BERTINORO ULTRASUONI

Tromboembolia polmonare

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Ospedale Generale Regionale F. Miulli, Acquaviva delle Fonti (BA)

EP :obiettivi

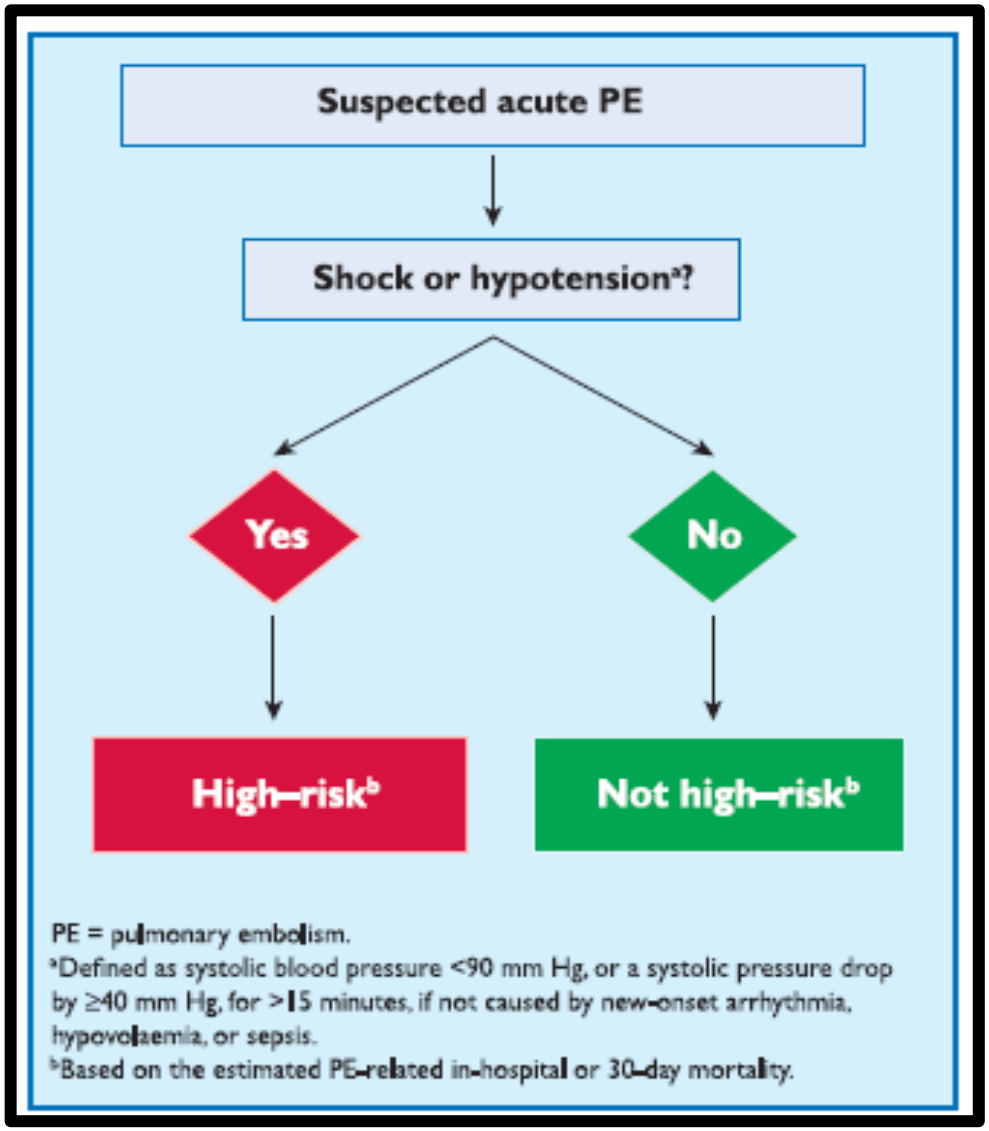
- **Corretto Iter Diagnostico**
- **Rapida Terapia in Fase Acuta**
- **Prevenzione delle Recidive**

Corretto iter diagnostico:

- **40%** di recidiva nel 1°mese
- **10%** al 2° e 3° mese
- **50%** di EP a 3 mesi

Hull, 1979
Hirsh,1992
Kearon, 1997

Initial risk stratification



ALGORITMO DIAGNOSTICO

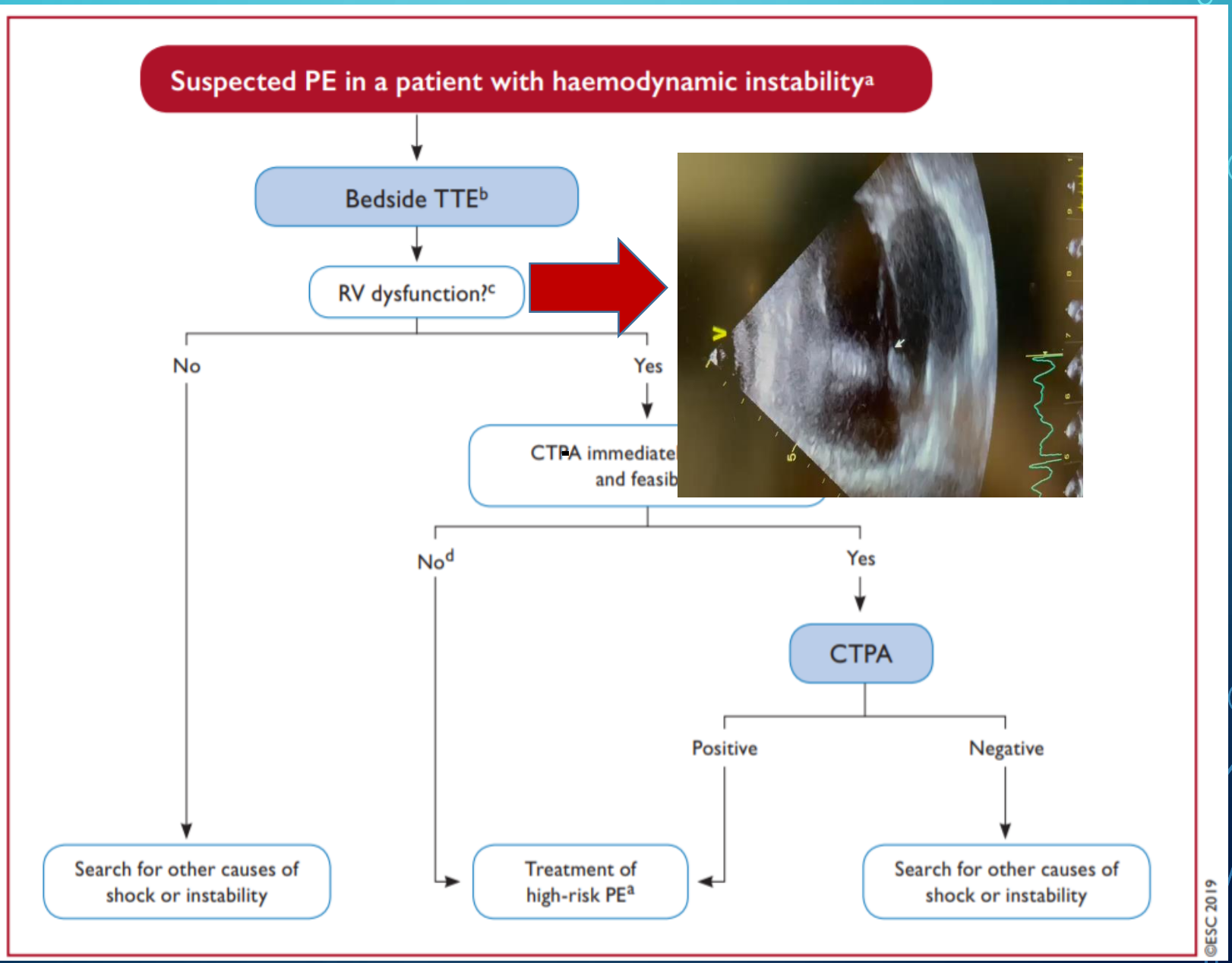
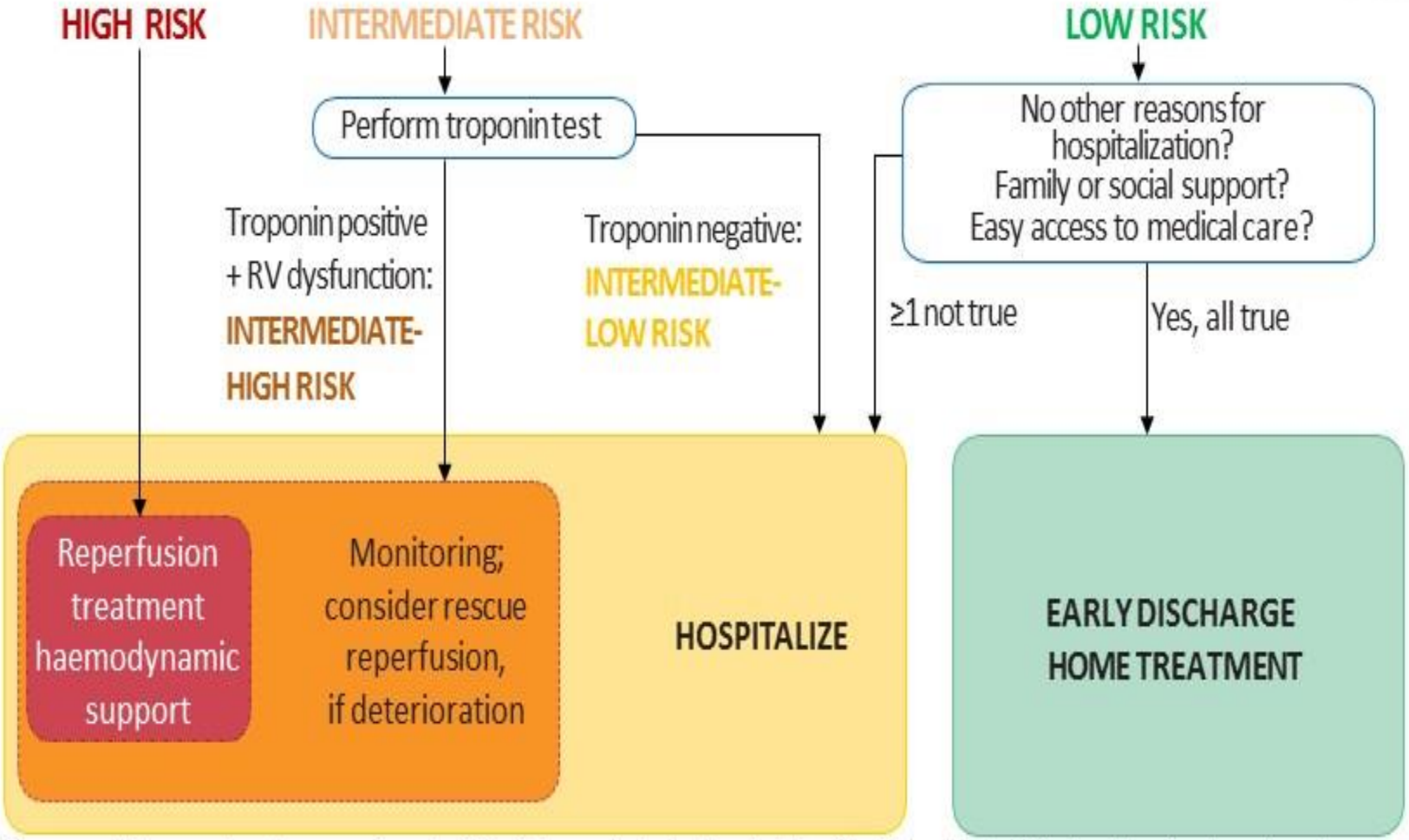


Figure 5 Risk-adjusted management strategy for acute PE (2)

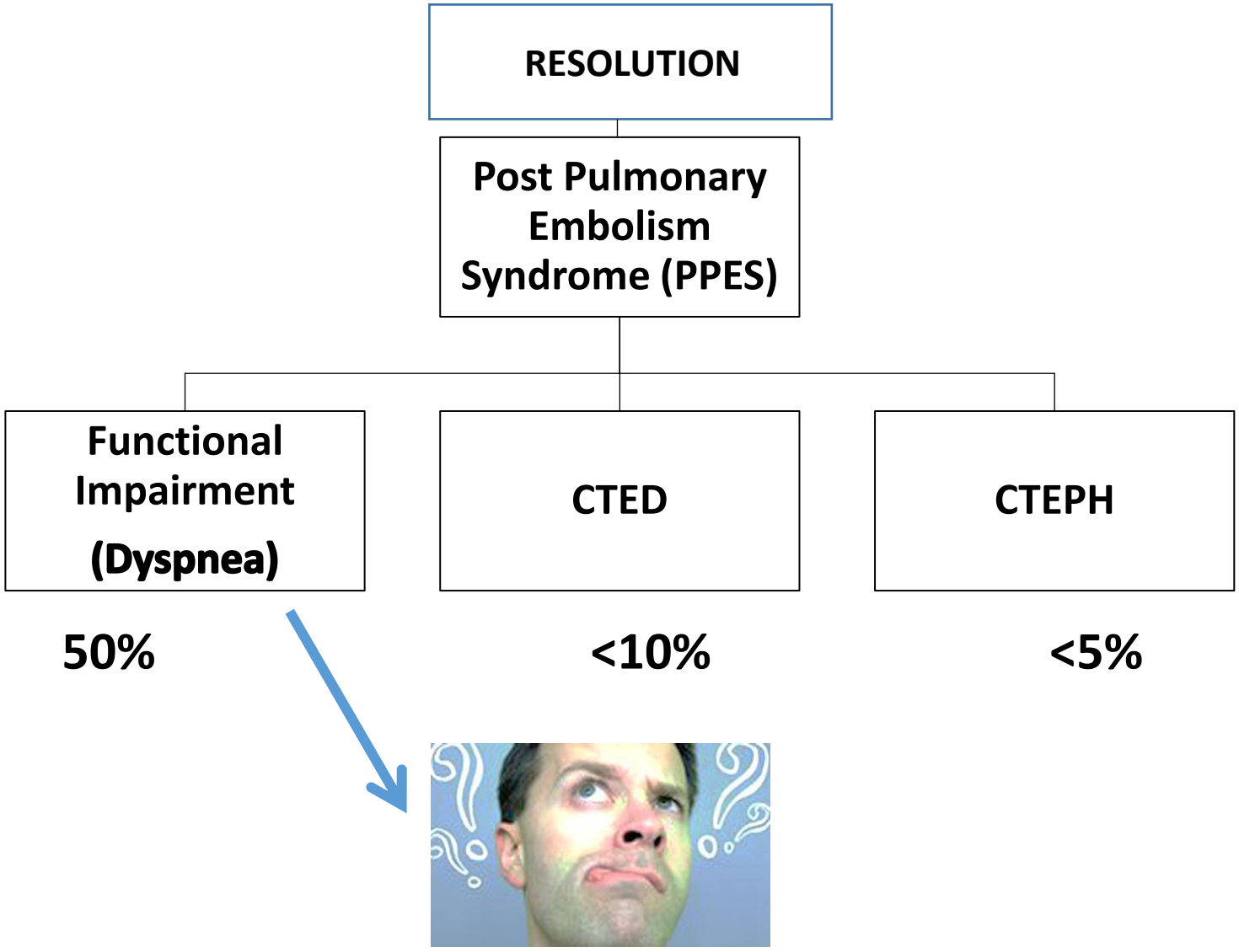
ESC European Society of Cardiology



CTPA = computed tomography pulmonary angiography; PESI = Pulmonary Embolism Severity Index; RV = right ventricular; TTE = transthoracic echocardiography.

