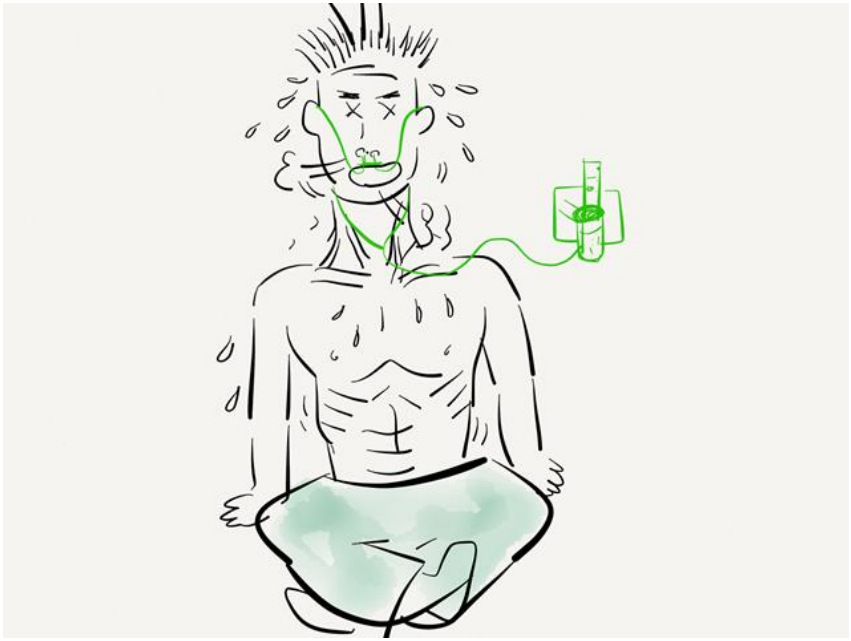
Treatment of Pulmonary Hypertension

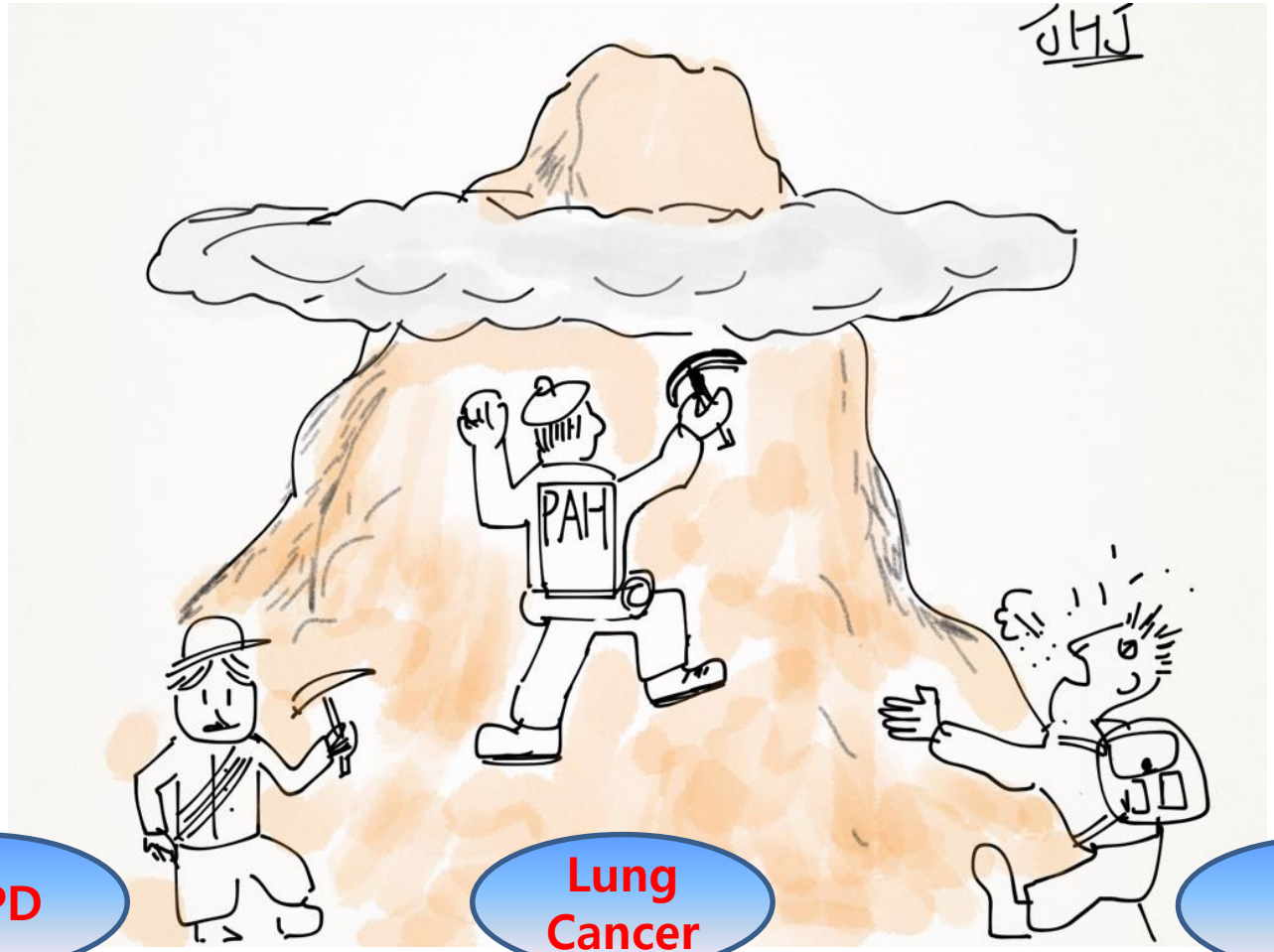
Updated Overview

"Can see **Dramatic improvement**"
in pulmonary diseases



Most developing area?

