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PALAZZO DELLE STELLINE

Migliorare l'outcome nell'ipertensione arteriosa polmonare: le nuove possibilità terapeutiche

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COI disclosure

- **Roche: investigator in trials, lectures, AB**
- **Actelion : investigator in trials, lectures, AB, grant for research**
- **Boehringer Ing. : investigator in trials, lectures, AB, grant for research**

Task Force #6: Risk Stratification and Medical Therapy of Pulmonary Arterial Hypertension

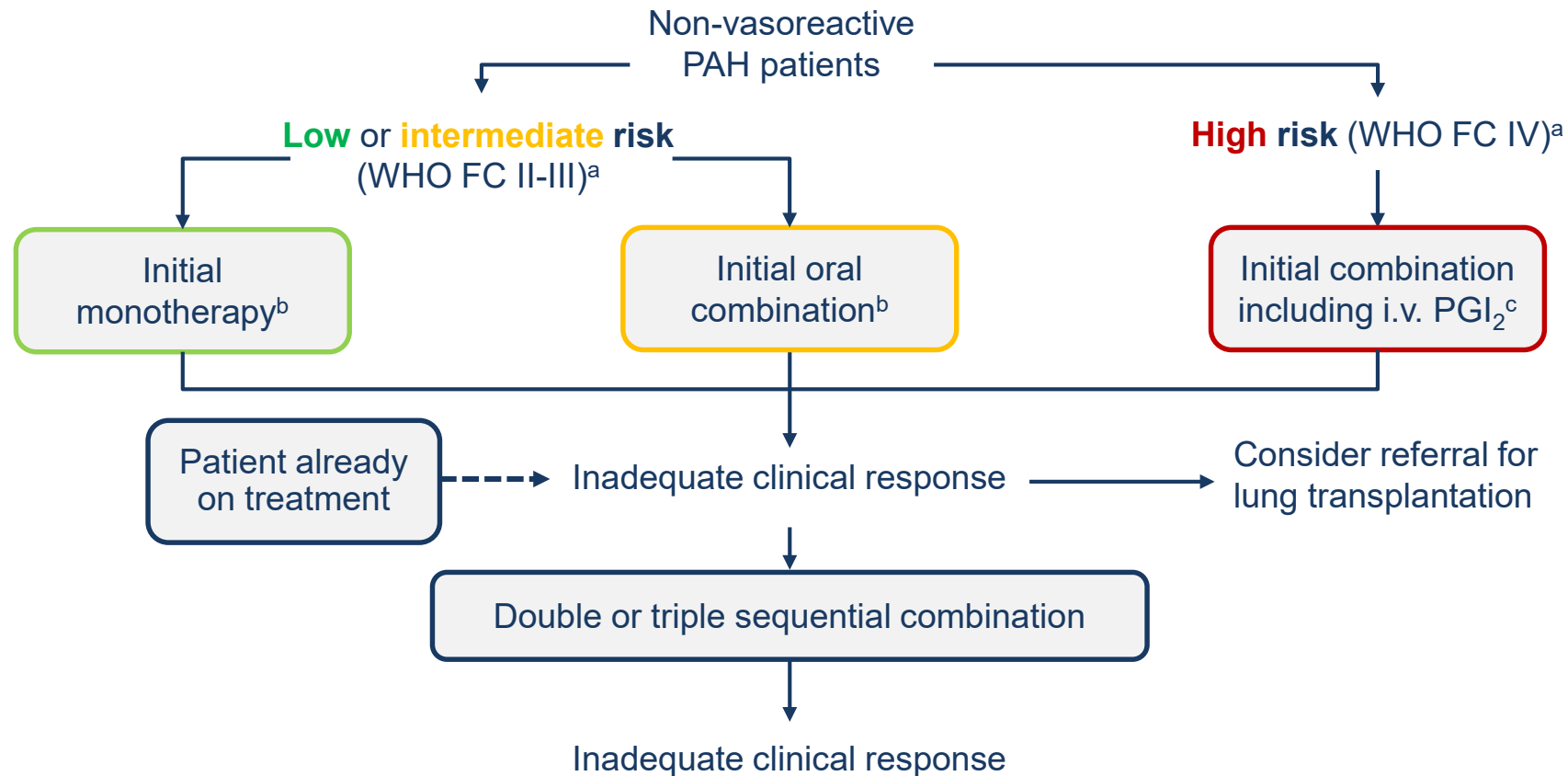


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Risk assessment is fundamental for the determination of an optimal treatment strategy



^a Some WHO-FC III patients may be considered high-risk;

^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 prioritized as it has reduced the 3 month rate for mortality in high-risk PAH patients also as monotherapy.

Risk Prediction Tools in PAH

Risk equations or models currently available to predict outcomes in PAH

1. **NIH registry equation¹**
2. **French network equation^{2,3}**
3. **PH Connection (PHC) equation^{4,5}**
4. **Scottish composite score⁶**
5. **REVEAL equation⁷ and risk score⁸**
6. **ESC/ERS risk stratification table⁹**

Recommendations for evaluation of PAH severity and response to therapy

Recommendations for evaluation of PAH severity and response to therapy		Class	Level
Risk Stratification	It is recommended to evaluate the severity of PAH patients with a panel of data derived from clinical assessment, exercise tests, biochemical markers and echocardiographic and hemodynamic evaluations	I	C
	It is recommended to perform regular follow-up assessments every 3 - 6 months in stable patients	I	C
Treatment goal	Achievement/maintenance of a low-risk profile is recommended as an adequate treatment response for patients with PAH	I	C
	Achievement/maintenance of an intermediate-risk profile should be considered an inadequate treatment response for most patients with PAH	IIa	C

Summary of four registries assessing risk scores

	REVEAL ¹	SPAHR ²	COMPERA ³	FPHN ⁴
Required variables, <i>n</i>	12 - 14	8	8	4
Patients at baseline, <i>n</i>	2716	530	1588	1017
Patients at follow up, <i>n</i>	2529	383	1094	1017
Associated-PAH included	Yes	Yes	Yes	No
Definition of low-risk	≤ 6 REVEAL score	<1.5 Average score	< 1.5 Average score	3-4 of 4 low-risk criteria
1-year mortality by risk group (low/intermediate/high), %	≤2.6 / 7.0 / ≥10.7	1.0 / 7.0 / 26.0	2.8 / 9.9 / 21.2	1.0 / NA / 13.0-30.0

1. Benza RL, et al. *J Heart Lung Transplant*. 2015;34:356–61.

2. Kylhammar D, et al. *Eur Heart J* 2017; ehx257.

3. Hoeper MM, et al. *Eur Respir J* 2017; 50:1700740.

4. Boucly A, et al. *Eur Respir J* 2017; 50:1700889.

The REVEAL score

REVEAL™	PAH Risk Score			
WHO Group I Subgroup	<div>APAH-CTD</div> <div>+1</div>	<div>APAH-PoPH</div> <div>+2</div>	<div>FPAH</div> <div>+2</div>	<input type="text"/>
Demographics & Comorbidities	<div>Renal Insufficiency</div> <div>+1</div>	<div>Males Age > 60yrs</div> <div>+2</div>		<input type="text"/>
NYHA/WHO Functional Class	<div>I</div> <div>-2</div>	<div>III</div> <div>+1</div>	<div>IV</div> <div>+2</div>	<input type="text"/>
Vital Signs	<div>SBP < 110 mm Hg</div> <div>+1</div>	<div>HR > 92 BPM</div> <div>+1</div>		<input type="text"/>
6-Minute Walk Test	<div>≥ 440 m</div> <div>-1</div>	<div>< 165 m</div> <div>+1</div>		<input type="text"/>
BNP	<div>< 50 pg/mL</div> <div>-2</div>	<div>> 180 pg/mL</div> <div>+1</div>		<input type="text"/>
Echocardiogram	<div>Pericardial Effusion</div> <div>+1</div>			<input type="text"/>
Pulmonary Function Test	<div>% pred. DLco ≥ 80</div> <div>-1</div>	<div>% pred. DLco ≤ 32</div> <div>+1</div>		<input type="text"/>
Right Heart Catheterization	<div>mRAP > 20 mm Hg within 1 yr</div> <div>+1</div>	<div>PVR > 32 Wood units</div> <div>+2</div>		<input type="text"/>
SUM OF ABOVE				<input type="text"/>
			+	<input type="text" value="6"/>
= RISK SCORE				<input type="text"/>

- Score from 0 (low risk) to 22 (high risk)
- Estimated survival at 1 year
- Incident/prevalent cases

Survival according to risk score at enrollment

2015 ESC/ERS Guidelines – Risk stratification in PAH

Clinical Evaluation

Exercise Capacity

Right Ventricular Function

Determinants of prognosis	Estimated 1-year mortality		
	Low risk < 5%	Intermediate risk 5-10%	High risk > 10%
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
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
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
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
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%

2015 ESC/ERS Guidelines – Risk stratification in PAH

Clinical Evaluation

Exercise Capacity

Right Ventricular Function

Determinants of prognosis	Estimated 1-year mortality		
	Low risk < 5%	Intermediate risk 5-10%	High risk > 10%
Clinical signs of right heart failure			
Progression of symptoms			
Syncope			
FC			
6MWD			
CPET			
NT-proBNP plasma levels			
Imaging (echo, CMR)			
Hemodynamics			

Validation of ESC/ERS risk stratification for PAH



European Heart Journal (2017) 0, 1-7
doi:10.1093/eur/ehx257

CLINICAL RESEARCH
Pulmonary circulation

A comprehensive risk stratification at early follow-up determines prognosis in pulmonary arterial hypertension

David Kylhammar^{1*}, Barbro Kjellström², Clara Hjalmarsson³, Kjell Jansson⁴, Magnus Nisell⁵, Stefan Söderberg⁶, Gerhard Wikström⁷, and Göran Rådegran¹, on behalf of SveFPH and SPAHR

Mortality in pulmonary arterial hypertension: prediction by the 2015 European pulmonary hypertension guidelines risk stratification model

Marius M. Hoeper^{1,2}, Tilmann Kramer^{3,4}, Zixuan Pan⁵, Christina A. Eichstaedt⁶, Jens Spiesshoefer⁶, Nicola Benjamin⁵, Karen M. Olsson^{1,2}, Katrin Meyer¹, Carmine Dario Vizza⁷, Anton Vonk-Noordegraaf⁸, Oliver Distler⁹, Christian Opitz¹⁰, J. Simon R. Gibbs¹¹, Marion Delcroix¹², H. Ardeschir Ghofrani¹³, Doerte Huscher¹⁴, David Pittrow¹⁵, Stephan Rosenkranz^{3,4} and Ekkehard Grünig^{2,5}

