Inovações Terapêuticas na Hipertensão Pulmonar

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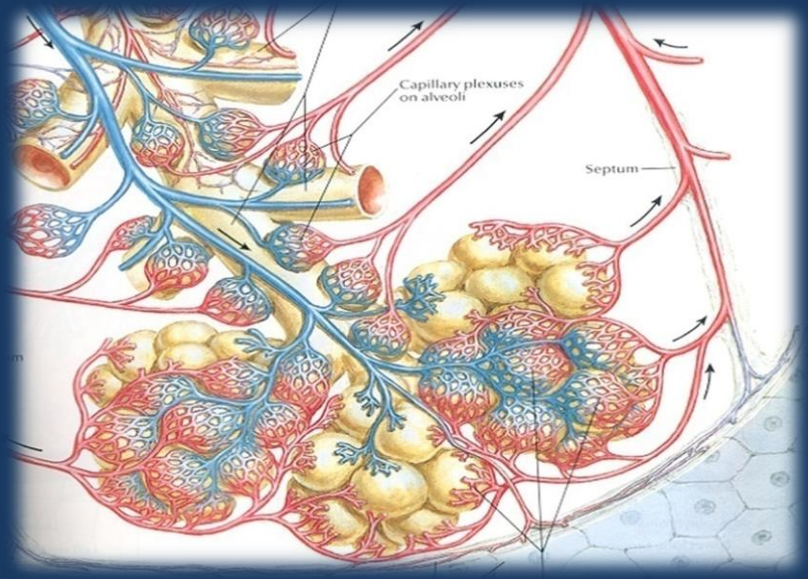
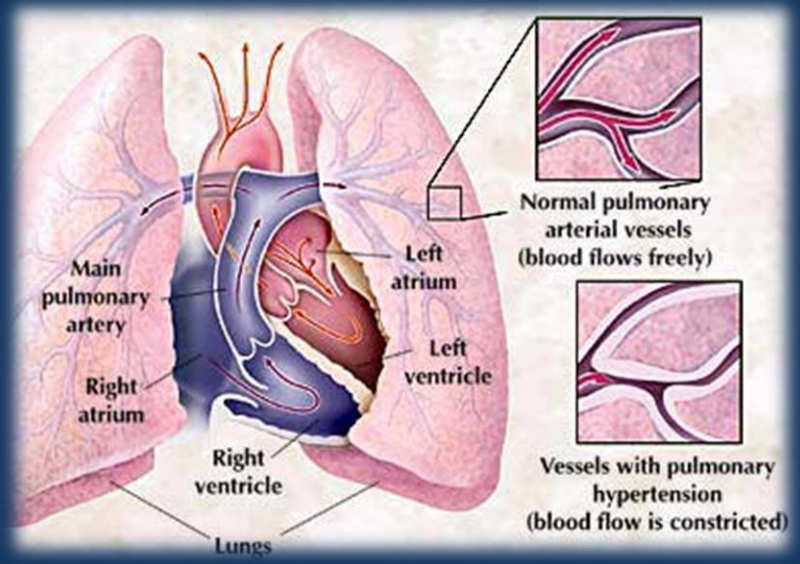
Definition of Pulmonary Hypertension (PH)

Not a disease, but a syndrome in which the pressure in the pulmonary circulation is raised and can be found in multiple clinical conditions

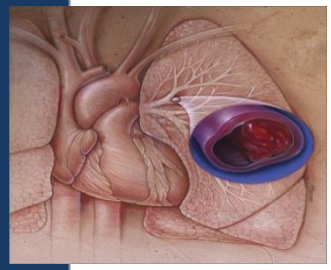
PH is defined haemodynamically by an increase in mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg at rest, as assessed by right heart catheterization (RHC).

PAH is defined by pre-capillary PH with CWP ≤ 15 mmHg and elevated PVR (≥ 3 U Wood) as decided by 5th World Symposium on PH

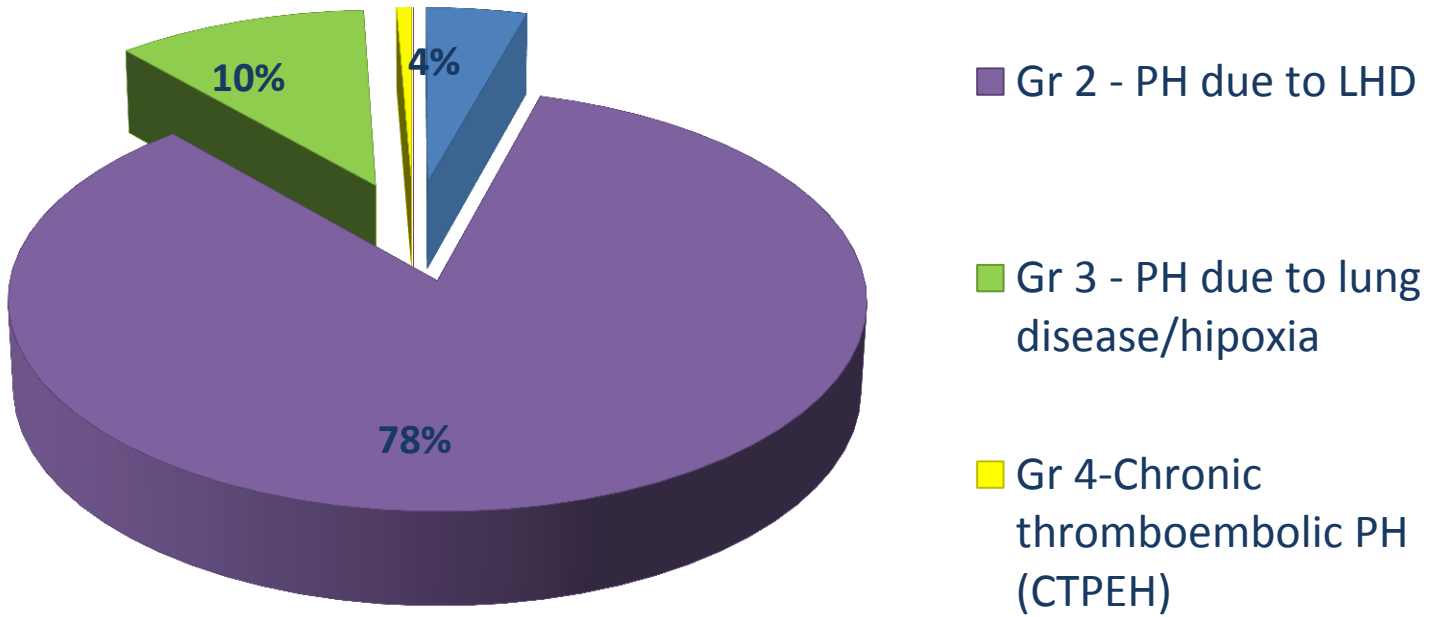




Pulmonary Arterial Hypertension (PAH) is an uncommon cause of PH in an unselected population[1]

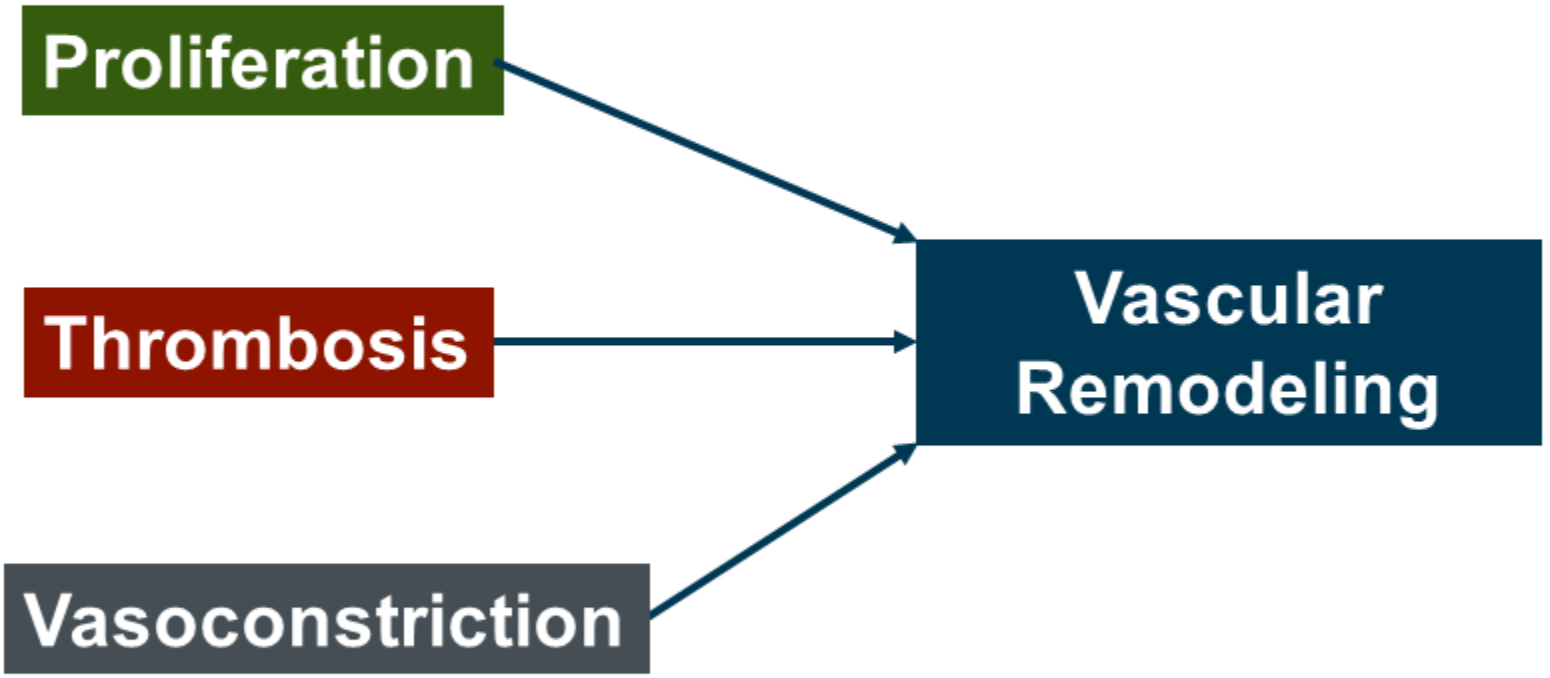


Clinical Classification of PH [2]

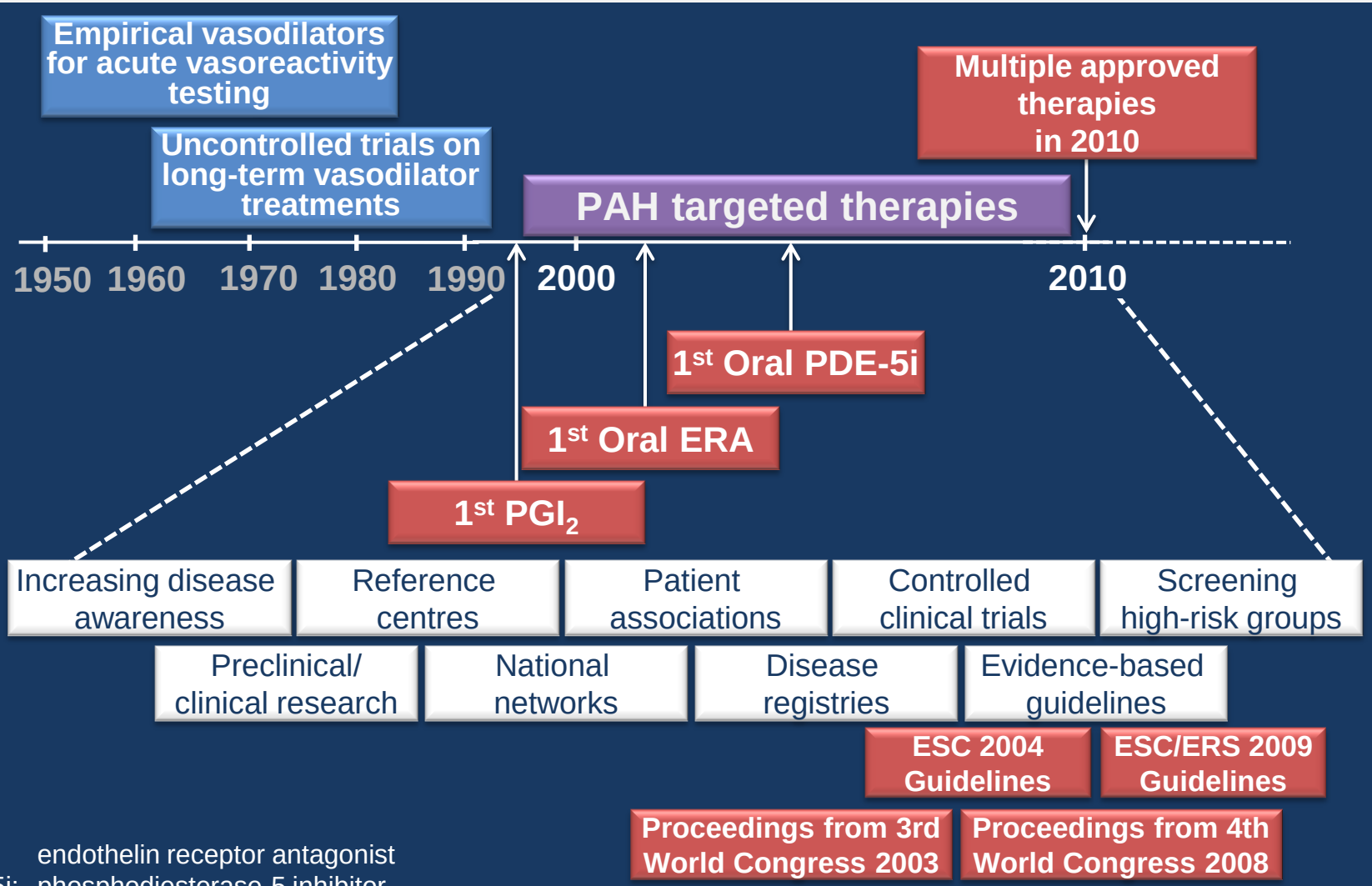


PH due to Left heart disease (LHD) is very common

Pathophysiology of PAH: Overview



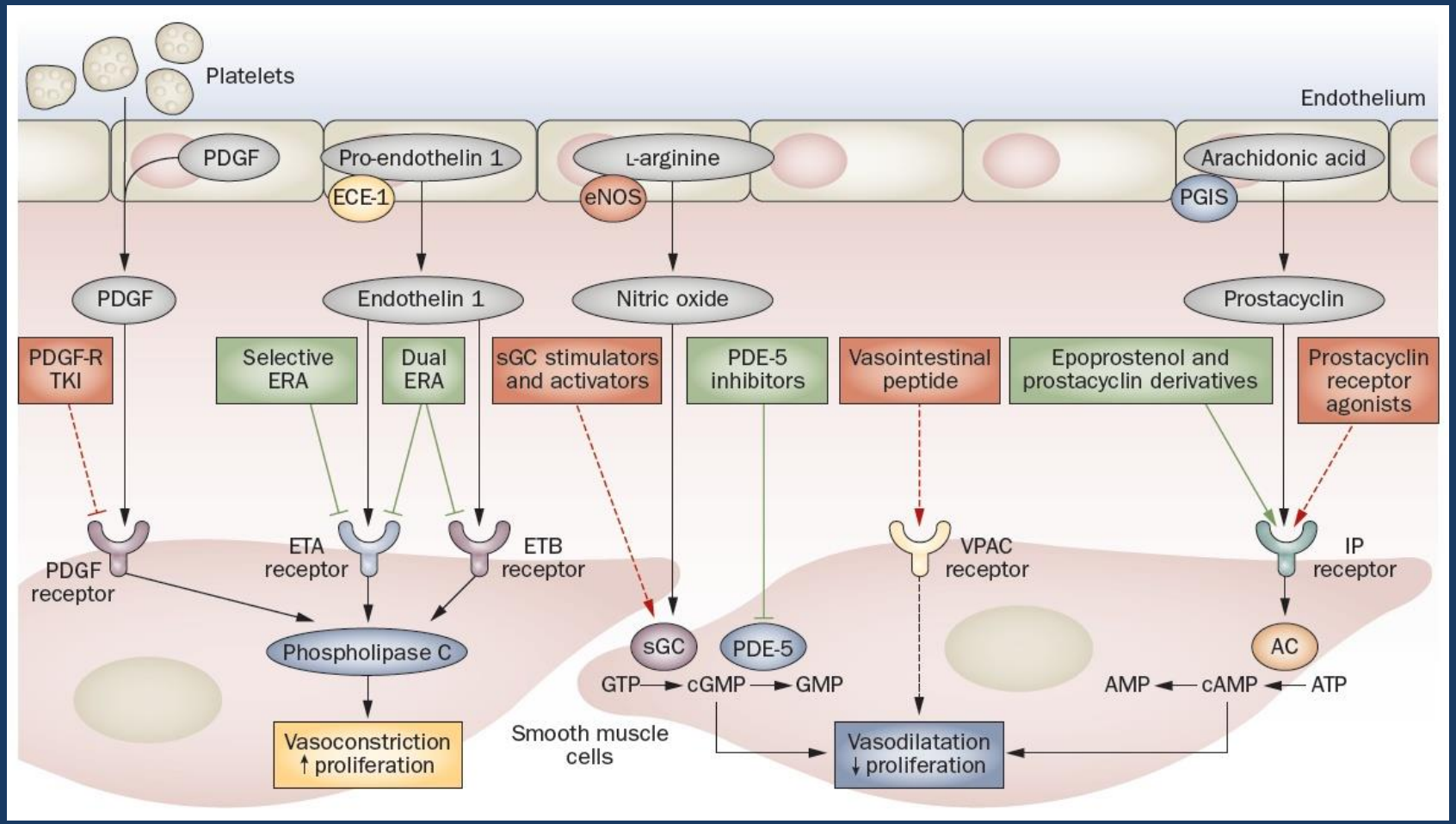
Significant progress has been made in the field of PAH



ERA: endothelin receptor antagonist
PDE-5i: phosphodiesterase-5 inhibitor
PGI_2: prostacyclin

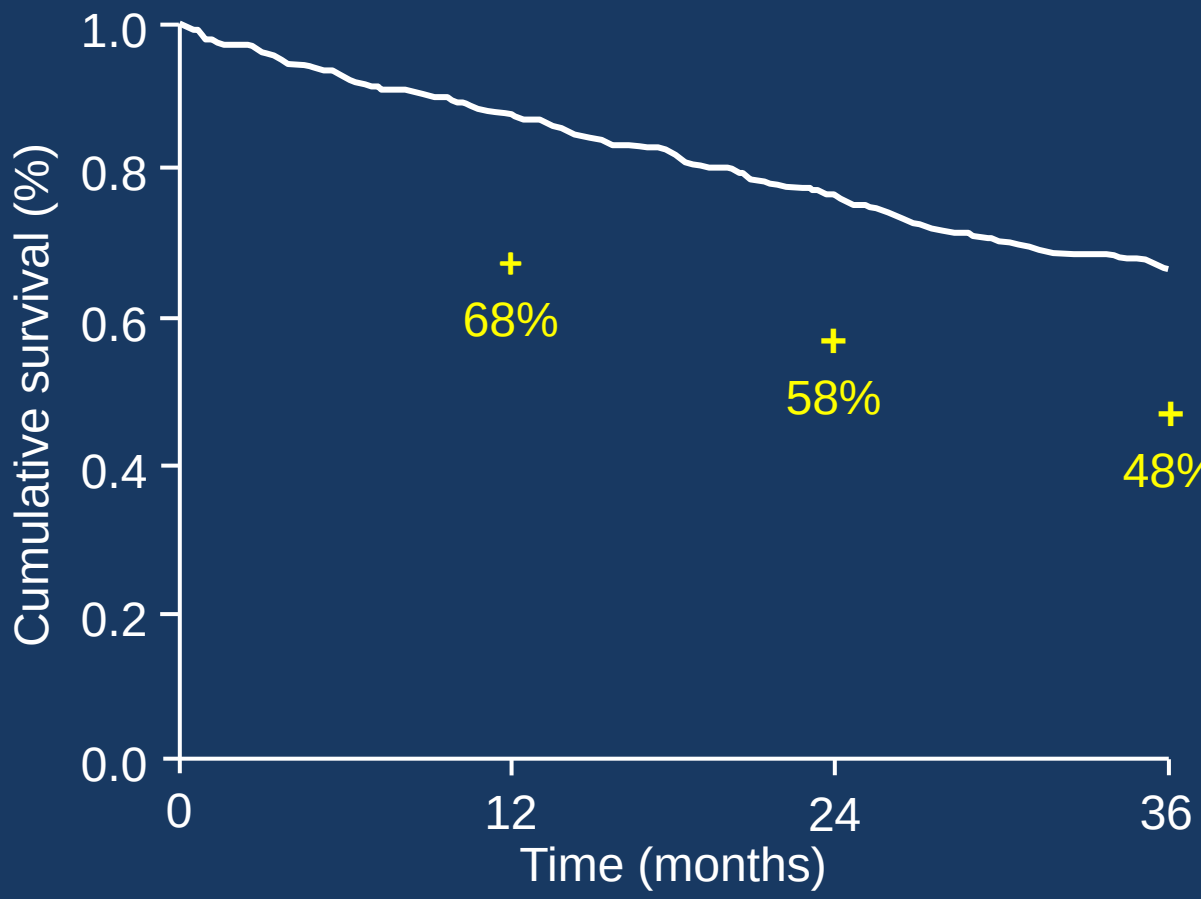
Galiè N, *et al. Eur Heart J* 2009; 30:2493-537.
The 4th World Symposium on Pulmonary Hypertension.*J Am Coll Cardiol* 2009; 54:S1-S117.

