What have we learned from national PAH registries?

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Disclosures – Olivier Sitbon, MD PhD

- Relevant financial relationships with a commercial interest:
    - **Actelion/J&J:** consultancy (current), board or advisory committee (current), speaker (current), research support (current)
    - **Bayer/Merck:** consultancy (current), board or advisory committee (current), speaker (current), research support (current)
    - **GSK:** consultancy (past), board or advisory committee (past), speaker (past), research support (current)
    - **United Therapeutics**: consultancy (current)
    - **Gossamer Bio**: board or advisory committee (current)

PAH Registries

Despite limitations due to their observational and uncontrolled nature, PAH registries may provide important information on:

- Incidence and / or prevalence of the disease
- Characteristics of patients in real life
- Practice patterns
- Long-term outcome and survival
- Variables predicting survival

Methodology of registries: A key issue!

- Ideally registries have to be prospective, multicentre and to include consecutive patients
- Quality control of data is essential
- Long period of observation with no loss to follow-up
- Finally, the design of registries should be adapted to the question we want to answer

Methodology of registries: 3 levels

Non-selective registries

Pros: epidemiology (prevalence) and clinical characteristics

Cons: survival analysis and prognosis

Registries of newly diagnosed patients

Pros: epidemiology (incidence), survival analysis, prognosis and risk equation from baseline variables

Cons: assessment of time-dependent variables and treatment goals

Interventional registries

Pros: assessment of time-dependent variables and treatment goals

Lewis J. Rubin*, Gerald Simonneau#, David Badesch¶, Nazzareno Galiè+, Marc Humbert#, Anne Keogh§, Joseph Massaro^f, Marco Matucci Cerinic**,##, Olivier Sitbon# and Steven Kymes¶¶

Eur Respir Rev 2012; 21: 125, 234–238

Available PH Registries

Registry	Duration of inclusion (years)	Study Population (n)	Prospective/ Retrospective	Multicentre (n)	Incident patients only
NIH (1987)[1]	5	IPAH (187)	Pro	Yes (32)	No
French (2006)[2]	1	PAH (674)	Pro	Yes (17)	No
Scottish (2007)[3]	9	PAH (374)	Retro	Yes	No
Chinese (2007)[4]	6	IPAH (72)	Pro	Yes	No
Swiss (2008)[5]	5	PH (250)	Pro	Yes	No
Chicago (2009)[6]	26	PAH (576)	Retro & Pro	Yes (3)	No
REVEAL (2010)[7]	4	PAH (2716)	Pro	Yes (54)	No
CTEPH (2011)[8]	2	CTEPH (679)	Pro	Yes	Yes
UK (2012)[9]	8	PAH (482)	Pro	Yes (8)	Yes
Spanish (2012)[10]	10	PAH & CTEPH (866)	Pro & Retro.	Yes (31)	No
COMPERA (2013)[11]	8	PAH (587, now 8700)	Pro & Retro.	Yes (28)	No
SPAHR (2017)[12]	9	PAH (457)	Pro	Yes (8)	Yes
French (current)	≈20 years	PH (≈12 800)	Pro	Yes (25)	Yes

1. Rich S, *et al. Ann Intern Med* 1987.
2. Humbert M, *et al. Am J Respir Crit Care Med* 2006.
3. Peacock AJ, *et al. Eur Respir J* 2007.
4. Jing Z-C, *et al. Chest* 2007.
5. Tueller C, *et al. Swiss Med Wkly* 2008.
6. Thenappan T, *et al. Eur Respir J* 2007.
7. Badesch DB, *et al. Chest* 2010.
8. Pepke-Zaba J, *et al. Circulation* 2011.
9. Ling Y, *et al. Am J Respir Crit Care Med* 2012.
10. Escribano-Subias P, *et al. Eur Respir J* 2012.
11. Hoeper MM, *et al. Int J Cardiol* 2013.
12. Kylhammar D, *et al. Eur Heart J* 2018.

The French PAH Registry (2002-2003 followed until 2006)

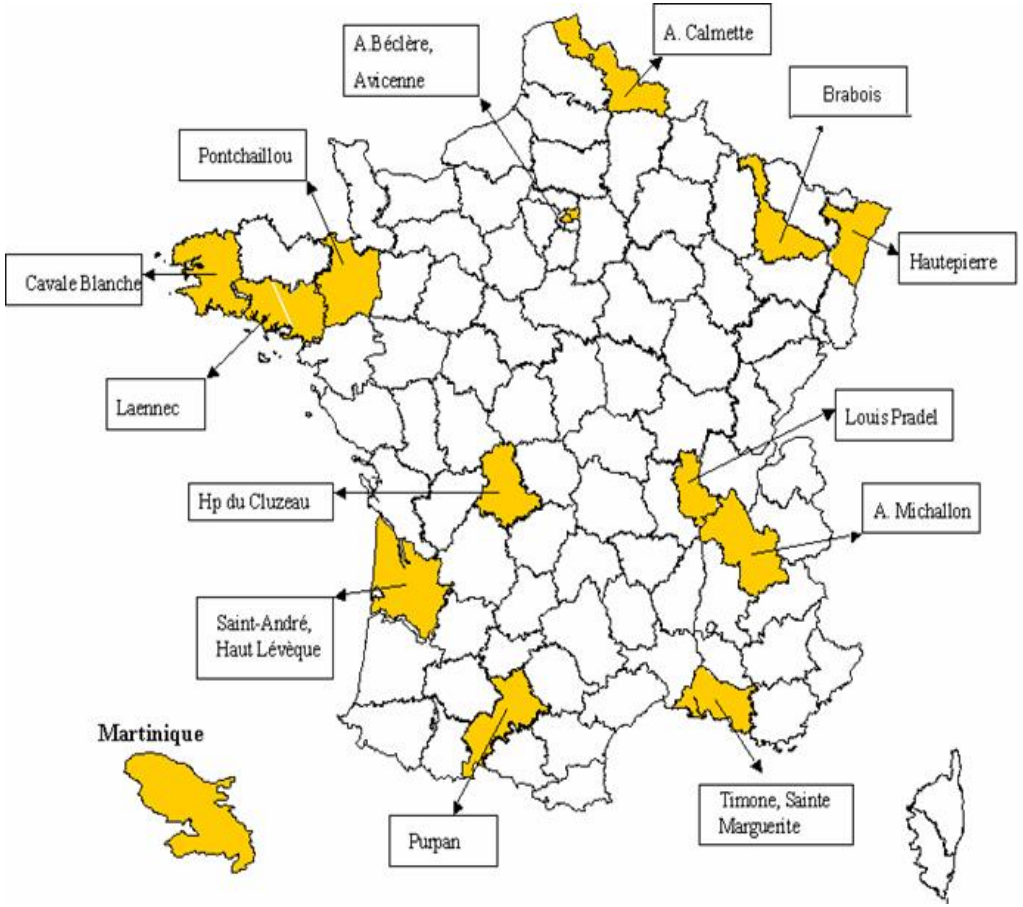
Pulmonary Arterial Hypertension in France

Results from a National Registry

Marc Humbert, Olivier Sitbon, Ari Chaouat, Michèle Bertocchi, Gilbert Habib, Virginie Gressin, Azzedine Yaici, Emmanuel Weitzenblum, Jean-François Cordier, François Chabot, Claire Dromer, Christophe Pison, Martine Reynaud-Gaubert, Alain Haloun, Marcel Laurent, Eric Hachulla, and Gérald Simonneau

Service de Pneumologie, Centre des Maladies Vasculaires Pulmonaires, Hôpital Antoine Béclère, Assistance-Publique–Hôpitaux de Paris, Université Paris-Sud, Clamart, France; Service de Pneumologie, Hôpital Hautepierre, Strasbourg; Service de Pneumologie, Hôpital Louis-Pradel, Lyon; Service de Cardiologie, Hôpital de la Timone; Service de Pneumologie, Hôpital Sainte Marguerite, Marseille; Actelion Pharmaceuticals France, Paris; Service de Pneumologie, Hôpital de Brabois, Vandoeuvre-les-Nancy; Service de Chirurgie Thoracique, Hôpital du Haut Levesque, Bordeaux; Département Médecine Aiguë Spécialisée, Hôpital Michallon, Grenoble; Service de Pneumologie, Hôpital Laennec, Nantes; Service de Cardiologie, Hôpital Pontchaillou, Rennes; and Service de Médecine Interne, Hôpital Claude Huriez, Lille, France

- 674 patients, 17 medical centres (respiratory medicine, cardiology, internal medicine) spread across France
- Adult patients (>18 years) suffering from PAH (idiopathic, familial or associated conditions)
- Prospective cohort monitored and on-site audits
- Enrolment: 2002-2003



Humbert M, *et al. Am J Respir Crit Care Med* 2006; 173:1023-30.

