Pulmonary Arterial Hypertension: Review and Updates

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Is it Primary vs Secondary Pulmonary Hypertension?

Today…

- **Nomenclature review - classification**
- **Diagnosis**
- **Prognosis**
- **Treatment**

No!!
Dated Nomenclature

Is it Pulmonary Arterial Hypertension (PAH) or Non-PAH?

The 2003 Venice Classification of Non-PAH Pulmonary Hypertension

- Pulmonary hypertension (PH) with left heart disease – WHO Class 2
  - ✓Trigger: High LA Pressure
- PH with lung disease/hypoxemia - WHO Class 3
  - ✓Trigger: Hypoxemia and Parenchyma Distortion
- PH due to chronic thrombotic and/or embolic disease – WHO Class 4
  - ✓Trigger: Obstruction

Pulmonary Hypertension Is a Disease of Triggers

The 2003 Venice Classification of PAH - WHO Class 1

- Pulmonary Arterial Hypertension
  - ✓ Familial PAH (FPAH)
  - ✓ Idiopathic PAH (IPAH)

    } Trigger: Mutation/Polymorphism
  - ✓ Associated PAH (APAH)
    - Connective tissue disease (CTD)
    - Human immunodeficiency virus (HIV)
    - Portal hypertension
    - Anorexigens

      } Trigger: Permissive Phenotype
    - Congenital heart disease (CHD)
  - ✓ Persistent pulmonary hypertension of the newborn (PPHN)
  - ✓ PAH with venule/capillary involvement

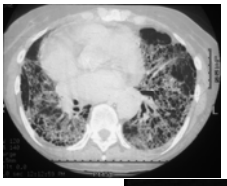
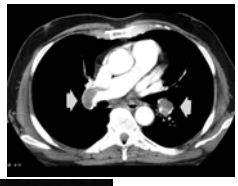
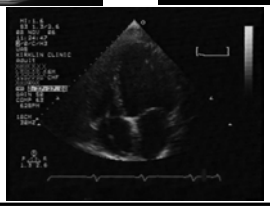
Importance of Classification: Why do it?

- Efficacy: What's the trigger? Can you change it?
- Safety: Can it hurt the patient?
- Cost: How much are we spending for limited efficacy and small changes in QOL?

Safety: Can it hurt the patient?

- LV dysfunction: Pulmonary edema
- ILD/COPD: Worsen V/Q mismatch
- CTEPH: Delay referral for thromboendarterectomy

Efficacy: What's the trigger? Can you change it?

Cost: How much are we spending for limited efficacy and small changes in QOL?

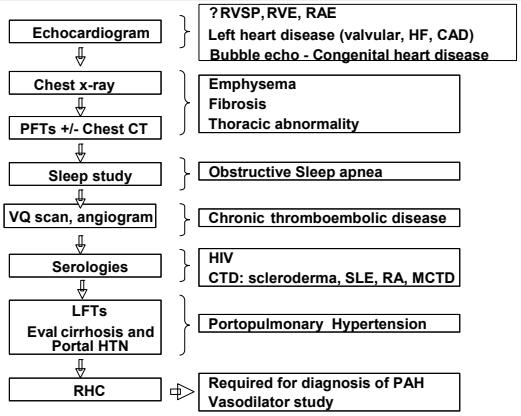
- Bosentan: ~35-40k per year
- Sildenafil: ~12-15k per year
- Inhaled Iloprost: ~60k per year
- IV Prostacyclins: ~60-120k per year

Pulmonary Arterial Hypertension

- Classification
- Diagnosis
- Prognosis
- Treatment

Diagnosis PAH = RHC

Schema for Patient Evaluation



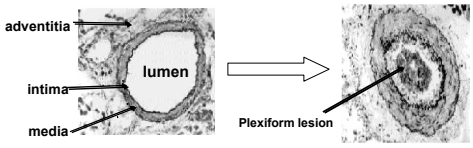
Cardiac Catheterization to Assess Severity and Prognosis of PAH

