Tratamento da Hipertensão Arterial Pulmonar

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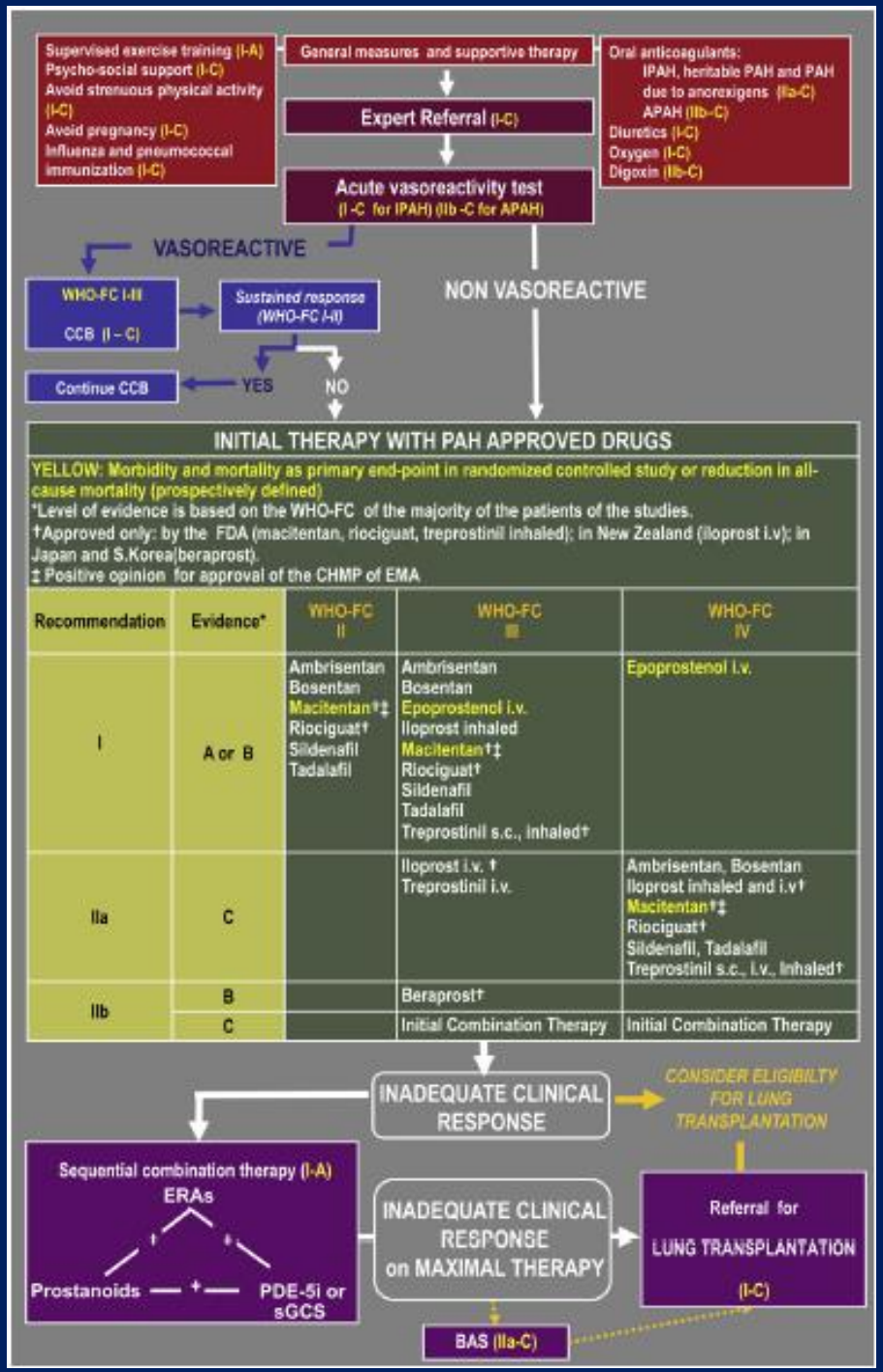
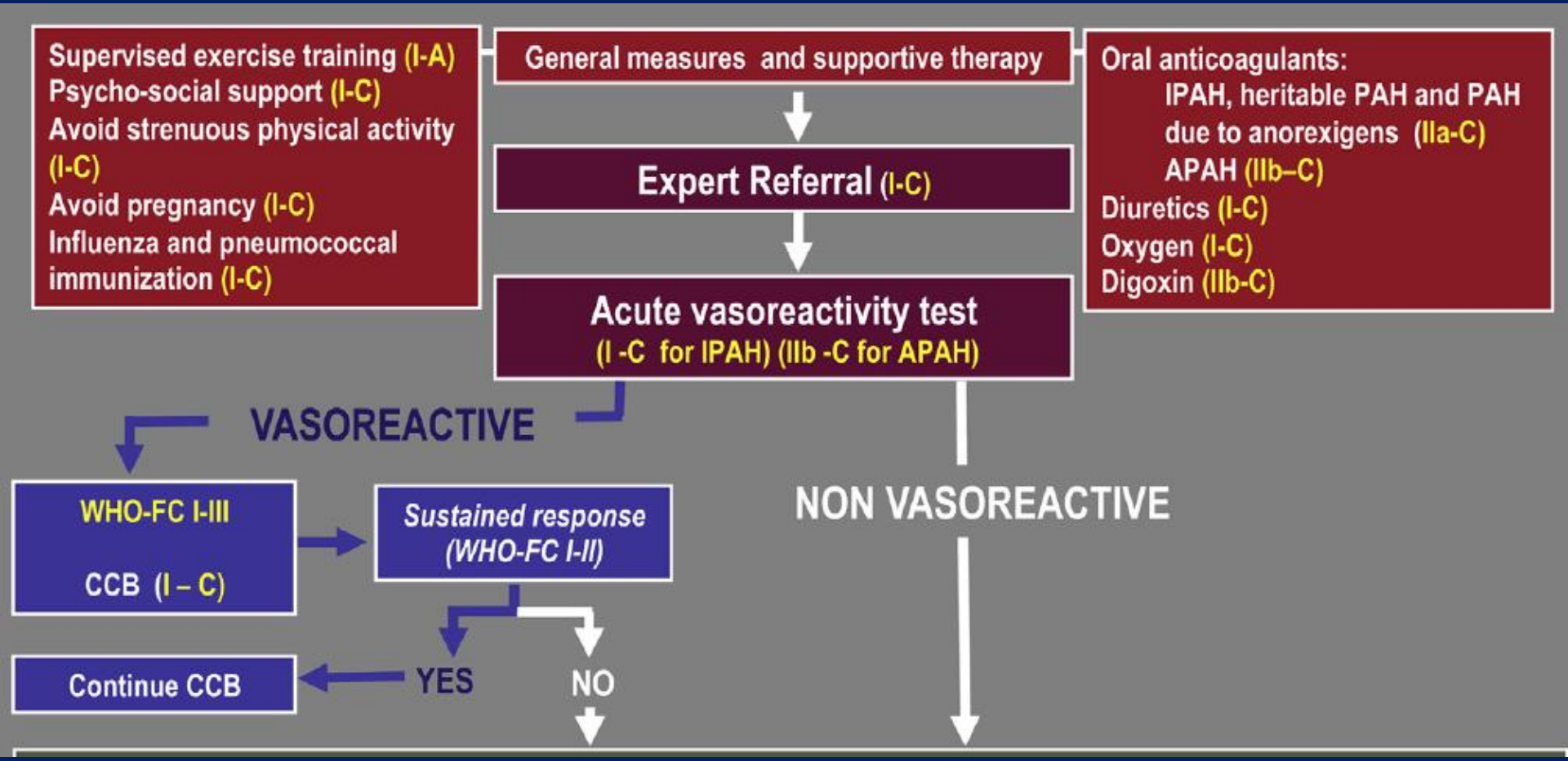


