

Pulmonary Arterial Hypertension: Diagnosis of Treatment

Namita Sood, MD, FCCP
 Director, Pulmonary Hypertension Program
 Associate Professor - Clinical
 Department of Internal Medicine
 The Ohio State University Wexner Medical Center

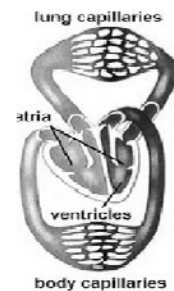
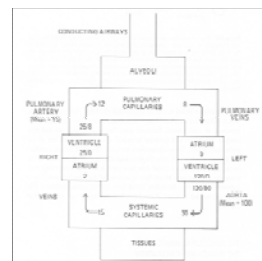
PAH

- Classification
- Diagnosis
- Current treatment

Pulmonary Circulation

- Originates from the RV
- Low Pressure, low resistance circuit
- Thin-walled vessels
- High compliance
- Receives entire CO from RV
- Accommodates wide range of CO without increase in PVR

Pulmonary circulation



Pulmonary Hypertension

- Mean PAP > 25 mmHg
- Not just one disease, but a large group of diverse diseases

Classification

1. Pulmonary arterial hypertension (PAH)
 - 1. Pulmonary arterial hypertension (PAH)
 - 1.1. Idiopathic (IPAH)
 - 1.2. Heritable
 - 1.2.1 BMPR2
 - 1.2.2 ALKI Endoglin (with or without HHT)
 - 1.2.3 Unknown
 - 1.3. Drugs and Toxins
 - 1.4. Associated with (APAH):
 - 1.4.1. Collagen vascular disease
 - 1.4.2. HIV
 - 1.4.3. Portal hypertension
 - 1.4.4. Congenital Heart Disease
 - 1.4.5. Schistosomiasis
 - 1'1 Pulmonary veno-occlusive disease (PVOD)/ Pulmonary capillary hemangiomatosis (PCH)
 - 1'2 Persistent pulmonary hypertension of the newborn

Classification

2. Pulmonary hypertension with left heart disease
 - 2.1. Left Ventricular Systolic Dysfunction
 - 2.2 Left Ventricular Diastolic Dysfunction
 - 2.3 Valvular Disease
 - 2,4 Congenital /Acquired Left Heart inflow tract obstruction and congenital cardiomyopathies
3. Pulmonary hypertension associated with lung diseases and/or hypoxemia
 - 3.1. Chronic obstructive pulmonary Ds
 - 3.2. Interstitial lung disease
 - 3.3. Sleep-disordered breathing
 - 3.4. Alveolar hypoventilation disorders
 - 3.5. Chronic exposure to high altitude
 - 3.6. Developmental abnormalities

Classification

4. Pulmonary hypertension due to chronic thromboembolic

Classification

- **5. Pulmonary Hypertension with unclear multifactorial mechanism**
 - 5.1 Hematologic disorders, myeloproliferative disorders, splenectomy
 - 5.2 Sarcoidosis, histiocytosis X, lymphangioleiomyomatosis
 - 5.3 Metabolic disorders, glycogen storage disease, Gaucher disease, thyroid
 - 5.4 Compression of pulmonary vessels tumor obstruction, fibrosing mediastinitis, Chronic renal failure

Pulmonary Arterial Hypertension

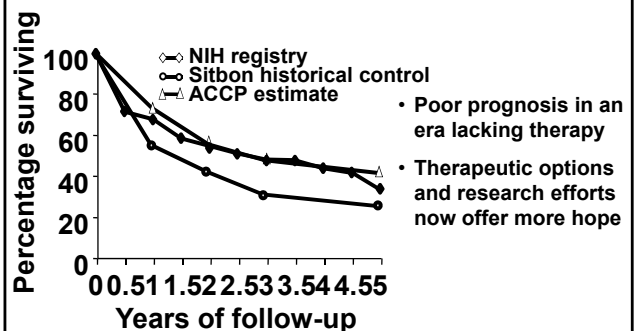
mean pulmonary artery pressure

- > 25 mm Hg
- Pulmonary artery wedge pressure <15

Incidence of PAH

- 187 patients followed over 7 years
- Mean age at diagnosis: 36 years
- Almost 2:1 female-to-male ratio
- Incidence: ~2 cases per 100,000
- Mean survival 2.8 yrs
- Mean duration of symptoms before diagnosis: 2 years
- 647 patients in 1 yr
- Prevalence increasing: 15 cases per million
 - IPAH = 5.9 per million
- Mean delay between enrollment and diagnosis: 6 ± 86 months

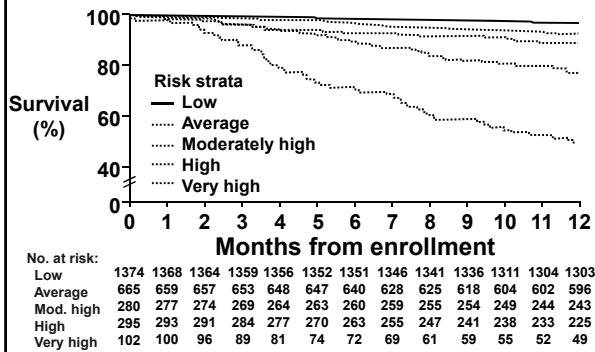
A Disease of Decline and Deterioration: IPAH Survival if Untreated



Adapted from: Sitbon O et al. *J Am Coll Cardiol.* 2002;40:780-788;
D'Alonzo GE. *Ann Intern Med.* 1991;115:343-349;
and McLaughlin VV et al. *Chest.* 2004;126:78S-91S.

