VI CORSO GUCH

L'ipertensione arteriosa polmonare nelle cardiopatie congenite

Il paziente adulto con cardiopatia congenita

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03 DICEMBRE 2022
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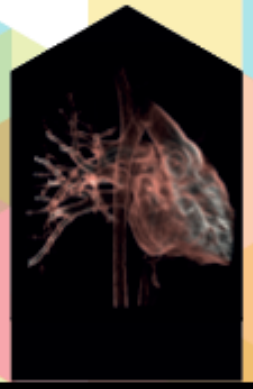


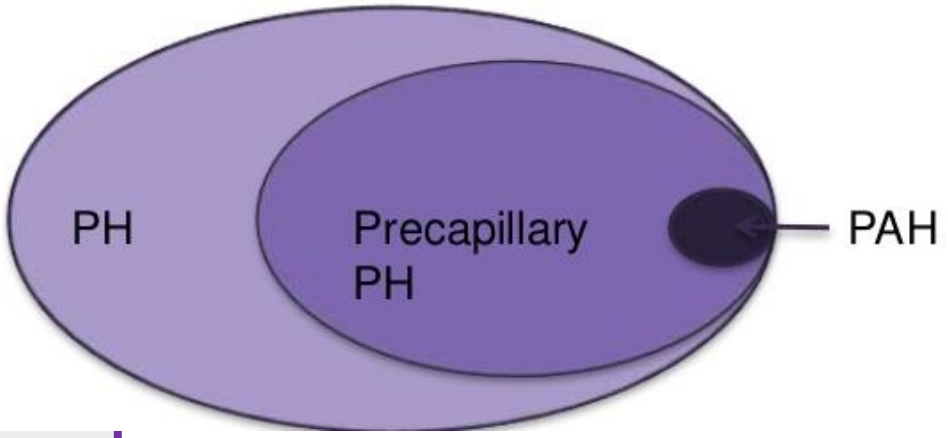
2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

GROUP 1 Pulmonary arterial hypertension (PAH)

- 1.1 Idiopathic
  - 1.1.1 Non-responders at vasoreactivity testing
  - 1.1.2 Acute responders at vasoreactivity testing
- 1.2 Heritable[a]
- 1.3 Associated with drugs and toxins[a]
- 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 disease
  - 1.4.5 Schistosomiasis
- 1.5 PAH with features of venous/capillary (PVOD/PCH) involvement
- 1.6 Persistent PH of the newborn

ESC/ERS GUIDELINES

Definition	Haemodynamic characteristics
PH	mPAP >20 mmHg
Pre-capillary PH	mPAP >20 mmHg PAWP <15 mmHg PVR >2 WU



PAH corresponds to Group 1 PH, defined by right-heart catheterisation as precapillary PH in the absence of other causes such as chronic lung disease or chronic thromboembolic disease

Clinical classification of PAH associated with congenital heart disease

(1) Eisenmenger syndrome

Includes all large intra- and extracardiac defects that begin as systemic-to-pulmonary shunts and progress to severely elevated PVR and to reverse (pulmonary-to-systemic) or bidirectional shunting. Cyanosis, secondary erythrocytosis, and multiple organ involvement are usually present. Closing the defects is contraindicated.

(2) PAH associated with prevalent systemic-to-pulmonary shunts

- Correctable[a]
- Non-correctable

Include moderate-to-large defects. PVR is mildly to moderately increased and systemic-to-pulmonary shunting is still prevalent, whereas cyanosis at rest is not a feature.

(3) PAH with small/coincidental[b] defects

Markedly elevated PVR in the presence of cardiac defects considered haemodynamically non-significant (usually ventricular septal defects <1 cm and atrial septal defects <2 cm of effective diameter assessed by echocardiography), which themselves do not account for the development of elevated PVR. The clinical picture is very similar to IPAH. Closing the defects is contraindicated.

(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, post-operative, haemodynamic lesions.

Epidemiology of PAH associated with congenital heart disease

- PAH associated with congenital heart disease is highly prevalent:
  - French cohort: 11.3% of all cases of PAH
  - Spanish cohort: 16% of of all cases of PAH
- PAH affects 5% to 10% of adults with CHD
- Women are affected more commonly by PAH-CHD and risk increases with increasing biological age and the age when defect closure occurred.

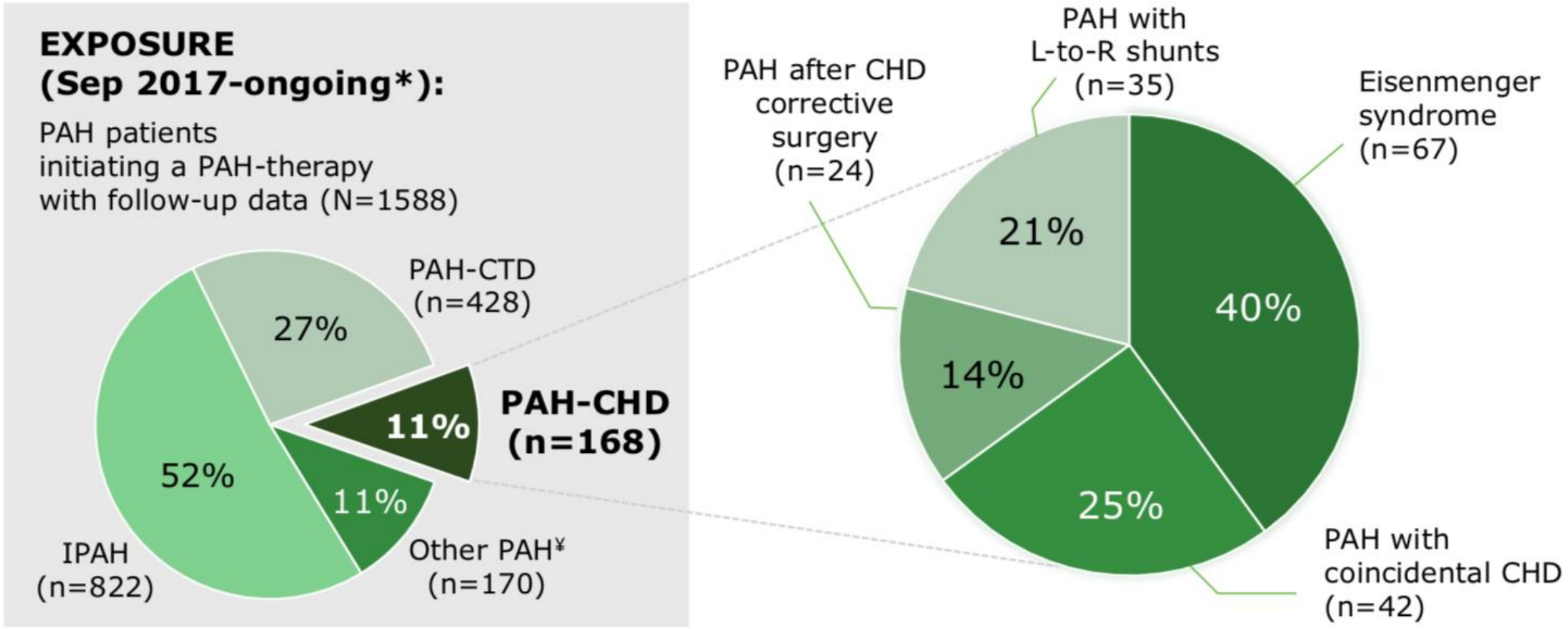
PAH associated with congenital heart disease

PAH-CHD patients referred to Bologna 1998-2011

Characteristic	Eisenmenger syndrome	PAH with systemic-to-pulmonary shunt	PAH with small defects	PAH after defect correction	P-value
Patients, *n* (%)	90 (47)	48 (25)	10 (5)	44 (23)	N/A
Age (years)	41 ± 16	47 ± 18	25 ± 21	36 ± 17	0.0002
Female sex, *n* (%)	56 (63)	34 (71)	6 (60)	20 (45)	0.08
PAH diagnosis to referral,[a] *n* (%)					
≥0 to <1 year	29 (33)	29 (60)	6 (60)	26 (59)	<0.001
≥1 to <5 year	2 (2)	4 (8)	1 (10)	8 (19)	
≥5 year	59 (65)	15 (31)	3 (30)	10 (22)	
Type of the defect, *n* (%)					
Atrial septal defect	10 (11)	22 (46)	4 (40)	12 (27)	0.0001
Ventricular septal defect	36 (40)	10 (21)	5 (50)	18 (41)	0.106
Patent ductus arteriosus	15 (17)	0	0	3 (7)	0.009
Partial APVR-isolated	0	3 (6)	0	0	0.035
Partial APVR + atrial septal defect	3 (3)	10 (21)	0	3 (7)	0.004
Other combined[b]	11 (12)	2 (4)	1 (10)	2 (5)	0.393
Complex[c]	15 (17)	1 (2)	0	6 (13)	0.058

Eur Heart J 2014. 35, 716–724

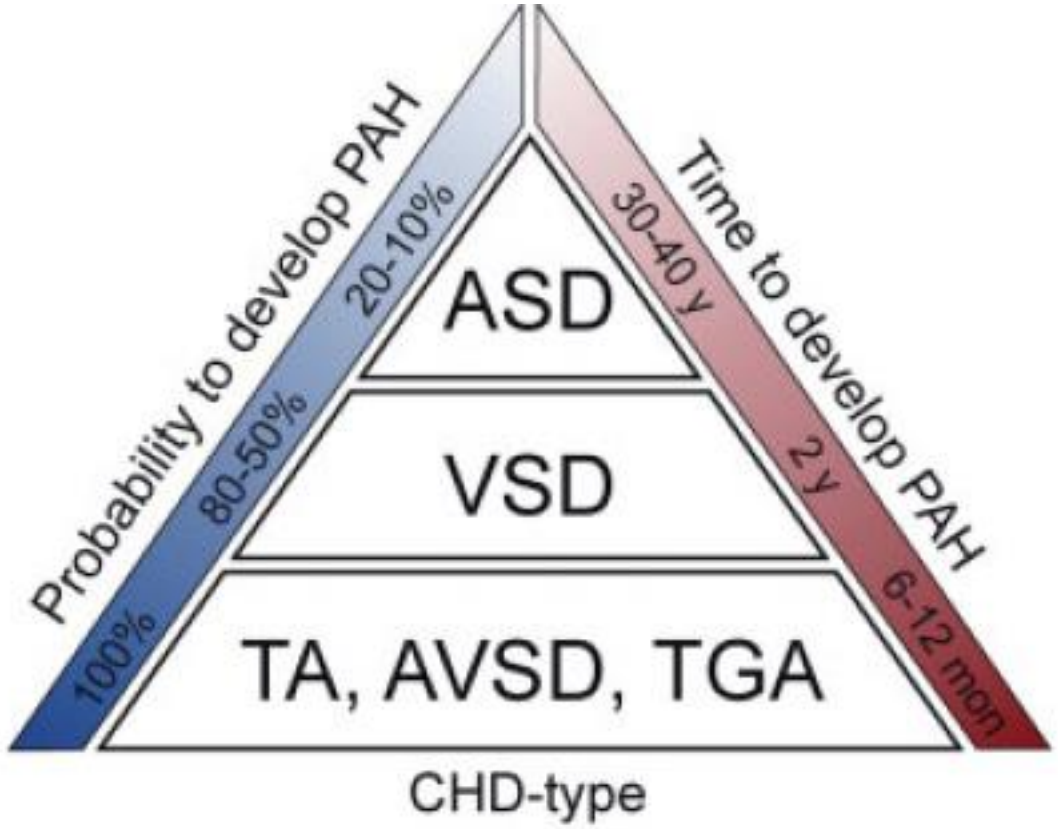
PAH associated with congenital heart disease



EXPOSURE is an ongoing, multicentre, prospective, observational study of PAH patients initiating a PAH-specific therapy in Europe and Canada

Escribano et al ESC 2022

CHD-type and shunt determine the progression of PAH

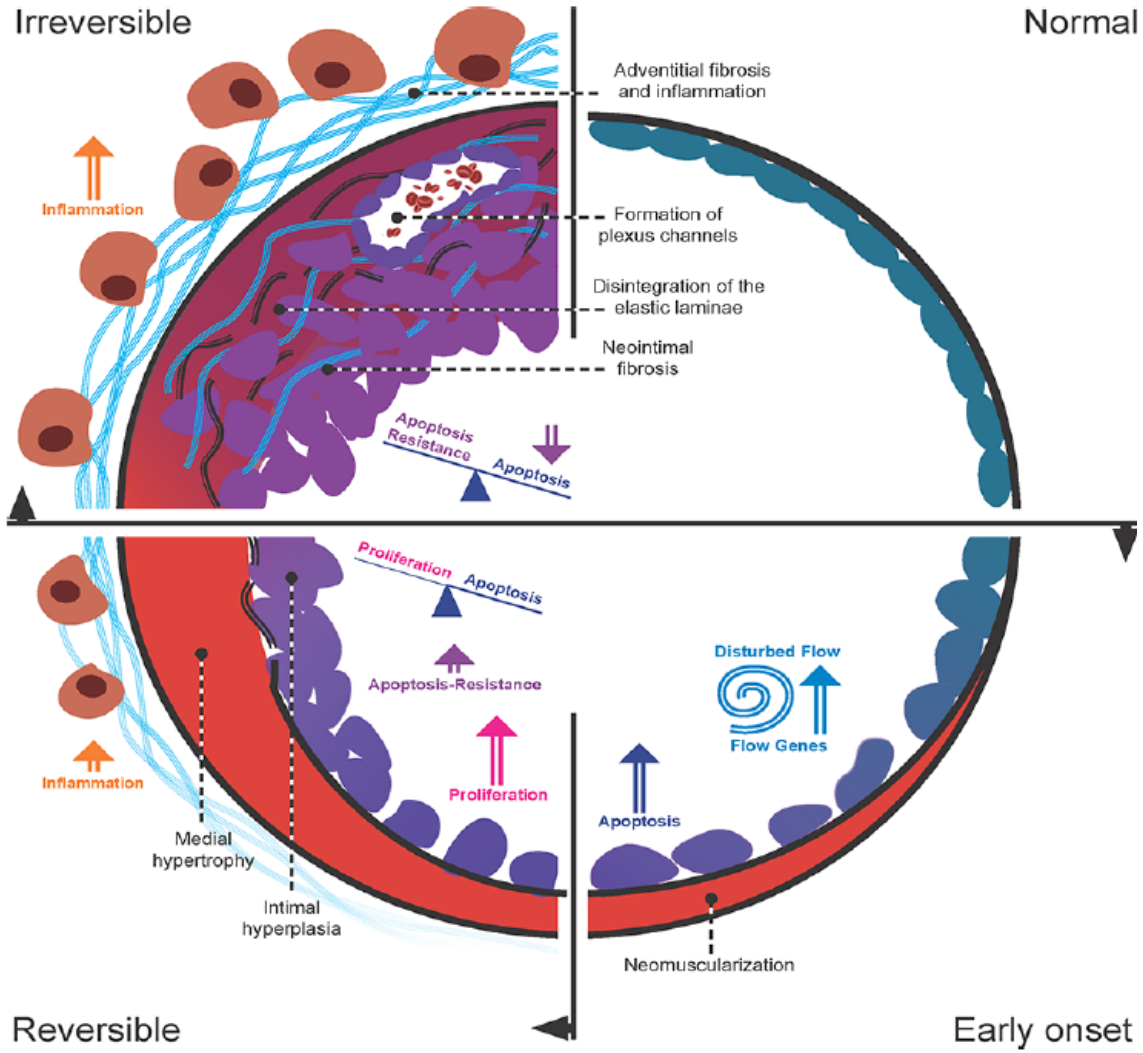


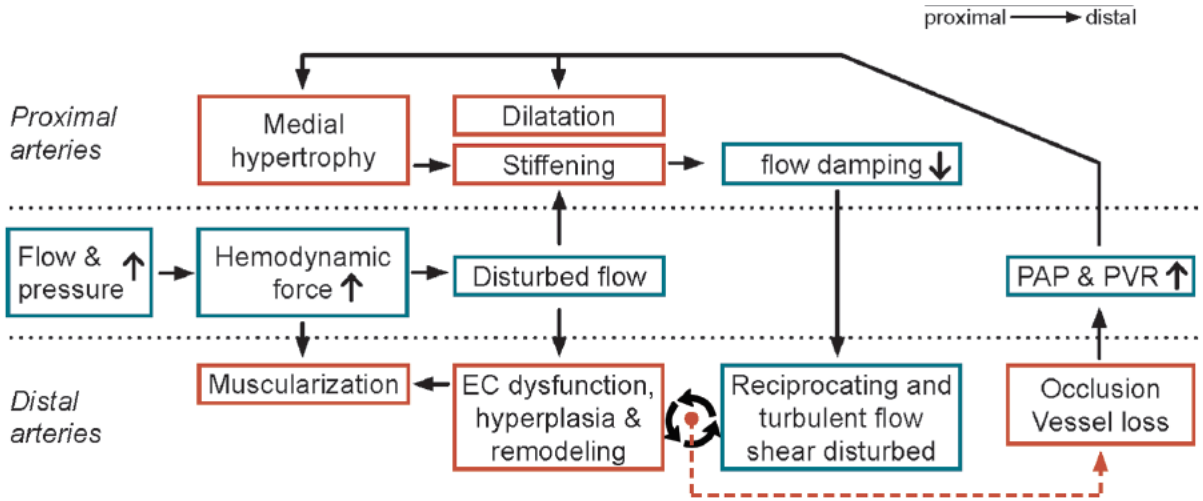
- The risk of developing PAH depends on the location and size of the shunt lesion, as well as concomitant factors, such as the presence of Down syndrome.

