


# Updates in Pulmonary Hypertension: What the ICU Pharmacist Needs to Know

 Jenny Shah, PharmD, BCCCP  
Clinical Pharmacy Manager - CCU  
NewYork - Presbyterian Hospital  
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AMAZING  
THINGS  
ARE  
HAPPENING  
HERE

## Disclosure

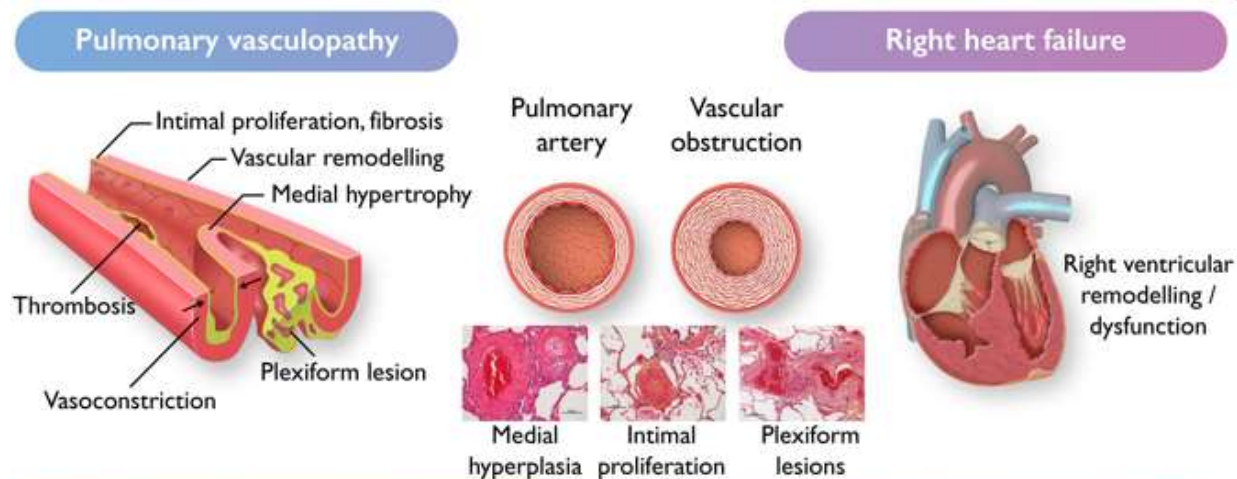
- I have nothing to disclose regarding the contents of this presentation.

## Objectives

- Describe pathophysiology of pulmonary arterial hypertension (PAH)
- Compare and contrast medications used in PAH and review dosing, adverse effects, and monitoring considerations
- Summarize the clinical considerations of PAH medications for patients presenting to the intensive care unit (ICU)
- Recognize precipitating factors for pulmonary hypertension (PH) crisis and management strategies

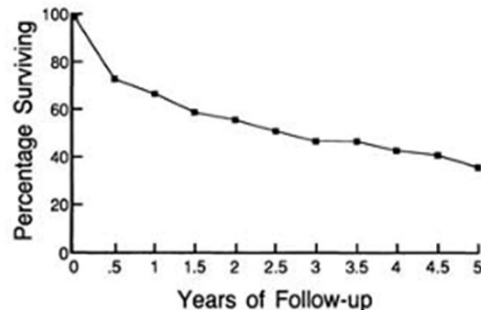
# Background and Epidemiology

- Pulmonary hypertension (PH) prevalence is estimated at ~1% of the global population
  - Higher in individuals aged >65 years
  - Most common causes are left heart disease, followed by lung disease
- PH is an increase in pressure within the pulmonary arteries
  - Defined by a mean pulmonary arterial pressure (mPAP) > 20 mm Hg at rest
  - Pulmonary arterial hypertension (PAH): pulmonary vascular resistance (PVR) >2 Wood Units and pulmonary arterial wedge pressure (PAWP): ≤ 15 mm Hg



# Survival in Patients with Pulmonary Hypertension

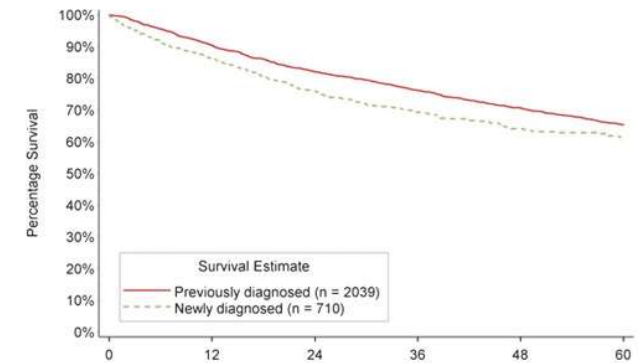
- National prospective registry of 32 clinical centers in the United States (US) supported by the National Heart, Lung, and Blood Institute
  - 194 patients between July 1981 – December 1985 followed through August 1988
  - Results
    - Median survival = 2.8 years
    - Survival at 1 year: 68%
    - Survival at 3 years: 48%
    - Survival at 5 years: 34%



**Figure 1.** Estimated percentage of patients surviving over time from the baseline catheterization. Number of patients at risk are shown for 0 through 5 years. Median survival is estimated at 2.8 years. Estimated percentages of patients surviving at 1, 3, and 5 years are 68%, 48%, and 34%, respectively.

- REVEAL registry: 55-center US registry of patients with PAH
  - Enrolled newly and previously diagnosed patients with PAH from March 2006-December 2009
  - Results for previously vs newly diagnosed patients:
    - 1-year survival: 90.4 vs 86.3%
    - 3-year survival: 76.2% vs 69.3%
    - 5-year survival: 65.4% vs 61.2% for newly diagnosed patients

## Kaplan-Meier Estimates of 5-year Survival



Number at risk	0	12	24	36	48	60
Previously dx	2039	1826	1616	1430	1262	1120
Newly dx	710	604	510	433	288	175

# Clinical Classifications of PH

## Group 1: Pulmonary Arterial Hypertension

- Idiopathic
- Heritable
- Associated with drugs/ toxins
- Associated with connective tissue disease, HIV, portal HTN, congenital heart disease, or schistosomiasis
- PAH with features of venous/ capillary involvement
- Persistent PH of the newborn

## Group 2: PH due to Left Heart Disease

- HFpEF/ HFrEF
- Valvular heart disease
- Congenital/ acquired cardiovascular conditions

## Group 3: PH due to Chronic Lung Disease/ Hypoxia

- Obstructive lung disease/ emphysema
- Restrictive lung disease
- Hypoventilation syndromes
- Chronic exposure to high altitude
- Developmental lung disorders

## Group 4: Chronic Thromboembolic Pulmonary Hypertension

- Chronic thromboembolic PH (CTEPH)
- Other pulmonary artery obstructions

## Group 5: PH with Unclear/ Other Mechanisms

- Hematological/ systemic/ metabolic disorders
- Chronic renal failure
- Pulmonary tumor thrombotic microangiopathy
- Fibrosing mediastinitis

HIV: human immunodeficiency virus; HTN: hypertension; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction

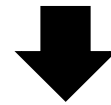
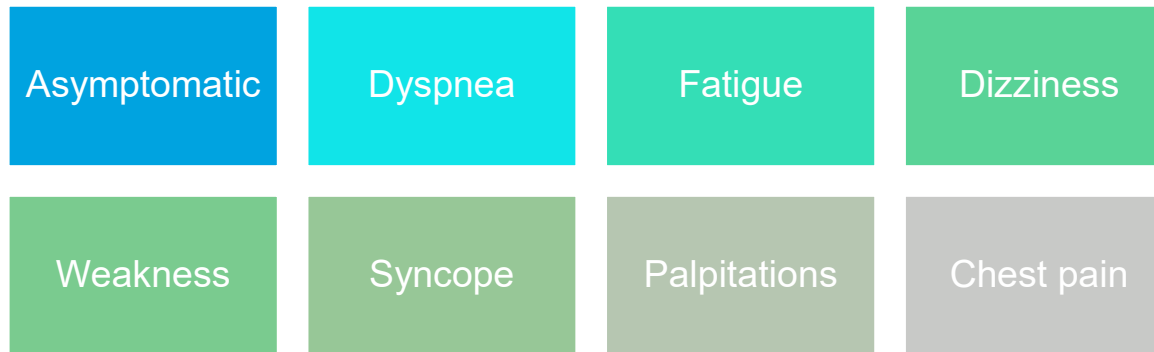
# World Health Organization (WHO) Functional Class

Class	Limitation of Physical Activity	Description
I	None	<ul style="list-style-type: none"><li>• No symptoms with normal activities</li></ul>
II	Mild	<ul style="list-style-type: none"><li>• No discomfort at rest</li><li>• Normal activity causes some symptoms</li></ul>
III	Marked	<ul style="list-style-type: none"><li>• No discomfort at rest</li><li>• Less than normal activity causes symptoms</li></ul>
IV	Severe	<ul style="list-style-type: none"><li>• Discomfort at rest</li><li>• Cannot perform activities of daily living</li><li>• Manifest signs of right heart failure</li></ul>

