Bridging the Gap in Pulmonary Arterial Hypertension in Connective Tissue Disease: Promoting Consistent Screening and Management Regimens
Learning Objectives

• Characterize the symptoms and signs of CTD-PAH and the screening algorithms indicated for early identification and initiation of appropriate treatment

• Summarize current treatment recommendations for PAH

• Formulate treatment regimens that are individualized to patients with CTD-PAH

CTD = connective tissue disease; PAH = pulmonary arterial hypertension.
Defining PH and PAH

- PH refers to the presence of abnormally high pulmonary artery pressure (PAP)

**Hemodynamic definition of PH:** mPAP >20 mmHg

- PAH results from structural changes in small pulmonary arteries resulting in an increase in PAP and reduction in flow

**Hemodynamic definition of PAH:**
- mPAP >20 mmHg
- PAWP ≤15 mmHg
- PVR >3 Wood units

- Pulmonary vascular resistance increases and:
  - Restricts blood flow through the pulmonary arterial circulation
  - Ultimately leads to right heart failure

PH Is Categorized Into 5 Groups

**Group 1 – PAH**
1.1 Idiopathic PAH
1.2 Heritable PAH
   1.2.1 BMPR2
   1.2.2 ALK-1, ENG, Smad9, CAV1, KCNK3
   1.2.3 Unknown
1.3 Drug- and Toxin-Induced
1.4 Associated With:
   1.4.1 CTD
   1.4.2 HIV Infection
   1.4.3 Portal Hypertension
   1.4.4 Congenital Heart Disease
   1.4.5 Schistosomiasis
1’ Pulmonary Veno-occlusive Disease (PVOD) and/or Pulmonary Capillary Hemangiomatosis
1” Persistent Pulmonary Hypertension of the Newborn (PPHN)

**Group 2 – PH Due to Left Heart Disease**
2.1 Left Ventricular Systolic Dysfunction
2.2 Left Ventricular Diastolic Dysfunction
2.3 Valvular Disease
2.4 Congenital/Acquired Left Heart Inflow/Outflow Tract Obstruction and Congenital Cardiomyopathies

**Group 3 – PH Due to Lung Disease and/or Hypoxia**
3.1 COPD
3.2 ILD
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

**Group 4 – Chronic Thromboembolic Pulmonary Hypertension (CTEPH)**

**Group 5 – PH With Unclear Multifactorial Mechanisms**
5.1 Hematologic Disorders: Chronic Hemolytic Anemia, Myeloproliferative Disorders, Splenectomy
5.2 Systemic Disorders: Sarcoidosis, Pulmonary Histiocytosis, Lymphangioleiomyomatosis
5.3 Metabolic Disorders: Glycogen Storage Disease, Gaucher Disease, Thyroid Disorders
5.4 Others: Tumoral Obstruction, Fibrosing Mediastinitis, Chronic Renal Failure, Segmental PH

BMPR2 = bone morphogenetic protein receptor type 2; CAV1 = caveolin 1; ENG = endoglin; KCNK3 = gene encoding K$^{+}$ channel; ILD = interstitial lung disease.
Patients With CTD Can Also Have Group 2, 3, 4 PH

- Group 1: PAH, PVOD
- Group 2: Pulmonary Hypertension Due To Left Heart Disease
  - Elevated Right Atrial Pressure
  - Hypoxia
  - Lung Scarring
- Group 3: ILD
  - Abnormal V/Q
- Group 4: CTEPH

WHO Functional Classification (WHO-FC)

**FC I**
- No limitation of usual physical activity
- Ordinary activity does not cause increased symptoms

**FC II**
- Mild limitation of usual physical activity
- No discomfort at rest but ordinary activity increases symptoms

**FC III**
- Marked limitation of usual physical activity
- No discomfort at rest but less than ordinary activity increases symptoms

**FC IV**
- Unable to perform physical activity without symptoms
- Symptoms may be present at rest
- May have signs of right heart failure

*Patients with CTD are often diagnosed only after disease has progressed significantly*

REVEAL Registry: Nearly 25% of PAH Is CTD-Related

Overall

- Heritable (2.7%)
- Pulmonary Veno-occlusive (0.4%)

Associated (50.7%)

- Idiopathic (46.2%)
- Associated (50.7%)
- Connective tissue/collagen vascular (49.9%)
- Congenital heart disease (19.5%)
- Portopulmonary Hypertension (10.6%)
- Drugs/Toxins (10.5%)
- Other (5.5%)