Socio-demographic data

Age	50 ± 15
Women	65%
Men	35%

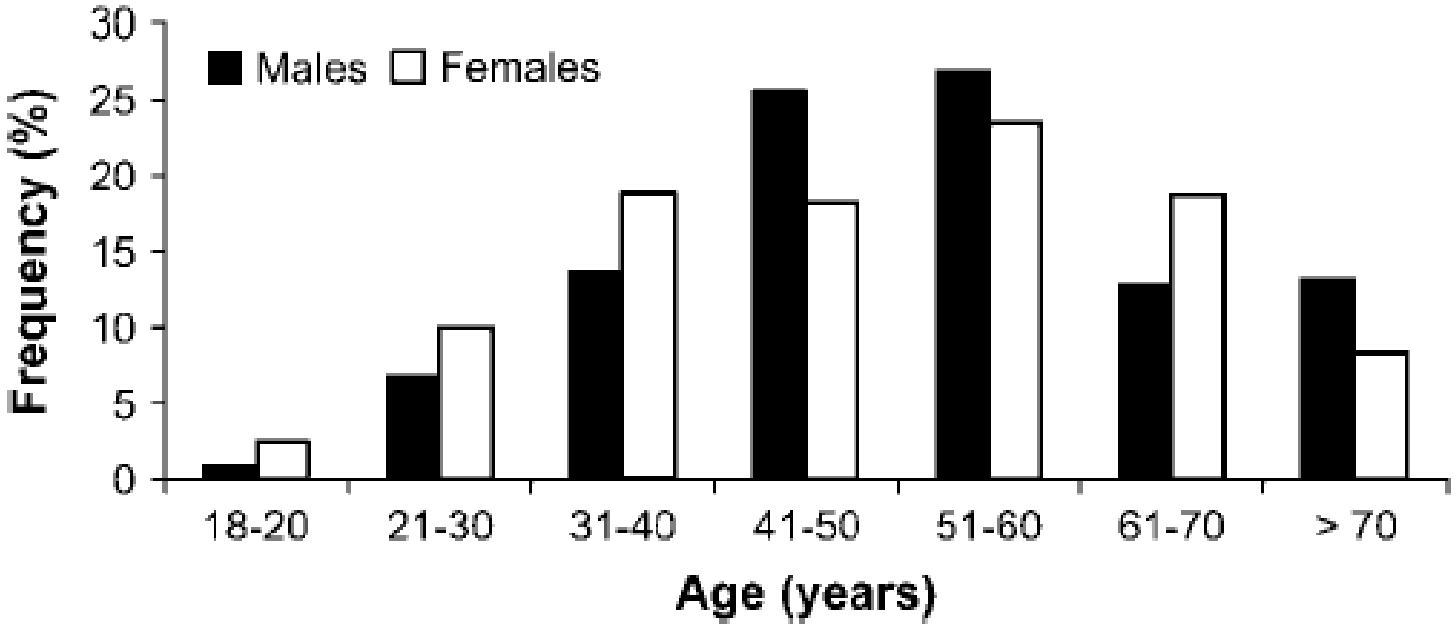
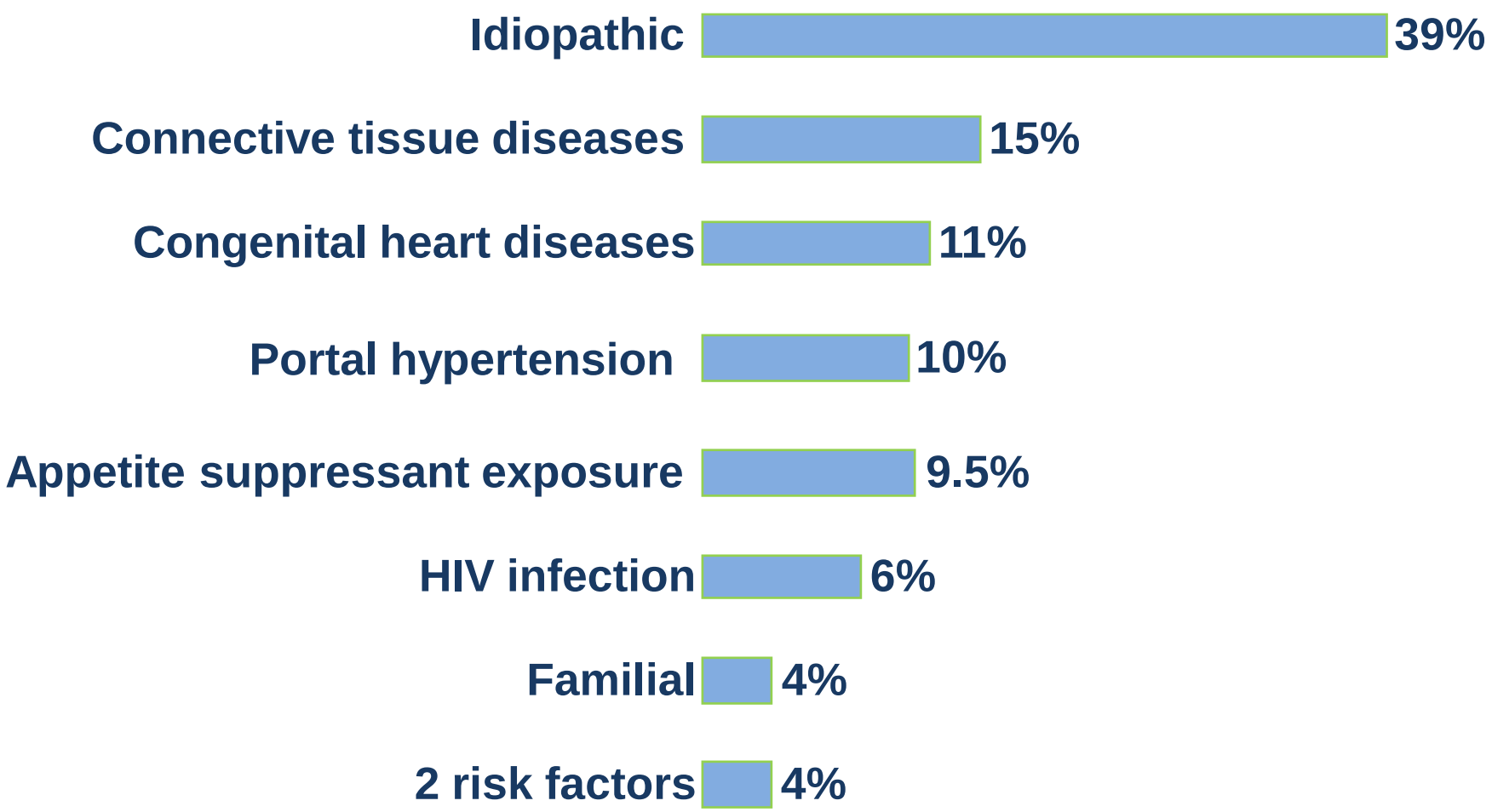


Figure 1. Distribution of patients with pulmonary arterial hypertension according to age based on sex.

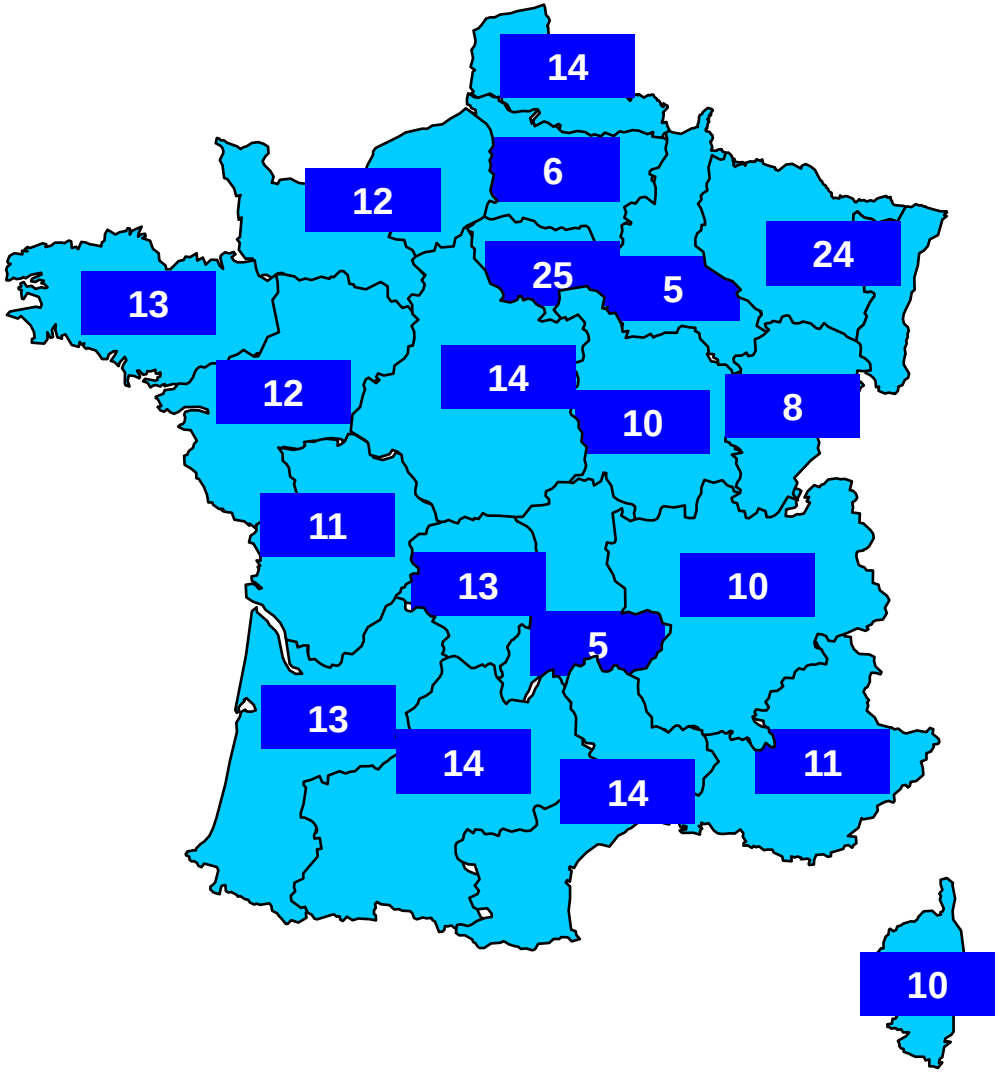
Humbert M, *et al. Am J Respir Crit Care Med* 2006; 173:1023-30.

Type of PAH at diagnosis



Humbert M, *et al. Am J Respir Crit Care Med* 2006; 173:1023-30.

