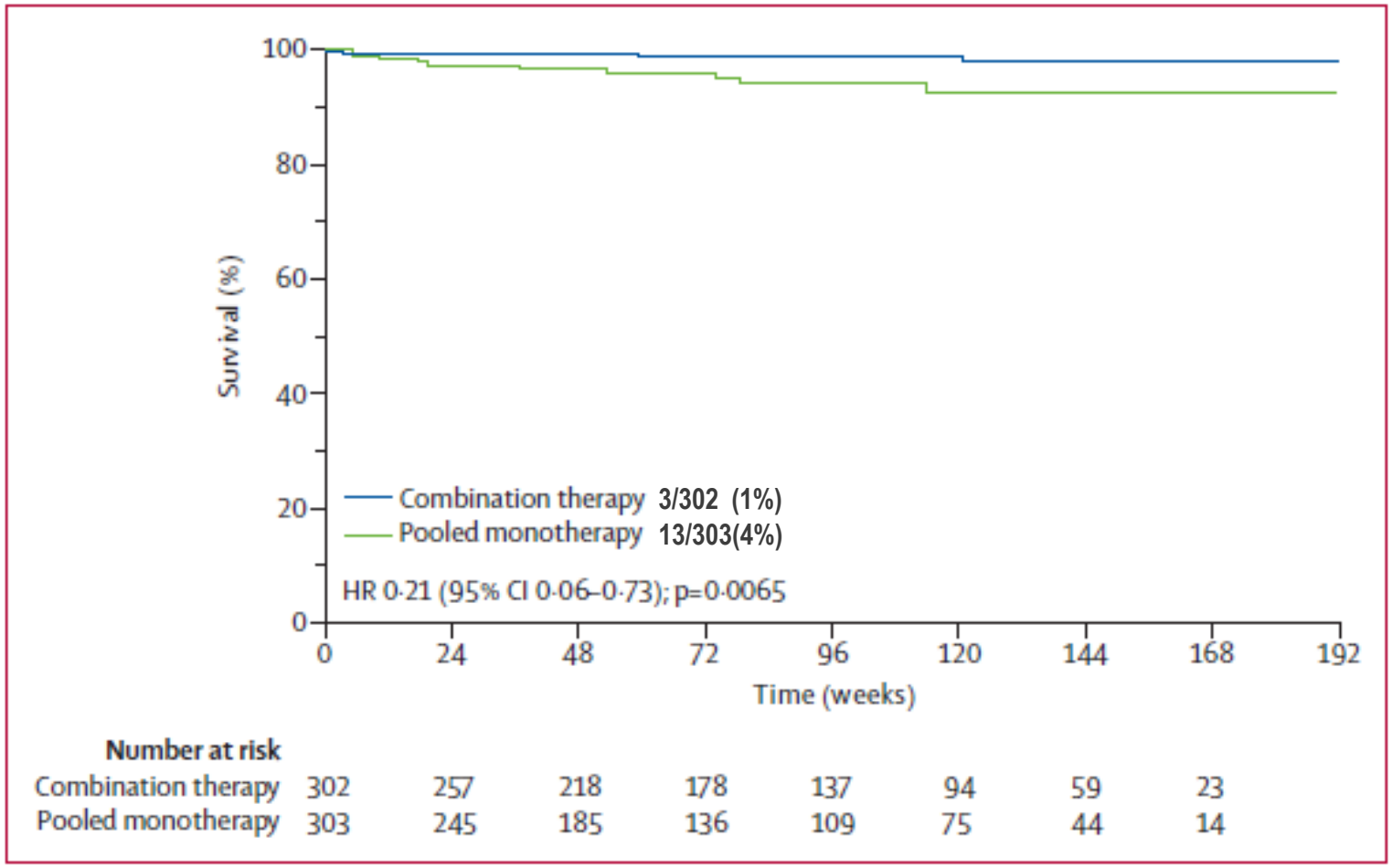
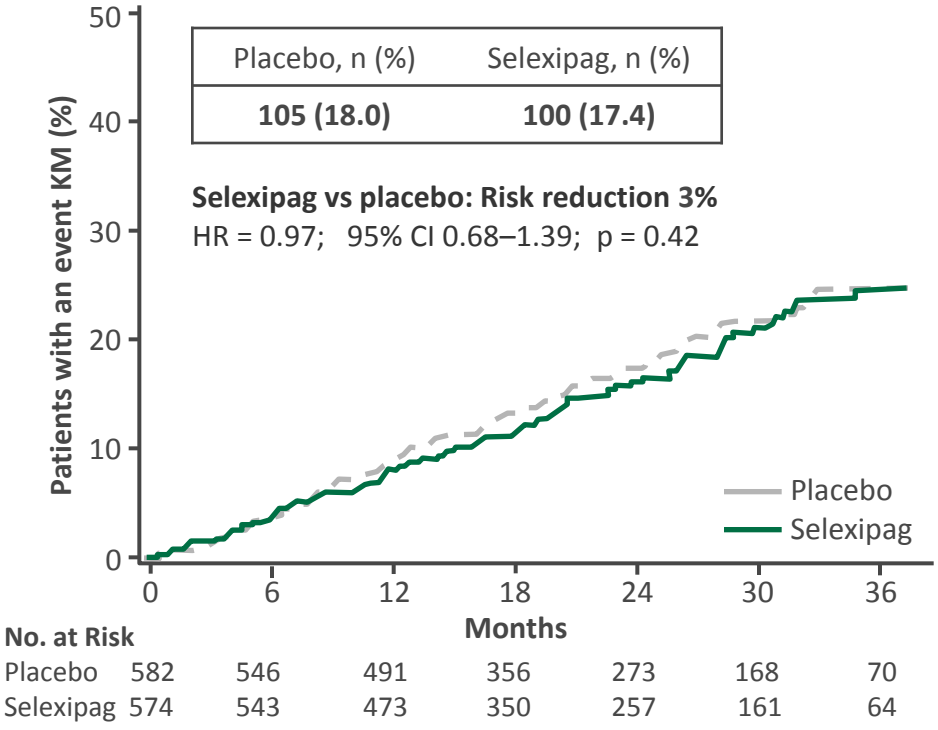


