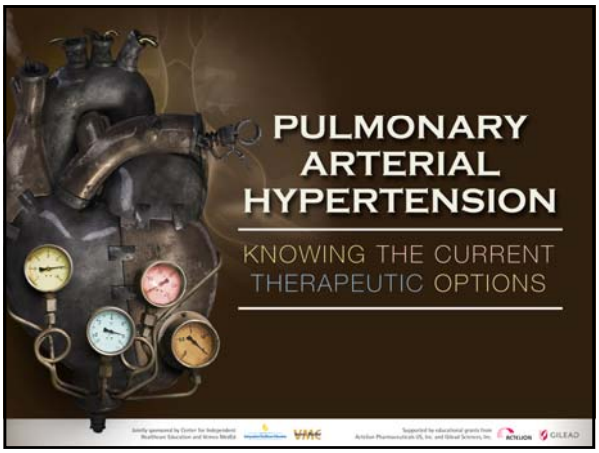
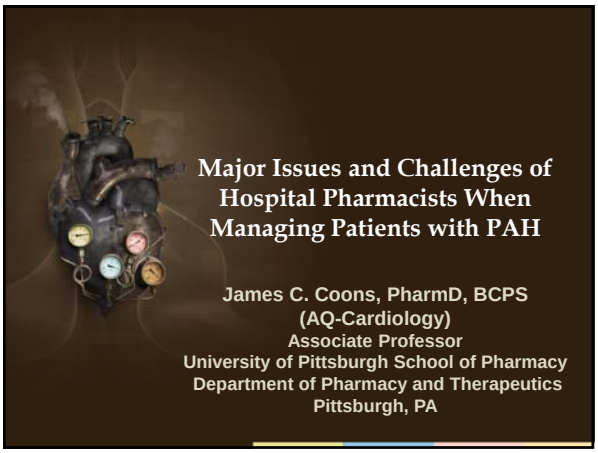




Current Challenges

- Expansion of therapeutic options
  - Medications
  - Delivery systems
- Complexity of regimens
- High-risk medications
- Patient acuity
- Educational needs

Pharmacotherapy Timeline

- **1960-1980… empiric/various vasodilators**
- **1980… oral anticoagulants, calcium channel blockers, lung/heart transplantation**
- **1996… epoprostenol**
- **2001… bosentan**
- **2002… treprostinil subcutaneous (SC)**
- **2004… treprostinil intravenous (IV), iloprost**
- **2005… sildenafil**
- **2007… ambrisentan**
- **2009… tadalafil, treprostinil inhaled**
- **2010… thermostable epoprostenol**

Evaluating Prostacyclin Safety

- Surveys of PAH centers
  - University Hospital Consortium (UHC)
  - Phone interview – 18 large PAH centers
  - Electronic survey – convenience sample of all PAH centers in US (n=97)

Kingman MS, et al. *J Heart Lung Transplant*. 2010;29:841-846.

Findings and Scope of Problem

- UHC and phone interviews
  - Baseline evaluation of policies
    - 8 of 18 kept patients on their home pumps
    - 10 of 18 patients did not keep back-up prostacyclin cassettes on the unit

Kingman MS, et al. *J Heart Lung Transplant*. 2010;29:841-846.

Findings and Scope of Problem

- Phone interview
  - Serious errors at 17 of 18 centers
    - Failure to restart CADD pump
    - Wrong patient
    - Wrong rate
    - Errors in dose calculations
    - Flushing of the prostacyclin line
  - 3 deaths

CADD, computerized ambulatory drug delivery

Kingman MS, et al. *J Heart Lung Transplant*. 2010;29:841-846.

Findings and Scope of Problem

- Electronic survey
  - Serious or potentially serious errors – 68%
    - Wrong patient
    - Wrong dose
    - Pump left off
    - Flushing the line
  - 9 deaths

Kingman MS, et al. *J Heart Lung Transplant*. 2010;29:841-846.

Examples of Medication Considerations

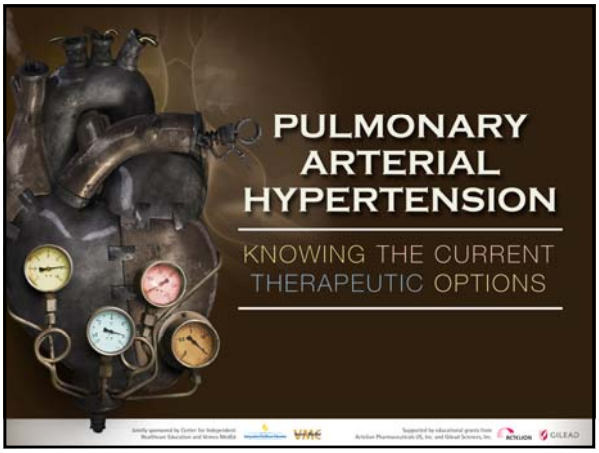
Treprostinil

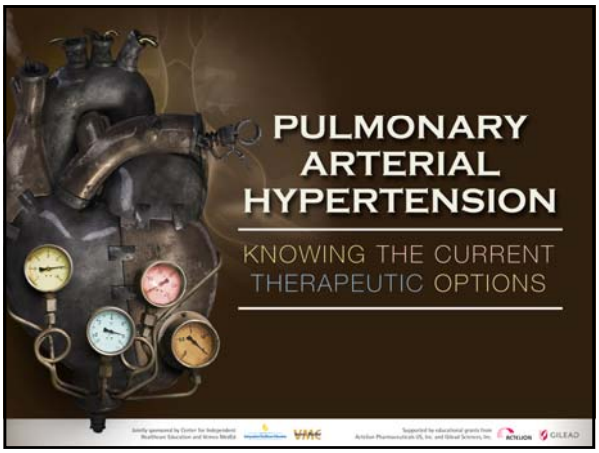
- Multiple vial concentrations
  - 1, 2.5, 5, & 10 mg/mL
- Multiple routes of administration
  - IV, SC, inhaled
- Multiple delivery systems
  - IV – CADD infusion pump, Crono-5 pump
  - SC – CADD-MS3 & MiniMed syringe pumps
  - Inhaled – Tyvaso inhalation system®

Examples of Medication Considerations

Epoprostenol

- Requires reconstitution
- Requires back-up cassette
- Multiple formulations
  - Epoprostenol (Flolan®)
  - Generic epoprostenol
  - "Room-temperature stable" epoprostenol (Veletri®)





Knowing the Pharmacist's Role in Managing PAH

Pathophysiology of PAH

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Overview

- Etiology
- Epidemiology
- Pathophysiology

Definition

- Mean pulmonary artery pressure (mPAP) >25 mmHg at rest in setting of:
  - Normal or decreased cardiac output
  - Normal fluid status

Badesch DB, et al. *J Am Coll Cardiol.* 2009;54(1 Suppl):S55.

Etiology (Dana Point, 2008)

1. Pulmonary arterial hypertension	1.1 Idiopathic	
	1.2 Heritable	1.2.1 $BMPR_2$
		1.2.2 ALK_1, endoglin
		1.2.3 Unknown
	1.3 Drug/toxin-induced	
	1.4 Associated with	1.4.1 Connective tissue disease
		1.4.2 HIV infection
		1.4.3 Portal hypertension
		1.4.4 Congenital heart disease
		1.4.5 Schistosomiasis
		1.4.6 Chronic hemolytic anemia
	1.5 Persistent pulmonary hypertension of the newborn	

Simonneau G, et al. *J Am Coll Cardiol.* 2009;54(1s1):S43-54.

Etiology (Dana Point, 2008)

1'. Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)	
2. PH due to left heart disease	2.1 Systolic dysfunction
	2.2 Diastolic dysfunction
	2.3 Valvular disease
3. PH due to lung diseases and/or hypoxia	3.1 COPD
	3.2 Interstitial lung disease
	3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
	3.4 Sleep-disordered breathing
	3.5 Alveolar hypoventilation disorders
	3.6 Chronic exposure to high altitude
	3.7 Developmental abnormalities

Simonneau G, et al. *J Am Coll Cardiol.* 2009;54(1s1):S43-54.

