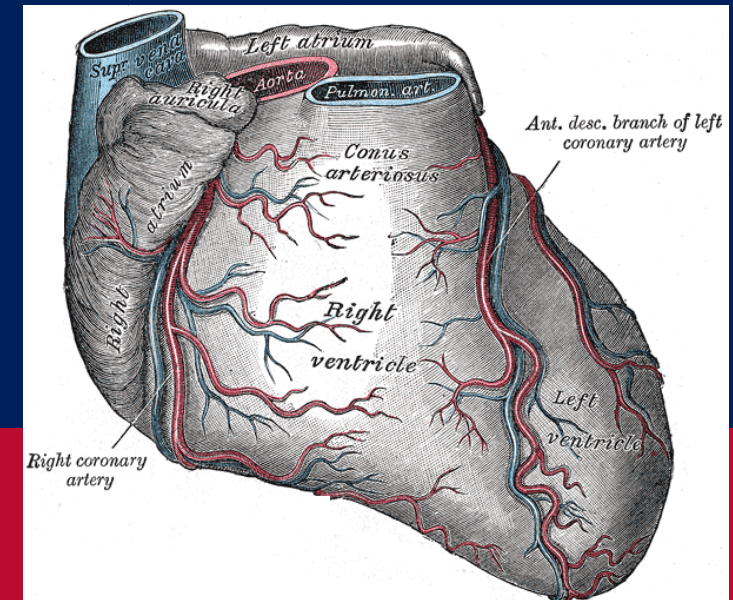


# Basic Principles in Pulmonary Arterial Hypertension

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# Conflicts of Interest

1. Merck Pharmaceuticals – Educational Speaker, Primary Investigator, and Consultant
2. Johnson and Johnson Pharmaceuticals – Educational Speaker and Consultant
3. United Therapeutics Pharmaceuticals – Primary Investigator and Consultant
4. Insmed – Primary Investigator

# Objectives

1. Distinguish Pulmonary Hypertension (PH) from Pulmonary Arterial Hypertension (PAH)
2. Define the hemodynamic profile of PAH
3. Describe the basic pathophysiology of PAH
4. Define the diagnostic strategy for PAH
5. Outline the basic treatment algorithm for PAH

# Case Vignette Part I – Initial Presentation

**Chief Complaint:** Sonya is 36-year-old woman presents to the internal medicine clinic with progressive shortness of breath over the past 6 months.

**History of Present Illness:** She reports that initially she noticed mild shortness of breath when walking quickly or climbing stairs, but more recently she has had difficulty keeping up with her coworkers during lunchtime walks. She denies chest pain, wheezing, or coughing. She has noticed the dyspnea more at night when she lays in bed or when tying her shoes. She mentions that her smart watch has been alarming due to high resting heart rates. There is no history of recent upper respiratory illness. She occasionally feels lightheaded when standing for long periods but denies syncope.

**Past Medical History:** Hypothyroidism, well-controlled on levothyroxine

**Social History:** Negative

**Family History:** Mother with SLE, No family history of cardiopulmonary disease

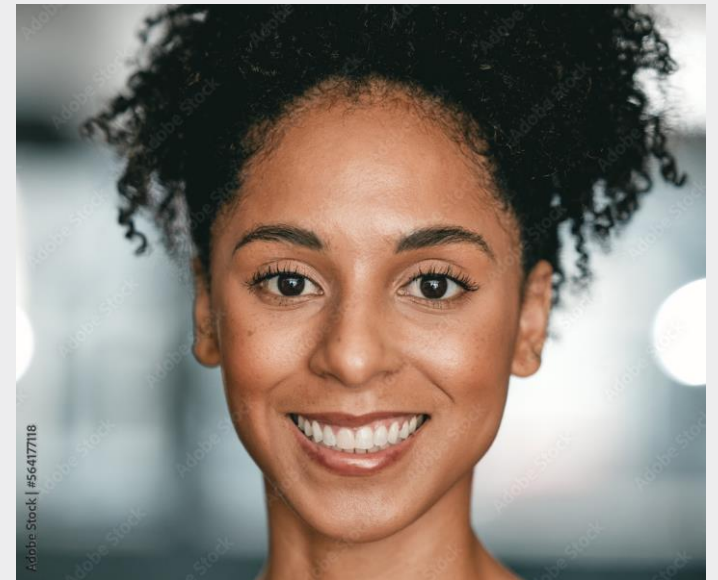
## **Physical Exam:**

Vitals: HR 92, BP 108/68, RR 18, SpO<sub>2</sub> 96% on room air

Regular rhythm, normal S1/S2, subtle increase in P2 with fixed splitting

Lungs Clear to auscultation bilaterally

Trace peripheral edema



# Group Discussion

1. What is your differential diagnosis for this patient?

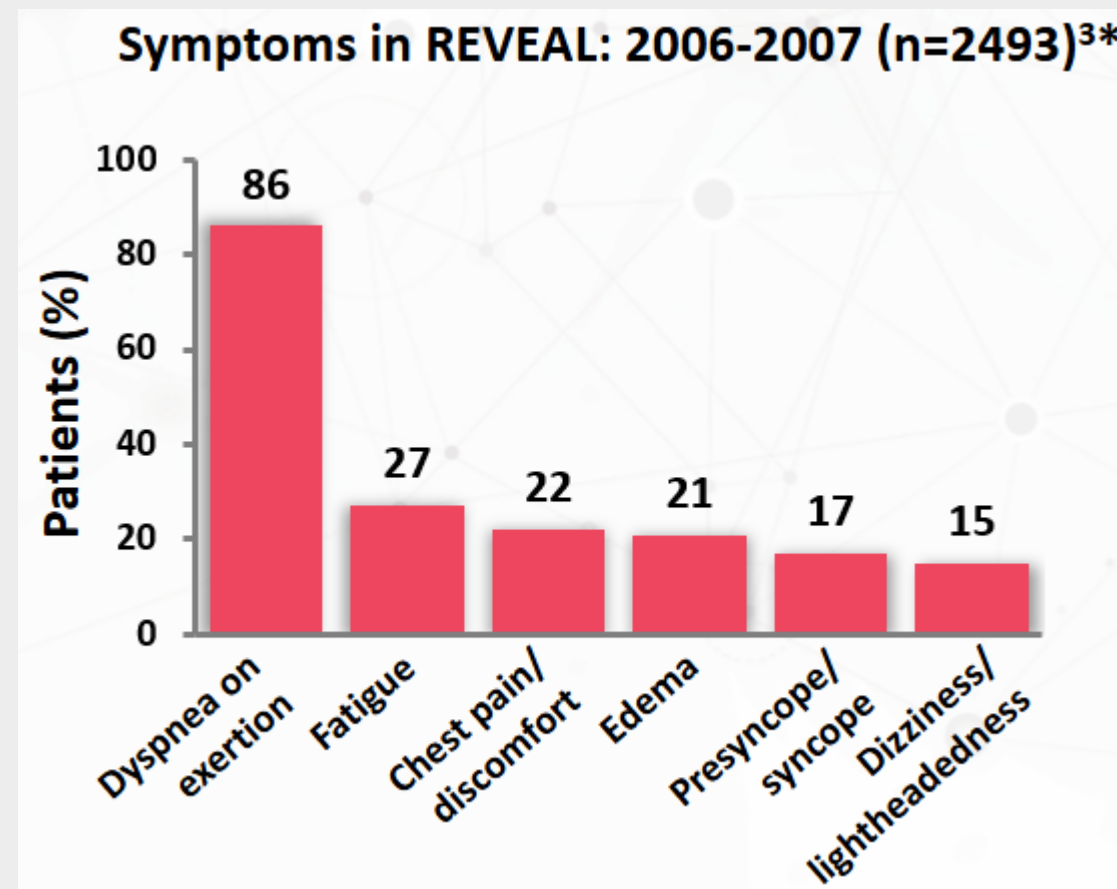
Wide

1. What is the next step in management?

Echocardiogram

# PAH Presenting symptoms are vague

- The most common presenting symptoms are... common
- Overlap with many other more common cardiopulmonary diseases
  - Asthma
  - Heart Failure
  - COPD
  - Angina/CAD



# Utilize Your Physical Exam

| Finding  | Significance in PAH  |
|--|--|
| <b>Loud/Accentuated P2</b>                         | Reflects elevated pulmonary artery pressures causing forceful pulmonic valve closure |
| <b>Right Ventricular Heave or Lift</b>             | Indicates right ventricular hypertrophy due to pressure overload                     |
| <b>Jugular Venous Distension (JVD)</b>             | Suggests elevated right atrial pressure and right-sided heart strain                 |
| <b>Peripheral Edema or Hepatomegaly</b>            | Signs of systemic venous congestion from right heart failure                         |
| <b>Clear Lung Fields on Auscultation</b>           | Absence of pulmonary congestion or bronchospasm despite dyspnea                      |
| <b>Tricuspid Regurgitation Murmur</b>              | Holosystolic murmur due to annular dilation from RV volume/pressure overload         |
| <b>Right-sided S3 Gallop</b>                       | May indicate RV volume overload or reduced compliance                                |
| <b>Cyanosis or Digital Clubbing (late finding)</b> | Seen in advanced disease with hypoxemia or chronic low cardiac output                |

## Case Vignette Part II – Initial Work-up

Given her subtle physical findings, her primary care physician refers her for a transthoracic echocardiogram to further evaluate her dyspnea. The findings are listed below

### **Echocardiogram Results:**

1. Left Ventricle: EF of 55-60%, Normal size and thickness
2. Right Ventricle: Mildly dilated, TAPSE 1.6
3. Right Atrium: Mild Enlargement
4. Left Atrium: Normal
5. Tricuspid Valve: Regurgitation Jet Velocity: 3.0 m/s
6. Inferior Vena Cava (IVC): Dilated with <50% inspiratory collapse