Figure 3: **Post-hoc Kaplan-Meier estimates of survival from baseline to 7 days after the end of each patient's assigned treatment**

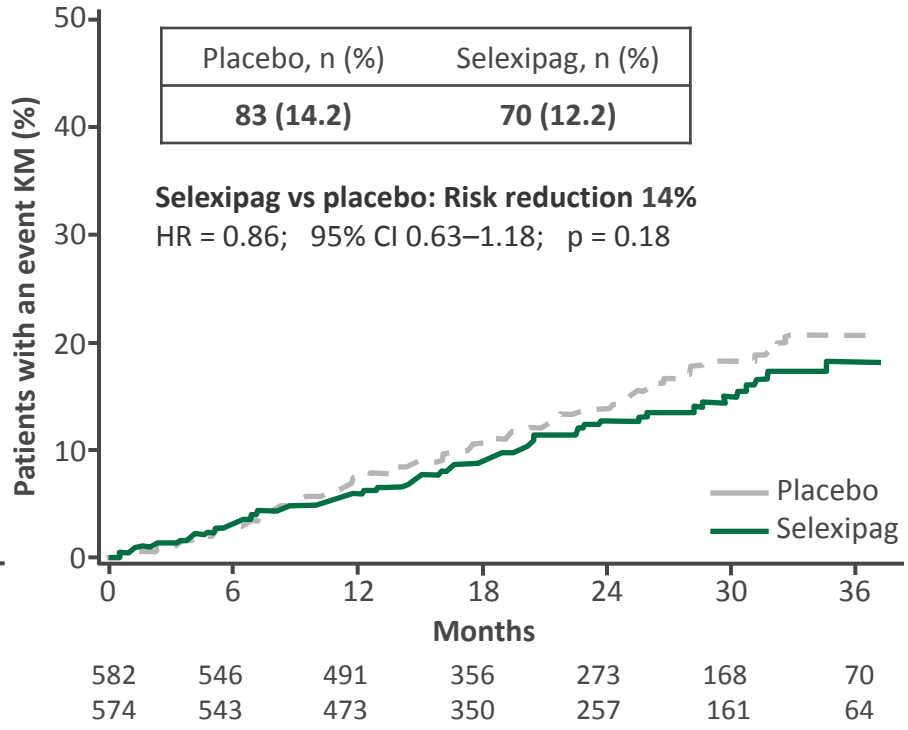
M Hoeper et al Lancet Respir Med 2016 (published online october 10th)

At the end of the study

Death from all causes



Death due to PAH



O Sitbon et al N Engl J Med 2015 suppl

NICE

6TH

February 27-28
March 1, 2018

WORLD SYMPOSIUM ON PULMONARY HYPERTENSION