

Prise en charge thérapeutique de l'HTAP

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Clinical classification of pulmonary hypertension (PH)

1. Pulmonary arterial hypertension

1.1 Idiopathic

1.2 Heritable

 1.2.1 BMPR2 mutation

 1.2.2 Other mutations

1.3 Drugs and toxins induced

1.4 Associated with:

 1.4.1 Connective tissue disease

 1.4.2 Human immunodeficiency virus (HIV) infection

 1.4.3 Portal hypertension

 1.4.4 Congenital heart disease (Table 6)

 1.4.5 Schistosomiasis

Hemodynamic classification of pulmonary hypertension (PH) – Group 2

PH associated with left heart diseases

Post-capillary PH	PAPm \geq 25 mmHg PAWP >15 mmHg
Isolated post-capillary PH (Ipc-PH)	DPG <7 mmHg and/or PVR \leq 3 WU ^c
Combined post-capillary and pre-capillary PH (Cpc-PH)	DPG \geq 7 mmHg and/or PVR >3 WU ^c

The use of PAH-approved therapies is not recommended in PH-LHD	III	C
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Hemodynamic classification of pulmonary hypertension (PH) – Group 3

PH associated with chronic lung diseases

Terminology	Haemodynamics (right heart catheterization)
COPD/IPF/CPFE without PH	PAPm <25 mmHg
COPD/IPF/CPFE with PH	PAPm ≥ 25 mmHg
COPD/IPF/CPFE with severe PH	PAPm >35 mmHg, or PAPm ≥ 25 mmHg in the presence of a low cardiac output (CI <2.5 L/min, not explained by other causes)

The use of drugs approved for PAH is
not recommended in patients with
PH due to lung diseases

III

C

Objectifs du traitement de l'HTAP

- Le traitement de l'HTAP tente de s'opposer aux effets délétères de :
 - la vasoconstriction,
 - l'obstruction vasculaire pulmonaire par remodelage et thrombose
 - l'insuffisance cardiaque droite.
- Objectifs
 - Amélioration symptômes (classe NYHA)
 - Amélioration qualité de vie
 - Amélioration capacités à l'effort (TM6, EF-X)
 - Amélioration fonction VD
 - BNP
 - Echo : TAPSE, S au Dti
 - KT droit : POD, Qc/IC, RVP, PAP ?
 - Amélioration de la survie

Objectifs
individualisés
+++

Les algorithmes de traitement de l'HTAP

Les années 80 (la préhistoire ...)

1990 - 2000

Oral anticoagulant

Oral anticoagulant

Acute

Positive

Oral CCB

Sustained Response

Yes

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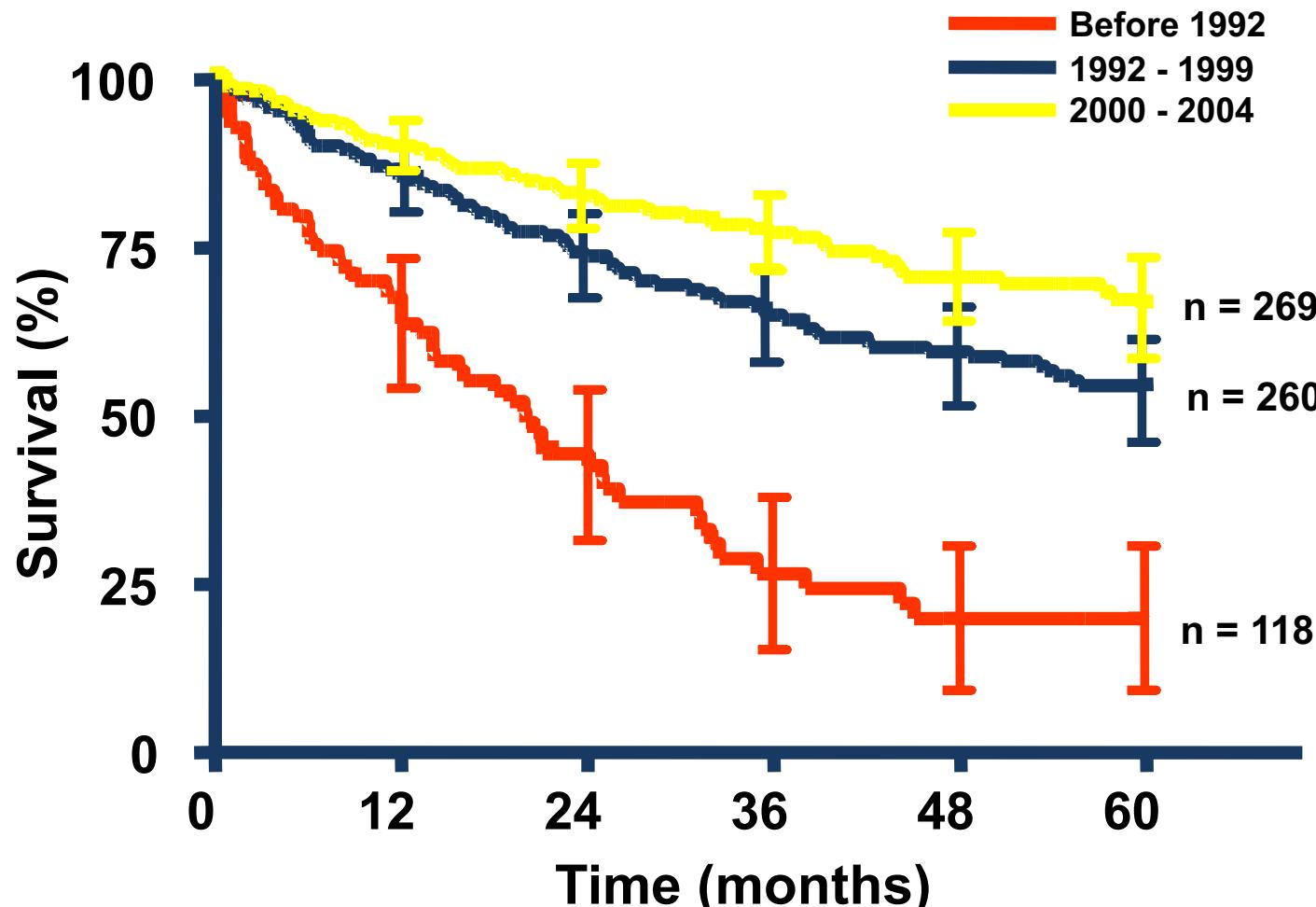
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Current therapeutic approaches

Impact on survival?



P<0.05, Log-Rank Test

Traitemen~~t~~ de l'HTAP : philosophie

- Stratégie thérapeutique qui inclut
 - L'évaluation initiale du risque
 - L'évaluation de la réponse au traitement

Évaluation du risque dans l'HTAP (1)

- À réaliser tous les 3 à 6 mois dans un centre de référence ou de compétences chez les patients stables (I-C)
- Sur la base d'un ensemble de paramètres (I-C)

Cliniques	Signes d'insuffisance ventriculaire droite, progression des symptômes, syncope	Taux plasmatique de NT-proBNP
Mesure de la capacité à l'effort	Classe fonctionnelle NYHA : marqueur pronostique +++ Distance parcourue au test de marche de 6 minutes et/ou épreuve d'effort	Évaluation de la fonction ventriculaire droite Imagerie (échocardiographie, IRM) Hémodynamique

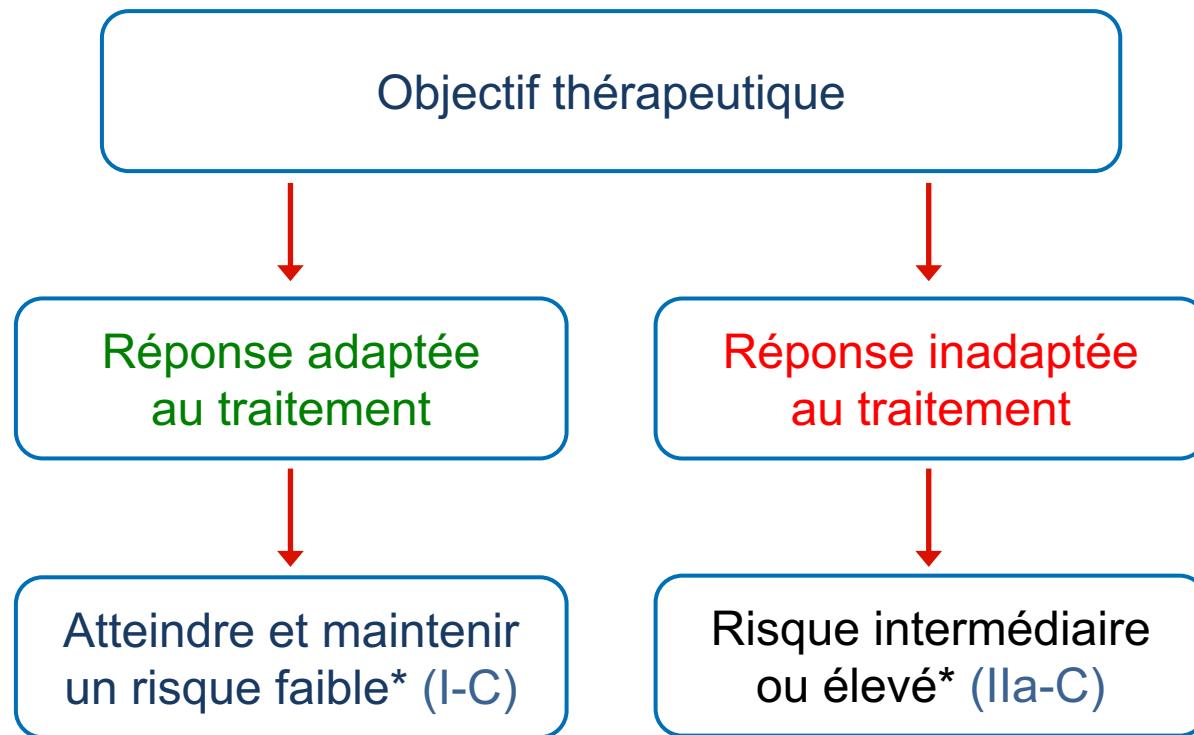
- **Information pronostique** (risque faible, intermédiaire, élevé) de décès à 1 an
- **À individualiser pour chaque patient** (étiologie de l'HTAP, rapidité de la progression de la maladie, symptômes, comorbidités, âge et traitements)

ESC/ERS 2015 Guidelines for risk assessment in PAH

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%

Évaluation de la réponse au traitement (1)

Objectif thérapeutique à individualiser pour chaque patient



* La plupart des valeurs utilisées pour l'évaluation du risque reposent sur des avis d'experts.
Les facteurs individuels du patient sont à prendre en compte.

Évaluation de la réponse au traitement (2)

Modalités de suivi à individualiser pour chaque patient

	Évaluation initiale (avant traitement)	Tous les 3-6 mois	Tous les 6-12 mois	3-6 mois après tout changement de traitement	En cas d'aggravation clinique
Examen clinique, CF NYHA, ECG	✓	✓	✓	✓	✓
TM6 et score de Borg	✓	✓	✓	✓	✓
Épreuve d'effort	✓		✓		✓
Échographie cardiaque	✓		✓	✓	✓
Biologie courante incluant BNP/NT-proBNP	✓	✓	✓	✓	✓
Biologie autre	✓		✓		✓
GDS (ou SpO ₂)	✓		✓	✓	✓
Cathétérisme cardiaque droit	✓		✓	✓	✓

Traitemen~~t~~ de l'HTAP

Trois étapes

1. Mesures générales, traitement conventionnel, adresser le patient à un centre de référence ou de compétences de l'HTP, test de vasodilatation en aigu (au NO)
2. Traitement médical
 - Antagonistes calciques chez les patients répondeurs au NO
 - Traitements approuvés pour l'HTAP chez les patients non répondeurs au NO, selon le risque et le niveau de preuve / la classe de recommandation des médicaments
3. Évaluation de la réponse au traitement
 - Association de médicaments approuvés
 - Transplantation pulmonaire

Mesures générales et traitement symptomatique

(2015 guidelines – Treatment algorithm)

Recommendations	Class ^a	Level ^b
It is recommended that PAH patients avoid pregnancy	I	C
Immunization of PAH patients against influenza and pneumococcal infection is recommended	I	C
Psychosocial support is recommended in PAH patients	I	C
Supervised exercise training should be considered in physically deconditioned PAH patients under medical therapy	IIa	B
In-flight O ₂ administration should be considered for patients in WHO-FC III and IV and those with arterial blood O ₂ pressure consistently < 8 kPa (60 mmHg)	IIa	C
In elective surgery, epidural rather than general anaesthesia should be preferred whenever possible	IIa	C
Excessive physical activity that leads to distressing symptoms is not recommended in PAH patients	III	C

Recommendations	Class ^a	Level ^b
Diuretic treatment is recommended in PAH patients with signs of RV failure and fluid retention	I	C
Continuous long-term O ₂ therapy is recommended in PAH patients when arterial blood O ₂ pressure is consistently < 8 kPa (60 mmHg) ^d	I	C
Oral anticoagulant treatment may be considered in patients with IPAH, HPAH and PAH due to use of anorexigens	IIb	C
Correction of anaemia and/or iron status may be considered in PAH patients	IIb	C
The use of angiotensin-converting enzyme inhibitors, angiotensin-2 receptor antagonists, beta-blockers and ivabradine is not recommended in patients with PAH unless required by co-morbidities (i.e. high blood pressure, coronary artery disease or left heart failure)	III	C

