ACTION

Pneumologi in azione
nell'ipertensione arteriosa polmonare (PAH)

Classificazione e Algoritmo diagnostico

Davide Elia

ACTION

Pneumologi in azione
nell'ipertensione arteriosa polmonare (PAH)

✓ L'ipertensione polmonare è una condizione emodinamica e fisiopatologica definita come aumento dei valori di **PAPm ≥25 mmHg** a riposo documentato mediante cateterismo cardiaco destro.

✓Pazienti con valori di mPAP compresi tra 21 e 24 mmHg devono essere controllati attentamente, specialmente se appartengono alle categorie a rischio di sviluppare PAH (es. pazienti affetti da connettivopatie o con familiarità per IPAH/HPAH), il termine **"borderline"** non deve essere più utilizzato.

✓L'**ipertensione arteriosa polmonare (PAH)** è definita dalla presenza di una IP pre-capillare con una pressione di incuneamento di fine espirazione (PAWP) ≤ 15 mmHg e resistenze vascolari polmonari (PVR) > 3 Unità Wood

European Heart Journal
doi:10.1093/eurheartj/ehv317

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)

Authors/Task Force Members: Nazzareno Galiè* (ESC Chairperson) (Italy), Marc Humbert*[a] (ERS Chairperson) (France), Jean-Luc Vachiery[c] (Belgium), Simon Gibbs (UK), Irene Lang (Austria), Adam Torbicki (Poland), Gérald Simonneau[a] (France), Andrew Peacock[a] (UK), Anton Vonk Noordegraaf[a] (The Netherlands), Maurice Beghetti[b] (Switzerland), Ardeschir Ghofrani[a] (Germany), Miguel Angel Gomez Sanchez (Spain), Georg Hansmann[b] (Germany), Walter Klepetko[c] (Austria), Patrizio Lancellotti (Belgium), Marco Matucci[d] (Italy), Theresa McDonagh (UK), Luc A. Pierard (Belgium), Pedro T. Trindade (Switzerland), Maurizio Zompatori[e] (Italy) and Marius Hoeper[a] (Germany)

Table 1 Updated Classification of Pulmonary Hypertension*

1. Pulmonary arterial hypertension
   - 1.1 Idiopathic PAH
   - 1.2 Heritable PAH
   - 1.2.1 BMPR2
   - 1.2.2 ALK-1, ENG, SMAD9, CAV1, KCNK3
   - 1.2.3 Unknown
   - 1.3 Drug and toxin induced
   - 1.4 Associated with:
   - 1.4.1 Connective tissue disease
   - 1.4.2 HIV infection
   - 1.4.3 Portal hypertension
   - 1.4.4 Congenital heart diseases
   - 1.4.5 Schistosomiasis

1′ Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis

1″. Persistent pulmonary hypertension of the newborn (PPHN)

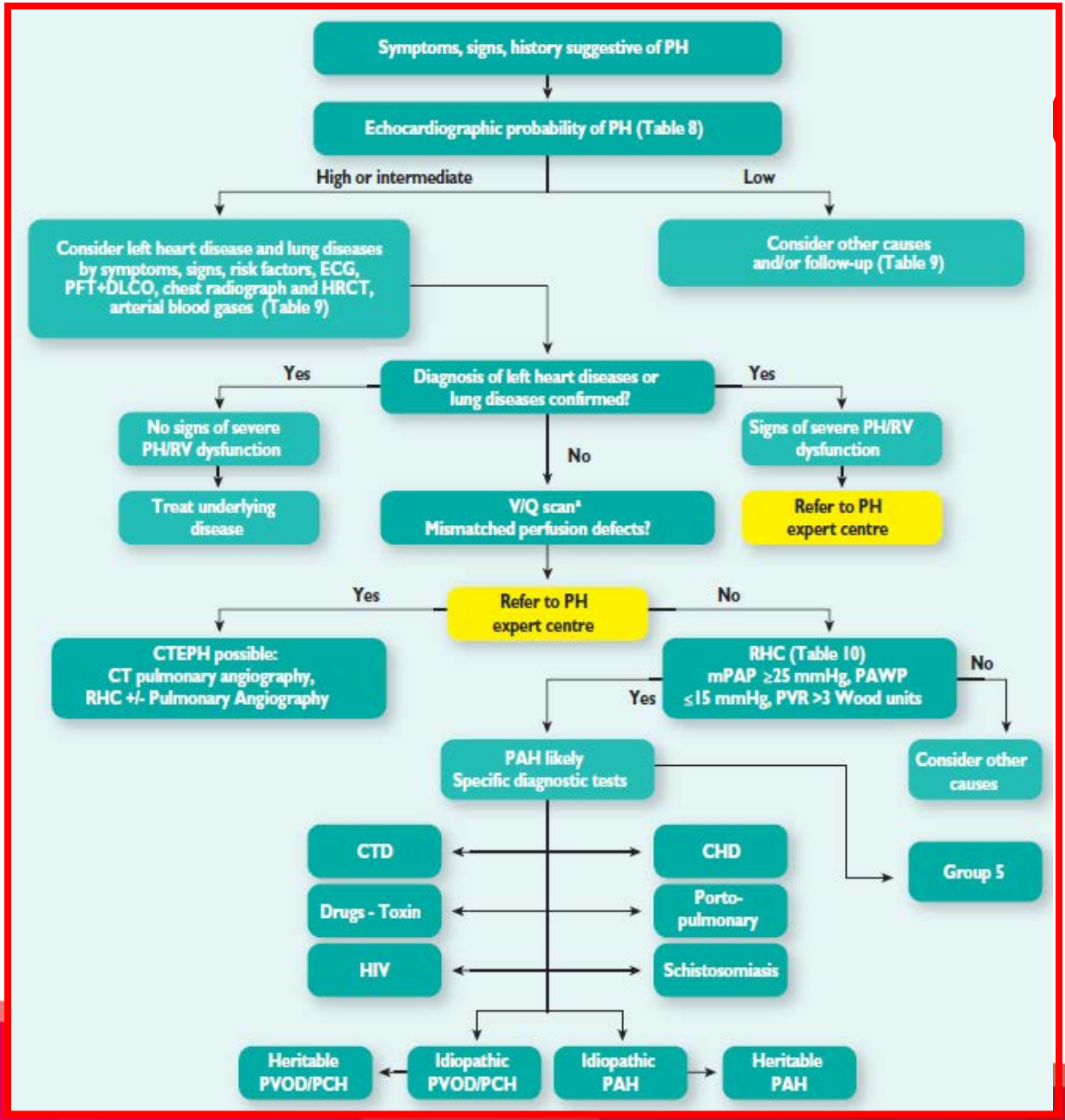
2. Pulmonary hypertension due to left heart disease
   - 2.1 Left ventricular systolic dysfunction
   - 2.2 Left ventricular diastolic dysfunction
   - 2.3 Valvular disease
   - 2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

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

4. Chronic thromboembolic pulmonary hypertension (CTEPH)

5. Pulmonary hypertension with unclear multifactorial mechanisms
   - 5.1 Hematologic disorders: chronic hemolytic anemia, 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: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

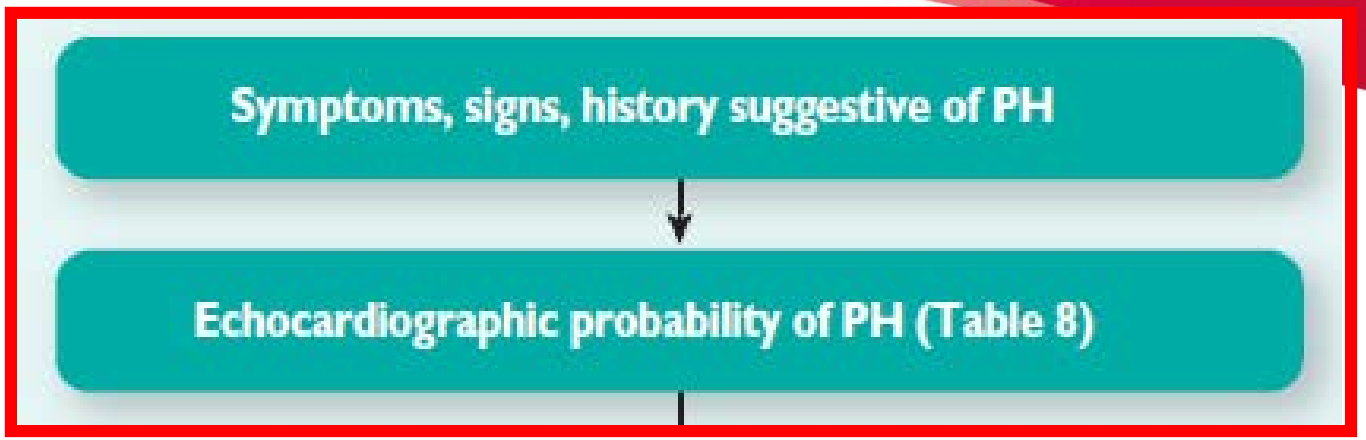
Simonneau G, *et al. J Am Coll Cardiol* 2013; 62:D34-41.



(1) confermare la diagnosi di IP

(2) identificare il gruppo clinico di IP e la specifica etiologia all'interno del gruppo dell'IAP

(3) valutare il grado di compromissione funzionale ed emodinamica del paziente.



"PH/PAH should be suspected in any patient with otherwise unexplained dyspnea on exertion, syncope, and/or signs of right ventricular dysfunction. Transthoracic echocardiography continues to be the most important noninvasive screening tool to assess the possibility of PH, but RHC remains mandatory to establish the diagnosis"

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

Table 8A Echocardiographic probability of pulmonary hypertension in symptomatic patients with a suspicion of pulmonary hypertension

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	

Table 8B Echocardiographic signs suggesting pulmonary hypertension used to assess the probability of pulmonary hypertension in addition to tricuspid regurgitation velocity measurement in *Table 8A*

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.	

