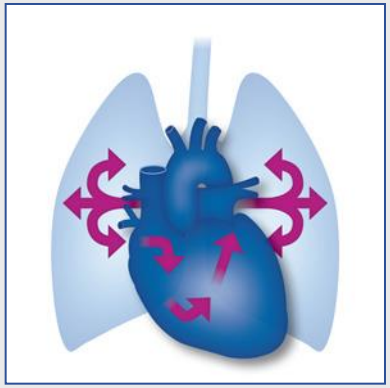
Pneumo Update Europe 2018

15-16 June, Budapest

Pulmonary Vascular Diseases

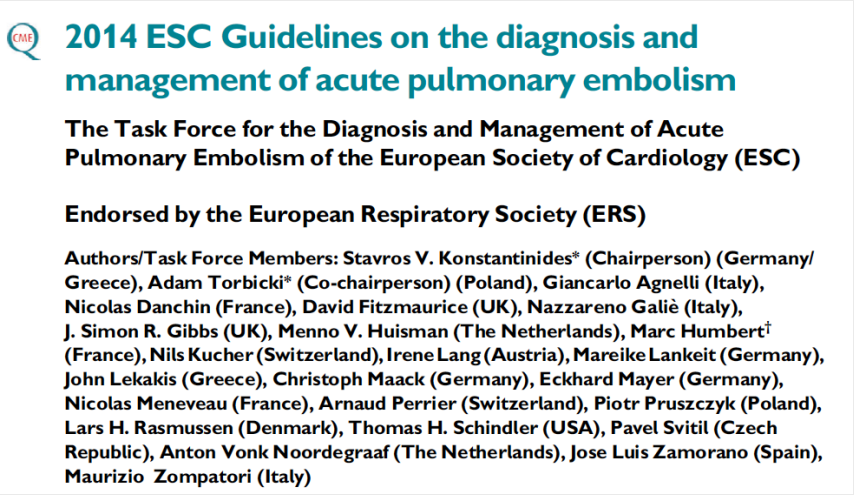


Marc Humbert, France

From acute pulmonary embolism to chronic thromboembolic pulmonary hypertension

State of the Art

- Pulmonary embolism and venous thromboembolic disease are fast-moving fields of cardiopulmonary medicine
- ESC PE Guidelines endorsed by ERS have been published in 2014
- Novel ESC PE Guidelines endorsed by ERS should be released in 2019



2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism

The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC)

Endorsed by the European Respiratory Society (ERS)

Authors/Task Force Members: Stavros V. Konstantinides* (Chairperson) (Germany/Greece), Adam Torbicki* (Co-chairperson) (Poland), Giancarlo Agnelli (Italy), Nicolas Danchin (France), David Fitzmaurice (UK), Nazzareno Galiè (Italy), J. Simon R. Gibbs (UK), Menno V. Huisman (The Netherlands), Marc Humbert† (France), Nils Kucher (Switzerland), Irene Lang (Austria), Mareike Lankeit (Germany), John Lekakis (Greece), Christoph Maack (Germany), Eckhard Mayer (Germany), Nicolas Meneveau (France), Arnaud Perrier (Switzerland), Piotr Pruszczyk (Poland), Lars H. Rasmussen (Denmark), Thomas H. Schindler (USA), Pavel Svitil (Czech Republic), Anton Vonk Noordegraaf (The Netherlands), Jose Luis Zamorano (Spain), Maurizio Zompatori (Italy)

Konstantinides et al. Eur Heart J 2014; 35:3033-80

Treatment of Pulmonary Embolism

Management Appropriateness and Outcomes of Patients with Acute Pulmonary Embolism

- treatment of PE = international guidelines / evidence-based medicine.
- Evolution of patients with PE according to respect with guidelines ?

- Two analyses :
  - One prospective monocentric cohort (Madrid)
  - External validation in a prospective multicentric registry (RIETE)

Jimenez et al. Eur Respir J 2018; 51:1800445

Treatment of Pulmonary Embolism

Management classified **unappropriateness** if :

- Use of **UFH*** in a patient i) without severe renal failure (i.e., creatinine clearance < 30 mL/min), ii) without severe obesity (i.e., body weight > 120 kilograms), and iii) without unstable PE (defined as cardiogenic shock, systolic blood pressure < 90 mmHg, or use of inotropic or vasopressor support);
- use of **LMWH**** in a patient i) with severe renal failure, ii) severe obesity, or iii) unstable PE.

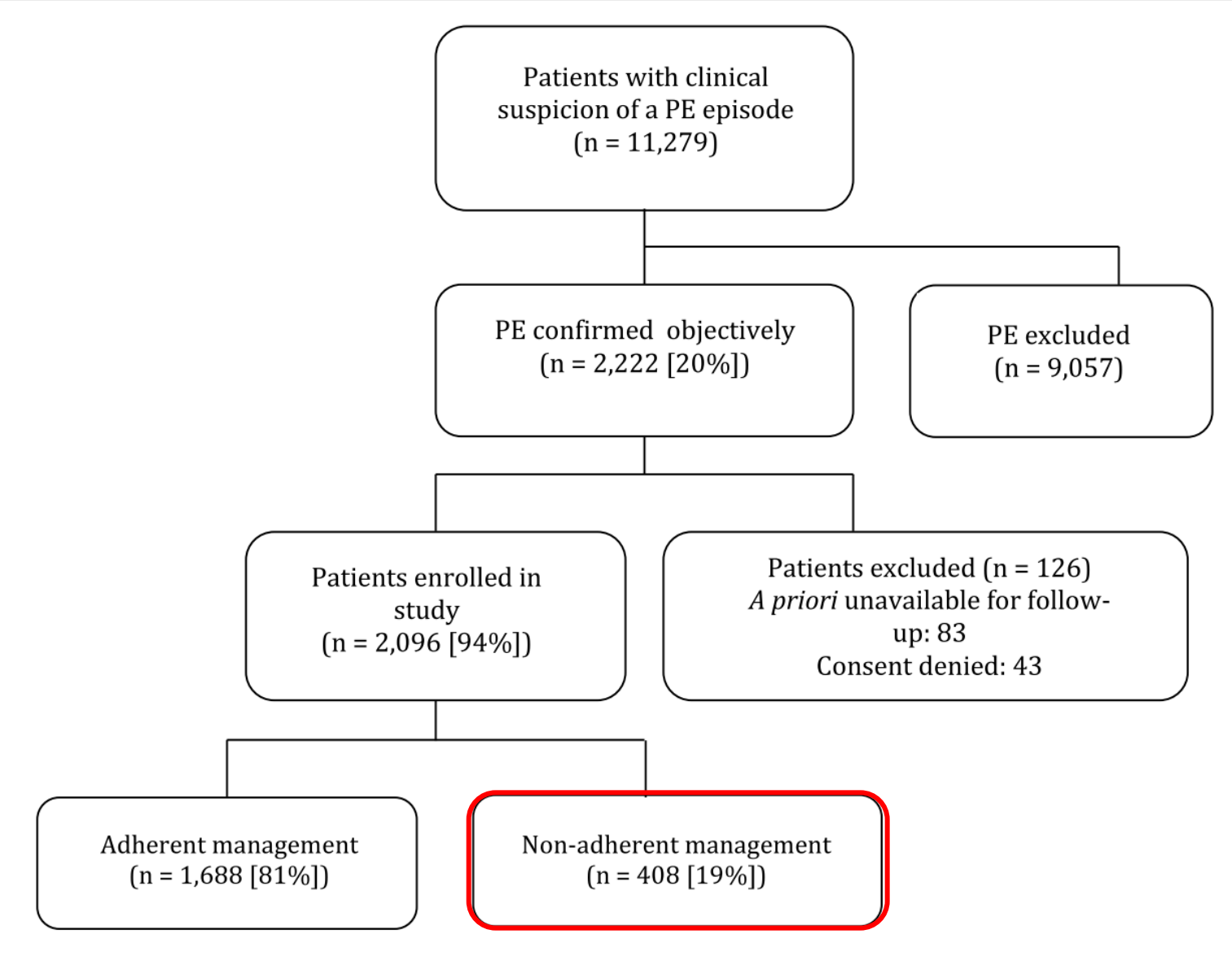
- Use of **thrombolytic therapy** in a hemodynamically stable patient who did not deteriorate soon after diagnosis; or **no use of thrombolytic therapy** in a hemodynamically unstable patient without major contraindications owing to bleeding risk.

- Insertion of an **inferior vena cava filter** in a patient without a contraindication to anticoagulant therapy; or **no insertion of an inferior vena cava filter** in a patient with a contraindication to anticoagulant therapy.

UFH: unfractionated heparin** * low moelcular weight heparin**

Jimenez et al. Eur Respir J 2018; 51:1800445

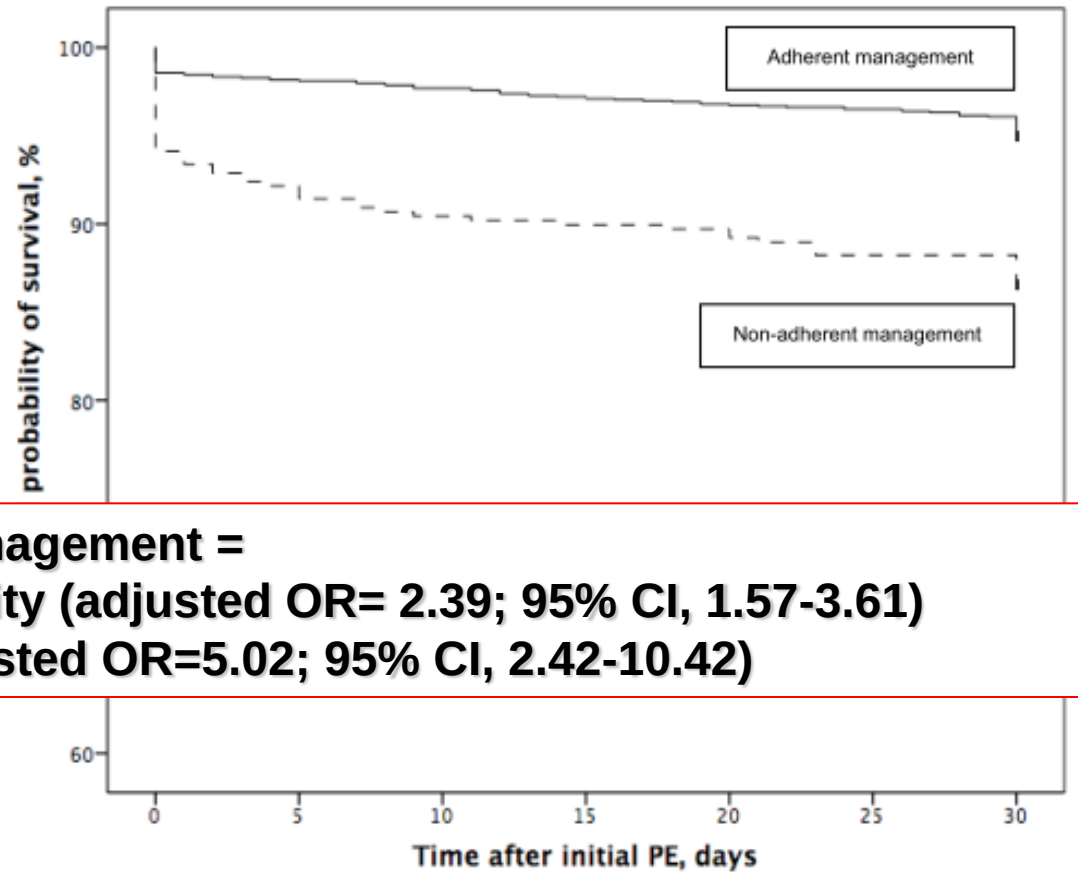
Treatment of Pulmonary Embolism



Jimenez et al. Eur Respir J 2018; 51:1800445

Treatment of Pulmonary Embolism

Figure 2.



No. at Risk

Non-adherent management	408	369	364	353
Adherent management	1,688	1,649	1,633	1,603

Log rank p < 0.001

Inappropriate management =
↗all-cause mortality (adjusted OR= 2.39; 95% CI, 1.57-3.61)
↗PE-related (adjusted OR=5.02; 95% CI, 2.42-10.42)

Jimenez et al. Eur Respir J 2018; 51:1800445

Treatment of cancer-associated PE

Recommendations for duration of anticoagulation after pulmonary embolism (cont.)	Class[a]	Level[b]
For patients with PE and cancer, weight adjusted subcutaneous LMWH should be considered for the first 3 to 6 months.	IIa	B
For patients with PE and cancer, extended anticoagulation (beyond the first 3 to 6 months) should be considered for an indefinite period or until the cancer is cured.	IIa	C

Konstantinides et al. Eur Heart J 2014; 35:3033-80

Edoxaban for the treatment of cancer-associated venous thromboembolism (HOKUSAI-VTE Cancer)

Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism

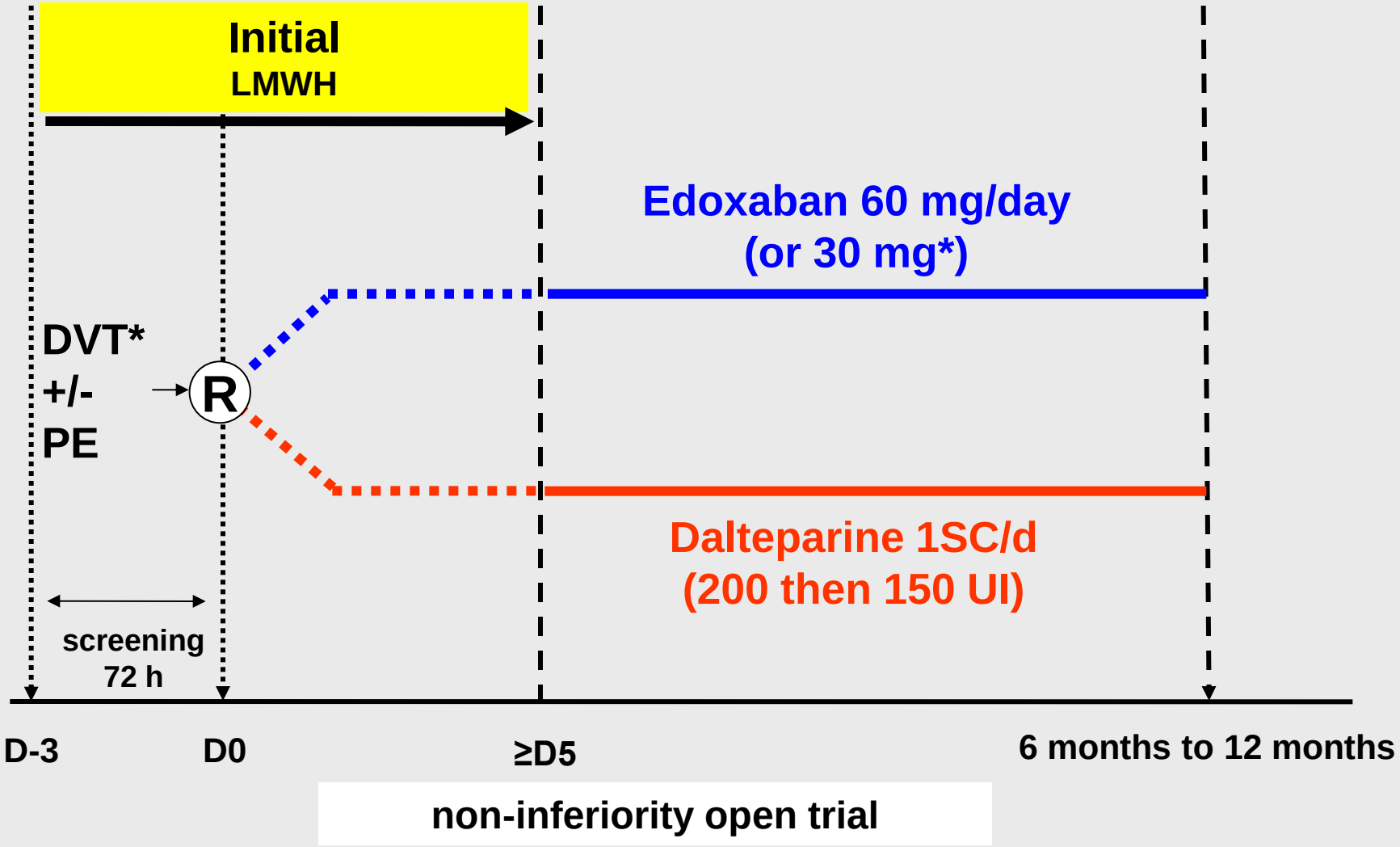
Gary E. Raskob, Ph.D., Nick van Es, M.D., Peter Verhamme, M.D., Marc Carrier, M.D., Marcello Di Nisio, M.D., David Garcia, M.D., Michael A. Grosso, M.D., Ajay K. Kakkar, M.B., B.S., Michael J. Kovacs, M.D., Michele F. Mercuri, M.D., Guy Meyer, M.D., Annelise Segers, M.D., Minggao Shi, Ph.D., Tzu-Fei Wang, M.D., Erik Yeo, M.D., George Zhang, Ph.D., Jeffrey I. Zwicker, M.D., Jeffrey I. Weitz, M.D., and Harry R. Büller, M.D., for the Hokusai VTE Cancer Investigators*

- Open-label, noninferiority trial
- Patients with cancer who had acute symptomatic or incidental VTE
- Receive either LMWH (at least 5 days) followed by oral edoxaban at a dose of 60 mg once daily (edoxaban group) or SC dalteparin, 200 IU/kg/day (one month), followed by dalteparin,150 IU/kg/d (dalteparin group).
- Treatment was given for at least six months and up to 12 months.
- Primary outcome = composite of recurrent VTE or major bleeding during the 12 months after randomization, regardless of treatment duration.

