The Pulmonary Circulation:
Pulmonary Embolism and
Pulmonary Arterial Hypertension

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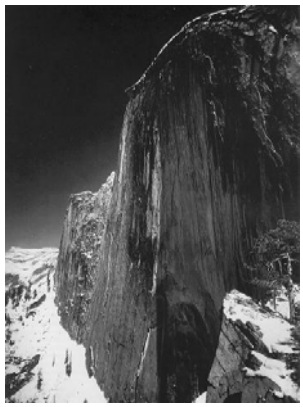
- **Ohm's Law- V=IR…. R=V/I**
  - **PVR= (mPA-LA)/CO**
  - **100 dynes/s/cm^{-5}**
- **R=8 (l) n / r^4 Π**



Control of the Pulmonary Circulation

- **Hypoxia**
- **Nervous**
- **Neurohormones**

Pulmonary Vasculature

- **Elastic pulmonary arteries (> 1-2 mm diameter)**
- **Muscular pulmonary arteries (100 µm-1 mm)**
- **Pulmonary arterioles (< 30 µm) no muscle**
- **7 times more compliant than systemic vasculature**

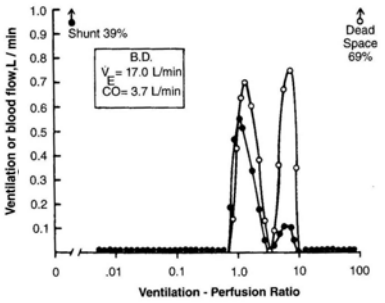
Pulmonary Hypertension

Increased pulmonary arterial pressure
- usually increased PVR
  - Vasoconstriction
  - Obstruction
  - Obliteration
  - Cor pulmonale

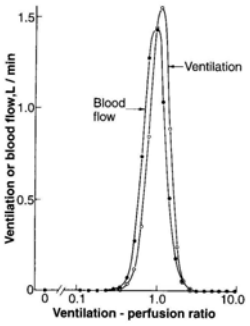
Acute Pulmonary Embolism

- ✓ Deep venous thrombosis is precursor
  - ✓ 5 mil DVT, 10% have PE, 10% die
- ✓ After embolus hits-
  - ✓ Alveolar dead space created
  - ✓ Hyperventilation ensues
  - ✓ Arterial hypoxemia ensues
    - ✓ Increased A-V difference from RV strain and decreased CO
    - ✓ Shunt (pulmonary or cardiac)
    - ✓ Increased PA pressure, hypoxic vasoconstriction is overcome and V/Q mismatch occurs
    - ✓ Late- loss of surfactant and reperfusion

Acute PE



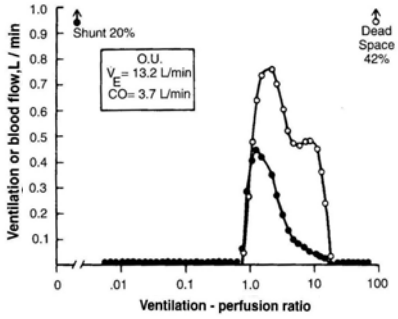
Normal V/Q Matching



Acute Pulmonary Embolism

- ✓ Obstruction by thrombus
  - ✓ < 20% ok
  - ✓ 30-40% less ok
  - ✓ > 40-50%- bad
- ✓ Response
  - ✓ No preexisting disease
  - ✓ Preexisting disease

Acute PE



Acute Pulmonary Embolism

- ✓ Symptoms
  - ✓ Dyspnea
  - ✓ Chest pain
  - ✓ Syncope
- ✓ Signs
  - ✓ Tachypnea
  - ✓ Tachycardia
  - ✓ Rales
  - ✓ RV findings
  - ✓ Legs

Acute Pulmonary Embolism

- ✓ Diagnosis
  - ✓ D-dimer
  - ✓ Chest radiograph
  - ✓ Ecg
  - ✓ Arterial blood gas
  - ✓ Duplex ultrasound
  - ✓ Ventilation-perfusion scan
  - ✓ CT scan of the chest with contrast

