A PHresh Overview of Pulmonary Hypertension (PH)

Emma Siegel, PharmD, BCACP

CMEPRO

Objectives

Recall the etiology of pulmonary hypertension

Identify treatment targets for pulmonary hypertension

List key considerations for the medications used in pulmonary hypertension

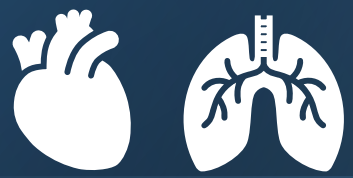
Abbreviations

- PH = pulmonary hypertension
- mPAP = mean pulmonary artery pressure
- ECHO = echocardiogram
- RV = right ventricle
- ECG = electrocardiogram
- BNP = B-type natriuretic peptide
- COPD = chronic obstructive pulmonary disease
- RHC = right heart catheterization
- PVR = pulmonary vascular resistance
- PCWP = pulmonary capillary wedge pressure
- WHO = World Health Organization
- PAH = pulmonary arterial hypertension
- CTEPH = chronic thromboembolic pulmonary hypertension
- CCB = calcium channel blockers
- LHD = left heart disease
- Cpc = combined pre-/post-capillary PH
- PEA = pulmonary endarterectomy
- BPA = balloon pulmonary angioplasty
- NO = nitric oxide
- cGMP = cyclic guanosine monophosphate

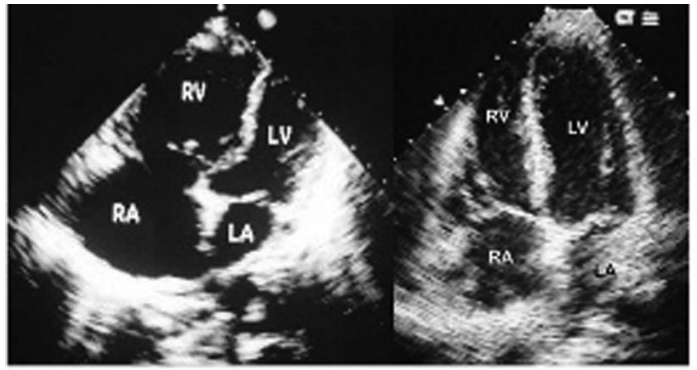
Abbreviations

- PDE-5is: phosphodiesterase-5 inhibitors
- sGC = soluble guanylate cyclase
- ERA = endothelin receptor antagonist
- PRA = prostacyclin agonist
- ADE = adverse drug effect
- DDI = drug drug interaction
- PO = by mouth
- BID = twice daily
- TID = three times daily
- REMS = risk evaluation and mitigation strategy
- LFT = liver function tests
- OCP = oral contraceptives
- AC/AP = anticoagulants/antiplatelets
- DPI = dry powder inhaler
- IV = intravenous
- SQ = subcutaneous
- 6MWT = 6 minute walk test
- PFTs = pulmonary function testing
- DLCO = diffusing capacity of lungs for carbon monoxide
- V/Q scan = ventilation/perfusion scan

What is Pulmonary Hypertension?



- **Mean pulmonary arterial pressure (mPAP) > 20 mmHg**
  - Diagnosed by right heart catheterization (RHC)
- Abnormal echocardiogram (ECHO) only “suggestive” of pulmonary hypertension
- Many different causes
  - 5 sub-groups
  - 3 hemodynamic classifications
- Prevalence: ~1% of global population



Signs/Symptoms of PH

- Fatigue
- Edema, bloating
- Dyspnea
- Cool extremities
- Loss of appetite
- Dizziness/lightheadedness
- Tachycardia
- **Syncope**

Suspicion for PH

- Abnormal RV on ECHO
- ECG changes
- Elevated biomarkers (BNP/NT-proBNP)
- Diseases associated with PH:
  - Drug use
  - Connective tissue disease
  - HIV
  - Family history
  - Left heart disease
  - COPD

Diagnostic Approach

Raise early suspicion of PH and ensure fast-track to specialists for patients with high likelihood of severe disease

Identify underlying diseases and comorbidities to ensure proper classification, risk assessment, and treatment

Patient Case

EC is a 30 YOF c/o dyspnea on minor exertion, rapid exhaustion with activity, and weight gain/swelling. Past medical history relevant for anxiety, depression, hx of substance use disorder (methamphetamines; abstinent x6mo).