Eur Heart J Cardiovasc Imaging 2015;16:233-271

Table 9 Diagnostic management suggested according to echocardiographic probability of pulmonary hypertension in patients with symptoms compatible with pulmonary hypertension, with or without risk factors for pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension

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]	Ref[c]
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	45, 46
	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	

CTEPH = chronic thromboembolic pulmonary hypertension; Echo = echocardiographic; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension; RHC = right heart catheterization.

[a]Class of recommendation.

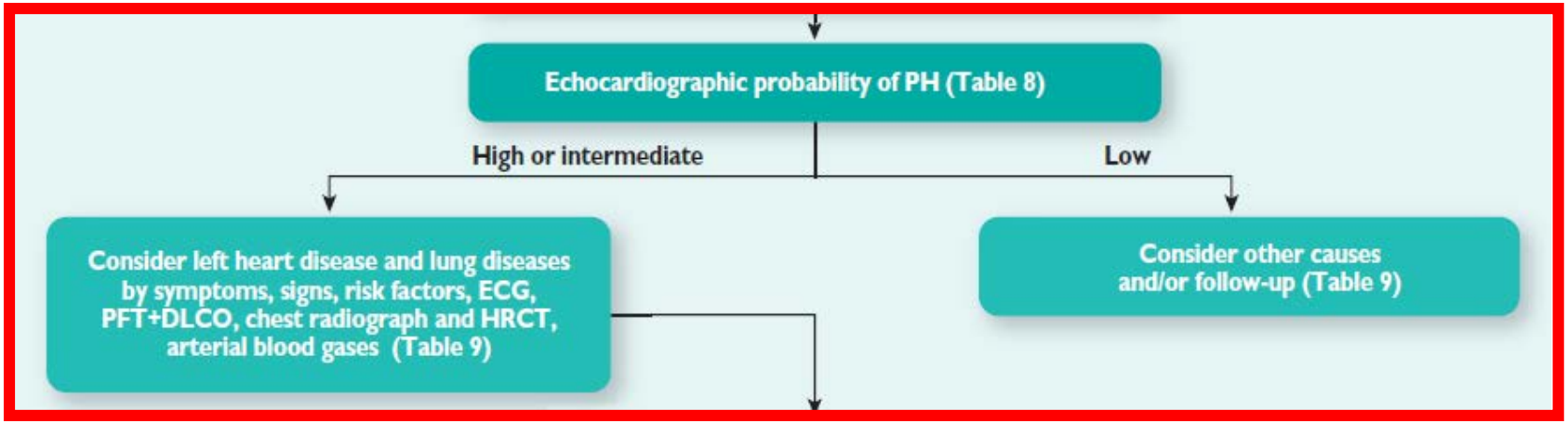
[b]Level of evidence.

[c]Reference(s) supporting recommendations.

[d]These recommendations do not apply to patients with diffuse parenchymal lung disease or left heart disease.

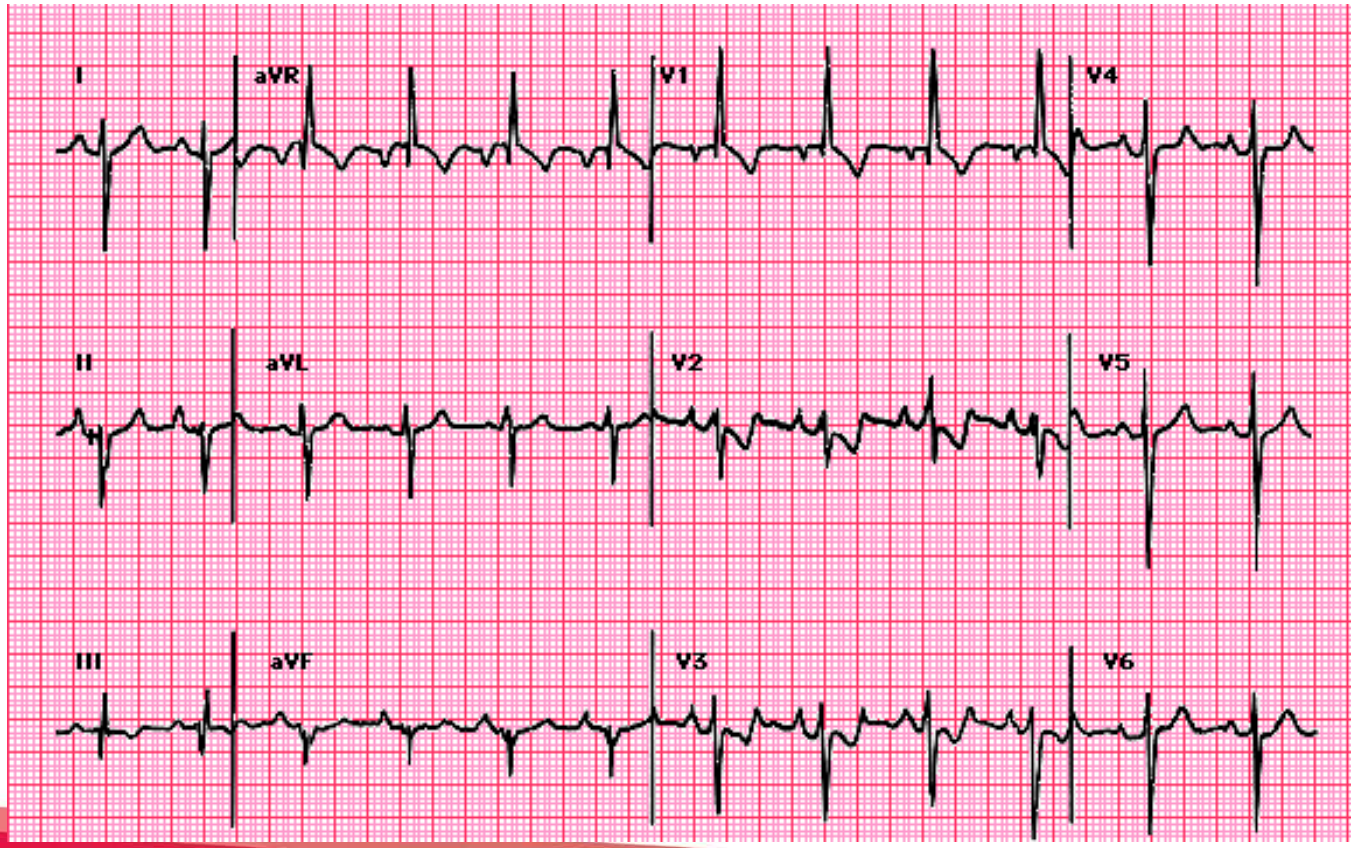
[e]Depending on the presence of risk factors for PH group 2, 3 or 5.

Further investigation strategy may differ depending on whether risk factors/associated conditions suggest higher probability of PAH or CTEPH – see diagnostic algorithm.


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)

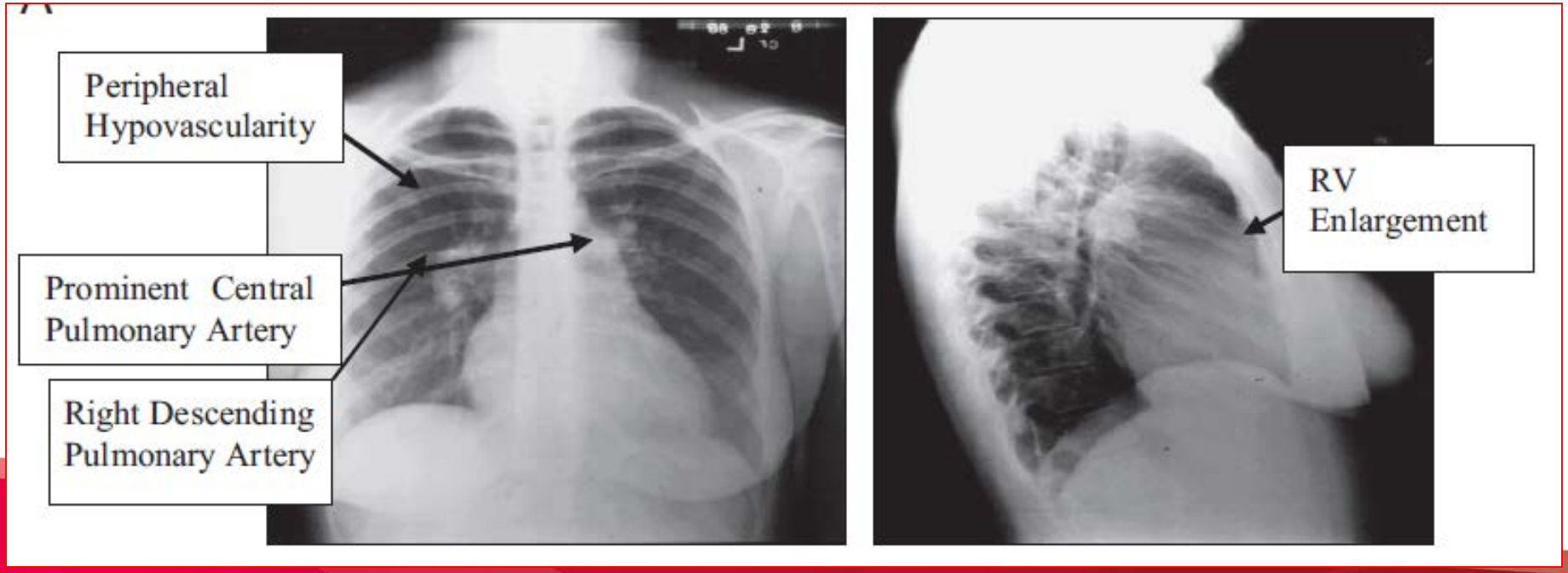
ECG

- Ipertrofia ventricolare destra con sovraccarico e dilatazione atriale destra
- L'assenza di questi aspetti non esclude la presenza di IP e nemmeno la presenza di un'importante compromissione emodinamica