Associated (50.7%)

Types of CTD-related PAH: SSc = 64.5%, SLE = 22.4%, rheumatoid arthritis = 8.9%

SLE = systemic lupus erythematosus; SSc = systemic sclerosis.
Based on Venice Clinical Classification 2003; 2967 patients. Adapted from Badesch. Chest. 2010;137:376.
Patients With PAH and SSc Have Worse Survival Than Those With PAH and SLE

- Registry study of N = 429 patients with CTD-PAH (73% with SSc-PAH)

Survival of Patients With Isolated SSc-PAH vs SLE-PAH

<table>
<thead>
<tr>
<th>Years From Diagnosis</th>
<th>Patients at risk</th>
<th>Cumulative Survival</th>
<th>SSc-PAH</th>
<th>SLE-PAH</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>259</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.0</td>
<td>21</td>
<td>0.82</td>
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</tr>
<tr>
<td>2.0</td>
<td>179</td>
<td>0.65</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>3.0</td>
<td>94</td>
<td>0.45</td>
<td></td>
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<td></td>
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<td>4.0</td>
<td>53</td>
<td>0.36</td>
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<td>5.0</td>
<td>27</td>
<td>0.25</td>
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<tr>
<td>6.0</td>
<td>6</td>
<td>0.15</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3-Year Survival Rate, %

<table>
<thead>
<tr>
<th></th>
<th>SSc-PAH</th>
<th>SLE-PAH</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-Year Survival</td>
<td>47</td>
<td>74</td>
<td>.01</td>
</tr>
</tbody>
</table>

Case Study: Susan

- 56-year-old postmenopausal woman
- Systemic sclerosis diagnosed 6 years ago (at age 50 years)
  - Severe Raynaud’s phenomenon
  - Severe digital ischemia
  - Cutaneous telangiectasias
    - Limited cutaneous disease
  - Positive anticentromere antibody
- Followed routinely in rheumatology clinic
- Echocardiogram shows enlarged right ventricle (RV) and poor RV contractility
- Pulmonary function test (PFT) results:
  - FVC = 85%
  - FEV₁/FVC = 85%
  - DLco = 50%
  - FVC/DLco = 1.7

DLco = diffusing capacity for carbon monoxide; FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity.
Clinical Risk Factors for PAH in SSc

<table>
<thead>
<tr>
<th>SSc-Related</th>
<th>Pulmonary</th>
<th>Autoantibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Long-standing disease</td>
<td>• Isolated low DLco &lt;50%</td>
<td>• Absence of anti–Scl-70 antibodies</td>
</tr>
<tr>
<td>• Older age at SSc onset</td>
<td>• Decrease in DLco/alveolar volume &lt;70%</td>
<td>• Anti-centromere antibodies</td>
</tr>
<tr>
<td>• Postmenopausal time period</td>
<td>• FVC/DLco &gt;1.6</td>
<td>• Anti-U1-ribonucleoprotein antibodies</td>
</tr>
<tr>
<td>• Severe Raynaud’s phenomenon</td>
<td>• Increasing RVSP &gt;2 mm Hg/year</td>
<td>• Nucleolar pattern of antinuclear antibodies</td>
</tr>
<tr>
<td>• Severe digital ischemia</td>
<td></td>
<td>– Anti-Th/To antibodies</td>
</tr>
<tr>
<td>• Cutaneous telangiectasias</td>
<td></td>
<td>– Anti-U3-ribonucleoprotein antibodies</td>
</tr>
</tbody>
</table>

*RVSP = right ventricular systolic pressure; Scl = scleroderma; Th= tyrosine hydroxylase.*

# Building a Clinical Suspicion of PAH

## General Symptoms (Nonspecific)
- Exertional dyspnea
- Weakness
- Chest pain
- Light-headedness/syncope
- Cough (less frequent)
- Fatigue

## Physical Findings
- Augmented second heart sound (P2 component)
- RV lift
- Jugular venous distension
- Hepatojugular reflux
- Ascites
- Hepatomegaly and/or splenomegaly
- Edema
- Tricuspid regurgitant or pulmonary regurgitant murmurs
- S3 gallop

## More Progressive Disease
- Progressive right-sided heart failure (edema, ascites, abdominal distension)
- Hemoptysis
- Ortner’s syndrome/hoarseness (unilateral vocal cord paralysis)
- Arrhythmias
- Syncope/light-headedness
Signs Indicative of Symptomatic PH/PAH on Echocardiogram