National and regional prevalences



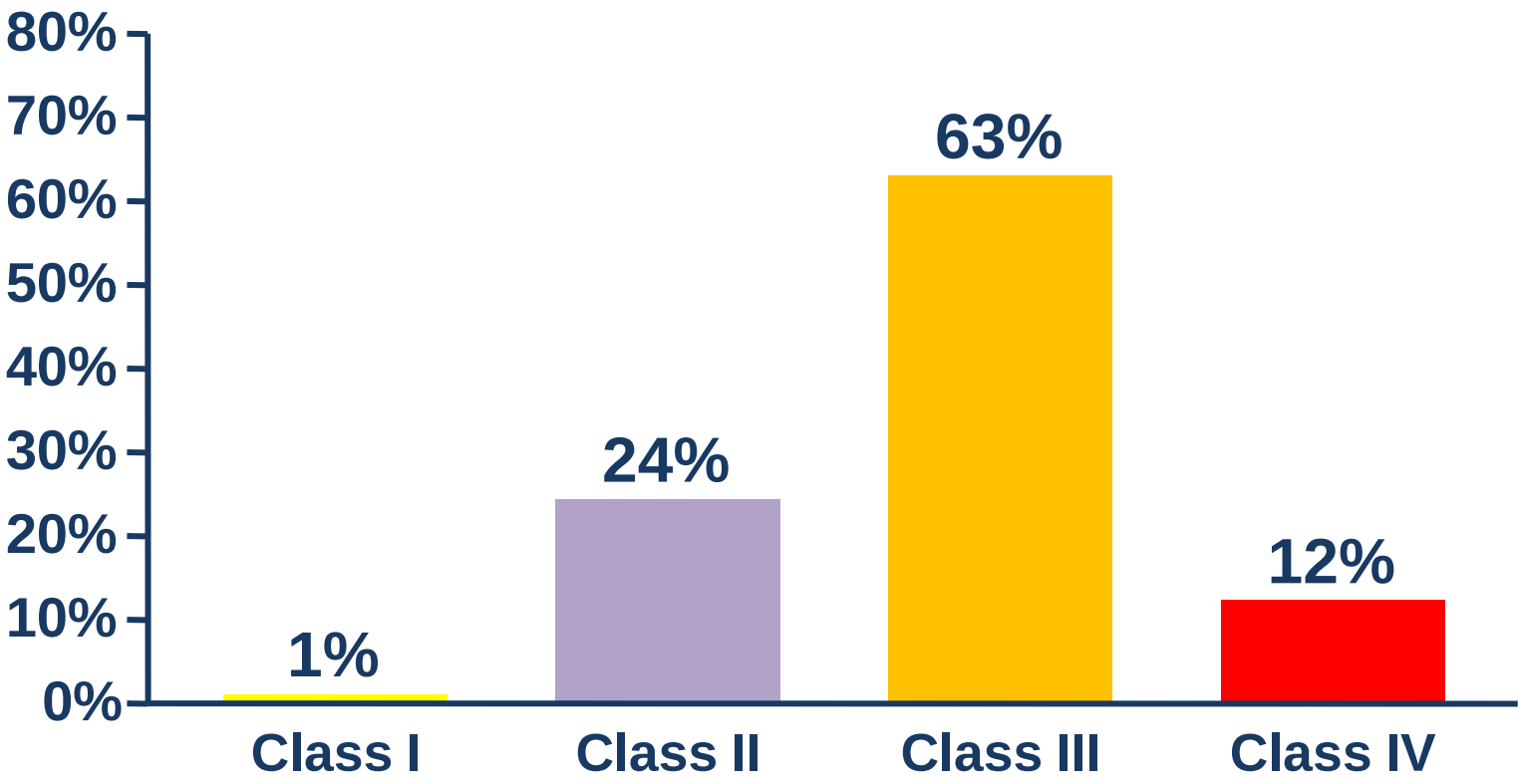
Average 15 / million

Range 5 to 25 / million

Humbert M, *et al. Am J Respir Crit Care Med* 2006; 173:1023-30.

Functional classes at diagnosis

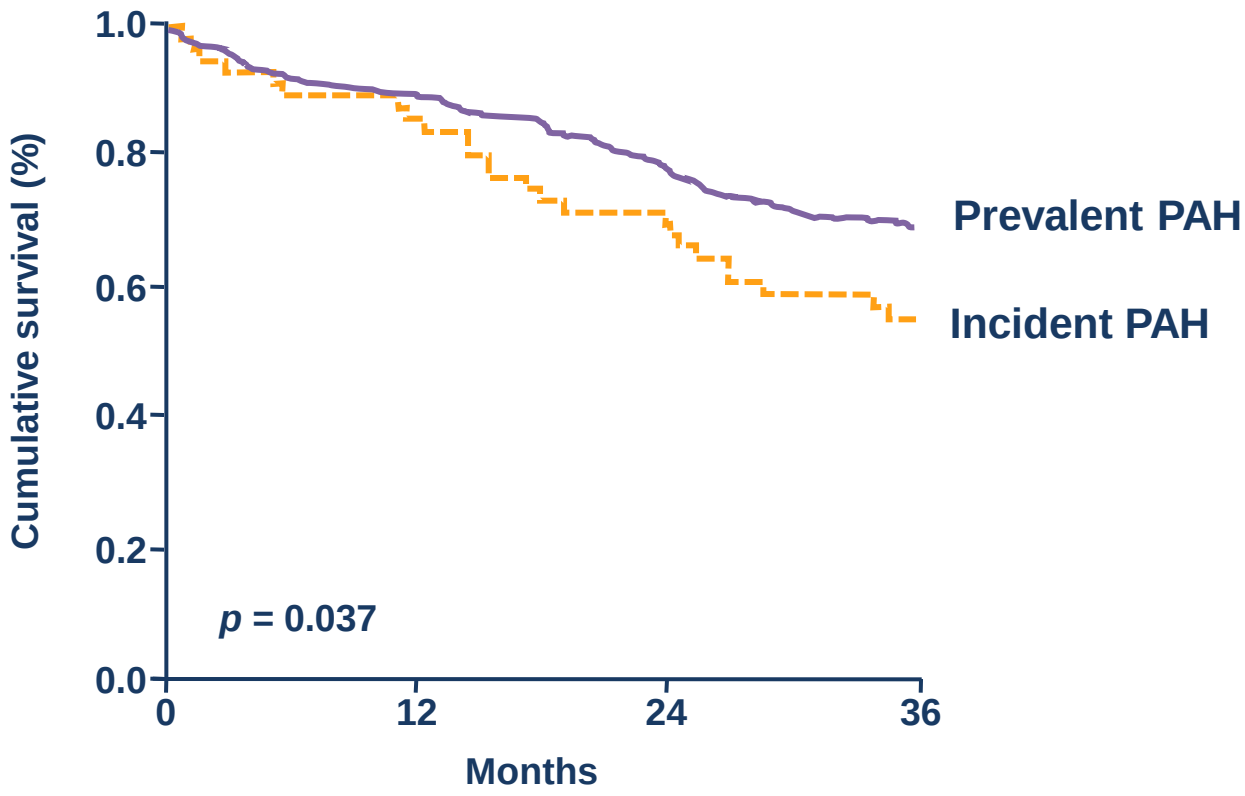
→ **Delay between onset of symptoms and diagnosis: 27 months**



Humbert M, *et al. Am J Respir Crit Care Med* 2006; 173:1023-30.

Survival in the French cohort

SURVIVAL OF PAH IN THE MODERN ERA (IDIOPATHIC, FAMILIAL & ANOREXIGEN-INDUCED PAH POPULATION)

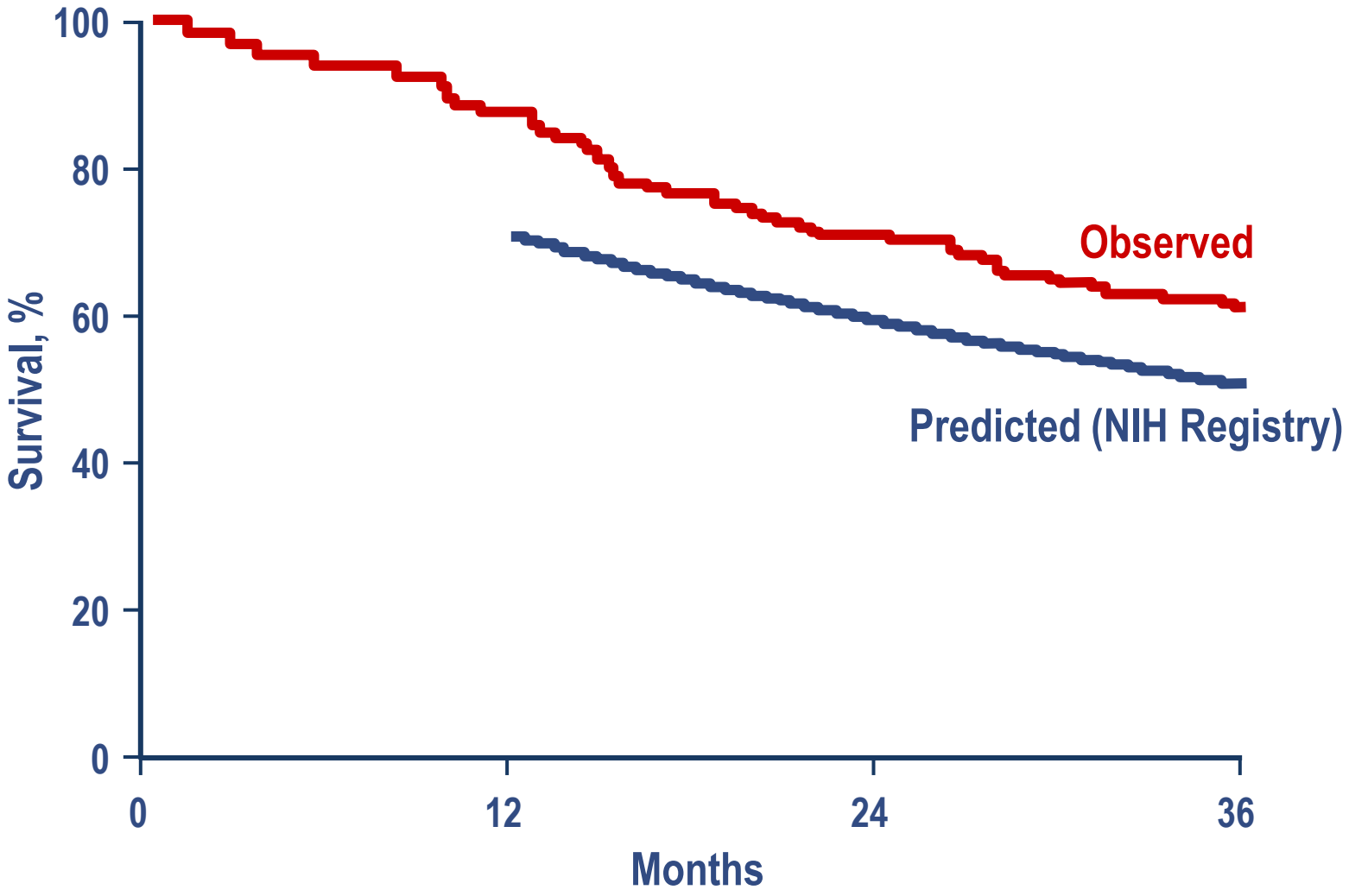


Humbert M, *et al*. *Eur Respir J* 2010; 36: 549–55.

