2015 State-of-the-Art Management of Pulmonary Hypertension Based on an Understanding of the Various Etiologies

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Disclosures

- Has served as a consultant and/or advisor for Actelion Pharmaceuticals US, Inc., Bayer, Gilead Sciences, Inc., and United Therapeutics Corporation
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Pulmonary Arterial Hypertension (PAH): Key Points

- Average 14-mo delay from initial presentation to diagnosis: need to diagnose early
- Evaluation must be methodical and include echocardiography and right heart catheterization
- To treat effectively and avoid harm, PAH must be differentiated from pulmonary venous hypertension
- Prognosis improves with therapy, but PAH remains a progressive fatal disease
- Therapies and management strategies continue to evolve

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 diseases
  - 1.4.2 HIV infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease (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 obstruction

3. PH due to lung diseases and/or hypoxia

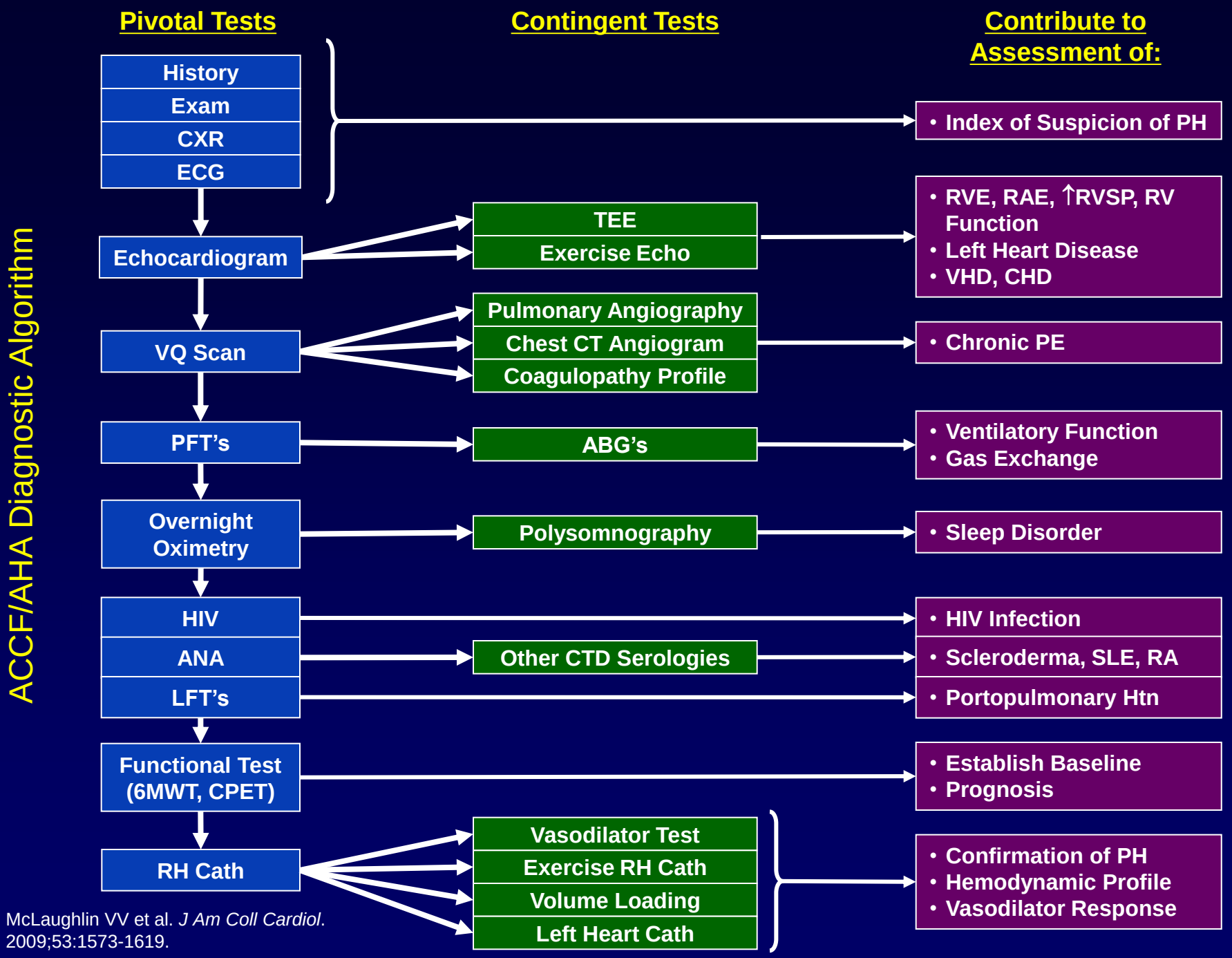
- 3.1 COPD
- 3.2 Interstitial lung disease
- 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
- 3.4 Sleep-disordered breathing
- 3.5 Alveolar hypoventilation disorders
- 3.6 Chronic exposure to high altitude
- 3.7 Developmental lung diseases (update)