Symptoms: dyspnea, fatigue, syncope, chest pain

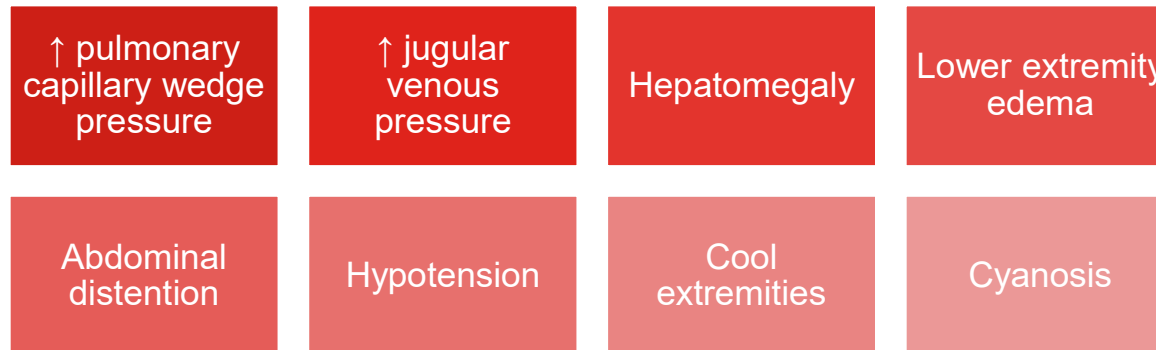
# Clinical Presentation

## Early Stages:



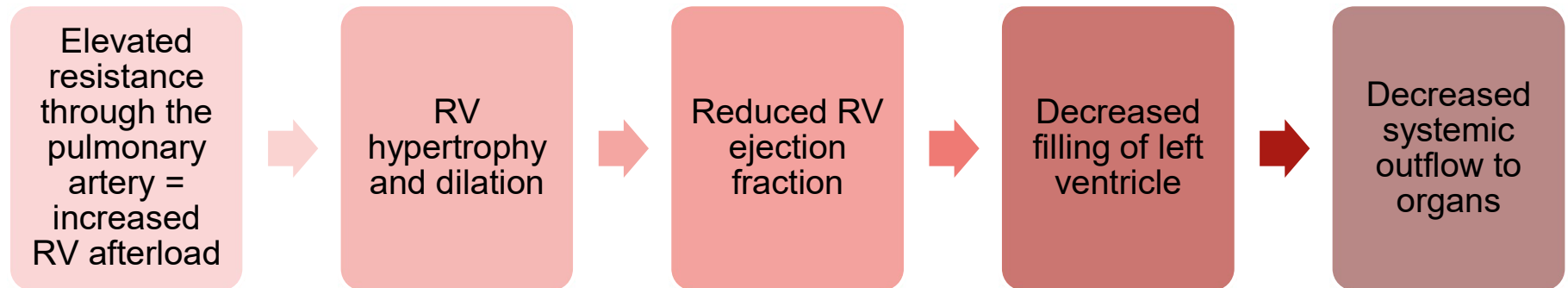
## Advanced Stages:

- Volume overload
- Cardiogenic shock



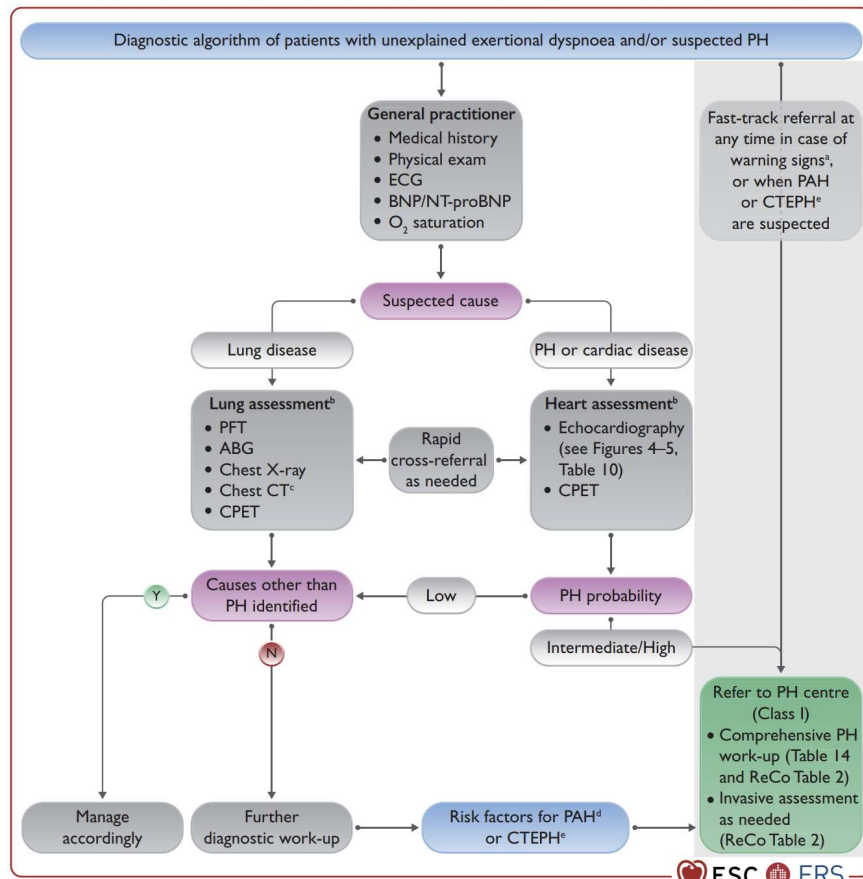
# Right Ventricular (RV) Dysfunction

- Complication of PH that contributes to decreasing functional capacity and worsening prognosis
- May occur in any of the PH groups but is mostly reported in groups 1 and 4
- RV failure remains leading cause of death in patients with PAH



# Diagnosis

- Goals are to raise early suspicion of PH + identify underlying diseases/comorbidities



**Echocardiography is recommended as the first-line , non-invasive, diagnostic investigation in suspected PH**

**Tricuspid regurgitant jet velocity >2.8 m/s corresponds to pulmonary artery systolic pressure ~35 mm Hg suggest PH (NOT 100% sensitive)**

**Right heart catheterization is the gold standard for diagnosing PH, clarifying PH subtype, and staging disease severity**

# Severity and Risk Assessment in PAH

Determinants of prognosis (1-year mortality)	Low Risk (<5%)	Intermediate Risk (5-20%)	High Risk (>20%)
Signs of right HF	Absent	Absent	Present
Progression of symptoms and manifestations	No	Slow	Rapid
Syncope	No	Occasional syncope	Repeated syncope
WHO-Functional Class	I, II	III	IV
6 min walk distance (meters)	>400	165-400	<165
Cardiopulmonary exercise testing	Peak VO <sub>2</sub> > 15 ml/min/kg (>65% predicted) VE/VCO <sub>2</sub> slope <36	Peak VO <sub>2</sub> 11-15 ml/min/kg (35-65% predicted) VE/VCO <sub>2</sub> slope 36-44	Peak VO <sub>2</sub> <11 ml/min/kg (<35% predicted) VE/VCO <sub>2</sub> slope >44
Biomarkers	BNP < 50 ng/L NT-proBNP <300 ng/L	BNP 50-800ng/L NT-proBNP 300-1100 ng/L	BNP >800 ng/L NT-proBNP >1100 ng/L
Echocardiography	RA area < 18 cm <sup>2</sup> No pericardial effusion	RA area 18-26 cm <sup>2</sup> Minimal pericardial effusion	RA area >26 cm <sup>2</sup> Mod/large pericardial effusion
Right Atrial Pressure Cardiac Index Stroke Volume Index Mixed Venous O <sub>2</sub> Sat	<8 mm Hg ≥2.5 L/min/m <sup>2</sup> >38 ml/m <sup>2</sup> >65%	8-14 mm Hg 2.0-2.4 L/min/m <sup>2</sup> 31-38 ml/m <sup>2</sup> 60-65%	>14 mm Hg <2.0 L/min/m <sup>2</sup> <31 ml/m <sup>2</sup> <60%

# Simplified Four-strata Risk Assessment Tool

Determinants of prognosis	Low Risk	Intermediate-Low Risk	Intermediate-High Risk	High Risk
<b>1-year mortality (%)</b>	0-3	2-7	9-19	20
<b>Points assigned</b>	1	2	3	4
<b>WHO-Functional Class</b>	I or II	-	III	IV
<b>6 min walk distance (meters)</b>	>440	320-440	165-319	<165
<b>BNP NT-pro-BNP (ng/L)</b>	< 50 ng/L <300 ng/L	50-199 300-649	200-800 650-1100	>800 >1100

BNP: brain natriuretic peptide; NT-proBNP: N-terminal pro-brain natriuretic peptide; WHO: World Health Organization  
Risk is calculated by dividing the sum of all grades by the number of variable and rounding to the next integer.