- Increased sPAP or TRV
- RA and RV hypertrophy/dilatation
- Flattening of intraventricular septum (IVS)
- Small LV dimension
- Dilated pulmonary artery
- Issues with RVSP pressure estimate
  - High frequency of false negatives in mild disease
  - High frequency of false positives in ILD

LA = left atrium; LV = left ventricle; RA = right atrium; sPAP = systolic pulmonary artery pressure; TRV = tricuspid regurgitant jet velocity.
ESC/ERS Screening Guidelines

- Positive screen on echocardiography (referral for RHC recommended)
  - TRV >3.4 m/sec
  or
  - TRV between 2.9 and 3.4 m/sec and symptoms (dyspnea, syncope or peripheral edema)
  or
  - TRV ≤2.8 and symptoms and additional echo variables, RV or RA enlargement (large RA area)
- Requires that echocardiogram report includes TRV, not just RVSP

ERS = European Respiratory Society; ESC = European Society of Cardiology; RHC = right heart catheterization.
ASIG Screening Protocol for PH/PAH

**Component A:**
- NT-proBNP ≥210 pg/mL

**Component B:**
- DLco <70% predicted with FVC/DLco ≥1.8

**Positive**
- Component A and/or Component B positive
  - RHC Referral

**Negative**
- Component A and Component B negative
  - Repeat screen in 6-12 months

**Other investigations as indicated**
- eg, echocardiogram, HRCT, 6MWT

**ASIG** = Australian Scleroderma Interest Group; 6MWT = 6-minute walk test; HRCT = high-resolution computed tomography; NT-proBNP = N-terminal pro-B type natriuretic peptide. Hao. Arthritis Res Ther. 2015;17:7.
In patients with DLco <60% predicted and diagnosis of SSc of >3 years from date of first non-Raynaud’s symptoms

**Step 1:** Non-echocardiographic variables
- FVC %/DLco % predicted
- Current/past telangiectasias
- Anti-centromere antibody
- NT-proBNP
- Urate
- ECG right axis deviation

**Total risk points >300?**

Urate and ECG may not be routine in rheumatology office

**Step 2:** Total risk points from Step 1 + Echocardiographic variables
- Right atrium area
- TRV

High Risk

Requires the echocardiogram report to include RA area and TRV

High Risk

RHC Referral

Predictive Accuracy of 3 Screening Models for PAH in SSc

<table>
<thead>
<tr>
<th></th>
<th>DETECT</th>
<th>ESC/ERS</th>
<th>ASIG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>100</td>
<td>96.3</td>
<td>100</td>
</tr>
<tr>
<td>Specificity</td>
<td>35.3</td>
<td>32.3</td>
<td>54.5</td>
</tr>
<tr>
<td>Positive Predictive Value</td>
<td>55.1</td>
<td>55.3</td>
<td>60</td>
</tr>
<tr>
<td>Negative Predictive Value</td>
<td>100</td>
<td>90.9</td>
<td>100</td>
</tr>
</tbody>
</table>

Cross-sectional and longitudinal study of consecutive patients diagnosed with SSc-PAH after having been identified by **routine practice (symptoms)** (n = 16) vs by **systematic screening program with echocardiography** (n = 16)

Compared with patients identified in routine practice, those identified by systematic screening program:

- More likely to have NYHA **FC I/II**
  - 50% vs 12.5%, *P* = .036

**Screening Permits Earlier Detection of PAH in SSc**

- Had **better survival**
  - HR = 4.15 (95% CI: 1.47 to 11.71)
  - *P* = .0037

**Functional Class Survival**

<table>
<thead>
<tr>
<th>Years of Follow-up</th>
<th>Routine Practice</th>
<th>Systematic Screening Program</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>3</td>
<td>75%</td>
<td>81%</td>
</tr>
<tr>
<td>5</td>
<td>31%</td>
<td>73%</td>
</tr>
<tr>
<td>8</td>
<td>17%</td>
<td>64%</td>
</tr>
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</table>

**Patients (%)**

<table>
<thead>
<tr>
<th>FC I</th>
<th>FC II</th>
<th>FC III</th>
<th>FC IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>12.5</td>
<td>69</td>
<td>18.5</td>
</tr>
</tbody>
</table>