- Large post-tricuspid shunts (high flow, high pressure) more frequently and quickly induce irreversible PAH than restrictive or pretricuspid shunts (high flow, normal pressure)

Eur Heart J 2017; 00:1–8

Pathophysiology of PAH-CHD



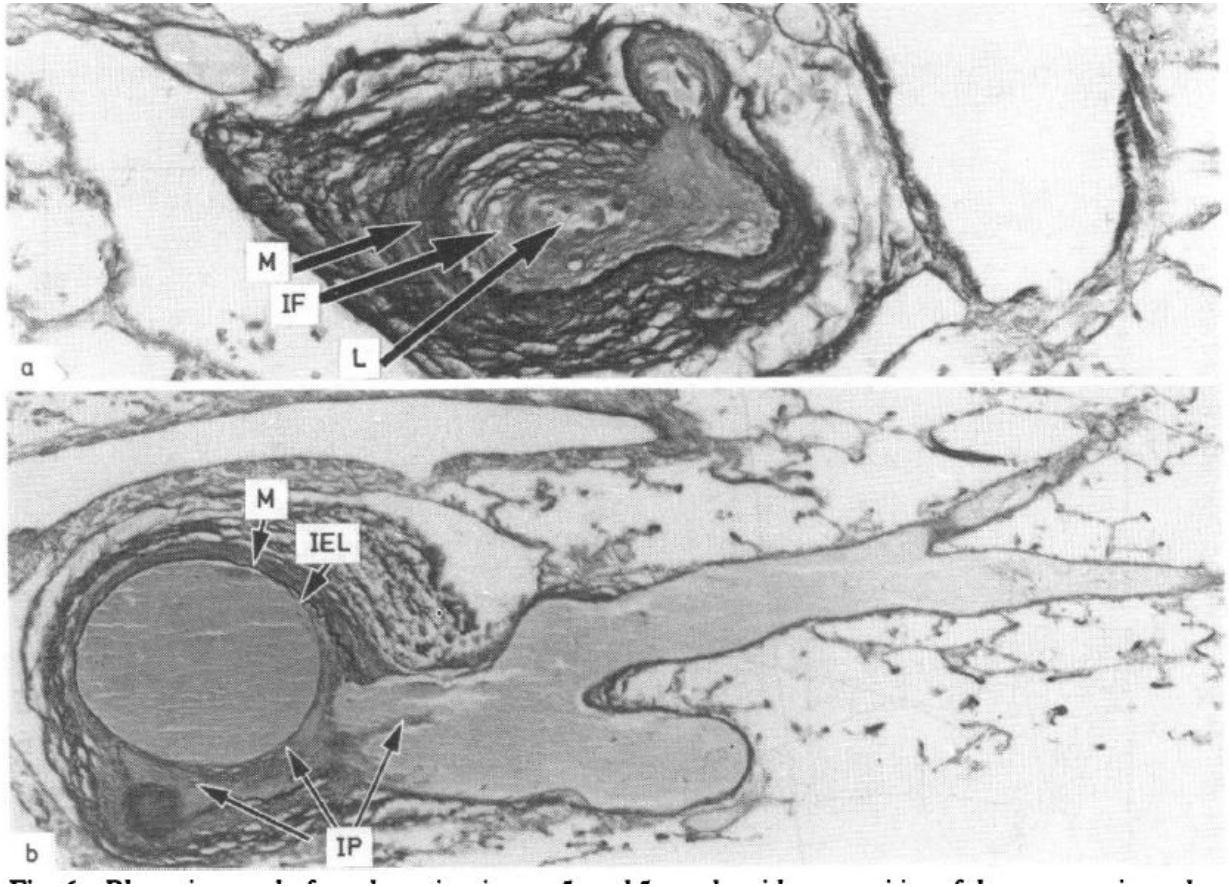


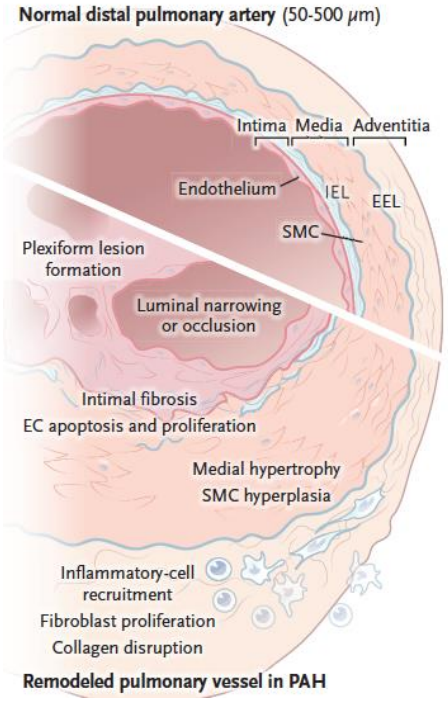
van der Feen DE, et al. Heart 2019

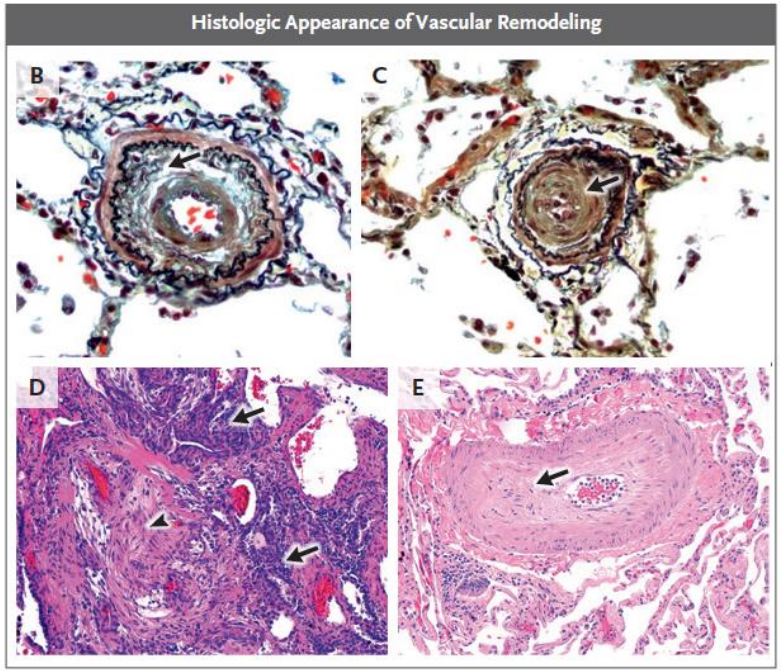
PAH associated with congenital heart disease

Br Heart J 1984; **52**: 557–71

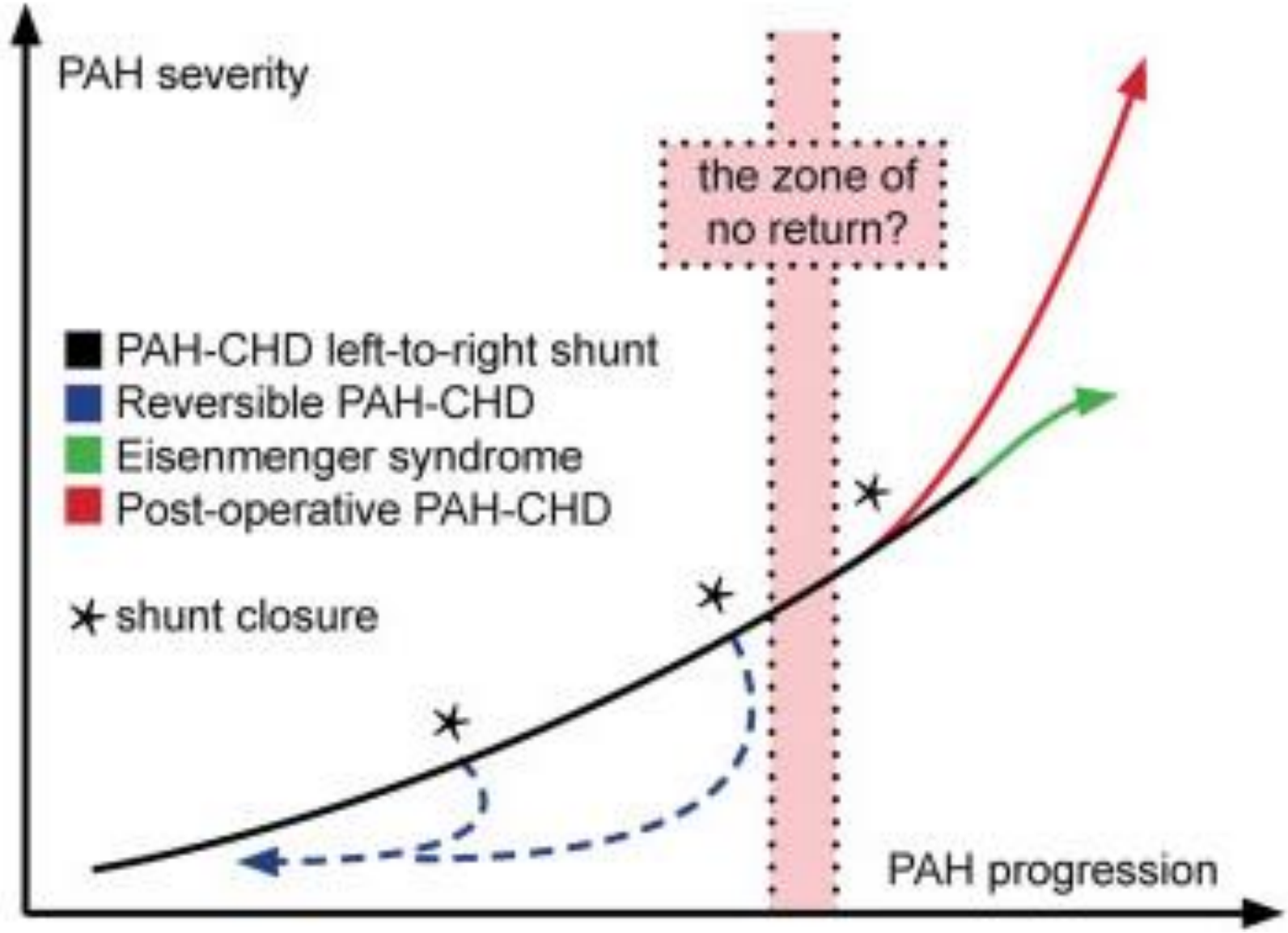
Pulmonary vascular disease in different types of congenital heart disease



