Pathophysiolgic Based Management of Pulmonary Hypertension

Vermont Cardiac Network
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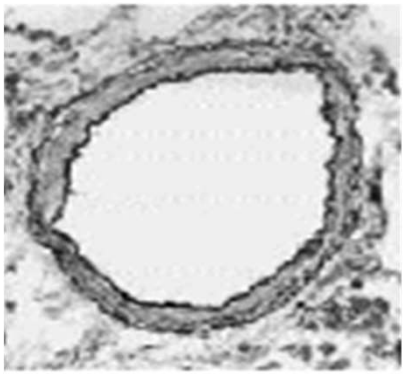
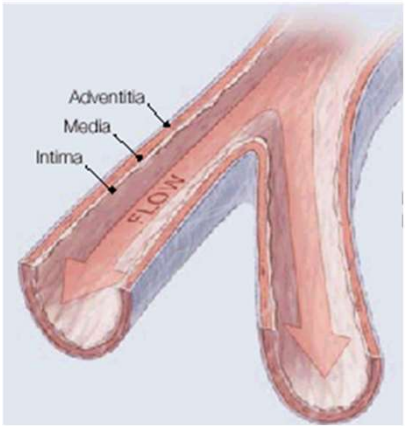
Learning Objectives

- Differentiate types of pulmonary hypertension according to the World Health Organization Classification System
- Understand the abnormalities in pulmonary vascular physiology seen in patients with pulmonary arterial hypertension
- Understand the pathologic changes in cell signaling pathways in the pulmonary arteries of patients with pulmonary arterial hypertension
- Relate treatment strategies for patients with pulmonary hypertension to pathophysiology

The Normal Pulmonary Circulation

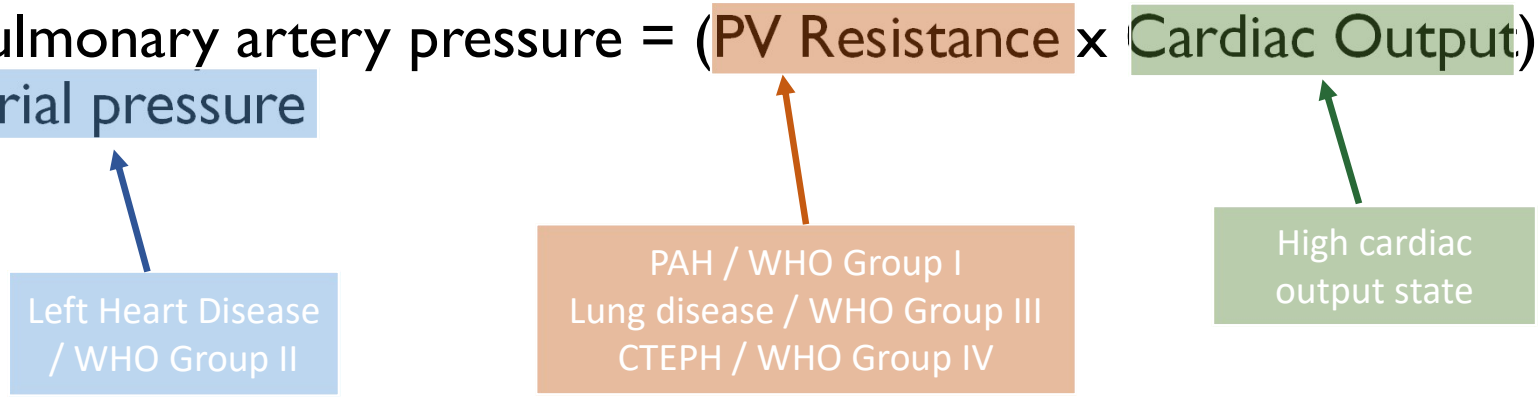
- Low resistance circulation
- Accommodating circulation
  - Only organ that receives 100% of the cardiac output
  - Pulmonary pressure increases very little as flow increases
  - Regulation of flow based V/Q matching, not on metabolism





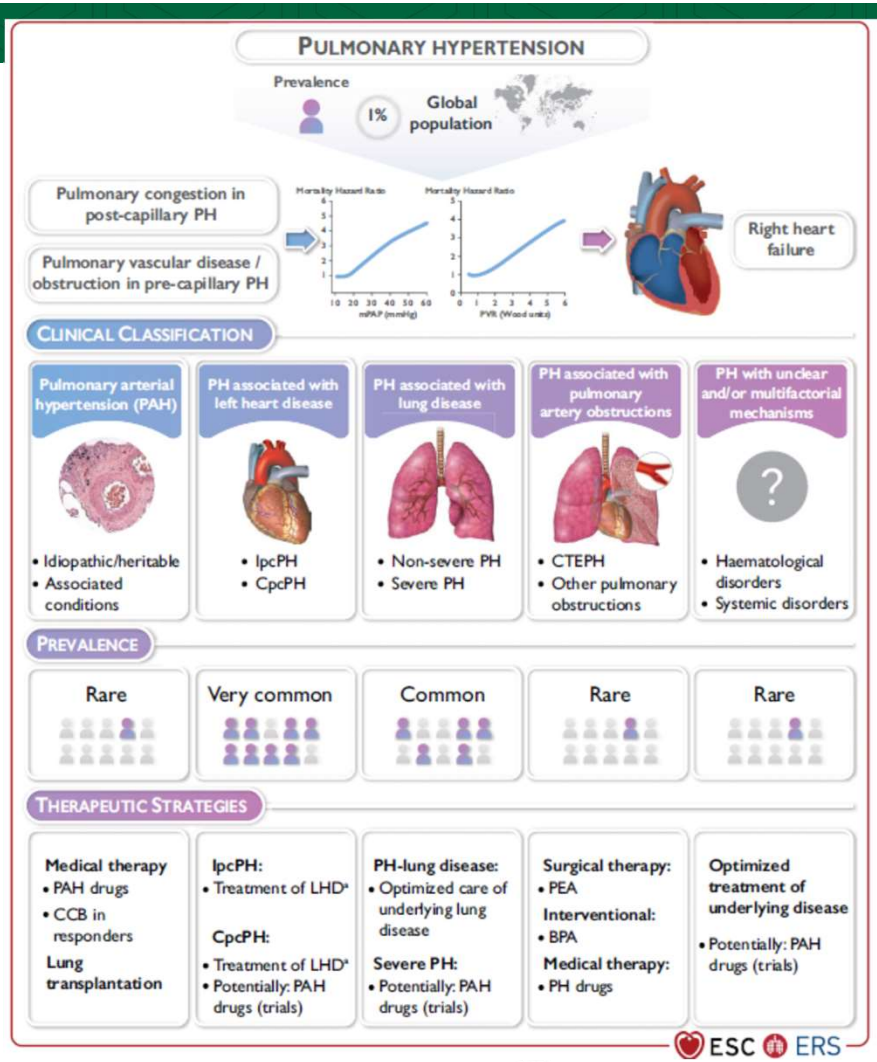
Classification of Pulmonary Hypertension

- What determines pulmonary artery pressure?
- Δ Pressure = Resistance x Flow
- Mean pulmonary pressure – left atrial pressure = PV Resistance x Cardiac Output
- Mean pulmonary artery pressure = (PV Resistance x Cardiac Output) + left atrial pressure



World Health organization (WHO) classification

- I: Pulmonary Arterial Hypertension (PAH)
- II: PH associated with Left Heart Disease
- III: PH associated with Lung Diseases and/or Hypoxia
- IV: PH associated with Pulmonary Artery Obstructions
- V: PH with Unclear and/or Multifactorial Mechanisms



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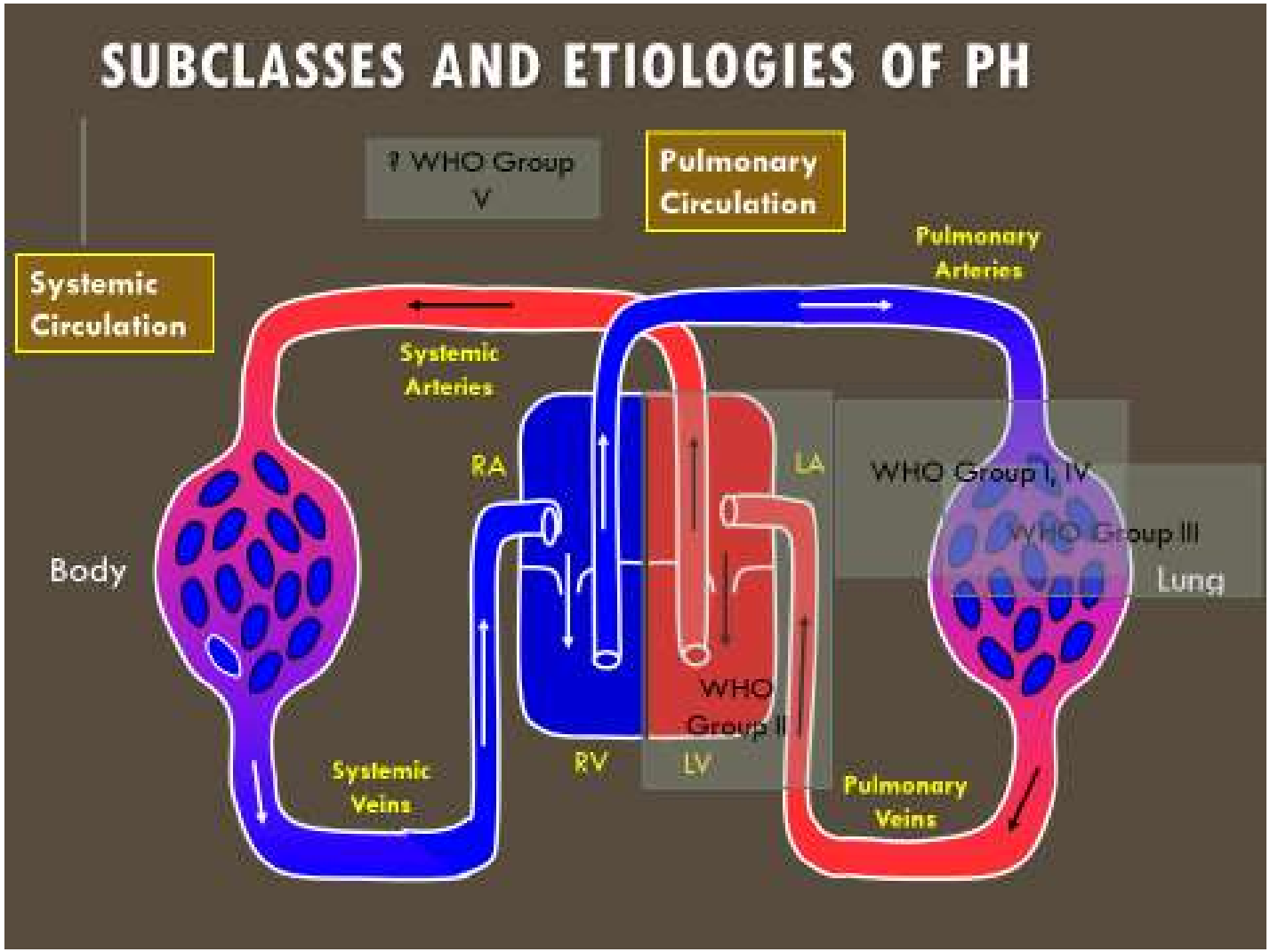

