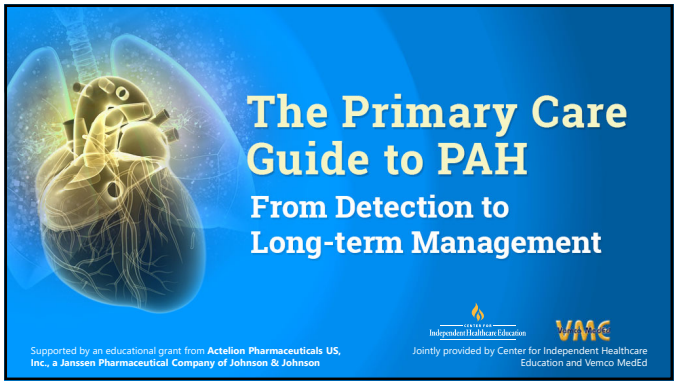


Outline

- Case presentation
- Pulmonary Hypertension definition and classification
- Clinical suspicion and screening for pulmonary hypertension
- Diagnostic strategy for PAH
- Basics of PAH management

Clinical Case: 27 y/o Woman with Chest Pain

She reports that one day prior to presentation she developed sharp, substernal chest pain during a walk with her son. This resolved after resting. Pain was 8 out of 10 without radiation and she had never experienced this previously. Chest pain was associated with shortness of breath and palpitations. She went to the clinic the following day and was referred to the hospital for complete evaluation.

Troponin was elevated at 0.16 and she was admitted to the hospital.

Clinical Case (cont.)

- **Past Medical History:**
  - Raynaud's syndrome
  - Migraine HA
  - Anemia
  - Gestational DM type 2
- **Past Surgical History:**
  - C-section last year
  - Appy 7 years ago
- **Allergies:**
  - PCN: facial swelling
- **Meds:**
  - None
- **Family History:**
  - Father: DM, HTN
  - Mother: healthy
  - Brother: DM
- **Social History:**
  - Lives with husband and 3 children
  - Works in daycare
  - Never smoker
  - Denies EtOH or illicits

Physical Exam

Temp 97.7/36.5 **BP** 103/77 **HR** 107 **RR** 20 **SpO2** 100% RA
Gen: NAD, alert and cooperative
HEENT: EOMI, PERRL, moist oral mucosa
Neck: no appreciable JVD, no LAD
Heart: S1/S2 normal, no murmurs
Lung: CTA b/l, no wheeze or focal adventitious sounds
Abd: soft, NT, DF, +BS
Ext: no LE edema, 2+ distal pulses
Skin: no rashes
Neuro: AOx3, sensation and strength intact grossly

ECG: Sinus tachycardia, nonspecific T wave inversion in infralateral leads

Plan: Admit to hospital, trend troponin, CT PE protocol, Echocardiogram

What is Pulmonary Hypertension[1]

- Diagnosed by RHC with mPAP ≥ 25mmHg
- Normal mPAP ≤ 20mmHg at rest
- Borderline (21-24) prognostic significance in lung disease and CTD[2,3]
- PVR >3 WU (PVR = ΔPressure/CO)
  - Normal PVR in some secondary PH
- PAH defined with PAWP ≤15mmHg
  - Normal ≤ 12 mmHg

[1]Hoeper et al. *J Am Coll Cardiol.* 2013; 62: D42-50.
[2]Kovacs et al. *Eur Res J.* 2009;34:888–94.
[3]Kovacs et al. *Am J Respir Crit Care Med.* 2009;180:881-6.

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. 2018

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.

Updated Hemodynamic Definitions of Pulmonary Hypertension

Table 1: Updated Hemodynamic Definitions of Pulmonary Hypertension

Definition	Hemodynamic Characteristics	Hemodynamic	Clinical Classification
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
[illegible]	DPG < 7 mmHg and/or PVR ≤ 3 WU	PVR < 3 WU	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

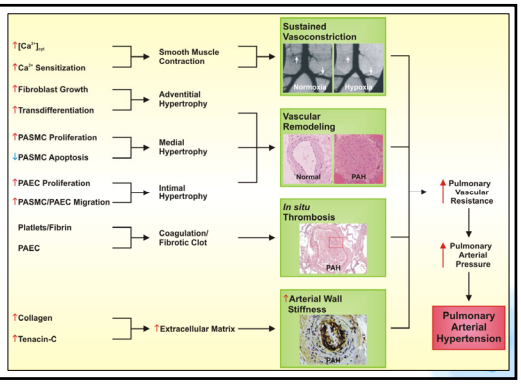
6th WSPH Consensus documents: Hemodynamic definition and clinical classification of PH. 2018

