III Simposio ICSI-Las Lomas
Cardiología de Precisión

Novedades en Hipertensión Pulmonar

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ESC/ERS GUIDELINES

2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS)

Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT)

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Guías → **Clínica**

Unidad Multidisciplinaria de Hipertensión Pulmonar

Enfoque Diagnóstico y Terapéutico

Unidad Multidisciplinaria

Medicina Interna

Reumatología

Neumonología

Cardiología

Hemodinamia

C. Congénitas

Imagenes

Unidad Coronaria

Infectología

Pruebas Funcionales

Anestesia

Hematología

Obstetricia

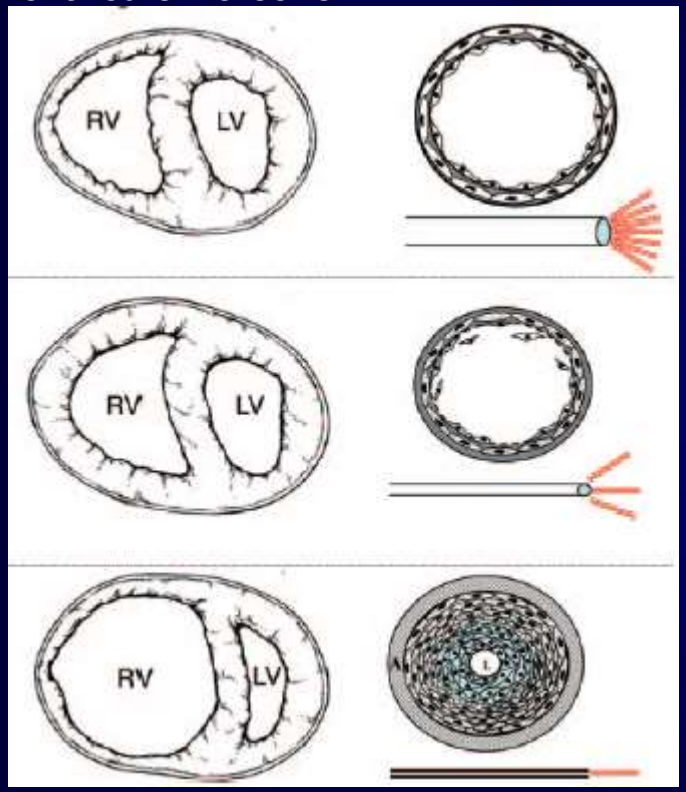
Psicología

Rehabilitación

PPM > 20 mm Hg

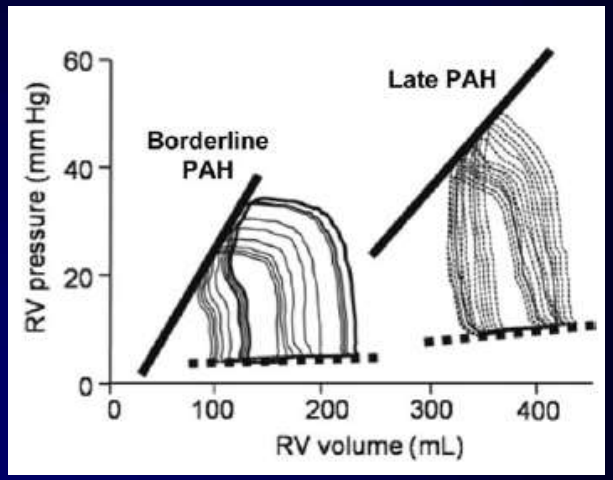
DE LA FISIOPATOLOGÍA A LA ANATOMIA PATOLÓGICA