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Update Definitions of Pulmonary Hypertension

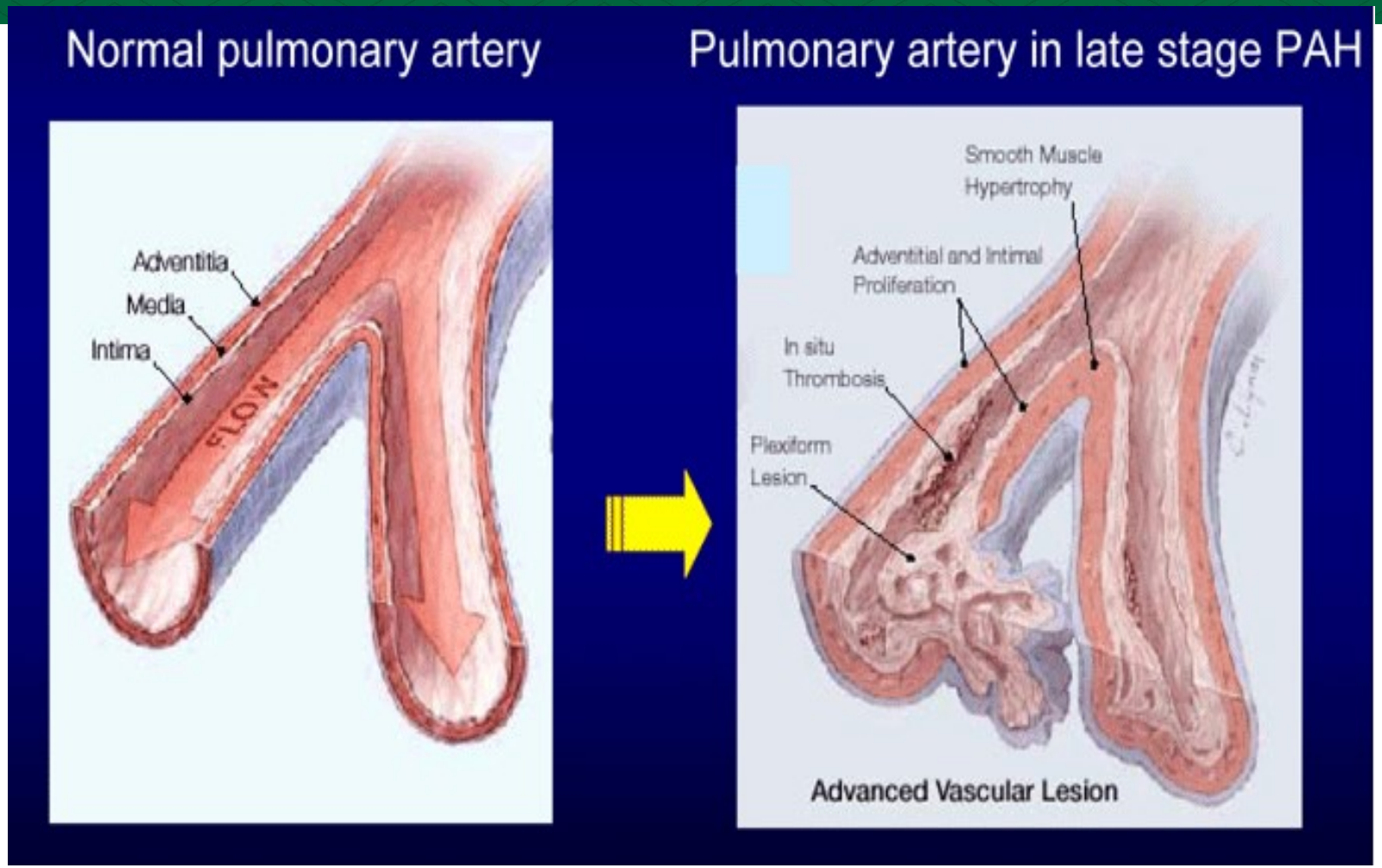
- Definition has evolved over the years
- Most recent: 2022 ESC/ERS Definitions:

Pulmonary Hypertension
- Mean PAP ≥ 20 mmHg at rest

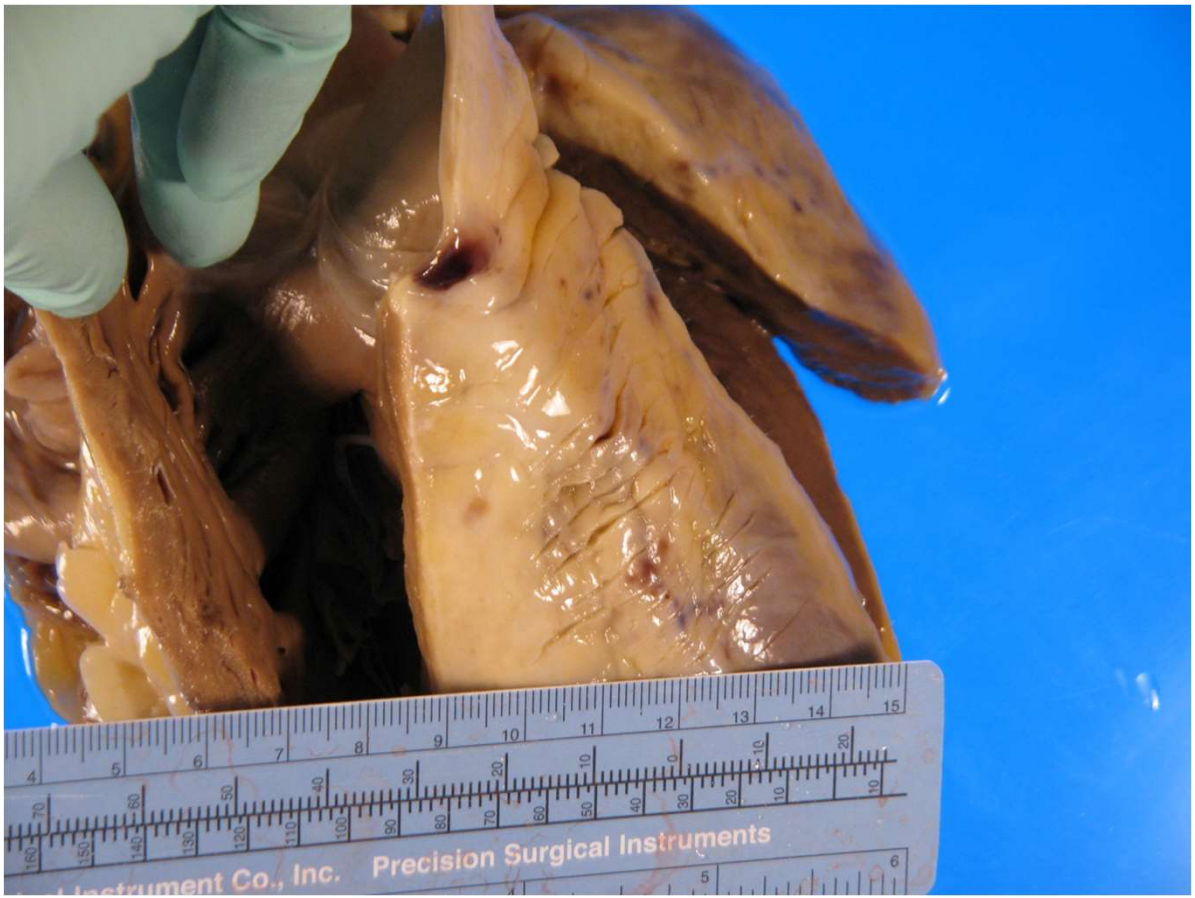
Pre-Capillary PH
- Mean PAP ≥ 20 mmHg at rest
- *PVR > 2 WU (160 dyn*s/cm^5)*
- *PAWP ≤ 15 mmHg (PAH)*

Combined Pre and Post Capillary PH (CpcPH)
- Mean PAP ≥ 20 mmHg at rest
- *PVR ≤ 2 WU (160 dyn*s/cm^5)*
- *PAWP > 15 mmHg (PAH)*

Isolated Post-Capillary PH (IpcPH)
- Mean PAP ≥ 20 mmHg at rest
- *PVR ≤ 2 WU (160 dyn*s/cm^5)*
- *PAWP > 15 mmHg (PAH)*

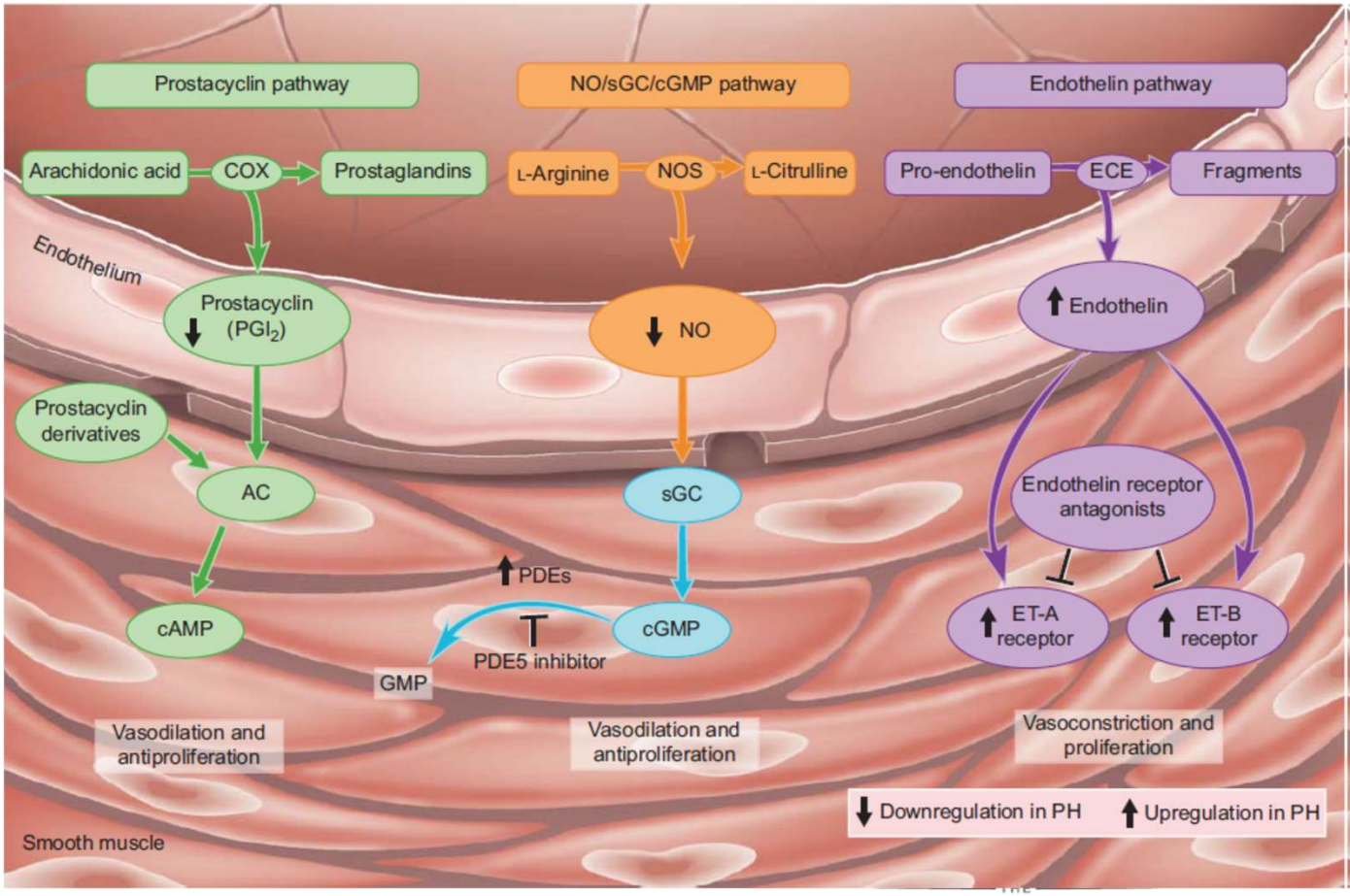

Normal pulmonary artery
Pulmonary artery in late stage PAH
Adventitia
Media
Intima
FLOW
Smooth Muscle Hypertrophy
Adventitial and Intimal Proliferation
In situ Thrombosis
Plexiform Lesion
Advanced Vascular Lesion

