Von Thrombose zu Fibrose

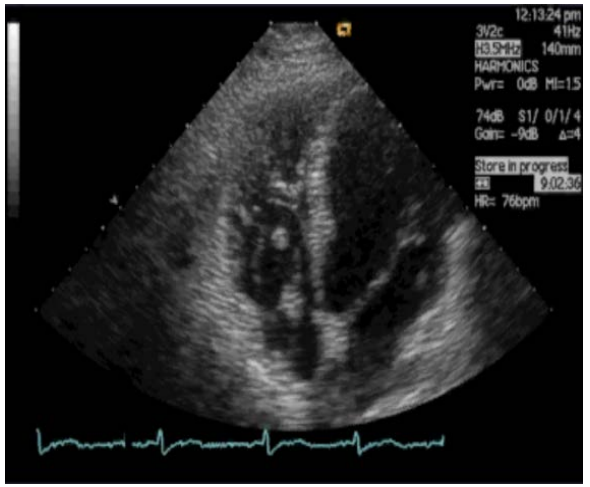
Irene M Lang
Medical University of Vienna, Austria
Irene.lang@meduniwien.ac.at

THROMBOSE FORUM 2019

Venöser Thromboembolismus

DVT

1 pro 1000



Embolus in transit

?

Akute PE

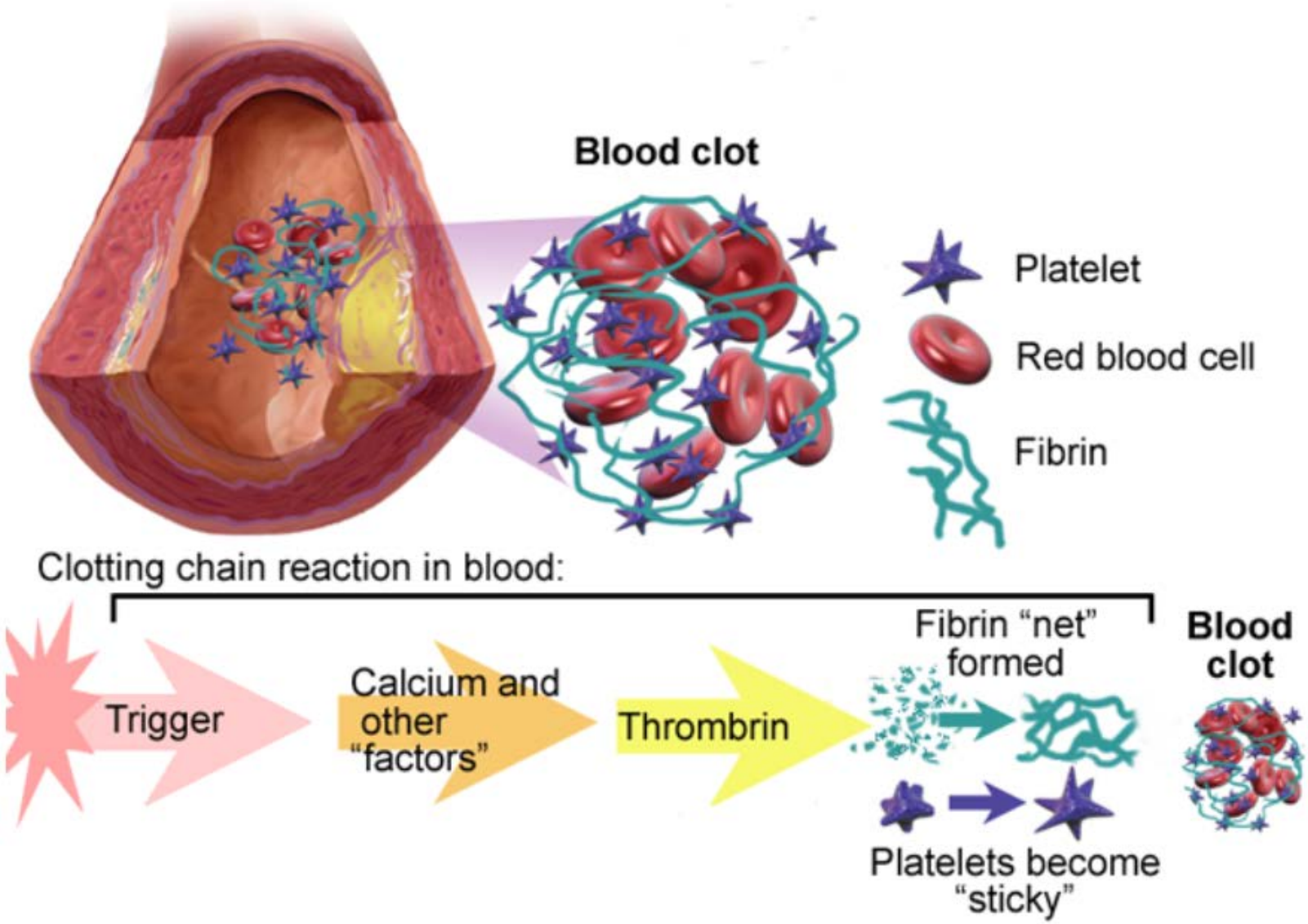
<1 pro 1000

CTEPH

45 pro Million

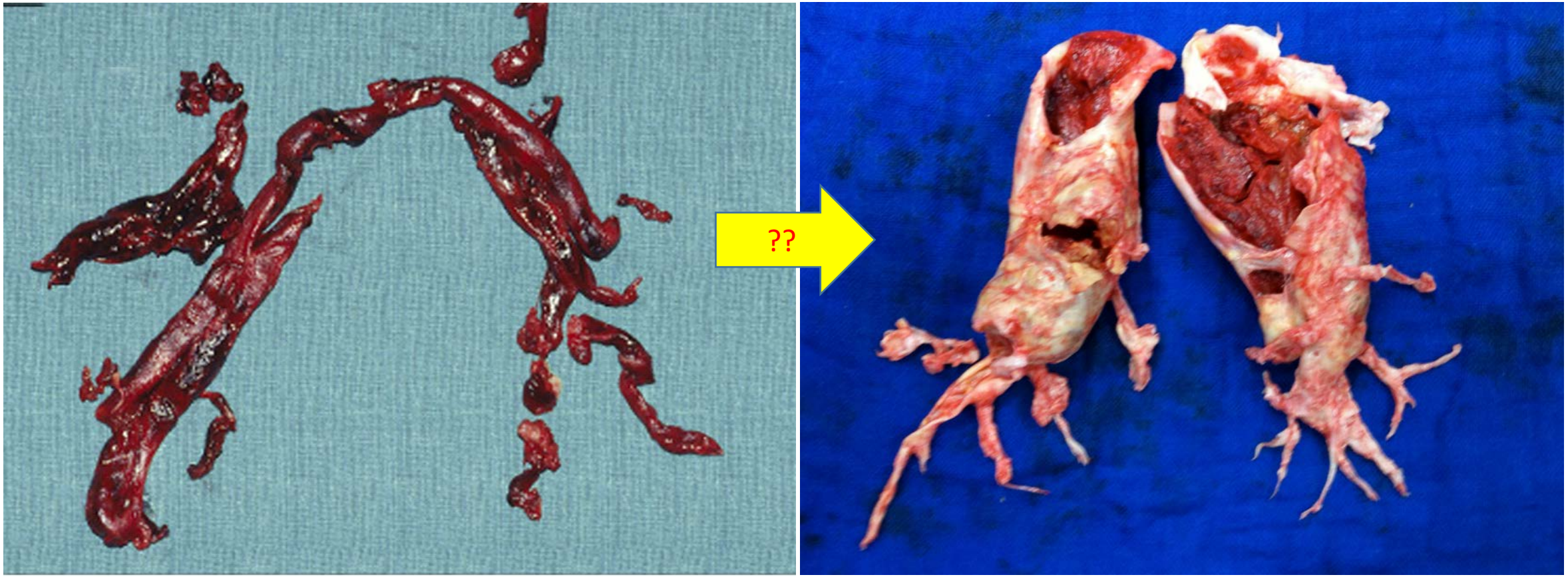
International CTEPH Registry. Pepke-Zaba J *Circulation* 2011;124:1973–81.

Thrombose



Adapted from *Medmovie.com*

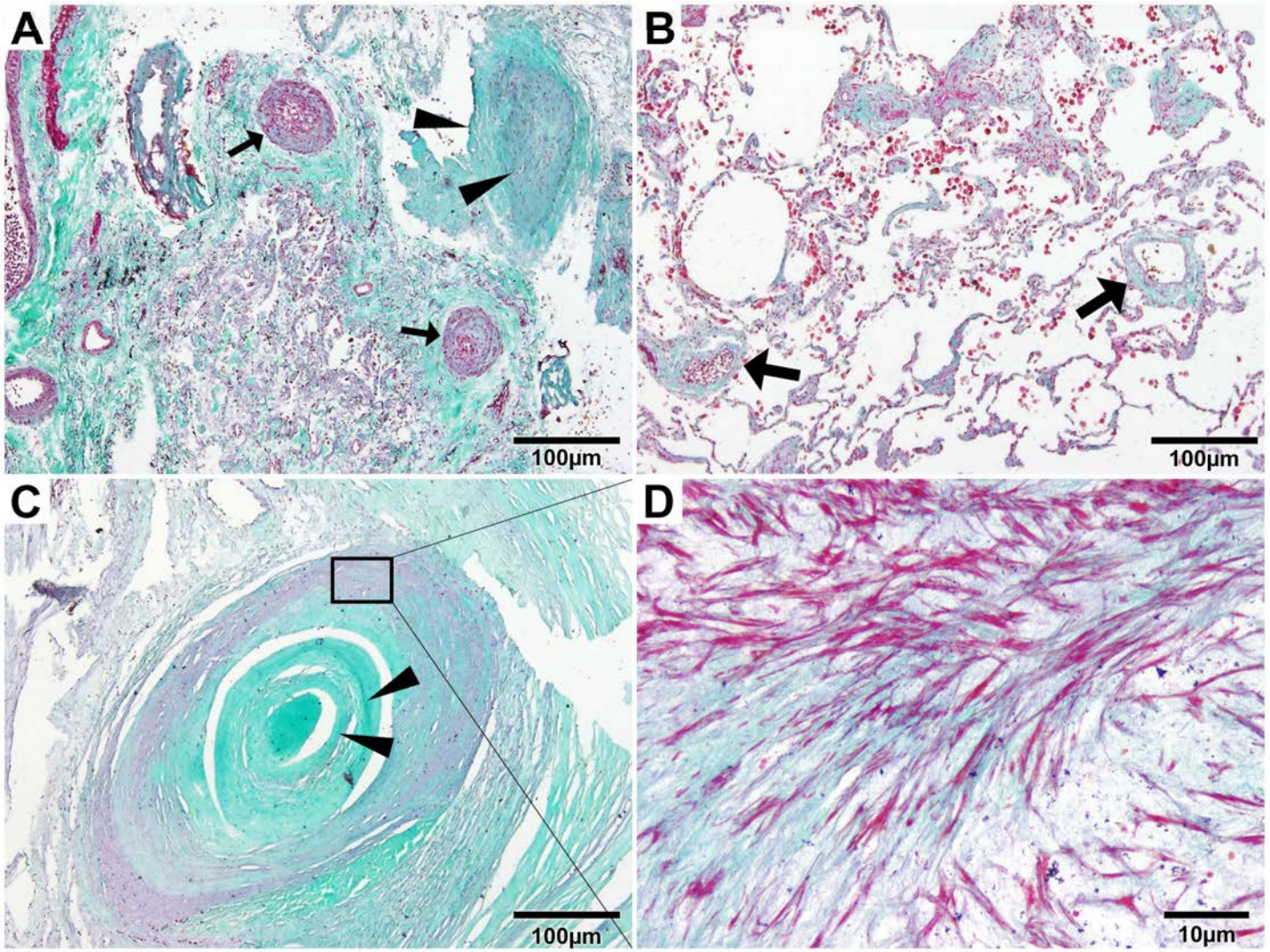
Von der Thrombose zur Fibrose



Acute PE

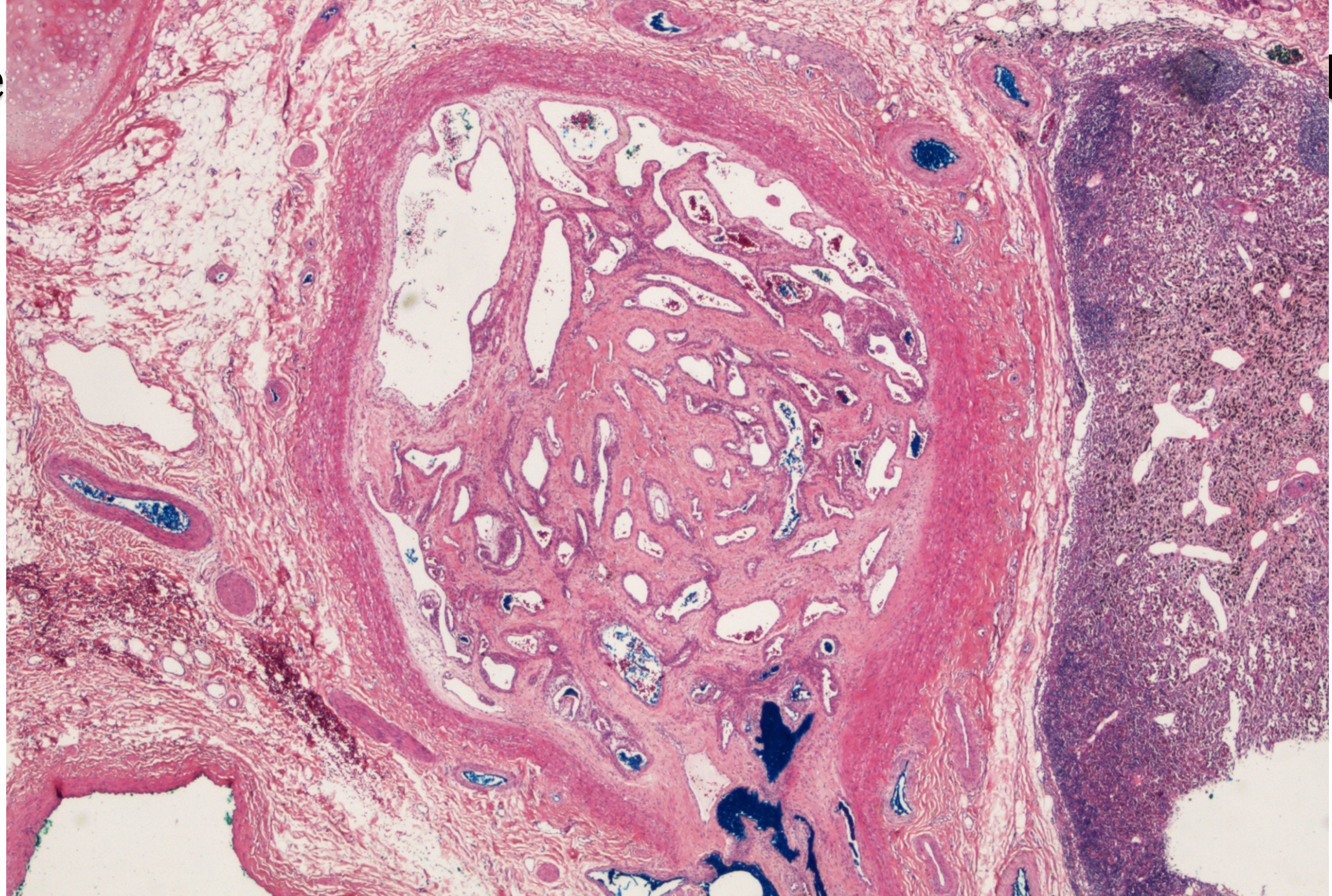
CTEPH

Fibrotisches vasculäres Remodeling



Lang IM and Madani M. *Circulation.* 2014 Aug 5;130(6):508-18.

