# Πνευμονική Υπέρταση

Ηρακλής Τσαγκάρης

Αναπληρωτής Καθηγητής Εντατικής Θεραπείας

Αττικό Νοσοκομείο

# Δήλωση συμφερόντων

Συμμετοχή σε συνέδρια, κλινικές μελέτες ή συμβουλευτικά των εταιρειών Actelion, Bayer, ELPEN, Galenica, Glaxo GSK, Lilly, MSD, Pfizer

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European Heart Journal
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ESC/ERS GUIDELINES

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

## The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS)

## Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT)

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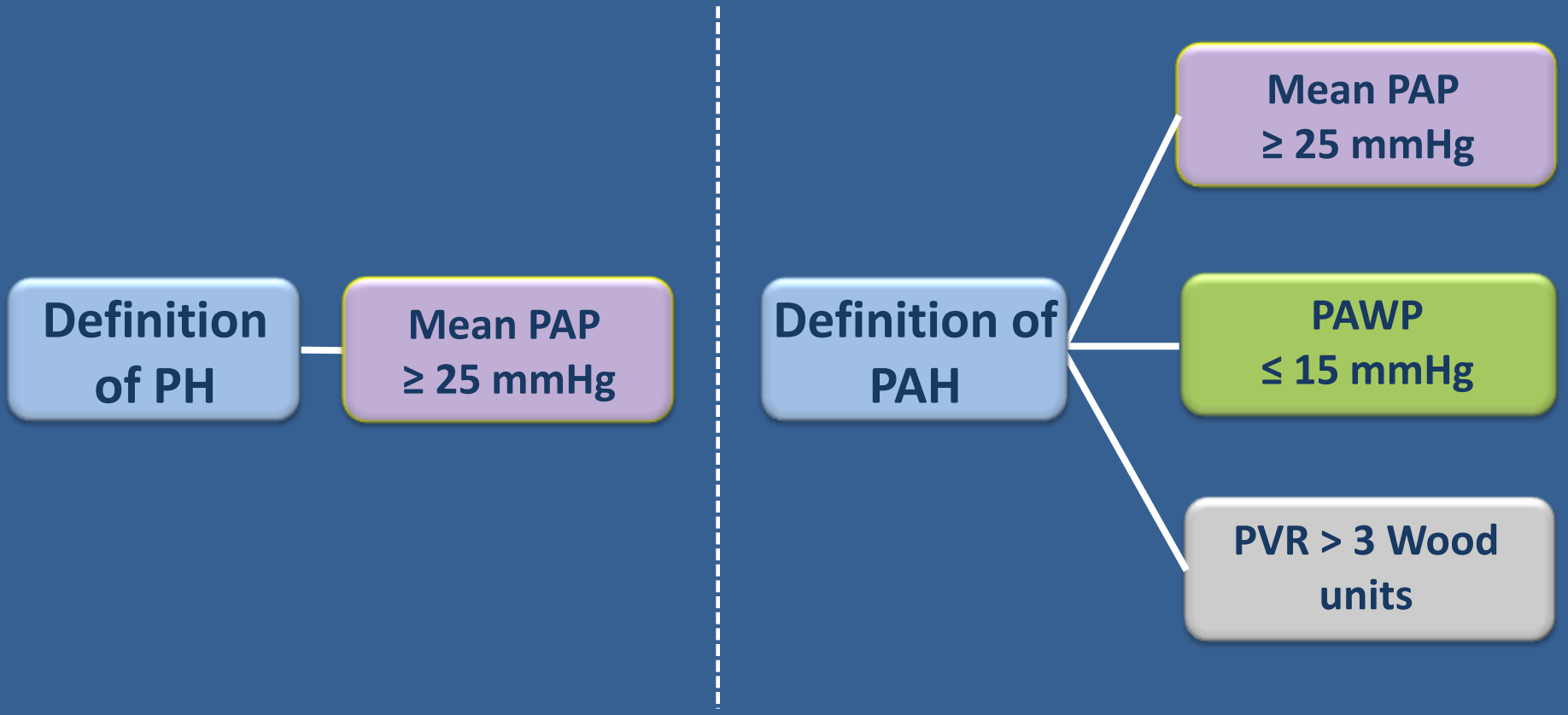
# 5th World Symposium on PH: Haemodynamic definition of PAH




PAP: pulmonary arterial pressure; PAWP: pulmonary artery wedge pressure; PVR: pulmonary vascular resistance

Hoeper MM, *et al. J Am Coll Cardiol* 2013; 62:D42-50.

| Definition | Characteristics[a] | Clinical group(s)[b] |
|---|---|---|
| PH | PAPm ≥25 mmHg | All |
| Pre-capillary PH | PAPm ≥25 mmHg<br>PAWP ≤15 mmHg | 1. Pulmonary arterial hypertension<br>3. PH due to lung diseases<br>4. Chronic thromboembolic PH<br>5. PH with unclear and/or multifactorial mechanisms |
| Post-capillary PH | PAPm ≥25 mmHg<br>PAWP >15 mmHg | 2. PH due to left heart disease<br>5. PH with unclear and/or multifactorial mechanisms |
| Isolated post-capillary PH (Ipc-PH) | DPG <7 mmHg and/or<br>PVR ≤3 WU[c] | |
| Combined post-capillary and pre-capillary PH (Cpc-PH) | DPG ≥7 mmHg and/or<br>PVR >3 WU[c] | |

## Etiologic classification of pulmonary hypertension

- **MPA - PCWP = CO * PVR**
- **MPA = CO * PVR + PCWP**

MPA: mean pulmonary artery, PCWP: pulmonary capillary wedge pressure, CO: cardiac output, PVR: pulmonary vascular resistance

# Pulmonary Hypertension: Define Lesion

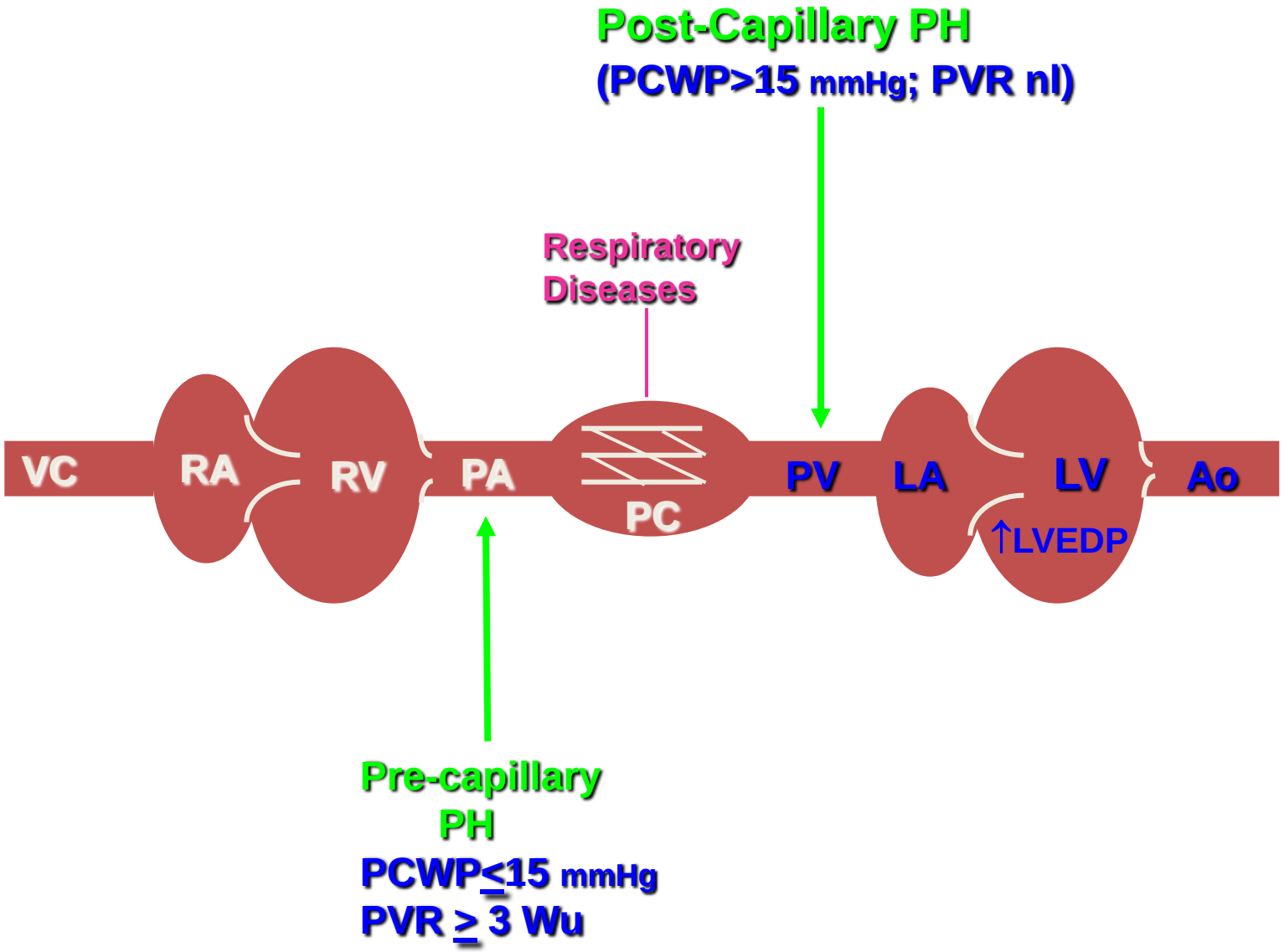


**Table 4** Comprehensive clinical classification of pulmonary hypertension (updated from Simonneau et al.[5])

**1. Pulmonary arterial hypertension**
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- 1.2 Heritable
  - 1.2.1 BMPR2 mutation
  - 1.2.2 Other mutations
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- 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)
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**1''. Persistent pulmonary hypertension of the newborn**

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| Definite | Likely | Possible |
|---|---|---|
| • Aminorex<br>• Fenfluramine<br>• Dexfenfluramine<br>• Toxic rapeseed oil<br>• Benfluorex<br>• Selective serotonin reuptake inhibitors[a] | • Amphetamines<br>• Dasatinib<br>• L-tryptophan<br>• Methamphetamines | • Cocaine<br>• Phenylpropanolamine<br>• St John's Wort<br>• Amphetamine-like drugs<br>• Interferon $\alpha$ and $\beta$<br>• Some chemotherapeutic agents such as alkylating agents (mytomycine C, cyclophosphamide)[b] |

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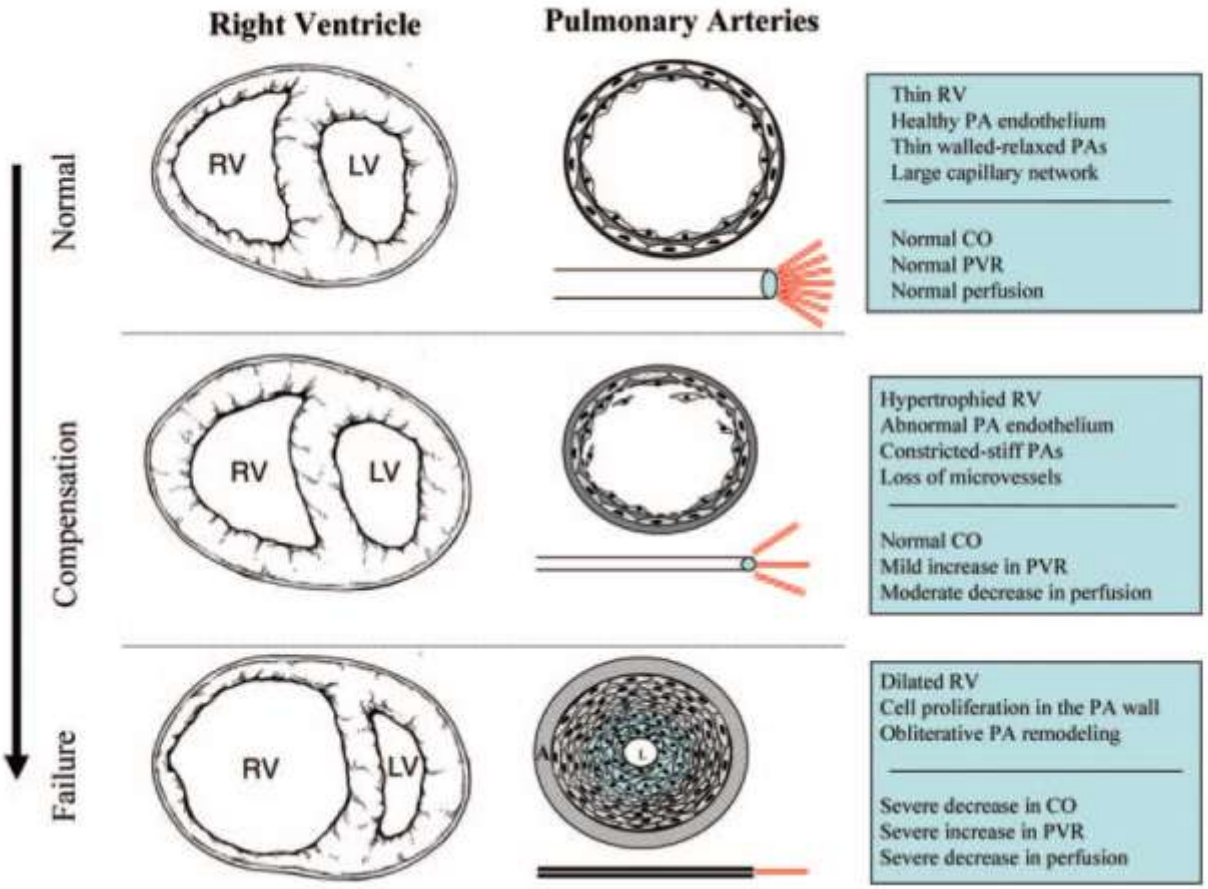
# PH epidemiology

- In the UK, a prevalence of 97 cases per million with a female:-male ratio of 1.8 has been reported.
- The age-standardized death rate in the USA ranges between 4.5 and 12.3 per 100,000 population.

# Progression of vascular disease

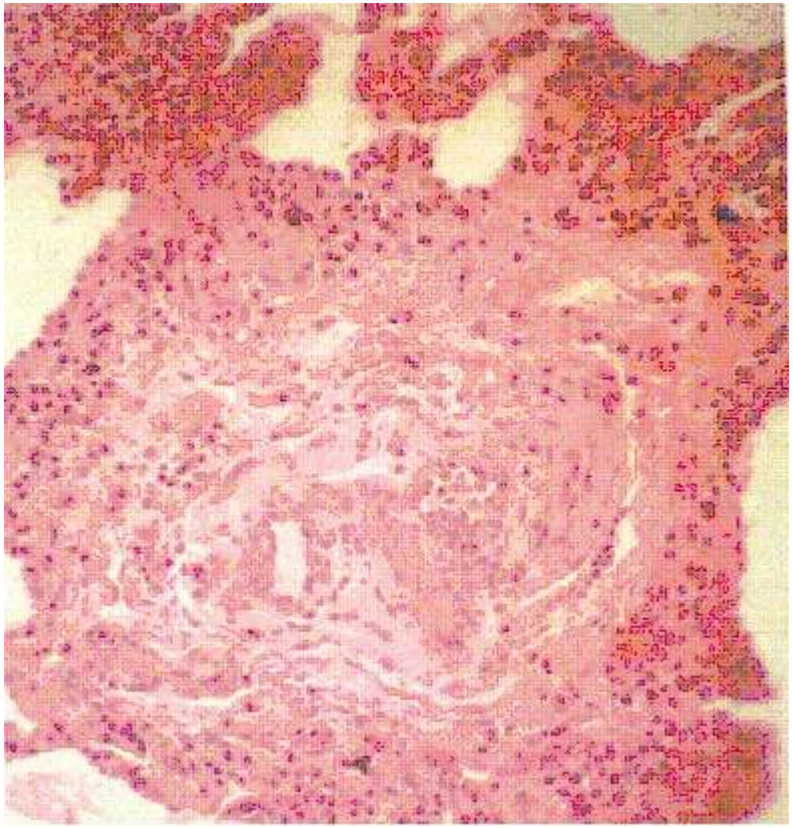



Hunter C. Champion, Evangelos D. Michelakis and Paul M. Hassoun

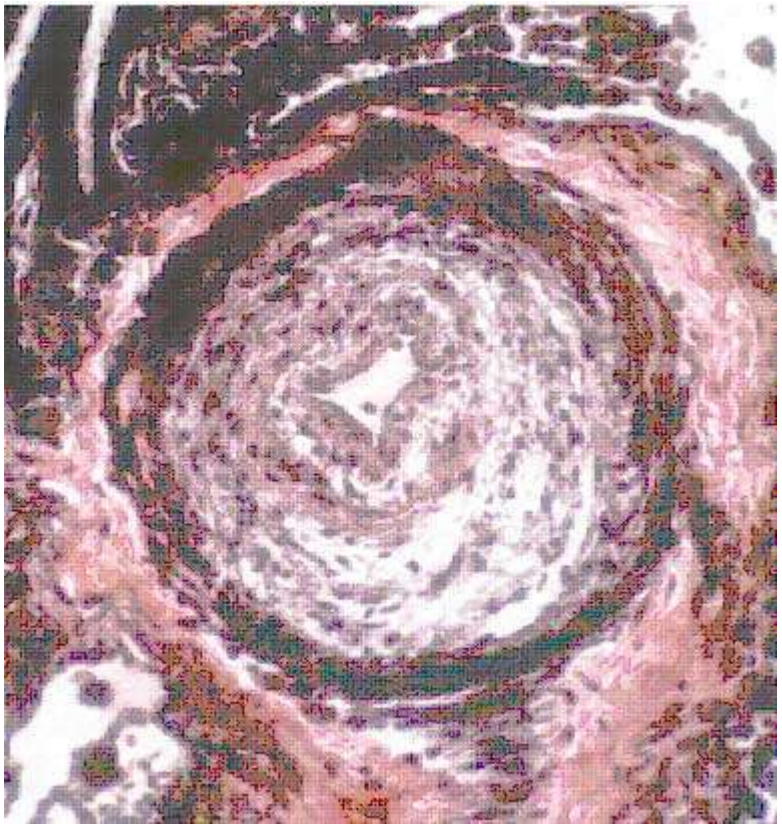
*Circulation* 2009;120;992-1007

# **PAH pathology:** The development of “plexiform lesions’ is a pathologic hallmark of PAH.

Plexiform lesion

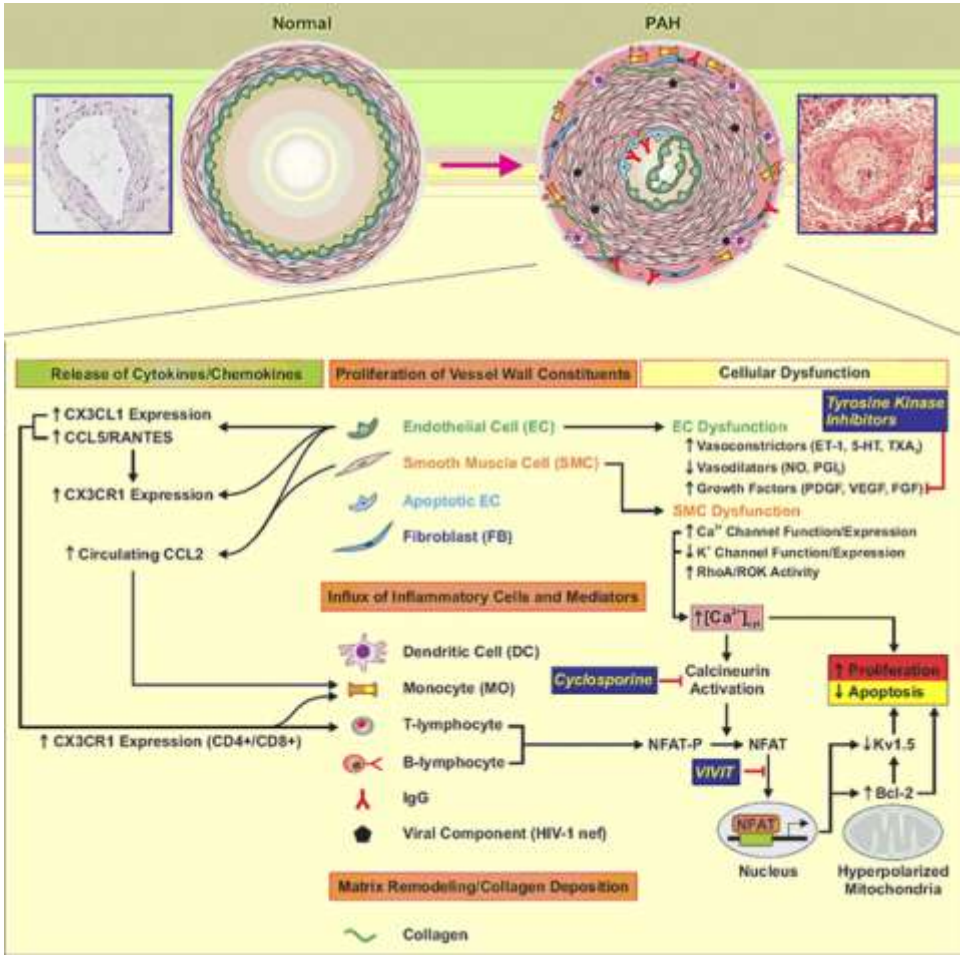


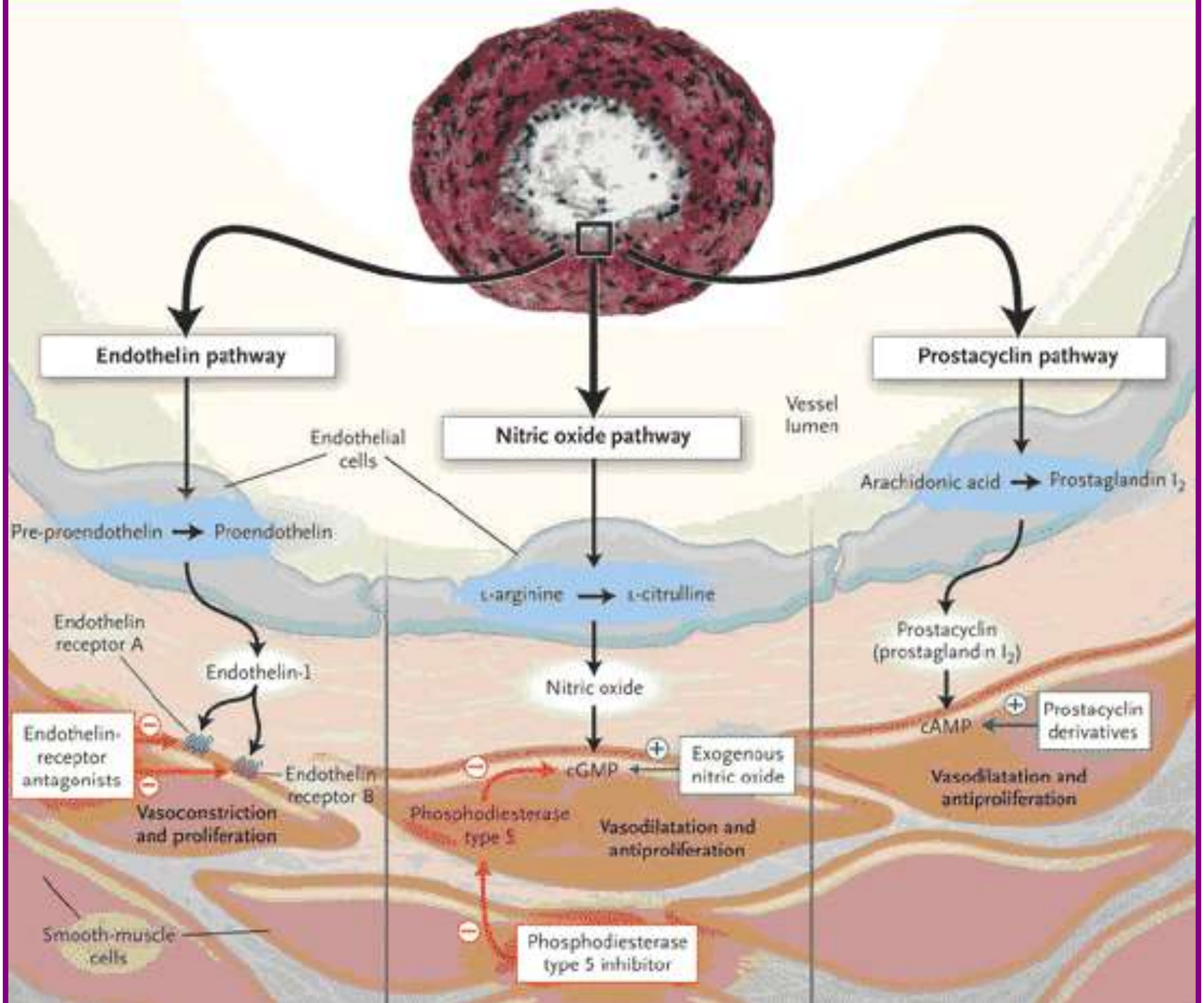
Occlusion of pulmonary artery



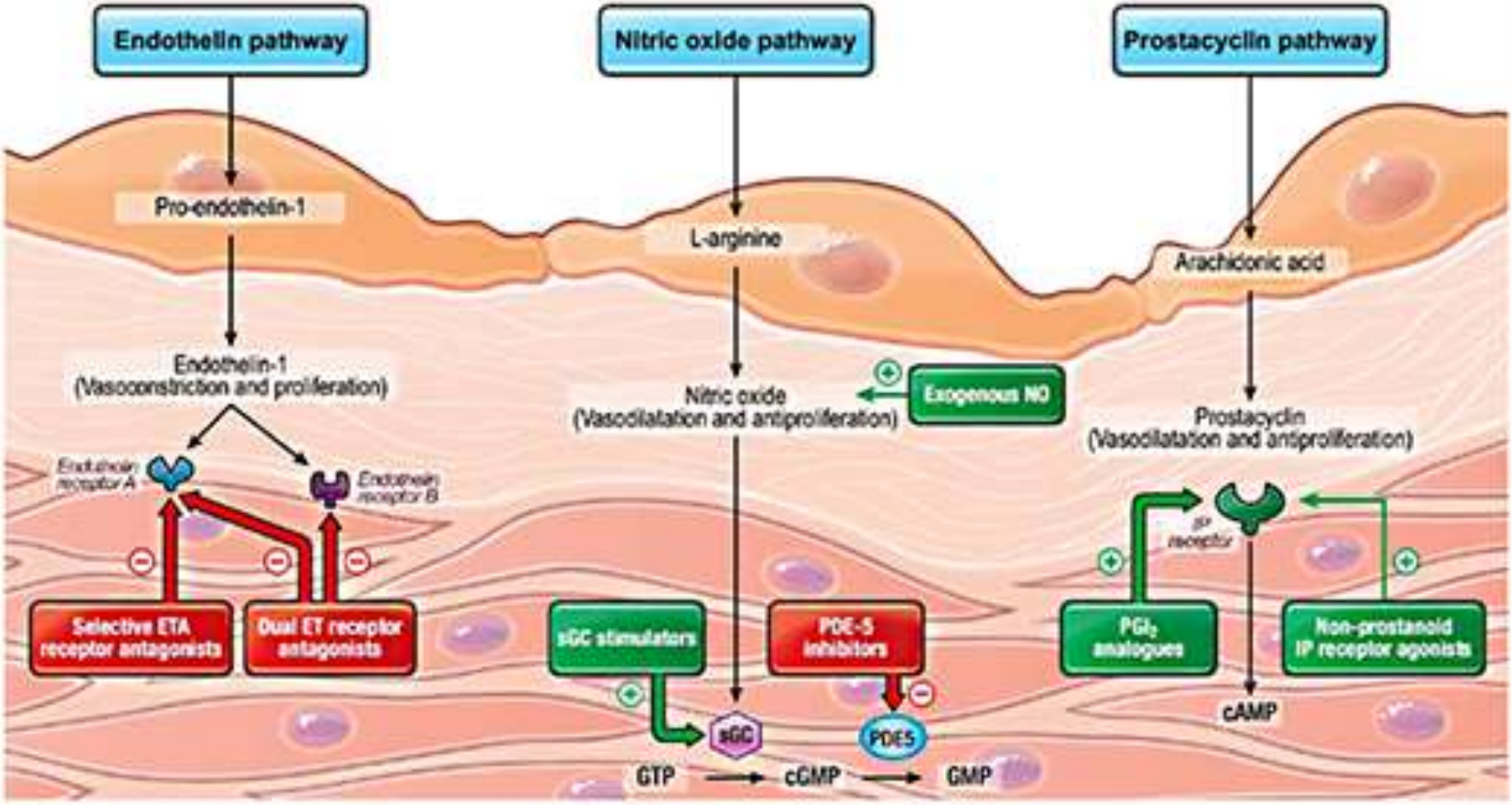
Fishman. Physiol Res 2000

# Mechanisms of Inflammation-Mediated Remodeling




Endothelin pathway
Nitric oxide pathway
Prostacyclin pathway
Vessel lumen
Endothelial cells
Pre-proendothelin
Proendothelin
Arachidonic acid
Prostaglandin $I_2$
L-arginine
L-citrulline
Endothelin receptor A
Endothelin-1
Nitric oxide
Prostacyclin (prostaglandin $I_2$)
Endothelin-receptor antagonists
Endothelin receptor B
Vasoconstriction and proliferation
cGMP
Exogenous nitric oxide
cAMP
Prostacyclin derivatives
Vasodilatation and antiproliferation
Phosphodiesterase type 5
Vasodilatation and antiproliferation
Smooth-muscle cells
Phosphodiesterase type 5 inhibitor