Raskob GE, et al. N Engl J Med 2018; 378:615-624

Edoxaban for the treatment of cancer-associated venous thromboembolism (HOKUSAI-VTE Cancer)

*DVT: deep vein thrombosis



non-inferiority open trial

Raskob GE, et al. N Engl J Med 2018; 378:615-624

Edoxaban for the treatment of cancer-associated venous thromboembolism (HOKUSAI-VTE Cancer)

- 1046 patients
- A primary-outcome event occurred in 67 of the 522 patients (12.8%) in the edoxaban group as compared with 71 of the 524 patients (13.5%) in the dalteparin group (P = 0.006 for noninferiority; P = 0.87 for superiority).
- Recurrent VTE occured in 41 patients (7.9%) in the edoxaban group and in 59 patients (11.3%) in the dalteparin group.
- Major bleeding occurred in 36 patients (6.9%) in the edoxaban group and in 21 patients (4.0%) in the dalteparin group.

Raskob GE, et al. N Engl J Med 2018; 378:615-624

Edoxaban for the treatment of cancer-associated venous thromboembolism (HOKUSAI-VTE Cancer)

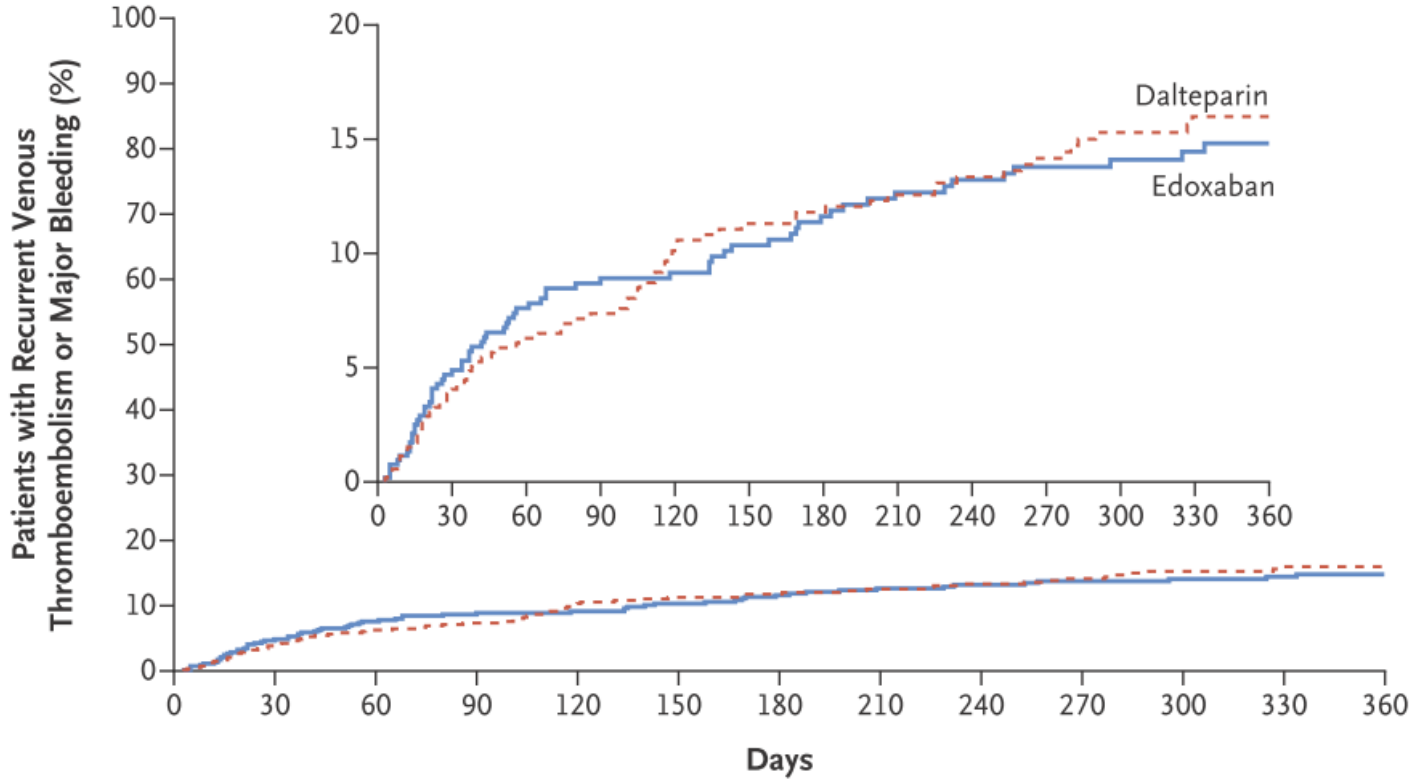
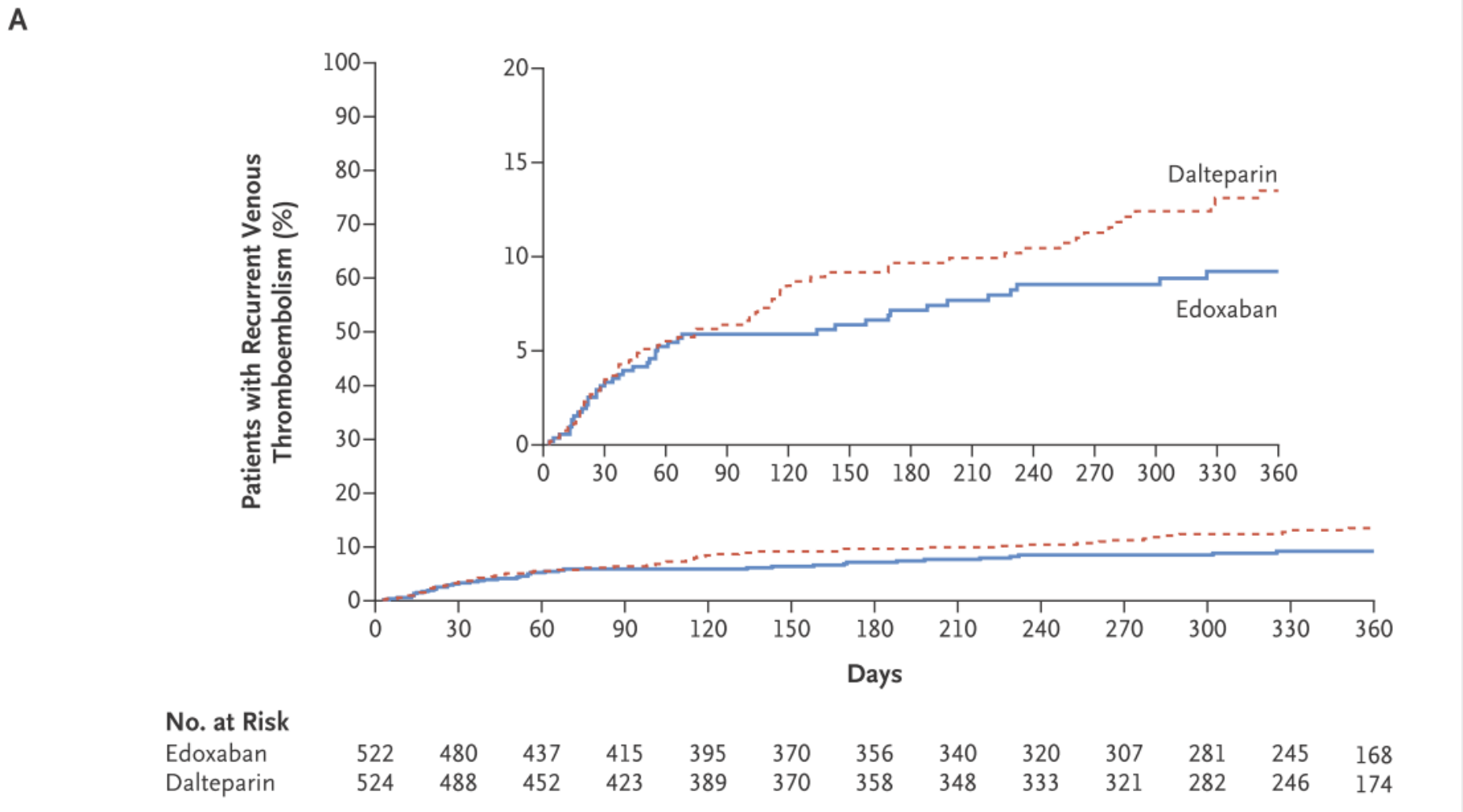


Figure 2. Kaplan–Meier Cumulative Event Rates for the Primary Outcome.

Raskob GE, et al. N Engl J Med 2018; 378:615-624

Edoxaban for the treatment of cancer-associated venous thromboembolism (HOKUSAI-VTE Cancer)

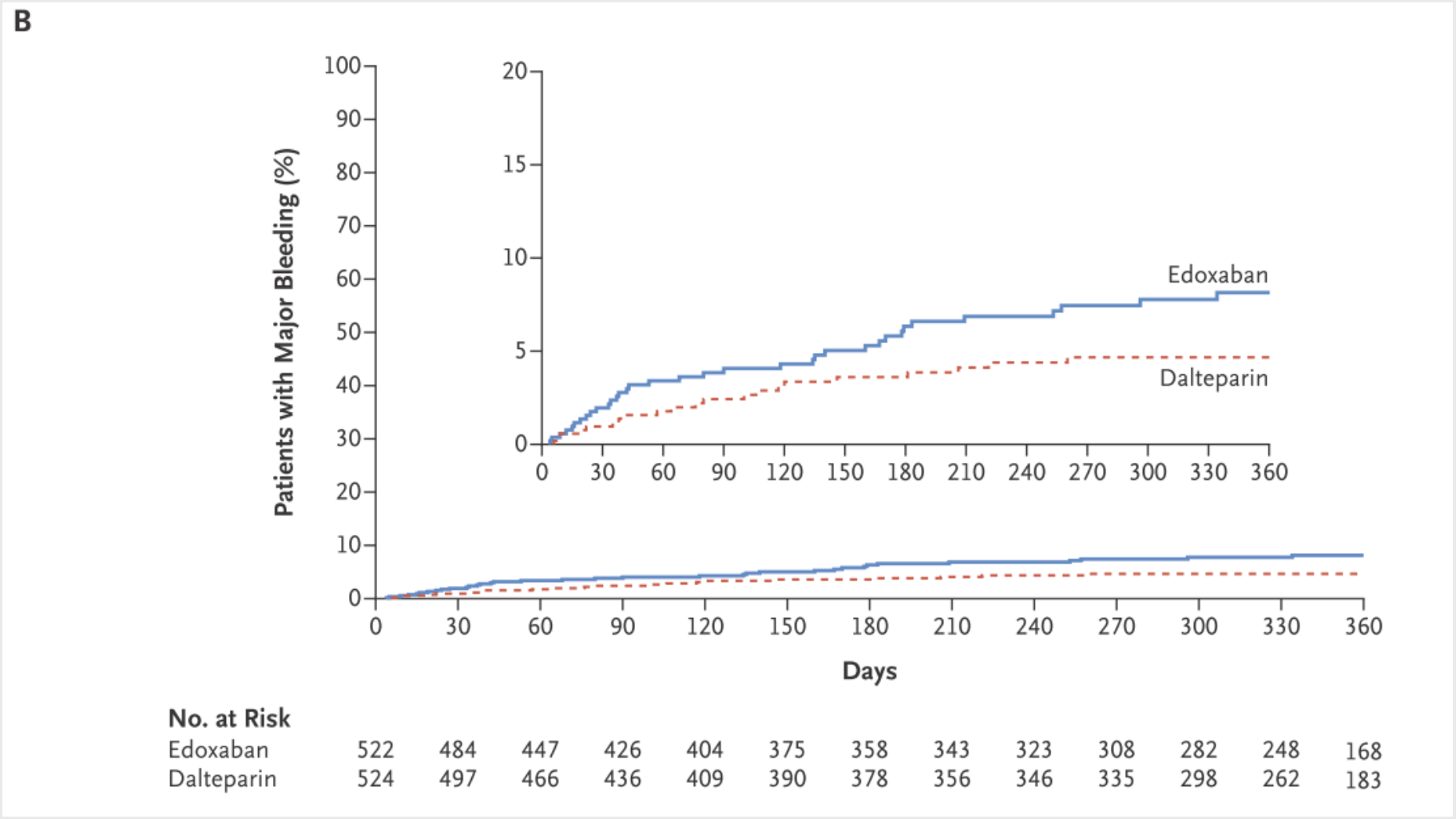
- Edoxaban : *less recurrent VTE* (mostly less DVT ?) ?



Raskob GE, et al. N Engl J Med 2018; 378:615-624

Edoxaban for the treatment of cancer-associated venous thromboembolism (HOKUSAI-VTE Cancer)

- Edoxaban : *more major bleeding* (gastro-intestinal ?) ?