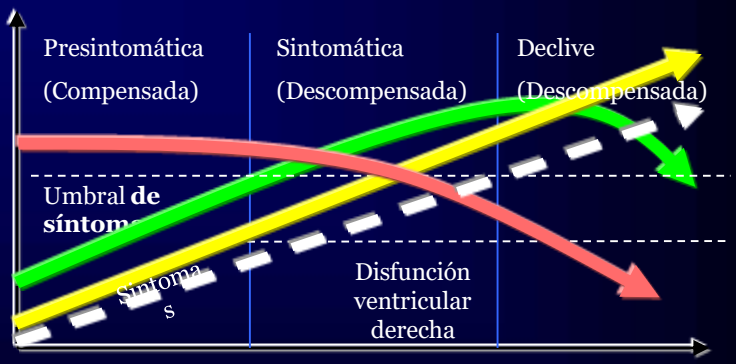
Ventrículo Derecho Arteria Pulmonar



Hipertrofia VD
Disfunción nendotelial
Constricción AP
Pérdida microvascular

Dilatación del VD
Hipertrofia vascular
Obliteración Vascular

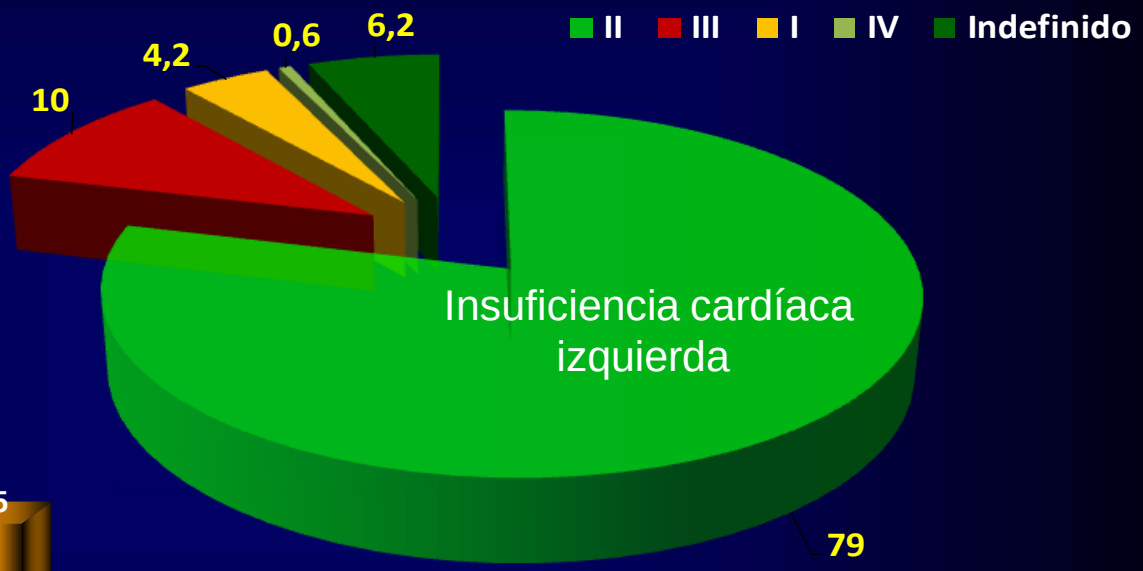


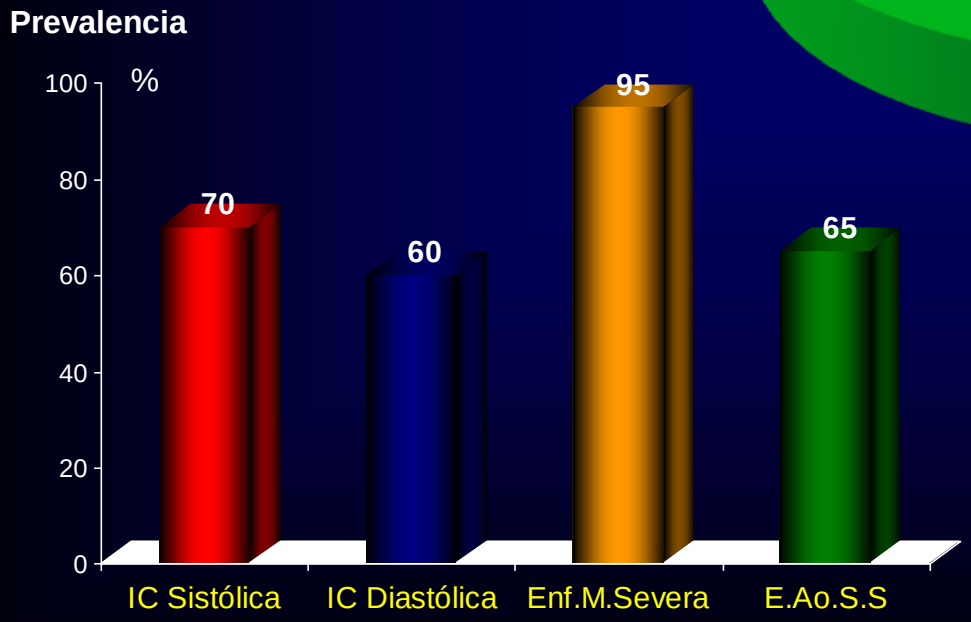


Champion y col. Circulation 2009;120:992-1007

Epidemiología de la Hipertensión Pulmonar

Prevalencia de 10,5% con una PSP > 40 mm Hg





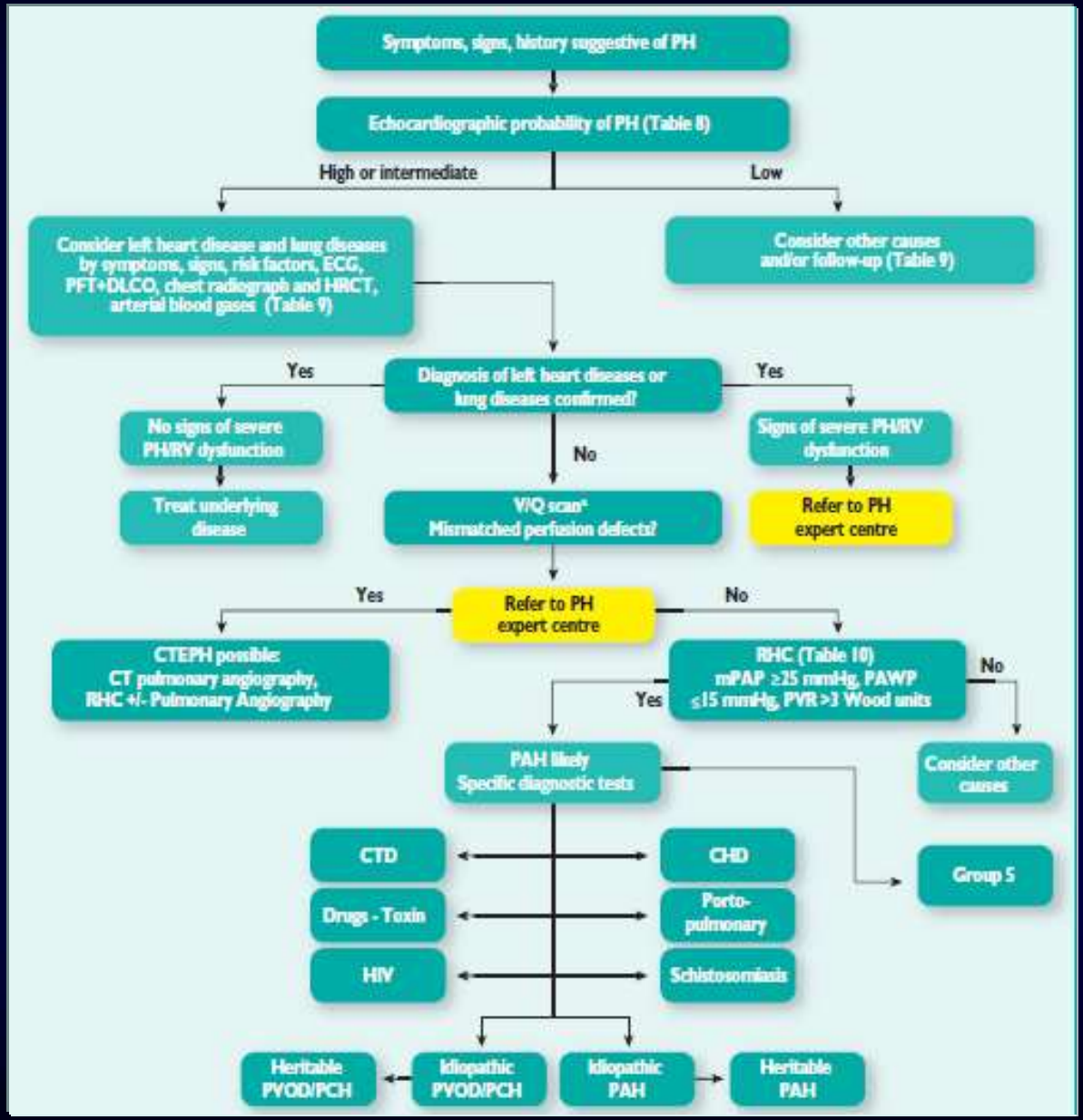
Anemia Hemolítica (6%)

1) Grupo I- 22,5%
2) Grupo II – 55 %
3) Hiperdinamia – 22,5%

JACC 2009;54:S85-96

Rev Esp cardiol 2010;63(5):583-96

Algoritmo Diagnóstico



SOSPECHA CLINICA

Poblaciones de riesgo

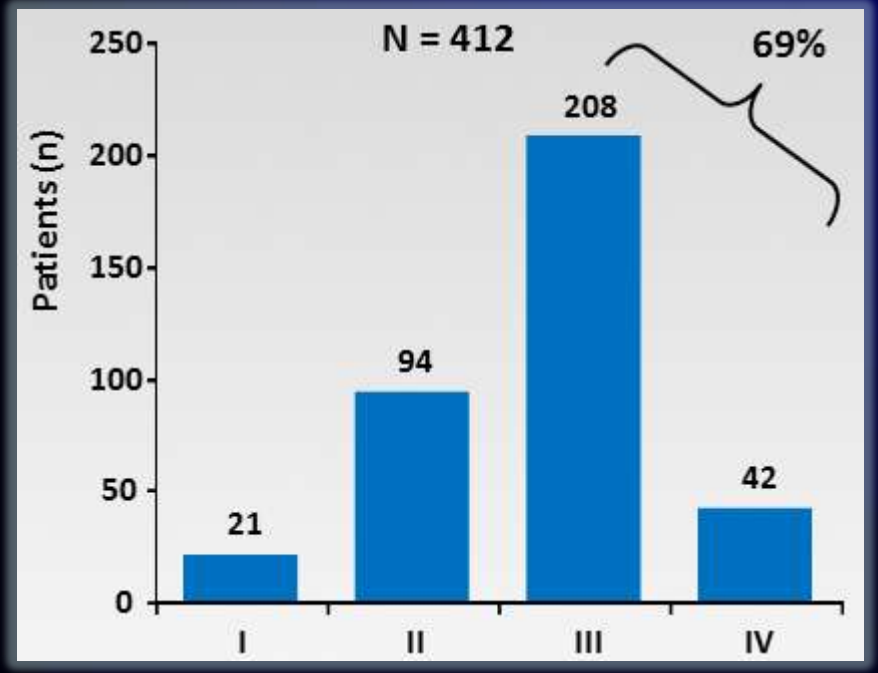
- HP familiar
- Exposición anorexígenos
- Enfermedades del colágeno (8-30%)
- VIH (0.5%)
- C.C: cortocircuitos sistémicos-pulmonares (20-40%)
- Antecedentes tromboembolismo pulmonar (3.8 %)
- Hepatopatías con hipertensión portal (0.5-4%)
- Anemía Hemolítica (6%)

15 casos por millón de habitantes

Diagnóstico Clínico

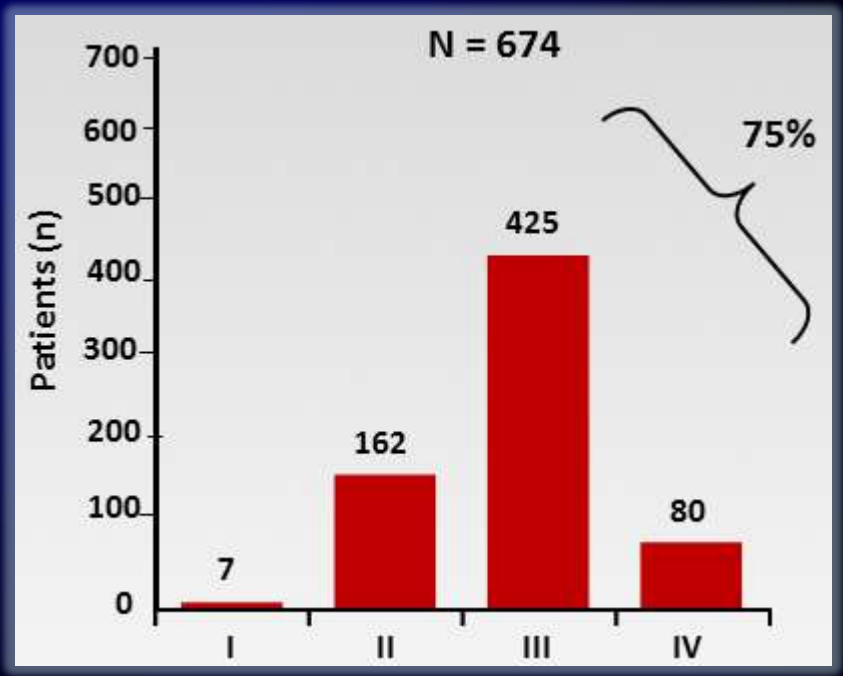
Demora entre el comienzo de los síntomas y el diagnóstico: 27 meses

REVEAL Registry



Functional Class

French National Registry



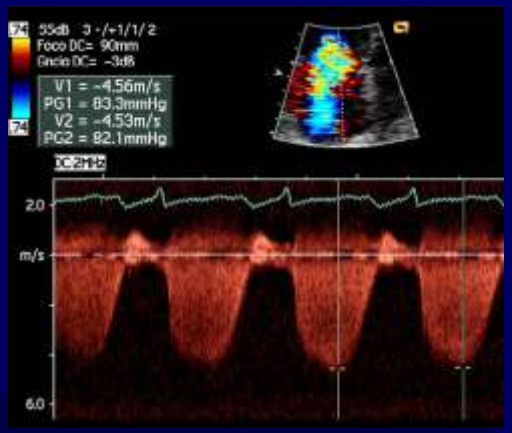
Functional Class

Benza RL and col. Circulation. 2010;122:164-172. Humbert M and col. Am J Respir Crit care 2006;173:1023-30.

Sospecha de Hipertensión Pulmonar
Ecocardiografía

ESC/ERS recomendaciones

Cuantificación del Reflujo Tricúspideo



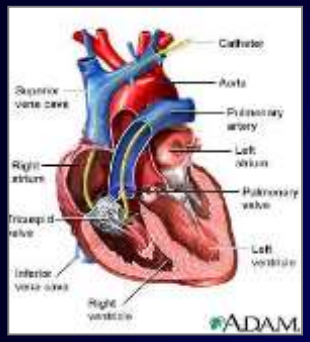
HAP no Probable:
Velocidad del RT pico < 2.8 m/s (PPS < 36 mmHg) y sin signos adicionales

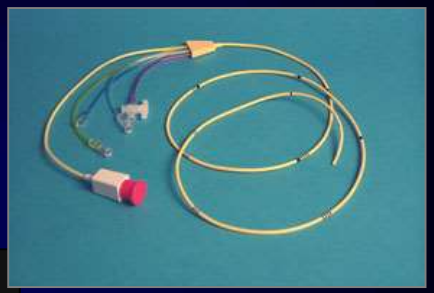
HAP Posible:
Velocidad del RT pico de 2.8 m/s (PPS 36 mmHg) con presencia adicional de variables ecocardiográficas sugestiva
VRT pico entre 2.9-3.4 m/s (PPS 37-50 mmHg) con/sin signos indirectos

HAP Probable:
Velocidad del RT pico > 3.4 m/s (PPS > 50 mmHg) con/sin signos indirectos

Galiè N, et al. Eur Heart J 2009; 30:2493-537. Rudski LG, et al. J Am Soc Echocardiogr 2010; 23:685-713.

