HIPERTENSION PULMONAR

Tratamientos no específicos

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Medidas generales

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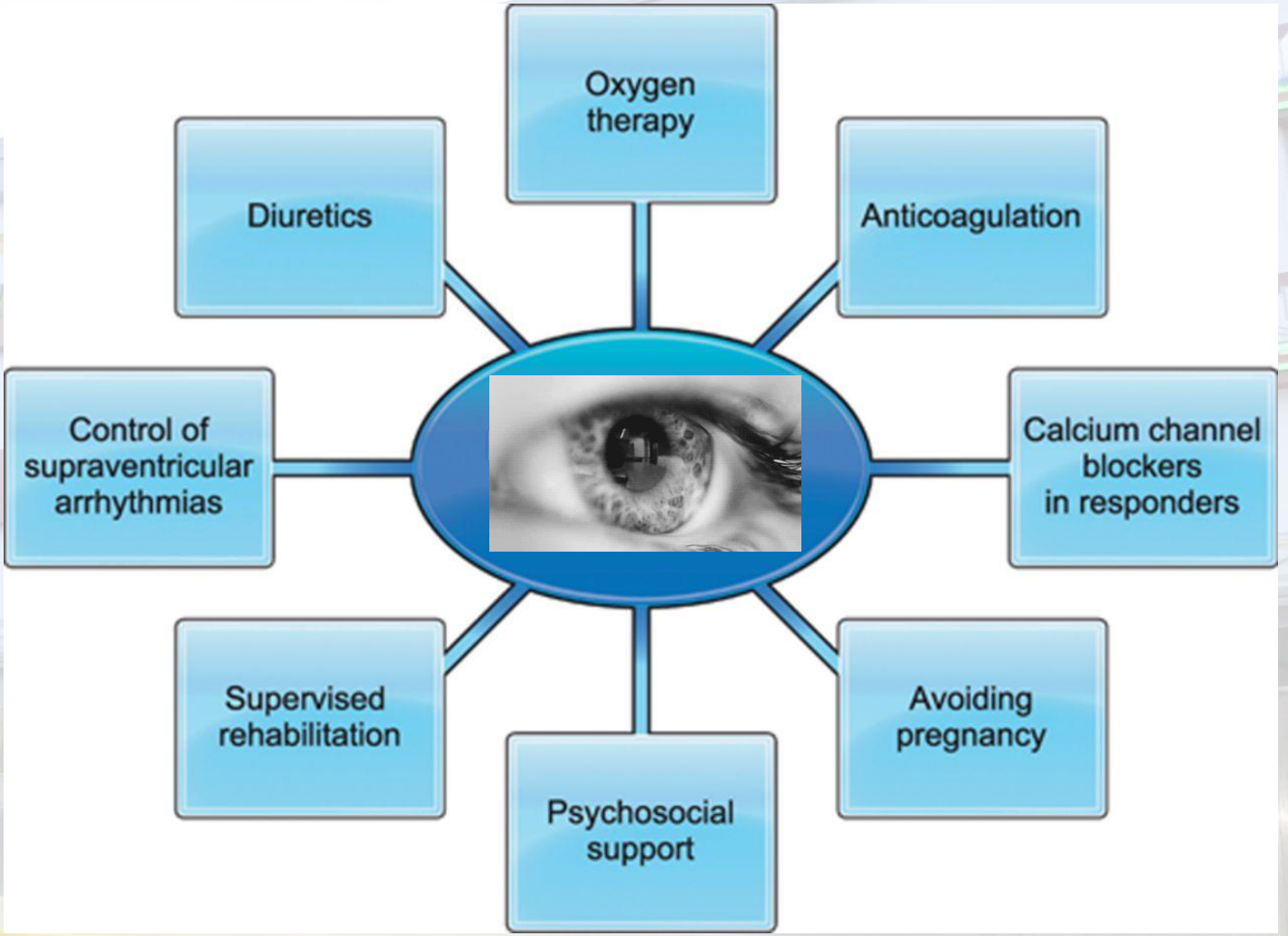
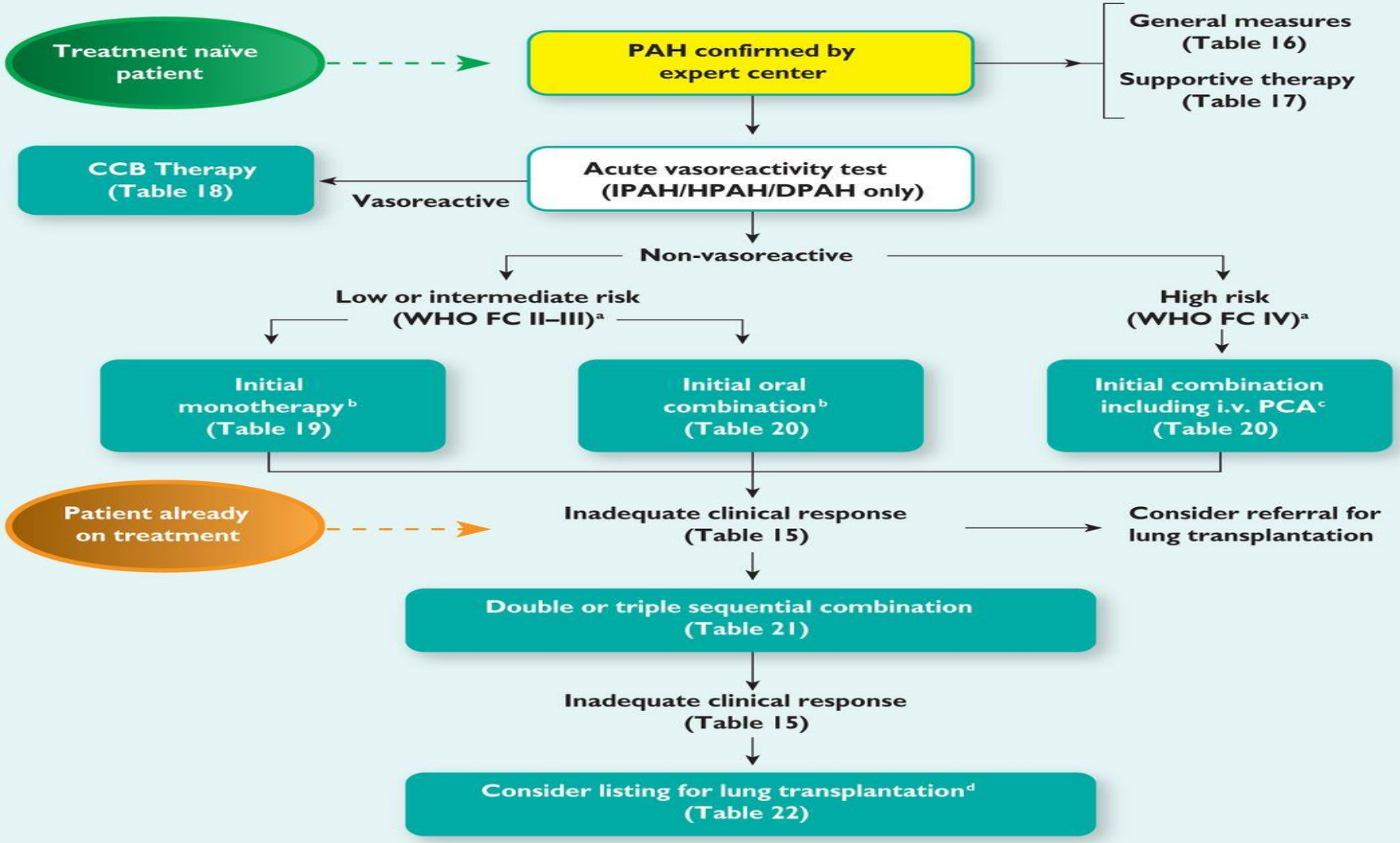
Basic measures and conventional therapies in PAH. The components of basic measures in the management of PAH are shown.



Humbert M et al. Circulation. 2014;130:2189-2208

Algorritmo de inicio terapeutico



CCB = calcium channel blockers; DPAH = drug-induced PAH; HPAH = heritable PAH; IPAH = idiopathic PAH; i.v. = intravenous; PAH = pulmonary arterial hypertension; PCA = prostacyclin analogues; WHO-FC = World Health Organization functional class.
[a]Some WHO-FC III patients may be considered high risk (see Table 13).
[b]Initial combination with ambrisentan plus tadalafil has proven to be superior to initial monotherapy with ambrisentan or tadalafil in delaying clinical failure.
[c]Intravenous epoprostenol should be prioritised as it has reduced the 3 months rate for mortality in high risk PAH patients also as monotherapy.
[d]Consider also balloon atrial septostomy.

Authors/Task Force Members: et al. Eur Heart J 2015;eurheartj.ehv317

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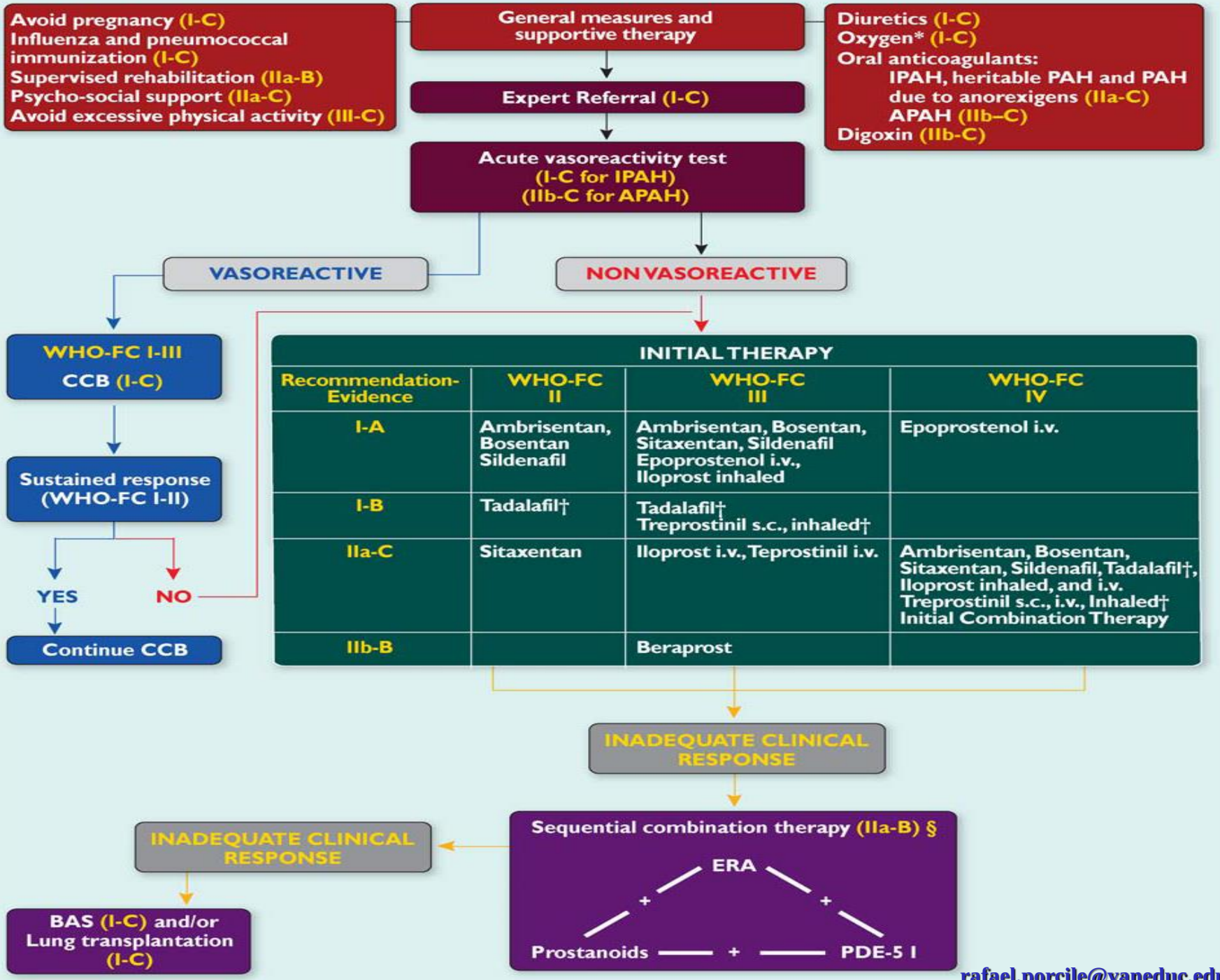

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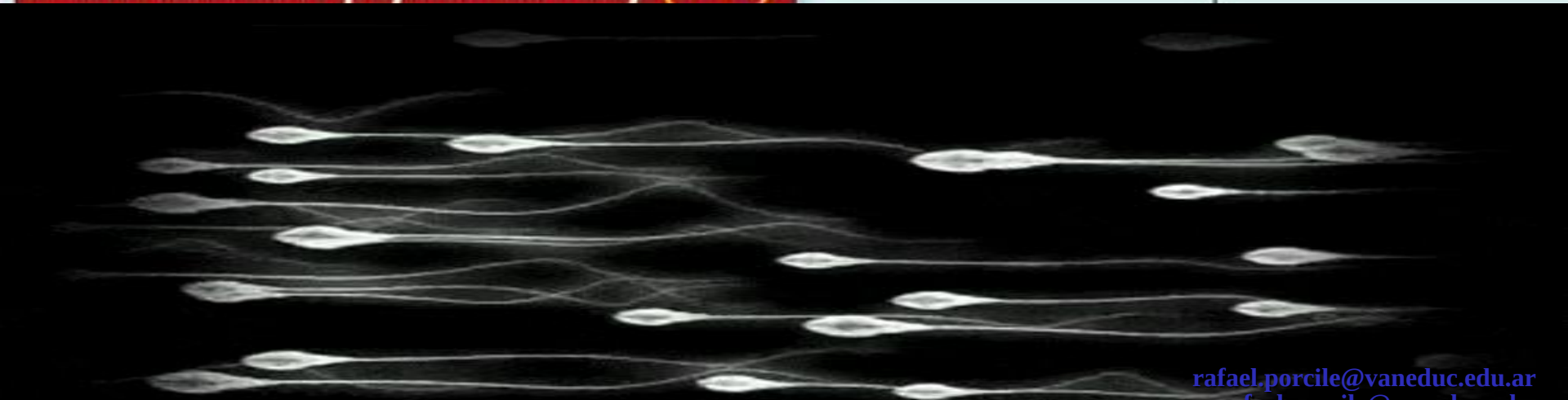
Medidas generales

Avoid pregnancy (I-C)
Influenza and pneumococcal immunization (I-C)
Supervised rehabilitation (IIa-B)
Psycho-social support (IIa-C)
Avoid excessive physical activity (III-C)

General measures and supportive therapy

Expert Referral (I-C)



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Medidas generales

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General measures and supportive therapy

Expert Referral (I-C)

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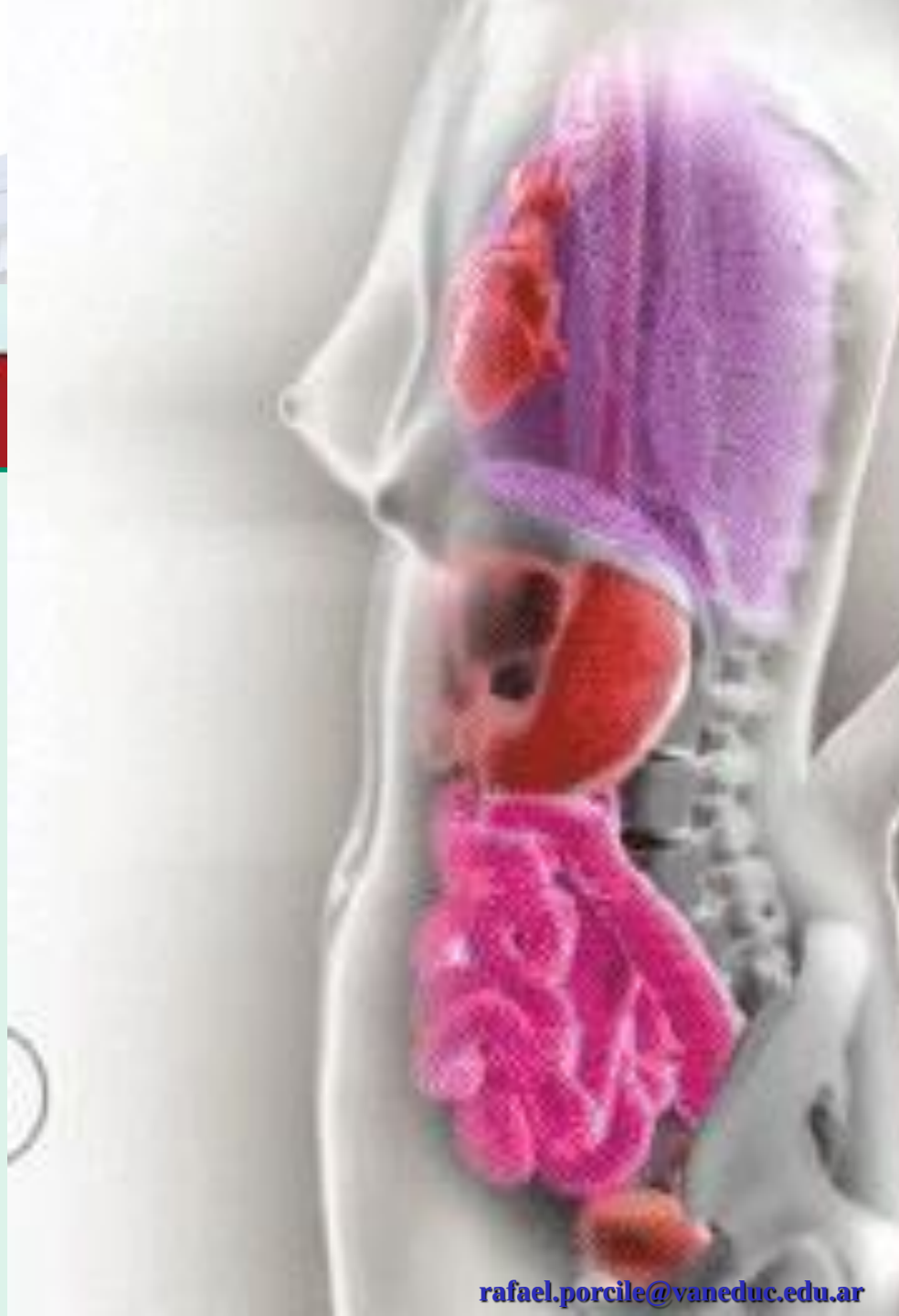
Medidas generales

Avoid pregnancy (I-C)

Los cambios hemodinámicos del embarazo comportan

1) **Aumento de la volemia**
2) **Aumento de la PVC**
3) **Reducción de la precarga del VD por compresión cava**
4) **Reducción de la capacidad pulmonar**
5) **Estatus pro coagulante de la progesterona**



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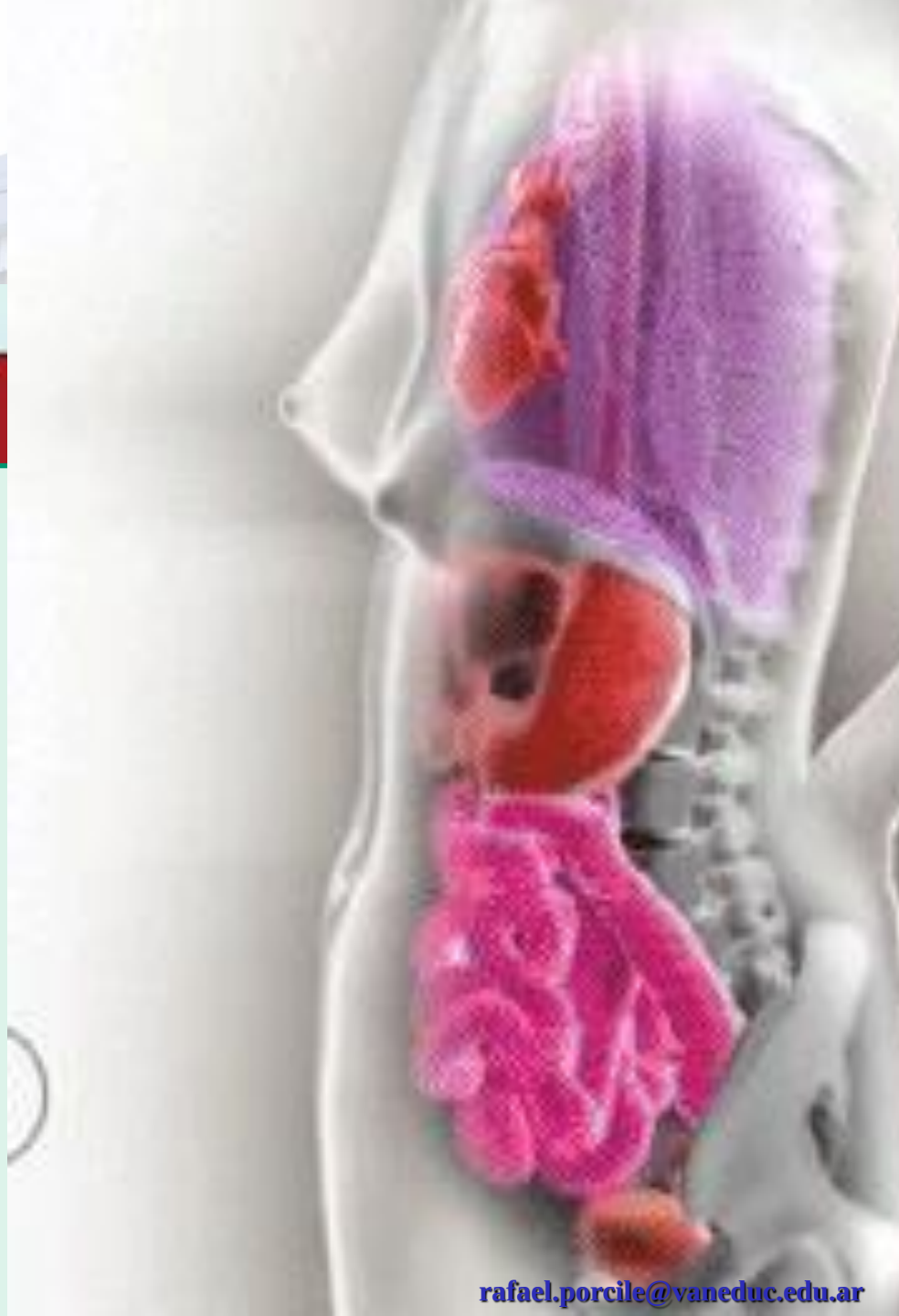
Medidas generales

Avoid pregnancy (I-C)

La mortalidad de las pacientes gestantes con hipertensión pulmonar aumenta entre el 12 al 17% por encima de la basal marcada por su CF



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Medidas generales

Barrera+ hormonar

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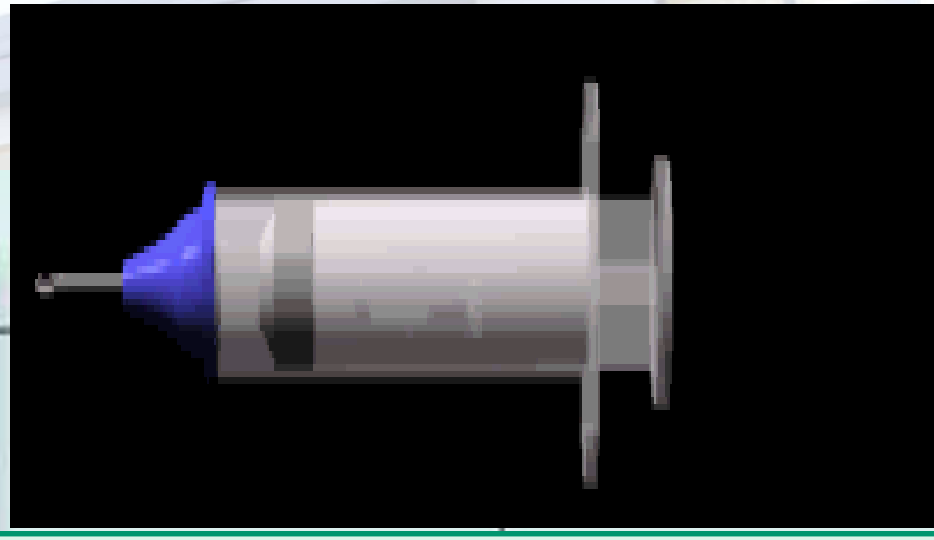
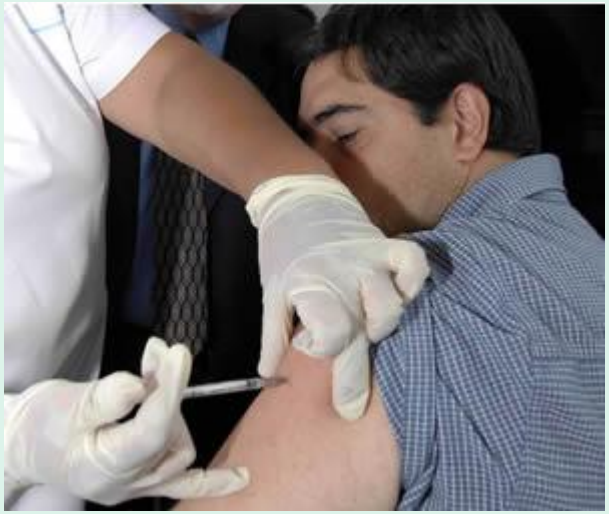
VACUNACIÓN

Avoid pregnancy (I-C)
Influenza and pneumococcal immunization (I-C)





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EJERCICIO

Avoid pregnancy (I-C)
Influenza and pneumococcal immunization (I-C)
Supervised rehabilitation (IIa-B)
Psycho-social support (IIa-C)
Avoid excessive physical activity (III-C)

No debe ser contraindicado el ejercicio aeróbico
No cualquier tipo de actividad física en cualquie condición
Debe ser rehabilitación supervisada programada

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General measures and supportive therapy

Expert Referral (I-C)

Diuretics (I-C)
Oxygen* (I-C)
Oral anticoagulants:
IPAH, heritable PAH and P
due to anorexigens (IIa-C)
APAH (IIb–C)
Digoxin (IIb-C)

Anticoagulación

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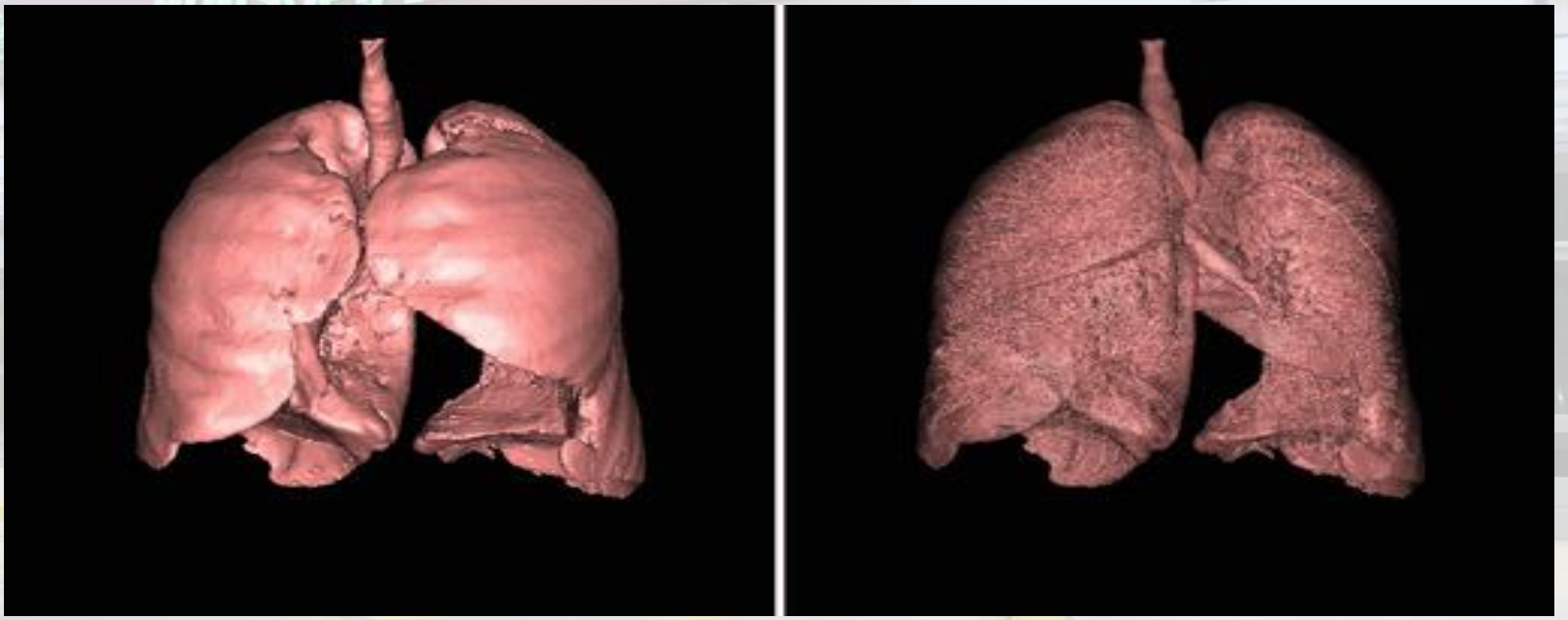
ANTICOAGULACIÓN EN HIPERTENSION PULMONAR

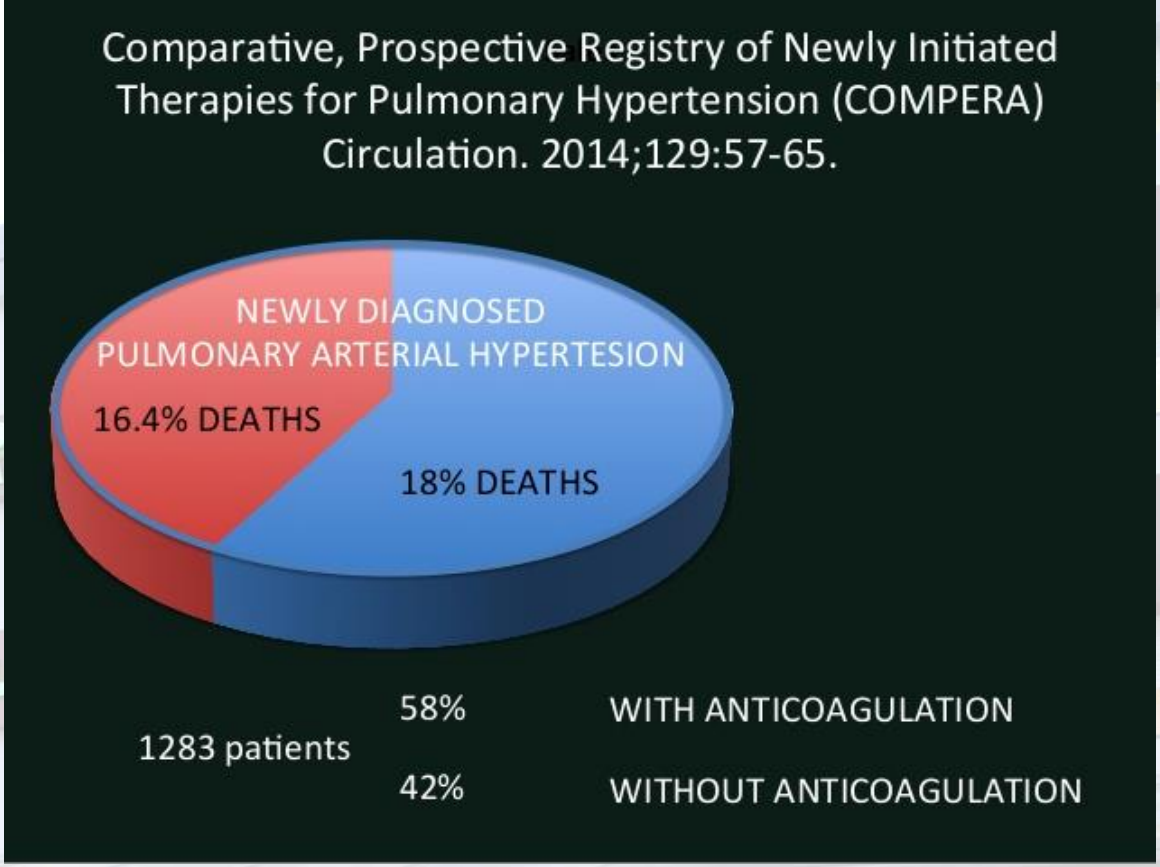


Anticoagulation and Survival in Pulmonary Arterial Hypertension Results From the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA)

Circulation. 2014 Jan 7;129(1):57-65.