Burden of PAH

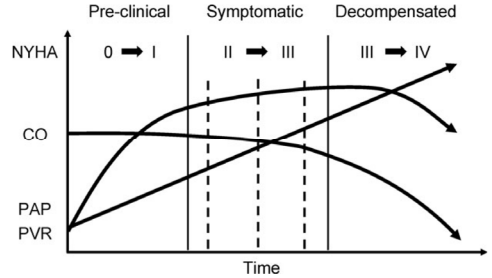
- Pulmonary arterial hypertension (PAH) is a serious and rapidly progressive cardiopulmonary disease
- Difficult to diagnose, symptoms are often non-specific
- Sustained PAH leads to right heart failure, the leading cause of death in this population
- Associated with 1-year mortality of 10–15%
- Rare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

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

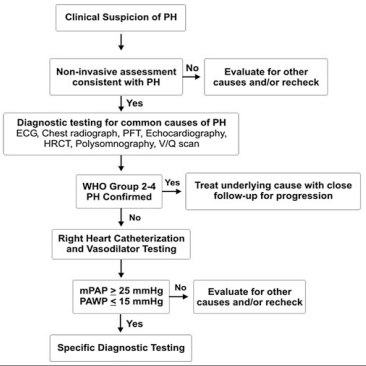
Pathogenesis of PAH



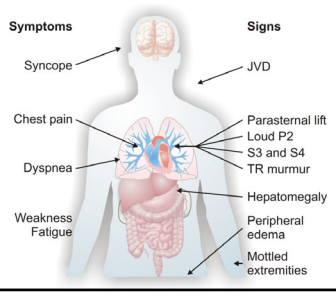
Clinical Course of PAH



Evaluation



Clinical Suspicion of Pulmonary Hypertension



Echocardiography for Screening

Noninvasive technique to evaluate cardiac structure and function

Echo diagnosis	Tricuspid regurgitation velocity	PA systolic pressure	Additional Variables
Unlikely	≤2.8 m/s	≤36 mmHg	None
Possible	≤2.8 m/s	≤36 mmHg	Yes
Possible	2.9 – 3.4 m/s	37-50 mmHg	Yes or No
Likely	≥3.4 m/s	≥50 mmHg	Yes or No

McLaughlin et al. *J Am Coll Cardiol.* 2009;53(17):1573-619.

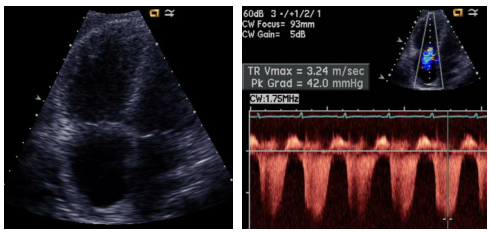
Echocardiography Use in PH

- TR jet velocity is most commonly used
  - $P_{RV} - P_{RA} = 4 (TR_V)^2$
- Decreased PAAT or TAPSE also predictive of pulmonary artery pressures[2,3]
- Can both under and overestimate
- Can be used prognostically and to monitor response to therapy

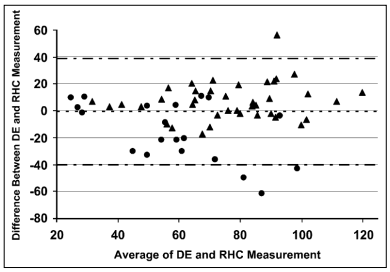
[1]Yock and Popp. *Circulation.* 1984; 70: 657–662.
[2]Yared et al. *J Am Soc Echocardiogr.* 2011; 24: 687–692.
[3]Ghio et al. *Int J Cardiol.* 2010; 140: 272–278.

Back to Clinical Case: 27 y/o Woman with Chest Pain

Echocardiogram is performed and pulmonary consulted following results.



