PULMONARY HYPERTENSION: NEW TREATMENT OPTIONS

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Disclosures

- None

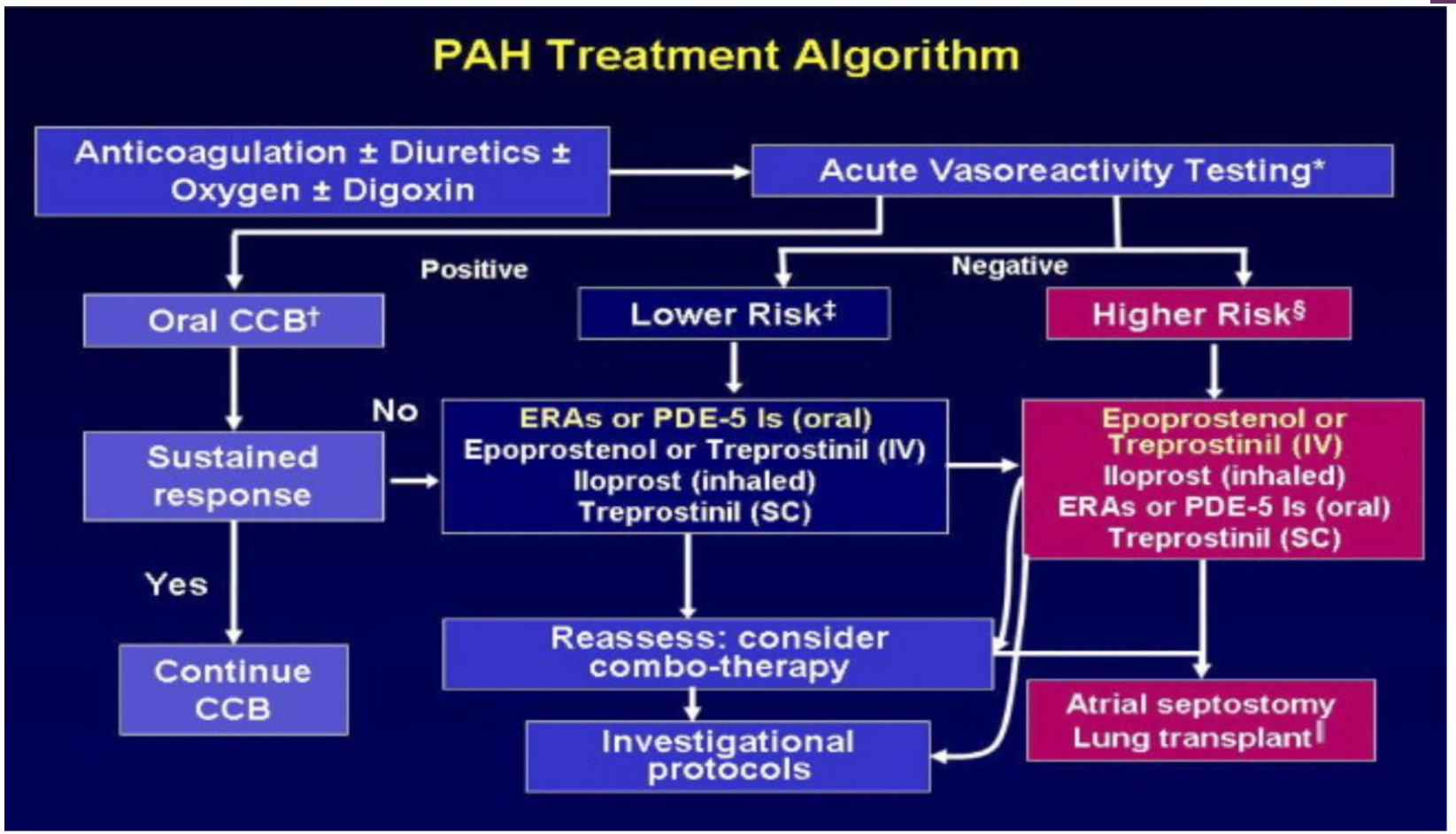
Learning Objectives

- Identify prognostic markers that determine treatment decisions in pulmonary hypertension
- Initiate treatment plans based on the updated algorithm
- Familiarize with ongoing trials of new therapies on the horizon

Outline

- Treatment Algorithm – Old and New
- Treatment Options
- Special Considerations
- New Therapies

Treatment – Old paradigm



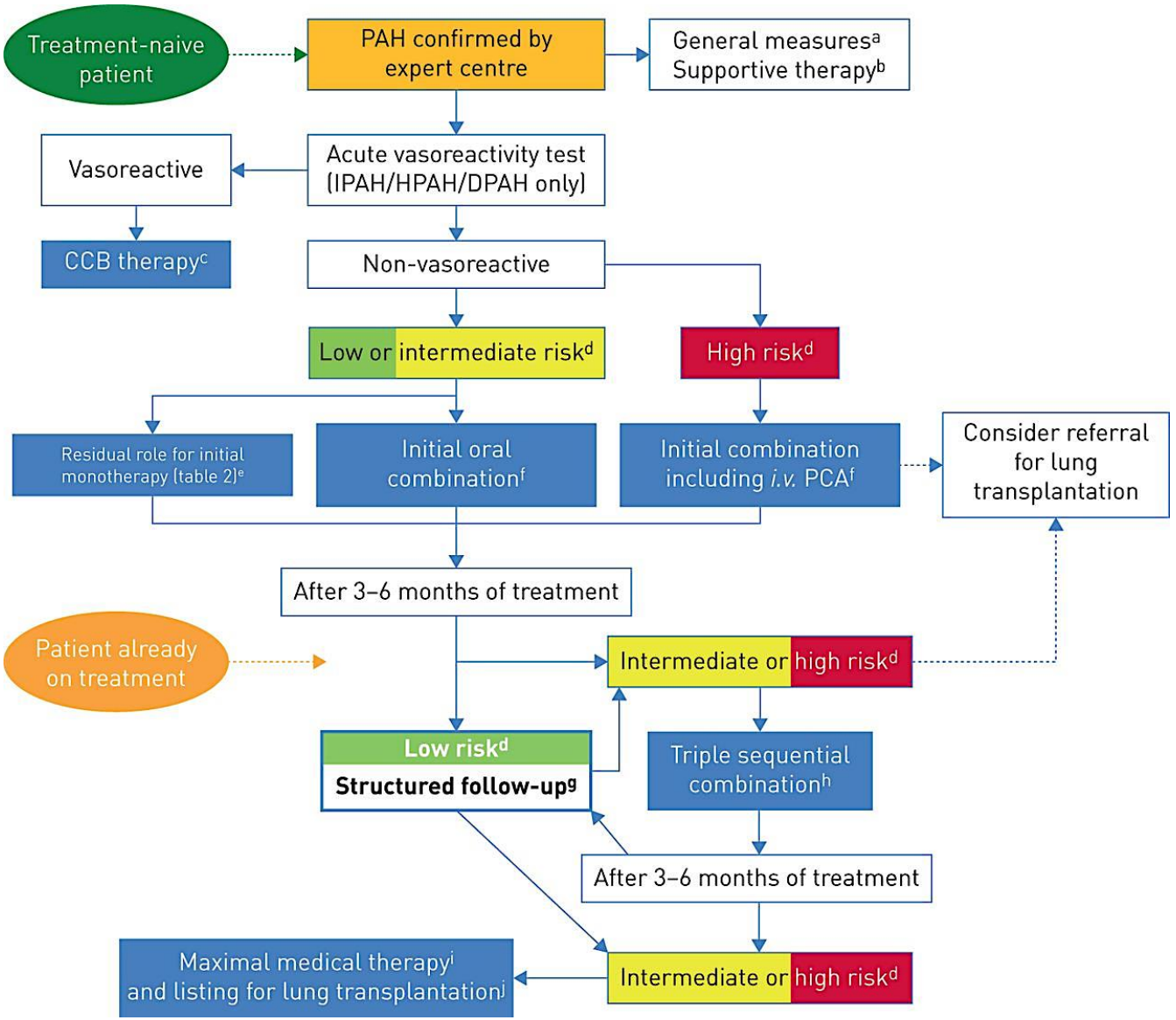
ACCF/AHA 2009 EXPERT CONSENSUS DOCUMENT
On PH. J Am Coll Cardiol 2009