WHO Classification

- o Pulmonary arterial hypertension
- o Pulmonary hypertension with left heart disease
- o Pulmonary hypertension associated with lung diseases and/or hypoxemia
- o Pulmonary hypertension due to chronic thrombotic and/or embolic disease
- o Miscellaneous

(Simonneau, JACC, 2004)

Acute Pulmonary Embolism

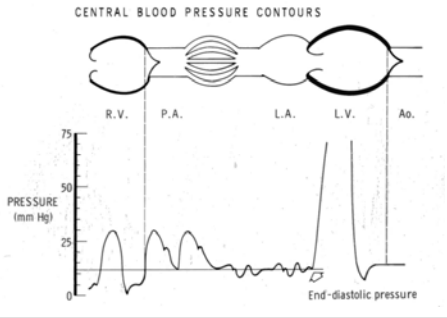
- ✓ Diagnosis
  - ✓ D-dimer
  - ✓ Chest radiograph
  - ✓ Ecg
  - ✓ Arterial blood gas
  - ✓ Duplex ultrasound
  - ✓ Ventilation-perfusion scan
  - ✓ CT scan of the chest with contrast
- ✓ Treatment
  - ✓ Heparin, warfarin- get therapeutic within 24 hours
  - ✓ Thrombolytic therapy
  - ✓ Inferior vena cava filter

WHO Classification

- **Left Heart Disease**
  - Atrial
  - Ventricular
  - Valvular
- **Hypoxemic**
  - COPD
  - ILD
  - Sleep-disordered breathing
  - Alveolar hypoventilation
  - High altitude
  - Developmental abnormalities
- **Thrombotic/embolic**
- **Miscellaneous**

(Simonneau, JACC, 2004)

Normal Pulmonary Artery Pressures

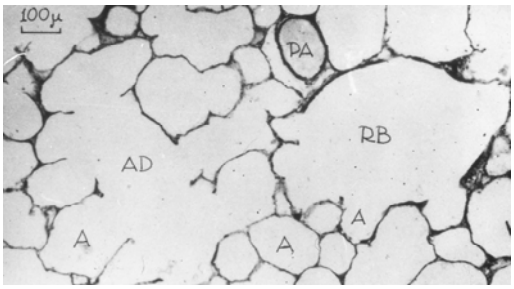


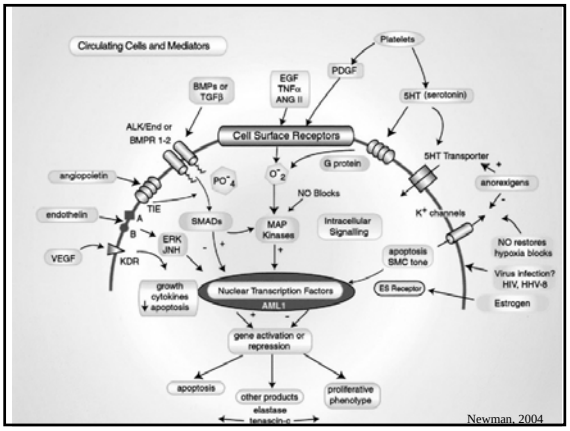
WHO Classification

- o **Pulmonary arterial hypertension**
  - o Idiopathic
  - o Familial
  - o Associated with:
    - o Drugs/Anorexigen use ("Fen-phen")
    - o Collagen vascular disease
    - o HIV infection
    - o Portal hypertension
    - o Congenital systemic-to-pulmonary cardiac shunts
    - o Other (glycogen storage dis, HHT, splenectomy)
  - o Associated with significant venous or capillary involvement (PVOD, PCH)

(Simonneau, JACC, 2004)

