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Treatment of Pulmonary Hypertension

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Disclosures

- This speaker has no potential or actual conflicts of interest to disclose in relation to this presentation.

Goals and Objectives

- Distinguish the etiologies and pathophysiology associated with the different WHO classification groups of pulmonary hypertension.
- Identify the pharmacological agents approved and under investigation for treatment of pulmonary arterial hypertension.
- Recognize the adverse drug reactions associated with the pharmacological agents used for treatment.
- Explain treatment algorithms for pulmonary arterial hypertension.

Overview

- Pulmonary hypertension
- Management of pulmonary arterial hypertension (PAH) (Group 1)
- Management of chronic thromboembolic pulmonary hypertension (CTEPH) (Group 4)
- Pulmonary arterial hypertension approved drugs
- Pipeline

Pulmonary Hypertension

Introduction

- Pulmonary hypertension (PH) is a disorder characterized by an increase in pulmonary artery pressure (PAP)
- Results from multifactorial pathophysiologic mechanisms with a wide variety in etiology
- Presentation can be nonspecific or attributed to comorbid conditions

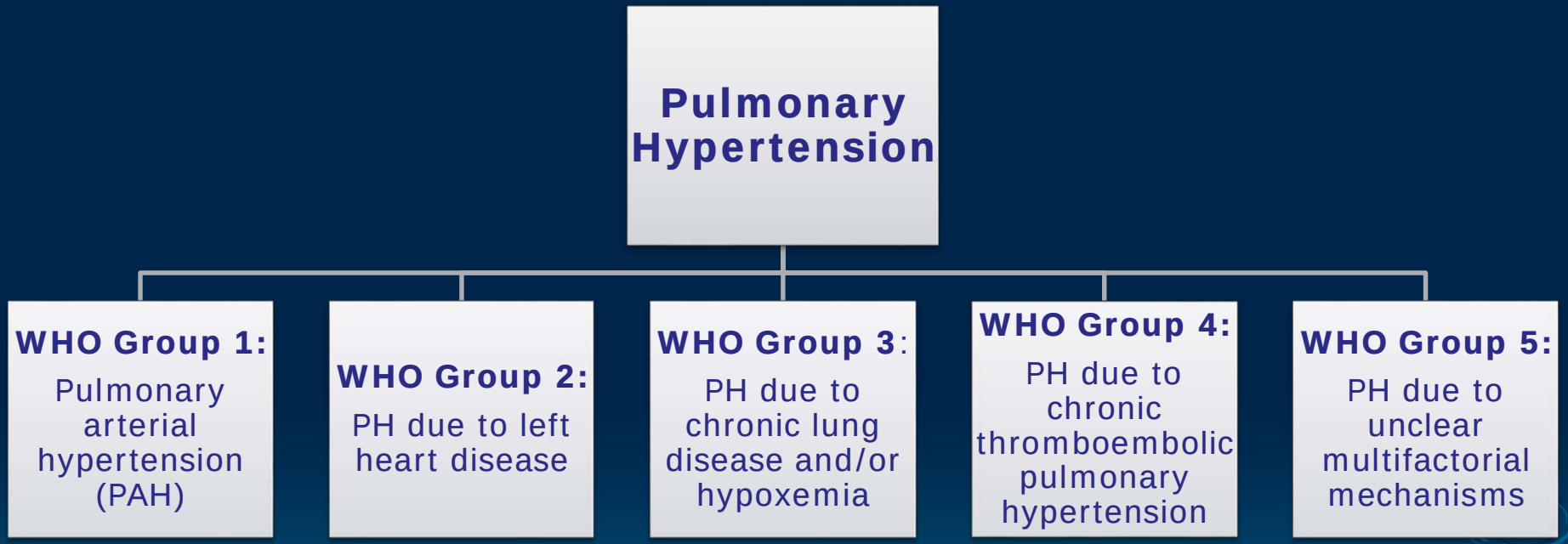
Galiè N, et al. *Eur Heart J.* 2016;37:67-119.; Newman J. *Am J Respir Crit Care Med*. 2005;172(9):1072-1077.

Epidemiology

- Global reporting on the incidence of PH is limited
  - Around 1% of the global population suffers from PH
- PAH incidence levels range from 1.1 – 7.6 cases per one million per year; prevalence ranges from 6.6 – 26.0 cases per million per year
- CTEPH incidence rates are 0.9 cases per million per year; prevalence rates 3.2 cases per million per year
- The most common cause of PH is left heart disease (LHD)

Galiè N, et al. *Eur Heart J.* 2016;37:67-119.; Hoeper M, et al. *Dtsch Arztebl Int.* 2017;114: 73–84.; Hoeper M, et al. *Lancet Respir Med* 2016;4: 306–322; Thenappan T, et al. *BMJ.* 2018;360:j5492.

Clinical Classifications



Adapted from: *Lancet Respir Med* 2016; 4:306–322.

Conditions

- Group 1: PAH
  - Idiopathic PAH (IPAH)
  - Heritable
  - Drugs and toxins
  - Connective tissue disease
  - Human immunodeficiency virus (HIV)
  - Portal hypertension
  - Congenital heart disease
  - Schistosomiasis

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

Drugs and Toxins

Definite	Likely	Possible
Aminorex	Amphetamine	Cocaine
Fenfluramine	Dasatinib	Phenylpropanolamine
Dexfenfluramine	L-tryptophan	St John's Wort
Rapeseed oil	Methamphetamines	Amphetamine-like drugs
Benfluorex		Interferon alpha and Beta
Selective serotonin reuptake inhibitors		Alkylating agents

Adapted from: *Eur Heart J.* 2016;37:67-119.

