HIPERTENSÃO ARTERIAL PULMONAR

29º CONGRESSO DE CARDIOLOGIA DO ESTADO DA BAHIA

10 a **13** de **maio** de 2017
Bahia Othon Palace

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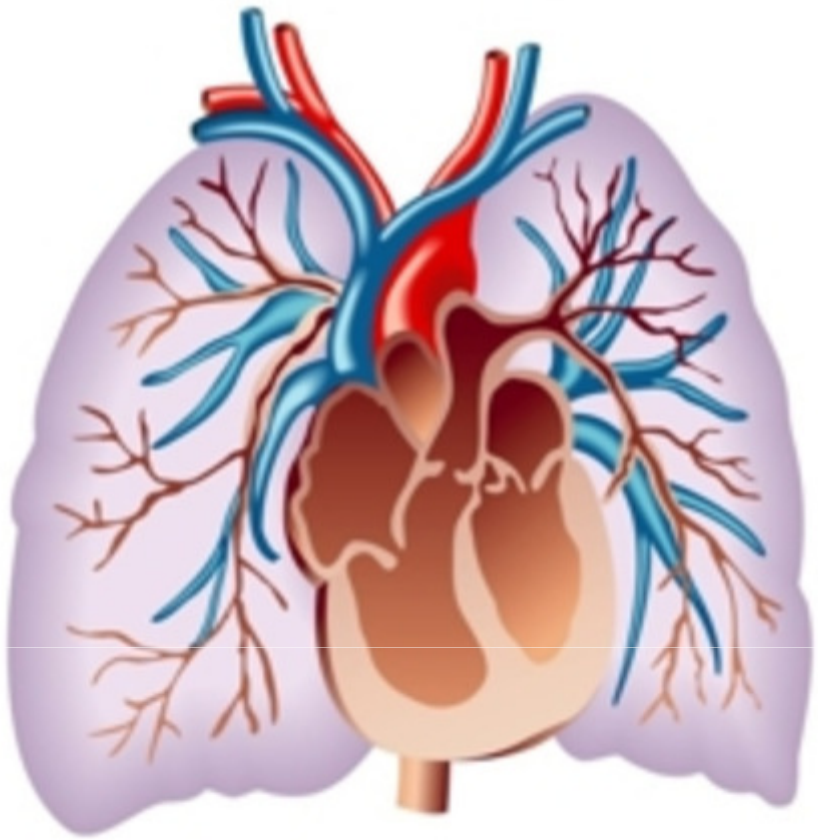


Ernst von Romberg, em 1891, publicou a primeira descrição de hipertensão arterial pulmonar (HAP) com dados da necropsia de um paciente com cardiomegalia e hipertrofia de ventrículo direito, classificando-a como esclerose da circulação pulmonar.

Rubin L J, et al. Chest. 1993;104(1):236-50.

Dtsch Archiv Klin Med, 48 (1891), pp. 197–206

HAP - Fisiopatologia

Suscetibilidade
. Gen BMPR2
. ALK1
. 5HTT
. Ec-NOS

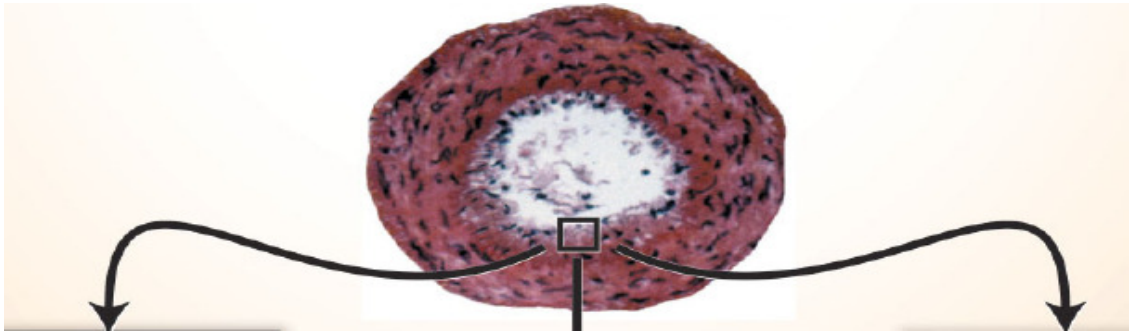
Fatores de risco e condições associadas
. Doenças do colágeno
. Doença cardíaca congênita
. Hipertensão porta
. Infecção HIV
. Drogas e toxinas

Injúria vascular
. Disfunção endotelial
↓ síntese oxido nítrico
↓ produção prostaciclina
↑ produção de tromboxano
↑ Produção de endotelina
. Disfunção musculatura lisa vascular
Defeito no canal de potássio
. Hipertrofia da musculatura lisa
. Proliferação da íntima

Doença
. Vasoconstricção **. Proliferação**
. Trombose **. Inflamação**

Artérias pulmonares distais (500 mm)
- Hipertrofia mediana
- Proliferação intimal
- Alterações fibróticas
- Espessamento adventício
- Leve a moderada infiltrados inflamatórios perivasculares
- Neogénese linfóide
- Lesões complexas (lesões plexiformes, dilatadas)
- Trombose

J Am Coll Cardiol 2004;43(Suppl 1):S25–S32 / J Am Coll Cardiol 2009;54(Suppl):S3–S9



Endotelina

ETA - ETB

Vasoconstrição
Proliferação

Inibidores da Endotelina

Bosentana
Ambrisentana
Macintentana

Óxido Nitrico

L-ARGININA -------- L-citrulina

NO

cGMP ⇐ NO

Fosfodisterase

Vasodilatação e
Anti-proliferativo

Inibidores da fosfodiesterase

Sildenafila
Tadalafila

ESTIMULADORES DA GUANIL CICLASE

Riociquat

Prostaciclina

Ac. Aracdônico -----Prostaglandina

cAMP

Vasodilatação e
Anti-proliferação

Prostaciclinas

Selexipag

Epoprostenol
Iloprost
Prostinil
Beroprost

HAP - Definição

- Definição Hemodinâmica

Cat. Cardíaco direito

PAPm > 25 mmHg repouso

PCP < 15 mmHg

Resistência vascular pulmonar ≥ 3 unidades woods

"Aumento progressivo da resistência vascular pulmonar, que culmina em falência VD e morte"

$$P = F \times R$$

TESTE DE VASORREATIVIDADE PULMONAR

Web Table IV **Route of administration, half-life, dose ranges, increments, and duration of administration of the most commonly used agents for pulmonary vasoreactivity tests**

Drug	Route	Half-life	Dose range[d]	Increments[e]	Duration[f]	Class[a]	Level[b]	Ref[c]
Nitric oxide	Inh	15–30 sec	10–20 ppm	-	5 min[g]	I	C	4, 5
Epoprostenol	i.v.	3 min	2–12 ng/kg/min	2 ng/kg/min	10 min	I	C	4, 6
Adenosine	i.v.	5–10 sec	50–350 μg/kg/min	50 μg/kg/min	2 min	IIa	C	7
Iloprost	Inh	30 min	5–20 μg	-	15 min	IIb	C	8

- REDUÇÃO 10 mmHg na mPAP
- Valor absoluto < 40 mmHg

ESC/ERS Guidelines(addendum) - 2015

HISTÓRIO TRATAMENTO HP - FDA

1995 – EPOPROSTENOL
2001 – BOSENTANA
2004 – ILOPROST
2005 – SILDENAFILA
2007 – AMBRISETANA
2009 – TADALAFILA
2013 – MACITENTAN
2015 – SELEXIPAG
2015 – TADALAFILA + AMBRISENTANA

www.fda.gov/drugs

Annals of Internal Medicine®

ORIGINAL RESEARCH | 1 APRIL 1990

Treatment of Primary Pulmonary Hypertension with Continuous Intravenous Prostacyclin (Epoprostenol): Results of a Randomized Trial

Lewis J. Rubin, MD; Jessica Mendoza, BSN; Michele Hood, BSPh; Michael McGoon, MD; Robyn Barst, MD; William B. Williams, MD; Jane Hall Diehl, MS; James Crow, PhD; Walker Long, MD

Table 3. *Hemodynamic Variables at Baseline and at 2 Months*

Treatment Group	Variable	Baseline	2 Months	95% CI	*P* Value
Prostacyclin ($n = 10$)*	Cardiac output, *L/min*	3.3	3.9	0.11 to 1.03	0.020
	Heart rate, *beats/min*	83	87	−4.1 to 12.7	0.34
	Mean pulmonary artery pressure, *mm Hg*	58.6	49.3	−17.7 to 0.91	0.057
	Mean systemic artery pressure, *mm Hg*	88.8	83.6	−11.8 to 1.41	0.157
	Systemic oxygen transport, *mL/min*	577	681	7.92 to 185.68	0.048
	Total pulmonary resistance, *units*	21.6	13.9	−13.1 to −2.2	0.022
	Total systemic resistance, *units*	29.1	22.9	−11.35 to −1.17	0.039
	6-Minute walk, *m*	246	378	49.8 to 212.6	0.011
Conventional therapy ($n = 9$)	Cardiac output, *L/min*	3.5	3.9	−0.51 to 1.38	0.393
	Heart rate, *beats/min*	85	83	−12.5 to 8.7	0.735
	Mean pulmonary artery pressure, *mm Hg*	62.2	62.2	−8.91 to 8.91	1.000
	Mean systemic artery pressure, *mm Hg*	102.9	95.7	−14.2 to −0.3	0.076
	Systemic oxygen transport, *mL/min*	704	751	−124 to 218	0.60
	Total pulmonary resistance, *units*	20.6	20.4	−6.2 to 5.9	0.96
	Total systemic resistance, *units*	34.1	30.3	−11.6 to 4.1	0.37
	6-Minute walk test, *m*	205	292	21.7 to 135.8	0.022