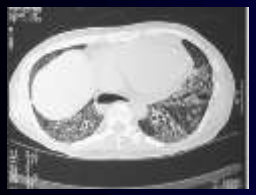
¿A TODOS CATETERISMO DERECHO BASAL?

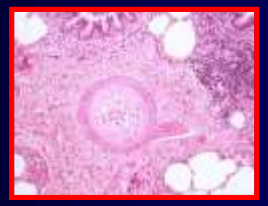


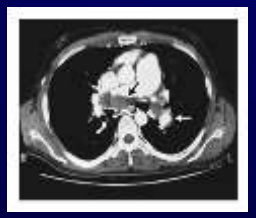


CONFIRMACION DIAGNOSTICA

PCP NORMAL ← RVP → **PCP ALTA**







1. PAPm >25 mmHg
2. PCP < 16 mmHg
3. RVP > 3 u Wood

GTPD ≥ 7
RVP ≥ 3

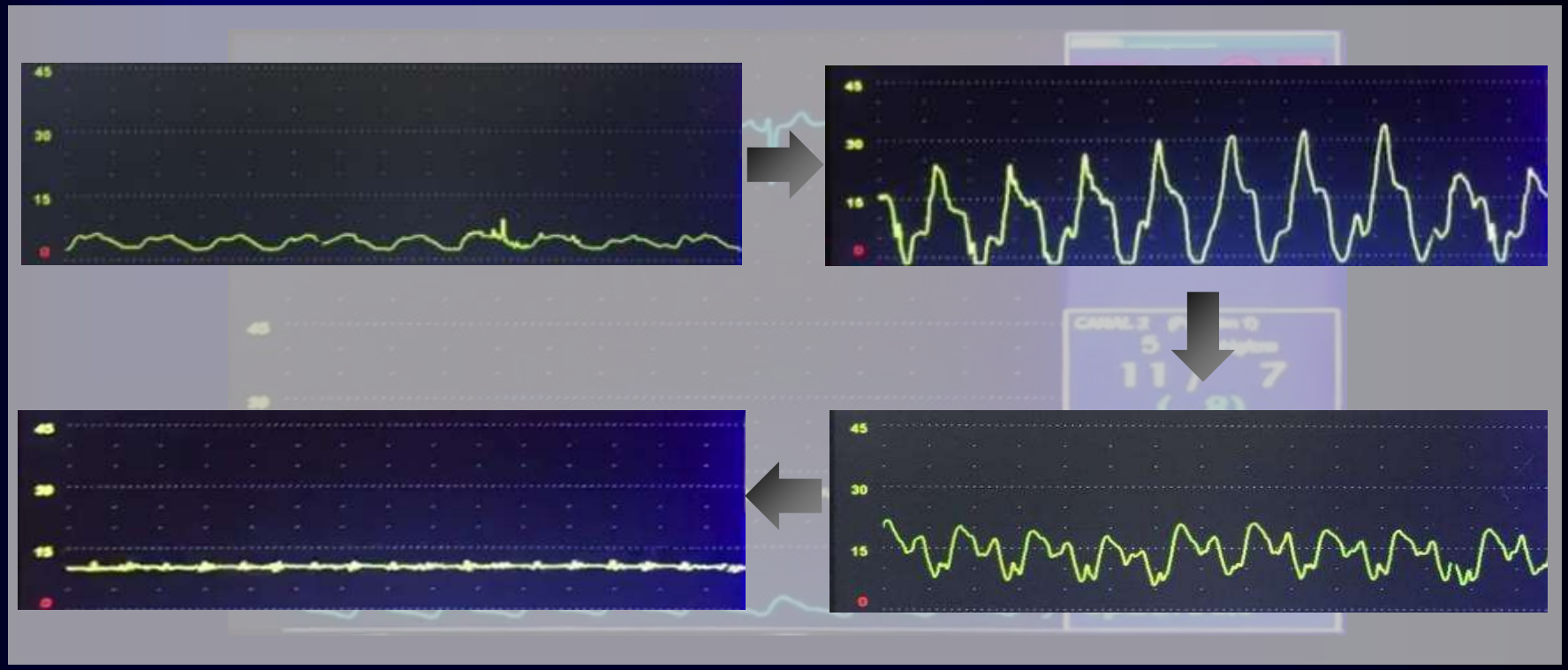
Combinada

GTPD < 7
RVP < 3

Aislada

¿A TODOS CATETERISMO DERECHO BASAL?

Vd y Ap (inflar y avanzar)



Pronóstico en Hipertensión Arterial Pulmonar

Variables Pronósticas (mortalidad 1/año)	Riesgo Bajo < 5%	Riesgo Intermedio 5-10%	Riesgo Alto > 10%
Insuficiencia cardíaca derecha	Ausente	Ausente	Presente
Progresión de síntomas	No	Lento	Rápido
Síncope	No	Ocasional	Recurrente
CF WHO	I – II	III	IV
TC6M (metros)	> 440	165 – 440	< 165
Test ejercicio cardiopulmonar VO2 pico (ml/kg/min) (predicho %) VE/VCO2	 >15 (>65%) < 36	 11 – 15 (35-65%) 36-44.9	 < 11 (<35%) ≥ 45
BNP (ng/l) NT-proBNP (ng/ml)	< 50 < 300	50 – 300 300 - 1400	> 300 > 1400
Imágenes (Ecocardiograma, RNM)	Area AD<18 cm^2 DP negativo	Area AD 18-26 cm^2 DP mínima	Area AD > 26 cm^2 DP
Hemodinámico	PAD < 8 mm Hg IC 2.5 l/min/m^2 SvO2 > 65%	PAD 8-14 mm Hg IC 2-2.4 l/min/m^2 SvO2 60-65%	PAD >14 mm Hg IC <2 l/min/m^2 SvO2 <60%

EHJ 2015;29 Agosto: 1-58

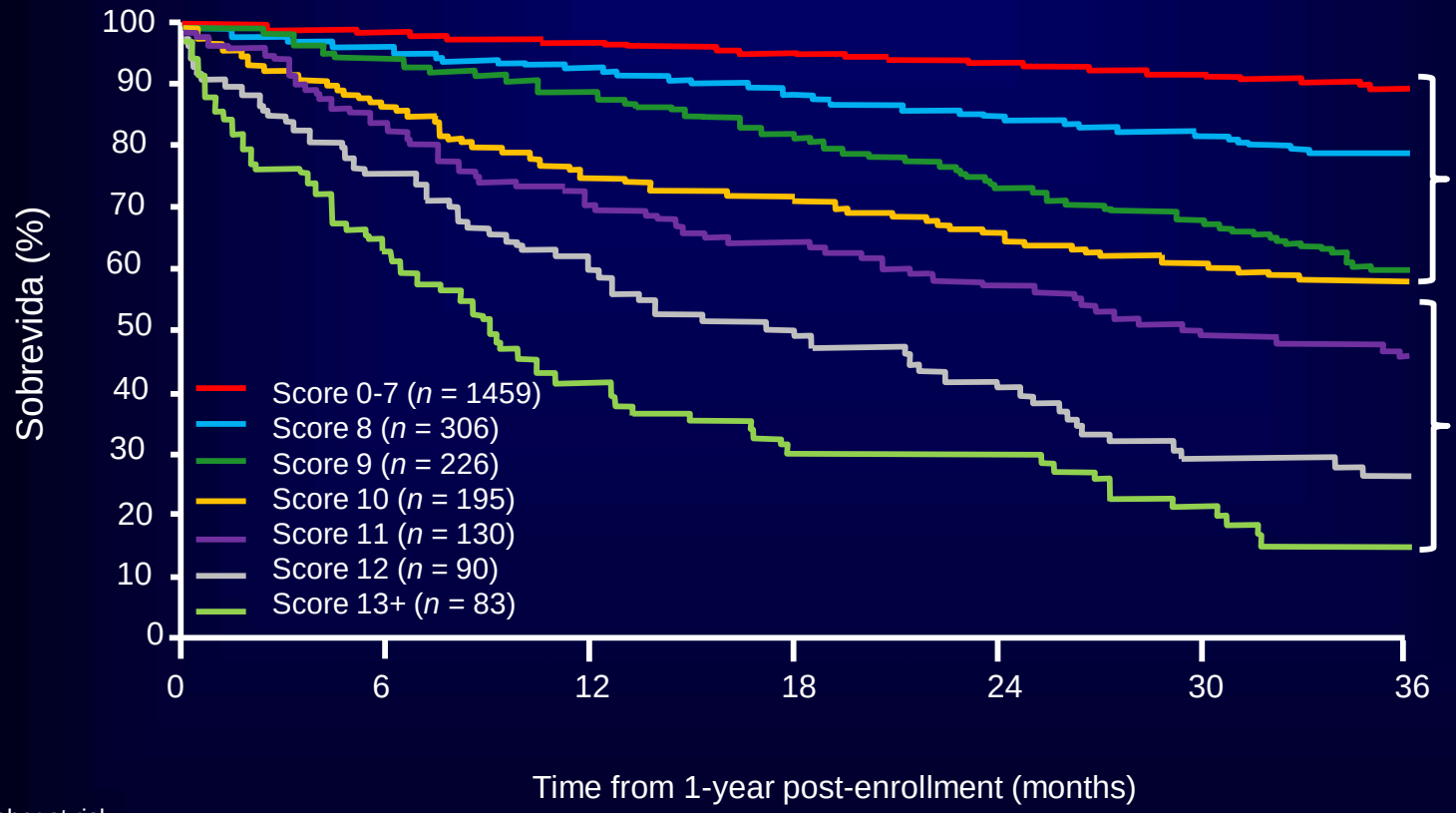
ESC/ERS Guidelines: Multi-parameter risk assessment

