Management of PAH

21.8.15 and 11.9.15

Seminar outline

- Definition and classification
- Treatment
  - Specific therapies for PAH
  - Role of combination therapy
  - Status of emerging therapies
- PAH 2^{o} to lung disease (Group 3)
- CTEPH (Group 4)
- Prognosis and prognosis assessment tools

PAH

- Pulmonary arterial hypertension (PAH) remains a highly morbid disease with high mortality.

- Despite a recent growth in therapeutic options, clinicians and their patients continue to struggle with questions regarding pharmacologic treatments and major uncertainties persist in the management of PAH.

Definition & Classification

Old definition

- Pulmonary arterial hypertension (PAH) was defined by
  - Mean PAP >25 mmHg at rest or >30 mmHg with exercise
  - PAWP ≤15 mmHg and
  - PVR >3 mmHg/L/min (Wood units) or >240 dyn·s/cm^5

ESC guidelines. Galie N et al. European Heart Journal (2004) 25, 2243–2278

New definition

- Pulmonary hypertension (PH) is defined as a resting mPAP ≥25 mmHg at right heart catheterization (RHC)
- PAH is defined as a subgroup of PH with:
  - PAWP ≤15 mmHg (Pre-capillary PH) with PVR ≤ 3 Wood units
  - Normal or reduced cardiac output
  - Absence of other causes of pre-capillary PH (PH due to lung diseases, CTEPH, or other rare diseases)

ESC guidelines. Galie N et al. European Heart Journal (2004) 25, 2243–2278

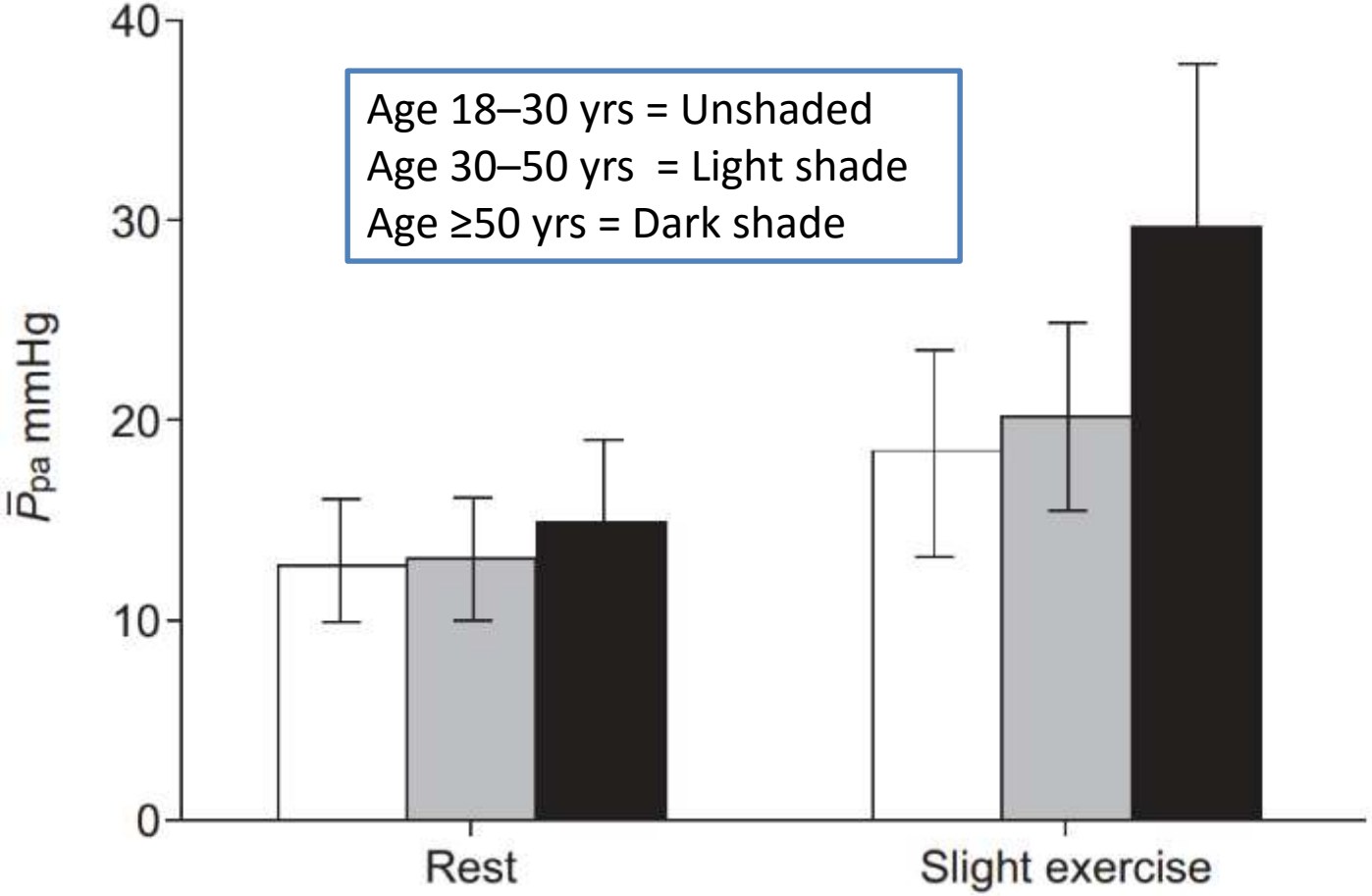
Why this cut-off?

- Systematic review of 47 studies describing 72 healthy populations (1187 patients)
  - Normal resting mPAP: 14 ± 3.3 mmHg
  - Upper limit of normal (ULN = Mean + 2SD): 20.6 m

mPAP 21-24 mmHg: Borderline PAH?

Kovacs G et al. Eur Respir J 2009; 34: 888–894

Why was exercise cut-off (>30mmHg) eliminated?



Kovacs G et al. Eur Respir J 2009; 34: 888–894

Table 1 Updated Classification of Pulmonary Hypertension*

1. Pulmonary arterial hypertension
   - 1.1 Idiopathic PAH
   - 1.2 Heritable PAH
   - 1.2.1 BMPR2
   - 1.2.2 ALK-1, 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
   - 1.4.5 Schistosomiasis

1′ Pulmonary veno-occlusive disease and/or pulm

1″. Persistent pulmonary hypertension of the ne

2. Pulmonary hypertension due to left heart disea
   - 2.1 Left ventricular systolic dysfunction
   - 2.2 Left ventricular diastolic dysfunction
   - 2.3 Valvular disease
   - 2.4 Congenital/acquired left heart inflow/out congenital cardiomyopathies

3. Pulmonary hypertension due to lung diseases
   - 3.1 Chronic obstructive pulmonary disease
   - 3.2 Interstitial lung disease
   - 3.3 Other pulmonary diseases with mixed restr
   - 3.4 Sleep-disordered breathing
   - 3.5 Alveolar hypoventilation disorders
   - 3.6 Chronic exposure to high altitude
   - 3.7 Developmental lung diseases

4. Chronic thromboembolic pulmonary hypertensi

5. Pulmonary hypertension with unclear multifact
   - 5.1 Hematologic 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

1. Pulmonary arterial hypertension (PAH)
   - 1.1. Idiopathic PAH
   - 1.2. Heritable
     - 1.2.1. BMPR2
     - 1.2.2. ALK1, endoglin (with or without hereditary hemorrhagic telangiectasia)
     - 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 diseases
     - 1.4.5. Schistosomiasis
     - 1.4.6. Chronic hemolytic anemia
   - 1.5 Persistent pulmonary hypertension of the newborn

1′. Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)

Simonneau et al. J Am Coll Cardiol 2013;62: D34–41

Disease burden

- Prevalence: 15–50 patients per million population
- Annual incidence: 2-7 cases per million population
- No systematic data on prevalence/incidence from India

Humbert M et al. Am. J. Respir. Crit. Care Med. 173, 1023–1030 (2006)
Peacock AJ et al. Eur. Respir. J. 30, 104–109 (2007)

Therapies for PAH

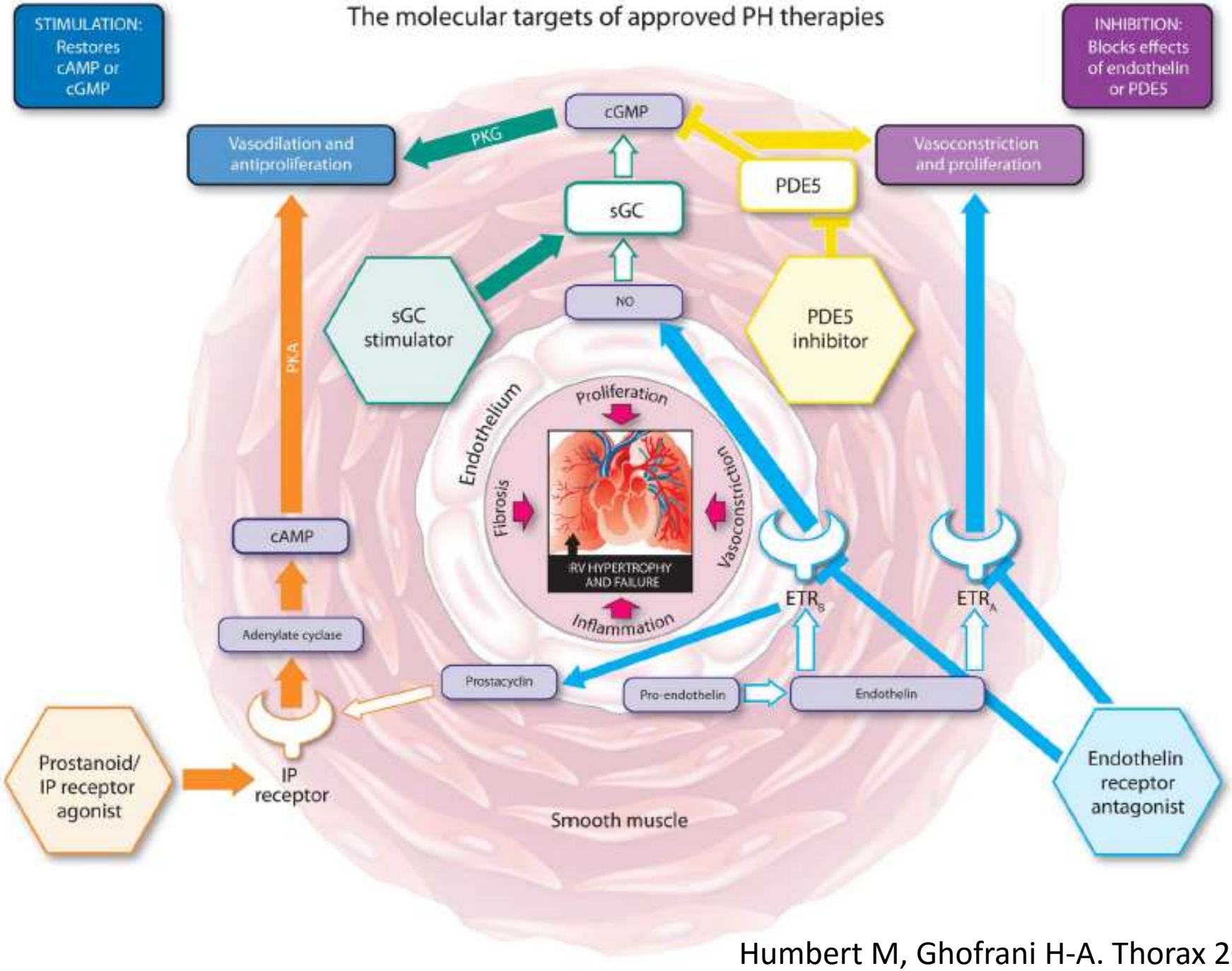
Therapy without RCT data

- CCBs
- Warfarin
- Oxygen
- Exercise
- Diuretics

Targeted Therapies

- Prostanoids
- Endothelin receptor antagonists
- PDE-5 inhibitors
- Prostanoids
- Riociguat
- Emerging therapies

Monotherapy vs Combination therapy?



Humbert M, Ghofrani H-A. Thorax 2015

CCBs

- Nifedipine and Diltiazem MC used > Amlodipine
- Verapamil avoided d/t negative inotropic effect
- HR > 100 → Ditiazem
- HR < 100 → Nifedipine/Amlodipine
- High dose CCBs required:
  - Nifedipine 180-240 mg/d
  - Diltiazem 720-960 mg/d
  - Amlodipine 20-30 mg/d

1. Taichman, Ornelas et al. CHEST 2014
2. McLaughlin, Archer et al. Circulation 2009

Vasoreactivity testing

- Done with short acting agent: Inhaled nitric oxide (iNO) is drug of choice
  - IV epoprostenol, acetylcholine, adenosine or tolazoline also used: may have systemic vasodilator effects
  - Inhaled iloprost has emerged as newer alternative

- Fall in mPAP > 10 mmHg to value < 40 mmHg cutoff for selecting patients for CCBs

1. Taichman, Ornelas et al. CHEST 2014
2. Galie et al. Journal of the American College of Cardiology 2013

CCBs

Rich et al. NEJM 1992

- 17/64 patients (26%) had acute pulmonary vasoreactivity (20% decrease in mPAP and PVR)
- Responders received CCBs: At 5 yrs CCB group had 94% survival compared with 55% in non-responders (p=0.003)

Sitbon et al. Circulation 2005.