Glob Cardiol Sci Pract. 2014 Jun 18;2014(2):10.5339/gcsp.2014.25. eCollection 2014.

Anticoagulation in pulmonary arterial hypertension: Contemporary data from COMPERA registry



The results of lend support to current recommendations for thCOMPERA e use of anticoagulant therapy in patients with idiopathic PAH, but not in other forms of PAH. Also, the study confirmed the previously reported concern that anticoagulant therapy may be harmful in patients with scleroderma-associated PAH

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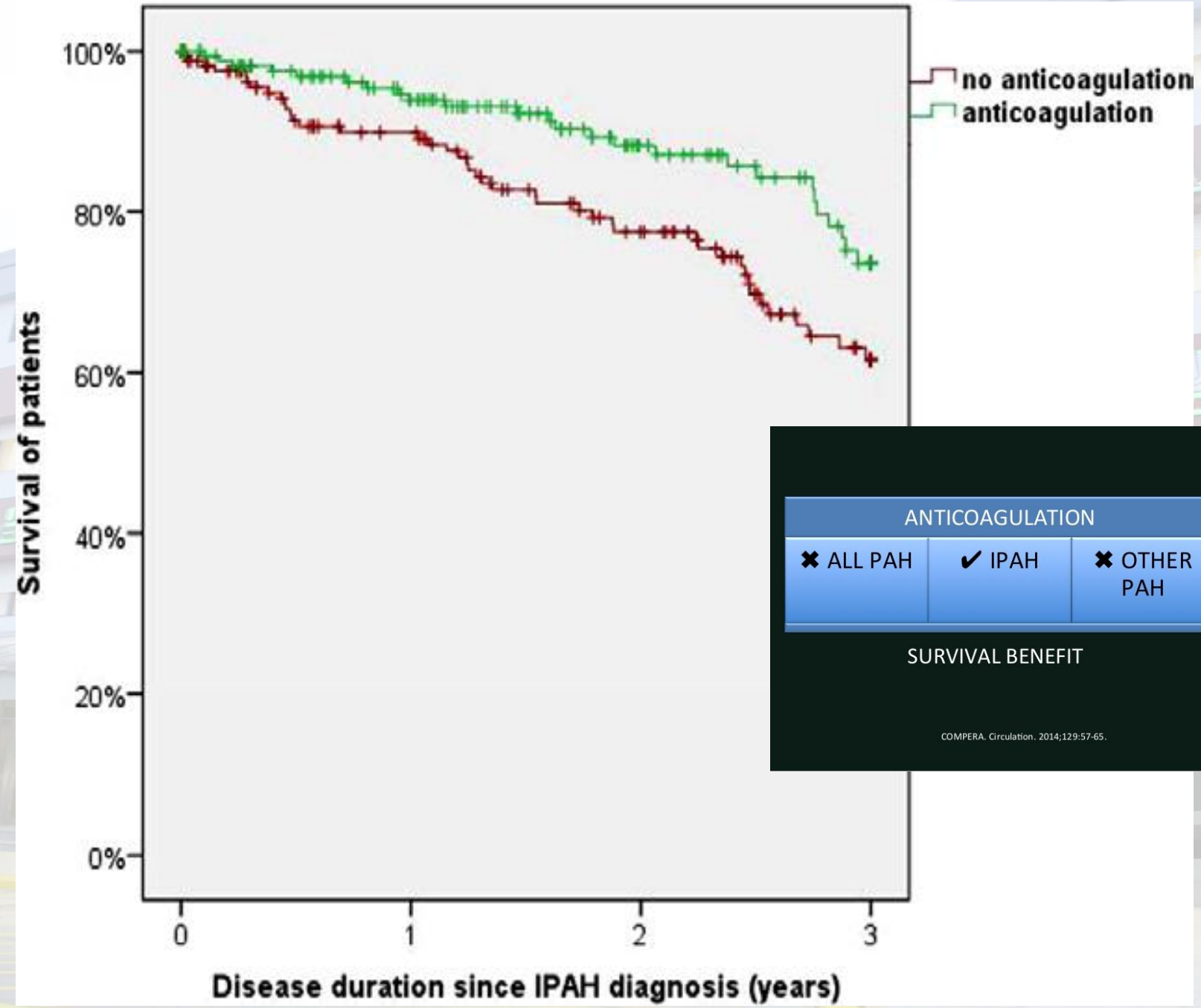

ANTICOAGULATION		
✖ ALL PAH	✔ IPAH	✖ OTHER PAH

SURVIVAL BENEFIT

COMPERA. Circulation. 2014;129:57-65.

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Anticoagulation Therapy for Pulmonary Arterial Hypertension

- Idiopathic PAH
  - Improved survival reported with oral anticoagulation in iPAH[1]
  - *In situ* microscopic thrombosis documented in patients with iPAH
  - RV failure and venous stasis increases risk of pulmonary thromboembolism
  - Recommended target INR1.5-2.5 but varies from center to center
- PAH associated with other diseases - controversial
  - Consider risk/benefit ratio
    - Scleroderma – risk of increased GI bleeding higher
    - Consider if right ventricle is enlarged and systolic dysfunction present

Badesch D et al. *Chest*. 2004;126.
[1]Rich S et al. *N Engl J Med*. 1992;327.

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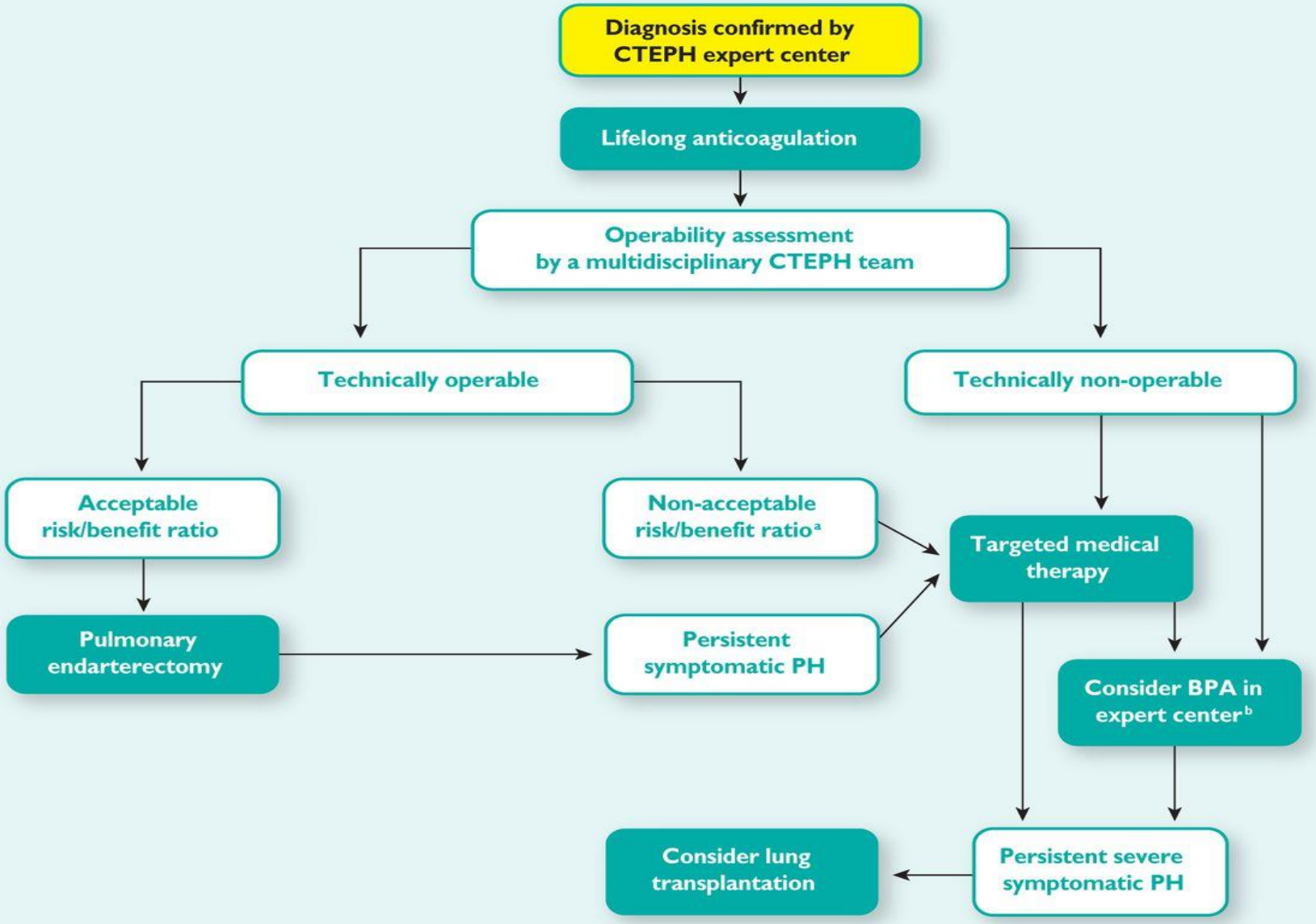
Treatment algorithm for chronic thromboembolic pulmonary hypertension.



BPA = balloon pulmonary angioplasty; CTEPH = chronic thromboembolic pulmonary hypertension; PH = pulmonary hypertension.
[a]Technically operable patients with non-acceptable risk/benefit ratio can be considered also for BPA.
[b]In some centers medical therapy and BPA are initiated concurrently.

Authors/Task Force Members: et al. Eur Heart J 2015;eurheartj.ehv317

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¿Beta bloqueantes en hipertensión pulmonar?

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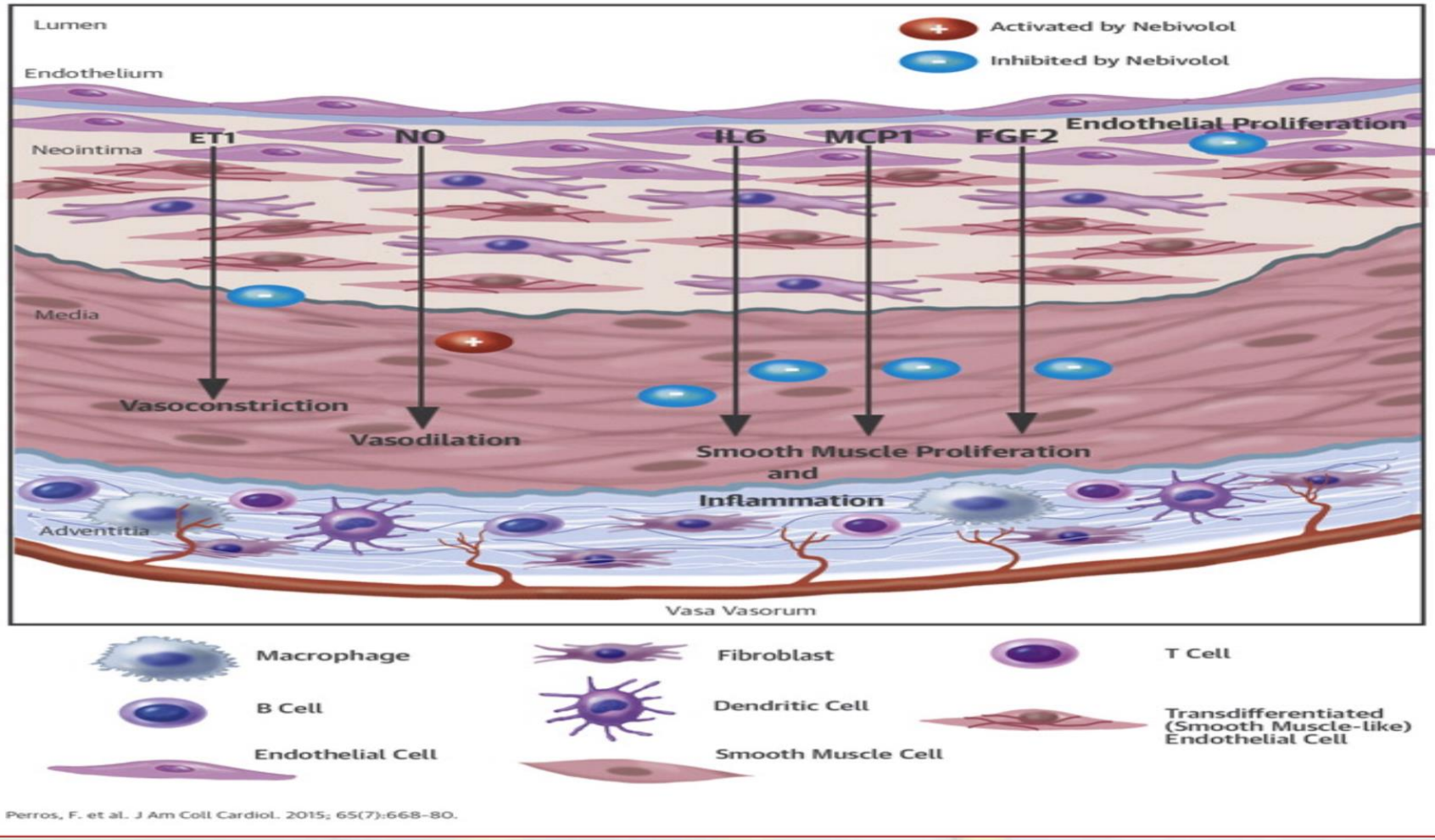
From: Nebivolol for Improving Endothelial Dysfunction, Pulmonary Vascular Remodeling, and Right Heart Function in Pulmonary Hypertension

J Am Coll Cardiol. 2015;65(7):668-680. doi:10.1016/j.jacc.2014.11.050



Perros, F. et al. J Am Coll Cardiol. 2015; 65(7):668–80.

Nebivolol for Improving Endothelial Dysfunction, Pulmonary Vascular Remodeling, and Right Heart Function in Pulmonary Hypertension

J Am Coll Cardiol. 2015;65(7):668-680. doi:10.1016/j.jacc.2014.11.050

1) la proliferación de CE pulmonares (P-CE) control y HAP en cultivo;
2) la producción de factores vasoactivos y proinflamatarios
3) la diafonía (*crosstalk*) con células musculares lisas de arteria pulmonar (AP). Asimismo, se evalúo los efectos de ambos β-bloqueantes en anillos de AP previamente contraídos y se compararon los efectos de ambos β-bloqueantes en HAP experimental.

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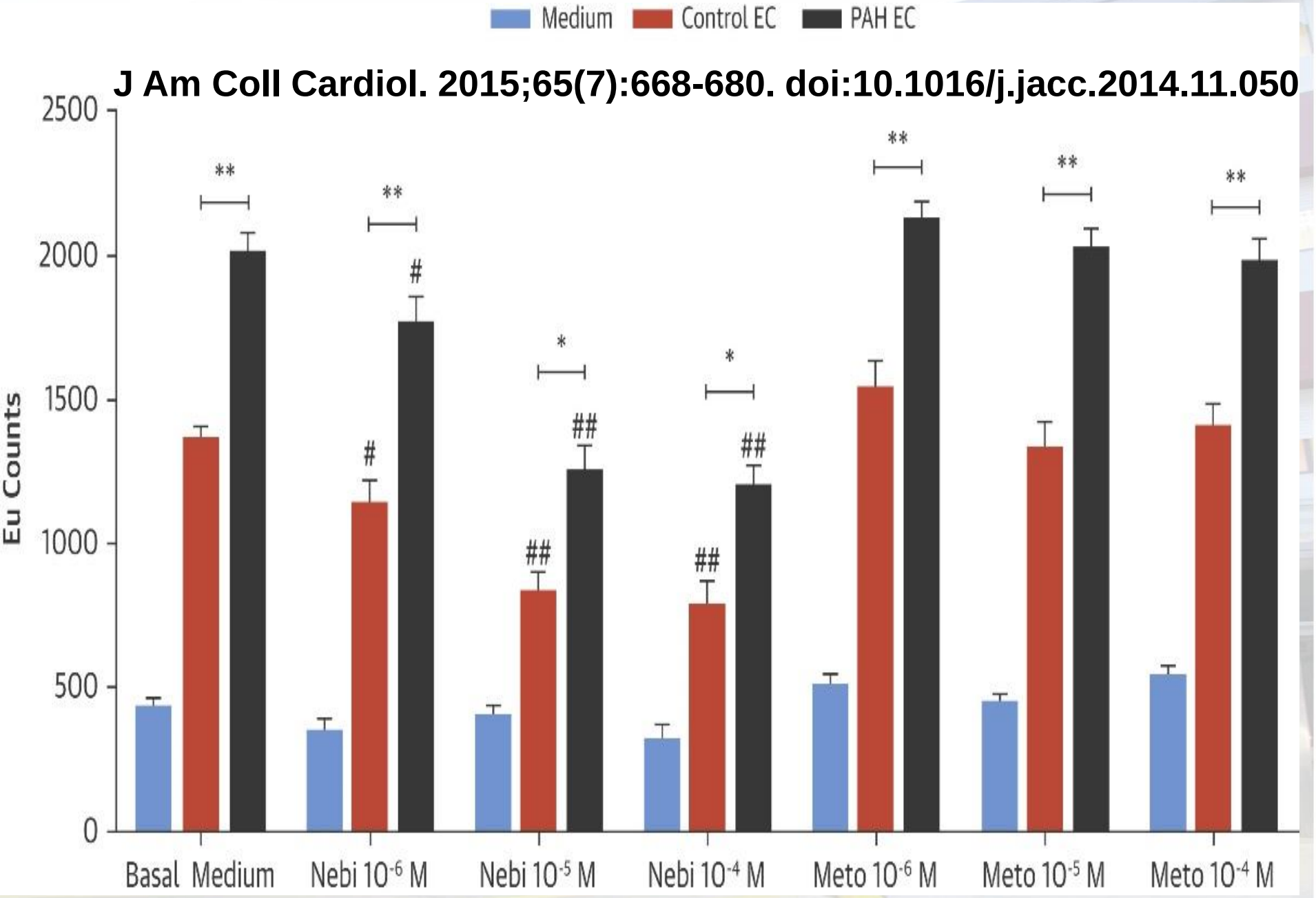

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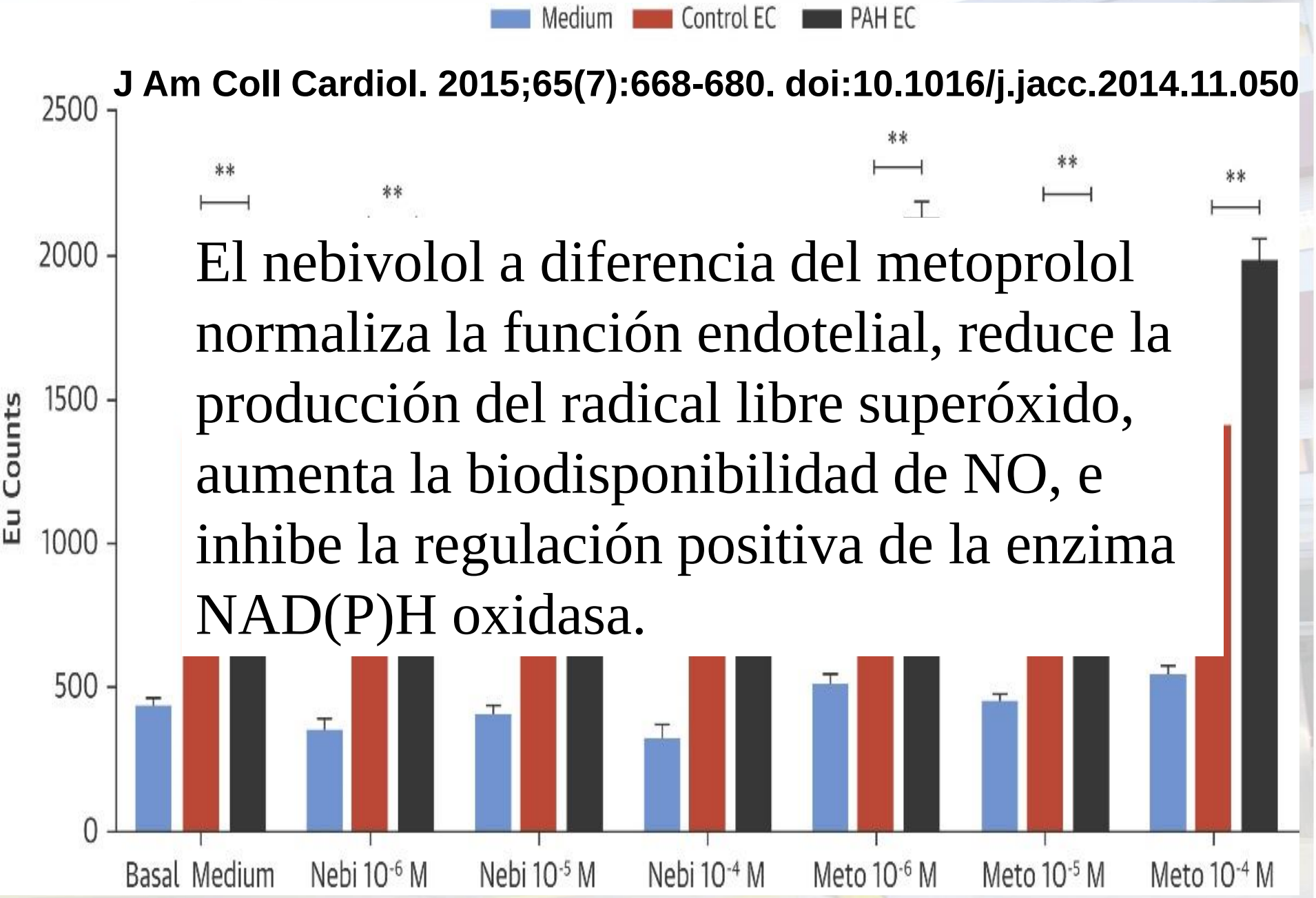

El nebivolol a diferencia del metoprolol normaliza la función endotelial, reduce la producción del radical libre superóxido, aumenta la biodisponibilidad de NO, e inhibe la regulación positiva de la enzima NAD(P)H oxidasa.

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Nebivolol for Improving Endothelial Dysfunction, Pulmonary Vascular Remodeling, and Right Heart Function in Pulmonary Hypertension

J Am Coll Cardiol. 2015;65(7):668-680. doi:10.1016/j.jacc.2014.11.050

Nebivolol could be a promising option for the management of PAH, improving endothelial dysfunction, pulmonary vascular remodeling, and right heart function. **Until clinical studies are undertaken, however, routine use of β-blockers in PAH cannot be recommended**

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¿Beta bloqueantes en hipertensión pulmonar?

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NO! si no son liberadores de oxido nitrico

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Reformulemos la pregunta …

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¿ Nebivolol hipertensión pulmonar?

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PODRIA SER…

Aun NO

NECESITAMOS MAS INFORMACIÓN

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Diuretics (I-C)
Oxygen* (I-C)

Diuréticos
Bloqueantes de la angiotensina
Antialdosteronicos siempre deben ser incluidos en el tratamiento

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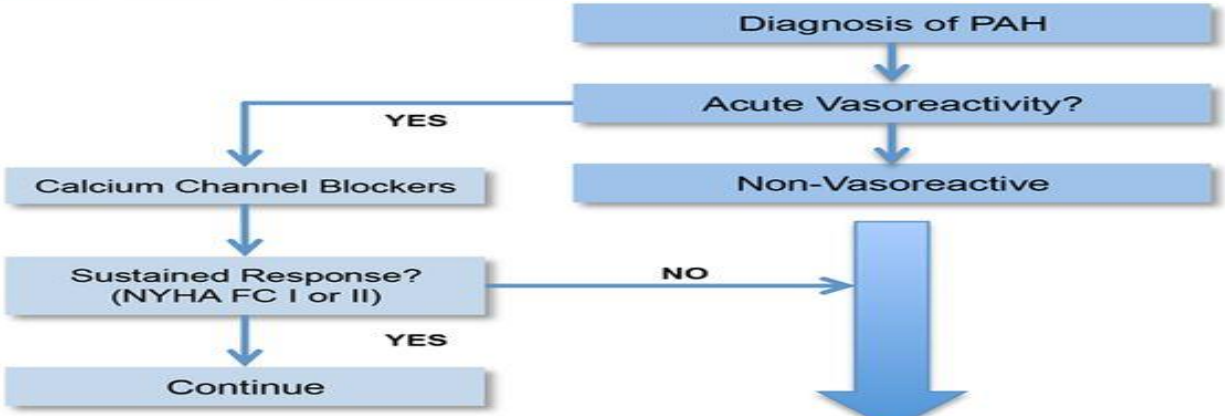

Therapy with Approved PAH Drugs

Recommendation	Evidence	FC II	FC III	FC IV
I	A or B	Ambrisentan Bosentan Macitentan# Riociguat Sildenafil Tadalafil	Ambrisentan Bosentan Epoprostenol IV* Iloprost inhaled Macitentan# Riociguat Sildenafil Tadalafil Treprostinil SC, inhaled	Epoprostenol IV*
IIa	C		Iloprost IV Treprostinil IV	Ambrisentan Bosentan Iloprost inhaled, IV Macitentan# Riociguat Sildenafil Tadalafil Treprostinil SC, IV
IIb	B		Beraprost	
	C		Upfront Combination	Upfront Combination

Acute vasoreactivity test
(I-C for IPAH)
(IIb-C for APAH)

VASOREACTIVE

NON VASOREACT

WHO-FC I-III
CCB (I-C)

Sustained response
(WHO-FC I-II)

YES

NO

Continue CCB

DATOS OBSERVACIONALES
SUGIERES QUE LOS BLOQUEANTES CALCICOS EN ALTAS DOSIS MEJORAN LA HEMODINAMIA PULMONAR Y LOS SINTOMAS DE LOS PACIENTES CON PRUEBAS DE VASOREACTIVIDAD POSITIVA

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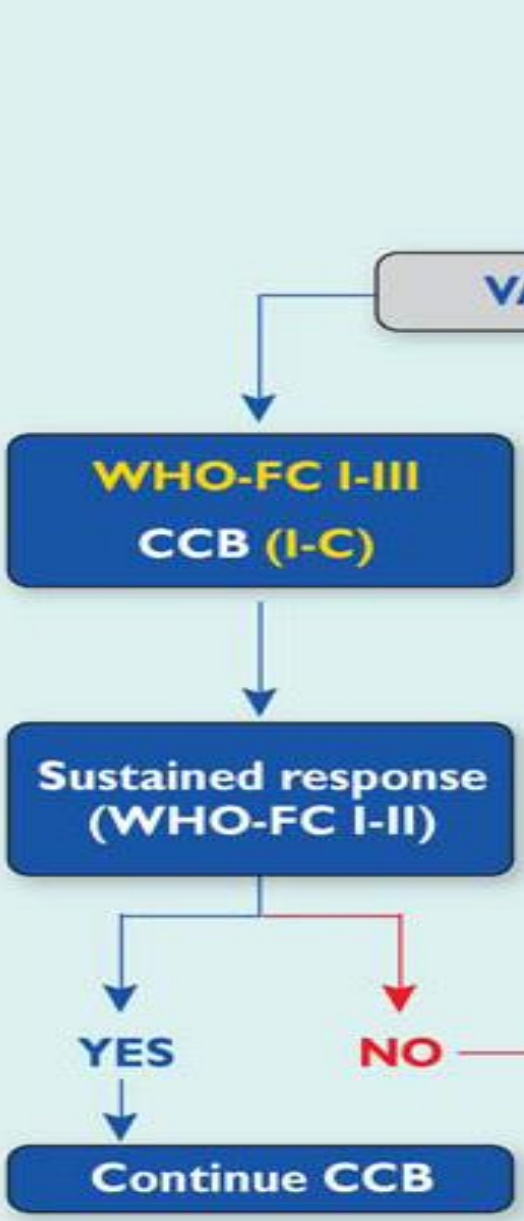

Diltiazem y la Nifedipina.
Las dosis son relativamente elevadas:
240-720mg/día de diltiazem y
120-240 mg/día de nifedipina.