Normal

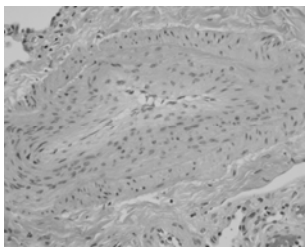




Newman, 2004

Pathology

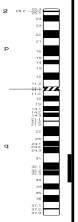
Endothelial thickening



Smooth muscle hypertrophy

Bone Morphogenetic Protein Receptor-II

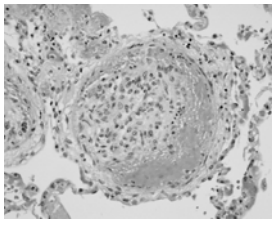
Columbia *(Deng et al., Am J Hum Gen, 2000)*
Vanderbilt *(Lane et al., Nat Gen, 2000)*

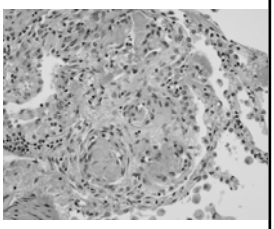


- TGF-β receptor superfamily, Chr 2q 31-33
- Heterozygous germ line mutation:
  frameshift, nonsense, and missense
- 25-50% of familial; 26% of sporadic cases
  (Thompson, J Med Gen, 2000; Machado, Am J Hum Gen, 2001)
- Inheritance: autosomal dominant
- Incomplete penetrance, genetic anticipation
- Mechanism: haplotype insufficiency vs. dominant negative

Pathology

Plexiform lesions





In situ thrombosis

Medical History and Labs

- Past medical history
- Exposures
- Drug use
- Family history
- Anti-nuclear antibodies
- HIV
- Anti-phospholipid antibodies

Evaluation

- Chest radiograph
- Electrocardiogram
- Pulmonary function testing
- Cardiopulmonary exercise testing
- Arterial blood gas
- HIV testing
- Serologies
- High-resolution computed tomography
- Polysomnography
- V/Q scan
- Pulmonary angiography
- Echocardiography
- Right heart catheterization

Right Heart Catheterization

•Diagnose pulmonary hypertension with normal PCWP

•Assess severity of pulmonary hypertension

•Assess acute vasoreactivity

Lung Function and Imaging

•Chest radiograph

•High-resolution CT scan

•V/Q scan

•Pulmonary arteriogram

•Arterial blood gas

•Pulmonary function testing

•Polysomnography

Right Heart Catheterization

•Mean right atrial pressure

•Mean pulmonary artery pressure

•Cardiac index

•Acute vasoreactivity

Echocardiography

•Tricuspid regurgitation

•Right a/v dilatation

•Right ventricular hypertrophy

•Right ventricular dysfunction

•Pulmonic insufficiency

•Intracardiac shunt

•Left heart

•Valvular morphology

•Pericardial effusion

Right Heart Catheterization

•RA-4 mm Hg

•PA- 90/60 mm Hg

•PCWP- 8 mm Hg

•CI- 2.4 $L/m/m^2$

•PVR- 1100 $d \cdot s \cdot cm^{-5}$

•RA-12 mm Hg

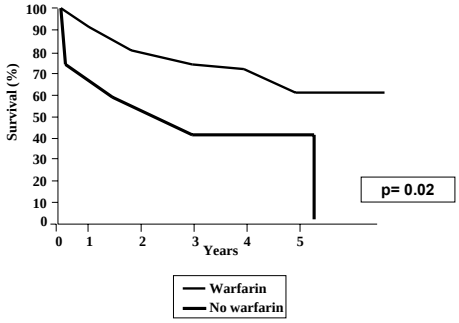
•PA- 50/25 mm Hg

•PCWP- 8 mm Hg

•CI- 1.0 L/m/m2

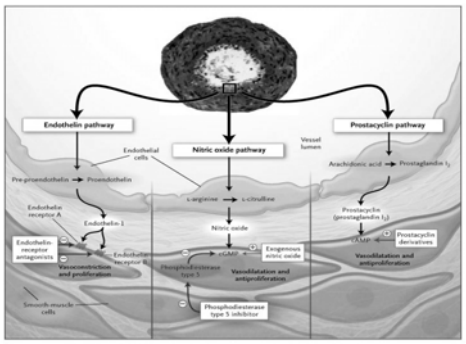
•PVR- 1100 $d \cdot s \cdot cm^{-5}$

Pulmonary Arterial Hypertension: Warfarin Use and Survival (1994-2002) (N=84)