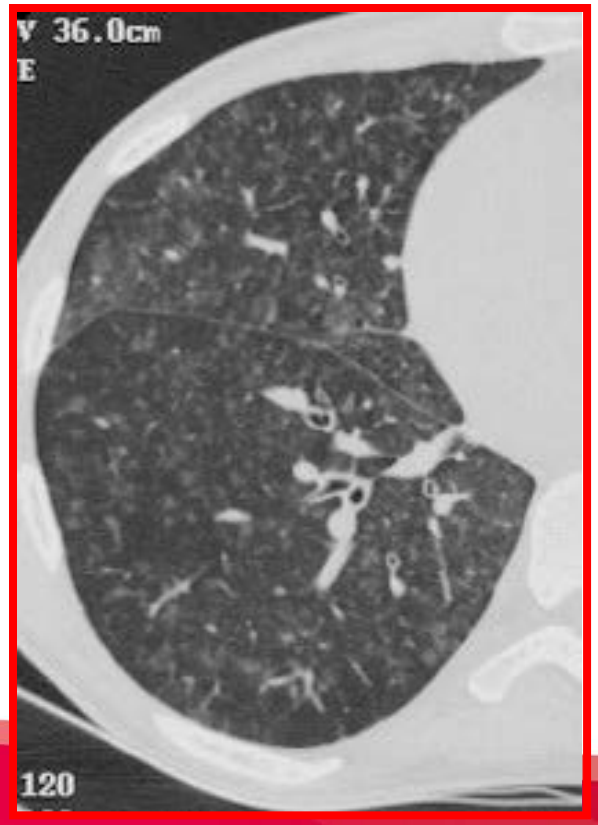
RX TORACE

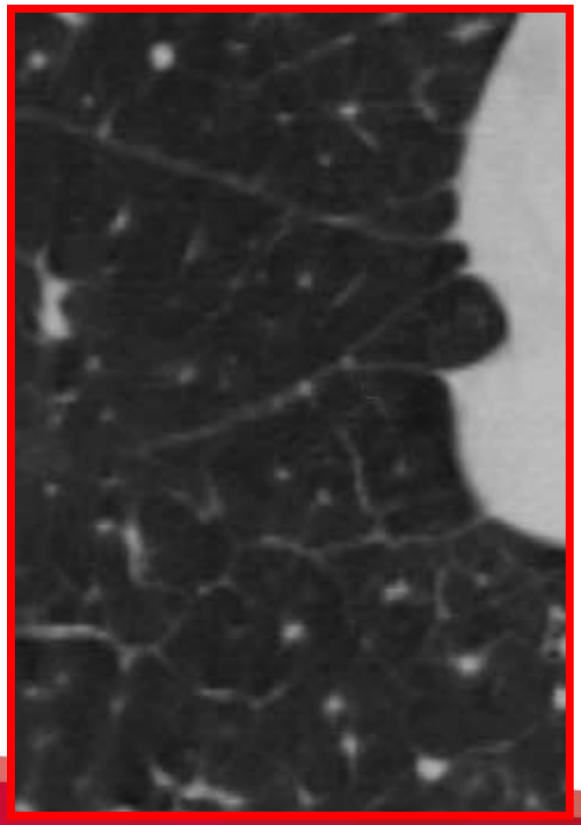
- Nel 90% dei pazienti anormale alla diagnosi
- Dilatazione delle AP centrali che contrasta con la povertà vascolare dei campi periferici (aspetto “ad albero potato”)
- Nei casi più avanzati dilatazione di atrio e ventricolo destro
- Consente di escludere ragionevolmente la presenza di patologie polmonari

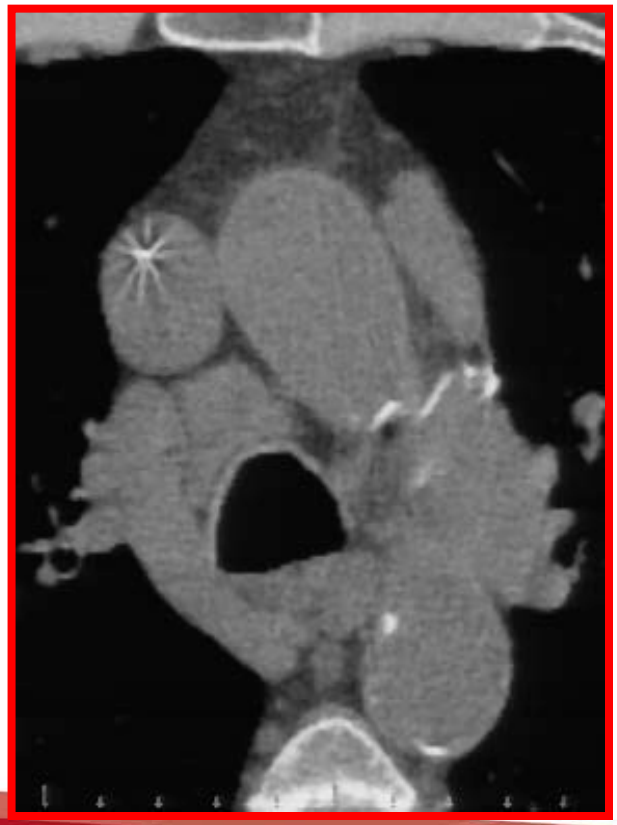


TC TORACE HR

- Diagnosi di malattie interstiziali ed enfisema
- Sospetto di IP: aumento del diametro dell'arteria polmonare (≥ 29 mm) e rapporto tra diametro a. polmonare e aorta ascendente (≥1.0)
- MVOP/angiomiomatosi capillare polmonare



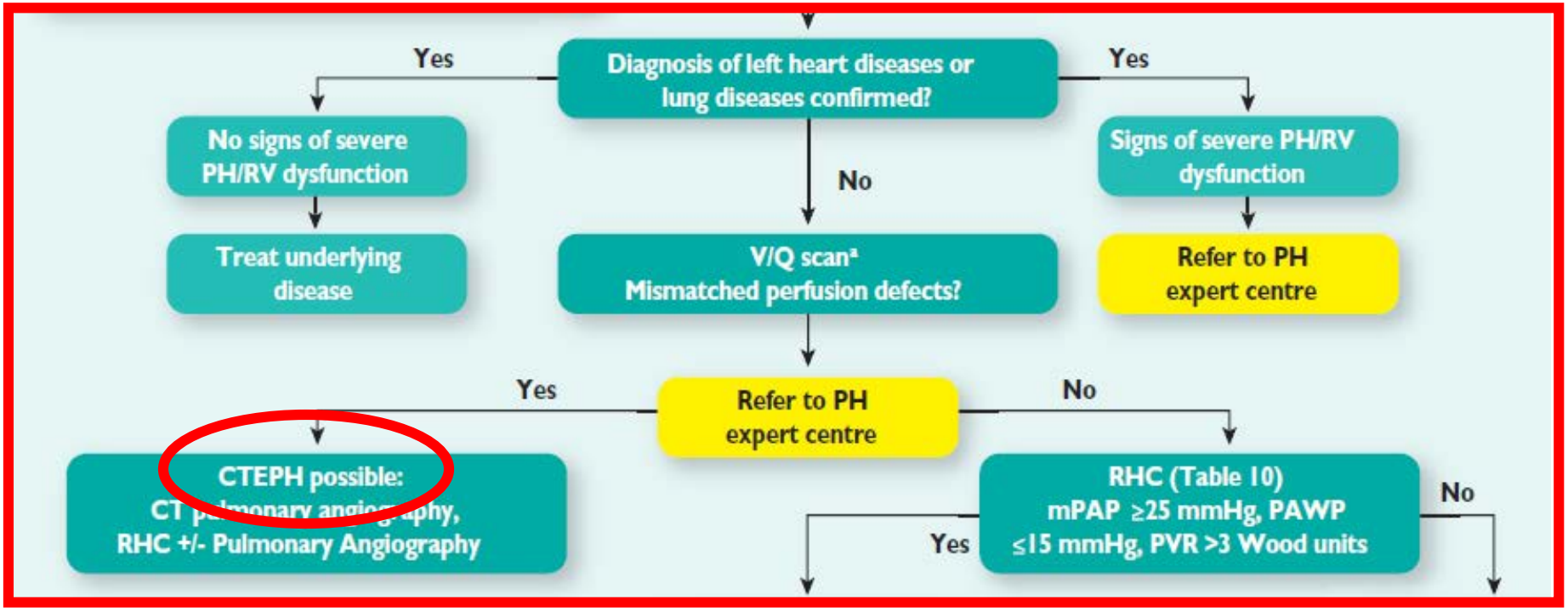




Resten et al.AJR 2004

RISONANZA MAGNETICA CARDIACA

- Valutazione diretta dimensioni, morfologia e funzione del VD.
- Quantificare in maniera non invasiva gittata sistolica, PC, distensibilità dell'AP e massa del VD.
- Angio-RM ruolo potenziale nei pazienti con sospetta CTEPH, soprattutto in particolari scenari clinici come donne in gravidanza, pazienti giovani o in cui vi sono controindicazioni al mdc iodato (Eur Radiol 2003;13:2365-2371).
- Può fornire informazioni prognostiche nei pazienti con IP sia alla diagnosi sia nel follow-up (Eur Heart J 2007;28:1250-1257. Ciec Cardiovasc Imaging 2014;7:107-114. J Am Coll Cardiol 2011;58:2511-2519).