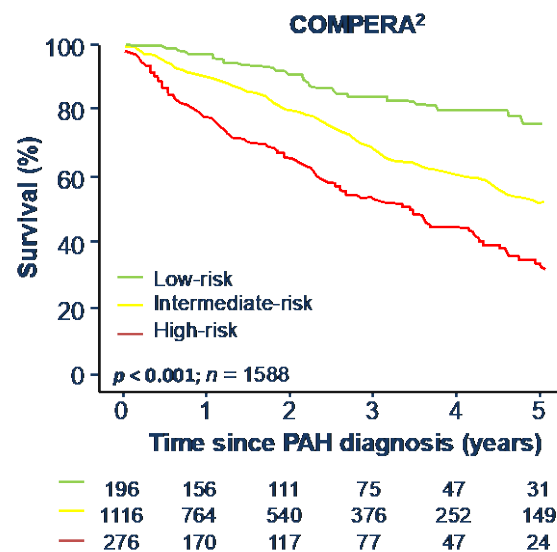
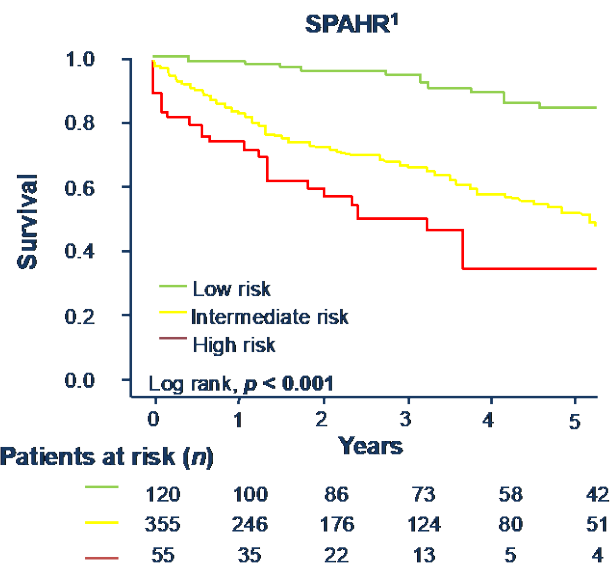
Risk assessment, prognosis and guideline implementation in pulmonary arterial hypertension

Athénaïs Boucly^{1,2,3}, Jason Weatherald^{2,3,4}, Laurent Savale^{1,2,3}, Xavier Jaïs^{1,2,3}, Vincent Cottin⁵, Grégoire Prevot⁶, François Picard⁷, Pascal de Groote⁸, Mitja Jevnikar^{1,2,3}, Emmanuel Bergot⁹, Ari Chaouat^{10,11}, Céline Chabanne¹², Arnaud Bourdin¹³, Florence Parent^{1,2,3}, David Montani^{1,2,3}, Gérald Simonneau^{1,2,3}, Marc Humbert^{1,2,3} and Olivier Sitbon^{1,2,3}

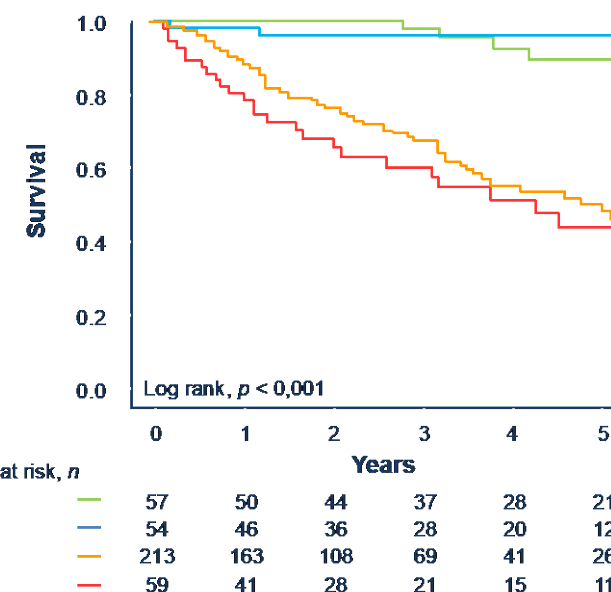
Kylhammar (8 variables)	Hoeper (6 variables)	Boucly (4 or 3 variables)
<i>n</i> = 530 PAH (2008-2016)	<i>n</i> = 1588 PAH (2009-2016)	<i>n</i> = 1017 IPAH (2006-2016)
WHO 6MWD BNP RA area Pericardial effusion RAP CI SvO ₂	WHO 6MWD BNP RAP CI SvO ₂	WHO 6MWD RAP CI WHO 6MWD BNP
Sum of grades (1 low-3 high) /number available variables	Sum of grades (1 low-3 high) /number available variables	Number of low risk variables

Validation of ESC/ERS risk stratification in large registries

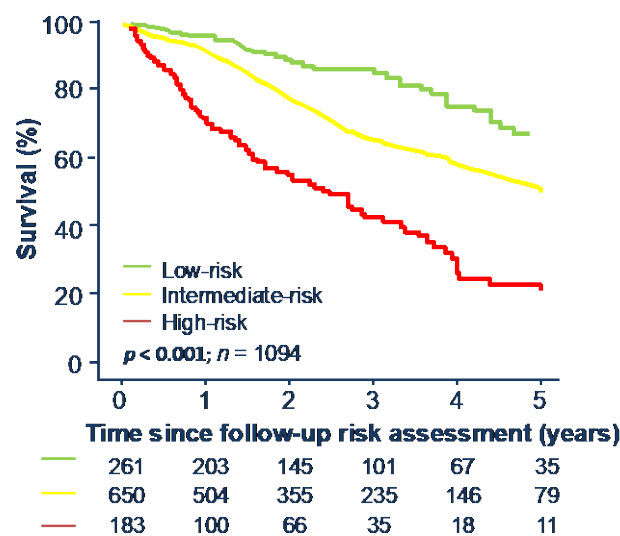
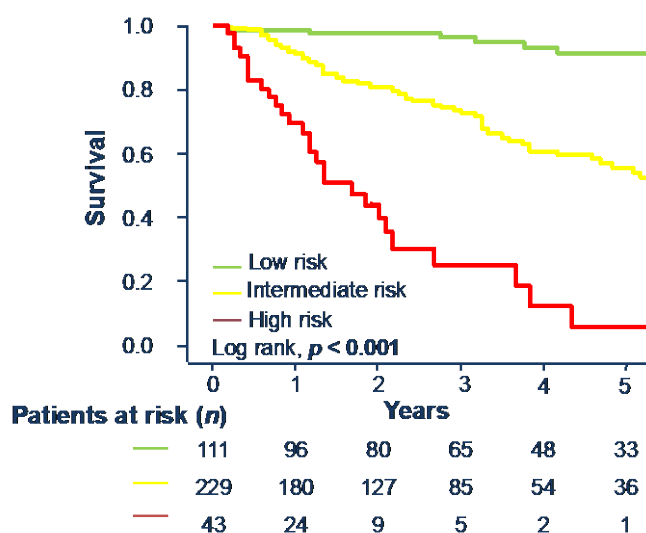
Baseline



SPAHR: change in risk status



Follow-up

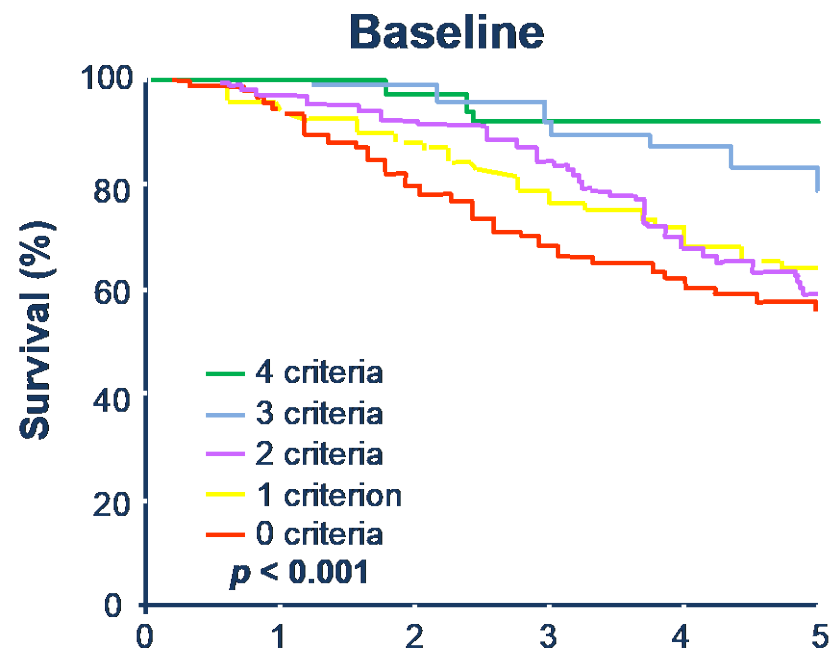


1. Kylhammar D, et al. *Eur Heart J* 2017; Epub ahead of print;
2. Hoeper MM, et al. *Eur Respir J* 2017; 50:1700740.

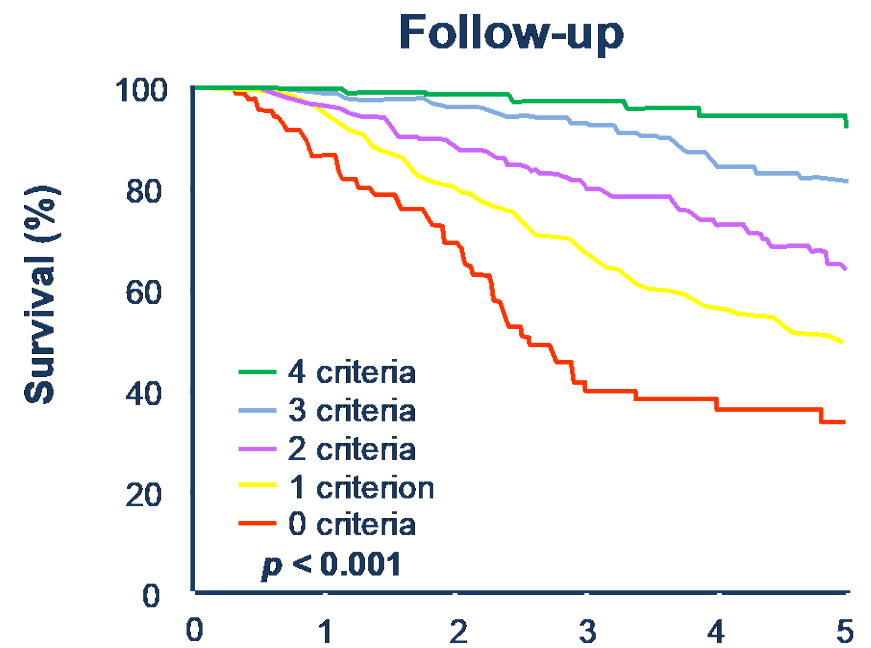
Achievement of multiple low risk criteria is associated with improved long-term outcomes

Low-risk criteria:

NYHA FC I-II
6MWD >440 m
RAP <8 mmHg
CI >2.5 L/min/m²

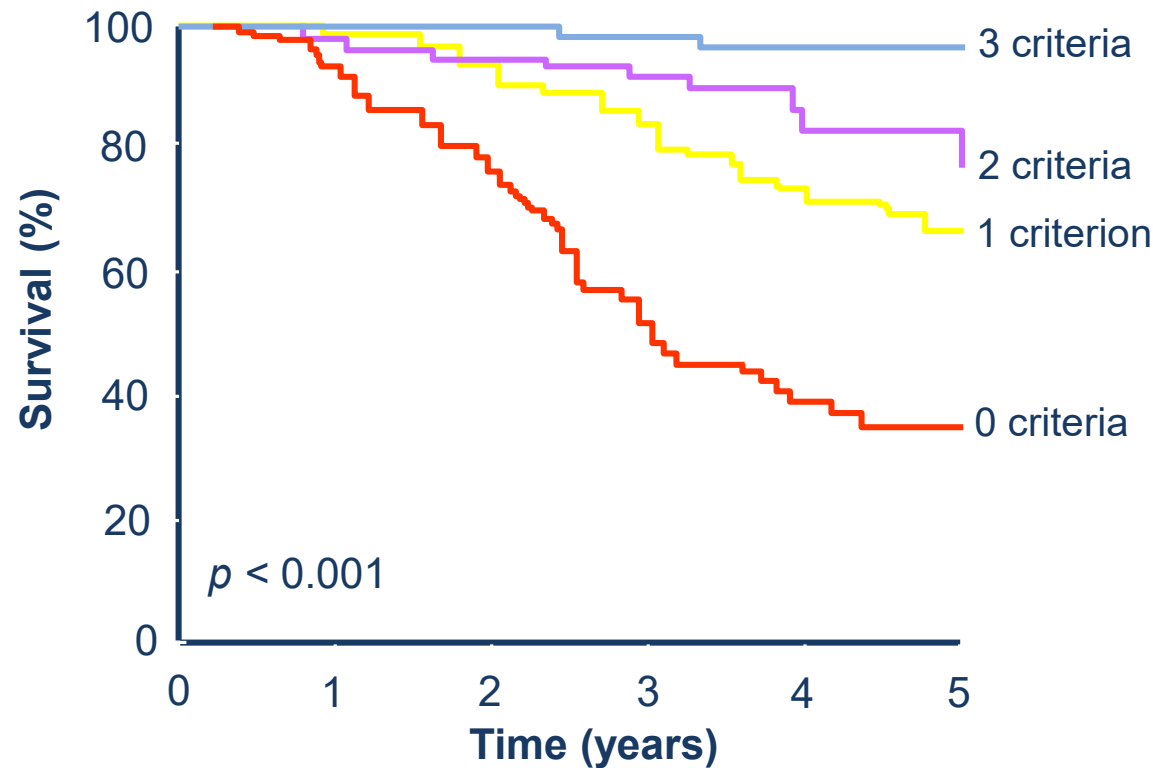


Patients at risk, <i>n</i>		Time (years)					
		0	1	2	3	4	5
4 criteria	59	52	46	35	26	20	
3 criteria	112	94	74	59	36	26	
2 criteria	217	173	149	104	63	45	
1 criterion	371	302	233	176	128	89	
0 criteria	258	212	158	117	76	53	



		Time (years)					
		0	1	2	3	4	5
4 criteria	175	153	128	102	63	48	
3 criteria	247	204	175	140	102	72	
2 criteria	275	219	171	122	78	49	
1 criterion	225	183	128	91	62	45	
0 criteria	95	61	44	22	18	14	

Number of non-invasive low-risk criteria at follow-up is also associated with prognosis



Non-invasive low-risk criteria:
 NYHA FC I-II
 6MWD >440 m
 BNP <50 ng/L or NT-proBNP <300 ng/L

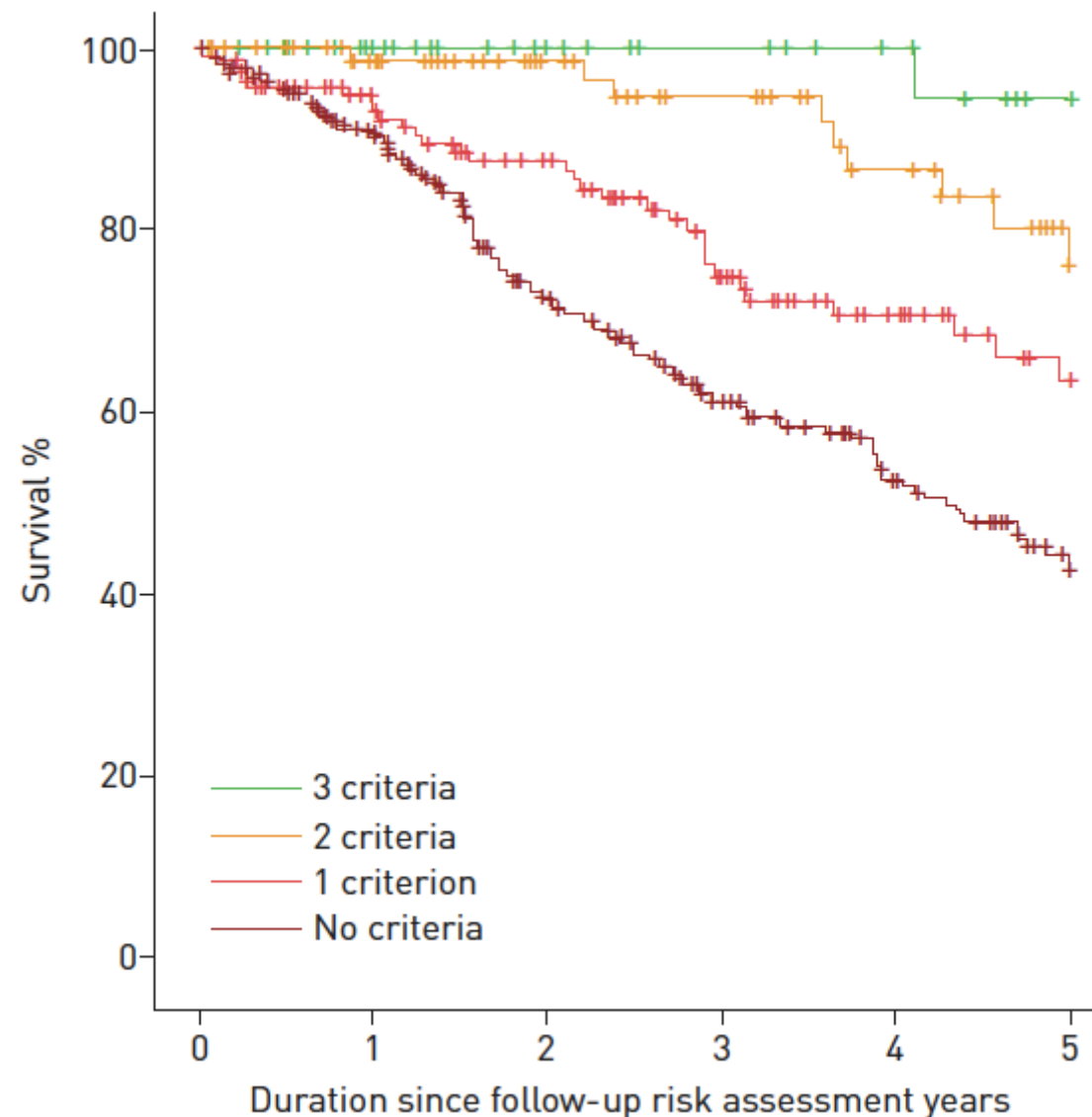
Patients with all 3 non-invasive low-risk criteria had a 2-, 3- and 5-year survival of 100%, 99% and 97%, respectively

Patients at risk, n ($n = 603$)

3 criteria	115	97	81	63	38	26
2 criteria	145	116	95	72	36	21
1 criterion	175	136	101	62	38	24
0 criteria	168	117	76	39	23	11

Validation of the french methodology in COMPERA

- 579 idiopathic PAH
- 1st f-up (median 4.6 months)
- 3 non invasive criteria:
 - NYHA FC I-II
 - 6MWD > 440m
 - BNP < 50 ng/L or
NT-proBNP < 300 ng/mL



Limitations of Risk Assessment

- Data derived from retrospective and prospective observational registries
- Data collection was not standardized in all published registries
- Significant missing data and patients lost to follow-up (SPAHR & COMPERA)
- Other important prognostic features, e.g. imaging, Echo, and CPET, were not collected systematically
- Intermediate risk patients is the largest group

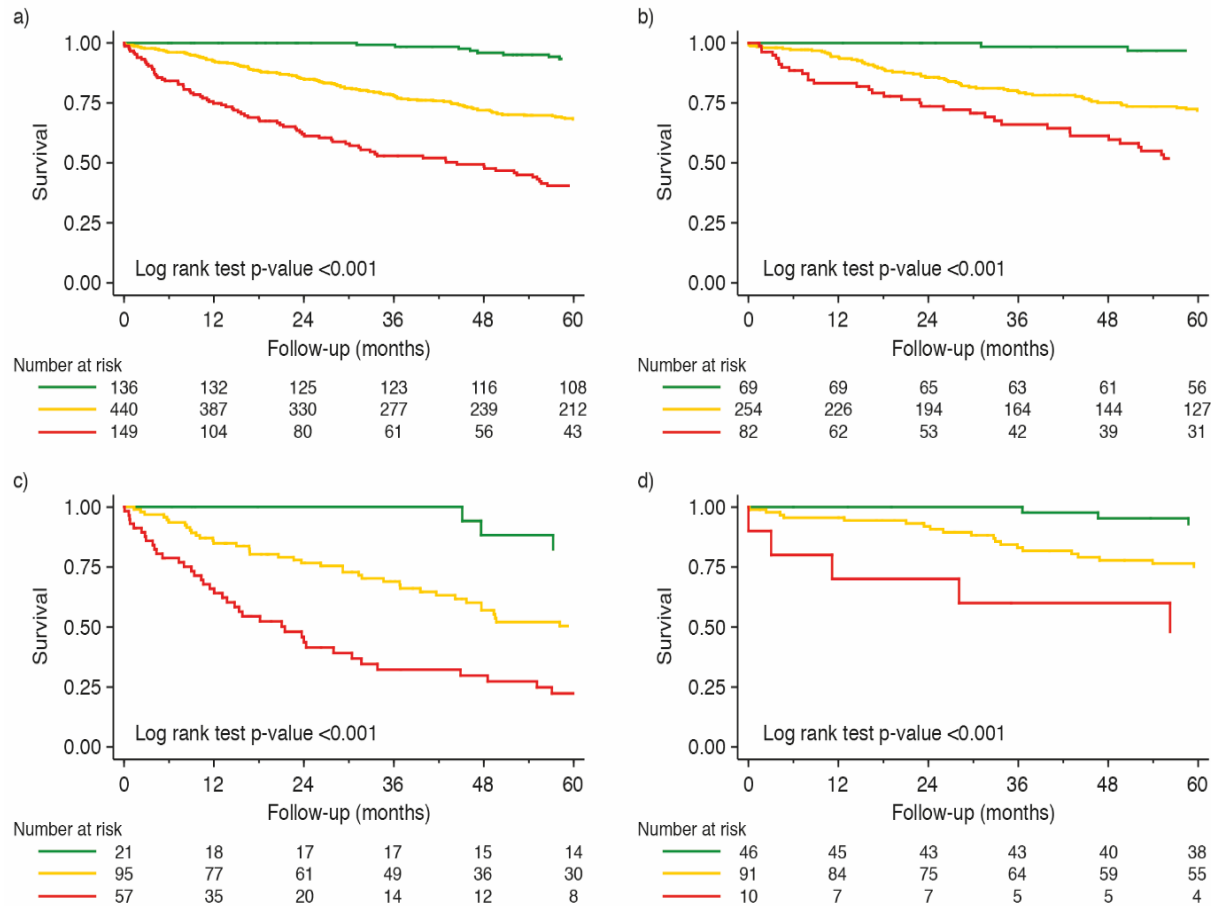
Proposal of a simplified risk assessment in pulmonary arterial hypertension

