Pulmonary Arterial Hypertension: Diagnosis of Treatment

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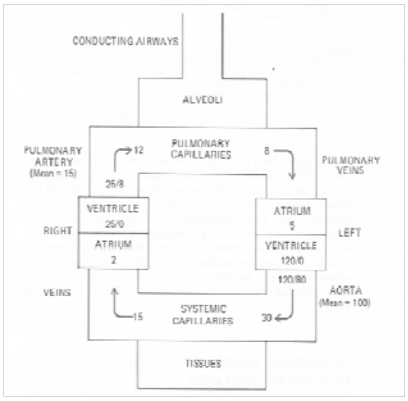
PAH

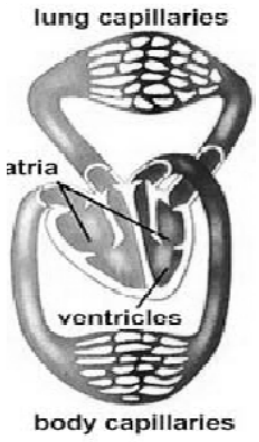
- Classification
- Diagnosis
- Current treatment

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)

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- **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**
- **2,4Congenital /Aquired 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

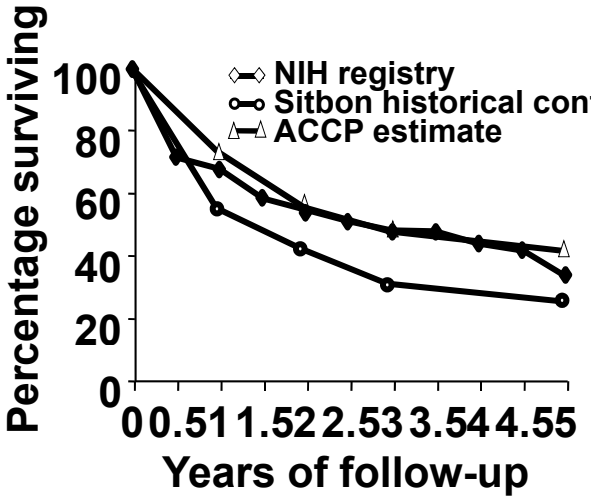
mean pulmonary artery pressure

- **> 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

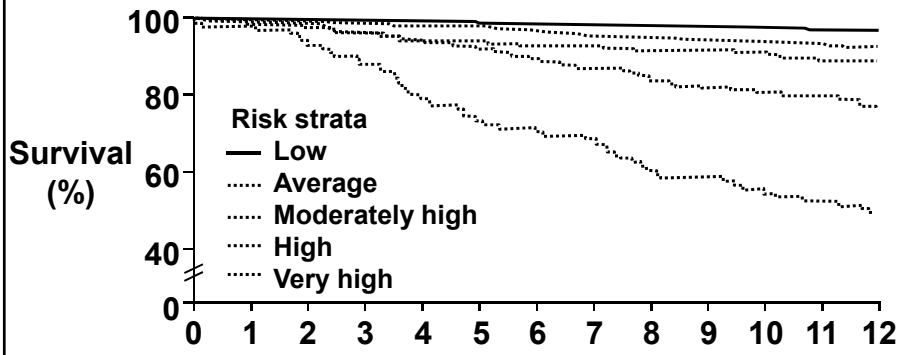
A Disease of Decline and Deterioration: IPAH Survival if Untreated



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

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.

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

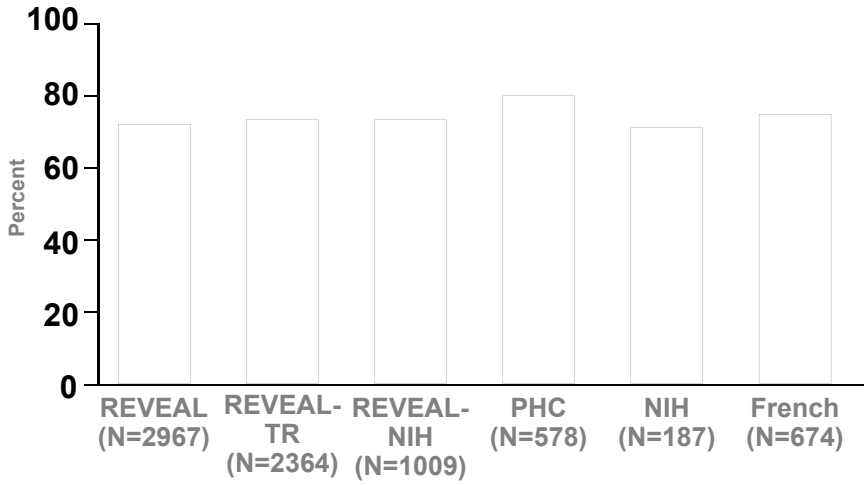


No. at risk:													
Low	1374	1368	1364	1359	1356	1352	1351	1346	1341	1336	1311	1304	1303
Average	665	659	657	653	648	647	640	628	625	618	604	602	596
Mod. high	280	277	274	269	264	263	260	259	255	254	249	244	243
High	295	293	291	284	277	270	263	255	247	241	238	233	225
Very high	102	100	96	89	81	74	72	69	61	59	55	52	49

Benza RL et al. *Circulation*. 2010;122:164-172.

PAH Registries: Functional Class at Diagnosis Indicates Delayed Diagnosis

% Patients NYHA Functional Class III-IV at Diagnosis



Frost AE. CHEST 2008. October 25-30, 2008, Philadelphia, PA. Session AP2217.