Diagnosis of left heart diseases or lung diseases confirmed?
Yes
No signs of severe PH/RV dysfunction
Treat underlying disease
Yes
Signs of severe PH/RV dysfunction
Refer to PH expert centre
No
V/Q scan[a] Mismatched perfusion defects?
Yes
Refer to PH expert centre
No
CTEPH possible:
RHC +/- Pulmonary Angiography
Yes
RHC (Table 10)
mPAP ≥25 mmHg, PAWP ≤15 mmHg, PVR >3 Wood units
No

SCINTIGRAFIA POLMONARE V/P

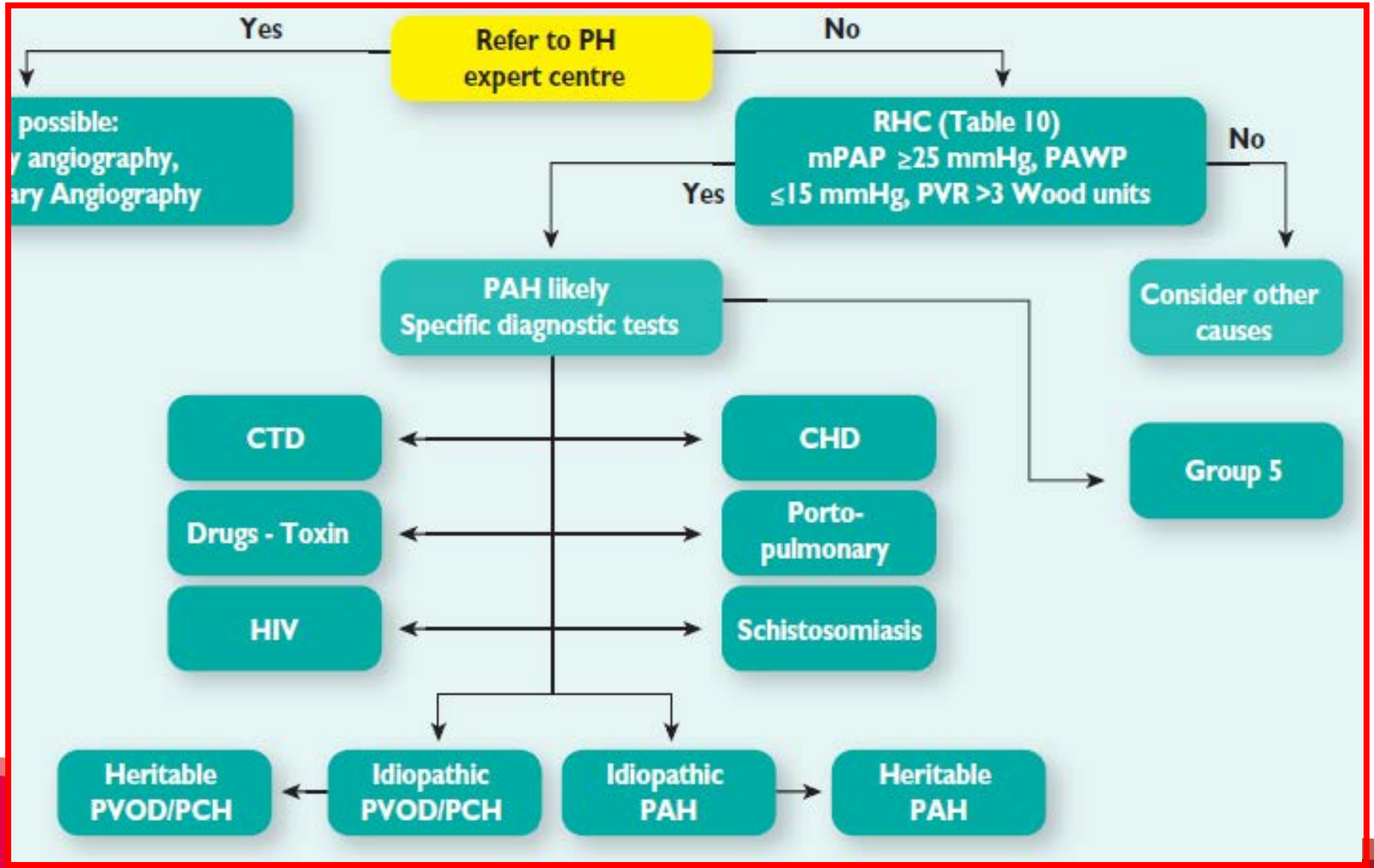
- Se normale o a bassa probabilità permette di escludere la diagnosi di CTEPH con una sensibilità del 90-100% e con una specificità del 94-100%.

- Rappresenta la metodica di elezione per lo screening del CTEPH, in quanto rispetto alla TC:

- maggiore sensibilità (Tunariu et al. J Nucl Med 2007)
- minor esposizione alle radiazioni, non rischi da mdc
- richiede minor training
- minor falsi positivi

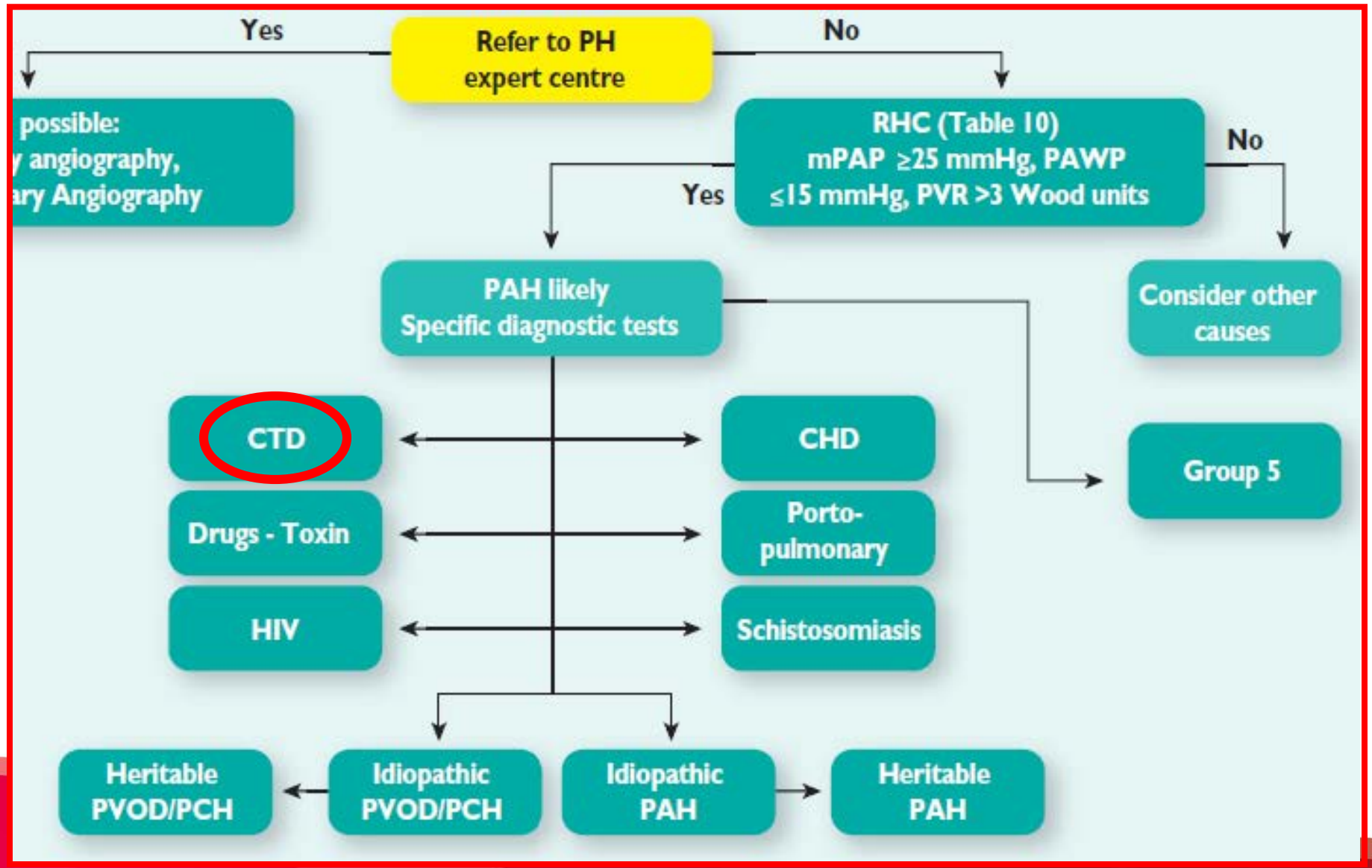
- Identificare pz affetti da CTEPH con lesioni ostruttive potenzialmente trattabili chirurgicamente (PEA).

- L'angiografia polmonare rimane il gold-standard per confermare la diagnosi di CTEPH e valutarne l'operabilità.


Yes
Refer to PH expert centre
No
possible:
y angiography,
ary 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

