Complex Therapy Management

- **General**
  - Accurate diagnosis
  - Initiation of therapy
  - Medication availability
  - Education and training
    - Staff
    - Patients
  - Cost and reimbursement
  - Limited distribution
  - Small populations
  - Contraindications
- **Prostacyclins (infused and inhaled):**
  - Unique devices and supplies
  - Complex dosing and titrations
  - Profound pharmacological effects
  - Specially-trained HCPs
- **Oral targeted therapies**
  - REMS
  - Drug interactions

Multidisciplinary Management

UI Health PAH Team

- Program Director
- PAH Nurse Coordinator
- Clinical Pharmacists
- Clinic Support Staff

Health-System Approach

- Physicians: pulmonary, critical care, cardiology
- Nurses: clinical and research
- Pharmacists: dispensing, clinical and research
- Research personnel
- Specialty services: rheumatology, hematology, hepatology, sleep medicine and cardiovascular imaging

What is the Hemodynamic Definition of Pulmonary Arterial Hypertension?

1. Mean PAP ≥25 mm Hg at rest or ≥30 mm Hg with exercise
2. Pulmonary artery systolic pressure >40 mm Hg
3. Mean PAP ≥25 mm Hg at rest, PCWP ≤15 mm Hg PVR, increased PVR
4. All of the above

PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance

Hemodynamic Definition of PH/PAH

PH	**Mean PAP ≥25 mm Hg**
PAH	**Mean PAP ≥25 mm Hg *plus* PCWP/LVEDP ≤15 mm Hg**
ACCF/AHA includes PVR >3 Wood Units	

LVEDP, left ventricular end diastolic pressure

Badesch D, et al. *J Am Coll Cardiol.* 2009;54:S55-S66.
Galiè N, et al. *Eur Heart J.* 2009;30:2493-2537.
McLaughlin VV, et al. *J Am Coll Cardiol.* 2009;53:1573-1619.

5th World Symposium on PH: Modified Classification of PH

1. Pulmonary arterial hypertension
- 1.1 Idiopathic PAH
- 1.2 Heritable PAH
  - 1.2.1 BMPR2
  - 1.2.2 ALK1, ENG, SMAD9, CAV1, KCNK3
  - 1.2.3 Unknown
- 1.3 Drug- and 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 diseases (update)
  - 1.4.5 Schistosomiasis
  - ~~1.4.6 Chronic hemolytic anemia~~

1'. Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis

1". PPHN

2. PH due to LHD
- 2.1 LV systolic dysfunction
- 2.2 LV diastolic dysfunction
- 2.3 Valvular disease
- 2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

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 lung diseases (update)

4. CTEPH

5. PH with unclear multifactorial mechanisms
- 5.1 Hematological disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
- 5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis,
- 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
- 5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

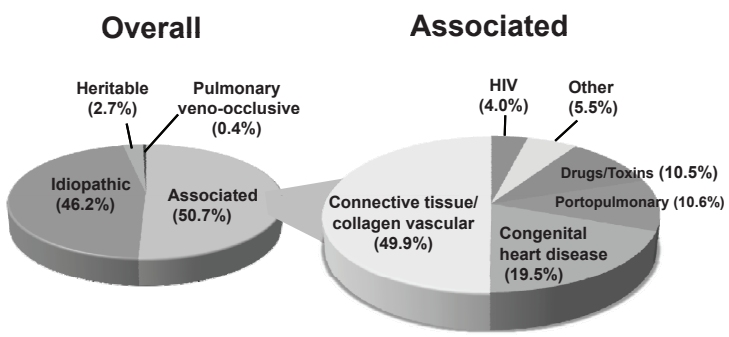
Simonneau G, et al. *JACC.* 2013;62:D34-D41.

Hemodynamic-Clinical Classification Relationships

Definition	Hemodynamic Characteristics	WHO Clinical Groups
PH	mPAP >25 mm Hg CO normal, reduced, or ↑	ALL
Pre-capillary PH	PCWP/LVEDP ≤15 mm Hg TPG ≥12–15 mm Hg	1. PAH 3. PH due to lung disease and/or hypoxemia 4. CTEPH 5. PH with unclear or multifactorial mechanisms
Post-capillary PH	PCWP/LVEDP >15 mm Hg TPG <12 mm Hg	2. PH owing to LHD
Mixed PH Reactive Non-reactive/fixed	PCWP/LVEDP >15 mm Hg TPG ≥12–15 mm Hg	2. PH owing to LHD

Adapted from Hoeper M, et al. *Eur Heart J.* 2009;30:2493-2537.

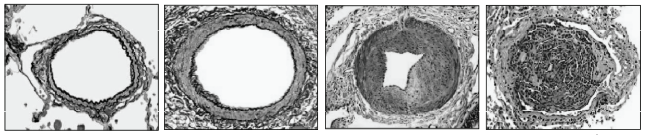
PAH Distributions in the US: REVEAL Registry



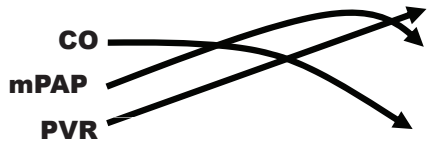
Based on Venice Clinical Classification (2003); 2967 patients.
Adapted from Badesch DB, et al. *Chest.* 2010;137:376-387.

Progressive and Life-limiting Disorder

Pathological changes in the pulmonary arteries



Hemodynamic impairment

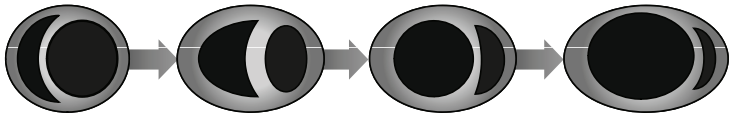


Decreasing mean PAP may not reflect improvement

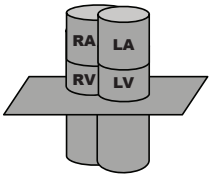
Adapted from Gaine S. *JAMA.* 2000;284:3160-3168.

The Right Ventricle in PAH

- RV pressure/volume overload
- RV failure

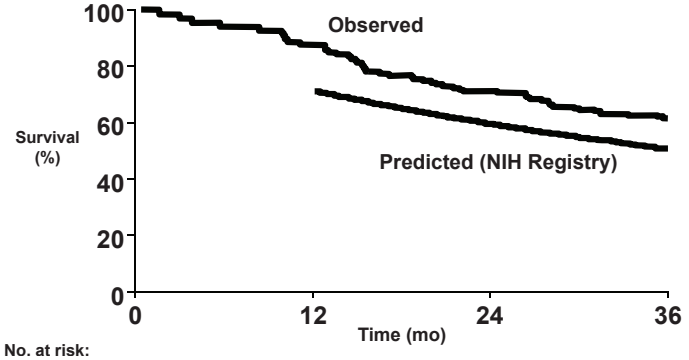


Progressive structural changes in the RV due to poor adaptation to increasing PVR



Cross-section

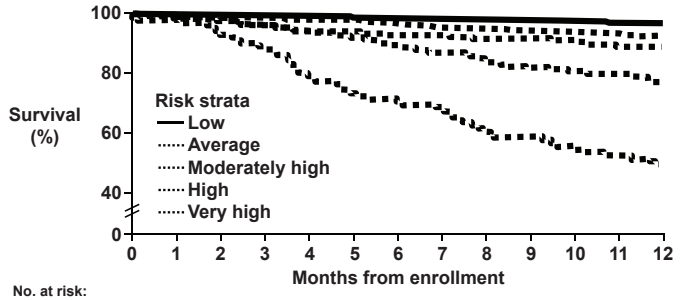
French Registry: Kaplan-Meier Survival Estimates in Combined PAH Population vs. NIH-predicted



No. at risk:							
All patients	56	69	98	113	120	127	133

Humbert M, et al. *Circulation*. 2010;122:156-163.