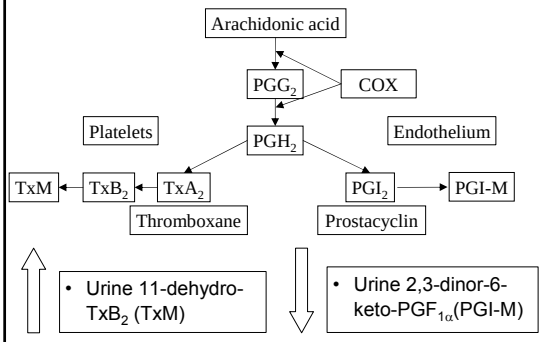


(Kawut, 2005)

Therapy Targets for PAH



Humbert M, Sitbon O, Simonneau G. *N Engl J Med* 2004;351:1425-36



(*Christman, 1991)*

Therapies for PAH

- **Preventative care**
- **Anticoagulation**
- **Supplemental oxygen**
- **Diuretics**
- **Inotropes**
- **Calcium channel blockers**
- **Prostacyclin analogues**
- **Endothelin-1 receptor antagonists**
- **PDE-5 inhibitors**
- **Cardiopulmonary rehabilitation**
- **Atrial septostomy**
- **Lung transplantation**

Intravenous Epoprostenol

Randomized, controlled trial, IPAH

NYHA III-IV

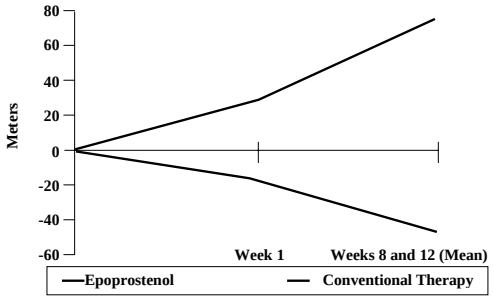
41 randomized to IV epoprostenol + conventional therapy

40 randomized to conventional therapy alone

All but 1 in each group were anticoagulated

(Barst, 1996)

Change from Baseline in 6-Minute Walk Test



(Barst, 1996)

Serious Complications

- Catheter-related infections
- Malfunction of the drug delivery system
- Systemic hypotension
- Ascites
- Coronary steal
- Thrombocytopenia

Changes from Baseline to 12 Weeks

Variable	Conv (N=40)	Conv + Epo (N=41)
RA, mm Hg	0.1 (1)	-2.2 (1)*
mPA, mm Hg	1.9 (2)	-4.8 (1)*
CI, L/min/m^2	-0.2 (0.1)	0.3 (0.1)*
PVR, d•s•cm^{-5}	120 (80)	-272 (56)*

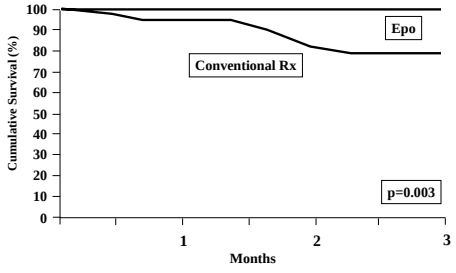
***P< 0.05** *(Barst, 1996)*

Inhaled Iloprost *(AIR)*

- **Randomized, double-blind, placebo-controlled**
- **12 weeks inhaled iloprost vs. placebo**
- **203 patients, NYHA Class III or IV**
  - **IPAH (50%)**
  - **Associated with connective tissue disease (17%) or anorexigen use (4.5%)**
  - **Chronic thromboembolic PH (28%)**