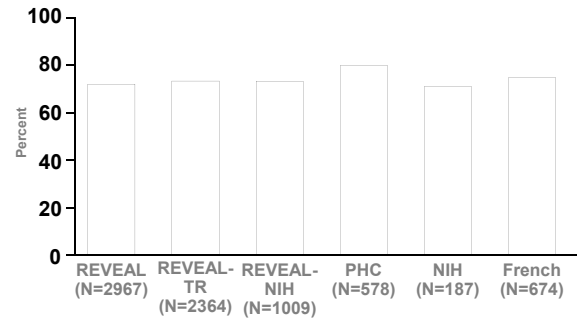
- Poor prognosis in an era lacking therapy
- Therapeutic options and research efforts now offer more hope

REVEAL: Observed 1-year Survival From Time of Enrollment According to Predicted Risk Strata



PAH Registries: Functional Class at Diagnosis Indicates Delayed Diagnosis

% Patients NYHA Functional Class III-IV at Diagnosis



Is There a Reason to Suspect PAH?

Clinical Presentation

Common Initial Symptoms (N=187)	Patients (%)
Dyspnea	60
Fatigue	19
Syncope or near syncope	13
Chest pain	7
Palpitations	5
Leg edema	3

McGoan M et al for the American College of Chest Physicians. *Chest*. 2004;126:14S-34S.
Rich S et al. *Ann Intern Med*. 1987;107:216-223.

Physical Exam

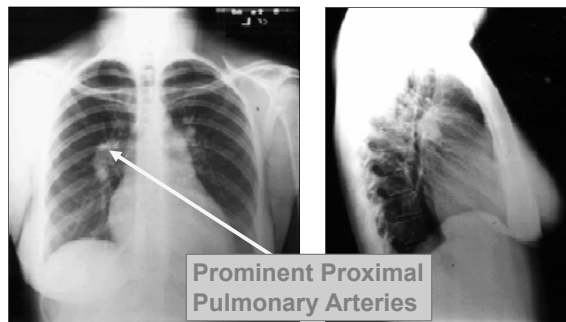
Presence of PH

- Loud P2
- RV lift
- Systolic murmur (TR)
- Diastolic murmur (PR)
- RV S4

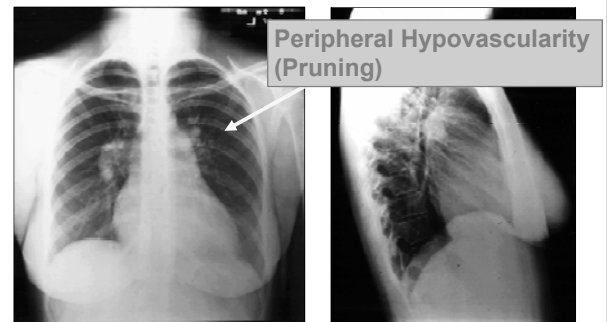
Presence of RV Failure

- JVD with V wave
- RV S3
- Hepatomegaly
- Edema
- Ascites

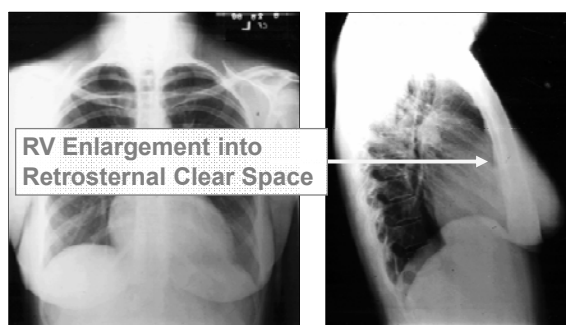
Chest X-Ray



Chest X-Ray



Chest X-Ray



Is There a Reason to Suspect PAH?

ECG

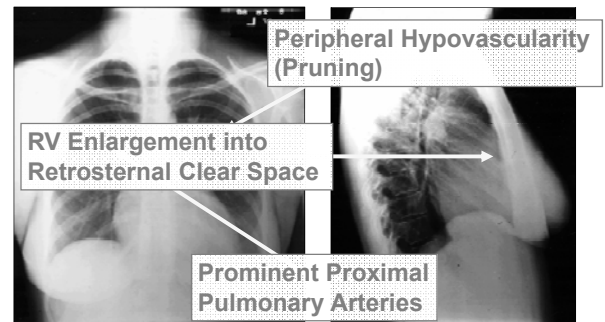


McGoan M et al for the American College of Chest Physicians. *Chest*. 2004;126:14S-34S.