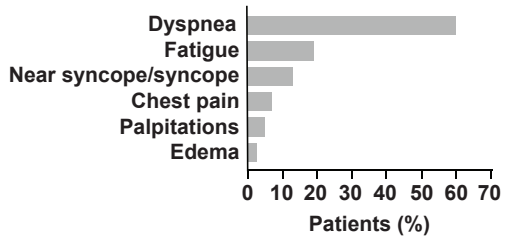
REVEAL: Observed 1-year Survival From Time of Enrollment According to Predicted Risk Strata



No. at risk:			
Low	1374	1351	1303
Average	665	640	596
Mod. high	280	260	243
High	295	263	225
Very high	102	72	49

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

Patient Presentation: Nonspecific Symptoms



Median Time From Symptom Onset to Diagnosis

NIH Registry (1981 to 1985)	1.3 years	***Multiple educational efforts***
REVEAL Registry (2006 to 2007)	1.1 years	

Rich A, et al. *Ann Intern Med.* 1987;107:216-223.
Badesch DB, et al. *Chest.* 2010;137:376-387.

Clinical Case: Meet Jane

- 37-year-old woman, previously healthy
- Delivered second child 14 mo previously
- Limited exercise tolerance since delivery, attributed to weight gain
- Dyspnea while playing with older child; syncope while walking up an incline

Jane's Initial Symptoms

- Currently has dyspnea with mild exertion, walks slowly in store
- Exertional light-headedness
- Atypical chest pain
- Occasional palpitations
- Lower extremity edema

Jane's Additional History

- PMH: 2 children, 4 yr and 14 mo
  - IBS: diet-controlled
- Meds: none
- Allergies: contrast dye
- FH: PAH in a paternal aunt, CAD, DM, HTN
- SH: rare ETOH, o/w unremarkable

CAD, coronary artery disease; DM, diabetes mellitus; ETOH, alcohol; FH, family history; HTN, hypertension; IBS, irritable bowel syndrome; PAH, pulmonary arterial hypertension; PMH, past medical history; o/w, otherwise; SH, social history

Jane: Physical Exam

- HR 90 bpm; BP 130/68 mm Hg; Wt 190 lb; Ht 5' 4"
- JVP ~15 cm, reduced carotid upstrokes
- Clear lungs
- Palpable RV heave, RRR, NL S, loud P_2, III/VI, TR murmur
- 2+ LE edema

JVP, jugular venous pressure; RRR, regular rate and rhythm; RV, right ventricular; TR, tricuspid regurgitation; LE, lower extremity

Is There a Reason to Suspect PAH?
Clinical Presentation

History	Exam (PH)	Exam (RV Failure)
• Dyspnea (86%) • Fatigue (27%) • Chest pain (22%) • Edema (22%) • Syncope (17%) • Dizziness (15%) • Cough (14%) • Palpitations (13%)	• Loud P2 (listen at apex) • RV lift (left parasternal – fingertips) • RV S3, S4 • Systolic murmur (TR; inspiratory augmentation) • Early systolic click • Midsystolic ejection murmur • Diastolic murmur (PR)	• JVD; increased A wave, V wave; hepatojugular reflex • Pulsatile liver • Hepatomegaly • Edema • Ascites • Low BP, low PP, cool extremities

REVEAL. Badesch DB, et al. *Chest.* 2010;137:376-87.
Adapted from McLaughlin VV, et al. *J Am Coll Cardiol.* 2009;53:1573-1619.

Pivotal Tests: RHC

- Refer to a PH center if:
  - accurate tracings (especially PCWP) are difficult to obtain
  - vasoreactivity testing is not available

Vasoreactivity Testing

- Patients with pre-capillary PH
- Inhaled nitric oxide is recommended (typically protocolized at PH centers)
- Decrease in mPAP by ≥10 mm Hg *and*
- Decrease of mPAP to <40 mm Hg *and*
- No significant decrease in CO

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

Jane: Right Heart Catheterization

	1/29/07 Baseline	Nitric Oxide 20 ppm
RAP (mm Hg)	19	20
PAP (mm Hg)	93/40, mean 63	93/46, mean 64
LVEDP (mm Hg)	10	
Oxygen saturation (%) Pulmonary artery Femoral artery	 52.9 91.4	 58.3 91.7
Cardiac output / Cardiac index (L/min) Fick	2.5/1.3	2.88/1.52
PVR (Wood units) Fick	21.2	15.2

LVEDP, left ventricular end diastolic pressure; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure

PAH Treatment Goals

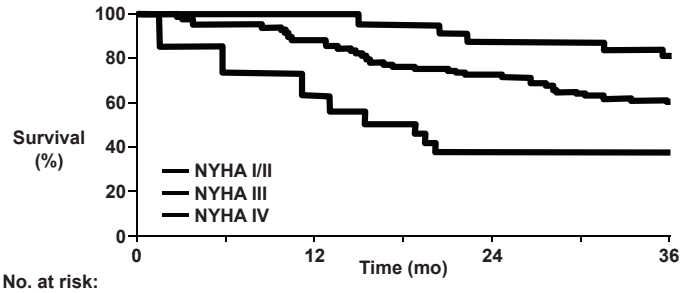
- Fewer/less severe symptoms
- Improve exercise capacity
  - 6MWD
  - WHO functional classification
- Improve hemodynamics
- Prevent clinical worsening
  - escalation of therapy
  - hospitalization
  - lung transplantation
  - death
- Improve quality of life
- Improve survival

6MWD, six-minute walk distance

Initial Therapy: Making the Right Decision

- Severity of disease
- Patient preference
- Trying to weigh the data
- When "comparing" trials, examine:
  - objective baseline characteristics of participants (age, functional class, 6MWD, hemodynamics)
  - outcome measures (6MWD, time to clinical worsening)

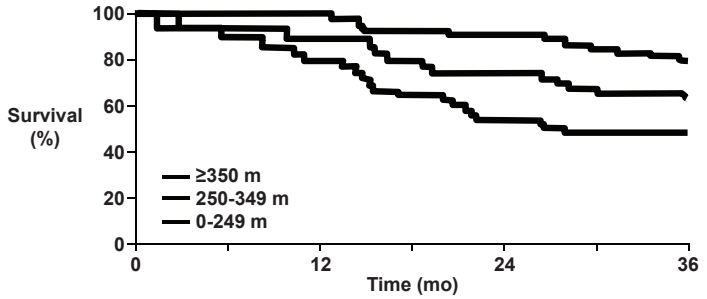
French Registry: Kaplan-Meier Survival Estimates According to Baseline NYHA Functional Class



No. at risk:							
NYHA I/II	12	15	19	23	24	26	27
NYHA III	37	48	70	79	86	88	89
NYHA IV	7	6	9	11	10	13	17

Combined idiopathic, familial, and anorexigen-associated PAH.
Humbert M, et al. *Circulation.* 2010;122:156-163.

