

TAKE HOME MESSAGES FROM THE 6TH WORLD SYMPOSIUM on PULMONARY HYPERTENSION

Risk assessment in pulmonary arterial hypertension

Olivier SITBON

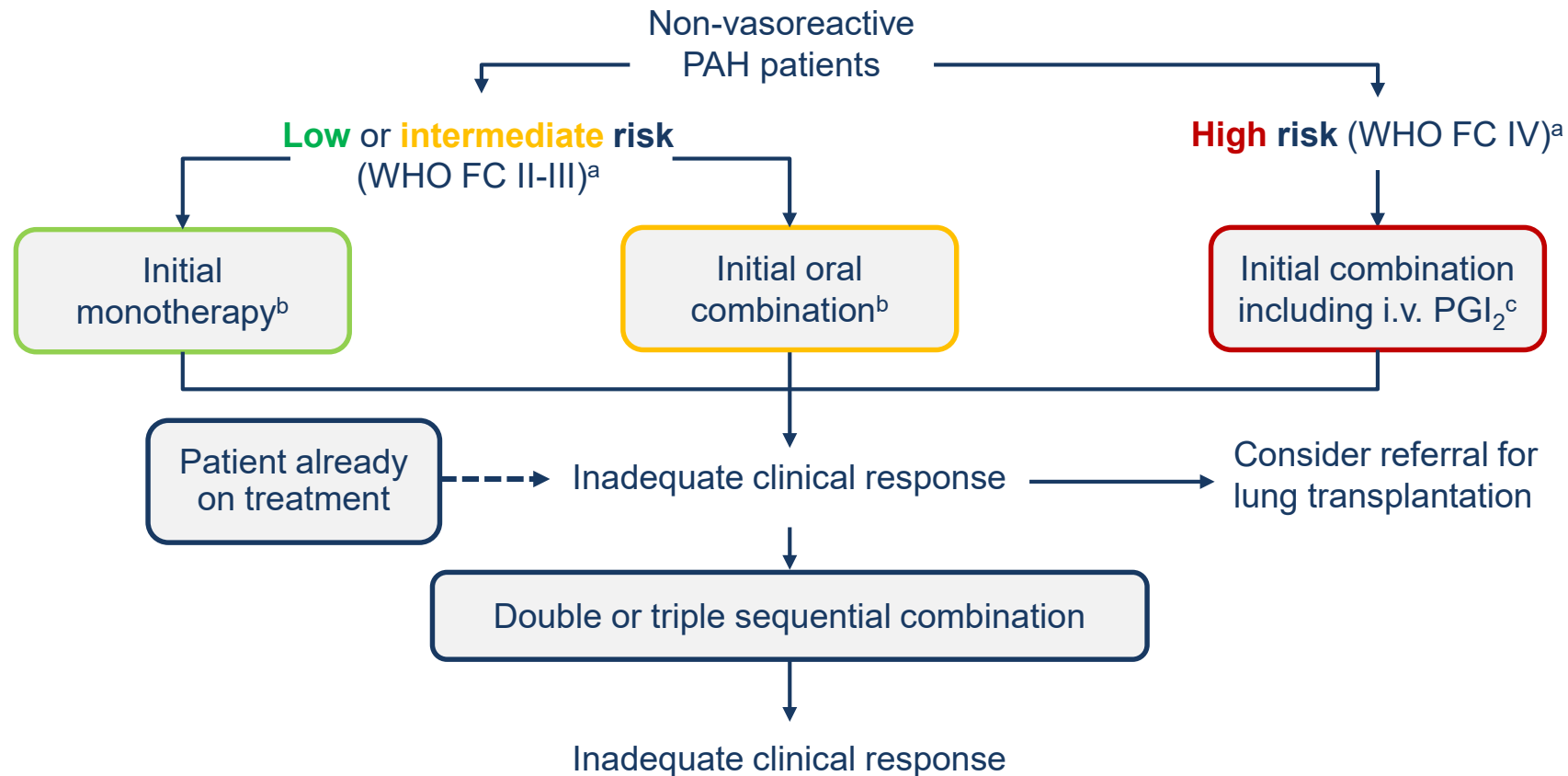
*Centre de Référence de l'Hypertension Pulmonaire – Service de Pneumologie
Hôpital Universitaire de Bicêtre – INSERM UMR S999 – Université Paris-Sud
Le Kremlin-Bicêtre – France*

Conflict of interest disclosure

I have the following real or perceived conflicts of interest that relate to this presentation:

Affiliation / Financial interest	Commercial Company
Grants/research support:	Actelion Pharmaceuticals, Bayer HealthCare, GlaxoSmithKline, Merck
Honoraria or consultation fees:	Actelion Pharmaceuticals, Acceleron Pharmaceuticals, Arena Pharmaceuticals, Bayer HealthCare, GlaxoSmithKline, Gossamer Bio, Merck
Participation in a company sponsored bureau:	No
Stock shareholder:	No
Spouse / partner:	No
Other support / potential conflict of interest:	No

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

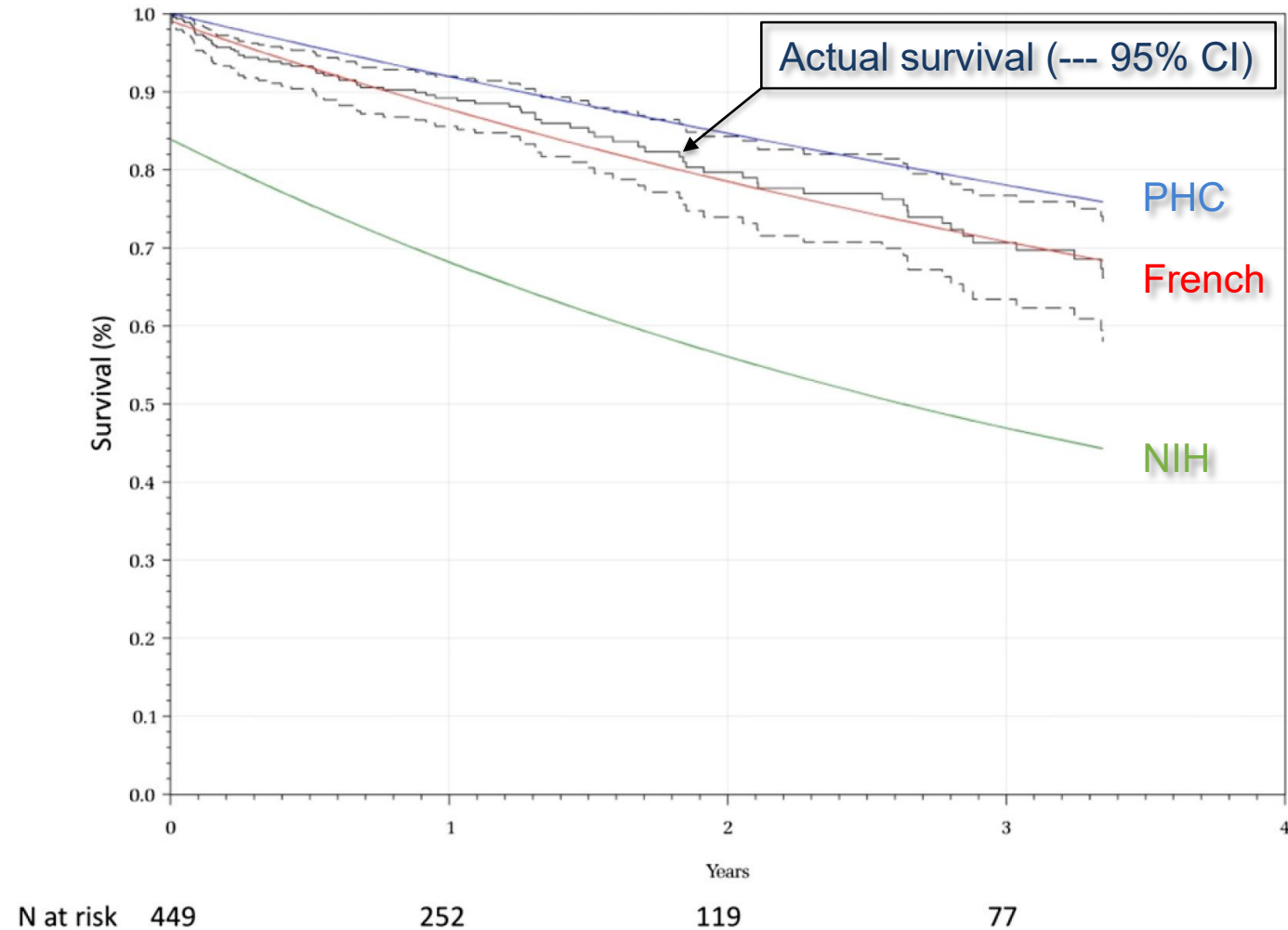
Risk equations or models currently available to predict outcomes in PAH

- | | |
|---|---|
| 1. NIH registry equation ¹ | Haemodynamic variables (RAP, mPAP, CI) |
| 2. French network equation ^{2,3} | Gender, 6MWD, CO |
| 3. PH Connection (PHC) equation ^{4,5} | Haemodynamic variables (RAP, mPAP, CI) |
| 4. Scottish composite score ⁶ | Gender, aetiology, Age, 6MWD, RAP, CO |
| 5. REVEAL equation ⁷ and risk score ⁸ | 12 variables (non-modifiable and modifiable) |
| 6. ESC/ERS risk stratification table ⁹ | 9 domains / Validated with 3 to 6 variables (FC, 6MWD, BNP/NT-proBNP, RAP, CI, SvO ₂) |

1. D'Alonzo. *Ann Intern Med* 1991. 2. Humbert. *Circulation* 2010. 3. Humbert. *Eur Respir J* 2010. 4. Thenappan. *Eur Respir J* 2010. 5. Thenappan. *Chest* 2012. 6. Lee. *Eur Respir J* 2012. 7. Benza. *Circulation* 2010. 8. Benza. *Chest* 2012. 9. Galiè N, *Eur Heart J* 2016 & *Eur Respir J* 2015.