Ve bus



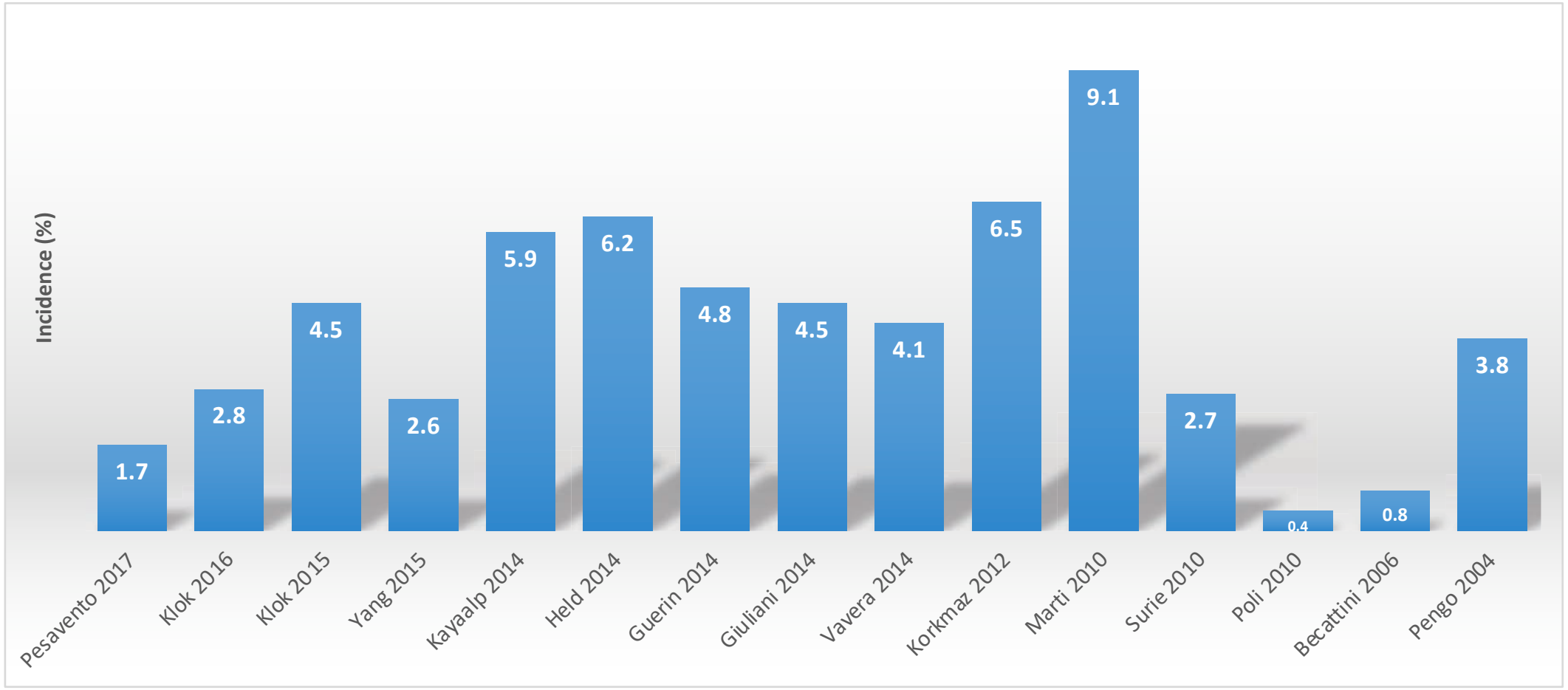

Fläche: 2.58mm²
Mittlerer Durchmesser: 1.79 mm
Min: 1.3
07.11.2017 12:49:57
0001

WHO Klassifikation

WHO group	Description
Group 1	Pulmonary arterial hypertension (PAH)
Group 2	Pulmonary hypertension (PH) with left heart disease
Group 3	PH associated with lung diseases and/or hypoxemia
Group 4	Chronic thromboembolic PH (CTEPH) and other pulmonary vascular obstructions
Group 5	Unclear or multifactorial mechanisms

Galié N, Humbert M, et al, *Eur Heart J*. 2016 Jan 1;37(1):67-119.

Wird aus einer PE CTEPH?

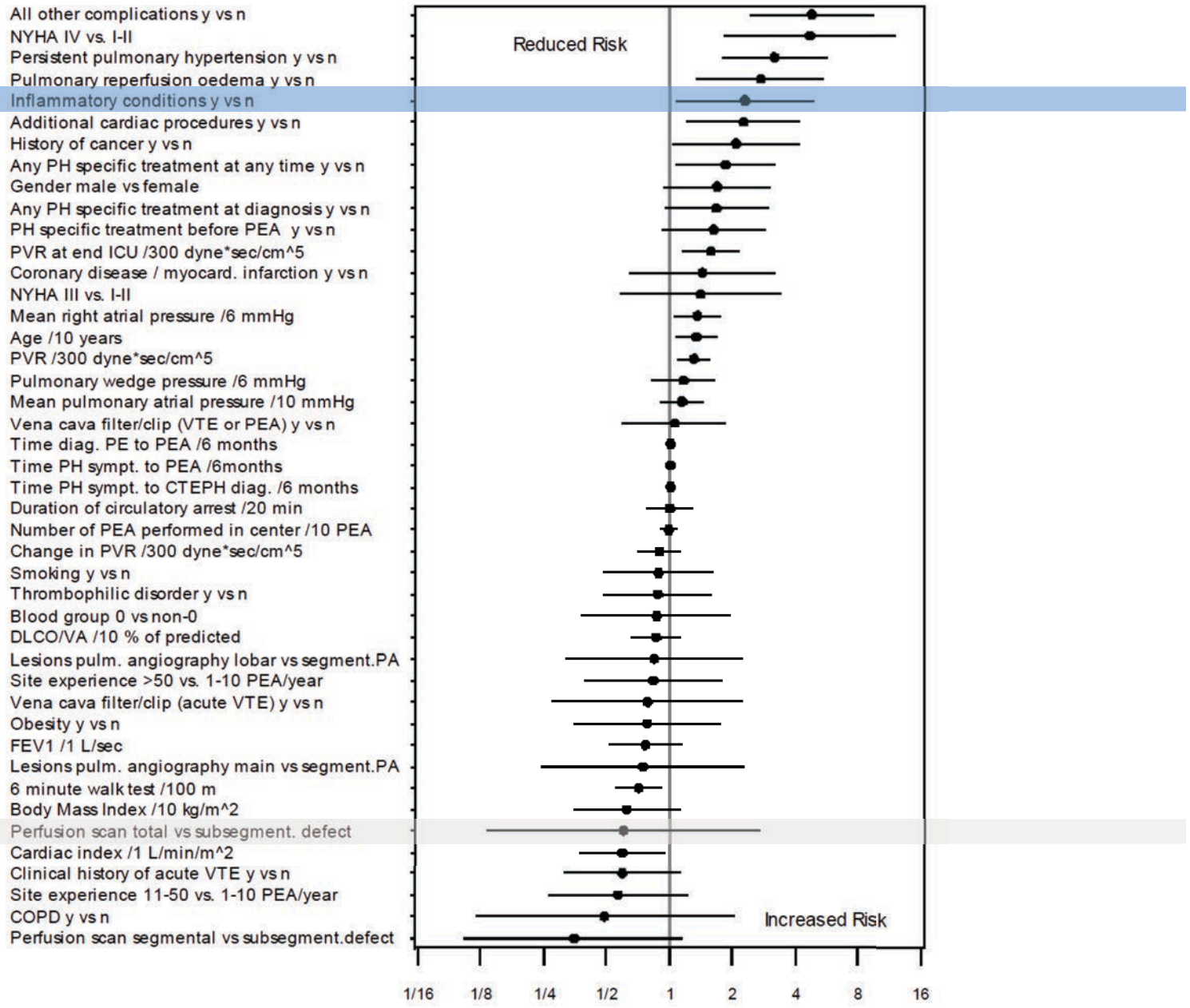


Wer kriegt CTEPH?

Associated condition	*Odds Ratios*
VA shunt/infected leads [1, 2]	13.00 [2.5-129] and 76.4 [7.67-10350.62]
Splenectomy [1, 2, 3]	13.00 [2.7-127] and 17.87 [1.56-2438]
Recurrent VTE [1]	14.4 [5.40-43.08]
Thyroid replacement therapy [1]	6.1 [2.73-15.05]
Previous VTE [1]	4.52 [2.35-9.12]
Antiphospholipid antibodies /LA [1]	4.20 [1.56-12.21]
Survived cancer [1]	3.76 [1.47-10.43]
Inflammatory bowel disease [1, 2]	3.19 [0.74-16.03]
Blood groups non-0 [1,4]	2.09 [1.12-3.94]
Fibrinogen Aα Thr312Ala polymorphism [5]	1.68 [1.13-2.49]
HLA-B*5201 (Japan) [6]	2.14 [1.29-3.55]
HLA-DPB1*0202 (Japan) [6]	3.41 [1.71-6.74]

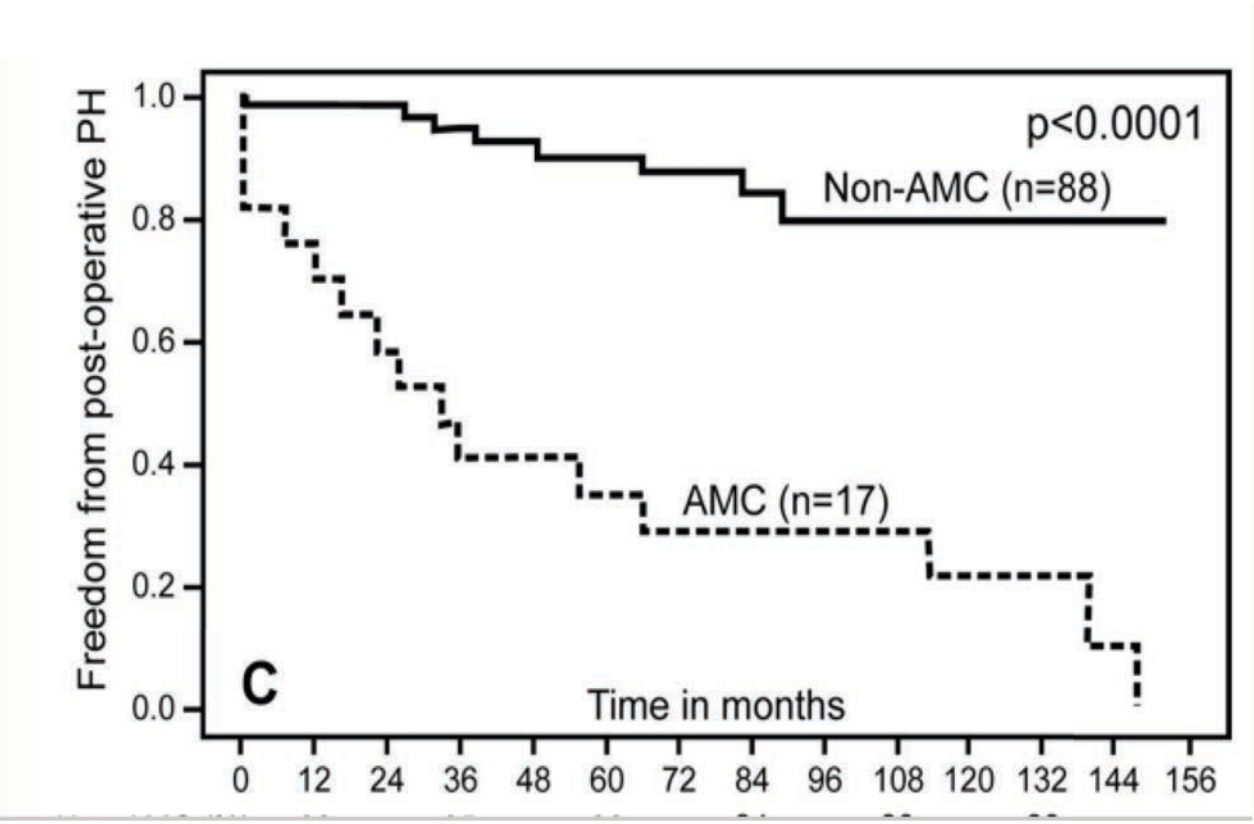
1 Bonderman D and Lang IM, et al. Eur Respir J. 2009; 33: 325-3, 2 Bonderman D et al Thromb Haemost. 2005;93:512-516, 3 Jais et al Thorax. 2005;60:1031-1034, 4 Bonderman D et al Thromb Haemost. 2003;90:372-376, 5 Suntharalingam J et al. Eur Respir J. 2008;31:736-741, 6 Tanabe N et al Eur Respir J. 2005;25:131-138.

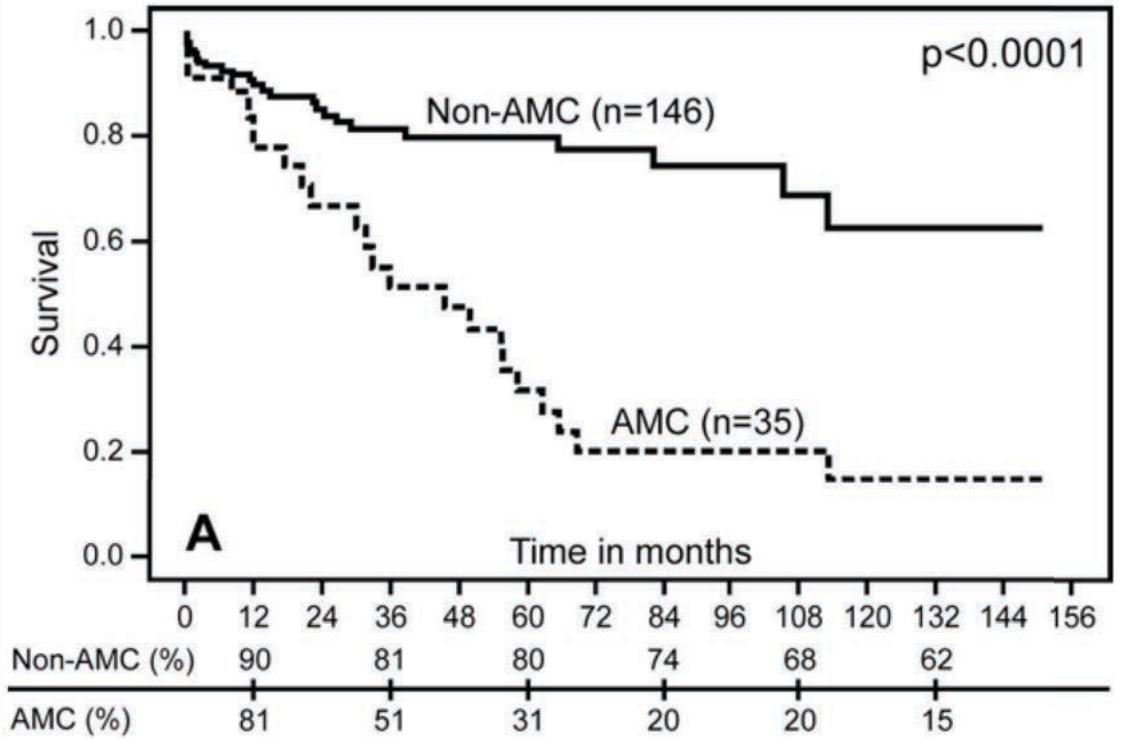
CTEPH



Delcroix M et al. *Circulation* 2016 Mar 1;133(9):859-71.

