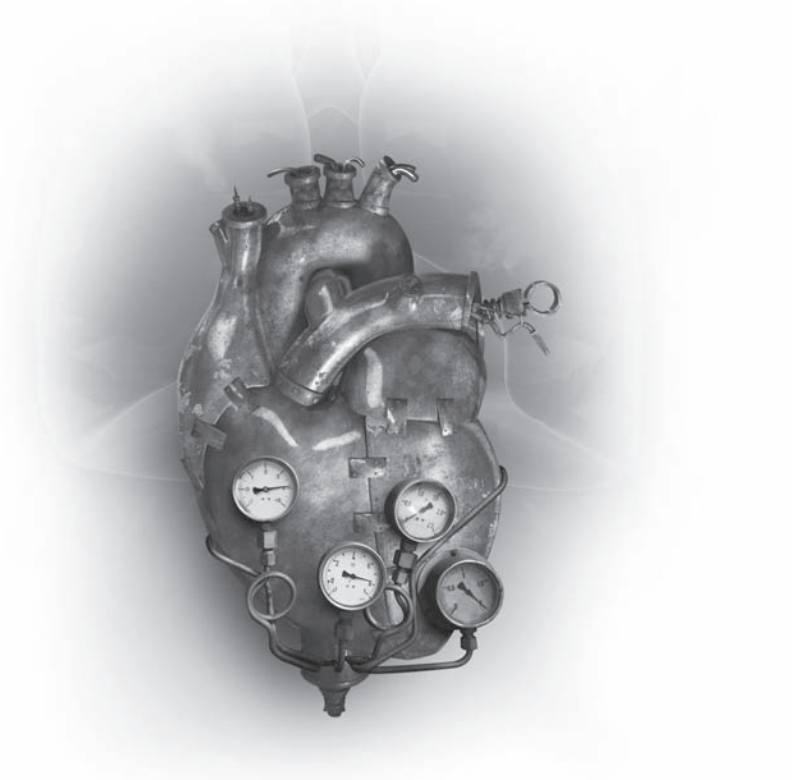


Emerging Solutions in Pulmonary Arterial Hypertension

EMPOWERING PHARMACISTS IN TREATMENT DECISIONS

Monday,
December 3, 2012
7:30 – 8:30 AM

Las Vegas, NV

Educational Overview

Pulmonary arterial hypertension (PAH) is a rare disease with significant consequences, including serious functional impairment and premature death. If left untreated, PAH is rapidly fatal. Fortunately, over the past decade, the knowledge and understanding of this disease has greatly expanded. Furthermore, the availability of effective and more convenient oral and inhaled medications has allowed clinicians to better individualize therapy to meet patient treatment goals. Though there is no cure for PAH, effective treatment can significantly slow disease progression and clinical worsening. Given the serious nature of this disease and its rapid progression, optimal management approaches are essential.

The Role of the Pharmacist

Optimal management of patients with PAH requires early detection and diagnosis followed by a patient-centered treatment plan. By increasing their competency, pharmacists can play an important role within the multidisciplinary team when encountering patients with this disease.

Given the complex and individualized nature of PAH therapy, pharmacists must have a full understanding of treatment algorithms, disease-specific therapies, and long-term monitoring recommendations based on evidence-based guidelines. As the armamentarium to treat PAH continues to expand, pharmacists must make efforts to stay informed of the latest finding in order to contribute to the optimal management of these patients.

Target Audience

This continuing pharmacy education activity is planned to meet the needs of pharmacists in a variety of practice settings, including large and small healthcare systems, outpatient clinics, managed care organizations, long-term care facilities, and academia. This program targets health-system pharmacists who are responsible for the safe and effective use of medications utilized for the treatment of patients with PAH.

Learning Objectives

Upon completing this activity, participants will be able to:

- Differentiate the safety and efficacy among the various classes of medications used in the treatment of PAH
- Utilize evidence-based guidelines to select appropriate therapy to meet individualized patient treatment goals
- Optimize management decisions based on pathophysiology of PAH
- Discuss the role of clinical pharmacists in the management of patients with PAH

Educational Program

7:30 – 7:35 AM

Managing Patients with PAH: Where to Start?
David Badesch, MD

7:35 – 8:05 AM

Utilizing Current Therapeutic Options and Treatment Algorithms to Optimize Outcomes
David Badesch, MD

8:05 – 8:25 AM

Individualizing Therapy to Meet Patient Goals: Recognizing the Pharmacist's Role
James Coons, PharmD

8:25 – 8:30 AM

Open Forum: Q&A

Faculty

David B. Badesch, MD, FACP, FCCP

Professor of Medicine
Divisions of Pulmonary Sciences, Critical Care Medicine and Cardiology
Clinical Director, Pulmonary Hypertension Center
University of Colorado at Denver and Health Sciences Center
Denver, CO

James C. Coons, PharmD, BCPS (AQ Cardiology)

Associate Professor
University of Pittsburgh School of Pharmacy
Cardiology Residency Program Director
Clinical Pharmacist, Cardiology
University of Pittsburgh Medical Center-Presbyterian Hospital
Pittsburgh, PA

Accreditation

Pharmacists

Center for Independent Healthcare Education is accredited by the Accreditation Council for Pharmacy Education as a provider for continuing pharmacy education. Center has assigned 1.0 contact hour (0.1 CEUs) of continuing pharmacy education credits for participating in this activity.

ACPE UAN: 0473-9999-12-007-L01-P

Type of Activity: Knowledge-based

Instructions for Credit

To receive a Statement of Credit, participants must register for the symposium, document attendance, and complete and return the evaluation form. You can access information about your completed CPE through MyCPEmonitor.net.

Disclosure of Conflicts of Interest

In accordance with policies set forth by the Accreditation Council for Continuing Medical Education (ACCME) and the Accreditation Council for Pharmacy Education (ACPE), Center for Independent Healthcare Education requires all faculty members and spouses/significant others with an opportunity to affect the content of a continuing education activity to disclose any relevent financial relationships during the past 12 months with commercial interests. A commercial interest is any entity producing, marketing, reselling or distributing healthcare goods or services consumed by or used on patients. Relationships with commercial interests and conflicts of interest resulting from those relationships must be revealed to the audience and resolved prior to the activity.

Relevant relationships include roles such as speaker, author, consultant, independent contractor (including research), employee, investor, advisory committee member, board member, review panelist, and investigator. If a potential speaker or author indicates a possible conflict of interest, the conflict will be resolved by choosing another speaker or author for that therapeutic area, or the slides, handouts, and/or monograph will be reviewed and approved by a qualified commercially-disinterested peer.

Planning Committee Members
David B. Badesch, MD
James C. Coons, PharmD
Paul DeLisle
Marco P. Cicero, PhD
Maja Drenovac, PharmD

Financial Interest Summary

David B. Badesch, MD (Faculty/Planner) has relevant financial relationships with commercial interests as follows:

- Advisory Board/Steering Committees: Actelion/CoTherix, Gilead/Myogen, Pfizer, United Therapeutics/Lung Rx, Lilly/ICOS, Bayer, Ikaria, Arena
- Consultant: Actelion/CoTherix, Gilead/Myogen, Pfizer, United Therapeutics/Lung Rx, Lilly/ICOS, Bayer, Ikaria, Arena
- Grant Recipient/Research Support: Actelion/CoTherix, Gilead/Myogen, Pfizer, United Therapeutics/Lung Rx, Lilly/ICOS, Novartis, Bayer, Ikaria, Arena

Dr. Badesch does not intend to discuss the off-label use of a product.

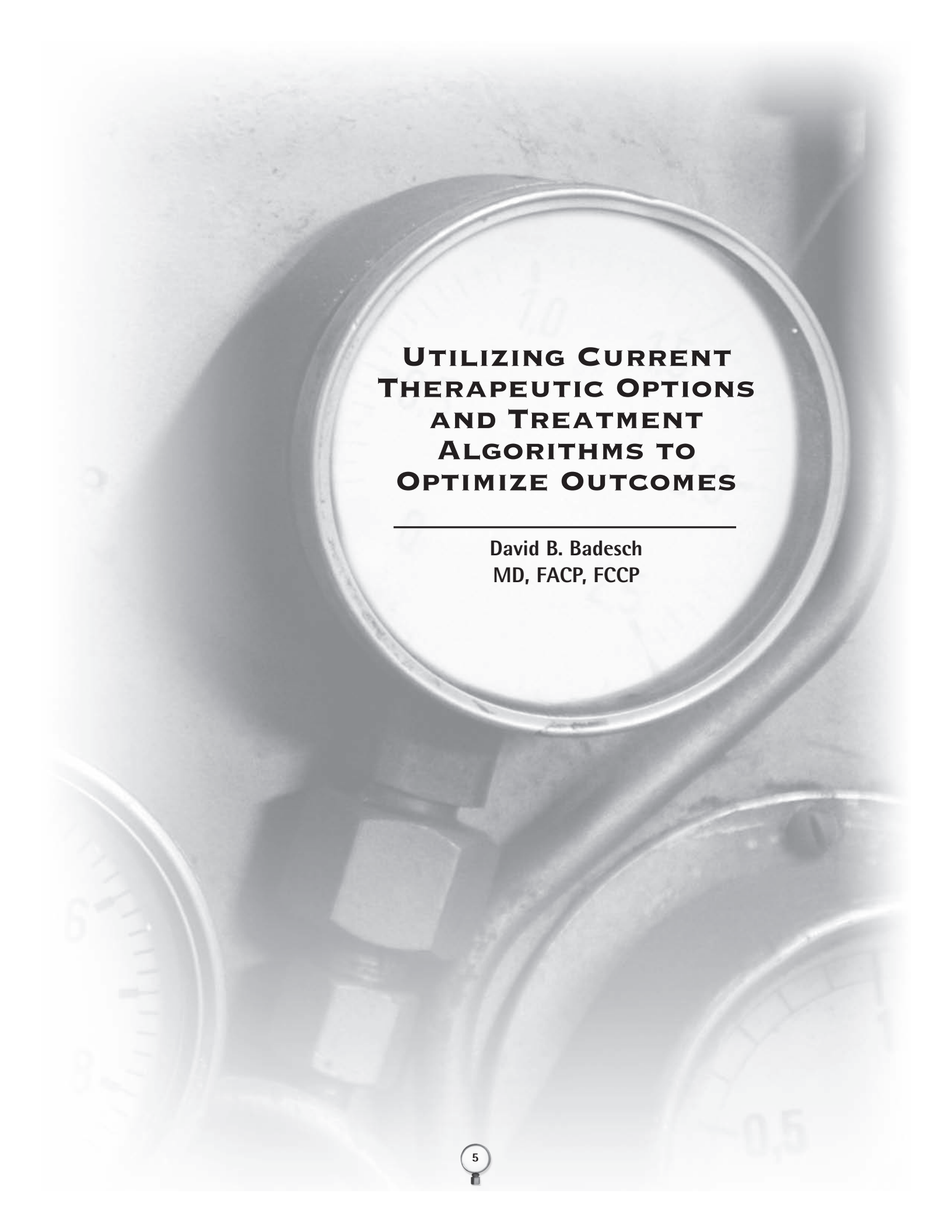
James C. Coons, PharmD (Faculty/Planner) has no relevant financial relationships with commercial interests. Dr. Coons does not intend to discuss the off-label use of a product.

