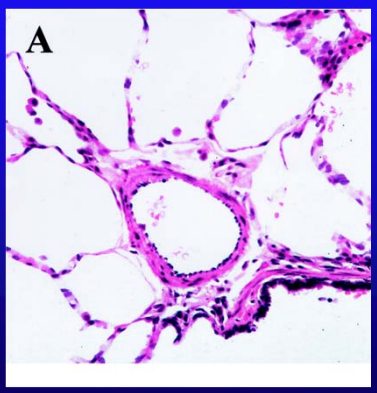
Pulmonary Hypertension: Etiology and Clinical Presentation Therapy 2017

Disclosures: None

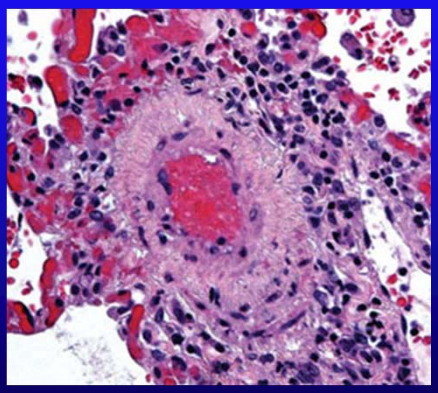
Pulmonary Arterial Hypertension: Clinicopathologic Definition

- Hemodynamic definition:
  - mPAP > 25 mm Hg at rest
  - PCWP or LVDP 15 mmHg
  - PVR ≥ 3.0 Wood Units
- Associated with biologic changes:
  - In pulmonary vasculature
    - Vasoconstriction
    - Cellular proliferation and apoptosis
  - In RV function, thickness, and size

Pulmonary Arterioles 70-500 Microns



Normal



Plexigenic Pulmonary Arteriopathy

Updated WHO Classification of Pulmonary Hypertension
2013 Nice World Symposium - J Am Coll Cardiol December 2013

Group 1: Pulmonary arterial hypertension (PAH)

- Idiopathic PAH
- Heritable – BMPR2, ALK1, ENG,SMAD9, CAV1, KCNK3, unknown
- Drugs and toxin-induced
- Associated with:
  - Connective tissue diseases
  - HIV infection
  - Portal hypertension
  - Congenital heart diseases
- Schistosomiasis
- Persistent pulmonary hypertension of the newborn
- **1' Pulmonary veno-occlusive disease** and/or pulmonary capillary hemangiomatosis

WHO Classification, Groups 2-5 PH

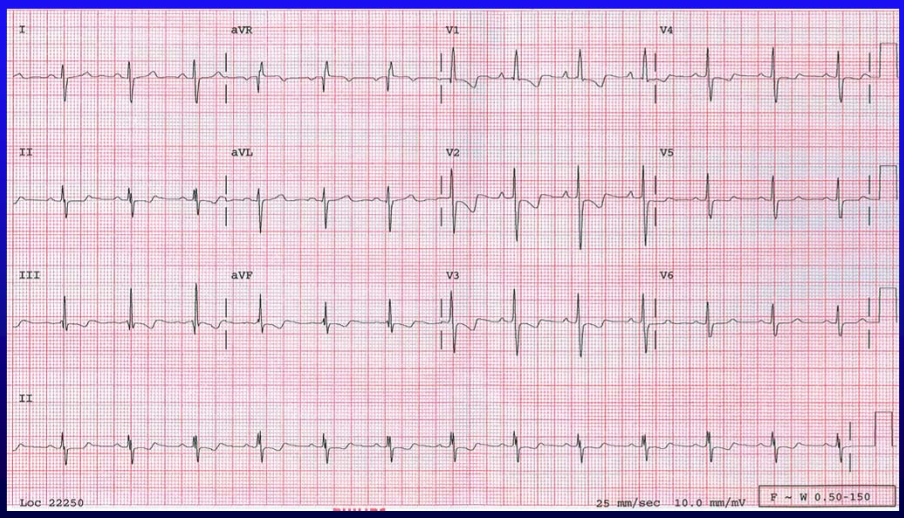
- **Group 2: Pulmonary hypertension due to left heart disease**
  (Incidence associated with HF/preserved EF "exploding" - Lindenfeld J, Mayo Clinic)
- Group 3: Pulmonary hypertension of lung disease and/or hypoxia
- Group 4: Chronic thromboembolic pulmonary hypertension (CTEPH)
- Group 5: Pulmonary hypertension with unclear multifactorial mechanisms
  Hemolytic anemia
  Sarcoidosis
  Chronic renal failure

