THE UNIVERSITY OF CHICAGO MEDICINE

Current Medical Therapy in PAH and CTEPH

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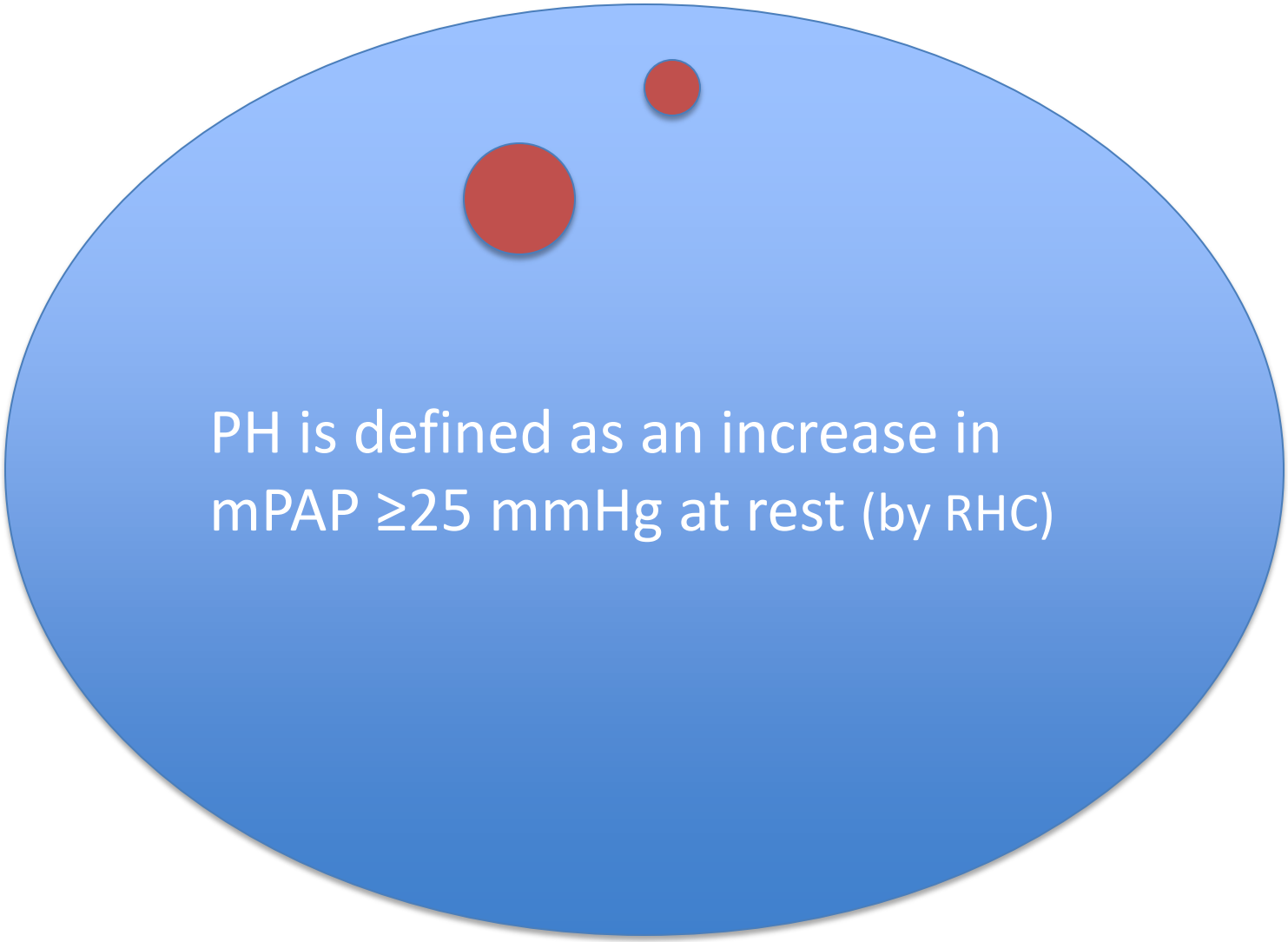
Disclosure

- Advisory board /Speakers Bureau : Gilead, Bayer, Actelion
- Research Support: Gilead, United Therapeutics, Lung Rx, Medtronics,

- I do not plan to discuss the investigational/unapproved use of a commercial product.
- If off-label, I will disclose that the use or indication in question is not currently approved by the FDA for labeling or advertising

Objectives

- Define PH, PAH and CTEPH
- Describe screening and diagnostic approaches to PAH
- Discuss management for PAH and CTEPH


PH is defined as an increase in
mPAP ≥25 mmHg at rest (by RHC)

Classification of PH

- WHO Gr 1- PAH
- WHO Gr 2- PH due to left heart disease
- WHO Gr 3- PH due to lung disease and/or hypoxia
- WHO Gr 4- CTEPH and other pulmonary artery obstruction
- WHO Gr 5- PH with unclear and /or multifactorial mechanisms

Classification of PH- PAH

5th WSPH
Simonneau et al.
JACC 2013

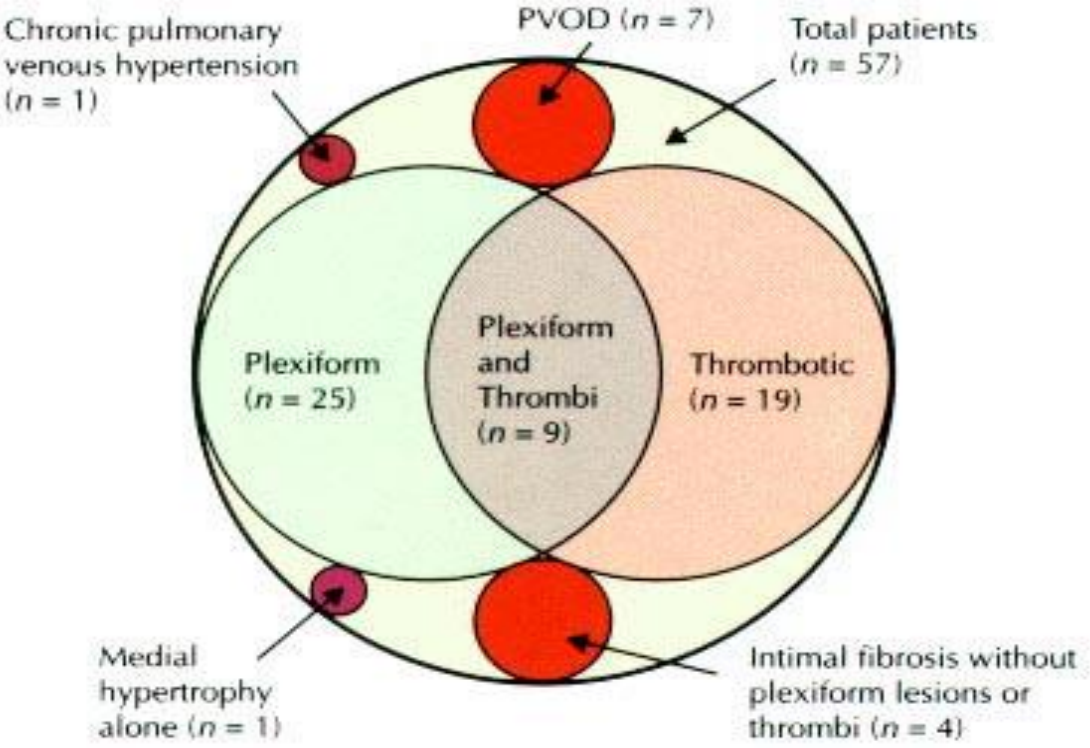
1. Pulmonary arterial hypertension
- **1.1 Idiopathic PAH**
- **1.2 Heritable PAH**
- **1.2.1 BMPR2**
- **1.2.2 ALK-1, ENG, SMAD9, CAV1, KCNK3**
- **1.2.3 Unknown**
- **1.3 Drug and toxin induced**
- **1.4 Associated with:**
- **1.4.1 Connective tissue disease**
- **1.4.2 HIV infection**
- **1.4.3 Portal hypertension**
- **1.4.4 Congenital heart diseases**
- **1.4.5 Schistosomiasis**

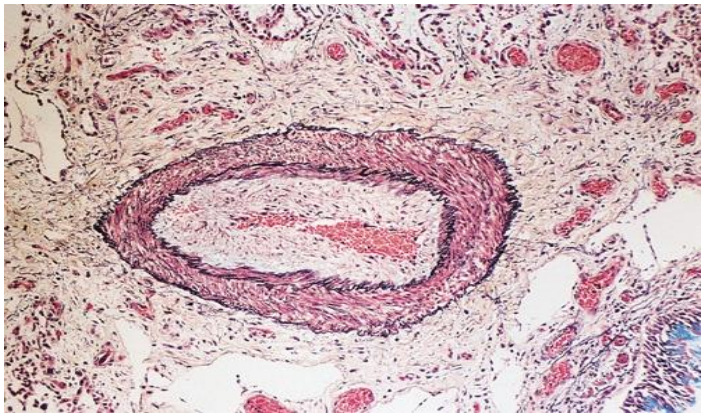
1′ Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis

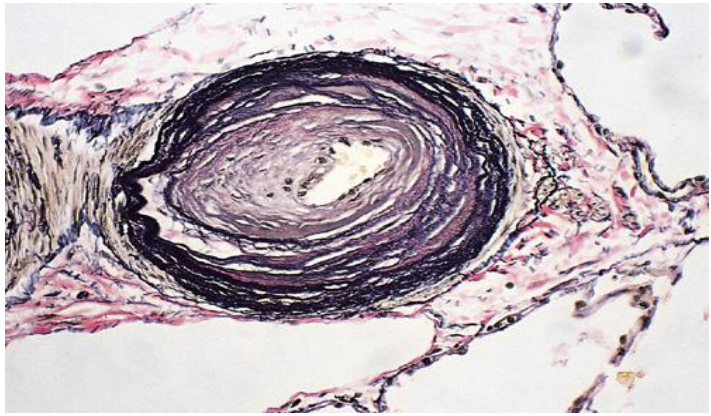
1″. Persistent pulmonary hypertension of the newborn (PPHN)

Histopathology Findings in NIH PPH Registry

Pietra et al Circulation 1989; 80:1198-1206

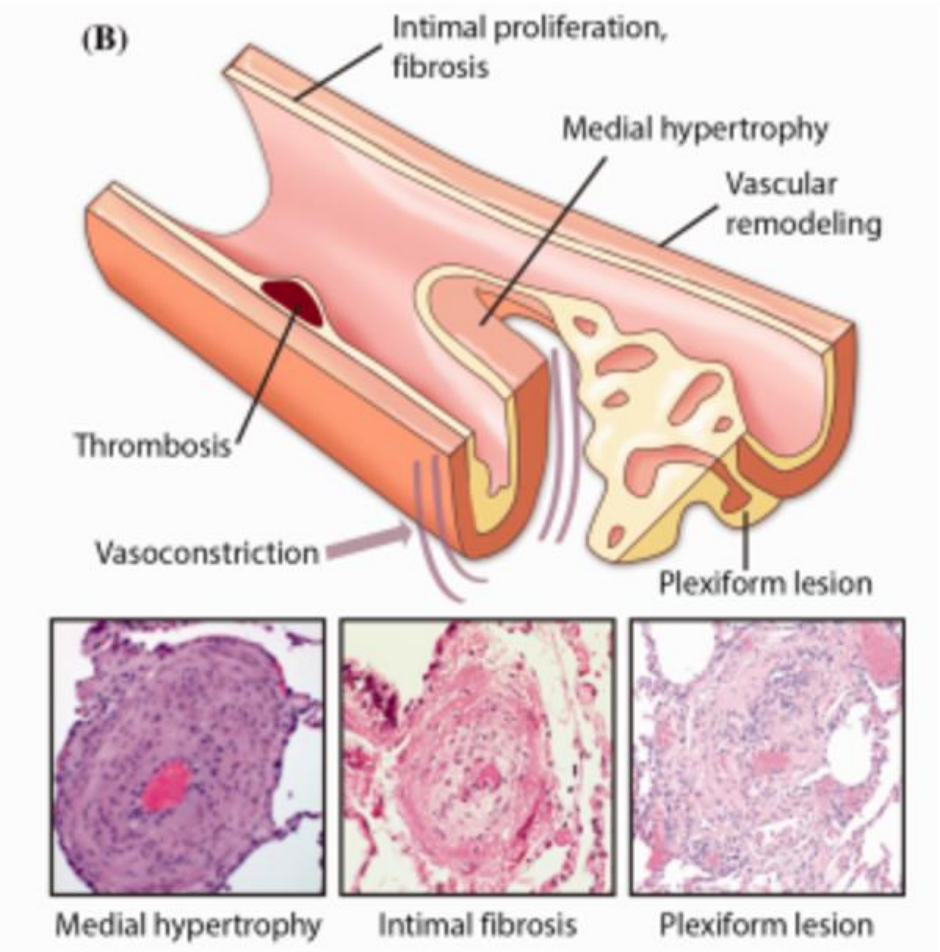






Histology of PAH

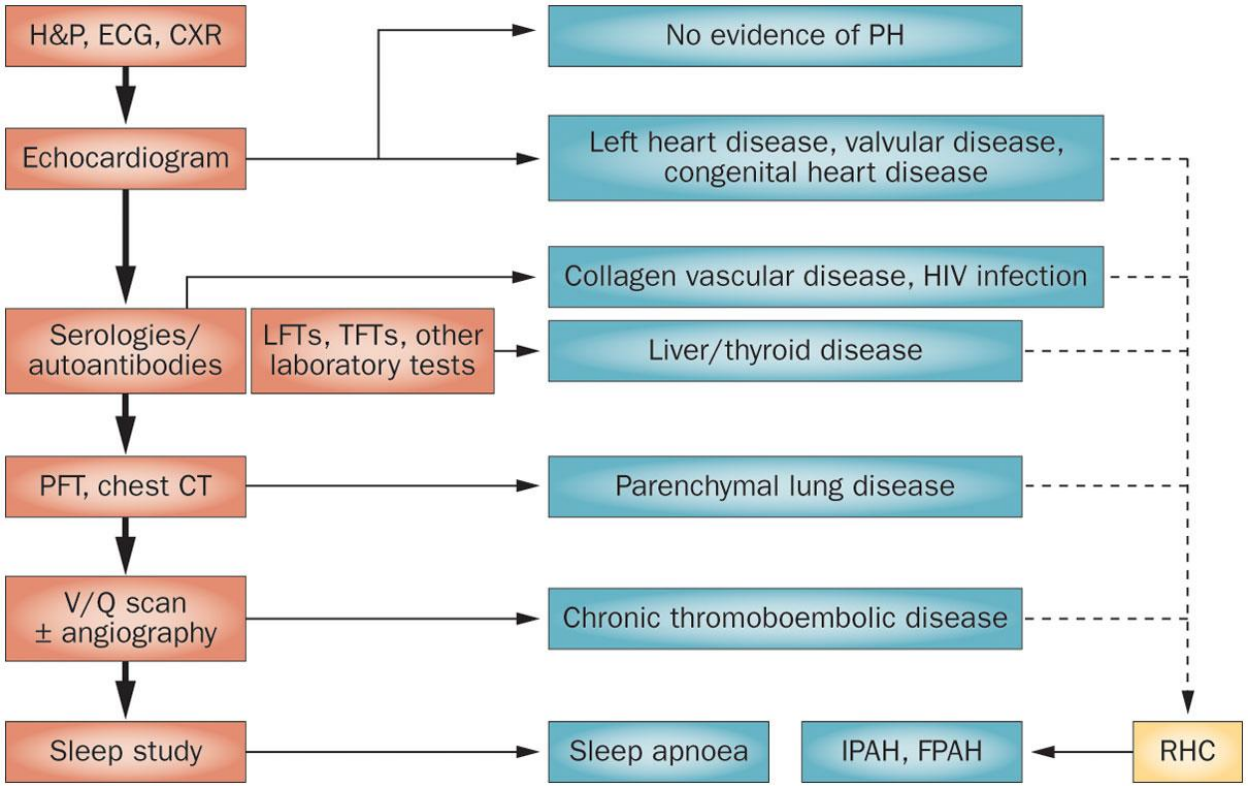
Dasgupta et. al. Clinical Pharmacology & Therapeutics 2015