Soprattutto SSc, LES, connettiviti indifferenziate

Meno frequenti: AR, dermatomiosite, Sjogren



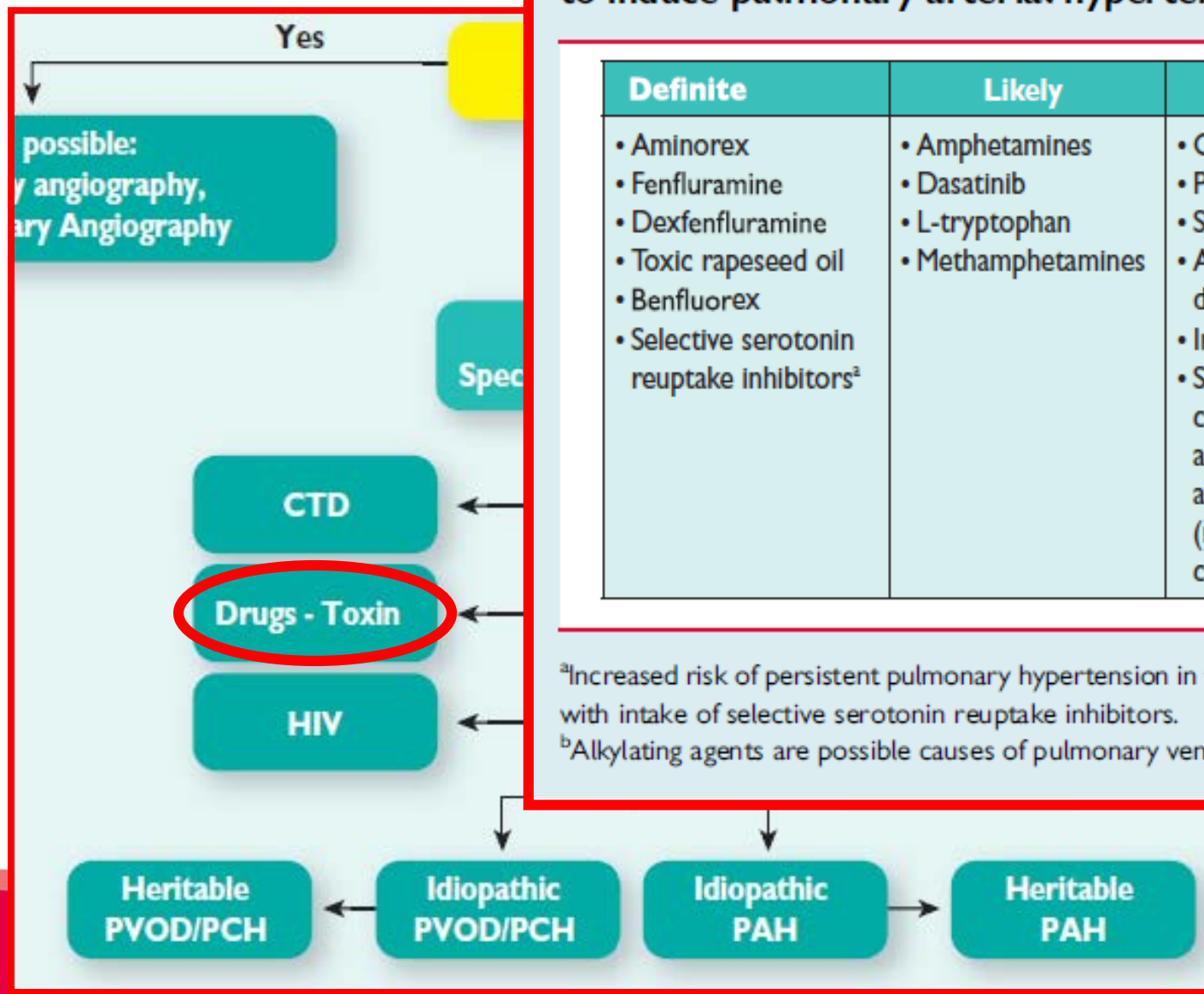
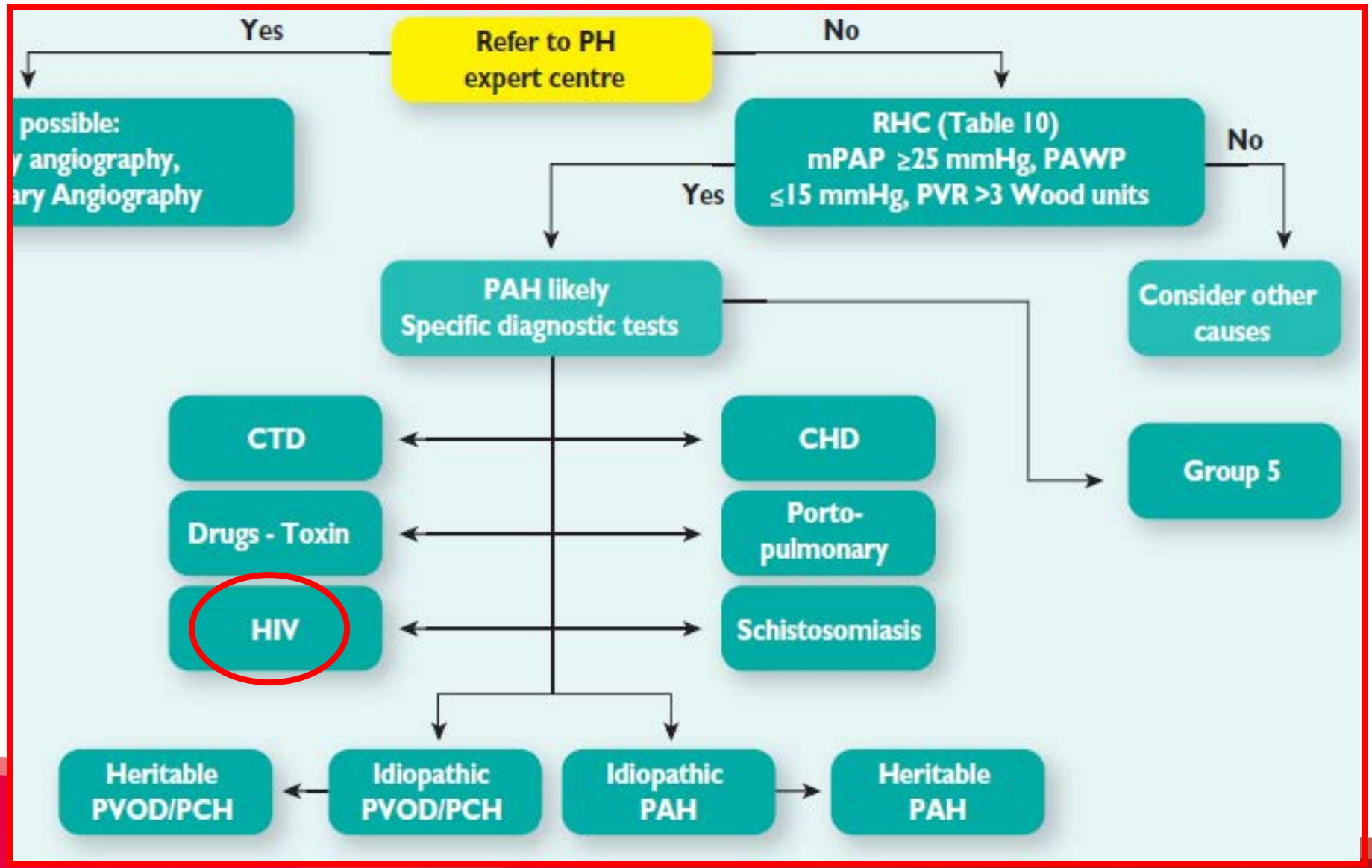


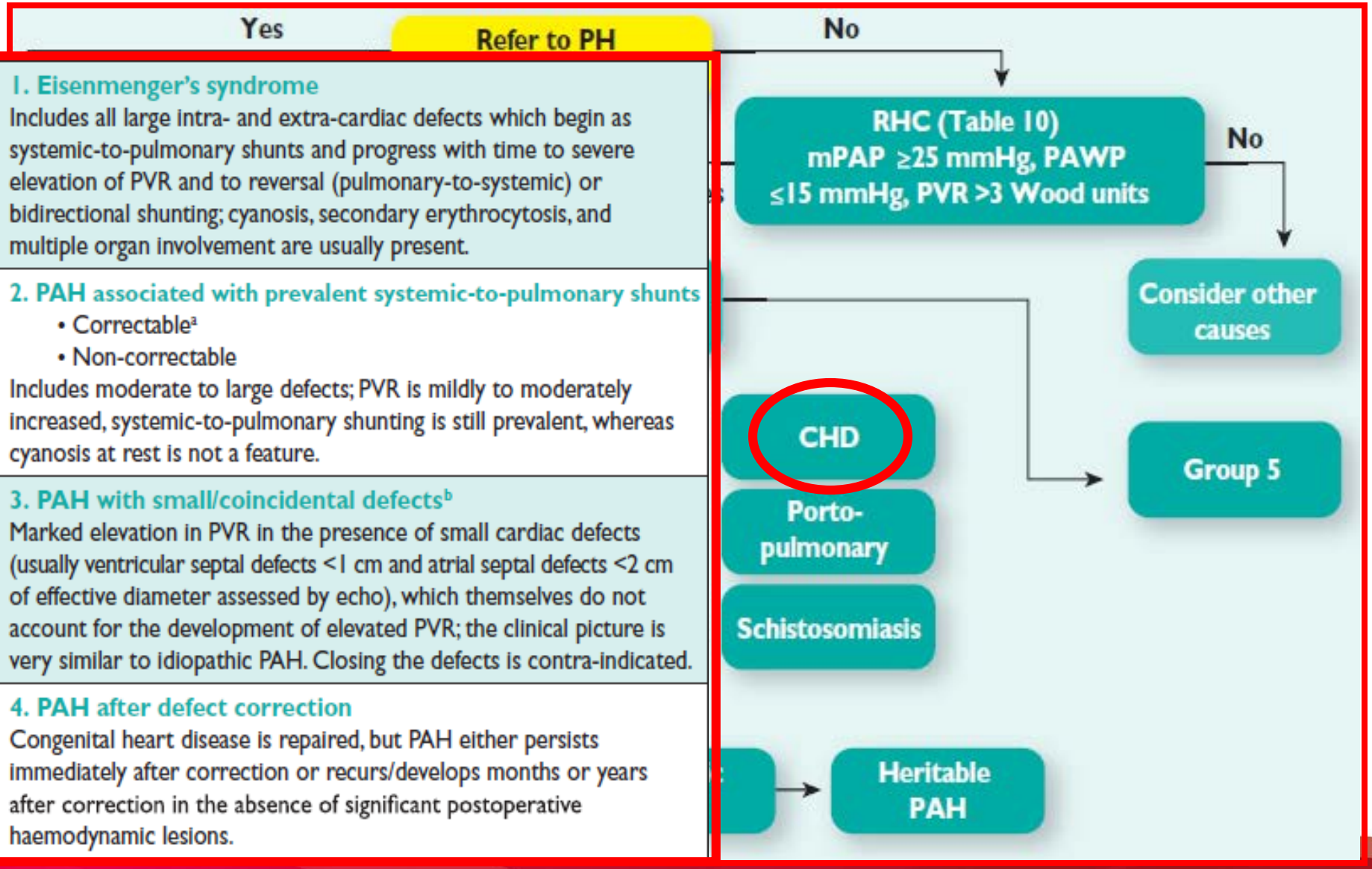
Table 7 Updated risk level of drugs and toxins known to induce pulmonary arterial hypertension

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

[a]Increased risk of persistent pulmonary hypertension in the newborns of mothers with intake of selective serotonin reuptake inhibitors.
[b]Alkylating agents are possible causes of pulmonary veno-occlusive disease.