Survival in the French cohort (incident)

Survival ($_{95\%}$CI)

- 1 year 83 % (72 – 95)
- 2 years 67 % (57 – 79)
- 3 years 58 % (49 – 69)



Humbert M, *et al. Circulation* 2010.

The modern age of PAH registries

- Several large, prospective, multicentre registries are now available worldwide (Europe, US, Canada, Latin America, China, Japan, Middle East & Africa, Australia & NZ etc…)
- Demographics have changed in the western world with increased age and comorbidities
- Increased number of approved therapies, availability of combination therapies and international guidelines have markedly changed management
- Registries have been a key tool for addressing novel questions such as risk stratification and treatment goals

French Idiopathic / Heritable / Associated PAH cohorts (2002 – 2003 & 2006 – 2009)

Group 1 (PAH) incident cases	PAH registry (2006 – 2009)	Previous registry (2002 – 2003)
n	718	121
Sex-Ratio F / M	1.33	1.70
Age, yrs (range)	56 ± 15 (18 – 86)	53 ± 17 (19 – 85)
Patients > 70 y-o	24 %	9 %
NYHA FC III-IV	73 %	81 %
6-min walk distance, m	325 ± 123	312 ± 114

Humbert M *et al*. *Am J Respir Crit Care Med* 2006.
Sitbon O *et al.* ERS Congress 2011.

French I / H / APAH cohorts (2002 - 2003 & 2006 - 2009)

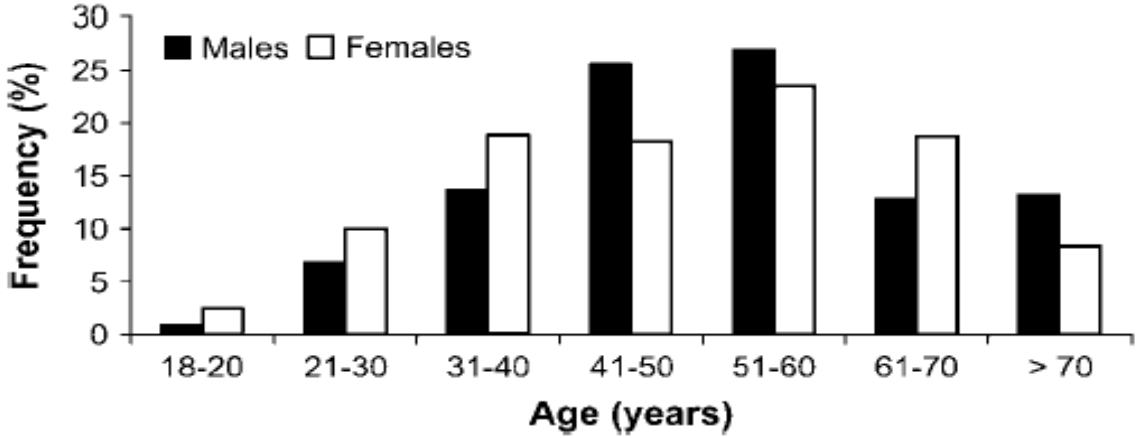
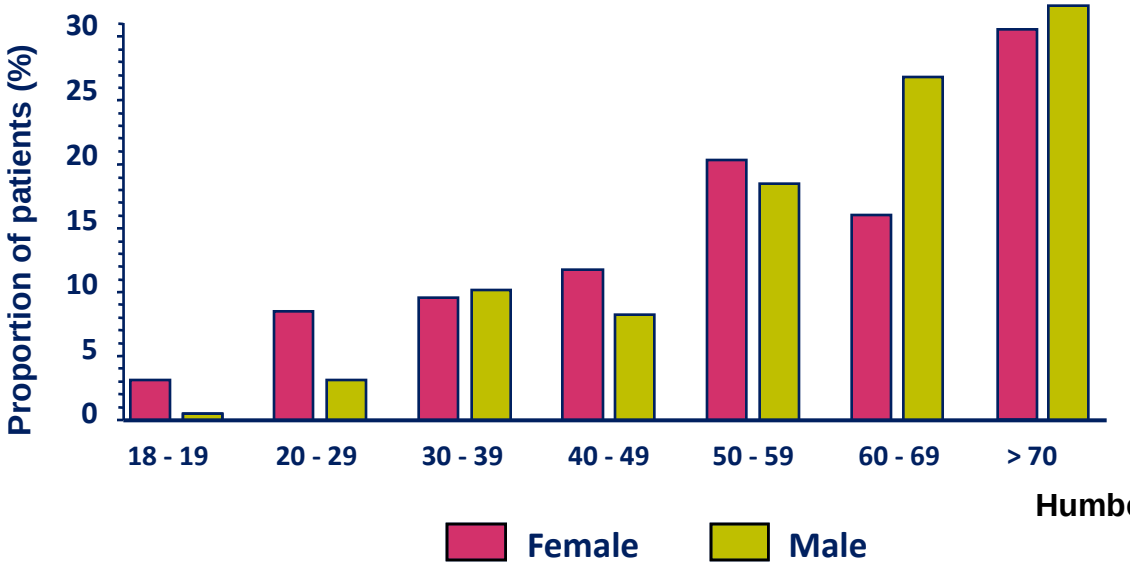


Figure 1. Distribution of patients with pulmonary arterial hypertension according to age based on sex.

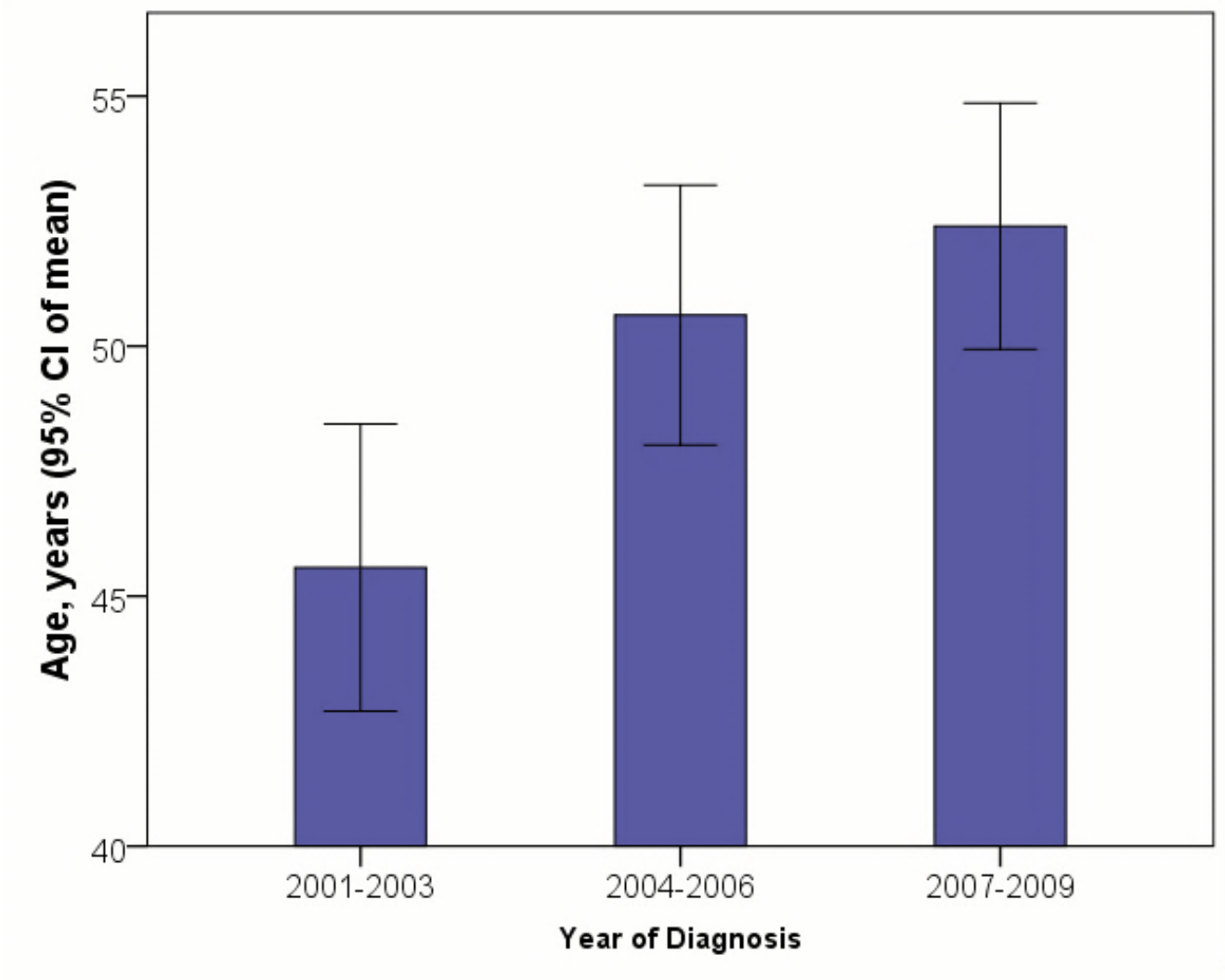
2002 - 2003



2006 - 2009

Humbert M *et al*. Am J Respir Crit Care Med 2006.
Sitbon O *et al.* ERS 2011.