Evaluation of Dyspnea

- Clinical Assessment
- CBC, CMP, TSH, NT-pro BNP
- Spirometry, DLCO, TLC
- 6MWT / ambulatory oximetry
- CXR→ HRCT
- EKG, ? EST
- Echocardiogram
- RHC
- PSG, Exercise echocardiogram, Exercise RHC, CPET, serum lactate

Figure 1 Flowchart for the diagnostic evaluation of suspected RV failure associated with suspected PH



Simon, M. A. (2013) Assessment and treatment of right ventricular failure
Nat. Rev. Cardiol. doi:10.1038/nrcardio.2013.12

nature REVIEWS CARDIOLOGY

CTD Associated PAH

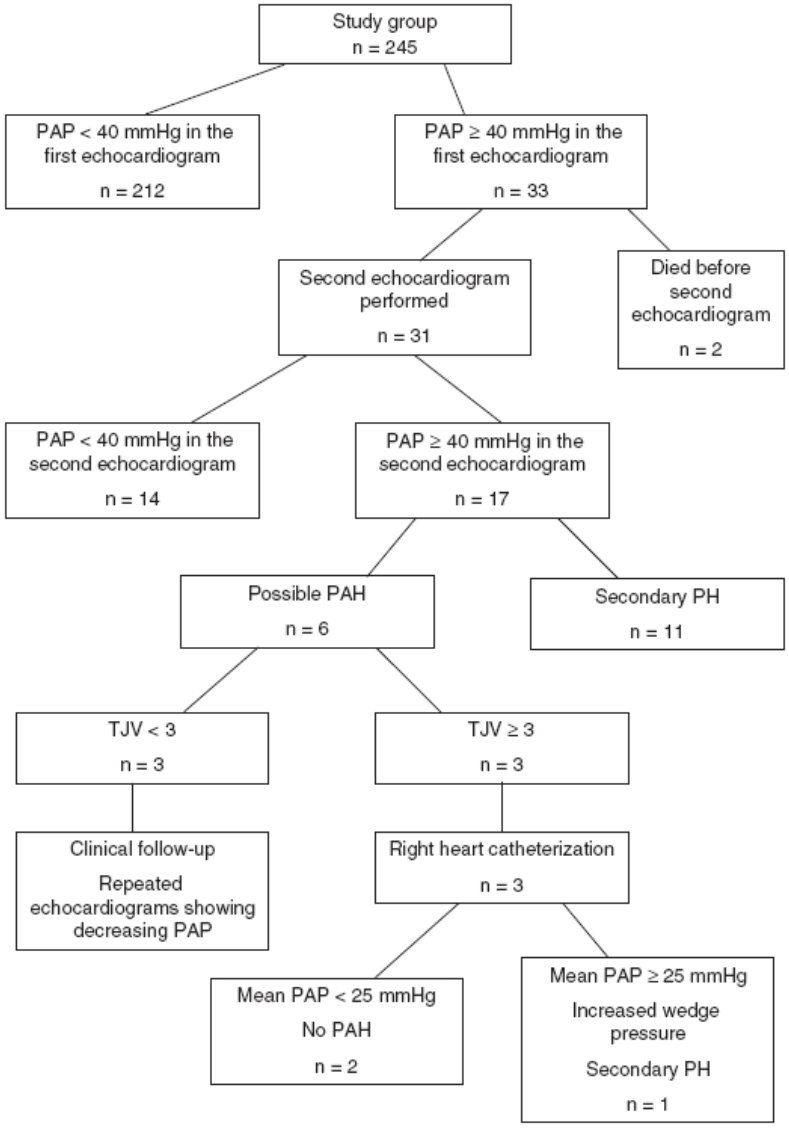
Chung L, Reveal, Chest 2010
Condliffe R AJRCCM 2009
Ngian GS, Arthritis Res Ther 2012

- CTD-PAH -- 15-30%
- Systemic Sclerosis (62-95%)
- SLE (8-17%)
- MCTD (8%)
- PM/DM (1-3%)
- Primary Sjogren's Syndrome 1-2%)
- RA (3-4%)
- Overlap (2%)
- Undifferentiated CTD (2%)

F:M ratio 4:1
mean age at diagnosis >60 y

Secondary PH More Prevalent in SLE

Ruiz Irastorza Autoimmunity Reviews 2013



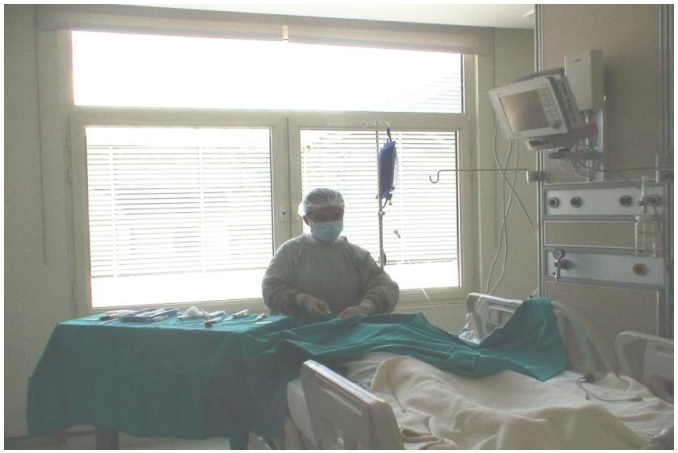
Echocardiographic Probability of PH in Symptomatic Patients

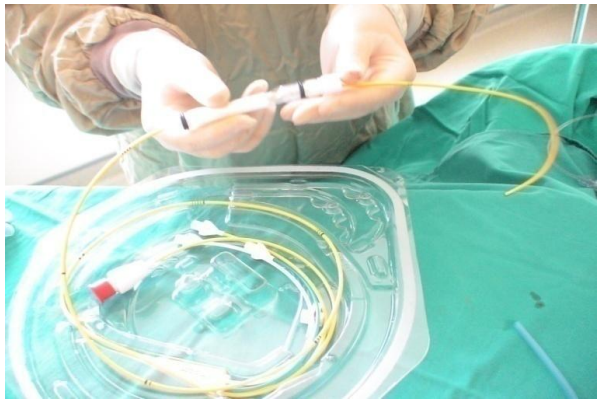
Eur Respir J 1998 12 (6) 1476-1478
2015 ERS/ ESC Guidelines

Peak tricuspid regurgitation velocity (m/s)	Presence of other echo 'PH signs'[a]	Echocardiographic probability of pulmonary hypertension
≤2.8 or not measurable	No	Low
≤2.8 or not measurable	Yes	Intermediate
2.9–3.4	No	
2.9–3.4	Yes	High
>3.4	Not required	

Gold Standard in PAH Diagnosis
Right Heart Catheterization

- Increased mPAP:
  - ≥25 mm Hg at rest, or
- PVR: ≥3 Wood units
- Severity
  - RAP
  - CI
  - SvO2
- Etiology





ESC Guidelines.

PH & PAH

- PH is defined as an increase in mPAP ≥25 mmHg at rest as assessed by RHC
- PAH describes a group of PH patients with pre-capillary PH (PAWP ≤15 mmHg and a PVR >3 WU in the absence of other causes of pre-capillary PH)

PH	PAPm ⩾25 mmHg	All
Pre-capillary PH	PAPm ⩾25 mmHg PAWP ⩽15 mmHg	1. Pulmonary arterial hypertension 3. PH due to lung diseases 4. Chronic thromboembolic PH 5. PH with unclear and/or multifactorial mechanisms
Post-capillary PH	PAPm ⩾25 mmHg PAWP >15 mmHg	2. PH due to left heart disease 5. PH with unclear and/or multifactorial mechanisms
Isolated post-capillary PH (Ipc-PH)	DPG <7 mmHg and/or PVR ⩽3 WU[c]	
Combined post-capillary and pre-capillary PH (Cpc-PH)	DPG ⩾7 mmHg and/or PVR >3 WU[c]	

Risk Assessment for PAH

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 >15 ml/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%

RV ejection fraction less than 35%
TAPSE less than 15 mm

Nazzareno Galiè et al. Eur Heart J 2016;37:67-119

WHO FC

- I No limitation of usual physical activity; ordinary physical activity does not cause dyspnea, fatigue, chest pain, or presyncope (>7 METs)
- II Mild limitation of physical activity; no discomfort at rest; but normal activity causes increased dyspnea, fatigue, chest pain, or presyncope (5 METs)
- III Marked limitation of activity; no discomfort at rest but less than normal physical activity causes increased dyspnea, fatigue, chest pain, or presyncope (2-3 METs)
- IV Unable to perform physical activity at rest; may have signs of RV failure; symptoms increased by almost any physical activity (1.6 METs)

- *MET (metabolic equivalent) is defined as the resting VO2 for a 40-year-old 70kg man.1 MET = 3.5mL O2 /min/kg body weight.

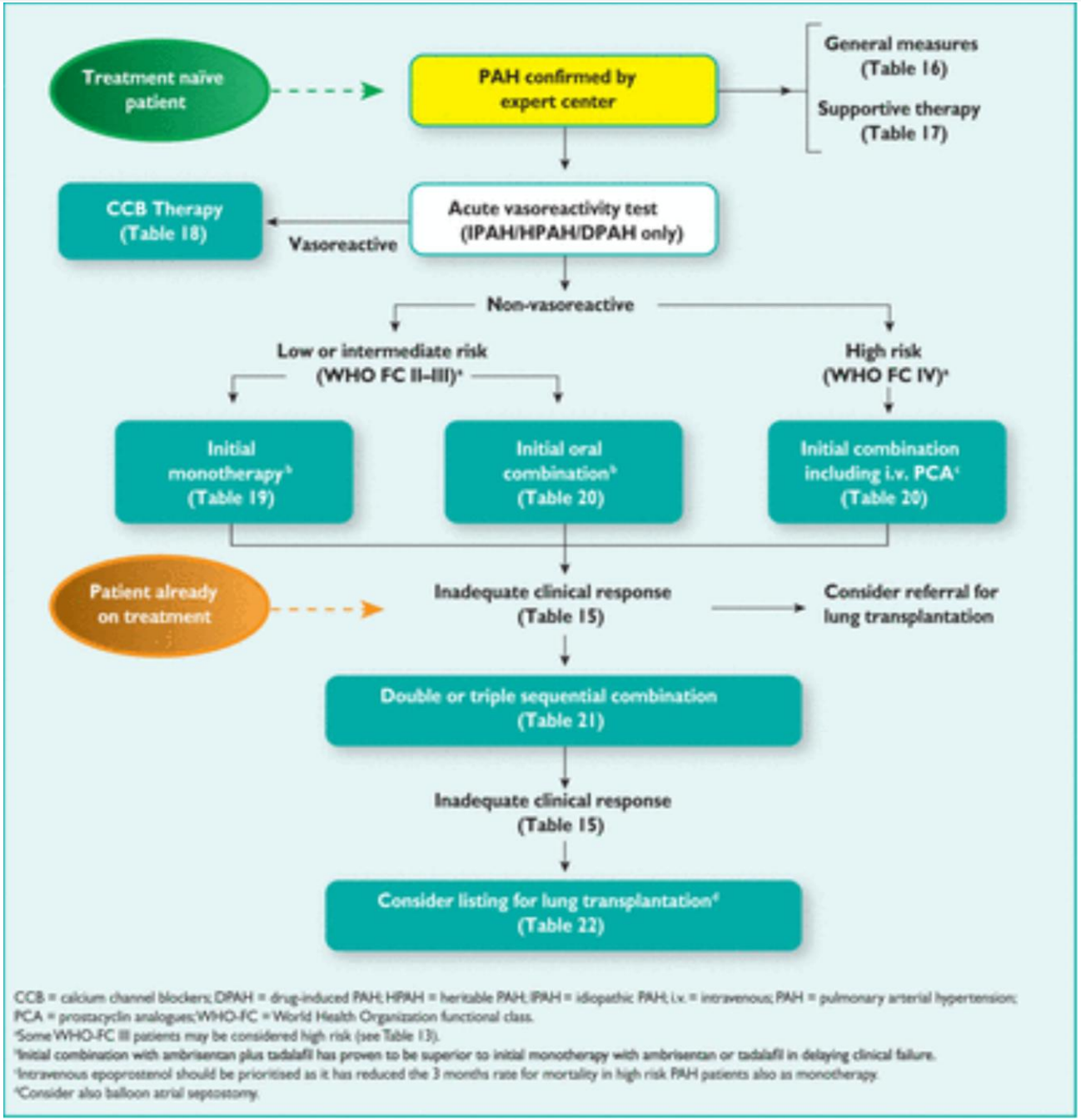
PAH Treatment Goals

- Improve symptoms and quality of life
- Improve exercise capacity
  - 6MWT
  - WHO FC
- Prevent Clinical Worsening
  - Hospitalizations
  - Transplantation
- Improve Survival
  - Biomarkers
  - Hemodynamics

Nonspecific Treatment

ERS/ESC Guidelines

- Supervised exercise training, Influenza & pneumococcal immunization, avoid pregnancy
- Digoxin
  - No RCT, no long term data
  - Advanced RV failure
  - Adjust to Renal function
- Hypoxemia: Oxygen
  - Rest, exercise, sleep, altitude
- Diuretics
- Anticoagulation
  - ? Benefit in IPAH (harmful in PH-SSc)
- Sleep apnea
  - Common co-morbidity



CCB = calcium channel blockers; DPAH = drug-induced PAH; HPAH = heritable PAH; IPAH = idiopathic PAH; i.v. = intravenous; PAH = pulmonary arterial hypertension; PCA = prostacyclin analogues; WHO-FC = World Health Organization functional class.