Approved and investigational target receptor stimulation (arrows) or blockade (crossed lines)



•Reprinted by permission from Macmillan Publishers Ltd: *Nature Reviews Cardiology* (O'Callaghan *et al.* 2011;8:526–38), copyright (2011).
•O'Callaghan DS *et al. Nat Rev Cardiol* 2011;8:526–38.

Although outcomes have improved over the past 15 years, long-term prognosis remains poor



67% 3-year survival estimates[1]

\+ Historical survival estimates[2]

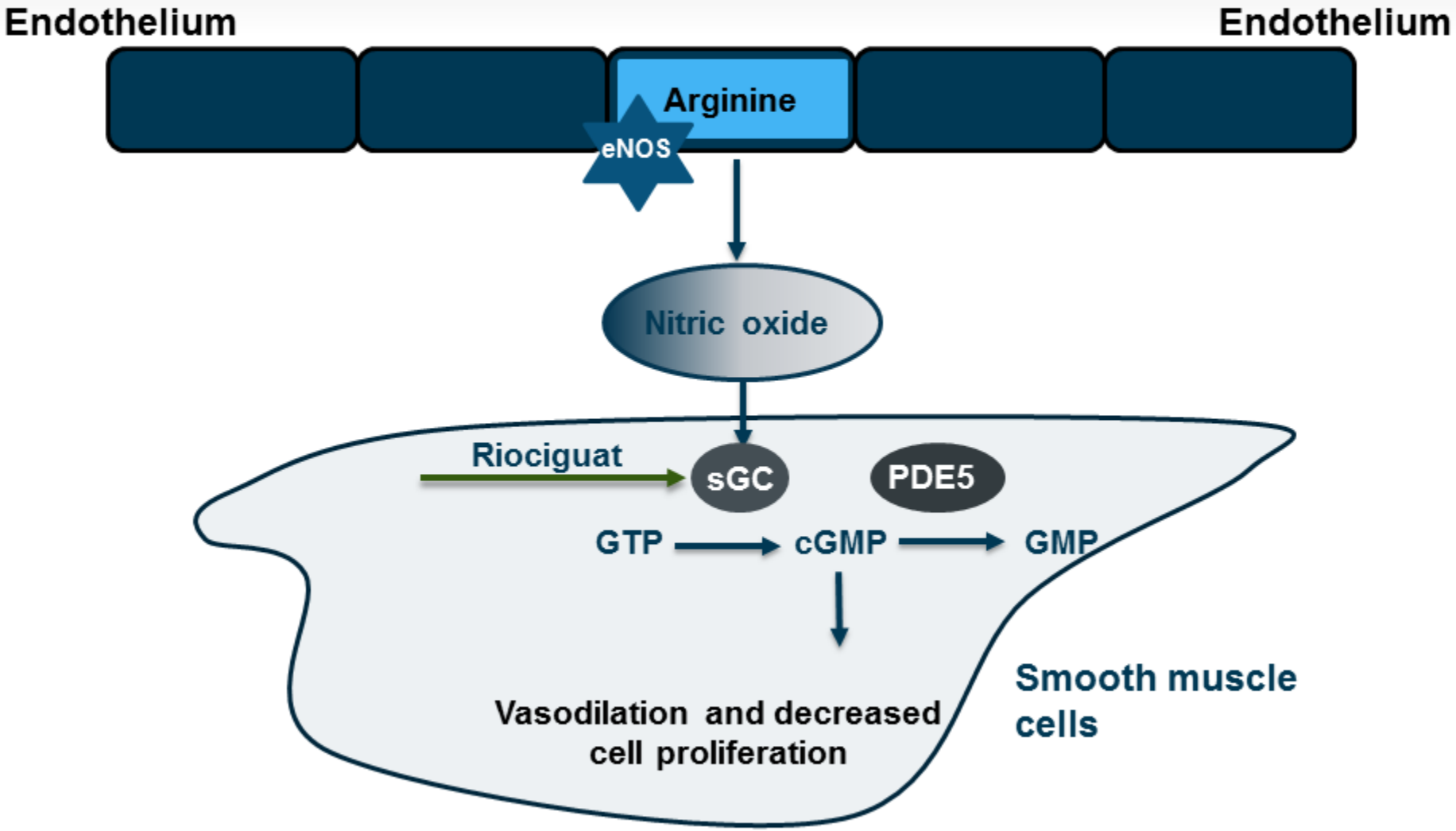
1. Humbert M, *et al*. *Eur Respir J* 2010; 36:549-55.
2. D'Alonzo GE, *et al. Ann Intern Med* 1991; 115:343-9.

No último ano
3 importantes estudos fase III
foram publicados no NEJM

Riociguat: A soluble guanylate cyclase stimulator

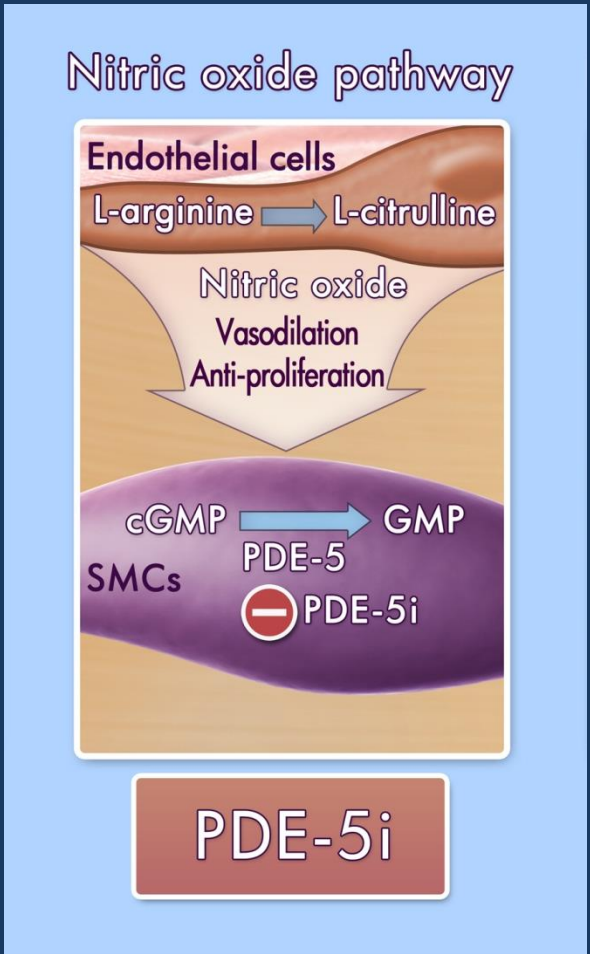
Clinical study data in PAH

Nitric Oxide Pathway: Modulation by Investigational Agents



O'Callaghan DS, et al. *Nat Rev Cardiol.* 2011;8:526-538.

Important milestones have included the identification of three pathophysiological pathways



- Riociguat is a soluble guanylase cyclase (cGC) whicht promotes vasodilatation, decreases fibrosis and inflammation.
- Riociguat has a dual mode of action: sensitizes sCG to engenous NO by stabilizing NO-sGC binding and it also directly stimulates sGC via a diferent site binding, independently of NO.

cAMP: cyclic adenosine monophosphate; cGMP: cyclic guanosine monophosphate; ERA: endothelin receptor antagonist; ET: endothelin; PDE-5: phosphodiesterase-5; PDE-5i: phosphodiesterase-5 inhibitor; PGI_2: prostacyclin

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

PATENT: Objectives and design

- **Objectives**
  - To evaluate the efficacy of riociguat in the treatment of PAH patients (treatment naïve or on stable treatment with an endothelin receptor antagonist or prostacyclin [oral, inhaled or subcutaneous])
- **Design**
  - Phase III, multicentre, double-blind, randomised, placebo-controlled study (PATENT-1)
    - 124 centres across 30 countries in Europe, South America, North America, Asia and Australia
  - Patients completing PATENT-1 could enrol in a long-term extension study (PATENT-2)

Ghofrani HA, *et al. New Engl J Med* 2013; 369:330-40.

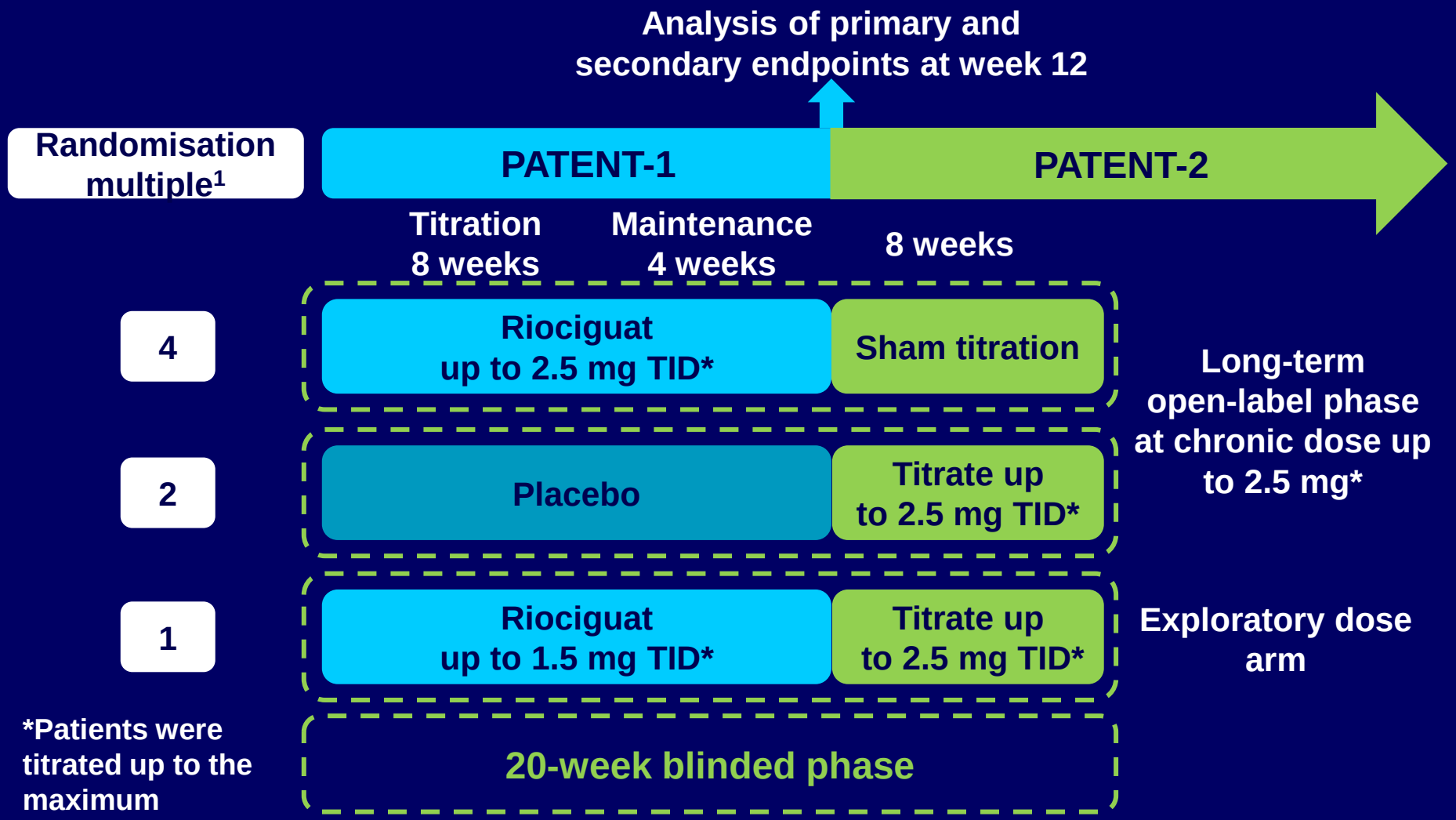
PATENT: Objectives and design

- 12 week, double blind, randomized, placebo-controlled international multicenter study.
- 445 PATIENTS WITH PAH
- Inclusion criteria:
- PVR > 300 dyn/sec/cm5
- MPAP > 25 mmHg
- 6 mWT distance of 150-450 m

- Primary endpoint was change in 6MWT
- Secondary endpoints included changes in PVR, NT-proBNP, WHO class, time to clinical worsening, Borg scales and QOL scores

Ghofrani HA, *et al. New Engl J Med* 2013; 369:330-40.

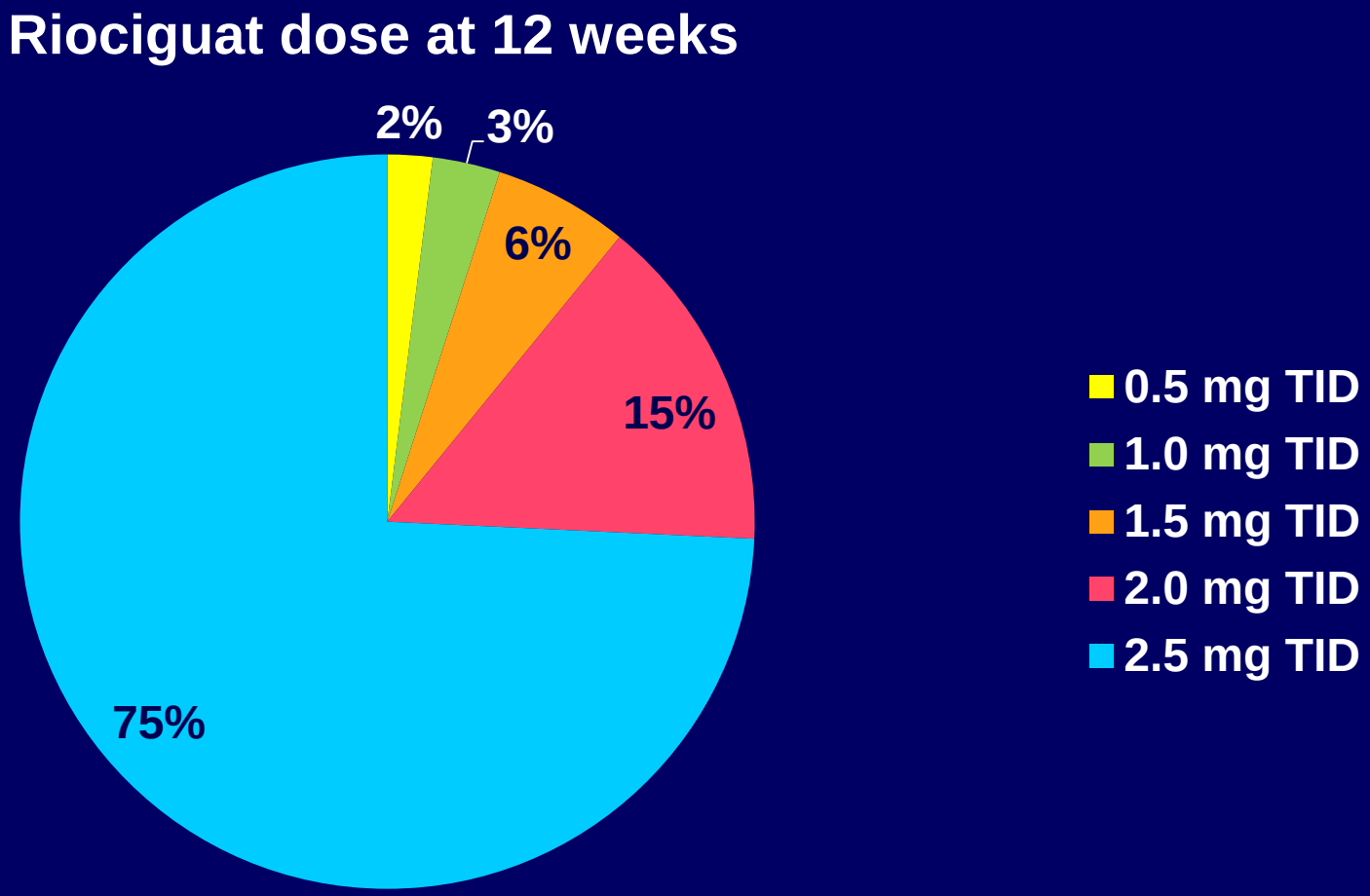
PATENT: Study design



*Patients were titrated up to the maximum tolerated dose

Ghofrani HA, *et al. New Engl J Med* 2013; 369:330-40.

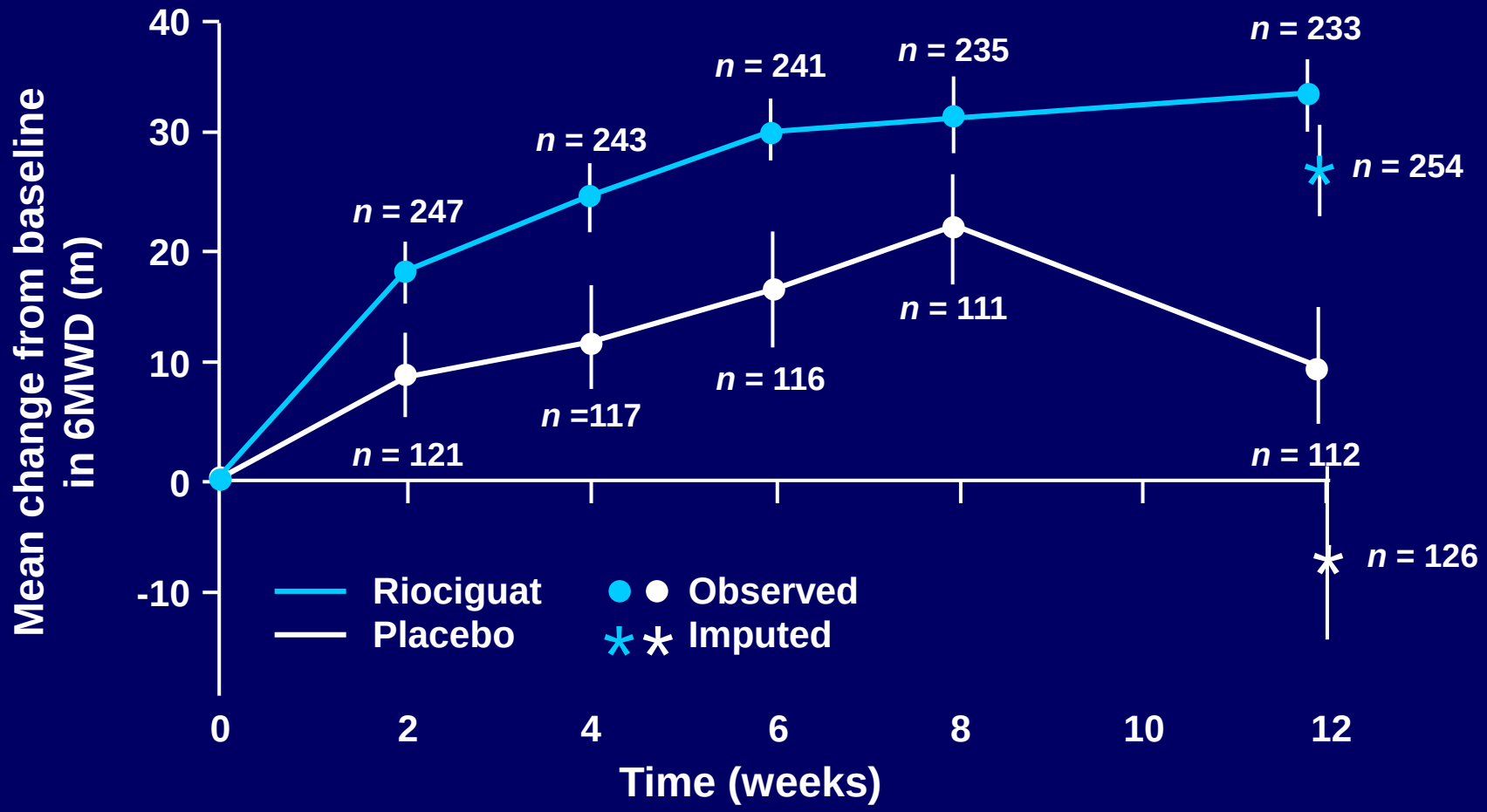
PATENT: Optimal dose achieved by individual dose titration



Ghofrani HA, *et al. New Engl J Med* 2013; 369:330-40.

PATENT-1: Analyses of primary endpoint (6MWD)

Significant incresae at 12 w = + 30 m (95% CI: 20 - 52 m; *p* < 0.001)



6MWD: 6-minute walk distance

Ghofrani HA, *et al. New Engl J Med* 2013; 369:330-40.