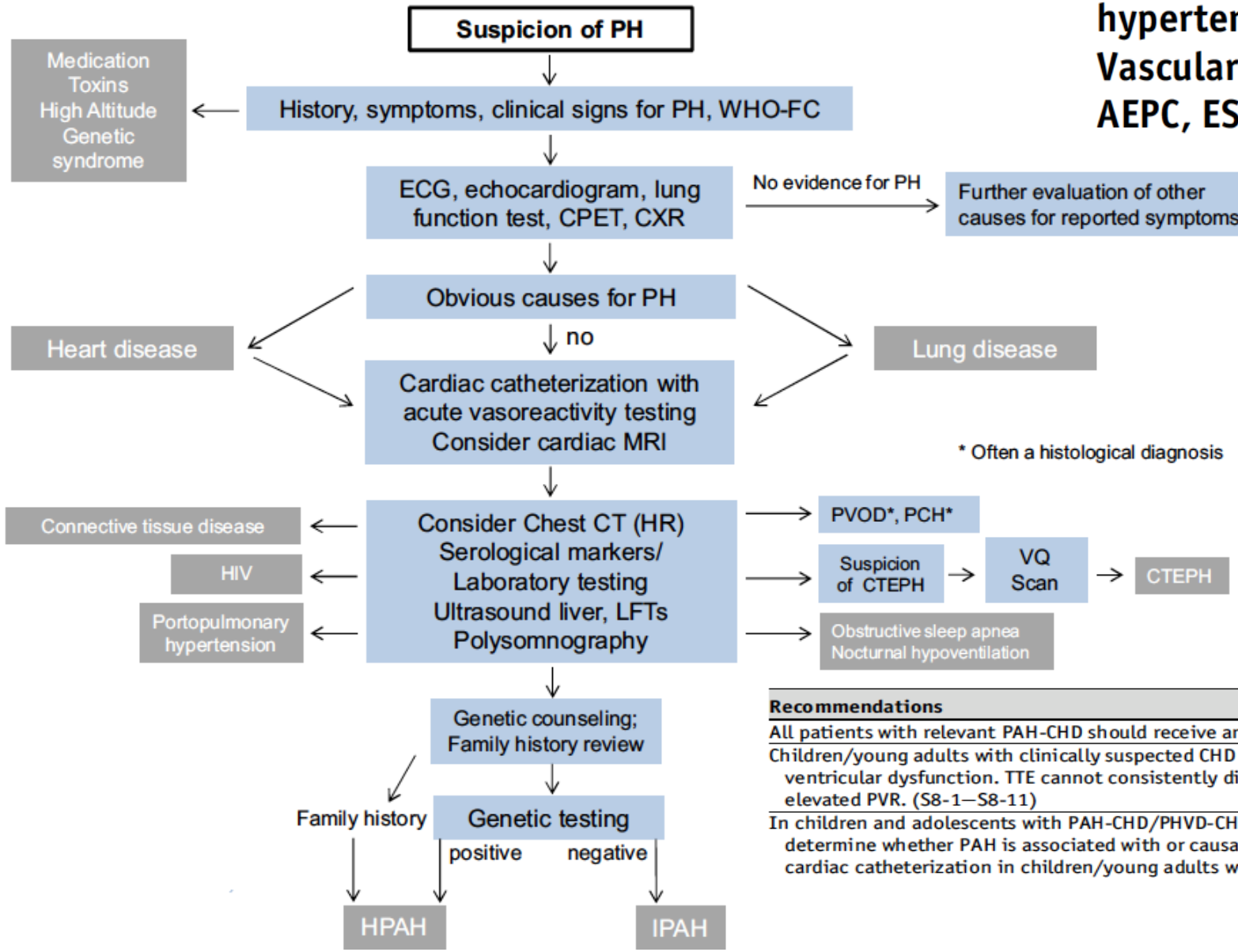




Pathophysiology of PAH-CHD



Diagnosis and evaluation of PAH associated with CHD



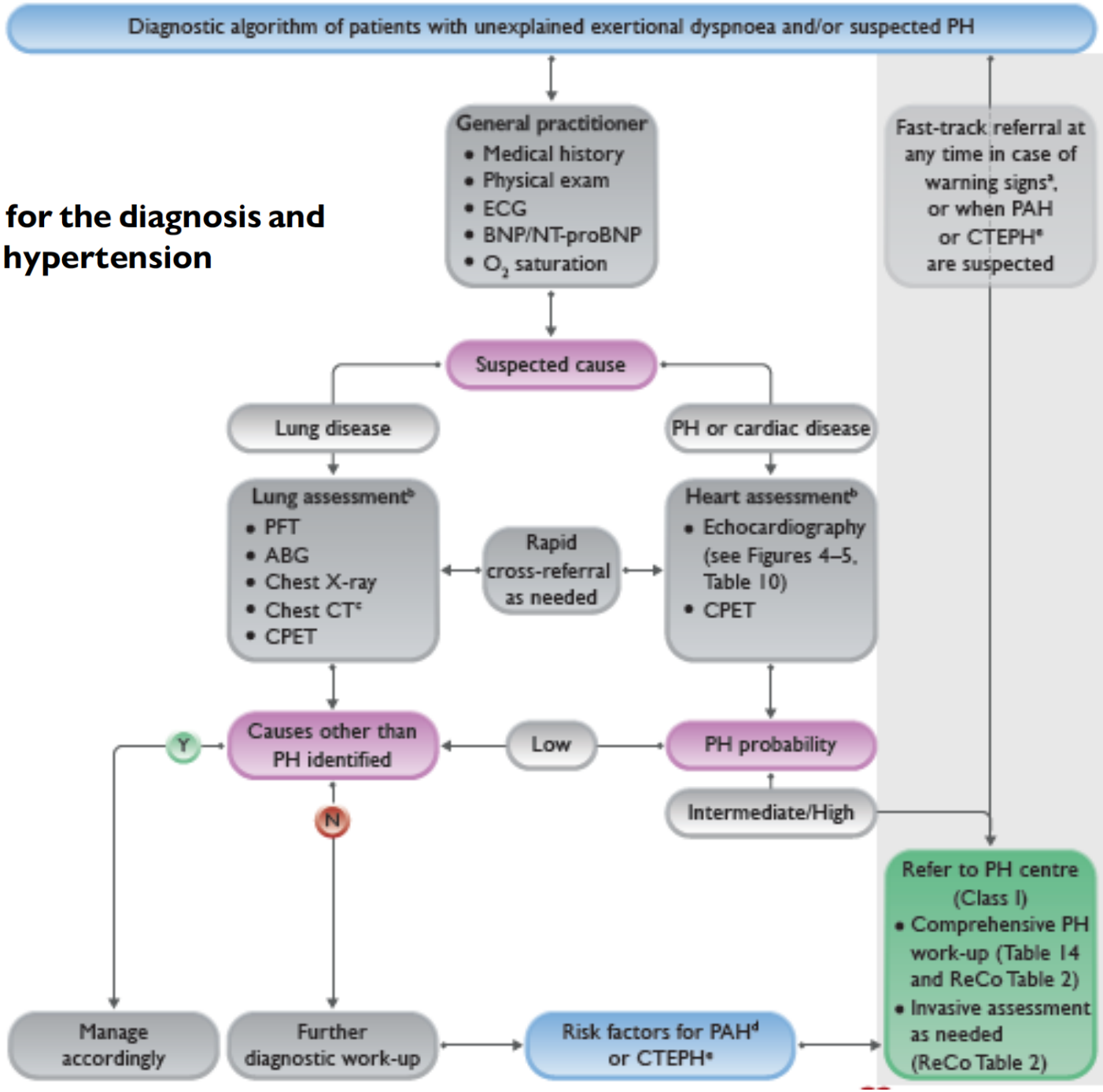
CONSENSUS STATEMENT

2019 updated consensus statement on the diagnosis and treatment of pediatric pulmonary hypertension: The European Pediatric Pulmonary Vascular Disease Network (EPPVDN), endorsed by AEPC, ESPR and ISHLT

Recommendations	COR	LOE
All patients with relevant PAH-CHD should receive and benefit from tertiary care. (S8-1, S8-2)	I	C
Children/young adults with clinically suspected CHD should undergo specific TTE screening for PAH and/or ventricular dysfunction. TTE cannot consistently distinguish between PH with increased PVR and PH without elevated PVR. (S8-1—S8-11)	I	C
In children and adolescents with PAH-CHD/PHVD-CHD, a complete diagnostic work-up needs to be performed to determine whether PAH is associated with or causally related to concomitant CHD. (S8-1—S8-3) For indications of cardiac catheterization in children/young adults with CHD and cardiovascular shunt, see Table 5 and Figure 3.	I	C

J Heart Lung Transplant 2019;38:879–901

2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension



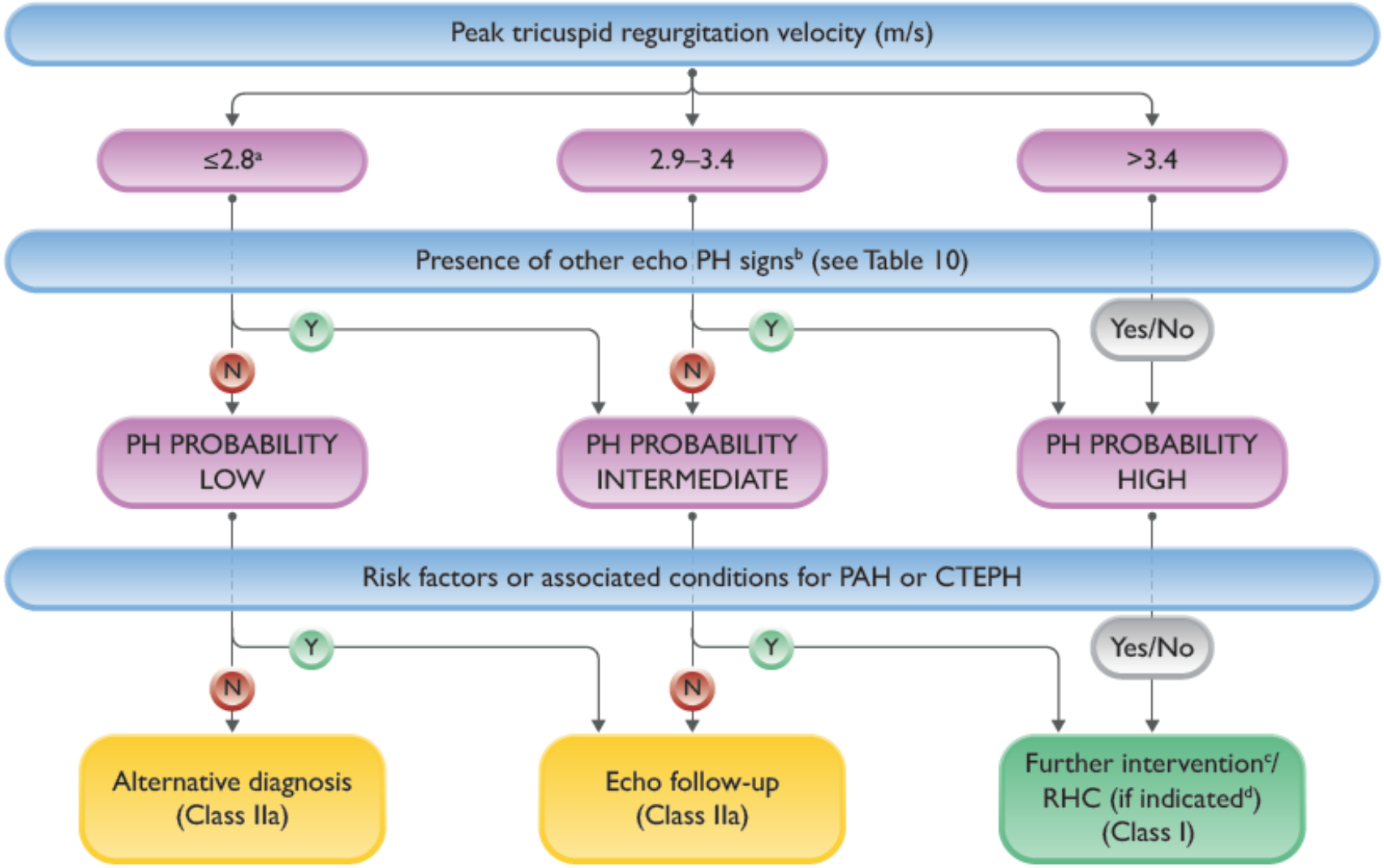
Eur Heart J 2022; 00: 1–114

2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

Diagnostic work-up: Echocardiography

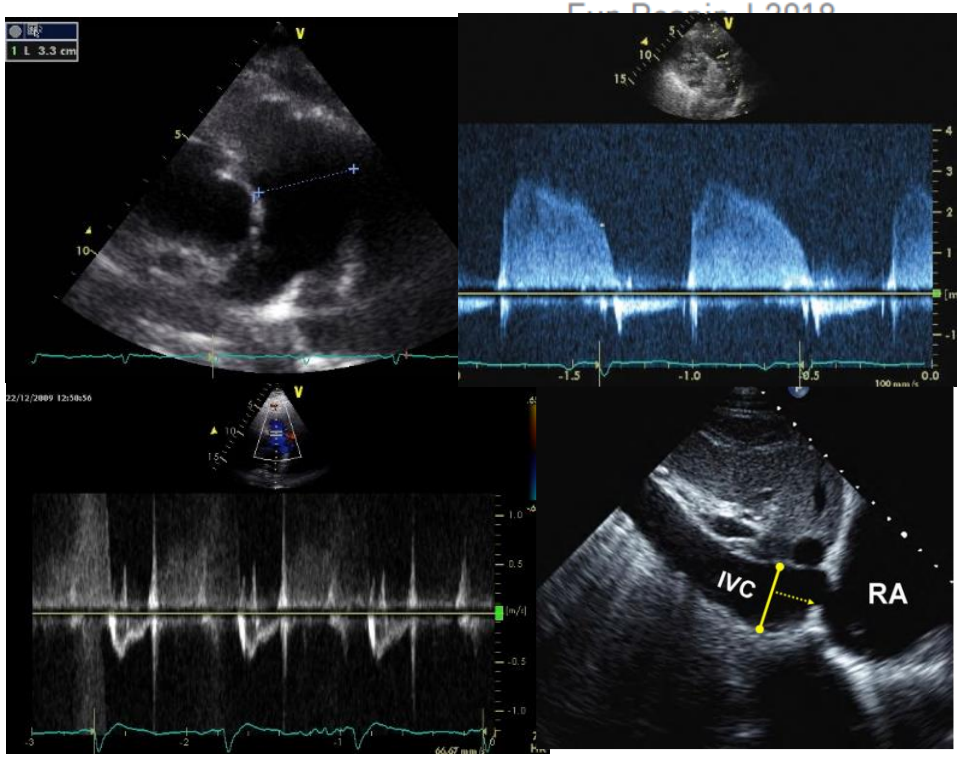
ESC/ERS GUIDELINES

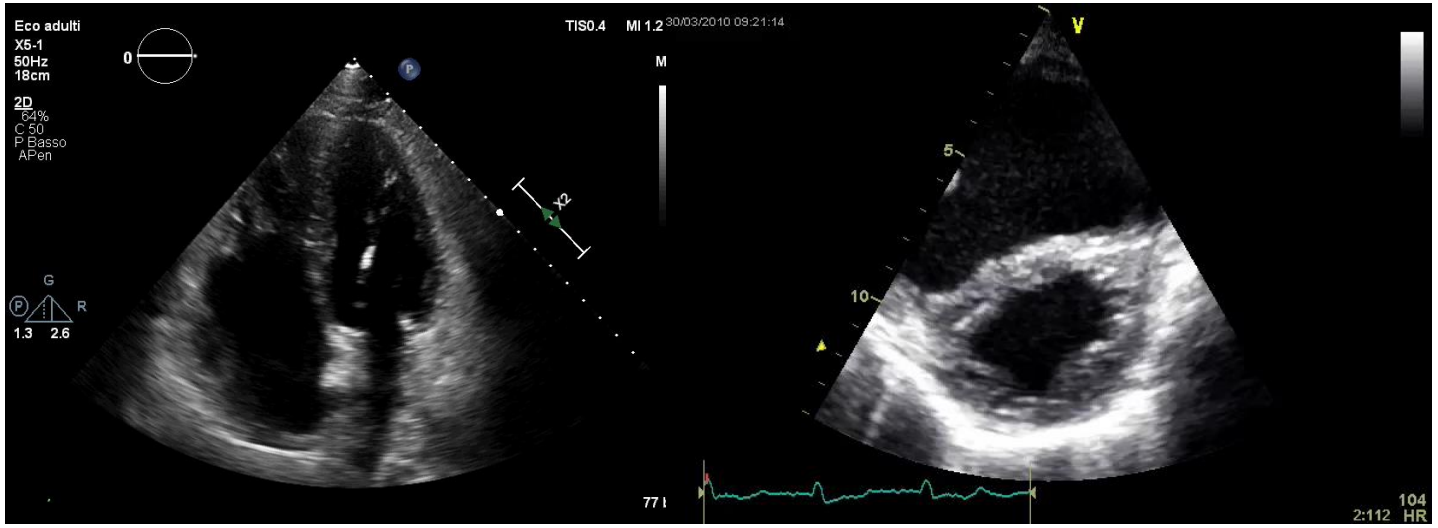
Recommendation	Class[a]	Level[b]
Echocardiography		
Echocardiography is recommended as the first-line, non-invasive, diagnostic investigation in suspected PH[82,84,91]	I	B
It is recommended to assign an echocardiographic probability of PH, based on an abnormal TRV and the presence of other echocardiographic signs suggestive of PH (see *Table 10*)[91,92,162]	I	B
It is recommended to maintain the current threshold for TRV (>2.8 m/s) for echocardiographic probability of PH according to the updated haemodynamic definition[88]	I	C

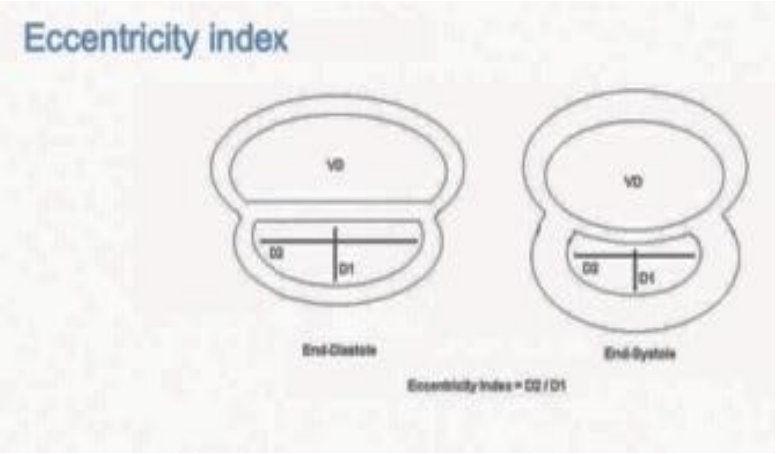


Echocardiographic signs suggestive of pre-capillary PH

A: The ventricles	B: Pulmonary artery	C: Inferior vena cava and RA
RV/LV basal diameter/ area ratio >1.0	RVOT AT <105 ms and/or mid-systolic notching	IVC diameter >21 mm with decreased inspiratory collapse (<50% with a sniff or <20% with quiet inspiration)
Flattening of the interventricular septum (LVEI >1.1 in systole and/or diastole)	Early diastolic pulmonary regurgitation velocity >2.2 m/s	RA area (end-systole) >18 cm^2
TAPSE/sPAP ratio <0.55 mm/mmHg	PA diameter >AR diameter PA diameter >25 mm	