## Treatment Goals

Alleviate  
symptoms

Improve  
quality of life

Prevent  
disease  
progression

Improve  
survival

## Overview of Management

### ■ General management

- Exercise
- Supplemental oxygen
- Diuretics
- Digoxin
- Anticoagulation in certain populations

### ■ Targeted Therapy

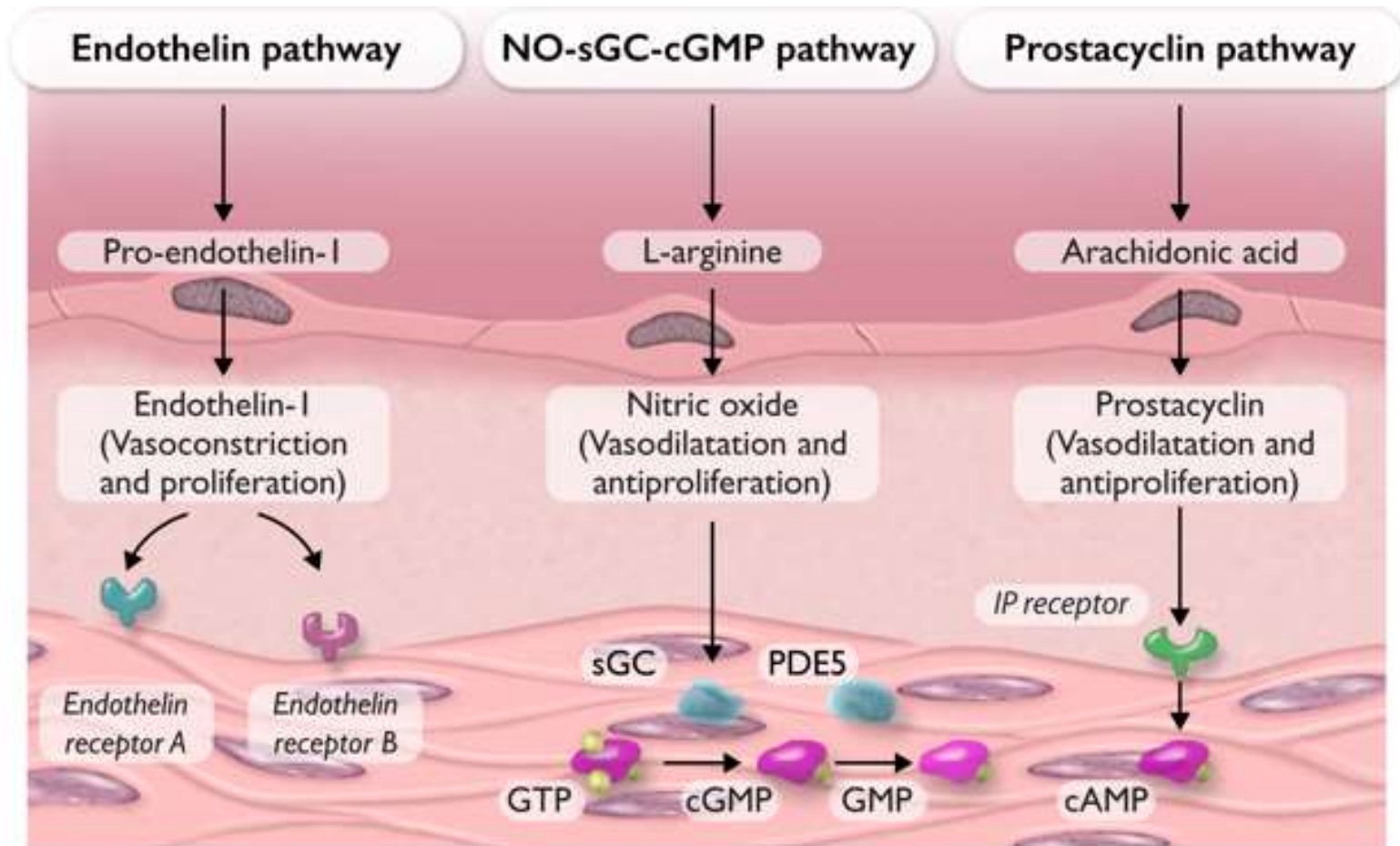
- Calcium channel blockers
- Endothelin receptor antagonists
- Phosphodiesterase-5 inhibitors
- Soluble guanylate cyclase stimulator
- Prostacyclin receptor agonists/analogues
- Nitric oxide
- Sotatercept

## Assessment Question

Which of the following is true with regards to the levels of endothelin, prostacyclin, and nitric oxide in patients with PAH?

- A. Levels of prostacyclin are increased; endothelin and nitric oxide are reduced
- B. Levels of endothelin are decreased; prostacyclin and nitric oxide are increased
- C. Levels of endothelin, prostacyclin, and nitric oxide are all reduced
- D. Levels of endothelin are increased; prostacyclin and nitric oxide are reduced

# Current Therapeutic Targets



# Therapeutic Targets for PAH

## Prostacyclin Pathway

- Epoprostenol
- Iloprost
- Treprostinil
- Selexipag

## Nitric Oxide Pathway

- Sildenafil
- Tadalafil
- Riociguat

## Endothelin Pathway

- Bosentan
- Ambrisentan
- Macitentan

# Vasoreactivity Testing for PAH

- Used to detect residual properties of vasodilation of small pulmonary arteries and arterioles
- Agents used for vasoreactivity testing: inhaled nitric oxide, inhaled iloprost
- Responders may be candidates for treatment with high dose calcium channel blockers (<10% of patients)
- Only recommended in patients with idiopathic, heritable, or drug/toxin associated PAH

Compound	Route	Half-Life	Dosage	Duration
Nitric oxide	Inhaled (INH)	15-30 s	10-20 ppm	5-10 min
Iloprost	INH	30 min	5-10 mcg	10-15 min

**Positive acute response: reduction in mPAP by  $\geq 10$  mm Hg to reach an absolute value  $\leq 40$  mm Hg with increased or unchanged cardiac output**

## Calcium Channel Blockers (CCB)

- Indication: patients with a positive vasoreactivity test
- Mechanism of action (MoA): directly acts on vascular smooth muscle to produce vasodilation
- Choice of CCB is based on patient's heart rate at baseline
  - Relatively bradycardia: nifedipine/amlodipine
  - Relative tachycardia: diltiazem

Agent	Starting Dose	Target Dose	Adverse Effects	Clinical Pearls
<b>Amlodipine</b>	5 mg daily	15-30 mg daily	Hypotension, peripheral edema	<ul style="list-style-type: none"> <li>• Higher doses than typically used in hypertension</li> <li>• Doses must be reached progressively</li> </ul>
<b>Diltiazem</b>	60 mg BID	120-360 mg BID		
<b>Felodipine</b>	5 mg daily	15-30 mg daily		
<b>Nifedipine</b>	10 mg TID	20-60 mg BID or TID		

- Re-assess (including RHC) after 3-6 months of therapy
  - If inadequate response (still WHO FC III/IV or mPAP >30 mm Hg and PVR >4WU), start additional PAH therapy

## Endothelin Receptor Antagonists (ERA)

- Rationale for use:
  - Endothelin receptor stimulation → vasoconstriction
  - This vasoconstriction is mediated through ET<sub>A</sub> and ET<sub>B</sub> receptors on the vascular endothelium and smooth muscles
    - ET<sub>A</sub> : located primary in the pulmonary vasculature and effect is muscular vasoconstriction and cellular proliferation
    - ET<sub>B</sub> :located in both the pulmonary vasculature and peripheral smooth muscles and effect is inhibition of apoptosis of vascular smooth muscle cells

**ERAs competitively block the action of endothelin from acting on endothelin receptors leading to vasodilation and a reduction in cell proliferation**

# Endothelin Receptor Antagonists (ERA)

Agent	Starting Dose	Adverse Reactions	Clinical Pearls
Bosentan (Tracleer®)	62.5 mg BID Target: 125 mg BID	<ul style="list-style-type: none"> <li>Peripheral edema</li> <li>Headache</li> <li>Hepatotoxicity</li> <li>Decreases in hemoglobin</li> </ul>	<ul style="list-style-type: none"> <li>Black Box Warning (BBW): embryo-fetal toxicity</li> <li>BBW: Increased liver function tests (bosentan only)</li> <li>DO NOT CRUSH</li> <li>As increase in generation → longer half-life and less hepatotoxicity</li> <li>Always check for drug interactions with these agents!</li> <li><b>Ambrisentan has a &gt;4,000-fold higher affinity for ET<sub>A</sub> than ET<sub>B</sub></b></li> </ul>
Ambrisentan (Letairis®)	5-10 mg daily		
Macitentan (Opsumit®)	10 mg daily		

## – REMS program:

- Female patients must adhere to pregnancy testing and contraception before beginning therapy and monthly
- Bosentan only (men and women): requires initial and monthly liver enzymes

## Phosphodiesterase-5 Inhibitors (PDE-5i)

- Rationale for use:
  - Inhibition of PDE-5 in smooth muscle of pulmonary vasculature where PDE-5 is responsible for degradation of cGMP
  - Increased cGMP results in **pulmonary vascular relaxation**

Agent	Dosing	Half-Life	Adverse Reactions	Clinical Pearls
Sildenafil (Revatio®)	20 mg PO TID (~10 mg IV = 20 mg PO) Max: 80 mg PO TID	4 hours	<ul style="list-style-type: none"> <li>• Hypotension</li> <li>• Flushing</li> <li>• Headache</li> <li>• Dyspepsia</li> </ul>	<ul style="list-style-type: none"> <li>• Major 3A4 substrate</li> <li>• Contraindicated with nitrate and riociguat use</li> <li>• Tadalafil requires dose adjustment for renal impairment (contraindicated in CrCl &lt;30)</li> </ul>
Tadalafil (Adcirca®)	40 mg daily	15 hours	<ul style="list-style-type: none"> <li>• Epistaxis</li> <li>• Visual alterations non-arteritic anterior ischemic optic neuropathy)</li> </ul>	

# Soluble Guanylate Cyclase (sGC) Stimulator

## ■ MoA:

- Sensitizes sGC to endogenous nitric oxide by stabilizing their binding and stimulates sGC independent of nitric oxide (NO) leading to increased cGMP causing vasodilation

