What You Need to Know About PAH

Empowering Pharmacists in Management Decisions

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Learning Objectives

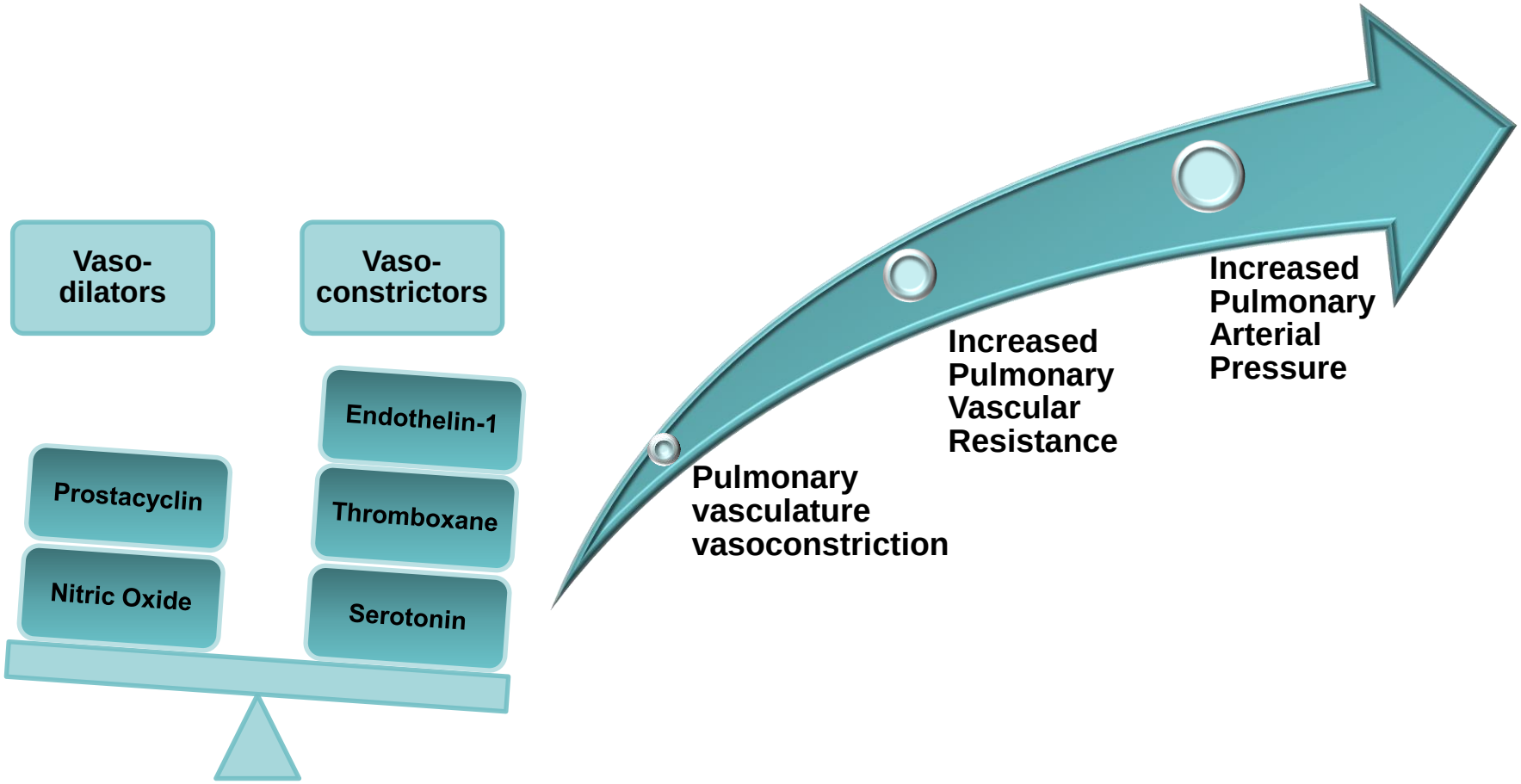
- Explain how treatment algorithms and prognostic factors can be used to individualize care for patients with PAH
- Describe the evolution of PAH therapy over the past 20 years and evaluate the role of the various therapeutic classes as monotherapy or combination therapy in the treatment of PAH
- Discuss how pharmacists can play an integral part of the inter-professional healthcare team when managing patients with PAH

Burden of Pulmonary Arterial Hypertension

- Pulmonary arterial hypertension (PAH) is a serious and rapidly progressive cardiopulmonary disease
- Difficult to diagnose, symptoms are often non-specific
- Sustained PAH leads to right heart failure, the leading cause of death in this population
- Associated with 1-year mortality up to 10–15%
- Rare disease, affects 15 to 26 people per million
- True burden may be underestimated:
  - Under-diagnosis
  - Misdiagnosis

Benza, et al. *Chest.* 2012;142(2):448-456.
Thenappan, et al. *Eur. Respir. J.* 2007;30(6):1103–1110.
Peacock, et al. *Eur Respir J.* 2007;30(1):104-9.
Humbert, et al. *Am J Respir Crit Care Med*. 2006;73:1023-30.
Badesch, et al. *Chest*. 2010;137:376-87.

Pathogenesis



Patient Case 1: Betty R.

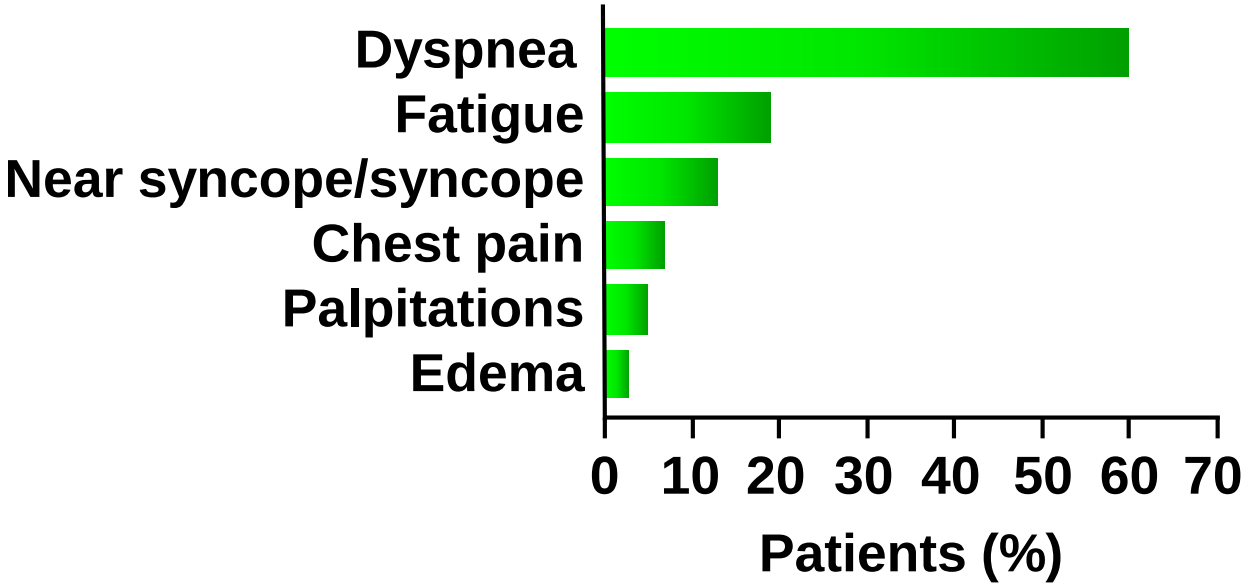
- Betty R. is a 48-year-old female patient who self-referred to pulmonary clinic for progressive DOE. States she has a h/o “heart failure” diagnosed at 27 years of age, with resolution after 2 years of treatment with ACE-I, ASA and diuretic. She brought OSH records with her, managed primarily by PCP.
- No remarkable symptoms until age of 46
  - DOE, can walk <1 block w/o SOB, LEE, occasional chest tightness, fatigue
  - 3 hospitalizations for HF exacerbation. Started on furosemide, potassium, carvedilol and spironolactone.

DOE, dyspnea on exertion; LEE, lower extremity edema; SOB, shortness of breath

Which of Betty R.'s symptoms are consistent with possible PH?

A. Dyspnea on exertion and fatigue
B. Lower extremity edema
C. Chest tightness
D. All of the above

Patient Presentation: Nonspecific Symptoms



Median Time From Symptom Onset to Diagnosis

NIH Registry (1981 to 1985)	1.3 years
REVEAL Registry (2006 to 2007)	1.1 years

Multiple educational efforts

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

Diagnostic and Monitoring Evaluation

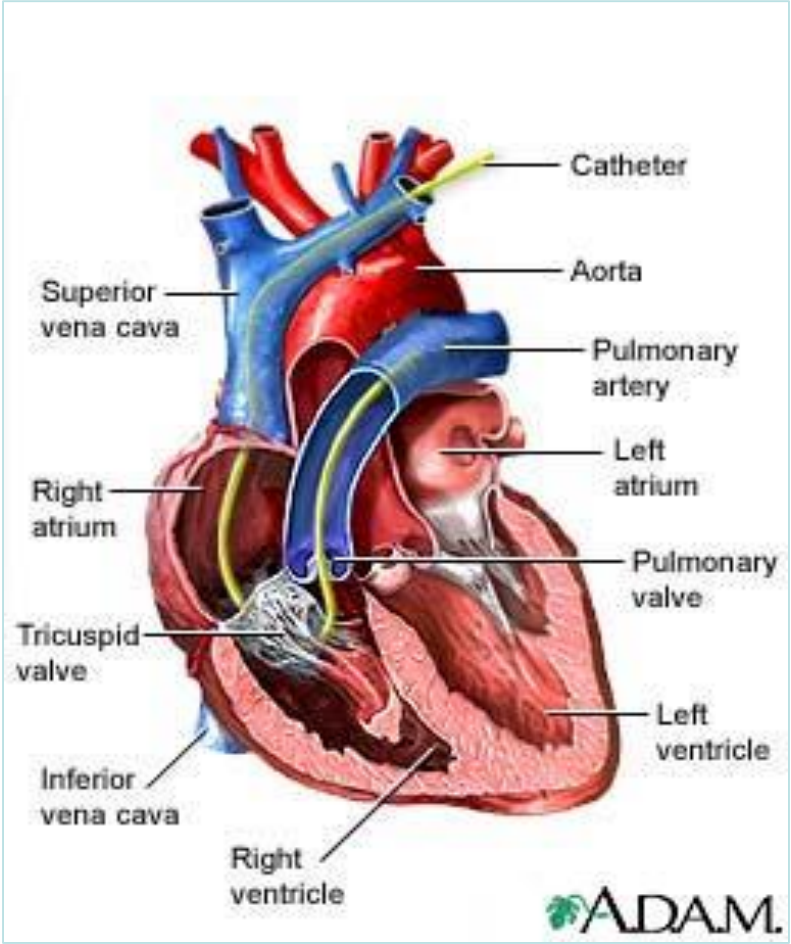
Test	Assessment/Finding
Physical examination and history	For suspected PH
Chest x-ray electrocardiography	For suspected PH
Echocardiogram	Evaluation of right ventricular function and screening tool
Ventilation perfusion scan	Screen for CTEPH
Overnight oximetry	Screen for sleep disorder or nocturnal hypoxia
Pulmonary function tests	Screen for obstructive/restrictive diseases Diffusing capacity
Blood work: ANA, LFT, HIV, BNP, UA, troponin	Screen for associated with: Connective tissue disease Liver disease Human immunodeficiency disease BNP: measure of RV failure and prognosis UA, troponin: prognosis
6-minute walk distance	Baseline exercise capacity, prognosis, response to treatment
Right heart catheterization	Used to confirm diagnosis Obtain baseline and ongoing hemodynamic profile Acute vasodilator response for CCB Determination of CO/CI, PCWP, RAP