Eficaz si : la clase funcional es I o II
PSAP cercana a los valores normales.

El 50% de los pacientes respondedores dejen de serlo al año

Si no se consiguen estos objetivos está indicado iniciar tratamiento con fármacos específicos

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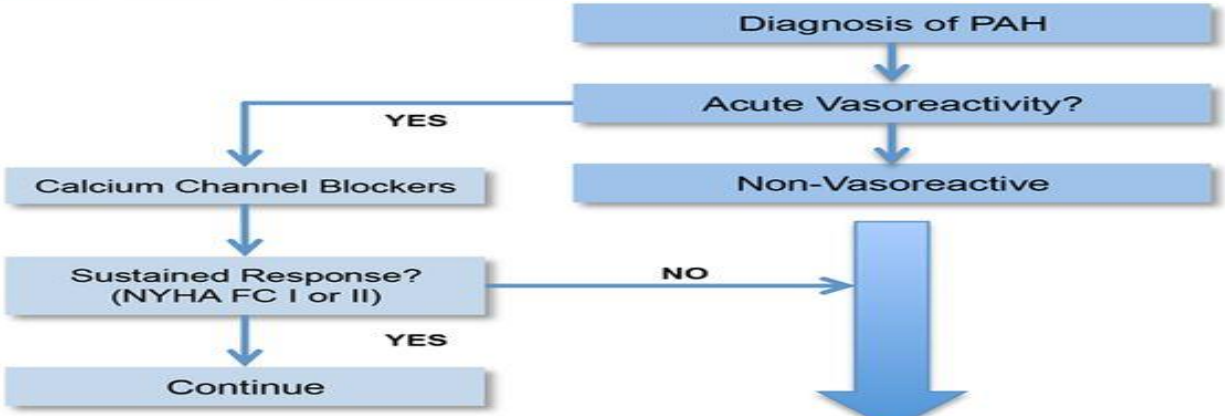

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IIb	B		Beraprost	
	C		Upfront Combination	Upfront Combination

HIPERTENSION PULMONAR

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Measure/treatment	Class[a]-Level[b]					
	WHO-FC II		WHO-FC III		WHO-FC IV	
Macitentan added to sildenafil[d]	**I**	**B**	**I**	**B**	**IIa**	**C**
Riociguat added to bosentan	**I**	**B**	**I**	**B**	**IIa**	**C**
Selexipag[e] added to ERA and/or PDE-5i[d]	**I**	**B**	**I**	**B**	**IIa**	**C**
Sildenafil added to epoprostenol	**–**	**–**	**I**	**B**	**IIa**	**B**
Treprostinil inhaled added to sildenafil or bosentan	**IIa**	**B**	**IIa**	**B**	**IIa**	**C**
Iloprost inhaled added to bosentan	**IIb**	**B**	**IIb**	**B**	**IIb**	**C**
Tadalafil added to bosentan	**IIa**	**C**	**IIa**	**C**	**IIa**	**C**
Ambrisentan added to sildenafil	**IIb**	**C**	**IIb**	**C**	**IIb**	**C**
Bosentan added to epoprostenol	**–**	**–**	**IIb**	**C**	**IIb**	**C**
Bosentan added to sildenafil	**IIb**	**C**	**IIb**	**C**	**IIb**	**C**
Sildenafil added to bosentan	**IIb**	**C**	**IIb**	**C**	**IIb**	**C**
Other double combinations	**IIb**	**C**	**IIb**	**C**	**IIb**	**C**
Other triple combinations	**IIb**	**C**	**IIb**	**C**	**IIb**	**C**
Riociguat added to sildenafil or other PDE-5i	**III**	**B**	**III**	**B**	**III**	**B**

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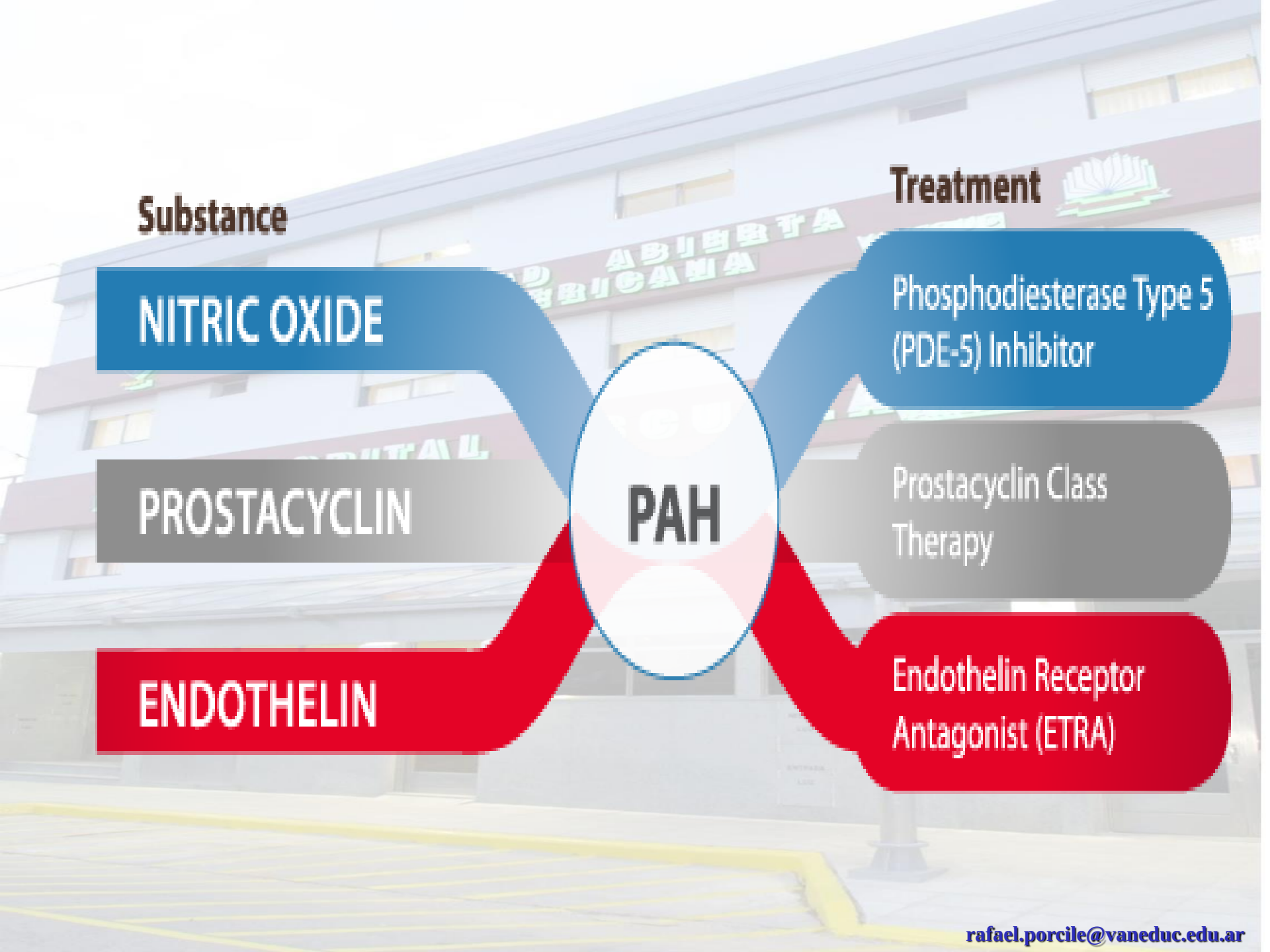

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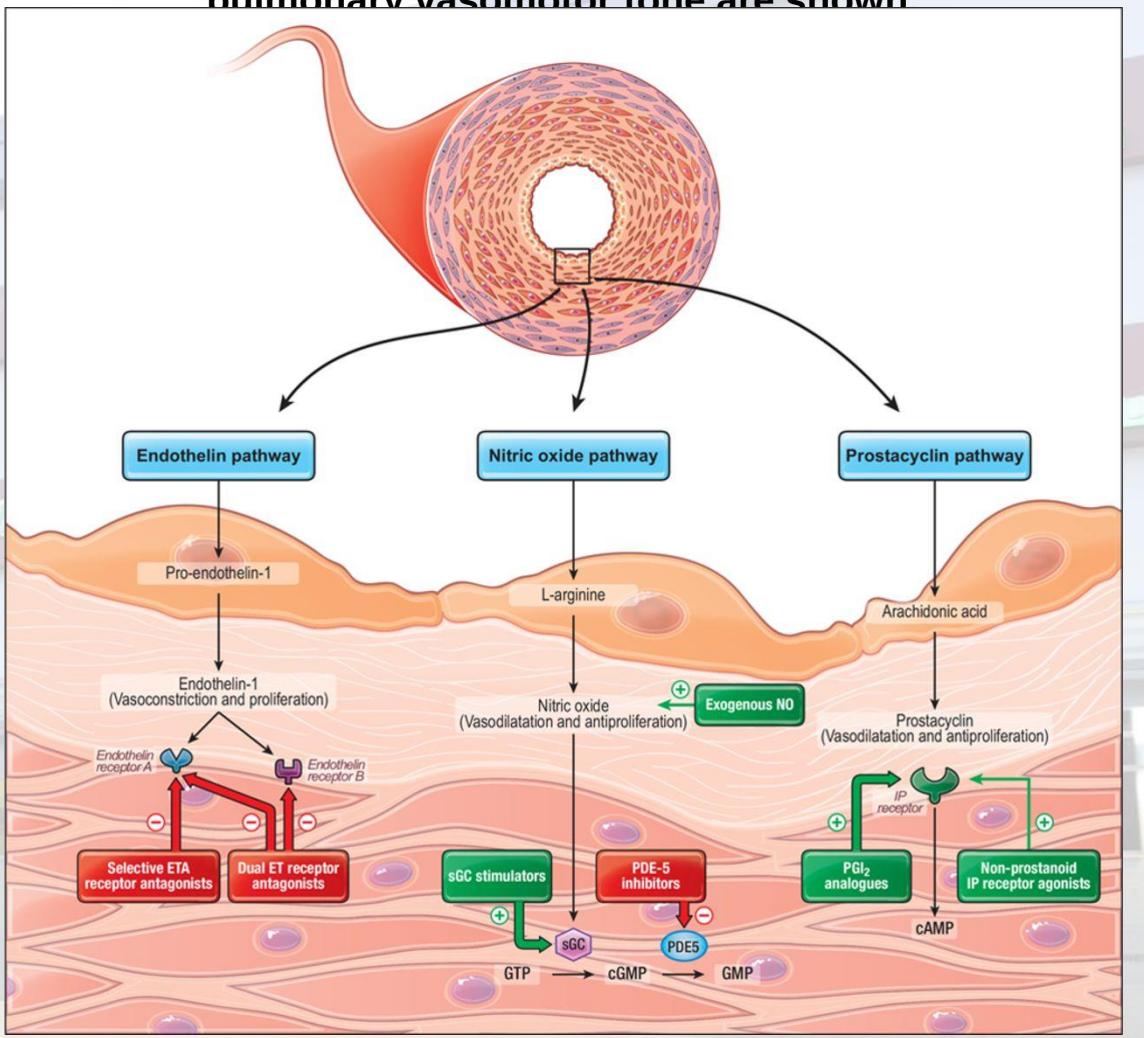
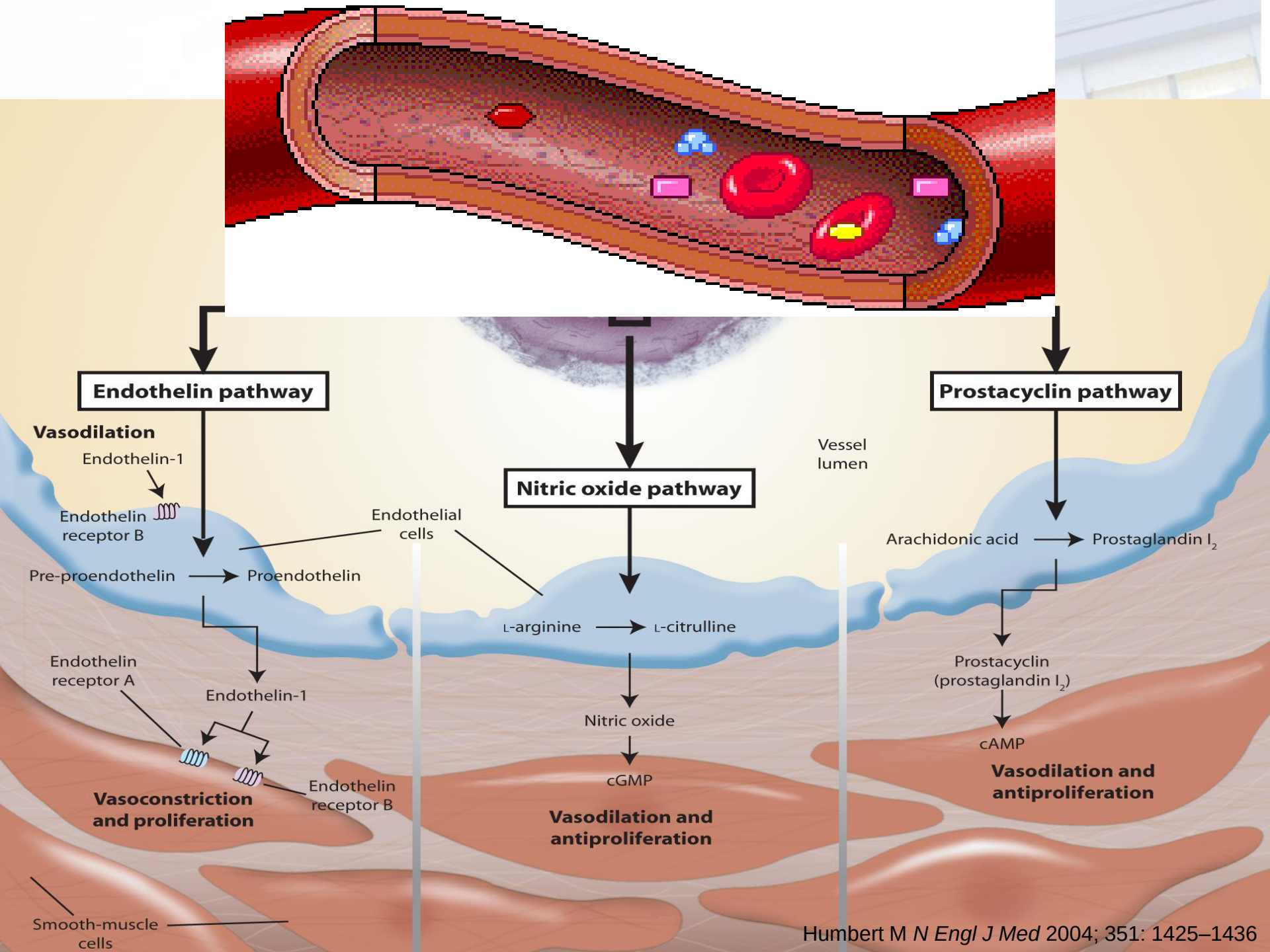
Established vasomotor pathways targeted by current and emerging therapies in PAH. The 3 major pathways (endothelin-1, nitric oxide, and prostacyclin) involved in the regulation of pulmonary vasomotor tone are shown.

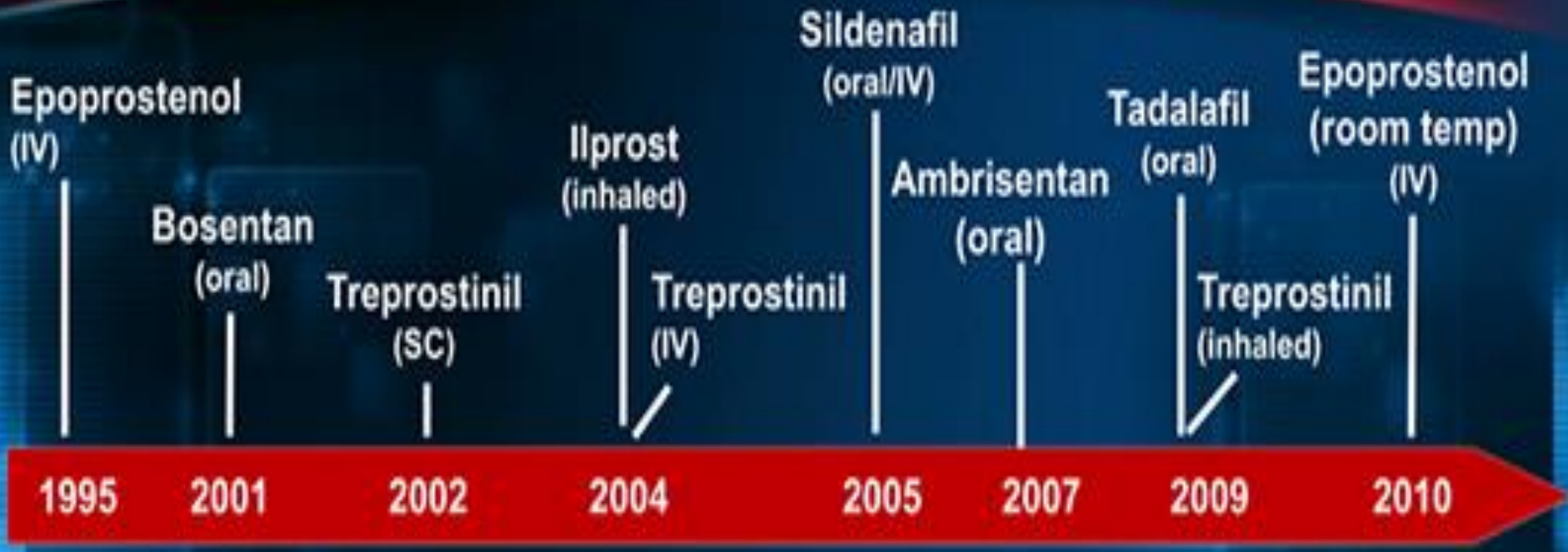


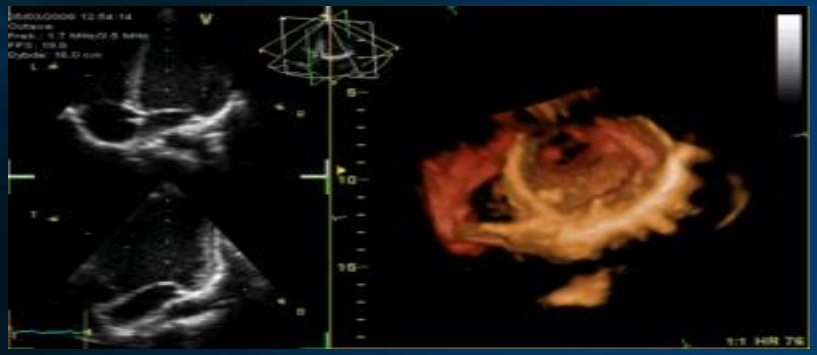
Humbert M et al. Circulation. 2014;130:2189-2208



Humbert M *N Engl J Med* 2004; 351: 1425–1436

PAH-Specific Therapies: US FDA Approvals





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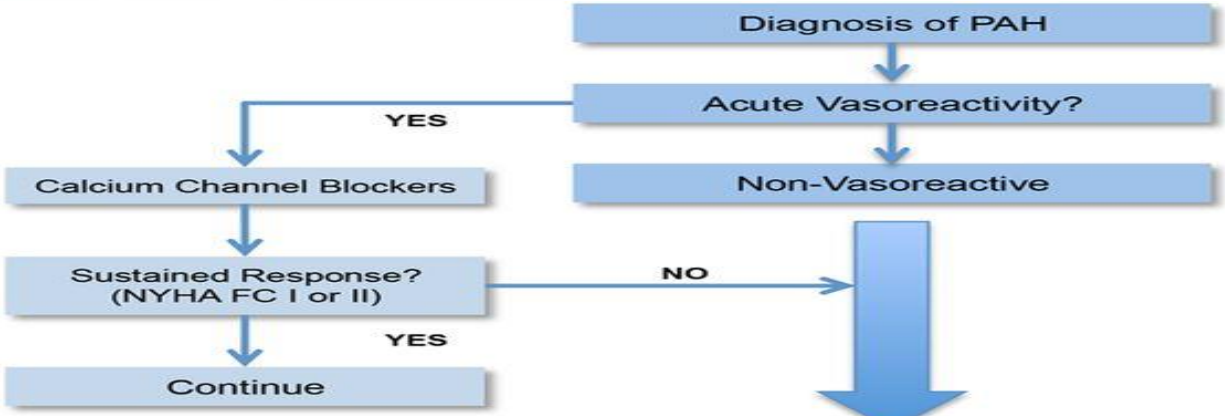

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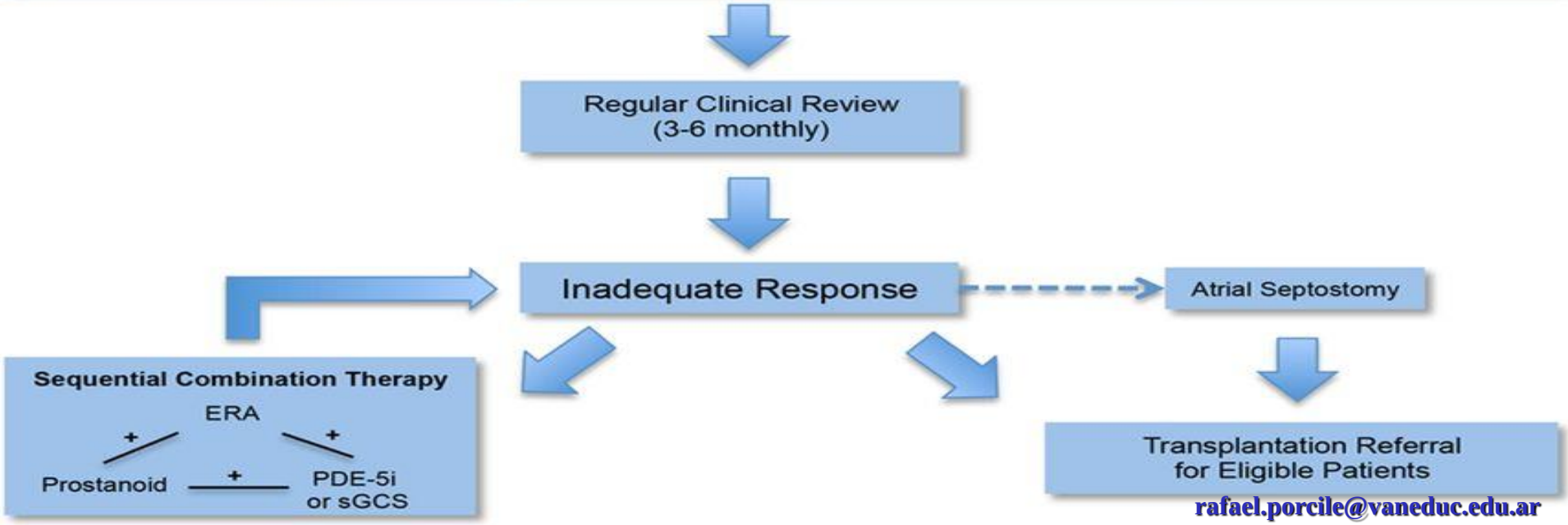

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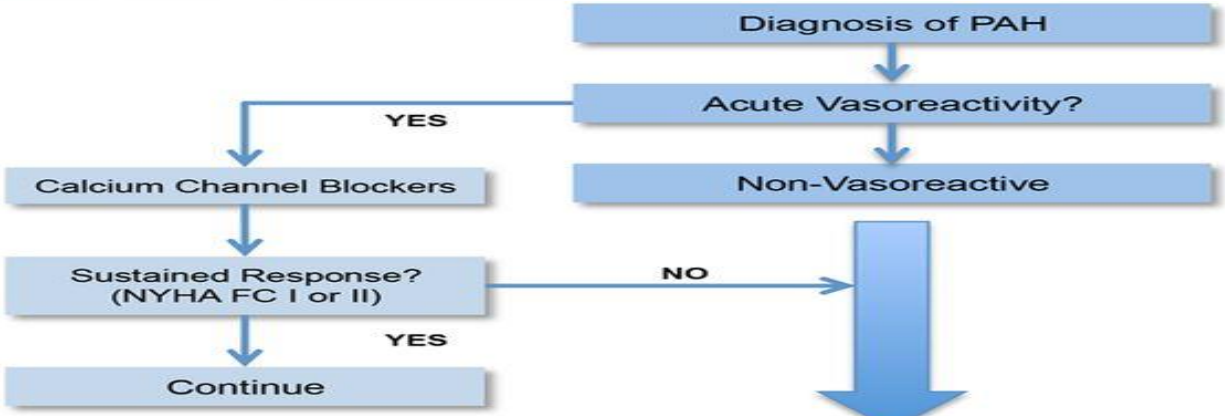

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IIb	B		Beraprost	
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Sustained Response?
(NYHA FC I or II)

NO

YES

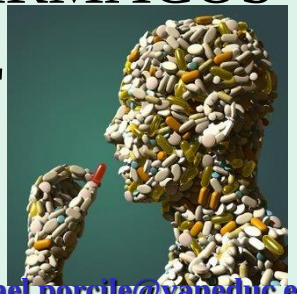
Continue

Therapy with Approved PAH Drugs

Recommendation	Evidence	FC II	FC III	FC IV
I	A or B	Ambrisentan Bosentan Macitentan# Riociguat Sildenafil Tadalafil	Ambrisentan Bosentan Epoprostenol IV* Iloprost inhaled Macitentan# Riociguat Sildenafil Tadalafil Treprostinil SC, inhaled	Epoprostenol IV*
IIa	C		Iloprost IV Treprostinil IV	Ambrisentan Bosentan Iloprost inhaled, IV Macitentan# Riociguat Sildenafil Tadalafil Treprostinil SC, IV
IIb	B		Beraprost	
	C		Upfront Combination	Upfront Combination

LA REVISION SISTEMATICA DEMUESTRA (EXEPTO EN EPOPROSTENOL) LA EFECTIVIDAD DE LOS FARMACOS CONSIDERADOS INDIVIDUALMENTE

NO DISMINUYEN LA MORTALIDAD



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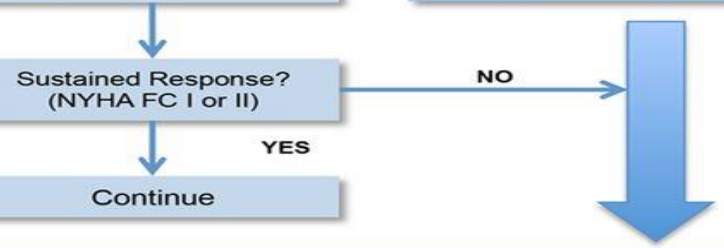

Therapy with Approved PAH Drugs

Recommendation	Evidence	FC II
I	A or B	Ambrisentan Bosentan Macitentan# Riociguat Sildenafil Tadalafil
IIa	C	
IIb	B	
	C	

WHO-FC II. 8 AÑOS
SOBREVIDA

EVIDENCIA PARA TERAPEUTICA EN CFII

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Effects of the dual endothelin-receptor antagonist **bosentan** in patients with pulmonary hypertension: a randomised placebo-controlled study

Lancet **2001**;358:1119-23.

- **Mejoría en Capacidad al ejercicio, clase funcional y variables ecocardiográficas**
- **10% de los pacientes aumentan los valores de transaminasas.**
- **Anemia, disminución de la espermatogénesis y efectos teratogénicos.**
- **Reduce por competencia efecto del sildenafil**

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Tasas de toxicidad hepática observadas con AREs

- Bosentan 11.2%
- Sitaxentan 7.0%
- Ambrisentan 2.1%

Todas los AREs requieren de un monitoreo mensual de funcionalidad hepática.