Traitemen~~t~~ de l'HTAP : mesures générales

Ce qui ne change pas

- La grossesse est contre-indiquée dans l'HTAP (I-C)
 - La mortalité est importante
 - Informer la patiente des risques
 - Pas de consensus sur la meilleure méthode de contraception
= progestatifs, DIU au lévonorgestrel (risque rare de réaction vagale à l'insertion chez les patientes avec HTAP sévère)
 - Discuter l'interruption médicale de grossesse
 - Suivi de grossesse par une équipe multidisciplinaire comportant des obstétriciens et des experts de l'HTAP
 - Les ARE sont contre-indiqués au cours de la grossesse

Traitement de l'HTAP : mesures générales

Ce qui ne change pas

- La grossesse est contre-indiquée dans l'HTAP (I-C)
- Une réadaptation supervisée est encouragée chez les patients déconditionnés (IIa-B)
 - Dans des centres de référence ou de compétences de l'HTAP et de réadaptation
 - Chez les patients stables cliniquement, sous un traitement pharmacologique optimisé
 - Méthode, intensité, durée du programme de réadaptation non encore définies

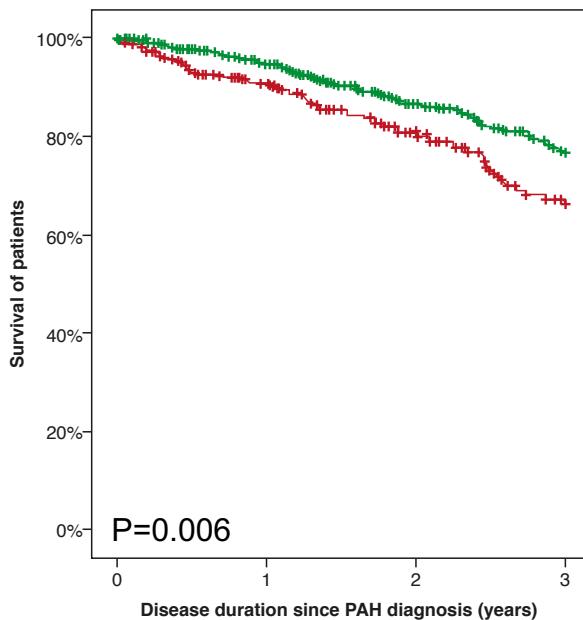
Quelle place pour les anticoagulants ?

EU COMPERA Registry: 2414 PAH, incl. 1283 incident cases

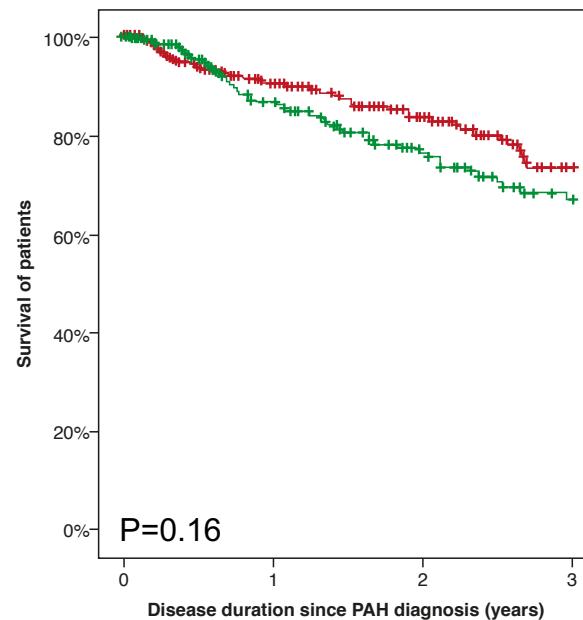
800 idiopathic PAH: Oral AC in 66%

483 other forms of PAH (incl. 208 PAH-SSc): Oral AC in 43%

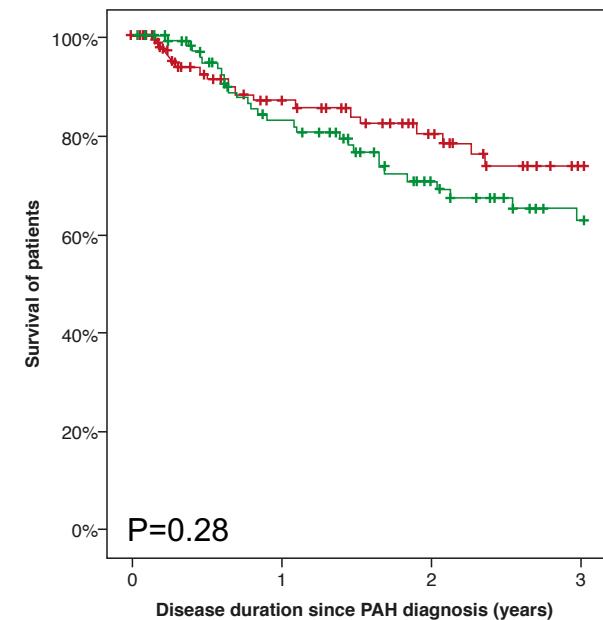
Idiopathic PAH



Non-idiopathic PAH



PAH-SSc



— no anticoagulation

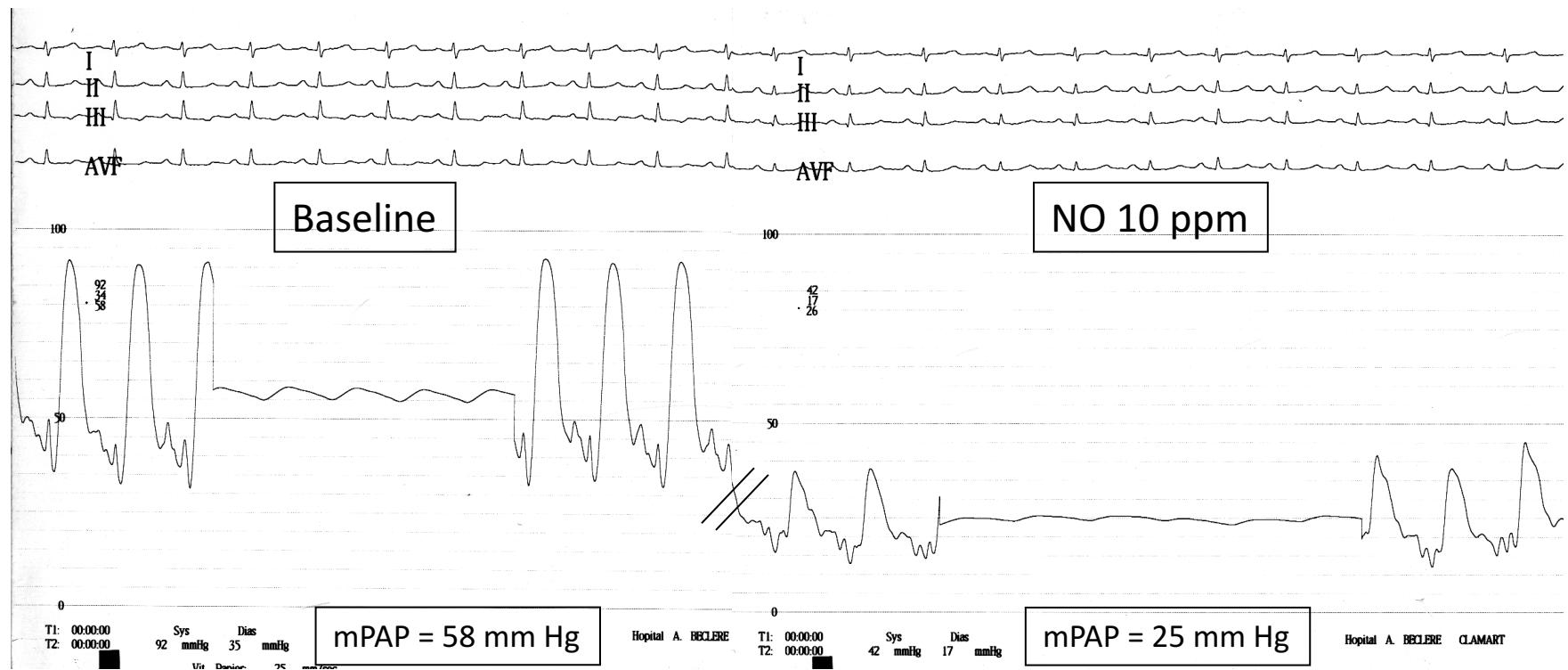
— anticoagulation

Olsson KM, et al. Circulation. 2014;129:57-65.

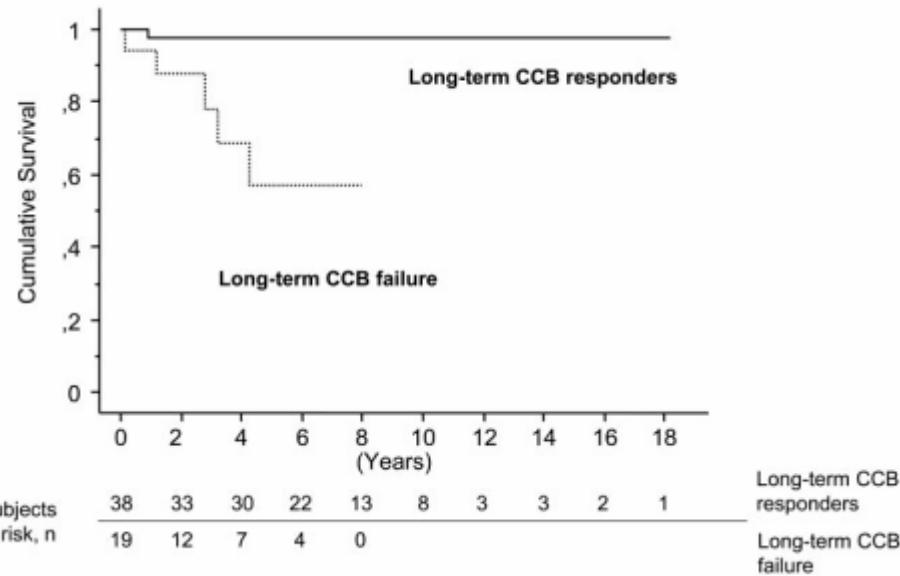
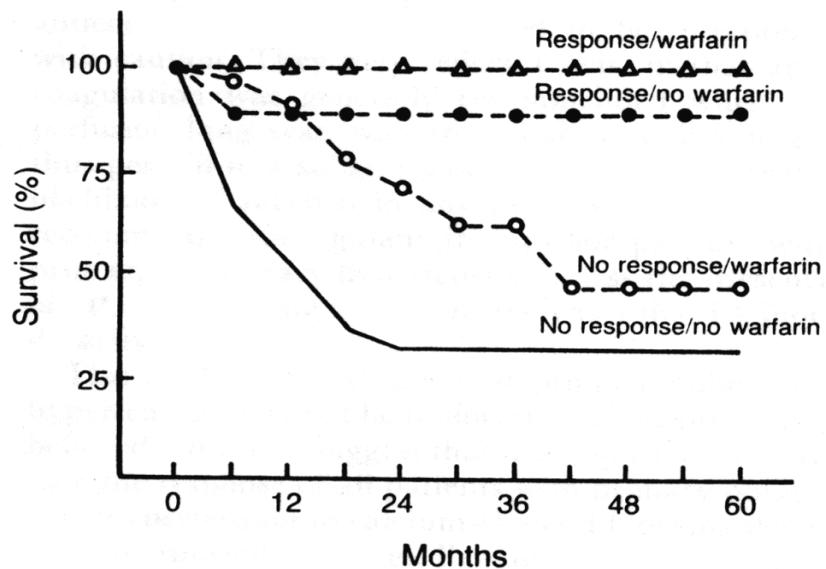
Test de vasoréactivité en aigu

Le but du test de vasoréactivité en aigu est de détecter les patients susceptibles de répondre favorablement aux inhibiteurs calciques au long cours.