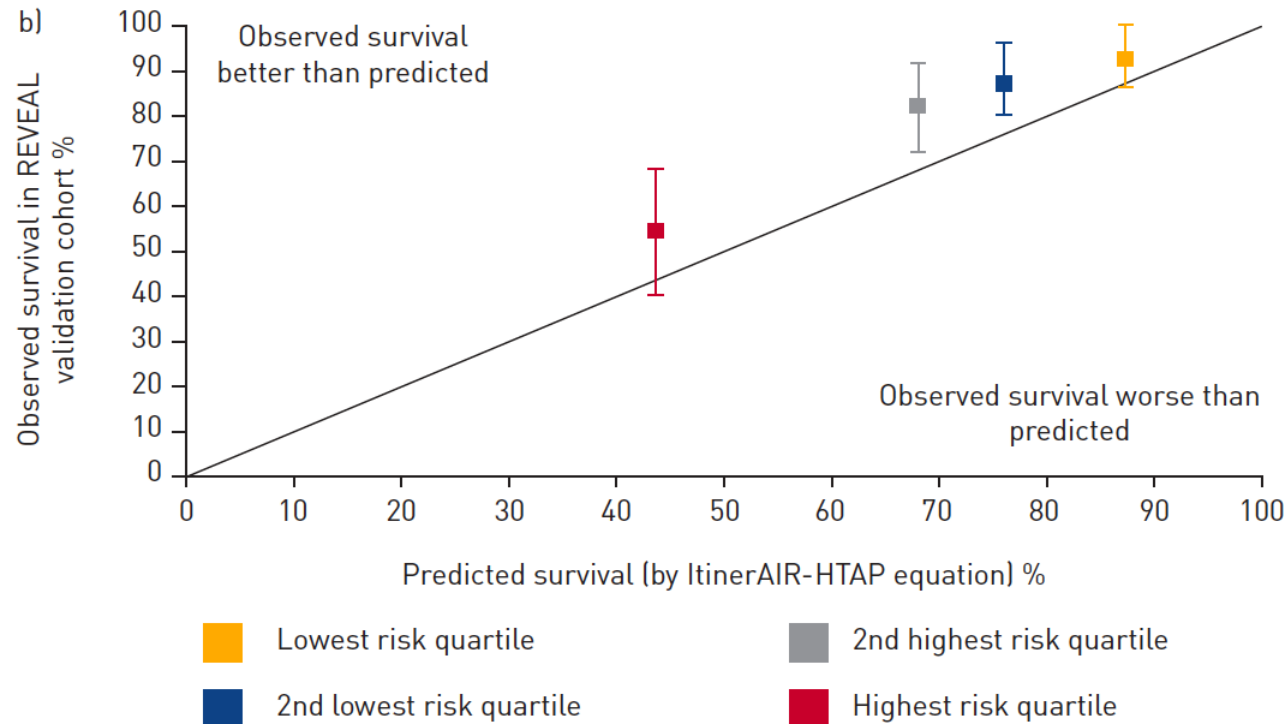
Validation and comparison of different tools

449 IHA-PAH patients from 4 RCTs and OLE (treprostinil and beraprost)

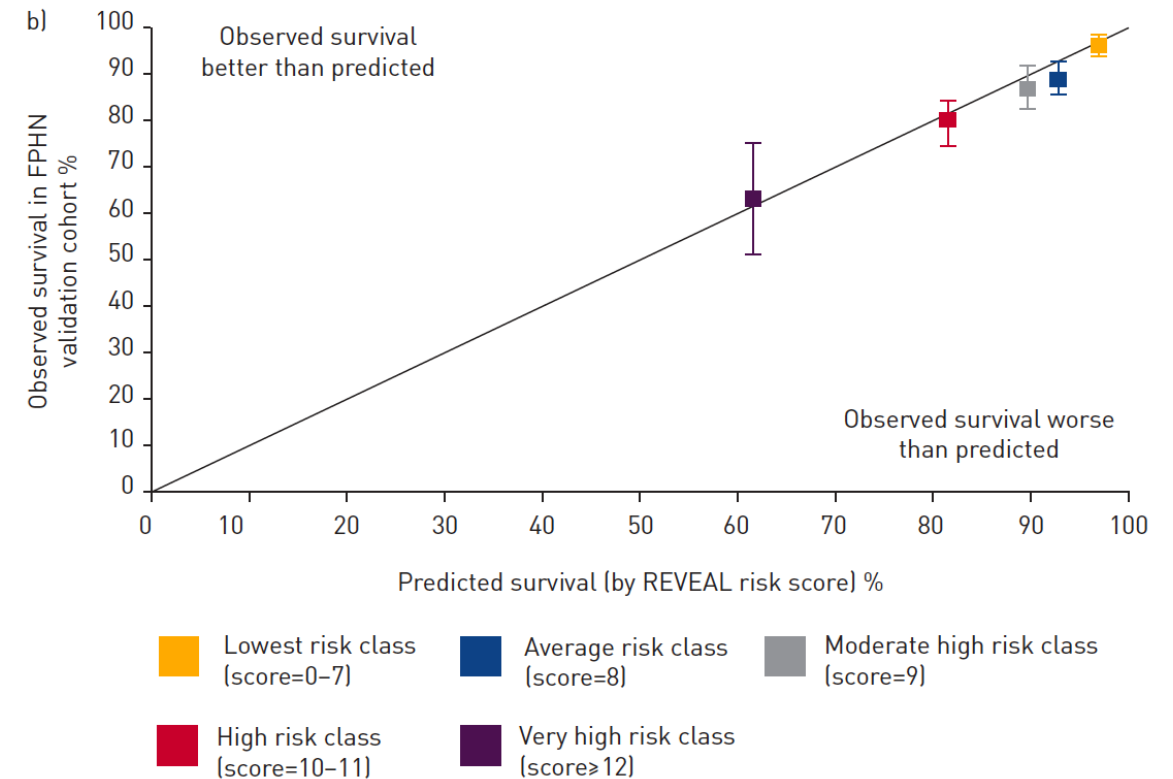


Cross validation of French equation and REVEAL score

Survival in REVEAL validation cohort by mortality risk quartiles (FPHN ItinerAIR-HTAP predicted risk).



Survival in the French Pulmonary Hypertension Network (FPHN) validation cohort by REVEAL risk score.



Four recent registries assessing risk stratification in PAH

REVEAL¹



Swedish PAH Registry²

COMPERA³

French PH Registry⁴

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.

Summary of four registries assessing risk scores

	REVEAL ¹	SPAHR ²	COMPERA ³	FPHN ^{4,5}
Required variables, n	12	8	6	4
Associated-PAH included	Yes	Yes	Yes	Only SSc ⁵
Methodology	Score	Sum of grades (1 low-3 high) /nb available variables	Sum of grades (1 low-3 high) /nb available variables	Number of low risk variables
Definition of low-risk	≤ 6 REVEAL score	<1.5 Average score	< 1.5 Average score	3-4 of 4 low-risk criteria
External validation	Yes	Yes	Yes	Yes

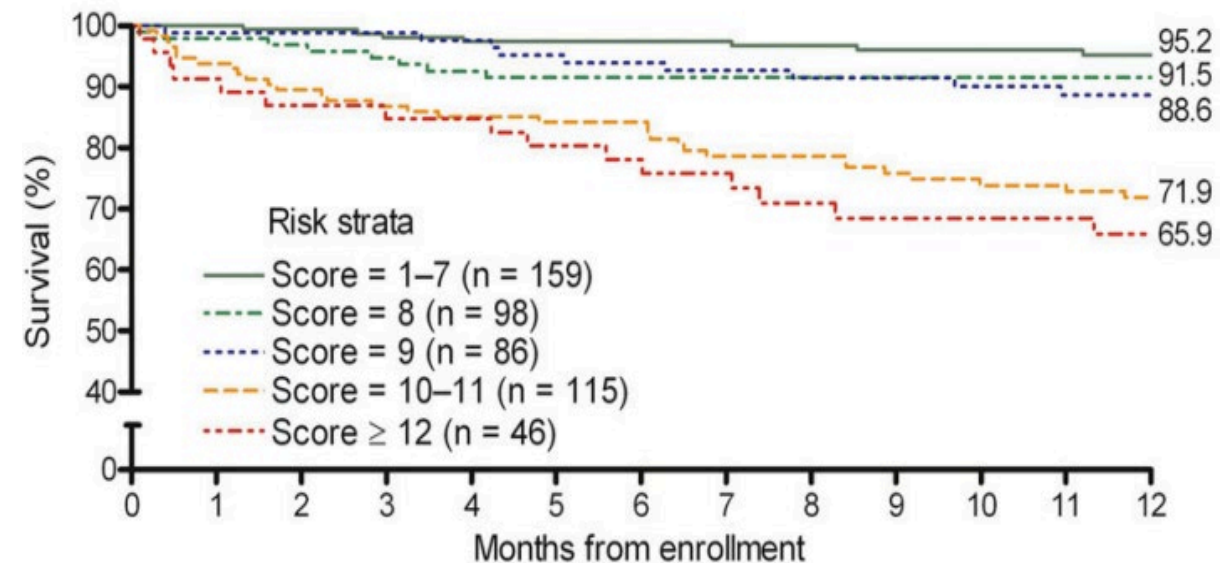
1. Benza RL, et al. *J Heart Lung Transplant*. 2015;34:356–61. 2. Kylhammar D, et al. *Eur Heart J* 2017; ehx257. 3. Hoeper MM, et al. *Eur Respir J* 2017; 50:1700740.
4. Boucly A, et al. *Eur Respir J* 2017; 50:1700889. 5. Weatherald J, Boucly A, et al, *Eur Respir J* 2018; 52: 1800678.

