State-of-the-Art Management of Pulmonary Hypertension Based on an Understanding of the Various Etiopathogenesis

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5th World Symposium on PH: Modified Classification of PH

1. Pulmonary arterial hypertension
- 1.1 Idiopathic PAH
- 1.2 Heritable PAH
  - 1.2.1 BMPR2
  - 1.2.2 ALK1, ENG, SMAD9, CAV1, KCNK3
  - 1.2.3 Unknown
- 1.3 Drug- and toxin-induced
- 1.4 Associated with
  - 1.4.1 Connective tissue diseases
  - 1.4.2 HIV infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease (update)
  - 1.4.5 Schistosomiasis
  - ~~1.4.6 Chronic hemolytic anemia~~

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

1''. PPHN

2. PH due to LHD
- 2.1 LV systolic dysfunction
- 2.2 LV diastolic dysfunction
- 2.3 Valvular disease
- 2.4 Congenital/acquired left heart inflow/outflow obstruction

3. PH due to lung diseases and/or hypoxia
- 3.1 COPD
- 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 (update)

4. CTEPH

5. PH with unclear multifactorial mechanisms
- 5.1 Hematological disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
- 5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
- 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. *JACC 2013*;62:D34-41.

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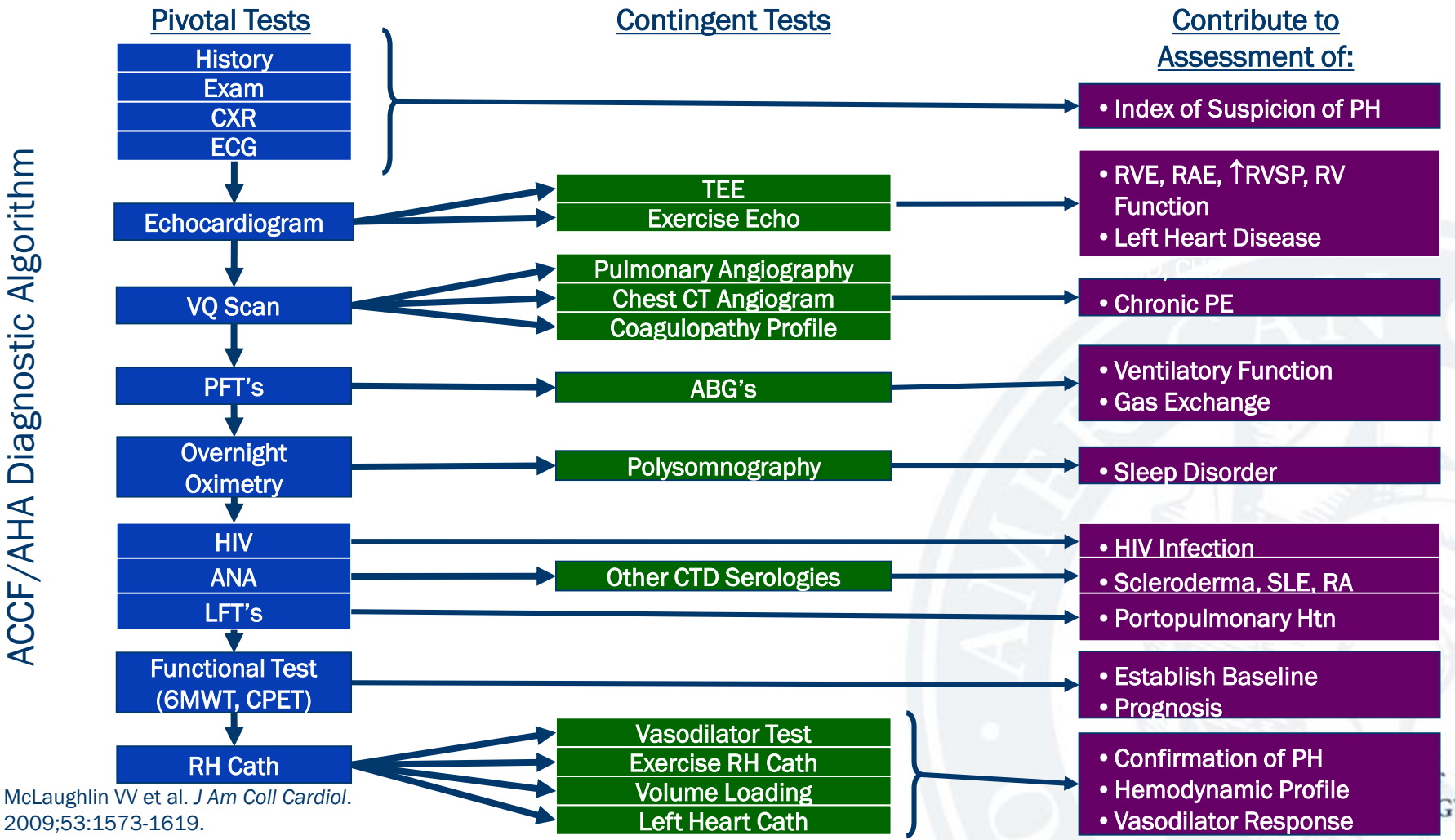
ACCF/AHA Diagnostic Algorithm