Annals of Internal Medicine®

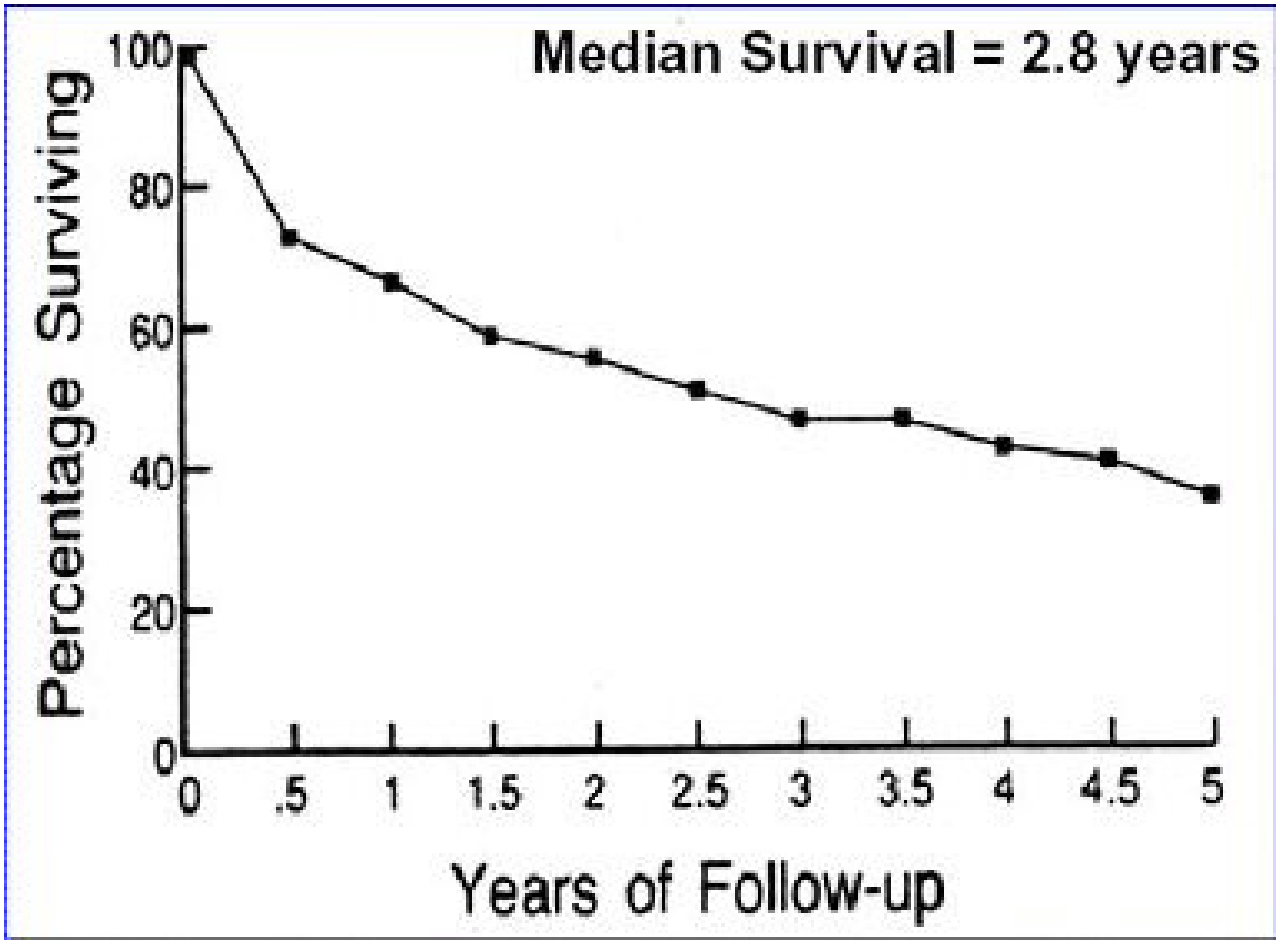
ORIGINAL RESEARCH |1 APRIL 1990

Treatment of Primary Pulmonary Hypertension with Continuous Intravenous Prostacyclin (Epoprostenol): Results of a Randomized Trial

Table 1. *Demographic and Clinical Characteristics of Patients in Study*

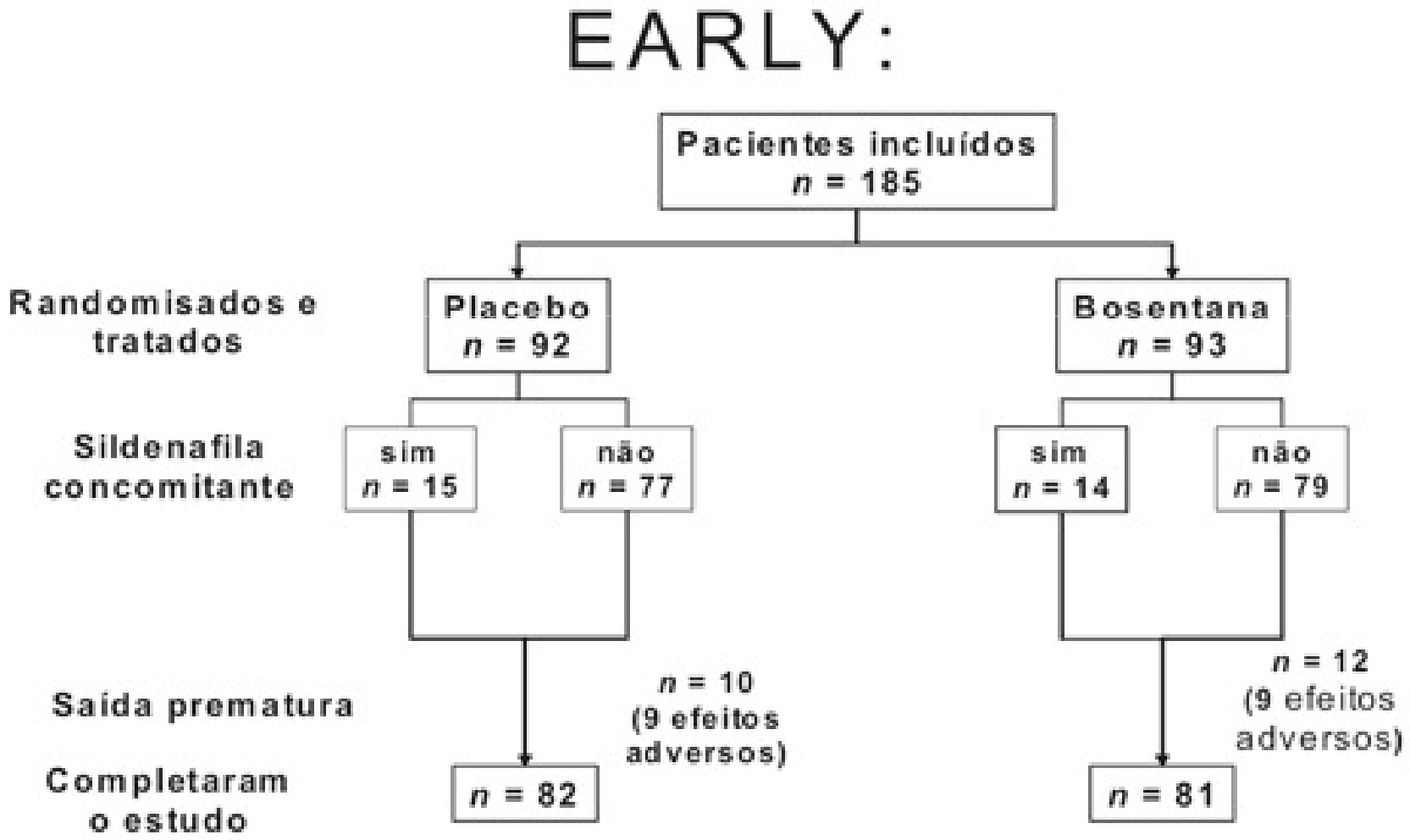
Patient Group	Sex, Age, *y*	Functional Class	Medications during 2-Month Study
Prostacyclin			
1	F, 53	III	digoxin, furosemide
2	F, 42	II	furosemide
3	M, 66	III	theophylline, prednisone
4	F, 31	IV	furosemide
5•	M, 21	III	furosemide, spironolactone
6	F, 34	III	. . .
7	F, 26	III	. . .
8	M, 34	III	. . .
9	F, 38	III	furosemide
10	F, 37	III	. . .
11	M, 30	III	. . .
Conventional			
1	M, 21	III	. . .
2	F, 60	IV	digoxin, diltiazem, furosemide
3	F, 29	II	diltiazem, furosemide
4†	F, 33	IV	nifedipine, digoxin, furosemide
5	F, 52	III	methyldopa
6	F, 25	III	nifedipine, thiazide
7	F, 52	IV	diltiazem, furosemide, spironolactone, metolazone
8	M, 23	III	nifedipine
9	M, 54	IV	diltiazem, furosemide
10	F, 35	III	diltiazem, furosemide
11†	F, 21	IV	nitropaste, bumetanide
12†	F, 15	III	digoxin
Not randomized			
1‡	F, 27	IV	. . .