Old Paradigm: Determinants of Risk

LOWER RISK	DETERMINANT	HIGHER RISK
No	CLINICAL EVIDENCE OF RV FAILURE	Yes
Gradual	PROGRESSION	Rapid
II, III	WHO FUNCTIONAL CLASS	IV
> 400 M	6 MWD	< 300 M
Minimally Elevated	BNP	Very Elevated
Minimal RV Dysfunction	ECHOCARDIOGRAM	Pericardial Effusion RV Dysfunction
Normal RAP and CI	HEMODYANAMICS	High RAP, Low CI

McLaughlin, McGoon. Circulation. 2006;114:1417

Treatment – New paradigm



Nazzareno Galiè et al. Eur Respir J 2019;53:1801889

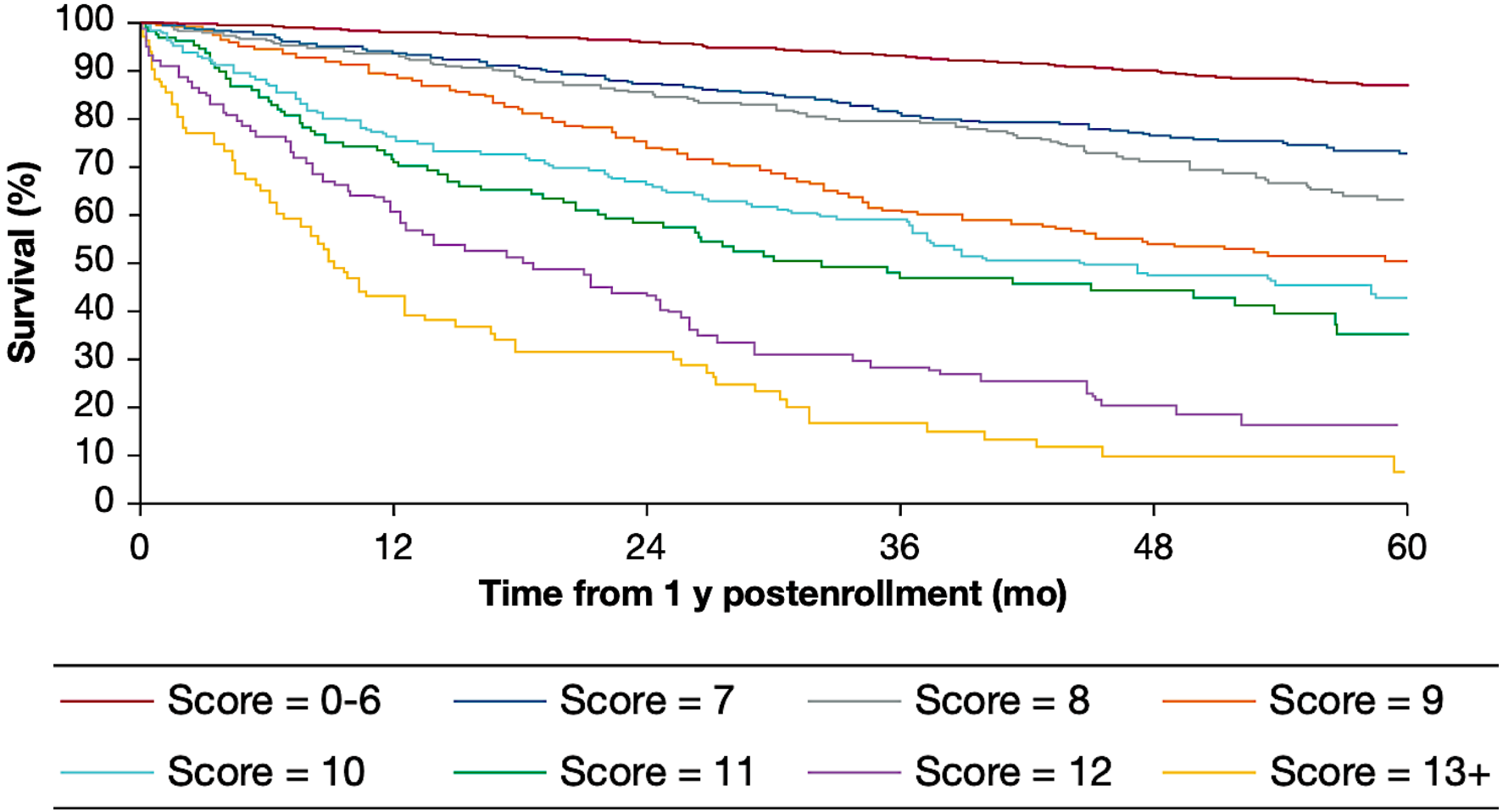
REVEAL 2.0 – PAH Risk Score

		Score
WHO Group 1 Subgroup	APAH-CTD +1 · APAH-PoPH +3 · FPAH +2	
Demographics	Males Age >60 yr +2	
Comorbidities	eGFR <60 mL/min/1.73 m² or renal inefficiency (if eGFR is unavailable) +1	
NYHA/WHO Functional Class	I -1 · III +1 · IV +2	
Vital Signs	SBP <110 mm Hg +1 · HR >96 BPM +1	
All-Cause Hospitalizations ≤6 mo	All-Cause Hospitalizations within 6 mo +1	
6-Minute Walk Test	≥440 m -2 · 320 to <440 m -1 · <165 m +1	
BNP	<50 pg/mL or NT-proBNP <300 pg/mL -2 · 200 to <800 pg/mL +1 · ≥800 pg/mL or NT-proBNP ≥1110 pg/mL +2	
Echocardiogram	Pericardial Effusion +1	
Pulmonary Function Test	% predicted DL_{CO} ≤40 +1	
Right Heart Catheterization	mRAP >20 mm Hg Within 1 Year +1 · PVR <5 Wood Units -1	
	Sum of above	
		+6

Risk score	Low risk	Intermediate risk	High risk	Risk score
	0-6	7-8	≥9	

Frantz, CHEST 2019; 156(2):323

5 year Survival Estimates



Frantz, CHEST 2019; 156(2):323

GOALS OF TREATMENT

- Improve WHO FC III and IV to FC I or II

OR

- At least maintain FC II in FC II patients

BARST.J Am Coll Cardiolo.2009;54:S78

TRANSPLANTATION GUIDELINES for IPAH

- Persistent NYHA class III or IV on maximal medical therapy
- Low (<350 meter) or declining 6-MWT
- Failing therapy with intravenous epoprostenol, or equivalent
- Cardiac index of less than 2 liters/min/m2
- Right atrial pressure exceeding 15 mm Hg