No other speakers, authors, planners or content reviewers have any relevant financial relationships to disclose. No other speakers or authors will discuss off-label use of a product.

Content review confirmed that the content was developed in a fair, balanced manner free from commercial bias. Disclosure of a relationship is not intended to suggest or condone commercial bias in any presentation, but it is made to provide participants with information that might be of potential importance to their evaluation of a presentation.

Commercial Support

This activity is supported by an educational grant from Actelion Pharmaceuticals, US, Inc.



Utilizing Current Therapeutic Options and Treatment Algorithms to Optimize Outcomes

David B. Badesch
MD, FACP, FCCP

David B. Badesch, MD, FACP, FCCP

Professor of Medicine
Divisions of Pulmonary Sciences, Critical Care Medicine, and Cardiology
Clinical Director, Pulmonary Hypertension Center
University of Colorado at Denver and Health Sciences Center
Denver, CO

Dr. David Badesch is Professor of Medicine, in the Divisions of Pulmonary Sciences and Critical Care Medicine, and Cardiology, and Clinical Director of the Pulmonary Hypertension Center, at the University of Colorado at Denver and Health Sciences Center (UCDHSC). He is also a Distinguished Advisor to the Scientific Leadership Council of the Pulmonary Hypertension Association (PHA) and a member of the Pulmonary Vascular Research Institute (PVRI).

Dr. Badesch received his undergraduate degree in Mathematics from Vanderbilt University in Nashville, TN and then went on to complete his medical degree from the University of Virginia School of Medicine, Charlottesville, VA. After completing his residency in Internal Medicine from Vanderbilt University School of Medicine, he went to complete a fellowship in Pulmonary Medicine from the University of Colorado School of Medicine, Denver, CO. He is board certified in Internal Medicine with a subspecialty in Examination in Pulmonary Diseases.

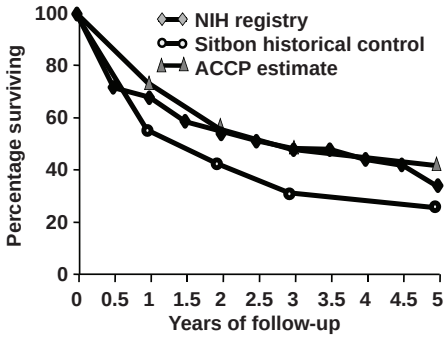
Dr. Badesch has published in numerous journals including the *Annals of Internal Medicine, New England Journal of Medicine, Lancet, Journal of the American College of Cardiology,* and *CHEST*. He serves as a reviewer for several scientific publications including the *American Review of Respiratory Diseases, Annals of the Rheumatic Diseases* and *Arthritis and Rheumatism*. Dr. Badesch is a fellow of the American College of Chest Physicians (ACCP) and the American College of Physicians (ACP) and a member of the American Thoracic Society (ATS). He serves on the Steering Committees (national and international) of many of the major clinical trials conducted in the field of pulmonary hypertension. Dr. Badesch has been listed among the Best Doctors in America 2001-2010.

Pulmonary Arterial Hypertension

Key Points:

- Non-specific symptoms → delayed diagnosis
- Poor prognosis without therapy
- Methodical evaluation, including catheterization required
- Evolving therapies → improved prognosis (but not yet normal)

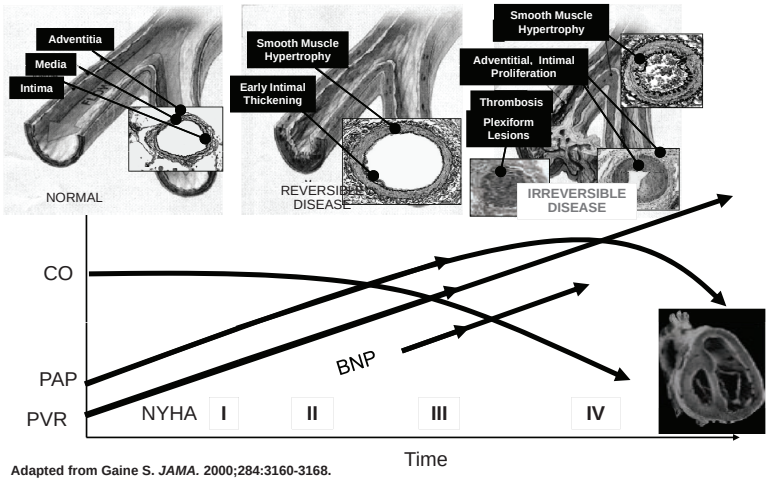
A Disease of Decline and Deterioration: IPAH Survival if Untreated



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

Adapted from: Sitbon O et al. *J Am Coll Cardiol.* 2002;40:780-788.
D'Alonzo GE. *Ann Intern Med.* 1991;115:343-349.
McLaughlin VV et al. *Chest.* 2004;126:78S-91S.

PAH: Hemodynamic and Clinical Course



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

Clinical Classification of Pulmonary Hypertension (Dana Point)

1. PAH

- Idiopathic PAH
- Heritable
- Drug- and toxin-induced
- Persistent PH of newborn
- Associated with:
  - CTD
  - HIV infection
  - portal hypertension
  - CHD
  - schistosomiasis
  - chronic hemolytic anemia

1'. PVOD and/or PCH

2. PH Owing to Left Heart Disease

- Systolic dysfunction
- Diastolic dysfunction
- Valvular disease

3. PH Owing to Lung Diseases and/or Hypoxia

- COPD
- ILD
- Other pulmonary diseases with mixed restrictive and obstructive pattern
- Sleep-disordered breathing
- Alveolar hypoventilation disorders
- Chronic exposure to high altitude
- Developmental abnormalities

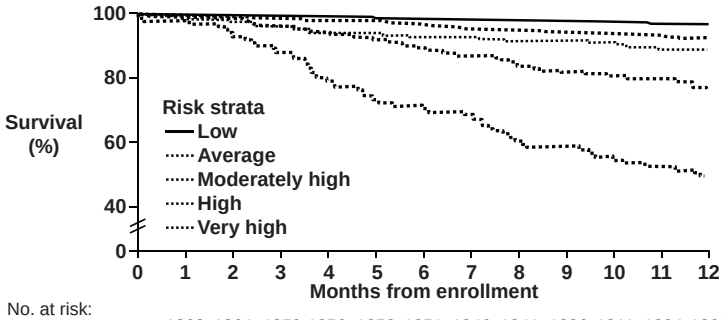
4. CTEPH

5. PH With Unclear Multifactorial Mechanisms

- Hematologic disorders
- Systemic disorders
- Metabolic disorders
- Others

Simonneau G, Robbins IM, Beghetti M, Channick RN, Delcroix M, Denton CP, Elliott CG, Gaine SP, Gladwin MT, Jing ZC, Krowka MJ, Langleben D, Nakanishi N, Souza R. *J Am Coll Cardiol.* 2009;54;S43-S54.

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

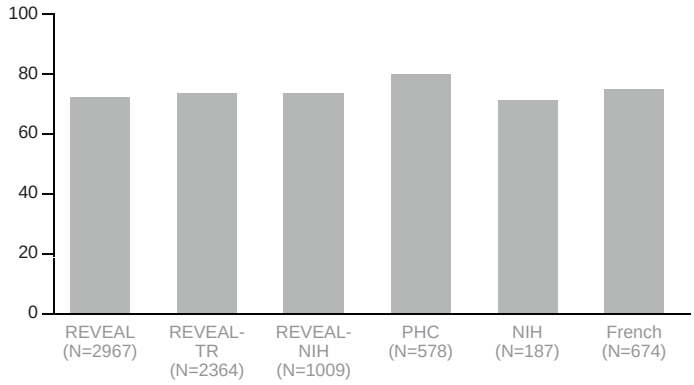


No. at risk:													
Low	1374	1368	1364	1359	1356	1352	1351	1346	1341	1336	1311	1304	1303
Average	665	659	657	653	648	647	640	628	625	618	604	602	596
Mod. high	280	277	274	269	264	263	260	259	255	254	249	244	243
High	295	293	291	284	277	270	263	255	247	241	238	233	225
Very high	102	100	96	89	81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

Benza RL, Miller DP, Gomberg-Maitland M, Frantz RP, Foreman AJ, Coffey CS, Frost A, Barst RJ, Badesch DB, Elliott CG, Liou TG, McGoon MD. Predicting Survival in Pulmonary Arterial Hypertension: Insights from the REVEAL Registry. *Circulation.* 2010 Jul 13;122(2):164-72.