HAP - Sobrevida



D'Alonzo et al. Ann Intern Med 1991; 115:343-9

EARLY -Endothelin Antagonist tRial in miLdlY symptomatic PAH patients
(Galié N, et al. Lancet 2008;37:2093-100)



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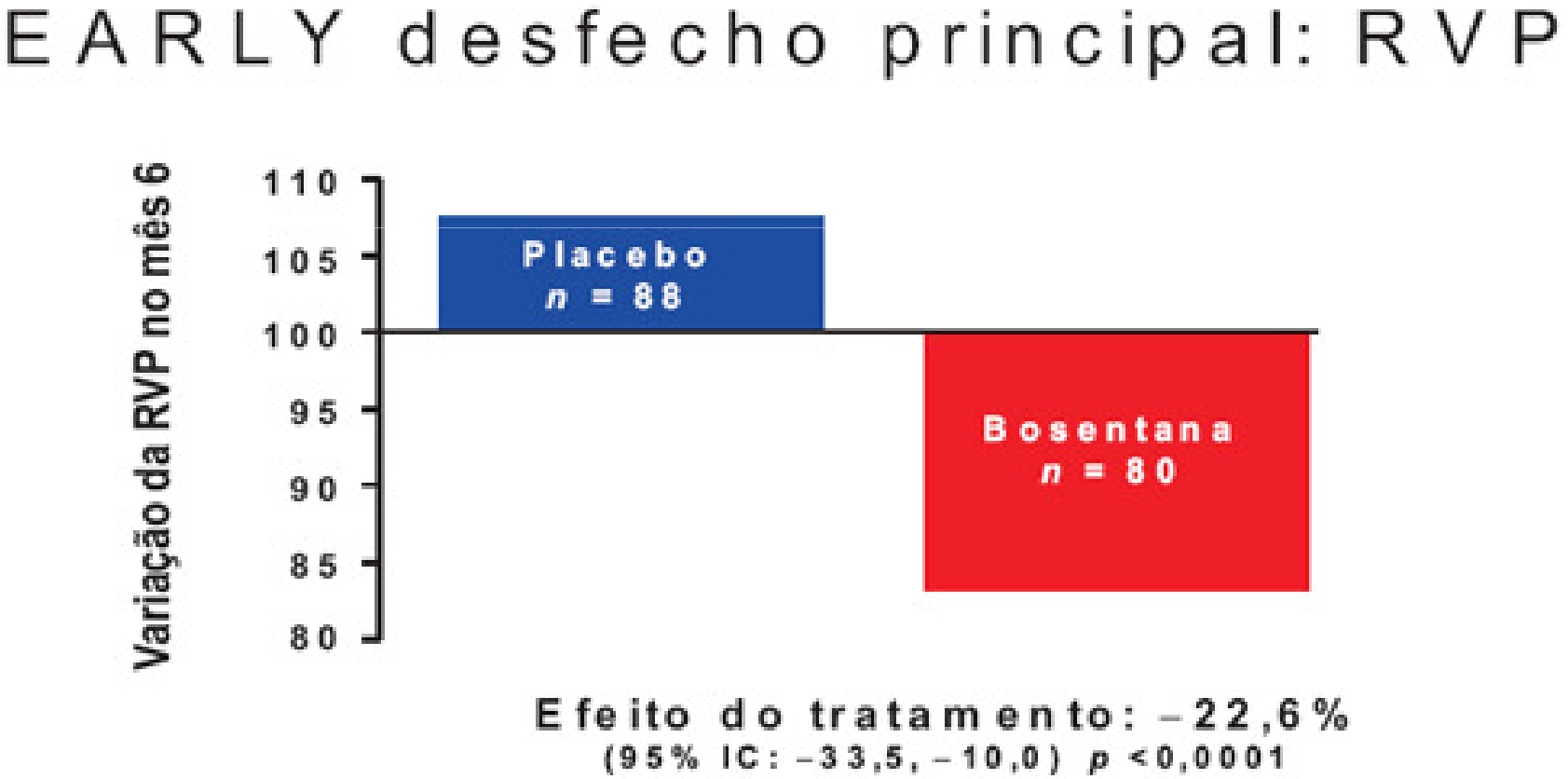


Antagonistas da endotelina em HAP

Bosentan - BREATHE-1 – 16 semanas

213 pacientes randomizados

- 74 – 125 mg 2 x dia
- 70 – 250 mg 2 x dia
- 69 – placebo

Pacientes: Classe funcional III (>90%) e IV

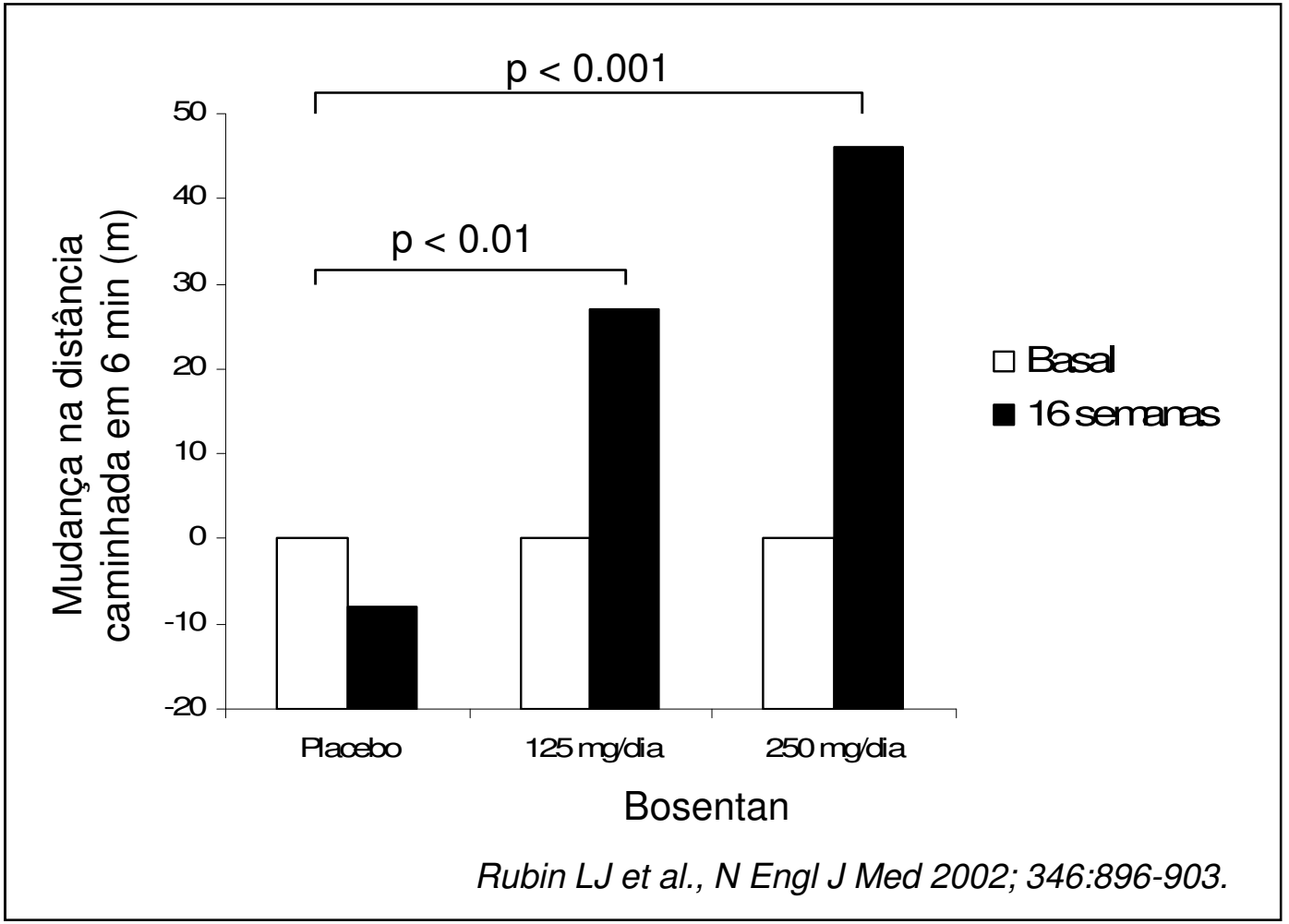
- 71% – HAPI
- 23% – Esclerodermia
- 6% – LES

Resultados:

Dist. 6 min	44 m vs. placebo
Melhora funcional	42% vs. 30% com placebo
Piora clínica	6% vs. 20% com placebo
Hospitalização	4% vs. 13% com placebo
Óbitos	1% vs. 3% com placebo
Sobrevida	93% e 84% em 1 e 2 a

Rubin LJ et al., N Engl J Med 2002; 346:896-903.

Bosentan - BREATHE-1 – Teste caminhada 6 min



Rubin LJ et al., N Engl J Med 2002; 346:896-903.