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

Conditions

- Group 2: Left heart disease (LDH)
  - Left ventricular systolic dysfunction
  - Left ventricular diastolic dysfunction
  - Valvular disease
  - Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
  - Congenital/acquired pulmonary veins stenosis

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

Conditions

- Group 3: Lung disease/hypoxemia
  - Chronic obstructive pulmonary disease
  - Interstitial lung disease
  - Other pulmonary diseases with mixed restrictive and obstructive pattern
  - Sleep-disordered breathing
  - Alveolar hypoventilation disorders
  - Chronic exposure to high altitude
  - Developmental lung diseases

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

Conditions

- Group 4: Chronic thromboembolic pulmonary hypertension (CTEPH)

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

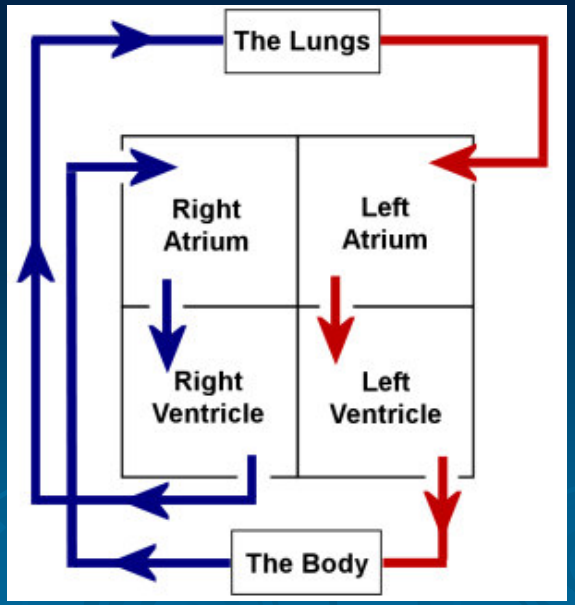
Conditions

- Group 5: Unclear multifactorial mechanisms
  - Hematologic disorders
  - Systemic disorders
  - Metabolic disorders
  - Others

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

Blood Flow Through the Cardiopulmonary Anatomy

- Vena Cava → Right Atrium → Right Ventricle → Pulmonary Artery → Pulmonary Capillaries → Pulmonary Vein → Left Atrium → Left Ventricle → Aorta → Systemic circulation



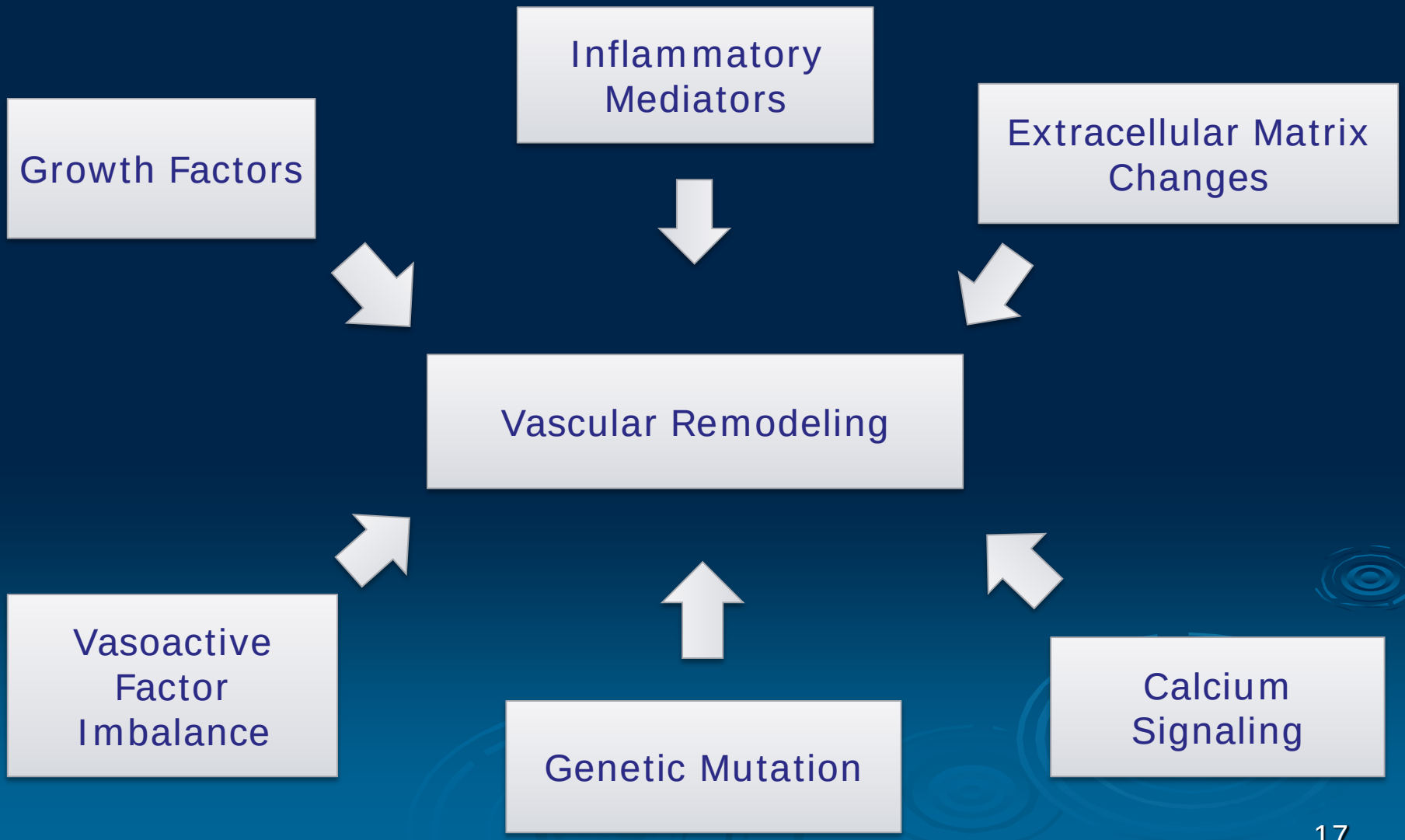
https://www.teachpe.com/anatomy-physiology/the-circulatory-system/the-heart

Hemodynamic Definitions:

- PH: Elevation of pulmonary arterial pressure (PAPm) ≥ 25 mmHg at rest
  - All groups
- Pre-capillary PH: PAPm ≥ 25 mmHg and pulmonary arterial wedge pressure (PAWP) ≤ 15 mmHg
  - Associated Groups: 1, 3, 4 & 5
- Post-capillary PH: PAPm ≥ 25 mmHg and PAWP > 15 mmHg
  - Associated Groups: 2, 5