- To measure wedge pressure or LVEDP
  - Scrutinize wedge tracings!!!!
  - Wedge sat; End expiration
- To exclude or evaluate CHD
- To establish severity and prognosis
- To test vasodilator therapy

Catheterization is required for every patient with suspected pulmonary HTN

Pulmonary Arterial Hypertension

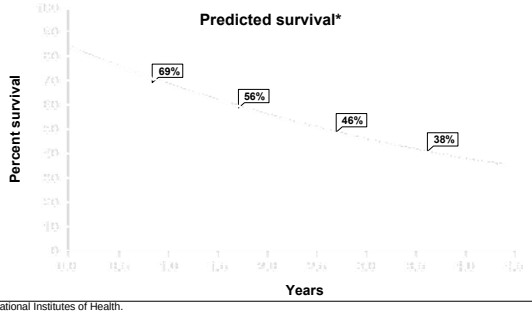
- Mean Pulmonary artery ≥ 25 mmHg
- Wedge pressure ≤ 15 mmHg
- PVR > 3 Woods units



Normal pulmonary arteriole Pulmonary arteriole in PAH

Barst et al. *J Am Coll Cardiol.* 2004;43:40S-47S.

Natural History of PAH: NIH Registry[1,2]



NIH = National Institutes of Health.
Predicted survival according to the NIH equation. Predicted survival rates were 69%, 56%, 46%, and 38% at 1, 2, 3, and 4 years, respectively. The numbers of patients at risk were 231, 149, 82, and 10 at 1, 2, 3, and 4 years, respectively. *Patients with primary pulmonary hypertension, now referred to as idiopathic pulmonary hypertension.
1. Rich et al. *Ann Intern Med.* 1987;107:216-223. 2. D'Alonzo et al. *Ann Intern Med.* 1991;115:343-349.

Pulmonary Arterial Hypertension

- Classification
- Diagnosis
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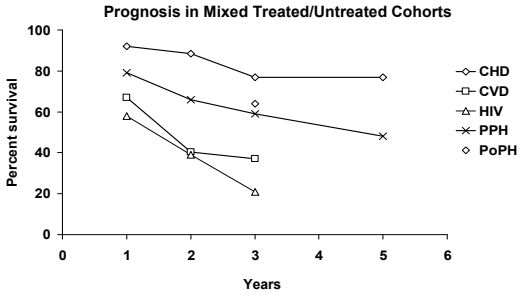
Survival by PAH Etiology



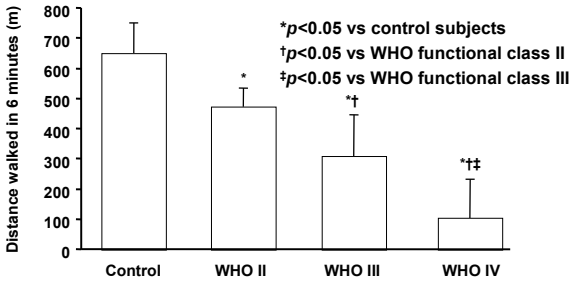
CHD = congenital heart disease; CVD = collagen vascular disease; HIV = human immunodeficiency virus; PAH = pulmonary arterial hypertension; PPH = primary pulmonary hypertension; PoPH = portopulmonary hypertension.
McLaughlin et al. *Chest.* 2004;126:78S-92S.