Symptoms and Physical Exam

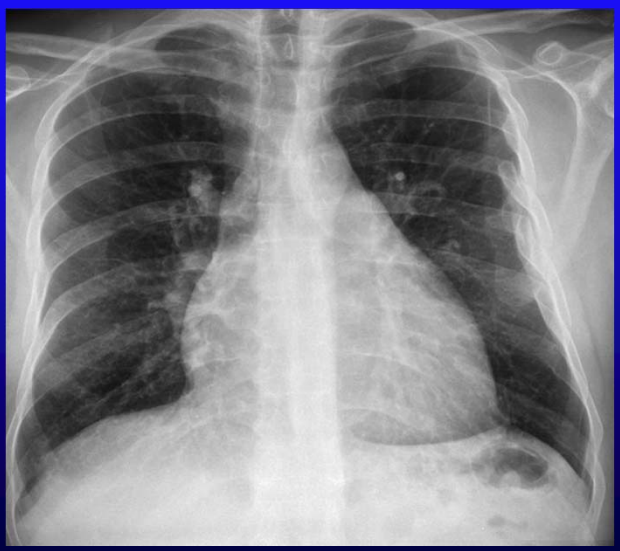
- Dyspnea
- Syncope, seizures
- Dizziness
- Fatigue
- Edema
- Chest discomfort
- Late presentation: it's anything but I'm sick, maybe deep-seated anxiety

- Loud P2, SEM
- Elevation of the venous pressure
- TR, high-pressure PI
- Palpable right ventricular impulse
- Parasternal S3 gallop
- Hepatomegaly
- Ascites
- Lower extremity edema

Electrocardiogram



Chest X-Ray



Echo – Parasternal Short Axis

- Assess RV size and contraction
- Estimate PA systolic pressure
- Assess RV pressure-volume ovewrload

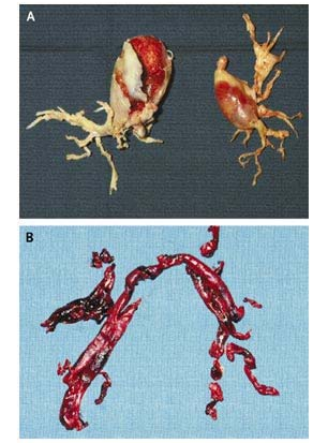
WHO Functional Classificiation

Modified NYHA HF Classification

- Class I: Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope
- Class II: Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope
- Class III: Marked limitation of physical activity. Comfortable at rest. Less than ordinary physical activity causes symptoms
- Class IV: Inability to carry out physical activity without symptoms. Manifest signs of right heart failure. Symptoms may be present at rest.

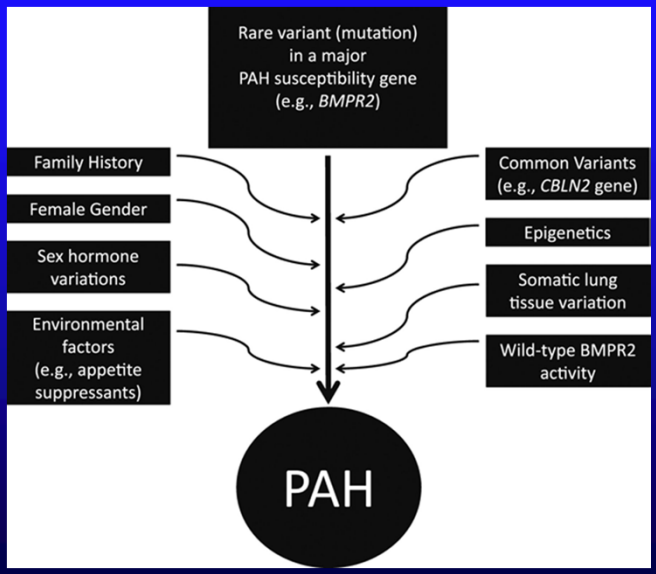
WHO 1998 (http://who.int/ncd/cvd/pph.html

Chronic Thromboembolic Pulmonary Hypertension (CTEPH): WHO Group PH



- About 20-30 CTEPH centers worldwide
- UCSD the largest experience
  - 2000+ cases operated
- Treatment of choice:
  - Hypothermic arrest (18° C)
  - Embolectomy
- Significance
  - High index of suspicion
  - Value PA angiography
  - Seek cause for venous thrombosis