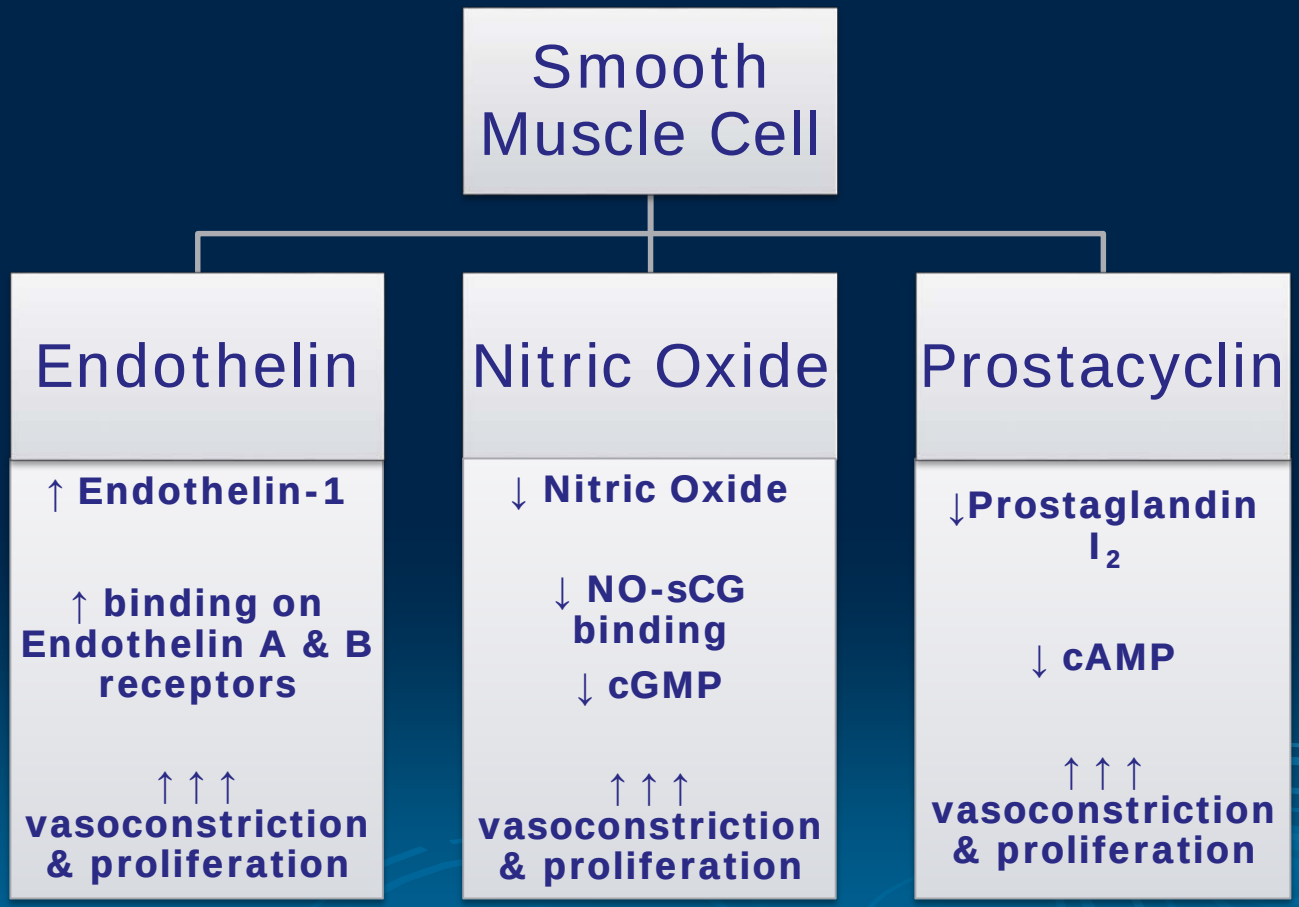
Galiè N, et al. *Eur Heart J.* 2016;37:67-119.

Pathophysiology



Toshner M, et al. *Br Med Bull.* 2010;94:21-32.

3 Major Pathways



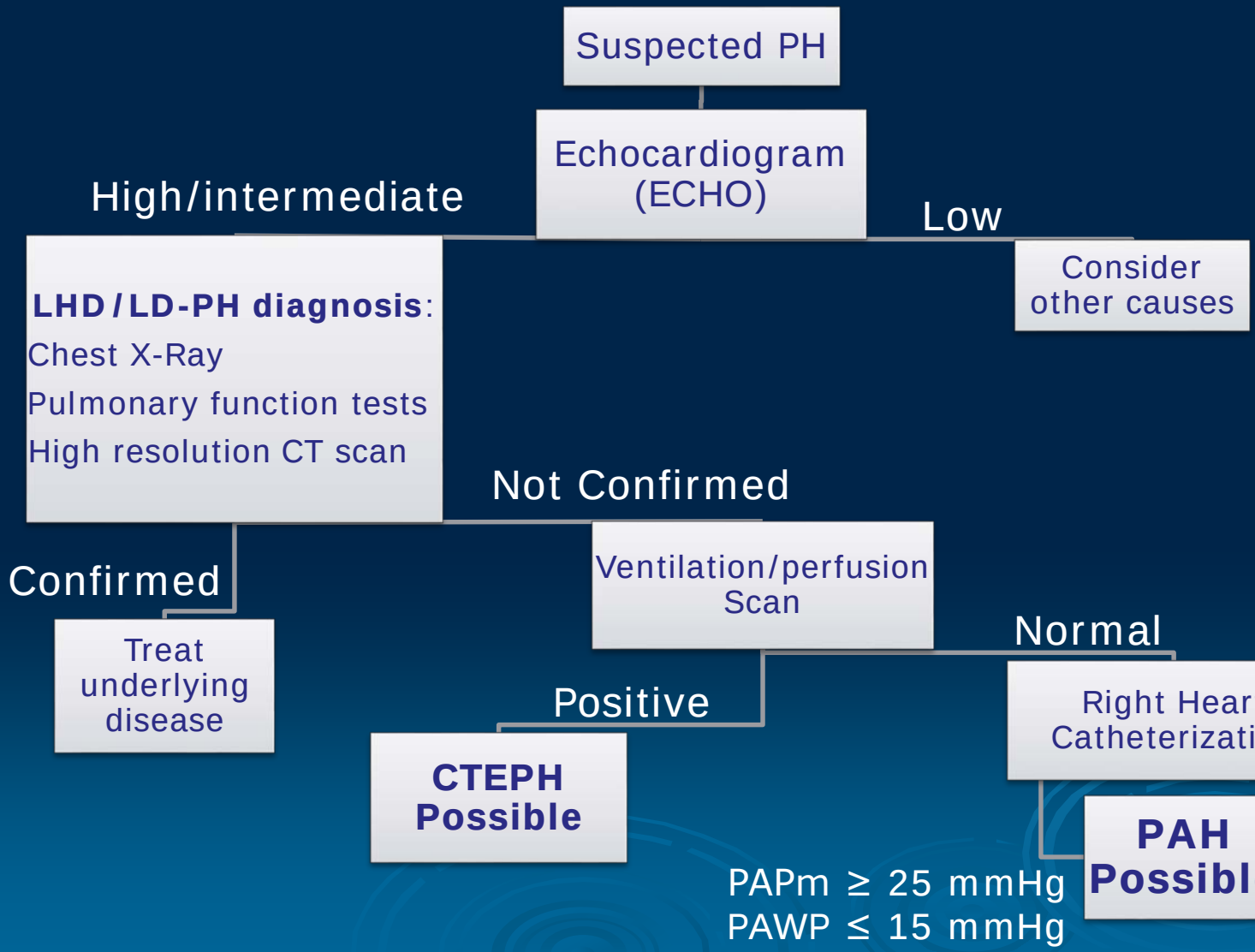
Toshner M, et al. *Br Med Bull.* 2010;94:21-32.; Humbert M, et al. *N Engl J Med*.2004;351:1425-1436.