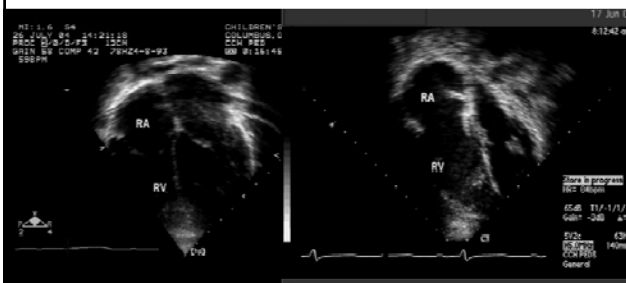
Diagnostic Evaluation

- Pulmonary function tests
 - Mild restrictive defects
 - Decreased DLCO
- Arterial Blood gas
 - Hypoxemia
 - Increased A-a gradient

Chest X-Ray

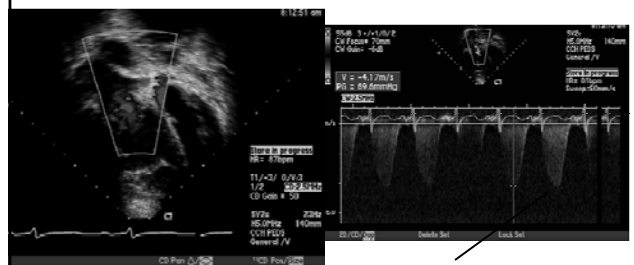


Cardiovascular Evaluation



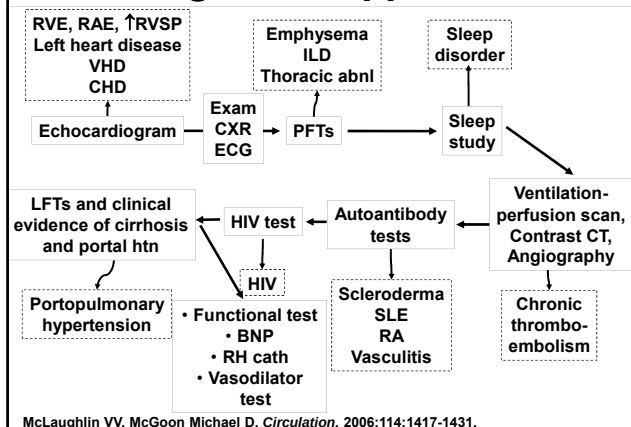
Chamber size
LV and RV systolic function
LV diastolic function
Valvular function
TR
Bubble study

Cardiovascular Evaluation



4.1 m/sec = 70 mmHg
+ RA Pressure = PA 80 mmHg

Diagnostic Approach



Exercise testing

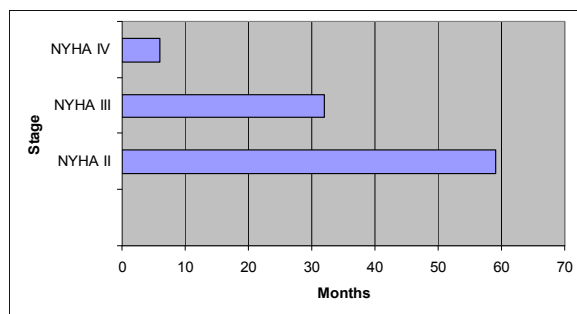
- Six – minute walk
- Cardiopulmonary exercise test
 - Assessment of functional status
 - Response to therapy

Functional Assessment

Class I	No limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain or near syncope.
Class II	Slight limitation of physical activity. Ordinary physical activity causes undue dyspnea or fatigue, chest pain or near syncope.
Class III	Marked limitation of physical activity. Less than ordinary physical activity causes undue dyspnea or fatigue, chest pain or near syncope.
Class IV	Inability to perform any physical activity without symptoms. Signs of right heart failure. Dyspnea and/or fatigue may be present at rest, and discomfort is increased by any physical activity.

* New York Heart Assoc./World Health Org. modification
 Rich S ed. Executive summary of the World Congress on PPH 1998.
<http://www.who.int/ncd/cvd/pph.html>

NYHA Staging / Survival in PPH



Right Heart Catheterization

Invasive measurement of :

- Right atrial Pressure
- Right ventricular Pressures
- PA Pressure
- Pulmonary capillary wedge pressure
- Mixed venous oxygen saturation
- Cardiac output
- Vasodilator challenge