PAH Registries: Functional Class at Diagnosis Indicates Delayed Diagnosis

% Patients NYHA Functional Class III-IV at Diagnosis



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

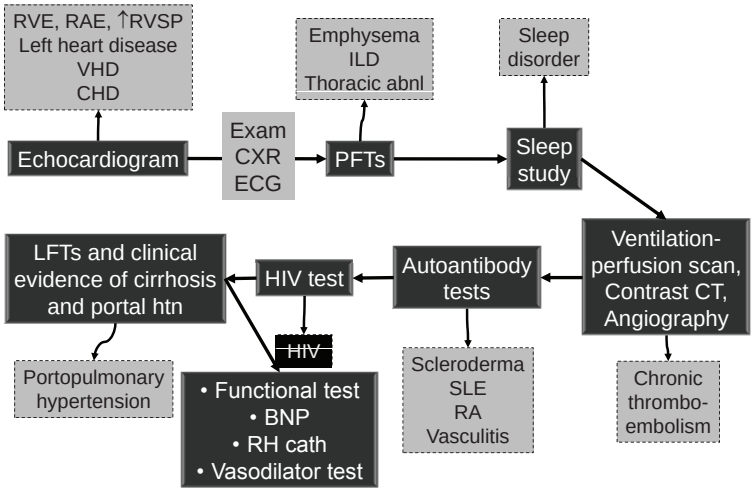
Is There a Reason to Suspect PAH?

Clinical Presentation

Common Initial Symptoms (N=187)	Patients (%)
Dyspnea	60
Fatigue	19
Syncope or near syncope	13
Chest pain	7
Palpitations	5
Leg edema	3

McGoon M, Gutterman D, Steen V, Barst R, McCrory DC, Fortin TA, Loyd JE. *Chest.* 2004;126:14S-34S.
Rich S et al. *Ann Intern Med.* 1987;107:216-223.

Diagnostic Approach



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

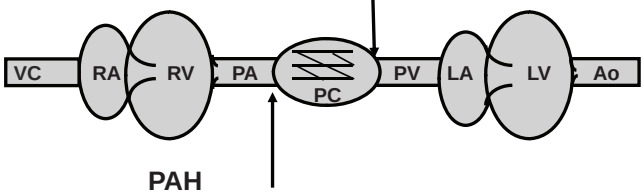
Dana Point Hemodynamic Definition of PH/PAH

PH	Mean PAP ≥25 mm Hg
PAH	Mean PAP ≥25 mm Hg *plus* PCWP/LVEDP ≤15 mm Hg

Badesch DB, Champion HC, Sanchez MA, Hoeper MM, Loyd JE, Manes A, McGoon M, Naeije R, Olschewski H, Oudiz RJ, Torbicki A. Diagnosis and assessment of pulmonary arterial hypertension. *J Am Coll Cardiol*. 2009 Jun 30;54(1 Suppl):S55-66.

PH: The Importance of Hemodynamics

Pulmonary venous hypertension
Elevated PCWP, normal PVR



PAH
PH with respiratory disease
CTEPH
Normal PCWP, elevated PVR

Other:
High CO

Cardiac Catheterization

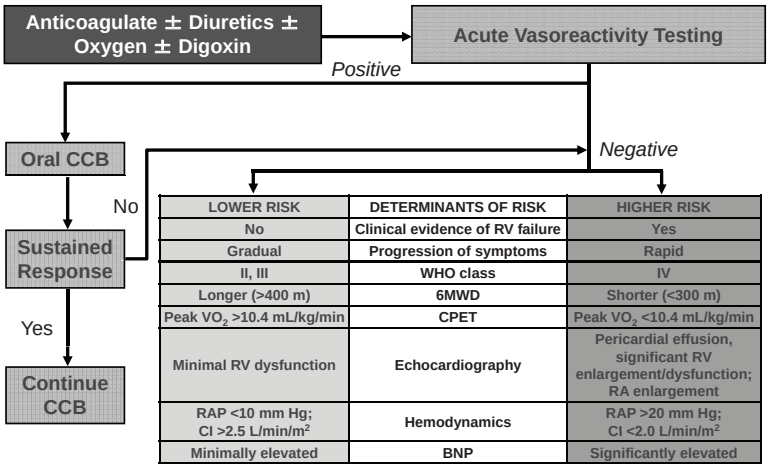
- Exclude congenital heart disease
- Measure wedge pressure or LVEDP
- Establish severity and prognosis
- Test vasodilator therapy

Catheterization is required when pulmonary hypertension is suspected

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?



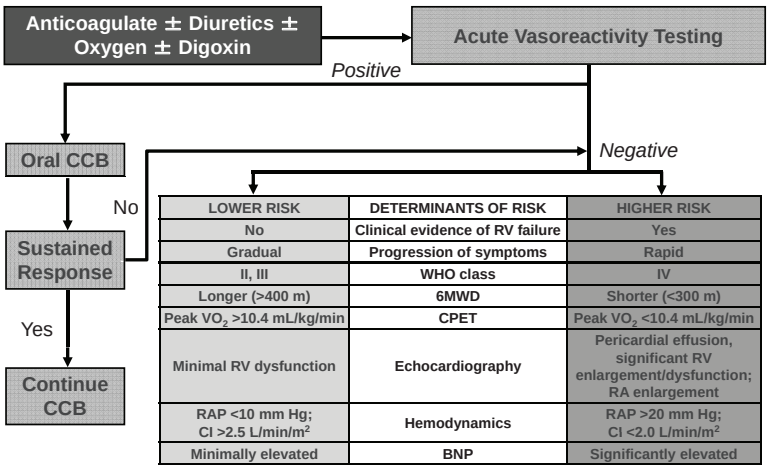
LOWER RISK	DETERMINANTS OF RISK	HIGHER RISK
No	Clinical evidence of RV failure	Yes
Gradual	Progression of symptoms	Rapid
II, III	WHO class	IV
Longer (>400 m)	6MWD	Shorter (<300 m)
Peak VO_2 >10.4 mL/kg/min	CPET	Peak VO_2 <10.4 mL/kg/min
Minimal RV dysfunction	Echocardiography	Pericardial effusion, significant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

McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, Mathier MA, McGoon MD, Park MH, Rosenson RS, Rubin LJ, Tapson VF, Varga J. American College of Cardiology Foundation Task Force on Expert Consensus Documents; American Heart Association. *J Am Coll Cardiol*. 2009 Apr 28;53(17):1573-619.

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?



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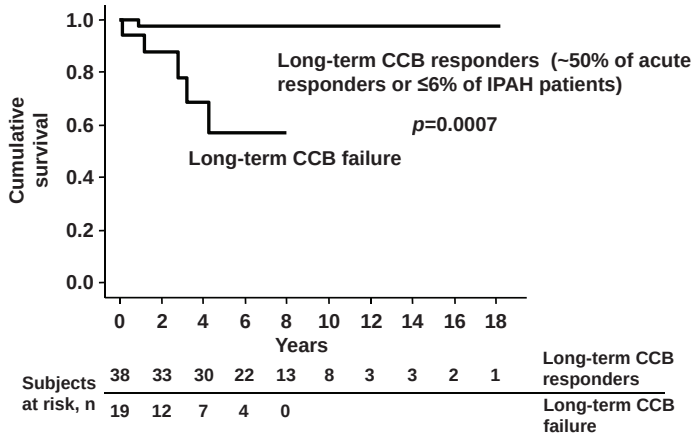
Calcium Channel Blockers Only If "Vasodilator Responsive"

"Vasodilator Response"

- Fall in mPAP ≥10 mm Hg
- + PAPm (absolute) <40 mm Hg
- + Normal CO

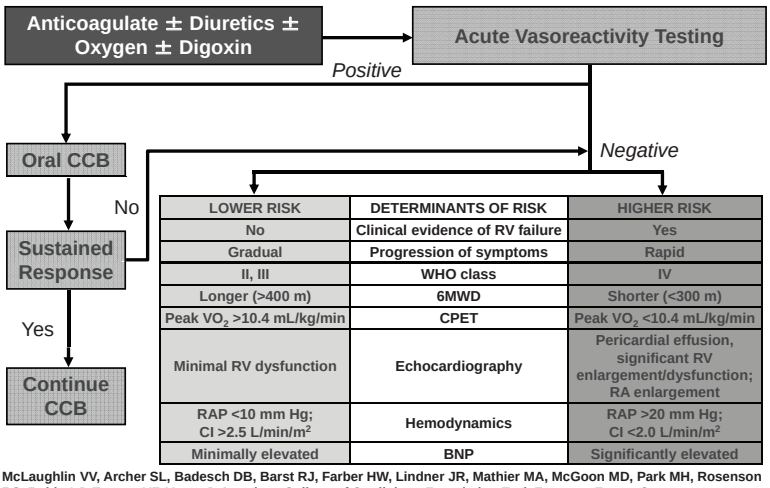
McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, Mathier MA, McGoon MD, Park MH, Rosenson RS, Rubin LJ, Tapson VF, Varga J; American College of Cardiology Foundation Task Force on Expert Consensus Documents; American Heart Association. *J Am Coll Cardiol*. 2009 Apr 28;53(17):1573-619.

Survival in IPAH
Long-term CCB Responders



Sitbon O, Humbert M, Jais X, Ioos V, Hamid AM, Provencher S, Garcia G, Parent F, Herve P, Simonneau G. *Circulation.* 2005;111:3105-3111.

What Is the Optimal Treatment Strategy?