# Group Discussion

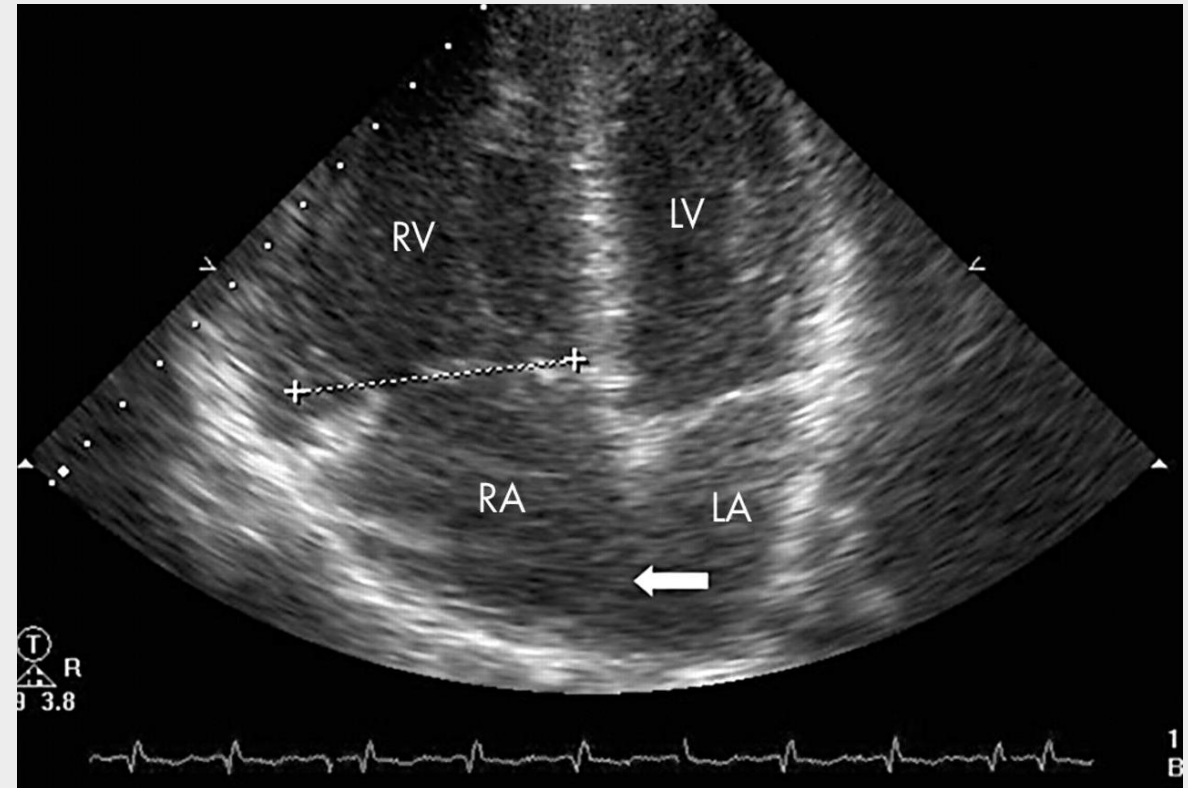
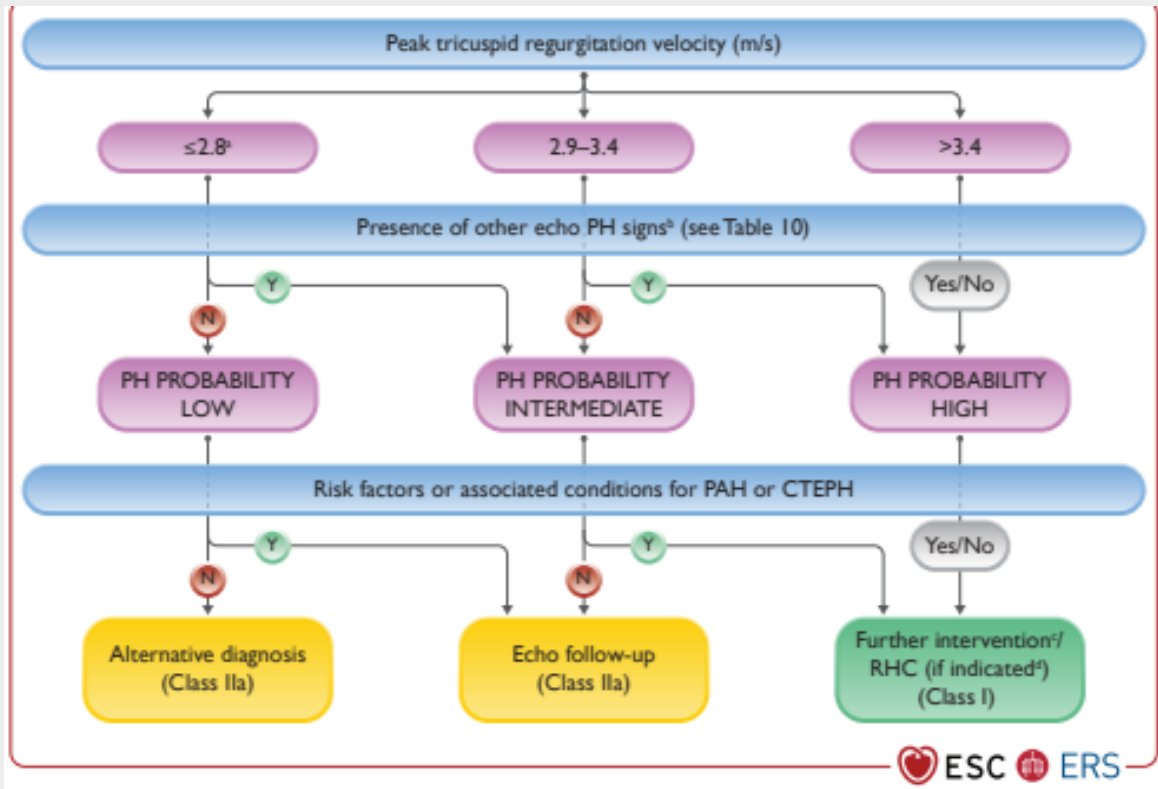
1. What is your top differential diagnosis now?

Pulmonary Hypertension

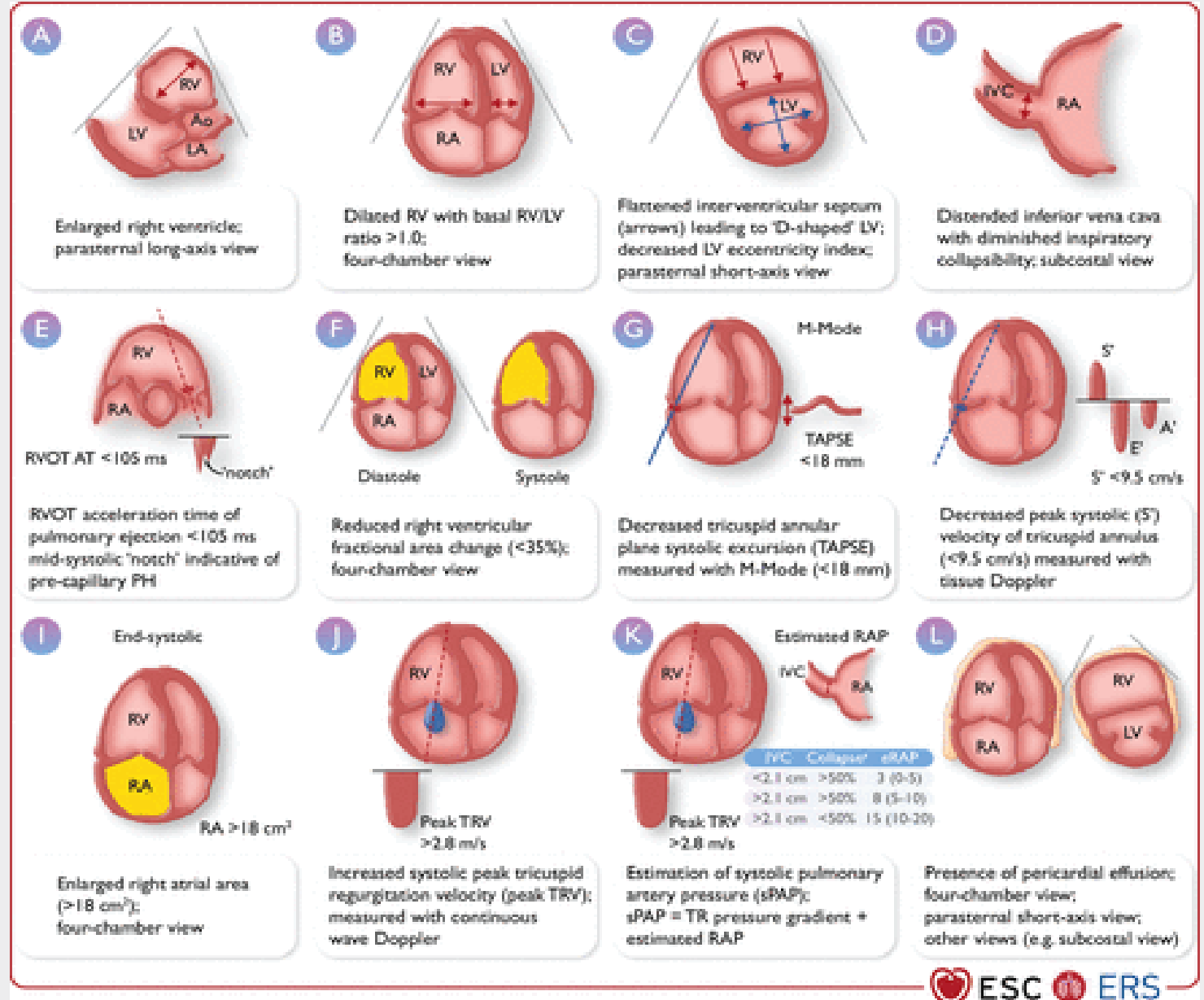
1. What is the next step in management?

RHC

# Echocardiogram Screening



# Other Echocardiographic Signs of Pulmonary Hypertension



# Case Vignette Part III – Right Heart Catheterization

Given her echocardiogram findings, she is referred to a pulmonary vascular clinic for further work-up. There it is decided that she will undergo a right heart catheterization to confirm the suspected diagnosis of PH. Her hemodynamic profile is shown below.

| Parameter  | Value                     |
|--|---------------------------|
| Right Atrial Pressure (RAP)                        | 10 mmHg                   |
| Right Ventricular Pressure (RVP)                   | 70/10 mmHg                |
| Pulmonary Artery Pressure (PAP)                    | 65/25 mmHg (mean 42 mmHg) |
| Pulmonary Capillary Wedge Pressure (PCWP)          | 10 mmHg                   |
| Cardiac Output (Thermodilution)                    | 3.5 L/min                 |
| Cardiac Index                                      | 1.9 L/min/m <sup>2</sup>  |
| Pulmonary Vascular Resistance (PVR)                | 9.1 Wood units            |
| Mixed Venous Oxygen Saturation (SvO <sub>2</sub> ) | 60%                       |

## Group Discussion

This hemodynamic profile is consistent with what type of pulmonary hypertension pattern?

Isolated Precapillary PH

What is the difference between Pulmonary Hypertension and Pulmonary Arterial Hypertension?

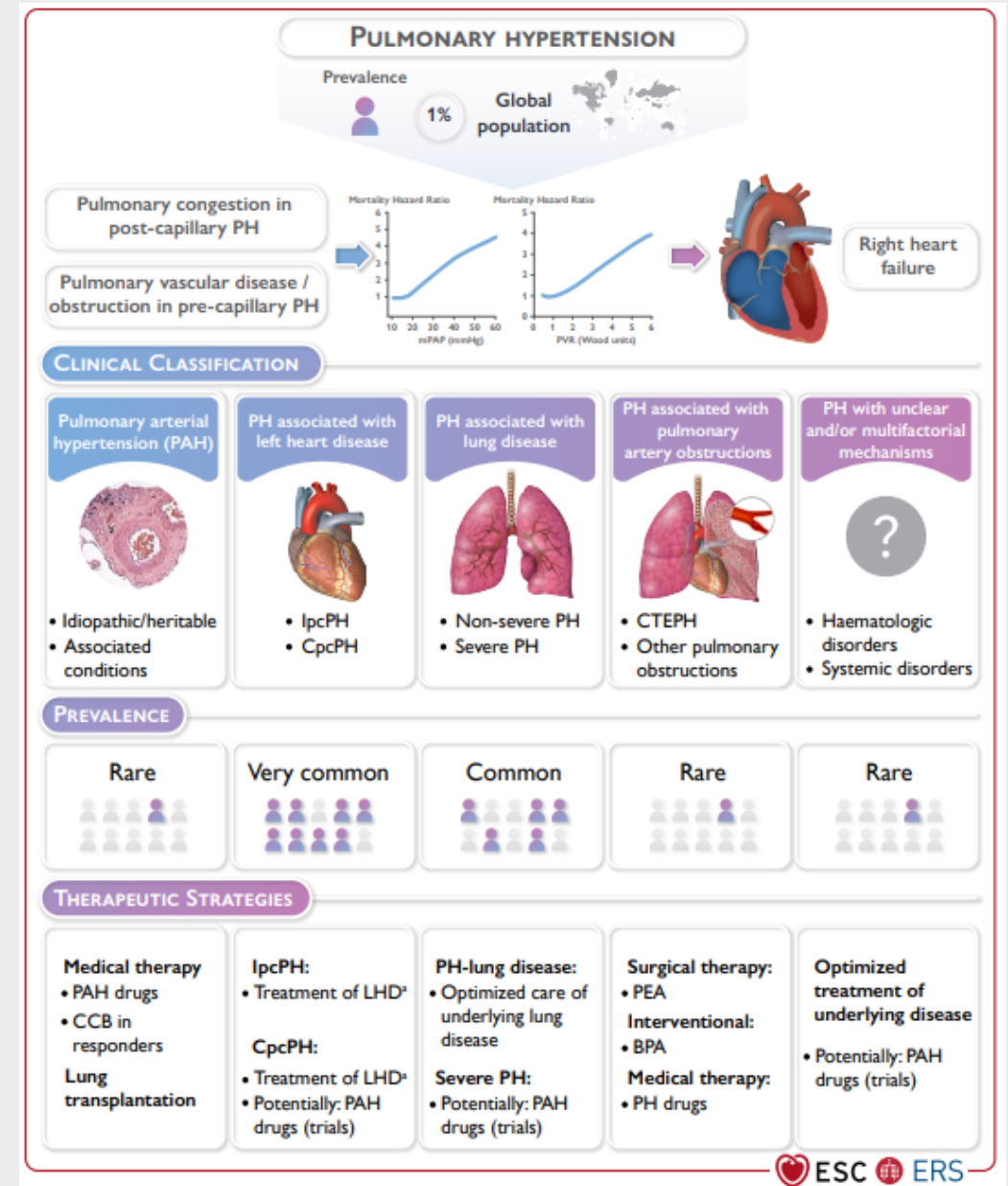
Pulmonary hypertension is defined by elevated RV afterload, PAH is specifically RV afterload due to maladaptive pulmonary vascular remodeling

What are the next steps?