4. CTEPH

5. PH with unclear multifactorial mechanisms

- 5.1 Hematological disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
- 5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
- 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:D34-41.

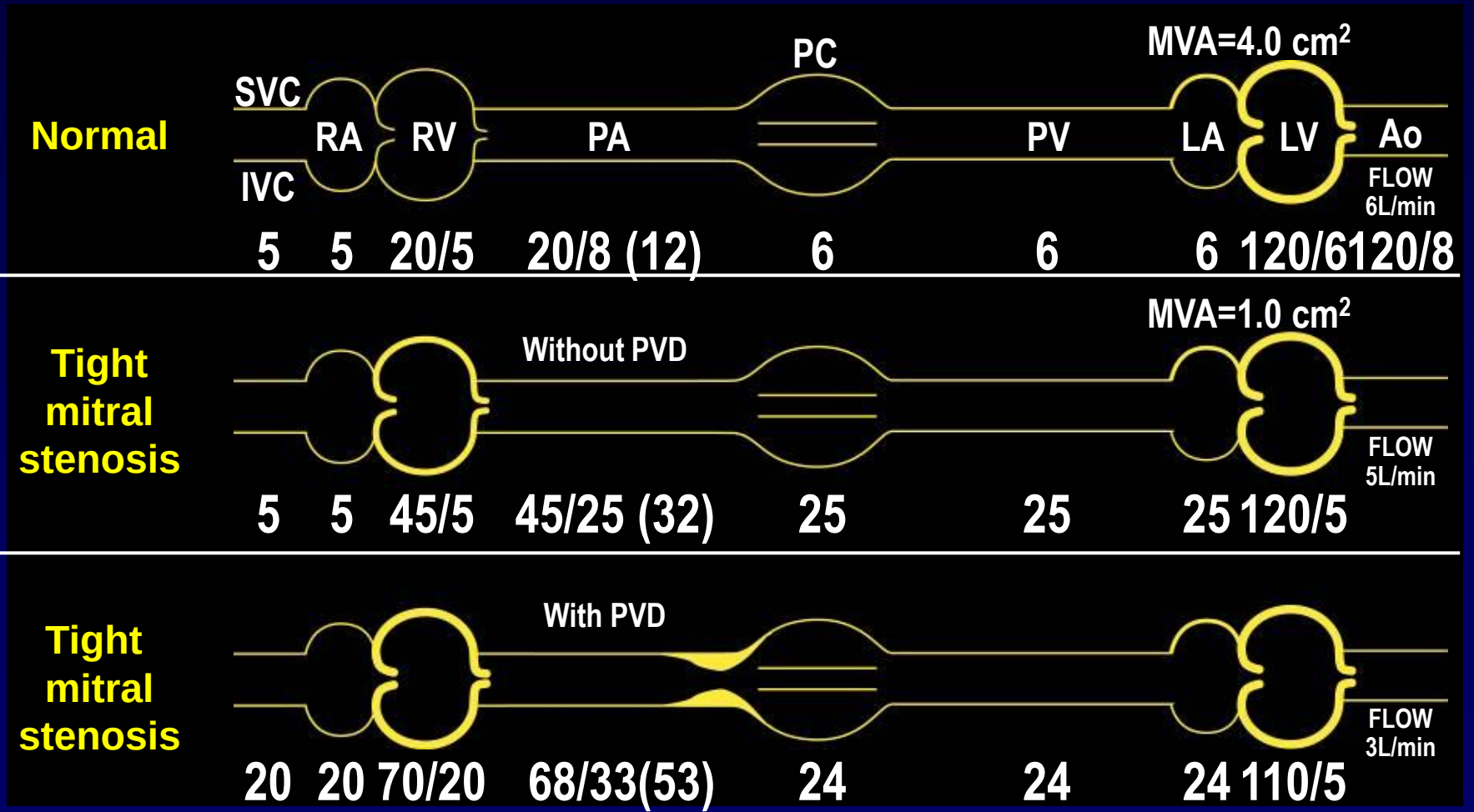


McLaughlin VV et al. *J Am Coll Cardiol*. 2009;53:1573-1619.