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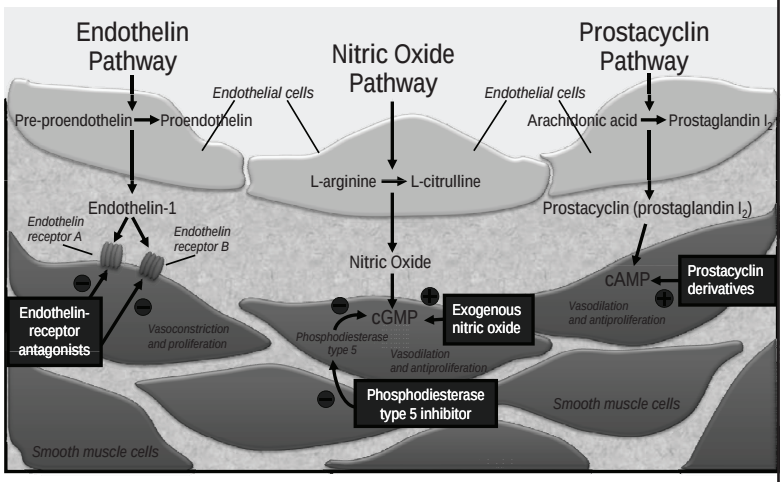
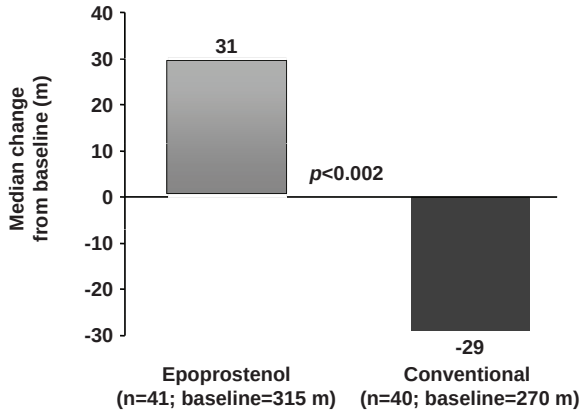
Approved Therapeutic Targets



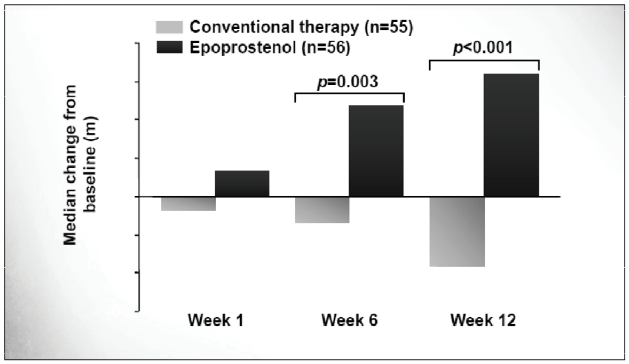
Humbert M, Sitbon O, Simonneau G. *N Engl J Med*. 2004;351:1425-1436.

IV Epoprostenol in IPAH: Change From Baseline in 6MWD



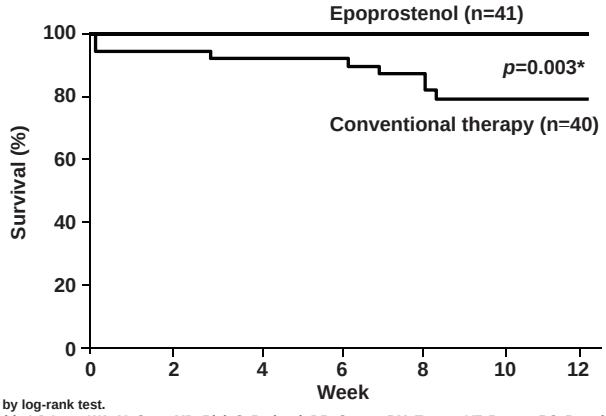
Barst RJ, Rubin LJ, Long WA, McGoon MD, Rich S, Badesch DB, Groves BM, Tapson VF, Bourge RC, Brundage BH, Koerner SK, Langleben D, Keller CA, Murali S, Uretsky BF, Clayton LM, Jobsis MM, Blackburn SD, Shortino D, Crow JW, for the Primary Pulmonary Hypertension Study Group. *N Engl J Med.* 334:296-301;1996.

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



Badesch DB, Tapson VF, McGoon MD, Brundage BH, LJ Rubin, Wigley FM, Rich S, Barst RJ, et al. Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease. A randomized controlled trial. *Annals of Internal Medicine*. 132:425-434;2000.

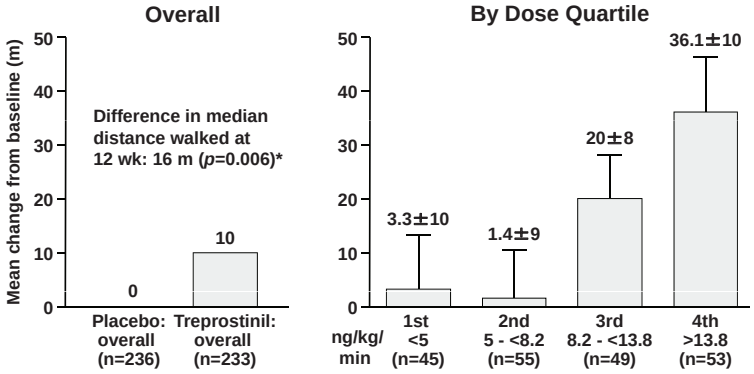
Survival Among Patients With IPAH: Epoprostenol vs Conventional Therapy



*Two-sided, by log-rank test.

Barst RJ, Rubin LJ, Long WA, McGoon MD, Rich S, Badesch DB, Groves BM, Tapson VF, Bourge RC, Brundage BH, Koerner SK, Langleben D, Keller CA, Murali S, Uretsky BF, Clayton LM, Jobsis MM, Blackburn SD, Shortino D, Crow JW, for the Primary Pulmonary Hypertension Study Group. *N Engl J Med.* 334:296-301;1996.

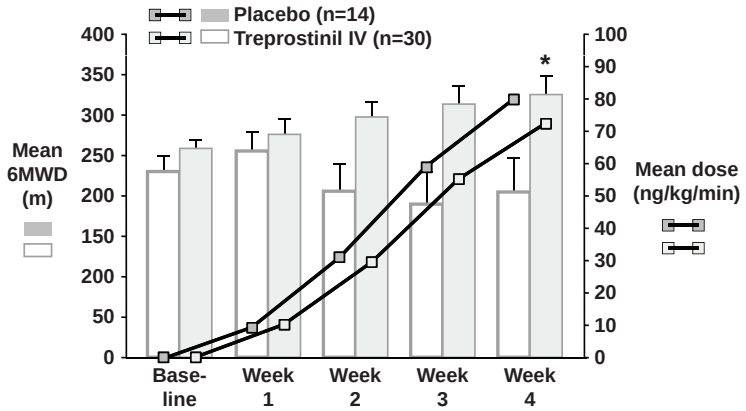
Subcutaneous Treprostinil: Change From Baseline in 6MWD Overall and by Dose Quartile



*Hodges-Lehmann estimate

Simonneau G, Barst RJ, Galie N, Naeije R, RichS, Bourge RC, Keogh A, Oudiz R, Frost A, Blackburn SD, Crow JW, Rubin LJ for the Treprostinil Study Group. *Am J Respir Crit Care Med*. 2002;165:800-804.

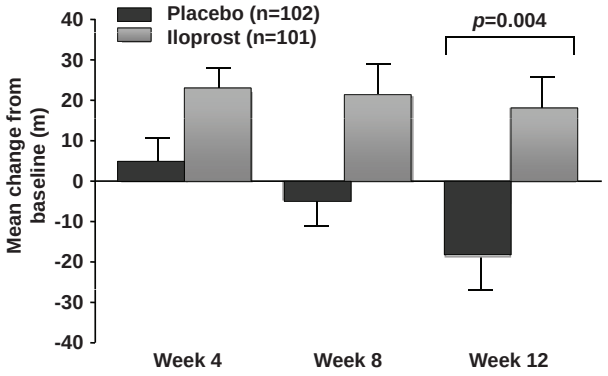
Treprostinil IV: 6MWD (TRUST)



*p=0.022. 6MWD values are mean+SE.

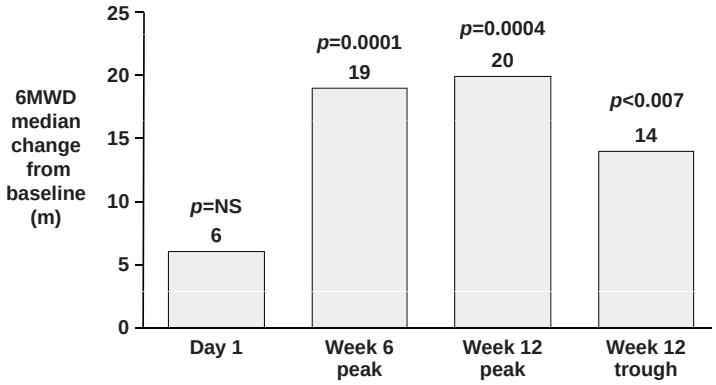
Hiremath J, Thanikachalam S, Parikh K, Shanmugasundaram S, Bangera S, Shapiro L, Pott GB, Vnencak-Jones CL, Arneson C, Wade M, White RJ; TRUST Study Group. *J Heart Lung Transplant*. 2010;29:137-149.

Inhaled Iloprost: Change From Baseline in 6MWD (AIR Trial)



6MWD was not the primary end point in the AIR trial.
Olschewski H, Simonneau G, Galiè N, Higenbottam T, Naeije R, Rubin LJ, Nikkho S, Speich R, Hoeper MM, Behr J, Winkler J, Sitbon O, Propov W, Ghofrani HA, Manes A, Kiely DG, Ewert R, Meyer A, Corris PA, Delcroix M, Gomez-Sanchez M, Siedentop H, SeegerW; Aerosolized Iloprost Randomized Study Group. *N Engl J Med*. 2002;347:322-329.