Secondary PH work-up and Risk assessment

# PAH is a Rare and Fatal form of PH

- PH is non-specific
  - characterized by elevated RV afterload and progressive RV failure
- PAH = PH with maladaptive vascular remodeling
- PAH low incidence/prevalence compared to other forms of PH
- PAH is progressive with 7 year survival without therapy



# Clinical Classification

## 1. PAH

### 1.1 Idiopathic

- 1.1.1 Non-responders at vasoreactivity testing
- 1.1.2 Acute responders at vasoreactivity testing

### 1.2 Heritable

### 1.3 Associated with drugs and toxins

### 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/capillaries (PVOD/PCH) involvement

### 1.6 Persistent PH of the newborn

## 2. PH associated with left heart disease

### 2.1 Heart failure

- 2.1.1 With preserved ejection fraction
- 2.1.2 With reduced or mildly reduced ejection fraction

### 2.2 Valvular heart disease

### 2.3 Congenital/acquired cardiovascular conditions leading to post-capillary PH

## 3. PH associated with lung diseases and/or hypoxia

### 3.1 Obstructive lung disease or emphysema

### 3.2 Restrictive lung disease

### 3.3 Lung disease with mixed restrictive/obstructive pattern

### 3.4 Hypoventilation syndromes

### 3.5 Hypoxia without lung disease (eg, high altitude)

### 3.6 Developmental lung disorders

## 4. PH associated with pulmonary artery obstructions

### 4.1 Chronic thromboembolic PH

### 4.2 Other pulmonary artery obstructions

## 5. PH with unclear and/or multifactorial mechanisms

### 5.1 Hematologic disorders

### 5.2 Systemic disorders

### 5.3 Metabolic disorders

### 5.4 Chronic renal failure with or without hemodialysis

### 5.5 Pulmonary tumor thrombotic microangiopathy

### 5.6 Fibrosing mediastinitis

# PAH Has a Specific Hemodynamic definition

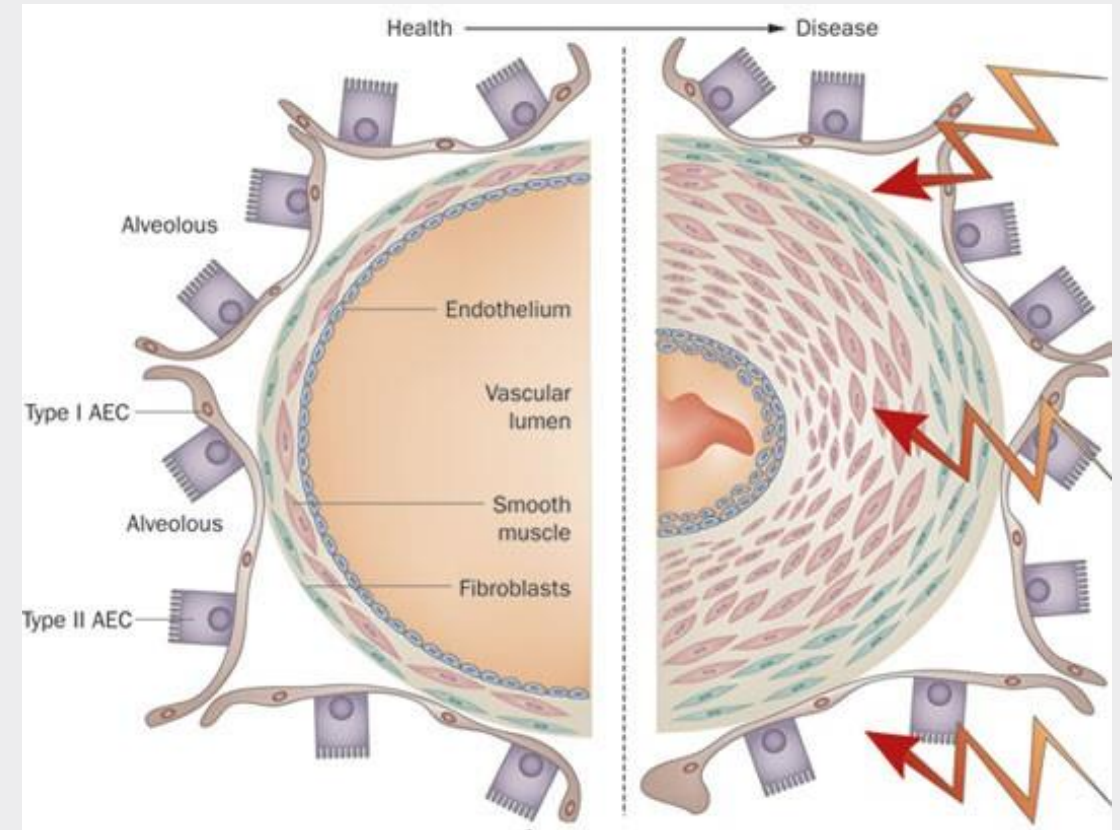
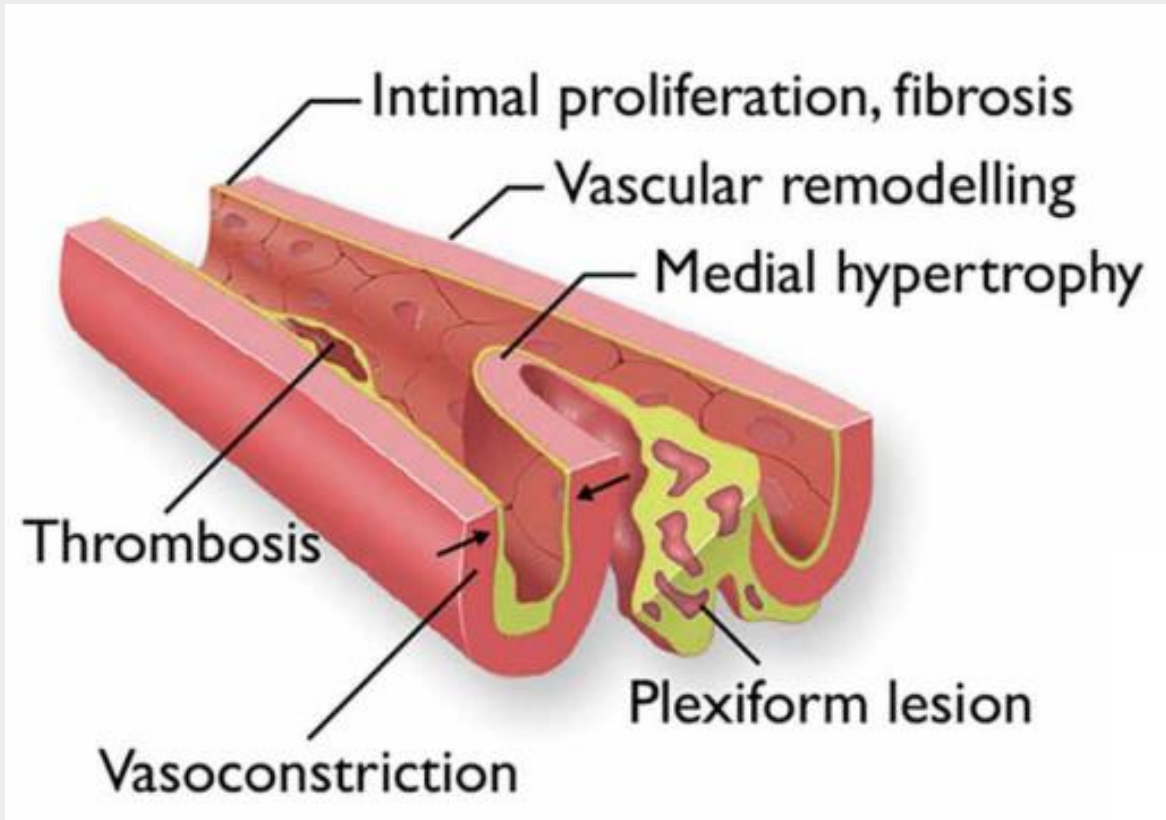
- All PH characterized by elevated RV afterload (mPAP >20 mmHg)
- PAH characterized by elevated pulmonary vascular resistance (PVR >2.0)
- Must exclude downstream (post-capillary) afterload
  - Hemodynamically estimated by normal LVEDP (PAWP ≤15)
- RHC is required to confirm the diagnosis of PAH

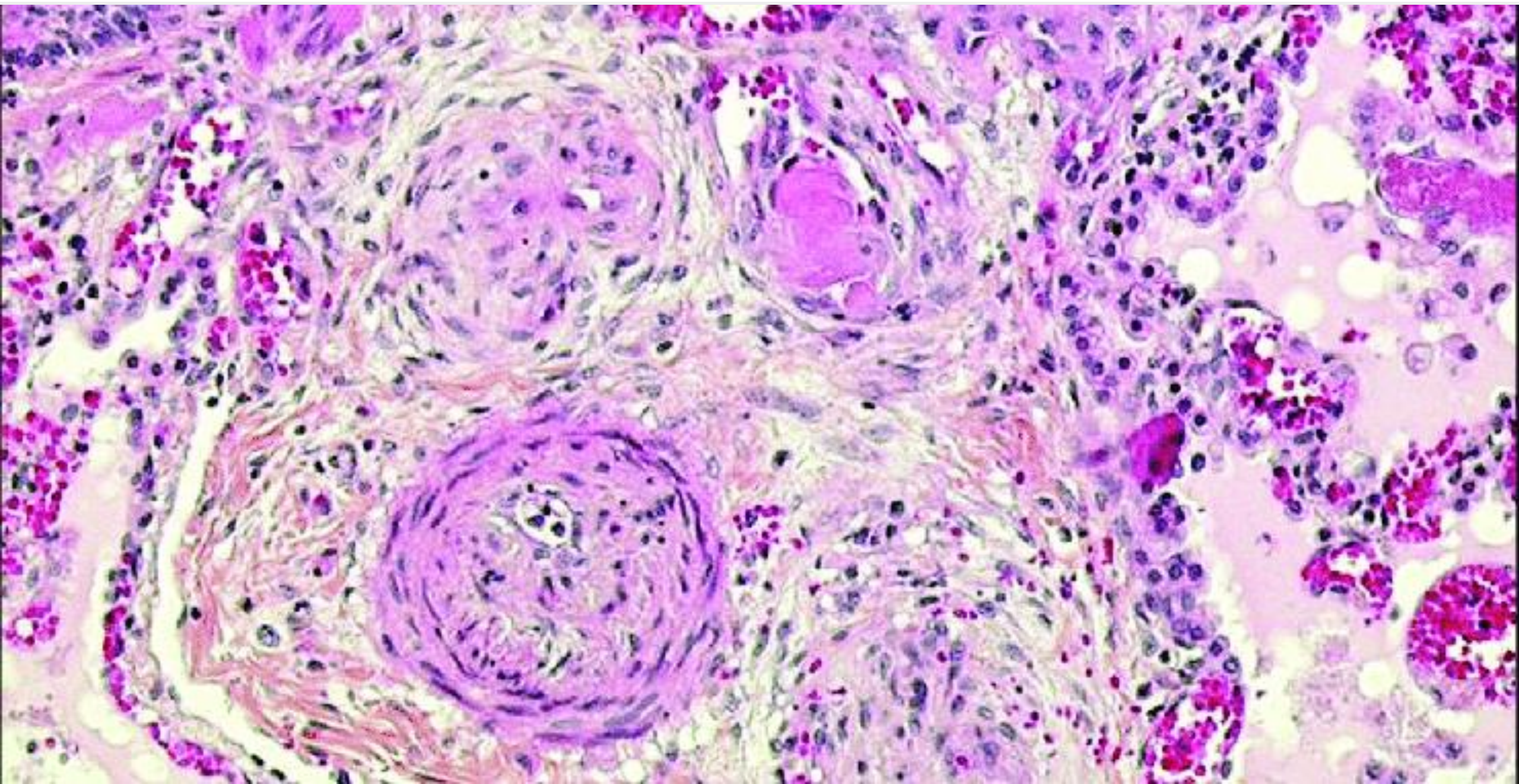
| Definition       | Haemodynamic characteristics                             |
|------------------|--|
| PH               | mPAP >20 mmHg  |
| Pre-capillary PH | mPAP >20 mmHg<br>PAWP ≤15 mmHg<br>PVR >2 WU              |
| lpcPH            | mPAP >20 mmHg<br>PAWP >15 mmHg<br>PVR ≤2 WU              |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

CO, cardiac output; CpcPH, combined post- and pre-capillary pulmonary hypertension; lpcPH, isolated post-capillary pulmonary hypertension; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; WU, Wood units.

