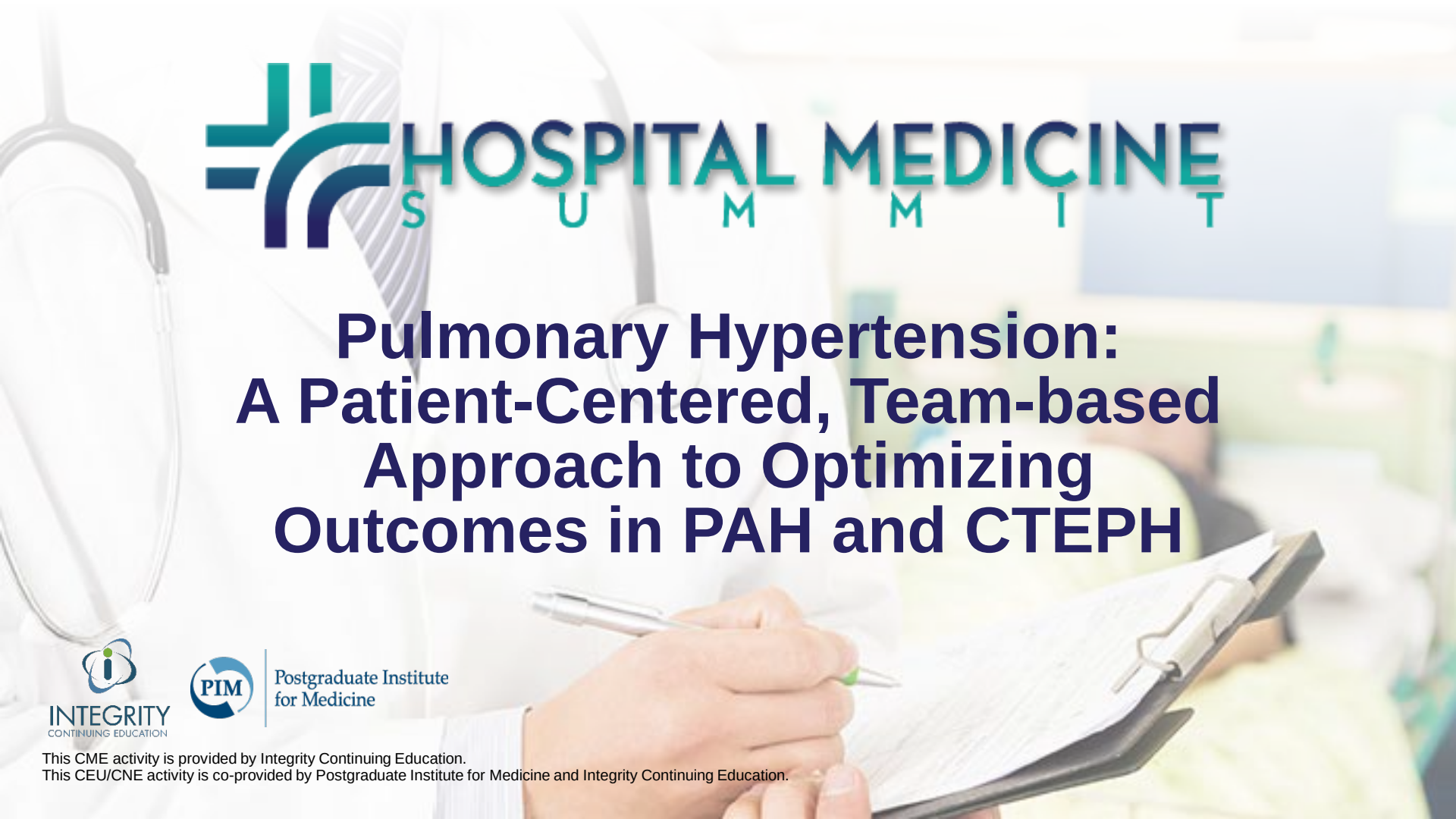
HOSPITAL MEDICINE SUMMIT

Pulmonary Hypertension: A Patient-Centered, Team-based Approach to Optimizing Outcomes in PAH and CTEPH



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Faculty Disclosures

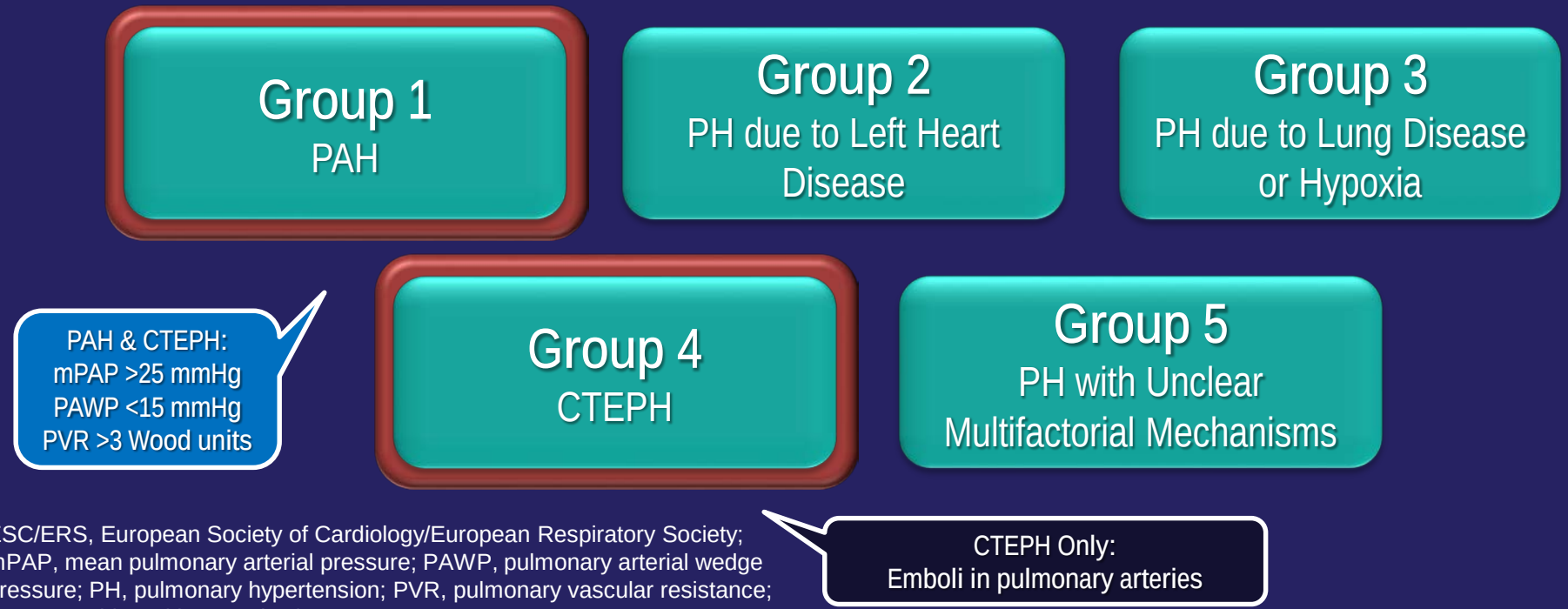
- Consultant: Acceleron, Actelion, Gilead, Liquidia, Pfizer, United Therapeutics
- Grants to TMC: Acceleron, Actelion, Bayer, Complexa, Gilead, Liquidia, United Therapeutics

Learning Objectives

- Identify strategies to screen and improve early recognition of pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH)
- Apply guideline recommendations to the accurate diagnosis of PAH and CTEPH
- Develop a guideline-directed, evidence-based management plan for PAH and CTEPH that includes consideration of novel therapies and current clinical trial data
- Establish a multidisciplinary, patient-centered approach to care for patients with PAH or CTEPH

Introduction

WHO Classification Groups



ESC/ERS, European Society of Cardiology/European Respiratory Society; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; WHO, World Health Organization.

Galiè N, et al. *Eur Heart J*. 2016;37(1):67-119.

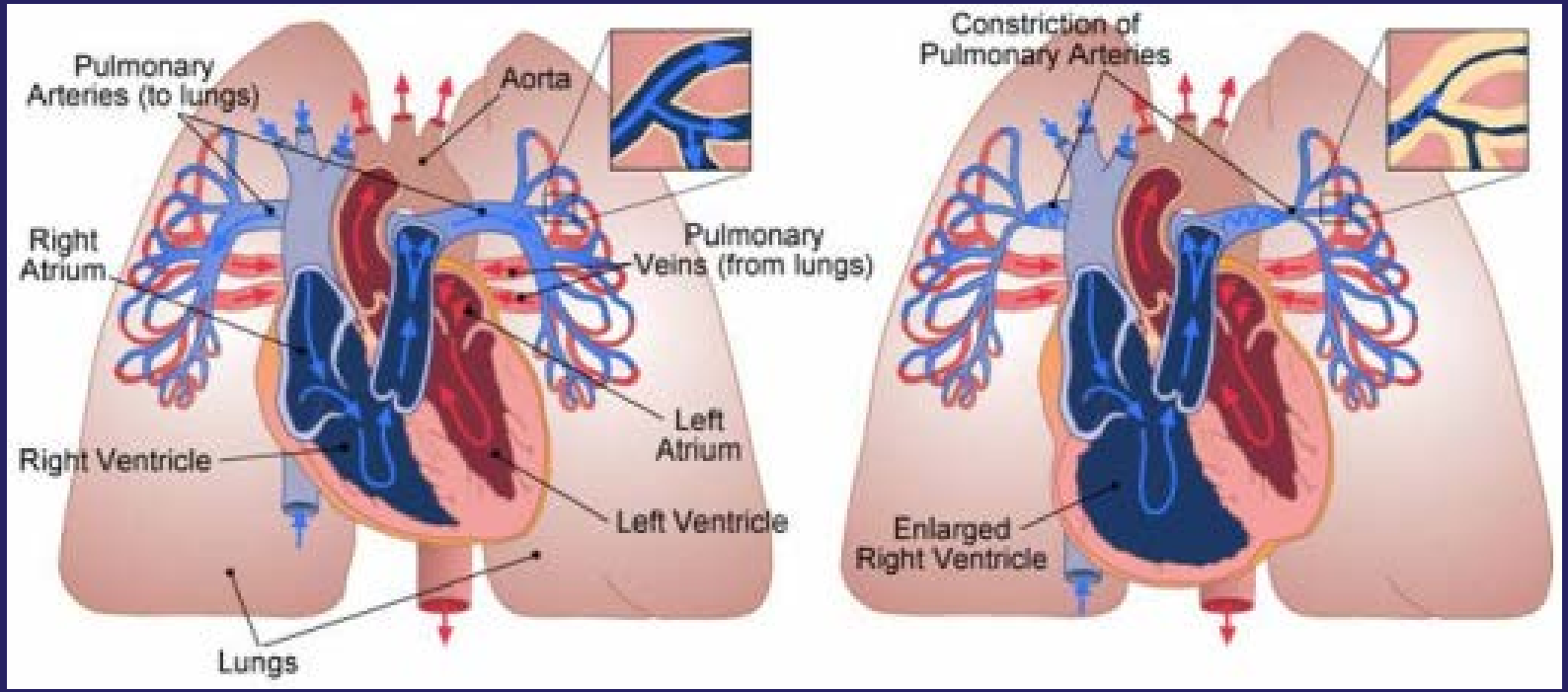
PAH Group I

- **Idiopathic (IPAH)**
- **Hereditary (HPAH)**
- **Associated with (APAH)**
  - Collagen vascular disease
  - Congenital systemic-to-pulmonary shunts
  - Portal hypertension
  - HIV infection
  - Drugs/toxins

- **Persistent pulmonary hypertension of the newborn**
- **Associated with venous or capillary involvement**
  - Pulmonary veno-occlusive disease (PVOD)
  - Pulmonary capillary hemangiomatosis (PCH)