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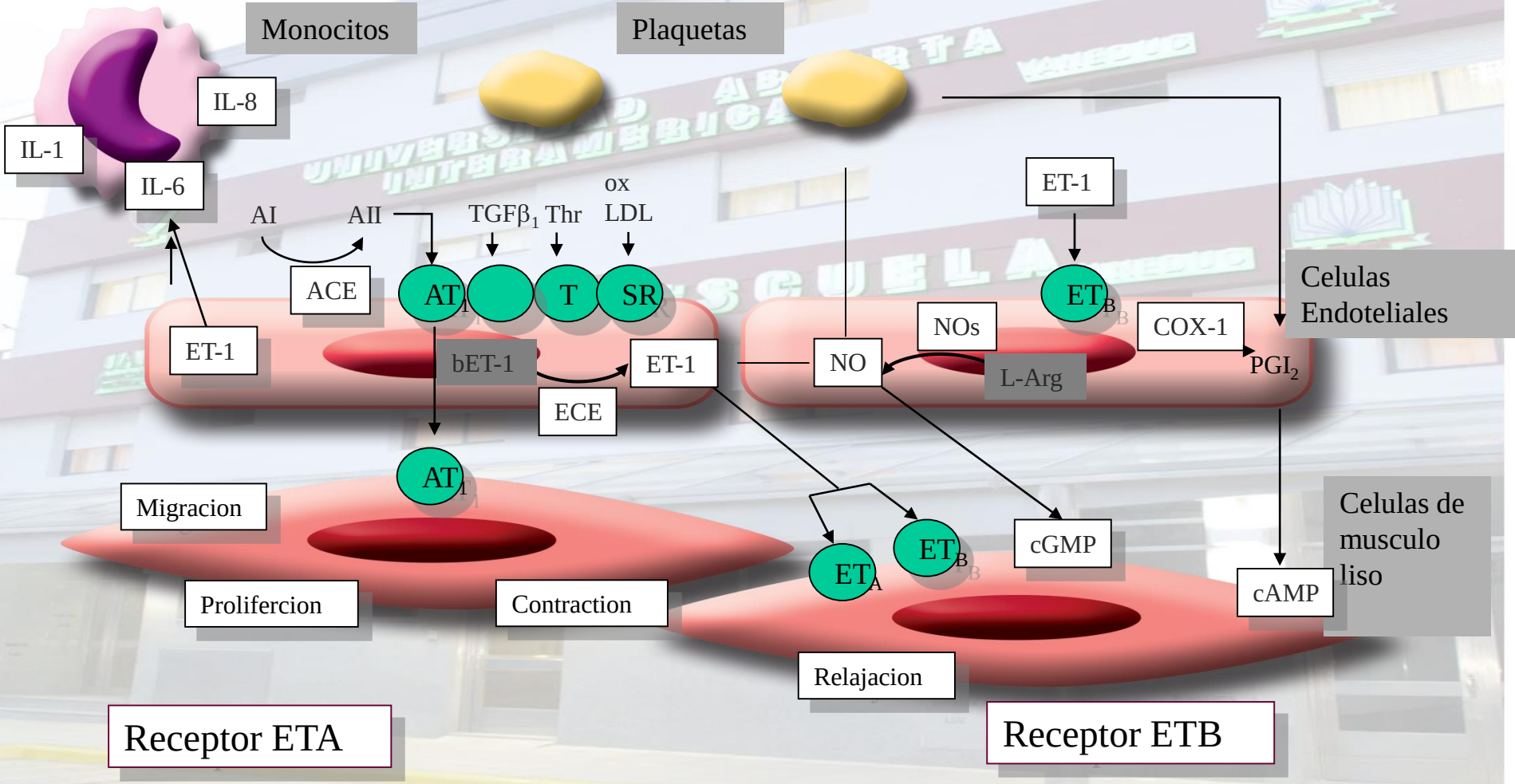
Endotelina 1 desempeña un papel importante en HAP

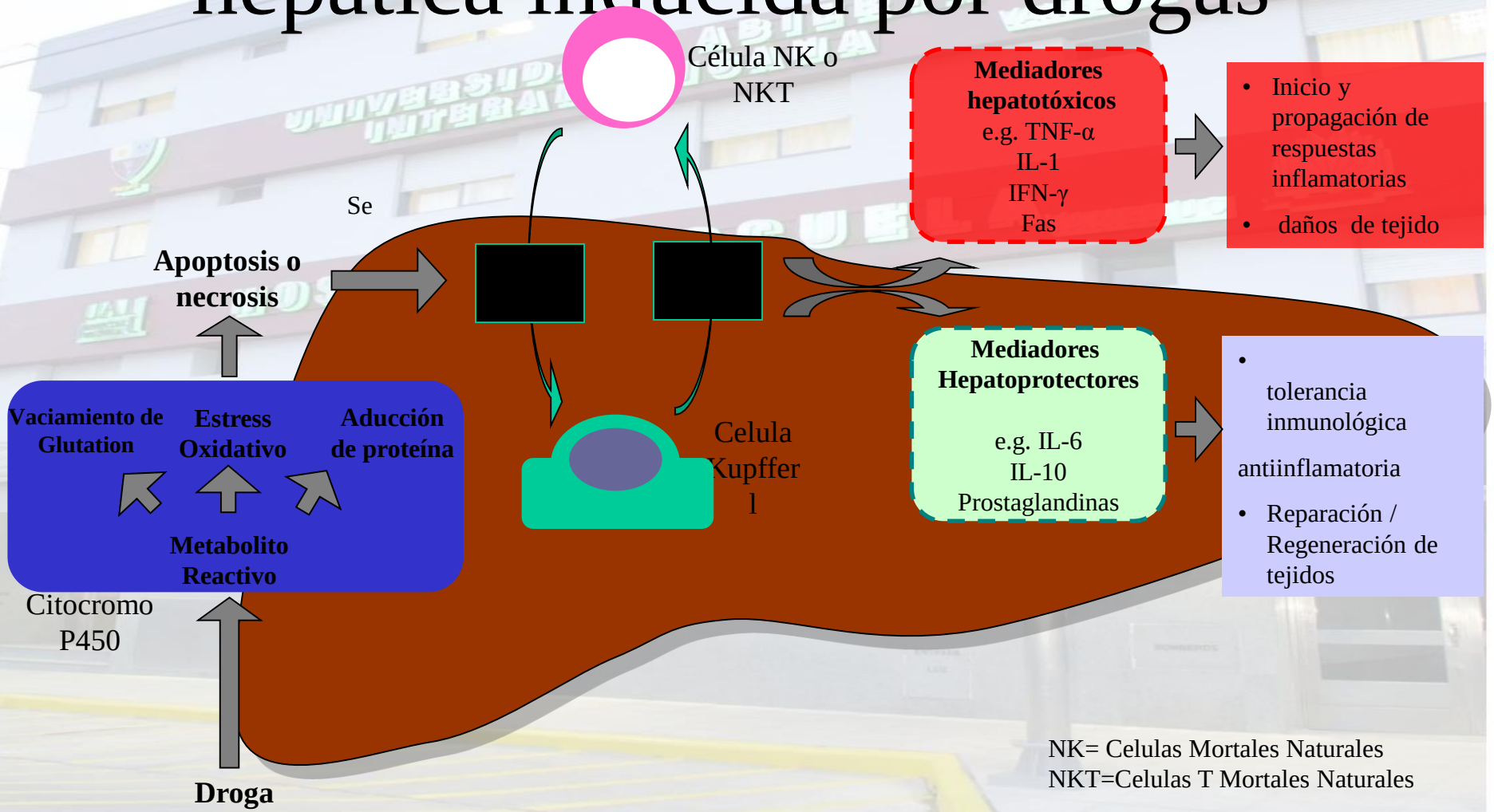


Vasoconstriccion
SMC migracion + proliferacion

ET-1 clearance
Vasodilacion/antiproliferativo

Spieker LE *et al J Am Coll Cardiol* 2001; 37: 1493–1505

Mecanismo propuesto de lesión hepática inducida por drogas



NK= Celulas Mortales Naturales
NKT=Celulas T Mortales Naturales

1. Holt MP, Ju C *AAPS J* 2006; 8: E48–E54

La inhibición de la bomba de exportación de sales biliares puede contribuir a las anomalías

1. Fattinger K *et al Clin Pharmacol Ther* 2001; 69: 223–231

Ther Adv Respir Dis. 2012 Aug 29. [Epub ahead of print]

An update on the use of ambrisentan in pulmonary arterial hypertension.

Meta analisis

improvement including time to clinical worsening, survival, functional class, quality of life and hemodynamic variables have been reported in clinical trials. A favorably low incidence of aminotransferase elevation indicating lower hepatic toxicity than other ERAs has been observed. Ambrisentan can be safely administered with warfarin or sildenafil .A once daily oral medication.

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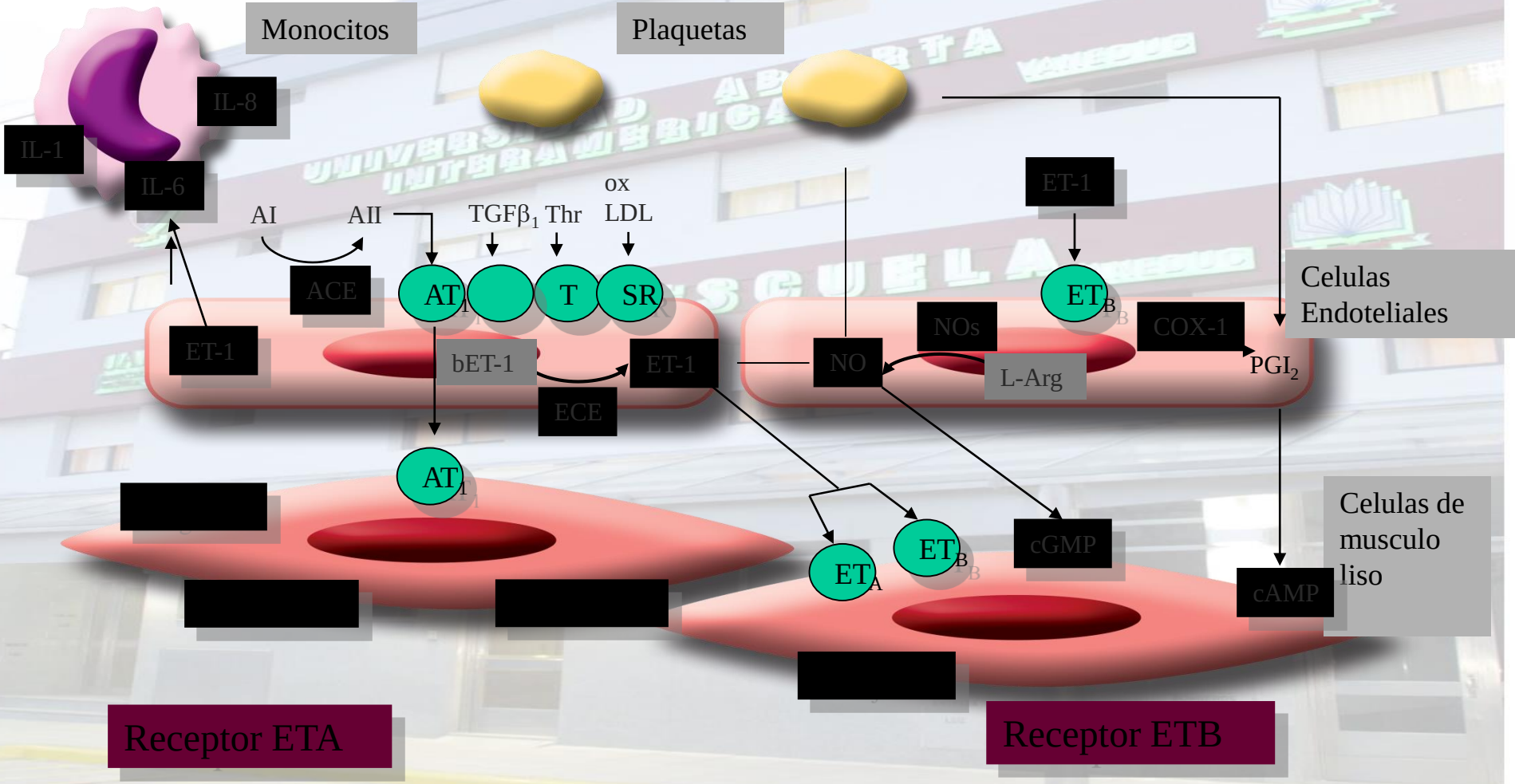
Endotelina 1 desempeña un papel importante en HAP



Vasoconstriccion
SMC migracion + proliferacion

ET-1 clearance
Vasodilacion/antiproliferativo

Spieker LE *et al J Am Coll Cardiol* 2001; 37: 1493–1505

Treatment of pulmonary arterial hypertension in connective tissue disease

The European treatment guidelines advocate the use of PAH-targeted therapies including Ambrisentan, sildenafil, inhaled iloprost, intravenous epoprostenol (I-A recommendations), tadalafil or treprostinil (I-B recommendations) for patients in WHO functional class II-III.

Drugs. 2012 May 28;72(8):1039-56.

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Long-term hepatic safety of ambrisentan in patients with pulmonary arterial hypertension

J Am Coll Cardiol. 2012 Jul 3;60(1):80-1. Epub 2012 May 9.

Compared with bosentan, ambrisentan seems to have a better safety profile with regards to hepatic safety and drug-drug interactions.

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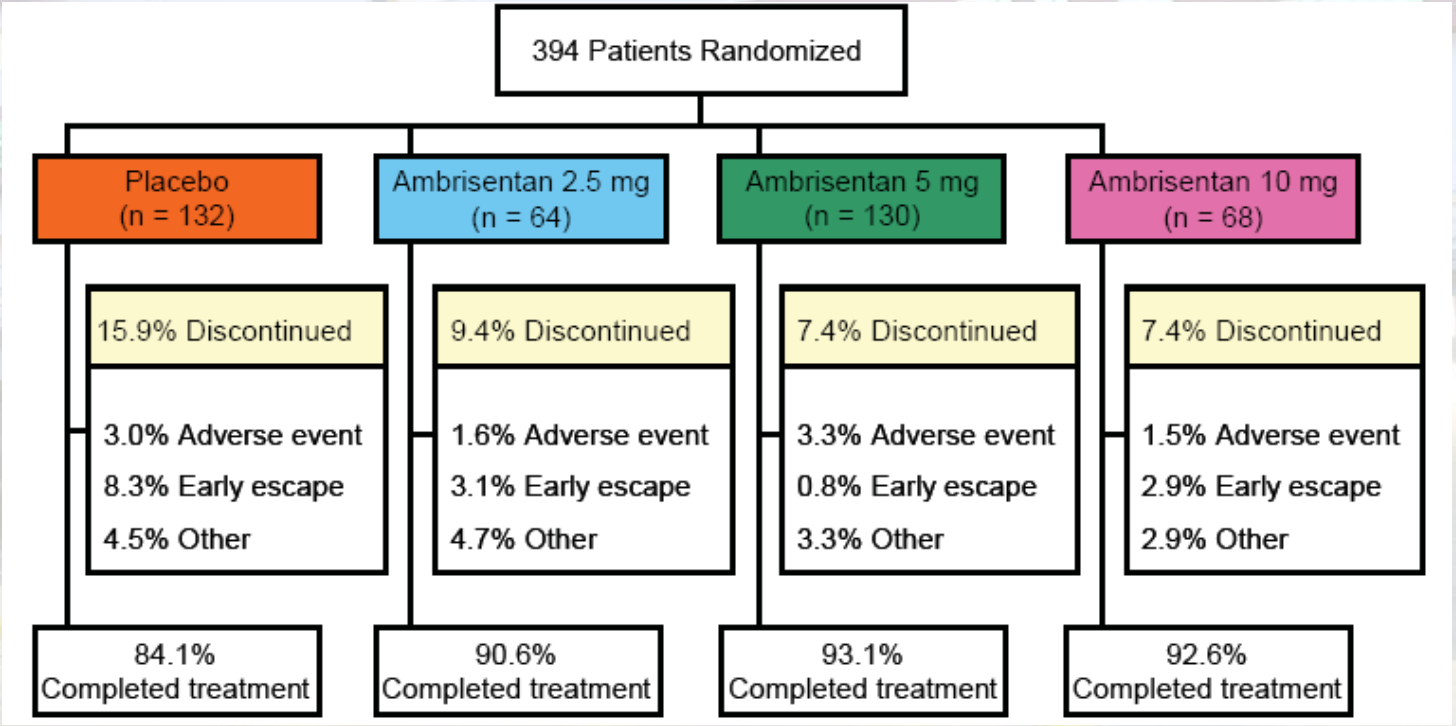
ARIES-C
Detalle de Analisis

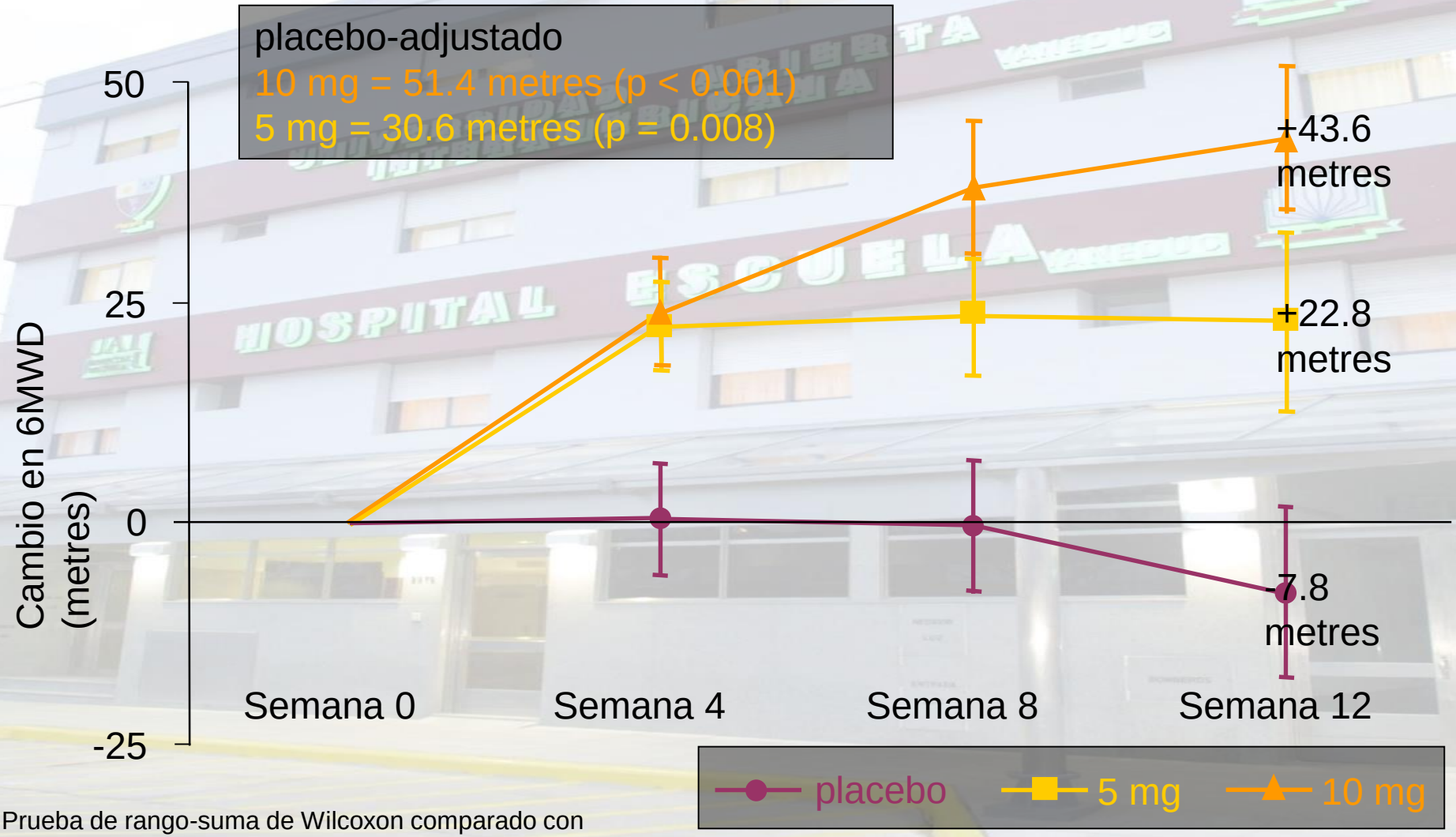
- Un análisis integrado de estudios ARIES-1 y ARIES-2 por OMS FC fue previamente especificado antes de develar alguno de los estudios
- Los análisis evaluaron la seguridad y eficacia de ambrisentan en OMS FC II y III en una población de HAP



Galiè N *et al* American Thoracic Society International Conference 2007 Poster 3192

Estudio ARIES-1

Ambrisentan mejora la capacidad de ejercicio en 12 semanas



Prueba de rango-suma de Wilcoxon comparado con barras de Error de placebo = error estándar de la media

Adapted from Galiè N *et al Circulation* 2008;117:3010-3019

Long-Term Pulmonary Hemodynamic Effects of Ambrisentan in Pulmonary Arterial Hypertension

- ..ambrisentan may provide sustained improvements in pulmonary hemodynamics in patients with PAH who receive long-term treatment and these changes correlate with improvements in exercise capacity.

Am J Cardiol. 2011 May 3.

Klinger JR, Oudiz RJ, Spence , Despain D Dufton C

Source

Division of Pulmonary, Sleep and Critical Care Medicine, Rhode Island Hospital and Alpert Medical School, Brown University, Providence, Rhode Island.

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Clinical safety, pharmacokinetics, and efficacy of ambrisentan therapy in children with pulmonary arterial hypertension

..initial experience with ambrisentan in children suggests that treatment is safe with similar pharmacokinetics to those in adults and may improve PAH in some children.

Takatsuki S,
Pediatric Cardiology, University of Colorado School of Medicine, Children's Hospital, Aurora, Colorado

Pulmonol. 2012 Apr 17. doi: 10.1002/ppul.22555

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A randomized, double-blind, multicenter study of first-line combination therapy with AMBrIsentan and Tadalafil in patients with pulmonary arterial hypertensION

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AMBITION

MUNICH--(BUSINESS WIRE)--Sep. 8, 2014-- Gilead Sciences, Inc. (Nasdaq:GILD) today announced results from the **AMBITION** study

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AMBITION

Combination of ambrisentan 10 mg and tadalafil 40 mg

Reduced the risk of clinical failure by fifty percent (50%) compared to pooled ambrisentan and tadalafil monotherapy arm (hazard ratio = 0.502; p=0.0002

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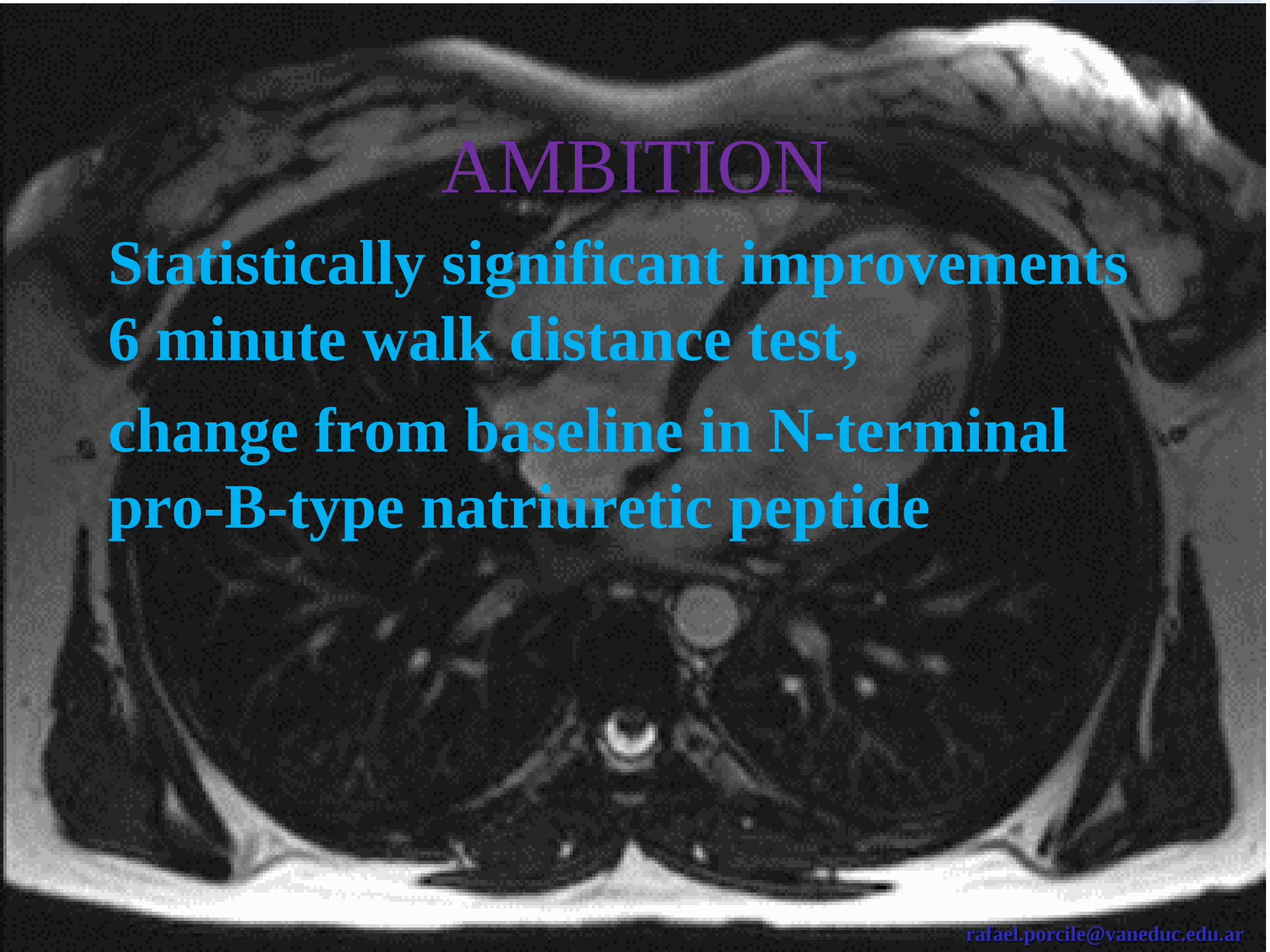

AMBITION

Statistically significant improvements
6 minute walk distance test,
change from baseline in N-terminal pro-B-type natriuretic peptide

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Macitentan and Morbidity and Mortality in Pulmonary Arterial Hypertension

n engl j med 369;9 nejm.org
august 29, 2013

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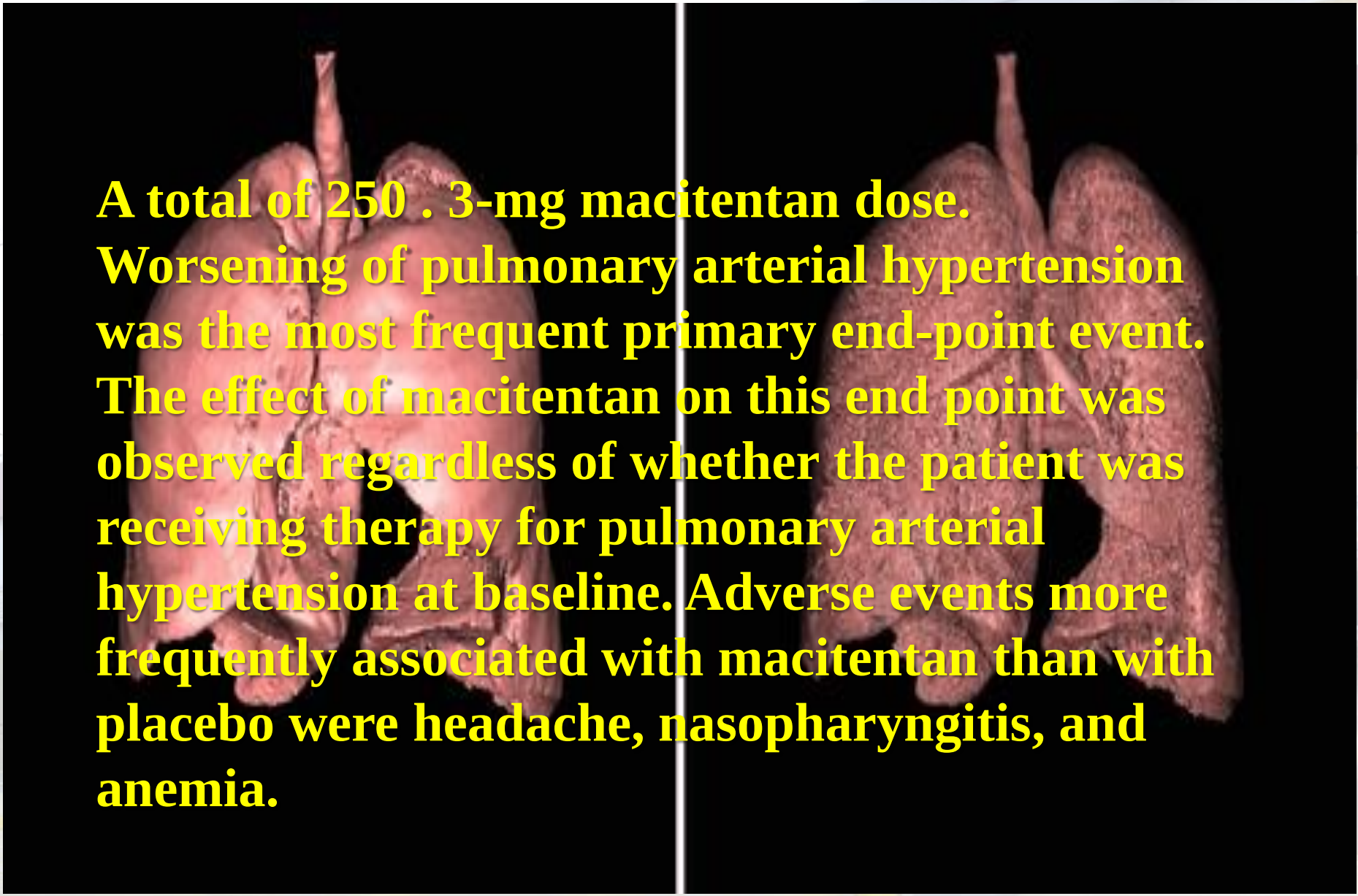

A total of 250 . 3-mg macitentan dose. Worsening of pulmonary arterial hypertension was the most frequent primary end-point event. The effect of macitentan on this end point was observed regardless of whether the patient was receiving therapy for pulmonary arterial hypertension at baseline. Adverse events more frequently associated with macitentan than with placebo were headache, nasopharyngitis, and anemia.