Some patients present with elevated mPAP (>20 mmHg) but low PVR (≤2 WU) and low PAWP (≤15 mmHg); this haemodynamic condition may be described by the term 'unclassified PH' (see text for further details).

# PAH is a Progressive Fatal Vasculopathy of the Pulmonary Arterioles





# Group Discussion

Where do you feel this patient is in her disease course (early, late, etc) and why?

Mid to late presentation given presence of symptoms (WHO-fc III)

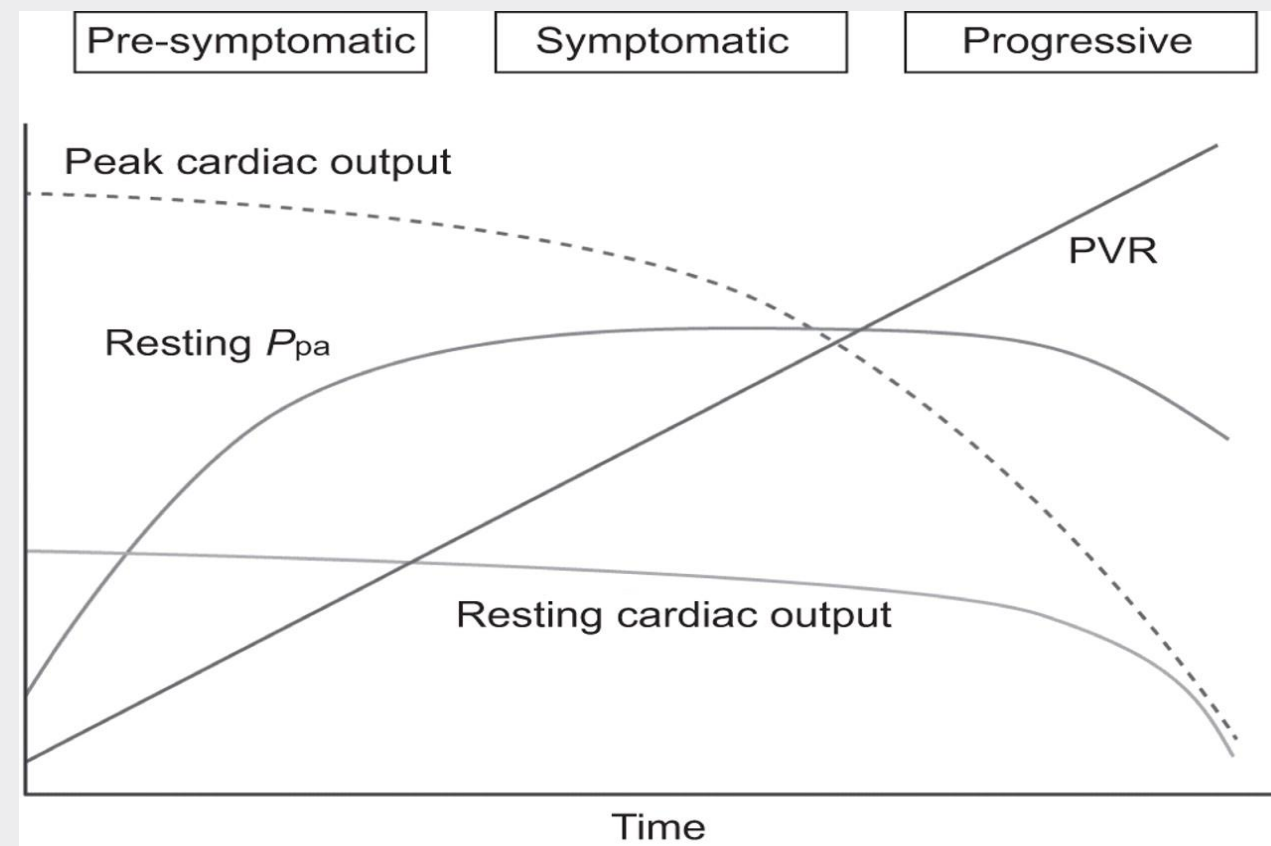
Why is early diagnosis of PAH important

Early diagnosis and treatment is associated with improved outcomes

# Why is early diagnosis of PAH important?

# Clinical Disease Course

- CO is maintained in early disease
- RV compensation is overwhelmed as PVR increases
- PAP initially increases, but then falls as CO is compromised
- RAP increases as RV failure progresses



# Refer Early to an expert PH center

## Triggers to refer for not expert centers:

- Rapid Progression
- Severe symptoms: eg Syncope
- Severe limitation (WHO-fc III/IV)
- Signs of right heart failure

## Triggers to refer for anyone else:

- Any suspicion for PH

## Why:

- Late presentation (and treatment) drive mortality
- Up to 1/3 of patients are misdiagnosed at time of referral
- Nearly 60% are on incorrect therapies

## Case Vignette Part IV – Follow-up

Two weeks after undergoing right heart catheterization, the patient returns to the pulmonary hypertension clinic to review her results.

She appears well and reports no significant change in her symptoms. She continues to experience exertional dyspnea with daily activities, such as walking from the parking lot to her office.

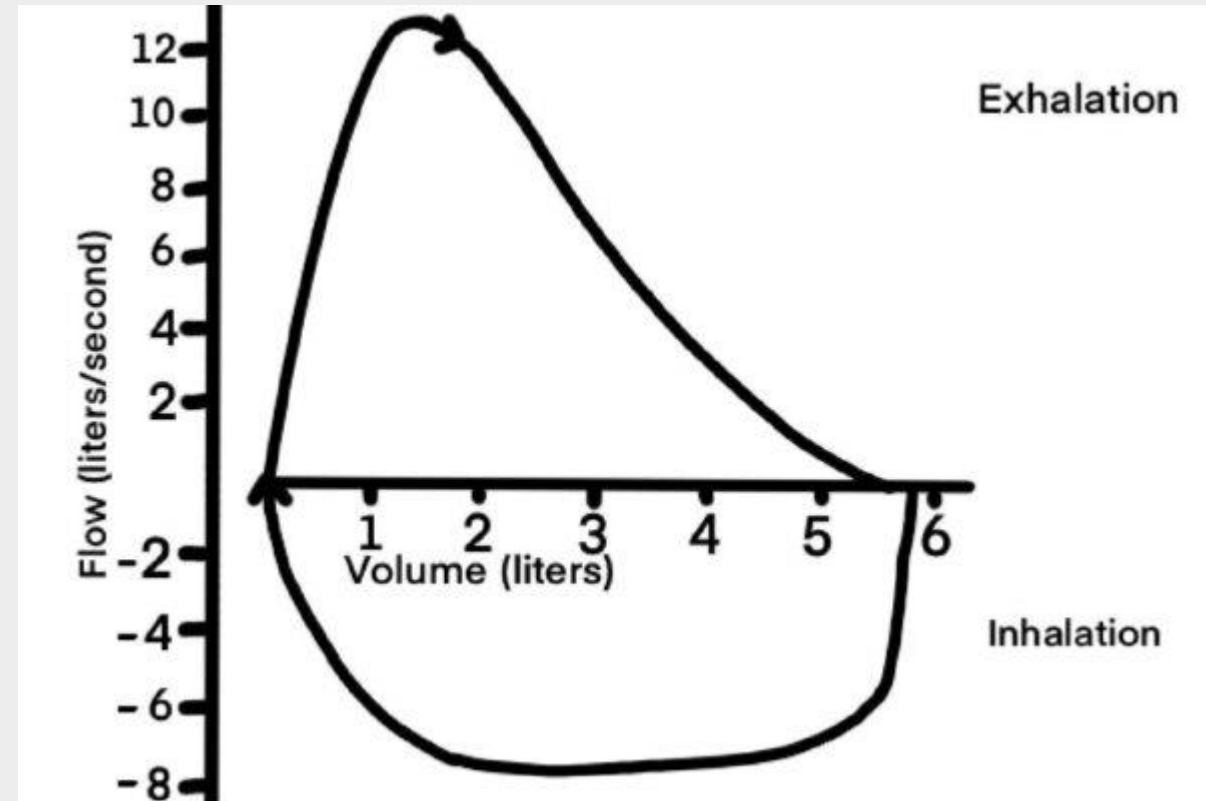
Based on her hemodynamics, symptom burden, and functional class (WHO FC III), a formal diagnosis of pulmonary arterial hypertension (Group 1) is made.

# Group Discussion

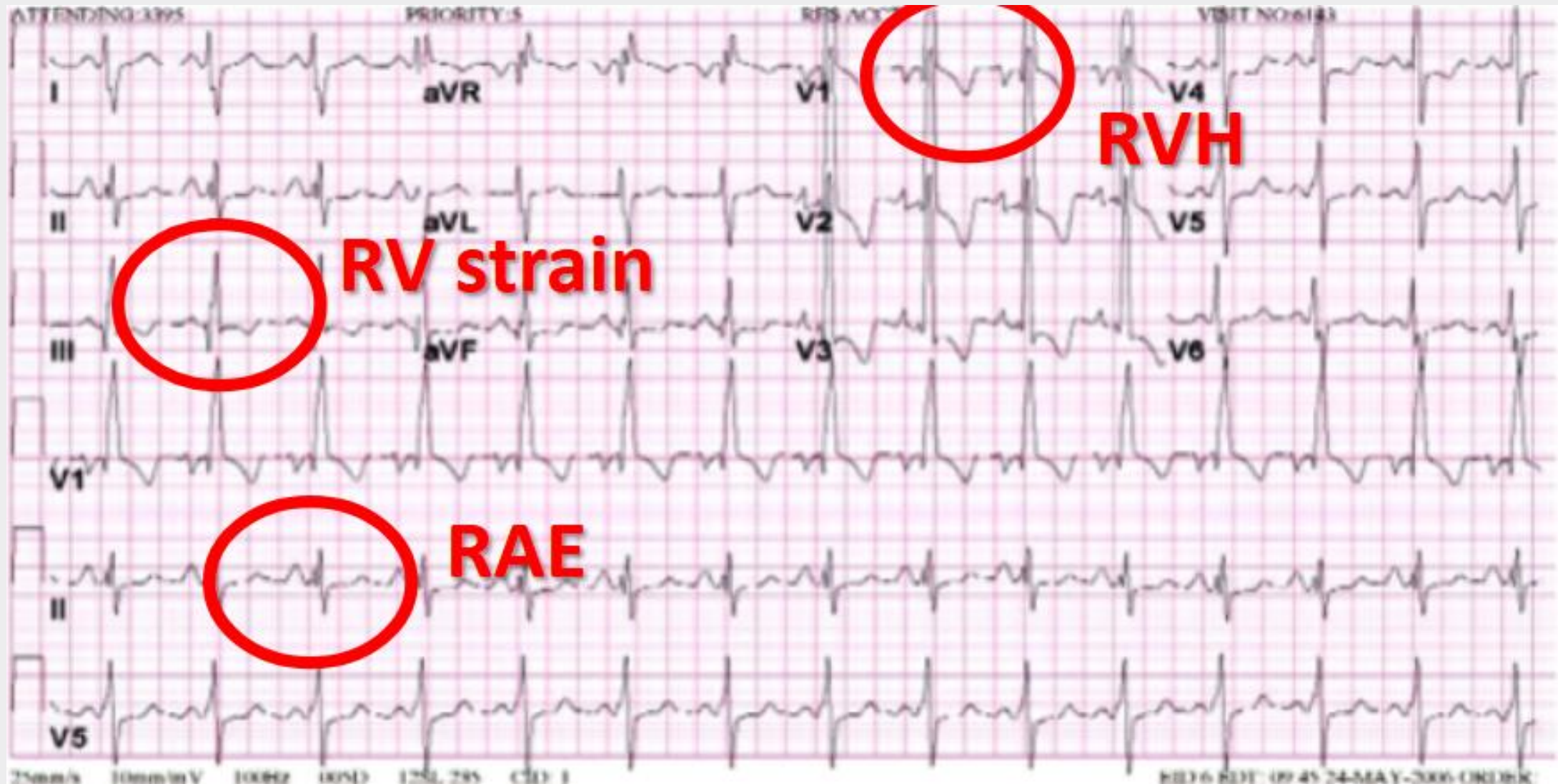
1. What additional ancillary testing should be performed for this patient?