PH → Right-sided Heart Failure

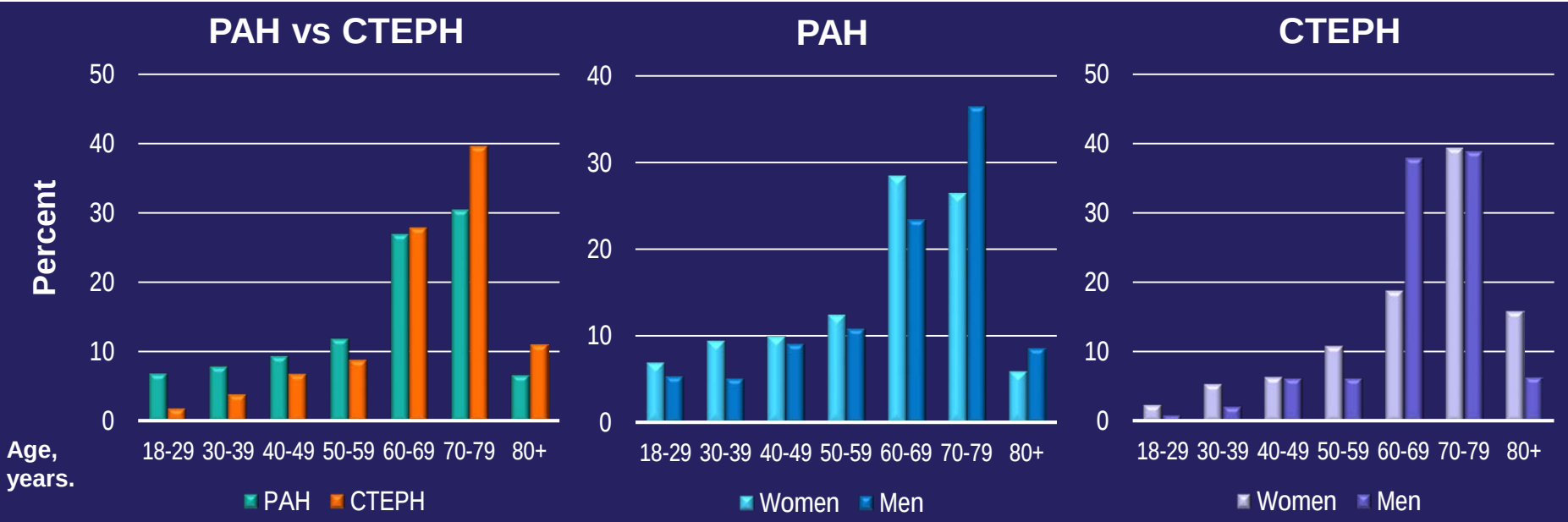
Normal Heart | **Pulmonary Hypertension**



Nationwide Children's Hospital. Pulmonary Hypertension. Available at: https://www.nationwidechildrens.org/conditions/pulmonary-hypertension.

Early Recognition of PAH and CTEPH

Diagnosed Patients: Age Distribution & Prevalence



PAH: 15 cases per million adults

CTEPH: 3.2 cases per million adults

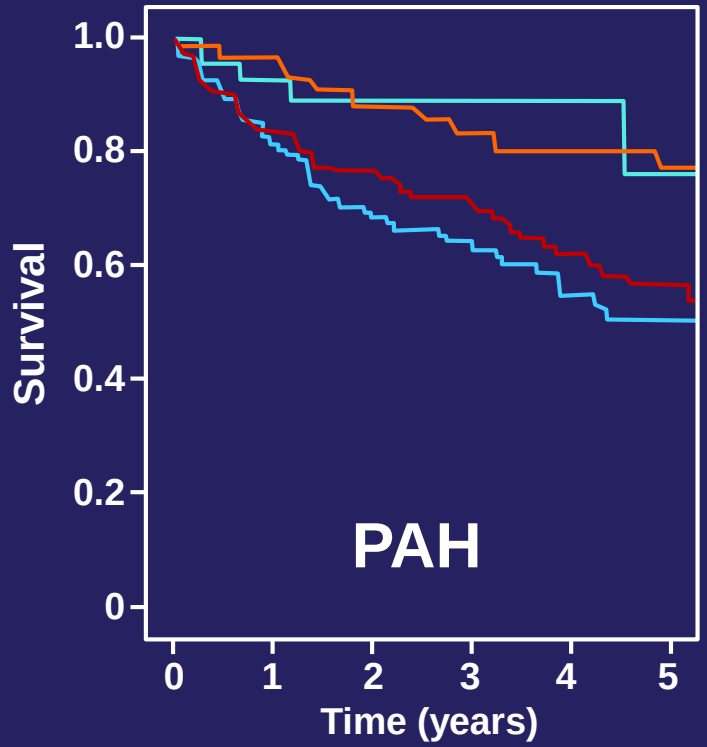
Rådegran G, et al. *Scand Cardiovasc J*. 2016;50(4):243-250.
Galiè N, et al. *Eur Heart J*. 2016;37(1):67-119.

WHO Functional Classes: PAH & CTEPH

Class	Description
I	**No limitation of usual physical activity**; ordinary physical activity does not cause increased dyspnea, fatigue, chest pain, or presyncope.
II	**Mild limitation of physical activity**. There is no discomfort at rest, but normal physical activity causes increased dyspnea, fatigue, chest pain, or presyncope.
III	**Marked limitation of physical activity**. There is no discomfort at rest, but less than normal physical activity causes increased dyspnea, fatigue, chest pain, or presyncope.
IV	**Unable to perform any physical activity at rest** and **may have signs of right ventricular (RV) failure**. Dyspnea and/or fatigue may be present at rest, and symptoms are increased by almost any physical activity.

Moote R, et al. In: DiPiro JT, et al, eds. *Pharmacotherapy: A Pathophysiologic Approach*, 10th ed. New York, NY: McGraw-Hill Education; 2017.

Importance of Early Recognition

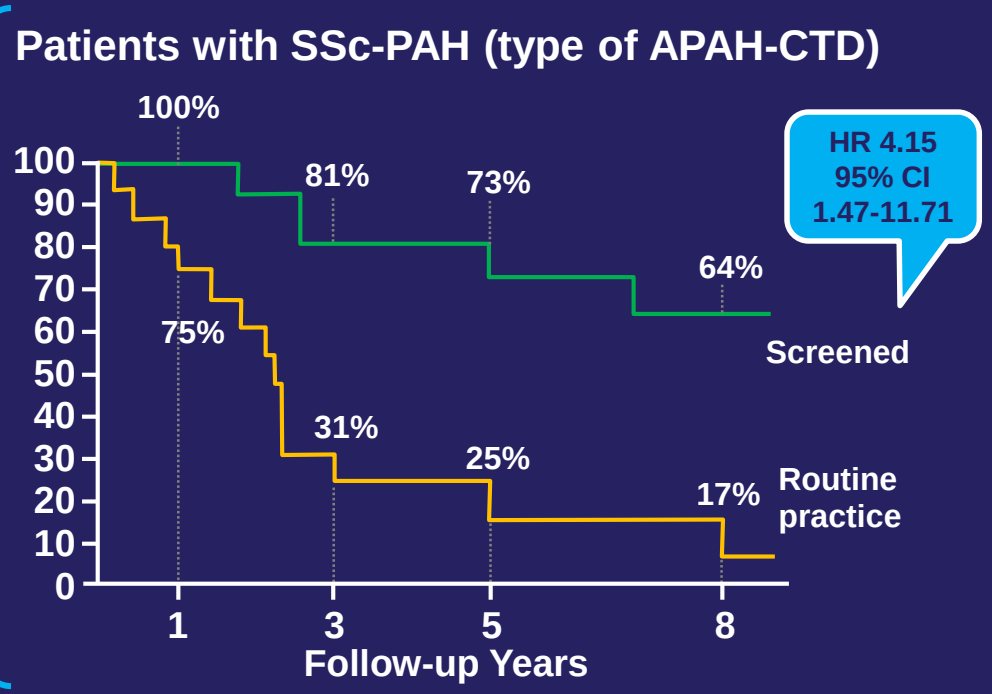


APAH-Other

APAH-CHD

IPAH/HPAH

APAH-CTD

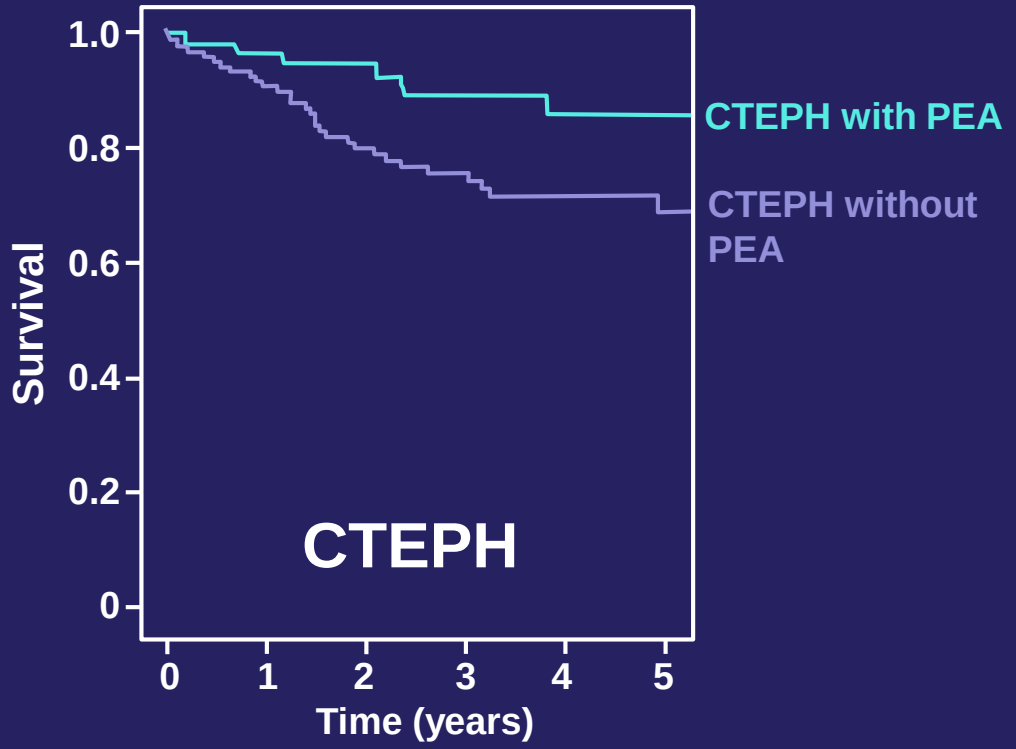


CHD, congenital heart disease; CTD, connective tissue disease; SSc, systemic sclerosis.

Rådegran G, et al. *Scand Cardiovasc J*. 2016;50(4):243-250.
Humbert M, Gerry Coghlan J, Khanna D. *Eur Respir Rev*. 2012;21(126):306-312.

Importance of Early Recognition (cont'd)

- **CTEPH is only PH with potential cure**
- Pulmonary endarterectomy (PEA)
  - 20%-40% are inoperable
  - 80%-90% cured with PEA
  - Procedure mortality
    - In-hospital mortality: 4.7%
    - 1-year postoperative mortality: 7%



Rådegran G, et al. *Scand Cardiovasc J*. 2016;50(4):243-250.
Mayer E. *Eur Respir Rev*. 2010;19 (115):64-7.