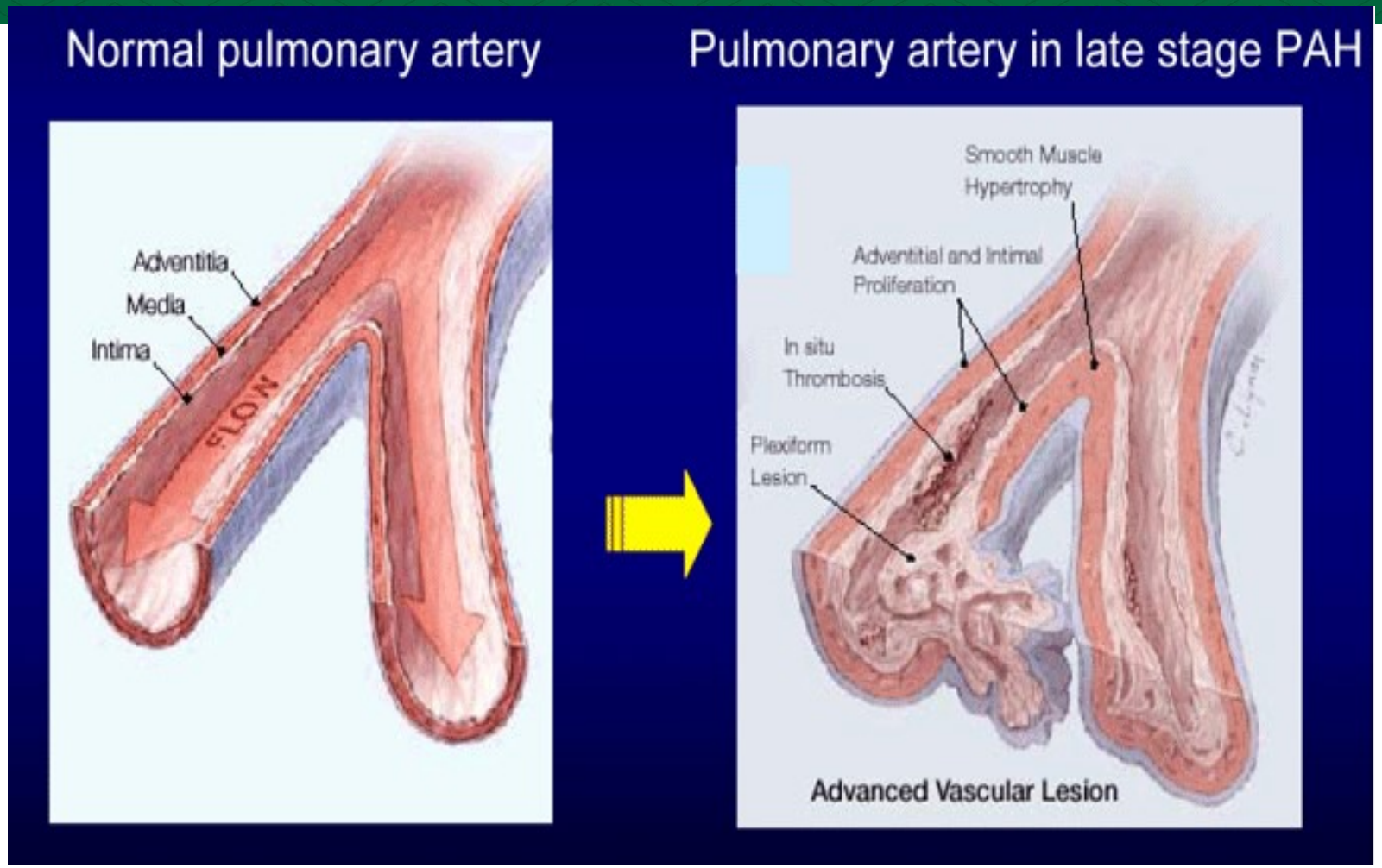
Right ventricular hypertrophy / failure



Abnormal Signaling Pathways in PAH

- Patients with PAH exhibit:
  - Lower levels of prostacyclin
  - Lower endogenous NO
  - Increased endothelin

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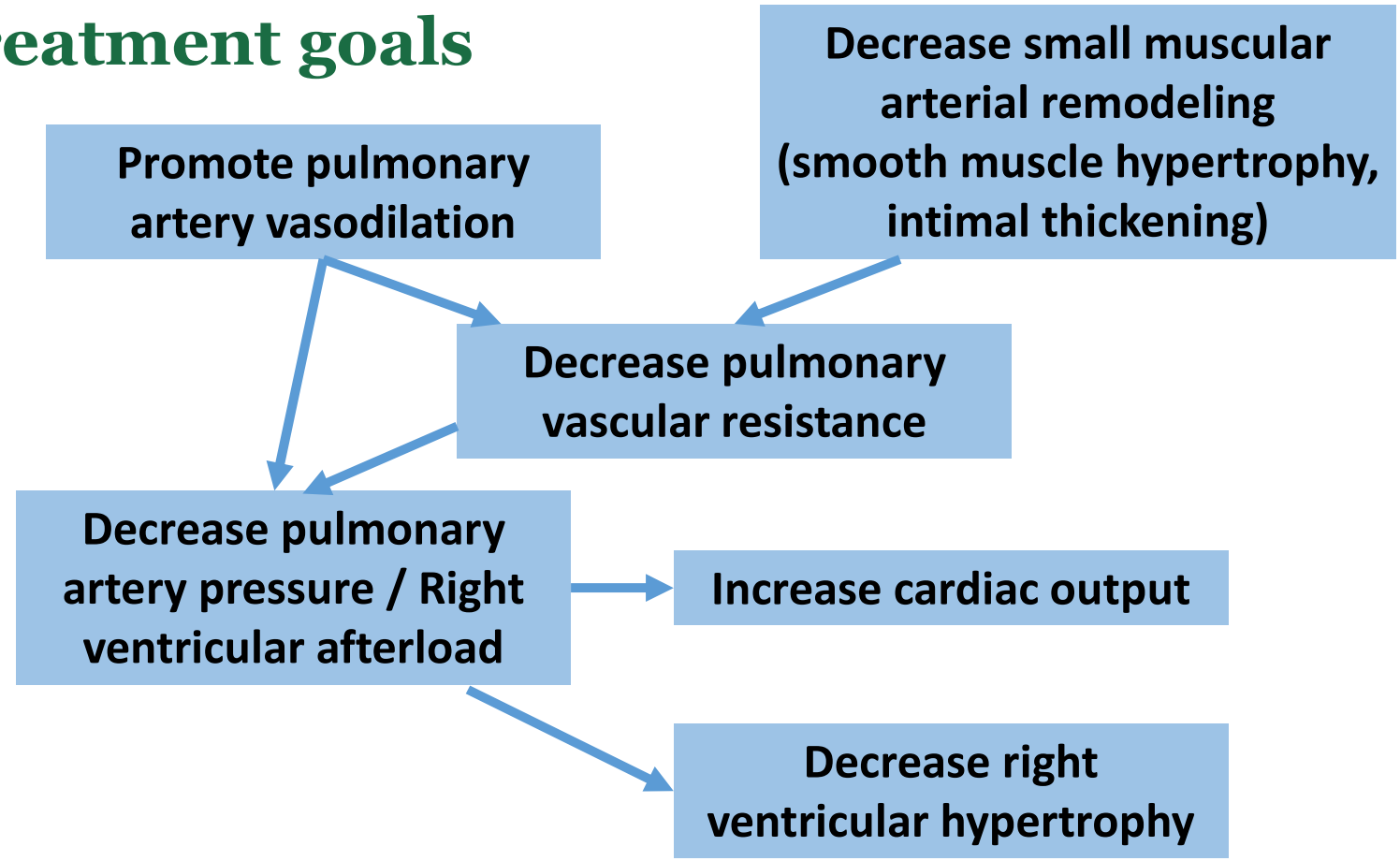
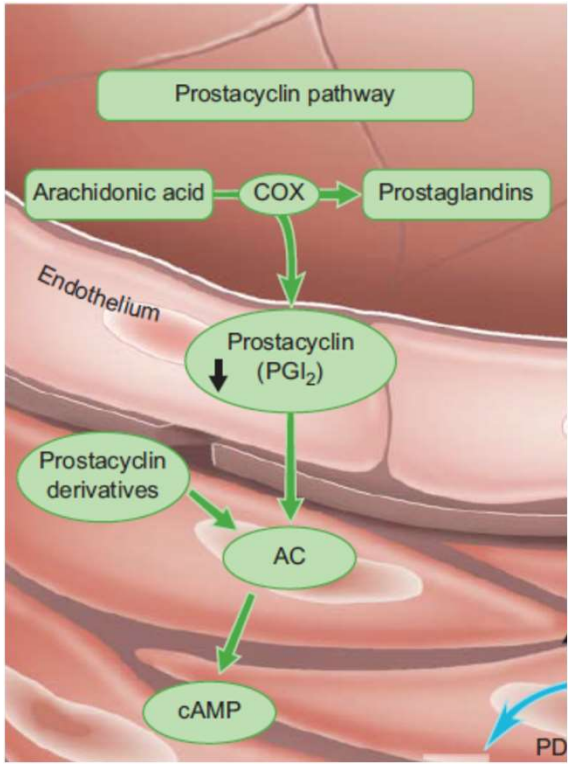
Treatment goals