**Patients (%)**

<table>
<thead>
<tr>
<th>FC I</th>
<th>FC II</th>
<th>FC III</th>
<th>FC IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>44</td>
<td>50</td>
<td>0</td>
</tr>
</tbody>
</table>

Screening for PAH in Patients With SSc

Recommendations from the 6th World Symposium on Pulmonary Hypertension Proceedings (2018):

**Annual screening** for PAH in patients with SSc and SSc spectrum of diseases (with uncorrected DLco <80% of predicted) should be considered. Appropriate screening tools include DETECT, the 2015 ESC/ERS recommendations for TTE or FVC/DLco ratio >1.6 (assuming none-to-mild ILD) and >2-fold upper limit of normal of NT-proBNP.

**ESC/ERS Guidelines (2015):**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Level&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting echo is recommended as a screening test in asymptomatic patients with SSc, followed by annual screening with echo, DLco and biomarkers</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Initial screening using the stepwise DETECT algorithm may be considered in patients with &gt;3 years disease duration and a DLco &lt;60% predicted*</td>
<td>IIb</td>
<td>B</td>
</tr>
</tbody>
</table>

<sup>a</sup>Class of recommendation; <sup>b</sup>Level of evidence. *The DETECT algorithm is not yet validated in patients with DLco >60%.

TTE = transthoracic echocardiogram.

Case Study (cont’d): Susan

- 56-year-old woman, postmenopausal
- Systemic sclerosis diagnosed 6 years ago (at age 50 years)
  - Severe Raynaud’s phenomenon
  - Severe digital ischemia
  - Cutaneous telangiectasias
    - Limited cutaneous disease
  - Positive anticentromere antibody
- Followed routinely in rheumatology clinic

“My energy level is down, and I’ve noticed I’m short of breath on stairs.”
Causes of Poor Exercise Tolerance in SSc

- Lung disease (ILD, PAH, respiratory muscle or chest wall disease)
- Left heart disease
- Anemia
- Musculoskeletal problems (arthritis, tendon rubs, myopathy)
- Deconditioning

Causes of Poor Exercise Tolerance in SSc

• Lung disease (ILD, PAH, respiratory muscle or chest wall disease)
• Left heart disease
• Anemia
• Musculoskeletal problems (arthritis, tendon rubs, myopathy)
• Deconditioning

“What’s the most physical activity that you do and what symptom limits your capabilities?”

How has this changed in the past 6-12 months?”

Case Study (cont’d): Susan’s Test Results

- Screening echocardiography and PFTs show high probability for PH:
  - FEV₁/FVC = normal
  - TLC = normal
  - DLco = 50% (low)
  - FVC/DLco = 1.7

- Referred for evaluation with RHC:
  - mPAP = 36 mmHg
  - PCWP = 5 mmHg
  - Mean RAP = 10 mmHg
  - Cardiac index = 2.3 L/min/m²
  - PVR = 6.8 Wood units

PCWP = pulmonary capillary wedge pressure; RAP = right arterial pressure.
Workup of PAH After Echo and RHC

• Ventilation perfusion scan (VQ scan) to rule out CTEPH

• PFTs and arterial blood gases (if not already done) to evaluate for lung diseases

• High-resolution CT

• Cardiopulmonary exercise testing (CPET)
  – 6MWT

• Overnight oximetry

• Blood tests and immunology, including HIV

• PVOD can be mistaken for PAH
  – Look for disproportionate hypoxemia, typical changes on chest CT

Case Study (cont’d): Susan Is Diagnosed With PAH

- Screening echocardiography and PFTs show high probability for PH:
  - \( FEV_1/FVC = \) normal
  - TLC = normal
  - DLco = 50% (low)
- 6MWD: 250 meters
- NT-proBNP: 420ng/L

- Referred for evaluation with RHC:
  - mPAP = 36 mmHg
  - PCWP = 5 mmHg
  - Mean RAP = 10 mmHg
  - Cardiac index = 2.3 L/min/m\(^2\)
  - PVR = 6.8 Wood units
- No ILD
- Diagnosis: PAH associated with scleroderma
- Functional Class III
A Multiparameter Tool Is Required To Assess Patient Risk

Risk Assessment

Biochemical Markers
- NT-proBNP
- WHO FC
- Progression of Symptoms
- Signs of Right Heart Failure