Agent	Dosing	Adverse Reactions	Clinical Pearls
Riociguat (Adempas®)	1-2.5 mg TID	<ul style="list-style-type: none"><li>• Hypotension</li><li>• Headache</li><li>• N/V/D</li><li>• Bleeding</li><li>• Pulmonary edema</li></ul>	<ul style="list-style-type: none"><li>• Approved for PAH and CTEPH</li><li>• Use should be avoided in Child-Pugh Class C or worse hepatic dysfunction</li><li>• Contraindicated for patients receiving nitrates and PDE5i's</li><li>• Caution with CYP3A4 inducers and inhibitors</li><li>• Tables should not be split, crushed, or chewed</li></ul>

## ■ REMS program:

- Female patients must adhere to pregnancy testing and contraception requirements (monthly pregnancy tests)
- Male patients are not enrolled but still need to be registered

# Prostacyclin Receptor Agonist/Analogue

- MoA: Mimics the action of endogenous prostacyclin
  - Direct vasodilation of pulmonary and systemic vascular beds
  - Inhibition of platelet aggregation
  - Also has anti-proliferative effects
- Dosing weight for these agents does NOT change
  - Prostacyclin dosing weight is determined at initiation of therapy
  - This weight is carried with the patient forever, regardless of any changes to their actual weight
  - The specialty pharmacy will send a dosing chart from their records
  - This dosing weight should be documented in a note in the medical chart

# Prostacyclin Receptor Agonist/Analogue

Agent	Route	Dosing	Half-life	Adverse Reactions	Clinical Pearls
<b>Epoprostenol</b>	IV (Flolan <sup>®</sup> , Veletri <sup>®</sup> )	Initial: 2 ng/kg/min Titrate: increase dose in increments of 1-2 ng/kg/min at intervals of 15 min	6 min	<ul style="list-style-type: none"> <li>• Hypotension</li> <li>• Flushing</li> <li>• Headache</li> <li>• Jaw pain</li> <li>• Nausea/ vomiting</li> <li>• Infection</li> <li>• Thrombo-cytopenia</li> </ul>	<ul style="list-style-type: none"> <li>• Treprostinil is a major CYP 2C8 substrate – caution with strong inhibitors</li> <li>• Area under the curve of oral treprostinil is increased by 49% with a high fat, high calorie meal</li> <li>• Oral treprostinil tablets should not be split, chewed, or crushed</li> </ul>
	Inhalation (not FDA approved)	Initial: 25 ng/kg/min Max: 50 ng/kg/min			
<b>Treprostinil</b>	IV (Remodulin <sup>®</sup> )	Initial: 1.25 ng/kg/min Titrate: increase dose in increments of 1.25 ng/kg/min per week for first 4 weeks, followed by increments of 2.5 ng/kg/min per week	4 hours	Inhalation product warnings: <ul style="list-style-type: none"> <li>• Bronchospasm</li> <li>• Pulmonary edema</li> <li>• Syncope</li> </ul>	
	SubQ (Remodulin <sup>®</sup> )				
	Inhalation (Tyvaso <sup>®</sup> )	Initial: 18 mcg QID Max: 54 mcg QID			
	Oral (Orenitram <sup>®</sup> )	Initial: 250 mcg q12h or 125 mcg q8h			
<b>Iloprost</b>	Inhalation (Ventavis <sup>®</sup> )	Initial: 2.5 mcg 6-9 times/day Maintenance: 2.5-5 mcg/dose Max: 45 mcg/day	20-30 minutes		

# Prostacyclin Receptor Agonist

- MoA:
  - Activates the prostacyclin receptor leading to vasodilation

Agent	Dosing	Adverse Reactions	Clinical Pearls
Selexipag (Uptravi®)	Initial: 200 mcg PO BID  Max: 1600 mcg PO BID	<ul style="list-style-type: none"><li>• Headache (65%)</li><li>• Flushing</li><li>• Nausea</li><li>• Diarrhea</li><li>• Jaw, limb, and muscle pain</li></ul>	<ul style="list-style-type: none"><li>• Selexipag is a major CYP2C8 substrate-contraindicated with strong inhibitors (ex: gemfibrozil)</li><li>• Use should be avoided in Child-Pugh Class C or worse hepatic dysfunction</li></ul>

# Management of Patients on Tyvaso<sup>®</sup> During Mechanical Ventilation (MV)

- Tyvaso inhalation system is not designed for use with MV
- Options for management include:
  - Transition to intravenous Treprostinil
  - Use of inhaled epoprostenol or inhaled nitric oxide
  - Continuing inhaled Treprostinil using vibrating mesh or jet nebulizers if available
- Single case report investigating use of Tyvaso via a tracheostomy



*The mouthpiece of the Tyvaso Inhalation System was removed. Adaptors were placed on both sides of tubing to connect the patient's artificial airway to the inhalation system.*

# Treprostinil Delivery Options



**Remunity®**

The small, simple, and safe SC pump that provides state-of-the-art dosing accuracy



**CADD-MS® 3 ambulatory infusion pump**

The all-in-one pump  
*LIMITED SUPPLY AVAILABLE*



**CADD®-Solis VIP ambulatory infusion pump**

A durable and easy-to-use IV pump

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**CADD-Legacy® ambulatory infusion pump**

Reliably delivering Remodulin since 2004  
*LIMITED SUPPLY AVAILABLE*

# Checklist for Patient Admitted on Home Prostacyclin

- ✓ Confirm plan to continue patient's own supply versus transition to hospital supply
  - ✓ Must have backup supply available at all times (particularly epoprostenol)
  - ✓ If patient using own supply, must have necessary supplies (remote, cassette, batteries/chargers, infusion sets/tubing)
- ✓ Confirm the following medication factors
  - ✓ Concentration
  - ✓ Dose
  - ✓ Dosing weight
  - ✓ Amount of drug in diluent
  - ✓ Type of diluent
  - ✓ Total volume of infusion
  - ✓ Infusion rate
  - ✓ Brand or generic medication used?
- ✓ Obtain patient's dosing spreadsheet from Accredo or CVS Caremark
- ✓ Should infusion through central catheter but peripheral infusion with backup IV access may be used until central line access established



Maintain prostacyclin as a dedicated infusion. Do not mix with other medications

# Limitations of Parenteral Prostacyclins

- Increased systemic vasodilation
  - Detrimental in patients with hypotension and/or right ventricular dysfunction/left heart failure
- Increased perfusion-ventilation mismatch
  - Vasodilates ventilated and non-ventilated area
  - Results in worsened gas exchange
- Increased side effects, including those related to parenteral access
- Medication safety

## How to approach prostacyclin infusion in a patient with bacteremia?

If catheter removed, alternative access **must** be obtained prior to catheter removal for continuous prostacyclin delivery. Options for transitioning the infusion from old catheter to new catheter:

- Quickly transfer infusion from old to new catheter without priming the new catheter
- Priming new catheter with medication prior to transferring infusion to the new catheter
  - Overlapping infusions

# Transitioning Epoprostenol to Treprostinil

- Epoprostenol should NEVER be abruptly turned off
- Must transition with overlap of treprostinil (typically takes 24-48 hours)
- SubQ treprostinil to IV treprostinil
  - No overlap is required but can be considered
  - SubQ treprostinil has 100% bioavailability → 1:1 conversion

Step	Epoprostenol Dose	Treprostinil Dose
1	Maintain current dose	Initiate at 10% initial epo dose
2	Decrease to 80% initial dose	Increase to 30% initial epo dose
3	Decrease to 60% initial dose	Increase to 50% initial epo dose
4	Decrease to 40% initial dose	Increase to 70% initial epo dose
5	Decrease to 20% initial dose	Increase to 90% initial epo dose
6	Decrease to 5% initial dose	Increase to 110% initial epo dose
7	Discontinue epoprostenol	Maintain current dose plus additional 5% - 10% as needed

# Nitric Oxide

- MoA:

- Relaxes vascular smooth muscle by binding to the heme moiety of cytosolic guanylate cyclase, activating guanylate cyclase, leading to vasodilation

Agent	Dosing	Adverse Reactions	Clinical Pearls
Inhaled nitric oxide (iNO)	1-20 parts per million	<ul style="list-style-type: none"><li>• Methemoglobinemia</li><li>• Airway injury from nitrogen dioxide and/or peroxynitrite</li></ul>	<ul style="list-style-type: none"><li>• Only used inpatient</li><li>• Tachyphylaxis occurs at ~24 hours</li></ul>

# Combination Therapy and Drug Interactions

Drug	Mechanism	Interacting drug	Interaction
<b>Ambrisentan</b>	Unknown	Cyclosporine	↑ ambrisentan
<b>Bosentan</b>	CYP3A4 inhibition	Cyclosporine, erythromycin, azoles, amiodarone, diltiazem, verapamil	↑ bosentan
	CYP3A4 induction	Rifampin, phenytoin, hormonal contraceptives	↓ bosentan
		Cyclosporine	↓ cyclosporine
	CYP2C9 inhibition	Fluconazole, amiodarone	↑ bosentan
	CYP2C9 induction	Rifampin, phenytoin, hormonal contraceptives	↓ bosentan
Statins, warfarin		↓ simvastatin, atorvastatin warfarin	
<b>Sildenafil</b>	3A4 inhibition	Statins, protease inhibitors, erythromycin, azoles, diltiazem, verapamil,	↑ sildenafil
	3A4 induction	Phenytoin, rifampin	↓ sildenafil
<b>Macitentan, Riociguat</b>	3A4 inhibition	Cyclosporine, erythromycin, ketoconazole, fluconazole, diltiazem, verapamil	↑ macitentan, riociguat
	CYP3A4 induction	Rifampin, phenytoin, hormonal contraceptives	↓ macitentan, riociguat

## Combination Therapy and Drug Interactions

Drug	Mechanism	Interacting drug	Interaction
Ambrisentan	Unknown	Cyclosporine	↑ ambrisentan
Bosentan	CYP3A4 inhibition	Cyclosporine, erythromycin, azoles, amiodarone, diltiazem, verapamil	↑ bosentan
Sildenafil			
	3A4 induction	Phenytoin, rifampin	↓ sildenafil
Macitentan, Riociguat	3A4 inhibition	Cyclosporine, erythromycin, ketoconazole, fluconazole, diltiazem, verapamil	↑ macitentan, riociguat
	CYP3A4 induction	Rifampin, phenytoin, hormonal contraceptives	↓ macitentan, riociguat

Use of riociguat and either sildenafil/tadalafil is **CONTRAINDICATED!**

## Assessment Question

Which of the following is true with regards to the levels of endothelin, prostacyclin, and nitric oxide in patients with PAH?