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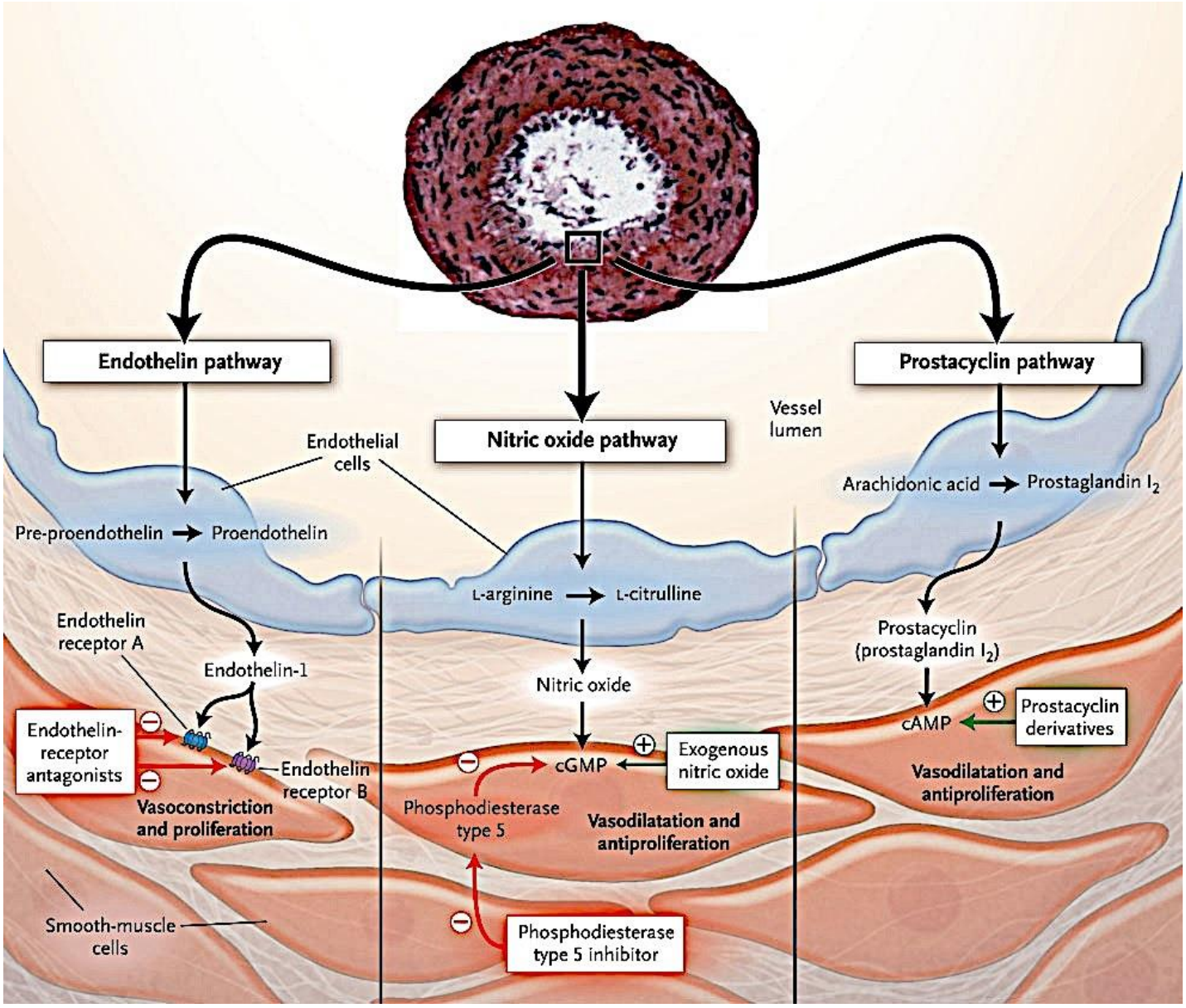
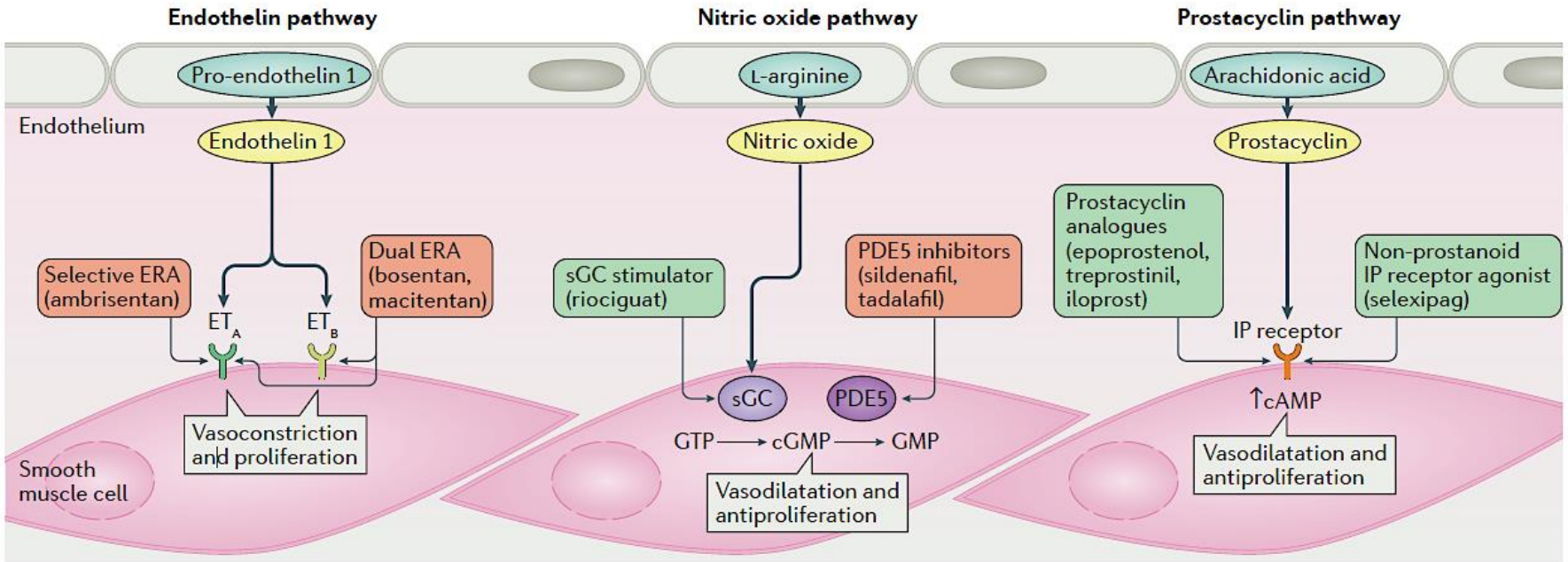
Treatment Options