- Retrospective study: 70/557 (12.6%) showed vasoreactivity and got CCB
- Only 38/70 (7% of total) had response to CCB
- CCB responders had better baseline NYHA Class, longer 6MWD and hemodynamic variables
- Also showed significant survival benefit (98% v 48%)

CCB responder group had reached a lower mPAP (<40 mmHg) and lower PVR on vasodilator testing when compared to CCB non-responder group

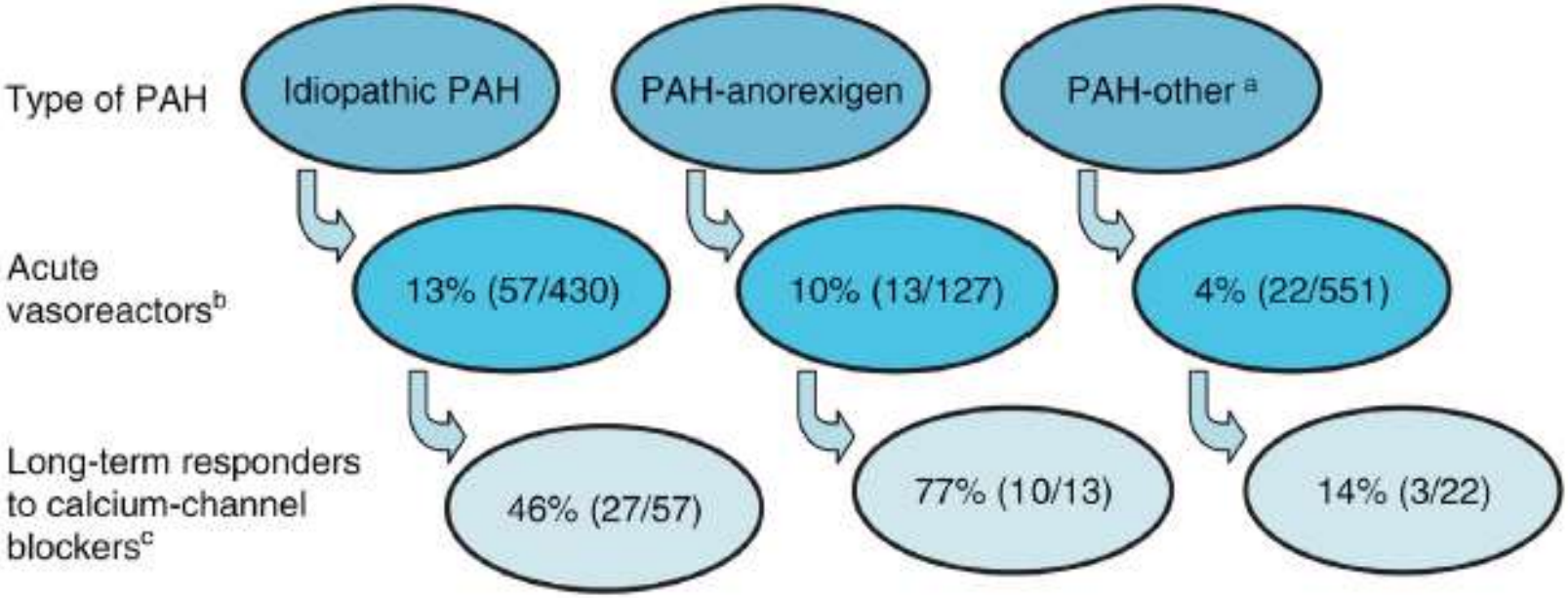


Figure 4. Breakdown of long-term responders to calcium channel blocker (CCB) monotherapy amongst those who are acutely vasoreactive, by type of PAH (data adopted from Sitbon et al. (2004)

Fallah. Global Journal of Health Science 2015

Factors predicting response to CCBs

TABLE 5. Odds Ratios for Variables Associated With Treatment Success on Long-Term CCB for Acute Responders (Univariate Analysis)

	Dichotomy/Median	Odds Ratio	95% CI	*P*
Baseline clinical variables				
Age, y	<42.8	2.18	0.83–5.75	0.115
History of RHF	No	3.48	0.95–12.68	0.059
NYHA functional class	II/III-IV	3.02	1.13–8.13	0.028
Hemodynamic variables measured at baseline				
Mean RAP, mm Hg	<7	2.36	0.89–6.21	0.083
Mean PAP, mm Hg	<56	3.02	1.13–8.13	0.028
Cardiac index, $L \cdot min^{-1} \cdot m^{-2}$	>2.5	3.21	1.20–8.54	0.015
PVR, Wood units	<11.5	4.24	1.55–11.49	0.005
Svo_2, %	>65	19.18	5.73–64.25	<0.0001
Variables achieved during acute vasodilator testing				
Mean PAP, mm Hg	<37	6.13	2.11–17.86	0.0009
Fall in mean PAP, %	>31	7.35	2.54–21.28	0.0002
PVR, Wood units	<6.7	7.35	2.54–21.28	0.0002
Fall in PVR, %	>45	3.27	1.22–8.77	0.018

RHF indicates right heart failure; RAP, right atrial pressure.

Sitbon et al. Circulation 2005.

CCBs: Use with Caution!

- Start with low dose and titrate upwards
- Edema
- Hypotension
- Reflex tachycardia → RV ischaemia
- Increasing CCB doses in patients who are not vasoreactive may be fatal
- As 93% patients are not likely to respond → Should not be used without vasoreactivity testing

Taichman, Ornelas et al. CHEST 2014

Prostanoids

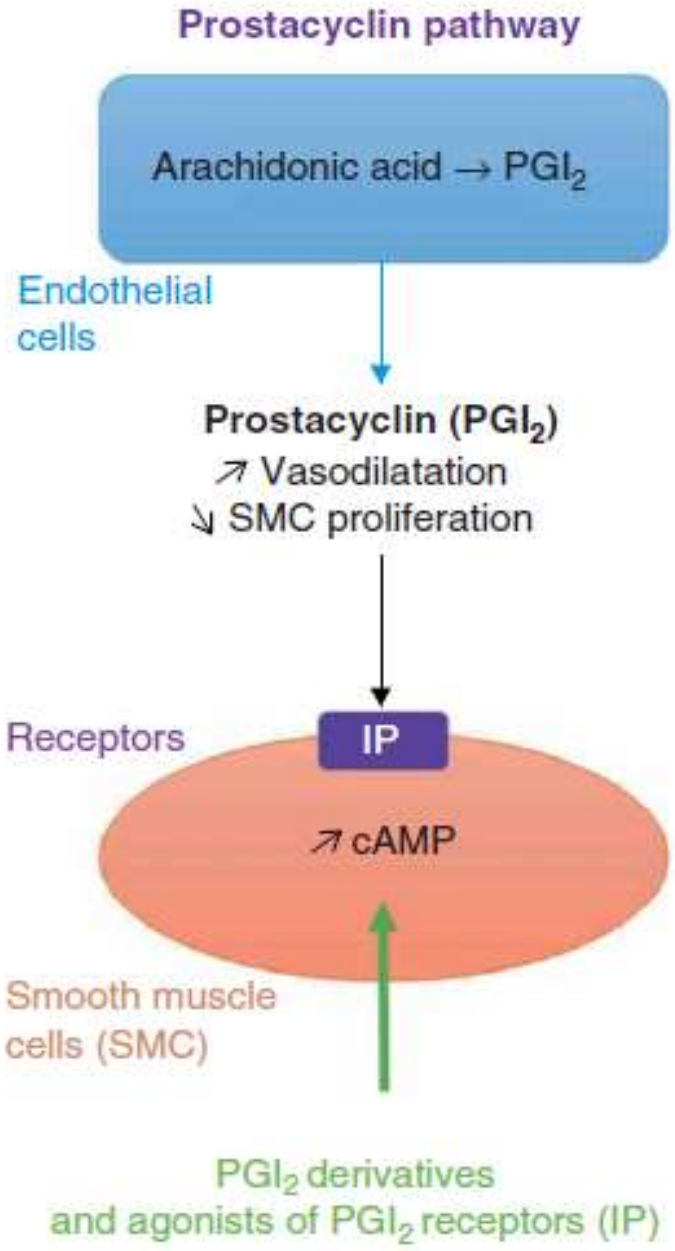
- Prostacyclin(PGI_2) – endogenous eicosanoid produced by endothelial cells.
- Epoprostenol is the synthetic equivalent of prostacyclin, and treprostinil and iloprost are both stable synthetic analogs.
- Deficiency of prostacyclin activity identified as an important part of the pathobiology of PAH.
- Loss of expression of prostacyclin synthase also been observed in lung tissue of PAH patients.

Richa Agarwal et al. AHJ 2011

Prostanoids - Mechanism of Action

- Primary target of prostacyclin → IP receptor on vascular smooth-muscle cells.
- Prostacyclin binds target receptors on smooth-muscle cells, intracellular signaling leads to adenylate cyclase activation and increase in cAMP levels.
- Results in smooth-muscle relaxation with vasodilation.
- Also believed to target pathologic vascular remodeling observed in PAH.
- Additional prostanoid effects include anti-proliferative, inhibition of platelet aggregation, anti-inflammatory, and augmentation of ventricular inotropy

LeVarge. Therapeutics and Clinical Risk Management 2015



Epoprostenol
Treprostenil
Iloprost
Beraprost
Selexipag

Perrin et al. Expert Opin. Pharmacother. 2015

Prostanoids – Dosing and administration

Drug	Preparation	Administration	Dosage
Epoprostenol GM (glycine-mannitol FLOLAN) 0.5 mg 1.5 mg lyophilised powder	Reconstituted solutions stable for up to 8 hrs. May be stored for up to 40 hrs refrigerated at 2°C to 8°C.	Continuous IV infusion via central line with ambulatory infusion pump	Start at 2 ng/kg/min (titrate upward 3-7 days) Mean dose: 12 wks = 11 ng/kg/min 1 yr = 21 ng/kg/min 1 ½ yr = 35 ng/kg/min
Epoprostenol AS (arginine-sucrose VELETRI) 0.5 mg 1.5 mg lyophilised powder	Reconstituted solutions stable for up to 48 hrs. May be stored for up to 8 days refrigerated at 2°C to 8°C.	do	do

Not to be exposed to direct sunlight

Prostanoids – Dosing and administration (contd)

Drug	Preparation	Administration	Dosage
Iloprost – Inhaled (VENTAVIS) 10 mcg/ml = 2.5 mcg 20 mcg/ml = 5 mcg	No dilution required	Oral inhalation via ultrasonic nebuliser	2.5-5 mcg per dose 6 to 9 times/day
Treprostenil – Inhaled (TYVASO) 1.74 mg/2.9 ml	No dilution required. One ampoule to be changed every 24 hrs.	Oral inhalation via Tyvaso Inhalational System	3-9 breaths per session (18-54 mcg) 4 times/day
Treprostenil - IV/SC (REMODULIN)	With sterile water: storage upto 4 hrs at room temp and 24 hrs refrigerated. With diluent: Maybe stored upto 14 days. Administer within 48 hrs	Continuous IV/SC infusion with ambulatory infusion pump	1.25 ng/kg/min and titrate upward *Dosage of 40ng/kg/min a/w improved survival
Treprostenil – Oral (ORENITRAM)	-	-	0.25 mg bd and increase 3-4 days *Mean dose 3.4 mg bd

Epoprostenol – Landmark Trial

- 12 week prospective randomized open label trial (epoprostenol vs standard care)
- IPAH, NYHA Class III/IV, n = 81 (41 Epoprostenol)
- 1^{o} outcome: mean 6MWD increased by 32 m in epoprostenol group (decrease by 25 m in std Rx)
- Other statistically significant outcomes:
  - Only randomised PAH trial to show improved survival
  - Improvement in hemodynamic parameters, FC, QoL and dyspnea scores

Barst et al. NEJM 1996

Comparison of RCTs in Epoprostenol

Study	n	Population	6MWD Improvement (compared to placebo)	Survival	Dyspnea	FC change	QoL	Hemodynamics	Serious Adverse Events
Rubin 1990 Barst 1994	25 18	IPAH	106 m at 6 mon 144 m at 18 mon	At 3 yrs 63% v 40% (p=.045)	-	-	-	Y	2 deaths d/t catheter complications 7 episodes of sepsis
Barst 1996	81	IPAH	60 m at 12 wks	8 vs 0 deaths (p =.003)	Y	Y	Y	Y	4 sepsis, 1 paradoxical embolism. No deaths.
Badesch 2000	111	SSc	108 m at 12 wks	5 vs 4 deaths (p=NS)	Y	Y	N	Y	2 sepsis, 2 cellulitis, 2 pneumothorax, 2 hemorrhage

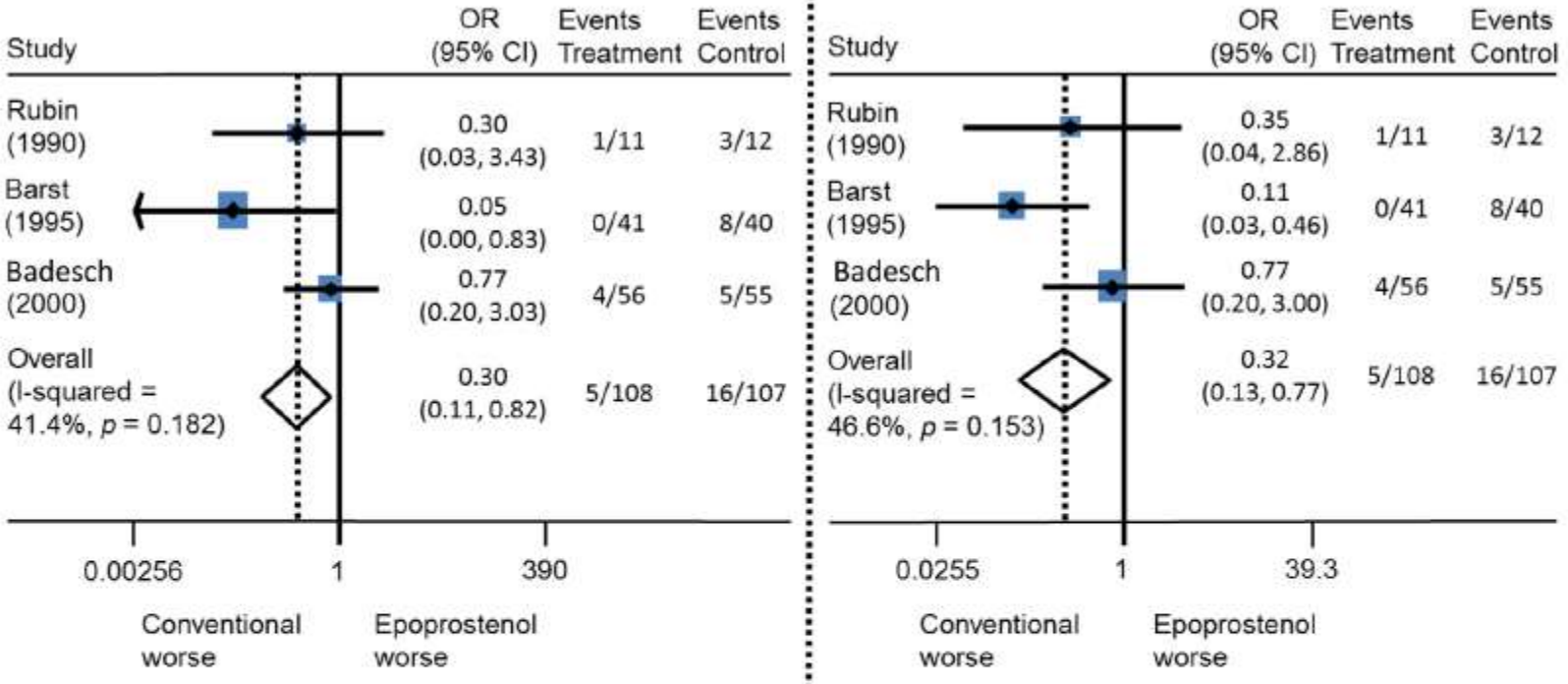


Figure 2 **Meta-Analysis of Published Randomized Controlled Studies (Identified by First Author and Year of Publication) With Epoprostenol in Pulmonary Arterial Hypertension by Mantel–Haenszel and Peto Methods**

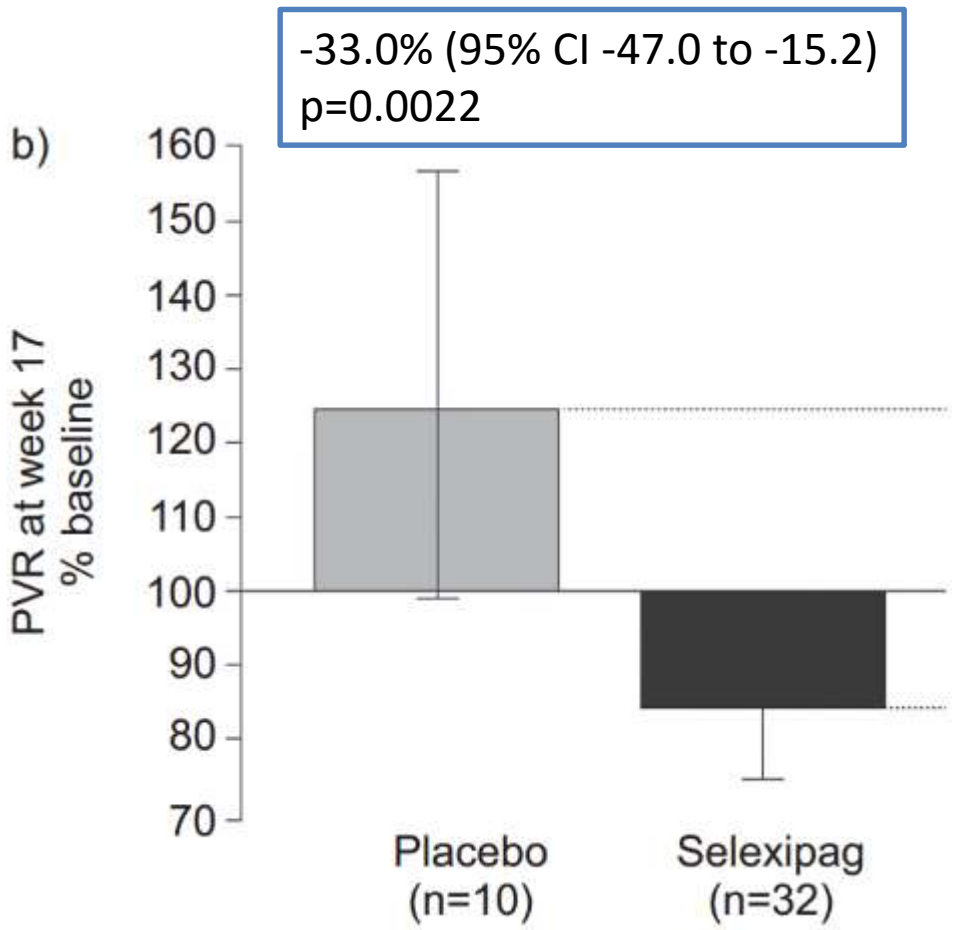
The analysis included 215 patients in 3 trials. The figure shows the cumulative relative risk (RR) estimate of death in active treatment groups when compared with control groups. An overall reduction of the risk of mortality of 70% (p = 0.019) and 68% (o = 0.012) is shown with Mantel–Haenszel and Peto methods, respectively. CI = confidence interval; OR = odds ratio.