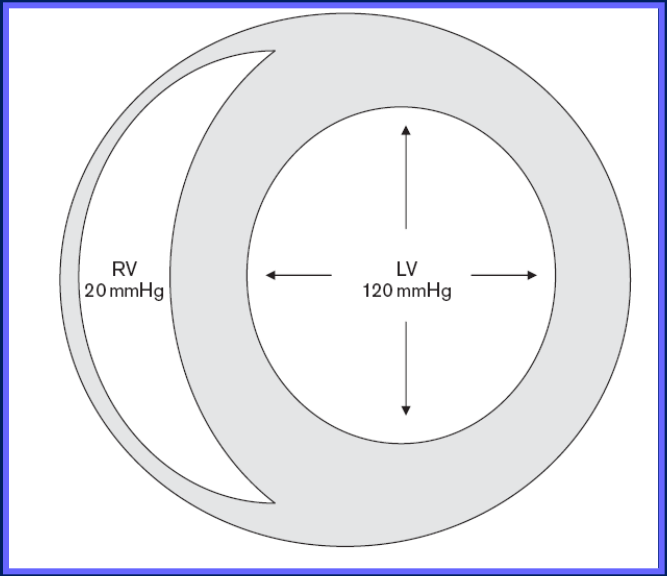
JACC 2013; 62:D60

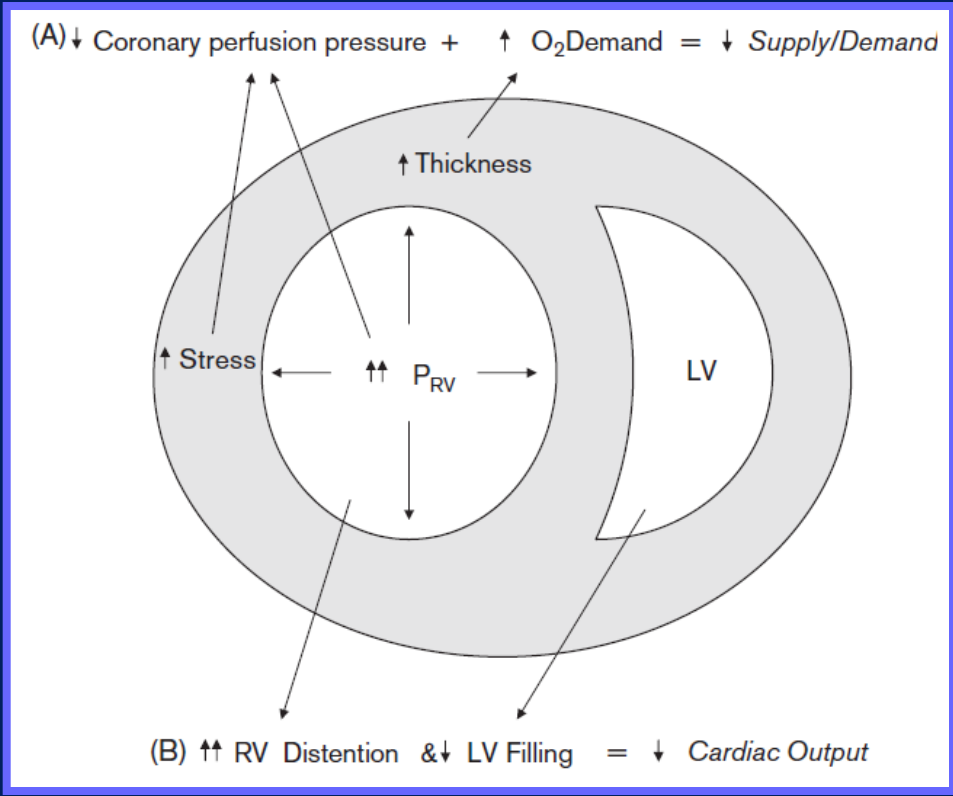


JACC 2013; 62:D60

Insuficiência de VD

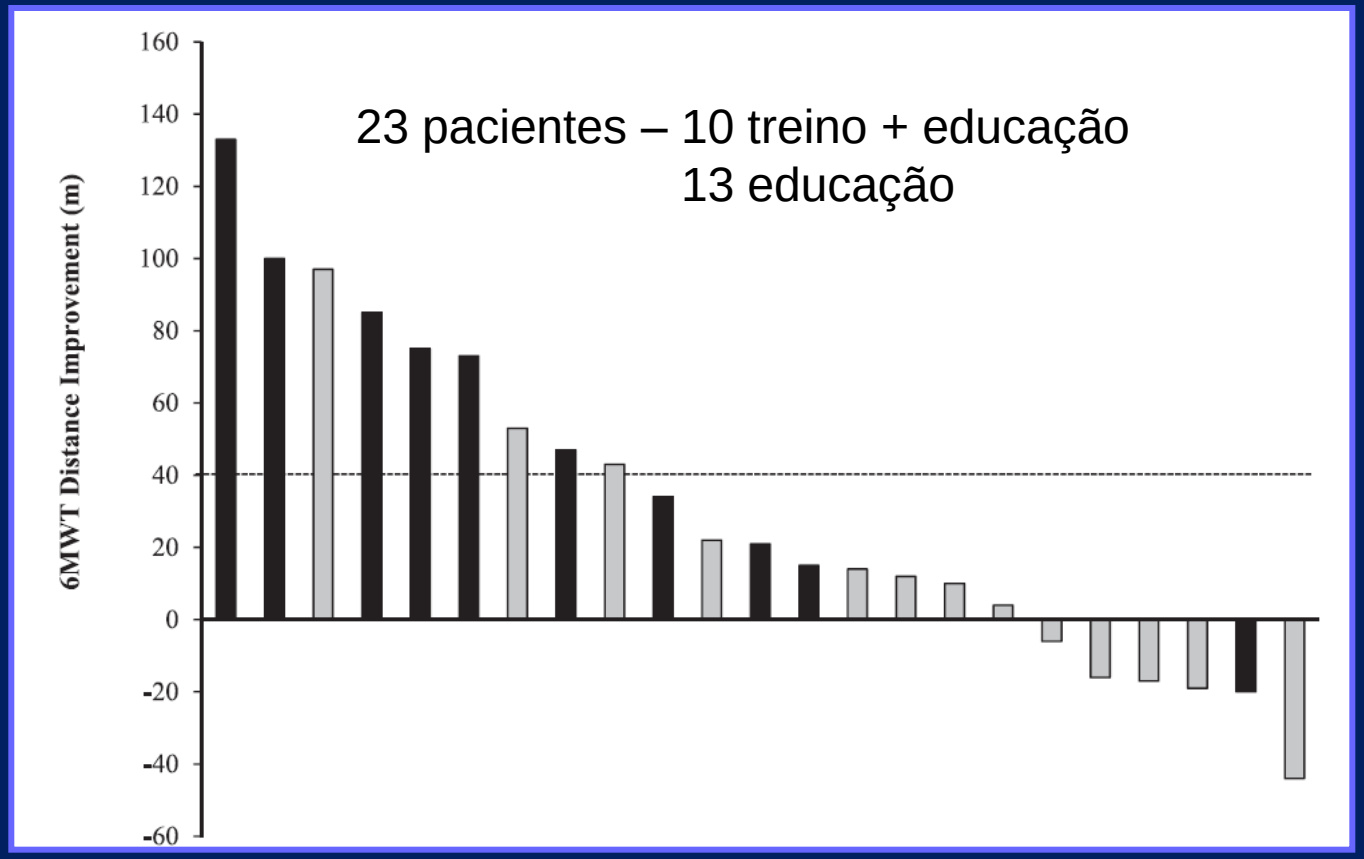
- Diuréticos
- Digital





Coron Artery Dis 2005; 16: 13

Reabilitação

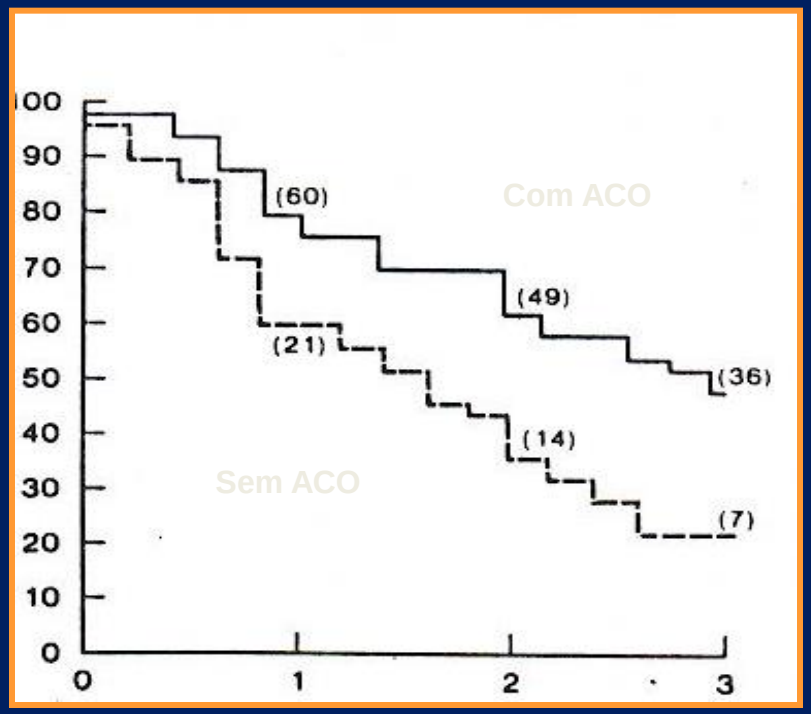


- Qualidade de vida

CHEST 2013; 143: 333

Fisiopatologia

Trombose *in situ*

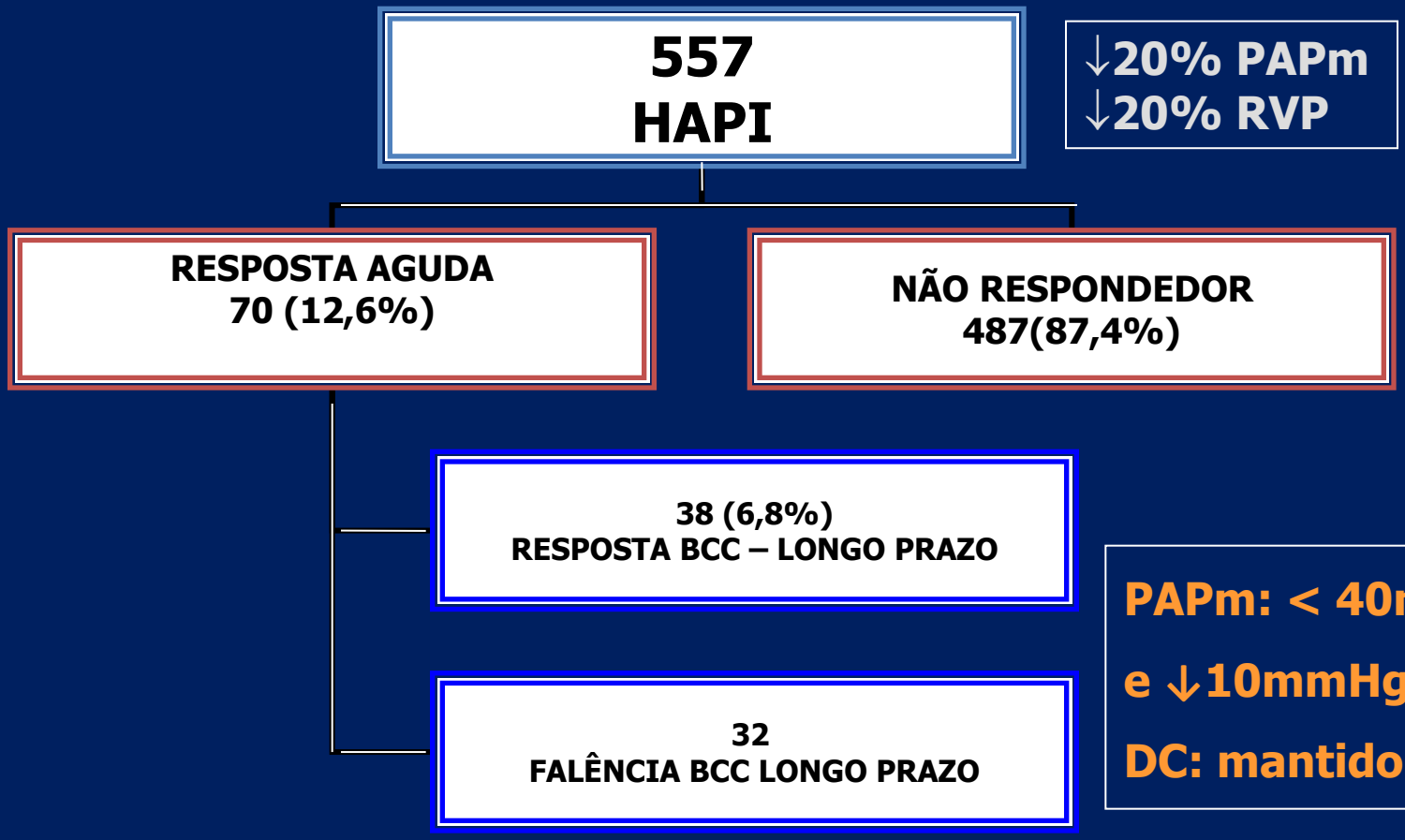


Clínica Mayo
Seguimento 120 pacientes
Mínimo 5 anos

Pacientes	
TROMBOSE	32 (57%)
ARTERIOPATIA	21 (38%)
VENOOCLUSIVA	3 (5%)