Farber & Loscalzo, NEJM, 2004

Pulmonary Vasodilators



ERAs
bosentan
ambrisentan
macitentan

PDE-5 inhibitors
sildenafil
tadalafil

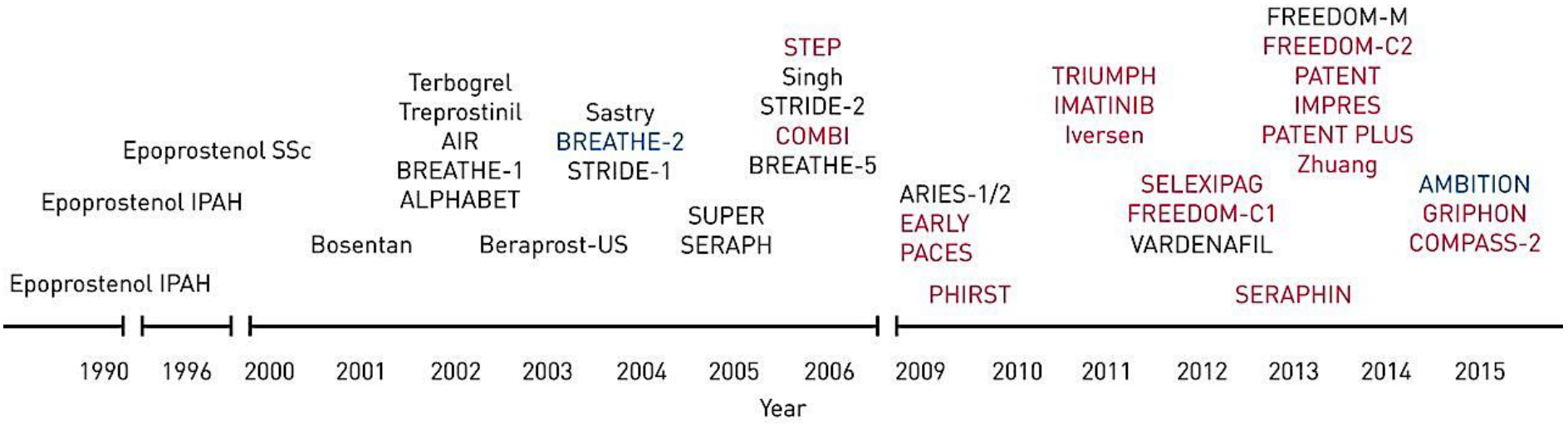
sGC
riociguat

Prostanoids
epoprostenol
treprostinil
iloprost

IP receptor agonist
selexipag

Lau, Nat Rev Cardiol 2017

Completed Trial in PAH

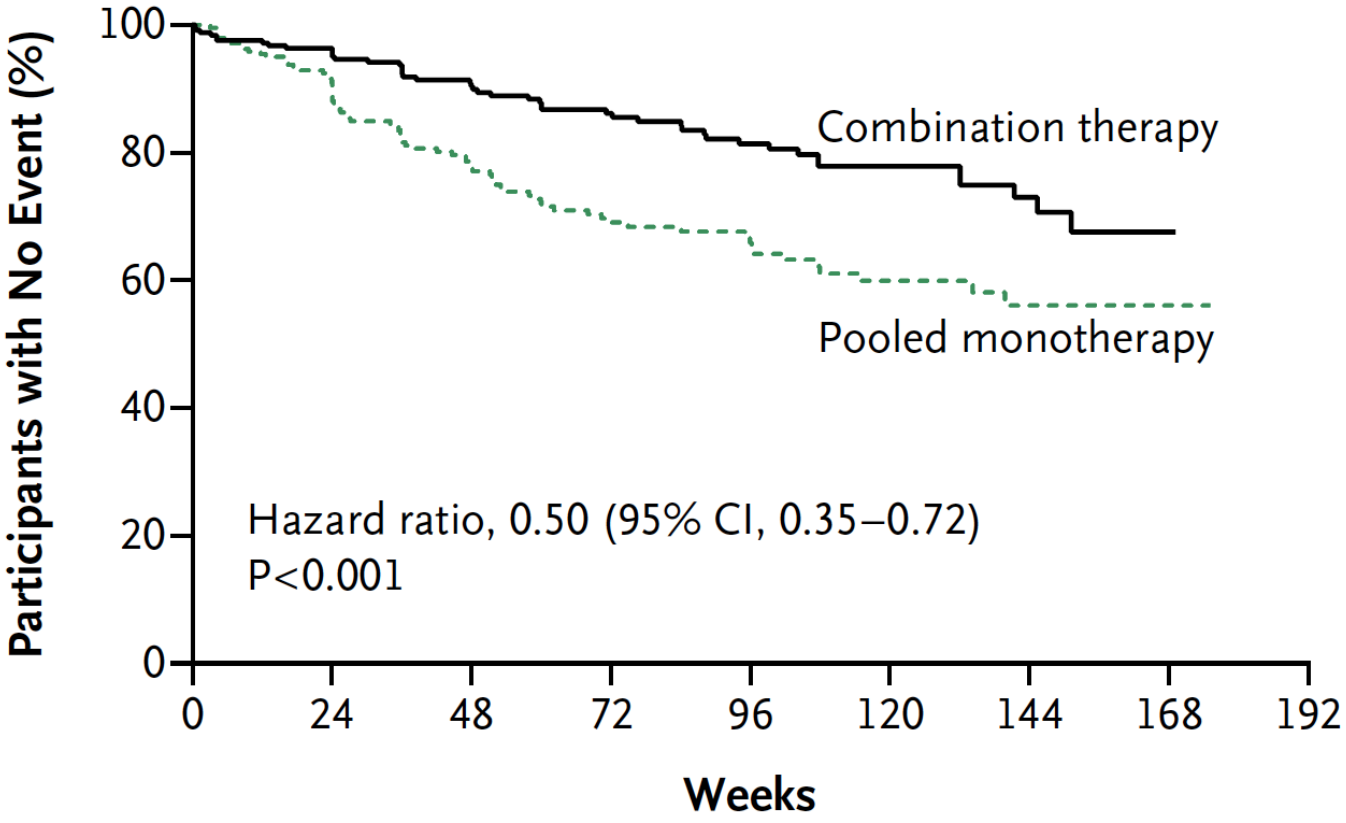


RCTs on monotherapy *versus* placebo or *versus* monotherapy (n=21)
RCTs on monotherapy and/or sequential combination *versus* placebo (n=18)
RCTs on initial combination *versus* monotherapy (n=2)