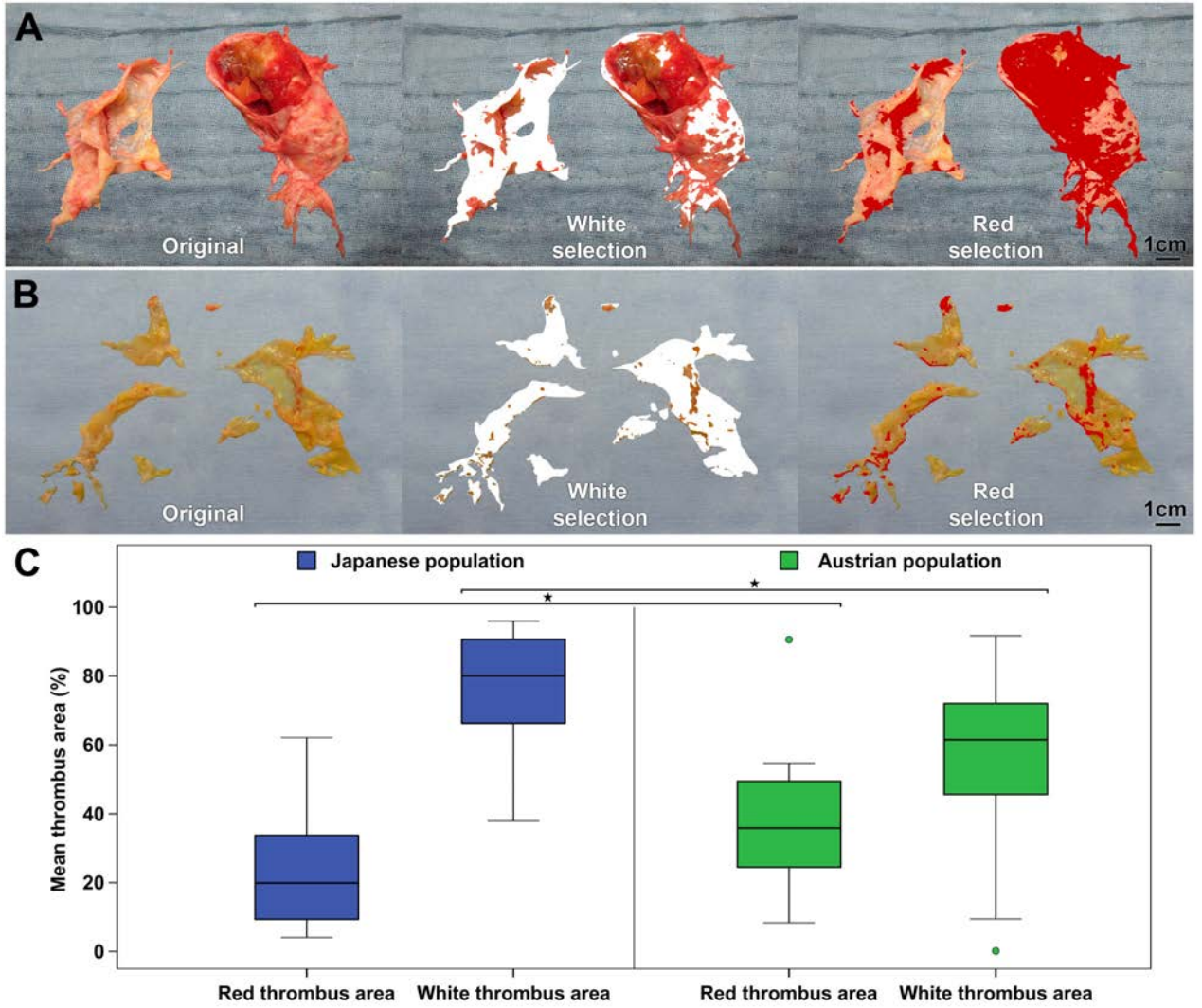
Ko-morbiditäten und Outcome





Bonderman D et al. *Circulation.* 2007;115:2153-2158

CTEPH in Europa und Japan



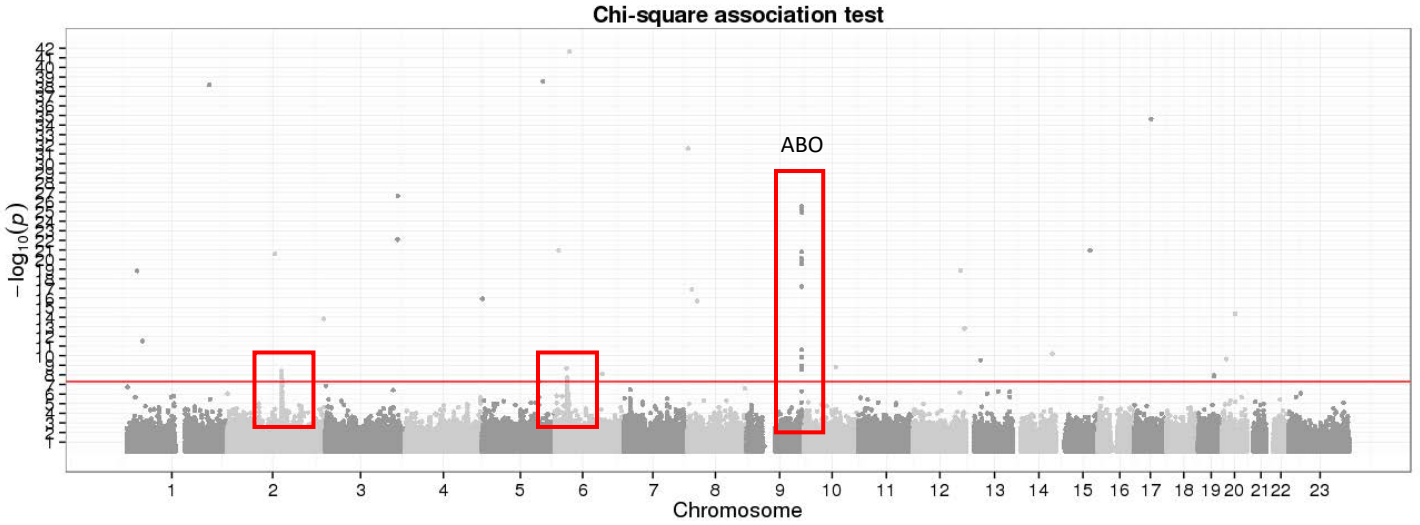
Chausheva S, Seilichiro Sakao et al. *J Thorac CardiovascSurg 2019*

CTEPH weltweit

Parameters	Japanese Registry [12]	International Registry [5]	UC San Diego PEA Registry [90]
Number of patients (*n*)	519	679	2700
Gender, % male	28.1	50.1	49.7
Age, years	67 [53;75]*	63 [51;72]*	52 [40;63]* (8-88)†
World Health Organization class, % I/II/III/IV	5.2/41.9/47.7/5.2	0.7/17.8/68.6/12.8	1.5/9.7/80.3/8.6
History of deep vein thrombosis, %	50.4	56.1	49.2
History of acute pulmonary embolism, %	37.2	74.8	70.6
Coagulopathies, %	11.7	31.9	30.1
Mean pulmonary arterial pressure, mmHg, median	38 [33;46]*	47 [38;55]*	46 [38;53]*
Pulmonary vascular resistance, dynes.s/cm^5, median	621 [439;916]*	709 [480;988]*	814 [476;1018]*
Pulmonary endarterectomy, %	13.9	56.8	100
Inferior vena cava filter, %	26.9	12.4	>90
PAH-targeted therapy, %	52.2	37.9 ‡	37.0 ‡

Lang IM and Madani M. *Circulation.* 2014 Aug 5;130(6):508-18.

Loci achieve genome wide significance



1457 Caucasian CTEPH patients were enrolled from 10 European and US Centers and compared to 1536 healthy Caucasian controls from the Wellcome Trust Case Control Consortium.

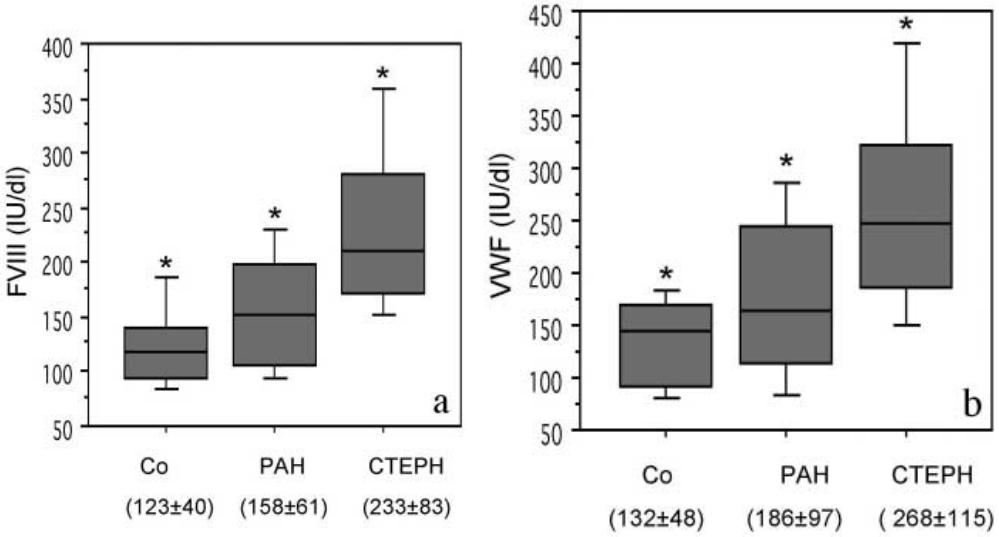
Toshner M et al, *Eur Respir J*. 2019 Jan 17. pii: 1801805.

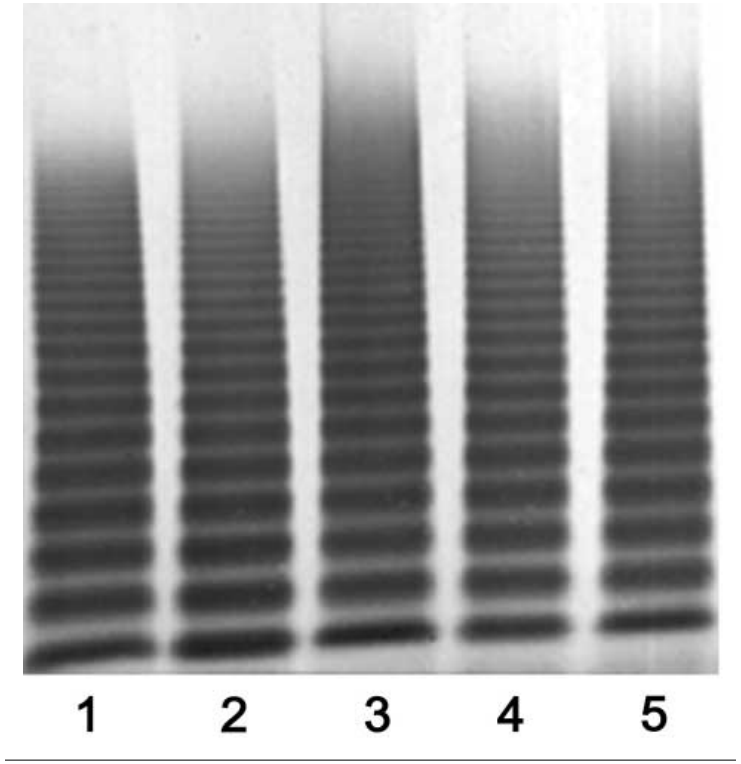
Blut Gruppen nicht-O und CTEPH

	country	FR	GB	DE	PL	AU	BE
Blood Group							
A	51.8	37.0	35.0	37.0	32.0	30.0	34.0
B	16.1	9.0	8.0	9.0	15.0	12.0	8.5
AB	8.2	3.0	3.0	4.0	7.0	6.0	4.1
0	24.0	36.0	37.4	35.0	31.0	33.0	38.0
Rhesus							
pos	81.1	85.0	82.0	82.0	85.0	81.0	84.6
neg	19.9	15.0	17.0	15.0	15.0	19.0	15.3

Lang I et al. *Thromb Haemost*. 2013; 110: 83-91

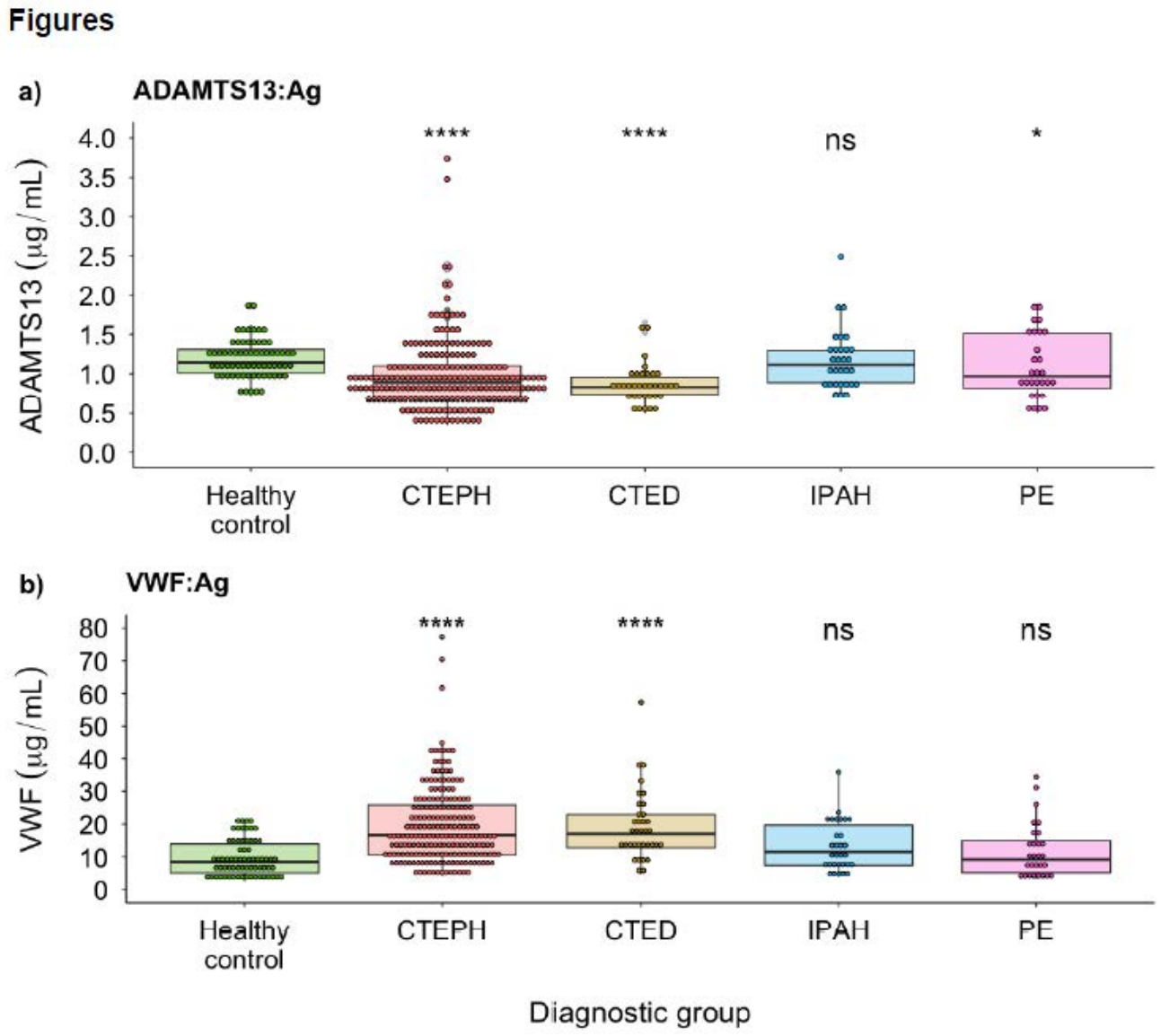
Faktor VIII





Bonderman D et al. *Thromb Haemost*. 2003 Sep;90(3):372-6.