PATENT-1: Effect on cardiopulmonary haemodynamics and biomarkers

	Riociguat		Placebo			
Parameter	Baseline	Mean change from baseline	Baseline	Mean change from baseline	Placebo-corrected LS-mean difference	Riociguat vs placebo: *p*-value
PVR ($dyn \cdot s \cdot cm^{-5}$)	791	- 223 (-28%)	834	- 9 (- 1%)	- 226	< 0.001
mPAP (mmHg)	47	- 4 (-8%)	49	- 0.5 (- 1%)	- 4	< 0.001
Cardiac index ($L/min/m^2$)	2.52	+ 0.54 (+ 21%)	2.49	- 0.02 (- 1%)	+ 0.56	< 0.0001
NT-proBNP (ng/L)	1027	- 198 (-19%)	1228	+ 232 (+ 19%)	- 432	< 0.001

mPAP: mean pulmonary arterial pressure
NT-proBNP: N-terminal pro-brain natriuretic peptide
PVR: pulmonary vascular resistance

Ghofrani HA, *et al. New Engl J Med* 2013; 369:330-40.

PATENT-1: Effect on WHO functional class

WHO functional class improvement, *n* (%) (*p* = 0.003)

	Riociguat (*n* = 254)	Placebo (*n* = 125)
Improved	53 (21%)	18 (14%)
Stable	192 (76%)	89 (71%)
Deteriorated	9 (4%)	18 (14%)

Ghofrani HA, *et al. New Engl J Med* 2013; 369:330-40.

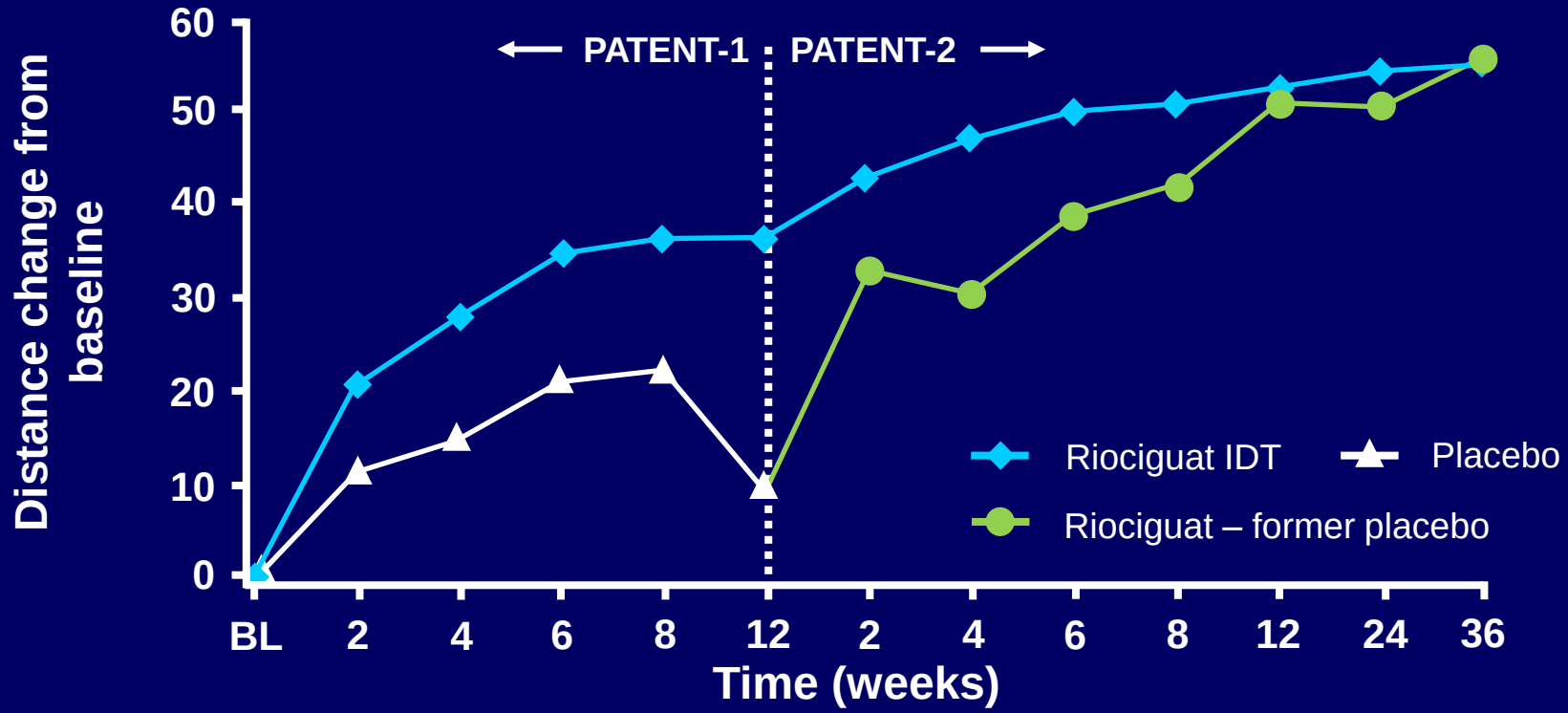
PATENT-1: Riociguat was well tolerated with a good safety profile as mono- or combination therapy

Adverse event, *n* (%) (treatment-emergent)	Riociguat *n* = 254	Placebo *n* = 126
Frequently reported adverse events		
Headache	69 (27)	25 (20)
Dyspepsia	48 (19)	10 (8)
Peripheral oedema	44 (17)	14 (11)
Nausea	40 (16)	16 (13)
Dizziness	40 (16)	15 (12)
Diarrhoea	35 (14)	13 (10)
Nasopharyngitis	26 (10)	14 (11)
Anaemia	21 (8)	3 (2)
Dyspnoea	16 (6)	14 (11)
Cough	12 (5)	13 (10)
Vomiting	26 (10)	11 (9)
Adverse events of special interest		
Hypotension	25 (10)	3 (2)
Syncope	3 (1)	5 (4)

Adapted from Ghofrani HA, *et al. New Engl J Med* 2013; 369:330-40.

PATENT-2: Further improvement in 6MWD from baseline

Mean change from baseline in 6MWD by visit in studies PATENT-1 and PATENT-2 (long-term safety population, observed cases)



n	BL	2	4	6	8	12	2	4	6	8	12	24	36
Placebo	121	117	116	111	112	91	91	91	92	89	77	68	
Riociguat	247	243	241	235	233	258	257	252	254	241	211	179	

6MWD: 6-minute walk distance
IDT: individual titration dose

Riociguat FDA Reviewer's Guide, August 2013.

PATENT PLUS

Pulmonary Arterial hyperTENsion sGC-stimulator Trial

A placebo-controlled, double-blind Phase II interaction study to evaluate blood pressure following addition of riociguat to patients with symtomatic PAH receiving sildenafil

PATENT PLUS: Conclusions

- In the 12-week study, addition of riociguat or placebo to sildenafil resulted in similar changes in blood pressure
- There were no clear clinical benefits with sildenafil/riociguat combination therapy in the exploratory efficacy variables
- In the long-term extension, the combination of sildenafil and riociguat was associated with a high rate of discontinuation (35%), predominantly due to hypotension
- Three patients (18%) died during the long-term extension (considered not drug-related by the investigators)
- The study was discontinued (withdrawal of riociguat) in December 2012, with a 3-month follow-up
- Overall, there was no evidence of a positive risk:benefit ratio with sildenafil/riociguat combination therapy

The study was discontinued

Concomitant use of riociguat with PDE-5 inhibitors should be avoided

PDE-5: phosphodiesterase-5

CHEST

Riociguat for the Treatment of Chronic Thromboembolic Pulmonary Hypertension

A Study to evaluate EFicacy and Safety of oral riociguat in Pts with CTEPH 16-week, multicenter, randomized, double blind, placebo controlled internacional

N Engl J Med
Volume 369(4):319-329
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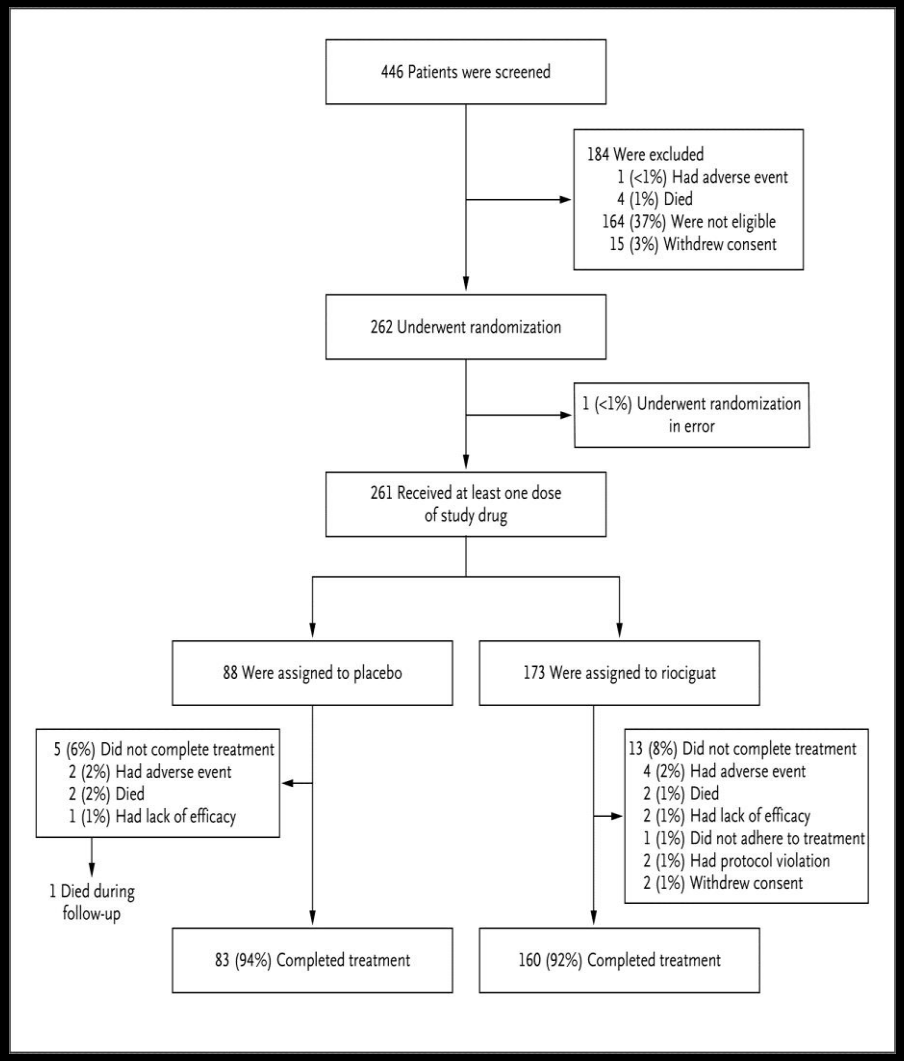
Study Overview

- As Study to evaluate Efficacy and Safety of Riociguat in pts with CTEPH
- PTS were either technically inoperable CTEPH or pts who had undergone pulmonary endartrerectomy but had persistent or recurrent PH
- Inclusion criteria were:
- PVR > 300 dyn/seg/cm5 and mPAP > 25 mmHg
- 6MWT of 150-450 m
- Primary and secondary endpoints were similar to PATENT
- In this trial, 261 patients with chronic thromboembolic pulmonary hypertension were assigned to placebo or to the soluble guanylate cyclase stimulator riociguat.
- At 16 weeks, riociguat had significantly improved the 6-minute walk distance and pulmonary vascular resistance.
- PTS were excluded if they had receive an ERA, PDE-5 inhibitor or NO donor 3 months previous to study

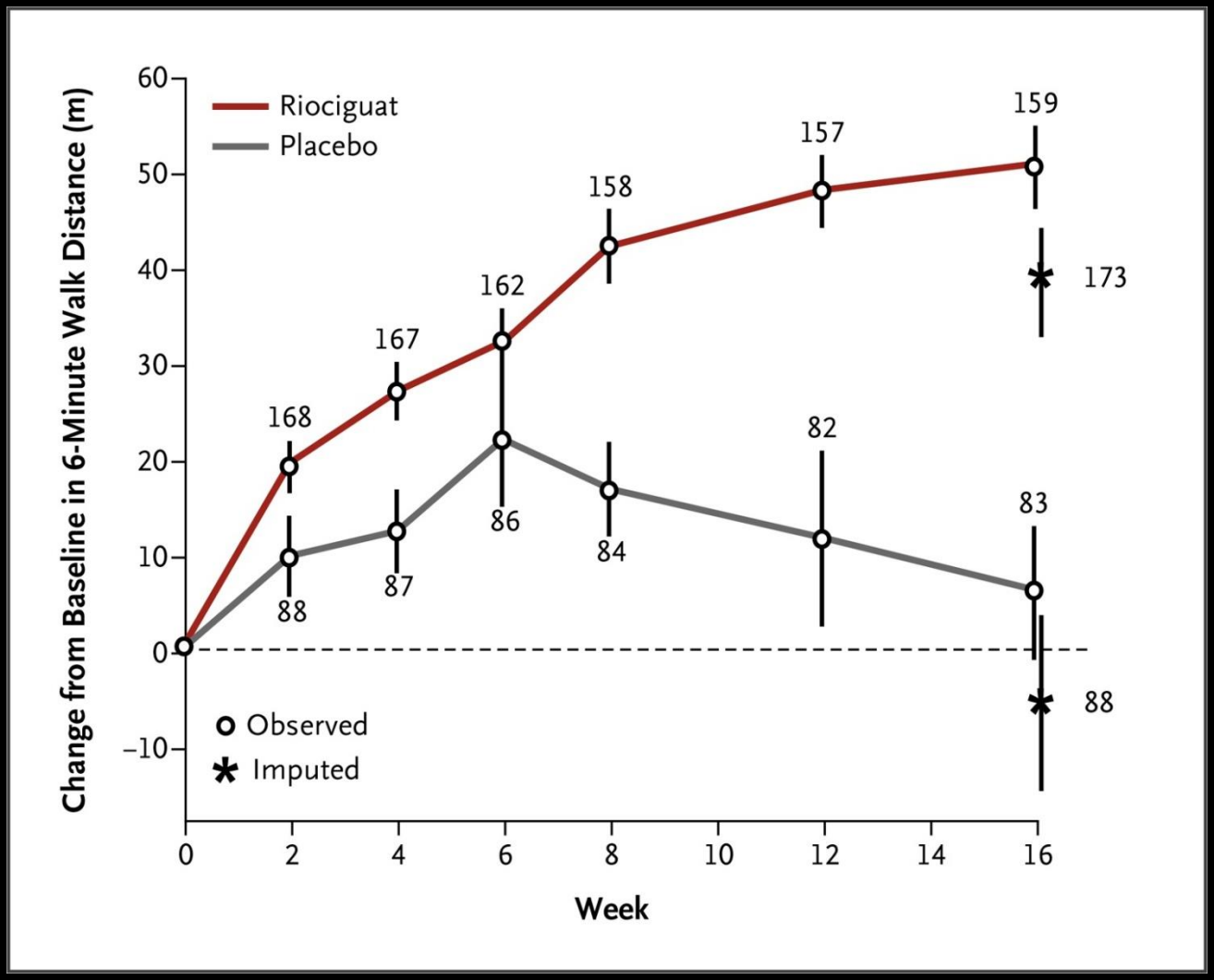
Screening, Randomization, and Follow-up.



- A total of 261 pts (173 with riociguat were randomized to receive different doses(1, 1,5, 2 and 2,5 mg TID) and the dose titration took 8 weeks

Ghofrani H-A et al. N Engl J Med 2013;369:319-329

Mean Change from Baseline in the 6-Minute Walk Distance.
There was a significant improved in 6WMT at 16 week in pts with riociguat



Ghofrani H-A et al. N Engl J Med 2013;369:319-329

Change from Baseline to End of Week 16 in Primary and Secondary End Points and in Hemodynamic Variables:

PVR and other hemodynamic parameters improved compared to placebo, as well as significantly decrease the level of NT-proBNP and improvements in functional class.

Table 2. Change from Baseline to End of Week 16 in Primary and Secondary End Points and in Hemodynamic Variables.*

End Point	Placebo			Riociguat			Least-Squares Mean Difference (95% CI)	P Value†
	No. of Patients	Baseline	Change	No. of Patients	Baseline	Change		
Primary end point								
6-Min walk distance (m)‡	88	356±75	−6±84	173	342±82	39±79	46 (25 to 67)	<0.001
Secondary end points								
Pulmonary vascular resistance (dyn·sec·cm^{-5})	82	779±401	23±274	151	791±432	−226±248	−246 (−303 to −190)	<0.001
NT-proBNP (pg/ml)	73	1706±2567	76±1447	150	1508±2338	−291±1717	−444 (−843 to −45)	<0.001
WHO functional class§	87	0 patients in class I, 25 (29%) in class II, 60 (69%) in class III, 2 (2%) in class IV	13 patients (15%) moved to lower class (indicating improvement), 68 (78%) stayed in same class, 6 (7%) moved to higher class	173	3 patients (2%) in class I, 55 (32%) in class II, 107 (62%) in class III, 8 (5%) in class IV	57 patients (33%) moved to lower class (indicating improvement), 107 (62%) stayed in same class, 9 (5%) moved to higher class	—	0.003
Borg dyspnea score¶	88	4±2	0.2±2.4	173	4±2	−0.8±2	—	0.004‖
EQ-5D score**	87	0.66±0.25	−0.08±0.34	172	0.64±0.24	0.06±0.28	0.13 (0.06 to 0.21)	<0.001‖
LPH score††	86	46±23	−2±19	170	41±22	−7±19	−6 (−10 to −1)	0.1‖
Hemodynamic variables‡‡								
Pulmonary-artery pressure (mm Hg)	84	44±10	0.8±7.3	156	45±13	−4±7	−5 (−7 to −3)	<0.001
Mean arterial pressure (mm Hg)	78	95±11	−0.3±11.8	155	95±12	−9±12	−9 (−12 to −6)	<0.001
Right atrial pressure (mm Hg)	84	9±6	−0.6±5.2	157	9±5	−1±5	−0.6 (−1.7 to 0.6)	0.4
Cardiac output (liters/min)	83	4±1	−0.03±1.07	155	4±1	0.8±1.1	0.9 (0.6 to 1.1)	<0.001
Pulmonary-capillary wedge pressure (mm Hg)	83	9±4	0.2±4.3	151	9±3	0.6±3.7	0.6 (−0.4 to 1.5)	0.2
Arterial oxygen saturation (%)	87§§	94±2	−3±8	172¶¶	94±3	−2±4	—	—
Heart rate (beats/min)	88	76±12	2±12	173	78±12	1±12	—	—
Pao_2 (mm Hg)	87‖‖	69±11	−5±12	172¶¶	70±12	−3±15	—	—

* Plus–minus values are means ±SD. The changes from baseline to the end of week 16 are arithmetic means. The least-squares mean difference was calculated by analysis of covariance for the change from baseline to the last visit. NT-proBNP denotes N-terminal pro–brain natriuretic peptide, and Pao_2 partial pressure of arterial oxygen.
† P values were calculated with use of the stratified Wilcoxon test for the change from baseline to the last visit.
‡ The primary end point was analyzed in the modified intention-to-treat population as the change from baseline to the last observed value (not including follow-up) among patients who completed the study or withdrew; the worst value (0 m) was imputed in the case of death or clinical worsening without a termination visit or without a measurement at the termination visit.
§ The change in the WHO functional class was analyzed with the use of a stratified Wilcoxon test.
¶ The Borg dyspnea scale ranges from 0 to 10, with 0 representing no dyspnea and 10 maximal dyspnea. The change in the Borg dyspnea score was analyzed with the use of a stratified Wilcoxon test; an analysis of covariance was not specified for this variable owing to the nonnormal distribution of the data.
‖ These analyses were only exploratory, owing to the hierarchical testing procedure.
** Scores on the EuroQol Group 5-Dimension Self-Report Questionnaire (EQ-5D) range from −0.6 to 1.0, with higher scores indicating a better quality of life.
†† Scores on the Living with Pulmonary Hypertension (LPH) questionnaire (an adaptation of the Minnesota Living with Heart Failure Questionnaire) range from 0 to 105, with higher scores indicating worse quality of life.
‡‡ All the analyses of hemodynamic variables were exploratory analyses, with the exception of heart rate, which was analyzed descriptively (and therefore has no P value associated with it).
§§ Data at week 16 were missing for 7 patients.
¶¶ Data at week 16 were missing for 20 patients.
‖‖ Data at week 16 were missing for 6 patients.

Ghofrani H-A et al. N Engl J Med 2013;369:319-329

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Table 3. Clinical Worsening and Adverse Events.*

Event	Placebo (N=88)	Riociguat (N=173)
	number of patients (percent)	
Clinical worsening		
All events	5 (6)	4 (2)†
Hospitalization due to pulmonary hypertension	1 (1)	0
Start of new treatment for pulmonary hypertension	1 (1)	2 (1)
Decrease in 6-min walk distance due to pulmonary hypertension	2 (2)	1 (1)
Persistent worsening of WHO functional class due to pulmonary hypertension	1 (1)	0
Death	3 (3)	2 (1)
Adverse events		
Any	76 (86)	159 (92)
Headache	12 (14)	43 (25)
Dizziness	11 (12)	39 (23)
Dyspepsia	7 (8)	31 (18)
Peripheral edema	18 (20)	27 (16)
Nasopharyngitis	8 (9)	26 (15)
Nausea	7 (8)	19 (11)
Vomiting	3 (3)	17 (10)
Diarrhea	4 (5)	17 (10)
Hypotension	3 (3)	16 (9)‡
Upper respiratory tract infection	4 (5)	10 (6)
Increase in international normalized ratio	4 (5)	10 (6)
Constipation	1 (1)	10 (6)
Prolonged activated partial-thromboplastin time	2 (2)	8 (5)
Cough	16 (18)	9 (5)
Chest pain	4 (5)	7 (4)
Dyspnea	12 (14)	8 (5)
Back pain	5 (6)	7 (4)
Increase in serum creatinine level	5 (6)	3 (2)
Pain in extremity	5 (6)	3 (2)
Insomnia	6 (7)	4 (2)
Syncope	3 (3)	4 (2)

* The adverse events listed are those that occurred in at least 5% of the patients in either group during the treatment period or up to 2 days after the end of treatment. The incidence of syncope as an adverse event of special interest is also reported.
† P=0.17 as compared with placebo, with the use of a stratified log-rank test.
‡ Of the 16 cases of hypotension reported in the riociguat group, 8 were reported as mild and 8 as moderate.