Major Factors in the Development of PAH



- Austin and Lloyd, Circ Research 2014

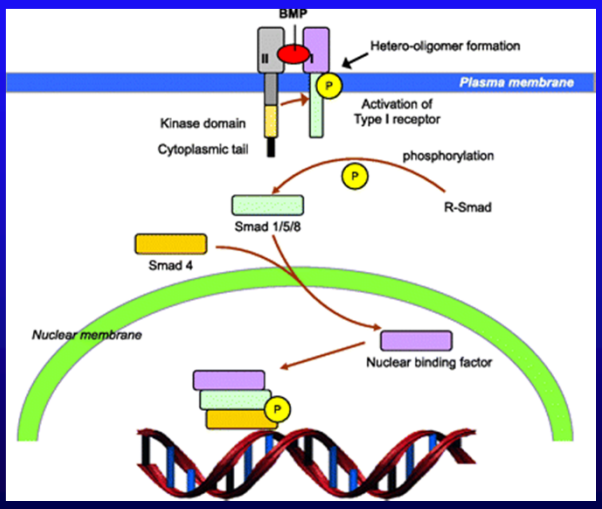
Group 1 PAH Conundrum

- In only 10% of PAH patients does reversal of vasoconstriction result in clinically meaningful reduction in pulmonary vascular resistance.
- In remainder, proliferative arteriopathy the driver of elevated pulmonary pressures
- Available drugs to date do not significantly impact proliferative arteriopathy.

A PH-Wide Conundrum

- Emerging Omics research demonstrates significant phenotypic and genotypic overlap in the different WHO Groups
- Effective treatment of PH may require a more “precise” definition of what is being treated.

Bone Morphogenetic Protein Receptor Pathway: Normally Inhibitory, Becomes Proliferative

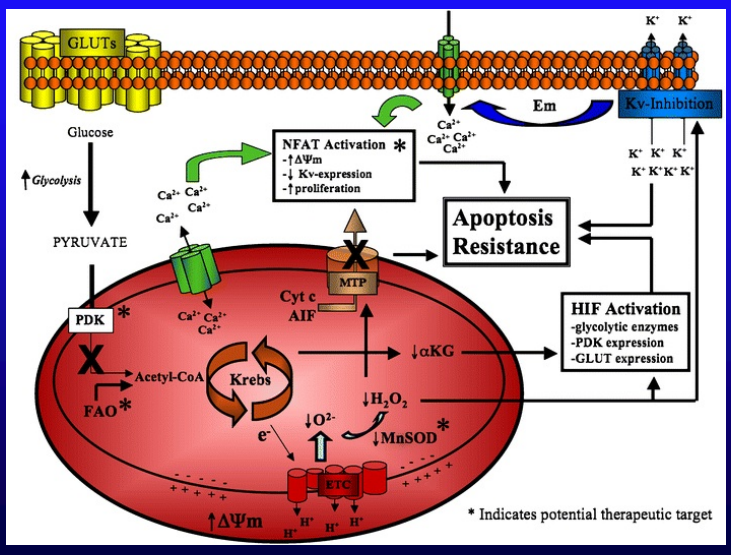


- Said S, Lung Cell Mol Physiol 2006

Metabolic Hypothesis in PAH

The Role Mitochondria in Pulmonary Vascular Remodeling

- "Warburg Effect"
- Erzurum et al., Am J Path 2010
- PDK induced by PAH state
- PDH inactivated by PDK
- Decreased pyruvate influx, hyperpolarized Δ membrance potential
- Reduced mitochondrial Kreb's cycle activity and mROS production close mitochondrial transition pore (MTP)
- Suppression of apoptosis, enhancement of cell proliferation
- Disordered mitochondrial O_2-sensing signals hypoxia in absence of hypoxemia

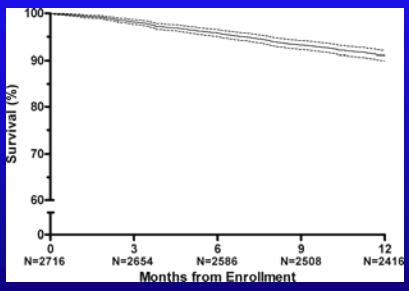


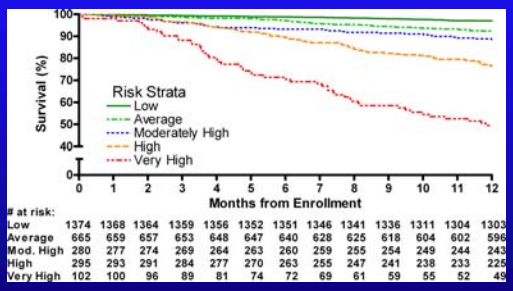
- Michelakis ED et al., Mol Med 2010

Incidence of Idiopathic Pulmonary Hypertension (IPAH)