Risk stratification table, based on PAH expert opinion

	Determinants of prognosis	Estimated 1-year mortality		
		Low risk < 5%	Intermediate risk 5-10%	High risk > 10%
Clinical assessment	Clinical signs of right heart failure	Absent	Absent	Present
	Progression of symptoms	No	Slow	Rapid
	Syncope	No	Occasional syncope	Repeated syncope
	FC	I, II	III	IV
Exercise tests	6MWD	> 440 m	165 - 440 m	< 165 m
	CPET	Peak VO_2 > 15 ml/min/kg (> 65% pred.) VE/VCO_2 slope < 36	Peak VO_2 11 - 15 ml/min/kg (35-65% pred.) VE/VCO_2 slope 36 - 44.9	Peak VO_2 < 11ml/min/kg (< 35% pred.) VE/VCO_2 slope ≥ 45
Biochemical markers	NT-proBNP plasma levels	BNP < 50 ng/l NT-proBNP < 300 ng/l	BNP 50–300 ng/l NT-proBNP 300–1400 ng/l	BNP > 300 ng/l NT-proBNP > 1400 ng/l
Echocardiographic evaluations	Imaging (echo, CMR)	RA area < 18 cm^2 No pericardial effusion	RA area 18–26 cm^2 No or minimal pericardial effusion	RA area > 26 cm^2 Pericardial effusion
Hemodynamic evaluations	Hemodynamics	RAP < 8 mmHg CI ≥ 2.5 l/min/m^2 SvO_2 > 65%	RAP 8–14 mmHg CI 2.0–2.4 l/min/m^2 SvO_2 60–65%	RAP > 14 mmHg CI < 2.0 l/min/m^2 SvO_2 < 60%

Galiè N, *et al. Eur Heart J* 2016; 37:67-119;
Galiè N, *et al. Eur Respir J* 2015; 46:903-75.

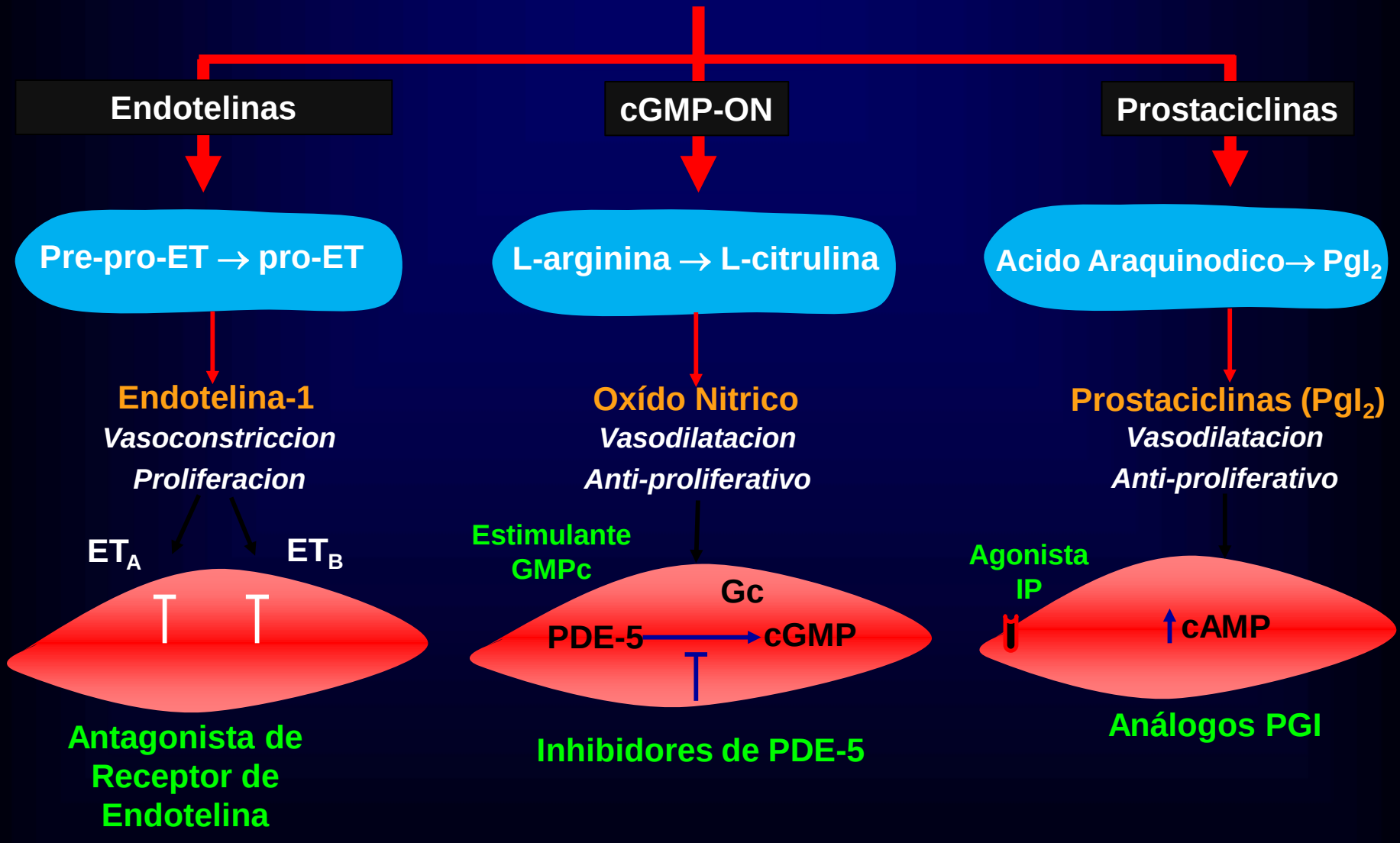
Score de Riesgo REVEAL
Discriminación de Sobrevida



Number at risk							
Score 0-7	1459	1424	1376	1323	1265	1189	1096
Score 8	306	292	275	256	236	216	194
Score 9	266	248	230	207	178	157	133
Score 10	195	166	142	127	116	99	88
Score 11	130	109	87	77	67	50	40
Score 12	90	68	54	41	34	23	21
Score 13+	83-	53	34	24	24	17	10

Benza R et al. Presented at ATS 2017; 195:A6899.

DIVERSAS VIAS FISIOPATOLOGICAS EN HIPERTENSION PULMONAR



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

CLASIFICACION DE HP

1- Hipertensión arterial pulmonar

1.1- Idiopática
1.2- Hereditaria : BMPR2 y otras mutaciones
1.3- Inducidos por drogas y toxinas
1.4- Asociada con: Enfermedades del tejido conectivo, Hipertensión portal
Infección por virus de inmunodeficiencia adquirida (HIV)
Cardiopatías congénitas, Esquistosomiasis,
1´ - Enfermedad pulmonar veno-oclusiva y/o hemangiomatosis capilar pulmonar
1`` Hipertensión pulmonar persistente del recién nacido

2- Hipertensión pulmonar asociada a enfermedades cardíacas izquierda

Disfunción sistólica / Disfunción diastólica / Enfermedad valvular
Obstrucción congénita/adquirida del TSVI/ Estenosis venas pulmonares

3- Hipertensión pulmonar asociada a enfermedades respiratorias y/o hipoxemia

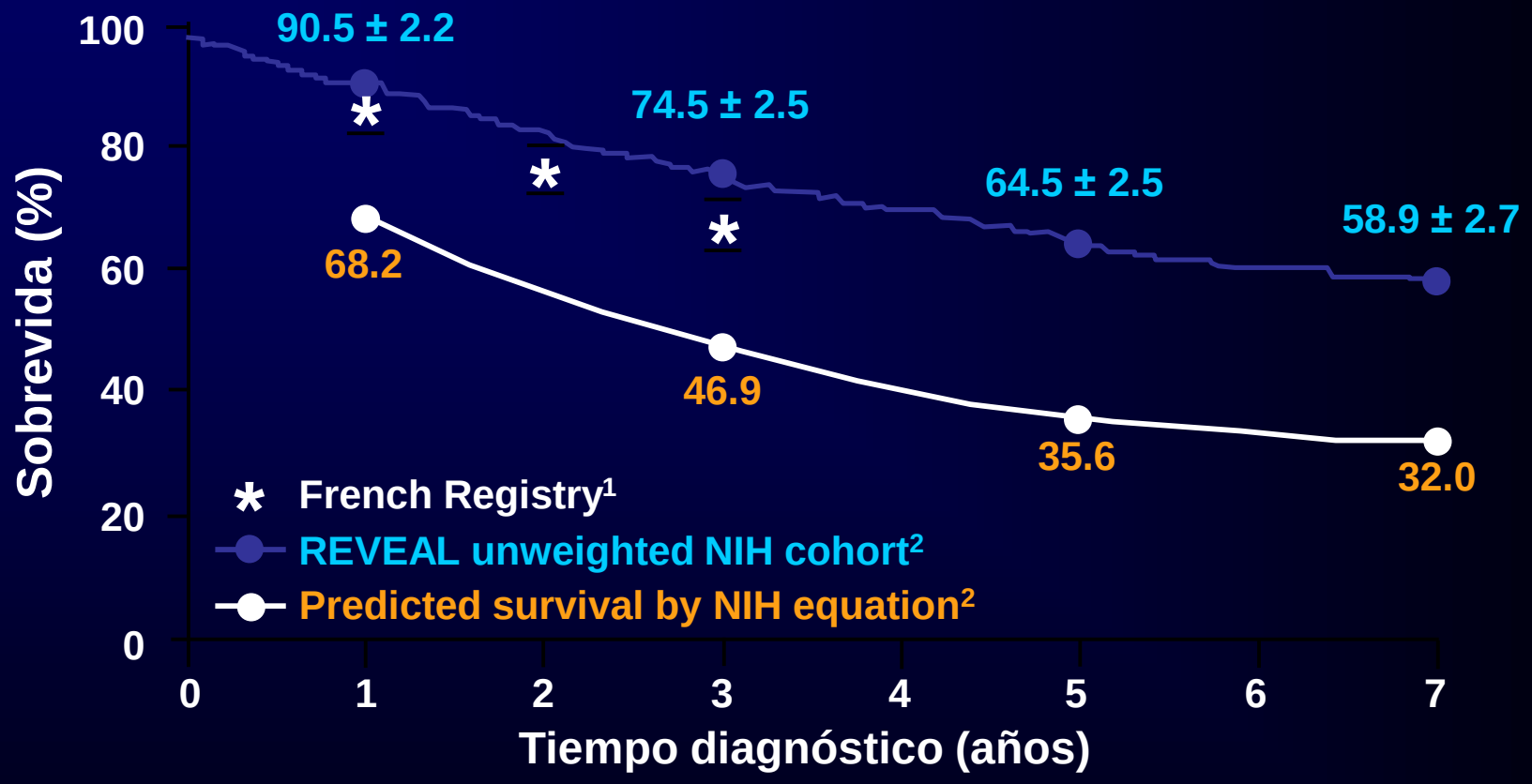
3.1- Enfermedad pulmonar obstructiva crónica
3.2- Enfermedad pulmonar intersticial
3.3- **Otras afecciones mixtas restrictiva/obstructiva**
3.4- Hipoventilación asociado a trastornos del sueño
3.5- Hipoventilación alveolar
3.6 Exposición crónica a grandes alturas
3.7 Anomalías del desarrollo