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

McGoon 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

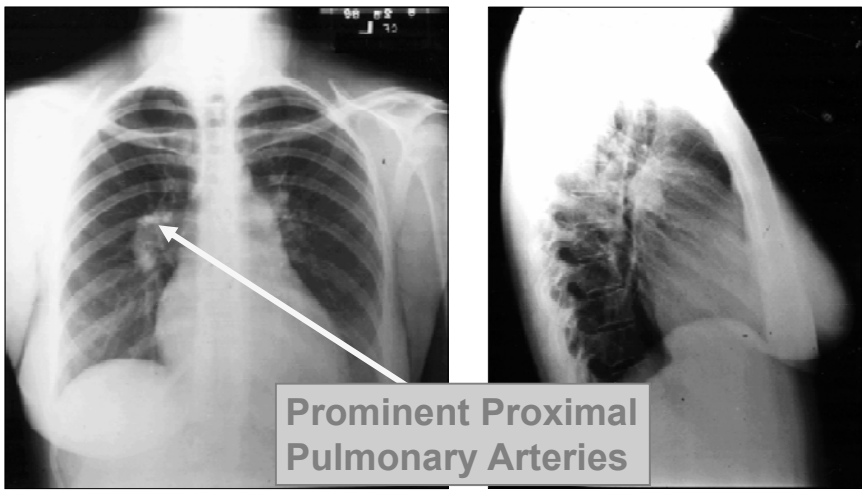
Presence of PH

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

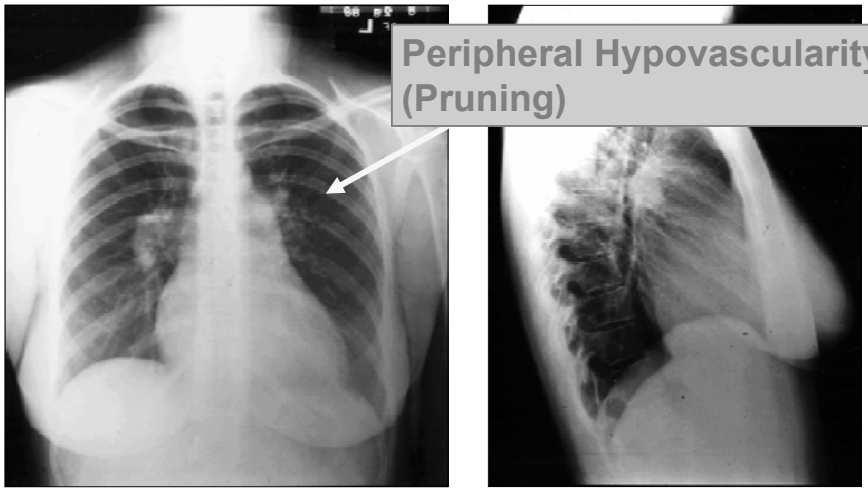
Presence of RV Failure

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

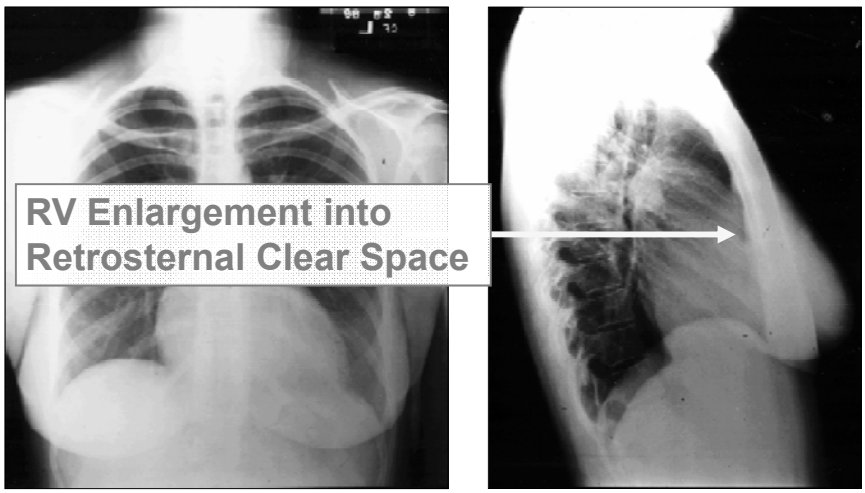
Chest X-Ray



Chest X-Ray

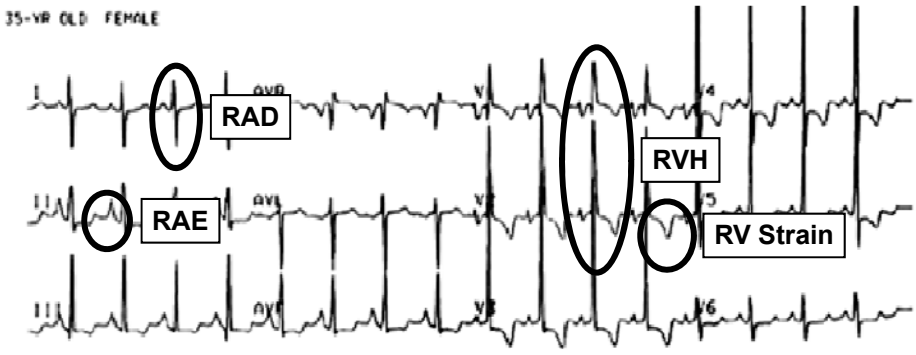


Chest X-Ray



Is There a Reason to Suspect PAH?

ECG

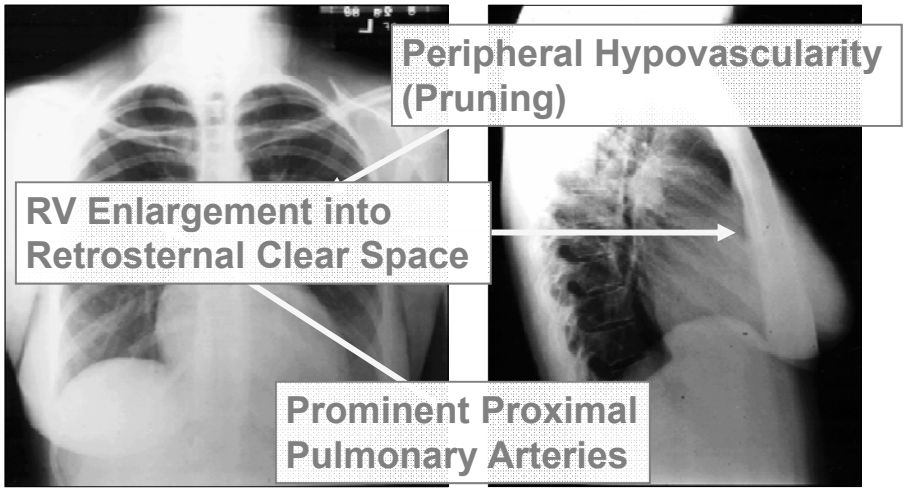


McGoon M et al for the American College of Chest Physicians. *Chest.* 2004;126:14S-34S.