# Endothelial Dysfunction in PAH




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

| Therapy | Clinical trial identifier | Clinical trial design | Primary end-points | Treatment duration | Status (October 2016) |
|---|---|---|---|---|---|
| **Therapies targeting inflammation and immunity** | | | | | |
| Ubenimex | NCT02664558 | Phase II, multicentre, randomised, double-blind, placebo-controlled trial in PAH patients | Change in PVR | 24 weeks | Recruiting [17] |
| | NCT02736149 | Phase II, open-label, multicentre, extension study in PAH patients | Frequency of adverse events | ~1 year | Not yet recruiting [18] |
| Rituximab | NCT01086540 | Phase II, randomised, double-blind, placebo-controlled trial in PAH-SSc patients | Change in PVR | 24 weeks | Recruiting [19] |
| Tocilizumab | NCT02676947 | Phase II, open-label trial in PAH patients | Incidence and severity of adverse events; change in PVR | 6 months | Recruiting [20] |
| **Therapies targeting mitochondrial dysfunction** | | | | | |
| Bardoxolone methyl | NCT02036970 | Phase II, double-blind, randomised, interventional trial in pulmonary hypertension Group I, II or V patients | Change in 6MWD | 16 weeks | Preliminary results published [21] |
| | NCT02657356 | Phase III, double-blind, early interventional trial in PAH-CTD patients | Change in 6MWD | 24 weeks | Recruiting [22] |
| GS-4997 | NCT02234141 | Phase II, dose-ranging, randomised, double-blind, placebo-controlled trial in PAH patients | Change in PVR | 24 weeks | Ongoing, not recruiting [23] |
| **Therapies targeting BMPR2 signalling** | | | | | |
| Tacrolimus | NCT01647945 | Phase II, double-blind, randomised trial in PAH patients | Frequency of adverse events | 16 weeks | Terminated due to limited funding/slow patient recruitment; follow-up multicentre phase IIb efficacy trial planned [24] |
| **Therapies targeting iron deficiency** | | | | | |
| Ferinject (ferric carboxymaltose) | NCT01447628 | Phase II, double-blind, randomised, interventional trial in IPAH, HPAH and anorexigen-associated PAH patients | Change in PVR and exercise capacity | 24 weeks | Recruiting [25] |
| | NCT01847352 | Single-blind, nonrandomised, interventional, trial in healthy volunteers who met iron-deficient or iron-replete criteria | Change in PASP following *i.v.* iron infusion | 1 week | Completed: April 2014 [26, 27] |
| Ferrous sulfate (oral dietary iron supplement) | NCT01446848 | Interventional, open-label study in IPAH patients with iron deficiency | Change in zinc protoporphyrin level; change in serum ferritin level | 12 weeks | Completed: August 2014 [28] |
| **Pulmonary artery denervation** | | | | | |
| Pulmonary arterial denervation procedure | chiCTR-ONC-12002085 | Phase II, observational, unblinded, nonrandomised study in PAH and PAH-CTD patients | Change in PASP and 6MWD | 24 weeks | Completed: April 2014 [29] |
| | NCT02525926 | Single-blind, randomised, interventional efficacy study in PAH patients | Mean pulmonary artery pressure | 26 weeks | Recruiting [30] |

Simonneau, ERR, 2016

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doi:10.1093/eurheartj/ehv317

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CME

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## The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS)

## Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT)

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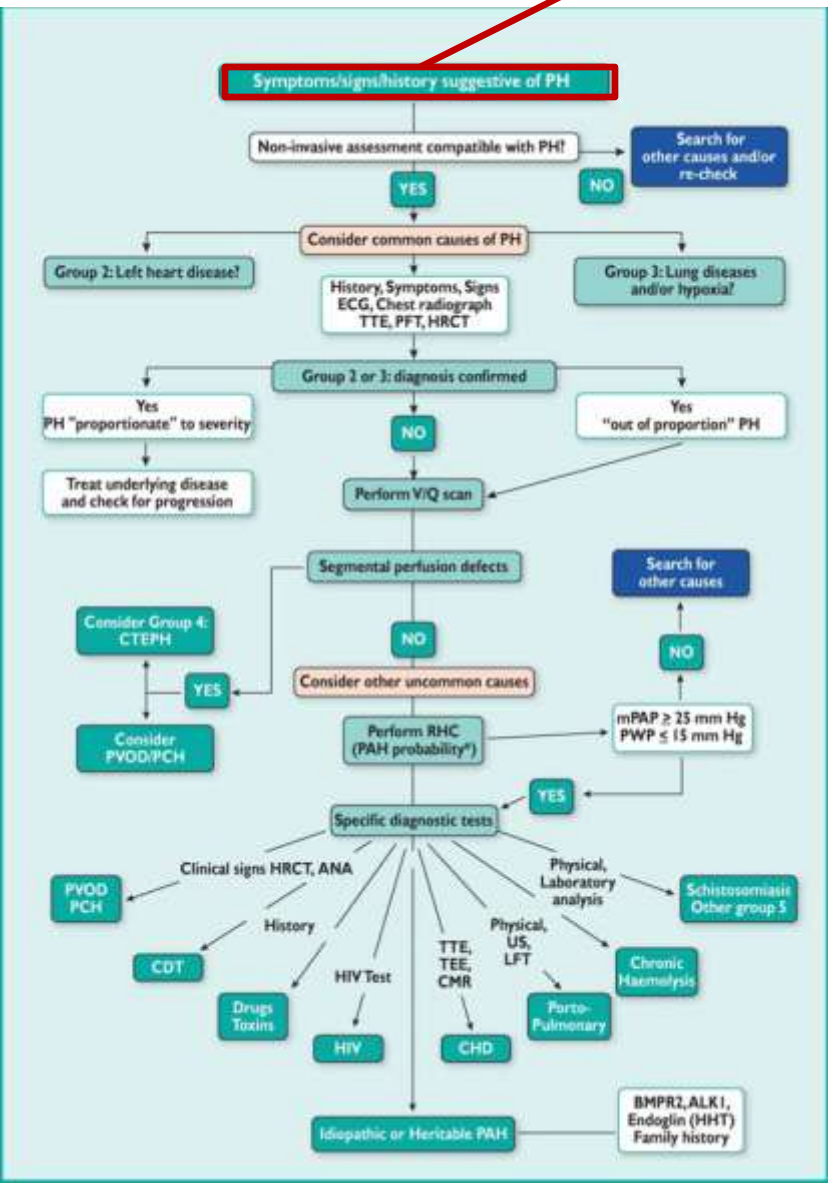
# Diagnostic approach

- Suspicion
- Detection
- Identification
- Classification

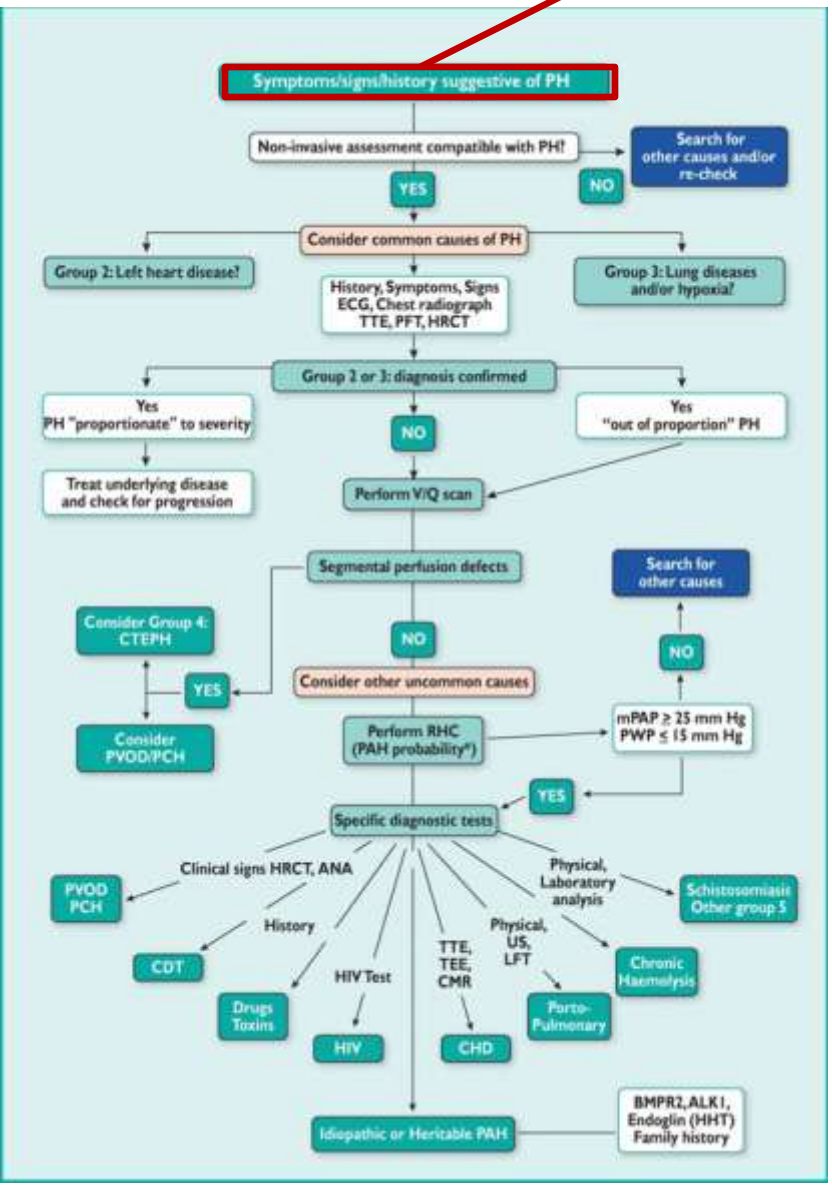
# Symptoms/signs/history




- Exertional dyspnea
- Chest pain
- Syncope
- Peripheral edema
- Raynaud

ESC/ERS GUIDELINES

# Symptoms/signs/history

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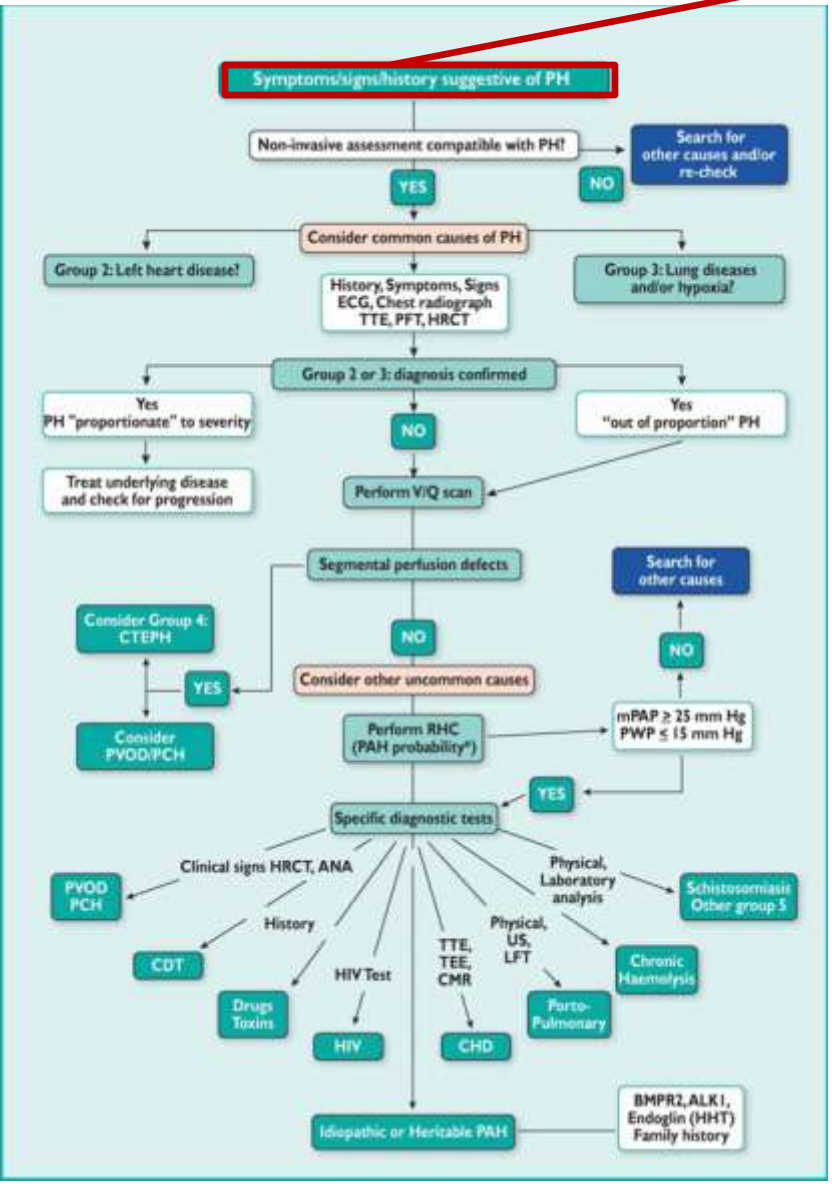
# 2 years delay

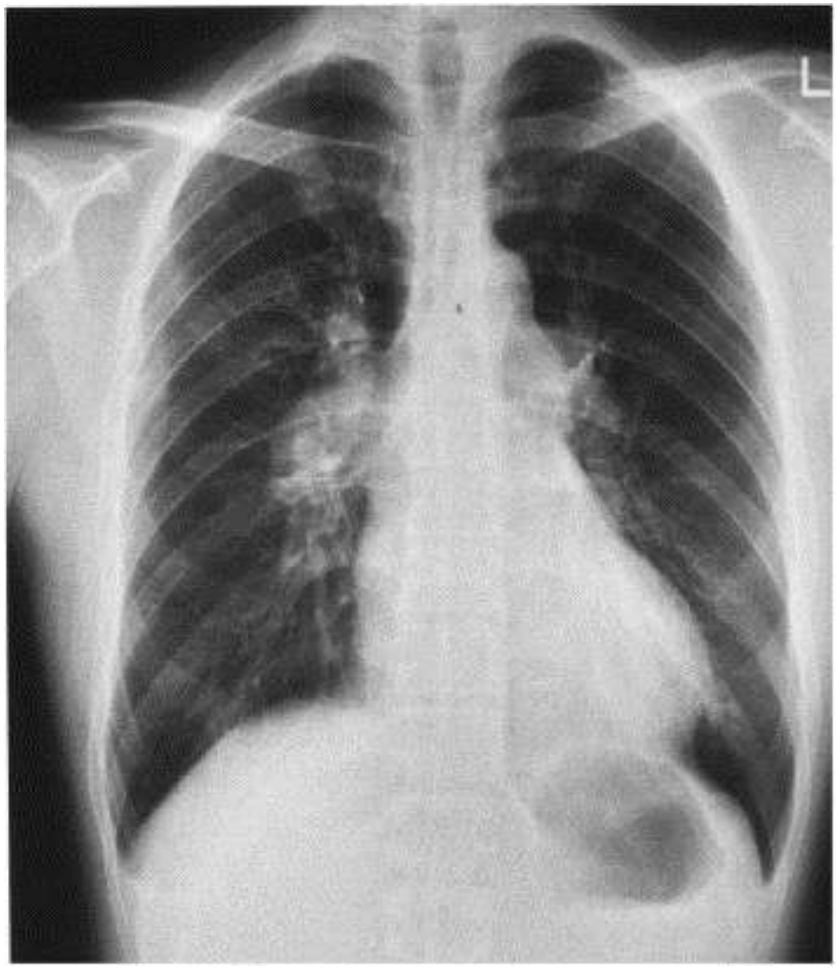
ESC/ERS GUIDELINES

# Symptoms/signs/history




- Physical examination
- Chest X-Ray
- ECG

ESC/ERS GUIDELINES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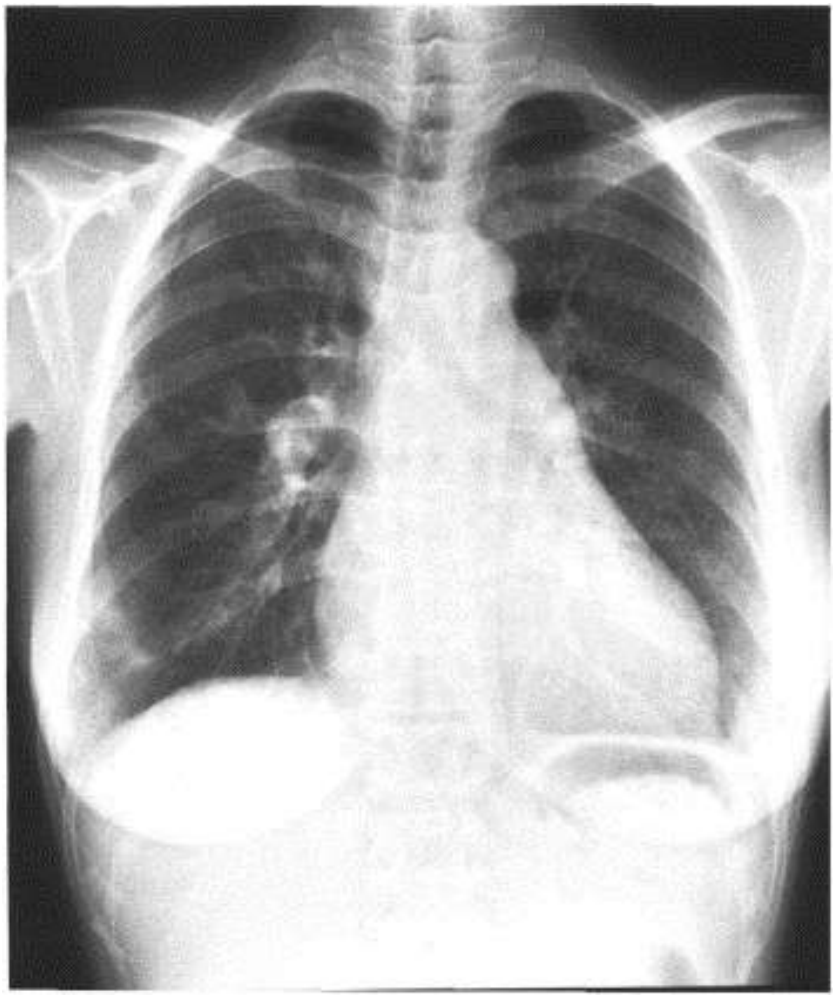
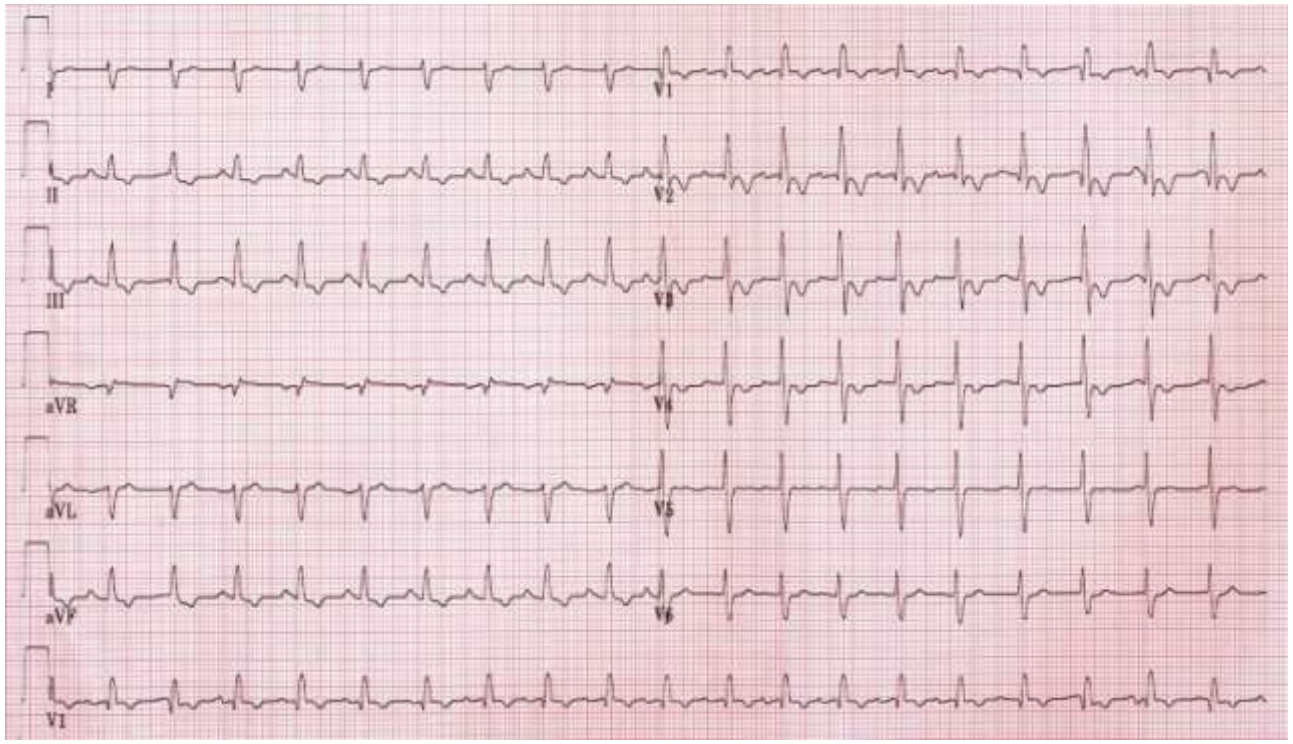


# ECG

**Often misinterpreted**

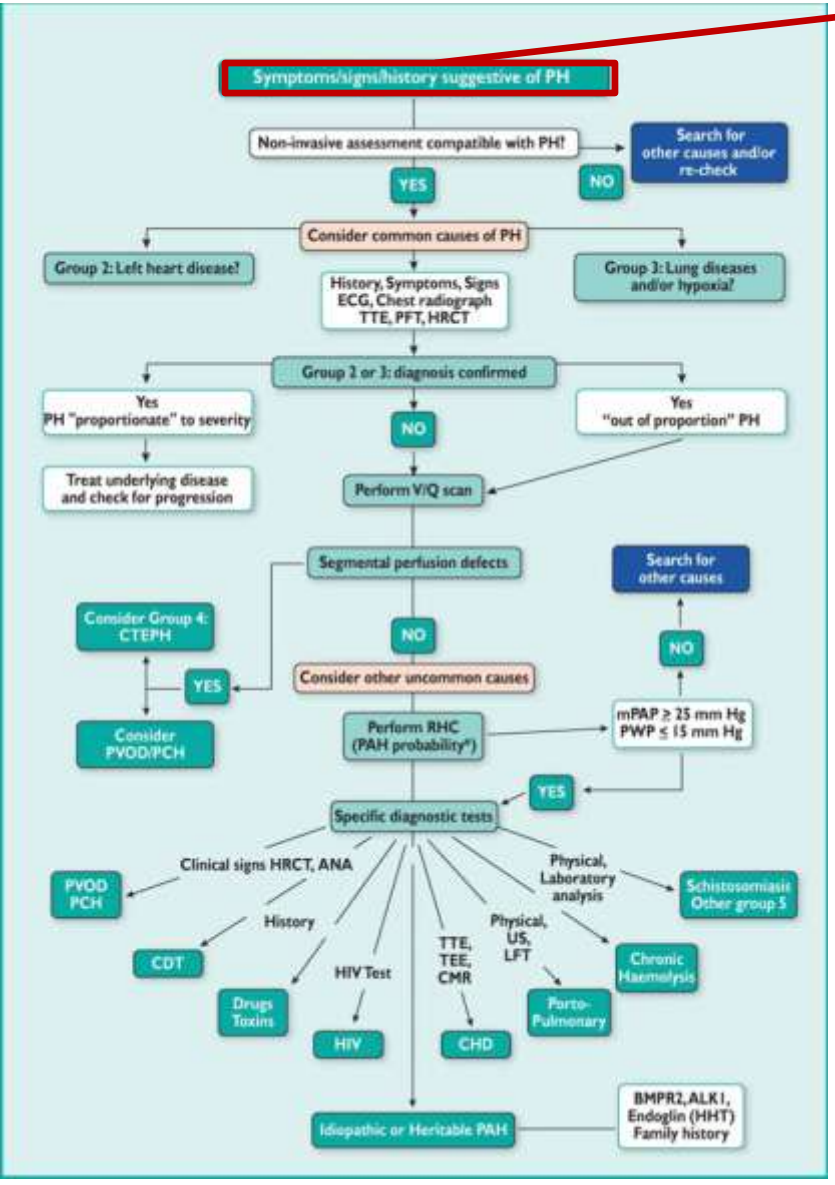
**Normal in one third of the patients**

**Does not parallel hemodynamics**

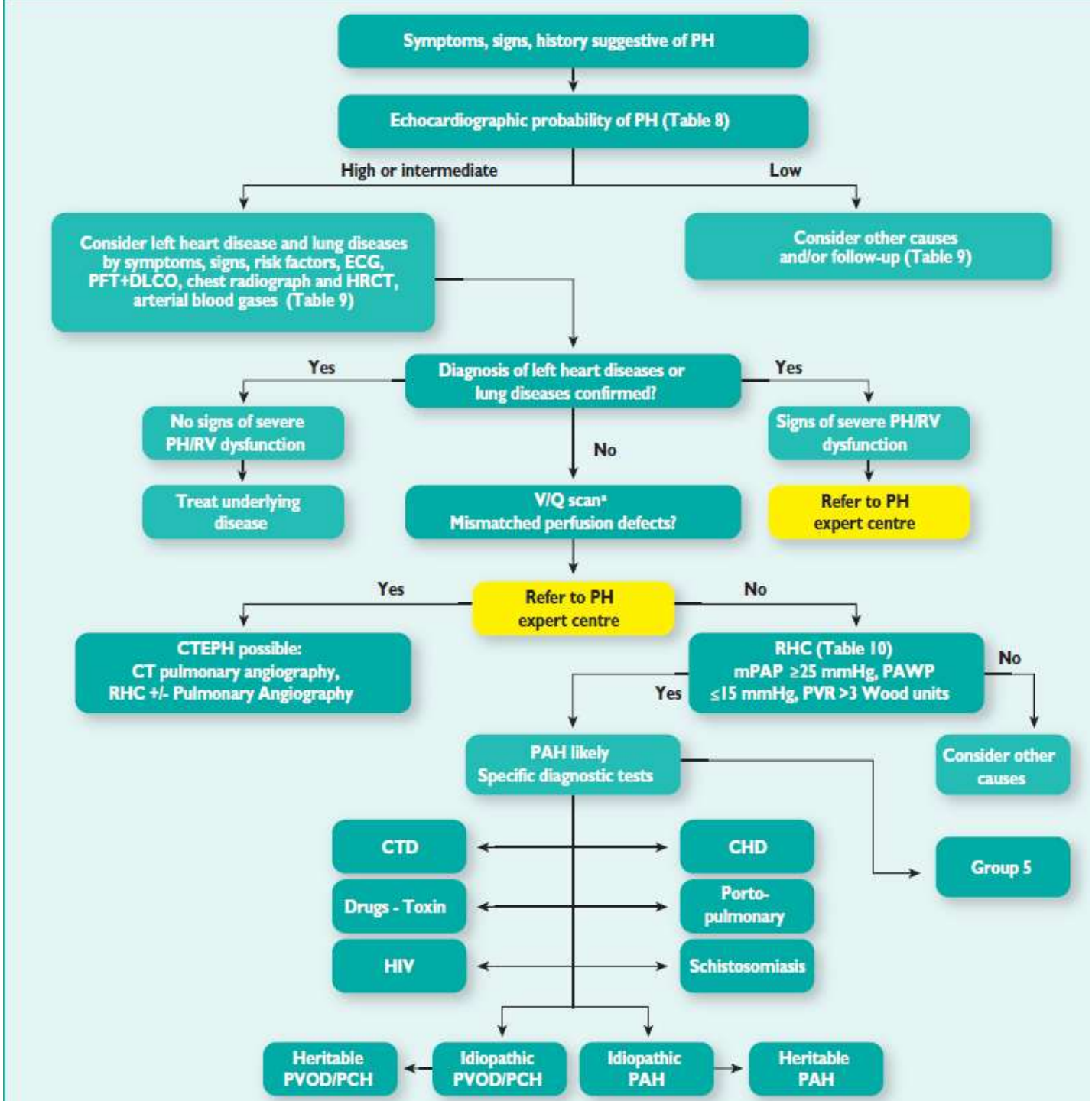



With permission of Prof. Ewert

# Symptoms/signs/history




- Family history
- Connective tissue disease
- Congenital heart disease
- Portal hypertension
- Venous thromboembolism/PE
- Anorexiogen use
- HIV


Symptoms, signs, history suggestive of PH
Echocardiographic probability of PH (Table 8)
High or intermediate
Low
Consider left heart disease and lung diseases by symptoms, signs, risk factors, ECG, PFT+DLCO, chest radiograph and HRCT, arterial blood gases (Table 9)
Consider other causes and/or follow-up (Table 9)
Yes
Diagnosis of left heart diseases or lung diseases confirmed?
Yes
No signs of severe PH/RV dysfunction
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Treat underlying disease
V/Q scan[a] Mismatched perfusion defects?
Refer to PH expert centre
Yes
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No
CTEPH possible: CT pulmonary angiography, RHC +/- Pulmonary Angiography
RHC (Table 10) mPAP ≥25 mmHg, PAWP ≤15 mmHg, PVR >3 Wood units
No
Yes
PAH likely Specific diagnostic tests
Consider other causes
CTD
CHD
Group 5
Drugs - Toxin
Porto-pulmonary
HIV
Schistosomiasis
Heritable PVOD/PCH
Idiopathic PVOD/PCH
Idiopathic PAH
Heritable PAH