Clinical Worsening and Adverse Events: There was no significant differences in the incidence of clinical worsening events between 2 groups..

Ghofrani H-A et al. N Engl J Med 2013;369:319-329

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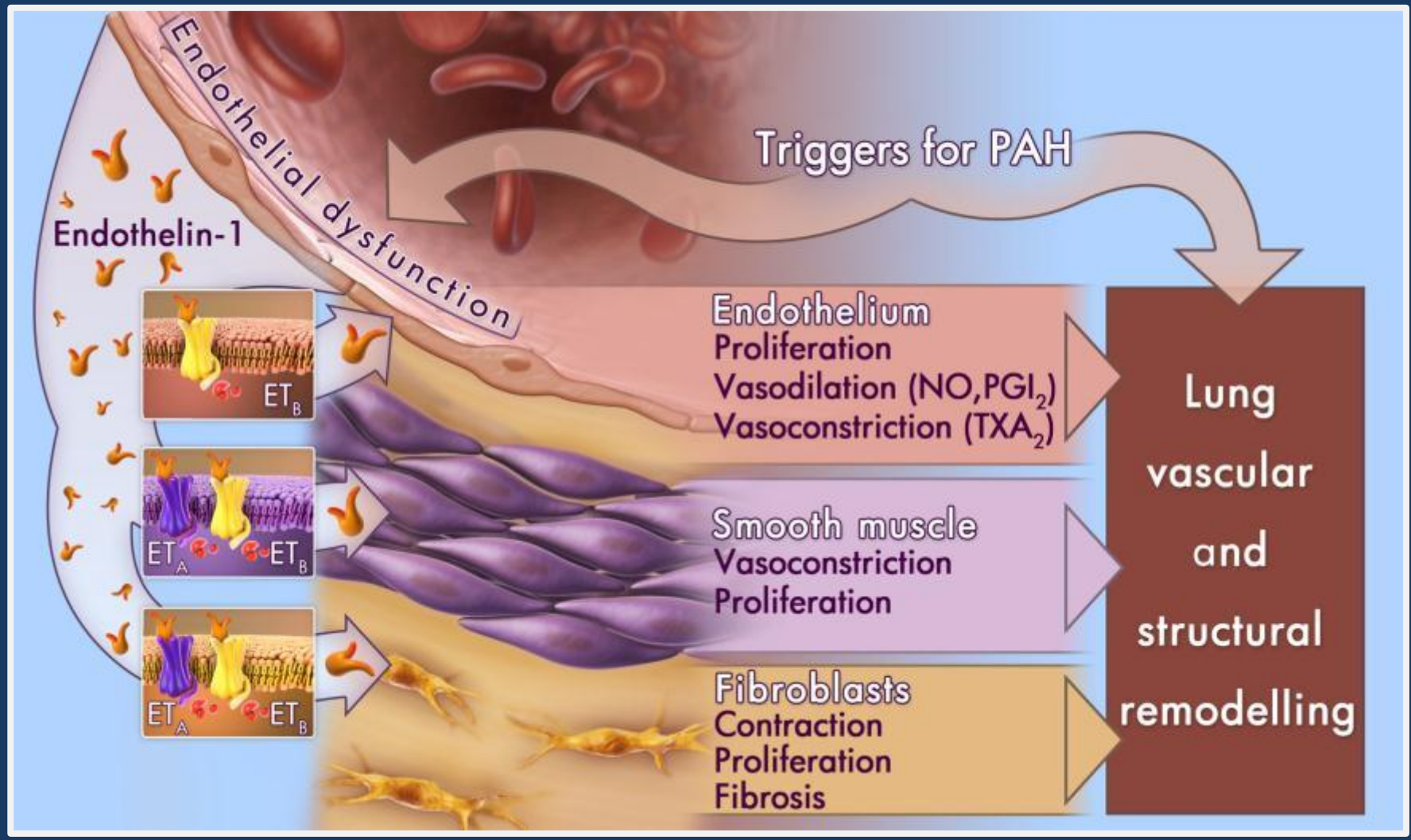
Conclusions

- CHEST 1 demonstrate that riociguat appears to be a safe oral theraphy for pts with inoperable CTEPH and for those with persistent PH after endarterectomy. Keeping in mind that pts should always be evaluated for CTEPH and that surgery must be the first opotion whenever possible, it would be a welcome additional treatment for these pts

- Riociguat significantly improved exercise capacity and pulmonary vascular resistance in patients with chronic thromboembolic pulmonary hypertension.

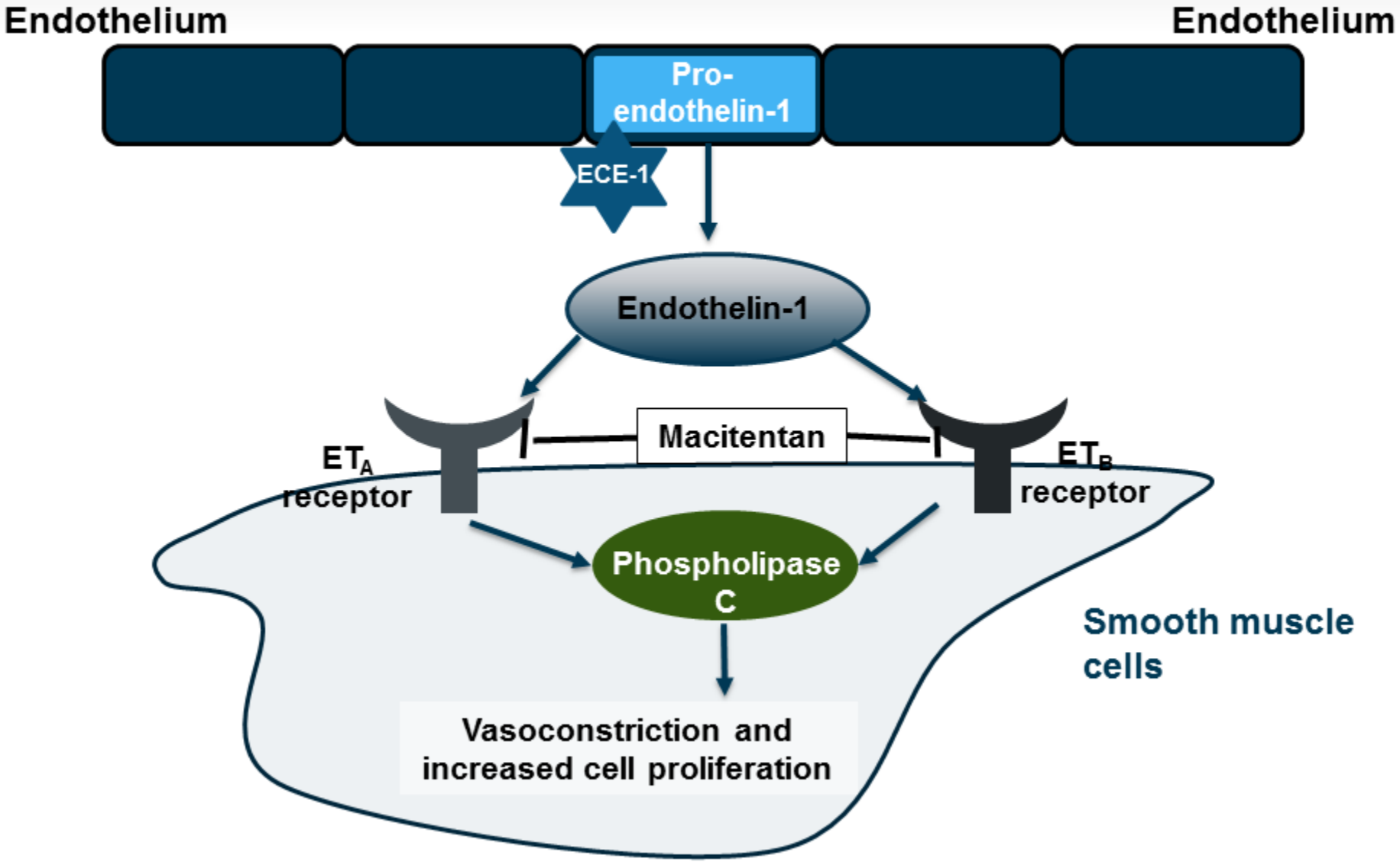
ET-1 plays an important role in tissue remodelling



ET: endothelin; NO: nitric oxide;
PGI_2: prostacyclin; TXA_2: thromboxane A_2

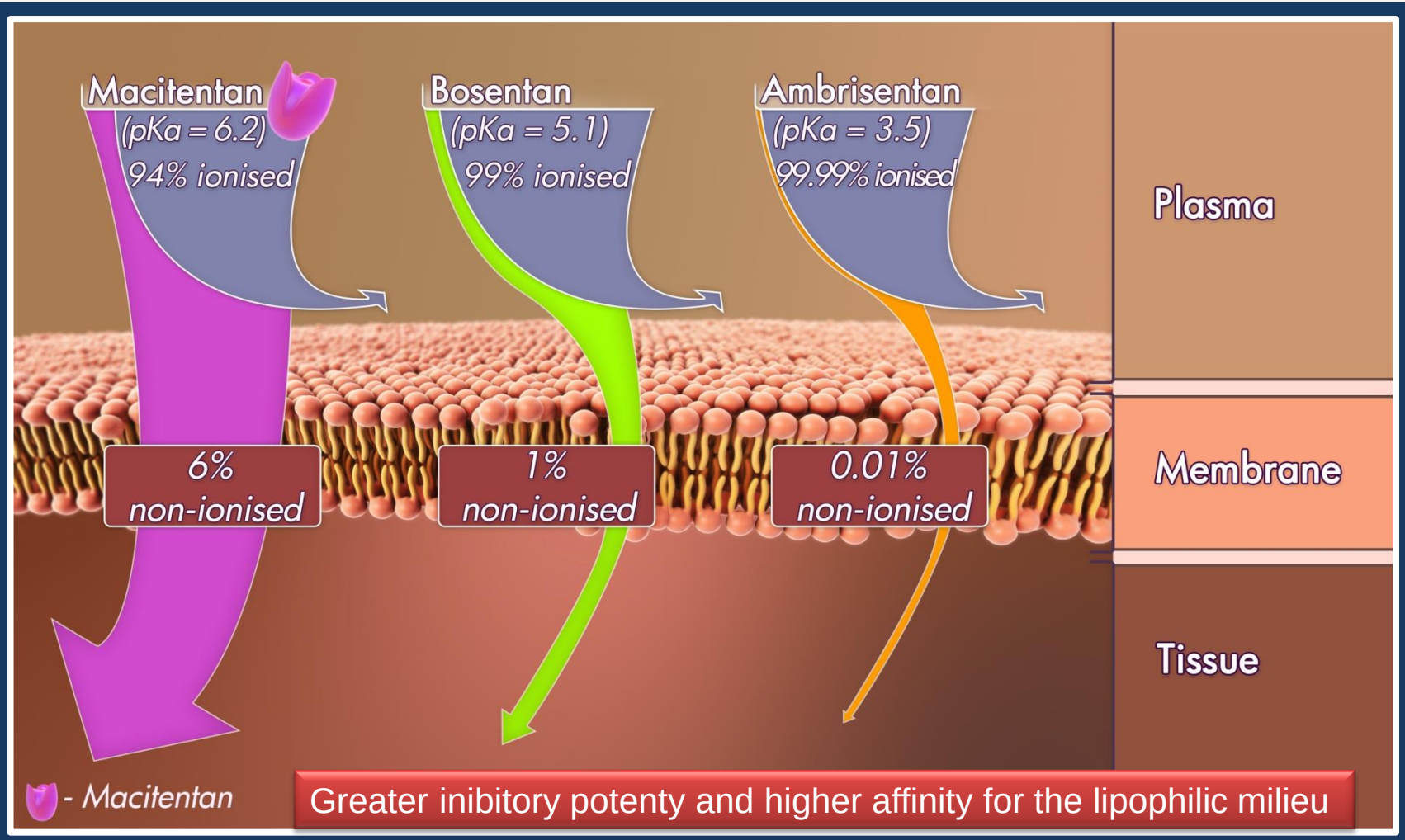
Adapted from Dupuis J & Hoeper MM. *Eur J Respir* 2008; 31:407-15.

Endothelin-1 Pathway: Modulation by Investigational Agents



O'Callaghan DS, et al. *Nat Rev Cardiol.* 2011;8:526-538.

Optimisation of the physicochemical properties of macitentan may favour its penetration into tissues



A higher pKa corresponds to greater lipophilicity and thus greater tissue targeting potential

pKa: ionisation dissociation constant

Adapted from Iglarz M, *et al. J Pharmacol Exp Ther* 2008; 327:736-45.

4 properties of macitentan at its target receptors

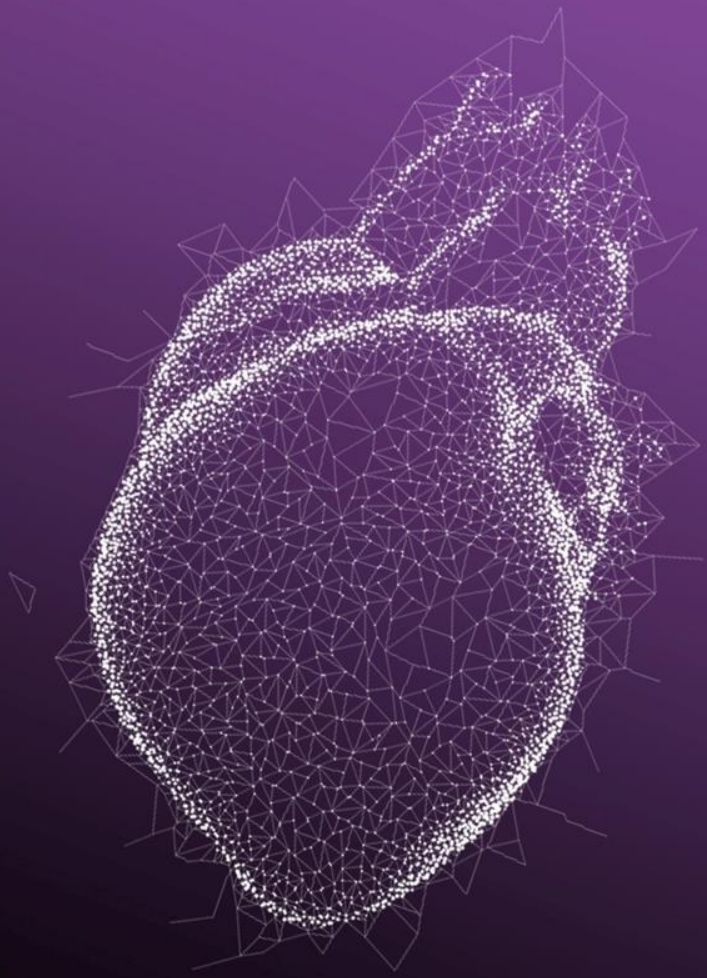
Dual	Macitentan targets ET_A and ET_B receptors
Potent	Macitentan blocks ET-1-induced calcium signaling at sub-nanomolar concentrations in human pulmonary arterial smooth muscle cells (PASMC)
Sustained	Macitentan has a 15-fold increased receptor occupancy time compared to bosentan and ambrisentan in human PASMCs
More effective	Macitentan has a more effective mode of antagonism than ambrisentan and bosentan: It is active irrespective of the ET-1 concentration

Macitentan is a dual, potent, slow-offset competitive endothelin receptor antagonist with a more effective mode of antagonism than bosentan and ambrisentan

This unique efficacy in cellular models is expected to contribute to increased efficacy in animals and humans

STUDY WITH ENDOTHELIN RECEPTOR ANTAGONIST IN PULMONARY ARTERIAL HYPERTENSION TO IMPROVE CLINICAL OUTCOME

Seraphin



Consenso médico pede há muito end-points mais robustos

- To date, SERAPHIN is the largest and longest conducted randomized, controlled study in PAH pts
- SERAPHIN is unique among PH trials in that it included a clearly define primary endpoint of morbidity and all cause mortality treatment vs placebo, making it the first event-driven Phase 3 trial
- The primary endpoint was a composited endpoint from the time of initiation therphy to the first ocurrence of death, atrial septopstomy, lung transplantation, inicition of iv or sc prostanoides, or worsening PAH
- Secondary endpoints included improvement in 6MWT or WHO at 6 moths or hospitalization for PAH up to the end of treatment and death from any cause

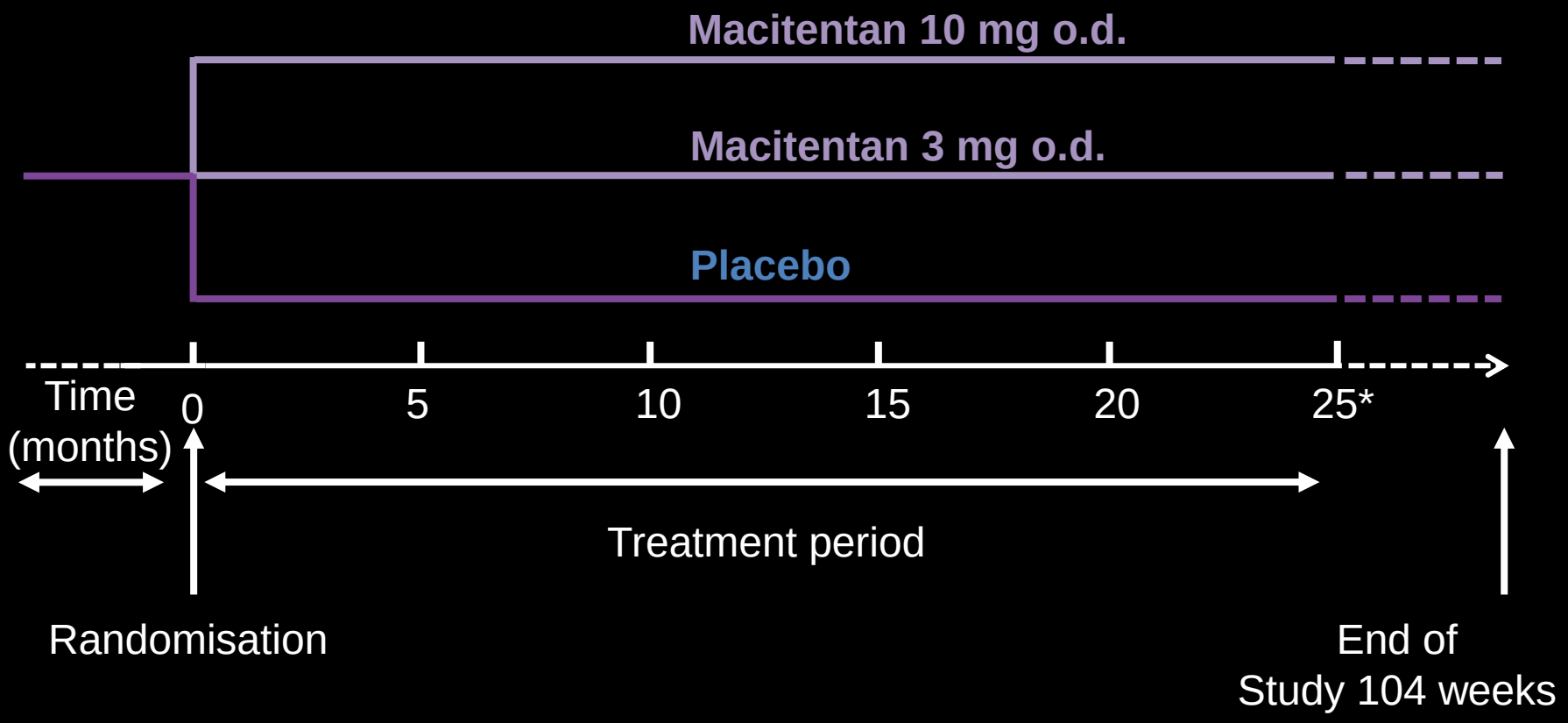
SERAPHIN – A nova referência em estudos da HAP
742 pts were randomized 1.1,1 into 3 groups of treatment: placebo, macitentan 3 mg and 10 mg

Drug	Study	Duration	Primary endpoint	No. of patients
Bosentan	Study-351[1,2]	12 wks	6-MWD	32
	BREATHE-1[3]	16 wks	6-MWD	213
	EARLY[4]	24 wks	PVR, 6-MWD	185
Ambrisentan	ARIES-1[5,6]	12 wks	6-MWD	202
	ARIES-2[5,7]	12 wks	6-MWD	192
Sildenafil	SUPER-1[8]	12 wks	6-MWD	277
Tadalafil	PHIRST[9]	16 wks	6-MWD	405
Macitentan	**SERAPHIN[10]**	**104 wks**	**Time to first morbidity/mortality event**	**742**