Increasing age of ‘pure IPAH’ in the UK and Ireland



Ling Y *et al*. *Am J Respir Crit Care Med* 2012.

Epidemiology of ‘pure IPAH’ has changed between 2001 and 2009 in the UK and Ireland

- Increasing
  - Incidence
  - Age
  - Body mass index and obesity
  - Co-morbidities

- Decreasing
  - DLCO

- No change
  - Duration
  - Severity

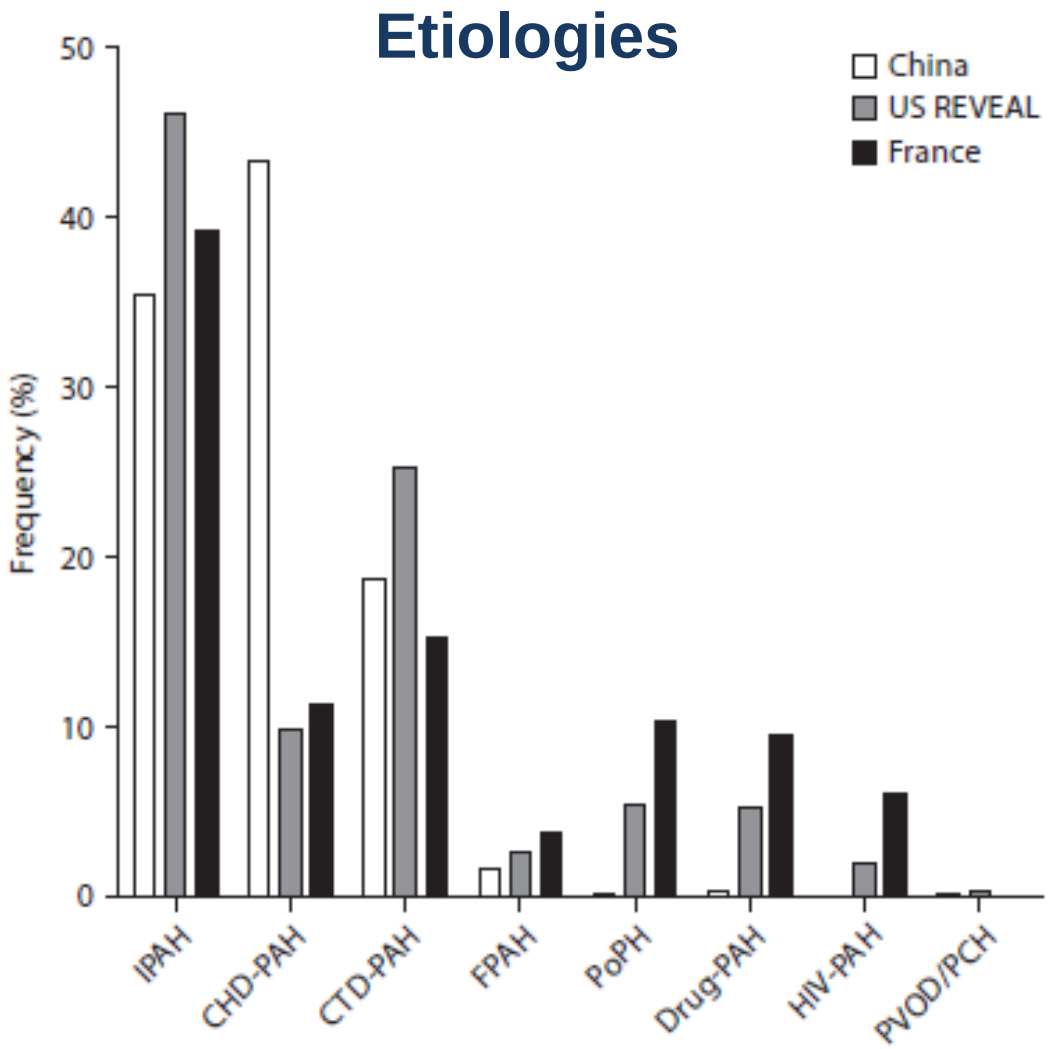
Ling Y *et al*. *Am J Respir Crit Care Med* 2012.

Baseline characteristics of PAH at the time of diagnosis from different registries

Registry	NIH[9]	French[7]	United States[6]	REVEAL[8]	United Kingdom/ Ireland[4]	ASPIRE[11,a]	COMPERA[5]
Year	1987	2006	2007	2010	2012	2012	2013
Subjects, *n*	187	674	578	2,525	482	175	587
Age, years	36 ± 15	50 ± 15	48 ± 14	50.1 ± 14.4	50.1 ± 17.1	55 ± 16	71 ± 16
Women, %	63	65.3	77	55.6	69.9	67	60.3
mPAP, mm Hg	60 ± 18	55 ± 15	52 ± 14	50.7 ± 13.6	54.1 ± 13.9	53 ± 13	44 ± 12
PAWP, mm Hg	[b]	8 ± 3	10 ± 4	9.1 ± 3.5	9.2 ± 3.5	10 ± 3	10 ± 3
RAP, mm Hg	9.7 ± 6	8 ± 5	11 ± 7	9.3 ± 5.6	10.1 ± 6.0	11 ± 6	8 ± 5
CI, L/min/m^2	2.27 ± 0.9	2.50 ± 0.8	2.3 ± 0.9	2.4 ± 0.8	2.1 ± 0.7	2.3 ± 0.8	2.2 ± 0.7
PVRi (WU·m^2)	26 ± 14	20.5 ± 10.2	–	21.1 ± 12.5	23.1 ± 10.3	–	–
PVR (WU)	–	–	12.5 ± 7.3	–	12.8 ± 6.3	12.0 ± 5.8	9.6 ± 5.5

Lador F & Hervé P. *Semin Respir Crit Care Med* 2013;34:654–64.

European, US & Chinese Registries in the modern management era



Jiang X; *Prog Resp Res*; Basel, Karger; 2012; 41:85-93

European, US & Chinese Registries in the modern management era

Clinical and hemodynamic characteristics

Characteristic	Overall Group 1 PAH			IPAH		
	China (n = 956)	USA (n = 2,525)	France (n = 674)	China (n = 383)	USA (n = 1,166)	France (n = 259)
Female, %	70	80	65	70	83	62
Age, years	36±13	50±14	50±15	38±13	50±15	52±15
Obesity (BMI ≥30), %	1.5	33.3	14.8	2.1	38.4	–
Median time from symptom onset to diagnosis, months	30	14	–	24	–	–
WHO FC III/IV, %	53.6	56	75	66	55	81
6MWD, m	378±125	366±126	329±109	353±127	374±129	328±112
mPAP, mm Hg	63±20	51±14	55±15	63±15	52±13	56±14
mRAP, mm Hg	8±5	9±6	8±5	8±6	10±6	9±5
PCWP, mm Hg	9±3	9±4	8±3	8±	9±4	8±3
CI, l/min/m^2	2.5±0.9	2.4±0.8	2.5±0.8	2.2±0.8	2.2±0.8	2.3±0.7
PVRI, Wood·m^2	25±14	21±13	21±10	27±12	23 ±11	23±10
SvO_2, %	66±12	63±10	63±9	60±11	62±10	61±10
Acute vasodilator responders, %	2.8	10.2	5.8	5.0	–	10.3

Jiang X; *Prog Resp Res*; Basel, Karger; 2012; 41:85-93

European, US & Chinese Registries in the modern management era

Comorbidities

Comorbid condition	Group 1 PAH		IPAH	
	US REVEAL (n = 2,438)	China (n = 956)	US REVEAL (n = 1,114)	China (n = 338)
Hypertension	980 (40.2)	44 (4.6)	466 (41.8)	10 (3.0)
Diabetes	293 (12.0)	16 (1.6)	158 (14.2)	4 (1.2)
Ischemic cardiovascular event[1]	227 (9.3)	15 (1.6)	114 (10.2)	8 (2.4)
Chronic parenchymal disease[2]	533 (21.9)	29 (3.0)	258 (23.2)	5 (1.5)
Renal insufficiency	109 (4.9)	8 (0.8)	48 (4.3)	2 (0.6)
Thyroid disease[3]	527 (21.6)	10 (1.0)	227 (20.4)	1 (0.3)
Cirrhosis	151 (6.2)	4 (0.4)	20 (1.8)	1 (0.3)
History of VTE[4]	313 (12.8)	11 (1.2)	164 (14.7)	0 (0)
Cancer	148 (6.1)	5 (0.5)	69 (6.2)	1 (0.3)

Jiang X; *Prog Resp Res*; Basel, Karger; 2012; 41:85-93

Four recent registries assessing risk stratification in PAH

REVEAL[1]

Swedish PAH Registry[2]