# PAH suspicion?

Echo

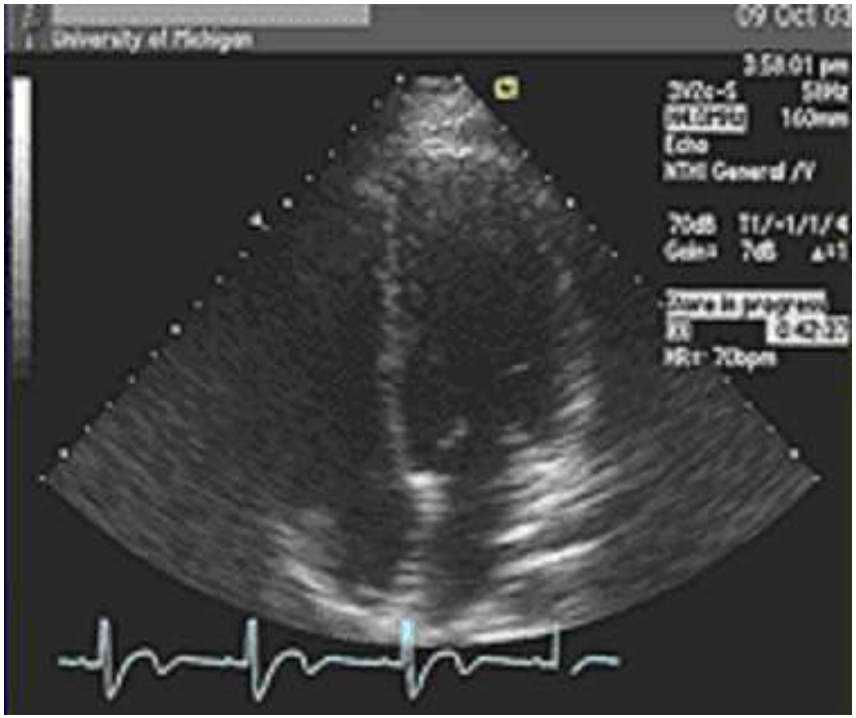
RV assessment

- TR Velocity >>>RVSP
- RAE, RVE, RV dysfunction

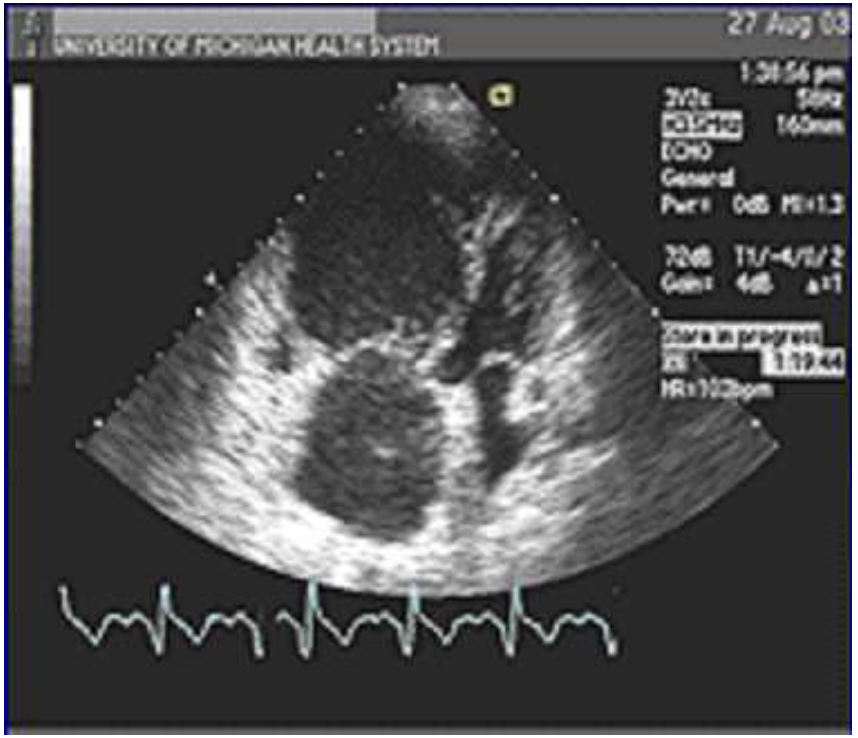
LV assessment

R/o congenital HD

# Apical 4-chamber

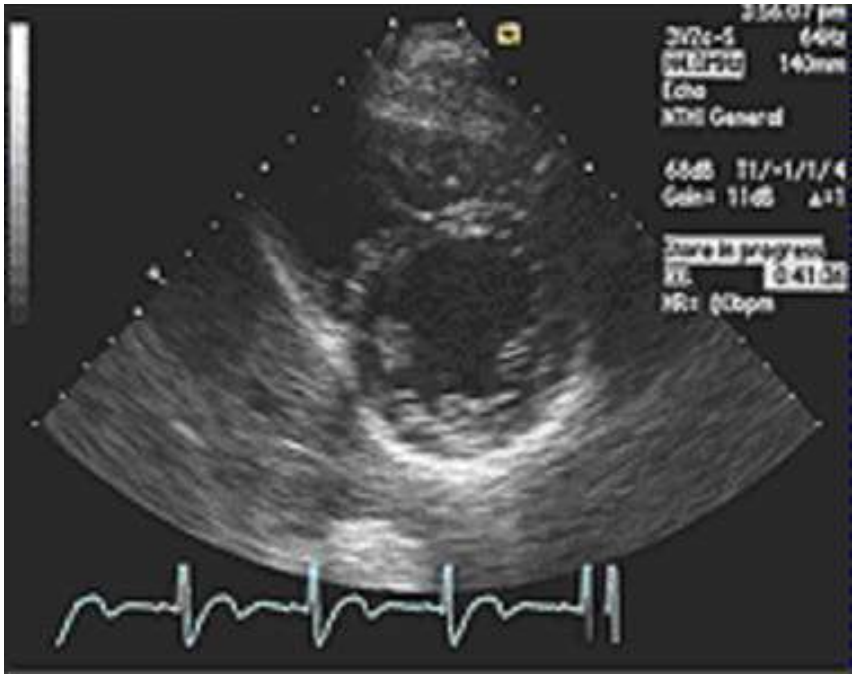


Normal



PAH

# Parasternal short axis



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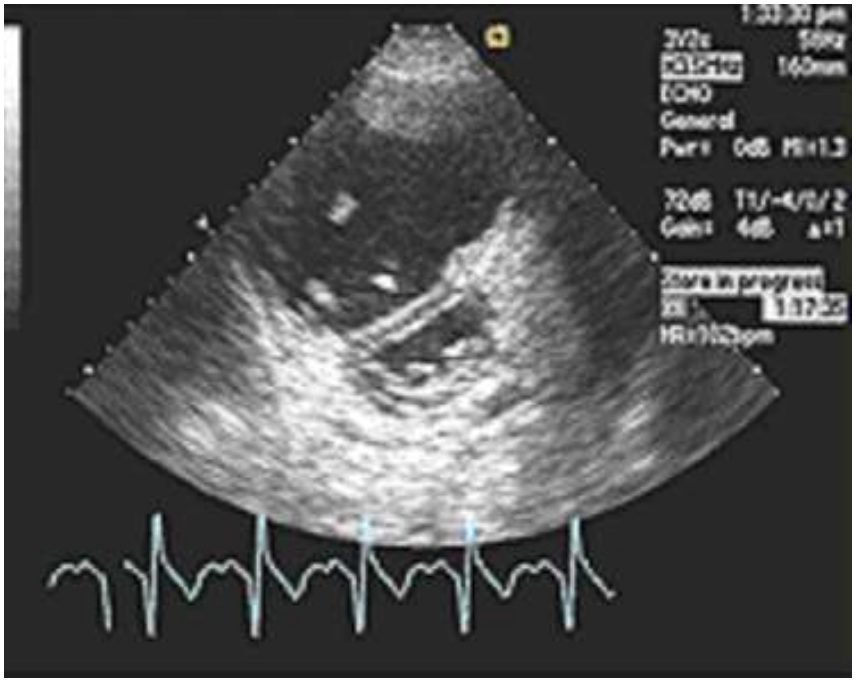
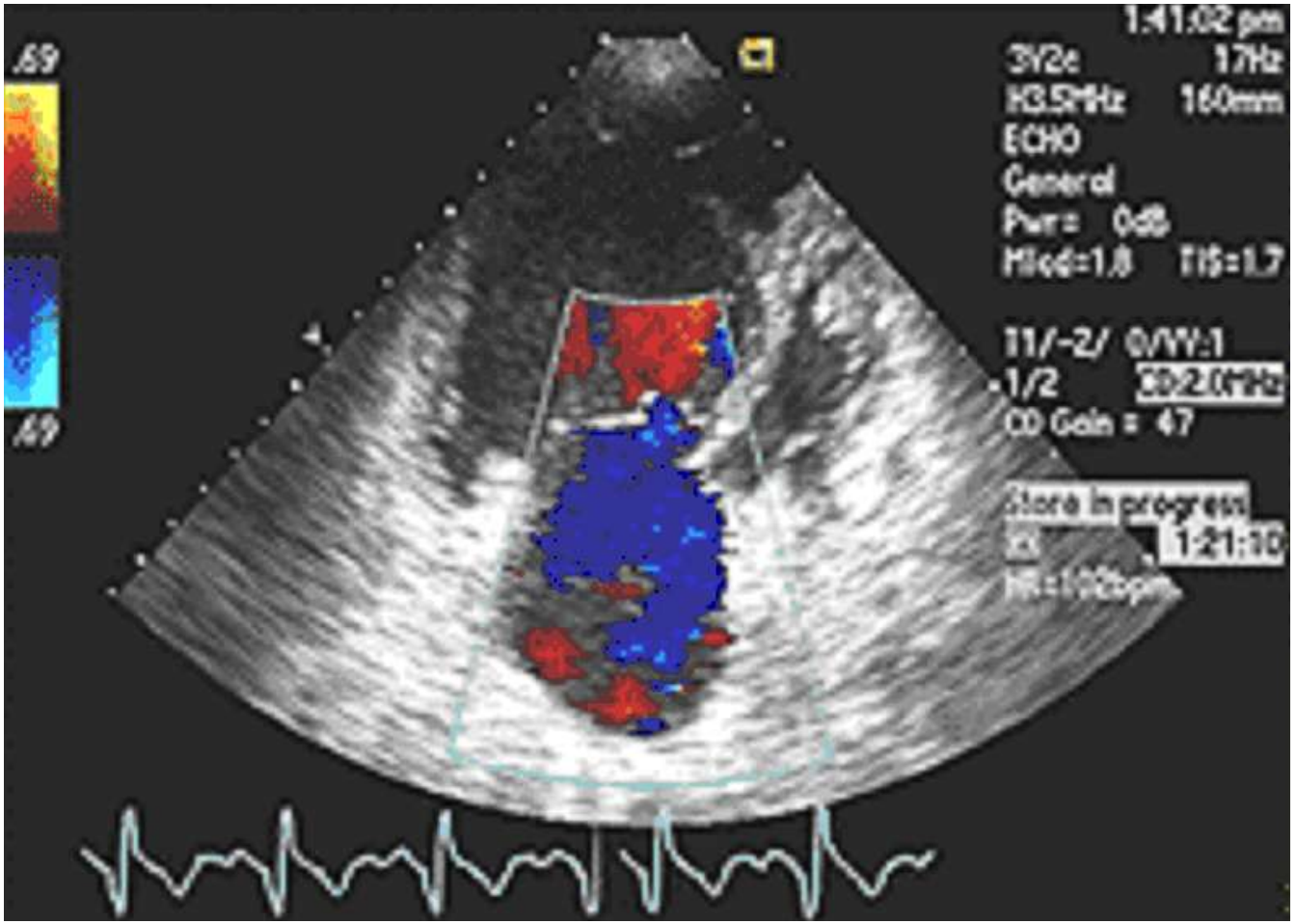
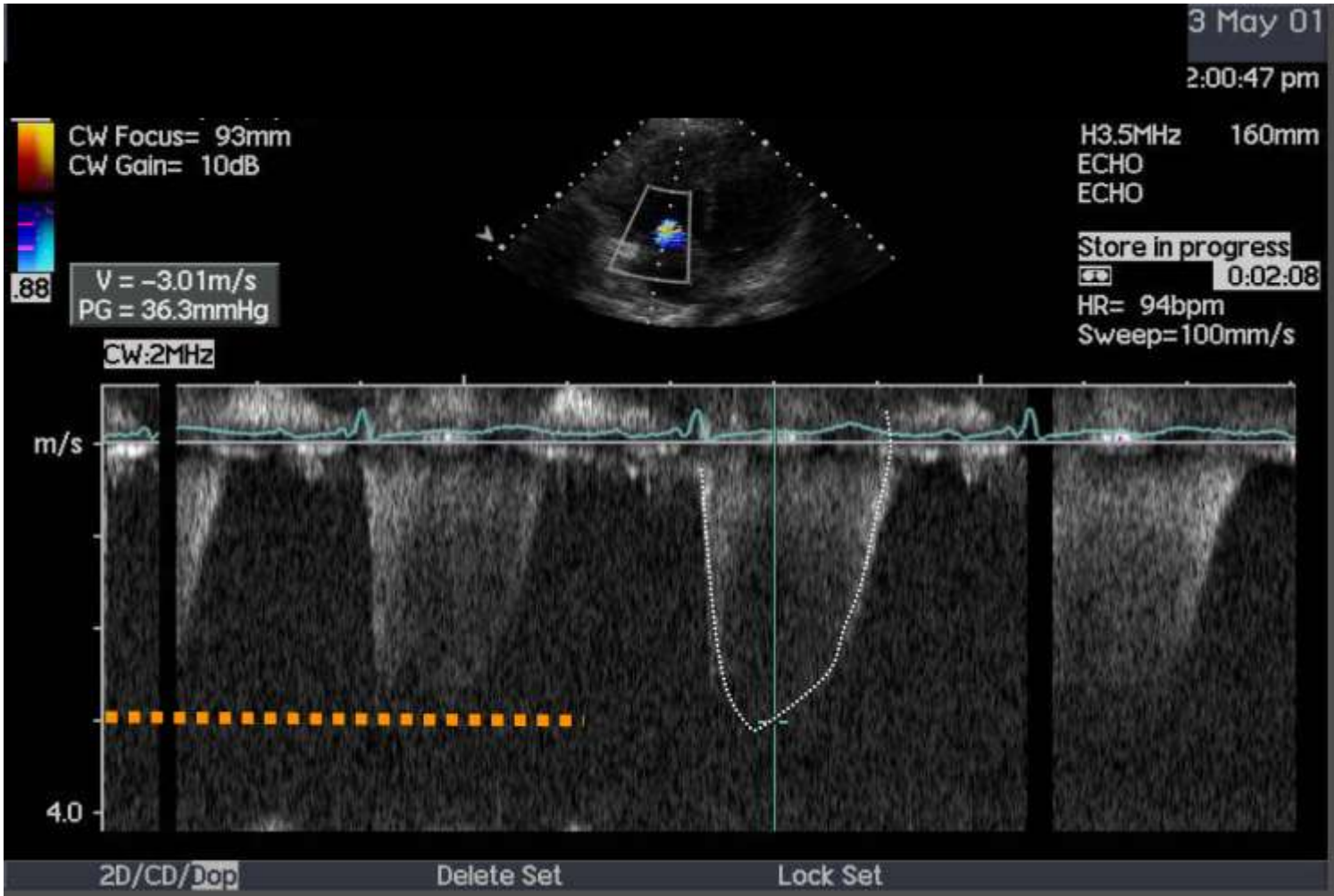


PAH

# Tricuspid Regurgitation

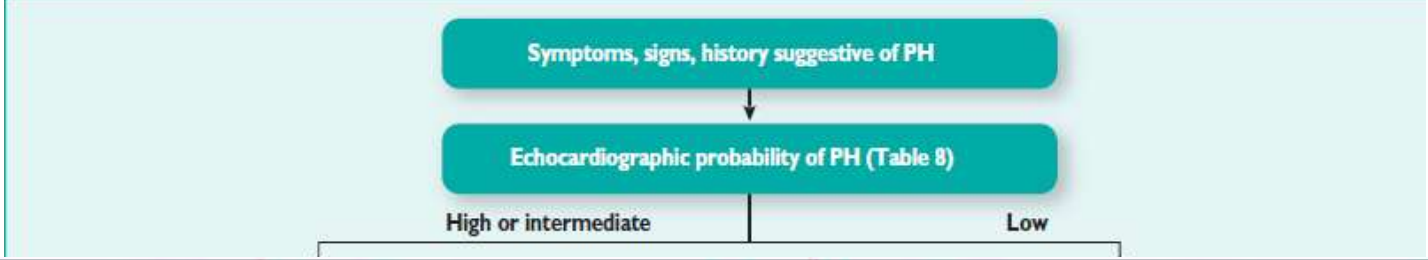





# Tricuspid insufficiency Vmax

## TI Pressure Gradient = 4 $Vmax^2$

## PASP = 4 x $Vmax^2$ + RAP*(est)*

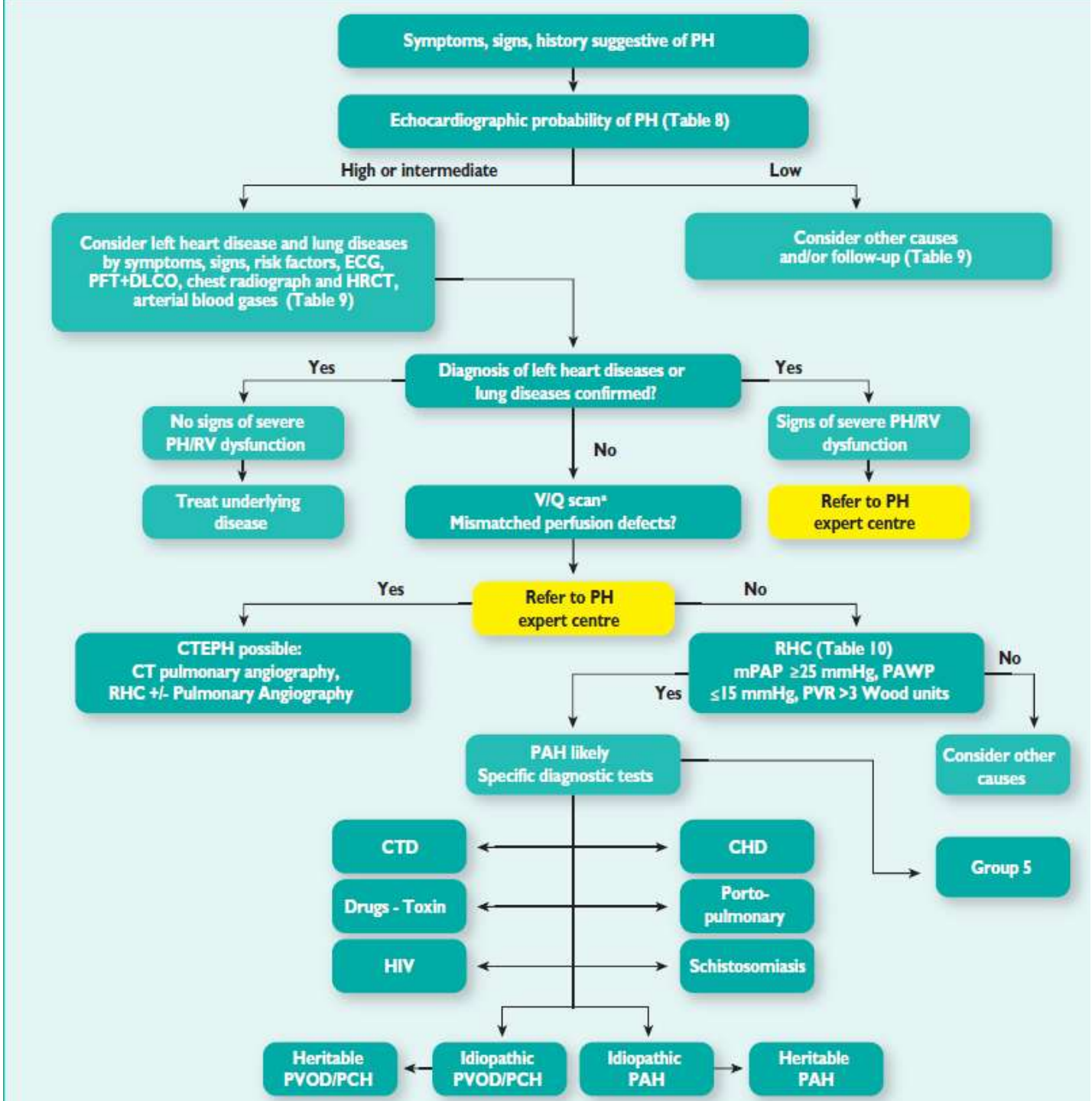



| Peak tricuspid regurgitation velocity (m/s) | Presence of other echo 'PH signs'[a] | Echocardiographic probability of pulmonary hypertension |
|---|---|---|
| ≤2.8 or not measurable | No | Low |
| ≤2.8 or not measurable | Yes | Intermediate |
| 2.9–3.4 | No | |
| 2.9–3.4 | Yes | High |
| >3.4 | Not required | |

| A: The ventricles[a] | B: Pulmonary artery[a] | C: Inferior vena cava and right atrium[a] |
|---|---|---|
| Right ventricle/ left ventricle basal diameter ratio >1.0 | Right ventricular outflow Doppler acceleration time <105 msec and/or midsystolic notching | Inferior cava diameter >21 mm with decreased inspiratory collapse (<50 % with a sniff or <20 % with quiet inspiration) |
| Flattening of the interventricular septum (left ventricular eccentricity index >1.1 in systole and/or diastole) | Early diastolic pulmonary regurgitation velocity >2.2 m/sec | Right atrial area (end-systole) >18 $cm^2$ |
| | PA diameter >25 mm. | |

# Diagnostic management

| Echocardiographic probability of PH | Without risk factors or associated condition for PAH or CTEPH[d] | Class[a] | Level[b] | With risk factors or associated conditions for PAH or CTEPH[c] | Class[a] | Level[b] |
|---|---|---|---|---|---|---|
| Low | Alternative diagnosis should be considered | IIa | C | Echo follow-up should be considered | IIa | C |
| Intermediate | Alternative diagnosis, echo follow-up, should be considered | IIa | C | Further assessment of PH including RHC should be considered[e] | IIa | B |
| | Further investigation of PH may be considered[e] | IIb | | | | |
| High | Further investigation of PH (including RHC[e]) is recommended | I | C | Further investigation of PH[e] including RHC is recommended | I | C |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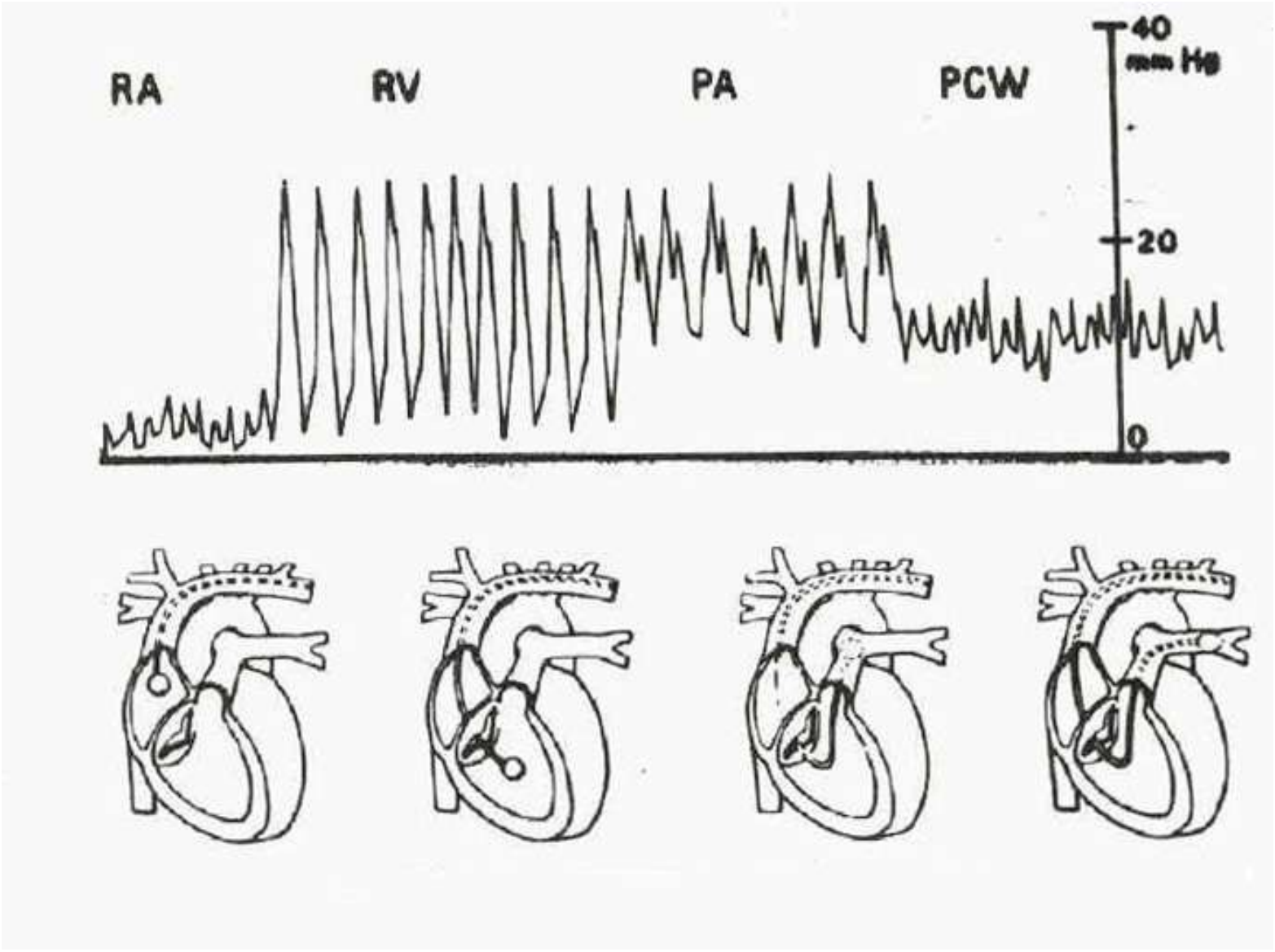
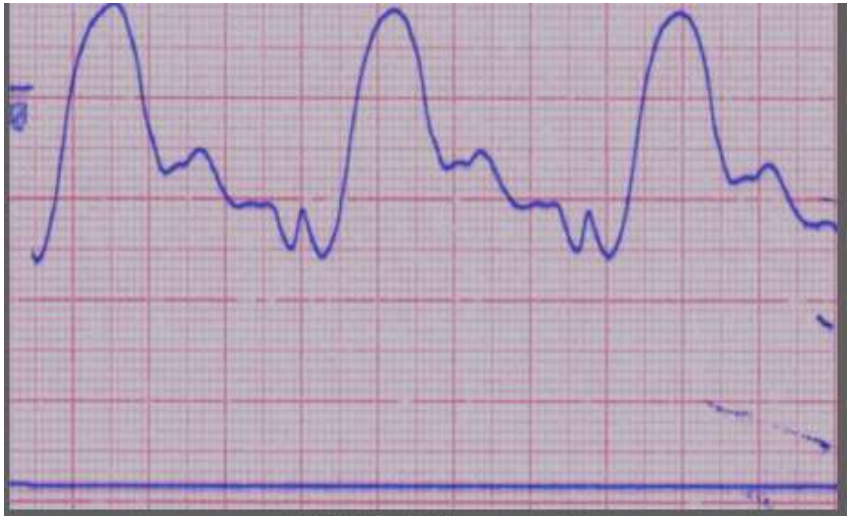
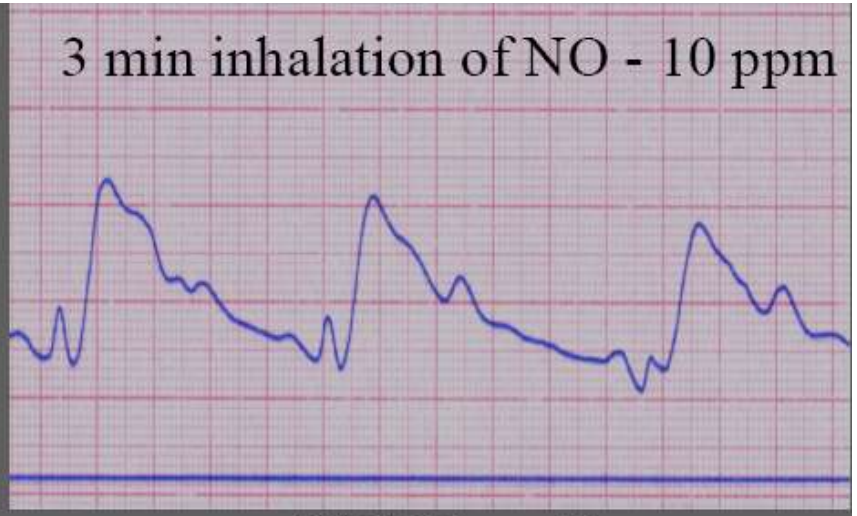
Heritable PVOD/PCH
Idiopathic PVOD/PCH
Idiopathic PAH
Heritable PAH

# Right heart catheterization





mPAP 51 mmHg
CO 5,14 l / min
PVR 8,75jW




mPAP 25 mmHg
CO 5,33 l / min
PVR 3,5 j. W.