Raskob GE, et al. N Engl J Med 2018; 378:615-624

Edoxaban for the treatment of cancer-associated venous thromboembolism (HOKUSAI-VTE Cancer)

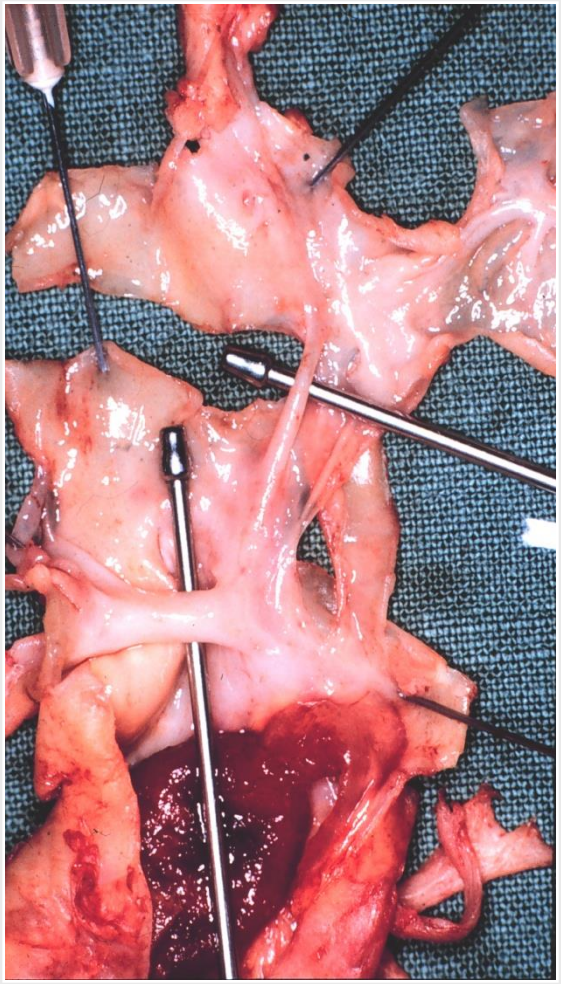
Table 2. Clinical Outcomes during the Overall Trial Period.*

Outcome	Edoxaban (N=522)	Dalteparin (N=524)	Hazard Ratio (95% CI)	P Value
Primary outcome				
Recurrent venous thromboembolism or major bleeding — no. (%)	67 (12.8)	71 (13.5)	0.97 (0.70–1.36)	0.006 for noninferiority; 0.87 for superiority
Secondary outcomes				
Recurrent venous thromboembolism — no. (%)	41 (7.9)	59 (11.3)	0.71 (0.48–1.06)	0.09
Recurrent deep-vein thrombosis — no. (%)	19 (3.6)	35 (6.7)	0.56 (0.32–0.97)	
Recurrent pulmonary embolism — no. (%)†	27 (5.2)	28 (5.3)	1.00 (0.59–1.69)	
Major bleeding — no. (%)	36 (6.9)	21 (4.0)	1.77 (1.03–3.04)	0.04
Severity of major bleeding among those with major bleeding — no./total no. (%)‡				
Category 1	0	0		
Category 2	24/36 (66.7)	8/21 (38.1)		
Category 3	12/36 (33.3)	12/21 (57.1)		
Category 4	0	1/21 (4.8)		
Clinically relevant nonmajor bleeding — no. (%)§	76 (14.6)	58 (11.1)	1.38 (0.98–1.94)	
Major or clinically relevant nonmajor bleeding — no. (%)§¶	97 (18.6)	73 (13.9)	1.40 (1.03–1.89)	
Death from any cause — no. (%)	206 (39.5)	192 (36.6)	1.12 (0.92–1.37)	
Event-free survival — no. (%)‖	287 (55.0)	296 (56.5)	0.93 (0.77–1.11)	

Raskob GE, et al. N Engl J Med 2018; 378:615-624

Definition of CTEPH

- Chronic thromboembolic pulmonary hypertension (CTEPH) is defined by a mean PAP ≥ 25 mmHg with persistent perfusion defects despite 3-6 months of adequate anti-coagulation
- CTEPH is a disease with:
  - a mechanical component which can be treated by surgery (endarterectmy) or interventional balloon pulmonary angioplasty
  - and variable small vessel disease which may require medical therapy with vasodilators



Simonneau et al. Eur Respir Rev 2016

CTEPH is a rare complication of acute PE

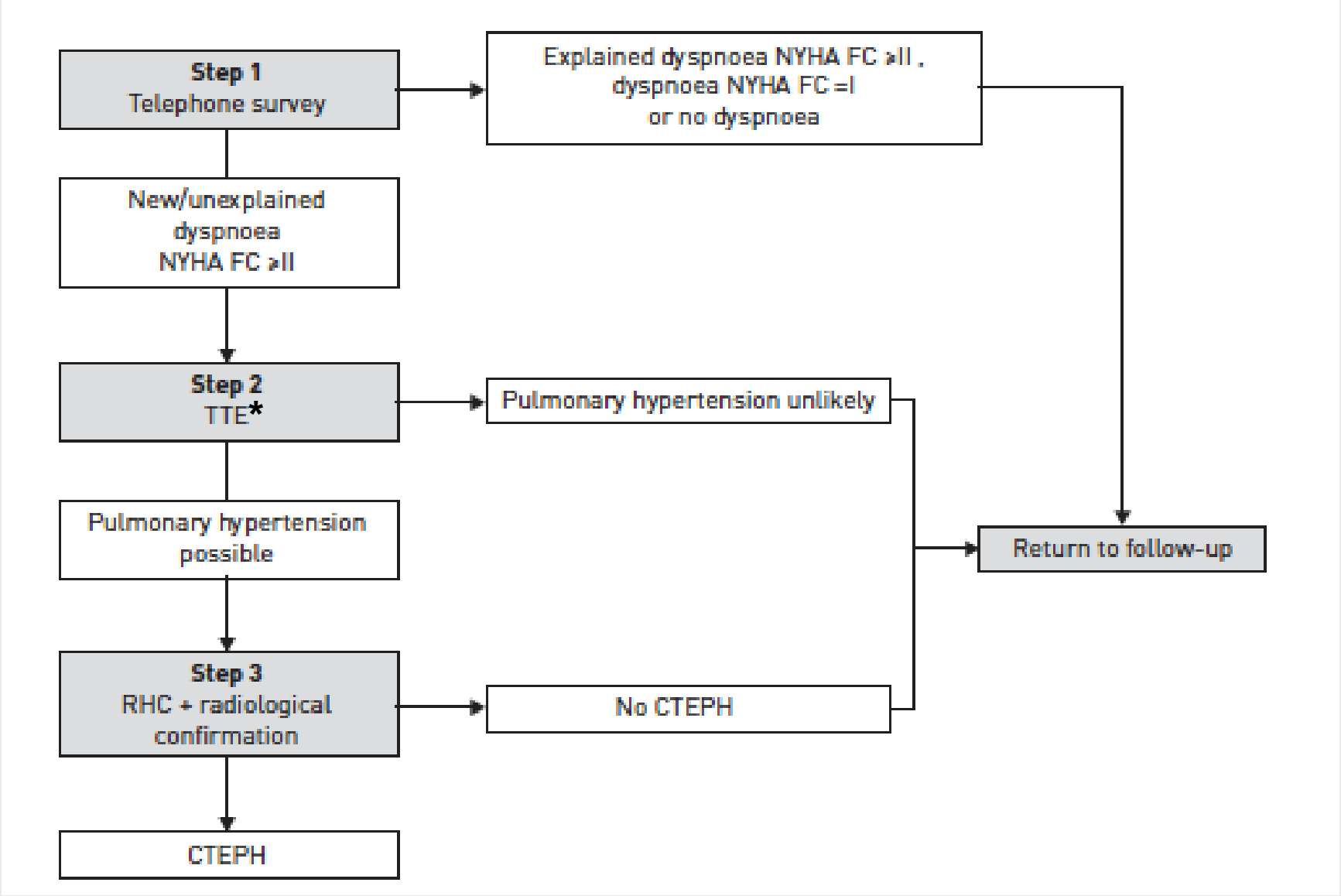
Multicentre observational screening survey for the detection of CTEPH following pulmonary embolism

Nicolas Coquoz[1,2], Daniel Weilenmann[3], Daiana Stolz[4], Vladimir Popov[5], Andrea Azzola[6], Jean-Marc Fellrath[7], Hans Stricker[8], Alberto Pagnamenta[9], Sebastian Ott[10], Silvia Ulrich[11], Sandor Györik[12], Jérôme Pasquier[13] and John-David Aubert[1,2,14]

- Prospective, multicentre, observational study
- Patients with acute pulmonary embolism from 11 centres in Switzerland from March 2009 to November 2016
- Screening for possible CTEPH was performed at 6, 12 and 24 months using a stepwise algorithm that included
  - a dyspnoea phone-based survey
  - transthoracic echocardiography
  - right heart catheterisation
  - and radiological confirmation of CTEPH

Coquoz N, et al. Eur Respir J 2018; 51: 1702505

CTEPH incidence after acute PE



*TTE: transthoracic echocardiogramm

Coquoz N, et al. Eur Respir J 2018; 51: 1702505

CTEPH is a rare complication of acute PE

Out of 1699 patients with acute PE 508 patients were assessed for CTEPH screening over 2 years

- CTEPH incidence following pulmonary embolism was 3.7 per 1000 patient-years
- with a 2-year cumulative incidence of 0.79%
- The Swiss pulmonary hypertension registry consulted in December 2016 did not report additional CTEPH cases in these patients.
- The survey yielded 100% sensitivity and 81.6% specificity.
- The second step echocardiography in newly dyspnoeic patients showed a negative predictive value of 100%.

	Patient			
	1	2	3	4
mPAP mmHg	25	25	31	27
PAWP mmHg	10	7	10	13
mRAP mmHg	10	2	10	12
PVR dyn·sec·cm^{-5}	317	360	232	151
CO L·min^{-1}	3.79	3.99	7.24	7.50
CI L·min^{-1}·m^{-2}	1.80	2.40	3.89	3.00
BMI kg·m^{-2}	28.2	25.2	26.0	52.7

Coquoz N, et al. Eur Respir J 2018; 51: 1702505

CTEPH is a rare complication of acute PE
Meta-analysis

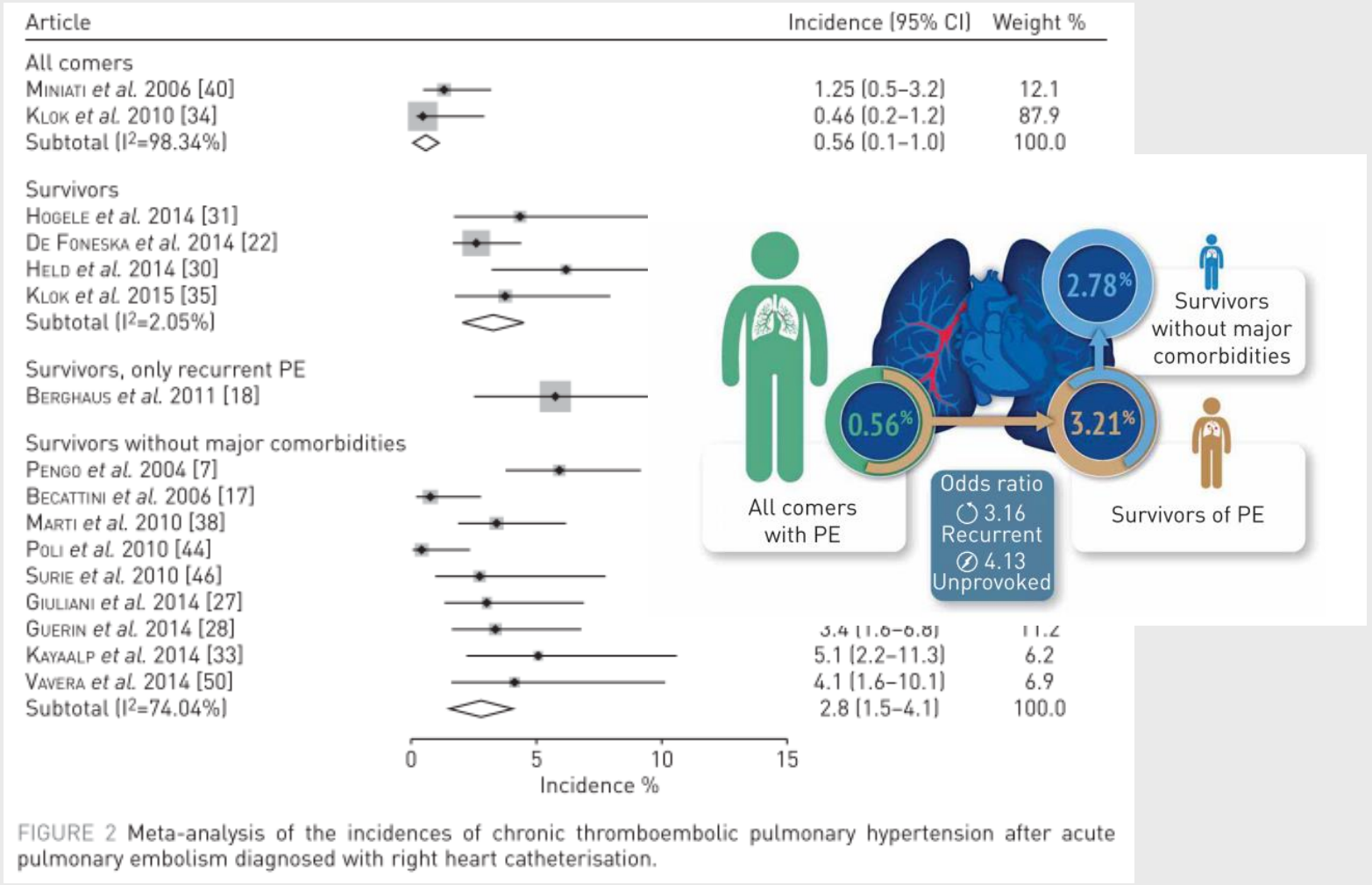


FIGURE 2 Meta-analysis of the incidences of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism diagnosed with right heart catheterisation.

Ende-Verhaar Y, et al. Eur Respir J 2017; 49: 1601792

Thrombolytic therapy does not prevent CTEPH

Impact of Thrombolytic Therapy on the Long-Term Outcome of Intermediate-Risk Pulmonary Embolism

Stavros V. Konstantinides, MD, PhD,[a,b] Eric Vicaut, MD, PhD,[c] Thierry Danays, MD,[d] Cecilia Becattini, MD,[e] Laurent Bertoletti, MD, PhD,[f] Jan Beyer-Westendorf, MD,[g] Helene Bouvaist, MD,[h] Francis Couturaud, MD, PH Claudia Dellas, MD,[j] Daniel Duerschmied, MD,[k] Klaus Empen, MD,[l] Emile Ferrari, MD,[m] Nazzareno Galiè, MD

- PEITHO trial = randomized comparison of thrombolysis with tenecteplase versus placebo in normotensive patients with acute PE, RV dysfunction on imaging, and a positive cardiac troponin test result. Both treatment arms received standard anticoagulation.
- Long-term (median 37.8 months) survival was assessed
- Overall mortality rates were 20.3% and 18.0%, respectively (NS).
- Between day 30 and long-term follow-up, 65 deaths occurred in the thrombolysis arm and 53 occurred in the placebo arm.
- At follow-up, persistent dyspnea (mostly mild) or functional limitation was reported by 36.0% versus 30.1% of the patients (NS).
- Echocardiography did not reveal significant differences in residual pulmonary hypertension or RV dysfunction.
- CTEPH was confirmed in 4 (2.1%) versus 6 (3.2%) cases (NS).

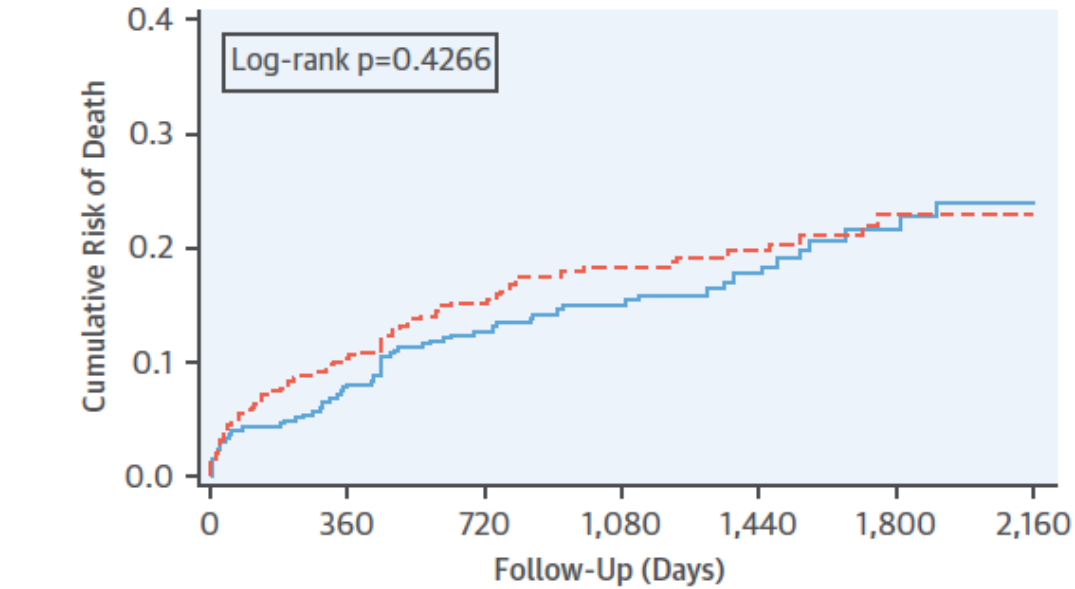
Konstantinides S et al. J Am Coll Cardiol 2017; 69:1536-44

Thrombolytic therapy does not prevent CTEPH

Impact of Thrombolytic Therapy on the Long-Term Outcome of Intermediate-Risk Pulmonary Embolism

Stavros V. Konstantinides, MD, PhD,[a,b] Eric Vicaut, MD, PhD,[c] Thierry Danays, MD,[d] Cecilia Becattini, MD,[e] Laurent Bertoletti, MD, PhD,[f] Jan Beyer-Westendorf, MD,[g] Helene Bouvaist, MD,[h] Francis Couturaud, MD, PH Claudia Dellas, MD,[j] Daniel Duerschmied, MD,[k] Klaus Empen, MD,[l] Emile Ferrari, MD,[m] Nazzareno Galiè, MD