PAH Determinants of Risk

Lower Risk	Determinants of Risk	Higher Risk
No	Clinical evidence of RV failure	Yes
Gradual	Progression	Rapid
II, III	NYHA class	IV
Longer (>400 m)	6MW distance	Shorter (<300 m)
Minimally elevated	BNP	Very elevated
Minimal RV dysfunction	Echocardiographic findings	Pericardial effusion, significant RV dysfunction
Normal/near normal RAP and CI	Hemodynamics	High RAP, low CI

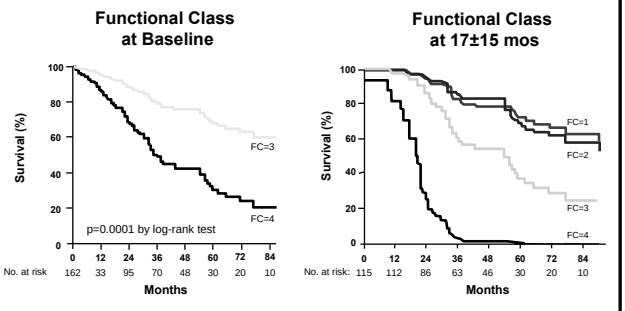
McLaughlin VV and McGoon M. *Circulation*. 2006;114:1417-1431.

Correlation of Six-minute-walk Test and WHO Functional Class



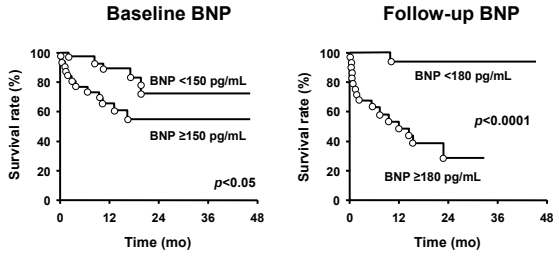
Miyamoto S et al. *Am J Respir Crit Care Med*. 2000;161:487-492.

Impact of Functional Class on Survival



McLaughlin VV, et al. *Circulation*. 2002;106:1477-1482.

Plasma BNP as a Prognostic Indicator of Mortality in Patients With PPH



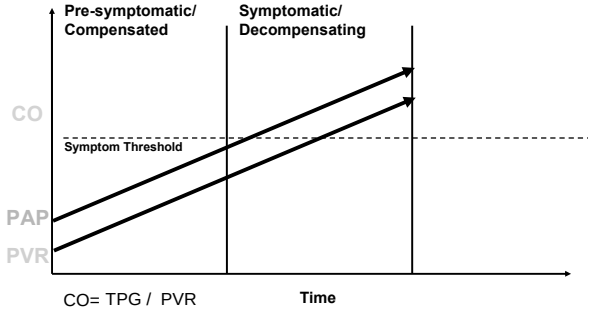
By multivariate analysis, higher BNP at baseline (RR=11.971, *p*=0.0348) and at follow-up (RR=25.880, *p*=0.0243) were independent predictors of mortality

Nagaya N et al. *Circulation*. 2000;102:865-870.

Predicting Survival and Following Therapy

- **Clinical parameters**
  - ✓ **functional class**
  - ✓ **exercise capacity**
  - ✓ **neurohormones**
- **Hemodynamics**
- **Imaging**
  - ✓ **right ventricle: function and size**
  - ✓ **pulmonary artery remodeling (future)**

Schematic Progression of PAH



PAP=pulmonary artery pressure; PVR=pulmonary vascular resistance; TPG=transpulmonary gradient.
Courtesy of: Vallerie V. McLaughlin, MD.

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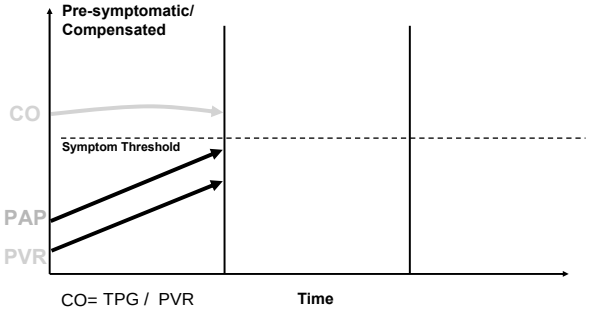

