Traitement de l'HTAP en 2014

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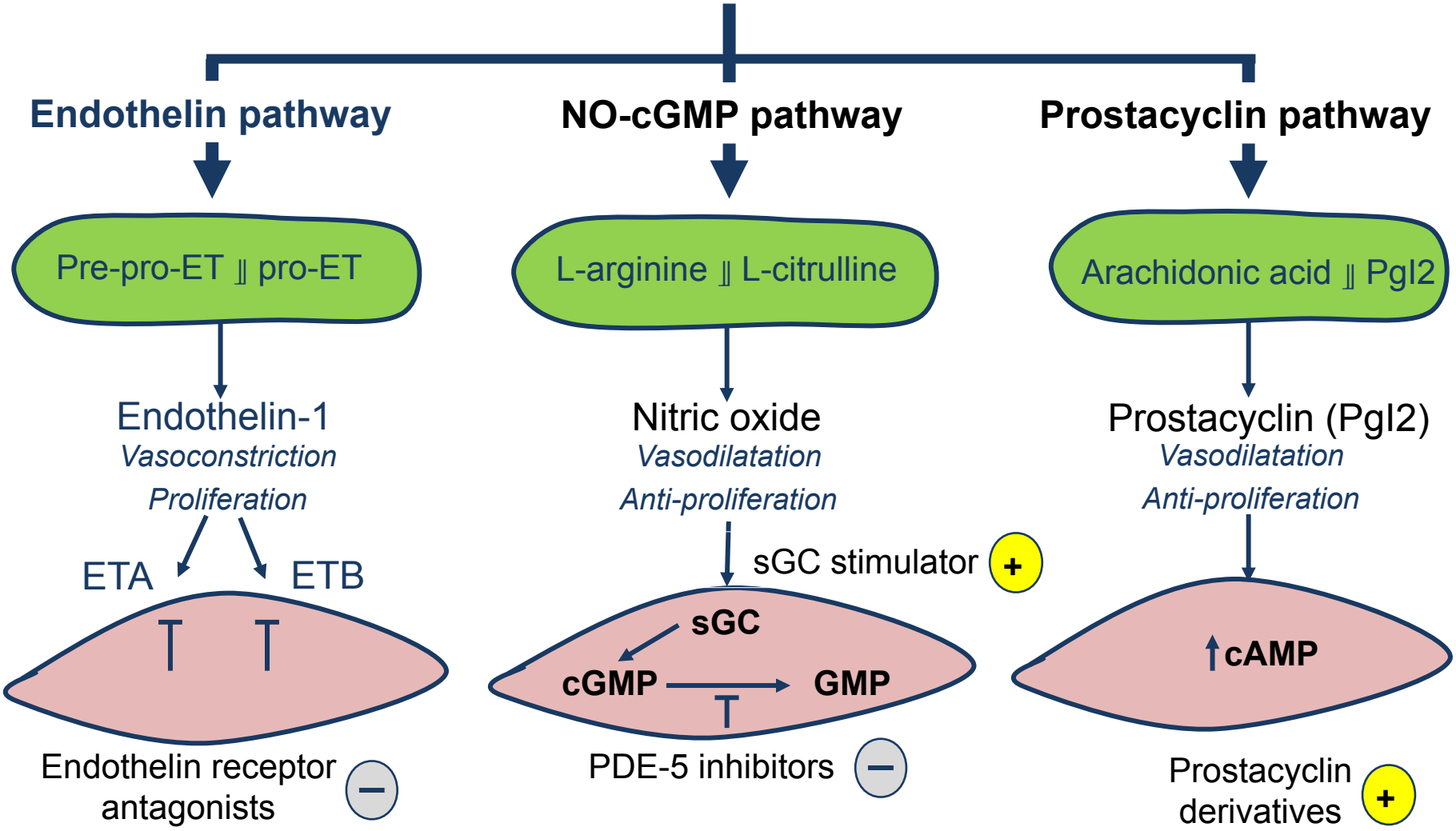
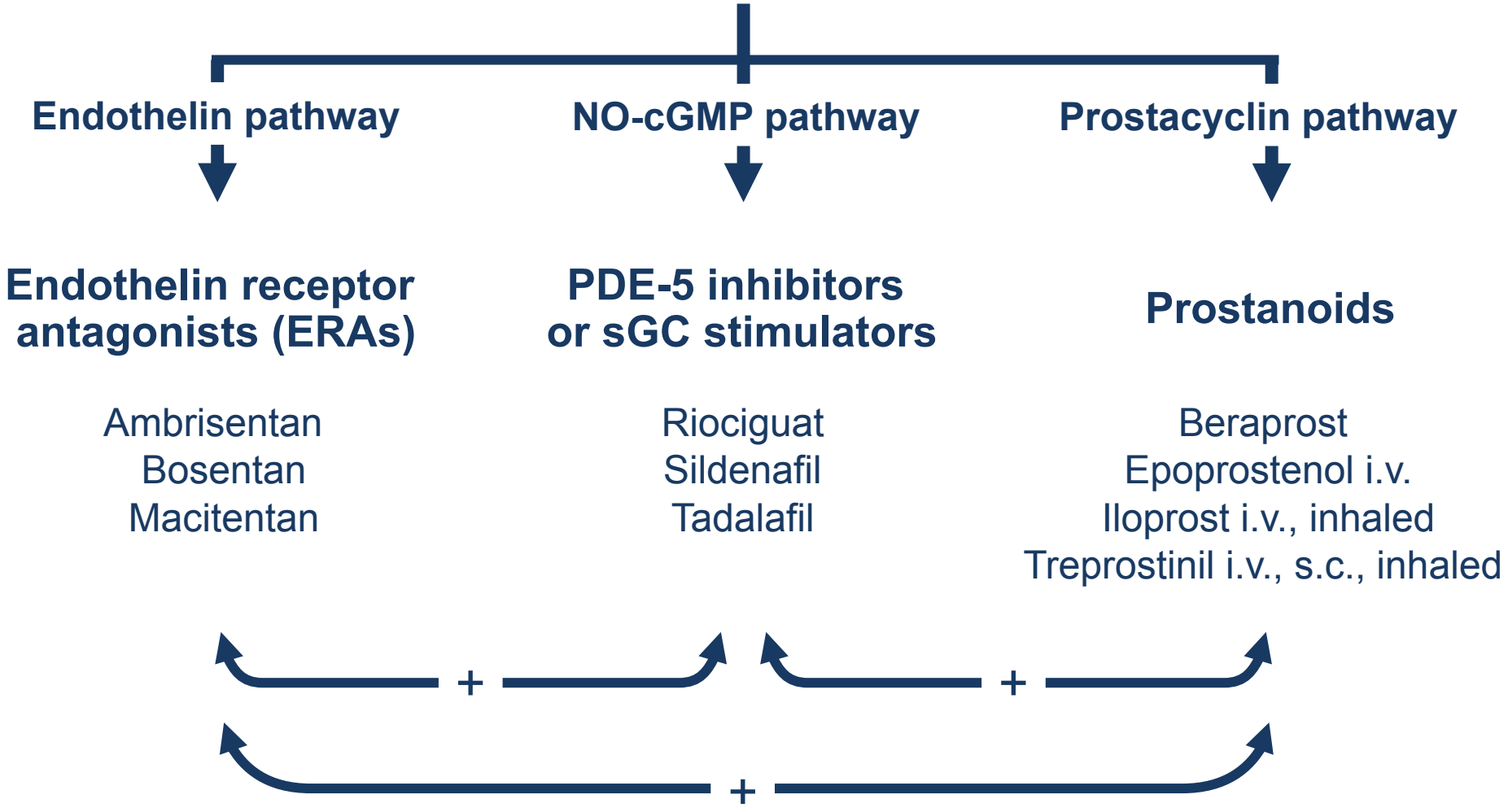
DHU Thorax Innovation

PAH-specific therapies target the three signalling pathways involved in PAH



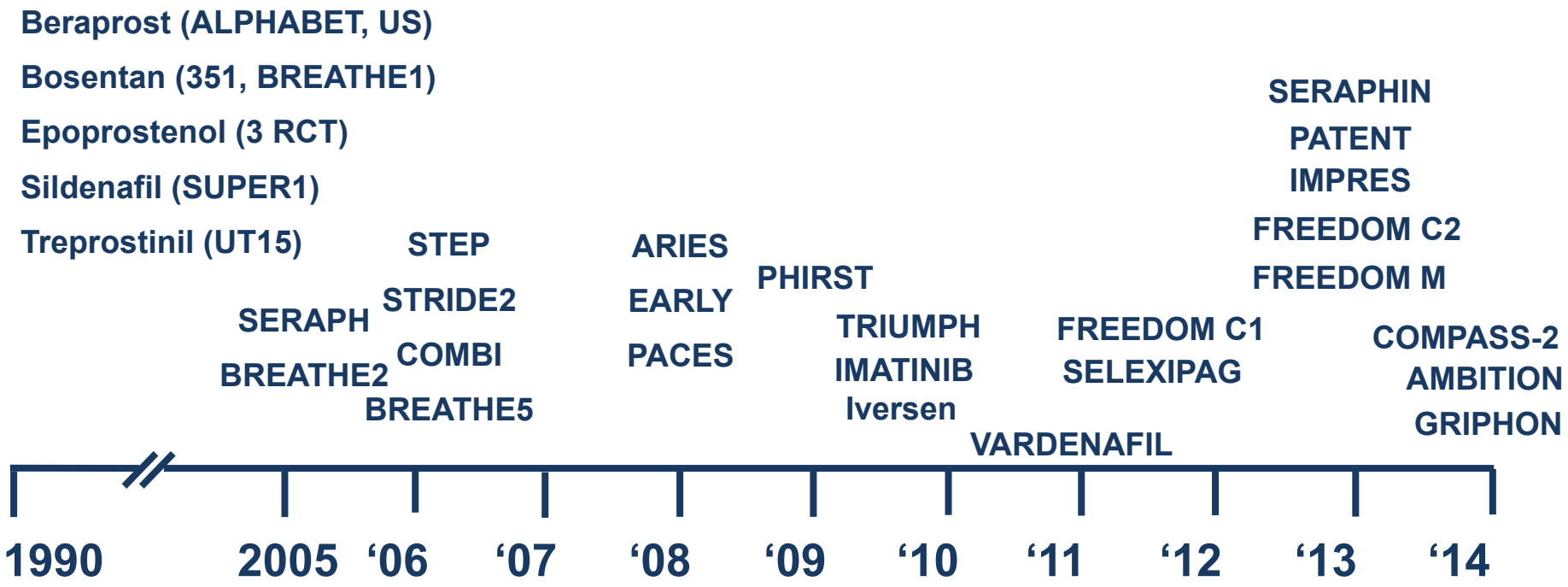
Adapted from Humbert M, *et al. N Engl J Med* 2004; 351:1425-36.