CTEPH, chronic thromboembolic pulmonary hypertension; PH, pulmonary hypertension; ANA, antinuclear antibody; BNP, B-type natriuretic peptide; CCB, calcium channel blocker; CO, cardiac output; CI, cardiac index; LFT, liver function tests; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure ; UA, uric acid.

McLaughlin VV, et al. *J Am Coll Cardiol*. 2009 Apr 28;53(17):1573-619. McGoon MD, Kane GC. *Mayo Clinic Proc*. 2009;84(2):191-207. Vachiery JL, et al. *Eur Respir Rev*. 2012;21(123):40-7.

Diagnosis of PH

- Pulmonary artery pressure can be estimated on echocardiogram
  - Using tricuspid regurgitation
- PH must be confirmed by right heart catheterization
  - PAP and pulmonary capillary wedge pressure (PCWP) are measured before and after vasodilator challenge
  - Along with echo, provides data needed to classify type of PH
    - Category of PH crucial to developing effective treatment plan



Right Heart Catheterization Hemodynamics

- mPAP >25 mm Hg *and*
- LVEDP/PCWP ≤15 mm Hg

"Acute Vasodilator Response"

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

- ACCF/AHA include PVR >3 Wood Units

LVEDP, left ventricular end diastolic pressure; mPAP, mean pulmonary arterial pressure; PCWP, pulmonary capillary wedge 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.

Patient Case 1 Betty R. Continued

- TTE: found severely dilated RA, severely enlarged RV, moderately elevated PASP, intraventricular septal flattening, normal LV function but reduced LV size, LVEF 55–60%
- MRI: Severe TR, moderate reduction in RV systolic function, RV severely enlarged, normal EF, no evidence of shunting
- Chest CT: severe cardiomegaly with enlarged PA
- RHC: mPAP 47 mm Hg, mRA 17 mm Hg, PCW 14 mm Hg, PVR 8.5 Wood units
- 6MWD 213 m, O_2 with exercise 3 LPM

→ Recommended to initiate infused prostacyclin ASAP

EF, ejection fraction; LPM, liters per minute; LVEF, left ventricular ejection fraction; mRA, mean right atrial; PA, pulmonary artery; PASP, pulmonary artery systolic pressure; PCW, pulmonary capillary wedge; RA, right atrium; RV, right ventricle; TR, tricuspid regurgitation; TTE, transthoracic echocardiogram

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.

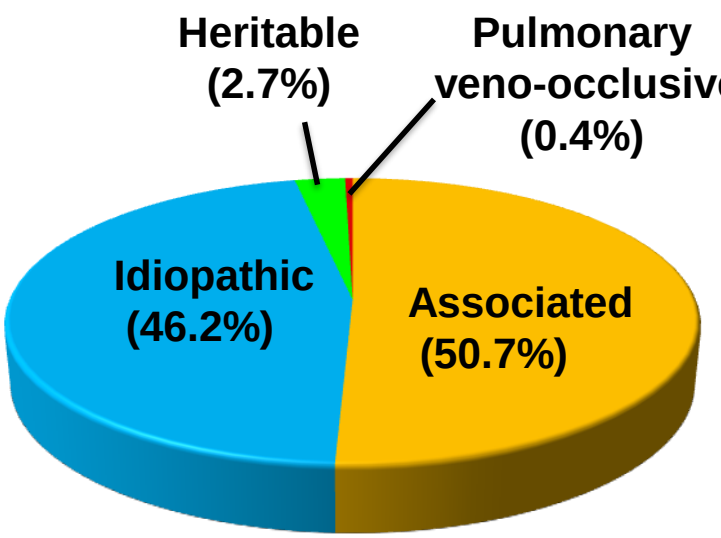
Group 1: Pulmonary Arterial Hypertension (PAH)

- Most well-known and well-studied type of PH
  - Actually a rare disease (15-26 cases/million)
- Involves components of vasoconstriction, proliferation, and inflammation
  - Imbalance of vasodilators (NO) and vasoconstrictors (ET-1) in pulmonary vasculature
  - Proliferation and inflammation lead to vascular fibrosis and narrowing of pulmonary arteries
- Tends to occur more commonly in women
- PAH can also be heritable
  - 80% from mutations in bone morphogenic protein receptor 2 (BMPR2)

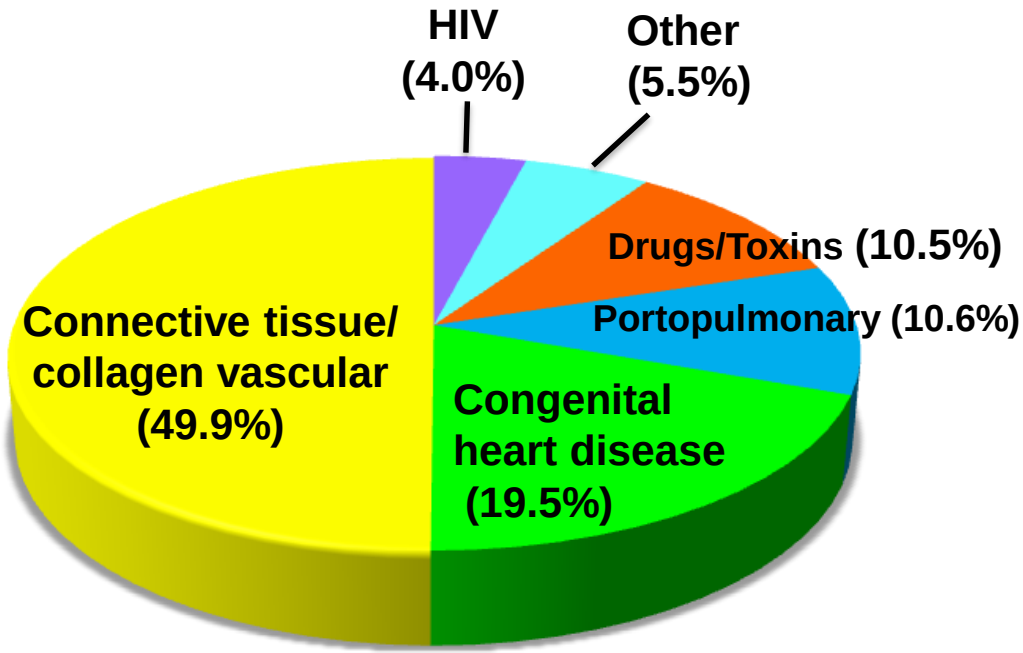
Humbert, et al. *Am. J. Respir. Crit. Care Med.* 173(9), 1023–1030 (2006).
Peacock, et al. *Eur. Respir. J.* 30(1), 104–109 (2007).
Machado, et al. *Hum. Mutat.* 27(2), 121–132 (2006).

PAH Distributions in the US: REVEAL Registry

Overall



Associated



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

Group 2: PH Due to Left Heart Disease

- Associated with pulmonary venous hypertension, which often leads to pulmonary arterial hypertension
  - mPAP ≥25mm Hg and PCWP ≥15 mm Hg
  - Most often from valvular disease or left heart failure
    - Estimated that 30-40% of heart failure patients have disproportionately high mPAP compared to degree of heart failure
    - Elevated mPAP in HF patients are associated with increased risk of death

Lam, et al. *J. Am. Coll. Cardiol.* 53(13), 1119–1126 (2009).
Schwartzenberg, et al, *J. Am. Coll. Cardiol.* 59(5), 442–451 (2012).
Bursi, et al. *J. Am. Coll. Cardiol.* 59(3), 222–231 (2012).

Group 3: PH Due to Lung Disease and/or Hypoxia

- Associated with hypoxic lung disease, often COPD or interstitial lung disease (ILD)
  - Thought to be common in advanced stage lung disease
  - Actual prevalence not well-defined
- Out-of-proportion PH is associated with 50% or greater increase in mortality
- No large RCTs exist addressing long-term effects of PH treatments in this patient population

Oswald-Mammosser, et al. *Chest* 107(5), 1193–1198 (1995).
Lettieri et al. *Chest* 129(3), 746–752 (2006).
Hoeper, et. al. *J. Am. Coll. Cardiol.* 54(Suppl. 1), S85–S96 (2009).

Group 4: Chronic Thromboembolic PH

- Defined as mPAP ≥25 mm Hg persisting longer than 6 months after diagnosis of pulmonary embolism
  - Found in approximately 4% of PE patients
- Can be curable by pulmonary thromboendarterectomy
- If inoperable, vasodilators, such as riociguat, may be beneficial

Condliffe, et al. *Am. J. Respir. Crit. Care Med.* 177(10), 1122–1127 (2008).