2019 ESC Guidelines on the diagnosis and management of acute pulmonary embolism
(European Heart Journal 2019 - doi/10.1093/eurheartj/ehz405)

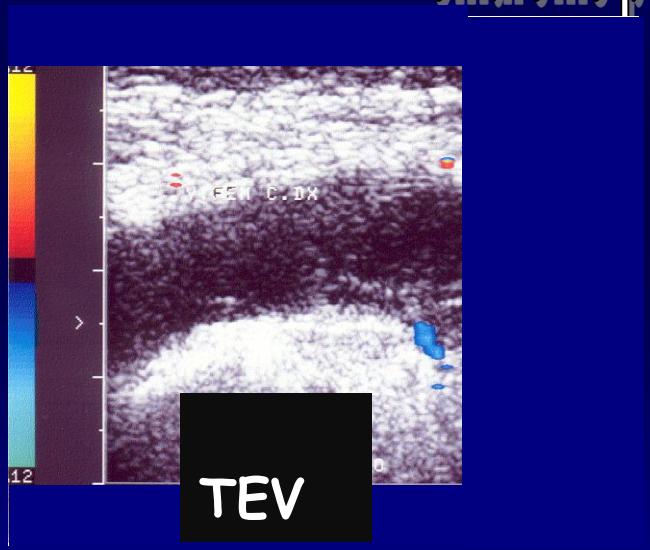
Natural and Pathologic History of Pulmonary Embolism



Fattori di rischio

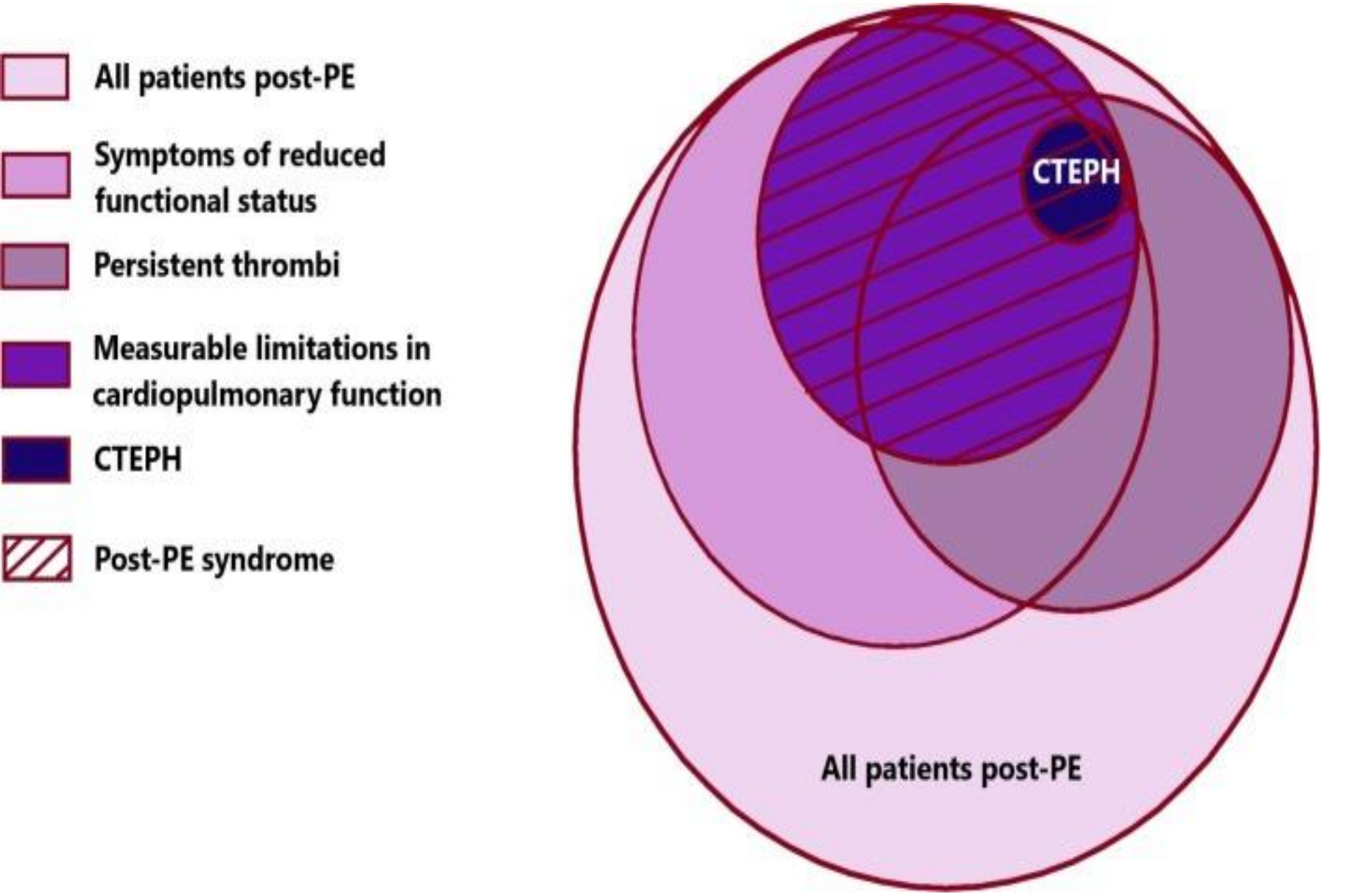
embolia polmonare

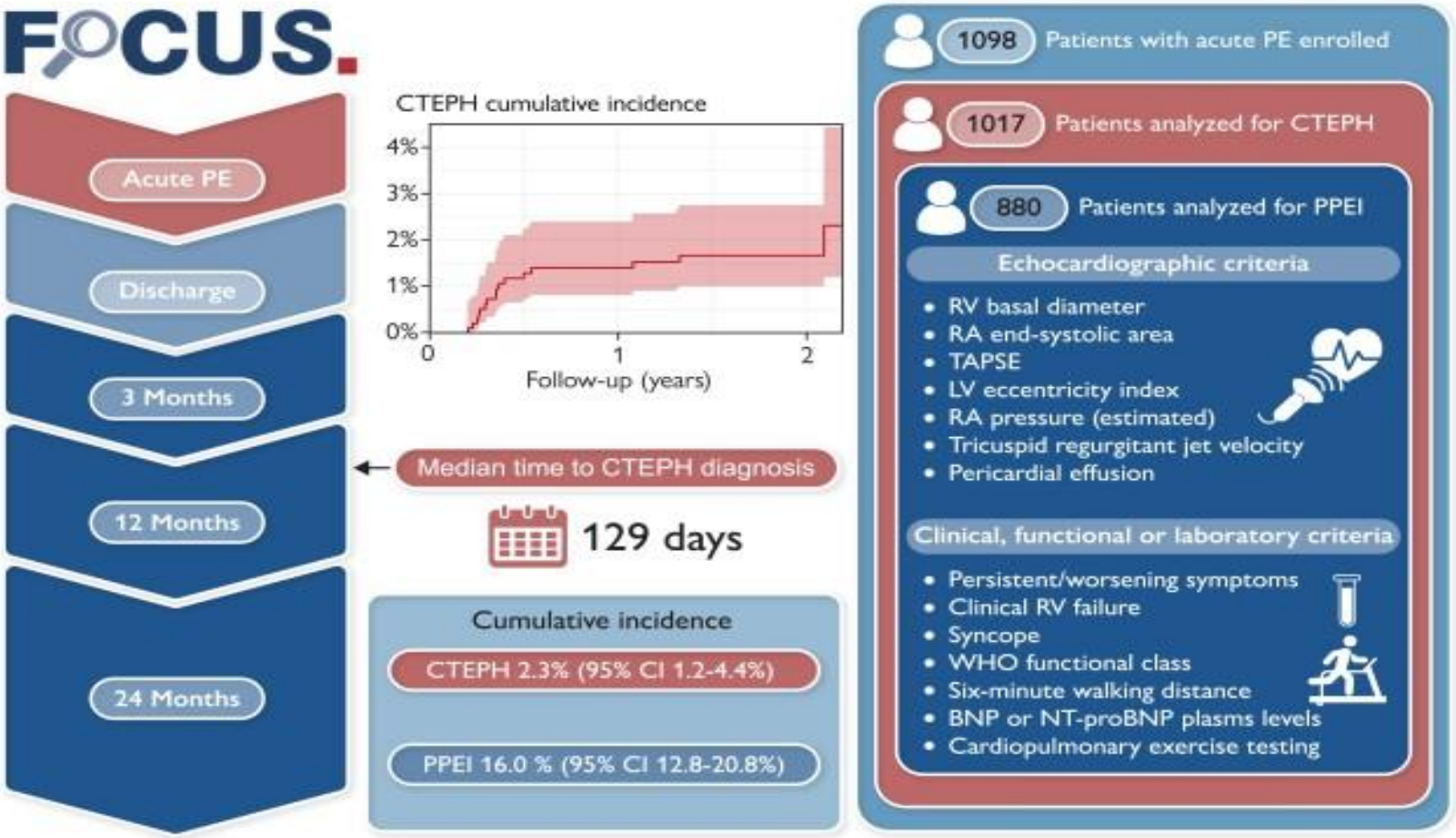
sindrome post-trombotica



Ipertensione Polmonare

Ulcera Venosa Cronica


All patients post-PE
Symptoms of reduced functional status
Persistent thrombi
Measurable limitations in cardiopulmonary function
CTEPH
Post-PE syndrome
CTEPH
All patients post-PE


FOCUS.
Acute PE
Discharge
3 Months
12 Months
24 Months
CTEPH cumulative incidence
4%
3%
2%
1%
0%
0
1
2
Follow-up (years)
Median time to CTEPH diagnosis
129 days
Cumulative incidence
CTEPH 2.3% (95% CI 1.2-4.4%)
PPEI 16.0 % (95% CI 12.8-20.8%)
1098 Patients with acute PE enrolled
1017 Patients analyzed for CTEPH
880 Patients analyzed for PPEI
Echocardiographic criteria
RV basal diameter
RA end-systolic area
TAPSE
LV eccentricity index
RA pressure (estimated)
Tricuspid regurgitant jet velocity
Pericardial effusion
Clinical, functional or laboratory criteria
Persistent/worsening symptoms
Clinical RV failure
Syncope
WHO functional class
Six-minute walking distance
BNP or NT-proBNP plasms levels
Cardiopulmonary exercise testing

Death 12 (2.9%) 6 (2.7%) 3 (2.4%) 6 (5.2%)*

Rehospitalization, n(%)120 (29%) 63 (29%)51 (40%)* 54 (47%)*

QL

Post-Pulmonary Embolism Syndrome (PPEs):

Predictors of post-PE syndrome

*** younger age**

*** higher BMI**

*** smoking**

*** Altered cardiopulmonary exercise testing or 6 min walk testing at 1 month may identify pts with a higher risk of post-PE syndrome at 1 year**

1.Lang IM, et a. Ann Am Thorac Soc 2016; 13: Suppl. 3, S215–S221.
2. Jenkins D et al. Respir Rev 2012;21:32–9.

Quality of Life, Dyspnea, and Functional Exercise Capacity Following a First Episode of Pulmonary Embolism: Results of the ELOPE Cohort Study n=100

*** female sex**

*** higher body mass index**

*** Dispnea Score**

*** percent-predicted VO2 peak <80% on 1 month cardiopulmonary exercise test**

***prior lung disease**

***higher pulmonary artery systolic pressure**

***higher main pulmonary artery diameter on baseline Computed Tomography Pulmonary Angiography**

Susan R. Kahn et al., *The American Journal of Medicine* (2017) 130,

Post-Pulmonary Embolism Syndrome (PPEs):

*** The inflammation and local vasoactive agents are responsible for the transition from acutely elevated pulmonary artery pressure and right ventricular dysfunction shortly after PE to persistent changes.**

***impaired angiogenesis**

*** hereditary or acquired predisposing pulmonary endothelial cell abnormalities**

***abnormal genetic variants of fibrinogen**

*** bacterial infection of fresh thrombi**

1.Lang IM, et a. Ann Am Thorac Soc 2016; 13: Suppl. 3, S215–S221.
2. Jenkins D et al. Respir Rev 2012;21:32–9.

CTHEP:

- Rare, progressive pulmonary vascular disease that is usually a chronic consequence of venous thromboembolism (VTE).

- Potentially fatal disease if left untreated [1]

  - Right ventricular heart failure is the most common cause of death.

- Potentially curable

  - Pulmonary endarterectomy surgery in eligible patients[2].

1.Lang IM, et a. Ann Am Thorac Soc 2016; 13: Suppl. 3, S215–S221.
2. Jenkins D et al. Respir Rev 2012;21:32–9.

European Heart Journal Advance Access published August 29, 2015

European Heart Journal
doi:10.1093/eurheartj/ehv317

ESC/ERS GUIDELINES

2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

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

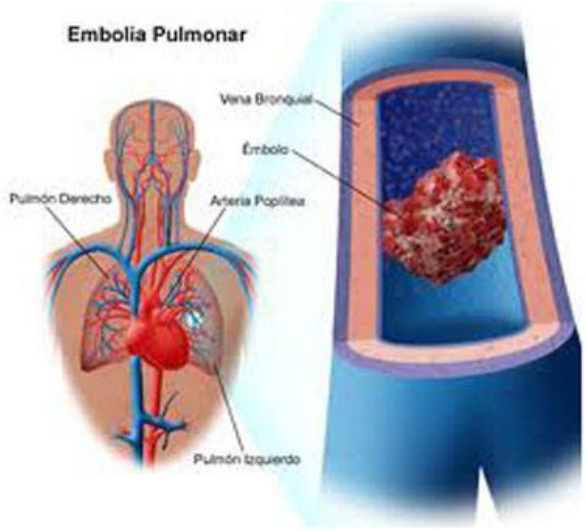
- 4.1 Chronic thromboembolic pulmonary hypertension
- 4.2 Other pulmonary artery obstructions
  - 4.2.1 Angiosarcoma
  - 4.2.2 Other intravascular tumors
  - 4.2.3 Arteritis
  - 4.2.4 Congenital pulmonary arteries stenoses
  - 4.2.5 Parasites (hydatidosis)

4%

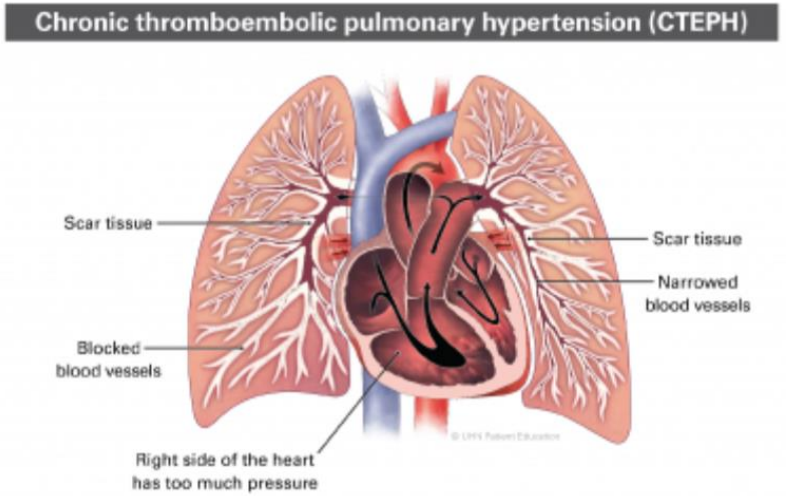
5. Pulmonary hypertension with unclear and/or multifactorial mechanisms

- 5.1 Haematological disorders: chronic haemolytic anaemia, myeloproliferative 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 Respir J* 2015;46:903–975.



