PULMONARY ARTERIAL HYPERTENSION

Practice Points for Pharmacists to Improve Patient Outcomes

Supported by an educational grant from Actelion Pharmaceuticals US, Inc., a Janssen Pharmaceutical Company of Johnson & Johnson.

Jointly provided by Center for Independent Healthcare Education and Vemco MedEd

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Introduction: Burden of PAH

- Pulmonary arterial hypertension (PAH) is a serious and rapidly progressive cardiopulmonary disease
- Associated with 5-year survival of 43.8% to 72.7% in newly diagnosed patients (based on functional class at time of diagnosis)
- Prevalence estimated at 6 to 26 people per million in US and Europe
- Higher incidence with some associated conditions (scleroderma, 6–60%)
- More common in women (65–80%)
- Recent registries show age at first diagnosis higher than previously thought (50+ years)
- Delay in symptom onset to diagnosis (1.9 to 3.9 years)

Benza RL, et al. *Chest.* 2012;142(2):448-456. ; Badesch DB, et al. *Chest*. 2010;137:376-87.; Farber, et al. *Chest*. 2015;148:1043-54.
McGoon MD, et al. *J Am Coll Cardiol*. 2013;62: D51-9.; Strange G, et al. *Pulm Circ*. 2013; 3:89-94.; Badlam JB, et al. *Chest*. 2021; 159:311-327.

6th World Symposium on PH: Modified Classification of PH

1. Pulmonary arterial hypertension

- 1.1 Idiopathic PAH
- 1.2 Heritable PAH
- 1.3 Drug- and toxin-induced PAH
- 1.4 PAH Associated with
  - 1.4.1 Connective tissue disease
  - 1.4.2 HIV infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart diseases
  - 1.4.5 Schistosomiasis
- 1.5 PAH long-term responders to calcium channel blocker therapy
- 1.6 PAH with overt features of venous/capillaries (PVOD/PCH) involvement
- 1.7 Persistent PH of the newborn syndrome

2. PH due to LHD

- 2.1 PH due to heart failure with preserved LVEF
- 2.2 PH due to heart failure with reduced LVEF
- 2.3 Valvular disease
- 2.4 Congenital/acquired cardiovascular conditions leading to post-capillary PH

3. PH due to lung diseases and/or hypoxia

- 3.1 Obstructive lung disease
- 3.2 Restrictive lung disease
- 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
- 3.4 Hypoxia without lung disease
- 3.5 Developmental lung diseases

4. PH due to pulmonary artery obstructions

- 4.1 Chronic thromboembolic PH
- 4.2 Developmental lung diseases

5. PH with unclear multifactorial mechanisms

- 5.1 Hematological disorders
- 5.2 Systemic disorders and metabolic
- 5.3 Others
- 5.4 Complex congenital heart disease

6th WSPH Consensus documents: Hemodynamic definition and clinical classification of PH. 2019.

United States Pulmonary Hypertension Scientific Registry (USPHSR)

- WHO Group 1 Classification by Clinical Criteria
  - 44% IPAH, 51% APAH (predominantly CTD), 4% FPAH, 1% PVOD/PCH
- WHO Group 1 Classification *AFTER* Genetic Testing
  - 36% IPAH, 49% APAH, 15% FPAH, 0.4% PVOD/PCH

IPAH, idiopathic PAH; APAH, associated PAH; CTD, connective tissue disease; FPAH, familial PAH; PVOD/PCH, PAH with overt features of venous/capillaries involvement

Badlam JB, et al. *Chest*. 2021;159:311-327.

Genetic Polymorphisms in PAH

- Genetic polymorphisms with causal association of developing PAH
  - Higher level of evidence:
    BMPR2; *EIF2AK4*; *TBX4*; *ATP13A3*; *GDF2*; *SOX17*; *AQP1*; *ACVRL1*; *SMAD9*; *ENG*; *KCNK3*; *CAV1*
  - Lower level of evidence:
    SMAD4; *SMAD1*; *KLF2*; *BMPR1B*; *KCNA5*

Morrell NW, et al. *Eur Respir J*. 2019;53:1801899; DOI: 10.1183/13993003.01899-2018.

Drug- and Toxin-Induced PAH

Definite	Possible
Aminorex	Cocaine
Fenfluramine	Phenylpropanolamine
Dexfenfluramine	L-tryptophan
Benfluorex	St. John's wort
Methamphetamines	Amphetamines
Dasatinib	Interferon α and β
Toxic rapeseed oil	Alkylating agents
	Bosutinib
	Direct-acting antiviral agents against HCV
	Leflunomide
	Indirubin (Chinese herb Ding-Dai)

6th WSPH Consensus documents: Hemodynamic definition and clinical classification of PH. 2019.

Updated Hemodynamic Definitions of Pulmonary Hypertension

Table 1: Updated Hemodynamic Definitions of Pulmonary Hypertension			
Definition	**Hemodynamic Characteristics per ESC/ERS 2015 Guidelines**	**Hemodynamic Characteristics per 6th WSPH**	**Clinical Classification of PH**
Pre-capillary PH	mPAP ≥25 mm Hg, PCWP ≤ 15 mm Hg	mPAP > 20 mm Hg, PCWP ≤ 15 mm Hg PVR ≥ 3 WU	1. PAH 3. PH due to lung disease and/or hypoxemia 4. CTEPH 5. PH with unclear or multifactorial mechanisms
Isolated post-capillary PH (IpcPH)	mPAP ≥25 mm Hg, PCWP > 15 mm Hg DPG < 7 mmHg and/or PVR ≤ 3 WU	mPAP > 20 mm Hg, PCWP > 15 mm Hg PVR < 3 WU	2. PH owing to LHD 5. PH with unclear or multifactorial mechanisms
Combined post- and pre-capillary PH (CpcPH)	mPAP ≥ 25 mm Hg, PCWP > 15 mm Hg DPG ≥ 7 mmHg and/or PVR > 3 WU	mPAP > 20 mm Hg, PCWP > 15 mm Hg PVR ≥ 3 WU	2. PH owing to LHD 5. PH with unclear or multifactorial mechanisms

CTEPH: chronic thromboembolic PH; DPG: diastolic pressure gradient; LHD: left heart disease; mPAP: mean pulmonary artery pressure; PCWP: pulmonary capillary wedge pressure; PH: pulmonary hypertension; PAH: pulmonary arterial hypertension; WU: wood units

6th WSPH Consensus documents: Hemodynamic definition and clinical classification of PH. 2019.

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.