SERAPHIN

A LONG-TERM, EVENT-DRIVEN RCT IN PAH

USE OF OTHER PAH THERAPIES WERE ALLOWED EXEPT ARA



*Estimated mean study drug exposure

- **INCLUSION CRITERIA**

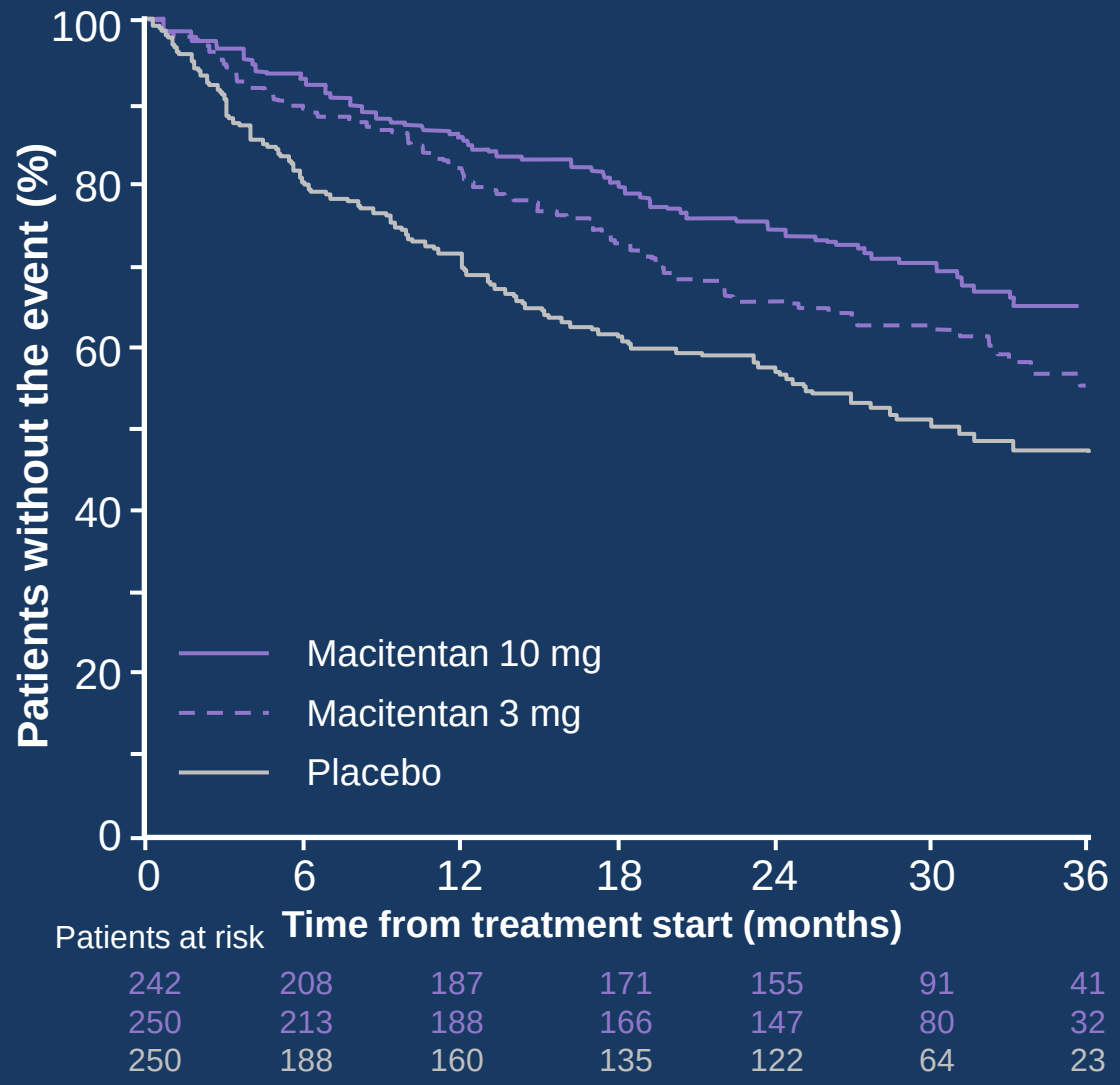
Pts older than 12 years with:

idiopathic PAH, hereditable PAH or PAH related to connective disorders, repaired congenited, systemic to pulmonary shunts, HIV or drug or toxine exposure, 6 mwt of 50 or more, and WHO class ii, iii, or iv

Oral PDE-5 inhibitors, oral or inhaled prostanoides, CCB were allowed.

Any sc or ev prostanoides were excluded

Primary endpoint: Morbidity and mortality up to end of treatment



Patients at risk

242	208	187	171	155	91	41
250	213	188	166	147	80	32
250	188	160	135	122	64	23

Macitentan 10 mg
Macitentan 3 mg
Placebo

Risk reduction of primary endpoint event vs placebo

Macitentan 10 mg: 45%

Macitentan 3 mg: 30%

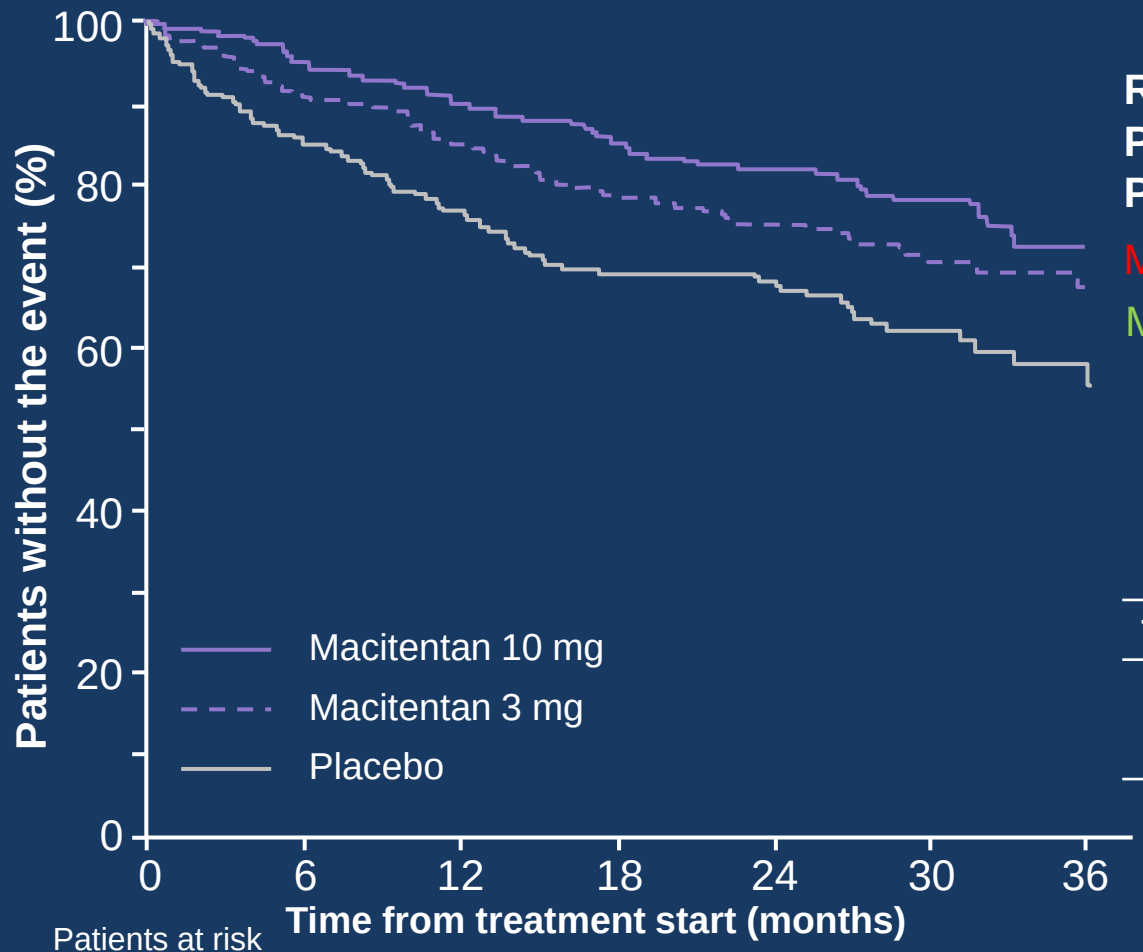
Treatment difference	3 mg	10 mg
Hazard ratio (HR)	0.70	0.55
Log-rank *p*-value	0.01	< 0.001

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

SECONDARY EFFICACY ENDPOINTS

- Dose-dependent effect ($p<0.05$ for either dose) on change from baseline to month 6 in six-minute walk-distance
- Dose-dependent effect ($p<0.05$ for either dose) on change from baseline to month 6 in WHO functional class and
- Dose-dependent effect ($p<0.05$ for either dose) on time -over the whole treatment period -to either death due to PAH or hospitalization due to PAH
- A trend in favor of 10 mg macitentan compared to placebo was observed on all-cause mortality (p=ns)

Secondary endpoint: Death due to PAH or hospitalisation for PAH



Patients at risk

242	203	183	166	152	86	39
250	208	181	159	144	77	31
250	188	155	132	119	62	22

Macitentan 10 mg
Macitentan 3 mg
Placebo

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

Macitentan 10 mg: 50%

Macitentan 3 mg: 33%

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

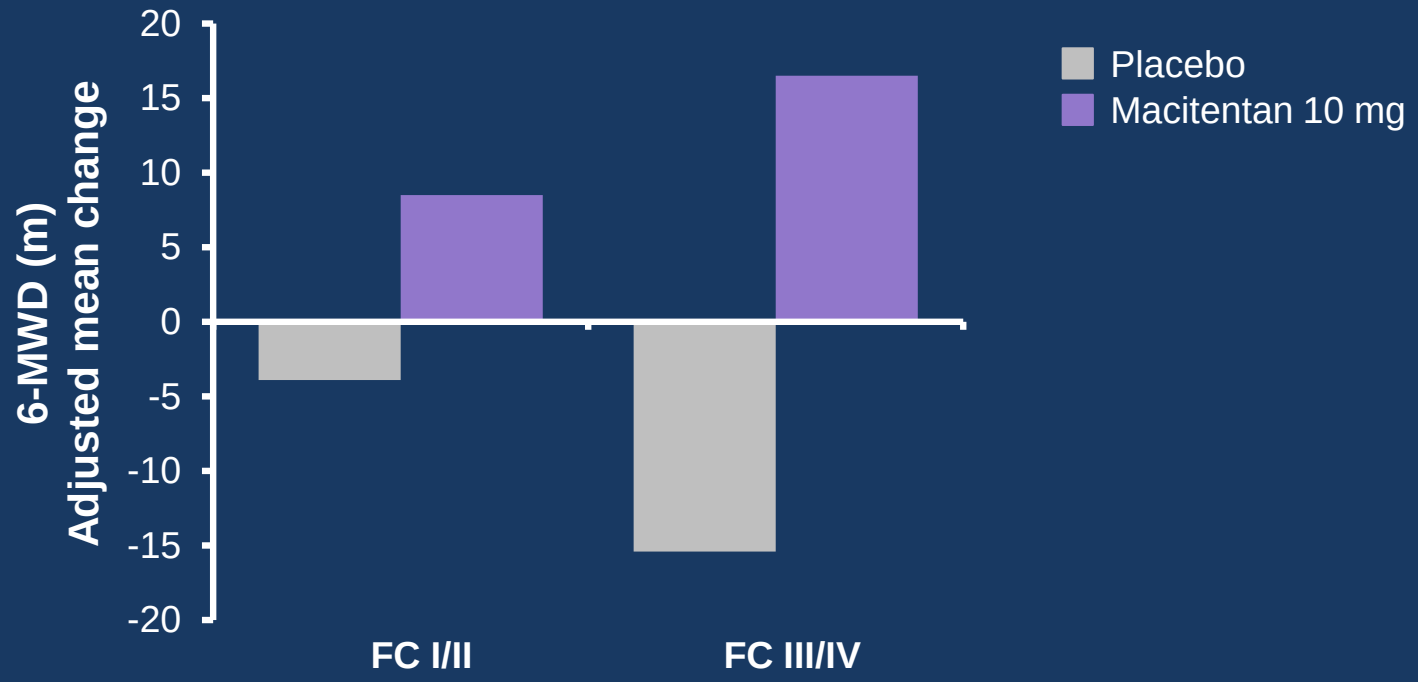
Pulido T, *et al. N Engl J Med* 2013; 369: 809-18.

Secondary endpoint: Change from baseline to month 6 in 6-MWD with macitentan 10 mg

	Macitentan 3 mg		Macitentan 10 mg	
Overall treatment effect baseline adjusted (mean)	17.7 m	$p = 0.04$	22.8 m	$p = 0.007$

Subgroup analysis by FC with macitentan 10 mg

+37.0 m, $p = 0.009$



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

SAFETY & TOLERABILITY

- **MACITENTAN WAS WELL TOLERATED**

- The number of adverse events reported and patients discontinuing treatment due to adverse events was similar across all groups

- Elevations of liver alanine or aspartate aminotransferases greater than three times the upper limit of normal were observed in:
  - 4.5 percent of patients receiving placebo
  - 3.6 percent of patients on 3 mg of macitentan
  - 3.4 percent of patients on 10 mg of macitentan

- No difference between macitentan and placebo on edema.
- A decrease in hemoglobin reported as an adverse event
  - observed more frequently on macitentan than placebo
    - with no difference in treatment discontinuation between groups

Benefícios Clínicos

- Reduz a morbi-mortalidade em 45%
- Reduz para metade o número hospitalizações por HAP
- Melhoria de + 37m no TM6M, adicionais a outras terapêuticas específicas
- Melhoria de 22% na Classe Funcional
- Perfil de Segurança semelhante ao placebo e superior aos ERA actuais
- Sem interacções farmacológicas relevantes
- Permitindo mais mais Tempo de Vida,
  com mais Qualidade de Vida, aos doentes com HAP

OPSUMIT STATUS

REGULAMENTAR

- **AIM centralizado: Q4/2013**

  => Aprovação local em janeiro de 2014

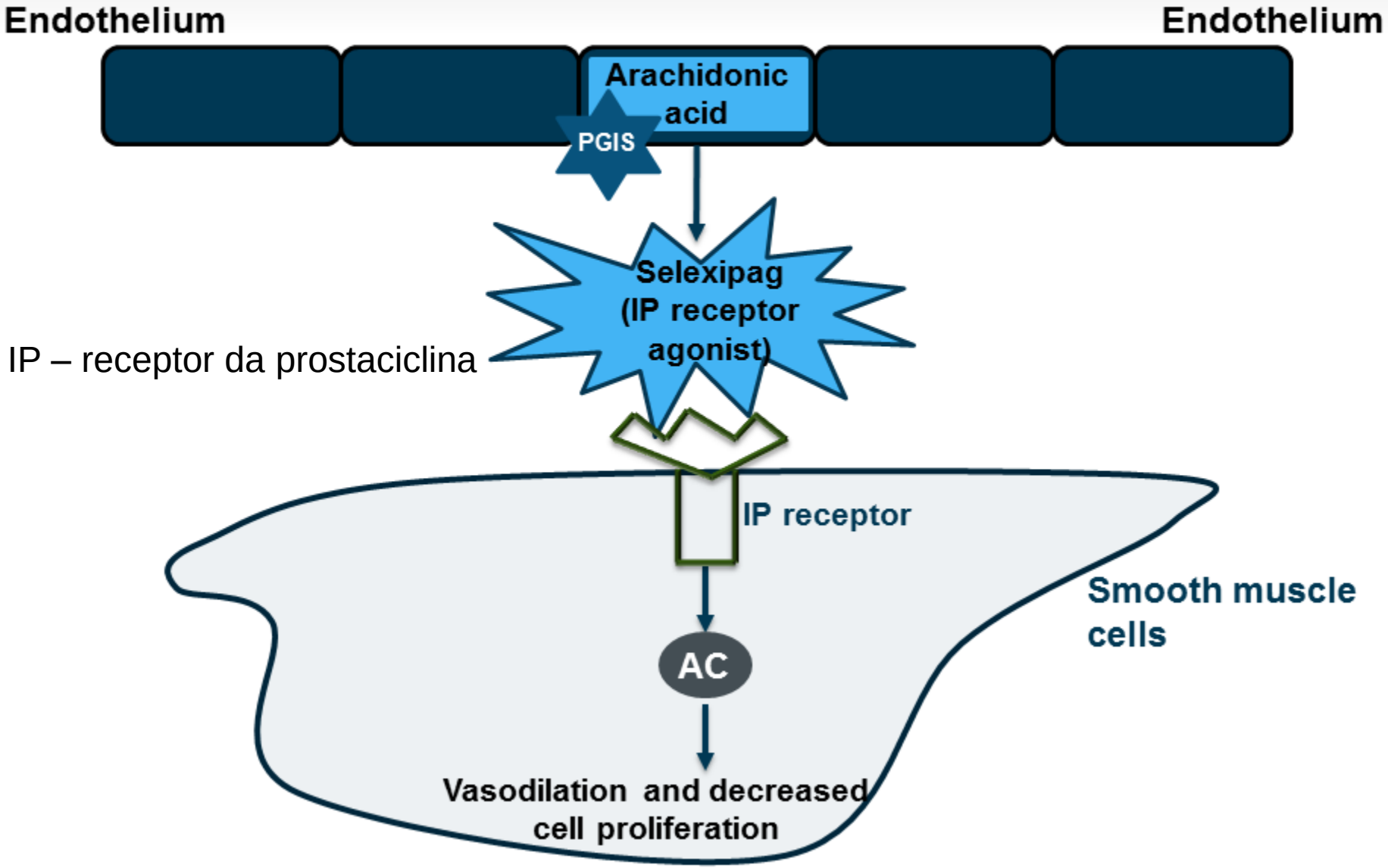
- **Avaliação fármaco-económica prévia:**

  - 200 dias revisão pelo Infarmed + acordo de partilha de risco + aprovação individual pelos hospitais = lançamento em 1Q2015

IMPROVING PATIENT'S DAILY LIFE

epoprostenol termo-estável

Prostacyclin Pathway: Modulation by Investigational Agents



IP – receptor da prostaciclina

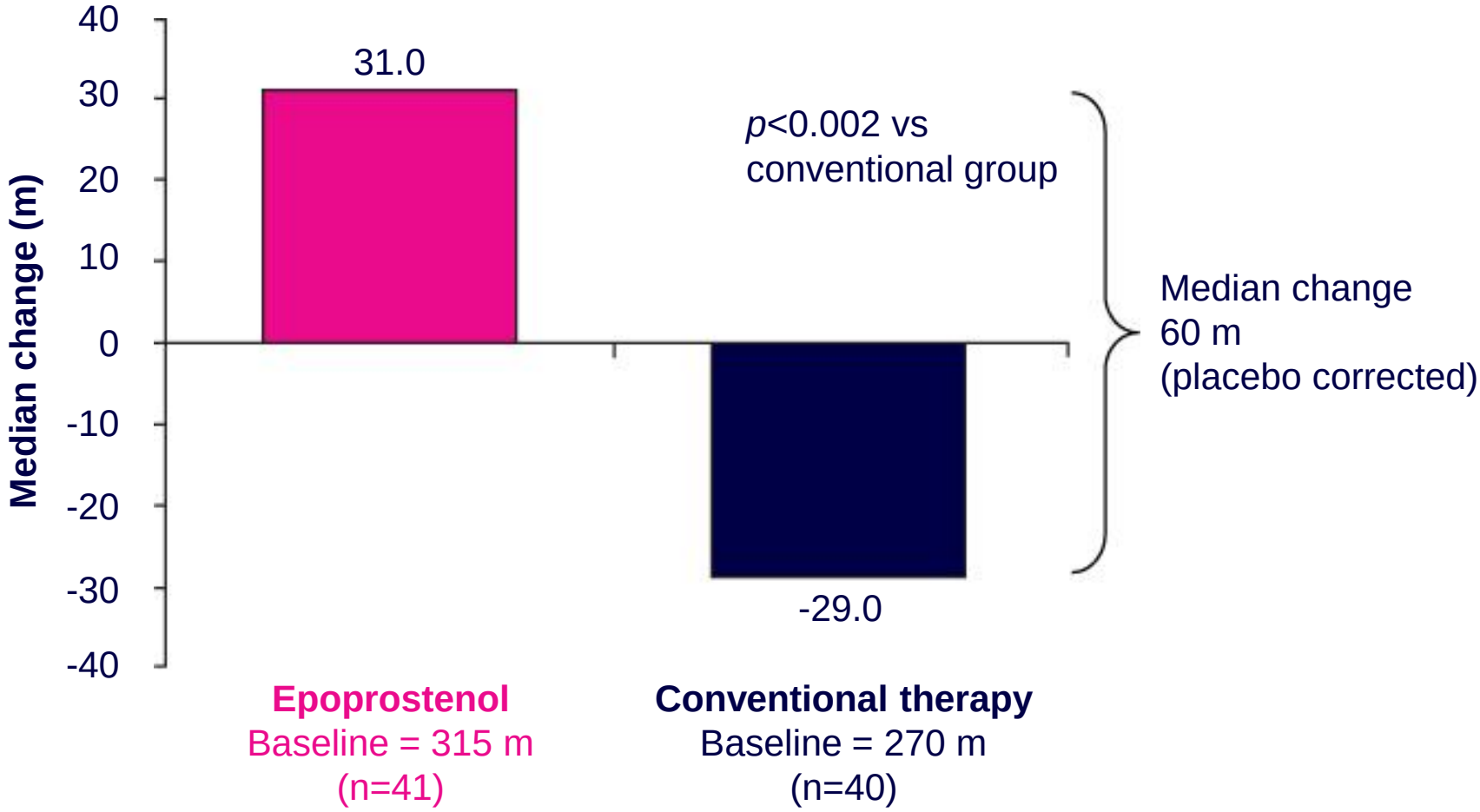
O'Callaghan DS, et al. *Nat Rev Cardiol.* 2011;8:526-538.