PAH Screening: ESC/ERS Recommendations

Symptoms of PH

Initial: Nonspecific, RV dysfunction

- Dyspnea
- Fatigue
- Weakness
- Angina
- Syncope
- Dry cough
- Exercise-induced N/V

Later: Progressive RV failure

PAH

- Resting echocardiogram
  - 1° relatives of HPAH
  - PoPH: liver transplant
- Annual echocardiogram
  - 1° relatives of HPAH
  - PAH mutation +
- Exercise echocardiogram **not recommended** in high-risk patients

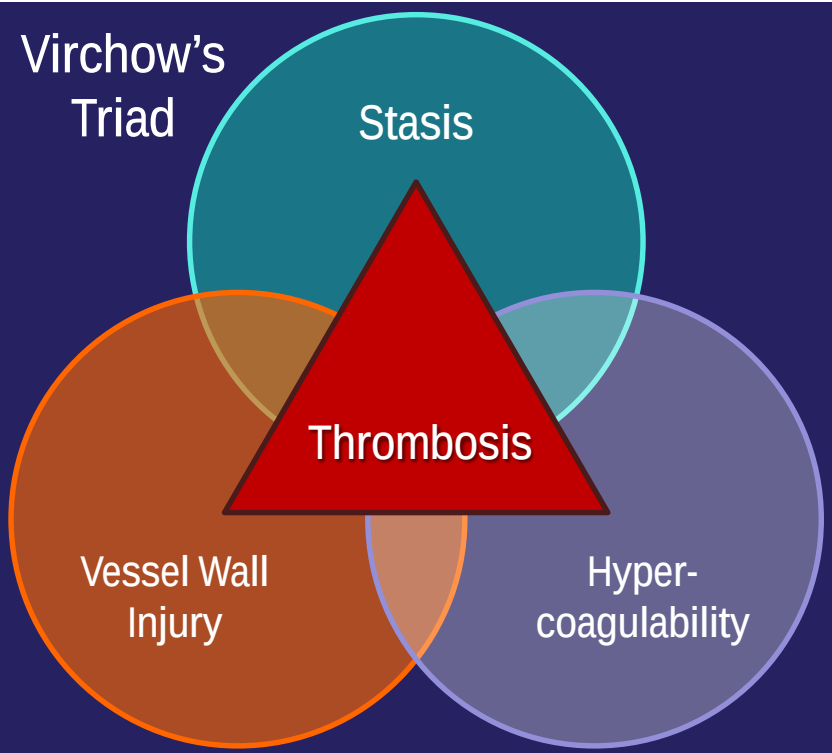
SSc-PAH (APAH-CTD)

- Resting echocardiogram
  - Asymptomatic patients
- Combined approach
- Annual screening
  - Echocardiograph, PFTs, biomarkers
- mPAP 21-24 mmHg
- DETECT algorithm
  - >3 years disease
  - DLCO <60% predicted

DLCO, diffusing lung capacity for carbon monoxide; PFT, pulmonary function test; PoPH, portopulmonary hypertension; RV, right ventricular.

Galiè N, et al. *Eur Heart J*. 2016;37(1):67-119.

Screening for CTEPH



Risk Factors for CTEPH

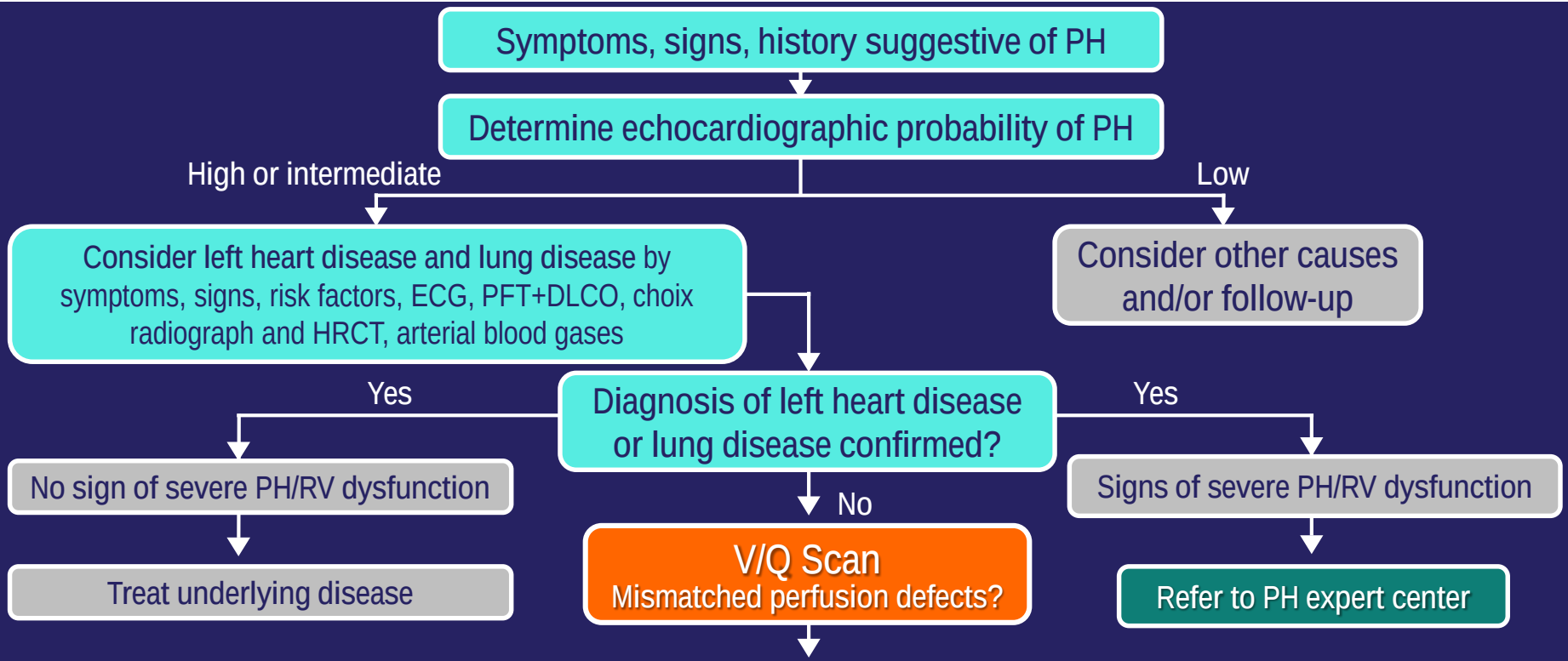
- History of pulmonary embolism (PE)
- Right-sided heart strain at initial PE
- Hypercoagulable states
  - Elevated factor VIII
  - Factor V Leiden mutation
  - Lupus
- Splenectomy
- Hypothyroidism
- Chronic inflammation
- History of malignancy
- Ventriculoarterial shunts or pacemakers
- Unexplained PH

Incidence after acute PE: 0.5% to 9%
History of acute PE in diagnosed: 75%

O'Connell C, et al. *Presse Med*. 2015;44(12):e409-e416.
Pepke-Zaba J, et al. *Circulation.* 2011;124:1973–1981.

Diagnosis of PAH and CTEPH

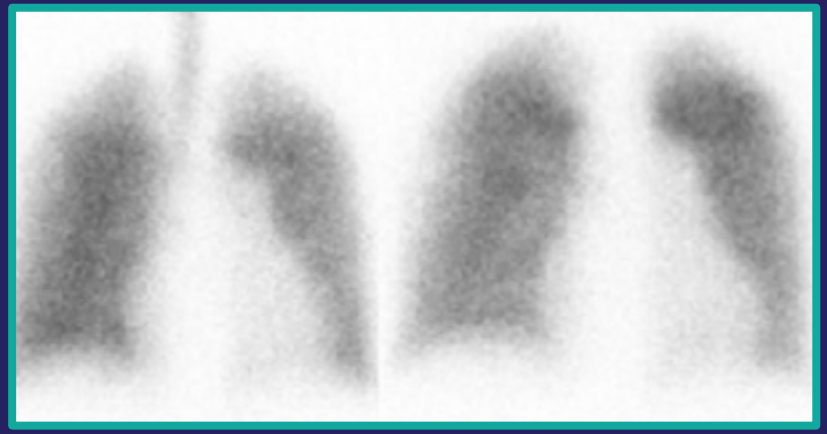
Diagnostic Algorithm: ESC/ERS Guidelines



Galiè N, et al. *Eur Heart J*. 2016;37(1):67-119.

V/Q Scan

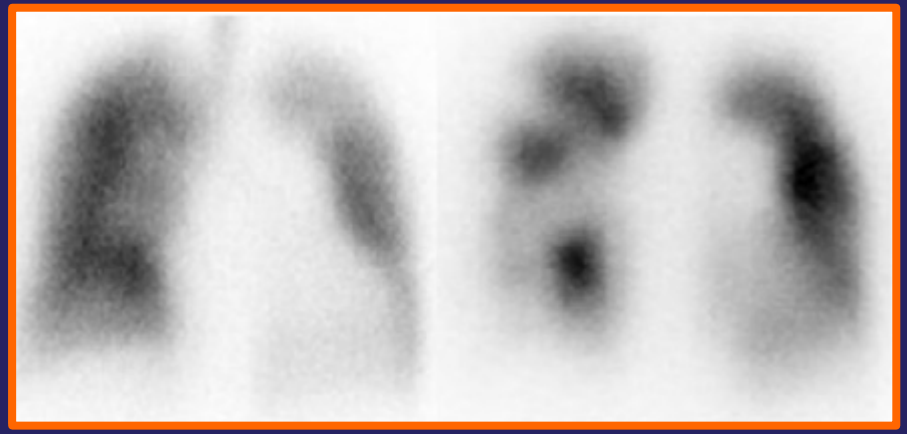
Ventilation **Perfusion**



Normal or Mottled Pattern

PAH

Ventilation **Perfusion**

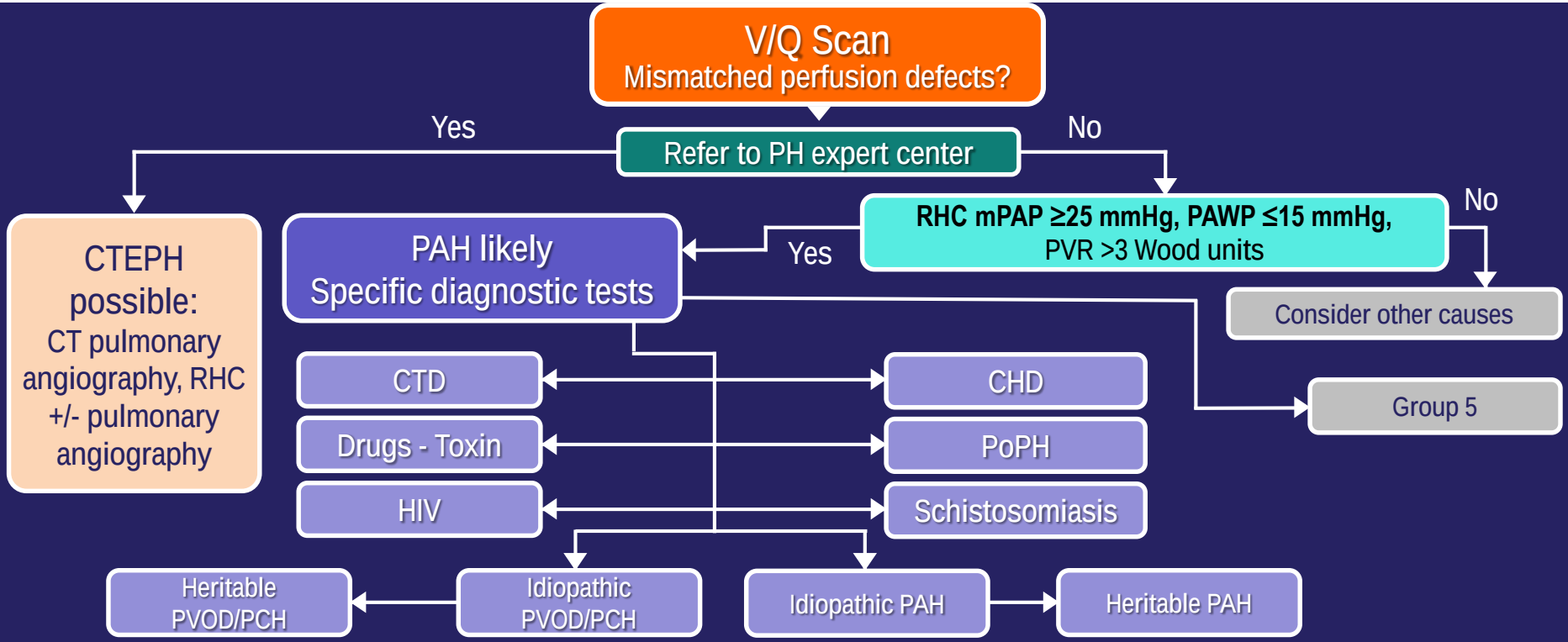


At least one segmental perfusion defect inconsistent with ventilation scan findings

CTEPH

Tanabe N, et al. *Respir Investig*. 2013;51(3):134-146.