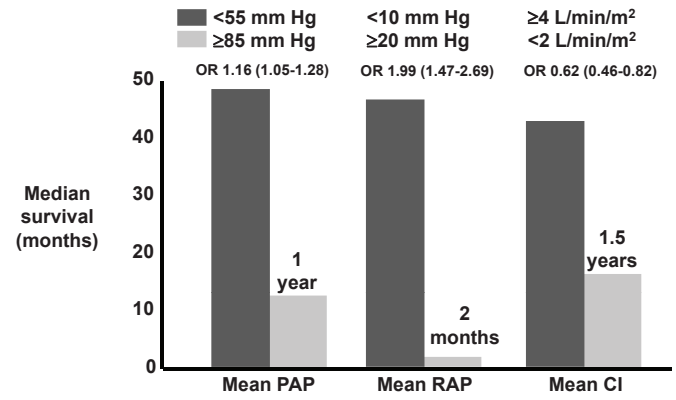
French Registry: Kaplan-Meier Survival Estimates According to Baseline 6MWD



No. at risk:							
0-249	17	19	29	30	28	32	35
250-349	16	19	21	27	31	33	35
≥350	17	23	37	45	50	52	53

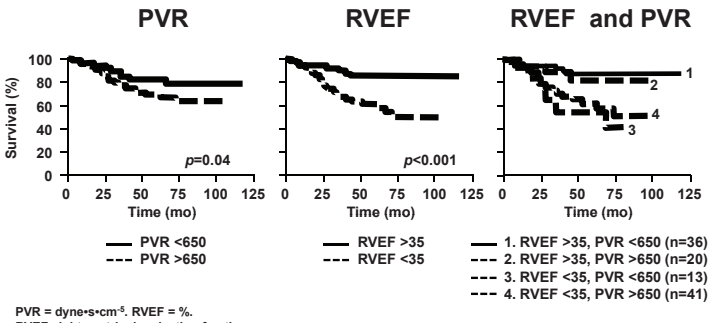
Combined idiopathic, familial, and anorexigen-associated PAH.
Humbert M, et al. *Circulation.* 2010;122:156-163.

Hemodynamic Abnormalities and Prognosis (IPAH)



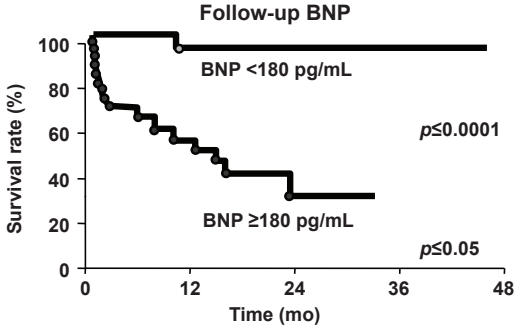
RAP, right atrial pressure; CI, cardiac index
D'Alonzo GE, et al. *Ann Intern Med.* 1991;115:343-349.

Survival Rates of Patients With PAH, Stratified by PVR and RVEF at Baseline



PVR = dyne•s•cm^{-5}. RVEF = %.
RVEF, right ventricular ejection fraction
van de Veerdonk MC, et al. *JACC.* 2011;58:2511-2519.

Plasma BNP as a Prognostic Indicator in Patients With IPAH



By multivariate analysis, higher BNP at *follow-up* (RR=25.880, *p*=0.0243) was an independent predictor of mortality.

Nagaya N, et al. *Circulation.* 2000;102:865-870.

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/m^2	Hemodynamics	RAP >20 mm Hg; CI <2.0 L/min/m^2
Minimally elevated	BNP	Significantly elevated

CPET, cardiopulmonary exercise testing; BNP, B-type natriuretic peptide
McLaughlin VV, et al. *J Am Coll Cardiol.* 2009;53:1573-1619.

5th World Symposium on PH Goals of Therapy: Setting the Bar Higher

Functional Class	• I or II
Hemodynamics	• Normalization of RV function (RAP <8 mm Hg and CI >2.5–3.0 L/min/m^2)
Echocardiography/ MRI	• Normal/near normal RV size and function
BNP level	• 'Normal'
6MWD	• 380–440 m, may not be aggressive enough
CPET	• Peak VO_2 >15 mL/kg/min • VE/VCO_2 @ AT <45

McLaughlin VV, et al. *J Am Coll Cardiol.* 2013.:62:D73-81.

5th World Symposium on PH: 2013 PAH Treatment Algorithm

- Supervised exercise training (I-A)
- Psycho-social support (I-C)
- Avoid strenuous physical activity (I-C)
- Avoid pregnancy (I-C)
- Influenza and pneumococcal immunization (I-C)

General measures and supportive therapy

↓

Expert Referral (I-C)

↓

- Oral anticoagulants:
  - IPAH, heritable PAH, and PAH due to anorexigens (IIa-C)
  - APAH (IIb-C)
- Diuretics (I-C)
- Oxygen (I-C)
- Digoxin (IIb-C)

Galiè N, et al. *J Am Coll Cardiol.* 2013;62:D60-D72.

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

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.

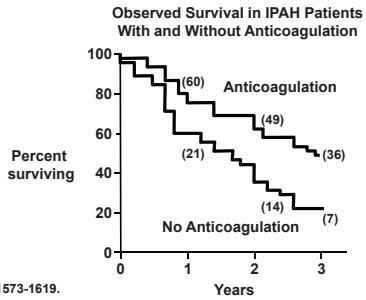
Chronic Adjuvant Treatment

Diuretics

- **Needed by most patients**
- **Hypotension not a contraindication**
- **Renal function and electrolytes must be monitored closely**

Anticoagulation

- **Recommended in IPAH**
- **Observational data only**
- **Need to balance unproven benefits with known risks**
- **INR goal 1.5–2.5**



Fuster V, et al. *Circulation.* 1984;70:580-587.
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
- Consider enrollment in a pulmonary rehabilitation program
- Immunizations
- Contraception
- Psycho-social support; role of support groups

5th World Symposium on PH: 2013 PAH Treatment Algorithm

- Supervised exercise training (I-A)
- Psycho-social support (I-C)
- Avoid strenuous physical activity (I-C)
- Avoid pregnancy (I-C)
- Influenza and pneumococcal immunization (I-C)

General measures and supportive therapy

↓

Expert Referral (I-C)

↓

Acute vasoreactivity test (I-C for IPAH) (IIb-C for APAH)

- Oral anticoagulants:
  - IPAH, heritable PAH, and PAH due to anorexigens (IIa-C)
  - APAH (IIb-C)
- Diuretics (I-C)
- Oxygen (I-C)
- Digoxin (IIb-C)

Galiè N, et al. *J Am Coll Cardiol.* 2013;62:D60-D72.

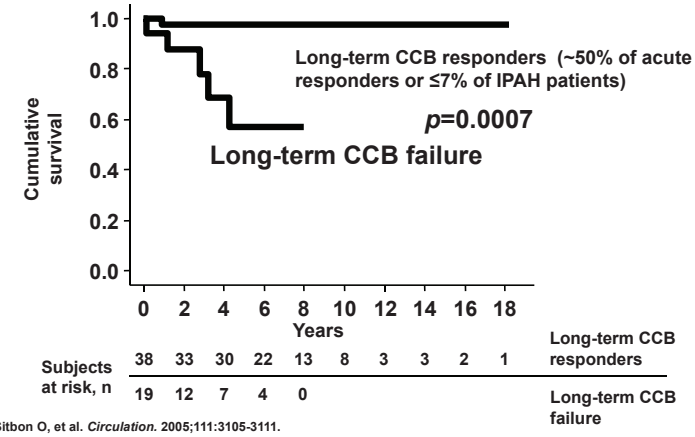
Vasodilator Challenge

- iNO (most commonly) at 40 ppm
- Positive if:
  - drop in mPAP >10 mm Hg to a mean <40 mm Hg
  - no decline in CO/CI
  - no rise in PCWP
- Suggests response to calcium channel blocker
- Caveats:
  - only indicated for IPAH patients
  - 50% lose vasoreactivity over time

Galiè N, et al. *J Am Coll Cardiol.* 2013;62:D60-72.