PAH-specific therapies target the three signalling pathways involved in PAH



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

Overview of RCTs in PAH



Monotherapy

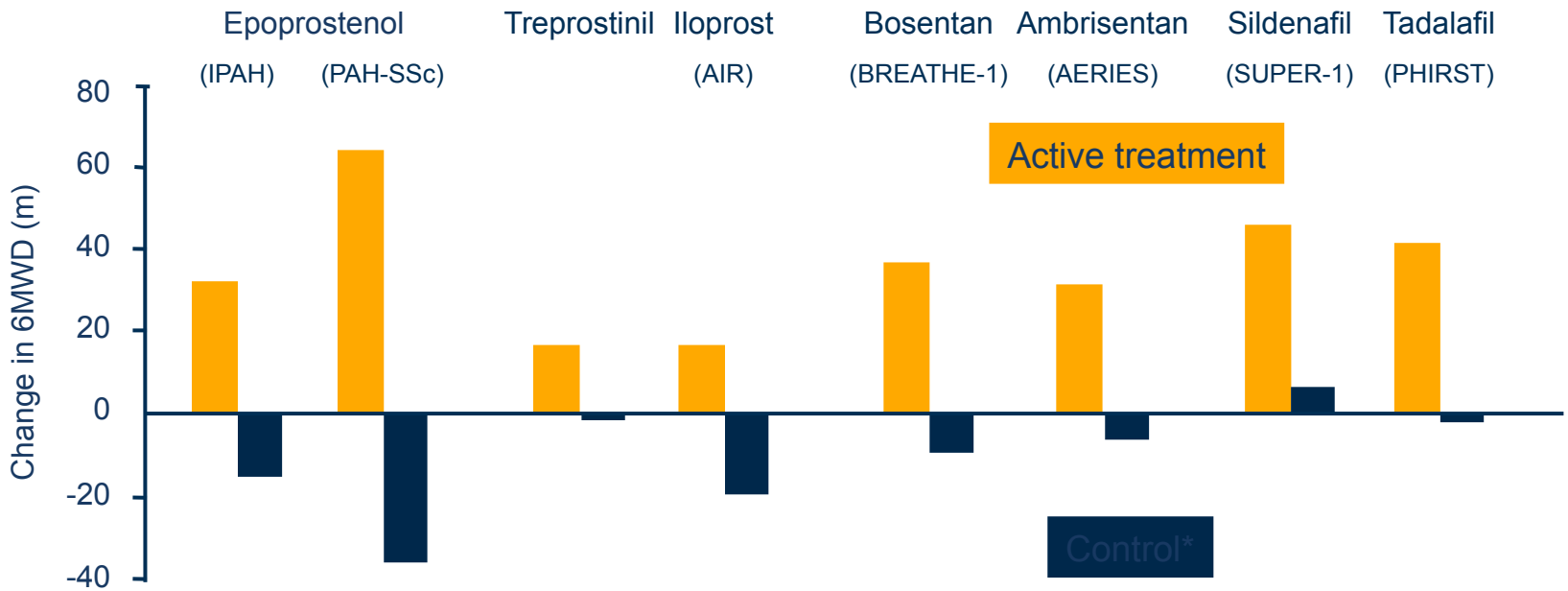
Monotherapy and/or sequential combination

Initial combination

Modified from Galiè N, *et al. Eur Heart J* 2010; 31:2080-2086.

RCTs with monotherapy in PAH

Improvement in exercise capacity (3-4 months)



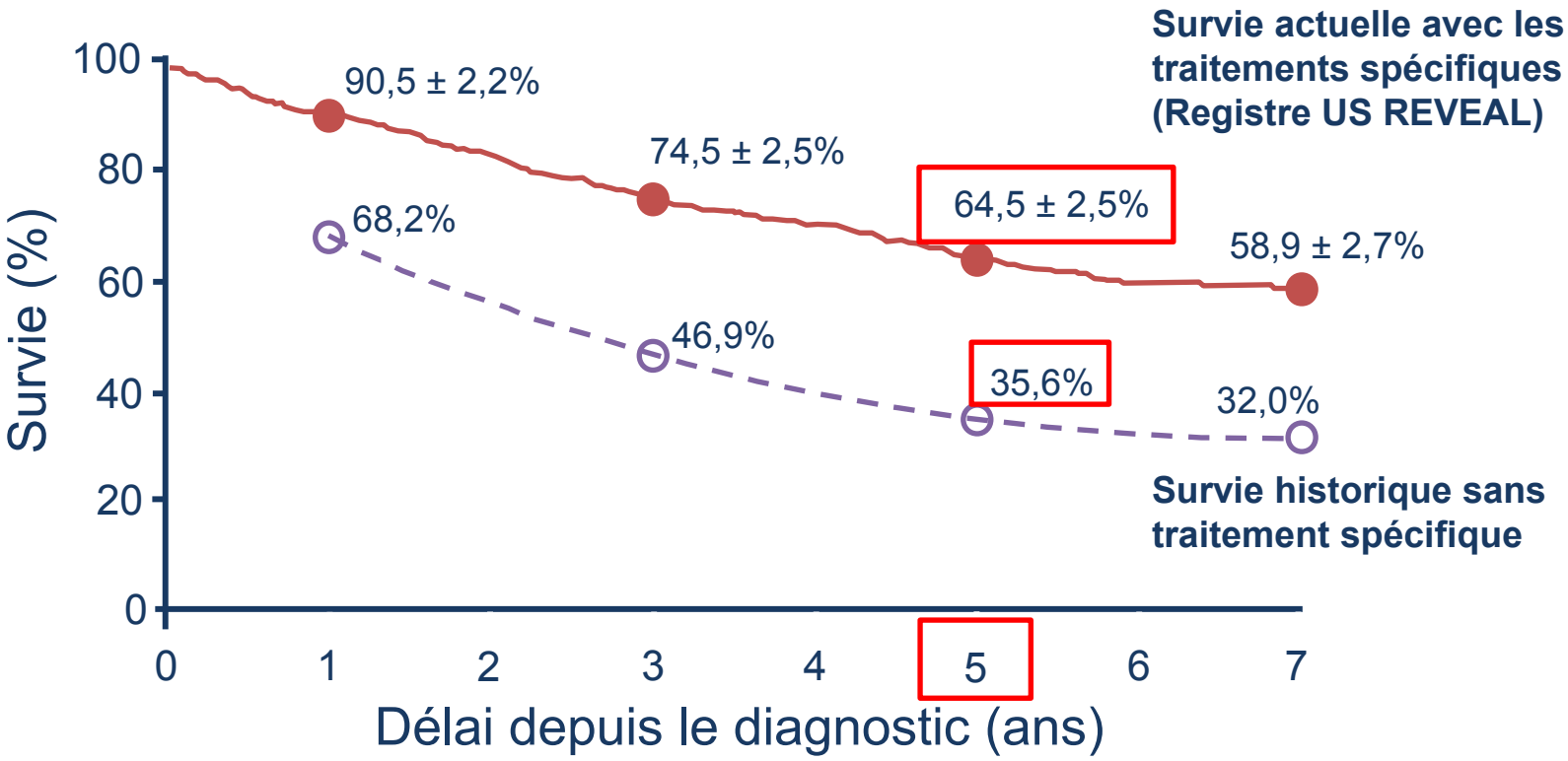
Treatment effect	+ 47 m	+ 108 m*	+ 18 m	+ 36 m	+ 44 m	+ 44 m	+ 42 m	+ 44 m#
p	< 0.003	< 0.001	0.005	0.004	0.0002	< 0.001	< 0.001	< 0.001

* 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.

Malgré les progrès thérapeutiques, le pronostic à long terme de l'HTAP est insatisfaisant



Comment faire mieux ?

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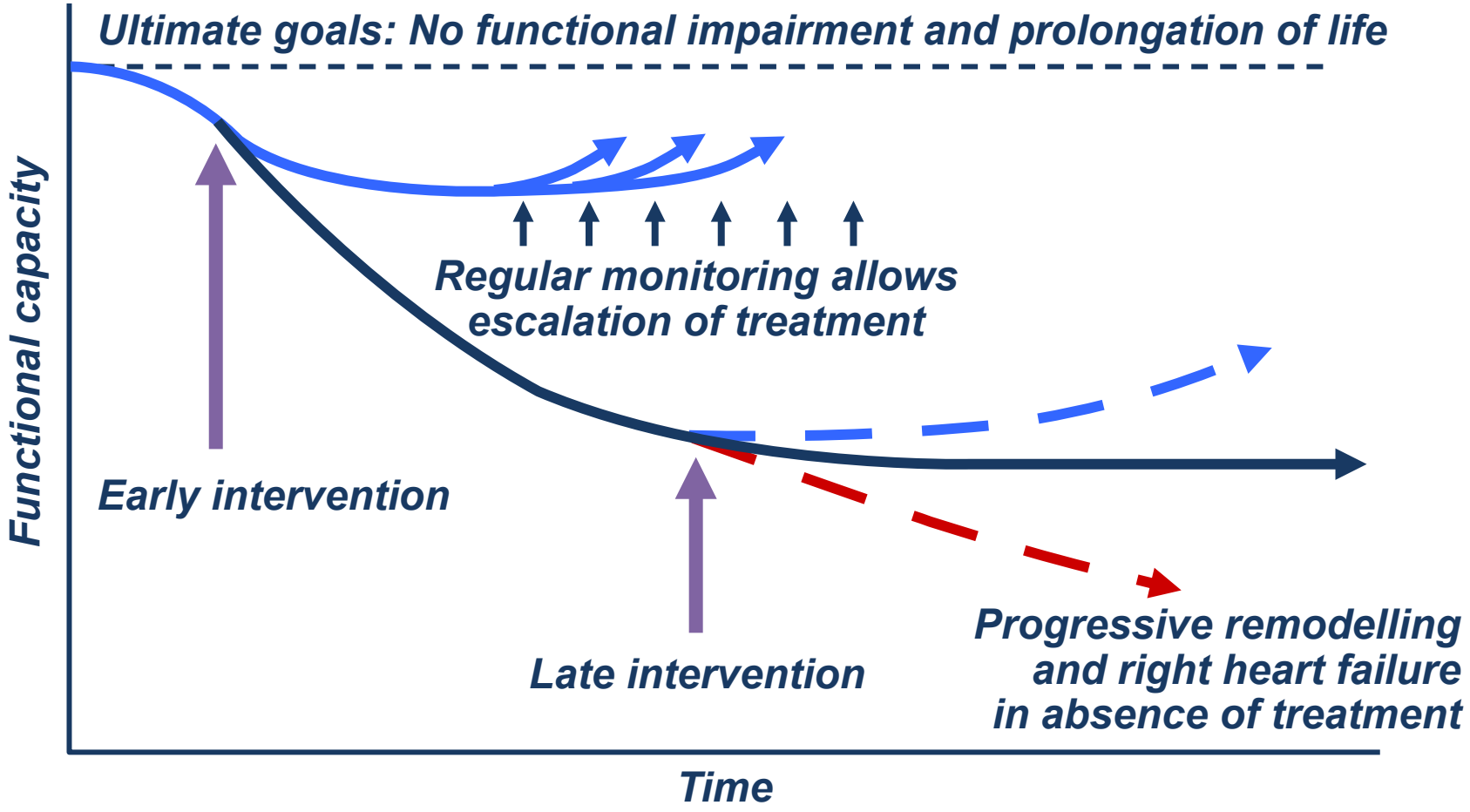
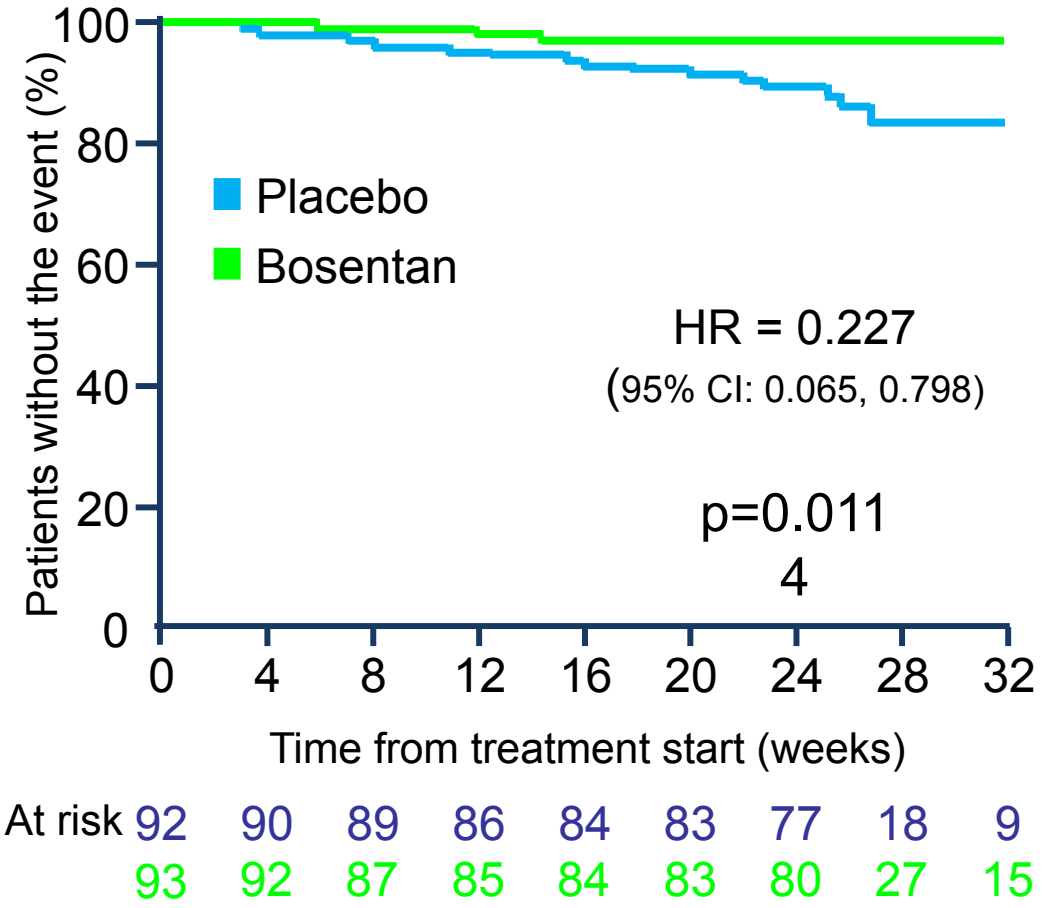
Traitement « précoce » et stratégie « goal-oriented » dans l'HTAP