The REVEAL score

REVEAL™ PAH Risk Score	
Aetiology	<div> <div>APAH-CTD</div> <div>+1</div> </div> <div> <div>APAH-PoPH</div> <div>+2</div> </div> <div> <div>FPAH</div> <div>+2</div> </div>
Demographics & Comorbidities	<div> <div>Renal Insufficiency</div> <div>+1</div> </div> <div> <div>Males Age>60yrs</div> <div>+2</div> </div>
NYHA FC	<div> <div>I</div> <div>-2</div> </div> <div> <div>III</div> <div>+1</div> </div> <div> <div>IV</div> <div>+2</div> </div>
sBP & HR	<div> <div>SBP<110 mm Hg</div> <div>+1</div> </div> <div> <div>HR>92 BPM</div> <div>+1</div> </div>
6MWD	<div> <div>≥440 m</div> <div>-1</div> </div> <div> <div><165 m</div> <div>+1</div> </div>
BNP	<div> <div><50 pg/mL</div> <div>-2</div> </div> <div> <div>>180 pg/mL</div> <div>+1</div> </div>
Echo (PE)	<div> <div>Pericardial Effusion</div> <div>+1</div> </div>
DLCO	<div> <div>% pred. DLco≥80</div> <div>-1</div> </div> <div> <div>% pred. DLco≤32</div> <div>+1</div> </div>
RAP & PVR	<div> <div>mRAP>20 mm Hg within 1 yr</div> <div>+1</div> </div> <div> <div>PVR>32 Wood units</div> <div>+2</div> </div>
SUM OF ABOVE	
+ 6	
= RISK SCORE	

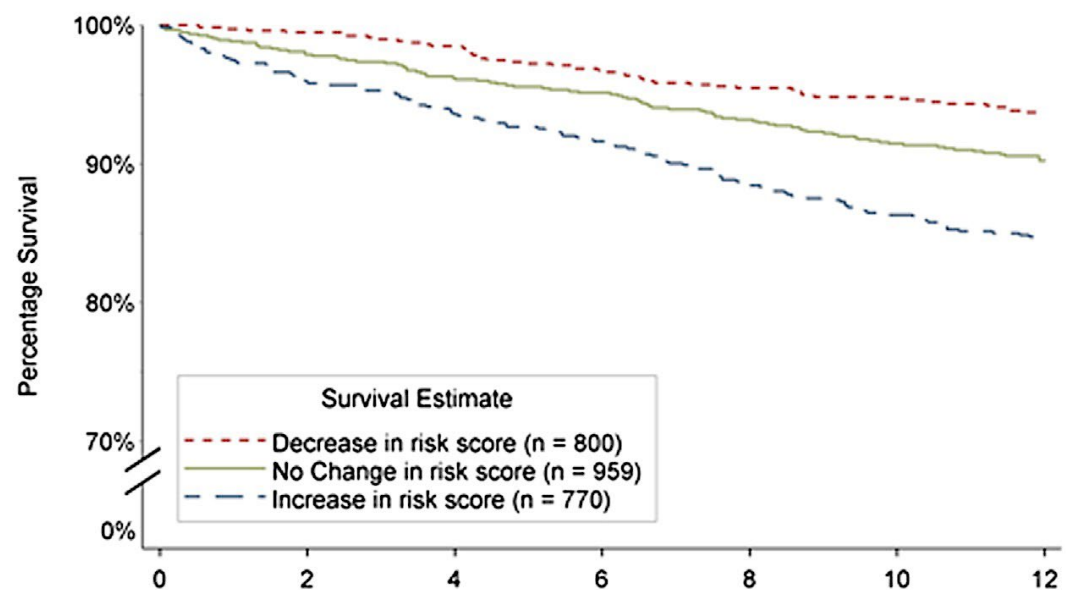
- Score from 0 (low risk) to 22 (high risk)
- Estimated survival at 1 year
- Incident/prevalent cases

Survival according to risk score at enrollment



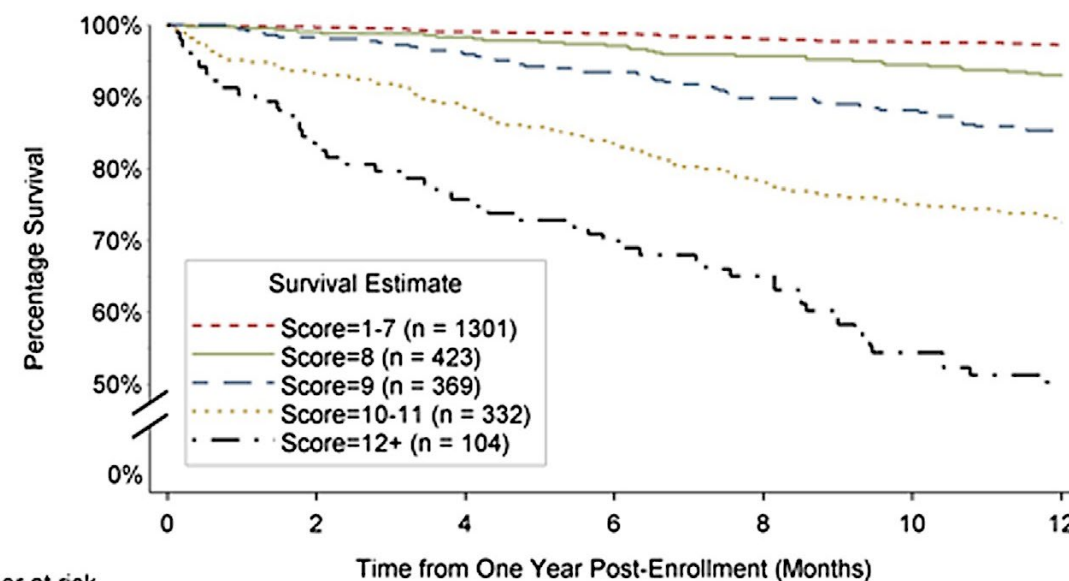
1-year survival according to REVEAL score at follow-up

Change in REVEAL score



	Time from One Year Post-Enrollment (Months)						
Number at risk	0	2	4	6	8	10	12
Decrease	800	794	784	769	757	750	741
No Change	959	930	906	893	860	837	823
Increase	770	736	714	698	667	650	634

REVEAL score at follow-up



	Time from One Year Post-Enrollment (Months)						
Number at risk	0	2	4	6	8	10	12
Score=1-7	1301	1289	1274	1270	1248	1239	1233
Score=8	423	417	412	406	394	388	381
Score=9	369	360	349	339	322	313	302
Score=10-11	332	308	291	273	253	242	233
Score=12+	104	86	78	72	67	55	49

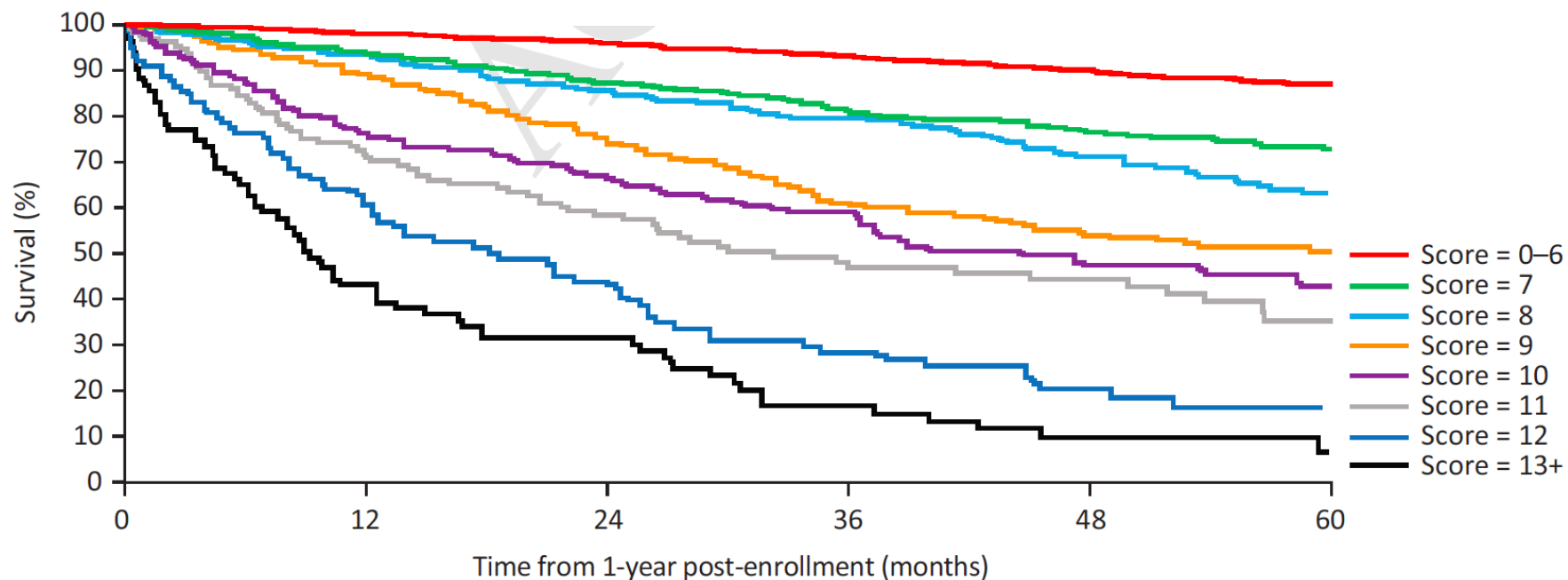
Updated REVEAL risk score calculator, n=2529

