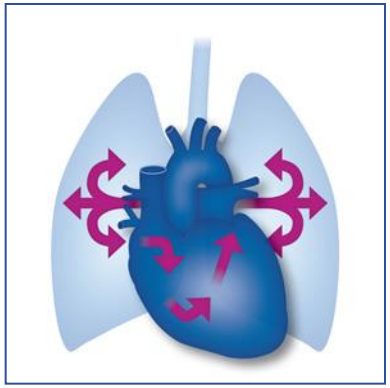
Pneumo Update Europe 2017

9-10 June, Vienna

Pulmonary Vascular Diseases



Marc Humbert, France

Pulmonary Embolism

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 information has been produced in the last year

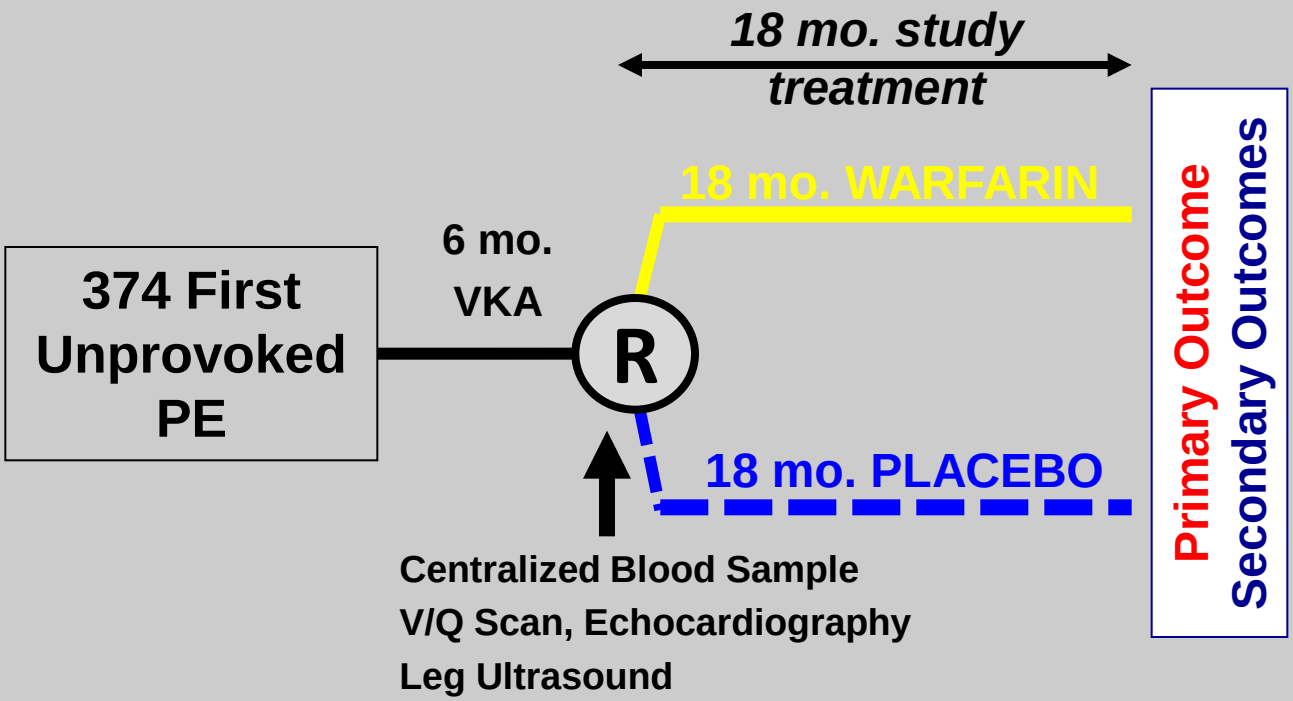
Konstantinides et al. Eur Heart J 2014; 35:3033-80

Original Investigation

Six Months vs Extended Oral Anticoagulation After a First Episode of Pulmonary Embolism

The PADIS-PE Randomized Clinical Trial

Francis Couturaud, MD, PhD; Olivier Sanchez, MD, PhD; Gilles Pernod, MD, PhD; Patrick Mismetti, MD, PhD; Patrick Jego, MD, PhD; Elisabeth Duhamel, MD; Karine Provost, MD; Claire Bal dit Sollier, MB; Emilie Presles, MS; Philippe Castellant, MD; Florence Parent, MD; Pierre-Yves Salaun, MD, PhD; Luc Bressollette, MD, PhD; Michel Nonent, MD, PhD; Philippe Lorillon, PharmD; Philippe Girard, MD; Karine Lacut, MD, PhD; Marie Guégan, MS; Jean-Luc Bosson, MD, PhD; Silvy Laporte, MS, PhD; Christophe Leroyer, MD, PhD; Hervé Décousus, MD; Guy Meyer, MD; Dominique Mottier, MD; for the PADIS-PE Investigators



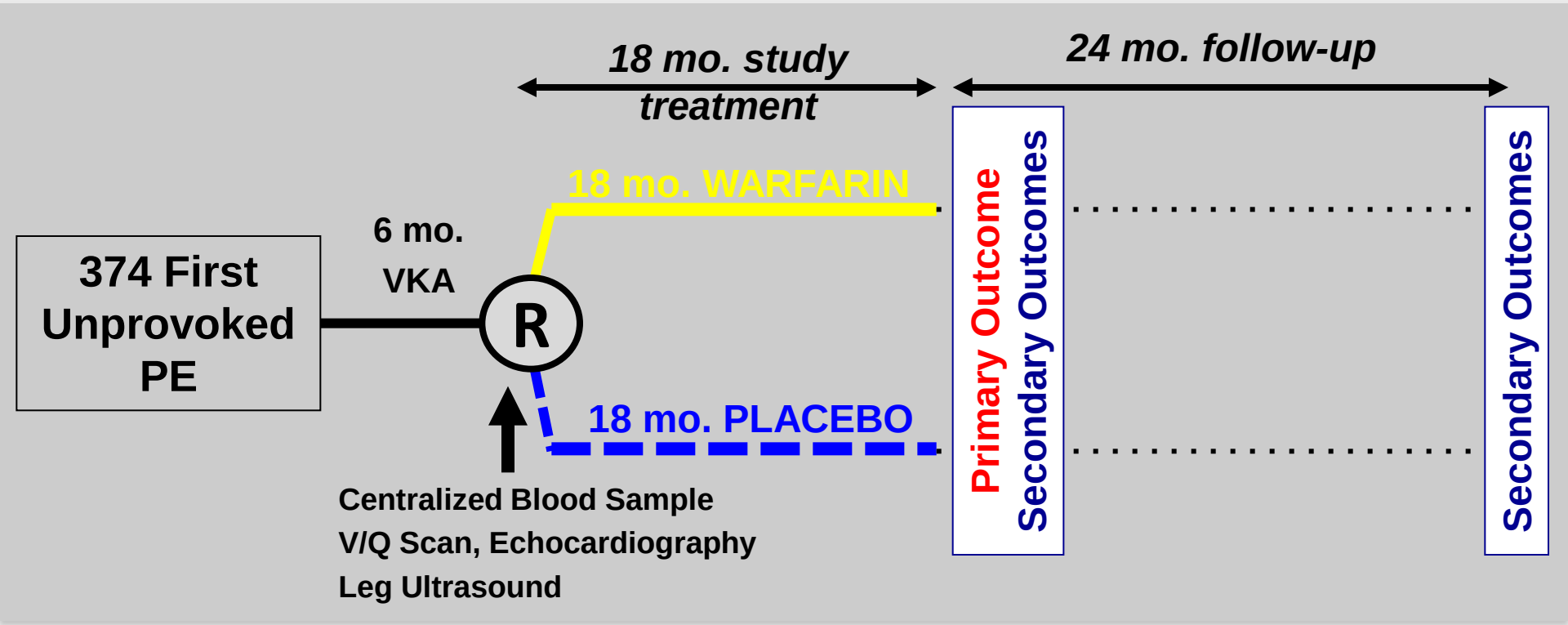
Couturaud F et al. JAMA 2015; 314:31–40

Original Investigation

Six Months vs Extended Oral Anticoagulation After a First Episode of Pulmonary Embolism

The PADIS-PE Randomized Clinical Trial

Francis Couturaud, MD, PhD; Olivier Sanchez, MD, PhD; Gilles Pernod, MD, PhD; Patrick Mismetti, MD, PhD; Patrick Jego, MD, PhD; Elisabeth Duhamel, MD; Karine Provost, MD; Claire Bal dit Sollier, MB; Emilie Presles, MS; Philippe Castellant, MD; Florence Parent, MD; Pierre-Yves Salaun, MD, PhD; Luc Bressollette, MD, PhD; Michel Nonent, MD, PhD; Philippe Lorillon, PharmD; Philippe Girard, MD; Karine Lacut, MD, PhD; Marie Guégan, MS; Jean-Luc Bosson, MD, PhD; Silvy Laporte, MS, PhD; Christophe Leroyer, MD, PhD; Hervé Décousus, MD; Guy Meyer, MD; Dominique Mottier, MD; for the PADIS-PE Investigators



Couturaud F et al. JAMA 2015; 314:31–40

Outcomes

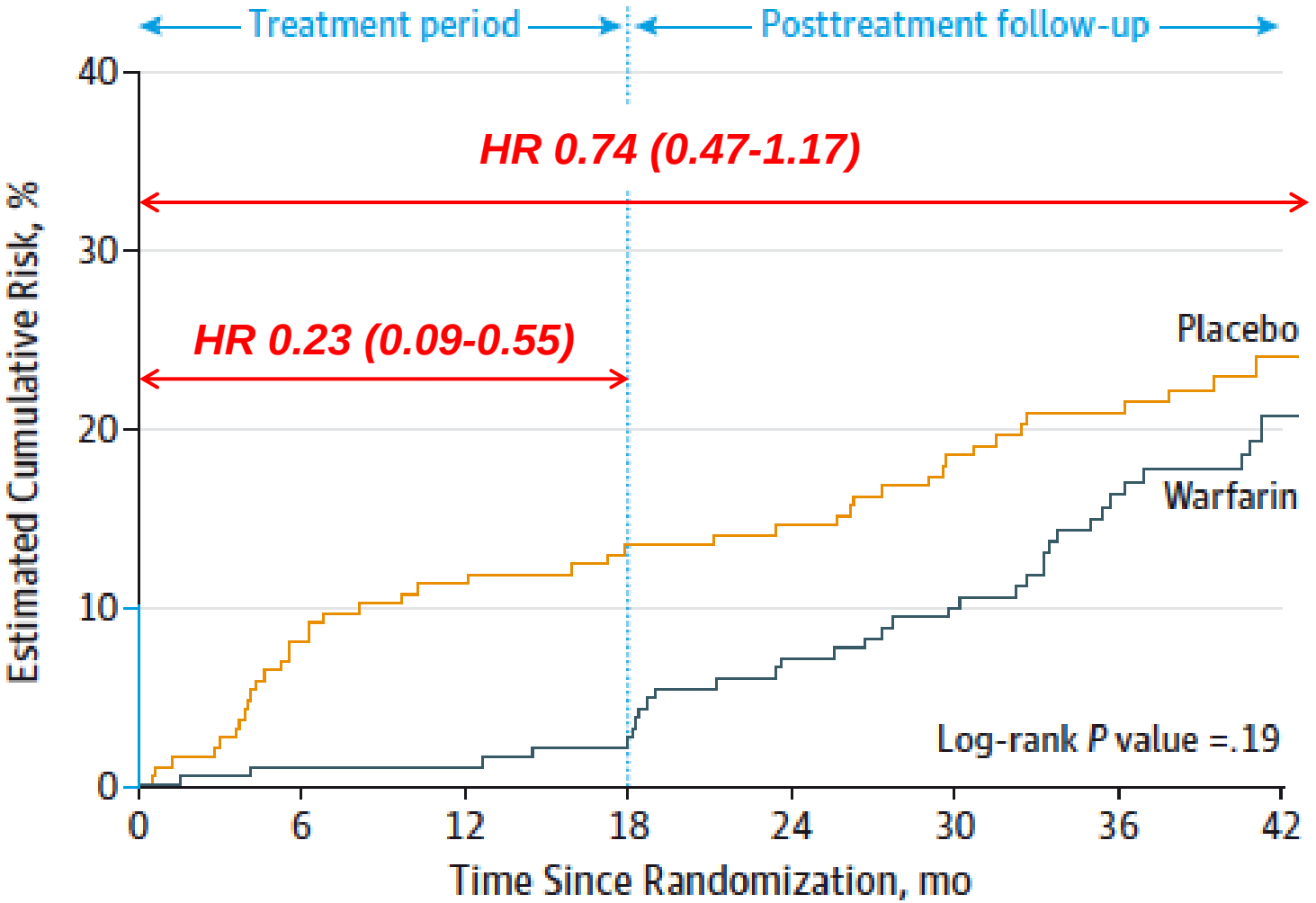
- **Primary outcome**:
  - **Composite of recurrent VTE or major bleeding during the 18 months study treatment period**

- **Secondary outcomes**:
  - Composite of recurrent VTE or major bleeding during the entire study period of 42 months
  - Recurrent VTE, major bleeding and deaths unrelated with the composite during the treatment period and the entire study period

All symptomatic events have been validated by the Critical Events Committee

Couturaud F et al. JAMA 2015; 314:31–40

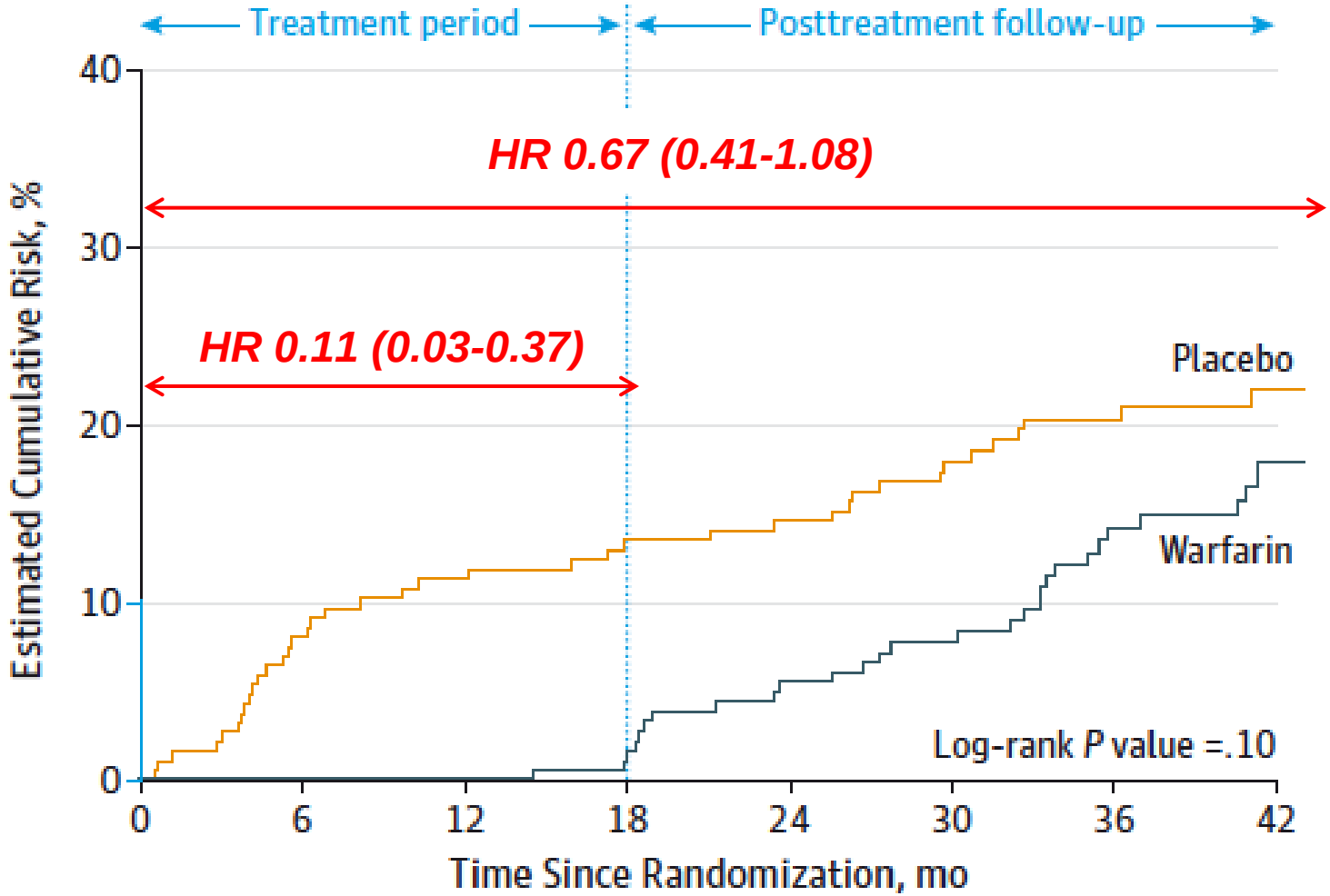
COMPOSITE: Recurrent VTE or Major Bleeding



No. at risk								
Placebo	187	170	162	158	155	140	117	104
Warfarin	184	182	180	174	168	150	120	110

Couturaud F et al. JAMA 2015; 314:31–40

Recurrent VTE



No. at risk								
Placebo	187	170	162	158	155	141	117	105
Warfarin	184	182	180	174	168	150	120	110

Couturaud F et al. JAMA 2015; 314:31–40

Clinical consequences of “PADIS-PE” trial

After a first episode of unprovoked PE initially treated during 6 months:

- Major reduction of recurrent VTE while anticoagulation is continued
- Loss of benefit after stopping anticoagulation

  → No impact of an extended but limited duration of anticoagulation

Recurrent VTE occurred:

- In 80% of cases as PE (8% fatal)
- In 90% of cases as unprovoked VTE

→ Clinical presentation of recurrence = initial episode

Couturaud F et al. JAMA 2015; 314:31–40

Clinical consequences

Reinforces recommendations ESC 2014 for indefinite anticoagulation

Recommendations for duration of anticoagulation after pulmonary embolism	Class[a]	Level[b]
For patients with PE secondary to a transient (reversible) risk factor, oral anticoagulation is recommended for 3 months.	I	B
For patients with unprovoked PE, oral anticoagulation is recommended for at least 3 months.	I	A
Extended oral anticoagulation should be considered for patients with a first episode of unprovoked PE and low bleeding risk.	IIa	B
Anticoagulation treatment of indefinite duration is recommended for patients with a second episode of unprovoked PE.	I	B
In patients who receive extended anticoagulation, the risk–benefit ratio of continuing such treatment should be reassessed at regular intervals.	I	C

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

Clinical consequences

Reinforces recommendations CHEST 2016 for indefinite anticoagulation

9. In patients with a first VTE that is an unprovoked proximal DVT of the leg or PE and who have a (i) low or moderate bleeding risk (see text), we suggest extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy (Grade 2B), and

Kearon C, et al. Chest 2016; 149: 315-52

Clinical consequences

Only 2 treatment options:

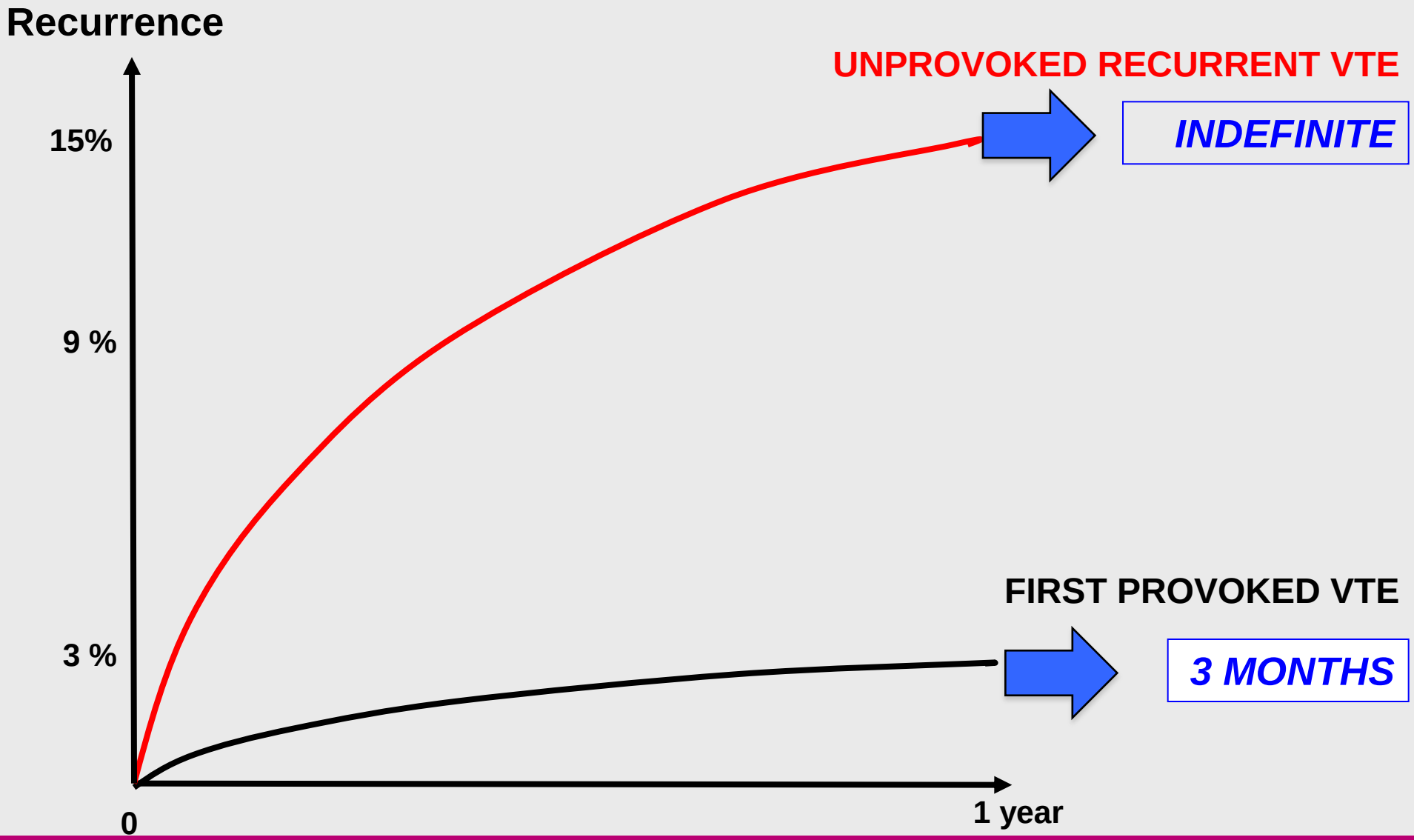
1- Short Treatment = 3 (or 6 months)