Diagnostic Algorithm: ESC/ERS Guidelines



PVOD/PCH, pulmonary veno-occlusive disease/pulmonary capillary hemangiomatosis; RHC, right heart catheterization.

Galiè N, et al. *Eur Heart J*. 2016;37(1):67-119.

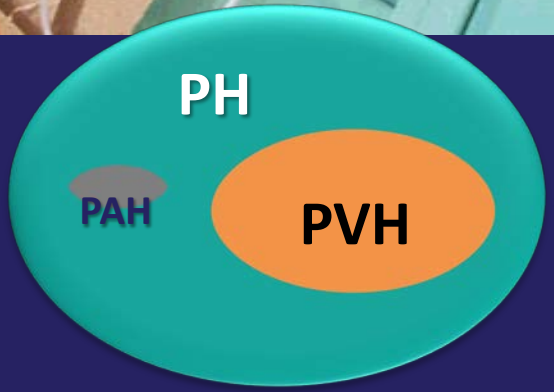
PAH:
Hemodynamic Definition (definitive diagnosis)

Mean pulmonary artery pressure (mPAP) of ≥25 mmHg at rest

AND

Mean pulmonary capillary wedge pressure (PCWP) of ≤15 mmHg

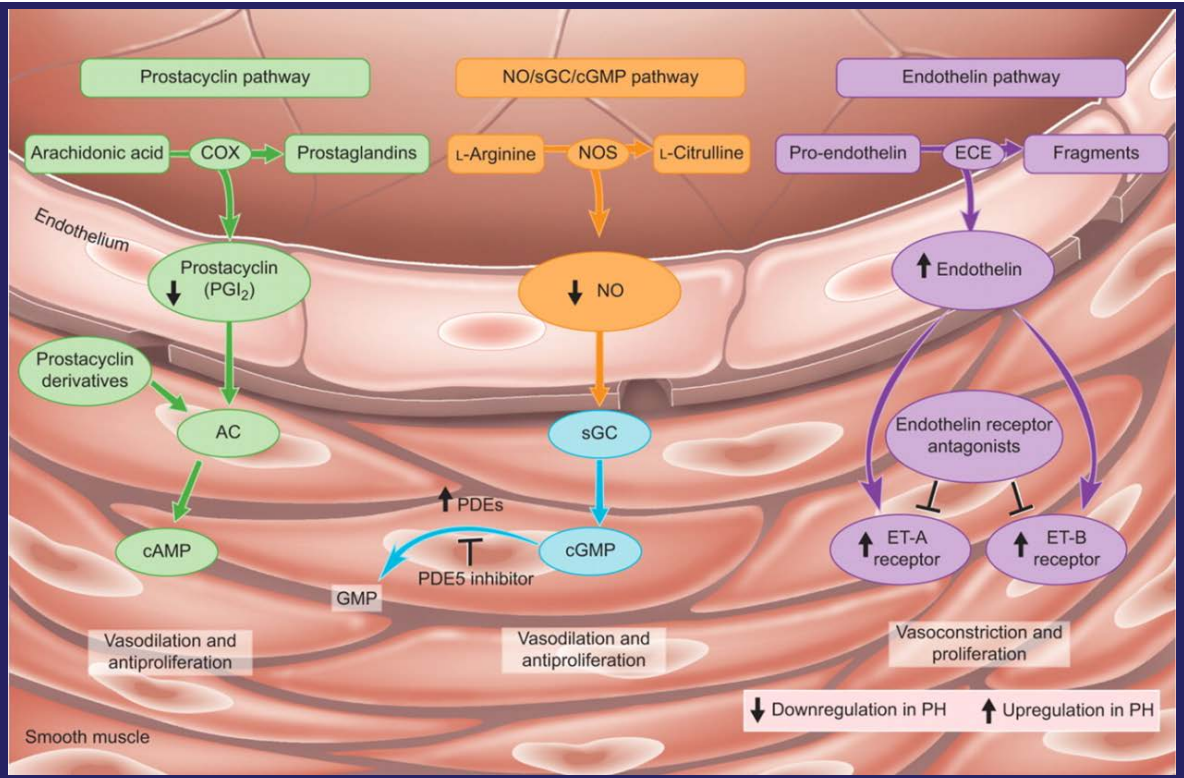
(No evidence of left-heart disease)
PVR >3 Wood units



- **Most PH cases are not in WHO group I!!!**
- **PAH**
  - ↑PVR
  - ↑Transpulmonary pressure gradient (TPG)
  - Normal left-sided filling pressures
- Pulmonary venous hypertension (PVH) characterized by
  - ↑PCWP, usually normal TPG, and PVR

Therapy for PAH

Targeting Multiple Pathologic Pathways Improves Response



Humbert M. Pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension: pathophysiology. European Respiratory Review 2010;19: 59-63.

Goals of Treatment in 2018: Improvement to a Goal

- However….**improvement** and **normalization** of **ALL clinical parameters** to make patients LOW RISK is the goal in PAH treatment
- Preservation or prevention of worsening is no longer the goal

Determinants of Prognosis (estimated 1-year mortality)	Low Risk (<5%) AT GOAL!!!	Intermediate Risk (5-10%) NOT AT GOAL	High Risk (>10%) NOT AT GOAL
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope	Repeated syncope
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% predicted) VE/VCO_2 slope <36	Peak VO_2 11-15 mL/min/kg (35%-65% predicted) VE/VCO_2 slope 36-44.9	Peak VO_2 <11 mL/min/kg (<35% predicted) VE/VCO_2 slope ≥45
NT-proBNP levels	BNP <50 ng/L NT-pro BNP <300 ng/L	BNP 50-300 ng/L NT-pro BNP 300-1400 ng/L	BNP >300 ng/L NT-pro BNP >1400 ng/L
Imaging (ECHO or CMR)	RA area <18 cm^2 No pericardial effusion	RA area 18-26 cm^2 No/minimal pericardial effusion	RA area >26 cm^2 Pericardial effusion
Hemodynamics	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%

6MWD, 6-minute walk distance; CI, pulmonary clearance; CMR, cardiovascular magnetic resonance; NT-pro BNP, N-terminal pro-B-type brain natriuretic peptide; RA, right atrial; RAP, right atrial pressure; SVO_2, mixed venous oxygen saturation VE/VCO_2, ventilation:carbon dioxide output; VO2, peak oxygen uptake.

Galiè N, et al. *Eur Heart J*. 2016;37(1):67-119.

Drug Monotherapy
Medications for PAH: ESC/ERS Guidelines

Recommendations			Class - Level					
Therapy			WHO FC II		WHO FC III		WHO FC IV	
Calcium channel blockers			I	C	I	C	—	—
Endothelin receptor antagonists (ERA)	Ambrisentan		I	A	I	A	IIb	C
	Bosentan		I	A	I	A	IIb	C
	Macitentan — NOVEL AGENT		I	B	I	B	IIb	C
Phosphodiesterase type-5 inhibitors (PDE-5i)	Sildenafil		I	A	I	A	IIb	C
	Tadalafil		I	B	I	B	IIb	C
	Vardenafil*		IIb	B	IIb	B	IIb	C
Guanylate cyclase stimulators	Riociguat — NOVEL AGENT		I	B	I	B	IIb	C
Prostacyclin analogues	Epoprostenol	Intravenous (IV)	—	—	I	A	I	A
	Iloprost	Inhaled	—	—	I	B	IIb	C
		IV*	—	—	IIa	C	IIb	C
	Treprostinil	Subcutaneous (SC)	—	—	I	B	IIb	C
		Inhaled	—	—	I	B	IIb	C
		IV	—	—	IIa	C	IIb	C
		Oral	—	—	IIb	B	—	—
	Beraprost*		—	—	IIb	B	—	—
Prostacyclin receptor (IP) agonists	Selexipag (oral) — NOVEL AGENT		I	B	I	B	—	—

*Included in recommendations but not yet approved for PAH indication

FC, functional class.

Galiè N, et al. *Eur Heart J*. 2016;37(1):67-119.

Initial Combination Therapy Medications for PAH: ESC/ERS Guidelines

Recommendations	Class - Level					
Therapy	WHO FC II		WHO FC III		WHO FC IV	
Ambrisentan + tadalafil	I	B	I	B	IIb	C
Other ERA + PDE-5i	IIa	C	IIa	C	IIb	C
Bosentan + sildenafil + IV epoprostenol	—	—	IIa	C	IIa	C
Bosentan + IV epoprostenol	—	—	IIa	C	IIa	C
Other ERA or PDE-5i + SC treprostinil	—	—	IIb	C	IIb	C
Other ERA or PDE-5i + other IV prostacyclin analogues	—	—	IIb	C	IIb	C

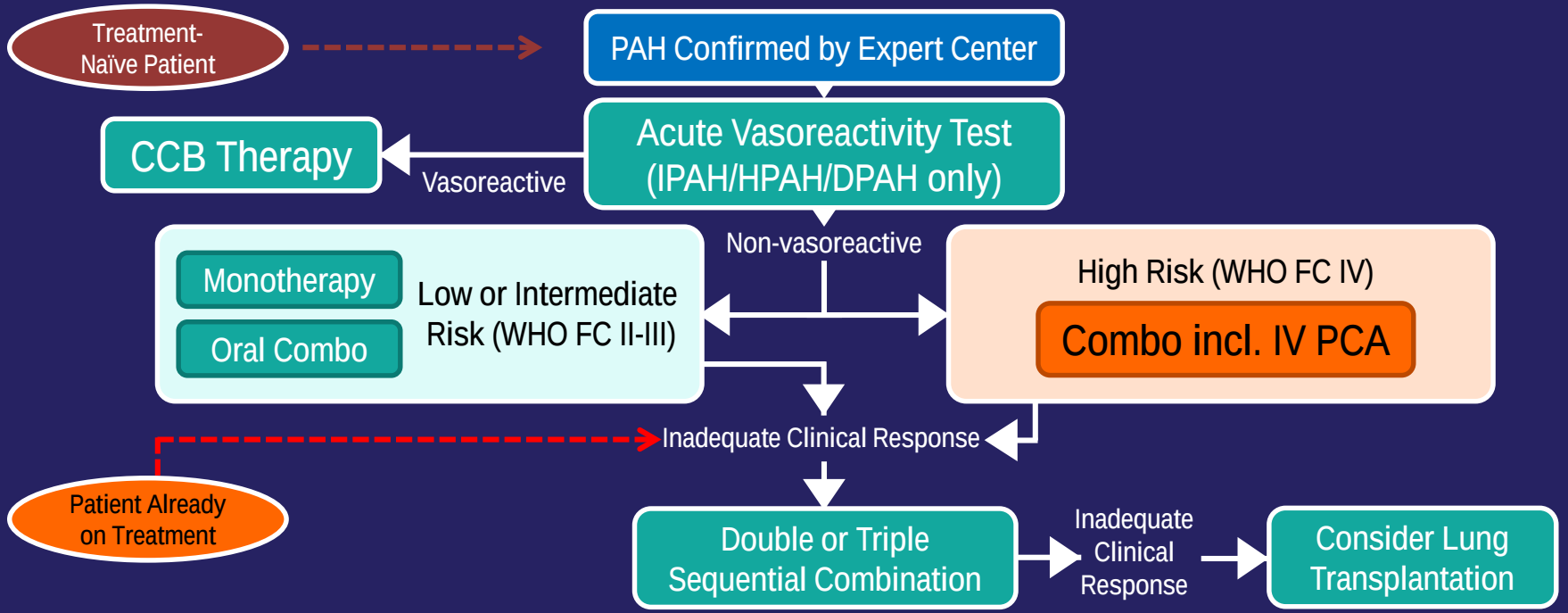
Galiè N, et al. *Eur Heart J*. 2016;37(1):67-119.