Nazzareno Galiè et al. Eur Respir J 2019;53:1801889

Upfront Dual Oral Combination Therapy

- AMBITION trial
- Tadalafil (PDE-5i) or Ambrisentan (ERA) vs combination



Galie, N Engl J Med 2015

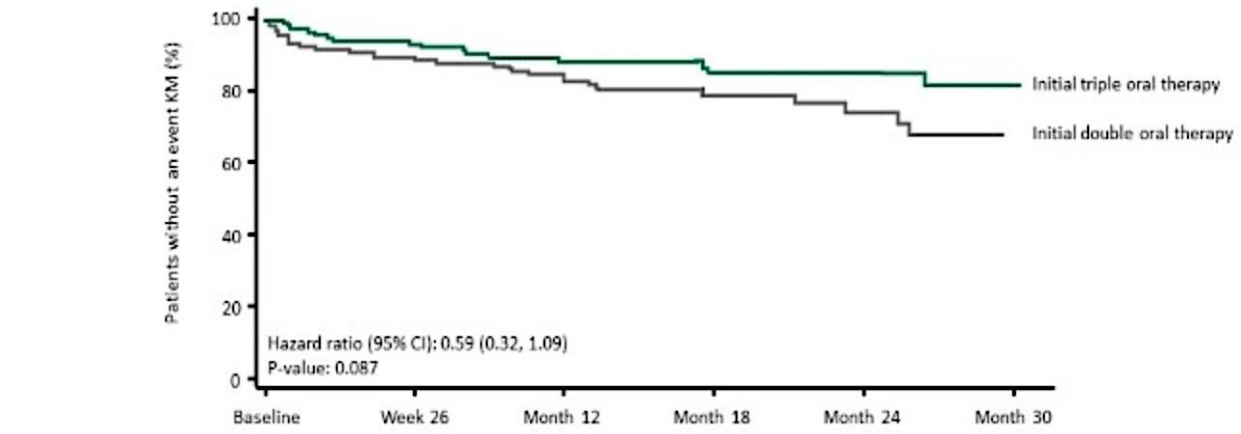
Upfront Triple Oral Combination Therapy

- TRITON trial

Tadalafil + Macitentan + Selexipag

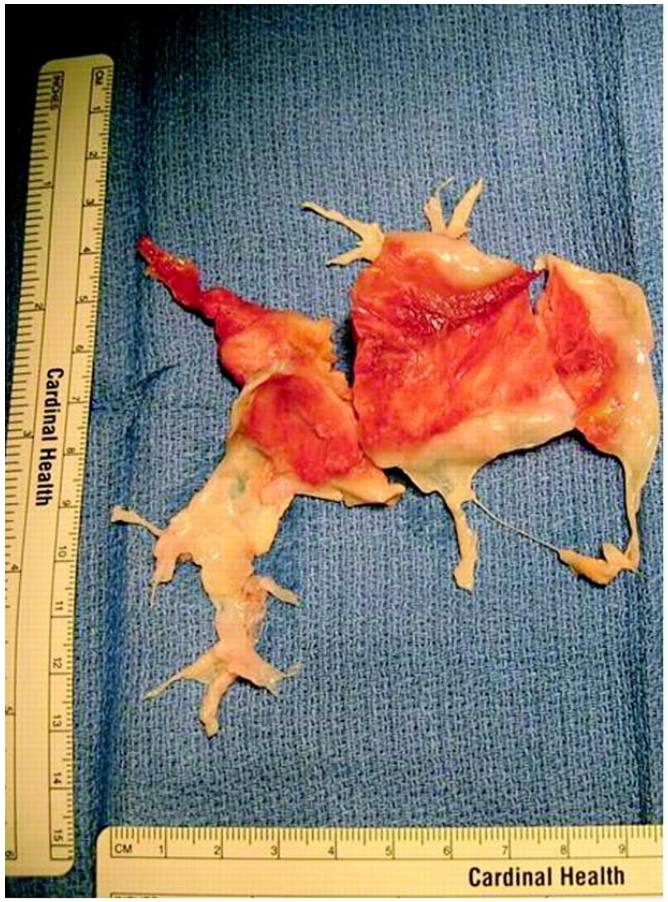
versus

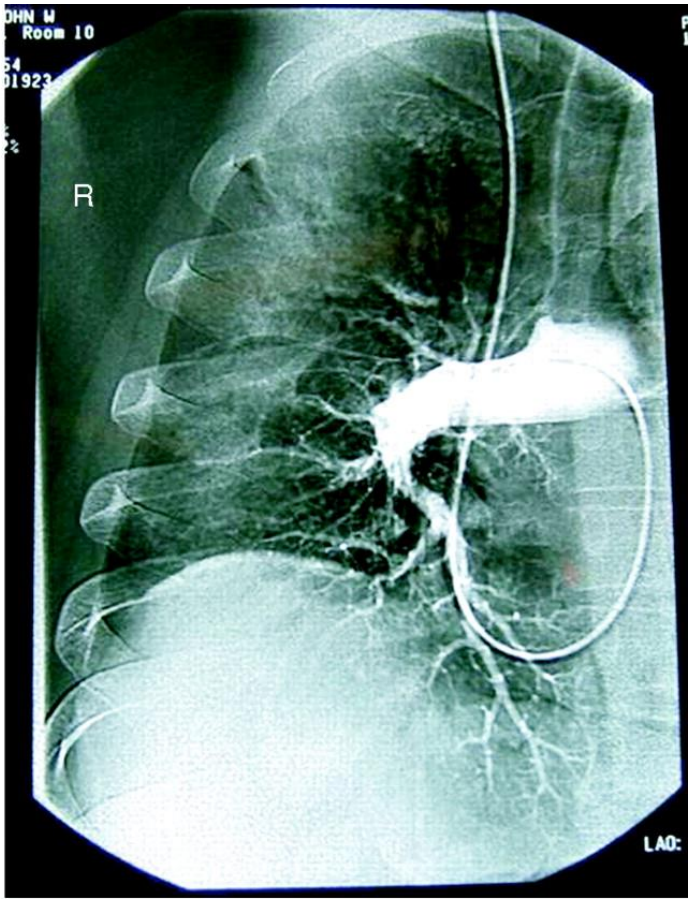
Tadalafil + Macitentan + Placebo



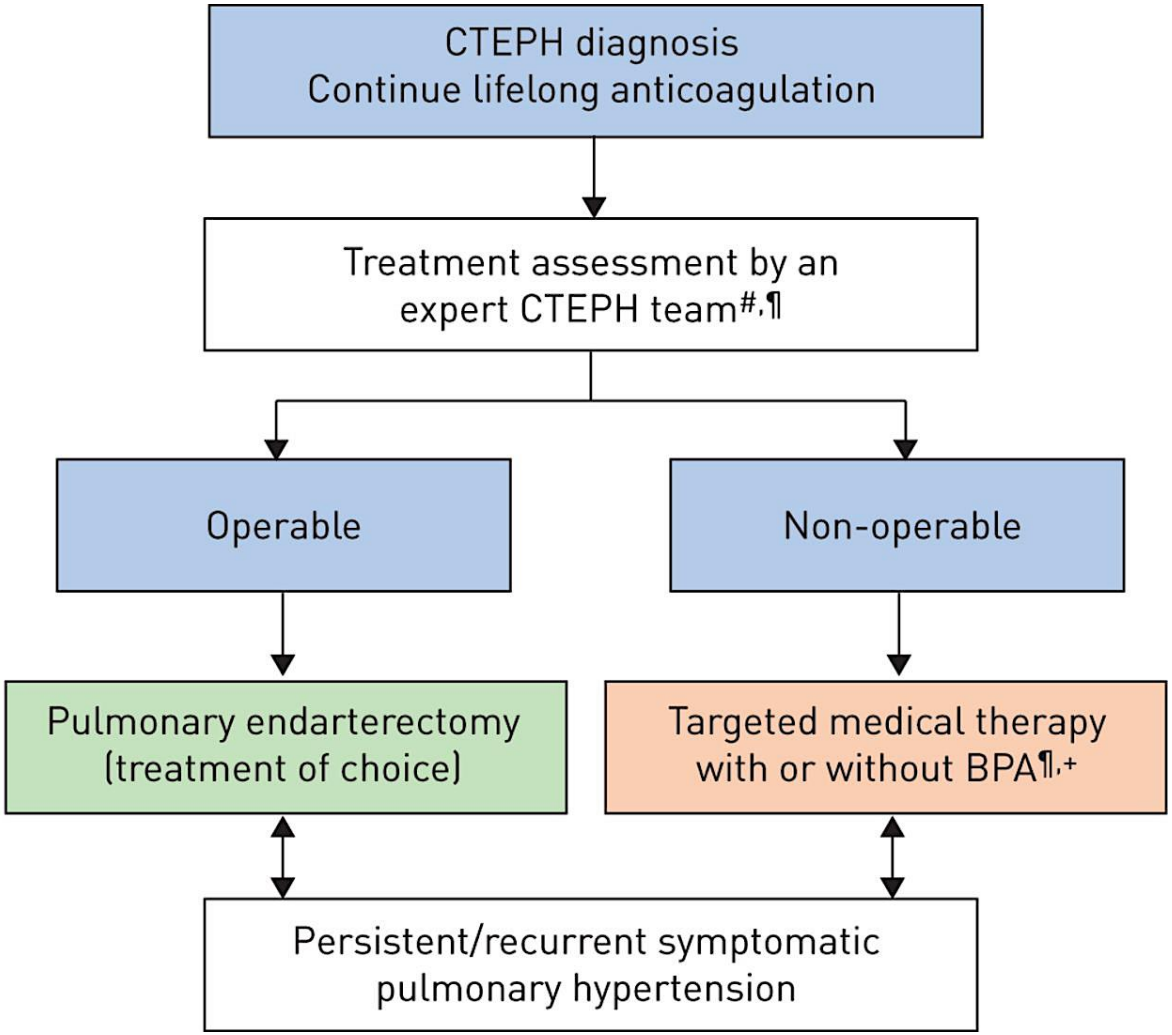
Galie, AJRCCM abstract 2020

Treatment of CTEPH





CTEPH Treatment Algorithm



Nick H. Kim et al. Eur Respir J 2019;53:1801915

RCTs for Medical Therapy in CTEPH

Trial [ref.]	Study drug	Duration weeks	Subjects n	NYHA FC	6MWD m	6MWD effect m	PVR baseline dyn·s·cm^{-5}	PVR effect %
BENEFIT [73]	Bosentan	16	157	II–IV	342±84	+2^{NS}	783 (95% CI 703–861)	−24
CHEST-1 [55]	Riociguat	16	261	II–IV	347±80	+46	787±422	−31
MERIT-1 [74]	Macitentan	16 (24$^{\#}$)	80	II–IV	352±81	+34	957±435	−16