Circulation 1984;70:580

Critério de resposta x Benefício a longo prazo

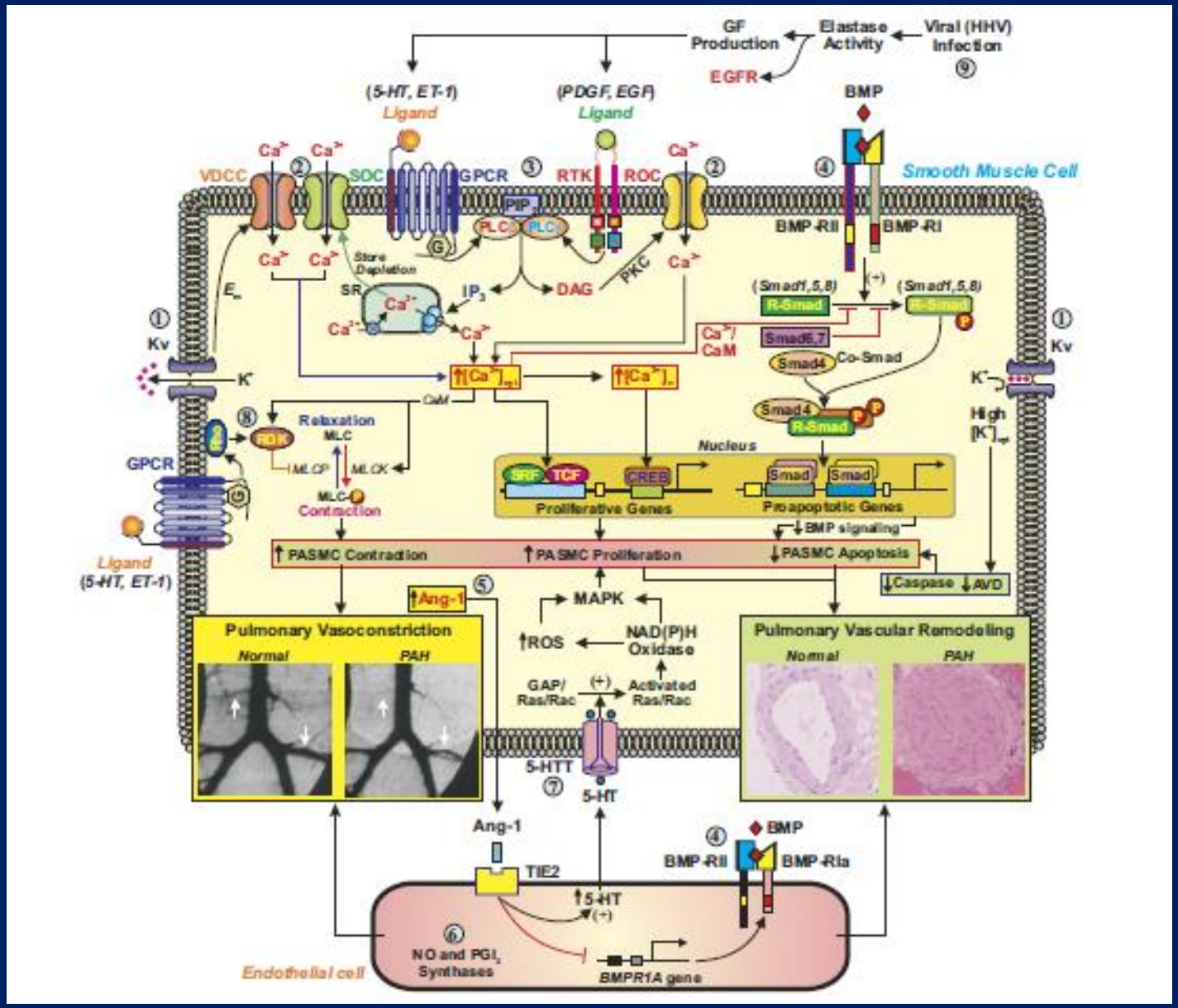


Sitbon O. et al. Circulation 2005

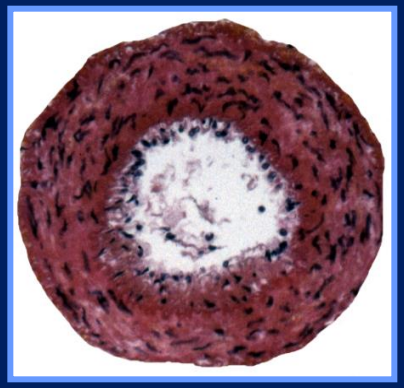
Benefício em longo prazo HAP

	Anorexígeno (n=127)	DTC (n168)	HPoP (n=153)	HIV (n=124)	CC (n=50)	DVOP/HP (n041)
Resposta aguda ↓ PAPm e RVP > 20%	17 (13,4)	17 (10,1)	2 (1,3)	2 (1,6)	0	5 (12,2)
Resposta longo prazo BCC (%entre respondedores agudos)	12 (70,6)	1 (5,8)	1 (50)	2 (100)	0	0
% resposta longo prazo BCC da população geral	9,4	0,6	0,7	1,6	0	0