Clinical Presentation

- Early Stages
  - Symptoms are non-specific, initially induced by exertion:
    - shortness of breath, fatigue, weakness, angina and syncope
- Advanced Stages
  - Abdominal distension, hepatomegaly, jugular venous pressure, edema
- Presentation of PH may be modified by diseases that cause or are associated with PH as well as other concurrent diseases

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

Diagnosis



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

Targeted Treatment?

WHO Group		
Group 1	Pulmonary arterial hypertension	**Yes**
Group 2	Pulmonary hypertension due to left sided heart disease	No
Group 3	Pulmonary hypertension associated with lung disease or chronic hypoxemia	No
Group 4	Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions	**Yes**
Group 5	Pulmonary hypertension with unclear and/or multifactorial mechanism	No

Dunlap, et al. *Am Fam Physician*. 2016;94(6):463-469

Management of Pulmonary Arterial Hypertension (Group 1)

Evaluation of Disease Severity

World Health Organization Functional Classification (WHO-FC)	
I	• No resulting limitations of physical activity • Ordinary physical activity does not cause undue fatigue or dyspnea, chest pain, or heart syncope
II	• Slight limitation of physical activity • Comfortable at rest • Ordinary physical activity results in undue fatigue or dyspnea, chest pain, or heart syncope
III	• Marked limitation of physical activity • Comfortable at rest • Less than ordinary physical activity causes undue fatigue or dyspnea, chest pain, or heart syncope
IV	• Inability to carry on any physical activity without symptoms • Dyspnea/fatigue may be present at rest • Physical activity increases discomfort

Adapted from: *Eur Heart J.* 2016;37:67-119

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

Evaluation of Disease Severity

Exercise capacity

- 6-minute walking test (6MWT)
- Cardiopulmonary exercise testing (CPET)

Imaging

- ECHO
- CMR

Hemodynamics

- Right atrial pressure (RAP)
- Cardiac Index (CI)
- Mixed venous oxygen saturation (SvO_2)

Biochemical Markers

- NT-proBNP

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

PAH Risk Assessment (Estimated 1-Year Mortality)

Prognosis Determinant	Low risk (<5%)	Intermediate risk (5-10%)	High risk (>10%)
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional	Repeated
WHO-FC	I, II	III	IV
6MWD	> 440 m	165 - 440 m	< 165 m
Cardiopulmonary exercise testing	Peak VO_2 >15 ml/min/kg (>65 % predicted) VE/VCO_2 slope <36	Peak VO_2 11–15 ml/min/kg (35-65 % predicted) VE/VCO_2 slope 36-44.9	Peak VO_2 <11 ml/min/kg (<35 % predicted) VE/VCO_2 slope ≥ 36
Imaging	RA area < 18 cm^2 No pericardial effusion	RA area 18 - 26 cm^2 No or minimal pericardial effusion	RA area > 26 cm^2 pericardial effusion
Hemodynamics	RAP <8 mmHg CI ≥ 2.5 L/min/m^2 SvO_2 > 65 %	RAP 8-14 mmHg CI ≥ 2.0 -2.4 L/min/m^2 SvO_2 60-65 %	RAP >14 mmHg CI <2.0 L/min/m^2 SvO_2 <60 %

Adapted from: *Eur Heart J.* 2016;37:67-119

PAH Treatment Goals

- Maintain patients with in WHO-FC I-II
- Preserve 6MWT distance

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

PAH Treatment

General Measures

- Fluid restrictions/ sodium restrictions
- Exercise training
- Influenza/ pneumococcal vaccination
- Contraceptive measures