Inhaled Treprostinil: Median Change in 6MWD (TRIUMPH)



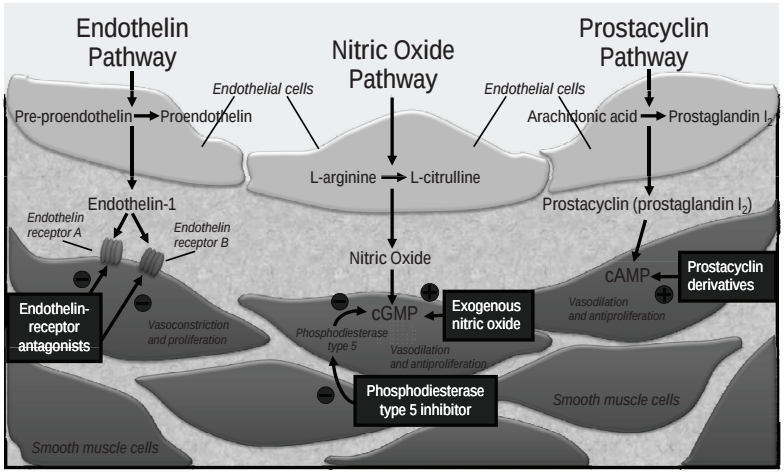
Hodges-Lehmann estimate of treatment effect.
Peak: between 10-60 min after dose. Trough: ≥4 hr after dose.
McLaughlin VV, Benza RL, Rubin LJ, Channick RN, Voswinckel R, Tapson VF, Robbins IM, Olshewski H, Rubenfire M, Seeger W. *J Am Coll Cardiol.* 2010;55:1915-1922.

Prostanoid Side Effects

- Flushing
- Headache
- Diarrhea, nausea, vomiting
- Jaw pain
- Leg pain
- Hypotension
- Dizziness
- Syncope
- Cough (inhaled)
- Delivery site complications

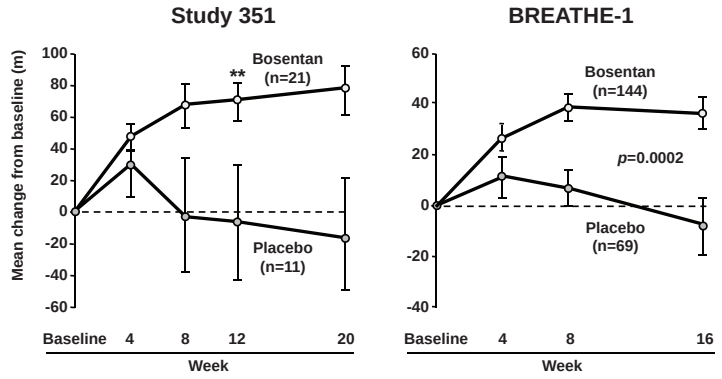
Vary according to drug and route of delivery

Approved Therapeutic Targets



Humbert M, Sitbon O, Simonneau G. *N Engl J Med*. 2004;351:1425-1436.

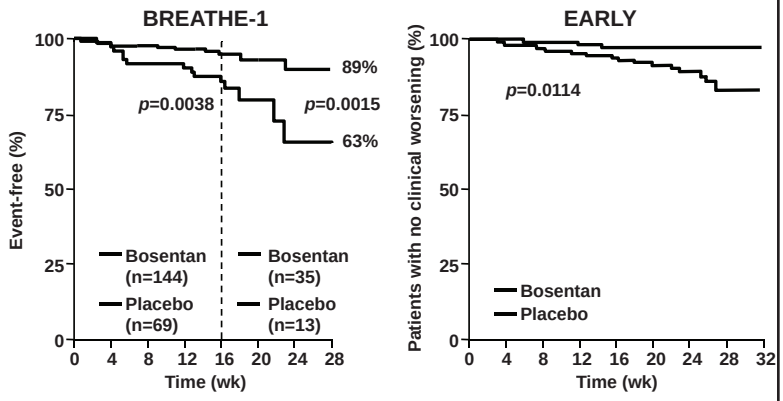
Bosentan: 6-MWD (351 and BREATHE-1)



**$p<0.05$ vs baseline; $p=0.021$ vs placebo. Values are mean±SEM.

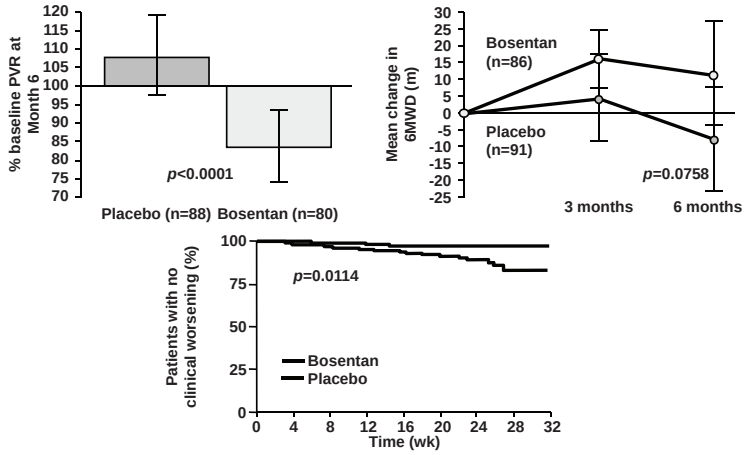
Channick, RN, Simonneau G, Sitbon O, Robbins IM, Frost A, Tapson VF, Badesch DB, et al. *Lancet.* 2001;358:1119-1123.
Rubin LJ, Badesch DB, Barst RJ, et al. *N Engl J Med.* 346:896-903;2002.

Bosentan: Time to Clinical Worsening (BREATHE-1 and EARLY)



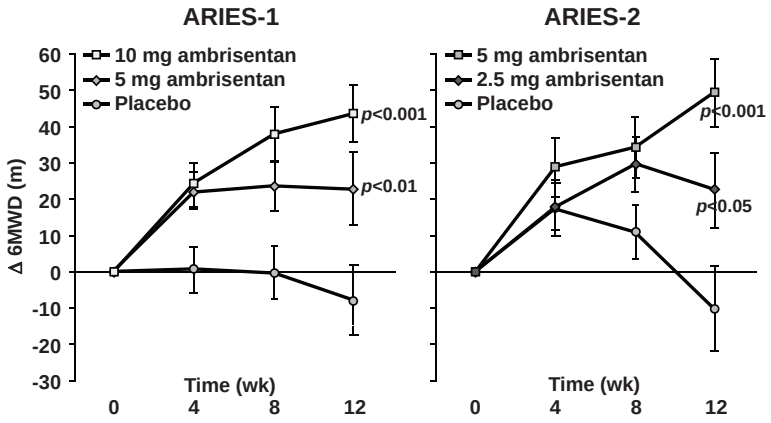
Adapted from Rubin LJ, Badesch DB, et al for the BREATHE Study Group. *N Engl J Med.* 2002;346;896-903.
Galiè N et al. *Lancet.* 2008;371:2093-2100.

Would Earlier Treatment Be Better?
The "EARLY" Study



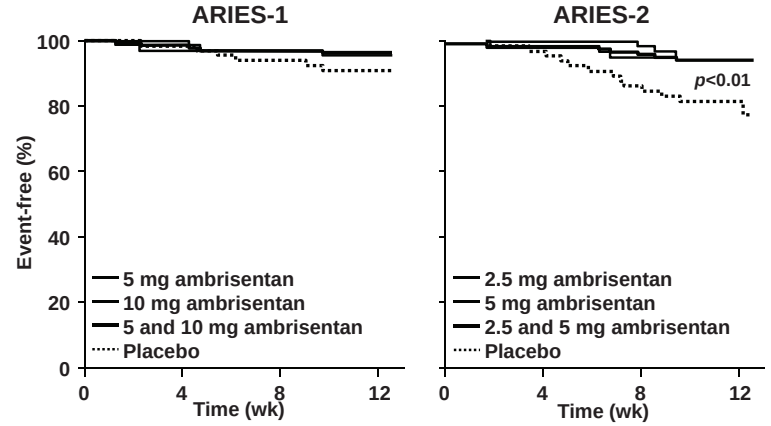
Galiè N, Rubin LJ, Hoeper M, Jansa P, Al-Hiti H, Meyer G, Chiossi E, Kusic-Pajic A, Simonneau G. *Lancet.* 2008;371:2093-2100.

Ambrisentan in PAH: 6MWD (ARIES)



Galiè N, Olschewski H, Oudiz RJ, Torres F, Frost A, Ghofrani HA, Badesch DB, McGoon MD, McLaughlin VV, Roecker EB, Gerber MJ, Dufton C, Wiens BL, Rubin LJ. *Circulation.* 2008; 117(23); 3010-9.

Ambrisentan in PAH: Time to Clinical Worsening (ARIES)

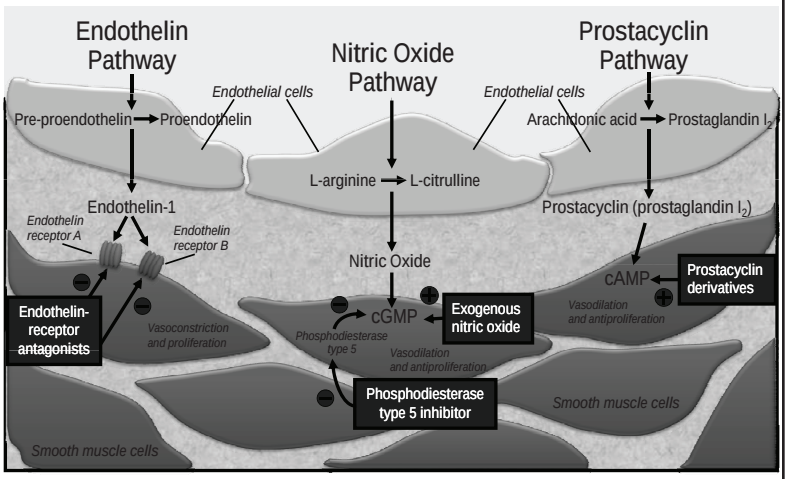


Galiè N, Olschewski H, Oudiz RJ, Torres F, Frost A, Ghofrani HA, Badesch DB, McGoon MD, McLaughlin VV, Roecker EB, Gerber MJ, Dufton C, Wiens BL, Rubin LJ. *Circulation.* 2008; 117(23); 3010-9.