2- Indefinite Anticoagulation

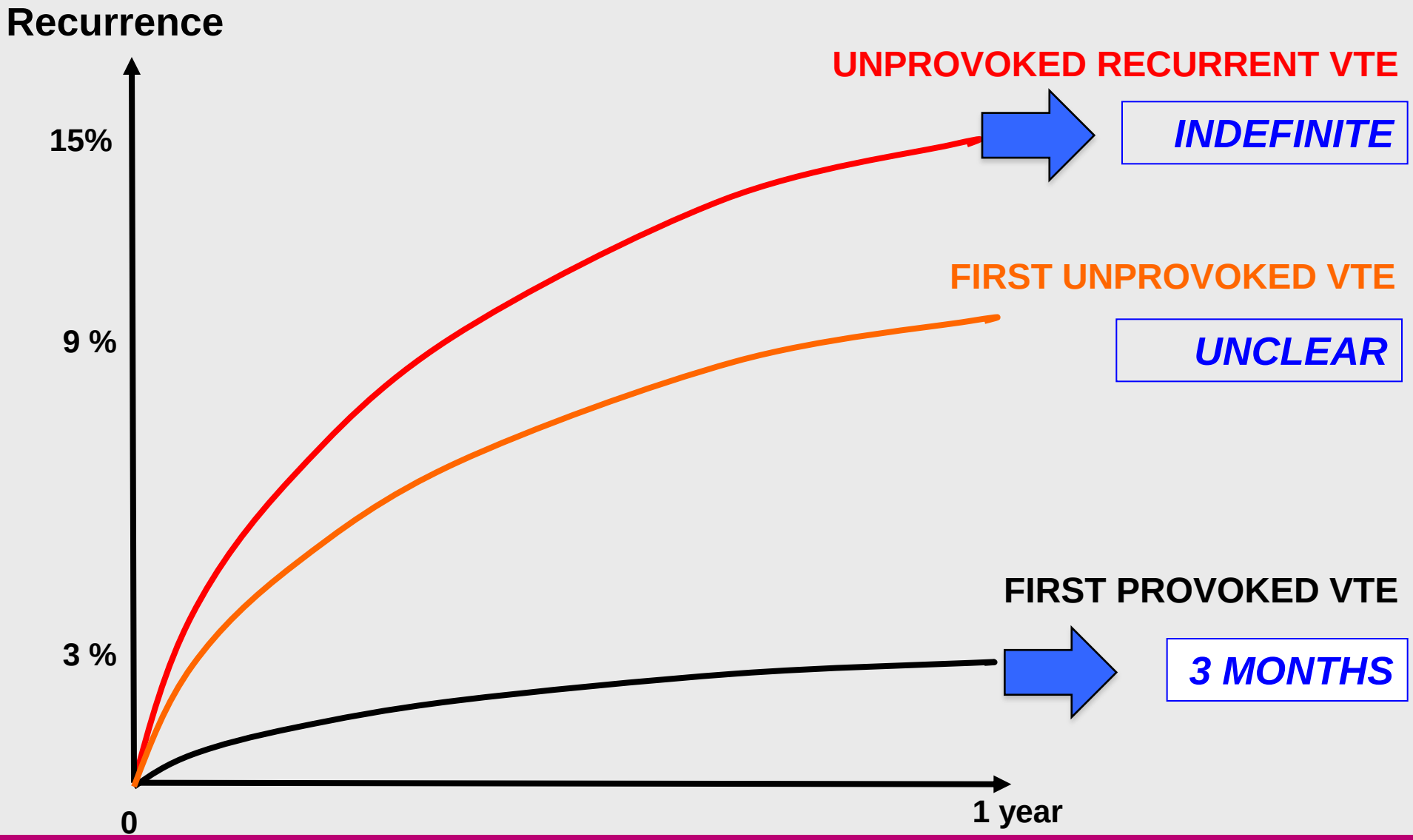
Based on what Criteria ?

Couturaud F et al. JAMA 2015; 314:31–40

VTE recurrence after interruption of anticoagulants



VTE recurrence after interruption of anticoagulants



Extended treatment in patients at “equipoise”with low-dose direct oral anticoagulants (DOACs)?

=

Patients where physicians are uncertain for indefinite anticoagulation

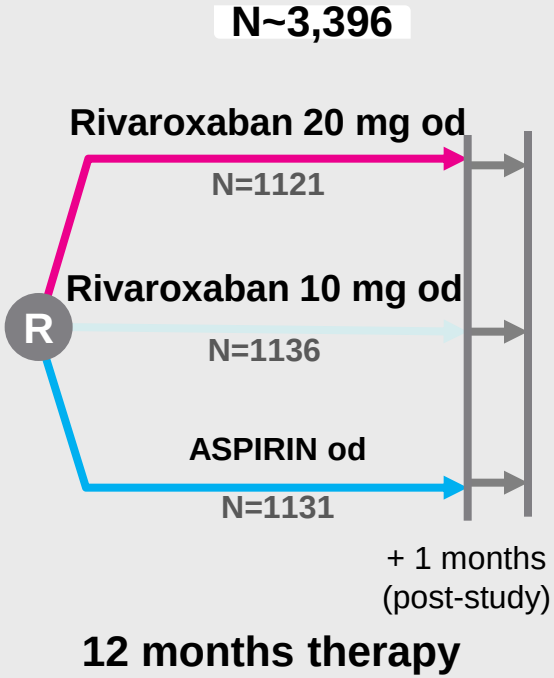
Rivaroxaban or Aspirin for Extended Treatment of Venous Thromboembolism

J.I. Weitz, A.W.A. Lensing, M.H. Prins, R. Bauersachs, J. Beyer-Westendorf, H. Bounameaux, T.A. Brighton, A.T. Cohen, B.L. Davidson, H. Decousus, M.C.S. Freitas, G. Holberg, A.K. Kakkar, L. Haskell, B. van Bellen, A.F. Pap, S.D. Berkowitz, P. Verhamme, P.S. Wells, and P. Prandoni, for the EINSTEIN CHOICE Investigators*

Weitz JI, et al. N Engl J Med 2017; 376:1211-22

Extended treatment in patients at “equipoise” with low-dose DOACs?

“Einstein-Choice Study”



Design: Multicentre, randomized, double-blind, superiority study

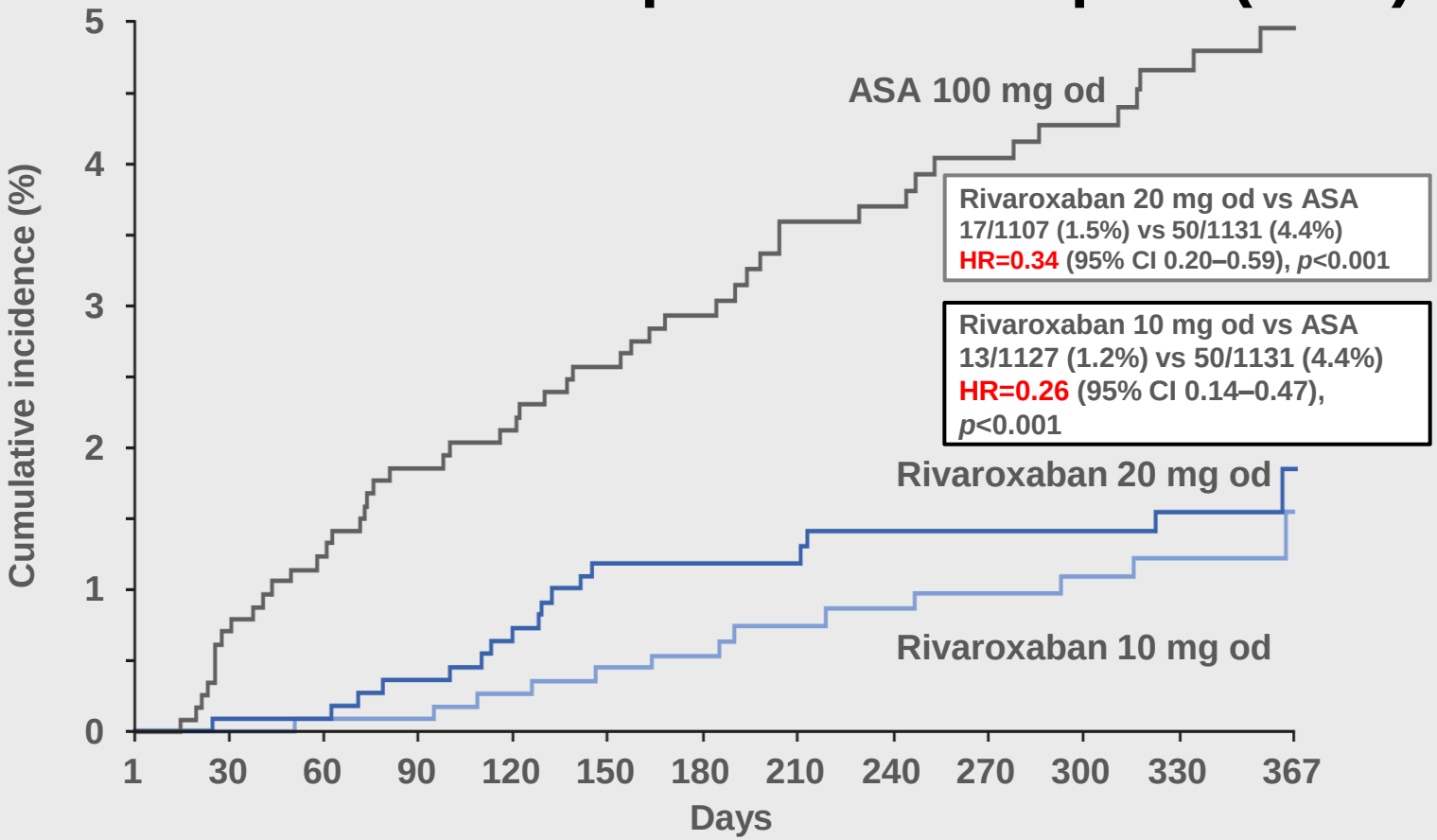
Weitz JI, et al. N Engl J Med 2017; 376:1211-22

Clinical Characteristics

Outcome		Rivaroxaban 20 mg (n=1107)	Rivaroxaban 10 mg (n=1127)	Aspirin 100 mg (n=1131)
Index event, n (%)	DVT	565 (51.0)	565 (50.1)	577 (51.0)
	PE	381 (34.4)	381 (33.8)	366 (32.4)
	Both	155 (14.0)	179 (15.9)	181 (16.0)
	Asymptomatic or unconf.	6 (0.5)	2 (0.2)	7 (0.6)
Classification of index VTE, n (%)	Unprovoked	441 (39.8)	480 (42.6)	468 (41.4)
	Provoked	666 (60.2)	647 (57.4)	663 (58.6)
History of prior VTE, n (%)		198 (17.9)	197 (17.5)	194 (17.2)
Known thrombophilia, n (%)		79 (7.1)	74 (6.6)	70 (6.2)
Active cancer, n (%)		25 (2.3)	27 (2.4)	37 (3.3)
Study drug duration (median days, IQR)		349 (189-362)	353 (190-362)	350 (186-362)

Weitz JI, et al. N Engl J Med 2017; 376:1211-22

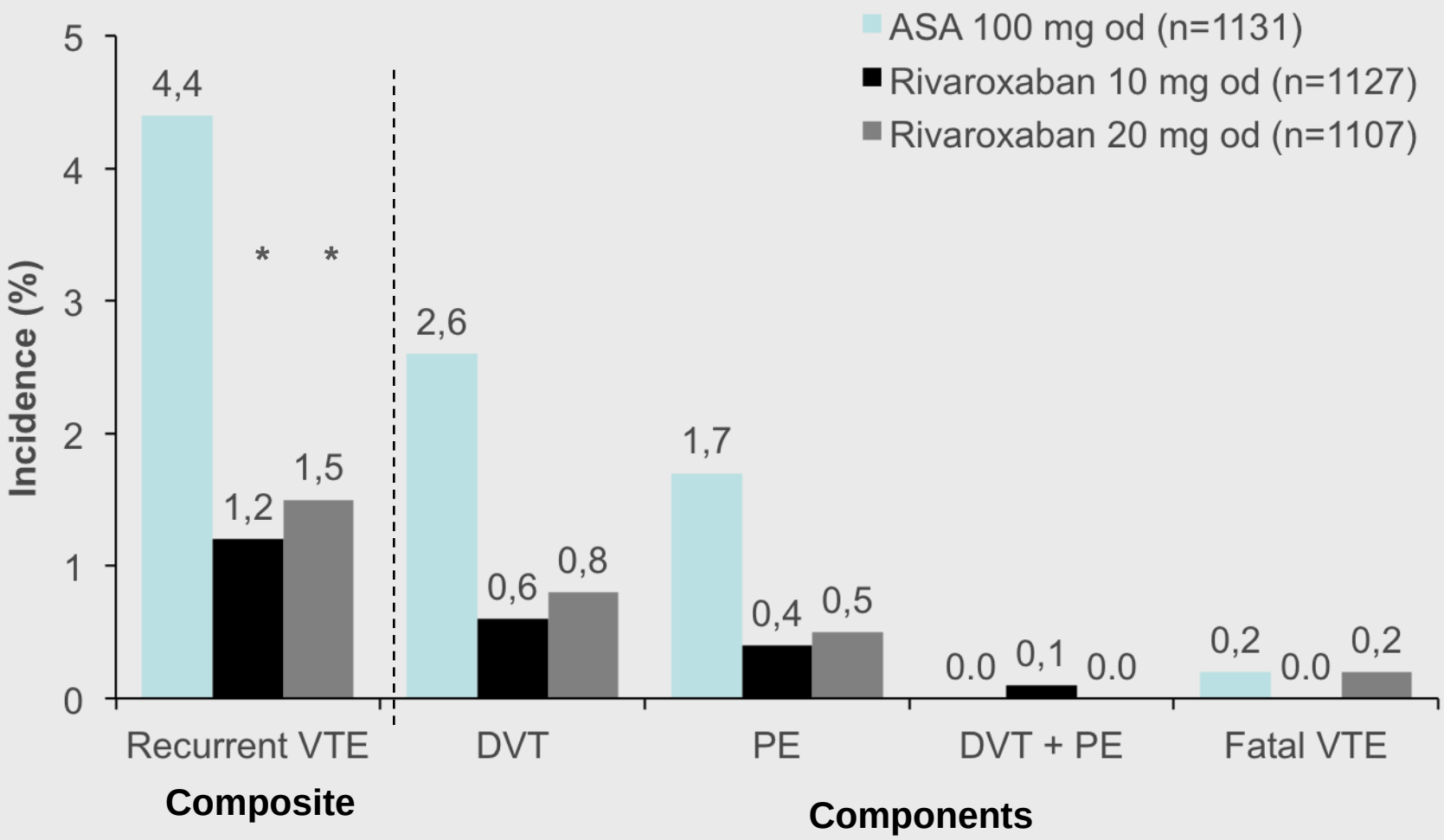
Both Rivaroxaban Doses Provided Superior Reduction in Recurrent VTE Rates Compared with Aspirin (ASA)



Number of patients at risk													
Rivaroxaban 20 mg od	1107	1102	1095	1090	1084	1079	997	876	872	860	794	718	0
Rivaroxaban 10 mg od	1126	1124	1119	1118	1111	1109	1029	890	886	867	812	723	0
ASA 100 mg od	1131	1121	1111	1103	1094	1088	1010	859	857	839	776	707	0

Weitz JI, et al. N Engl J Med 2017; 376:1211-22

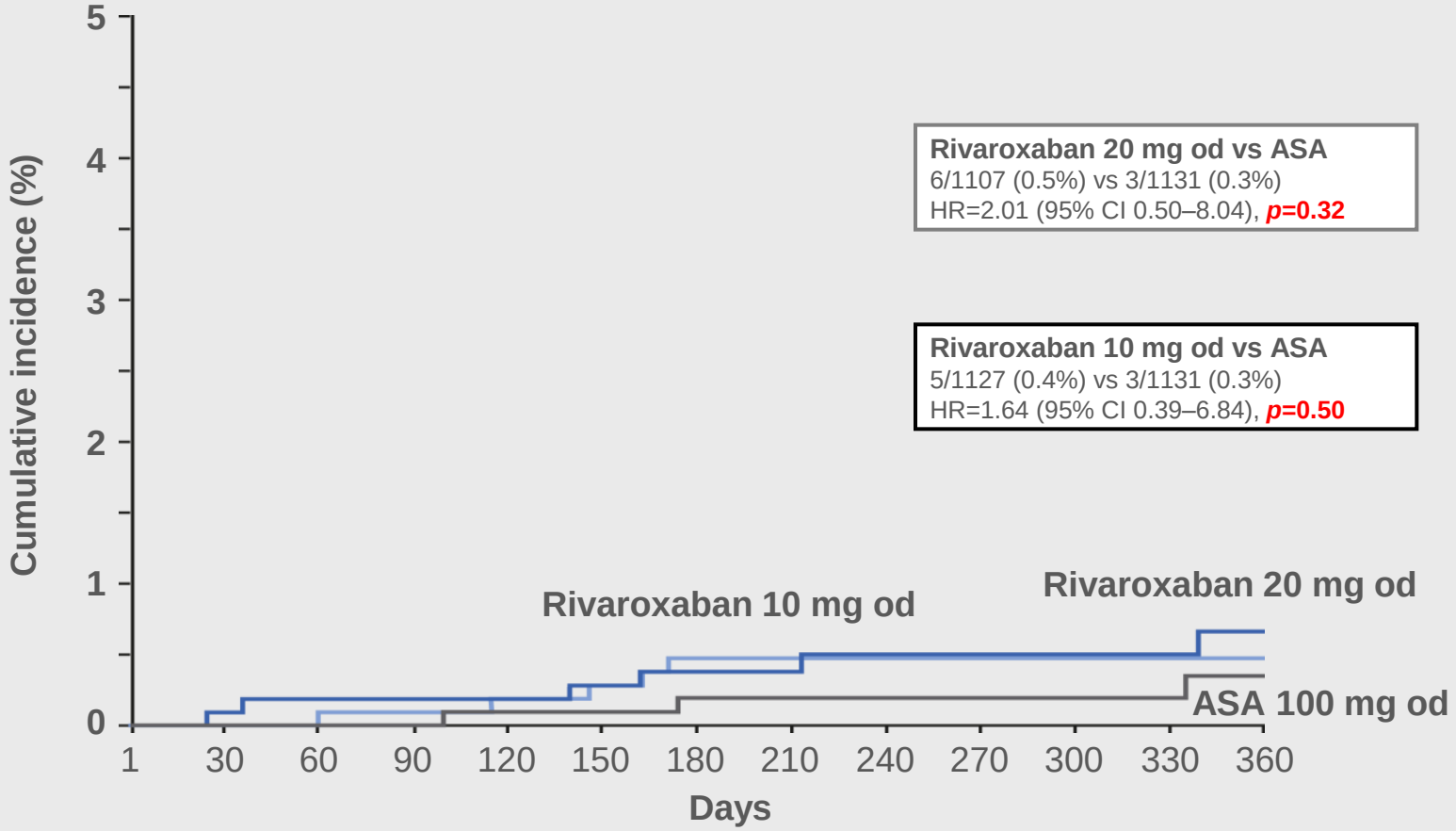
Primary Efficacy Outcome Results Components



Intention-to-treat analysis. *p<0.001 versus ASA 100 mg od

Weitz JI, et al. N Engl J Med 2017; 376:1211-22

Rates of Major Bleeding Were ≤0.5% and Similar to ASA

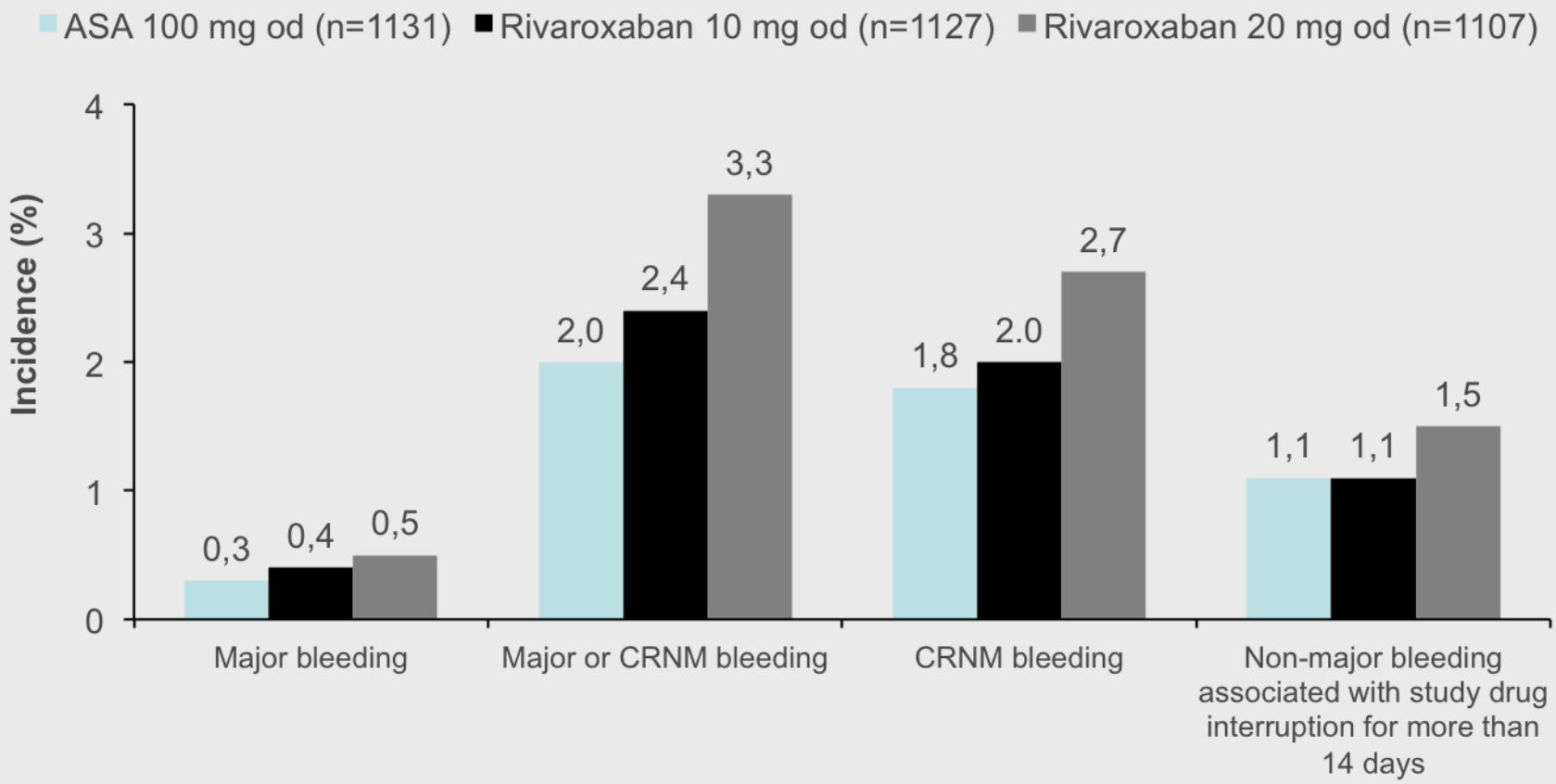


Number of patients at risk													
Rivaroxaban 20 mg od	1107	1081	1063	1048	1036	1024	963	818	801	780	712	642	449
Rivaroxaban 10 mg od	1126	1103	1080	1070	1058	1046	988	823	812	790	733	653	469
ASA 100 mg od	1131	1096	1075	1058	1040	1023	970	800	791	768	709	645	445