ADAMTS13 and VWF antigen concentration

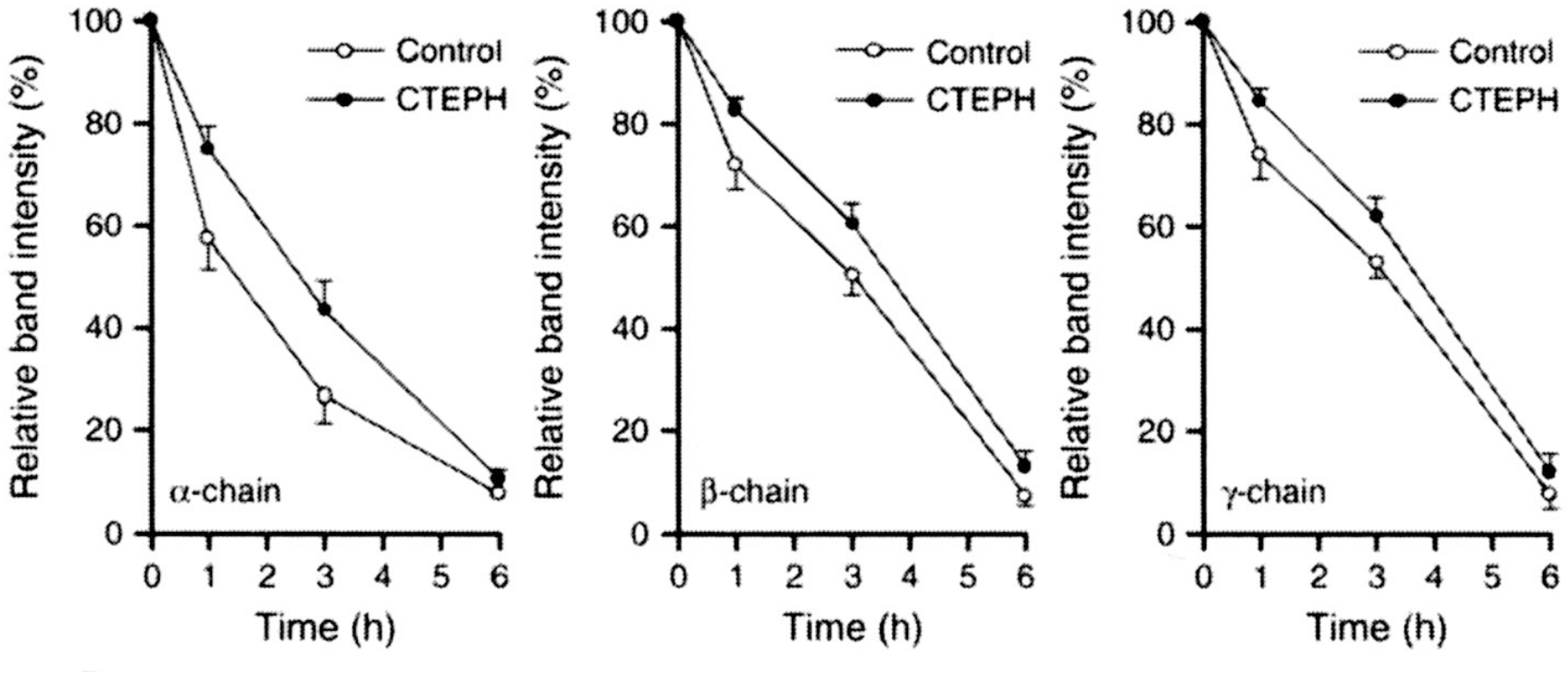


- ADAMTS13 antigen levels were decreased in CTEPH patients (0.889 ± 0.397µg/mL; $p<0.001$) compared to healthy controls (1.15 ± 0.300µg/mL)
- ADAMTS13 was also reduced in CTED (0.831 ± 0.224µg/ml, $p<0.001$) but levels were similar to CTEPH ($p=0.205$)
- No difference in ADAMTS13 levels between IPAH (1.12 ± 0.413µg/mL; $p=0.373$) and healthy controls

Published range for healthy ADAMTS13 antigen levels: 0.740 – 1.420µg/ml with a median of 1.080µg/ml!

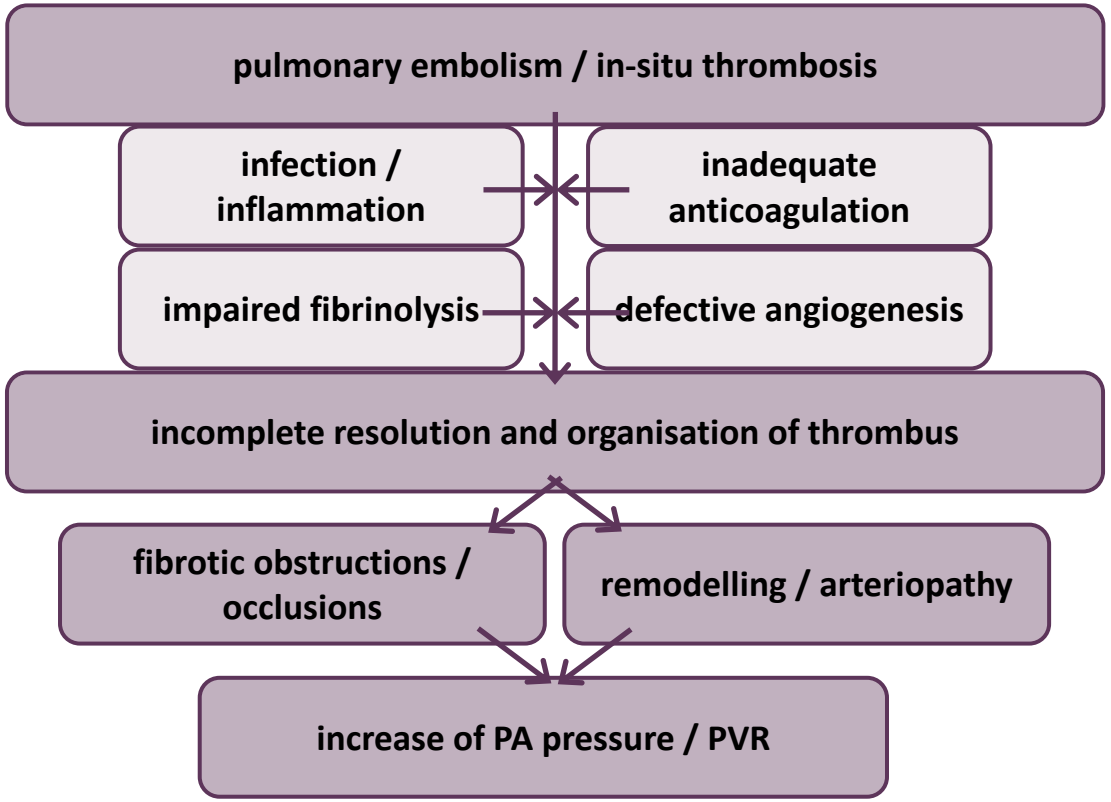
Toshner M et al, *Eur Respir J*. 2019 Jan 17. pii: 1801805.

CTEPH Fibrinogen ist lyse-resistent



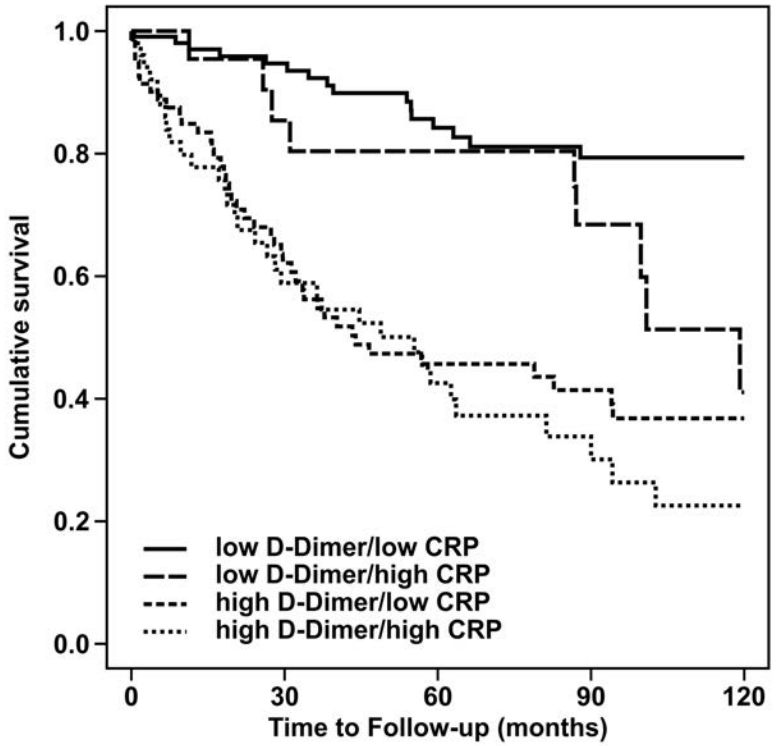
Morris TA et al, *Am J Resp Crit Care Med* 2006; 173: 1270-5.

Pathophysiologie



Galiè N et al., *Eur Heart J* 2016; 37:67-119; Lang IM et al., *Eur Respir J* 2013; 41:462-468;
Wilkens H […] Lankeit M et al., *Dtsch Med Wochenschr* 2016; 141:S62-S69

CRP, D-Dimer und CTEPH

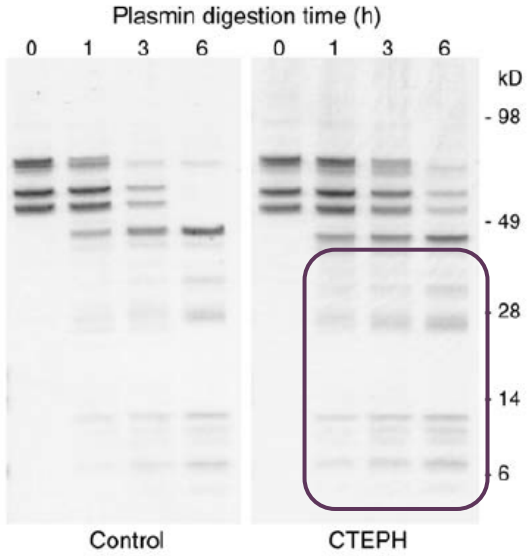


D-Dimer	CRP	Patients at risk				
low	low	111	82	66	52	35
low	high	23	19	16	16	7
high	low	84	47	30	23	13
high	high	51	31	22	13	7

Skoro N et al. *J Heart Lung Transplant 2018*

Thrombolyse kann CTEPH nicht verhindern

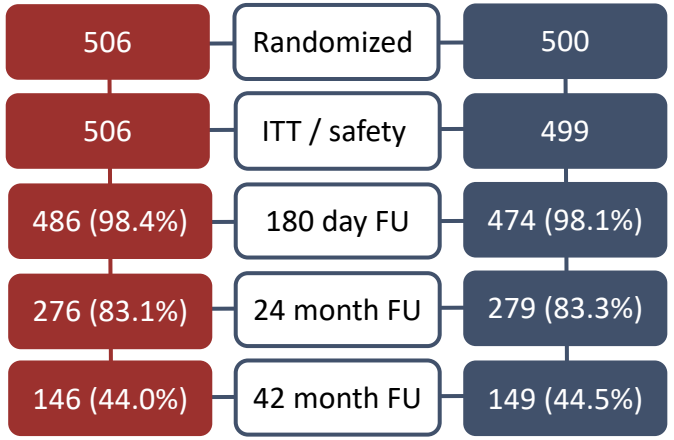
Fibrin from patients with CTEPH is resistant to plasmin-mediated lysis



delayed degradation of the intact α-, β- and γ-chains of CTEPH fibrin

DPEITHO

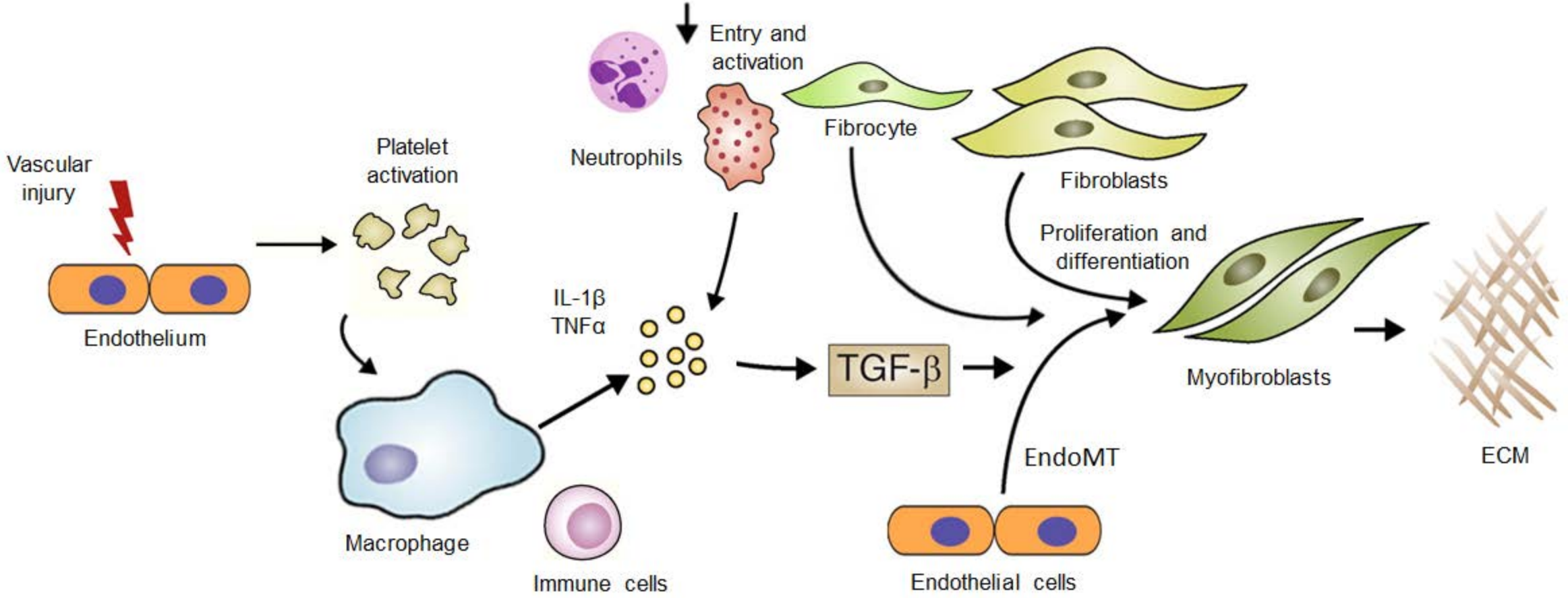
ClinicalTrials.gov: NCT00639743



long-term follow-up (41.6±15.7 months)	Tenecteplase (n=146)	Placebo (n=149)	*P* value
confirmed CTEPH	**4 (2.7%)**	**6 (4.0%)**	**0.541**

Meyer G, […] Lankeit M et al., *N Engl J Med* 2014; 370:1402-1411
Konstantinides S, […] Lankeit M et al., *J Am Coll Cardiol* 2017; 69:1536-1544

Inflammatory drivers of vascular fibrosis



Sharma Smriti et al. Thesis

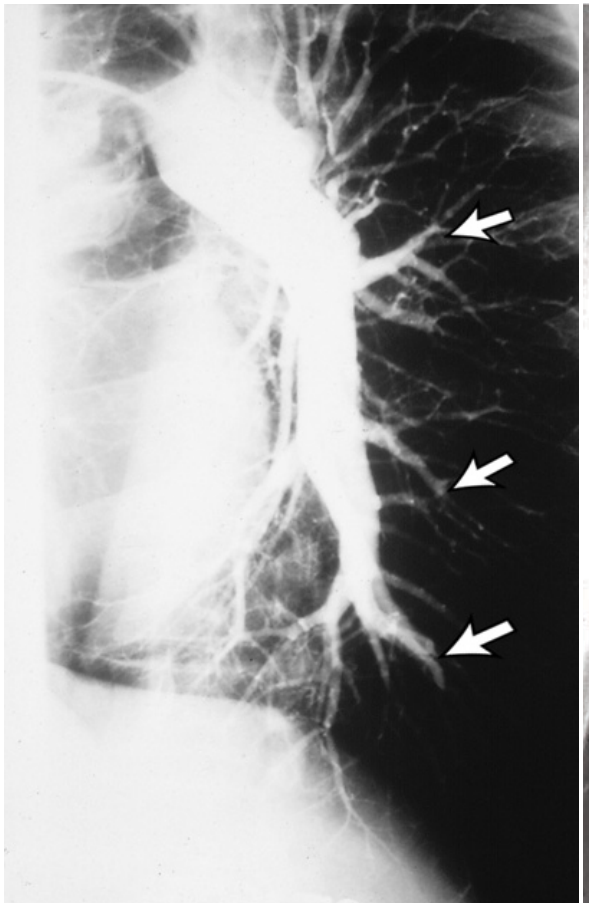
CTEPH Diagnose

- **Imaging criteria**
  - Invasively measured mean pulmonary artery pressure (mPAP) ≥25mmHg
  - On V/Q at least one larger defect (at least~1/3 of a segment)
  - Typical vascular changes on CT or conventional PA angiography
- **At least 3 months of effective anticoagulation**

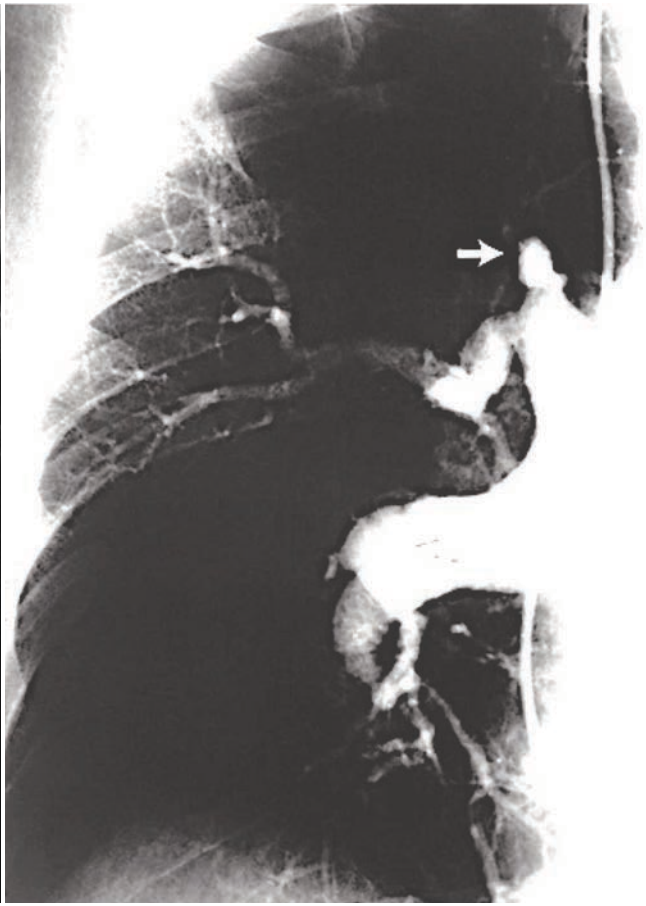
Kim, N. *et al. J Am Coll Cardiol* 2013;62:D92–9.