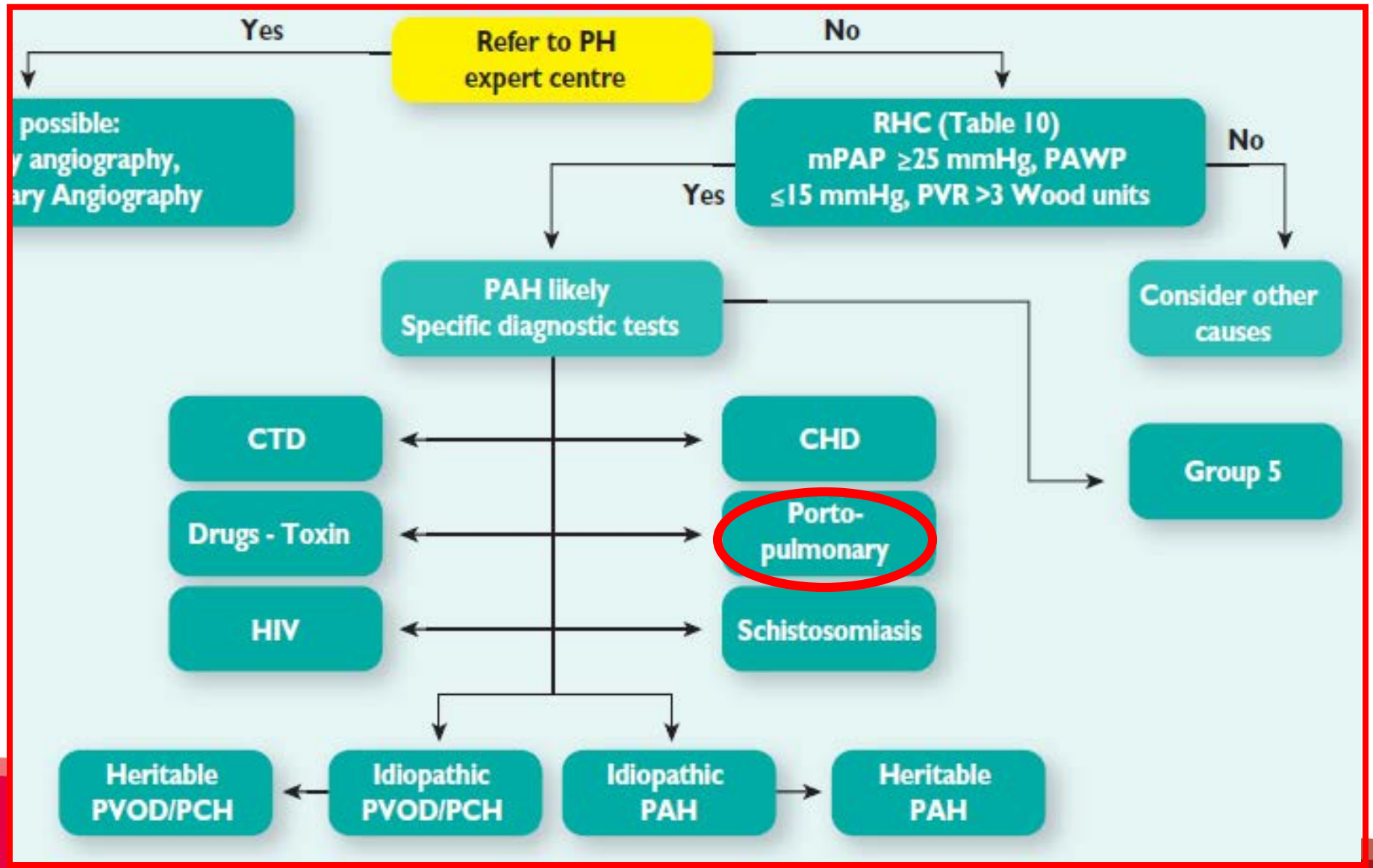
Prevalenza minima pari allo 0.47% anche nell'era HAART
(Sitbon et al. Am J Respir Crit Care Med 2008)




Yes
Refer to PH
No
1. Eisenmenger's syndrome
Includes all large intra- and extra-cardiac defects which begin as systemic-to-pulmonary shunts and progress with time to severe elevation of PVR and to reversal (pulmonary-to-systemic) or bidirectional shunting; cyanosis, secondary erythrocytosis, and multiple organ involvement are usually present.
2. PAH associated with prevalent systemic-to-pulmonary shunts
• Correctable[a]
• Non-correctable
Includes moderate to large defects; PVR is mildly to moderately increased, systemic-to-pulmonary shunting is still prevalent, whereas cyanosis at rest is not a feature.
3. PAH with small/coincidental defects[b]
Marked elevation in PVR in the presence of small cardiac defects (usually ventricular septal defects <1 cm and atrial septal defects <2 cm of effective diameter assessed by echo), which themselves do not account for the development of elevated PVR; the clinical picture is very similar to idiopathic PAH. Closing the defects is contra-indicated.
4. PAH after defect correction
Congenital heart disease is repaired, but PAH either persists immediately after correction or recurs/develops months or years after correction in the absence of significant postoperative haemodynamic lesions.
RHC (Table 10)
mPAP ≥25 mmHg, PAWP ≤15 mmHg, PVR >3 Wood units
No
Consider other causes
CHD
Porto-pulmonary
Schistosomiasis
Group 5
Heritable PAH

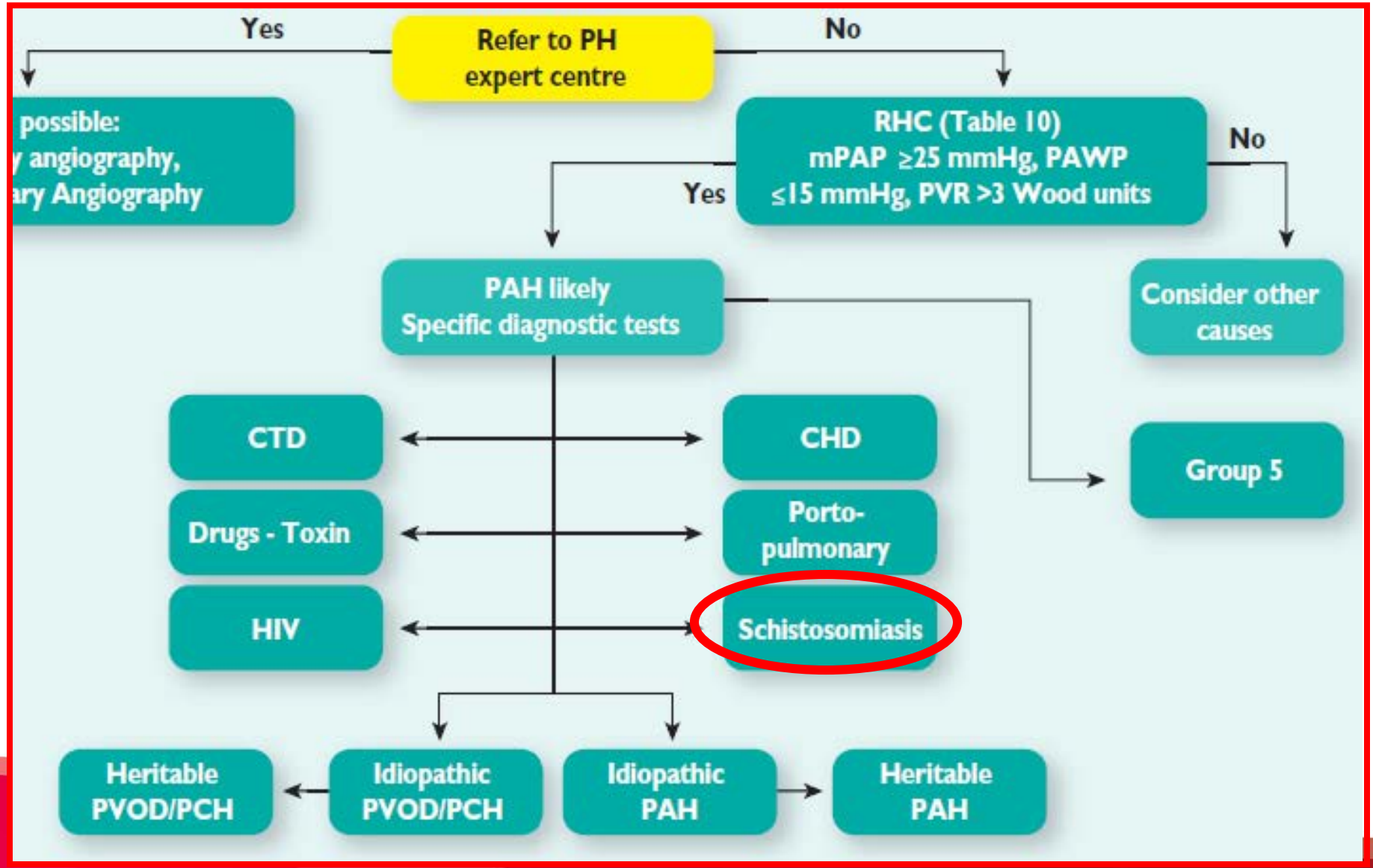
Ecografia addome, marker di funzionalità epatica,