# Evaluation of right heart size and function

- Echo is the mainstay for right heart evaluation in routine clinical practice
- However, MRI is the most accurate method for evaluating RV mass, RV volume, RVEF
- In addition MRI can quantify:
  - Regurgitant volumes
  - Delayed enhancement (focal scars)
  - Myocardial strain, coronary perfusion, pulmonary pulsatility
- RVEF and TAPSE are markers of ventriculo-arterial coupling, rather than ventricular contractility

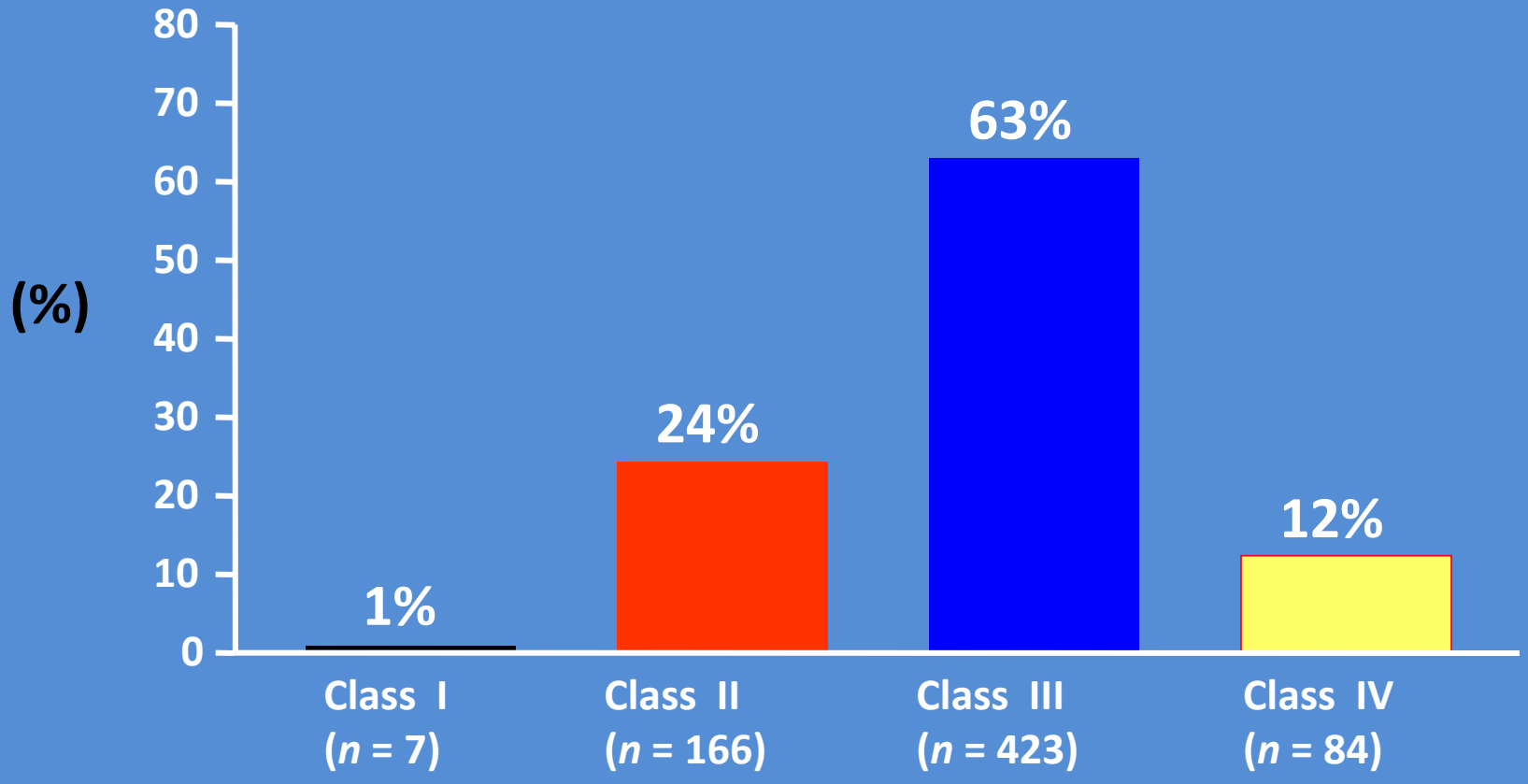
# Diagnostic – work up

- Suspicion
- Detection
- Identification
- Assessment-Classification

# NYHA Functional Class

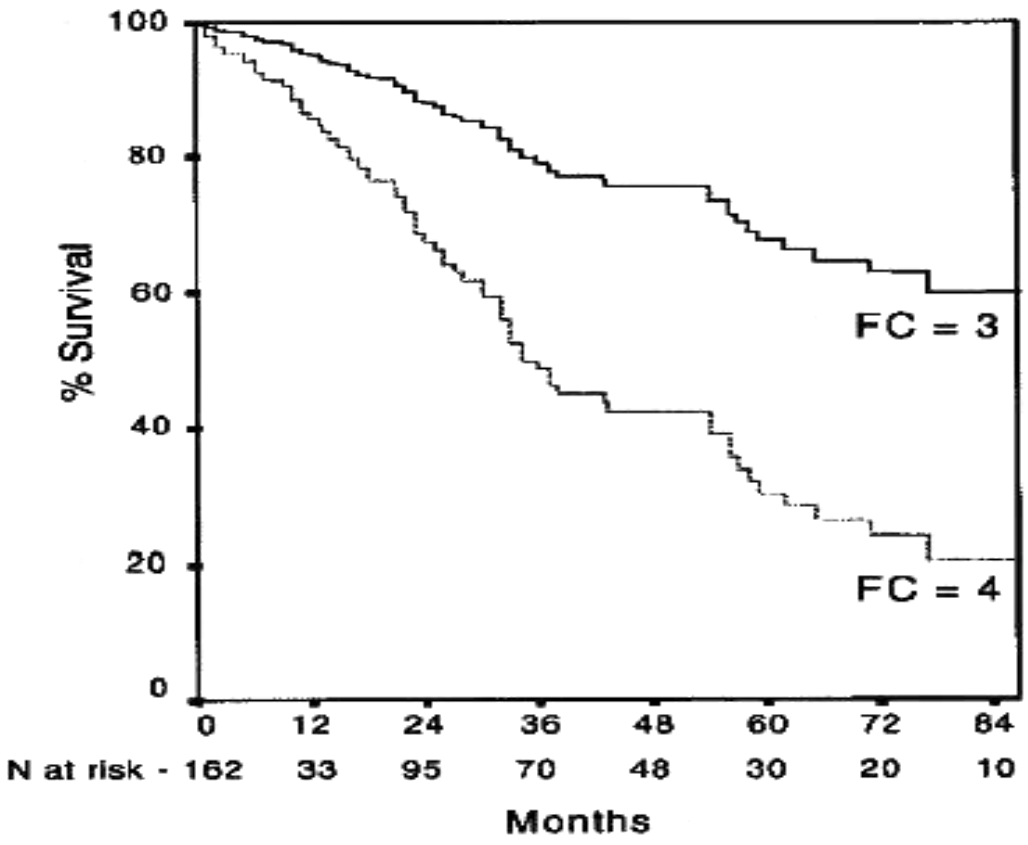
| Class | Patient Symptoms |
| --- | --- |
| Class I (Mild)  | No limitation of physical activity. Ordinary physical activity does not cause undue symptoms |
| Class II (Mild)  | Slight limitation of physical activity. Comfortable at rest, ordinary physical activity results in symptoms. |
| Class III (Moderate)  | Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms. |
| Class IV (Severe)  | Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased. |

# NYHA functional class at diagnosis



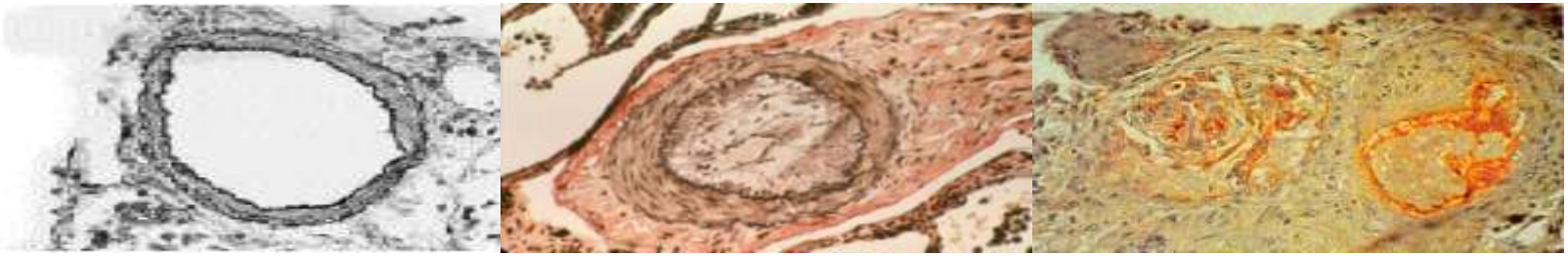

*Humbert M, et al. Am J Respir Crit Care Med 2006; 173:1023-30.*

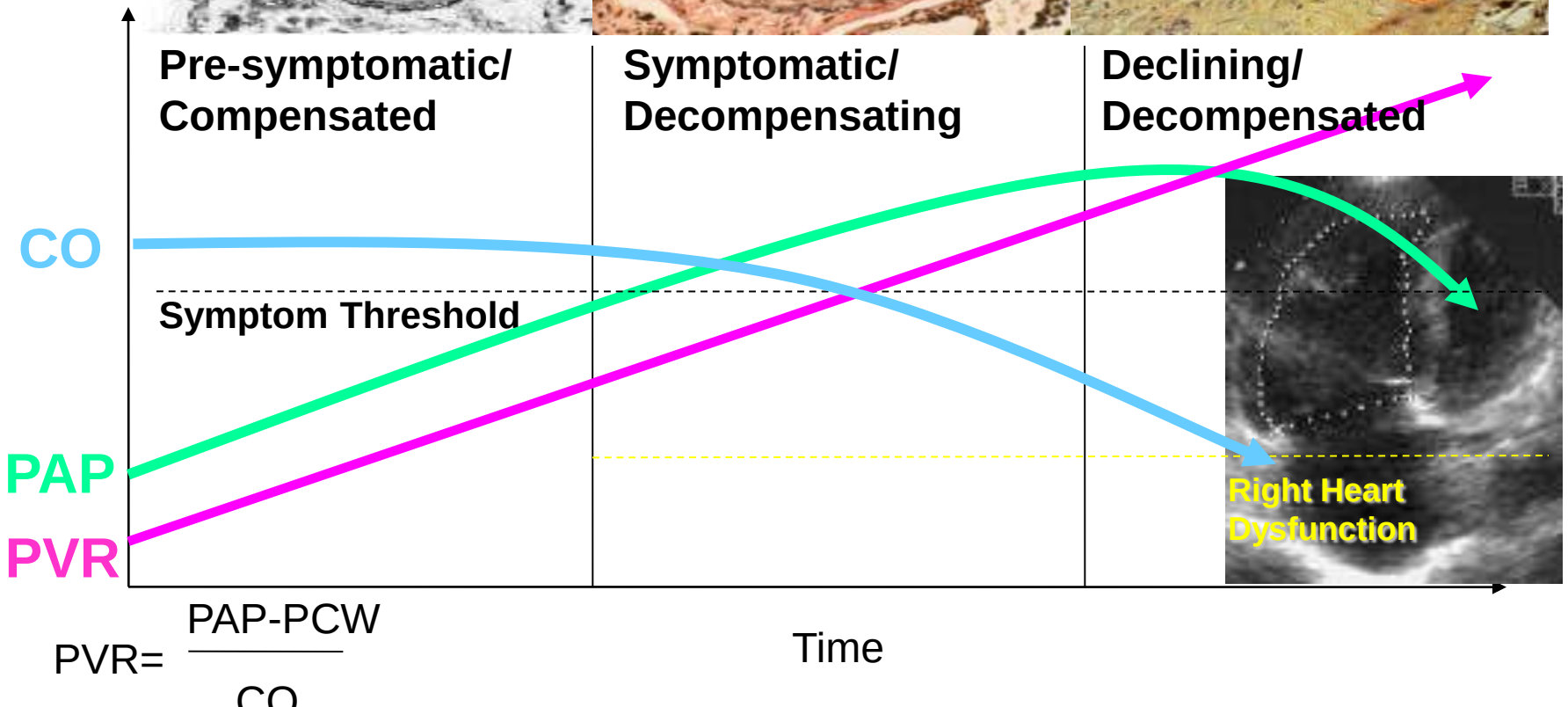
# **Severity of PAH**: NYHA Functional Class (Predictor of survival in PAH)




McLaughlin, Circulation 2002

# Schematic Progression of PAH






$$PVR = \frac{PAP - PCW}{CO}$$

# Risk Assessment in PAH

| 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 % |

[a]Most of the proposed variables and cut-off values are based on expert opinion.
[b]Occasional syncope during brisk or heavy exercise, or occasional orthostatic syncope in an otherwise stable patient.
[c]Repeated episodes of syncope, even with little or regular physical activity.

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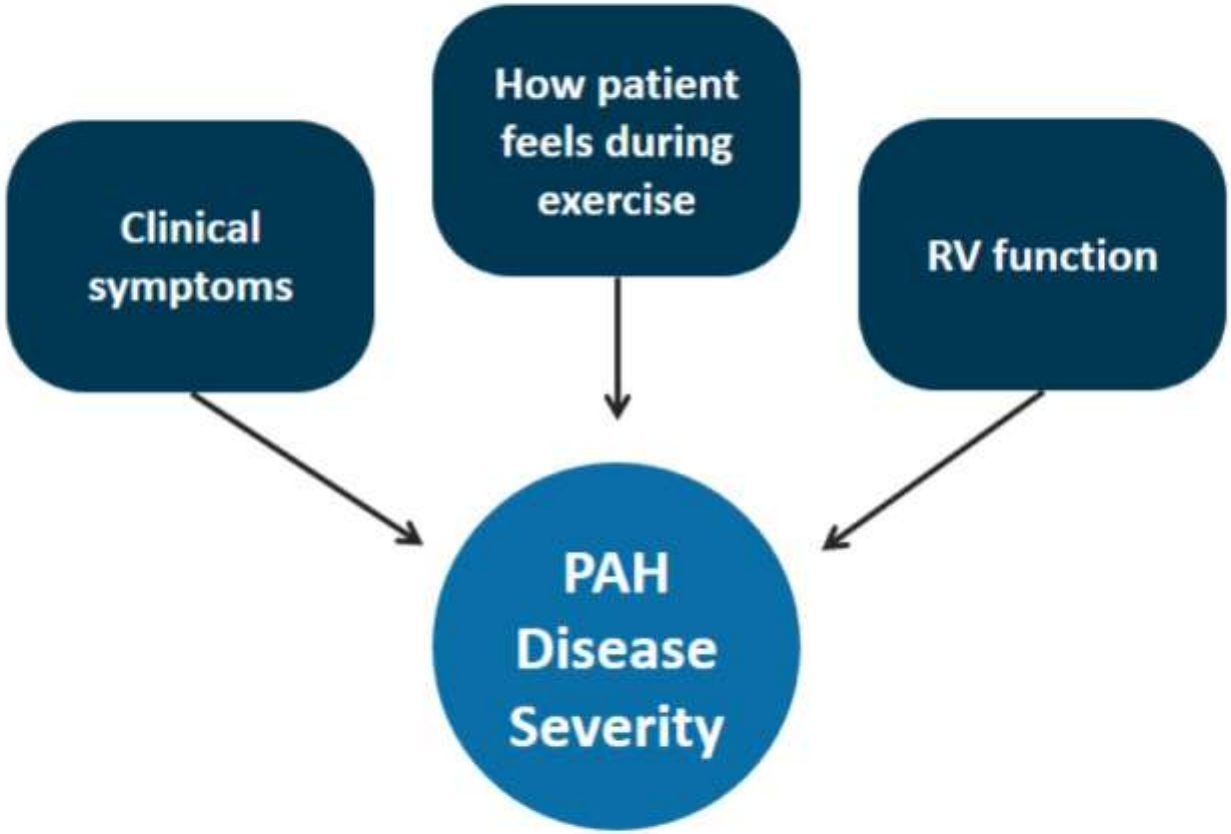
# Components of a Comprehensive Risk Assessment




It is important to be comprehensive and use all components of the risk assessment to determine disease severity.

Galie N, et al. *Eur Heart J*. 2016;37:67-119.

# Definition of Patient Status

- In many cases, all of the variables that determine a patient's status will fall into different risk categories (ie, low, intermediate, or high)
  - It is the overall assessment that should drive therapeutic decisions

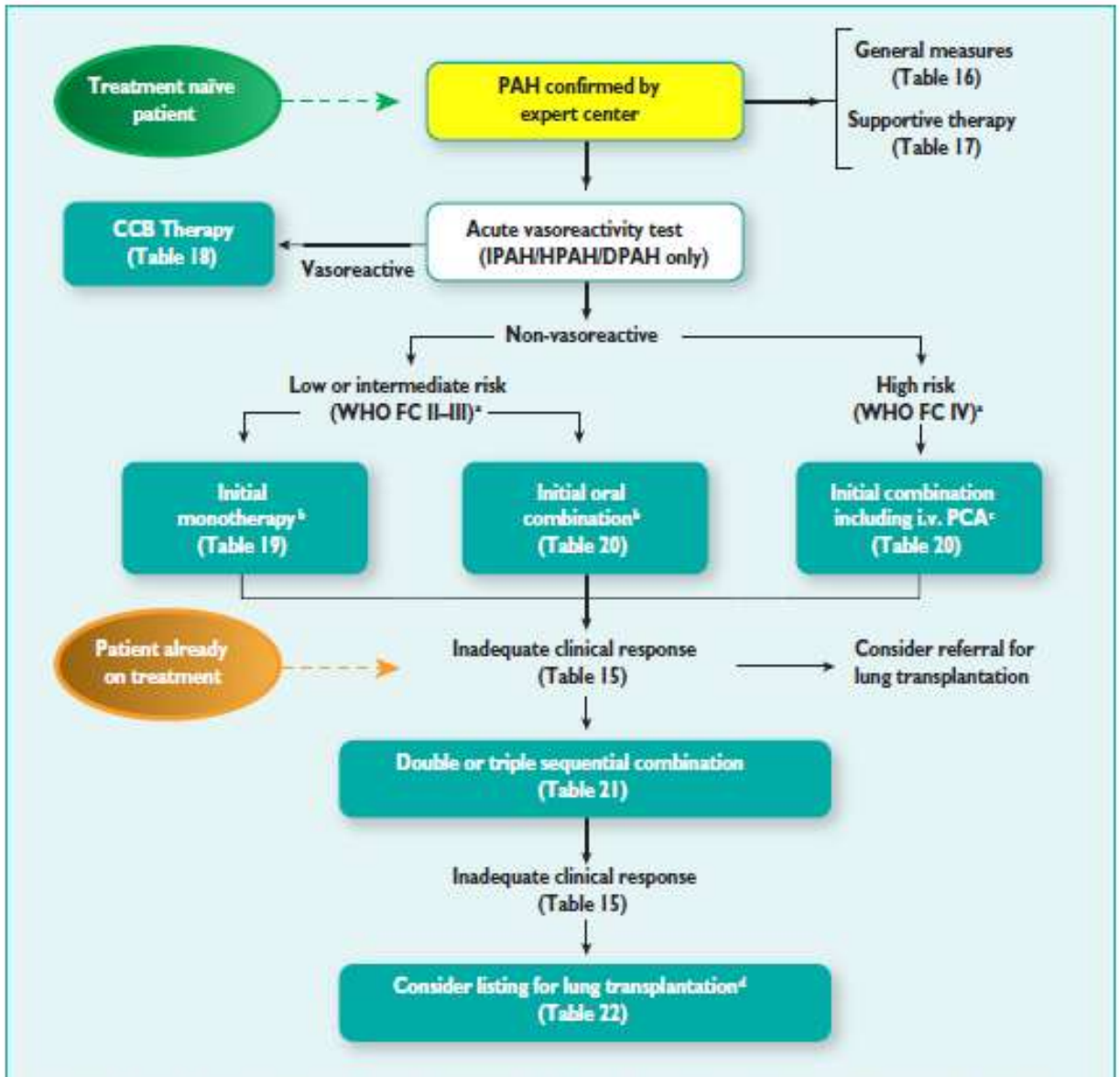
Galie N, et al. *Eur Heart J*. 2016;37:67-119.

# Raising the bar on treatment goals

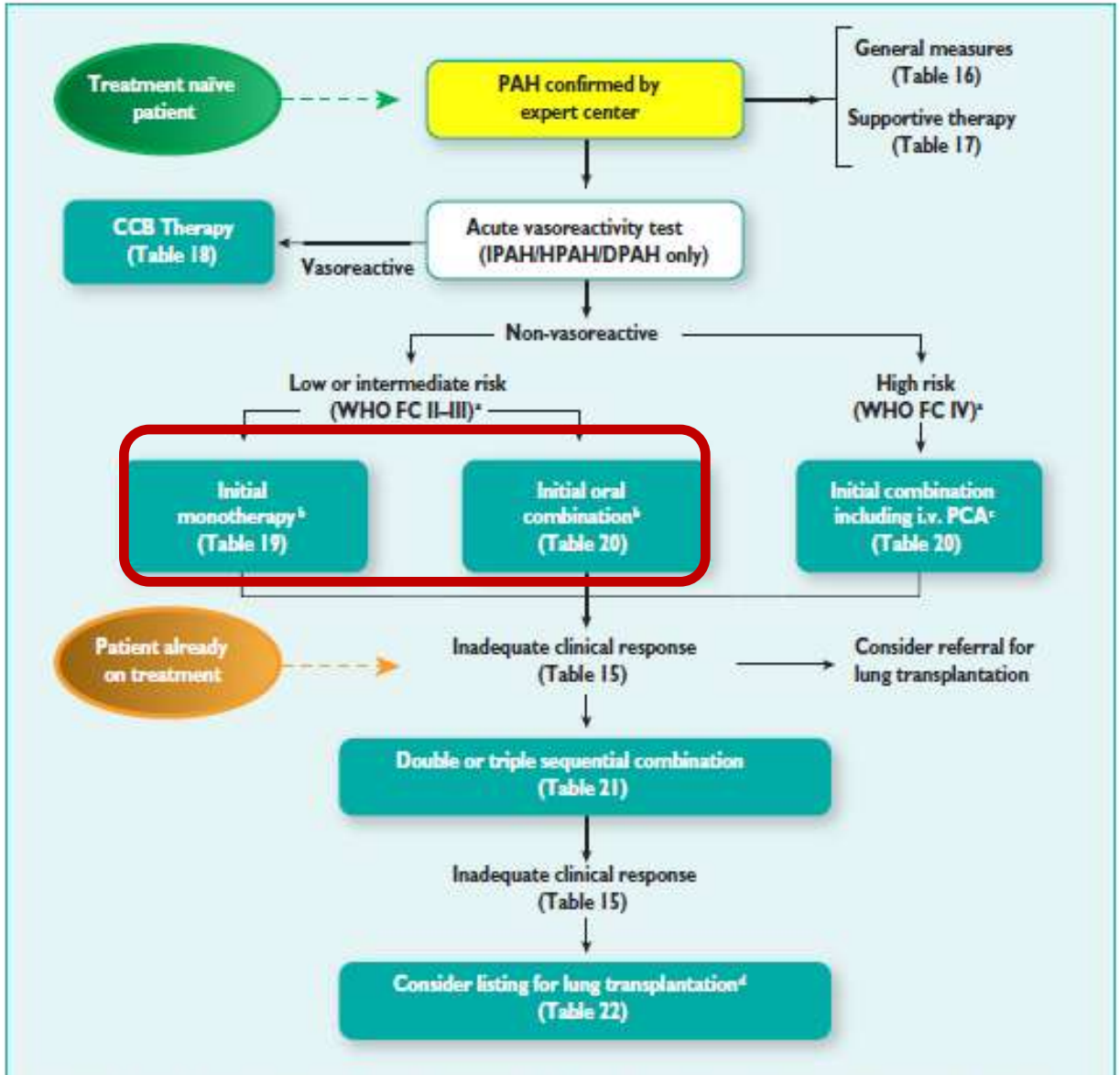
**Table 1** Variables Used in Clinical Practice to Determine Response to Therapy and Prognosis in Patients With PAH

| |
|---|
| Functional class |
| I or II |
| Echocardiography/CMR |
| Normal/near-normal RV size and function |
| Hemodynamics |
| Normalization of RV function (RAP $<$8 mm Hg and CI $>$2.5 to 3.0 l/min/m$^2$) |
| 6-min walk distance |
| $>$380 to 440 m; may not be aggressive enough in young individuals |
| Cardiopulmonary exercise testing |
| Peak $VO_2$ $>$15 ml/min/kg and $EqCO_2$ $<$45 l/min/l/min |
| B-type natriuretic peptide level |
| Normal |

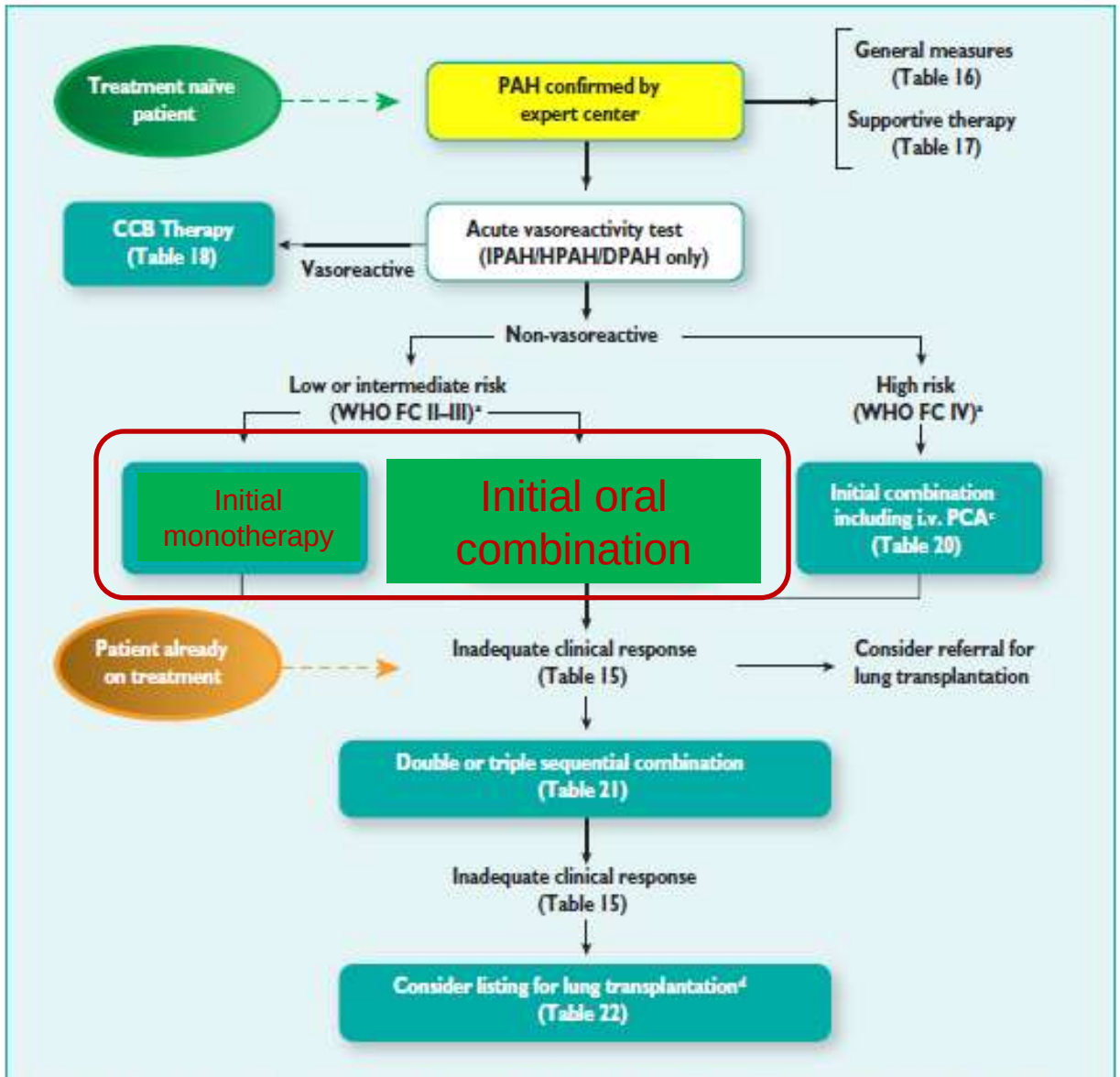
# ESC/ERS GUIDELINES 2015.Treatment algorithm



# ESC/ERS GUIDELINES 2015.Treatment algorithm changes



# ESC/ERS GUIDELINES 2015.Treatment algorithm changes



# Monotherapy Is Frequently Inadequate

- Retrospective analysis of medical records of patients with PAH at Skåne University Hospital 2000 to 2011

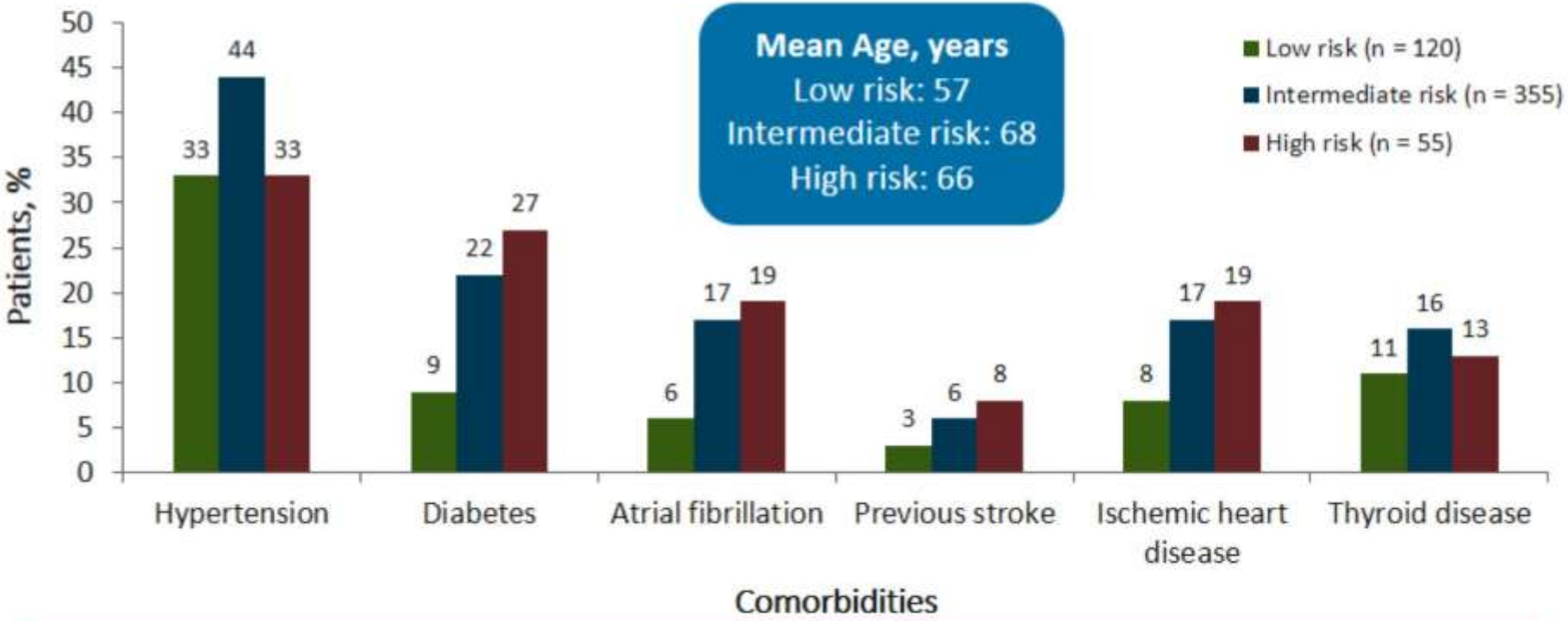
**Patient Who Started and Remained on Monotherapy**

| 1-Year Survival | 2-Year Survival | 3-Year Survival |
|---|---|---|
| 58% | 41% | 24% |

Kylhammar D, et al. *Scand Cardiovasc J*. 2014;48:223-233.