Differentiating PAH and HFpEF

characteristic	PAH more likely	HFpEF more likely
age	younger	older
Comorbidities-DM, HTN , CAD, obesity (metabolic syndrome)	Often absent	Often multiple present
Symptoms-PND, orthopnea	Often absent	Often present
Cardiac Examination	RV heave, loud P2, TR murmur	Sustained LV impulse, RS4,
CXR	Clear lung fields	Pulmonary vascular congestion, pleural effusions, pulmonary edema
Chest CT	Often clear lungs	Mosaic perfusion pattern, ground-glass opacities consistent with chronic interstitial edema
ECG	RAD, RVE	LAE, LVE, Atrial Fibrillation, no RAD
Naturetic peptides	Often elevated	Often elevated
Echo-LAE, LVH	Absent	Often present
Echo-diastolic dysfunction	Grade 1 common	Grade 2, 3 common
Echo-RV	Often enlarged, may share the apex	Often normal, mildly enlarged
Echo-pericardial effusion	sometimes	rare

Cardiopulmonary Circulation in Patients With Tight Mitral Stenosis With and Without Pulmonary Vascular Disease



PAH-Specific Therapies: Studies On PH-LV Dysfunction: Adverse Effects Trump Efficacy

Treatment		
Prostacyclin[1]	↑PVR, ↓SVR, ↓PAWP, ↑CO	↑Mortality
Sildenafil[2-8]	↓PVR, ↓PAWP, ↓MPAP, ↑CO	Lower PAP, Improved endothelial function and exercise tolerance
Bosentan[9-11]	↓PVR	↑Transaminases, ↑Fluid Retention
Darusentan[12-13]	↓SVR	No Benefits
Tezosentan[14]	↓PVR, ↓SVR, ↓PAWP, ↑CI	No Benefits

No therapies that are approved for WHO Group 1 PAH are FDA approved for PH resulting from left heart failure.

1. Califf RM, *et al*, Am Heart J; 1997; 134-44-54, 2. Galie N, *et al*, N Engl J Med; 2005; 353:2148–57, 3. Alaeddini J, *et al*, Am J Cardiol; 2004; 94:1475–7, 4. Lepore JJ, *et al*, Chest; 2005; 127:1647–53, 5. Lewis GD, *et al*, Circulation; 2007; 115:59–66, 6. Guazzi M,*et al*, Circ Heart Fail; 2011; 4:8–17, 7. Guazzi M, *et al*, Eur J Heart Fail; 2012; 14:82–90, 8. Guazzi M, *et al,* Circulation; 2011; 124:164–74, 9. Cowburn PJ and Cleland JG, Eur Heart J; 2001; 22:1772–84, 10. Kelland NF and Webb DJ, Heart 2007;93(1):2–4, 11. Sutsch G, *et al*, Circulation; 1998; 98:2262–8, 12. Luscher TF, *et al*, Circulation; 2002; 106:2666–72, 13. Anand PI, *et al*, Lancet; 2004; 364:347–54, 14. Kaluski E, *et al*, J Am Coll Cardiol; 2003; 41:204–10

PAH Determinants of Risk

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

McLaughlin VV et al. *J Am Coll Cardiol*. 2009;53:1573-1619.