Lungengefässerkrankungen

Normal



IPAH



CTEPH

Symptoms

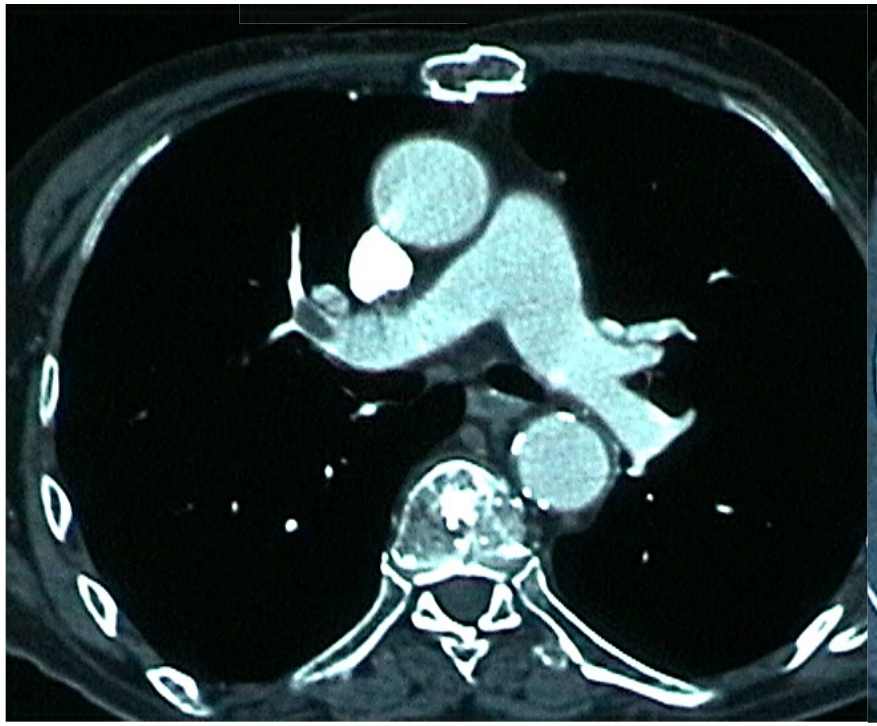
CTEPH Chronic Thromboembolic Pulmonary Hypertension REGISTRY

Type of symptom	iPAH n=158		CTEPH n=436	
	n	%	n	%
number of patients with available data	158	100.0	436	100.0
Dyspnea	157	99.4	431	98.9
Edema	43	27.2	176	40.4
Fatigue	25	15.8	103	23.6
Dizziness	27	17.1	23	5.3
Chest pain	31	19.6	60	13.8
Hemoptysis	1	0.6	21	4.6

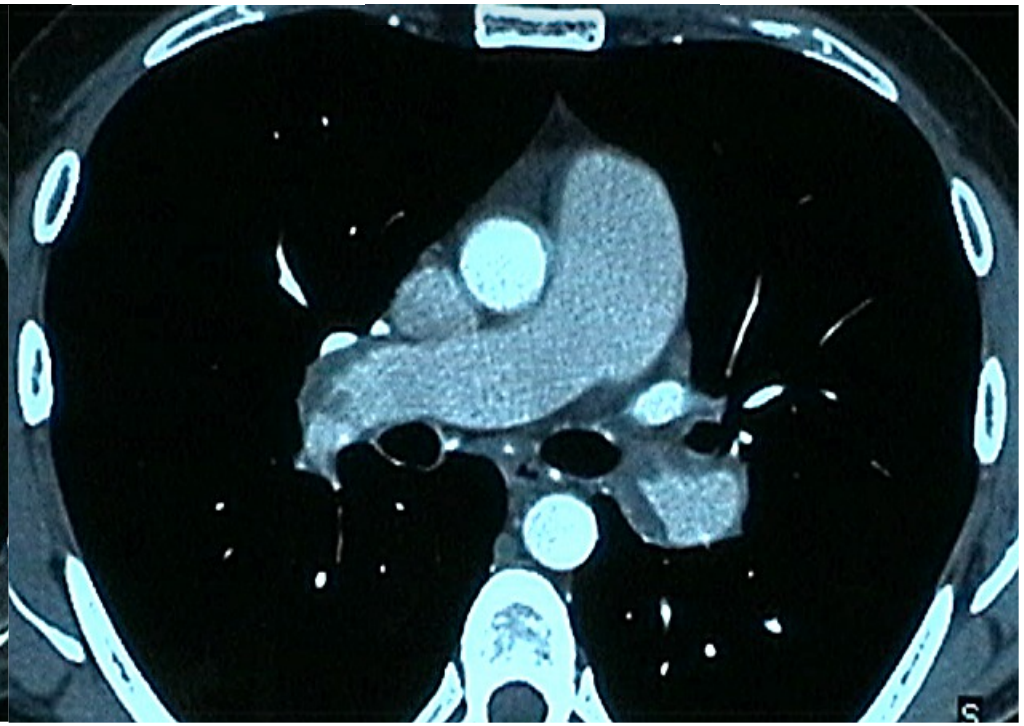
International CTEPH Registry. Pepke-Zaba J *Circulation* 2011;124:1973–81.

Acute pulmonary embolism versus CTEPH

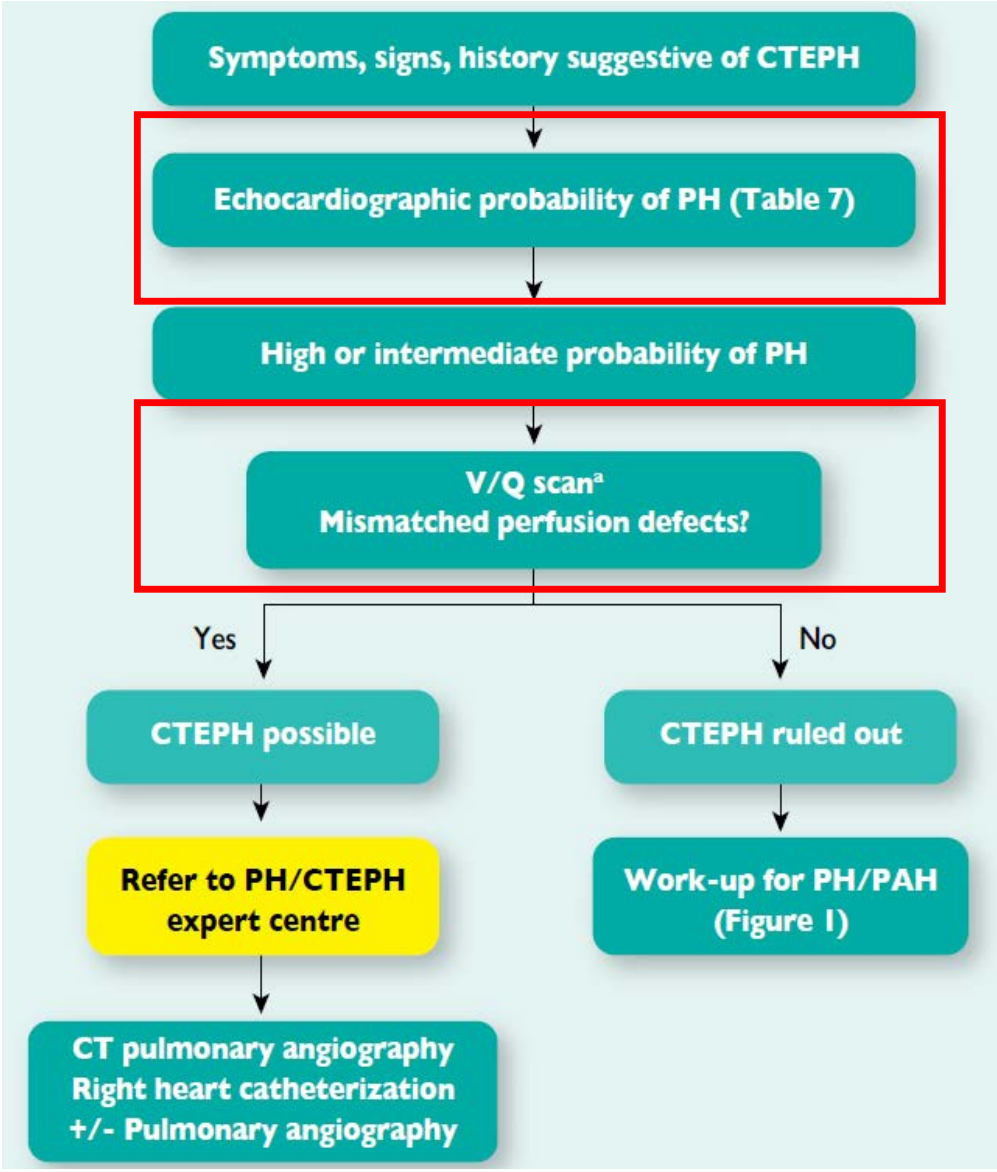
Acute PE



CTEPH



Diagnosis



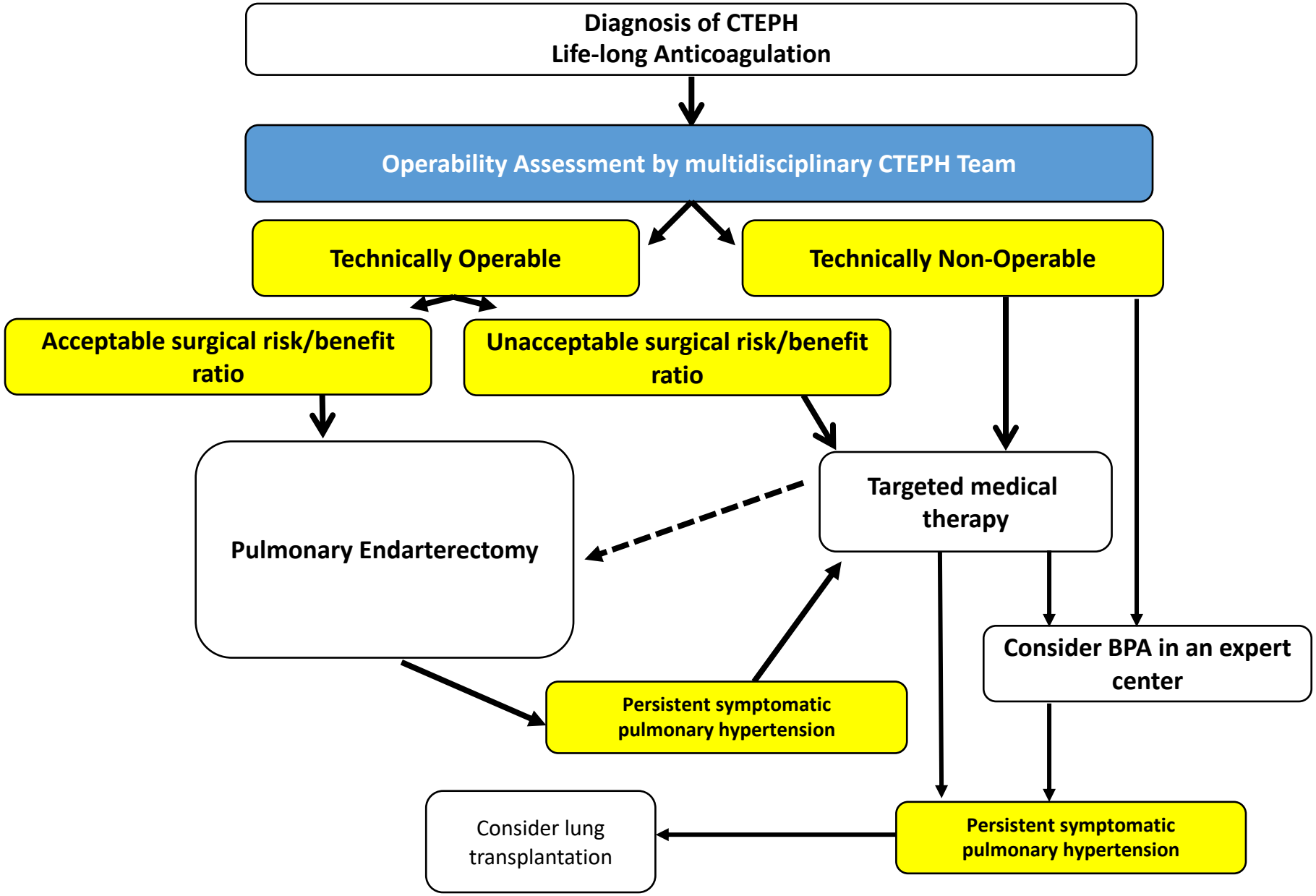
European Heart Journal (2014):doi:10.1093/eurheartj/ehu283

Guidelines

Recommendations	Class[a]	Level[b]
In PE survivors with exercise dyspnoea, CTEPH should be considered.	IIa	C
Life-long anticoagulation is recommended in all patients with CTEPH.	I	C
It is recommended that in all patients with CTEPH the assessment of operability and decisions regarding other treatment strategies be made by a multidisciplinary team of experts.	I	C
Surgical PEA in deep hypothermia circulatory arrest is recommended for patients with CTEPH.	I	C
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 persistent/recurrent CTEPH after surgical treatment, or inoperable CTEPH by a CTEPH team including at least one experienced PEA surgeon.	IIb	B
Interventional BPA may be considered in patients who are technically non-operable, or carry an unfavourable risk-benefit ratio for PEA.	IIb	C
Screening for CTEPH in asymptomatic survivors of PE is currently not recommended.	III	C

Galié N, Humbert M, et al, *Eur Heart J*. 2016 Jan 1;37(1):67-119.