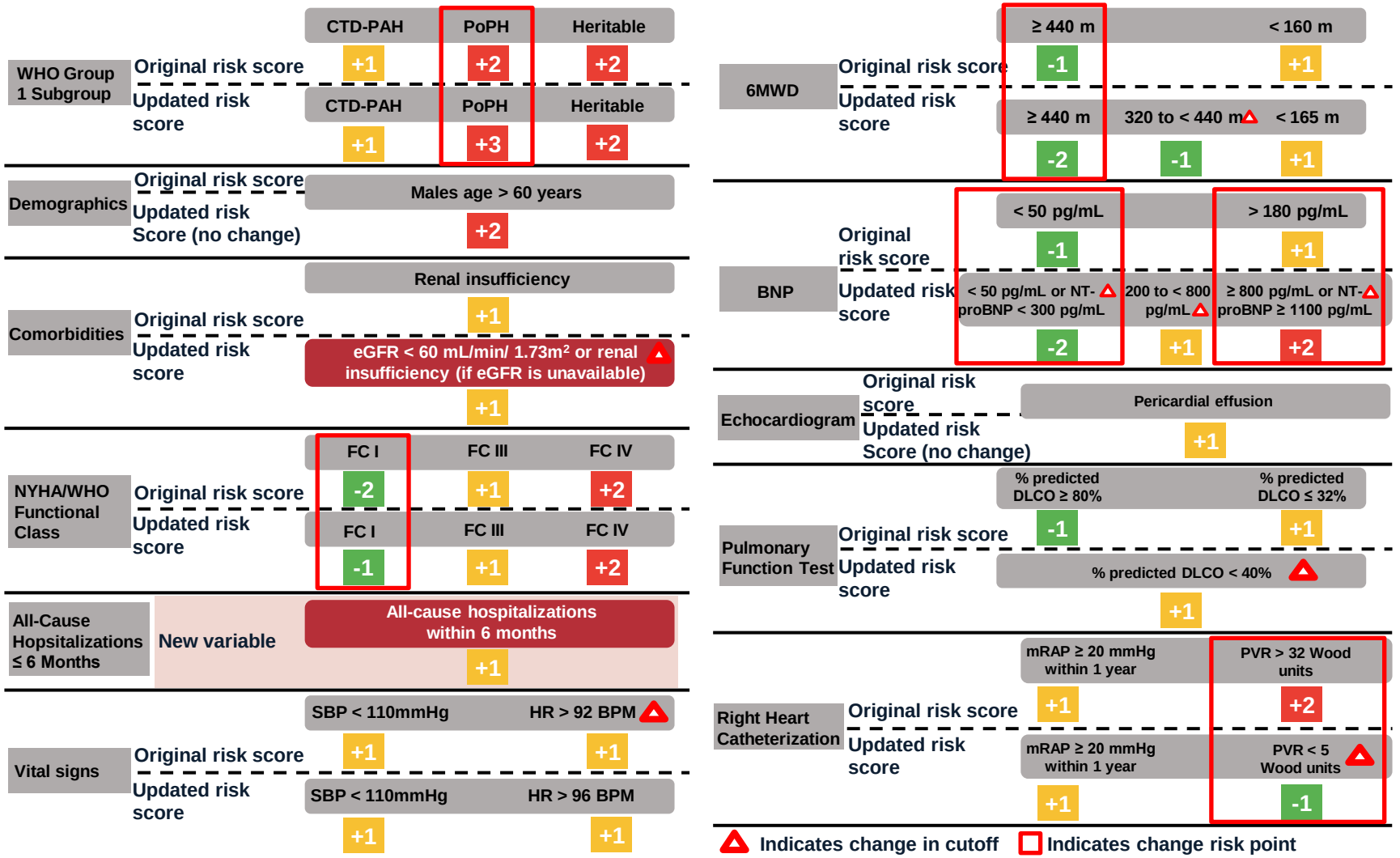
COMPERA[3]

French PH Registry[4]

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.

REVEAL Registry: Risk score

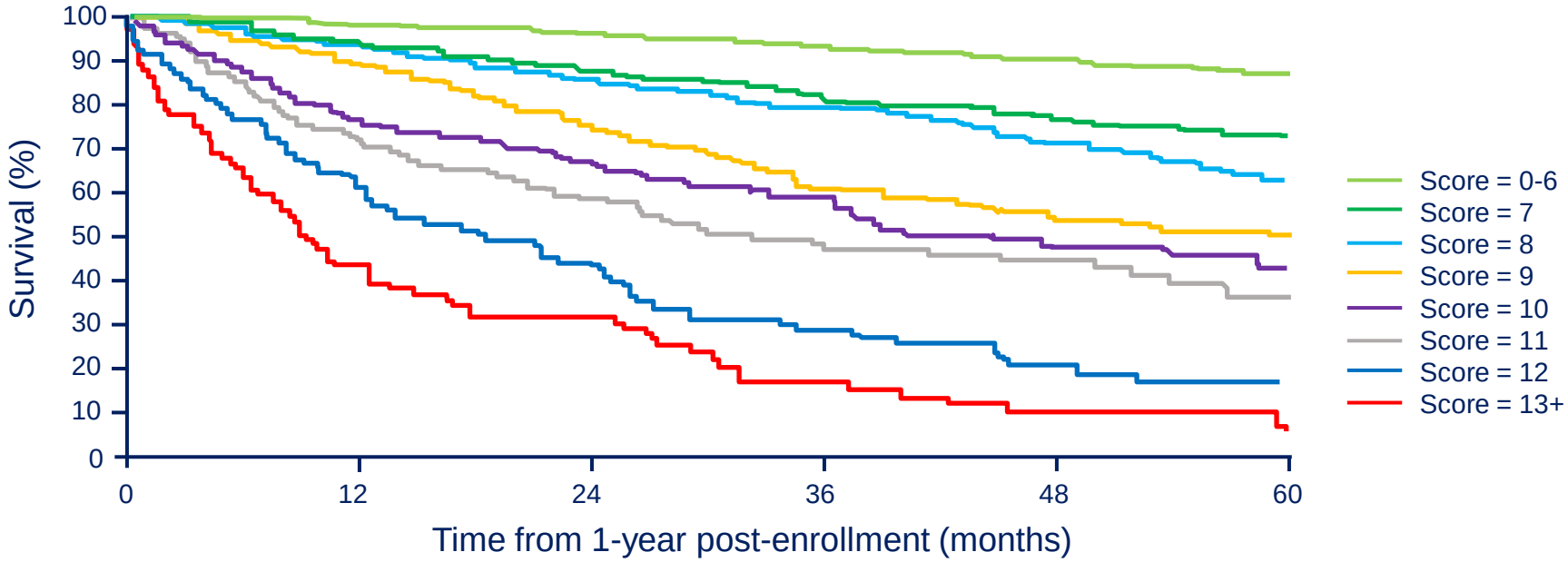
- Multivariable model coefficients replaced with integer values to create calculator[1]
- Risk calculator allows easy tabulation of risk score[1]
- REVEAL 2.0 can predict survival and clinical worsening[2]



REVEAL: Registry to Evaluate Early and Long-term PAH disease management.

1. Benza R, *et al. CHEST* 2012; 141:354-62;
2. Benza R, *et al. Chest* 2019 [Epub ahead of print].

Survival according to REVEAL 2.0 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: Registry to Evaluate Early and Long-term PAH disease management.

Benza R, *et al. Chest* 2019 [Epub ahead of print].

REVEAL PAH risk score considerations

- Large number of variables (-)
- Incorporates non-modifiable variables (-)

- Weighted variables (+)
- Validated across many different patient groups (+)
- Highly discriminatory for both survival and clinical worsening (+)
- Works in both incident and prevalent cases (+)
- External validation (French PAH Registry cohort) (+)

1. Benza R, *et al. J Heart Lung Transplant* 2017; 36:S19;
2. Benza R, *et al. Eur Respir J* 2017; 50:1701353;
3. Benza R, *et al. Chest* 2019; article in press;
4. Sitbon O, *et al. Eur Respir J* 2015; 46:152-164.

2015 ESC/ERS Guidelines – Risk stratification in PAH

	Determinants of prognosis	Estimated 1-year mortality		
		Low risk < 5%	Intermediate risk 5-10%	High risk > 10%
Clinical Evaluation	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 Capacity	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
Right Ventricular Function	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%

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

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 Kjellström[2], Clara Hjalmarsson[3], Kjell Jansson[4], Magnus Nisell[5], Stefan Söderberg[6], Gerhard Wikström[7], and Göran Rådegran[1], 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 Pan[5], Christina A. Eichstaedt[5], Jens Spiesshoefer[6], Nicola Benjamin[5], Karen M. Olsson[1,2], Katrin Meyer[1], Carmine Dario Vizza[7], Anton Vonk-Noordegraaf[8], Oliver Distler[9], Christian Opitz[10], J. Simon R. Gibbs[11], Marion Delcroix[12], H. Ardeschir Ghofrani[13], Doerte Huscher[14], David Pittrow[15], Stephan Rosenkranz[3,4] and Ekkehard Grünig[2,5]

Risk assessment, prognosis and guideline implementation in pulmonary arterial hypertension

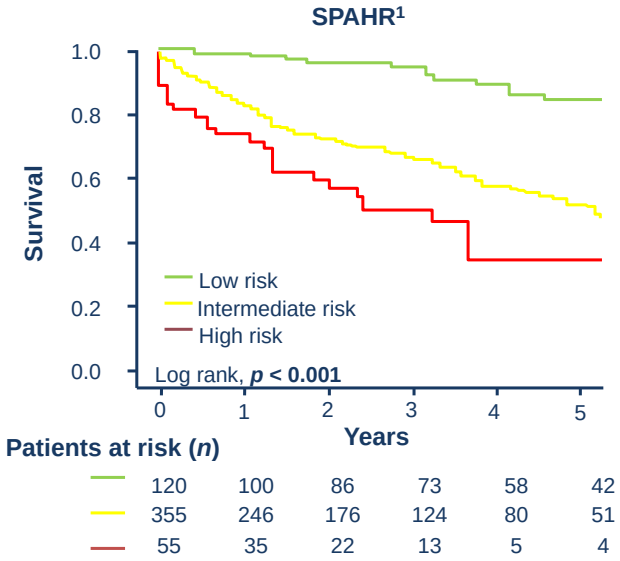
Athénaïs Boucly[1,2,3], Jason Weatherald[2,3,4], Laurent Savale[1,2,3], Xavier Jaïs[1,2,3], Vincent Cottin[5], Grégoire Prevot[6], François Picard[7], Pascal de Groote[8], Mitja Jevnikar[1,2,3], Emmanuel Bergot[9], Ari Chaouat[10,11], Céline Chabanne[12], Arnaud Bourdin[13], Florence Parent[1,2,3], David Montani[1,2,3], Gérald Simonneau[1,2,3], Marc Humbert[1,2,3] and Olivier Sitbon[1,2,3]