McLaughlin VV et al. *J Am Coll Cardiol*. 2009;53:1573-1619.

Haemodynamic definitions of pulmonary hypertension

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

CO = cardiac output; DPG = diastolic pressure gradient (diastolic PAP – mean PAWP); mPAP = mean pulmonary arterial pressure; PAWP = pulmonary arterial wedge pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; WU = Wood units.

[a]All values measured at rest; see also section 7.

[b]According to Table 4.

[c]Wood Units are preferred to dynes.s.cm^{-5}.

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Differentiating PAH and HFpEF

characteristic	PAH more likely	HFpEF more likely
age	younger	older
Comorbidities-DM, HTN , CAD, obesity (metabolic syndrome)	Often absent	Often multiple present
Symptoms-PND, orthopnea	Often absent	Often present
Cardiac Examination	RV heave, loud P2, TR murmur	Sustained LV impulse, RS4,
CXR	Clear lung fields	Pulmonary vascular congestion, pleural effusions, pulmonary edema
Chest CT	Often clear lungs	Mosaic perfusion pattern, ground-glass opacities consistent with chronic interstitial edema
ECG	RAD, RVE	LAE, LVE, Atrial Fibrillation, no RAD
Naturetic peptides	Often elevated	Often elevated
Echo-LAE, LVH	Absent	Often present
Echo-diastolic dysfunction	Grade 1 common	Grade 2, 3 common
Echo-RV	Often enlarged, may share the apex	Often normal, mildly enlarged
Echo-pericardial effusion	sometimes	rare

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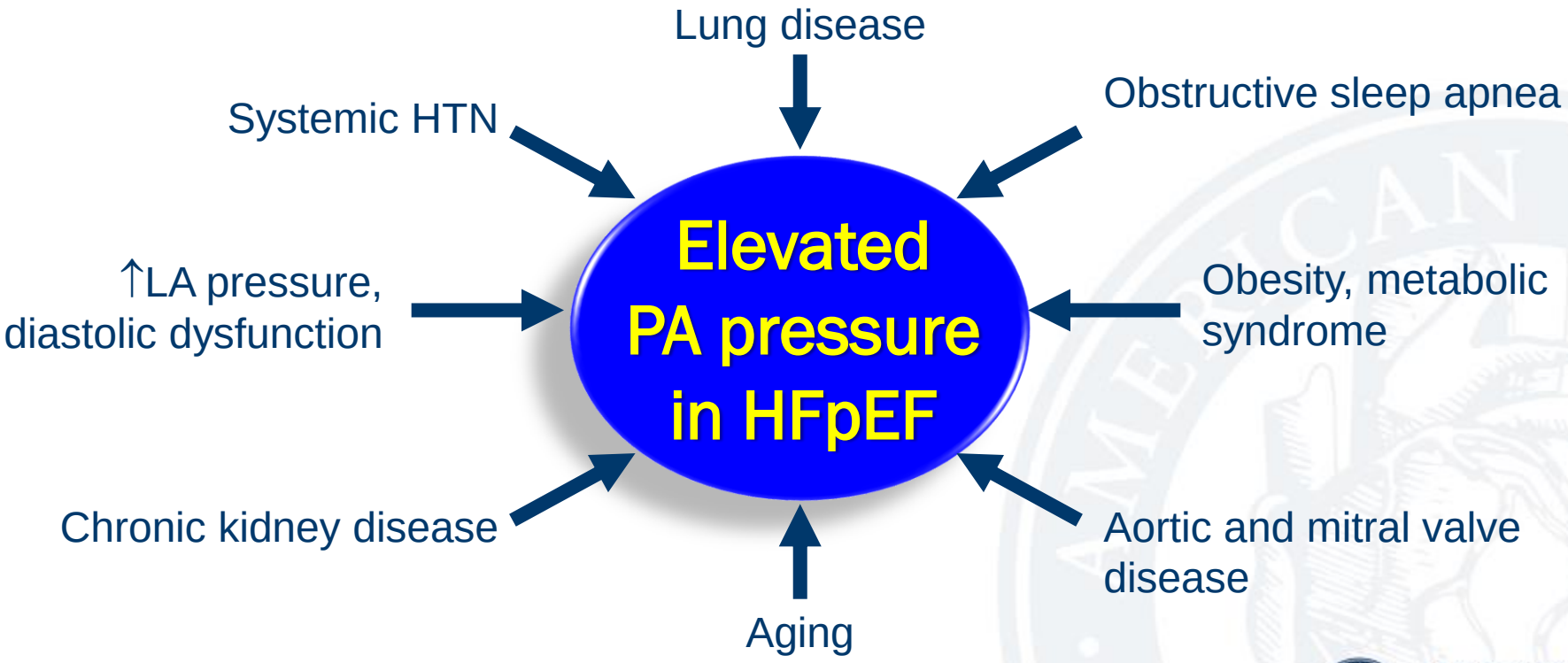
Adapted from McLaughlin and Humbert, Braunwald's Heart Disease, 10th Edition, 2015