Etiology (Dana Point, 2008)

4. CTEPH		
5. PH with unclear multifactorial mechanisms	**5.1 Hematologic disorders**	**Myeloproliferative disorders**
		Splenectomy
	5.2 Systemic disorders	**Sarcoidosis**
		Pulmonary Langerhans cell histiocytosis
		Lymphangioleiomyomatosis
		Neurofibromatosis type 1
		Vasculitis
	5.3 Metabolic disorders	**Glycogen storage disease**
		Gaucher disease
		Thyroid disorders
	5.4 Others	**Tumoral obstruction**
		Fibrosing mediastinitis
		CKD on dialysis

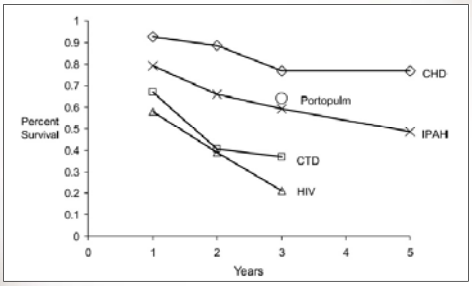
Simonneau G, et al. *J Am Coll Cardiol*. 2009;54(1s1):S43-54.

Epidemiology

- PAH prevalence[1]
  - Estimated 50,000–100,000 Americans
  - 15,000–20,000 diagnosed and receiving treatment
- Diagnosed typically 3rd–4th decade of life[2]
  - Female:male ratio 1.7:1
- 2.8-year median survival without treatment[3]

[1] DeMarco T. *Cardiol Rev*. 2006;14:312–8.
[2] Rich S, et al. *Ann Intern Med*. 1987;107:216-23.
[3] D'Alonzo GE, et al. *Ann Intern Med*. 1991;115:343-9.

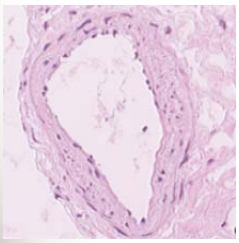
Mean Survival by Etiology



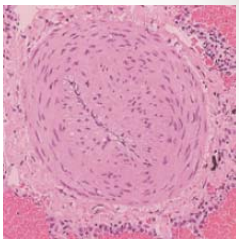
CHD, congenital heart disease; CTD, connective tissue disease; IPAH, idiopathic pulmonary arterial hypertension; Portopulm, portopulmonary hypertension

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

Pathophysiology



Normal



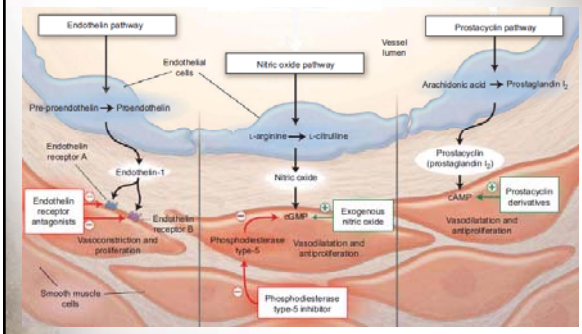
PAH

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

Pathophysiology

- Endothelin-1
- Nitric oxide
- Prostacyclin
- Serotonin
- Vasoactive intestinal peptide (VIP)
- Inflammation

PAH Therapy Targets



Schulze-Neick I, Beghetti M. *Eur Respir Rev*. 2010;19:331–9.

Serotonin

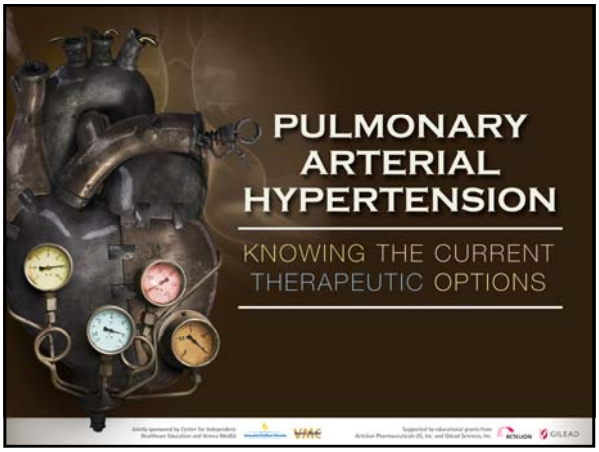
- Effects
  - Vasoconstriction
  - Smooth muscle cell hyperplasia and hypertrophy
- Impaired platelet serotonin storage in PAH
  - Dexfenfluramine
- No PAH-SSRI association

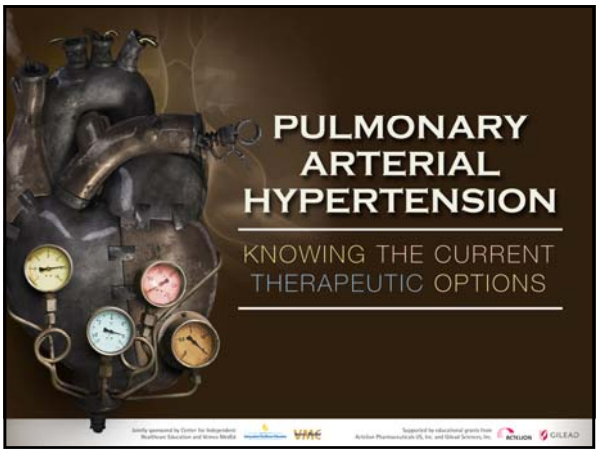
McLaughlin VV, et al. *Curr Probl Cardiol.* 2011;36:461-517.
Marcos E, et al. *Am J Respir Crit Care Med.* 2003;168:487-93.

VIP

- Effects
  - Vasodilatation
  - Inhibition of vascular smooth muscle cell proliferation
- Low levels in PAH population

McLaughlin VV, et al. *Curr Probl Cardiol.* 2011;36:461-517.





Knowing the Pharmacist's Role in Managing PAH

Knowing Your Therapeutic Options: Current Medications and Their Effectiveness

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Section of Pulmonary, Critical Care Medicine, Sleep and Allergy
Institute for Personalized Respiratory Medicine
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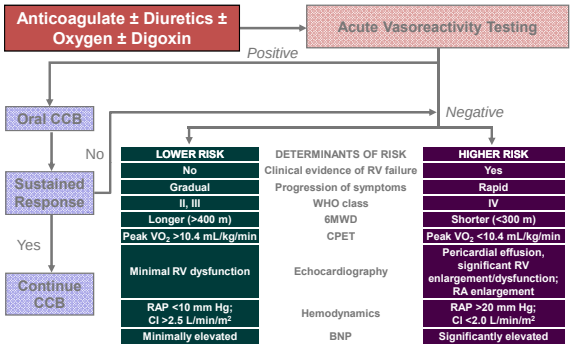
Chicago, IL

PAH Treatment Goals

- Fewer/less severe symptoms
- Improved exercise capacity
- Improved hemodynamics
- Prevention of clinical worsening
- Improved quality of life
- Improved survival

What Is the Optimal Treatment Strategy?



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

Chronic Adjuvant Therapies in PAH

Digoxin
- Variable inotropic effect and use
- No long-term data; need to balance unproven benefits with known risks

Oxygen
- Use to prevent hypoxic vasoconstriction
- Consider exercise, sleep, altitude
- Aim for target saturation >90%
- May not correct hypoxia with shunt

Diuretics
- Most need; hypotension not a contraindication (may need BP support)
- Renal function and electrolytes must be monitored closely

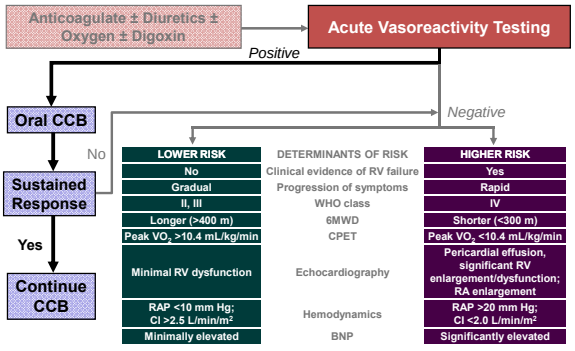
Anticoagulation
- Recommended in IPAH
- Retrospective data only; need to balance unproven benefits with known risks
- INR 1.5–2.5

Adapted from: Badesch DB, et al. *Chest*. 2004;126:35S-62S.
Badesch DB, et al. *Chest*. 2007;131:1917-1928.
McLaughlin VV, et al. *J Am Coll Cardiol*. 2009;53:1573-1619.

Other Management Issues

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

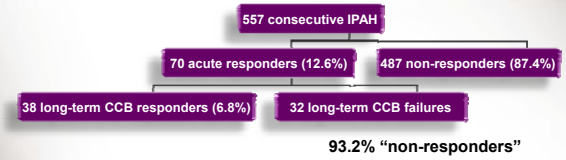
What Is the Optimal Treatment Strategy?