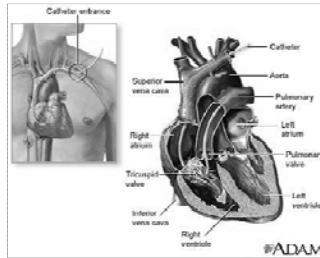
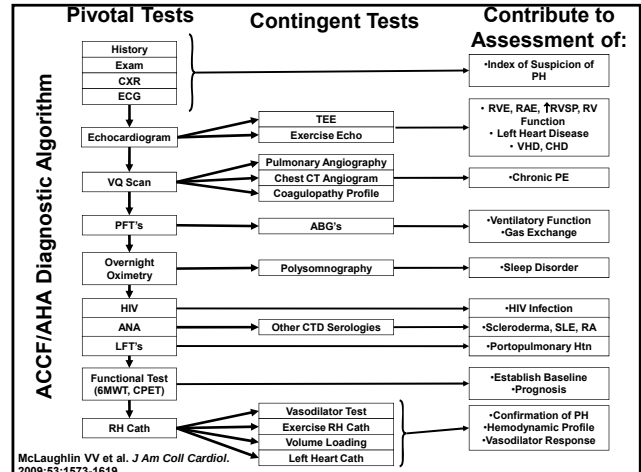
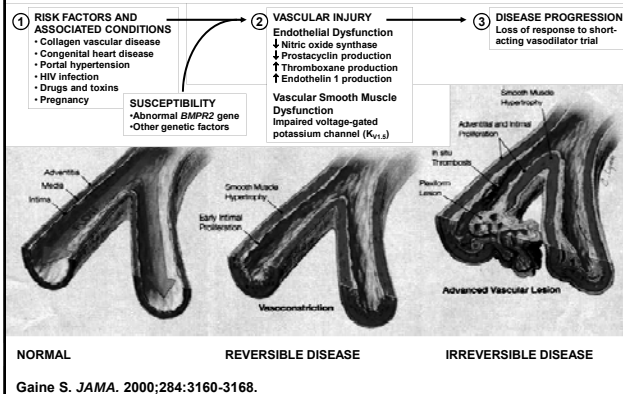


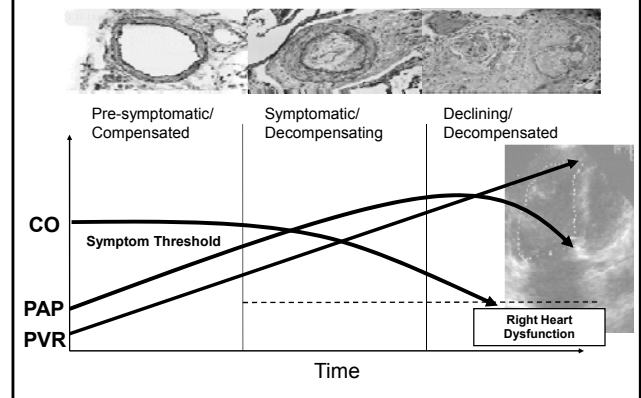
Image from A.D.A.M.



Mechanisms of Disease Pathology



Progression of PAH



Treatment

General measures

- Supplemental oxygen
- Diuretics
- Digoxin
- Anticoagulation

Anticoagulation

Rationale:

- Fresh intrapulmonary clots
- High risk for thromboembolic event
- Improved survival

Treatment

- Warfarin- goal INR 1.6-2.5

Digoxin

- Inotropic effect: variable
- Used in varying number of patients in major center trials of PAH
- Short-term administration associated with an increase in cardiac output and reduced circulating catecholamines
- No long-term data available

Rich S et al. *Chest*. 1998;114:787-792.

Diuretics

- Majority of patients require them
- Variable response
- Follow renal and electrolyte parameters
- Individual patient assessment

Oxygen

- Hypoxemia is detrimental: results in vaso-constriction
- Altitude and sleep may result in hypoxemia
- In congenital heart disease, probably no benefit

Other Management Issues

- Encourage exercise and activity within the limits of disease and ability to maintain O₂ levels
- Immunizations
- Contraception

Calcium Channel Blockers

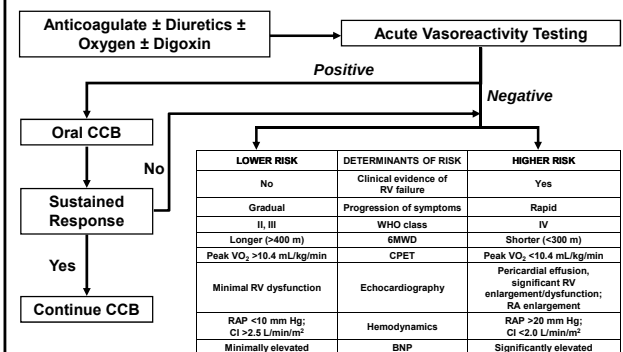
Rationale:

- Rich et al NEJM 1992;327:76-81
- 64 patients with PPH
 - 17 Significant vasoreactivity
 - 13 treated with Nifedipine 172mg + 41 mg/day
 - 4 treated with Diltiazem 720 + 208 mg/day
 - 94% alive at 5 years

Treatment

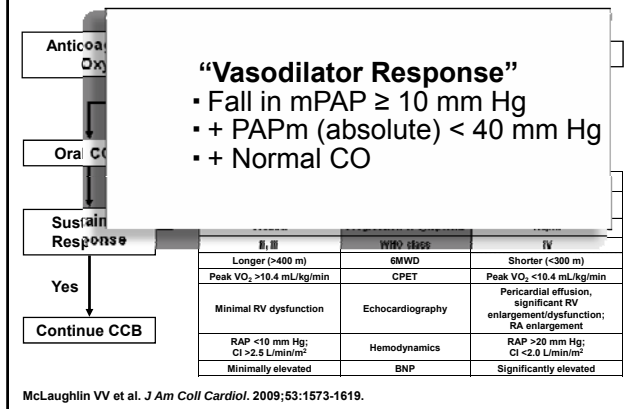
- Diltiazem 360-900 mg/day
- Nifedipine 90-180 mg/day
- ? Amlodipine 20-40 mg/day

What Is the Optimal Treatment Strategy?