# PAH Population Is Heterogeneous

- Baseline patient characteristics from SPAHR




Aggressive initial therapy may not be possible in elderly patients with comorbidities as in younger patients without comorbidities

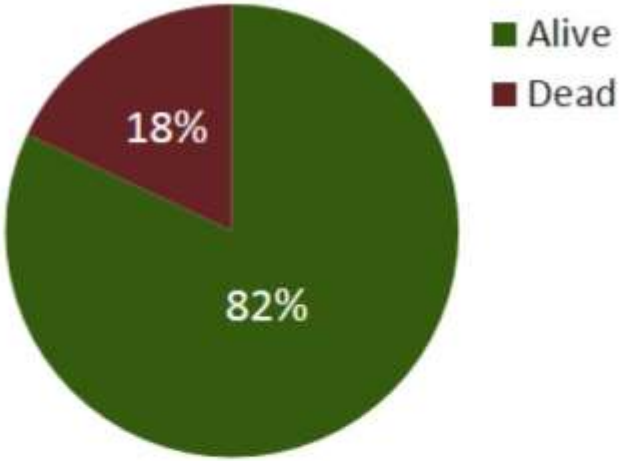
Kylhammar D, et al. *Eur Heart J.* 2017

# French PH Registry

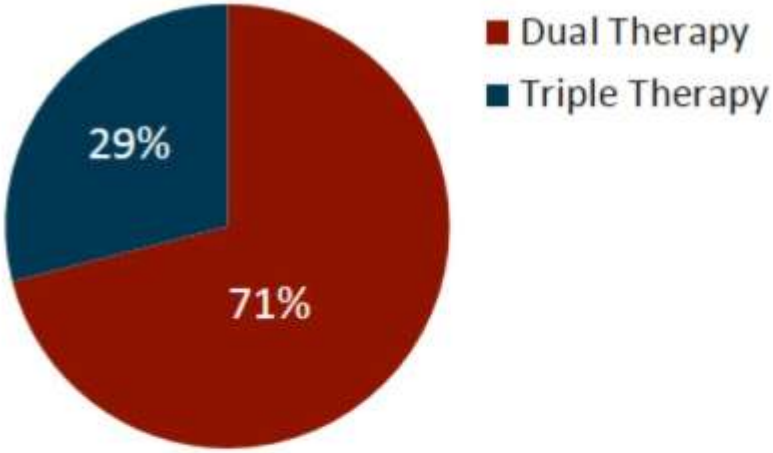
## *Early Combination Treatment Leads to Better Long-Term Survival*

- 97 patients with newly diagnosed PAH (86% in NYHA FC III to IV)
- Enrolled between January 2007 and December 2013
- All patients treated with initial oral combination therapy with additional prostanoid treatment if condition deteriorated or inadequate response

**30-Month Follow-Up**




**Among Alive Patients**




**Shorter follow-up intervals are appropriate in patients who do not reach treatment goals**

Sitbon O, et al. *Eur Respir J.* 2016;47:1727-1736.

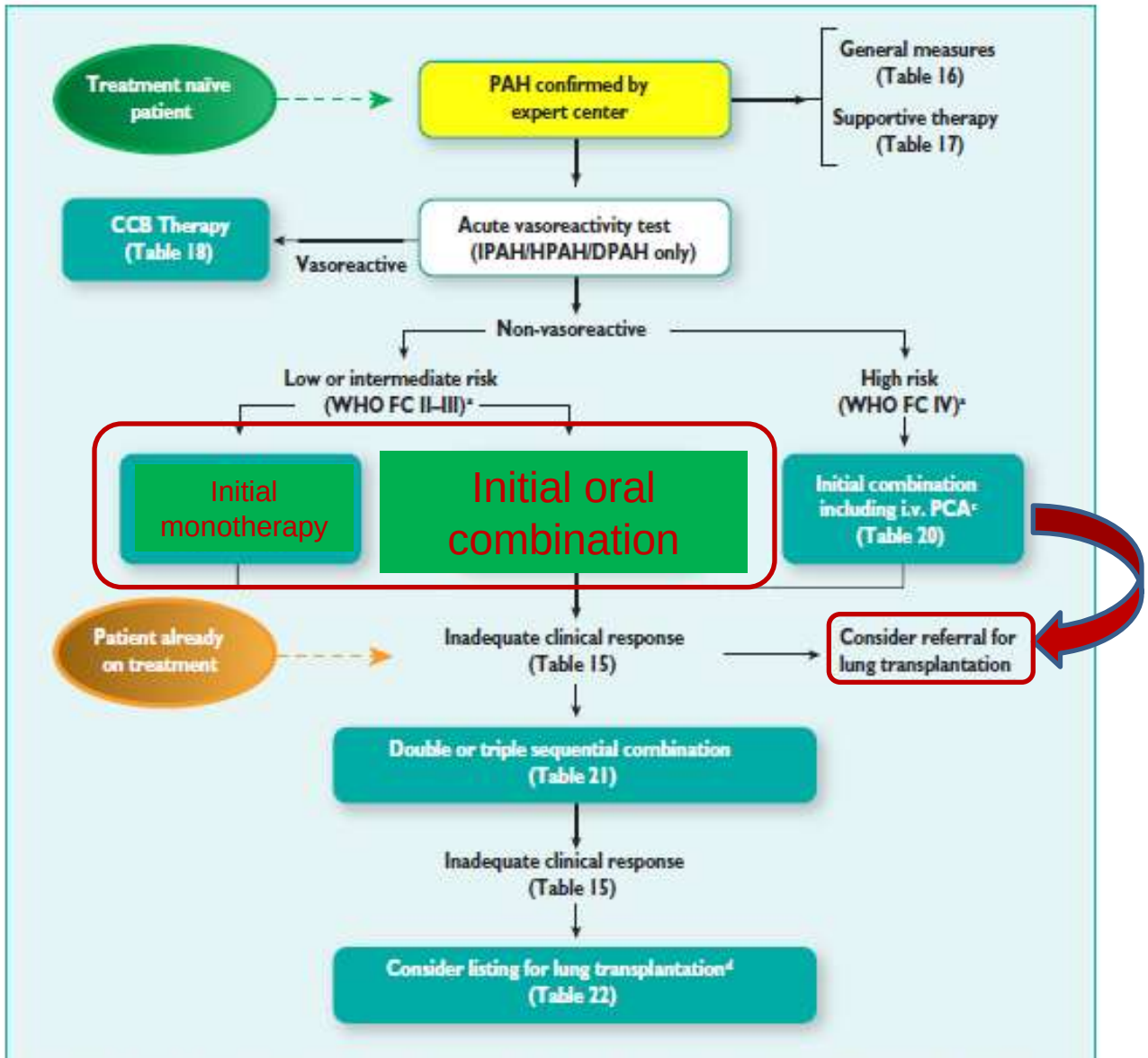
# Pilot Study
## *Initial Triple Combination Therapy*

- Retrospective analysis of NYHA FC III/IV PAH* patients (N=19) admitted to French center
  - Severe hemodynamic impairment: CI <2.0 L/min/$m^2$ and/or mean RAP >20 mmHg and/or PVR ≥1000 dyn/s/$cm^5$
  - Initiated on upfront triple combination therapy IV epoprostenol, bosentan, and sildenafil
  - Mean follow-up 41.2 months
- Resulted in improvements in FC, exercise capacity, cardiopulmonary hemodynamics, and survival prospects
  - Overall survival estimates were 100% and transplant-free survival estimates were 94% at 1, 2, and 3 years

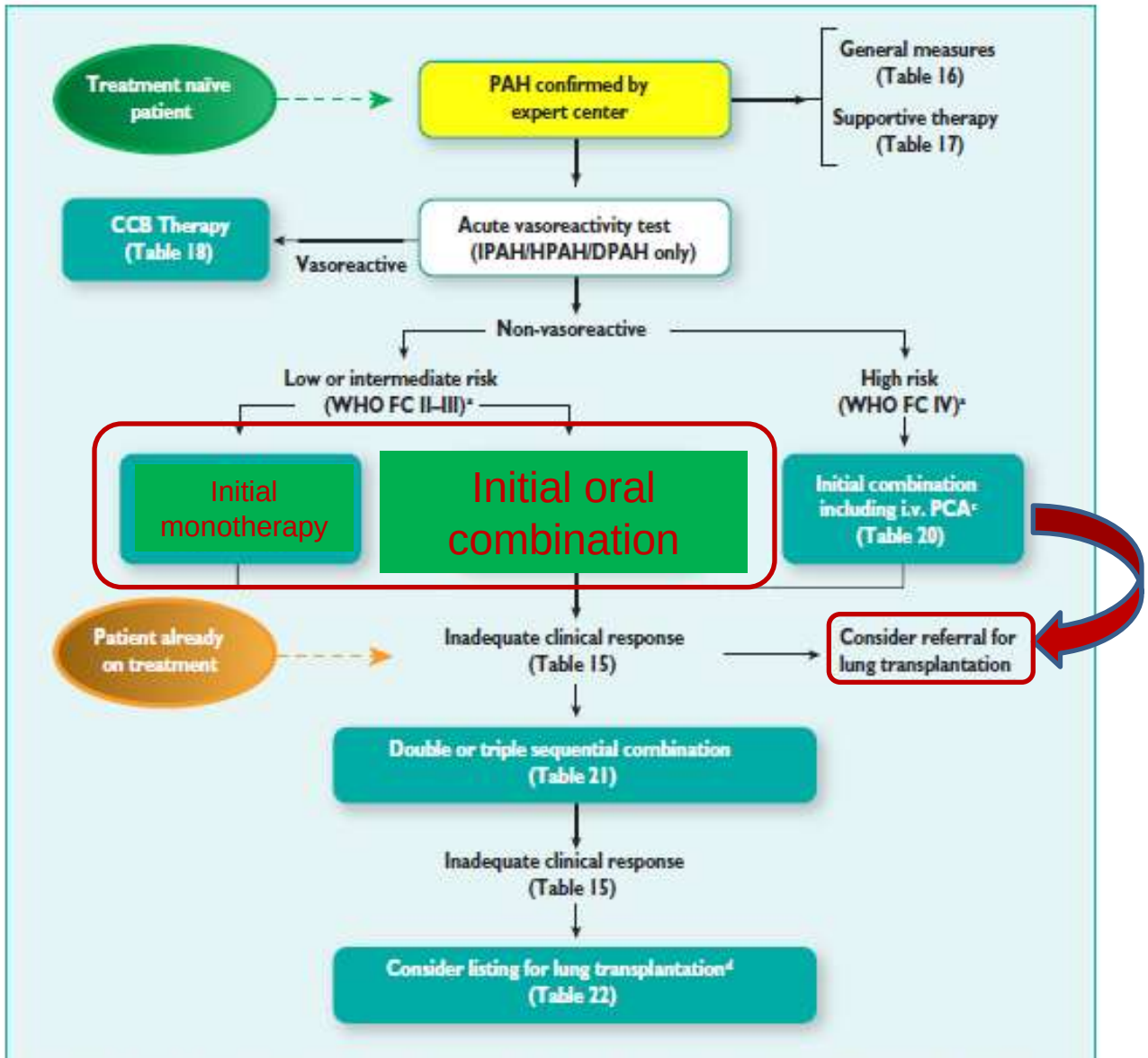
*Idiopathic, heritable or anorexigen-associated PAH.

Sitbon O, et al. *Eur Respir J*. 2014; 43:1691–1697.

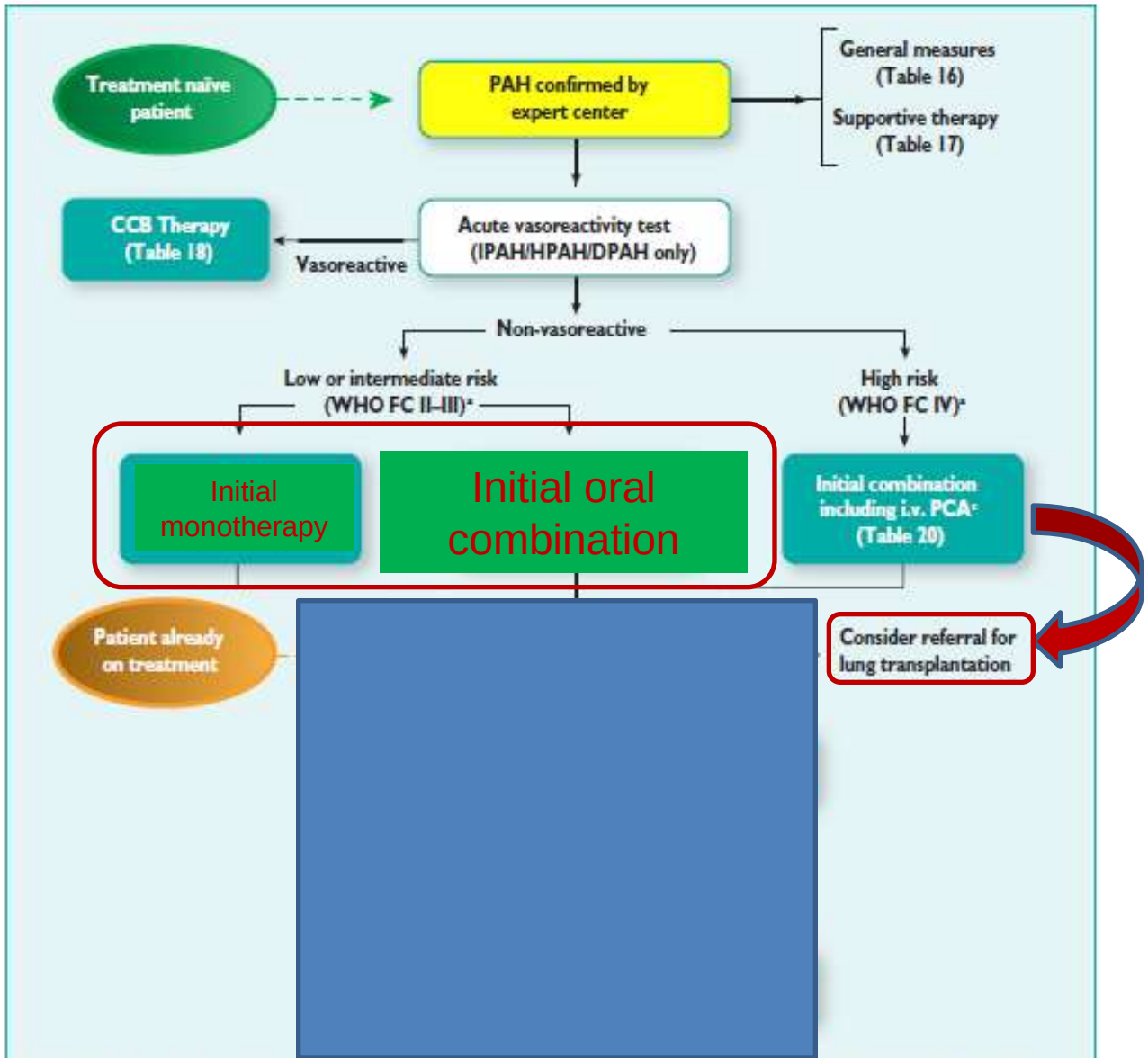
# ESC/ERS GUIDELINES 2015.Treatment algorithm changes



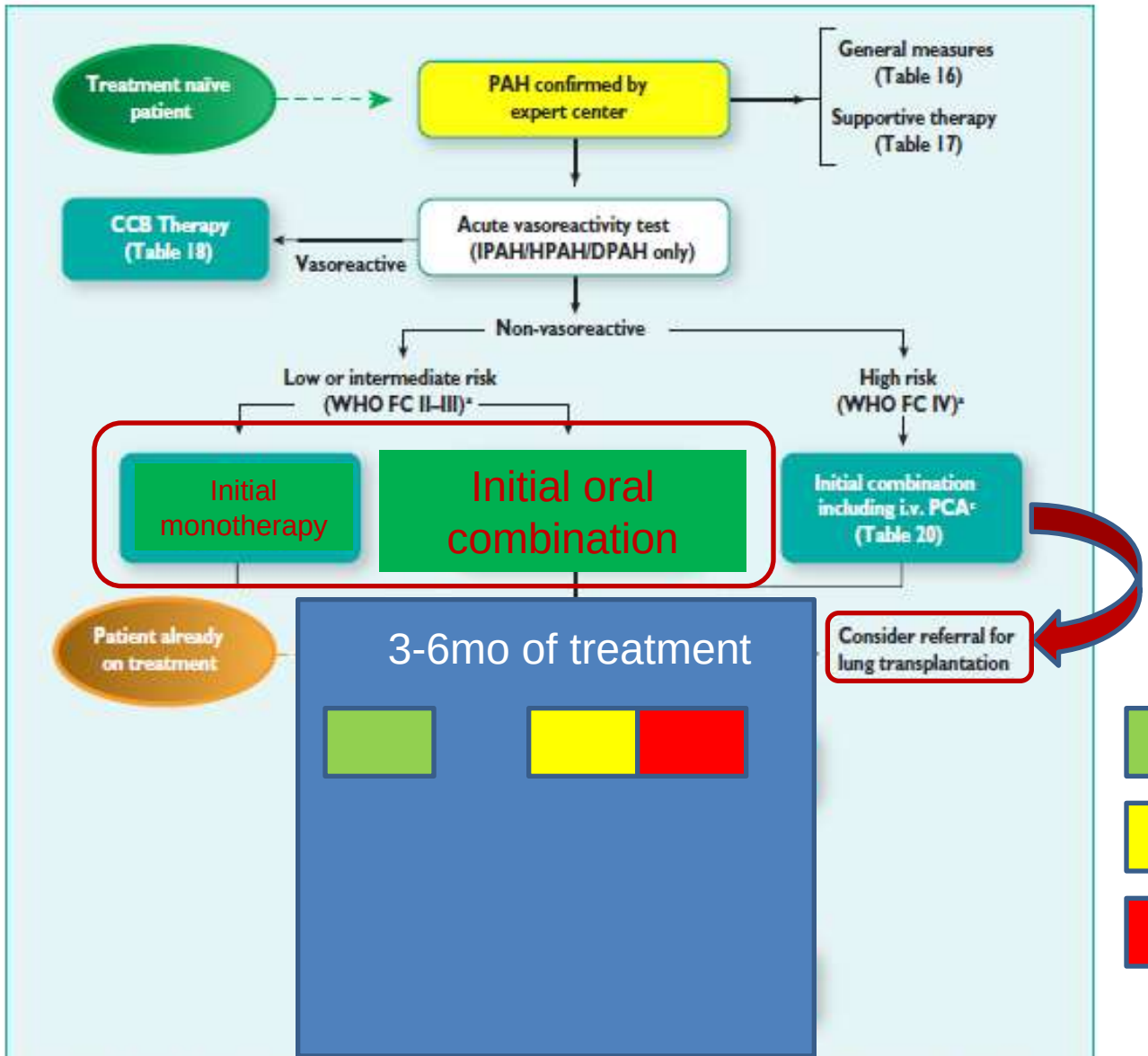
# ESC/ERS GUIDELINES 2015.Treatment algorithm changes



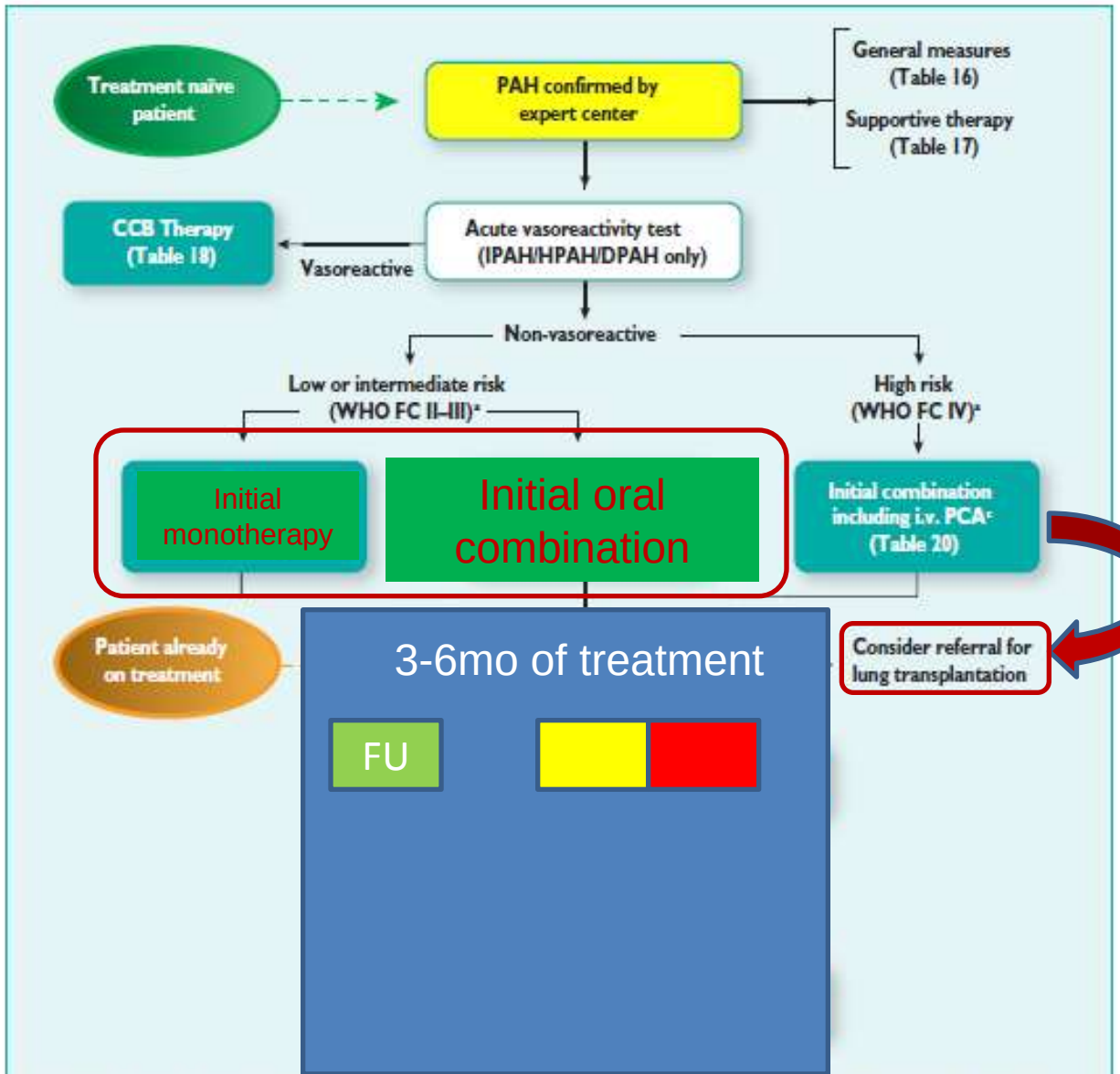
# ESC/ERS GUIDELINES 2015.Treatment algorithm changes



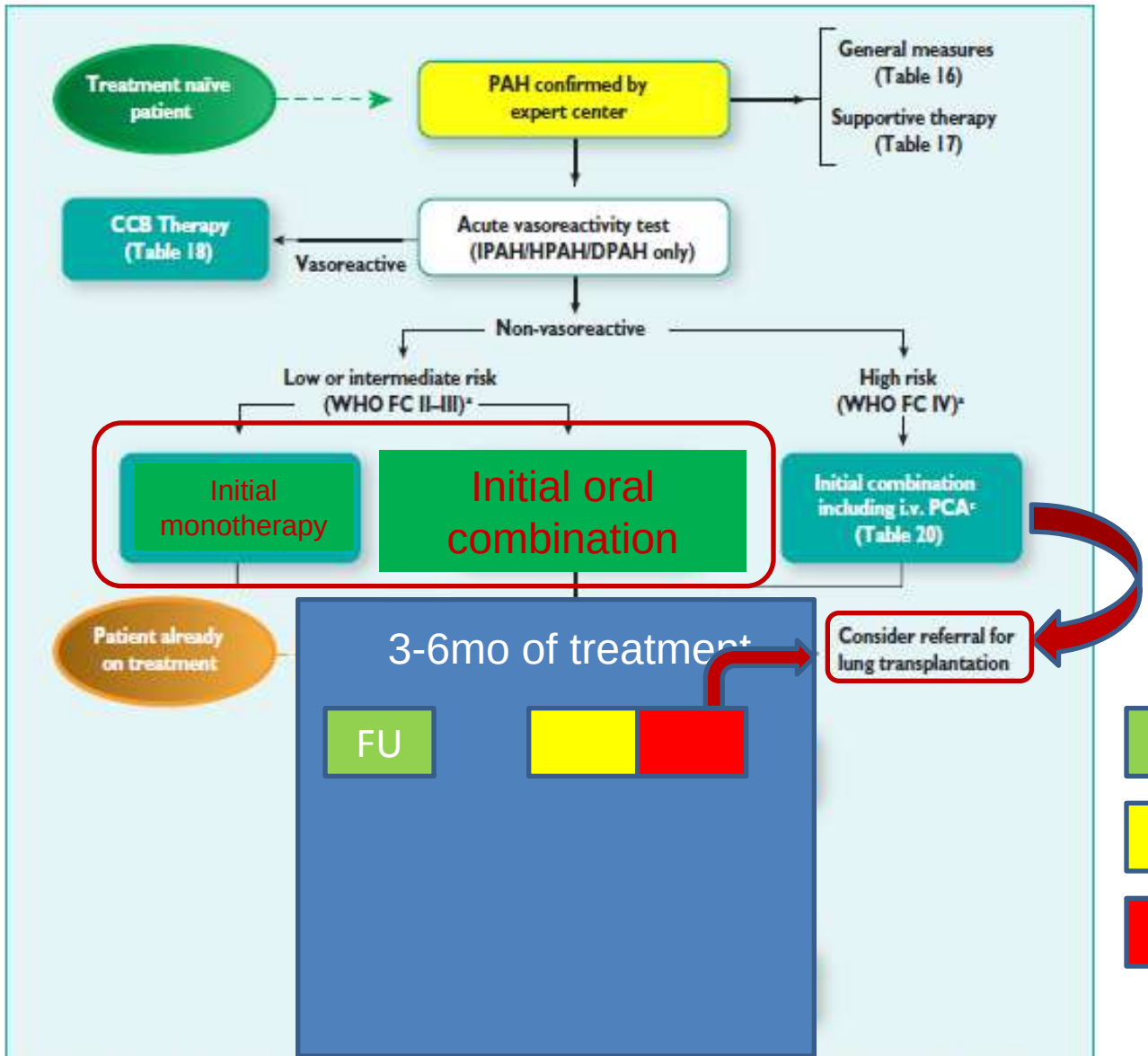
# ESC/ERS GUIDELINES 2015.Treatment algorithm changes