"Multi-hit" Causes of PH in HFpEF



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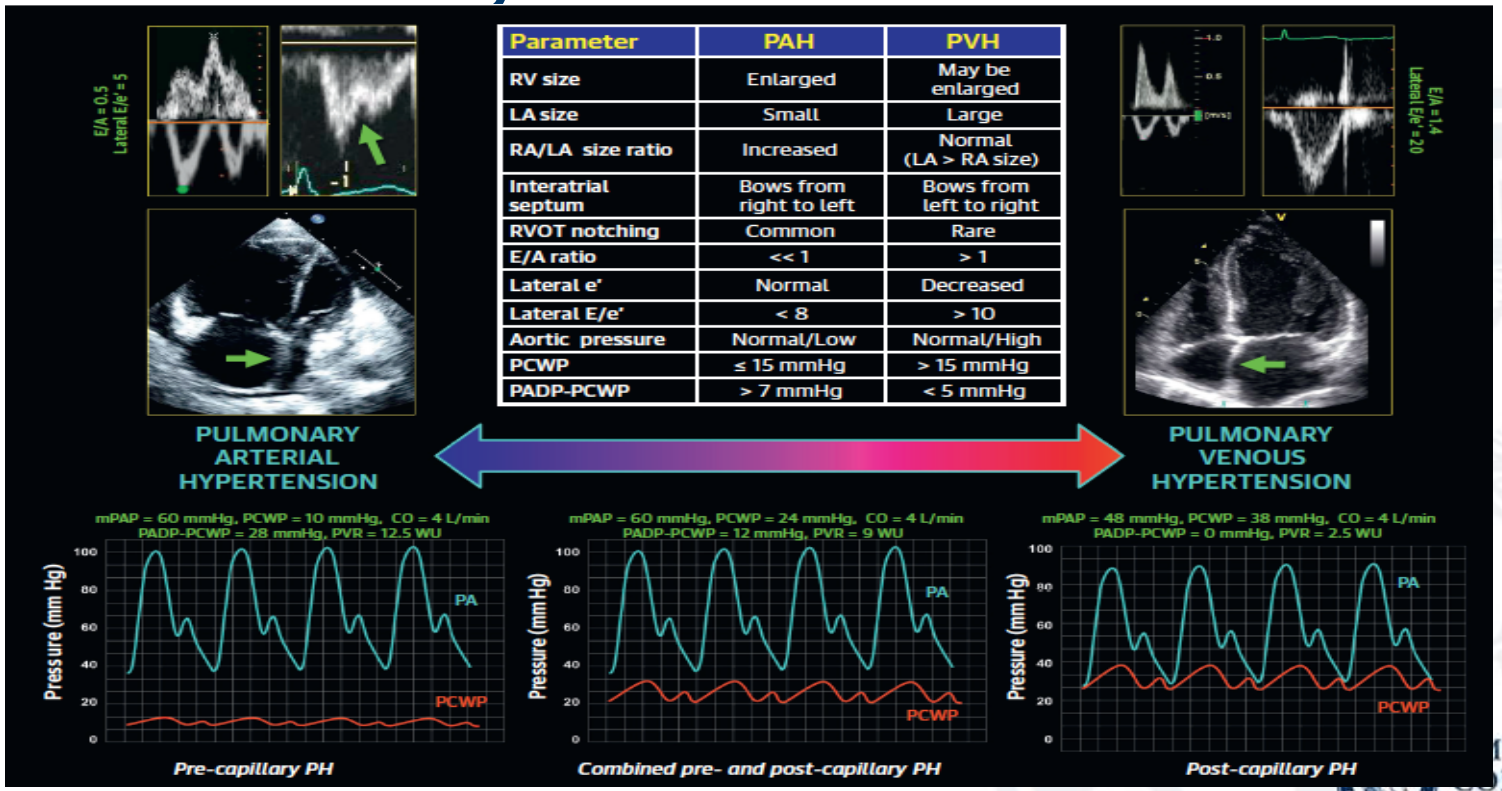
PAH Versus PVH: Echo and Invasive Hemodynamic Differentiation