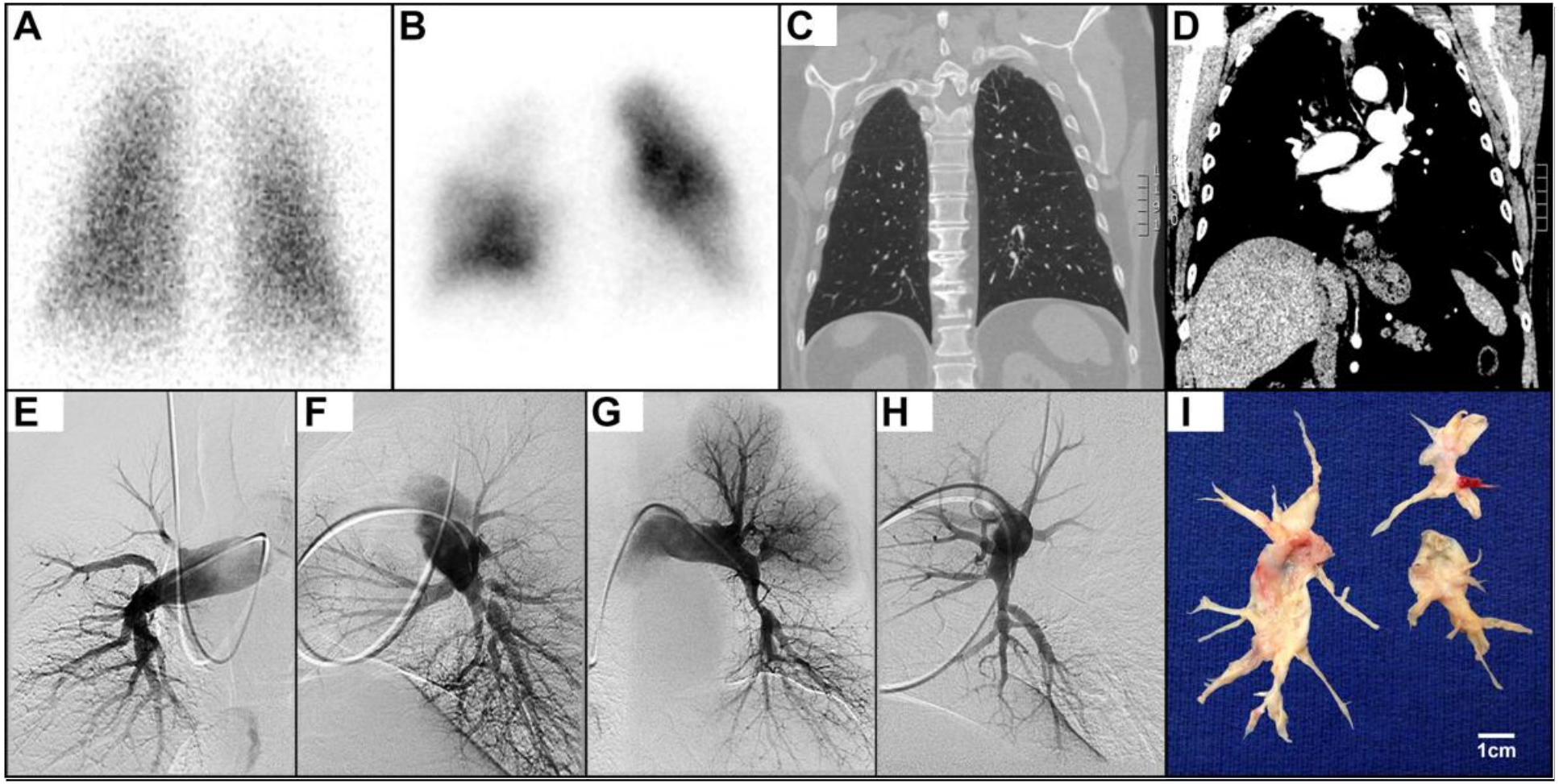
The CTEPH TEAM



BPA, balloon pulmonary angioplasty.

Lang IM and Madani M. *Circulation.* 2014 Aug 5;130(6):508-18.
Galiè N *et al. Eur Heart J* 2015:doi:10.1093/eurheart/ehv317.

Der “operable” Patient



Lang IM and Madani M. *Circulation* 2014;130:508–18.

Pulmonale (Thrombo)-endarterektomie (PEA)

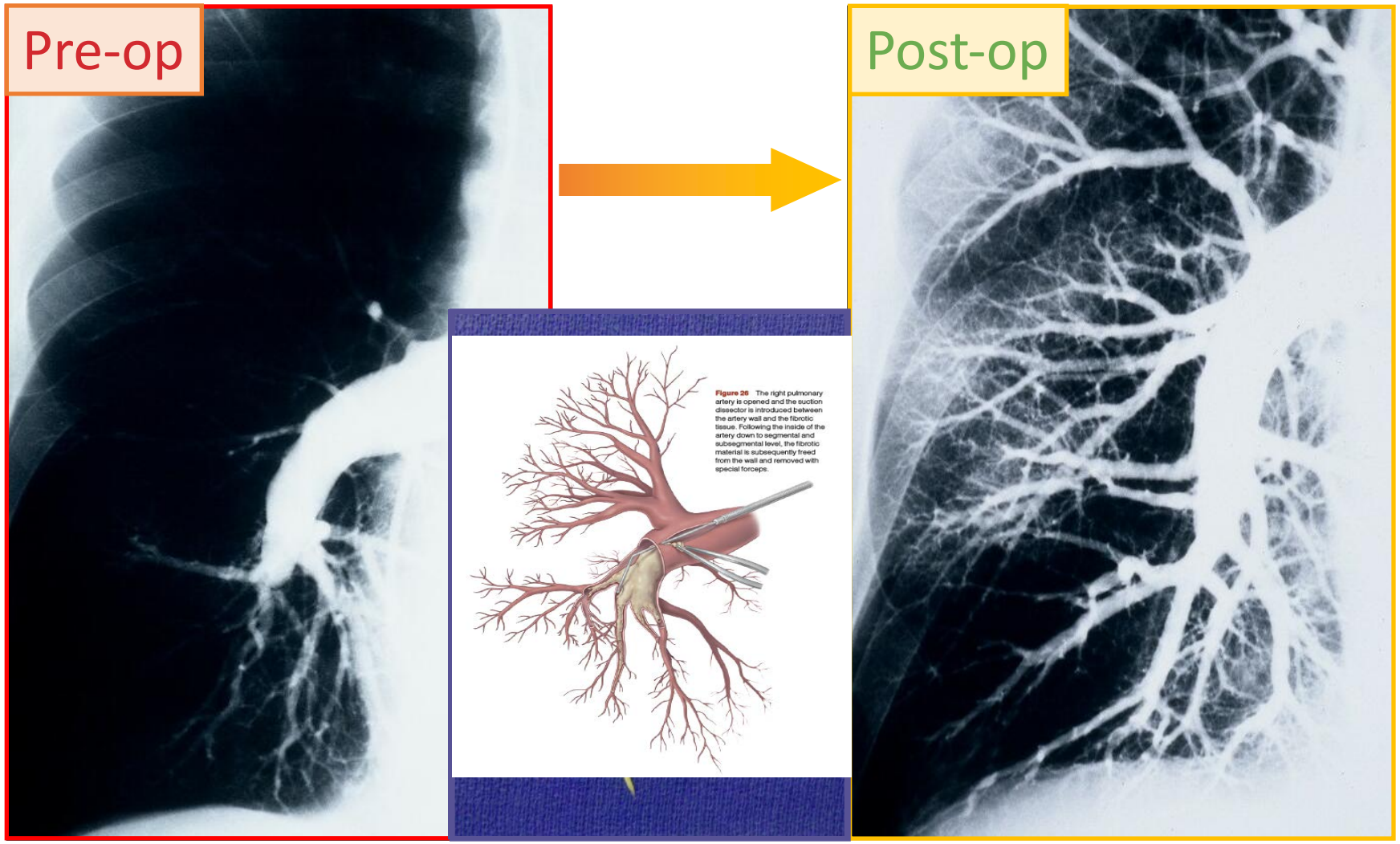
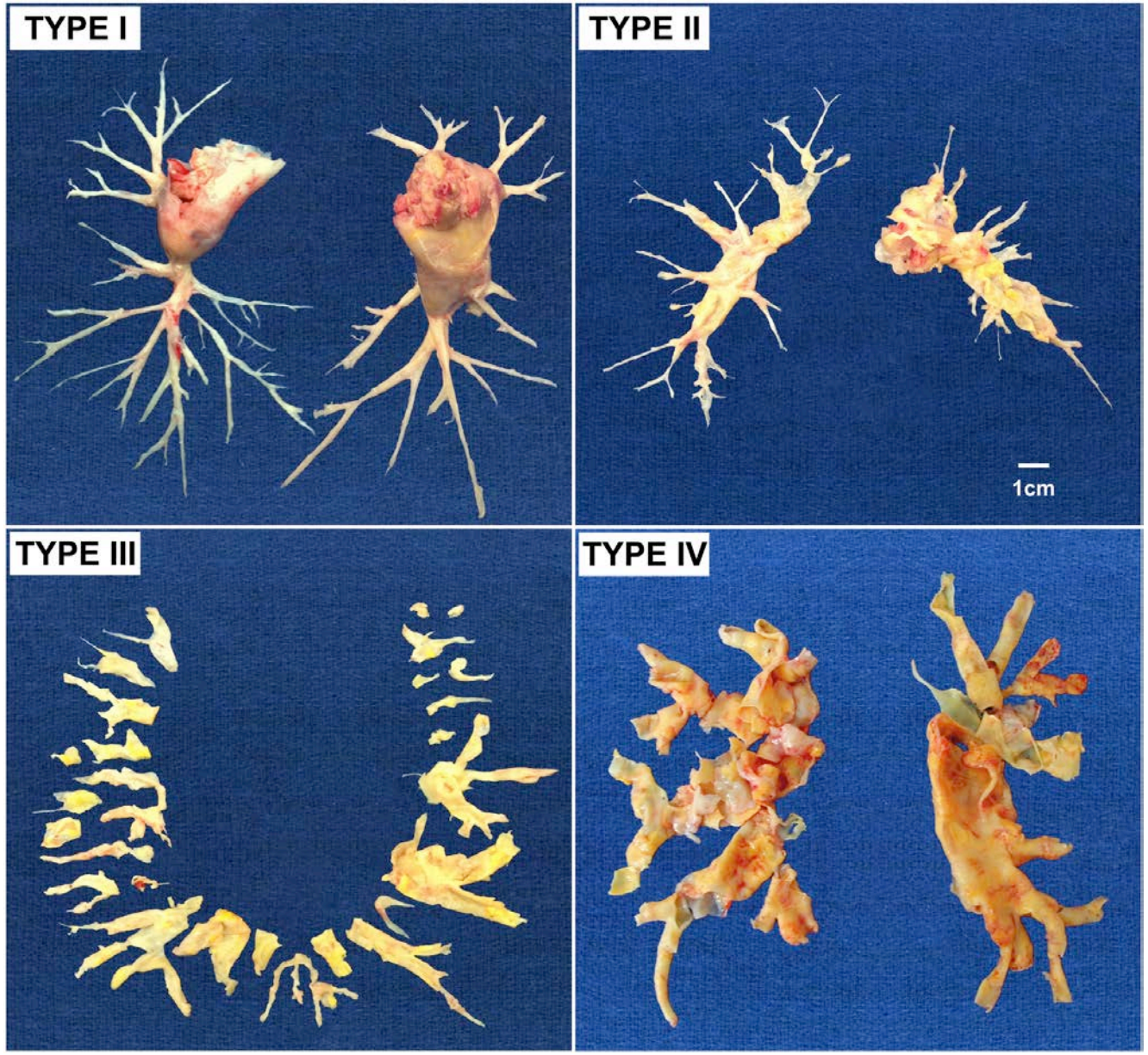


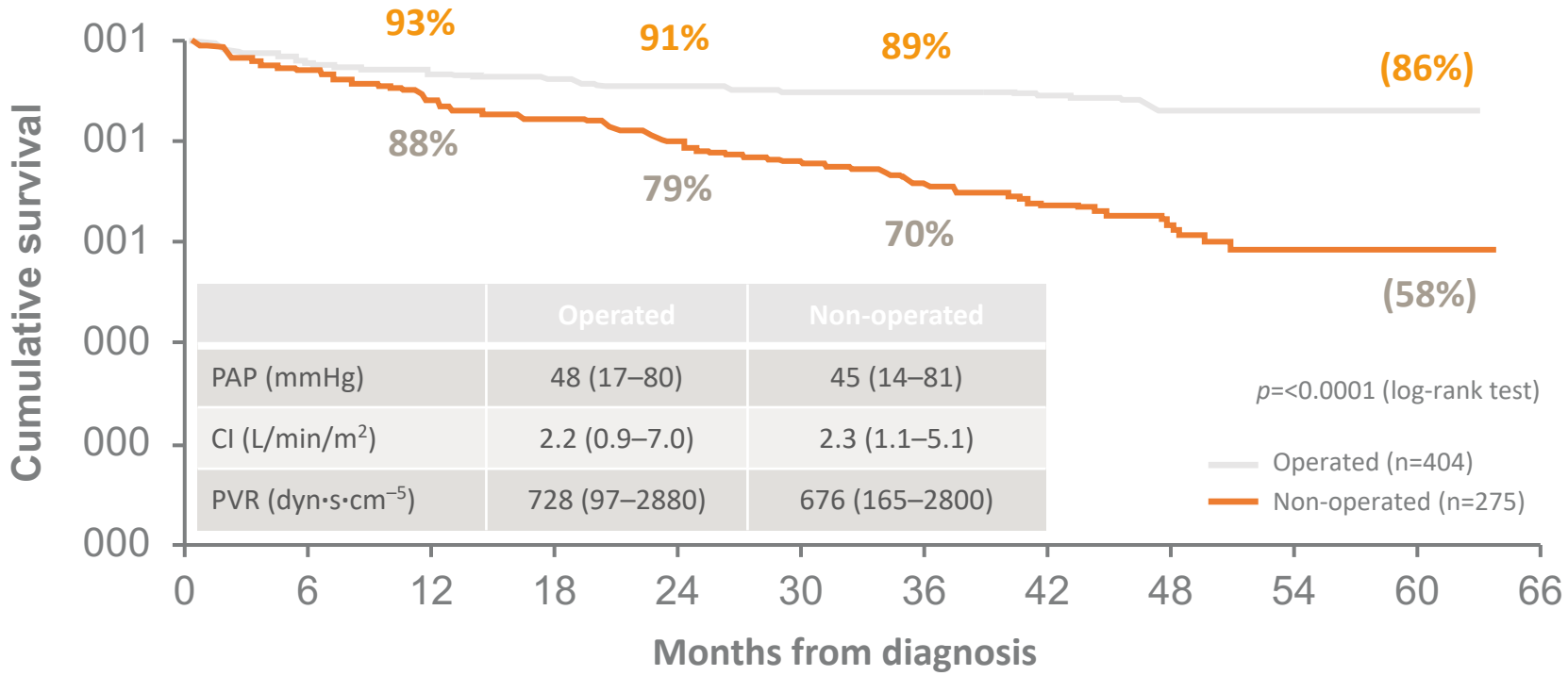
Illustration courtesy of Hotten, M. Thesis, Master Scientific Illustration, 2016., and Nick Kim, MD.

Chirurgische Klassifikation



Kaplan–Meier survival estimates of operated and non-operated patients

CTEPH Chronic Thromboembolic Pulmonary Hypertension REGISTRY



	Operated	Non-operated
PAP (mmHg)	48 (17–80)	45 (14–81)
CI (L/min/m^2)	2.2 (0.9–7.0)	2.3 (1.1–5.1)
PVR (dyn·s·cm^{-5})	728 (97–2880)	676 (165–2800)

Number of patients at risk at the end of the time period:

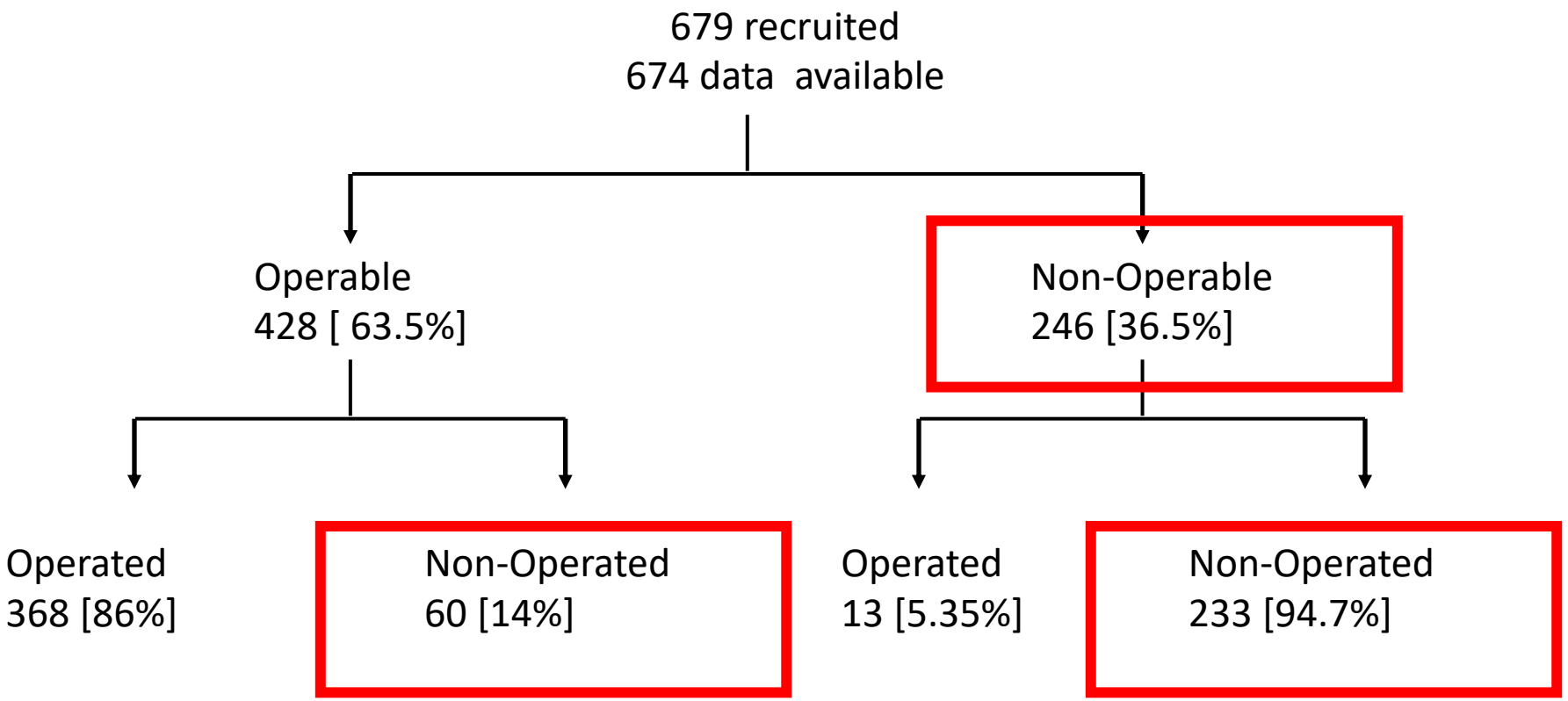
Operated	404	382	374	366	361	355	336	244	158	62	3	0
Non-operated	275	246	228	214	200	188	164	120	58	20	2	0

CI, cardiac index; PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance.