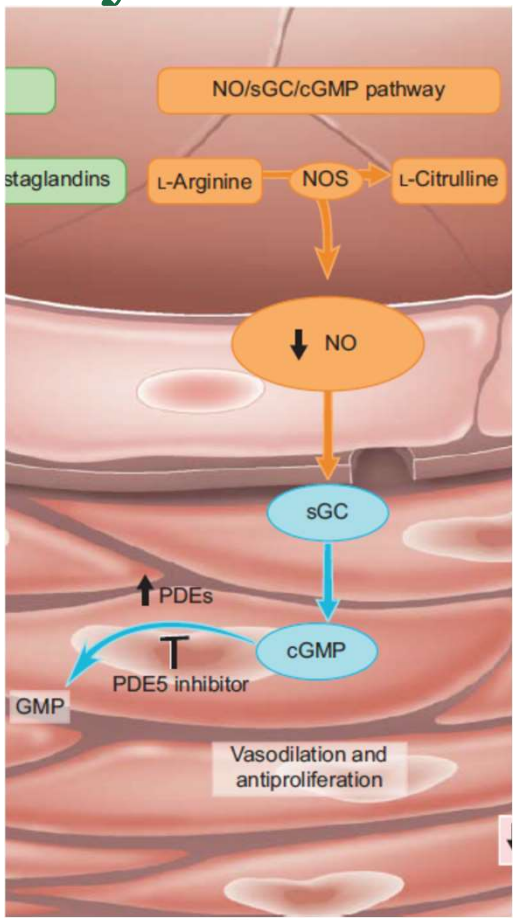
Targeting the prostacyclin pathway

- First treatment for PAH (Epoprostenol)
- Parental therapy remains SOC for advanced disease
- Now includes 5 agents
- Multiple routes of administration:
  - IV
  - Subcutaneous
  - Oral
  - Inhaled



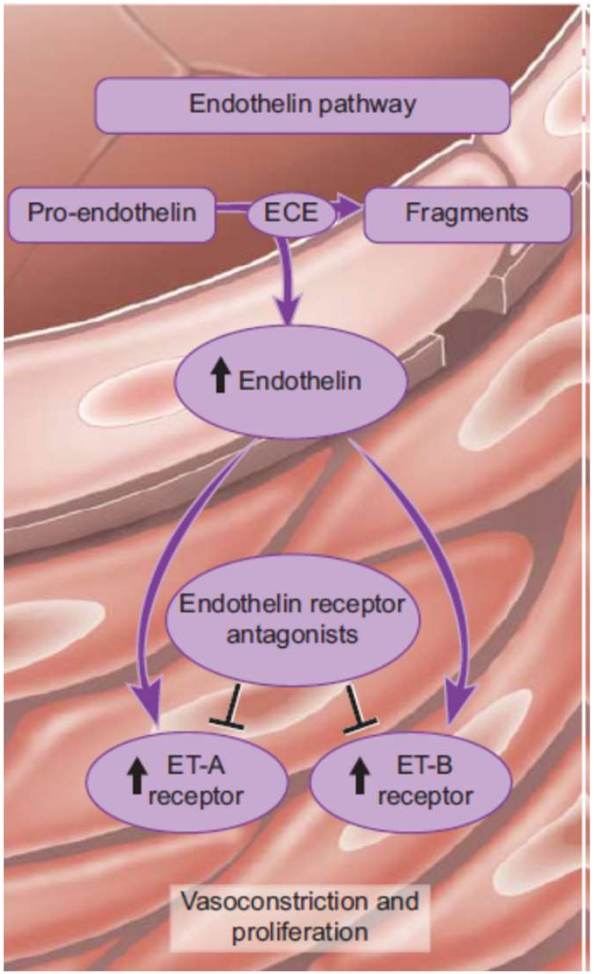
Targeting the nitric oxide/ cGMP pathway

- Goal is to stimulate production of cGMP
  - Stimulate soluble guanylate cyclase
- *OR* inhibit breakdown to GMP
  - Inhibit phosphodiesterase 5
- Three agents
  - All oral route of admin
- Typically started in combination with endothelin receptor antagonists

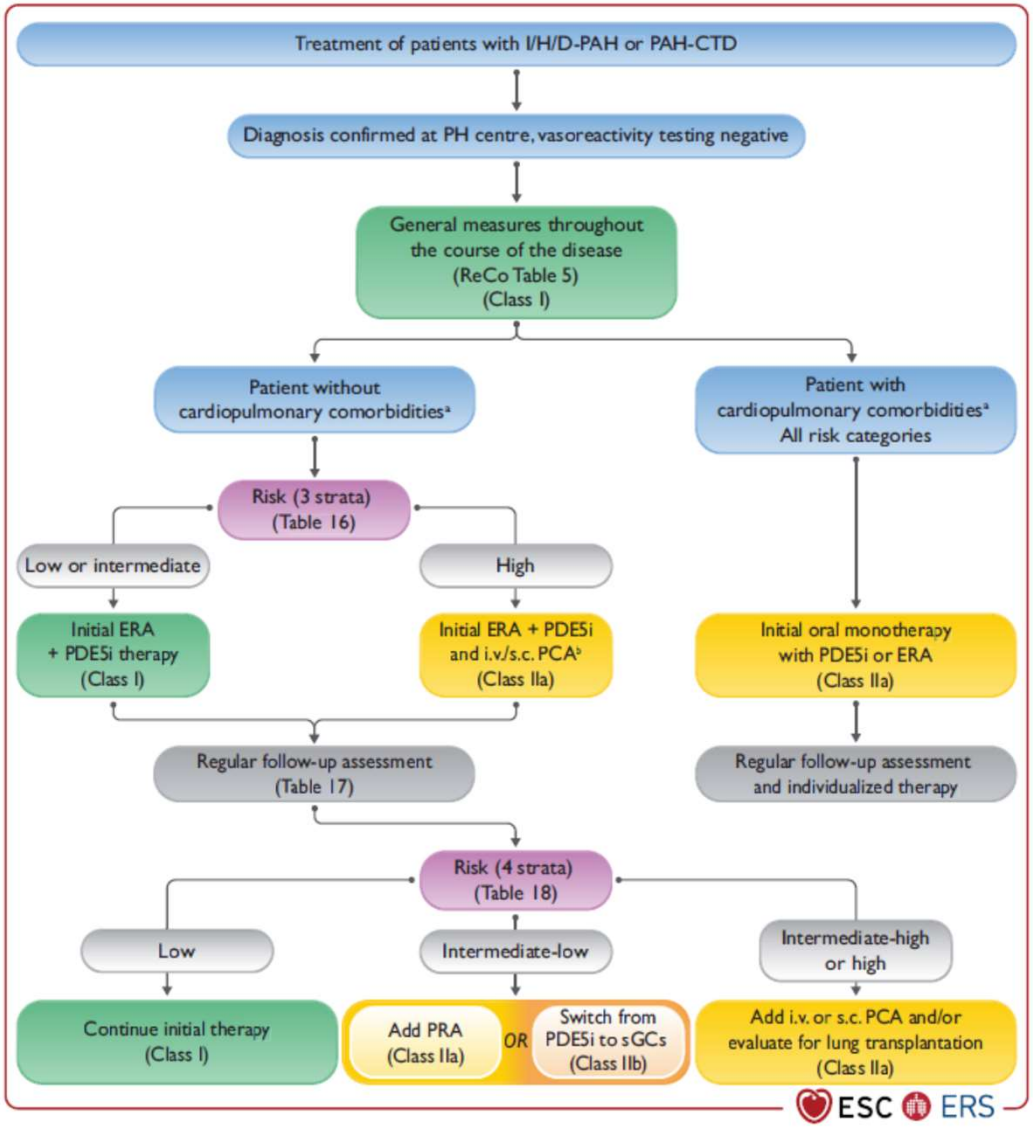


Targeting the endothelin pathway

- In contrast to the other two pathways, goal is to inhibit / downregulate endothelin pathway
- Three agents available
  - All oral route of admin
- Typically started in combination with endothelin receptor antagonists



Choosing Treatment Options



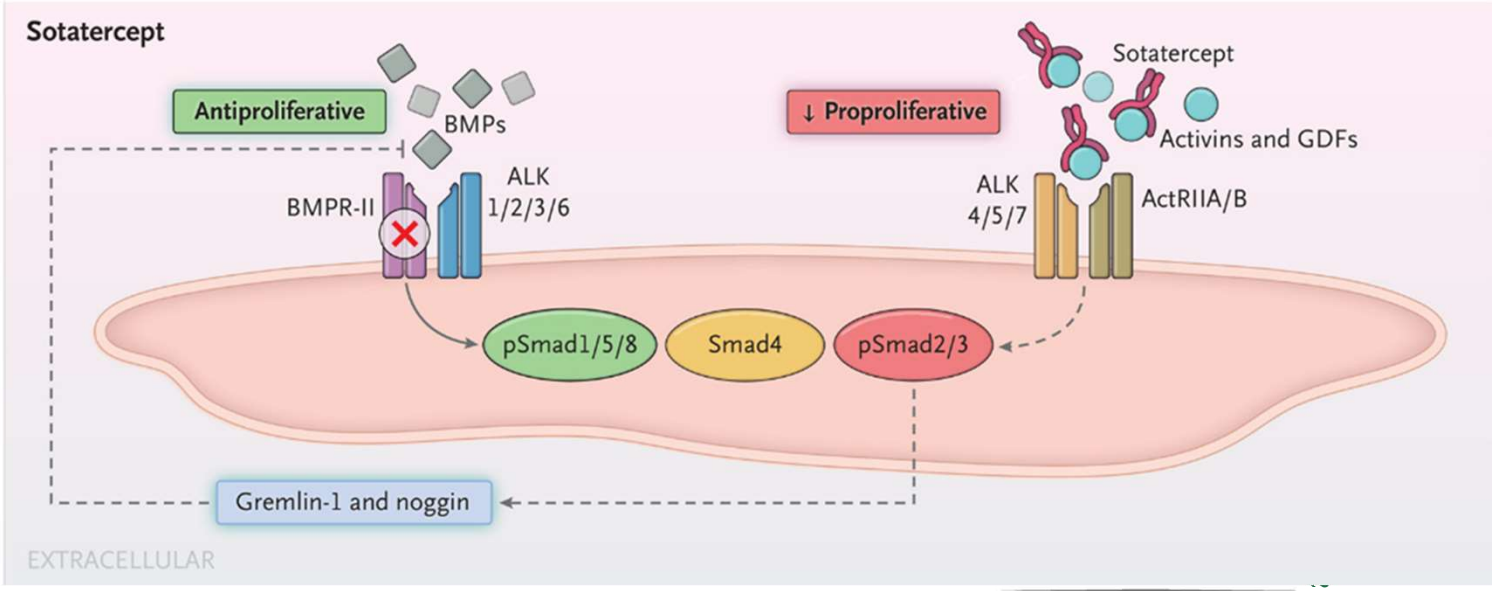
Determining treatment strategies

- Guided by risk assessment
  - Several assessment tools: REVEAL, ESC/ERS, COMPERA
  - Assess patients as Low, Intermediate, High Risk
  - Range from very extensive / detailed / invasive to simple non-invasive
  - Newest non-invasive breaks risk into 4 categories

Determinants of prognosis	Low risk	Intermediate–low risk	Intermediate–high risk	High risk
Points assigned	1	2	3	4
WHO-FC	I or II[a]	-	III	IV
6MWD, m	>440	320–440	165–319	<165
BNP or NT-proBNP,[a] ng/L	<50 <300	50–199 300–649	200–800 650–1100	>800 >1100