SELEXIPAG

SELEXIPAG

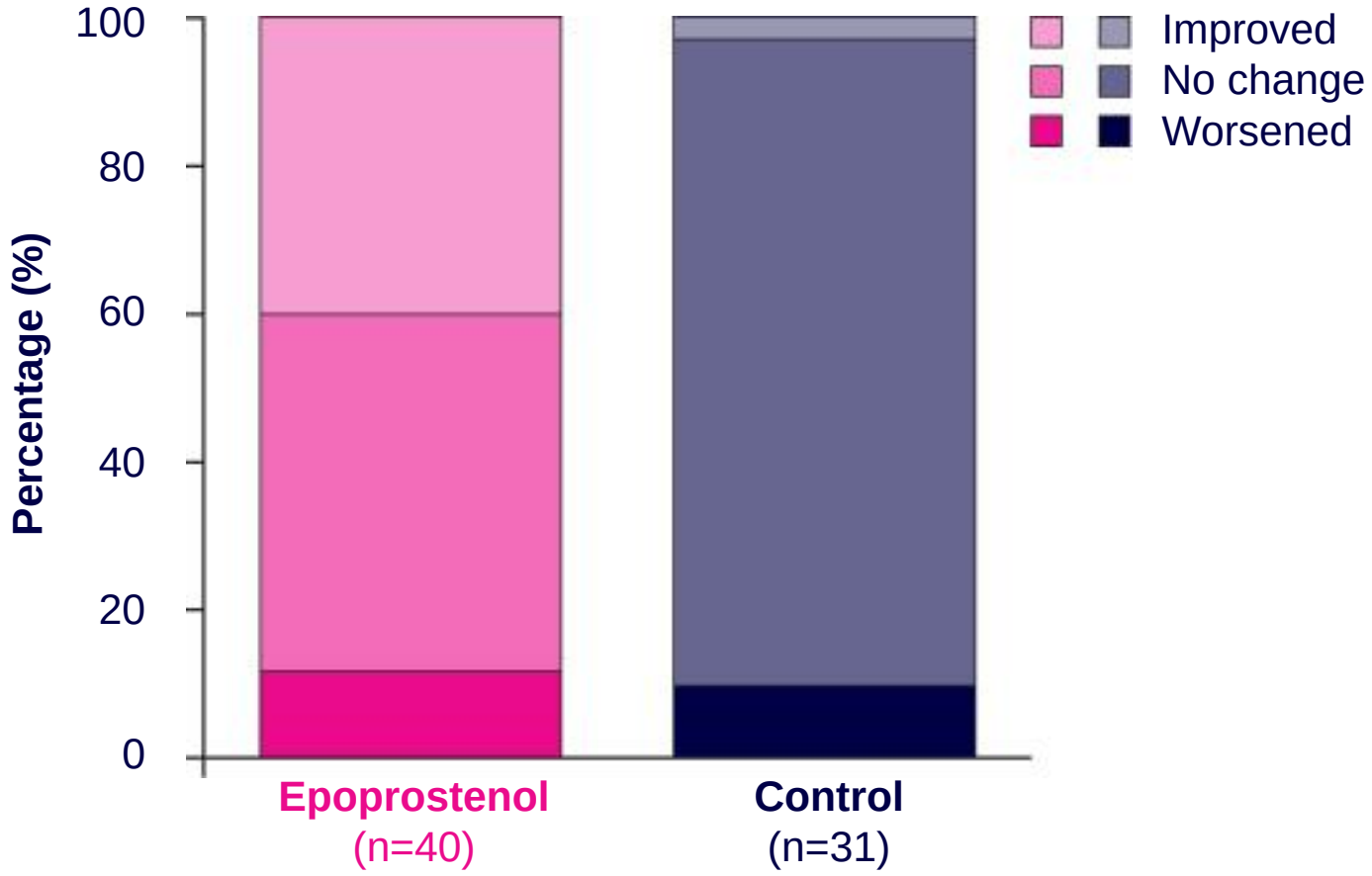
- Agonista selectivo, não prostanoide, do recetor da Prostaciclina (IP)
  - elevada afinidade e selectividade para o recetor IP
- Eficaz por via oral
  - vias de administração actuais (in, iv, sc) limitam a administração de prostanoides: utilizados em menos de 10K doentes em todo o Mundo
- Administrado 2xd
- Baixo potencial para interações farmaco-fármaco
- Menor incidência de taquifilaxia

Epoprostenol in iPAH: 12 weeks' therapy improves exercise capacity



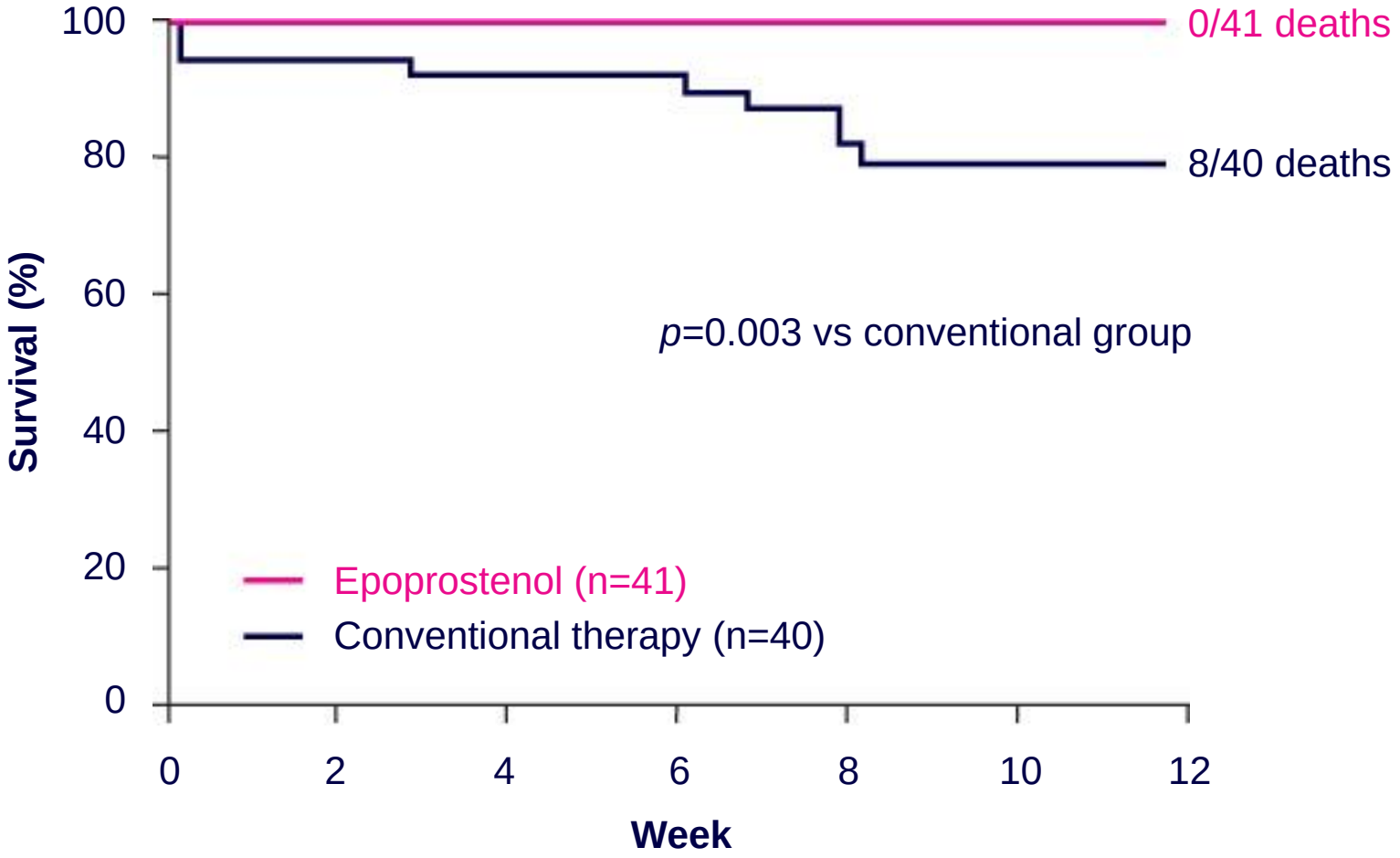
Barst et al. *N Engl J Med* 1996

Epoprostenol in iPAH: Improved NYHA FC



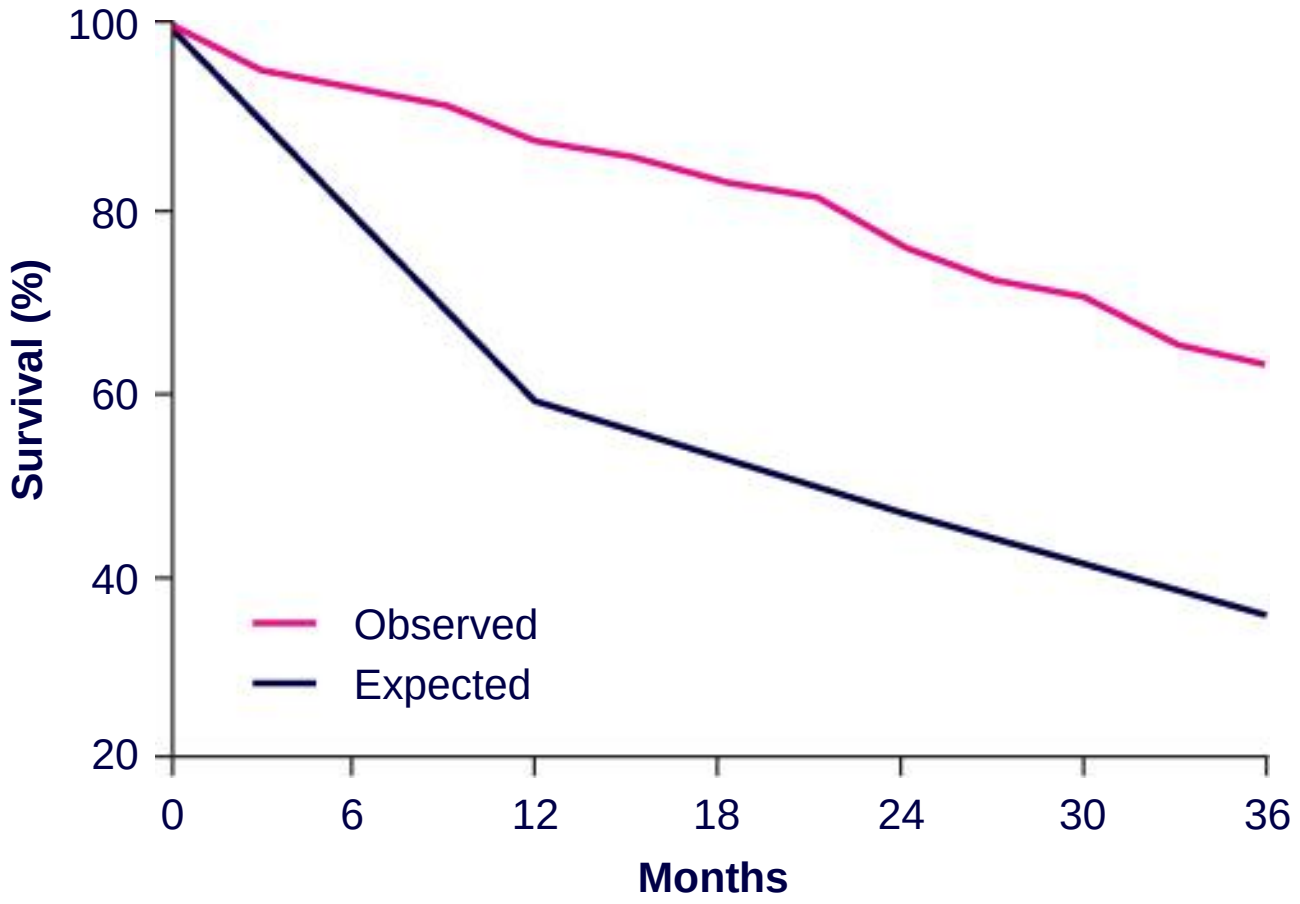
Barst et al. *N Engl J Med* 1996

Epoprostenol in iPAH: Improved survival with 12 weeks' therapy



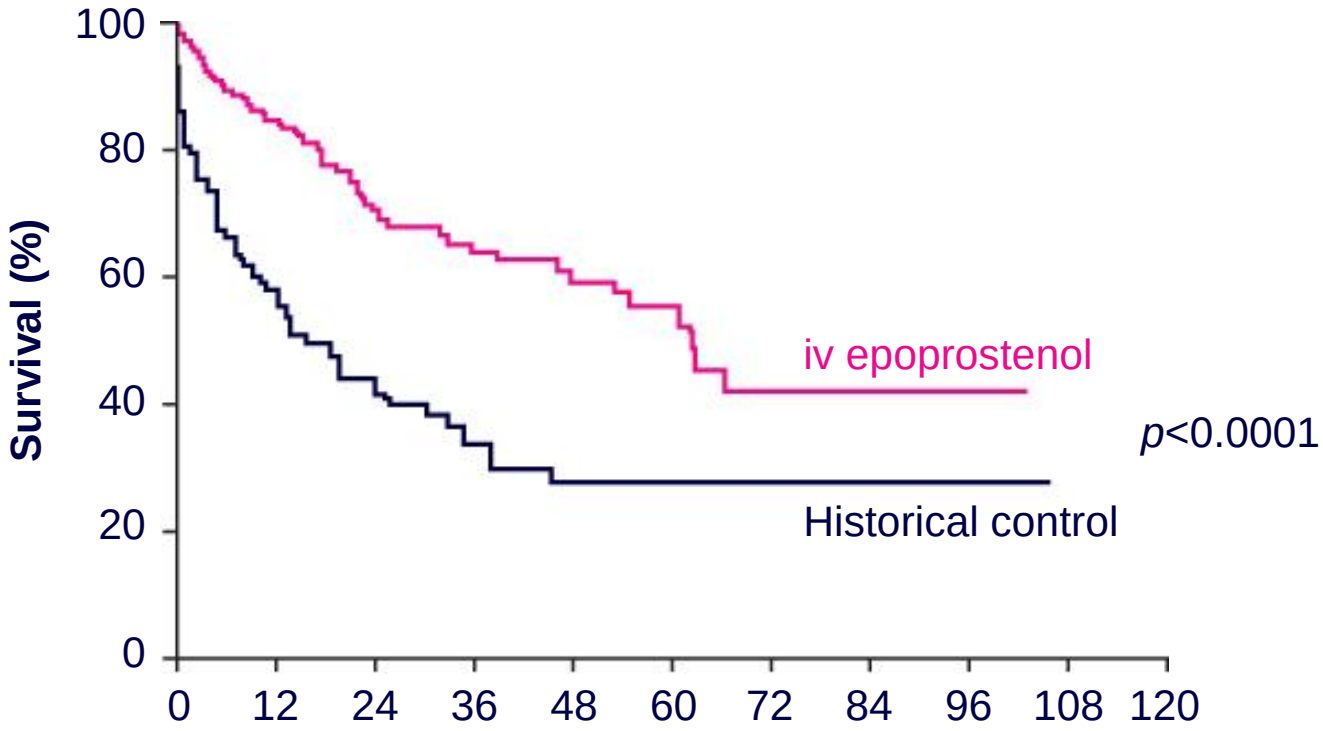
Barst et al. *N Engl J Med* 1996

Epoprostenol in iPAH: Evidence of improved survival (McLaughlin study)



McLaughlin et al. *Circulation* 2002; D'Alonzo et al. *Ann Intern Med* 1991

Epoprostenol in iPAH: Evidence of improved survival (Sitbon study)

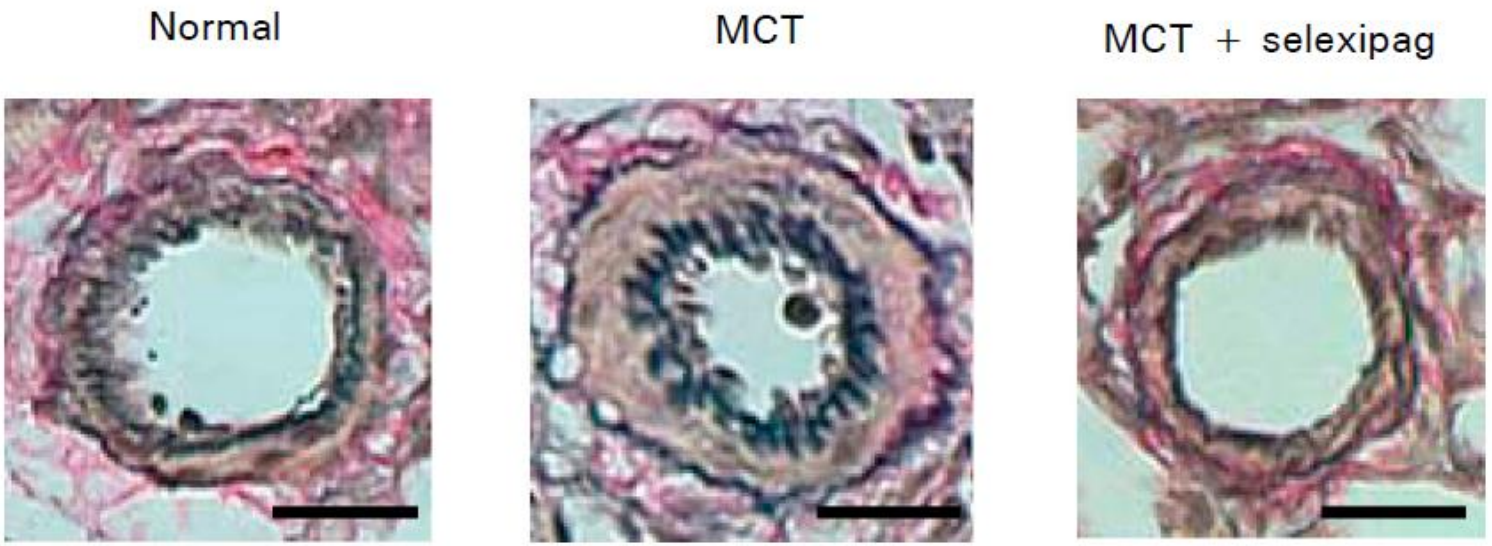


Patients at risk, n									
iv epoprostenol	178	129	85	57	36	21	7	3	1
Historical control	135	59	34	20	11	4	2	2	1

Sitbon et al. *J Am Coll Cardiol* 2002

Selexipag

REDUÇÃO DA HIPERTROFIA DA ARTÉRIA PULMONAR (ESTUDO EM ANIMAIS)



Representative photomicrographs of cross-sections of peripheral pulmonary arteries. Bar = 25 μM. Selexipag was orally administered to MCT-treated rats at 1 mg/kg twice daily for 19 days.

