12:30 – 1:45 pm

Pulmonary Arterial Hypertension (PAH) Management in the Primary Care Setting

SPEAKER
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Presenter Disclosure Information

The following relationships exist related to this presentation:

- Stuart Rich, MD: No financial relationships to disclose.

Off-Label/Investigational Discussion

- In accordance with pmiCME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

Pulmonary Arterial Hypertension Management in the Primary Care Setting

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Introduction

- Pathogenesis of pulmonary arterial hypertension
- Prevalence of pulmonary hypertension
- Case presentations

Vascular Mechanisms That Can Lead to Pulmonary Hypertension

- Vasoconstriction
- Thrombosis
- Toxins/drugs
- Inflammation
- Metabolic dysfunction
- Genetic predisposition

How common is pulmonary hypertension?

- Pulmonary hypertension from all causes is estimated at >3000 per million
  - Australian screening study. Heart: 2012
- Pulmonary arterial hypertension (PAH) is estimated at:
  - 71-149/million <65 yrs
  - 384-519/million >65 yrs
- Pulmonary hypertension from chronic pulmonary embolism is estimated at:
  - 34-91/million <65 yrs
  - 94-111/million >65 yrs

Curr Med Res Opin. 2011

Clinical Diagnosis of PH

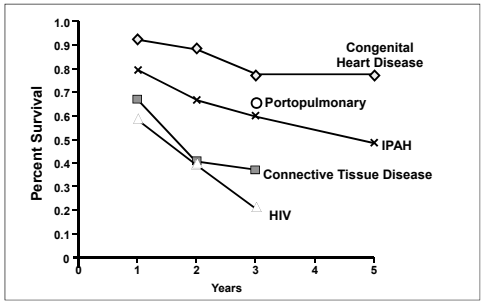
- Importance of early diagnosis
- Diagnostic classification of PH
- Signs and symptoms
- How to diagnose

Natural History of PAH

- Progressive increase in pulmonary artery pressure and pulmonary vascular resistance
- Right ventricular failure
- Death
  - Median life expectancy of untreated idiopathic PAH is 2.8 years from diagnosis

Mark MH. In: Harrison's Internal Medicine; McGraw-Hill Companies. 2007.
D'Alonzo GE, et al. *Ann Intern Med*. 1991;115:343-349.

Survival in PAH



IPAH, idiopathic pulmonary arterial hypertension.
McLaughlin VV, et al. *Chest*. 2004;126:78S-92S.

Revised Clinical Classification of Pulmonary Hypertension

Category 1) PAH
- Idiopathic (IPAH)
- Familial (FPAH)
- Associated with (APAH)
  - Connective tissue disease
  - Congenital systemic-to-pulmonary shunts
  - Portal hypertension
  - HIV infection
  - Drugs and toxins

Revised Clinical Classification of Pulmonary Hypertension

Category 2) Pulmonary hypertension with left heart disease
- Left-sided atrial or ventricular heart disease
- Left-sided valvular heart disease

Category 3) Pulmonary hypertension associated with lung diseases and/or hypoxemia
- Chronic obstructive pulmonary disease
- Interstitial lung disease
- Sleep-disordered breathing
- Developmental abnormalities

.

Revised Clinical Classification of Pulmonary Hypertension

Category 4) Pulmonary hypertension due to chronic thrombotic and/or embolic disease

Category 5) Miscellaneous
- Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels
  - Adenopathy, tumor, fibrosing mediastinitis

Simonneau G, et al. *J Am Coll Cardiol*. 2004;43:5S-12S.