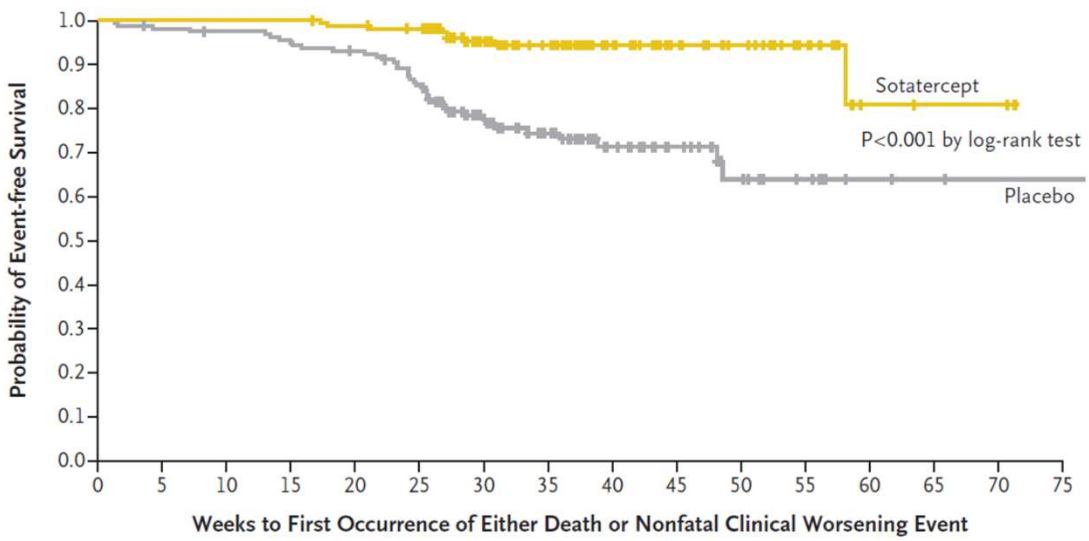
Genetic Mutations in PAH

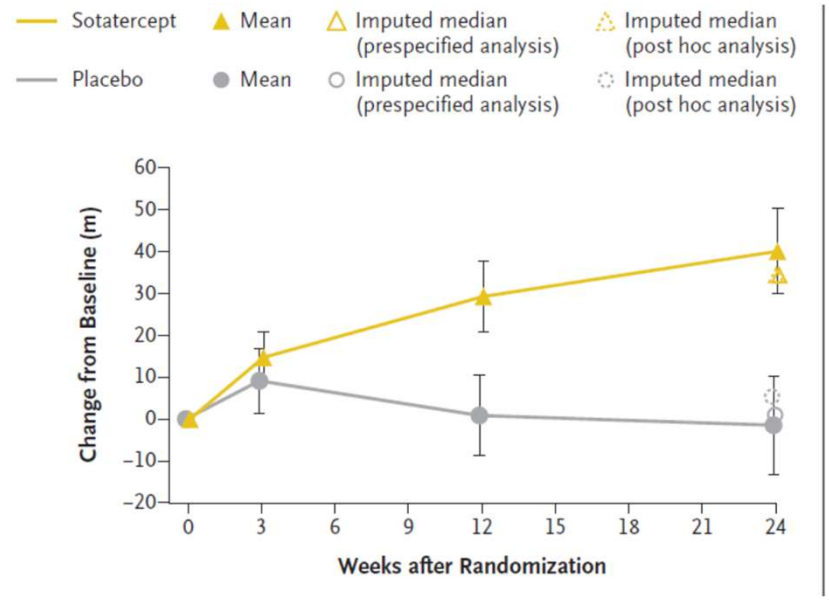
- Most commonly identified are mutations in the BMPR-II receptor
  - Significant role in metabolism and vascular proliferation
- Multiple identified
- Observed in heritable and idiopathic PAH
- Many are subjects of active research



ORIGINAL ARTICLE

Phase 3 Trial of Sotatercept for Treatment of Pulmonary Arterial Hypertension



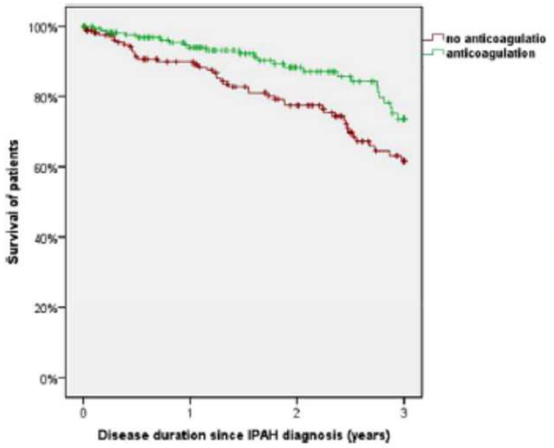


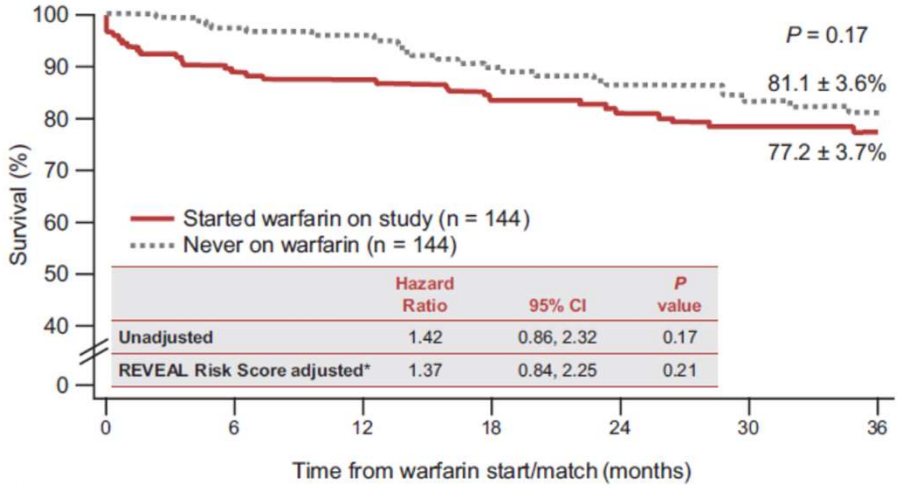
Anticoagulation in PAH?

- Physiologic basis established early after recognition of "PPH"
- 8 major trials
- All data observational, mostly retrospective
- 6 pos trials, 2 neg