# Pulmonary Function testing

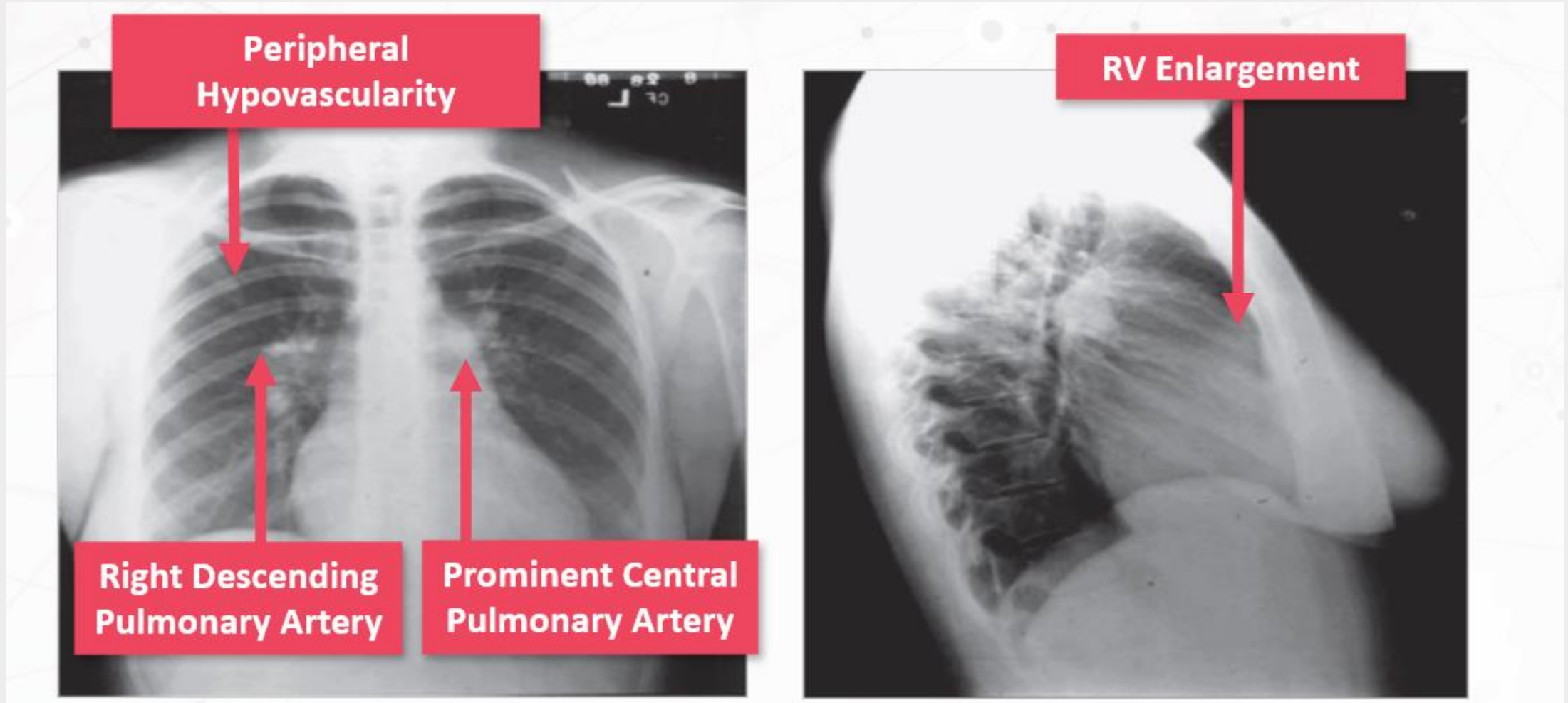
1. Typically, normal with isolated diffusion restriction (low DLCO)
2. Help distinguish between PH groups (group I vs III)
3. Prognosticate disease severity
4. COPD and ILD related PH (Group III) may look identical on RHC and echocardiogram
5. Advanced thoracic imaging (CT/HRCT) should be considered where structural lung disease is suggested



# EKG

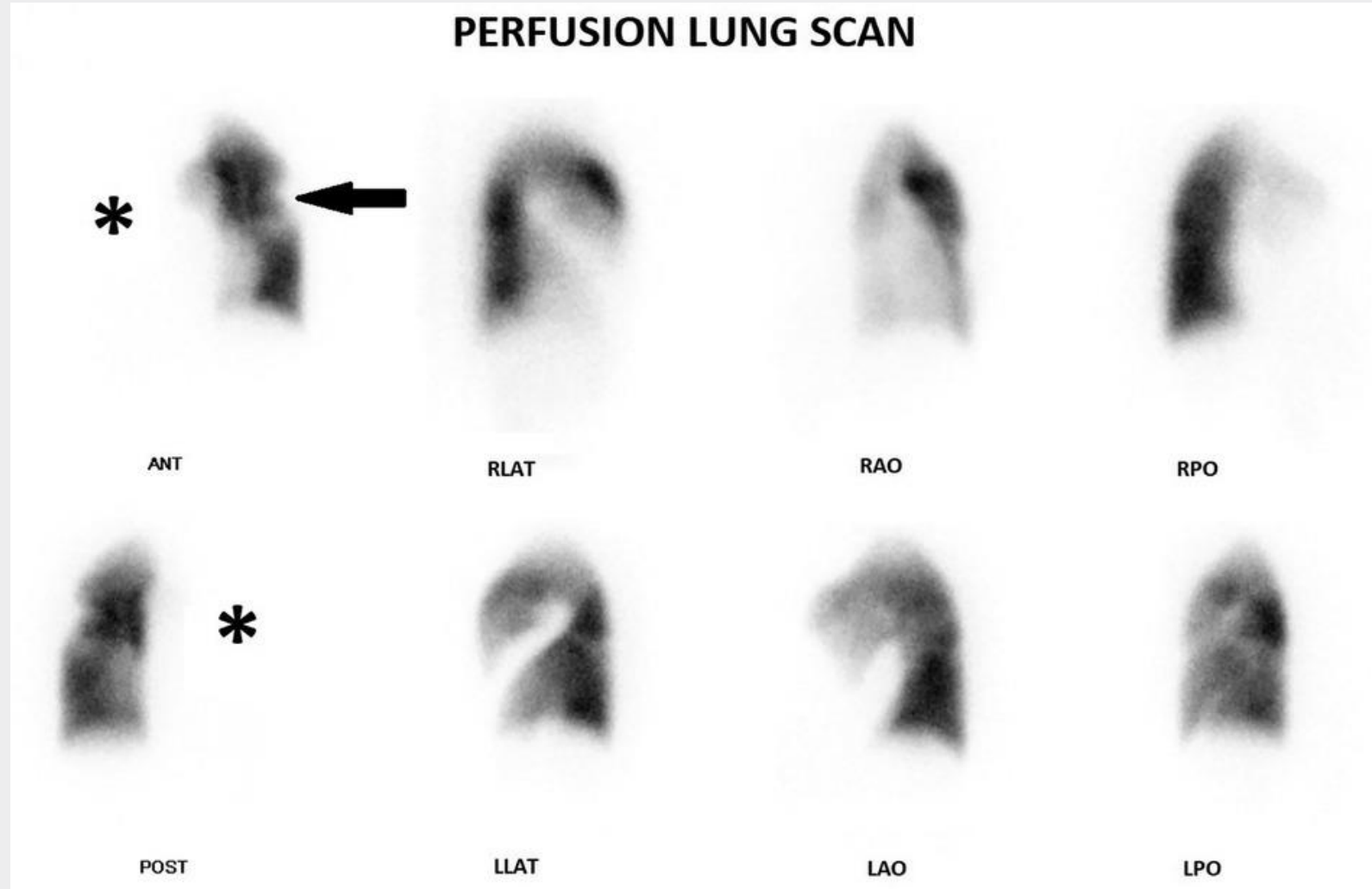


# Chest X-Ray



# Ventilation/Perfusion Scan

- Normal V/Q excludes CTEPH
- Matched perfusion defects seen in structural/chronic lung disease
- May need confirmation with pulmonary angiogram



# Other testing to consider

- CPET
- Arterial Blood Gas
- Nocturnal Oximetry (or polysomnogram in high-risk patients for OSA)
- HIV
- Urine Drug Screen
- Hepatitis Panel
- Connective Tissue Disease Panel
- Thyroid Function Testing
- Cardiac MRI

## Case Vignette Part V – Disease Phenotyping

The patient returns for follow-up after completion of the standard pulmonary hypertension work-up. Her results are below:

1. Pulmonary Function Testing (PFTs): Normal Spirometry/Lung Volumes
2. Moderately reduced DLCO at 38% predicted
3. Electrocardiogram (EKG): NSR, Right axis deviation
4. Laboratory Testing:
  - Normal CBC, CMP, and TSH
  - HIV negative
  - NT-proBNP: 485 pg/mL
  - ANA: Positive (1:320, speckled pattern)
  - Anti-RNA Polymerase III antibody: Positive
  - EGFR: 95

Upon further questioning, the patient reports occasional episodes of cold-induced finger discoloration, which she previously dismissed as poor circulation. Her hands are shown



# Group Discussion

In addition to pulmonary arterial hypertension, what is her diagnosis?

Scleroderma

What diagnostic markers are commonly associated with this diagnosis?

Anti-topoisomerase Ab (Anti-Scl 70), Anti-RNA Polymerase III, Anti-Centromere

| Connective Tissue Disease                     | Common Autoantibodies   | Notes  |
|---|---|--|
| <b>Systemic Sclerosis (SSc)</b>               | <ul style="list-style-type: none"> <li>- Anti-centromere (ACA)</li> <li>- Anti-topoisomerase I (Scl-70)</li> <li>- Anti-RNA Polymerase III</li> </ul> | Most common CTD-associated PAH<br>PAH more common in limited cutaneous form (ACA+)<br>Anti-RNA Pol III also associated with scleroderma renal crisis |
| <b>Systemic Lupus Erythematosus (SLE)</b>     | <ul style="list-style-type: none"> <li>- Anti-dsDNA</li> <li>- Anti-Sm</li> <li>- Anti-U1 RNP</li> </ul>  | PAH is less common but can be reversible with immunosuppression in some cases  |
| <b>Mixed Connective Tissue Disease (MCTD)</b> | <ul style="list-style-type: none"> <li>- Anti-U1 RNP</li> </ul>   | Often overlaps with SLE/SSc features<br>PAH may develop even in patients with mild systemic disease  |
| <b>Rheumatoid Arthritis (RA)</b>              | <ul style="list-style-type: none"> <li>- Rheumatoid factor (RF)</li> <li>- Anti-CCP</li> </ul>  | Rare, typically associated with advanced lung disease (group 3 overlap possible)   |
| <b>Sjogren's Syndrome</b>                     | <ul style="list-style-type: none"> <li>- Anti-Ro (SSA)</li> <li>- Anti-La (SSB)</li> </ul>  | Rare; may co-occur with SLE or MCTD  |
| <b>Dermatomyositis/Polymyositis</b>           | <ul style="list-style-type: none"> <li>- Anti-Jo-1</li> <li>- Anti-Mi-2</li> </ul>  | Rare, may be seen in overlap syndromes or with ILD   |

## Case Vignette Part VI – Risk Assessment and Therapy

You inform Sonya that you will refer her to rheumatology to partner in the treatment of her newly diagnosed scleroderma.