CCB, calcium-channel blocker
McLaughlin VV, et al. *J Am Coll Cardiol.* 2009;53:1573-1619.

Criteria for "Responders"

Criteria for Long-term Beneficial Effect of CCB?



93.2% "non-responders"

- Acute vasodilator testing with PgI2 (n=156) or NO (n=401)
- Acute response = fall in mPAP and PVR >20% → initiation of chronic CCB
- Long-term CCB responders = NYHA FC I/II after at least one year on oral CCB without need for prostanoids and/or ERAs

CCB, calcium-channel blocker
Sitbon O, et al. *Circulation.* 2005;111:3105-3111.

Revised Definition of Vasodilator Responder

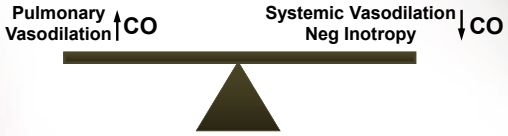
"Vasodilator Response"

- Fall in mPAP **≥10 mmHg**
- **+** mPAP (absolute) **<40 mmHg**
- **+** Normal CO

Only acute vasodilator responders should be tried on CCB therapy to treat PAH

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

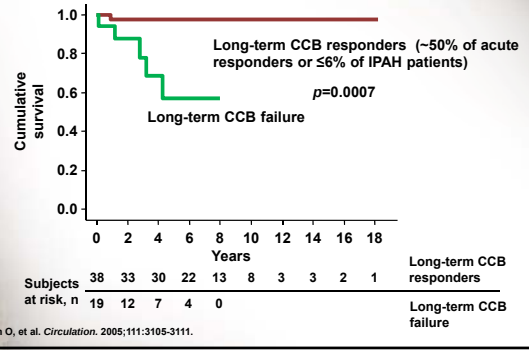
Net Effect of Vasodilator Challenge with CCB?



- Effects of CCB challenge are highly variable, unpredictable, and include death
- CCBs should NOT be used empirically

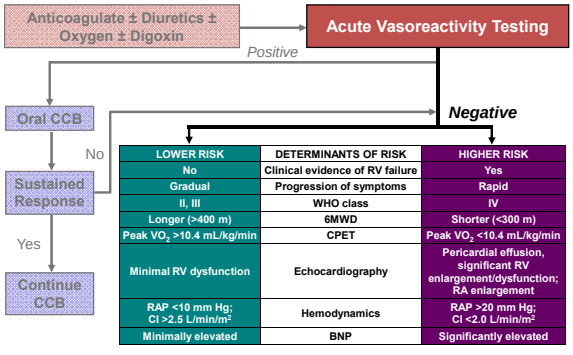
Survival in IPAH

Long-term CCB Responders



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

What Is the Optimal Treatment Strategy?



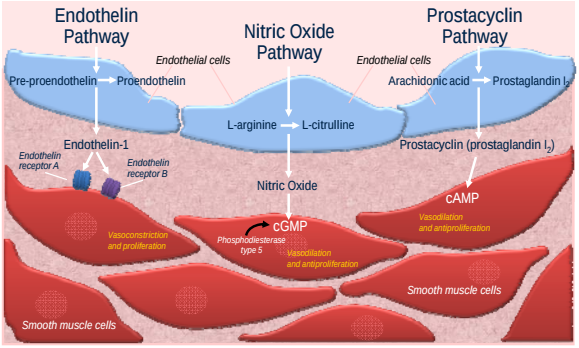
McLaughlin VV, et al. *J Am Coll Cardiol.* 2009;53:1573-1619.

PAH Determinants of Risk

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/m²	Hemodynamics	RAP >20 mm Hg; CI <2.0 L/min/m²
Minimally elevated	BNP	Significantly elevated

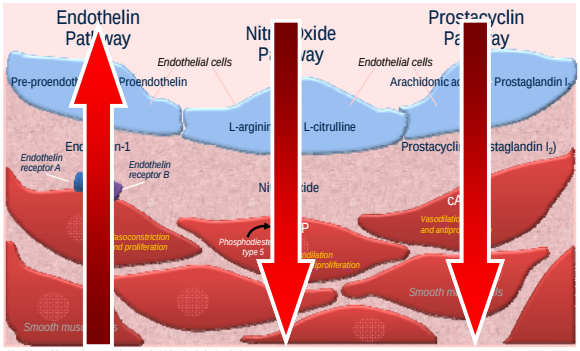
McLaughlin VV, et al. *J Am Coll Cardiol.* 2009;53:1573-1619.

Key Pathways Implicated in PAH Pathogenesis



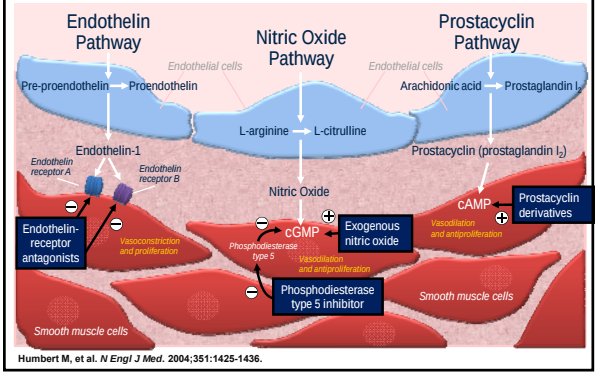
Humbert M, et al. *N Engl J Med.* 2004;351:1425-1436.

Key Pathways Implicated in PAH Pathogenesis



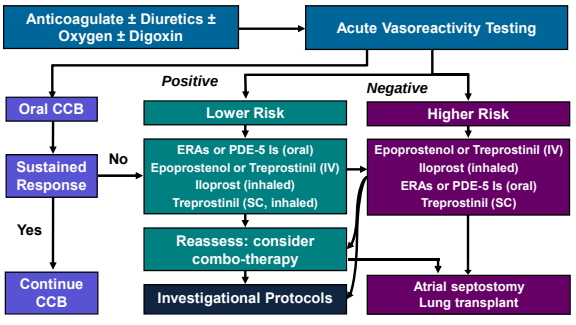
Humbert M, et al. *N Engl J Med.* 2004;351:1425-1436.

Mechanisms of Action of Approved Therapies for PAH



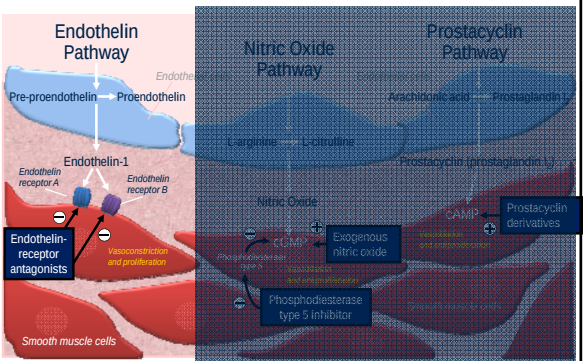
Humbert M, et al. *N Engl J Med.* 2004;351:1425-1436.

ACCF/AHA Consensus PAH Treatment Algorithm



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

Approved Therapeutic Targets



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

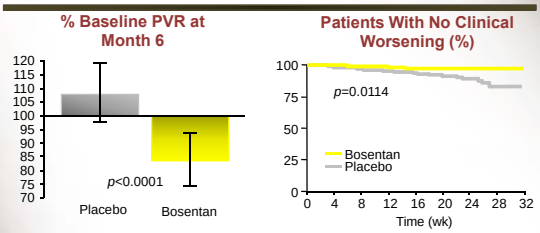
Endothelin Receptor Antagonists: Pivotal Trials

Study Name Drug	N Etiology Class	Design	Positive Results
BREATHE-1 Oral bosentan* vs placebo	213 PAH III, IV	Double-blind 16-week	• 6MWD • Delay clinical worsening • Symptoms
EARLY Oral bosentan vs placebo	185 PAH II	Double-blind 6-month	• Delay clinical worsening • Hemodynamics
ARIES-1&2 Oral ambrisentan § vs placebo	394 PAH II, III	Double-blind 12-week	• 6MWD • Delay clinical worsening

*Bosentan = Tracleer®. Approved for FC II-IV. 62.5-125 mg po bid.
§ Ambrisentan = Letairis®. Approved for FC II-III. 5-10 mg po qd

Rubin L, et al. *N Engl J Med.* 2002;346:896-903.
Channick RN, et al. *Lancet.* 2001;358:1119-1123.
Galiè N, et al. *Lancet,* 2008;371:2093-2100.
Galiè N, et al. *Circulation.* 2008;117:3010-3019.