Risk Criteria	Determinants of <u>Prognosis</u> ^a (estimated 1-year mortality)	Low Risk Variables (<5%)	Intermediate Risk Variables (5-10%)	High Risk Variables (>10%)
A.	WHO functional class	I, II	III	IV
B.	6MWD	> 440 m	165–440 m	< 165 m
C.	<u>NT-proBNP/BNP</u> plasma levels or RAP	BNP < 50 ng/l NT-proBNP < 300 ng/l or RAP < 8 mmHg	BNP 50–300 ng/l <u>NT-proBNP</u> 300–1400 ng/l or RAP 8–14 mmHg	BNP > 300 ng/l NT-proBNP > 1400 ng/l or RAP > 14 mmHg
D.	CI or SvO ₂	CI ≥ 2.5 l/min/m ² or SvO ₂ > 65%	CI 2.0–2.4 l/min/m ² or SvO ₂ 60–65%	CI < 2.0 l/min/m ² or SvO ₂ < 60%
Individual Risk Category Definition		Low Risk Definition	Intermediate Risk Definition	High Risk Definition
		At least 3 low risk criteria and no high risk criteria	Definitions of low or high risk not fulfilled	At least 2 high risk criteria including CI or SvO ₂

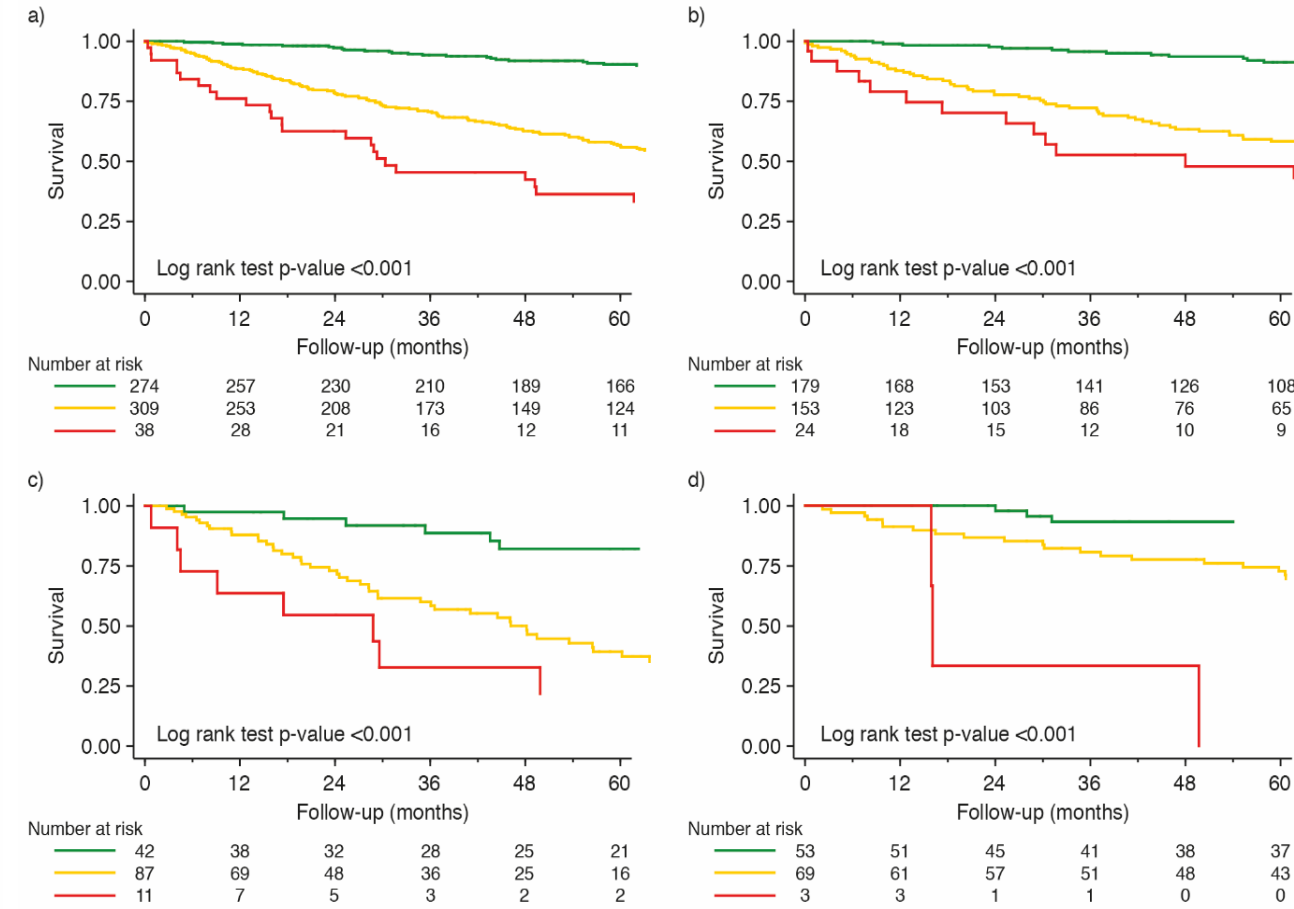


Risk stratification at baseline and follow-up

BASELINE EVALUATION



TREATMENT RESPONSE



— Low — Intermediate — High

Recommendations for evaluation of PAH severity and response to therapy



**Risk
Stratification**

Recommendations for evaluation of PAH severity and response to therapy

Class

Level

It is recommended to evaluate the severity of PAH patients with a panel of data derived from clinical assessment, exercise tests, biochemical markers and echocardiographic and hemodynamic evaluations

I

C > B

It is recommended to perform regular follow-up assessments every 3 - 6 months in stable patients

I

C > B

**Treatment
goal**

Achievement/maintenance of a low-risk profile is recommended as an adequate treatment response for patients with PAH

I

C > B

Achievement/maintenance of an intermediate-risk profile should be considered an inadequate treatment response for most patients with PAH

IIa

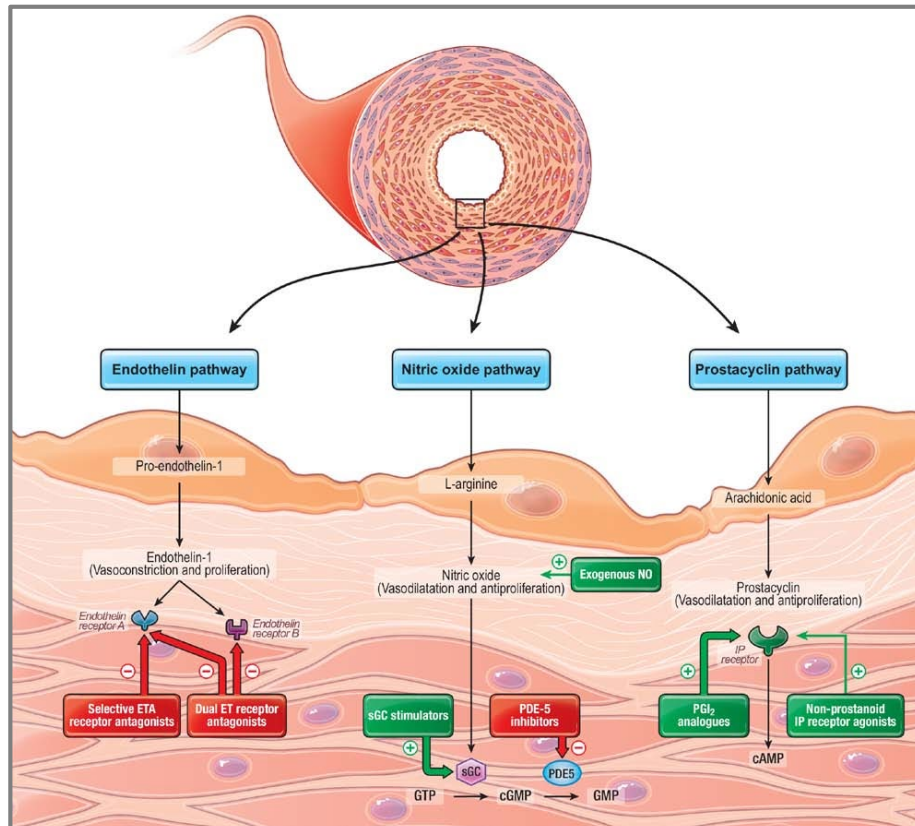
C > B

Current PAH-targeted medications:

Targeting 3 major pathways of endothelial dysfunction

Advances in Therapeutic Interventions for Patients With Pulmonary Arterial Hypertension

Marc Humbert, MD, PhD; Edmund M.T. Lau, MD, PhD; David Montani, MD, PhD;
Xavier Jaïs, MD; Oliver Sitbon, MD, PhD; Gérald Simonneau, MD



Circulation. 2014;130:2189-208.

Endothelin pathway

Endothelin receptor antagonists (ERAs)

- Ambrisentan
- Bosentan
- Macitentan

NO–cGMP pathway

PDE5 inhibitors

- Sildenafil
- Tadalafil

sGC stimulators Riociguat

Prostacyclin pathway

Prostanoids

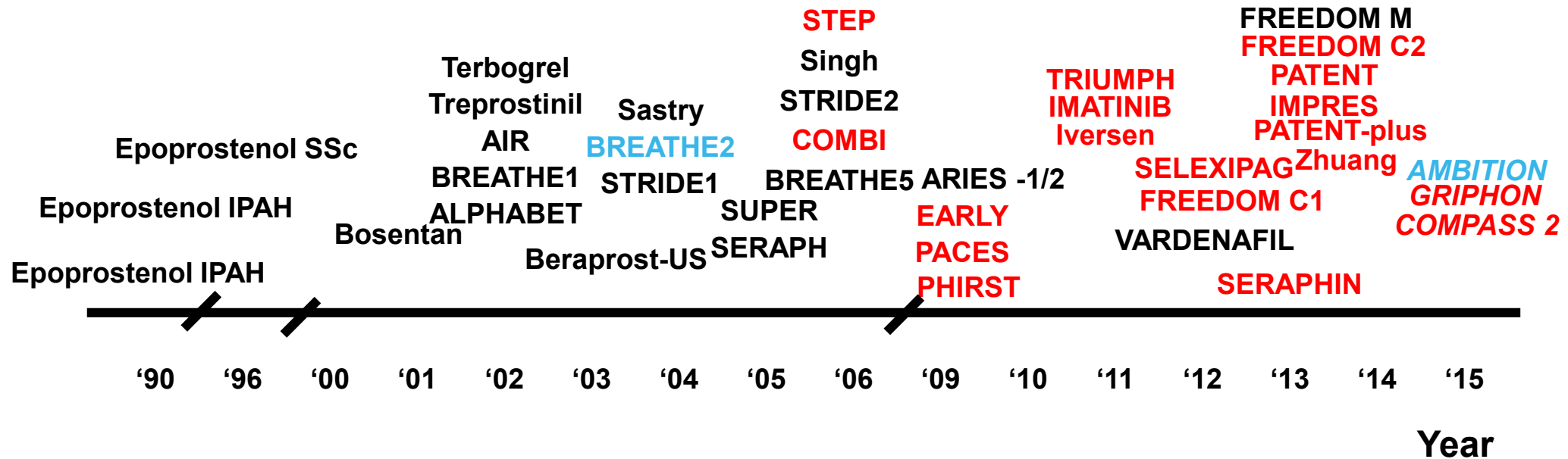
- Epoprostenol iv
- Iloprost inhaled, iv
- Treprostinil sc, iv, (inhaled, oral)*
- (Beraprost)**