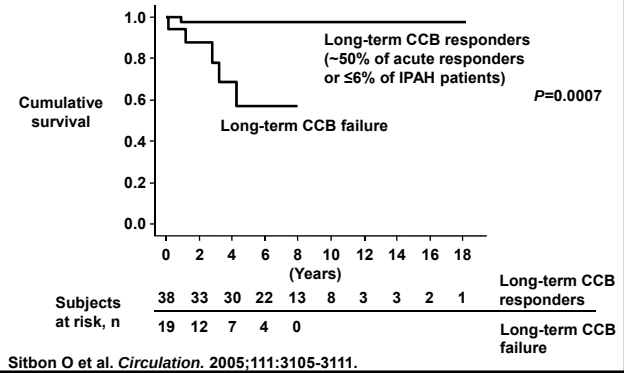


McLaughlin VV et al. J Am Coll Cardiol. 2009;53:1573-1619.

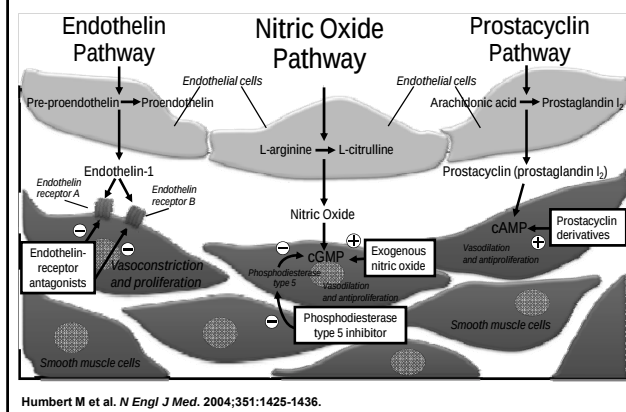
What Is the Optimal Treatment Strategy?



Survival in IPAH Long-term CCB Responders



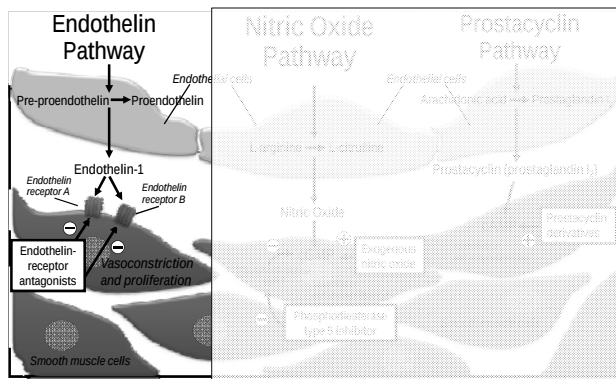
Approved Therapeutic Targets



End points used in trials

- 6 minute walk distance
- VO₂
- QOL
- Hemodynamics
- Time to clinical worsening

Approved Therapeutic Targets



Humbert M et al. *N Engl J Med*. 2004;351:1425-1436.

Endothelin receptor Blocker

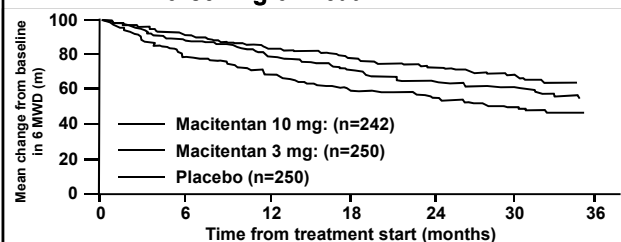
- **Ambrisentan** : selective (ET_A) antagonist
Approved doses: 5 mg and 10 mg qd
- **Bosentan** dual (ET_A and ET_B) antagonist
 - Approved doses: 62.5 mg bid starting dose for 4 weeks increased to 125 mg bid maintenance dose
- **Macitentan** dual (ET_A and ET_B) antagonist

Endothelin receptor blockers vs Placebo in PH

- **Bosentan and Ambrisentan**
 - Increased exercise capacity
 - Delayed the time to clinical worsening
 - Improved dyspnea score
 - WHO Functional Class

Macitentan for PAH: Time To Clinical Worsening or Death

Abstract



Macitentan 10 mg: Hazard ratio=0.55; log-rank p<0.0001
Macitentan 3 mg: Hazard ratio=0.70; log-rank p=0.0108

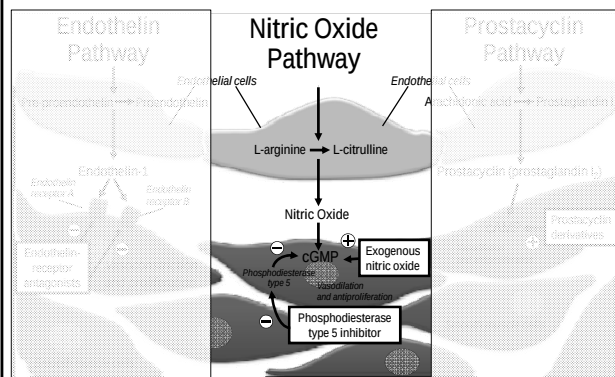
N=742. Double-blind, placebo-controlled Phase III study. Primary endpoint composite endpoint of death, atrial septostomy, lung transplantation, initiation of intravenous/subcutaneous prostanoids or 'other worsening' of PAH.