Is Treatment of Less Symptomatic (FC II) Patients Justified?



Baseline 6MWD: Placebo: 438±86 m (n=92) Bosentan: 431±91 m (n=93)

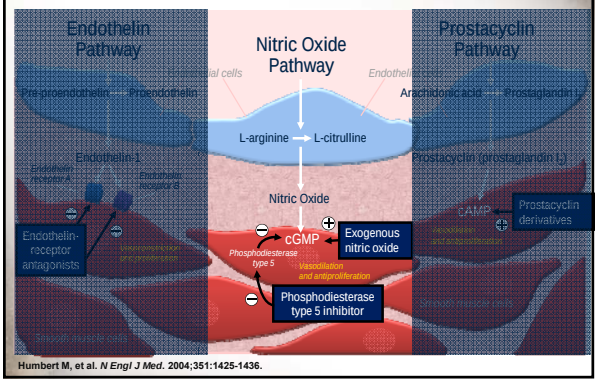
Other studies with FC I or II patients, though not in nos. adequate for analysis, include ARIES 1&2 (40%), SUPER (39%), PHIRST (33%), IV epo (5%), and SC treprostinil (11%).

Galiè N, et al. *Lancet.* 2008;371:2093-2100.

Endothelin Receptor Antagonists: Adverse Effects

- **Nasal congestion**
- **Abnormal hepatic function**
  - monthly LFTs required for bosentan
- **Anemia**
  - monitor CBC quarterly
- **Edema**
  - lower extremity edema may require diuretic adjustment
- **Teratogenic**
  - use requires dual contraceptive methods (hormonal plus barrier)

Approved Therapeutic Targets



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

PDE-5 Inhibitor Pivotal Trials

Study Name Drug	N Etiology Class	Design	Positive Results
SUPER-1 Oral sildenafil* vs placebo	278 PAH I-IV	Double-blind 12-week	• 6MWD • Symptoms • Hemodynamics
PHIRST-1 Oral tadalafil § vs placebo	405 PAH I-IV	Double-blind 16-week	• 6MWD • Delay clinical worsening • Hemodynamics • HRQoL

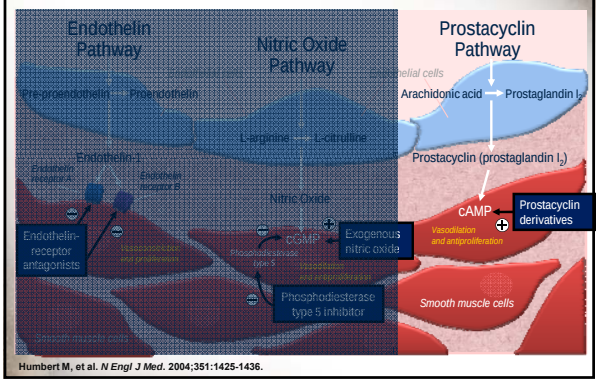
*Sildenafil = Revatio®. Approved for FC II-III. 20 mg po tid.
§ Tadalafil = Adcirca®. Approved for FC I-IV. 40 mg po qd.

Galiè N, et al. *N Engl J Med.* 2005:353:2148-2157.
Galiè N, et al. *Circulation.* 2009;119;2894-2903.

PDE-5 Inhibitor Adverse Effects

- Nose bleed
- Headache
- Dyspepsia
- Flushing
- Diarrhea
- Visual changes
- Contraindicated with use of nitrates

Approved Therapeutic Targets



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

Prostacyclin Analogues: Intravenous, Subcutaneous, or Inhaled

Epoprostenol (Flolan® or Veletri®)
Treprostinil (Remodulin®)

Treprostinil (Remodulin®)
Iloprost

Iloprost (Ventavis®)
Treprostinil (Tyvaso®)

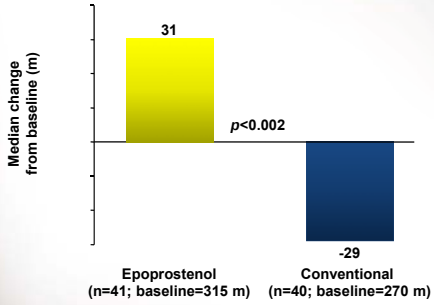
Approved uses: Epoprostenol IV: FC III-IV, 2 ng/kg/min titrated to desired clinical response in 1-2 ng/kg/min increments. Treprostinil IV / SC: FC II-IV, 1.25-2.5 ng/kg/min/wk. IV=diluted. Inhaled: FC III, to 54 mcg, 4 inh/d. Iloprost Inhaled: FC III-IV, 2.5-5 mcg, 6-9 inh/d.

Prostacyclin Analogues: Pivotal Trials

Study Name / Drug	N / Etiology / Class	Design	Positive Results
AIR Inhaled iloprost vs placebo	203 PH III-IV	Double-blind 12-week	• Composite end point • 6MWD • Symptoms • Hemodynamics
TRIUMPH 1 Inhaled treprostinil vs placebo[§]	235 PAH III-IV*	Double-blind 12-week on background oral Rx	• 6MWD
SQ treprostinil vs SQ placebo	470 PAH II-IV	Double-blind 12-week	• 6MWD • Symptoms • Hemodynamics
TRUST IV treprostinil vs placebo	44 PAH III	Double-blind, placebo-controlled 2-week	• 6MWD • Symptoms
IV epoprostenol vs conventional Rx	81 IPAH/FPAH III,IV	Open-label 12-week	• 6MWD • Symptoms • Hemodynamics • **Survival**
IV epoprostenol vs conventional Rx	111 APAH **SSc** III,IV	Open-label 12-week	• 6MWD • Hemodynamics • Symptoms

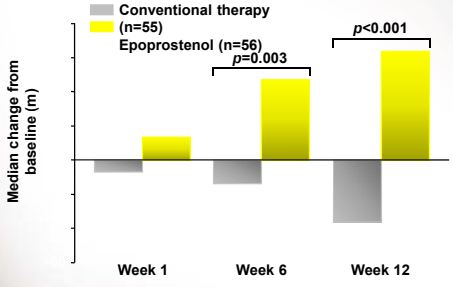
***Approved for class III only. §Included background therapy with ERA or PDE5-I.**
Olschewski H, et al. *N Engl J Med*. 2002;347:322-329; Simonneau G, et al. *Am J Respir Crit Care Med*. 2002;165:800-804; Barst RJ, et al. *N Engl J Med*. 1996;334:296-301; McLaughlin VV, et al. *Am J Respir Crit Care Med*. 2008;177:A965. McLaughlin VV, et al. *J Am Coll Cardiol*. 2010;55:1915-1922. Badesch D, et al. *Ann Intern Med* 2000;132(6):425-432. Hiremath J, et al. *J Heart Lung Transplant*. 2010;29:137-149.

IV Epoprostenol in IPAH: Change From Baseline in 6MWD



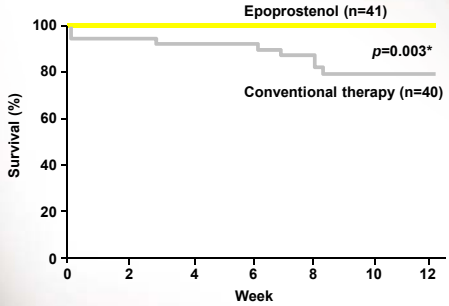
Barst RJ, et al for the PPH Study Group. *N Engl J Med*. 1996;334:296-301.

IV Epoprostenol in PAH Due to Scleroderma: Change From Baseline in 6MWD



Badesch D, et al. *Ann Intern Med*. 2000;132:425-434.