Parameter	PAH	PVH
RV size	Enlarged	May be enlarged
LA size	Small	Large
RA/LA size ratio	Increased	Normal (LA > RA size)
Interatrial septum	Bows from right to left	Bows from left to right
RVOT notching	Common	Rare
E/A ratio	<< 1	> 1
Lateral e'	Normal	Decreased
Lateral E/e'	< 8	> 10
Aortic pressure	Normal/Low	Normal/High
PCWP	≤ 15 mmHg	> 15 mmHg
PADP-PCWP	> 7 mmHg	< 5 mmHg

McLaughlin VV et al. *J Am Coll Cardiol*. 2015;65:1976–97.

PAH-Specific Therapies: Studies On PH-LV Dysfunction: Adverse Effects Trump Efficacy

Treatment	Acute Response	LT Outcome
Prostacyclin[1]	↑PVR, ↓SVR, ↓PAWP, ↑CO	↑Mortality
Sildenafil[2-8]	↓PVR, ↓PAWP, ↓MPAP, ↑CO	Lower PAP, Improved endothelial function and exercise tolerance
Bosentan[9-11]	↓PVR	↑Transaminases, ↑Fluid Retention
Darusentan[12-13]	↓SVR	No Benefits
Tezosentan[14]	↓PVR, ↓SVR, ↓PAWP, ↑CI	No Benefits

No therapies that are approved for WHO Group 1 PAH are FDA approved for PH resulting from left heart failure.

1. Califf RM, *et al*, Am Heart J; 1997; 134-44-54, 2. Galie N, *et al*, N Engl J Med; 2005; 353:2148–57, 3. Alaeddini J, *et al*, Am J Cardiol; 2004; 94:1475–7, 4. Lepore JJ, *et al*, Chest; 2005; 127:1647–53, 5. Lewis GD, *et al*, Circulation; 2007; 115:59–66, 6. Guazzi M,*et al*, Circ Heart Fail; 2011; 4:8–17, 7. Guazzi M, *et al*, Eur J Heart Fail; 2012; 14:82–90, 8. Guazzi M, *et al,* Circulation; 2011; 124:164–74, 9. Cowburn PJ and Cleland JG, Eur Heart J; 2001; 22:1772–84, 10. Kelland NF and Webb DJ, Heart 2007;93(1):2–4, 11. Sutsch G, *et al*, Circulation; 1998; 98:2262–8, 12. Luscher TF, *et al*, Circulation; 2002; 106:2666–72, 13. Anand PI, *et al*, Lancet; 2004; 364:347–54, 14. Kaluski E, *et al*, J Am Coll Cardiol; 2003; 41:204–10

Management of pulmonary hypertension in left heart disease

Recommendations	Class[a]	Level[b]
Optimization of the treatment of the underlying condition is recommended before considering assessment of PH-LHD (i.e. treating structural heart disease).	I	C
It is recommended to identify other causes of PH (i.e. COPD, SAS, PE, CTEPH) and to treat them when appropriate before considering assessment of PH-LHD.	I	C
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 center for a complete diagnostic work-up 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
The use of PAH approved therapies is not recommended in PH-LHD.	III	C