Echocardiographic probability of pulmonary hypertension

2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

Recommendation	Class[a]	Level[b]
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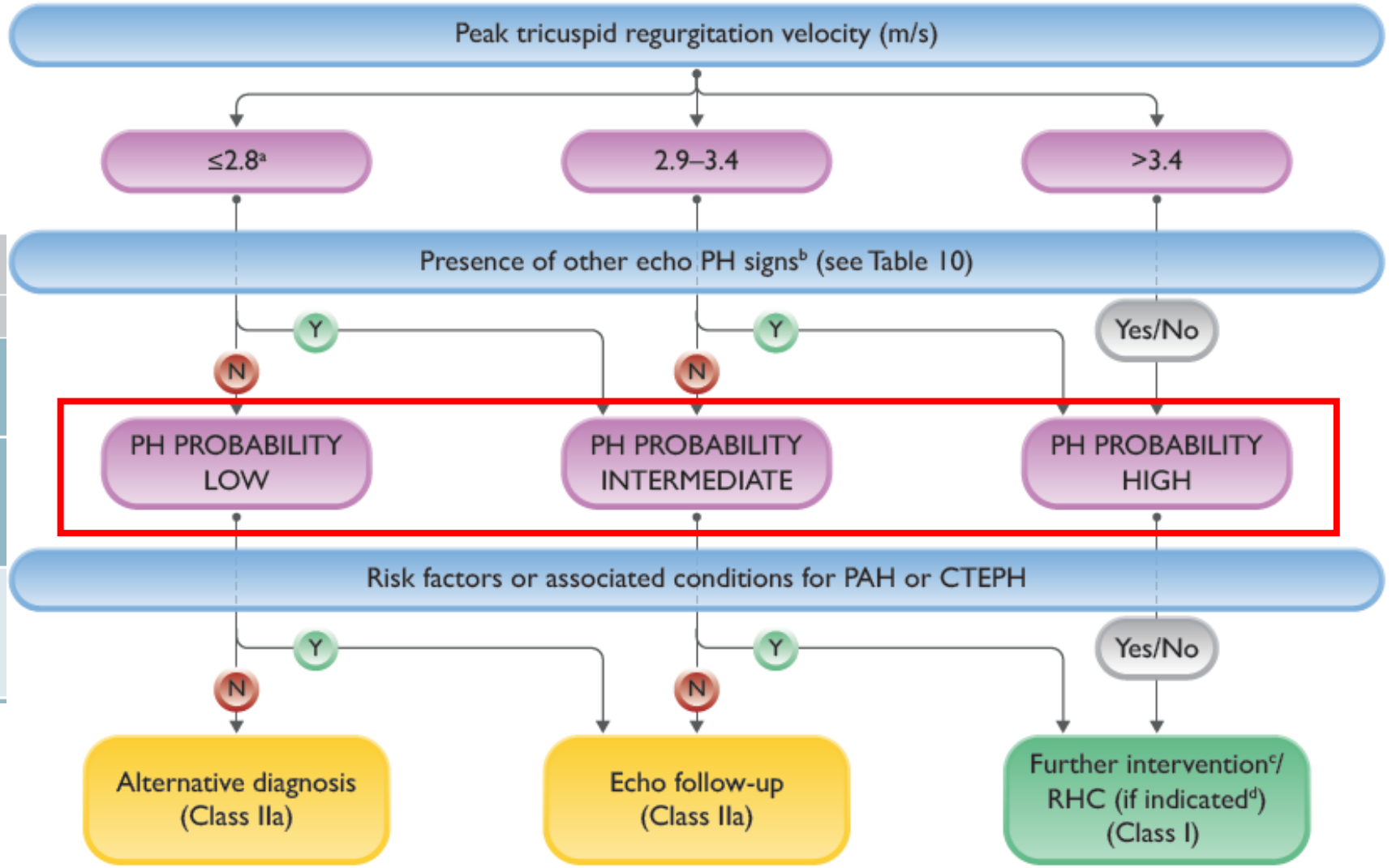
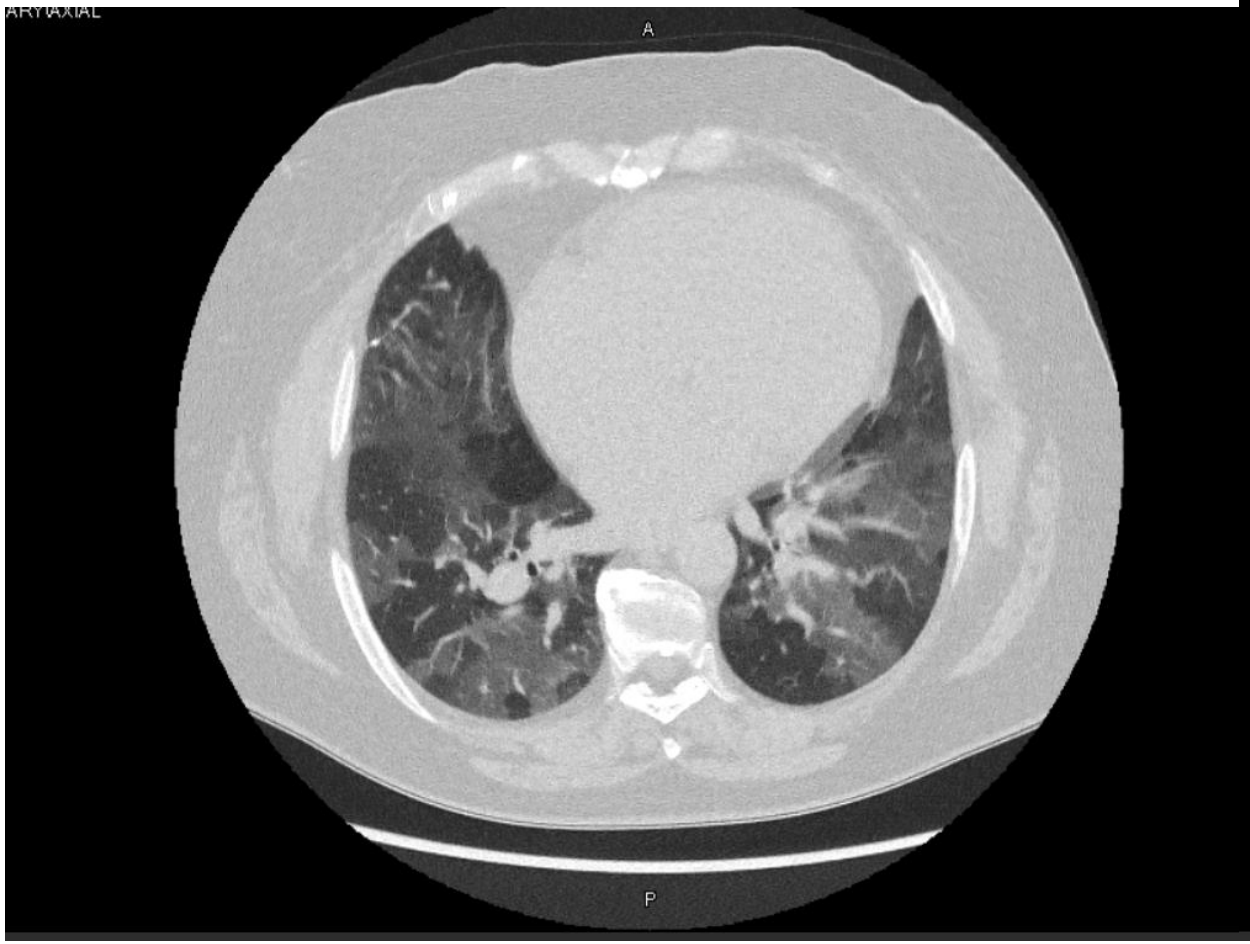


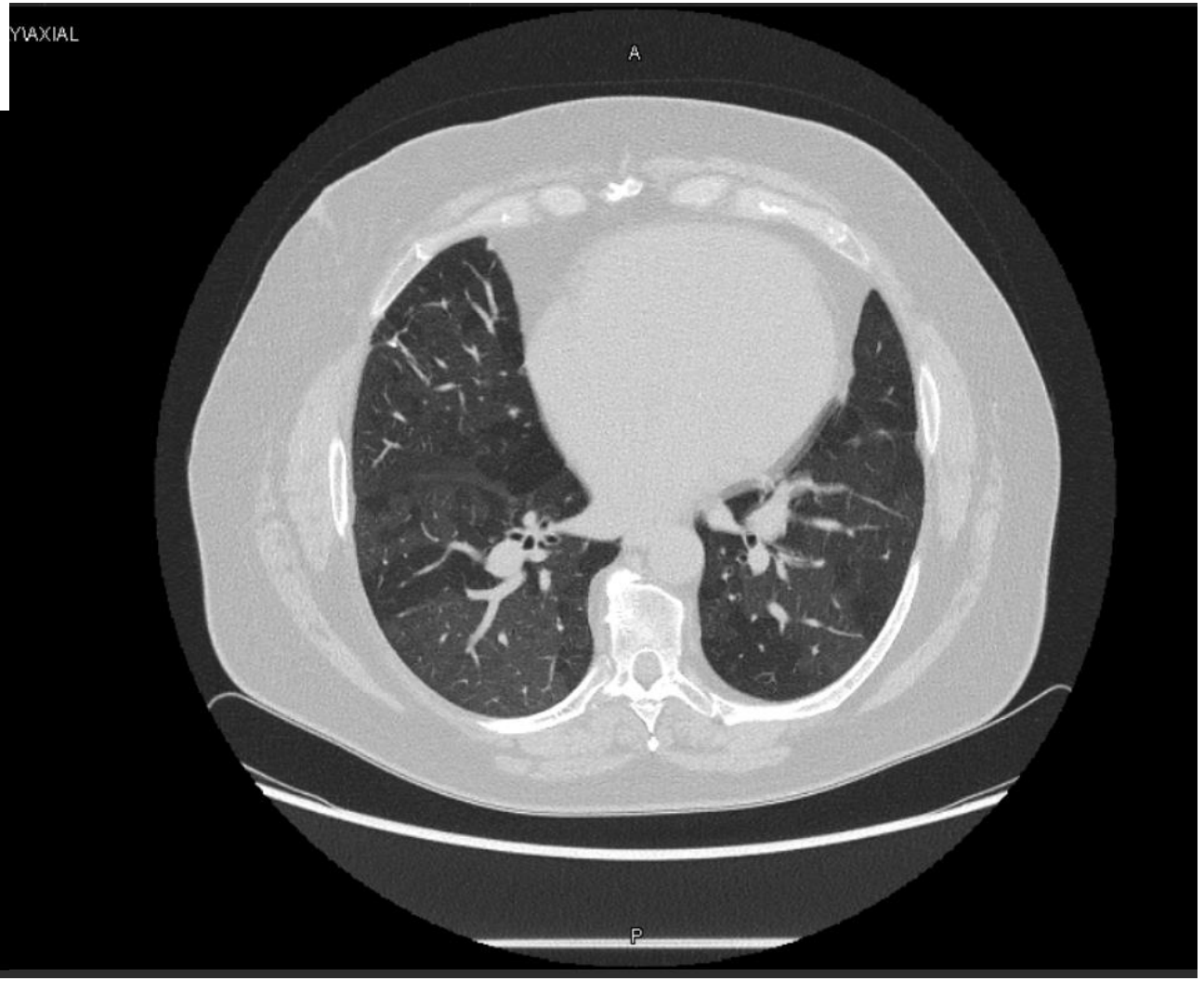
Sig.ra A-L, anni 50

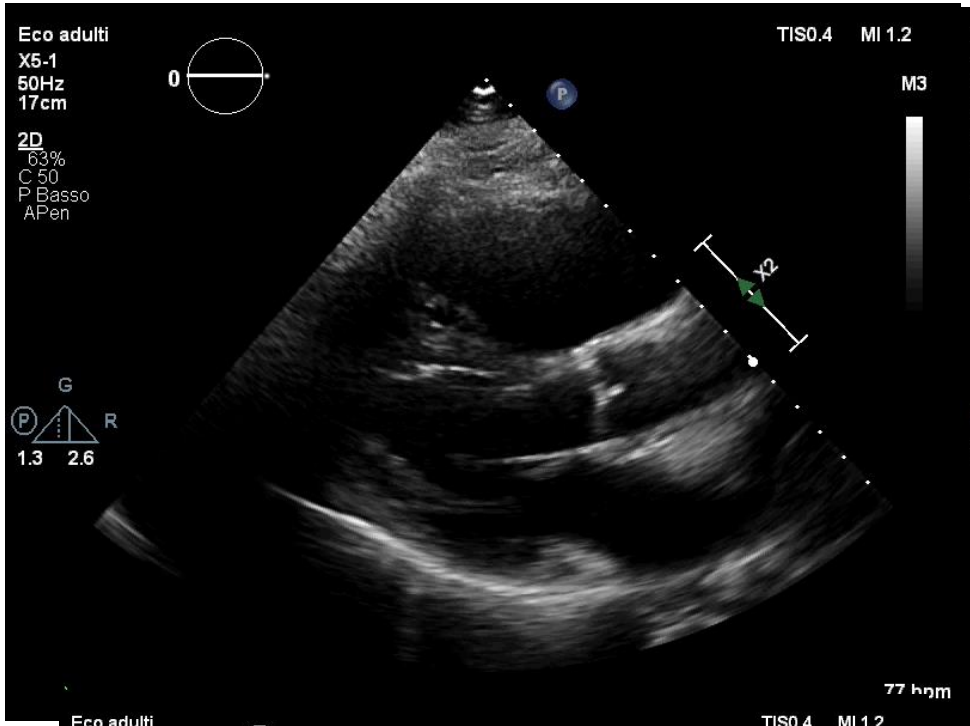
FRCV: obesità (BMI 38), ipertensione arteriosa