Endothelin Receptor Antagonists: Side Effects

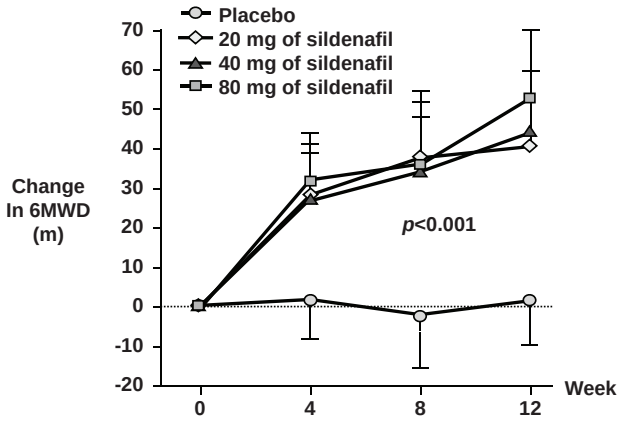
- Nasal congestion
- Abnormal hepatic function
  - reversible transaminase elevations >3X ULN
  - may require dose adjustments or discontinuations
  - monthly LFTs required
- Edema
  - lower extremity edema may require diuretic adjustment
- Use requires dual contraceptive methods (hormonal plus barrier)

Approved Therapeutic Targets



Humbert M, Sitbon O, Simonneau G. *N Engl J Med*. 2004;351:1425-1436.

Effect of Sildenafil on 6MWD (SUPER)



Galiè N, Ghofrani HA, Torbicki A, Barst, RJ, Rubin LJ, Badesch DB, Fleming T, Parpia T, Burgess G, Branzi A, Grimminger F, Kurzyna M, Simonneau G., Sildenafil Use in Pulmonary Arterial Hypertension (SUPER) Study Group. *New Engl J Med.* 353:2148-2157;2005.

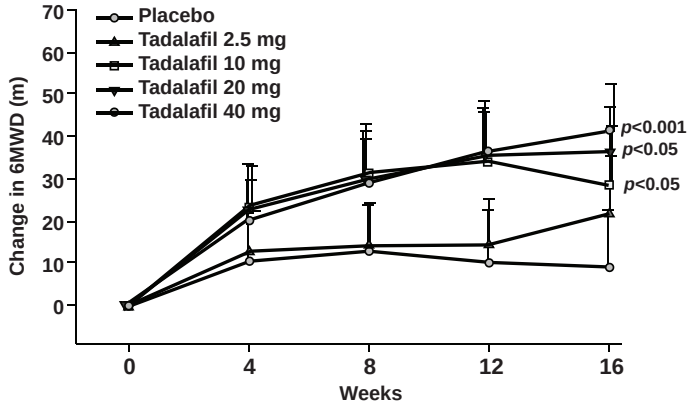
Sildenafil: Incidence of Clinical Worsening (SUPER)

		Sildenafil		
	Placebo (n=70)	20 mg tid (n=69)	40 mg tid (n=67)	80 mg tid (n=71)
Event	Incidence, n (%)			
Clinical worsening	7 (10)	3 (4)	2 (3)	5 (7)
– death	1 (1)	1 (1)	0	2 (3)
– hospitalization for PAH	7 (10)	2 (3)	2 (3)	2 (3)
– initiation of prostacyclin	1 (1)	0	0	0
– initiation of bosentan	0	0	1 (1)	2 (3)

p=NS. Clinical worsening defined as death, transplantation, hospitalization for PAH, or initiation of additional therapies for PAH.

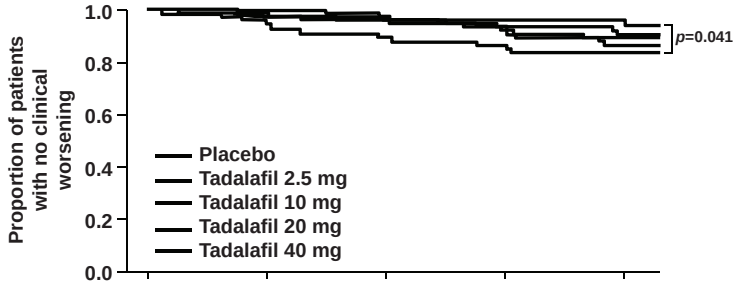
Galiè N, Ghofrani HA, Torbicki A, Barst RJ, Rubin LJ, Badesch DB, Fleming T, Parpia T, Burgess G, Branzi A, Grimminger F, Kurzyna M, Simonneau G., Sildenafil Use in Pulmonary Arterial Hypertension (SUPER) Study Group. *New Engl J Med.* 353:2148-2157;2005.

Effect of Tadalafil* on 6MWD (PHIRST)



*Adcirca®
Galiè N et al. *Circulation.* 2009;119;2894-2903..

Effect of Tadalafil on Time to Clinical Worsening (PHIRST)



Patients at risk:

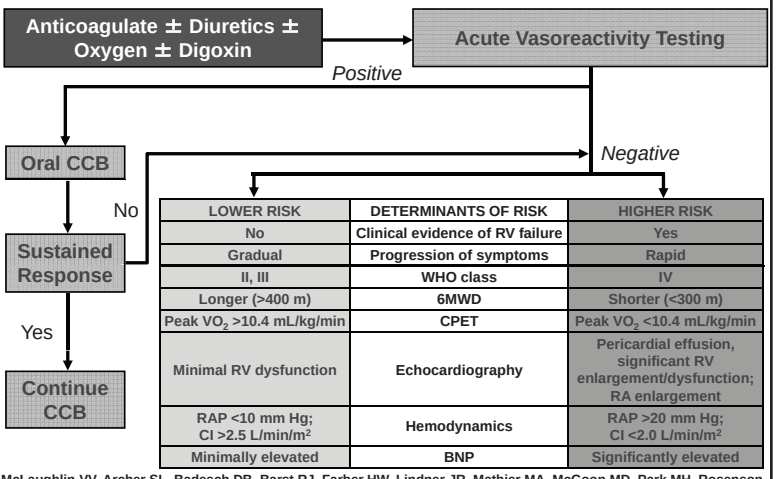
Placebo	82	78	73	68	30
Tadalafil 2.5 mg	82	80	75	69	29
Tadalafil 10 mg	80	76	75	72	32
Tadalafil 20 mg	82	77	74	69	37
Tadalafil 40 mg	79	75	73	72	48

Galiè N, Brundage BH, Ghofrani HA et al. *Circulation.* 2009;119;2894-2903.

PDE-5 Side Effects

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

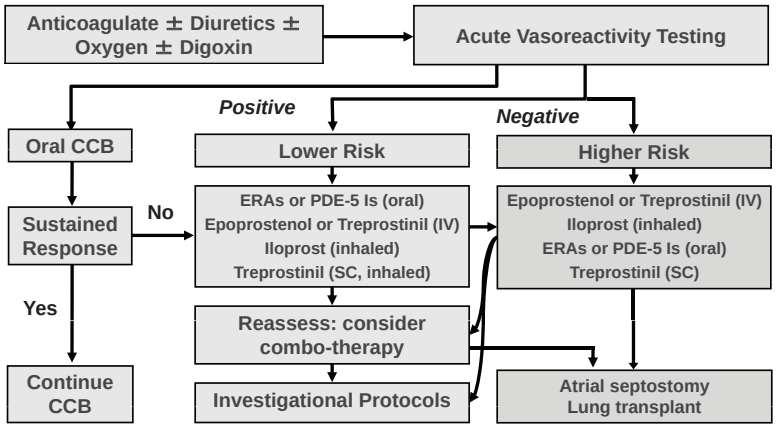
What Is the Optimal Treatment Strategy?



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

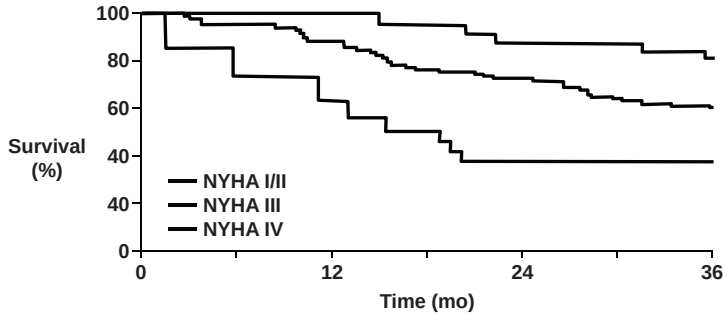
McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, Mathier MA, McGoon MD, Park MH, Rosenson RS, Rubin LJ, Tapson VF, Varga J. American College of Cardiology Foundation Task Force on Expert Consensus Documents; American Heart Association. *J Am Coll Cardiol*. 2009 Apr 28;53(17):1573-619.

ACCF/AHA Consensus PAH Treatment Algorithm



Modified from McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, Mathier MA, McGoon MD, Park MH, Rosenson RS, Rubin LJ, Tapson VF, Varga J; American College of Cardiology Foundation Task Force on Expert Consensus Documents; American Heart Association. *J Am Coll Cardiol*. 2009 Apr 28;53(17):1573-619.

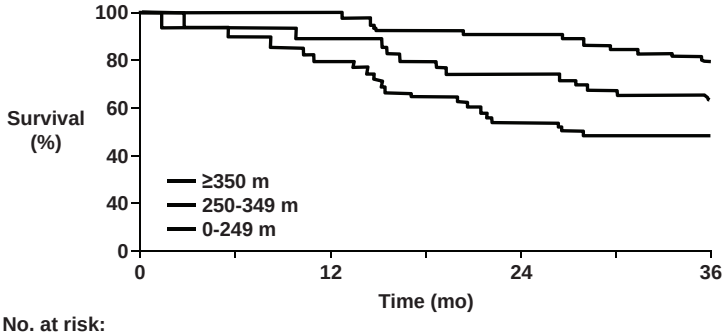
French Registry: Kaplan-Meier Survival Estimates According to Baseline NYHA Functional Class



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.