4- Hipertensión pulmonar tromboembólica crónica (CTEPH) y otras obstrucciones

5- Hipertensión pulmonar con mecanismos multifactoriales no claros.

Desordenes hematológicos: trastornos mieloproliferativos, esplenectomía, Anemia hemolitica crónica
Desordenes sistémicos: Sarcoidosis, histiocitosis, linfangiomatosis, neurofibromatosis, vasculitis.
Desordenes metabólicos: enfermedad por depósito de glucógeno, Gaucher, desordenes tiroideos.
Otros: Tumores obstructivos, mediastinitis fibrosante, insuficiencia renal crónica en diálisis, segmentación PH

Eventos a largo plazo
Beneficios en la era moderna



Nro riesgo:	279	377	390	388	328	240	153	88

1. Humbert M, et al. Eur Respir J 2010; 36:549–555. 2. Benza RL, et al. Chest 2012

General measures for patients with pulmonary hypertension

Avoid pregnancy

Influenza and pneumococcal immunisation according to STIKO

Psychological counselling Frequent depression, anxiety disorders

Supervised exercise training

Supplemental oxygen

Regional anaesthesia should be preferred over general anaesthesia whenever possible

Supportive therapy

Diuretic administration loop diuretics, aldosterone antagonists

Long-term oxygen therapy Saturation <90%; PaO_2 <8 kPa (60 mmHg)

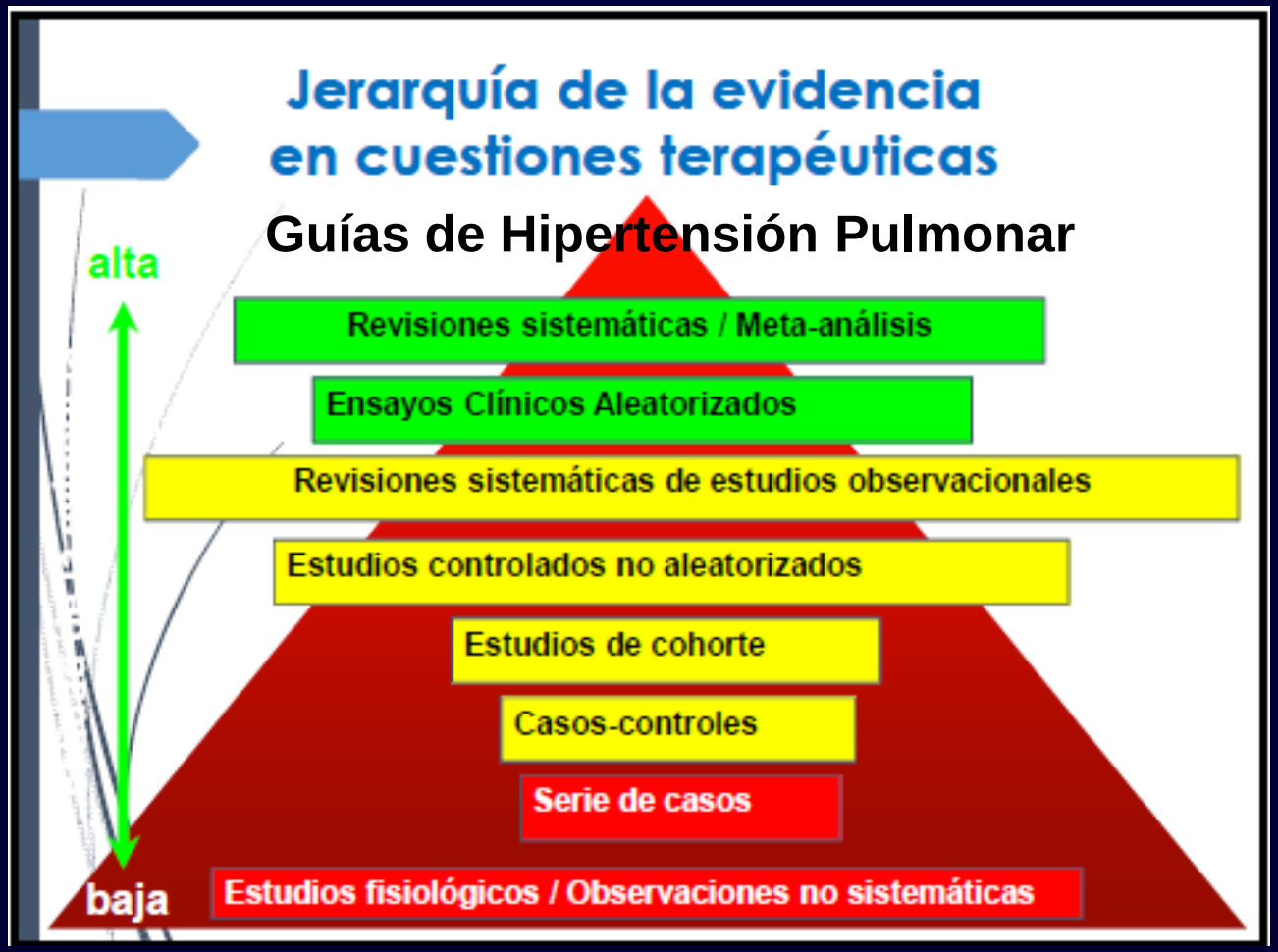
Anticoagulation CTEPH Not routinely recommended in PAH

Iron deficiency Correction

Use of ACE inhibitors, AT_1-antagonists, β-blockers, ivabradine only if specifically indicated, e.g., comorbidity

Treatment of arrhythmias Electrical cardioversion /ablation for atrial fibrillation

Medicina basada en Opiniones



Medicina basada en Evidencia

Historia de los Ensayos Clinicos en HAP(41)

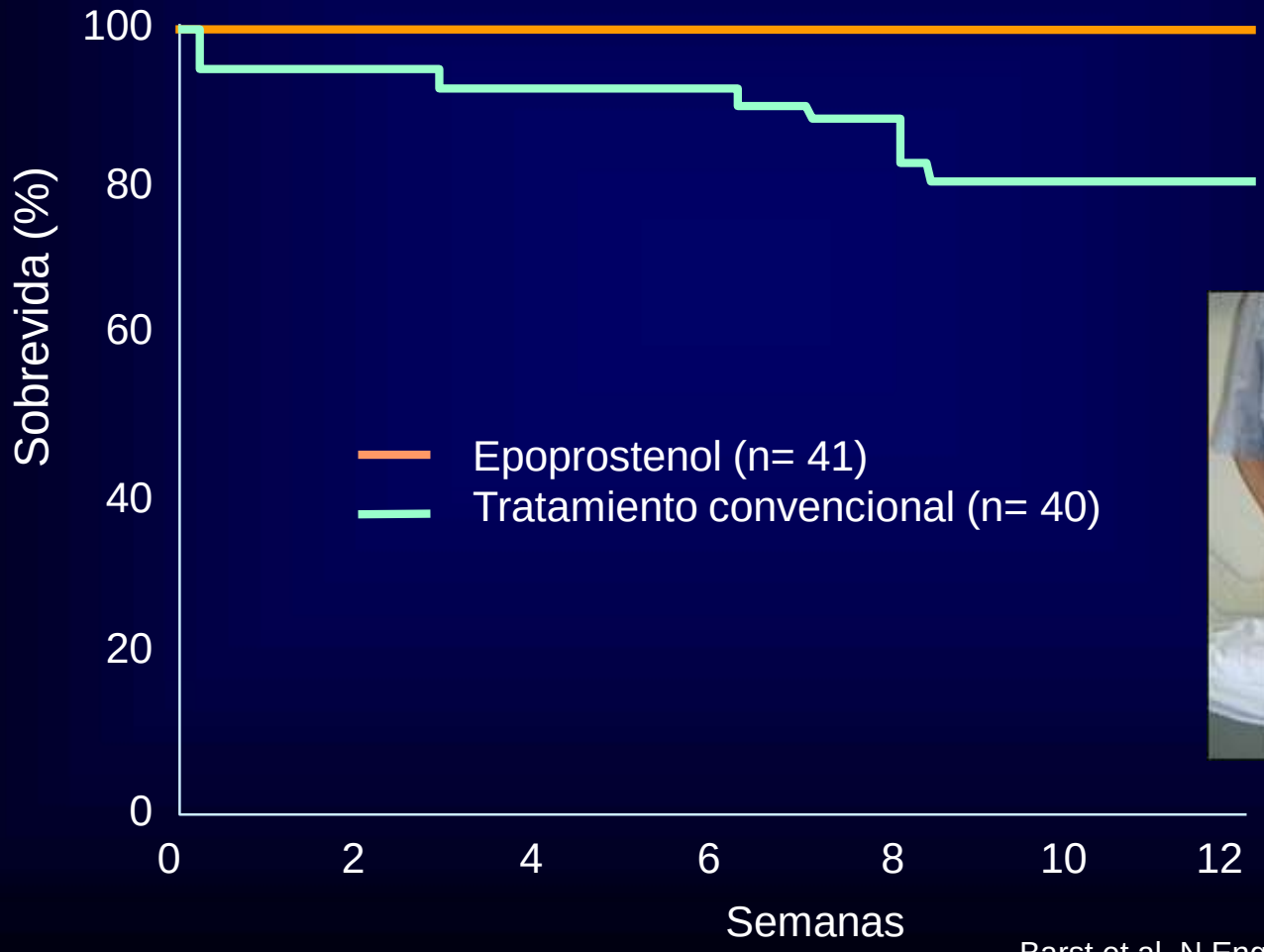
- ✓ **Pacientes incluídos en RCT: 9061**
- ✓ **Prevalencia en HAP: 50 / millón**