Galie et al. Journal of the American College of Cardiology 2013

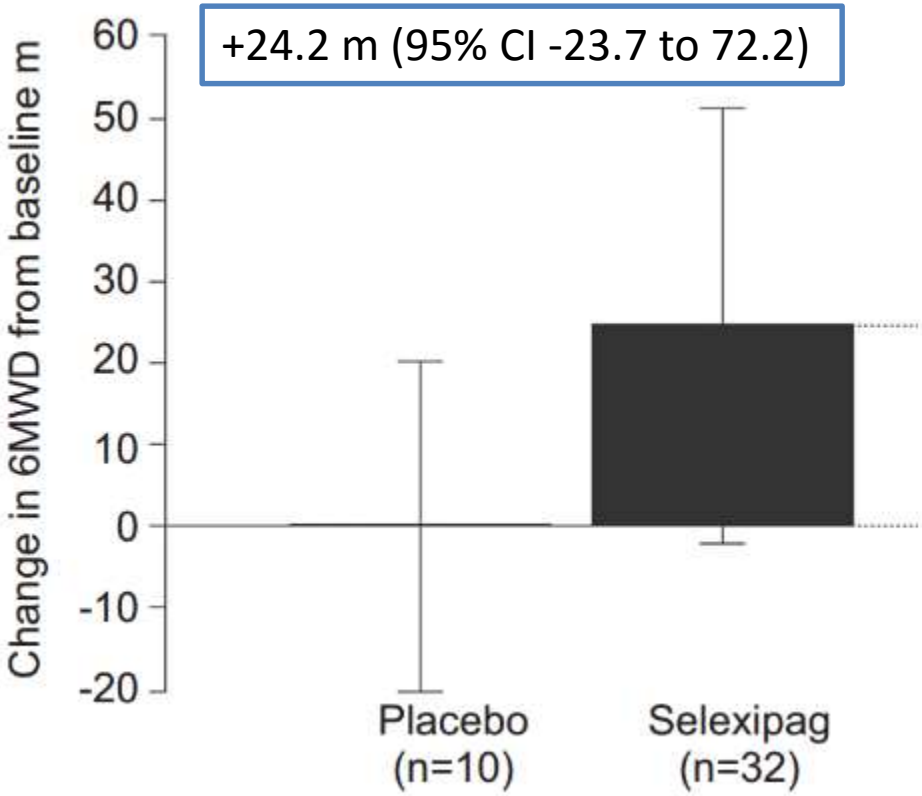
RCTs with iloprost/treprostenil

Study	n	Population	6MWD Improvement (compared to placebo)	Survival	Dyspnea	FC change	QoL	Hemodynamics	Serious Adverse Events
Olschewski 2002 (AIR-Double blind RCT)	203	IPAH, CTEPH NYH 3 or 4	36 m at 12 wk (p=.004) (59 in IPAH, 12 in CTEPH p=NS)	4 vs 1 (p=NS)	Y	Y	Y	Y	Increased syncope, flushing, cough
Simonneau 2002	470	Grp 1 PAH NYH 2/3/4	16 m at 12 wks (p=.006)	7 vs 7		N	Y	Y	3 GI bleed
Jing 2013 Freedom-M	349	Grp 1 PAH	26 m at 12 wks (p=.012)	10 vs 6 (p=NS)	N	N	N	-	2 syncope, 2 pul edema

Selexipag



-33.0% (95% CI -47.0 to -15.2)
p=0.0022



+24.2 m (95% CI -23.7 to 72.2)

Simonneau G et al. Eur Respir J. 2012 Oct;40(4):874-80

Adverse events with prostacyclins

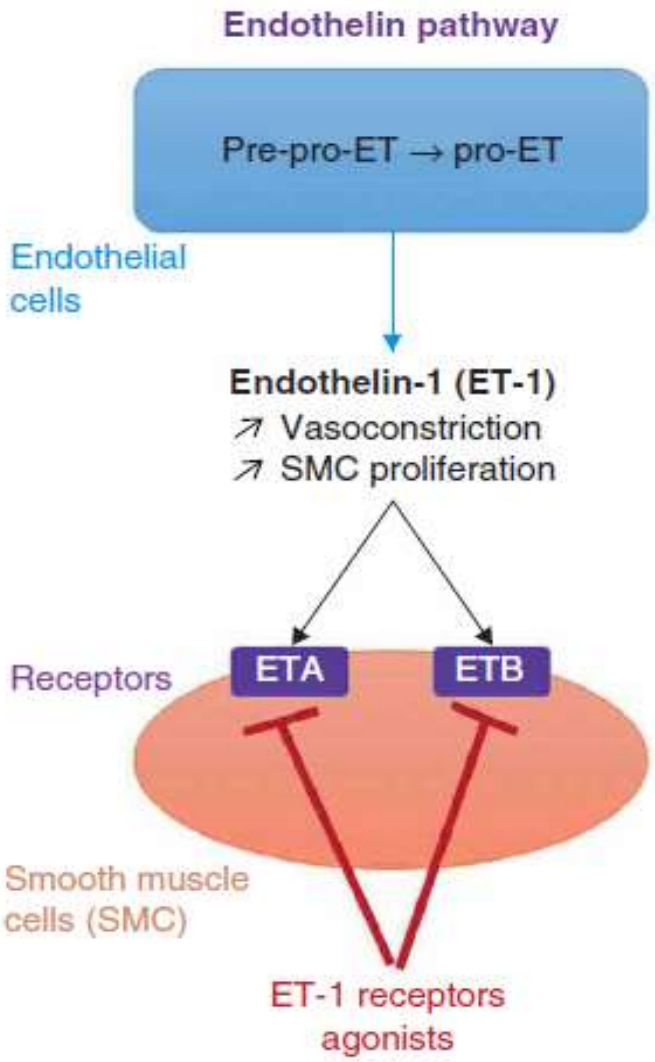
Drug Related

- Flushing
- Headache
- Diarrhea
- Nausea/Vomiting
- Jaw pain
- Flu-like symptoms
- Syncope/hypotension
- Cough
  (with inhaled)

Catheter Related

- Sepsis
- Thrombosis
- Bleeding
- Drug interruption and rebound PAH
- Paradoxical embolism

Endothelin pathway



Perrin et al. Expert Opin. Pharmacother. 2015

Endothelin receptor antagonists

- ET-1 → potent vasoconstrictor that promotes smooth muscle proliferation and contributes to disease progression in PAH.
- ET-1 levels increased in PAH, levels correlate with PVR in IPAH.
- 2 receptors, endothelin-A (ETA) and endothelin-B (ETB).
- ETA receptors, found on smooth muscle cells only, induce vasoconstriction and cellular proliferation.
- ETB receptors on smooth muscle cells, when activated, also stimulate vasoconstriction; **however, ETB receptors on endothelial cells have the counter-effect of vasodilation and clearance of ET-1**.
- Whether selective ETA receptor antagonism offers greater benefit in PAH? – Inconclusive data

Richa Agarwal et al. AHJ 2011

Comparison of ERAs

Drug	Dose	Selectivity	Main Adverse Affects	Interactions	Monitoring
Bosentan BOSENTAS/ LUPIBOSE Rs 110: 62.5 mg	Initially 62.5 mg bd, If LFT normal increase to 125 mg bd	Non-selective	Transaminitis, Teratogenic, Edema, Anemia	Glyburide, Cyclosporine, CYP450 inhibitors/inducers	Monthly LFT, Monthly pregnancy testing
Ambrisentan AMBRICAN/ ENDOBLOC Rs 140: 5mg Rs 230: 10mg	5 mg to 10 mg od	ET-A	<Transaminitis, Teratogenic, Nasal congestion, edema, Anemia	Cyclosporine, CYP450 inhibitors/inducers	Monthly pregnancy testing
Macitentan	10 mg od	Non-selective	do	do	

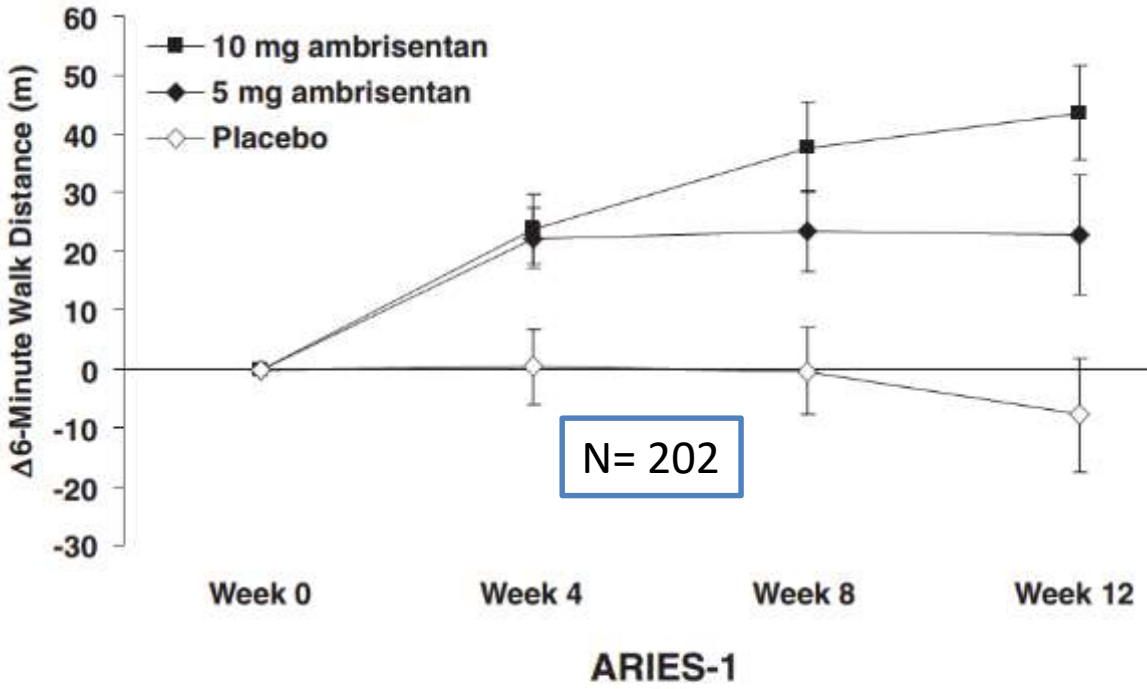
Sitaxsentan withdrawn after reports of ALF

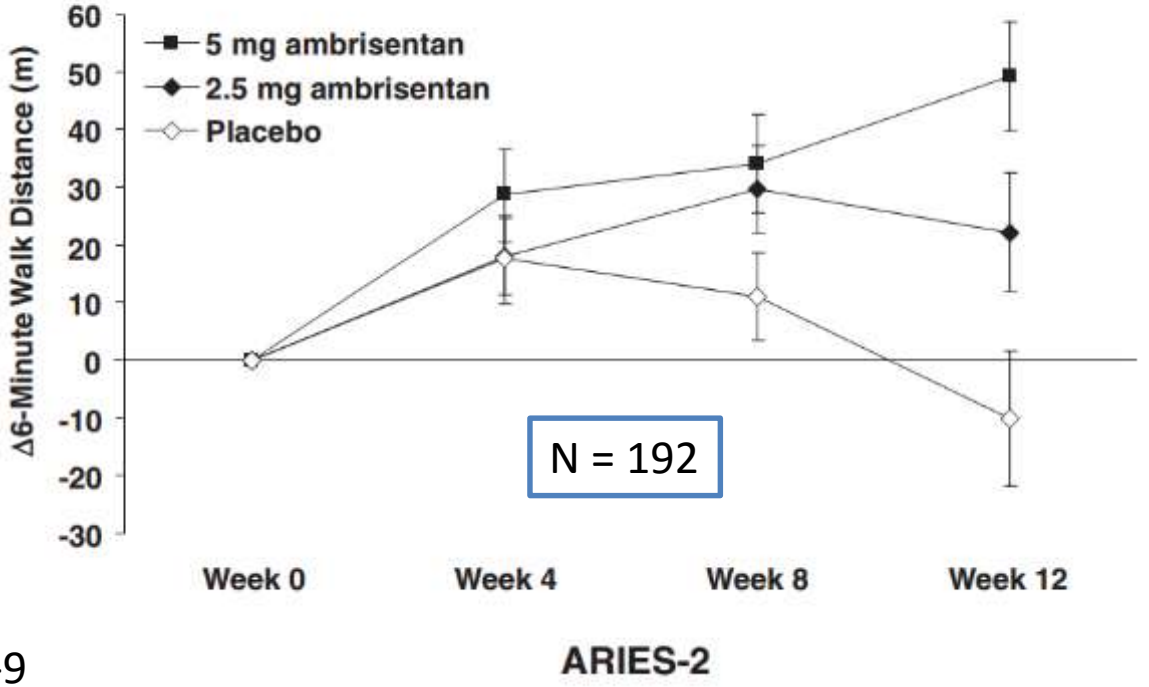
RCTs with ERA monotherapy

Study	n	Population	6MWD Improvement (compared to placebo)	Death/Clinical Worsening	Dyspnea	FC change	QoL	Hemodynamics	Serious Adverse Events
Channik 2001	32 (Bosentan 125 mg bd)	Grp 1 PAH NYH 3	76 m at 12 wks (p=.021)	No deaths (CW p=.03)	Y	Y	-	Y	Nil
Rubin 2002 (BREATHE-1)	213 (Bosentan 125 vs 250)	NYHA -4 also	44 m at 12 wks (p=.001), 250 mg better, IPAH group better	CW (p=.004)	Y	Y	-	Y	Transaminitis in 9%, dose dependent
Galie 2006 (BREATHE-5)	51 (Bosentan 125 bd)	Eisenmengers	53 m at 16 wks (p=.008)	-	-	Y	-	Y	Chest pain, palpitation, edema
Galie 2008 ARIES-1 and ARIES-2 (Ambrisentan)	202 (5 vs 10 mg)	Grp 1 PAH, 6MWD 150-450m	10mg=51m 5mg=31 m at 12 wks	No diff death or CW	Y	Y	N	Cath not done, NT-BNP improved	Nasal congestion, edema
	192 (2.5 vs 5 mg)		5mg=59 2.5mg=32 m at 12 wks	CW (p<0.05 in both doses	Y	Y	Y		do