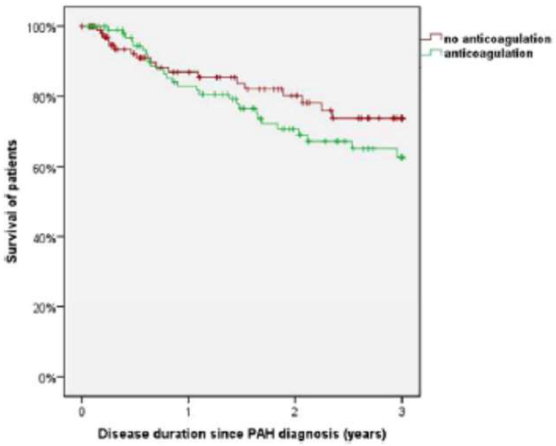
COMPERA REVEAL

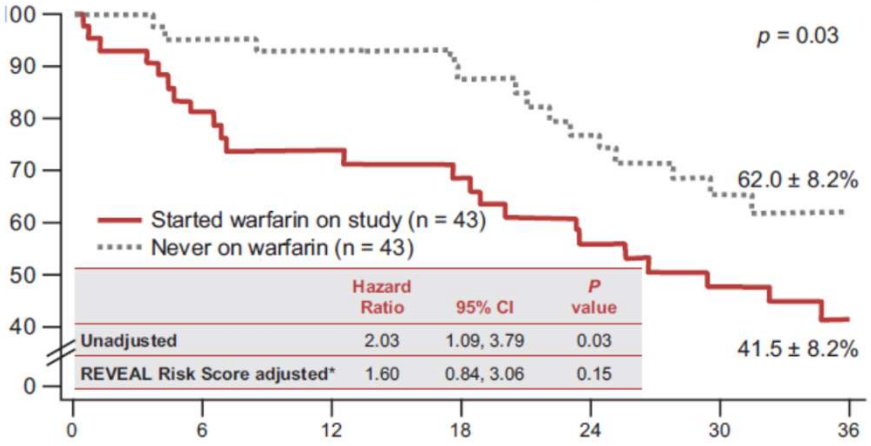
IPAH





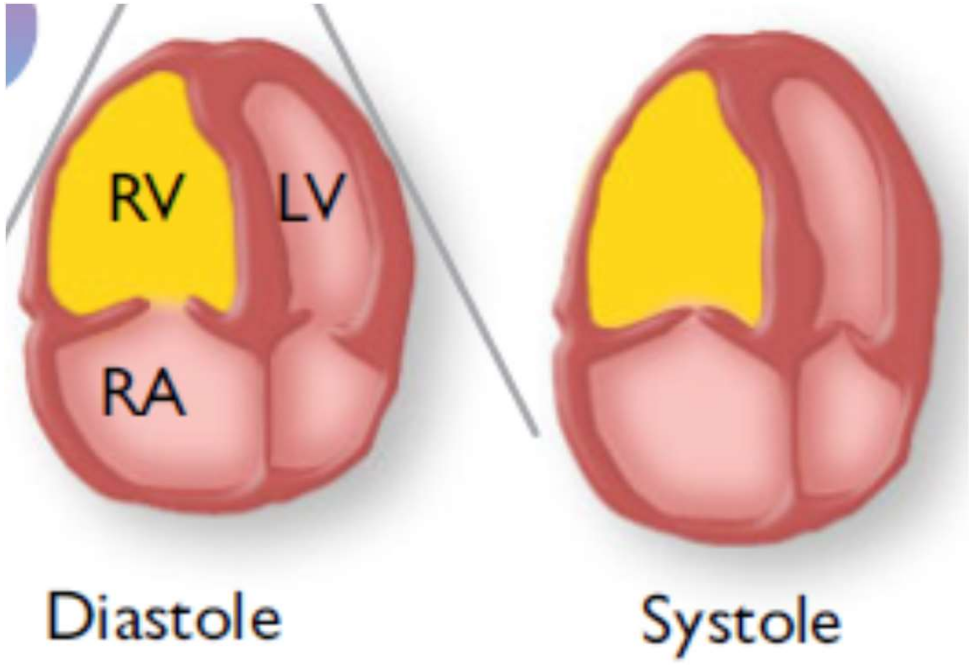
SSC-PAH



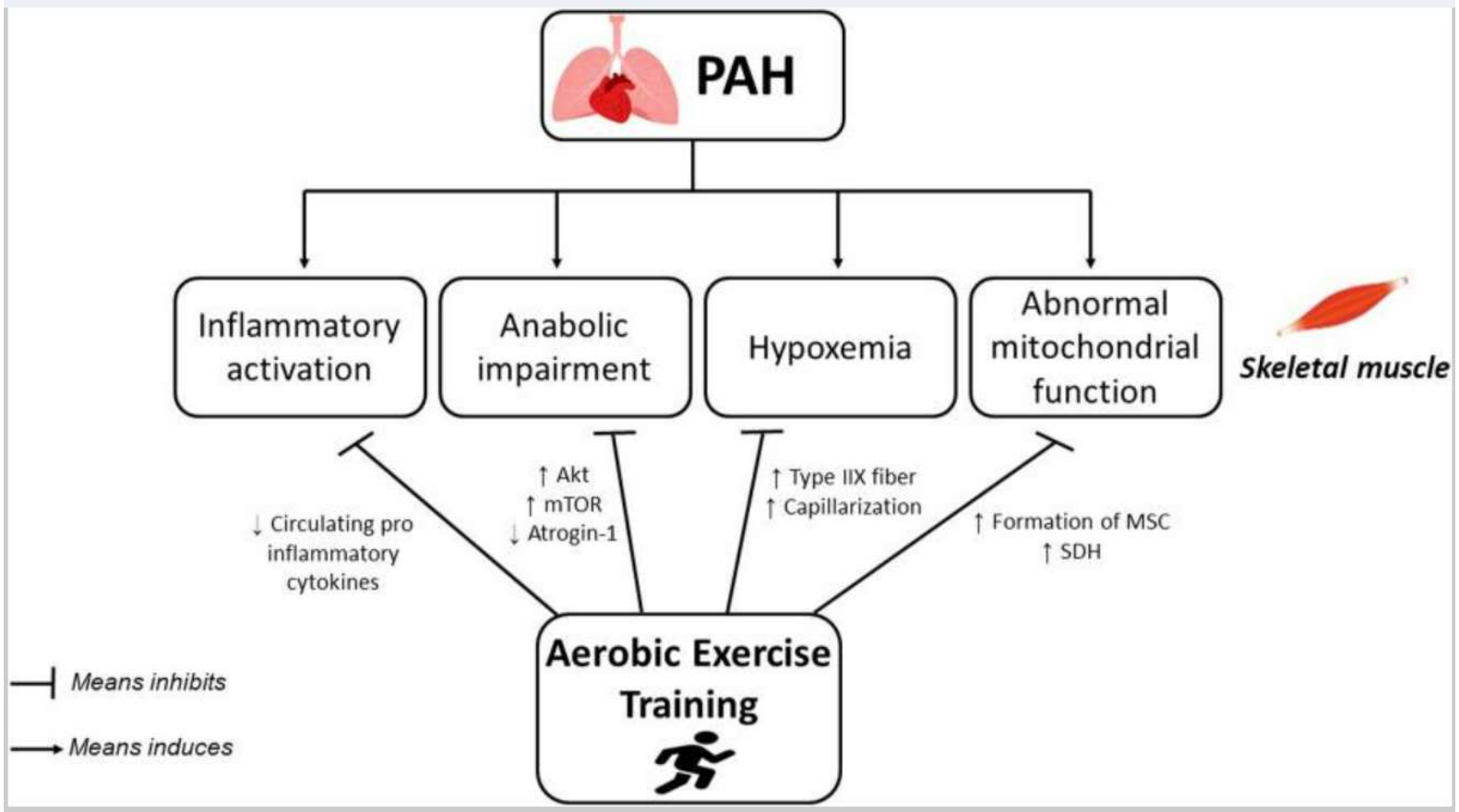


Fluid balance in PAH

- Significantly elevated RV preload in severe PAH
- Exacerbates RV dilation
  - Septal bowing
  - LV underfilling
  - Decreased septal contribution to LVEF
  - Increased RV wall tension- increased RV ischemia
  - Renal Venous congestion / dysfunction



Extra-pulmonary changes in PAH



Exercise in PAH

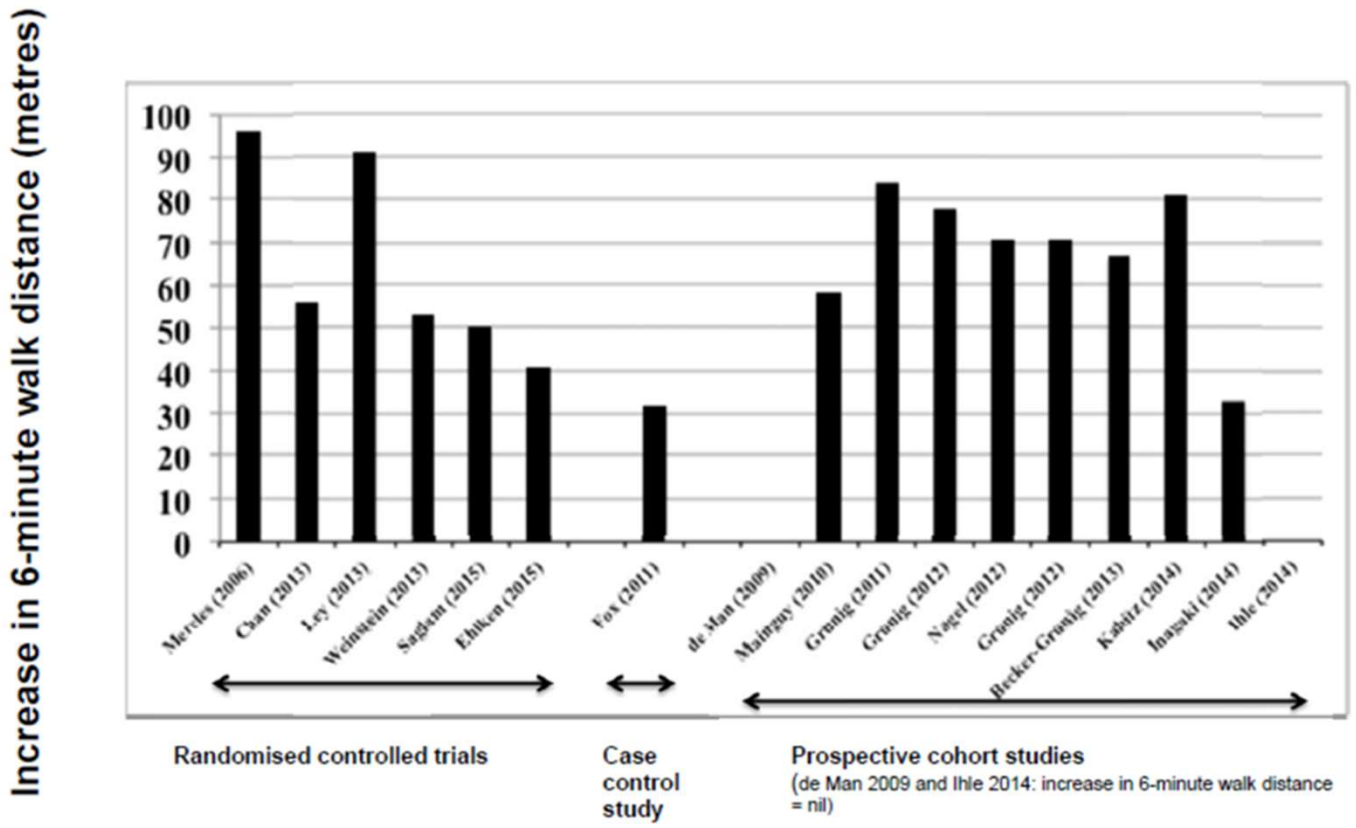
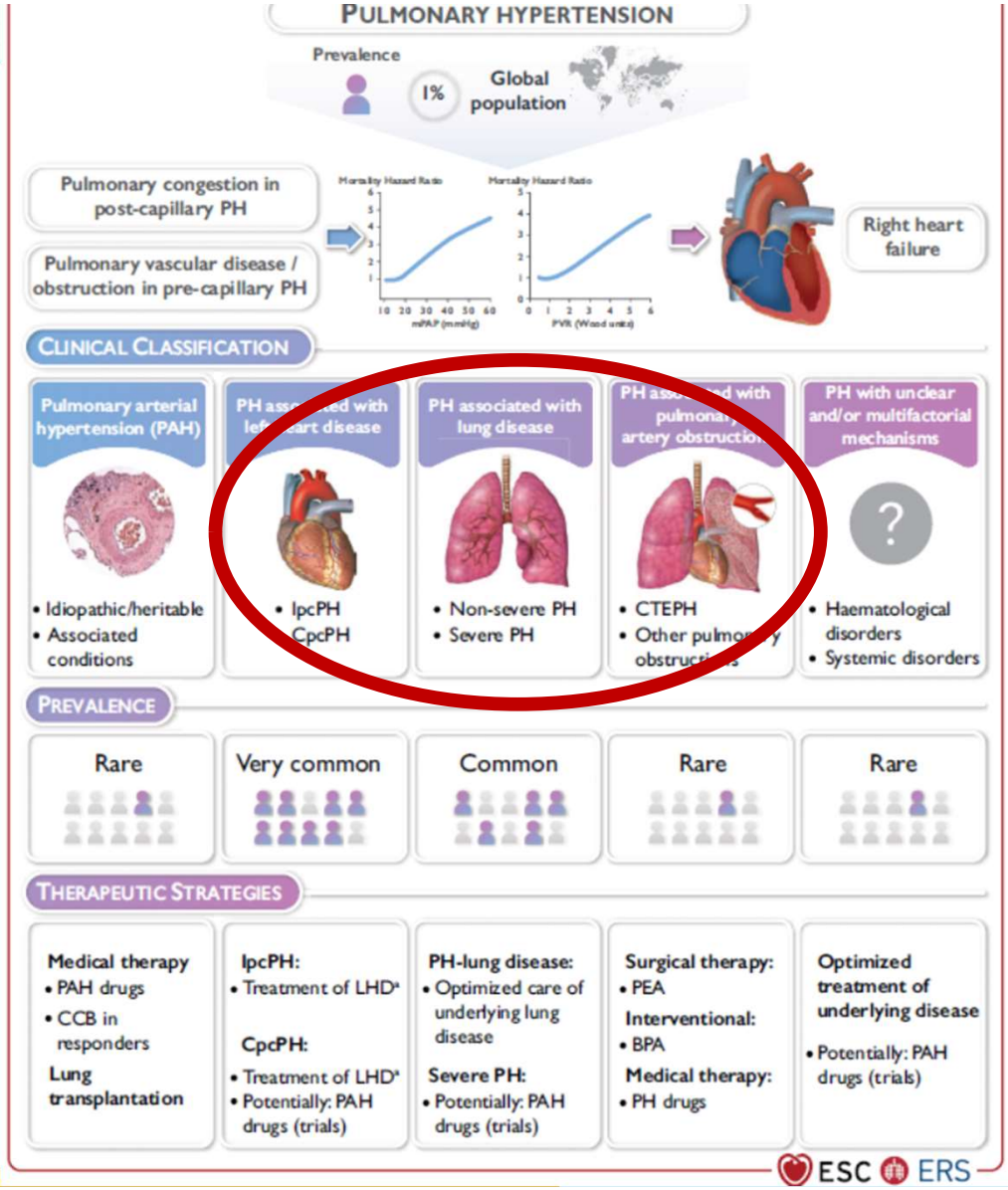


Figure 1: Trials of exercise intervention showing magnitude of increase in 6-minute walk test distance in metres

How do manage patients with other groups of PH?