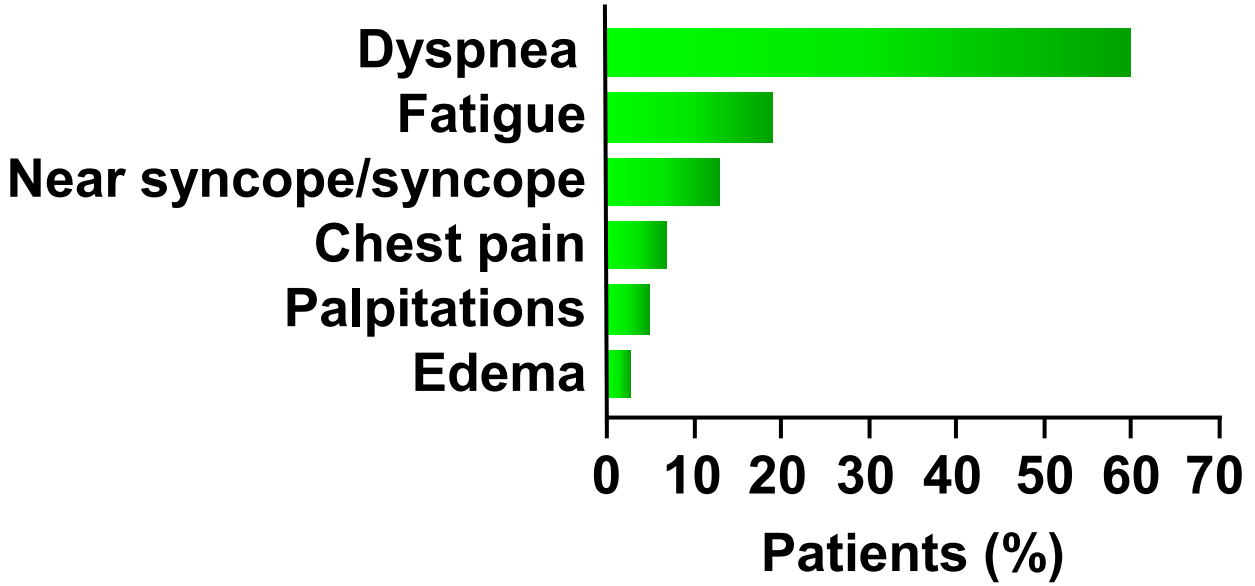
DOE, dyspnea on exertion; LEE, lower extremity edema; SOB, shortness of breath

Question

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

1. Dyspnea on exertion and fatigue
2. Lower extremity edema
3. Chest tightness
4. 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

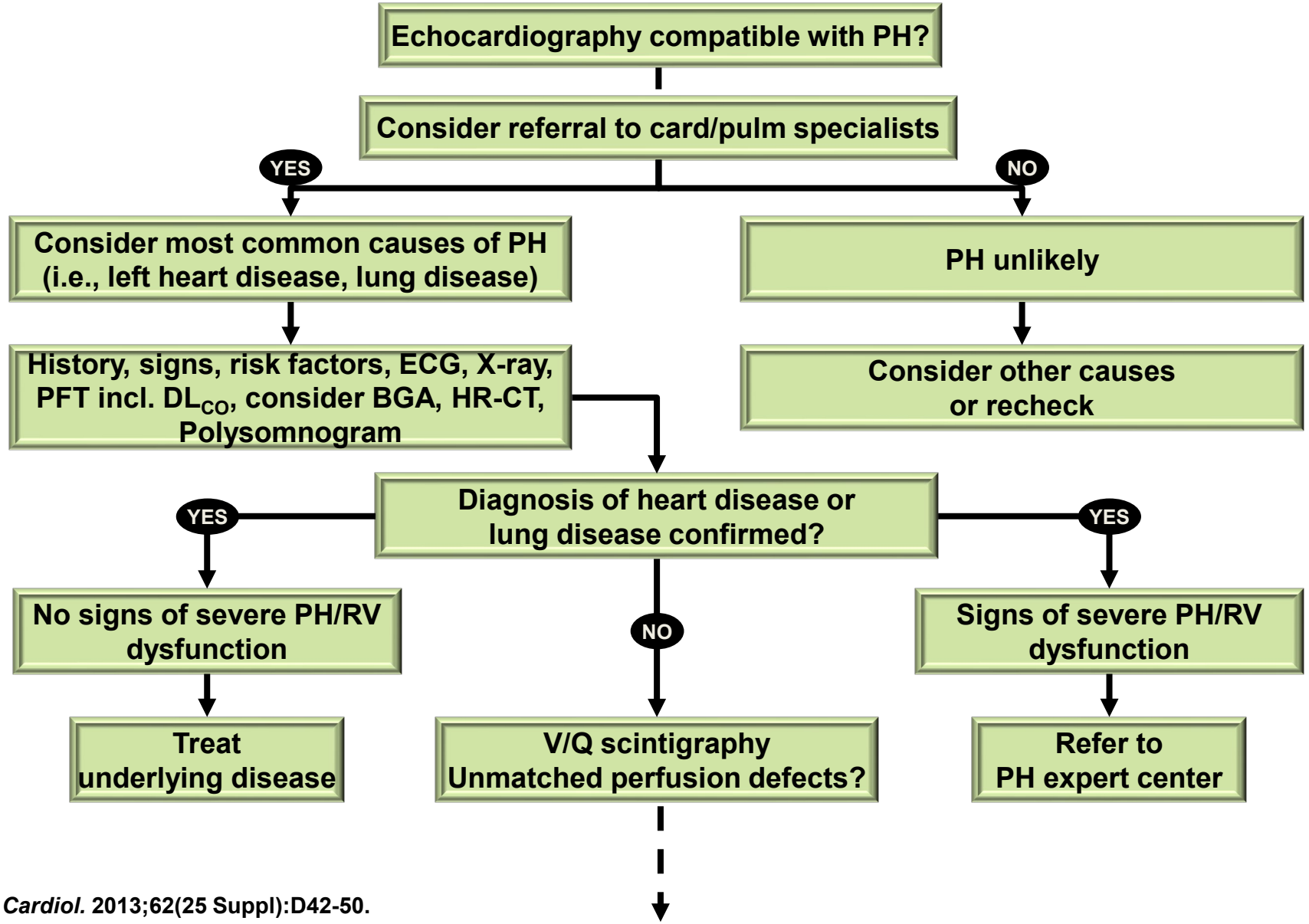
Multiple educational efforts

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

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

1. Dyspnea on exertion and fatigue
2. Lower extremity edema
3. Chest tightness
4. **All of the above**

PAH Diagnostic Algorithm



Hoeper MM, et al. *J Am Coll Cardiol.* 2013;62(25 Suppl):D42-50.

Right Heart Catheterization

- Mandatory for definitive diagnosis of PAH
  - mPAP >20 mm Hg ***(prior clinical trials used ≥25 mm Hg threshold)***
  - PCWP ≤15 mm Hg
  - PVR ≥3 WU
- Assess for: Acute Vasodilator Response
  - Fall in mPAP ≥10 mm Hg
  - mPAP (absolute) ≤40 mm Hg
  - No change in CO (normal 2.5–4.0 L/min/m^2)

6th WSPH Consensus documents: Hemodynamic definition and clinical classification of PH. 2019.