ARIES 1 & 2: Ambrisentan

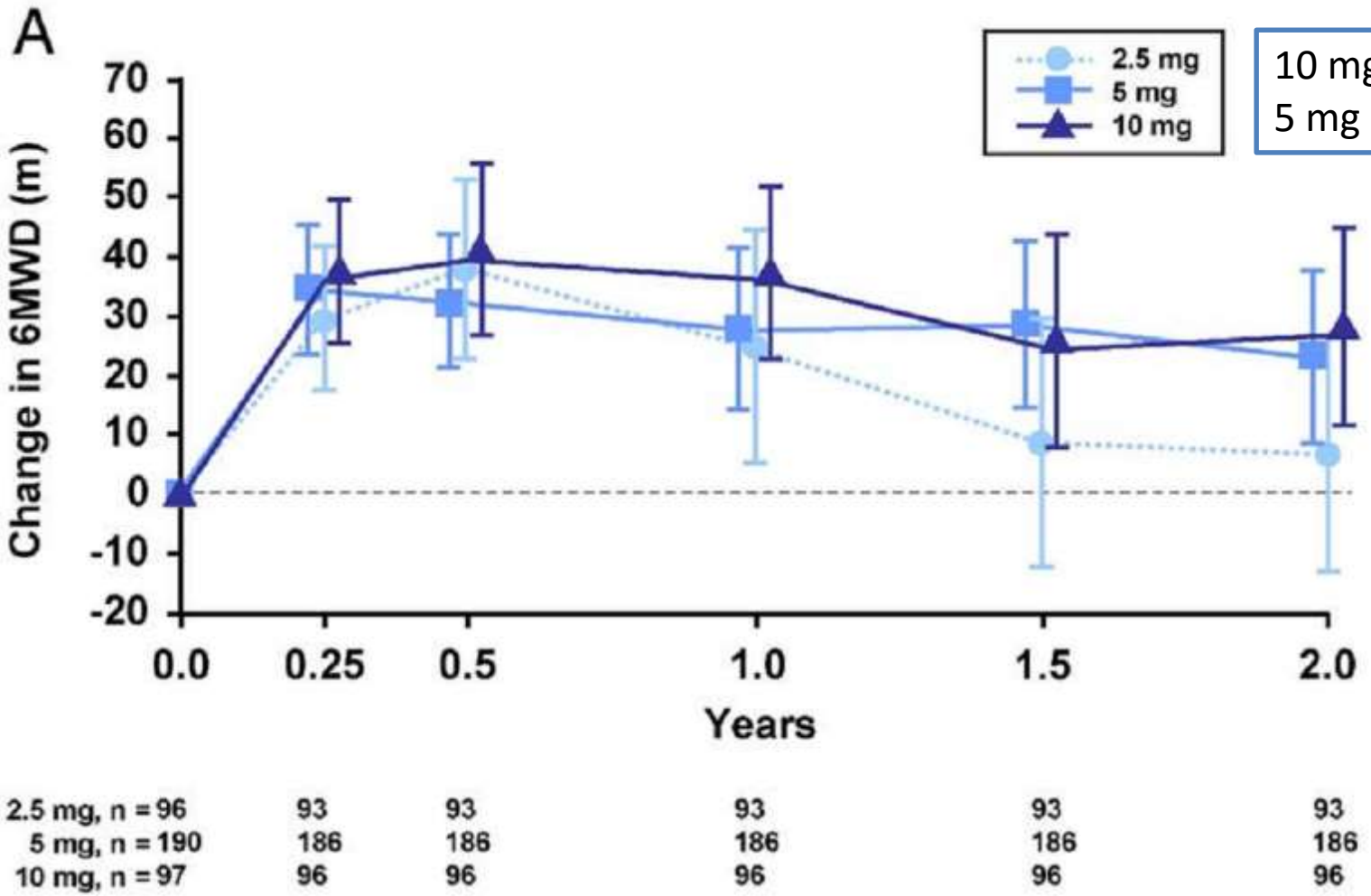
All WHO FC included, but consisted predominantly of WHO FC II, III





Circulation. 2008 Jun 10;117(23):3010-9

ARIES extension

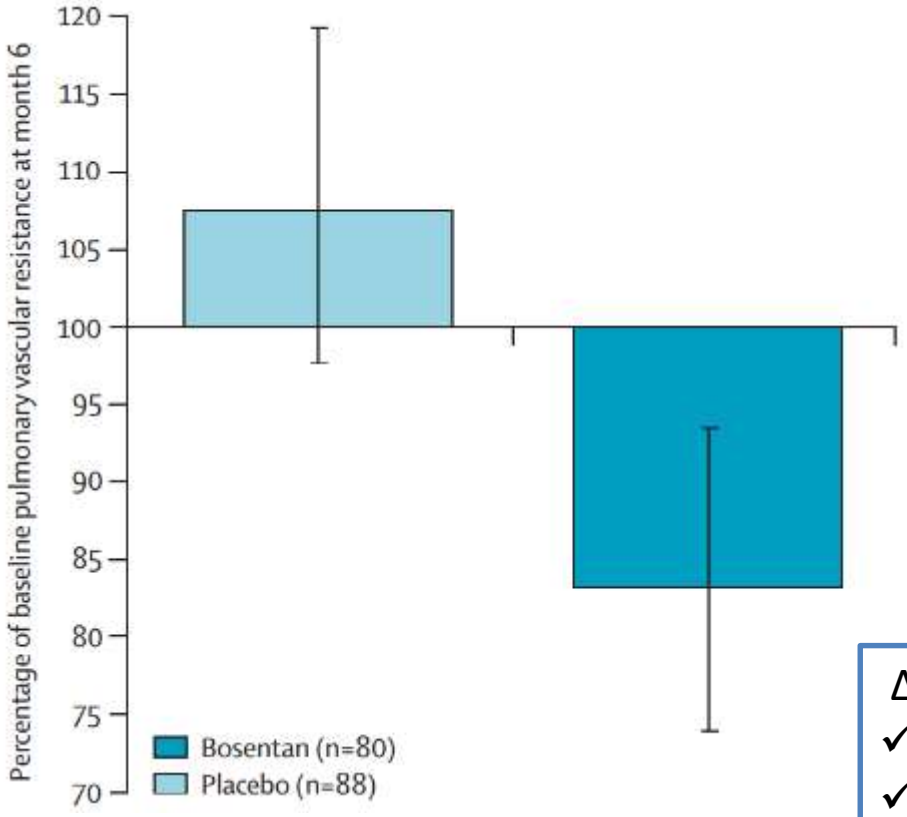


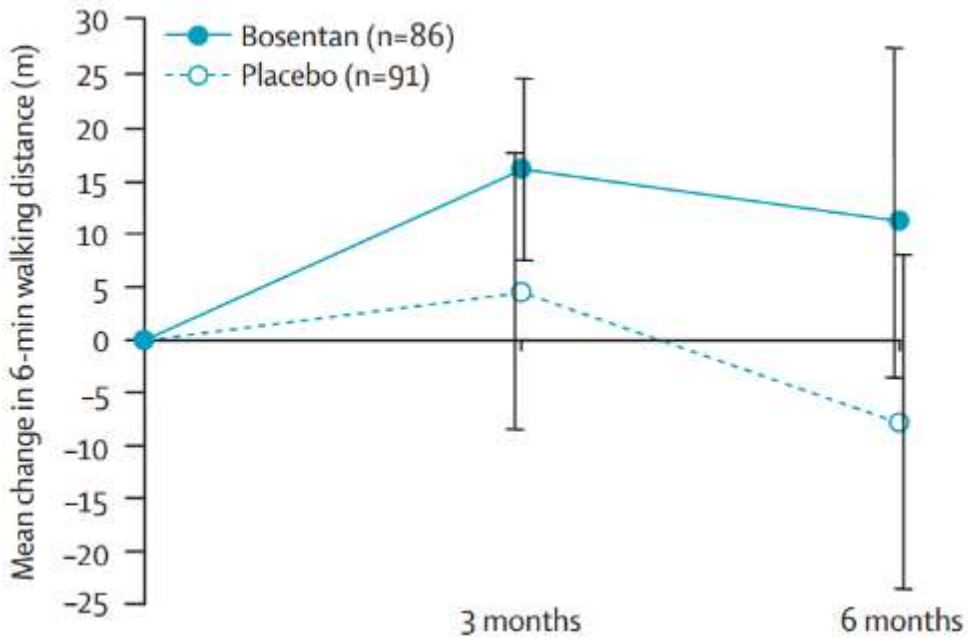
10 mg = 28 m
5 mg = 23 m

Dyspnea scores improved in 5mg & 10 mg, Survival better when compared with NIH registry

Oudiz et al.J Am Coll Cardiol. 2009

EARLY: Bosentan in WHO FC II





Δ6MWD = 19 m, p=ns
✓FC improvement
✓Time to CW improved
✓nT-BNP

N = 185

Galie N et al. Lancet 2008; 371: 2093–100.

Macitentan – SERAPHIN trial

- Multicentre, double blind RCT, n=742
- 250 = placebo, 250 = 3 mg, 242 = 10 mg
- Group 1, NYHA class II or III
- 61% PDE-5, 5% prostanoids as additional Rx
- Follow-up for 2 yrs
- Primary outcome = composite of mortality and morbidity

Pulido et al. NEJM 2013

Table 2. Primary and Secondary End Points for Events Related to Pulmonary Arterial Hypertension and Death.*

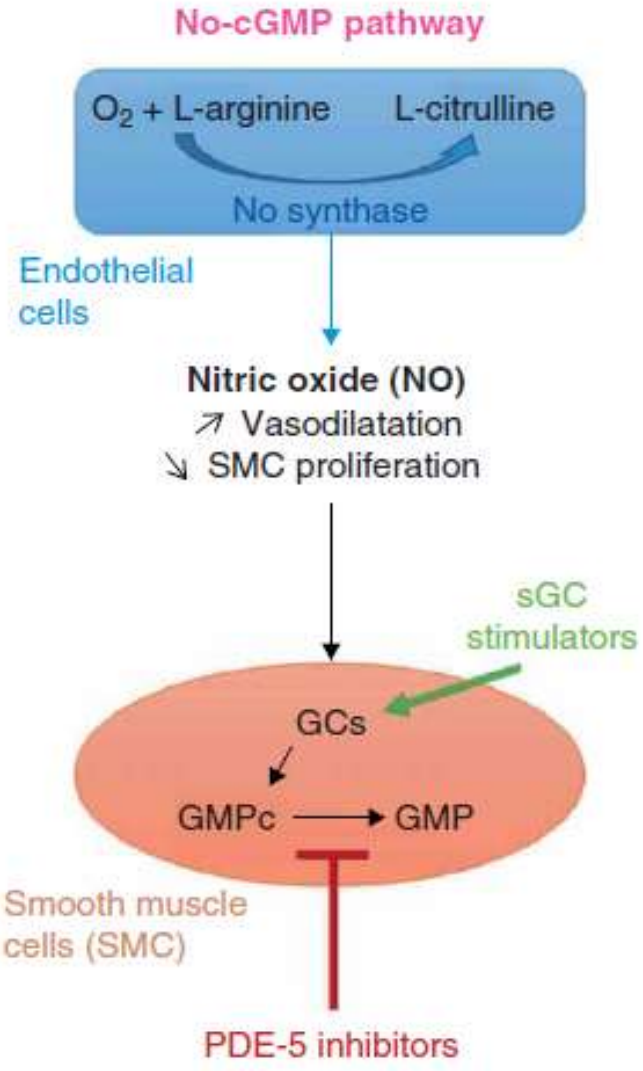
End Point	Placebo (N=250)	Macitentan, 3 mg (N=250)	Macitentan, 10 mg (N=242)	Macitentan, 3 mg, vs. Placebo		Macitentan, 10 mg, vs. Placebo	
				Hazard Ratio (97.5% CI)	P Value	Hazard Ratio (97.5% CI)	P Value
	number of patients (percent)						
Event related to PAH or death as the first event							
All events	116 (46.4)	95 (38.0)	76 (31.4)	0.70 (0.52–0.96)	0.01	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							
All events	84 (33.6)	65 (26.0)	50 (20.7)	0.67 (0.46–0.97)	0.01	0.50 (0.34–0.75)	<0.001
Hospitalization for PAH	79 (31.6)	56 (22.4)	45 (18.6)				
Death due to PAH‡	5 (2.0)	9 (3.6)	5 (2.1)				
Death from any cause	19 (7.6)	21 (8.4)	14 (5.8)	0.97 (0.48–1.98)	0.92	0.64 (0.29–1.42)	0.20
Death due to PAH§	14 (5.6)	14 (5.6)	7 (2.9)	0.87 (0.37–2.04)	0.72	0.44 (0.16–1.25)	0.07
Death from any cause by the end of the study¶	44 (17.6)	47 (18.8)	35 (14.5)	1.05 (0.65–1.67)	0.83	0.77 (0.46–1.28)	0.25

Treatment effect maintained across subgroups including those receiving background therapy

Other outcomes and status

- 6MWD (vs placebo): 3 mg-16.8m, 10 mg-22m
- Significant change in FC (20 and 22% resp)
- Better cardiac hemodynamics at 6 months
- ADR: Headache, anemia (4.3% in 10mg arm), nasal congestion
- 10 mg received FDA approval in October 2013
- India - NA

PDE-5 inhibitors - mechanism



Perrin et al. Expert Opin. Pharmacother. 2015

PDE-5 inhibitors - mechanism

- NO → vasodilator, antiproliferative, and antithrombotic.
- Its activity is mediated by second messenger, cGMP.
- cGMP rapidly degraded by PDE-5 isoenzyme.
- PDE-5 inhibition thus acts to enhance cGMP levels and prolong its vasodilating effects.
- Also, increased myocardial PDE-5 expression, facilitated by pressure-overloaded myocytes, occurs in the hypertrophied RV but not in normal hearts.
- PDE5 inhibitors may directly target RV function and acutely improve contractility in RV failure patients who express elevated PDE5 levels.