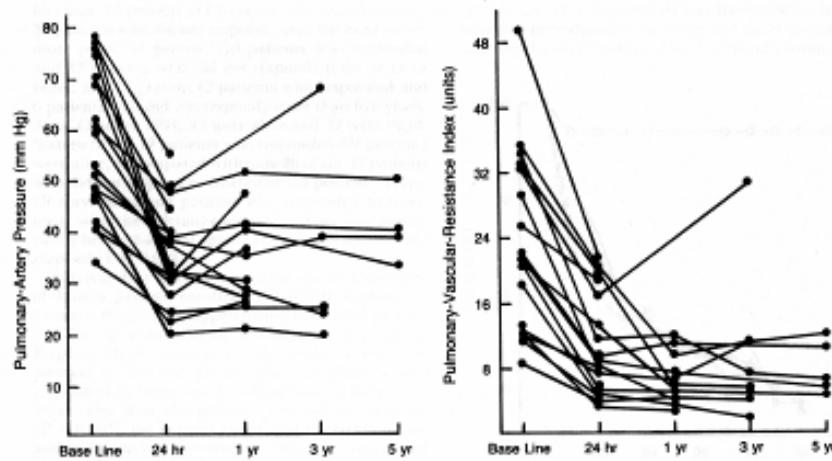
Il permet d'identifier les patients ayant le meilleur pronostic



HTAP : Effets des inhibiteurs calciques



Sitbon O, et al. *Circulation* 2005

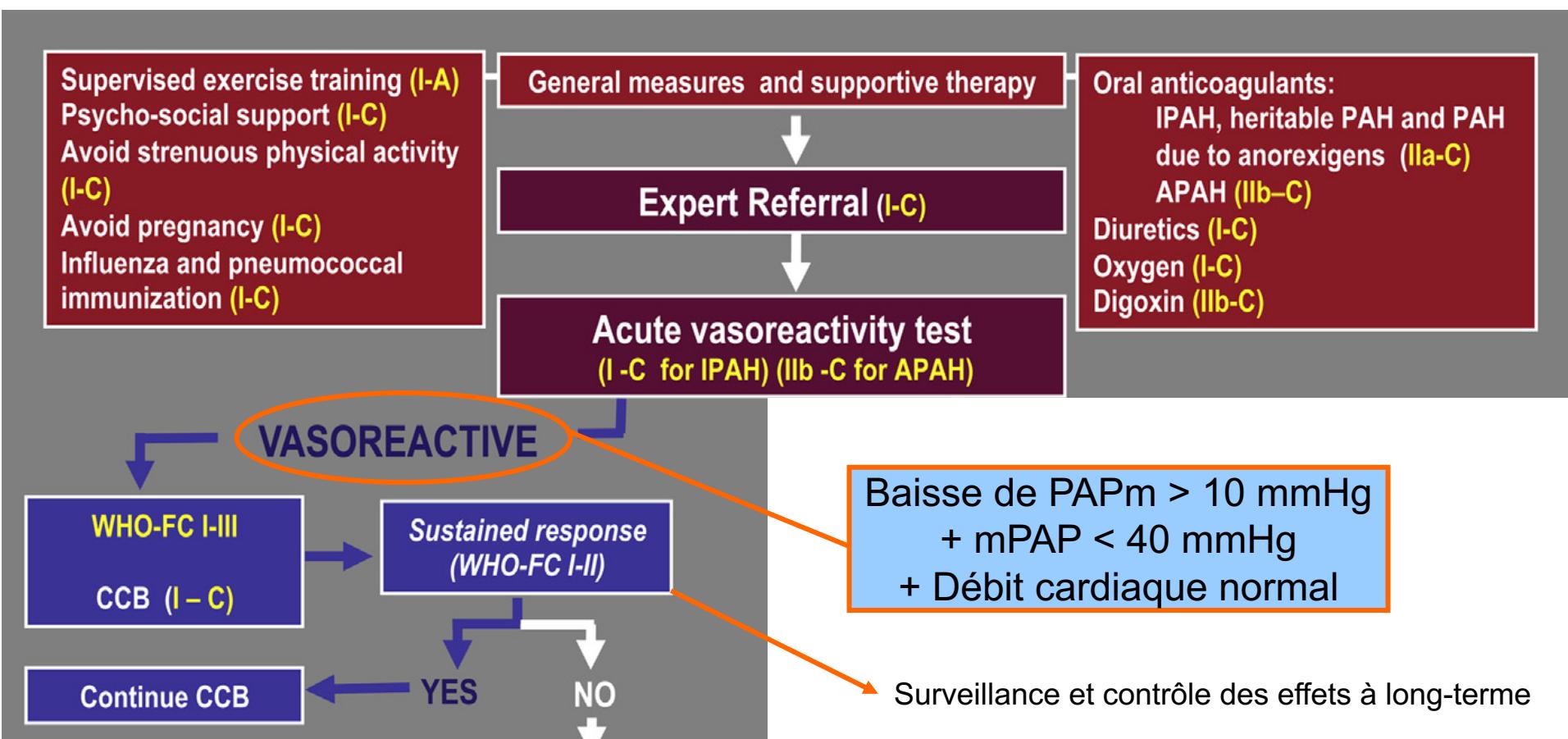


Rich et al. *N Engl J Med* 1992

Only a minority of iPAH patients respond favorably to CCBs (<10%)

Vasoréactivité / Traitement par inhibiteurs calciques

(2013 5th WSPH – Treatment algorithm)



Sitbon O, et al. Circulation. 2005;111:3105-3111.

3rd World PAH Symposium. J Am Coll Cardiol 2004;43:1S-90S.

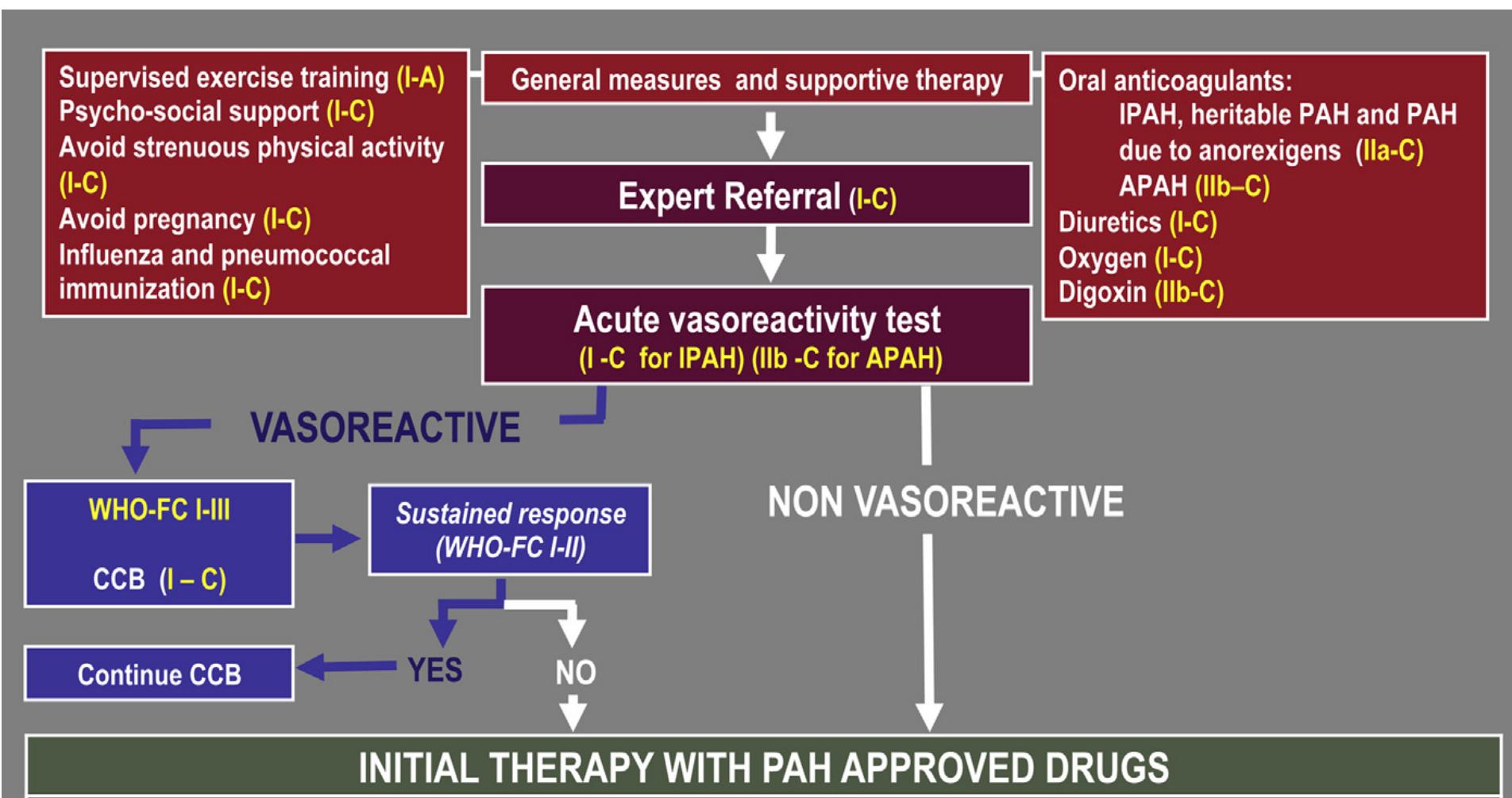
ACCP Guidelines. Chest 2004;126:1S-92S.

Galiè N, et al. ESC Guidelines. Eur Heart J 2004;25:2243-78.

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

Vasoréactivité / Traitement par inhibiteurs calciques

(2013 5th WSPH – Treatment algorithm)



PAH treatment: Targeting 3 major dysfunctional pathways (2004 – 2014)

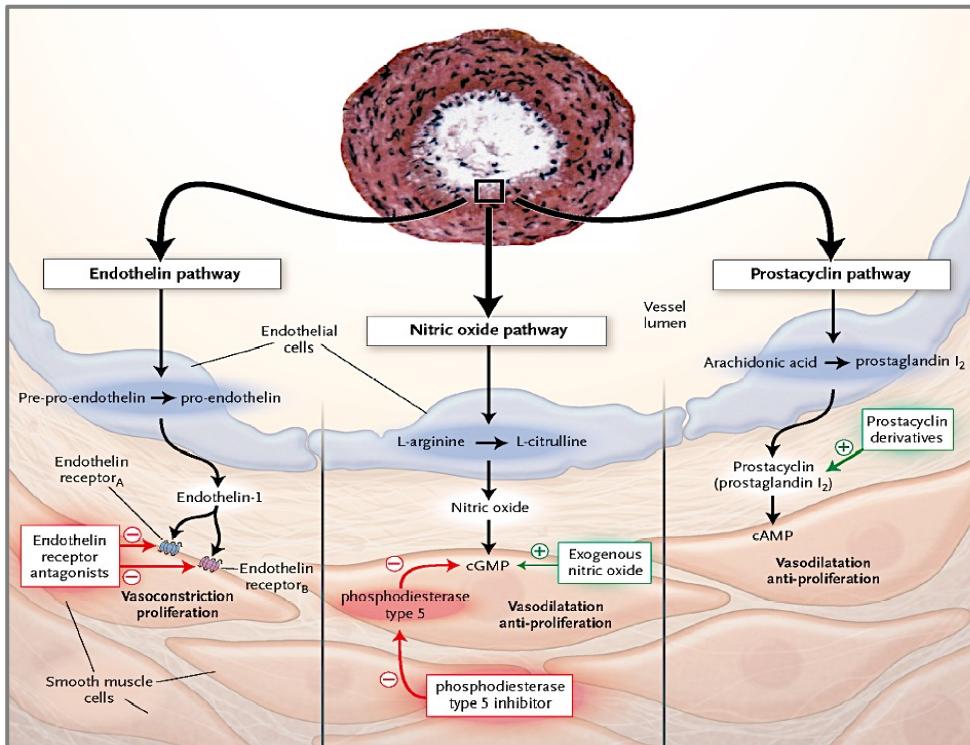
DRUG THERAPY

Treatment of Pulmonary Arterial Hypertension

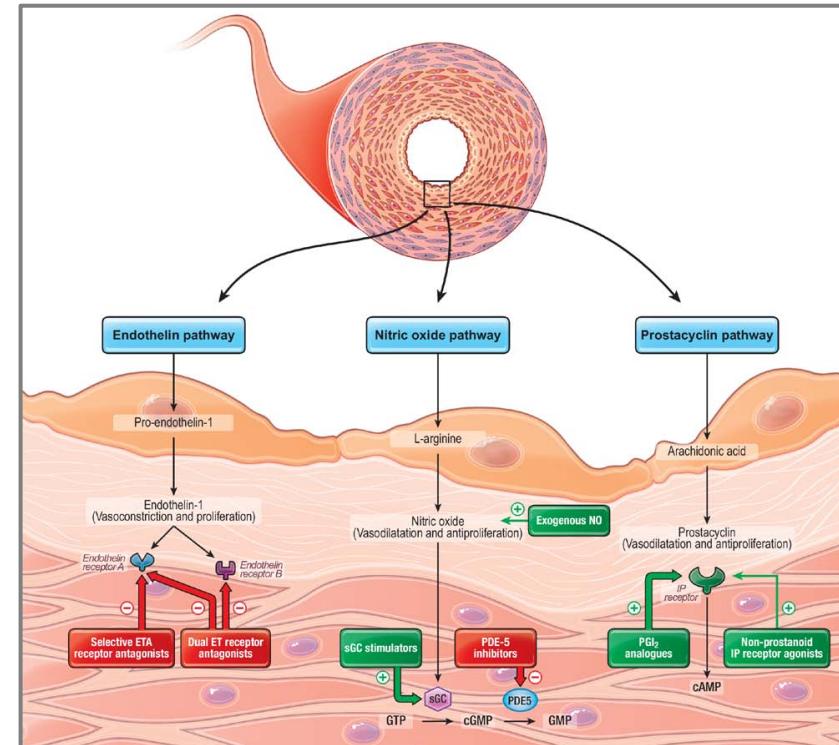
Marc Humbert, M.D., Ph.D., Olivier Sitbon, M.D., and Gérald Simonneau, M.D.