- Sporadic and heritable (formerly primary)
  - Approximately 1-10 per million
  - Females 1.7/1
- Other Group 1 etiologies
  - Also rare per 100,000 underlying diagnoses

Survival in Idiopathic Pulmonary Arterial Hypertension: The REVEAL Registry





- Median survival from diagnosis 2.8 years untreated
- Highly dependent upon right ventricular function
- One year or less in the presence of RV failure

American Heart Association.

Raymond L. Benza et al. Circulation. 2010;122:164-172

PAH in Scleroderma Systemic Sclerosis (SSc): Facts

- The worst of PAH: 4 times more likely to die than IPAH patients
- 240 cases/million in U.S.
- 10-15% of SSc patients
- 1.5-1.7% family history
- Older population compared to IPAH
- Predominantly female
- Responsible for 18-28% of SSc deaths (pulmonary fibrosis 42% of SSc deaths)

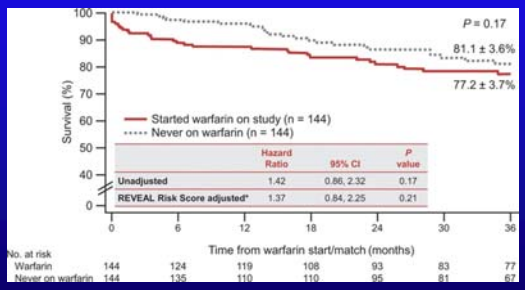
PAH Diagnosis

- Suspect on clinical grounds
- Right heart catheterization: THE SINE QUA NON for the diagnosis of PAH
- Right internal jugular approach
- U/S guidance - warfarin cessation not necessary
- Meticulous attention to accuracy of PCWP
  - Distinguish primary from secondary etiology

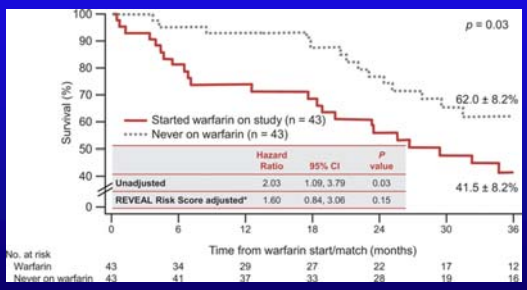
Warfarin and Survival: REVEAL Registry

Kaplan-Meier estimates at 36 Months

IPAH



SSc-PAH

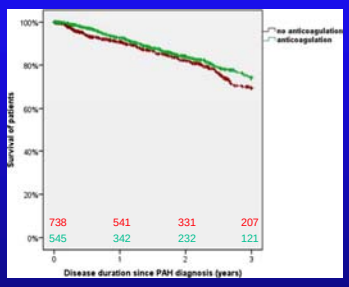


American Heart Association

- Preston IR, Roberts KE, Farber et al. Circulaton 2015

Anticoagulation in COMPERA: European Registry

All PAH Patients



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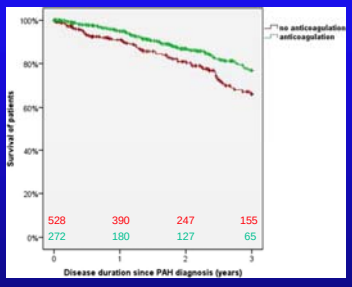
IPAH



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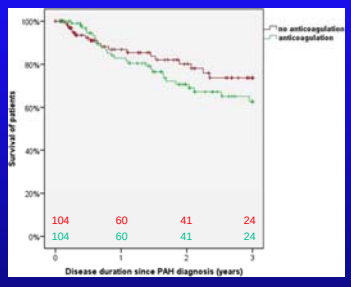
SSc