WHO Functional Classification

Class	Description	Example
I	No limitation of usual physical activity; ordinary physical activity does not cause dyspnea, chest pain, fatigue or other symptoms.	The patient with no symptoms of PAH with exercise, regular daily activity, or at rest
II	Slight limitations of physical activity; ordinary physical activity produces dyspnea, fatigue, chest pain, or near syncope; no symptoms at rest	The patient may be slightly limited by normal activities such as housecleaning, walking, or climbing stairs; but generally, not enough to avoid activities
III	Marked limitation of physical activity, less than ordinary physical activity produces dyspnea, fatigue, chest pain, or near syncope; no symptoms at rest	The patient is generally substantially limited by normal activities and may need to take frequent breaks or avoid certain activities
IV	Unable to perform any physical activity without symptoms; dyspnea and/or fatigue present at rest; symptoms are increased by almost any physical activity	The patient is severely limited with normal activity and most often has symptoms while at rest.

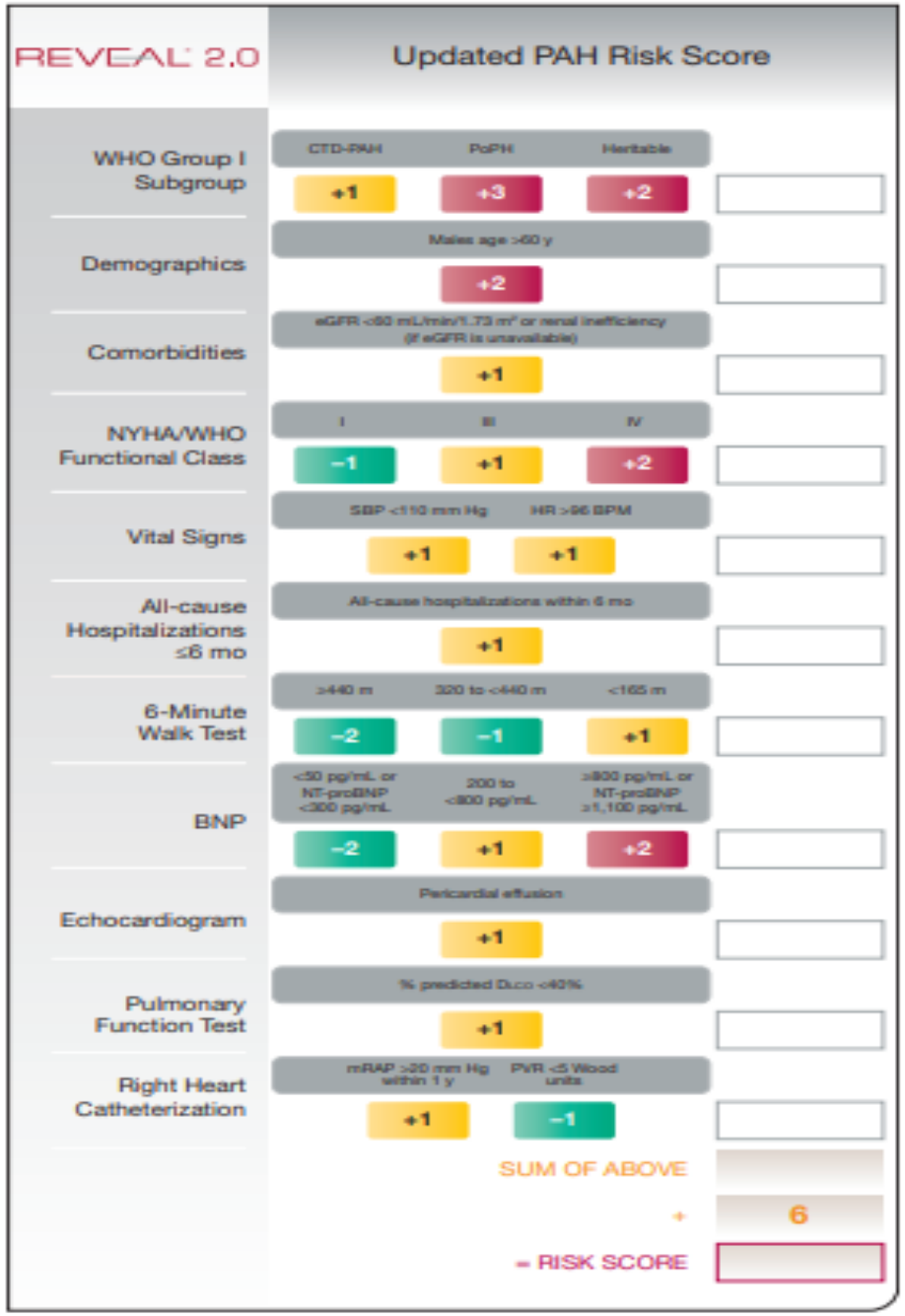
McLaughlin VV, et al. *Circulation*. 2009;119; 2250-2294.
McGoon M, et al. *CHEST*. 2004; 126:14S-34S.

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 >15ml/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%

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

REVEAL 2.0 Risk Calculator



Existing variables with unchanged risk points/cut-points

- PAH associated with connective tissue disease
- Heritable PAH
- Renal insufficiency
- Males age >60 y
- Systolic blood pressure <110 mm Hg
- Pericardial effusion
- Mean right atrial pressure ≥20 mm Hg within 1 y