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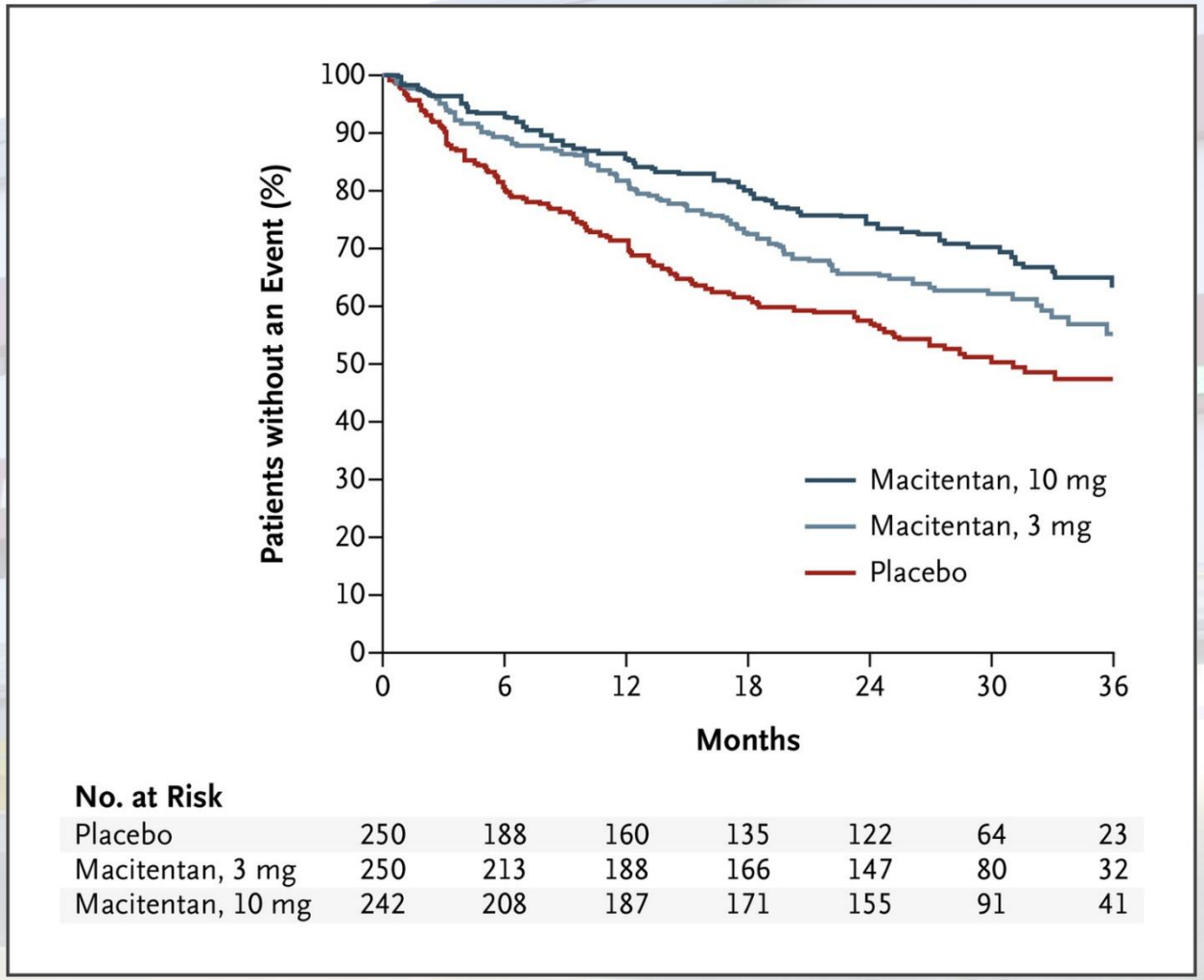
Effect of Macitentan on the Composite Primary End Point of a First Event Related to Pulmonary Arterial Hypertension or Death from Any Cause



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

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

The NEW ENGLAND JOURNAL of MEDICINE

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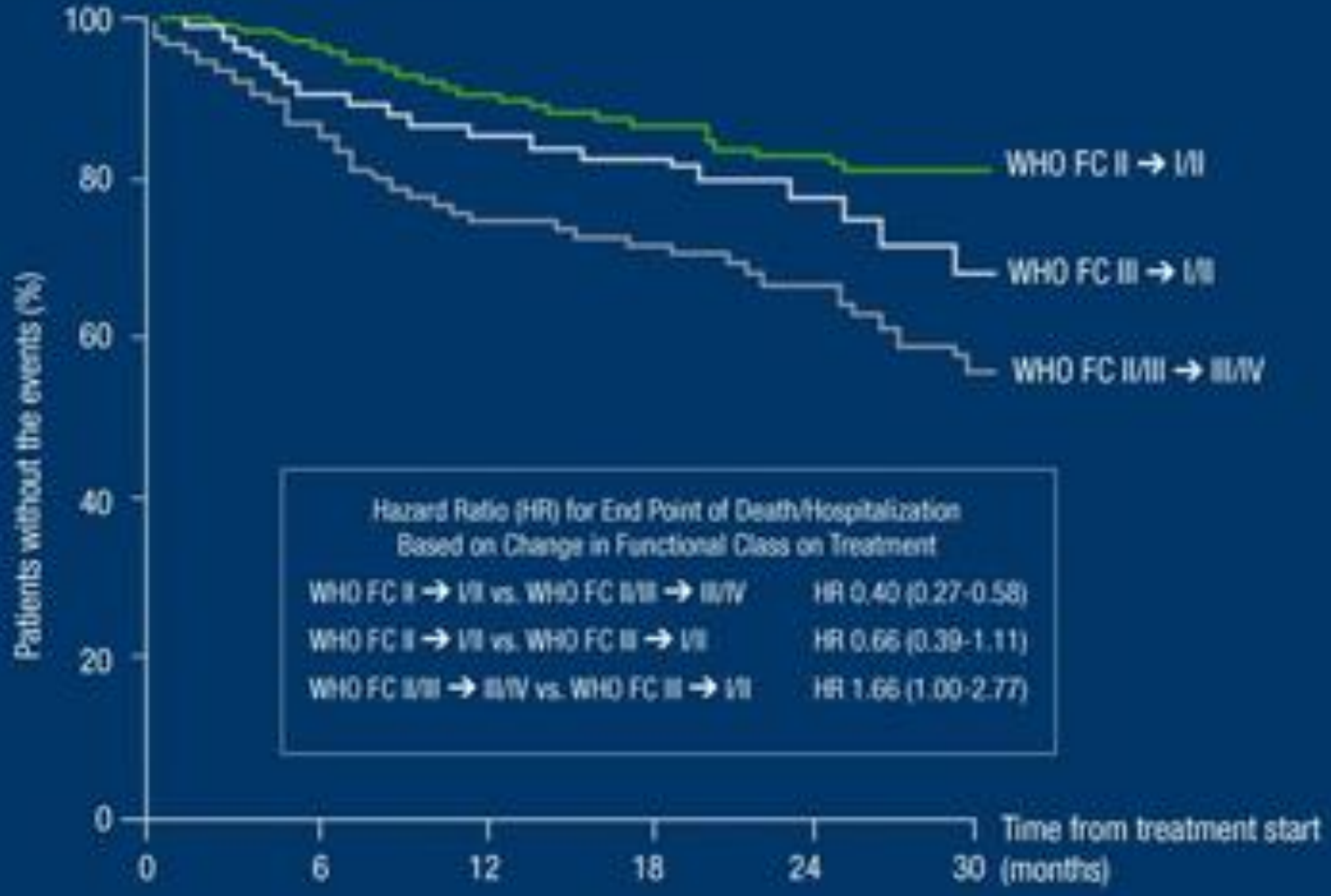
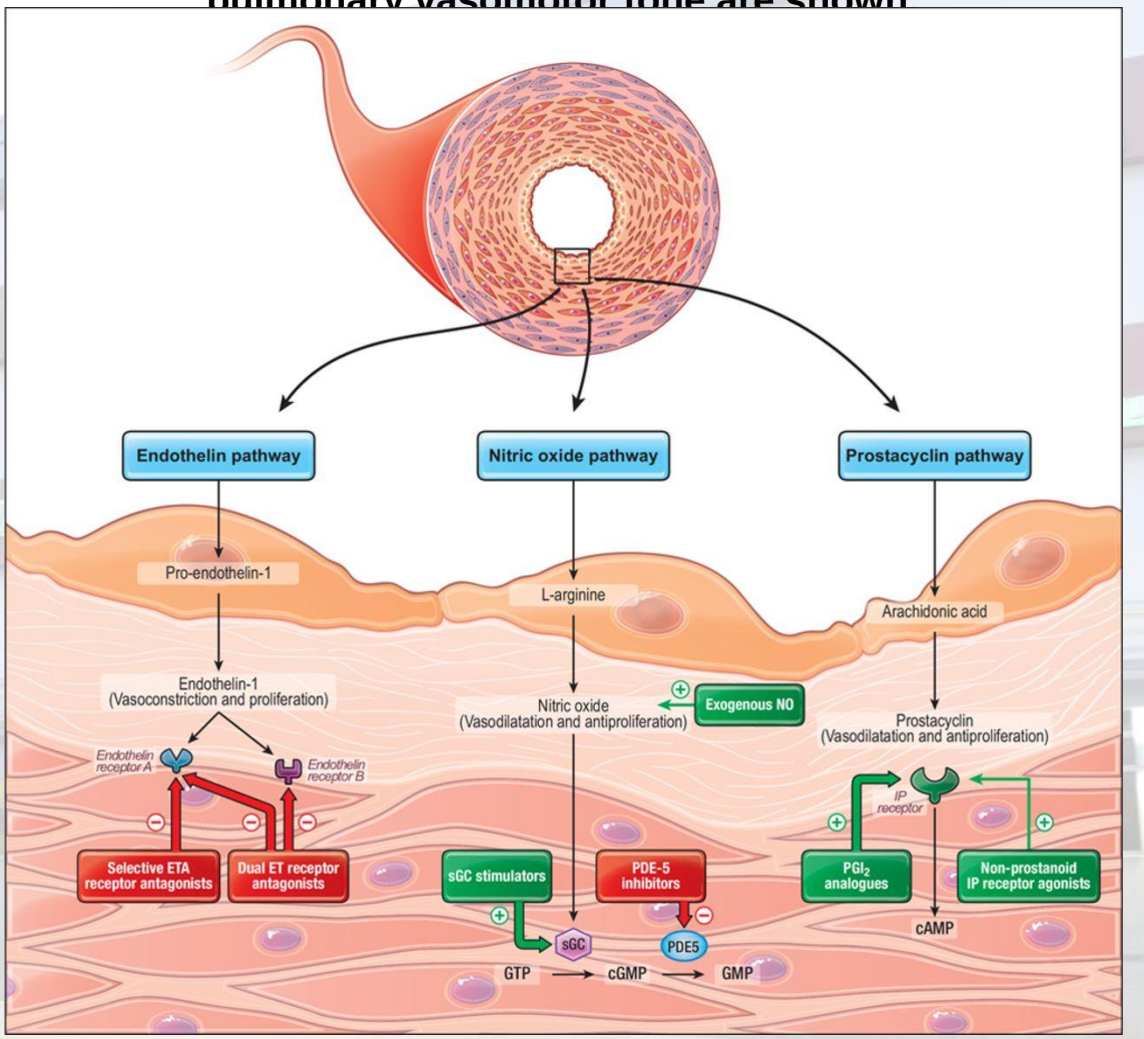
Death Due to PAH or Hospitalization for PAH



Adapted from Souza et al. Chest 2013 Annual Meeting.

Established vasomotor pathways targeted by current and emerging therapies in PAH. The 3 major pathways (endothelin-1, nitric oxide, and prostacyclin) involved in the regulation of pulmonary vasomotor tone are shown



Humbert M et al. Circulation. 2014;130:2189-2208

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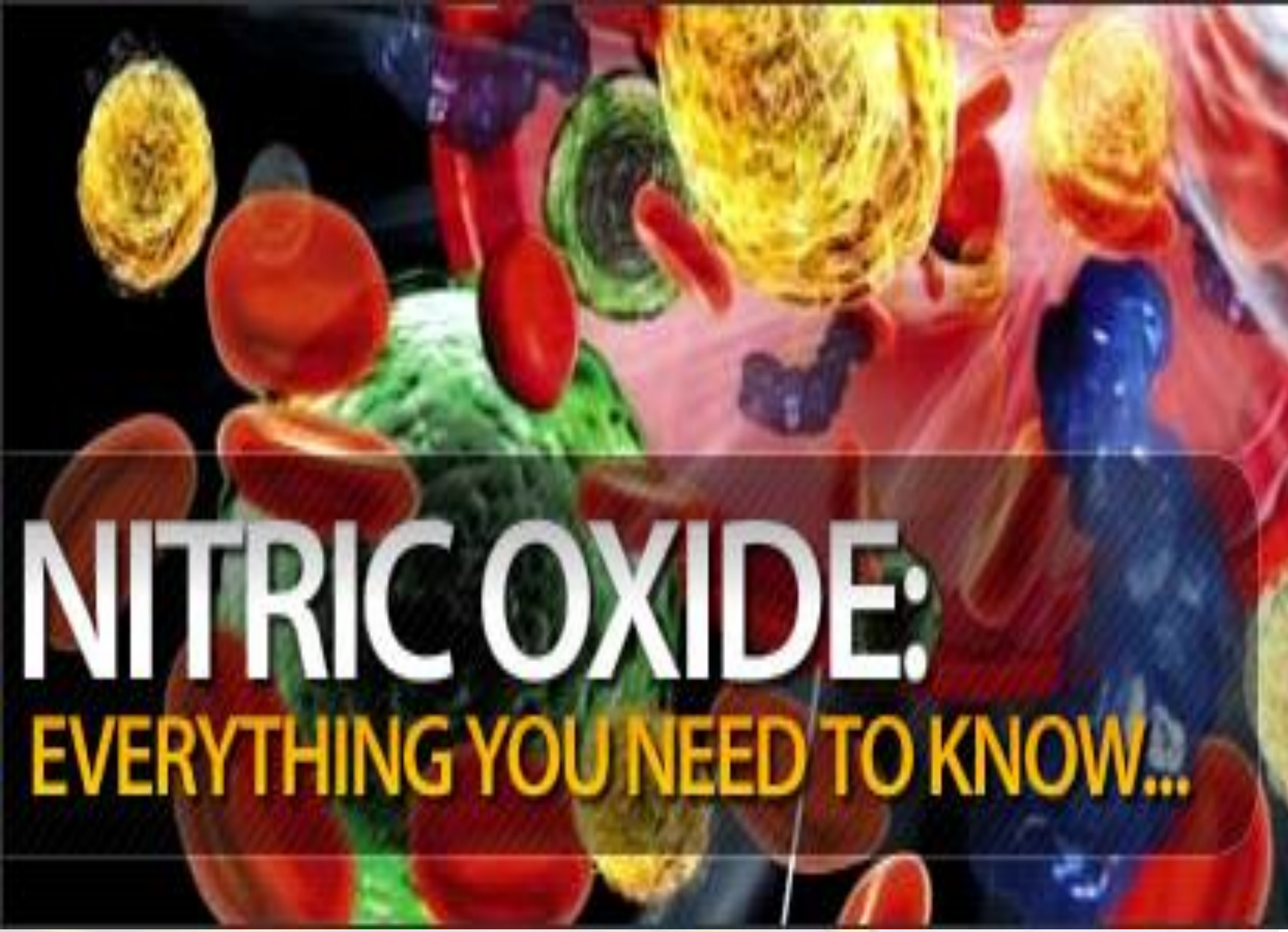
NITRIC OXIDE:
EVERYTHING YOU NEED TO KNOW...

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¿SILDENAFIL?

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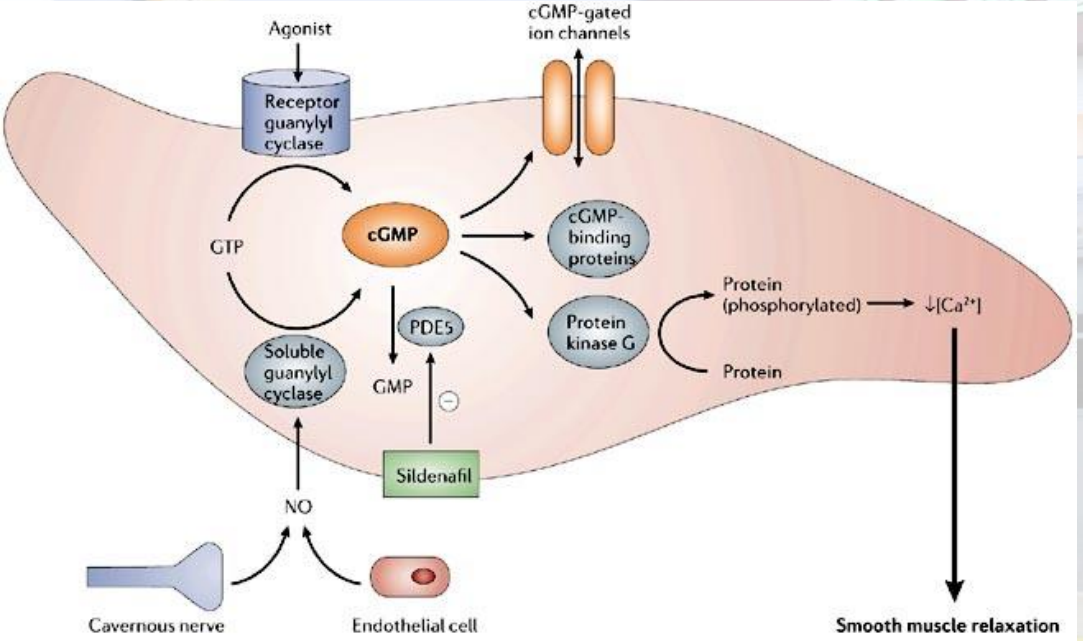
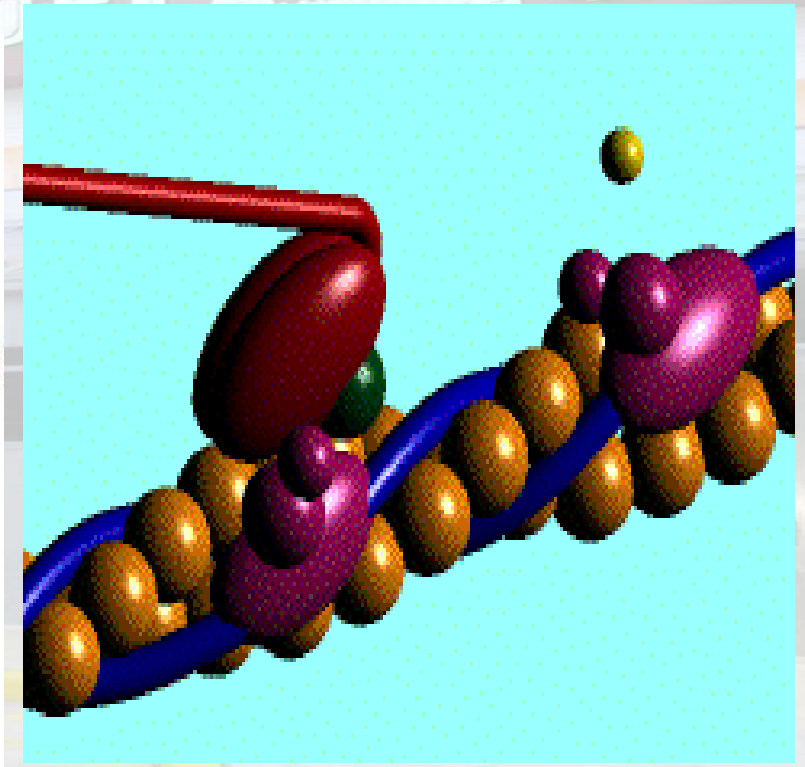
Sildenafil

WHO Clase II/III

100-300 mg día





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Sildenafil in PAH: SUPER-1
Incidence of Clinical Worsening

	Placebo (n=70)	Sildenafil 20mg (n=69)	Sildenafil 40mg (n=67)	Sildenafil 80mg (n=71)
Proportion Worsened (%) (95% CI)	10 (3,17)	4 (0,9)	3 (0,7)	7 (1,13)
Incidence of Clinical Worsening Events				
Death	1 (1)	1 (1)	0 (0)	2[1] (3)
Transplantation	0 (0)	0 (0)	0 (0)	0 (0)
Hospitalization due to PAH	7 (10)	2 (3)	2 (3)	2 (3)
Initiation of Prostanoid	1 (1)	0 (0)	0 (0)	0 (0)
Initiation of Bosentan	0 (0)	0 (0)	1 (2)	2 (3)

N=277.

[1]One patient died during the 1st week while receiving sildenafil 40 mg

Galie N et al. *N Engl J Med.* 2005;353:2148-2157.

Long-Term Treatment with Sildenafil Citrate in Pulmonary Arterial Hypertension: SUPER-2.

CHEST 2011 May 5.

Long-term treatment of PAH initiated as sildenafil monotherapy was generally well tolerated.

After 3 years, the majority of patients who entered the SUPER-1 trial improved or maintained their functional status

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Tadalafil for the treatment of pulmonary arterial hypertension

Expert Rev Respir Med. 2011 Jun;5(3):315-28.

The longer half-life of tadalafil allows for once-daily dosing 5-40mg as compared with three-times daily dosing for sildenafil

cialis

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Tadalafil for the treatment of pulmonary arterial hypertension.

- EXPERT OPINION: Tadalafil is an efficacious drug with a favorable side-effect profile and convenient mode of administration. More studies are needed to analyze its impact on ***survival*** and to substantiate its role in an upfront combination treatment strategy.

Expert Opin Pharmacother. **2012 Apr;13**(5):747-55. Epub 2012 Feb 23

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Vardenafil in pulmonary arterial hypertension: a randomized, double-blind, placebo-controlled study.

Vardenafil is effective and well tolerated in patients with PAH at a dose of 5 mg twice daily

Am J Respir Crit Care Med. 2011 Jun 15;183(12):1723-9

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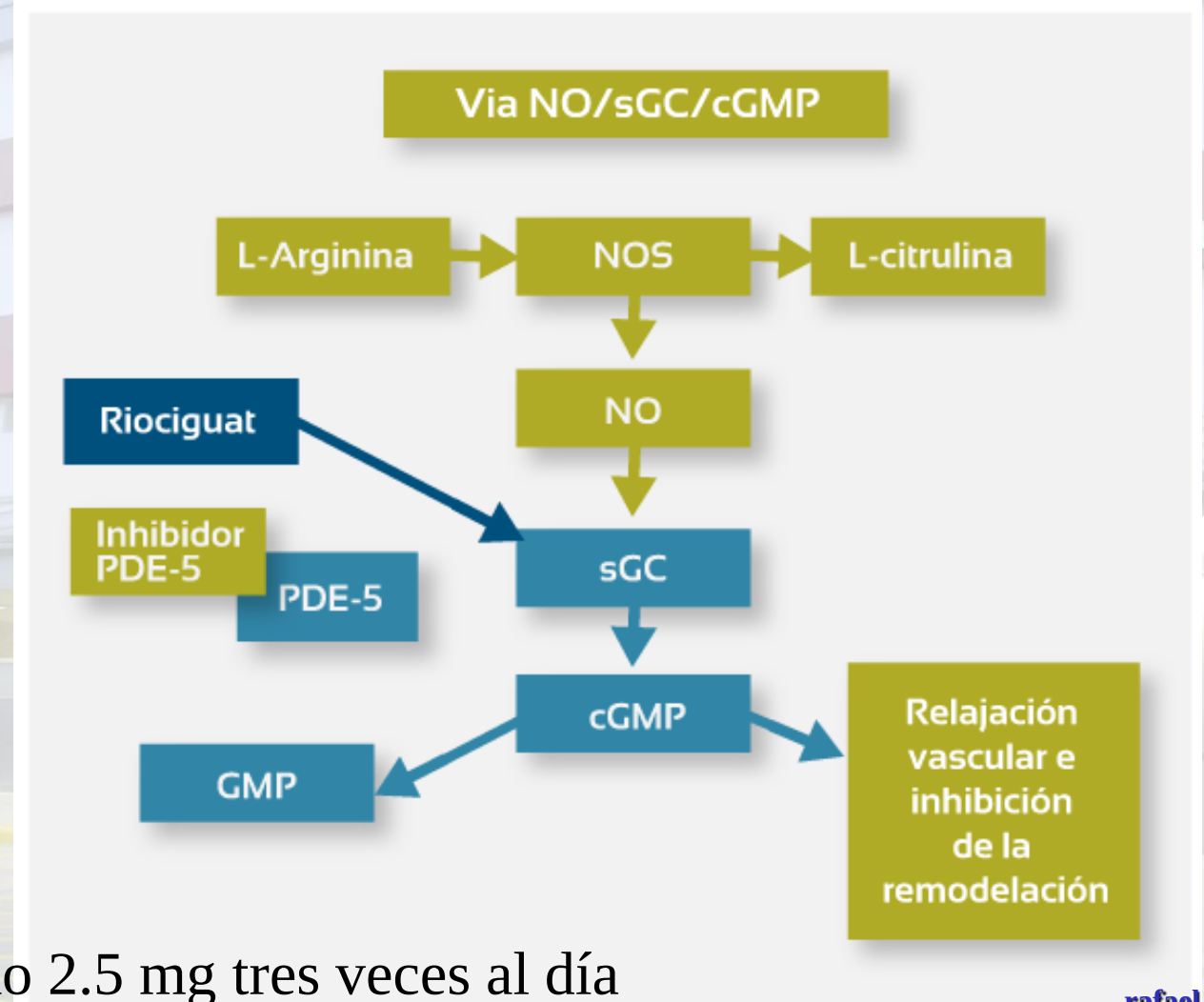
RIOCIGUAT



Máximo 2.5 mg tres veces al día

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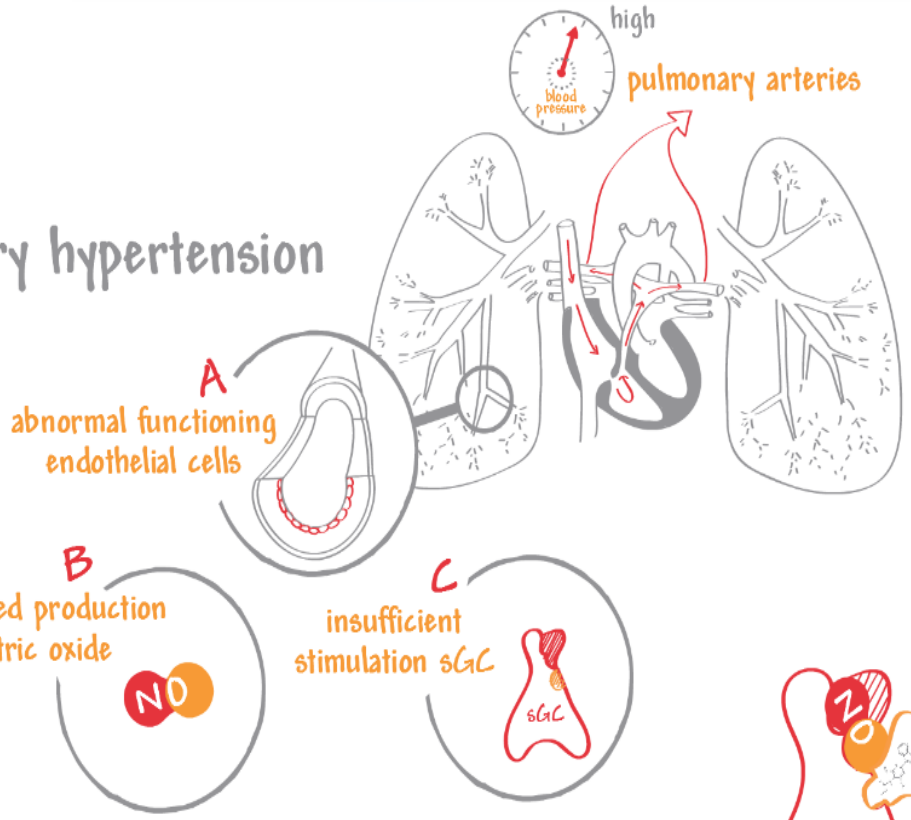
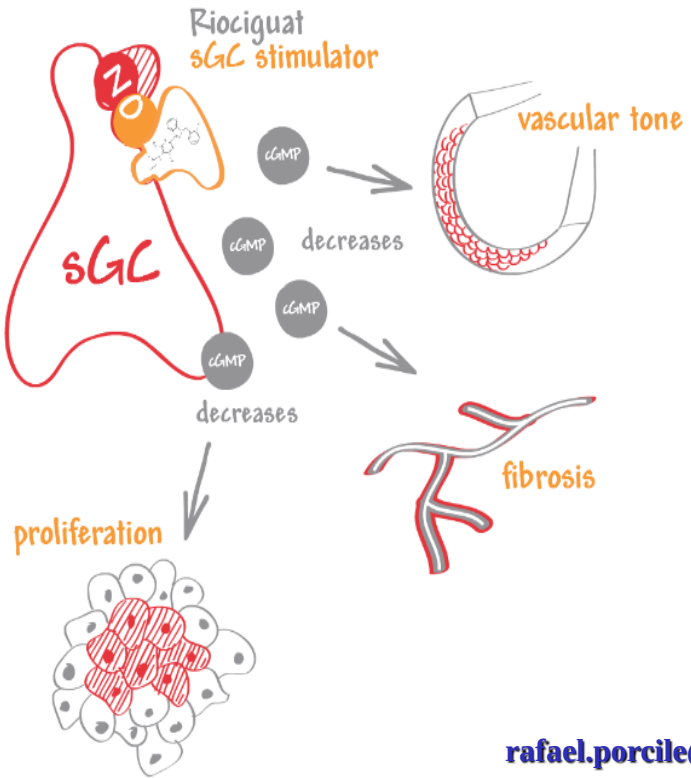
The Mode of Action of Riociguat

pulmonary hypertension





Riociguat sGC stimulator

- increases sensitivity of sGC to NO
- stimulates sGC directly independently of NO
- leading to increased generation of cGMP