CTEPH is different from pulmonary embolism



Relationship between PE and CTEPH

CTEPH occurs in **~0.5–4%** of patients with history of PE[5]

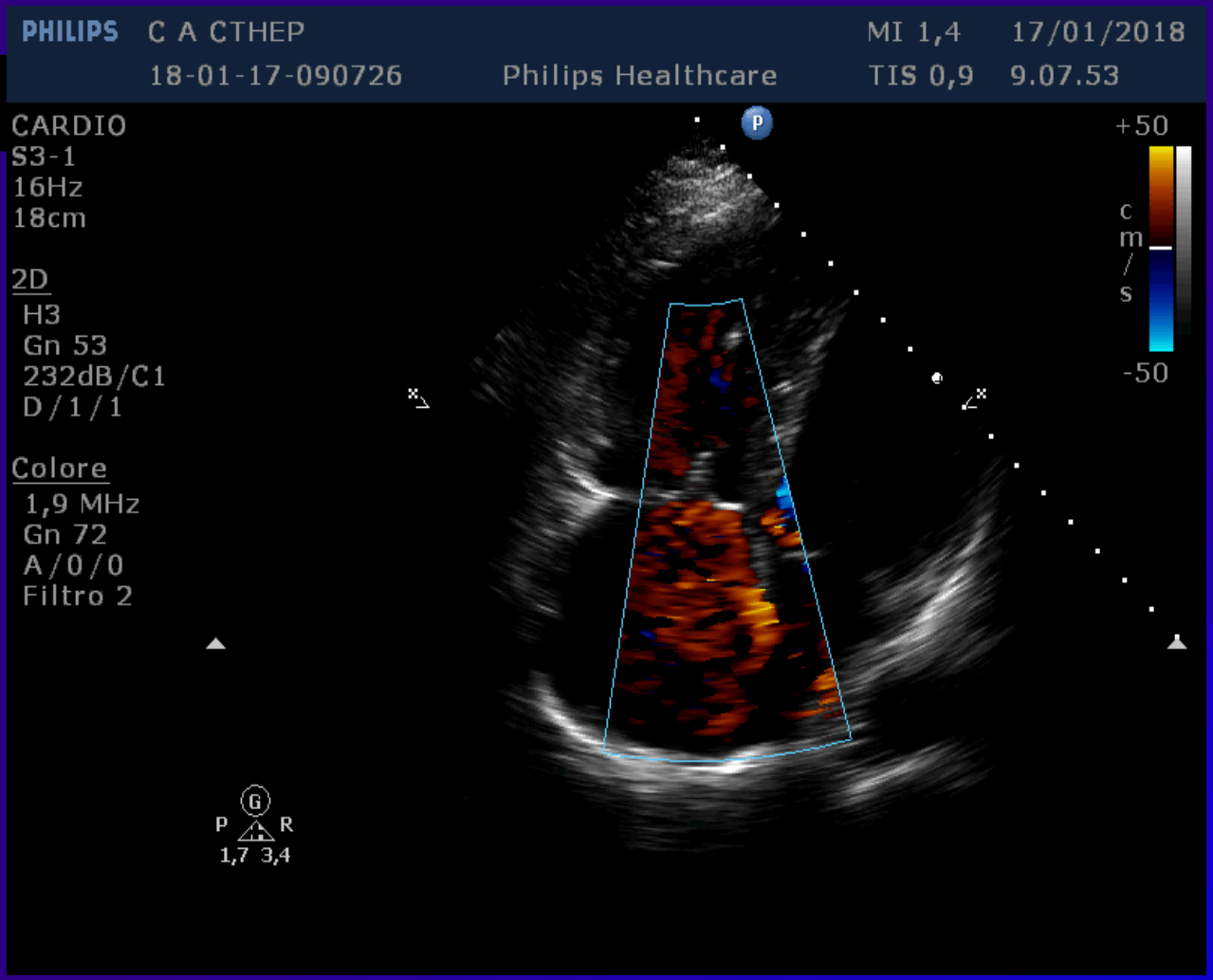
- Previous PE confirmed for approximately **75%** of CTEPH patients[6]
- PE not necessary for diagnosis as no history of PE in some patients[7]

  - Undiagnosed PE may be a factor in patients with no history of PE

Diagnostic delay: *2 years*

5. Galiè N *et al. Eur Heart J* 2009;30:2493–537. 2. Pengo V *et al. N Engl J Med* 2004;350:2257–64.
6. Pepke-Zaba J *et al. Circulation* 2011;124:1973–81. 5. Bonderman D *et al. Eur Respir J* 2009;33:325–31.

Clinical Feature



No PE no DVT!!!

CTEPH - DVT

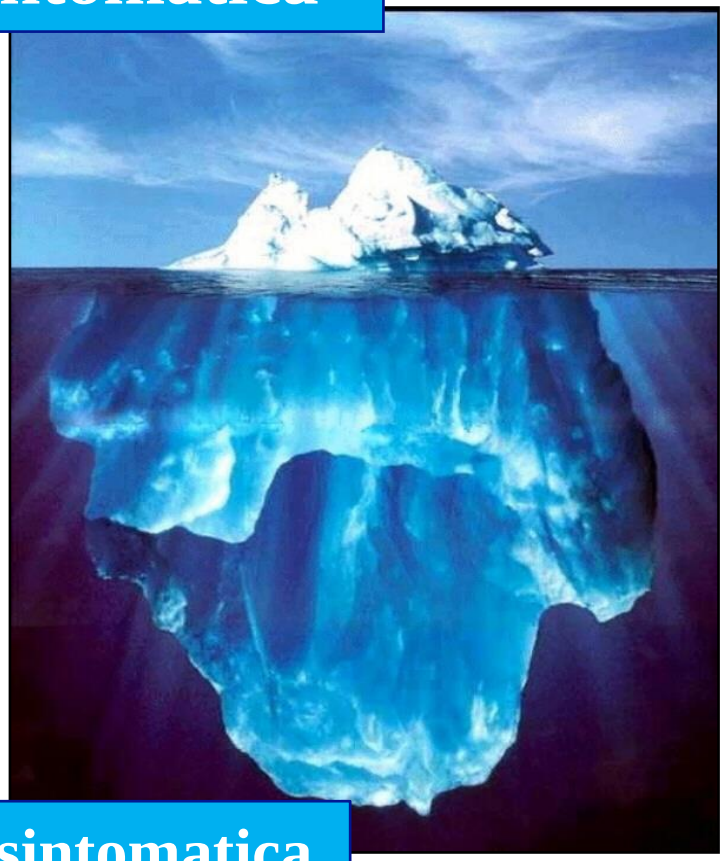
63% dei Pz con CTEPH
Anamnesi negativa
per TVP sintomatica

Lang IM. N Engl J Med 2004

50% delle TVP Prossimali si complica
con EP asintomatiche
rilevate con TAC

Moser KM., JAMA 2004

TEV Sintomatica



TEV asintomatica
(alto rischio!)

Risk Factors/Predisponing Conditions for CTEPH

Findings related to the acute PE event (obtained at PE diagnosis)	Concomitant chronic diseases and conditions predisposing to CTEPH (documented at PE diagnosis or at 3–6-month follow-up)
Previous episodes of PE or DVT	Ventriculo-atrial shunts
Large pulmonary arterial thrombi on CTPA	Infected chronic i.v. lines or pacemakers
Echocardiographic signs of PH/RV dysfunction	History of splenectomy
CTPA findings suggestive of pre-existing chronic thromboembolic disease	Thrombophilic disorders, particularly antiphospholipid antibody syndrome and high coagulation factor VIII levels

CTEPH = chronic thromboembolic pulmonary hypertension; CTPA = computed tomography pulmonary angiography; DVT = deep vein thrombosis; PH = pulmonary hypertension; RV = right ventricular.

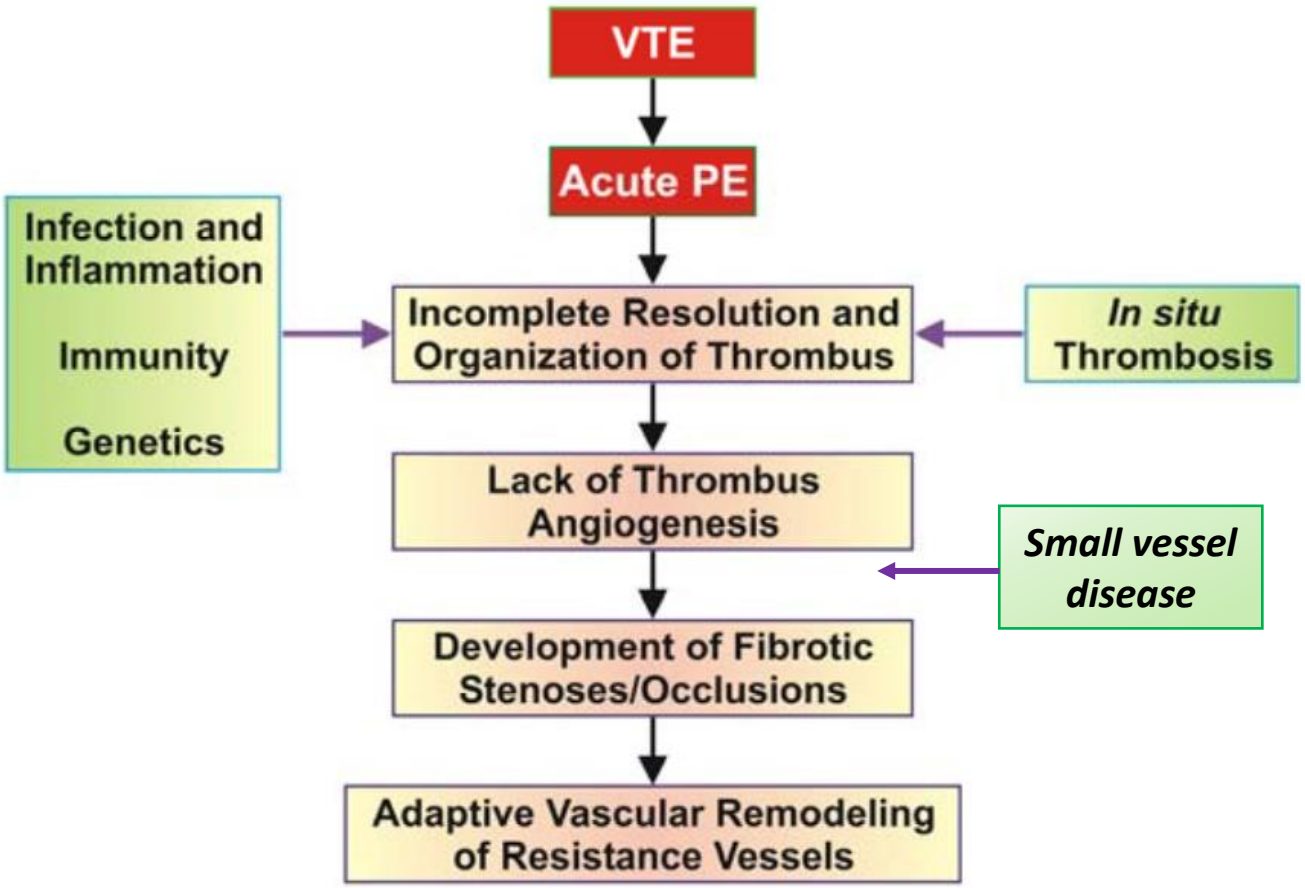
2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). European Heart Journal (2019) 00, 1 61 doi:10.1093/eurheartj/ehz405

Risk Factors/Predisponing Conditions for CTEPH

Findings related to the acute PE event (obtained at PE diagnosis)	Concomitant chronic diseases and conditions predisposing to CTEPH (documented at PE diagnosis or at 3–6-month follow-up)
	Non-O blood group
	Hypothyroidism treated with thyroid hormones
	History of cancer
	myeloproliferative disorders
	Inflammatory bowel disease
	Chronic osteomyelitis

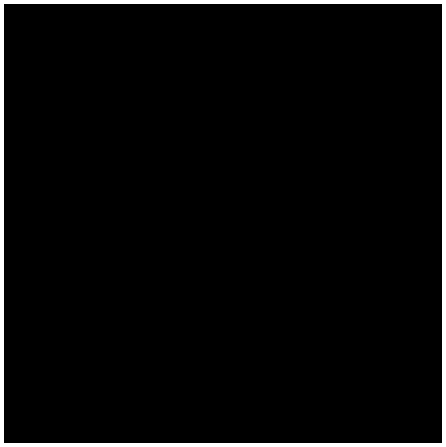
2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). European Heart Journal (2019) 00, 1 61 doi:10.1093/eurheartj/ehz405

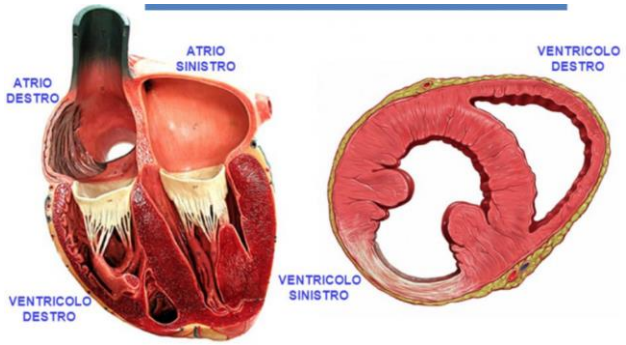
CTEPH Pathophysiology



Simonneau G, Torbicki A, Dorfmüller P, et al. The pathophysiology of chronic thromboembolic pulmonary hypertension. Eur Respir Rev 2017; 26: 160112

RV in patients with PH





PH

RV dilatation

Systolic dysfunction

RV hypertrophy

Diastolic dysfunction

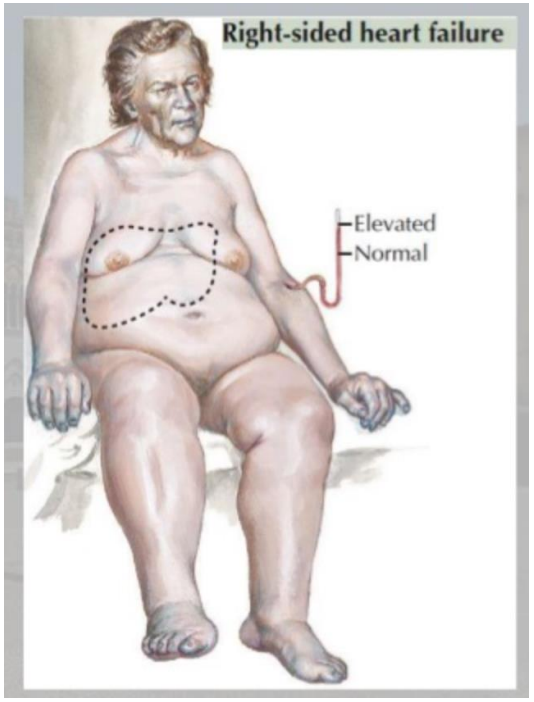
Preload-Aferload mismatch

Right ventricular heart failure

Pulmonary Arterial Hypertension and Women. De Marco, Teresa MD, FACC
Cardiology in Review: November-December 2006 - Volume 14 - Issue 6 - p 312-318
doi: 10.1097/01.crd.0000240529.49704.2e

Clinical Presentation of CTEPH -1

- Early nonspecific clinical symptoms
  - Unexplained exertional dyspnea
  - Atypical chest pain
  - Episodic hemoptysis
  - Non-productive cough
  - Fatigue
  - Palpitations
- Presentation can be initially subtle, but can progress to similar manifestations as PAH



Auger WR et al. Clin Chest Med 2010;31:741–758

Clinical Presentation of CTEPH -2

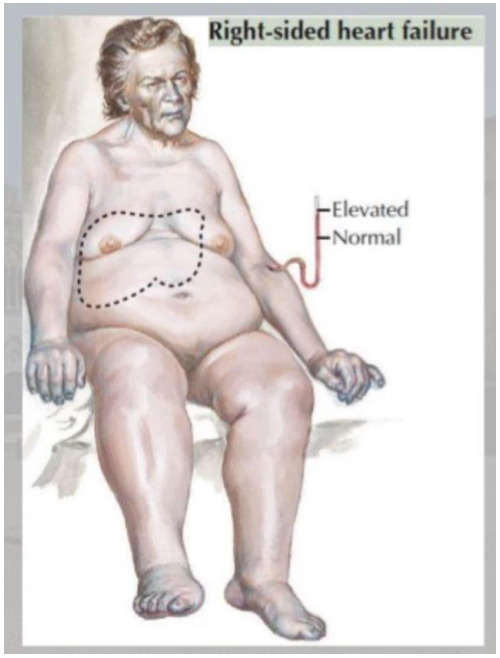
- Pulmonary Embolism
- "Honeymoon Period"
- Evidence of Right Ventricular dysfunction

– Peripheral edema

– Severe exercise limitation

– Chest discomfort/pain

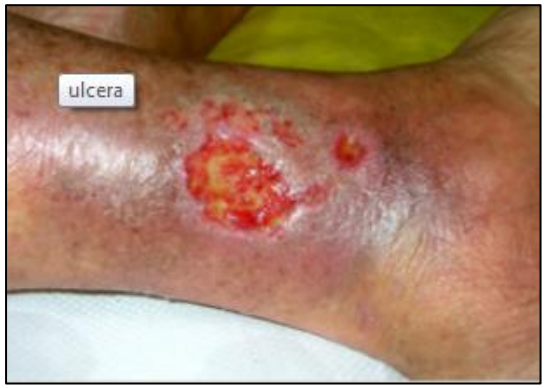
– Exertional dizziness or syncopal episodes