Existing variables with revised risk points/cut-points

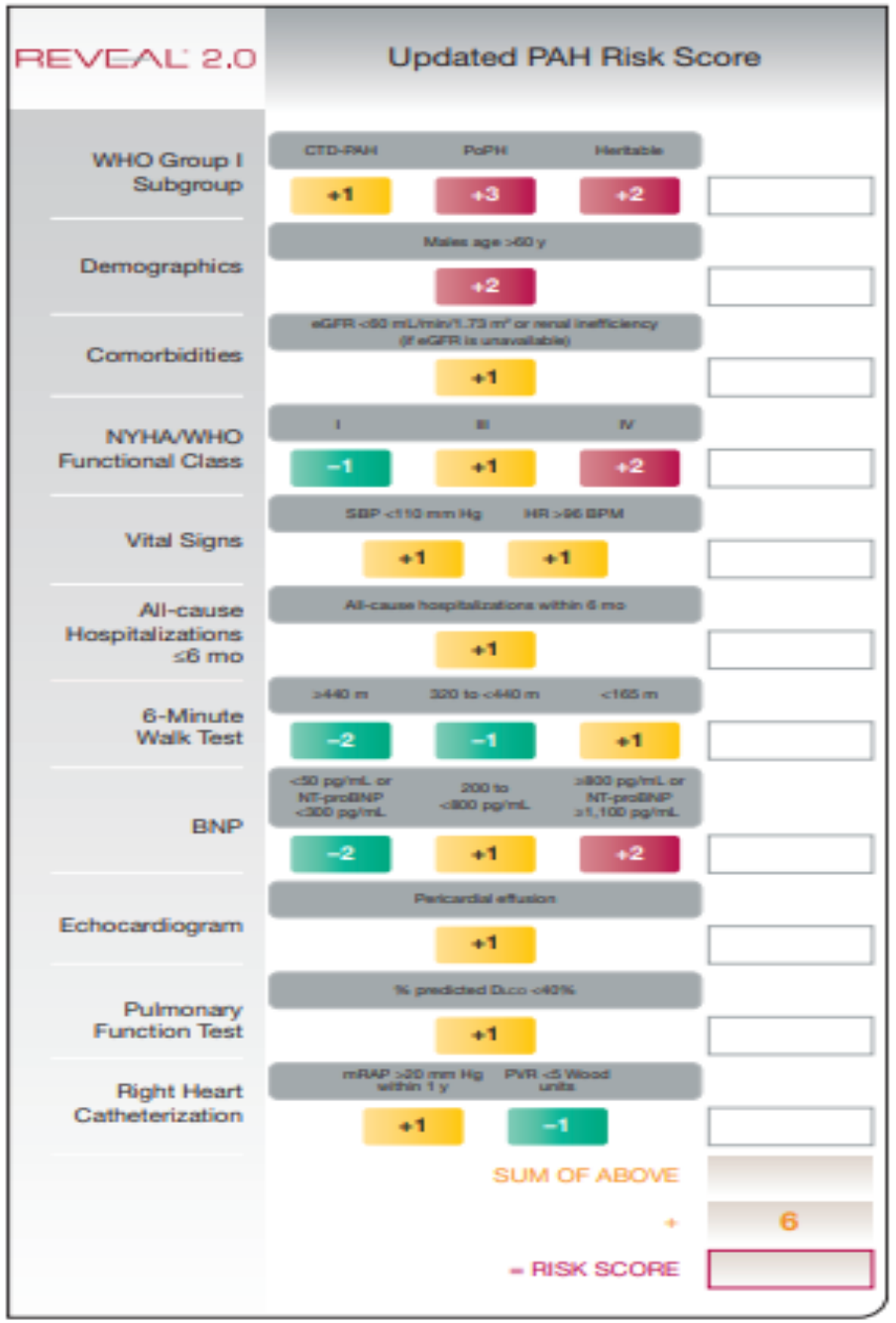
- BNP/NT-proBNP
- Heart rate
- 6MWD
- Pulmonary vascular resistance
- PAH associated with portopulmonary hypertension
- Percent predicted DLco
- NYHA/WHO functional class

New/revised variables

- Hospitalizations within the last 6 mo
- eGFR <60 mL/min/1.73 m^2 or renal insufficiency if missing eGFR

Risk score		Predicted 1-year mortality
≤ 6	LOW RISK	< 5%; 1.9% (1.1-2.7%)
7-8	INTERMEDIATE RISK	5 to 10%; 6.5% (4.7-8.4%)
≥9	HIGH RISK	>10%; 25.8% (22.7-28.9%)

Chest 2019;156:323-37.



REVEAL Lite 2 Risk Calculator

- Simplified method for routine use
- Uses fewer variables:
  - WHO FC
  - SBP
  - HR
  - 6MWD
  - BNP/nT-pro BNP
  - Renal insufficiency

Benza RL, et al. *CHEST*. 2021;159:337-346.

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, **CKD**
- 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. (cont'd)

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, PVR 10 Wood units
- **6MWD ~100 m**, frequent stops and continuous O_2 requirement
- No other tests available for review

Using the information available, calculate Donna K's 1-year mortality risk according to REVEAL 2.0.

Donna K.'s REVEAL Score UDPATE

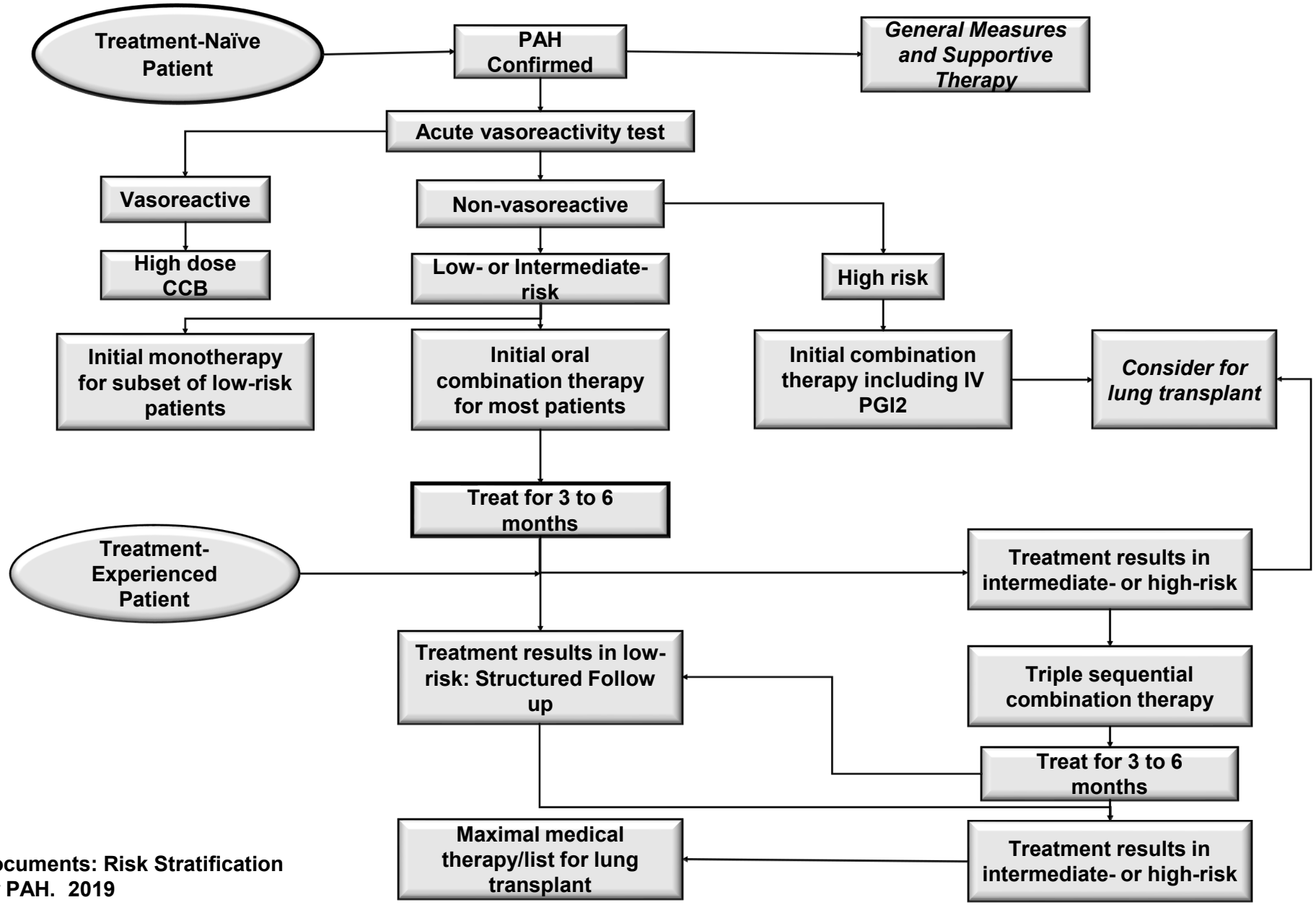
WHO Group I Subgroup	
☑ CTD-PAH	1
☐ PoPH	0
☐ Heritable	0
Comorbidities	
☑ eGFR < 60 ml/min/1.73m3 or Renal Insufficiency	1
Demographics	
☐ Males Age > 60 yrs	0
NYHA/WHO Functional Class	
☐ I	0
☐ III	0
☑ IV	2
Vital Signs	
☑ SBP < 110 mmHg	1
☐ HR > 96 BPMs	0
All-Cause Hospitalizations ≤6 mo	
☑ All-cause hospitalization within 6 mo	1
6-Minute Walk Test	
☐ ≥ 440 m	0
☐ 320 to < 440 m	0
☑ < 165 m	1
BNP	
☐ < 50 pg/mL or NT-proBNP < 300 pg/mL	0
☐ 200 to < 800 pg/mL	0
☑ ≥ 800 pg/mL or NT-proBNP ≥ 1,100 pg/mL	2
Echocardiogram	
☐ Pericardial Effusion	0
Pulmonary Function Test	
☐ % pred. DLco <40%	0
Right Heart Catheterization	
☐ mRAP > 20 mmHg within 1 year	0
☐ PVR < 5 Wood units	0
	15