Non prostanoids IP receptor agonist Selexipag (oral)

*Only approved in the US; **Only approved in Japan and South Korea

Time-course of completed and published RCTs in PAH (41): Therapy Strategy

9061: PAH patients in RCTs



RCTs on monotherapy vs placebo or vs monotherapy (21)

RCTs on monotherapy and/or sequential combination vs placebo (18)

RCTs on initial combination vs monotherapy (2)

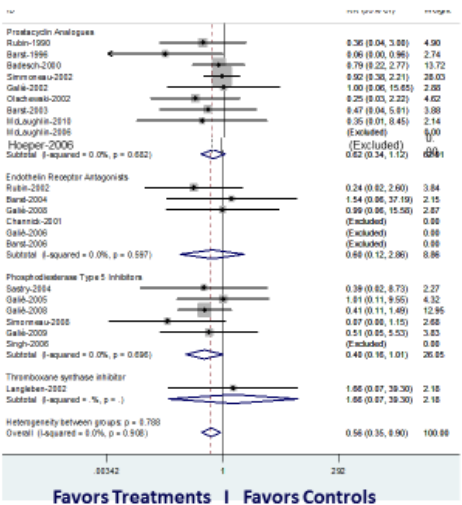
Meta-analyses comparison on all-cause mortality

MONOTHERAPY

Pulmonary arterial hypertension: from the kingdom of the near-dead to multiple clinical trial meta-analyses

All Cause Mortality

RR = - 44%
P = 0.016



N.Galiè, M.Palazzini, A.Manes, Eur Heart J 2010

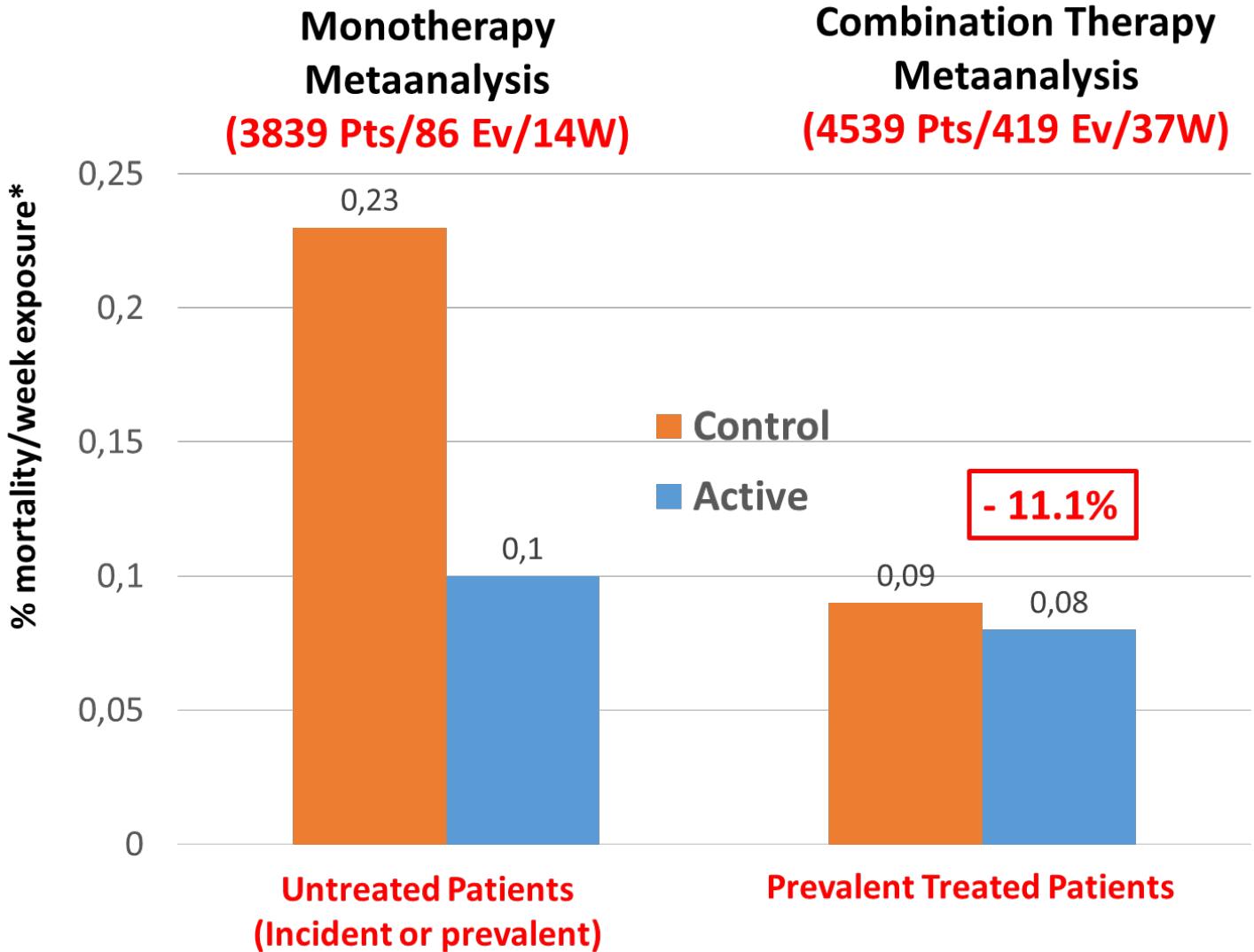
SEQUENTIAL COMBINATION

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

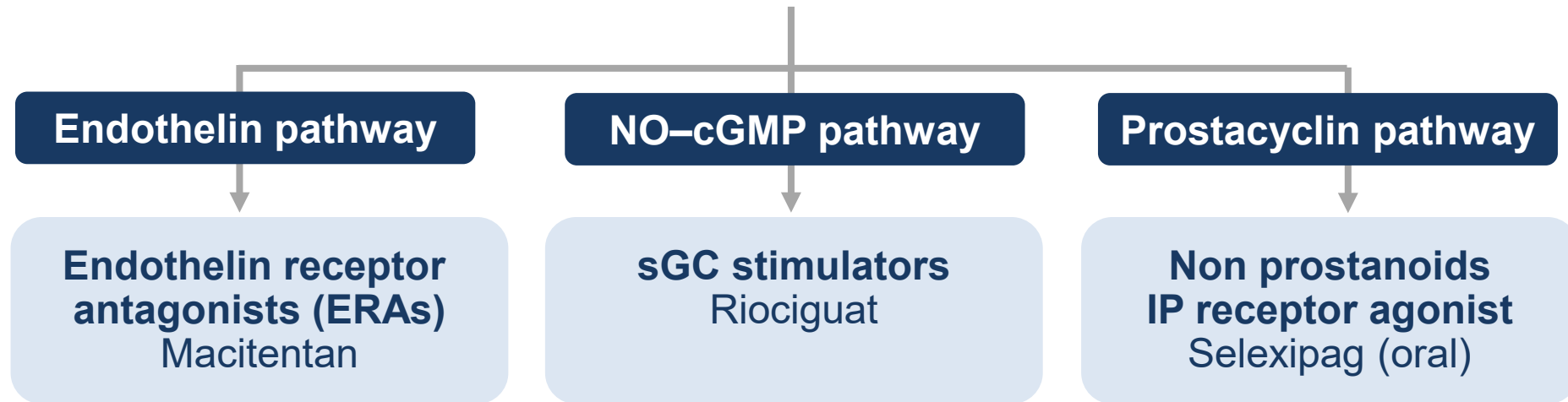
Annie Christine Leleu*, Gabriel Luzzini*, Jean-Christophe Lega, Yves Lacasse, Sylvie Martin, Serge Simard, Sébastien Bounnet†, Stéve Provencher†

	Number of studies	Proportion of events (%)
		With combined therapy
Primary outcome		
Clinical worsening (all events)	15 ^{1,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100,101,102,103,104,105,106,107,108,109,110,111,112,113,114,115,116,117,118,119,120,121,122,123,124,125,126,127,128,129,130,131,132,133,134,135,136,137,138,139,140,141,142,143,144,145,146,147,148,149,150,151,152,153,154,155,156,157,158,159,160,161,162,163,164,165,166,167,168,169,170,171,172,173,174,175,176,177,178,179,180,181,182,183,184,185,186,187,188,189,190,191,192,193,194,195,196,197,198,199,200,201,202,203,204,205,206,207,208,209,210,211,212,213,214,215,216,217,218,219,220,221,222,223,224,225,226,227,228,229,230,231,232,233,234,235,236,237,238,239,240,241,242,243,244,245,246,247,248,249,250,251,252,253,254,255,256,257,258,259,260,261,262,263,264,265,266,267,268,269,270,271,272,273,274,275,276,277,278,279,280,281,282,283,284,285,286,287,288,289,290,291,292,293,294,295,296,297,298,299,300,301,302,303,304,305,306,307,308,309,310,311,312,313,314,315,316,317,318,319,320,321,322,323,324,325,326,327,328,329,330,331,332,333,334,335,336,337,338,339,340,341,342,343,344,345,346,347,348,349,350,351,352,353,354,355,356,357,358,359,360,361,362,363,364,365,366,367,368,369,370,371,372,373,374,375,376,377,378,379,380,381,382,383,384,385,386,387,388,389,390,391,392,393,394,395,396,397,398,399,400,401,402,403,404,405,406,407,408,409,410,411,412,413,414,415,416,417,418,419,420,421,422,423,424,425,426,427,428,429,430,431,432,433,434,435,436,437,438,439,440,441,442,443,444,445,446,447,448,449,450,451,452,453,454,455,456,457,458,459,460,461,462,463,464,465,466,467,468,469,470,471,472,473,474,475,476,477,478,479,480,481,482,483,484,485,486,487,488,489,490,491,492,493,494,495,496,497,498,499,500,501,502,503,504,505,506,507,508,509,510,511,512,513,514,515,516,517,518,519,520,521,522,523,524,525,526,527,528,529,530,531,532,533,534,535,536,537,538,539,540,541,542,543,544,545,546,547,548,549,550,551,552,553,554,555,556,557,558,559,560,561,562,563,564,565,566,567,568,569,570,571,572,573,574,575,576,577,578,579,580,581,582,583,584,585,586,587,588,589,590,591,592,593,594,595,596,597,598,599,600,601,602,603,604,605,606,607,608,609,610,611,612,613,614,615,616,617,618,619,620,621,622,623,624,625,626,627,628,629,630,631,632,633,634,635,636,637,638,639,640,641,642,643,644,645,646,647,648,649,650,651,652,653,654,655,656,657,658,659,660,661,662,663,664,665,666,667,668,669,670,671,672,673,674,675,676,677,678,679,680,681,682,683,684,685,686,687,688,689,690,691,692,693,694,695,696,697,698,699,700,701,702,703,704,705,706,707,708,709,710,711,712,713,714,715,716,717,718,719,720,721,722,723,724,725,726,727,728,729,730,731,732,733,734,735,736,737,738,739,740,741,742,743,744,745,746,747,748,749,750,751,752,753,754,755,756,757,758,759,760,761,762,763,764,765,766,767,768,769,770,771,772,773,774,775,776,777,778,779,780,781,782,783,784,785,786,787,788,789,790,791,792,793,794,795,796,797,798,799,800,801,802,803,804,805,806,807,808,809,810,811,812,813,814,815,816,817,818,819,820,821,822,823,824,825,826,827,828,829,830,831,832,833,834,835,836,837,838,839,840,841,842,843,844,845,846,847,848,849,850,851,852,853,854,855,856,857,858,859,860,861,862,863,864,865,866,867,868,869,870,871,872,873,874,875,876,877,878,879,880,881,882,883,884,885,886,887,888,889,890,891,892,893,894,895,896,897,898,899,900,901,902,903,904,905,906,907,908,909,910,911,912,913,914,915,916,917,918,919,920,921,922,923,924,925,926,927,928,929,930,931,932,933,934,935,936,937,938,939,940,941,942,943,944,945,946,947,948,949,950,951,952,953,954,955,956,957,958,959,960,961,962,963,964,965,966,967,968,969,970,971,972,973,974,975,976,977,978,979,980,981,982,983,984,985,986,987,988,989,990,991,992,993,994,995,996,997,998,999,1000,1001,1002,1003,1004,1005,1006,1007,1008,1009,1010,1011,1012,1013,1014,1015,1016,1017,1018,1019,1020,1021,1022,1023,1024,1025,1026,1027,1028,1029,1030,1031,1032,1033,1034,1035,1036,1037,1038,1039,1040,1041,1042,1043,1044,1045,1046,1047,1048,1049,1050,1051,1052,1053,1054,1055,1056,1057,1058,1059,1060,1061,1062,1063,1064,1065,1066,1067,1068,1069,1070,1071,1072,1073,1074,1075,1076,1077,1078,1079,1080,1081,1082,1083,1084,1085,1086,1087,1088,1089,1090,1091,1092,1093,1094,1095,1096,1097,1098,1099,1100,1101,1102,1103,1104,1105,1106,1107,1108,1109,1110,1111,1112,1113,1114,1115,1116,1117,1118,1119,1120,1121,1122,1123,1124,1125,1126,1127,1128,1129,1130,1131,1132,1133,1134,1135,1136,1137,1138,1139,1140,1141,1142,1143,1144,1145,1146,1147,1148,1149,1150,1151,1152,1153,1154,1155,1156,1157,1158,1159,1160,1161,1162,1163,1164,1165,1166,1167,1168,1169,1170,1171,1172,1173,1174,1175,1176,1177,1178,1179,1180,1181,1182,1183,1184,1185,1186,1187,1188,1189,1190,1191,1192,1193,1194,1195,1196,1197,1198,1199,1200,1201,1202,1203,1204,1205,1206,1207,1208,1209,1210,1211,1212,1213,1214,1215,1216,1217,1218,1219,1220,1221,1222,1223,1224,1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Meta-analyses comparison on all-cause mortality