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Haemodynamic classification of pulmonary hypertension associated with lung disease

Terminology	Haemodynamics (right heart catheterization)
COPD/IPF/CPFE without PH	PAPm <25 mmHg
COPD/IPF/CPFE with PH	PAPm ≥25 mmHg
COPD/IPF/CPFE with severe PH	PAPm >35 mmHg, or PAPm ≥25 mmHg in the presence of a low cardiac output (CI <2.5 L/min, not explained by other causes)

CI = cardiac index; COPD = chronic obstructive pulmonary disease; CPFE = combined pulmonary fibrosis and emphysema; IPF = idiopathic pulmonary fibrosis; PAP = pulmonary artery pressure; PAPm = mean pulmonary arterial pressure; PH = pulmonary hypertension.

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Recommendations for pulmonary hypertension due to lung diseases

Recommendations	Class[a]	Level[b]
Echocardiography is recommended for the non-invasive diagnostic assessment of suspected PH in patients with lung disease.	I	C
In patients with echocardiographic signs of severe PH and/or severe right ventricular dysfunction referral to an expert center is recommended.[c]	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
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
The use of drugs approved for PAH is not recommended in patients with PH due to lung diseases.	III	C

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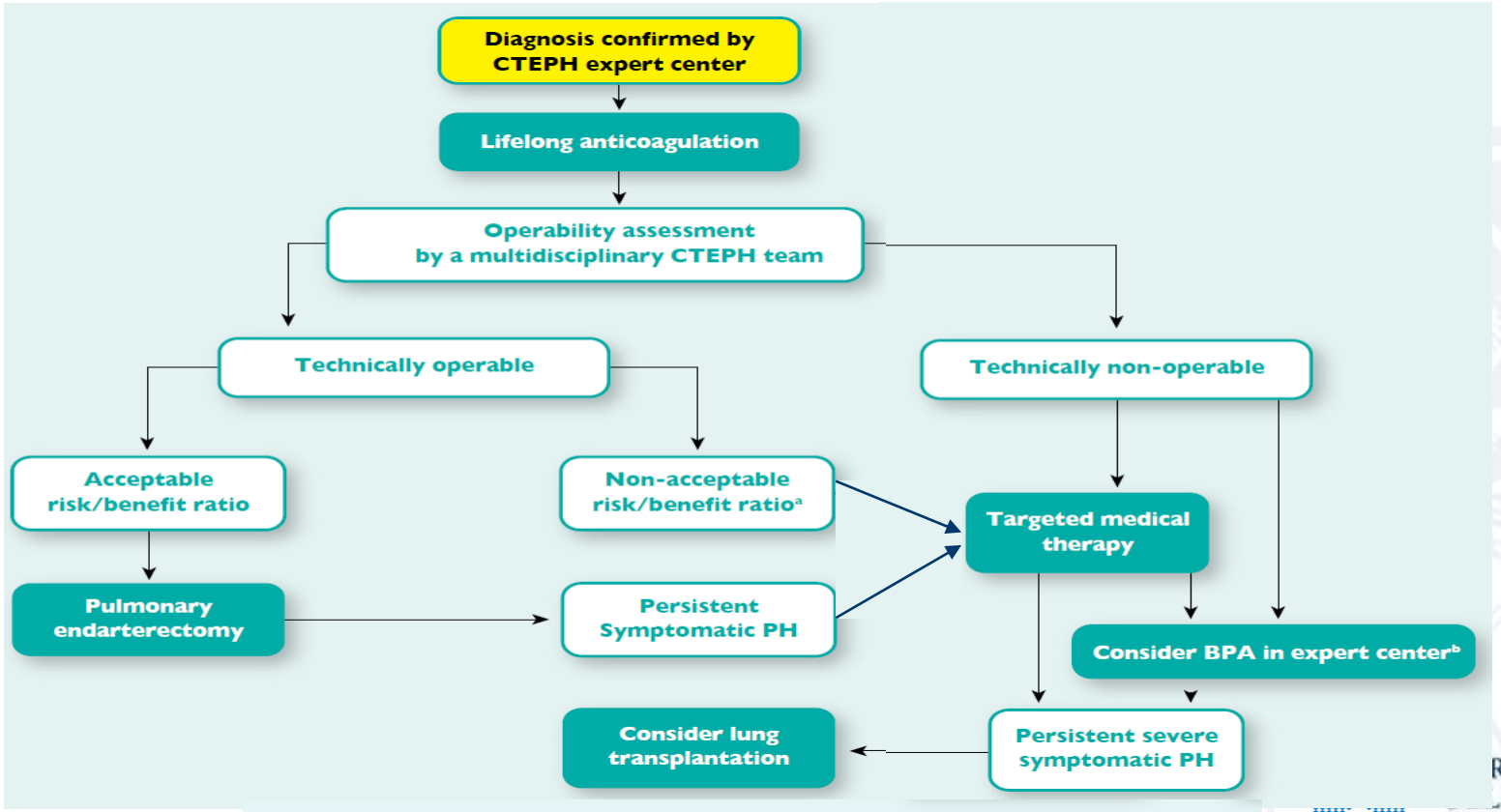
Treatment algorithm for chronic thromboembolic pulmonary hypertension