MCT: monocrotaline

Selexipag: estudo de fase III

Drug	Study	Duration	Primary endpoint	No. of subjects
Bosentan	Study-351[29, 30]	12 weeks	6-MWD	32
	BREATHE-1[31]	16 weeks	6-MWD	213
	BREATHE-5[122]	16 weeks	SpO_2, PVRI	54
	EARLY[32]	24 weeks	PVR, 6-MWD	185
Ambrisentan	ARIES-1[33, 123]	12 weeks	6-MWD	202
	ARIES-2[33, 124]	12 weeks	6-MWD	192
Ambrisentan and tadalafil	AMBITION[53]	Event-driven	Time to clinical failure	352
Sildenafil	SUPER-1[34]	12 weeks	6-MWD	277
	PACES[35]	16 weeks	6-MWD	267
Tadalafil	PHIRST[36]	16 weeks	6-MWD	405
Macitentan	SERAPHIN	Event-driven (103.9 weeks*)	Time to first morbidity/mortality event	742
Selexipag	GRIPHON	Event-driven (0.7 to 4.3 years‡)	Time to first morbidity/mortality event	1150†

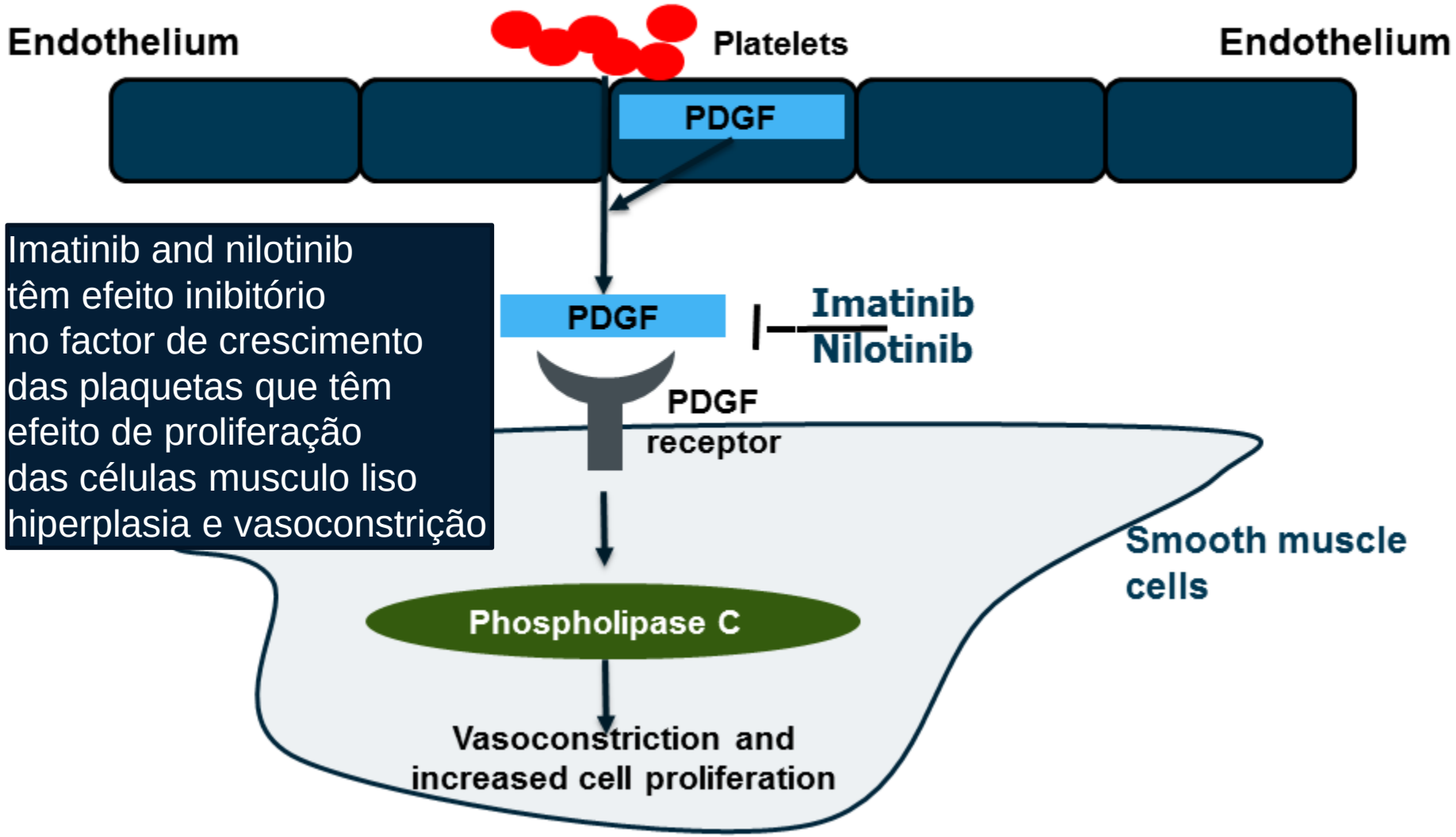
ESTUDO DE FASE III: GRIPHON

- Endpoint relevante e robusto: tempo até ao primeiro evento de morbilidade/mortalidade
- Selexipag em monoterapia ou associação, CF III e IV
- Estudo a longo prazo com duração de tratamento até mais de 4 anos
- Resultados
  - análise interina para eficácia e futilidade : final de 2013
    - Positiva para continuação do estudo
  - resultados finais esperados em meados de 2014

SELEXIPAG EM PORTUGAL

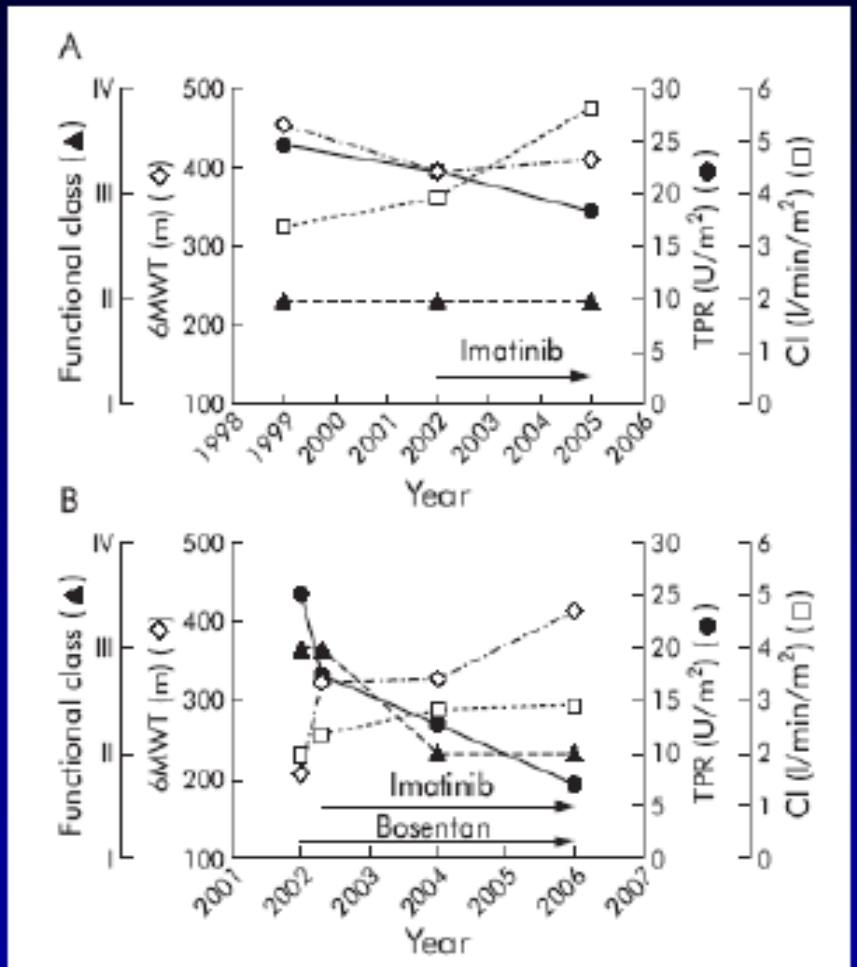
- Ponto da situação
  - AIM Nacional: - 6 Dezembro 2013
  - Avaliação farmacoeconómica prévia e preço: - 1º Semestre 2014
  - Lançamento: - 2º trimestre 2014

Angiogenesis and PDGF: Modulation by Investigational Agents



PDGF = platelet derived growth factor.

PLATELET-DERIVED GROWTH FACTOR INHIBITION WITH IMATINIB IN HUMAN PAH



Two patients with PAH and CML

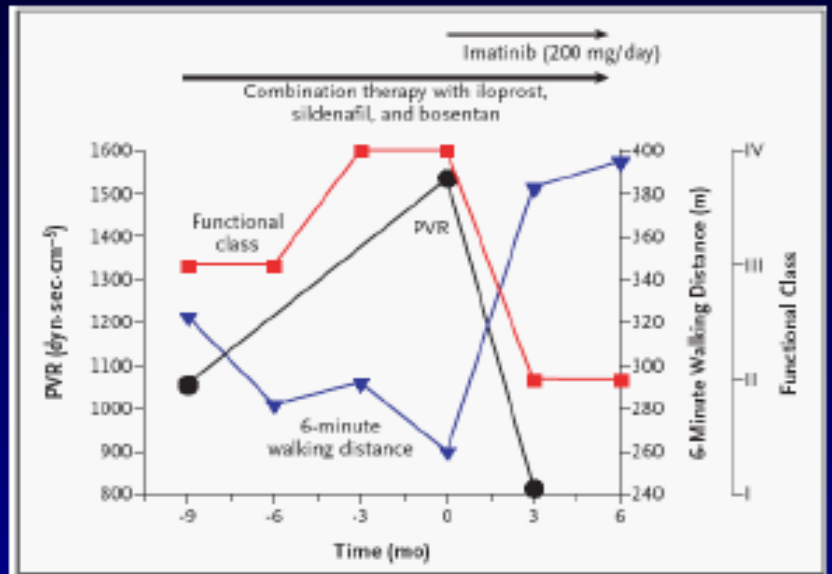


Figure 1. Time Course of Clinical Status, Exercise Capacity, and Hemodynamics before and after Initiation of Imatinib Treatment.

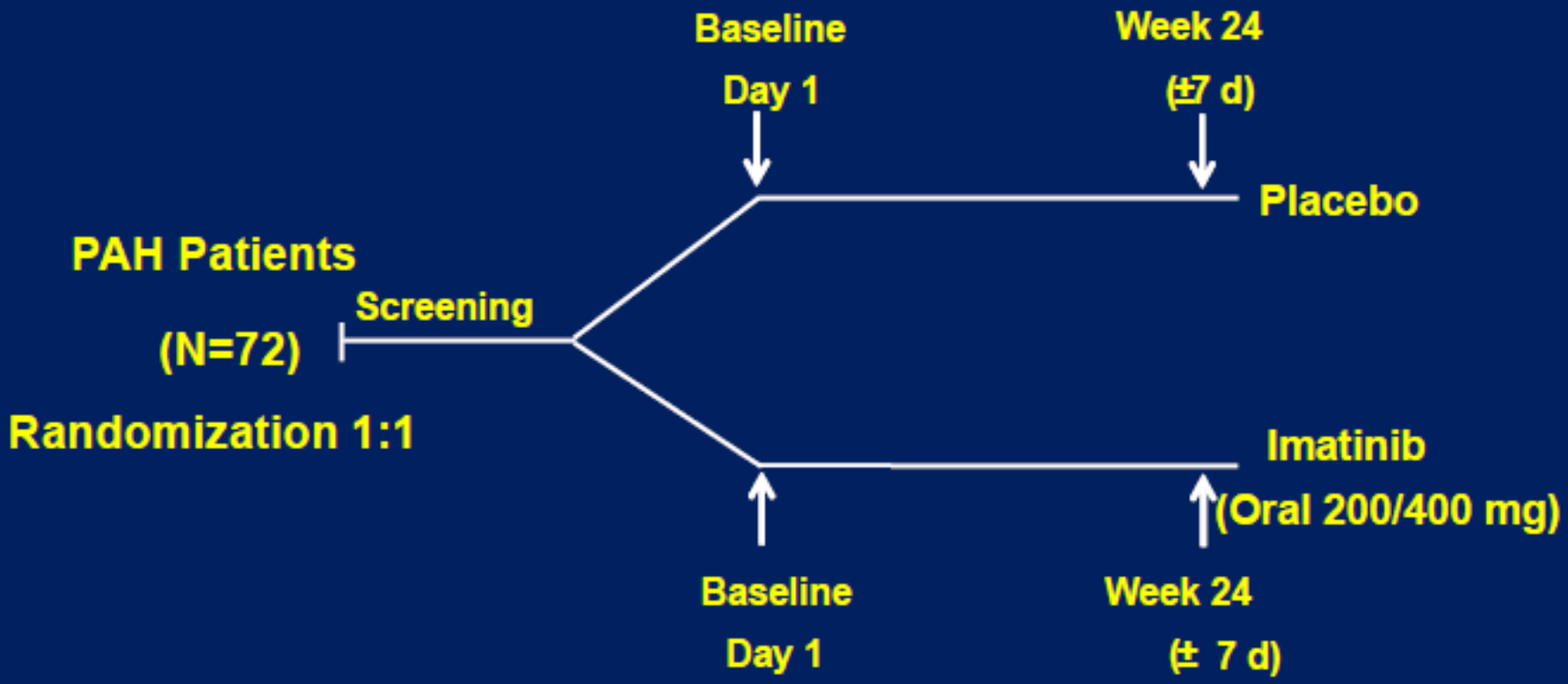
Pulmonary vascular resistance (PVR), New York Heart Association functional class, and six-minute walking distance are shown. Invasive assessment for PVR values was not undertaken at six months. The long horizontal arrow represents the continuation of combination therapy with iloprost, sildenafil, and bosentan.

Compassionate use in refractory PAH

Ghofrani et al, N Engl J Med 2005
Farber et al, Ann Int Med 2006
Souza et al, Thorax 2006

Tyrosine Kinase Inhibitors: Imatinib

Phase II Study



Ghofrani et al, Am J Resp Crit Care Med 2010

Tyrosine Kinase Inhibitors: Imatinib

Change in Key variables Baseline to study end. Per Protocol analysis mean (percent)

	mPAP (mmHg)	CO (l/min)	PVR (dyne/s · cm)$^{-5}$	PCWP (mmHg)	6MW
Gleevec N=19	-6.42 (-11%)	0.83 (20%)	-300 (-29%)	-0.4 (-4%)	18.1 (5%)
Placebo N=21	-2.66 (-4%)	0.11 (3%)	-81 (-8%)	1.4 (19%)	-12 (-3%)
Gleevec - Placebo	-3.75 (7%)	0.71 (17%)	218 (-21%)	1.8 (23%)	30 (8%)
P Value	0.27	0.017	0.029	0.07	0.06

Phase III: IMPRES

Ghofrani et al, Am J Resp Crit Care Med 2010

Vasoactive Intestinal Peptide (VIP)

Member of the glucagon growth-hormone releasing superfamily

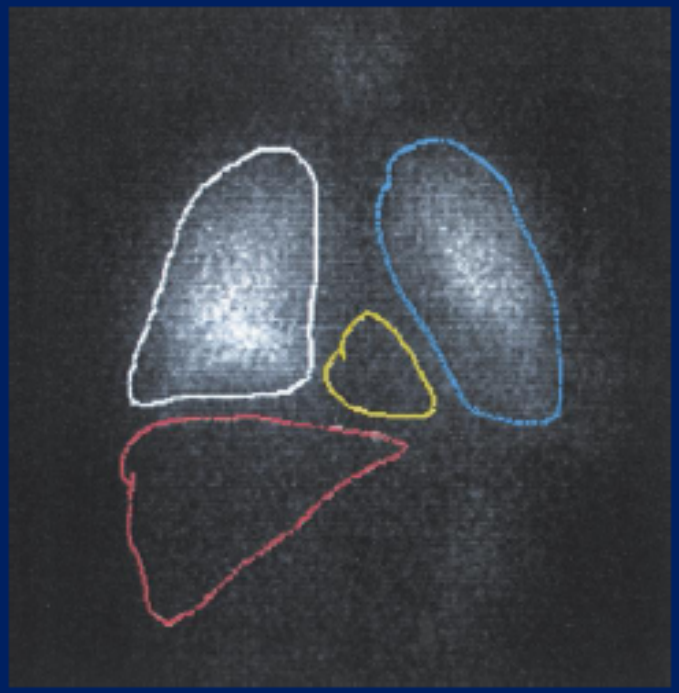
Pharmacologic profile similar to epoprostenol:

- Endogenous vasodilator
- Inhibitor of smooth muscle cell proliferation
- Inhibitor of platelet aggregation

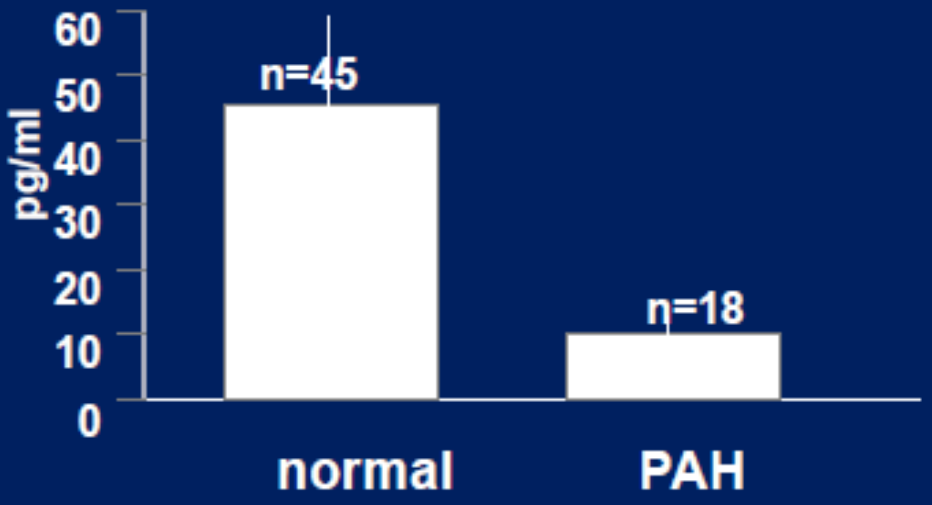
Said SI, et al. *Circulation*. 2007;115:1260-1268; Petkov V, et al. *J Clin Invest.* 2003;111:1339-1346.

Vasoactive Intestinal Peptide

VIP is actively concentrated in the Lung



VIP serum concentration



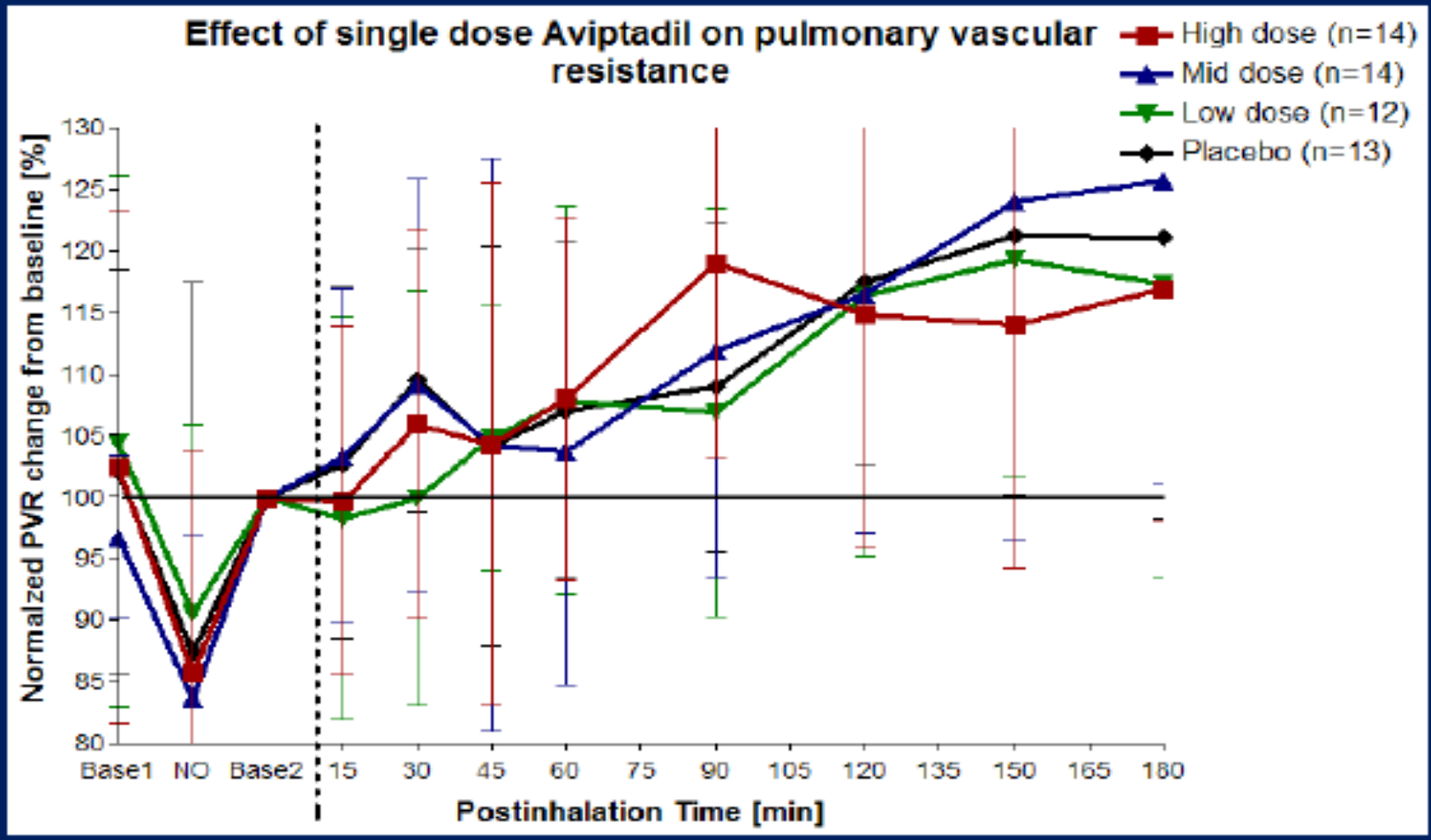
J. Clin. Invest. 111:1339–1346 (2003).