ERJ 2010;31:1898



JACC 2009; 54, suppl



VIA ENDOTELINA

Pre-ET→ pro-ET

Antagonistas Receptor Endotelina

Endotelina 1-1

ET_A ET_B

\-

Vasoconstrição
Proliferação

VIA ÓXIDO NÍTRICO

L-arginina→ L-citruline

Òxido Nítrico

\-

cGMP *Vasodilatação*
Anti-proliferação

PDE5

Inibidor fosfodiesterase

VIA PROSTACICLINA

Ácido aracdonico → PgI_2

Prostaciclina (PgI_2)

Derivados da Prostaciclina

\+

cAMP *Vasodilatation*
anti-proliferation

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

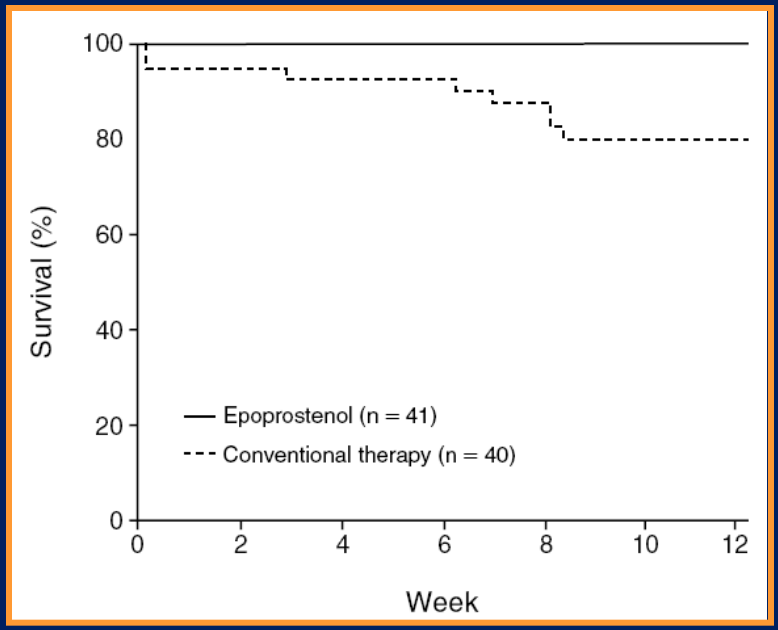
Recommendation	Evidence*	WHO-FC II	WHO-FC III	WHO-FC IV
I	A or B	Ambrisentan Bosentan Macitentan†‡ Riociguat† Sildenafil Tadalafil	Ambrisentan Bosentan Epoprostenol i.v. Iloprost inhaled Macitentan†‡ Riociguat† Sildenafil Tadalafil Treprostinil s.c., inhaled†	Epoprostenol i.v.
IIa	C		Iloprost i.v. †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

JACC 2013; 62:D60

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

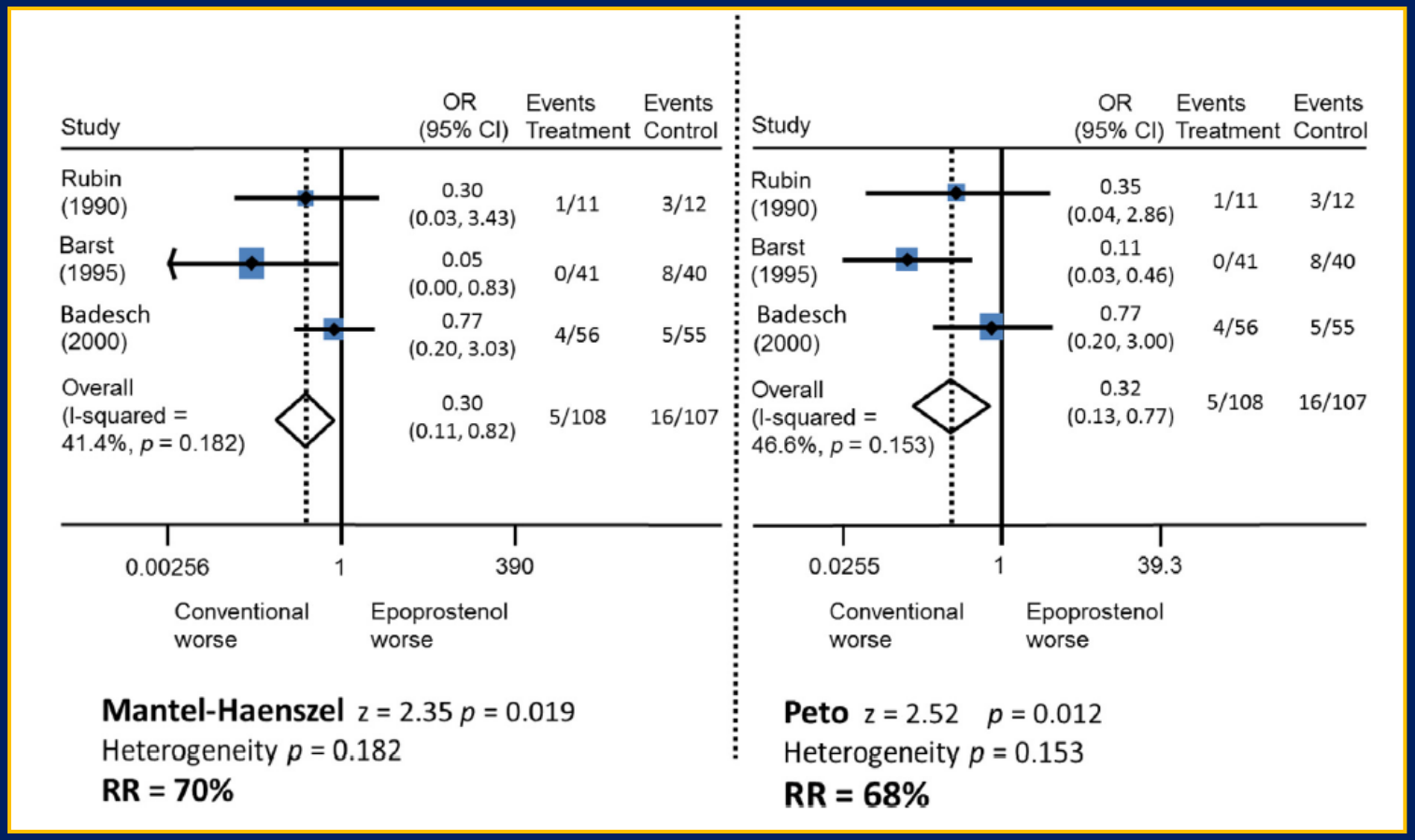
ROBYN J. BARST, M.D., LEWIS J. RUBIN, M.D., WALKER A. LONG, M.D., MICHAEL D. MCGOON, M.D., STUART RICH, M.D., DAVID B. BADESCH, M.D., BERTRON M. GROVES, M.D., VICTOR F. TAPSON, M.D., ROBERT C. BOURGE, M.D., BRUCE H. BRUNDAGE, M.D., SPENCER K. KOERNER, M.D., DAVID LANGLEBEN, M.D., CESAR A. KELLER, M.D.,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

- 80 pacientes c/ HAPi, WHO III e IV, 12 semanas
  - 6MWT: epoprostenol 315 → 362 (p<0,002)
    controle 270 → 204