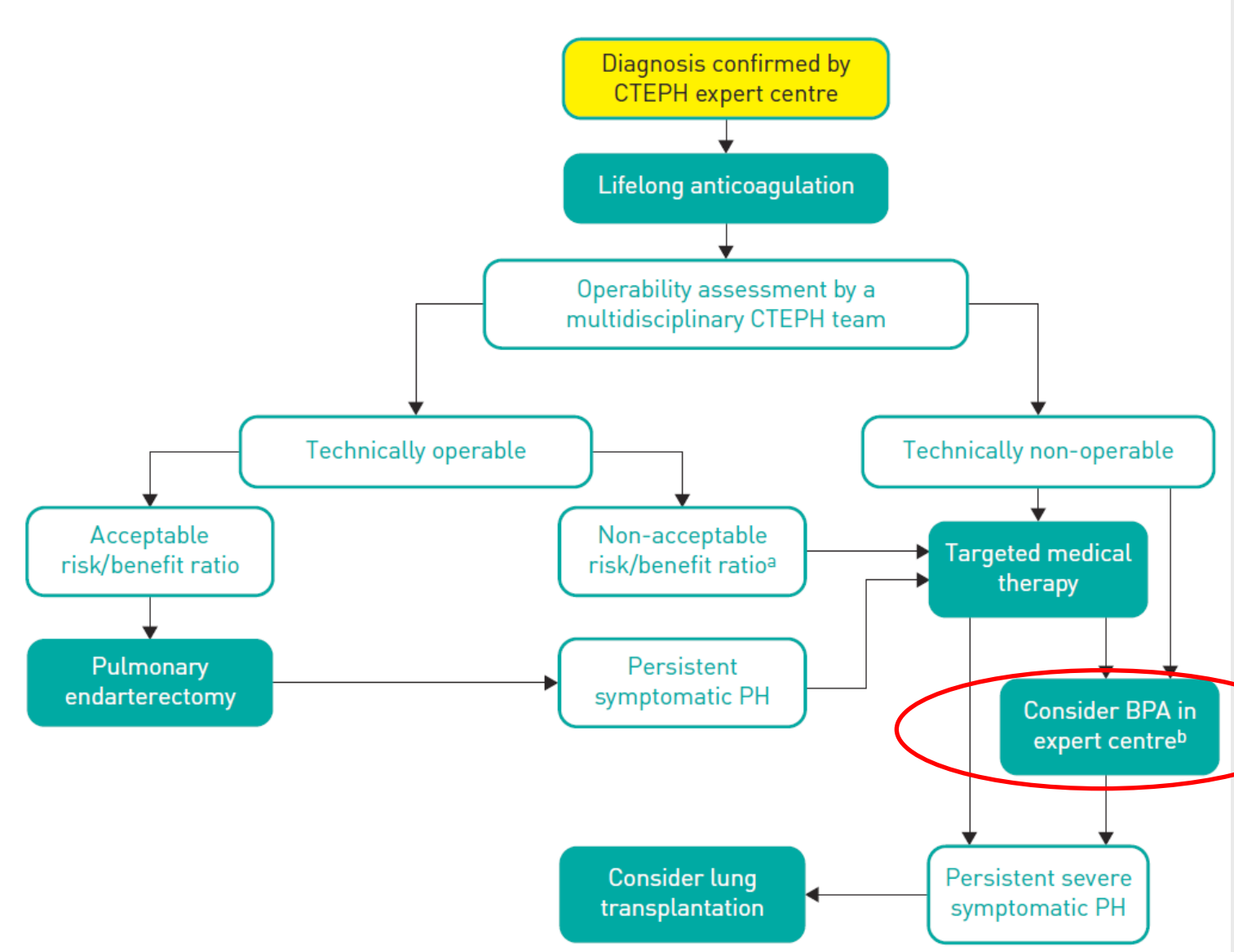
CENTRAL ILLUSTRATION Thrombolysis for Pulmonary Embolism: Kaplan-Meier Survival Curves of Patients Randomized to Tenecteplase Compared With Placebo



Konstantinides, S.V. et al. J Am Coll Cardiol. 2017;69(12):1536–44.

Konstantinides S et al. J Am Coll Cardiol 2017; 69:1536-44

CTEPH Treatment Algorithm



BPA= balloon pulmonary angioplasty

Galiè et al. Eur Heart J 2016; Eur Respir J 2015

The largest European experience of balloon pulmonary angioplasty for CTEPH

- Description of all consecutive patients with inoperable CTEPH who underwent BPA at the French Reference Centre for Pulmonary Hypertension.
- All cases were discussed in a multidisciplinary meeting (experienced surgeons for pulmonary endarterectomy, interventional radiologists/cardiologists, radiologists experienced in pulmonary vascular imaging and pulmonologists with expertise in PH).
- 154 patients had a complete evaluation after a median duration of 6.1 months after the first session.

BPA for inoperable CTEPH

- Overall, there was a significant improvement in
  - WHO functional class
  - 6-min walk distance (mean change, +45 m)
  - and a significant decrease in mPAP by 26% and PVR by 43%
- The percentage decrease of mPAP and PVR (pulmonary vascular restistance) were 22% and 37% in the early period versus 30% and 49% in the recent period, respectively ($p<0.005$).
- The main complications included lung injury which occurred in 9.1% of 1006 sessions (10.4% in the early period versus 1.8% in the recent period, $p<0.001$) and hemoptysis (7.1%).
- Three-year survival was 95.1%.
- Safety and efficacy improve over time, underscoring the unavoidable learning curve period for this complex interventional procedure
- Long-term results and the respective roles of medical therapy and BPA are currently evaluated in a prospective, multicenter study comparing medical therapy with guanylate cyclase stimulator riociguat versus BPA in inoperable CTEPH (RACE study, NCT 02634203).

Brenot P, et al. American Thoracic Society Conference; San Diego 23 May 2018

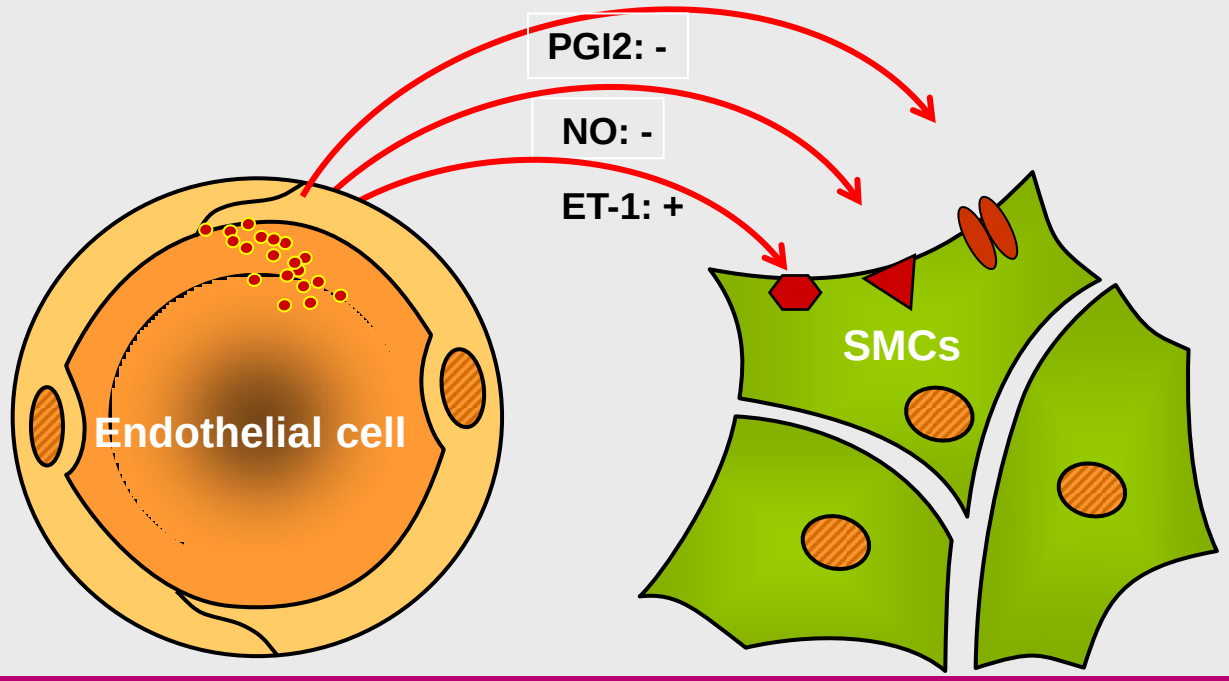
Pulmonary Arterial Hypertension

State of the Art

- Pulmonary hypertension is another fast-moving field of cardiopulmonary medicine
- ESC/ERS Guidelines have been released in 2015
- Novel information have been produced in the last year

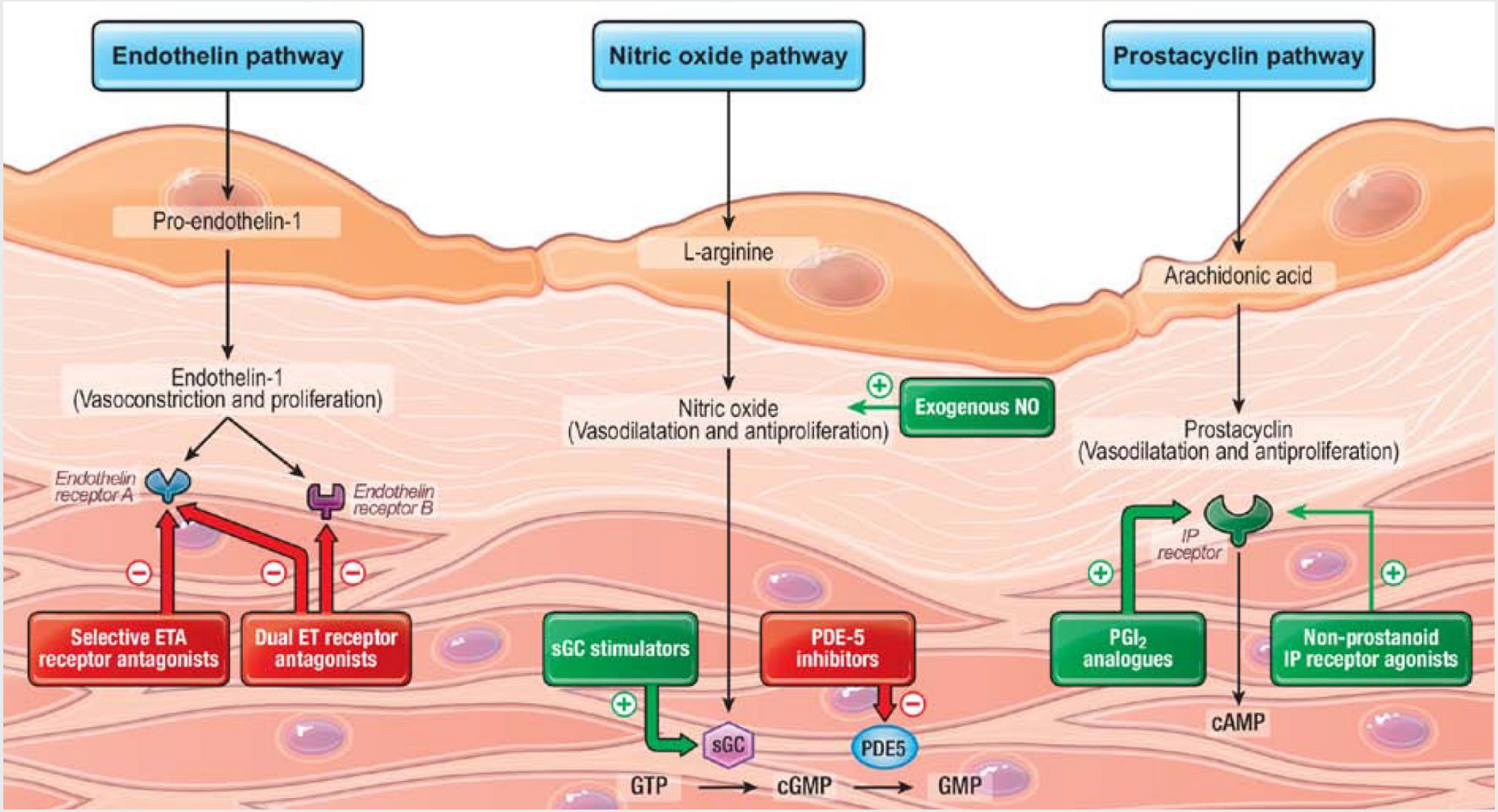
Pulmonary arterial hypertension: a rare, but not an orphan, disease

- Rare: prevalence 15–50/million (incidence 6/million/year)
- Pathophysiology: pulmonary artery endothelial cell dysfunction
- Drugs: 14 agents approved in the last 15 years (orphan drug status)
- Lung/heart–lung transplantation: if refractory to medical therapy



Galiè et al. Eur Heart J 2016; Eur Respir J 2015

Targeting endothelial dysfunction in PAH



Humbert et al. Circulation 2014

Recommendations for evaluation of severity of pulmonary arterial hypertension and clinical response to therapy

Recommendations	Class[a]	Level[b]
It is recommended to evaluate the severity of PAH patients with a panel of data derived from clinical assessment, exercise tests, biochemical markers, echocardiographic and haemodynamic evaluations (Tables 12 and 13).	I	C

Galiè et al. Eur Heart J 2016; Eur Respir J 2015

ESC/ERS Guidelines Risk Assessment

Determinants of prognosis[a] (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[b]	Repeated syncope[c]
WHO functional class	I, II	III	IV
6MWD	>440 m	165–440 m	<165 m
Cardiopulmonary exercise testing	Peak VO_2 >15ml/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 <11 ml/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 (echocardiography, CMR imaging)	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
Haemodynamics	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: 903–975

Validation of the ESC/ERS Tool

- 3 recent studies
  - Kylhammar et al. – Swedish SPHAR registry
  - Hoeper et al. – COMPERA registry
  - Boucly et al. French PH Registry

Kylhammar D, Kjellstrom B, Hjalmarsson C, et al. Eur Heart J 2017
Hoeper MM, Kramer T, Pan Z, et al. Eur Respir J; 50: 1700740
Boucly A, Weatherald J, Savale L, et al. Eur Respir J 2017; 50: 1700889

Recent Publications Addressing Application of ESC/ERS Guidelines for Risk Stratification

COMPERA

ORIGINAL ARTICLE
PULMONARY VASCULAR DISEASES

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

Marius M. Hoeper[1,2], Tim Kramer[3,4], Zixuan Pan[5], Christina A. Eichstaedt[5], Jens Spiesshoefer[4], Nicola Benjamin[5], Karen M. Olsson[1,2], Katrin Meyer[1], Carmine Dario Vizza[6], 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[4,5]

@ERSpublications
The risk stratification strategy proposed by the current European PH guidelines allows accurate survival prediction http://ow.ly/KsWk30c6InK

Cite this article as: Hoeper MM, Kramer T, Pan Z, *et al*. Mortality in pulmonary arterial hypertension: prediction by the 2015 European pulmonary hypertension guidelines risk stratification model. *Eur Respir J* 2017; 50: 1700740 [https://doi.org/10.1183/13993003.00740-2017].

ABSTRACT The 2015 European pulmonary hypertension (PH) guidelines propose a risk stratification strategy for patients with pulmonary arterial hypertension (PAH). Low-, intermediate- and high-risk strata are defined by estimated 1-year mortality risks of <5%, 5–10% and >10%, respectively. This risk assessment strategy awaits validation.

We analysed data from patients with newly diagnosed PAH enrolled into COMPERA (Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension), a European-based PH registry. An abbreviated version of the risk assessment strategy proposed by the European PH guidelines was applied, using the following variables: World Health Organization functional class, 6-min walking distance, brain natriuretic peptide or its N-terminal fragment, right atrial pressure, cardiac index and mixed venous oxygen saturation.

Data from 1588 patients were analysed. Mortality rates were significantly different between the three risk strata (p<0.001 for all comparisons). In the entire patient population, the observed mortality rates 1 year after diagnosis were 2.8% in the low-risk cohort (n=496), 9.9% in the intermediate-risk cohort (n=1116) and 21.2% in the high-risk cohort (n=276). In addition, the risk assessment strategy proved valid at follow-up and in major PAH subgroups.

An abbreviated version of the risk assessment strategy proposed by the current European PH guidelines provides accurate mortality estimates in patients with PAH.