Combination therapy: New endpoints/ New strategies

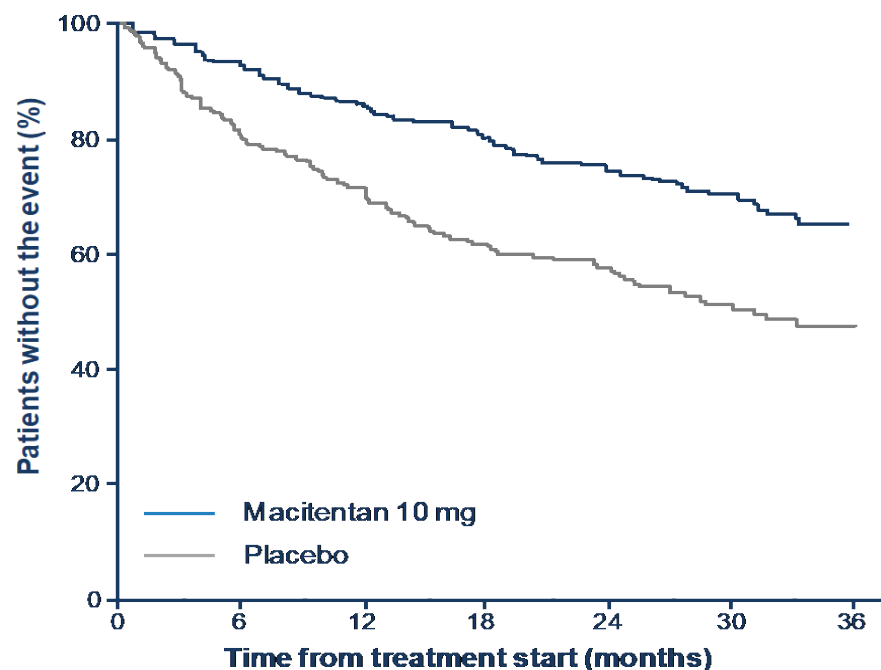


Drug tested	Study	Background	N	Duration (weeks)	Primary endpoint
Bosentan	COMPASS-2 ¹	Sildenafil	334	92	Time to first occurrence of death or morbidity event (NEG)
Macitentan	SERAPHIN ²	None (36%), PDE5i (61%) or oral/inhaled prostanoids	742	≈ 100	Time to first occurrence of death or morbidity event (POS)
Selexipag	GRIPHON ³	None (21%), ERA (13%), PDE5i (32%) or both (34%)	1156	≈ 70	Time to first occurrence of death or morbidity event (POS)
Ambrisentan + tadalafil	AMBITION ⁴	None (incident cases)	500	≈ 74	Time to first occurrence of clinical failure event (POS)

1. McLaughlin VV, et al. *Eur Respir J* 2015. 2. Pulido T, et al. *N Engl J Med* 2013. 3. Sitbon O, et al. *N Engl J Med* 2015. 4. Galié N, et al. *N Engl J Med* 2015.

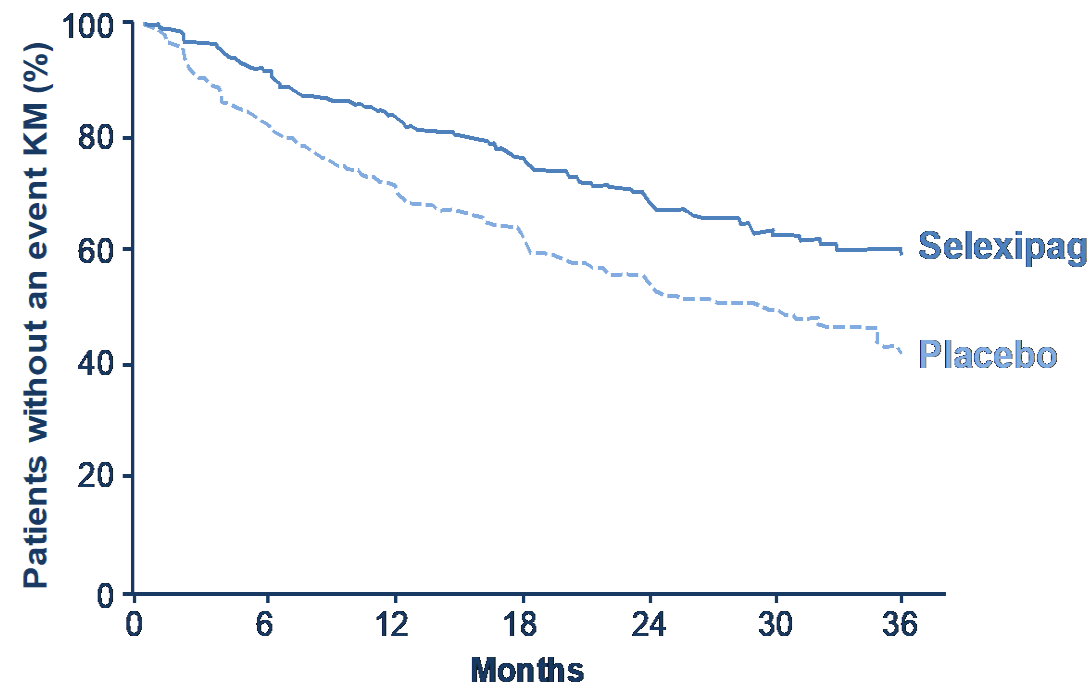
SERAPHIN & GRIPHON: macitentan and selexipag reduced the risk of the primary outcome composite of death or morbidity due to PAH