Prostacyclin Analogues: Pivotal Trials for IV and SC Formulations

Study Name / Drug	N / Etiol / Class	Design	Positive Results
TRUST IV treprostinil vs placebo	44 PAH III	Double-blind, placebo-controlled 12-week	• 6MWD • Symptoms
IV epoprostenol vs conventional Rx	81 IPAH/FPAH III,IV	Open-label 12-week	• 6MWD • Symptoms • Hemodynamics • **Survival**
IV epoprostenol vs conventional Rx	111 APAH **SSc** III,IV	Open-label 12-week	• 6MWD • Hemodynamics • Symptoms
SQ treprostinil vs SQ placebo	470 PAH II-IV	Double-blind 12-week	• 6MWD • Symptoms • Hemodynamics

Hiremath J et al. *J Heart Lung Transplant*. 2010;29:137-149.
Barst RJ et al. *N Engl J Med*. 1996;334:296-301.
Badesch D et al. *Ann Intern Med* 2000;132(6):425-432.
Simonneau G et al. *Am J Respir Crit Care Med*. 2002;165:800-804

Prostacyclin Analogues: Pivotal Trials for Inhaled and Oral Formulations

Study Name / Drug	N / Etiol / Class	Design	Positive Results
AIR Inhaled iloprost vs placebo	203 PH III-IV	Double-blind 12-week	• Composite end point • 6MWD • Symptoms • Hemodynamics
TRIUMPH 1 Inhaled treprostinil vs placebo §	235 PAH III-IV*	Double-blind 12-week on background oral Rx	• 6MWD
FREEDOM-M Oral treprostinil vs placebo	228 PAH II-III	Double-blind, placebo-controlled 12-week	• 6MWD

*Approved for class III only. § Included background therapy with ERA or PDE5-I.

Olschewski H et al. *N Engl J Med*. 2002;347:322-329.
McLaughlin VV et al. *J Am Coll Cardiol.* 2010;55:1915-1922*Heart Lung Transplant*. 2010;29:137-149.
Jing Z-C et al. *Circulation*. 2013;127:624-633.

Endothelin Receptor Antagonists: Pivotal Trials

Study Name Drug	N Etiology Class	Design	Positive Results
BREATHE-1 Oral bosentan* vs placebo	213 PAH III, IV	Double-blind 16-week	• 6MWD • Delay clinical worsening • Symptoms
EARLY Oral bosentan vs placebo	185 PAH **II**	Double-blind 6-month	• Delay clinical worsening • Hemodynamics
ARIES-1&2 Oral ambrisentan § vs placebo	394 PAH II, III	Double-blind 12-week	• 6MWD • Delay clinical worsening
SERAPHIN Oral macitentan† vs placebo	742 PAH II,III	Morbidity and Mortality Endpoint Driven	• Delay disease progression • 6MWD • Symptoms

***Bosentan = Tracleer®. Approved for FC II-IV. 62.5-125 mg po bid.**
§ Ambrisentan = Letairis®. Approved for FC II-III. 5-10 mg po qd
†Macitentan = Opsumit®. Approved for FC II-III. 10 mg po qd.

Rubin L et al. *N Engl J Med.* 2002;346:896-903. Channick RN et al. *Lancet.* 2001;358:1119-1123. Galiè N et al. *Lancet,* 2008;371:2093-2100. Galiè N et al. *Circulation.* 2008;117:3010-3019. Pulido T et al. *N Engl J Med*. 2013;369:809-18

PDE-5 Inhibitor Pivotal Trials

Study Name Drug	N Etiol Class	Design	Positive Results
SUPER-1 Oral sildenafil* vs placebo	278 PAH I-IV	Double-blind 12-week	• 6MWD • Symptoms • Hemodynamics
PHIRST-1 Oral tadalafil § vs placebo	405 PAH I-IV	Double-blind 16-week	• 6MWD • Delay clinical worsening • Hemodynamics • HRQoL

***Sildenafil = Revatio®. Approved for FC II-III. 20 mg po tid.**
§ Tadalafil = Adcirca®. Approved for FC I-IV. 40 mg po qd.

Galiè N et al. *N Engl J Med*. 2005:353:2148-2157.
Galiè N et al. *Circulation.* 2009;119;2894-2903.