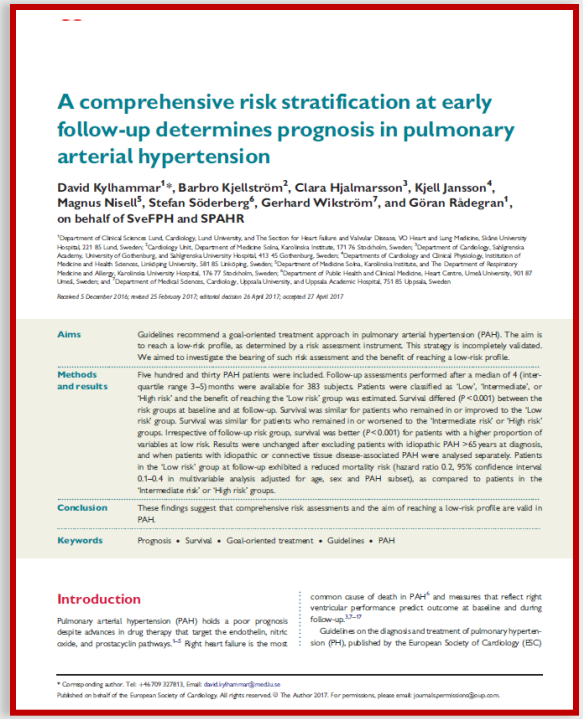
This article has supplementary material available from erj.ersjournals.com

Received: April 10 2017 | Accepted after revision: May 20 2017

Support statement: This work was supported by the German Centre for Lung Research (DZL) and the Deutsche Forschungsgemeinschaft (M.M. Hoeper, HO 1599/2-1). COMPERA is funded by unrestricted grants from Actelion Pharmaceuticals, Bayer and GSK. These companies were not involved in data analysis or the writing of this manuscript. Funding information for this article has been deposited with the Crossref Funder Registry.

Conflict of interest: Disclosures can be found alongside this article at erj.ersjournals.com

SPAHR



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

[1]Department of Clinical Sciences Lund, Cardiology, Lund University, and The Section for Heart Failure and Valvular Disease, VO Heart and Lung Medicine, Skåne University Hospital, 221 85 Lund, Sweden; [2]Cardiology Unit, Department of Medicine Solna, Karolinska Institute, 171 76 Stockholm, Sweden; [3]Department of Cardiology, Sahlgrenska Academy, University of Gothenburg, and Sahlgrenska University Hospital, 413 45 Gothenburg, Sweden; [4]Departments of Cardiology and Clinical Physiology, Institution of Medicine and Health Sciences, Linköping University, 581 85 Linköping, Sweden; [5]Department of Medicine Solna, Karolinska Institute, and The Department of Respiratory Medicine and Allergy, Karolinska University Hospital, 176 77 Stockholm, Sweden; [6]Department of Public Health and Clinical Medicine, Heart Centre, Umeå University, 901 87 Umeå, Sweden; and [7]Department of Medical Sciences, Cardiology, Uppsala University, and Uppsala Academic Hospital, 751 85 Uppsala, Sweden

Received 5 December 2016; revised 25 February 2017; editorial decision 28 April 2017; accepted 27 April 2017

Aims Guidelines recommend a goal-oriented treatment approach in pulmonary arterial hypertension (PAH). The aim is to reach a low-risk profile, as determined by a risk assessment instrument. This strategy is incompletely validated. We aimed to investigate the bearing of such risk assessment and the benefit of reaching a low-risk profile.

Methods and results Five hundred and thirty PAH patients were included. Follow-up assessments performed after a median of 4 (interquartile range 3–5) months were available for 383 subjects. Patients were classified as 'Low', 'Intermediate', or 'High risk' and the benefit of reaching the 'Low risk' group was estimated. Survival differed (P<0.001) between the risk groups at baseline and at follow-up. Survival was similar for patients who remained in or improved to the 'Low risk' group. Survival was similar for patients who remained in or worsened to the 'Intermediate risk' or 'High risk' groups. Irrespective of follow-up risk group, survival was better (P<0.001) for patients with a higher proportion of variables at low risk. Results were unchanged after excluding patients with idiopathic PAH >65 years at diagnosis, and when patients with idiopathic or connective tissue disease-associated PAH were analysed separately. Patients in the 'Low risk' group at follow-up exhibited a reduced mortality risk (hazard ratio 0.2, 95% confidence interval 0.1–0.4 in multivariable analysis adjusted for age, sex and PAH subset), as compared to patients in the 'Intermediate risk' or 'High risk' groups.

Conclusion These findings suggest that comprehensive risk assessments and the aim of reaching a low-risk profile are valid in PAH.

Keywords Prognosis • Survival • Goal-oriented treatment • Guidelines • PAH

Introduction

Pulmonary arterial hypertension (PAH) holds a poor prognosis despite advances in drug therapy that target the endothelin, nitric oxide, and prostacyclin pathways.[1–3] Right heart failure is the most common cause of death in PAH[4] and measures that reflect right ventricular performance predict outcome at baseline and during follow-up.[3,7–17]

Guidelines on the diagnosis and treatment of pulmonary hypertension (PH), published by the European Society of Cardiology (ESC)

* Corresponding author. Tel: +46 709 327813, Email: david.kylhammar@medsi.se

French

ORIGINAL ARTICLE
PULMONARY VASCULAR DISEASES

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]

Affiliations: [1]Université Paris-Sud, Faculté de Médecine, Université Paris-Saclay, Le Kremlin-Bicêtre, France. [2]AP-HP, Service de Pneumologie, Hôpital Bicêtre, Le Kremlin-Bicêtre, France. [3]INSERM UMR_S 999, Hôpital Marie Lannelongue, Le Plessis Robinson, France. [4]Department of Medicine, Division of Respirology, University of Calgary, Calgary, AB, Canada. [5]Université Lyon-1, Hospices Civils de Lyon, Centre de Référence des Maladies Pulmonaires Rares, Centre de Compétences de l'Hypertension Pulmonaire, Hôpital Louis Pradel, Lyon, France. [6]Service de Pneumologie, Hôpital Larrey, Toulouse, France. [7]Service de Cardiologie, Hôpital Haut-Lévêque, Pessac, France. [8]Hôpital Cardiologique de Lille, Centre de Compétences de l'Hypertension Pulmonaire, Lille, France. [9]Hôpital Côte de Nacre, Centre de Compétences Basse Normandie de l'Hypertension Pulmonaire, Université de Caen-Basse Normandie, Caen, France. [10]CHU Nancy, Pôle des Spécialités Médicales, Département de Pneumologie, Vandoeuvre-lès-Nancy, France. [11]Université de Lorraine, INGRES, EA 7298, Vandoeuvre-lès-Nancy, France. [12]CHU de Rennes, Service de Cardiologie et Maladies Vasculaires, INSERM U1099, Rennes, France. [13]Service de Pneumologie, Université de Montpellier; INSERM U1046, UMR 9214, Hôpital Arnaud de Villeneuve, Montpellier, France.

Correspondence: Olivier Sitbon, Service de Pneumologie, Hôpital Bicêtre, 78 rue du Général Leclerc, 94275 Le Kremlin-Bicêtre, France. E-mail: olivier.sitbon@bct.aphp.fr

@ERSpublications
Simplified risk assessment using the number of low-risk criteria predicts prognosis at baseline and follow-up in PAH http://ow.ly/KMsj30cPNbm

Cite this article as: Boucly A, Weatherald J, Savale L, *et al*. Risk assessment, prognosis and guideline implementation in pulmonary arterial hypertension. *Eur Respir J* 2017; 50: 1700889 [https://doi.org/10.1183/13993003.00889-2017].

ABSTRACT Current European guidelines recommend periodic risk assessment for patients with pulmonary arterial hypertension (PAH). The aim of our study was to determine the association between the number of low-risk criteria achieved within 1 year of diagnosis and long-term prognosis.

Incident patients with idiopathic, heritable and drug-induced PAH between 2006 and 2016 were analysed. The number of low-risk criteria present at diagnosis and at first re-evaluation were assessed: World Health Organization (WHO)/New York Heart Association (NYHA) functional class I or II, 6-min walking distance (6MWD) >440 m, right atrial pressure <8 mmHg and cardiac index ≥2.5 L·min^{-1}·m^{-2}.

1017 patients were included (mean age 57 years, 59% female, 75% idiopathic PAH). After a median follow-up of 34 months, 238 (23%) patients had died. Each of the four low-risk criteria independently predicted transplant-free survival at first re-evaluation. The number of low-risk criteria present at diagnosis (p<0.001) and at first re-evaluation (p<0.001) discriminated the risk of death or lung transplantation. In addition, in a subgroup of 603 patients with brain natriuretic peptide (BNP) or N-terminal pro-brain natriuretic peptide (NT-proBNP) measurements, the number of three noninvasive criteria (WHO/NYHA functional class, 6MWD and BNP/NT-proBNP) present at first re-evaluation discriminated prognostic groups (p<0.001).

A simplified risk assessment tool that quantifies the number of low-risk criteria present accurately predicted transplant-free survival in PAH.

Kylhammar D, Kjellstrom B, Hjalmarsson C, et al. Eur Heart J 2017
Hoeper MM, Kramer T, Pan Z, et al. Eur Respir J; 50: 1700740
Boucly A, Weatherald J, Savale L, et al. Eur Respir J 2017; 50: 1700889

French Registry

- French Registry incident patients from 2006 – 2016
- Only included idiopathic, heritable PAH, drug and toxin-induced PAH
- Only included patients with a complete follow-up including RHC, 6MWD, assessment of NYHA/WHO functional class within first year of diagnosis

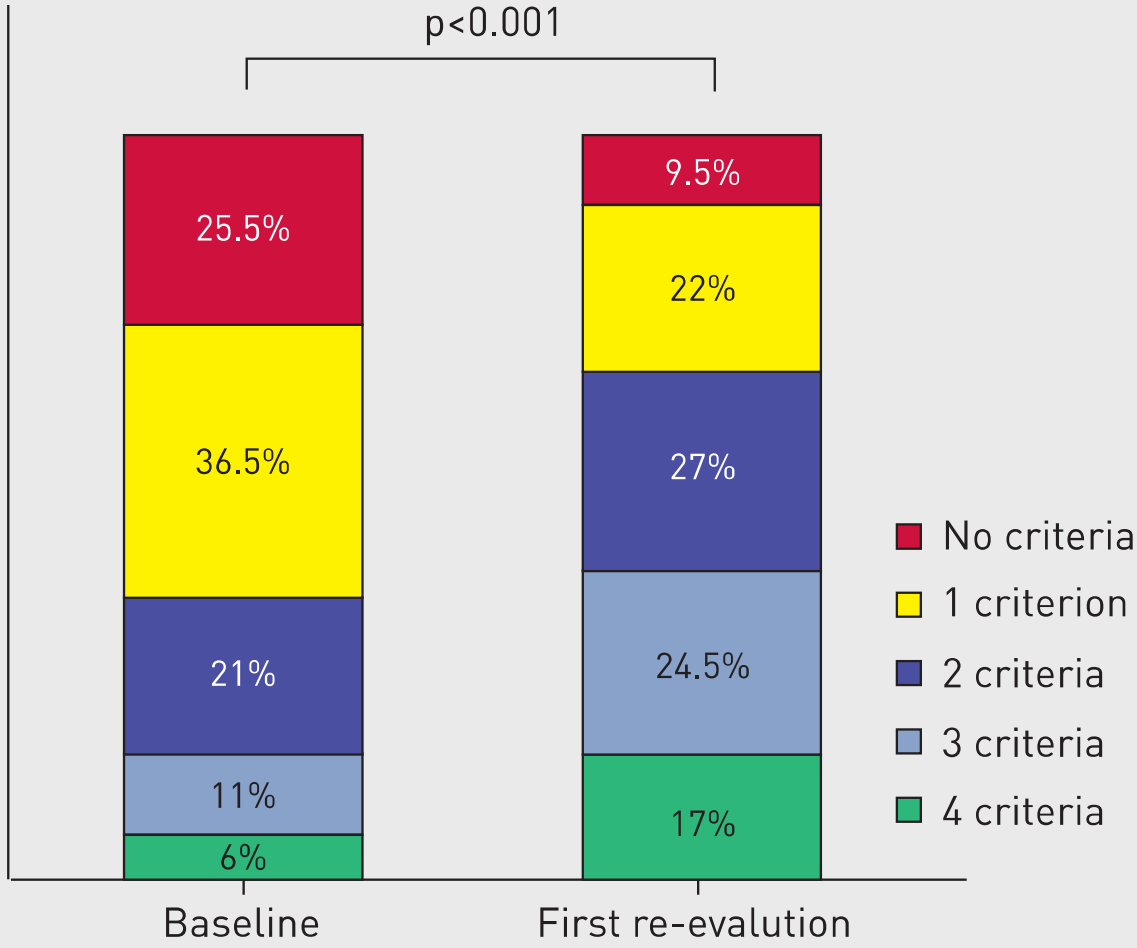
Boucly A, Weatherald J, Savale L, et al. Eur Respir J 2017; 50: 1700889

French Registry

- Methods
  - Calculated number of low-risk criteria present for each patient:
    1. NYHA/WHO functional class I or II
    2. 6MWD > 440 m
    3. Right atrial pressure (RAP) < 8 mmHg
    4. Cardiac index (CI) ≥ 2.5 L/min/m2
  - Exploratory analysis looked at only non-invasive criteria including BNP/NT-proBNP at follow-up

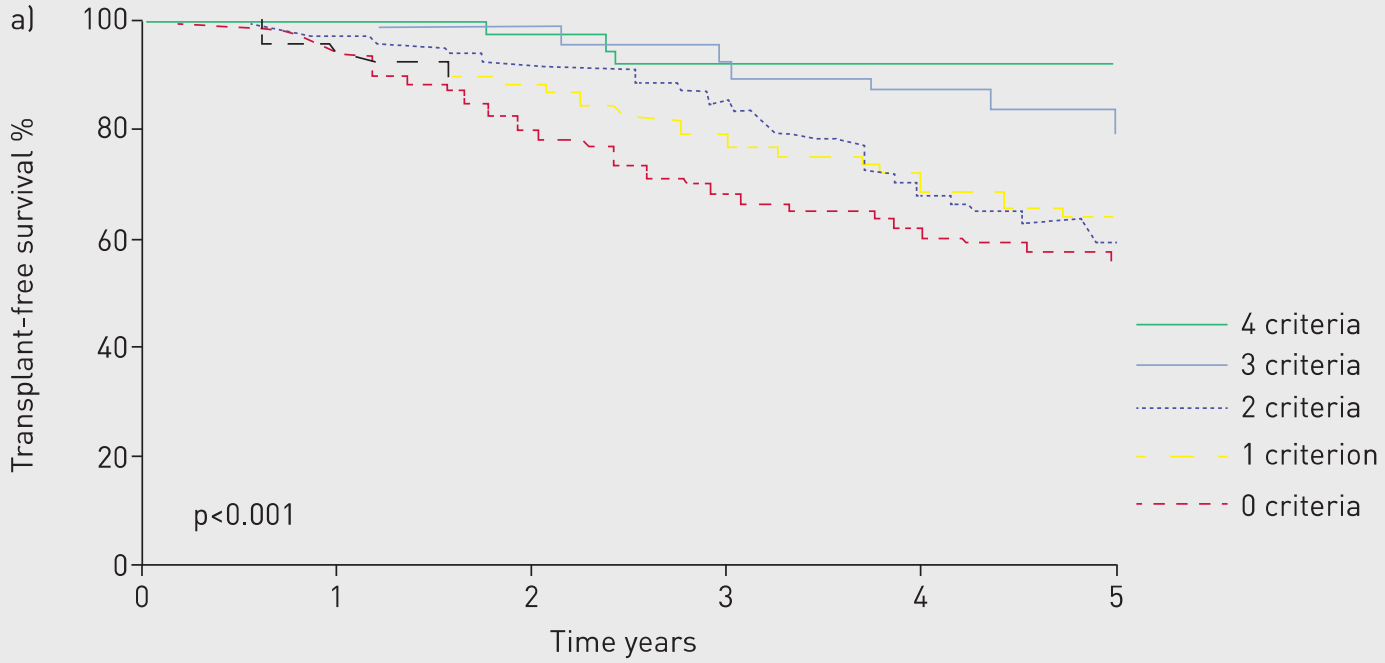
Boucly A, Weatherald J, Savale L, et al. Eur Respir J 2017; 50: 1700889

French Registry



Boucly A, Weatherald J, Savale L, et al. Eur Respir J 2017; 50: 1700889

French Registry (from diagnosis/baseline)