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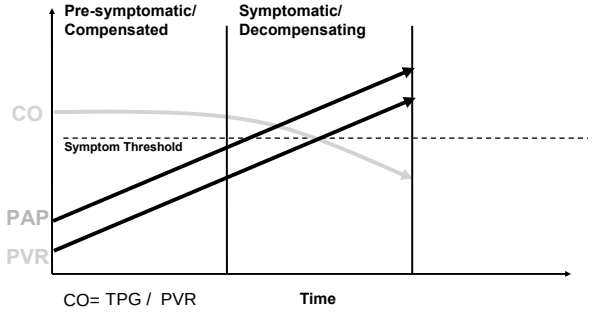

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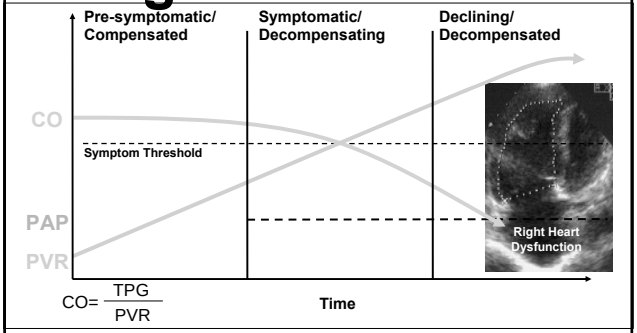
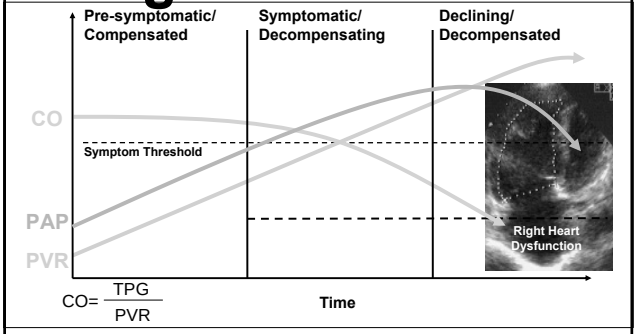


PAP=pulmonary artery pressure; PVR=pulmonary vascular resistance; TPG=transpulmonary gradient.
Courtesy of: Vallerie V. McLaughlin, MD.

Goals of Therapy

- Improve symptoms
  - ✓ 6-minute walk (>380 m)
  - ✓ functional class (I or II)
  - ✓ CPET (VO_2 max >10.4)
  - ✓ quality of life
- Improve hemodynamics
- Improve survival

Schematic Progression of PAH



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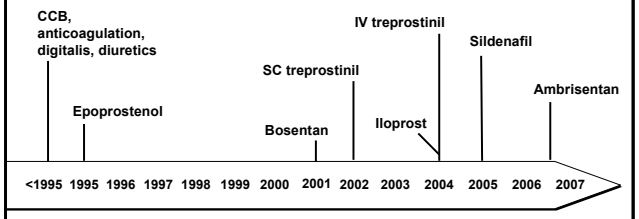
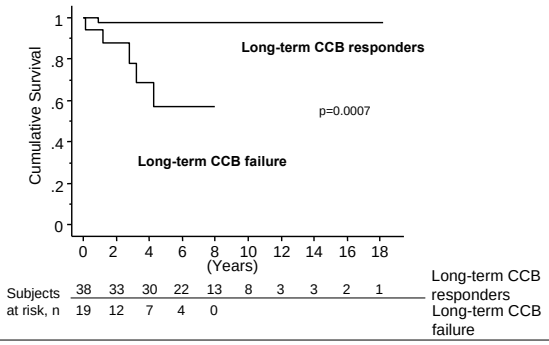
What Drug and When