Sequential Combination Therapy Medications for PAH: ESC/ERS Guidelines

Recommendations	Class - Level					
Therapy	WHO FC II		WHO FC III		WHO FC IV	
Macitentan added to sildenafil	I	B	I	B	IIa	C
Riociguat added to bosentan	I	B	I	B	IIa	C
Selexipag added to ERA and/or PDE-5i	I	B	I	B	IIa	C
Sildenafil added to epoprostenol	—	—	I	B	IIa	B
Treprostinil inhaled added to sildenafil or bosentan	IIa	B	IIa	B	IIa	C
Iloprost inhaled added to bosentan	IIb	B	IIb	B	IIb	C
Tadalafil added to bosentan	IIa	C	IIa	C	IIa	C
Ambrisentan added to sildenafil	IIb	C	IIb	C	IIb	C
Bosentan added to epoprostenol	—	—	IIb	C	IIb	C
Bosentan added to sildenafil	IIb	C	IIb	C	IIb	C
Sildenafil added to bosentan	IIb	C	IIb	C	IIb	C
Other double combinations	IIb	C	IIb	C	IIb	C
Other triple combinations	IIb	C	IIb	C	IIb	C
Riociguat added to sildenafil or other PDE-5i	III	B	III	B	III	B

Galiè N, et al. *Eur Heart J*. 2016;37(1):67-119.

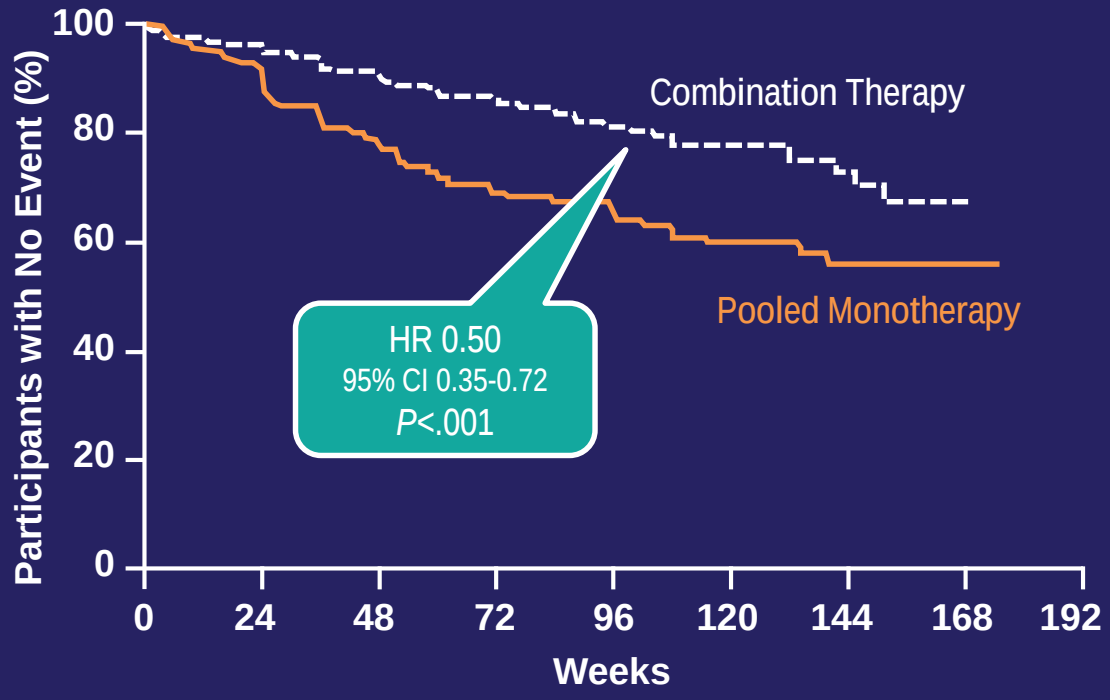
PAH Treatment Algorithm: ESC/ERS Guidelines

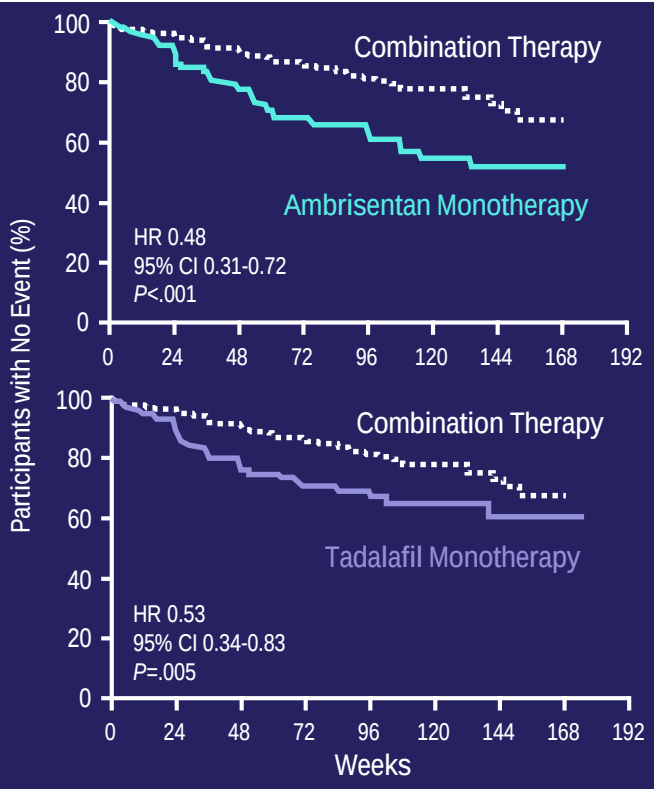


CCB, calcium channel blocker; PCA, patient-controlled analgesia.

Galiè N, et al. *Eur Heart J*. 2016;37(1):67-119.

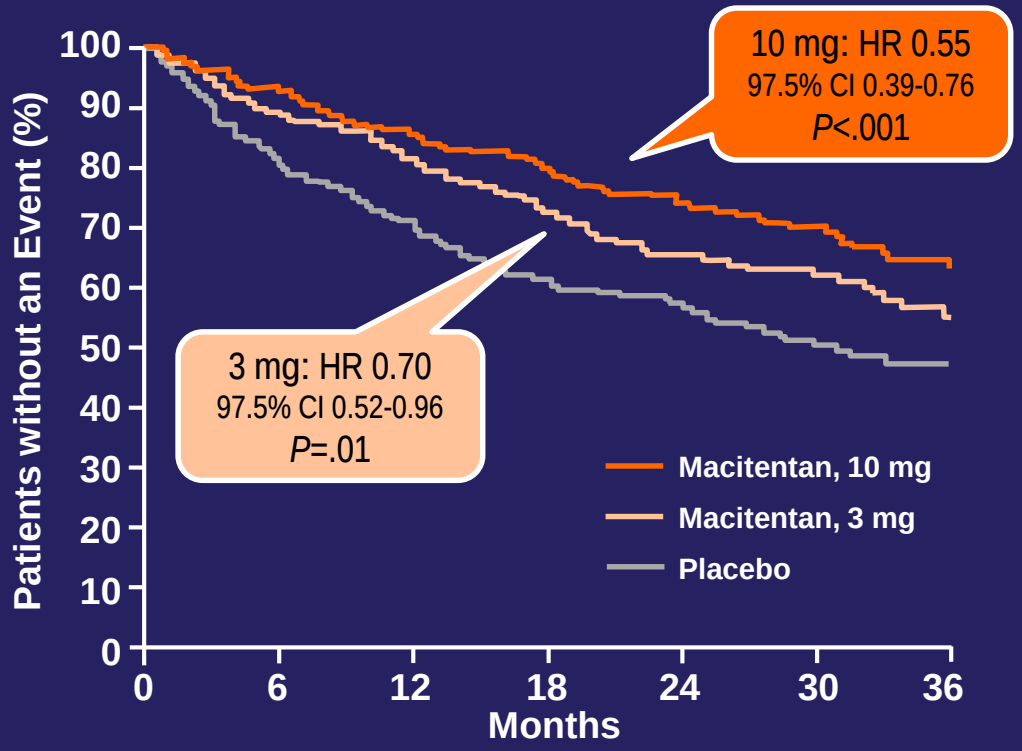
The AMBITION Trial: Evidence for Combination Therapy

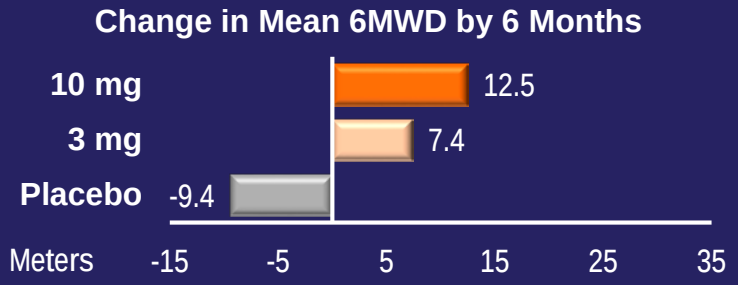




Galiè N, et al. *N Engl J Med*. 2015;373(9):834-844.

Macitentan: SERAPHIN Trial
Novel Agent for PAH

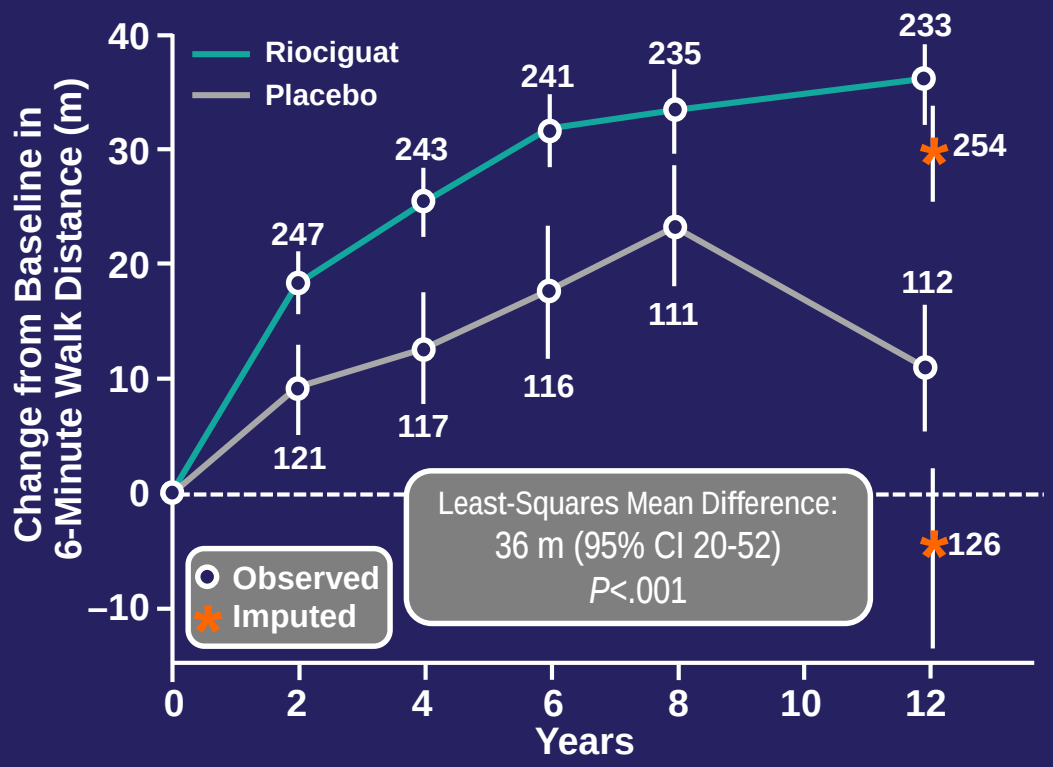


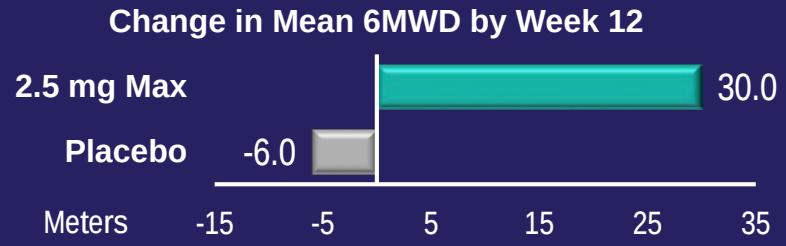


Adverse Events	3 mg (n=250)	10 mg (n=242)	Placebo (n=249)
Worsening PAH	30%	22%	35%
Upper resp. tract infect.	20%	15%	13%
Peripheral edema	16%	18%	18%
Nasopharyngitis	15%	14%	10%
RV failure	15%	13%	23%
Headache	13%	14%	9%

Pulido T, et al. *N Engl J Med*. 2013;369(9):809-818.