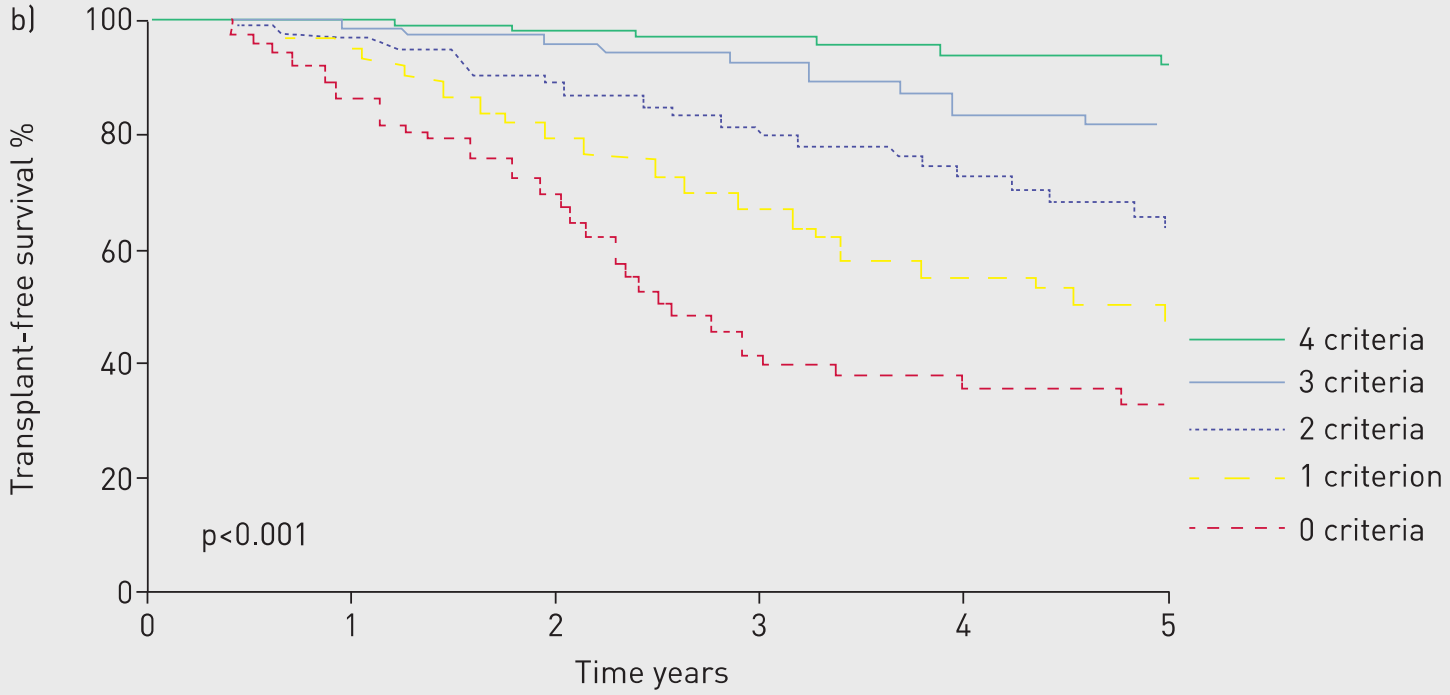


Patients at risk n

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

Boucly A, Weatherald J, Savale L, et al. Eur Respir J 2017; 50: 1700889

French Registry (from first re-evaluation)



Patients at risk n

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

Boucly A, Weatherald J, Savale L, et al. Eur Respir J 2017; 50: 1700889

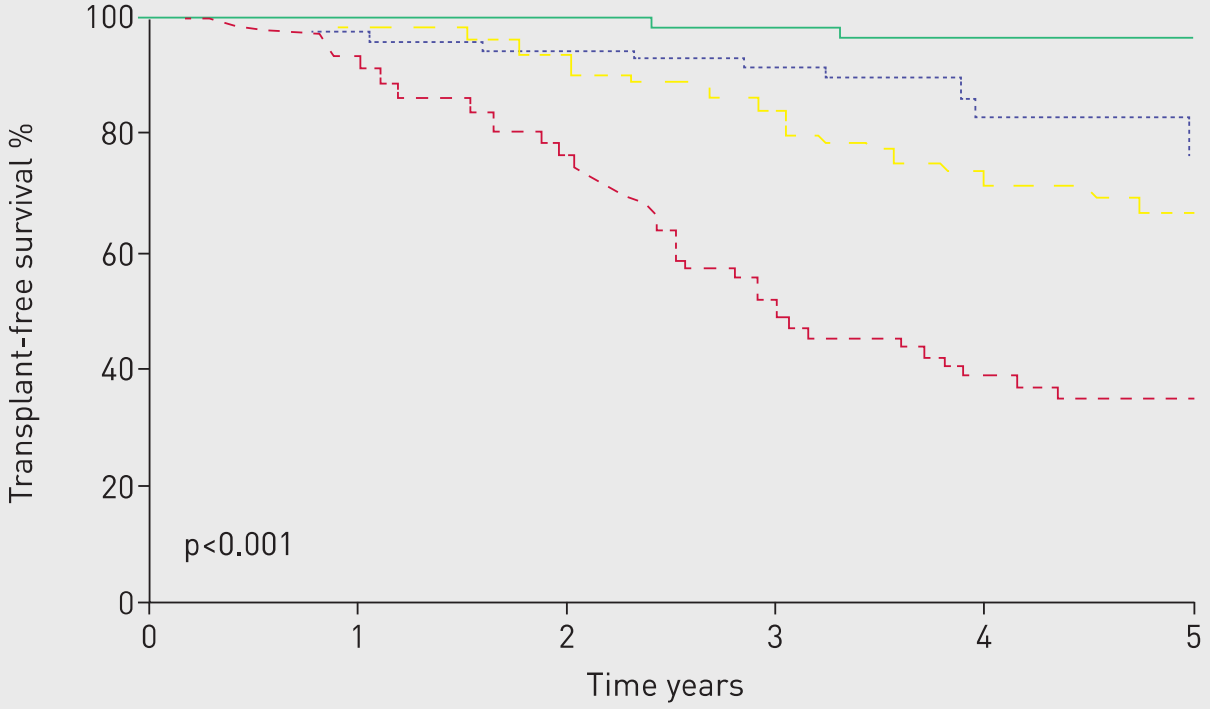
French Registry

	Univariable analysis		Multivariable analysis	
	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
WHO/NYHA FC I–II	0.28 (0.19–0.42)	<0.001	0.47 (0.32–0.71)	<0.001
6-min walking distance >440 m	0.17 (0.09–0.31)	<0.001	0.32 (0.17–0.60)	<0.001
BNP <50 ng·L^{-1} or NT-proBNP <300 ng·mL^{-1}	0.21 (0.13–0.34)	<0.001	0.31 (0.19–0.52)	<0.001
Right atrial pressure <8 mmHg	0.45 (0.31–0.65)	<0.001		
Cardiac index ⩾2.5 L·min^{-1}·m^{-2}	0.44 (0.30–0.65)	<0.001		

WHO: World Health Organization; NYHA: New York Heart Association; FC: functional class.

Boucly A, Weatherald J, Savale L, et al. Eur Respir J 2017; 50: 1700889

French Registry



1. **WHO FC I or II**
2. **6MWD > 440m**
3. **NT-proBNP<300 or BNP < 50**

Patients at risk n						
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

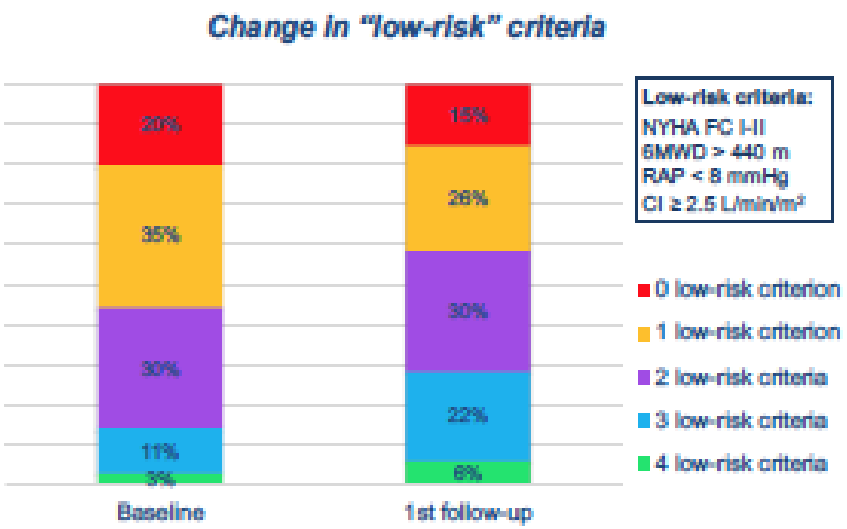
Boucly A, Weatherald J, Savale L, et al. Eur Respir J 2017; 50: 1700889

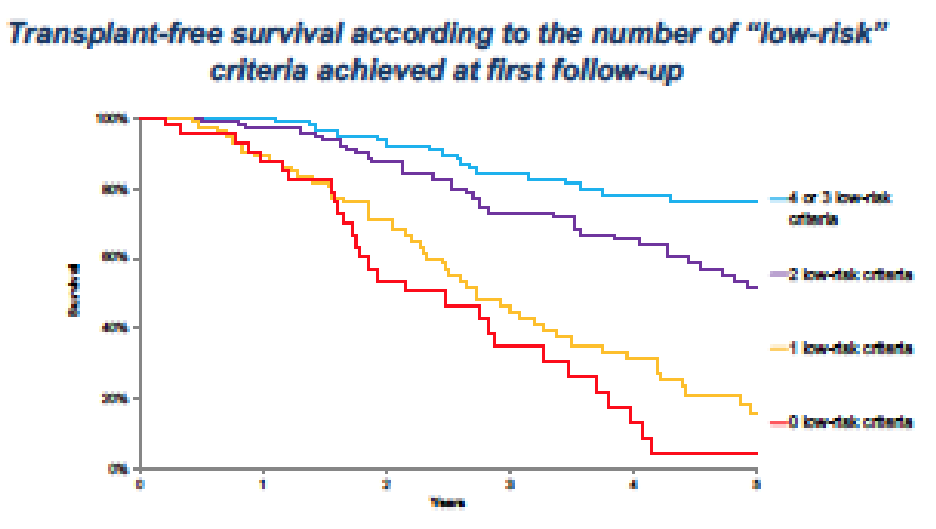
Recent validation of the ESC/ERS Risk Tool

	Swedish[1]	COMPERA[2]	French[3]
Number of patients at Baseline	530	1588	1017
Number of patients at Follow-up	383	1094	1017
Associated-PAH Included	Yes	Yes	No
Definition of Low-Risk	Average Score <1.5	Average Score < 1.5	3-4 of 4 low-risk criteria
1-year mortality % by Risk Group	1/7/26	2.8/9.9/21.2	1/NA/13-30
% Low-Risk at Baseline	23%	12.3%	17%
% Low-Risk at Follow-up	29%	24%	41.5%
Non-invasive Assessment	No	No	Yes
Initial Combination Therapy	12%	17%	50%
Monotherapy	86%	83%	50%

1. Kylhammar D et al. Eur Heart J 2017
2. Hoeper M et al. Eur Respir J 2017
3. Boucly A et al. Eur Respir J 2017

Recent validation of the ESC/ERS Risk Tool in patients wih systemic sclerosis-associated PAH



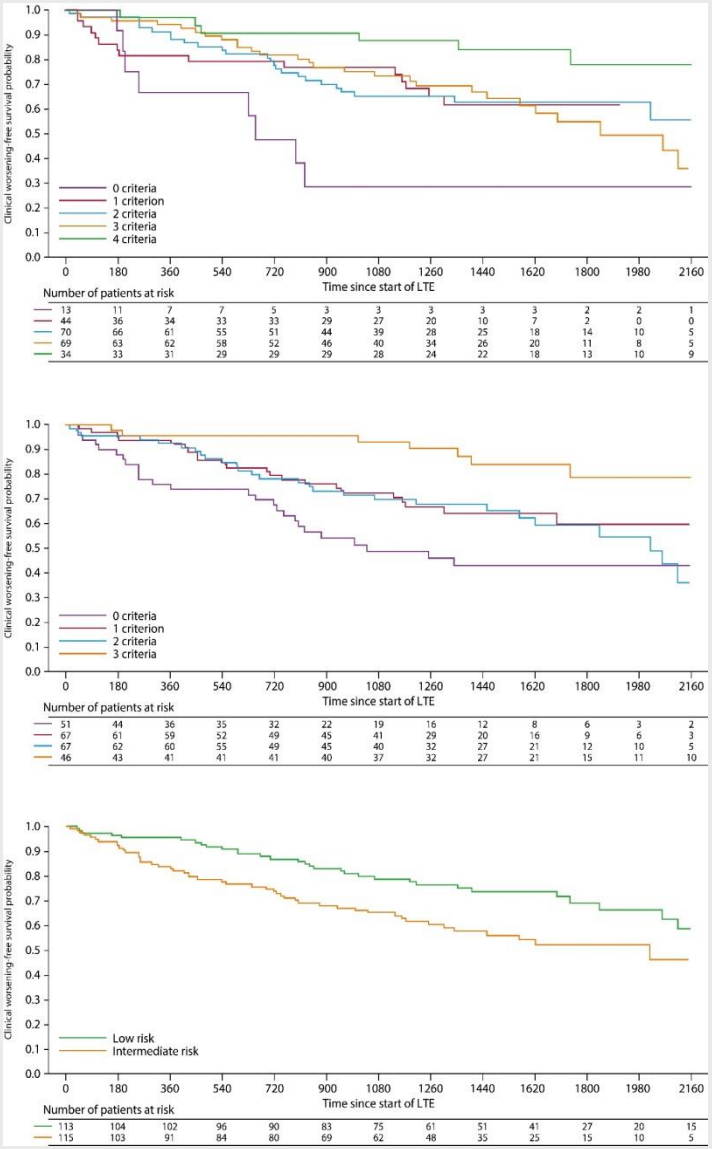


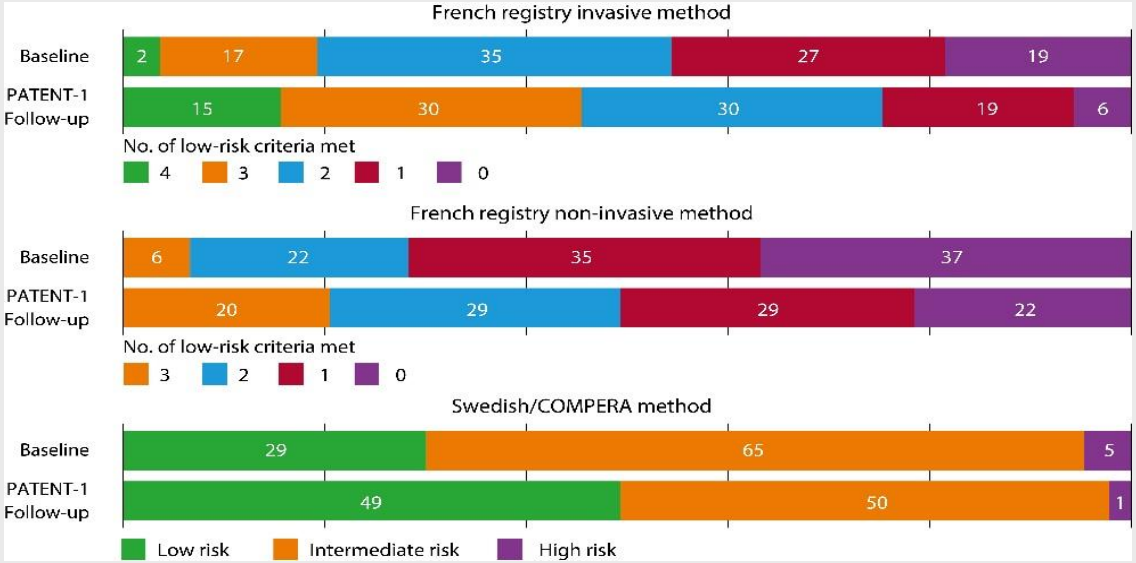
Boucly et al. American Thoracic Society Conference; San Diego 20 May 2018

ESC/ERS Risk Assessment Tool

- The ESC/ERS Risk assessment tool is a simple and easy way to estimate short and long-term risk of death in incident PAH patients.
- Risk assessment after starting initial treatment discriminated prognosis better than baseline risk assessment in all 3 recent European studies.
- The tool can be applied by assigning a value of 1, 2, or 3 to each available variable and calculating the average score OR by calculating the number of criteria in the low-risk zone.
- A simple, non-invasive version using only 3 variables (NYHA/WHO FC, 6MWD, and BNP/NT-proBNP) accurately identifies a truly low-risk group.
- Had not yet been validated in a prevalent cohorts (> 1 year from diagnosis).