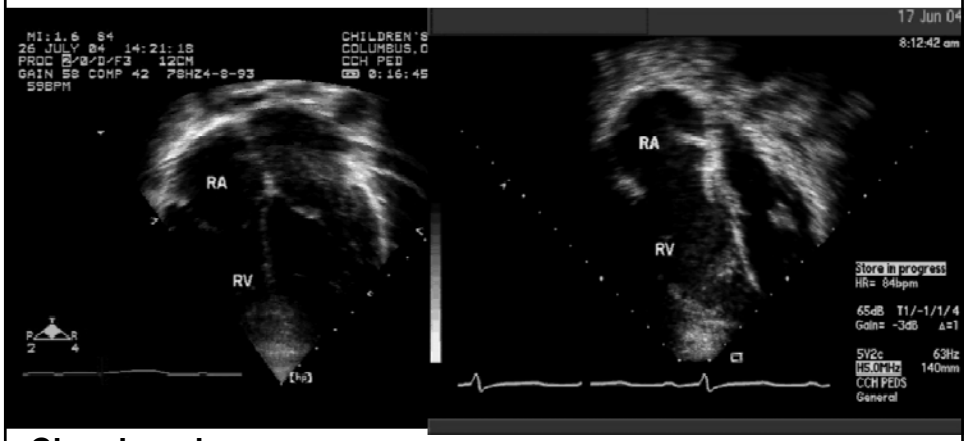
Diagnostic Evaluation

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

Chest X-Ray

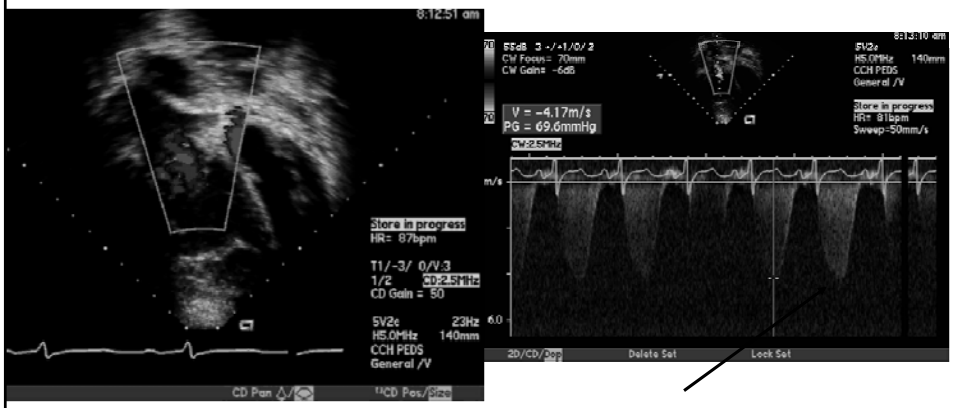


Cardiovascular Evaluation



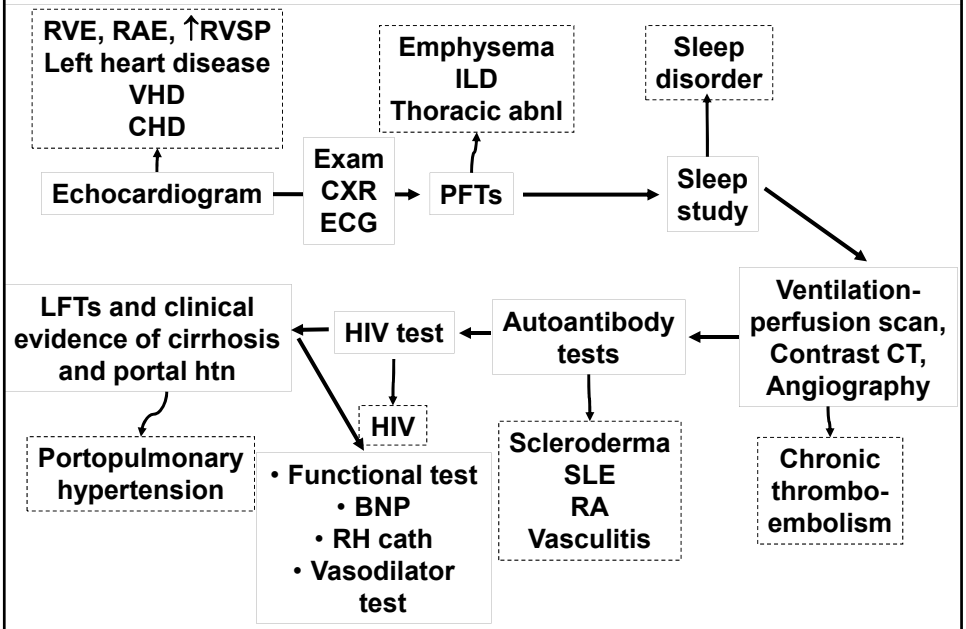
Chamber size
LV and RV systolic function
LV diastolic function
Valvular function
TR
Bubble study

Cardiovascular Evaluation



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

Diagnostic Approach



McLaughlin VV, McGoon Michael D. *Circulation.* 2006;114:1417-1431.

Exercise testing

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

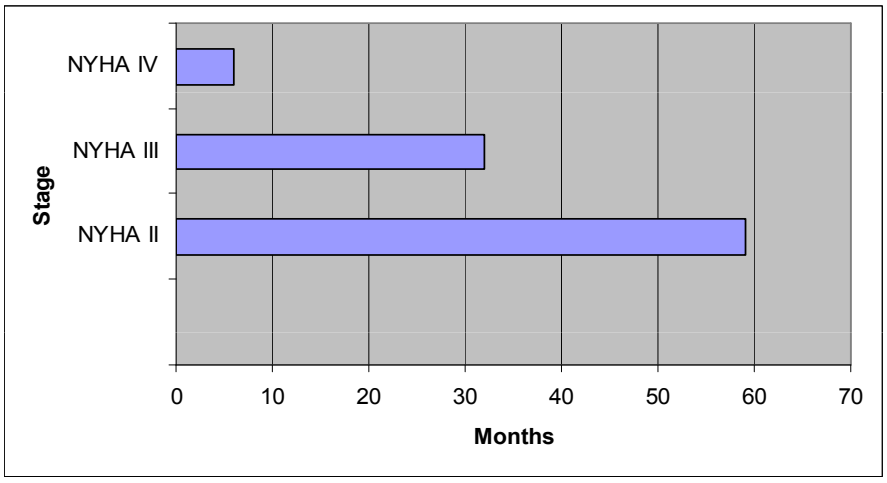
Functional Assessment

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**
-

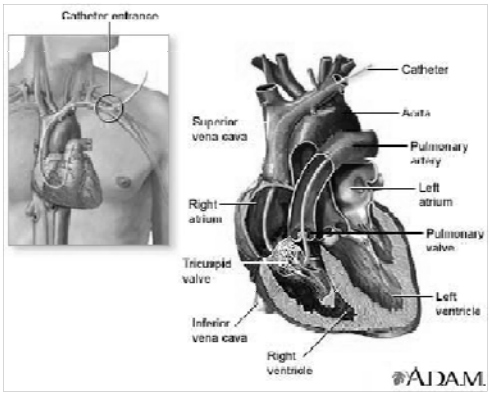
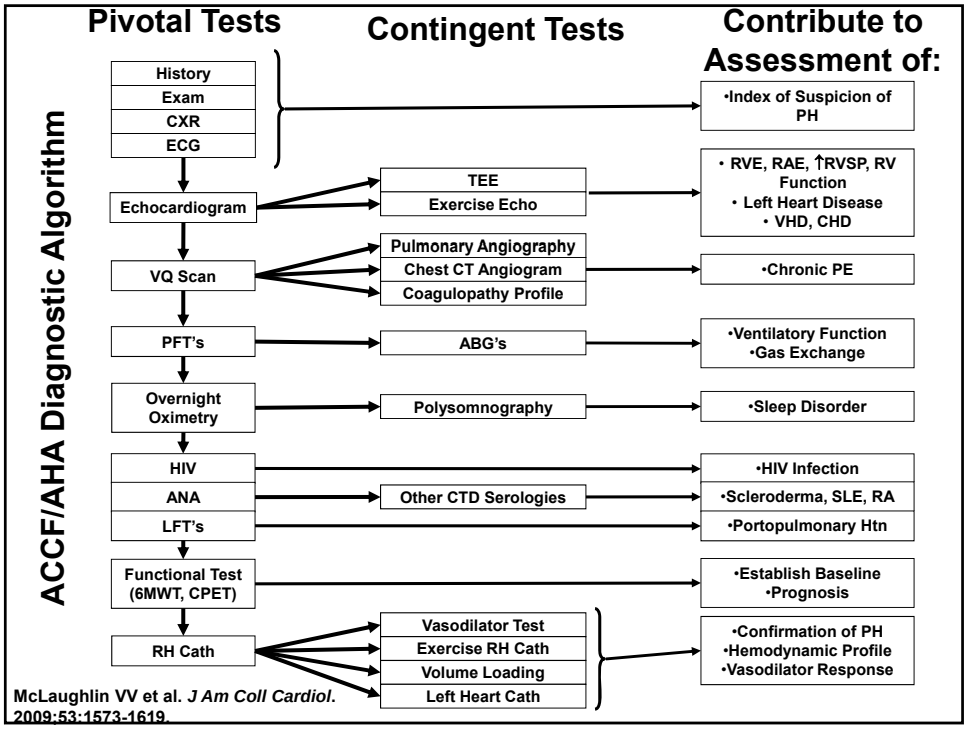
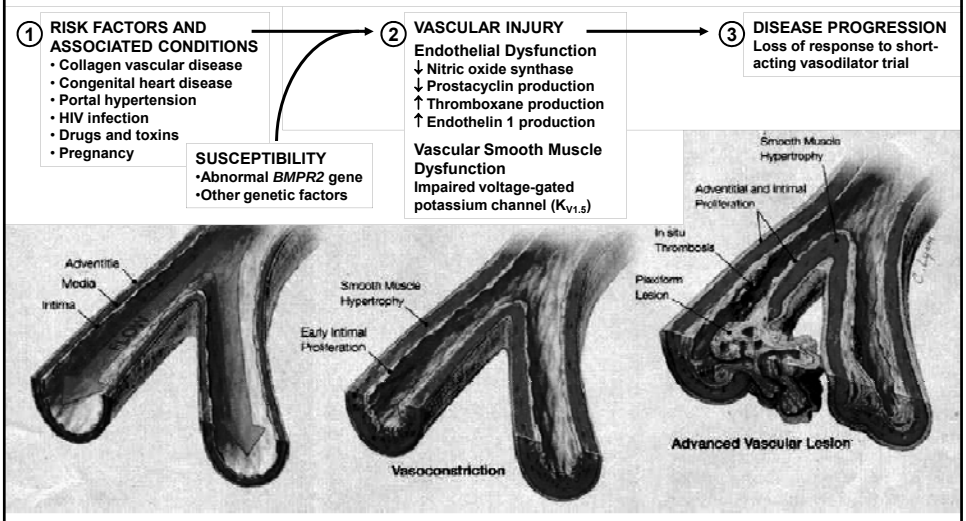