Safety analysis. No events after Day 360 up to Day 480

Weitz JI, et al. N Engl J Med 2017; 376:1211-22

Bleeding Outcome Analyses



Similar rates of bleeding were observed in the rivaroxaban and ASA treatment groups

Safety analysis. All treatment comparisons p>0.05

Weitz JI, et al. N Engl J Med 2017; 376:1211-22

Extended treatment in patients at “equipoise”with low-dose Rivaroxaban ? “Einstein-Choice Study”

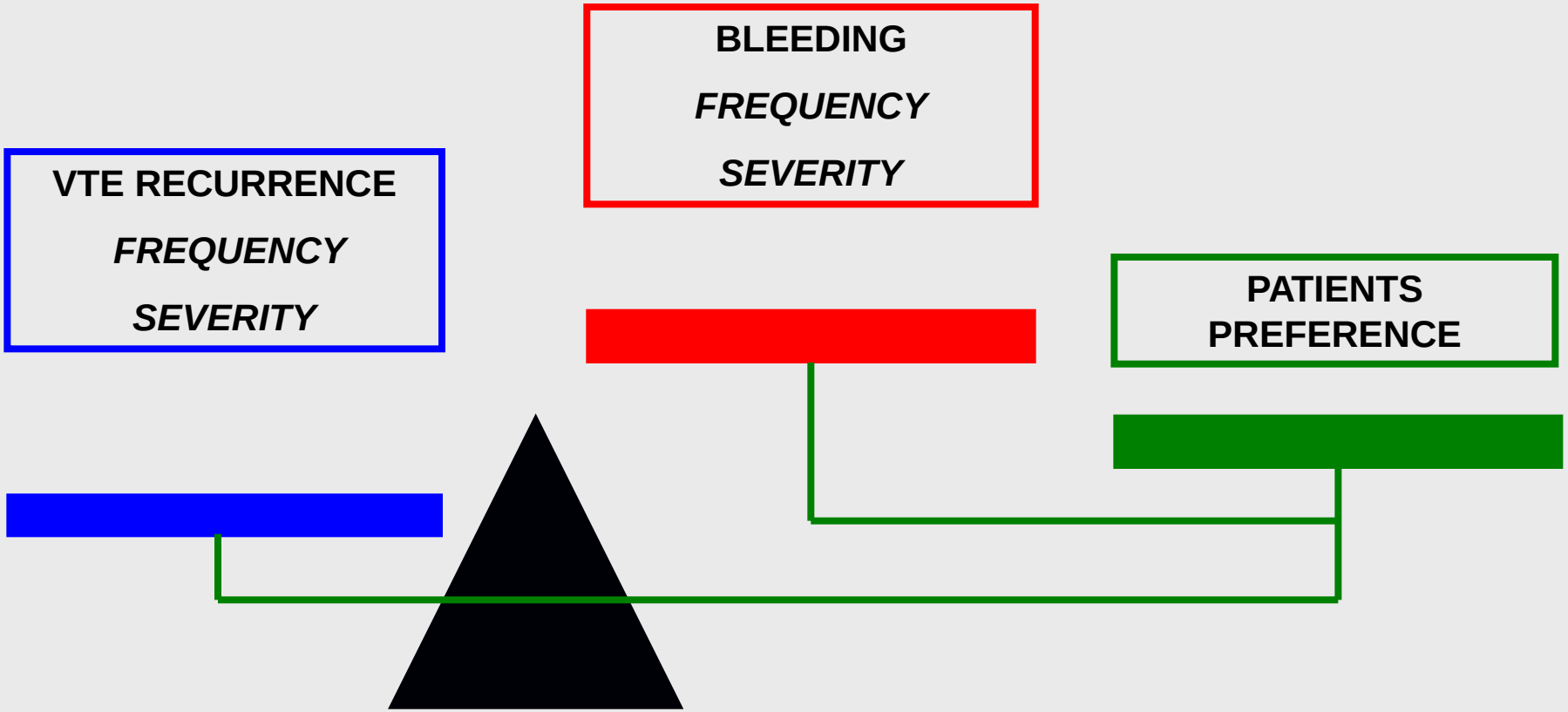
- **Interpretation**

In patients where physicians are uncertain for extended anticoagulation:

  - Rivaroxaban low-dose or full-dose is more effective than aspirin
  - Bleeding risks are low and not different between the groups
  - No heterogeneity among strata analyses
  - What optimal dose for what patient ?

Weitz JI, et al. N Engl J Med 2017; 376:1211-22

Optimal anticoagulant therapy duration is a compromise



CONCLUSION

Treatment duration

- Only two possibilities: short / indefinite
- Determine:
  - Major risk factors of recurrence / mortality
  - Major risk factors of bleeding/ mortality
  - Benefit / Risk balance
  - Patients preference

Conclusion

Indefinite treatment:

- ANTICOAGULANT > ASPIRINE : Yes
- DOAC > VKA : Probable (but little evidence available yet)
- ½ DOSE > FULL DOSE DOAC ? Possible (but not demonstrated)

Perspectives

- Validate RISK SCORES OF VTE RECURRENCE
- Define TRANSIENT RISK FACTOR
- Validate BLEEDING RISK SCORES
- High risk patients: validate optimal treatment intensity anticoagulation full dose *versus* DOAC half-dose

Pulmonary Hypertension

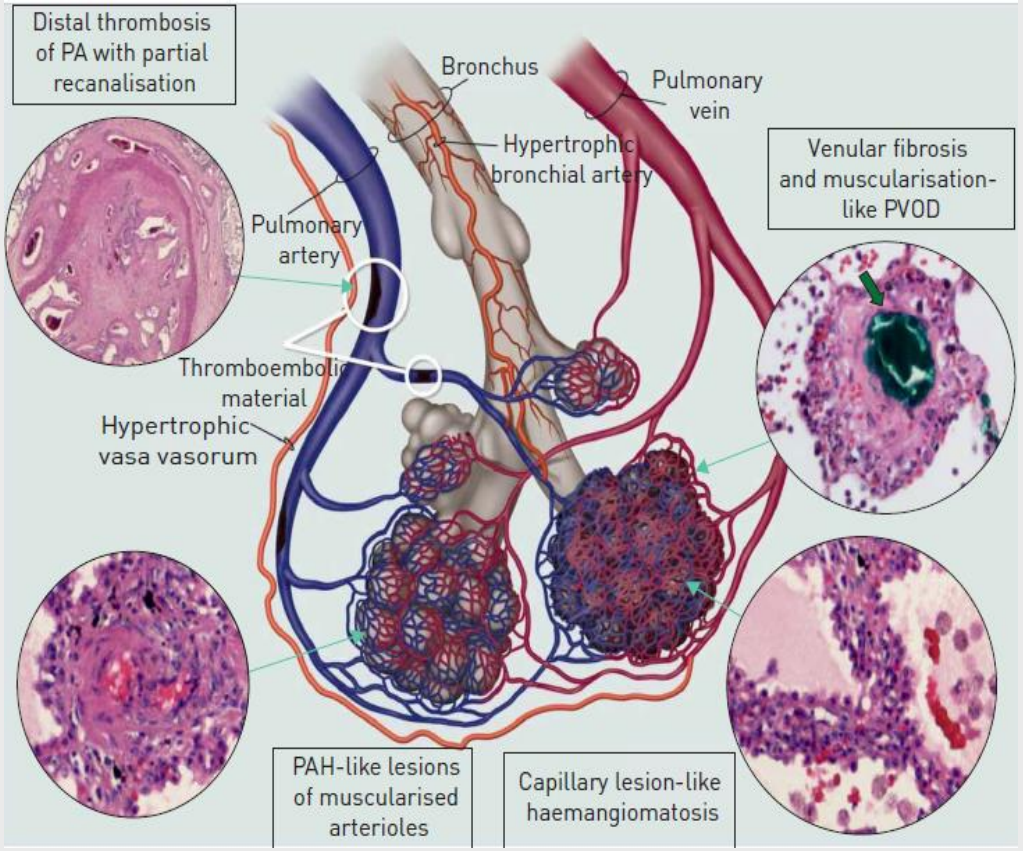
State of the Art

- 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

Medical therapy and balloon pulmonary angioplasty in chronic thromboembolic pulmonary hypertension (CTEPH)

Chronic thromboembolic pulmonary hypertension (CTEPH)

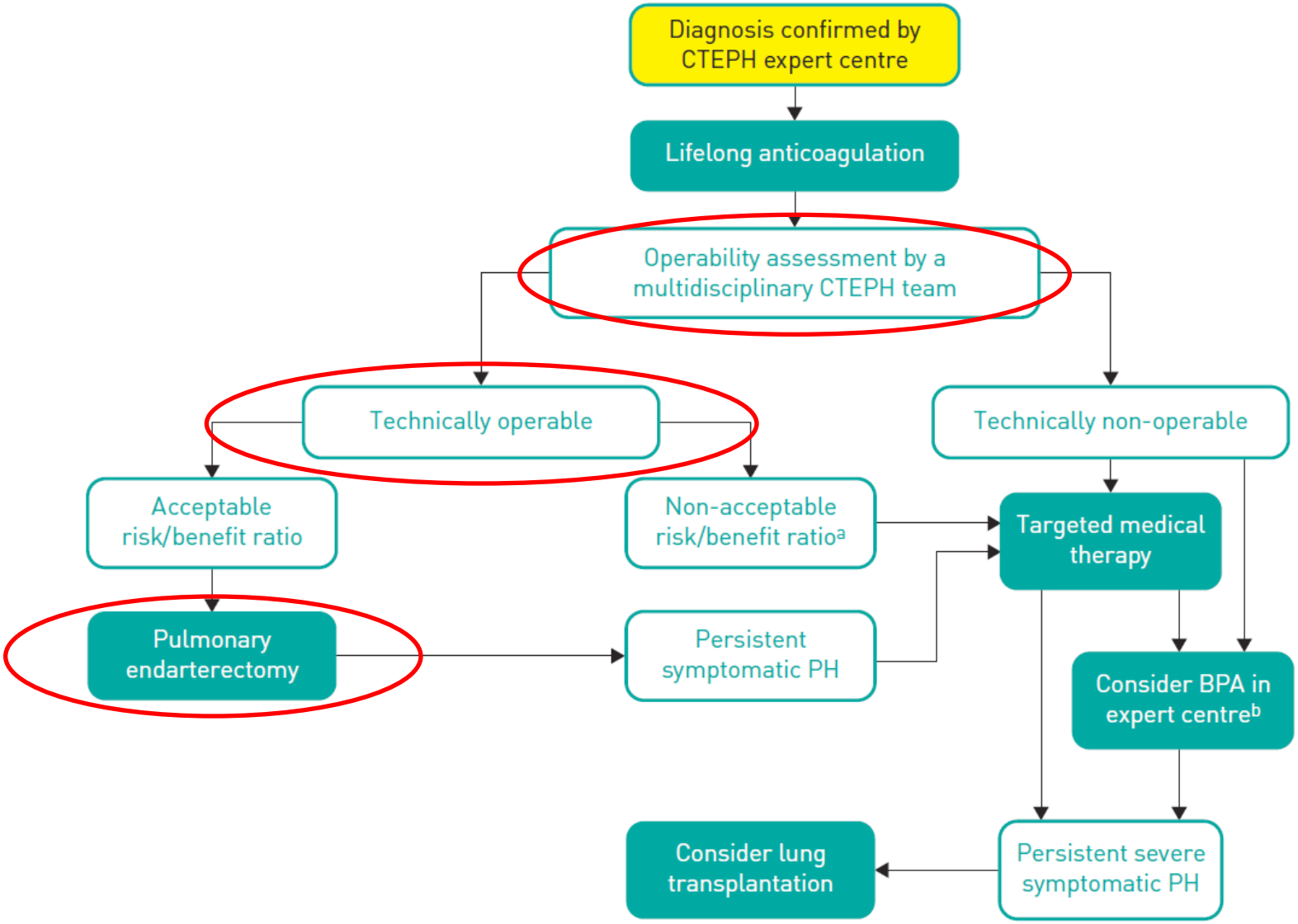
- CTEPH is characterized by macroscopic and microscopic changes in the pulmonary vasculature and has a poor prognosis
- Pulmonary endarterectomy to remove macrovascular thromboembolic material is recommended, but many patients are not operable
- Microscopic vasculopathy may be amenable to treatment with medical therapies



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

Simonneau et al. Eur Respir Rev 2017 26: 160112

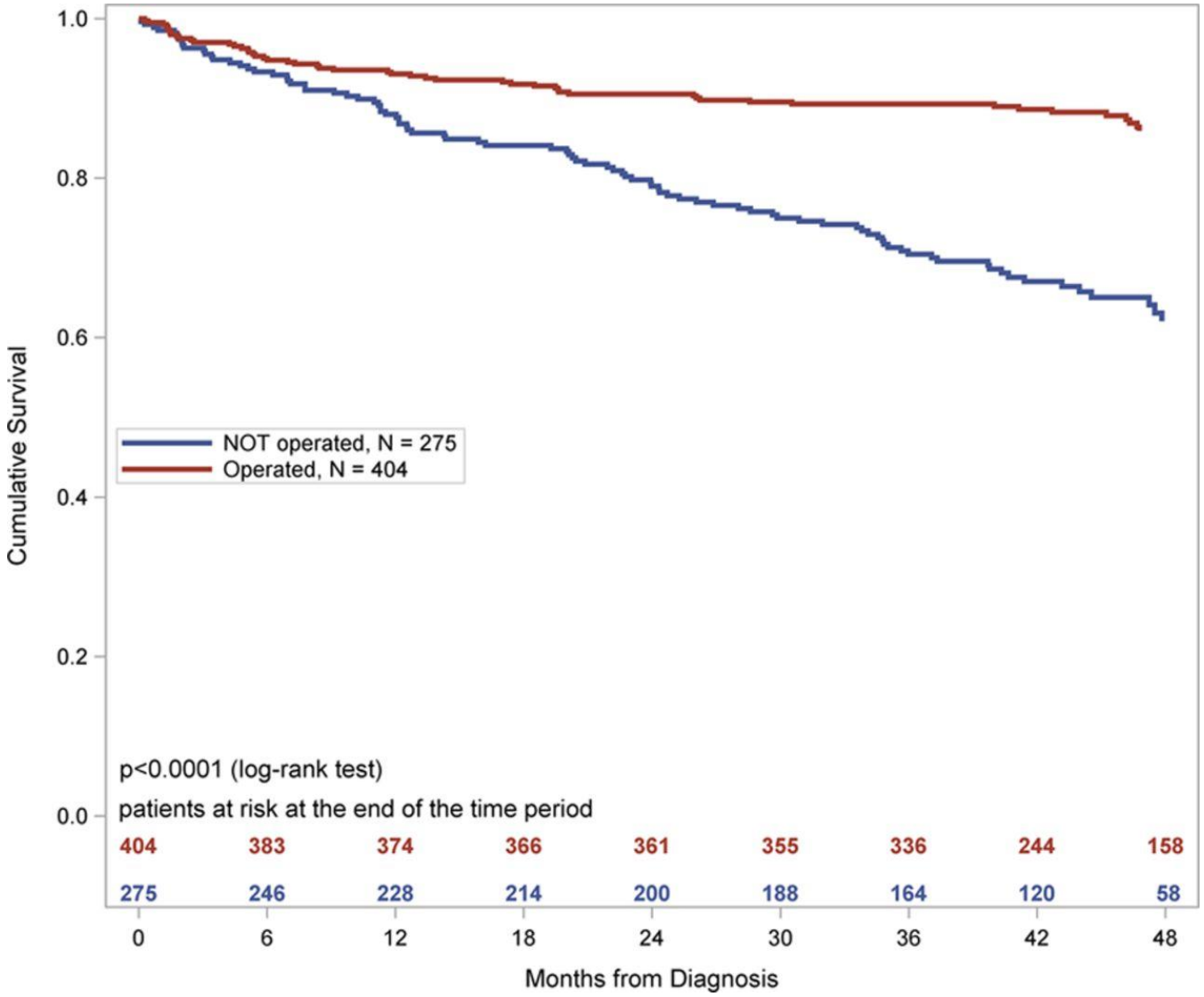
CTEPH Treatment Algorithm



BPA= balloon pulmonary angioplasty

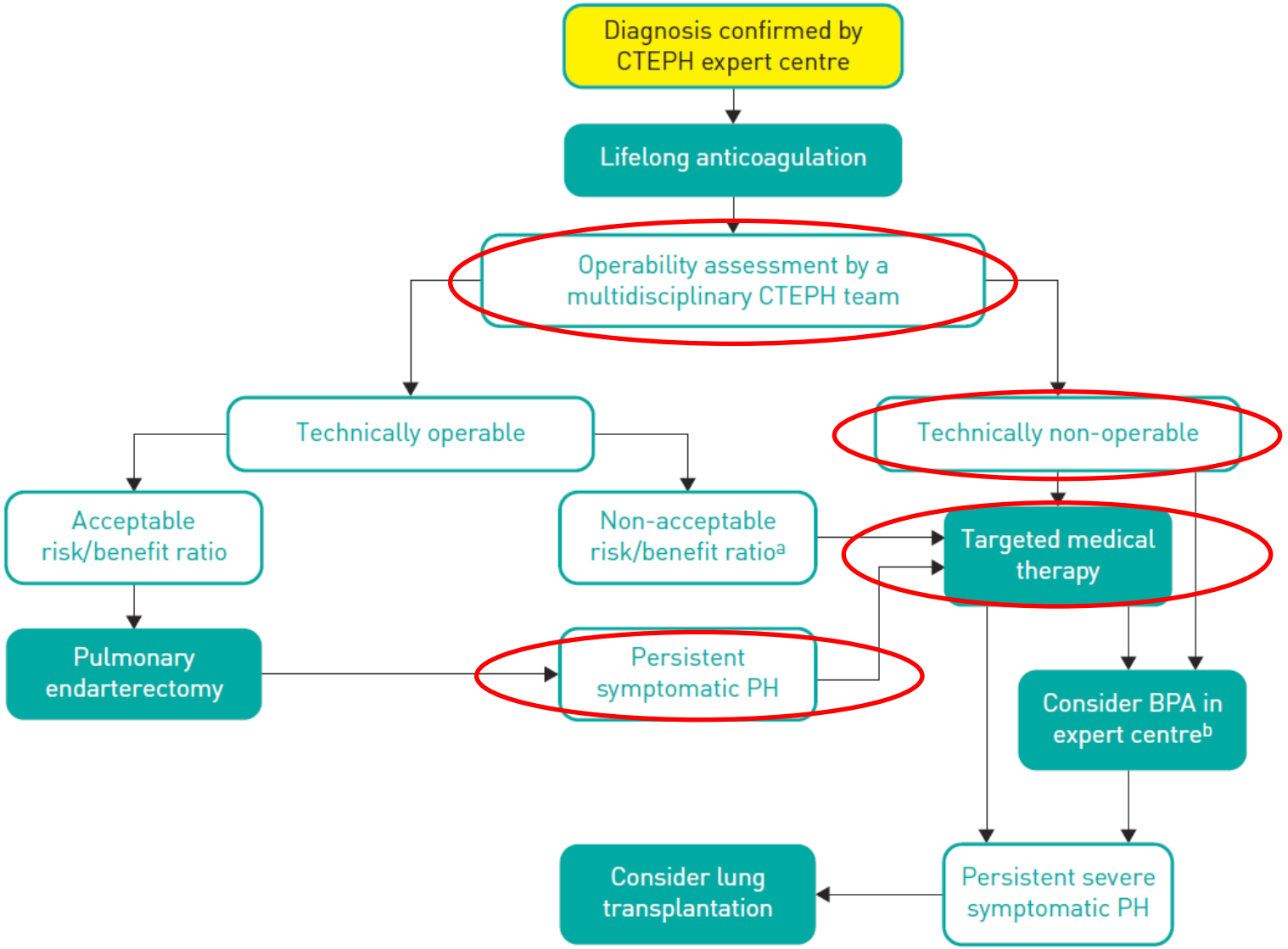
Galiè N *et al. Eur Heart J* 2016;37:67–119. Galiè N *et al. Eur Respir J* 2015;46:903–75

Survival according to treatment



Delcroix M et al. Circulation 2016; 133:859-71

CTEPH Treatment Algorithm



BPA= balloon pulmonary angioplasty

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

Randomized controlled trials in CTEPH

	Drug	Patients (n)	Study duration	Primary endpoint	Primary EP met	Secondary EP met
BENEFIT[1]	Bosentan	157	16 weeks	6-MWD PVR	No **Yes**	(TTCW) No
-	Sildenafil[2]	19	12 weeks	6-MWD	No	(PVR) **Yes**
CHEST[3]	Riociguat	261	16 weeks	6-MWD	**Yes**	(PVR) **Yes** (TTCW) No

- 3 RCTs showed beneficial effects of PAH drugs on hemodynamics but only 1 study (CHEST) demonstrated an improvement in 6-MWD
- No treatment effect on time to clinical worsening

1. Jais X, J Am Coll Cardiol. 2008 Dec 16;52(25):2127-34
2. Suntharalingam J, Chest 2008 Aug;134(2):229-236.
3.Ghofrani HA, NEJM 2013 Dec 5;369(23):2268

Randomized controlled trials in CTEPH: Hemodynamic changes in patients receiving study drug

	N	Baseline PVR (dyn.s.cm^{-5})	Change (dyn.s.cm^{-5})	Treatment effect
Jaïs[1] 2008	66	778±323	-146	-19%
Suntharaligam[2] 2008	9	814±385	-179±245	-22%
Ghofrani[3] 2013	151	791±432	-226±248	-29%

1. Jais X, J Am Coll Cardiol. 2008 Dec 16;52(25):2127-34
2. Suntharalingam J, Chest 2008 Aug;134(2):229-236.
3.Ghofrani HA, NEJM 2013 Dec 5;369(23):2268