[a]Some WHO-FC III patients may be considered high risk (see Table 13).

[b]Initial combination with ambrisentan plus tadalafil has proven to be superior to initial monotherapy with ambrisentan or tadalafil in delaying clinical failure.

[c]Intravenous epoprostenol should be prioritised as it has reduced the 3 months rate for mortality in high risk PAH patients also as monotherapy.

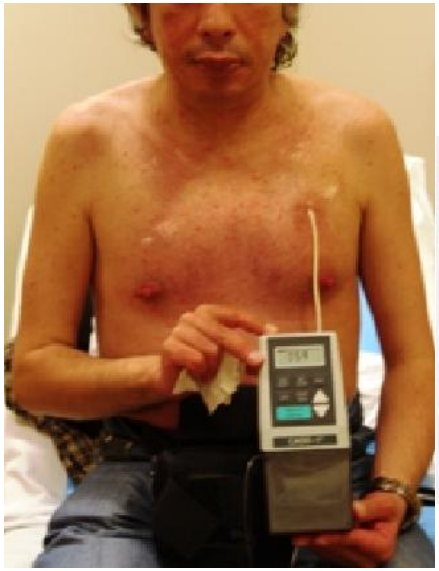
[d]Consider also balloon atrial septostomy.

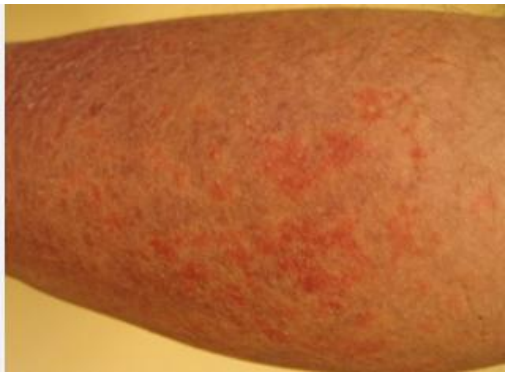
From: 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension
Eur Heart J. 2015;37(1):67-119.

IV Epoprostenol vs Conventional Therapy for IPAH

Barst et al N Engl J Med 1996;334:296-301

- RCT – 81 pts, 12 weeks
- Improved HD, 6MWT, Survival
- Epoprostenol: 315 m->362m
- Conventional: 270->204 m





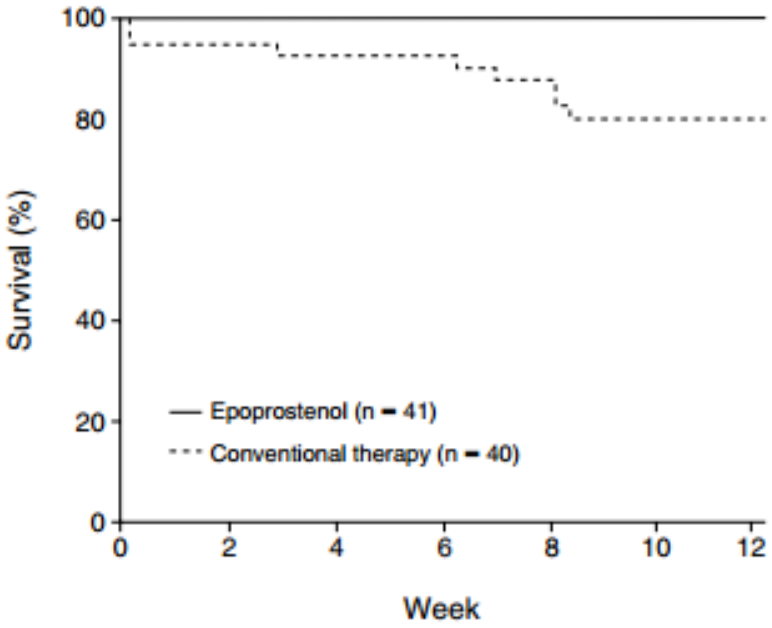


Figure 1. Survival among the 41 Patients Treated with Epoprostenol and the 40 Patients Receiving Conventional Therapy.

Data on patients who underwent transplantation during the 12-week study were censored at the time of transplantation. Estimates were made by the Kaplan–Meier product-limit method. The two-sided P value from the log-rank test was 0.003. Survival analysis with data on patients receiving transplants not censored at transplantation resulted in the same level of significance (two-sided P = 0.003 by the log-rank test).

Metaanalysis : RRR for mortality 70%

PH Specific Medications

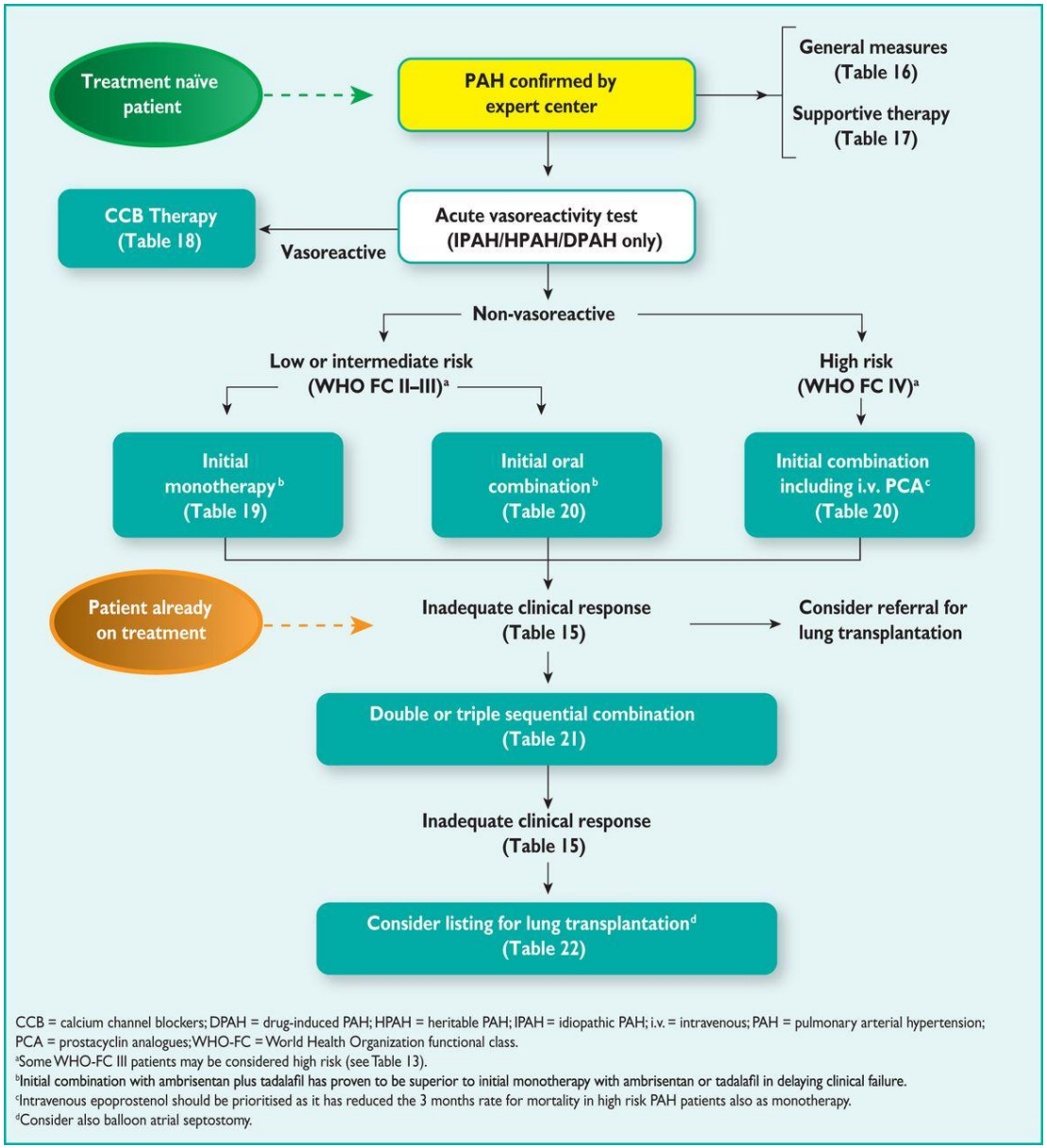
Klinger et al Ann Am Thorac Soc Vol 11, No 5, pp 811

Ca channel blockers

Name	Drug Class	Action	Route of Administration	Terminal Half-Life
Ambrisentan	Endothelin receptor antagonist	Blocks endothelin receptor A	Oral	15 h
Bosentan	Endothelin receptor antagonist	Blocks endothelin receptor A and B	Oral	5.4 h
Macitentan	Endothelin receptor antagonist	Blocks endothelin receptor A	Oral	14–18 h
Sildenafil	Phosphodiesterase type-5 inhibitor	Slows metabolism of intracellular cGMP	Oral or intravenous	4 h orally
Tadalafil	Phosphodiesterase type-5 inhibitor	Slows metabolism of intracellular cGMP	Oral	17.5 h
Epoprostenol	Prostacyclin	Increases intracellular cAMP	Intravenous or inhaled*	<6 min
Treprostinil	Prostacyclin derivative	Increases intracellular cAMP	Intravenous, subcutaneous, inhaled, or oral	4 h
Iloprost	Prostacyclin derivative	Increases intracellular cAMP	Inhaled	20–30 min
Nitric oxide	Soluble guanylate cyclase stimulator	Increases intracellular cGMP	Inhaled	Seconds
Riociguat	Soluble guanylate cyclase stimulator	Increases intracellular cGMP	Oral	7–12 h

Selexipag

Evidence based treatment algorithm for pulmonary arterial hypertension patients (for group 1 patients only).



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Nazzareno Galiè et al. Eur Heart J 2016;37:67-119

How to choose initial therapy

- PAH type
- Disease severity
- Drug availability / approval status,
- Route of administration, patients' preference,
- Side effect profile,
- Drug–drug interactions,
- Physicians' experience /preference

Risk Assessment for PAH

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TAPSE less than 15 mm

Nazzareno Galiè et al. Eur Heart J 2016;37:67-119

Upfront triple combination therapy

- Retrospective analysis of prospective French reference centers
- IV epoprostenol, bosentan and sildenafil
- n=19, 17 F, 10/13 w BMPR2, 11 NYHA FC 4, 8 NYHA FC 3
- 18 pts w 100% 3 yr survival estimate (estimated 49% survival)

	Baseline	Month 4 visit	Final follow-up visit[#]
NYHA FC I/II/III/IV n	0/0/8/10	1/16/1/0**	4/14/0/0**
6MWD m	227±171	463±94**	514±105**,¶
Haemodynamics			
RAP mmHg	11.9±5.2	4.9±4.9**	5.2±3.5**
mPAP mmHg	65.8±13.7	45.7±14.0**	44.4±13.4**
PCWP mmHg	8.4±3.5	6.7±3.2	7.9±2.8
Cardiac index $L \cdot min^{-1} \cdot m^{-2}$	1.66±0.35	3.49±0.69**	3.64±0.65**
PVR $dyn \cdot s \cdot cm^{-5}$	1718±627	564±260**	492±209**
Mean BP mmHg	92.1±12.5	80.1±11.7**	84.9±19.4
HR beats per min	92.3±10.7	83.9±9.8**	79.9±13.4**
Sv_{O_2} %	51.0±8.5	69.7±5.2**	72.2±4.0**
Dose of epoprostenol achieved $ng \cdot kg^{-1} \cdot min^{-1}$	0	15.9±1.9	19.6±6.0

Olivier Sitbon et al. Eur Respir J 2014;43:1691-1697

Web Table VIA Characteristics of randomised controlled trials with pulmonary arterial hypertension drugs interfering with the endothelin pathway (Endothelin receptors antagonists)

Drugs tested	Study	Number of patients	Duration (weeks)	Background therapy	Primary endpoint	Main results
Ambrisentan	ARIES-1 [10]	202	12	No	6MWD	6MWD improved TTCW not improved
	ARIES-2 [10]	192	12	No	6MWD	6MWD improved TTCW improved
Bosentan	Study-351 [11]	32	12	No	6MWD	6MWD improved TTCW improved
	BREATHE-5 [12]	213	16	No	6MWD	6MWD improved TTCW improved
	EARLY [13]	185	24	No, or Sildenafil [16%]	PVR, 6MWD	PVR improved TTCW improved 6MWD not improved
	BREATHE-5 [14]	54	12	No	SaO_2, PVR	PVR improved 6MWD improved
	COMPASS-2 [15]	334	99	Sildenafil	TTCW	TTCW not improved 6MWD improved NT-proBNP improved
Macitentan	SERAPHIN [16]	742	115	No, or Sildenafil, or Inh iloprost	TTCW	TTCW improved in monotherapy and combination

Web Table VIB Characteristics of randomised controlled trials with pulmonary arterial hypertension drugs interfering with the nitric oxide pathway (Soluble guanylate cyclase stimulators, Phosphodiesterase type-5 inhibitors)