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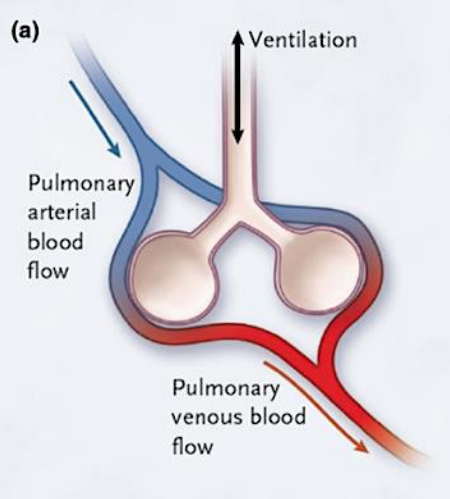
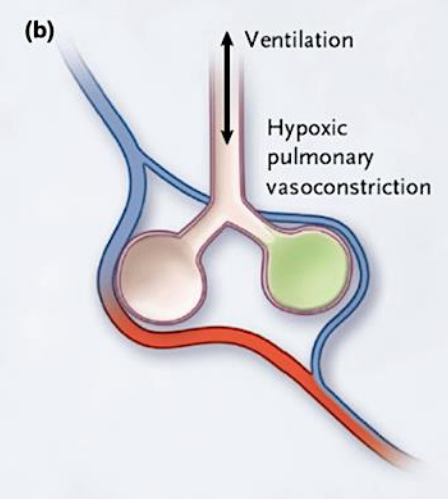
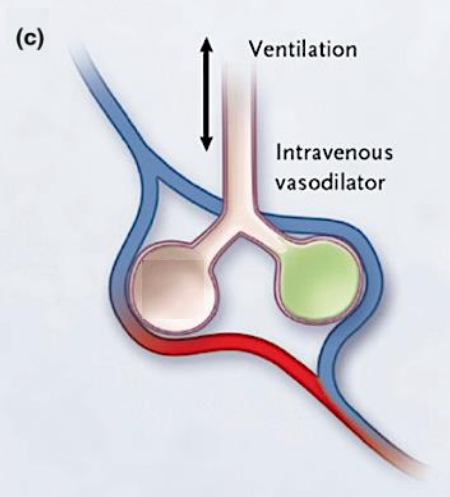
Pulmonary Vasodilator Considerations

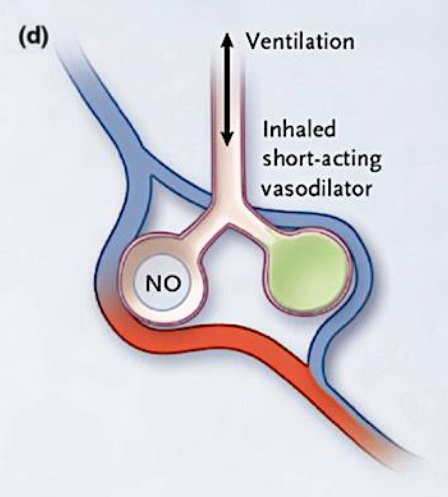
- Decrease SVR → systemic hypotension
  - cautious use in hypotensive patients
- Abrupt medication withdrawal → rebound pulmonary hypertension
  - always wean gradually
- Worsen V/Q matching → hypoxemia
  - cautious use in intrinsic lung disease

Worsening V/Q Mismatch









RCTs with PAH-therapy in ILD

Han (2013) [90]	119	IPF with echo available (66% of the whole cohort)	RCT	Echo: RVSD	Not available	FVC 57%, D_{LCO} 26%	Sildenafil 20 mg 3 times daily	12 weeks	6MWD, less decline in patients with RVSD on sildenafil	Improvement in QoL in patients with RVSD
Corte (2014) [60]	60	IPF or idiopathic fibrotic NSIP	RCT (2:1)	RHC: mPAP ⩾25 mmHg	mPAP 37±9.9 mmHg, CI 2.2±0.5 $L \cdot min^{-1} \cdot m^{-2}$	FVC 55.7±20%, K_{CO} 45±22%	Bosentan	16 weeks	PVRI decrease of 20%, negative	Secondary end-points all negative; no change in functional capacity or symptoms
Raghu (2015) [14]¶	68	IPF with group 2 PH (14% of whole cohort)	RCT (2:1)	RHC	mPAP 30±8 mmHg	FVC 67±12%, D_{LCO} 39±15%	Ambrisentan 10 $mg \cdot day^{-1}$	Event-driven study terminated early	Disease progression, unfavourable trend	More hospitalised ambrisentan arm
Nathan (2017) [57]	147	IIP, FVC >45%, mPAP >25 mmHg	RCT	RHC	mPAP 33.2±8.2 mmHg, CI 2.6±0.7 $L \cdot min^{-1} \cdot m^{-2}$	FVC 76.3±19%, D_{LCO} 32±12%	Riociguat 2.5 mg 3 times daily	26 weeks	6MWD, no difference at study halt	Study stopped early for increased harm to riociguat arm (death and hospitalisation)