Group 5: PH with Unclear Multifactorial Mechanisms

- Multiple miscellaneous etiologies, most of which are not well-studied
  - Most common etiology in North America is thought to be sarcoidosis
    - PH is estimated to be present in nearly ¾ of patients with advanced sarcoidosis
    - Etiology not well understood, but may involve pulmonary fibrosis or formation of vascular flow-inhibiting granulomas
- Few treatment studies have been done in these patient populations

Shigemitsu et al. *Curr. Opin. Pulm. Med.* 13(5), 434–438 (2007).
Baughman et al. *Am. J. Respir. Crit. Care Med.* 183(5),573–581 (2011).

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

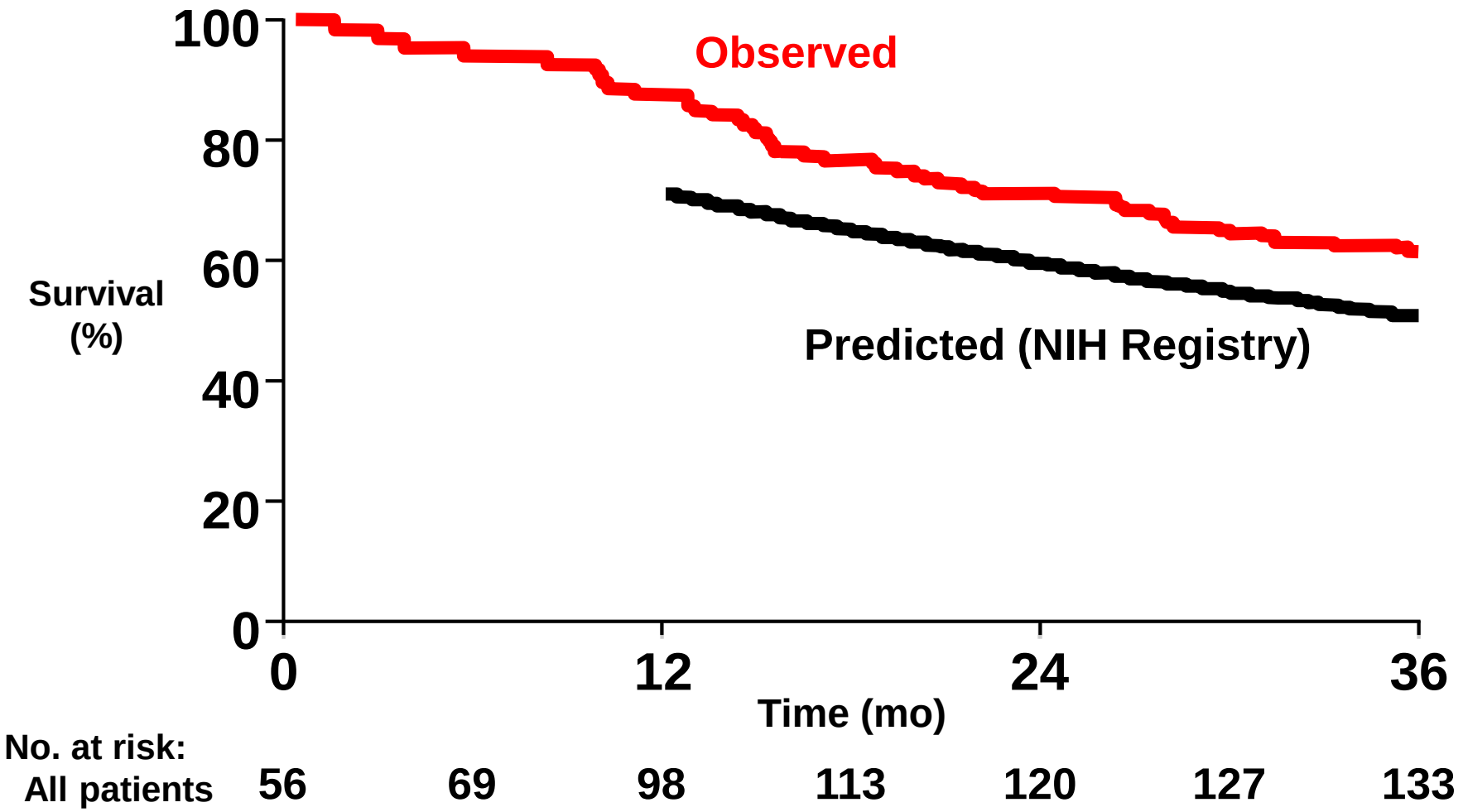
Adapted from Hoeper M, et al. *Eur Heart J.* 2009;30:2493-2537.

WHO Functional Classification

Class	Description
I	No limitation of usual physical activity; ordinary physical activity does not cause dyspnea, fatigue or other symptoms.
II	Mild limitations of physical activity; ordinary physical activity produces dyspnea, fatigue, chest pain, or near syncope; no symptoms at rest
III	Marked limitation of physical activity, less than ordinary physical activity produces dyspnea, fatigue, chest pain, or near syncope; no symptoms at rest
IV	Unable to perform any physical activity without symptoms; dyspnea and/or fatigue present at rest; symptoms are increased by almost any physical activity

McLaughlin VV, et al. *Circulation*. 2009;119; 2250-2294.
McGoon M, et al. *CHEST*. 2004; 126:14S-34S.

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



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

Patient Case 2: Donna K.

- Donna K. is a 42-year-old female who presents for worsening DOE with rapid progression of symptoms x 4 months. Recently diagnosed with PAH via RHC at OSH, discharged 3 days ago. Can walk only 5 to 10 feet w/o severe SOB.
- PMH: SLE, PE on warfarin, hypothyroidism
- FH/SH: ex-smoker, 1 daughter
- Meds: warfarin, prednisone, hydroxychloroquine, albuterol, metoprolol

DOE, dyspnea on exertion; PE, pulmonary embolism; RHC, right heart catheterization; SLE, systemic lupus erythematosus; SOB, shortness of breath;

Patient Case 2 Donna K. Continued

From OSH records:

- BP 85/60 mm Hg, HR 86, RR 22
- CrCl ~24 mL/min, CBC WNL, LFTs elevated
- BNP 2378 pg/mL
- PE: 1+ pitting edema, loud P2
- TTE: EF 40-45%, RV overload, systolic and diastolic septal flattening, RV severely dilated
- RHC: mPAP 48 mm Hg, PCWP 7 mm Hg, RA 13 mm Hg
- 6MWD ~100 m, frequent stops and continuous O_2 requirement

No other tests available for review

What is Donna K.’s 1-year mortality risk?

A. Average, predicted 1-year survival 90–100%
B. Medium, predicted 1-year survival 90–< 95%
C. High, predicted 1-year survival 70–< 85%
D. Very high, predicted 1-year survival <70%

PAH Determinants of Risk

Determinants of prognosis[a] (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope[b]	Repeated syncope[c]
WHO functional class	I, II	III	IV
6MWD	>440 m	165–440 m	<165 m
Cardiopulmonary exercise testing	Peak VO_2 >15 ml/min/kg (>65% pred.) VE/VCO_2 slope <36	Peak VO_2 11–15 ml/min/kg (35–65% pred.) VE/VCO_2 slope 36–44.9	Peak VO_2 <11 ml/min/kg (<35% pred.) VE/VCO_2 slope ≥45
NT-proBNP plasma levels	BNP <50 ng/l NT-proBNP <300 ng/l	BNP 50–300 ng/l NT-proBNP 300–1400 ng/l	BNP >300 ng/l NT-proBNP >1400 ng/l
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2 No pericardial effusion	RA area 18–26 cm^2 No or minimal, pericardial effusion	RA area >26 cm^2 Pericardial effusion
Haemodynamics	RAP <8 mmHg CI ≥2.5 l/min/m^2 SvO_2 >65%	RAP 8–14 mmHg CI 2.0–2.4 l/min/m^2 SvO_2 60–65%	RAP >14 mmHg CI <2.0 l/min/m^2 SvO_2 <60%

6MWD = 6-minute walking distance; BNP = brain natriuretic peptide; CI = cardiac index; CMR = cardiac magnetic resonance; NT-proBNP = N-terminal pro-brain natriuretic peptide; pred. = predicted; RA = right atrium; RAP = right atrial pressure; SvO_2 = mixed venous oxygen saturation; VE/VCO_2 = ventilatory equivalents for carbon dioxide; VO_2 = oxygen consumption; WHO = World Health Organization.