Drugs tested	Study	Number of patients	Duration (weeks)	Background therapy	Primary endpoint	Main results
Riociguat	PATENT [17]	443	12	No, or bosentan, or prostanoids	6MWD	6MWD improved Haemodynamics improved
	PATENT plus [18]	30	18	Sildenafil	Supine SBP	Terminated for excess of SAE in the treated group
Sildenafil	SUPER-I [19]	227	12	No	6MWD	6MWD improved TTCW not improved
	Sastry [20]	22	12	No	TT	TT improved
	Singh [21]	20	6	No	6MWD	6MWD improved
	PACES [22]	264	16	Epoprostenol	6MWD	6MWD improved TTCW and haemodynamics improved
	Iversen [23]	20	12	Bosentan	6MWD	6MWD not improved
	Pfizer study A1481243	103	12	Bosentan	6MWD	6MWD not improved
Tadalafil	PHIRST [24]	405	16	No, or bosentan (54%)	6MWD	6MWD improved (In bosentan treated patients +23 m, 95% CI -2 to 48 m) TTCW improved
Vardenafil[a]	EVALUTATION [25]	66	12	No	6MWD	6MWD improved TTCW improved

Web Table VIC Characteristics of randomised controlled trials with pulmonary arterial hypertension drugs interfering with the prostacyclin pathway (Prostacyclin analogues and prostacyclin receptors agonists)

Drugs tested	Study	Number of patients	Duration (weeks)	Background therapy	Primary endpoint	Main results
Beraprost[a]	ALPHABET [26]	130	12	No	6MWD	6MWD improved Haemodynamics not improved
	Barst [27]	116	52	No	CW	CW not improved
Epoprostenol	Rubin [28]	23	12	No	6MWD	6MWD improved Haemodynamics improved
	Barst [29]	81	12	No	6MWD	6MWD improved Haemodynamics improved Survival improved
	Badesch [30]	111	12	No	6MWD	6MWD improved
Inhaled Iloprost	AIR [31]	203	12	No	6MWD and FC	6MWD and WHO-FC improved Haemodynamics improved at peak
	STEP [32]	67	12	Bosentan	6MWD	6MWD improved (p=0.051) TTCW improved
	COMBI [33]	40	12	Bosentan	6MWD	Terminated for futility 6MWD not improved No clinical improvement

Web Table VIC Characteristics of randomised controlled trials with pulmonary arterial hypertension drugs interfering with the prostacyclin pathway (Prostacyclin analogues and prostacyclin receptors agonists)

Drugs tested	Study	Number of patients	Duration (weeks)	Background therapy	Primary endpoint	Main results
Treprostinil	SC–Pivotal study [34]	470	12	No	6MWD	6MWD improved Haemodynamics improved Pain at infusion site
	Inhal[a] TRIUMPH [35]	235	12	Bosentan or sildenafil	6MWD	6MWD improvement (+20 m at peak, +12 m at trough) TTCW not improved
	PO[a]-Freedom M [36]	185	16	No	6MWD	6MWD improvement (+26 m at peak, +17 m at trough) TTCW not improved
	PO[a]-Freedom CI [37]	354	16	ERA and/or PDE-5i	6MWD	6MWD not improved TTCW not improved
	PO[a]-Freedom CI [38]	310	16	ERA and/or PDE-5i	6MWD	6MWD not improved TTCW not improved
Selexipag[a]	Phase - 2 [39]	43	17	ERA and/or PDE-5i	PVR	PVR improved 6MWD not improved
	Griphon [40]	1156	74	ERA and/or PDE-5i	TTCW	TTCW improved

Monotherapy per ERS//ESC Guidelines

Measure/treatment			Class[a]-Level[b]					
			WHO-FC II		WHO-FC III		WHO-FC IV	
Calcium channel blockers			I	C[d]	I	C[d]	-	-
Endothelin receptor antagonists	Ambrisentan		I	A	I	A	IIb	C
	Bosentan		I	A	I	A	IIb	C
	Macitentan[e]		I	B	I	B	IIb	C
Phosphodiesterase type 5 inhibitors	Sildenafil		I	A	I	A	IIb	C
	Tadalafil		I	B	I	B	IIb	C
	Vardenafil[g]		IIb	B	IIb	B	IIb	C
Guanylate cyclase stimulators	Riociguat		I	B	I	B	IIb	C
Prostacyclin analogues	Epoprostenol	Intravenous[e]	-	-	I	A	I	A
	Iloprost	Inhaled	-	-	I	B	IIb	C
		Intravenous[g]	-	-	IIa	C	IIb	C
	Treprostinil	Subcutaneous	-	-	I	B	IIb	C
		Inhaled[g]	-	-	I	B	IIb	C
		Intravenous[f]	-	-	IIa	C	IIb	C
		Oral[g]	-	-	IIb	B	-	-
	Beraprost[g]		-	-	IIb	B	-	-
IP receptor agonists	Selexipag (oral)[g]		I	B	I	B	-	-

Combination Therapy in PAH

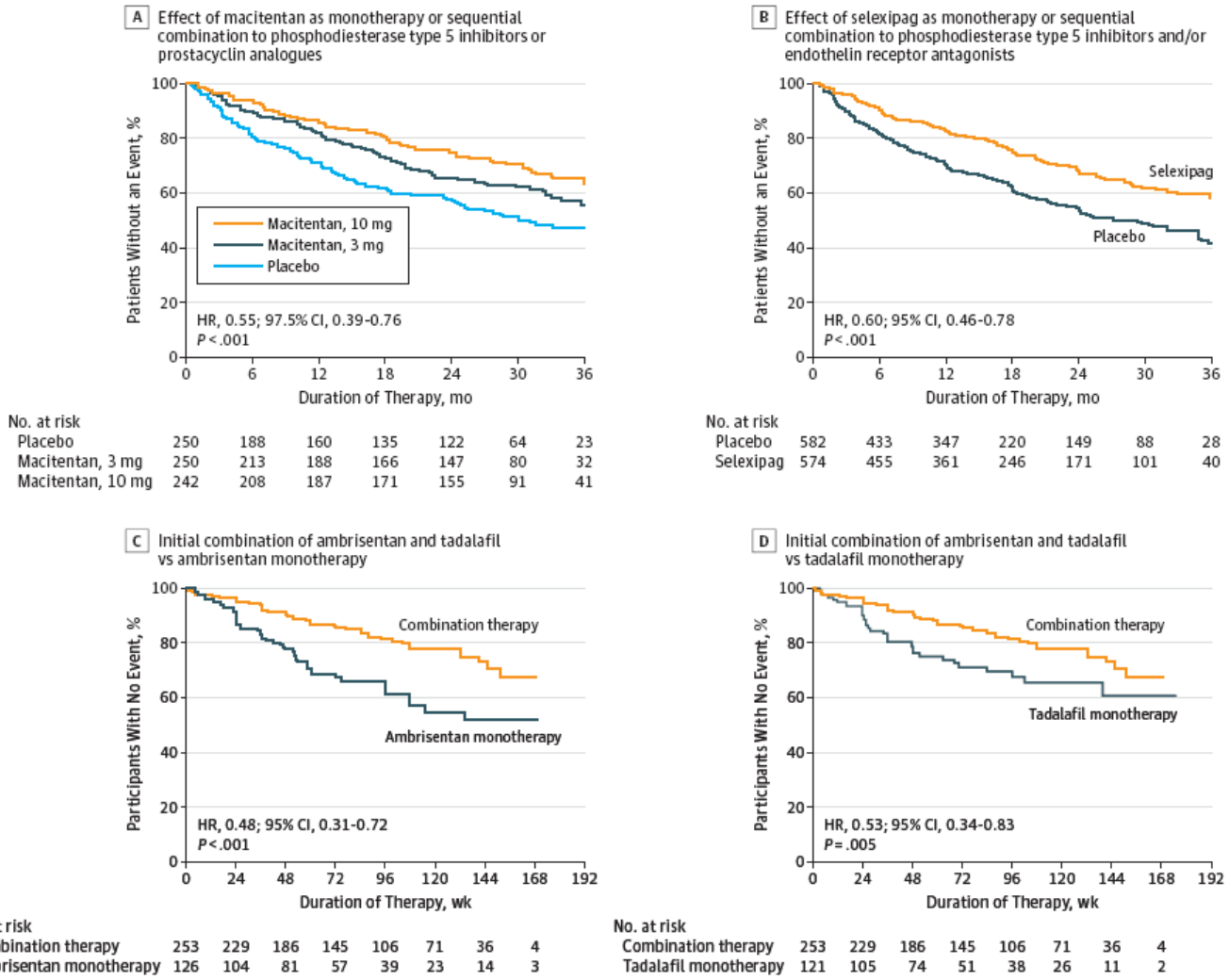
- Sequential
  - Dual
  - Triple
- Upfront
  - Ambrisentan + Tadalafil

Sequential Combination Therapy in PAH

Measure/ treatment	Class[a]-Level[b]					
	WHO-FC II		WHO-FC III		WHO-FC IV	
Macitentan added to sildenafil[d]	I	B	I	B	IIa	C
Riociguat added to bosentan	I	B	I	B	IIa	C
Selexipag[e] added to ERA and/or PDE-5i[d]	I	B	I	B	IIa	C
Sildenafil added to epoprostenol	–	–	I	B	IIa	B
Treprostinil inhaled added to sildenafil or bosentan	IIa	B	IIa	B	IIa	C
Riociguat added to sildenafil or other PDE-5i	III	B	III	B	III	B

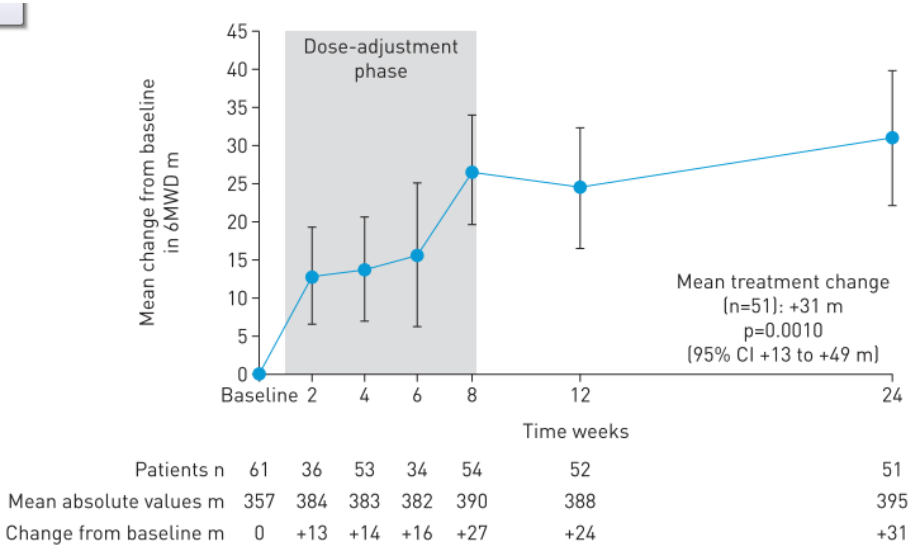
KM Curves for the Effect of Various Therapies for PH

Galie JAMA Cardiology 2016

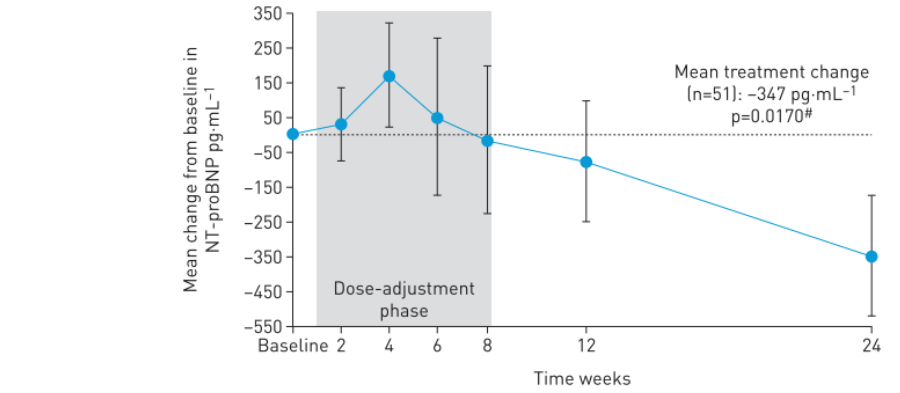


RESPITE: switching to riociguat in pulmonary arterial hypertension patients with inadequate response to phosphodiesterase-5 inhibitors

Marius M. Hoeper[1], Gérald Simonneau[2], Paul A. Corris[3], Hossein-



Patients n	61	36	53	34	54	52	51
Mean absolute values m	357	384	383	382	390	388	395
Change from baseline m	0	+13	+14	+16	+27	+24	+31



Patients¶ n	60	61	59	56	55	54	52
Mean absolute values pg·mL⁻¹	1190	1277	1388	1218	1120	1066	737
Change from baseline¶ pg·mL⁻¹	0	+29	+171	+52	−16	−77	−347