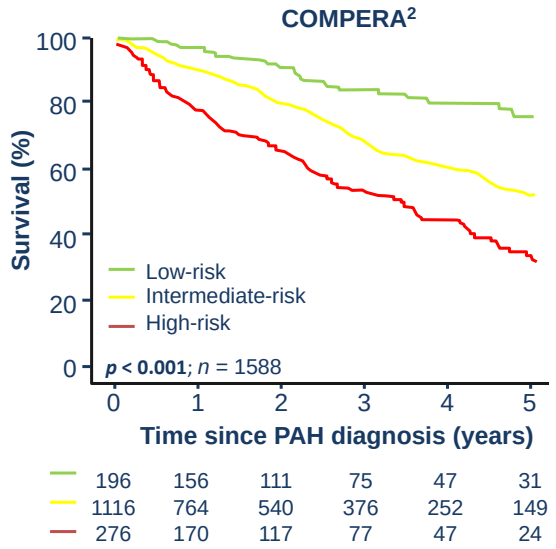
Kylhammar (8 variables)	Hoeper (6 variables)	Boucly (4 or 3 variables)
n = 530 PAH (2008-2016)	n = 1588 PAH (2009-2016)	n = 1017 IPAH (2006-2016)
WHO 6MWD BNP RA area Pericardial effusion RAP CI SvO_2	WHO 6MWD BNP RAP CI SvO_2	WHO 6MWD RAP CI WHO 6MWD BNP
Sum of grades (1 low-3 high) /number available variables	Sum of grades (1 low-3 high) /number available variables	Number of low risk variables

Kylhammar D, *et al. Eur Heart J* 2017; ehx257; Hoeper MM, *et al. Eur Respir J* 2017; 50:1700740; Boucly A, *et al. Eur Respir J* 2017; 50:1700889.

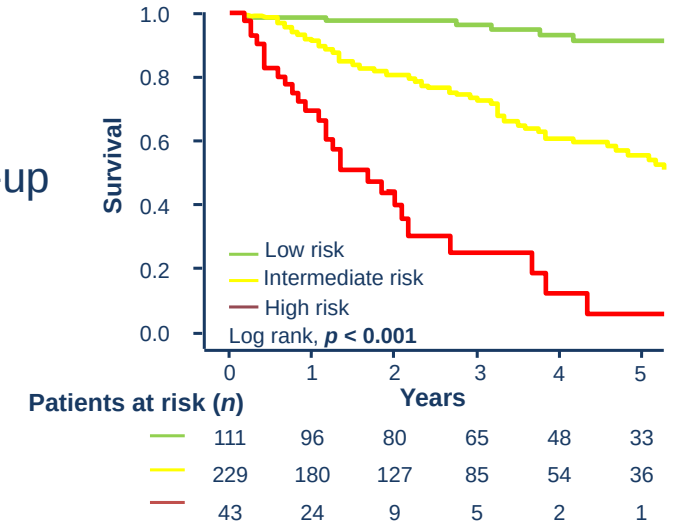
Validation of ESC/ERS risk stratification in large registries

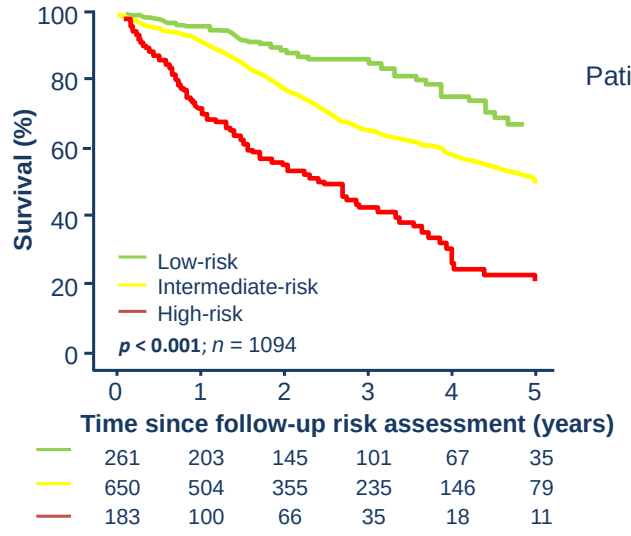
Baseline

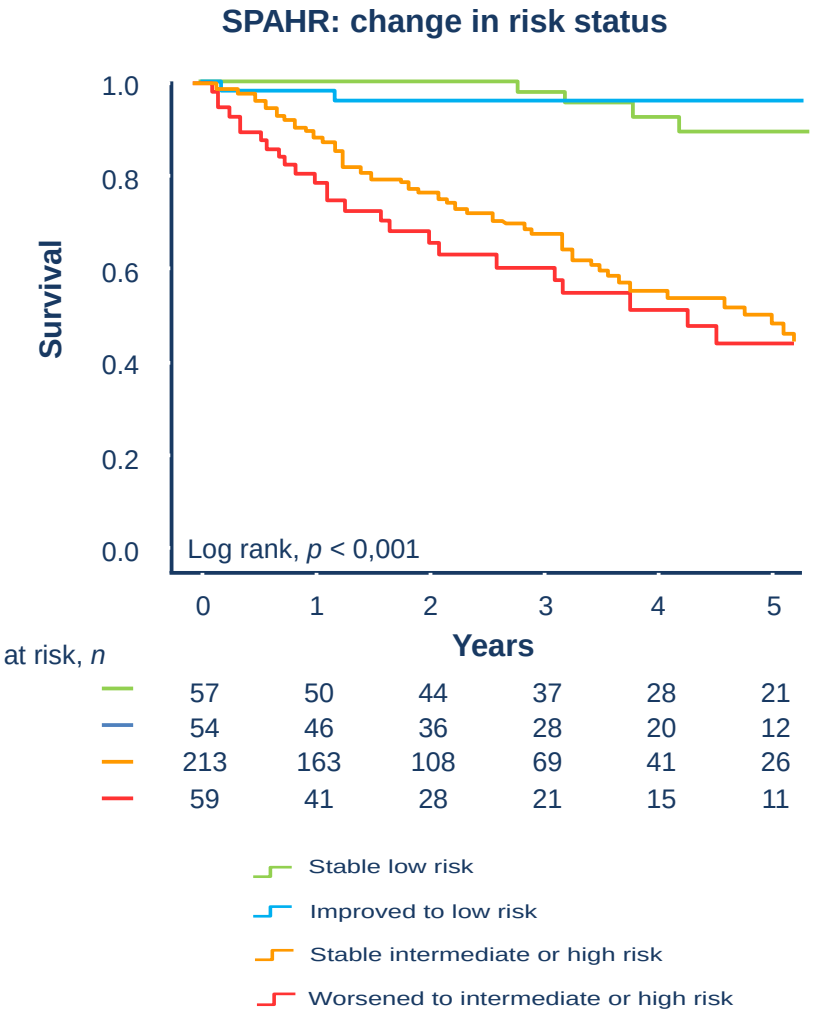




Follow-up







1. Kylhammar D, *et al. Eur Heart J* 2017; ; ehx257;
2. Hoeper MM, *et al. Eur Respir J* 2017; 50:1700740.

French Registry approach: association between the number low-risk criteria and survival

- Incident patients with idiopathic, heritable and drug-induced PAH between 2006-2016 were analysed

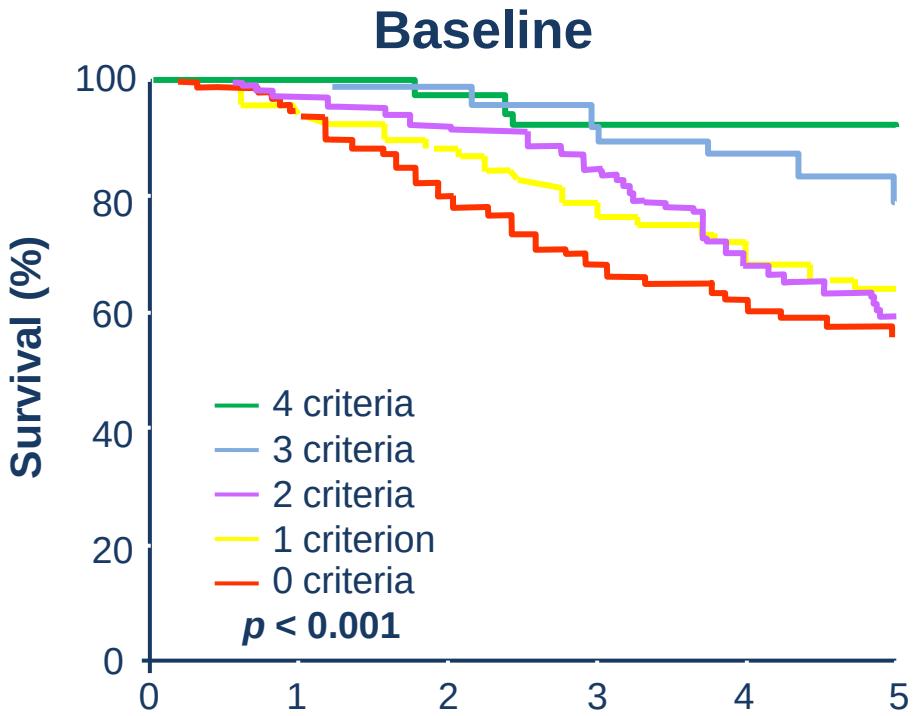
- The number of low-risk criteria present at diagnosis and at first re-evaluation were assessed:
  1. WHO/NYHA functional class I or II
  2. 6-minute walk distance (6MWD) > 440m
  3. right atrial pressure < 8 mmHg
  4. cardiac index ≥ 2.5 L/min/m^2