Survival Among Patients With IPAH: Epoprostenol vs Conventional Therapy



***Two-sided, by log-rank test.**
Barst RJ, et al for the PPH Study Group. *N Engl J Med*. 1996;334:296-301.

Prostanoid Adverse Effects

- Flushing
- Headache
- Diarrhea, nausea, vomiting
- Jaw pain
- Leg pain
- Hypotension
- Dizziness
- Syncope
- Delivery site complications (pain, infection, cough, thrombosis, infusion interruption)

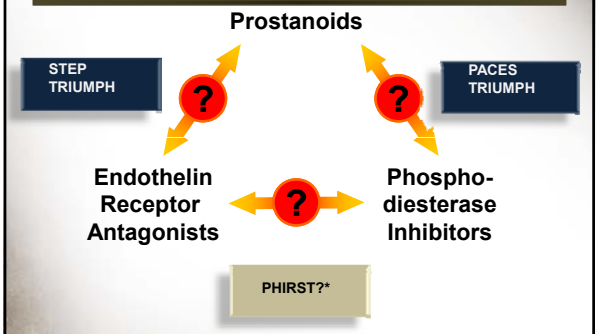
Vary according to drug and route of delivery

On-therapy Favorable 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

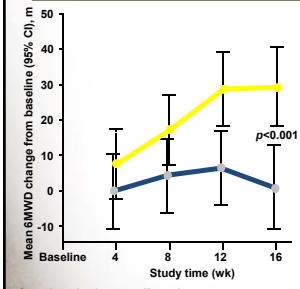
Sitbon O, et al. *J Am Coll Cardiol*. 2002;40:780-788.
McLaughlin VV, et al. *Circulation*. 2002;106:1477-1482.
Wensel R, et al. *Circulation*. 2002;106:319-324.

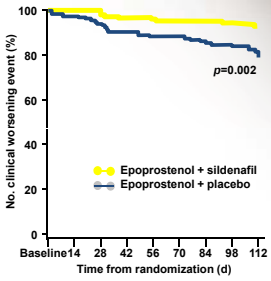
Combination Therapy



*Only half of patients on combination therapy

Sildenafil Added to Epoprostenol (PACES)



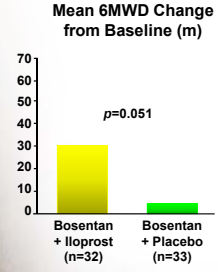


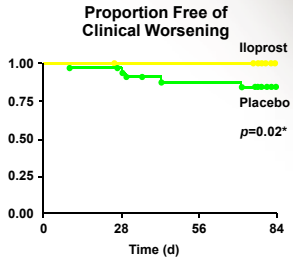
Opposite order than "usual" practice.
Different approach to epo dosing.
Most pts on 80 mg TID (not approved).
Simonneau G, et al. *Ann Intern Med*. 2008;149:521-530.
Erratum: *Ann Intern Med*. 2009;150:63; 2009;151:435.

Persons at Risk (Censored), n

	Base-line	Day 28	Day 56	Day 84	Day 112
Epo + placebo	131	123(1)	116(0)	111(2)	70(36)
Epo + sildenafil	134	134(0)	128(2)	125(2)	78(44)

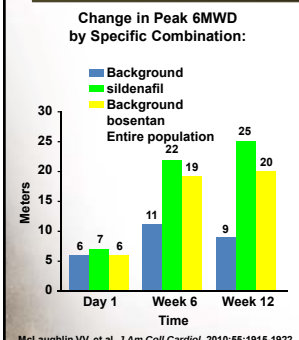
Inhaled Iloprost Added to Bosentan (STEP)

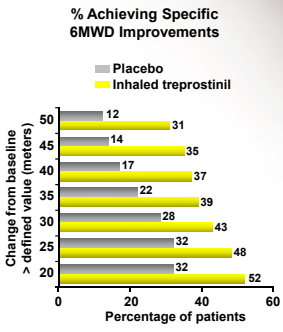




*log-rank test.
McLaughlin VV, et al. *Am J Respir Crit Care Med*. 2006;174:1257-1263.

Inhaled Treprostinil Added to Bosentan or Sildenafil (TRIUMPH)





McLaughlin VV, et al. *J Am Coll Cardiol*. 2010;55:1915-1922.

Combination Therapy Caveats

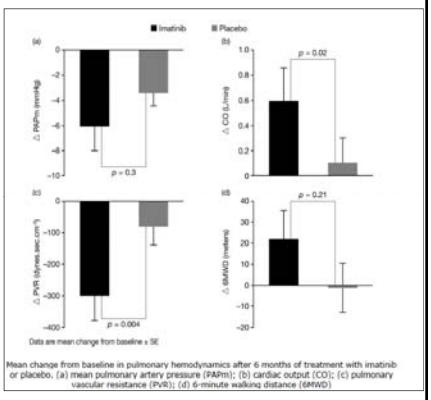
- Experience evolving
- Most data from 'add-on' - ? De novo? Order?
- More drugs available
  - more options
  - more ways to get it wrong
- More questions than answers
- Costs/expenditures; third-party hurdles

Taichman DB. *Ann Intern Med*. 2008;149:583-585.

Antiproliferative Therapy in PAH

- Abnormal endothelial and smooth muscle cell proliferation is a hallmark of PAH lesions
- Endothelial cells in PAH are hyperproliferative, apoptosis-resistant, and display abnormalities in cell cycle regulation
- Plexogenic lesions can have monoclonal origin
- Several experimental studies support this approach:
  - Statins
  - Tyrosine kinase inhibitors (e.g. imatinib)
  - SSRIs
  - DCA
  - Carbon monoxide
- Humans studies are underway

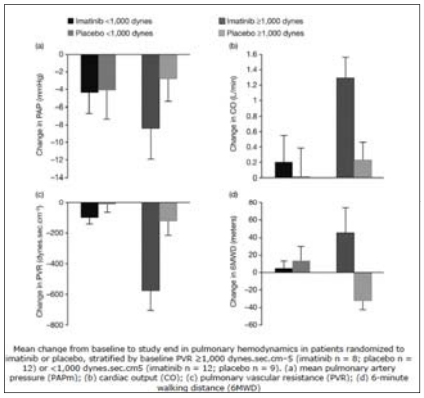
Imatinib in PAH



Mean change from baseline in pulmonary hemodynamics after 6 months of treatment with imatinib or placebo. (a) mean pulmonary artery pressure (PAPm); (b) cardiac output (CO); (c) pulmonary vascular resistance (PVR); (d) 6-minute walking distance (6MWD)

Ghofrani HA, et al. *Am J Respir Crit Care Med*. 2010;182:1171-1177.

Imatinib in PAH

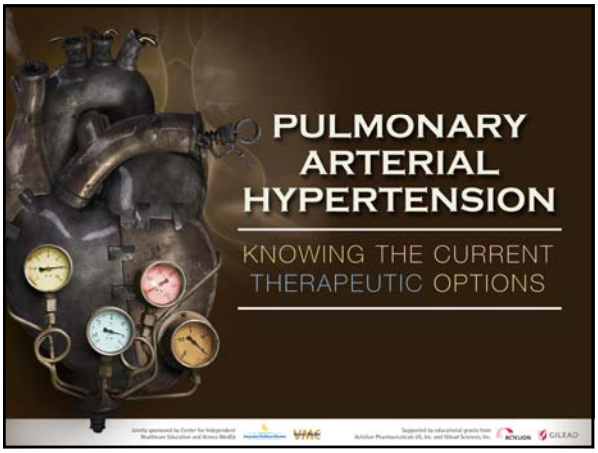


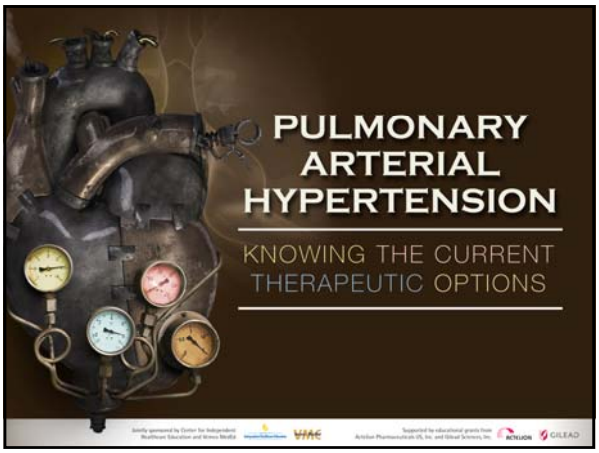
Mean change from baseline to study end in pulmonary hemodynamics in patients randomized to imatinib or placebo, stratified by baseline PVR ≥1,000 dynes.sec.cm−5 (imatinib n = 8; placebo n = 12) or <1,000 dynes.sec.cm5 (imatinib n = 12; placebo n = 9). (a) mean pulmonary artery pressure (PAPm); (b) cardiac output (CO); (c) pulmonary vascular resistance (PVR); (d) 6-minute walking distance (6MWD)

Ghofrani HA, et al. *Am J Respir Crit Care Med*. 2010;182:1171-1177.