Rubin L, et al. *Chest*. 2012;142(4_MeetingAbstracts):1026A.

Endothelin Receptor Antagonists: Side Effects

- Nasal congestion
- Abnormal hepatic function
 - reversible transaminase elevations >3X ULN
 - may require dose adjustments or discontinuations
 - monthly LFTs required
- Edema
 - lower extremity edema may require diuretic adjustment
 - Use requires dual contraceptive methods (hormonal plus barrier)

Approved Therapeutic Targets



Humbert M et al. *N Engl J Med*. 2004;351:1425-1436.

Phosphodiesterase-5 Inhibitors

- Sildenafil
 - Approved dose: 20 mg tid
 - Approved for PAH (all classes)
- Tadalafil
 - Approved dose 40 mg once a day

PDE-5 Inhibitor

- Sildenafil Improved
 - Exercise capacity
 - Functional class
 - Hemodynamics
- Tadalafil Improved
 - Exercise capacity
 - Quality of life measures
 - Delayed clinical worsening

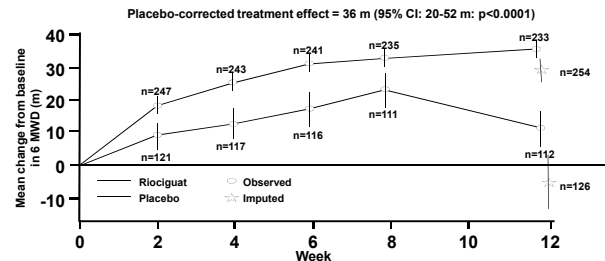
Riociguat

- It is a stimulator of soluble guanylate cyclase(sGC)
- Stimulates NO production
- Does not require endogenous NO
- Initiate at 1 mg taken 3 times a day and titrate by 0.5 mg every 2 weeks as tolerated to 2.5 mg

PATENT-1: Riociguat for PAH

Abstract

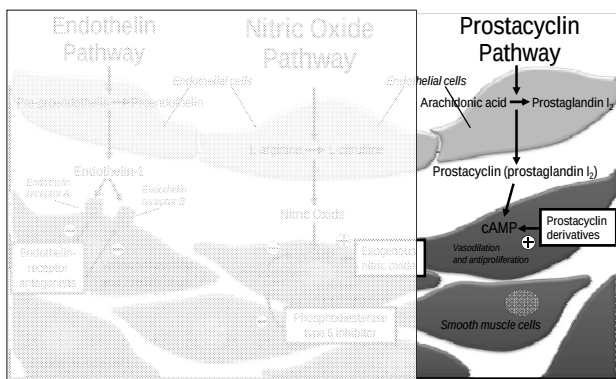
Change in 6MWD At Week 12



N=445. Double-blind, placebo-controlled Phase III trial. 50% of patients were on stable background PAH therapy with ERAs (43%) or prostacyclin (7%)

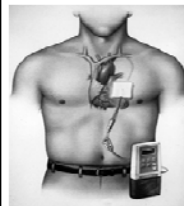
Ghofrani H, et al.

Approved Therapeutic Targets



Humbert M et al. *N Engl J Med*. 2004;351:1425-1436.

Prostacyclin Analogues: Intravenous Subcutaneous, Inhaled



Epoprostenol (Flolan®)
Treprostinil (Remodulin®)

Prostacyclin Analogues: Intravenous Subcutaneous, Inhaled

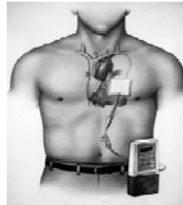


Epoprostenol (Flolan®)
Treprostinil (Remodulin®)



Treprostinil
(Remodulin®)

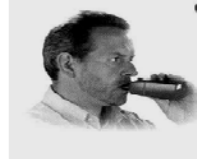
Prostacyclin Analogues: Intravenous Subcutaneous, Inhaled



Epoprostenol (Flolan®)
Treprostinil (Remodulin®)



Treprostinil
(Remodulin®)



Iloprost (Ventavis®)
Treprostinil (Tyvaso®)



Prostanoid Side Effects

- Flushing
- Headache
- Diarrhea, nausea, vomiting
- Jaw pain
- Leg pain
- Hypotension
- Dizziness
- Syncope
- Cough (inhaled)
- Delivery site complications

Vary according to drug and route of delivery

Epoprostenol

- Synthetic salt of prostacyclin
- Rapid efficacy; short, 3- to 5-min half-life
- Approved for Class III and IV
- Invasive: requires continuous IV infusion
- Initiate at low dose 2ng /kg/min



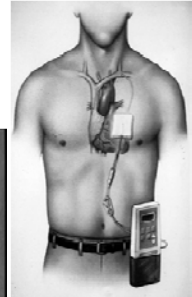
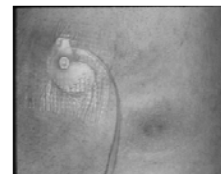
Flolan® (epoprostenol sodium) package insert. GlaxoSmithKline. Research Triangle Park, NC.