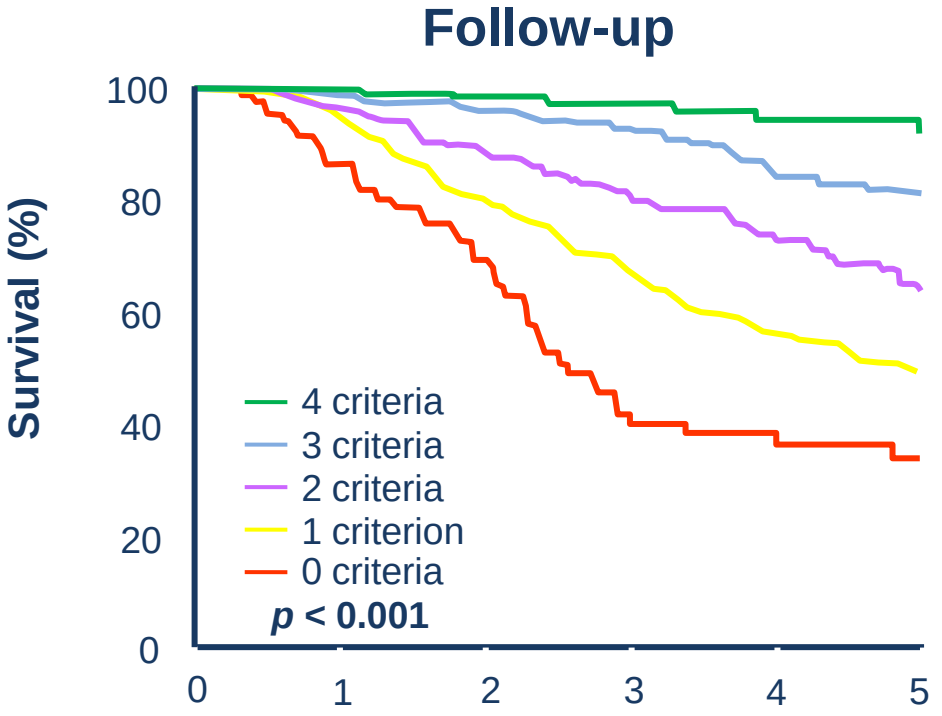
- 1017 / 1591 patients having all parameters available at both baseline and first re-evaluation

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%

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

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





Patients at risk, *n*

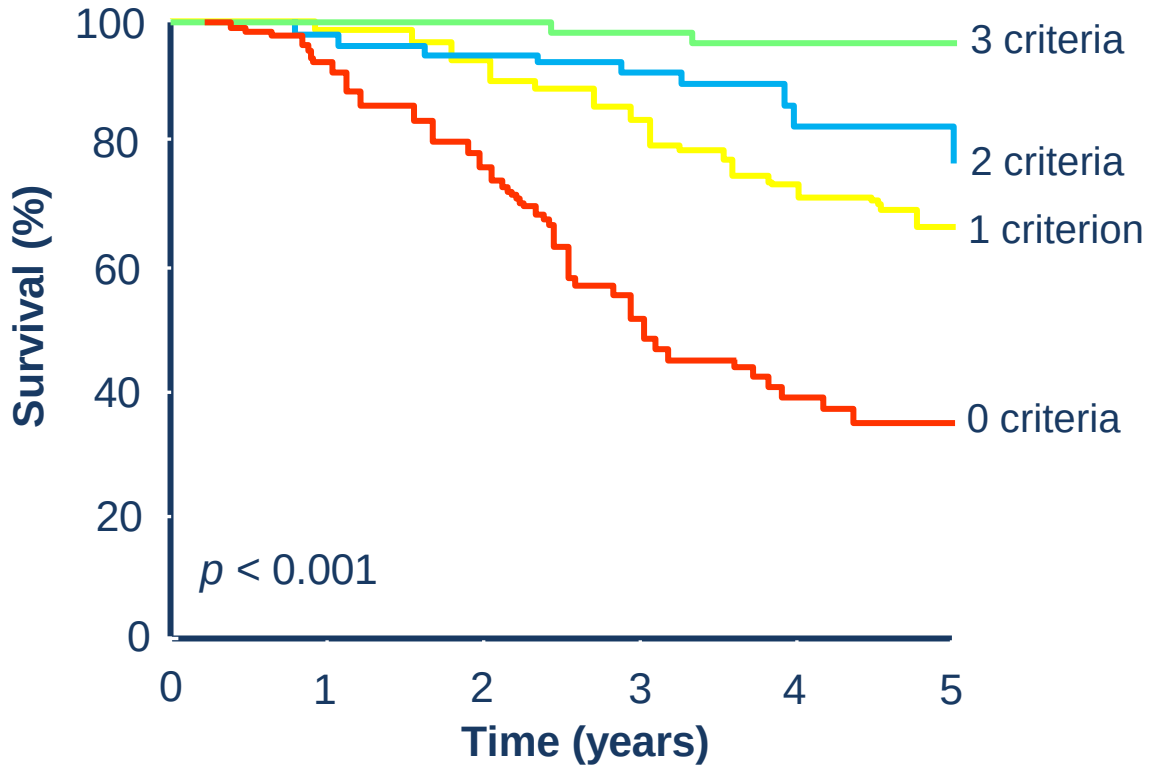
4 criteria	59	52	46	35	26	20
3 criteria	112	94	74	59	36	26
2 criteria	217	173	149	104	63	45
1 criterion	371	302	233	176	128	89
0 criteria	258	212	158	117	76	53

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

Incident patients enrolled in the French registry

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

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

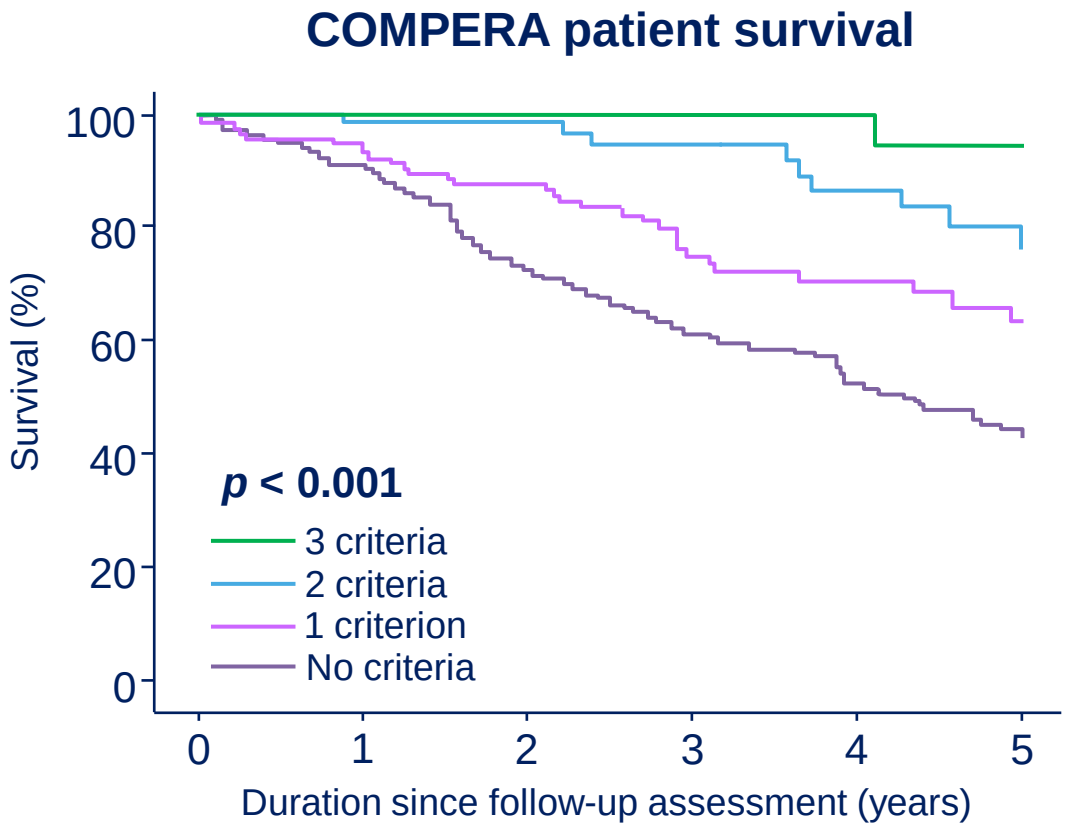
Patients with all 3 non-invasive low-risk criteria (≈ 20%) had a 2-, 3- and 5-year survival of 100%, 99% and 97%, respectively

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

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

When the French registry risk score was applied to the COMPERA population…

…Comparable survival rates for COMPERA and French Registry patients were observed



	Number of low-risk criteria at follow up	1 Year survival estimate	3 Year survival estimate	5 Year survival estimate
COMPERA	3 low-risk criteria	100%	100%	95%
	2 low-risk criteria	99%	95%	76%
	1 low-risk criterion	93%	75%	64%
	0 low-risk criteria	90%	61%	43%
French registry	3 low-risk criteria	100%	97%	96%
	2 low-risk criteria	98%	90%	77%
	1 low-risk criterion	98%	83%	66%
	0 low-risk criteria	94%	52%	35%

n = 579; IPAH patients for whom complete data sets of FC, 6MWD and BNP/NT-proBNP were available at first follow-up (median 4.6 months, interquartile range 3.1-9.5 months) after treatment initiation.

Hoeper MM, *et al. Eur Respir J* 2018; 51:1702606.

Conclusions

- Registries are unique tools allowing a better understanding of PAH epidemiology
- PAH registries have been very useful (PAH incidence, prevalence, etiologies, patients' characteristics, survival, …)
- Risk stratification and treatment goals can be tested in registries

Guidelines for Registries Implementation

- The process of registry development

  - **Keep the registry simple**
    - A database should include the minimal number of variables that are necessary to answer the questions that we are asking to ourselves (the simpler the registry, the less prone to errors)

  - **Adequate selection of participating centers**
    - One of the major criticisms of some registries is that some participating centres had a very low recruitment rate, thus reflecting high variability with regards the experience with the diagnosis and management of the disease.

McGoon M, et al. J Am Coll Cardiol 2013