PH associated with Left Heart Disease

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- Δ Pressure = Resistance x Flow
- Mean pulmonary pressure – left atrial pressure = PV Resistance x Cardiac Output
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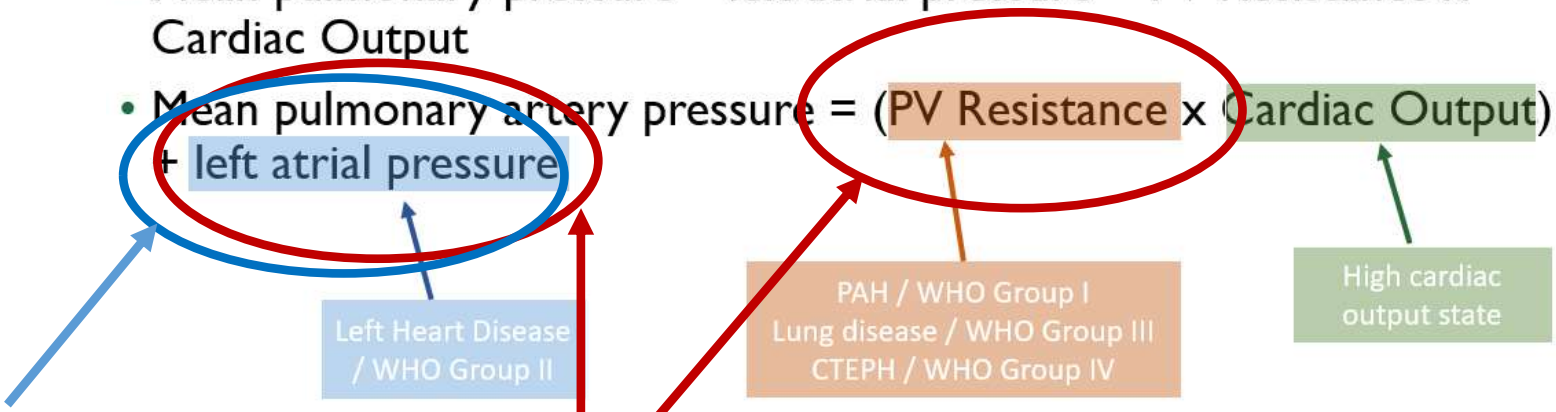


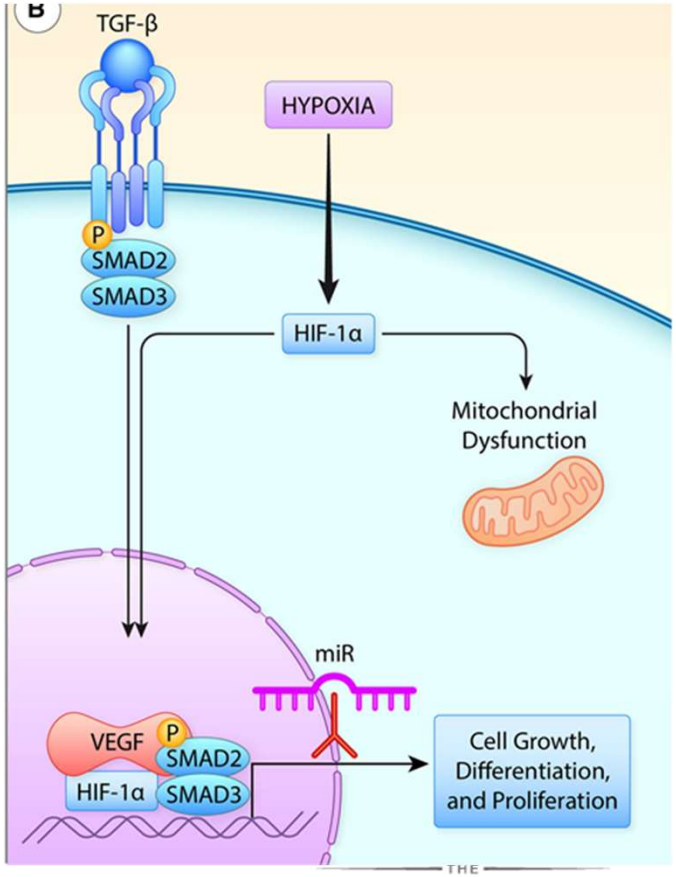
- Isolated Post Capillary PH
- Combined Pre and Post Capillary PH

PH associated with Left Heart Disease

- Reduce LVEDP / LAP
- Diuretics
- Address valvular dysfunction, ischemia
- GDMT for HFrEF
- Optimize HFpEF
- ? Address PVR / pre-capillary component ?
  - Refer to clinical trials
  - Select cases in PH centers

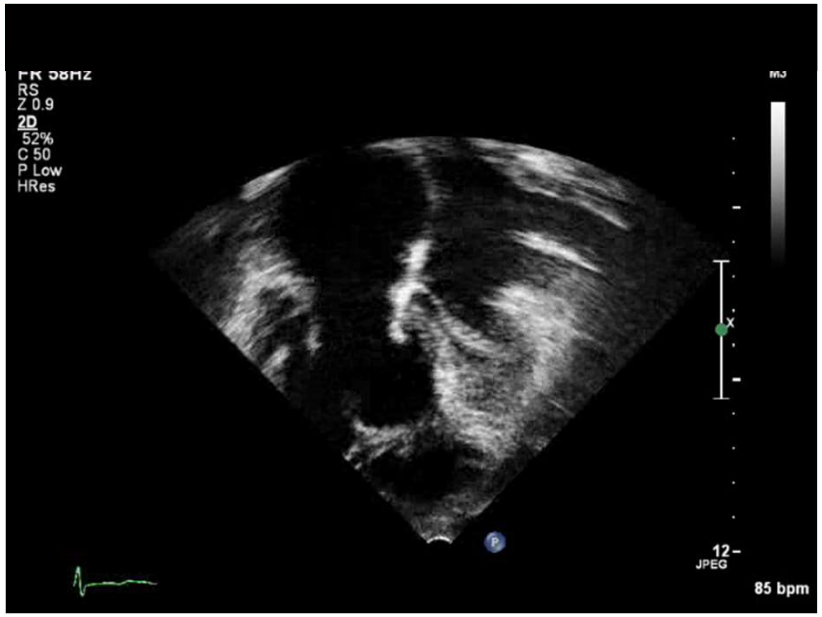
PH associated with Lung Diseases and/or hypoxia

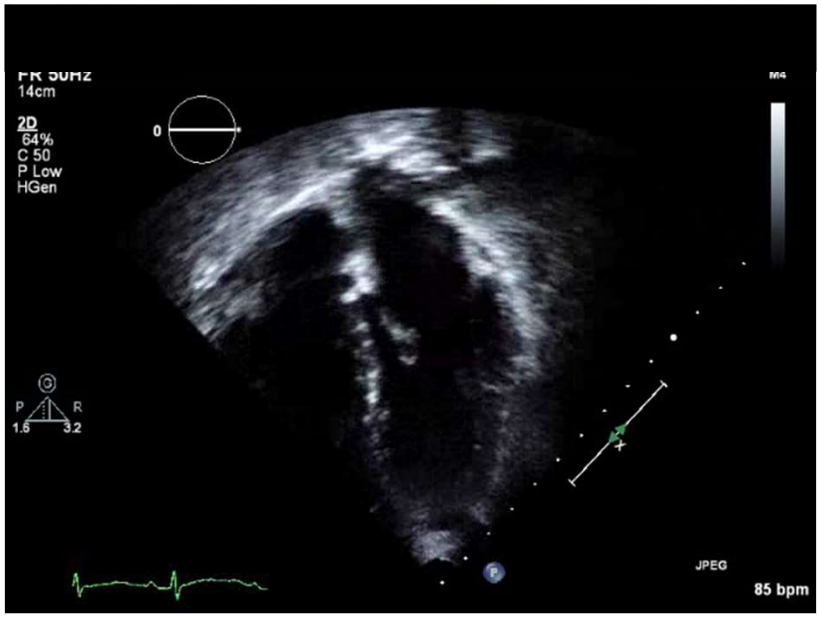
- Most common and severe in patients with combined fibrosis and emphysema (CPFE)
- Mechanisms:
  - Hypoxic and Hypercapnic induced vasocontriction
  - Vascular destruction with progressive parenchymal destruction
  - Vascular remodeling, similar to some findings in PAH
    - Smooth muscle hypertrophy
    - Intimal and advential thickening



Address Hypoxia:

- Patient with previously undx Interstitial Lung Disease
- Repeat echo 8 months post initiating supplemental O_2 and optimization of ILD



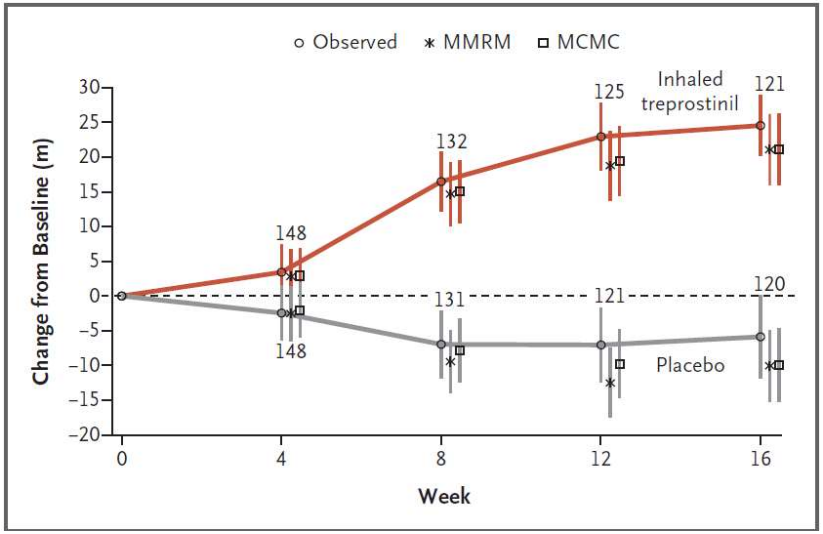


PH associated with Lung Diseases and/or hypoxia

- Treat hypoxia
- Treat sleep disordered breathing
- Smoking cessation
- Optimize lung disease management
- ? Pulmonary vasodilator treatment
  - Mixed data with PDE5i
  - Trials with ERAs and sGC stimulator terminated for futility and trend towards harm
  - Possibility of worsening hypoxia w/ systemic (parental and oral) tx

Solution? Inhaled pulmonary vasodilator?