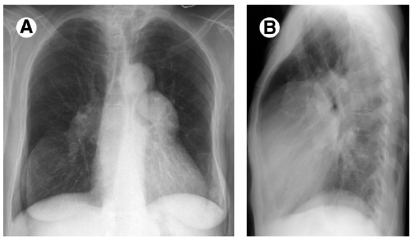
Echocardiography



Fisher et al. *Am J Respir Crit Care Med.* 2009; 179(7):615-21.

Chest Radiograph

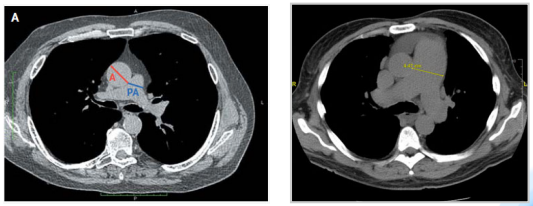
Can suggest PH and help elucidate underlying cardiopulmonary diseases



Frazier and Burke. *Semin Ultrasound CT MR.* 2012;33(6):535-51.

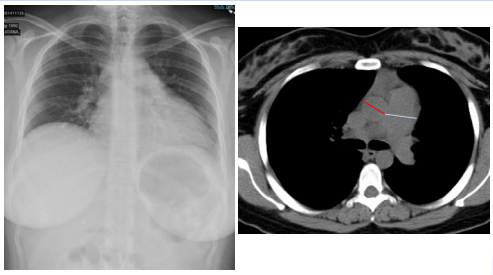
CT Thorax

PA : Ao ratio > 1

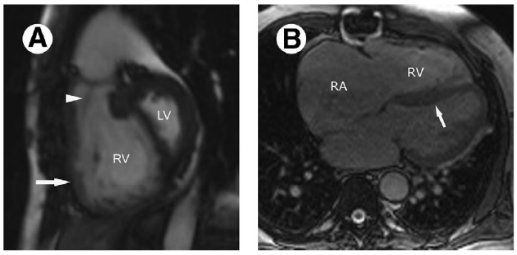


Wells et al. *N Engl J Med.* 2012; 367: 913-21.

Back to Clinical Case: 27 y/o Woman with Chest Pain



Cardiac MR



Frazier and Burke. *Semin Ultrasound CT MR.* 2012;33(6):535-51.

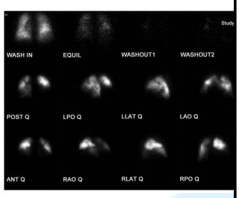
Cardiac MR

- Best use is for evaluating RV size and function i.e. RVEF[1]
- Ratio of RV:LV mass shown to predict PH[2]
- Elevated RV end-diastolic volume associated with mortality[3]
- Myocardial enhancement associated with fibrosis/scar – may be related to RV dysfunction[4]

[1]Fakhri et al. *Heart Fail Clin.* 2012 Jul;8(3):353-72.
[2]Saba et al. *Eur Respir J.* 2002;20(6):1519–24.
[3]van Wolferen et al. *Eur Heart J.* 2007;28(10):1250–7.
[4]McCann et al. *AJR Am J Roentgenol.* 2007;188(2): 349–55.

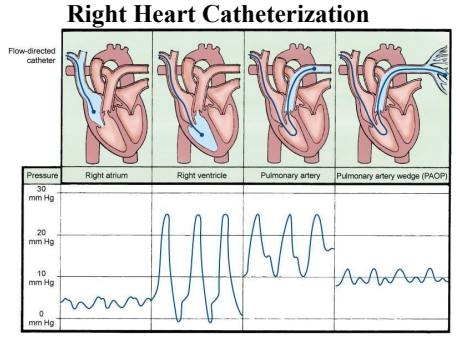
V/Q Scan

- Sensitivity better than CT for CTEPH[1]
  - 97.4% vs 51%
- Can delineate proximal vs distal disease
- Several mismatched defects are common
- Normal perfusion excludes operable CTEPH



[1]Tunariu et al. *J Nucl Med* 2007; 48:680-4.
Auger et al. *Pulm Circ.* 2012; 2:155-62

Right Heart Catheterization



Braunwald E et al. Braunwald's Heart Disease. 8th edition.

Right Heart Catheterization

- Necessary to diagnosis of PAH
- Prognostic value
  - RAP, CO, PVR
- Important for therapeutic decisions
  - Vasoreactivity testing
- Important that data is accurate
  - Review tracings

Back to Clinical Case: 27 y/o Woman with Chest Pain

Concern for pulmonary hypertension given elevated PASP and RV dysfunction; referred for RHC.