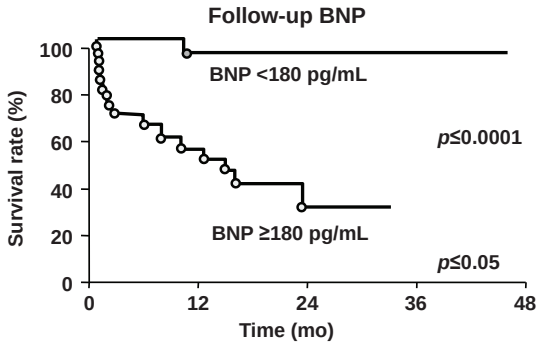
French Registry: Kaplan-Meier Survival Estimates According to Baseline 6MWD



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.

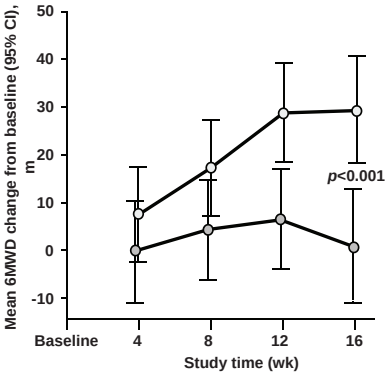
Plasma BNP as a Prognostic Indicator in Patients With IPAH

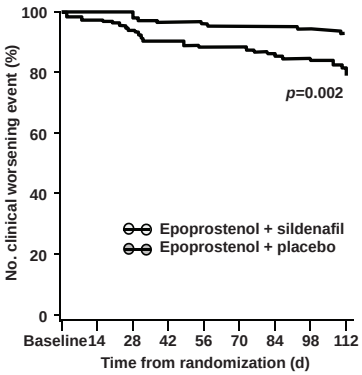


By multivariate analysis, higher BNP at *follow-up* (RR=25.880, *p*=0.0243) was an independent predictor of mortality.

Nagaya N, Nishikimi T, Uematsu M, Satoh T, Kyotani S, Sakamaki F, Kakishita M, Fukushima K, Okano Y, Nakanishi N, Miyatake K, Kangawa K. *Circulation.* 2000;102:865-870.

Sildenafil Added to Epoprostenol (PACES)





Simonneau G, Rubin LJ, Galiè N, Barst RJ, Fleming TR, Frost AE, Engel PJ, Kramer MR, Burgess G, Collings L, Cossons N, Sitbon O, Badesch DB; PACES Study Group. Addition of sildenafil to long-term intravenous epoprostenol therapy in patients with pulmonary arterial hypertension: a randomized trial. *Ann Intern Med*. 2008 Oct 21;149(8):521-30.

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)

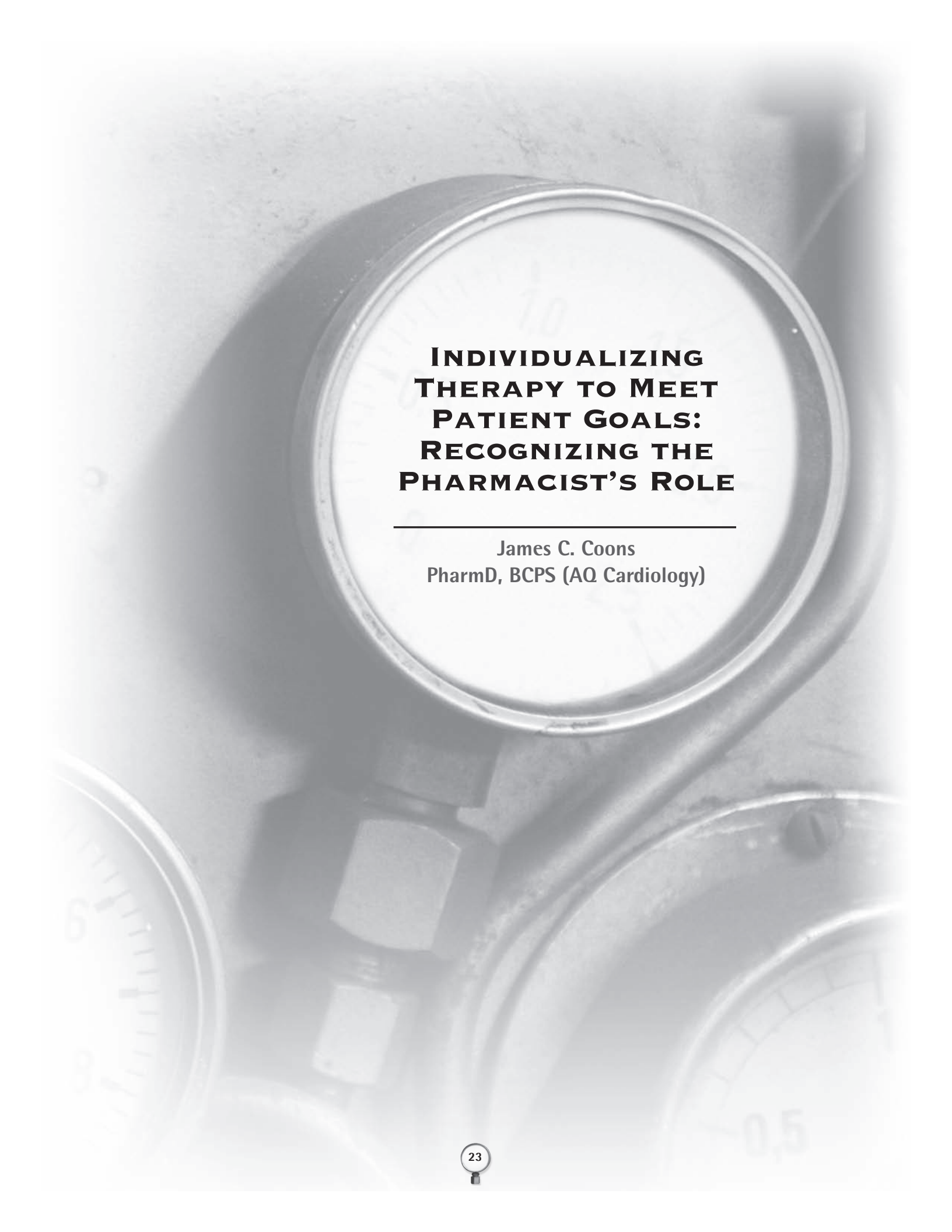
Combination Therapy: Other Ongoing or Recently Completed Clinical Trials

	Current therapy	Added therapy	Patients (*n*)	Study duration	Primary end point
FREEDOM-C	Bosentan and/ or sildenafil	Treprostinil oral	300	16 weeks	6MWD
AMBITION	Ambrisentan/ tadalafil/combo	Combo vs mono	300	Event-driven	Morbidity/mortality event
Pfizer	Bosentan	Sildenafil	106	12 weeks	6MWD
COMPASS-1	Bosentan	Sildenafil	45	Single dose	PVR
COMPASS-2	Sildenafil	Bosentan	250	Event-driven	Morbidity/mortality event
COMPASS-3	Bosentan	Sildenafil	100	16 weeks	6MWD
ATHENA-1	Sildenafil or tadalafil	Ambrisentan	40	24 weeks	PVR
SERAPHIN	Naïve/PDE-5/PGI/combo	Macitentan	742	Event-driven	Morbidity/mortality event
PATENT	Naïve/PGI/ERA	Riociguat	462	12 weeks	6MWD
IMPRES	≥2 current therapies	Imatinib	200	24 weeks	6MWD
ATPAHSS	Ambrisentan/ tadalafil/combo	Combo vs mono	63	36 weeks	RV mass/PVR
GRIPHON	ERA, PDE5 or both	Selexipag	670	Event-driven	Morbidity/mortality event

It Takes a Team

A truly <u>multidisciplinary</u> approach

- Pulmonary
- Cardiology
  - Cath Lab Team
  - Echo
  - Congenital Heart Disease
- Rheumatology
- Interventional Radiology
- Pharmacy
- Nursing
- Research
  - COMIRB
  - CCTSI
  - HHRC
- Respiratory Therapy
- Cardiothoracic Surgery / Lung Transplantation
- Hepatology / Transplant Surgery / Liver Tx
- Pediatric PH Program at Children's Hospital Colorado
- Basic and translational research



Individualizing Therapy to Meet Patient Goals: Recognizing the Pharmacist's Role

James C. Coons
PharmD, BCPS (AQ Cardiology)

James C. Coons,
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Cardiology Residency Program Director
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Dr. James Coons is an Associate Professor, Pharmacy and Therapeutics at the University of Pittsburgh School of Pharmacy in Pittsburgh, PA. After receiving his Doctor of Pharmacy from the University of Pittsburgh, he completed a PGY-1 residency in pharmacy practice at the University of Virginia Health System in Charlottesville, VA. This was followed by a PGY-2 specialty residency in cardiology pharmacy practice at the University of Pittsburgh.

Until August 2012, Dr. Coons was a clinical pharmacy specialist in cardiology at Allegheny General Hospital in Pittsburgh. During that time, he managed patients in the cardiac intensive care unit and those under the care of the advanced heart failure service. He also served as the PGY-1 residency program director.

Dr. Coons' research interests focus on the optimal use of antiplatelets and anticoagulants in the setting of acute coronary syndromes and percutaneous coronary intervention, as well as the application of pharmacogenomics in improving outcomes in this patient population.

Objective:
Discuss the role of clinical pharmacists in the management of patients with PAH.