Conclusions

- PAH therapy improves hemodynamics, functional capacity, morbidity and possibly mortality
- Despite progress, PAH is still incurable and current therapies do not alter vascular remodeling characteristic of the disease
- New therapies for PAH are needed



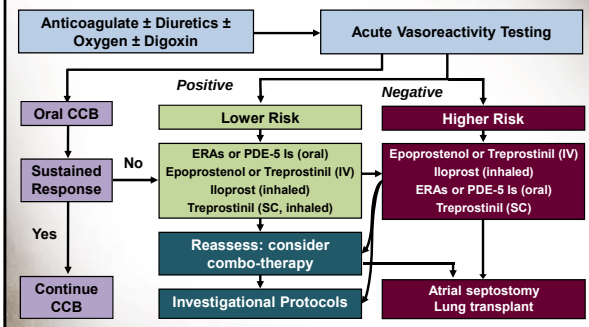


Knowing the Pharmacist's Role in Managing PAH

Utilizing Treatment Algorithms in Practice

James C. Coons, PharmD, BCPS (AQ-Cardiology)
Associate Professor
University of Pittsburgh School of Pharmacy
Department of Pharmacy & Therapeutics
Pittsburgh, PA

ACCF/AHA Consensus PAH Treatment Algorithm



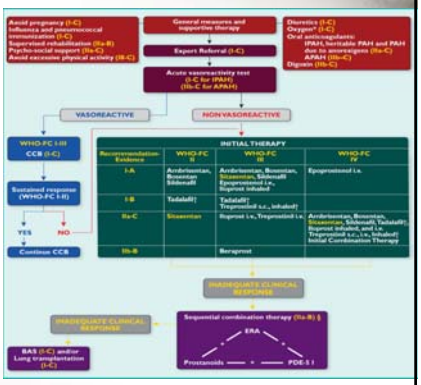
Modified from McLaughlin VV, et al. *J Am Coll Cardiol*. 2009;53:1573-1619.

Risk Assessment

Risk Factor	Lower Risk	Higher Risk
Evidence of RV failure	No	Yes
Symptom progression	Gradual	Rapid
Functional class	II, III	IV
6-min walk distance	>400 meters	<300 meters
Exercise testing	Peak VO_2 >10.4 mL/kg/min	Peak VO_2 <10.4 mL/kg/min
Echocardiogram	Minimal RV dysfunction	Pericardial effusion; RV enlargement/dysfunction; right atrial enlargement
Hemodynamics	RAP <10 mm Hg; CI >2.5 L/min/m²	RAP >20 mm Hg; CI <2 L/min/m²
BNP	Minimal elevation	Significant elevation

RV, right ventricle; VO2 , peak exercise oxygen consumption; RAP, right atrial pressure; CI, cardiac index.
McLaughlin VV, et al. *J Am Coll Cardiol*. 2009;53:1573-1619.

ESC/ERS Guidelines



Galie N, et al. *Eur Heart J*. 2009;30:2493-2537.

Pharmacotherapy Considerations

- Most clinical experience in PAH trials with idiopathic disease or associated with connective tissue disease or anorexigen use
- Limited long-term data
- Limited experience with combination therapy

REVEAL Registry: Summary of Treatments at Enrollment

All Patients	ERA	PDE-5 Inhibitor	Prostacyclin
Overall	47%	49%	42%
Monotherapy	18.5%	17.1%	12.1%
Combo with 1 oral therapy	11.9%	11.9%	21.7%
Combo with 1 prostacyclin	9.2%	12.5%	0.4%
Combo with >1 other therapy	7.4%	7.5%	7.8%

Badesch DB, et al. *CHEST*. 2010;137(2):376-387.

REVEAL Registry: Summary of Treatments at Enrollment

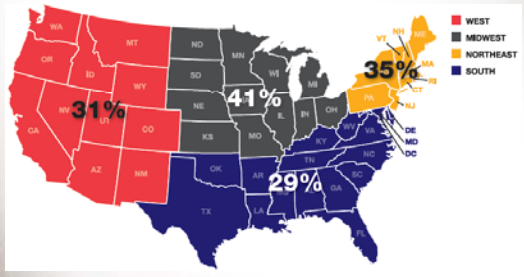
Class IV	ERA	PDE-5 Inhibitor	Prostacyclin
Overall	44.4%	49.2%	58.9%
Monotherapy	4%	11.3%	19.3%
Combo with 1 oral therapy	12.9%	12.9%	26.6%
Combo with 1 prostacyclin	14.5%	12.1%	---
Combo with >1 other therapy	12.9%	12.9%	12.8%

13% of patients were not treated with any PAH medication

Badesch DB, et al. *CHEST*. 2010;137(2):376-387.

Are Treatment Patterns the Same Throughout the US?

Use of Any Continuous Prostanoid in WHO Class III/IV Patients, by Region



Frantz, et al. Presented at the American Thoracic Society International Conference, San Diego, CA, May 15-20, 2009.

Combination Therapies

- Which medication is most effective and when?
- "Front-loaded" vs. "step-wise" approach?
- Does treating patients earlier make a difference?

Rationale for a "Step-Wise Approach"

- PAH is a progressive, insidious disease
- Addition of new medications may be needed to achieve and maintain goals
- Analogous to "CHF approach"

Evidence for Combination Therapy in PAH

Author	Study	Background Rx	Study Drug	Design
Humbert M. *Eur Resp J.* 2004	BREATHE-2	Epoprostenol	Bosentan	Up-front RCT
McLaughlin V. *Am J Resp Crit Care Med.* 2006	STEP	Bosentan	Iloprost	Sequential RCT
Hoeper M. *Eur Resp J.* 2006	COMBI	Bosentan	Iloprost	Sequential open label
Simonneau G. *Ann Intern Med.* 2008	PACES	Epoprostenol	Sildenafil	Sequential RCT
McLaughlin V. *J Am Coll Cardiol.* 2010	TRIUMPH 1	Sildenafil, bosentan, or both	Treprostinil (inhaled)	Sequential RCT
Tapson V. American Thoracic Society 2008	FREEDOM C	Sildenafil, ERA, or both	Treprostinil (oral)	Sequential RCT

RCT: randomized, controlled trial

Evidence for Combination Therapy in PAH

Author	Study	Patients	N	Duration (wks)	I EP	I EP	TCW
Humbert M. *Eur Resp J.* 2004	BREATHE-2	IPAH SSc SLE	33	16	TPR	-	ND
McLaughlin V. *Am J Resp Crit Care Med.* 2006	STEP	PAH	67	12	6MWD	-	+
Hoeper M. *Eur Resp J.* 2006	COMBI	IPAH	40	12	6MWD	-	-
Simonneau G. *Ann Intern Med.* 2008	PACES	IPAH CTD, CHD	267	16	6MWD	+	+
McLaughlin V. *J Am Coll Cardiol.* 2010	TRIUMPH 1	PAH	235	12	6MWD	+	-
Tapson V. ATS 2008	FREEDOM C	PAH	354	16	6MWD	-	-

CHD, congenital heart disease; CTD, connective tissue disease; IEP, initial endpoint; IPAH, idiopathic PAH; ND, no significant difference; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; TPR, total pulmonary resistance; TCW, time to clinical worsening

Rationale for "Front-Loaded" Approach

- PAH not always a "one drug" disease
- Redundancy of pathways
- Chemotherapeutic or induction approach

AMBITION Trial

A randomized, multicenter study of first-line AMBrisentan and Tadalafil combination therapy in subjects with pulmonary arterial hypertensION

To compare 2 treatment strategies upfront combo (amb + tad) vs. mono (amb or tad)

↓

Event-driven trial

↓

Primary objective: time to clinical failure
Secondary objectives: safety & tolerability, 6MWD at peak and trough levels

NCT01178073. http://www.clinicaltrials.gov/ct2/show/NCT01178073. Accessed Feb 2012.

REVEAL Registry: Independent Predictors of Mortality Based on a Multivariate Model

Parameter[a]	Hazard ratio	*P* value
Connective tissue–associated PAH	1.59	<0.001
Portal hypertension	3.60	<0.001
NYHA/WHO FC III/IV	1.41/3.13	0.008/<0.001
6MWD <165 m	1.68	<0.001
BNP >180 pg/mL	1.97	<0.001
PVR >32 Wood units	4.08	<0.001

[a] Other significant predictors of increased mortality include FPAH, renal insufficiency, male age >60 y, HR >92 bpm, SBP <110 mm Hg, any pericardial effusion, % predicted DLCO ≤32, and mRAP >20 mm Hg.