SERAPHIN¹



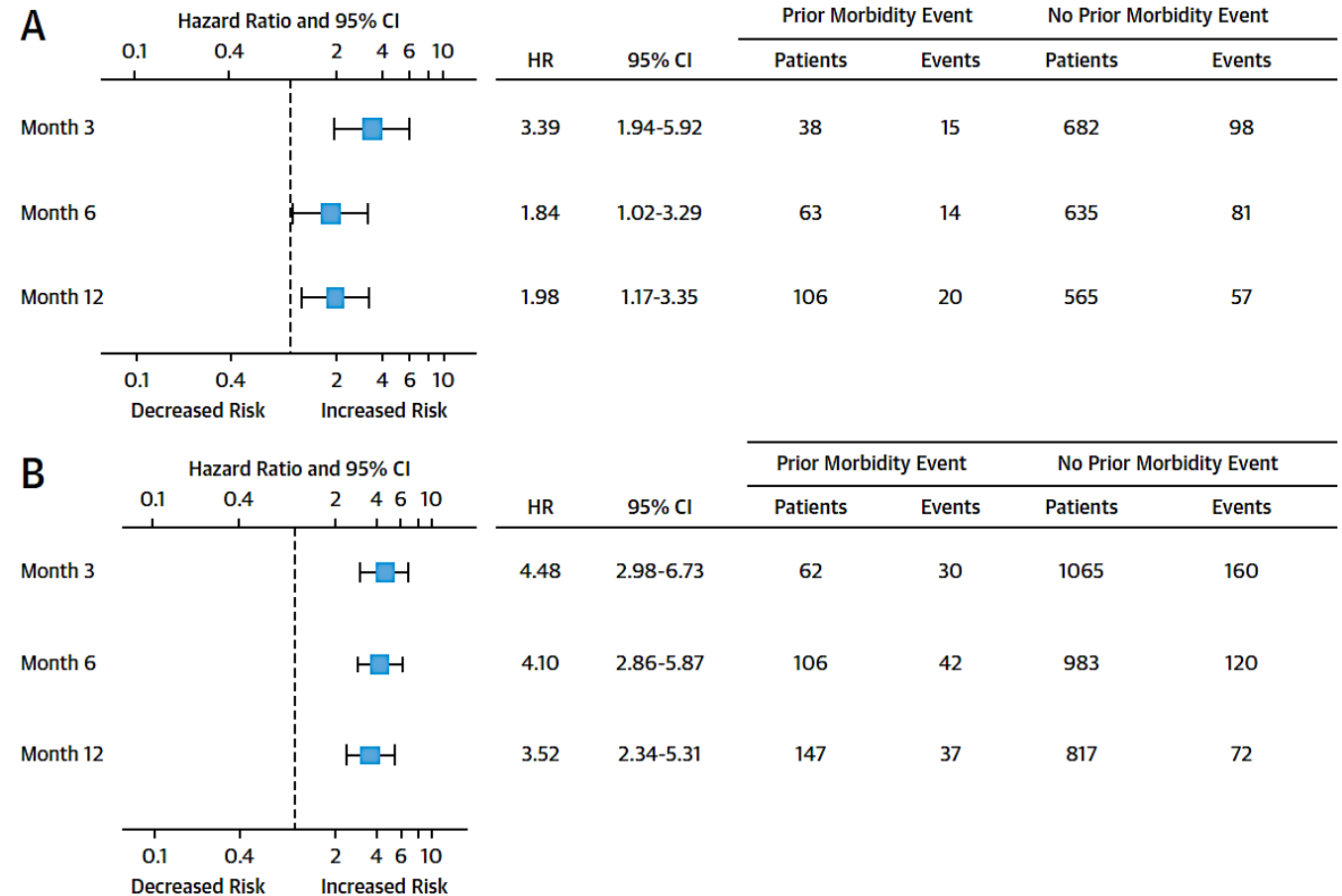
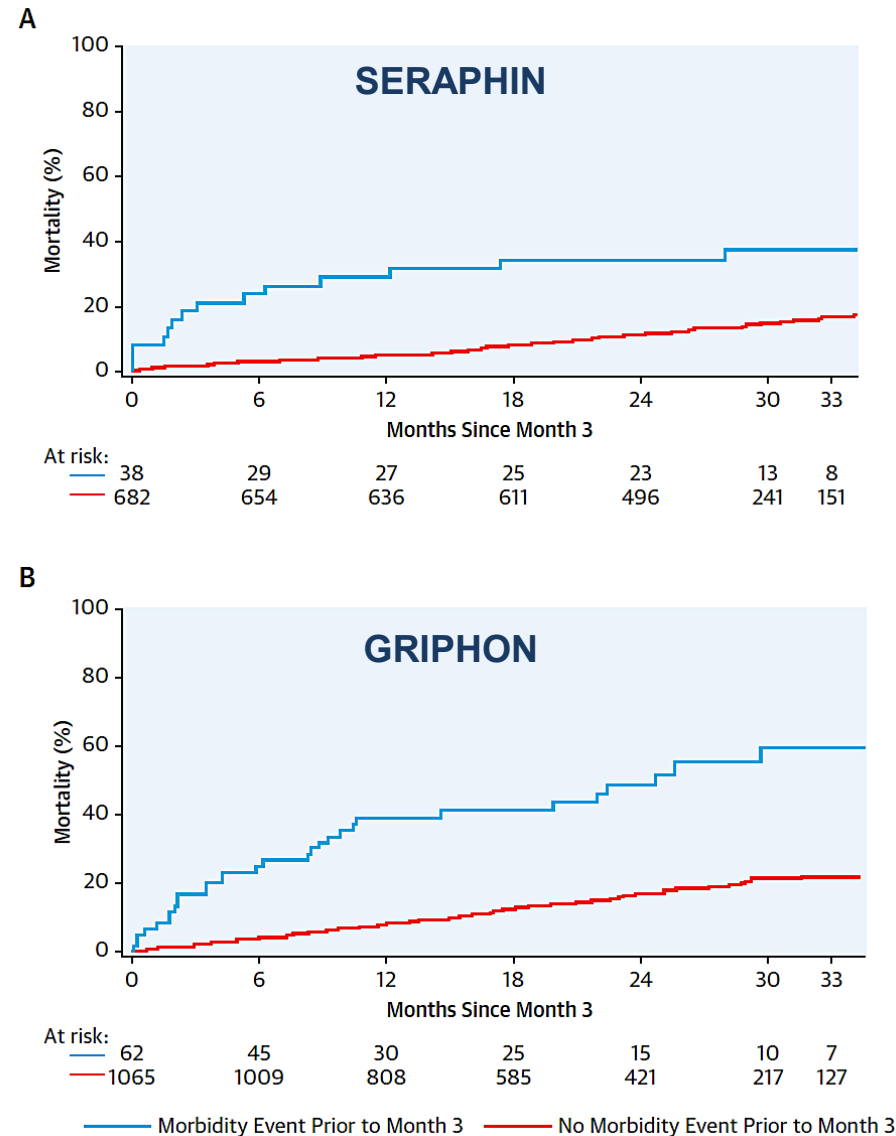
Risk reduction of primary endpoint event vs placebo
Macitentan 10 mg: 45% ($p < 0.001$)

GRIPHON²



Risk reduction of primary endpoint event vs placebo
Selexipag: 40% ($p < 0.0001$)

SERAPHIN & GRIPHON Landmark analysis: Morbidity events were prognostic for mortality



Initial combination therapy: What is the evidence?

Measure/ treatment	Class ^a -Level ^b					
	WHO-FC II		WHO-FC III		WHO-FC IV	
Ambrisentan + tadalafil ^d	I	B	I	B	IIb	C
Other ERA + PDE-5i	IIa	C	IIa	C	IIb	C
Bosentan + sildenafil + i.v. epoprostenol	-	-	IIa	C	IIa	C
Bosentan + i.v. epoprostenol	-	-	IIa	C	IIa	C
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

AMBITION: Galiè N, *et al. N Engl J Med* 2015;273:834-44.

Sitbon O, *et al. Eur Respir J* 2016;47:1727-36.

Sitbon O, *et al. Eur Respir J.* 2014;43:1691-7.

BREATHE-2: Humbert M, *et al. Eur Respir J.* 2004;24:353-9.

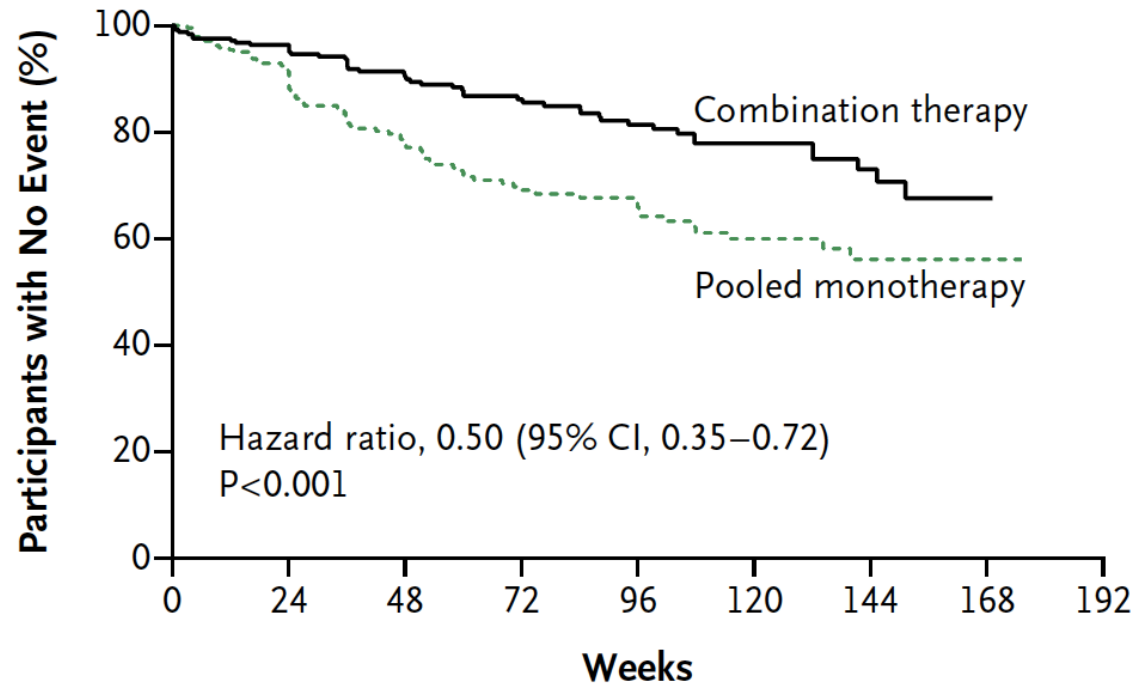
Kemp K, *et al. J Heart Lung Transplant* 2012;31:150-8.

TRITON study (macitentan, tadalafil, ± selexipag) ongoing

RCTs

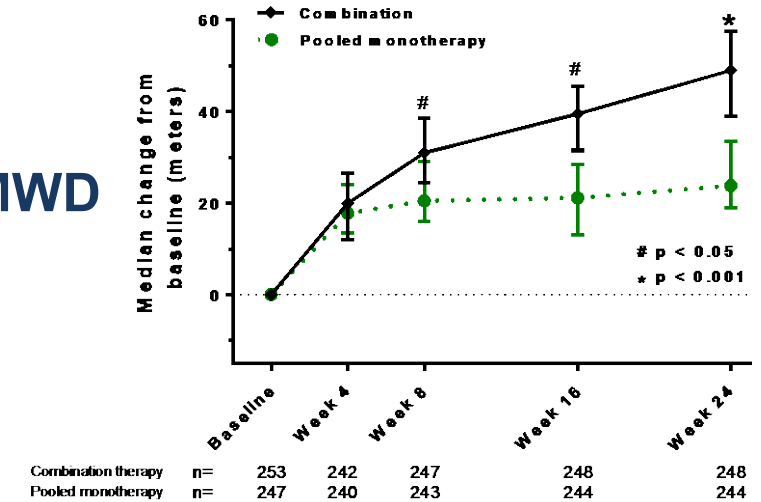
AMBITION: Initial combo of ambrisentan AND tadalafil is superior to monotherapy with ambrisentan OR tadalafil

- N=500 treatment-naïve patients with PAH (31% FC II)
- **Primary endpoint:** Time to the first occurrence of a composite endpoint of death, hospitalization for PAH worsening, disease progression, or unsatisfactory long-term clinical response

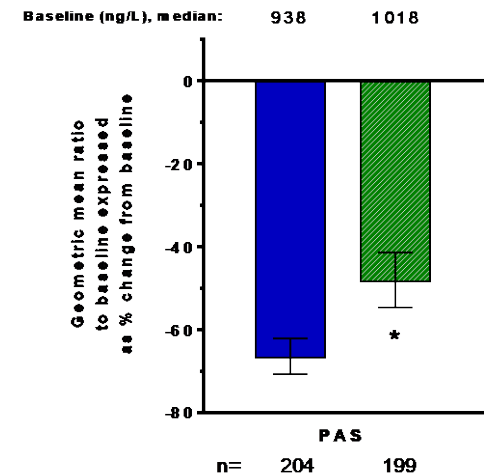


Hospitalisation for PAH worsening was the main component of the primary endpoint

6MWD



NT-ProBNP



Initial dual oral combination in PAH: *A matter of drugs or a question of strategy?*

	AMBITION–BONSAI* Ambrisentan + tadalafil (n=19) ¹	Joint–INTENTION# Bosentan + sildenafil (n=23) ²	French Network Cohort ERA + PDE5i (n=97) ³	OPTIMA Macitentan + tadalafil (n=16) ⁴
Δ RAP (%)	-17	- 36	-29	-10
Δ mPAP (%)	-33	- 21	-16 (-10 mmHg)	-22 (-10 mmHg)
Δ CI (%)	+56	+63	+46 (+1 L/min/m ²)	+45 (+1 L/min/m ²)
Δ PVR (%)	-61	-60	-45 (from 12.7 WU)	-54 (from 10 WU)
Δ 6MWD (%)	+25	+ 42	+22 (+71 m)	+8 (+27 m)