Clinical Assessment
- Syncope

Exercise Tests
- CPET
- 6MWD

Hemodynamic Evaluations
- RA area
- Pericardial Effusion
- Mixed Venous Saturation
- CI
- RAP

Echocardiographic Evaluations

CI = cardiac index.
## Determinants of Prognosis

<table>
<thead>
<tr>
<th>Determinants of Prognosis</th>
<th>Low (&lt;5%)</th>
<th>Intermediate Risk (5%-10%)</th>
<th>High Risk (&gt;10%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Signs of Right Heart Failure</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Progression of Symptoms</td>
<td>No</td>
<td>Slow</td>
<td>Rapid</td>
</tr>
<tr>
<td>Syncope</td>
<td>No</td>
<td>Occasional syncope</td>
<td>Repeated syncope</td>
</tr>
<tr>
<td>WHO Functional Class</td>
<td>I, II</td>
<td>III</td>
<td>IV</td>
</tr>
<tr>
<td>6MWD</td>
<td>&gt;440 m</td>
<td>165-440 m</td>
<td>&lt;165 m</td>
</tr>
<tr>
<td>Cardiopulmonary Exercise Testing</td>
<td>Peak VO$_2$ &gt;15 mL/min/kg (&gt;65% predicted) VE/VCO$_2$ slope &lt;36</td>
<td>Peak VO$_2$ 11-15 mL/min/kg (35%-65% predicted) VE/VCO$_2$ slope 36.0-44.9</td>
<td>Peak VO$_2$ &lt;11 mL/min/kg (&lt;35% predicted) VE/VCO$_2$ slope ≥45</td>
</tr>
<tr>
<td>NT-proBNP Plasma Levels</td>
<td>BNP &lt;50 ng/L NT-pro BNP &lt;300 ng/L</td>
<td>BNP 50-300 ng/L</td>
<td>BNP &gt;300 ng/L NT-proBNP &gt;1400 ng/L</td>
</tr>
<tr>
<td>Imaging (ECHO or CMR)</td>
<td>RA area &lt;18 cm$^2$ No pericardial effusion</td>
<td>RA area 18-26 cm$^2$ No/minimal pericardial effusion</td>
<td>RA area &gt;26 cm$^2$ Pericardial effusion</td>
</tr>
<tr>
<td>Hemodynamics</td>
<td>RAP &lt;8 mm Hg Cl ≥2.5L/min/m$^2$ SvO$_2$ &gt;65%</td>
<td>RAP 8-14 mmHg Cl 2.0-2.4 L/min/m$^2$ SvO$_2$ 60%-65%</td>
<td>RAP &gt;14 mm Hg Cl &lt;2.0 L/min/m$^2$ SvO$_2$ &lt;60%</td>
</tr>
</tbody>
</table>

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ERS/ESC Guidelines: Goal Is Improvement, Not Just Preservation of Risk Status

Don’t settle for just halting disease progression!
Summary of 3 European Registries Assessing PAH Risk Scores

<table>
<thead>
<tr>
<th></th>
<th>Swedish PAH Registry</th>
<th>COMPERA</th>
<th>French Pulmonary Hypertension Network</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required variables, n</td>
<td>8</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Patients at baseline, n</td>
<td>530</td>
<td>1588</td>
<td>1017</td>
</tr>
<tr>
<td>Patients at follow-up, n</td>
<td>383</td>
<td>1094</td>
<td>1017</td>
</tr>
<tr>
<td>Associated PAH included</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Definition of low risk</td>
<td>&lt;1.5 average score</td>
<td>&lt;2 average grade</td>
<td>3-4 out of 4 low-risk criteria</td>
</tr>
<tr>
<td>1-year mortality by risk group (low/intermediate/high), %</td>
<td>1.0/7.0/26.0</td>
<td>2.8/9.9/21.2</td>
<td>1.0/NA/13.0-30.0</td>
</tr>
</tbody>
</table>