Case Presentation: Meet CJ

- CC/HPI: CJ is a 33-year-old female who presents to the PH clinic with c/o progressive dyspnea and fatigue x 3 weeks with 15 lbs. weight gain since last visit (3 months ago). Symptoms noted with minimal activities.
- PMH: idiopathic PAH (diagnosed at age 29 yrs), GERD, type 2 diabetes mellitus, depression
- Meds: sildenafil 20 mg tid, bosentan 125 mg bid, omeprazole 20 mg qd, glyburide 5 mg bid, metformin 500 mg bid, sertraline 50 mg qd

Case Presentation

- Pertinent labs (1 week ago):
  BUN/SrCr: 40/1.6 mg/dL (20/1.1 at last visit)
  NT-proBNP: 800 pg/mL
- Vital signs: BP: 95/50 mmHg; HR: 110 bpm
- Current weight: 80 kg
- 6MWD: 280 meters (440 meters at last visit)
- **Plan:** Admit for right heart catheterization (RHC) and possible initiation of prostacyclin therapy

Case Presentation

- **Summary of RHC findings:**
  - PAP: 80/40 mmHg (mPAP: 53 mmHg)
  - CI: 1.9 L/min/m^2
  - PvO_2: 50%
  - PCWP: 12 mmHg; CVP: 15 mmHg
  - SVR: 1250 dynes × sec/cm^5
  - PVR: 1025 dynes × sec/cm^5
- **Next steps:**
  - Admit to cardiac ICU for initiation of IV epoprostenol at 2 ng/kg/min continuous IV infusion

NOTES

Current Challenges in PAH Care

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

Considerations by Medication

Epoprostenol

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

Considerations by Medication

Epoprostenol (Veletri®)

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

Considerations by Medication

Treprostinil (Remodulin®)

- 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® & Mini-Med® syringe pumps
  - Inhaled – Tyvaso inhalation system®

Parenteral Treprostinil Delivery

IV CADD

- **Continuous IV infusion**
- **Titration**
- **Requires dilution**
- **Rate provided in mL/day**
- **48 hour stability**

CRONO-5

- **Continuous IV infusion**
- **Not generally for titration**
- **Requires dilution**
- **Stable doses of medication**
- **20 mL syringe**
- **Rate provided in mcL/hr**
- **48 hour stability**

SC

- **Continuous SC infusion**
- **CADD-MS3®**
- **Mini-Med 407c® *(being phased out)***
- **Not diluted**
- **Rate provided in mL/hr**
- **72 hour stability**

Inhalational Treprostinil Delivery

Treprostinil (Tyvaso®)

- Supplied as foil packs
  - Each pack contains 4 ampules
  - 1 ampule (1.74 mg/2.9 mL)
  - 1 ampule per day regardless of total dose
  - Opened foil pack stable for 7 days
- Dispense as multi-dose vs. single-dose?

Considerations by Medication

Endothelin-1 Receptor Antagonists

- Special enrollment
  - Bosentan (Tracleer®)
    - Tracleer Access Program (T.A.P.)
  - Ambrisentan (Letairis®)
    - Letairis Education and Access Program (L.E.A.P.)
- New initiation vs. maintenance

Scope of Problem

- 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. for the Prostacyclin Safety Group. *J Heart Lung Transplant*. 2010;29:841-46.

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. for the Prostacyclin Safety Group. *J Heart Lung Transplant*. 2010;29:841-46.

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

Kingman MS, et al. for the Prostacyclin Safety Group. *J Heart Lung Transplant.* 2010;29:841-46.

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. for the Prostacyclin Safety Group. *J Heart Lung Transplant.* 2010;29:841-46.

Role of the Pharmacist

- Medication safety
- Quality improvement
- Optimizing medical regimens
- Patient education and adherence

Proposed Solutions

- Potential pharmacy policies
  - Contact PAH clinic or specialty pharmacy for:
    - Current dose, dosing weight, concentration, rate
  - Double-check all calculations
  - Obtain copy of titration schedule
  - Ensure pharmacy labels are clear
  - Ensure all relevant information is in medication administration record

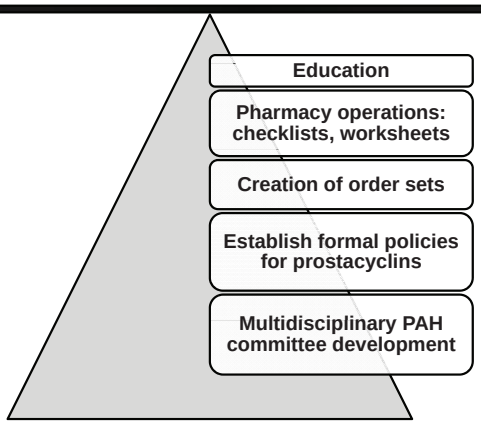
Kingman MS, et al. for the Prostacyclin Safety Group. *J Heart Lung Transplant*. 2010;29:841-46.

Proposed Solutions

- Potential hospital/nursing policies
  - Develop formal prostacyclin administration policies
  - Provide ongoing staff education
  - Double-check cassette and rate changes regularly
  - Re-evaluate placement of back-up cassettes
  - Place markers near connection sites ("do not flush" or "dedicated line")

Kingman MS, et al. for the Prostacyclin Safety Group. *J Heart Lung Transplant*. 2010;29:841-46.

A Model for Practice Change



Multidisciplinary Committee

- Identify stakeholders
  - Key physicians
  - Nursing
  - Pharmacy
  - Administrators
- Define current problems
- Delegate responsibilities

Prostacyclin Policies

- Interdisciplinary medication manual
- Key nursing resources
- Key pharmacy resources
- Readily accessible

Order Set Development

- Computerized physician order entry
- Required data elements
  - Route of administration
  - Correct formulation and vial concentration
  - Dosing weight
  - Dose
  - Final concentration
  - Base solution
  - Rate
  - Attending physician

Order Set Development

- Consider restricting by prescribing service/prescriber
- Location

Pharmacy Operations

- New order: initiation vs. maintenance
  When is first dose due?
- Obtain patient-specific dosing chart
- Double-check all calculations to verify current order
  Compare with patient-specific dosing chart
- Documentation: Create patient packet
  (patient-specific dosing chart, order checklist, dispensing log)
- Preparation and dispensing
- Continuity of care

Pharmacy Operations

- Prostacyclin flowchart
- Checklist
  (treprostinil vs. epoprostenol)
- Dispensing log
  (treprostinil vs. epoprostenol)
- Continuity of care

Pharmacy Operations

- Streamline appropriate product selection and related supplies
- Meetings between specialty pharmacy supplier and hospital pharmacy team (clinical/operations/supply chain team)
- Centralize location
- Establish par levels
- Creation of product kits

Other Operational Pearls

- Use patient weight provided by specialty pharmacy vs. inpatient weight
- CADD® pumps vs. regular IV pumps
- Need for back-up cassettes (epoprostenol)

Education

- Mandatory monthly education with annual competency
  - Pharmacists & pharmacy technicians: pharmacotherapy, prostacyclin policies, order sets, pharmacy operations
  - Nursing: pathophysiology, hemodynamic monitoring, pharmacotherapy, equipment

Back to the Patient Case

CC/HPI: CJ is a 33-year-old female who presents to the PH clinic with c/o progressive dyspnea and fatigue x 3 weeks with 15 lbs. weight gain since last visit (3 months ago). Symptoms noted with minimal activities.

Initiate epoprostenol

- 2 ng/kg/min continuous IV infusion
- New order entered by heart failure fellow
- ICU pharmacist receives order

As the pharmacist in this case, what additional information would be important to know before proceeding?

Patient Case: Next Steps

- Contact physician that entered order and/or PAH clinical nurse
  - When is therapy to start?
  - Has IV CADD® pump been obtained?
- Locate "prostacyclin flowchart"
- Obtain documents for "patient packet"
  - "Patient-specific dosing chart"
    - Contact specialty pharmacy to determine dosing scheme
  - Veletri® "order checklist"
  - Veletri® "dispensing log"

Patient Case: Next Steps

- Verify dose and rate on "patient-specific dosing chart"
- Verify accuracy and completeness of inpatient order vs. "patient-specific dosing chart"
  - Vial amount, patient weight, rate, dose, final concentration, diluent

Patient Case: Final Steps

- Send Patient Packet to IV room pharmacist
- Notify IV room of time first dose is due
- IV room pharmacist serves as double-check
- Complete Veletri® "dispensing log"
- Maintain "patient packet" on file in pharmacy
- "Continuity-of-care" sheet
    - Note titration schedule (possible changes in cassette concentrations)

What additional opportunities exist for optimizing medications in this patient?

Please remember to complete and return the "Activity Evaluation"

Upcoming Educational Activity

Online Learning Activity

For healthcare professionals who were unable to participate in the presentation, an online learning activity based on the live program will be available.

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Continuing Professional Development (CPD): Reflect | Plan | Do | Evaluate

Emerging Solutions in Pulmonary Arterial Hypertension:
Empowering Pharmacists in Treatment Decisions

Center for Independent Healthcare Education is committed to supporting pharmacists in their Continuing Professional Development (CPD) and lifelong learning. Please use this form to incorporate the learning from this educational activity into your everyday practice.

Continuing Professional Development: a self-directed, ongoing, systematic and outcomes-focused approach to learning and professional development that assists individuals in developing and maintaining continuing competence, enhancing their professional practice, and supporting achievement of their career goals.

CPD Value Statement:

"Pharmacists who adopt a CPD approach accept the responsibility to fully engage in and document their learning through reflecting on their practice, assessing and identifying professional learning needs and opportunities, developing and implementing a personal learning plan, and evaluating their learning outcomes with the goal of enhancing the knowledge, skills, attitudes and values required for their pharmacy practice."

REFLECT

Consider my current knowledge and skills in managing PAH, and self-assess my professional development needs and goals.

PLAN

Develop a "Personal Learning Plan" to achieve intended outcomes, based on what and how I want or need to learn.

Develop objectives that are specific for you, measurable, achievable, relevant to the learning/practice topic, and define the time frame to achieve them.

DO

Implement my learning plan utilizing an appropriate range of learning activities and methods.

List learning activities that you will engage in to meet your goals.
List resources (e.g. materials, other people) that you might use to help achieve your goal.

EVALUATE

Consider the outcomes and effectiveness of each learning activity and my overall plan, and what (if anything) I want or need to do next.

Monitor progress regularly toward achievement of your goal.