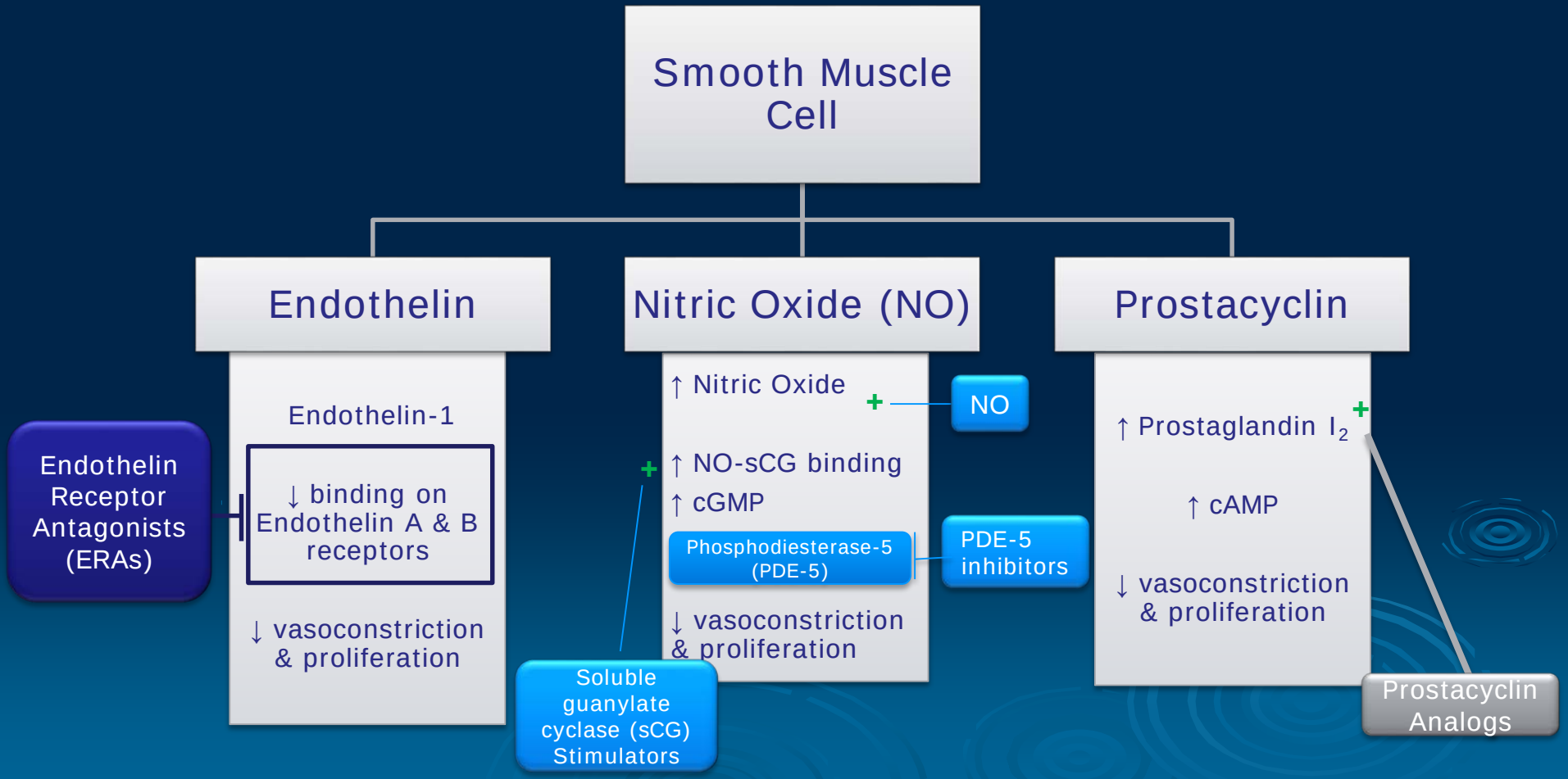
Supportive Therapies

- Diuretics
- Supplemental O_2
- Digoxin
- Anticoagulation
- Iron supplementation

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

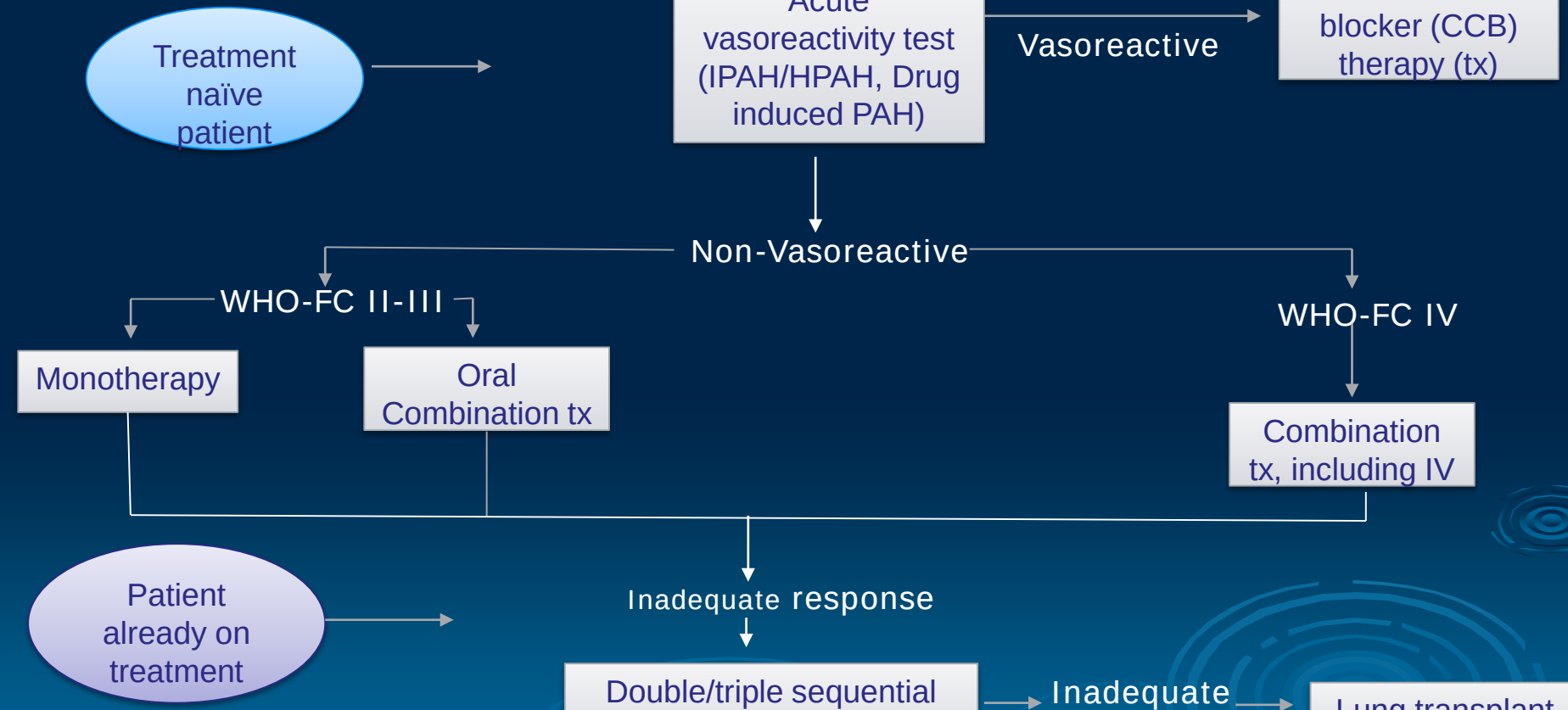
PAH Treatment

Specific Drug Therapy



Galiè N, et al. *Eur Heart J.* 2016;37:67-119.; Toshner M, et al. *Br Med Bull.* 2010;94:21-32.; Humbert M, et al. *N Engl J Med.*2004;351:1425-1436.

PAH Treatment Algorithm



Adapted from: *Eur Respir J* 2015; 46: 879–882.