RA: 10/8/7 (a/v/end diastolic)
RV: 60/0/13 (s/d/m)
PA: 73/30/46 (s/d/m)
PAWP: 9/7/7 (a/v/end diastolic)
Fick CO 2.69 Fick CI: 1.72
AO sat: 96 Pa Sat: 48
PVR: 12 Woods units

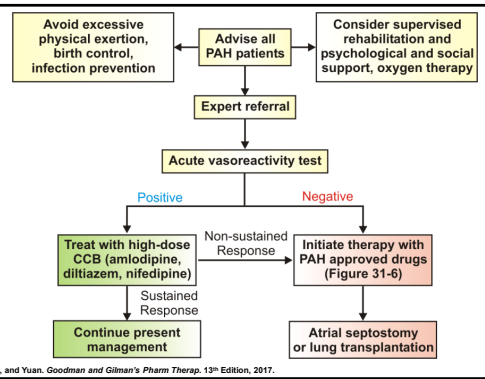
Clinical Case (cont.)

Work-up completed for PAH associated conditions:

- No history/evidence of congenital heart disease
- HIV negative
- Liver function tests normal, RUQ U/S normal
- No history using agents associated with drug/toxin associated PAH
- Anti-Scl70 and Anti-centromere antibody neg
- ANA positive with 1:640 titer
- Anti-RNP and Anti-Ro positive

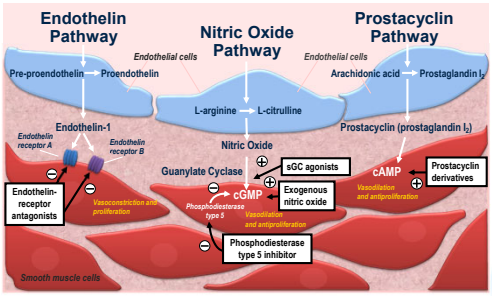
} Diagnosed with mixed connective tissue disease and started on hydroxychloroquine

I have diagnosed PAH, now what do I do?



Fraidenburg, Desai, and Yuan. *Goodman and Gilman's Pharm Therap.* 13th Edition, 2017.

Therapeutic Targets for PAH



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

PAH Approved Therapies

- PDE-5 inhibitors
  - Sildenafil, Tadalafil
- Endothelin Receptor Antagonists
  - Bosentan, Ambrisentan, Macitentan
- Prostacyclin Analogs
  - Epoprostenol, Treprostinil (oral, inhalation, subQ, IV)
  - IP receptor agonist – Selexipag
- Soluble Guanylate Cyclase Stimulator
  - Riociguat

The Evolution of PAH Therapy

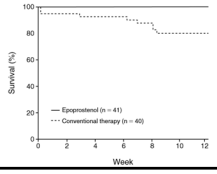
Our First Therapy - Epoprostenol

296 THE NEW ENGLAND JOURNAL OF MEDICINE Feb. 1, 1996

A COMPARISON OF CONTINUOUS INTRAVENOUS EPOPROSTENOL (PROSTACYCLIN) WITH CONVENTIONAL THERAPY FOR PRIMARY PULMONARY HYPERTENSION

ROBYN J. BARST, M.D., LEWIS J. RUBIN, M.D., WALKER A. LONG, M.D., MICHAEL D. MCGOON, M.D., STUART RICH, M.D., DAVID B. BADESCH, M.D., BERTRON M. GROVES, M.D., VICTOR F. TAPSON, M.D., ROBERT C. BOURGE, M.D., BRUCE H. BRUNDAGE, M.D., SPENCER K. KOERNER, M.D., DAVID LANGLEBEN, M.D., CESAR A. KELLER, M.D., SRINIVAS MURALI, M.D., BARRY F. URETSKY, M.D., LINDA M. CLAYTON, PHARM.D., MARIA M. JÖBSIS, B.A., SHELMER D. BLACKBURN, JR., B.A., DENISE SHORTINO, M.S., JAMES W. CROW, PH.D., FOR THE PRIMARY PULMONARY HYPERTENSION STUDY GROUP*