Riociguat: PATENT Trials
Novel Agent for PAH

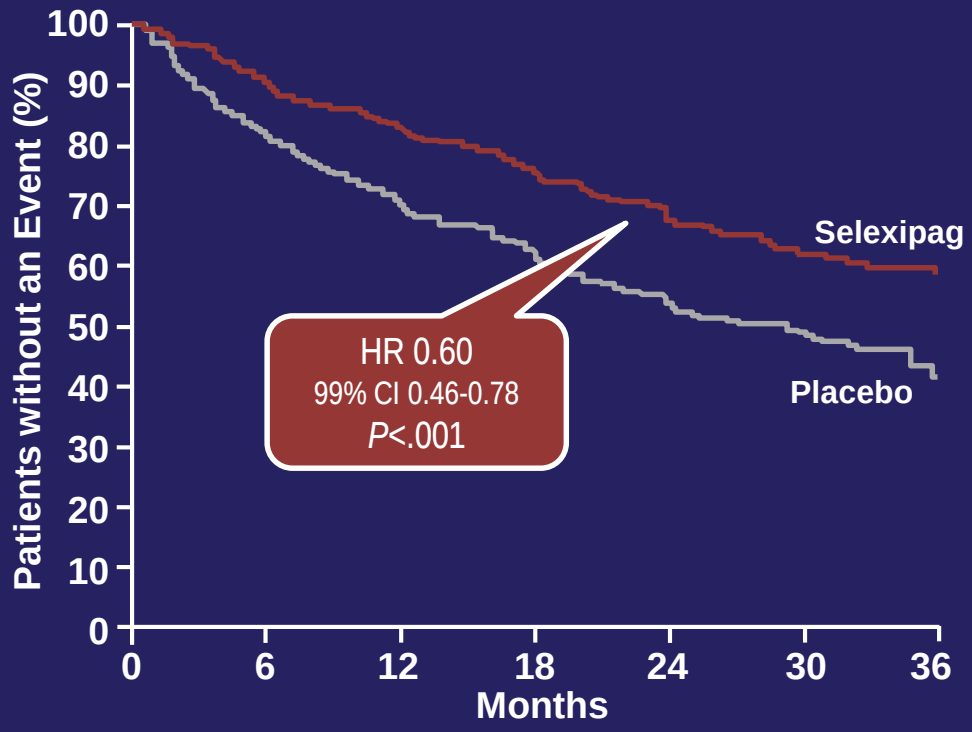


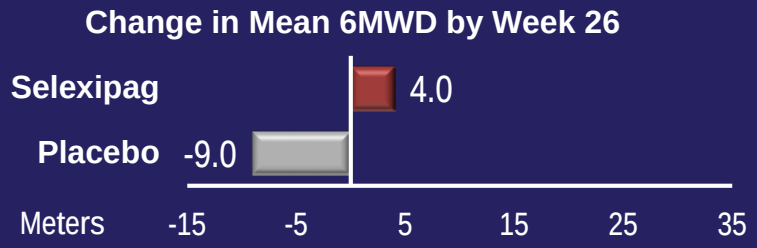


Adverse Events	1.5 mg max (n=63)	2.5 mg max (n=254)	Placebo (n=126)
Headache	32%	27%	20%
Dyspepsia	13%	19%	8%
Peripheral edema	22%	17%	11%
Nausea	16%	16%	13%
Dizziness	24%	16%	12%
Diarrhea	10%	14%	10%

Ghofrani H-A, et al. *N Engl J Med*. 2013;369(4):330-340.

Selexipag: GRIPHON Trial
Novel Agent for PAH





Adverse Events	Selexipag (n=575)	Placebo (n=577)	*P*-value
Headache	65%	33%	*P*<.001
Diarrhea	42%	19%	*P*<.001
Nausea	34%	19%	*P*<.001
Pain in jaw	26%	6%	*P*<.001
Worsening of PAH	22%	36%	*P*<.001
Vomiting	18%	9%	*P*<.001

Sitbon O, et al. *N Engl J Med*. 2015;373(26):2522-2533.

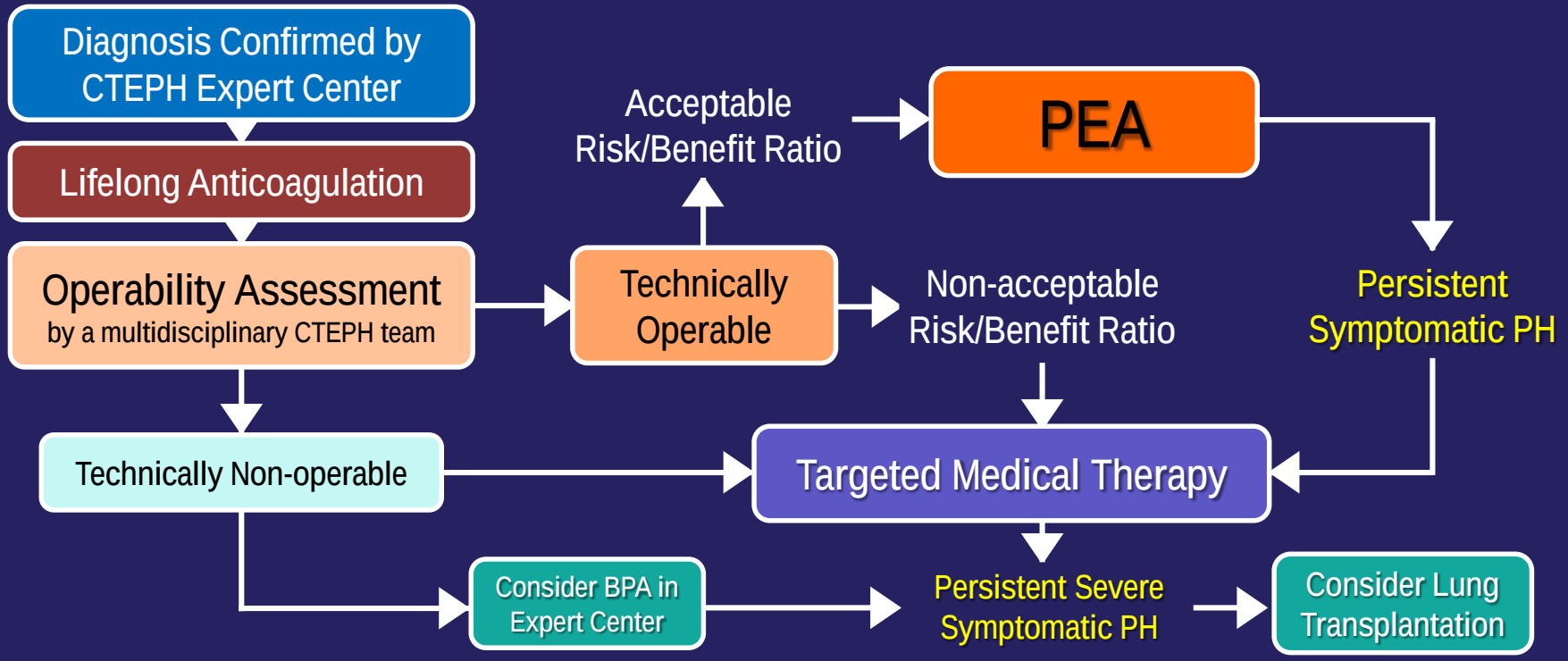
The TRITON Trial

Evidence for Combination Therapy

- The Efficacy and Safety of Initial Triple Versus Initial Dual Oral Combination Therapy in Patients With Newly Diagnosed Pulmonary Arterial Hypertension (TRITON)

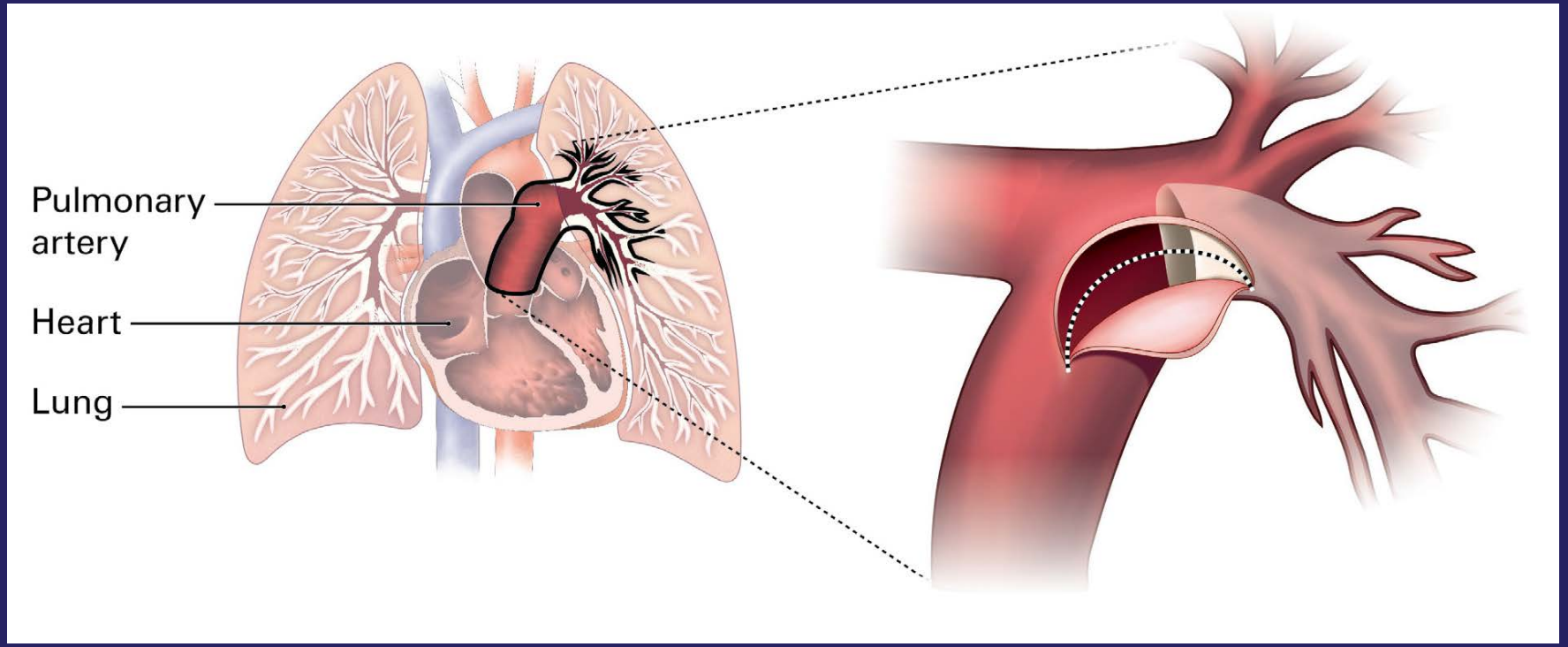
Therapy for CTEPH

CTEPH Treatment Algorithm: ESC/ERS Guidelines



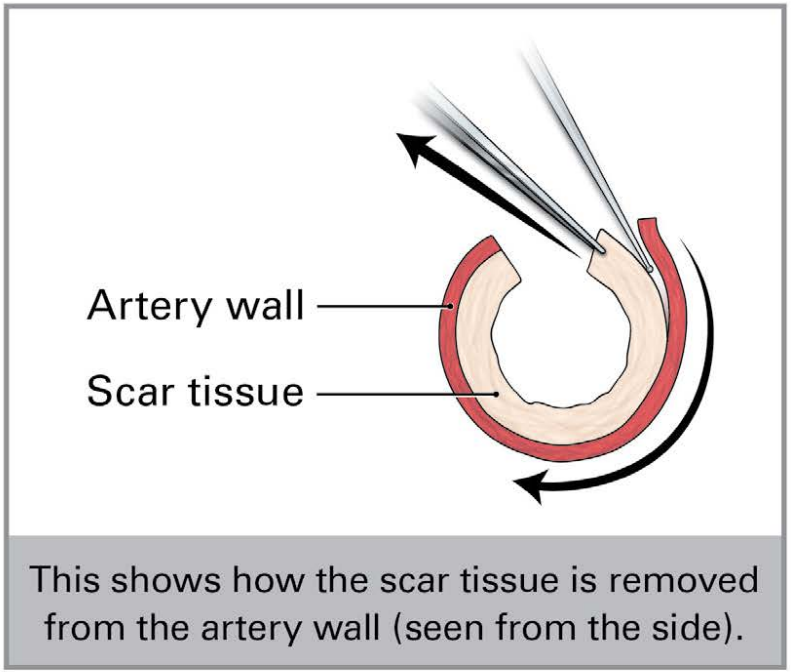
Galiè N, et al. *Eur Heart J*. 2016;37(1):67-119.