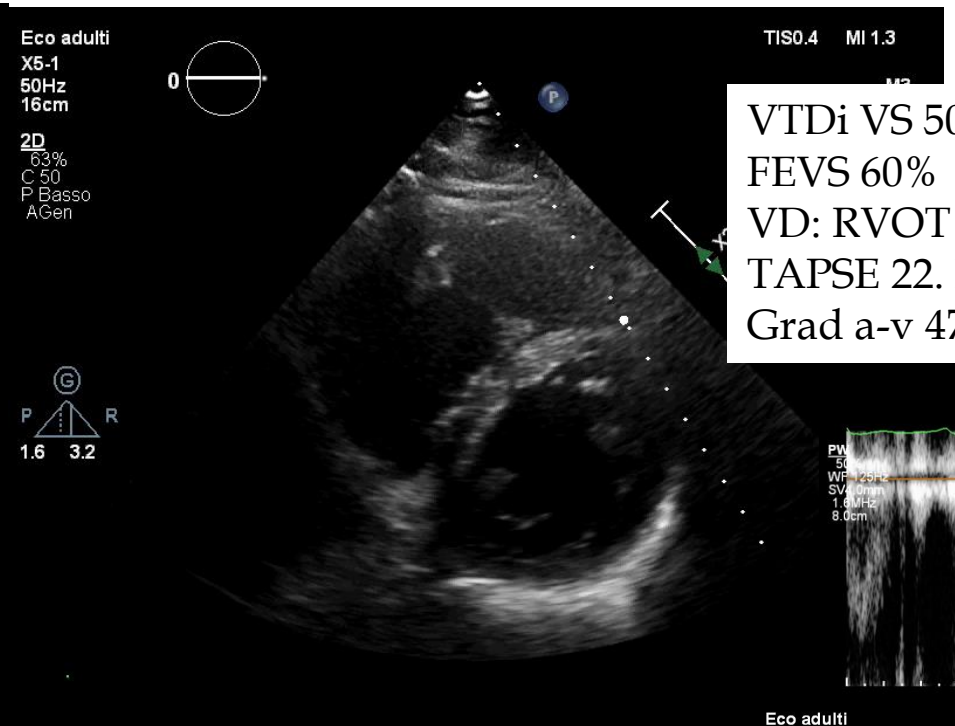
Pneumopatia grave

Dispnea da sforzo lieve

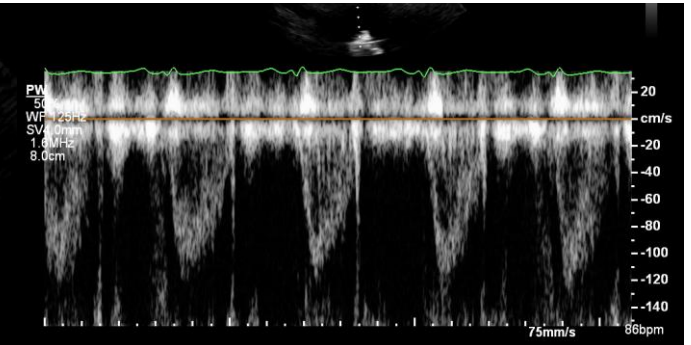


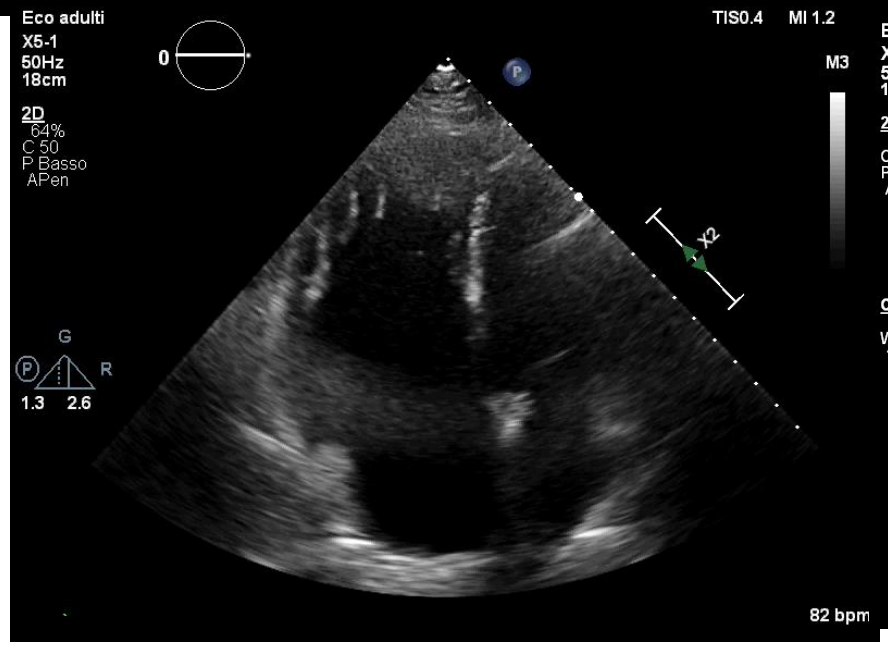


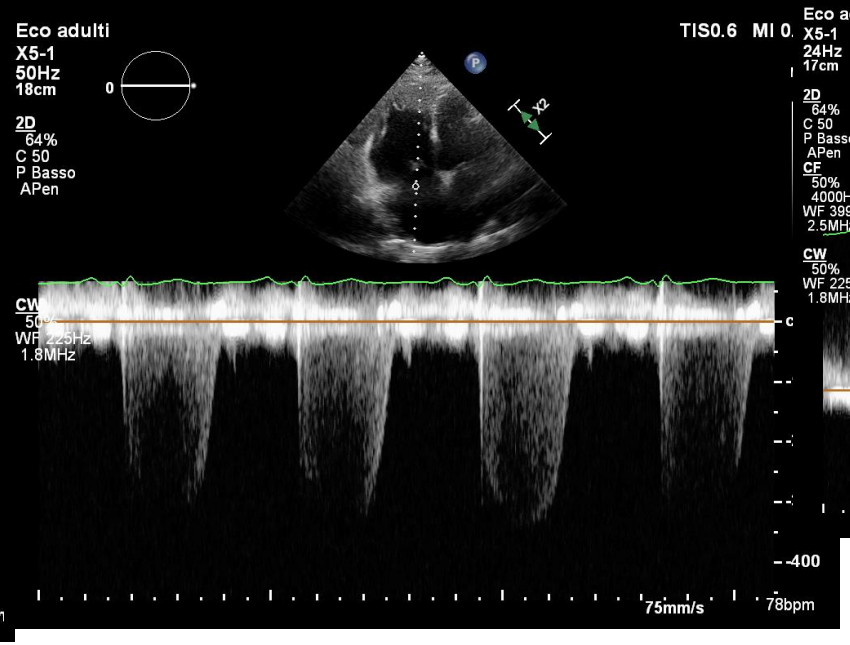


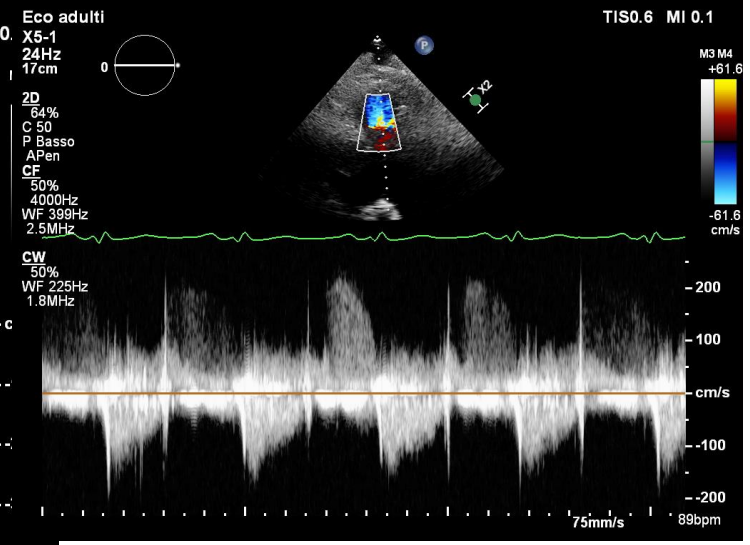


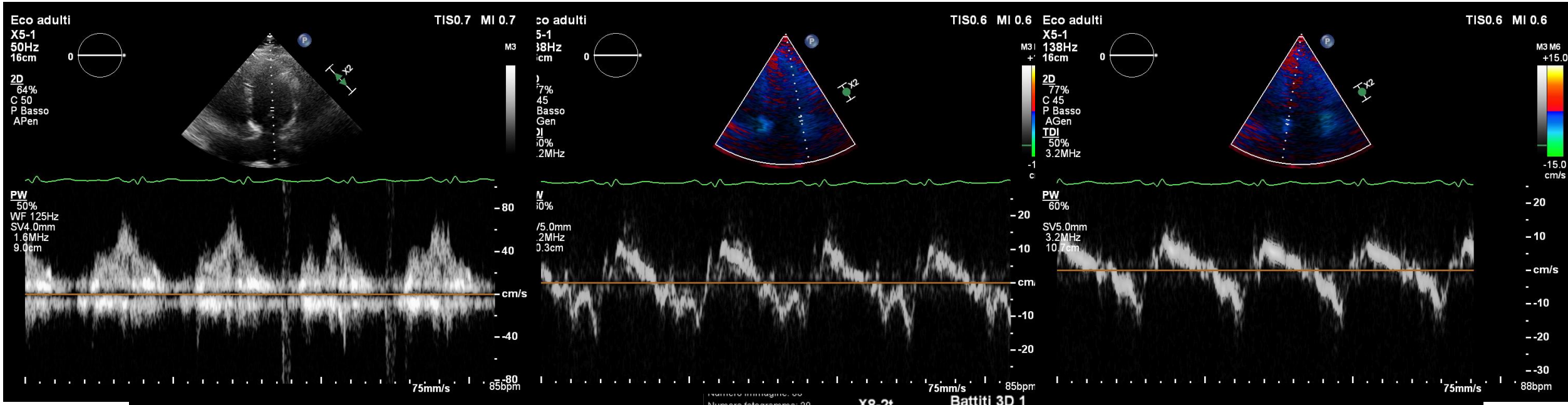
VTDi VS 50 ml/mq
FEVS 60%
VD: RVOT plax 43mm, Area Td 43 cmq
TAPSE 22. FAC 41%
Grad a-v 47 mmhg

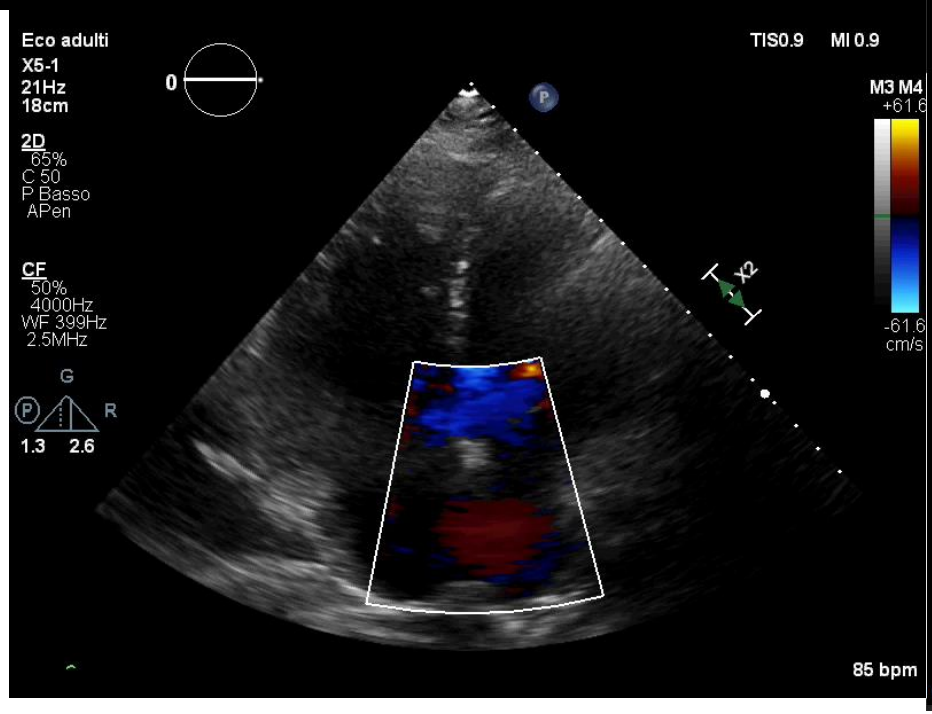


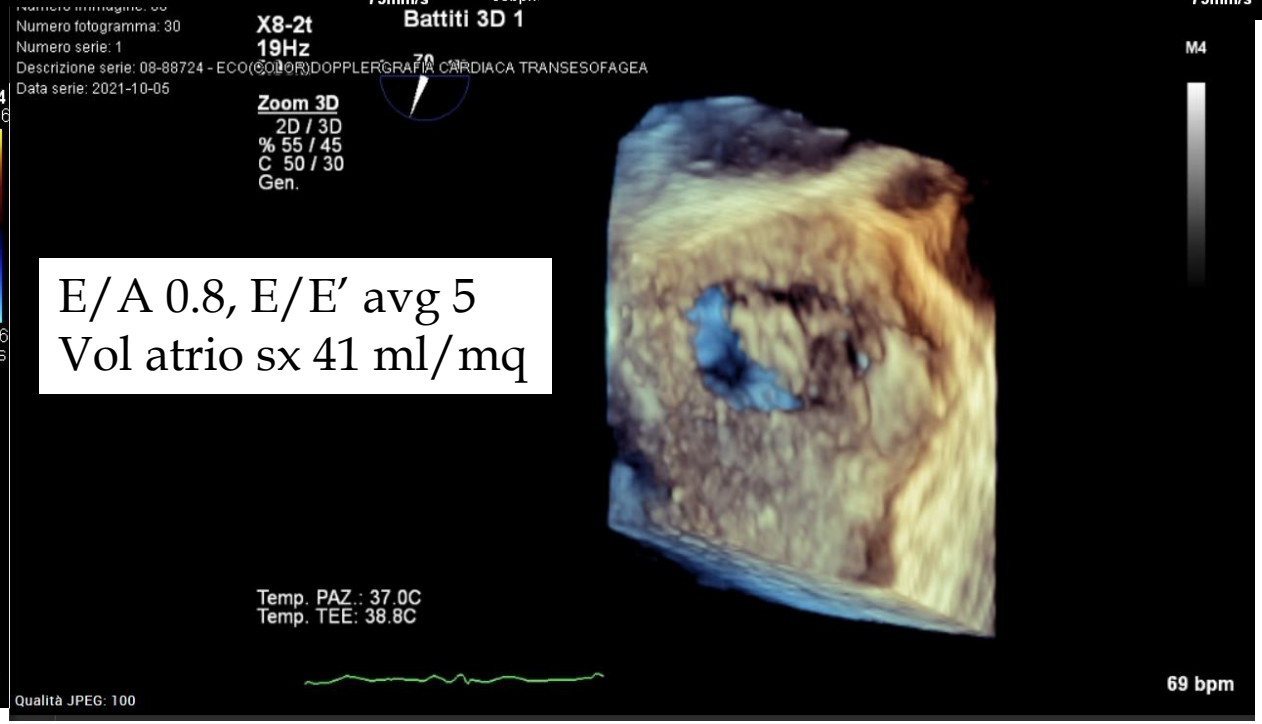










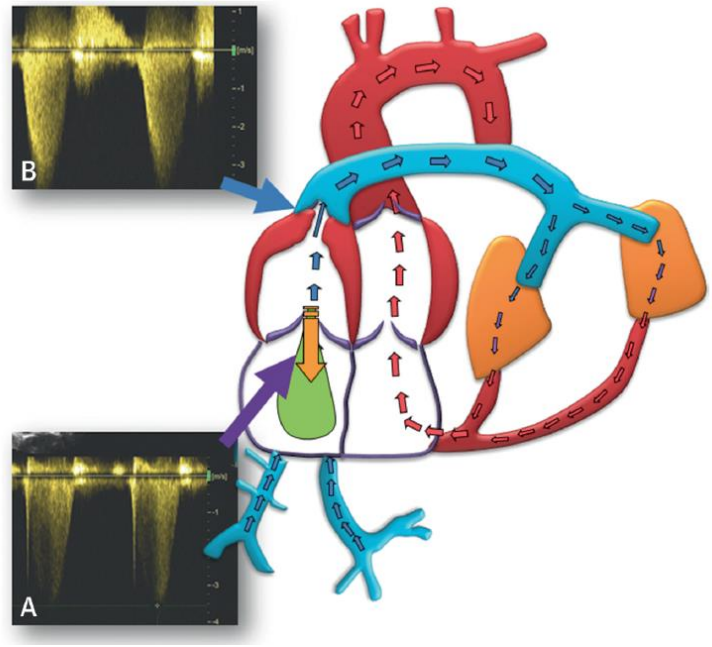


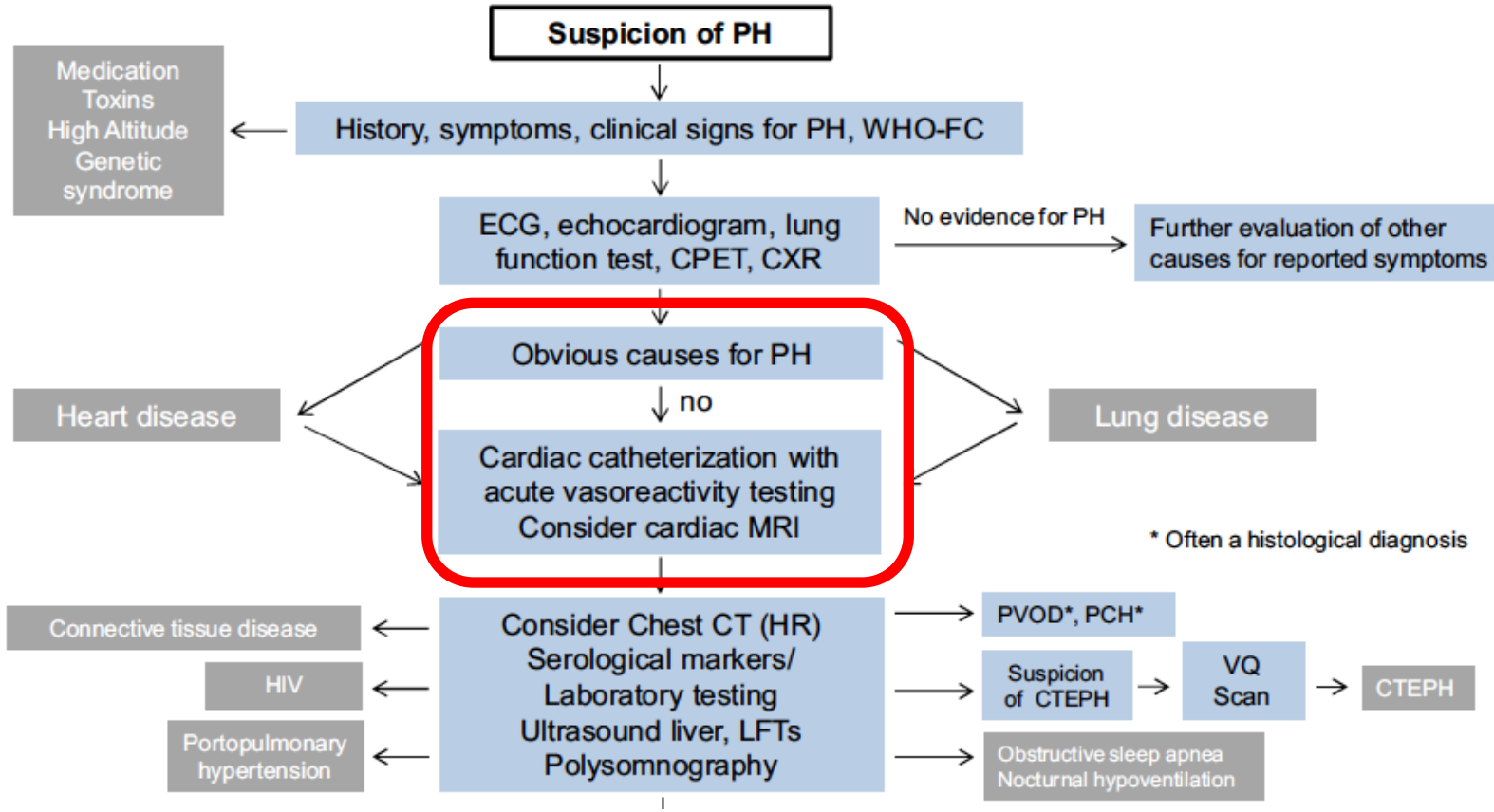
E/A 0.8, E/E' avg 5
Vol atrio sx 41 ml/mq