- FC III-IV
- Mean PA pressure ~ 60mmHg
- PVR 16 WU

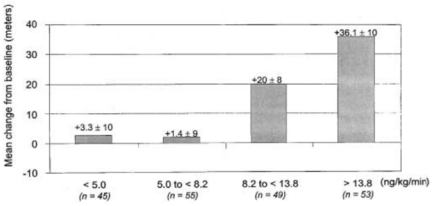


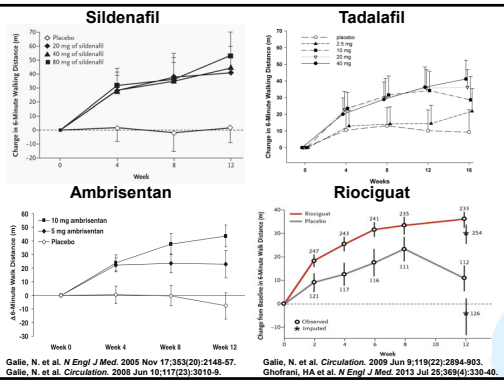
Subcutaneous Treprostinil

Continuous Subcutaneous Infusion of Treprostinil, a Prostacyclin Analogue, in Patients with Pulmonary Arterial Hypertension

A Double-blind, Randomized, Placebo-controlled Trial

GERALD SIMONNEAU, ROBYN J. BARST, NAZZARENO GALIE, ROBERT NAEIJE, STUART RICH, ROBERT C. BOURGE, ANNE KEOGH, RONALD OUDIZ, ADAANI FROST, SHELMER D. BLACKBURN, JAMES W. CROW, and LEWIS J. RUBIN, for the Treprostinil Study Group





Galie, N. et al. *N Engl J Med.* 2005 Nov 17;353(20):2148-57.
Galie, N. et al. *Circulation.* 2008 Jun 10;117(23):3010-9.
Galie, N. et al. *Circulation.* 2009 Jun 9;119(22):2894-903.
Ghofrani, HA et al. *N Engl J Med.* 2013 Jul 25;369(4):330-40.

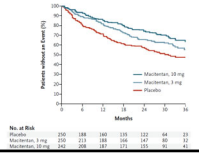
The Dawn of Event-Driven Studies in PAH

ORIGINAL ARTICLE

Macitentan and Morbidity and Mortality in Pulmonary Arterial Hypertension

Tomás Pulido, M.D., Igor Adzerikho, M.D., Richard N. Channick, M.D., Marion Delcroix, M.D., Nazzareno Galiè, M.D., Hossein-Ardeschir Ghofrani, M.D., Pavel Jansa, M.D., Zhi-Cheng Jing, M.D., Franck-Olivier Le Brun, M.Sc., Sanjay Mehta, M.D., Camilla M. Mittelholzer, Ph.D., Loic Perchenet, Ph.D., B.K.S. Sastry, M.D., Olivier Sitbon, M.D., Rogério Souza, M.D., Adam Torbicki, M.D., Xiaofeng Zeng, M.D., Lewis J. Rubin, M.D., and Gérald Simonneau, M.D., for the SERAPHIN Investigators*

- 742 subjects randomized
  - 1:1:1 placebo vs macitentan 3mg or 10mg
- FC II > III >>> IV
- PVR ~ 12 WU
- 64% on background therapy
  - 61% PDE-5i, 5% oral or inh prostacyclin
- Combined primary outcome
  - Event related to PAH worsening
  - Death



End Point	Placebo (N=250)	Macitentan, 3 mg (N=250)	Macitentan, 10 mg (N=242)	Macitentan, 10 mg vs. Placebo: Hazard Ratio (97.5% CI)	P Value
	number of patients (percent)				
Event related to PAH or death as the first event					
All events	116 (46.4)	95 (38.0)	76 (31.4)	0.55 (0.32–0.76)	<0.001
Worsening of PAH	93 (37.2)	72 (28.8)	59 (24.4)		
Death from any cause†	17 (6.8)	21 (8.4)	16 (6.6)		
Prostanoid initiation	6 (2.4)	1 (0.4)	1 (0.4)		
Lung transplantation	0	1 (0.4)	0		
Death due to PAH or hospitalization for PAH as the first event					