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

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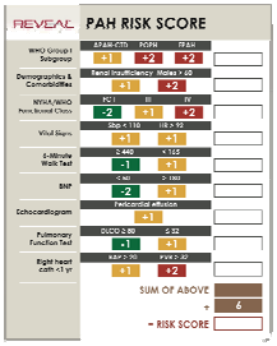
REVEAL Registry: Risk Score

- Composite Assessment of Risk
  - 19 easily obtained variables
    - 10 variables from demographics and exam
    - 9 from diagnostic tests
- Useful at any point during therapy
- Applicable for all PAH subgroups
- Multivariable model coefficients were replaced with integer values to create calculator
- Risk Calculator allows easy tabulation of risk score



BNP, B-type natriuretic peptide; NYHA, New York Heart Association; REVEAL, Registry to Evaluate Early and Long-term PAH disease management; WHO, World Health Organization.

Benza RL, et al. *Chest.* 2012;141:354-362.

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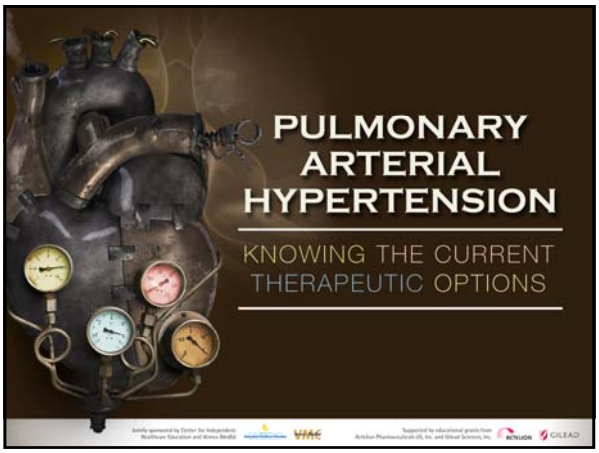
Implications for Use of REVEAL Score

- Incorporating score into therapeutic decision-making
- Practical considerations:
  - Goal REVEAL score <8
  - Consider PO or inhaled add-on therapy if score 7-9
  - Strong consideration to IV prostacyclin if score ≥10
  - Re-evaluate scores between 8 and 16 weeks



Challenges with PAH Treatments

- Identifying the pharmacists role in PAH management
- Complexity of regimen
- Infusion-related safety requirements
- Availability of medications and administration devices
- Education and training needs
- Reimbursement

Pharmacists Role in PAH Management

Medication Safety

- Hospital policy
- Dose verification
- Order entry
- Safety requirements
- Monitoring
- Side effect management
- Device use

Optimizing Medical Regimens

- Anticoagulation services
- Prevention
- Health maintenance
- Medication reconciliation

Pharmacists Role in PAH Management

Patient Education/Adherence

- Medication education
- Prescription and refill management
- Ongoing assessments and training

Transitions in Care

- Outpatient to inpatient conversion (and vice versa)
- Admission/discharge med review and education
- Access available resources
- Discharge planning
- Coverage coordination

Complex Regimens

- Initiation in controlled setting by experienced clinicians
- Titrated to symptoms improvement or signs of excessive effects
- Titrated in small increments

Complex Regimens

- **Dosing and administration**
  - Route
  - Vial concentration
  - Calculated dose
  - Dilution and reconstitution (concentration and total volume)
  - Rate (units of delivery specific to device)
  - Importance of dosing weight
  - Titration orders
  - Timing of next reservoir change

Epoprostenol Sodium

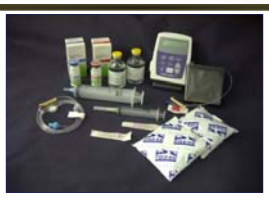
Generic, Flolan, Veletri * (0.5-mg and 1.5-mg lyophilized powder)

Dosing and Administration	Drug Properties
Requires reconstitution and further dilution: mixed concentration is rate/dose dependent	Short T ½ = ~4 to 6 min; must be protected from light
Initiated at 2 ng/kg/min and titrated q15 min Ongoing: 1-2 ng/kg/min q1-2wk Range: 20-40 ng/kg/min	Prior to reconstitution: stored at room temperature
Required CVC and continuous infusion pump (CADD Legacy) Requires back-up pump	Diluted: 8 hours at room temperature; 24 hours on ice; 48 hours maximum refrigerated*

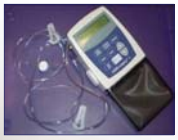
*Veletri:
- Not bioequivalent to Flolan® or generic
- Improved stability
- Reconstitute with sterile water or 0.9% sodium chloride, not sterile diluent for epoprostenol

Flolan Package insert. 2011. Veletri Package insert. 2011.

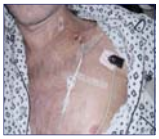
Epoprostenol Sodium: Administration



CADD pump



Central line



IV/SQ Treprostinil Sodium

Remodulin MDV: multiple concentrations

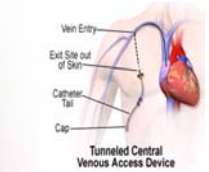
Dosing and Administration	Drug Properties
SQ: undiluted, q72h cartridge change IV: requires further dilution q48h	T½: ~4 hours
New: 1.25 ng/kg/min, titrated to response Conversion: 10% reduction Ongoing: weekly	Unopened vials stored at room temperature Opened: store up to 30 days
IV: CVC required, 3 pumps options SQ: CADD MS3	During administration Diluted: 48 h Undiluted: 72 h

Available Vial Sizes

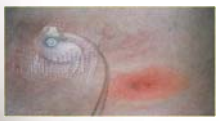
20mg/20ml (yellow) **100mg/20ml (green)**
50mg/20ml (blue) **200mg/20ml (pink)**

Remodulin Package Insert. 2011.

IV/SQ Treprostinil Sodium: Administration



Tunneled Central Venous Access Device



Parenteral Prostacyclin Delivery Systems

Intravenous

- CADD-Legacy
  - mL/24 hr
  - 50 or 100 mL cassettes
  - Dilution required
  - 24 hrs epoprostenol, 48 hrs treprostinil
- CRONO-Five*
  - microL/hr
  - 20 mL cartridge
  - Dilution required
  - 48 hrs treprostinil
- CADD MS3*
  - mL/hr
  - 3 mL cartridge
  - Dilution required
  - 48 hrs treprostinil

Subcutaneous

- CADD MS3
  - mL/hr in increments of 0.002
  - 3 mL cartridge
  - Drug **not** diluted
  - 72-hr administration intervals
- Mini-Med 407c *(being phased out)*

*Additional notes for micro-infusions:
1. Anticoagulation recommended due to low infusion rates
2. Transition recommended only after stable dose achieved
3. Consider priming volume with smaller volume reservoirs

Subcutaneous Treprostinil Dose Guide

CADD MS3 Infusion Pump (3 mL medication reservoir)

Patient Name:	RR
Date of Birth:	11/11/1951
MRN:	1111111111
Dosing Weight (kg):	102.0 kg
Date Printed:	12/27/2012
Cartridge Change (hrs):	48
Vial Concentration:	10.0 mg/mL 20 mL MDV

Calculated Dose (ng/kg/min)	Infusion Rate (in 0.002 mL/hr increments)	Total Cartridge Volume (mL)
65.0 ng/kg/min	0.040 mL/hr	2.4 mL

Intravenous Treprostinil Dose Guide

CADD Legacy 1 Infusion Pump (50 mL or 100 mL medication cassettes)

Patient Name:	RR	Starting Dose:	63.0 ng/kg/min
Date of Birth:	11/11/1951	Titration Increment:	2.0 ng/kg/min
MRN:	1111111111	Total Volume:	100 mL
Dosing Weight (kg):	102.0 kg	Starting Date:	12/2/2012
Todays Date:	12/27/2012	Interval:	2 days
Vial Concentration:	10.0 mg/mL 20 mL MDV	Number of Titrations:	10

Titration Date	Calculated Dose (ng/kg/min)	Pump Rate (CADD Legacy in mL/24hr)	Treprostinil Mix Volume (mL)	Diluent Mix Volume (mL)	Mixed Concentration (mg/mL)
12/02/12	63	31	3	97.0	0.3
12/04/12	65	32	3	97.0	0.3
12/06/12	67	33	3	97.0	0.3
12/08/12	69	34	3	97.0	0.3
12/10/12	71	35	3	97.0	0.3
12/12/12	73	36	3	97.0	0.3
12/14/12	75	37	3	97.0	0.3
12/16/12	77	38	3	97.0	0.3
12/18/12	79	39	3	97.0	0.3
12/20/12	81	40	3	97.0	0.3