		PAH risk score		
		APAH-CTD	APAH-PoPH	FPAH
WHO Group 1 Subgroup	Original risk score	+1	+2	+2
	Updated risk score	APAH-CTD +1	POPH +3	FPAH +2
Demographics	Original risk score	Males age >60 years		
	Updated risk score (no change)	+2		
Comorbidities	Original risk score	Renal insufficiency		
	Updated risk score	+1		
All-cause Hospitalizations ≤6 months	Original risk score	eGFR <60 ml/min/1.73 m ² or "renal insufficiency" if eGFR unavailable		
	New variable	All-cause hospitalisations within 6 months		
Vital signs	Original risk score	SBP <110 mm Hg +1	HR >92 BPM +1	
	Updated risk score	SBP <110 mm Hg +1	HR >96 bpm +1	

6MWD	Original risk score	≥440m -1	<165m +1
	Updated risk score	≥440m -2	320 to <440m -1
BNP	Original risk score	<50 pg/mL -1	>180 pg/mL +1
	Updated risk score	< 50 pg/mL or NTproBNP <300 -2	200 to <800 pg/mL +1
Echocardiogram	Original risk score	Pericardial effusion	
	Updated risk score (no change)	+1	
Pulmonary function test	Original risk score	% predicted DLCO ≥80% -1	% predicted DLCO ≤32% +1
	Updated risk score	DLCO <40% predicted +1	
Right heart catheterization	Original risk score	mRAP ≥20 mm Hg within 1 year +1	PVR > 32 UW +2
	Updated risk score	mRAP ≥20 mm Hg within 1 year +1	PVR < 5 UW -1

△ Indicates change in cutoff □ Indicates change in risk point

Survival according to the updated REVEAL score



Number at risk

Score = 0–6	1073	1032	961	839	743	343
Score = 7	386	344	304	257	217	114
Score = 8	306	275	236	194	155	79
Score = 9	266	230	178	133	100	46
Score = 10	195	142	116	88	58	32
Score = 11	130	87	67	40	30	13
Score = 12	90	54	34	21	11	5
Score = 13+	83	34	24	10	5	2

REVEAL score

PRO	CON
All forms of PAH	12 variables Including non modifiable variables
Incident and prevalent cases	Predicts survival at 1 year only (now up to 5 years with REVEAL 2.0)
At any time	
External validation (French Registry)	

2015 ESC/ERS Guidelines – Risk stratification in PAH

Clinical Evaluation

Exercise Capacity

Right Ventricular Function

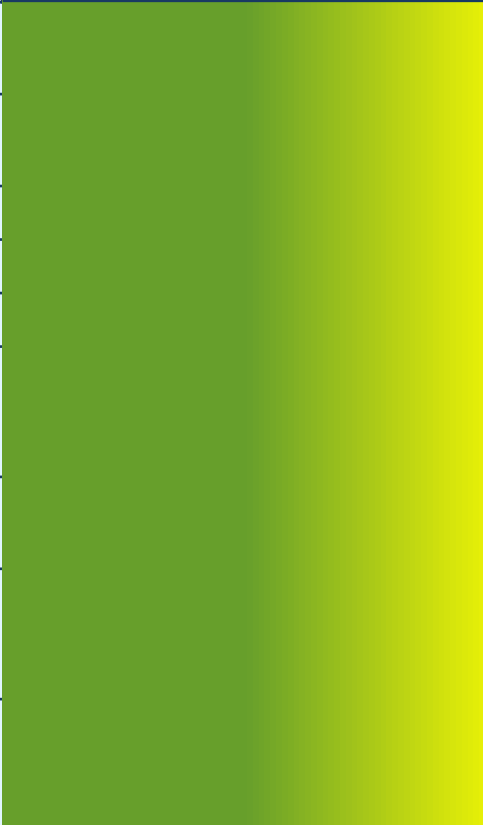

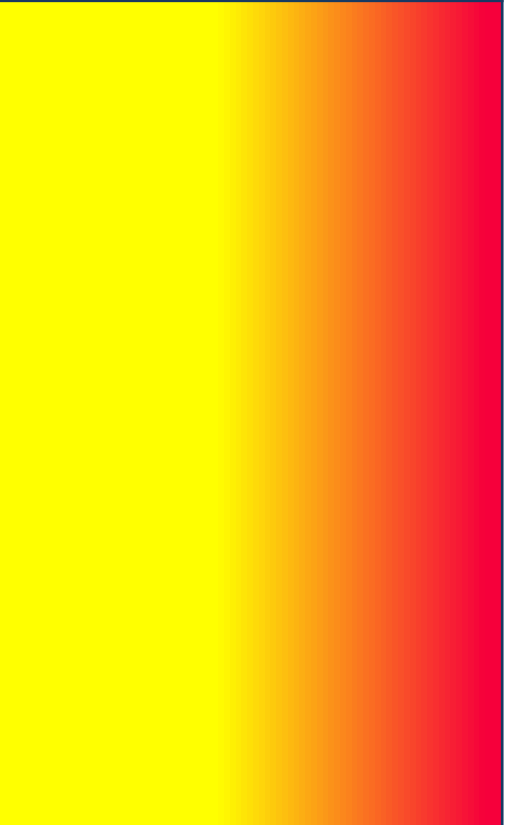
Determinants of prognosis	Estimated 1-year mortality		
	Low risk < 5%	Intermediate risk 5-10%	High risk > 10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope	Repeated syncope
FC	I, II	III	IV
6MWD	> 440 m	165 - 440 m	< 165 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/eurheartj/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 Benjamin³, 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

Methodology used in The Swedish PAH Registry and COMPERA

- **Incident population of PAH:** n= 530 (SPAHR), n= 1588 (COMPERA)
- Assigned a score of 1 (low-risk), 2 (intermediate-risk) or 3 (high-risk) for each variable available;
- Calculated average score, rounded to nearest integer to define the patient's risk group.

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 1	Peak VO ₂ 11 - 15 ml/min/kg (35-65% pred) VE/VCO ₂ slope 2	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 3
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%

Score = 1 + 1 + 2 + 2 + 3 = 9

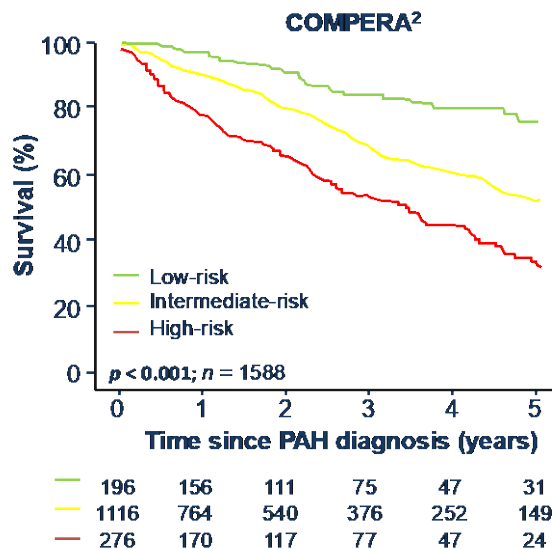
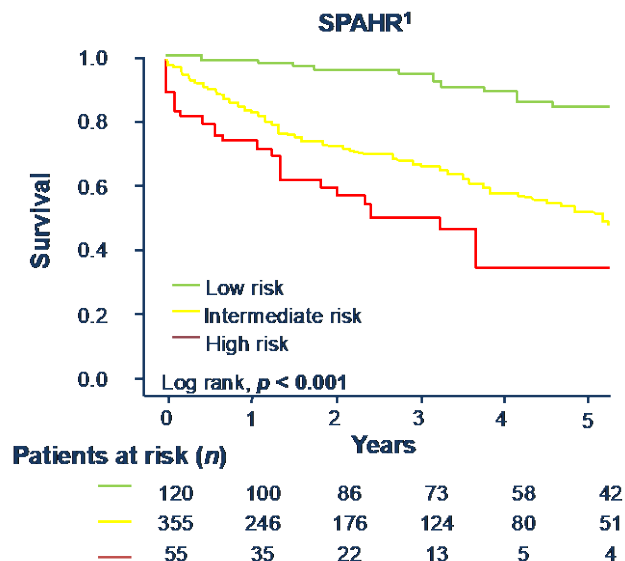
Score divided by the number of available variables = 9 / 5 = 1.8