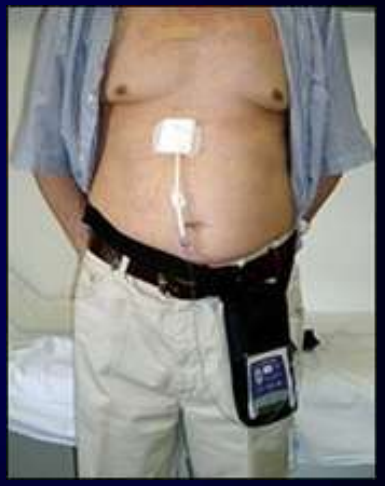
EVIDENCIA DE EPOPROSTENOL EN HAP

Estudio randomizado a 12 semanas

81 pacientes en HAPI CF III-IV

Evaluación: capacidad al ejercicio, hemodinámico, CF, sobrevida y seguridad

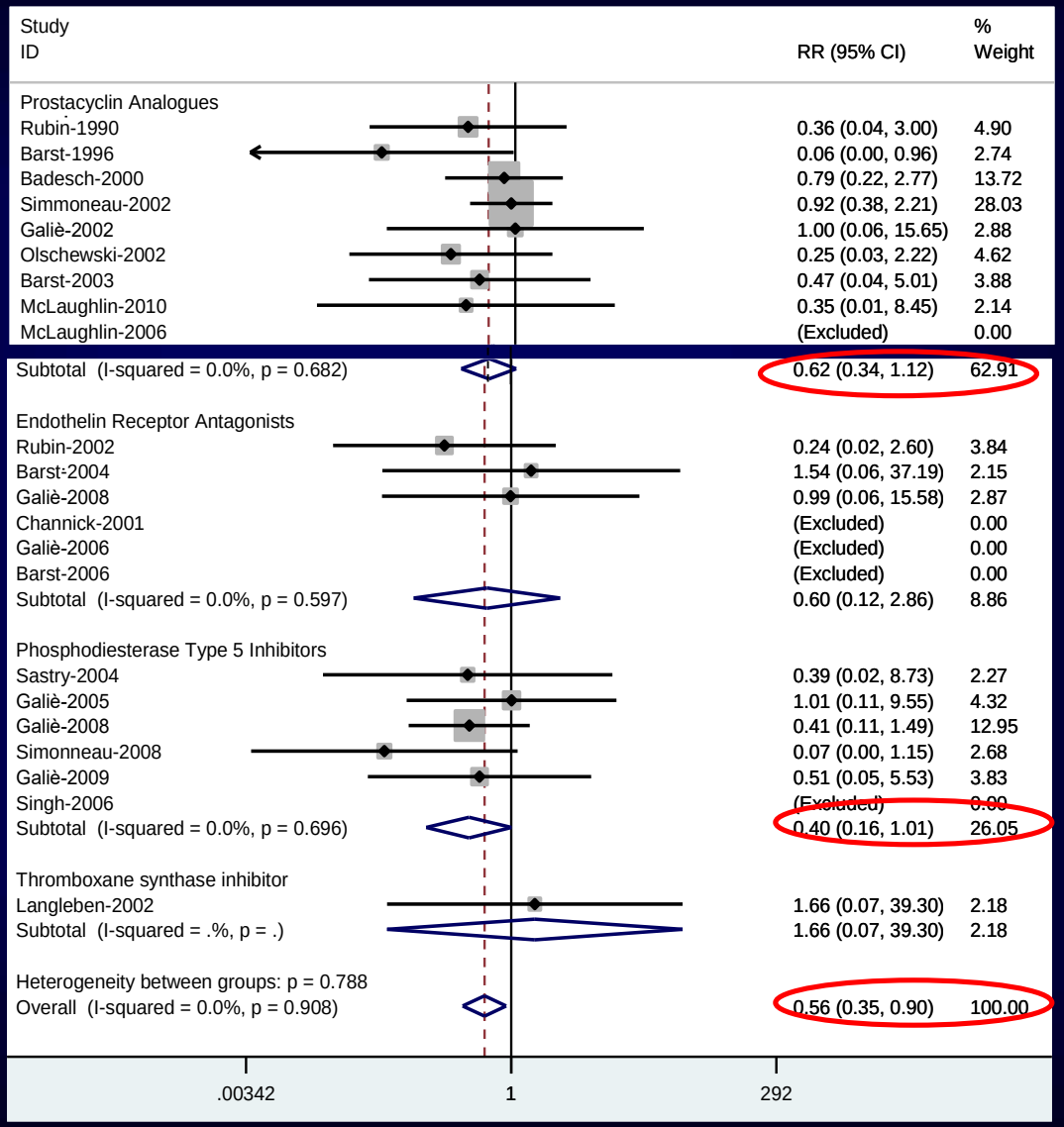




Barst et al. N Engl J Med 1996;334:296–301.

Monoterapia en HAP: “Mortalidad Global”

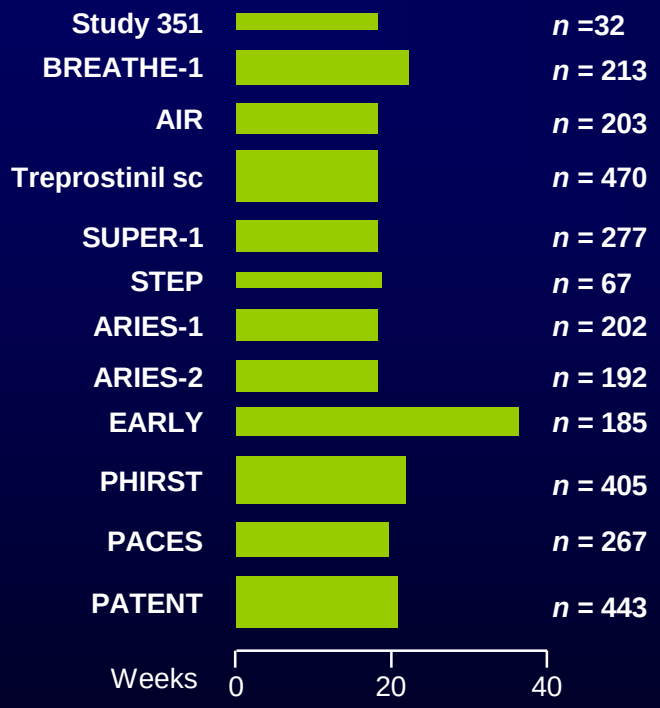
RR = - 44%
P = 0.016



N.Galié and col. Eur Heart J 2010

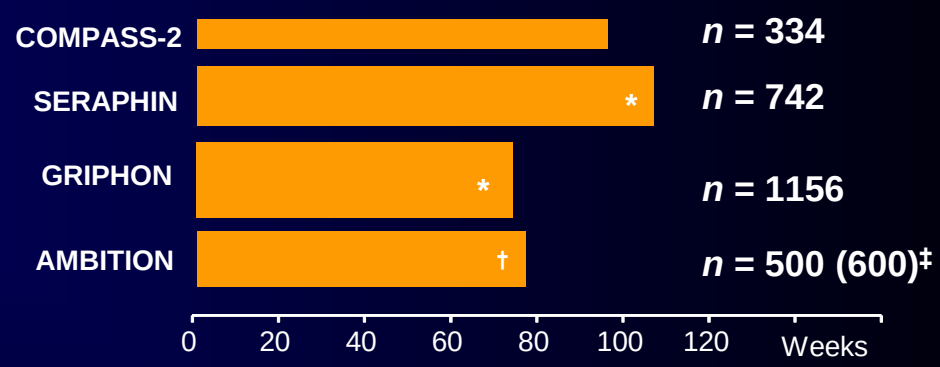
Objetivo Primario de los Ensayos Clínicos Randomizados

6MWD trials (2001 – 2013)



20 semanas
2956 pacientes

Outcome trials (2013 – 2015)