Image from A.D.A.M.



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

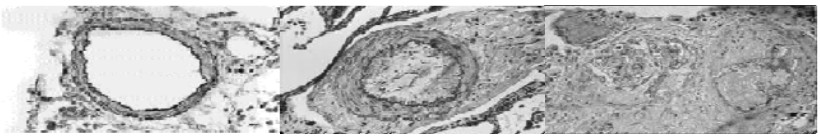
Mechanisms of Disease Pathology

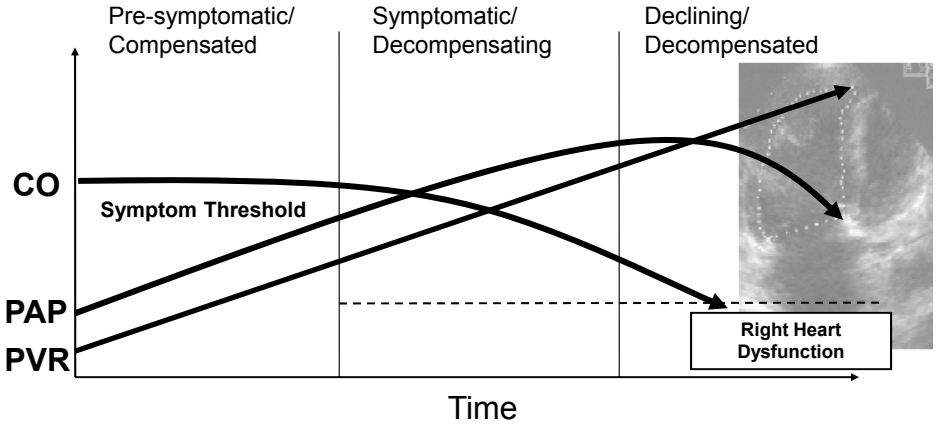


NORMAL **REVERSIBLE DISEASE** **IRREVERSIBLE DISEASE**

Gaine S. *JAMA.* 2000;284:3160-3168.

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

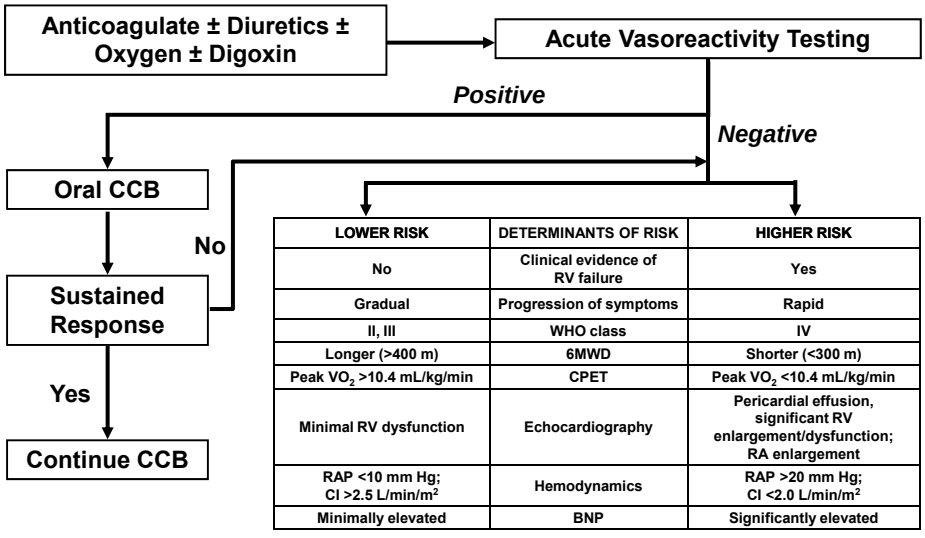
- Encourage exercise and activity within the limits of disease and ability to maintain O_2 levels
- Immunizations
- Contraception

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
- ? Amilodipine 20-40 mg/day

What Is the Optimal Treatment Strategy?