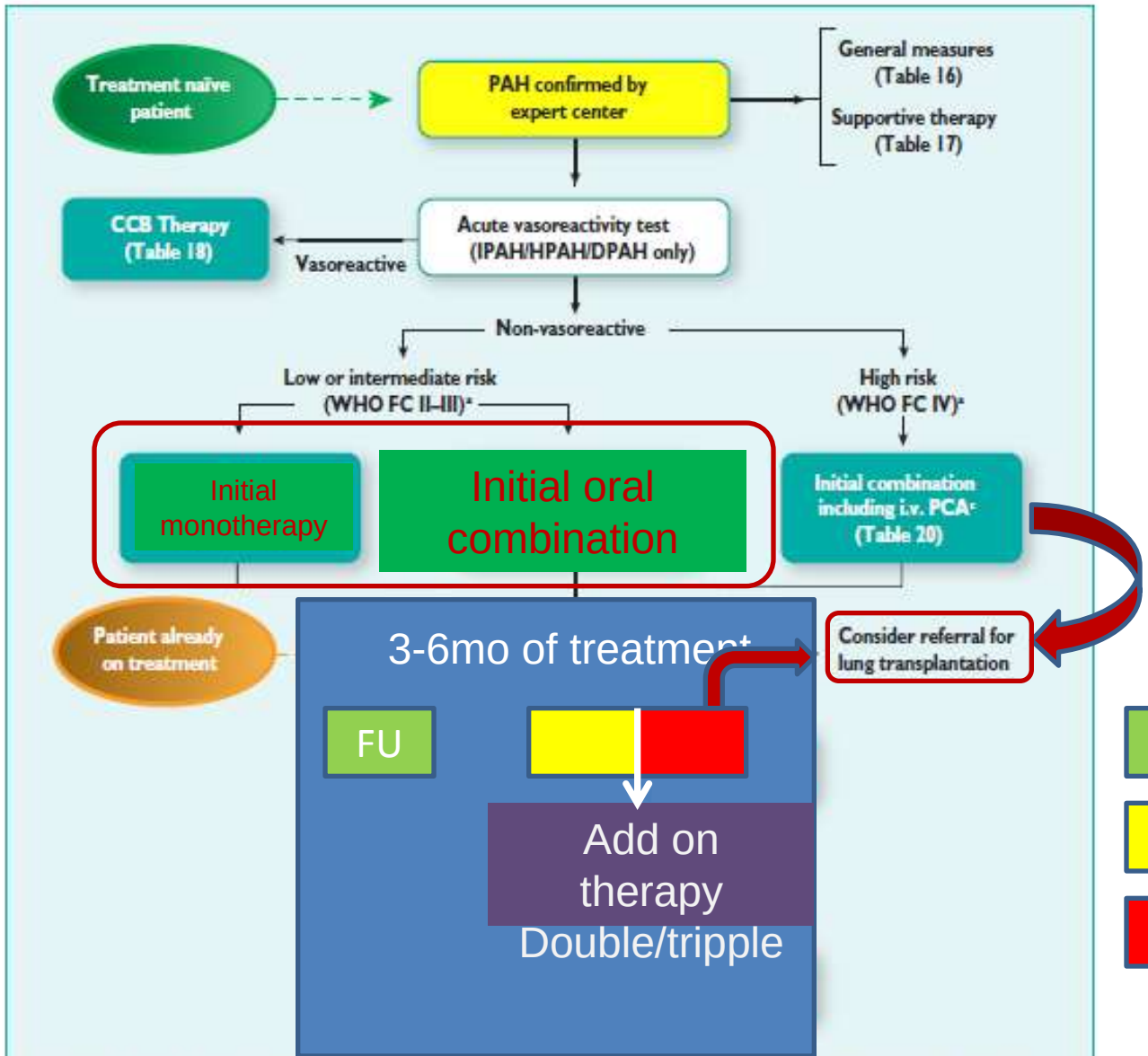
# ESC/ERS GUIDELINES 2015.Treatment algorithm changes



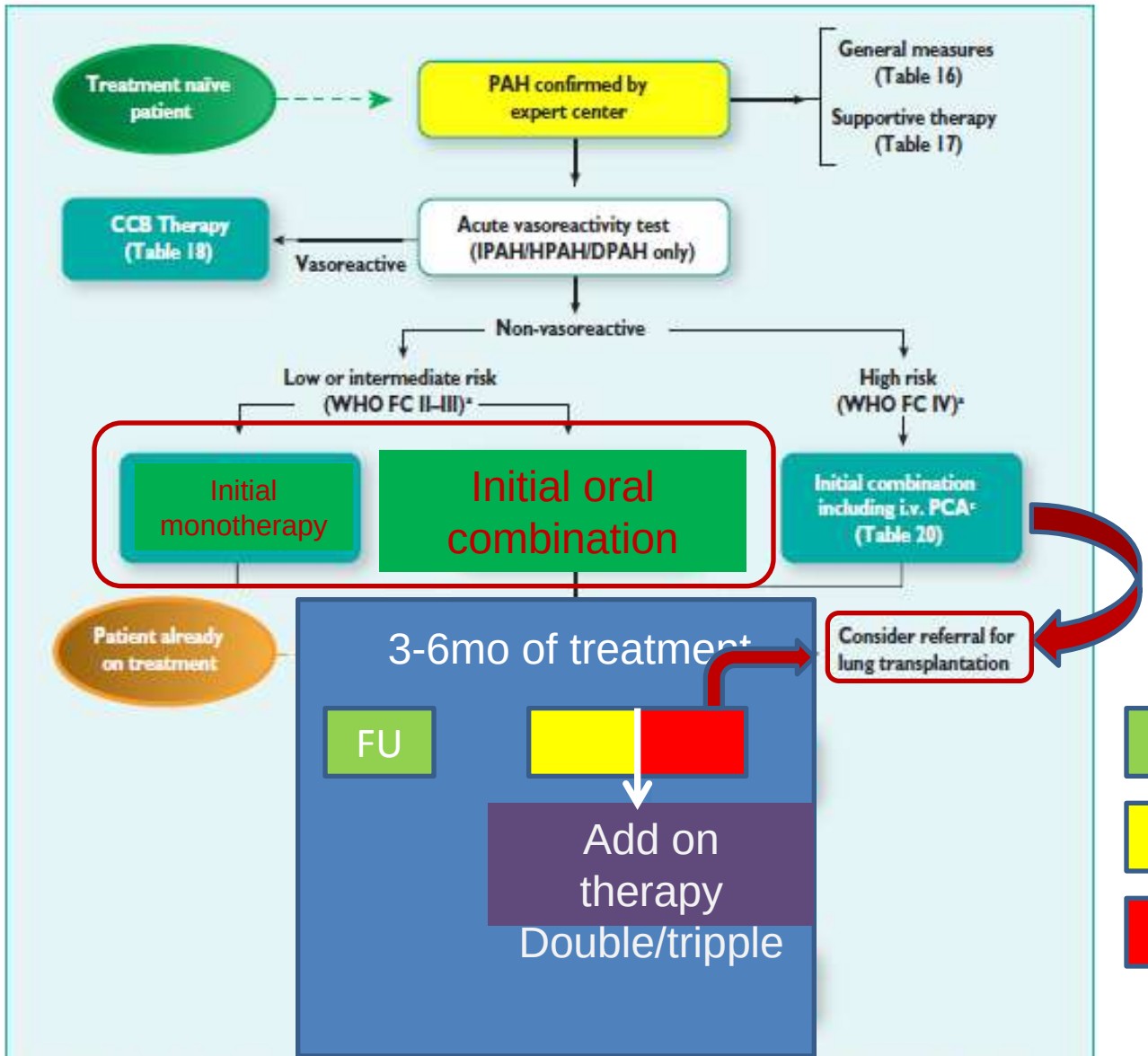
# ESC/ERS GUIDELINES 2015.Treatment algorithm changes



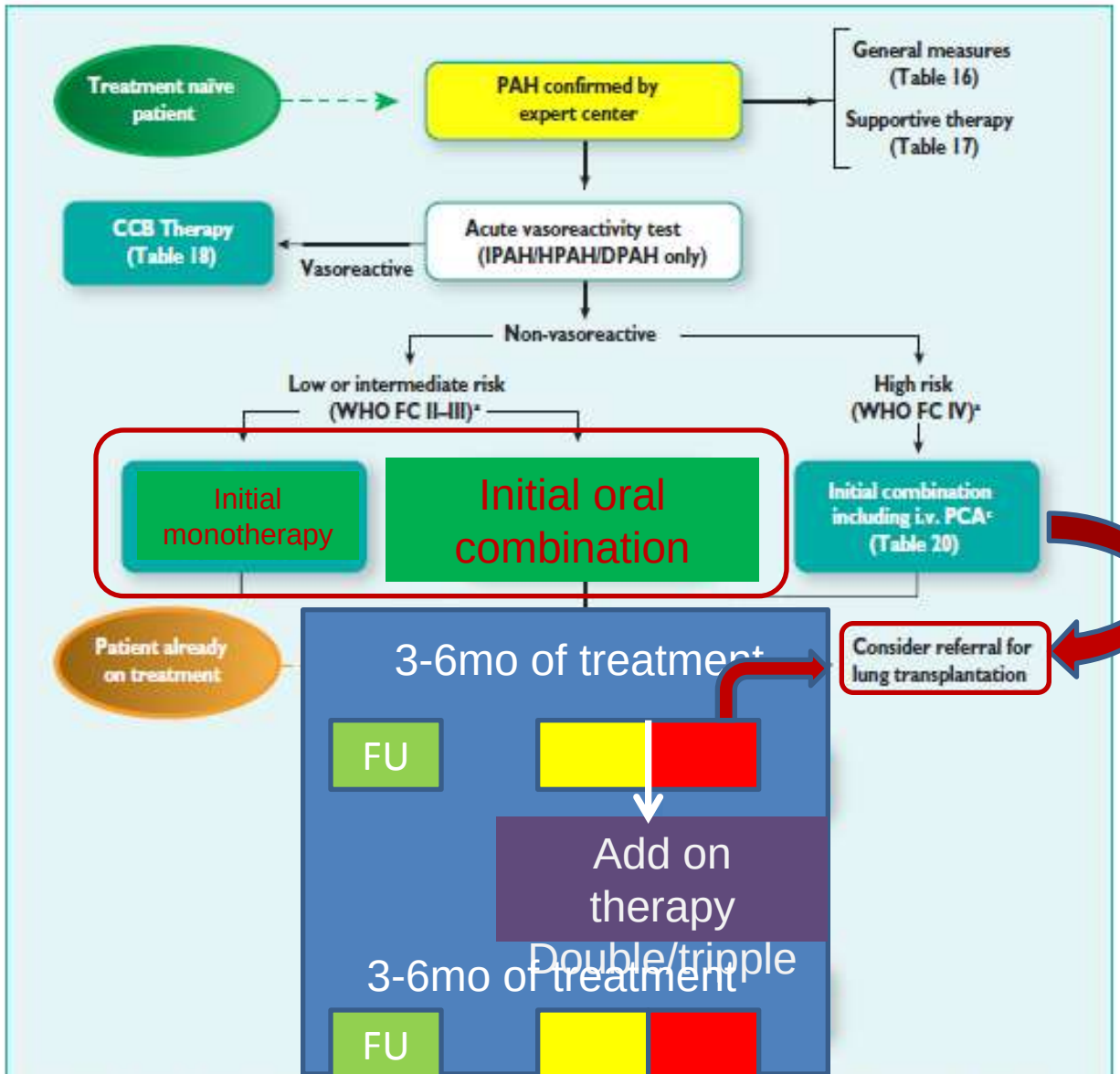
# ESC/ERS GUIDELINES 2015.Treatment algorithm changes



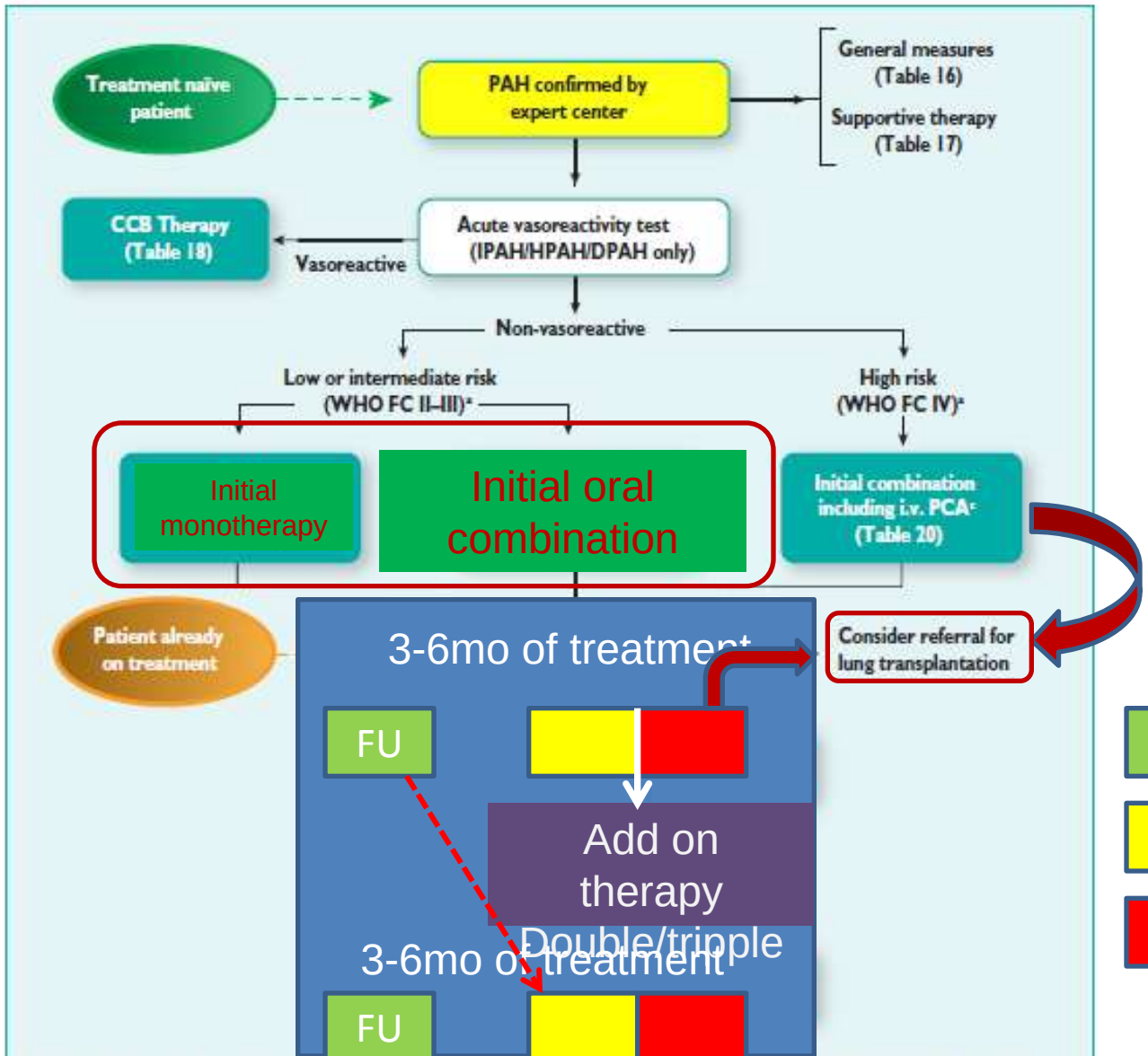
# ESC/ERS GUIDELINES 2015.Treatment algorithm changes



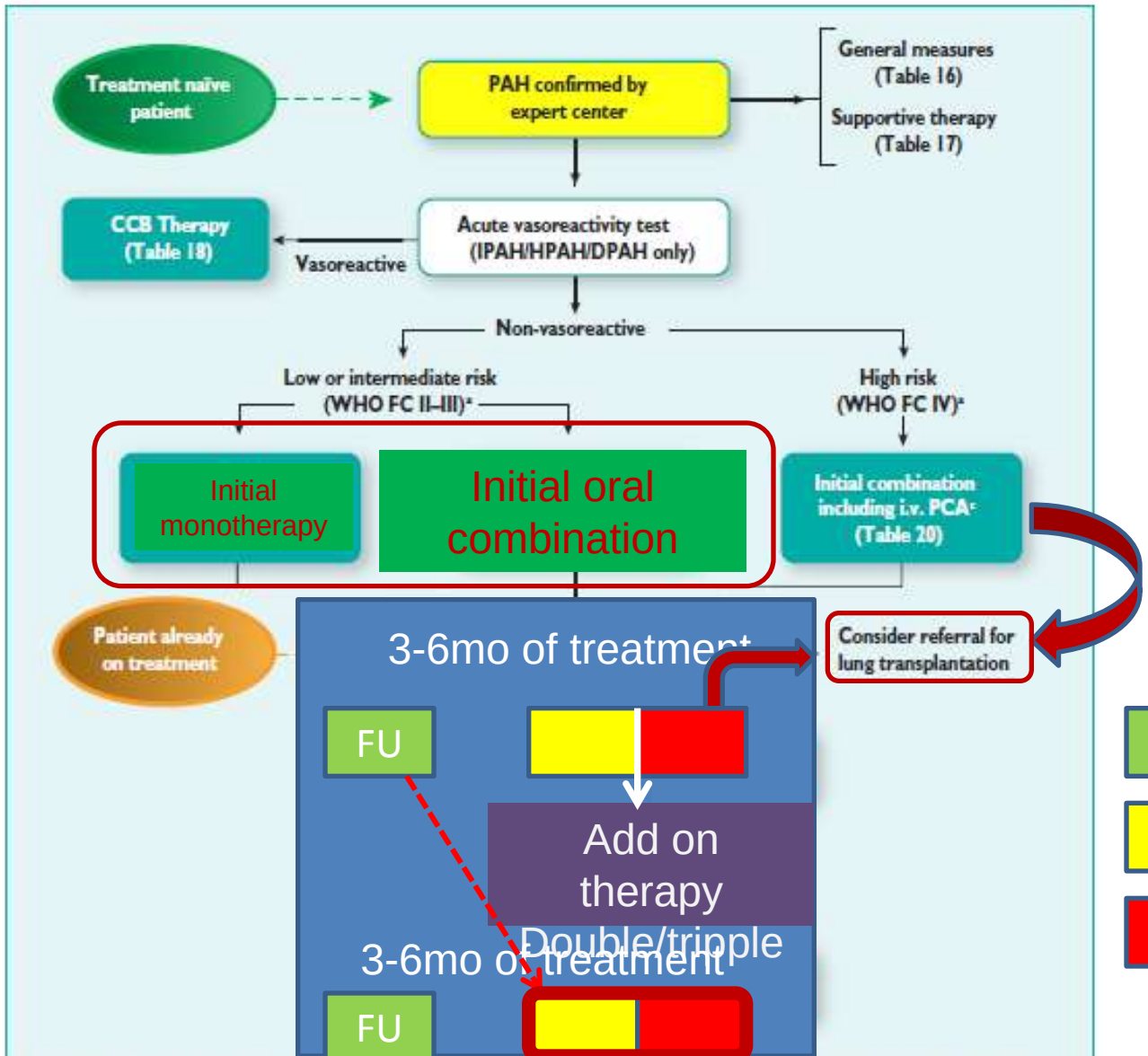
# ESC/ERS GUIDELINES 2015.Treatment algorithm changes



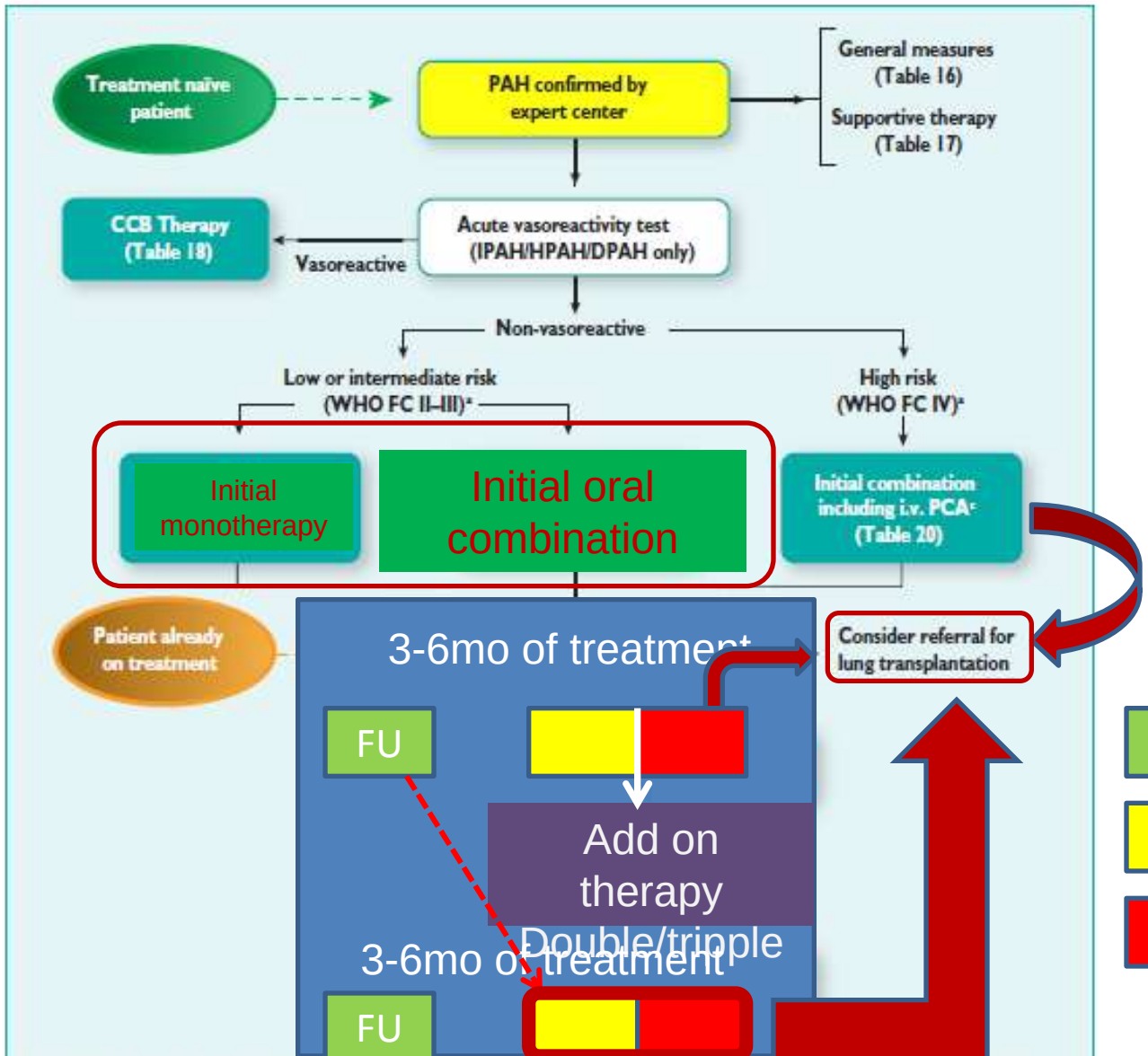
# ESC/ERS GUIDELINES 2015.Treatment algorithm changes



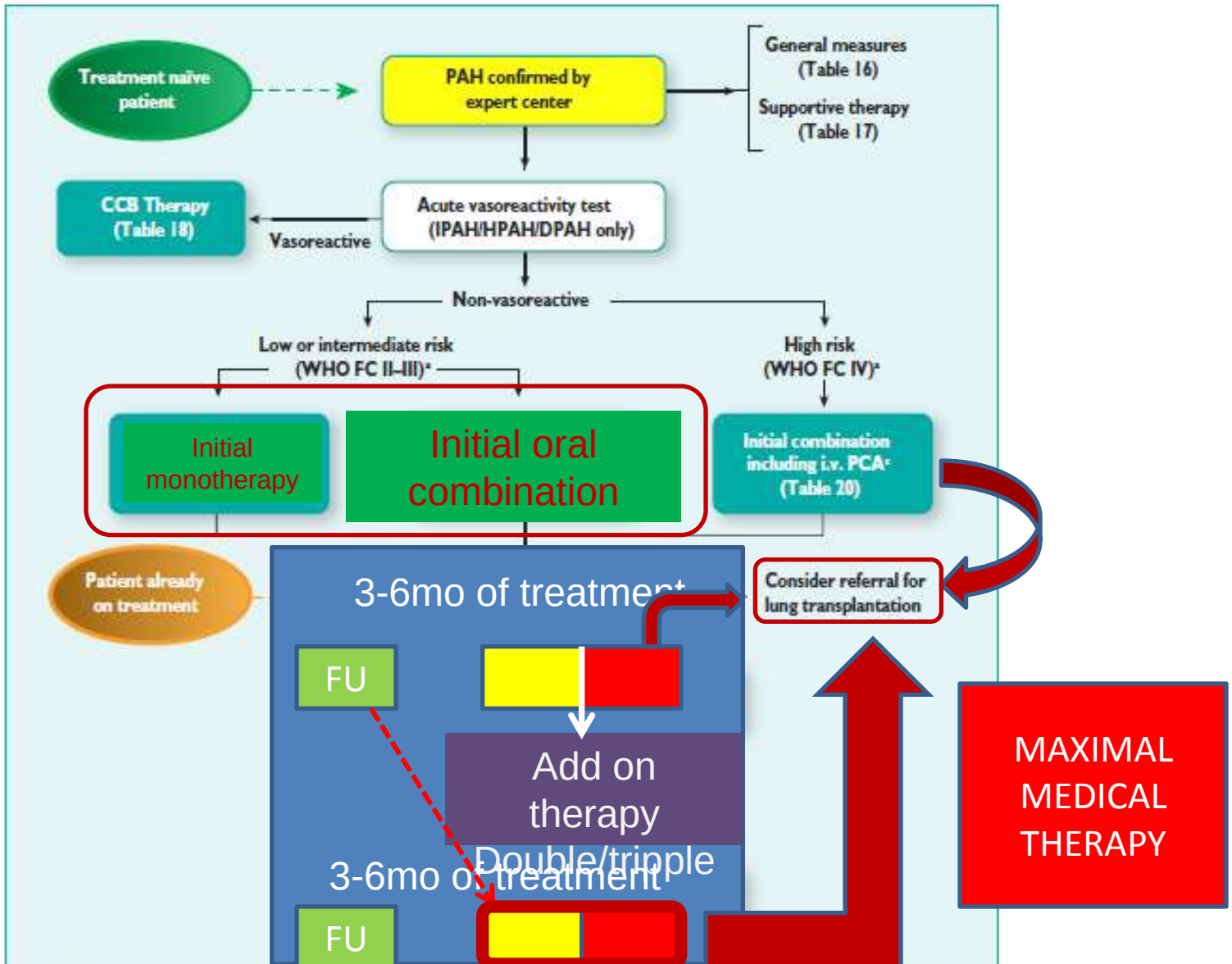
# ESC/ERS GUIDELINES 2015.Treatment algorithm changes