Risk score		Predicted 1-year mortality
≤ 6	LOW RISK	< 5%; 1.9% (1.1-2.7%)
7-8	INTERMEDIATE RISK	5 to 10%; 6.5% (4.7-8.4%)
≥9	HIGH RISK	>10%; 25.8% (22.7-28.9%)

REVEAL 2.0 score: 15

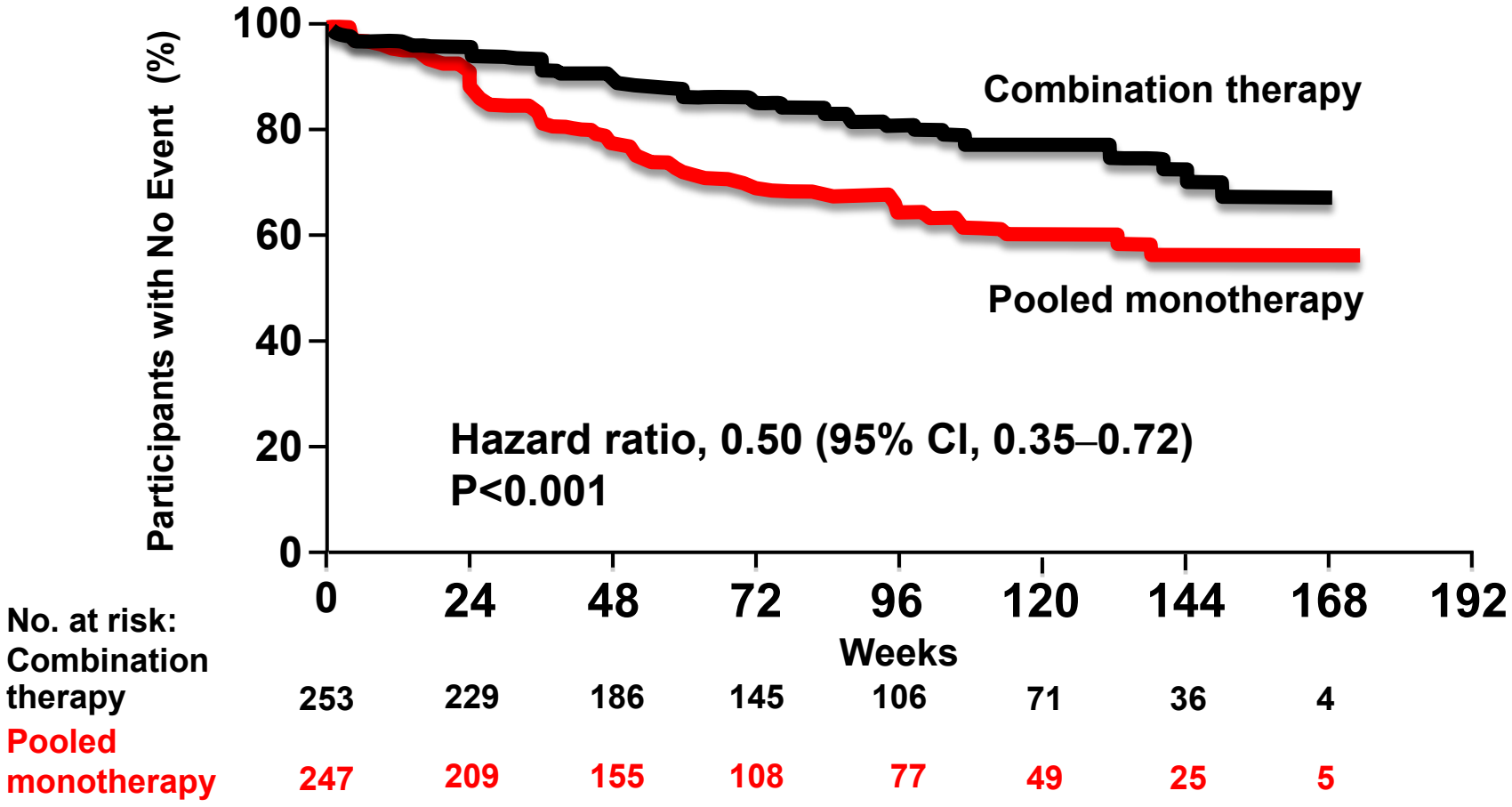
REVEAL Lite 2: 13

6th WSPH Updated Treatment Algorithm



6th WSPH Consensus documents: Risk Stratification and Medical Therapy for PAH. 2019

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



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

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

Additional Combination Therapy Evidence

SERAPHIN

- Event-driven phase 3 trial evaluating long-term effects of macitentan in patients on "background therapy" compared to placebo
  - 97.4% on PDE-5i and 5.4% inhaled or oral PGI2
  - 38% RR in morbidity and mortality events
  - Background therapy + macitentan had 37% RR in risk of hospitalization (HR 0.63; 95% CL 0.41–0.96)

GRIPHON

- 1156 patients randomized to placebo (n=582) or selexipag (n=574)
  - 20% naïve, 47% on ERA or PDE-5i; 33% on ERA+PDE-5i
  - 376 pts on dual combo tx had treatment effect consistent with overall population 37% RR in morbidity/mortality events

Coghlan JG, et al. *Am J Cardiovasc Drugs*. 2018;18(1):37-47.
Jansa P, et al. *Am J Cardiovasc Drugs*. 2018;18(1):1-11.

What About Upfront Triple Combination Therapy?