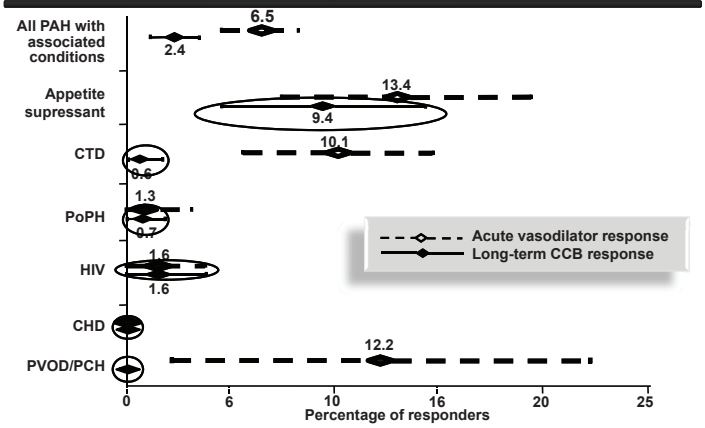
Why Is It Important? Survival in IPAH

Long-term CCB Responders



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

Long-term Response to CCBs in Non-idiopathic PAH

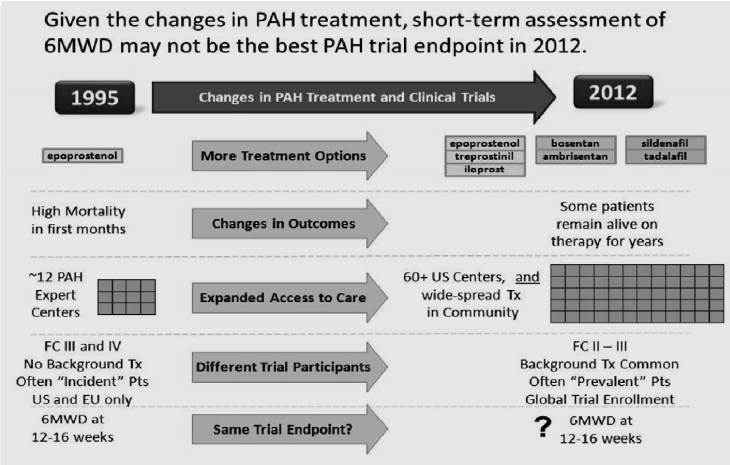


Montani D, et al. *Eur Heart J.* 2010;31:1898-1907.

How Do I Treat a Responder?

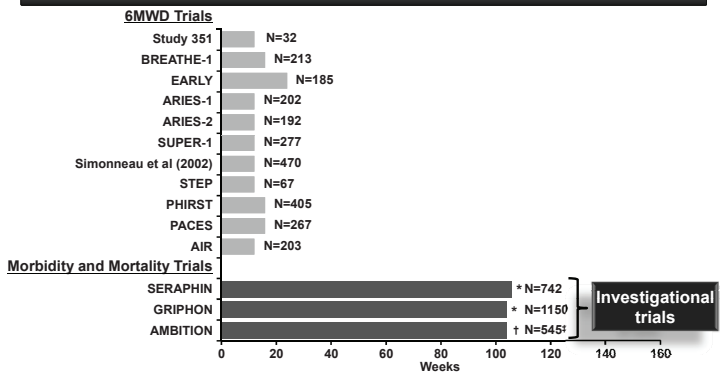
- High-dose calcium channel blockers
  - nifedipine 180–240 mg/d
  - diltiazem 720–960 mg/d
  - amlodipine 20–30 mg/d
- Must re-catheterize after 3–6 months of therapy to assess sustained response
  - 50% will lose vasoreactivity over time
    - Treat as other PAH patients

Changes in PAH Trials Over Time



McLaughlin VV. *Chest.* 2012;142:1363-1364.

Evolution From Exercise Capacity to Morbidity and Mortality RCTs



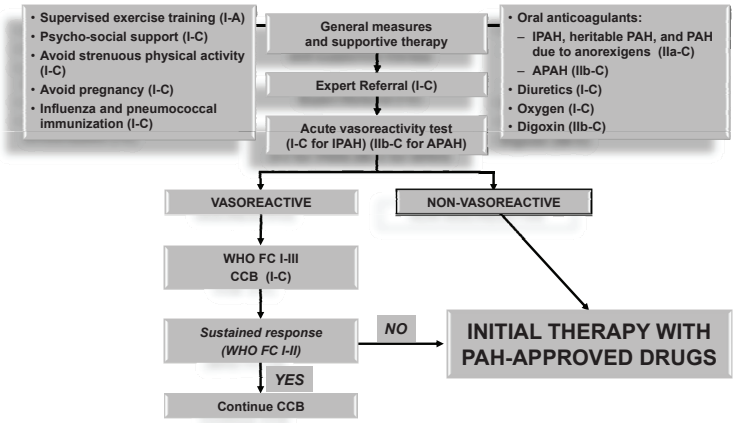
*Estimated mean study drug exposure. †Estimated median study drug exposure. ‡Estimated target enrollment.
PAH=pulmonary arterial hypertension; RCT=randomized controlled trial.
Channick RN et al. *Lancet.* 2001;358:1119-1123. Rubin LJ et al. *N Engl J Med.* 2002;346:896-903. Galiè N et al. *Lancet.* 2008;371:2093-2100. Galiè N et al. *Circulation.* 2008;117:3010-3019. Galiè N et al. *N Engl J Med.* 2005;353:2148-2157. Simonneau G et al. *Am J Respir Crit Care Med.* 2002;165:800-804. McLaughlin VV et al. *Am J Respir Crit Care Med.* 2006;174:1257-1263. Galiè N et al. *Circulation.* 2009;119:2894-2903. Simonneau G et al. *Ann Intern Med.* 2008;149:521-530. Olschewski H et al. *N Engl J Med.* 2002;347:322-329. SERAPHIN, GRIPHON, and AMBITION study designs available at: www.clinicaltrials.gov. Accessed 23 November 2015.

Time to Clinical Worsening: The Spectrum in PAH Trials

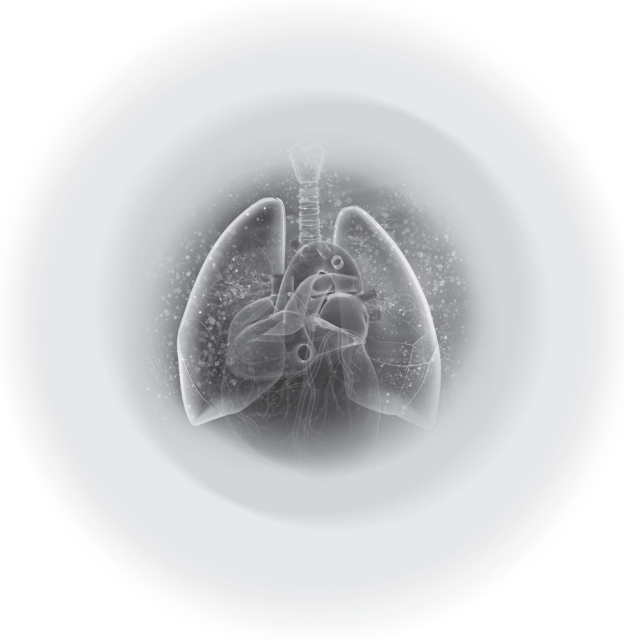
	Death	Hospital	Lung Tx	AS	Symptom	No Δ	Add therapy
BREATHE-1	X	X	X	X	X	X	X
EARLY	X	X	-	-	X	X	-
ARIES-1	X	X	X	X	X	X	X
ARIES-2	X	X	X	X	X	X	X
SERAPHIN	X	X	X	X	X	X	X
SUPER-1	X	X	X	-	-	-	X
PHIRST	X	X	X	X	X	-	X
TRIUMPH	X	X	X	-	-	-	X
PATENT-1	X	X	X	X	X	-	X
STEP	X	X	X	-	-	X	X
PACES	X	X	-	-	-	-	X
GRIPHON	X	X	X	X	X	-	X

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. Pulido T et al. *N Engl J Med.* 2013;369:809-818. Galiè N et al. *N Engl J Med.* 2005:353:2148-2157. Galiè N et al. *Circulation.* 2009;119;2894-2903. McLaughlin VV et al. *Am J Respir Crit Care Med.* 2006;174:1257-1263. Simonneau G et al. *Ann Intern Med.* 2008;149:521-530. Erratum: *Ann Intern Med.* 2009;150:63; 2009;151:435. McLaughlinVV et al. *J Am Coll Cardiol.* 2015;65(10_S):. doi:10.1016/S0735-1097(15)61538-8.