Current medications: none

Relevant testing:

- ECHO w/ RVSP 90 mmHg
- NT-proBNP 1081 ng/mL

Patient is referred for RHC….

RHC Hemodynamics

mPAP = mean pulmonary artery pressure	PVR = pulmonary vascular resistance	PCWP = pulmonary capillary wedge pressure
• Mean pressure in pulmonary arteries	• Measure of resistance to blood flow in pulmonary arteries	• Surrogate for preload on left side of heart

Hemodynamics

Definition	Hemodynamic Characteristic
PH	mPAP >20 mmHg
Pre-capillary PH	mPAP >20 mmHg PCWP ≤15 mmHg PVR >2 WU
Isolated Post-capillary PH	mPAP >20 mmHg PCWP >15 mmHg PVR ≤2 WU
Combined Pre/post-capillary PH	mPAP >20 mmHg PCWP >15 mmHg PVR >2 WU

WHO Groups

1. **WHO 1:** Pulmonary arterial hypertension (PAH)
   - Idiopathic/heritable
   - Associated conditions: HIV, cirrhosis, connective tissue disease, drug use, congenital heart disease
2. **WHO 2:** Associated with left heart disease
3. **WHO 3:** Associated with lung disease
4. **WHO 4:** Associated with pulmonary artery obstructions
   - CTEPH
5. **WHO 5:** Unclear/multifactorial mechanisms

Hemodynamics…Again

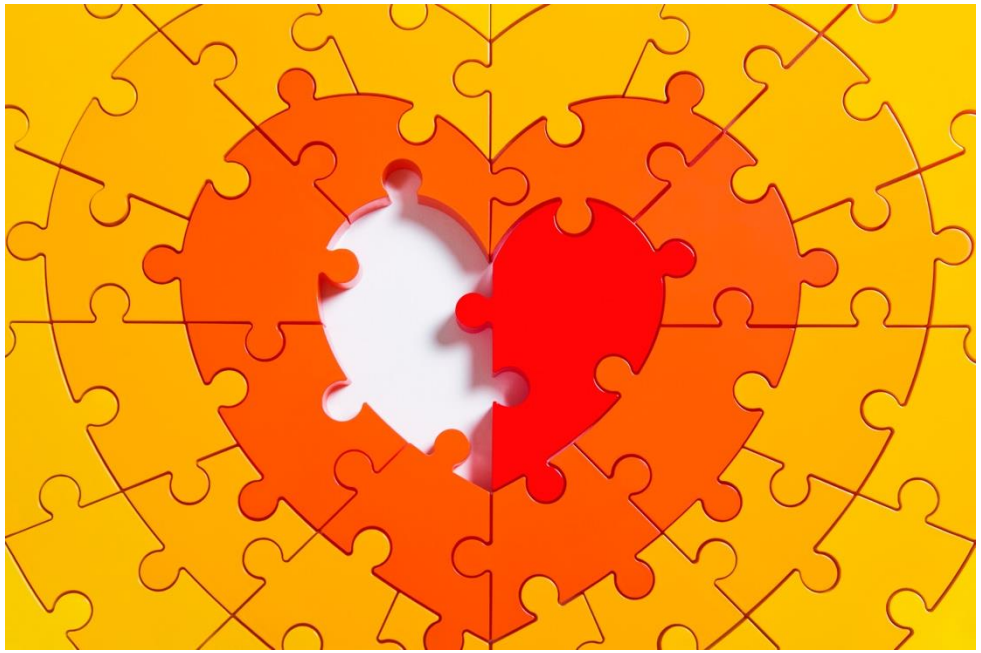
Pre-capillary PH:

- WHO 1
- WHO 3
- WHO 4

Post-capillary PH:

- WHO 2

WHO 5: any



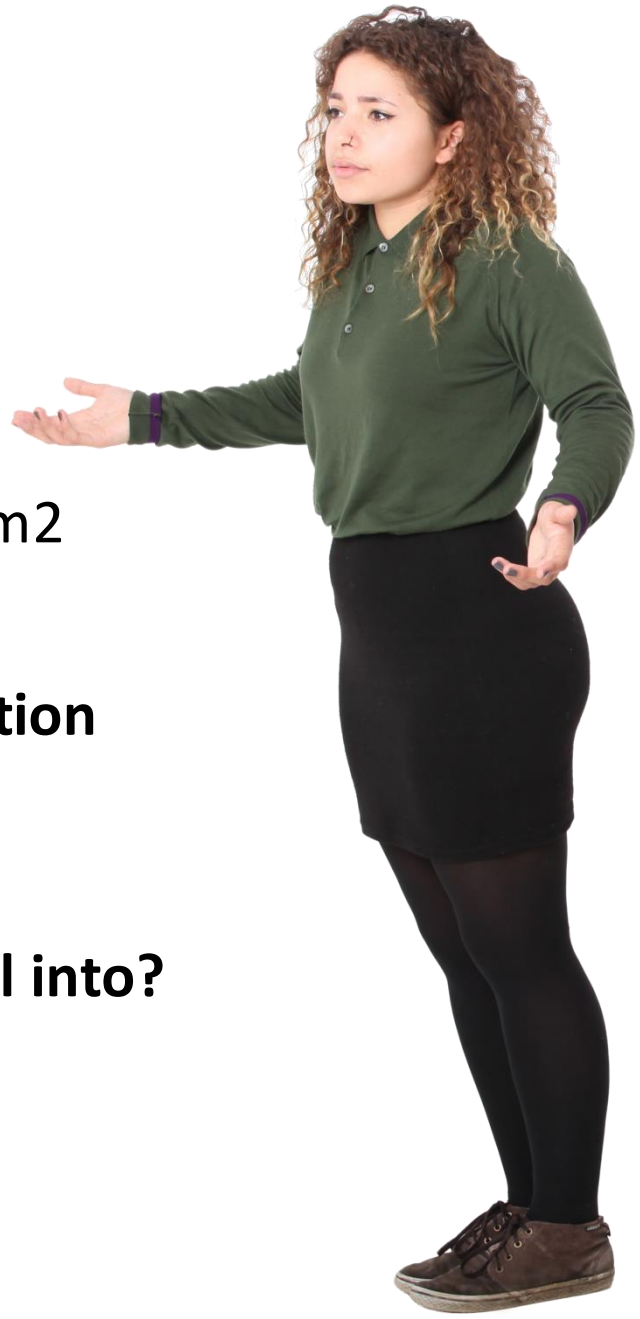
Patient Case

EC RHC results:

- mPAP 57 mmHg
- PVR 7 WU
- PCWP 12 mmHg
- Cardiac index 1.8 L/min/m2

What hemodynamic classification does ES fall into?

What WHO group might ES fall into?