PAH Treatments - a Historical Overview



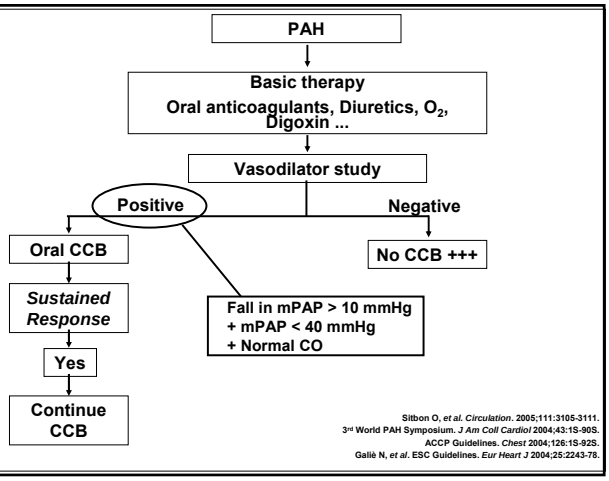
CCB = calcium channel blocker.

Survival in IPAH
Long-term CCB Responders

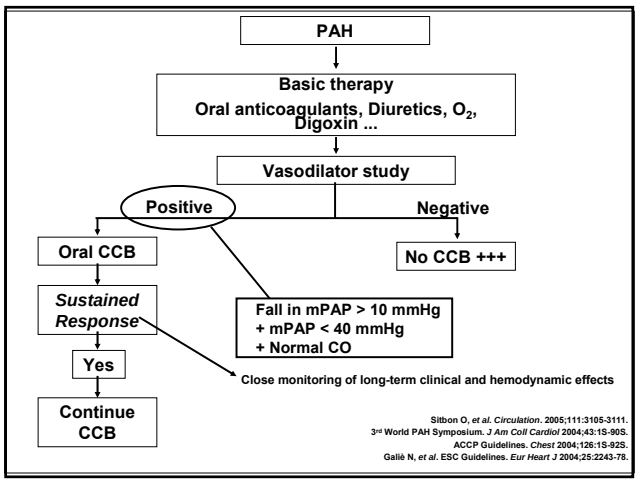


O. Sitbon et al. Circulation 2005;111:3105-3111

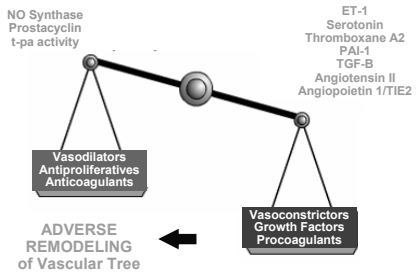
When to use a Calcium Antagonist ?



Sitbon O, *et al. Circulation*. 2005;111:3105-3111.
3rd World PAH Symposium. *J Am Coll Cardiol* 2004;43:1S-90S.
ACCP Guidelines. *Chest* 2004;126:1S-92S.
Galiè N, *et al*. ESC Guidelines. *Eur Heart J* 2004;25:2243-78.