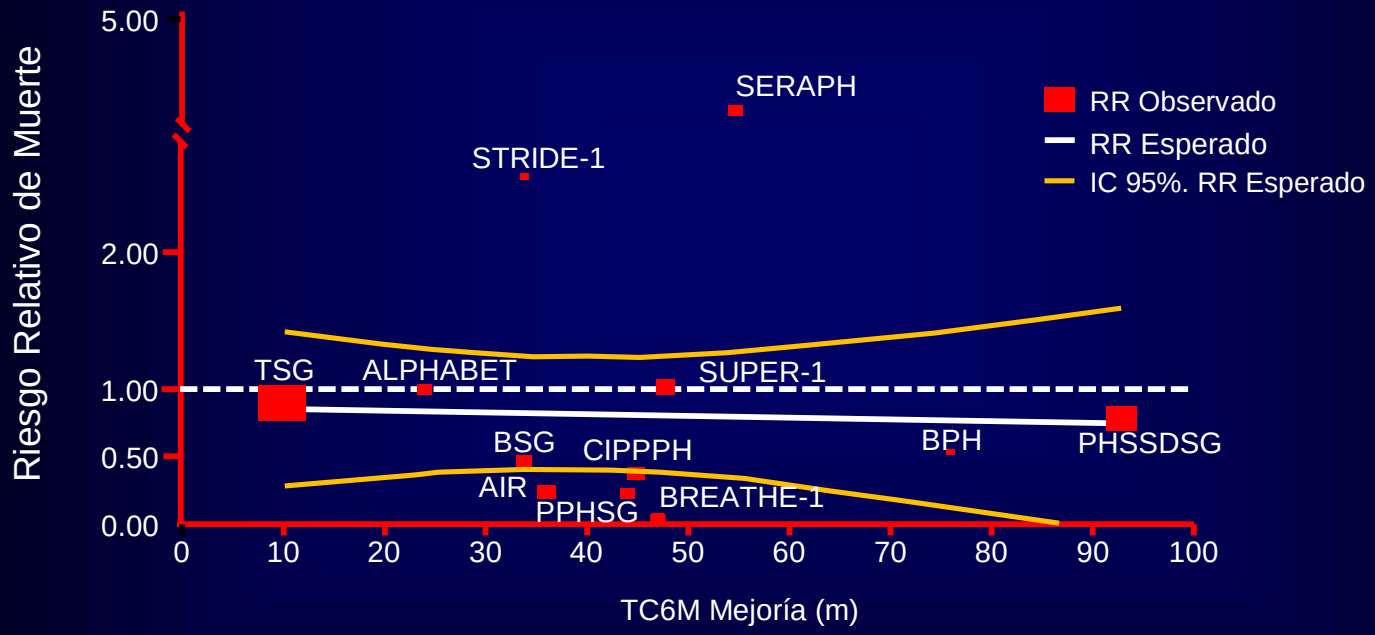
90 semanas
2732 pacientes

• Exposición media a la droga
† Mediana de exposición a la droga.
‡ Objetivo de enrolamiento.

Channick RN, *et al. Lancet* 2001; Rubin LJ, *et al. N Engl J Med* 2002; Galiè N, *et al. Lancet* 2008; Galiè N, *et al. Circulation* 2008; Galiè N, *et al. N Engl J Med* 2005; Simonneau G, *et al. Am J Respir Crit Care Med* 2002; McLaughlin VV, *et al. Am J Respir Crit Care Med* 2006; Galiè N, *et al. Circulation* 2009; Simonneau G, *et al. Ann Intern Med* 2008; Olschewski H, *et al. N Engl J Med* 2002; McLaughlin VV, *et al. Eur Respir J* 2015; Pulido S, *et al. New Engl J Med* 2013; Sitbon O, *et al. Eur Respir J* 2015; Galiè N, *et al. New Engl J Med* 2015.

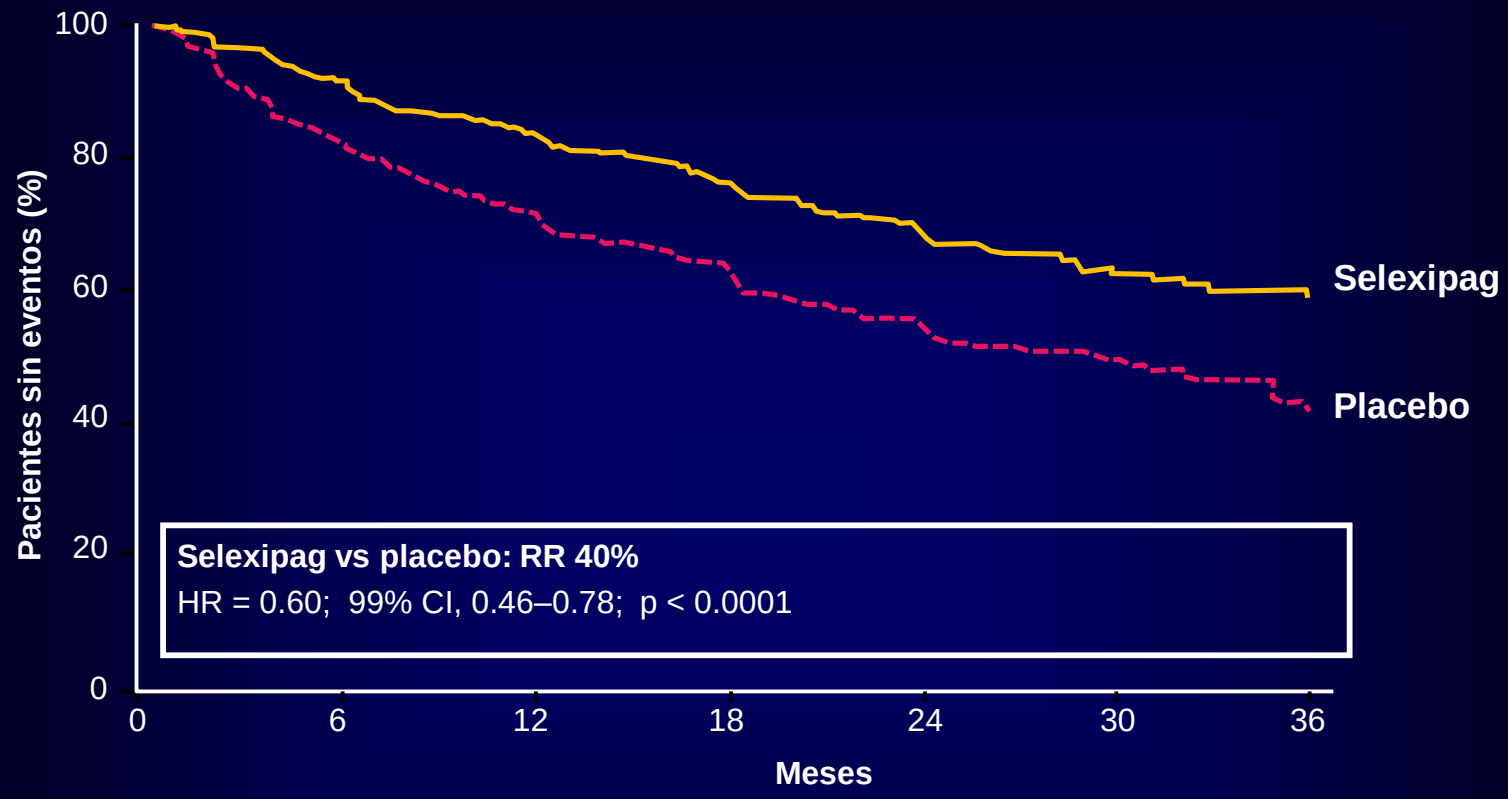
Relación entre el Riesgo de Mortalidad y Test de Caminata de 6 Minutos

Meta-análisis de 16 trials en HAP (*n* = 1962)



Macchia A, et al. Am Heart J 2007; 153:1037-47.

GRIPHON
PGI oral y Morbimortalidad

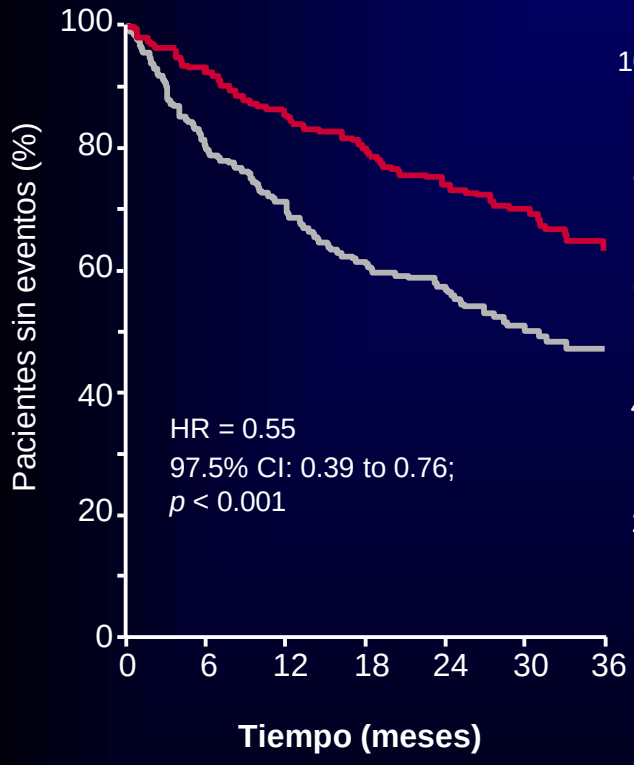


Nro							
Placebo	582	433	347	220	149	88	28
Selexipag	574	455	361	246	171	101	40

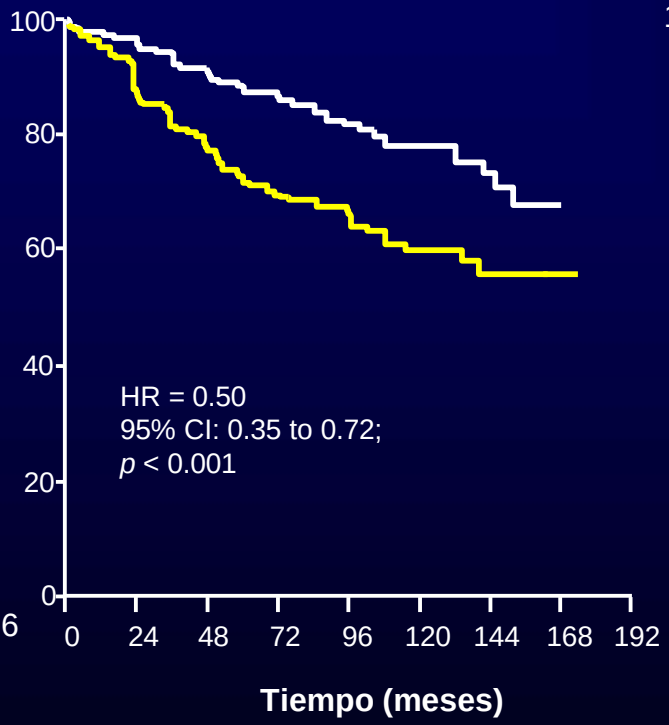
Sitbon O, et al. N Engl J Med 2015;373:2522–33.