Pre-referral Diagnoses Compared With Diagnoses Obtained at PAH Tertiary Care Centers

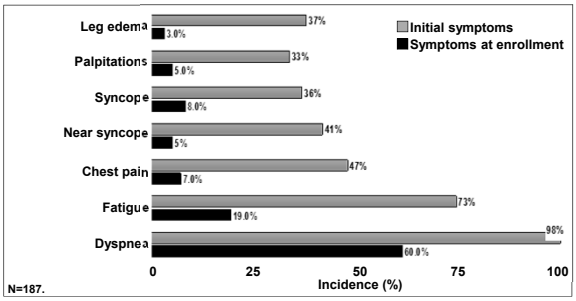
		Post Referral Diagnosis				
		Group 1	Group 2	Group 3	No PH	Unk.
Pre-Referral Diagnosis	Group 1	41 (73%)	3 (5%)	4 (7%)	7 (12%)	1 (18%)
	Group 2	0	8 (61%)	1 (8%)	4 (31%)	0
	Group 3	4 (17%)	4 (17%)	13 (56%)	2 (9%)	0
	Unk.	12 (29%)	13 (31%)	1 (2%)	14 (33%)	2 (5%)

■ = correct pre-referral diagnosis ■ = incorrect pre-referral diagnosis

N=141 patients referred over a 10-month period for PH evaluation.
39% of patients initiated on PAH-specific mediation prior to referral did not have Group I PAH.

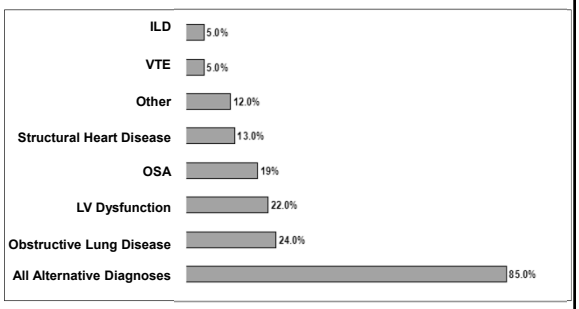
Deano RC et al. JAMA Int Med 2013

NIH Registry: Initial Symptoms of IPAH Compared With Symptoms at Time of Enrollment in Registry



Rich S, et al. *Ann Intern Med*. 1987;107:216-223.

Alternative Diagnoses of Patients Referred to PAH Specialty Clinic



Moghbelli MH, et al. *Am J Respir Crit Care Med*. 2008;177:A923.

Screening for PAH Requires High Index of Suspicion for Clinician

- Diagnosis is complex
  - IPAH is a diagnosis of exclusion
- Early symptoms likely to be attributed to variety of more-common conditions
- Echocardiography is most commonly used screening tool
- Cardiac catheterization required for confirmation

McGoon M, et al. *Chest*. 2004;126:14S-34S.

PAH Diagnostic Guidelines Decision Analysis

Patient Presents With Dyspnea, Syncope, etc → **Clinical History, Examination, Chest X-Ray, ECG**

McGoon M, et al. *Chest*. 2004;126:14S-34S.

Examination clues in PH

Clues from the examination:

- telangiectasias
- Raynaud's phenomena
- Palmar erythema/sequelae of liver disease
- JVP elevation
- RV heave
- Murmurs (most often tricuspid regurgitation)
- Prominent P2 from elevated PA pressure
- Clubbing
- Peripheral edema

Electrocardiogram

Does not provide sufficient sensitivity to serve as a screening tool but pay attention when you see[1]:

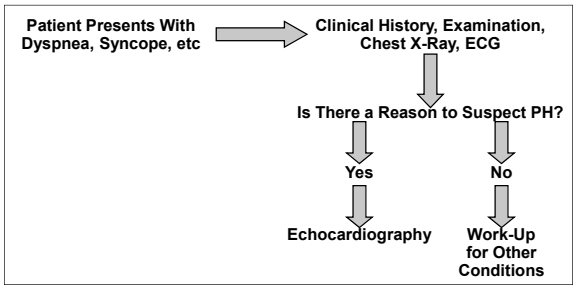
- RVH – 87% of PH cases
- RAD – 79% of PH cases
- RAE – *P* wave > 2.5 mm in II, III, aVF

[1]Rich S et al. *Ann Intern Med* 1987;107:216-23.