Open label background tx with ERAs
n=61, FC III

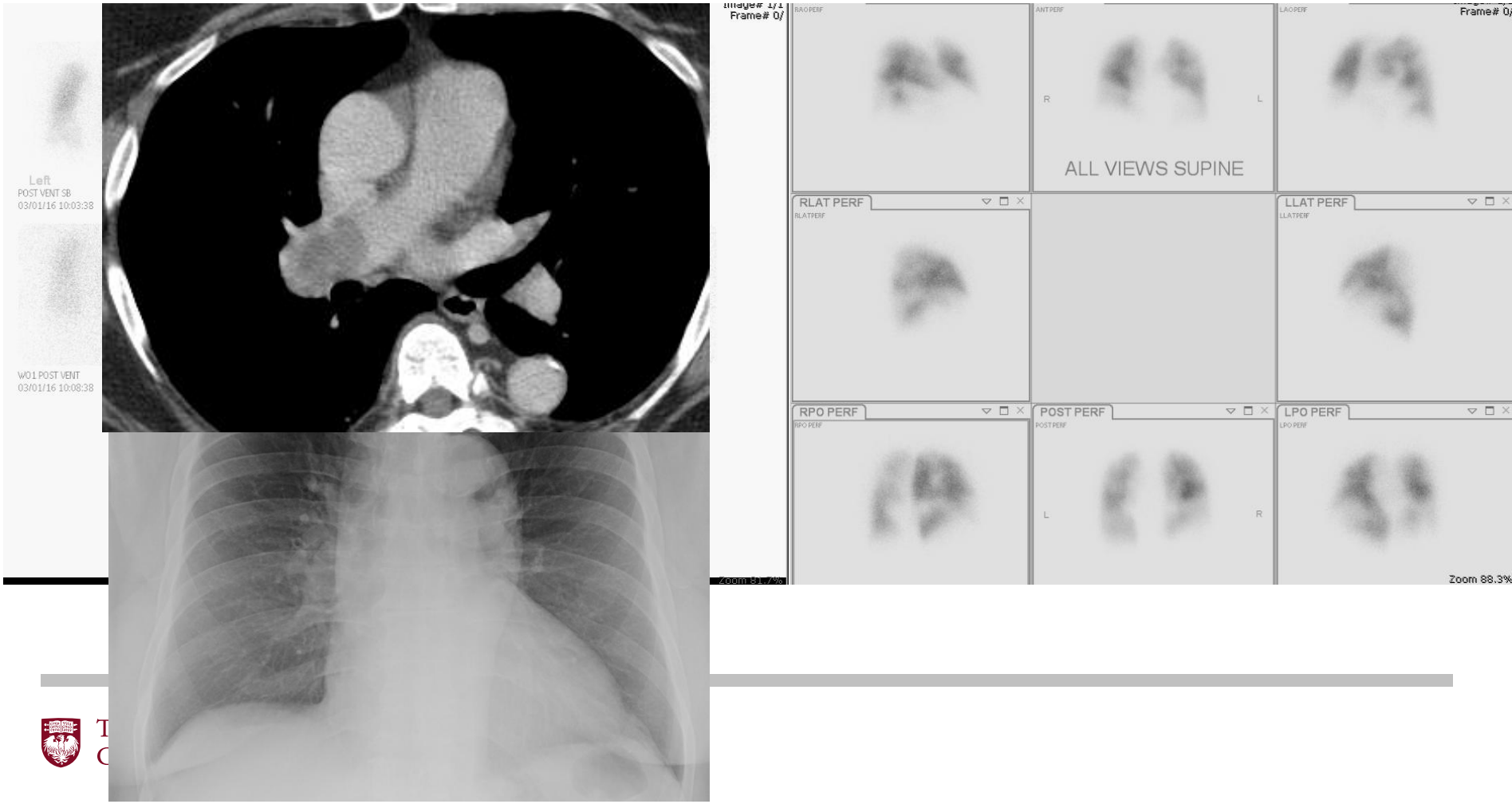
Eur Respir J 2017; 50

Toxicity:

- Embryo-fetal: Ambrisentan, Bosentan, Macitentan, Riociguat
- Liver: Bosentan , Ambrisentan, Macitentan
- Edema: Ambrisentan
- Anemia: Macitentan
- Line infection , thrombosis
- Multiple SE: HA, GI, diarrhea

Case

- DVT & PE 2/12/2016
- RHC 2/2016 : mRAP 8, PAP 80/30, mPAP 42, no PCWP, Fick CO 6.4

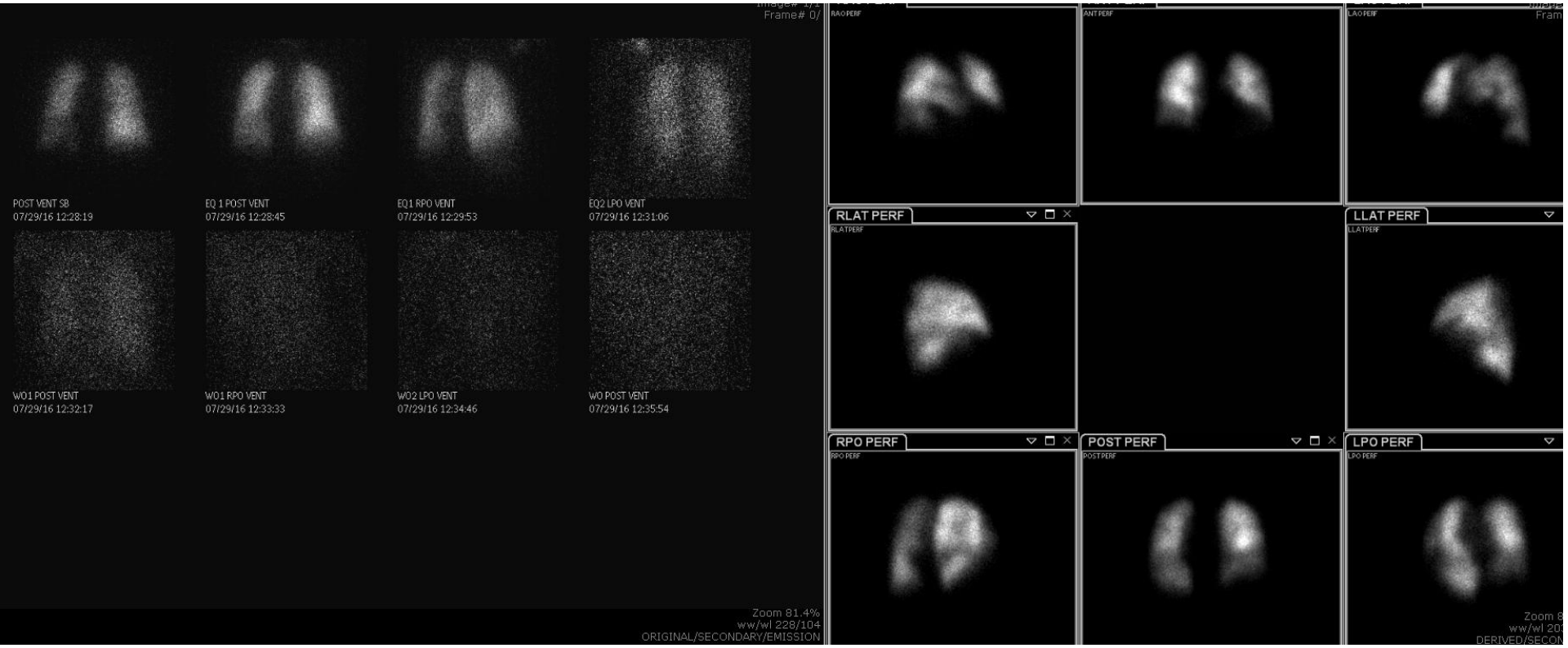


Case in ~ 6 mo

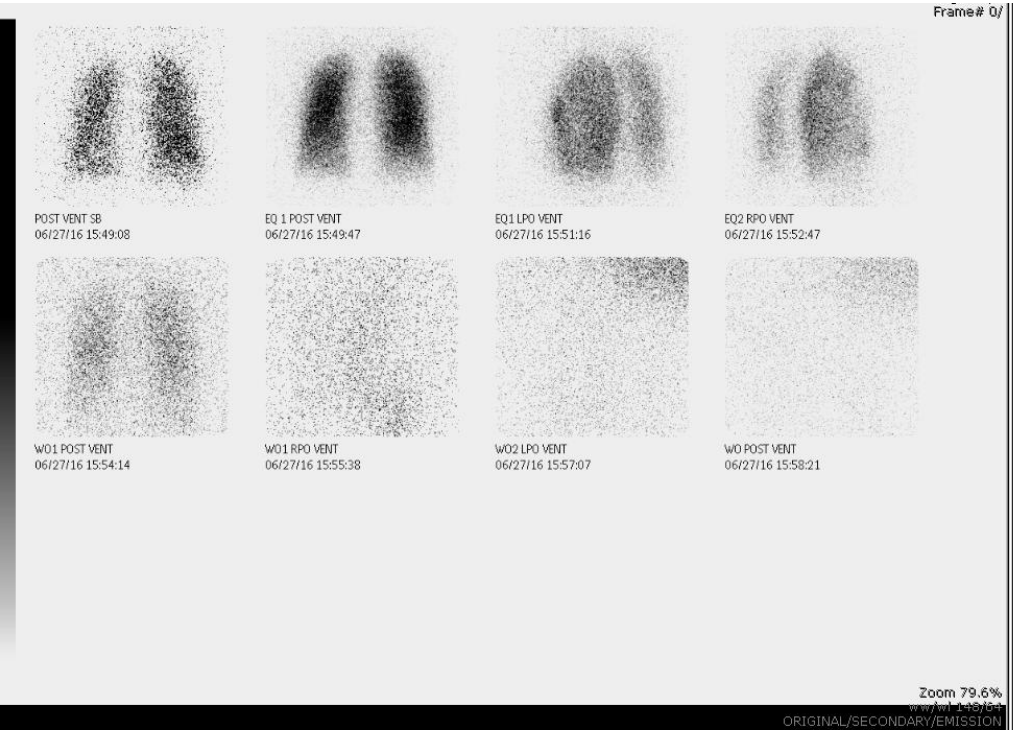
WHO FC 3, 6MWT 357 m , min SpO2 90%

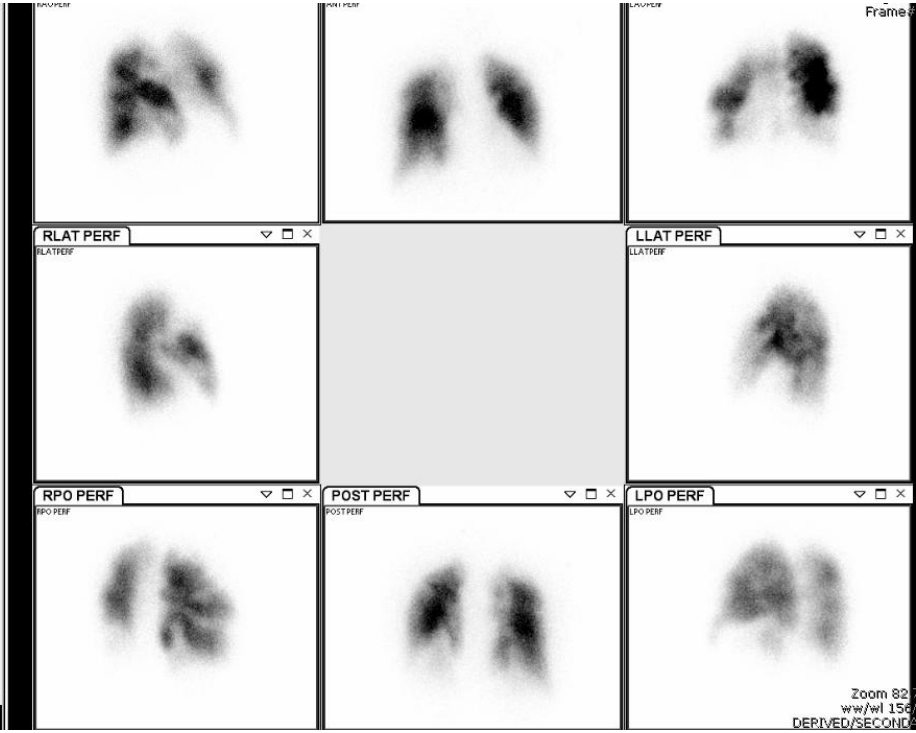
VQ 7/29/2016- 6 mo

RHC (after CPAP use):RA 6, RV 75/10, PA 75/25 (38), PCW 10, TD CO 3.7, PVR= 7.5

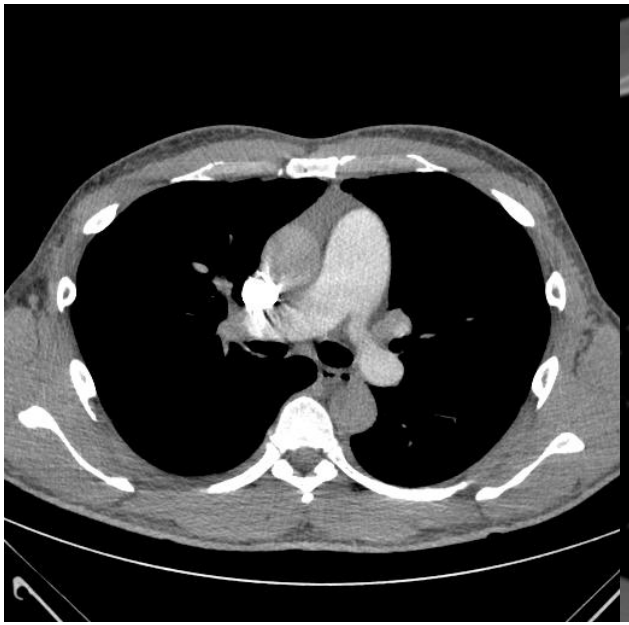


VQ

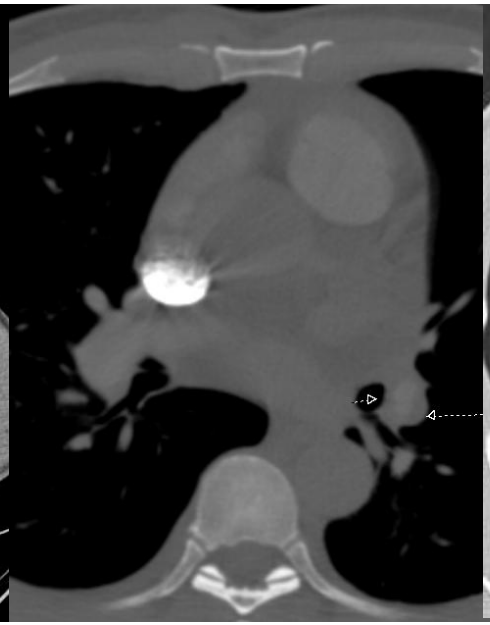

POST VENT SB
06/27/16 15:49:08
EQ 1 POST VENT
06/27/16 15:49:47
EQ1 LPO VENT
06/27/16 15:51:16
EQ2 RPO VENT
06/27/16 15:52:47
W01 POST VENT
06/27/16 15:54:14
W01 RPO VENT
06/27/16 15:55:38
W02 LPO VENT
06/27/16 15:57:07
W0 POST VENT
06/27/16 15:58:21
Zoom 79.6%
ORIGINAL/SECONDARY/EMISSION