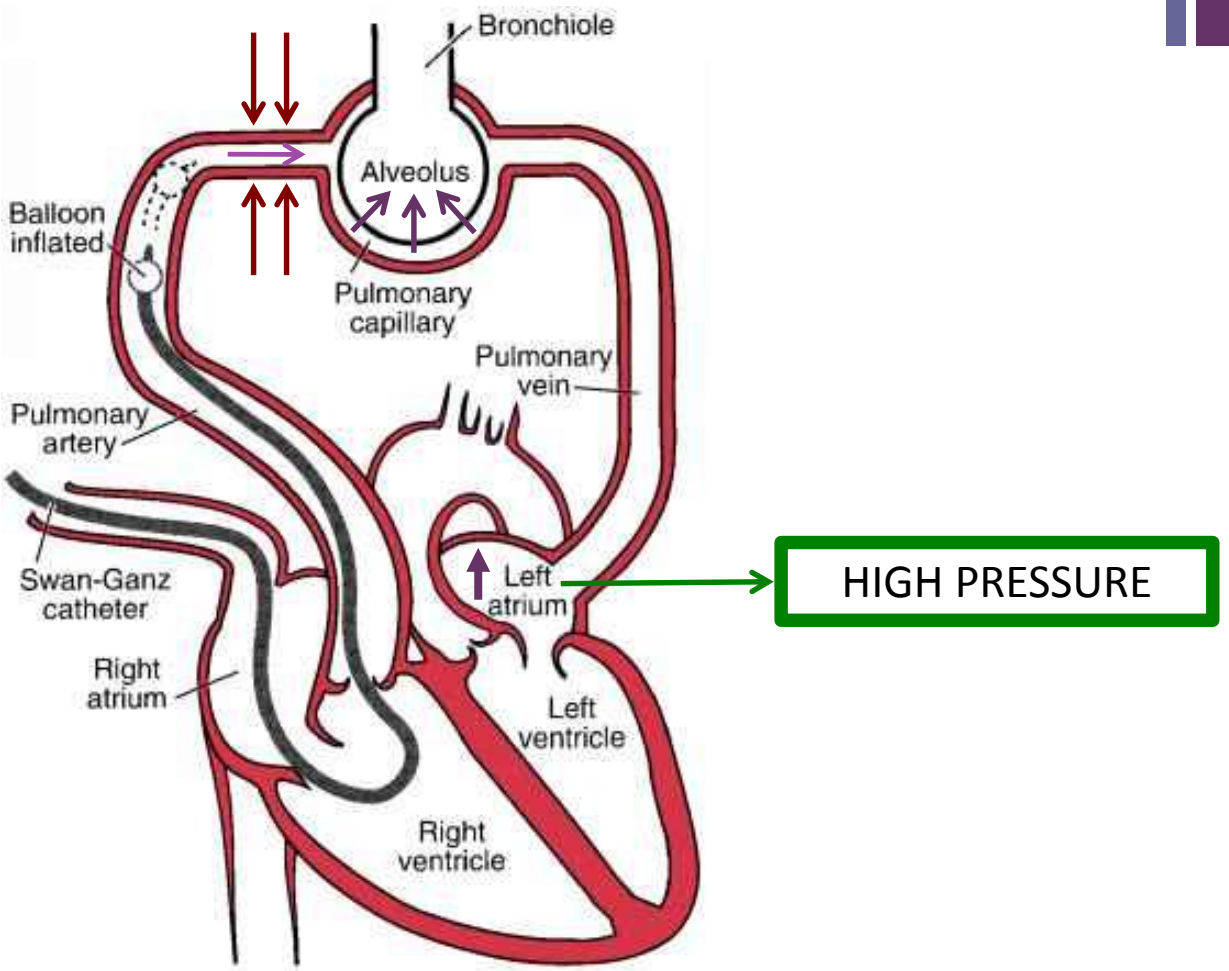
RCTs with PAH-therapy in COPD

First author (year) [ref.]	Subjects n	Inclusion criteria	Study design	Diagnosis of PH	Baseline haemodynamics#	Baseline PFTs#	Therapy	Duration	Primary end-point result	Other outcomes
COPD										
Vonbank (2003) [86]	40	COPD on supplemental oxygen with PH by RHC	RCT (open label)	RHC: mPAP ⩾25 mmHg	mPAP 27.6±4.4 mmHg, CI 2.7±0.6 L·min^{-1}·m^{-2}	FEV_1 1.09±0.4 L, FEV_1/FVC 44.5%	"Pulsed" nitric oxide with oxygen *vs* oxygen	3 months	PVRI, improved	Improved mPAP, CO and PVR; no worsened hypoxaemia
Stolz (2008) [53]	30	GOLD III–IV; no haemodynamic requirement	RCT (2:1)	Echo	sPAP 32 (29–38) mmHg	Not reported	Bosentan 125 mg 2 times daily	12 weeks	6MWD, no change	Worsened hypoxaemia and health-related QoL
Valerio (2009) [50]	32	COPD with PH by RHC	RCT (open label)	RHC	mPAP 37±5 mmHg	FEV_1 37±18%	Bosentan 125 mg 2 times daily	18 months	No defined primary	mPAP, PVR, BODE index and 6MWD improved
Rao (2011) [87]	33	GOLD III–IV	RCT	Echo: sPAP >40 mmHg	sPAP 52.7±11.9 mmHg	FEV_1 32.5±11.1%	Sildenafil 20 mg 3 times daily	12 weeks	6MWD, increased 190 m	Decrease in sPAP
Blanco (2013) [88]	60	COPD with PH by RHC or echo	RCT	RHC: mPAP ⩾25 mmHg; echo: sPAP ⩾35 mmHg	sPAP 42±10 mmHg, mPAP 31±5 mmHg	FEV_1 32±11%	Sildenafil 20 mg or placebo 3 times daily and PR	3 months	Exercise endurance time, no change	No change in 6MWD, peak V'_{O_2}, QoL or oxygenation
Goudie (2014) [89]	120	COPD with PH by echo	RCT	Echo: pulmonary acceleration time <120 ms or sPAP >30 mmHg	Echo: sPAP 42±10 mmHg	FEV_1 41±16%	Tadalafil 10 mg daily	12 weeks	6MWD, no change	Decreased sPAP compared with placebo; no difference in QoL, BNP or S_{aO_2}
Vitulo (2016) [49]	28	COPD with PH by RHC	RCT (2:1)	RHC: mPAP >35 mmHg (if FEV_1 <30%), mPAP ⩾30 mmHg (if FEV_1 ⩾30%)	mPAP 39±8 mmHg, CI 2.4±0.5 L·min^{-1}·m^{-2}, PVR 7±2.6 WU	FEV_1 54±22%, D_{LCO} 33±12%	Sildenafil 20 mg 3 times daily	16 weeks	PVR, decreased 1.4 WU	Improved CI, BODE scores and QoL; no effect on gas exchange

Pulmonary Vasodilator Considerations

- Decrease SVR → systemic hypotension
  - cautious use in hypotensive patients
- Abrupt medication withdrawal → rebound pulmonary hypertension
  - always wean gradually
- Worsen V/Q matching → hypoxemia
  - cautious use in intrinsic lung disease
- Increase pulmonary capillary pressure → pulmonary edema
  - cautious use in elevated left atrial pressure

Inducing Pulmonary Edema



Prior RCTs of PDE-5i and ERA in LHD

First author or study [ref.]	Study drug	Dose	Subjects n	Duration	Population	Primary outcome	Result
Guazzi [74]	Sildenafil	50 mg 3 times a day	44	12 months	HFpEF	PVR, RV performance, CPET	Improvement
LEPHT [75]	Riociguat	0.5, 1 or 2 mg 3 times a day	201	16 weeks	HFrEF	mPAP *versus* placebo	No change
Hoendermis [73]	Sildenafil	60 mg 3 times a day	52	12 weeks	HFpEF	mPAP *versus* placebo	No change
SIOVAC [77]	Sildenafil	40 mg 3 times a day	231	24 weeks	VHD	Composite clinical score#	Worsening in active group
MELODY-1 [76]	Macitentan	10 mg once daily	48	12 weeks	HF (EF >30%); 75% HFpEF	Safety and tolerability	+10% fluid retention in active group

Ongoing Trials in PH due to LHD

Study#	Study drug	Dose	Subjects n	Duration	Population	Primary outcome
SERENADE (NCT03153111)	Macitentan	10 mg once daily	300	52 weeks	LVEF ≥40% and ESC-defined HFpEF; HF hospitalisation within 12 months and/or PAWP or LVEDP >15 mmHg within 6 months; elevated NT-proBNP; PVD or RVD	% change from baseline in NT-proBNP at week 24
SOPRANO (NCT02554903)	Macitentan	10 mg once daily	78	12 weeks	LVAD within 45 days; PH by RHC with PAWP ≤18 mmHg and PVR >3 WU	PVR ratio of week 12 to baseline
DYNAMIC (NCT02744339)	Oral riociguat	1.5 mg 3 times a day	114	26 weeks	HFpEF; mPAP >25 mmHg and PAWP >15 mmHg	Change in CO
Oral treprostinil (NCT03037580)	Oral treprostinil		310	24 weeks	LVEF ≥50%; RHC within 90 days of randomisation; 6MWD >200 m	Change in 6MWD from baseline to week 24
PASSION (not registered)	Oral tadalafil	40 mg once daily	320	NA	HFpEF; PH with PAWP >15 mmHg and mPAP >25 mmHg and PVR >3 WU	Time to first event defined as HF-associated hospitalisation (independently adjudicated) or death from any cause

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Targeting Metabolic Dysfunction