Rounded to nearest integer = 2 → **Intermediate risk**

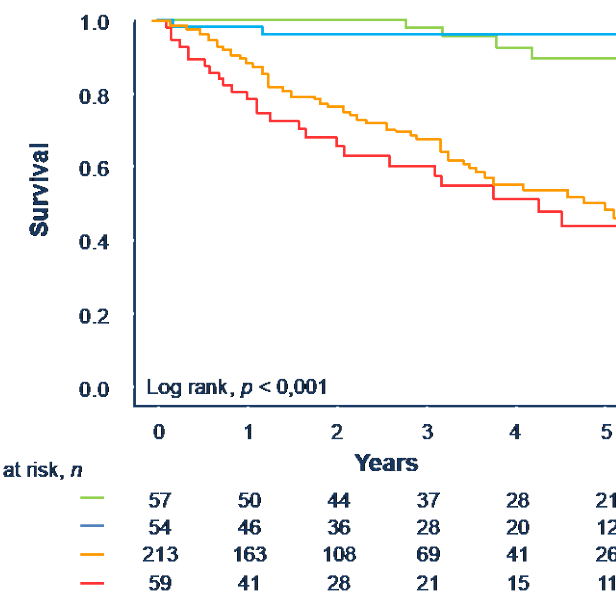
Kylhammar D, et al. *Eur Heart J* 2017; (Epub ahead of print).

Validation of ESC/ERS risk stratification in large registries

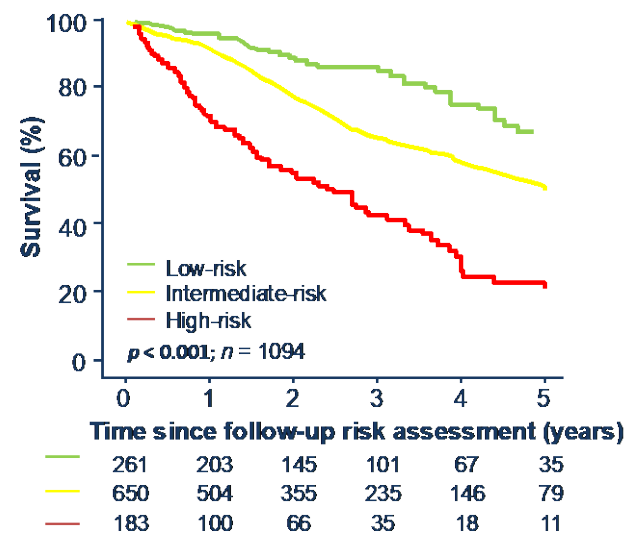
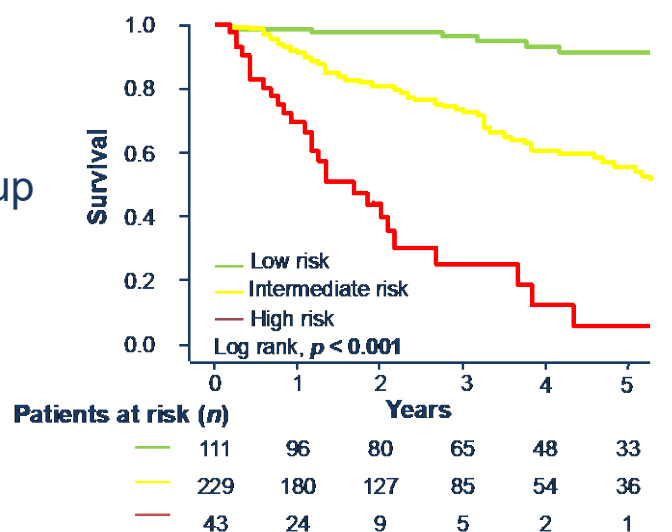
Baseline