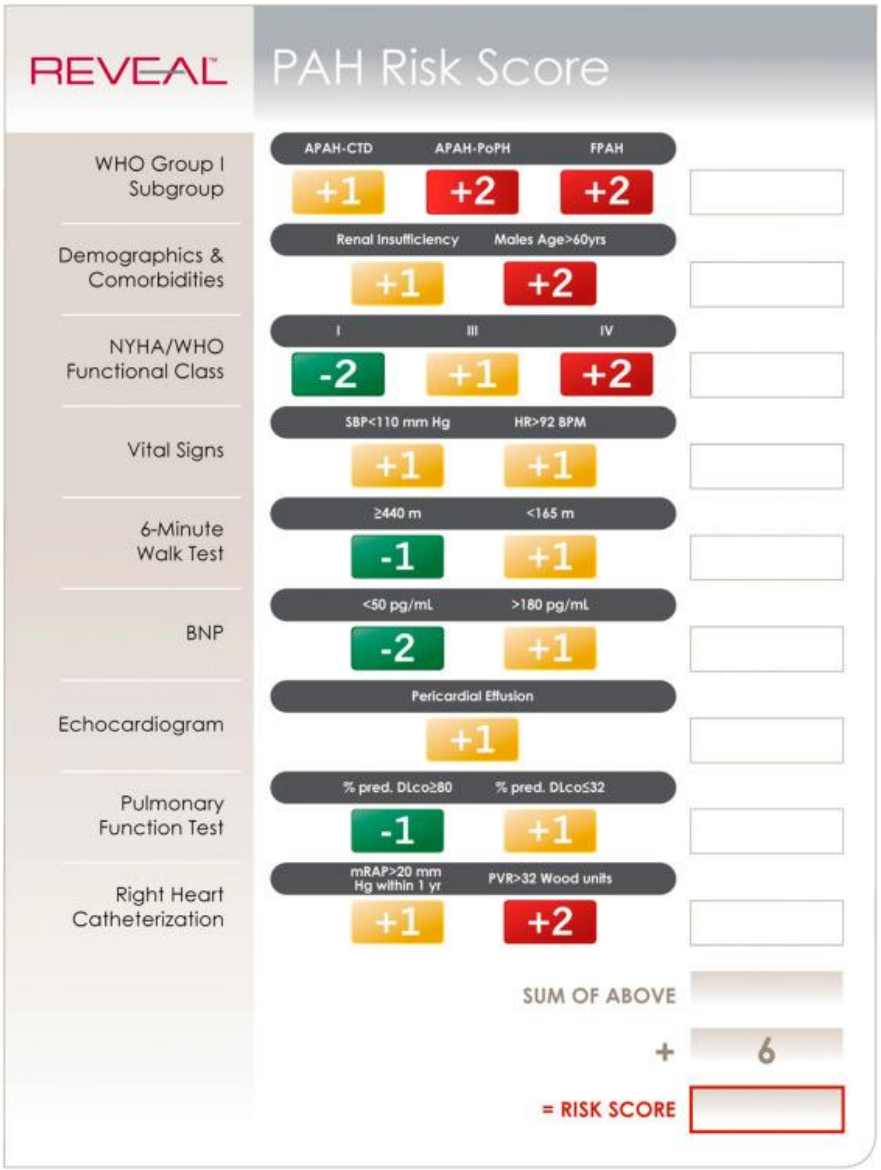
[a]Most of the proposed variables and cut-off values are based on expert opinion. They may provide prognostic information and may be used to guide therapeutic decisions, but application to individual patients must be done carefully. One must also note that most of these variables have been validated mostly for IPAH and the cut-off levels used above may not necessarily apply to other forms of PAH. Furthermore, the use of approved therapies and their influence on the variables should be considered in the evaluation of the risk.

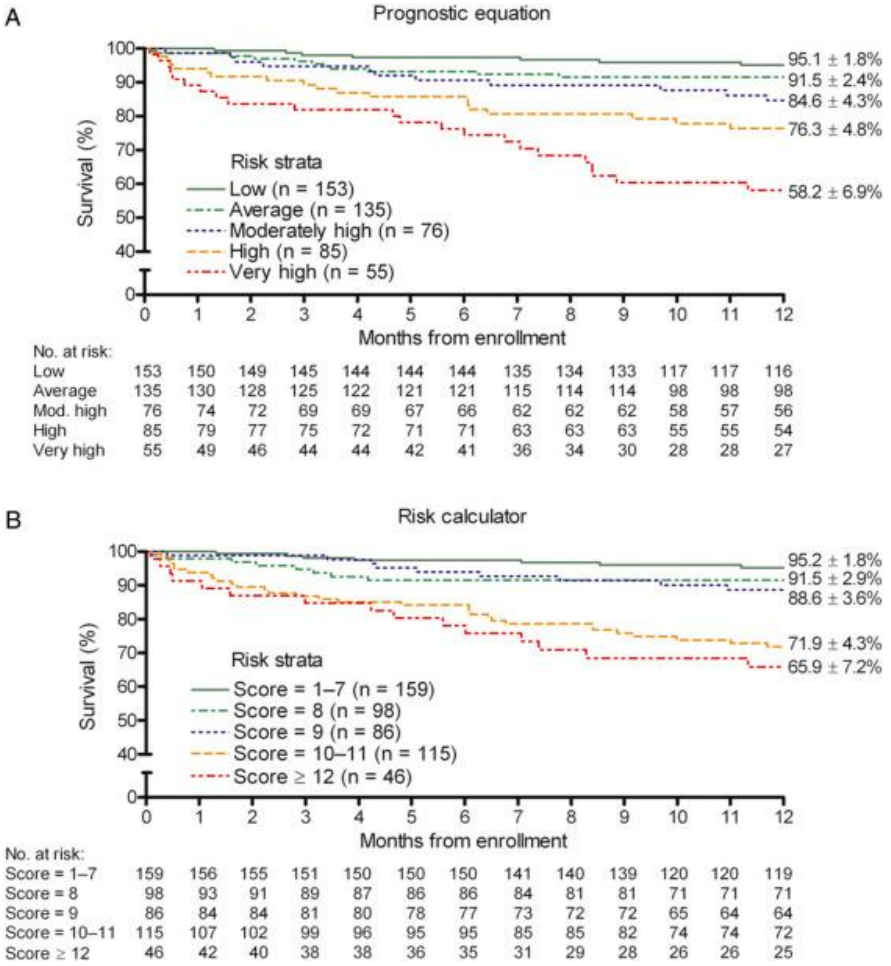
[b]Occasional syncope during brisk or heavy exercise, or occasional orthostatic syncope in an otherwise stable patient.

[c]Repeated episodes of syncope, even with little or regular physical activity.

Galiè N, et al. *Eur Heart J*. 2016;37:67-119.

The REVEAL Registry Risk Score Calculator in Patients Newly Diagnosed With Pulmonary Arterial Hypertension





One-year survival in the validation cohort stratified according to estimated probability of surviving 1 year. Predicted 1-year survival is 95% to 100% in the low-risk group, 90% to < 95% in the average-risk group, 85% to < 90% in the moderately high-risk group, 70% to < 85% in the high-risk group, and < 70% in the very high-risk group. B, One-year survival in the validation cohort stratified according to risk score. The average predicted 1-year survival is 95% to 100% (low risk) for patients with risk scores of 1 to 7. Similarly, the ranges specified for average risk, moderately high risk, high risk, and very high risk correspond to risk scores of 8, 9, 10 to 11, and ≥ 12.

Benza RL, et al. *Chest.* 2012;141(2):354-62.

Patient Case 2 Donna K. Continued

	B	C	D
	WHO Group I Subgroup		
☑	APAH-CTD	TRUE	1
☐	APAH-PoPH	FALSE	0
☐	FPAH	FALSE	0
	Demographics & Comorbidities		
☑	Renal Insufficiency	TRUE	1
☐	Males Age > 60 yrs	FALSE	0
	NYHA/WHO Functional Class		
☐	I	FALSE	0
☐	III	FALSE	0
☑	IV	TRUE	2
	Vital Signs		
☑	SBP < 110 mmHg	TRUE	1
☐	HR > 92 BPMs	FALSE	1
	6-Minute Walk Test		
☐	≥ 440 m	FALSE	0
☑	< 165 m	TRUE	1
	BNP		
☐	< 50 pg/mL	FALSE	0
☑	> 180 pg/mL	TRUE	1
	Echocardiogram		
☐	Pericardial Effusion	FALSE	0
	Pulmonary Function Test		
☐	% pred. DLco ≥ 80	FALSE	0
☐	% pred. DLco ≤ 32	FALSE	0
	Right Heart Catheterization		
☐	mRAP > 20 mmHg within 1 year	FALSE	0
☐	PVR ≥ 32 Wood units	FALSE	0
		Sum of above +	14

Risk score		Predicted 1-year survival
1–7	LOW RISK	95% to 100%
8	AVERAGE RISK	90% to <95%
9	MODERATE HIGH RISK	85% to <90%
10–11	HIGH RISK	70% to <85%
≥12	VERY HIGH RISK	<70%

The reveal registry risk score calculator in patients newly diagnosed with pulmonary arterial hypertension

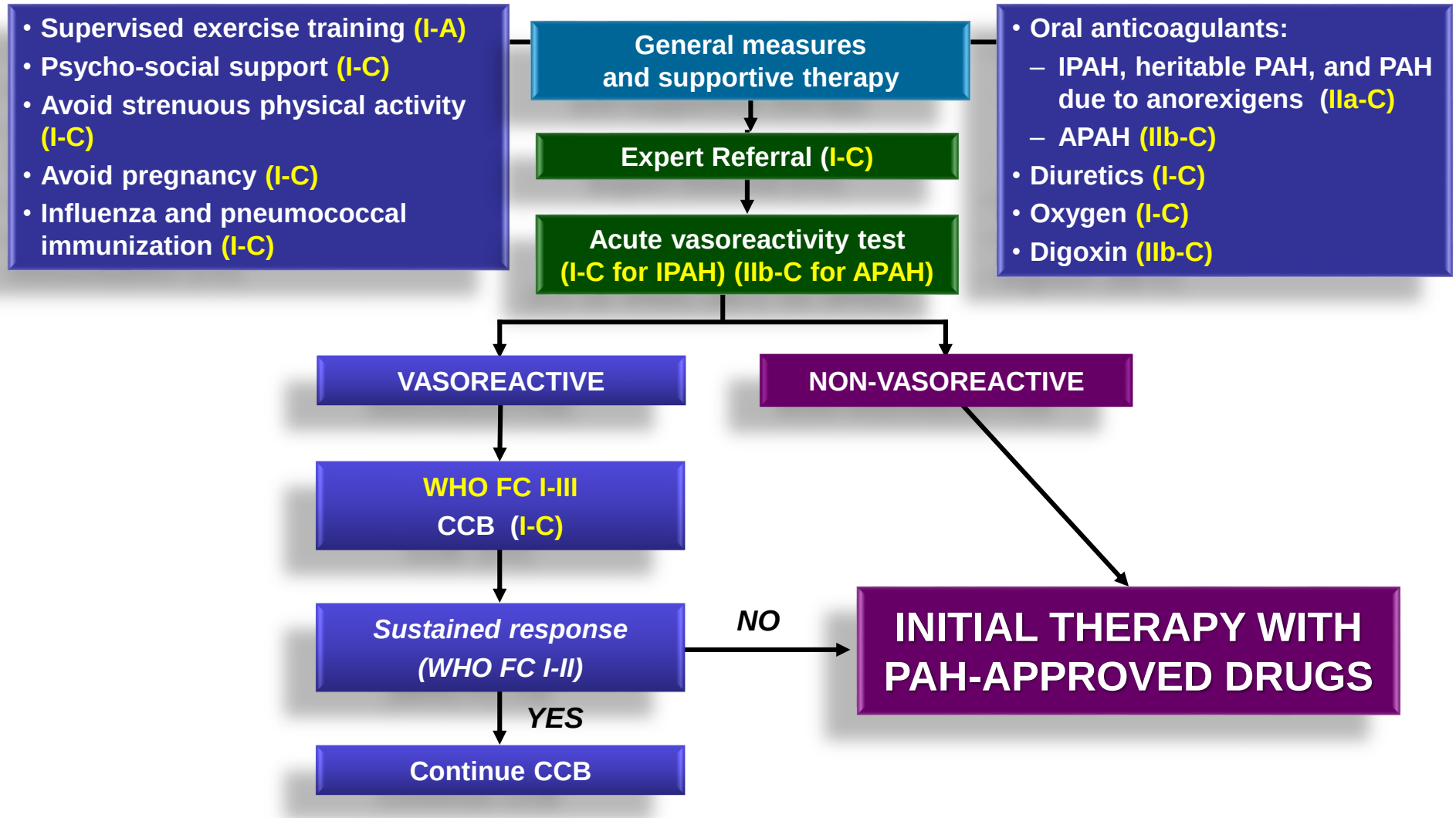
Benza RL, Gomberg-Maitland M, Miller DP, et al.