5th World Symposium on PH: 2013 PAH Treatment Algorithm



Galiè N, et al. *J Am Coll Cardiol.* 2013;62:D60-D72.



PAH Drug Classes

- **Prostacyclin Derivatives**
- **Endothelin Receptor Antagonists**
- **Soluble Guanylate Cyclase Stimulators**
- **Phosphodiesterase Inhibitors**
- ***Calcium Channel Blockers***

5th World Symposium on PH: 2013 PAH Treatment Algorithm

INITIAL THERAPY WITH PAH-APPROVED DRUGS					
RED: Morbidity and mortality as primary end point in randomized controlled study or reduction in all-cause mortality (prospectively defined) Level of evidence based on WHO-FC of majority of patients of studies					
		Evidence	WHO FC II	WHO FC III	WHO FC IV
Recommendation	I	A or B	•Ambrisentan, Bosentan •Macitentan •Riociguat •Sildenafil •Tadalafil	•Ambrisentan, Bosentan, Epoprostenol IV •Iloprost inh •Macitentan •Riociguat •Sildenafil •Tadalafil •Treprostinil SC, inh	•Epoprostenol IV
	IIa	C		•Iloprost IV*, Treprostinil IV	•Ambrisentan, Bosentan, Iloprost inh and IV* •Macitentan •Riociguat •Sildenafil, Tadalafil •Treprostinil SC, IV, Inh*
	IIb	B		•Beraprost*	
		C		•Initial Combination Therapy	•Initial Combination Therapy

Galiè N, et al. *J Am Coll Cardiol.* 2013;62:D60-D72.

*Not approved in in US.

In patients with IPAH, which agent(s) have been shown to increase survival in a randomized clinical trial?

1. Calcium channel blockers
2. Epoprostenol
3. Bosentan
4. Treprostinil
5. All of the above

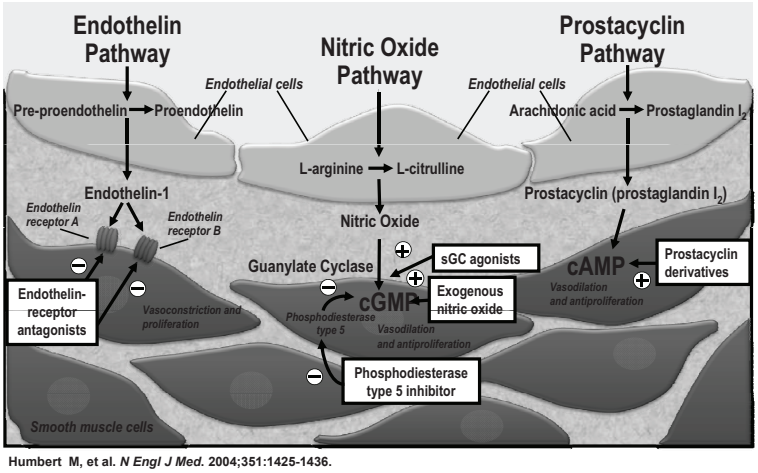
Which of the following agents would you choose to treat Jane's PAH?

1. Amlodipine
2. Epoprostenol
3. Bosentan
4. Riociguat
5. Tadalafil

Jane: Initial Management

- Admitted to hospital following RHC
- IV diuresis
- IV epoprostenol initiation

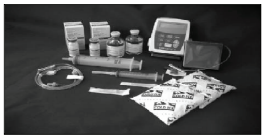
Therapeutic Targets for PAH



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

Prostacyclin General Characteristics

- Often considered gold standard for advanced disease
- Unique administration devices
- Interruptions must be avoided
- Differ in stability, half-life, and method of delivery
- Available only through restricted drug distribution system (RDDS)
- Titrated to response and tolerability
- ***High-risk, error-prone medications***



Prostacyclin Analogues: IV and SQ Formulations

How Supplied	Administration	FC	Dose	Properties	CI/P/Misc
Epoprostenol Sodium **Generic, Flolan®, or Veletri® 0.5mg, 1.5mg**	Continuous IV infusion via infusion pump. Requires tunneled CVC. Flolan requires use of ice packs. Requires reconstitution.	III, IV	Initiated at 2 ng/kg/min and titrated based on response. Ongoing: 1-2 ng/kg/min q1-2 wk.	$T_{½}$ <6 min. Temp and light sensitive. Reconstituted stability dependent on formulation. Rapidly hydrolyzed in the blood.	CHF due to severe LVD. Avoid abrupt withdrawals or interruption in infusion: may result in rebound PH or death.
Treprostinil Sodium **Remodulin® 1mg/mL, 2mg/mL, 5mg/mL, 10mg/mL in 20mL vials**	Continuous IV or SubQ infusion via infusion pump. IV requires tunneled CVC.	II-IV	Initiated at 1.25 ng/kg/min and titrated based on response Ongoing: 1.25 ng/kg/min every week or as tolerated	$T_{½}$ ~4 hours. Metabolized by CYP 2C8. Diluted: 48-hour infusion duration. Undiluted: 72-hour infusion duration.	Initiated in controlled setting. Monitor for signs of BSI.

Veletri® (epoprostenol) US Prescribing Information. Actelion Pharmaceuticals US, Inc. June 2012.
Remodulin® (treprostinil) US Prescribing Information. United Therapeutics Corp. December 2014.

Prostacyclin Analogues: Pivotal Trials for IV and SC Formulations

Study Name / Drug	N / Etiol / Class	Design	Positive Results
TRUST **IV treprostinil vs placebo**	**44** **PAH** **III**	**Double-blind, placebo-controlled 12-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**
SC treprostinil vs SC placebo	**470** **PAH** **II–IV**	**Double-blind 12-week**	**• 6MWD** **• Symptoms** **• Hemodynamics**

Hiremath J, et al. *J Heart Lung Transplant.* 2010;29:137-149.
Barst RJ, et al. *N Engl J Med.* 1996;334:296-301.
Badesch D, et al. *Ann Intern Med* 2000;132:425-432.
Simonneau G, et al. *Am J Respir Crit Care Med.* 2002;165:800-804.

Oral and Inhaled Prostacyclins					
How Supplied	Administration	FC	Dose	Properties	CI/P/Misc
Iloprost **Ventavis® 10 mcg/mL and 20 mcg/mL unit dose ampules**	Intermittent inhalation via dedicated inhalation device	III, IV	2.5 mcg once, then 5 mcg per dose if tolerated for 6 to 9 x/day	$T_{½}$ ~20 to 30 min.	Caution if underlying lung disease or symptomatic hypotension. Bronchospasm Store at RT Discard unused solution One ampule used per treatment session (20 mcg/mL = 5 mcg dose only!)
Treprostinil Tyvaso® for inhalation 0.6 mg/mL in 2.9 mL ampules	Intermittent inhalation via dedicated inhalation device	III	3 breaths QID, titrated to goal 9 breaths QID	$T_{½}$ ~4 hours. Metabolized by CYP 2C8.	One inhaled ampule provides multiple doses/day Once opened: discard remaining solution after 24 hours, protect ampules from light during storage
Treprostinil Orenitram® 0.125 mg, 0.25 mg, 1 mg and 2.5 mg ER tablets	Oral extended release osmotic tablets	II, III	Initial: 0.25 mg BID or 0.125 mg TID, titrate every 3 to 4 days	$T_{½}$ ~4 hours. Metabolized by CYP 2C8. Food increases bioavailability	Abrupt discontinuation, Diverticulitis Severe hepatic impairment Avoid alcohol

Ventavis® (iloprost) US Prescribing Information. Actelion Pharmaceuticals US, Inc. November 2013.
Tyvaso® (treprostinil) US Prescribing Information. United Therapeutics Corp. August 2014.
Orenitram® (treprostinil) US Prescribing Information. United Therapeutics Corp. October 2014.