RLAT PERF
LLAT PERF
RPO PERF
POST PERF
LPO PERF

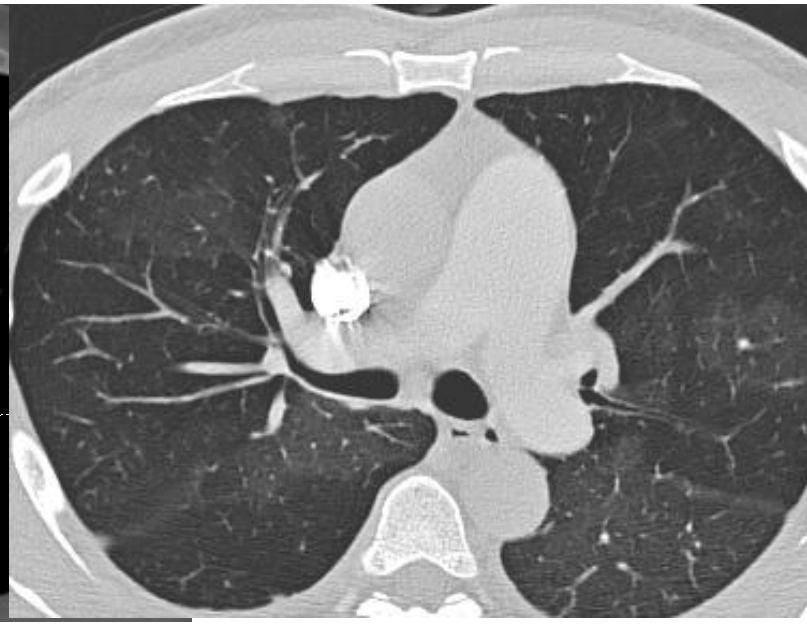
CT



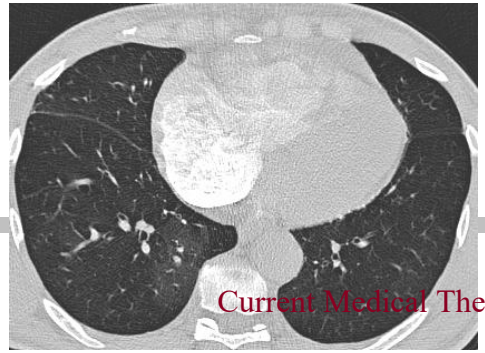
PAD 38 mm

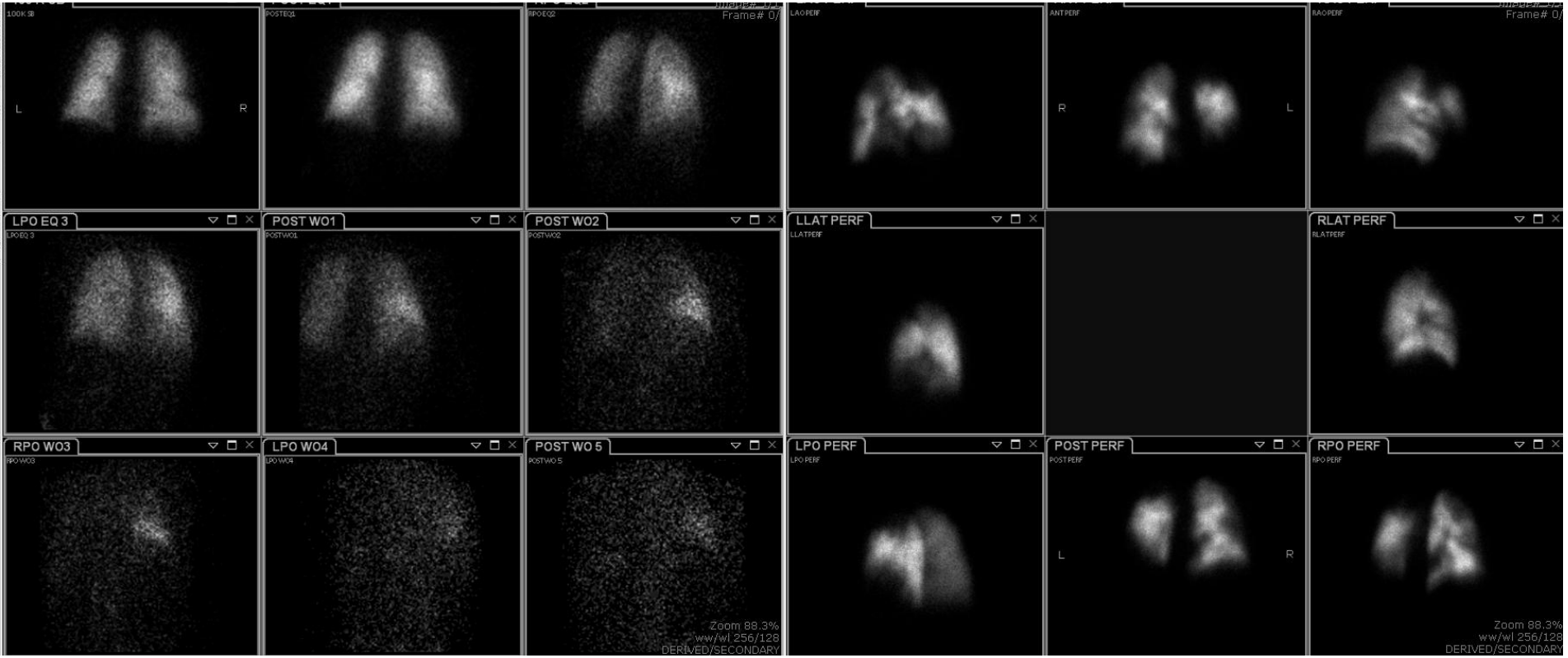


Web-like filling defect and circumferential narrowing

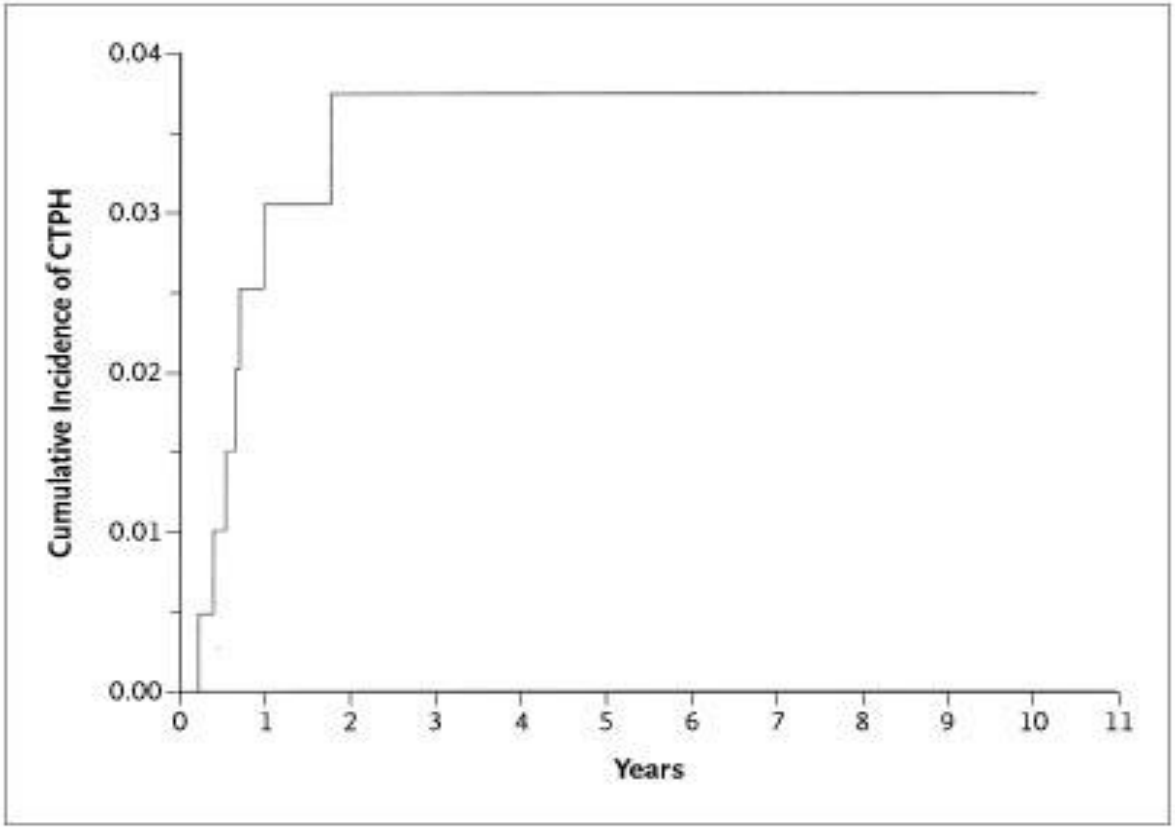


Mosaic pattern




L
R
LPO EQ 3
POST W01
POST W02
LLAT PERF
RLAT PERF
RPO W03
LPO W04
POST W0 5
LPO PERF
POST PERF
RPO PERF
L
R
Zoom 88.3%
ww/wl 256/128
DERIVED/SECONDARY

The Cumulative Incidence of CTEPH after a First Episode of PE

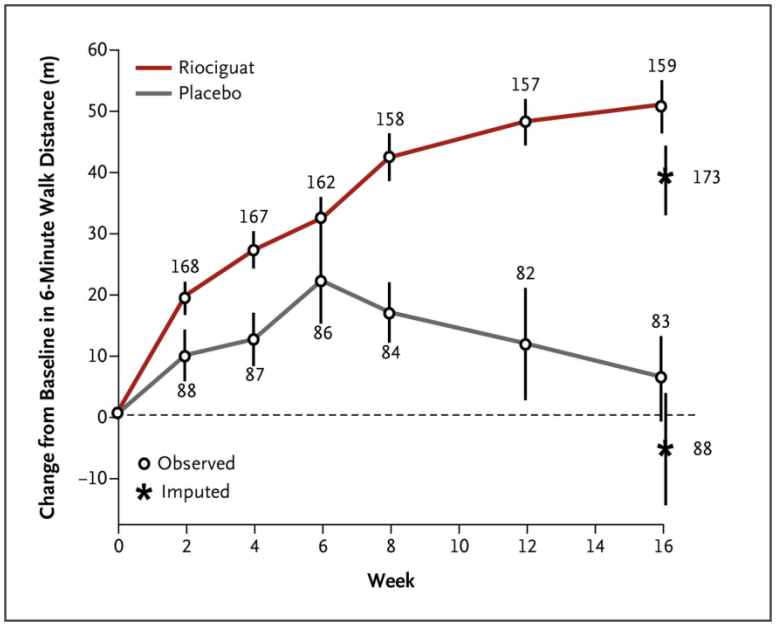


Pengo V et al. N Engl J Med 2004;350:2257-2264

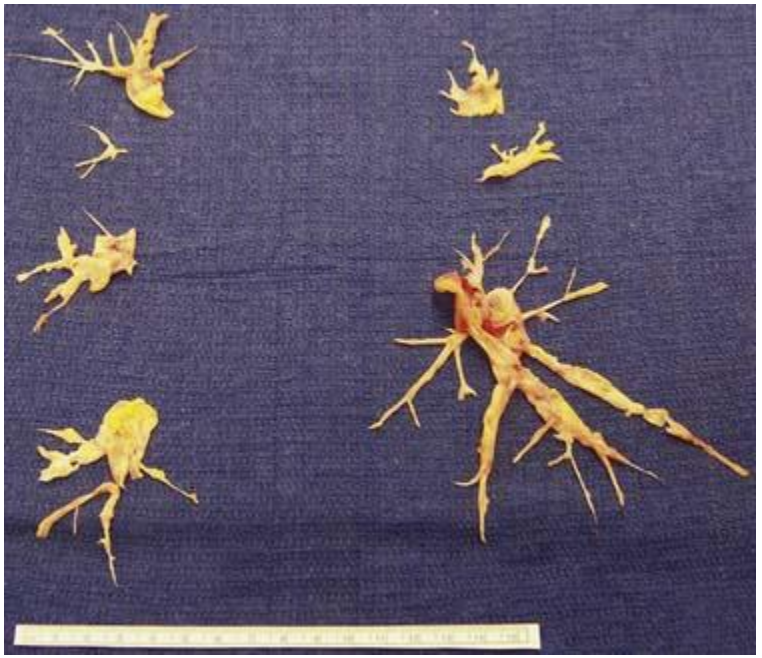
The NEW ENGLAND JOURNAL of MEDICINE

CTEPH Treatment

- CHEST-1 n=261, Riociguat



Thromboendaterectomy
N= ~500/year in the US



N Engl J Med 2013; 369:319-329

BPA for CTEPH

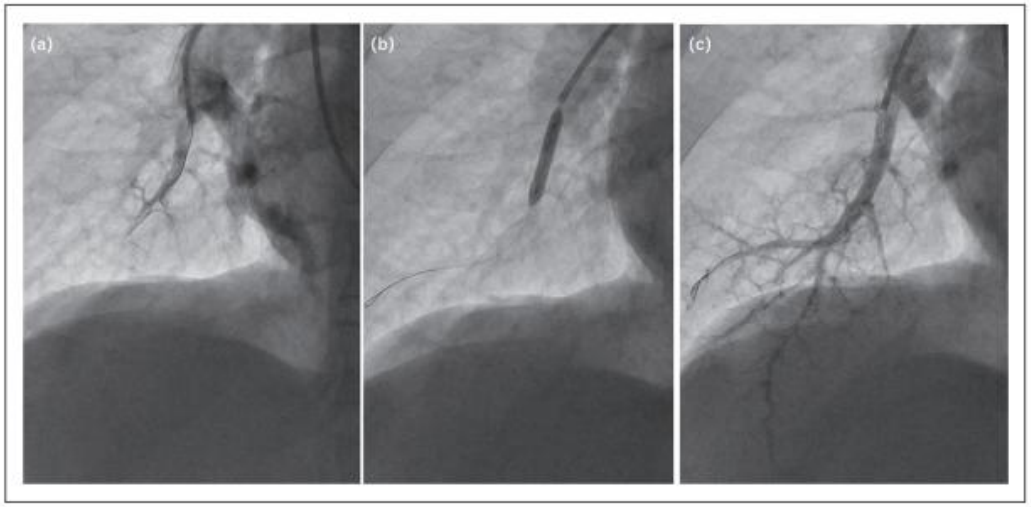


Table 2. Recent haemodynamic results from balloon pulmonary angioplasty

		PVR, dyn/s/cm^{-5}		
	n	**Before BPA**	**After BPA**	**BPA effect in PVR**
Sugimura *et al.* [10]	12	627 ± 236	310 ± 73	−54%
Mizoguchi *et al.* [12]	68	942 ± 367	327 ± 151	−65%
Andreassen *et al.* [13]	20	704 ± 320	472 ± 288	−33%
Fukui *et al.* [14▪]	20	889 ± 365	490 ± 201	−45%
Taniguchi *et al.* [16]	29	763 ± 308	284 ± 128	−63%

Data are presented as mean ± standard deviation unless otherwise noted. BPA, balloon pulmonary angioplasty; PVR, pulmonary vascular resistance.