→ Direct admission from clinic for initiation of IV epoprostenol

Initial Therapy: Making the Right Decision

- Severity of disease
- Patient preference
- Patient characteristics
- 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)

5th World Symposium on PH: 2013 PAH Treatment Algorithm



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

ESC/ERS 2015 Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension

- **Important 2015 updates:**
  - New parameters for definition of post-capillary PH subgroups
  - Adult and pediatric common clinical classification
  - Updated diagnostic algorithm and screening recommendations
  - Recommendations for referral to centers of excellence
  - **Treatment recommendations/goals based on risk and severity**
  - Combination therapy
  - Additional recommendations in Groups 2–5 PH

Galiè N, et al. *Eur Heart J*. 2016;37:67-119.

ESC/ERS 2015 Recommendations Regarding Initial and Sequential Combination Therapy

Key Points:

- Sequential using goal-oriented therapy is most commonly used strategy
- Upfront combination therapy generally based on mortality risk
- RCTs for initial combination therapy
- Cost and coverage

Table 20 Recommendations for efficacy of initial drug combination therapy for pulmonary arterial hypertension (group 1) according to World Health Organization functional class. Sequence is by rating

Measure/ treatment	Class[a]-Level[b]						Ref.[c]
	WHO-FC II		WHO-FC III		WHO-FC IV		
Ambrisentan + tadalafil[d]	I	B	I	B	IIb	C	247
Other ERA + PDE-5i	IIa	C	IIa	C	IIb	C	-
Bosentan + sildenafil + i.v. epoprostenol	-	-	IIa	C	IIa	C	246
Bosentan + i.v. epoprostenol	-	-	IIa	C	IIa	C	198, 245
Other ERA or PDE-5i + s.c. treprostinil			IIb	C	IIb	C	-
Other ERA or PDE-5i + other i.v. prostacyclin analogues			IIb	C	IIb	C	-

ERA = endothelin receptor antagonist; i.v. = intravenous; PDE-5i = phosphodiesterase type 5 inhibitor; RCT = randomized controlled trial; s.c. = subcutaneous; WHO-FC = World Health Organization functional class.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.
[d]Time to clinical failure as primary endpoint in RCTs or drugs with demonstrated reduction in all-cause mortality (prospectively defined).

Table 21 Recommendations for efficacy of sequential drug combination therapy for pulmonary arterial hypertension (group 1) according to World Health Organization functional class. Sequence is by rating and by alphabetical order

Measure/ treatment	Class[a]-Level[b]						Ref.[c]
	WHO-FC II		WHO-FC III		WHO-FC IV		
Macitentan added to sildenafil[d]	I	B	I	B	IIa	C	201
Riociguat added to bosentan	I	B	I	B	IIa	C	214
Selexipag[e] added to ERA and/or PDE-5i[d]	I	B	I	B	IIa	C	241, 248
Sildenafil added to epoprostenol	-	-	I	B	IIa	B	209
Treprostinil inhaled added to sildenafil or bosentan	IIa	B	IIa	B	IIa	C	237
Iloprost inhaled added to bosentan	IIb	B	IIb	B	IIb	C	230, 231
Tadalafil added to bosentan	IIa	C	IIa	C	IIa	C	211
Ambrisentan added to sildenafil	IIb	C	IIb	C	IIb	C	249
Bosentan added to epoprostenol	-	-	IIb	C	IIb	C	250
Bosentan added to sildenafil	IIb	C	IIb	C	IIb	C	251, 252
Sildenafil added to bosentan	IIb	C	IIb	C	IIb	C	252
Other double combinations	IIb	C	IIb	C	IIb	C	-
Other triple combinations	IIb	C	IIb	C	IIb	C	-
Riociguat added to sildenafil or other PDE-5i	III	B	III	B	III	B	215

EMA = European Medicines Agency; ERA = endothelin receptor antagonist; PAH = pulmonary arterial hypertension; PDE-5i = phosphodiesterase type 5 inhibitor; RCT = randomized controlled trial; WHO-FC = World Health Organization functional class.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.
[d]Time to clinical worsening as primary endpoint in RCTs or drugs with demonstrated reduction in all-cause mortality (prospectively defined).
[e]This drug was not approved by the EMA at the time of publication of these guidelines.

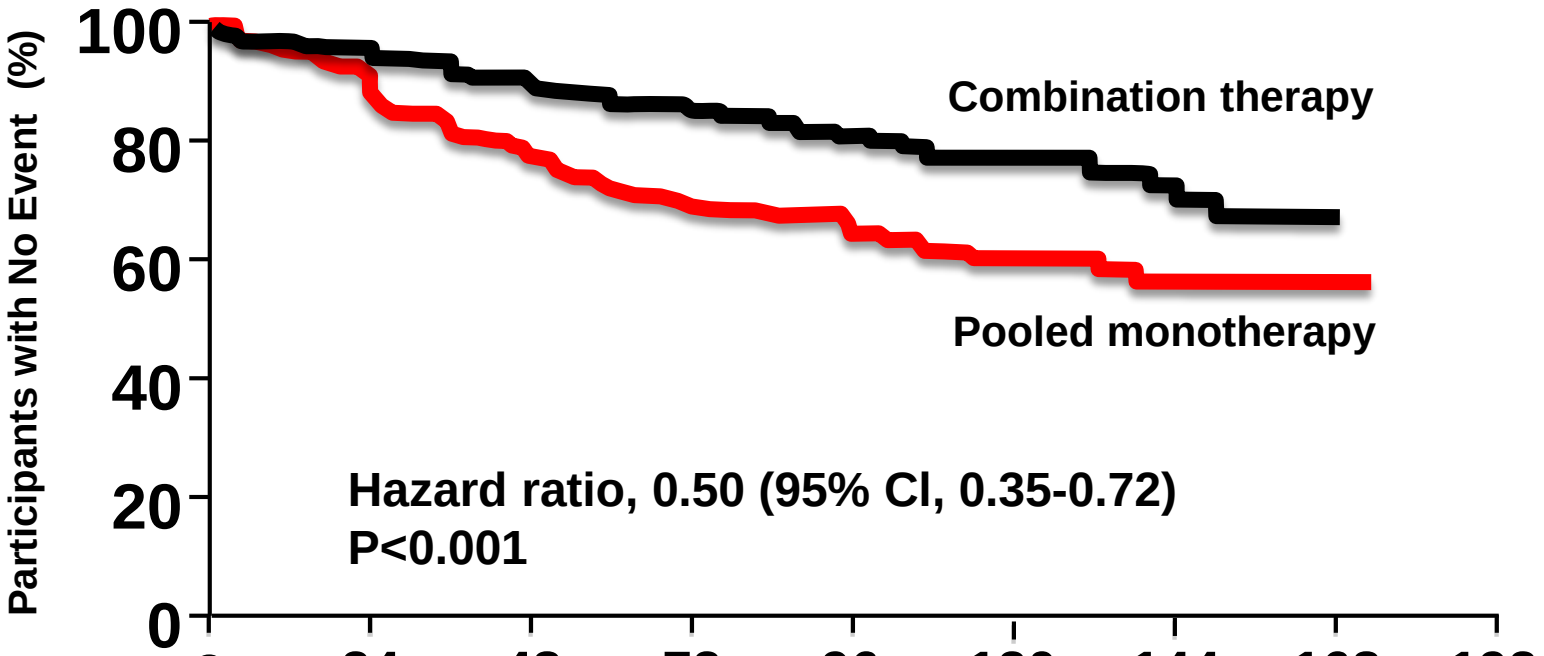
Galiè N, et al. *Eur Heart J*. 2016;37:67-119.

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/

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

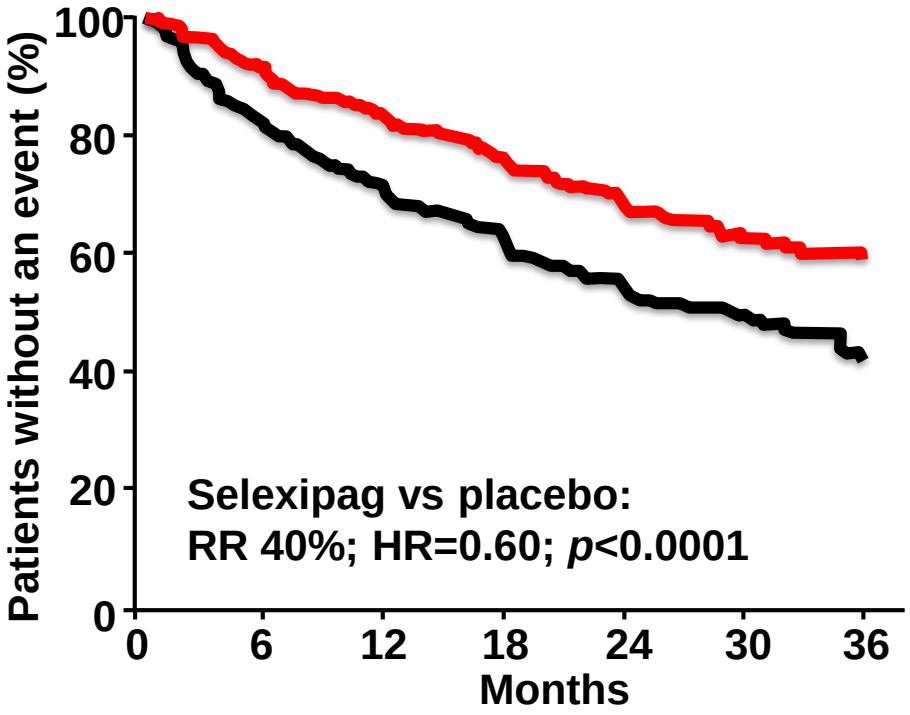


No. at risk:								
Combination therapy	253	229	186	145	106	71	36	4
Pooled monotherapy	247	209	155	108	77	49	25	5

*Death, hospitalization for worsening PAH, disease progression, unsatisfactory long-term clinical response.