ESC/ERS PH 2015 guidelines

Riociguat is recommended in symptomatic patients who have been classified as having persistent/recurrent CTEPH after surgical treatment or inoperable CTEPH by a CTEPH team including at least one experienced PEA surgeon	I	B
Off-label use of drugs approved for PAH may be considered in symptomatic patients who have been classified as having inoperable CTEPH by a CTEPH team including at least one experienced PEA surgeon	IIb	B

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

Medical therapy in CTEPH

- There is only one medical therapy (riociguat) approved for CTEPH (in inoperable CTEPH or persistent/recurrent CTEPH after pulmonary endarterectomy)
- Although not approved, other PAH therapies may be considered for inoperable CTEPH
- Controlled data on combination therapy in CTEPH are lacking

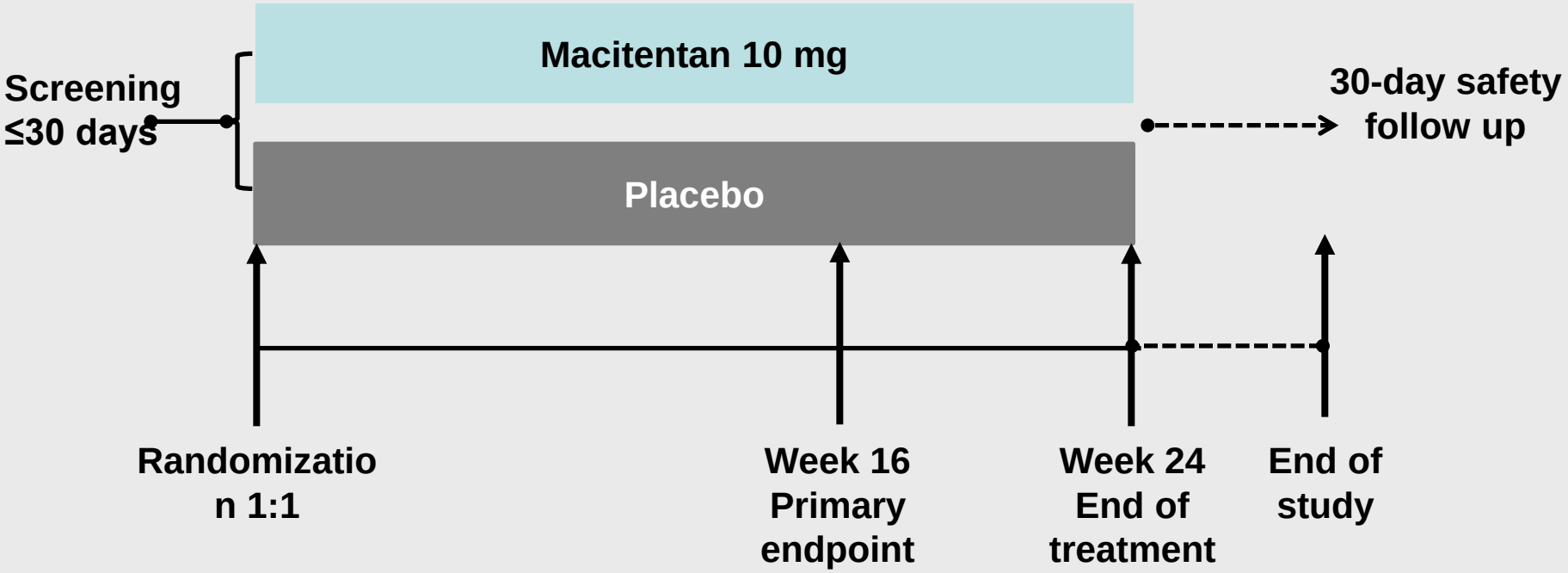
Galiè N *et al. Eur Heart J* 2016;37:67–119. Galiè N *et al. Eur Respir J* 2015;46:903–75

Macitentan and the MERIT-1 study

- Macitentan
  - A dual endothelin-receptor antagonist shown to delay disease progression in PAH patients[1,2]
- MERIT-1
  - Multicenter, double-blind, randomized, placebo-controlled phase 2 study
  - To evaluate the efficacy and safety of macitentan in patients with inoperable CTEPH
  - Inoperability was confirmed by independent pre-inclusion adjudication
  - Treatment with PDE-5i and/or inhaled/oral prostanoid at baseline was allowed for patients in NYHA FC III and IV

1. Gatfield J, *et al. PLoS ONE* 2012; 7:e47662; 2. Pulido T, *et al. N Engl J Med* 2013; 369:809-18.

MERIT-1 study design



Study endpoints

- Primary endpoint
  - Change in PVR from baseline to week 16 expressed as percentage of baseline
- Secondary endpoints
  - Change in 6MWD from baseline to week 24
  - Change in Borg dyspnea index from baseline to week 24
  - Proportion of patients with worsening in WHO FC at week 24
- Exploratory endpoints included
  - Change in other hemodynamic parameters from baseline to week 16
  - Change in NT-proBNP from baseline to week 24 expressed as a percentage of baseline

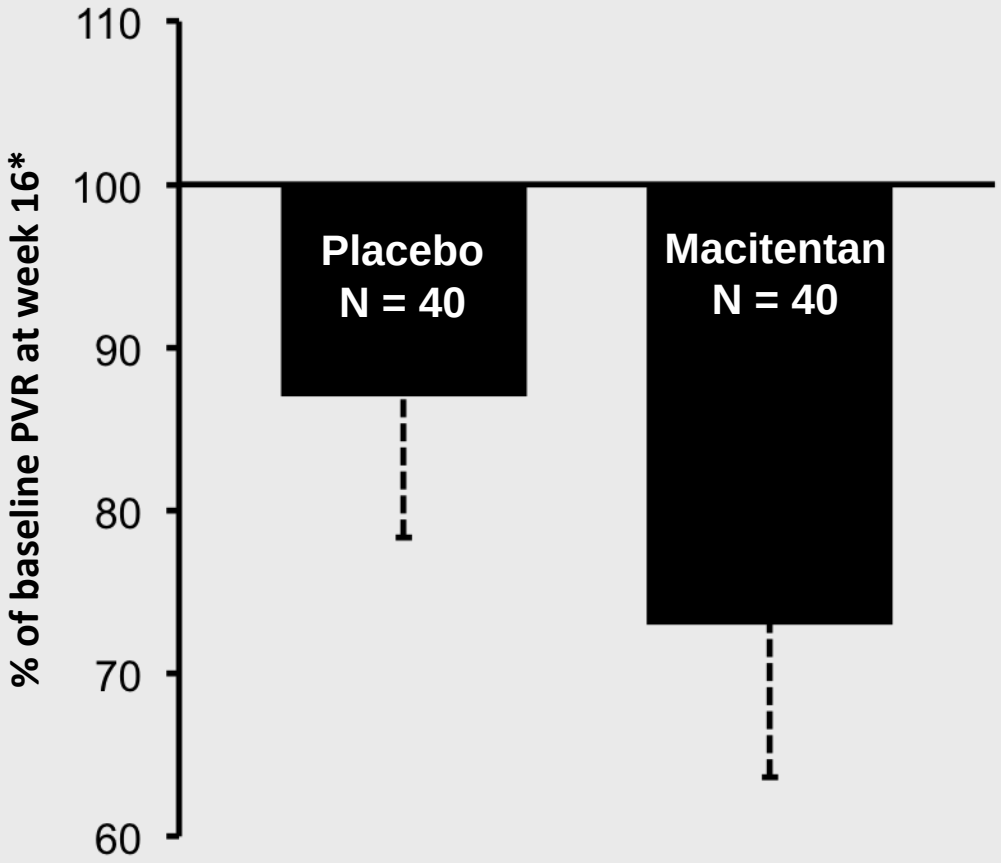
Baseline characteristics

Characteristic	Placebo (N = 40)	Macitentan (N = 40)	All patients (N = 80)
Female sex – n (%)	25 (62.5)	26 (65.0)	51 (63.8)
Age, years – mean ± SD	56.9 ± 13.9	58.2 ± 14.0	57.5 ± 13.9
Time from diagnosis, years – mean ± SD	1.2 ± 1.95	1.7 ± 2.36	1.5 ± 2.16
6MWD, meters – mean ± SD	351 ± 74	353 ± 88	352 ± 81
WHO FC – n (%)			
II	6 (15.0)	12 (30.0)	18 (22.5)
III-IV	34 (85.0)	28 (70.0)	62 (77.5)
PVR, dyn·sec·cm^{-5} – mean ± SD	984 ± 487	929 ± 380	957 ± 435
Use of PAH medications* – n (%)			
No PAH medication	15 (37.5)	16 (40.0)	31 (38.8)
PAH medication	25 (62.5)	24 (60.0)	49 (61.3)
PDE-5i	19 (47.5)	18 (45.0)	37 (46.3)
Oral/inhaled prostanoids	1 (2.5)	1 (2.5)	2 (2.5)
PDE-5i plus oral/inhaled prostanoids	5 (12.5)	5 (12.5)	10 (12.5)

Ghofrani HA, et al. 2017 ATS Conference

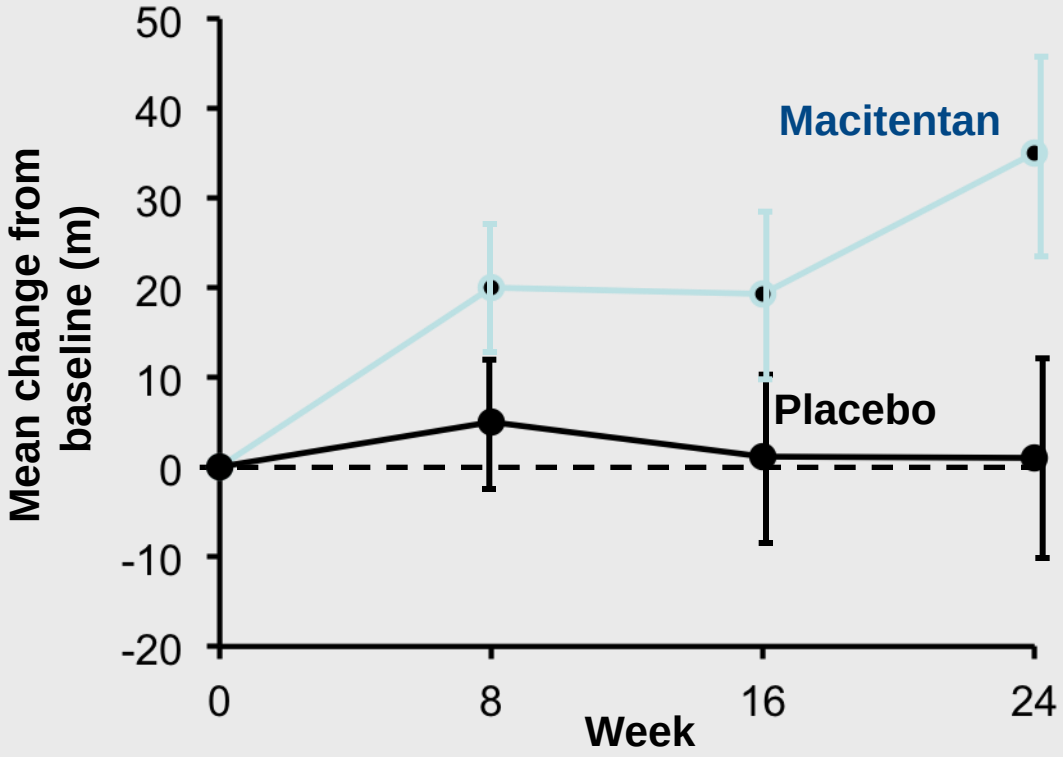
Primary endpoint
Change in PVR at week 16

Macitentan vs placebo: PVR reduction 16%
Ratio of geometric means (95% CL): 0.84 (0.70, 0.99), P=0.04



Ghofrani HA, et al. 2017 ATS Conference

Secondary endpoint
Change in 6MWD at week 24



No. of patients				
	40	40	40	40
	40	40	40	40

Treatment effect (95% CL):
34.0 m (2.9, 65.2), P=0.03

Consistent treatment effect with or without baseline PAH therapy*

Yes: 32.4 m (-7.0, 71.7)
No: 37.8 m (-19.7, 95.4)

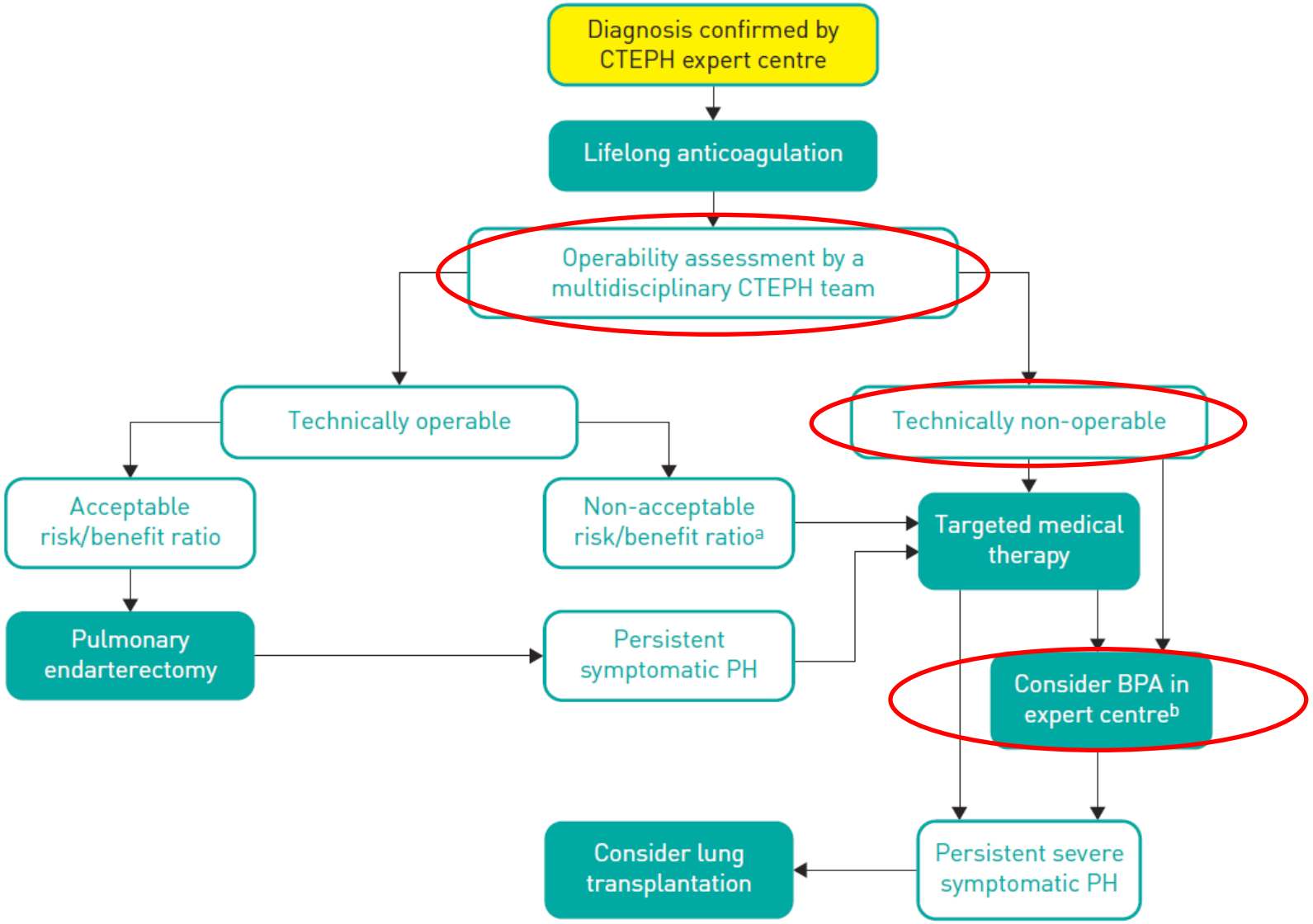
Ghofrani HA, et al. 2017 ATS Conference

Conclusions

- Macitentan significantly improved PVR and exercise capacity in patients with inoperable CTEPH
  - Treatment effects were consistent in patients receiving other PAH therapies at baseline
- Macitentan also improved other clinically relevant parameters and was well tolerated

Balloon Pulmonary Angioplasty (BPA) for treatment of CTEPH

CTEPH Treatment Algorithm

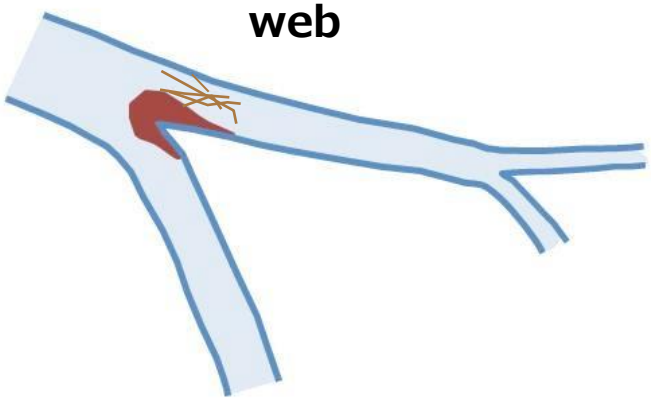


BPA= balloon pulmonary angioplasty Galiè N *et al. Eur Heart J* 2016;37:67–119. Galiè N *et al. Eur Respir J* 2015;46:903–75