Sitbon O and Galiè N. *Eur Respir Rev* 2010.

Traiter « précocement »
Etude EARLY: bosentan dans l'HTAP de CF II



	Placebo	Bosentan
6-MWD (m)	431 ± 91	438 ± 86
PVR (dyn.sec.cm□5)	805 ± 369	839 ± 531

Galiè N, *et al. Lancet* 2008.

Définir les objectifs à partir des facteurs pronostiques connus

Assessment parameter	Stable and satisfactory	Stable and not satisfactory	Unstable and deteriorating
Clinical evidence of RV failure	No	Only some of the "green" parameters are fulfilled (Grey zone)	Yes
Rate of progression	Slow		Rapid
Syncope	No		Yes
WHO-FC	I, II		IV
6-MWD	Longer (> 500 m)		Shorter (< 300 m)
CPET	Peak VO2 > 15 ml/min/kg		Peak VO2 < 12 ml/min/kg
BNP/NT-proBNP plasma levels	Normal or near-normal		Very elevated and rising
Echocardiographic findings	No pericardial effusion TAPSE > 2.0 cm		Pericardial effusion TAPSE < 1.5 cm
Haemodynamics	RAP < 8 mmHg and CI ≥ 2.5 l/min/m2		RAP > 15 mmHg or CI ≤ 2.0 l/min/m2

Adapted from Galiè N, *et al. Eur Heart J* 2009 and Eur Respir J 2009.

Objectifs thérapeutiques dans l'HTAP
Placer la barre plus haut…

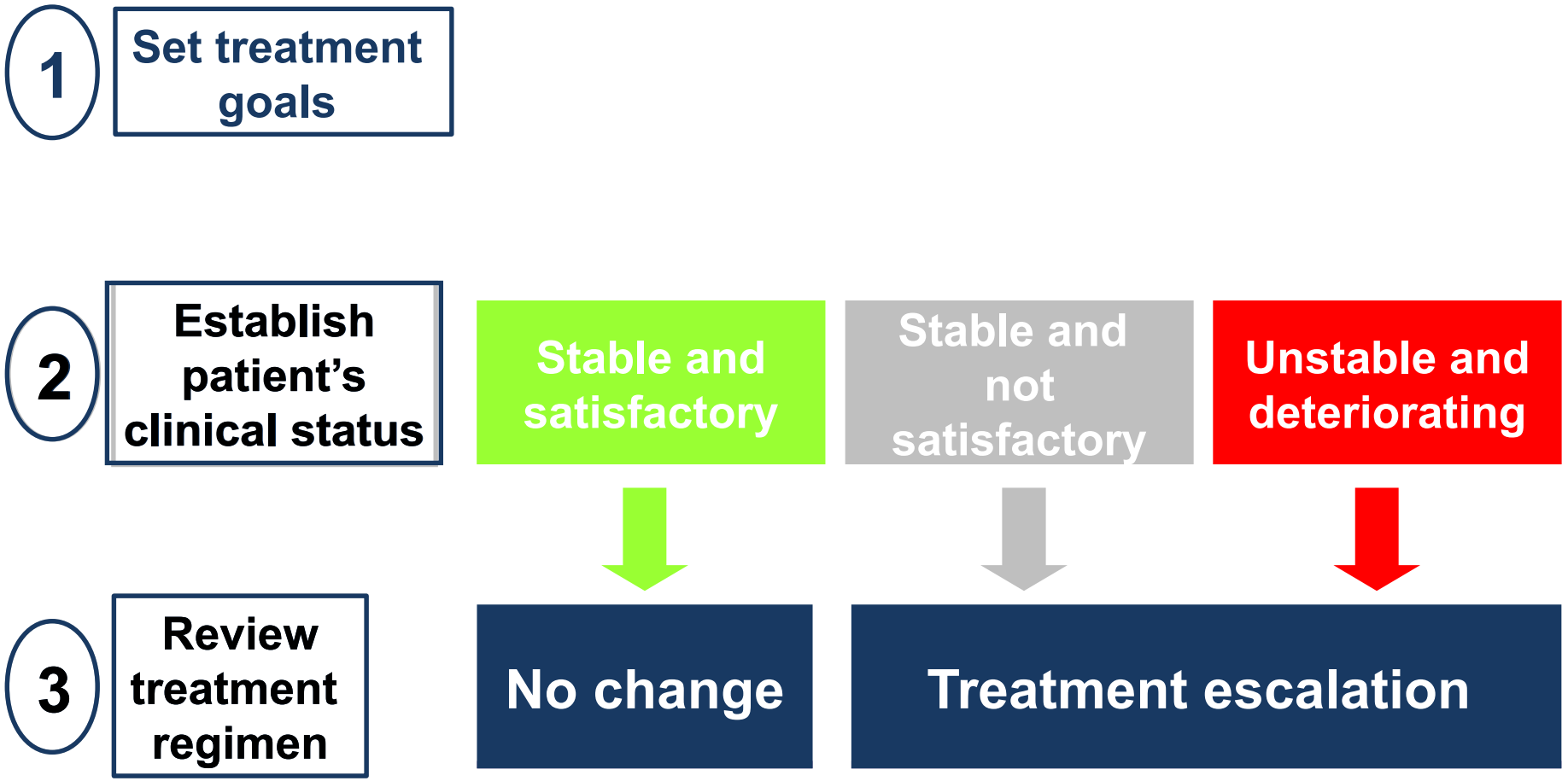
Treatment Goals of Pulmonary Hypertension

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

McLaughlin VV, *et al. J Am Coll Cardiol* 2013; 25 (Suppl): D73-D81.

Stratégie « goal-oriented » dans l'HTAP

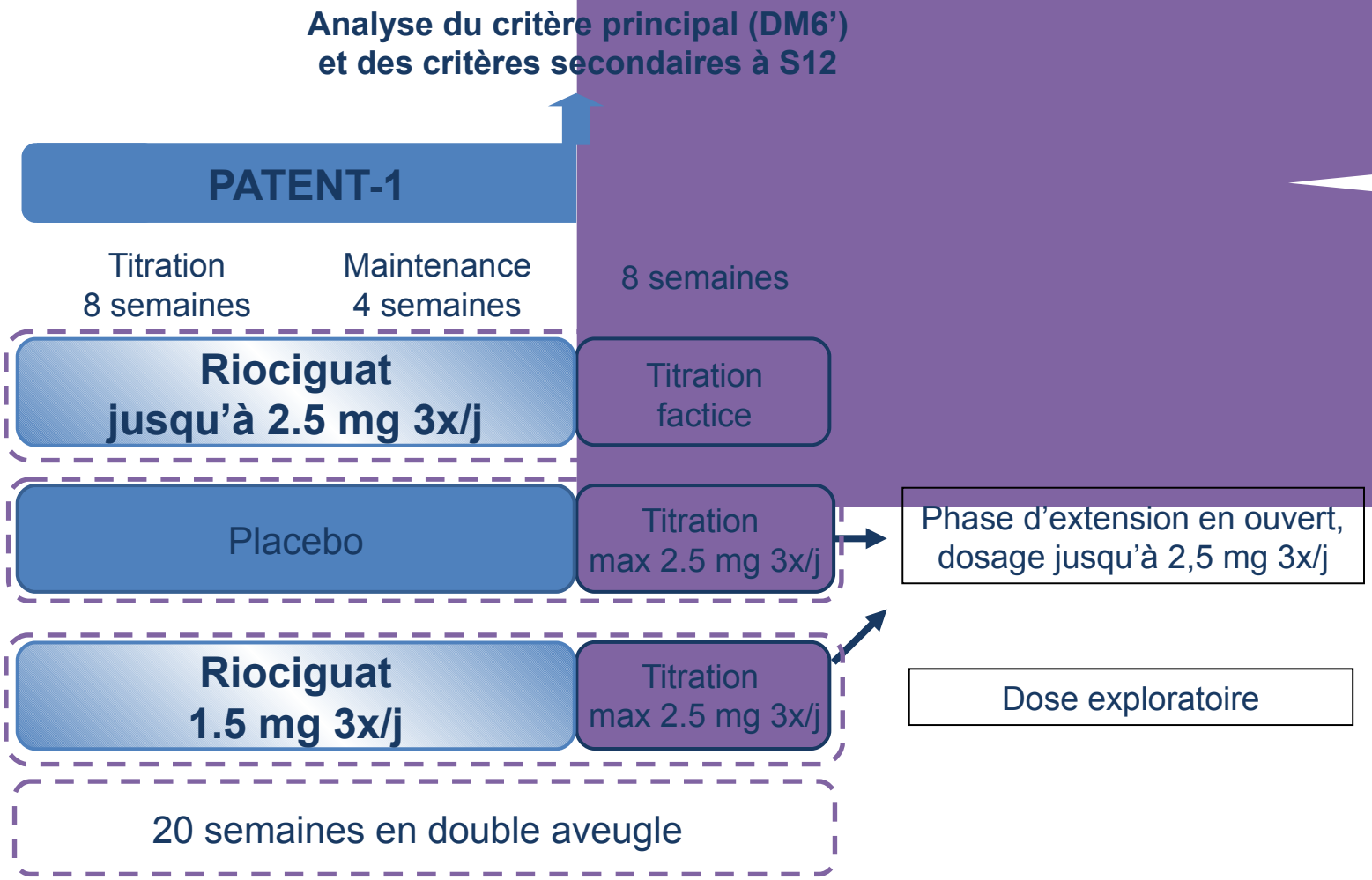


Adapted from Galiè N, *et al. Eur Heart J* 2009 and Eur Respir J 2009.