- TRITON Study
  - N=247 newly diagnosed, treatment naïve PAH patients
  - Randomized to initial triple (macitentan+tadalafil+selexipag) or initial double therapy (macitentan+tadalafil)
  - Primary outcome: change in PVR at 26 weeks
  - Secondary outcomes: change in 6MWD, BNP, time to first disease progression event
  - RESULTS:
    - Both dual and triple regimens similarly improved PVR and 6MWD at 26 weeks
    - Further research recommended:
      - 41% reduction in risk of first disease progression events was observed with initial triple vs initial double **(p=0.087)**
      - 2 deaths in triple group, 9 in double group

Chin KM, et al. *Am J Resp Crit Care Med*. 2020;201:A2928.

Treatment Goal: Low Risk

- Achieving/maintaining low risk status is linked with improved survival
- Achieving low risk status within the first year of diagnosis appears to be most indicative of long-term risk status

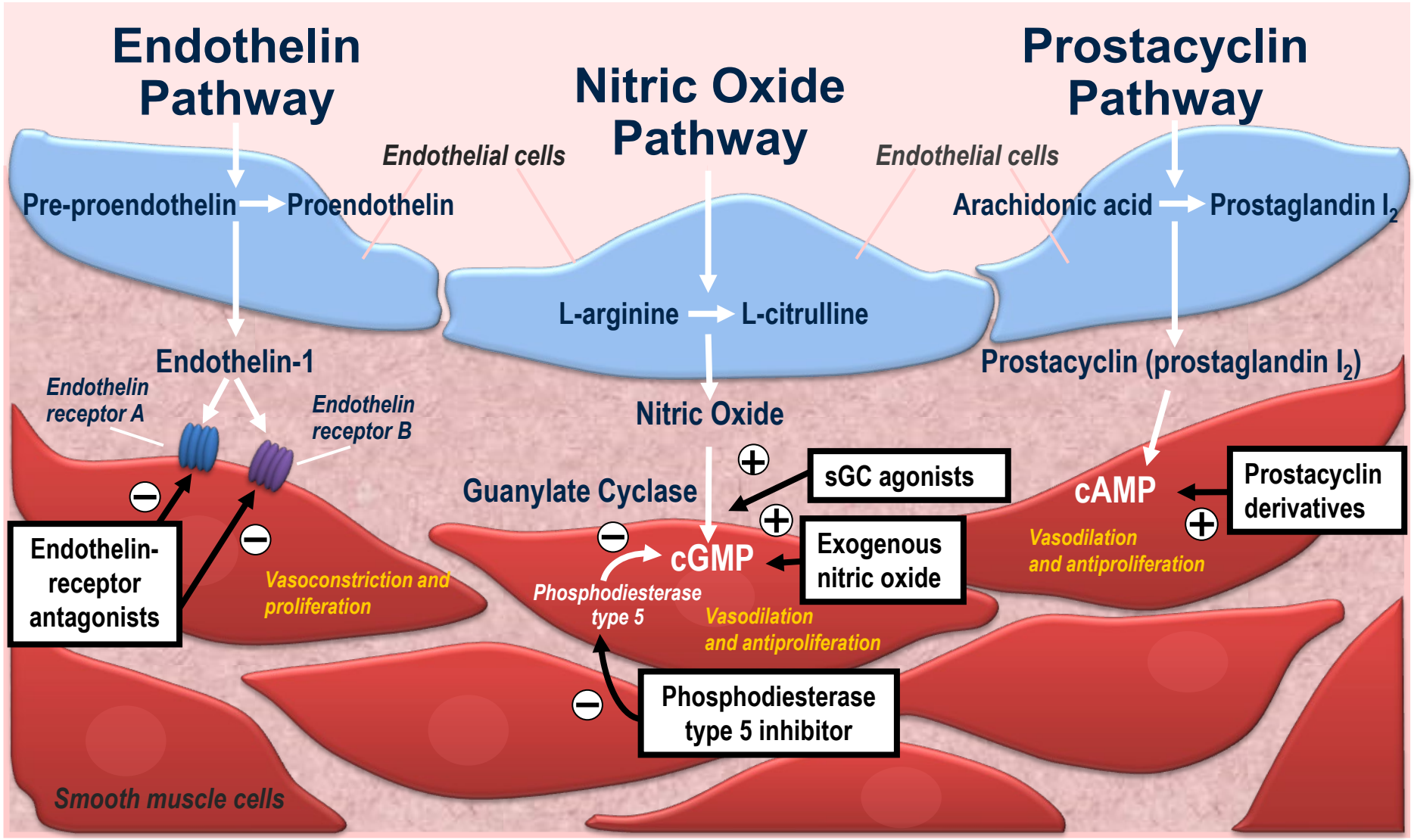
Hoeper MM, et al. *Eur Resp J*. 2017;50:1700740.
Bouzina H, et al. *ESC Heart Failure*. 2020;8:680-690.

PAH and SARS-CoV-2

- Recent US survey of 77 Care Centers for PH found reported associated mortality rate ~12% in patients with PAH with COVID-19, reported incidence similar to general population
- Big shift towards virtual visits but determining “risk status” dependent on specific tests/evaluations

Lee J, et al. *Ann Am Thorac Soc* 2020;Jul 29.

Therapeutic Targets for PAH



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

Patient Case 3: Roberta M.

- 51-year-old female with PAH admitted for worsening DOE. Currently on tadalafil and ambrisentan × 6 months with little to no improvement in symptoms, ECHO or recent RHC performed
- Plan is to schedule a hospital admission and initiate subcutaneous treprostinil

Question

Which of the Following is Most Important to Determine <u>Prior</u> to *Initiating* Infused Treprostinil?

1. Dosing weight
2. Ambulatory infusion pump type
3. Treprostinil vial concentration
4. Titration plan

Prostacyclin Analogues: IV and SQ Formulations

How Supplied	Administration	FC	Dose	Properties	CI/P/Misc
Epoprostenol Sodium **Generic, Flolan®, or Veletri® 0.5mg, 1.5mg**	Continuous IV infusion via infusion pump. Requires tunneled CVC. Flolan requires use of ice packs. Requires reconstitution.	III, IV	Initiated at 2 ng/kg/min and titrated based on response. Ongoing: 1-2 ng/kg/min q1-2 wk.	$T_{½}$ <6 min. Temp and light sensitive. Reconstituted stability dependent on formulation. Rapidly hydrolyzed in the blood.	CHF due to severe LVD. Avoid abrupt withdrawals or interruption in infusion: may result in rebound PH or death. Initiated in controlled setting. Monitor for signs of BSI.
Treprostinil Sodium **Generic, Remodulin® 1mg/mL, 2.5mg/mL, 5mg/mL, 10mg/mL in 20mL vials**	Continuous IV or SubQ infusion via infusion pump. IV requires tunneled CVC.	II-IV	Initiated at 1.25 ng/kg/min and titrated based on response Ongoing: 1.25 ng/kg/min every week or as tolerated	$T_{½}$ ~4 hours. Metabolized by CYP 2C8. Diluted: 48-hour infusion duration. Undiluted: 72-hour infusion duration.	