SGC Stimulator Pivotal Trials

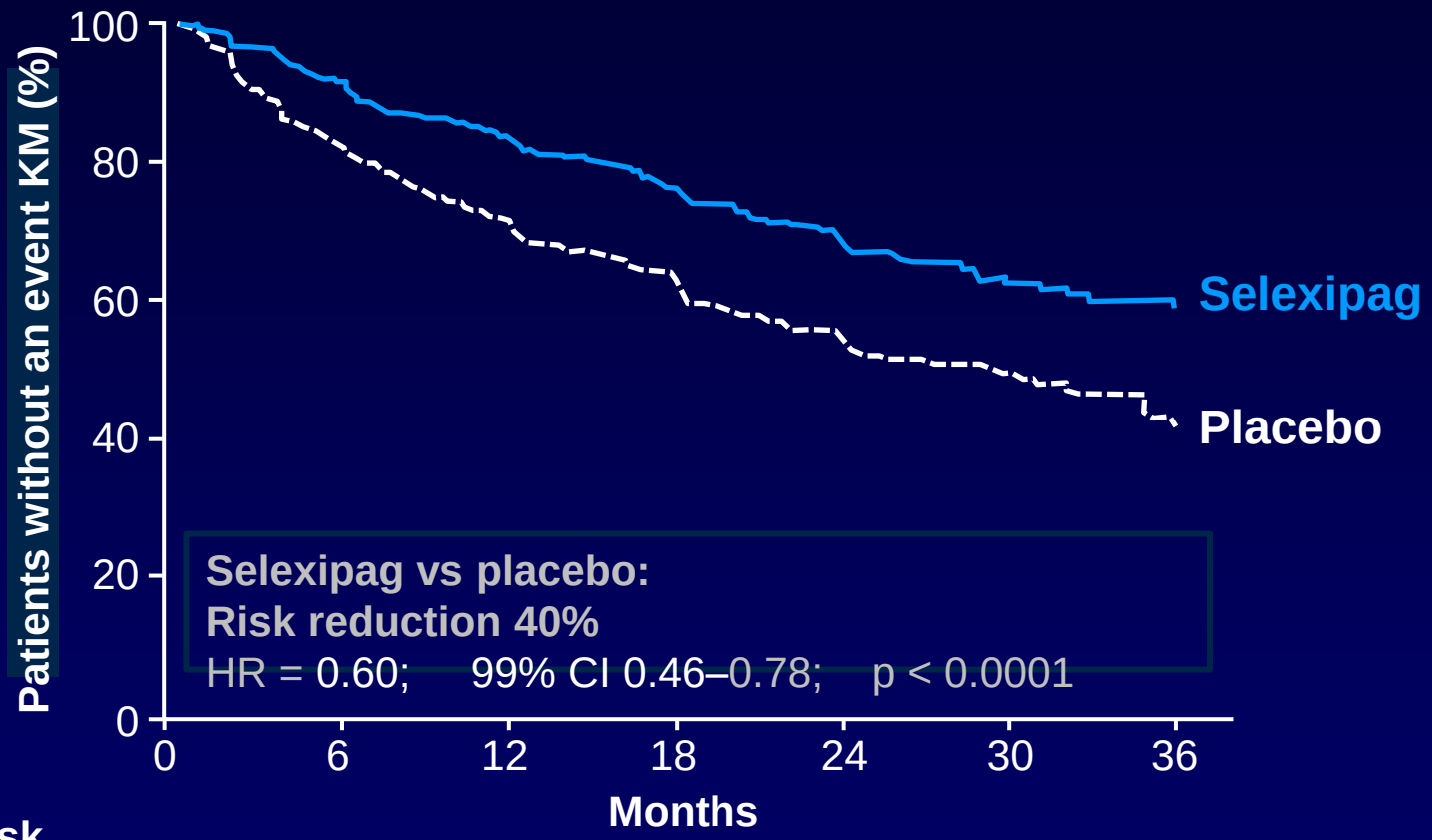
Study Name Drug	N Etiol Class	Design	Positive Results
PATENT-1 Oral riociguat* vs placebo	443† PAH I-IV	Double-blind 12-week	• 6MWD • Symptoms • Hemodynamics • Delay clinical worsening
CHEST-1 Oral riociguat vs placebo	261 CTEPH I-IV	Double-blind 16-week	• 6MWD • Symptoms • Hemodynamics

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

†63 patients on exploratory 1.5 mg tid were excluded from efficacy analysis.