- A. Levels of prostacyclin are increased; endothelin and nitric oxide are reduced
- B. Levels of endothelin are decreased; prostacyclin and nitric oxide are increased
- C. Levels of endothelin, prostacyclin, and nitric oxide are all reduced
- D. Levels of endothelin are increased; prostacyclin and nitric oxide are reduced

# Summary of Physiochemical and Pharmacokinetic Properties of Oral PAH Medications

Drug	Molecular Size (g/mol)	Protein Binding (%)	Log P	Volume of Distribution (L)	Hepatic Metabolism	Renal Elimination
Ambrisentan	378.4	99	1.21	35-40	X	
Bosentan	551.6	98	1.3	30	X	
Macitentan	588.27	>99	2.9	50	X	X
Sildenafil	474.58	96	2.7	105	X	
Tadalafil	392.4	94	1.42	63	X	X
Riociguat	422.4	95	2.3	32.3	X	X
Selexipag	496.6	99	2.2	11.73	X	X
Treprostinil	390.5	91-96	4.5	14	X	X

**How does extracorporeal membrane oxygenation (ECMO) influence PAH medication dosing?**

# Summary of Physiochemical and Pharmacokinetic Properties of Oral PAH Medications

Drug	Molecular Size (g/mol)	Protein Binding (%)	Log P	Volume of Distribution (L)	Hepatic Metabolism	Renal Elimination
Ambrisentan	378.4	<b>99</b>	1.21	35-40	X	
Bosentan	551.6	<b>98</b>	1.3	30	X	
Macitentan	588.27	<b>&gt;99</b>	<b>2.9</b>	50	X	X
Sildenafil	474.58	<b>96</b>	<b>2.7</b>	105	X	
Tadalafil	392.4	<b>94</b>	1.42	63	X	X
Riociguat	422.4	<b>95</b>	<b>2.3</b>	32.3	X	X
Selexipag	496.6	<b>99</b>	<b>2.2</b>	11.73	X	X
Treprostinil	390.5	<b>91-96</b>	4.5	14	X	X

Lipophilic medications + highly protein bound drugs (>70%) are more likely to be sequestered in the ECMO circuit, resulting in decreased drug levels. Hydrophilic medications may be reduced due to the increased Vd at the start of ECMO.

## Assessment Question

JM is a 58-year old man with a past medical history of PAH, diabetes mellitus, and hyperlipidemia who presents to the emergency department with shortness of breath, fever, and oxygenation saturation of 80%, requiring mechanical ventilation. His home medications include ambrisentan and tadalafil. Which of the following is true regarding administration of his PAH medications through a nasogastric (NG) tube?

- A. Both ambrisentan and tadalafil may not be crushed and administered through an NG tube
- B. Both ambrisentan and tadalafil can be crushed and administered through an NG tube
- C. Only ambrisentan can be crushed and administered through an NG tube
- D. Only tadalafil can be crushed and administered through an NG tube
- E. Tadalafil is available in an intravenous formulation

# Evaluation of Alternate Routes of PAH Medications

- Endothelin receptor antagonists + riociguat: tablets should not be split, crushed, or chewed
  - If patient has a feeding tube, can prepare suspension from the tablets
  - Considered hazardous drugs by NIOSH due to risk of birth defects so need double gloving, protective gown and preparation in a controlled device
  - Bosentan has a dispersible tablet that can be used to prepare a solution
  
- Sildenafil
  - Can be changed to IV
  - Oral suspension available
  
- Tadalafil
  - May be compounded extemporaneously as an oral suspension or converted to sildenafil
  
- Selexipag
  - IV available, dosing is not an exact 1:1 conversion
  - Tablets should be swallowed whole
  - Short-term (<3 days) interruption may be safe
  
- Treprostinil
  - IV available
  - 1 mg TID of PO Treprostinil ~ 5-6 ng/kg/min  
Treprostinil infusion in a 70 kg patient

Remodulin (ng/kg/min) =	$\frac{139 \times \text{Orenitram total daily dose (mg)}}{\text{weight (kg)}}$
	weight (kg)

Chakinala et al. J Heart Lung Transplant. 2017;36(2):193-201.  
 Cramer et al. J Pediatr Pharmacol Ther. 2021;26(3):265-270.  
 Malik et al. Hosp Pharm. 2016;51(5):389-395.  
 Muzevich et al. Crit Care. 2014;18(5):523.  
 Pettit et al. Am J Health Syst Pharm. 2012;69(7):592-594.

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## Starting Therapy

- When PH medications are started, patients require close initial monitoring
- Must assess for tolerability and adequate response
  - Consider medication half-life and steady state
- Must ensure patients are well educated on each of their medications and are set up to receive medications outpatient
- Selecting initial therapy
  - Consider functional class, data, adverse effect profile, and administration of agents
  - If patients have a positive vasoreactivity test, high dose CCB should be considered
- Combination therapy
  - Able to target different pathways in PAH while minimizing toxicity of higher medication doses
    - Sequential approach: potentially may avoid unnecessary medication exposure if a patient responds well
    - Up-front: potential benefit from targeting multiple mechanisms earlier

# Initial Use of Ambrisentan plus Tadalafil in PAH (AMBITION)

<b>Objective</b>	To evaluate initial combination therapy vs monotherapy in treatment-naïve PAH patients
<b>Patient Population</b>	500 patients with treatment-naïve WHO-FC II-III PAH <ul style="list-style-type: none"><li>Excluded patients with <math>\geq 3</math> of the following risk factors: BMI <math>\geq 30</math> kg/m<sup>2</sup>, hypertension, diabetes, coronary artery disease (CAD)</li></ul>
<b>Comparison Groups</b>	Ambrisentan 10 mg PO + tadalafil 40 mg PO daily (n=253) Ambrisentan 10 mg PO daily (n=126) Tadalafil 40 mg PO daily (n=121)
<b>Results</b>	<i>Reported as: combination vs ambrisentan vs tadalafil</i> Time-to-event analysis of a composite of first event of clinical failure, which was defined as the first occurrence of a composite of death, hospitalization for worsening PAH, disease progression, or unsatisfactory long-term clinical response <ul style="list-style-type: none"><li>18% vs 34% vs 28% (31% in the pooled monotherapy group)</li><li>HR of combination vs pooled monotherapy: 0.50 (CI: 0.35-0.72, p &lt; 0.001)</li><li>Mainly driven by reduction in hospitalization for worsening PAH</li></ul>

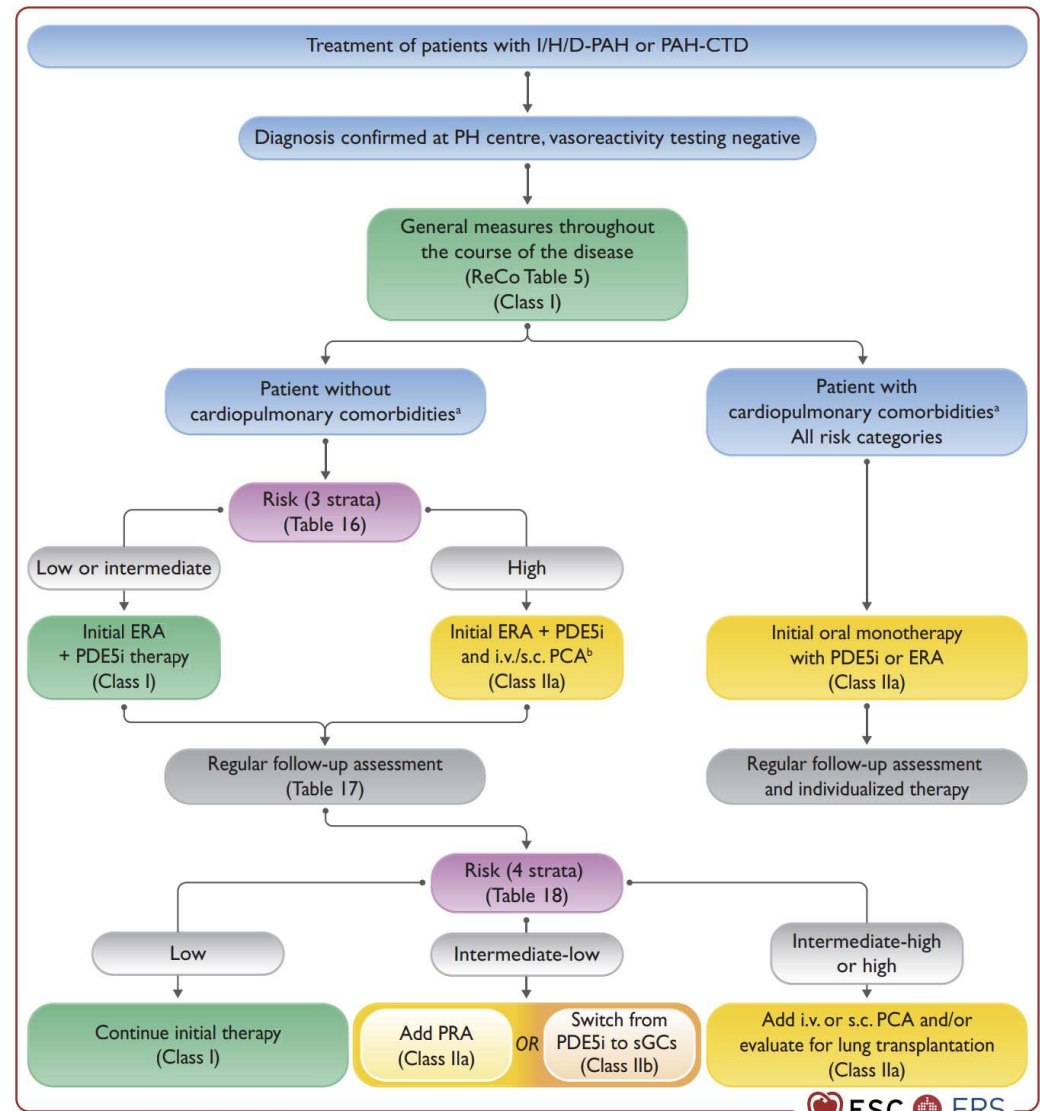
**Among patients with PAH who had not received previous treatment, initial combination therapy with ambrisentan and tadalafil resulted in a significantly lower risk of clinical-failure events than the risk with either monotherapy.**