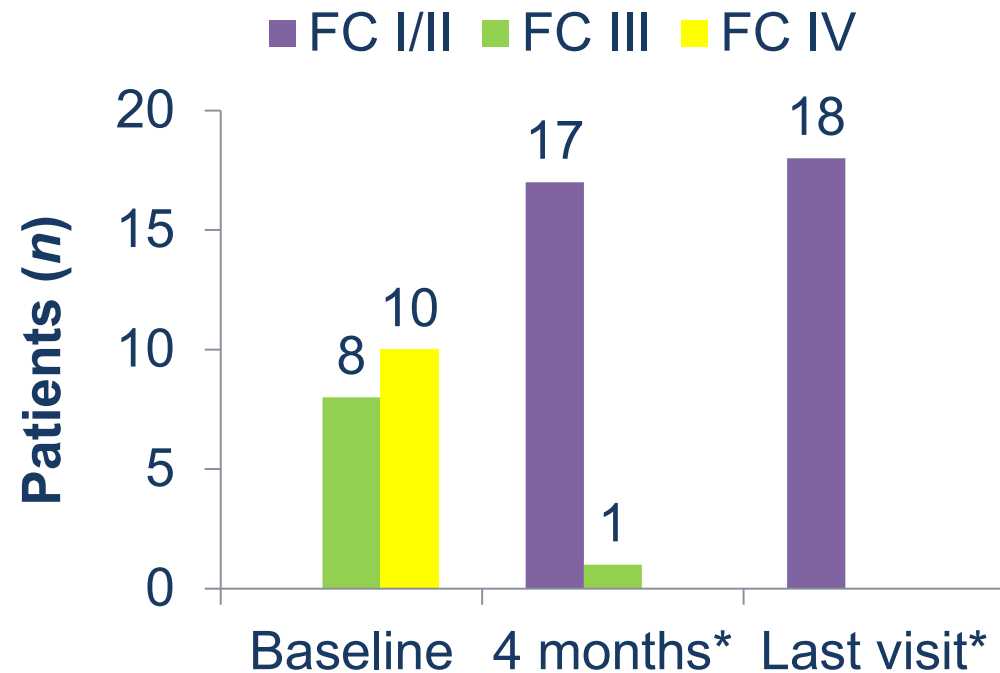
*BONSAI: **BO**log**Na** **S**ub-study on **hA**emodynam**ics**

#**Joint** Bologna and Calgary study on **INi**Tial bos**ENT**an plus sildenafil in pulmonary arterial hypertension.

1. Bachetti C *et al.* *Am J Respir Crit Care Med* 2015;191:A479.
2. Palazzini M *et al.* *Am J Respir Crit Care Med* 2016;193:A6317.
3. Sitbon O *et al.* *Eur Respir J* 2016;47:1727–36.
4. Sitbon O *et al.* Presented as poster at ATS conference 2017.

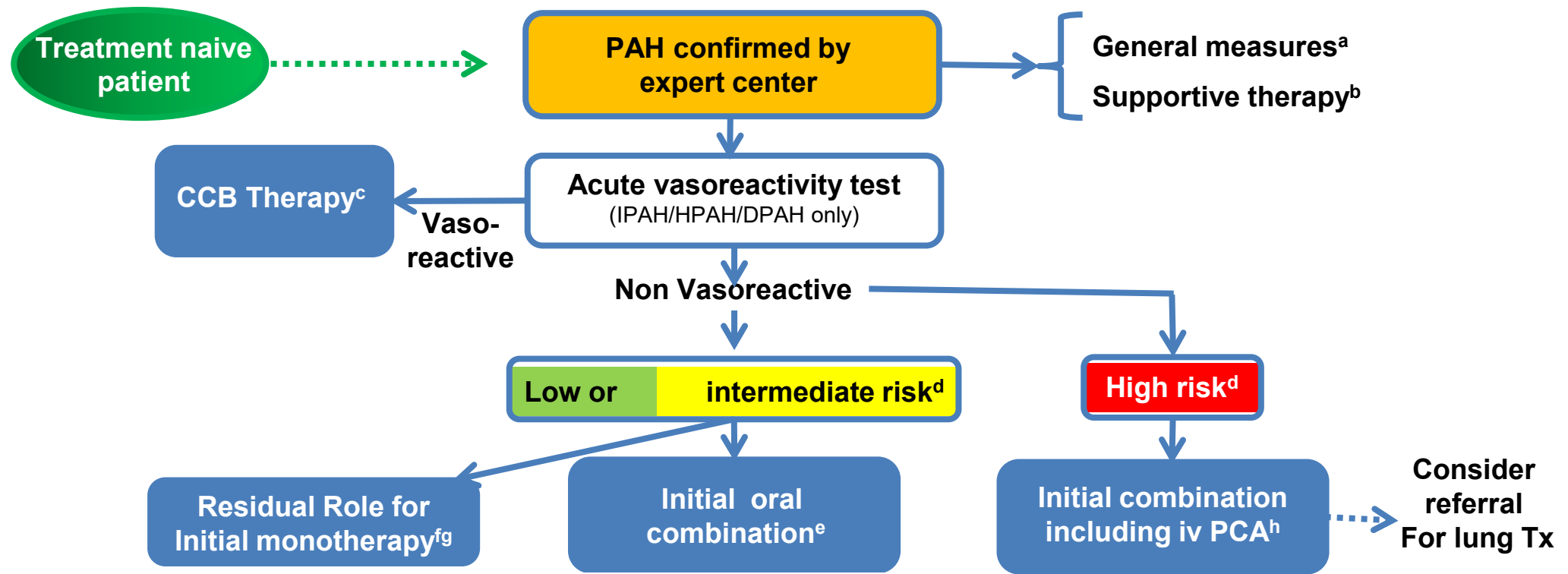
Initial triple combination therapy in severe PAH: Treatment benefit on FC and hemodynamics

Prospective, observational analysis of idiopathic or heritable PAH patients ($n = 19$) treated with triple initial combination therapy (epoprostenol, bosentan and sildenafil)



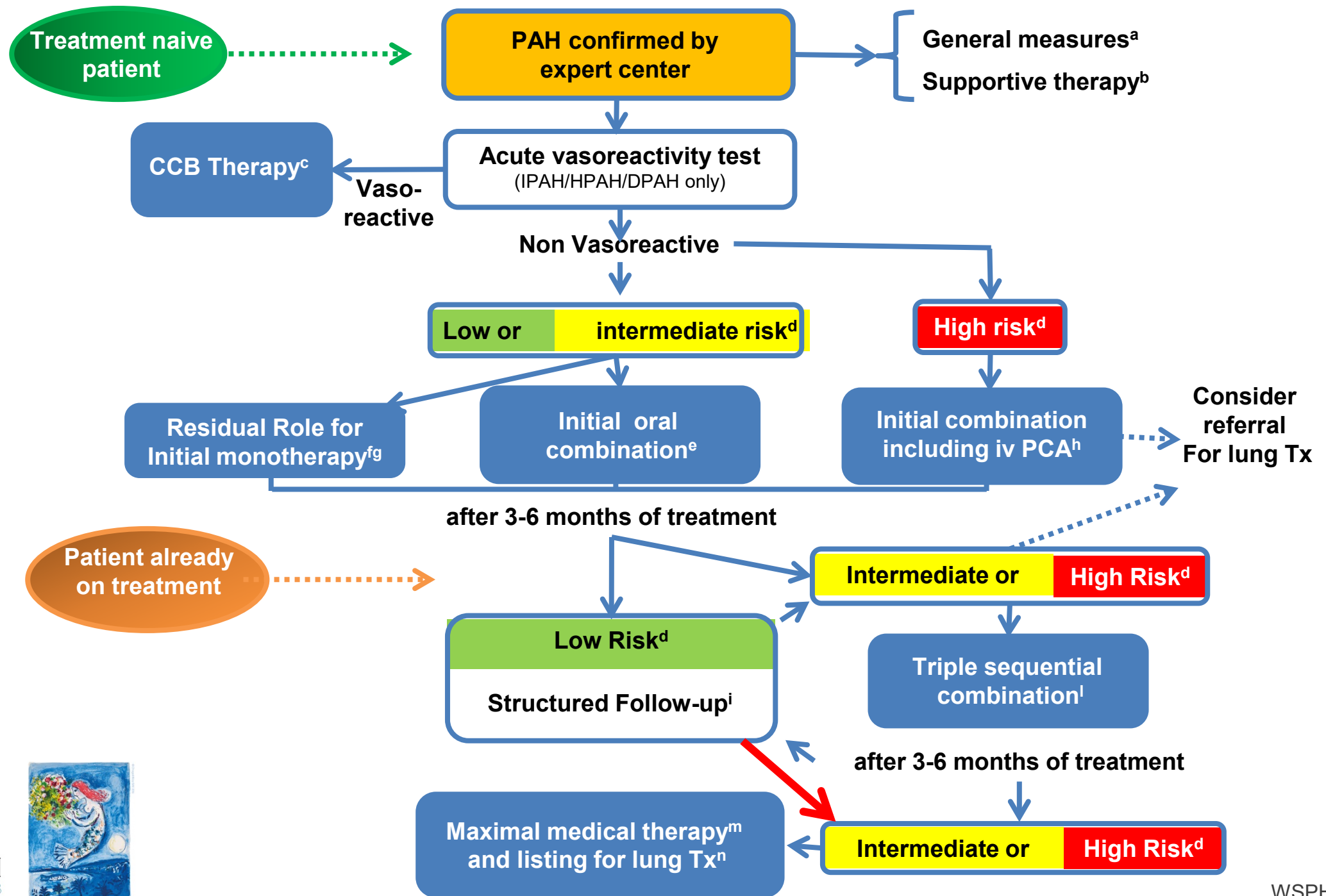
	Baseline	4-month	Last visit (32 ± 19 months)
RAP (mmHg)	11.9 ± 5.2	4.9 ± 4.9*	5.2 ± 3.5*
mPAP (mmHg)	65.8 ± 13.7	45.7 ± 14.0*	44.4 ± 13.4*
CI (l/min/m²)	1.66 ± 0.35	3.49 ± 0.69*	3.64 ± 0.65*
PVR (d.s.cm⁻⁵)	1718 ± 627	564 ± 260*	492 ± 209*
SvO₂ (%)	51.0 ± 8.5	69.7 ± 5.2*	72.2 ± 4.0*

* $p < 0.01$ versus baseline



Residual role for monotherapy

- I/H/D PAH patients **responders to acute vasoreactivity tests** and with near-normalization of symptoms, exercise capacity, PAP and PVR on highest tolerated doses of CCBs
- **Long-term treated historical PAH patients with monotherapy** (> 5-10 years) stable with low risk profile
- **PAH patients > 75 yo with multiple risk factors for HFpEF** (high blood pressure, diabetes mellitus, coronary artery disease, atrial fibrillation, obesity)
- PAH patients with suspicion or high probability of **PVOD/PCH**
- Patients with PAH associated with **HIV** or **portal hypertension** or **uncorrected CHD** as they were not included in RCTs of initial combination therapy
- PAH patients with **very mild disease** (e.g. FC I, PVR < 4 WU, mPAP < 30 mmHg, normal RV)
- **Combination therapy unavailable** or contraindicated (e.g. severe liver disease)



Conclusions

- Multiparametric evaluation is essential to evaluate prognosis and optimal therapeutic strategy
- Low risk category need a clear definition and could be a status to attend and maintain
- Intensive follow up is necessary for all pts to adapt and ev. Increase (combination) therapy
- Double therapy is now the most appropriate therapy for the vast majority of intermediate risk pts
- For more severe pts a parenteral PC associated to 2 oral drugs is recommended