Reasons to suspect PH

- CXR: also not sufficiently sensitive to serve as screening tool, but look for:
  - Attenuated peripheral vasculature
  - Enlarged mediastinal and hilar PA size

PAH Diagnostic Guidelines: Decision Analysis



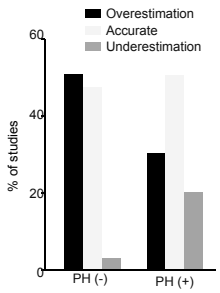
McGoon M, et al. *Chest*. 2004;126:14S-34S.

Echocardiography to diagnose pulmonary hypertension

- A normal echo excludes all but trivial pulmonary hypertension
- An echocardiogram allows for assessment of etiologies
  - Valvular heart disease
  - Congenital heart disease
  - LV systolic/diastolic dysfunction
- The severity of PH is best reflected by the RV function rather than the estimated PAP

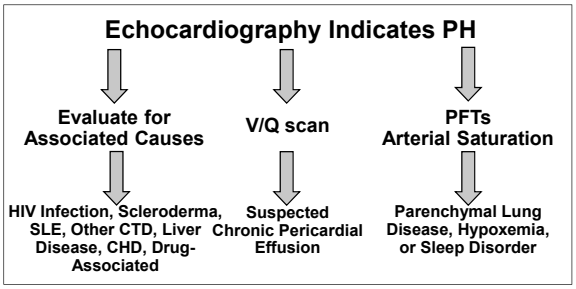
Accuracy of PH diagnosis by echocardiography in advanced lung disease

- Cohort study of 374 lung transplant candidates
- Doppler echo typically 24 – 48 h prior to RHC
- Prevalence of PH: 25%
- Echo frequently inaccurate for PAP, leading to overdiagnosis of AP in patients with advanced lung disease



Arcasoy SM et al. *Am J Respir Crit Care Med*. 2003;167:735-740.

PAH Diagnostic Guidelines: Further Evaluation of Patients



McGoon M, et al. *Chest*. 2004;126:14S-34S.

Blood Tests for Evaluation of PAH

- Antinuclear antibody (ANA)
- Antiphospholipid antibodies
  - Lupus anticoagulant, anticardiolipin antibodies
- HIV serology
- CBC with platelets
- Liver function
- Thyroid function
- Hemoglobin electrophoresis, if indicated

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

PAH and HIV Disease

- Seen in approximately 0.5% of HIV-infected patients
- Etiology appears related to HIV itself
  - No evidence for direct infection of HIV of vascular endothelium
  - Higher prevalence among injection drug users
- PAH incidence and course unaffected by HIV disease (stage or use of antiretrovirals)
  - ~66% of mortality related to PAH

Limsukon A, et al. *Mt Sinai J Med*. 2006;73:1037-1044.

PAH Associated With Connective Tissue Disorders

- Overall prevalence: 10% to 15%
  - ~20% in limited or diffuse systemic sclerosis
  - ~9% mixed connective tissue disease
  - ~7% systemic lupus erythematosus
- Systemic sclerosis accounts for up to 75% of CTD-associated PAH
- Rapidly progressive PAH disease course
  - 1-year survival: 45% to 69%
  - Therapy improves disease status and may increase survival

Coghlan JG, et al. *Lupus*. 2006;15:138-142.

Chronic thromboembolic pulmonary hypertension (CTEPH): screening

- It is crucial to exclude this form of PH in every suspected case of IPAH
  - **50% have no history of VTE**
- A ventilation-perfusion scan is the preferred screening test in CTEPH![1]
  - Validated with sensitivities from 90%-100% and specificity of 94%-100%[2-4]

[1]McGoon M et al. *Chest*. 2004;126:14S-34S.
[2]Fishman AJ et al. *Chest*.1983;84:679-683.
[3]D'Alonzo GE et al. *Chest*. 1984;85:457-461.
[4]Worsley DF et al. *J Nucl Med*. 1994;35:793-796.