During the rest of the visit, you ascertain the following:

- Symptoms: occur with normal activities but not with ADLS
- 6MWD: 300m without desaturation
- Vitals: BP 105/91, HR 92, SpO2 95% on RA
- NT-ProBNP (from prior labs): 485

# Group Discussion

How would you determine this patient's risk for disease progression?

Risk calculation (REVEAL, 4-Strata, etc)

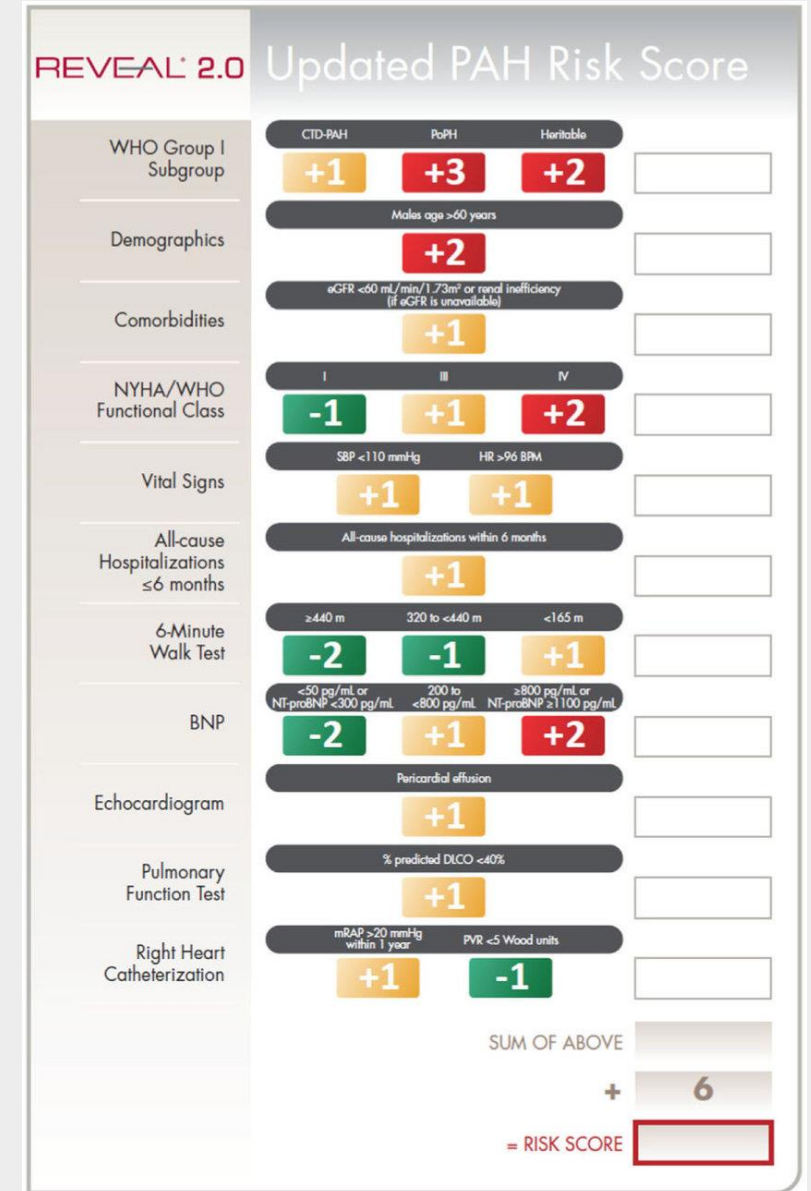
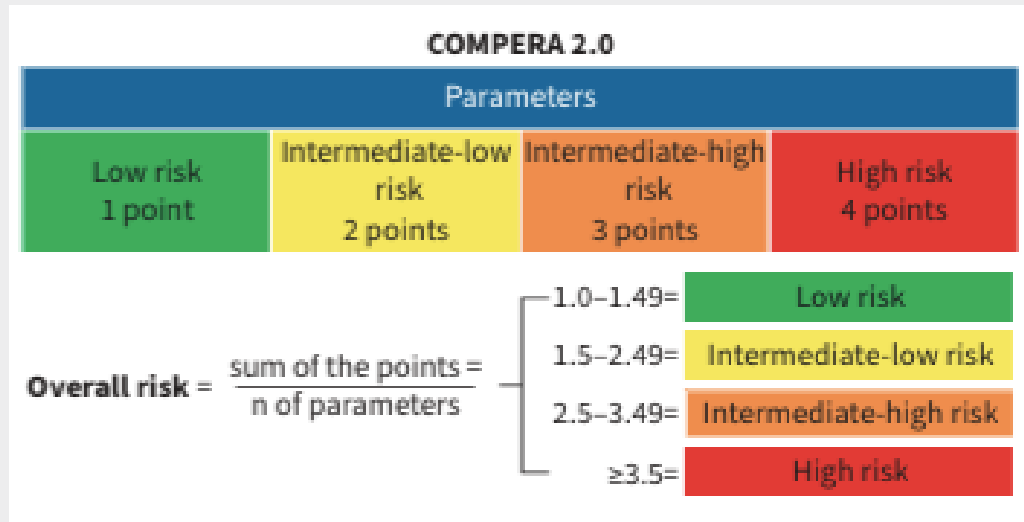
What should be our initial treatment strategy?

Dual oral combination therapy with PDE-5i/ERA

# Multimodal Risk Assessment

## Tools

1. REVEAL 2.0 Risk Tool
2. REVEAL-lite 2.0 Risk Tool
3. Compera 2.0 4-Strata Tool
4. REVEAL-Echo Risk Tool
5. French Registry Risk Tool



Source: Benza, R. et al (2019). Chest

COMPERA: Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension

# Our Patient

## REVEAL Lite 2 Risk Calculator

Print 

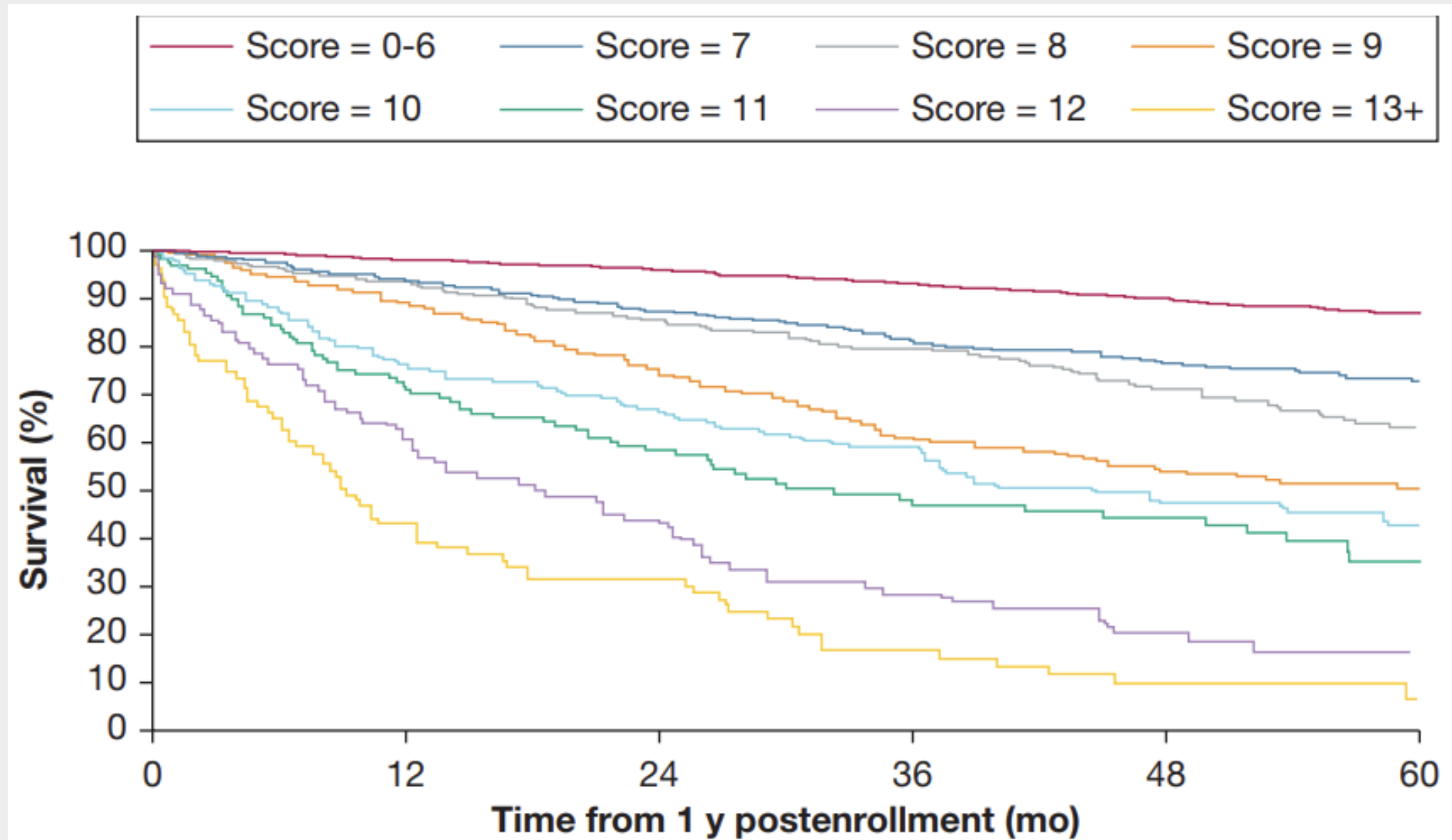
Reset

Select all variables that apply. A minimum of 3 variables are required to generate a score where at least 2 are of the most predictive variables - denoted \*\*.