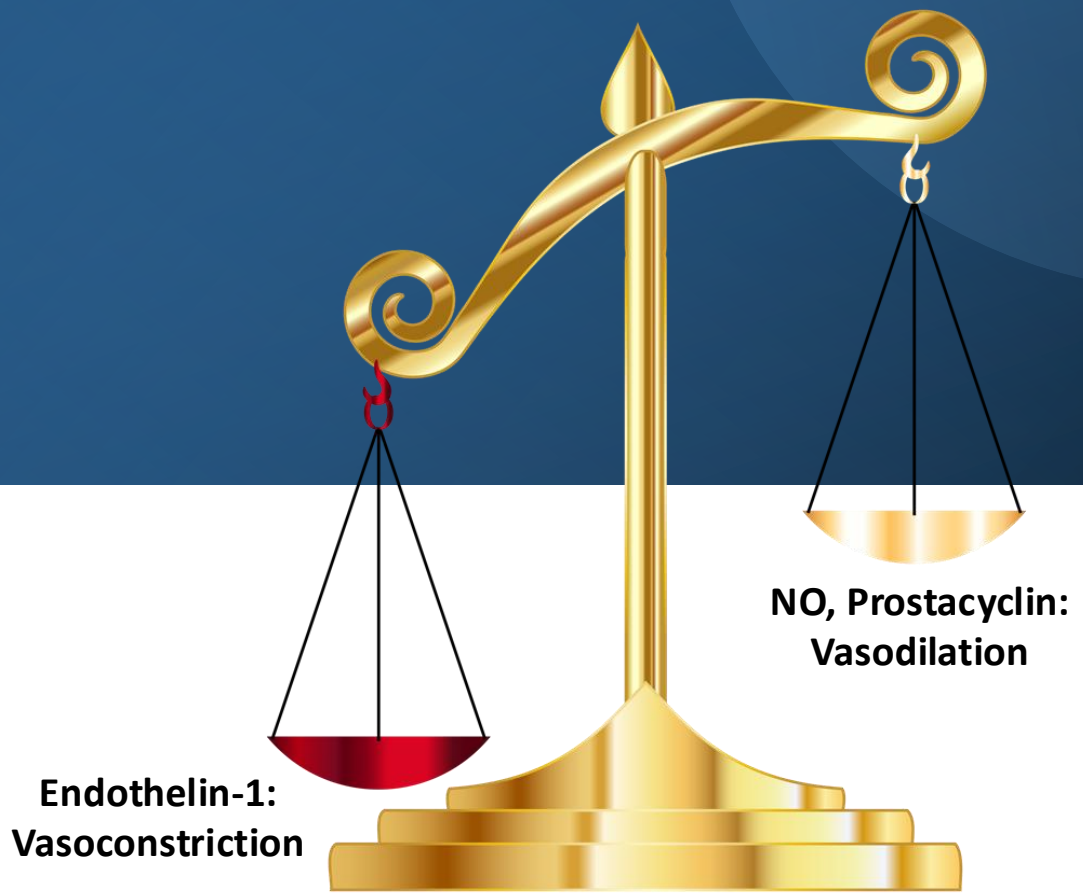


Group 1	Group 2	Group 3	Group 4	Group 5
• PAH drugs • CCBs in responders	• Treatment of LHD • Potentially PAH drugs in CpcPH (trials)	• Optimized care of underlying lung disease • Potentially PAH drugs in severe disease (trials)	• PEA • BPA • PAH drug: riociguat (Adempas®)	• Optimized treatment of underlying disease • Potentially PAH drugs (trials)

Treatment of PH

- Dependent on WHO group/underlying cause…
- Goal: normalize pressure, improve right heart function

WHO 1 PAH: Pulmonary Vasodilators



Pulmonary Vasodilators

1	2	3	4
NO/cGMP Pathway	**Endothelin Pathway**	**Prostacyclin Pathway**	**Activin Signaling Pathway**
PDE-5is: Inhibit PDE-5-based degradation of cGMP in pulmonary smooth muscle sCG stimulator: Enhances cGMP production Cause vasodilation and inhibit proliferation of pulmonary arteries	Block endothelin-mediated vasoconstriction and proliferation in pulmonary vasculature	PRA: Acts as prostacyclin agonist Prostacyclin analogue: mimics endogenous prostacyclin Cause potent vasodilation, inhibition of platelet aggregation, and inhibition of smooth muscle cell proliferation	Fusion protein that binds Activin A to balance pro-proliferative and anti-proliferative signaling to modulate vascular proliferation

PDE-5is

Recommend searching by BRAND name when ordering!

Drug	Route	Dosing	ADE	Relevant DDIs	Key Considerations
Sildenafil (Revatio®)	PO	20 mg TID	• Headache • Flushing • Rhinitis • Hypotension • Myalgias • Epistaxis *(generally well-tolerated)*	• Nitrates/sGC stimulator – risk of life-threatening hypotension	• Can be dispensed by local retail pharmacy • Generally affordable without insurance
Tadalafil (Adcirca®)	PO	40 mg daily			

sGC Stimulator

Drug	Route	Dosing	ADE	Relevant DDIs	Key Considerations
Riociguat (Adempas®)	PO	Start at 0.5 mg TID (or 1 mg TID), titrate by 0.5 mg TID q2wks to max dose of 2.5 mg TID	• Hypotension • Headache • GERD-like sx (may require H2RA/PPI)	• Nitrates/PDE-5is – risk of life-threatening hypotension • Cigarette smoking decreases concentration by 50-60% • Separate from antacids by 1h	• REMS program (pregnancy) • Can only be dispensed by specialty pharmacy