# Three vs Two Drug Therapy for Patients with Newly Diagnosed PAH (TRITON)

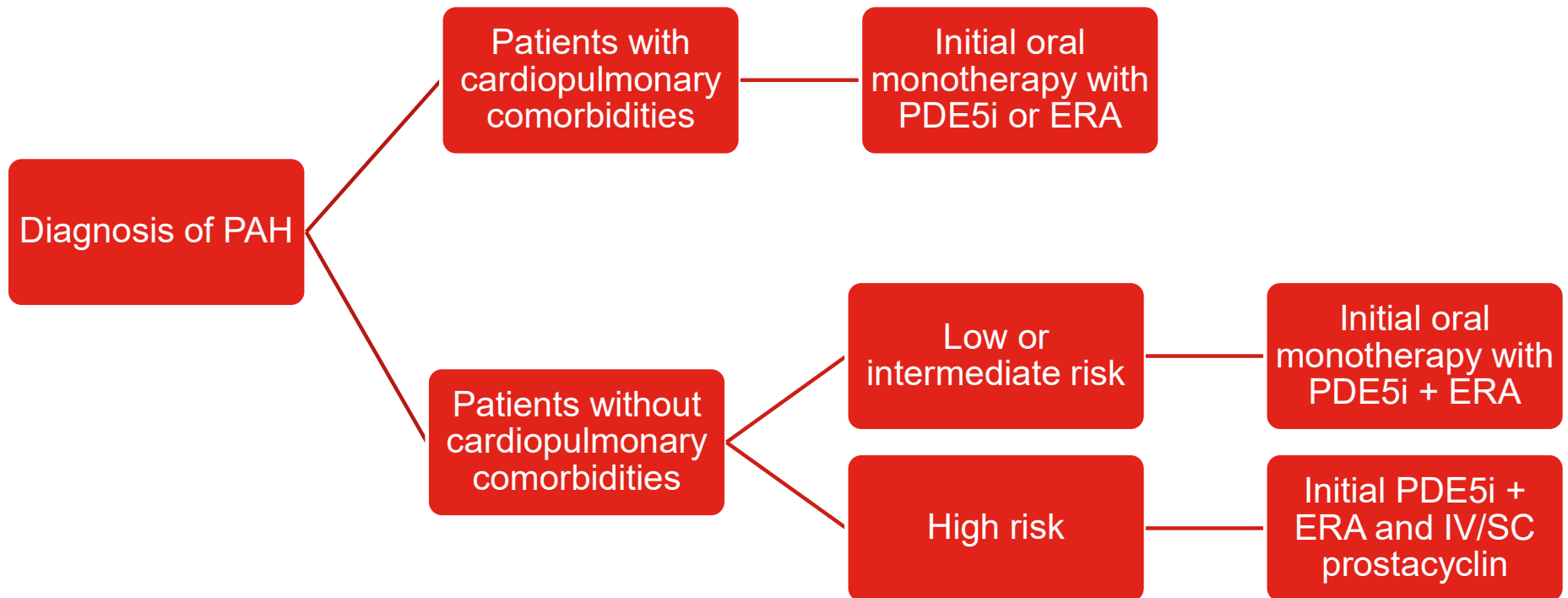
<b>Objective</b>	To evaluate initial triple vs double oral therapy in treatment-naïve PAH patients
<b>Patient Population</b>	247 patients with treatment-naïve PAH <ul style="list-style-type: none"><li>Excluded patients with <math>\geq 3</math> of the following risk factors: BMI <math>\geq 30</math> kg/m<sup>2</sup>, hypertension, diabetes, coronary artery disease (CAD)</li></ul>
<b>Comparison Groups</b>	Macitentan + tadalafil + selexipag (n = 123) Macitentan + tadalafil + placebo (n = 124)
<b>Results (at week 26)</b>	<ul style="list-style-type: none"><li>PVR decreased by 54% for initial triple therapy vs 52% for initial double therapy</li><li>Six-minute walk distance and N-terminal pro-brain natriuretic peptide improved by week 26, with no difference between groups</li><li>Risk for disease progression was reduced with initial triple versus initial double therapy (hazard ratio: 0.59; 95% CI: 0.32-1.09).</li><li>Most common AEs with initial triple therapy included headache, diarrhea, and nausea</li></ul>

**In patients with newly diagnosed PAH, both treatment strategies markedly reduced PVR by week 26, with no significant difference between groups.**

# 2022 ESC/ERS Guidelines Recommendations



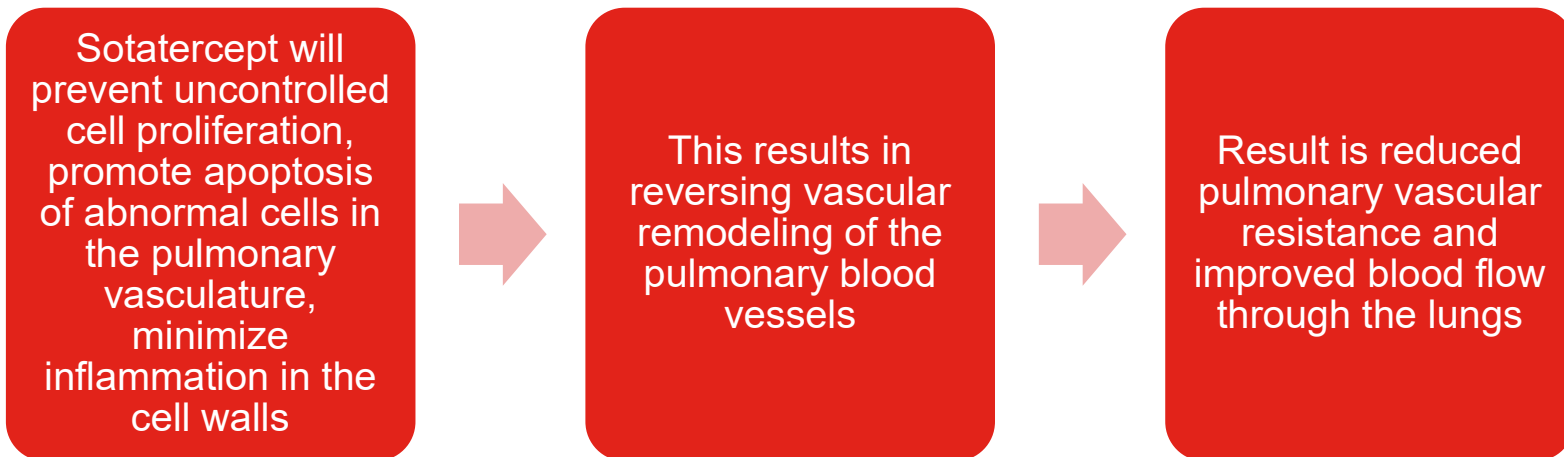
# Recommendations for Initial Oral Drug Combination Therapy



Cardiopulmonary comorbidities are conditions associated with an increased risk of left ventricular diastolic dysfunction, and include obesity, hypertension, diabetes mellitus, and coronary heart disease

## Novel Therapy: Sotatercept

- Recombinant fusion protein that has the Fc domain of human IgG-linked to activin receptor type IIA which is a ligand trap for transforming growth factor (TGF)-beta
  - TGF beta is thought to cause proliferation and prevent cell death that contributes to pulmonary vascular remodeling
  - Inhibiting TGF-beta will prevent proliferation and allow for cell death, preventing excessive cell proliferation and minimize inflammation



## Phase 3 Trial of Sotatercept for Treatment of PAH (STELLAR)

<b>Design</b>	Phase 3, multicenter, double-blind, randomized, placebo-controlled trial
<b>Objective</b>	To evaluate efficacy, safety, and adverse event profile of sotatercept in combination with stable background therapy in adult patients with symptomatic PAH
<b>Patient Population</b>	323 patients with confirmed diagnosis of PAH in WHO functional class II or III <ul style="list-style-type: none"><li>• 61.3% were receiving triple combination therapy</li><li>• 39.9% were receiving parenteral prostacyclins</li></ul>
<b>Comparison Groups</b>	Sotatercept 0.3 mg/kg (escalated to 0.7 mg/kg for 2 <sup>nd</sup> dose at day 21) vs placebo Treatment duration: 24 weeks
<b>Results</b>	<i>Reported as: sotatercept vs placebo</i> <ul style="list-style-type: none"><li>• Change from baseline at week 24 in the 6-minute walk distance: 40.1 m vs -1.4 m</li><li>• Patients meeting all 3 criteria of multicomponent improvement end point at week 24: 38.9% vs 10.1% (p &lt; 0.001)</li><li>• Adverse events reported in at least 10% of patients in either group. Epitaxis, telangiectasia, and dizziness were more frequent in sotatercept group</li></ul>

In patients with PAH who were receiving stable background therapy, sotatercept resulted in a greater improvement in exercise capacity, hemodynamics, and clinical outcomes, compared with placebo.