Target lesions for BPA

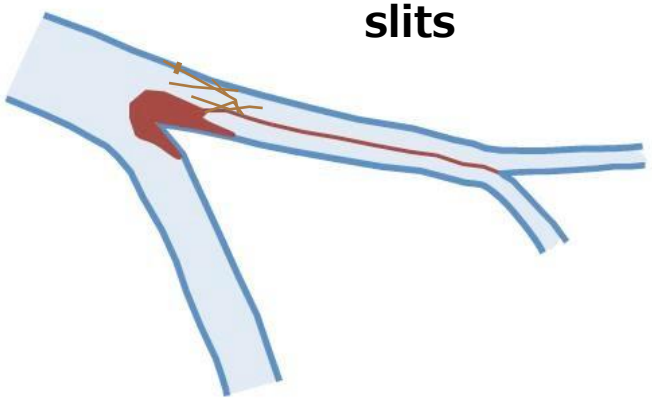
Type 1: Webs

→Ballooning to web



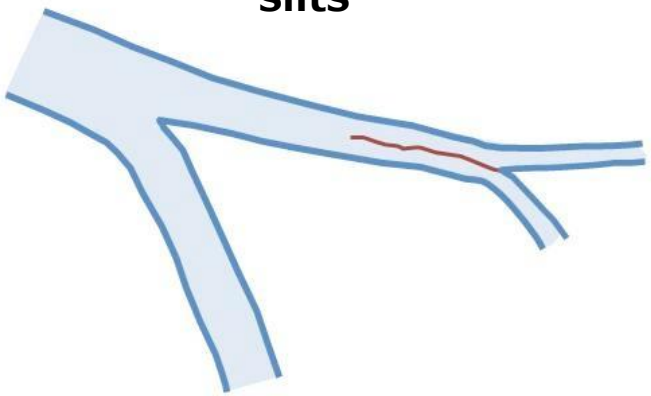
Type 2: Web＋slits

→Ballooning to web as well as slits



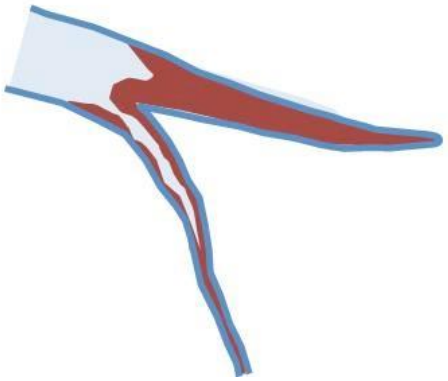
Type 3: Slits

→Ballooning to slits



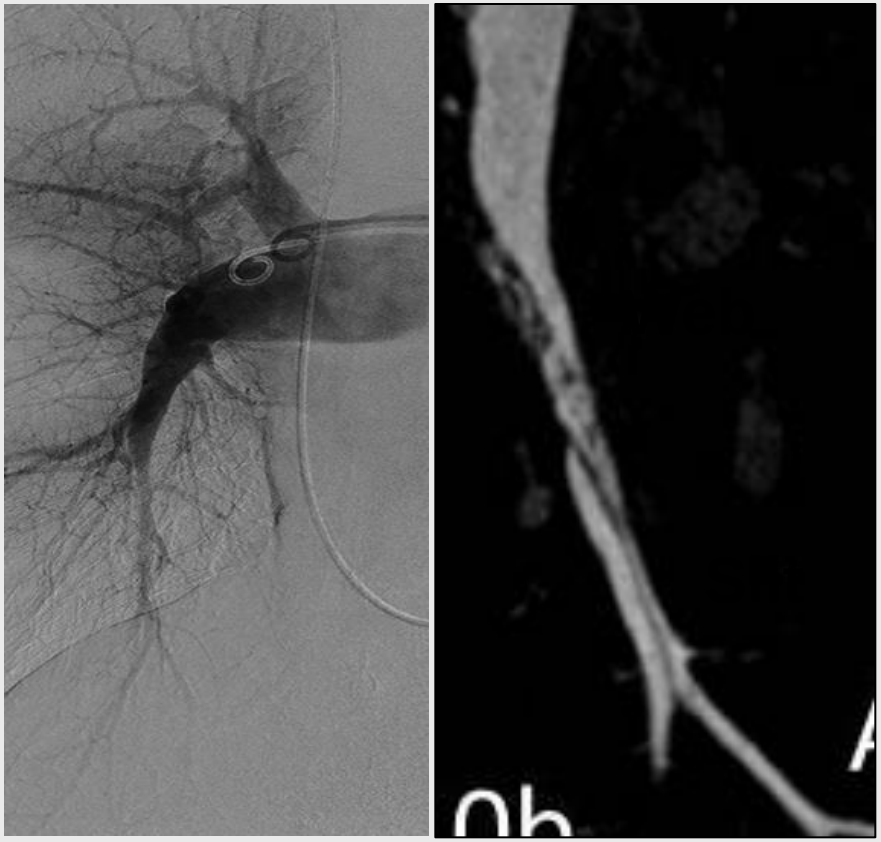
Type 4: Narrowing or complete occlusion

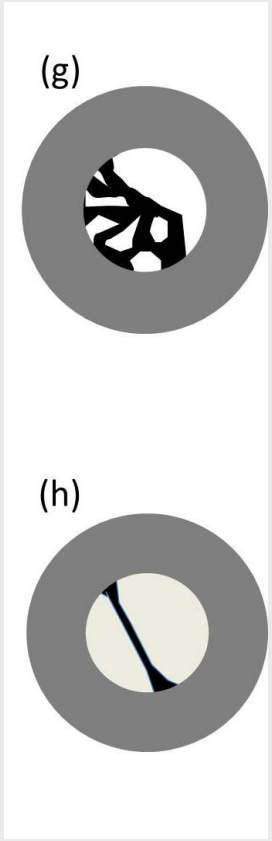
→not candidate for BPA

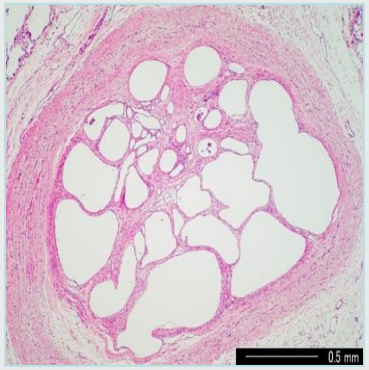


Kawakami et al. Circ Cardiovasc Interv 2016; 9(10). pii: e003318

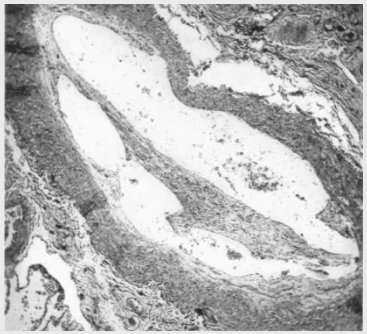
Target lesions for BPA







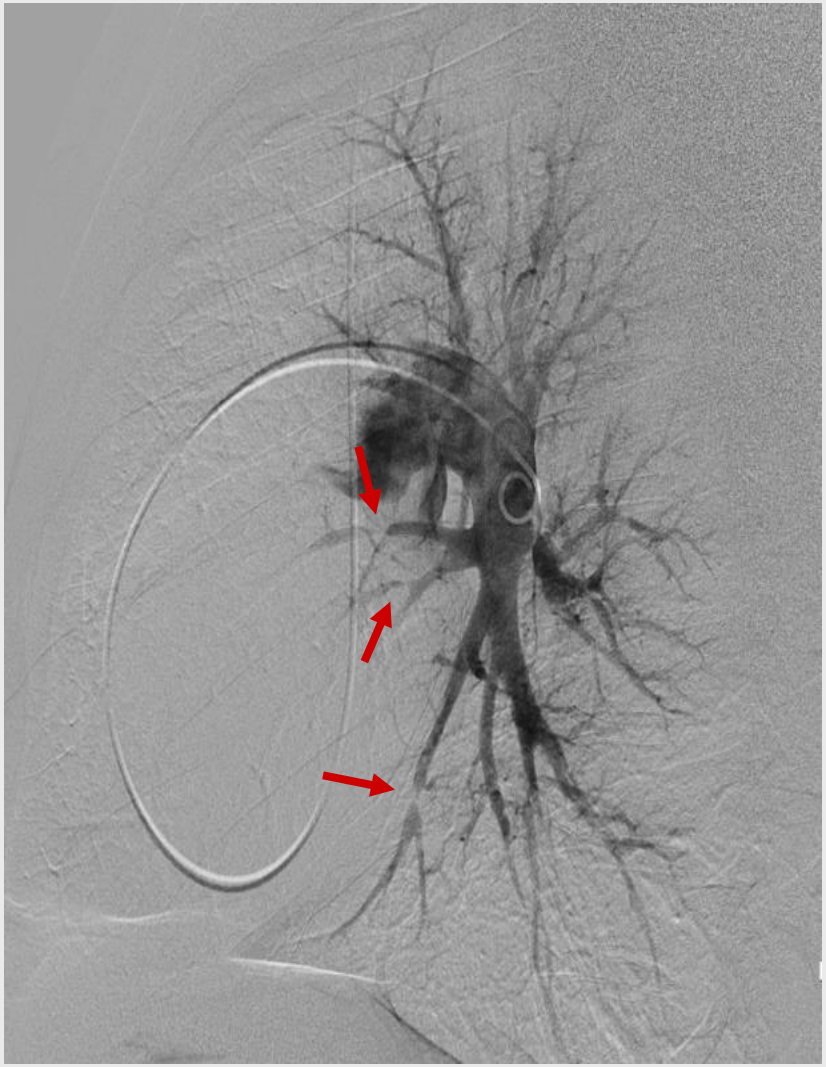
Histopathology

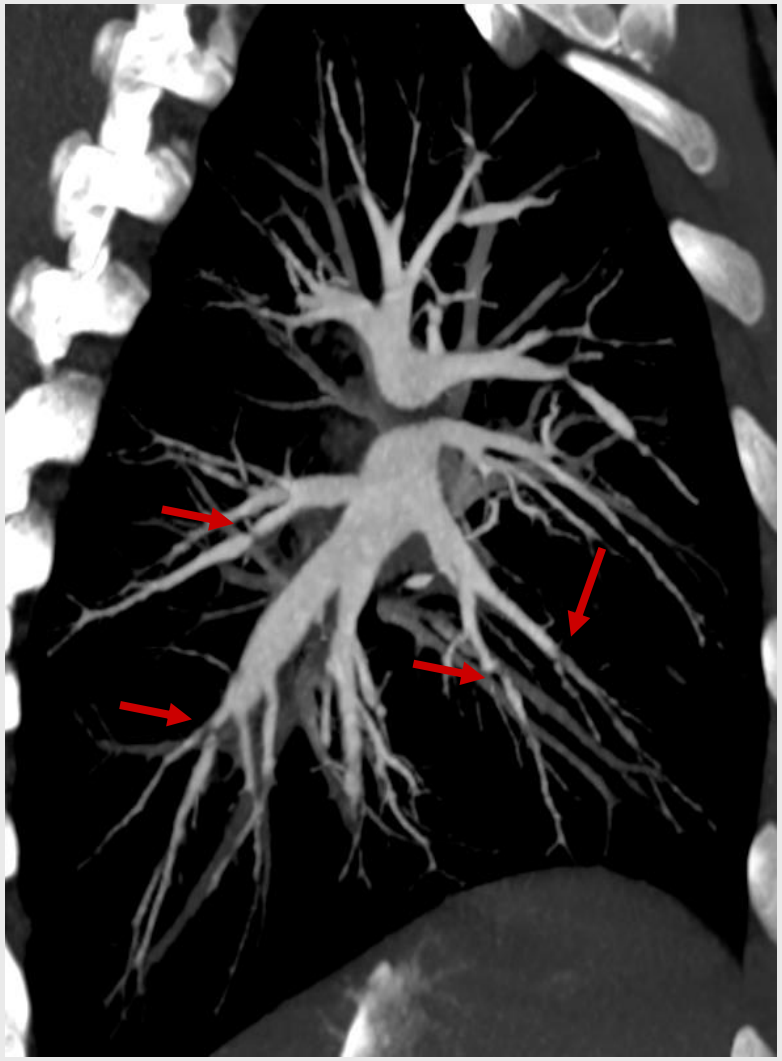


Sugiyama M, Fukuda T, Ogo T et al. 2014 Jul;32(7):375-82 Jpn J Radiol

Images Dr. Ueda, Dr. Ogo-Ohta, Department of Pathology,NCVC

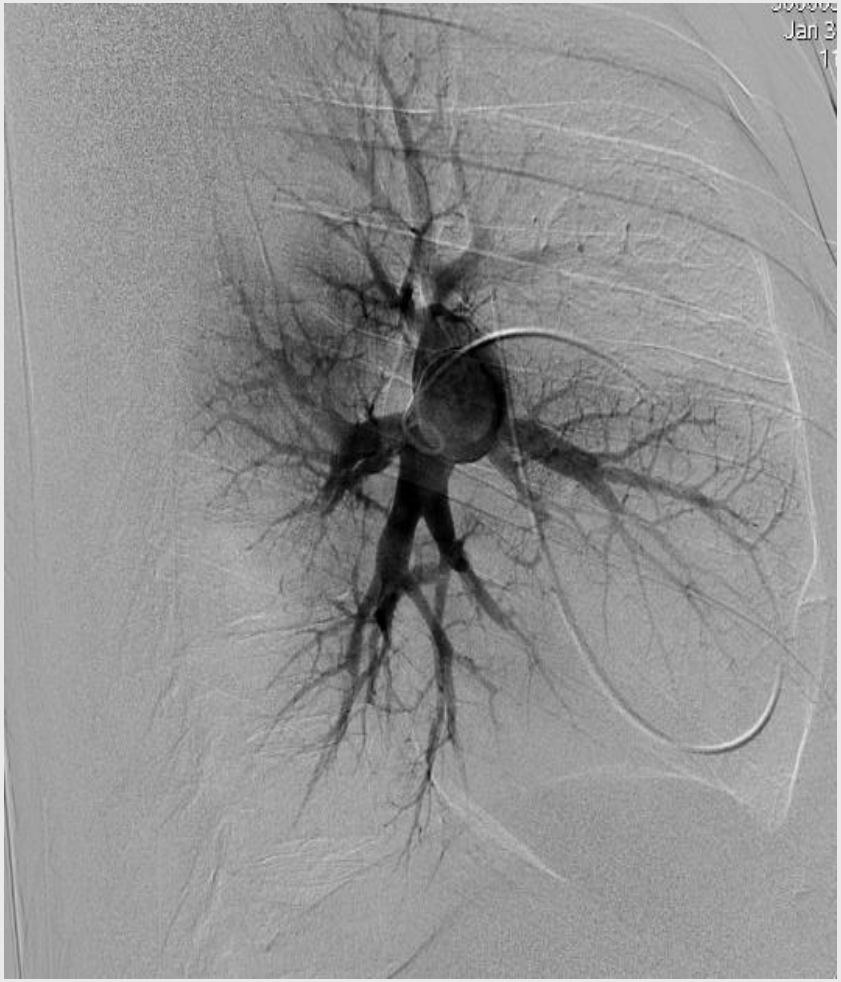
Eligible for BPA

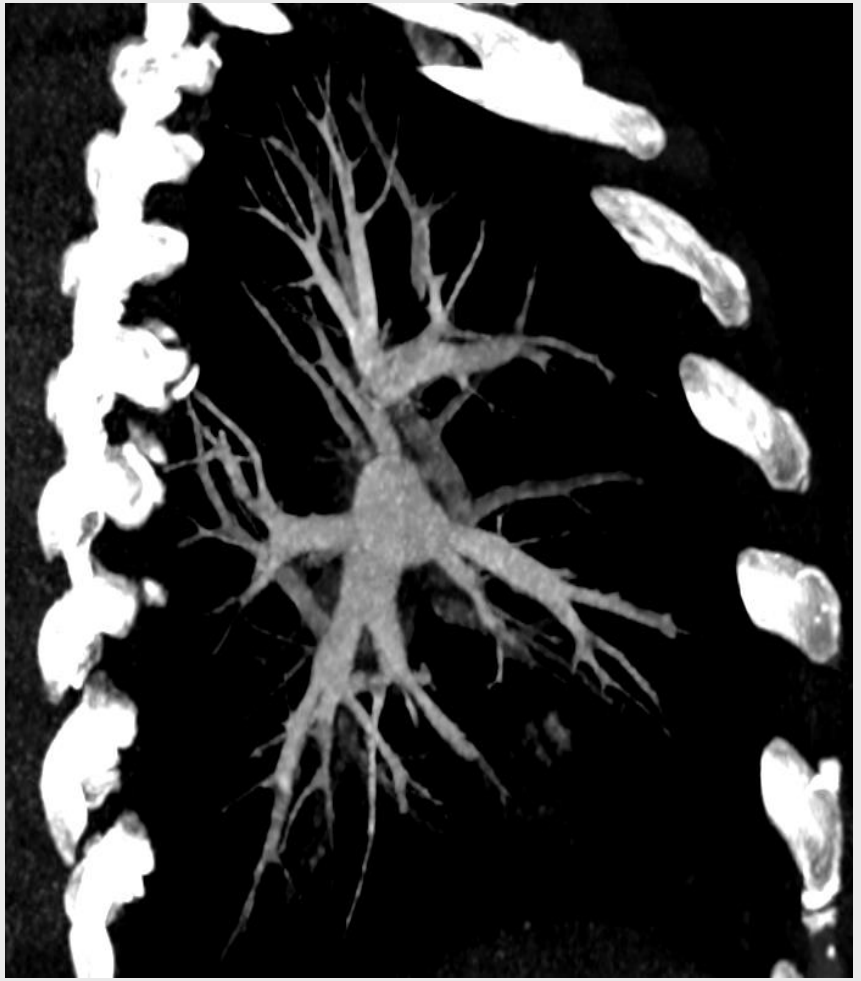




Courtesy: M. Humbert

Non-Eligible for BPA





Courtesy: M. Humbert

Current indication of BPA

- Diagnosed as CTEPH
- Inoperable
- ≥ NYHA II
- No contraindication for catheter intervention (Severe renal failure…)
- A case in which Type 1, 2, or 3 lesions confirmed at the periphery of the segmental branch

BPA in CTEPH : Main publications

	Inami 2014	Taniguchi 2014	Fukui S 2014	Paris AP-HP experience
Patient population	68 inop distal, age, comorbidity	13 inop distal 14 age, comorbidity 2 residual PH	16 inop distal, 2 comorbidity 1 residual PH 1 refusal	18 inop distal, 6 comorbidity 1 residual PH
Method	Angio	Angio, IVUS	Angio, CT	Angio
Medical treatment before BPA (%)	0%	100%	75%	75%
Procedures (n)	3.1	3.0	3.2	3.3
Severe BPA-related lung injury	7%	3.5%	0%	2.9%
Perforation	0.9%	4.7%	0%	2.9%
Follow-up	2 years	1 year	4 months	5 months
Mortality	1.5%	3.4%	0%	4%

Fukui S et al, Eur Respir J 2014 May;43(5):1394-402
Inami T et al, PLoS One 2014 Apr 11;9(4):e94587
Taniguchi Y et al, EuroIntervention 2014 Aug;10(4):518-25

Incidence, avoidance, and management of pulmonary artery injuries in percutaneous transluminal pulmonary angioplasty

Takumi Inami [a,1], Masaharu Kataoka [a,b,*,1], Nobuhiko Shimura [a], Haruhisa Ishiguro [a], Ryoji Yanagisawa [a], Takashi Kawakami [b], Keiichi Fukuda [b], Hideaki Yoshino [a], Toru Satoh [a]

[a] Division of Cardiology, Second Department of Internal Medicine, Kyorin University School of Medicine, Tokyo, Japan
[b] Department of Cardiology, Keio University School of Medicine, Tokyo, Japan

- Between 2009-2015, 540 BPA sessions in 143 patients, 55 pulmonary artery injuries (38% of patients)

- 10.2% of sessions
  - 8% guidewire perforations (too deep insertion)
  - 1.3% pulmonary artery dissection
  - 0.6% pulmonary artery rupture (oversized balloon catheter)
  - 0.3% high-pressure perfusion injury

- 2.4% spontaneous resolution and 7.8% active treatment (balloon sealing, embolization, stents)

Inami et al., Int J Cardiol. 2015 Dec 15;201:35-7

BPA in CTEPH: Haemodynamic results

	N	Before BPA PVR (dyn.s.cm^{-5})	After BPA PVR (dyn.s.cm^{-5})	Treatment effect
Mizoguchi 2012	68	942±367	327±151	-65%
Sugimura 2012	12	672±236	310±73	-54%
Andreassen 2013	20	704±320	472±288	-33%
Fukui 2014	20	889±365	490±201	-45%
Taniguchi 2014	29	763±308	284±128	-63%
Bicêtre AP-HP	25	675	370	-45%

Mizoguchi H, Circ Cardiovasc Interv 2012 Dec;5(6):748-55; Sugimura K, Circ J. 2012;76(2):485-8; Andreassen A, Heart 2013 Oct;99(19):1415-20; Fukui S et al, Eur Respir J 2014 May;43(5):1394-402; Taniguchi Y et al, EuroIntervention 2014 Aug;10(4):518-25

Diverse therapies for CTEPH

	Pulmonary Endarterectomy SURGICAL	Angioplasty INTERVENTIONAL	Drugs MEDICAL
Experience	>7000 cases	~400 cases reported	~1000 cases reported 4 RCT
Procedures	1	Multiple (3-5)	-
Invasiveness	High	Moderate	Low
Treatment effect (decrease in PVR)	-65% (San Diego and CTEPH registry)[1,2]	-33-65% [4,5,6,7,8]	-19-29% (RCT)[9,10,11,]
Long-term outcome	- Better 3-year survival compared to medical treatment[3] - >5-year survival reported	3-4 years	5 years
Cost	~ 50 000 euros	~ 25 000 euros	30 000 euros/year

1. Madani M, Ann Thorac Surg 2012; 2. Mayer E, J Thorac Cardiovasc Surg 2011; 3. Simonneau G, ATS 2013; 4. Sugimura K, Circ J 2012; 5. Mizoguchi H, Circ Cardiovasc Interv 2012; 6. Andreassen A, Heart 2013; 7. Fukui S, Eur Respir J 2014; 8. Taniguchi Y et al, EuroIntervention 2014; 9. Jais X, JACC 2008; 10. Suntharalingam J, Chest 2008; 11. Ghofrani A, New Engl J Med 2013; 12. Ghofrani A, ATS 2017

Main issues in non-operable CTEPH patients

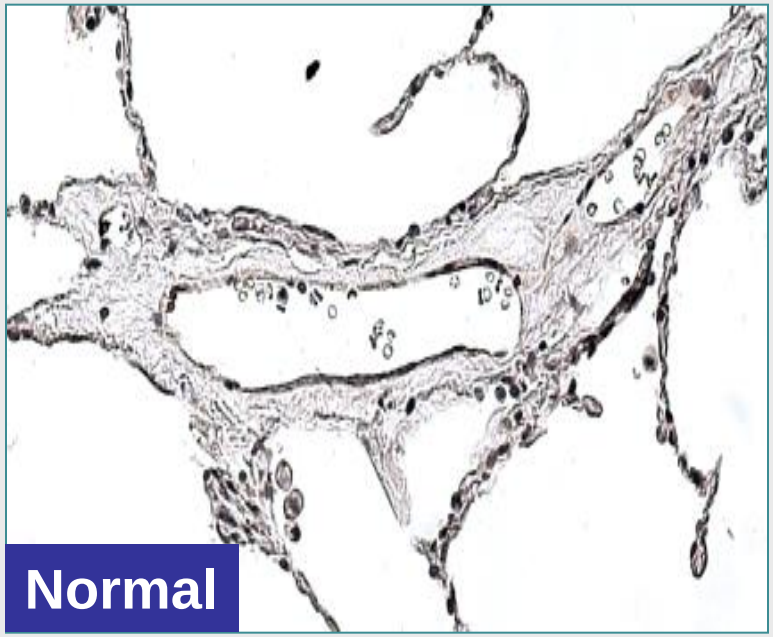
- BPA has never been prospectively evaluated
- No trial comparing safety and efficacy of medical therapy with riociguat vs BPA (RACE Study currently enrolling: BPA or Riociguat for inoperable patients)
- Respective places of medical treatment and BPA need to be further evaluated

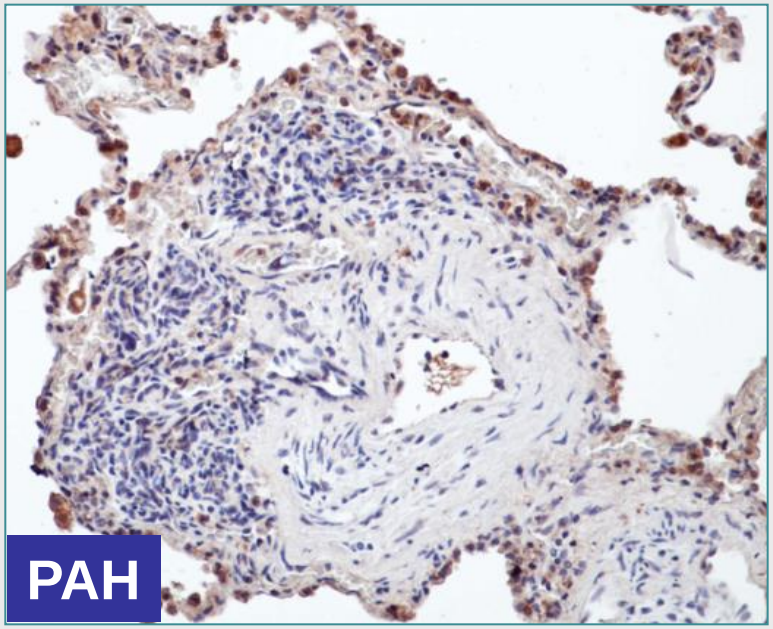
Conclusion

- Pulmonary endarterectomy remains the treatment of choice for CTEPH
- There is currently only one approved medical therapy (riociguat) for inoperable CTEPH or residual postoperative PH
- Impact of medical therapy on survival remains unlear
- Medical therapy should not be started before referral for PEA and should not delay time to referral
- BPA requires further evaluation before it can be recommended as an established treatment for CTEPH
- Further studies are needed to better determine the respective roles of medical therapy and BPA in the management of CTEPH

Pulmonary arterial hypertension: A severe pulmonary vascular disease

- Definition: chronic pre-capillary pulmonary hypertension (PAPm $\geq$ 25 mmHg, PAPO $\leq$ 15 mmHg
- Cause: progressive structural remodeling of the small pulmonary arteries
- Consequence: right heart failure and death





PAH, pulmonary arterial hypertension. Images are presenter's own.
Galiè N *et al. Eur Heart J* 2016;37:67–119. Galiè N *et al. Eur Respir J* 2015;46:903–75.