Olschewski H, Simonneau G, Galiè N, et al, AIR Study Group. *N Engl J Med* 2002;347:322-9

Survival on Epoprostenol



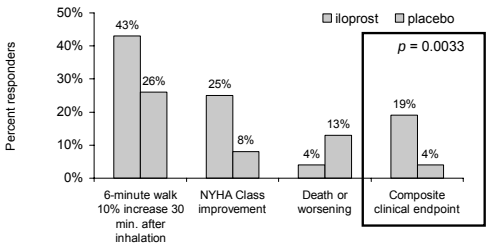
(Barst, 1996)

Inhaled Iloprost *(AIR)*

- **2.5 or 5 mcg, 6 to 9 times/day while awake**
- **median inhaled dose, 30 mcg/day**
- **mean inhalations/day = 7.3**
- **90% of patients never inhaled iloprost during sleeping hours**

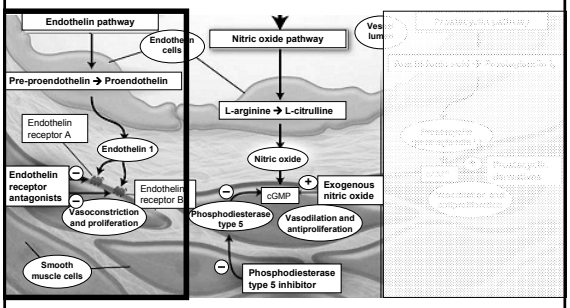
Olschewski H, Simonneau G, Galiè N, et al, AIR Study Group. *N Engl J Med* 2002;347:322-9

Inhaled Iloprost: *Composite Primary Endpoint*



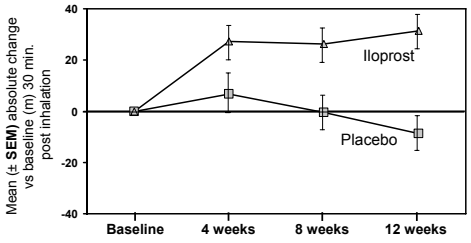
Composite response definition: 6 minute walk 10% increase **plus** NYHA class improvement **without** death or clinical worsening

Therapy Targets for PAH



Humbert M, Sitbon O, Simonneau G. *N Engl J Med* 2004;351:1425-36

Inhaled Iloprost: *PAH Patients*



Placebo-corrected mean difference at 12 weeks = 40 meters (p<0.01)

BREATHE-1
Bosentan Randomized Trial of Endothelin Receptor Antagonist Therapy for Pulmonary Hypertension

11 countries, 27 sites randomized 214 patients

from mid- July 2000 to Dec 2000

Patients were rolled over to an Open-Label study (n=198)

(Rubin, 2002)
Slide courtesy of Actelion

Prostacyclin Analogues- IV Epo, Iloprost, Treprostinil

Findings:

Different Δ 6MWT over short term

Different Δ dyspnea over 12 weeks

Improved time to clinical endpoints (epo, ilo)

Problems:

Success of masking subjects, investigators

Variable hemodynamic benefits

No clear survival benefits

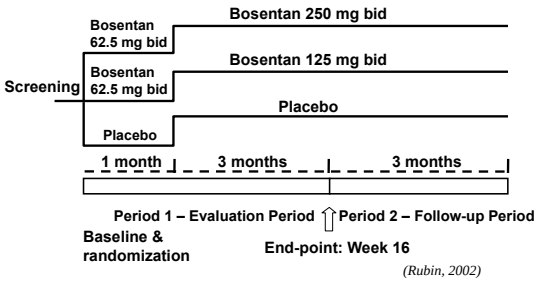
Suboptimal delivery systems

BREATHE-1: Main Inclusion Criteria

- **Males or females ≥ 12 years old**
- **PAH:**
  - **Idiopathic**
  - **Connective tissue or autoimmune diseases such as scleroderma (SSc/PHT) or systemic lupus erythematosus (SLE)**
- **WHO Class III-IV**
- **Baseline 6 minute walk test of ≥ 150 m and ≤ 450 m**