Traitement combiné séquentiel

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 +
Macitentan	SERAPHIN	None, PDE5i or inhaled iloprost	742	100	Morbi-mortality +
Riociguat	PATENT	None, bosentan or prostanoids	443	12	Δ6MWD +
Selexipag	GRIPHON	None, ERA and/or PDE5i	1156		Morbi-mortality +
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)**

PATENT : Riociguat dans l'HTAP
Design de l'étude

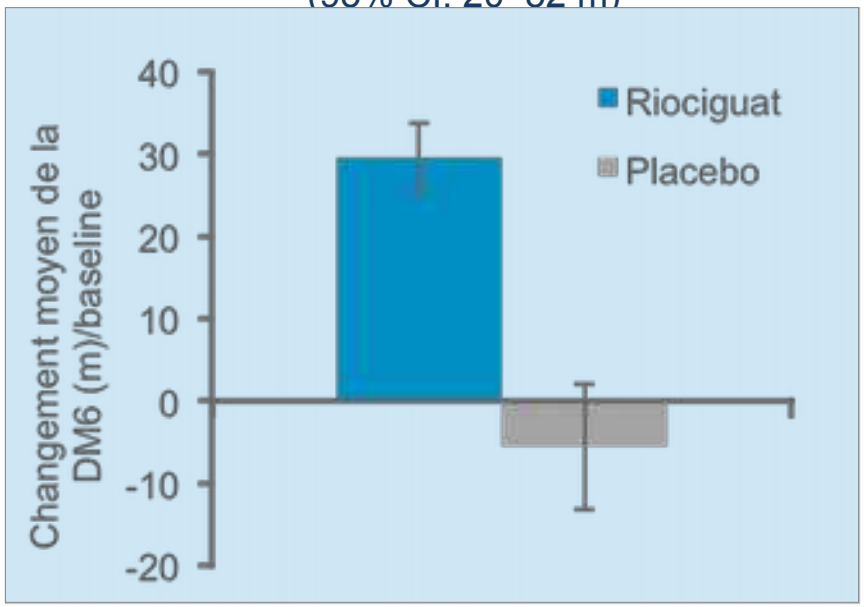


Ghofrani HA, *et al. N Engl J Med* 2013.

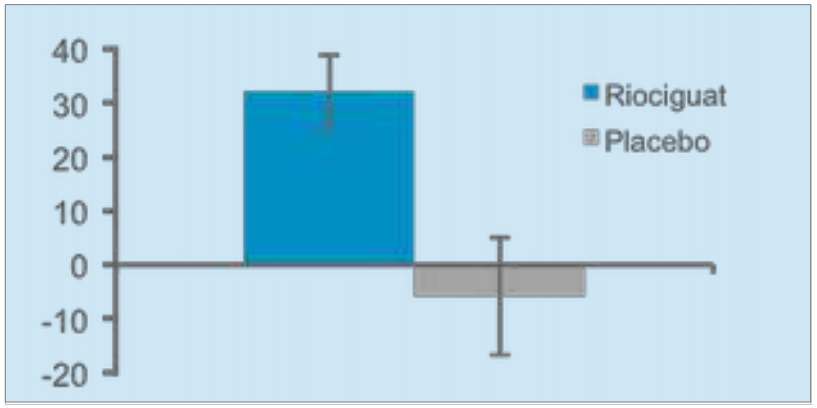
Amélioration de la DM6 chez les patients naïfs de traitement ou pré-traités

Critère principal: Population totale (n=254/126)

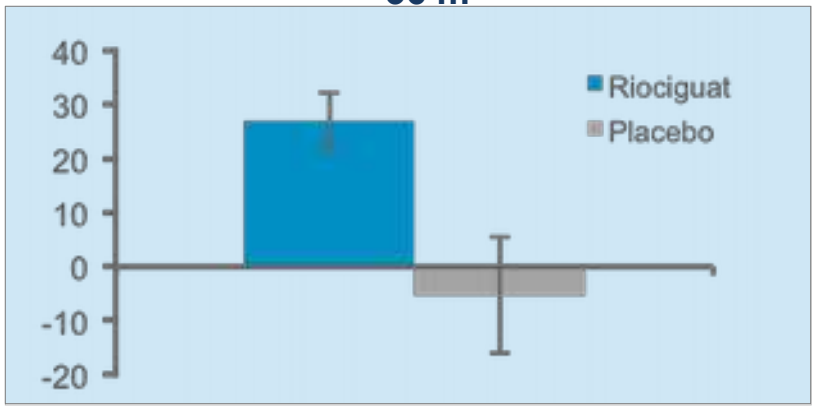
+36 m
p<0.0001
(95% CI: 20–52 m)



Population naïve de traitement (n=123/66)
+38 m



Population pré-traitée (n=131/60)
+36 m



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

Critères de jugement dans les études cliniques dans l'HTAP

Test de Marche de 6 mn

- Méthode simple, reproductible et valide pour évaluer les capacités d'exercice à court terme
- ΔDM6' initialement considéré comme prédictif de l'évolution
- Initialement accepté par les Autorités pour enregistrement des médicaments

Test de Marche de 6 mn

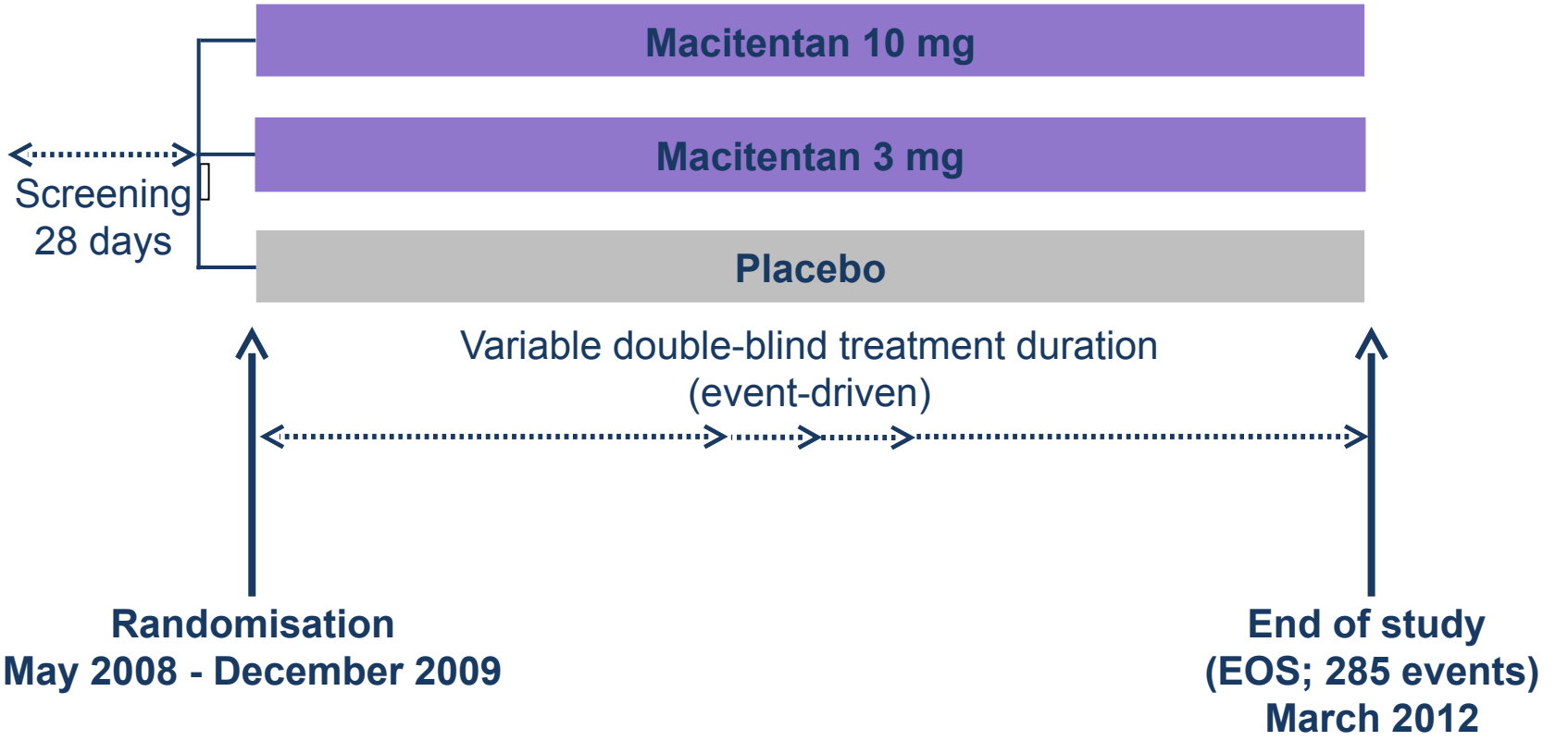
- ΔDM6' n'est pas prédictif de la morbi-mortalité
- Etudes à court terme non adaptées pour l'évaluation des médicaments dans une maladie grave et évolutive

4th World Symposium on Pulmonary Hypertension

Recommandations internationales : nécessité de conduire des études de morbi-mortalité dans l'HTAP