Classification

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 diseases (Table 5)
  - 1.4.5 Schistosomiasis

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

- 1'.1 Idiopathic
- 1'.2 Heritable
  - 1'.2.1 EIF2AK 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

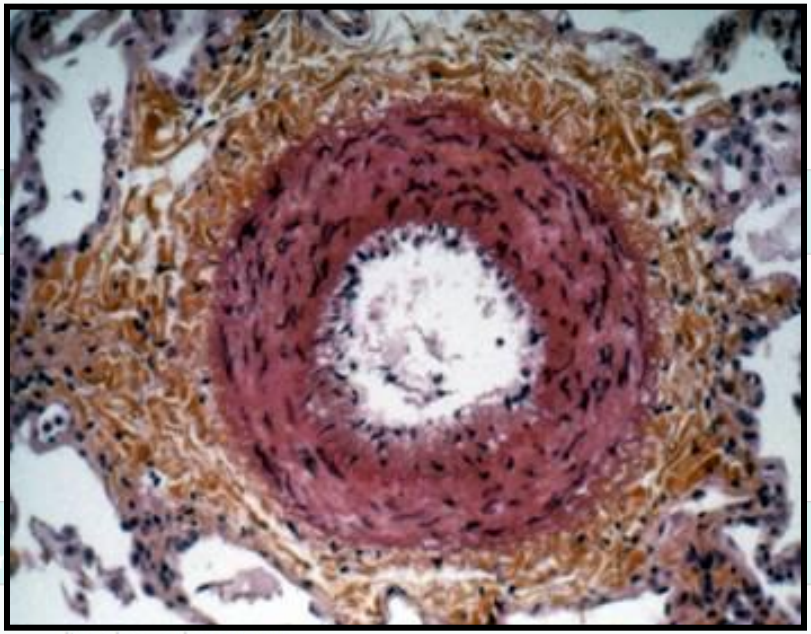
1''. Persistent pulmonary hypertension of the newborn

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

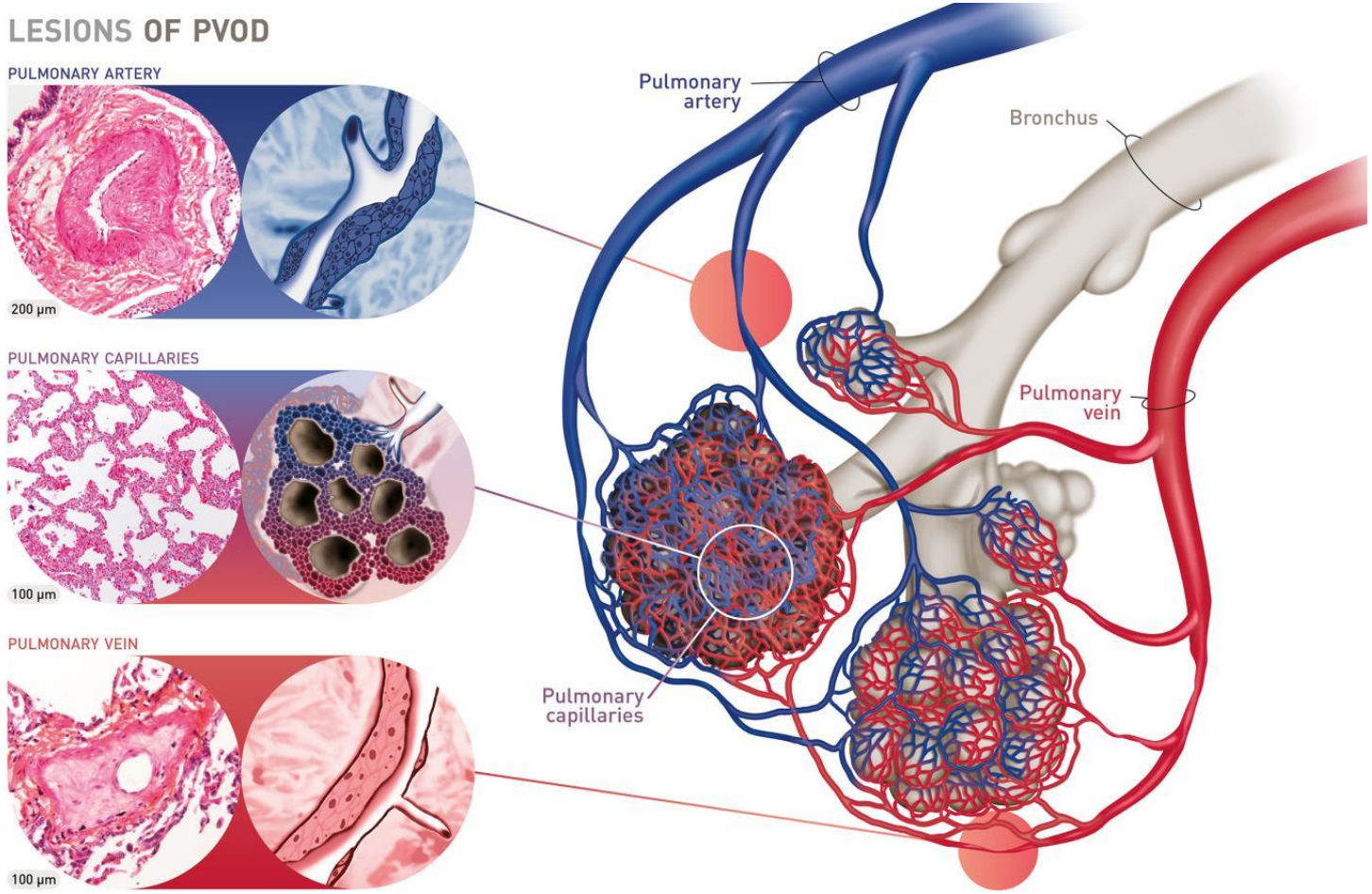


disorders, splenectomy.

- 5.2 Systemic disorders, sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
- 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
- 5.4 Others: pulmonary tumoral thrombotic microangiopathy, fibrosing mediastinitis, chronic renal failure (with/without dialysis), segmental pulmonary hypertension

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

Pulmonary veno-occlusive disease (PVOD)



Montani D et al. Eur Respir J 2016: 49(5)

PVOD versus idiopathic PAH

(all patients had histological confirmation)

Characteristic	PVOD (n = 24)	PAH (n = 24)	p Value
Sex			
Male	12	4	0.02
Female	12	20	
Age at diagnosis†, yr	40.1 ± 19.5	36.7 ± 13.3	0.49
Time to diagnosis†, mo	12.7 ± 11.7	15.0 ± 17.9	0.59
NYHA class at diagnosis			NS
Class II	2 (8.3%)	4 (16.7%)	
Class III	12 (50%)	15 (62.5%)	
Class IV	10 (41.7%)	5 (20.8%)	
Hemoptysis	1 (4.2%)	2 (8.3%)	NS
Raynaud phenomenon	2 (8.3%)	4 (16.7%)	NS
Syncope/near syncope	11 (45.8%)	11 (45.8%)	NS
Right heart failure	13 (54.2%)	14 (58.3%)	NS
Clubbing	4 (16.7%)	2 (8.3%)	NS

Montani D, et al. Medicine 2008 Jul;87(4):220-33

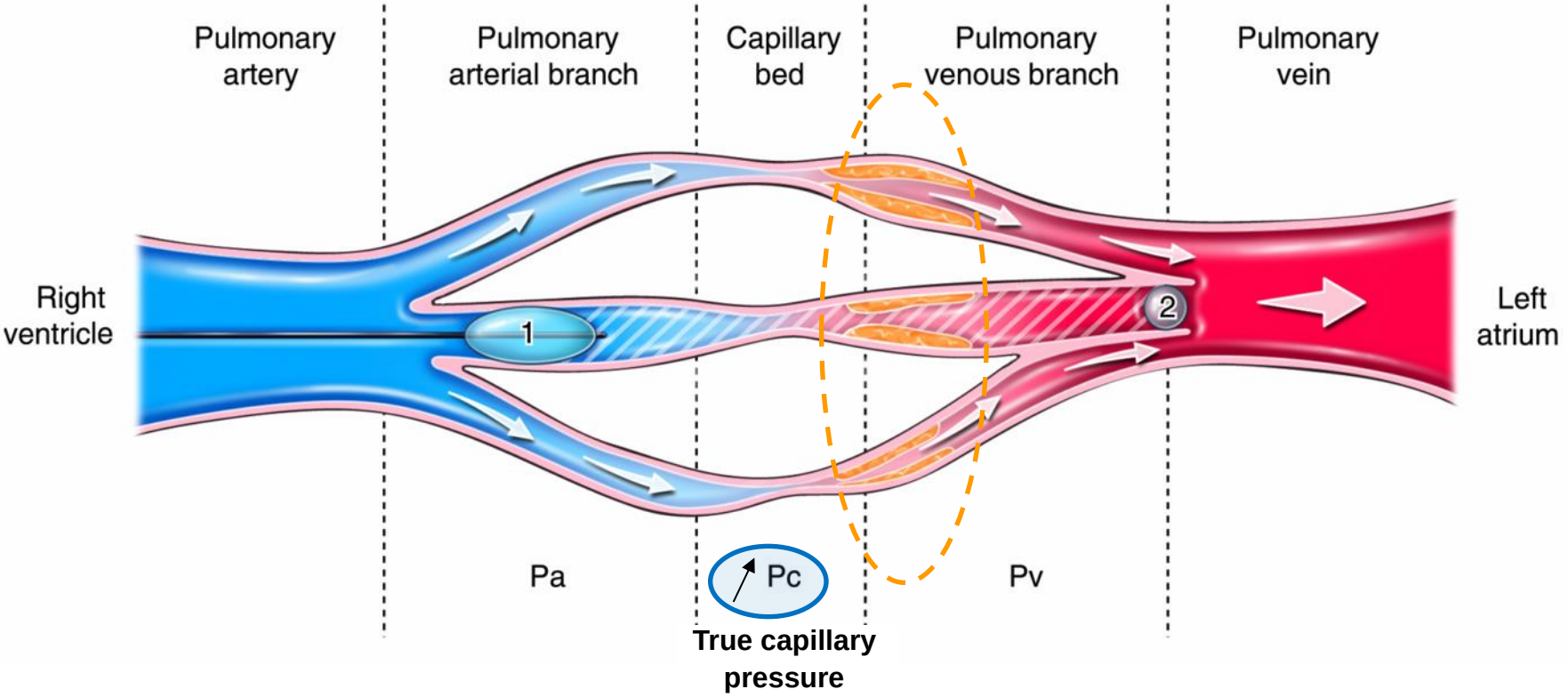
PVOD versus idiopathic PAH

(all patients had histological confirmation)

	PVOD (n = 24)	PAH (n = 24)	p Value
mPAP (mm Hg)	58.3 ± 12.4	62.9 ± 15.3	0.29
PCWP (mm Hg)	7.3 ± 3.1	7.8 ± 3.2	0.63
CI (L/min/m^2)	2.3 ± 0.8	2.1 ± 0.6	0.28
Systolic index (mL/min/m^2)	25.7 ± 10	24.3 ± 7.2	0.61
TPRi (U/m^2)	29.2 ± 13.5	31.9 ± 11.2	0.44
PVRi (U/m^2)	24.6 ± 12.6	25.7 ± 7.7	0.75
SvO2 (%)	59.7 ± 8.9	59.9 ± 10.7	0.94
Acute NO responders	1 (4.2%)	0	NS

Montani D, et al. Medicine 2008 Jul;87(4):220-33

Normal Pulmonary Artery Wedge Pressure in PVOD



True capillary pressure is increased but PCWP is normal because it is a reflection of the pressure in the large veins that are not affected by obstruction

Montani D et al. Eur Respir J 2016: 49(5)

PVOD versus idiopathic PAH

(all patients had histological confirmation)

Result	PVOD (n = 24)	PAH (n = 24)	p Value
PaO2 (mm Hg)	61.3 ± 17.3	75.4 ± 13.8	0.0085
PaCO2 (mm Hg)	30.6 ± 5.9	30 ± 3.5	0.71
FEV1 (% pred)	84.8 ± 14.7	90.2 ± 14.3	0.24
VC (% pred)	86.5 ± 17.6	93.8 ± 14.5	0.16
FEV1/VC (% pred)	80.7 ± 10.4	82 ± 6.4	0.63
TLC (% pred)	94.8 ± 18.0	98.1 ± 11.7	0.50
DLCO (% pred)	51.9 ± 19.3	70.5 ± 15.2	0.005
DLCO/VA (% pred)	41.8 ± 23.9	63.2 ± 13.6	0.002
Six-minute walk test			
Distance, m	273.7 ± 137.2	283.3 ± 127.8	0.81
Nadir SpO2, %	80.3 ± 8.9	87.2 ± 7.1	0.015

FEV1, forced expiratory volume in 1 second; PFT, pulmonary function test; VA, alveolar volume; VC, vital capacity; TLC, total lung capacity.

Montani D, et al. Medicine 2008 Jul;87(4):220-33

PVOD versus idiopathic PAH

(HRCT of the chest)

Pulmonary Hypertension:
CT of the Chest in Pulmonary Venoocclusive Disease

American Journal of Roentgenology 2004

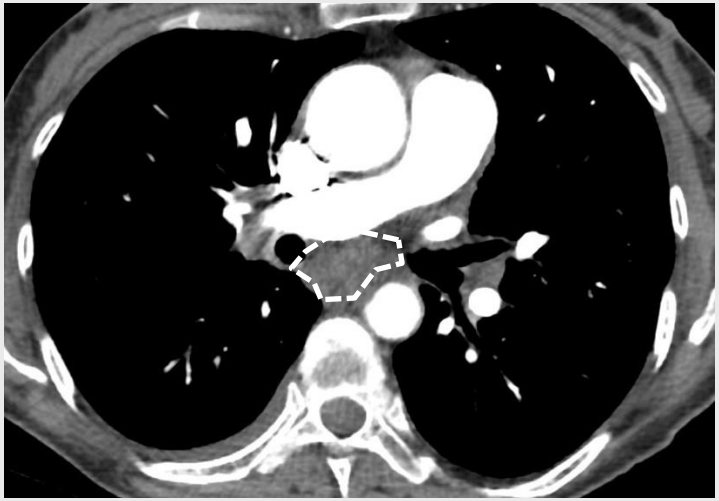
Arnaud Resten[1]
Sophie Maitre[1]
Marc Humbert[2]
Anne Rabiller[2]
Olivier Sitbon[2]
Frédérique Capron[3]
Gérald Simonneau[2]
Dominique Musset[1]

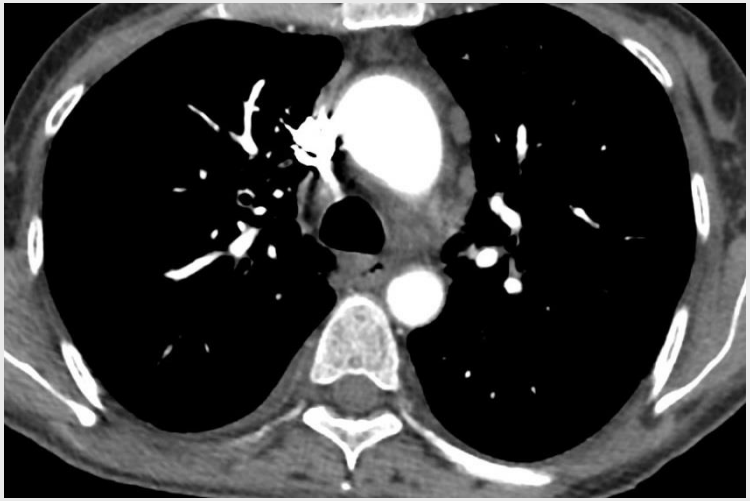
- **15 PVOD patients vs 15 idiopathic PAH patients**
- **3 radiologic abnormalities associated with PVOD**
  - **Lymph node enlargement**
  - **Septal lines**
  - **Centrilobular ground-glass opacities**

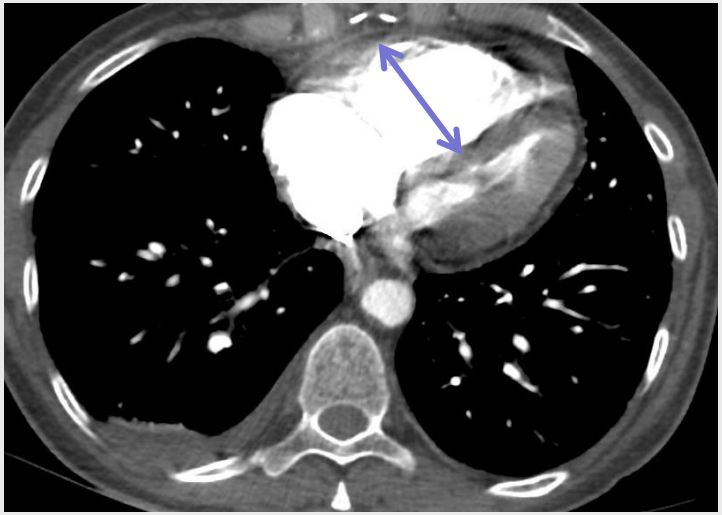
Resten A *et al.* AJR 2004 Jul;183(1):65-70

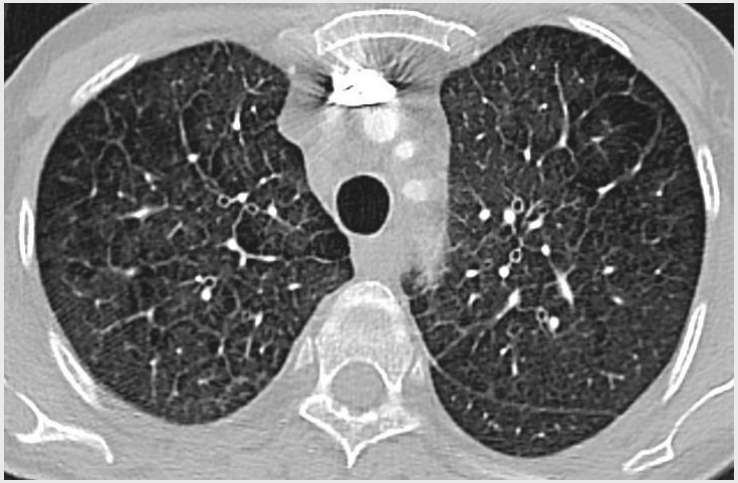
Signs of PVOD

(HRCT of the chest)



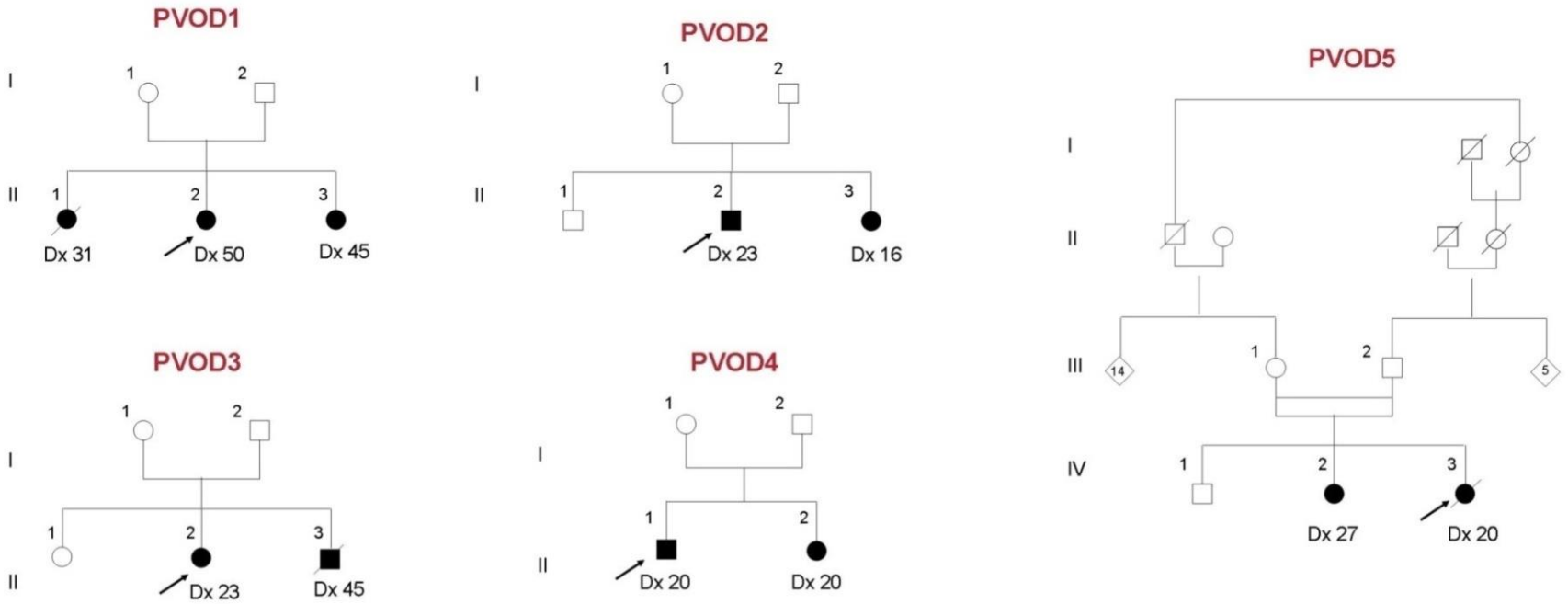






Montani D et al., Medicine (Baltimore) 2008; 87:220-233

Heritable pulmonary veno-occlusive disease

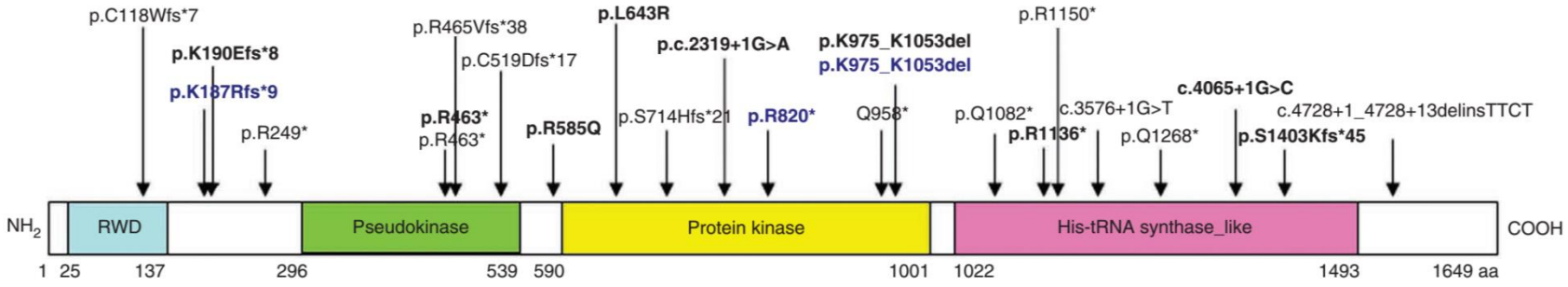


Eyries et al. Nat Genet 2014 Jan;46(1):65-9.

Bi-allelic EIF2AK4 mutations

EIF2AK4 mutations cause pulmonary veno-occlusive disease, a recessive form of pulmonary hypertension

Mélanie Eyries[1–3], David Montani[4–6], Barbara Girerd[4–6], Claire Perret[3,7], Anne Leroy[2], Christine Lonjou[8], Nadjim Chelghoum[8], Florence Coulet[2,3], Damien Bonnet[9,10], Peter Dorfmüller[6,11], Elie Fadel[6,12], Olivier Sitbon[4–6], Gérald Simonneau[4–6], David-Alexandre Tregouët[3,7], Marc Humbert[4–6] & Florent Soubrier[1–3]



Eyries et al. Nat Genet 2014 Jan;46(1):65-9.