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

GRIPHON primary endpoint: Time to first morbidity or mortality event up to EOT



No. at Risk							
Placebo	582	433	347	220	149	88	28
Selexipag	574	455	361	246	171	101	40

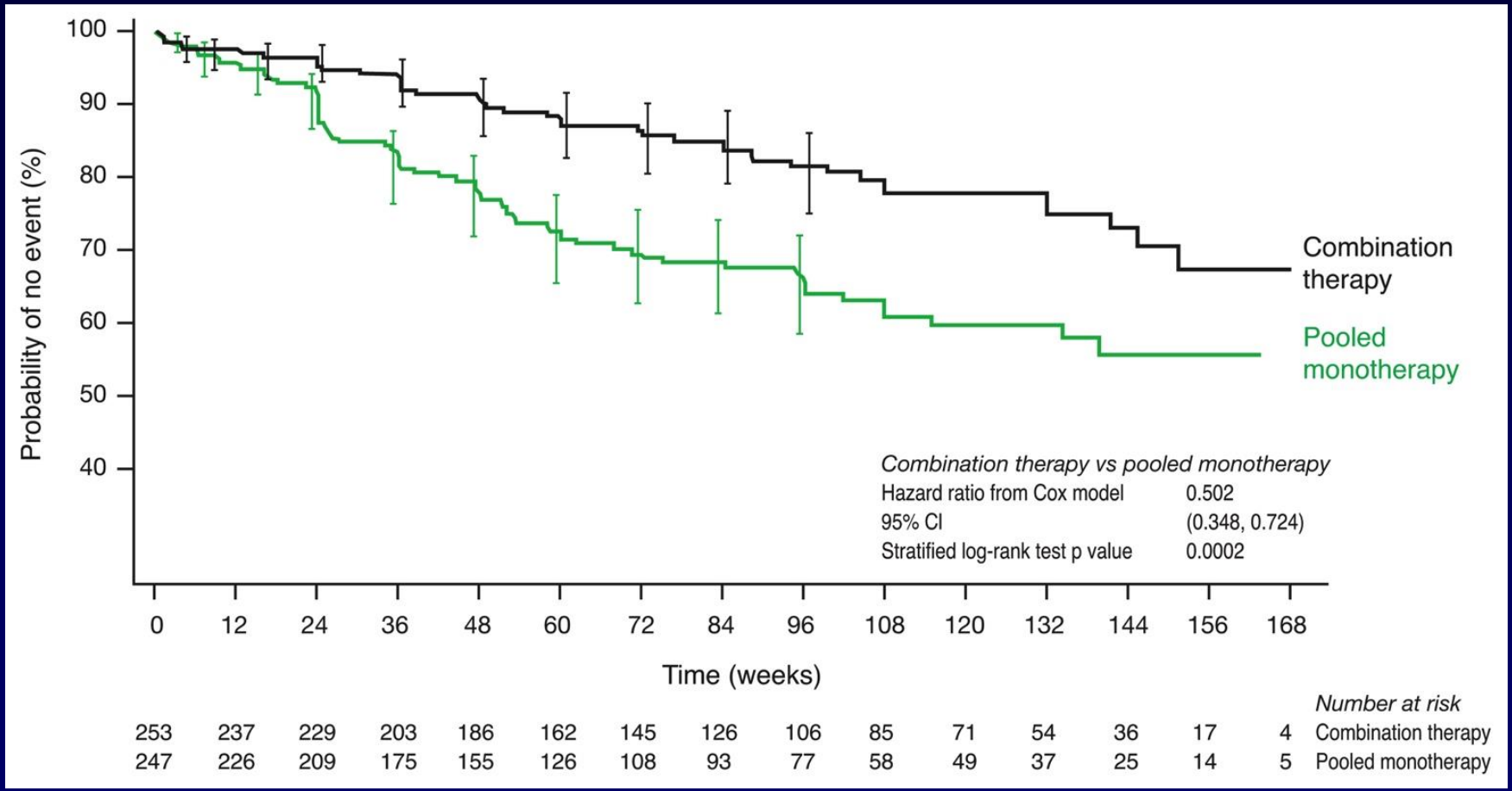
EOT: End of double-blind treatment; KM: Kaplan-Meier