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<b>Patient Population</b>	<b>Recruiting</b> ⓘ Study of Sotatercept in Newly Diagnosed Intermediate- and High-Risk PAH Participants (MK-7962-005/A011-13) (HYPERION)
<b>Comparison Group</b>	ClinicalTrials.gov ID ⓘ NCT04811092
<b>Results</b>	<b>Sponsor</b> ⓘ Acceleron Pharma, Inc., a wholly-owned subsidiary of Merck & Co., Inc., Rahway, NJ USA <b>Information provided by</b> ⓘ Acceleron Pharma, Inc., a wholly-owned subsidiary of Merck & Co., Inc., Rahway, NJ USA (Responsible Party) <b>Last Update Posted</b> ⓘ 2024-10-24 <ul style="list-style-type: none"><li>Adverse events reported in at least 10% of patients in either group. Epitaxis, telangiectasia, and dizziness were more frequent in sotatercept group</li></ul>

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# Considerations for Sotatercept Use in the Inpatient Setting

- Hospitals will need to decide about formulary addition
  - Nursing training for administration and monitoring
  - Protocol development for appropriate use
  - Storage/handling and dispensing considerations

Patients presenting to the hospital while on sotatercept outpatient

- Weigh risks vs benefits of continuing sotatercept according to outpatient administration schedule (ex: consider delay administration in patients with thrombocytopenia, angioectasia, major CV event, major bleeding)
- Ideally want to avoid delays >1 week
- If currently in acute decompensation, consider dose increase to 0.7 mg/kg if patient was previously on 0.3 mg/kg

Hospitalized patients not on sotatercept outpatient

- Unclear exactly when to start sotatercept
- Benefits of sotatercept seen when added to triple background therapy, however since this agent is a disease modifying agent, it is expected that it would take longer than pulmonary vasodilators to provide a substantial effect
- Very unlikely to provide rapid benefits to patients during acute decompensation
- If initiating inpatient, ensure appropriate outpatient coverage to ensure no interruptions after discharge

- Additional considerations
  - Subcutaneous absorption may be impaired in patients with acute decompensation and shock
  - PULSAR and STELLAR trials excluded patients with acute liver failure and eGFR <30 mL/min

# Treatment of Pulmonary Hypertension Crisis

- Combination of low central venous oxygenation saturation (<60%) with rising lactate levels and low or absent urine production signals imminent right heart failure
- Presentation
  - Right ventricular overload and failure
  - Hypotension/shock
  - Supraventricular arrhythmias
- Goals
  - Reduce pulmonary vascular resistance
  - Resolve hypotension
  - Avoid tachyarrhythmias

# Management of Acute Decompensations

1. Treat triggering factors and provide supportive care

- Treat infections, anemia, arrhythmias, comorbidities, etc
- Rule out pulmonary embolism, myocardial infarction, other conditions

2. Optimize fluid balance

- Administer fluids if hypovolemia is present/suspected
- Administer IV diuretics if fluid overload is present

3. Reduce RV afterload

- IV prostacyclins are treatment of choice
- Alternatives include IV or oral PDE-5 inhibitors or inhaled vasodilators (nitric oxide, iloprost)

4. Optimize cardiac output

- Consider dobutamine or milrinone

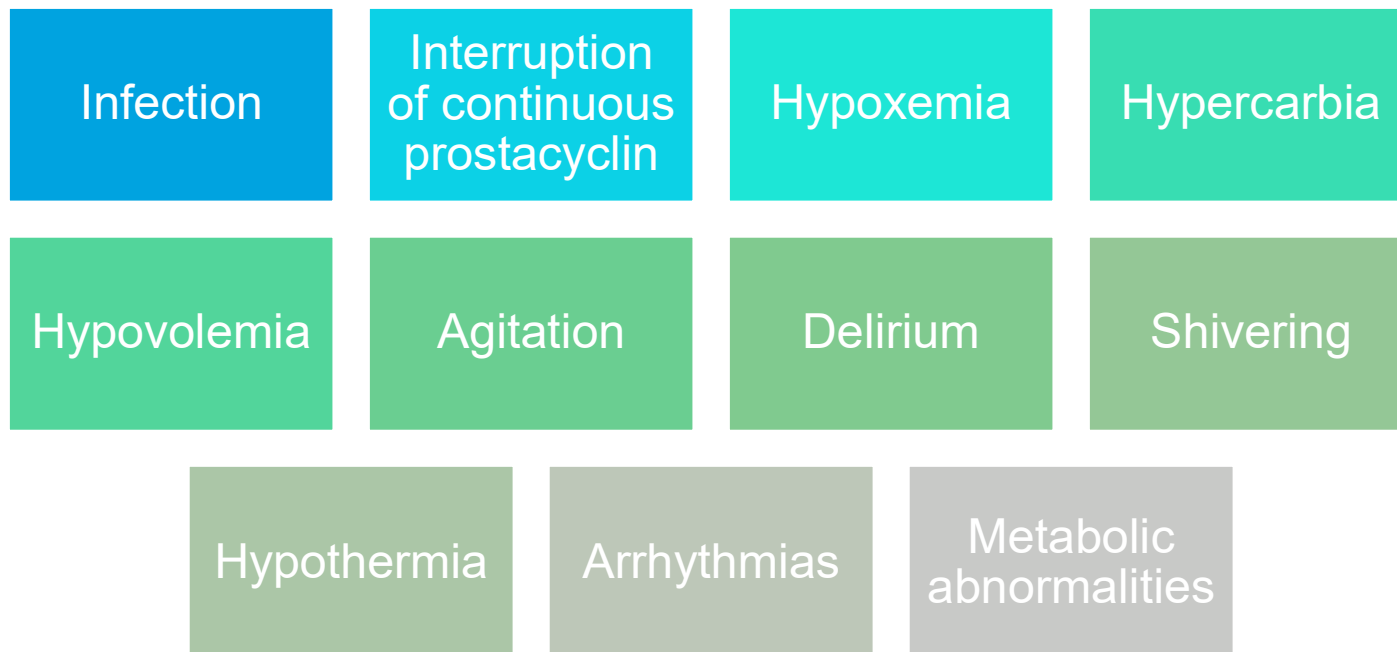
5. Optimize perfusion pressure

- Consider norepinephrine or vasopressin

6. Consider rescue therapies

- Consider lung transplantation or extracorporeal membrane oxygenation (ECMO)

# Management of Acute Decompensations: Triggering Factors



# Determination of Fluid balance

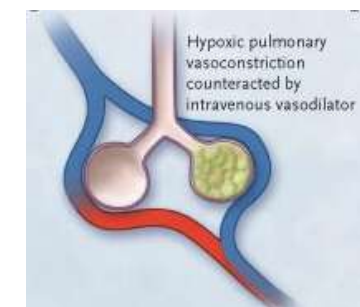
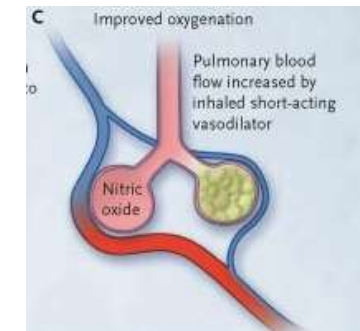
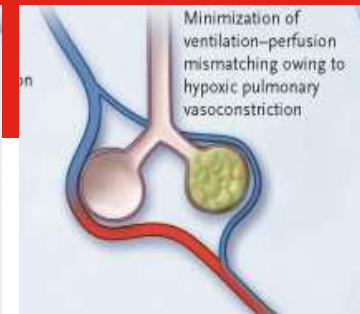
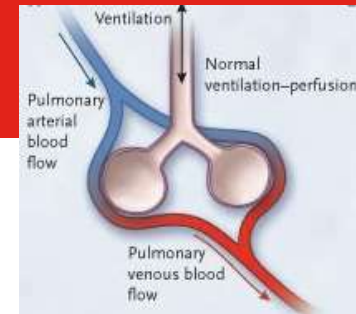
- Assessment of fluid responsiveness: dynamic measures preferred



- RV failure often involves volume overload, requiring diuretics or hemodialysis
  - Targeting initial RV filling pressure of 8–12 mmHg has been suggested
  - Achieving a normal superior vena cava O<sub>2</sub> (SVO<sub>2</sub>) saturation of 70–80%
  - Diuretic choice
    - Loop diuretics given as bolus or continuous infusion
    - May add on thiazide diuretic