**REVEAL 2.0 and REVEAL Lite 2 Assessing PAH Risk Scores**

### REVEAL 2.0

**Updated PAH Risk Score**

<table>
<thead>
<tr>
<th>WHO Group I Subgroup</th>
<th>Demographics</th>
<th>Comorbidities</th>
<th>NYHA/WHO Functional Class</th>
<th>Vital Signs</th>
<th>All-cause Hospitalizations ≤6 mo</th>
<th>6MWT</th>
<th>BNP (pg/mL)**</th>
<th>NT-proBNP (pg/mL)**</th>
<th>6MWT (m)**</th>
<th>NYHA/WHO Functional Class**</th>
<th>SBP (mm Hg)</th>
<th>Heart Rate (BPM)</th>
<th>eGFR&lt;60 mL/min or renal insufficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Median age &gt;60 y</td>
<td>eGFR&lt;60 mL/min/1.73 m² or renal insufficiency</td>
<td>II-IV</td>
<td>SBP&lt;110 mmHg, HR&gt;96 BPM</td>
<td>≤440 m, 220 to 440 m, &lt;165</td>
<td>&lt;50 pg/mL or NT-proBNP &lt;300 pg/mL</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>≥2</td>
<td>≥2</td>
<td>≥2</td>
<td>≥2</td>
<td>+1</td>
<td>+1</td>
<td>+1</td>
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<td>+1</td>
<td>+1</td>
<td>+1</td>
<td>+1</td>
<td>+1</td>
</tr>
</tbody>
</table>

**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.**

**Score**

- BNP (pg/mL)**
  - <50: -2
  - 50 to <100: 0
  - 100 to <200: 0
  - 200 to <400: 1
  - ≥400: 2
- NT-proBNP (pg/mL)**
  - <300: -2
  - 300 to <1100: 0
  - 1100 to <2000: 0
  - ≥2000: 2
- 6MWT (m)**
  - >440: -2
  - 320 to 440: -1
  - <320: -1
- NYHA/WHO Functional Class**
  - I: 0
  - II: 0
  - III: 1
  - IV: 1
- SBP (mm Hg)
  - SBP<110: 0
  - SBP≥110: 1
- Heart Rate (BPM)
  - HR<95: 0
  - HR≥95: 1
- eGFR<60 mL/min or renal insufficiency
  - No: 0
  - Yes: 1

**Sum of Above + Risk Score**

- Low: 0-6
- Intermediate: 7-8
- High: ≥9

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56-year-old woman with systemic sclerosis

Under care of rheumatology, screening echocardiography and PFTs show high probability for PH:
- FEV₁/FVC = normal
- TLC = normal
- DLco = 55% (low)

Referred for evaluation with RHC:
- mPAP = 36 mmHg
- PCWP = 5 mmHg
- Mean RAP = 10 mmHg
- Cardiac index = 2.3 L/min/m²
- PVR = 6.8 Wood units

No ILD

Diagnosis: PAH associated with scleroderma

Risk assessment: Intermediate risk
Revised PAH Treatment Algorithm: World Symposium on Pulmonary Hypertension 2018

- Treatment-naive Patient
  - Vasoreactive
    - CCB Therapy
  - Potential Role for Initial Monotherapy
    - Low or Intermediate Risk
      - Initial Oral Combination
        - After 3-6 Months of Treatment
          - Low Risk
            - Structured Follow-Up
          - Intermediate to High Risk
            - Consider Referral for Lung Transplantation
          - High Risk (WHO FC)
            - Initial Combination Including IV PCA
              - Intermediate to High Risk
                - Add-on Therapy (double/triple)
      - Non-Vasoreactive
        - Maximal Medical Therapy and Listing for Lung Transplantation
    - Non-Vasoreactive
      - Low or Intermediate Risk
        - Initial Oral Combination
          - After 3-6 Months of Treatment
            - Low Risk
              - Structured Follow-Up
            - Intermediate to High Risk
              - Add-on Therapy (double/triple)
      - High Risk (WHO FC)
        - Initial Combination Including IV PCA
          - Intermediate to High Risk
            - Add-on Therapy (double/triple)
    - Initial Combination Including IV PCA
      - Intermediate to High Risk
        - Add-on Therapy (double/triple)
      - After 3-6 Months of Treatment
        - Intermediate to High Risk
  - Patient Already on Treatment
    - General Measures
      - Supportive Therapy
      - Consider Referral for Lung Transplantation
Targets for Current Therapies in PAH

**Endothelin Pathway**

Endothelium → Pro-endothelin-1 → Endothelin-1

**Nitric Oxide Pathway**

L-arginine → Nitric oxide

**Prostacyclin Pathway**

Arachidonic acid → Prostacyclin

Agents:
- **Enoximone (ERA)**
- **sGCstimulator**
- **PDE5i**
- **IP receptor agonist**
- **Prostacyclin derivative**

**Endothelin receptor A**
**Endothelin receptor B**

cAMP = cyclic adenosine monophosphate; GMP = guanosine monophosphate; GTP = guanosine-5'-triphosphate; sGC, soluble guanylate cyclase.