- Improved 6MWD
- Lower rates of clinical worsening
- Improved pulmonary function testing



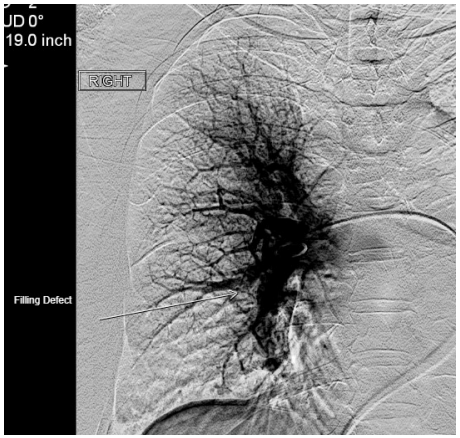
The NEW ENGLAND JOURNAL of MEDICINE

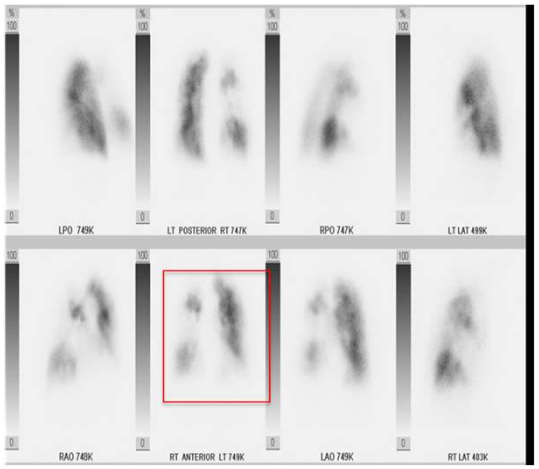
ORIGINAL ARTICLE

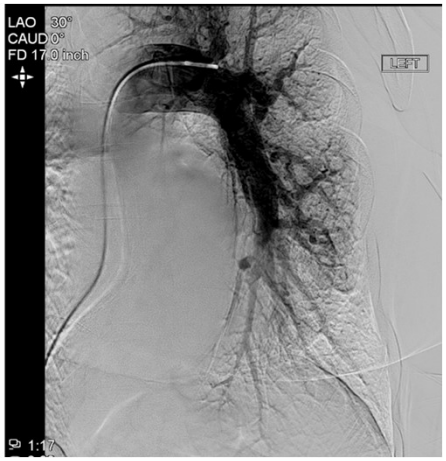
Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease

PH associated with Pulmonary Artery Obstructions

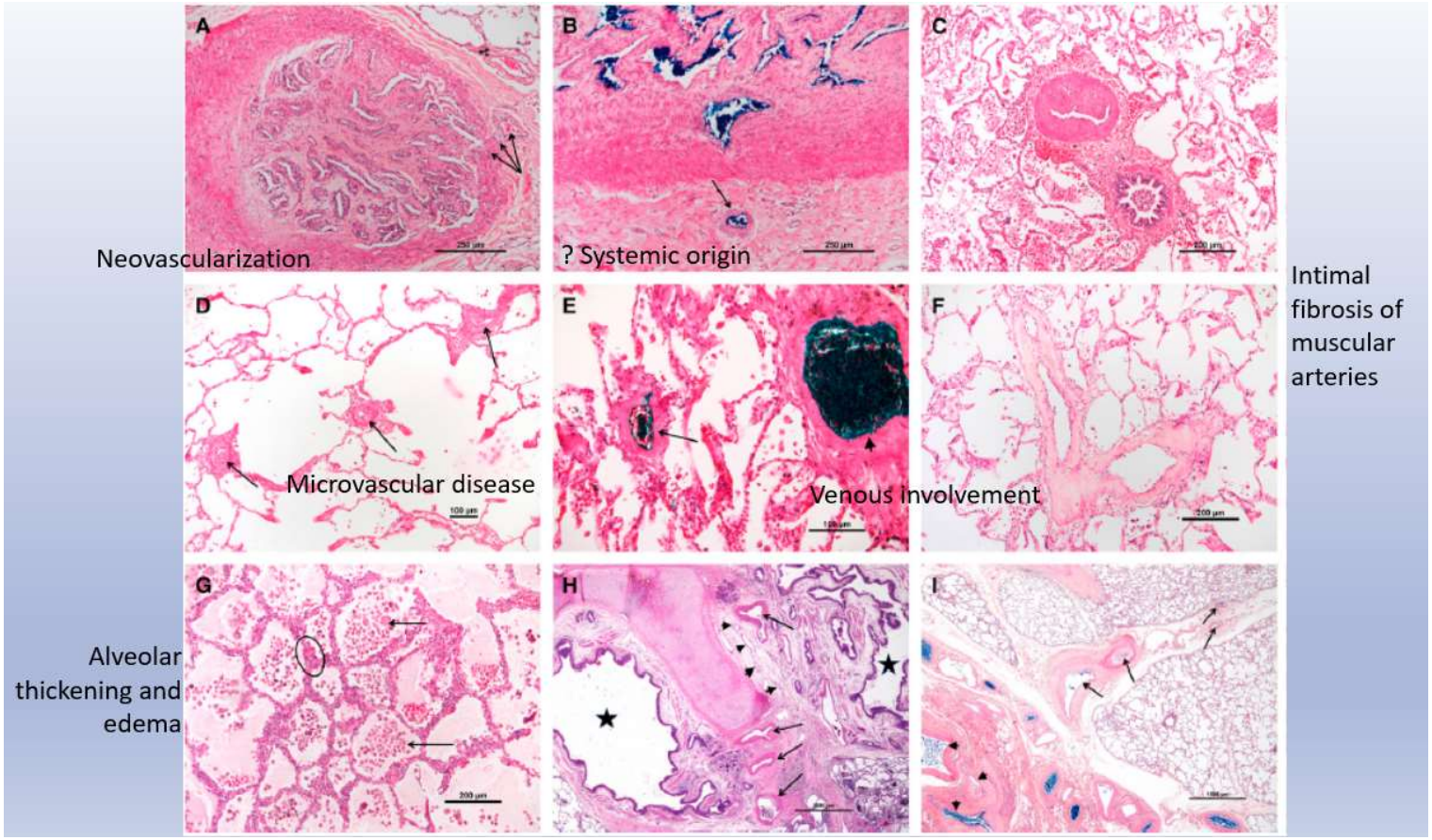
- Most commonly Chronic Thromboembolic Pulmonary Hypertension (CTEPH)
  - Years of progressive unrecognized thrombosis found during evaluation of dyspnea
  - Incomplete resolution of acute pulmonary emboli, formation of scar adherent to pulmonary arterial wall







CTEPH: More than just chronic clots



Surgical Management of CTEPH: Pulmonary Thromboendarterectomy

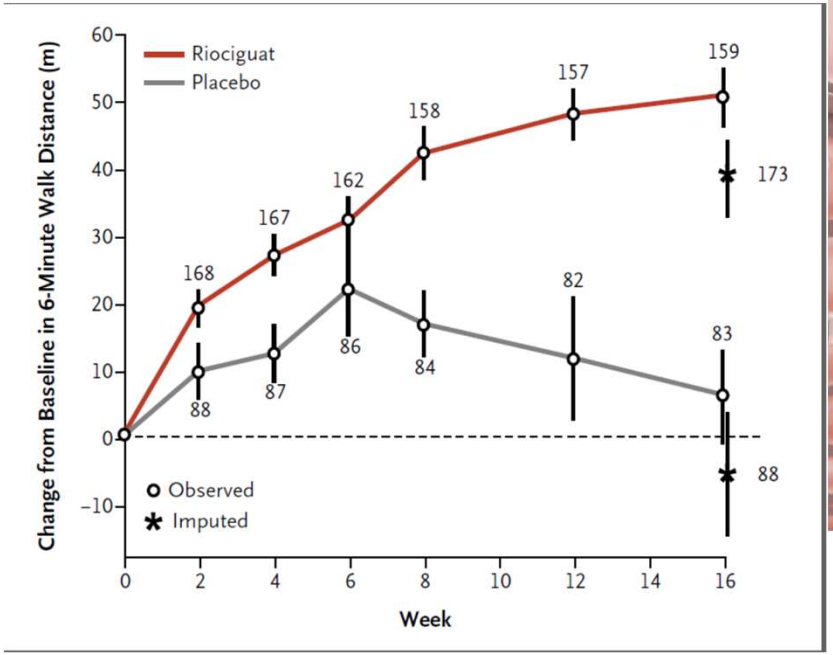
Management of CTEPH: Balloon Pulmonary Angioplasty

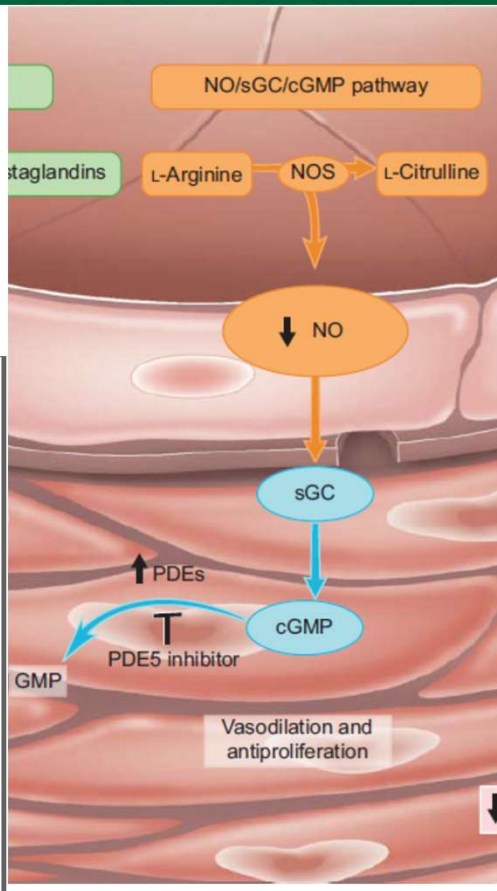
- Patients with smaller vessel disease
- Patients with significant comorbidities

	Survival, %				
	1 yr	2 yr	3 yr	5 yr	10 yr
Multicenter Registry Data	96.8	96.8	94.5		
308 pts, 1408 sessions					
Okayama Medical Center	98.6		94	92.5	89.5
418 pts, Data through 2019					

Medical therapy for CTEPH

- Riociguat- soluble guanylate cyclase stimulator
- CHEST-1: 261 CTEPH pts
  - Inoperable (~75%)
  - Persistent post-operative (~25%)
  - ~45 m difference in 6MWD,
  - Improved HD, WHO FC, QOL scores





Medical therapy vs BPA? Or both?

Randomization RACE Trial	PVR (WU) at inclusion in RACE	PVR (WU) at 6 months End of RACE	PVR (WU) at 1 year, end of the extension study (intention to treat analysis)
BPA (n=52)	9.1 ± 1.4	3.6 ± 1.5	3.0 ± 1.4 **(65 % decrease from baseline)** Add on therapy with riociguat
Riociguat (n=53)	7.9 ± 1.5	5.4 ± 1.6	3.2 ± 1.5 **(61% decrease from baseline)** Add on therapy with BPA 2nd line

- Rates of SAE much higher in BPA vs Riociguat (42 vs 9 %)
- Extension Arm:
  - Patients pretreated with 6 months of riociguat prior to BPA:
  - Lower rates of SAE than those tx w/ upfront BPA (14 vs 42 %)

Summary

- The are numerous causes of pulmonary hypertension
- Understanding the pathophysiology of pulmonary arterial hypertension and other pulmonary hypertension groups is critical to managing these patients
- Identifying pathophysiologic changes has also helped patients and providers identify supportive care strategies to improve quality of life
- Research continues to identify new mutations and pathways that may be targets for novel therapies, and to identify treatment strategies for patients with non-PAH forms of pulmonary hypertension