LOWER RISK	DETERMINANTS OF RISK	HIGHER RISK
No	Clinical evidence of RV failure	Yes
Gradual	Progression of symptoms	Rapid
II, III	WHO class	IV
Longer (>400 m)	6MWD	Shorter (<300 m)
Peak VO_2 >10.4 mL/kg/min	CPET	Peak VO_2 <10.4 mL/kg/min
Minimal RV dysfunction	Echocardiography	Pericardial effusion, significant RV enlargement/dysfunction; RA enlargement
RAP <10 mm Hg; CI >2.5 L/min/m^2	Hemodynamics	RAP >20 mm Hg; CI <2.0 L/min/m^2
Minimally elevated	BNP	Significantly elevated

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

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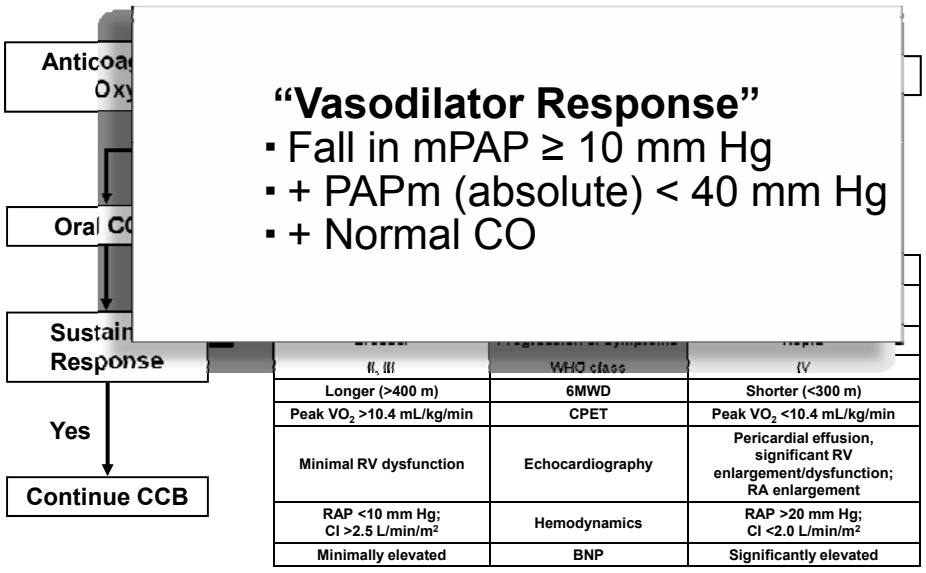

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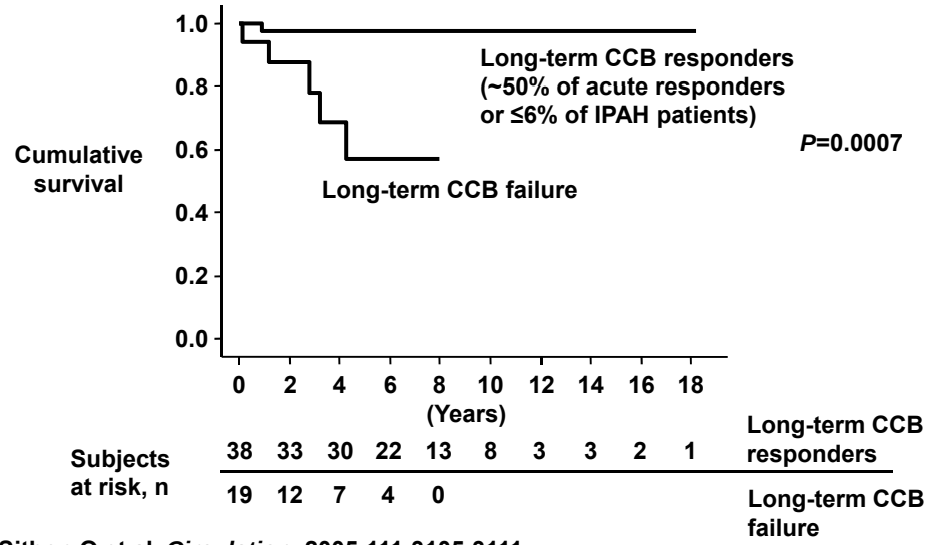
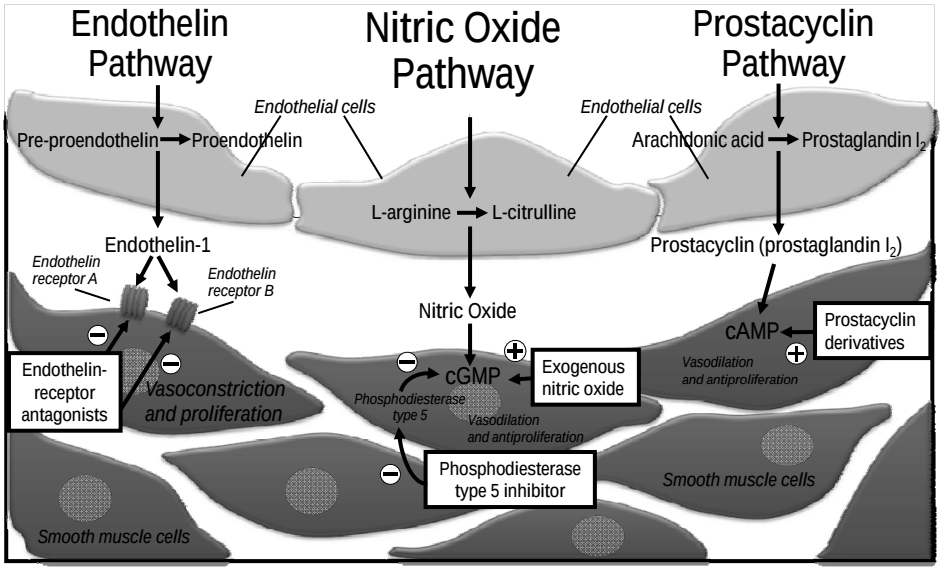
Survival in IPAH
Long-term CCB Responders



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

Approved Therapeutic Targets

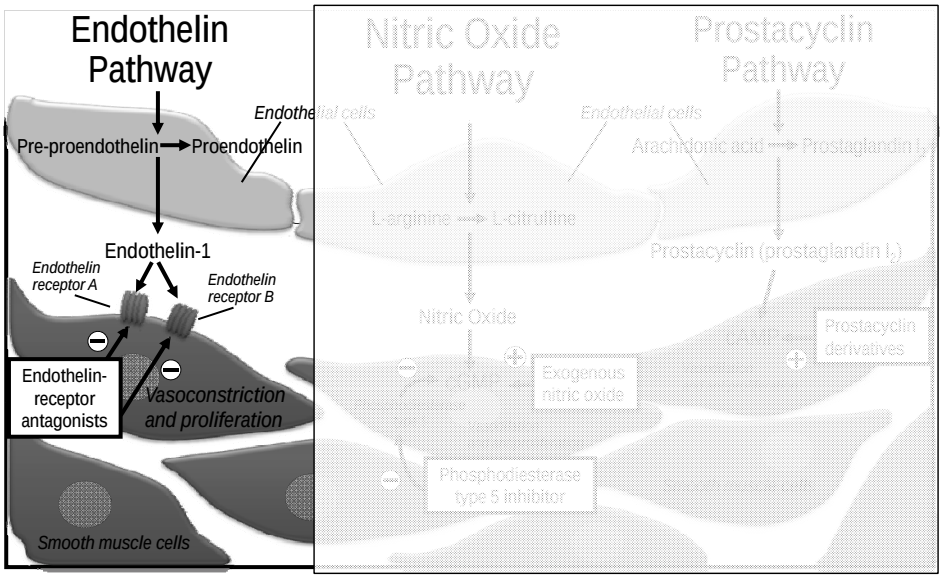


Humbert M et al. *N Engl J Med*. 2004;351:1425-1436.