Initial Management of PAH in the Current Era

- Most patients in the **low and intermediate risk** categories should be started on **dual therapy** with an ERA + either a PDE5 inhibitor or sGC stimulator.

  - **Low Risk**
    - Monotherapy or combination therapy*

  - **Intermediate Risk**
    - Combination therapy including ERA + PDE5 inhibitor/sGC stimulator, oral prostacyclin receptor agonist

  - **High Risk**
    - Combination therapy including IV prostacyclins

*Monotherapy has a role in certain situations, not necessarily defined only by low risk status.
# Drug Treatment of PAH

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Route of Administration</th>
<th>Additional Class Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERAs</td>
<td>Ambrisentan</td>
<td>Oral</td>
<td>Contraindicated in pregnancy</td>
</tr>
<tr>
<td></td>
<td>Bosentan</td>
<td>Oral</td>
<td>Hepatotoxicity, peripheral edema, decreases in hemoglobin, drug-drug interactions</td>
</tr>
<tr>
<td></td>
<td>Macitentan</td>
<td>Oral</td>
<td></td>
</tr>
<tr>
<td>PDE5 inhibitors</td>
<td>Sildenafil</td>
<td>Oral, IV injection</td>
<td>Hearing or vision changes, hypotension, contraindicated to use with organic nitrates</td>
</tr>
<tr>
<td></td>
<td>Tadalafil</td>
<td>Oral</td>
<td></td>
</tr>
<tr>
<td>Soluble cGMP stimulators</td>
<td>Riociguat</td>
<td>Oral</td>
<td>Contraindicated in pregnancy, Avoid with PDE-5 inhibitors; bleeding risk</td>
</tr>
<tr>
<td>Prostacyclin derivatives</td>
<td>Epoprostenol</td>
<td>IV infusion</td>
<td>Avoid abrupt interruptions, Pulmonary edema, hypotension, bleeding, infection risk with chronic indwelling catheters, drug-drug interactions</td>
</tr>
<tr>
<td></td>
<td>Iloprost</td>
<td>Inhaled</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Treprostinil</td>
<td>Oral, inhaled, SC/IV infusion</td>
<td></td>
</tr>
<tr>
<td>Prostacyclin receptor agonists</td>
<td>Selexipag</td>
<td>Oral, IV infusion</td>
<td>Drug-drug interactions</td>
</tr>
</tbody>
</table>

Ambrisentan PI. Bosentan PI. Epoprostenol PI. Iloprost PI. Macitentan PI; Riociguat PI. Selexipag PI. Sildenafil PI. Tadalafil PI. Treprostinil PI.
## Most Common Adverse Events

<table>
<thead>
<tr>
<th>ERAs</th>
<th>PDE5 Inhibitors</th>
<th>Prostanoids</th>
<th>Soluble Guanylate Cyclase Stimulators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid retention</td>
<td>Headache</td>
<td>Headache</td>
<td>Headache</td>
</tr>
<tr>
<td>Anemia</td>
<td>Nasal congestion</td>
<td>Jaw pain</td>
<td>Syncope</td>
</tr>
<tr>
<td>Abnormal LFTs (bosentan)</td>
<td>GERD</td>
<td>Bone pain</td>
<td>Dyspepsia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(especially if IV)</td>
<td></td>
</tr>
<tr>
<td>Embryo-fetal toxicity (REMS required)</td>
<td>Flushing</td>
<td>Flushing/rash</td>
<td>Peripheral edema</td>
</tr>
<tr>
<td>Hypotension</td>
<td></td>
<td>Line infections(IV)</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Hearing or vision changes</td>
<td></td>
<td>Cough (inhaled form)</td>
<td>Embryo-fetal toxicity (REMS required)</td>
</tr>
</tbody>
</table>

Case Study (cont’d): Susan Begins an ERA and PDE5 Inhibitor

- 56-year-old woman with systemic sclerosis
- Screening echocardiography and PFTs show high probability for PH
- Diagnosis after RHC: PAH associated with scleroderma
- Risk assessment: Intermediate risk