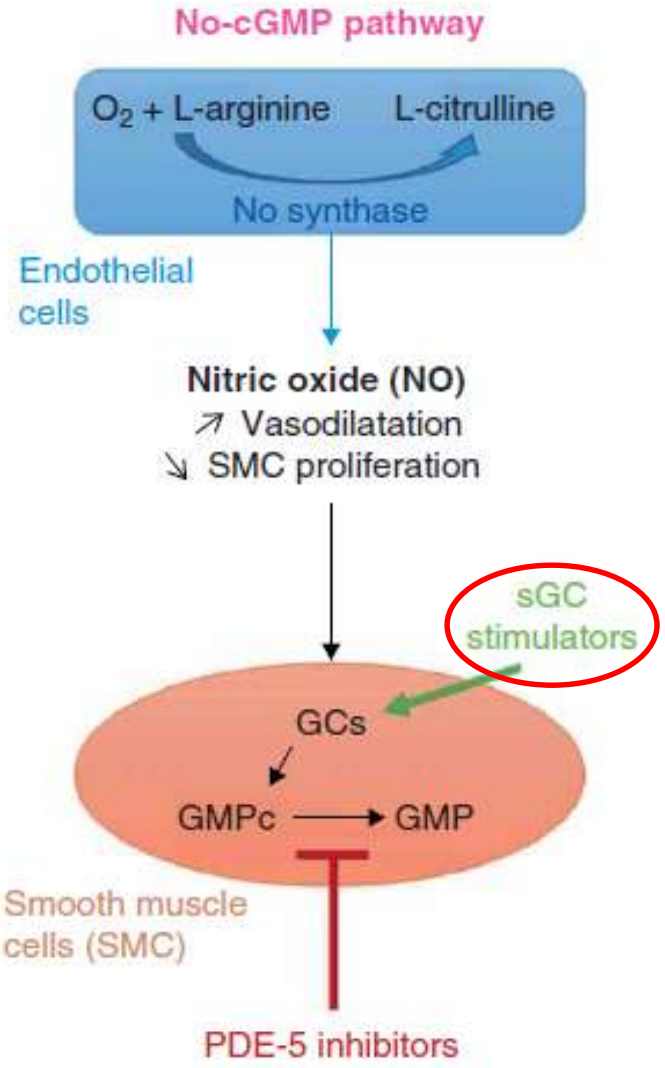
Richa Agarwal et al. AHJ 2011

Comparison of PDE-5 inhibitors

Drug	Dose	Main Adverse Affects	Interactions	Contraindications
Sildenafil	Only 20 mg tds FDA approved (higher doses used off-label)	Flushing, dyspepsia, myalgia, visual changes, epistaxis, nasal congestion, headache	Concomitant nitrates avoided (hypotension), Cy450 inhibitors	MI in past 3 mon, hypotension, AION
Tadalafil	40 mg od	do	do	do

Study	n	Population	6MWD Improvement (compared to placebo)	Death/Clinical Worsening	Dyspnea	FC change	QoL	Hemodynamics	Serious Adverse Events
Galie 2005 SUPER (Sildenafil)	278 (20, 40, 80 mg tds)	Grp 1 PAH, NYH II or III	45, 46 and 50 m for the 3 doses at 12 wks (p<.001)	P= NS	N	Y	-	Y	MI, LV dysfunction, postural hypotension (1 each), frequent mild ADR
Galie 2009 PHIRST (Tadalafil)	405 (2.5, 10, 20, 40 mg od)	Grp 1 PAH, NYH II or III, **53% on bosentan**	33 m at 16 wks (p=.01) Sig benefit seen in 40 mg & bosentan naïve	CW (p=.04 for 40 mg)	N	N in whole, Y in bosentan naive	Y	Y	Nil, frequent mild ADR (49%) – MC headache
Galie 2012 PHIRST Extn (Tadalafil)	357 (63 in 20 mg, 293 in 40 mg)		Effect maintained at 52 wks, but no improvement in dose escalated patients	No diff in 20 or 40 mg,	N	Y	Y	-	do

Guanylyl cyclase activator - Riociguat



Perrin et al. Expert Opin. Pharmacother. 2015

Guanylyl cyclase activator - Riociguat

- Soluble guanylyl cyclase stimulator → increases cGMP levels → Vasodilation
- Pyrimidine derivative
- First-in-its class drug
- Good oral bioavailability
- T ½ = 5-10 hrs
- Dose = 1-2.5 mg tds

- MC adverse effects:

  Hypotension, syncope, transaminitis, supraventricular tachycardia, edema, headache, nasal congestion, neck pain
- Dose to be reduced by 0.5-1 mg in case of ADR

Meis et al. Expert Opin. Pharmacother. 2015

RCTs with Riociguat

Study	n	Population	6MWD Improvement (compared to placebo)	Death/Clinical Worsening	FC change	QoL	Hemodynamics	Serious Adverse Events
Ghofrani 2013 (PATENT)	443	Grp 1 PAH, NYHA II,III>IV	36m at 12 wks, 55m at 24 wks (p=.001), NYHA III/IV had more benefit	Y	Y	N	Y	Hypotension (10%, p=.005))
Ghofrani 2013 (CHEST-1)	261	CTEPH, NYH II or III	46m at 12 wks, (p=.001)	N	Y	Y (Dyspnea scores also improved)	Y	do
Ghofrani 2015	22	COPD with PAH, GOLD II-IV, FEV1<70, pO2>50	-	-	-	-	Y	-

Combination therapy for PAH

- Strong rationale for combining drugs as different drugs act on different pathways
- Beyond a simple additive effect, certain combinations may also have a synergistic action (eg Sildenafil and prostanoid/Selective ETRA)
- REVEAL registry – 52% pts on combination Rx
- The general treatment paradigm has been to add drugs sequentially
- In an early open-label trial using a step-wise goal-directed approach, sildenafil and iloprost added sequentially after 1st line therapy with bosentan (n=123) showed significant benefit

Hoeper et al. Eur Respir J 2005; 26: 858–863

Sequential vs. upfront combination

Emerging concept

- Mortality and Morbidity similar to many rheumatologic and oncologic disorders
- Multi-mechanistic approach from the start, in which physicians use several drug combinations to effectively treat the disease and gain disease remission.
- Several large trials testing the upfront multi-drug combination therapy are ongoing, AMBITION trial recently published

BREATHE-2: Bosentan + IV epoprostenol

ABSTRACT: The efficacy and safety of combining bosentan, an orally active dual endothelin receptor antagonist and epoprostenol, a continuously infused prostaglandin, in the treatment of pulmonary arterial hypertension (PAH) was investigated.

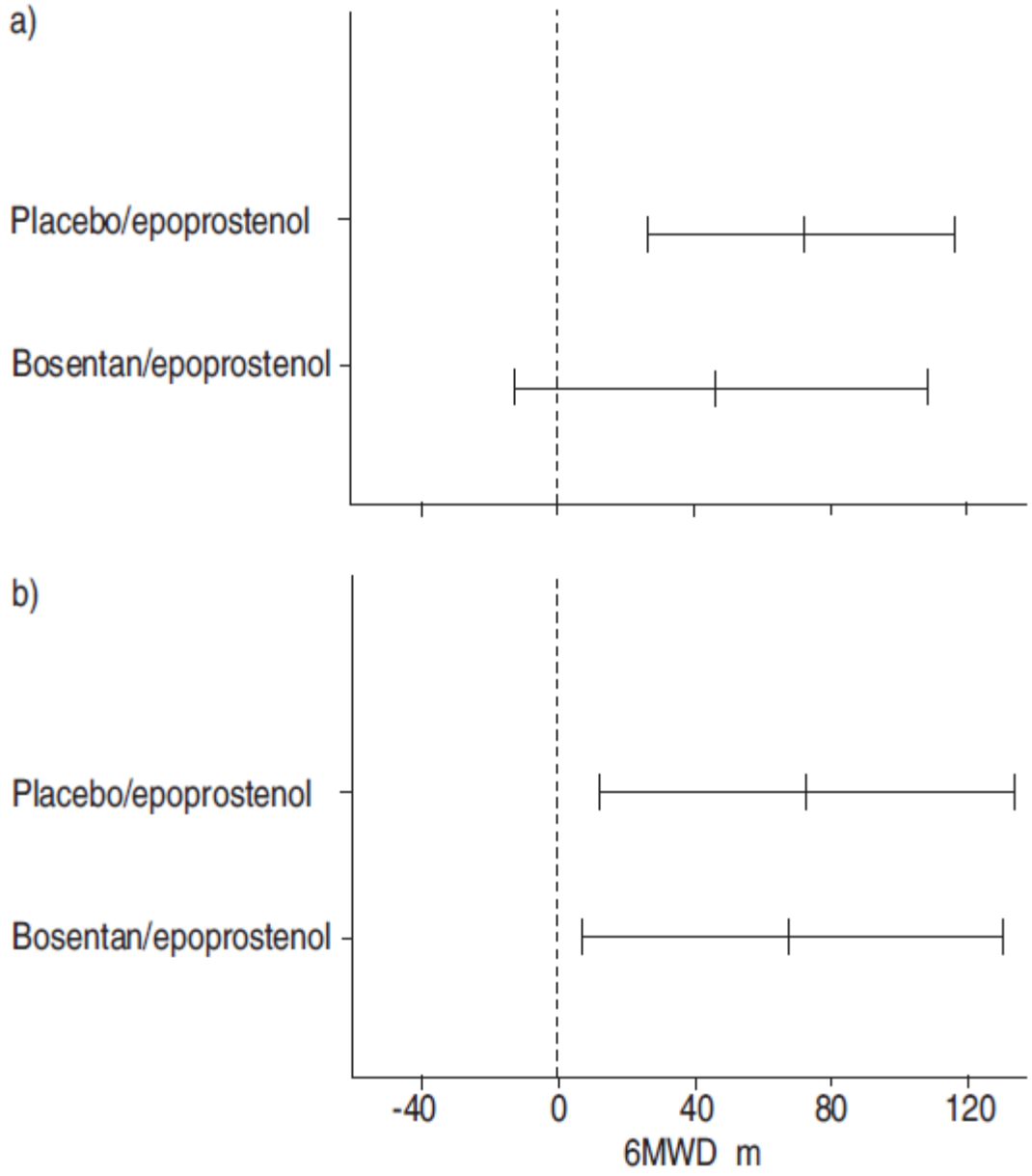
In this double-blind, placebo-controlled prospective study, 33 patients with PAH started epoprostenol treatment (2 $ng \cdot kg^{-1}min^{-1}$ starting dose, up to 14 ± 2 $ng \cdot kg^{-1}min^{-1}$ at week 16) and were randomised for 16 weeks in a 2:1 ratio to bosentan (62.5 mg *b.i.d* for 4 weeks then 125 mg *b.i.d*) or placebo.

Haemodynamics, exercise capacity and functional class improved in both groups at week 16. In the combination treatment group, there was a trend for a greater (although nonsignificant) improvement in all measured haemodynamic parameters. There were four withdrawals in the bosentan/epoprostenol group (two deaths due to cardiopulmonary failure, one clinical worsening, and one adverse event) and one withdrawal in the placebo/epoprostenol group (adverse event).

This study showed a trend but no statistical significance towards haemodynamics or clinical improvement due to the combination of bosentan and epoprostenol therapy in patients with pulmonary arterial hypertension. Several cases of early and late major complications were reported. Additional information is needed to evaluate the risk/benefit ratio of combined bosentan-epoprostenol therapy in pulmonary arterial hypertension.

Eur Respir J 2004; 24: 353–359.

Humbert et al. Eur Respir J 2004



Baseline

Week 16

COMBI Trial: Iloprost + Bosentan

ABSTRACT: Addition of inhaled iloprost to bosentan may have beneficial effects in patients with idiopathic pulmonary arterial hypertension (IPAH). A multicentre, open, randomised, controlled trial was performed to assess the safety and efficacy of inhaled iloprost in patients with IPAH who had already been treated with bosentan.

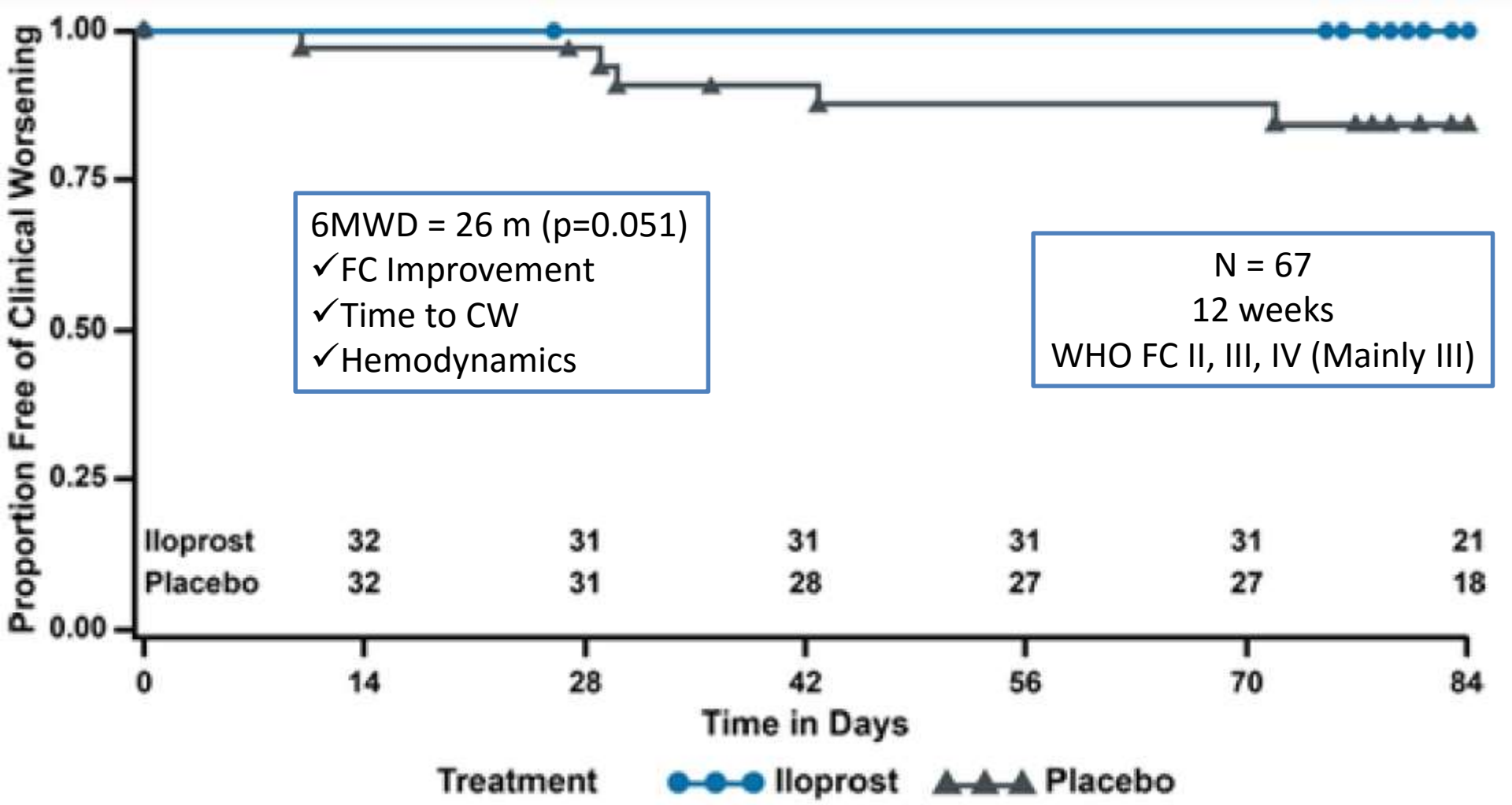
The trial was terminated early after a futility analysis predicted failure with respect to the predetermined sample size. At that time, 40 patients were randomised to receive either bosentan alone (control group) or bosentan plus inhaled iloprost (combination group) for a 12-week period.

The primary end-point, change in 6-min walking distance, was not met (mean changes +1 m and -9 m in the control and combination group, respectively). These results may have been skewed by three outliers in the iloprost group who presented with severe clinical worsening. None of the secondary end-points including functional class, peak oxygen uptake, and time to clinical worsening differed significantly between groups.

The current study failed to show a positive effect of adding inhaled iloprost to bosentan in idiopathic pulmonary arterial hypertension patients. Further studies involving larger sample sizes and long-term follow-up are needed to determine the efficacy of adding inhaled iloprost to bosentan in patients with idiopathic pulmonary arterial hypertension.