# ESC/ERS GUIDELINES 2015.Treatment algorithm changes

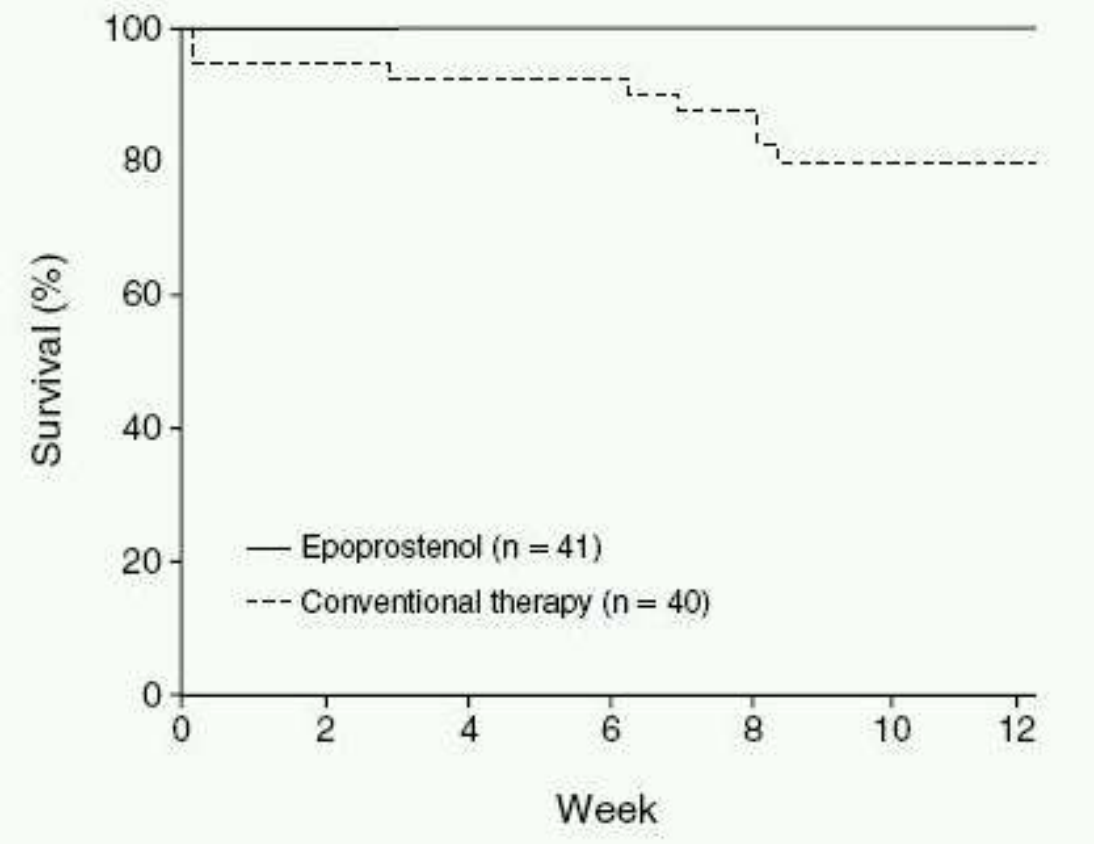


# ESC/ERS GUIDELINES 2015.Treatment algorithm changes



# A COMPARISON OF CONTINUOUS INTRAVENOUS EPOPROSTENOL (PROSTACYCLIN) WITH CONVENTIONAL THERAPY FOR PRIMARY PULMONARY HYPERTENSION

ROBYN J. BARST, M.D., LEWIS J. RUBIN, M.D., WALKER A. LONG, M.D., MICHAEL D. MCGOON, M.D., STUART RICH, M.D., DAVID B. BADESCH, M.D., BERTRON M. GROVES, M.D., VICTOR F. TAPSON, M.D., ROBERT C. BOURGE, M.D., BRUCE H. BRUNDAGE, M.D., SPENCER K. KOERNER, M.D., DAVID LANGLEBEN, M.D., CESAR A. KELLER, M.D., SRINIVAS MURALI, M.D., BARRY F. URETSKY, M.D., LINDA M. CLAYTON, PHARM.D., MARIA M. JÖBSIS, B.A., SHELMER D. BLACKBURN, JR., B.A., DENISE SHORTINO, M.S., JAMES W. CROW, PH.D.,




*

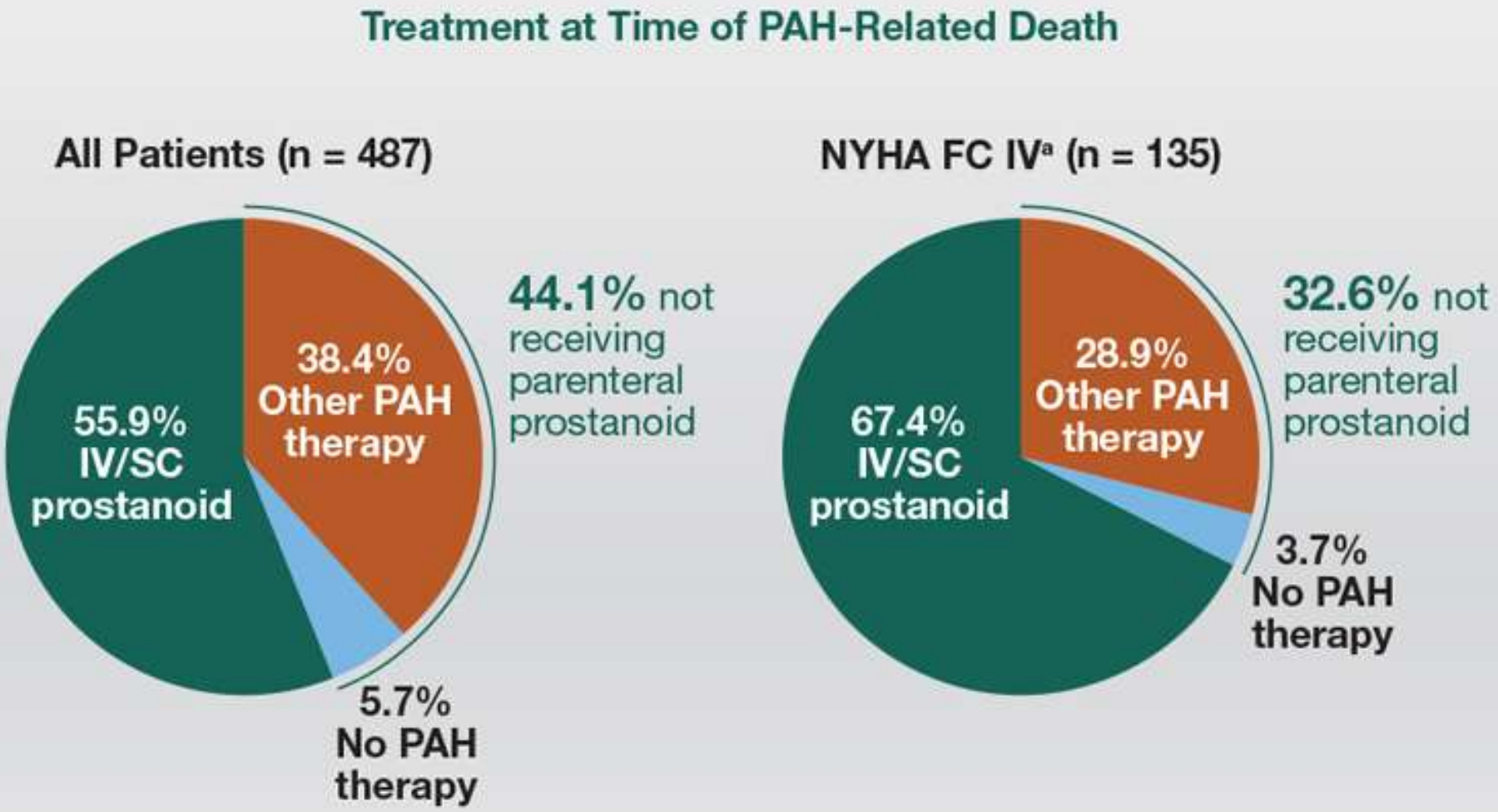
**Anticoagulation and Survival in Pulmonary Arterial Hypertension: Results From the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA)**

Karen M. Olsson, Marion Delcroix, H. Ardeschir Ghofrani, Henning Tiede, Doerte Huscher, Rudolf Speich, Ekkehard Grünig, Gerd Staehler, Stephan Rosenkranz, Michael Halank, Matthias Held, Tobias J. Lange, Juergen Behr, Hans Klose, Martin Claussen, Ralf Ewert, Christian F. Opitz, C. Dario Vizza, Laura Scelsi, Anton Vonk-Noordegraaf, Harald Kaemmerer, J. Simon R. Gibbs, Gerry Coghlan, Joanna Pepke-Zaba, Uwe Schulz, Matthias Gorenflo, David Pittrow and Marius M. Hoeper

*Circulation.* 2014;129:57-65; originally published online September 30, 2013;

| | All PAH Patients n=1283 | Patients Receiving Anticoagulants n=738 (58%) | Patients Not Receiving Anticoagulants n=545 (42%) | *P* Value |
|---|---|---|---|---|
| Age, y (median, Q1-Q3) | 68 (55–75) | 70 (58–76) | 66 (52–75) | 0.001 |
| Female, n (%) | 819 (64%) | 474 (64%) | 345 (63%) | 0.77 |
| Diagnosis | | | | |
| Idiopathic PAH | 800 (62%) | 528 (66%) | 272 (34%) | <0.001 |
| Other forms of PAH* | 483 (38%) | 210 (43%) | 273 (57%) | |
| Functional class, n (%) | | | | |
| I/II | 165 (13%) | 75 (10%) | 90 (17%) | < 0.001 |
| III | 934 (73%) | 539 (73%) | 395 (73%) | |
| IV | 174 (14%) | 120 (16%) | 54 (10%) | |
| 6MWD, m | 303±132 | 293±127 | 317±138 | 0.003 |
| Hemodynamics | | | | |
| RAP, mm Hg | 8.3±5.1 | 8.7±5.2 | 7.8±4.8 | 0.001 |
| PAPm, mm Hg | 44±12 | 45±12 | 43±13 | 0.002 |
| PAWP, mm Hg | 9.5±3.4 | 9.7±3.5 | 9.3±3.4 | 0.06 |
| CI, l/min/m$^2$ | 2.3±0.8 | 2.3±0.8 | 2.4±0.8 | <0.001 |
| PVR, dyn·s·cm$^{-5}$ | 763±445 | 798±468 | 716±408 | 0.001 |
| $SvO_2$ (%) | 63±9 | 62±9 | 65±8 | <0.001 |
| Initial PAH treatment, n (%)† | | | | |
| ERA | 559 (44%) | 309 (42%) | 250 (46%) | 0.16 |
| PDE-5 inhibitors | 738 (58%) | 441 (60%) | 297 (54%) | 0.07 |
| PCA | 27 (2%) | 18 (2%) | 9 (2%) | 0.43 |
| Combination therapy during follow-up, n (%) | 581 (45%) | 389 (53%) | 192 (35%) | <0.001 |

# REVEAL: Use of Parenteral Prostanoids at Time of PAH-Related Death




[a] Among patients assessed <6 months prior to death (n = 308), 135 (43.8%) were in NYHA FC IV.

| 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.)<br>$VE/VCO_2$ slope <36 | Peak $VO_2$<br>11–15 ml/min/kg (35–65% pred.)<br>$VE/VCO_2$ slope 36–44.9 | Peak $VO_2$ <11 ml/min/kg (<35% pred.)<br>$VE/VCO_2$ ≥45 |
| NT-proBNP plasma levels | BNP <50 ng/l<br>NT-proBNP <300 ng/ml | BNP 50–300 ng/l<br>NT-proBNP 300–1400 ng/l | BNP >300 ng/l<br>NT-proBNP >1400 ng/l |
| Imaging (echocardiography, CMR imaging) | RA area <18 $cm^2$<br>No pericardial effusion | RA area 18–26 $cm^2$<br>No or minimal, pericardial effusion | RA area >26 $cm^2$<br>Pericardial effusion |
| Haemodynamics | RAP <8 mmHg<br>CI ≥2.5 l/min/$m^2$<br>$SvO_2$ >65% | RAP 8–14 mmHg<br>CI 2.0–2.4 l/min/$m^2$<br>$SvO_2$ 60–65% | RAP >14 mmHg<br>CI <2.0 l/min/$m^2$<br>$SvO_2$ <60% |

# Proposed Simpified Risk Stratification in PAH

| Prognostic Criteria | Low risk variables | Intermediate risk variables | High risk variables |
|---|---|---|---|
| A. WHO FC | I, II | III | IV |
| B. 6MWT | >440m | 165-440m | <165m |
| C. BNP/NT-proBNP plama levels OR RAP | BNP<50ng/L NT-proBNP<300ng/L OR <8mmHg | BNP 50-300ng/L NT-proBNP 300-1400ng/L OR 8-14mmHg | BNP >300ng/L NT-proBNP>1400ng/L OR >14mmHg |
| D. CI OR SvO2 | >2.5L/min/$m^2$ OR >65% | 2-2.4L/min/$m^2$ OR 60-65% | <2L/min/$m^2$ OR <60% |

# Proposed Simpified Risk Stratification in PAH

| Low risk | Intermediate risk variables | High risk variables |
|---|---|---|
| At least 3 low risk criteria and no high risk criteria | Definitions of high or low risk criteria not fullfiled | At least 2 high risk criteria including CI or $SvO_2$ |

**Table 4** Comprehensive clinical classification of pulmonary hypertension (updated from Simonneau et al.[5])

**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

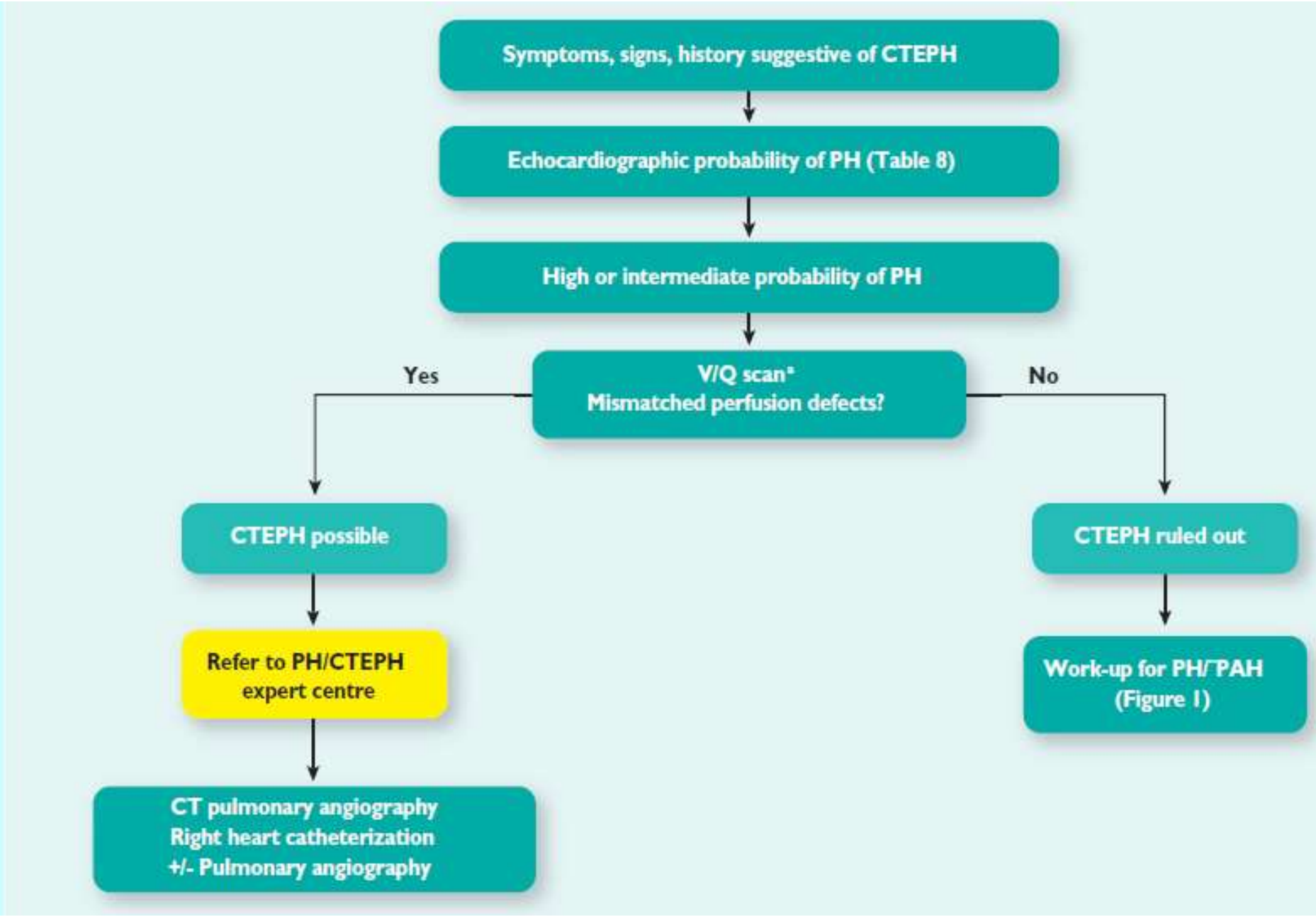
**3. Pulmonary hypertension due to lung diseases and/or hypoxia**
- 3.1 Chronic obstructive pulmonary disease
- 3.2 Interstitial lung disease
- 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
- 3.4 Sleep-disordered breathing
- 3.5 Alveolar hypoventilation disorders
- 3.6 Chronic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

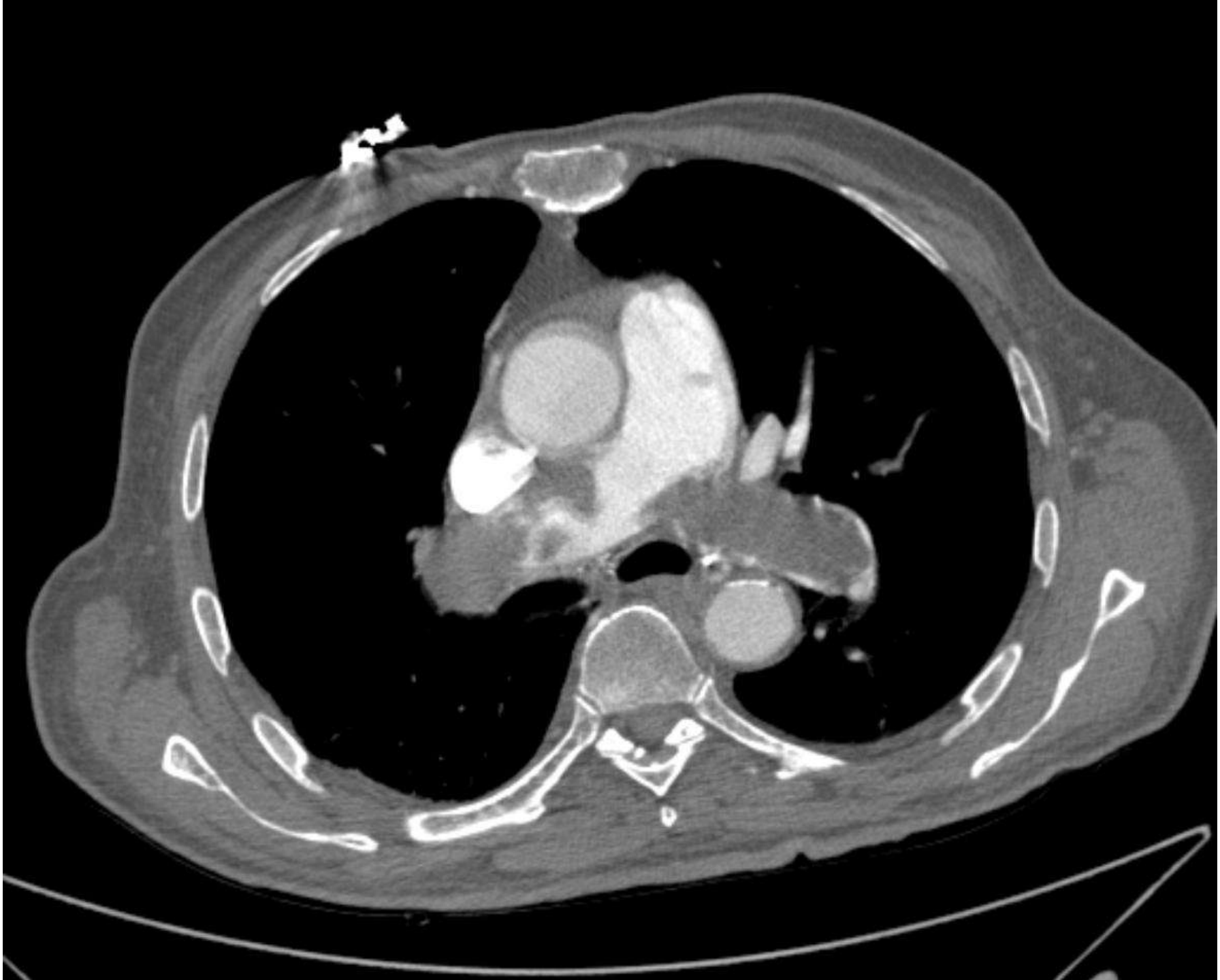
**4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions**
- 4.1 Chronic thromboembolic pulmonary hypertension
- 4.2 Other pulmonary artery obstructions
  - 4.2.1 Angiosarcoma
  - 4.2.2 Other intravascular tumors
  - 4.2.3 Arteritis
  - 4.2.4 Congenital pulmonary arteries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

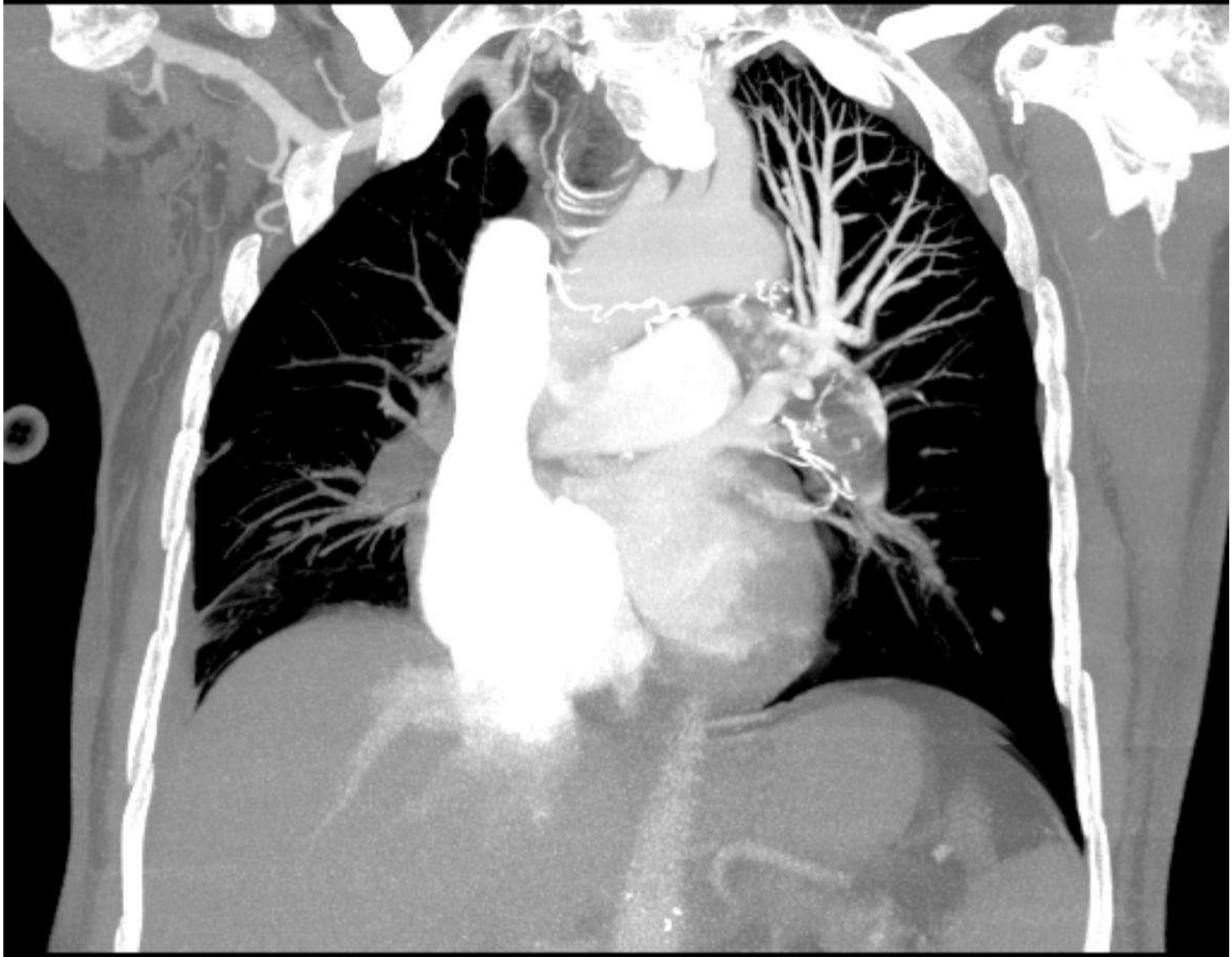
**5. Pulmonary hypertension with unclear and/or multifactorial mechanisms**
- 5.1 Haematological disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy
- 5.2 Systemic disorders, sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
- 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
- 5.4 Others: pulmonary tumoral thrombotic microangiopathy, fibrosing mediastinitis, chronic renal failure (with/without dialysis), segmental pulmonary hypertension

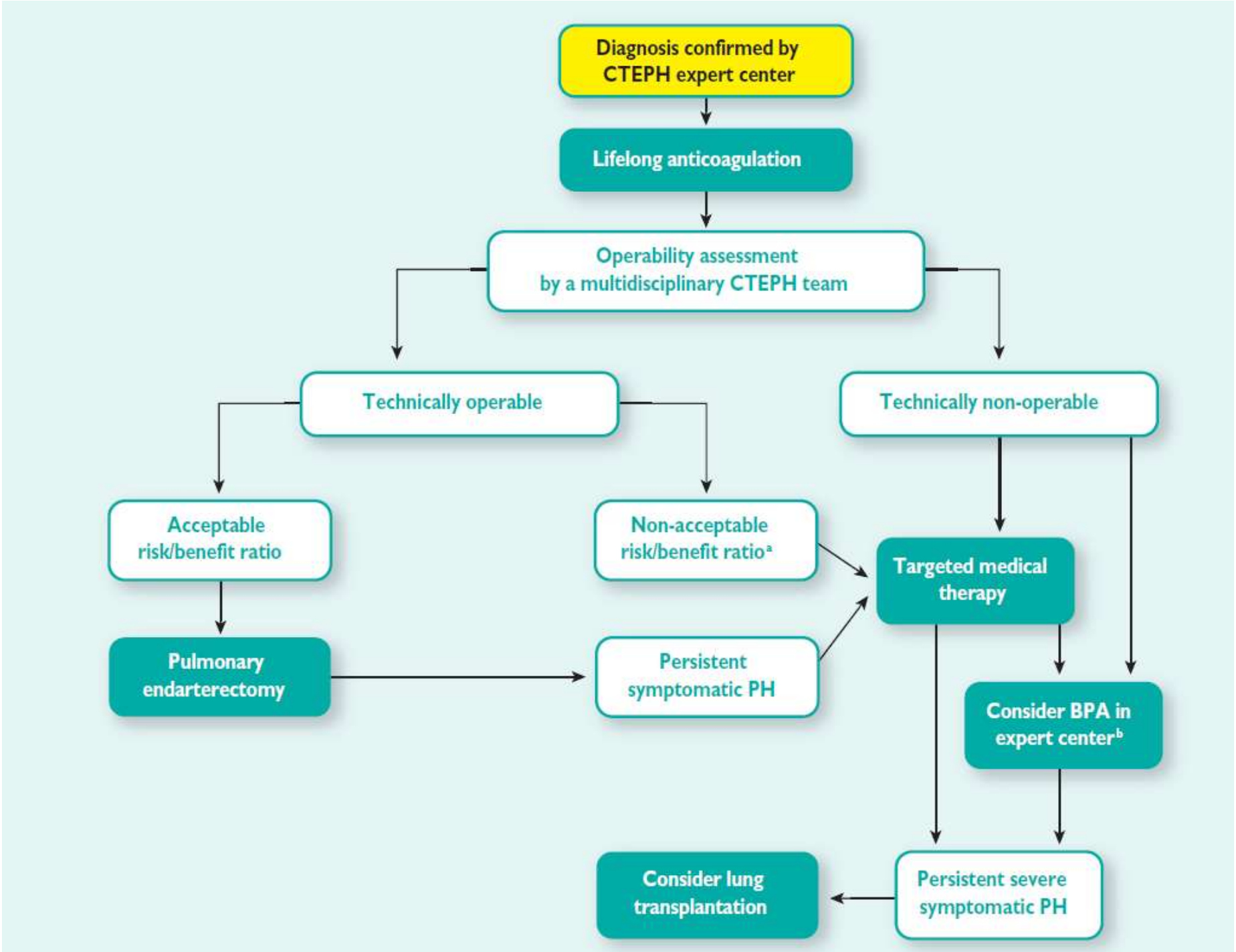
**4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions**

- 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)


Symptoms, signs, history suggestive of CTEPH
Echocardiographic probability of PH (Table 8)
High or intermediate probability of PH
V/Q scan*
Mismatched perfusion defects?
Yes
No
CTEPH possible
Refer to PH/CTEPH expert centre
CT pulmonary angiography
Right heart catheterization
+/- Pulmonary angiography
CTEPH ruled out
Work-up for PH/PAH (Figure 1)






Diagnosis confirmed by CTEPH expert center
Lifelong anticoagulation
Operability assessment by a multidisciplinary CTEPH team
Technically operable
Technically non-operable
Acceptable risk/benefit ratio
Non-acceptable risk/benefit ratio[a]
Targeted medical therapy
Pulmonary endarterectomy
Persistent symptomatic PH
Consider BPA in expert center[b]
Consider lung transplantation
Persistent severe symptomatic PH