(Rubin, 2002)
Slide courtesy of Actelion

BREATHE-1: Study Design



(Rubin, 2002)
Slide courtesy of Actelion

Endothelin Receptor Antagonists

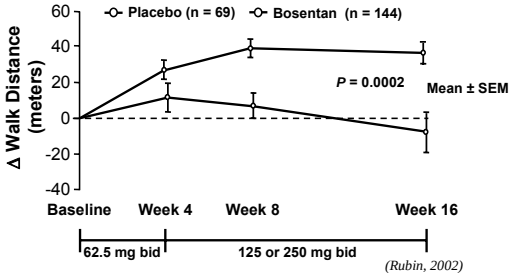
Findings:

- Different Δ 6MWT over short term
- Different Δ hemodynamics over short term

Questions:

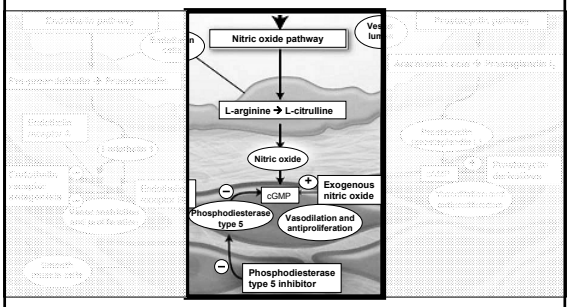
- No clear benefit on survival, transplant, or epo
- ET-A vs. dual receptor antagonism?
- Durability of effects?
- Is combination therapy effective?

6-Minute Walk Test
Change From Baseline to Week 16



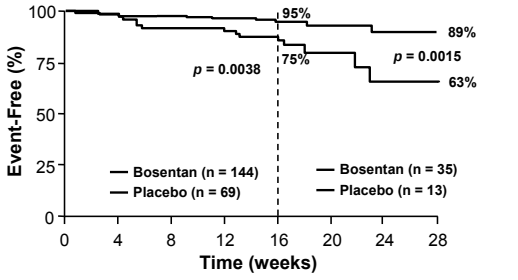
(Rubin, 2002)
Slide courtesy of Actelion

Therapy Targets for PAH



Humbert M, Sitbon O, Simonneau G. *N Engl J Med* 2004;351:1425-36

BREATHE-1: Results
Time to Clinical Worsening



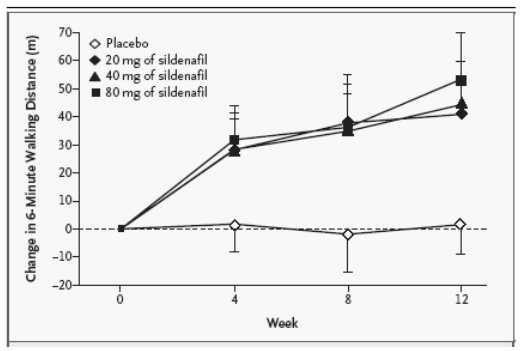
(Rubin, 2002)
Slide courtesy of Actelion

The NEW ENGLAND JOURNAL of MEDICINE

Sildenafil Citrate Therapy for Pulmonary Arterial Hypertension NOVEMBER 17, 2005

- **PAH due to:**
  - **Idiopathic**
  - **Connective tissue disease**
  - **CHD**
- **Baseline 6 minute walk test of ≥ 100 m and ≤ 450 m**
- **53 centers**
- **Placebo, 20, 40, 80 mg TID**
- **360 patients screened, 278 randomized**

(Galie, 2005)



ADULT LUNG TRANSPLANTATION

Actuarial Survival By Diagnosis (1990-2001)