ERAs

Drug	Route	Dosing	ADE	Relevant DDIs	Key Considerations
Ambrisentan (Letairis®)	PO	Initiate at 5 mg daily, can increase to 10 mg	• Fluid retention • Nasal congestion • Flushing • Hemoglobin/ hematocrit decrease • Decreases in sperm count • LFT elevations (most significant with bosentan)	• Cyclosporine increases exposure	• Contraindicated in pregnancy (REMS recently removed) • Bosentan REMS program for hepatotoxicity still in effect • Can only be dispensed by specialty pharmacy
Macitentan (Opsumit®)	PO	Initiate at 10 mg daily		• Major substrate of CYP3A4	
Bosentan (Tracleer®)	PO	Initiate at 62.5 mg PO BID; for patients > 40 kg, increase to 125 mg PO BID after 4 weeks		• Decreases efficacy of OCP	

PRA

Drug	Route	Dosing	ADE	Relevant DDIs	Key Considerations
Selexipag (Uptravi®)	PO	Initial: 200mcg BID, titrate by 200/200 at weekly intervals Max (goal): 1600 mcg BID *Tolerability determines dose*	• Headache • Diarrhea • Nausea • Jaw pain • Nausea • Myalgias • Arthralgias	• CYP2C8 substrate (i.e. gemfibrozil, clopidogrel) • Increased bleeding risk on AC/AP	• Avoid in severe hepatic impairment (dose adjust for Child-Pugh B) • Do NOT stop abruptly • Can only be dispensed by specialty pharmacy

Prostacyclin Analogues

Drug	Route	Dosing	ADE	Relevant DDIs	Key Considerations
Treprostinil (Remodulin®)	IV/SQ	Initial: 1.25 ng/kg/min; increase as directed to target dose of 40 ng/kg/min	• SQ: infusion site pain • IV: infection • Inhaled: cough • Headache • N/V/D • Jaw pain • Flushing • Hypotension	• CYP2C8 substrate • Increased bleeding risk on AC/AP	• **Do NOT stop abruptly** • Can only be dispensed by specialty pharmacy (RNs provide education) • Orenitram: Contraindicated in Child-Pugh C
Treprostinil (Tyvaso®, Yutrepia®)	Inhaled	Dosing differs between DPI & nebulizer formulations + branded products BOTTOM LINE: 4x/d			
Treprostinil (Orenitram®)	PO	Initial: 0.25 mg BID or 0.125 mg TID; increase by 0.25-0.5 mg BID or 0.125 mg TID ~q7d (max dose determined by tolerability) *must be taken with food			