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**

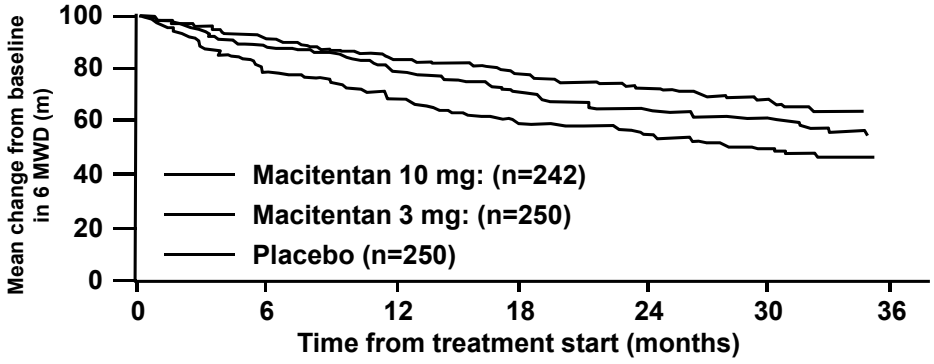
Endothelin receptor blockers vs Placebo in PH

- **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

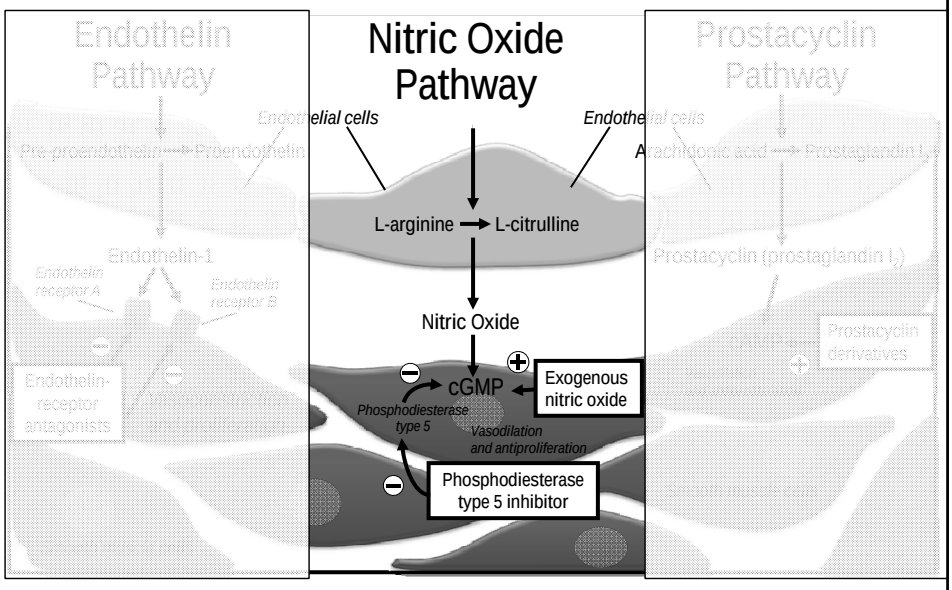
N=742. Double-blind, placebo-controlled Phase III study. Primary endpoint composite endpoint of death, atrial septostomy, lung transplantation, initiation of intravenous/subcutaneous prostanoids or 'other worsening' of PAH.

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 cyclace(sGC)
- Stimulates NO production
- Does not require endogenous NO

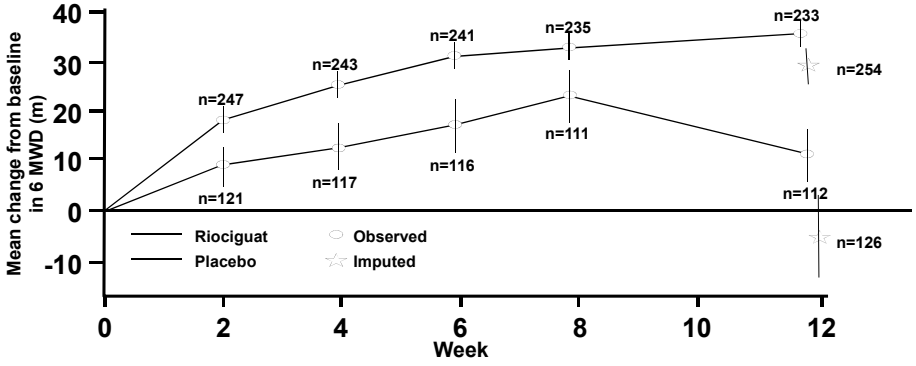
- Initiate at 1 mg taken 3 times a day and titrate by 0.5 mg every 2 weeks as tolerated to 2.5 mg

PATENT-1: Riociguat for PAH Change in 6MWD At Week 12

Abstract

Six-minute Walk Distance

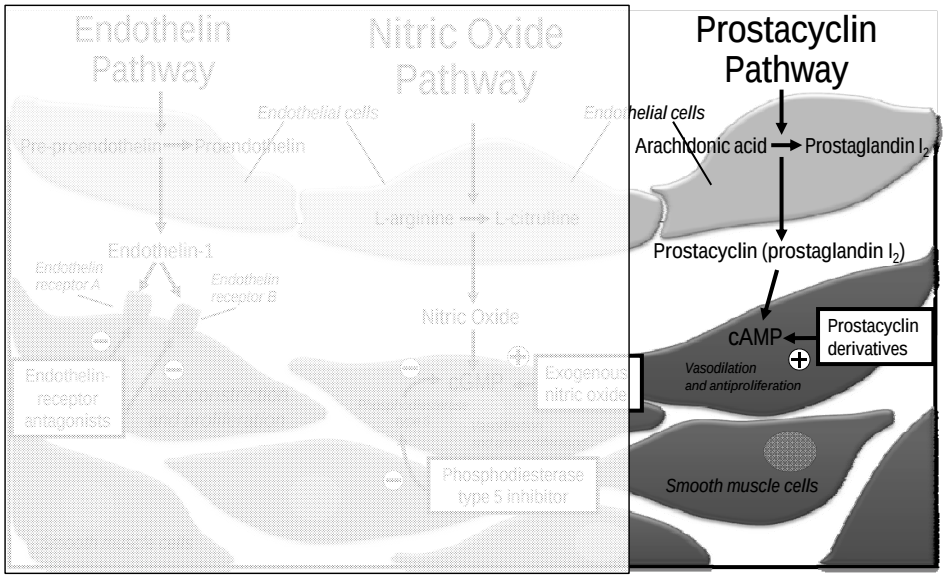
Placebo-corrected treatment effect = 36 m (95% CI: 20-52 m: p<0.0001)



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



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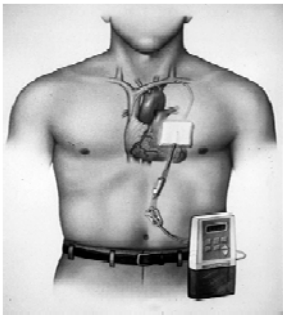
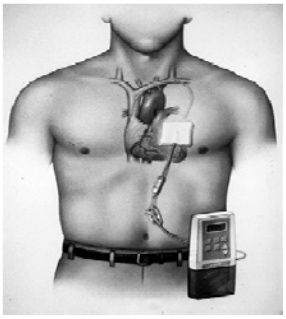
Prostacyclin Analogues: Intravenous Subcutaneous, Inhaled