**Treatment:**
Dual oral combination therapy with ERA and PDE5 inhibitor
Other Considerations in CTD-PAH

- Be more aggressive with treatment due to poorer prognosis
- Benefit from referral to pulmonary rehabilitation
- Make sure vaccinations are up to date
- Diuretics frequently needed to maintain volume status
- Manage comorbidities
  - GERD, ILD, diastolic dysfunction, Raynaud’s phenomenon, digital ulcers, sleep disordered breathing
- Oxygen therapy for O\textsubscript{2} sats less than 90% (finger oximetry may not be accurate)
- Lung transplantation should be considered in carefully selected patients
### ACCF/AHA 2009 Expert Consensus: Follow-up: Longitudinal Evaluation of PAH

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Low Risk</th>
<th>Intermediate-High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms/decompensation</td>
<td>No increase</td>
<td>Increase</td>
</tr>
<tr>
<td>FC</td>
<td>I/II</td>
<td>IV</td>
</tr>
<tr>
<td>6MWD</td>
<td>&gt;400 m</td>
<td>&lt;300 m</td>
</tr>
<tr>
<td>RH failure</td>
<td>None</td>
<td>Signs</td>
</tr>
<tr>
<td>RV size/function</td>
<td>Normal</td>
<td>Enlargement/dysfunction</td>
</tr>
<tr>
<td>Hemodynamics</td>
<td>RAP, CI normal</td>
<td>RAP high, CI low</td>
</tr>
<tr>
<td>BNP</td>
<td>Near normal/stable or decreasing</td>
<td>Elevated or increasing</td>
</tr>
</tbody>
</table>

**Frequency of Evaluations**

<table>
<thead>
<tr>
<th></th>
<th>Every 3-6 Months</th>
<th>Every 1-3 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Echocardiogram</td>
<td>Every 12 mo or center-dependent</td>
<td>Every 6-12 months or center dependent</td>
</tr>
<tr>
<td>• RHC</td>
<td>Clinical deterioration and center-dependent</td>
<td>Every 6-12 months or clinical deterioration</td>
</tr>
<tr>
<td>• BNP evaluation</td>
<td>Center dependent</td>
<td></td>
</tr>
<tr>
<td>• FC assessment, 6MWD</td>
<td>Every clinic visit</td>
<td></td>
</tr>
</tbody>
</table>

For high-risk patients, consider referral to PH specialty center for advanced therapies, clinical trials, and/or lung transplantation

Case Study (cont’d): Susan 4 Months Later

- 56-year-old woman with systemic sclerosis
- Screening echocardiography and PFTs show high probability for PH
- Diagnosis after RHC: PAH associated with scleroderma
- Treatment: Dual oral combination therapy with ERA and PDE5 inhibitor
- Feels better but, after 4 months, symptoms return to pretreatment levels, plus new symptoms:
  - Light-headed
  - Lower extremity edema
- Repeat risk assessment: High risk
Case Study (cont’d): Susan 4 Months Later

- 56-year-old woman with systemic sclerosis
- Screening echocardiography and PFTs show high probability for PH
- Diagnosis after RHC: PAH associated with scleroderma
- Treatment: Dual oral combination therapy with ERA and PDE5 inhibitor
- Feels better but, after 4 months, symptoms return to pretreatment levels, plus new symptoms:
  - Light-headed
  - Lower extremity edema
- Repeat risk assessment: High risk
- IV prostacyclin added to regimen (triple therapy)
- Lung transplant considered
Summary

Screening
- CTD-PH is a common form of PAH, most commonly in SSc
- Annual screening is critical to identify patients with SSc who are at high risk for PAH

Management
- CTD-PH requires comanagement with rheumatology and PH treating specialist
- PAH risk status should be assessed using an objective tool at every visit
- Most patients are started on ≥2 PAH-specific medications at time of diagnosis
  - Most patients in the **low- and intermediate-risk** categories should be started on **dual therapy**
    with an ERA + either a PDE5 inhibitor or sGC stimulator
- Many patients with CTD-PAH also have some degree of Group 2 PH from diastolic dysfunction
  and/or Group 3 PH from ILD
  - May face some added challenges when being evaluated for lung transplantation
Be alert to risk factors and signs/symptoms to identify PAH
- Ensure patients with SSc at high risk for PAH are screened annually
- Strive to attain and maintain low risk status in your patients with PAH
- Use a formal risk assessment tool to get your patient at goal
- Use dual drug therapy for patients with typical PAH categorized as low and intermediate risk at baseline, while high-risk patients could be considered for more advanced therapy

PCE Promotes Practice Change