Pulmonary Function Testing for PAH Suspected by Doppler Echo

- Lung volumes 60% to 80% of predicted
- Nocturnal hypoxemia occurs in >75% of patients with IPAH
- Desaturation may increase during exercise
- DL_{CO} <55% of predicted associated with future development of PAH in limited systemic sclerosis

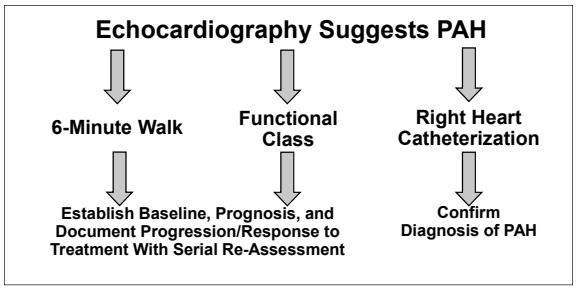
McGoon M, et al. *Chest*. 2004;126:14S-34S.
Barst RJ, et al. *J Am Coll Cardiol*. 2004;43:40S-47S.

PH in Patients With Obstructive Sleep Apnea

- Tends to be much milder than PH from other causes
  - Prevalence range: 17% to 53%
- Spirometric abnormalities strongly associated with PH
- PH in patients with OSA is strongly associated with other risk factors
  - Left-sided heart disease
  - Parenchymal lung disease
  - Nocturnal desaturation
  - Obesity

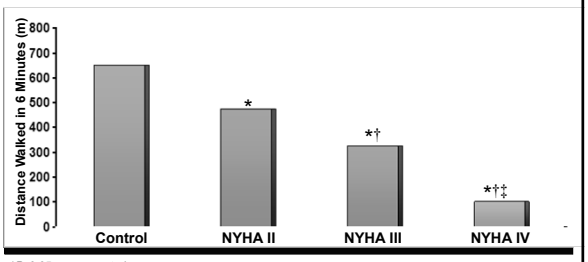
Atwood CW, et al. *Chest*. 2004;126:72S-77S.

PAH Diagnostic Workup



McGoon M, et al. *Chest*. 2004;126:14S-34S.

6-Minute Walk Distance Correlates With IPAH Disease Severity



*P<0.05 versus control.
†P<0.05 versus NYHA Class II.
‡P<0.05 vs NYHA Class III.

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

Right Heart Catheterization

- Required to confirm diagnosis, calculate resistance, and guide therapy for PAH
- Excludes other etiologies for PH
  - Intracardiac or extracardiac shunts
  - Left-heart disease
- Measures degree of right-heart dysfunction
  - Right atrial pressure
  - Cardiac output

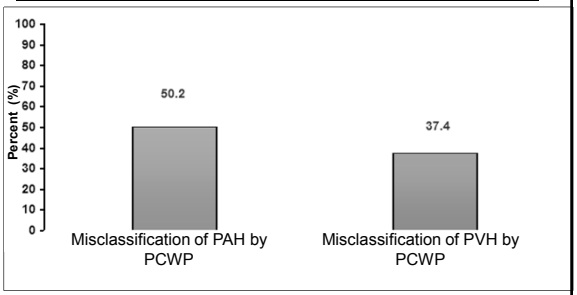
McGoon M, et al. *Chest*. 2004;126:14S-34S.

Pulmonary arterial hypertension: **WHO** definition

- Requires[1,2]:
  - A *mean* pulmonary artery pressure
    - ≥ 25 mm Hg at rest AND
  - PCWP (LVEDP, LAP)
    - ≤ 15 mm Hg
- Also important to look for true alterations of pulmonary vascular resistance (PVR)
  - ≥240 dyne·sec·cm^{-5} or
  - 3 Wood units

[1]Rich S et al. *Am Intern Med* 1987;107:216-223.
[2]Badesch DB et al. *Chest* 2007;131:1917-1928.