Recent validation of the ESC/ERS Risk Tool in a prevalent population treated with riociguat (PATENT)





Humbert et al. American Thoracic Society Conference; San Diego 20 May 2018

Pulmonary hypertension in systemic sclerosis: different phenotypes

David Launay[1,2,3,4], Vincent Sobanski[1,2,3,4], Eric Hachulla[1,2,3,4] and Marc Humbert[5,6,7]

1. Pulmonary arterial hypertension
1.1 Idiopathic
1.2 Heritable
1.2.1 BMPR2 mutation
1.2.2 Other mutations
1.3 Drugs and toxins induced
1.4 Associated with:
1.4.1 Connective tissue disease
1.4.2 Human immunodeficiency virus (HIV) infection
1.4.3 Portal hypertension
1.4.4 Congenital heart disease (Table 6)
1.4.5 Schistosomiasis
1'. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis
1'.1 Idiopathic
1'.2 Heritable
1'.2.1 EIF2AK4 mutation
1'.2.2 Other mutations
1'.3 Drugs, toxins and radiation induced
1'.4 Associated with:
1'.4.1 Connective tissue disease
1'.4.2 HIV infection
1''. Persistent pulmonary hypertension of the newborn

2. Pulmonary hypertension due to left heart disease
2.1 Left ventricular systolic dysfunction
2.2 Left ventricular diastolic dysfunction
2.3 Valvular disease
2.4 Congenital / acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
2.5 Congenital /acquired pulmonary veins stenosis
3. Pulmonary hypertension due to lung diseases and/or hypoxia
3.1 Chronic obstructive pulmonary disease
3.2 Interstitial lung disease
3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4 Sleep-disordered breathing
3.5 Alveolar hypoventilation disorders
3.6 Chronic exposure to high altitude
3.7 Developmental lung diseases (Web Table III)
4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions

Galiè N *et al.* Eur Respir J 2015 & Eur Heart J 2016

Launay et al. Eur Respir Rev 2017; 26:170056

Pulmonary hypertension in systemic sclerosis: different phenotypes

David Launay[1,2,3,4], Vincent Sobanski[1,2,3,4], Eric Hachulla[1,2,3,4] and Marc Humbert[5,6,7]

1. Pulmonary arterial hypertension

- 1.1 Idiopathic
- 1.2 Heritable
  - 1.2.1 BMPR2 mutation
  - 1.2.2 Other mutations
- 1.3 Drugs and toxins induced
- 1.4 Associated with:
  - 1.4.1 Connective tissue disease
  - 1.4.2 Human immunodeficiency virus (HIV) infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease (Table 6)
  - 1.4.5 Schistosomiasis

1'. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis

- 1'.1 Idiopathic
- 1'.2 Heritable
  - 1'.2.1 EIF2AK4 mutation
  - 1'.2.2 Other mutations
- 1'.3 Drugs, toxins and radiation induced
- 1'.4 Associated with:
  - 1'.4.1 Connective tissue disease
  - 1'.4.2 HIV infection

1''. Persistent pulmonary hypertension of the newborn

Post-capillary PH due to left heart disease (group 2)

Pre-capillary PAH (group 1 PAH)

Pre-capillary PH due to ILD (group 3)

PVOD

CTEPH (group 4)

2. Pulmonary hypertension due to left heart disease

- 2.1 Left ventricular systolic dysfunction
- 2.2 Left ventricular diastolic dysfunction
- 2.3 Valvular disease
- 2.4 Congenital / acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
- 2.5 Congenital /acquired pulmonary veins stenosis

3. Pulmonary hypertension due to lung diseases and/or hypoxia

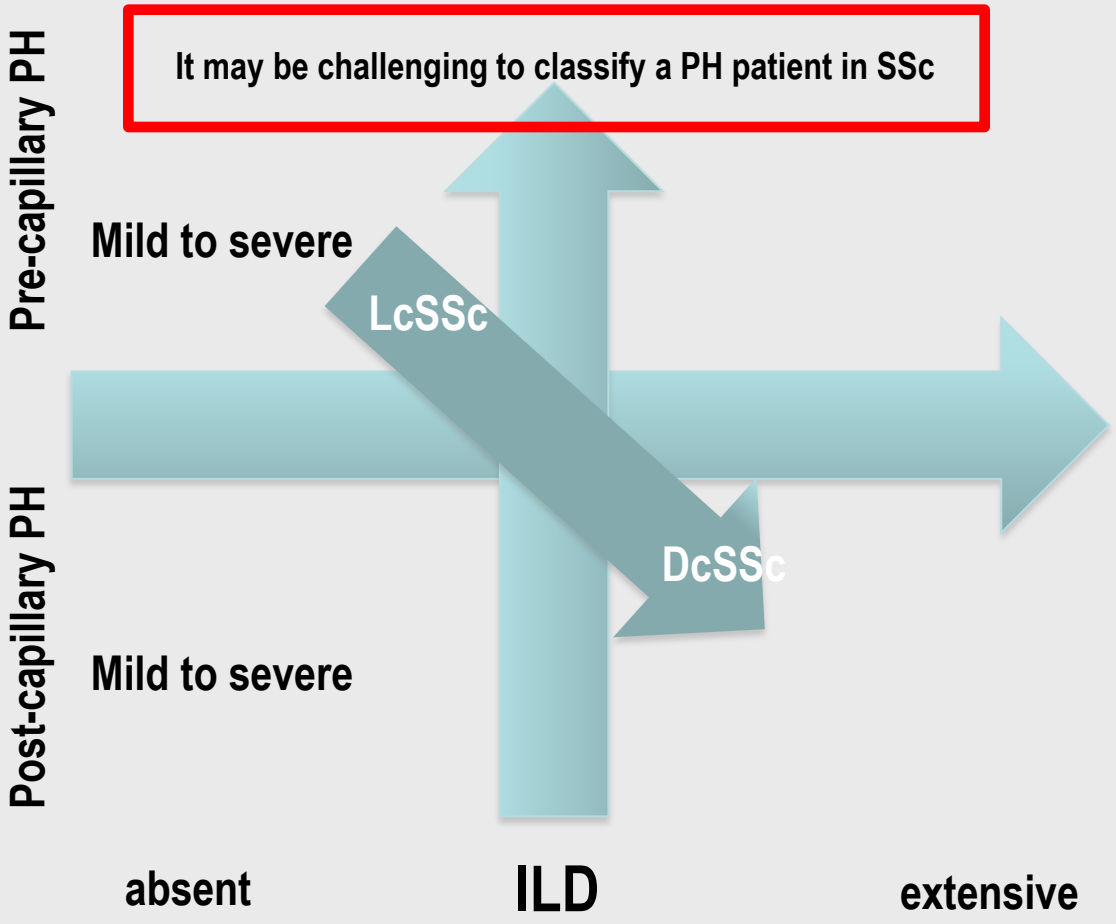
- 3.1 Chronic obstructive pulmonary disease
- 3.2 Interstitial lung disease
- 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
- 3.4 Sleep-disordered breathing
- 3.5 Alveolar hypoventilation disorders
- 3.6 Chronic exposure to high altitude
- 3.7 Developmental lung diseases (Web Table III)

4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions

Galiè N *et al.* Eur Respir J 2015 & Eur Heart J 2016

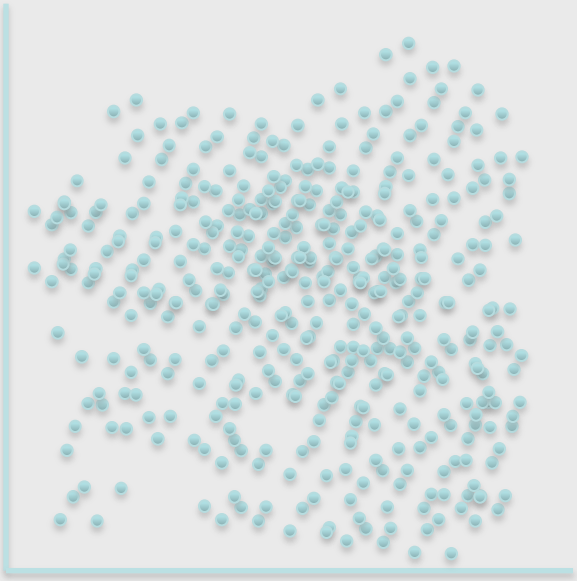
Launay et al. Eur Respir Rev 2017; 26:170056

Different phenotypes of PH in SSc



Launay et al. Eur Respir Rev 2017; 26:170056

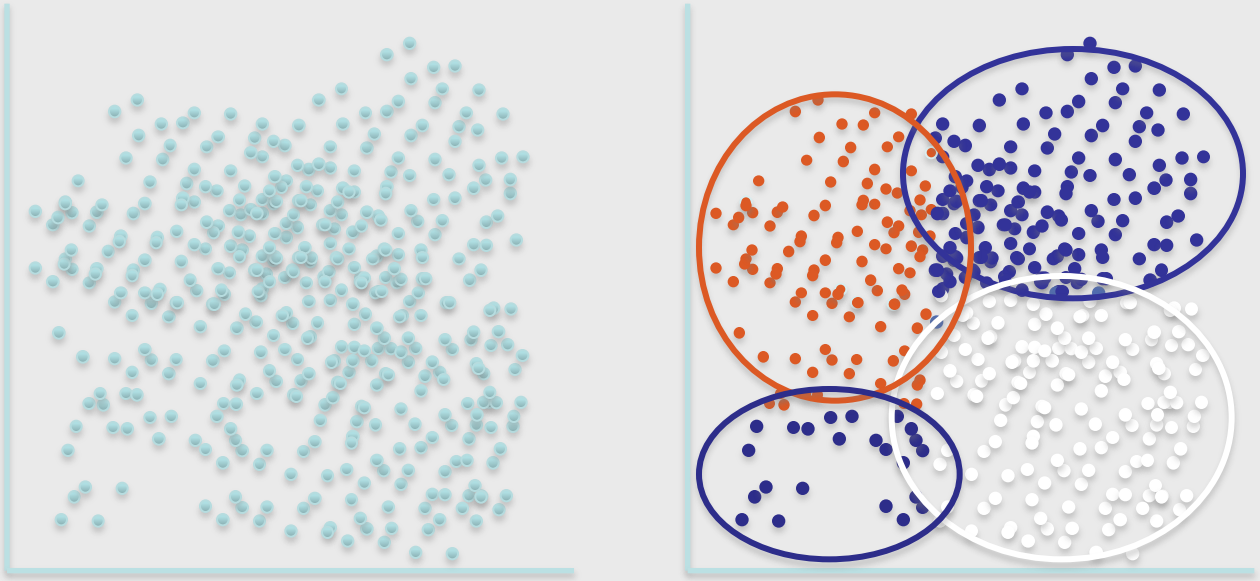
How to define homogeneous PH phenotypes in SSc ? = Cluster analysis



1. Definition of clustering variables
2. The analysis detects homogeneous clusters according to these variables
3. Comparison of the different clusters characteristics

Launay et al. PLoS One; 2018; 13:e0197112

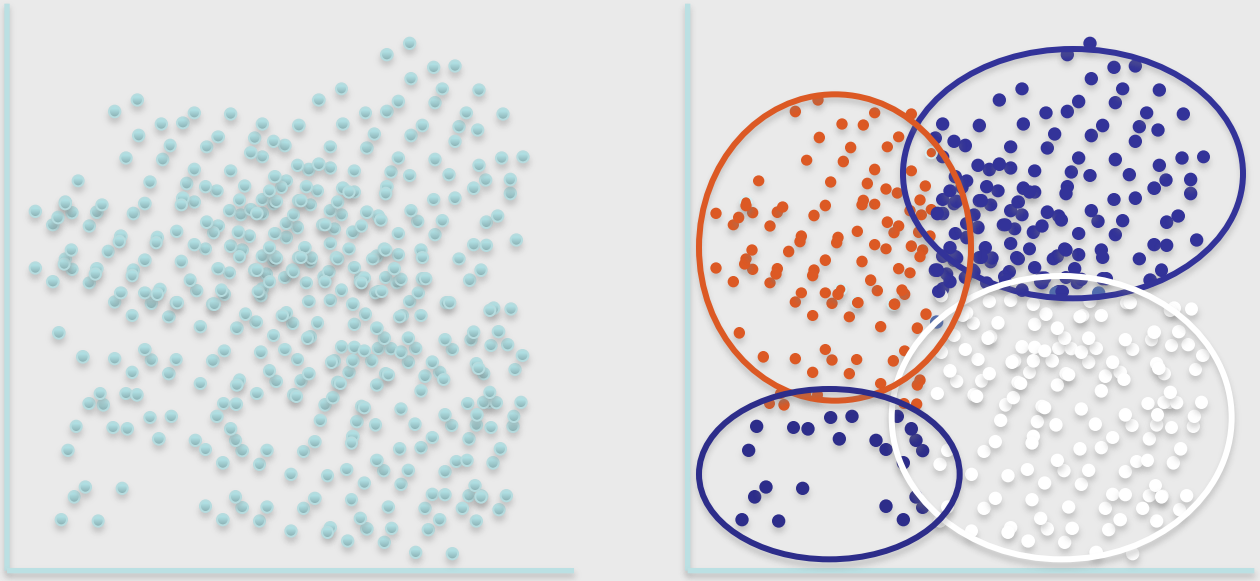
How to define homogeneous PH phenotypes in SSc ? = Cluster analysis



Launay et al. PLoS One; 2018; 13:e0197112

How to define homogeneous PH phenotypes in SSc ? = Cluster analysis

➔ **May contribute to better understanding of the disease and support personalised medicine**



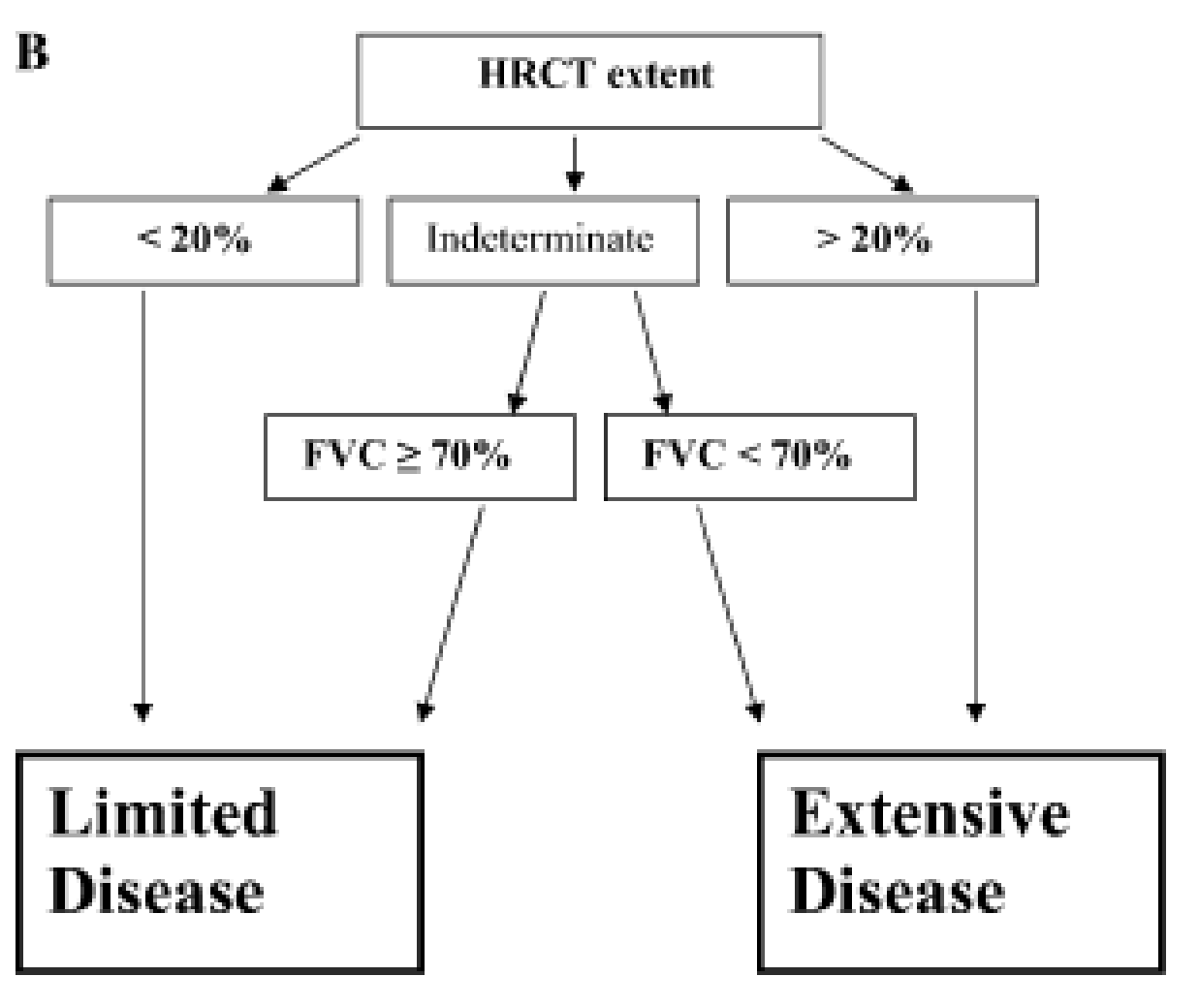
Launay et al. PLoS One; 2018; 13:e0197112