Major PVOD subtypes

1’ PVOD (=PCH)

Idiopathic
Heritable
Drugs and toxins induced :
- ***chemotherapy***
- ***occupational exposure***

Associated with CTD *(systemic sclerosis)*

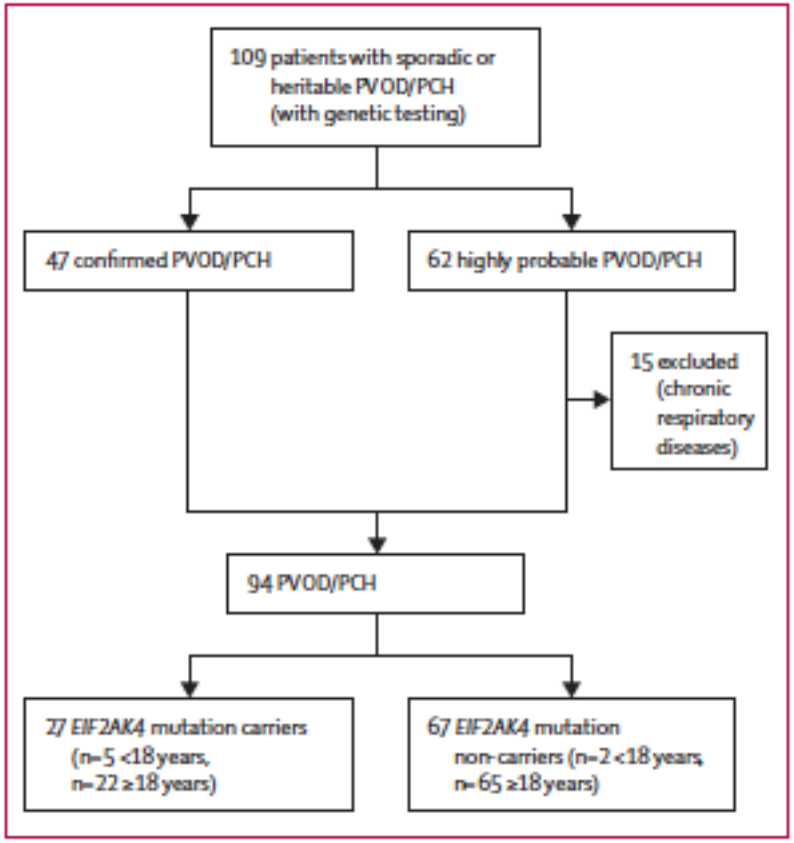
Galiè N *et al. Eur Heart J* 2016;37:67–119. Galiè N *et al. Eur Respir J* 2015;46:903–75

Clinical phenotypes and outcomes of heritable and sporadic pulmonary veno-occlusive disease: a population-based study

David Montani*, Barbara Girerd*, Xavier Jaïs, Marilyne Levy, David Amar, Laurent Savale, Peter Dorfmüller, Andrei Seferian, Edmund M Lau, Mélanie Eyries, Jérôme Le Pavec, Florence Parent, Damien Bonnet, Florent Soubrier, Elie Fadel, Olivier Sitbon, Gérald Simonneau, Marc Humbert

Summary

Background **Bi-allelic mutations of the *EIF2AK4* gene cause heritable pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis (PVOD/PCH). We aimed to assess the effect of *EIF2AK4* mutations on the clinical phenotypes and outcomes of PVOD/PCH.**



Montani D, Lancet Resp Med 2017;5:125-34

PVOD patients carrying *EIF2AK4* mutations were younger at diagnosis and at death compared to non carriers

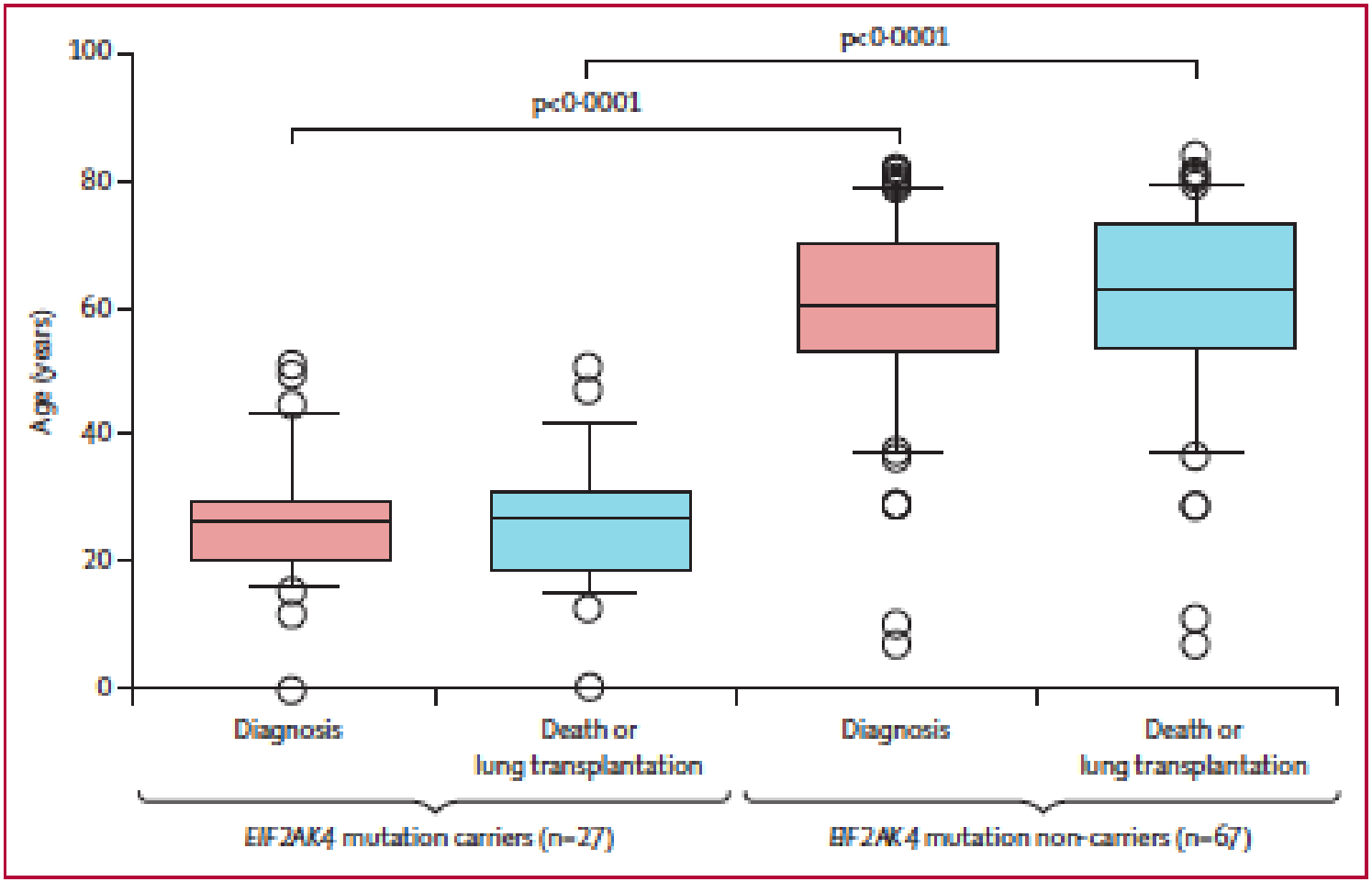


Figure 2: Age at PVOD/PCH diagnosis and age at death or lung transplantation

Montani D, Lancet Resp Med 2017;5:125-34

PVOD patients carrying *EIF2AK4* mutations were more likely to be transplanted as compared to noncarriers

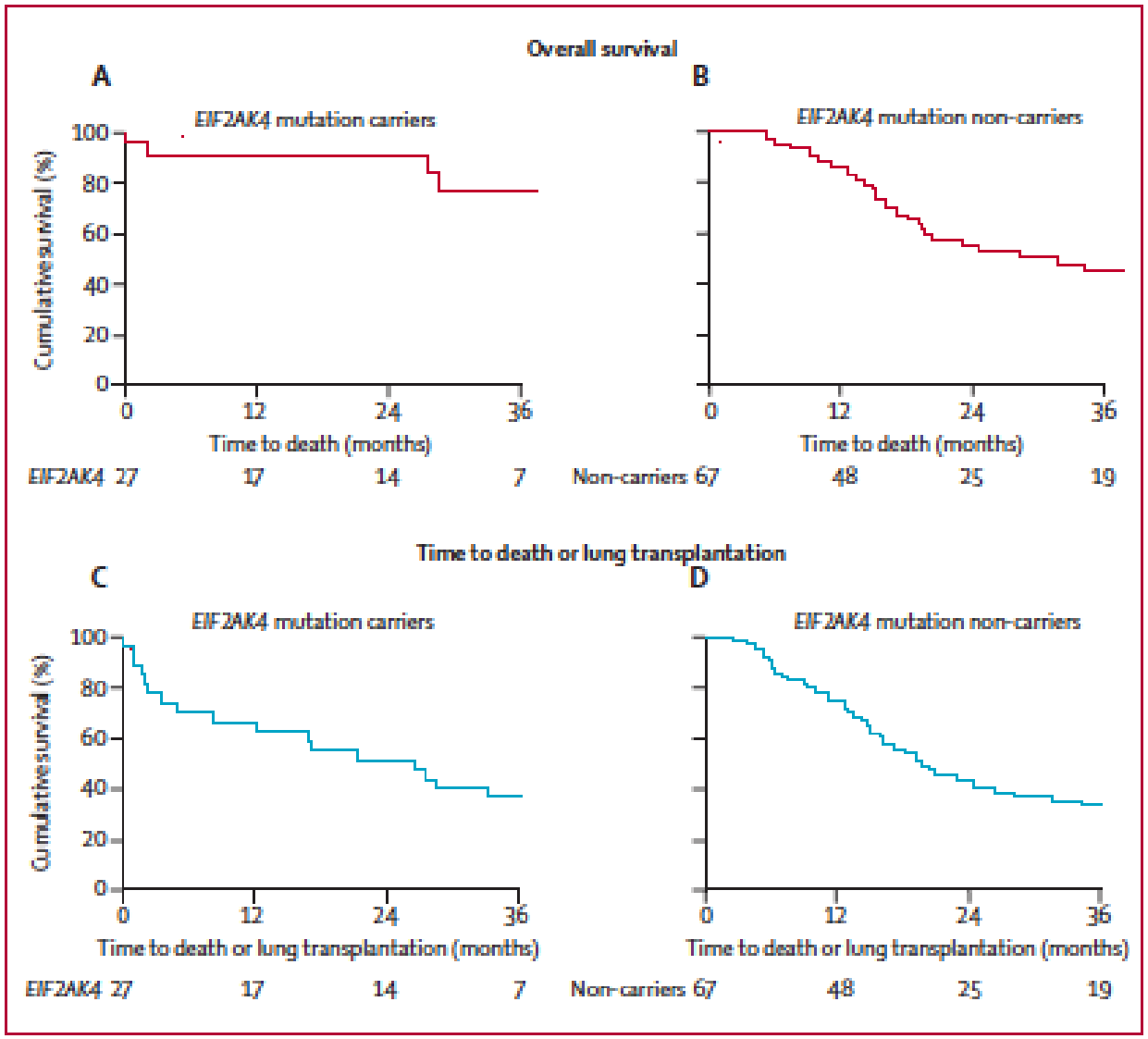


Figure 5: Overall survival and time to death or lung transplantation of *EIF2AK4* bi-allelic mutation carriers and non-carriers

Montani D, Lancet Resp Med 2017;5:125-34

PVOD in pediatric patients was often discovered in *EIF2AK4* mutations carriers

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
EIF2AK4 bi-allelic mutations	Yes	Yes	Yes	Yes	No	No	Yes
Age at diagnosis (years)	17	16	15	12	10	7	Birth
Sex	Male	Female	Female	Male	Male	Female	Male
NYHA functional class	III	III	IV	I–II	III	IV	–
mPAP (mm Hg)	75	39	54	24	49	73	–
PAWP (mm Hg)	8	8	7	11	8	5	–
Cardiac Index (L/min per m^2)	1·94	4·49	1·68	3·8	1·54	3·2	–
PVR (wood units)	24·7	4·4	18·8	2·3	26·3	21	–
High-resolution CT of the chest							
Lymph node enlargement	No	Yes	Yes	Yes	Yes	Yes	–
Centrilobular ground-glass opacities	Yes	Yes	Yes	Yes	Yes	Yes	–
Interlobular septal lines	Yes	Yes	Yes	Yes	Yes	Yes	–
Medical therapy for pulmonary arterial hypertension	ERA	ERA plus PDE5 inhibitor	Prostacyclin derivatives	ERA plus PDE5 inhibitor	ERA	PDE5 inhibitor	No
Outcome	Lung transplantation at 4 months	Lung transplantation at 21 months	Lung transplantation at 5 months	Lung transplantation at 17 months	Death at 17 months	Lung transplantation at 7 months	Death at 10 days

PVOD/PCH=pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis. NYHA=New York Heart Association. mPAP=mean pulmonary artery pressure. PAWP=pulmonary artery wedge pressure. PVR=pulmonary vascular resistance. ERA=endothelin receptor antagonist. PDE5=phosphodiesterase type 5. –=data not available.

Table 3: Clinical, functional, and haemodynamic characteristics at diagnosis, and outcomes of paediatric cases of PVOD/PCH

Montani D, Lancet Resp Med 2017;5:125-34

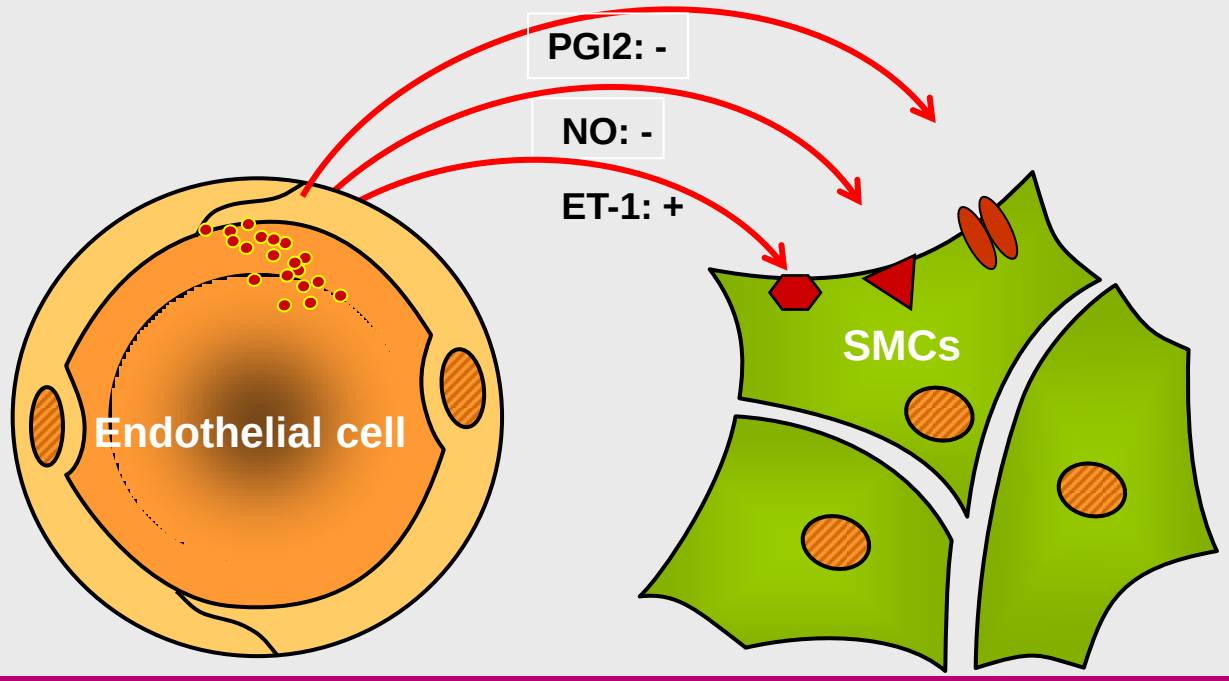
Conclusions

- PVOD may be idiopathic, heritable (autosomal recessive), drug/toxin-induced, or associated with connective tissue disease (systemic sclerosis)
- PVOD is characterized by hypoxaemia, low DLCO, HRCT showing ground-glass opacities, septal lines and lymph node enlargement
- PVOD is rare but severe (refractory to PAH therapy and sometimes with pulmonary edema induced by therapy)
- Eligible PVOD patients should be considered for lung transplantation

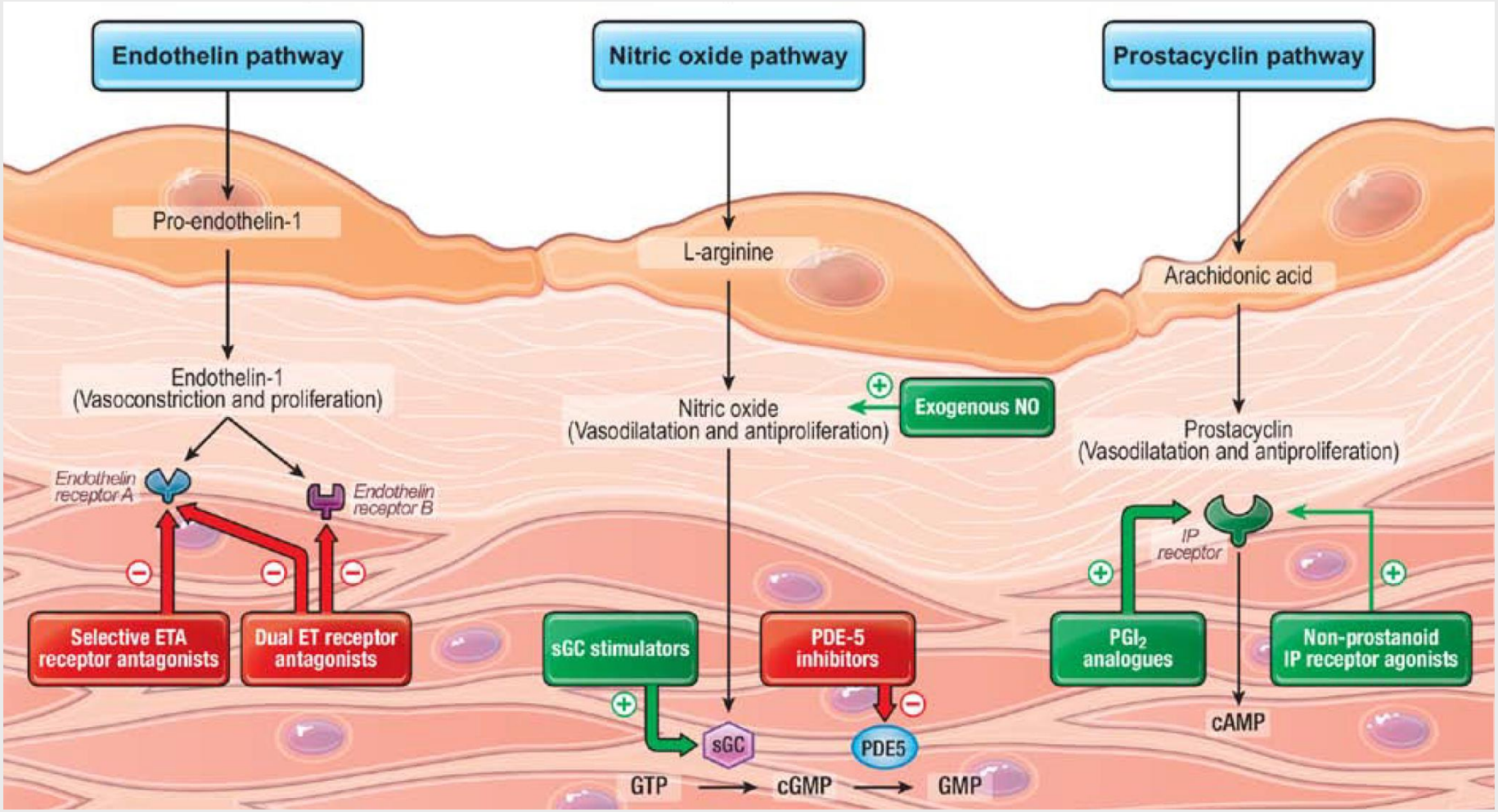
Pulmonary arterial hypertension: a rare, but not an orphan, disease

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

- Rare: prevalence 15–50/million (incidence 6/million/year)
- Pathophysiology: pulmonary artery endothelial cell dysfunction
- Drugs: 10 agents approved in the last 15 years (orphan drug status)
- Lung/heart–lung transplantation: if refractory to medical therapy



Targeting endothelial dysfunction in PAH



Humbert et al. Circulation 2014;130:2189-2208

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

Risk assessment in pulmonary arterial hypertension

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 >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 <11 ml/min/kg (<35 % pred.) VE/VCO_2 ≥45
NT-proBNP plasma levels	BNP <50 ng/l NT-proBNP <300 ng/ml	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 Heart J* 2016;37:67–119. Galiè N *et al. Eur Respir J* 2015;46:903–75

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
It is recommended to perform regular follow-up assessments every 3–6 months in stable patients (Table 12).	I	C
Achievement/maintenance of a low-risk profile (Table 13) is recommended as an adequate treatment response for patients with PAH.	I	C
Achievement/maintenance of an intermediate-risk profile (Table 13) should be considered an inadequate treatment response for most patients with PAH.	IIa	C

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

2015 ESC/ERS Pulmonary Hypertension Guidelines: risk assessment

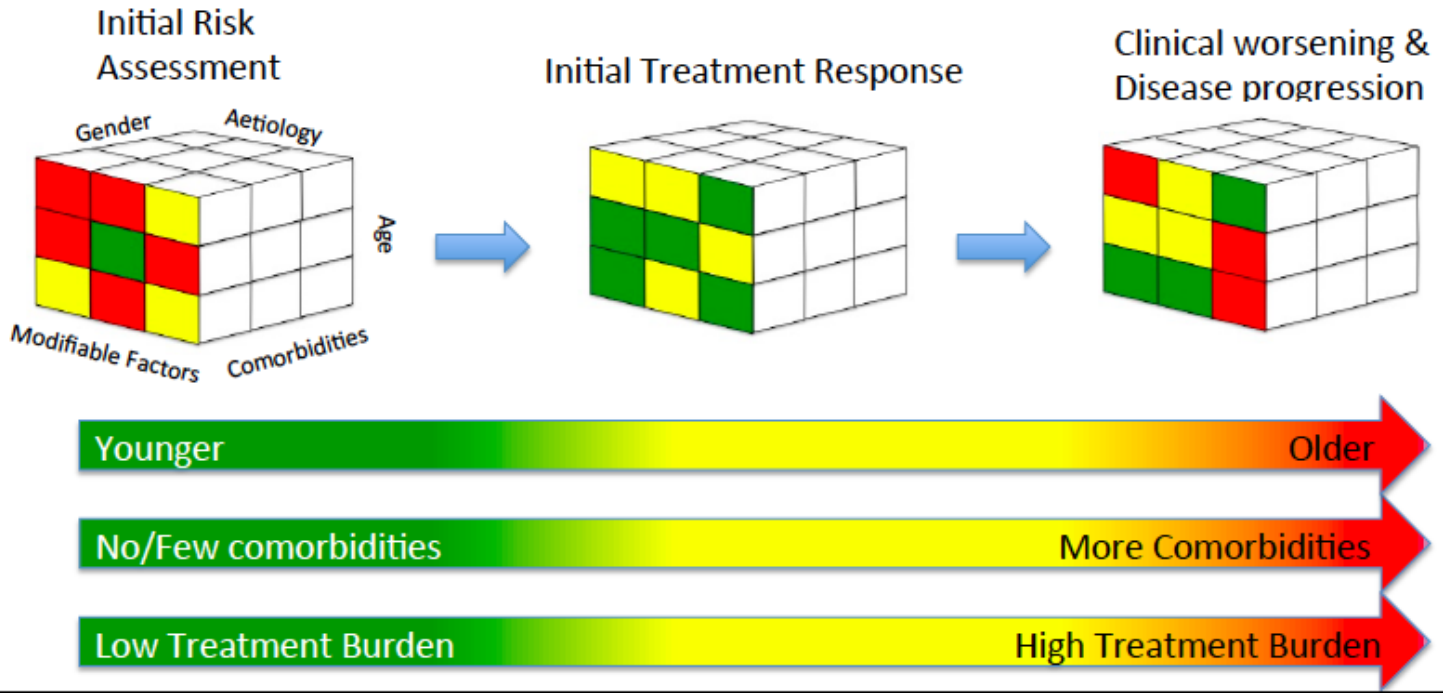
Determinants of prognosis[a] (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope[b]	Repeated syncope[c]
WHO functional class	I, II	III	IV
6MWD	>440 m	165–440 m	<165 m
Cardiopulmonary exercise testing	Peak VO_2 >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 <11 ml/min/kg (<35% pred.) VE/VCO_2 ≥45
NT-proBNP plasma levels	BNP <50 ng/l NT-proBNP <300 ng/ml	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%

ESC: European Society of Cardiology; ERS: European Respiratory Society

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

Risk assessment in pulmonary arterial hypertension

Modifiable Prognostic Variables	Low (<5%)	Intermediate (5-10%)	High (>10%)
Symptoms/ Functional Class			
Exercise Capacity			
Right ventricular function			



Weatherald, Sitbon & Humbert. Eur Heart J 2017; in press

Objectives and hypothesis

- To apply the risk assessment criteria from the 2015 ESC/ERS guidelines to an incident cohort of patients with PAH.
- To determine survival according to the number of low risk criteria at diagnosis and the number achieved during the first year of treatment.
- We hypothesised that survival would be better in patients achieving all low risk criteria compared to those who achieved fewer criteria.