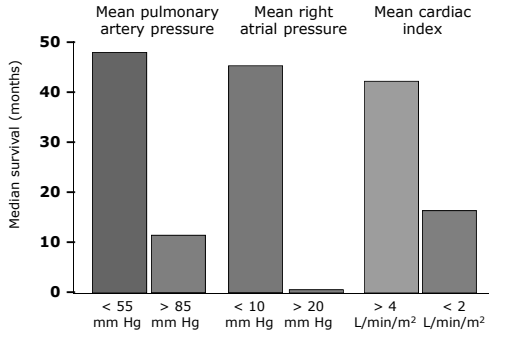
Misclassification of PAH and PVH Through Use of PWCP vs LVEDP



N = 4,666, all patients undergoing LHC and RHC over 10 years at single center.

Halpern SD, et al. *Am J Respir Crit Care Med*. 2008;177:A259.

Median survival for patients with PPH compared with 3 hemodynamic variables[1]



[1]D'Alonzo GE et al. *Ann Intern Med*. 1991;115:343-349.

Summary: PAH Epidemiology and Diagnosis

- PAH is rare, serious, and progressive
- PAH/PH has a wide range of etiologies
- Symptoms of PAH are nonspecific
- Screening for suspected PH can be done in local communities
- Consider referral to specialty centers for PAH confirmation and initiation of PAH specific therapy

Treatment of PAH

- Current approved medications
- How to evaluate drug efficacy
- How to recognize drug failure
- Alternatives to medications

Therapeutic Choices for Treating Pulmonary Hypertension

- Anticoagulants
- Calcium channel blockers
- Endothelin receptor antagonists
- Phosphodiesterase inhibitors
- Prostacyclins

New predictors of outcome in idiopathic pulmonary arterial hypertension

Kawut SM, et al. The American Journal of Cardiology 2005, 95: 199-203

- Warfarin use was associated with a reduced risk of death.
- Warfarin use:
  - Hazard ratio 0.35
  - 95% CI 0.12–0.99
  - P value <0.05

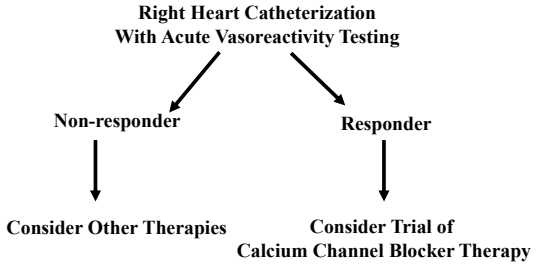
Anticoagulation for Pulmonary Hypertension

- recommended for patients with idiopathic pulmonary arterial hypertension
- may prolong survival by preventing thrombin induced vascular proliferation
- not likely to affect symptoms
- suggested INR 2.0-3.0

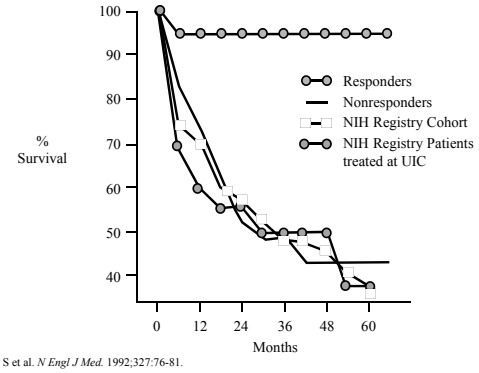
Therapeutic Choices for Treating Pulmonary Hypertension

- Anticoagulants
- Calcium channel blockers
- Endothelin receptor antagonists
- Phosphodiesterase inhibitors
- Prostacyclins