McLaughlin V, et al. *J Am Coll Cardiol.* 2015;65(10S):A1538

ITT population

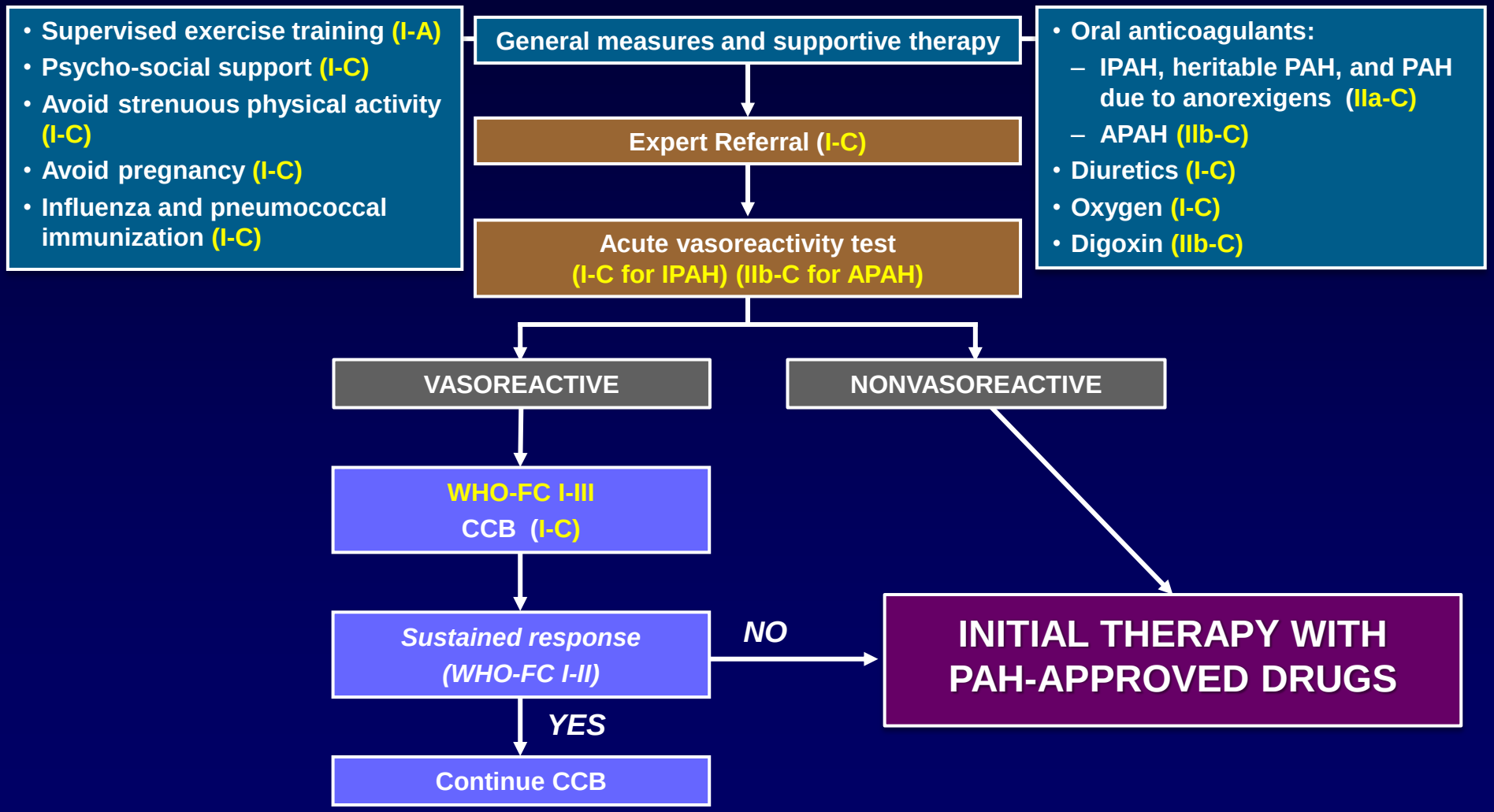
AMBITION Trial
Kaplan-Meier cumulative curve for time to first adjudicated clinical failure-Primary Analysis Set

Combination vs pooled monotherapy



95% CIs (using log-log transform method) are presented for each treatment group at weeks 4, 8, 16, 24, and then every 12 weeks up to week 96.

5th World Symposium on PH: 2013 Treatment Algorithm



Galiè N et al. *JACC*. 2013;62:D60-D72.