Galiè N, et al. *N Engl J Med*. 2015;373:834-44.

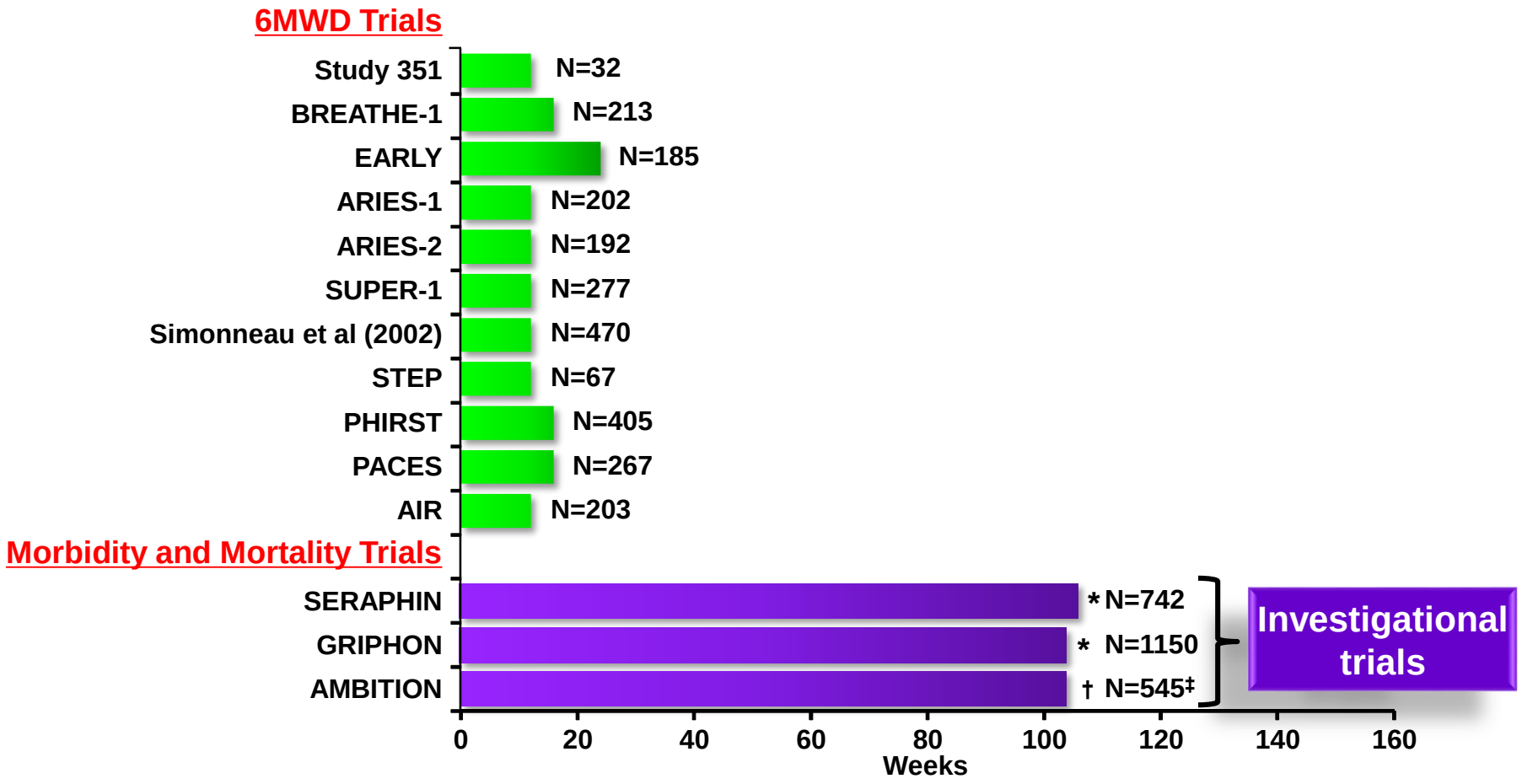
Oral Prostacylin Therapy: Time to First Morbidity or Mortality Event—GRIPHON



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.

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.

Patient Case 3: John W.

- John W. is a 56-year-old male with h/o scleroderma, Raynaud's disease, COPD, and PAH who presents today for follow-up. Has been on triple therapy for approximately 1 year. Can now climb 3 flights of stairs before SOB.
- Current medications include:
  - Albuterol prn
  - Omeprazole 40 mg BID
  - Macitentan 10 mg daily
  - Sildenafil 20 mg TID
  - Treprostinil IV current dose 76 ng/kg/min

Patient Case 3 John W. Continued

- ROS/PE unremarkable
- Vitals: WNL
- Recent 6 MWD 427 m, O_2 requirement with exertion
- Repeat RHC mPAP 14 mm Hg, PCWP 12 mm Hg, RA 4 mm Hg, PVR <1 Wood Unit, CI 1.9 (compared to baseline mPAP 45 mm Hg, PCWP 11 mm Hg, RA 14 mm Hg, PVR 11 Wood Units, CI 2.0)
- ECHO: no evidence of RV failure, small pericardial effusion
- BNP 190 pg/mL

What is the Best Recommendation Regarding PAH Therapy for John W?

A. Continue current regimen, patient has reached goal and can now follow-up annually
B. Continue current regimen, patient has demonstrated improvement but follow-up in 3 to 4 months to assess clinical status
C. Patient is not at goal, continue titrating IV treprostinil to a goal dose of 100 ng/kg/min
D. Patient is not at goal, add riociguat 1 mg TID for quadruple therapy

General treatment goals (*J Am Coll Cardiol*. 2013;62(25_S) and *Eur Respir J.* 2015 Oct;46(4):903-75)	
Outcome	**Recommended Goal**

• Fewer/less severe symptoms
• Improve exercise capacity
	• Functional Class I or II
	• 6MWD 380-440 m
	• CPET
	  ○ Peak VO_2 >15 mL/kg/min
	  ○ VE/VCO_2 @ AT <45

• Improve hemodynamics, imaging, and other measures of disease severity	• Hemodynamics: normalization of RV function
	  ○ RAP <8 mmHg and CI >2.5-3.0 L/min/m^2
	• Echocardiography/MRI:
	  ○ Normal/near normal RV size and function
	• BNP level “normal”

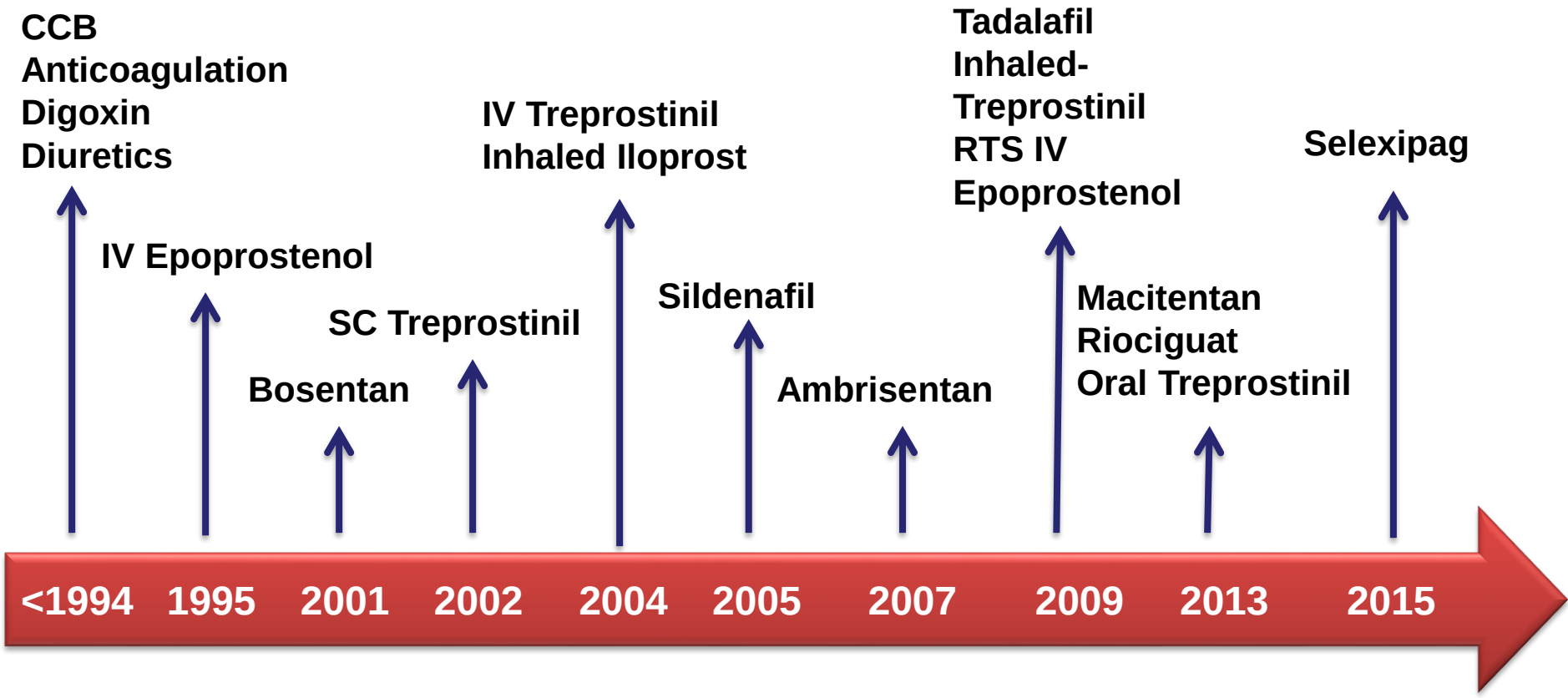
• Prevent clinical worsening and improve quality of life	• Prevention of:
	  ○ Escalation of therapy
	  ○ Hospitalization
	  ○ Lung transplantation
	  ○ Death