Inibidores de fosfodiesterases em HAP

Sildenafil - SUPER-1 – 12 semanas

277 pacientes tratados

- 69 – 20 mg 3 x dia
- 67 – 40 mg 3 x dia
- 71 – 80 mg 3 x dia
- 70 – placebo

Pacientes: Classe funcional II e III

- 63% – HAPI
- 30% – D. tecido conectivo
- 6% – Cardiopatias congênitas

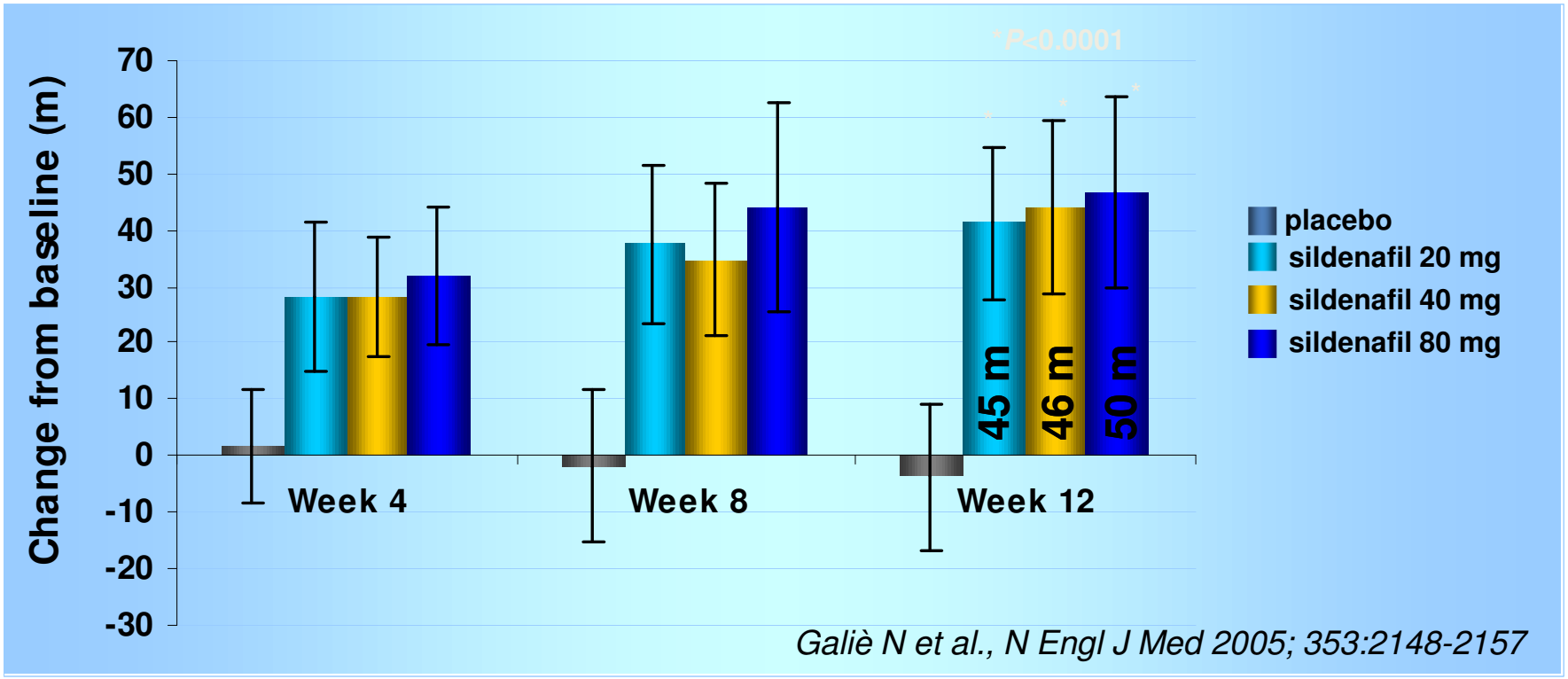
Resultados:

Dist. 6 min	45, 48, 51 m (20, 40, 80 mg)	vs. placebo
Melhora funcional	42% dos pcs. em CFIII	vs. 3,4% com placebo
RVP (din/seg/cm^{-5})	-122, -143, -261	vs. +49
Piora clínica	4%, 3%, 7%	vs. 10%
Hospitalização	3%, 3%, 3%	vs. 10%
Óbitos	1%, 0%, 3%	vs. 1%

Ef. adversos: epistaxes, cefaleia, dispepsia, “flushing”, insônia

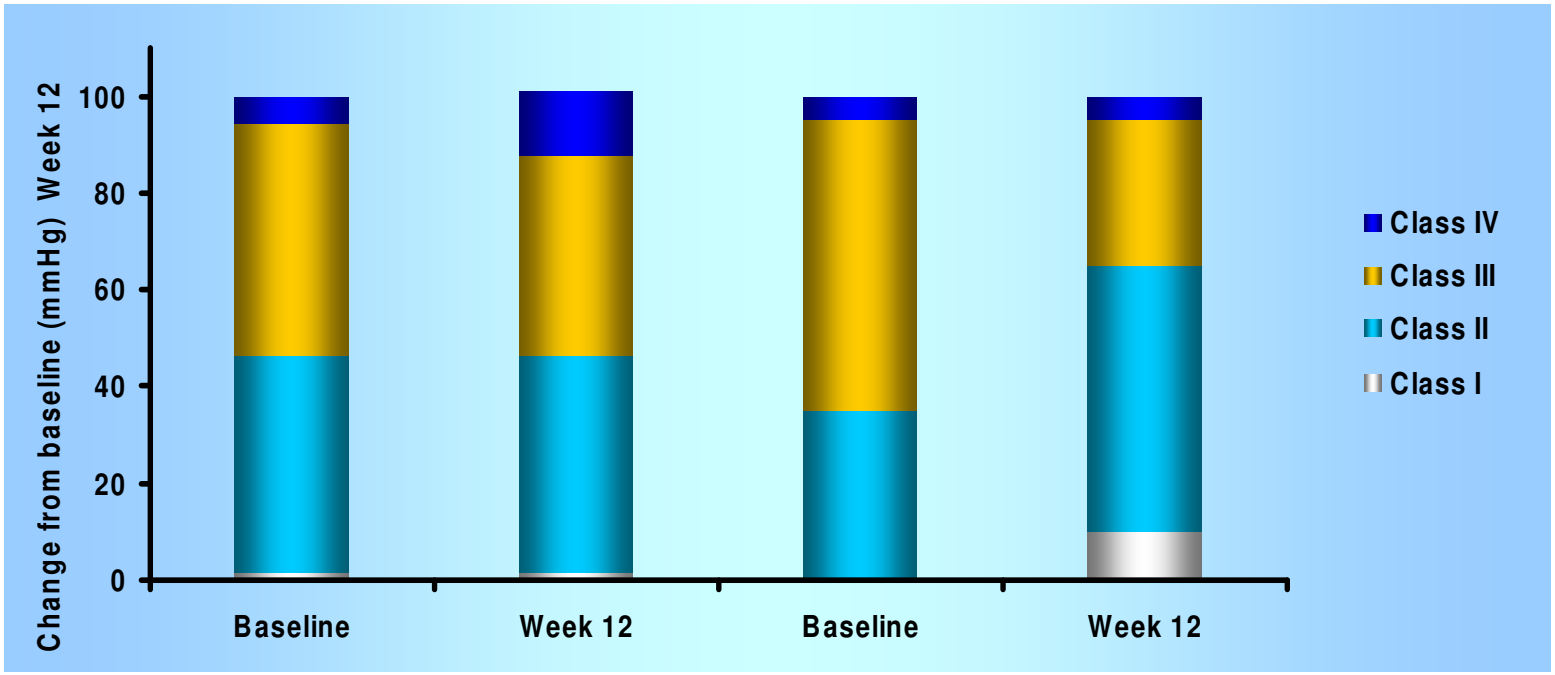
Galiè N et al., N Engl J Med 2005; 353:2148-2157.

Sildenafil - SUPER-1 – 12 semanas



Galiè N et al., N Engl J Med 2005; 353:2148-2157

Sildenafil - SUPER-1 – 12 semanas



Galiè N et al., N Engl J Med 2005; 353:2148-2157

Macitentan and Morbidity and Mortality in Pulmonary Arterial Hypertension
SERAPHIN

Multicêntrico (151 centros, 39 países, entre maio-2008 a dez-2009, Randomizado, duplo cego e placebo controlado.
HAP CF II e III
Redução de risco para morbimortalidade
742 pacintes (1:1:1) – Macitentana 03 mg / 10 mg / Placebo
Média de duração do estudo foi de 96,2 semanas.
36,3% - Sem tratamento prévio
63,7% - Recebiam algum tratamento (61,4% inibidores da PDE-5, 5,4% prostanóide, 58% sildenafila)

Evento de morbimortalidade:

Morte, atrial septostomia, transplante pulmonar, inicio de prostanoide EV ou SC e piora da HAP.