Algorithm for Assessment of Vasoreactivity in Patients with PH

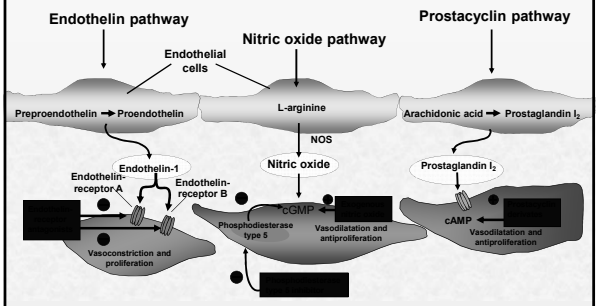


Effect of High-Dose CCBs on Survival in PPH



Rich S et al. *N Engl J Med.* 1992;327:76-81.

Targets for PAH Therapy



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

Current Approved Treatments of Pulmonary Hypertension

- Endothelin receptor blockers
  - Oral agents
  - No head to head comparisons
- Phosphodiesterase-5 inhibitors
  - Oral agents
  - No head to head comparisons
- Soluble guanylate cyclase stimulator
  - Riociguat
- Prostacyclins
  - iv, subQ, inhaled, oral
  - Marked differences in bioavailability and efficacy

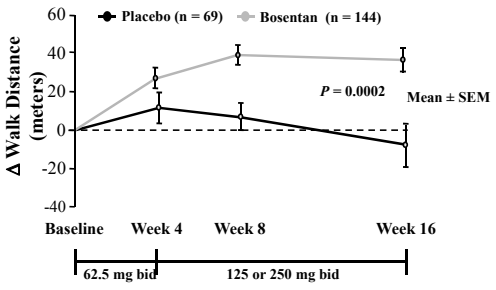
Endothelin Receptor Blockers

- Bosentan (Tracleer®)
  - Twice daily
  - Liver toxicity
- Ambrisentan (Letaris®)
  - Once daily
  - 5mg and 10mg doses
- Macitentan (Opsumit®)
  - Once daily

BREATHE-1: Results

6-Minute Walk Test

Change From Baseline at Week 16

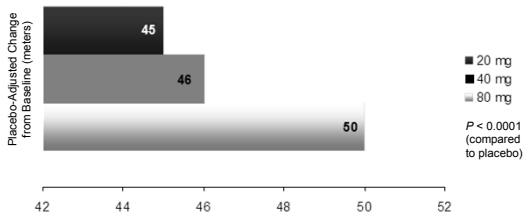


Phosphodiesterase-5 Inhibitors

- Sildenafil (Revatio®)
  - 3 times daily
  - Dose response
  - Only 20mg TID "approved"
- Tadalafil (Adcirca®)
  - Once daily
  - One dose
- Most effective oral therapy
  - Lowers PAP and increases Cardiac Output

Sildenafil for PAH: SUPER Clinical Trial

Change in 6-MWD (from Baseline to Week 12)

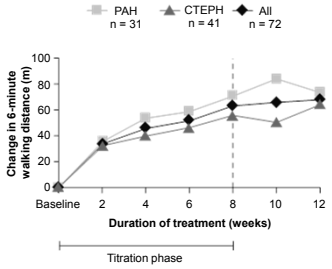


Galie, et al. *N Engl J Med.* 2005;353:2148-57.

Riociguat (Adempas®)

- Soluble guanylate cyclase stimulator
- Works independent of nitric oxide production
- No data to suggest better efficacy than PDE5i
- Hypotension a clinical problem
- Approved for PAH and CTEPH

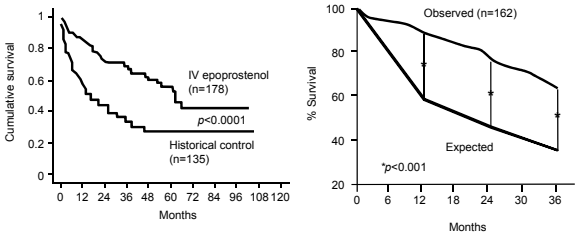
Six-minute walking distance: all patients