Effects of inhaled aviptadil (vasoactive intestinal peptide) in patients with pulmonary arterial hypertension (PAH): results from a phase II study

N. Galie[1], D. Badesch[2], T. Fleming[3], G. Simonneau[4], L. Rubin[5], R. Ewert[6], A. Boonstra[7], JA. Barbera[8], MA. Gomez-Sanchez[9], A. Torbicki[10]

(1) University of Bologna, Institute of Cardiology, Bologna, Italy (2) University of Colorado Health Sciences Center , Denver, United States of America (3) University of Washington, Seattle, United States of America (4) Paris-Sud University-Antoine Béclere Hospital, Clamart, France (5) University of California, San Diego, United States of America (6) Ernst Moritz Arndt University of Greifswald, Greifswald, Germany (7) Academic Medical Center, Amsterdam, Netherlands (8) University of Barcelona, Department of Pulmonary Medicine, Barcelona, Spain (9) University Hospital "12 de Octubre", Department of Cardiology, Madrid, Spain (10) Institute of Tuberculosis and Lung Diseases, Warsaw, Poland

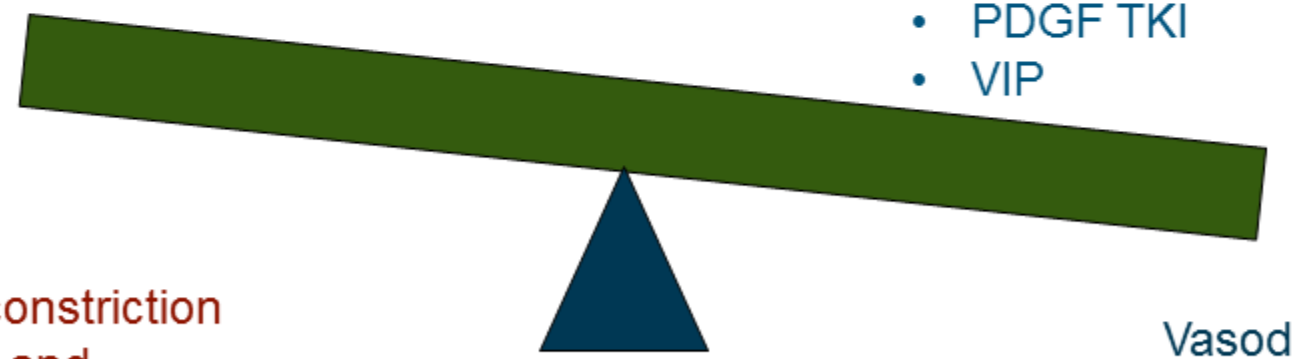
Time-course of PVR change



Restoring the Balance in PAH: Combining Synergistic Pathways

- ET-1 levels
- PDE5
- PDGF
- Serotonin

- ERAs
- Oral sGC stimulators
- PDE5 inhibitors
- Prostacyclin receptor agonists
- Prostanoids
- PDGF TKI
- VIP



Vasoconstriction
and
Increased proliferation

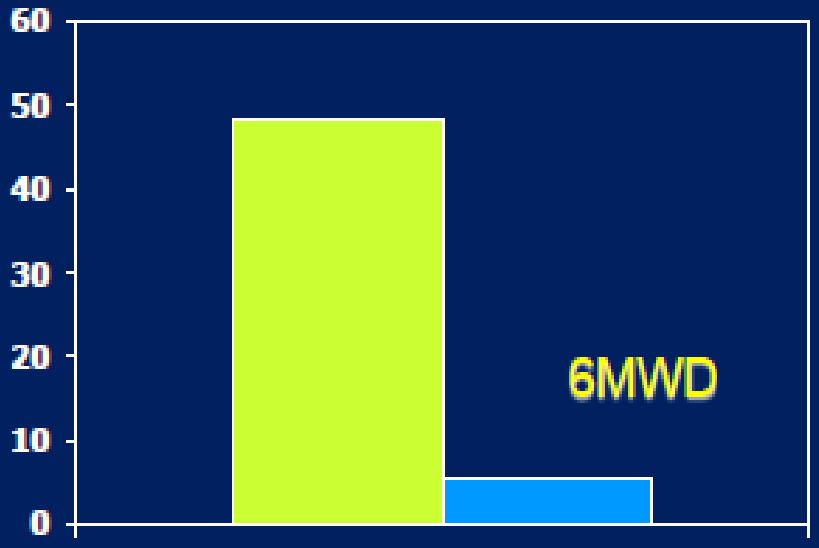
Vasodilation
and
Decreased proliferation

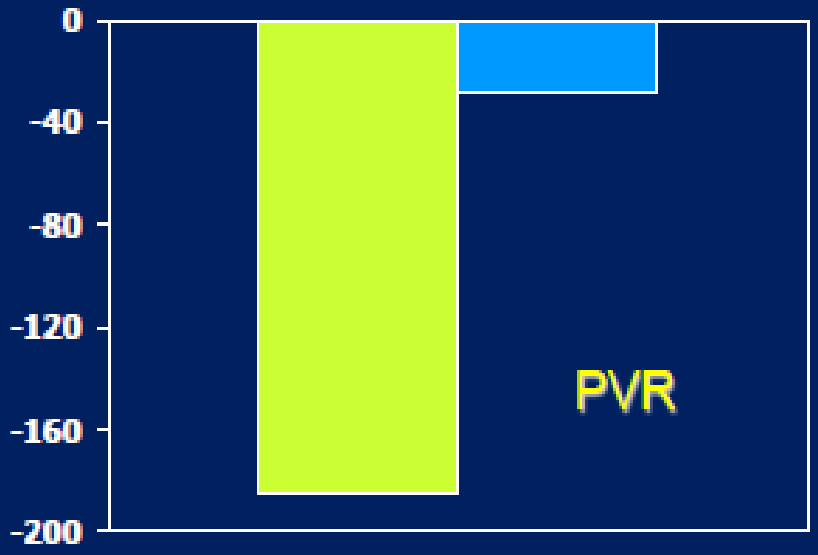
TKI = tyrosine kinase inhibitor.

Transplantation of Autologous Endothelial Progenitor Cells May Be Beneficial in Patients With Idiopathic Pulmonary Arterial Hypertension

A Pilot Randomized Controlled Trial

N=31 FC II/III on therapy (PGE1, sild)
EPC delivered IV – 12 weeks assessment



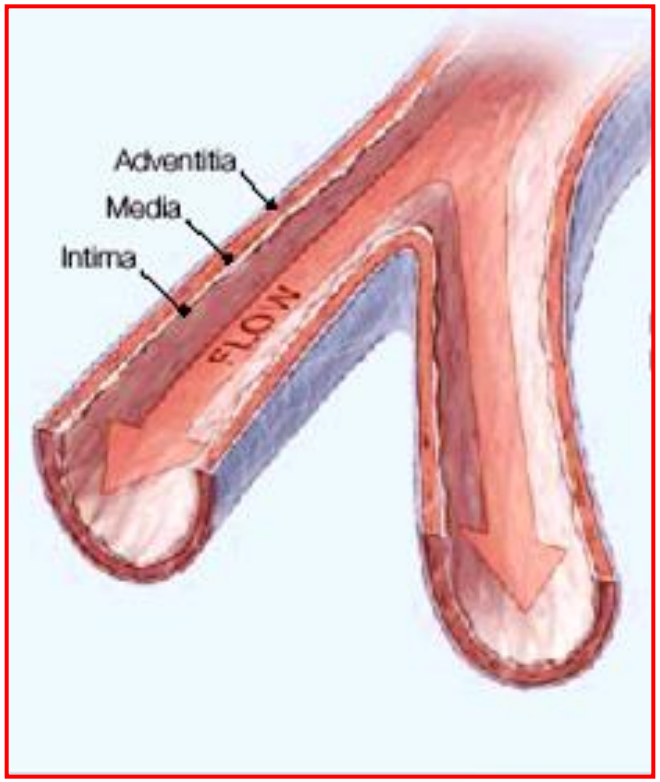


Wang XX et al J Am Coll Cardiol 2007;49:

PARADIGM SHIFT ????

OVER TIME, FUNCTIONAL AND STRUCTURAL CHANGES IN THE PULMONARY VASCULATURE OCCUR, INITIALLY IN THE CAPILLARIES AND LATER IN THE ARTERIOLES AND ARTERIES, WITH ABNORMALITIES OF THE ELASTIC FIBERS, INTIMAL PROLIFERATION AND MEDIAL HYPERTROPHY THAT RESULT IN INCREASED VASCULAR STIFFNESS[1]

Normal



Elevated left ventricular filling pressure

↓

Elevated left atrial pressure

↓

Elevated pulmonary artery diastolic and systolic pressure

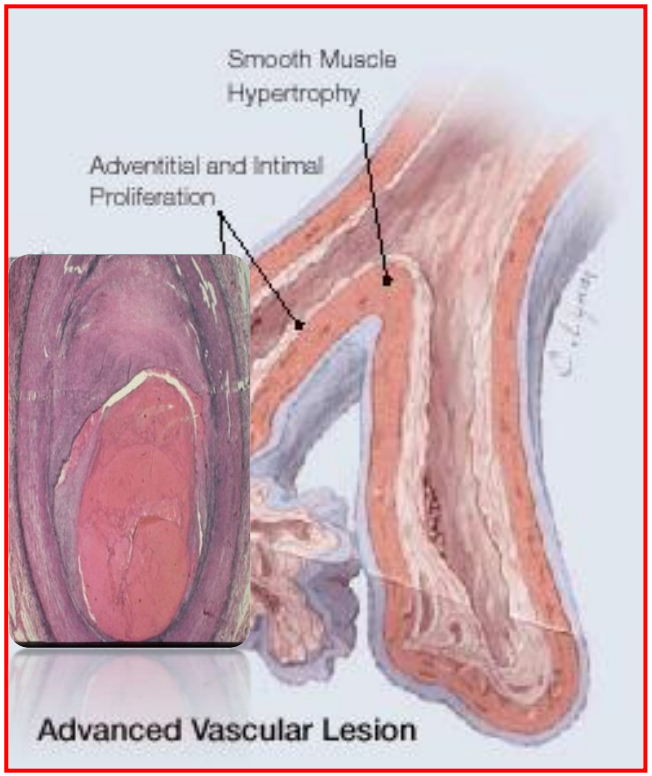
↓

Pulmonary vasoconstriction and remodeling

↓

Further increase in pulmonary pressures and loss of reversibility

PH

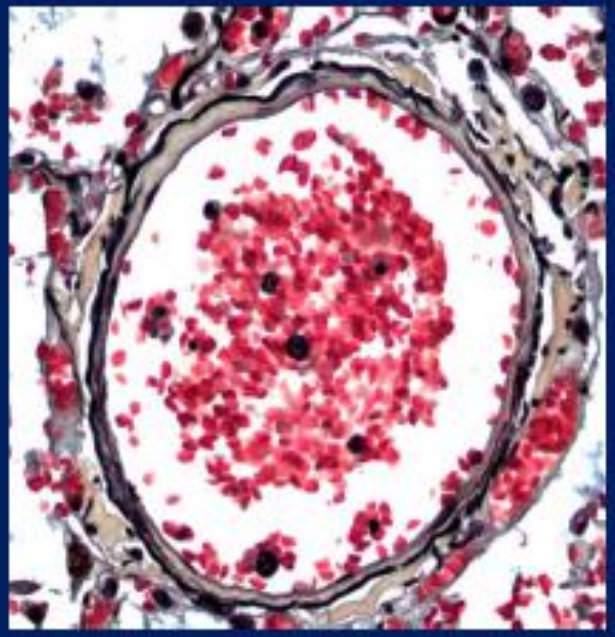


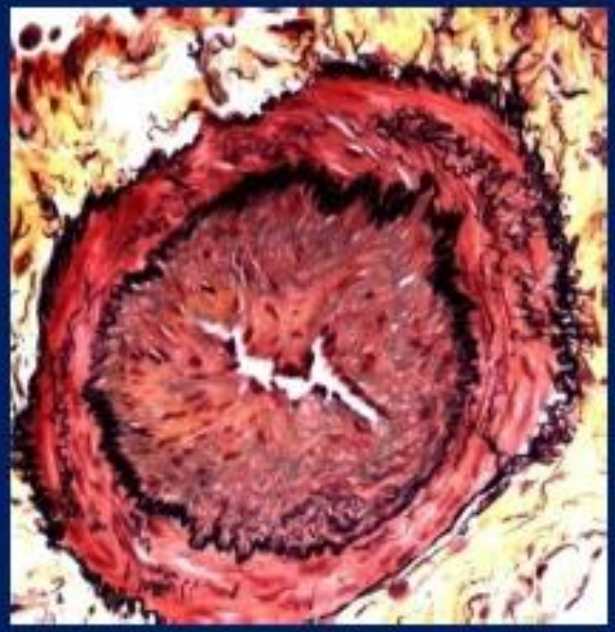
high flow
low resistance

low flow
high resistance

1. Adapted from Gaine S. JAMA 2002

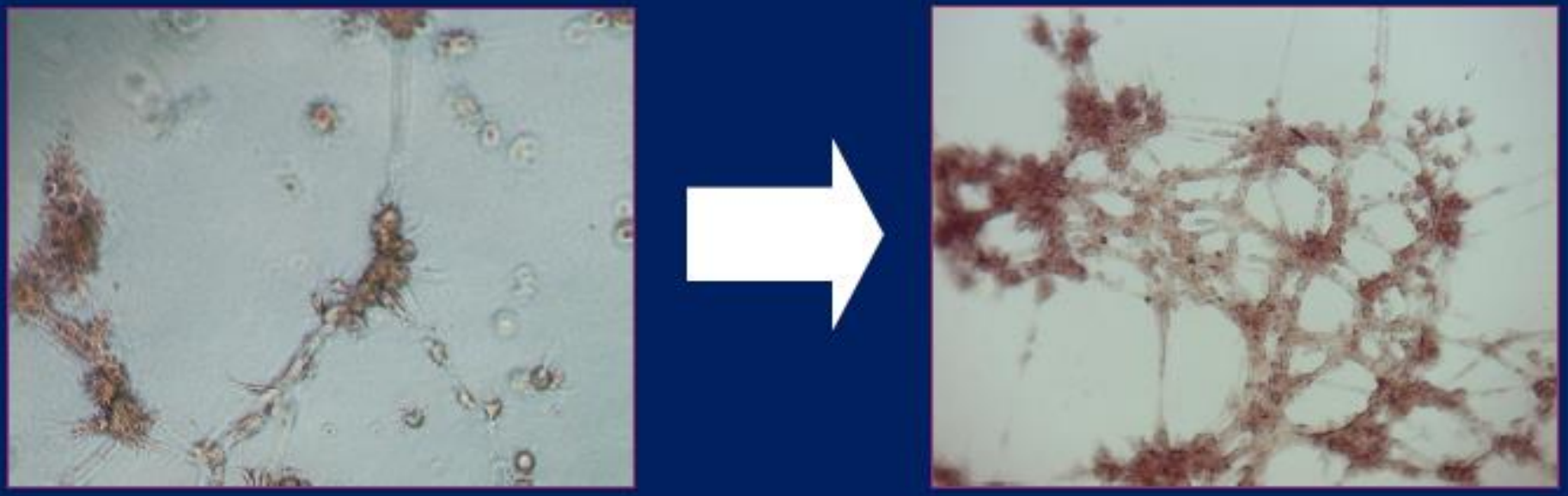
From Reverse-remodeling





Drugs

To Regenerative Vasculogenesis?



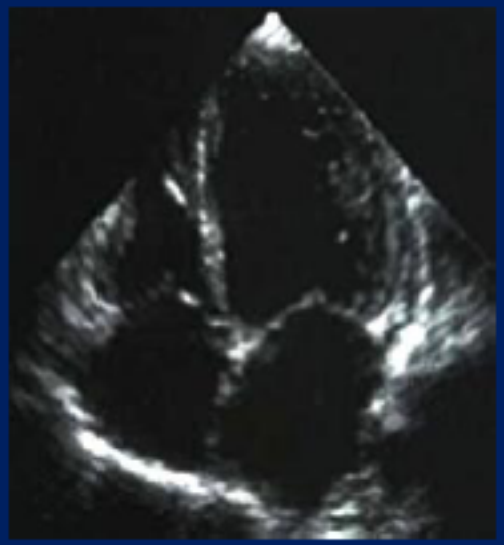
Control

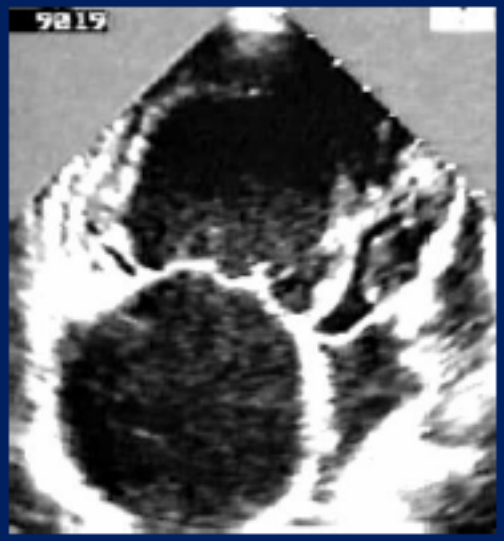
Stem Cells

+ HBR

Courtesy of Prof Carlo Ventura

Reverse-remodeling induction





Stem Cells
(myocites)

From „bricks“ to „repairing machines“

GALIÈ (2013): UPDATED PAH TREATMENT ALGORITHM

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

CHMP, Committee for Medicinal Products for Human Use; EMA, European Medicines Agency; FDA, Food and Drug Administration; PAH, pulmonary arterial hypertension; WHO-FC, World Health Organization functional class

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

CONCLUSÃO

- Os recentes e vastos progressos da compreensão fisiopatológica, avanços nas potencialidades diagnósticas e novas áreas de intensa investigação com terapêuticas promissoras, conferem a esta área um contexto previligiado e único.

- A mortalidade continua a ser elevada, com marcada limitação funcional, pelo que as novas terapêuticas emergentes podem conferir modificação significativa do prognóstico destes doentes.

GATA ESCONDIDA (MIRÓ)

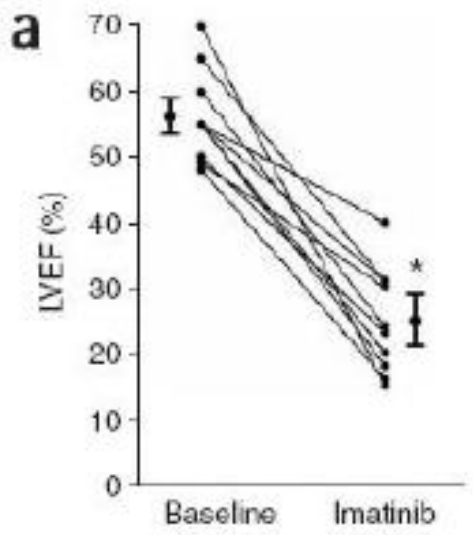

Mais importante do que a obra de arte propriamente dita é o que ela vai gerar. A arte pode morrer; um quadro desaparecer. O que conta é a semente.
(Joan Miró Ferrà)
kdfrases.com

Cardiac Toxicity of Imatinib

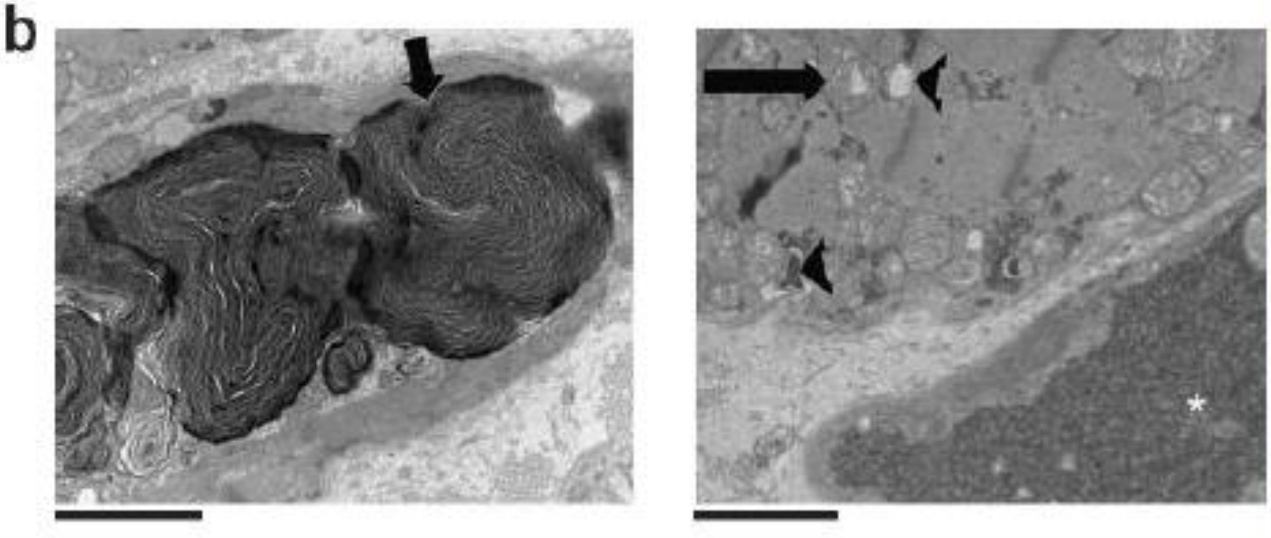
Cardiotoxicity of the cancer therapeutic agent imatinib mesylate

nature medicine

Change in LVEF from pretreatment to heart failure while on imatinib



Electron micrographs of cardiac biopsies from individuals presenting with presumed imatinib-induced heart failure



Mitochondrial and reticulum abnormalities

Kerkela R, *et al. Nat Med* 2006; 12:908-16.