McLaughlin VV, *et al*. *J Am Coll Cardiol* 2009

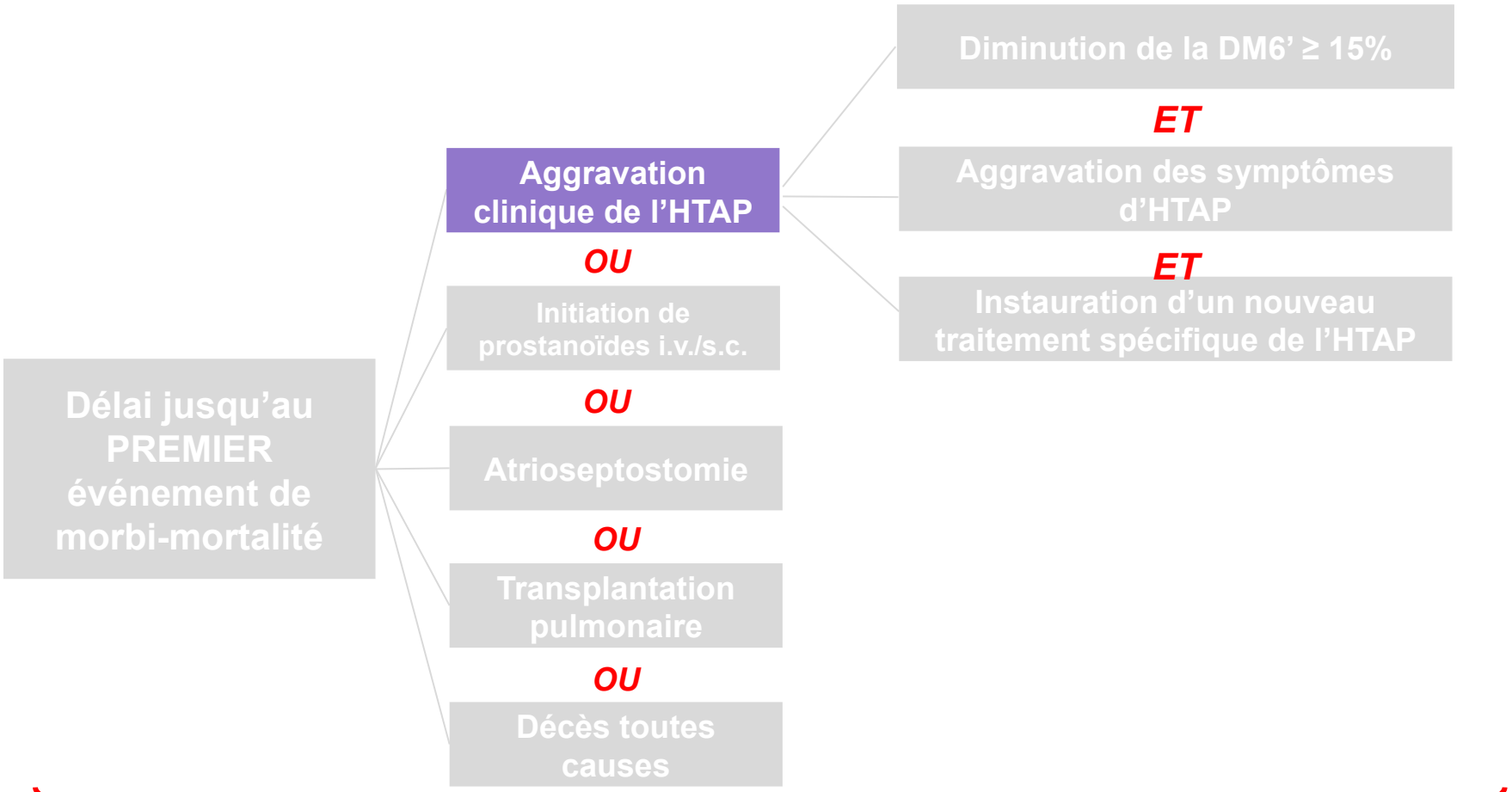
SERAPHIN : Schéma de l'étude



Patients were censored at end of double-blind treatment

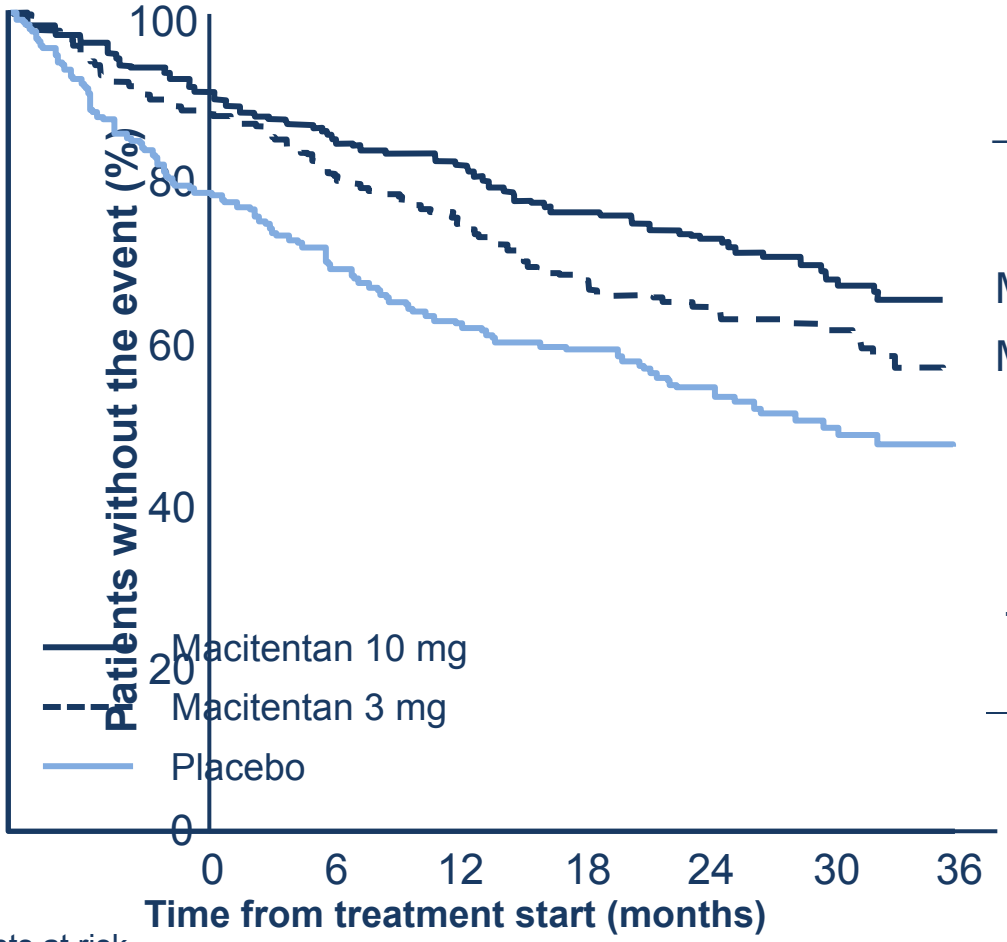
Pulido T, *et al. N Engl J Med* 2013; 369: 809-18.

SERAPHIN : Critère principal de jugement



Tous les événements ont été confirmés en aveugle par un comité d'adjudication indépendant

SERAPHIN : Critère principal de jugement



Macitentan 10 mg: 45%

Macitentan 3 mg: 30%

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

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**

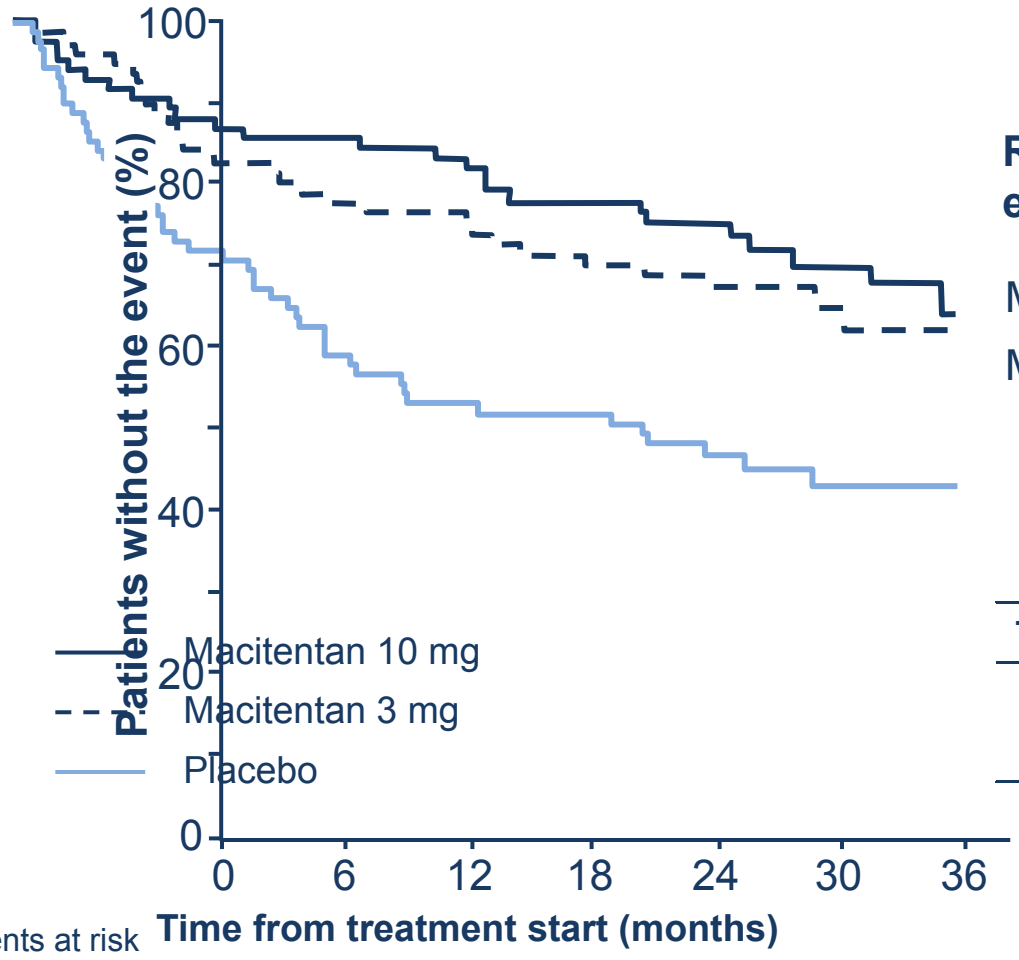
Pulido T, *et al. N Engl J Med* 2013; 369: 809-18.

SERAPHIN : Evénements composant le critère de principal de jugement

	Placebo *n* = 250	Macitentan 10 mg *n* = 242
Patients avec un événement, n (%)	116 (46,4)	76 (31,4)
Type de 1er événement, n (%)		
Aggravation de l'HTAP	93 (37,2)	59 (24,4)
Initiation d'un prostanoïde IV ou SC	6 (2,4)	1 (0,4)
Décès toutes causes	17 (6,8)	16 (6,6)

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

SERAPHIN : Patients SANS traitement spécifique préalable



Risk reduction of primary endpoint event vs placebo

Macitentan 10 mg: 55%

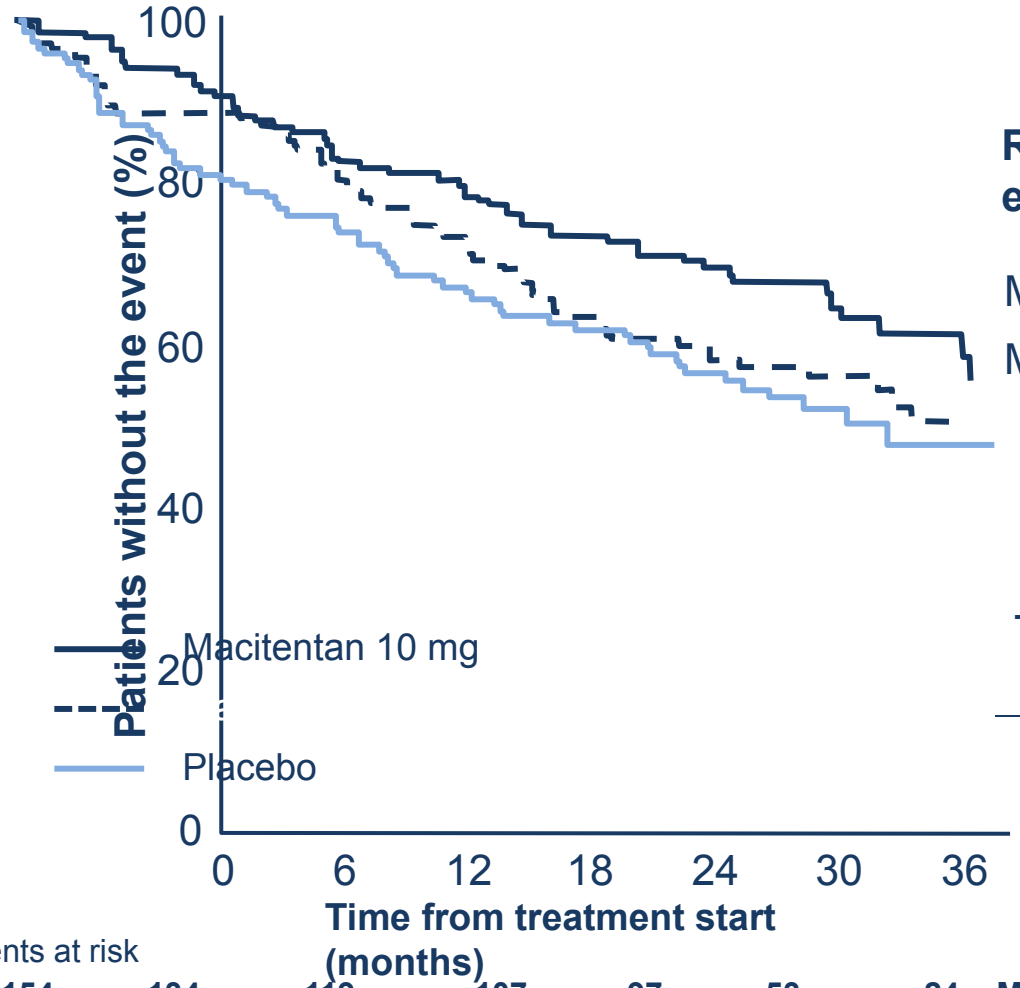
Macitentan 3 mg: 47%

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	Macitentan 10 mg
86	74	63	59	56	29	13	Macitentan 3 mg
96	66	54	45	42	24	13	Placebo