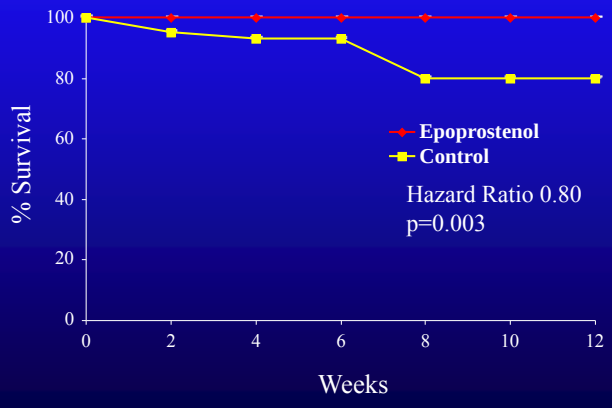
p = 0.28

American Heart Association

- Karen M. Olsson et al. Circulation. 2014;129:57-65

Karen M. Olsson et al. Circulation. 2014;129:57-65

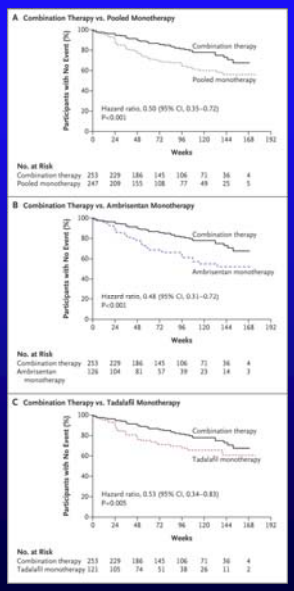
Continuous Intravenous Epoprostenol versus Conventional Therapy



- 12-week prospective randomized trial
- Epoprostenol vs. conventional therapy
- 81 patients, PA 60 mm Hg, WHO III-IV
- Mean max. dose 9.5 + 0.5 ng/kg/min
- Approximate 2% reduction in mPAP
- Improved 6-minute walk & WHO Class
- Improved survival

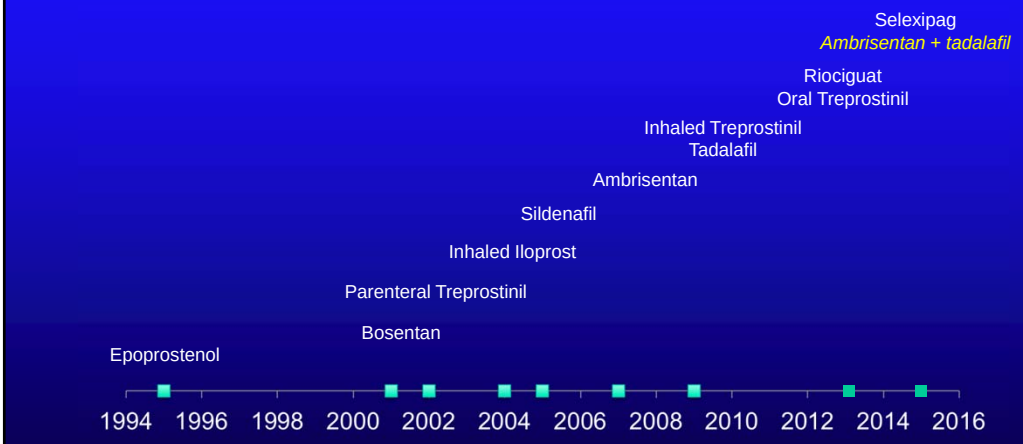
Barst et al., N Engl J Med 1996

AMBITION Trial/Ambrisenan+Tadalafil: Probability of a First Adjudicated Primary End-Point Event