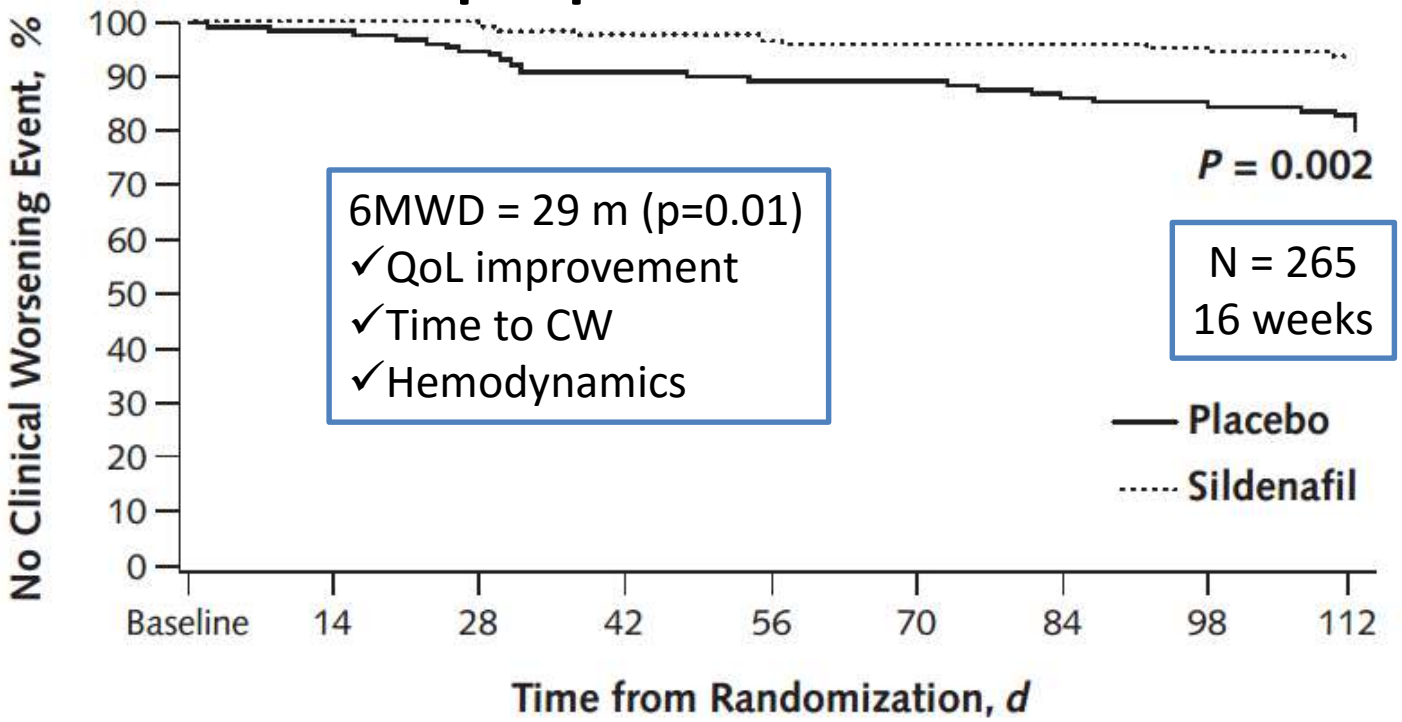
Hoeper et al. Eur Respir J 2006

STEP trial: Addition of Inhaled Iloprost to Bosentan



McLaughlin et al Am J Respir Crit Care Med. 2006

PACES: Addition of sildenafil to epoprostenol



6MWD = 29 m (p=0.01)
✓QoL improvement
✓Time to CW
✓Hemodynamics

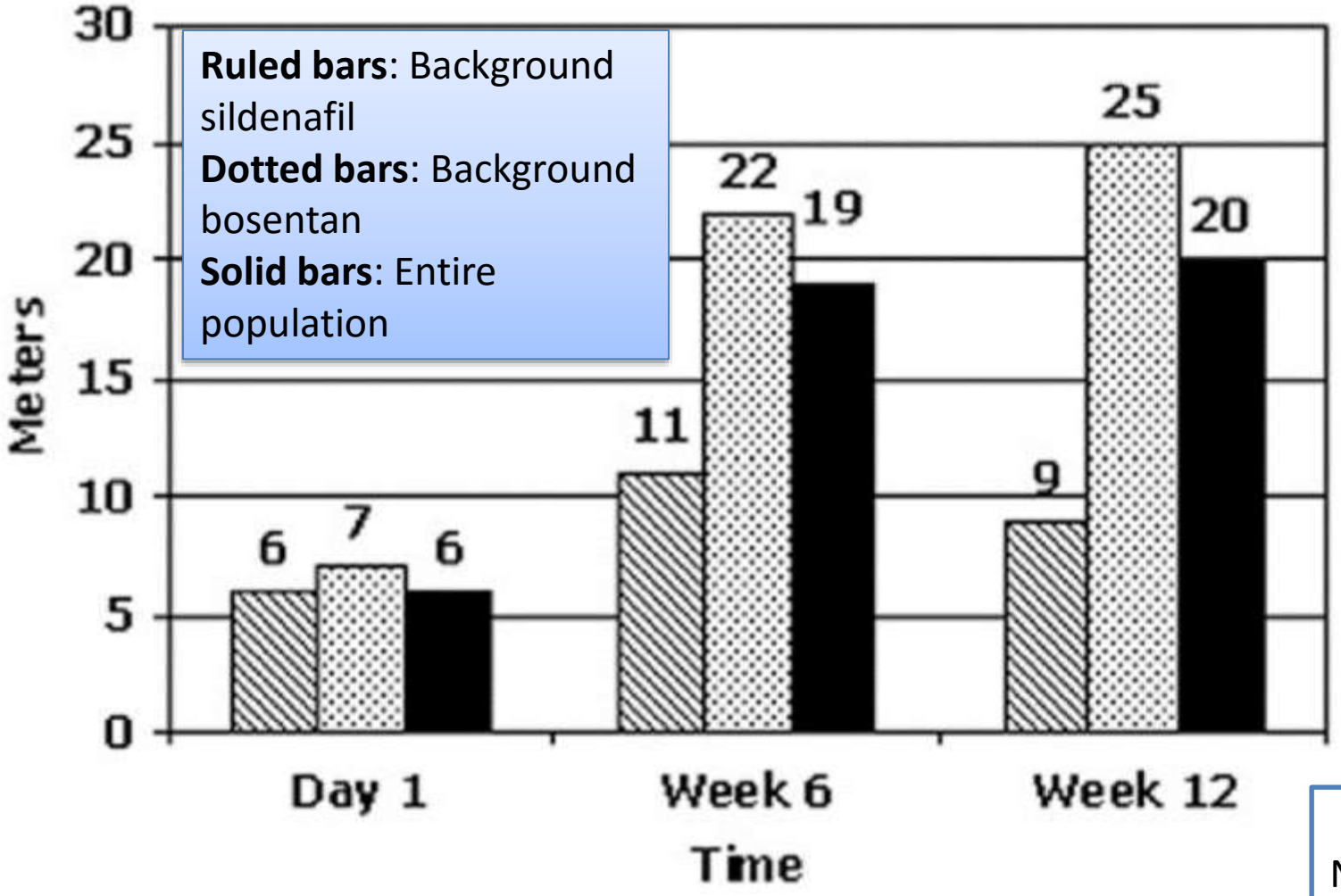
N = 265
16 weeks

Treatment	Persons at Risk (Censored), *n*				
	Baseline	Day 28*	Day 56†	Day 84‡	Day 112§
Epoprostenol + placebo	131	123 (1)	116 (0)	111 (2)	70 (36)
Epoprostenol + sildenafil	134	134 (0)	128 (2)	125 (2)	78 (44)

All WHO FC included, but predominantly II, III

Simonneau et al. Ann Intern Med. 2008

TRIUMPH I: Addition of inhaled treprostinil to oral therapy



N = 235
NYHA III/IV

McLaughlin VV et al. J Am Coll Cardiol. 2010 May 4;55(18):1915-22

Tadalafil + Bosentan in PHIRST: 6MWD

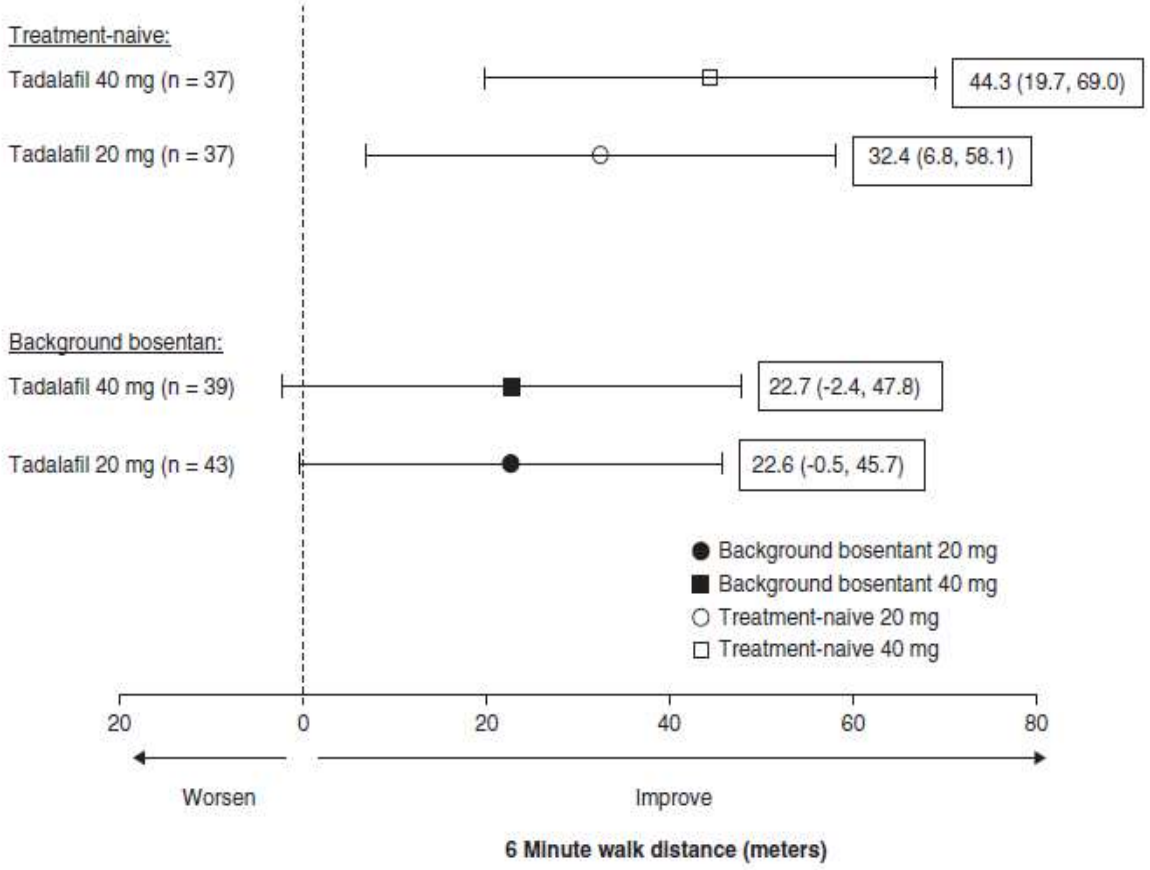


Figure 1. Placebo-adjusted treatment differences in 6-min walk distance (meters) from baseline to week 16 by bosentan use.

Tadalafil + Bosentan in PHIRST: clinical worsening

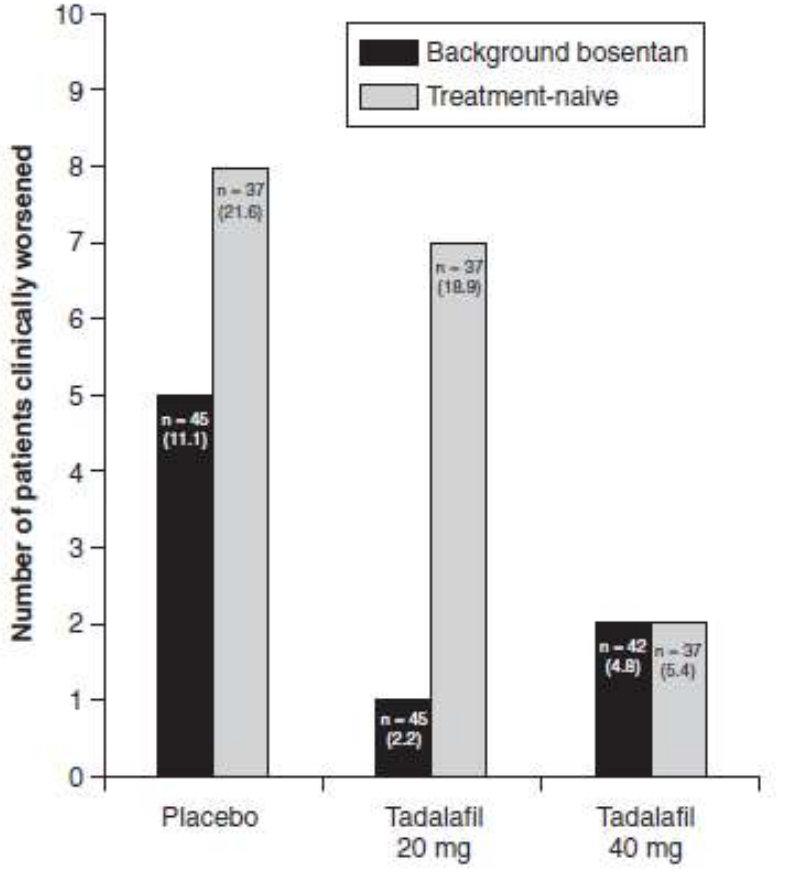


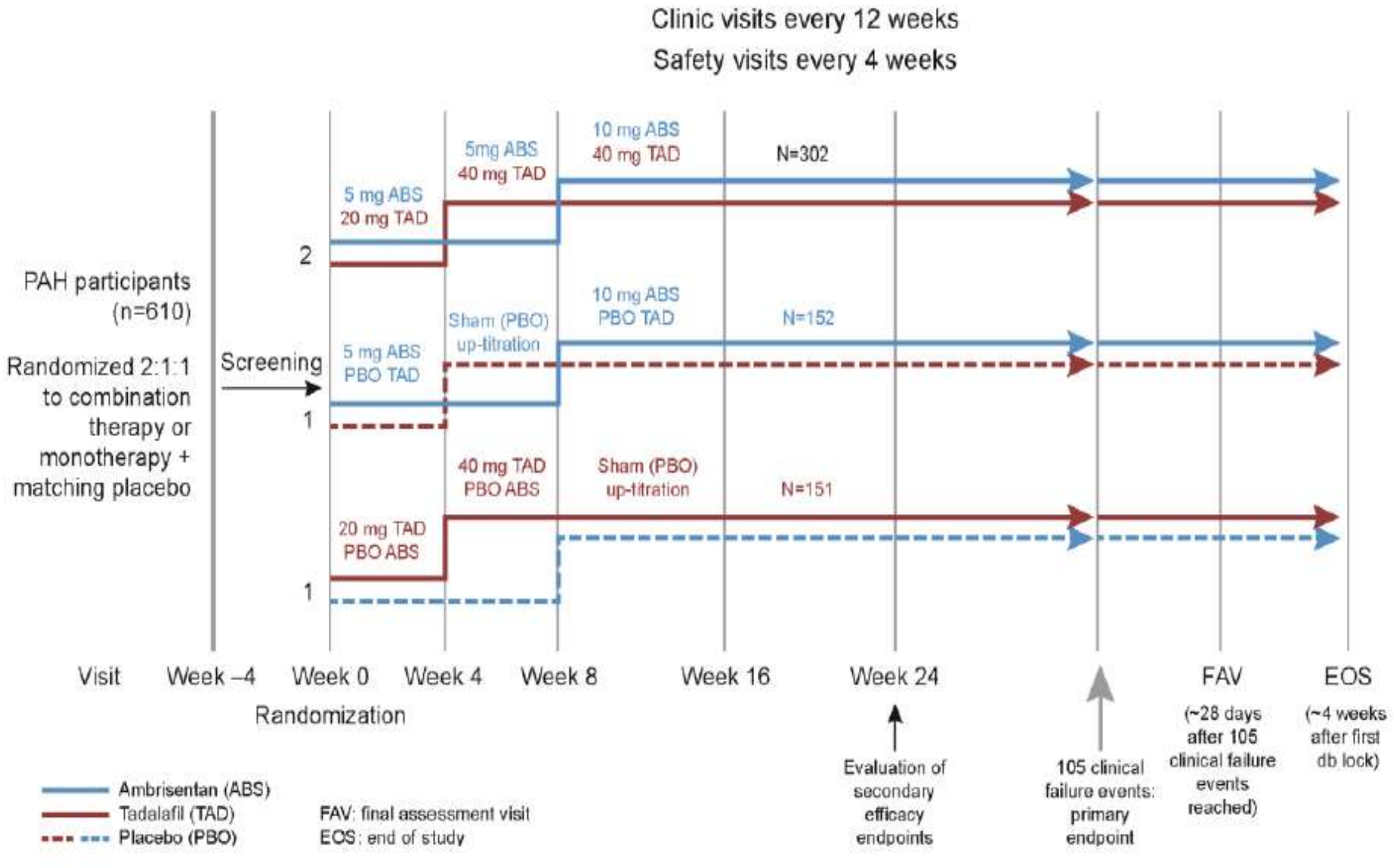
Figure 2. Clinical worsening by bosentan use and tadalafil treatment subgroup.