SPAHR: change in risk status

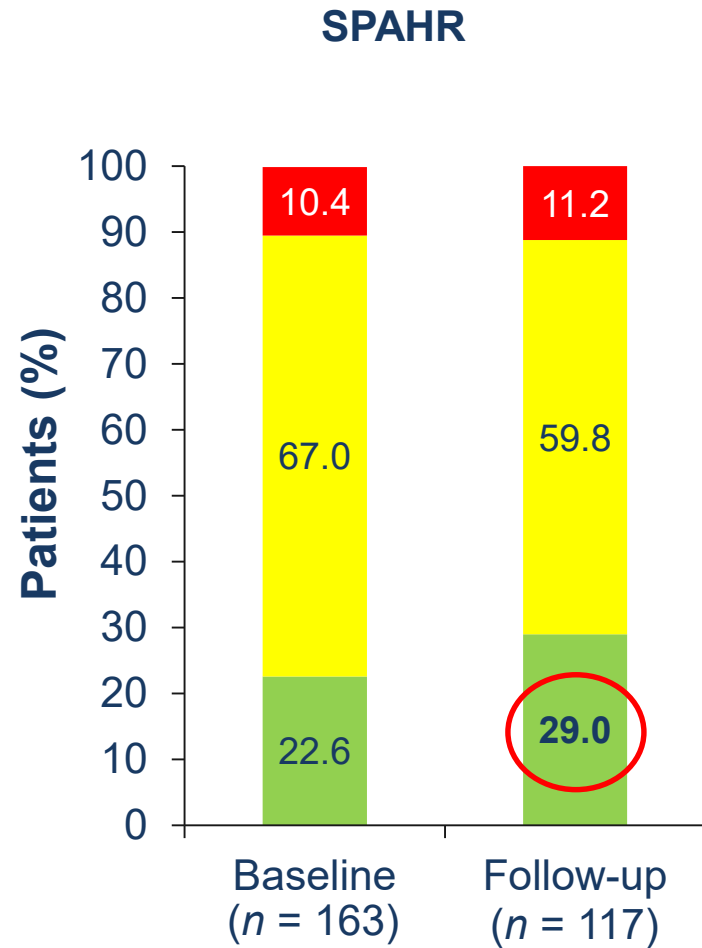


Follow-up

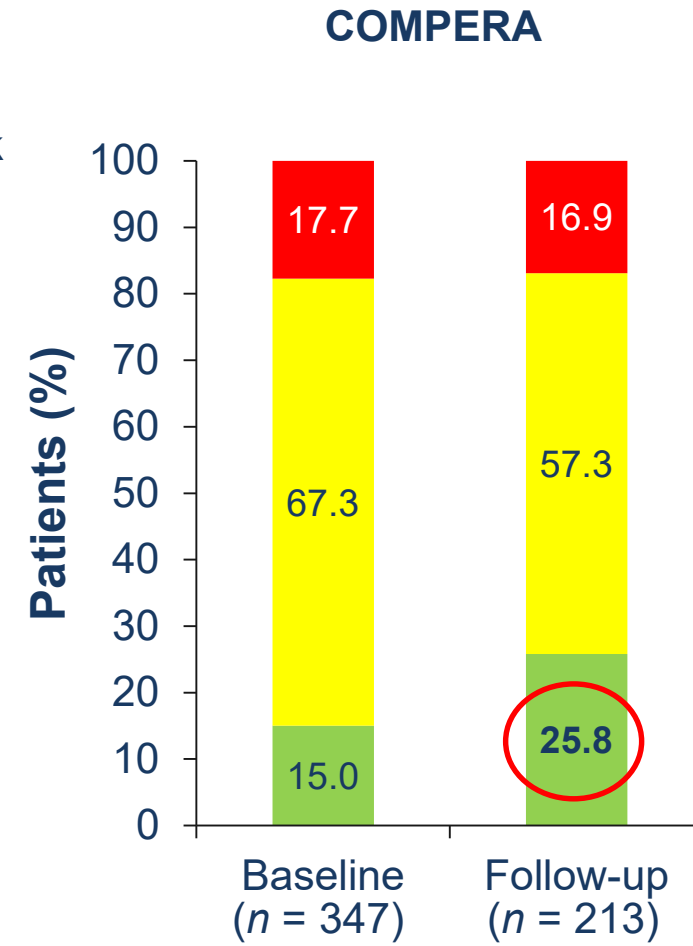


1. Kylhammar D, et al. *Eur Heart J* 2017; Epub ahead of print;
2. Hoeper MM, et al. *Eur Respir J* 2017; 50:1700740.

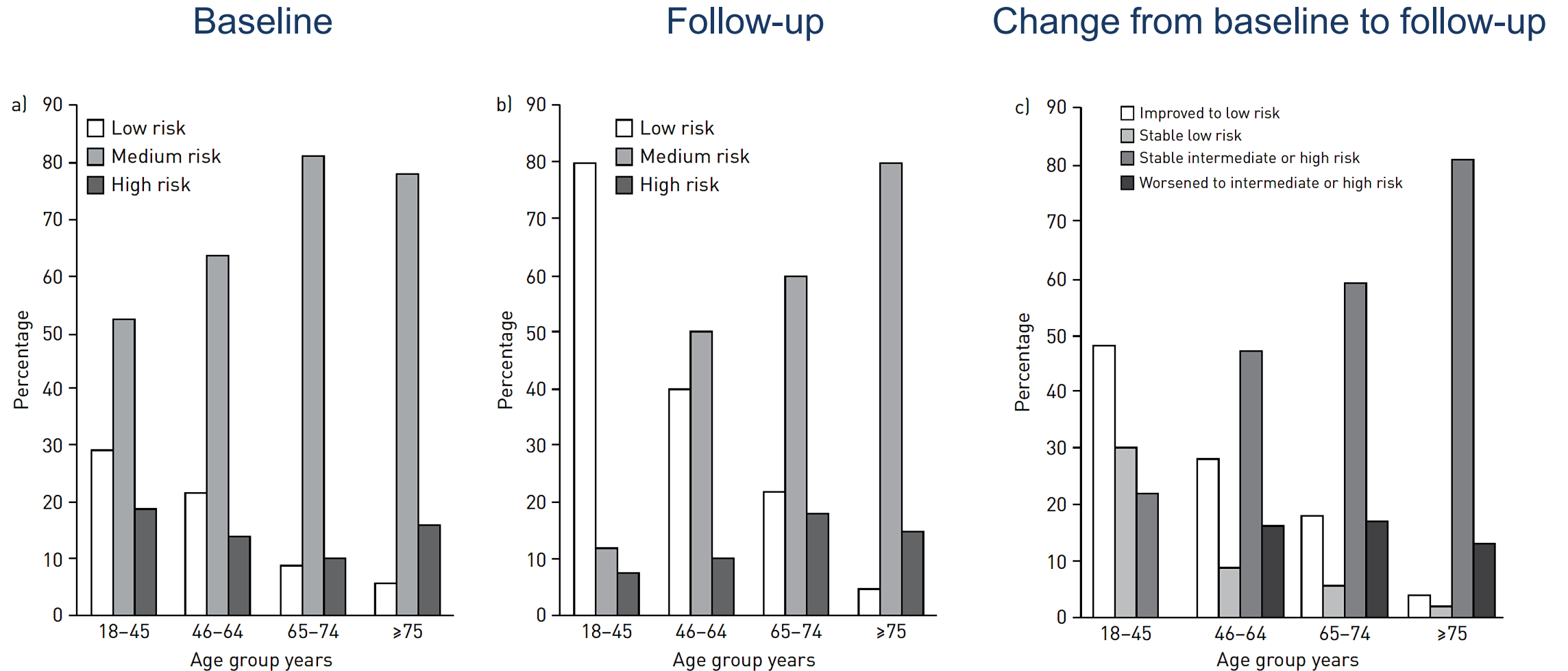
Around 75% of PAH patients did not achieve a low risk profile at follow-up



■ High risk
■ Intermediate risk
■ Low risk



Impact of age and comorbidities on risk stratification




SPAHR and COMPERA methodology

PRO	CON
6 – 8 variables (less than REVEAL)	Only incident cases
All forms of PAH	Lot of missing data
Predicts 5 year-survival	Estimated risk could be calculated with 2 variables only (misclassification)
Risk status at 1 year predicts survival irrespective of baseline status	High mortality rate in patients at low risk (COMPERA)

Association between the number low-risk criteria and survival

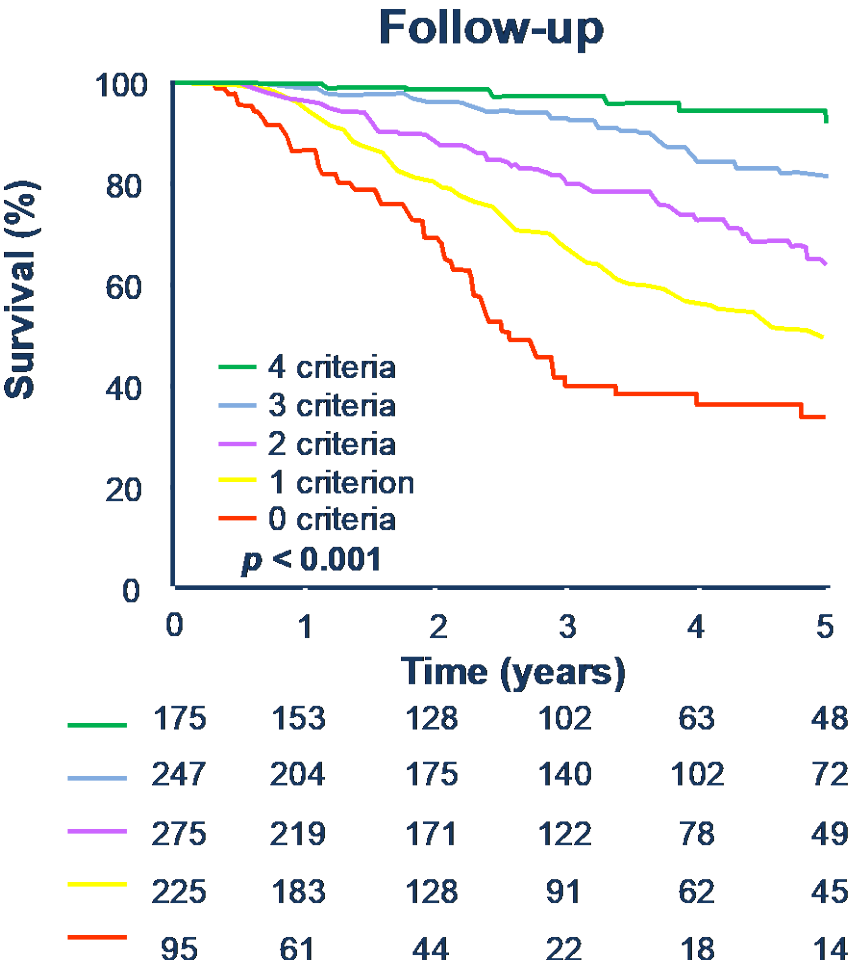
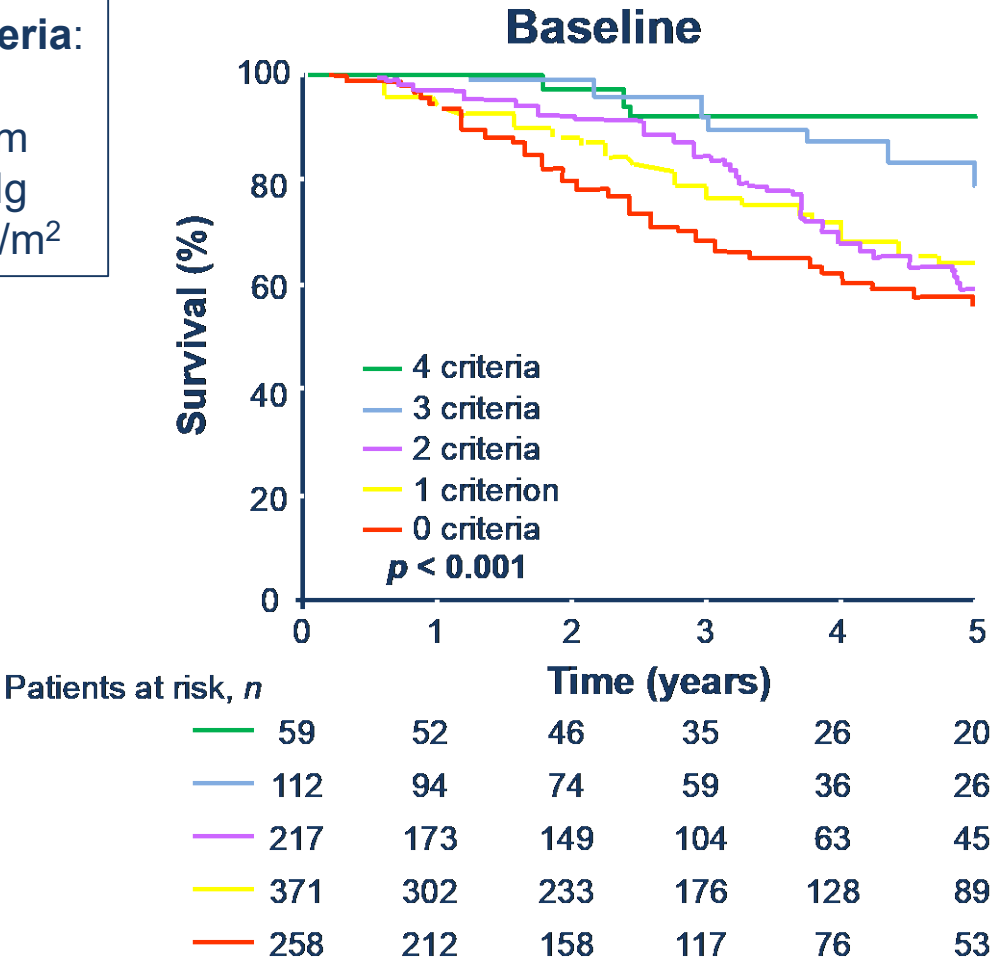
- Retrospective study from French Registry
- Incident patients with idiopathic, heritable and drug-induced PAH between 2006-2016 were analysed
- The number of low-risk criteria present at diagnosis and at first re-evaluation were assessed:
 1. WHO/NYHA functional class I or II
 2. 6-minute walk distance (6MWD) > 440m
 3. right atrial pressure < 8 mmHg
 4. cardiac index ≥ 2.5 L/min/m²
- 1017 / 1591 patients having all parameters available at both baseline and first re-evaluation