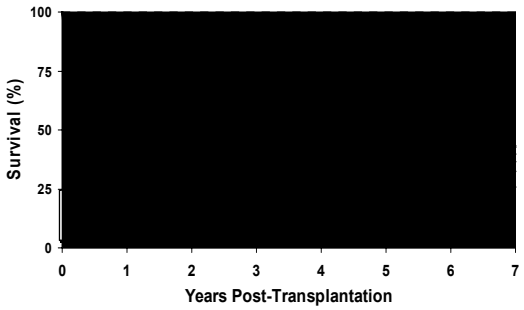
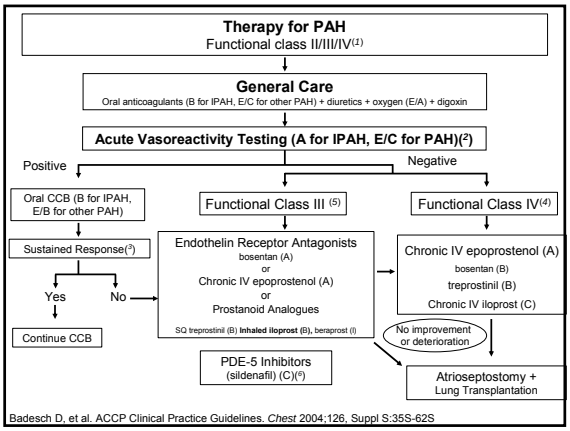


Table 2. **Mean Change in Hemodynamic Variables from Baseline to Week 12.***

Variable	Placebo (N=65)	Sildenafil					
		20 mg (N=65)	P Value	40 mg (N=63)	P Value	80 mg (N=65)	P Value
Heart rate — beats/minute	−1.3 (−4.1 to 1.4)	−3.7 (−5.9 to −1.4)	0.18	−3.3 (−5.5 to −1.0)	0.27	−4.7 (−7.3 to −2.2)	0.05
Mean pulmonary artery pressure — mm Hg	0.6 (−0.8 to 2.0)	−2.1 (−4.3 to 0.0).	0.04	−2.6 (−4.4 to −0.9)	0.01	−4.7 (−6.7 to −2.8)	<0.001
Cardiac index — liters/min/m²	−0.02 (−0.17 to 0.13)	0.21 (0.04 to 0.8).	0.06	0.24 (0.05 to 0.42)	0.03	0.37 (0.20 to 0.55)	0.001
Pulmonary vascular resistance — dyn·sec·cm⁻⁵	49 (−54 to 153)	−122 (−217 to −27)	0.01	−143 (−218 to −69)	0.01	−261 (−365 to −157)	<0.001
Right atrial pressure — mm Hg	0.3 (−0.9 to 1.5)	−0.8 (−1.9 to 0.3)	0.19	−1.1 (−2.4 to 0.2)	0.10	−1.0 (−2.1 to 0.1)	0.11



Badesch D, et al. ACCP Clinical Practice Guidelines. *Chest* 2004;126, Suppl S:35S-62S

Table 3. **Incidence of Clinical Worsening and of the Most Frequent Adverse Events in the Placebo and Sildenafil Groups.***

Event	Placebo (N=70)	Sildenafil		
		20 mg (N=69)	40 mg (N=67)	80 mg (N=71)
	number (percent)			
Clinical worsening	7 (10)	3 (4)	2 (3)	5 (7)
Death	1 (1)	1 (1)	0	2 (3)
Hospitalization for pulmonary arterial hypertension	7 (10)	2 (3)	2 (3)	2 (3)
Initiation of prostacyclin	1 (1)	0	0	0
Initiation of bosentan	0	0	1 (1)	2 (3)
Adverse event†				
Headache	27 (39)	32 (46)	28 (42)	35 (49)
Flushing	3 (4)	7 (10)	6 (9)	11 (15)
Dyspepsia	5 (7)	9 (13)	6 (9)	9 (13)
Back pain	8 (11)	9 (13)	9 (13)	6 (8)
Diarrhea	4 (6)	6 (9)	8 (12)	7 (10)
Limb pain	4 (6)	5 (7)	10 (15)	6 (8)
Myalgia	3 (4)	5 (7)	4 (6)	10 (14)
Cough	4 (6)	5 (7)	3 (4)	6 (8)
Epistaxis	1 (1)	6 (9)	5 (7)	3 (4)
Pyrexia	2 (3)	4 (6)	2 (3)	7 (10)
Insomnia	1 (1)	5 (7)	4 (6)	3 (4)
Influenza	2 (3)	4 (6)	4 (6)	3 (4)
Visual disturbance	0	0	3 (4)	5 (7)
Gastritis	0	2 (3)	2 (3)	3 (4)