Methods

Evaluation of low-risk criteria

- NYHA functional class I or II
- 6MWD > 440 m
- right atrial pressure (RAP) < 8 mmHg
- cardiac index ≥ 2.5 L/min/m^2

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

At baseline

At first follow-up

Classification according to number of low-risk criteria present

Univariate and multivariate stepwise Cox proportional hazards regression

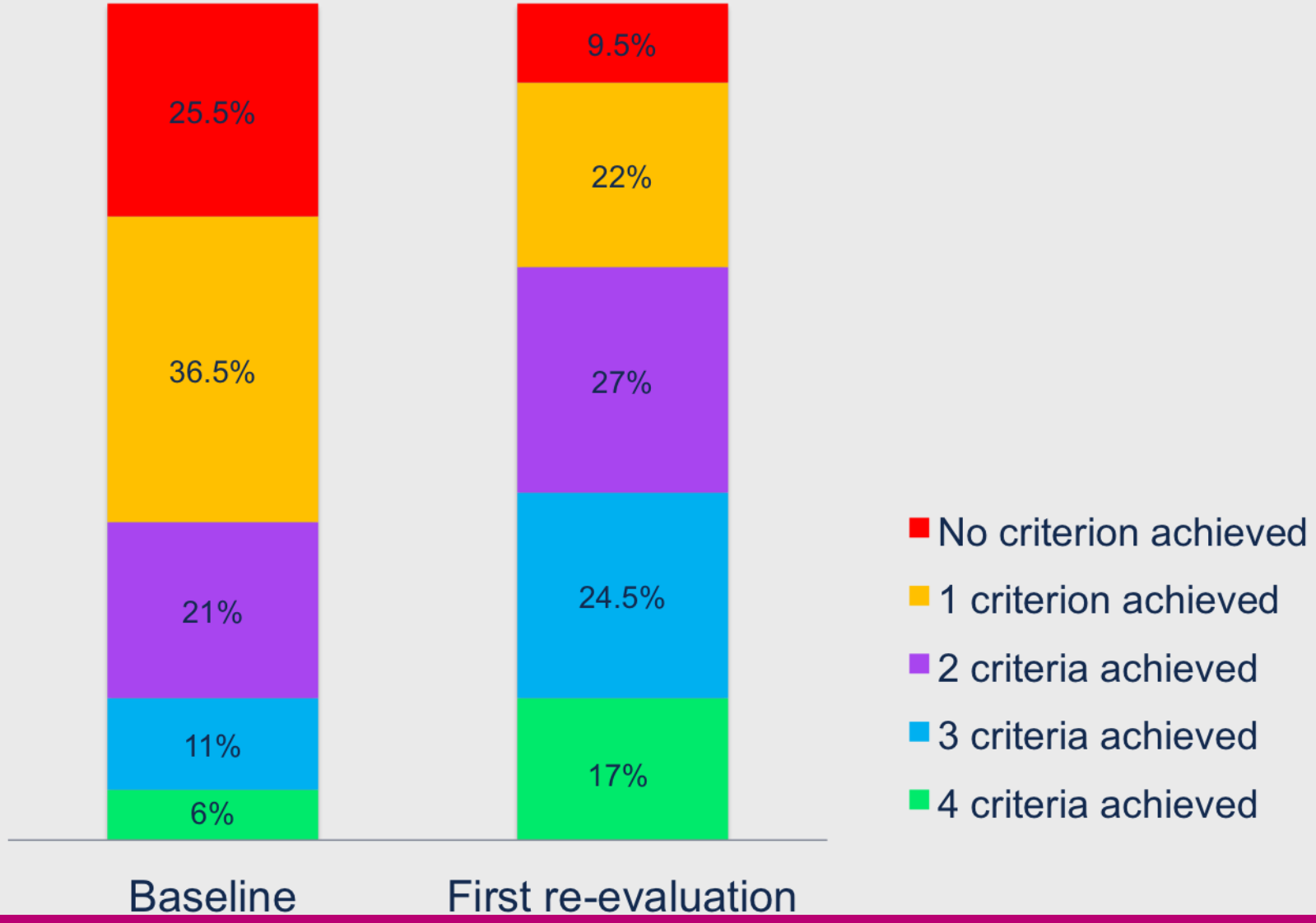
Kaplan-Meier survival curves Transplant free-survival according to the number of low-risk criteria

Change in NYHA class, 6MWD and haemodynamics at first re-evaluation

n = 1017	Baseline	First re-evaluation (4.4 months)	p value
NYHA FC, n (%) **I-II** **III** **IV**	 261 (26) 624 (61) 132 (13)	 595 (59) 349 (34) 73 (7)	 <0.0001
6 MWD, m	311 ± 145	354 ± 145	<0.0001
RAP, mmHg **mPAP**, mmHg **Cardiac output**, L/min **Cardiac index**, L/min/m^2 **PVR**, WU **SvO$_2$**, %	8.6 ± 5.0 50 ± 13 4.4 ± 1.4 2.4 ± 0.7 10.5 ± 5.9 63 ± 10	7.5 ± 4.8 44 ± 13 5.3 ± 1.6 2.9 ± 0.8 7.1 ± 4.6 67 ± 8	<0.0001 <0.0001 <0.0001 <0.0001 <0.0001 <0.0001

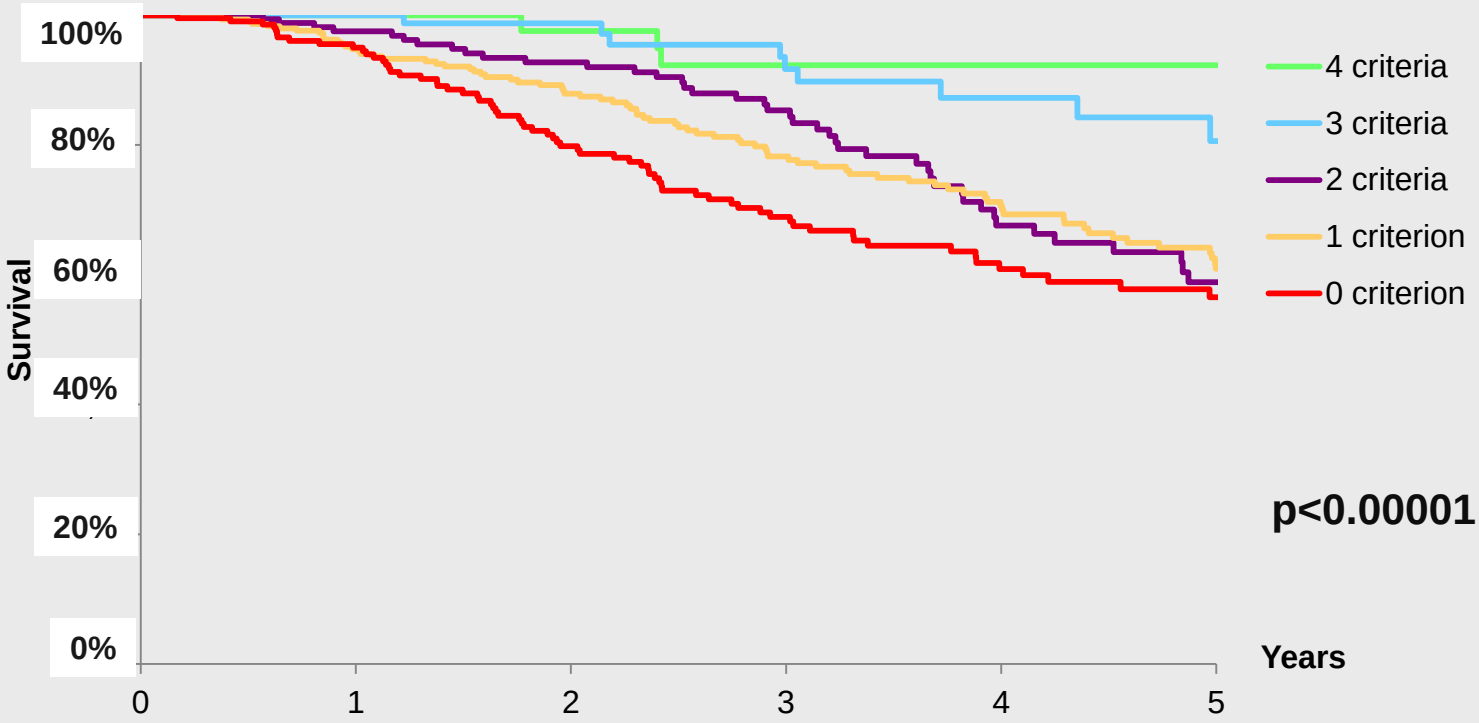
Boucly A, et al. 2017 ATS Conference

Change in “low-risk” criteria



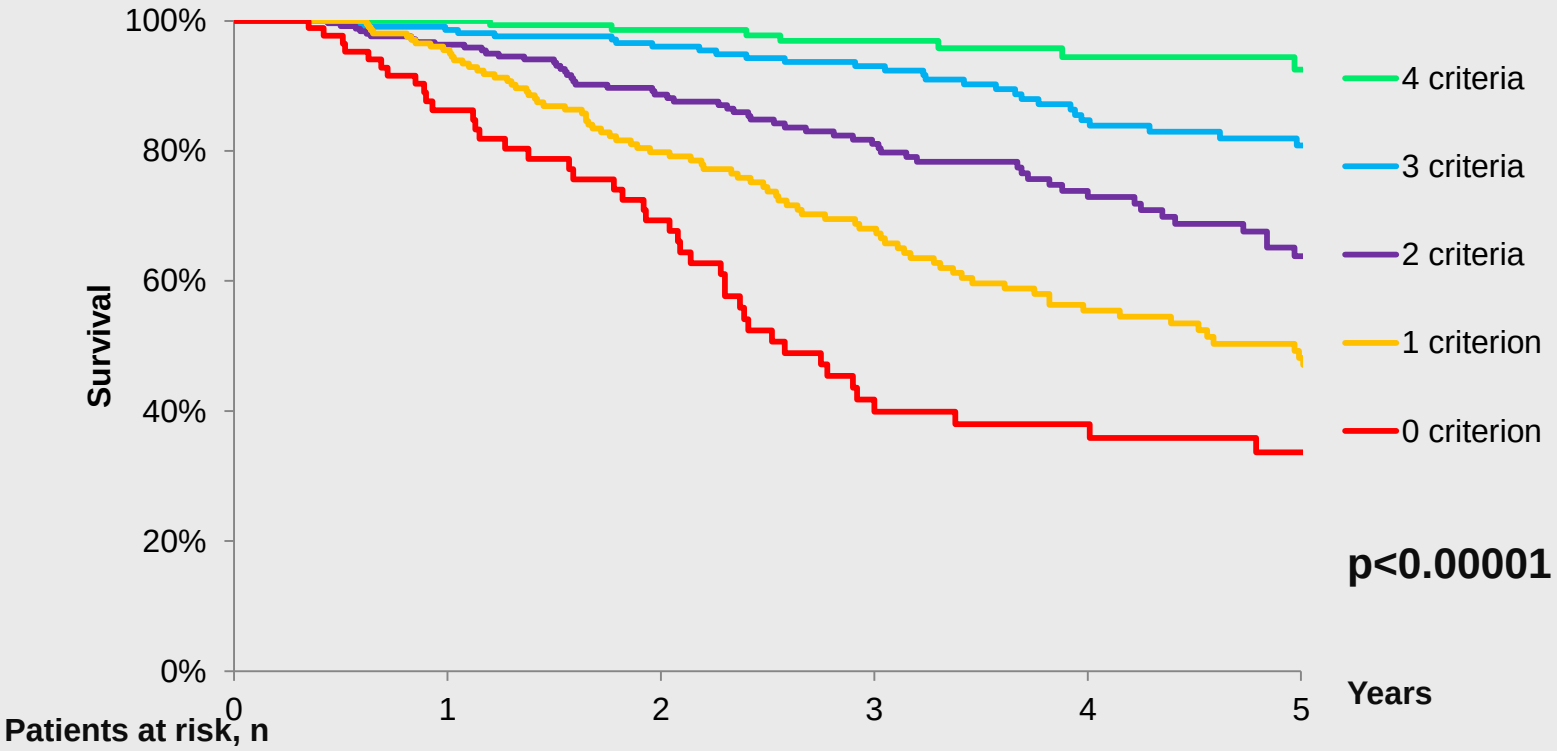
Boucly A, et al. 2017 ATS Conference

Transplant-free survival according to the number of “low-risk” criteria present at baseline



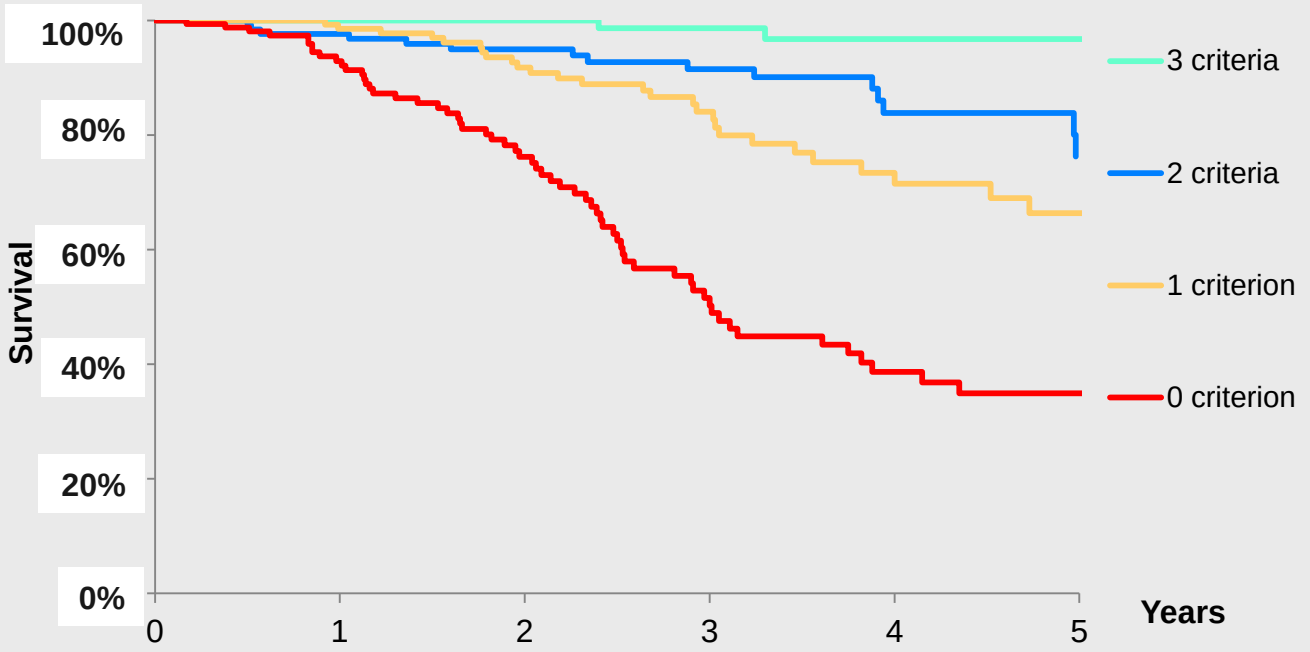
Boucly A, et al. 2017 ATS Conference

Transplant-free survival according to the number of "low-risk" criteria achieved at first re-evaluation



Boucly A, et al. 2017 ATS Conference

Transplant-free survival according to the number of non-invasive "low-risk" criteria achieved at first re-evaluation



Low-risk criteria analysed:

- NYHA FC I-II
- 6MWD > 440 m
- BNP <50 ng/L or NT-proBNP <300 ng/mL

p<0.00001

Patients at risk, n=603

Boucly A, et al. 2017 ATS Conference

Conclusions

- A multidimensional approach is essential for risk assessment of patients with PAH

- The more the low-risk criteria is achieved, the better is the survival → the ideal treatment goal is to obtain and maintain a maximum number of clinical and hemodynamic low-risk criteria

- The presence of simple non-invasive low-risk criteria such as NYHA functional class I-II, 6MWD > 440 m and normal level of BNP/NT-proBNP could identify a subset of patients for whom an invasive haemodynamic follow-up is questionnable

Relevant new aspects

1. Couturaud F, at al. Six months vs extended anticoagulation after a first episode of pulmonary embolism: the PADIS-PE randomized controlled trial. JAMA 2015; 314:31-40.
2. Weitz JI, et al. Rivaroxaban or aspirin for extended treatment of venous thromboembolism. N Engl J Med 2017; 376:1211-22
3. Kearon C, et al. Antithrombotic therapy for VTE disease: CHEST guidelines and expert panel report. Chest 2016; 149:315-52.
4. Galiè N, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J 2015; 46: 903-75 and Eur Heart J 2016; 37:67-119.
5. Kawakami T, et al. Novel angiographic classification of each vascular lesion in chronic thromboembolic pulmonary hypertension based on selective angiogram and results of balloon pulmonary angioplasty. Circ Cardiovasc Interv 2016; 9(10). pii: e003318.
6. Ghofrani HA, et al. Efficacy and safety of macitentan for inoperable chronic thromboembolic pulmonary hypertension: results from the randomized controlled MERIT-1 study. ATS Conference (Washington May 2017)
7. Montani D, et al. Clinical phenotypes and outcomes of heritable and sporadic pulmonary veno-occlusive disease: a population-based study. Lancet Respir Med 2017; 5:125-34.
8. Boucly A, et al. Risk assessment and prognosis in pulmonary arterial hypertension: implementation of the 2015 European pulmonary hypertension guidelines. ATS Conference (Washington May 2017)

List of References

1. Konstantinides et al. Eur Heart J 2014; 35:3033-80
2. Couturaud F et al. JAMA 2015; 314:31–40
3. Kearon C, et al. Chest 2016; 149: 315-52
4. Weitz JI, et al. N Engl J Med 2017; 376:1211-22
5. Galiè N *et al. Eur Heart J* 2016;37:67–119. Galiè N *et al. Eur Respir J* 2015;46:903–75
6. Delcroix M et al. Circulation 2016; 133:859-71
7. Jais X, J Am Coll Cardiol. 2008 Dec 16;52(25):2127-34
8. Suntharalingam J, Chest 2008 Aug;134(2):229-236.
9. Ghofrani HA, NEJM 2013 Dec 5;369(23):2268
10. Gatfield J, *et al. PLoS ONE* 2012; 7:e47662
11. Pulido T, *et al. N Engl J Med* 2013; 369:809-18
12. Ghofrani HA, et al. 2017 ATS Conference
13. Kawakami et al. Circ Cardiovasc Interv 2016; 9(10). pii: e003318
14. Sugiyama M et al. Jpn J Radiol 2014 Jul;32(7):375-82
15. Fukui S et al, Eur Respir J 2014 May;43(5):1394-402
16. Inami T et al, PLoS One 2014 Apr 11;9(4):e94587
17. Taniguchi Y et al, EuroIntervention 2014 Aug;10(4):518-25
18. Inami et al., Int J Cardiol. 2015 Dec 15;201:35-7
19. Mizoguchi H, Circ Cardiovasc Interv 2012 Dec;5(6):748-55
20. Sugimura K, Circ J. 2012;76(2):485-8
21. Andreassen A, Heart 2013 Oct;99(19):1415-20
22. Madani M, Ann Thorac Surg 2012 Jul;94(1):97-103
23. Mayer E, J Thorac Cardiovasc Surg 2011 Mar;141(3):702-10
24. Simonneau G, ATS 2013

List of References

25. Montani D et al. Eur Respir J 2016: 49(5
26. Montani D et al., Medicine (Baltimore) 2008; 87:220-233
27. Resten A *et al.* AJR 2004 Jul;183(1):65-70
28. Eyries et al. Nat Genet 2014 Jan;46(1):65-9.
29. Montani D, Lancet Resp Med 2017;5:125-34
30. Humbert et al. Circulation 2014;130:2189-2208
31. Weatherald, Eur Heart J 2017; in press
32. Boucly A, et al. 2017 ATS Conference