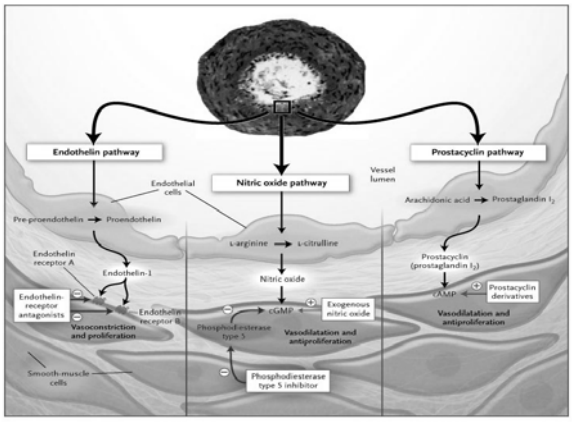


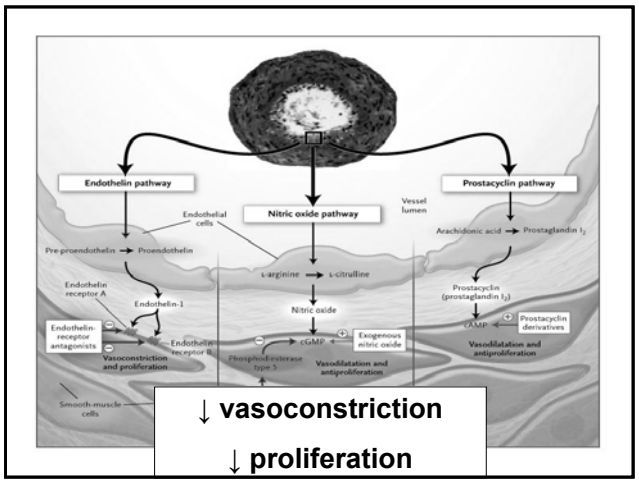
Vascular Pathology: Balance of Powers



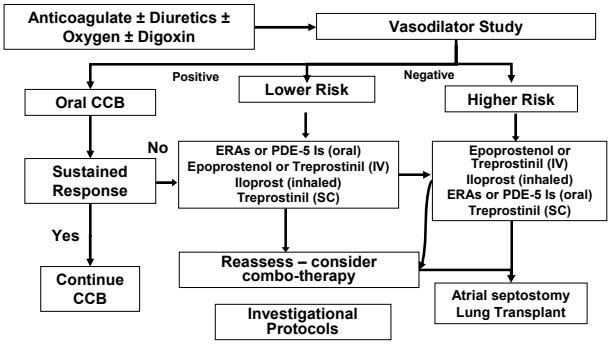
Courtesy of: Ronald J. Oudiz, MD.

Other Medications?





What is the Optimal Treatment Strategy?



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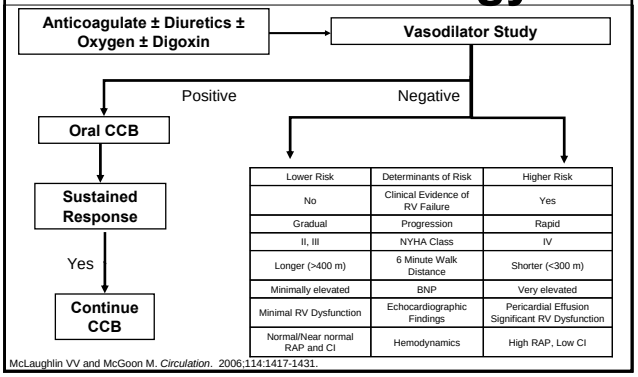

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Minimally elevated	BNP	Very elevated
Minimal RV Dysfunction	Echocardiographic Findings	Pericardial Effusion Significant RV Dysfunction
Normal/Near normal RAP and CI	Hemodynamics	High RAP, Low CI

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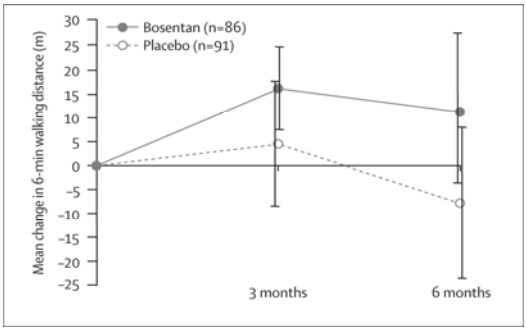
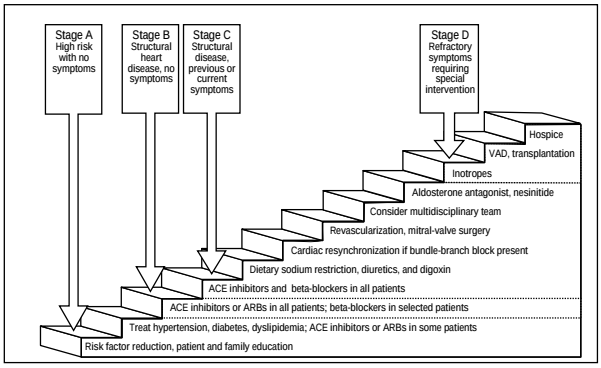
EARLY trial: Bosentan in NYHA class II