Epoprostenol (Flolan®)
Treprostinil (Remodulin®)

Prostacyclin Analogues: Intravenous Subcutaneous, Inhaled



Epoprostenol (Flolan®)
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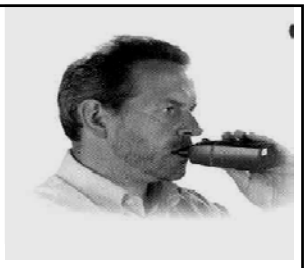
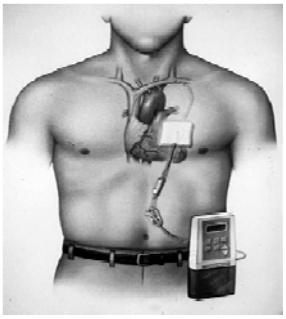


Iloprost (Ventavis®)
Treprostinil (Tyvaso®)



Epoprostenol (Flolan®)
Treprostinil (Remodulin®)

Treprostinil (Remodulin®)

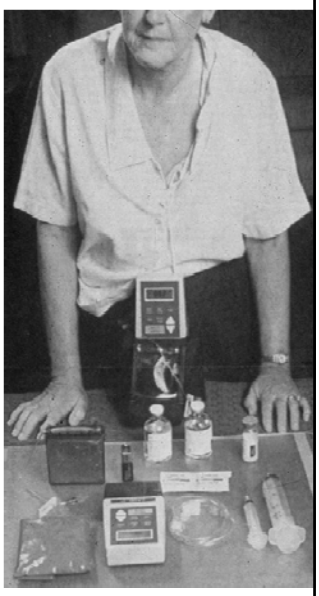
Prostanoid Side Effects

- 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



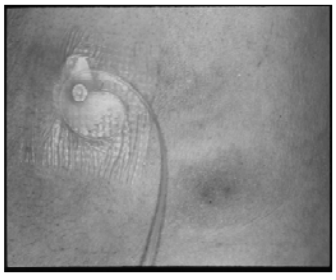
Flolan® (epoprostenol sodium) package insert. GlaxoSmithKline. Research Triangle Park, NC.

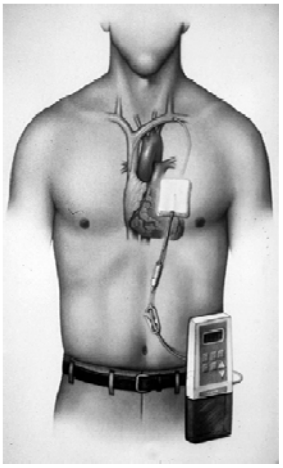
Continuous IV Epoprostenol vs conventional therapy in IPAH

- 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.

Inhalated Treprostinil

1. Inhalation device assembled

Mouthpiece

Inhalation piece

Filter shell

Device base

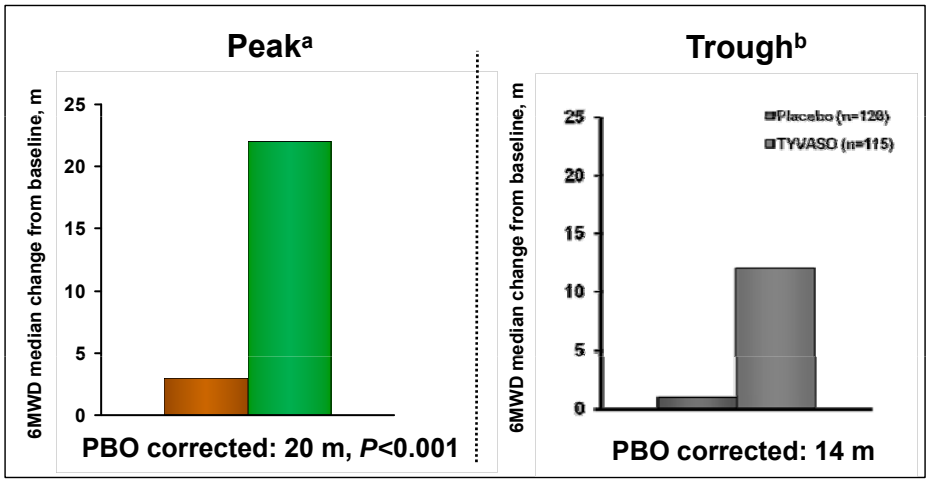
2. Measuring cup

3. One inhaled treprostinil ampule

4. Carrying case provided

Dosage delivery of 6 µg per breath .
Start at 3 breaths QID to upto 9 breaths QID

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 ≥4 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

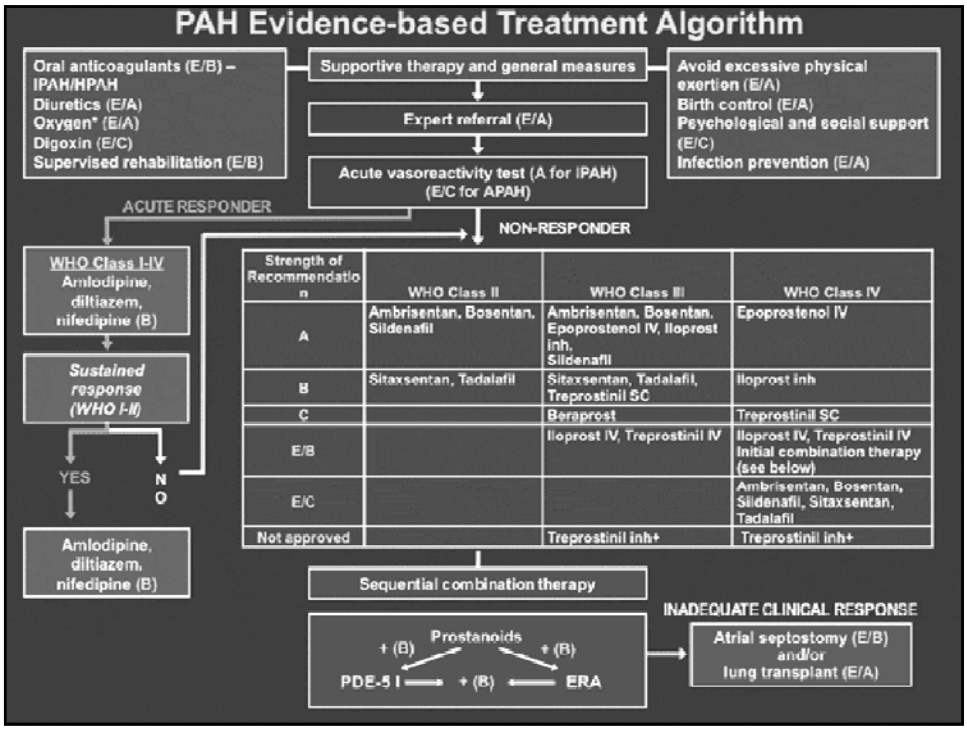
After treatment, remove USED mesh and place it in Red case

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.



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 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.