PEA Procedure

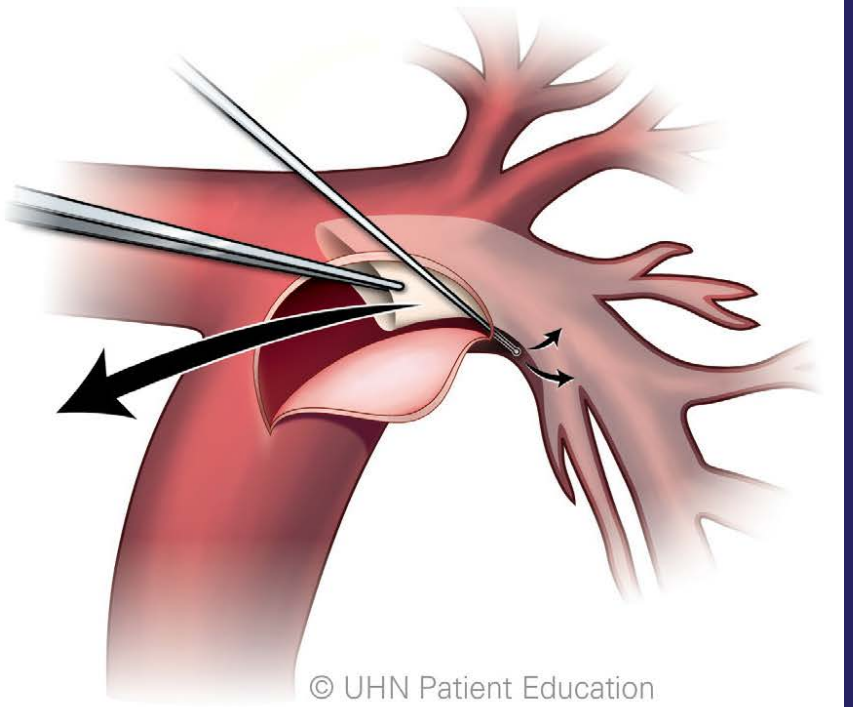


Pulmonary Hypertension Association of Canada. CTEPH – During the Surgery. Available at: http://www.phacanada.ca/cteph/treatment/; http://www.phacanada.ca/index.php/download_file/view_inline/2919/.

PEA Procedure (cont'd)



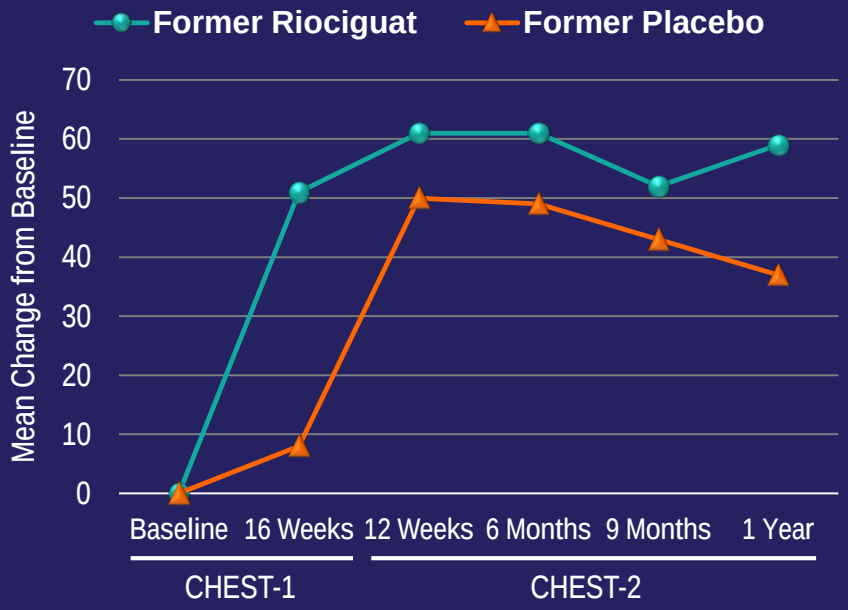
This shows how the scar tissue is removed from the artery wall (seen from the side).



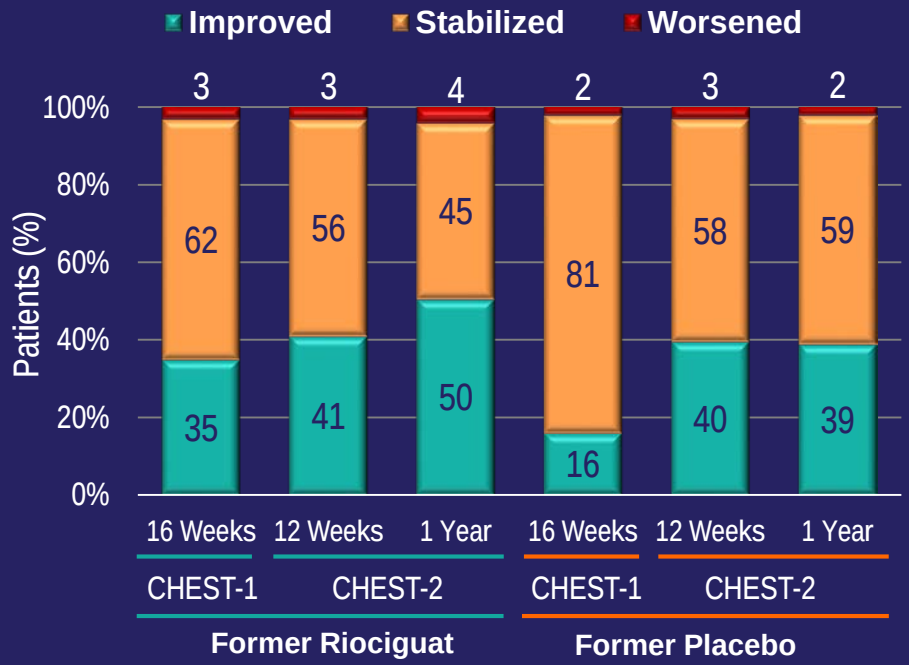
Pulmonary Hypertension Association of Canada. CTEPH – During the Surgery. Available at: http://www.phacanada.ca/cteph/treatment/; http://www.phacanada.ca/index.php/download_file/view_inline/2919/.

Riociguat: CHEST-1 & CHEST-2 Trials
CTEPH Targeted Medical Therapy: ESC/ERS Guidelines

Mean Change in 6MWD



Change in WHO FC



Simonneau G, et al. *Eur Respir J*. 2015;45(5):1293-1302.

Importance of a Team-based, Patient-centered Approach to Care

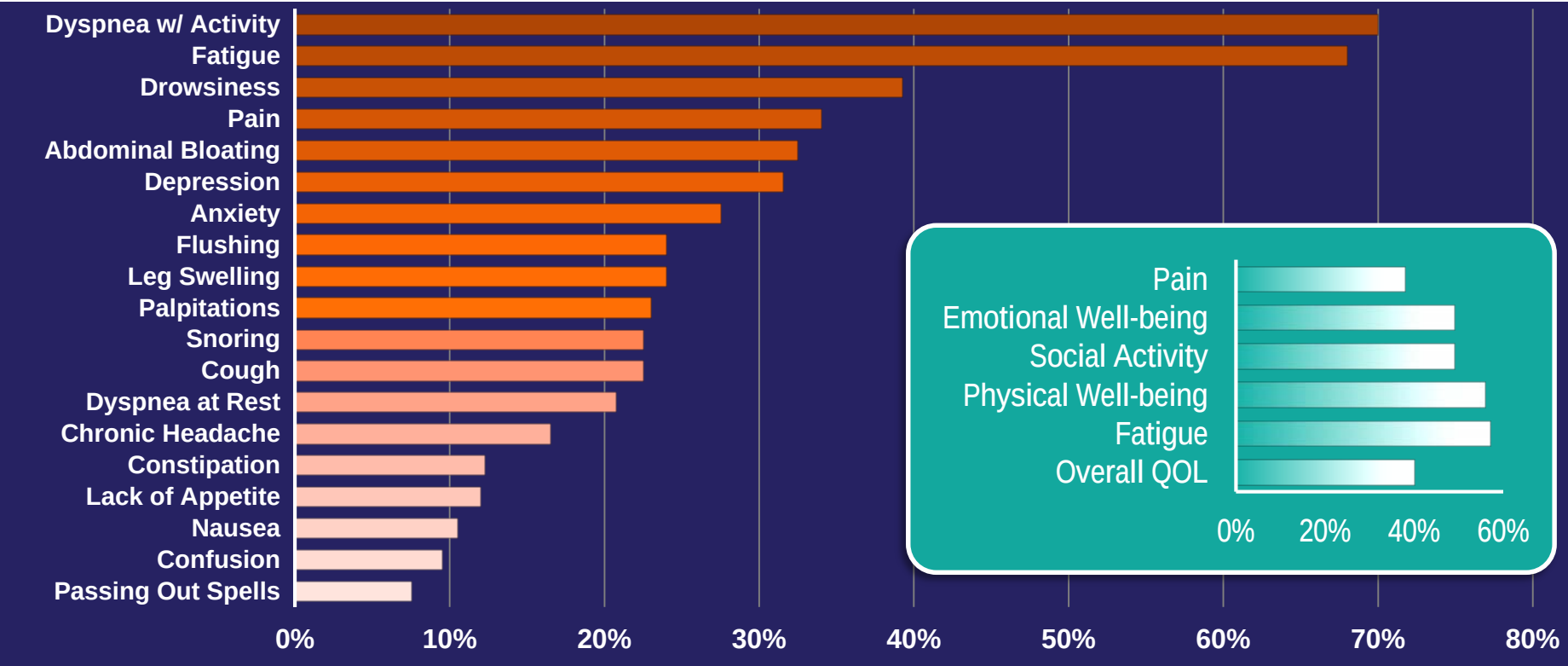
Multidisciplinary Team

- Cardiologist
- Pulmonologist
- Clinical Nurse Specialist
- Radiologist
- Psychologist
- Social Worker
- Gastroenterologist
- Infectious Disease Specialist
- Rheumatologist

Referral center should have direct links and quick referral patterns to additional services

- **CTD**
- **Family Planning**
- **PEA**
- **Transplant Center**
- **Adult CHD services**

Palliative Care:
Patient Perspectives from a Cross-sectional Survey



Swetz KM, et al. *J Heart Lung Transplant*. 2012;31(10):1102-1108.