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

SERAPHIN : Patients AYANT un traitement spécifique préalable



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

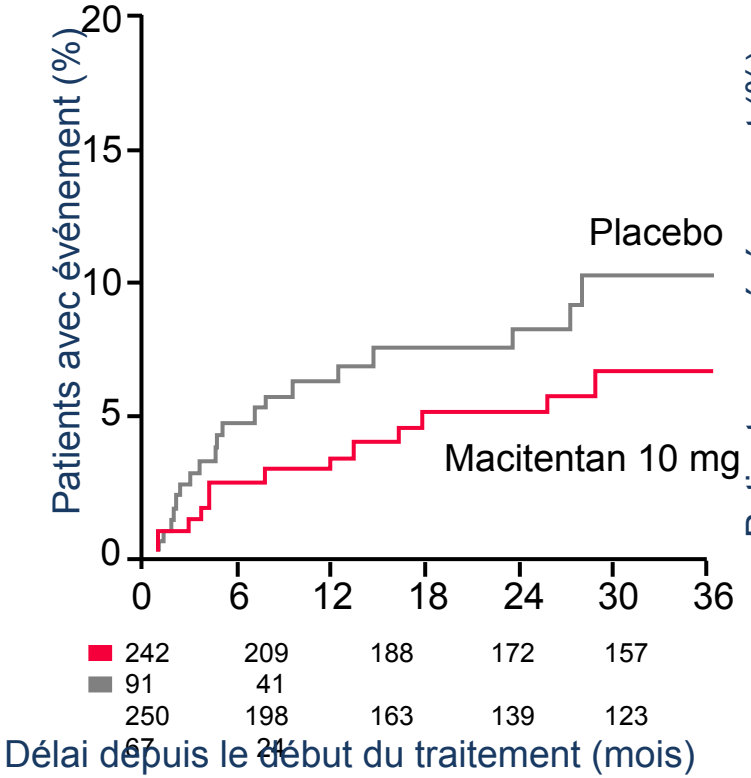
Patients at risk

154	134	119	107	97	53	24	Macitentan 10 mg
164	139	125	107	91	51	19	Macitentan 3 mg
165	122	106	90	80	40	10	Placebo

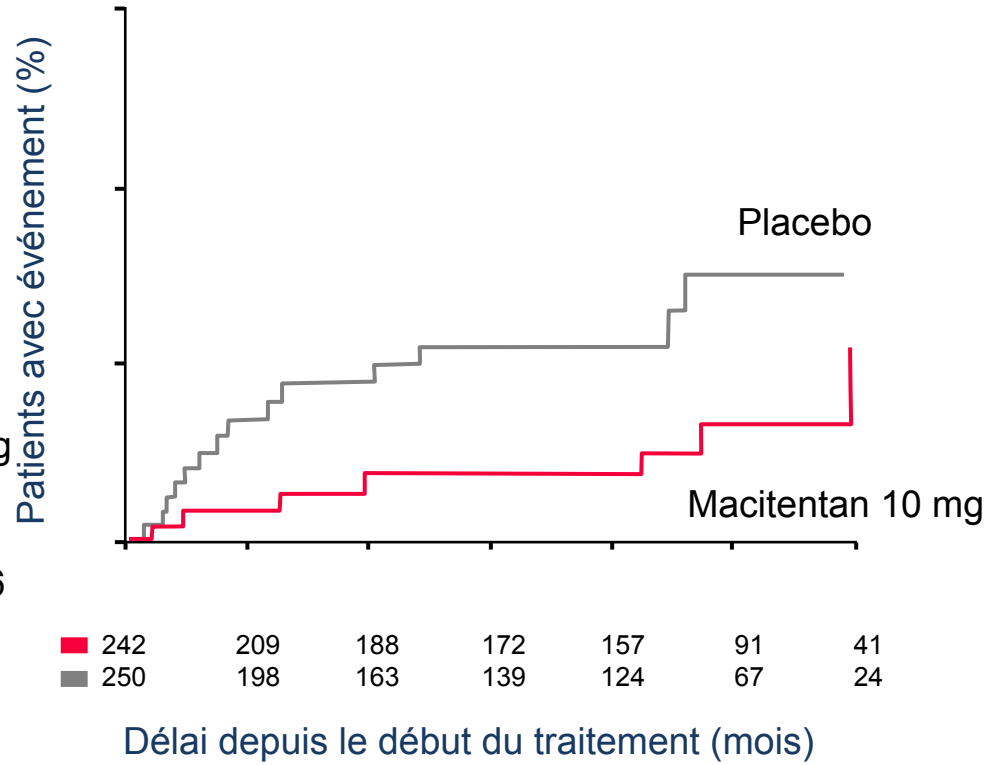
Pulido T, *et al. N Engl J Med* 2013; 369: 809-18.

SERAPHIN : Décès jusqu'à la fin du traitement

Décès toutes causes :
réduction du risque de 36%
(p = 0,20)



Décès liés à l'HTAP (post hoc) :
réduction du risque de 56%
(p = 0,07)



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

GRIPHON study (phase III): ProstaGlandin I2 Receptor agonist In Pulmonary arterial HypertensiON

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Actelion press release, 16 June 2014.

NCT01106014: *www.clinicaltrials.gov*

Changing strategy – Initial combination therapy: What is the evidence?

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1. Humbert M, et al. Eur Respir J 2004; 24:353-9.
2. 2. Kemp K, et al. J Heart Lung Transplant 2012; 31:150-8.
3. Sitbon O, et al. Eur Respir J. 2014; 43: 1691–1697.
4. GSK Press Release – 8 September 2014.

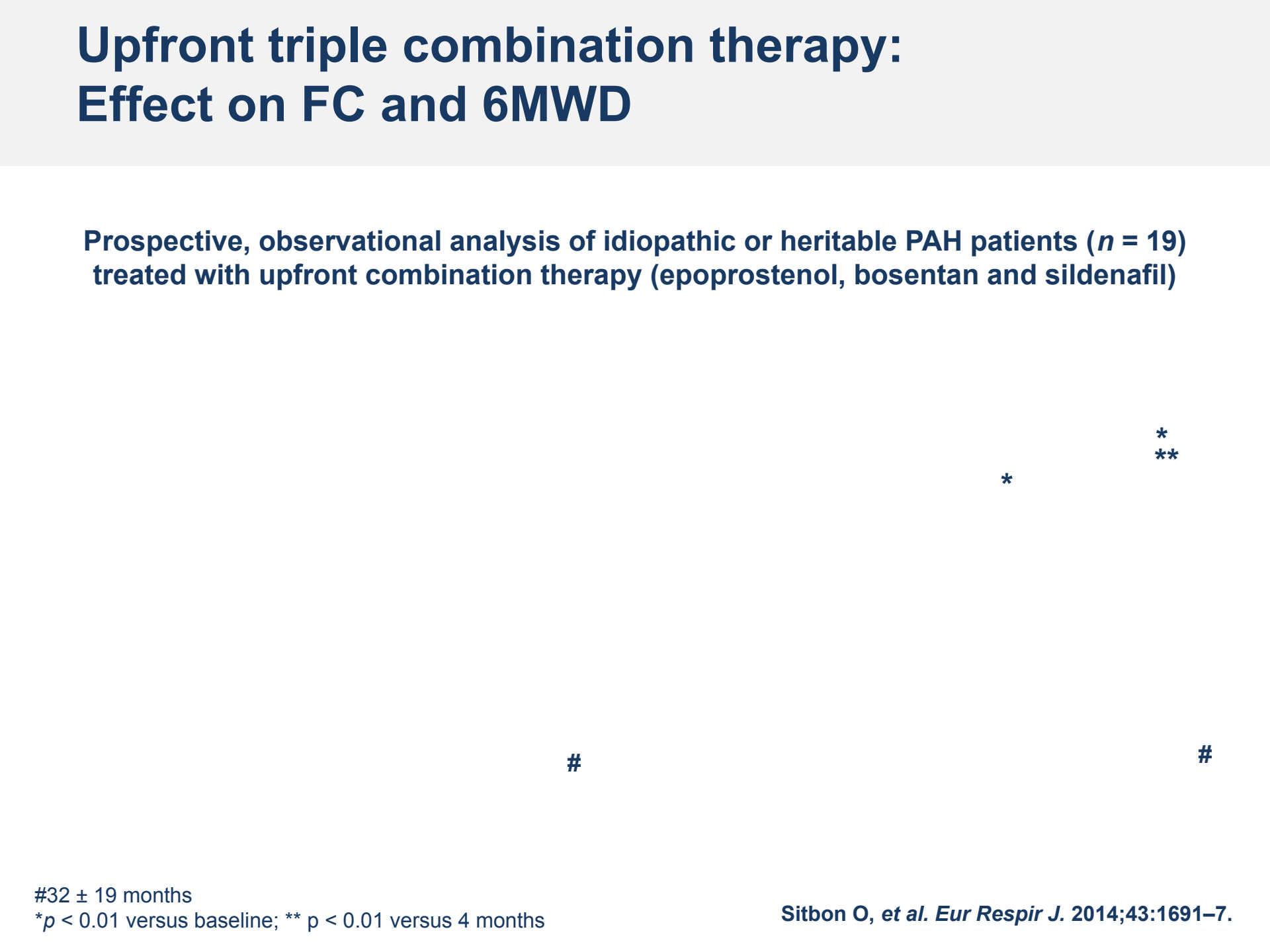
Upfront triple combination therapy in pulmonary arterial hypertension: a pilot study

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]

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

Upfront triple combination therapy: Effect on FC and 6MWD

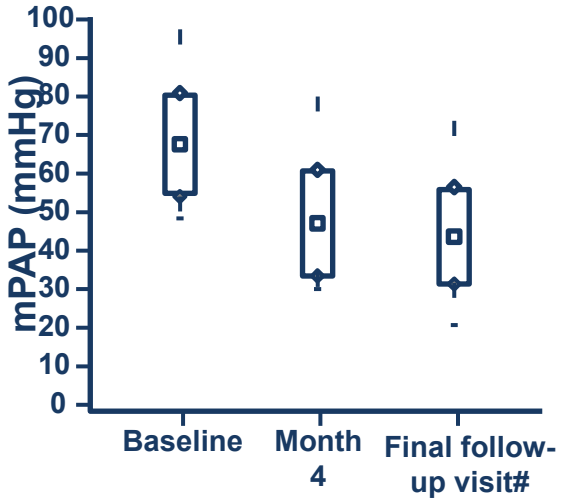
Prospective, observational analysis of idiopathic or heritable PAH patients (*n* = 19) treated with upfront combination therapy (epoprostenol, bosentan and sildenafil)

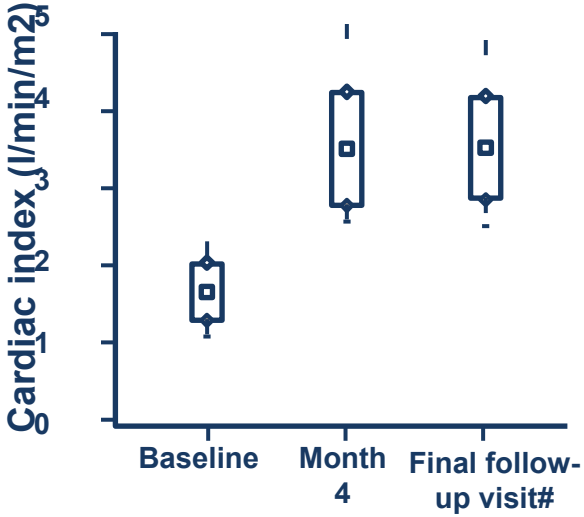


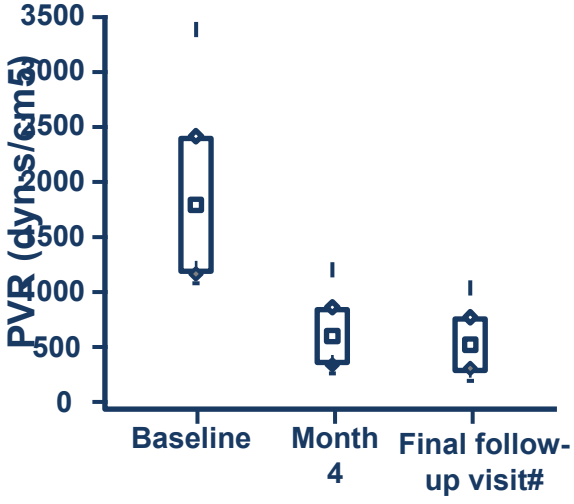
#32 ± 19 months
*p < 0.01 versus baseline; ** p < 0.01 versus 4 months