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; Olivier Sitbon, MD, PhD; Gérald Simonneau, MD

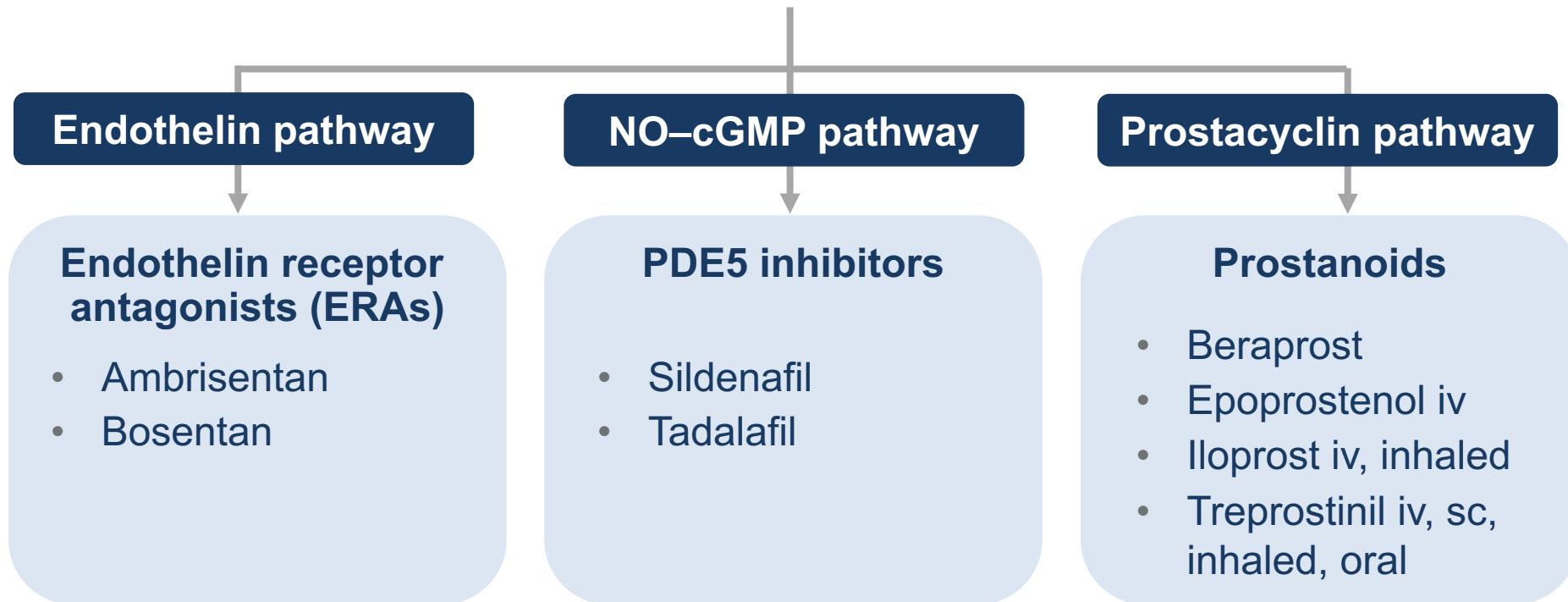


N Engl J Med 2004;351:1425–36.

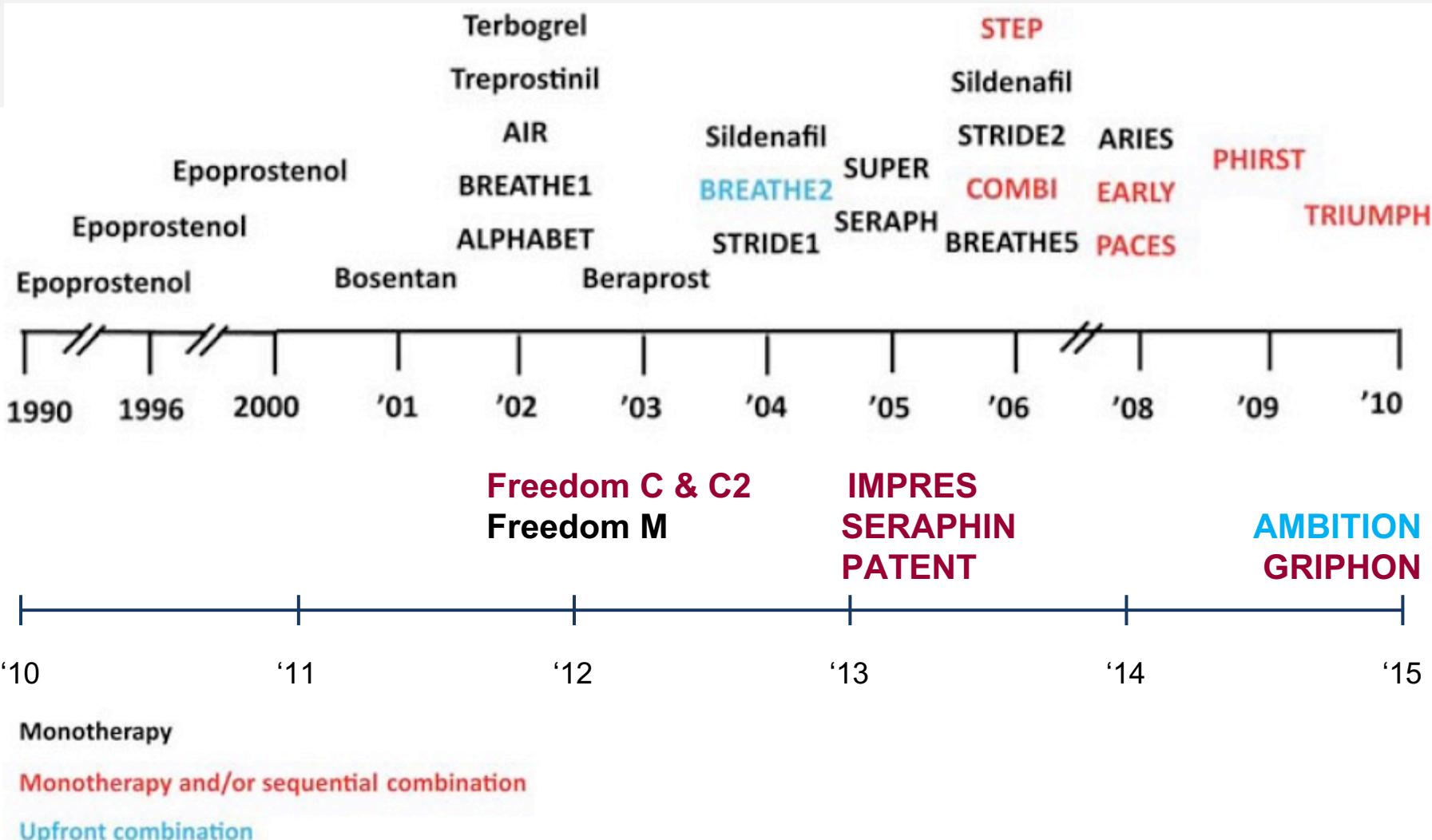


Circulation 2014;130:2189–208.

PAH-specific therapies target the 3 signaling pathways involved in PAH: “Old drugs”



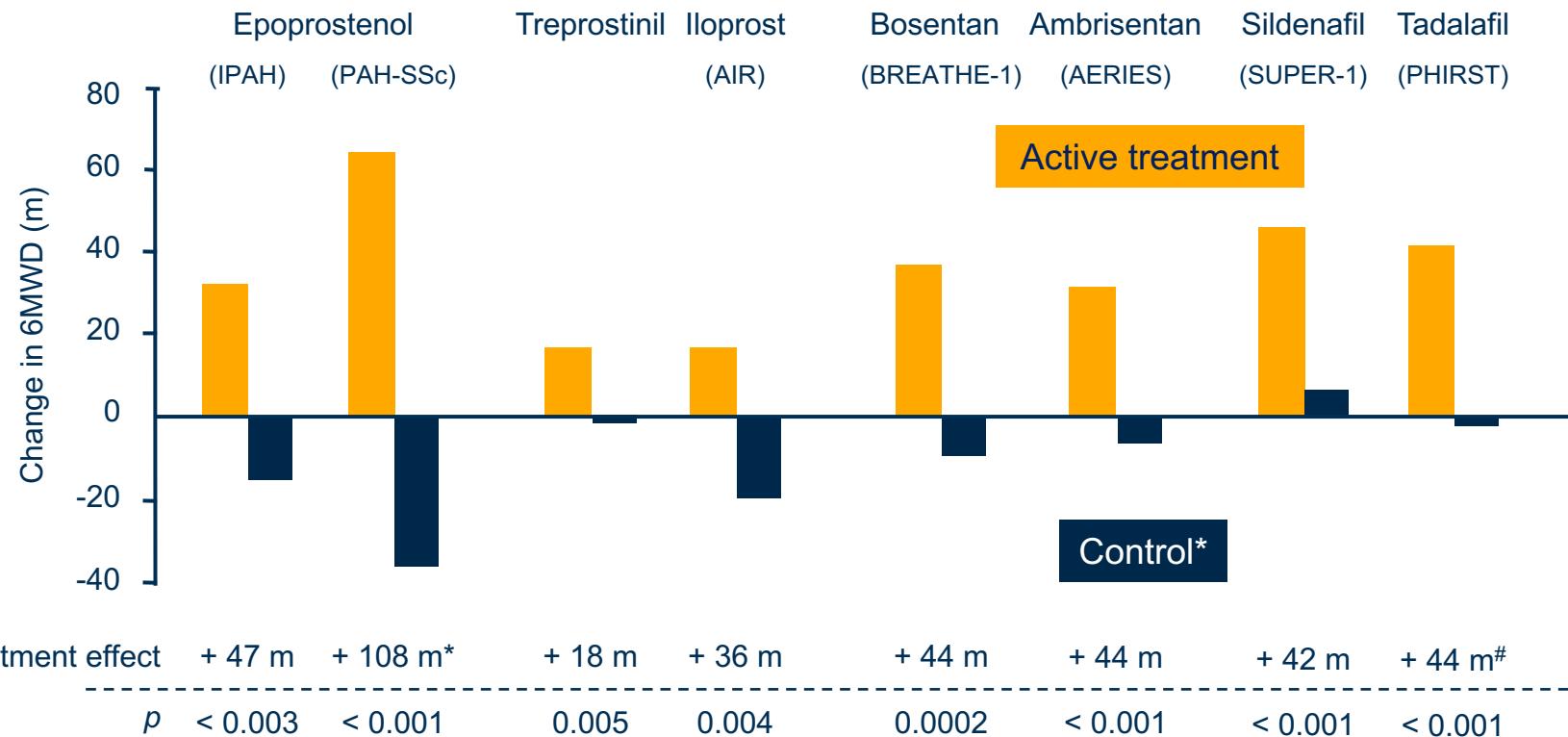
Supporting evidence in PAH: 2 decades of clinical trials



- N=33 published studies. > 6,700 patients with PAH (all FC/etiologies)
- 3 time periods: prostacyclins, oral drugs and combination therapies

RCTs with monotherapy in PAH

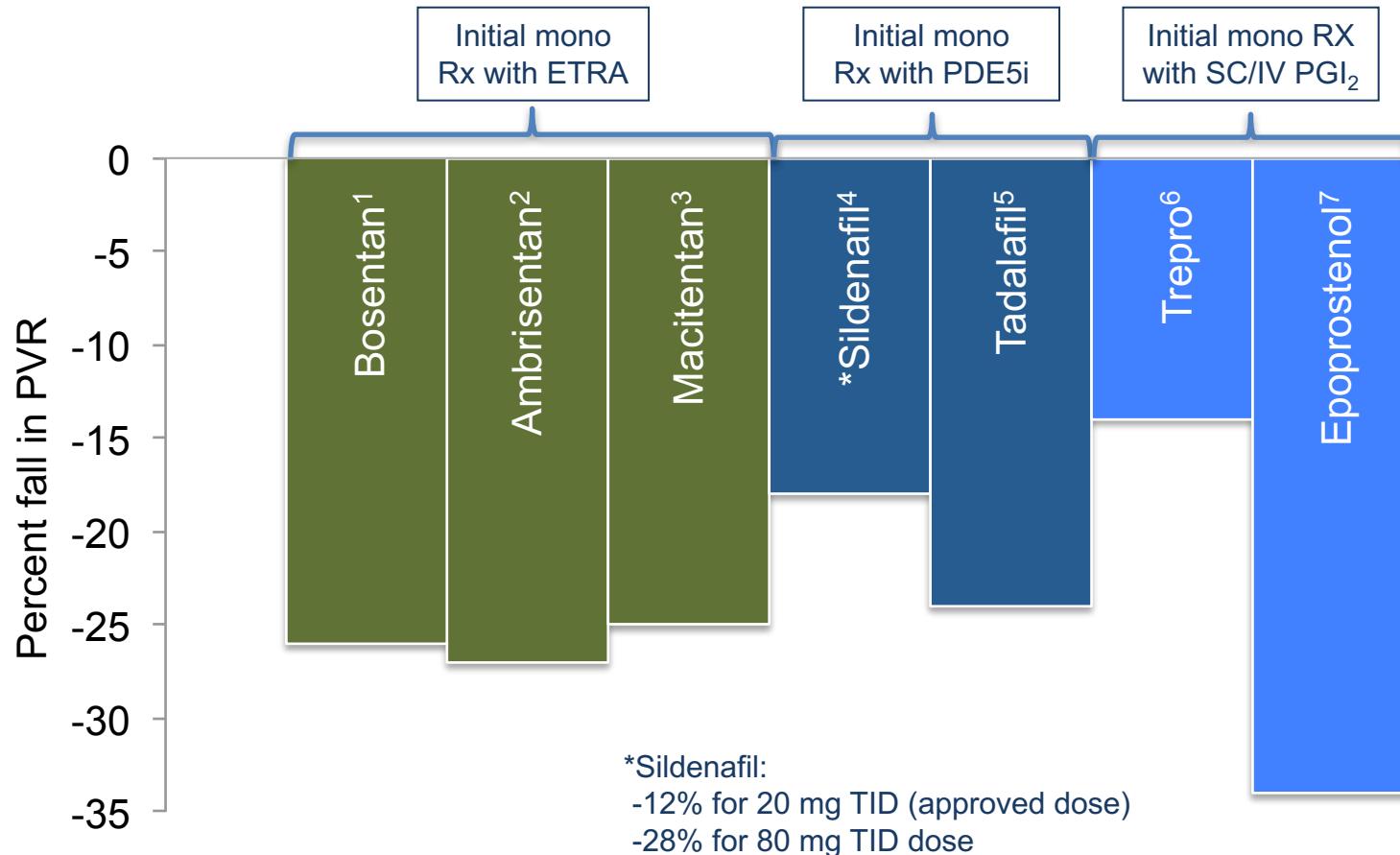
Improvement in exercise capacity (3-4 months)