NEJM 1996; 334:296-301

Epoprostenol

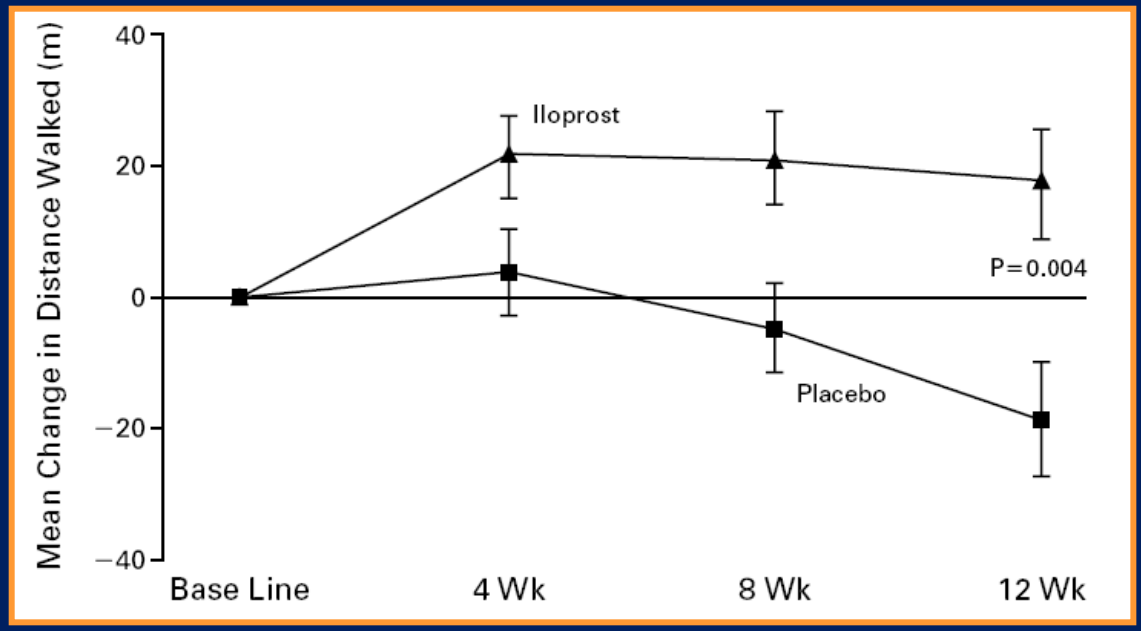


JACC 2013; 62:D60

INHALED ILOPROST FOR SEVERE PULMONARY HYPERTENSION

HORST OLSCHEWSKI, M.D., GERALD SIMONNEAU, M.D., NAZZARENO GALIÈ, M.D., TIMOTHY HIGENBOTTAM, M.D., ROBERT NAEIJE, M.D., LEWIS J. RUBIN, M.D., SYLVIA NIKKHO, M.D., RUDOLF SPEICH, M.D., MARIUS M. HOEPER, M.D., JÜRGEN BEHR, M.D., JÖRG WINKLER, M.D., OLIVIER SITBON, M.D., WLADIMIR POPOV, M.D., H. ARDESCHIR GHOFRANI, M.D., ALESSANDRA MANES, M.D., DAVID G. KIELY, M.D., RALPH EWERT, M.D., ANDREAS MEYER, M.D., PAUL A. CORRIS, F.R.C.P., MARION DELCROIX, M.D., MIGUEL GOMEZ-SANCHEZ, M.D., HARALD SIEDENTOP, DIPL.STAT., AND WERNER SEEGER, M.D., FOR THE AEROSOLIZED ILOPROST RANDOMIZED STUDY GROUP*

- 203 pacientes: HAPi, anorexígenos, colagenoses e CTEPH
- NYHA III e IV
- Dose: 2,5 – 5 mcg 6 a 9 vezes ao dia

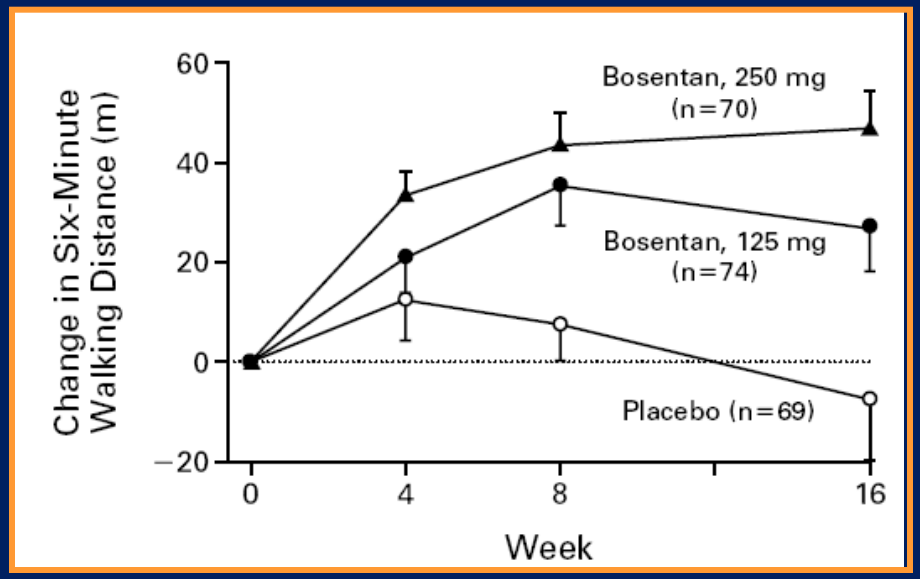


NEJM 2002; 347:322-9

BOSENTAN THERAPY FOR PULMONARY ARTERIAL HYPERTENSION

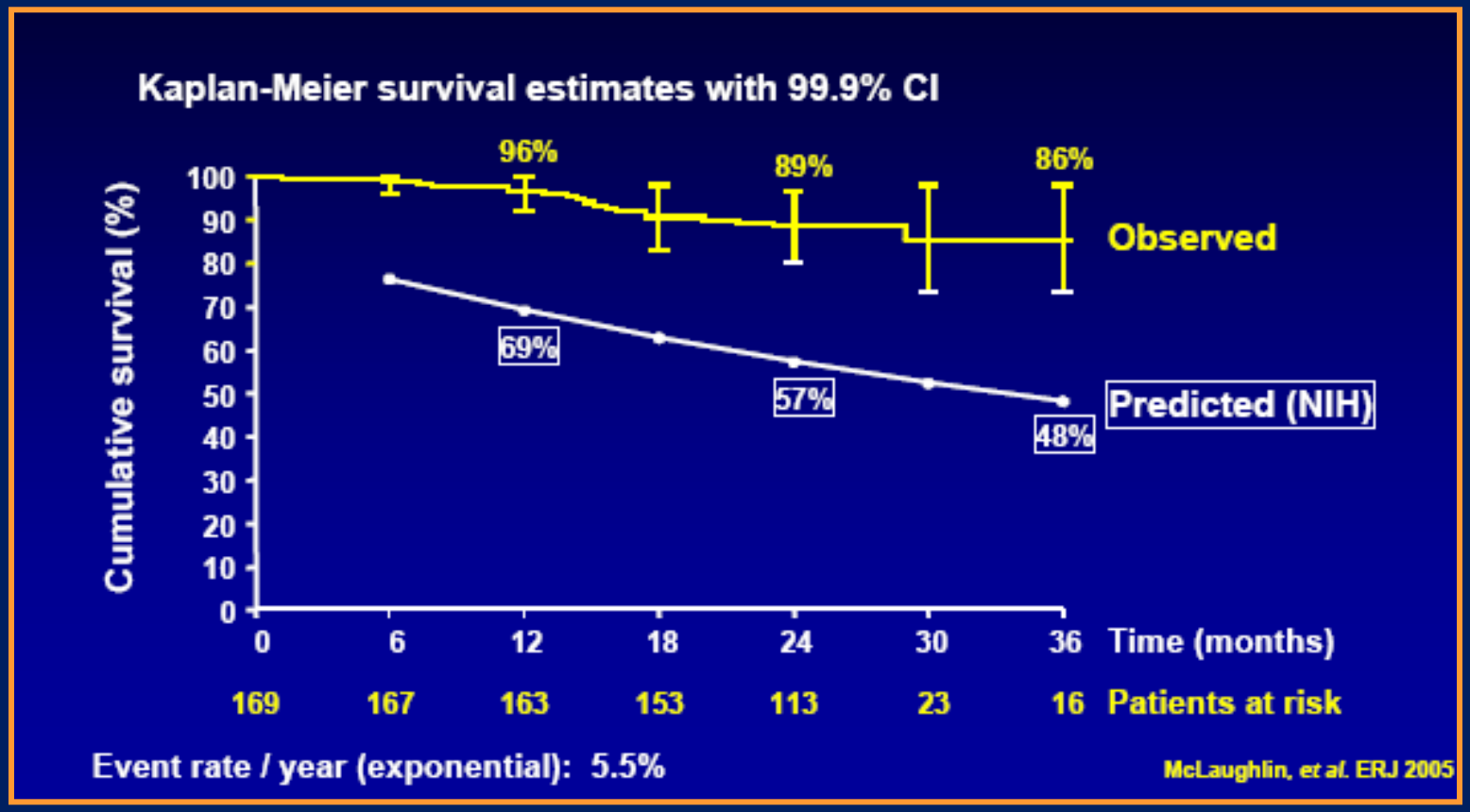
LEWIS J. RUBIN, M.D., DAVID B. BADESCH, M.D., ROBYN J. BARST, M.D., NAZZARENO GALIÈ, M.D., CAROL M. BLACK, M.D., ANNE KEOGH, M.D., TOMAS PULIDO, M.D., ADAANI FROST, M.D., SÉBASTIEN ROUX, M.D., ISABELLE LECONTE, PH.D., MICHAEL LANDZBERG, M.D., AND GÉRALD SIMONNEAU, M.D., FOR THE BOSENTAN RANDOMIZED TRIAL OF ENDOTHELIN ANTAGONIST THERAPY STUDY GROUP