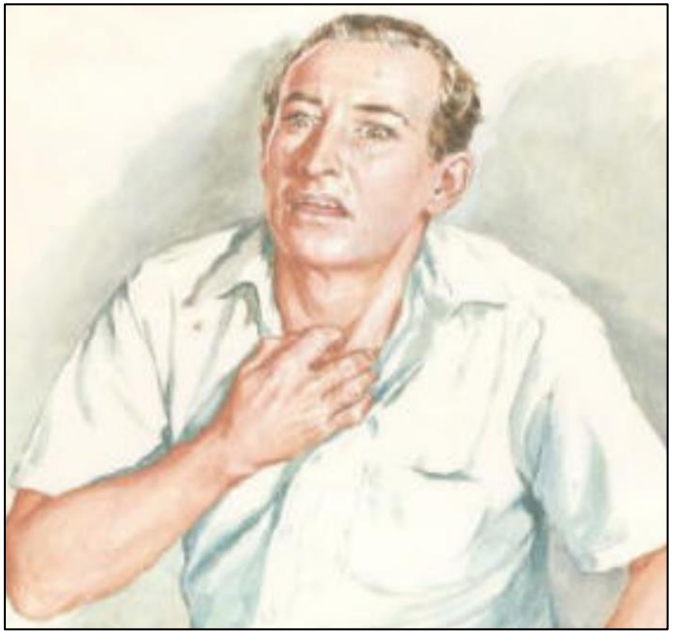
Auger WR et al. Pulmonary Circ 2012;2:155-161

Clinical Presentation of CTEPH -3

Post-thrombotic Syndrome

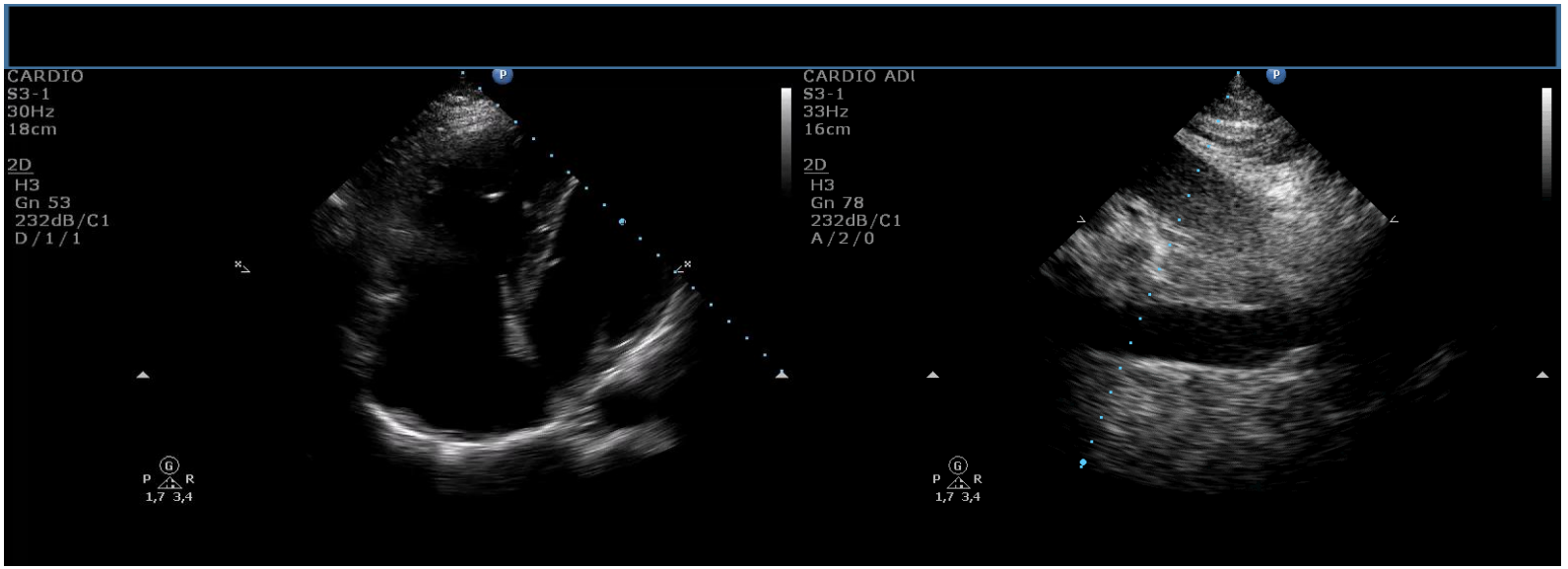


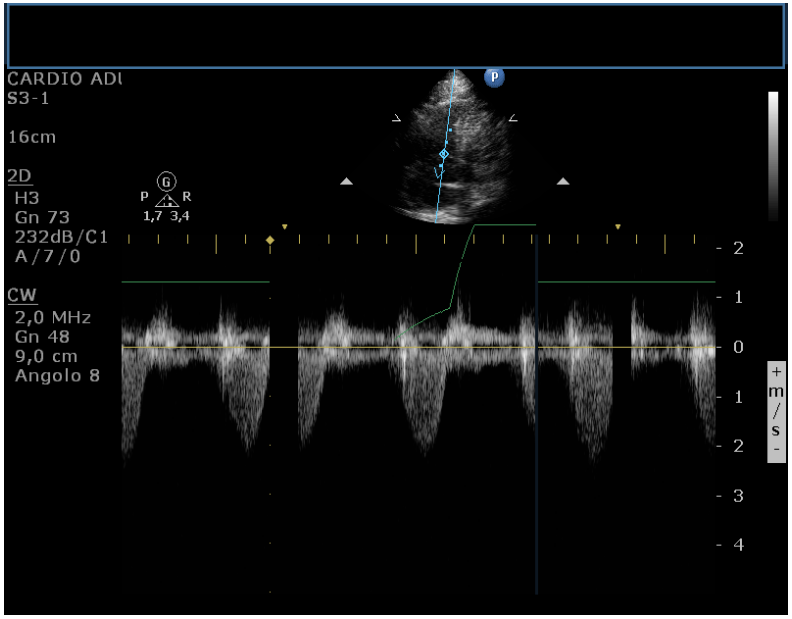
Dyspnea

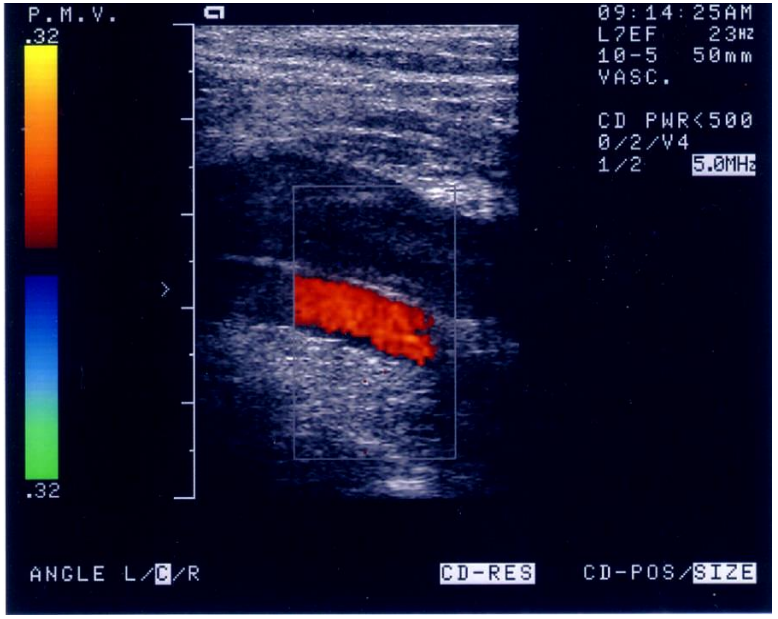


CTEPH

Integrated analysis : TTE-US







TTE follow-up

ANMCO Position Paper: long-term follow-up of patients with pulmonary thromboembolism

Carlo D'Agostino (Coordinator)[1]*, Pietro Zonzin (Coordinator)[2], Iolanda Enea (Coordinator)[3], Michele Massimo Gulizia, FACC, FESC (Coordinator)[4], Walter Ageno[5], Piergiuseppe Agostoni[6], Michele Azzarito[7], Cecilia Becattini[8], Amedeo Bongarzoni[9], Francesca Bux[10], Franco Casazza[11], Nicoletta Corrieri[12], Michele D'Alto[13], Nicola D'Amato[10], Andrea Maria D'Armini[14], Maria Grazia De Natale[8], Giovanni Di Minno[15], Giuseppe Favretto[16], Lucia Filippi[17], Valentina Grazioli[14], Gualtiero Palareti[18], Raffaele Pesavento[17], Loris Roncon[19], Laura Scelsi[20], Antonella Tufano[15]

Table 3 Recommendations for TTE

Transthoracic echocardiography (TTE) is useful to assess the presence of pulmonary arterial hypertension (PAH). However, the gold standard technique remains the cardiac catheterization.
TTE should always be performed at discharge to evaluate PAH and if present, FU at 3 and 6 months must be considered;
TTE follow-up should be considered only for those patients with a right ventricle-right atrium (RV-RA) gradient >45 mmHg or in the presence of both dyspnoea and a RV-RA gradient ranging between 32 and 45 mmHg at discharge.

Diagnosis-2

Table 12 Recommendations for diagnostic strategy

Recommendations	Class[a]	Level[b]	Ref.[c]
Echocardiography is recommended as a first-line non-invasive diagnostic investigation in case of suspicion of PH	I	C	
Ventilation/perfusion or perfusion lung scan is recommended in patients with unexplained PH to exclude CTEPH	I	C	47

V/Q scan is the gold standard technique for diagnosing CTEPH:

- "Sensitive but not specific"… can rule out CTEPH but not confirm
- Need more specific imaging techniques

Galiè N et al, Eur Heart J, 2015

TABLE 2 Diagnostic Tests Used for CTEPH

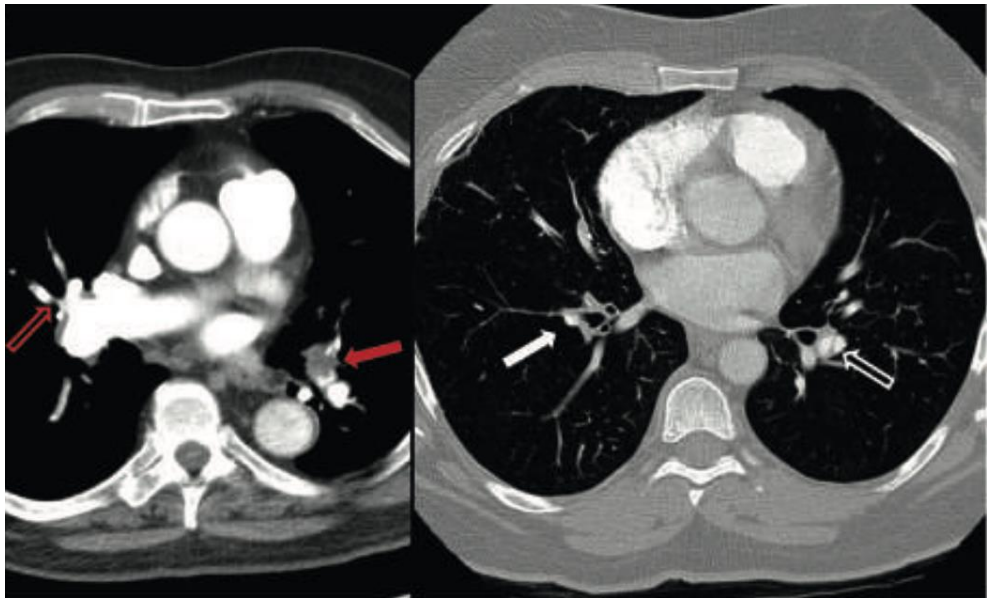
Diagnostic Technique	Features and Supportive Findings
Chest radiography	• Chronic pulmonary embolism: avascular lung areas; asymmetric central pulmonary artery enlargement; evidence of pleural disease • Pulmonary hypertension: dilatation of main pulmonary arteries, right atrial or right ventricular enlargement in advanced disease
Electrocardiography	• Right ventricular hypertrophy with right axis deviation
Pulmonary function tests	• Reduction in DLCO • Mild restrictive defect due to parenchymal scarring
Echocardiography	• Pulmonary hypertension • Right atrial enlargement • Right ventricular hypertrophy • Increased tricuspid regurgitation velocity
V/Q scan	• Preferred initial test with high sensitivity to detect CTEPH • Normal ventilation scan with a wedge-shaped perfusion defect
CTPA	• Lower sensitivity than V/Q scan • Right ventricular enlargement • Recanalized thromboembolic material associated with attenuated pulmonary arteries beyond the obstruction • Bronchial artery collateral flow • Mosaic perfusion of the pulmonary parenchyma
MRI	• Evaluation of pulmonary hemodynamics, and right ventricular size and function • MRA with contrast enhancement has similar sensitivity to CTPA
Pulmonary angiography and right heart catheterization	• "Gold standard" technique to assess the location and extent of disease; more sensitive at segmental and subsegmental level than CTPA • Determine surgical accessibility • Hemodynamic evaluation to confirm the diagnosis

J Am Coll Cardiol 2018;71:2468–86

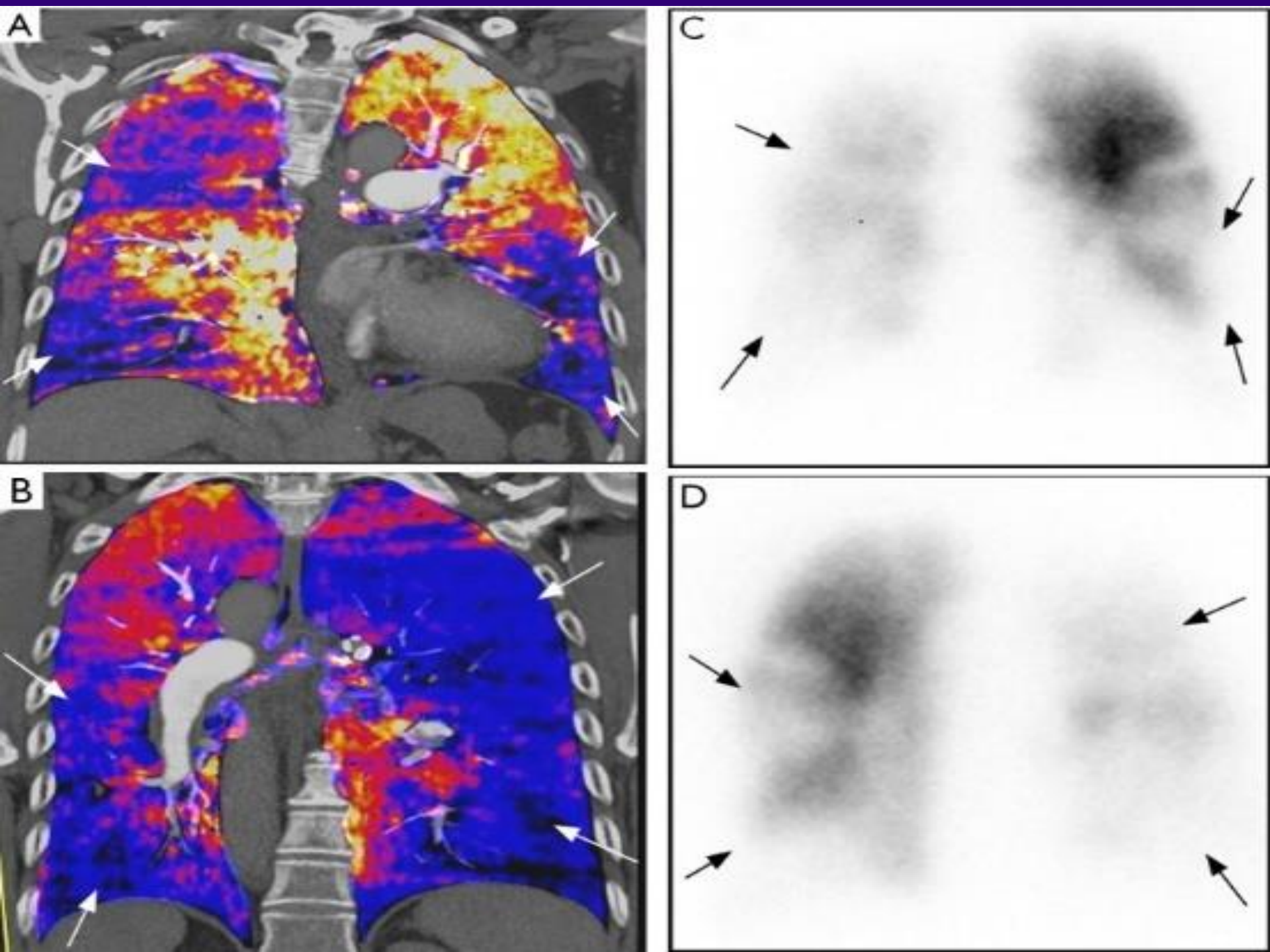
Diagnosis-3

Modern imaging modalities such as CT pulmonary angiography can provide useful clinical information in conjuction with V/Q scan:

- Cannot replace V/Q scan due to its lack of diagnostic specific



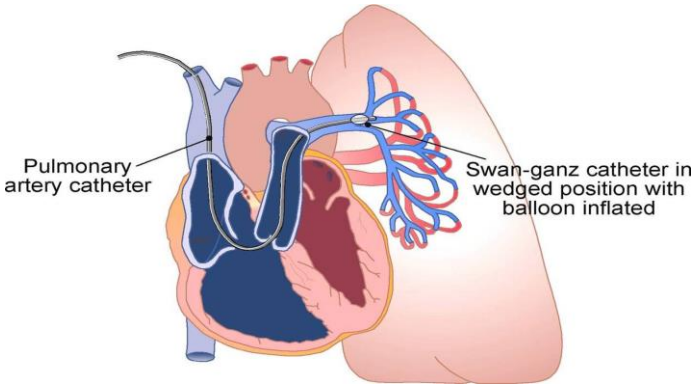
J Am Coll Cardiol 2018;71:2468–86


A
B
C
D

Diagnosis-4

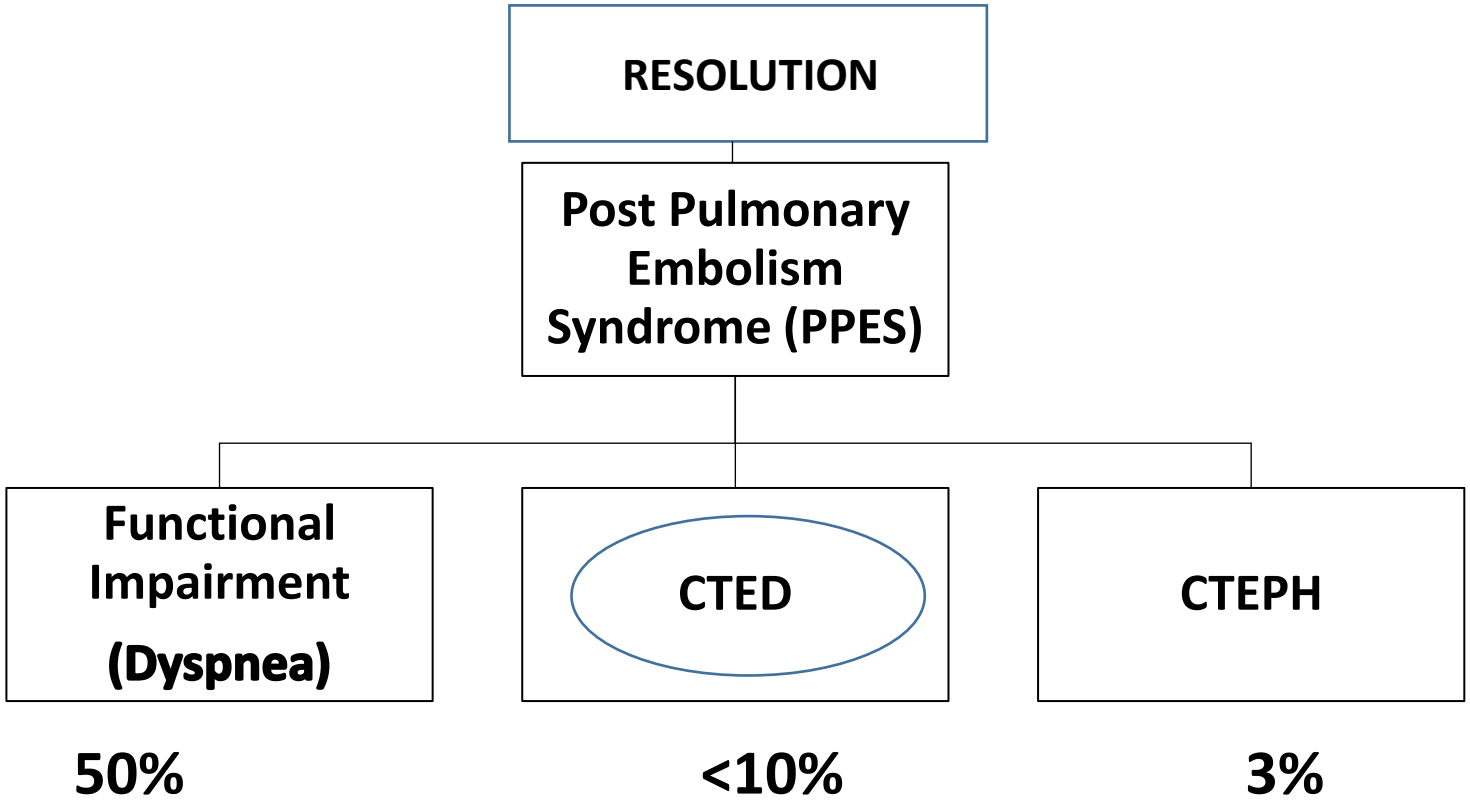
Right Heart Catheterization (**RHC)** is the diagnostic **gold standard** for pulmonary hypertension.

RHC is indicated in patients with Chronic Thromboembolic Pulmonary Hypertension (Group 4) to confirm diagnosis and support treatment decisions.	I	C



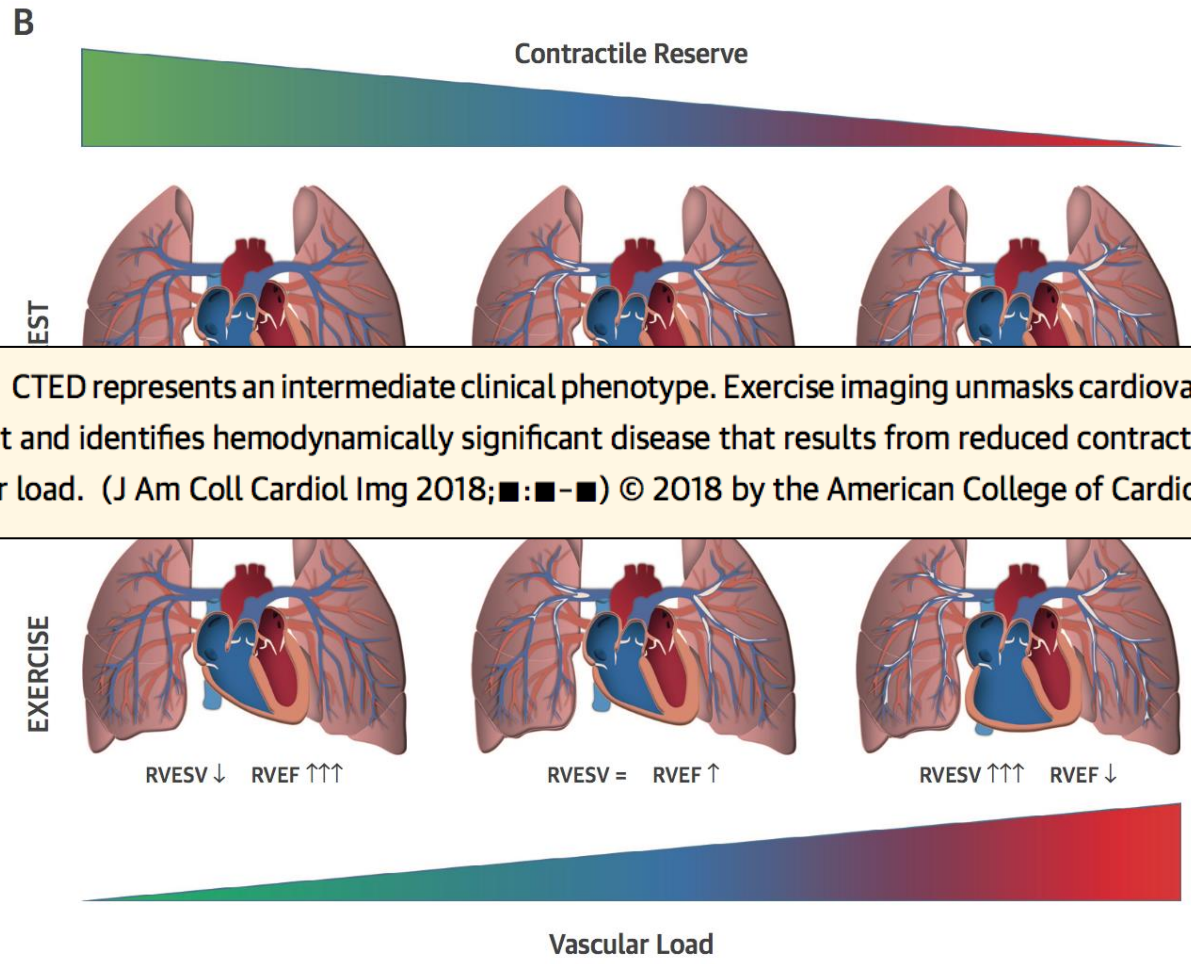
Galiè N *et al. Eur Respir J* 2015;46:903–975.
European Respiratory Journal Oct 2015, 46 (4) 903-975

Natural and Pathologic History of Pulmonary Embolism



Impaired Cardiac Reserve and Abnormal Vascular Load Limit Exercise Capacity in Chronic Thromboembolic Disease

Mathias Claeys, MD,[a,b] Guido Claessen, MD, PhD,[a,b] Andre La Gerche, MD, PhD,[a,c] Thibault Petit, MD,[a,b] Catharina Belge, MD, PhD,[d,e] Bart Meyns, MD, PhD,[a,f] Jan Bogaert, MD, PhD,[g,h] Rik Willems, MD, PhD,[a,b] Piet Claus, MSc, PhD,[a] Marion Delcroix, MD, PhD[d,e]



CONCLUSIONS CTED represents an intermediate clinical phenotype. Exercise imaging unmasks cardiovascular dysfunction not evident at rest and identifies hemodynamically significant disease that results from reduced contractile reserve or increased vascular load. (J Am Coll Cardiol Img 2018;■:■–■) © 2018 by the American College of Cardiology Foundation.

J Am Coll Cardiol Img 2018

CTED - Chronic ThromboEmbolic Disease (?)

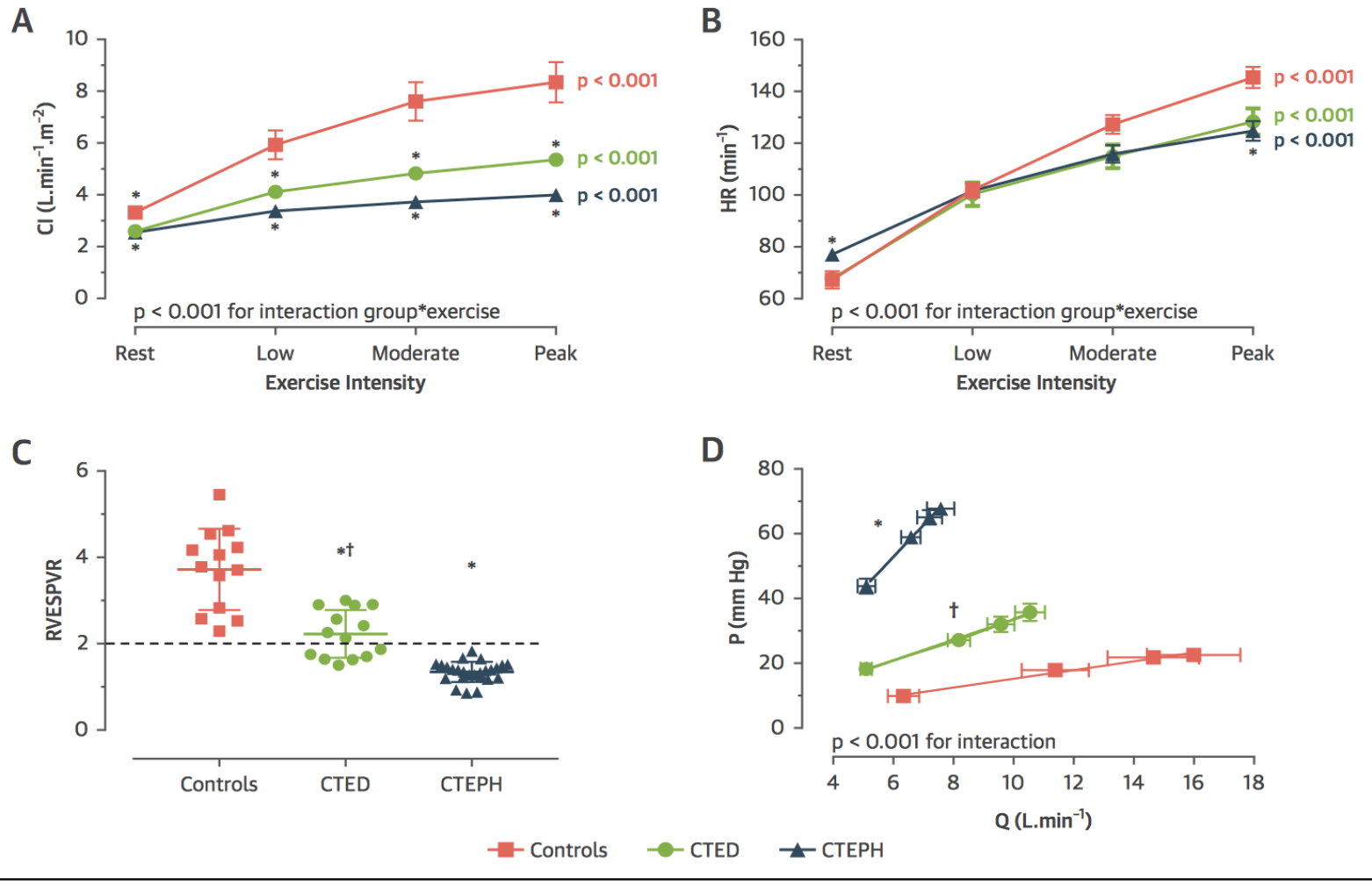
- CTEPH...but without the PH (mPAP < 25 mmHg at rest)
- Partial or complete obstruction of pulmonary vascular segments does NOT always mean you will have PH
- PV obstruction in areas of normal ventilation will lead to dead space ventilation (V/Q>>1) which contributes to dyspnea

Impaired Cardiac Reserve and Abnormal Vascular Load Limit Exercise Capacity in Chronic Thromboembolic Disease

Mathias Claeys, MD,[a,b] Guido Claessen, MD, PhD,[a,b] Andre La Gerche, MD, PhD,[a,c] Thibault Petit, MD,[a,b] Catharina Belge, MD, PhD,[d,e] Bart Meyns, MD, PhD,[a,f] Jan Bogaert, MD, PhD,[g,h] Rik Willems, MD, PhD,[a,b] Piet Claus, MSc, PhD,[a] Marion Delcroix, MD, PhD[d,e]