Tomás Pulido, et al. N Engl J Med 2013; 369:809-818

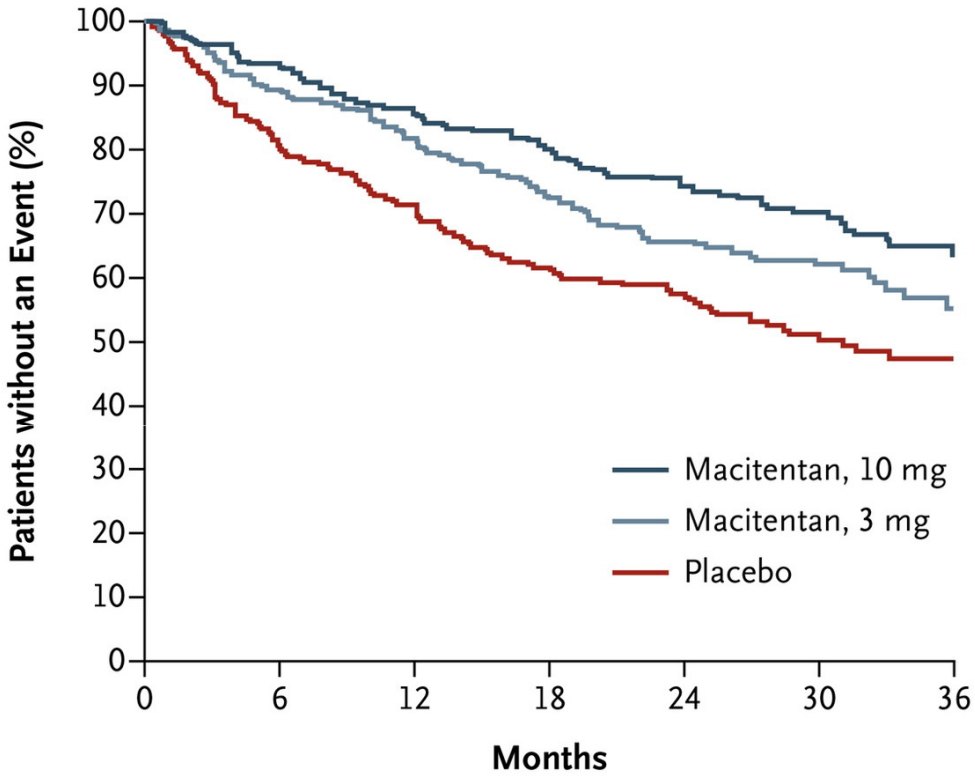
Macitentan and Morbidity and Mortality in Pulmonary Arterial Hypertension SERAPHIN

Table 2. Primary and Secondary End Points for Events Related to Pulmonary Arterial Hypertension and Death.*

End Point	Placebo (N=250)	Macitentan, 3 mg (N=250)	Macitentan, 10 mg (N=242)	Macitentan, 3 mg, vs. Placebo		Macitentan, 10 mg, vs. Placebo	
				Hazard Ratio (97.5% CI)	P Value	Hazard Ratio (97.5% CI)	P Value
	number of patients (percent)						
Event related to PAH or death as the first event							
All events	116 (46.4)	95 (38.0)	76 (31.4)	0.70 (0.52–0.96)	0.01	0.55 (0.32–0.76)	<0.001
Worsening of PAH	93 (37.2)	72 (28.8)	59 (24.4)				
Death from any cause†	17 (6.8)	21 (8.4)	16 (6.6)				
Prostanoid initiation	6 (2.4)	1 (0.4)	1 (0.4)				
Lung transplantation	0	1 (0.4)	0				
Death due to PAH or hospitalization for PAH as the first event							
All events	84 (33.6)	65 (26.0)	50 (20.7)	0.67 (0.46–0.97)	0.01	0.50 (0.34–0.75)	<0.001
Hospitalization for PAH	79 (31.6)	56 (22.4)	45 (18.6)				
Death due to PAH‡	5 (2.0)	9 (3.6)	5 (2.1)				
Death from any cause	19 (7.6)	21 (8.4)	14 (5.8)	0.97 (0.48–1.98)	0.92	0.64 (0.29–1.42)	0.20
Death due to PAH§	14 (5.6)	14 (5.6)	7 (2.9)	0.87 (0.37–2.04)	0.72	0.44 (0.16–1.25)	0.07
Death from any cause by the end of the study¶	44 (17.6)	47 (18.8)	35 (14.5)	1.05 (0.65–1.67)	0.83	0.77 (0.46–1.28)	0.25

Tomás Pulido, et al. N Engl J Med 2013; 369:809-818

Effect of Macitentan on the Composite Primary End Point of a First Event Related to Pulmonary Arterial Hypertension or Death from Any Cause - SERAPHIN



No. at Risk							
Placebo	250	188	160	135	122	64	23
Macitentan, 3 mg	250	213	188	166	147	80	32
Macitentan, 10 mg	242	208	187	171	155	91	41

Tomás Pulido, et al. N Engl J Med 2013; 369:809-818

MACITENTANA

REAÇÕES ADVERSAS

Anemia: (13.2% versus 3.2%)
Cefaléia: (13.6% versus 8.8%)
Infecções respiratórias (15.3% versus 13.3%)
ITU (8.7% versus 5.6%)
Bronquite (11.6% versus 5.6%)
Influenza (5.8% versus 1.6%)
Trombocitopenia (5.0% versus 2.8%)
Alteração hepática (8.7% versus 14.5%)

Tomás Pulido, et al. N Engl J Med 2013; 369:809-818

CHEST- 1

Chronic Thromboembolic Pulmonary Hypertension Soluble Guanylate Cyclase–Stimulator Trial 1 (CHEST-1) is a randomized, double-blind, multinational, multicenter, placebo-controlled, phase 3 study.

***Inoperable and persistent/recurrent CTEPH after surgery in adults.**

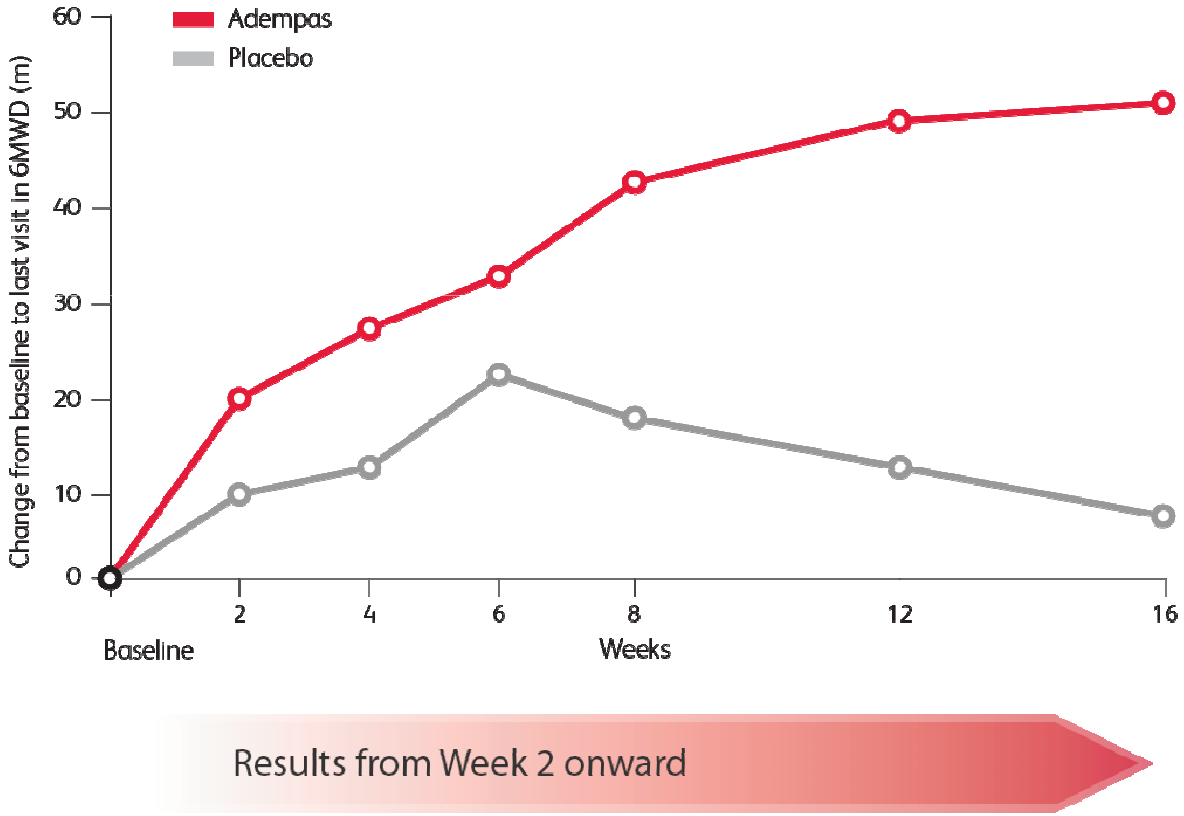
- **Dosing characteristics:**
  - Patients were initiated at 1.0 mg 3x a day
  - 77% were titrated to 2.5 mg 3x a day by Week 16
  - Adempas titrated every 2 weeks based on SBP and signs or symptoms of hypotension
- **Treatment characteristics:**
  - Concomitant medications: Stable dosages of oral anticoagulants, diuretics, digitalis, calcium channel blockers, and oxygen were allowed, but not NO donors, ERAs, PCAs, specific PDE-5 inhibitors (such as sildenafil, tadalafil, or vardenafil), and nonspecific PDE inhibitors (for example, dipyridamole or theophylline)
- **Baseline demographics:**
  - CTEPH: Inoperable for PEA† with PVR >300 dyn·sec·cm-5, mPAP >25 mm Hg measured at least 90 days after the start of full anticoagulation, or recurrent/persisting PH with PVR >300 dyn·sec·cm-5 measured at least 180 days following PEA
  - Mean age 59 years (range: 18-80)
  - CTEPH: Inoperable (72%), recurrent or persisting PH following PEA (28%)
  - WHO FC: II (31%); III (64%)
  - Mean 6MWD was 347m
  - Patients with SBP <95 mm Hg were excluded from study

Ghofrani A-H, et al. N *Engl J Med.* 2013;369(4):319-329

CHEST- 1

Chronic Thromboembolic Pulmonary Hypertension Soluble Guanylate Cyclase–Stimulator Trial 1 (CHEST-1) is a randomized, double-blind, multinational, multicenter, placebo-controlled, phase 3 study.
***Inoperable and persistent/recurrent CTEPH after surgery in adults.**

In CTEPH* (WHO Group 4): patients walked 46m farther at Week 16



143 riociguat patients (83%) had an improvement in 6MWD compared with 50 placebo patients (57%)

Ghofrani A-H, et al. N *Engl J Med.* 2013;369(4):319-329

CHEST- 1

Chronic Thromboembolic Pulmonary Hypertension Soluble Guanylate Cyclase–Stimulator Trial 1 (CHEST-1) is a randomized, double-blind, multinational, multicenter, placebo-controlled, phase 3 study.