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

#: monotherapy only

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

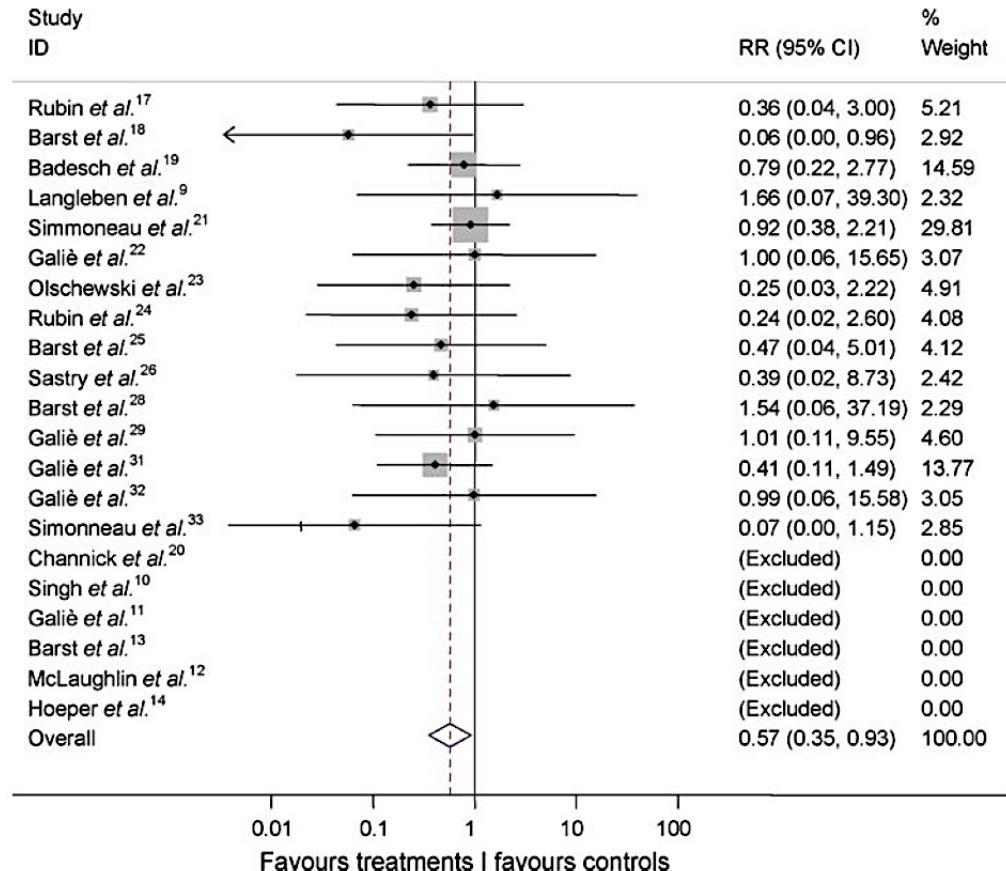


1. Channick RN. *Lancet* 2001; 2. Galie N. *J Am Coll Cardiol* 2005; 3. Pulido T. *N Engl J Med* 2013; 4. Galie N. *N Engl J Med* 2005;
5. Galie N. *Circulation* 2009; 6. Simonneau G. *Am J Respir Crit Care Med* 2002; 7. Barst RJ. *N Engl J Med* 1996.

A meta-analysis of randomized controlled trials in pulmonary arterial hypertension

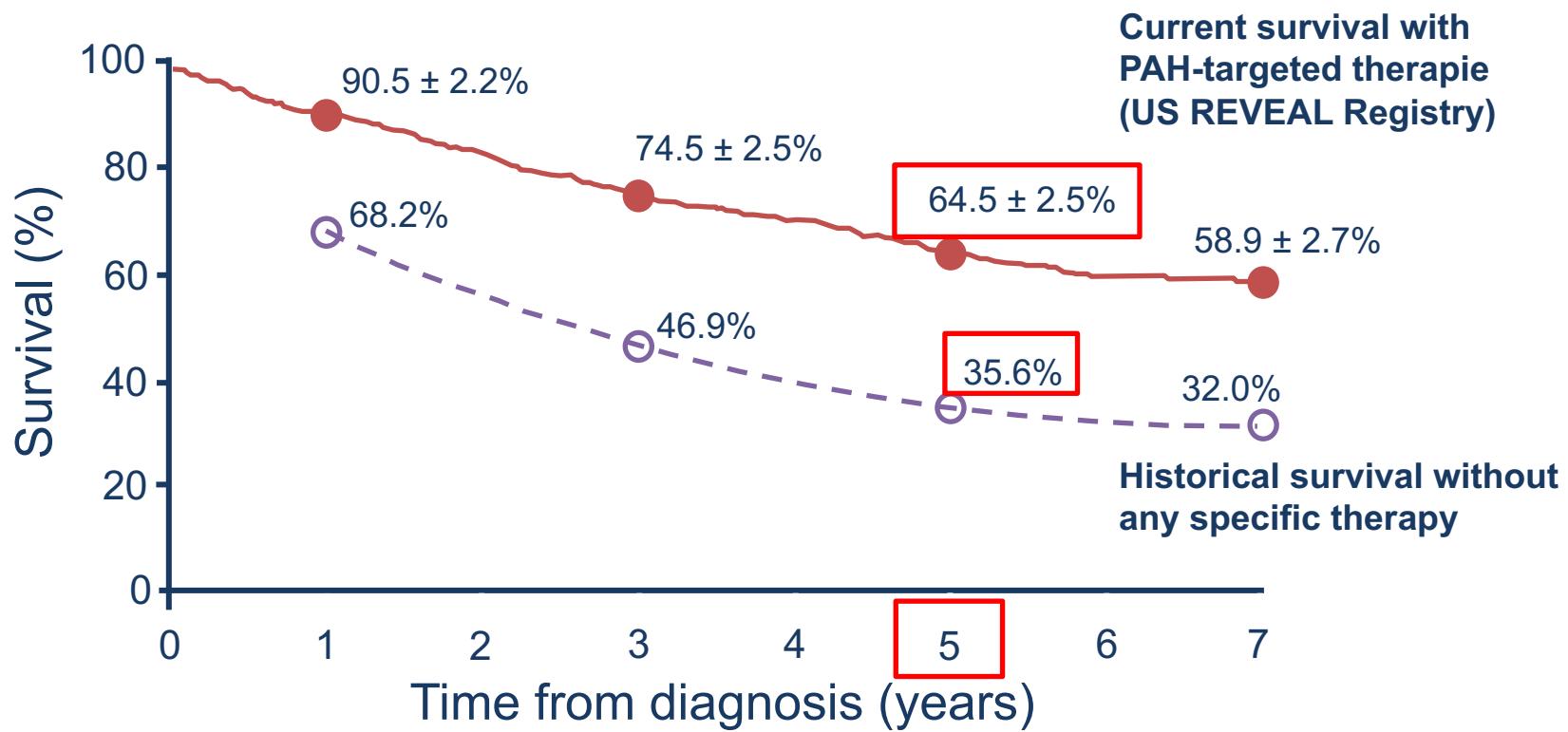
Nazzareno Galiè*, Alessandra Manes, Luca Negro, Massimiliano Palazzini,
Maria Letizia Bacchi-Reggiani, and Angelo Branzi

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

Despite drug discovery and development PAH remains a devastating condition



How to do better?

- Do better with what we have
 - Prevention: Detect and treat “early”
 - Treat more aggressively and be ambitious!
 - Goal-oriented treatment strategy and sequential combination therapy
 - Changing strategy: Initial combination therapy
- Consider new drugs targeting novel pathways (TKIs? Statins? 5-HT? Oxidative stress?...)

Strategies for combination therapy in PAH

1. Sequential combination after clinical deterioration

- Slow sequential combo
- Add drug B sometimes months/years after drug A
- Likely the worst strategy...

2. Sequential combination if treatment goals are not met (goal-oriented treatment strategy)

- Rapid (“aggressive”) sequential combo
- Add drug B rapidly (3-6 months) after drug A

3. Initial (“upfront”) combination therapy

- Treatment initiation with 2 or 3 drugs
- Really different than option 2?
- Some physicians are reluctant
 - “I prefer to keep a drug with me if my patient deteriorates...”
 - “I’m afraid by side effects...”

Sequential combination therapy with 6MWD as primary endpoint: results are not uniform...

Drug tested	Study	Background	N	Duration (weeks)	Primary endpoint
Bosentan ¹	EARLY	None or sildenafil (16%)	185	24	PVR +, Δ6MWD (NS)
Iloprost ²	STEP	Bosentan	67	12	Δ6MWD (NS)
Iloprost ³	COMBI	Bosentan	40	12	Δ6MWD (NS)
Sildenafil ⁴	PACES	Epoprostenol	264	16	Δ6MWD (POS)
Sildenafil ⁵	NCT00323297	Bosentan	104	12	Δ6MWD (NS)
Tadalafil ⁶	PHIRST	None or bosentan (54%)	405	16	Δ6MWD (NS)
Treprostинil ⁷	Inhaled- TRIUMPH	Bosentan or sildenafil	235	12	Δ6MWD (POS)
Treprostинil ⁸	Oral- FREEDOM C1	Bosentan &/or sildenafil	354	16	Δ6MWD (NS)
Treprostинil ⁹	Oral- FREEDOM C2	Bosentan &/or sildenafil	310	16	Δ6MWD (NS)