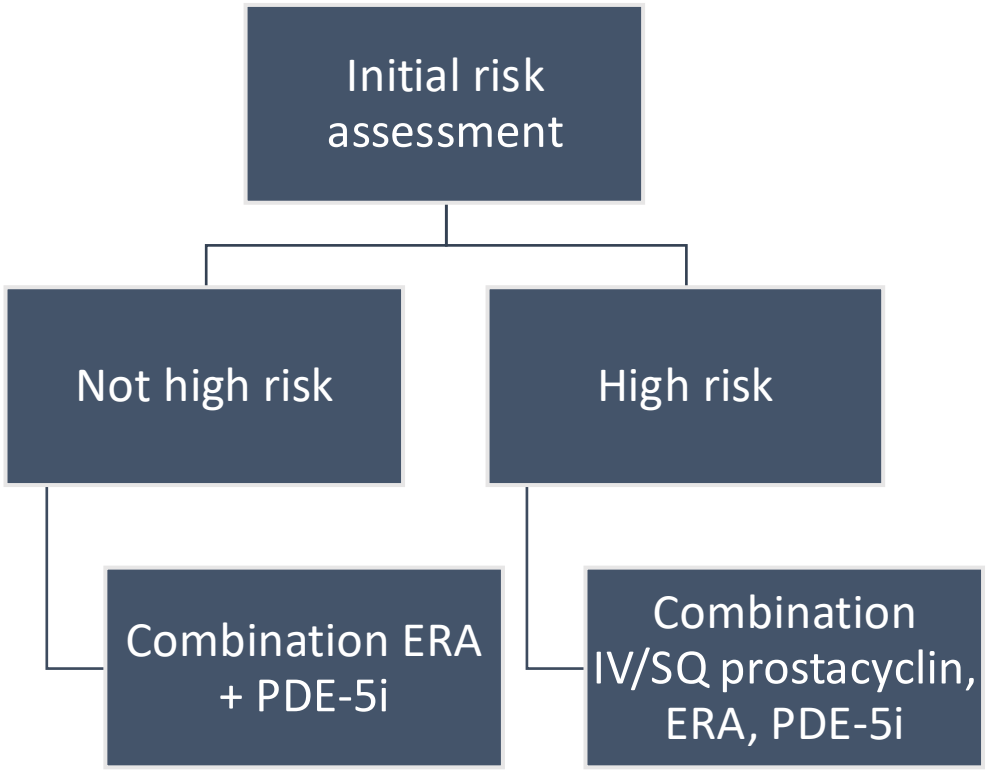
More on Treprostinil (IV/SQ)

- High-risk medication: interruption in therapy can be life-threatening (rebound PH, cardiogenic shock)
  - Half-life ~4h
- Dosing weight = **initial** weight (does not change)
- Pump rate (mcL/h) ≠ dose (ng/kg/min)
- Best friend = specialty pharmacy

Activin Signaling Therapy

Drug	Route	Dosing	ADE	Relevant DDIs	Key Considerations
Sotatercept (Winrevair®)	SQ	Initial: 0.3 mg/kg Q3weeks Target: 0.7 mg/kg Q3weeks (based on lab monitoring)	• Erythrocytosis • Thrombocytopenia • Epistaxis • Headache • Telangiectasia • Diarrhea	• Increased bleeding risk on AC/AP	• Can only be dispensed by specialty pharmacy • Can cause fetal harm/infertility • Do not initiate treatment if platelet count is <50k • Check Hgb & platelets before each dose for first 5 doses

PAH Treatment Algorithm



Risk Assessment:

- Functional class, 6 minute walk distance, natriuretic peptides as part of validated risk calculator (i.e. REVEAL score)
- Hemodynamics, right ventricle imaging to supplement
- Perform at BASELINE + within 3-4 months after therapy initiation + periodically thereafter