Intravenous Treprostinil Dose Guide

CADD Legacy 1 Infusion Pump (50 mL or 100 mL medication cassettes)

Patient Name:	RR	Starting Dose:	63.0 ng/kg/min
Date of Birth:	11/11/1951	Titration Increment:	2.0 ng/kg/min
MRN:	1111111111	Total Volume:	100 mL
Dosing Weight (kg):	109.0 kg	Starting Date:	12/2/2012
Todays Date:	12/27/2012	Interval:	2 days
Vial Concentration:	10.0 mg/mL 20 mL MDV	Number of Titrations:	10

Titration Date	Calculated Dose (ng/kg/min)	Pump Rate (CADD Legacy mL/24hr)	Treprostinil Mix Volume (mL)	Diluent Mix Volume (mL)	Mixed Concentration (mg/mL)
12/02/12	63	33	3	97.0	0.3
12/04/12	65	34	3	97.0	0.3
12/06/12	67	35	3	97.0	0.3
12/08/12	69	36	3	97.0	0.3
12/10/12	71	37	3	97.0	0.3
12/12/12	73	38	3	97.0	0.3
12/14/12	75	39	3	97.0	0.3
12/16/12	77	40	3	97.0	0.3
12/18/12	79	41	3	97.0	0.3
12/20/12	81	42	3	97.0	0.3

Inhaled Treprostinil Sodium

Tyvaso 0.6-mg/mL; 2.9-mL ampules

Dosing and Administration	Drug Properties
Administer undiluted, 1 ampule/day. 1 breath = 6 mcg	T ½: ~4 hours
Initial dosage: 3 breaths/tx QID Inc by 3 breaths/tx every 1-2 wks as tolerated to goal 9 breaths QID	Packaged 4 ampules per 1 foil pack Protect from light during storage at RT 7d once foil opened
Requires use of Optineb inhalation device.	Discard remaining solution from amp after 24 hrs.

Tyvaso package insert. 2011

Inhaled Iloprost Sodium

Ventavis 10- and 20- mcg/mL; 1-mL ampules

Dosing and Administration	Drug Properties
Administer undiluted, 1 ampule/treatment session.	T½: ~ 20 to 30 min
Initial: 2.5 mcg x 1 dose then increase to 5mcg per dose if tolerated 6 to 9 tx/day (20 mcg/mL = 5 mcg dose only!)	Stored at RT
Requires use of I-Neb inhalation device Dose is determined by medication chamber	Discard remaining solution

Ampule Concentration	Dose	Chamber/Disc Color
10 mcg/mL	2.5 mcg	Red
10 mcg/mL	5 mcg	Purple
20 mcg/mL	5 mcg	Gold

Ventavis package insert. 2012.

Inhaled Prostacyclin Delivery Systems

Inhaled treprostinil

- OptiNeb
  - 1 ampule provides 24 hrs of treatment sessions
  - Dosed in breaths per session
  - Requires use of distilled water

Inhaled iloprost

- I-Neb AAD
  - 1 ampule per treatment session
  - Dosed in treatment sessions per day
  - Two concentrations = KNOW DIFFERENCE!

Prostacyclin Patient Considerations

Infusion

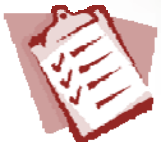
- Visual acuity
- Motor skills
- Environment
- Location
- Support
- Anticoagulation

Inhaled

- Compliance
  - Cleaning
  - Multiple treatment sessions
- Lung disease
- Disease severity

ERA Patient Considerations

- Reproduction
- Ability or willingness to comply with mandatory labs and enrollments (REMS requirements)
- Drug interactions
- Special enrollment
  - Bosentan (Tracleer®)
    - Tracleer Access Program (T.A.P.)
  - Ambrisentan (Letairis®)
    - Letairis Education and Access Program (L.E.A.P.)



Elevated LFT >3× ULN: Adjustment and Monitoring for Bosentan

ALT/AST level	Treatment and monitoring recommendations
>3 and ≤5 x ULN	• Repeat test; if confirmed, decrease dose to 62.5 mg twice daily or hold, monitor LFT q 2 wk • If LFTs normalize, continue or reintroduce at starting dose (recheck LFTs w/in 3 days and q 2wk as above)
>5 and ≤8 x ULN	• Repeat test; if confirmed, stop treatment and monitor LFTs q 2 wk • Once LFTs normalize, consider reintroduction at starting dose (recheck LFTs w/in 3 days and q 2 wk as above)
>8 x ULN	• Stop treatment and do not re-challenge

ULN=upper limit of normal.
Tracleer Package Insert. 2012.

PDE-5 Inhibitors: Patient Considerations

- Need for organic nitrates
- Other drug interactions
- Combination therapy
- Concomitant conditions

Transitioning Therapy

- Rationale
  - Recurrent bacteremia
  - Intolerable side effects
  - Profound improvement (benefits vs. risks)
  - Limitations with therapy management
  - Lifestyle, patient preference

Transitioning Therapy

- Potential concerns
  - Intermittent vs. continuous dosing of prostacyclin
  - Dose limitations with inhaled therapy
  - Patient compliance
  - Follow up
  - Patient selection

Transitioning Therapy

- Types
  - Transitioning parenteral prostacyclins
    - Titration
    - Rapid
  - Transitioning inhaled prostacyclins
  - Parenteral to or from inhaled prostacyclin
  - Prostacyclin to oral

Prostacyclin Infusion Related Safety Considerations

- Drug interactions and drug stability
- Never stop or turn off pump
- Never flush or prime the line
- No blood draws from dedicated line: consider labeling catheter and tubing
- Do not infuse with other medications
- Line dislodgement or obstruction → place peripheral line temporarily
- "Dead-space" and priming needs
- Need for MRI or X-Ray managing pumps
- Backup pump, drug, supplies
- Signs of infection
- Contact PH specialist

Potential Complications with Infused Prostacyclins

- Non-compliance
- CVC infection, leak, occlusion, or bleed
- Systemic infection
- Pump malfunction
- Mixing error
- Accidental bolus
- Any interruption in therapy
- Delivery delay
- Supply misuse
- Sudden worsening in symptoms
- Development of new symptoms
- SQ site infection, dislodgement, pain, or bleed
- Side effects

Adjunctive Medications for Side Effect Management

- Antiemetic
- Antidiarrheal
- Antidepressant
- Antiseizure meds
- Narcotics or other pain meds
- Topical creams/ointments
- Cough suppressants
- Diuretics
- Nasal decongestant sprays

Recommendations for Safe Use

- Detailed hospital policies for pharmacy and nursing
- Create checklists/order sets
- Annual staff training and education (consider demonstration component
- PH Specialist and specialty pharmacy contact info
- Limit management to certain HCP's

Availability and Other Resources

- Limited distribution/restricted access/REMS
- Specialty pharmacy contact info for 24/7/365
  - Hospital requests for information (concentration, dose, rate, weight, etc.)
  - Emergency needs of medication, devices or supplies
  - Therapy and device/supplies troubleshooting (e.g., occlusions, migrations, need for repair/leak, bleeding, suspected infection)
  - Inpatient use
- Patient's home supply (caution regarding reimbursement) and pumps
- Advocacy groups

Education of Patient and Caregiver

- Patients (preparation is key)
  - Be familiar with disease state and therapy
  - Know medications (paper list, luggage tag, thumb drive, electronic records, etc.)
  - Keep back-up of drug and supplies
  - Educate local emergency medical service teams
  - Know local hospital info, PCP, emergency contact
  - Compliance and regular follow-up (i.e. labs)
  - Diet and Exercise
  - Immunizations
  - Pregnancy and contraception
  - Patient expectations

Education of Staff

- Mandatory education and competency
  - Goal: ensure all staff members are comfortable and confident with the management of PAH therapies
  - Consider demonstration, written or oral competencies
    - Nursing: prostacyclin policies and procedures, equipment, monitoring, medication use, and disease state
    - Pharmacists & pharmacy technicians: prostacyclin policies and procedures, monitoring, pharmacotherapy, order sets, operational duties, and disease state

Reimbursement

- High-cost medications
- Pharmacy vs. medical vs. both
- Co-pay assistance programs
- Manufacturer PAP
- Drug approval before initiation