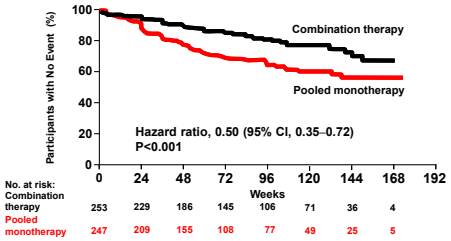
Combination Therapy

Initial Use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension

N. Galiè, J.A. Barberà, A.E. Frost, H.-A. Ghofrani, M.M. Hoeper, V.V. McLaughlin, A.J. Peacock, G. Simonneau, J.-L. Vachiery, E. Grünig, R.J. Oudiz, A. Vonk-Noordegraaf, R.J. White, C. Blair, H. Gillies, K.L. Miller, J.H.N. Harris, J. Langley, and L.J. Rubin, for the AMBITION Investigators*

- All PAH except PoPH
- FC II-III
- mPAP ~ 50 mmHg, PVR ~ 10 WU

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.

Additional Combination Therapy Evidence

SERAPHIN

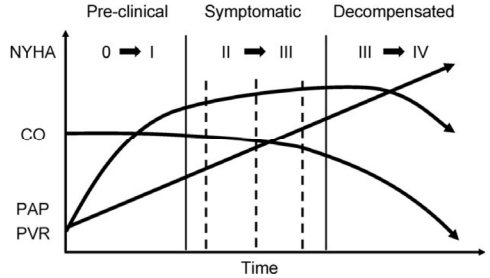
- Event-driven phase 3 trial evaluating long-term effects of macitentan in patients on "background therapy" compared to placebo
  - 97.4% on PDE-5i and 5.4% inhaled or oral PGI2
  - 38% RR in morbidity and mortality events
  - Background therapy + macitentan had 37% RR in risk of hospitalization (HR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

GRIPHON

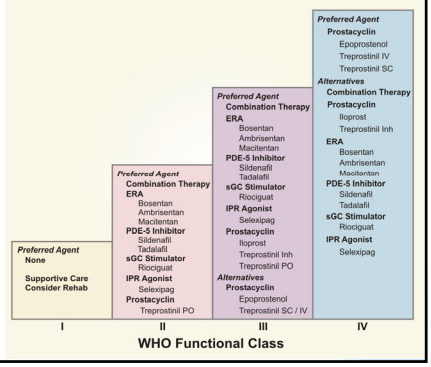
- 1156 patients randomized to placebo (n=582) or selexipag (n=574)
  - 20% naïve, 47% on ERA or PDE-5i; 33% on ERA+PDE-5i
  - 376 pts on dual combo tx had treatment effect consistent with overall population 37% RR in morbidity/mortality events

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.

Clinical Course of PAH



Treatment Strategy



Fraidenburg, Desai, and Yuan. *Goodman and Gilman's Pharm Therap*. 13th Edition, 2017.

Special Circumstances

- Warfarin considered for IPAH/HPAP
  - no clear data in other PAH
- Digoxin rarely used
- ERA class are teratogens
- Do not use riociguat with PDE-5
- IV/SC prostacyclin most potent therapy
  - Goal is highest tolerable dose

Goals of Therapy

- Symptomatic improvements
- Improved functional class
  - FC I-II better prognosis than III-IV
- Longer walk distance
  - Prognostic cutoffs of 250, 332, and 380 m
- Normalized RV function
  - RAP < 8mmHg and C.I. > 2.5 mg/kg/min
- Improving / normalized BNP

McLaughlin et al. *JACC.* 2013 Dec 24; 62: D73-81.

Goals of Therapy

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%

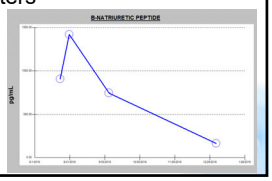
Galie N. et al. *Eur Heart J.* 2016 Jan 1;37(1):67-119.

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

Back to Clinical Case: 27 y/o Woman with Chest Pain

- Patient started on combination PDE-5 inhibitor and ERA as well as diuretics.
- Functional class improved from 3 -> 2
- Walk distance increased by 107 meters
- RVSP 54 mmHg -> 33 mmHg
- RV dysfunction improved



Conclusions

- The symptoms and signs of PH are often subtle, requiring high level of suspicion for diagnosis
- PAH diagnosis requires exclusion of associated syndromes i.e. non-Group 1 classes
- Therapy choice depends on functional class and RV function / dysfunction
- Goal of therapy is to improve symptoms, FC, walk distance and RV function
  - This ultimately slows PAH progression and improves morbidity and mortality


THANK YOU