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/m2)	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

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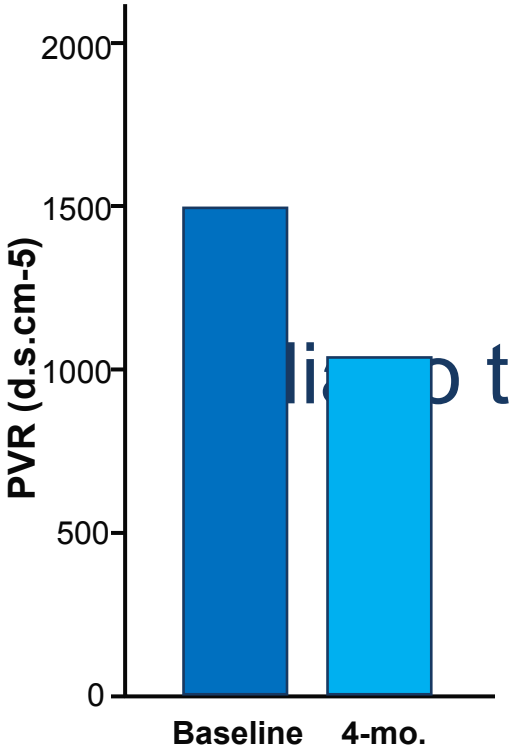
	1-year	2-year	3-year
Actual	100%	100%	100%
Transplant-free	94%	94%	94%
Expected* [95% CI]	75% [68%-82%]	60% [50%-70%]	49% [38%-60%]

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

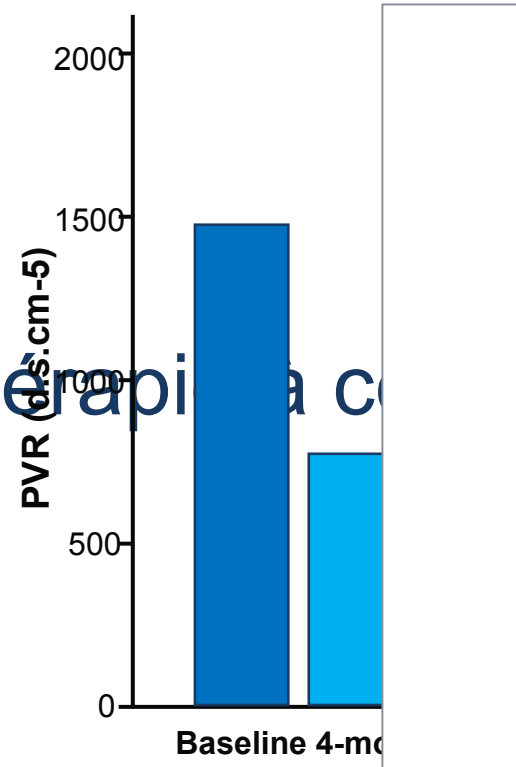
Upfront triple combination therapy

Epoprostenol monotherapy (n=46)



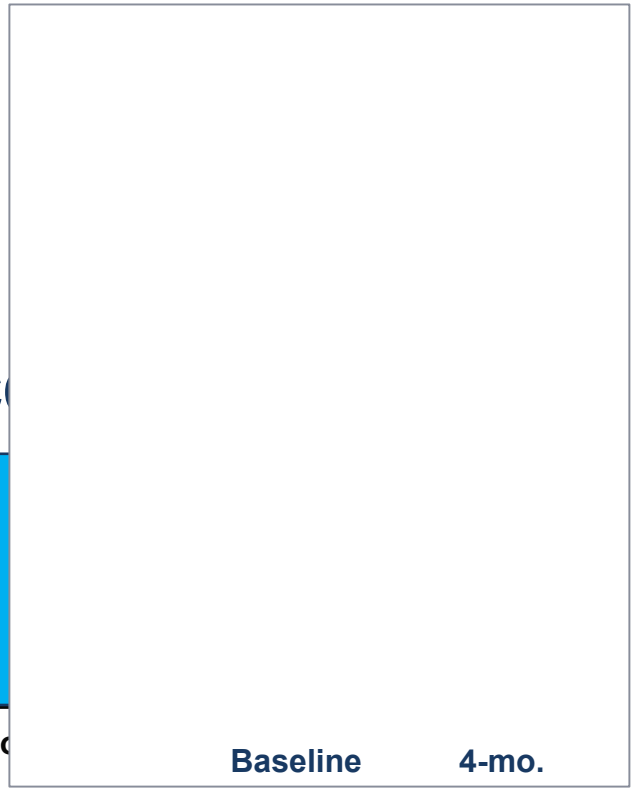
-29 ± 17%

Epoprostenol + bosentan combination therapy (n=23)



-48 ± 17%

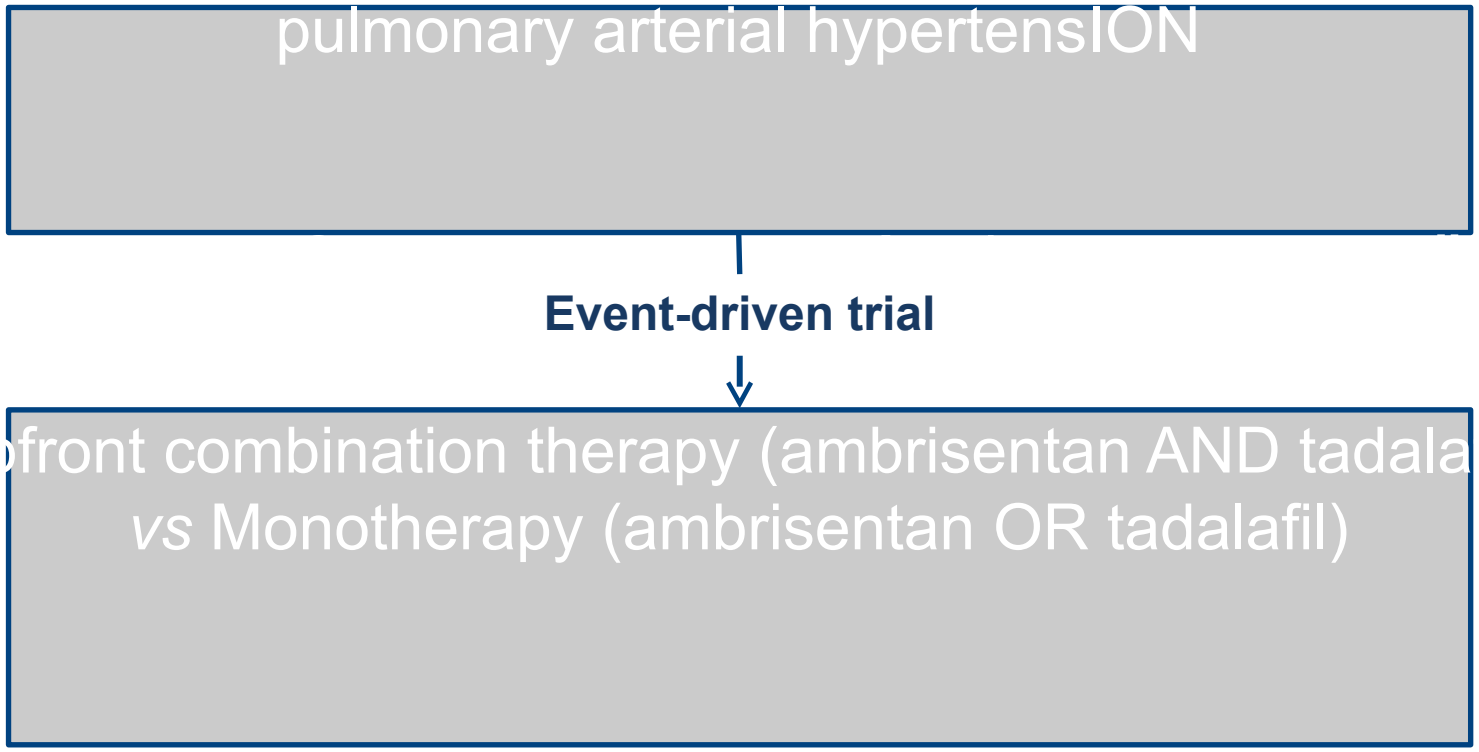
Epo + bosentan + sildenafil combination therapy (n=18)



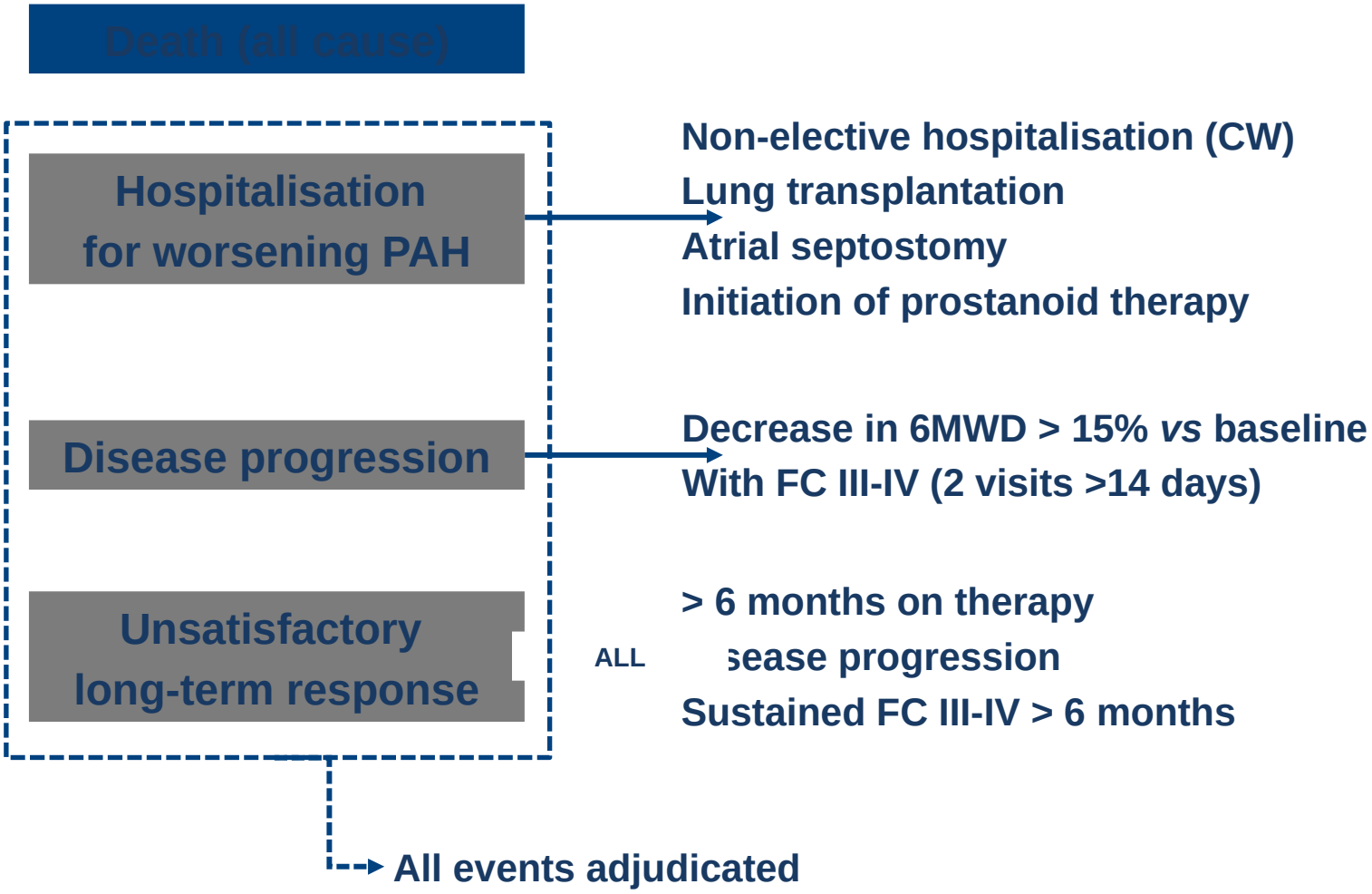
- 69 ± 8%

Kemp K, *et al*. J Heart Lung Transplant 2012;31:150–8.
Sitbon O, *et al. Eur Respir J.* 2014;43:1691–7.