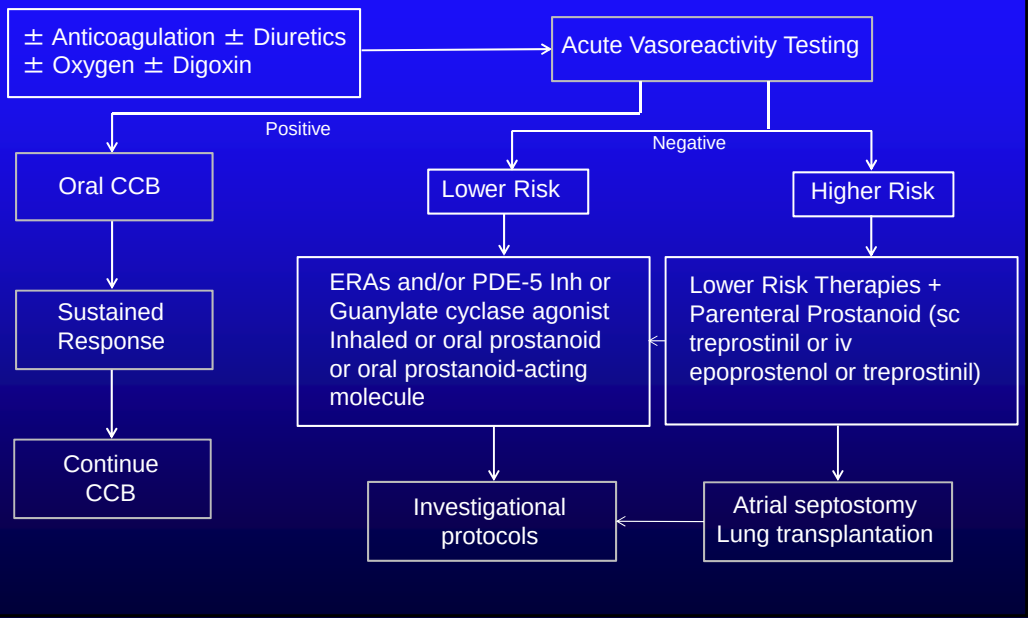


- Galie et al. N Engl J Med 2015

FDA-Approved Drug Timeline



PAH Treatment Algorithm



Pulmonary Veno-Occlusive Disease and Pulmonary Capillary Hemangiomatosis

- Virtually clinical diagnoses
- Mediastinal lymphadenopathy
- Pulmonary osteoarthropathy
- Deterioration/death in response to epoprostenol
- The PCWP is usually normal

Acutely Decompensating PH: Treatment

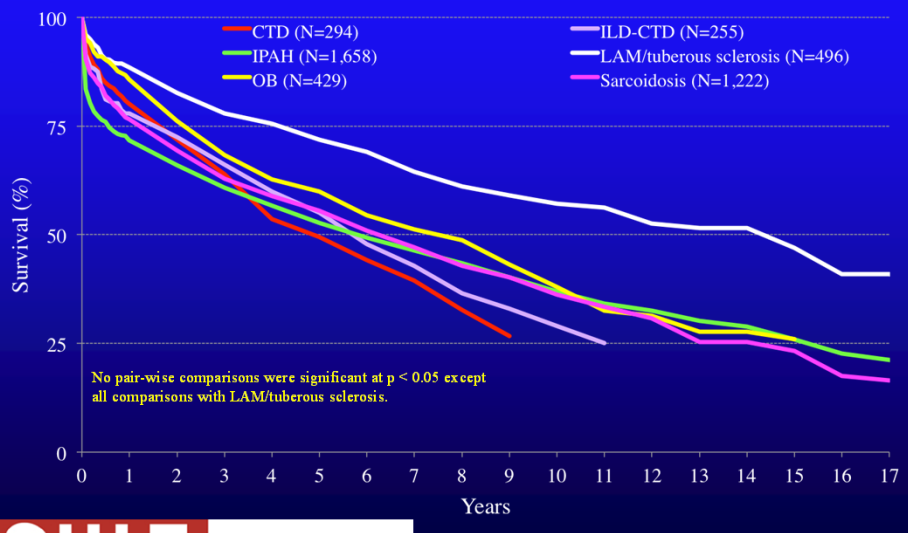
- Oxygen
- Phenylephrine – raise arterial pressure, improve coronary perfusion pressure
- Inotropic support: probably dobutamine
- Diuretics
- Inhaled nitric oxide
- Initiation of prostacyclin - be careful of hypotension
- Intubation: uniformly associated with mortality

Lung, Heart/Lung Transplantation

- Symptomatic progressive disease despite optimal treatment
- Bridging strategies: ECMO
- Optimal prostacyclin dosing: the presence of side effects
- Hemodynamic parameters:
  - CI < 2 L/min/m2
  - RA mean > 18 mm Hg
- Echo evidence of RV failure

Adult Lung Transplants Kaplan-Meier Survival by Diagnosis Conditional on Survival to 1 Year

(Transplants: January 1990 – June 2014)



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Conclusions

- Untreated, Group 1 PAH a deadly disease
- With WHO Group 1 PAH therapy, significant survival benefit (idiopathic PAH better than other sub-types)
- CTEPH: Pulmonary endarterectomy under deep hypothermic arrest
- Patients better managed by the PH specialist