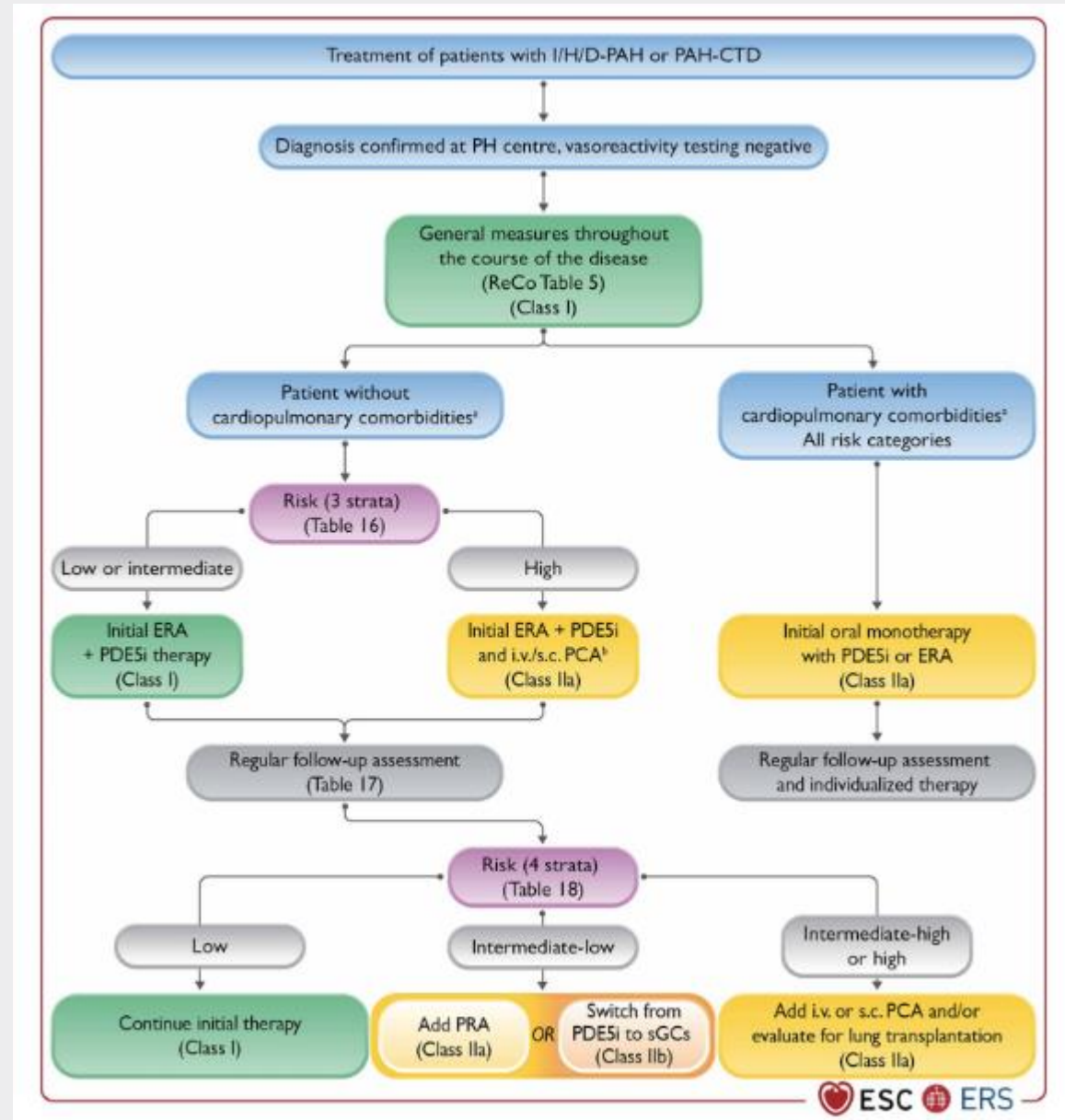
|   |            |                   |                  | Score     |                     |
|---|------------|-------------------|------------------|-----------|---------------------|
| BNP (pg/mL)**   | <50<br>-2  | 50 to <200<br>0   | 200 to <800<br>1 | ≥800<br>2 | --                  |
| — or —  |            |                   |                  |           |                     |
| NT-proBNP (pg/mL)**                                     | <300<br>-2 | 300 to <1100<br>0 | ≥1100<br>2       |           | 0                   |
| 6-Minute Walk Test (m)**                                | ≥440<br>-2 | 320 to 440<br>-1  | <320 to 165<br>0 | <165<br>1 | 0                   |
| NYHA/WHO Functional Class**                             | I<br>-1    | II<br>0           | III<br>1         | IV<br>2   | 0                   |
| Systolic BP (mm Hg)                                     |            | SBP≥110<br>0      | SBP<110<br>1     |           | 1                   |
| Heart Rate (BPM)  |            | HR≤96<br>0        | HR>96<br>1       |           | 0                   |
| eGFR<60mL/min/1.73m <sup>2</sup> or renal insufficiency |            | No<br>0           | Yes<br>1         |           | 0                   |
|   |            |                   |                  |           | +6                  |
|   |            |                   |                  |           | Risk score <b>7</b> |



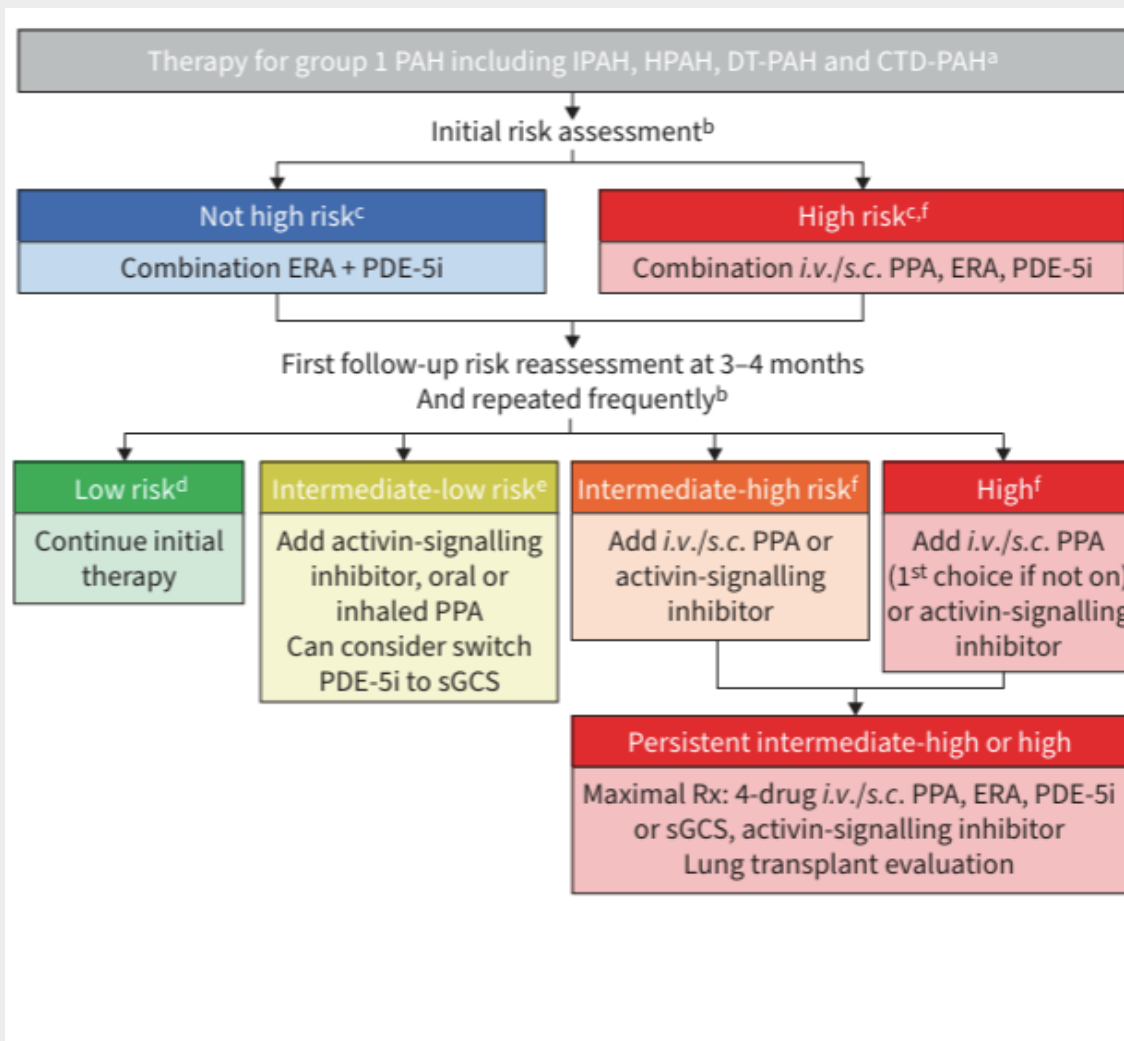
# Risk Drives Outcomes



# 2022 ERS Treatment Algorithm

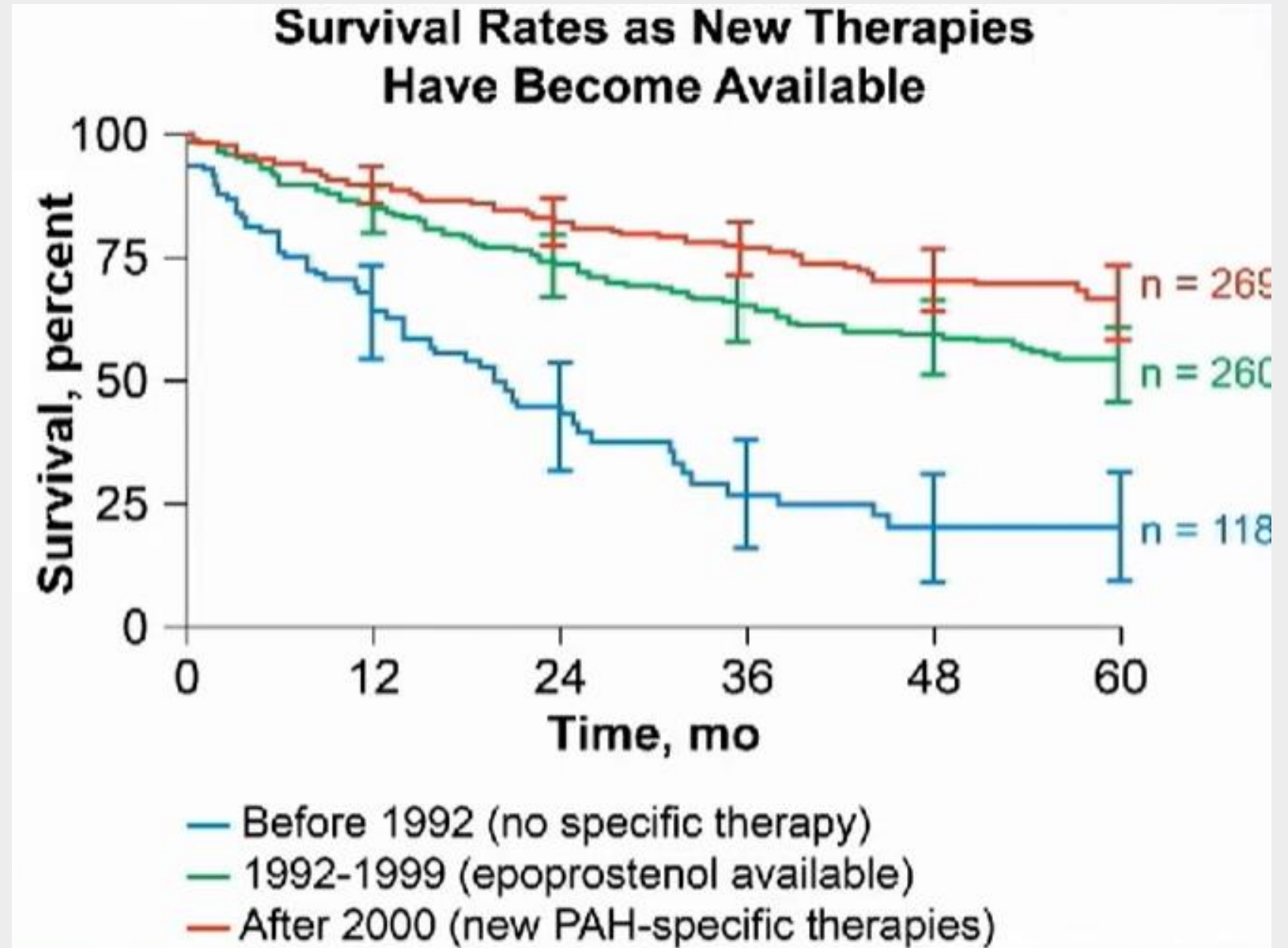


# 7<sup>th</sup> WSPH Treatment Algorithm



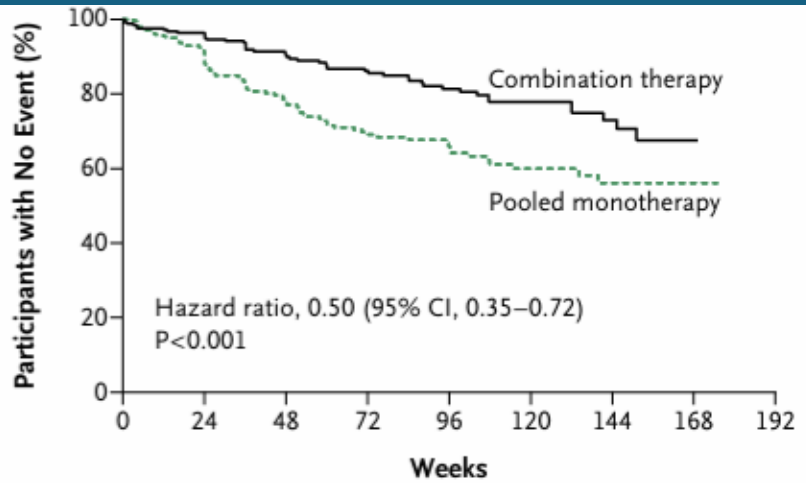
- Treatment algorithm key points
- The treatment algorithm is intended for patients with confirmed group 1 PAH (phenotypically clear-cut, including **mPAP ≥25 mmHg and PVR >3 Wood Units** and no significant response on acute vasoreactivity testing). See text for treatment in PAH with complex phenotypes.
  - Risk assessment** should be performed at baseline, within 3–4 months and periodically thereafter, and using FC, 6MWD and natriuretic peptides as a part of a validated risk calculator. Haemodynamics, RV imaging and other measures should be used to supplement risk assessment.
  - Initial triple therapy** with an *i.v./s.c.* PPA is recommended in high-risk patients and may be considered in non-high risk with severe haemodynamics and/or poor RV function.
  - Most **low-risk patients** at follow-up should continue initial therapy.
  - Clinical trials with oral and inhaled treprostinil included **only patients on monotherapy**, while studies of selexipag and sotarcept included patients on combination therapy.
  - Transplant referral** should be considered for select high-risk patients at diagnosis, and for intermediate-high and high-risk patients at first or subsequent follow-up.