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

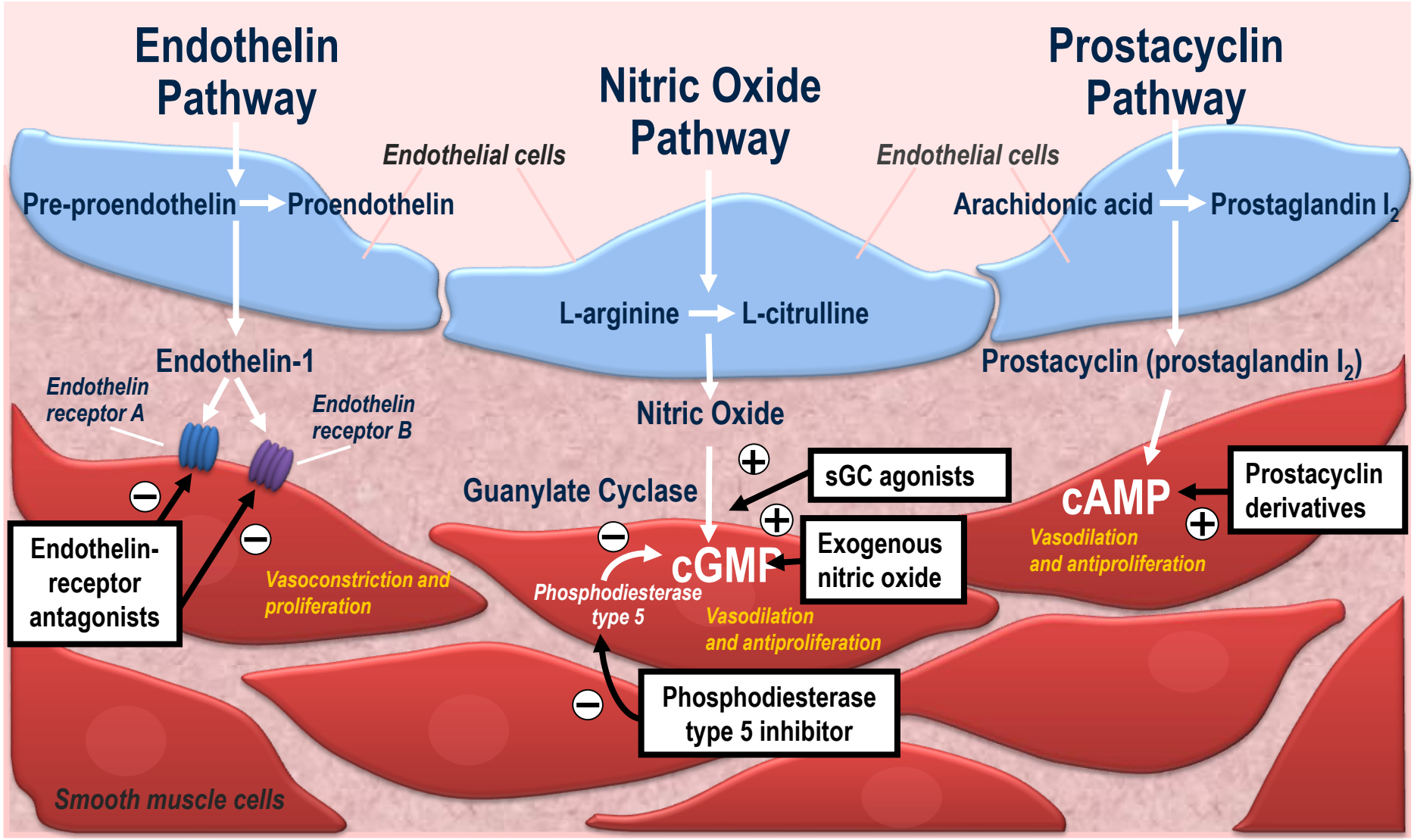
Galiè N, et al. *J Am Coll Cardiol.* 2013;62:D60-D72.

*Not approved in in US.



PAH Treatment Timeline

Therapeutic Targets for PAH



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

Prostacyclin Analogues: Overview

- Prostacylin pathway: prostacylin is a naturally-occurring vasodilator
  - Activates process that promotes vasodilatory, anti-platelet, and anti-proliferative effects
- Differ in stability, half-life, and method of delivery
- Typically initiated with close supervision in clinical setting
- Infusions titrated to response and tolerability
- Require extensive patient education and training
- Interruptions should be avoided = rebound symptoms

Patient Case 4: Roberta M.

- 51-year-old female with PAH admitted for worsening DOE. Currently on tadalafil and inhaled treprostinil x 8 months with little to no improvement in symptoms, ECHO or recent RHC performed
- Plan is to initiate subcutaneous treprostinil and stop inhaled treprostinil

Which of the following are most important to determine prior to initiating infused treprostinil?

A. Dosing weight and plan for transition from inhaled treprostinil
B. Dosing weight and plan for discharge
C. Vial concentration and plan for discharge
D. Next reservoir change and vial concentration

Prostacyclin Overview

- Prostacylin pathway: prostacylin is a naturally-occurring vasodilator
  - Activates process that promotes vasodilatory, anti-platelet, and anti-proliferative effects
- Gold standard for advanced disease
- Unique administration devices
- Interruptions must be avoided
- Limited distribution
- Titrated to response and tolerability
- ***High-risk, error-prone medications***

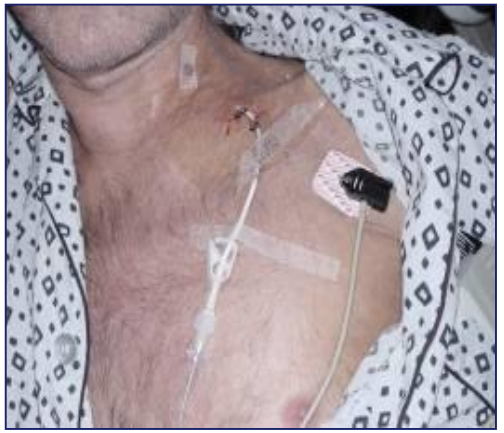
Prostacyclin Analogues: IV and SQ Formulations

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.

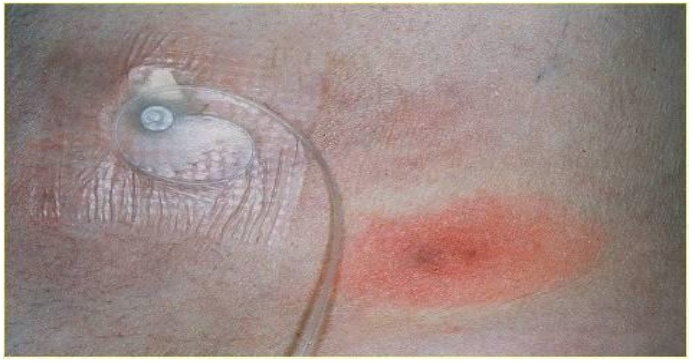
Veletri® (epoprostenol) US Prescribing Information. Actelion Pharmaceuticals US, Inc. July 2016.
Remodulin® (treprostinil) US Prescribing Information. United Therapeutics Corp. December 2014.

Infused Administration

Central line for IV



Subcutaneous Catheter



Parenteral Prostacyclin Delivery Systems

Intravenous

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

Subcutaneous

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

***Additional notes for micro-infusions:**

1. Anticoagulation recommended due to low infusion rates
2. Transition recommended only after stable dose achieved
3. Consider priming volume with smaller volume reservoirs

Administration Considerations

- **Dosing and administration**
  - Route
  - Vial concentration
  - Calculated dose
  - Concentration and total volume
  - Device specific infusion rate
  - **Dosing weight**
  - Titration orders
  - Timing of next reservoir change
  - Other PAH therapies

Potential Complications with Infused Prostacyclins

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

Patient Case 4 Roberta M. Continued

- Dosing weight = 81.7 kg
- Inpatient transition orders: Initiate infusion at 2 ng/kg/min, increase by 2 ng/kg/min daily x 4 days while simultaneously reducing dose of inhaled treprostinil by 25% daily then d/c.
- Discharge to home on 8 ng/kg/min.
- Ongoing titrations: increase by 2 ng/kg/min every 3 days to a goal dose of 20 ng/kg/min. Then follow-up with MD.

Subcutaneous treprostinil dose guide			
CADD MS3 Infusion Pump (3 mL medication reservoir)			
Name:	Case #4	Titration Orders	
Date of Birth:	51 yo	Start Date:	1/15/20146
MRN:	1111111111	Increment:	0.004 ml/hr
Dosing Weight (kg):	81.7 kg	Interval:	1 days
Cartridge Change (hrs):	72	Number of Titrations:	20
Vial Concentration:	2.5 mg/ml 20ml MDV		
Initiation Dose:	2.0 ng/kg/min		
Initiation Rate:	0.004 ml/hr		

Inpatient Titration Plan			
Date	Dose (ng/kg/min)	Infusion Rate (ml/hr)	Notes
01/15/16	2	0.004	9 breaths QID
01/16/16	4	0.008	6 breaths QID
01/17/16	6	0.012	3 breaths QID
01/18/16	8	0.016	stop inhaled

Subcutaneous treprostinil dose guide			
CADD MS3 Infusion Pump (3 mL medication reservoir)			
Name:	Case #4	Titration Orders	
Date of Birth:	51 yo	Start Date:	1/18/2016
MRN:	1111111111	Increment:	0.004 ml/hr
Dosing Weight (kg):	81.7 kg	Interval:	3 days
Cartridge Change (hrs):	72	Number of Titrations:	7
Vial Concentration:	2.5 mg/ml 20ml MDV		

Outpatient Titration Plan			
Date	Calculated Dose (ng/kg/min)	Infusion Rate (ml/hr)	Notes
01/18/16	8	0.016	Date of discharge
01/21/16	10	0.020	
01/24/16	12	0.024	
01/27/16	14	0.028	
01/30/16	16	0.032	
02/02/16	18	0.036	
02/05/16	20	0.040	f/u at MD appt.