EVIDENCIA EN TRATAMIENTO COMBINADO

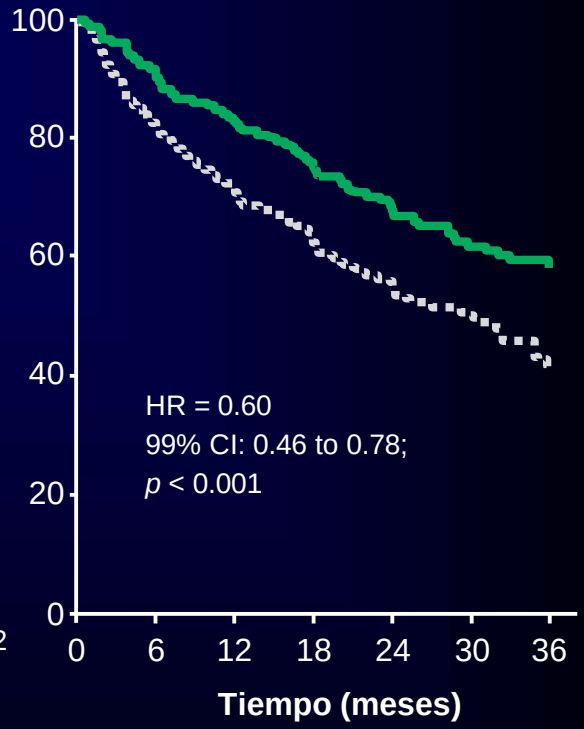
SERAPHIN[1]



AMBITION[2]



GRIPHON[3]



1. Pulido T, *et al. N Engl J Med* 2013; 369:809-18;
2. Galiè N, *et al. N Engl J Med* 2015; 373:834-44;
3. Sitbon O, *et al. N Engl J Med* 2015; 373:2522-33.

Terapia Combinada versus Monoterapia: Meta-análisis

16 ECR, 4538 pacientes. Seguimiento 37 semanas (%)

	Number of studies	Proportion of events (%)			Fixed-effect model		Random-effects model		Homogeneity	
		With combined therapy	With monotherapy	Total	Pooled RR	95 % CI (p value)	Pooled RR	95% CI (p value)	P value	I^2 (%)
Primary outcome										
Clinical worsening (all events)	15[11-14,29-32,34-40]	332/1940 (17%)	517/1862 (28%)	849/3802 (22%)	0·65	0·58–0·72 (p<0·00001)	0·65	0·56–0·76 (p<0·00001)	0·25	18%
Secondary outcomes as first event of clinical worsening										
All-cause mortality	12[11-14,30,33,34-40]	54/1711 (3%)	60/1712 (4%)	114/3423 (3%)	0·92	0·65–1·32 (p=0·65)	0·97	0·63–1·49 (p=0·88)	0·33	13%
Admission to hospital (PAH-related)†	8[11-13,32,34-37]	172/1658 (10%)	245/1680 (15%)	417/3338 (13%)	0·71	0·60–0·85 (p=0·0002)	0·71	0·53–0·96 (p=0·03)	0·12	37%

RR=rate ratio. PAH=pulmonary arterial hypertension. *Atrial septostomy were not reported in any study. †Data from the combination subgroup of the SERAPHIN trial are included in this analysis because they were available in a subsequent article.[45] However, these data were not included in the primary analysis because admission to hospital was not included in the definition of clinical worsening in SERAPHIN. ‡All deaths, including those as first event of clinical worsening and those after censoring for another event. Data from PHIRST,[31] EARLY,[40] PATENT-1,[29] and SERAPHIN[35] for the subgroup of patients already on background therapy were not available. Therefore, data from the entire study population were included for this secondary analysis. However, the exclusion of these studies did not modify the results for the all-cause mortality (RR 0·88 [95% CI 0·72–1·06], p=0·18). §Data from SERAPHIN[35] for the subgroup of patients already on background therapy were not available. The exclusion of this study yielded similar RRs for PAH-related mortality (RR 0·81 [95% CI 0·61–1·08]).

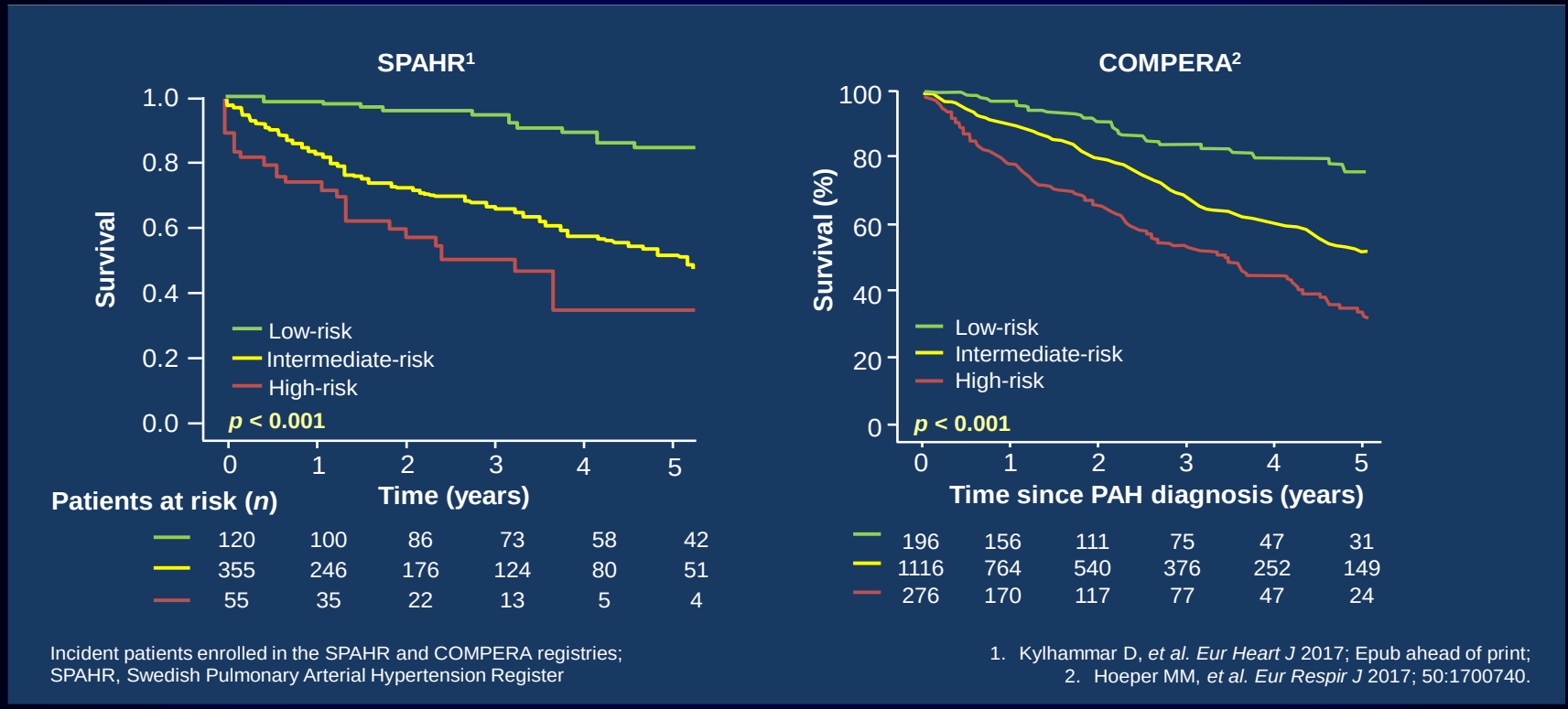
Table 3: **Primary and secondary outcomes***

	RRR(%)	valor de p
Empeoramiento clínico	-35	0.00001
1ra Hospitalización IC	-29	0.0002
Mortalidad Global	-14	0.09

Lajoie AC and col. Lancet Respir Med 2016

Objetivos Terapéuticos en los Registros

Bajo Riesgo en el Seguimiento



Incident patients enrolled in the SPAHR and COMPERA registries;
SPAHR, Swedish Pulmonary Arterial Hypertension Register

1. Kylhammar D, *et al. Eur Heart J* 2017; Epub ahead of print;
2. Hoeper MM, *et al. Eur Respir J* 2017; 50:1700740.

Menos del 30% alcanza el bajo riesgo clínico

“ Evolución de la Hipertensión Pulmonar”

Final

Desarrollo

Principio

Diagnóstico

Eventos

CF

TC6M

IC

Pronóstico

VM

PAD

BNP

¿Disminución de Eventos?

Tratamiento Cumpliendo Objetivos

Tratamiento Precoz
CF II - CF I ?

Detect Precoz
Screening en riesgo

Conciencia de enfermedad
Síntomas o riesgo

Cambiando la Historia Natural