PAH Treatment

Oral calcium channel blockers dosing:

- Nifedipine 120–240 mg total daily dose (TDD)
- Diltiazem 240–720 mg TDD
- Amlodipine 20 mg TDD

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

Management of Chronic Thromboembolic Pulmonary Hypertension (Group 4)

Etiology of CTEPH

- Major vessel thromboembolism causes pulmonary artery remodeling
- CTEPH has been reported with a cumulative incidence of 0.1–9.1% within the first 2 years after asymptomatic pulmonary embolisms (PE) event
- Other pulmonary artery obstructions can also lead to remodeling

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

CTEPH Treatment Goals

- Remove obstructions
- Restore blood circulation in the lungs

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

CTEPH Treatment

- Pulmonary endarterectomy (PEA) is the treatment of choice
- Anticoagulants, diuretics, and O_2 in cases of heart failure or hypoxemia
- Lifelong anticoagulation
- In symptomatic patients classified as having persistent/recurrent CTEPH after surgical treatment or with inoperable CTEPH, sCG stimulators are recommended

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

Pulmonary Arterial Hypertension Approved Drugs

Endothelin Receptor Antagonists (ERAs)

Medication	Ambrisentan	Bosentan	Macitentan
Route	Oral	Oral	Oral
Mechanism of Action	In PAH ↑ endothelin-1 (ET-1) concentrations, action of ET-1 at ET_A receptors causes vasoconstriction and cell proliferation. Action at ET_B receptors causes vasodilation, antiproliferation, and ET-1 clearance.		
	Blocks the action of ET-1 at ET_A receptor	Blocks the action of ET-1 at ET_A and ET_B receptor	
Warnings/Precautions	• Pregnancy category X (REMs Programs) • Not recommended in breast feeding • Liver toxicity • ↓ Hemoglobin • ↓ Sperm counts • Fluid retention		

Tracleer [prescribing information]. South San Francisco, CA: Actelion Pharmaceuticals US, Inc; 2017; Letairis [prescribing information]. Foster City, CA: Gilead Sciences, Inc; 2015; Opsumit [prescribing information]. South San Francisco, CA: Actelion Pharmaceuticals US, Inc; 2018

Letairis® (ambrisentan)

Indication	For treatment of pulmonary arterial hypertension (PAH) (WHO Group 1): • Improves exercise ability and delay clinical worsening • Used in combination with tadalafil to reduce the risks of disease progression and hospitalization for worsening PAH and to improve exercise ability	
Initial Dose	5 mg PO daily	
Adverse Drug Reactions (ADRs)	Common • Peripheral edema • Nasal congestion/sinusitis • Flushing	Severe • Embryo-fetal toxicity • Fluid retention • Decreased hemoglobin
Interactions	• Cyclosporine (Max dose 5 mg)	
Contraindications	• Pregnancy • Idiopathic pulmonary fibrosis	
Considerations	• Medication guide & REMs requirement • Tablets should not be split, crushed, or chewed	
FDA Approval	2007	

Letairis [prescribing information]. Foster City, CA: Gilead Sciences, Inc; 2015

Tracleer® (bosentan)

Indication	For treatment of PAH (WHO Group 1): • Improves exercise ability and decreases clinical worsening • In pediatric patients aged ≥3 yo with idiopathic or congenital PAH to improve pulmonary vascular resistance (PVR)	
Initial Dose	• ≤ 12 yo: 2 mg/kg PO BID • > 12 yo & > 40 kg: 62.5 mg PO BID x 4wks, then 125 mg PO BID • > 12 yo & < 40 kg: 62.5 mg PO BID	
Adverse Drug Reactions (ADRs)	Common • Respiratory tract infections • Pyrexia • Anemia	Severe • Embryo-fetal toxicity • Hepatotoxicity • Fluid retention
Interactions	• Cyclosporine (contraindicated) • Glyburide (contraindicated) • Hormonal contraceptives • CYP2C9 & CYP3A4 metabolites	
Contraindications	• Pregnancy • Use with Cyclosporine • Use with Glyburide • Hypersensitivity	
Considerations	• Medication guide & REMs requirement • Available as film coated tablets and tablet for oral suspension • Film coated tablets should not be split, crushed, or chewed • Missed doses should be taken ASAP unless the next dose is with in 6 hrs	
FDA Approval	2001	

Tracleer [prescribing information]. South San Francisco, CA: Actelion Pharmaceuticals US, Inc; 2017

Opsumit® (macitentan)

Indication	For treatment of pulmonary arterial hypertension (PAH) (WHO Group 1): • Reduces risk of disease progression and hospitalization	
Initial Dose	10 mg PO daily	
Adverse Drug Reactions (ADRs)	Common • Anemia • Nasopharyngitis/pharyngitis • Bronchitis • Headache • Influenza • Urinary tract infection	Severe • Embryo-fetal toxicity • Hepatotoxicity • Fluid retention • Decreased hemoglobin
Interactions	• Strong CYP3A4 inhibitors and inducers	
Contraindications	• Pregnancy	
Considerations	• Medication guide & REMs requirement • Tablets should not be split, crushed, or chewed	
FDA Approval	2013	

Opsumit [prescribing information]. South San Francisco, CA: Actelion Pharmaceuticals US, Inc; 2018

Soluble Guanylate Cyclase (sGC) Stimulators

Medication	Riociguat
Route	Oral
Mechanism of Action	• Stimulates sGC via a different binding site, independent of NO. • Sensitizes sGC to endogenous NO by stabilizing the NO-sGC binding. • Overall, it stimulates the NO-sGC-cGMP pathway and leads to increased generation of cGMP with subsequent vasodilation.
Warnings/Precautions	• Symptomatic hypotension • Bleeding • Pulmonary edema (in veno-occlusive disease)

Adempas [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc; 2013

Adempas® (riociguat)

Indication	**Treatment of adults with PAH (WHO Group 1):** • Improves exercise capacity, WHO functional class and to delays clinical worsening **Treatment of CTEPH (WHO Group 4) after surgical treatment or in inoperable CTEPH** • Improves exercise capacity and WHO functional class
Initial Dose	1 mg PO TID
Adverse Drug Reactions (ADRs)	Headache, dyspepsia/gastritis, dizziness, nausea, diarrhea, hypotension, vomiting, anemia, gastroesophageal reflux, constipation, embryo-fetal toxicity
Interactions	• Strong CYP and PGP/BCRP inhibitors: consider a starting dose of 0.5 mg PO TID • Antacids: separate administration by 1 hr
Contraindications	• Phosphodiesterase (PDE) inhibitors
Considerations	• REMs requirement & medication guide • Not recommended in breast feeding • If therapy is missed for ≥3 days, restart at lower dose
FDA Approval	2013

Adempas [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc; 2013

Phosphodiesterase-5 (PDE-5) Inhibitors

Medication	Sildenafil	Tadalafil
Route	Oral Intravenous (IV)	Oral
Mechanism of Action	• Inhibit PDE-5, preventing the breakdown of cGMP in smooth muscle cells • Increased levels of cGMP induces vascular relaxation and vasodilation	
Warnings/Precautions	• Hearing impairment • Vision impairment • Pulmonary edema	