Echocardiographic Parameters and Signs Suggestive of PH: Considerations for Patients With CHD

Parameter	Comments Related to ACHD	Parameters Do Not Apply In:
Peak TR velocity/gradient	Assumes that: The RV is directly communicating with the pulmonary circulation (see pulmonary atresia); There is no RVOTO or peripheral pulmonary stenosis RA pressure is adequately estimated and added to the TR gradient	Pulmonary atresia Pulmonary stenosis (valvular, subvalvular, or supravalvular) Double-chambered RV Torrential TR, in which the Bernoulli equation does not appl
Ventricles RV/LV basal diameter ratio Eccentricity index (systolic and/or diastolic)	Assumes that: There is biventricular circulation There is no other cause for pressure (or volume) overload to the RV (or to the LV in patients with a systemic RV)	Univentricular hearts, both unrepaired and repaired (Fontan circulation) Pulmonary stenosis Double-chambered RV ccTGA or post-atrial switch for transposition of great arteri Atrial septal defects
PA RV outflow Doppler acceleration time/midsystolic notching Early PR velocity PA diameter	Assumes that: There is no RVOTO There is no other cause for PA dilatation (e.g., a left-to-right shunt), pulmonary stenosis/regurgitation, congenitally abnormal PA	Pulmonary stenosis Absent pulmonary valve syndrome Severe PR Atrial septal defects
Inferior vena cava Diameter Inspiratory collapse RA area	Assumes that: There is no other cause for raised RA pressure (e.g., tricuspid valve disease, left-to-right shunt, restrictive RV physiology)	Tricuspid stenosis or severe regurgitation Pulmonary stenosis Restrictive RV physiology in tetralogy of Fallot Atrial septal defects Persistent RA dilation after repair of the defect or arrhythmia (atrial fibrillation)

Patient With RVOTO





CONSENSUS STATEMENT

2019 updated consensus statement on the diagnosis and treatment of pediatric pulmonary hypertension: The European Pediatric Pulmonary Vascular Disease Network (EPPVDN), endorsed by AEPC, ESPR and ISHLT

Recommendations	COR	LOE
Cardiac catheterization is indicated in all pediatric patients with PH to confirm diagnosis and to determine severity, and anytime when PH-specific drug therapy is considered. Exceptions may apply to infants with PH and low body weight (<2–5 kg), in which case cardiac catheterization may be postponed or even omitted. Classical PPHN is a contraindication for cardiac catheterization. (S5-1–S5-5)	I	C
Initial cardiac catheterization should include right and left heart catheterization to establish the diagnosis (not only RHC), if there is no contraindication. (S5-3–S5-5)	I	C
Cardiac catheterization for the diagnosis of PH should include AVT.(S5-3–S5-5,S5-12,S5-13)	I	C

J Heart Lung Transplant 2019;38:879–901

ESC European Society of Cardiology
European Heart Journal (2021) 42, 563–645
doi:10.1093/eurheartj/ehaa554

2020 ESC Guidelines for the management of adult congenital heart disease

Pulmonary Hypertension subtypes and their occurrence in Adult CHD

Pulmonary Hypertension in Adult Congenital Heart Disease		
Definition	**Haemodynamic characteristics[a]**	**Clinical settings**
Pulmonary Hypertension (PH)	Mean PAP >20 mmHg	All
Pre-capillary PH (PAH)	Mean PAP >20 mmHg PAWP ≤15 mmHg PVR ≥3 WU	Shunt lesions prior to and after repair (including Eisenmenger syndrome) Complex CHD (including UVH, segmental PAH)
Isolated post-capillary PH	Mean PAP >20 mmHg PAWP >15 mmHg PVR <3 WU	Systemic ventricular dysfunction Systemic AV valve dysfunction Pulmonary vein obstruction Cor triatriatum
Combined pre- and post-capillary PH	Mean PAP >20 mmHg PAWP >15 mmHg PVR ≥3 WU	Settings listed under isolated post-capillary PH Settings listed under isolated post-capillary PH in combination with shunt lesions/complex CHD

CONSENSUS STATEMENT

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Table S3a. Hemodynamic Definitions of Pulmonary Hypertension

Definition [a, b, c, d]	Invasive measures [a, b, c]	PH-group
Pulmonary hypertension (PH) [a, b]	mPAP > 20 mmHg	1-5
Pre-capillary PH [a, b]	mPAP > 20 mmHg PAWP ≤ 15 mmHg PVRi ≥ 3 WU · m^2	1, 3, 4 and 5
• Isolated post-capillary PH (Ipc-PH, as defined for adults) [a, b] or	mPAP > 20 mmHg PAWP > 15 mmHg PVRi < 3 WU · m^2 DPD < 7mmHg (adults) [c]	2 and 5
• Combined post-capillary and pre-capillary PH (Cpc-PH, as defined for adults)	mPAP > 20 mmHg PAWP > 15 mmHg PVRi ≥ 3 WU · m^2 DPD ≥ 7mmHg (adults) [c]	2 and 5

2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

Definition	Haemodynamic characteristics
PH	mPAP >20 mmHg
Pre-capillary PH	mPAP >20 mmHg PAWP ≤15 mmHg PVR >2 WU
IpcPH	mPAP >20 mmHg PAWP >15 mmHg PVR ≤2 WU
CpcPH	mPAP >20 mmHg PAWP >15 mmHg PVR >2 WU
Exercise PH	mPAP/CO slope between rest and exercise >3 mmHg/L/min

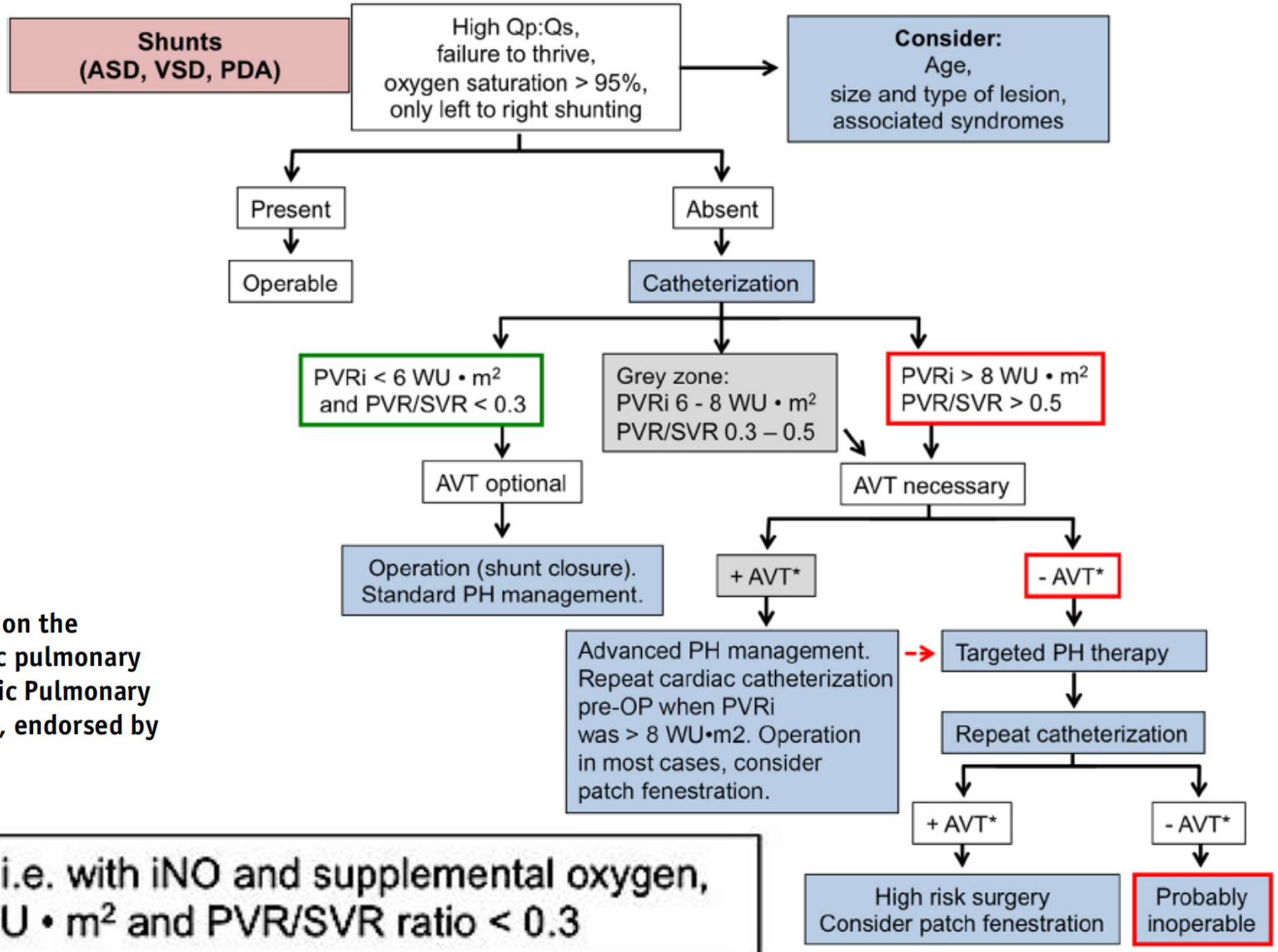
the criterion of pulmonary vascular resistance index (PVRI) ≥3 WU·m^2 in the definition for PAH in children remains unchanged.[599]

2019 updated consensus statement on the diagnosis and treatment of pediatric pulmonary hypertension: The European Pediatric Pulmonary Vascular Disease Network (EPPVDN), endorsed by AEPC, ESPR and ISHLT

Invasive Measures and clinical Implications

Measure [a-f]	Abnormality	Clinical implications
Mean RAP	Mean RAP >15mmHg	"Higher risk", RV failure, higher mortality
	Mean RAP >20mmHg	Contraindication for atrial septostomy
mPAP (mmHg) [a, b, e]	mPAP > 20mmHg	Definition of PH (WSPH, 2018)
mPAP/mSAP	mPAP/mSAP >0.3	Adjunct criterion for presence of PH
	mPAP/mSAP >0.75	Higher mortality
PAWP (mmHg)	PAWP > 15 mmHg	Criterion for post-capillary component [c]
PVR index (Wood units · m^2) [b, e]	PVR index >3 WU · m^2	Criterion for pre-capillary component [c]
	PVR index >8 WU · m^2	Inoperability in PAH-CHD
	PVR index >15 WU · m^2	"Higher risk", higher mortality
Cardiac index (L/min · m^2) by Fick principle or thermodilution	CI < 2.5 L/min · m^2	"Higher risk", low cardiac output, higher mortality
SVO_2, %	SVO_2 < 55%	Low cardiac output, higher mortality
Acute vasoreactivity testing [f]	AVT negative	see Tables 5 and 8; Figures 2, 3 and S1

Algorithm for the management of patients with CHD associated with PAH/PHVD and congenital shunt lesions



CONSENSUS STATEMENT

2019 updated consensus statement on the diagnosis and treatment of pediatric pulmonary hypertension: The European Pediatric Pulmonary Vascular Disease Network (EPPVDN), endorsed by AEPC, ESPR and ISHLT

* Positive AVT pre OP, i.e. with iNO and supplemental oxygen, PVRi decreases < 6 WU • m² and PVR/SVR ratio < 0.3

2019 updated consensus statement on the diagnosis and treatment of pediatric pulmonary hypertension: The European Pediatric Pulmonary Vascular Disease Network (EPPVDN), endorsed by AEPC, ESPR and ISHLT

Children with PVRi < 6 WU × m^2 and a PVR/SVR ratio < 0.3, in the absence of additional risk factors, are eligible for standard management/surgical shunt closure/percutaneous interventional device closure (Figure 3 and Table 5). (S8-13)	I	C
Children with PVRi ≥ 6 WU × m^2 and a PVR/SVR ratio ≥ 0.3 should be evaluated by AVT (Figure 3 and Table 5). (S8-13, S8-17).	I	C
Individual patient assessment in tertiary pediatric PH centers is particularly needed when PVRi is between 6 and 8 WU × m^2 (gray zone) (Figure 3 and Table 5). (S8-13)	I	C
A treat-to-close (treat-and-repair) approach (defined as PAH-targeted pharmacotherapy with 1–2 medications followed by partial or complete defect closure) might be considered in highly selected patients with pre- or post-tricuspid shunt (ASD, VSD, PDA) from the gray zone (PVRi 6–8 WU × m^2), and potentially even in children with PAH with PVRi > 8 WU x m^2, with the goal to decrease PVRi << 8 WU x m^2. After (complete or partial) closure, such patients must stay under long-term tertiary follow-up and be reassessed by cardiac catheterization, in addition to non-invasive measures, to assess for PVR after shunt closure. (S8-13, S8-18)	IIb	C
A partial defect closure (fenestrated patch or device) may be considered in selected patients with PAH-CHD from the gray zone (PVRi 6–8 WU × m^2), with or without preceding treat-to-close (treat-and-repair) approach. The impact of PVR numbers alone for clinical decision making differs between patients at different ages (e.g., infants with VSD vs young adults with ASD). (S8-18–S8-20)	IIb	C

2020 ESC Guidelines for the management of adult congenital heart disease

Shunt repair.

N	In patients with shunt lesions and non-invasive signs of PAP elevation, invasive measurement of PVR is mandatory.
N/R	Adjusted recommendations for shunt closure (when Qp:Qs >1.5) according to calculated PVR:
	<3 WU: class I for ASD, VSD, and PDA
	3–5 WU: class IIa for ASD, VSD, and PDA
	≥5 WU but decreasing to <5 WU after targeted PAH treatment: class IIb for ASD (fenestrated closure only)
	≥5 WU for VSD and PDA (careful individual decision in expert centres); class IIb
	≥5 WU despite targeted PAH treatment: class III for ASD.
N	In patients with ASD and LV disease, it is recommended to perform balloon testing and carefully weigh the benefit of eliminating L–R shunt against the potential negative impact of ASD closure on outcome due to increase in filling pressure (taking closure, fenestrated closure, and no closure into consideration).