Determinants of prognosis	Low risk < 5%
Clinical signs of right heart failure	Absent
Progression of symptoms	No
Syncope	No
FC	I, II
6MWD	> 440 m
CPET	Peak VO ₂ > 15 ml/min/kg (> 65% pred.) VE/VCO ₂ slope < 36
NT-proBNP plasma levels	BNP < 50 ng/l NT-proBNP < 300 ng/l
Imaging (echo, CMR)	RA area < 18 cm ² No pericardial effusion
Hemodynamics	RAP < 8 mmHg CI ≥ 2.5 l/min/m ² SvO ₂ > 65%

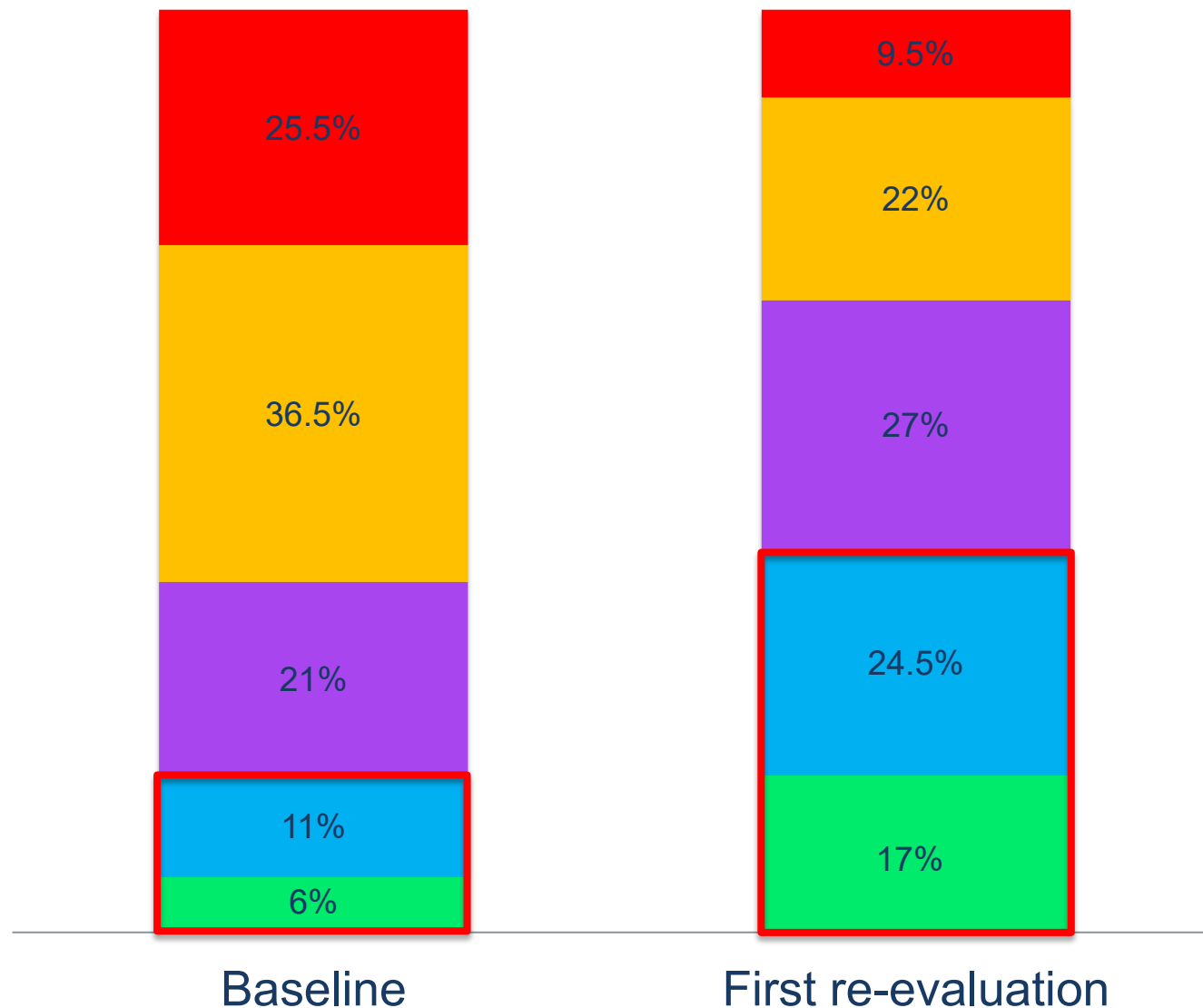


Achievement of multiple low risk criteria is associated with improved long-term outcomes

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



Change in “low-risk” criteria



Low-risk criteria:

NYHA FC I-II

6MWD > 440 m

RAP < 8 mmHg

CI \geq 2.5 L/min/m²

■ No criterion achieved

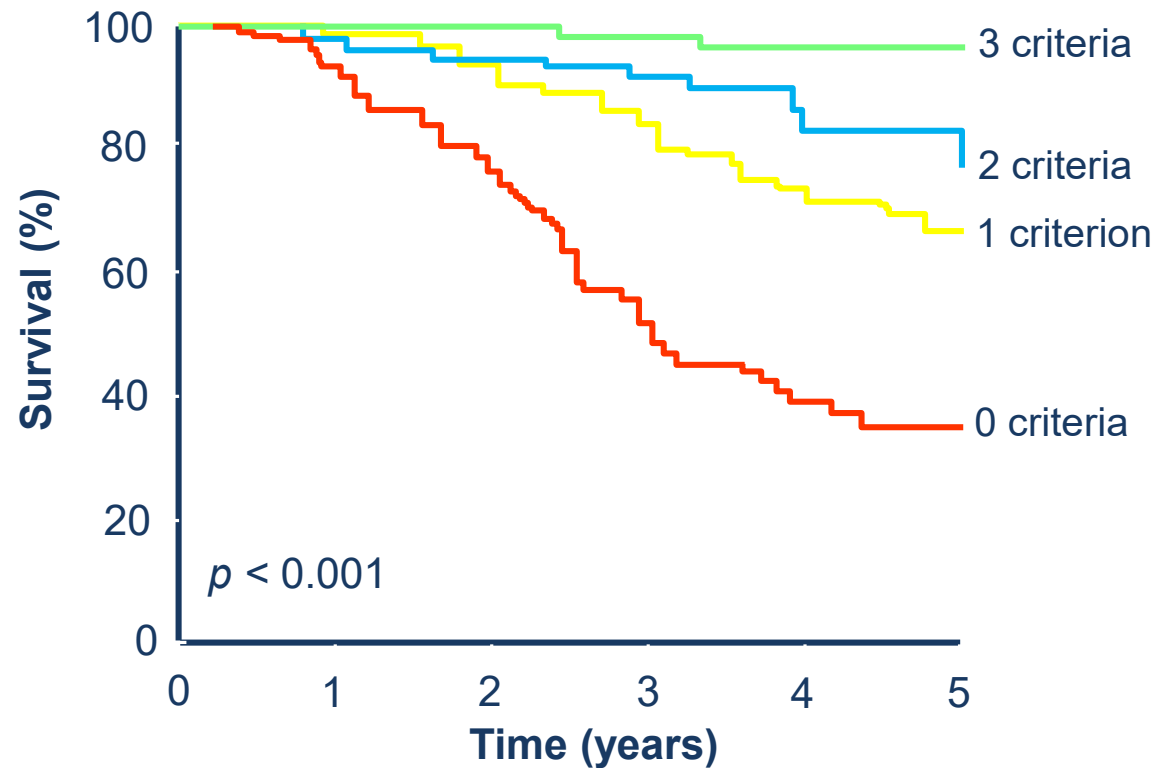
■ 1 criterion achieved

■ 2 criteria achieved

■ 3 criteria achieved

■ 4 criteria achieved

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



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

Non-invasive low-risk criteria:

NYHA FC I-II

6MWD >440 m

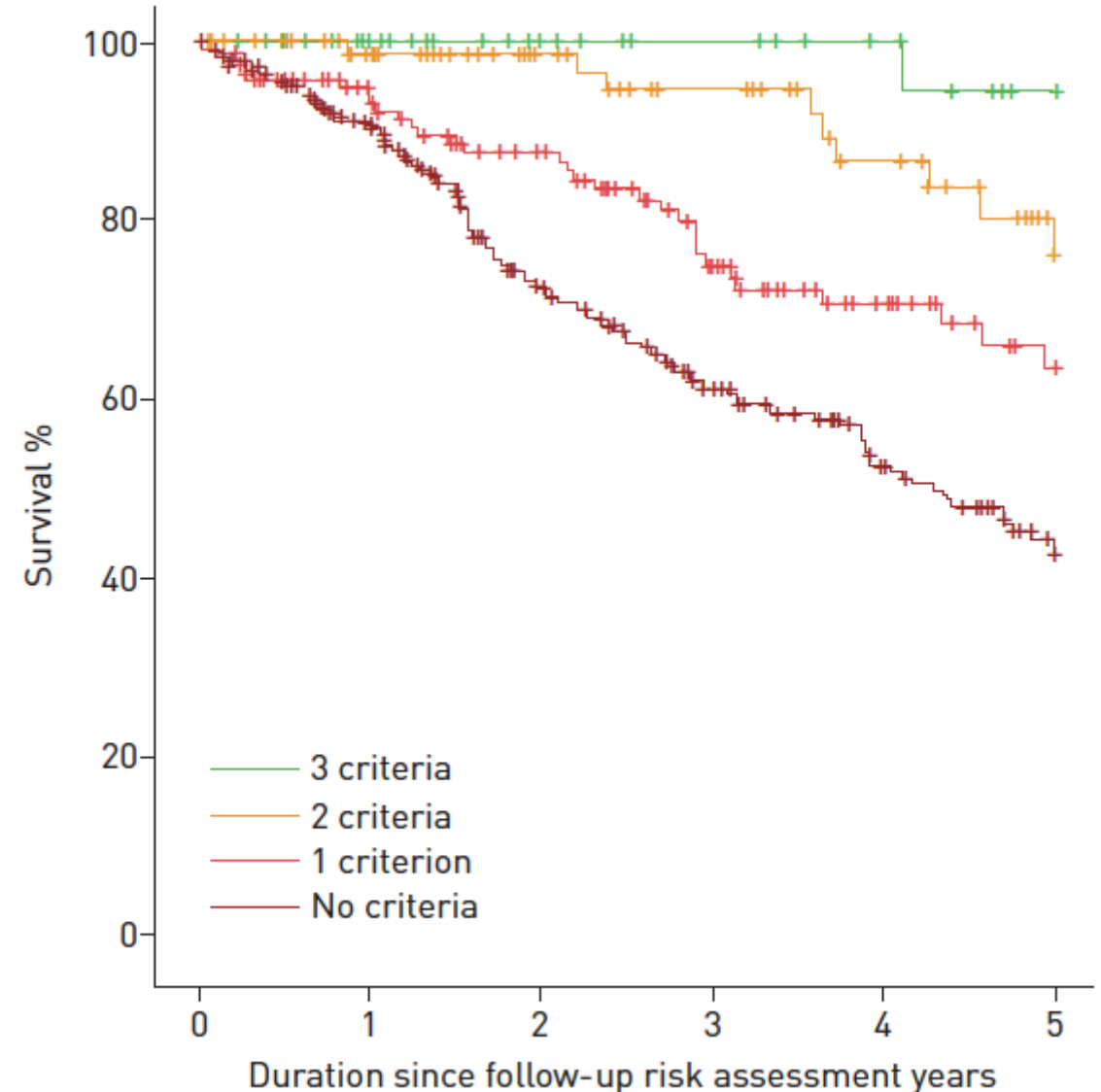
BNP <50 ng/L or NT-proBNP <300 ng/L

Patients with all 3 non-invasive low-risk criteria ($\approx 20\%$) had a 2-, 3- and 5-year survival of 100%, 99% and 97%, respectively

➔ Invasive hemodynamic risk assessment provides important prognostic information in patients who do not achieve 3 non-invasive low-risk criteria

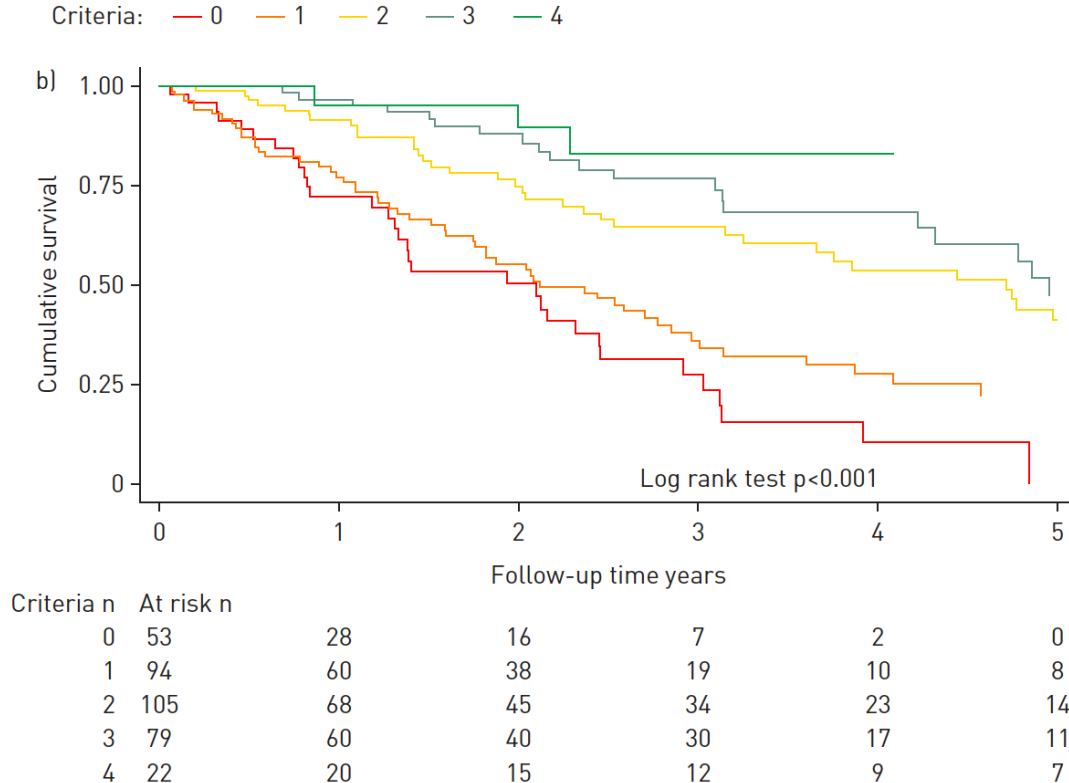
Validation of the simplified French methodology in COMPERA

- 579 idiopathic PAH
- 1st follow-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

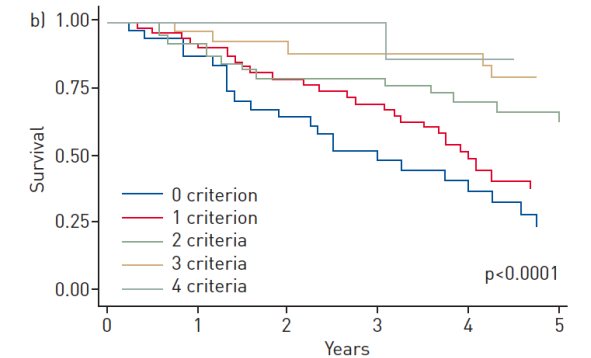


In PAH-SSc patients, achievement of multiple low-risk criteria at first re-evaluation leads to improved long-term outcomes

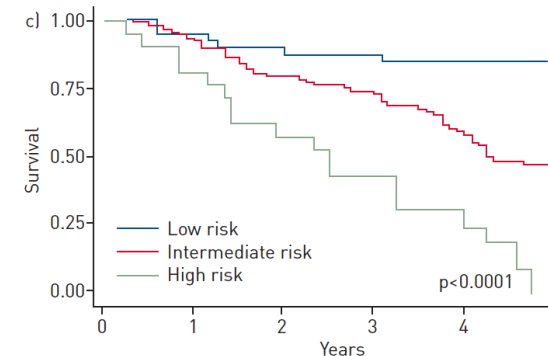
French Registry¹ PAH-SSc *n* = 352



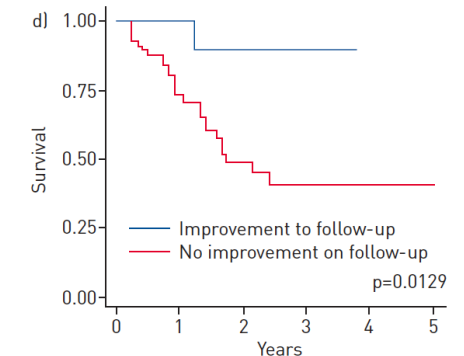
Johns Hopkins² PAH-SSc *n* = 151



At risk n	31	27	20	14	10	5
0 criterion	48	43	36	31	22	16
1 criterion	38	35	30	27	20	18
2 criteria	26	25	23	22	20	17
3 criteria	8	8	7	7	6	5
4 criteria						



At risk n	41	39	35	33	28	25
Low risk	89	82	69	61	46	36
Intermediate risk	21	17	12	7	5	0
High risk						



At risk n	20	10	4	3	0	0
Low risk at follow-up	72	31	13	6	3	3
Intermediate or high risk at follow-up						

French PH Network methodology

PRO	CON
4 variables including haemodynamics	Only incident cases
Simplified tool with 3 non-invasive variables	Not analysed in non-SSc CTD-PAH, CHD-PAH, PoPH, HIV-PAH
No missing data	
Predicts survival at 5 years	

To achieve 3-4 low-risk criteria could be considered as treatment goal

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

Recommendations for evaluation of PAH severity and response to therapy



Risk Stratification

Treatment goal

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

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

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

Conclusions

- Multi-parameter risk assessment is essential to determine prognosis and to define the optimum treatment strategy for all patients with PAH
- Recent studies have provided strong evidence to support multi-parameter risk assessment in PAH patients, at baseline and follow-up, irrespective of the methodology utilised
- Therefore, the ultimate goal of treatment should be to achieve a low risk profile at any time
- Finally, less is more...