Patient Case

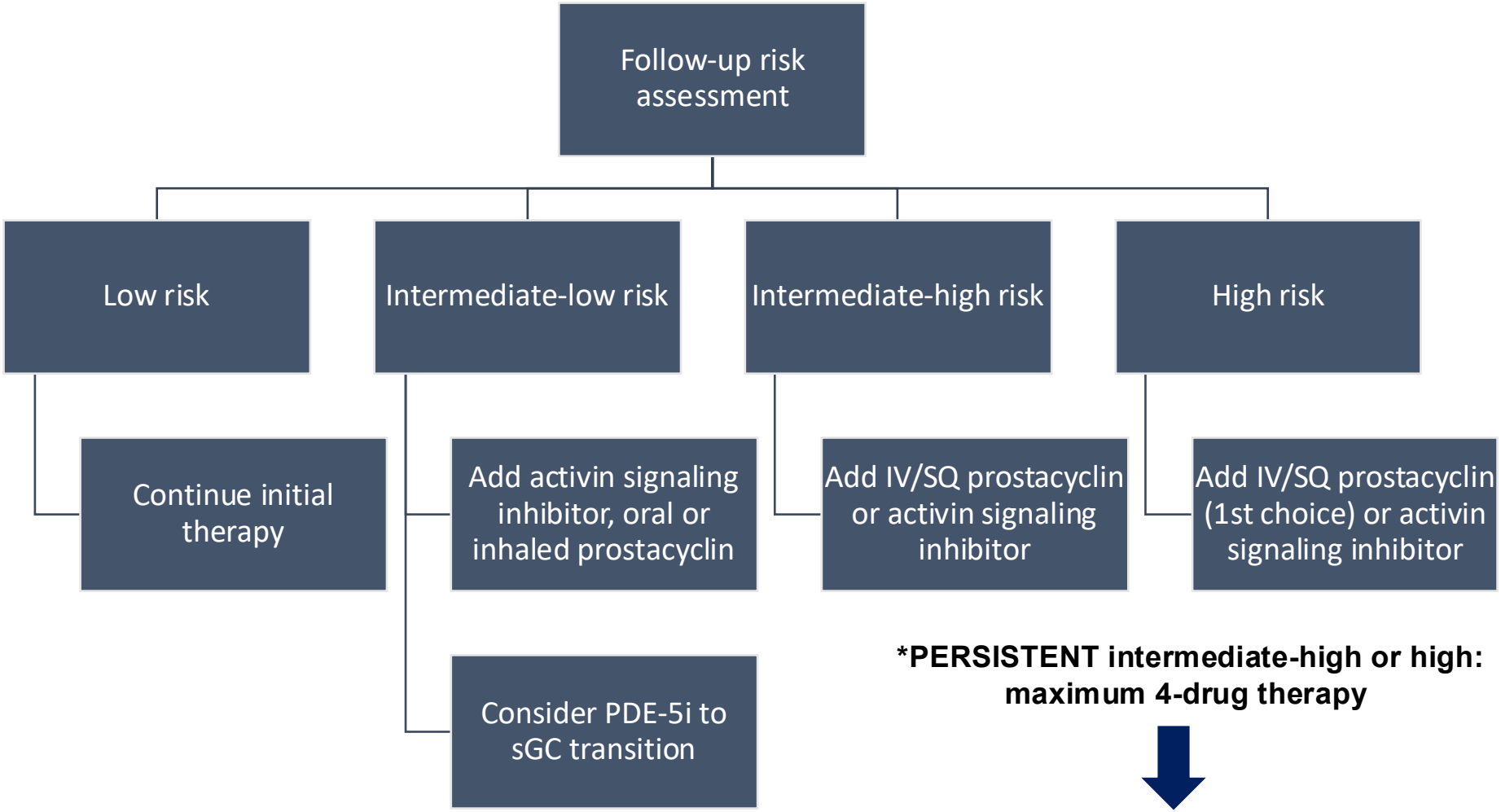
EC = HIGH risk

- mPAP 57 mmHg
- PVR 7 WU
- Cardiac index 1.8 L/min/m2
- WHO functional class III
- Elevated NT-proBNP
- Dilated RV on ECHO

What medications should ES be initiated on?

What are some important considerations when starting these medications?

PAH Treatment Algorithm



Patient Case

EC = 3 months later

- Medications:
  - Tadalafil 40 mg daily
  - Opsumit 10 mg daily
  - Remodulin 37 ng/kg/min
- 6MWT 450 m
- NT-proBNP <50 ng/mL
- Repeat ECHO with normalized RV

Determined to be LOW risk!

Next steps for EC?

PAH Treatment Recap

- PDE5-is → ERAs→ riociguat → prostacyclin receptor agonist → prostacyclin analogues
  - Sotatercept?
- Considerations when initiating therapy:
  - Risk classification
  - Side effect profiles
  - Pregnancy status
  - Drug interactions
  - Route of administration

WHO 2: LHD

- **Most** common cause of PH
  - HFrEF, HFmrEF, HFpEF, left-sided valvular heart disease, congenital/acquired CV conditions
  - Treat underlying condition!
- Vasodilators can WORSEN disease
  - Exception: PDE-5is? (CpcPH)

WHO 3: Lung Disease

- Common cause
  - COPD, emphysema, ILD, hypoventilation syndrom
- Severe vs non-severe
  - PVR >5 WU
- Testing: PFTs, including DLCO
- Treatment:
  - Optimize treatment of underlying lung condition
  - Supplementary O2 if indicated
  - Inhaled treprostinil for ILD
  - PDE-5is in COPD?