1. Galiè N. *Lancet* 2008. 2. McLaughlin V. *Am J Respir Crit Care Med* 2006. 3. Hoeper M. *Eur Respir J* 2006.

4. Simonneau. *Ann Intern Med* 2008. 5. NCT00323297. 6. Galiè N. *Circulation* 2009.

7. McLaughlin V. *J Am Coll Cardiol* 2010. 8. Tapson V. *Chest* 2012. 9. Tapson V. *Chest* 2013.

Combination therapy in PAH: New drugs / New strategies

Endothelin pathway

Endothelin receptor antagonists (ERAs)
Macitentan

NO–cGMP pathway

sGC stimulators
Riociguat

Prostacyclin pathway

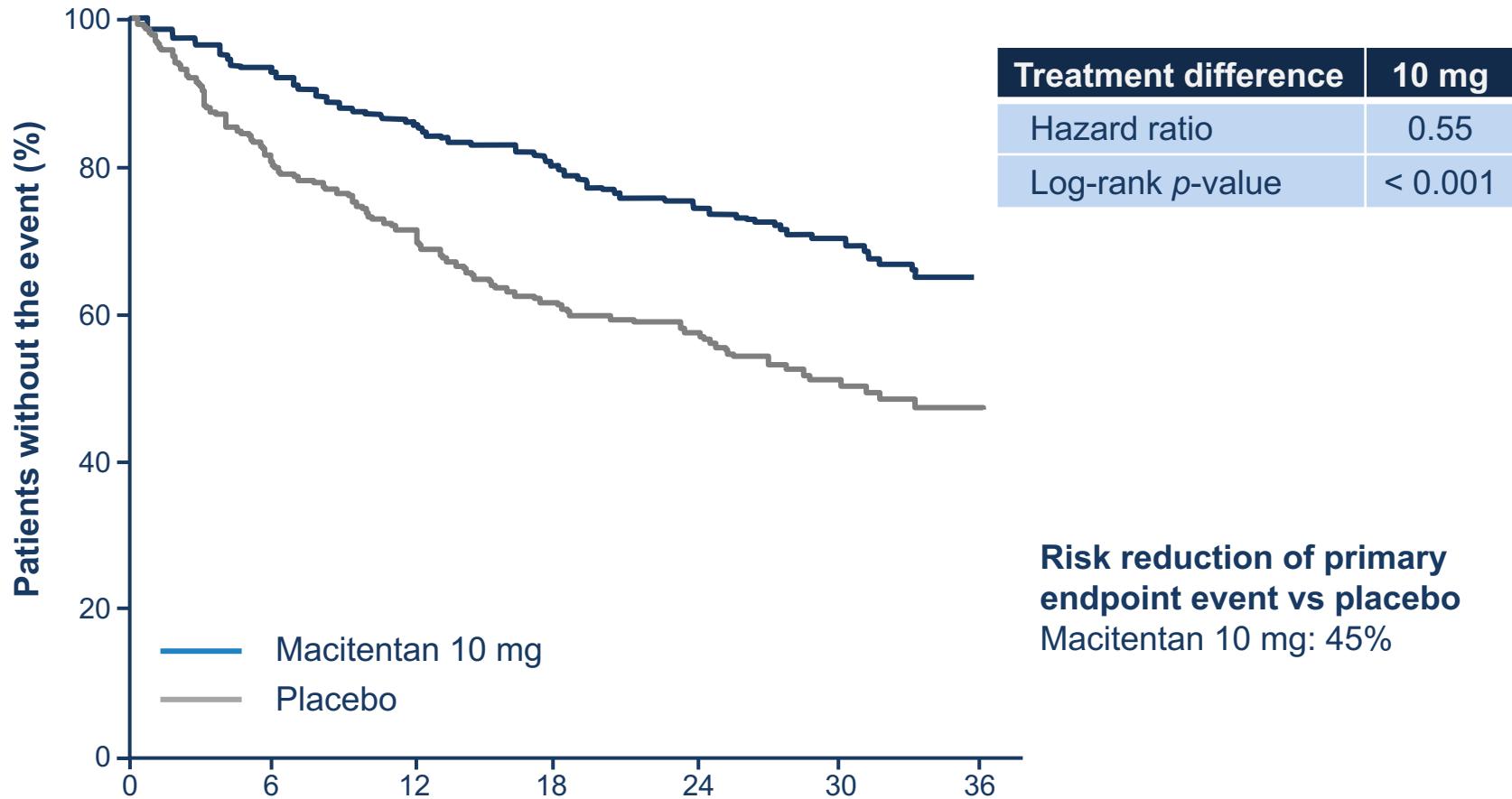
Non prostanoids
IP receptor agonist
Selexipag (oral)

Drug tested	Study	Background	N	Duration (weeks)	Primary endpoint
Bosentan	COMPASS-2 ¹	Sildenafil	334	92	Time to first event of death or morbidity (NS)
Macitentan	SERAPHIN ²	None (36%), PDE5i (61%) or oral/inhaled prostanoids	742	≈ 100	Time to first event of death or morbidity (POS)
Selexipag	GRIPHON ³	None (21%), ERA (13%), PDE5i (32%) or both (34%)	1156	≈ 70	Time to first event of death or morbidity (POS)
Ambrisentan + tadalafil	AMBITION ⁴	None (incident cases)	500	≈ 74	Time to clinical failure event (POS)

1. McLaughlin VV, et al. *Eur Respir J* 2015. 2. Pulido T, et al. *N Engl J Med* 2013.

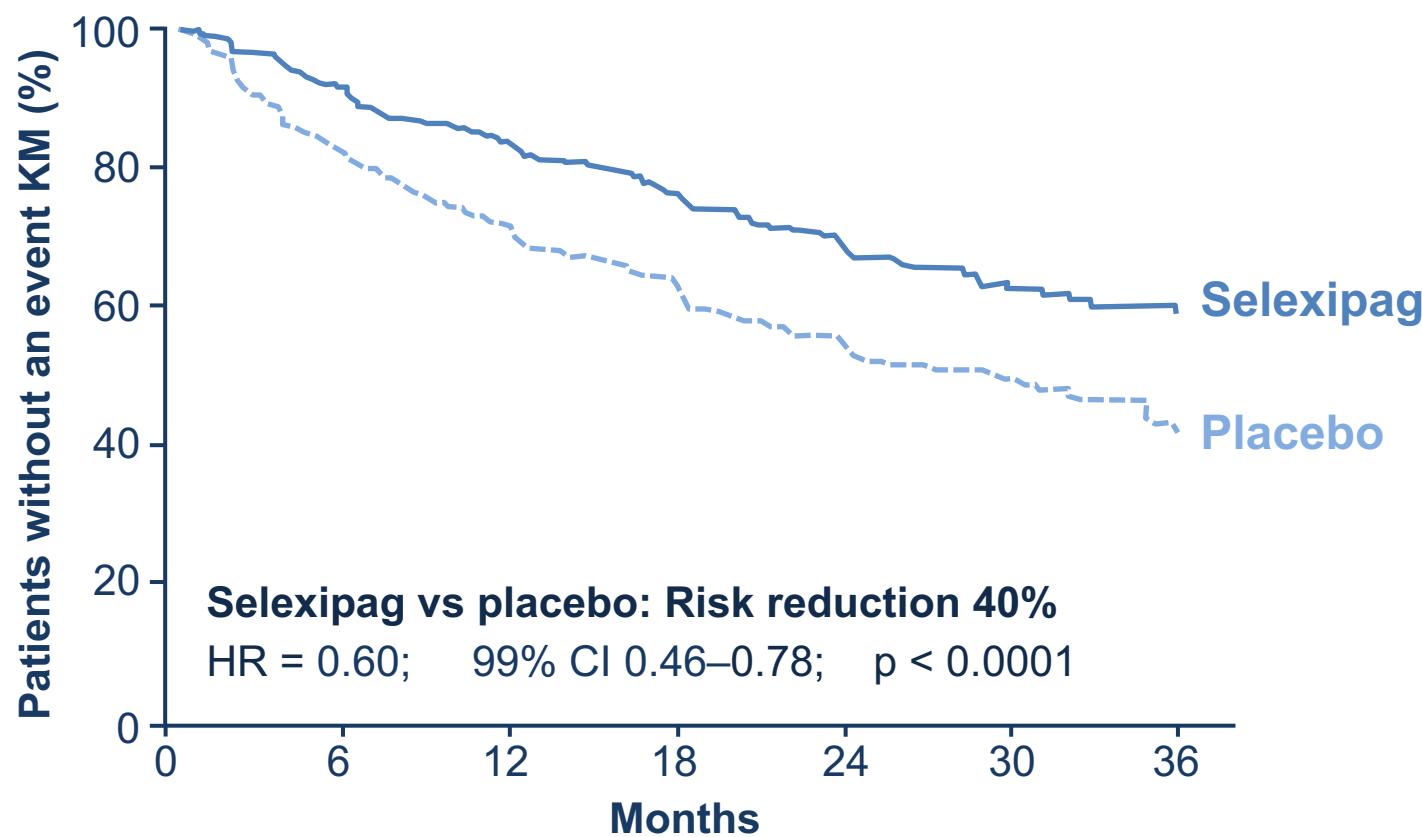
3. Sitbon O, et al. *N Engl J Med* 2015. 4. Galié N, et al. *N Engl J Med* 2015.

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



PAH worsening was the main component of the primary endpoint

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



Hospitalisation for PAH worsening and disease progression were the main components of the primary endpoint

ESC/ERS 2015 Guidelines for risk assessment in PAH

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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%

Survie globale selon objectifs atteints à la première réévaluation sous traitement (6 mois)

French PH Registry

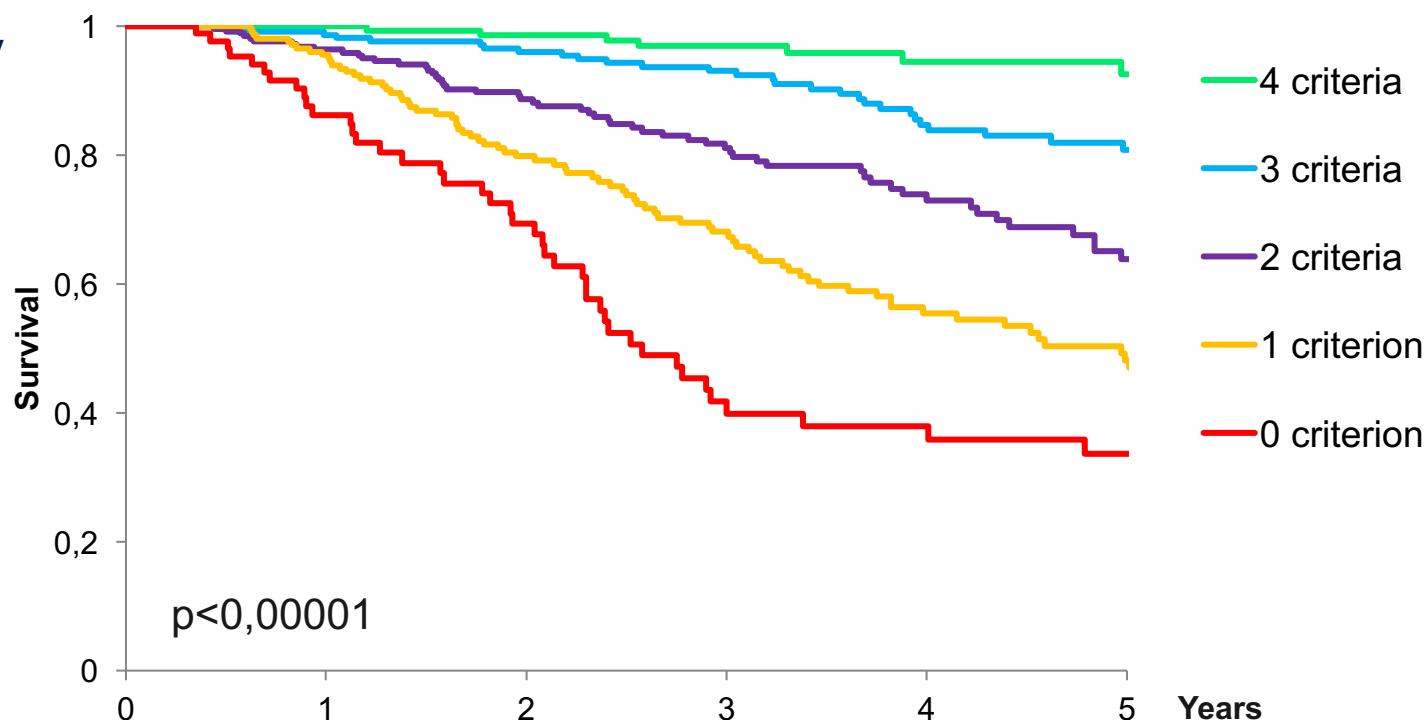
2006-2016

N = 1017

IHA PAH

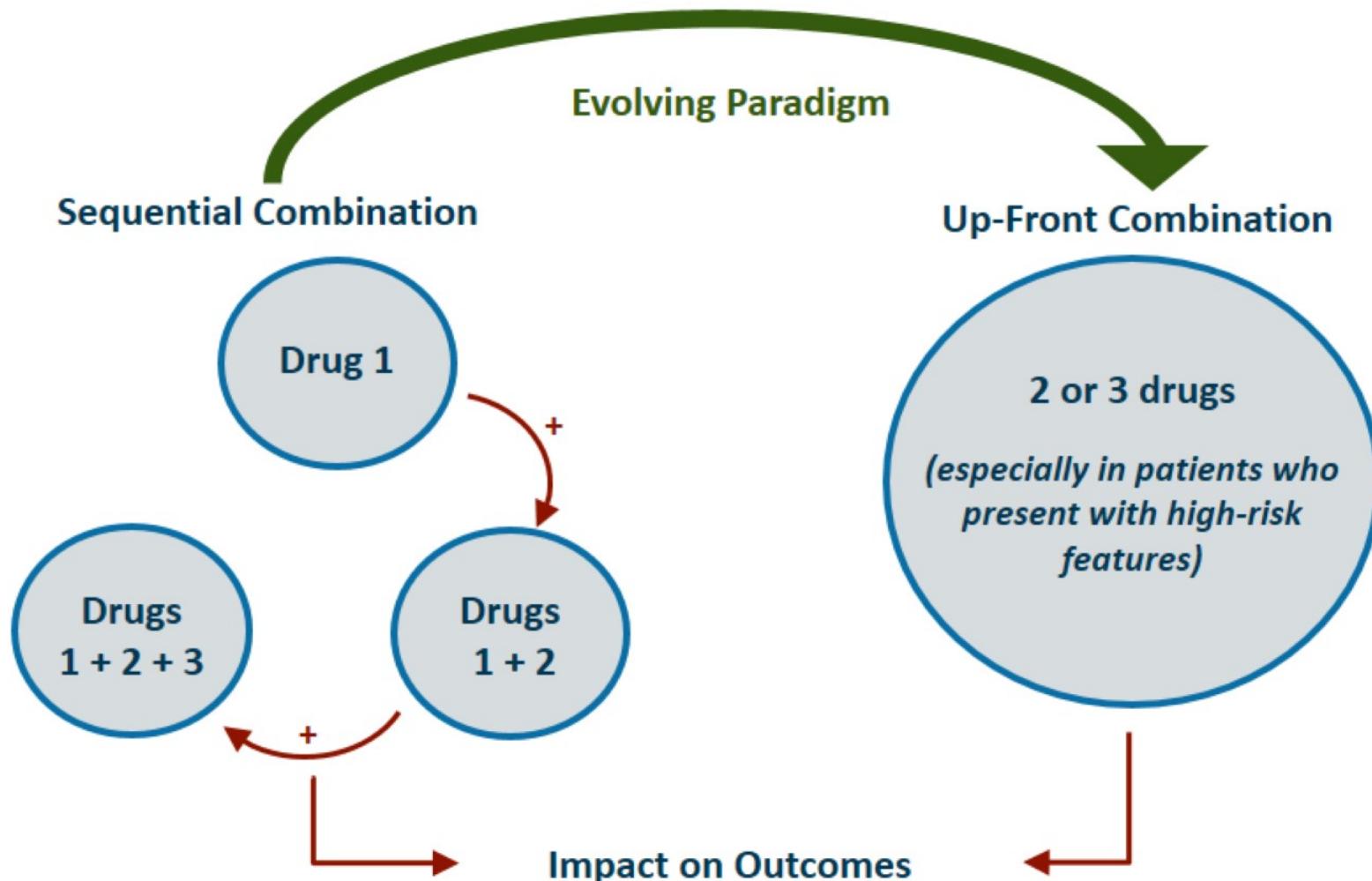
Criteria:

- FC I-II
- 6MWD >440 m
- RAP <8 mmHg
- CI >2.5 L/min/m²



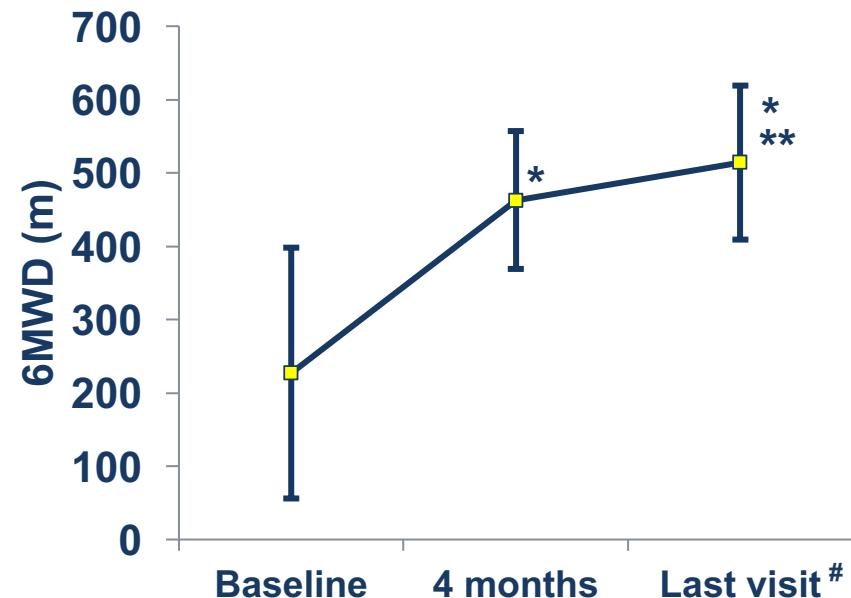
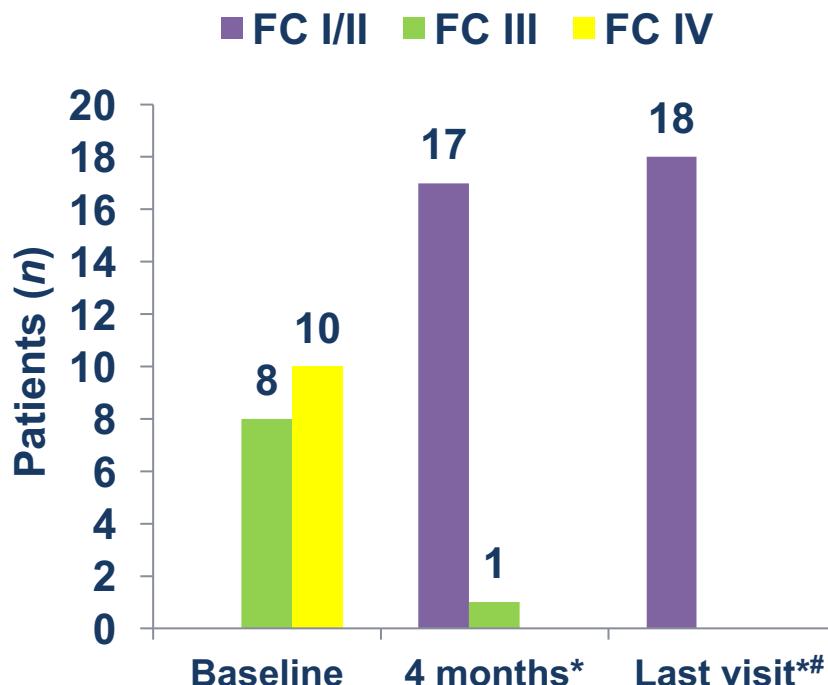
4 criteria	175	153	128	102	63	48
3 criteria	247	204	175	140	102	72
2 criteria	275	219	171	122	78	49
1 criterion	225	183	128	91	62	45
0 criterion	95	61	44	22	18	14

Evolving paradigm: From sequential to initial combination therapy



Upfront triple combination therapy: Effect on FC and 6MWD

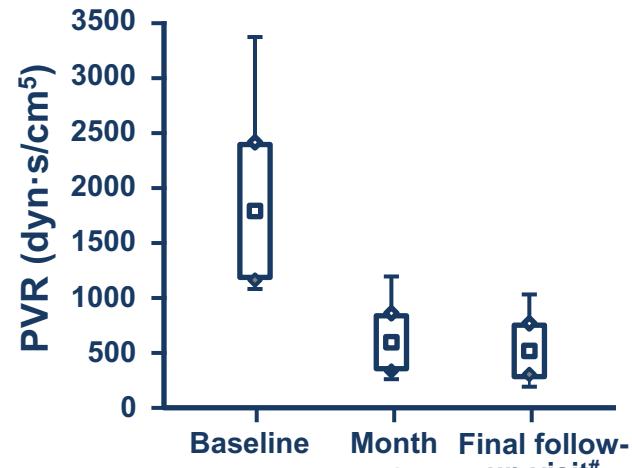
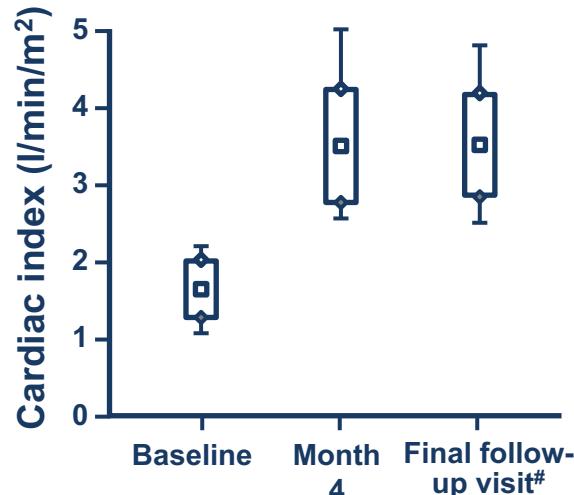
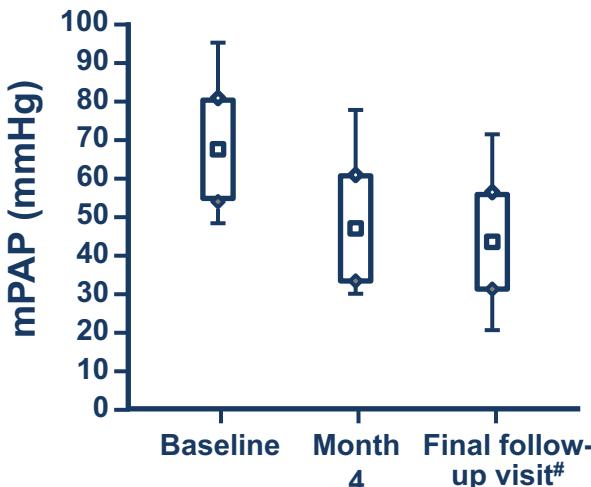
Prospective, observational analysis of idiopathic or heritable PAH patients ($n = 19$)
treated with upfront combination therapy (epoprostenol, bosentan and sildenafil)



32 ± 19 months

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

Upfront triple combination therapy: Effect on haemodynamics



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

#32 ± 19 months

* $p < 0.01$ versus baseline

The AMBITION trial

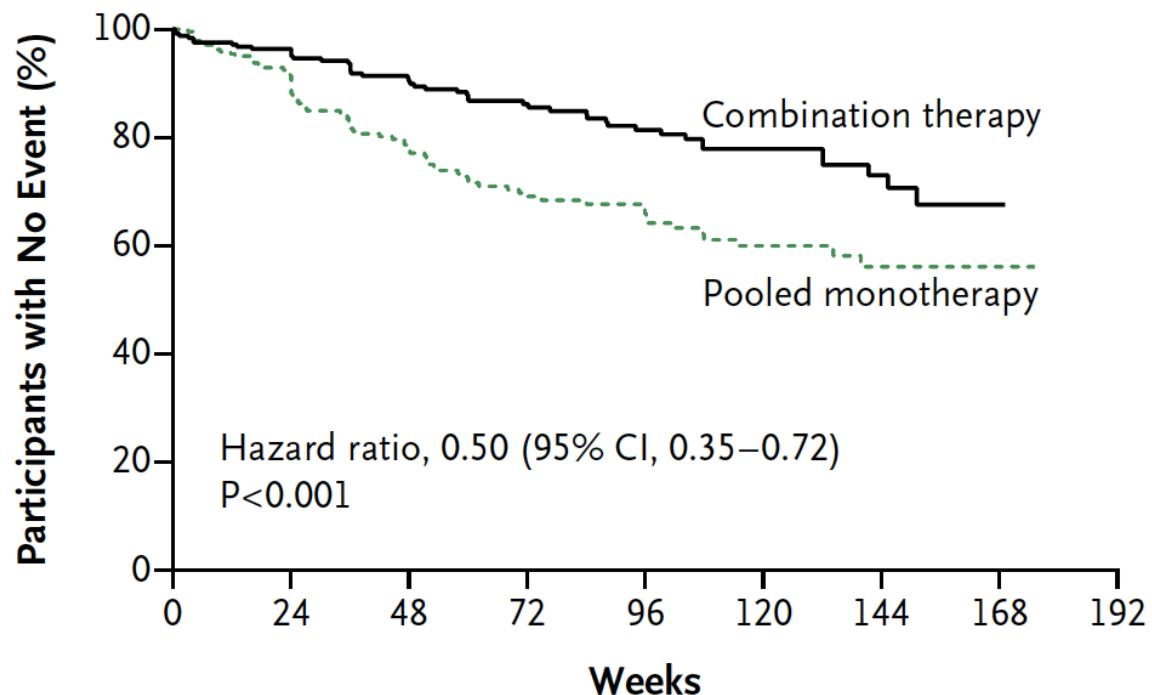
Initial Use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension

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: main result

A Combination Therapy vs. Pooled Monotherapy

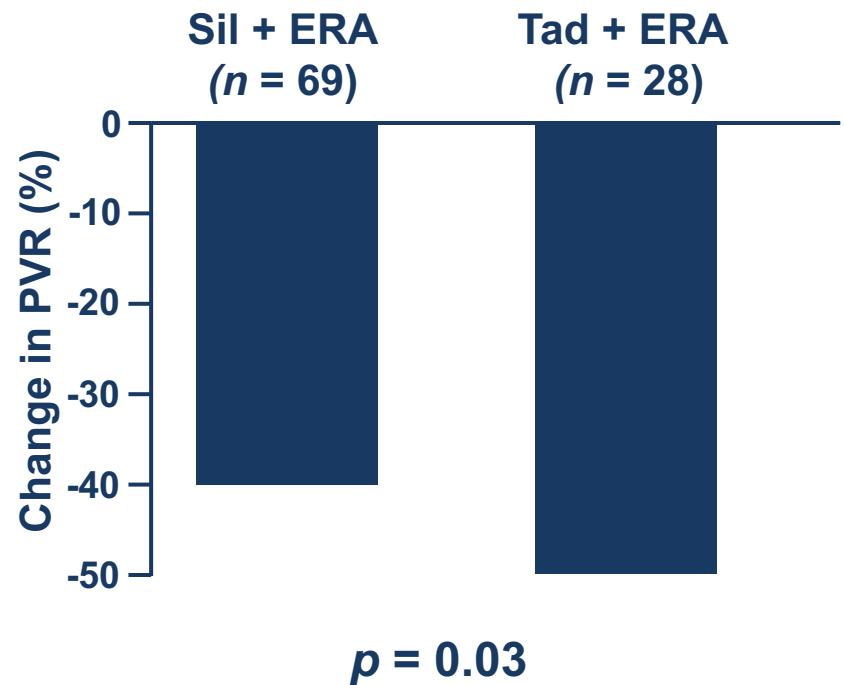
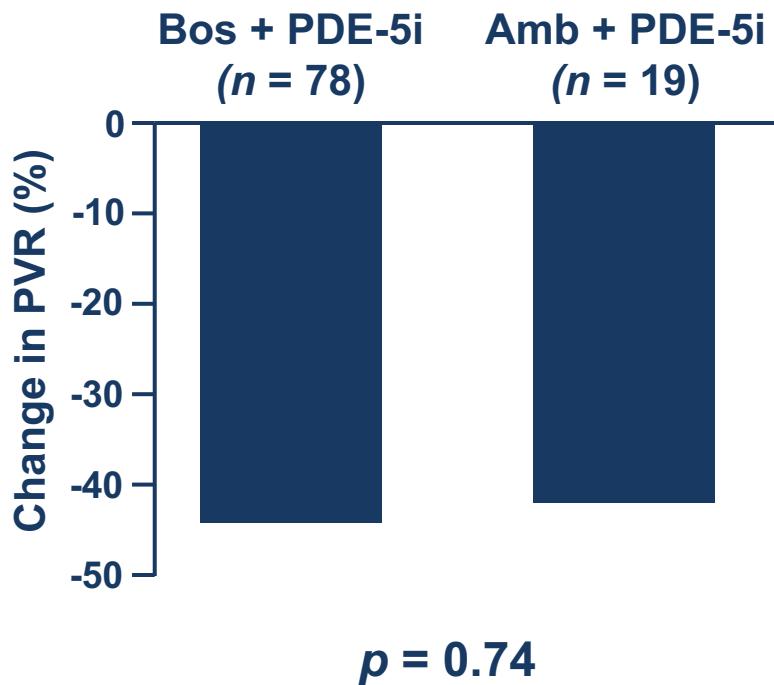