BPA = balloon pulmonary angioplasty; CTEPH = chronic thromboembolic pulmonary hypertension; PH = pulmonary hypertension.
[a]Technically operable patients with non-acceptable risk/benefit ratio can be considered also for BPA.
[b]In some centers medical therapy and BPA are initiated concurrently.

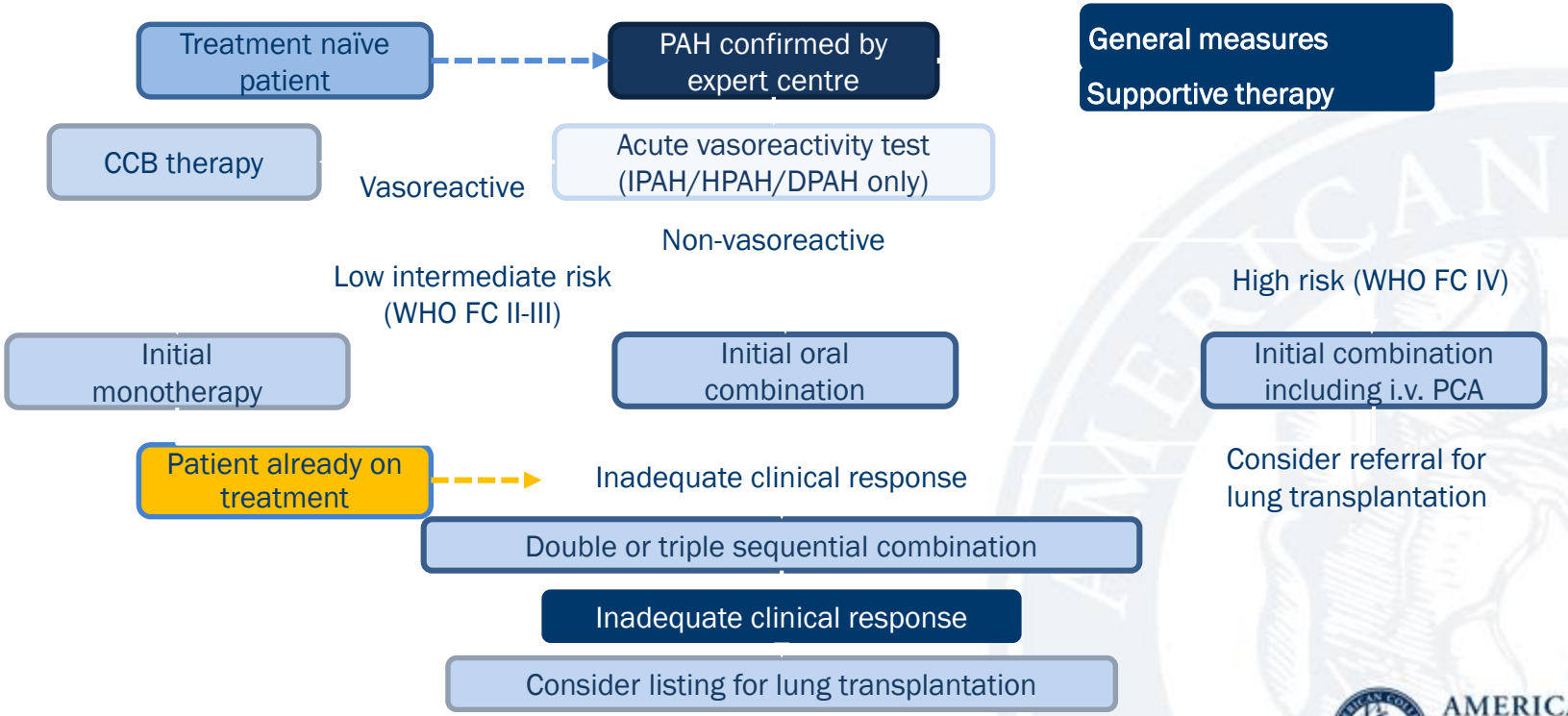
2015 ESC/ERS guidelines: Risk assessment