How to define homogeneous PH phenotypes in SSc ? = Cluster analysis

- Collaborative study between the French PH Registry and Johns Hopkins
  Primary objective : cluster analysis to define homogeneous groups of SSc-PH patients
- Secondary objective: analyse survival in the different clusters
- 200 patients studied
  - ACR-EULAR 2013 criteria for SSc
  - Pre-capillary PH at RHC
  - Baseline HRCT of the chest and Lung Function Test (LFTs)
  - CTEPH excluded
- ILD classified as absent/limited/extensive (Goh's staging system)
- Statistical method
  - Cluster analysis : K-means using 4 variables : FVC, DLCO, PVR et presence / extension ILD
  - Survival analysis

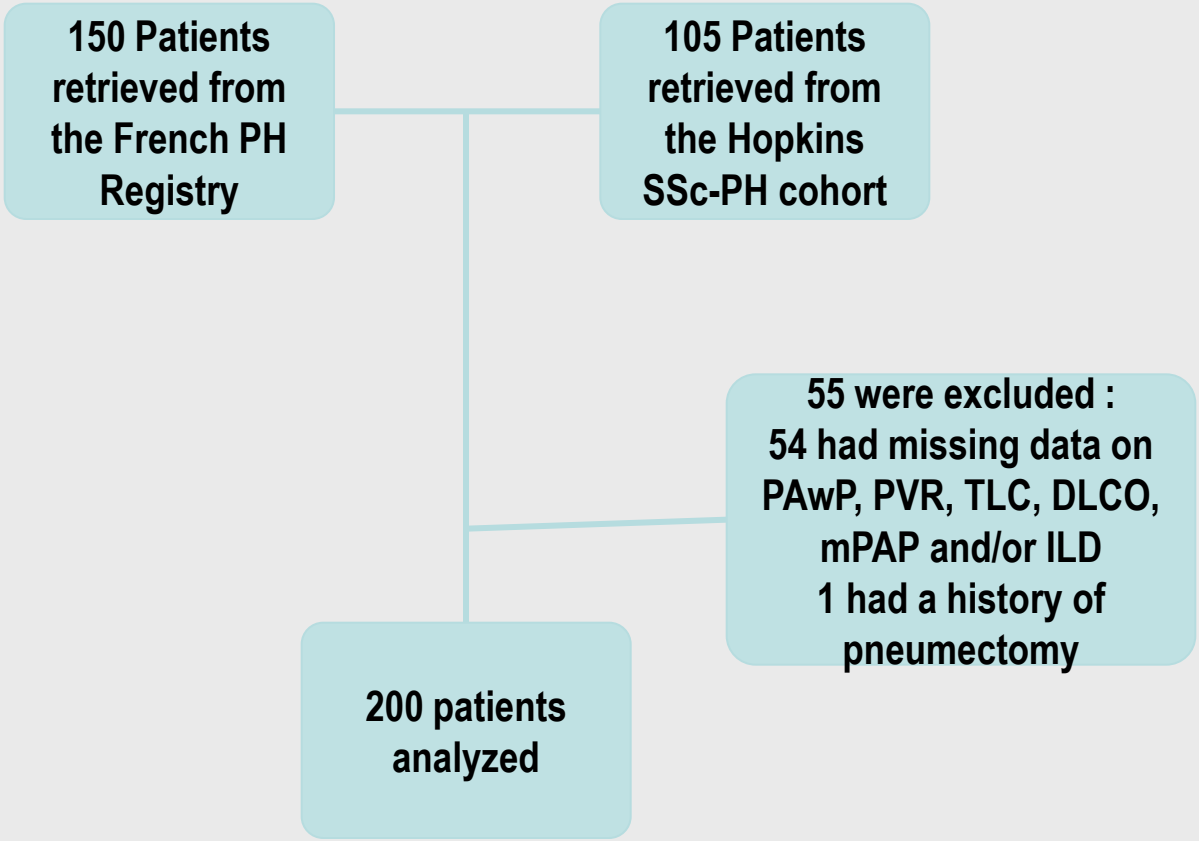
Launay et al. PLoS One; 2018; 13:e0197112

ILD classification (Goh's staging system)



Goh et al. Am J Respir Crit Care Med 2008

Flowchart



Launay et al. PLoS One; 2018; 13:e0197112

Cluster analysis : 4 clusters

- C4 :
  - 29 patients
  - Moderate PH (PVR : 6 ± 2 WU)
  - 100 % no ILD or limited ILD
  - Normal FVC and DLCO : 76±16 %
  - 75 % LcSSc ; 25 % ACA ; 20 % anti-topo 1

moderate PAH with normal DLCO without extensive ILD

- C1 :
  - 94 patients
  - Moderate PH (RVP : 8 ± 3 WU)
  - 98 % no ILD or limited ILD
  - Normal FVC but DLCO : 45±13 %
  - 84 % LcSSc ; 50 % ACA ; 5 % anti-topo 1

moderate PAH with low DLCO without extensive ILD

- C3 :
  - 16 patients
  - Severe PH (PVR : 19 ± 5 WU)
  - 94 % no ILD or limited ILD
  - Normal FVC but DLCO : 37±12 %
  - 81 % LcSSc ; 50 % ACA ; 12 % anti-topo 1

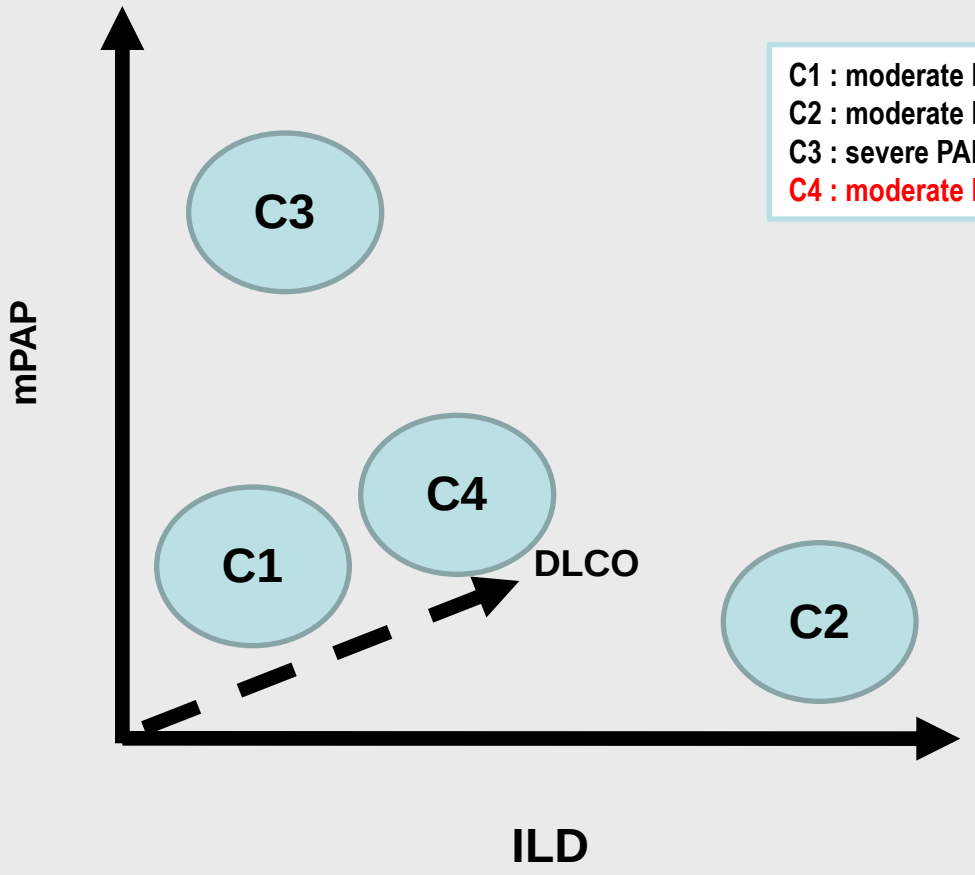
severe PAH with low DLCO without extensive ILD

- C2 :
  - 61 patients
  - Moderate PH (PVR : 6 ± 3 WU)
  - 100 % of extensive ILD
  - FVC : 61 % and DLCO : 37±16 %
  - 46 % DcSSc ; 12 % ACA ; 41 % anti-topo 1

moderate PH due to extensive ILD with low DLCO

Launay et al. PLoS One; 2018; 13:e0197112

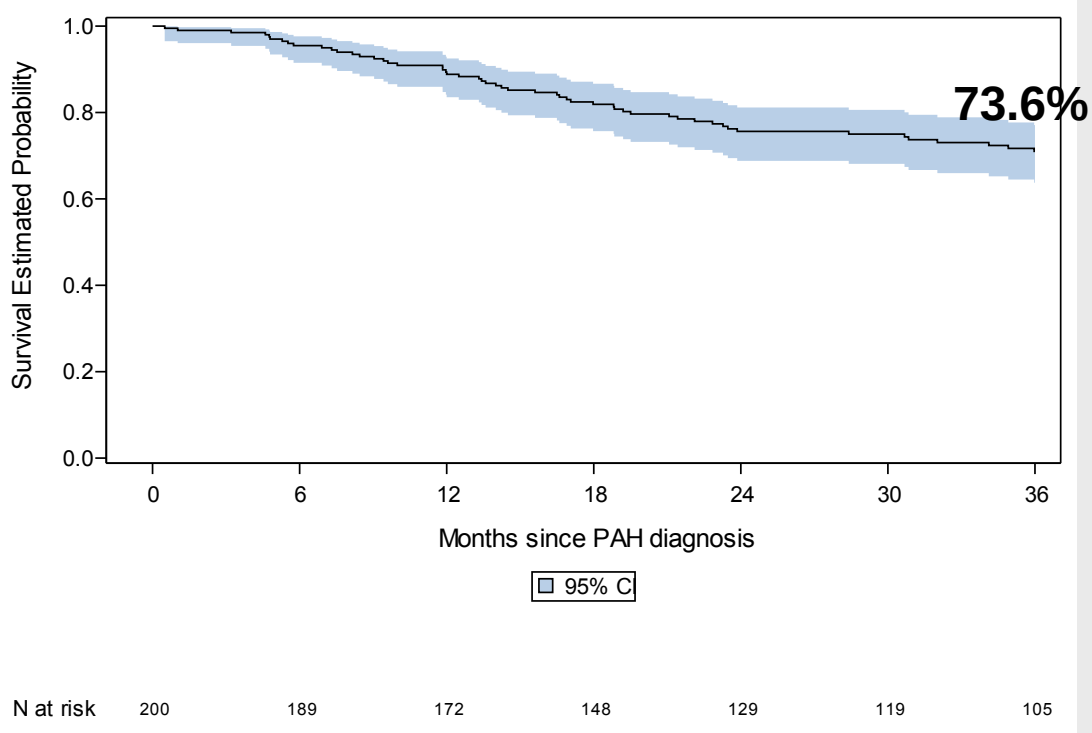
Cluster analysis : 4 clusters



C1 : moderate PAH with low DLCO without extensive ILD
C2 : moderate PH due to extensive ILD with low DLCO
C3 : severe PAH with low DLCO without extensive ILD
C4 : moderate PAH with normal DLCO without extensive ILD

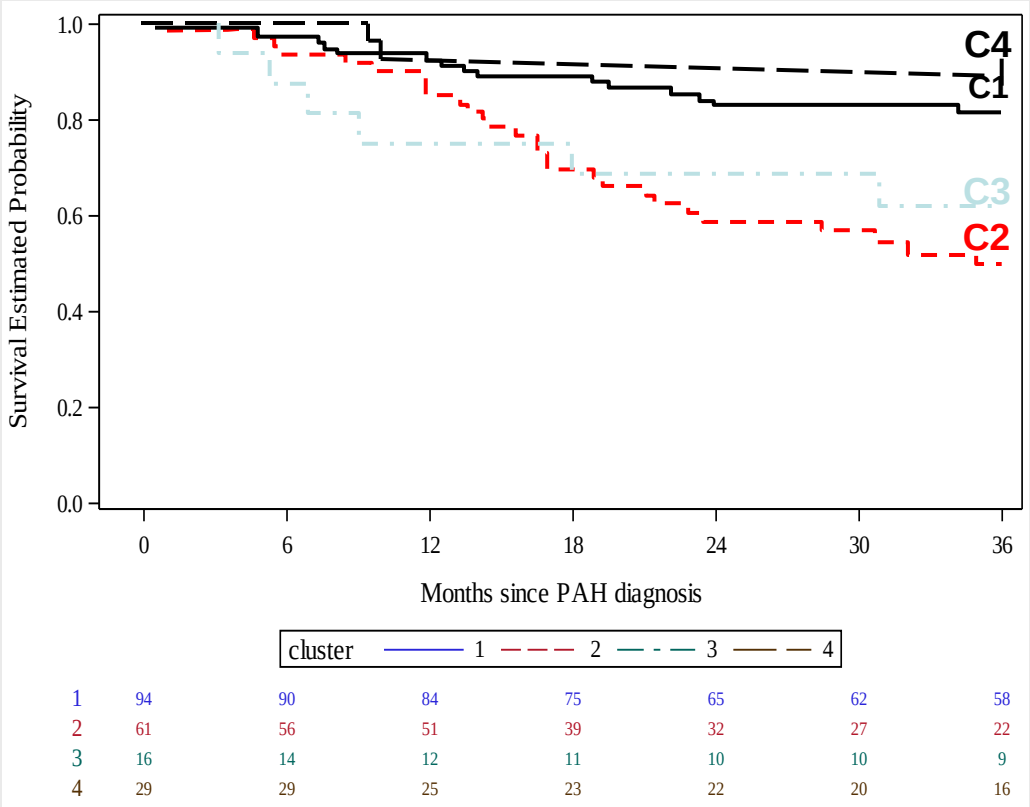
Launay et al. PLoS One; 2018; 13:e0197112

Overall survival



Launay et al. PLoS One; 2018; 13:e0197112

Survival in the 4 clusters



C1 : moderate PAH with low DLCO without extensive ILD
C2 : moderate PH due to extensive ILD with low DLCO
C3 : severe PAH with low DLCO without extensive ILD
C4 : moderate PAH with normal DLCO without extensive ILD

Launay et al. PLoS One; 2018; 13:e0197112

Take home messages

- Four simple SSc-PH clusters can be identified according to hemodynamics severity, extent of ILD and DLCO
- Eligible patients in clusters C2 (group 3 PH with extensive ILD) and C3 (group 1 PH with severe PAH) should be considered for lung transplantation
- Limited ILD has no strong impact on outcomes in SSc-PH

Launay et al. PLoS One; 2018; 13:e0197112

Relevant new aspects

1. Jimenez et al. Eur Respir J 2018; 51:1800445
2. Raskob GE, et al. N Engl J Med 2018; 378:615-624
3. Coquoz N, et al. Eur Respir J 2018; 51: 1702505
4. Ende-Verhaar Y, et al. Eur Respir J 2017; 49: 1601792
5. Konstantinides S et al. J Am Coll Cardiol 2017; 69:1536-44
6. Brenot P, et al. American Thoracic Society Conference; San Diego 23 May 2018
7. Boucly A, et al. Eur Respir J 2017; 50: 1700889
8. Boucly et al. American Thoracic Society Conference; San Diego 20 May 2018
9. Humbert et al. American Thoracic Society Conference; San Diego 20 May 2018
10. Launay et al. PLoS One; 2018; 13:e0197112