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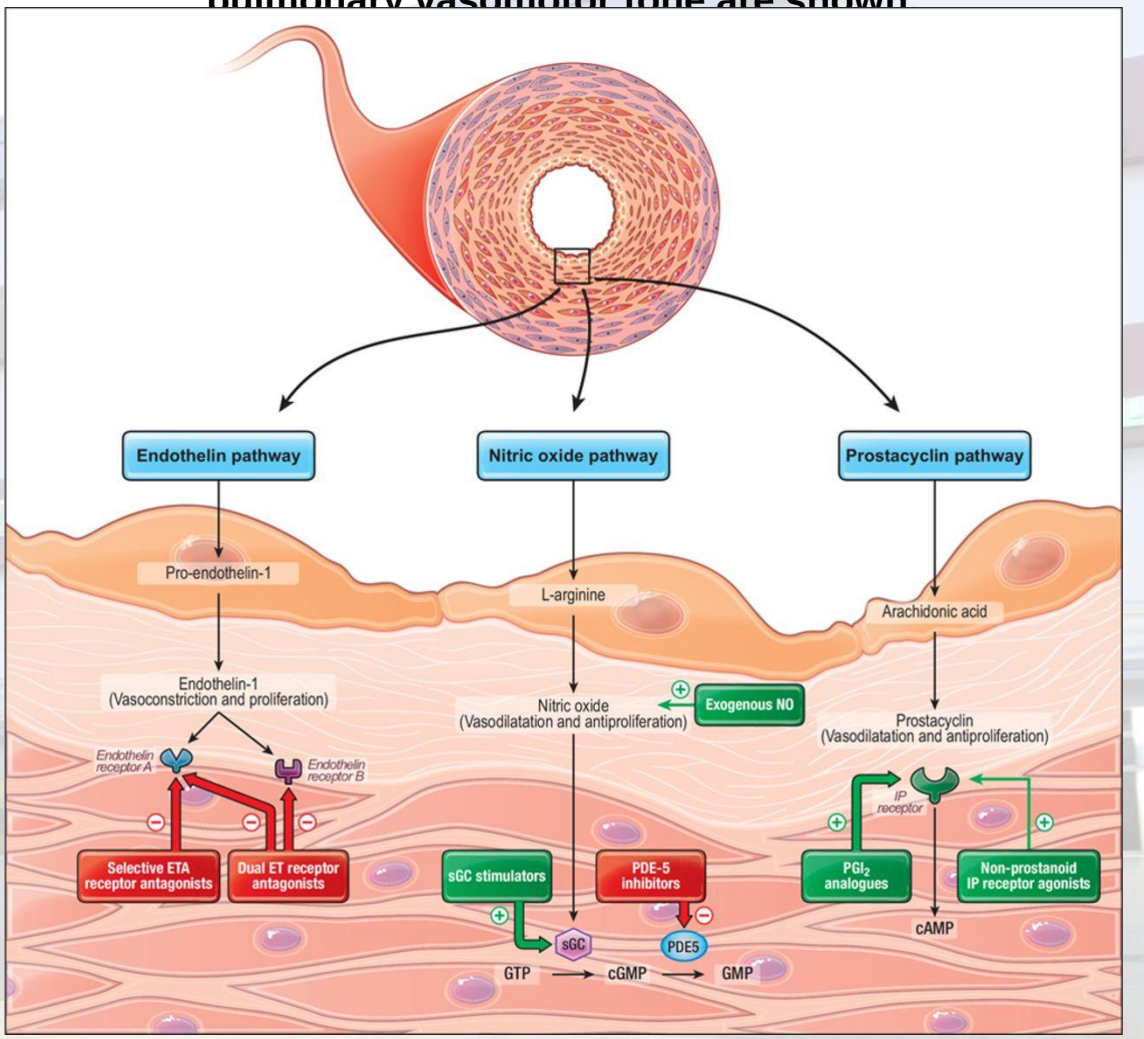
Established vasomotor pathways targeted by current and emerging therapies in PAH. The 3 major pathways (endothelin-1, nitric oxide, and prostacyclin) involved in the regulation of pulmonary vasomotor tone are shown



Humbert M et al. Circulation. 2014;130:2189-2208

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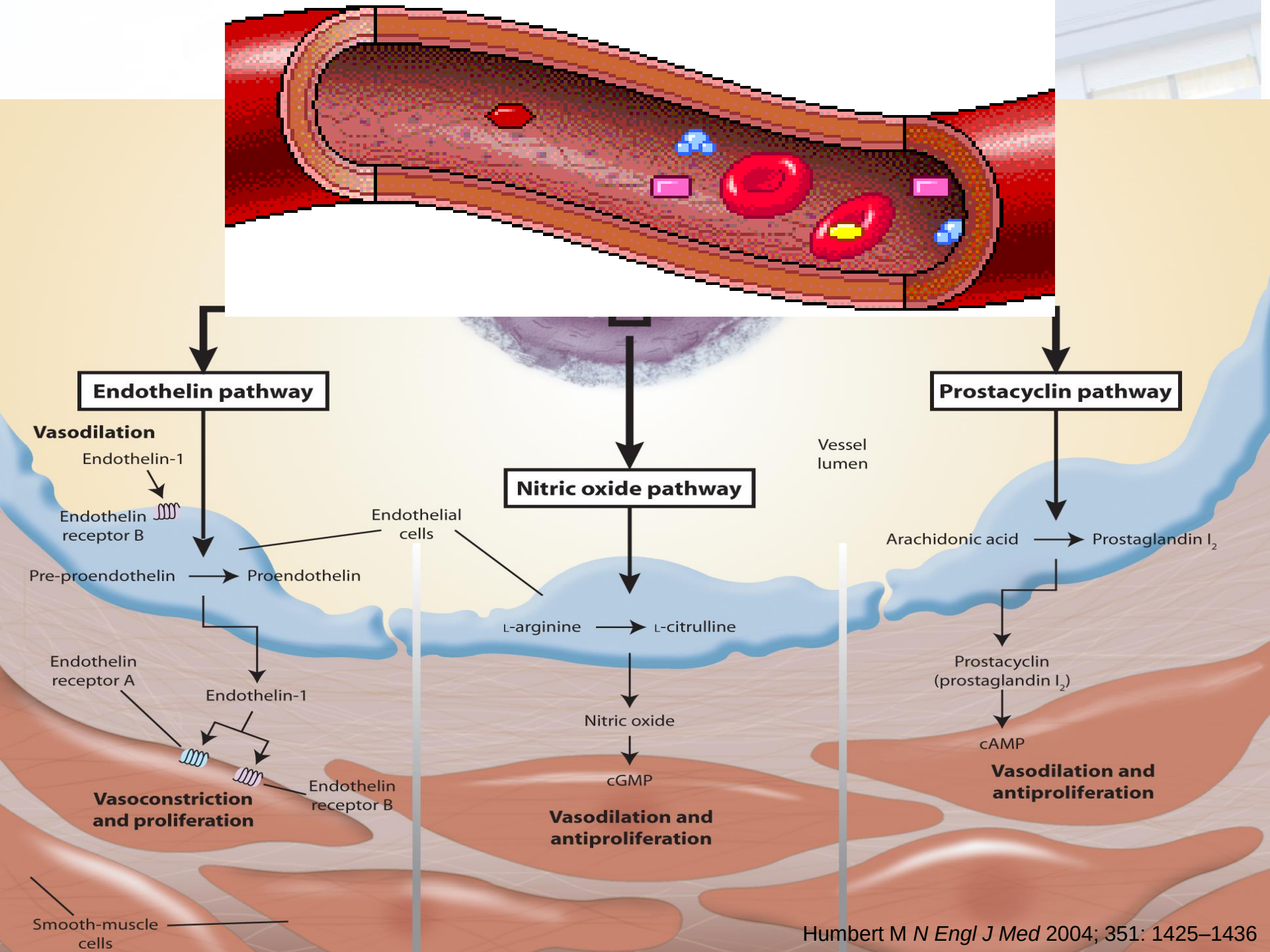

Humbert M *N Engl J Med* 2004; 351: 1425–1436

Chronic Thromboembolic Pulmonary Hypertension Soluble Guanylate Cyclase–Stimulator Trial 1 CHEST 1

Los pacientes que recibieron riociguat mostraron una **mejoría de la** 6MWD **estadísticamente significativa respecto del valor basal** +39 metros riociguat vs. -6 metros placebo

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Chronic Thromboembolic Pulmonary Hypertension Soluble Guanylate Cyclase–Stimulator Trial 2

dosis diarias de 2.5mg. Este estudio demuestra la seguridad y eficacia clínica a largo plazo de riociguat. Un análisis preliminar de los datos de 194 individuos, en la semana 12º, mostró la continuidad de la ganancia de metros en la prueba de 6MWD en los tratados con riociguat versus placebo.

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PATENT-1 *Pulmonary Arterial Hypertension Soluble Guanylate Cyclase–Stimulator Trial 1*

Mejoría estadísticamente significativa de la 6MWD **respecto del valor inicial** en comparación con placebo (promedio +30 metros riociguat 2.5 mg vs. -6 metros placebo; diferencia 36 metros; p< 0.001).

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Left Ventricular Systolic Dysfunction Associated With Pulmonary Hypertension

Riociguat *Trial*

A Phase IIb Double-Blind, Randomized, Placebo-Controlled, Dose-Ranging Hemodynamic Study

201 pacientes con insuficiencia cardiaca causada por HAP secundaria a disfunción sistólica ventricular izquierda.

Bonderman D et al. Circulation. 2013;128:502-511

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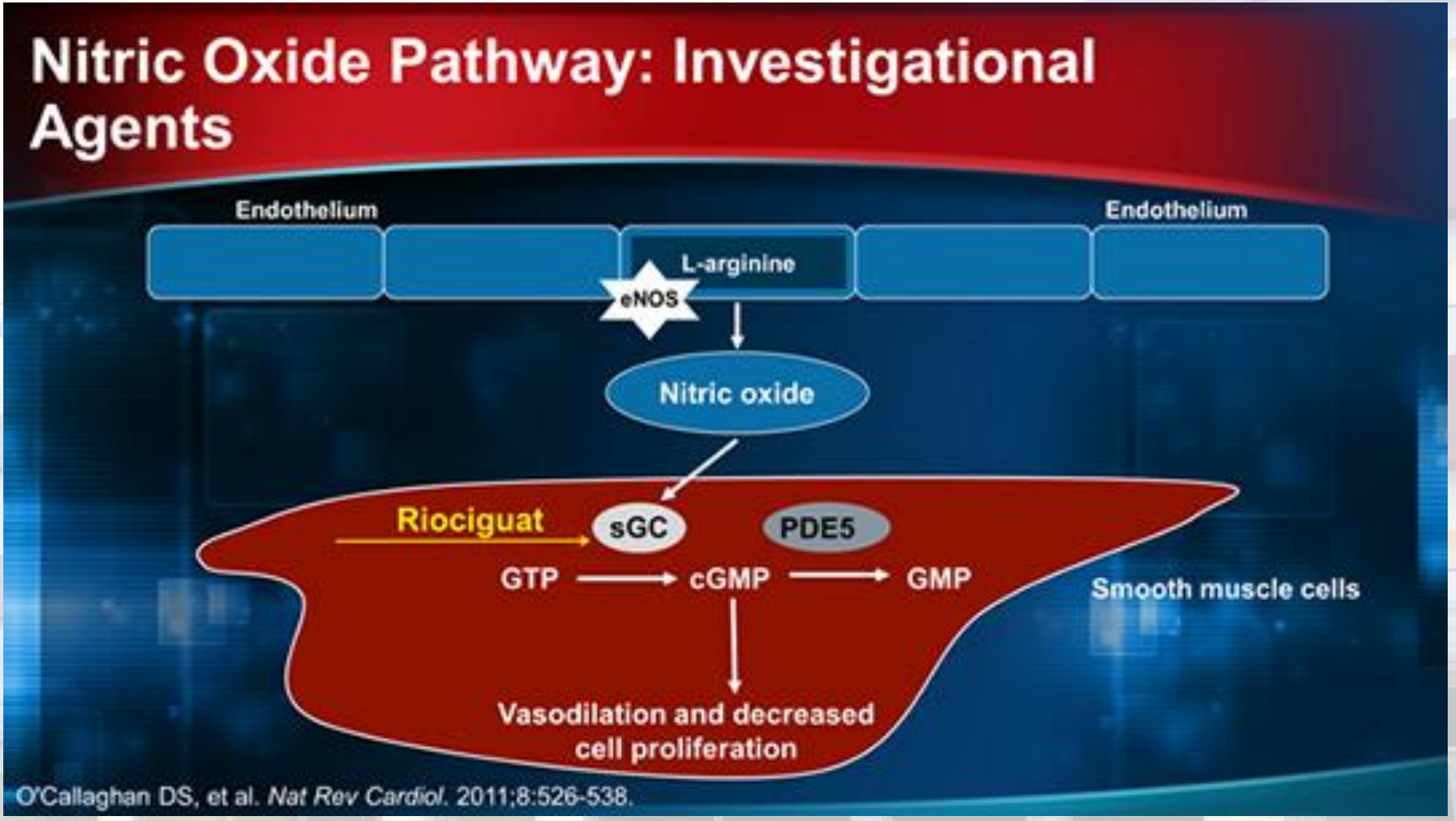
Nitric Oxide Pathway: Investigational Agents



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

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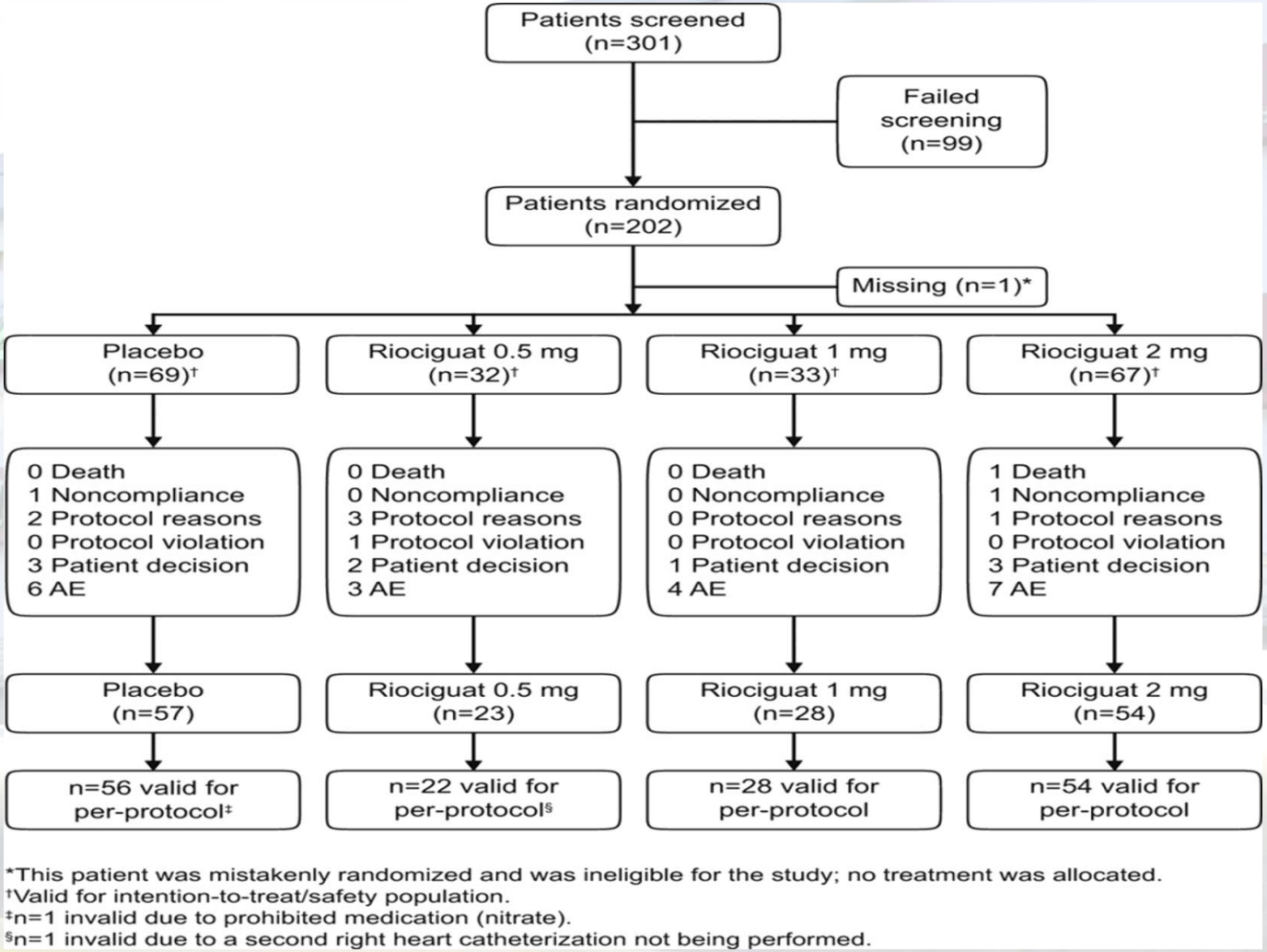
Patient flow.



*This patient was mistakenly randomized and was ineligible for the study; no treatment was allocated.
†Valid for intention-to-treat/safety population.
‡n=1 invalid due to prohibited medication (nitrate).
§n=1 invalid due to a second right heart catheterization not being performed.

Bonderman D et al. Circulation. 2013;128:502-511

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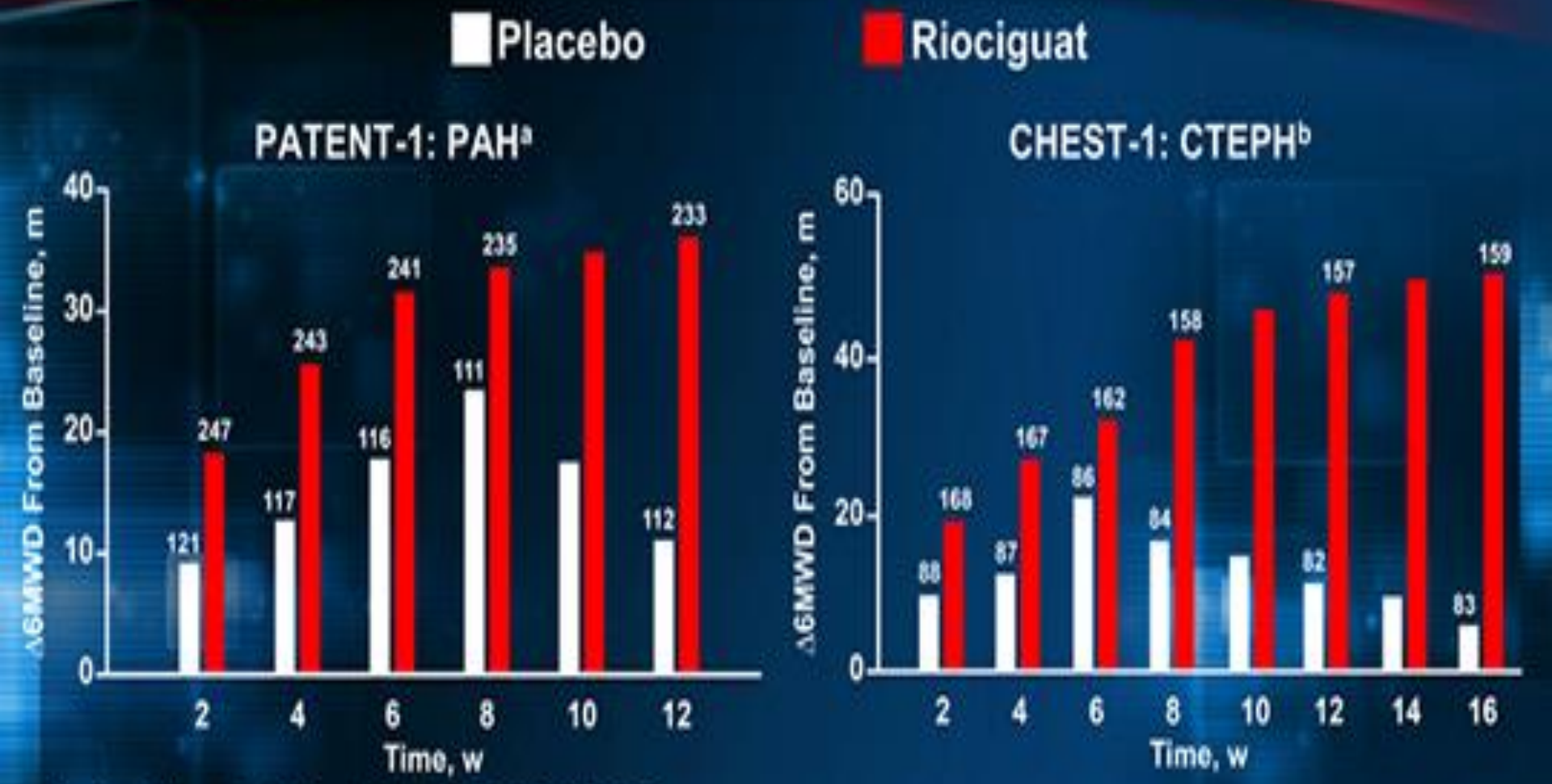
Efficacy in 2 Types of PH



a. Ghofrani HA, et al. *N Engl J Med.* 2013;369:330-340.

b. Ghofrani HA, et al. *N Engl J Med.* 2013;369:319-329.

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Left Ventricular Systolic Dysfunction Associated With Pulmonary Hypertension

Riociguat *Trial*

En el grupo tratado con tres dosis diarias de 2 mg de riociguat la mPAP disminuyó 6.1 mmHg versus la inicial ($p < 0.0001$), no obstante esta diferencia no resultó significativa respecto del placebo.

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Left Ventricular Systolic Dysfunction Associated With Pulmonary Hypertension

Riociguat *Trial*

Aumentaron el índice cardiaco (0.4 L⋅min^{-1}⋅m^{-2}; p= 0.0001) y el índice de volumen de eyección (5.2 ml⋅m^{-2}; p= 0.0018) sin que se observaran cambios en la frecuencia cardiaca ni la presión sistólica sistémica.

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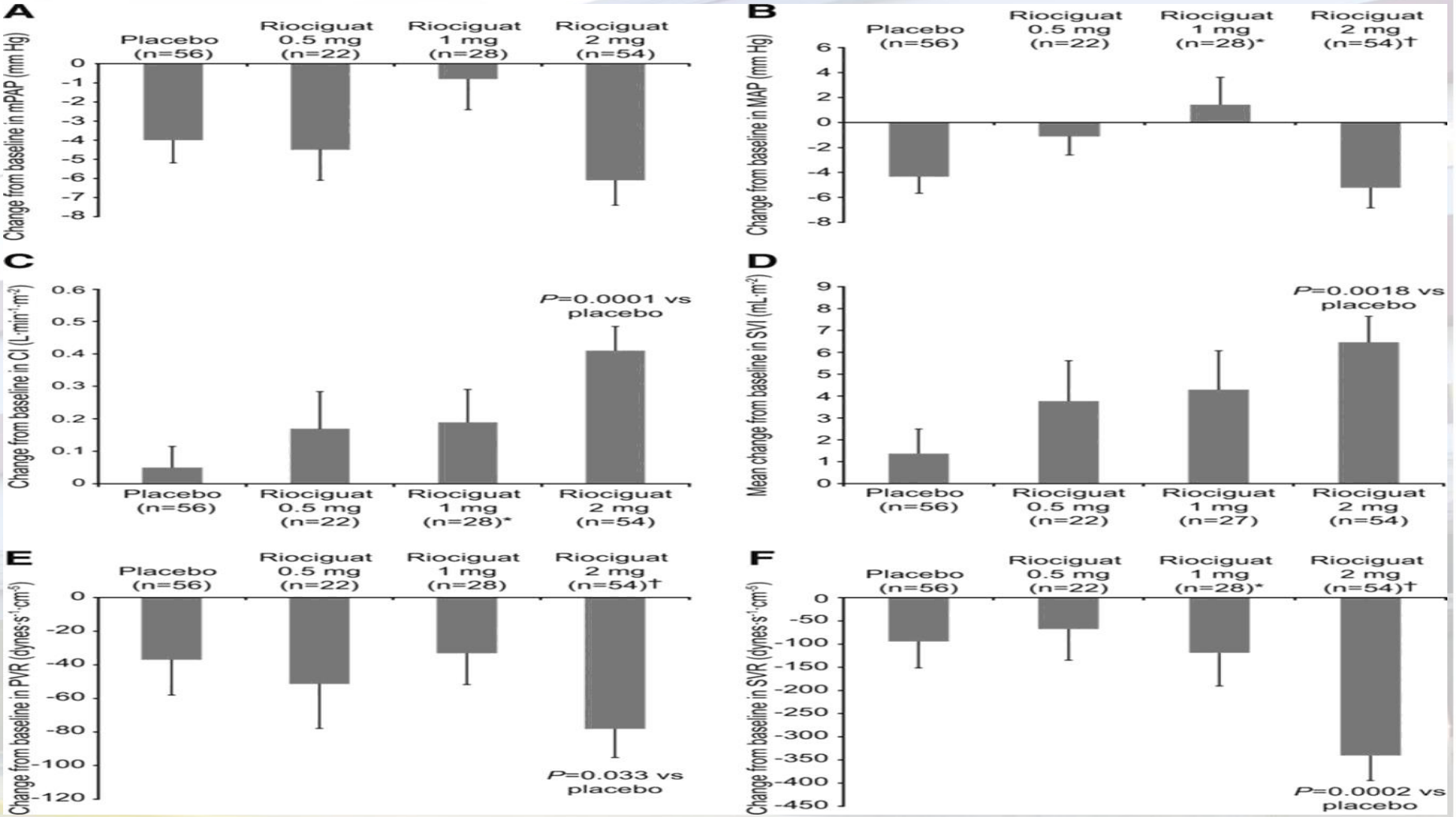
Mean±SEM changes from baseline at 16 weeks in hemodynamic parameters (per-protocol population).



Bonderman D et al. Circulation. 2013;128:502-511

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Left Ventricular Systolic Dysfunction Associated With Pulmonary Hypertension
***Riociguat** Trial*

Asimismo se registró una mejoría de la calidad de vida asociada al tratamiento con riociguat reflejada en una disminución de la puntuación del *Minnesota Living With Heart Failure Score* (p= 0.0002)

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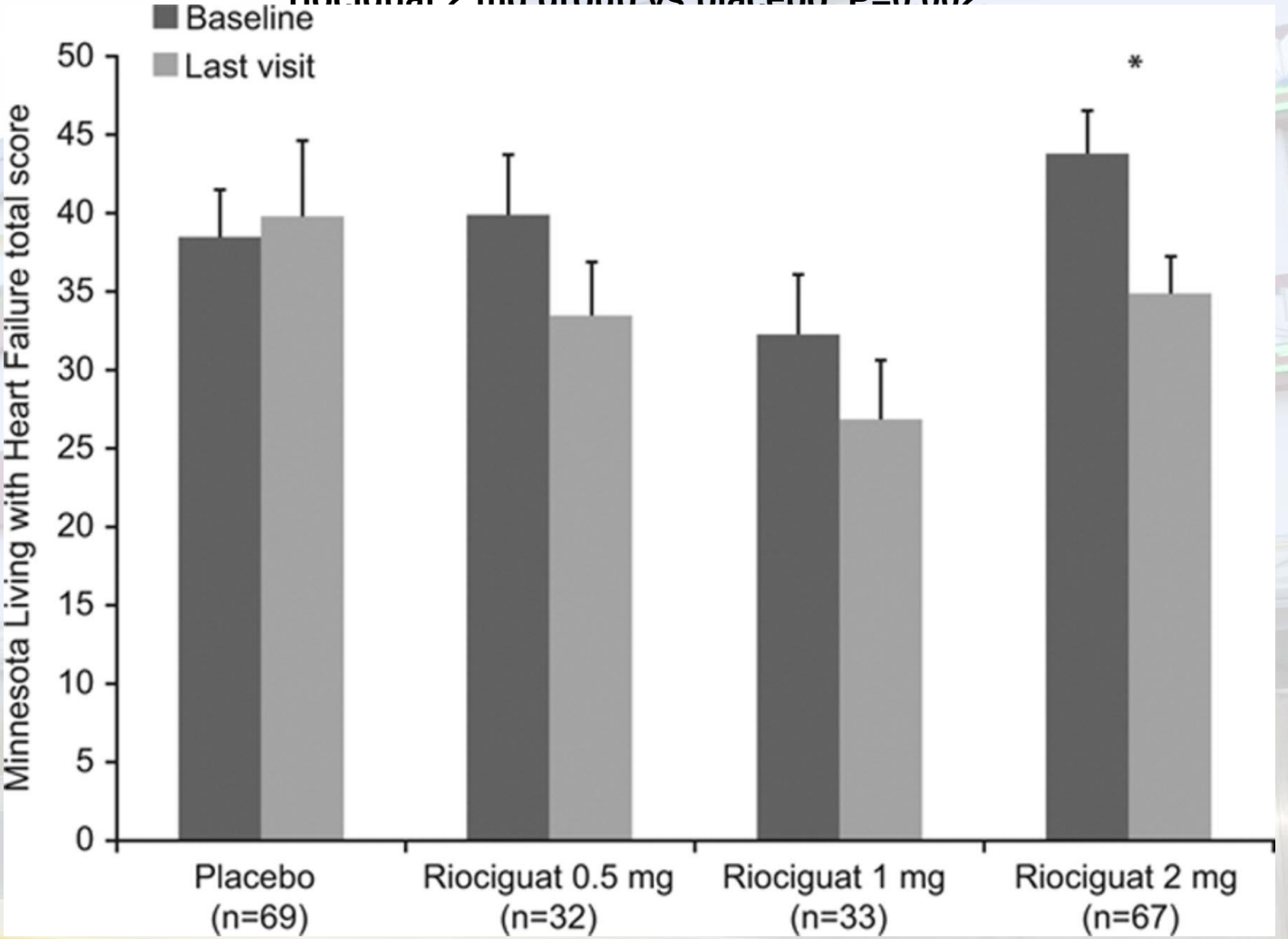
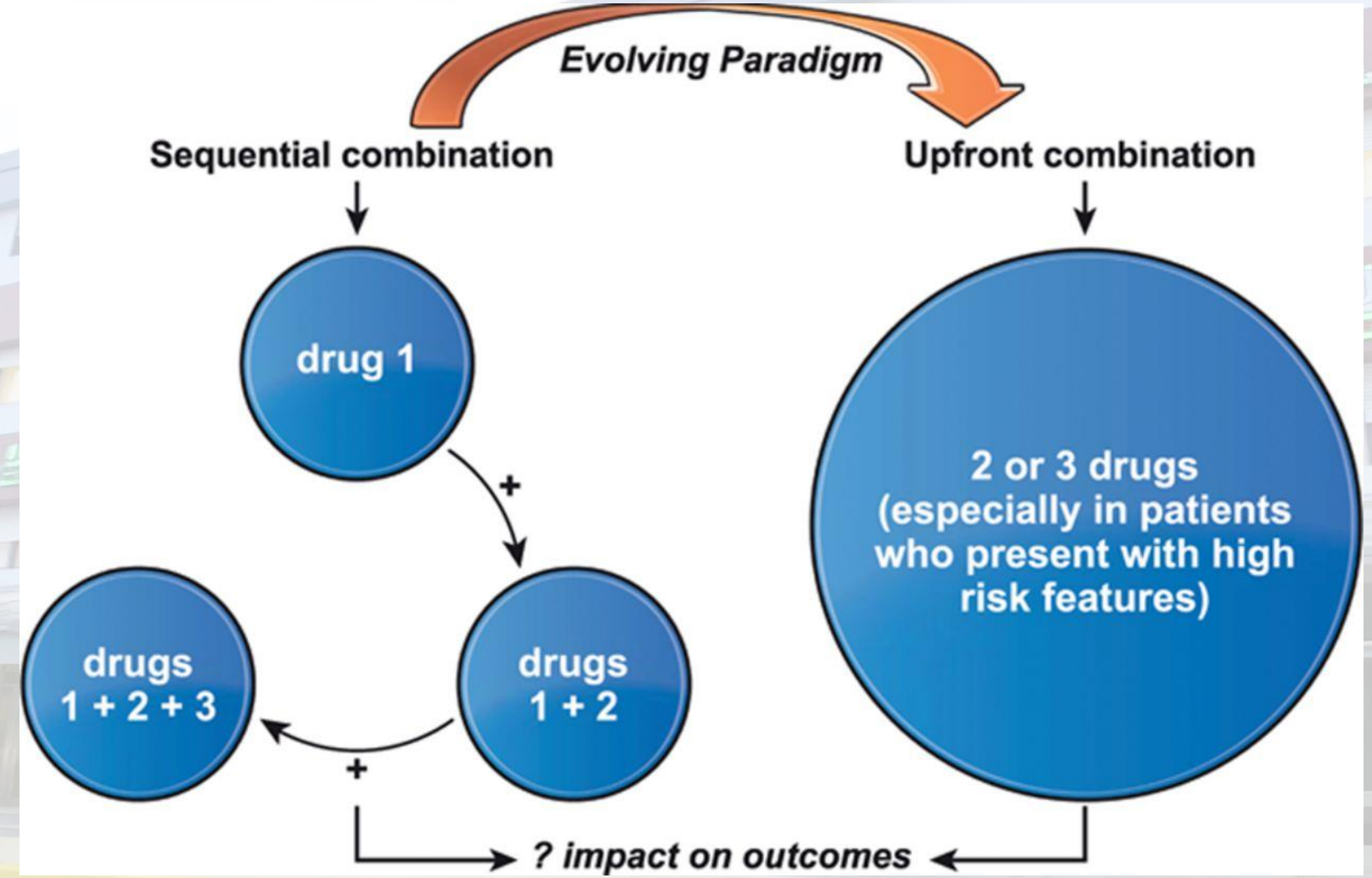
Minnesota Living With Heart Failure questionnaire total scores at baseline and last visit (intention-to-treat population). *Pairwise comparison of change from baseline (ANCOVA) for riociguat 2 mg group vs placebo, P=0.002



Bonderman D et al. Circulation. 2013;128:502-511

Paradigm of combination therapy in PAH. Combination therapy can be given by either sequentially adding agents if treatment response is unsatisfactory or by upfront combination.