Continuous IV Epoprostenol vs conventional therapy in IPAH

- Improved
 - Exercise Capacity
 - Hemodynamics
 - NYHA Class
 - Survival

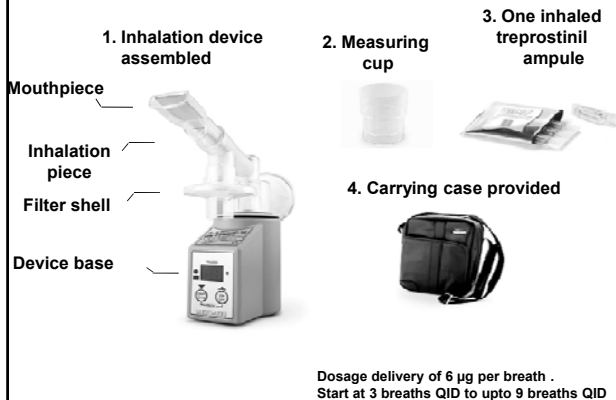
Treprostinil

- Longer-acting prostacyclin analogue
- Subcutaneous and IV infusion;
- Approved for Class II-IV
- Efficacy slower than epoprostenol, requires higher doses

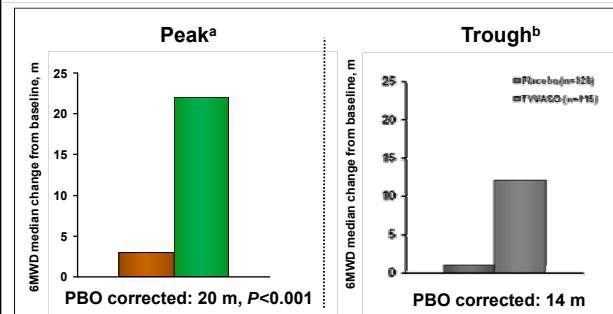


Remodulin® (treprostinil sodium) package insert. United Therapeutics Corp. Research Triangle Park, NC.

Inhaled Treprostinil



TYVASO (treprostinil) Improved Peak and Trough 6MWD at Week 12



6MWD, 6-minute walk distance; PBO, placebo.

^a Peak defined as measure between 10 and 60 minutes after dose. ^b Trough defined as measure 24 hours after dose.

Iloprost

- Longer-acting prostacyclin analogue (20- to 30-min half-life)
- Aerosolized delivery system
- Approved for Class III and IV
- Requires frequent inhalations (6-9x/d)



Ventavis® (Iloprost) package insert. CoTherix Inc. South San Francisco, CA.

I-neb® AAD® Once Daily Routine

At the beginning of each day, load Blue case with 6 CLEAN meshes



Administer therapy



After treatment, remove USED mesh and place it in Red case



At the end of each day, remove the USED meshes from the Red case and wash along with the mouthpiece and drug chamber in distilled water with 1 drop of liquid detergent

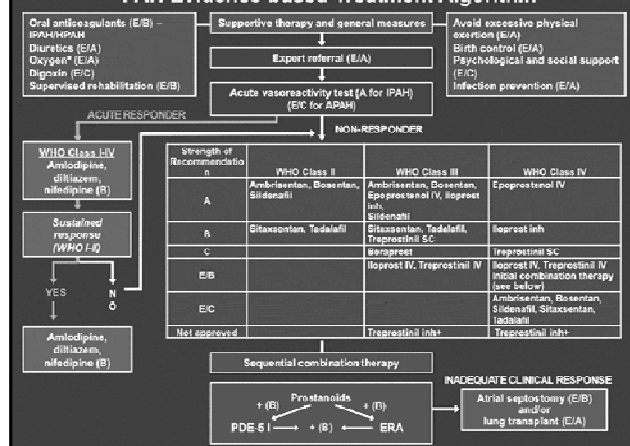


PAH Determinants of Risk

Lower Risk	Determinants of Risk	Higher Risk
No	Clinical evidence of RV failure	Yes
Gradual	Progression	Rapid
II, III	WHO 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. In press.

PAH Evidence-based Treatment Algorithm



Treatment

Monitoring Response to Treatment

- 6 min walk
- Echocardiogram
- BNP
- Right heart Catheterization

On-therapy Prognostic Indicators

- Functional Class I or II
- 6MWD > 380 m
- Hemodynamics
 - Normal cardiac index ($> 2.2 \text{ L/min/m}^2$)
 - Normal RA pressure
- Positive response to CCB
- BNP <180 pg/mL
- Tricuspid Annular plane systolic excursion > 1.8 cm

Sitbon O, et al. *J Am Coll Cardiol.* 2002;40:780-788.
McLaughlin VV, et al. *Circulation.* 2002;106:1477-1482.
Wensel R, et al. *Circulation.* 2002;106:319-324.