Drug tested	ClinicalTrials.gov identifier	Study design	Study duration	Main inclusion criteria	Primary outcome measure	Secondary outcome measures
Fatty acid oxidation: ranolazine and trimetazidine						
Ranolazine	NCT02829034	Multicentre RCT *versus* placebo	26 weeks	PH on stable specific therapies but with RV dysfunction (RVEF <45%)	Percentage change in RVEF (assessed by MRI)	
Ranolazine	NCT01839110	Multicentre RCT *versus* placebo	26 weeks	PH on stable specific therapies but with RV dysfunction (RVEF <45%)	Number and percentage of subjects with high-risk profile at end of the study	Baseline comparison of the metabolic profiling, microRNA and iPSCs of subjects with and without RV dysfunction
Ranolazine	NCT02133352	Single-centre open-label phase 4	26 weeks	PH with LV diastolic dysfunction	Percentage change in mPAP, PAOP and PVR (RHC)	Other haemodynamic variables, 6MWD, MRI, echocardiography and NT-proBNP
Ranolazine	NCT01757808	Phase 1	12 weeks	PAH on one or more background specific therapies (including *i.v./ s.c.* prostacyclins)	Change in PVR (RHC)	Change in CPET, RV echocardiography parameters and 6MWD
Trimetazidine	NCT03273387	Single-centre phase 2 and 3	12 weeks	PAH	Changes in RV function (MRI)	Changes in cardiac fibrosis level (MRI), NYHA FC and LDH level
Glycolysis: dichloroacetate						
Dichloroacetate	NCT01083524	Two-centre open-label phase 1	16 weeks	PAH on one or more background oral specific therapies	Safety and tolerability	Change in PVR, 6MWD, RV size and function (MRI), NT-proBNP and lung/RV metabolism (FDG-PET)
Modulation of Nrf2 pathway/NF-κB pathway: bardoxolone methyl						
Bardoxolone methyl	NCT02036970 (LARIAT)	Multicentre phase 2 RCT *versus* placebo	16 weeks	PAH, PH-ILD, subset of patients with group 3 or 5 PH	Change in 6MWD	Determine recommended dose range
Bardoxolone methyl	NCT02657356 (CATALYST)	Multicentre phase 3 RCT *versus* placebo	24 weeks	PAH-CTD	Change in 6MWD	
Bardoxolone methyl	NCT03068130 (RANGER)	Multicentre phase 3 open-label extension	Up to 5 years	Patients with PH who previously participated in RCTs with bardoxolone	Long-term safety	
Metabolic syndrome: AMPK signalling and metformin						
Hormonal, metabolic and signalling interactions in PAH	NCT01884051	Observational	5 years	PAH and healthy subjects	Safety and biomarkers of mechanism	
Metformin	NCT03349775	Early phase 1	12 weeks	PH and obesity	Pulmonary vascular haemodynamics at rest and on exercise	Effect on PA endothelial cell phenotypes

Targeting Inflammation

Drug tested	ClinicalTrials.gov identifier	Study design	Study duration	Main inclusion criteria	Primary outcome measures	Secondary outcome measures
Modulation of cytokines pathway: anakinra and tocilizumab						
Anakinra	NCT01479010	Single-centre open-label pilot study: phase 1 and 2	4 weeks	PAH (excluding PAH-CTD, ILD, POPH) in FC III despite optimal PAH therapy	Change in peak V'_{O_2} and in V'_E/V'_{CO_2} slope (CPET)	Change in biomarkers; correlation between changes in biomarkers and CPET measures
Anakinra	NCT03057028	Single-centre open-label pilot study: phase 1	14 days	PAH (excluding PAH-CTD) in FC II or III despite optimal PAH therapy	Change in peak V'_{O_2} and ventilatory efficiency (CPET)	Change in hs-CRP, NT-proBNP, IL-6 and symptoms of heart failure (MLHFQ); correlation between biomarkers and measures of exercise capacity
Tocilizumab	NCT02676947	Open-label: phase 2 (TRANSFORM-UK)	24 weeks	PAH (excluding PAH-CTD due to SLE, RA and MCTD)	Safety (incidence and severity of adverse events); change in PVR (RHC)	Change in 6MWD, NT-proBNP, WHO FC and QoL
Inflammation: ubenimex						
Ubenimex	NCT02736149	Multicentre open-label extension study: phase 2 (LIBERTY-2)	Variable (average 1 year)	PAH on ⩾1 PAH-specific therapies, in FC II or III, who completed the phase 2 study	Safety (adverse events)	Change in PVR, 6MWD, WHO FC and BNP/NT-proBNP
Ubenimex	NCT02664558	Multicentre double-blind RCT *versus* placebo: phase 2 (LIBERTY)	24 weeks	PAH on ⩾1 PAH-specific therapies in WHO FC II or III	Change in PVR	Change in 6MWD, WHO FC, TTCW, QoL and NT-proBNP

Targeting PA Innervation

Intervention	ClinicalTrials.gov identifier	Study design	Study duration	Main inclusion criteria	Primary outcome measures	Secondary outcome measures
Therapeutic Intra-Vascular UltraSound (TIVUS) system	NCT02516722	Multicentre open-label study (TROPHY)	12 months	PAH in WHO FC III on stable double combination therapy other than parenteral PGI_2	Safety (procedure-related AE: 1 month); safety (PAH-related AEs and all-cause death: 12 months)	Change in mPAP, PVR, 6MWD and QoL at 4 months
Therapeutic Intra-Vascular UltraSound (TIVUS) system	NCT02835950	Multicentre open-label study (TROPHY-US)	12 months	PAH in WHO FC III on stable double combination therapy other than parenteral PGI_2	Safety (procedure-related AE: 1 month); safety (AEs, PAH-related AEs and all-cause death: 12 months)	Change in mPAP, PVR, 6MWD, QoL, NT-proBNP and RV function (MRI and echocardiography) at 6 months
Pulmonary artery denervation	NCT02525926	Multicentre single-blinded RCT *versus* placebo (DENERV'AP)	24 weeks	PAH patients in WHO FC III–IV despite dual therapy including a PGI_2 or dual oral therapy in patients unable to receive PGI_2 therapy	Change in mPAP (RHC)	Change in mPAP (3 months), PVR and other haemodynamic variables (6 months), FC, 6MWD, oxygen dependence, supraventricular arrhythmia, BNP, cardiac troponin, and RV function (echocardiography)
PA denervation (+sildenafil)	NCT03282266	Multicentre single-blinded RCT *versus* placebo (PADN-CFDA)	24 weeks	PAH	Change in 6MWD	Change in haemodynamic variables (RHC), RV function (echocardiography) and PAH-related events

Cell Therapy

Cells	ClinicalTrials.gov identifier	Study design	Study duration	Main inclusion criteria	Primary outcome measures	Secondary outcome measures
Autologous EPCs transfected with human eNOS	NCT03001414	Multicentre double-blind crossover RCT *versus* placebo: phase 2 (SAPPHIRE)	24 weeks	PAH in WHO FC II–IV on stable PAH-specific therapy	Change in 6MWD	Change in 6MWD (3, 9 and 12 months) and PVR; number of deaths or clinical worsening of PAH; change in RV function (echocardiography and MRI) and QoL (SF-36)
Allogeneic human cardiosphere-derived stem cells	NCT03145298	Phase 1a: open-label; phase 1 (ALPHA) Phase 1b: double-blind RCT *versus* placebo: phase 1 (ALPHA)	1 year 1 year	PAH in WHO FC II–III on stable PAH-specific therapy	Safety (gas exchange, haemodynamics); arrhythmia; sudden death; mortality and morbidity	Long-term safety end-points; TTCW (including death)

Summary

- Guidelines are available to achieve optimal response in patients with PAH with FDA approved medications
- The treatment of WHO Group 2 and WHO Group 3 PHTN is mostly geared towards treating underlying conditions
- Exciting ongoing trials targeting metabolic dysfunction, inflammation and innervation are ongoing

Thank you!