# Therapy Works

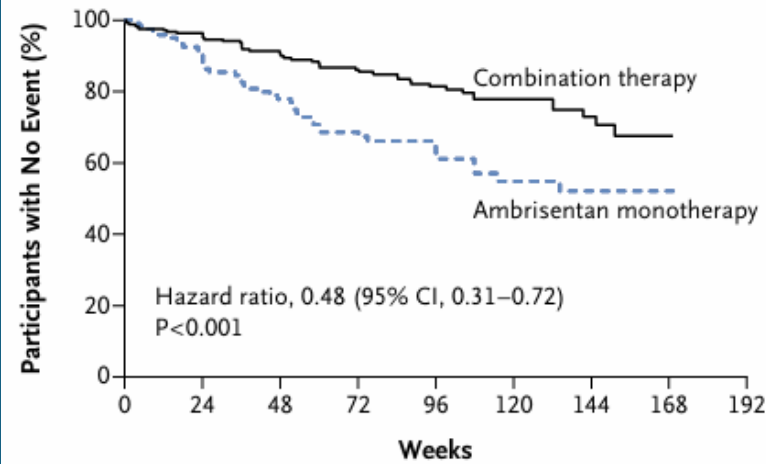


# Early Combination Therapy is Key

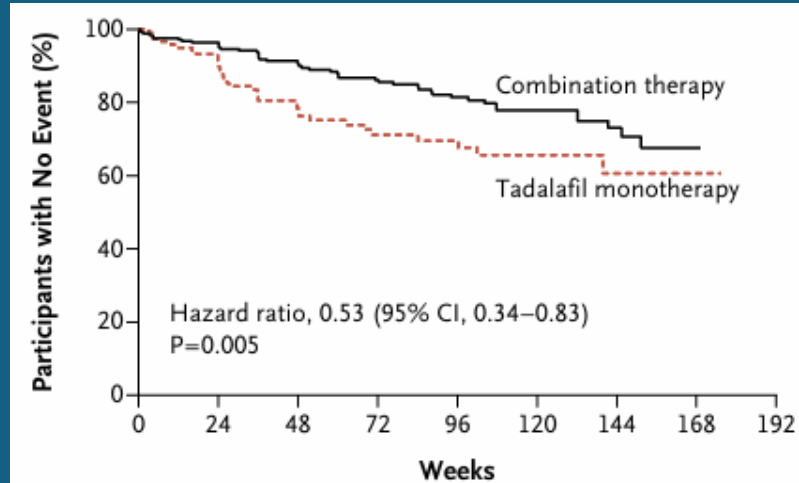
Combination Therapy vs. Pooled Monotherapy



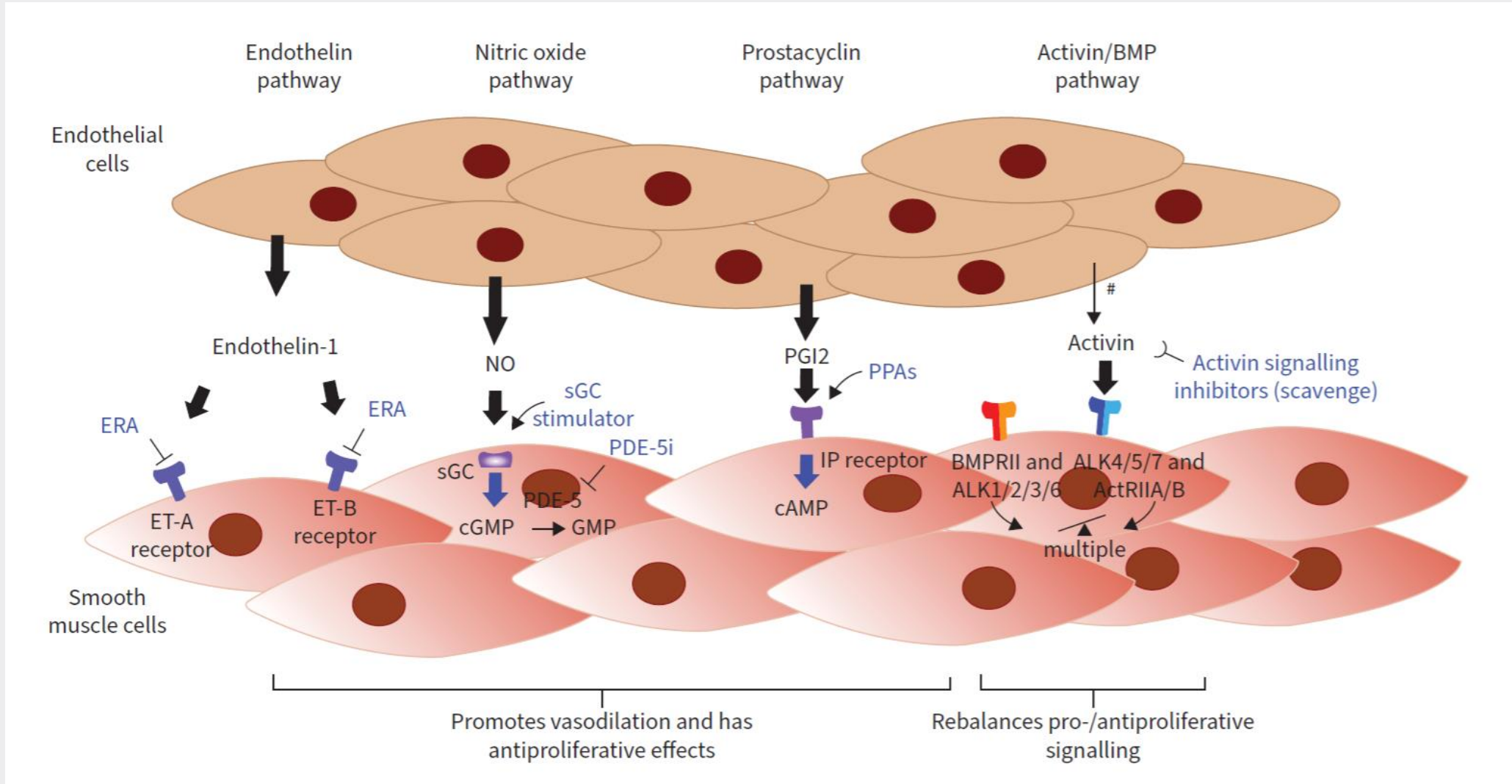
Combination Therapy vs. Ambrisentan Monotherapy



Combination Therapy vs. Tadalafil Monotherapy



# Therapeutic Targets



# Drugs and Common Adverse Affects

| Drug Class   | Common Medications   | Common Side Effects  |
|--|--|--|
| <b>Phosphodiesterase-5 Inhibitors (PDE-5i)</b>                         | - Sildenafil (Revatio)- Tadalafil (Adcirca)  | - Headache- Flushing- Nasal congestion- Dyspepsia- Visual disturbances- Hypotension          |
| <b>Endothelin Receptor Antagonists (ERA)</b>                           | - Ambrisentan (Letairis)- Bosentan (Tracleer)- Macitentan (Opsumit)  | - Hepatotoxicity (esp. bosentan)- Anemia- Peripheral edema- Nasal congestion- Headache       |
| <b>Prostacyclin Analogues / IP Receptor Agonists</b>                   | - Epoprostenol (Flolan, Veletri) (IV)- Treprostinil (Remodulin, Tyvaso, Orenitram) (SC, IV, inhaled, oral)- Iloprost (Ventavis) (inhaled)- Selexipag (Uptravi) (oral IP agonist) | - Jaw pain- Headache- Flushing- Diarrhea- Nausea- Site pain (SC)- Hypotension                |
| <b>Activin Signaling Inhibitors</b>                                    | - Sotatercept (Winrevair) (subq)   | - Headache- Increased hemoglobin- Thrombosis risk- Muscle pain- Injection site reaction      |
| <b>Calcium Channel Blockers</b> <i>(only in vasoreactive patients)</i> | - Amlodipine- Diltiazem- Nifedipine (PO)   | - Lower extremity edema- Bradycardia (diltiazem)- Hypotension- Constipation (esp. verapamil) |

# Calcium Channel Blockers

Appropriate Phenotypes:

1. Idiopathic
2. Heritable
3. Toxin Associated

**RECOMMENDATION TABLE 7** Recommendations for the treatment of vasoreactive patients with idiopathic, heritable, or drug-associated pulmonary arterial hypertension

| Recommendations  | Class <sup>a</sup> | Level <sup>b</sup> |
|--|--------------------|--------------------|
| High doses of CCBs are recommended in patients with IPAH, HPAH, or DPAH who are responders to acute vasoreactivity testing   | I                  | C                  |
| Close follow-up with complete reassessment after 3–4 months of therapy (including RHC) is recommended in patients with IPAH, HPAH, or DPAH treated with high doses of CCBs       | I                  | C                  |
| Continuing high doses of CCBs is recommended in patients with IPAH, HPAH, or DPAH in WHO-FC I or II with marked haemodynamic improvement (mPAP <30 mmHg and PVR <4 WU)           | I                  | C                  |
| Initiating PAH therapy is recommended in patients who remain in WHO-FC III or IV or those without marked haemodynamic improvement after high doses of CCBs                       | I                  | C                  |
| In patients with a positive vasoreactivity test but insufficient long-term response to CCBs who require additional PAH therapy, continuation of CCB therapy should be considered | IIa                | C                  |
| CCBs are not recommended in patients without a vasoreactivity study or non-responders, unless prescribed for other indications (e.g. Raynaud's phenomenon)                       | III                | C                  |

## Case Vignette Part VII – Follow-up Risk Assessment

The patient is initiated on dual oral therapy with PDE-5i and ERA therapy. You see her in clinic at a 3-month follow-up appointment. She mentions that she is still short of breath although less so (WHO-fc II). 4-Strata risk assessment calculates that she is still at intermediate risk

# Group Discussion

What should your next steps be?

Escalate therapy (Options are transition PDE-5i for GCS, Initiate PCA, or Initiate an activin signaling agent)

## Case Vignette Part VIII – Case conclusion

You initiate the patient on an oral PCA and titrate to the appropriate goal dose. The patient on 3-month follow-up feels much better. She is now asymptomatic with limitations consistent with WHO-fc I. Her 4-Strata risk is low.

# Q&A



# Thank you!

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