Prostacyclins

- Epoprostenol (Flolan®/Veletri®)
  - i.v. only
  - Only therapy to show improved survival
- Treprostinil (Remodulin®)
  - i.v./sub-Q/inhaled/oral
  - Oral treprostinil has limited use
- Iloprost (Ventavis®)
  - Inhaled only

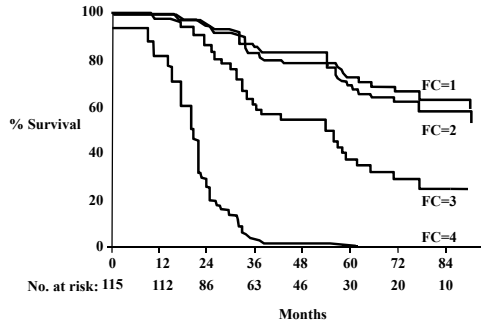
Long-Term Outcome in PPH With Epoprostenol



Sitbon O et al. *J Am Coll Cardiol.* 2002;40:780-788.

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

Impact of Functional Class at Period 1 on Subsequent Survival



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

Clinical efficacy by change in functional class after 3 months

Therapy	Clinically improved (FC)	Increase in 6MW distance (meters)
Bosentan*	12%	40
Iloprost*	11%	30
Sildenafil*	20%	35
Epoprostenol (i.v.)	99.4%	125

*From published RCTs

Epoprostenol would be the Ideal Treatment for Pulmonary Arterial Hypertension

- Improves symptoms
- Improves exercise tolerance
- Improves hemodynamics
- Improves survival
- Works on appropriate biologic pathways

if it were not for...

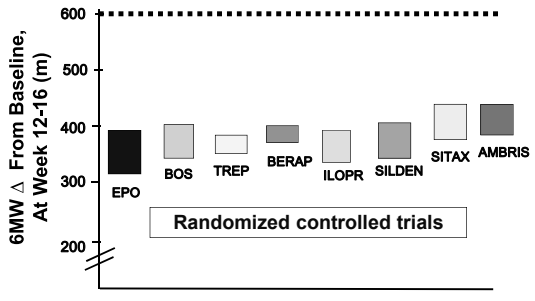
Required Supplies for Epoprostenol Administration

- Supply of epoprostenol
- Glycine Buffer Diluent
- Portable Infusion Pump (2)
- Medication cassettes 50 or 100ml
- IV extension sets with 0.22 micron filter to connect to subclavian catheter
- Insulated carrying pouch
- Cold Packs
- 9 volt batteries for pumps
- Normal Saline for injection
- Antimicrobial Soap
- Povidone-Iodine Solution
- 70% Alcohol
- Dressing Change Kits
- Betadine prep pads
- Alcohol Prep pads
- Needles (18 and 23 gauge)
- Syringes (3ml, 10ml, 60ml Luer Lok®)
- Other, as needed

Inhaled treprostinil

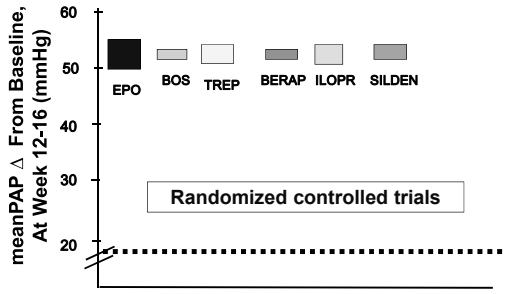
- 4 nebulizations daily
- Increase 6MW 14 meters
- Causes acute PG side effects and coughing
- Approved only in the USA

Mean Improvements on Monotherapy Do Not Restore Normal 6MW



Barst 1996, 2003, 2003; Rubin 2002; Simmoneau 2002; Galie 2002, 2005; Ghofrani 2004