Palliative Care: Physician Perspectives from a Cross-sectional Survey

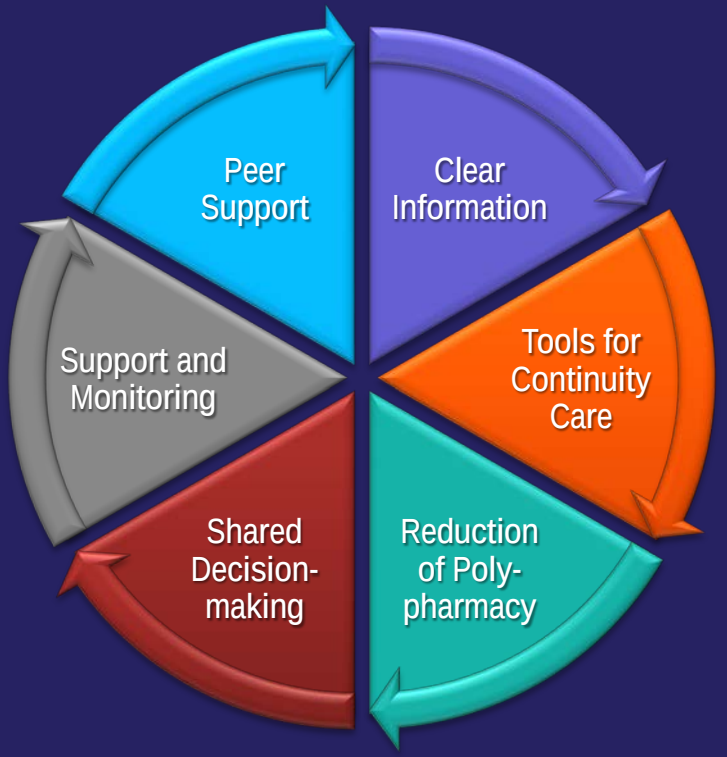
Reasons for Referral to PC	%
End of life/active dying	59%
Hospice referral	46%
Dyspnea management	39%
Impaired quality of life	39%
Goals-of-care discussion	32%
Pain management	25%
Other symptoms	14%

Perceived Barriers to Referral	%
Patient/Family not agreeable to consultation	51%
Patient will view as “giving up hope”	43%
Physician believes PC unnecessary	36%
Believes patients not eligible	28%
Gets in the way of PAH treatment	20%
“Palliative” has negative connotation	17%
Same as hospice and patient not ready	6%

PC, palliative care.

Fenstad ER, et al. *Pulm Circ.* 2014;4(3):504-510.

Addressing Adherence Issues



- Patient-centered care
- Self-efficacy is KEY
- Awareness of limitations in older patients
- Help with low health literacy
  - Simple language
  - Larger font sizes
  - Pictures/diagrams

Nurse-specific Training

- IV prostacyclin therapy
  - Medication orders
  - IV access
  - Initiation of therapy
  - Safety measures
  - Catheter priming for concentration changes or line changes
  - Pump management and maintenance
  - Care of central line and patient education
- Transitioning from one IV prostacyclin to another

Kingman MS, Lombardi S. *J Infus Nurs*. 2014;37(6):442-451.

Resources for Patients & Caregivers

- PHA association: www.phassociation.org
  - Resources for patients
  - Resources for clinicians
  - Clinical research

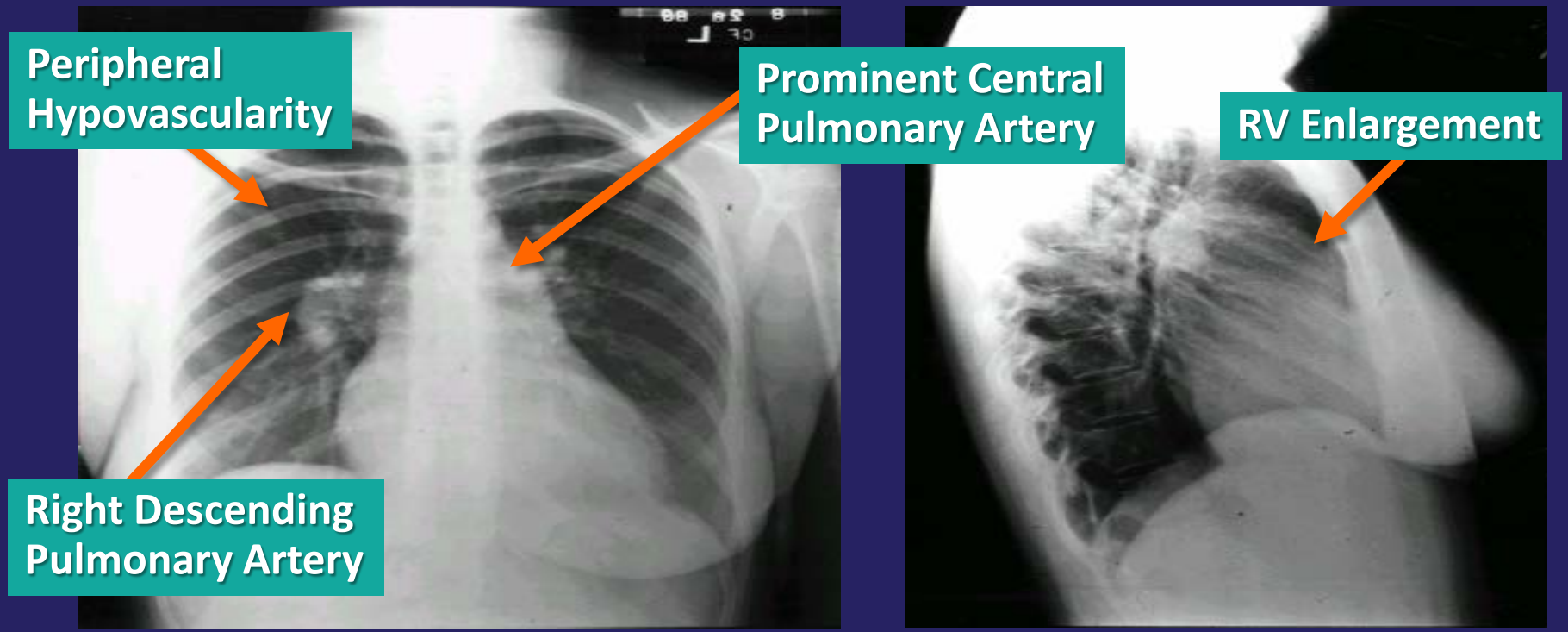
Case Evaluation

Case Evaluation: Patient Description

- 58-year-old female with scleroderma (>10 years)
- Evidence of progressive dyspnea over the preceding 6 months
- NYHA FC III
- Comorbidities
  - Smoker (>40 years)
  - Cough
  - Raynaud's syndrome (>9 years)
- Cool extremities with evidence of peripheral edema
- Pansystolic murmur indicating tricuspid regurgitation

NYHA FC: New York Heart Association functional class.

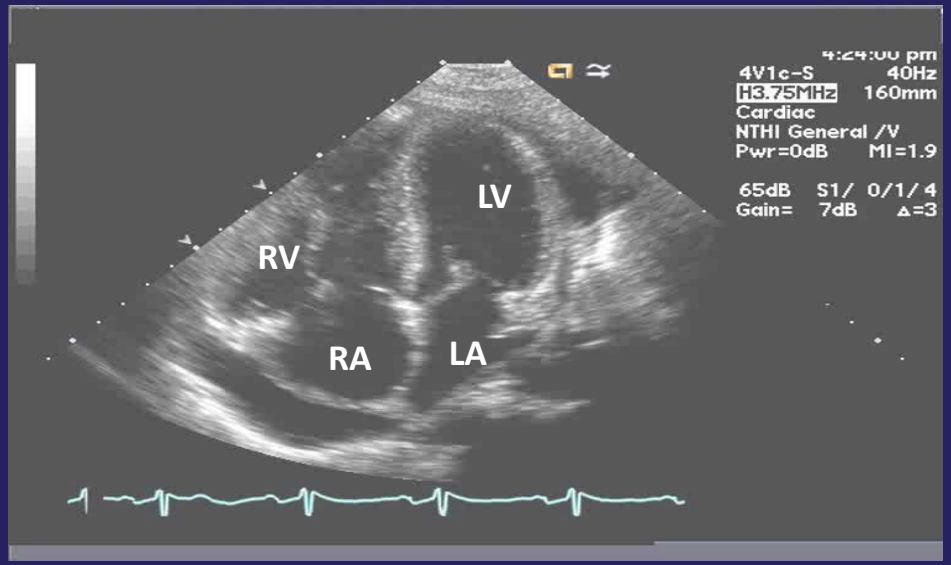
The CXR



CXR, chest X-ray.

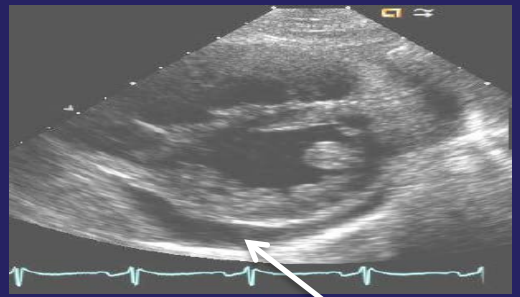
McLaughlin VV, et al. *JACC.* 2009;53:1573-1619.

Echocardiographic Characteristics of Our Patient (Apical View)



LA=left atrium/atrial
LV=left ventricle/ventricular
RA=right atrium/atrial
RV=right ventricle/ventricular

- Irrespective of the pressure measurement, this heart is highly suspicious for PAH, based on structural changes



Pericardial effusion

Our Patient's Initial Test Results

- DLCO 54%
- FVC%/DLC%=1.7
- 6MWD=268 meters
- CXR reveals enlarged cardiac silhouette
- Right Heart Catheterization
  - mRAP: 12 mmHg
  - mPAP: 45 mmHg
  - CI: 2.3 L/min/m^2
  - PVR: 12 Wood units

How would you treat this patient?

Goals of Treatment in 2018

- NYHA Functional Class is an important predictor of survival
- If PAH therapy is effective, improvement in NYHA FC from FC III/IV to FC II is consistent with improved PAH prognosis

Variables Used in Clinical Practice to Determine Responses to Therapy and Prognosis in PAH Patients	
Functional class	I or II
Echocardiography	Normal/near-normal RV size and function
Hemodynamics	Normalization of RV function (RAP <8 mmHg and CI >2.5-3.0 L/min^2)
6MWD	>380 to 440 m (or more in younger patients)
Cardiopulmonary exercise testing	Peak VO_2 >15 mL/min/kg and $EqCO_2$ <45 L/min/L/min
B-type natriuretic peptide levels	Normal

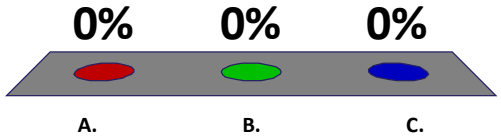
$EqCO_2$, ventilatory equivalent for carbon dioxide.

McLaughlin VV, et al. *JACC.* 2013;62(25 suppl D):D73-D81.

Case Evaluation: Discussion Question

What is the initial therapy for a high risk patient with Group I PAH (Functional Class II-III)?

A. Oral monotherapy
B. **Oral dual combination therapy**
C. IV infusion prostacyclin therapy



Summary

- PAH and CTEPH are chronic, life-threatening conditions
  - Require early recognition and accurate diagnosis
- Diagnosis
  - V/Q scan important to distinguish between PAH and CTEPH
- Complex therapeutic management
  - Guideline recommendations
  - Novel therapies
- Multidisciplinary, patient-centered approach is critical
  - PH referral centers
  - Cardiologists and pulmonologists
  - Adherence issues
  - High level of nursing competency

Clinical Pearls

- Diagnosis
  - Chest X-ray is inferior to ECG in diagnosing PAH
  - Structural changes may indicate PAH irrespective of pressure
- Treatment
  - PAH: Combination therapy is currently the standard of care
    - Targeting multiple pathways improves therapeutic response
    - Goal: Improvement and normalization to make patients LOW RISK
  - CTEPH: Patients ineligible for PEA should receive riociguat
- Patient resources are important to ensuring outcomes!

Questions and Answers

Thank You!