Prostacyclin Analogues: Pivotal Trials for Inhaled and Oral Formulations

Study Name / Drug	N / Etiol / 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**
FREEDOM-M **Oral treprostinil vs placebo**	**228** **PAH** **II-III**	**Double-blind, placebo-controlled** **12-week**	• **6MWD**

*Approved for class III only. §Included background therapy with ERA or PDE-5I.
Olschewski H, et al. *N Engl J Med.* 2002;347:322-329.
McLaughlin VV, et al. *J Am Coll Cardiol.* 2010;55:1915-1922
Hiremath J, et al. *J Heart Lung Transplant.* 2010;29:137-149.
Jing Z-C, et al. *Circulation.* 2013;127:624-633.

Jane's epoprostenol titrations are underway. Which of the following is a potential dose-related effect of epoprostenol?

1. Urticaria
2. Hypotension
3. Anemia
4. Constipation

Management of Prostacyclin-Related Effects

Adverse Effect	Management Strategy
Headache	OTC analgesics, Tramadol, opiates if severe
Diarrhea	Loperamide, Lomotil, adjust titrations
Nausea	Ondansetron or other anti-emetics, food (oral formulation)
Hypotension Dizziness	Adjust antihypertensive drugs, diuretics. Adjust titrations
Jaw Pain	Start first meal with bland food, "exercise jaw"
Leg Pain	Elevate legs, gabapentin, pregabalin, amitriptyline, other pain meds
Flushing	Adjust titrations

Management of SC Prostacyclin Effects

- Topical Agents
- Systemic Management
  - H1 and H2 blockers
  - OTC analgesics, opioids if severe
  - GABA analogs
  - Others
- Non-pharmacologic management
  - Catheter dwell times
  - Catheter type
  - Dry insertion
- Other strategies:
  - Pre-medicate
  - Rapid titration
  - Increase concentration

Endothelin Receptor Antagonists: General Characteristics

- ERAs antagonize ET_A receptors*
- Available only through limited distribution
- Risk Evaluation and Mitigation Strategies (REMS)
  - Inpatient and outpatient requirements
- Oral formulation

* Bosentan and macitentan are dual ET_A and ET_B receptor antagonist.

Bosentan				
How Supplied	REMS		Properties	CI/P
Tracleer® 62.5 mg, 125 mg tablets	Teratogenicity, liver toxicity. Must enroll in Tracleer REMS Program		$T_{½}$ ~5 hours Metabolized and strong inducer of CYP3A4 and CYP2C9, possibly CYP2C19; Caution with drug intx.	CI: Pregnancy and use of cyclosporine or glyburide. Caution with liver disease.
	FC	Dose		
Administration	II-IV	Initial: 62.5 mg BID x 4 weeks, then increase to 125 mg BID thereafter if tolerated and wt >40 kg.		
Oral tablets. Can be dissolved into soln.				

Ambrisentan				
How Supplied	REMS		Properties	CI/P
Letairis® 5 mg, 10 mg tablets	Teratogenicity. FRP must enroll in Letairis REMS Program		$T_{½}$ up to ~15 hours Metabolized by CYP3A4 and CYP2C19, substrate of P-glyco-protein	CI: pregnancy and IPF. Caution with anemia, fluid retention, PVOD.
	FC	Dose		
Administration	II-III	Initial: 5 mg daily, increase to 10 mg daily if tolerated		
Oral tablets				

Macitentan				
How Supplied	REMS		Properties	CI/P
Opsumit® 10 mg tablets	Teratogenicity. FRP must enroll in Opsumit REMS Program		$T_{½}$ ~16 hrs (48 hrs for active metabolite) Metabolized by CYP3A4 and CYP2C19; active metabolite contributes ~40% of activity.	CI: Pregnancy Caution with anemia, liver disease.
	FC	Dose		
Administration	Mostly II-III	10 mg po daily		
Oral tablets				

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
SERAPHIN Oral macitentan† vs placebo	742 PAH II,III	Double-blind Event-driven morbidity/mortality	• Delay disease progression • 6MWD • Symptoms

*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
†Macitentan = Opsumit®. Approved for FC II-III. 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. Pulido T, et al. *N Engl J Med.* 2013;369:809-818.

Guanylate Cyclase Stimulator

- Novel mechanism
- First non-WHO Group 1 approved indication
- Available only through RDDS
- Risk Evaluation and Mitigation Strategies (REMS) for teratogenicity
- Requires blood pressure monitoring and titration

Riociguat				
How Supplied	REMS		Properties	CI/P
Adempas® 0.5 mg, 1 mg, 1.5 mg, 2 mg, 2.5 mg tablets	Teratogenicity. FRP must enroll in Adempas REMS Program		T ½ ~12 hrs in PAH pts. Substrate of P-gp and BCRP, metabolized by CYP-1A1, 3A, 2C8, 2J2.	CI: Pregnancy, nitrates, PDE-5i. Caution with hypotension, PVOD, bleeding, smokers.
	FC	Dose		
Administration	II-III	0.5 to 1 mg TID, titrated q2weeks to max 2.5 mg TID		
Oral tablets				

Adempas® (riociguat) US Prescribing Information. Bayer Healthcare. September 2014.

sGC Stimulator Pivotal Trials

Study Name Drug	N Etiology Class	Design	Positive Results
PATENT-1 Oral riociguat* vs placebo	278 PAH I-IV	Double-blind 12-week	• 6MWD • Symptoms • Hemodynamics • Delay clinical worsening
CHEST-1 Oral riociguat vs placebo	261 CTEPH I-IV	Double-blind 16-week	• 6MWD • Symptoms • Hemodynamics

***Riociguat = Adempas®. Approved for WHO Group 1; persistent CTEPH (WHO Group 4) after surgical treatment, or inoperable CTEPH; titrated to maximum 2.5 mg po tid.**

Ghofrani HA, et al. *N Engl J Med.* 2013;369:319-329.
Ghofrani HA, et al. *N Engl J Med.* 2013;369:330-340.

Sildenafil				
How Supplied	REMS		Properties	CI/P
generic Revatio® 20 mg tablets **Revatio® 10 mg/12.5 mL soln for injection** **Powder for suspension**	n/a		$T_{½}$ ~4 hours Metabolized by CYP3A4 and CYP2C9 (minor)	CI: use with organic nitrates. Increased mortality risk in peds. Caution with SCD, PVOD. Post marketing AE: NAION
	FC	Dose		
Administration **Oral tablets or suspension. Solution for injection used for NPO.**	Mostly II-III	Oral: 20 mg TID Inj.: 10 mg TID		

Tadalafil				
How Supplied	REMS		Properties	CI/P
Adcirca® 20 mg tablets	n/a		$T_{½}$ ~35 hrs Metabolized by CYP3A4	CI: use with organic nitrates Caution with SCD, PVOD.
	FC	Dose		
Administration **Oral tablets**	II-III	40mg daily		

Revatio® (sildenafil) US Prescribing Information. Pfizer Labs. January 2014.
Adcirca® (tadalafil) US Prescribing Information. Eli Lilly and Company. April 2015.

PDE-5 Inhibitor Pivotal Trials

Study Name Drug	N Etiol 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.