- 213 pacientes, randomizado, duplo cego
- NYAH III/IV
- HAPi, colagenoses (havia pacientes com cardiopatias congênitas)



NEJM 2002;346:896-903

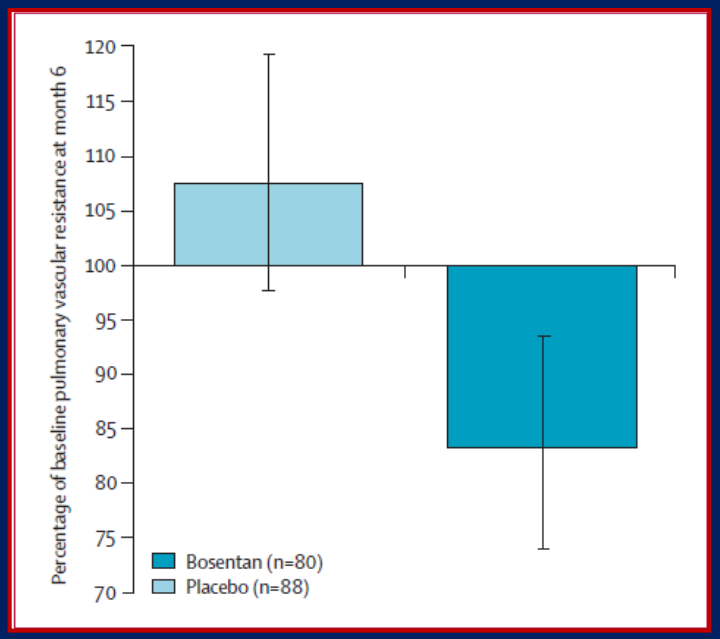
Bosentana – longo prazo

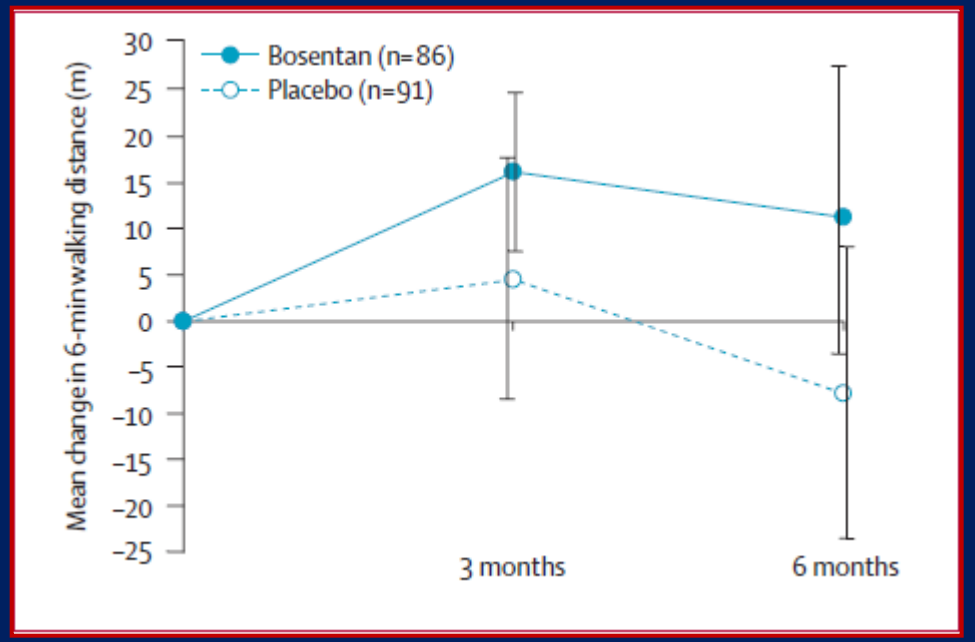


Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial

N Galiè, L J Rubin, M M Hoeper, P Jansa, H Al-Hiti, G M B Meyer, E Chiossi, A Kusic-Pajic, G Simonneau

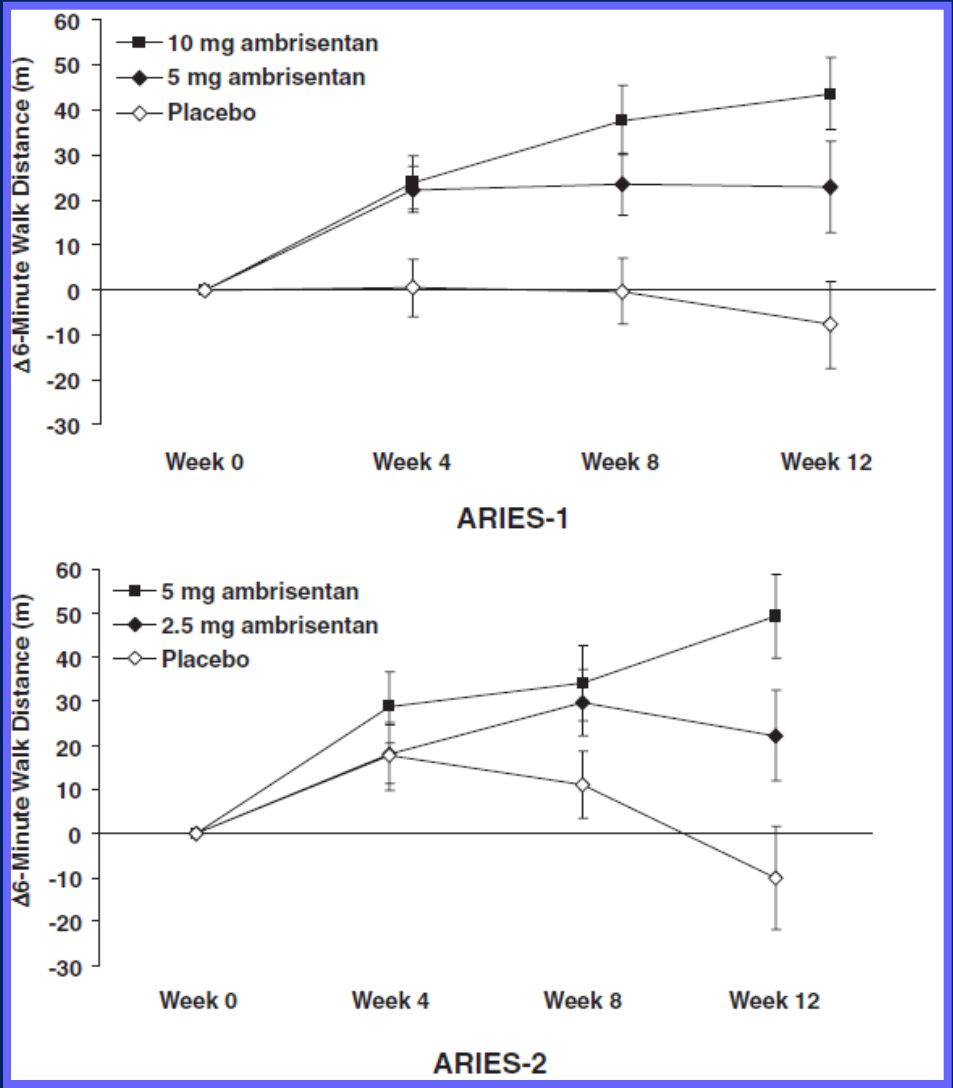
- 80 pacientes bosentan x 88 placebo em CF II