Curr Opin Pulm Med 2015, 21:425–431

Monitoring / Follow-up

Evaluation of Disease Severity and Monitoring in PAH

2015 ESC/ERS Guidelines

- Objective and multiparameter evaluation
- Baseline and ongoing to assess disease progression and treatment effect
- Symptoms and signs of R HF, volume status, syncope, hospitalization,
- WHO FC
- 6MWT / CPET
- BNP/ NT-proBNP
- Hemodynamics
- Imaging (ECHO, cardiac MR)

Risk Assessment for PAH

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 >15 ml/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%

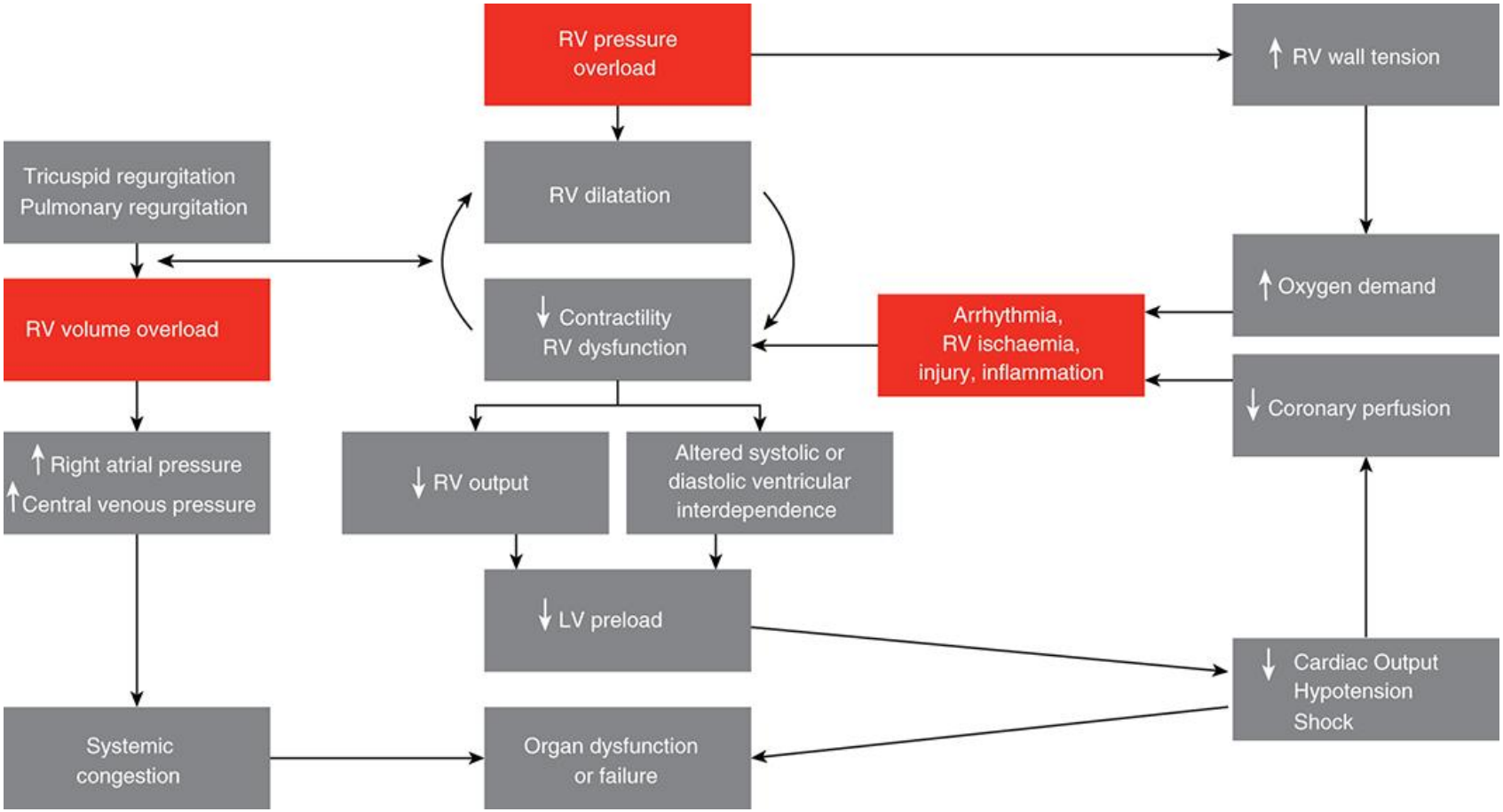
Nazzareno Galiè et al. Eur Heart J 2016;37:67-119

Common Pitfalls in the Management of PAH

- Diagnosis too late
- Patients at risk not screened
- Diagnostic work-up incomplete
  - Primary / associated / secondary not discerned
- Diagnosis relies on echocardiographic findings only
- Right heart catheterization and vasodilator test are not performed
- Inappropriate 6-min walk test
- Inappropriate use of calcium channel blockers/sildenafil
- Inappropriate use of combination therapy
- Too late to refer for lung transplantation

Approach to Acute RV Failure

Contemporary management of acute right ventricular failure: a statement from the Heart Failure Association and the Working Group on Pulmonary Circulation and Right Ventricular Function of the European Society of Cardiology



European Journal of Heart Failure
Volume 18, Issue 3, pages 226-241, 15 MAR 2016 DOI: 10.1002/ejhf.478
http://onlinelibrary.wiley.com/doi/10.1002/ejhf.478/full#ejhf478-fig-0001

Approach to Acute Decompensated RVF

- (1) Determine the cause of the decompensation
- (3) Avoid hypoxia, hypercapnia, acidosis
- (3) maximize cardiac output and systemic blood pressure
- (4) RV afterload reduction.

Approach to Acute Decompensated RVF

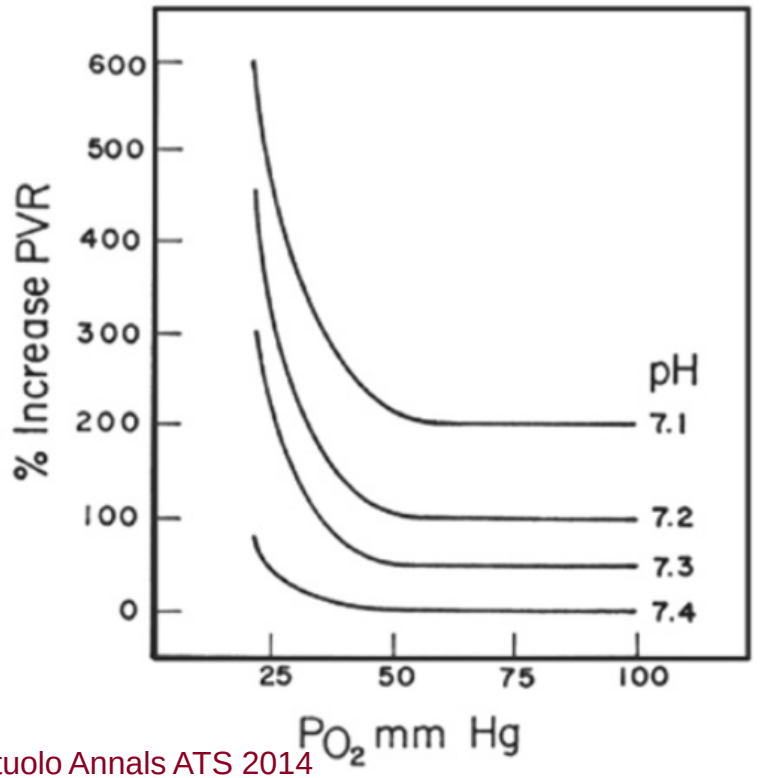
1-Cause of the decompensation

- Interruption of pulmonary vasodilator therapy
- Sepsis
- Pneumonia,
- Arrhythmia
- Pregnancy
- Volume Overload /dietary indiscretion
- PE, RV Ischemia

Eur Respir J 35(6):1286–1293

Approach to Acute Decompensated RVF

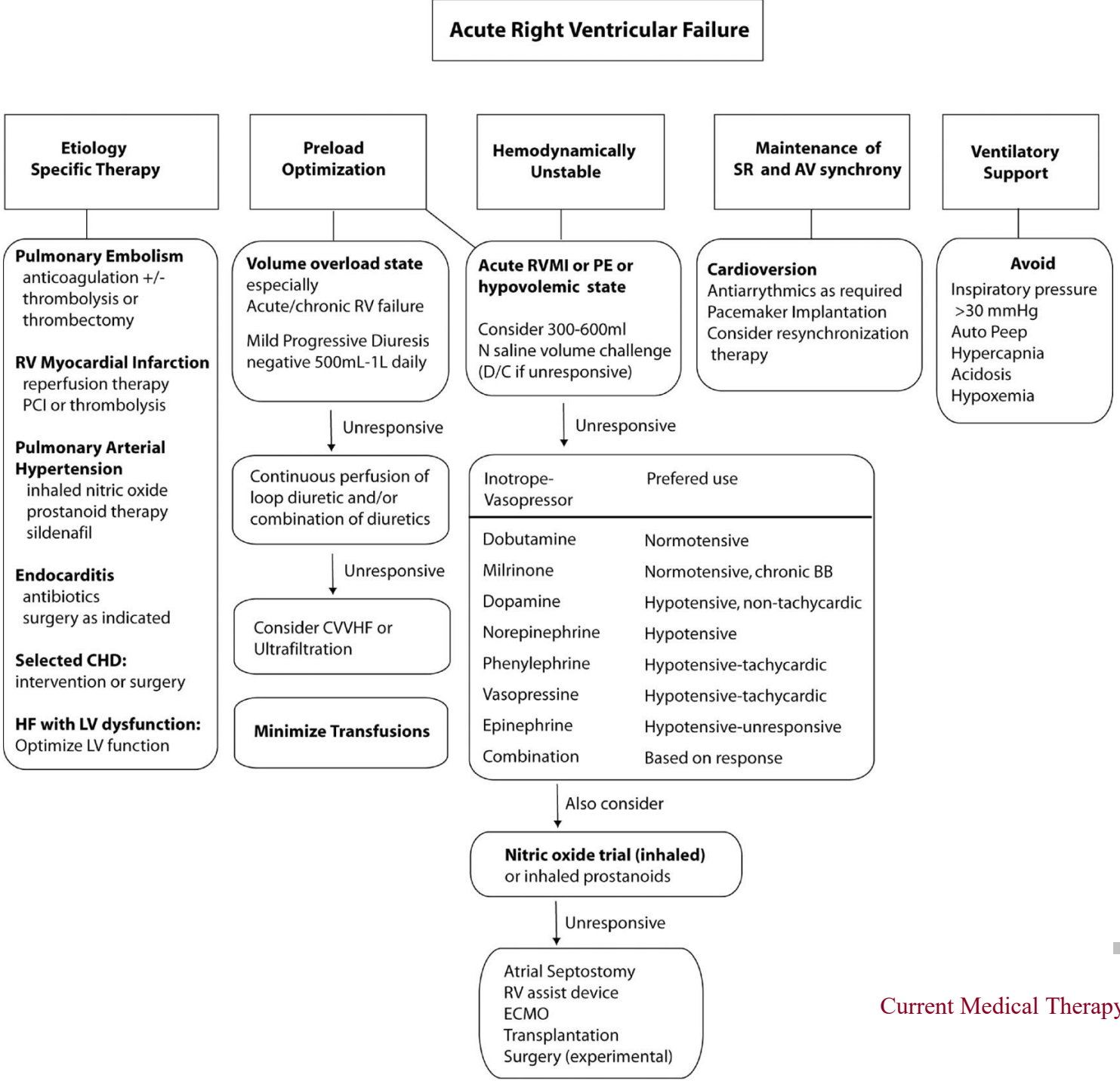
- (1) Determine the cause of the decompensation
- **(3) Avoid hypoxia, hypercapnia, acidosis**
- (3) maximize cardiac output and systemic blooc
- (4) RV afterload reduction.



Ventetuolo Annals ATS 2014

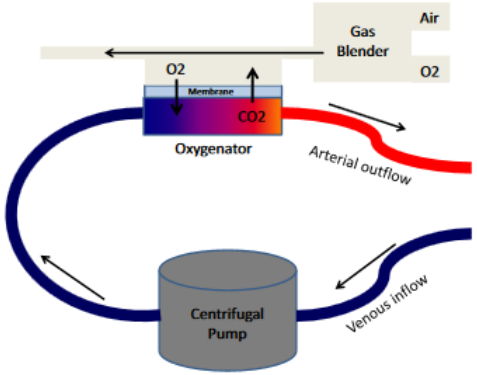
Vasoactive Drugs Used in RVF

Inotropes	Effect on PVR	Effect on SVR	PVR/SVR Ratio
Dobutamine[58-60,81-83]	↓↔[a]	↓↔[a]	↔
Milrinone[59,60,84,85]	↓↓	↓	↓
Norepinephrine[65,92]	↑	↑	↔
Dopamine	↑	↑	↔
Epinephrine	↑	↑	↔
Vasopressin[85,86]	↓	↑	↓
Phenylephrine[65,92]	↑↑	↑	↑


Acute Right Ventricular Failure
Etiology Specific Therapy
Preload Optimization
Hemodynamically Unstable
Maintenance of SR and AV synchrony
Ventilatory Support
Pulmonary Embolism
anticoagulation +/- thrombolysis or thrombectomy
RV Myocardial Infarction
reperfusion therapy
PCI or thrombolysis
Pulmonary Arterial Hypertension
inhaled nitric oxide
prostanoid therapy
sildenafil
Endocarditis
antibiotics
surgery as indicated
Selected CHD:
intervention or surgery
HF with LV dysfunction:
Optimize LV function
Volume overload state
especially
Acute/chronic RV failure
Mild Progressive Diuresis
negative 500mL-1L daily
Unresponsive
Continuous perfusion of loop diuretic and/or combination of diuretics
Unresponsive
Consider CVVHF or Ultrafiltration
Minimize Transfusions
Acute RVMI or PE or hypovolemic state
Consider 300-600ml
N saline volume challenge
(D/C if unresponsive)
Unresponsive
Inotrope-Vasopressor
Prefered use
Dobutamine
Normotensive
Milrinone
Normotensive, chronic BB
Dopamine
Hypotensive, non-tachycardic
Norepinephrine
Hypotensive
Phenylephrine
Hypotensive-tachycardic
Vasopressine
Hypotensive-tachycardic
Epinephrine
Hypotensive-unresponsive
Combination
Based on response
Also consider
Nitric oxide trial (inhaled)
or inhaled prostanoids
Unresponsive
Atrial Septostomy
RV assist device
ECMO
Transplantation
Surgery (experimental)
Cardioversion
Antiarrythmics as required
Pacemaker Implantation
Consider resynchronization therapy
Avoid
Inspiratory pressure >30 mmHg
Auto Peep
Hypercapnia
Acidosis
Hypoxemia