# Management of RV Afterload

- RV is vulnerable to increased afterload
- Correct hypercapnia, acidemia, and alveolar hypoxia
- Mainstay of treatment = prostacyclins
  - Epoprostenol IV infusion at 1-2 ng/kg/min
    - Increase 1–2 ng/kg/min every 15–30 minutes until a favorable hemodynamic response or maximum tolerability
  - May cause systemic vasodilation, hypotension, and impair V/Q matching
- Inhaled prostacyclins cause less hypotension
  - Only delivered to ventilated alveoli, may **reduce V/Q mismatch**
  - Inhaled epoprostenol shown to increase cardiac index (CI) and SVO<sub>2</sub> while also reducing mPAP and central venous pressure (CVP), without decreasing systemic blood pressure (SBP)
- Avoid use of PDE5 inhibitors, ERAs, and riociguat in hemodynamic instability



# Optimizing Cardiac Output: Inotropes

Milrinone

- Phosphodiesterase-3 (PDE-3) inhibition will increase cAMP, leading to vasodilation and increased contractility
  - Associated with decreased pulmonary vascular resistance (PVR)
  - May cause hypotension (inhaled milrinone may be used to avoid this)
- IV milrinone with inhaled nitric oxide (iNO) will have selective and additive pulmonary vasodilation

Dobutamine

- Shown to improve RV infarction-induced PH and PH in HFpEF
- Dobutamine in combination with iNO can increase CI and PaO<sub>2</sub> and decrease PVR and systemic vascular resistance (SVR), without changing the mPAP or mean arterial pressure (MAP)

Dopamine

- May cause tachycardia, increase risk of arrhythmias, and increase mortality in cardiogenic shock

- Akagi et al: Administration of low-dose dopamine and/or dobutamine (starting at 3 mcg/kg/min) when starting epoprostenol was safe and did not increase mPAP
- Dobutamine doses >5 mcg/kg/min → may cause systemic hypotension and should be avoided

# Vasopressor Choice in PH Crisis

- **Ideal vasopressor**: increases SVR to maintain MAP without increasing PVR

Norepinephrine (NE)	<ul style="list-style-type: none"><li>• Causes systemic and pulmonary vasoconstriction through <math>\alpha</math>-1 stimulation, increasing SVR and PVR</li><li>• Low doses (0.5 mcg/kg/min) unlikely to significantly impact PVR</li><li>• Slight inotropic effects can increase RV contractility and increase cardiac output</li></ul>
Phenylephrine	<ul style="list-style-type: none"><li>• In patients with chronic PH, it increases SVR, PVR, MAP, and mPAP</li><li>• At higher doses, phenylephrine decreases cardiac index, compared to NE</li><li>• Although phenylephrine may improve the coronary blood flow, it may have deleterious effects on the RV function and cardiac output</li><li>• Generally avoid use</li></ul>
Vasopressin	<ul style="list-style-type: none"><li>• Exerts its effects through V1 receptors on vascular smooth muscle cells</li><li>• Causes systemic vasoconstriction, and at low doses, it causes selective pulmonary <b>vasodilation</b>, resulting in decreased or preserved PVR</li><li>• Conflicting information regarding its pulmonary vasodilatory role and effects on RV function</li><li>• At higher doses (1.16 units/kg/h), it seems to produce pulmonary <i>vasoconstriction</i></li></ul>


# Arrhythmias

- Supraventricular tachycardias (SVTs) are most common arrhythmias in PAH
- SVTs are associated with impaired RV function, clinical deterioration, and increased mortality (atrial fibrillation)
- Rhythm control should be prioritized in PAH
- Electric cardioversion and ablation therapy are both safe and effective in rhythm control
- Sinus rhythm should be maintained using antiarrhythmic drugs, taking care to avoid negative inotropic activity
- Bradycardia in PAH is highly associated with cardiopulmonary arrest
- Oral anticoagulation should be initiated in *all* patients with SVTs

## Conclusion

- Management of PH requires understanding of the pathophysiology of the disease process and medication targets
- RV dysfunction is an independent predictor of survival in PH
- Sotatercept is a novel therapy and the first medication for PAH that targets mechanisms underlying the structural changes in the blood vessels
- Data regarding use of PAH medications in critically ill patients is limited, but decisions to initiate and discontinue therapies should be made with careful consideration

# Updates in Pulmonary Hypertension: What the ICU Pharmacist Needs to Know

 Jenny Shah, PharmD, BCCCP  
Clinical Pharmacy Manager - CCU  
NewYork - Presbyterian Hospital  
January 28, 2025

AMAZING  
THINGS  
ARE  
HAPPENING  
HERE

# Risk Stratification Evidence

## French Pulmonary Hypertension Registry (FPHR)

- Assesses risk based on the number of low-risk criteria present
- Uses both invasive and non-invasive models:
  - Invasive model: WHO Functional Class (FC), 6-minute walk distance (6MWD), cardiac index (CI), and mean right atrial pressure (mRAP)
  - Non-invasive model: WHO-FC, 6MWD, and NT-proBNP or BNP

## Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA)

- Uses a three-strata model based on the 2015 ESC/ERS guidelines
- Assigns scores (1=low risk, 2=intermediate risk, 3=high risk) to various parameters
- Calculates overall risk by averaging scores of available parameters<sup>1</sup>
- Recently updated to COMPERA 2.0, a simplified four-strata model using three parameters: WHO-FC, NT-proBNP, and 6MWD<sup>45</sup>

## Swedish Pulmonary Arterial Hypertension Register (SPAHR)

- Similar to COMPERA, uses a three-strata model based on the 2015 ESC/ERS guidelines
- Includes modifiable parameters such as WHO-FC, 6MWD, NT-proBNP, right atrial area, pericardial effusion, mRAP, CI, and mixed venous oxygen saturation
- Also considers clinical observations like signs of right heart failure, symptom progression, and syncope
- Recently updated to include a divided intermediate risk category, offering more comprehensive assessment at follow-ups

## REVEAL 2.0

- Uses 14 variables to calculate risk<sup>1</sup>
- Provides a more discriminating risk stratification compared to other models<sup>1</sup>
- Risk categories correspond to the following scores:
  - Low risk: REVEAL score  $\leq 6$
  - Intermediate risk: REVEAL score 7-8
  - High risk: REVEAL score  $\geq 9$

## Emerging Therapies: Imatinib

- Rationale for use: provides antiproliferative effects to reverse lung vascular remodeling; inhibition of platelet-derived growth factor receptor will prevent proliferation of smooth muscle cells in pulmonary arteries
  - In animal models, imatinib reversed PH and showed pulmonary vasodilatory effects
- N Engl J Med case report (2005) reporting on add-on imatinib for idiopathic PAH showed improvement in 6MWD, PVR, mPAP, CI, and functional class at 3-month and 6-month follow up
- Imatinib in PAH, a Randomized Efficacy Study (IMPRES) (2013)
  - Phase 3 RCT of 202 patients showed significant improvement in 6MWD (32 m) and hemodynamics in PAH patients on background therapies
  - Serious adverse effects and study drug discontinuation were common
  - Long-term follow up study completed in 2015 showed high rates of discontinuation and significant adverse effects (subdural hematoma, death)
- Inhaled imatinib PAH Clinical Trial (IMPAHCT) (2024)
  - Did not meet primary endpoint of change in PVR for any of the studied doses

# Emerging Therapies: Ralinepag

- Rationale for use: oral prostacyclin receptor agonist
- 2019 Phase II randomized, double-blind, placebo-controlled study (22 weeks):
  - Significant reduction in PVR compared to placebo (29.8% reduction,  $p=0.03$ )
  - Median PVR reduction: 163.9 dyn.s/cm<sup>5</sup> for ralinepag vs 0.7 dyn.s/cm<sup>5</sup> for placebo ( $p=0.02$ )
  - No significant difference in 6-minute walk distance (6MWD) compared to placebo
- 2024 Phase II open-label extension study:
  - 45 patients enrolled (30 from ralinepag group, 15 from placebo group)
  - At 24 months:
    - Significant increase in 6MWD by 36.3 m ( $p=0.004$ )
    - Median PVR decrease of 52.2 dyn.s/cm
    - Median mean pulmonary arterial pressure decrease of 2.0 mmHg ( $p=0.05$ )
- ADVANCE OUTCOMES study evaluating effects of adding Ralinepag to patients' current PAH therapies is currently recruiting

## Macitentan/Tadalafil Combination Tablet (Opsynvi®)

- FDA-approved for the chronic treatment of PAH in adults who are treatment-naïve or already taking an ERA, PDE5 inhibitor, or both
- OPSYNVI® has a Boxed Warning due to the risk of embryo-fetal toxicity and requires female patients to enroll in the Macitentan REMS program
- Randomized Trial of Macitentan/Tadalafil Single-Tablet Combination Therapy for PAH (A DUE Study) (2024)
  - Double-blind, randomized, active-controlled, multi-center trial of 187 adult PAH patients with WHO FC II-III Patients were either treatment-naïve or on a stable dose of an ERA or PDE5i
  - PVR reduction at 16 weeks: 45% for combination therapy vs. 23% for macitentan and 22% for tadalafil monotherapy ( $p \leq 0.0001$  for both comparisons)
- Dosing:
  - Treatment naïve to any PAH therapy or transitioning from ERA monotherapy:
    - Start with macitentan 10 mg-tadalafil 20 mg orally once daily x 1 week
    - If tolerated can uptitrate to macitentan 10 mg-tadalafil 40 mg daily
  - If transitioning from PDE5i monotherapy or PDE5i/ERA combination therapy:
    - Macitentan 10 mg-tadalafil 40 mg daily