AMBITION trial

- Multicenter, randomized, double-blind, phase 3 trial, n=500
- 126 pts = Ambrisentan 10 mg monotherapy
- 121 pts = Tadalafil 40 mg monotherapy
- 253 pts = Combination
- Follow-up 517 days
- Group I PAH
- NYHA II (30%), III (70%)

Galie et al. NEJM. Aug 2015

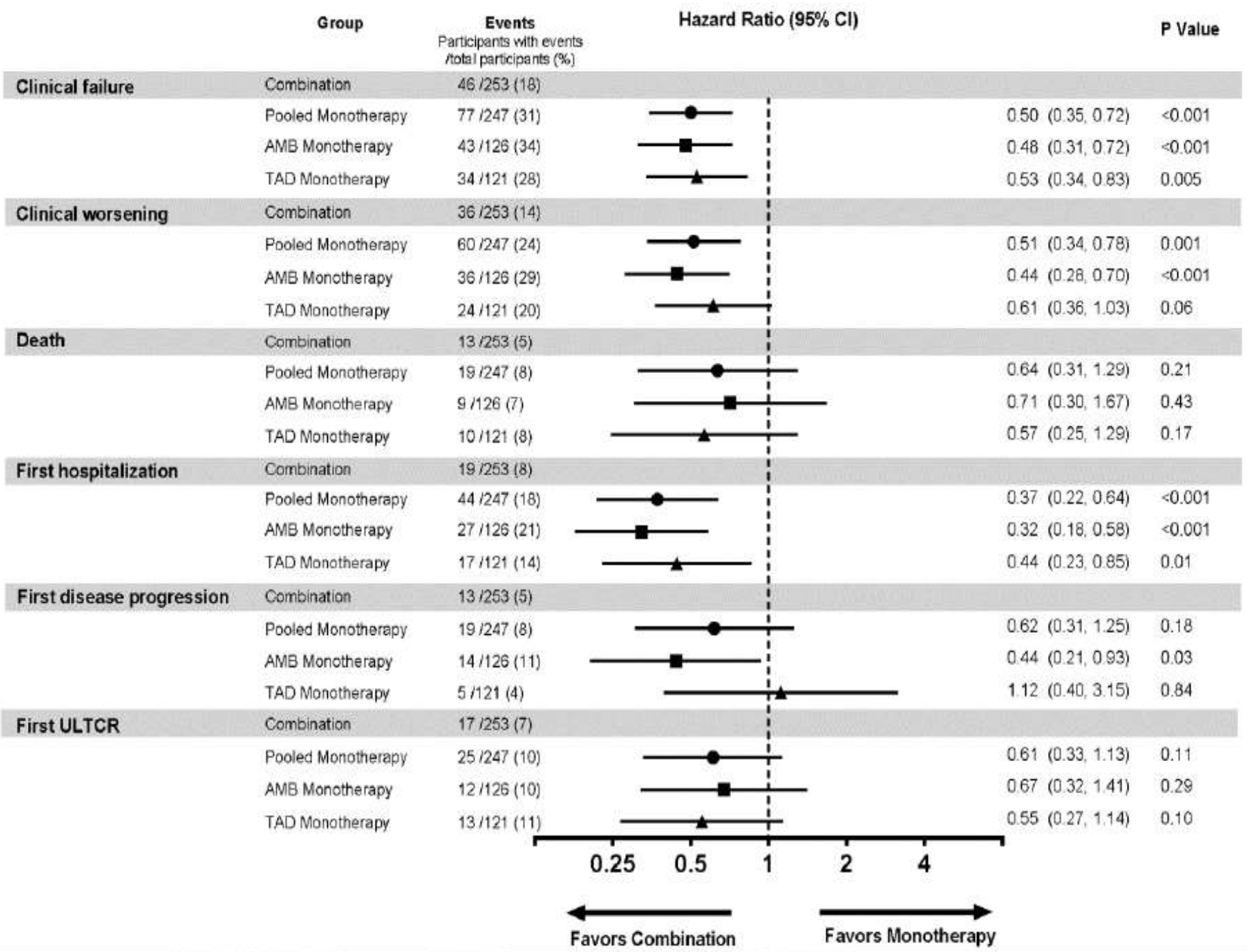
Study Design



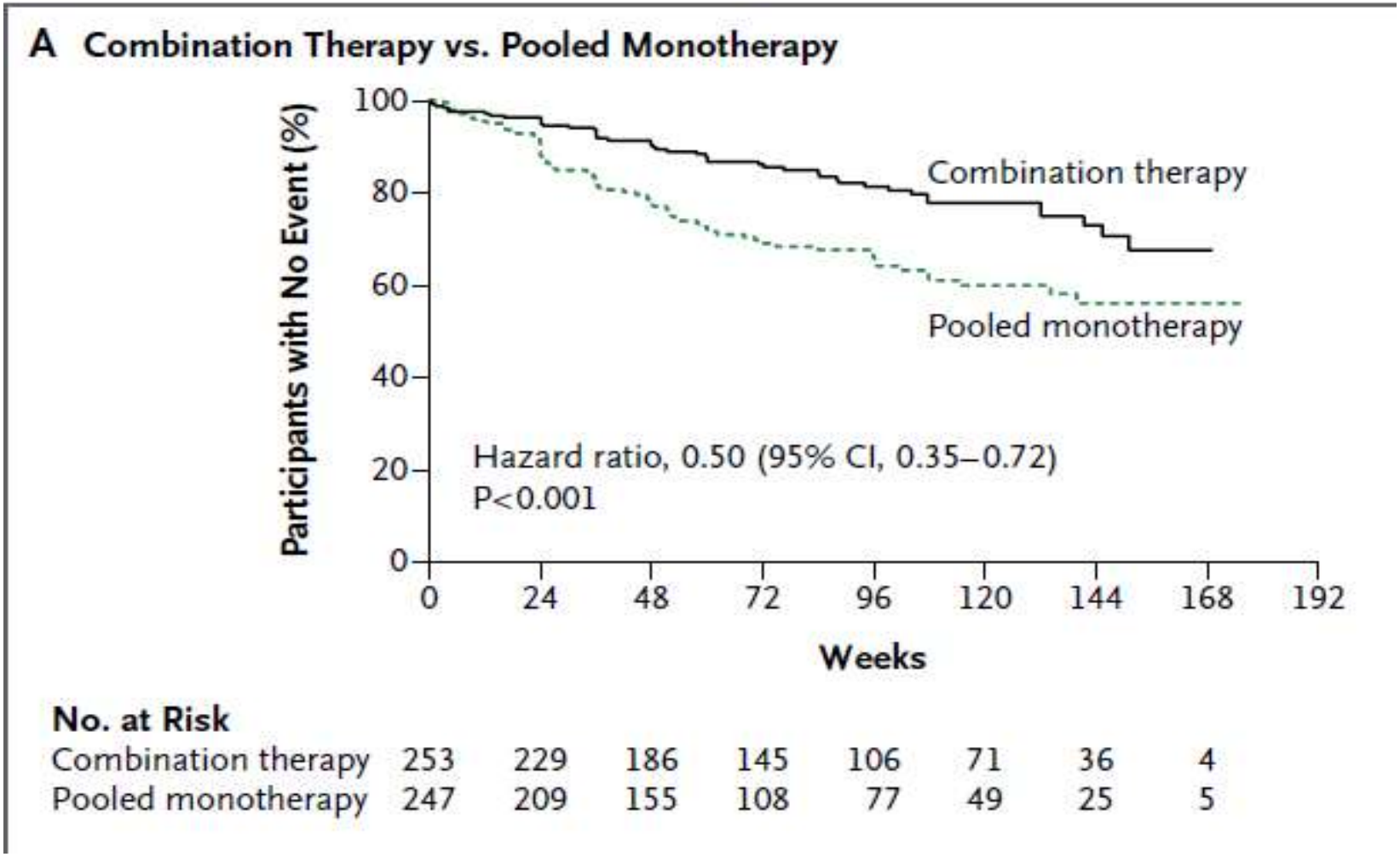
Results

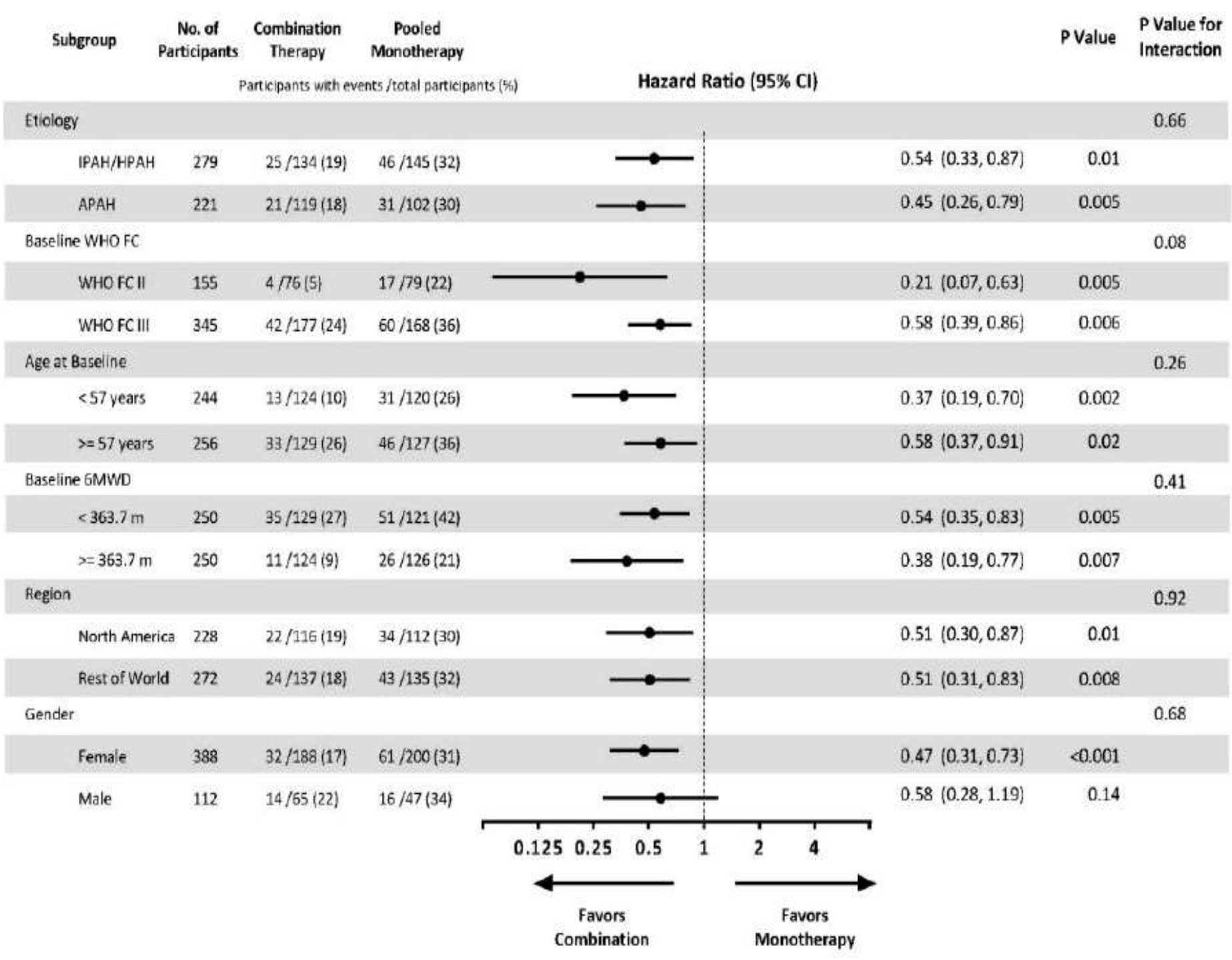
Table 4. Primary and Secondary Efficacy End Points.*

End Point	Combination-Therapy Group (N=253)	Pooled-Monotherapy Group (N=247)	Ambrisentan-Monotherapy Group (N=126)	Tadalafil-Monotherapy Group (N=121)
Primary end point				
First event of clinical failure — no. of participants (%)	46 (18)	77 (31)	43 (34)	34 (28)
Death	9 (4)	8 (3)	2 (2)	6 (5)
Hospitalization for worsening pulmonary arterial hypertension	10 (4)	30 (12)	18 (14)	12 (10)
Disease progression	10 (4)	16 (6)	12 (10)	4 (3)
Unsatisfactory long-term clinical response	17 (7)	23 (9)	11 (9)	12 (10)
Hazard ratio, combination therapy vs. monotherapy (95% CI)	Reference	0.50 (0.35 to 0.72)	0.48 (0.31 to 0.72)	0.53 (0.34 to 0.83)
P value	—	<0.001	<0.001	0.005


Group
Events
Participants with events /total participants (%)
Hazard Ratio (95% CI)
P Value
Clinical failure
Combination 46 /253 (18)
Pooled Monotherapy 77 /247 (31) 0.50 (0.35, 0.72) <0.001
AMB Monotherapy 43 /126 (34) 0.48 (0.31, 0.72) <0.001
TAD Monotherapy 34 /121 (28) 0.53 (0.34, 0.83) 0.005
Clinical worsening
Combination 36 /253 (14)
Pooled Monotherapy 60 /247 (24) 0.51 (0.34, 0.78) 0.001
AMB Monotherapy 36 /126 (29) 0.44 (0.28, 0.70) <0.001
TAD Monotherapy 24 /121 (20) 0.61 (0.36, 1.03) 0.06
Death
Combination 13 /253 (5)
Pooled Monotherapy 19 /247 (8) 0.64 (0.31, 1.29) 0.21
AMB Monotherapy 9 /126 (7) 0.71 (0.30, 1.67) 0.43
TAD Monotherapy 10 /121 (8) 0.57 (0.25, 1.29) 0.17
First hospitalization
Combination 19 /253 (8)
Pooled Monotherapy 44 /247 (18) 0.37 (0.22, 0.64) <0.001
AMB Monotherapy 27 /126 (21) 0.32 (0.18, 0.58) <0.001
TAD Monotherapy 17 /121 (14) 0.44 (0.23, 0.85) 0.01
First disease progression
Combination 13 /253 (5)
Pooled Monotherapy 19 /247 (8) 0.62 (0.31, 1.25) 0.18
AMB Monotherapy 14 /126 (11) 0.44 (0.21, 0.93) 0.03
TAD Monotherapy 5 /121 (4) 1.12 (0.40, 3.15) 0.84
First ULTCR
Combination 17 /253 (7)
Pooled Monotherapy 25 /247 (10) 0.61 (0.33, 1.13) 0.11
AMB Monotherapy 12 /126 (10) 0.67 (0.32, 1.41) 0.29
TAD Monotherapy 13 /121 (11) 0.55 (0.27, 1.14) 0.10
0.25
0.5
1
2
4
Favors Combination
Favors Monotherapy

Kaplan–Meier Curves for the Probability of a First Adjudicated Primary End-Point Event.