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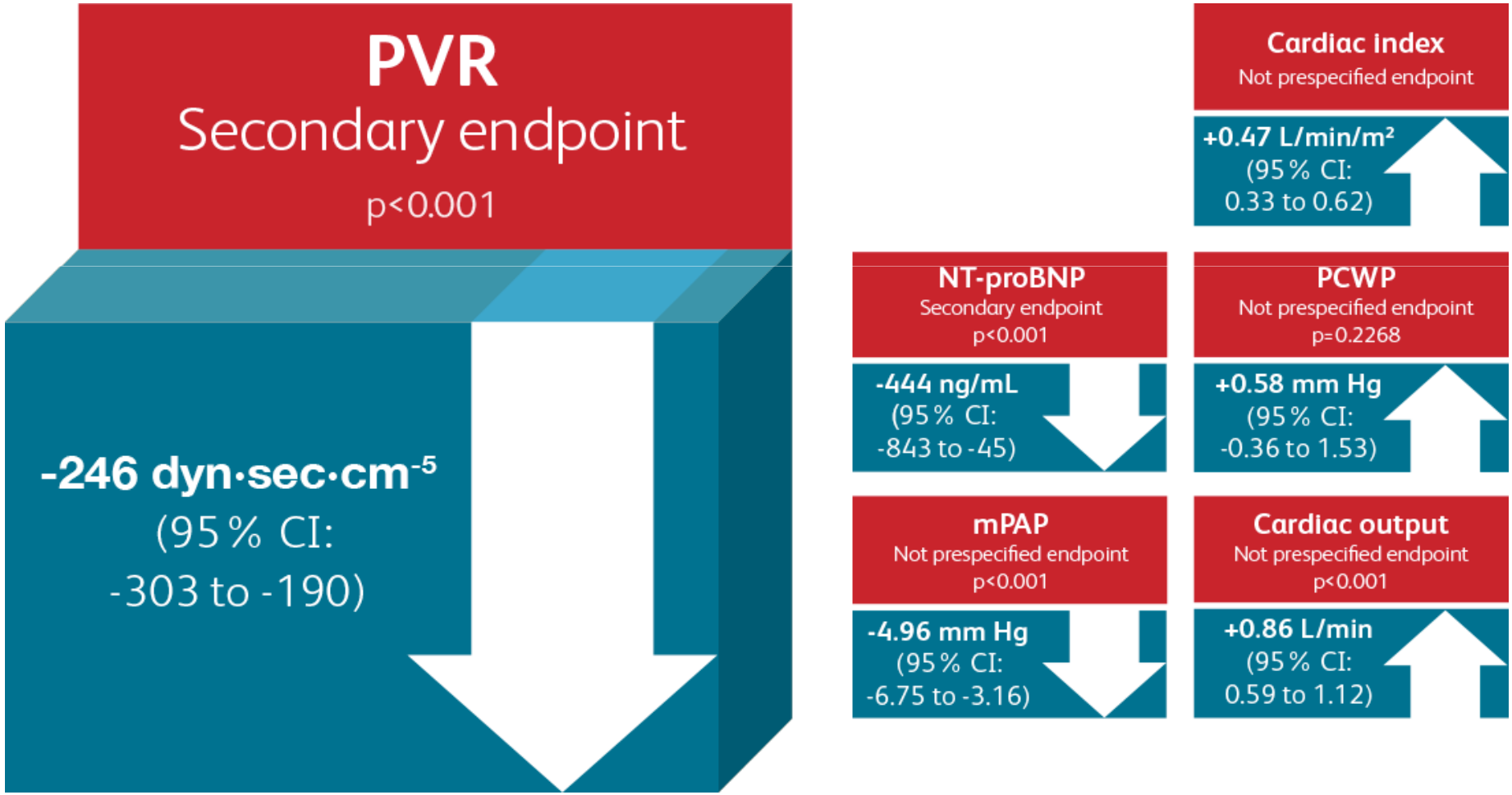


Ghofrani A-H, et al. N *Engl J Med.* 2013;369(4):319-329

Selexipag for the Treatment of Pulmonary Arterial Hypertension
GRIPHON

Estudo multicêntrico, duplo-cego, randomizado, de grupos paralelos, controlado por placebo, conduzido por evento.
1156 pacientes - 181 centros - 39 paises – dez 2009 a maio2013.
Placebo - 582 or selexipag - 574

HAP idiopatica, hereditária, HIV, droga ou toxina, DTC, Card cong.
CATE – no mínimo 05 WOOD (400 $dyn \cdot sec \cdot cm^{-5}$)
TC6M - 50 to 450 m.

Pacientes novos Tto ou com ERA e Inibidores da fosfodiesterase.

And Points:
- Morte
- Complicações:
  Eventos - hospitalização, Terapia EV, oxigenoterapia, septostomia e tramsplante pulmonar.
  Progressão doença - < 15 TC6M, Piora CF e + outra droga.

Selexipag: 200mcg – 1600 mcg 2 x dia - VO

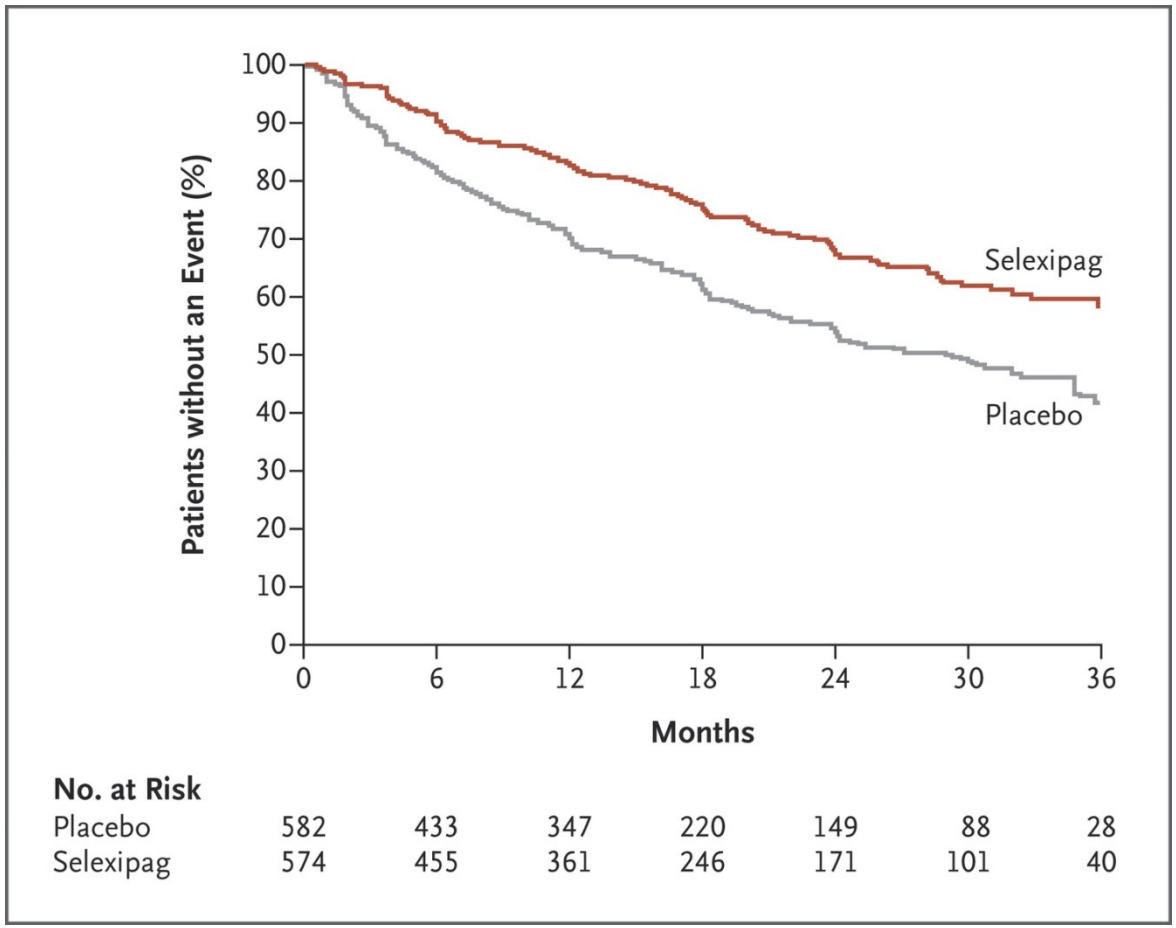
Olivier Sitbon, at al. N Engl J Med 2015; 373:2522-2533

Selexipag for the Treatment of Pulmonary Arterial Hypertension
GRIPHON

Baseline Characteristics	
Age	48 years
Female	80%
WHO Functional Class III	69%
Average 6 minute walk distance	353 meters
Background PAH treatments	20.4% none 14.7% ERA 32.4% PDE5i 32.5% ERA + PDE5i

Olivier Sitbon, at al. N Engl J Med 2015; 373:2522-2533

Kaplan–Meier curves for the primary composite end point of death (from any cause) or a complication related to pulmonary arterial hypertension



397 pacientes com eventos.