J Am Coll Cardiol Img 2018

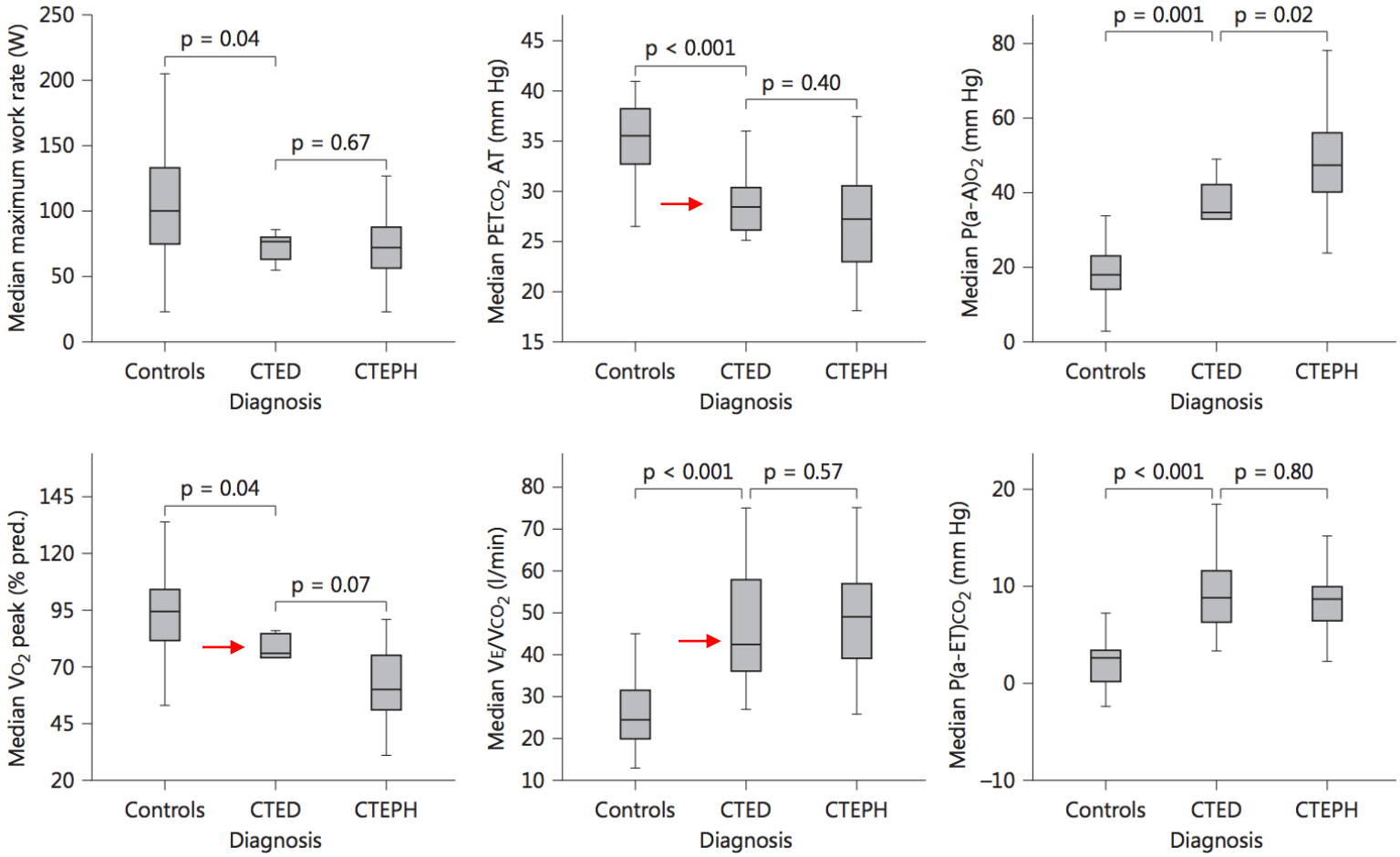
FIGURE 5 Cardiac Reserve and Pulmonary Vascular Load



Functional Characterization of Patients with Chronic Thromboembolic Disease

Matthias Held[a] Philipp Kolb[f] Maria Grün[a, b] Berthold Jany[a] Gudrun Hübner[a]
Aleksandar Grgic[c] Regina Holl[a] Hans-Joachim Schaefers[d] Heinrike Wilkens[e]

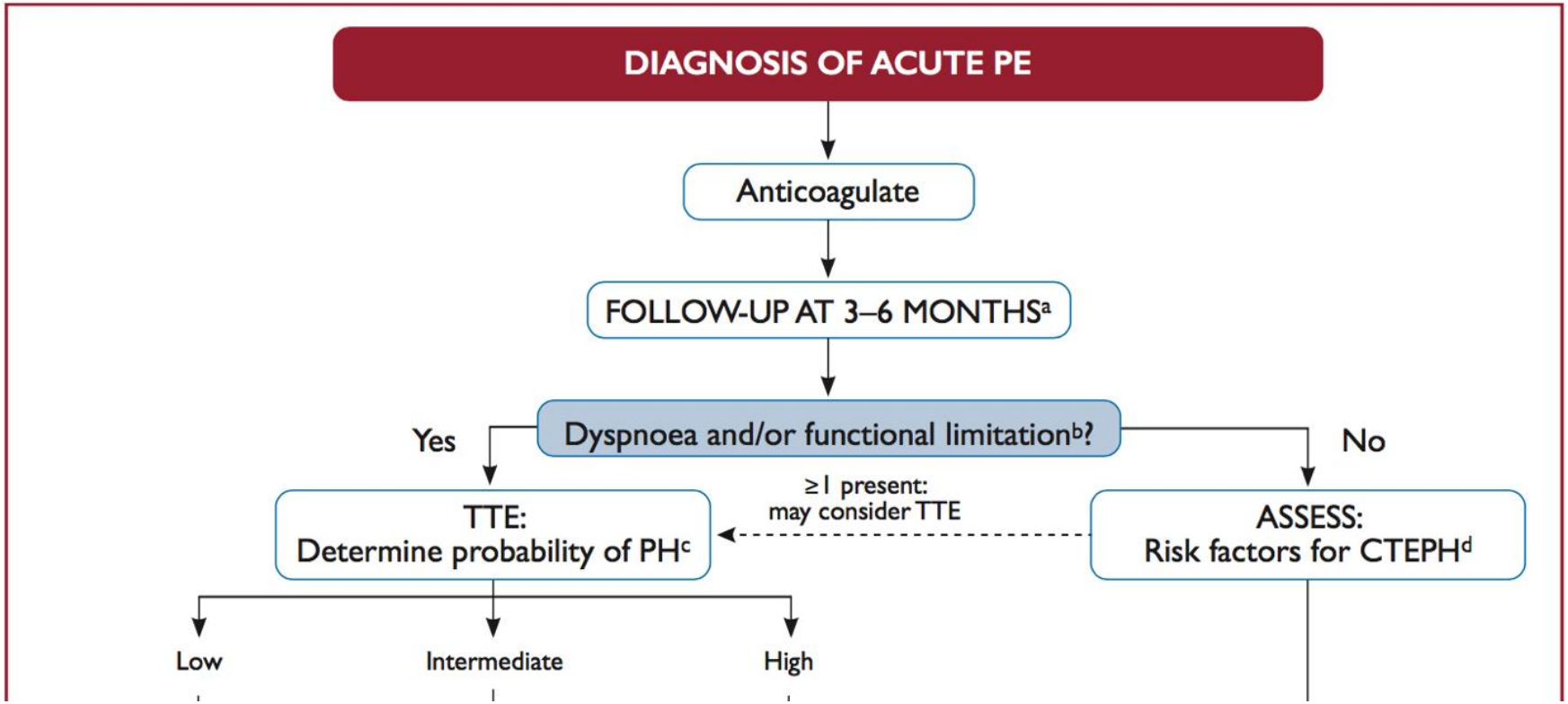
Chronic ThromboEmbolic Disease



Respiration 2016;91:503–509

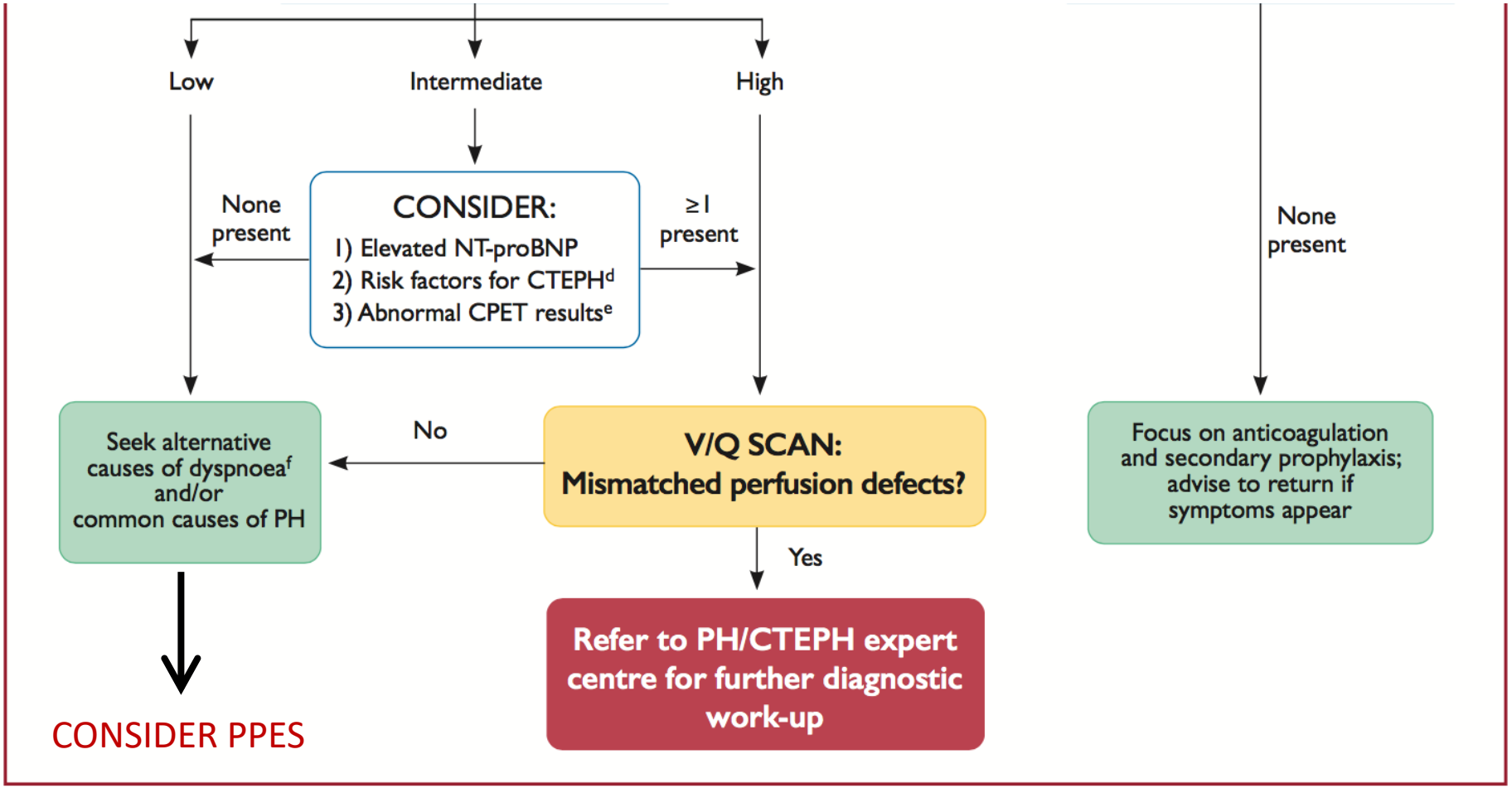
IL RUOLO DEL MEDICO

Follow-up strategy and diagnostic workup for long-term sequelae of pulmonary embolism



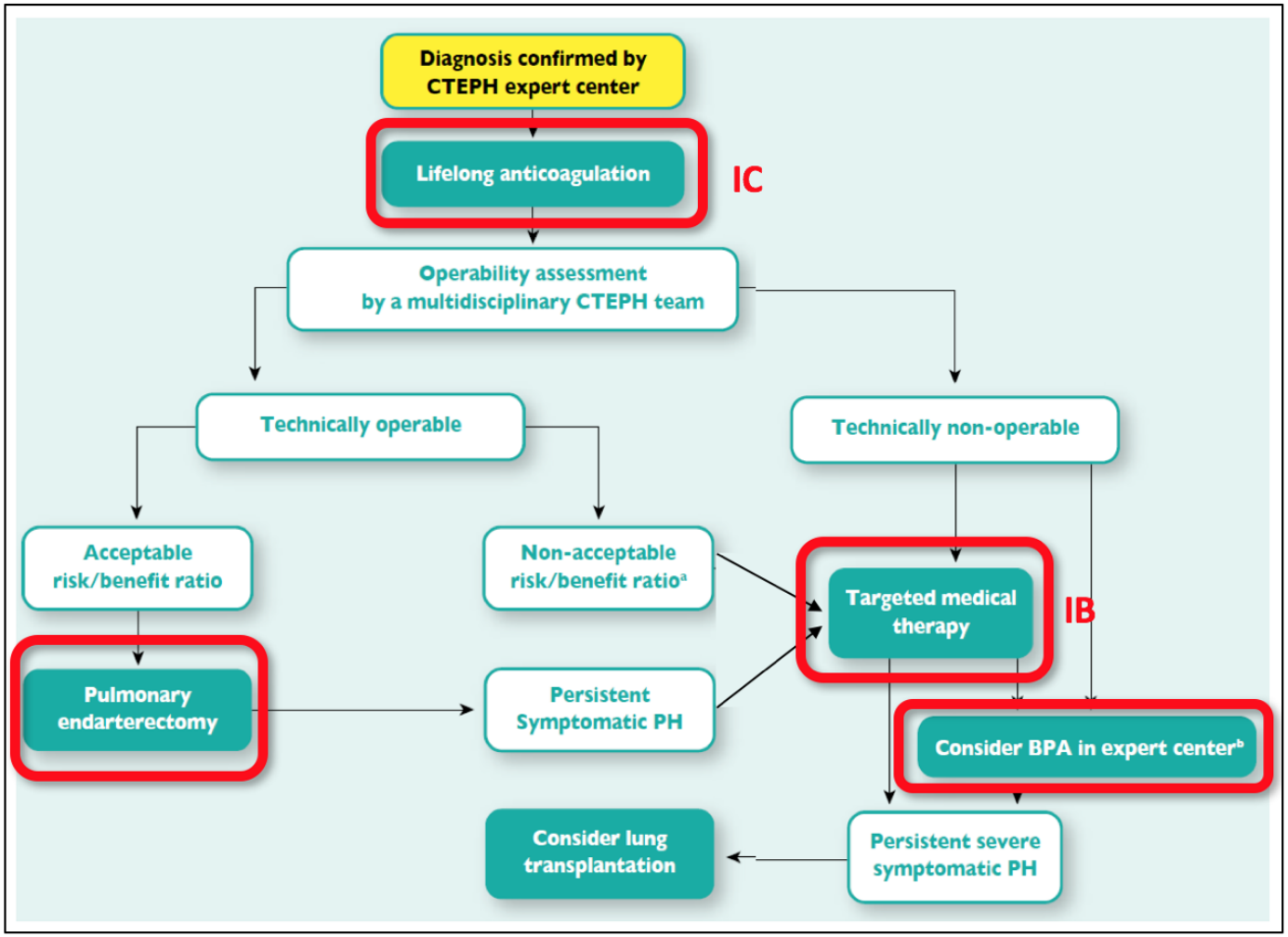
2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). European Heart Journal (2019) 00, 1 61 doi:10.1093/eurheartj/ehz405

Follow-up strategy and diagnostic workup for long-term sequelae of pulmonary embolism