Determinants of prognosis[a]	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 < 2.01 l/min/m^2 SvO_2 < 60%

[a]Estimated 1-year mortality. [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.

Galiè N, *et al. Eur Respir J* 2015; 46:903-75., Galiè N, *et al. Eur Heart J* 2016; 37:67-119

2015 ESC/ERS guidelines: Update to treatment algorithm



Galiè N, *et al. Eur Respir J* 2015; 46:903-75.
Galiè N, *et al. Eur Heart J* 2016; 37:67-119.

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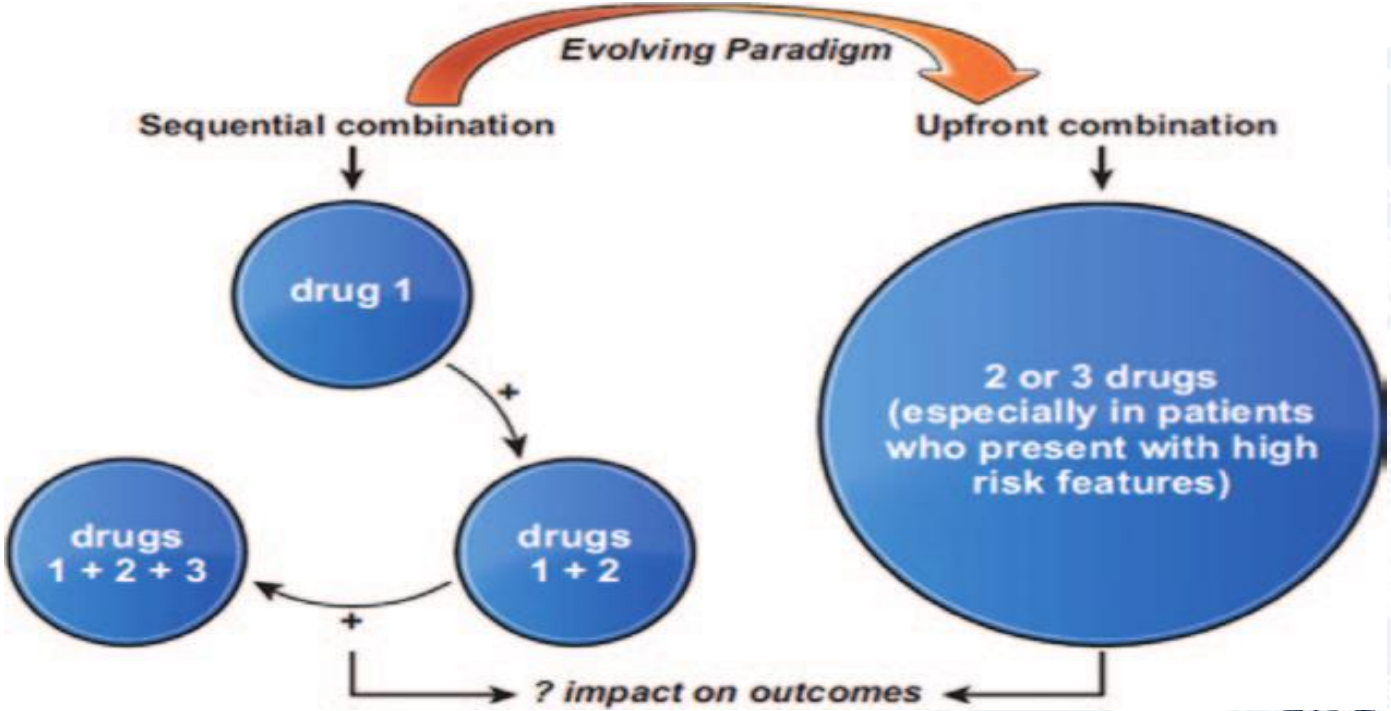
Evolving paradigm: From sequential to initial combination therapy



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Humbert M, *et al. Circulation* 2014;130:2189–208.