The AMBITION trial



AMBITION: Primary endpoint
Time to first clinical failure event



AMBITION: Primary endpoint
Time to f rst adjudicated clinical failure event

- First-line treatment of PAH with the combination of ambrisentan 10 mg and tadalafil 40 mg **reduced the risk of clinical failure by 50%** compared to pooled ambrisentan and tadalafil monotherapy arm (hazard ratio = 0.502; p=0.0002).
- Hospitalisation for worsening of PAH was the main component of the primary endpoint
- The combination was also statistically significant *vs* the individual ambrisentan and tadalafil monotherapy groups for the primary endpoint.

Expert consensus recommendations for combination therapy have improved with increasing experience

Venice, 20031	Dana Point, 20082,3	Nice, 20134
Sequential combination therapy may be considered in patients who fail to show improvement or who deteriorate on a single drug (monotherapy)	Combination therapy should be considered in patients on monotherapy with 'inadequate clinical response' Evidence level: IIa-B In FC IV, initial combination should be considered Evidence level: IIa-C	In case of inadequate clinical response, sequential therapy is recommended Evidence level: I-A In FC III/IV patients initial combination therapy may be considered Evidence level: IIb-C

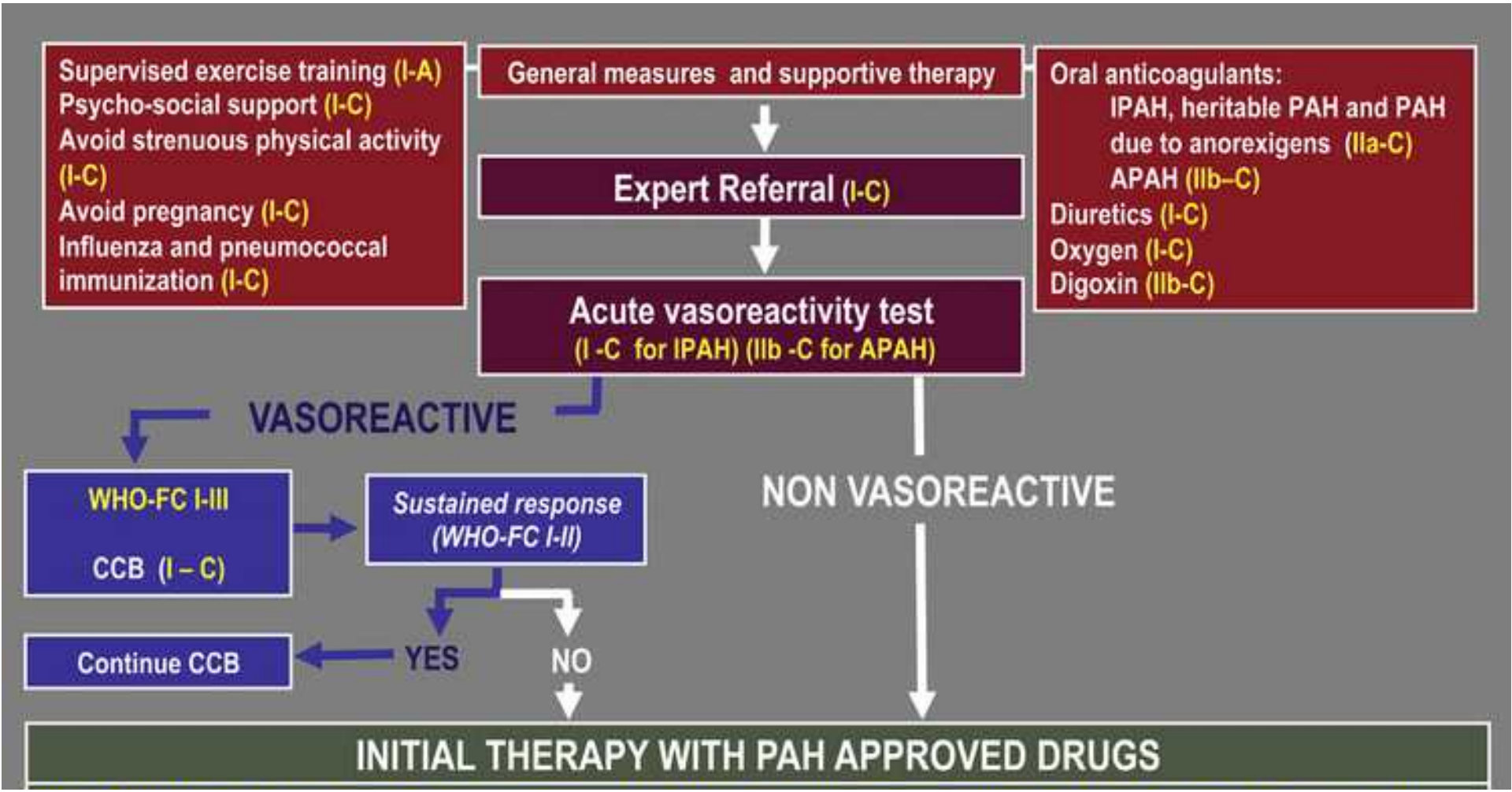
1. Galiè N, *et al. J Am Coll Cardiol* 2004; 43:81S-88S. 2. Barst RJ, *et al. J Am Coll Cardiol* 2009; 54:S78-84.
3.Galiè N, *et al. Eur Heart J* 2009; 30:2493-537. 4. Galiè N, *et al. J Am Coll Cardiol* 2013; 62:D60-72.

9 traitements approuvés dans l'HTAP

Voie de l'ET-1	Voie de la PGI2 / AMPc	Voie du NO / GMPc	
Antagonistes récepteurs ET-1 (oral)	Prostacyclines et dérivés	Inhibiteurs PDE-5 (oral)	Activateur GC soluble (oral)
Bosentan (Tracleer®)	Epoprostenol (Flolan® et génériques, Veletri®) – *IV*	Sildenafil (Revatio®)	Riociguat (Adempas®)
Ambrisentan (Volibris®)	Iloprost (Ventavis®) – *Inhalation*	Tadalafil (Adcirca®)	
Macitentan (Opsumit®)	Treprostinil (Remodulin®) – *SC, IV, inhalation*, oral**		
	Beraprost** – *oral*		

*Approuvé uniquement aux Etats Unis ; Non approuvé en Europe
**Approuvé uniquement au Japon et en Corée du Sud

2013 5th WSPH – Treatment Algorithm



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

INITIAL THERAPY WITH PAH APPROVED DRUGS

YELLOW: Morbidity and mortality as primary end-point in randomized controlled study or reduction in all-cause mortality (prospectively defined)

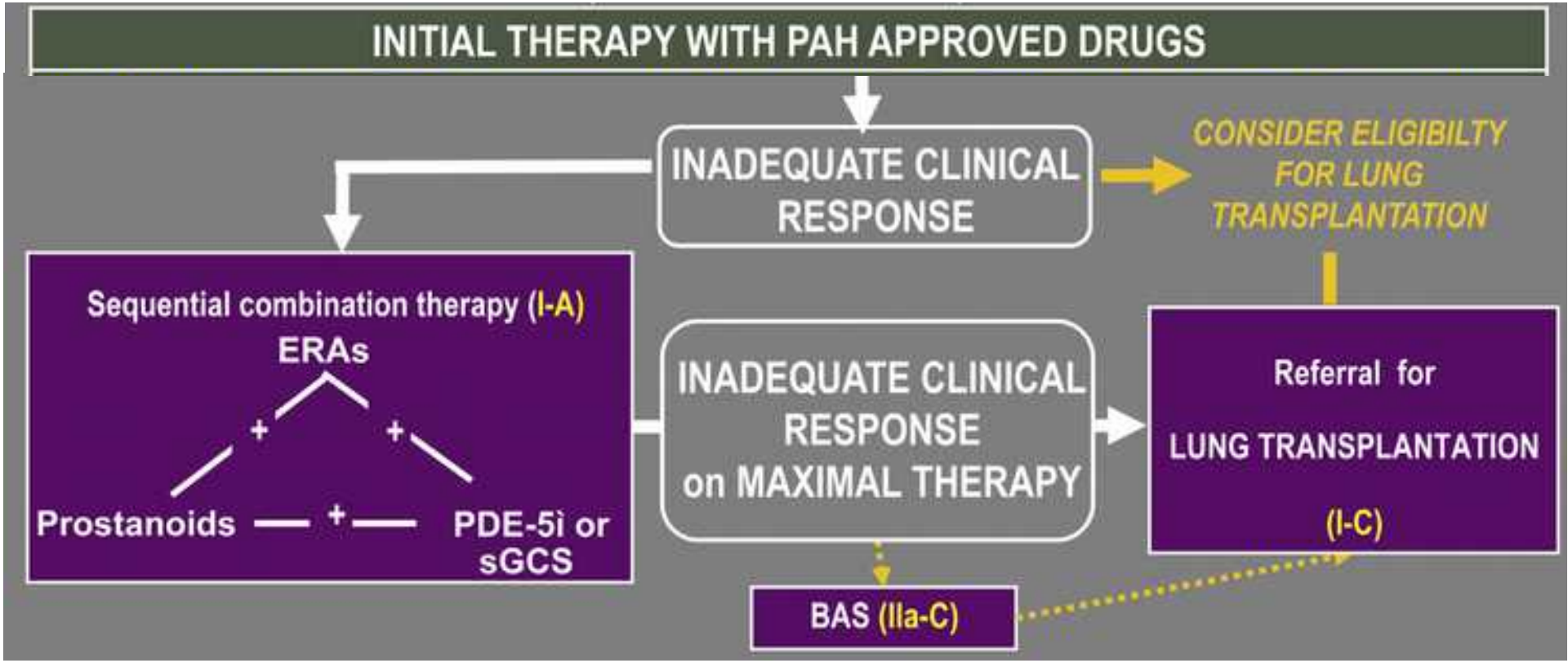
*Level of evidence is based on the WHO-FC of the majority of the patients of the studies.

†Approved only: by the FDA (macitentan, riociguat, treprostinil inhaled); in New Zealand (iloprost i.v); in Japan and S.Korea(beraprost).

‡ Positive opinion for approval of the CHMP of EMA

Recommendation	Evidence*	WHO-FC II	WHO-FC III	WHO-FC IV
I	A or B	Ambrisentan Bosentan Macitentan†‡ Riociguat† Sildenafil Tadalafil	Ambrisentan Bosentan Epoprostenol i.v. Iloprost inhaled Macitentan†‡ Riociguat† Sildenafil Tadalafil Treprostinil s.c., inhaled†	Epoprostenol i.v.
IIa	C		Iloprost i.v. † Treprostinil i.v.	Ambrisentan, Bosentan Iloprost inhaled and i.v† Macitentan†‡ Riociguat† Sildenafil, Tadalafil Treprostinil s.c., i.v., Inhaled†
IIb	B		Beraprost†	
	C		Initial Combination Therapy	Initial Combination Therapy

2013 5th WSPH – Treatment Algorithm



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