Revatio [prescribing information]. New York, NY: Pfizer Labs; 2014; Adcirca [prescribing information]. Indianapolis, IN: Eli Lilly and Company; 2017

Revatio® (sildenafil)

Indication	For treatment of PAH (WHO Group 1): • Improves exercise ability and delays clinical worsening
Dosage	• Tablet/suspension: 5 mg-20 mg PO TID • Injection: 2.5 mg or 10 mg as IV bolus TID
Adverse Drug Reactions (ADRs)	Epistaxis, headache, dyspepsia, flushing, insomnia, erythema, dyspnea, rhinitis, priapism
Interactions	• Alpha blockers or amlodipine • PDE-5 inhibitors • CYP3A4 inhibitors (not recommended)
Contraindications	• Use with nitrates • Use with sCG stimulators • Hypersensitivity
Considerations	• Space doses 4-6 hours apart • Available as 20 mg tablets, 10 mg/mL suspension, and 10 mg/12.5 mL single use vial
FDA Approval	2005

Revatio [prescribing information]. New York, NY: Pfizer Labs; 2014

Adcirca® (tadalafil)

Indication	For treatment of PAH (WHO Group 1): • Improves exercise ability
Dosage	40 mg PO daily
Adverse Drug Reactions (ADRs)	Headache, flushing, myalgia, erythema, rhinitis, priapism
Interactions	• Alpha blockers or amlodipine • Alcohol • PDE-5 inhibitors • CYP3A4 inhibitors (not recommended) • Use with ritonavir requires dose adjustments
Contraindications	• Use with nitrates • Use with sCG stimulators • Hypersensitivity
Considerations	• Available as 20 mg tablets • Administered with out regard to meals • Dividing dose over the course of the day is not recommended
FDA Approval	2009

Adcirca [prescribing information]. Indianapolis, IN: Eli Lilly and Company; 2017

Prostacyclin Analogs

Medication	Eporostenol	Illoprost	Treprostinil	Selexipag
Route	IV continuous infusion	Inhalation	• Oral • Inhalation • IV continuous infusion • SC continuous infusion	Oral
Mechanism of Action	Analogs of endogenous prostacyclin (PGI_2): • Promote direct vasodilation of pulmonary vasculature • Inhibit platelet aggregation			
Warnings/Precautions	• Risk of rebound pulmonary hypertension, doses should not be discontinued or changed abruptly • Increased risk of bleeding • Vasodilation reactions			

Flolan [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; 2018;
Veletri [prescribing information]. South San Francisco, CA: Actelion Pharmaceuticals US, Inc; 2012;
Ventavis [prescribing information]. South San Francisco, CA: Actelion Pharmaceuticals US, Inc; 2013;
Remodulin [prescribing information]. Research Triangle Park, NC: United Therapeutics Corp; 2018;
Tyvaso [prescribing information]. Research Triangle Park, NC: United Therapeutics Corp; 2016;
Orenitram [prescribing information]. Research Triangle Park, NC: United Therapeutics Corp; 2016;
Uptravi [prescribing information]. South San Francisco, CA: Actelion Pharmaceuticals US, Inc; 2017

Flolan® (epoprostenol)

Indication	For treatment of pulmonary arterial hypertension (PAH) (WHO Group 1): • Improves exercise capacity	
Initial Dose	• Initiate intravenous infusion through a central venous catheter at 2 ng/kg/min • Change dose in 1-to 2-ng/kg/min increments at intervals of at least 15 minutes based on clinical response	
Adverse Drug Reactions (ADRs)	Common • Dizziness • Jaw pain • Headache • Musculoskeletal pain • Nausea/vomiting	Severe • Catheter occlusions • Injection site infections • Pump malfunctions
Interactions	• Anticoagulants • Antihypertensive	
Contraindications	• Heart failure with reduced ejection fraction • Hypersensitivity	
Considerations	• Diluent used (sterile diluent vs pH 12 sterile diluent) affects stability • Reconstituted solutions may be used immediately; otherwise must be refrigerated • Requires protection from light • Requires infusion pump	
FDA Approval	1995	

Flolan [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; 2018

Veletri® (epoprostenol)

Indication	For treatment of pulmonary arterial hypertension (PAH) (WHO Group 1): • Improves exercise capacity	
Initial Dose	• Initiate intravenous infusion through a central venous catheter at 2 ng/kg/min • Increments at intervals sufficient to allow assessment of clinical • response; intervals should be at least 15 minutes	
Adverse Drug Reactions (ADRs)	Common • Dizziness • Jaw pain • Headache • Flu-like symptoms • Nausea/vomiting	Severe • Catheter occlusions • Injection site infections • Pump malfunctions
Interactions	• Anticoagulants • Antihypertensive	
Contraindications	• Heart failure due to severe left ventricular systolic dysfunction • Pulmonary edema • Hypersensitivity	
Considerations	• Must be used at temperatures > 77° F – 104° F • Infusion rate calculation • Requires protection from light • Requires infusion pump	
FDA Approval	2008	

Veletri [prescribing information]. South San Francisco, CA: Actelion Pharmaceuticals US, Inc; 2012

Ventavis® (iloprost)

Indication	For treatment of pulmonary arterial hypertension (PAH) (WHO Group 1): • Improves composite endpoint consisting of exercise tolerance, NYHA Class, and lack of deterioration	
Initial Dose	• Starting dose: 2.5 mcg • Maintenance dose: 5 mcg • 6 to 9 doses (inhalations) daily	
Adverse Drug Reactions (ADRs)	Common • Vasodilation (flushing) • Headache • Insomnia • Nausea/vomiting • Hypotension • Flu syndrome	Severe • Alkaline phosphatase increased • Hemoptysis • Pneumonia • Pulmonary edema
Interactions	• Anticoagulants • Antihypertensive	
Contraindications	• None	
Considerations	• Requires use of I-neb® AAD® System • Minimum of 2 hours between doses during waking hours	
FDA Approval	2004	

Ventavis [prescribing information]. South San Francisco, CA: Actelion Pharmaceuticals US, Inc; 2013

Remodulin® (treprostinil)