Humbert M et al. Circulation. 2014;130:2189-2208

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Nuestra experiencia Con terapia combinada inicial bloquentes cálcicos , sildenafil, ambrisentan

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Once fueron tratados con ambrisentan por hipertensión arterial pulmonar del 2004 a la fecha todo perteneciente al grupo UAI salud o circuitos de seguridad social atendidos por nuestro sistema

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6,7 años de seguimiento promedio

Los resultados globales de los 11 pacientes son muy similares.

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¿Que herramientas utilizar
Para una evaluación ESTIMATIVA
De la evolución de esta pequeña población ?

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5 herramientas de estimación

- Calculador de riesgo del REVEAL
- Evaluación de corte de la evolución clínica a los 36 meses
- Curva Kaplan Meier del REVEAL
- Mortalidad prevista según test de caminata inicial
- Mortalidad prevista según clase funcional OMS.

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Reflexiones…

A los **12 meses** de

seguiminto

AÑOS
2005/2006

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2004-2005

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The REVEAL Registry risk score calculator in patients newly diagnosed with pulmonary arterial hypertension.

Chest. 2012 Feb;141(2):354-62. doi: 10.1378/chest.11-0676. Epub 2011 Jun 16.

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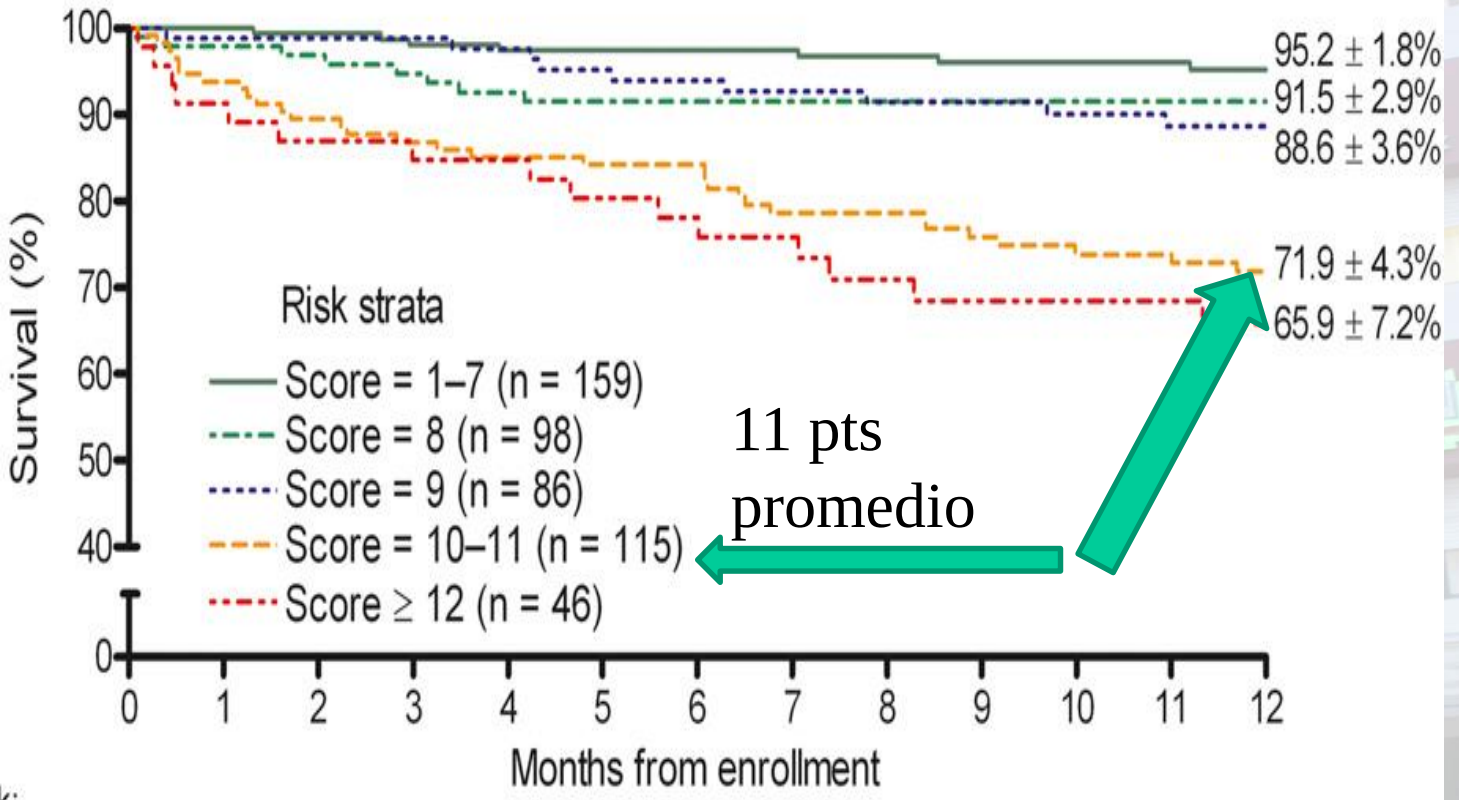
B

Risk calculator



11 pts promedio

No. at risk:													
Score = 1–7	159	156	155	151	150	150	150	141	140	139	120	120	119
Score = 8	98	93	91	89	87	86	86	84	81	81	71	71	71
Score = 9	86	84	84	81	80	78	77	73	72	72	65	64	64
Score = 10–11	115	107	102	99	96	95	95	85	85	82	74	74	72
Score ≥ 12	46	42	40	38	38	36	35	31	29	28	26	26	25

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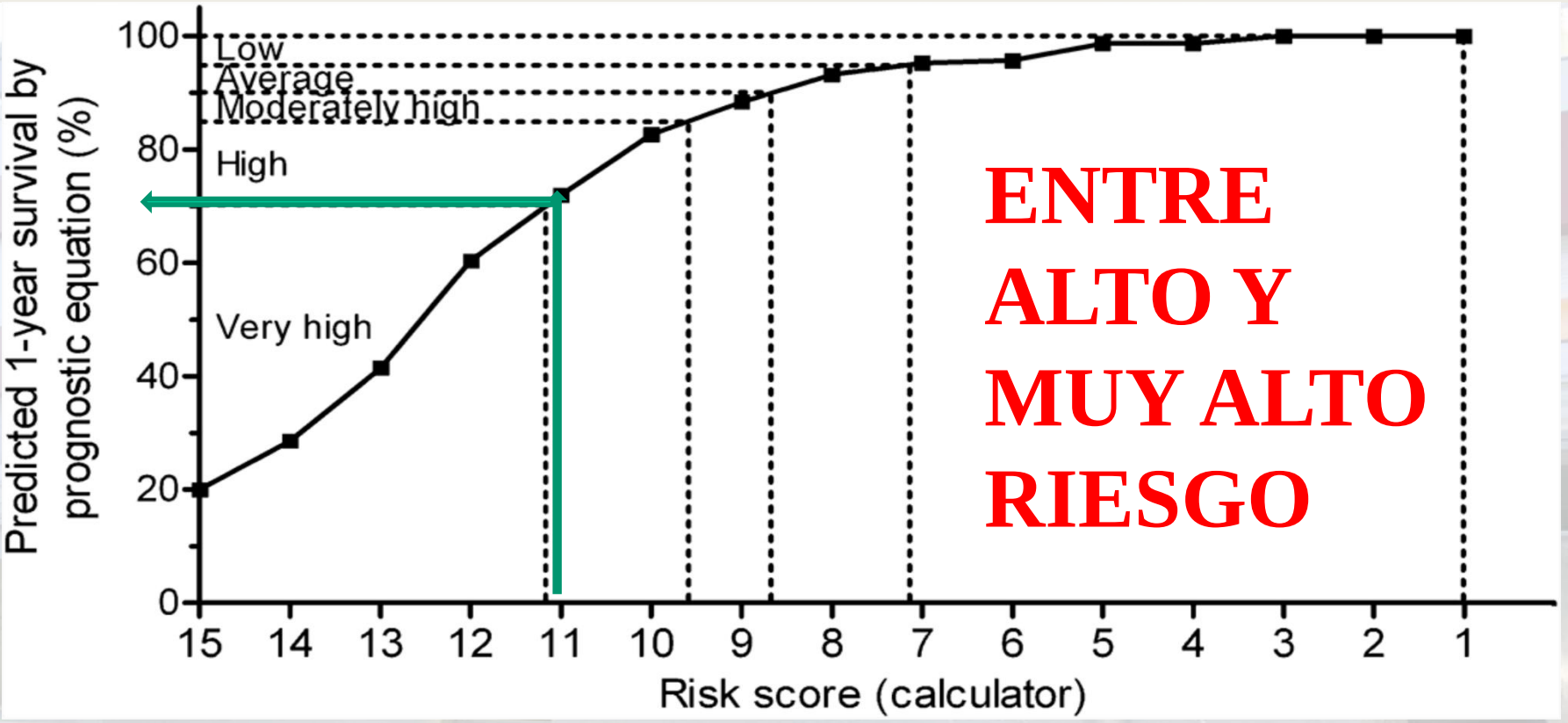
From: The REVEAL Registry Risk Score Calculator in Patients Newly Diagnosed With Pulmonary Arterial HypertensionValidation of the REVEAL Registry Risk Calculator

Chest. 2012;141(2):354-362. doi:10.1378/chest.11-0676



Twelve-month Kaplan-Meier survival estimate for the REVEAL Registry development cohort with predicted risk score. Risk strata are indicated by the lines: predicted 1-year survival is 95% to 100% in the low-risk group, 90% to < 95% in the average-risk group, 85% to < 90% in the moderately high-risk group, 70% to < 85% in the high-risk group, and < 70% in the very high-risk group. See Figure 1 legend for expansion of abbreviation.

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Reflexiones… No Conclusiones

- Sobrevida esperada promedio de los 5 pacientes al año subestimada por no ponderar BNP según REVEAL **71.9.%**

- **Sobrevida UAI observada al**
  - **1 año 100 %**

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Reflexiones…

A los

Tres años de

seguimiento

AÑOS
2007/2008

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EVOLUCIÓN CLINICA

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- **Buena tolerancia al fármaco sin hepatotoxicidad**
- **Caída del test de caminata respecto del mejor histórico en todos los casos mayor al 6-11 % que mejora al agregarle sildenafil a partir del ingreso a Aries Ext.**
- **Reducción de la presión arterial pulmonar a expensas predominantemente de la presión sistólicas**

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Reflexiones…

A los **4 años** de seguimiento

AÑOS
2008/2009

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Survival estimates of patients in REVEAL using Kaplan–Meier estimates stratified by newly versus previously diagnosed patients and survival estimated by a delayed entry model accounting for truncation

M.D. McGoon, and D.P. Miller
Eur Respir Rev 2012;21:8-18

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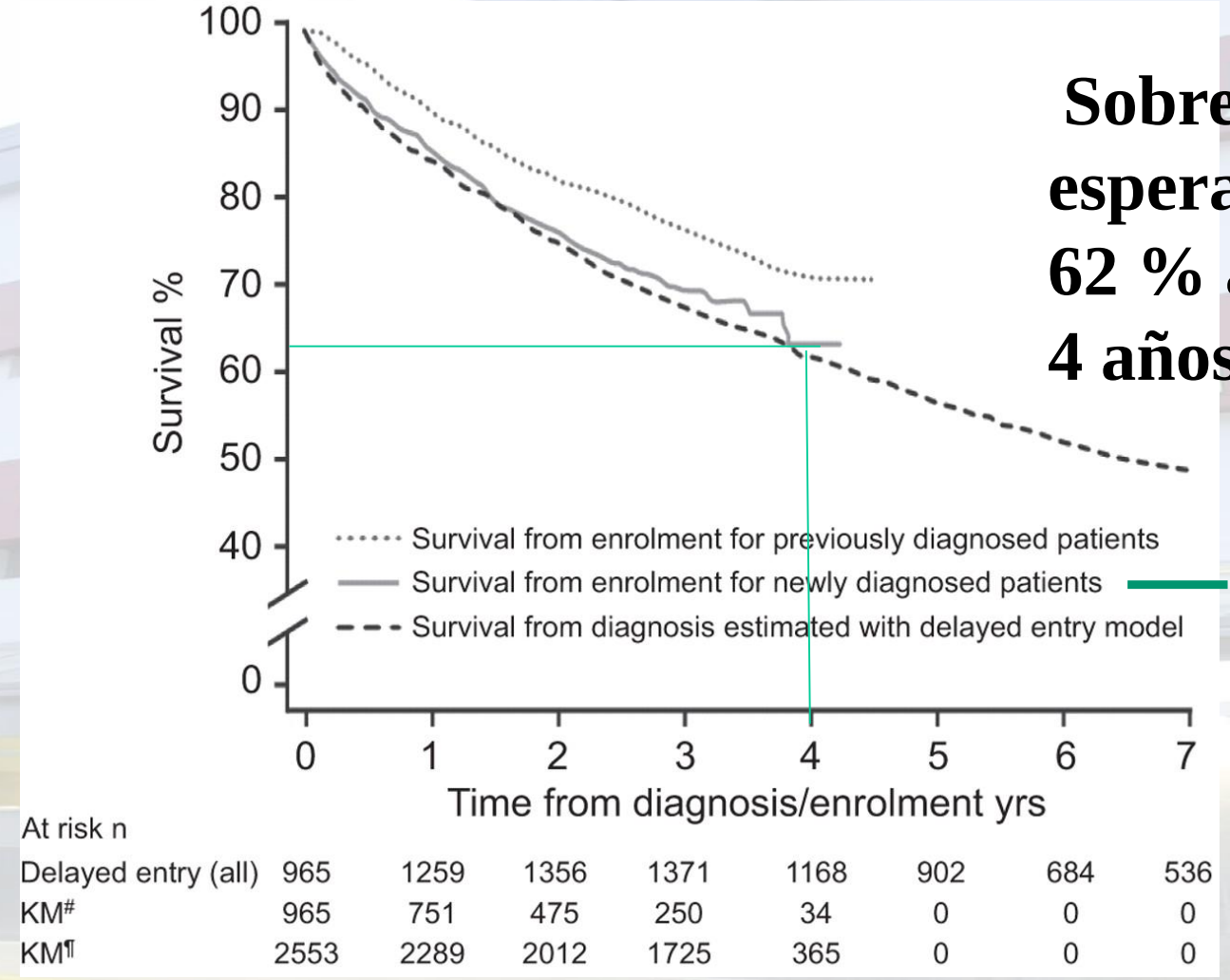
Survival estimates of patients in REVEAL using Kaplan–Meier estimates stratified by newly versus previously diagnosed patients and survival estimated by a delayed entry model accounting for truncation.



At risk n								
Delayed entry (all)	965	1259	1356	1371	1168	902	684	536
KM#	965	751	475	250	34	0	0	0
KM¶	2553	2289	2012	1725	365	0	0	0

Sobrevida esperada 62 % a los 4 años

M.D. McGoon, and D.P. Miller Eur Respir Rev 2012;21:8-18

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Reflexiones… No Conclusiones

- Sobrevida esperada promedio a los 4 años

62%

- Sobrevida UAI observada al
  - 1 año 100 %
  - 2 años 80%
  - 3 años 80 %
  - **4 años 80%**
  - 5 años 60 %
  - 11 años 60%

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Reflexiones…

A los **6 años** de seguimiento

AÑOS
2010/2011

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SOBREVIDA

O.M.S: 199876

Expectativa de vida según clase funcional

WHO-FC IV, 2.5 AÑOS

WHO-FC III, 6 AÑOS

WHO-FC I and II. 8 AÑOS

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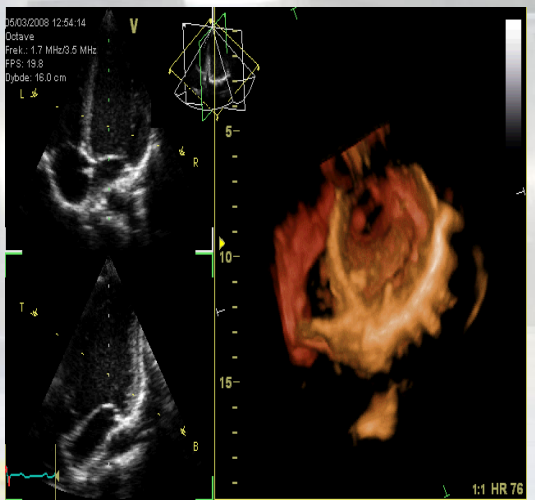
Clasificación funcional según New York Heart Association de acuerdo a O.M.S: 199876

WHO-FC IV, 2.5 AÑOS

WHO-FC III, 6 AÑOS

WHO-FC I and II. 8 AÑOS

Se esperaría que todos los pacientes hubiesen fallecido a los seis años



Reflexiones… No Conclusiones

- Mortalidad esperada promedio a los 11 años

100%

- Sobrevida observada al
  - 1 año 100 %
  - 2 años 80%
  - 3 años 80 %
  - 4 años 80%
  - 5 años 60 %
  - **11 años 60%**

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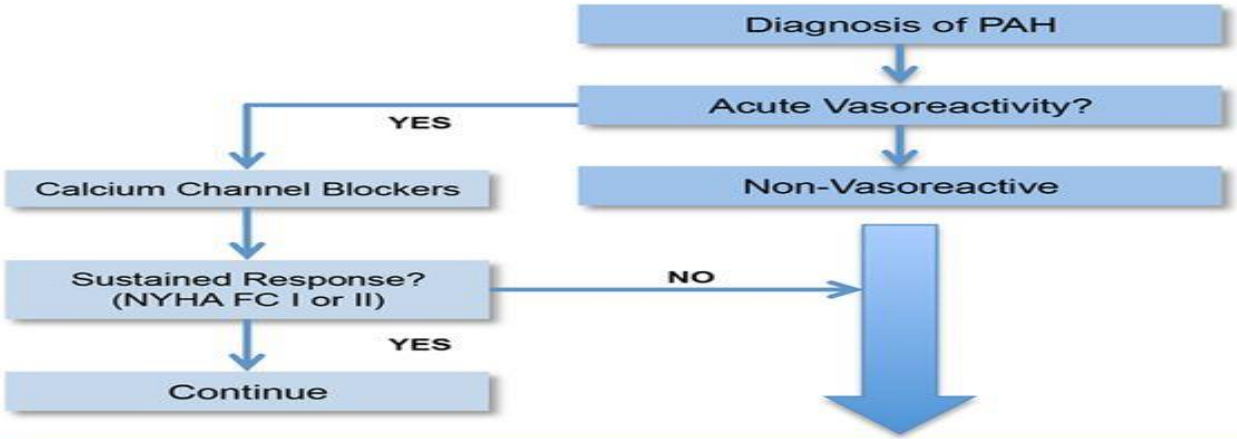
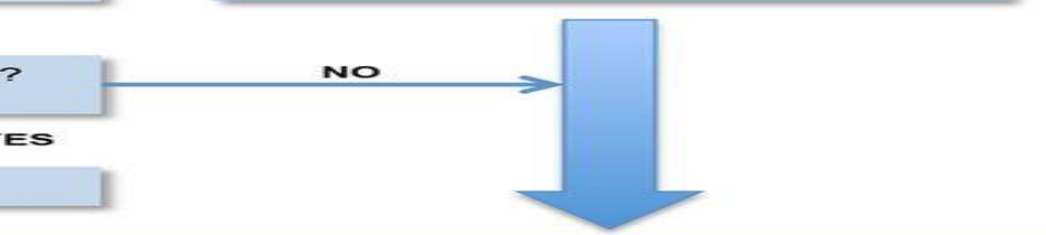


Therapy with Approved PAH Drugs

Recommendation	Evidence	FC II	FC III	FC IV
I	A or B	Ambrisentan Bosentan Macitentan# Riociguat Sildenafil Tadalafil	Ambrisentan Bosentan Epoprostenol IV* Iloprost inhaled Macitentan# Riociguat Sildenafil Tadalafil Treprostinil SC, inhaled	Epoprostenol IV*
IIa	C		Iloprost IV Treprostinil IV	Ambrisentan Bosentan Iloprost inhaled, IV Macitentan# Riociguat Sildenafil Tadalafil Treprostinil SC, IV
IIb	B		Beraprost	
	C		Upfront Combination	Upfront Combination



Therapy with Approved PAH Drugs		
Evidence		FC III
A or B		Ambrisentan Bosentan Epoprostenol IV* Iloprost inhaled Macitentan# Riociguat Sildenafil Tadalafil Treprostinil SC, inhaled
C		Iloprost IV Treprostinil IV
B		Beraprost
C		Upfront Combination

WHO-FC III, 6 AÑOS

EVIDENCIA PARA TERAPEUTICA EN CFIII

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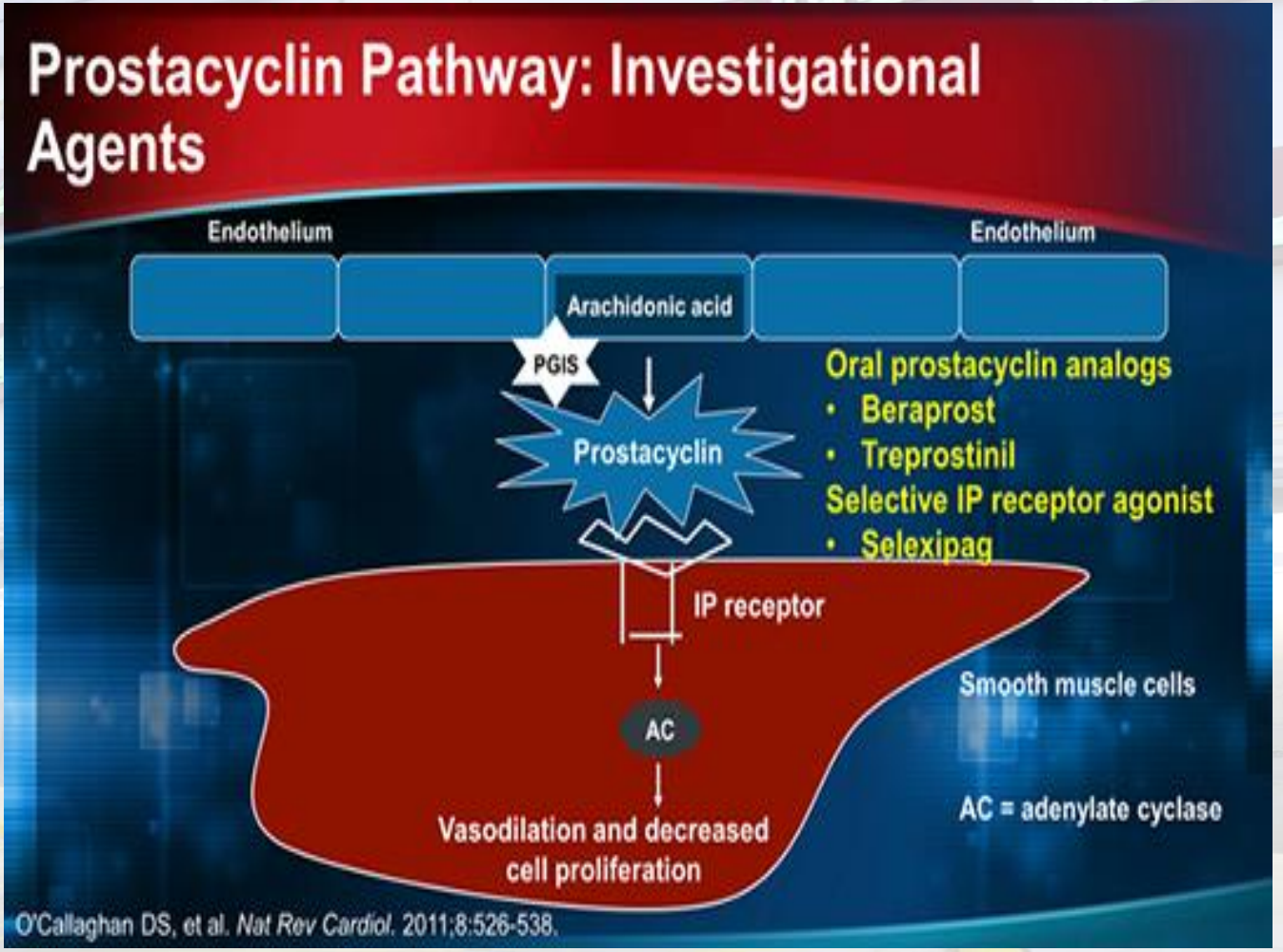
Análogos de las prostaciclinas



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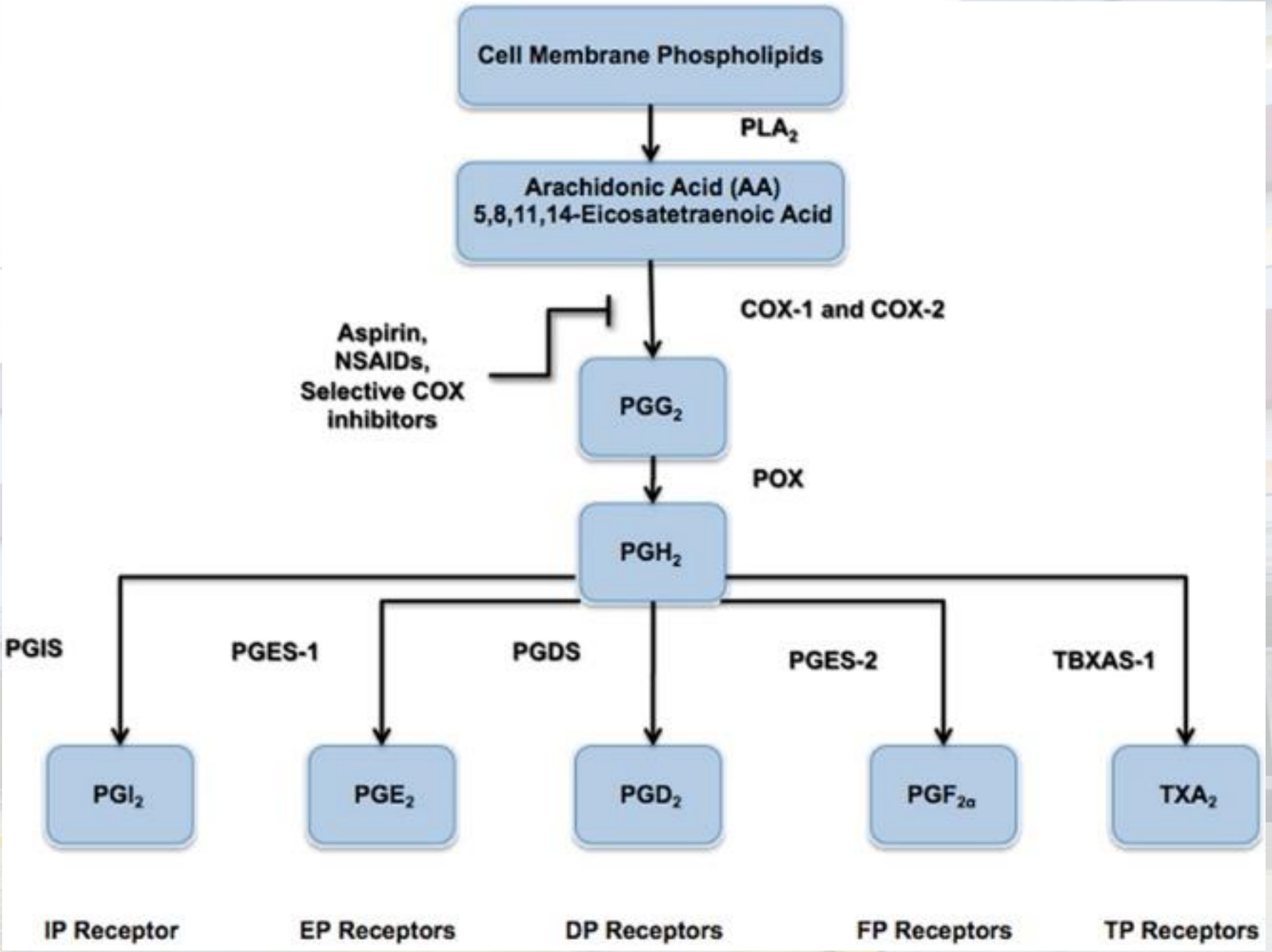