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. June 2016.
Orenitram® (treprostinil) US Prescribing Information. United Therapeutics Corp. January 2016.

Inhaled Prostacyclin Delivery Systems

Inhaled treprostinil

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

Inhaled iloprost

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

IP Agonist

- Novel mechanism
- Oral, selective prostacyclin receptor (IP) agonist
- Structurally distinct from prostacyclin
- Studied in combination therapy
- Available only through RDDS

<table>
<tr><th colspan="4">Selexipag</th></tr>
<tr><td>How Supplied</td><td colspan="2">REMS</td><td>Properties</td><td>CI/P</td></tr>
<tr><td rowspan="2">Uptravi® 200 mcg, 400 mcg, 600mcg, 800mcg, 1000 mcg, 1200 mcg, 1400 mcg, 1600 mcg</td><td colspan="2">N/A</td><td rowspan="3">T½ ~6 to 13.5 hrs for active metabolite

Substrate of 2C8, 3A4, P-gp, BRCP, UGT1A3, UGT2B7, OATP1B1, OATP1B3</td><td rowspan="3">CI: none
Caution with moderate liver disease (dose adjustment may be necessary).
Avoid with severe liver disease</td></tr>
<tr><td>FC</td><td>Dose</td></tr>
<tr><td>Administration

Oral tablets</td><td>Mostly II-III</td><td>Start at 200 mcg BID, titrate by 200 mcg BID once weekly to highest tolerated dose (max 1600 mcg BID)</td></tr>
</table>

Uptravi® (selexipag) US Prescribing Information. Actelion Pharmaceuticals. January 2016.

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

Prostacyclin Patient Considerations

Infusion

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

Inhaled

- Adherence
  - Cleaning
  - Multiple treatment sessions
- Lung disease
- Disease severity
- Own use devices

Endothelin Receptor Antagonists: Overview

- Endothelin pathway: endothelin binds to ET_A and ET_B receptors → regulation of vascular tone
  - ET_A activation = vasoconstriction and cellular proliferation
- ERAs antagonize ET_A receptors*

*** Bosentan is a 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				

ERA Patient Considerations

- Females of reproductive potential
- Ability or willingness to comply with mandatory labs and enrollments (REMS requirements)
- Drug interactions
- Special enrollments for REMS programs

PDE-5 Inhibitor Overview

- Nitric oxide (NO) pathway: Release of NO → increase intracellular cGMP → vasodilation
  - PDE-5, predominant PDE in pulmonary vasculature, responsible for degradation of cGMP
- PDE-5 inhibitors increase concentration of cGMP resulting in vasodilation

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. April 2015.
Adcirca® (tadalafil) US Prescribing Information. Eli Lilly and Company. April 2015.

PDE-5 Inhibitors: Patient Considerations

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

Guanylate Cyclase Stimulator

- Novel mechanism
- First non-WHO Group 1 approved indication
- Nitric oxide (NO) pathway: NO → guanylate cyclase → increase cGMP → vasodilation
  - Riociguat: soluble guanylate cyclase stimulator (sGC); works both independently of NO or to augment endogenous NO

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

<table>
<tr><th colspan="4">Riociguat</th></tr>
<tr><th>How Supplied</th><th colspan="2">REMS</th><th>Properties</th><th>CI/P</th></tr>
<tr><td rowspan="2">Adempas® 0.5 mg, 1 mg, 1.5 mg, 2 mg, 2.5 mg tablets</td><td colspan="2">Teratogenicity. FRP must enroll in Adempas REMS Program</td><td rowspan="3">T½ ~12 hrs in PAH pts. Substrate of P-gp and BCRP, metabolized by CYP-1A1, 3A, 2C8, 2J2.</td><td rowspan="3">CI: Pregnancy, nitrates, PDE-5i. Caution with hypotension, PVOD, bleeding, smokers.</td></tr>
<tr><td>FC</td><td>Dose</td></tr>
<tr><td>Administration
Oral tablets</td><td>II-III</td><td>0.5 to 1 mg TID, titrated q2weeks to max 2.5 mg TID</td></tr>
</table>

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

sGC Patient Considerations

- Females of reproductive potential
- Ability or willingness to comply with mandatory labs and enrollments (REMS requirements)
- Special enrollment for REMS programs
- Need for organic nitrates or PDE-5 inhibitors
- Titrations

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 (riociguat) 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 LFTs	Monitor LFTs monthly (bosentan) Reduce dose or discontinue drug

Patient Case 5: Jane W.

- 55-year-old African American female for evaluation of PH. Referred from rheumatology for worsening SOB. Can do most daily activities but dyspnea with exertion.
- COPD, OSA, DVT/PE, Hep C, DM, SLE, hiatal hernia, diverticulitis, fibromyalgia
- SH: Tobacco 2 ppd x 35 yrs, now quit; negative EtOH; previous marijuana use
- NKDA
- FH: VTE

COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; DVT, deep vein thrombosis; NKDA, no known drug allergies; OSA, obstructive sleep apnea; PE, pulmonary embolism; SLE, systemic lupus erythematosus; VTE, venous thromboembolism

Patient Case 5 Jane W. Continued

Medications:

- Singulair 10 mg daily
- Advair 250/50 mg BID
- Albuterol as needed
- Lansoprazole 30 mg BID
- Spiriva 1 puff daily
- Warfarin 5 mg daily
- Prednisone 5 mg daily
- Simvastatin 20 mg daily
- Amitriptyline 50 mg daily
- Bupropion 150 mg daily
- Calcium carbonate 3 TID
- Cyclobenzaprine 10 mg daily
- Dicyclomine 20 mg TID
- Vitamin D 50,000 units once weekly
- Gabapentin 300 mg TID
- Insulin glargine 14 units subcutaneously once daily
- Plaquenil 400 mg daily

Patient Case 5 Jane W. Continued

- Labs/Vitals/PE
  - BP 100/64 mm Hg, HR 95 bpm
  - **BNP: 4**
  - TSH, T4 normal
  - C3 elevated
  - Hep B surface ag and Hep C Ab positive
  - ANA not detected
  - PE: **LEE**

Patient Case 5 Jane W. Continued

Pertinent Procedure Results

- ECHO: RV fx normal. PASP not assessed. **Impaired LV relaxation. c/w** DD. EF ~55 to 60%
- RHC: **mPAP 27 mm Hg**, mPCWP 12 mm Hg, **LVEDP 19 mm Hg**, RAP 11 mm Hg, RVP 13 mm Hg. CO 4.7 (fick) CI 2.5. PVR 3.2 Wood Units. Negative vasodilator challenge.
- Negative V/Q scan, of previous PE
- PFTs: Low FEV_1, normal FVC, reduced ratio. DLCO 37% pred.
- 6MWD **approximately 280 m**, no O_2 requirement

What is the most appropriate therapeutic recommendation for Jane W.?

A. Initiate tadalafil 40 mg daily
B. Initiate infused prostacyclin
C. Maximize fluid status and BP control. Ensure adherence to CPAP
D. Initiate tadalafil + ambrisentan as upfront combination therapy

WHO Group 2 Pulmonary Hypertension

Drug Class	Strength of Evidence[1]: Treatment Effects of PAH Targeted Therapies
Prostacyclin Analogues	Harmful (moderate)
Endothelin Receptor Antagonists	Harmful (weak)
Phosphodiesterase Inhibitors	Beneficial (weak)
Soluble Guanylate Cyclase Agonist	Neutral (weak)

[1] Strong: supported by multiple randomized clinical trials; moderate: supported by one clinical trial or multiple trials conflict; weak: only small or non-randomized trials available; unknown: not enough data to determine benefit

Duarte J, et al. *Future Cardiol*. 2013 May;9(3):335-49.
Bonderman D, et al. *Circulation*. 2013;128:502-511.

WHO Group 3 Pulmonary Hypertension

Drug Class	Strength of Evidence[1]: Treatment Effects of PAH Targeted Therapies
Prostacyclin Analogues	Neutral (weak)
Endothelin Receptor Antagonists	Neutral (weak)
Phosphodiesterase Inhibitors	Harmful (weak)
Soluble Guanylate Cyclase Agonist	Unknown

[1] Strong: supported by multiple randomized clinical trials; moderate: supported by one clinical trial or multiple trials conflict; weak: only small or non-randomized trials available; unknown: not enough data to determine benefit

Duarte J, et al. *Future Cardiol*. 2013 May;9(3):335-49.

WHO Group 4 Pulmonary Hypertension

Drug Class	Strength of Evidence[1]: Treatment Effects of PAH Targeted Therapies
Prostacyclin Analogues	Beneficial (weak)
Endothelin Receptor Antagonists	Neutral (moderate)
Phosphodiesterase Inhibitors	Beneficial (weak)
Soluble Guanylate Cyclase Agonist	Beneficial (strong)

[1] Strong: supported by multiple randomized clinical trials; moderate: supported by one clinical trial or multiple trials conflict; weak: only small or non-randomized trials available; unknown: not enough data to determine benefit

Duarte J, et al. *Future Cardiol*. 2013 May;9(3):335-49.
Ghofrani H, et al. *N Engl J Med*. 2013;369:319-29.

WHO Group 5 Pulmonary Hypertension

Drug Class	Strength of Evidence[1]: Treatment Effects of PAH Targeted Therapies
Prostacyclin Analogues	Unknown
Endothelin Receptor Antagonists	Unknown
Phosphodiesterase Inhibitors	Unknown
Soluble Guanylate Cyclase Agonist	Unknown

[1] Strong: supported by multiple randomized clinical trials; moderate: supported by one clinical trial or multiple trials conflict; weak: only small or non-randomized trials available; unknown: not enough data to determine benefit

Duarte J, et al. *Future Cardiol*. 2013 May;9(3):335-49.

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

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**

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

Education of Patient and Caregiver

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

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

Summary

- Evolution in PAH therapy options has created new opportunities for individualizing therapy
- PAH therapies require a multi-disciplinary team of healthcare providers with specialized training
- Selection of initial therapy largely depends upon severity of disease at diagnosis
- Pharmacists are an important part of the inter-professional PAH team and many opportunities are available to promote improved patient care