Mean Improvements on Monotherapy Do Not Restore Normal PAP



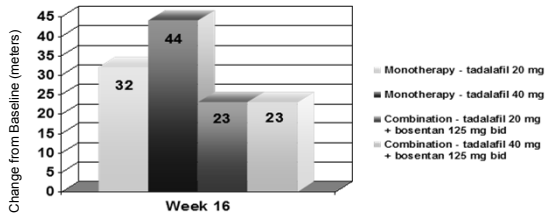
Barst 1996, 2003, 2003; Rubin 2002; Simmoneau 2002; Galie 2002, 2005; Ghofrani 2004

Combination Therapies

- ERB + PG = worse
  - Breathe-2
- ERB + PDE-5i = worse
  - PHIRST
- PDE-5i + PG = better
  - PACES
- Each therapy costs approx. $85,000/yr.

Combination Therapy with Tadalafil: PHIRST Clinical Trial

Change in 6-MWD (from Baseline to Week 16)



Galie, et al. *Circulation*. 2009;119(22):2894-903.
Barst, et al. *J Heart Lung Transplant*. 2011:1:Epub.

Survival in patients with PPH

Impact of the current treatment era

- **NIH Registry on PPH**
- 1981-1985
- No approved drugs
- 1 yr = 68%
- 3 yr = 48%

- **French National PH Registry**
- 2002-2009
- All patients treated with approved drugs
- 1 yr = 83%
- 3 yr = 58%

What we have learned

- Therapies hardly lower PA pressure
  - Vasodilators for non-reactive patients!
- Changes in 6 minute walk do not correlate with very much
- RV function predicts survival
  - Regardless of etiology
- Current therapies do not protect the pulmonary vasculature from disease progression
  - 4 published pathology studies

How to know if medical therapy is working

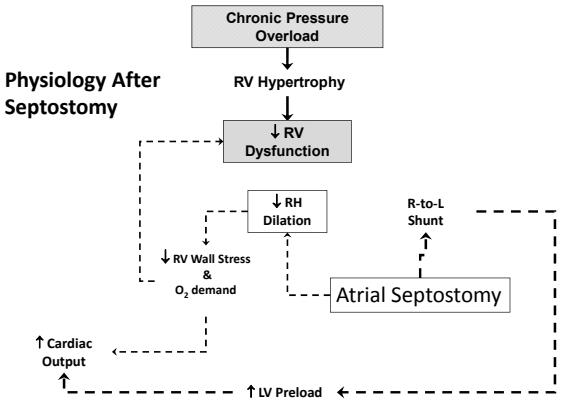
- Symptoms should improve
- Exercise tests should improve/not worsen
- Signs of RV failure should resolve
- Echocardiograms should improve/remain stable

How to know if medical therapy is NOT working

- Symptoms progress
- Exercise tests worsen
- Signs of RV failure persist/worsen
- Echocardiograms remain unchanged/worsen

PAH – Non-medical Treatments

- **Atrial septostomy**
- **Lung transplantation**



Graded balloon dilation atrial septostomy in severe primary pulmonary hypertension

A therapeutic alternative for patients nonresponsive to vasodilator treatment

	1 year Survival	2 year survival	3 year survival
Atrial septostomy	92%	92%	92%
Historical Controls	73%	59%	52%
NIH Registry	61%	49%	38%

Sandoval, et al. JACC 32:1998;297-304

Role of the Primary Care Physician in Diagnosis and Management of PH

- Recognize possible PH in patient with unexplained dyspnea on exertion
- Initiate screening
- Facilitate referral
- Provide regular local follow-up
  - Assess volume status, vital signs, and oxygenation
  - Monitor laboratory tests
  - Manage anticoagulation with warfarin, if indicated
- Provide local emergency care

Rubin LJ, et al. *Ann Intern Med.* 2005;143:282-292.