The window for reversibility is critical in patients with PAH-CHD

- Grey zone: individual patient evaluation in tertiary centres
- Recommendations are predominantly based on expert opinion
- No prospective studies have yet identified reliable haemodynamic cut-offs that predict reversal of pulmonary vascular disease and normalisation of haemodynamics after cardiac correction.
- Post-operative progressive PAH-CHD:
  - Pediatric 2-6%
  - Adult 7-13%

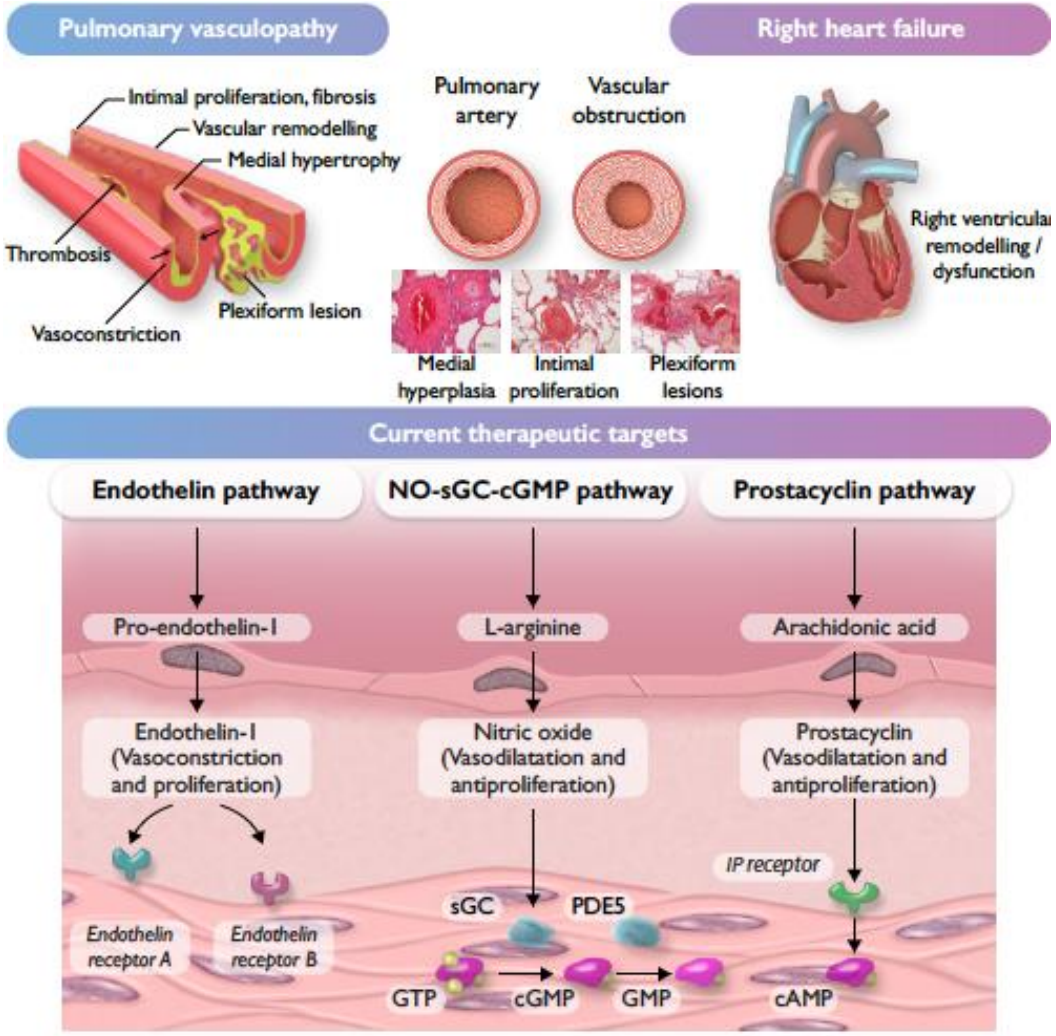
Additional indices for the assessment of reversibility in PAH-CHD

Contemporary indices		
Age and CHD type	Younger age at shunt correction favours reversibility. High flow+high pressure lesions more rapidly lead to irreversible PAH than high flow only. *Age below which reversible PAH is likely.* *TA, AVSD, TGA: <6–12 months. VSD, PDA: <1–2 years. ASD: 30–40 years.*	C
Comorbidities	Comorbidities such as Down syndrome, congenital diaphragmatic hernia, bronchopulmonary dysplasia, arteriovenous malformations, hereditary telangiectasia, hyperthyroidism or rheumatoid arthritis are associated with increased risk to develop irreversible PAH in CHD.	C
Physical examination	*Indicative of irreversible PAH:* cyanosis at exertion, peripheral oxygen saturation <90%, clubbing, RV heave, accentuated pulmonary 2° heart sound component, fading of ventricular murmur.	C
Echocardiographic evaluation	*Indicative of reversible PAH:* Net shunt direction is left-to-right. Pulmonary to systemic blood flow ratio (Qp/Qs) is 2:1.	C
Right heart catheterisation	*Indicative of reversible PAH: PVR<4 WU.* *Indicative of irreversible PAH: PVR>8 WU.* PVR 4–8 WU: further evaluation in tertiary centres.	B
Evaluated indices		
Genetic evaluation	BMPR2 and Sox17 mutations predispose to PAH in CHD. Other mutations associated with PAH, but not (yet) with PAH-CHD include: BMPR1B, ACVRL1, TBX4, EIF2AK4, KCNK3, ALK5, SMAD4, SMAD9, AGTR1, CAV1, EDN1, EDNRA, ENG, KCNA5, NOS2, NOTCH3, SERPINE1, SIRT3, THBS1, TOPBP1, TRPC6.	C
PA stiffness indices	*Indicative of reversible PAH:* PA-distensibility>0.95 %/mm Hg. PA-compliance>0.08 mm^2/mm Hg.	C

van der Feen DE, et al. Heart 2019;105:276–282.

Treatment PAH with small/coincidental defect or persistent PAH after defect closure

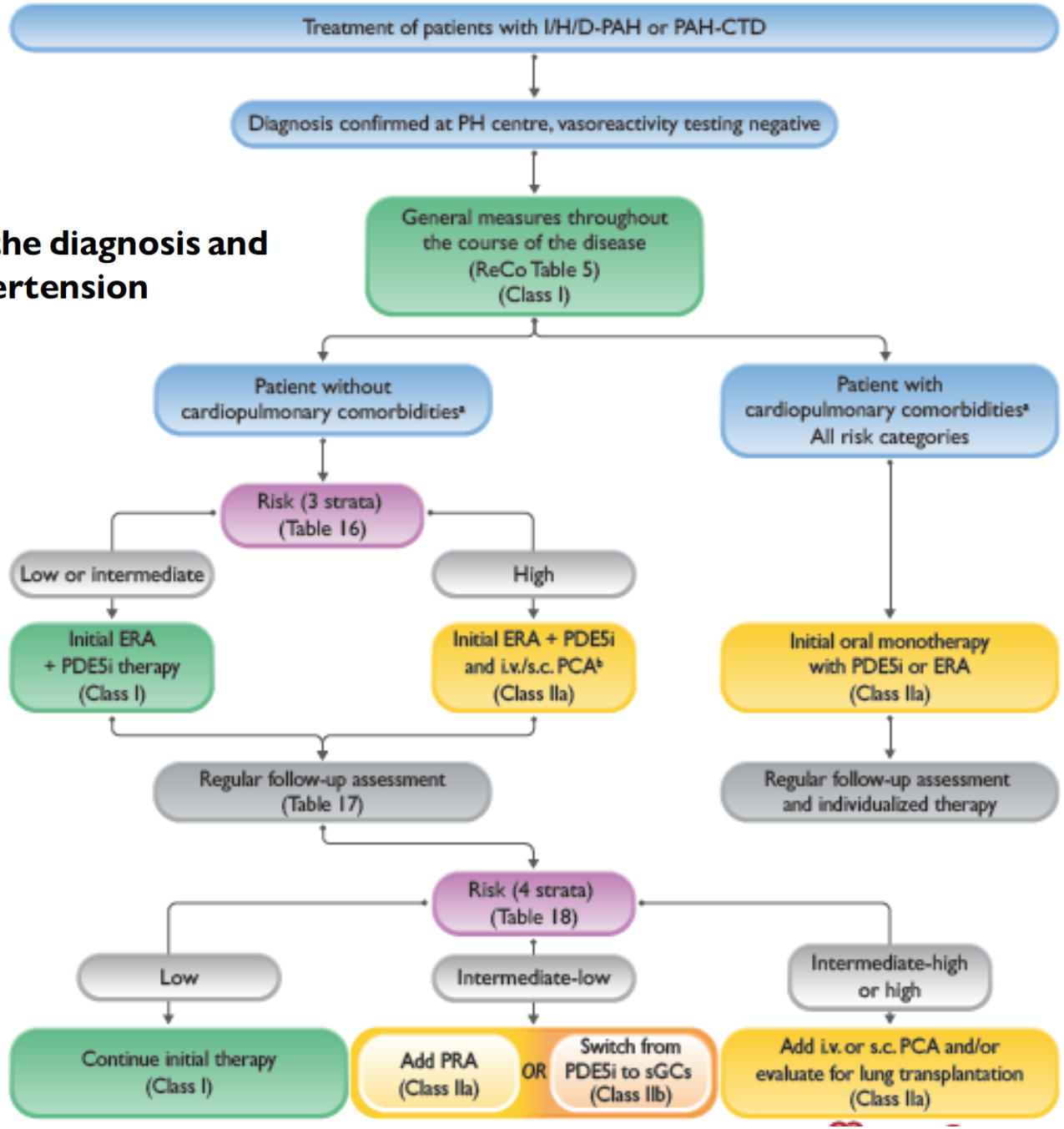
Recommendations	Class[a]	Level[b]
Risk assessment		
Risk assessment is recommended for patients with persistent PAH after defect closure	I	C
In patients with PAH after corrected adult CHD, initial oral combination therapy with drugs approved for PAH should be considered for patients at low and intermediate risk, while initial combination therapy including i.v./s.c. prostacyclin analogues should be considered for patients at high risk	IIa	C[c]



ESC/ERS GUIDELINES

EUROPEAN SOCIETY OF CARDIOLOGY

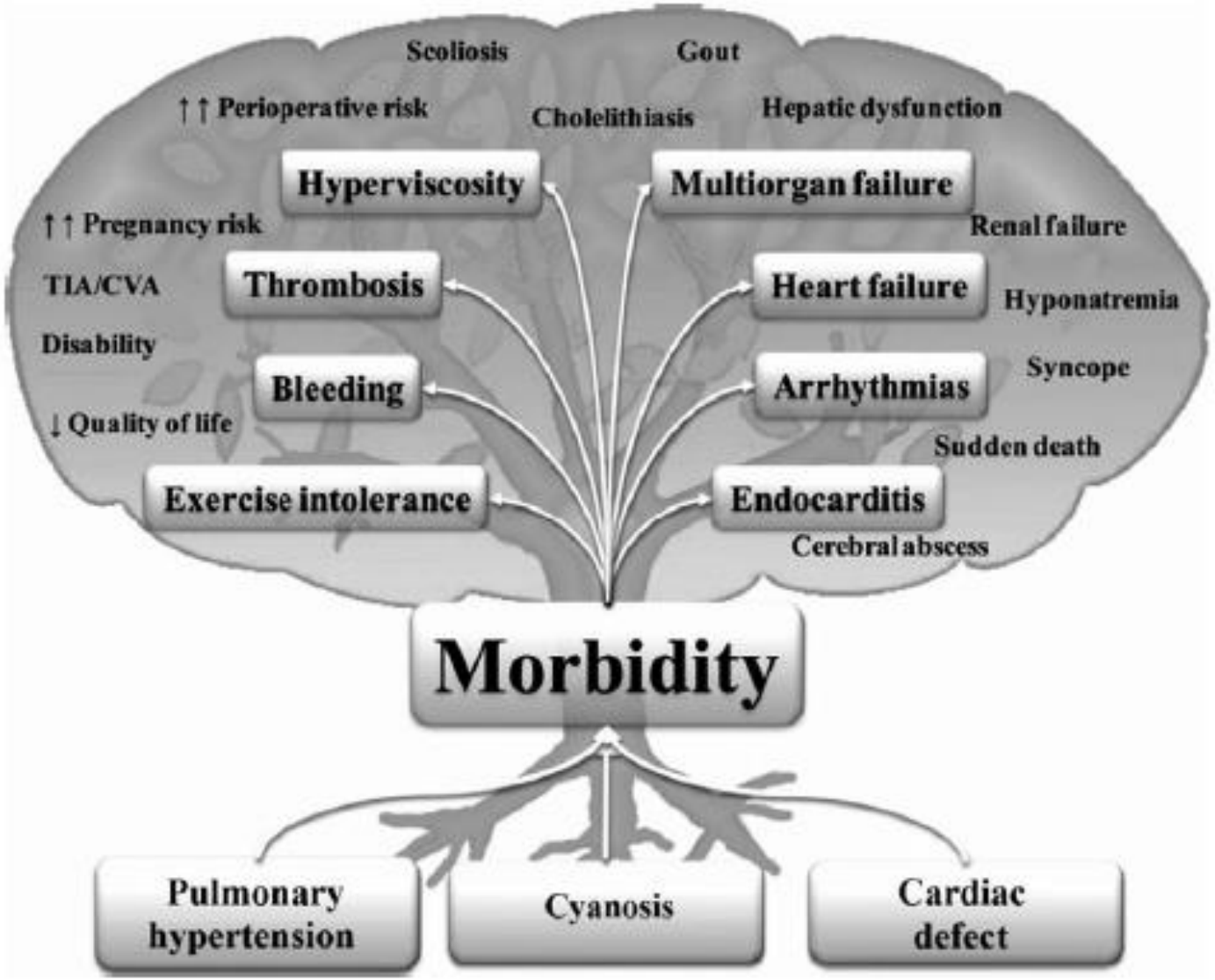
2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension



Eur Heart J 2022; 00: 1–114

Eisenmenger syndrome

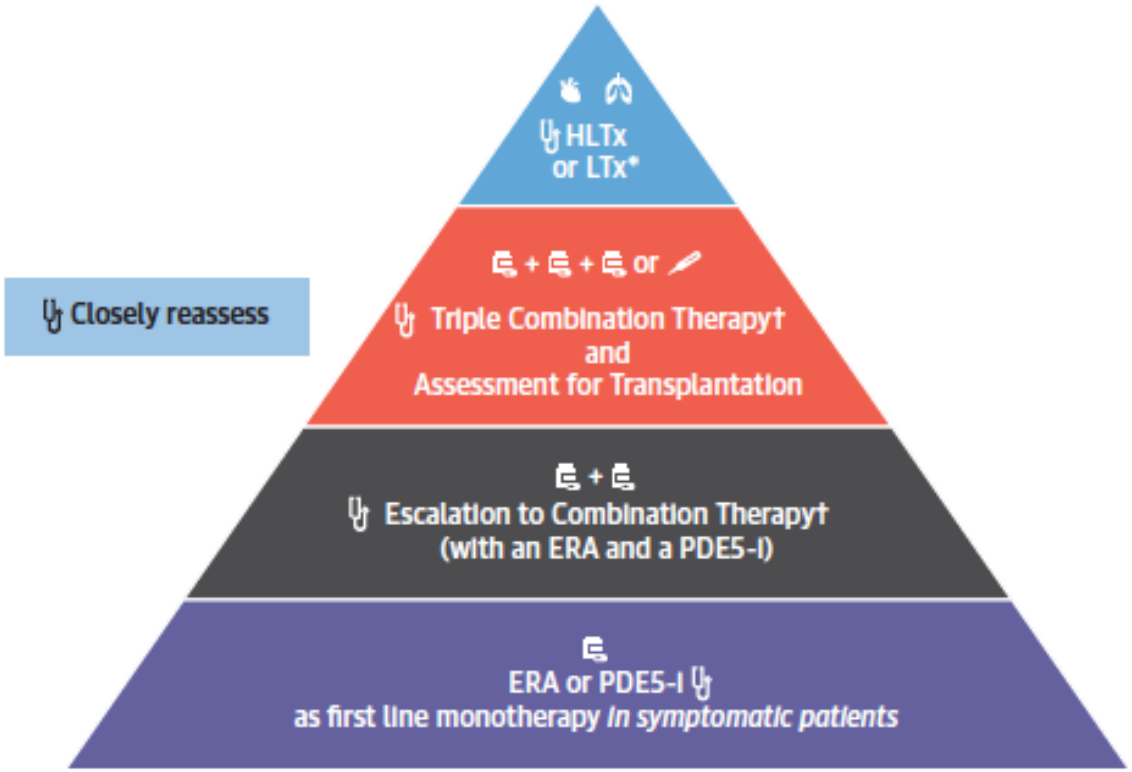
Issues	Suggestions/Recommendations
Secondary erythrocytosis	No place for routine venesections If a trial of venesection is considered • Only in expert centers • In patients with hemoglobin >22 g/dL and hematocrit >65% presenting with severe hyperviscosity symptoms in the absence of dehydration • At small volumes (250-500 mL) with simultaneous fluid replacement to avoid hemodynamic imbalance
Iron deficiency	Check iron profile (transferrin saturation <20%, best marker of iron deficiency anemia) Oral iron supplementation • Consider gastrointestinal side-effects Intravenous supplementation • Administer at a slow rate • Take care to avoid air emboli Periodic blood tests (iron profile/full blood count)
Thrombotic diathesis	Oral anticoagulation should be recommended in case of atrial arrythmia and in the presence of PA thrombus or emboli Vitamin K antagonists remain the oral anticoagulants of choice pending safety and efficacy data on direct oral anticoagulants
Hemoptysis	Anticoagulation is not recommended in patients with active or recurrent hemoptysis Supportive treatment • Manage concomitant respiratory tract infections, suppress coughing reduce physical activity, treat hypovolemia and (relative) anemia CTPA to determine the presence and location/origin of intrapulmonary hemorrhage Coil embolization of causative bronchial arteries in selected patients Inhaled tranexamic acid may be considered
Arrhythmias	Prompt restoration and maintenance of sinus rhythm recommended Catheter ablation in specialized centers may be considered in patients with intractable arrhythmia Transvenous pacing requires anticoagulation. Alternative pacing strategies, including epicardial and leadless systems, may be considered and tailored according to individual patient risk assessment S-ICD may be considered for secondary prevention of sudden cardiac death and for high-risk patients (primary prevention, eg, severe ventricular dysfunction and syncope) S-ICD should be favored in suitable candidates with ICD indications not needing antibradycardia pacing.
Advanced PAH therapies	Risk stratification for all patients based on available predictors and risk scores (Figure 1) Consider starting with an ERA monotherapy in symptomatic (>I WHO FC) patients with reduced functional capacity followed by a combination therapy (with a PDE5 inhibitor) to optimize patient Consider escalating to triple combination therapy in selected high-risk patients