Simonneau G *et al. Am J Respir Crit Care Med* 2013;187:A5365.

Delcroix M et al. *Circulation* 2016 Mar 1;133(9):859-71.

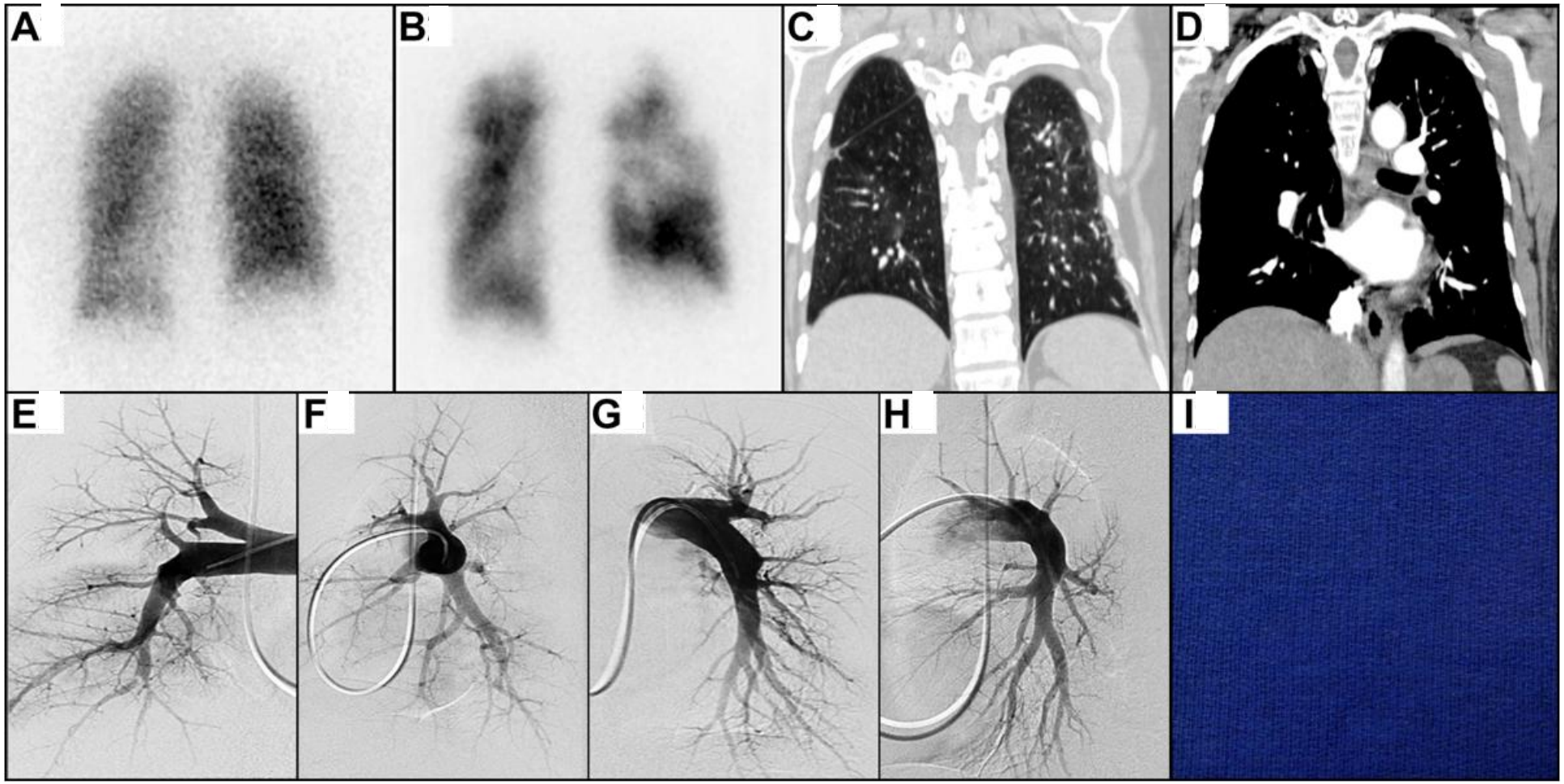
The European CTEPH Registry



Wenigstens 50% aller CTEPH Patienten werden nicht operiert!

Pepke-Zaba J et al. *Circulation*. 2011 Nov 1;124(18):1973-81

Der “nicht-operable” Patient



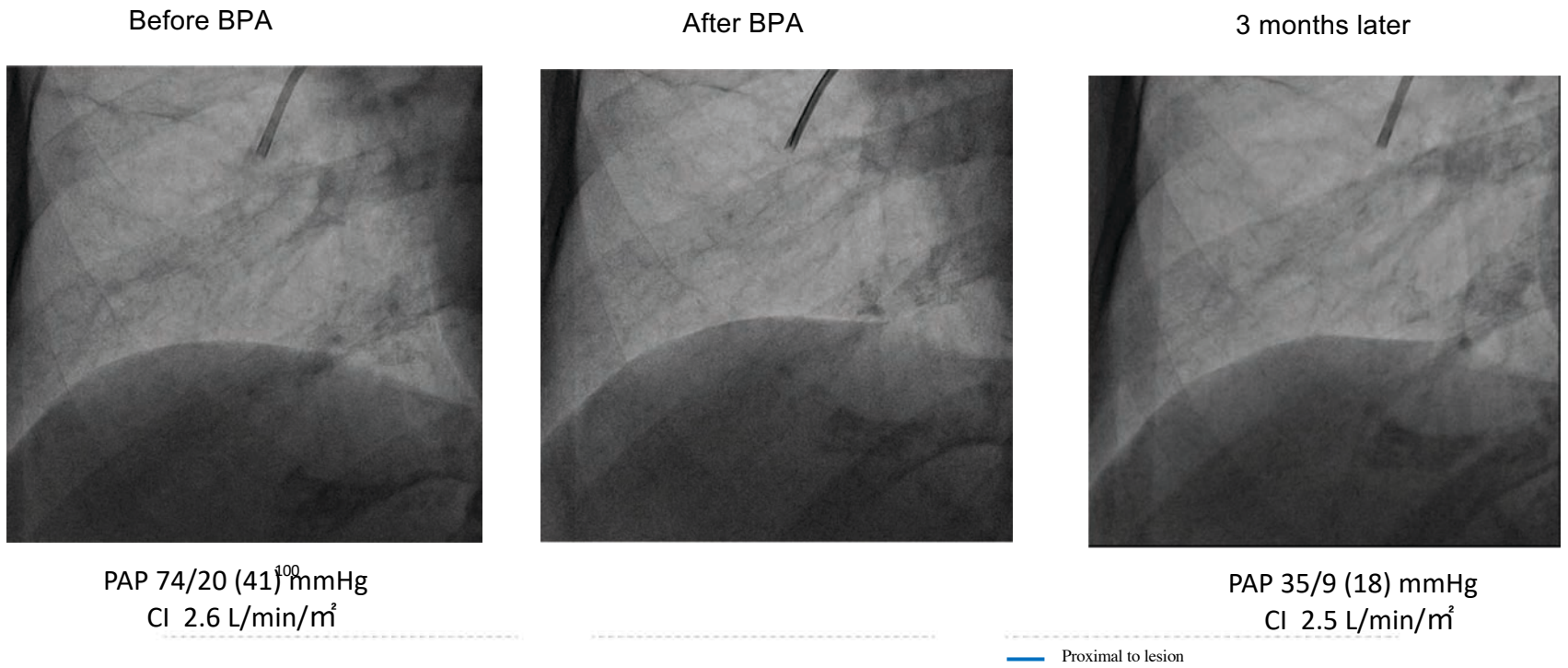
Lang IM and Madani M. *Circulation* 2014;130:508–18.

Guidelines

Recommendations	Class[a]	Level[b]
In PE survivors with exercise dyspnoea, CTEPH should be considered.	IIa	C
Life-long anticoagulation is recommended in all patients with CTEPH.	I	C
It is recommended that in all patients with CTEPH the assessment of operability and decisions regarding other treatment strategies be made by a multidisciplinary team of experts.	I	C
Surgical PEA in deep hypothermia circulatory arrest is recommended for patients with CTEPH.	I	C
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 persistent/recurrent CTEPH after surgical treatment, or inoperable CTEPH by a CTEPH team including at least one experienced PEA surgeon.	IIb	B
Interventional BPA may be considered in patients who are technically non-operable, or carry an unfavourable risk-benefit ratio for PEA.	IIb	C
Screening for CTEPH in asymptomatic survivors of PE is currently not recommended.	III	C

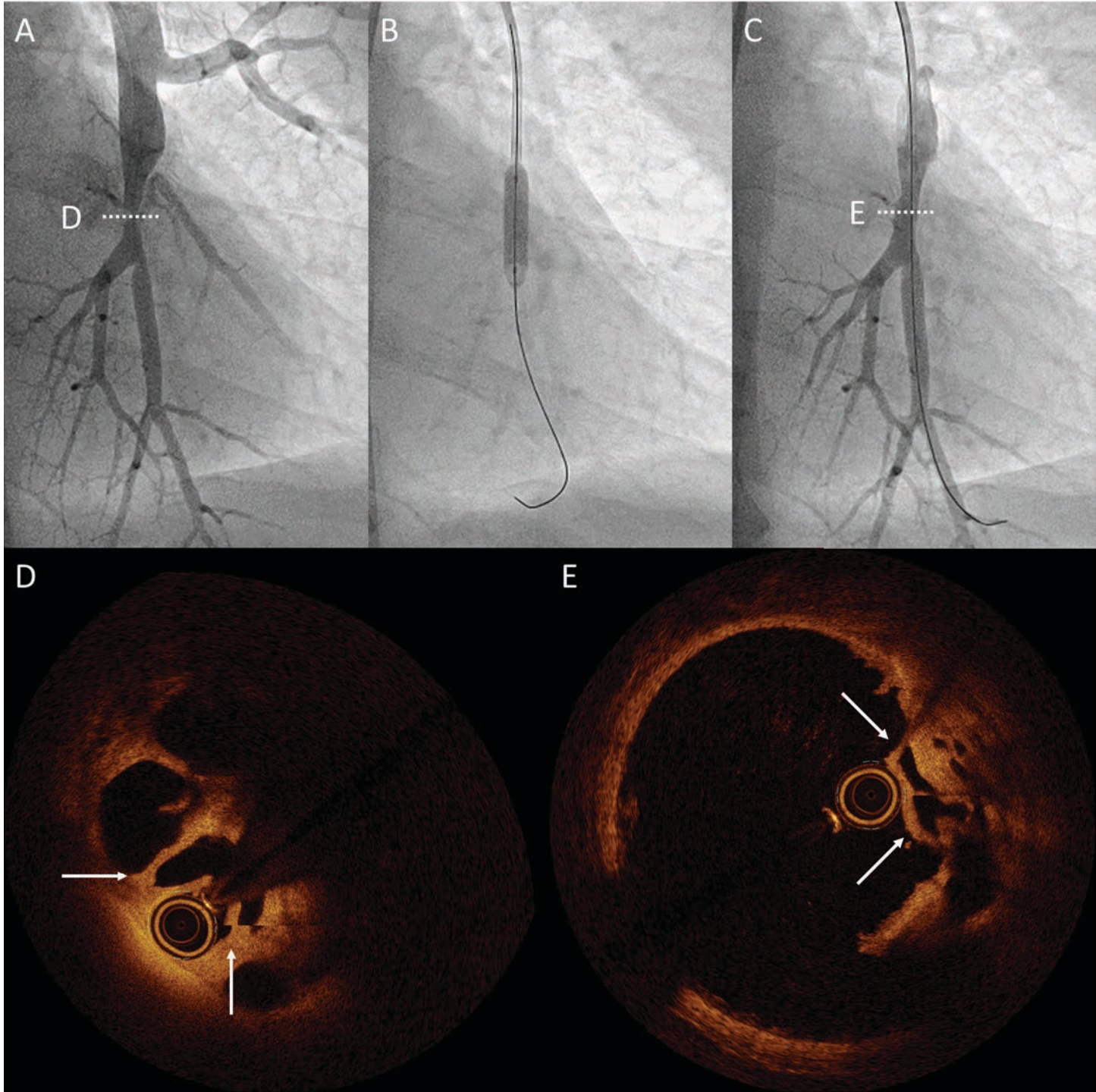
Galié N, Humbert M, et al, *Eur Heart J*. 2016 Jan 1;37(1):67-119.

Balloon Pulmonary Angioplasty (BPA)



Nagayoshi S et al. EuroIntervention. 2016 Dec 10;12(11):e1435.

Das Prinzip von BPA



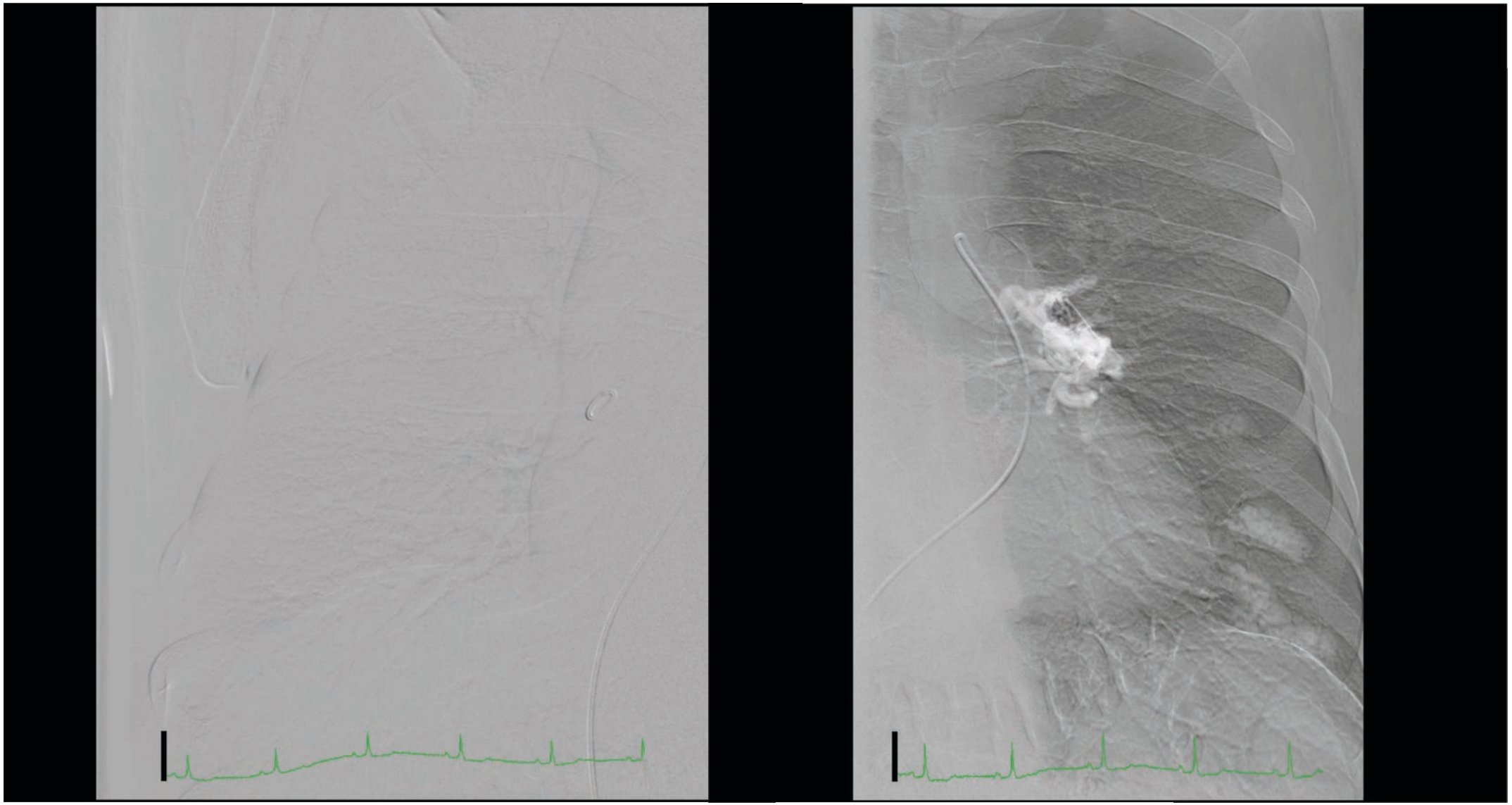
Balloon Angioplastie der Pulmonalarterien in Europa