Survival in Pulmonary Arterial Hypertension

Cohort	Years		
	1	2	3
NIH[1] (1981-1985)	68%	~58%	48%
New York[2] (1994-2002)	87%	77%	75%
Chicago[3] (1991-2001)	88%	76%	63%
Nashville[4] (1995-2001)	85%	76%	65%
Philadelphia[5] (1997-2001)	84%	71%	71%
Clamart[6] (1992-2001)	85%	70%	63%
Germany[7] (1996-2001)	68%	--	--

[1] *D'Alonzo, Ann Int Med, 1991*
[2] *Kawut, AJC, 2005*
[3] *McLaughlin, Circ, 2002*
[4] *Kuhn, AJRCCM, 2003*
[5] *Kawut, Chest, 2003*
[6] *Sitbon, JACC, 2002*
[7] *Wensel, Circ, 2002*

Survival Determinants of Patients with PAH at New York Presbyterian Hospital (1994-2002)

Retrospective cohort study of 84 consecutive adult patients

Mean age: 42 (14) years

Female: 68 (81%)

Hispanic: 9 (11%) Black: 6(7%) Asian: 9 (11%)

IPAH: 66 (78%) Familial: 14 (17%) Anorexigen: 4 (5%)

IV Epoprostenol: 38 (45%)

SC Treprostinil: 12 (14%)

Bosentan: 23 (27%)

Warfarin: 79 (94%)

Digoxin: 72 (86%)

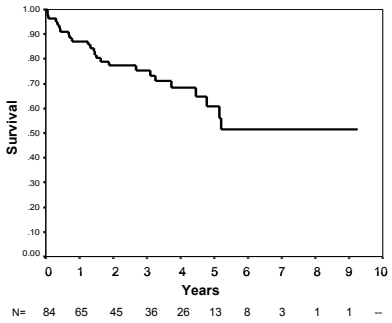
(Kawut, AJC, 2005)

Multivariate Survival Model

	HR	95% CI	p value
Black or Asian	4.3	1.7-11	0.002
Serum albumin	0.37	0.16-0.84	0.031
Warfarin use	0.35	0.12-0.99	0.05
CI	0.41	0.19-0.90	0.026
Acute vasoreactivity	0.13	0.02-0.96	0.046

(Kawut, AJC, 2005)

Kaplan-Meier Survival Estimate



Conclusions

Identification of BMPR2 has changed the paradigm of disease in PAH.

There are new effective therapies for PAH.

Innovative treatments may be on the horizon.

Survival has improved for patients with PAH.

Right heart function continues to be a primary determinant of outcome.

Reactivity of the pulmonary vascular bed is a phenotype which portends good outcomes.

Hemodynamic Survival Determinants

	HR	95% CI	p value
HR	1.06	1.02-1.1	0.005
SvO_2	0.94	0.90-0.98	0.003
RA	1.05	0.99-1.1	0.09
mPA	1.02	0.98-1.05	0.29
CI	0.36	0.17-0.76	0.005
PVRI	1.03	1.01-1.03	0.005
Acute vasoreactivity	0.11	0.01-0.81	0.03

(Kawut, AJC, 2005)

What is the Future of Treatment of Pulmonary Arterial Hypertension?

Better Prediction of Outcomes

Innovative and Combination Therapies

Improvements in Outcome after Lung Transplantation

Anti-platelet therapies