Subgroup
No. of Participants
Combination Therapy
Pooled Monotherapy
Participants with events /total participants (%)
Hazard Ratio (95% CI)
P Value
P Value for Interaction
Etiology 0.66
IPAH/HPAH 279 25 /134 (19) 46 /145 (32) 0.54 (0.33, 0.87) 0.01
APAH 221 21 /119 (18) 31 /102 (30) 0.45 (0.26, 0.79) 0.005
Baseline WHO FC 0.08
WHO FC II 155 4 /76 (5) 17 /79 (22) 0.21 (0.07, 0.63) 0.005
WHO FC III 345 42 /177 (24) 60 /168 (36) 0.58 (0.39, 0.86) 0.006
Age at Baseline 0.26
< 57 years 244 13 /124 (10) 31 /120 (26) 0.37 (0.19, 0.70) 0.002
>= 57 years 256 33 /129 (26) 46 /127 (36) 0.58 (0.37, 0.91) 0.02
Baseline 6MWD 0.41
< 363.7 m 250 35 /129 (27) 51 /121 (42) 0.54 (0.35, 0.83) 0.005
>= 363.7 m 250 11 /124 (9) 26 /126 (21) 0.38 (0.19, 0.77) 0.007
Region 0.92
North America 228 22 /116 (19) 34 /112 (30) 0.51 (0.30, 0.87) 0.01
Rest of World 272 24 /137 (18) 43 /135 (32) 0.51 (0.31, 0.83) 0.008
Gender 0.68
Female 388 32 /188 (17) 61 /200 (31) 0.47 (0.31, 0.73) <0.001
Male 112 14 /65 (22) 16 /47 (34) 0.58 (0.28, 1.19) 0.14
0.125 0.25 0.5 1 2 4
Favors Combination
Favors Monotherapy

Secondary end points

Secondary end points	Combination	Pooled Monotherapy	Ambrisentan	Tadalafil
NT-proBNP level†				
Percentage change in geometric mean from baseline to week 24	−67.2	−50.4	−56.2	−43.8
P value	Reference	<0.001	0.01	<0.001
Satisfactory clinical response at week 24 — no. of participants/total no. (%)‡				
Yes	91/234 (39)	66/226 (29)	35/113 (31)	31/113 (27)
No	143/234 (61)	160/226 (71)	78/113 (69)	82/113 (73)
Unknown	19/253 (8)	21/247 (9)	13/126 (10)	8/121 (7)
Odds ratio, combination therapy vs. monotherapy (95% CI)	Reference	1.56 (1.05 to 2.32)	1.42 (0.88 to 2.31)	1.72 (1.05 to 2.83)
P value	—	0.03	0.15	0.03
6-Minute walk distance — m§				
Median (IQR) change from baseline to week 24	48.98 (4.63 to 85.75)	23.80 (−12.25 to 64.53)	27.00 (−14.00 to 63.25)	22.70 (−8.25 to 66.00)
P value	Reference	<0.001	<0.001	0.003
Change in WHO functional class at week 24 — no. of participants/total no. (%)§				
Improved	94/252 (37)	81/244 (33)	42/124 (34)	39/120 (33)
No change	146/252 (58)	147/244 (60)	73/124 (59)	74/120 (62)
Deteriorated	12/252 (5)	16/244 (7)	9/124 (7)	7/120 (6)
P value	Reference	0.24	0.30	0.36

Combination Therapy:

Ongoing or Recently Completed Clinical Trials

	Current therapy	Added therapy	Patients (*n*)	Study duration	Primary end point
FREEDOM-C	Bosentan and/ or sildenafil	Treprostinil oral	300	16 weeks	6MWD
AMBITION	Ambrisentan/ tadalafil/combo	Combo vs mono	300	Event-driven	Morbidity/mortality event
Pfizer	Bosentan	Sildenafil	106	12 weeks	6MWD
COMPASS-1	Bosentan	Sildenafil	45	Single dose	PVR
COMPASS-2	Sildenafil	Bosentan	250	Event-driven	Morbidity/mortality event
COMPASS-3	Bosentan	Sildenafil	100	16 weeks	6MWD
ATHENA-1	Sildenafil or tadalafil	Ambrisentan	40	24 weeks	PVR
SERAPHIN	Naïve/PDE-5/PGI/combo	Macitentan	742	Event-driven	Morbidity/mortality event
PATENT	Naïve/PGI/ERA	Riociguat	462	12 weeks	6MWD
IMPRES	≥2 current therapies	Imatinib	200	24 weeks	6MWD
Gilead	Stable PAH therapy	Cicletanine	160	12 weeks	6MWD
ATPAHSS	Ambrisentan/ tadalafil/combo	Combo vs mono	63	36 weeks	RV mass/PVR
GRIPHON	ERA, PDE5 or both	Selexipag	670	Event-driven	Morbidity/mortality event
Novartis	Stable PAH therapy	Nilotinib	66	6 months	PVR

Warfarin – role in Group 1 PAH

- Retrospective data show benefit, No prospective RCT in modern PAH therapy era
- But used in 50-85% patients in US/European registries
- Rationale for use:
  - Many endothelial cell abnormalities that predispose patients to PAH also predispose thrombosis
  - Microscopic throbi well documented on pathology
  - Heart failure, immobilisation, Central venous lines

McLaughlin et al. ACCF/AHA 2009 Expert Consensus Document on PAH

Warfarin in PAH – meta-analysis

- No RCTs found
- 9 cohort studies were selected (2 prospective)
- 31% mortality risk reduction with warfarin (HR = 0.69, CI 0.57-0.82)
- “Pooled results from cohort studies suggest a survival benefit, but the moderate study quality, the high risk of publication bias, and the methodological limitations inherent in the analysis of observational studies preclude a definite conclusion.”
- Need for quality RCT

Caldeira et al. Canadian Journal of Cardiology 30 (2014)

Guidelines on Warfarin

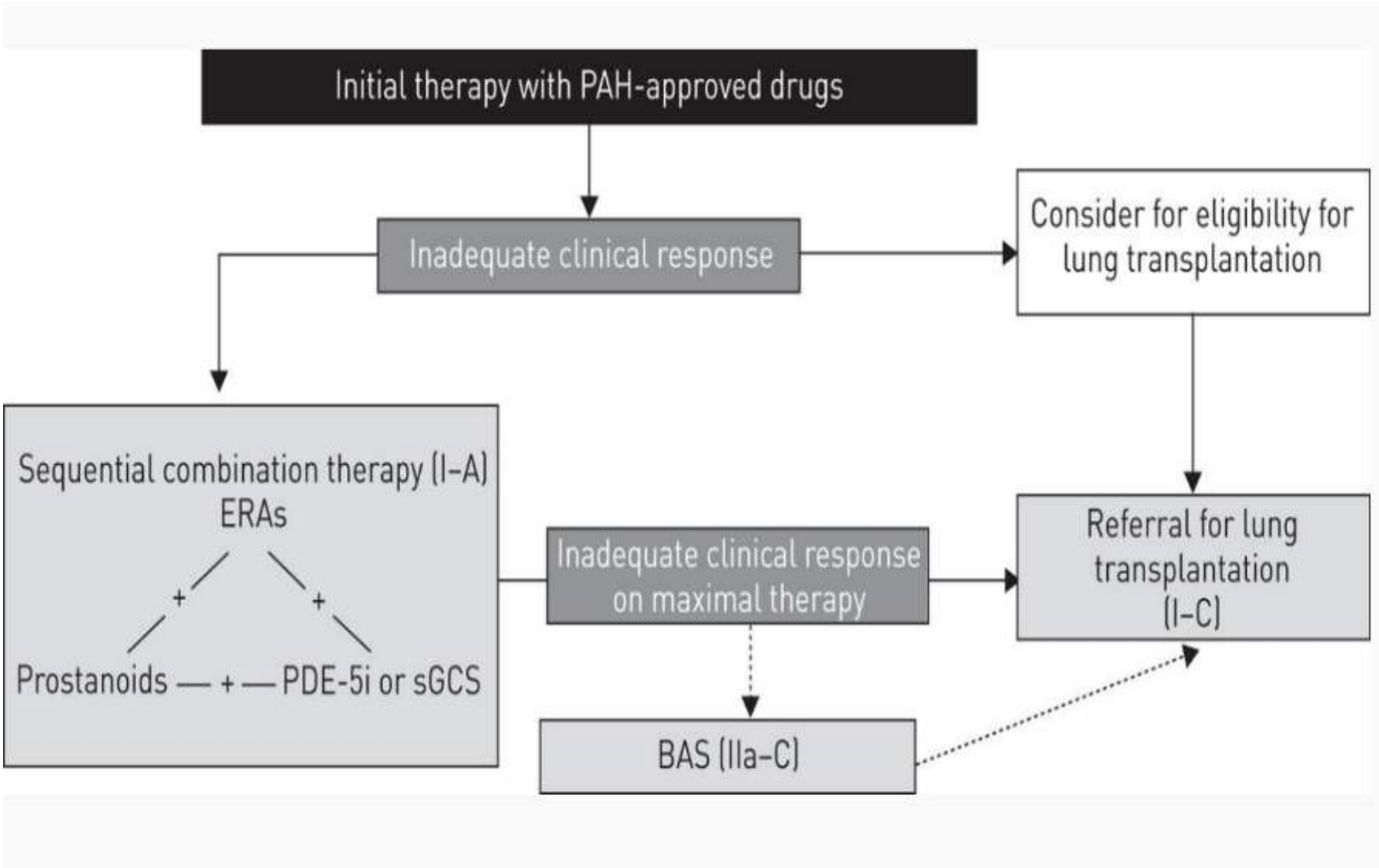
- Warfarin anticoagulation is recommended in all patients with IPAH.
- Updated guidelines have not changed this recommendation.
- However should be used with caution in patients with hemoptysis or bleeding
- Also interactions with other PAH specific drugs must be kept in mind

McLaughlin et al. ACCF/AHA 2009 Expert Consensus Document on PAH

Other supportive therapy

- Oxygen: sO2< 90% or pO2<60 should receive supplemental oxygen.
- Diuretics
- A sodium restricted diet (<2400 mg per day) advised and is important to manage volume status in patients with RV failure.
- Routine Immunizations (influenza and pneumococcal)
- Avoid:
  - Pregnancy
  - High altitude
  - Heavy exercise (aerobic exercises allowed)

McLaughlin et al. ACCF/AHA 2009 Expert Consensus Document on PAH



Galiè Net al. Updated Treatment Algorithm of Pulmonary Arterial Hypertension. Journal of the American College of Cardiology 2013.

Approach to PAH specific therapy based on NYHA class

- Class I: Wait and watch, assess 6 monthly
- Class II/III/IV: Vasoreactivity testing → If positive try CCB
- Class II: Oral monotherapy
    - Riociguat
    - Ambrisentan/bosentan/macitentan
    - Sildenafil/Tadalafil

  Add second drug if no response

  May consider upfront combination therapy

Contd.

- Class III: Consider combination oral therapy upfront
  - For Class III with:
    - Poor prognostic markers*
    - Progression despite 2 oral therapies

    Add IV or inhaled prostanoid
- Class IV
  - IV Prostanoid drug of choice
  - Inhaled prostanoid + ETRA in unwilling patients
  - Combination oral therapy if prostanoids NA

Prognostic markers in PAH

Lower	Determinants of Risk	Higher
No	**Clinical Evidence of RV Failure**	Yes
Gradual	**Progression**	Rapid
II, III	**WHO Class**	IV
Longer (>400 m)	**6 Minute Walk Distance**	Shorter (<300 m)
Minimally elevated	**BNP**	Very elevated
Minimal RV Dysfunction	**Echocardiographic Findings**	Pericardial Effusion Significant RV Dysfunction
Normal/Near normal RAP and CI	**Hemodynamics**	High RAP, Low CI

ACCF-AHA Expert Consensus. J Am Coll Cardiol 2009;53:1573– 619

Follow-up

	At baseline (prior to therapy)	Every 3–6 months[a]	3–4 months after initiation or changes in therapy	In case of clinical worsening
Clinical assessment WHO-FC ECG	✓	✓	✓	✓
6MWT[b]	✓	✓	✓	✓
Cardio-pulmonary exercise testing[b]	✓		✓	✓
BNP/NT-proBNP	✓	✓	✓	✓
Echocardiography	✓		✓	✓
RHC	✓[c]		✓[d]	✓[d]

European Heart Journal (2009)30, 2493–2537

Lung Transplantation

- NYHA Class III or IV despite a trial of at least 3 months of combination therapy including prostanoids.
- Cardiac index ≤ 2 liters/min/m2.
- Mean right atrial pressure ≥ 15 mm Hg.
- 6-minute walk test ≤ 350 m.
- Development of significant hemoptysis, pericardial effusion, or signs of progressive right heart failure (renal failure, increasing bilirubin, brain natriuretic peptide, or recurrent ascites)

Weill et al. ISHLT consensus guidelines. January 2015

Lung Tx only or Heart-lung Tx?

- In most patients with pulmonary hypertension associated with RV failure, isolated bilateral lung transplantation is associated with comparable or better results than heart-lung transplantation

- Most commonly, patients with irreversible myocardial dysfunction or congenital defects with irreparable defects of the valves or chambers in conjunction with intrinsic lung disease or severe PAH are considered for heart-lung transplantation

Weill et al. ISHLT consensus guidelines. January 2015

CTEPH

- Endarterectomy recommended in all patients who are fit for surgery and show evidence of PAH at rest or exercise
- Warfarin in all
- Those not-operable or those with residual PAH after surgery may be put on PAH specific Rx

PAH secondary to lung disease

- Only short term hemodynamic benefits of PAH specific Rx (ERA, PDE-5) demonstrated in both ILD/COPD
- Long term benefits not seen
- IPF patients with bosentan and ambrisentan showed worse outcomes
- Likely due to worsening hypoxia due to reversal of protective vasoconstriction → V/Q mismatch
- Patients with CTD with disproportionate PAH to lung disease may benefit with PAH specific therapy

Take Home message

- No approved therapy for PAH shown to prevent progression of the underlying pulmonary vascular disease - PAH remains an incurable disease
- Correct diagnosis (PAH and group) and ruling out treatable causes is must
- Stepwise approach to Rx based on WHO FC
- Rational combination therapy maybe helpful in those with progressive disease
- Lung Tx for those symptomatic despite maximal Rx