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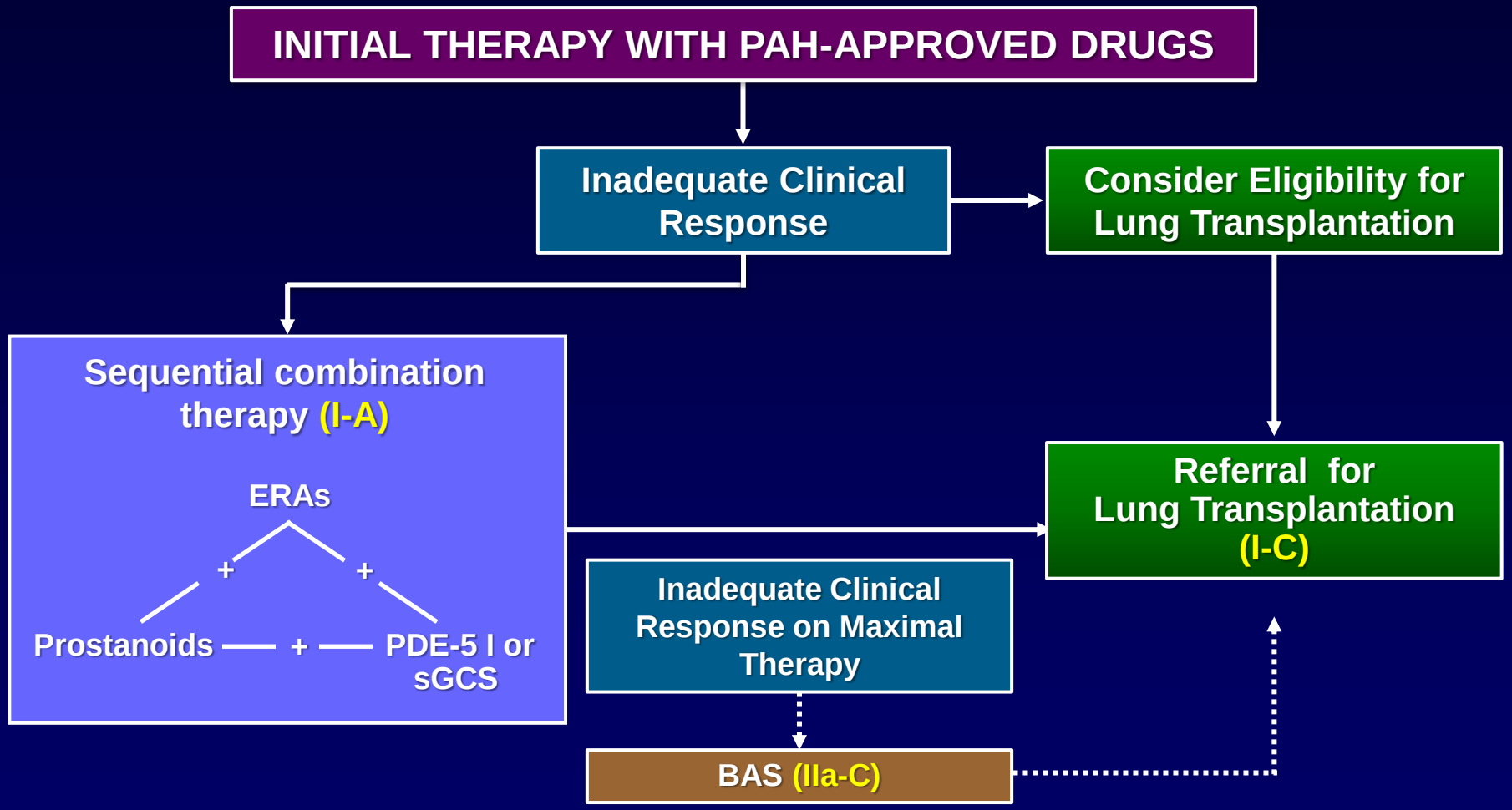
INITIAL THERAPY WITH PAH-APPROVED DRUGS					
YELLOW: Morbidity and mortality as primary end point in randomized controlled study or reduction in all-cause mortality (prospectively defined) Level of evidence is based on WHO-FC of majority of patients of studies					
		Evidence	WHO-FC II	WHO-FC III	WHO-FC 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

*Not approved in US.

Galiè N et al. *JACC.* 2013;62:D60-D72.

5th World Symposium on PH: 2013 Treatment Algorithm



Galiè N et al. *JACC*. 2013;62:D60-D72.

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

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

McLaughlin VV et al. *JACC 2013*.:62:D73-81.