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Functional Class	• I or II
Hemodynamics	• Normalization of RV function (RAP < 8 mm Hg and CI > 2.5-3.0 L/min/m^2)
Echocardiography/ MRI	• Normal/near normal RV size and function
BNP level	• 'Normal'
6-MWD	• 380-440 m, may not be aggressive enough
CPET	• Peak VO_2 > 15 mL/kg/min • VE/VCO_2 @ AT < 45

McLaughlin VV et al. *JACC 2013*.:62:D73-81.

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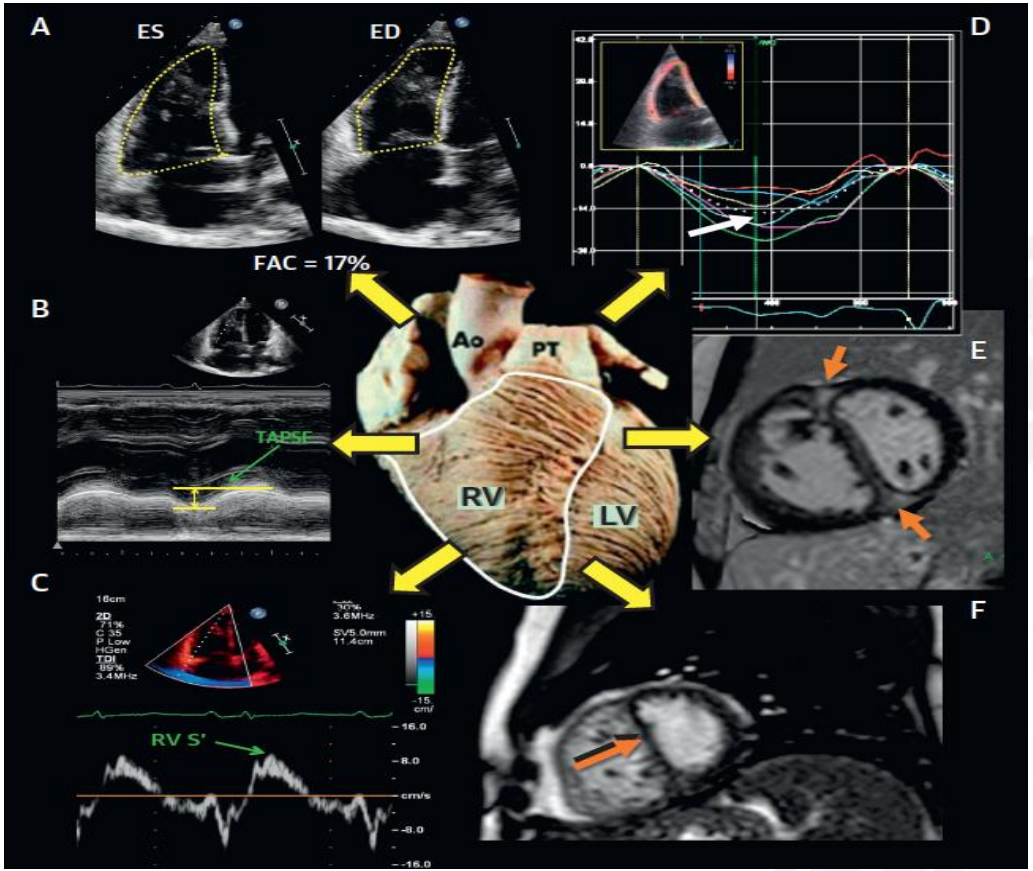
Echo and CMR Evaluation of RV in PH

RV fractional area

TAPSE

RV Doppler longitudinal (s') velocity



RV global longitudinal strain on speckle-track echo

Late gad-enhanced RV insertion point on CMR

"D Sign" of LV due to RV overload during peak inspiration

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Summary

- Pulmonary hypertension is common and has multiple different etiologies
- Evaluation must be methodical and include echocardiography and right heart catheterization
- To treat effectively and avoid harm, PAH must be differentiated from pulmonary venous hypertension
- For PH due to other heart and lung diseases, treatment should be directed towards the underlying process
- Specific therapies available for CTEPH, do not miss this diagnosis