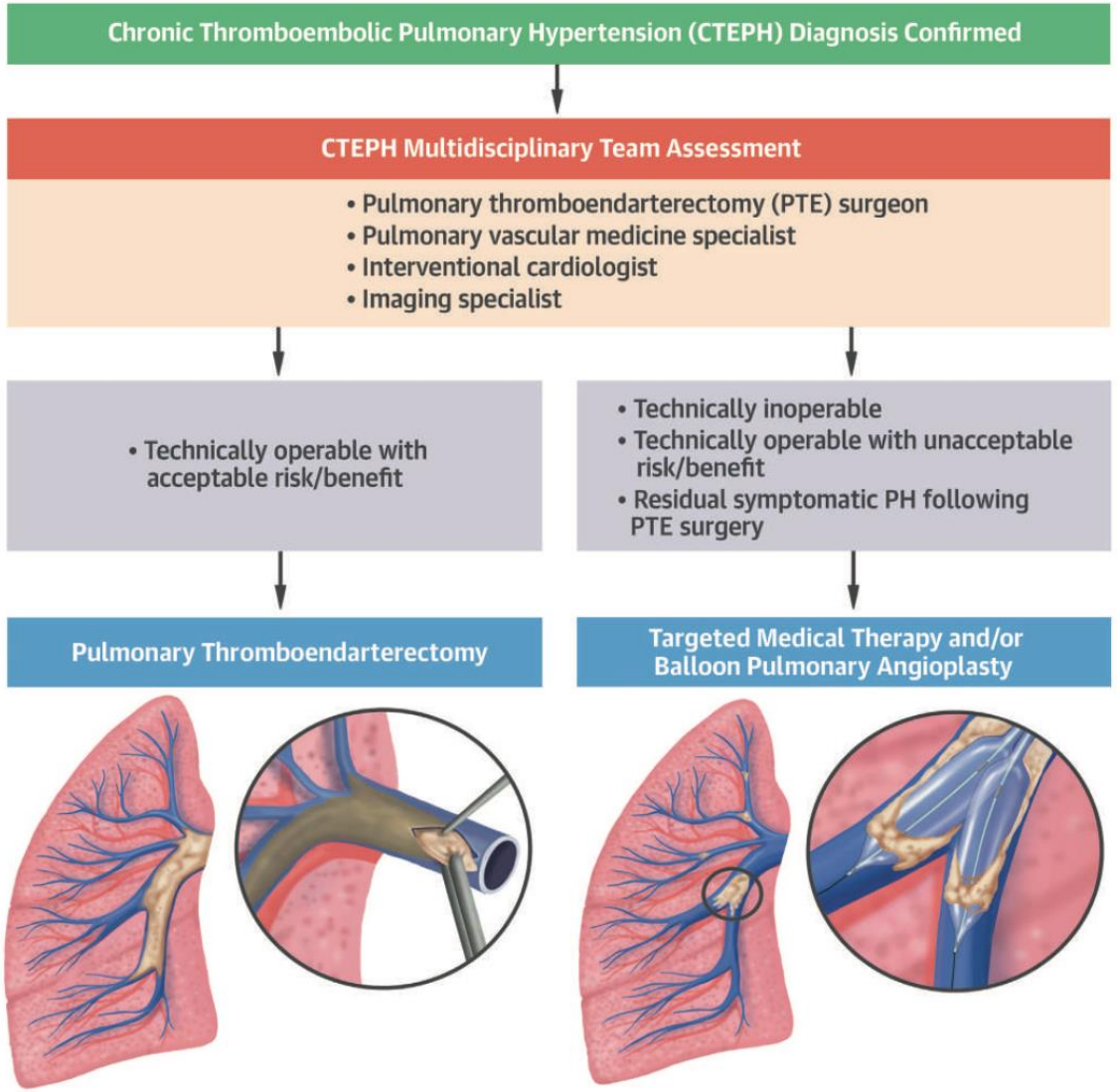
2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). European Heart Journal (2019) 00, 1 61 doi:10.1093/eurheartj/ehz405

Treatment algorithm for CTEPH



Galiè N et al, Eur Heart J, 2015

CTEPH Management-1



Mahmud, E. et al. J Am Coll Cardiol. 2018;71(21):2468-86.

Take home messages (1)

- ✓ Idiopathic or recurrent TEV, Large Prossimal Defect at CT and high RV-AD Gradient at discharge are at risk for CTHEP

- ✓ Echocardiography is the recommended first diagnostic step.

- ✓ V/Q scintigraphy is the imaging methodology of choice to exclude CTEPH.

Treatment of CTEPH

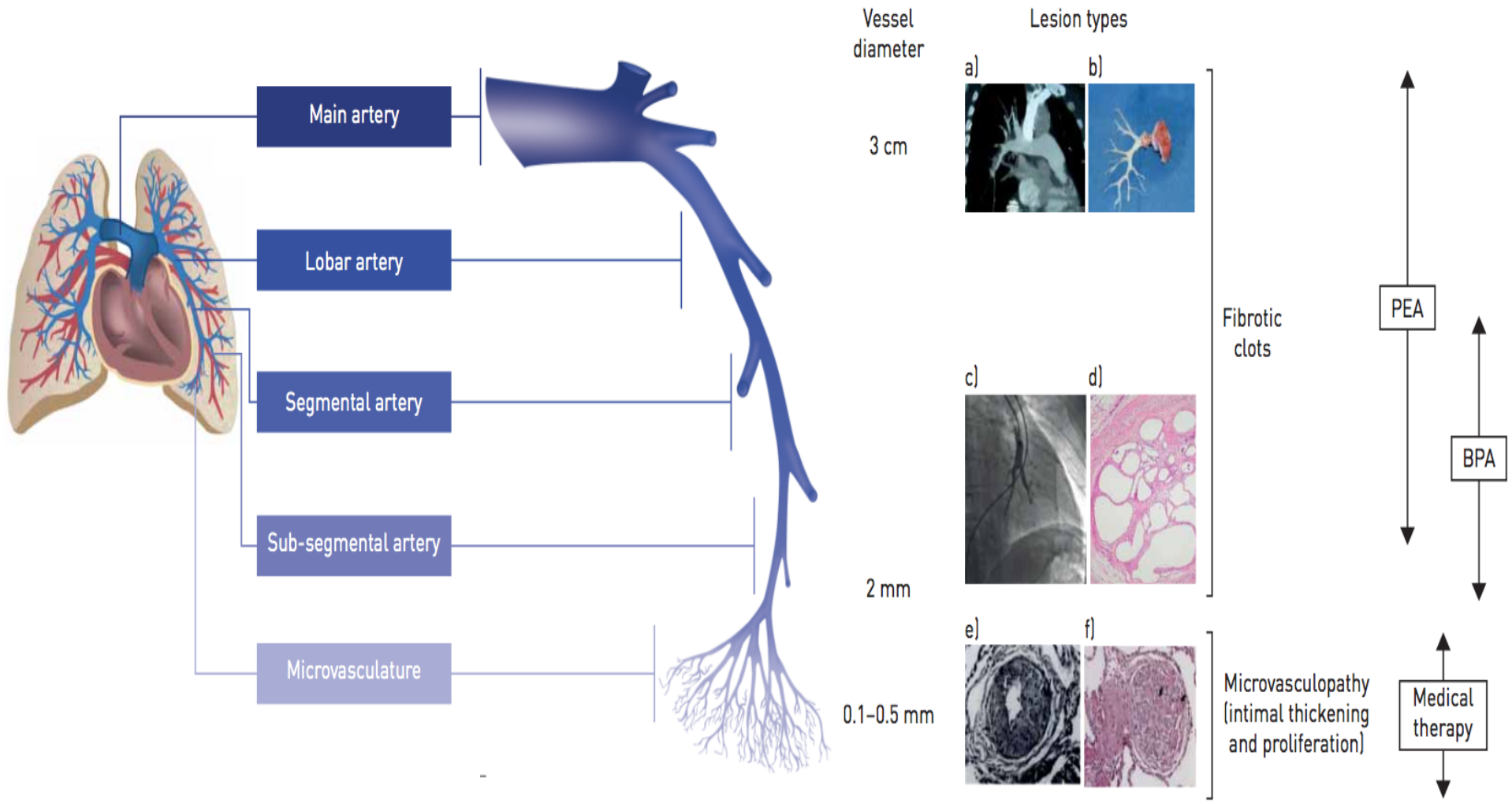
Supportive medical therapy

- **Anticoagulants** may reduce the risk of recurrent thromboembolism;
- ESC/ERS guidelines recommend lifelong anticoagulation in CTEPH patients;
- **Diuretics**;
- **Oxygen**.

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 should 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 inoperable CTEPH by a CTEPH team including at least one experienced PEA surgeon	IIb	B

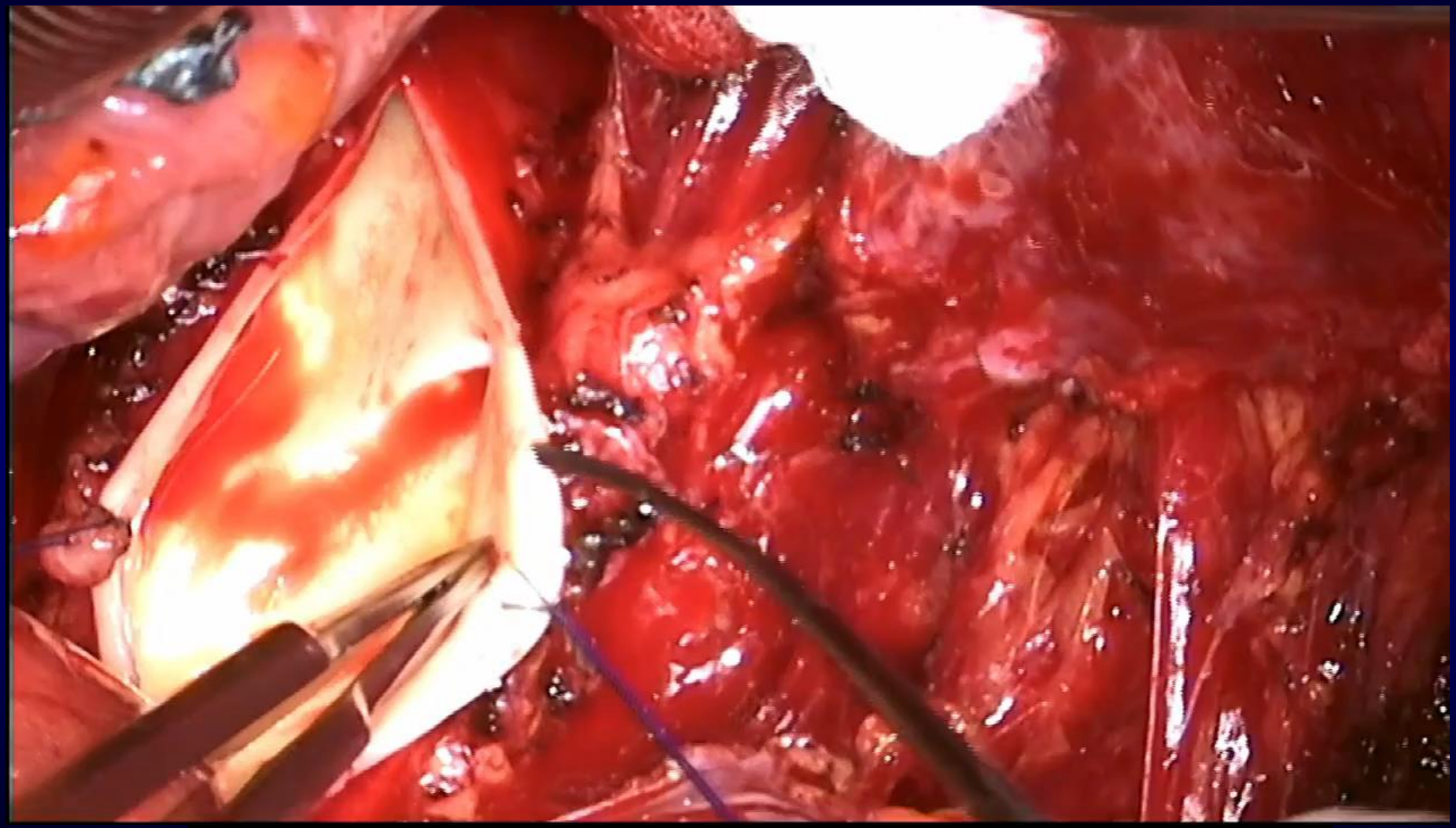
Galiè N *et al. Eur Respir J* 2015;46:903–975.
European Respiratory Journal Oct 2015, 46 (4) 903-975.

CTEPH Management-2

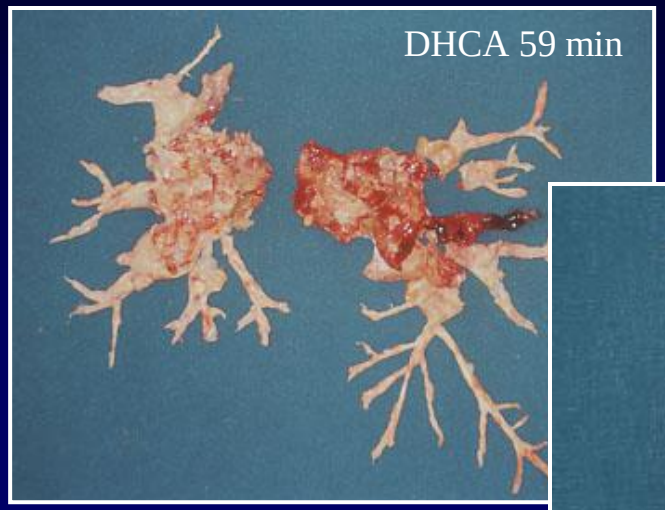


Madani M, Ogo T, Simonneau G. The changing landscape of chronic thromboembolic pulmonary hypertension management. Eur Respir Rev 2017; 26: 170105

SURGICAL TECHNIQUE



JAMIESON TYPE 1 vs. TYPE 2 vs. TYPE 3
RISULTATI EMODINAMICI

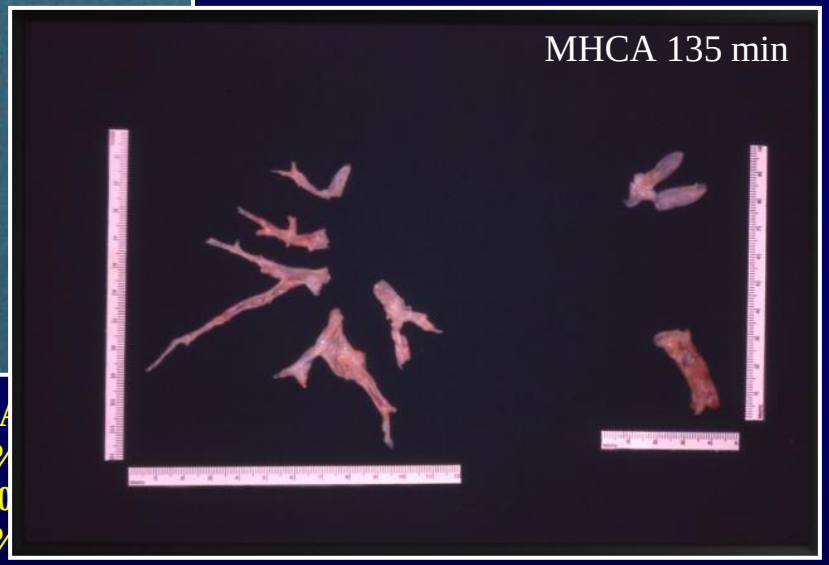


L.M.E.L. - 65 yrs M - Oct 2004 - PE

mPAP	**39**	→	**19**	**(-51%)**
CO	**4.4**	→	**5.4**	**(+23%)**
PVR	**665**	→	**222**	**(-66%)**

G.A.C. - 52 yrs F - Jul 2003 - PE

mPAP	**48**	→	**27**	**(-44%**
CO	**2.1**	→	**4.2**	**(+100**
PVR	**1638**	→	**381**	**(-77%**



B.A. - 43 yrs F - May 2009 - PEA #233

mPAP	**49**	→	**19**	**(-61%)**
CO	**3.3**	→	**5.0**	**(+52%)**
PVR	**1067**	→	**224**	**(-79%)**

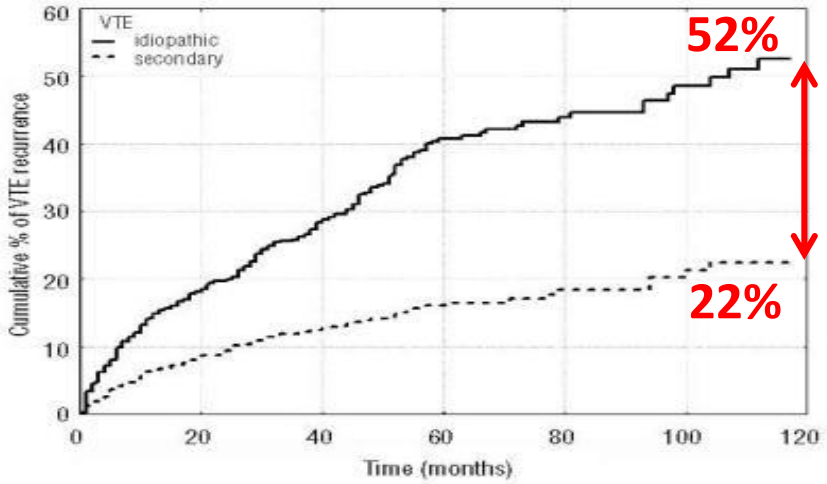
DHCA: Deep Hypothermic Circulatory Arrest