242 pacientes [41.6%] - placebo

155 pacientes [27.0%]- selexipag

Olivier Sitbon, at al. N Engl J Med 2015; 373:2522-2533

Selexipag for the Treatment of Pulmonary Arterial Hypertension
GRIPHON

Table 2. End Points Related to Pulmonary Arterial Hypertension and Death.*

End Point	Placebo (N=582)	Selexipag (N=574)	Hazard Ratio (99% or 95% CI)†	P Value‡
	no. of patients (%)			
Primary end point: composite of death or a complication related to PAH up to the end of the treatment period§				
All events	242 (41.6)	155 (27.0)	0.60 (0.46–0.78)	<0.001
Hospitalization for worsening of PAH	109 (18.7)	78 (13.6)		
Disease progression	100 (17.2)	38 (6.6)		
Death from any cause	18 (3.1)	28 (4.9)		
Initiation of parenteral prostanoid therapy or long-term oxygen therapy for worsening of PAH	13 (2.2)	10 (1.7)		
Need for lung transplantation or balloon atrial septostomy for worsening of PAH¶	2 (0.3)	1 (0.2)		
Secondary end point: death due to PAH or hospitalization for worsening of PAH up to the end of the treatment period§‖				
All events	137 (23.5)	102 (17.8)	0.70 (0.54–0.91)	0.003
Hospitalization for worsening of PAH	123 (21.1)	86 (15.0)		
Death due to PAH	14 (2.4)	16 (2.8)		
Secondary end point: death up to the end of the study‖**				
Death due to PAH	83 (14.3)	70 (12.2)	0.86 (0.63–1.18)	0.18
Death from any cause	105 (18.0)	100 (17.4)	0.97 (0.74–1.28)	0.42

Olivier Sitbon, at al. N Engl J Med 2015; 373:2522-2533

Table 3. Most Frequent Adverse Events and Abnormal Laboratory Results.*

Variable	Placebo (N=577)	Selexipag (N=575)	P Value
Adverse events — no.	3937	4607	
Patients with ≥1 adverse event — no. (%)	559 (96.9)	565 (98.3)	0.18
Patients with ≥1 serious adverse event — no. (%)†	272 (47.1)	252 (43.8)	0.26
Patients with adverse events leading to discontinuation of study agent — no. (%)	41 (7.1)	82 (14.3)	<0.001
Adverse event — no. of patients (%)‡			
Headache	189 (32.8)	375 (65.2)	<0.001
Diarrhea	110 (19.1)	244 (42.4)	<0.001
Nausea	107 (18.5)	193 (33.6)	<0.001
Pain in jaw	36 (6.2)	148 (25.7)	<0.001
Worsening of PAH	206 (35.7)	126 (21.9)	<0.001
Vomiting	49 (8.5)	104 (18.1)	<0.001
Pain in extremity	46 (8.0)	97 (16.9)	<0.001
Dyspnea	121 (21.0)	92 (16.0)	0.03
Myalgia	34 (5.9)	92 (16.0)	<0.001
Dizziness	85 (14.7)	86 (15.0)	0.93
Peripheral edema	104 (18.0)	80 (13.9)	0.06
Upper respiratory tract infection	80 (13.9)	75 (13.0)	0.73
Nasopharyngitis	63 (10.9)	75 (13.0)	0.28
Flushing	29 (5.0)	70 (12.2)	<0.001
Arthralgia	44 (7.6)	62 (10.8)	0.07
Cough	67 (11.6)	56 (9.7)	0.34
Fatigue	59 (10.2)	46 (8.0)	0.22
Right ventricular failure	58 (10.1)	46 (8.0)	0.26
Other adverse events and laboratory findings of interest — no. of patients (%)§			
Hyperthyroidism	0	8 (1.4)	0.004
Hypotension	18 (3.1)	29 (5.0)	0.10
Anemia	31 (5.4)	48 (8.3)	0.05
Syncope	51 (8.8)	37 (6.4)	0.15
Major bleeding event¶	12 (2.1)	14 (2.4)	0.70
Hemoglobin <8 g/dl‖	4 (0.7)	7 (1.3)	0.38

Olivier Sitbon, at al. N Engl J Med 2015; 373:2522-2533

THE LANCET
Respiratory Medicine

Combination therapy versus monotherapy for pulmonary arterial hypertension: a meta-analysis

Annie Christine Lajoie*, Gabriel Lauzière*, Jean-Christophe Lega, Yves Lacasse, Sylvie Martin, Serge Simard, Sebastien Bonnet†, Steeve Provencher†

Jan – 1990 a Maio – 2015
Piora clínica – and point
De 2017 estudos pesquisados - 17 (4095 patients)

A terapia combinada foi associada redução significativa do risco de piora clínica em relação à monoterapia.

- Terapia combinada 17% [332 de 1940 doentes]
- Vs monoterapia 28% [517 de 1862 doentes]
- Risco relativo [RR] 0,65 [95% IC 0 58-0 72], p <0 00001).

The Lancet -Volume 4, No. 4, p291–305, April 2016

Initial Use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension
AMBITION

Estudo duplo-cego, multricêntrico (120 centros, 14 países), randomizado, conduzido por evento – 500 pacientes

- 2: 1: 1 - 10 mg ambrisentan + 40mg tadalafila – combinado (253)
  10 mg ambrisentana – mono (126)
  40 mg tadalafila - mono (126)

Desfecho primário: primeiro evento de falência clínica
óbito – hospitalização – progressão doença – resposta clínica insatisfatória

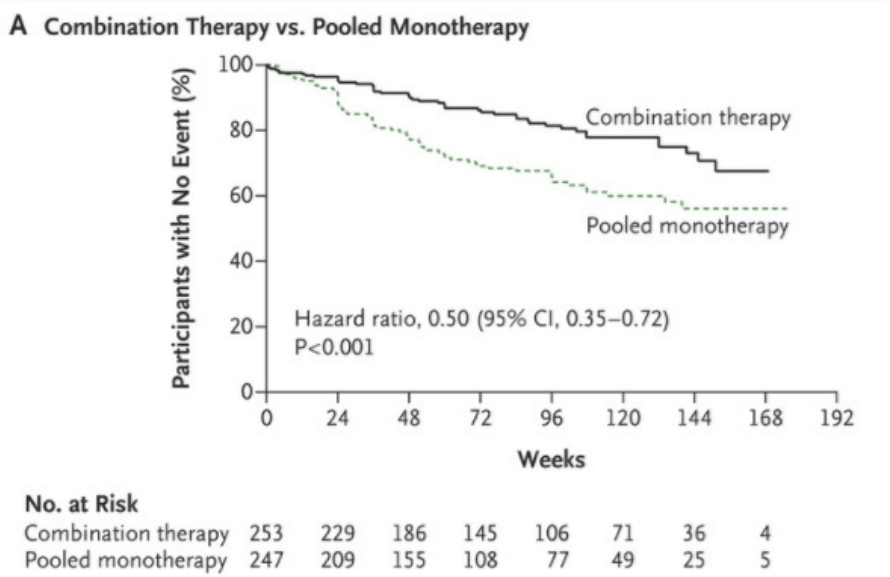
RESULTADOS:

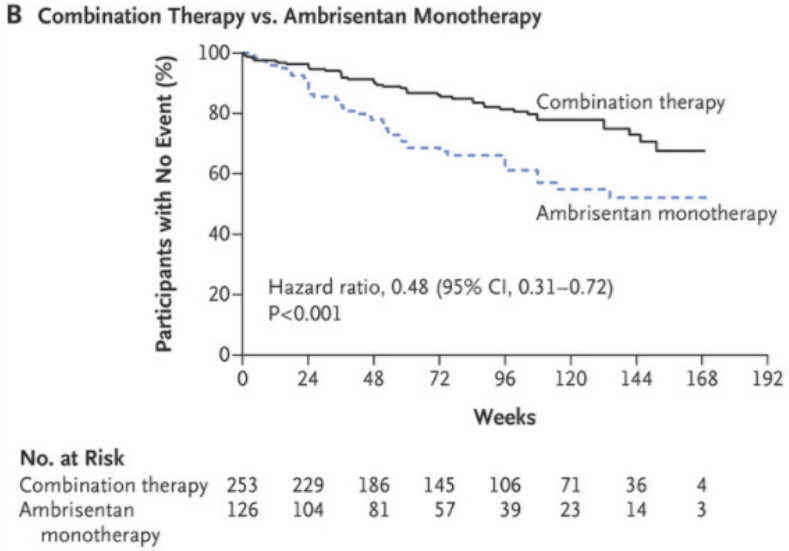
- 18%, 34%, e 28% (31% nos dois grupos de mono)
- HR 0.50 (95% confidence interval [CI], 0.35 to 0.72; P<0.001).