Management of Oral Therapy Effects

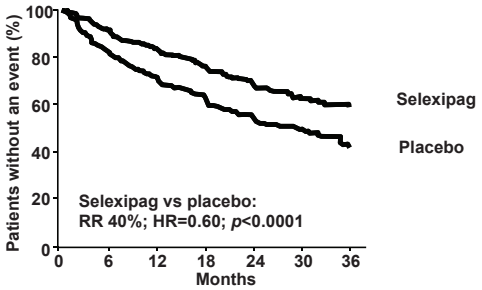
Adverse Effect	Management Strategy
Headache	OTC analgesics, Tramadol, opiates if severe
Peripheral Edema	Add or adjust diuretics, salt and fluid restrictions
Anemia	Periodic CBC monitoring Reduce dose or discontinue drug
Hemorrhagic events Epistaxis (sildenafil)	Caution with anticoagulants Monitor for bleeding/bruising
Nausea	Anti-emetics
Hypotension, Dizziness	Monitor BP in between dose titrations Adjust antihypertensive drugs, diuretics Reduce dose or hold titration if needed (riociguat)
Dyspepsia	PRN OTC agents if infrequent H2 blocker or PPI
Nasal congestion	Saline nasal spray
Teratogenicity	Obtain negative pregnancy test monthly for women of reproductive age Contraception mandatory
Elevated LFT's	Monitor LFT's monthly (bosentan) Reduce dose or discontinue drug

Recently Completed or Ongoing Clinical Trials of Combination Therapy

	Current Therapy	Added Therapy	Patients (*n*)	Study Duration	Primary Endpoint
AMBITION	Ambrisentan/ tadalafil/ combo	Combo vs mono	500	Event-driven	Morbidity/mortality event
Pfizer	Bosentan	Sildenafil	104	12 weeks	6MWD
COMPASS-2	Sildenafil	Bosentan	250	Event-driven	Morbidity/mortality event
ATPAHSS	Ambrisentan/ tadalafil/ combo	Combo vs mono	63	36 weeks	RV mass/PVR
GRIPHON	ERA, PDE-5I, or both	Selexipag	1156	Event-driven	Morbidity/mortality event
Ikaria	≥1 current therapies	Inhaled NO	78	16 weeks	PVR
FREEDOM-Ev	PDE-5I or ERA	Oral treprostinil	858	24 weeks (6MWD)/event driven	6MWD/ 1st clinical worsening event

https://clinicaltrials.gov/

Investigational Oral Prostacylin Therapy: Time to First Morbidity or Mortality Event—GRIPHON

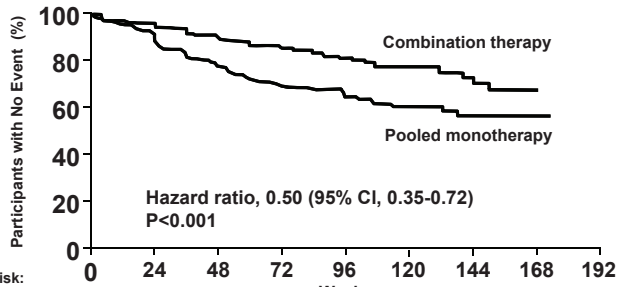


No. at Risk

Placebo	582	433	347	220	149	88	28
Selexipag	574	455	361	246	171	101	40

McLaughlin VV, et al. *J Am Coll Cardiol.* 2015;65(10_S):. doi:10.1016/S0735-1097(15)61538-8.

AMBITION: Effect of Ambrisentan Plus Tadalafil Versus Monotherapy on Clinical Worsening*



No. at risk:								
Combination therapy	253	229	186	145	106	71	36	4
Pooled monotherapy	247	209	155	108	77	49	25	5

*Death, hospitalization for worsening PAH, disease progression, unsatisfactory long-term clinical response.
Galiè N, et al. *N Engl J Med.* 2015;373:834-44.

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.

Transitioning Therapy

Rationale

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

Potential concerns

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

Types

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

Targeted Therapies: Use With Caution

Other drugs

- Multiple anti-hypertensive drugs
- Anti-platelet or anti-coagulants
- Sympathomimetic agents
- Strong inhibitors or inducers of specific CYP P450 enzymes

Co-Morbidities

- Liver or renal impairment
- Congestive heart failure
- Depression
- Cognitive impairment
- Substance abuse disorder
- Dexterity/mobility impairment
- Significant hypotension
- Immunosuppression

Transitions in Care

- Know your institution's policies and procedures
  - Be prepared and prioritize patient safety
  - Discharge planning
  - Contacting PAH specialists and specialty pharmacy
- Special enrollments and medication access process
  - REMS requirements
- Be familiar with significant drug interactions and AEs
- Engage the patient and caregiver, they are very well-trained and knowledgeable
  - Most patients carry backup meds/devices with them

Opportunities for Pharmacists

- Comprehensive medication reconciliation and history
- Education and training on targeted therapies and devices
- Participation in therapy selection and therapeutic alternatives
- Policies and procedure development
- Coordinate medication access
- Program enrollment for REMS or restricted distribution therapies
- Ongoing safe-use monitoring
- Dose verification, order entry and drug interactions
- Health maintenance
- Medication titration and adverse effect management
- Resource for other healthcare providers

Jane: Return Visit in May & September

- Significantly improved
- No limitations
- Functional class I
- Meds
  - epoprostenol 30 ng/kg/min
  - warfarin
  - furosemide 20 mg
  - KCl 10 mEq qd

Jane: Follow-up Physical Exam

- HR 80; BP 103/59 mm Hg; Wt 144.8 lb
- JVP 6 cm, carotid upstrokes NL
- Clear lungs
- Palpable RV heave, NL S, loud P_2, II/VI TR murmur
- No LE edema

Jane: 6MWD

- 222 m: 99–96% in January
- 486 m: 99–97% in May
- 556 m: 99–97% in September

Summary

- PAH-specific therapies promote vasodilation, leading to reduction in pulmonary vascular resistance and improved RV function
- Therapies are highly individualized and require a multi-disciplinary team of healthcare providers with specialized training
- Selection of initial therapy largely depends upon severity of disease at diagnosis
  - low-risk patients can be treated with oral agents
  - high-risk patients require parenteral prostacyclins
- Lack of improvement or worsening of parameters should trigger escalation of therapy
- There are a number of challenges associated with these complex therapies
- Pharmacists are an important part of the PAH therapy team and many opportunities are available to promote improved patient care

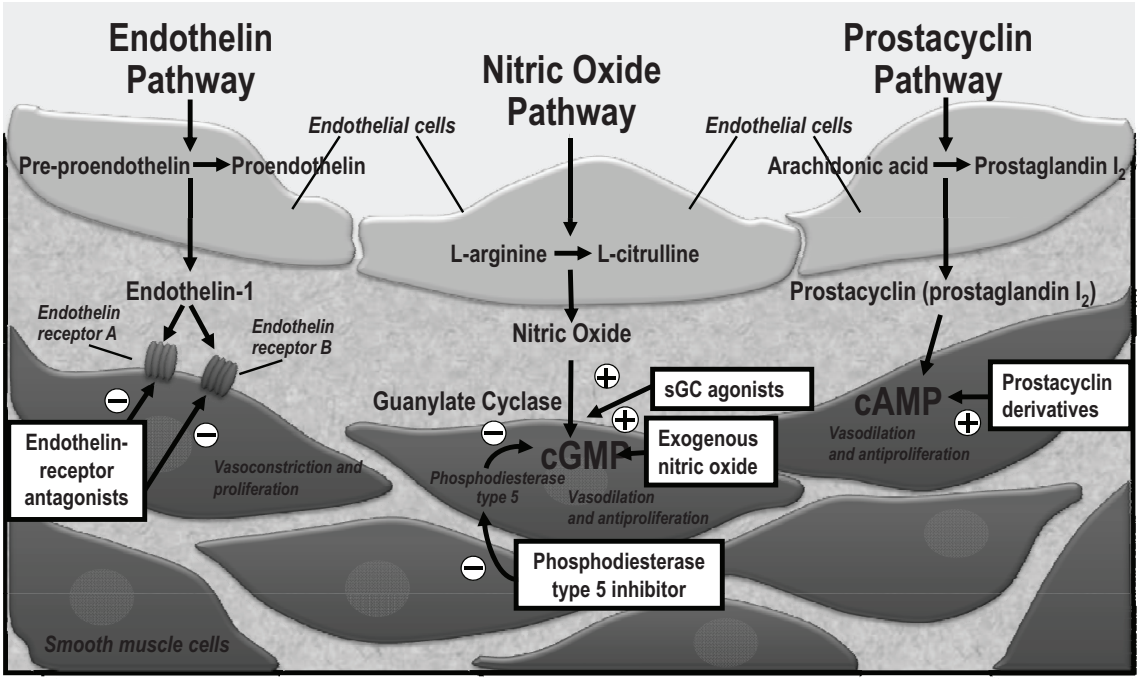
5th World Symposium on PH: 2013 PAH Treatment Algorithm