LANCET 2008;371: 2093

Ambrisentan



202 Pacientes – HAP
CF II e III

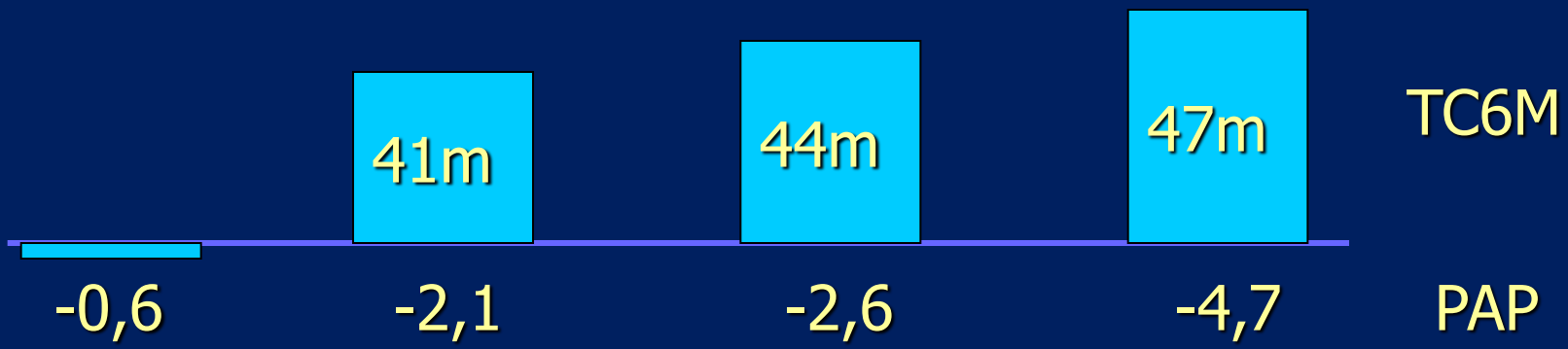
192 Pacientes – HAP
CF II e III

Circulation 2008; 117:3010

Sildenafil

278
HAPI, cardiopatia congênita, colagenose
NYHA I-II-III-IV

Placebo 68	20mg 3x/d 67	40mg 3x/d 65	80mg 3x/d 65

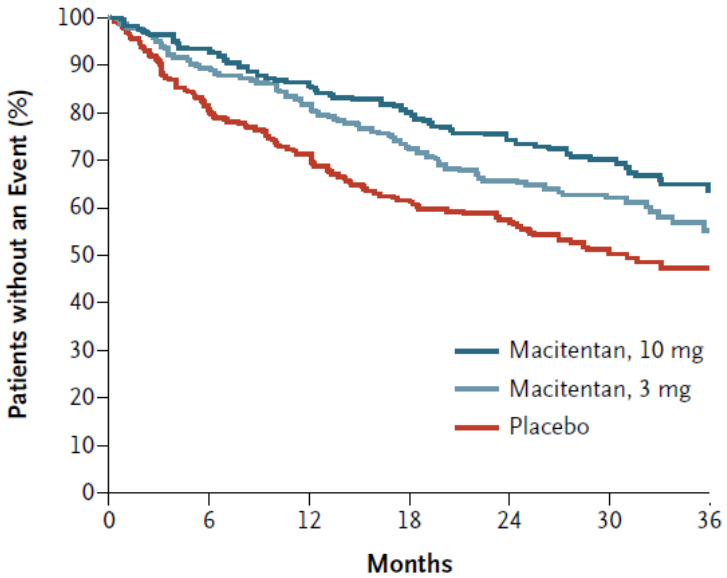


NEJM 2005;353:2148

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Macitentan and Morbidity and Mortality in Pulmonary Arterial Hypertension



No. at Risk

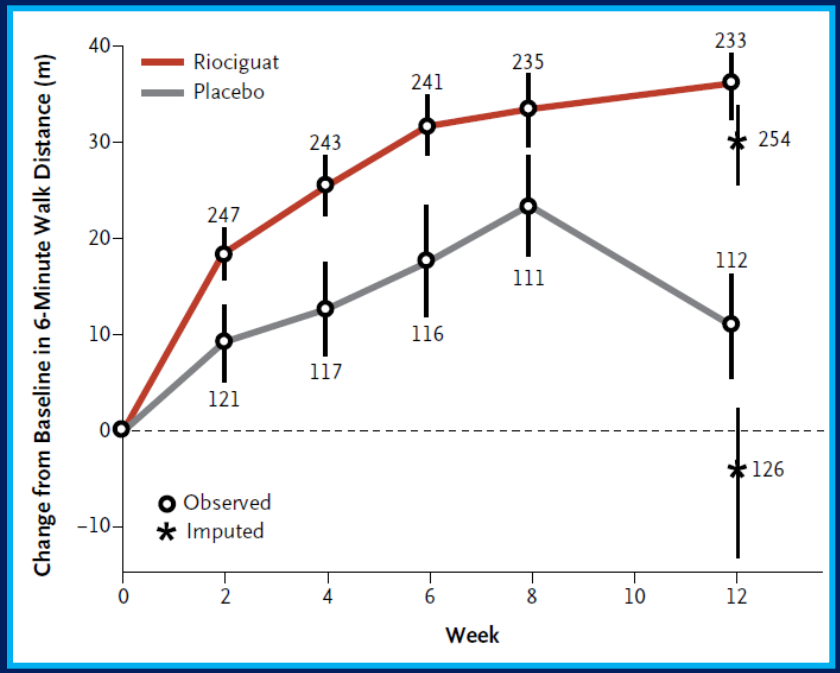
Placebo	250	188	160	135	122	64	23
Macitentan, 3 mg	250	213	188	166	147	80	32
Macitentan, 10 mg	242	208	187	171	155	91	41

NEJM 2013;369:809

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Riociguat for the Treatment of Pulmonary Arterial Hypertension



NEJM 2013;369:330

INITIAL THERAPY WITH PAH APPROVED DRUGS

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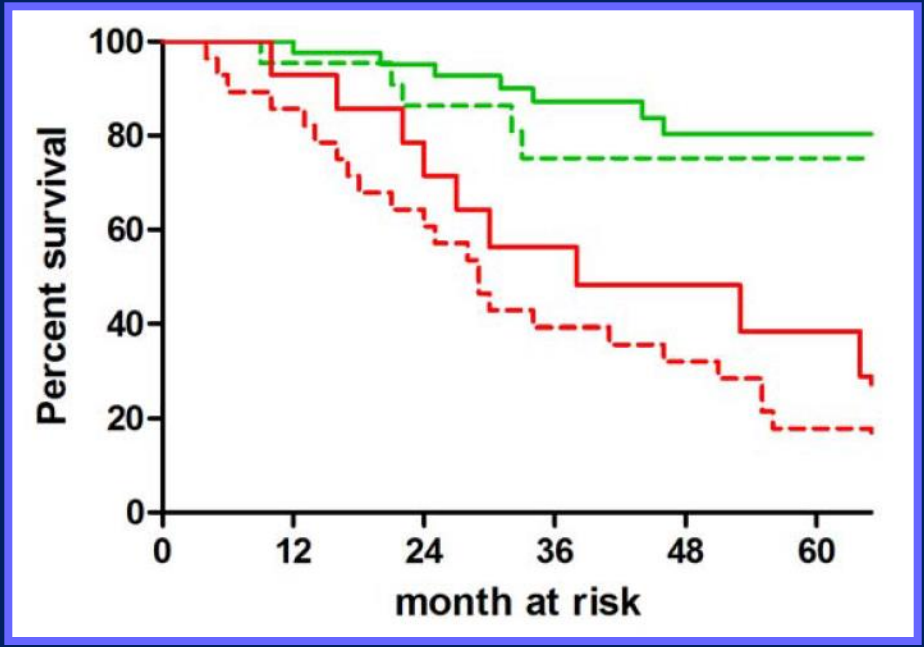
IIa	C		Iloprost i.v. † Treprostinil i.v.	Ambrisentan, Bosentan Iloprost inhaled and i.v† Macitentan†‡ Riociguat† Sildenafil, Tadalafil Treprostinil s.c., i.v., Inhaled†
IIb	B		Beraprost†	
	C		Initial Combination Therapy	Initial Combination Therapy

JACC 2013; 62:D60

Melhor prognóstico	Determinantes do prognóstico	Pior prognóstico
Não	Sinais clínicos de IVD	Sim
Lenta	Progressão da doença	Rápida
Não	Síncope	Sim
I,II	CF WHO	IV
>500m	TC6M	< 300m
Pico VO2 > 15mL/min/Kg	Ergoespiromatria	Pico VO2 < 12mL/min/Kg
Normal ou quase normal	BNP e NT-pró-BNP	Muito elevado e subindo
TAPSE > 2,0 cm Derrame pericárdico -	Ecocardiograma	TAPSE < 1,5 cm Derrame pericárdico +
PAD < 8 mmHg IC ≥ 2,5 L/min/m2	Hemodinâmica	PAD > 15mmHg IC ≤2,0 L/min/m2