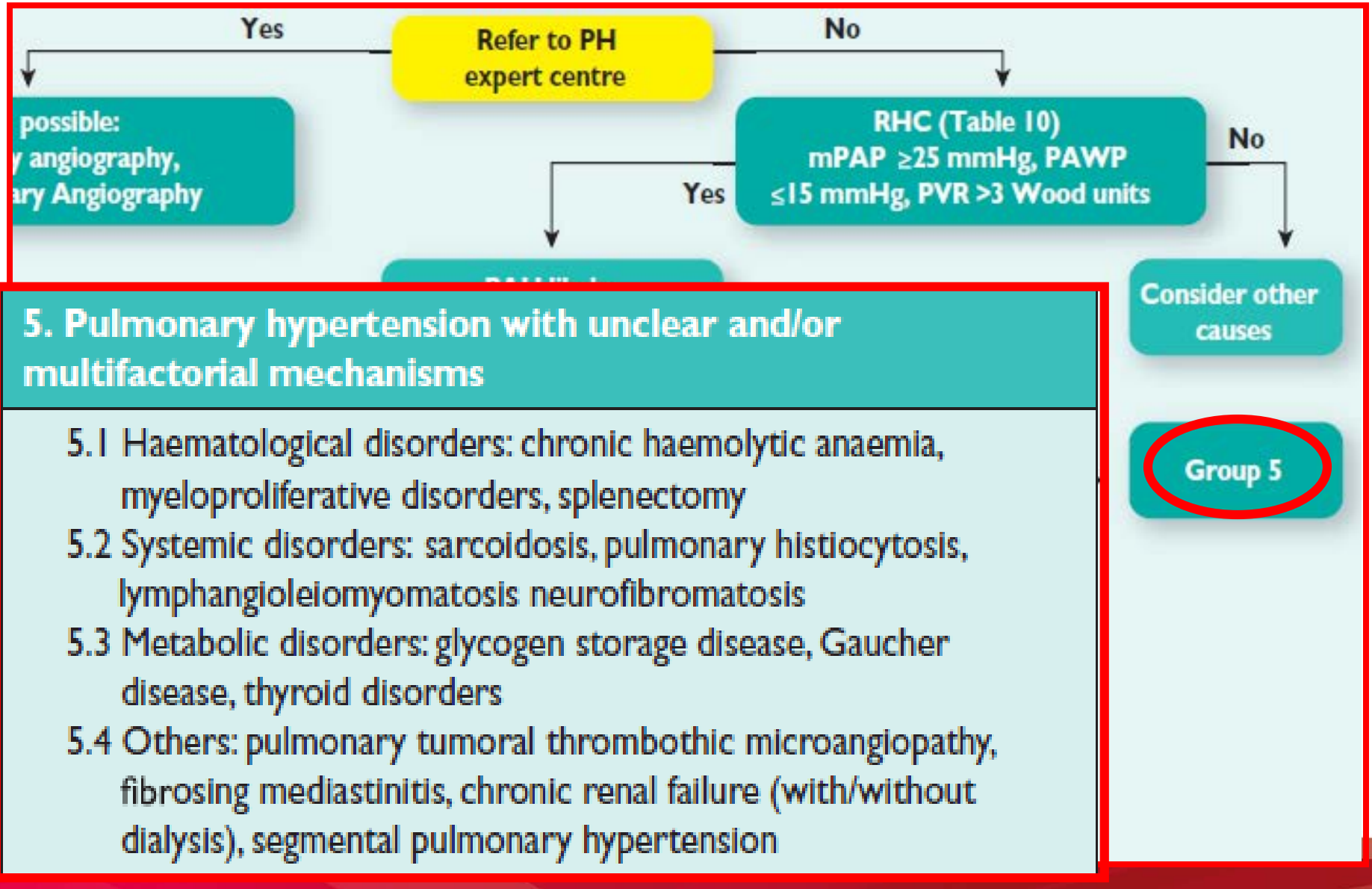
Sierologia per epatite virale e immunomediata



Più di 200 milioni di persone infette

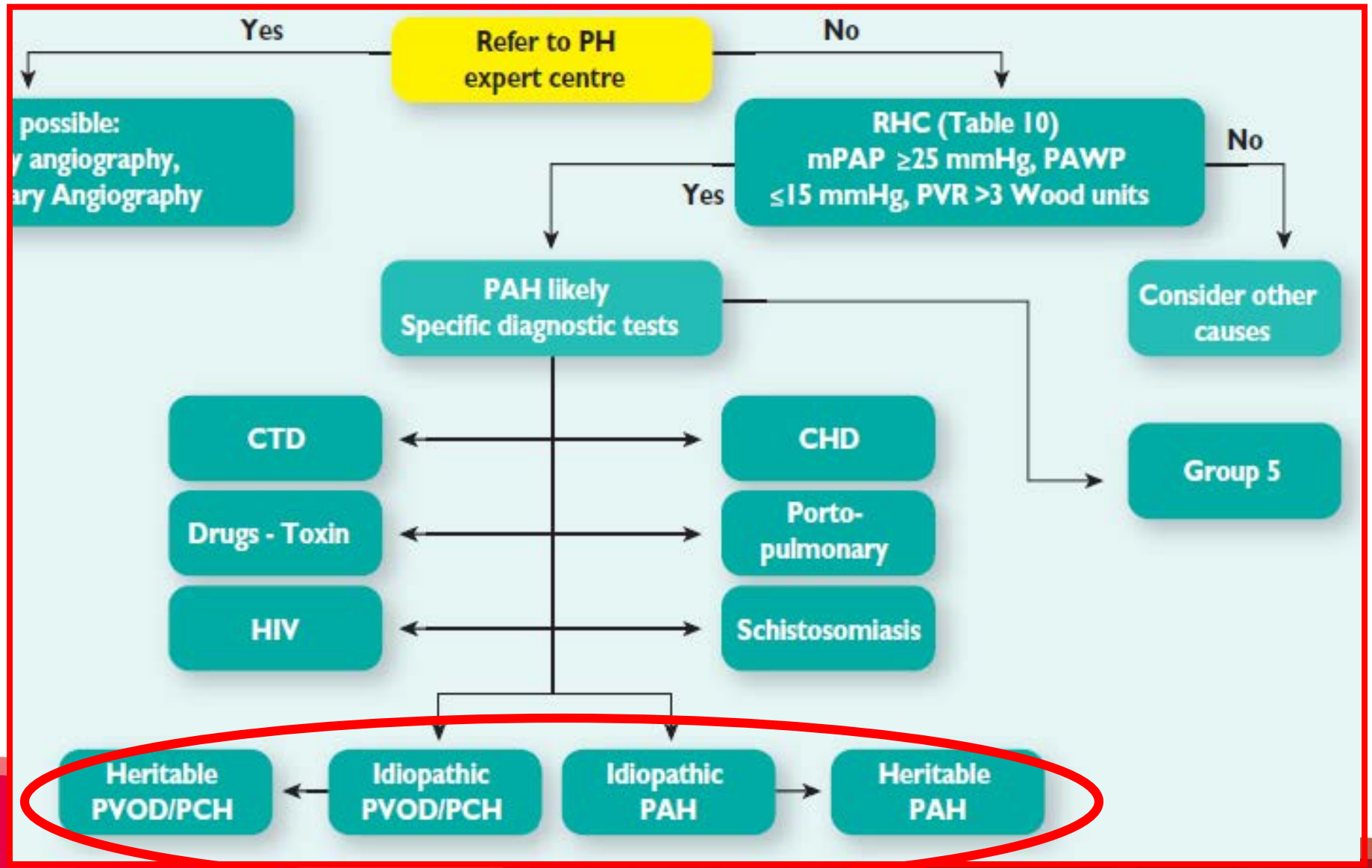
Prevalenza di IAP nei pazienti con malattia epatosplenica del 4.6% (Ross 2002, Figueiredo 2003, ATS–Dias 2008)