PAH treatment in Eisenmenger syndrome

2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

Treatment		
Bosentan is recommended in symptomatic patients with Eisenmenger syndrome to improve exercise capacity[574]	I	B
In patients with adult CHD, including Eisenmenger syndrome, other ERAs, PDE5is, riociguat, prostacyclin analogues, and prostacyclin receptor agonists should be considered	IIa	C
In patients with adult CHD, including Eisenmenger syndrome, sequential combination therapy should be considered if patients do not meet treatment goals	IIa	C



ESC/ERS GUIDELINES

Prognostication in Eisenmenger syndrome

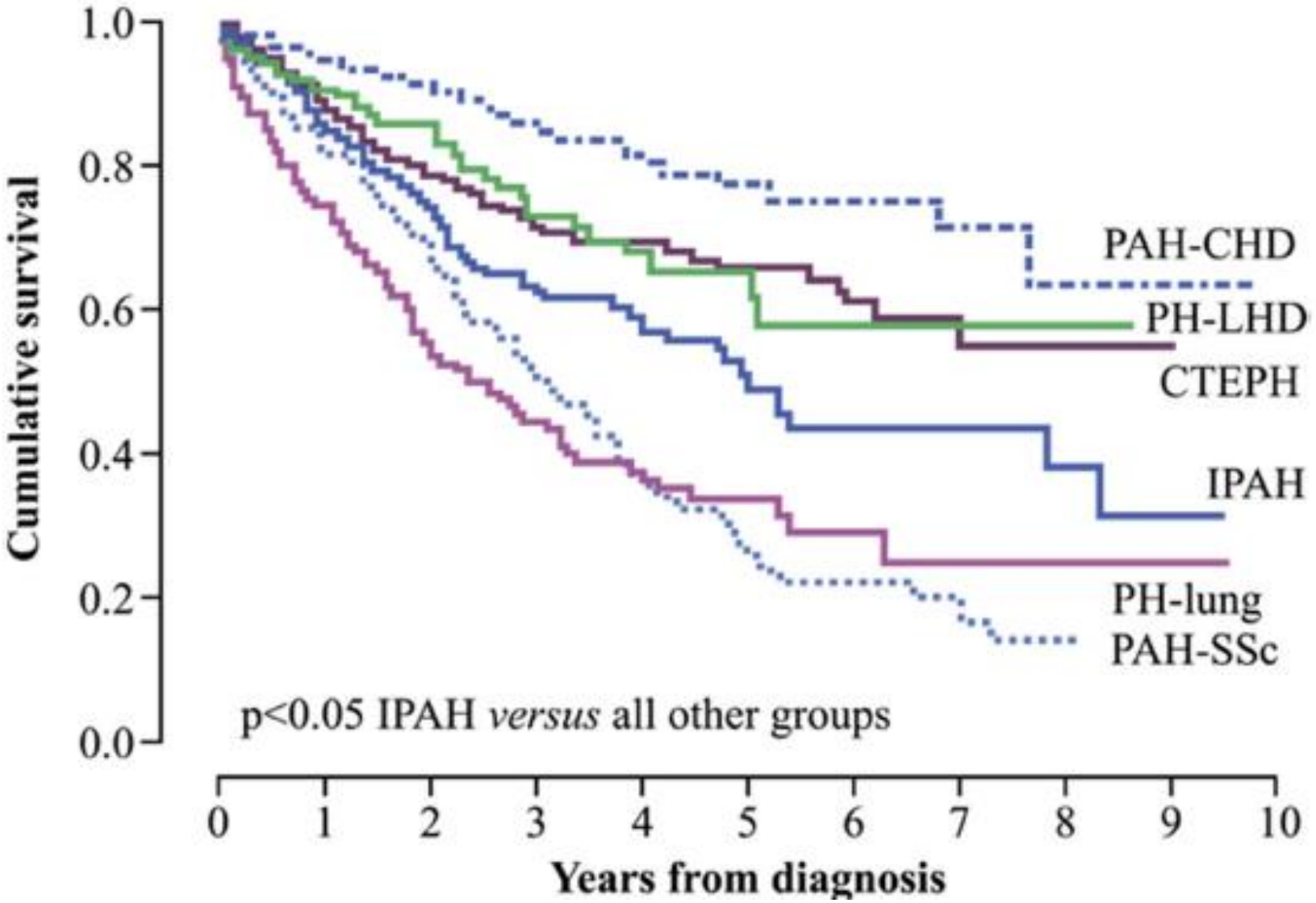
Better Prognosis	Determinants of Prognosis	Worse Prognosis
Post-tricuspid shunt	Level of shunt [8]	Pre-tricuspid shunt
Simple defect (i.e. VSD, PDA)	Complexity of CHD [11]	Complex defect (i.e. single ventricle)
Mild Resting O_2 saturations 85-90%	Cyanosis [8, 10]	Moderate / severe Resting O_2 saturations <85%
Transferrin saturation of >20%	Iron deficiency anaemia [18]	Transferrin saturation of <20%
I, II	NYHA functional class [12]	II, IV
Slow	Rate of symptoms progression	Rapid
No	Right ventricle failure	Guarded prognosis
Longer (> 400 m)	6 minute walk distance [10]	Shorter (< 300 m)
BNP plasma levels <13.9 pmol/L Normal CRP levels	Biomarkers (BNP, CRP) [13, 14]	BNP plasma levels > 30 pmol/L CRP levels >10 mg/L
TAPSE ≥ 1.5 cm RA area < 25 cm^2 RA/LA < 1.5 No pericardial effusion	Echocardiographic markers [8, 15]	TAPSE < 1.5 cm RA area ≥ 25 cm^2 RA/LA ≥ 1.5 Pericardial effusion
RAP < 8 mmHg and CI ≥2.5 L/min/m^2	Baseline haemodynamics	RAP > 15 mmHg and CI ≤ 2.0 L/min/m^2
Decrease in PVRi ≥ 25%	Acute vasoreactivity testing [16]	No changes or decrease in PVRi ≤ 25%

Heart 2018

Recommendations, Evidence Gaps, and Future Perspectives on Management of Patients With Eisenmenger Syndrome

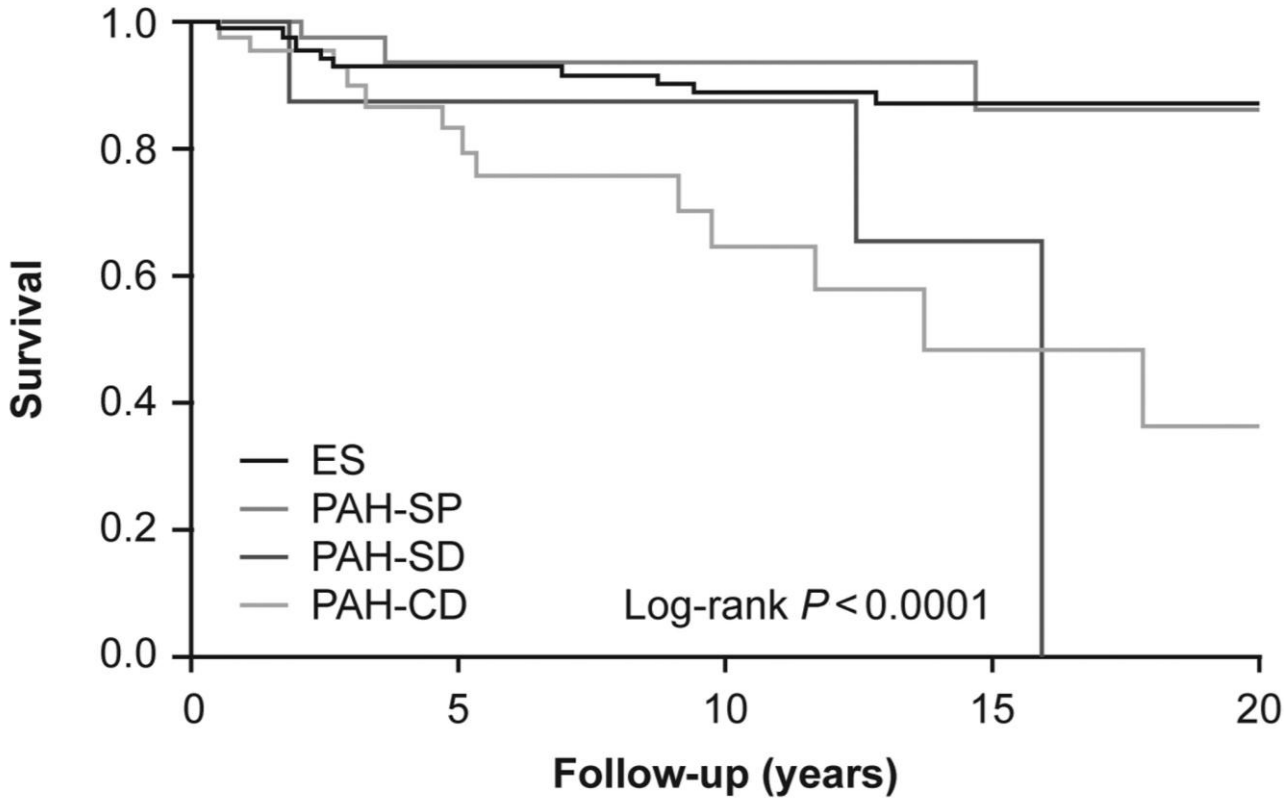
ESC GUCH guidelines 2010[44]	AHA/ACC ACHD guidelines 2018[45]	Therapeutic gaps and ambiguities
Bosentan should be initiated in WHO-FC III patients (IB)	Bosentan is beneficial in symptomatic adults with ASD or VSD (IA) Bosentan is a reasonable therapy to treat symptomatic adults with PDA or aortopulmonary window (IIa C Expert Opinion), or complex lesions or Down syndrome (IIa—B non-randomised trials)	▶ What about mildly symptomatic patients in WHO FC II? ▶ Are symptoms the only criterion for initiating a PAH-specific therapy? ▶ Should patients be stratified according to their risk for adverse outcomes? ▶ No RCTs to establish the use of bosentan in patients with shunts other than ASD or VSD
Other ERAs, PDE-5 inhibitors and prostanoids should be considered in WHO-FC III patients (IIa C)	It is reasonable to use PDE-5 inhibitors to treat symptomatic adults with ASD, VSD or great artery shunt (IIa B)	▶ No RCTs for the use of PDE-5 inhibitors in patients with shunts other than ASD, VSD or great artery shunt ▶ No comparative studies between different agents ▶ Should these agents be used in less symptomatic patients?
Combination therapy may be considered in WHO-FC III patients (IIb C)	Bosentan and PDE-5 inhibitors are reasonable in combination if symptomatic improvement does not occur with either medication alone (IIa B)	▶ Are symptoms the only criterion to guide escalation of PAH-specific therapy? ▶ No specific agents are recommended to be used in combination ▶ No discrimination among WHO FC III patients who need monotherapy or add-on combination therapy ▶ No evidence for the use of upfront combination therapy ▶ Lack of a risk score to guide therapeutic decisions

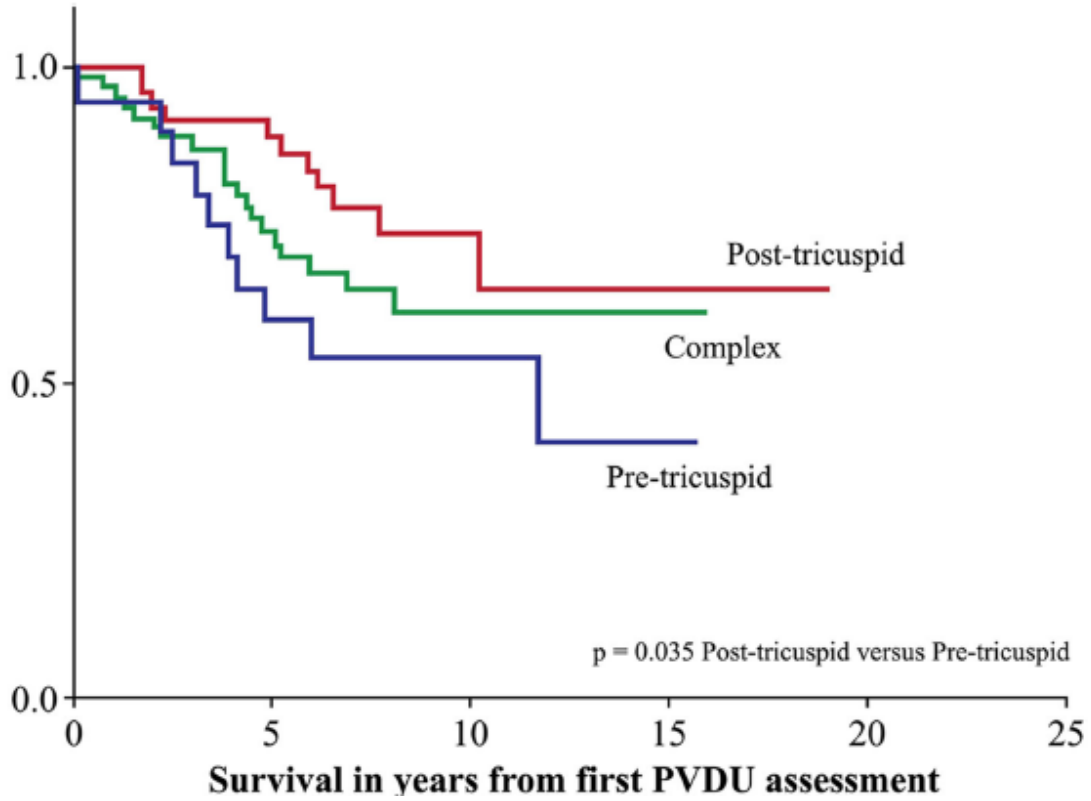
Survival in PAH associated with CHD



Eur Respir J 2012; 39: 945–955

Survival in Eisenmenger Syndrome according to type of defect





- Survival estimates at 20 years for ES, SP (systemic-to-pulmonary shunt), and CD (after defect correction) were 87%, 86% and 36%
- Survival estimates at 15 years for SD (small defects) was 66%

Eur Heart J. 2014;35(11):716–24.

Summary

- PAH is a frequent complication of congenital heart disease
- Prognosis varies depending on the type and size of the congenital heart defect, the timing of the development of PAH, and the response to treatment.
- High suspicion of PAH, and regular assessment for the presence of PAH in patients with shunt lesions, after defect closure is recommended.
- Proactive treatment is required in all PAH patients, including those with Eisenmenger syndrome.
- Women with CHD and confirmed pre-capillary PH should becounselled against pregnancy.

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