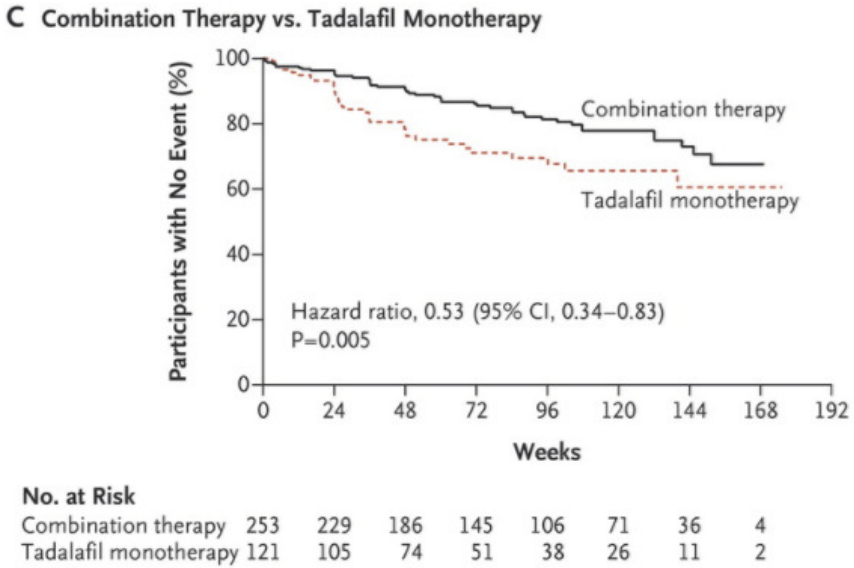
- Entre os pacientes com HAP sem tratamento prévio, a combinação inicial com ambrisentan e tadalafil resultou em um risco significativamente menor de eventos de falha clínica, quando comparados com ambrisentana ou tadalafila em monoterapia.

Nazzareno Galiè, at al. N Engl J Med 2015

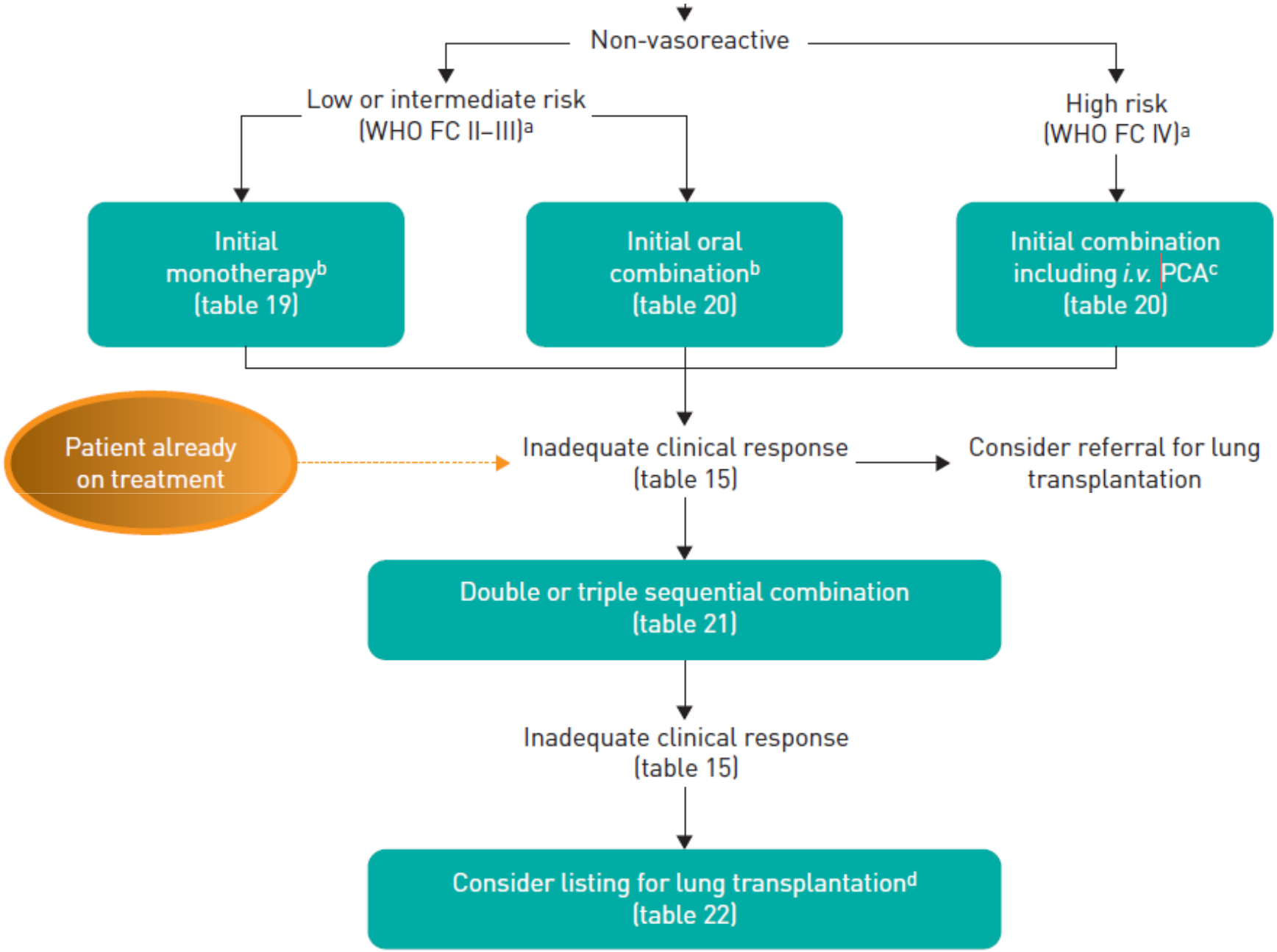
Initial Use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension







Nazzareno Galiè, at al. N Engl J Med 2015



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HAP – TERAPIA COMBINADA

TABLE 20 Recommendations for efficacy of initial drug combination therapy for pulmonary arterial hypertension (group 1) according to World Health Organization functional class. Sequence is by rating

Measure/treatment	Class[a]-Level[b]						Ref.[c]
	WHO-FC II		WHO-FC III		WHO-FC IV		
Ambrisentan + tadalafil[d]	I	B	I	B	IIb	C	[247]
Other ERA + PDE-5i	IIa	C	IIa	C	IIb	C	–
Bosentan + sildenafil + *i.v.* epoprostenol	–	–	IIa	C	IIa	C	[246]
Bosentan + *i.v.* epoprostenol	–	–	IIa	C	IIa	C	[198, 245]
Other ERA or PDE-5i + *s.c.* treprostinil			IIb	C	IIb	C	–
Other ERA or PDE-5i + other *i.v.* prostacyclin analogues			IIb	C	IIb	C	–

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HAP - Tratamento

- **Bosentan** (Tracleer 125 e 62,5 mg)
- Via Oral
- Metabolização Hepática (Citocromo P450)
- Efeitos colaterais:
    - Hepatotoxidade
    - Anemia, cefaleia, diarreia,
    - Edema
    - teratogênese
    - Pode reduzir efeito do anticoncepcional hormonal
    - Pode interferir na farmacocinética do Warfarina

HAP - Tratamento

- **SILDENAFIL** (Revatio 20 mg)
- Crianças/adolescentes (20 Kg): 10 mg 3x dia (0,75 – 1,5 mg/Kg/dose. 3 x dia
- VO
- Metabolização hepática (CYP3A4, P450 2C9)
- Uso de nitratos contra-indicado
- Efeitos colaterais:
  - Retinopatia (PDE6) – azul/verde
  - cefaleia / flushing
  - Epistaxis / parestesias
  - Dispepsia

Cost of Therapy With Orally Administered Or Inhaled PAH-Approved Agents

Drug	Usual Adult Maintenance Dose[9–17]	Cost[a]
Soluble guanylate cyclase (sGC) stimulator		
Riociguat (Adempas, Bayer)	2.5 mg by mouth three times daily	$9,270
Endothelin receptor antagonists		
Ambrisentan (Letairis, Gilead)	5–10 mg by mouth once daily	$8,272
Bosentan (Tracleer, Actelion)	125 mg by mouth twice daily	$9,126
Macitentan (Opsumit, Actelion)	10 mg by mouth once daily	$8,208
Phosphodiesterase type-5 (PDE-5) inhibitors		
Sildenafil (Revatio, Pfizer) (generic: multiple manufacturers)	20 mg by mouth three times daily	$2,751 $1,710[b]
Tadalafil (Adcirca, Eli Lilly)	40 mg by mouth once daily	$2,486
Prostanoids		
Iloprost (Ventavis, Actelion)	2.5–5 mcg/inhalation six to nine times per day	$21,049[c]
Treprostinil (Tyvaso, United Therapeutics)	Nine inhalations (54 mcg) four times daily	$15,622[d]
Treprostinil (Orenitram, United Therapeutics)	Oral dosing, individualized according to response[e]	$9,828[e]

[a]Cost is calculated for a 30-day supply unless otherwise specified. Cost is based on average wholesale price (AWP) at the usual ad
[b]The lowest AWP noted in Red Book Online is provided.
[c]Cost is based on 180 ampules of either the 10-mcg/mL or 20-mcg/mL ampule.
[d]Cost for a 28-day supply of the refill kit containing seven foil pouches each with four 2.9-mL ampules.
[e]The mean dose in a 12-week study was 3.4 mg twice daily.[17] Cost is based on a dose of 3.5 mg twice daily (2.5-mg and 1-mg tab

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P T. 2014 Nov; 39(11): 749-751, 755-758.

HIPERTENSÃO ARTERIAL PULMONAR

- Prolonga a sobrevida
- Melhora os sintomas
- Previne a progressão da doença
- Aumento o tempo para a piora clínica
- Avaliação dos grupos de riscos (SSc, mutação BMPR2 ou parentes, SCD, poHP)
- Terapia combinada

- **Endarterectomia**
- **Angioplastia pulmonar**

"A vida é curta,
a arte é longa,
a oportunidade é fugaz,
a experiência enganosa,
o julgamento difícil."

OBRIGADO!

Hipócrates, Aforismos, I,1 Apud SOUZA, A. Tavares, Curso de História da Medicina, Lisboa: Fund.Calouste Gulbenkian, 1981, p.56