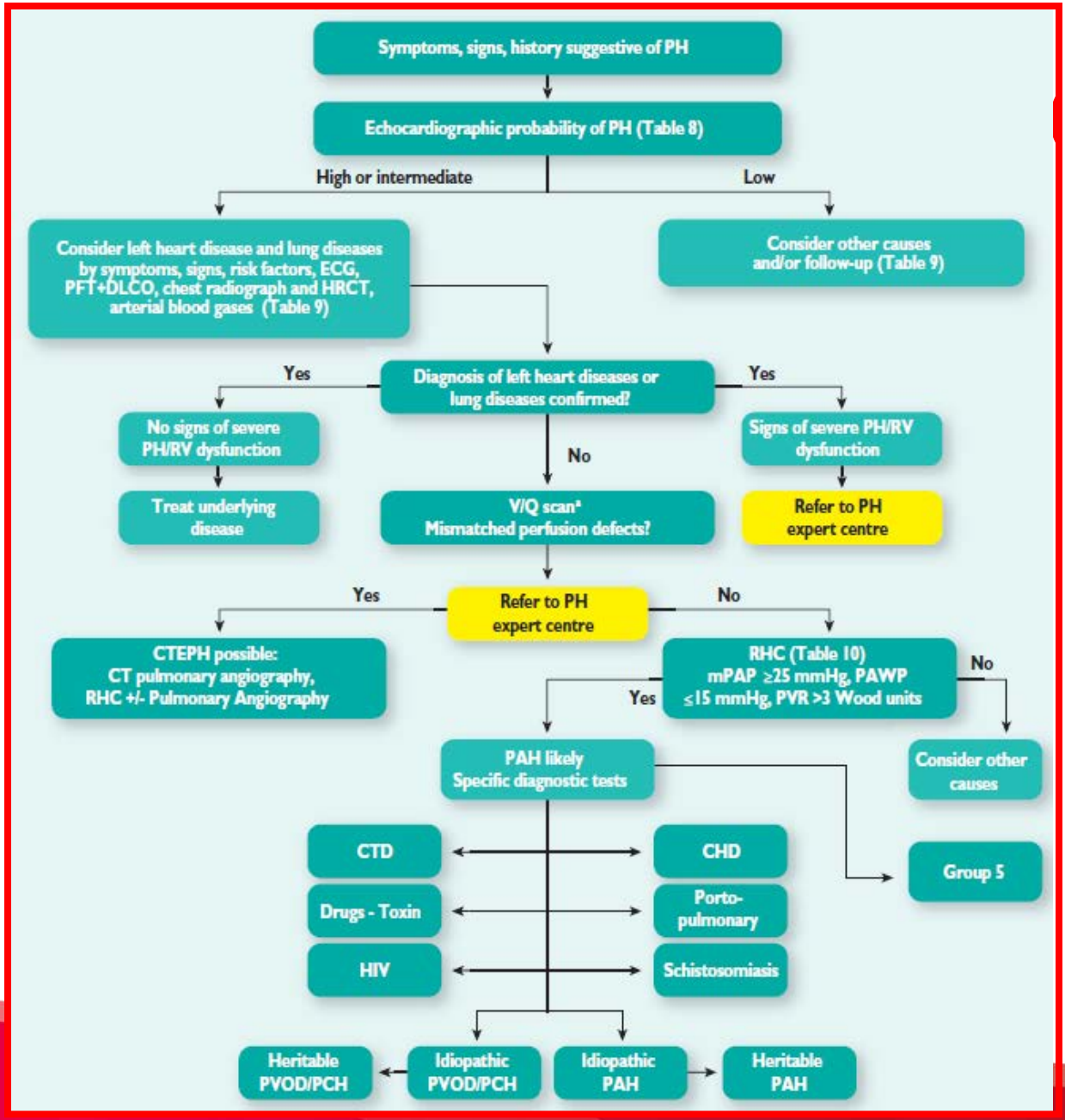



Yes
Refer to PH expert centre
No
possible:
y angiography,
ary Angiography
RHC (Table 10)
mPAP ≥25 mmHg, PAWP ≤15 mmHg, PVR >3 Wood units
No
Yes
Consider other causes
5. Pulmonary hypertension with unclear and/or multifactorial mechanisms
5.1 Haematological disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy
5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis neurofibromatosis
5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4 Others: pulmonary tumoral thrombothic microangiopathy, fibrosing mediastinitis, chronic renal failure (with/without dialysis), segmental pulmonary hypertension
Group 5

Counseling genetico

Screening pre-natale





(1) confermare la diagnosi di IP

(2) identificare il gruppo clinico di IP e la specifica etiologia all'interno del gruppo dell'IAP

(3) valutare il grado di compromissione funzionale ed emodinamica del paziente.

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 slope ≥45
NT-proBNP plasma levels	BNP <50 ng/l NT-proBNP <300 ng/l	BNP 50–300 ng/l NT-proBNP 300–1400 ng/l	BNP >300 ng/l NT-proBNP >1400 ng/l
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2 No pericardial effusion	RA area 18–26 cm^2 No or minimal, pericardial effusion	RA area >26 cm^2 Pericardial effusion
Haemodynamics	RAP <8 mmHg CI ≥2.5 l/min/m^2 SvO_2 >65%	RAP 8–14 mmHg CI 2.0–2.4 l/min/m^2 SvO_2 60–65%	RAP >14 mmHg CI <2.0 l/min/m^2 SvO_2 <60%

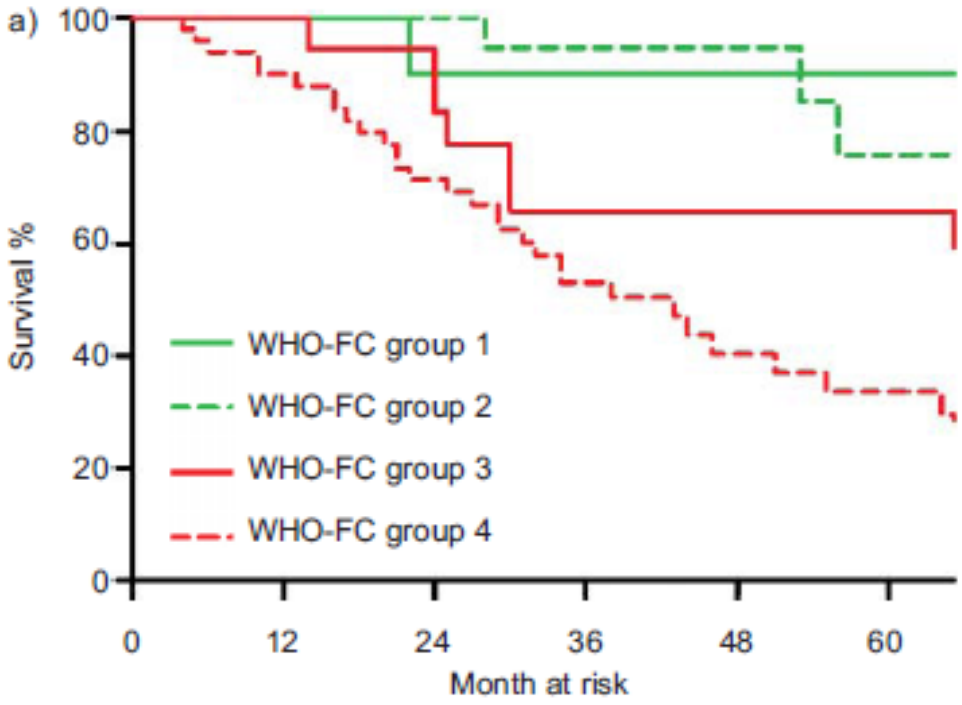
Determinants of prognosis[a] (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope[b]	Repeated syncope[c]
WHO functional class	I, II	III	IV

Class I – Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain or near syncope.

Class II – Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnoea or fatigue, chest pain or near syncope.

Class III – Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnoea or fatigue, chest pain or near syncope.

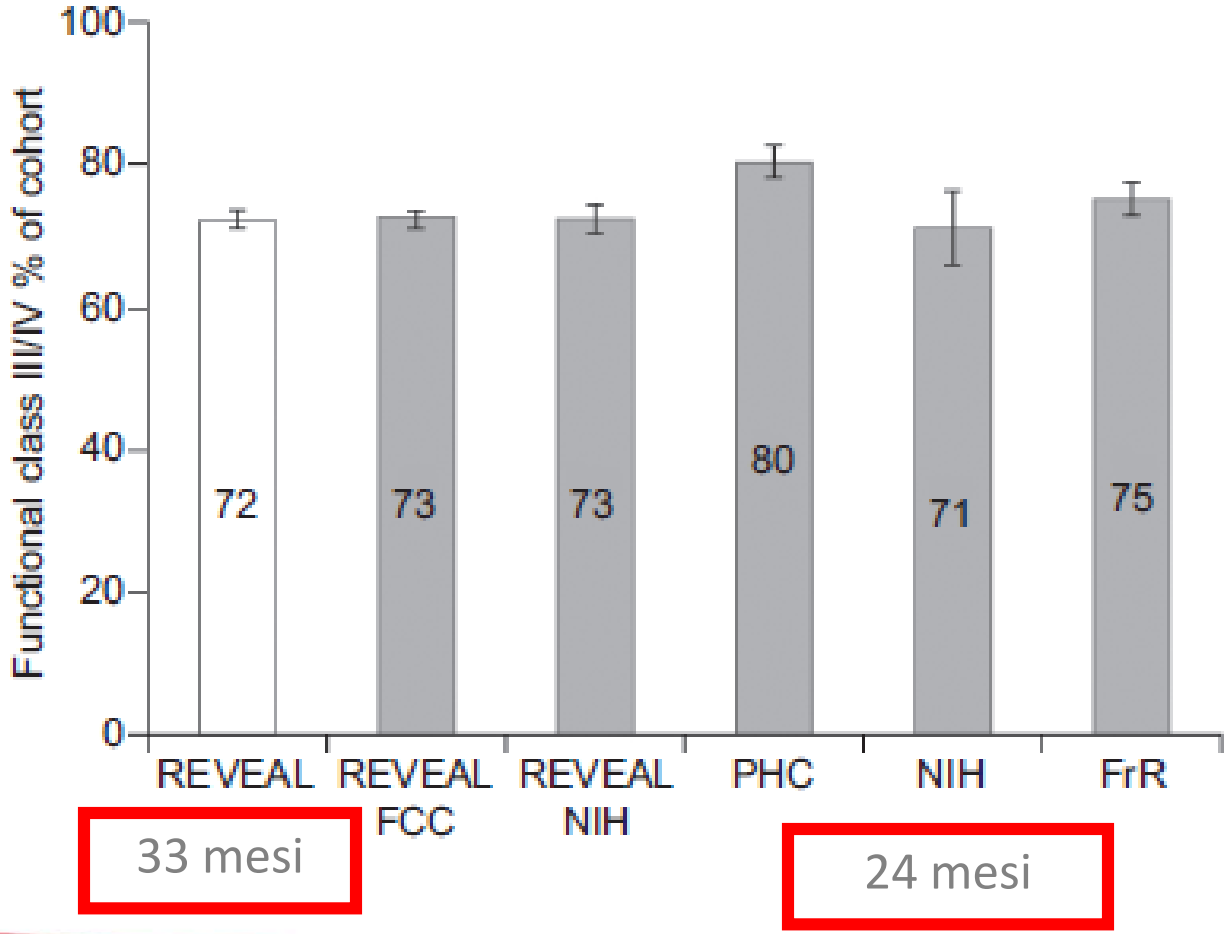
Class IV – Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnoea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.



Nickel N.Eur Respir J 2012

DIAGNOSI PRECOCE

Il 70–80% dei pazienti è in classe funzionale (WHO-FC) III-IV al momento della diagnosi




grazie
merci
arigatô
danke
gracias
shukran
thank you
obrigado
hvala
tak
takk
dank u
kiitos
faleminderit
благодаря
tänan
dankie
a dank
grazzi
mahalo
gràcies
köszönöm
terima kasih
dhanyavād
xièxiè
choukrane
paldies
diolch
mh'gōi
dziękuję
ďakujem
děkuji
ačiū
tack
дякую
спасибо
хвала
баярлалаа
ngiyabonga
mulţumesc
teşekkür ederim
nandri
kop khun