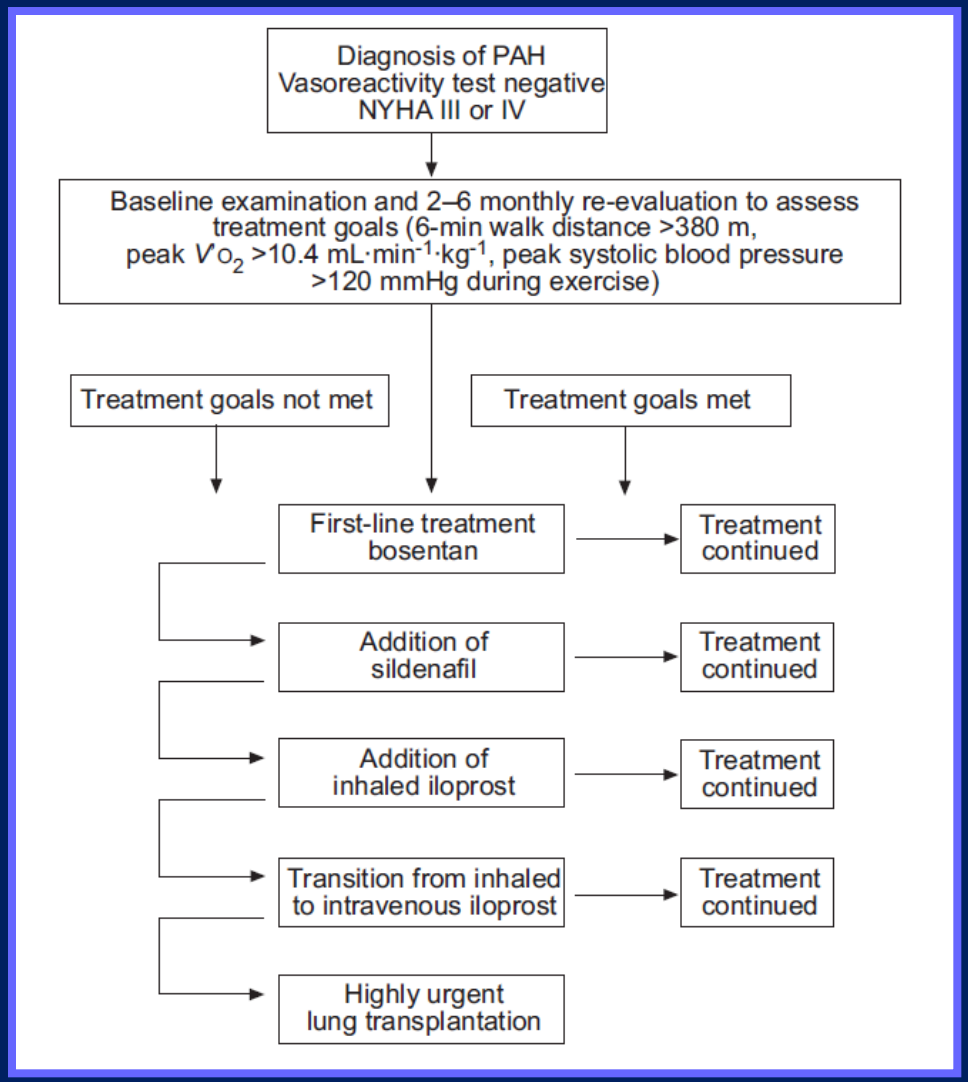
ERJ 2009

	Stable/satisfactory		Unstable/deteriorating	
	Group 1	**Group 2**	**Group 3**	**Group 4**
WHO functional class	WHO functional class I or II at baseline and during follow up	WHO functional class III-IV at baseline, WHO functional class I-II during follow up	WHO functional class I-II at baseline, WHO functional class III-IV during follow up	WHO functional class III-IV at baseline and during follow up
Cardiac index	CI ≥ 2.5 l/min/m^2 at baseline and during follow up	CI < 2.5 l/min/m^2 at baseline, but ≥ 2.5 during follow up	CI ≥ 2.5 l/min/m^2 at baseline, but <2.5 during follow up	CI < 2.5 l/min/m^2 at baseline and during follow up
SvO_2	SvO_2 ≥ 65% at baseline and during follow up	SvO_2 < 65% at baseline but ≥ 65 % during follow up	SvO_2 ≥ 65% at baseline, but < 65% during follow up	SvO_2 < 65% at baseline and during follow up
NT-proBNP	NT-proBNP < 1,800 ng/l at baseline and during follow up	NT-proBNP ≥ 1,800 ng/l at baseline, but < 1,800 ng/l during follow up	NT-proBNP < 1,800 ng/l at baseline, but ≥ 1,800 ng/l during follow up	NT-proBNP ≥ 1,800 ng/l at baseline and during folllow up



ERJ 2012; 39: 589

Tratamento combinado



Tratamento sequencial

x início com duas

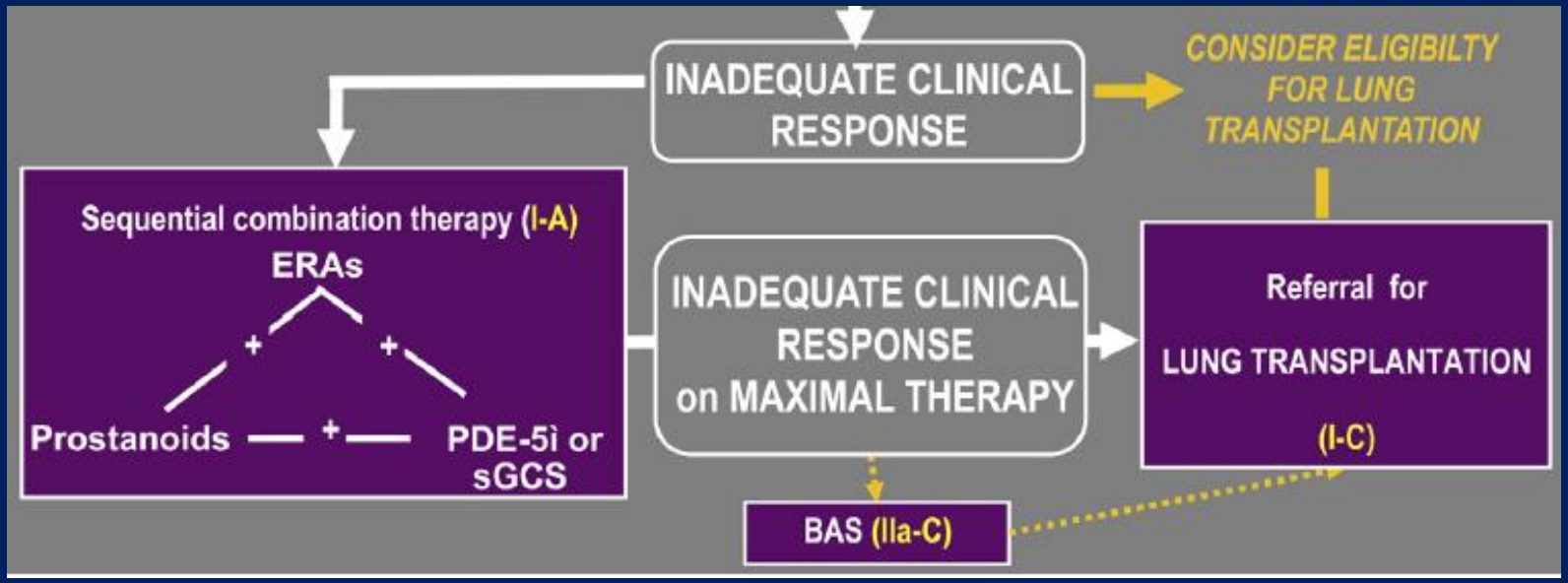
drogas concomitantes

ERJ 2012; 25: 858

Transplante de pulmão

- Pacientes em classe funcional III e IV
- Considerar para fila quando em terapêuica combinada

	1 year	5 years	10 years
Pittsburgh (Toyoda et al., 2008 [74])	86	75	66
Paris (Fadel et al., 2010 [75])	79	52	43
Toronto (de Perrot et al., 2012 [76])	78	60	45
Vienna (Klepetko, unpublished data, 2011)	73	71	—



JACC 2013; 62:D60