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

Diluent Options

Epoprostenol IV

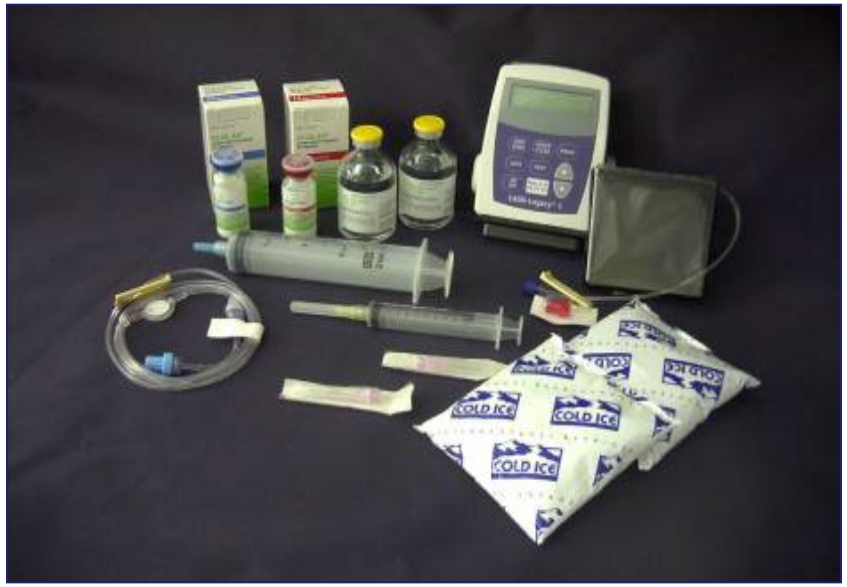
- Formulation dependent, not interchangeable
- Veletri
  - Sodium chloride 0.9% injection
  - Sterile water for injection
- Flolan*
  - Sterile diluent for Flolan
  - pH 12 sterile diluent for Flolan
- Generic epoprostenol
  - Flolan reference product:
    - sterile diluent for epoprostenol
  - Veletri reference product:
    - Sodium chloride 0.9% injection
    - Sterile water for injection

Treprostinil IV

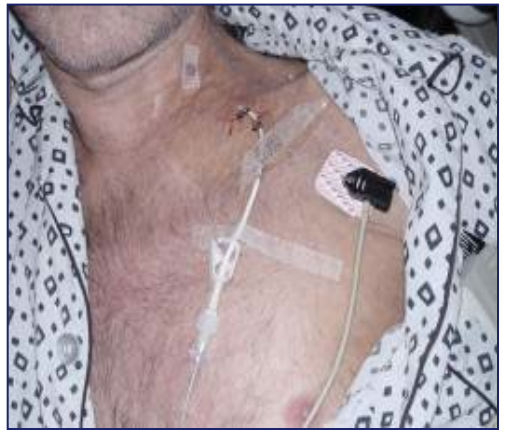
- Sodium chloride 0.9% injection
- Sterile water for injection
- High pH glycine diluent (Sterile diluent for Remodulin, treprostinil, Flolan, or epoprostenol)
  - Preferred diluent for IV treprostinil, reduced risk of Gram-negative line infections

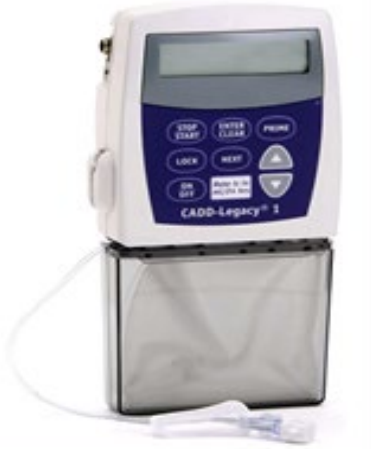
***Storage and administration recommendations differ depending on diluent selection**

Infused Administration

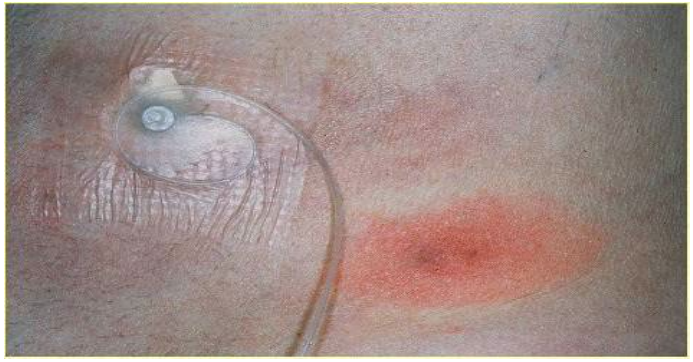


Central line for IV





Subcutaneous Catheter



Parenteral Administration Considerations

- **Dosing and administration**
  - Route/parenteral access
  - **Dosing weight**
  - Vial concentration
  - Diluent
  - Mixed concentration and total volume
  - Device specific infusion rate/units of measure
  - Titration orders
  - Timing of next reservoir change
  - Other PAH therapies

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, 2.5 mg and 5mg 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

Ventavis® (iloprost) US Prescribing Information. Actelion Pharmaceuticals US, Inc.
Tyvaso® (treprostinil) US Prescribing Information. United Therapeutics Corp.
Orenitram® (treprostinil) US Prescribing Information. United Therapeutics Corp.

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

IP Agonist

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

<table>
<tr><th colspan="4">Selexipag</th></tr>
<tr><th>How Supplied</th><th colspan="2">REMS</th><th>Properties</th><th>CI/P</th></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">$T_{½}$ ~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
Orally</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.

Which of the Following is Most Important to Determine <u>Prior</u> to *Initiating* Infused Treprostinil?

1. **Dosing weight**
2. Ambulatory infusion pump type
3. Treprostinil vial concentration
4. Titration plan

Management of Prostacyclin-Related Effects

Adverse Effect	Management Strategy
Headache	OTC analgesics, tramadol, opiates if severe
Diarrhea	Loperamide, diphenoxylate/atropine, 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 Site Pain

- Topical Agents
  - Corticosteroids
  - Anesthetic agents
  - PLO gel
- Systemic Management
  - H1 and H2 blockers
  - OTC analgesics, opioids if severe
  - GABA analogs
  - Others
- Non-pharmacologic management
  - Catheter dwell times
  - Dry insertion method
  - Cold compress
- Other strategies:
  - Pre-medicate
  - Rapid titration
  - Increase concentration

Endothelin Receptor Antagonists

Bosentan

How Supplied	REMS		Properties	CI/P
Generic, Tracleer® 62.5 mg, 125 mg tablets; 32mg tablets for oral suspension	Teratogenicity, liver toxicity. Must enroll in bosentan 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 Orally	II-IV	Initial > 12 yoa and wt > 40kg: 62.5 mg BID x 4 weeks, then increase to 125 mg BID thereafter (max 62.5mg BID if < 40 kg) Initial </= 12 yoa: weight based		

Ambrisentan

How Supplied	REMS		Properties	CI/P
Generic, Letairis® 5 mg, 10 mg tablets	Teratogenicity. FRP must enroll in ambrisentan 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 Orally	II-III	Initial: 5 mg daily, increase to 10 mg daily if tolerated		

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 Orally	Mostly II-III	10 mg po daily		

Tracleer® (bosentan) US Prescribing Information. Actelion Pharmaceuticals. Opsumit® (macitentan) US Prescribing Information. Actelion Pharmaceuticals. Letairis® (ambrisentan) US Prescribing Information. Gilead Sciences.