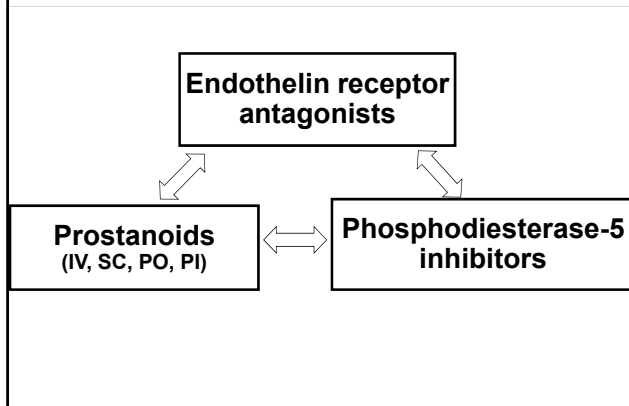
Goal oriented therapy

- Improve functional status
- RA pressure less than 10 mmHg
- BNP less than 100
- 6 minute walk > 350 m

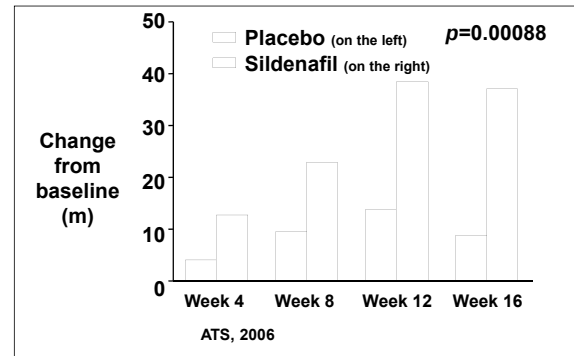
Goal Oriented Therapy

- If patient does not improve, what would you do?
 - Substitute therapy
 - Add therapies

Combination Therapy in PAH

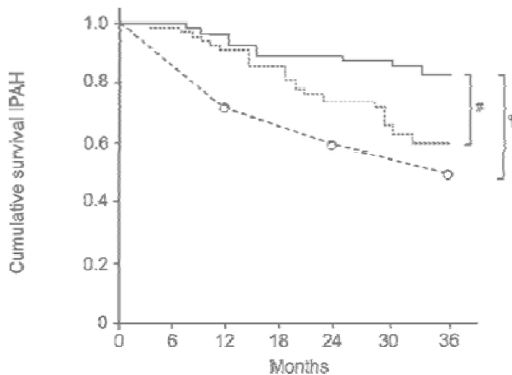


PACES: Change From Baseline in 6MWD after adding Sildenafil to IV Epoprostenol

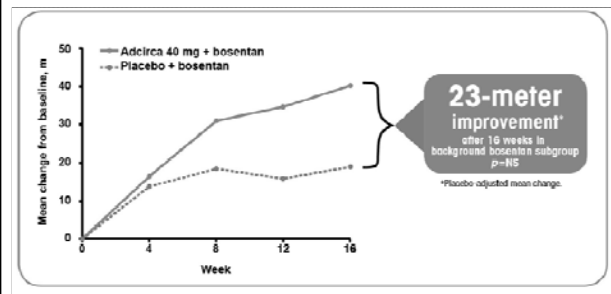


Simonneau. Annals Int Med.

Goal Oriented Treatment and Combination Therapy for PAH

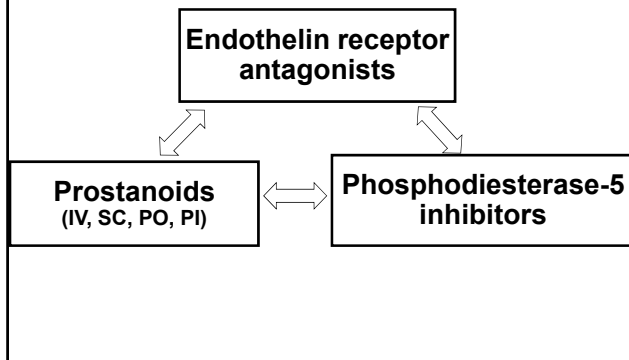


Tadalafil Improved 6MWD in the Bosentan Treatment Subgroup



6MWD, 6-minute walk distance; NS, not significant.

Combination Therapy in PAH



Atrial Septostomy

- Percutaneous catheter based technique
- Allows shunting from Right to left
- Shown to improve
 - clinical status
 - Long lasting benefit
- Carries a mortality of 5- 6%
- Reserved for patients with refractory right heart failure or recurrent syncope despite maximal medical therapy
- Acceptable baseline oxygenation
- Poor outcome
 - mRA > 20mmHg
 - PVRI > 55u/m²
 - Not indicated in patients with hemodynamic instability

Transplantation

- Symptomatic, Progressive Ds
- NYHA class III or IV
- Hemodynamic parameters
 - Cardiac index < 2L/min/m²
 - RA pressures > 15 mmHg
 - mPA pressure > 55mmHg



1951

“Primary Pulmonary Hypertension”

• “Runs a malignant course, characterized by right heart failure, frequently ending in sudden death”

• “There is no effective treatment”

Dresdale DT Am J Med 1951: 11: 686-705