Indication	For treatment of pulmonary arterial hypertension (PAH) (WHO Group 1): • Diminishes symptoms associated with exercise • Reduces rate of clinical deterioration, in patients who require transition from Flolan	
Initial Dose	New to therapy: • 1.25 ng/kg/min; increase based on clinical response (increments of 1.25 ng/kg/min/wk x4 wks, then 2.5 ng/kg/min/wk) Transition from Flolan: • Increase dose gradually as the Flolan dose is decreased	
Adverse Drug Reactions (ADRs)	Common • SC infusion site pain & reaction • Headache • Jaw pain • Vasodilatation • Edema • Hypotension	Severe • Hemoptysis • Pneumonia • GI hemorrhage • Sepsis
Interactions	• Anticoagulants • Antihypertensive • CYP2C8 inhibitors/inducers	
Contraindications	• None	
Considerations	• Indicated for SC or IV use only as a continuous infusion • Use central catheter for IV route	
FDA Approval	2002	

Remodulin [prescribing information]. Research Triangle Park, NC: United Therapeutics Corp; 2018

Tyvaso® (treprostinil)

Indication	For treatment of pulmonary arterial hypertension (PAH) (WHO Group 1): • Improves exercise ability	
Initial Dose	• Initial dosage: 3 breaths (18 mcg) per treatment session. If 3 breaths are not tolerated, reduce to 1 or 2 breaths • Titrate to target maintenance dosage of 9 breaths or 54 mcg per treatment session as tolerated	
Adverse Drug Reactions (ADRs)	Common • Cough • Headache • Throat irritation • Diarrhea • Edema • Hypotension	Severe • Hemoptysis • Pneumonia
Interactions	• Anticoagulants • Antihypertensive • CYP2C8 inhibitors/inducers	
Contraindications	• None	
Considerations	• Use only with the Tyvaso® Inhalation System • Administer undiluted, as supplied • Separate sessions approximately four hours apart, during waking hours • Sterile solution for oral inhalation available in 2.9 mL ampule containing 1.74 mg treprostinil (0.6 mg per mL)	
FDA Approval	2009	

Tyvaso [prescribing information]. Research Triangle Park, NC: United Therapeutics Corp; 2016

Orenitram® (treprostinil)

Indication	For treatment of pulmonary arterial hypertension (PAH) (WHO Group 1): • Improves exercise capacity	
Initial Dose	• Starting dose: 0.25 mg PO BID or 0.125 mg PO TID • Titrate by 0.25 mg or 0.5 mg BID or 0.125 mg TID, not more than every 3 to 4 days as tolerated • Maximum dose is determined by tolerability	
Adverse Drug Reactions (ADRs)	Common • Headache • Nausea • Diarrhea	Severe • Hemoptysis • Syncope
Interactions	• Anticoagulants • Antihypertensive • CYP2C8 inhibitors/inducers	
Contraindications	• Severe hepatic impairment (Child Pugh Class C)	
Considerations	• Give with food • Swallow tablet whole; use only intact tablets • Available as extended-release tablets: 0.125 mg, 0.25 mg, 1 mg & 2.5 mg • Should not be taken with alcohol • Never discontinue abruptly	
FDA Approval	2013	

Orenitram [prescribing information]. Research Triangle Park, NC: United Therapeutics Corp; 2016

Uptravi® (selexipag)

Indication	For treatment of pulmonary arterial hypertension (PAH) (WHO Group 1): • Delays disease progression and reduces the risk of hospitalization	
Initial Dose	• Starting dose: 200 mcg PO BID • Increase the dose by 200 mcg BID at weekly intervals to the highest tolerated dose up to 1600 mcg BID • Maintenance dose is determined by tolerability	
Adverse Drug Reactions (ADRs)	Common • Headache • Diarrhea • Jaw pain • Nausea/vomiting • Myalgia • Pain in extremity • Flushing	Severe • Pulmonary edema
Interactions	• CYP2C8 inhibitors/inducers	
Contraindications	• Concomitant use with strong CYP2C8 inhibitors	
Considerations	• Tablet strengths: 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1000 mcg, 1200 mcg, 1400 mcg, 1600 mcg • Avoid use in severe hepatic impairment • Not recommended in breastfeeding	
FDA Approval	2015	

Uptravi [prescribing information]. South San Francisco, CA: Actelion Pharmaceuticals US, Inc; 2017

Pipeline – Agents Under Investigation

Agents Under Investigation

BPS-314d-MR	Phase 3 study; BPS-314d-MR + inhaled treprostinil (Tyvaso) in PAH • Beraprost sodium 314d modified release tablets • Prostacyclin analog
Bardoxolone Methyl	Phase 3 study, bardoxolone methyl + standard of care in patients with WHO Group 1 connective tissue disease PAH • Bardoxolone methyl, activator of NRF2 → decrease in oxidative damage
Ubenimex	Phase 2 study; treatment of PAH • Ubenimex, an oral inhibitor of LTA4H, the enzyme responsible for the formation of the pro-inflammatory mediator LTB4
CXA-10	Phase 2 study; CXA-10 + background therapy in PAH • CXA-10, nitrated fatty acid compound with multiple mechanisms of action
ABI-009	Phase 1 study • ABI-009, mTOR inhibitor, for PAH

https://www.clinicaltrials.gov/ct2/show/NCT01908699?term=Beraprost+added-on+to+Tyvaso&rank=1;
https://reatapharma.com/our-science/pipeline/pivotal-programs/ctd-pah-bardoxolone/;
https://clinicaltrials.gov/ct2/show/record/NCT02664558?term=ubenimex+pulmonary&rank=1;
https://www.complexarx.com/pipeline;
https://clinicaltrials.gov/ct2/show/NCT02587325

POP QUIZ !

Test Question:

True or False:

- The World Health Organization (WHO) classification for pulmonary hypertension is delineated as follows:
  - **Group 1** – Pulmonary Arterial Hypertension
  - **Group 2** – Pulmonary hypertension due to left sided heart disease (LHD)
  - **Group 3** – Pulmonary hypertension due to lung disease or hypoxia (or both)
  - **Group 4** – Pulmonary hypertension with unclear multifactorial mechanisms
  - **Group 5** – Chronic thromboembolic pulmonary hypertension

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  - Phosphodiesterase-5 inhibitors (PDE-5i) and soluble guanylate cyclase (sGC) stimulators are recommended for use as combination therapy for the treatment of pulmonary arterial hypertension (PAH).

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Test Questions:

- True or False:
  - The endothelin receptor antagonists ambrisentan, bosentan, and macitentan all have respective risk evaluation and mitigation strategy (REMS) programs due to the risk of causing embryo-fetal toxicity.

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Treatment of Pulmonary Hypertension

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