Atrial Septostomy, VA ECMO, RVAD, Lung Transplantation

- Inadequate clinical response to maximal combination therapy



PAH : Timing of referral

- NYHA FC III or IV symptoms during escalating therapy.
- Rapidly progressive disease
- Use of parenteral targeted PAH therapy regardless of symptoms or NYHA FC
- Any PVOD or pulmonary capillary hemangiomatosis

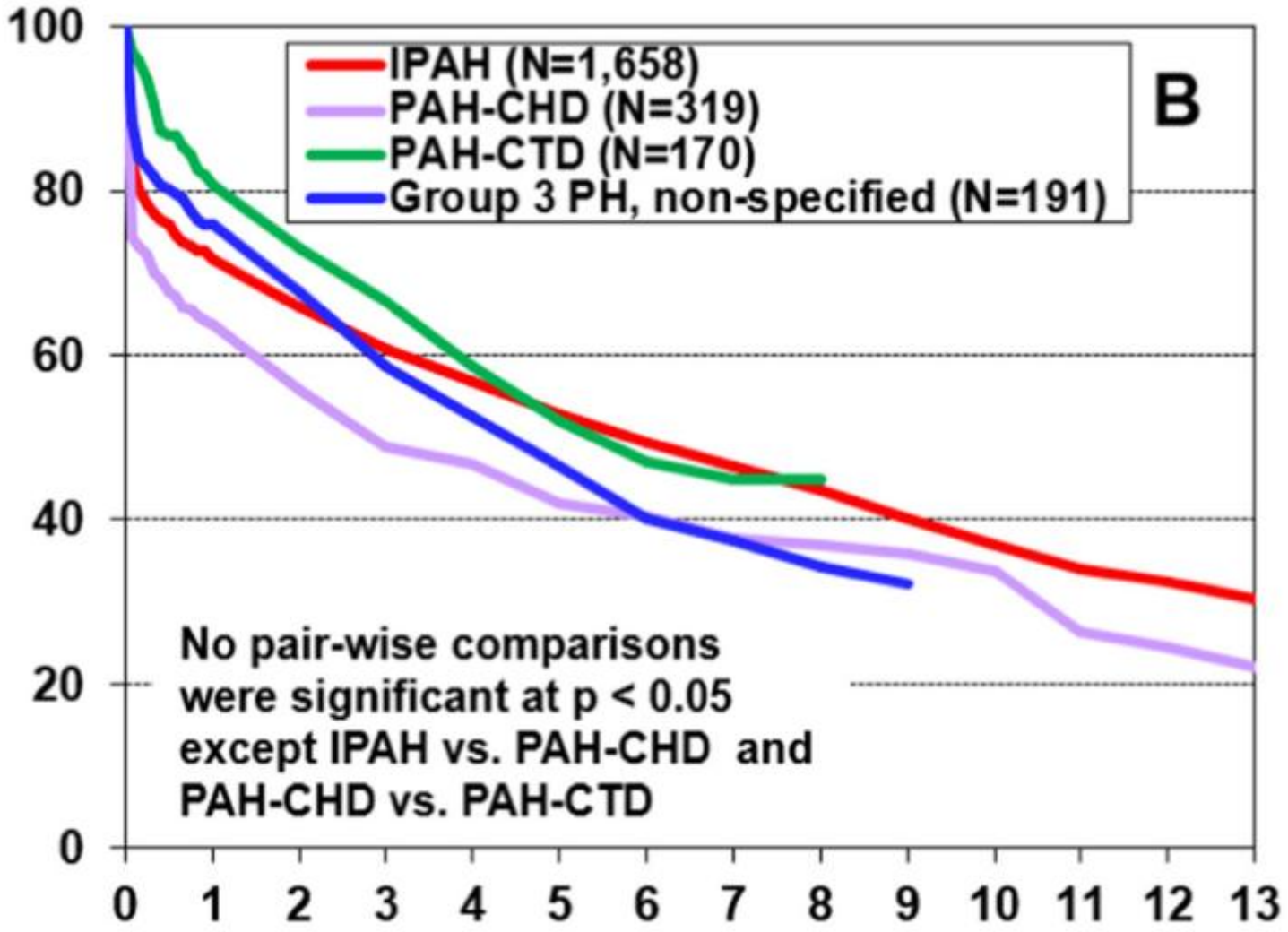
Weil et al. International Consensus Guidelines JHLT, January2015

PAH : Timing of Listing

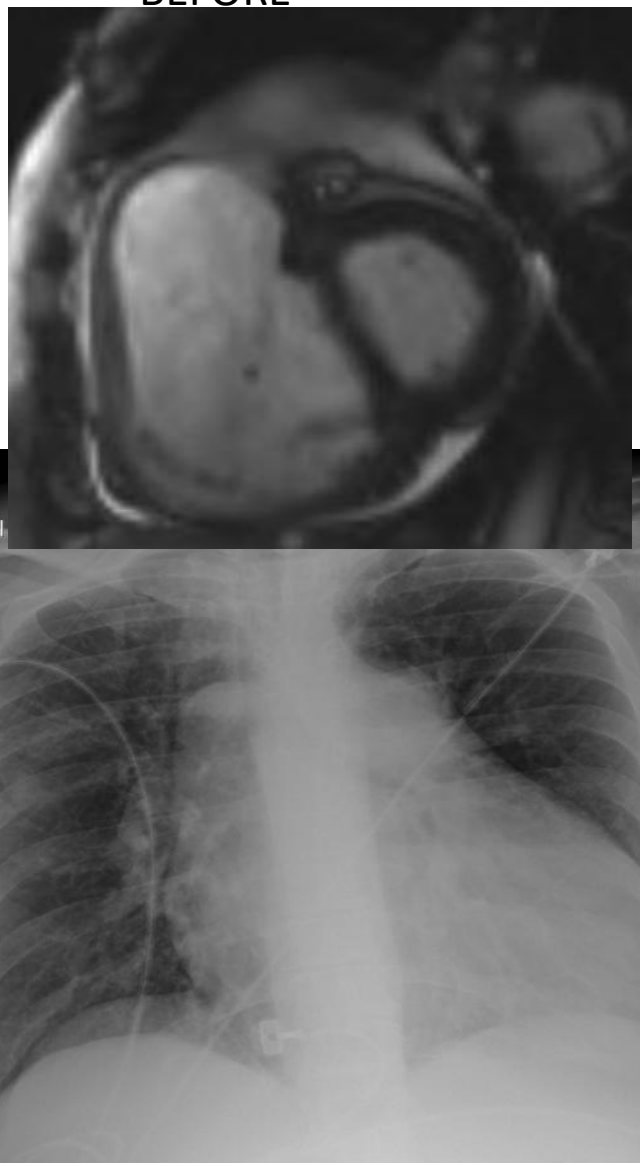
- NYHA FC III or IV symptoms despite a trial of at least 3 mo of combination Rx including prostanoids
- Cardiac index of <2 liters/min/m2
- Mean RAP >15 mmHg
- 6-MWT <350 m.
- Significant hemoptysis, pericardial effusion, or signs of progressive right heart failure(renal insufficiency, increasing bilirubin, BNP, recurrent ascites)

Weil et al. International Consensus Guidelines JHLT, January2015

Survival with Lung Tx – ISHLT Registry 2016



BEFORE



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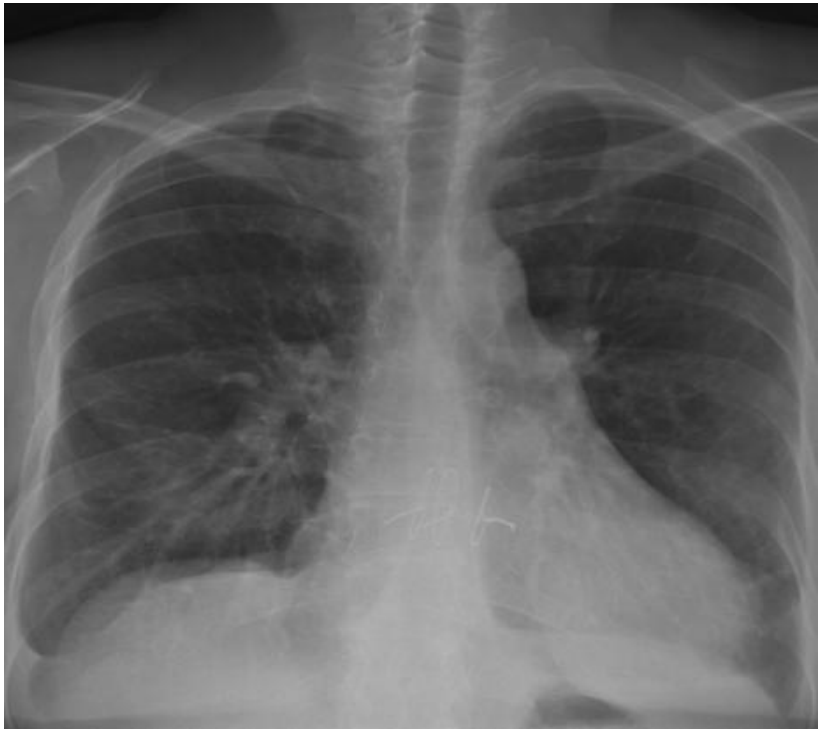
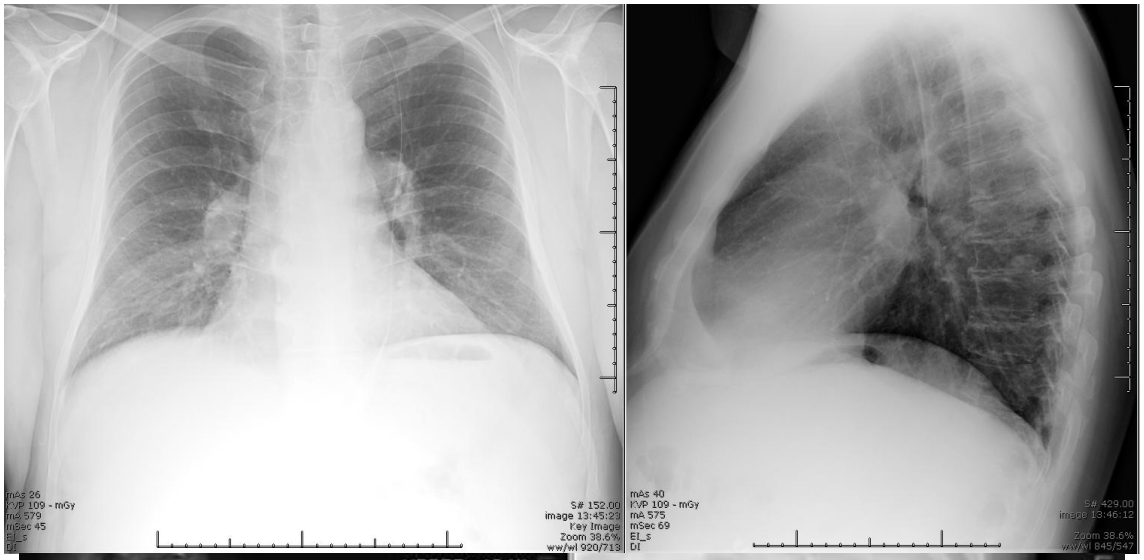
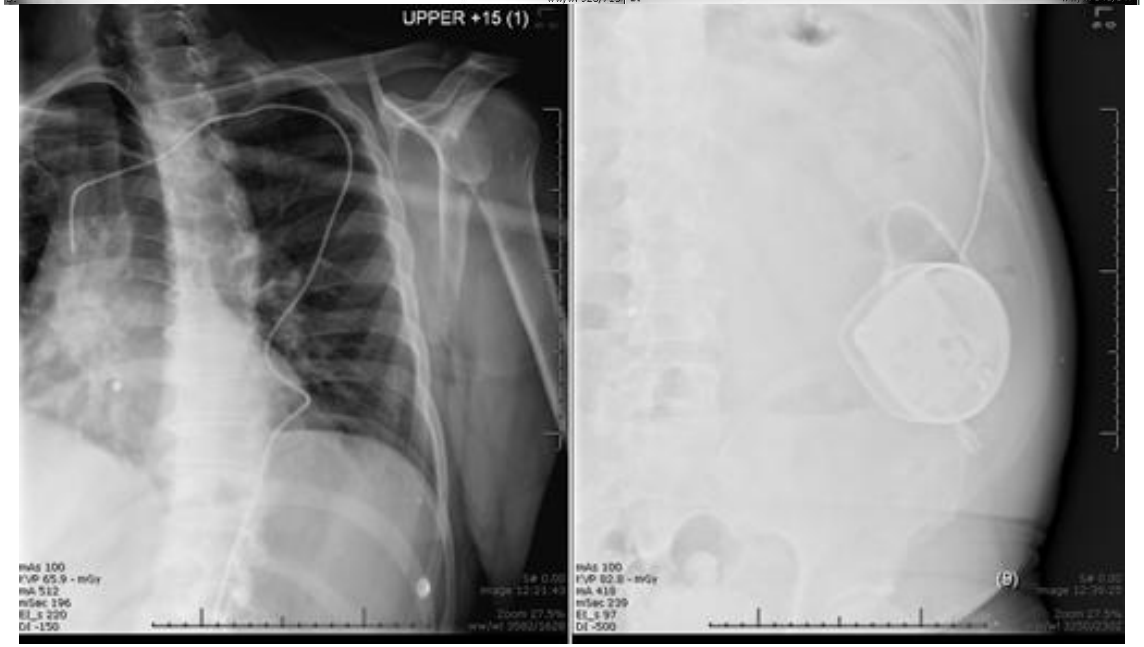


Summary

- PAH is characterized by vascular proliferation, hypertrophy, and fibrosis, leading to HD and RV abnormalities
- PAH progresses rapidly and has poor prognosis
- Echo is good screening tool for PAH
- RHC is required for confirmation of dx
- Endothelin, prostacyclin, and nitric oxide are key mediators and key targets for therapy



April
2012



Sept
2013