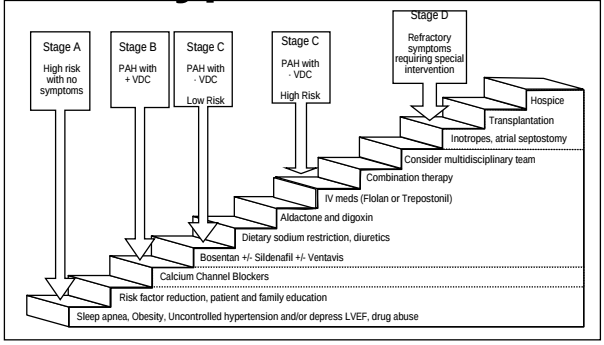
Galie N et al. Lancet 2008; 371: 2093-2100

Rx of Heart Failure



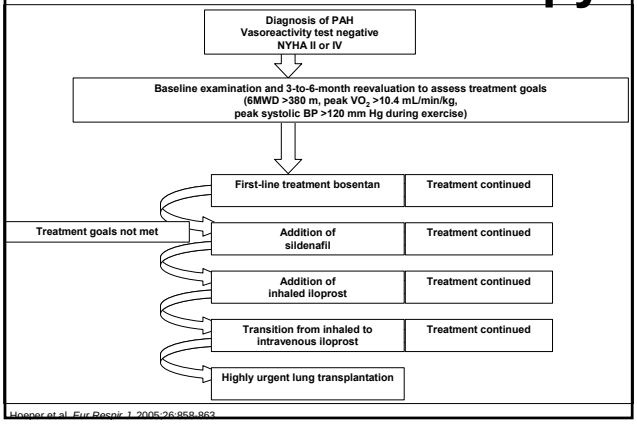
Jessup M, Brozena S. *N Engl J Med*. 2003;348:2007-2018.

Rx of Pulmonary Hypertension



Early, Risk-based and Combination Therapy: Changing Paradigms for PAH?

Goal-Oriented Therapy



Hoeper et al. *Eur Respir J*. 2005;26:858-863.

Summary: Treatment

- Traditional therapies; diuretics, oxygen, phlebotomy still used as indicated; anticoagulants recommended
- Calcium Channel Blockers should be used in Class II or III acute responders but followed closely for safety & efficacy
- Newer agents are tailored to WHO class – ACCP Guidelines
  - ✓ Class IV – Infused prostacyclins
  - ✓ Class III – Oral endothelin receptor antagonists (ERAs), phosphodiesterase (PDE) 5 inhibitors, infused or inhaled prostacyclins
  - ✓ Class II – PDE 5 inhibitors, or ERAs
    - Consider therapy if evidence of Right Ventricular Dysfunction
- Combination therapies and an array of investigational therapies hold hope for the future
- Role of transplantation/septostomy now diminished because of new effective pharmacologic therapies

Indications for Referral to a Specialized Center for Rx of PAH

- Unexplained dyspnea on exertion with evidence of PH on Echo
- Evidence of moderate to sever PH
  - ✓ Estimate PAS pressure > 45 mm Hg on Echo
  - ✓ Symptoms consistent with NYHA functional class II or worse
  - ✓ Near-syncope or syncope
- Absence of substantial left sided cardiac disease or parenchymal lung disease
- Clinical or echocardiographic evidence of RV dysfunction
  - ✓ Lower-extremity edema
  - ✓ Ascites
  - ✓ Right ventricular enlargement or systolic dysfunction on echocardiography

Rubin, L. J. et. al. Ann Intern Med 2005;143:282_292