Patient Case 4: Susie Q

- Susie Q is a 38-yo female recently diagnosed with PAH. MD recommends initiation of tadalafil and macitentan.
- She has 2 children (2 yoa and 4 yoa) with no intention of having more children.
- Her primary birth control method is barrier (male condoms)
- What REMS steps must be taken prior to initiating macitentan?

REMS Management

- PAH therapies with REMS:
  - Liver injury
    - Bosentan
  - Teratogenicity
    - Bosentan, ambrisentan, macitentan and riociguat
- Key components:
  - Mandatory enrollment, education and ongoing counseling
  - Required provider certifications
  - Patient ability or willingness to comply with mandatory labs
  - Pharmacy dispensing restrictions
  - Baseline and monthly evaluation of safe-use conditions

Patient Case 4: Susie Q

- REMS:
  - Patient consent and enrollment in Opsumit REMS program
  - Education on teratogenicity
  - Baseline negative pregnancy test
  - 2 effective/1 highly-effective contraception
    - Barrier + hormonal contraception OR tubal ligation
  - Ongoing monthly pregnancy testing

Phosphodiesterase Type-5 Inhibitors

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		$T_{1/2}$ ~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
Generic, Adcirca® 20 mg tablets	n/a		$T_{1/2}$ ~35 hrs Metabolized by CYP3A4	CI: use with organic nitrates Avoid CrCl <30 mL/min and severe hepatic impairment Caution with SCD, PVOD.
	FC	Dose		
Administration	II-III	40mg daily		
Orally				

Revatio® (sildenafil) US Prescribing Information. Pfizer Labs.
Adcirca® (tadalafil) US Prescribing Information. United Therapeutics.

Guanylate Cyclase Stimulator

- **Novel mechanism**
- **First non-WHO Group 1-approved indication**
- **Available only through restricted distribution**
- **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">$T_{½}$ ~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
Orally</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.

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

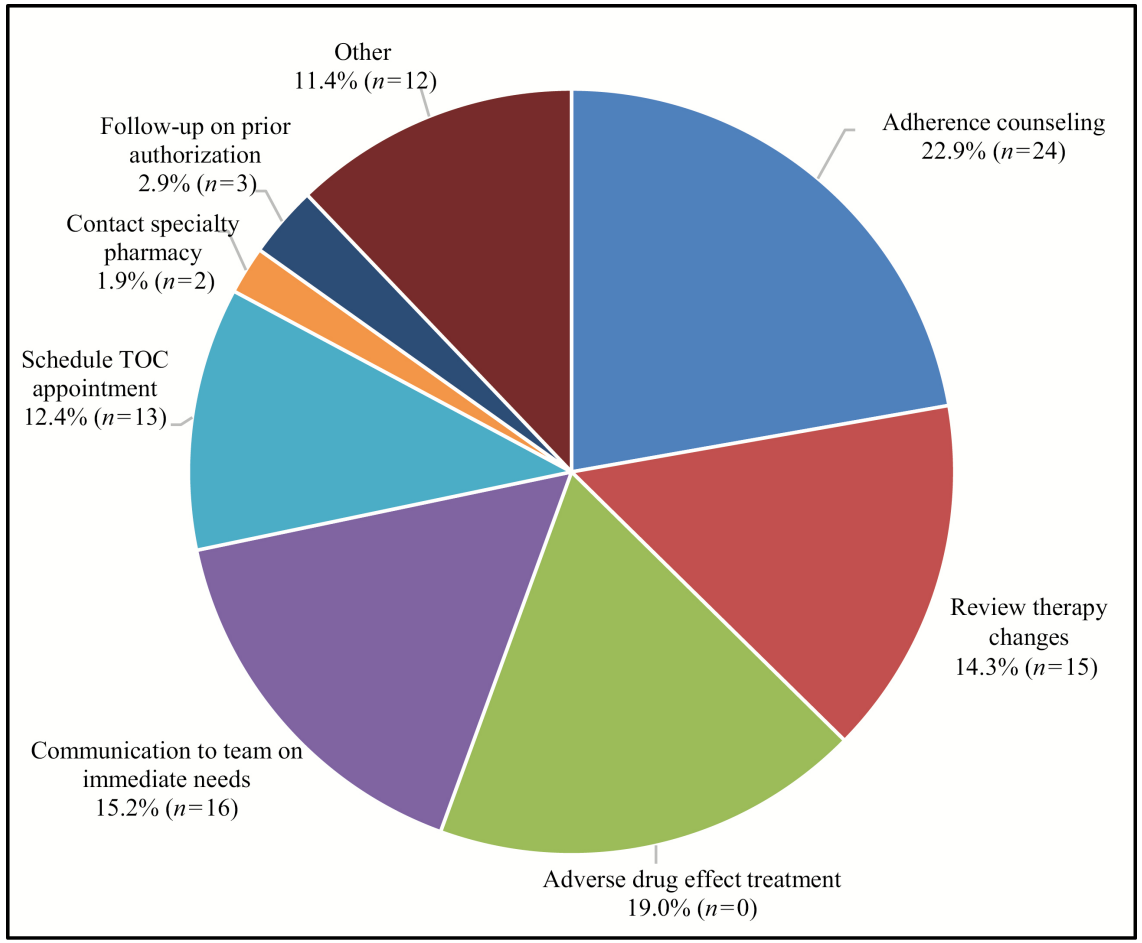
Opportunities for Pharmacists

- Medication reconciliation and history
- Education and training on targeted therapies and devices
- 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

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

Ambulatory Care Pharmacist's Transitions of Care Activities (n=105 instances)



Martirosov AL, et al. *Am J Health Syst Pharm.* 2020;77:958–965, https://doi.org/10.1093/ajhp/zxaa079.

Impact of Medication Adherence

- Medication adherence is critical!
- Non-adherence can result in:
  - Potential for rebound PAH or uncontrolled symptoms
  - Hospitalizations
  - Potential unnecessary escalation in therapy
  - Increased oxygen use
  - Worsening disease/progression
  - Death

Special Needs and Social Issues

- High rates of depression and other co-morbidities
- Patient and drug/route specific considerations
- Medication costs and lack of financial assistance resources
- Lack of necessary family or social support
- High morbidity and mortality rates
- Pregnancy generally = contraindication, high maternal mortality rates

Summary

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