DANGER
MINES

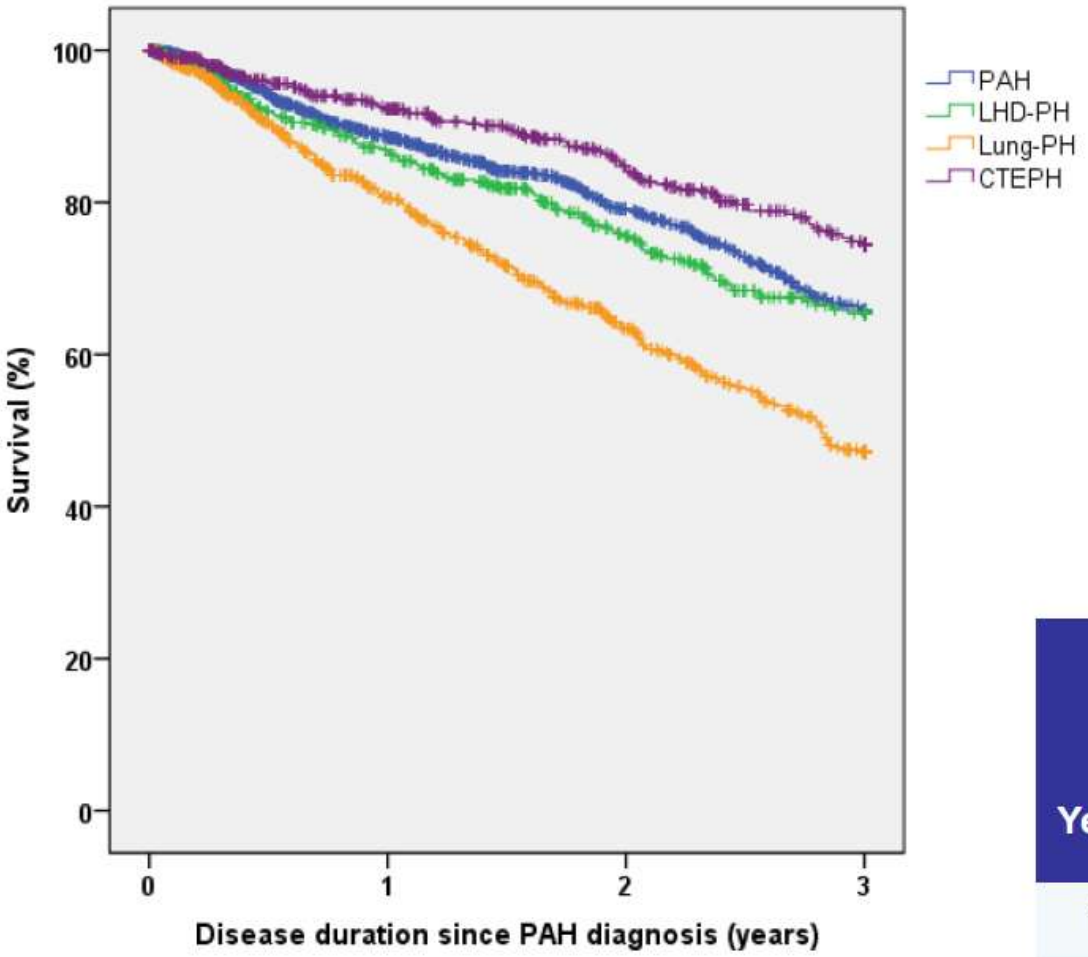
**Table 31 Management of pulmonary hypertension in left heart disease**

| Recommendations | Class[a] | Level[b] | Ref.[c] |
|---|---|---|---|
| Optimization of the treatment of the underlying condition is recommended before considering assessment of PH-LHD (i.e. treating structural heart disease) | I | B | 396 |
| It is recommended to identify other causes of PH (i.e. COPD, sleep apnoea syndrome, PE, CTEPH) and to treat them when appropriate before considering assessment of PH-LHD | I | C | 396 |
| It is recommended to perform invasive assessment of PH in patients on optimized volume status | I | C | |
| Patients with PH-LHD and a severe pre-capillary component as indicated by a high DPG and/or high PVR should be referred to an expert PH centre for a complete diagnostic workup and an individual treatment decision | IIa | C | |
| The importance and role of vasoreactivity testing is not established in PH-LHD, except in patients who are candidates for heart transplantation and/or LV assist device implantation | III | C | 396 |
| The use of PAH-approved therapies is not recommended in PH-LHD | III | C | 396 |

**Table 33 Recommendations for pulmonary hypertension due to lung diseases**

| Recommendations | Class[a] | Level[b] | Ref.[c] |
|---|---|---|---|
| Echocardiography is recommended for the non-invasive diagnostic assessment of suspected PH in patients with lung disease | I | C | 403, 405 |
| Referral to an expert centre is recommended[d] in patients with echocardiographic signs of severe PH and/or severe right ventricular dysfunction | I | C | |
| The optimal treatment of the underlying lung disease, including long-term $O_2$ therapy in patients with chronic hypoxaemia, is recommended in patients with PH due to lung diseases | I | C | 169 |
| Referral to PH expert center should be considered for patients with signs of severe PH/severe RV failure for individual-based treatment | IIa | C | |
| RHC is not recommended for suspected PH in patients with lung disease, unless therapeutic consequences are to be expected (e.g. lung transplantation, alternative diagnoses such as PAH or CTEPH, potential enrolment in a clinical trial) | III | C | 169 |
| The use of drugs approved for PAH is not recommended in patients with PH due to lung diseases | III | C | 411–416 |

# Survival of PAH vs Non-PAH patients




| Number of cases | | | | |
|---|---|---|---|---|
| Year | PAH | LHD -PH | Lung- PH | CTEPH |
| 0 | 1,495 | 528 | 733 | 541 |
| 1 | 914 | 336 | 446 | 361 |
| 2 | 615 | 212 | 269 | 251 |
| 3 | 403 | 124 | 142 | 158 |

| Survival after diagnosis | | | | |
|---|---|---|---|---|
| Year | PAH | LHD- PH | Lung- PH | CTEPH |
| 1 | 88.6% | 86.7% | 80.5% | 92.3% |
| 2 | 79.1% | 75.5% | 63.4% | 84.1% |
| 3 | 65.7% | 65.5% | 47.1% | 74.4% |

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# Pre-Capillary, Combined, and Post-Capillary Pulmonary Hypertension

## A Pathophysiological Continuum

Christian F. Opitz, MD,[a,b] Marius M. Hoeper, MD,[c] J. Simon R. Gibbs, MD,[d] Harald Kaemmerer, MD, VMD,[e] Joanna Pepke-Zaba, MD,[f] J. Gerry Coghlan, MD,[g] Laura Scelsi, MD,[h] Michele D'Alto, MD,[i] Karen M. Olsson, MD,[c] Silvia Ulrich, MD,[j] Werner Scholtz, MD,[k] Uwe Schulz, MD,[l] Ekkehard Grünig, MD,[m] Carmine D. Vizza, MD,[n] Gerd Staehler, MD,[o] Leonhard Bruch, MD,[p] Doerte Huscher, MSc, PhD,[q,r] David Pittrow, MD,[s] Stephan Rosenkranz, MD[t,u]

mPAP>25, W≤15

Atypical (≥ 3 risk factors for left heart disease)

- Arterial hypertension
- Coronary artery dis
- Diabetes
- Atrial fibrillation
- BMI>30 kg/m2

HEFpEF

- mPAP>25, W>15
- EF>45%
- Diastolic dysfunction

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**TABLE 1** Baseline Characteristics

| | All Patients (N = 786) | Typical IPAH (n = 421) | Atypical IPAH (n = 139) | Typical vs. Atypical IPAH p Value | PH-HFpEF (n = 226) | Typical IPAH vs. PH-HFpEF p Value | Atypical IPAH vs. PH-HFpEF p Value |
|---|---|---|---|---|---|---|---|
| Age, yrs | 66.6 ± 15.0 | 61.5 ± 17.3 | 71.3 ± 9.2 | <0.001 | 73.2 ± 8.3 | <0.001 | 0.434 |
| Female | 467 (59.4) | 250 (59.4) | 77 (55.4%) | 1.000 | 140 (61.9) | 1.000 | 0.686 |
| BMI, kg/m$^2$ | 28.1 (24.5-32.6) | 26.0 (23.3-29.8) | 32.2 (28.3-36.0) | <0.001 | 29.6 (25.7-34.0) | <0.001 | 0.002 |
| WHO-FC | | | | 0.089 | | <0.001 | 0.315 |
| I/II | 91 (11.8) | 71 (17.4) | 12 (8.8) | | 8 (3.6) | | |
| III | 540 (70.3) | 275 (67.6) | 96 (70.6) | | 169 (75.1) | | |
| IV | 137 (17.8) | 61 (15.0) | 28 (20.6) | | 48 (21.3) | | |
| 6MWD, m | 289.5 ± 121.8 | 319.0 ± 123.5 | 250.5 ± 104.2 | <0.001 | 260.0 ± 115.0 | <0.001 | 0.787 |
| RAP, mm Hg | 9.8 ± 5.4 | 8.5 ± 5.2 | 8.9 ± 4.8 | 0.615 | 12.9 ± 4.8 | <0.001 | <0.001 |
| PAPm, mm Hg | 46.0 ± 11.9 | 46.9 ± 13.3 | 43.9 ± 10.7 | 0.025 | 45.7 ± 9.4 | 0.437 | 0.326 |
| PAWP, mm Hg | 12.5 ± 6.0 | 9.3 ± 3.4 | 10.0 ± 3.6 | 0.186 | 19.9 ± 4.4 | <0.001 | <0.001 |
| TPG, mm Hg | 33.5 ± 13.1 | 37.6 ± 13.6 | 33.9 ± 11.1 | 0.006 | 25.8 ± 9.1 | <0.001 | <0.001 |
| Cardiac index, l/min/m$^2$ | 2.2 ± 0.8 | 2.3 ± 0.8 | 2.2 ± 0.8 | 0.629 | 2.2 ± 0.7 | 0.653 | 0.988 |
| PVR, Wood Units | 9.6 ± 6.7 | 10.8 ± 6.0 | 9.8 ± 10.6 | 0.309 | 7.0 ± 3.4 | <0.001 | <0.001 |
| $SvO_2$, % | 62.2 ± 9.0 | 62.1 ± 9.9 | 62.7 ± 9.0 | 0.804 | 62.1 ± 6.9 | 0.999 | 0.863 |
| BNP, pg/ml | 269 (127-541) | 287 (119-543) | 200 (115-469) | 1.000 | 310 (186-638) | 0.963 | 0.312 |
| NT-proBNP, pg/ml | 1,738 (621-3,891) | 1,435 (541-3,888) | 1,683 (478-2,815) | 1.000 | 2,196 (1,125-4,285) | 0.021 | 0.066 |
| Arterial hypertension | 66.5 | 43.2 | 98.6 | <0.001 | 91.9 | <0.001 | 0.021 |
| CAD | 32.0 | 15.7 | 59.7 | <0.001 | 46.4 | <0.001 | 0.049 |
| Diabetes mellitus | 30.6 | 10.7 | 74.8 | <0.001 | 41.2 | <0.001 | <0.001 |
| AF | 28.9 | 10.7 | 42.4 | <0.001 | 54.4 | <0.001 | 0.187 |
| BMI >30 kg/m$^2$ | 37.6 | 23.5 | 65.2 | <0.001 | 47.1 | <0.001 | 0.002 |

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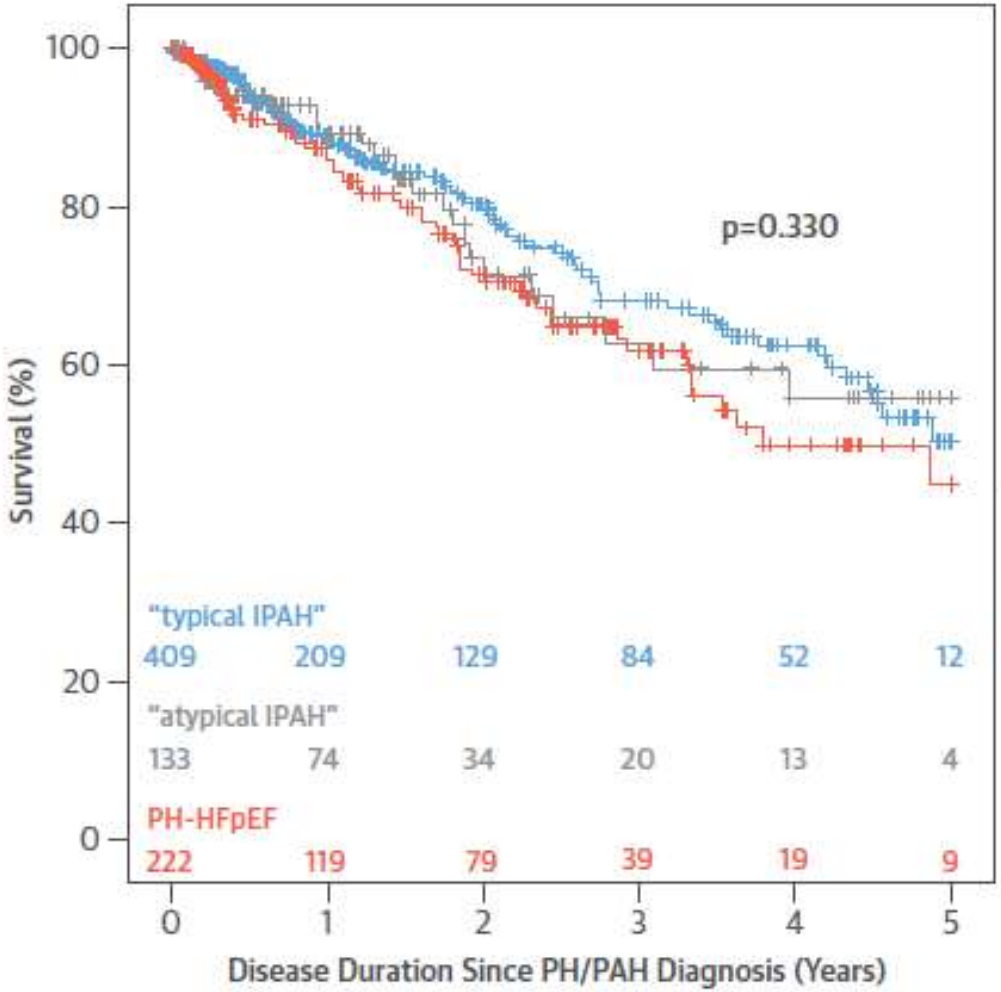
**FIGURE 2** 5-Year Overall Survival




| Years after diagnosis | "typical IPAH" | "atypical IPAH" | $p_1$ | HFpEF | $p_2$ | $p_3$ |
|---|---|---|---|---|---|---|
| 0 | 100% | 100% | | 100% | | |
| 1 | 88.5% | 89.1% | | 86.7% | | |
| 2 | 80.3% | 73.4% | 1.000 | 71.2% | 0.384 | 1.000 |
| 3 | 68.0% | 62.6% | | 61.7% | | |
| 4 | 62.4% | 55.7% | | 49.8% | | |
| 5 | 50.2% | 55.7% | | 44.8% | | |

# PAH in elderly patients – Why are so many male patients affected?

- Is there a smoking-related pulmonary vasculopathy presenting as a vanishing capillary syndrome?

# Loss of pulmonary capillaries due to apoptosis?

## Inducible NOS Inhibition Reverses Tobacco-Smoke-Induced Emphysema and Pulmonary Hypertension in Mice

Michael Seimetz,[1,5] Nirmal Parajuli,[1,5] Alexandra Pichl,[1] Florian Veit,[1] Grazyna Kwapiszewska,[1] Friederike C. Weisel,[1] Katrin Milger,[1] Bakytbek Egemnazarov,[1] Agnieszka Turowska,[4] Beate Fuchs,[1] Sandeep Nikam,[2] Markus Roth,[1] Akylbek Sydykov,[1] Thomas Medebach,[1] Walter Klepetko,[3] Peter Jaksch,[3] Rio Dumitrascu,[1] Holger Gam,[4] Robert Voswinckel,[2] Sawa Kostin,[2] Werner Seeger,[1] Ralph T. Schermuly,[2] Friedrich Grimminger,[1] Hossein A. Ghofrani,[1] and Norbert Weissmann[1,*]

Cell *147*, 293–305, October 14, 2011

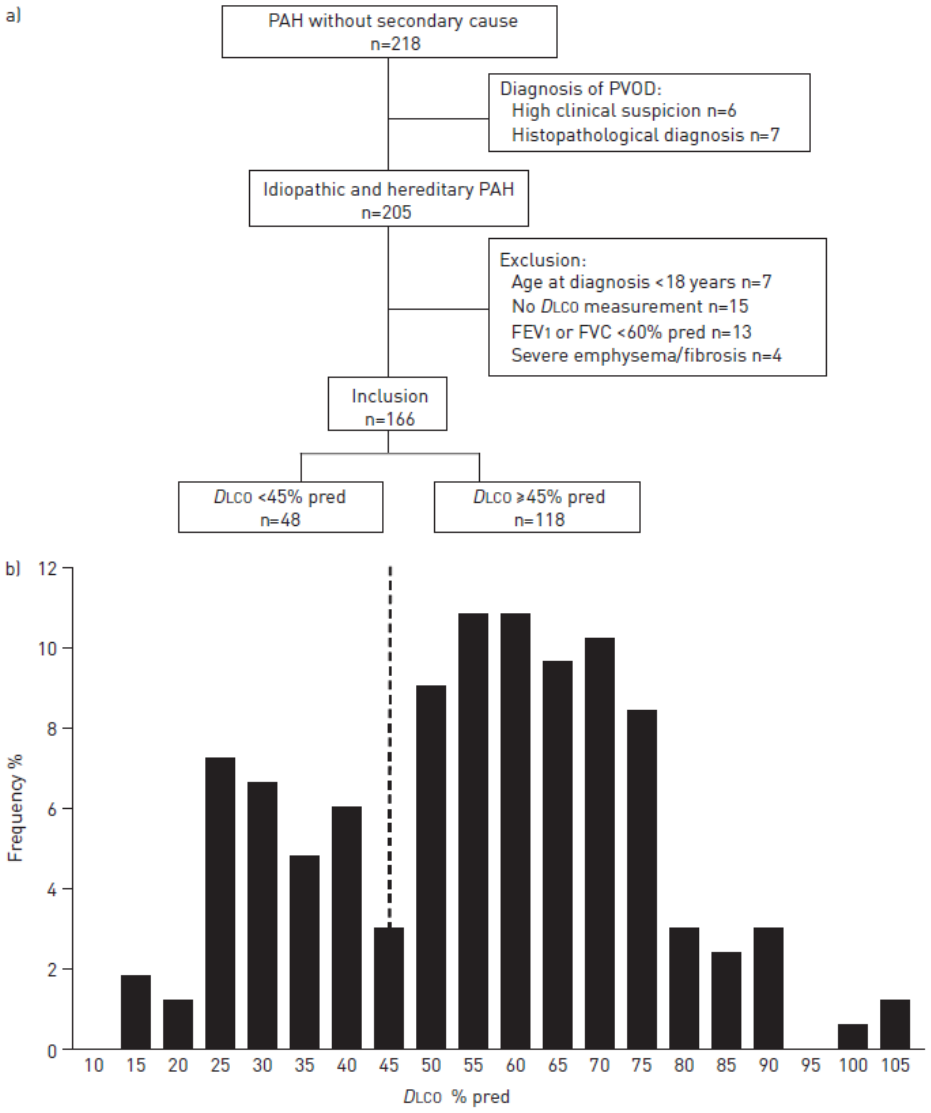
# PAH with a low DLCO

ORIGINAL ARTICLE
PULMONARY VASCULAR DISEASES

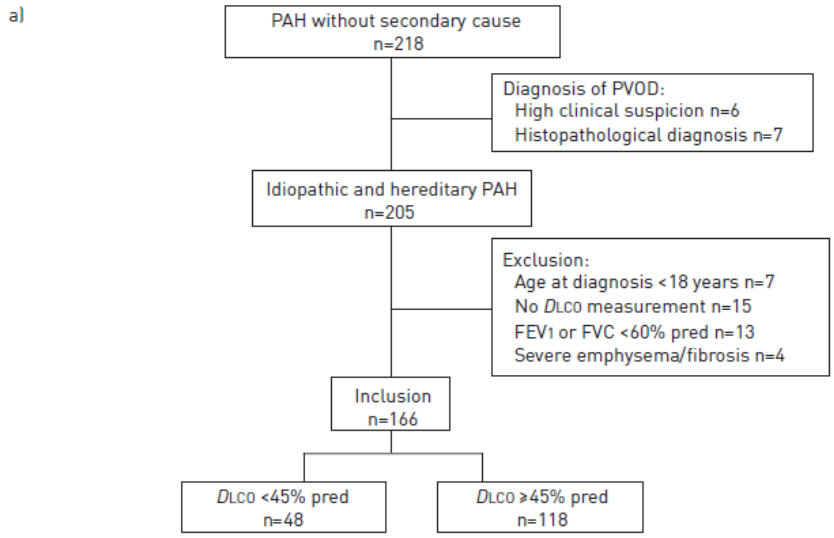
## Severely reduced diffusion capacity in idiopathic pulmonary arterial hypertension: patient characteristics and treatment responses

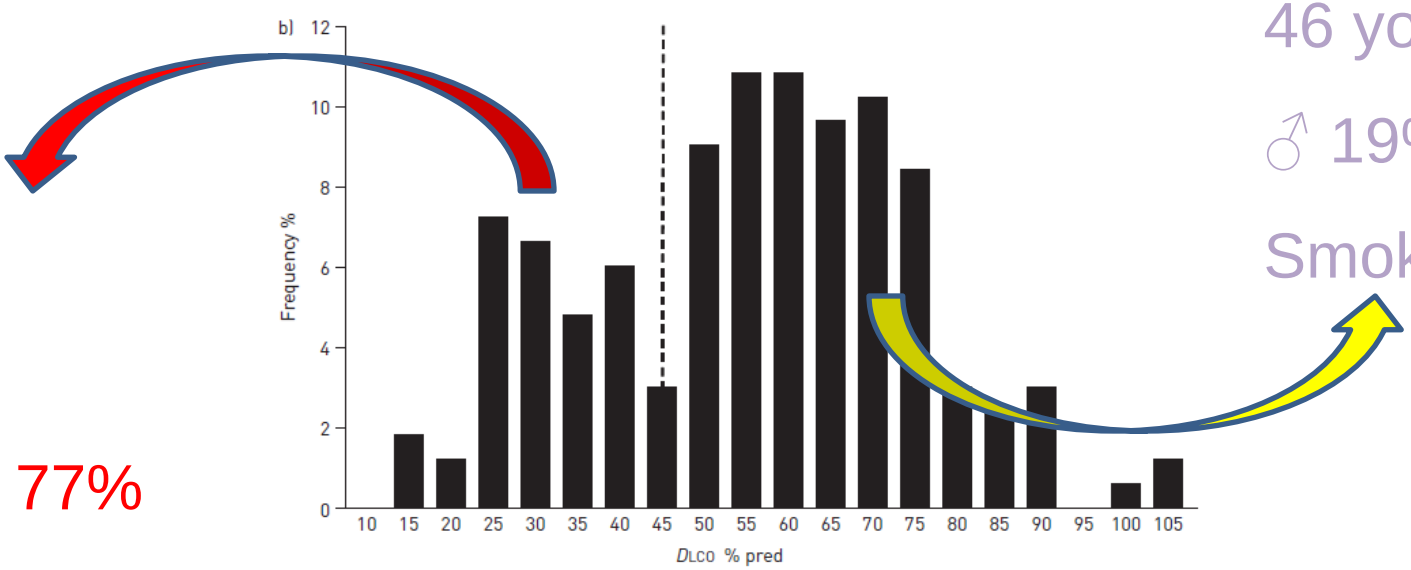
Pia Trip[1], Esther J. Nossent[1], Frances S. de Man[1,2], Inge A.H. van den Berk[3], Anco Boonstra[1], Herman Groepenhoff[1], Edward M. Leter[4], Nico Westerhof[1,2], Katrien Grünberg[5], Harm-Jan Bogaard[1] and Anton Vonk-Noordegraaf[1]

# PAH with a low DLCO



# PAH with a low DLCO




67 yo

♂ 50%

Smoking 77%

46 yo

♂ 19%

Smoking 48%

# Similar treatment response regardless of DLCO

Research Article

Pulmonary Circulation

## Treatment response in patients with idiopathic pulmonary arterial hypertension and a severely reduced diffusion capacity

Cathelijne E. van der Bruggen[1,*], Onno A. Spruijt[1,*], Esther J. Nossent[1], Pia Trip[1], J. Tim Marcus[2], Frances S. de Man[1], Harm Jan Bogaard[1] and Anton Vonk Noordegraaf[1]

[1]Department of Pulmonary Medicine, VU University Medical Center, Amsterdam, The Netherlands; [2]Department of Physics and Medical Technology, VU University Medical Center, Amsterdam, The Netherlands

**Abstract**

Patients with idiopathic pulmonary arterial hypertension (IPAH) and a reduced diffusion capacity of the lung for carbon monoxide (DLCO) have a worse survival compared to IPAH patients with a preserved DLCO. Whether this poor survival can be explained by unresponsiveness to pulmonary hypertension (PH)-specific vasodilatory therapy is unknown. Therefore, the aim of this study was to evaluate the hemodynamic and cardiac response to PH-specific vasodilatory therapy in patients with IPAH and a reduced DLCO. Retrospectively, we studied treatment naïve hereditary and IPAH patients diagnosed between January 1990 and May 2015 at the VU University Medical Center. After exclusion of participants without available baseline DLCO measurement or right heart catheterization data and participants carrying a BMPR2 mutation, 166 participants could be included in this study. Subsequently, hemodynamics, cardiac function, exercise capacity, and oxygenation at baseline and after PH-specific vasodilatory therapy were compared between IPAH patients with a preserved DLCO (DLCO >62%), IPAH patients with a moderately reduced DLCO (DLCO 43–62%), and IPAH patients with a severely reduced DLCO (DLCO <43%). Baseline hemodynamics and right ventricular function were not different between groups. Baseline oxygenation was worse in patients with IPAH and a severely reduced DLCO. Hemodynamics and cardiac function improved in all groups after PH-specific vasodilatory therapy without worsening of oxygenation at rest or during exercise. Patients with IPAH and a severely reduced DLCO show a similar response to PH-specific vasodilatory therapy in terms of hemodynamics, cardiac function, and exercise capacity as patients with IPAH and a moderately reduced or preserved DLCO.

**Keywords**

diffusion capacity of the lung for carbon monoxide (DLCO), oxygenation, pulmonary arterial hypertension (PAH), right ventricular (RV) function

Date received: 24 June 2016; accepted: 25 October 2016

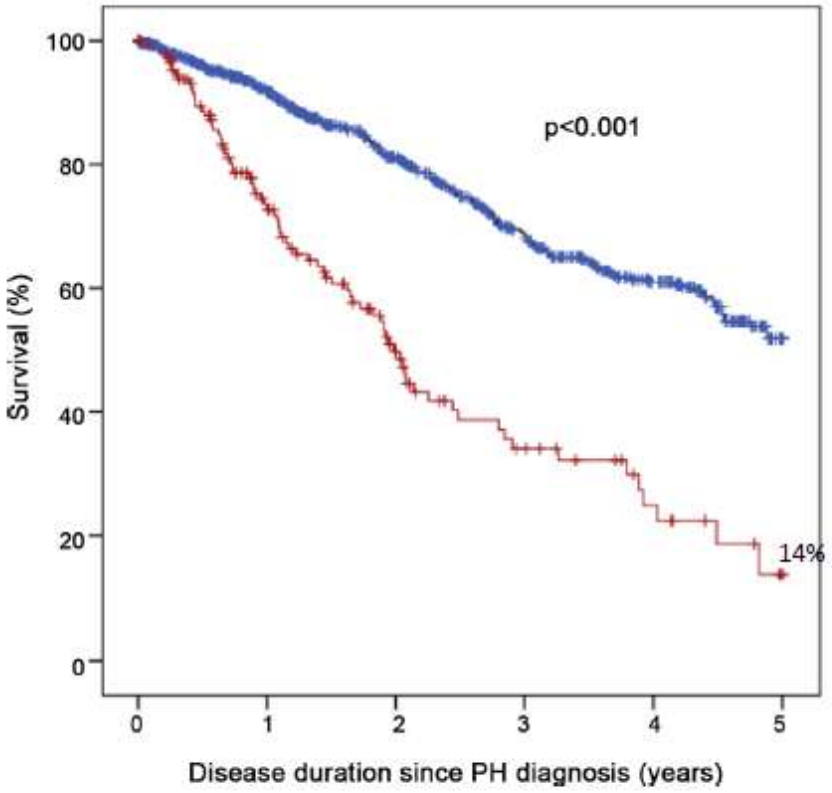
Pulmonary Circulation 2017; 7(1) 137–144

# Pulmonary Hypertension in Patients with Chronic Fibrosing Idiopathic Interstitial Pneumonias

Marius M. Hoeper[1]*, Juergen Behr[2], Matthias Held[3], Ekkehard Grunig[4], C. Dario Vizza[5], Anton Vonk-Noordegraaf[6], Tobias J. Lange[7], Martin Claussen[8], Christian Grohé[9], Hans Klose[10], Karen M. Olsson[1], Thomas Zelniker[11], Claus Neurohr[2], Oliver Distler[12], Hubert Wirtz[13], Christian Opitz[14], Doerte Huscher[15], David Pittrow[16], J. Simon R. Gibbs[17]

PLOS ONE

Dec 2015




**COMPERA** registry

PH-IIP n=151 (IPF: 113, NSIP:38)

79% severe PH (mPAP>35mmmHg)

FVC 62.9±20.0, DLco 28.5±15.8

- 88% PDE5i
- Short-term response to therapy (6MWT & FC) comparable to that of IPAH
- Dismal survival

# In conclusion

- An individual comprehensive risk assessment should guide the management of patient with PAH
- Combination therapy has become the mainstay for our approach to treatment
- A proactive approach is necessary to reach our treatment goals (move patients into low risk category and ensure long term outcome).

# Thank you for your attention