Year	First author, [ref.]	Country	Patient number	Procedures	Complications (%)	In-hospital death rate (%)	Follow-up Period (months)	Mean PAP (mmHg)	
								Baseline	Effect
2001	Feinstein [1]	USA	18	48	61[a]	5.6	34	42.0±12.0	-9.0
2013	Andreasen [2]	Norway	20	73	35.0[a]	10.0	51	45.0±11.0	-12.0
2015	KURZYNA [3]	Poland	20	37	10[a]	10	-	58±6.0	-17.0
2016	Roik [4]	Poland	9	27	5.5[a]	0	5	40	-5.4
2017	Olsson [5]	Germany	56	266	9.4[a]	1.8	24	40.0±12.0	-7.0
2017	Wiedenroth [6]	Germany	36/123	195	13.8	0	6	43.0 ± 12.0	-9.0
2018	Wiedenroth [7]	Germany	10	35	2.9	0	6	21.0 ± 2.0	-0
2018	**Okayama**	**Japan**	**373**	**2163**	**4.5[b]**	**1.8**	**28.8**	**41.8±11.7**	**-20.7**

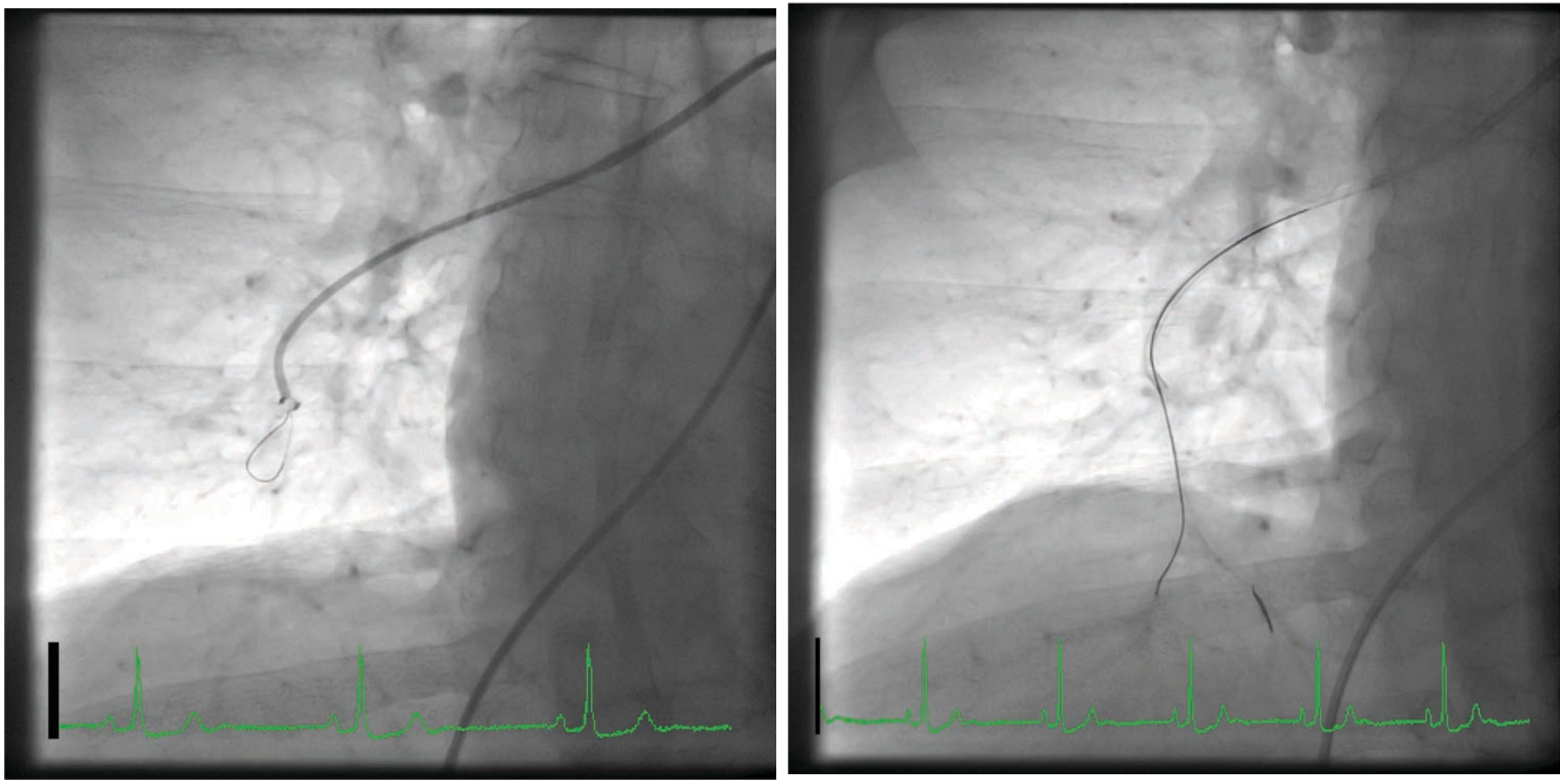
[1]: Circulation 2001; 103: 10–13. [2]: Heart 2013; 99: 1415–1420. [3]: Postepy Kardiol Interwencyjnej 2015; 11: 1–4.
[4]: Int J Cardiol 2016; 203: 228–235. [5]: Eur Respir J. 2017; 8;49(6). [6]: Pulm Circ. 2018 Jul-Sep;8(3):2045894018783996. [7]: Pulm Circ. 2018 Jan-Mar;8(1):2045893217753122
a: Reperfuison pulmonary edema, b: Severe lung injury

Fall

DSA pulmonary angiography



1st BPA session: right A10



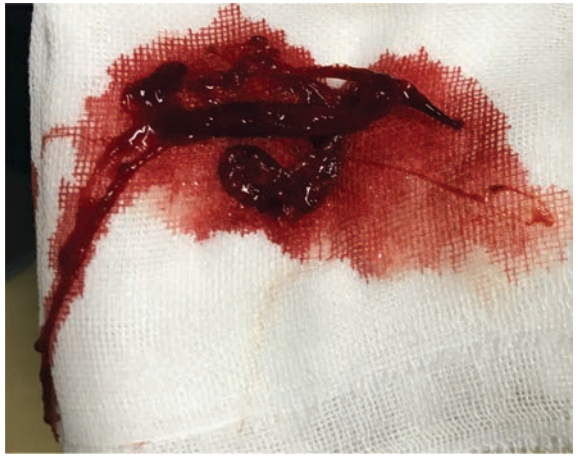
DSA pulmonary angiography after 3 BPAs

Summary

	baseline	after 3 BPAs
WHO FC	II	I
mPAP – mmHg	36	22
PVR – WU	5.4	2.3
6-MWD – m	500	697
Nt-proBNP – pg/mL	763.1	78.5

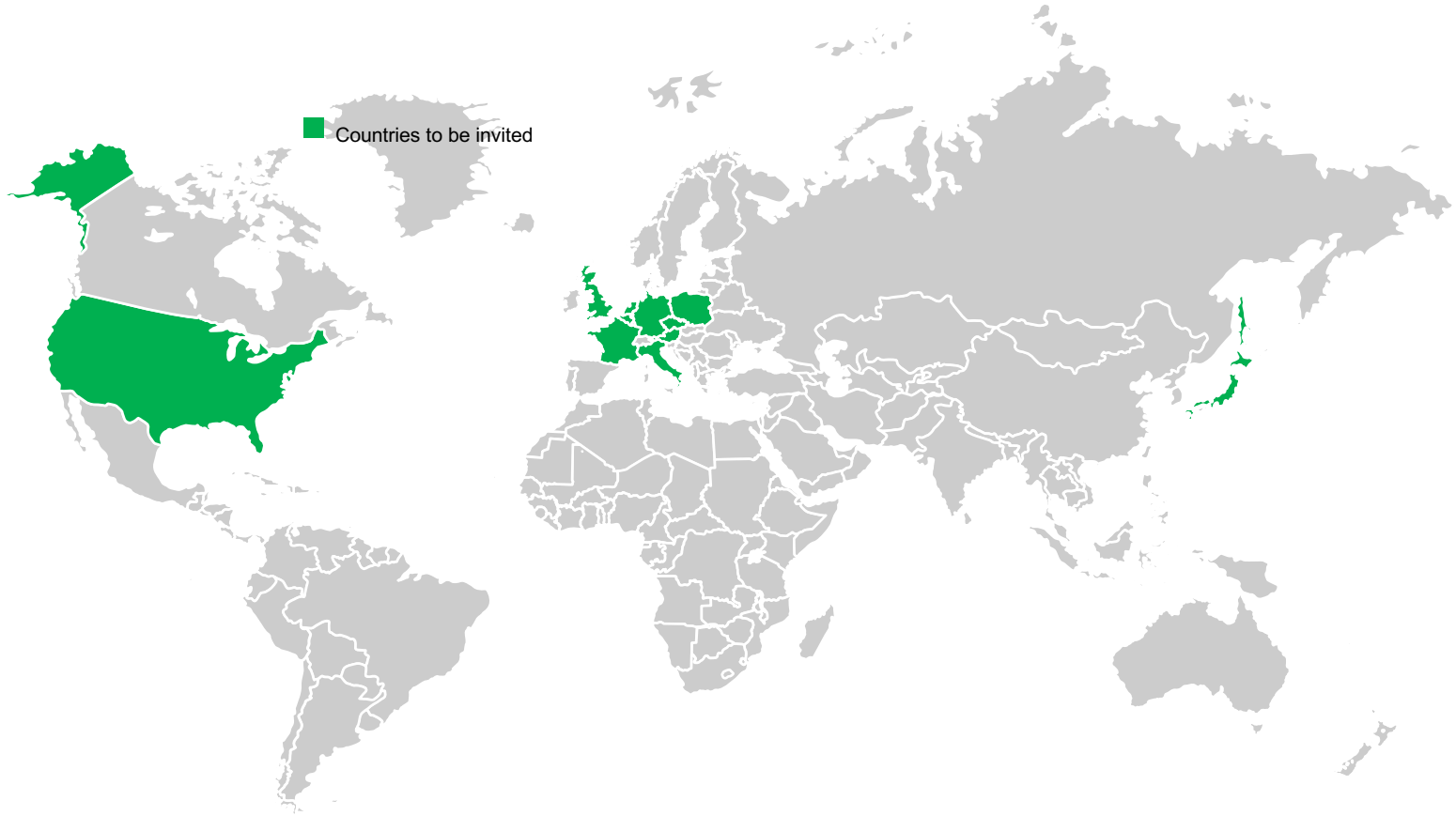
BPA-Komplikationen

	Diagnositic Criteria	Total	First 128 Sessions	Most Recent 127 Sessions	*P* Value
Reperfusion pulmonary injury	Hemo sputum	40	27	13	
	Chest X-ray or desaturation	36	19	17	
	Chest CT only	145	82	63	
	Total	221	128	93	<0.01
Pulmonary artery perforation		5	4	1	1.00



Mizuguchi H et al. *Circ Cardiovasc Interv*. 2012;5:748-755

International BPA Registry



Von Thrombose zu Fibrose

- CTEPH ist eine thromboembolische Erkankung
- Das Link zwischen akuter Pulmonalembolie und CTEPH ist Entzündung
- CTEPH Phänotypen sind
  - Thrombotic versus Inflammatory
  - Proximal versus Distal
  - Western versus Eastern

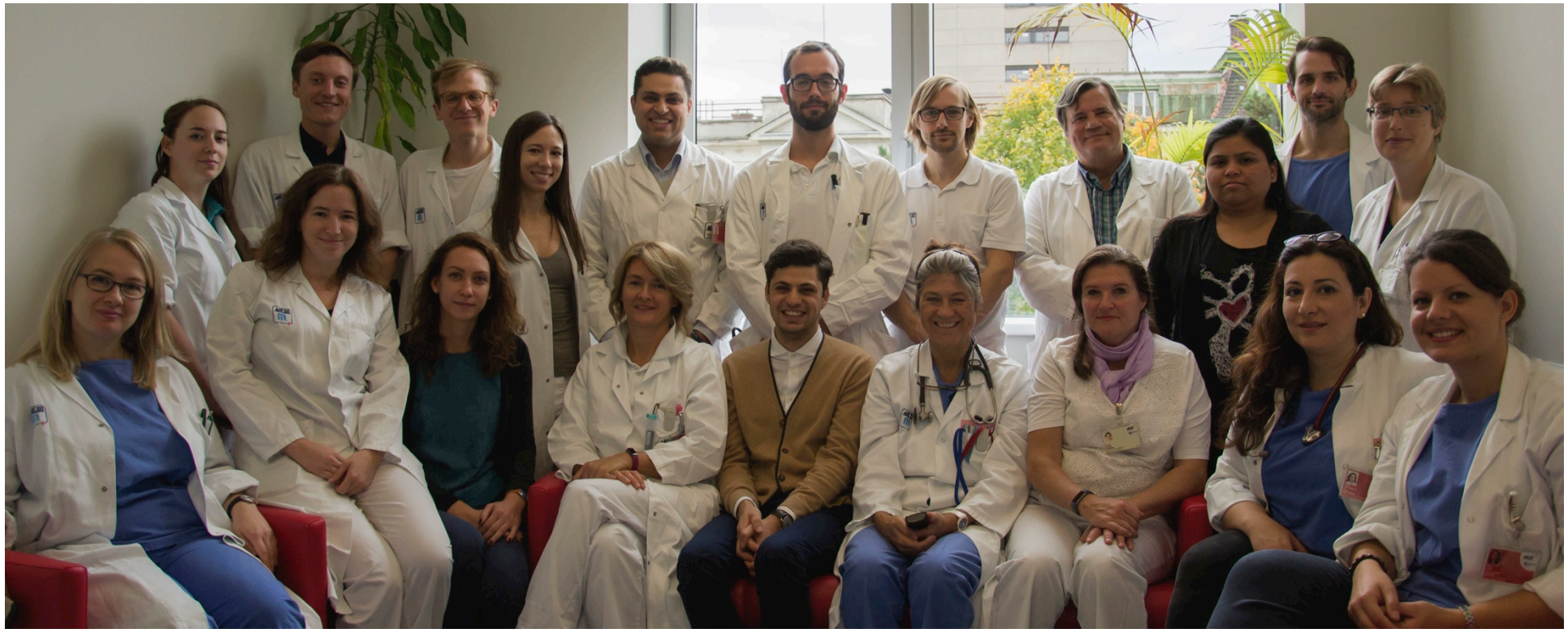
➢ Lebenslange Antikoagulation mit VKA ist Standard, die Rolle der NOACS ist ungesichert

➢ Als Therapien stehen zu Verfügung
  ➢ Pulmonale Endarterektomie
  ➢ Ballonangioplastie der Lungenarterien
  ➢ Medikamentöse Therapie mit Riociguat

➢ Riociguat erhöht den CO um 20% des Ausgangswerts

➢ BPA senkt den Mitteldruck um 20% des Ausgangswerts

Danke!



SIXTH FRAMEWORK PROGRAMME ICA International CTEPH Association

MEDICAL UNIVERSITY OF VIENNA

AKH Vienna General Hospital

FWF SFB-F54 InThro

CHD