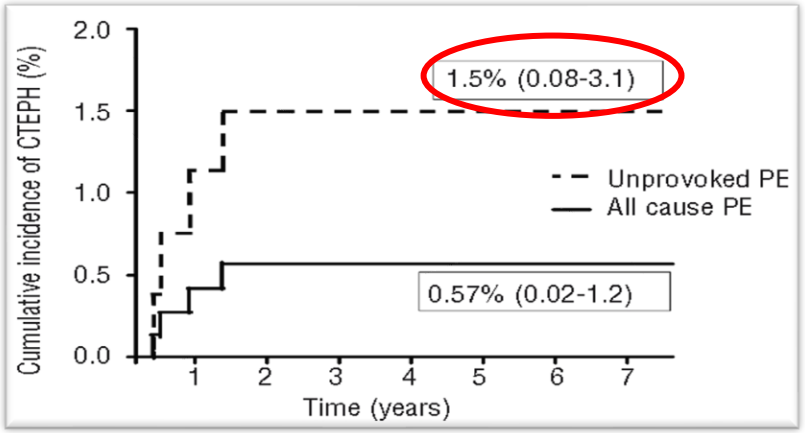
MHCA: Moderate Hypothermic Circulatory Arrest

TEV: Idiopathic vs Secondary

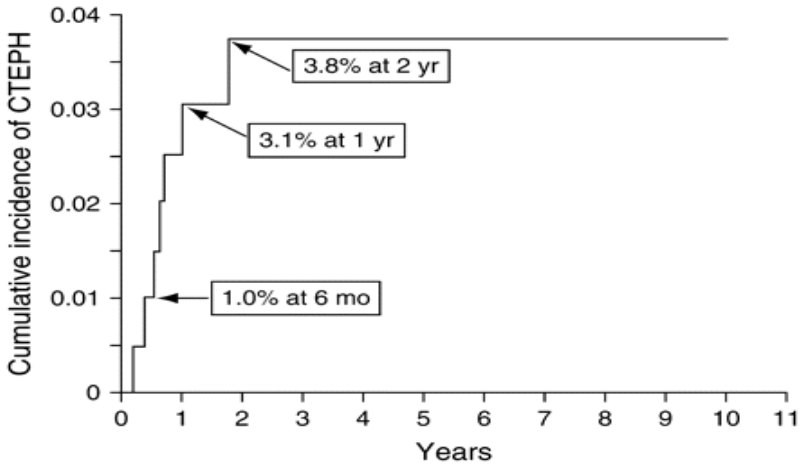
The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism. A prospective cohort study in 1,626 patients

Paolo Prandoni, Franco Noventa, Angelo Ghirarduzzi, Vittorio Pengo, Enrico Bernardi, Raffaele Pesavento, Matteo Iotti, Daniela Tormene, Paolo Simioni, Antonio Pagnan





F.A.KloK et al., Hematologica 2010



El da Pengo V et al., N Engl J Med 2004

Medical therapy-2

Drug Class	Evidence and Effects
Soluble guanylate cyclase stimulants (riociguat)	• CHEST-1 trial (randomized, double-blind, placebo-controlled study) (74); Improved pulmonary vascular resistance and 6-min walk distance after 16 weeks • CHEST-2 trial (follow-up extension study) (75); Persistent efficacy for up to 1 yr
Endothelin receptor antagonists (macitentan and bosentan)	Macitentan • MERIT-1 trial (randomized, double-blind, placebo-controlled study) (76); Improved pulmonary vascular resistance after 16 weeks Bosentan • BENEFiT trial (randomized, double blind, placebo-controlled study) (77); Improved pulmonary vascular resistance and cardiac index after 16 weeks • Systematic review of BENEFiT and 10 observational studies (78); Similar results were reported
Phosphodiesterase 5 inhibitors (sildenafil)	• Randomized, double blind, placebo-controlled pilot study (79); Improvement in World Health Organization functional class and pulmonary vascular resistance after 12 weeks
Prostanoids (epoprostenol and treprostinil)	Epoprostenol • Retrospective cohort study in severe inoperable CTEPH (80); Improvement in pulmonary vascular resistance, pulmonary artery pressure, and exercise capacity after 3 months Iloporost • AIR study (randomized, double-blind, placebo-controlled study) (81); Improvement in New York Heart Association functional class and 6-min walk distance at 12 weeks Treprostinil • Uncontrolled trial in severe inoperable CTEPH (82); Improved pulmonary vascular resistance after 20 months, and higher 5-yr survival rate (53% vs. 16% in historical controls)

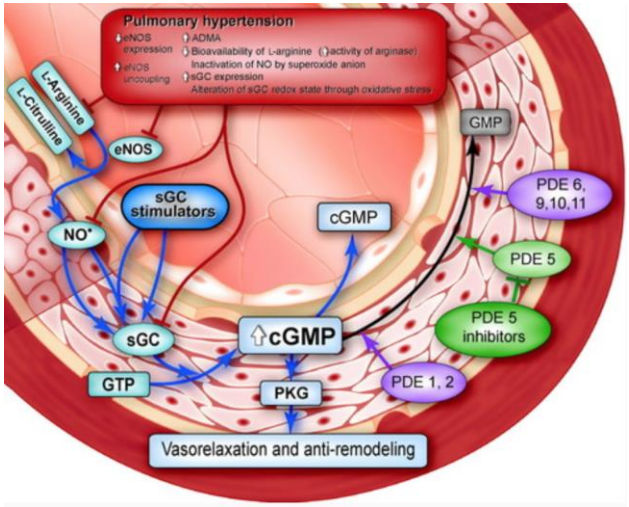
J Am Coll Cardiol 2018; 71:2468–86

Medical therapy-1

CTEPH-targeted medical therapy

Riociguat, a soluble guanylate cyclase stimulator, is the only therapy approved for inoperable CTEPH or patients with persistent/recurrent PH after PEA.

Riociguat directly stimulates sGC via a different binding site, independently of NO and sensitizes sGC to endogenous NO by stabilizing the NO–sGC binding.



Stasch J-P *et al. Circulation* 2011;123:2263–73.
Schermuly R *et al. Expert Opin Invest Drugs* 2011;20:567–76.

Riociguat for the Treatment of Chronic Thromboembolic Pulmonary Hypertension

Hossein-Ardeschir Ghofrani, M.D., Andrea M. D'Armini, M.D., Friedrich Grimminger, M.D., Marius M. Hoeper, M.D., Pavel Jansa, M.D., Nick H. Kim, M.D., Eckhard Mayer, M.D., Gerald Simonneau, M.D., Martin R. Wilkins, M.D., Arno Fritsch, Ph.D., Dieter Neuser, M.D., Gerrit Weimann, M.D., and Chen Wang, M.D., for the CHEST-1 Study Group*

New Engl J Med 2013

Inclusion criteria in CHEST-1

- Patients with CTEPH adjudicated to be technically inoperable or with persistent PH after PEA
- Age 18–80 years
- 6MWD at baseline 150–450 m
- PVR >300 dyn·sec·cm^{-5} and mPAP ≥25 mmHg

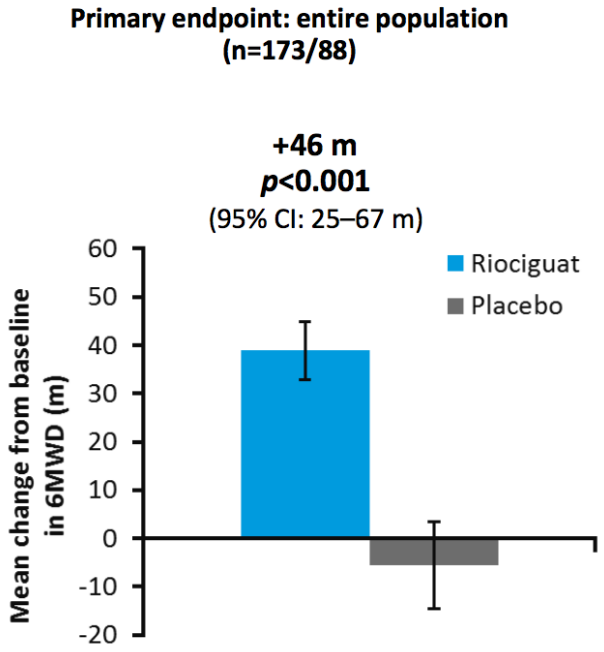
Patients excluded if treated with ERAs, prostacyclin analogs, PDE5i, and/or NO donors within 3 months prior to study entry

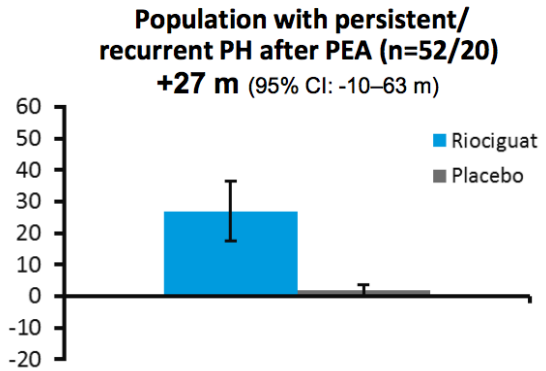
Maximum Dose allowed : Riociguat 2.5 mg TID

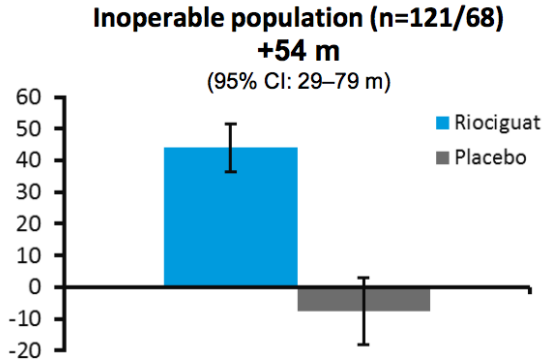
Riociguat in CTEPH: CHEST-1 and CHEST-2 Study Design[1,2]

CHEST Study Population: 261 Patients aged 18-80 years with technically inoperable CTEPH or persistent/recurrent PH following PEA.

CHEST-1: Primary endpoint achieved







1. Ghofrani H et al. *N Engl J Med*. 2013; 369:319-329.

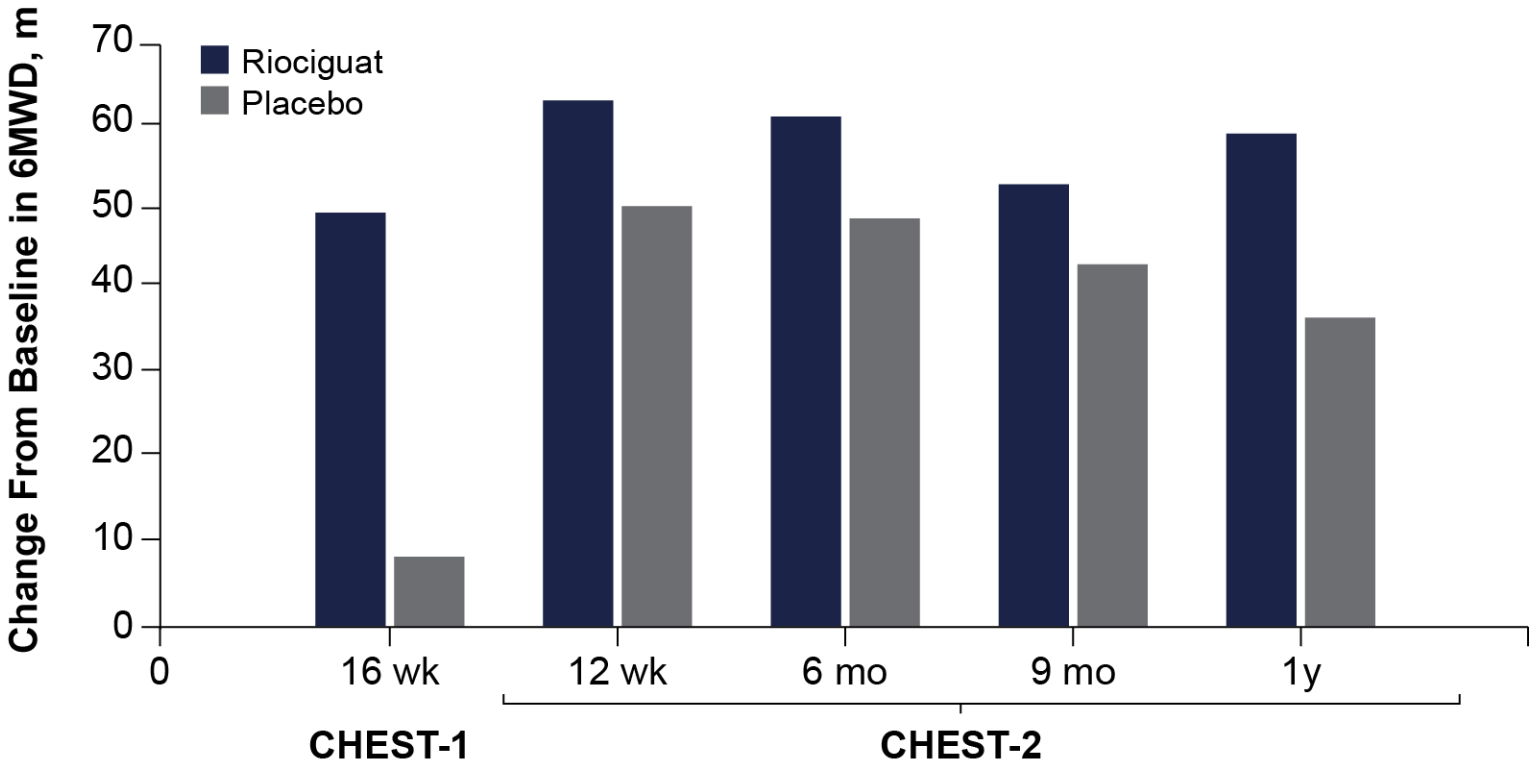
Riociguat in CTEPH: CHEST-1 and CHEST-2 Study Design[1,2]

Cardiopulmonary hemodynamics and biomarkers

	Riociguat		Placebo			
Parameter	**Baseline**	**Mean change from baseline**	**Baseline**	**Mean change from baseline**	**Placebo-corrected LS-mean difference**	**Riociguat vs placebo; p-value**
PVR ($dyn \cdot s \cdot cm^{-5}$)	791	-223 (-28%)	834	-9 (-1%)	-226	**<0.0001**
mPAP (mmHg)	47.1	-3.9 (-8%)	48.9	-0.5 (-1%)	-3.8	**0.0002**
CI ($L/min/m^2$)	2.52	+0.54 (+21%)	2.49	-0.02 (-1%)	+0.56	**<0.0001**
NT-proBNP (ng/L)	1027	-198 (-19%)	1228	+232 (+19%)	-432	**<0.0001**

1. Ghofrani H et al. *N Engl J Med*. 2013; 369:319-329.

CHEST-2: Long-Term Extension Study of Riociguat in CTEPH[1]



1. Simonneau G et al. *Eur Respir J.* 2015;45:1211-1213.

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J Am Coll Cardiol 2018; 71:2468–86

CTHEP: Apulia Experience

64 VTE patients (2008-2019):

A median of **14.8±8.4 months** had passed since first symptoms to confirme diagnosis

Etiology of VTE: "*Provoked VTE (30%)*"

TEV e non ottimale Terapia

No Parenterale
20% a 3 mesi

Durata trattamento
<3 mesi
10%

Trattamento
3-6 mesi
10% ad un anno

Fase Acuta	Long-term treatment	Extended treatment
≥ 5 days	at least 3 months	indefinite???

vitamin K antagonists (INR 2.0-3.0) or NOACs