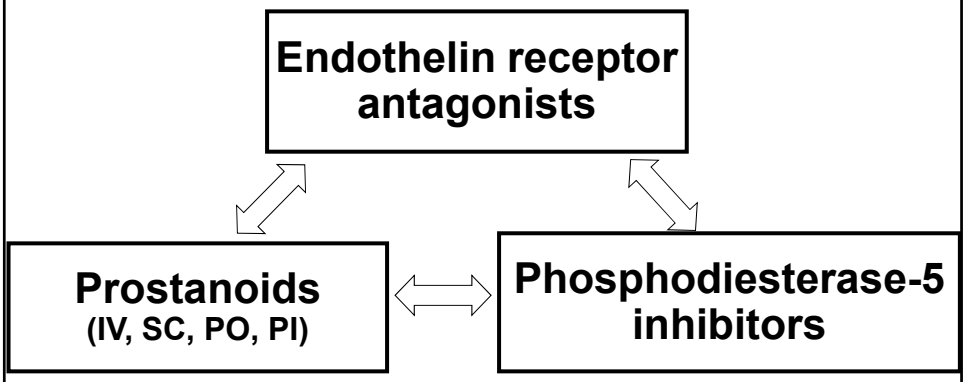
Goal oriented therapy

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

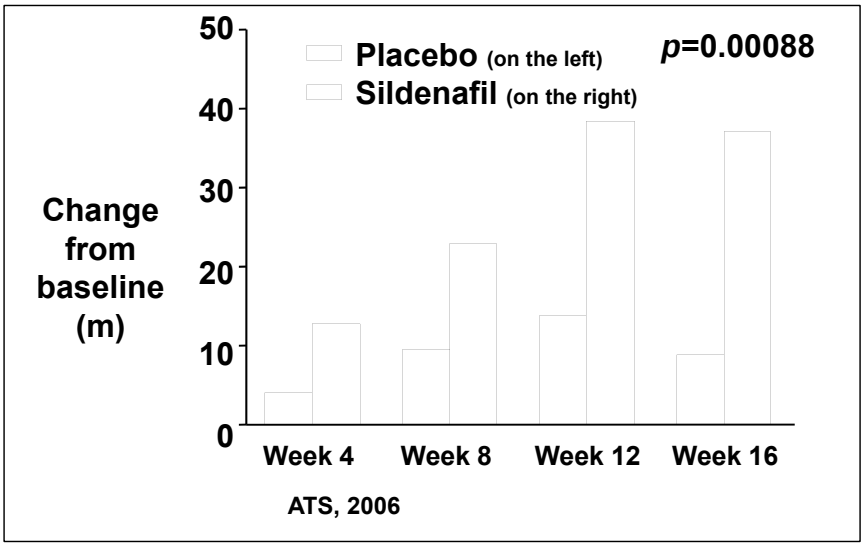
Goal Oriented Therapy

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

Combination Therapy in PAH

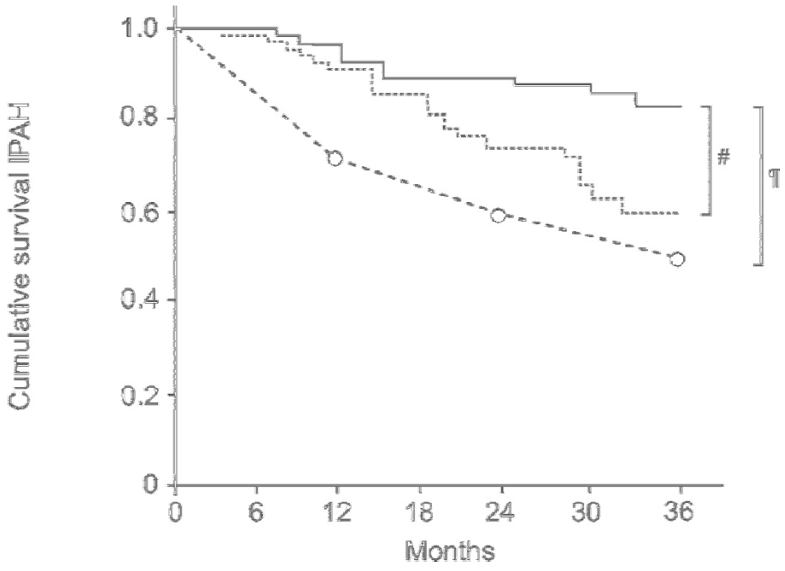


PACES: Change From Baseline in 6MWD after adding Sildenafil to IV Epoprostenol

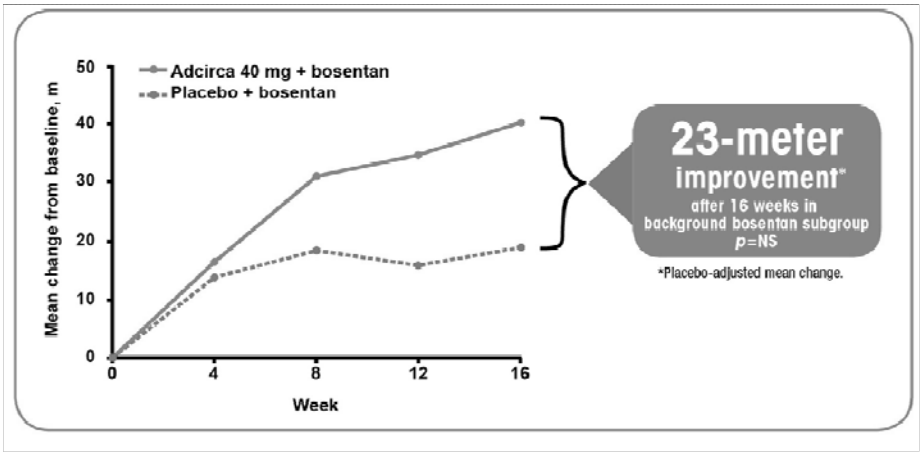


Simonneau. Annals Int Med.

Goal Oriented Treatment and Combination Therapy for PAH

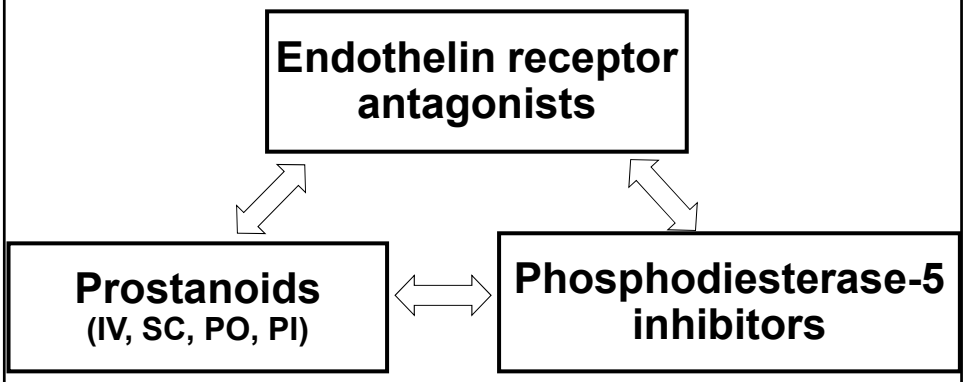


Tadalafil Improved 6MWD in the Bosentan Treatment Subgroup



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/m^2
  - 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