INITIAL THERAPY WITH PAH-APPROVED DRUGS					
RED: Morbidity and mortality as primary end point in randomized controlled study or reduction in all-cause mortality (prospectively defined) Level of evidence based on WHO-FC of majority of patients of studies					
		Evidence	WHO FC II	WHO FC III	WHO FC IV
Recommendation	I	A or B	•Ambrisentan, Bosentan •Macitentan •Riociguat •Sildenafil •Tadalafil	•Ambrisentan, Bosentan, Epoprostenol IV •Iloprost inh •Macitentan •Riociguat •Sildenafil •Tadalafil •Treprostinil SC, inh	•Epoprostenol IV
	IIa	C		•Iloprost IV*, Treprostinil IV	•Ambrisentan, Bosentan, Iloprost inh and IV* •Macitentan •Riociguat •Sildenafil, Tadalafil •Treprostinil SC, IV, Inh*
	IIb	B		•Beraprost*	
		C		•Initial Combination Therapy	•Initial Combination Therapy

Galiè N, et al. *J Am Coll Cardiol.* 2013;62:D60-D72.

*Not approved in in US.

Therapeutic Targets for PAH



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

Prostacyclin Analogues: IV and SQ Formulations					
How Supplied	Administration	FC	Dose	Properties	CI/P/Misc
Epoprostenol Sodium **Generic, Flolan®, or Veletri®** **0.5mg, 1.5mg**	Continuous IV infusion via infusion pump. Requires tunneled CVC. Flolan requires use of ice packs. Requires reconstitution.	III, IV	Initiated at 2 ng/kg/min and titrated based on response. Ongoing: 1-2 ng/kg/min q1-2 wk.	$T_{½}$ <6 min. Temp and light sensitive. Reconstituted stability dependent on formulation. Rapidly hydrolyzed in the blood.	CHF due to severe LVD. Avoid abrupt withdrawals or interruption in infusion: may result in rebound PH or death. Initiated in controlled setting. Monitor for signs of BSI.
Treprostinil Sodium **Remodulin®** **1mg/mL, 2mg/mL, 5mg/mL, 10mg/mL in 20mL vials**	Continuous IV or SubQ infusion via infusion pump. IV requires tunneled CVC.	II-IV	Initiated at 1.25 ng/kg/min and titrated based on response Ongoing: 1.25 ng/kg/min every week or as tolerated	$T_{½}$ ~4 hours. Metabolized by CYP 2C8. Diluted: 48-hour infusion duration. Undiluted: 72-hour infusion duration.	

Veletri® (epoprostenol) US Prescribing Information. Actelion Pharmaceuticals US, Inc. June 2012.
Remodulin® (treprostinil) US Prescribing Information. United Therapeutics Corp. December 2014.

Oral and Inhaled Prostacyclins					
How Supplied	Administration	FC	Dose	Properties	CI/P/Misc
Iloprost **Ventavis® 10 mcg/mL and 20 mcg/mL unit dose ampules**	Intermittent inhalation via dedicated inhalation device	III, IV	2.5 mcg once, then 5 mcg per dose if tolerated for 6 to 9 x/day	$T_{½}$ ~20 to 30 min.	Caution if underlying lung disease or symptomatic hypotension. Bronchospasm Store at RT Discard unused solution One ampule used per treatment session (20 mcg/mL = 5 mcg dose only!)
Treprostinil Tyvaso® for inhalation 0.6 mg/mL in 2.9 mL ampules	Intermittent inhalation via dedicated inhalation device	III	3 breaths QID, titrated to goal 9 breaths QID	$T_{½}$ ~4 hours. Metabolized by CYP 2C8.	One inhaled ampule provides multiple doses/day Once opened: discard remaining solution after 24 hours, protect ampules from light during storage
Treprostinil Orenitram® 0.125 mg, 0.25 mg, 1 mg and 2.5 mg ER tablets	Oral extended release osmotic tablets	II, III	Initial: 0.25 mg BID or 0.125 mg TID, titrate every 3 to 4 days	$T_{½}$ ~4 hours. Metabolized by CYP 2C8. Food increases bioavailability	Abrupt discontinuation, Diverticulitis Severe hepatic impairment Avoid alcohol

Ventavis® (iloprost) US Prescribing Information. Actelion Pharmaceuticals US, Inc. November 2013.
Tyvaso® (treprostinil) US Prescribing Information. United Therapeutics Corp. August 2014.
Orenitram® (treprostinil) US Prescribing Information. United Therapeutics Corp. October 2014.

Bosentan				
How Supplied	REMS		Properties	CI/P
Tracleer® 62.5 mg, 125 mg tablets	Teratogenicity, liver toxicity. Must enroll in Tracleer REMS Program		$T_{½}$ ~5 hours Metabolized and strong inducer of CYP3A4 and CYP2C9, possibly CYP2C19; Caution with drug intx.	CI: Pregnancy and use of cyclosporine or glyburide. Caution with liver disease.
	FC	Dose		
Administration	II-IV	Initial: 62.5 mg BID x 4 weeks, then increase to 125 mg BID thereafter if tolerated and wt >40 kg.		
Oral tablets. Can be dissolved into soln.				

Ambrisentan				
How Supplied	REMS		Properties	CI/P
Letairis® 5 mg, 10 mg tablets	Teratogenicity. FRP must enroll in Letairis REMS Program		$T_{½}$ up to ~15 hours Metabolized by CYP3A4 and CYP2C19, substrate of P-glyco-protein	CI: pregnancy and IPF. Caution with anemia, fluid retention, PVOD.
	FC	Dose		
Administration	II-III	Initial: 5 mg daily, increase to 10 mg daily if tolerated		
Oral tablets				

Macitentan				
How Supplied	REMS		Properties	CI/P
Opsumit® 10 mg tablets	Teratogenicity. FRP must enroll in Opsumit REMS Program		$T_{½}$ ~16 hrs (48 hrs for active metabolite) Metabolized by CYP3A4 and CYP2C19; active metabolite contributes ~40% of activity.	CI: Pregnancy Caution with anemia, liver disease.
	FC	Dose		
Administration	Mostly II-III	10 mg po daily		
Oral tablets				

Sildenafil				
How Supplied	REMS		Properties	CI/P
generic Revatio® 20 mg tablets Revatio® 10 mg/12.5 mL soln for injection Powder for suspension	n/a		$T_{½}$ ~4 hours Metabolized by CYP3A4 and CYP2C9 (minor)	CI: use with organic nitrates. Increased mortality risk in peds. Caution with SCD, PVOD. Post marketing AE: NAION
	FC	Dose		
Administration	Mostly II-III	Oral: 20 mg TID Inj.: 10 mg TID		
Oral tablets or suspension. Solution for injection used for NPO.				

Tadalafil				
How Supplied	REMS		Properties	CI/P
Adcirca® 20 mg tablets	n/a		$T_{½}$ ~35 hrs Metabolized by CYP3A4	CI: use with organic nitrates Caution with SCD, PVOD.
	FC	Dose		
Administration	II-III	40mg daily		
Oral tablets				

Revatio® (sildenafil) US Prescribing Information. Pfizer Labs. January 2014.
Adcirca® (tadalafil) US Prescribing Information. Eli Lilly and Company. April 2015.