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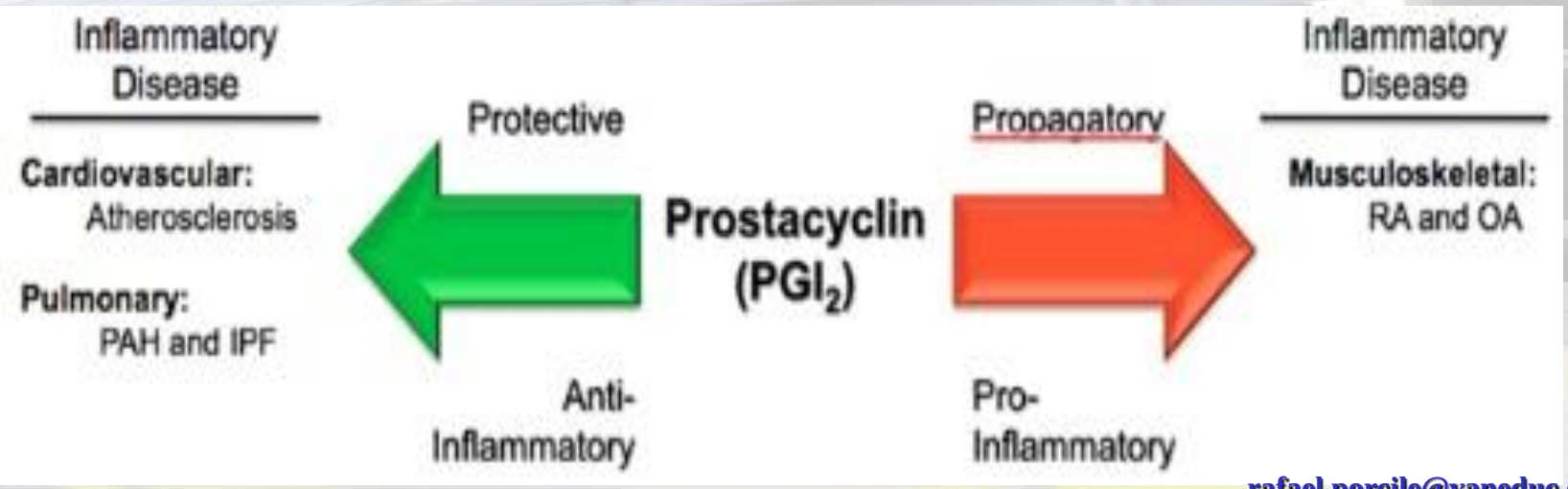
Selexipag

Selexipag is a prostacyclin IP receptor agonist. It is not prostacyclin or a prostacyclin analog. It is orally available and undergoes rapid hydrolysis to the active metabolite, ACT-333679



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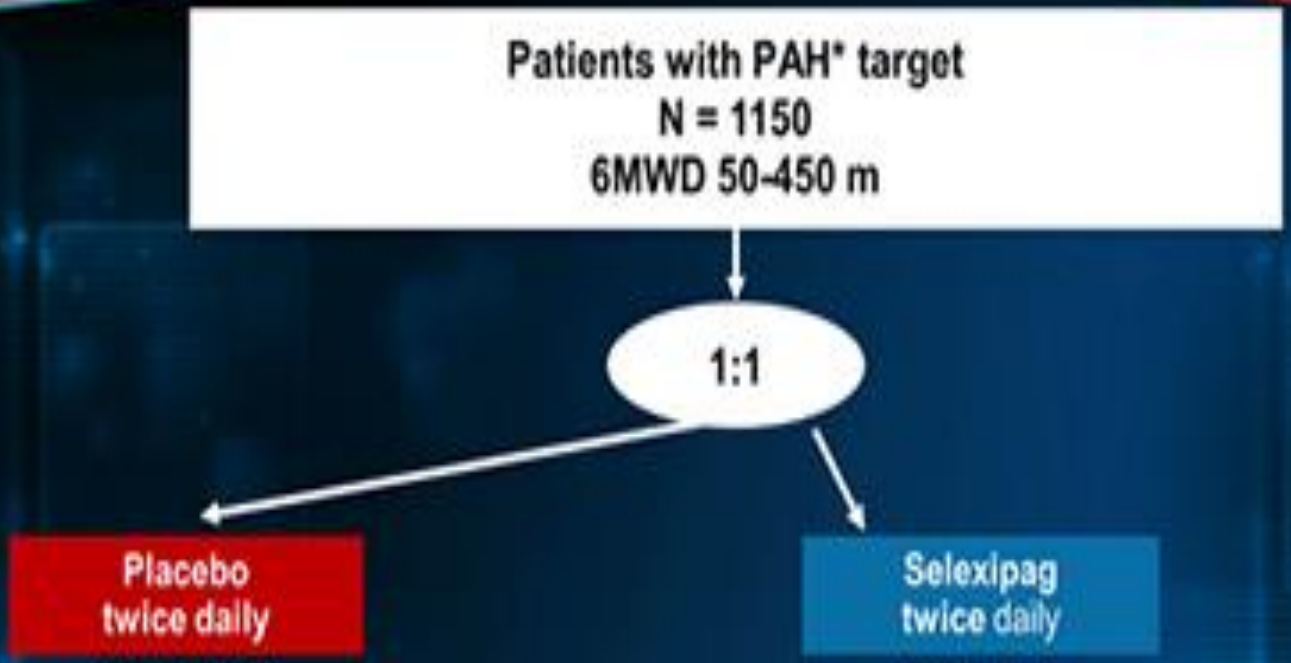
GRIPHON



Primary efficacy end point: time to first morbidity/mortality event

*IPAH; FPAH; APAH-CTD; simple, congenital systemic-to-pulmonary shunts ≥1 year postsurgical repair; HIV infection; or drugs and toxins.

http://clinicaltrials.gov/ct2/show/NCT01106014

Selexipag

Selective prostacyclin IP receptor agonist

The GRIPHON study was the largest outcome trial ever conducted in PAH, enrolling patients in 181 centers from 39 countries in North and Latin America, Europe, Asia-Pacific and Africa.
GRIPHON enrollment was completed in May 2013 with 1’156 patients. Patients received twice daily administration of selexipag or placebo and were also permitted to receive background therapy of endothelin receptor antagonist and/or a phosphodiesterase-5 inhibitor when on a stable dose for at least 3 months prior to enrollment. At baseline, 80% of patients were receiving oral medication specific for PAH: either an ERA, a PDE-5 inhibitor, or a combination of the two.

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Selexipag

Selective prostacyclin IP receptor agonist

The GRIPHON study

Designed to demonstrate a prolongation of time to the first morbidity/mortality event for selexipag compared to placebo and to evaluate the safety of the selexipag in PAH patients.

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Selexipag

Selective prostacyclin IP receptor agonist

The GRIPHON study

.

Selexipag decreased the risk of a morbidity/mortality event versus placebo by 39% ($p<0.0001$). Efficacy observed was consistent across the key subgroups: age, gender, WHO Functional Class, PAH etiology and background PAH therapy. Patients were treated for up to 4.3 years. The overall tolerability profile of selexipag in GRIPHON was consistent with prostacyclin therapies

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Iloprost nebulizado

WHO Class III

3-4hrly nebulisers

En argentina solo forma inhalatoria

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Inhaled iloprost for severe pulmonary hypertension

There were increases in the distance walked in six minutes of 36.4 m in the iloprost group

N Engl J Med. 2002 Aug 1;347(5):322-9

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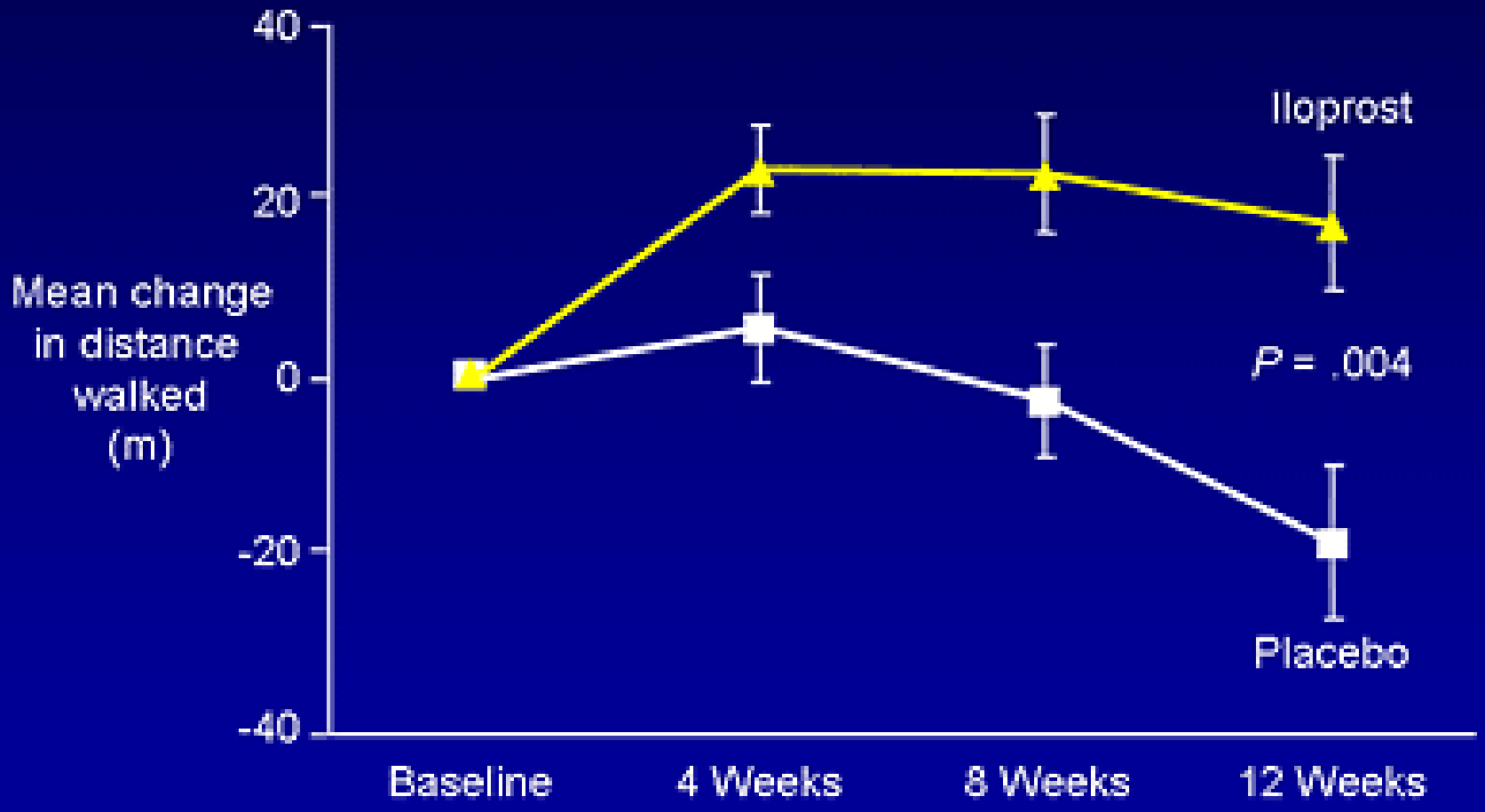
Effect of Inhaled Iloprost and Placebo on Mean Change in 6-Minute Walk



Olschewski H et al. *N Engl J Med*. 2002;347:322-329.

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Does the Outcome Justify an Oral-First Treatment Strategy for Management of Pulmonary Arterial Hypertension?

Guidelines for treatment of World Health Organization (WHO) functional class (FC) III pulmonary arterial hypertension (PAH) allow for oral therapy or parenteral prostacyclins at the discretion of expert clinicians.

Chest.2011 May 26

Cornwell WK McLaughlin VV Krishnan SM Rubenfire M

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Does the Outcome Justify an Oral-First Treatment Strategy for Management of Pulmonary Arterial Hypertension?

the clinical decision for treatment with an oral-first strategy is associated with a high survival rate when patients are appropriately risk-stratified prior to initiation of therapy. **The more potent prostacyclins can be reserved for high-risk patients or evidence of disease progression or treatment failure.**

Chest.2011 May 26

rafael.porcile@vaneduc.edu.ar

The potential for inhaled treprostinil in the treatment of pulmonary arterial hypertension.

Ther Adv Respir Dis. 2011 Jun ;5(3):195-206. Epub 2011 Feb 7.

Demonstrated pronounced pulmonary selectivity of vasodilatory effects, improved physical capacity and excellent tolerability and safety following aerosol administration

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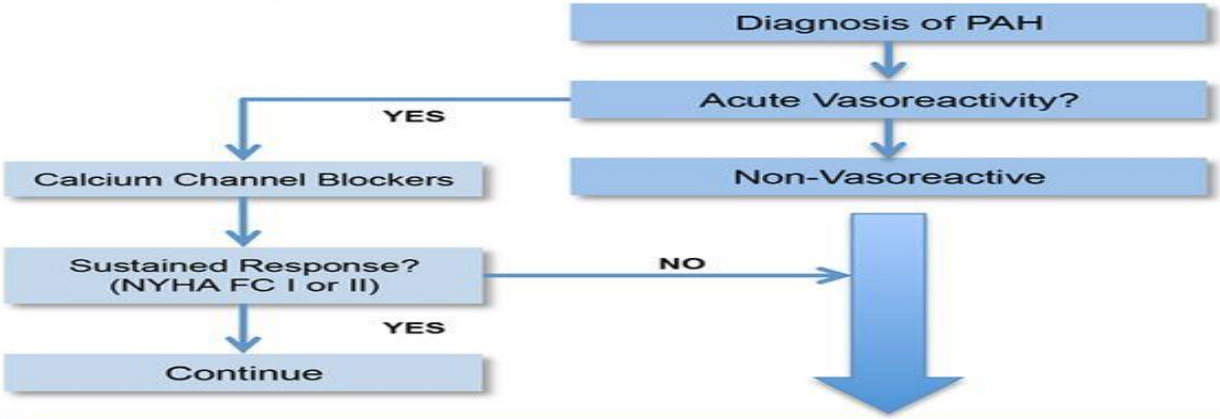

Therapy with Approved PAH Drugs

Recommendation	Evidence	FC II	FC III	FC IV
I	A or B	Ambrisentan Bosentan Macitentan# Riociguat Sildenafil Tadalafil	Ambrisentan Bosentan Epoprostenol IV* Iloprost inhaled Macitentan# Riociguat Sildenafil Tadalafil Treprostinil SC, inhaled	Epoprostenol IV*
IIa	C		Iloprost IV Treprostinil IV	Ambrisentan Bosentan Iloprost inhaled, IV Macitentan# Riociguat Sildenafil Tadalafil Treprostinil SC, IV
IIb	B		Beraprost	
	C		Upfront Combination	Upfront Combination

Therapy with Approved PAH Drugs

Evidence			FC IV
A or B			Epoprostenol IV*
C			Ambrisentan Bosentan Iloprost inhaled, IV Macitentan# Riociguat Sildenafil Tadalafil Treprostinil SC, IV
B			
C			Upfront Combination

WHO-FC IV
2.5 AÑOS

EVIDENCIA PARA TERAPEUTICA EN CFIV

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Epoprostenol (Flolan)

WHO Class III / IV

Intravenous via central venouscatheter

Half life approx 4

Minutes

DIFICIL

DISPONIBILIDAD

EN ARGENTINA

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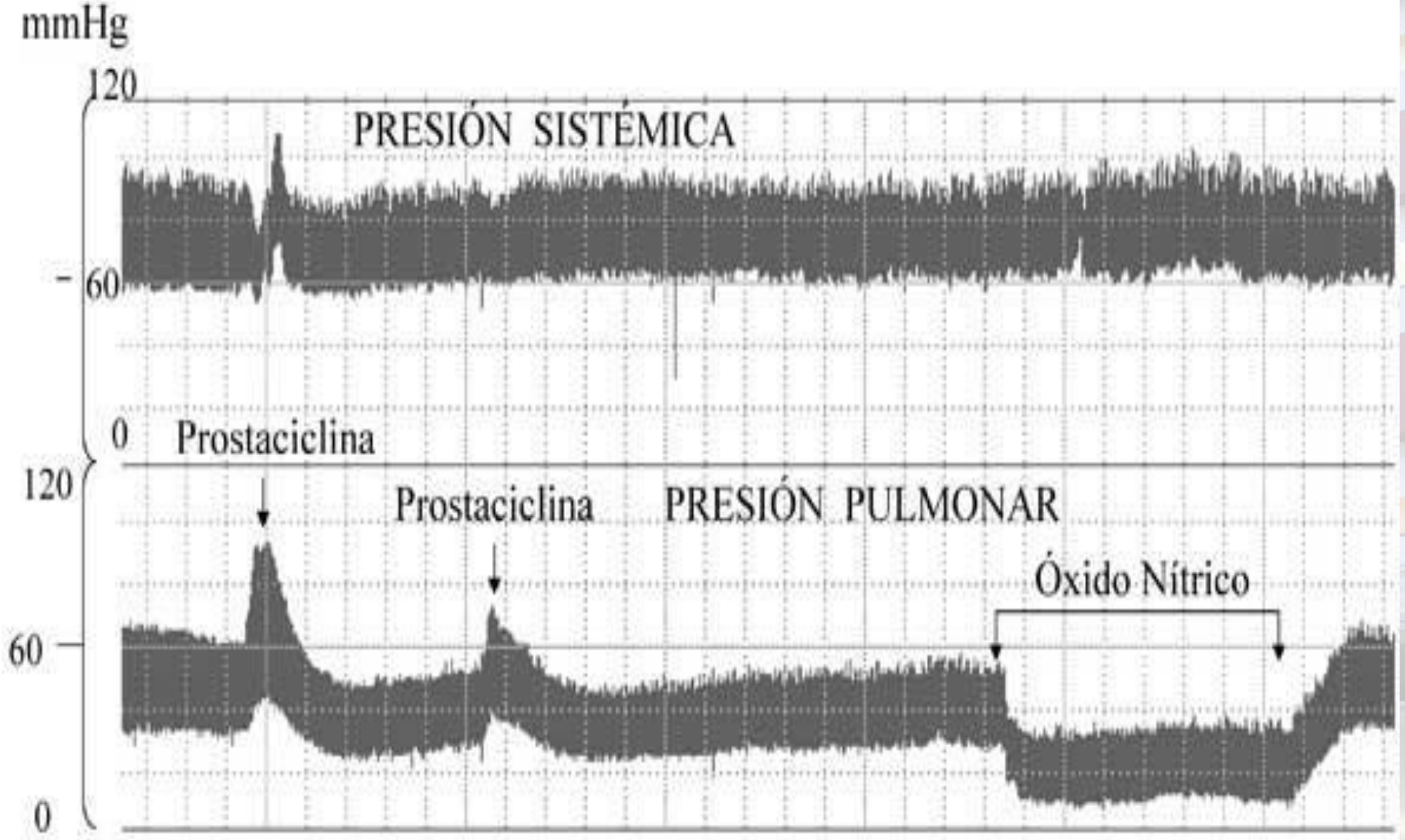

Figura 3. Evolución de la presión sistémica y pulmonar con la administración de prostaciclinas y óxido nítrico. Se observó que la desconexión que se realiza para administrar el fármaco agrava la hipertensión pulmonar por hipoxia. Gentileza del Departamento básico de Neonatología. Hospital de Clínicas.

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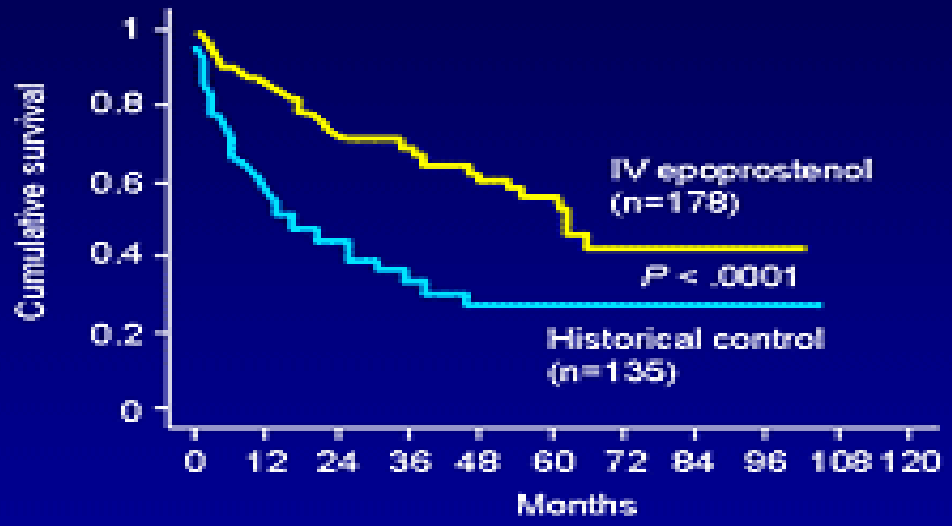
EPOPROSTENOL A LARGO PLAZO

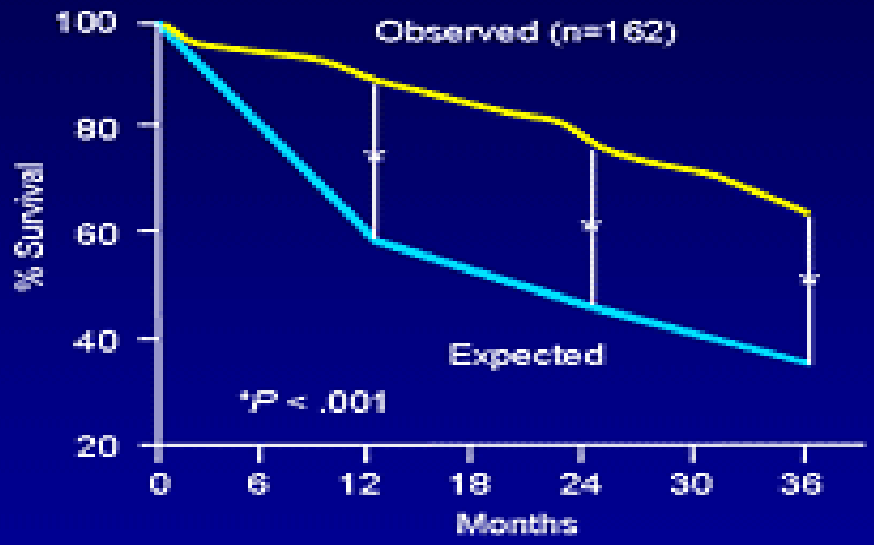
Long-term Outcome in IPAH With Epoprostenol



No. at risk

178	129	85	57	36	21	7	3	1	IV epo
135	59	34	20	11	4	2	2	1	Hist. control

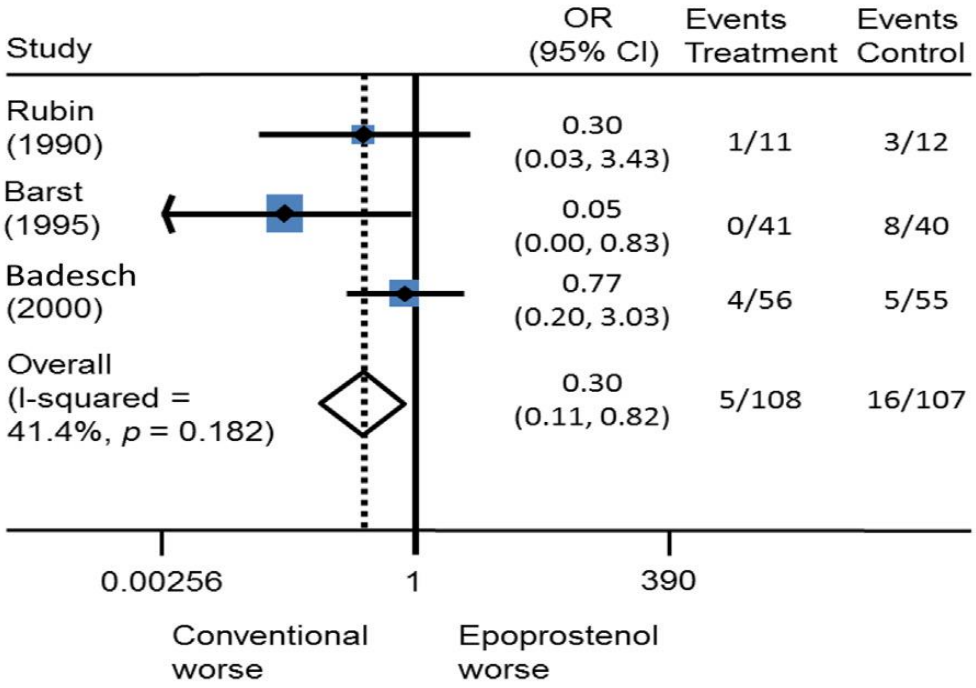
Sitbon O et al. *J Am Coll Cardiol.* 2002;40:780-788.



McLaughlin VV et al. *Circulation.* 2002;106:1477-1482.

Meta-Analysis of Published Randomized Controlled Studies (Identified by First Author and Year of Publication) With Epoprostenol in Pulmonary Arterial Hypertension by Mantel–Haenszel and Peto Methods

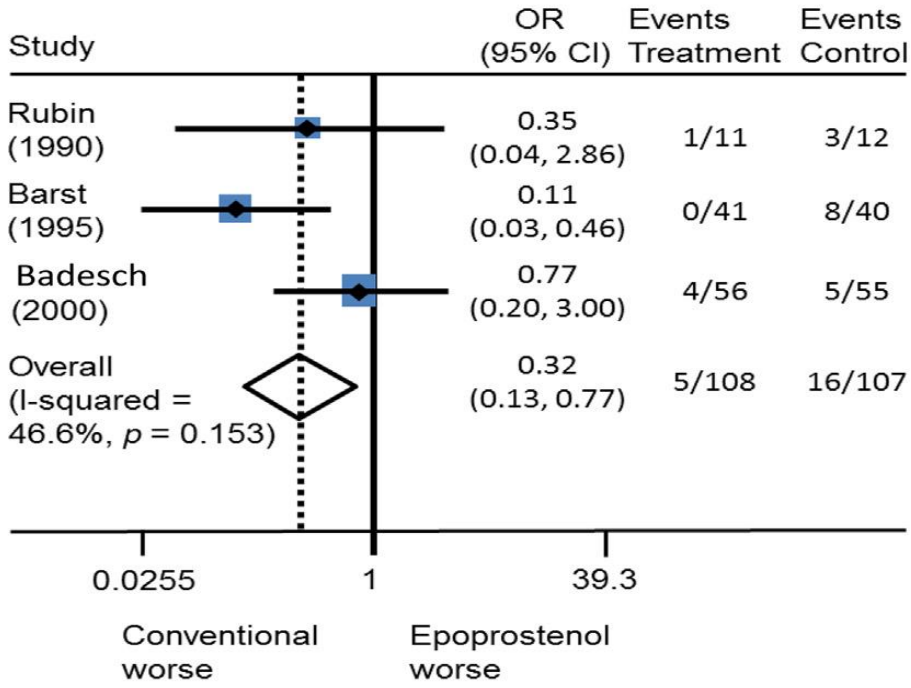
The analysis included 215 patients in 3 trials.



Mantel-Haenszel z = 2.35 $p = 0.019$

Heterogeneity $p = 0.182$

RR = 70%



Peto z = 2.52 $p = 0.012$

Heterogeneity $p = 0.153$

RR = 68%

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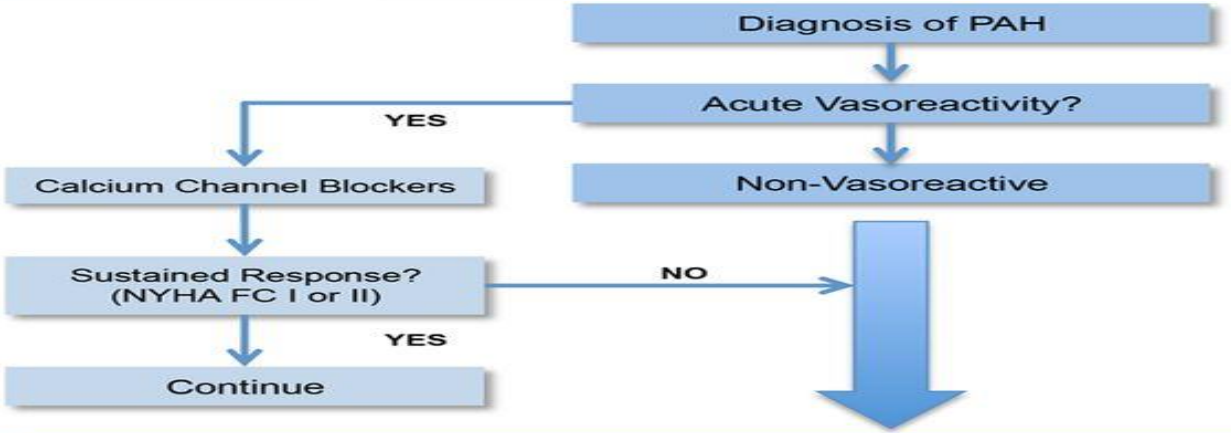

Therapy with Approved PAH Drugs

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IIa	C		Iloprost IV Treprostinil IV	Ambrisentan Bosentan Iloprost inhaled, IV Macitentan# Riociguat Sildenafil Tadalafil Treprostinil SC, IV
IIb	B		Beraprost	
	C		Upfront Combination	Upfront Combination

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MUCHAS GRACIAS POR SU ATENCIÓN

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