No. at Risk

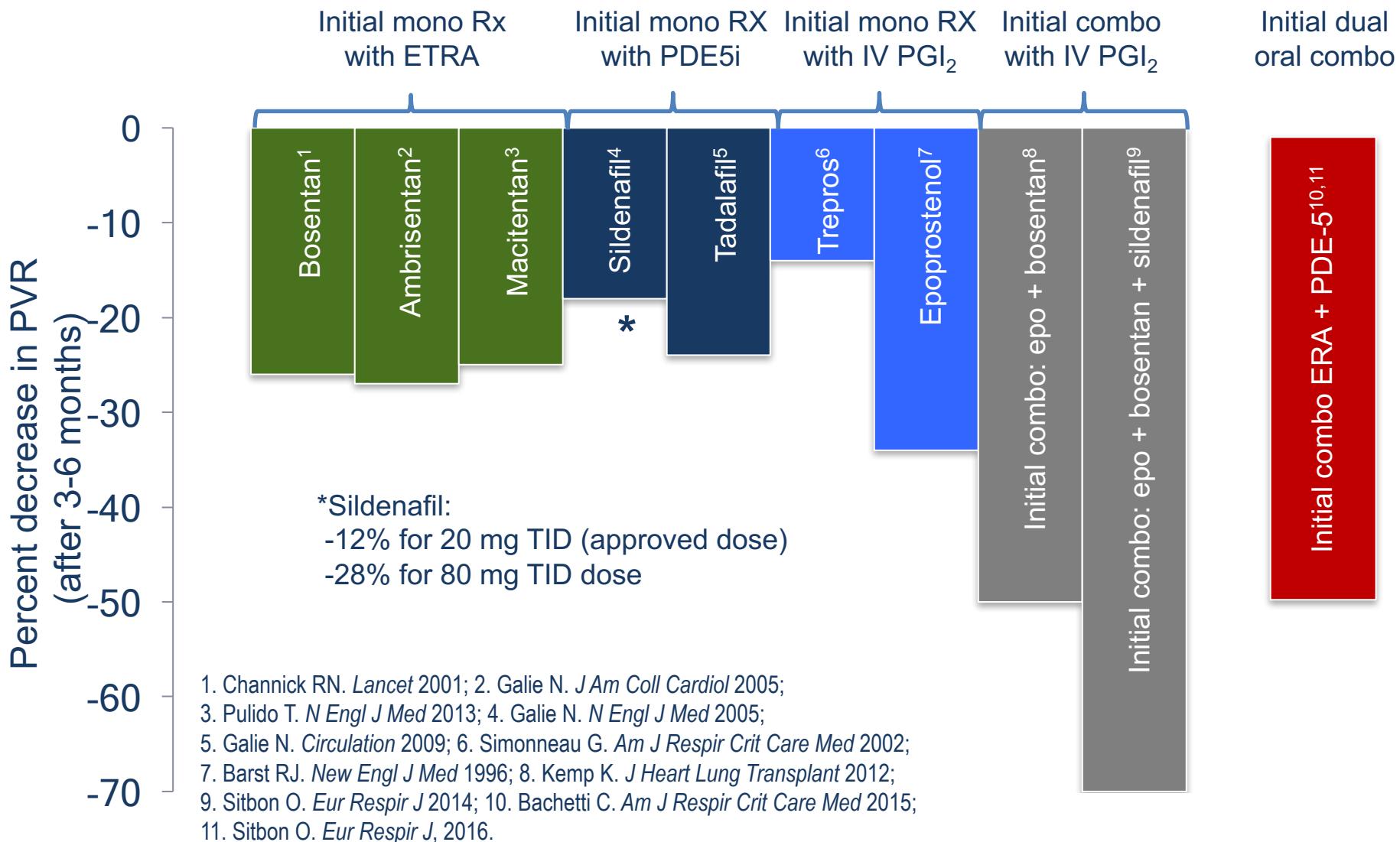
Combination therapy	253	229	186	145	106	71	36	4
Pooled monotherapy	247	209	155	108	77	49	25	5

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

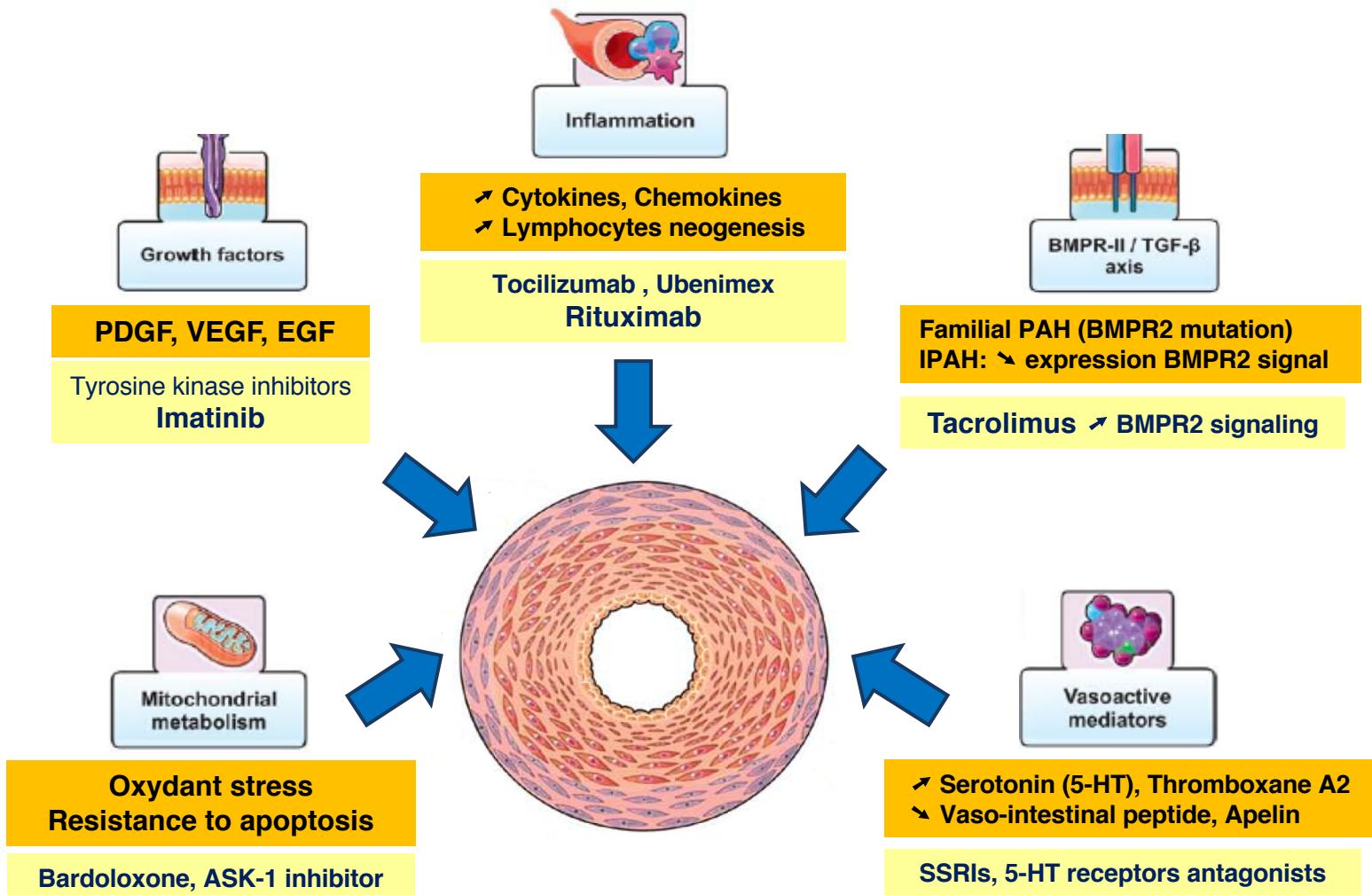
The strategy works with different combinations



Initial therapy: The more the better



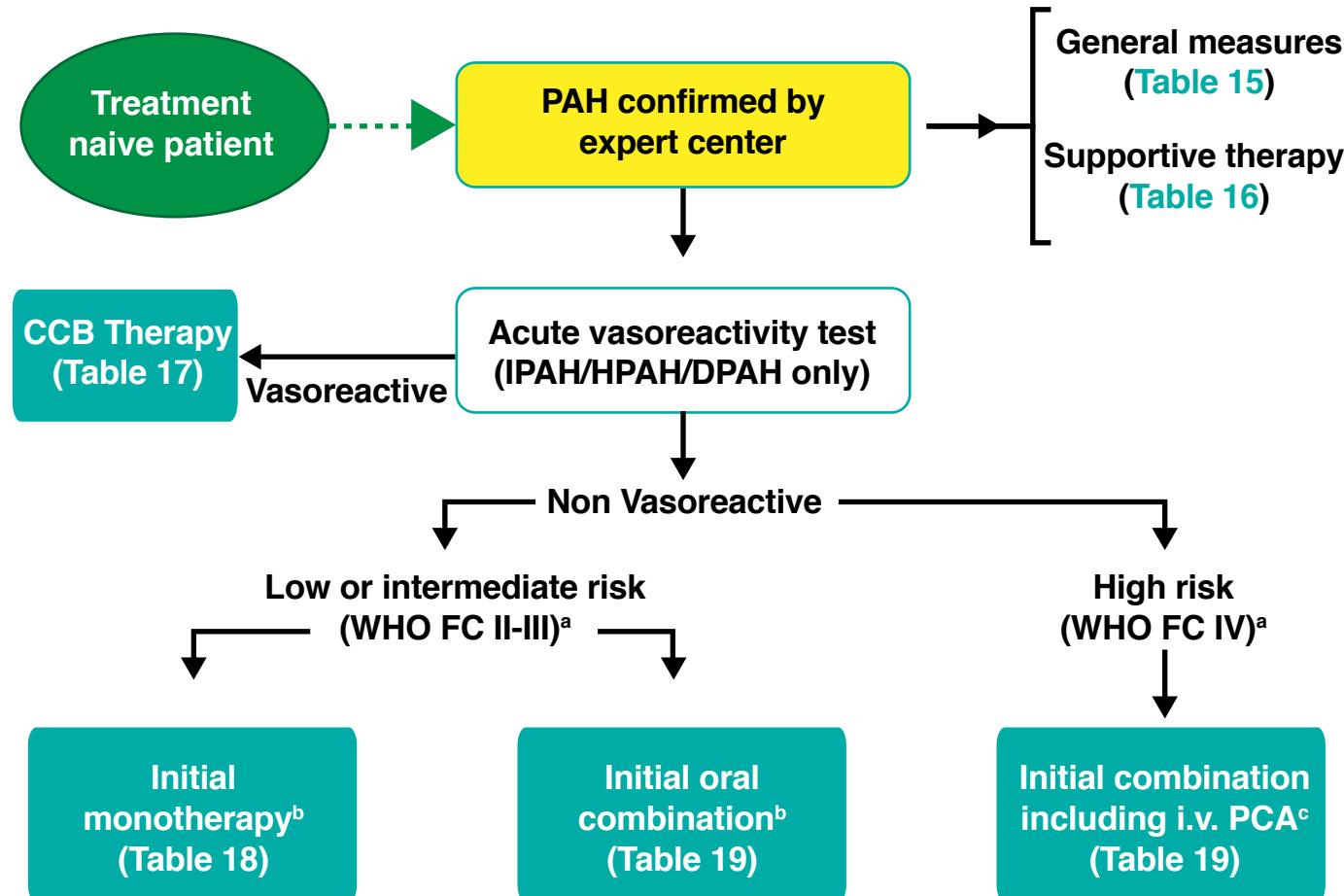
Des nouvelles cibles thérapeutiques ?



Over the last 10 years, many failures in trials with therapies targeting new pathways

- Anti thromboxane A2 (Trebogrel)
- Vasointestinal Peptide (VIP)
- Statins (Simvastatin)
- Specific serotonin reuptake inhibitors
- 5HT 2B/2A receptors antagonists (Terguride)
- Multiple TKI (Sorafenib)
- TKI (Imatinib)
- β -blockers (Bisoprolol)
-and maybe some others?

2015 ESC/ERS guidelines treatment algorithm



2015 ESC/ERS guidelines treatment algorithm