WHO 4: CTEPH

- Mismatched perfusion defects on V/Q scan
- Treatment:
  - Pulmonary endarterectomy (PEA) = treatment of choice with accessible PA lesions
  - Inoperable/recurrent:
    - Balloon pulmonary angioplasty (BPA)
    - Medical therapy: riociguat
- Lifelong therapeutic anticoagulation
  - Warfarin: antiphospholipid syndrome (10% of patients)

WHO 5: Multifactorial

- Includes:
  - Hematological disorders (i.e. sickle cell)
  - Systemic disorders (i.e. sarcoidosis)
  - Metabolic disrders (i.e. glycogen storage disease)
  - Chronic renal failure with/without hemodialysis
  - Pulmonary tumor thrombotic microangiopathy
  - Fibrosis mediastinitis
- Poorly understood mechanisms
- Treatment based on underlying cause, data from small RCTs

Assessment Question #1

Which of the following is commonly associated with WHO Group 2 PAH?

A. Connective tissue disease
B. Dialysis
C. HFpEF
D. Sickle cell disease

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Assessment Question #2

Which of the following represents a medication from the endothelin pathway for the treatment of PAH?

A. Sildenafil
B. Riociguat
C. Macitentan
D. Selexipag

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Assessment Question #3

Which of the following is a common side effect of treprostinil (parenteral/oral)?

A. Diarrhea
B. Fluid retention
C. Cough
D. Hypertension

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Questions?

References

- Adcirca (tadalafil). Prescribing information. Eli Lilly; 2020. Accessed January 2, 2026. adcirca-pi.pdf (lilly.com).
- Adempas (riociguat). Prescribing information. Bayer; 2013. Accessed January 2, 2026. Adempas_PI.pdf (bayerhealthcare.com).
- Humbert M, Galiè N, Rubin LJ, et al. The Seventh World Symposium on Pulmonary Hypertension: Our journey to Barcelona. *Eur Respir J* 2024; in press: 2401222. DOI: 10.1183/ 13993003.01222-2024.
- Humbert M, Kovacs G, Hoeper M, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: Developed by the task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). Endorsed by the International Society for Heart and Lung Transplantation (ISHLT) and the European Reference Network on rare respiratory diseases (ERN-LUNG). *Eur Heart J.* 2022 Oct 7;43(38):3618-3731. https://doi.org/10.1093/eurheartj/ehac237
- Letairis (ambrisentan). Prescribing information. Gilead; 2019. Accessed January 2, 2026. label (gilead.com).
- Opsumit (macitentan). Prescribing information. Actelion; 2013, Accessed January 2, 2026. OPSUMIT-pi.pdf (janssenlabels.com).
- Orenitram (trespostinil). Prescribing information. United Therapeutics; 2023. Accessed January 2, 2026. Orenitram-Prescribing-Information.pdf.
- Remodulin (trepostinil). Prescribing information. United Therapeutics; 2023. Accessed January 2, 2026. remodulin-pi.pdf.
- Revatio (sildenafil). Prescribing information. Pfizer; 2014. Accessed January 2, 2026. REVATIO (sildenafil) Label (fda.gov).
- Tello K, Yogeswaran A, Majeed RW, et al.; Pulmonary Vascular Research Institute GoDeep Consortium. Association of Phosphodiesterase-5 Inhibitor Treatment with Improved Survival in Pulmonary Hypertension Associated with COPD in the Pulmonary Vascular Research Institute GoDeep Meta-Registry. *CHEST*. 2025 Jan;167(1):224-240. doi: 10.1016/j.chest.2024.08.016. Epub 2024 Sep 7. PMID: 39182575; PMCID: PMC11864130.
- Tracleer (bosentan). Prescribing information. Actelion; 2017. Accessed January 2, 2026. TRACLEER (bosentan) tablets.
- Tyvaso (trepostinil). Prescribing information. United Therapeutics; 2022. Accessed January 2, 2026. TYVASO Prescribing Information.
- Uptravi (selexipag). Prescribing information. Actelion; 2022. Accessed January 2, 2026. . UPTRAVI-pi.pdf.
- Winrevair (sotatercept). Prescribing information. Merck; 2025. Accessed January 2, 2026. winrevair_pi.pdf.

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