in pulmonary diseases



COPD

Lung Cancer

ILD

Progress in PH

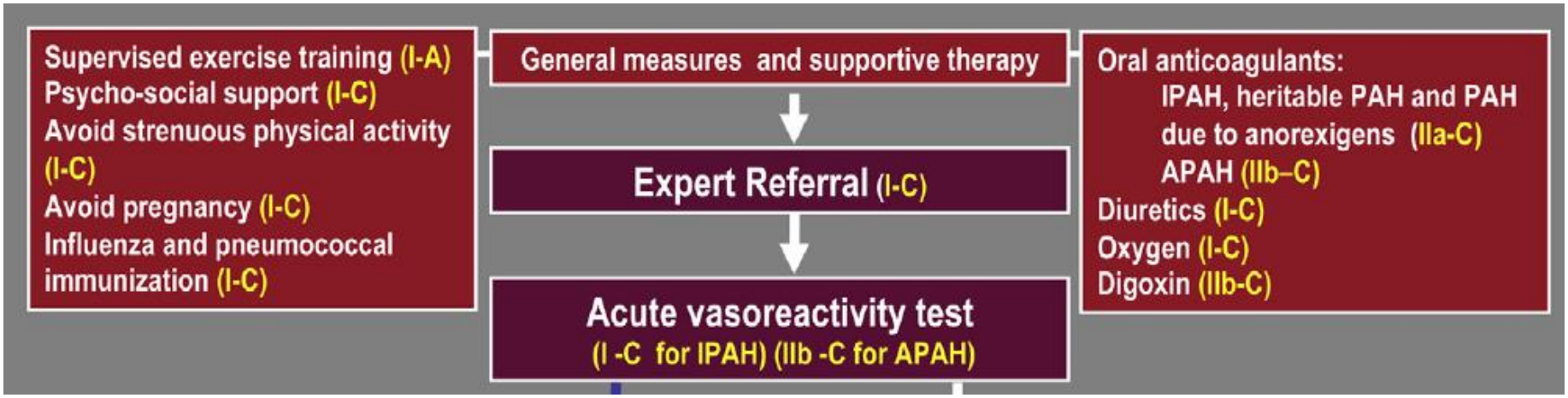
2nd World Symposium on PH in Evian, France, 1998

3rd World Symposium on PH in Venice, 2003

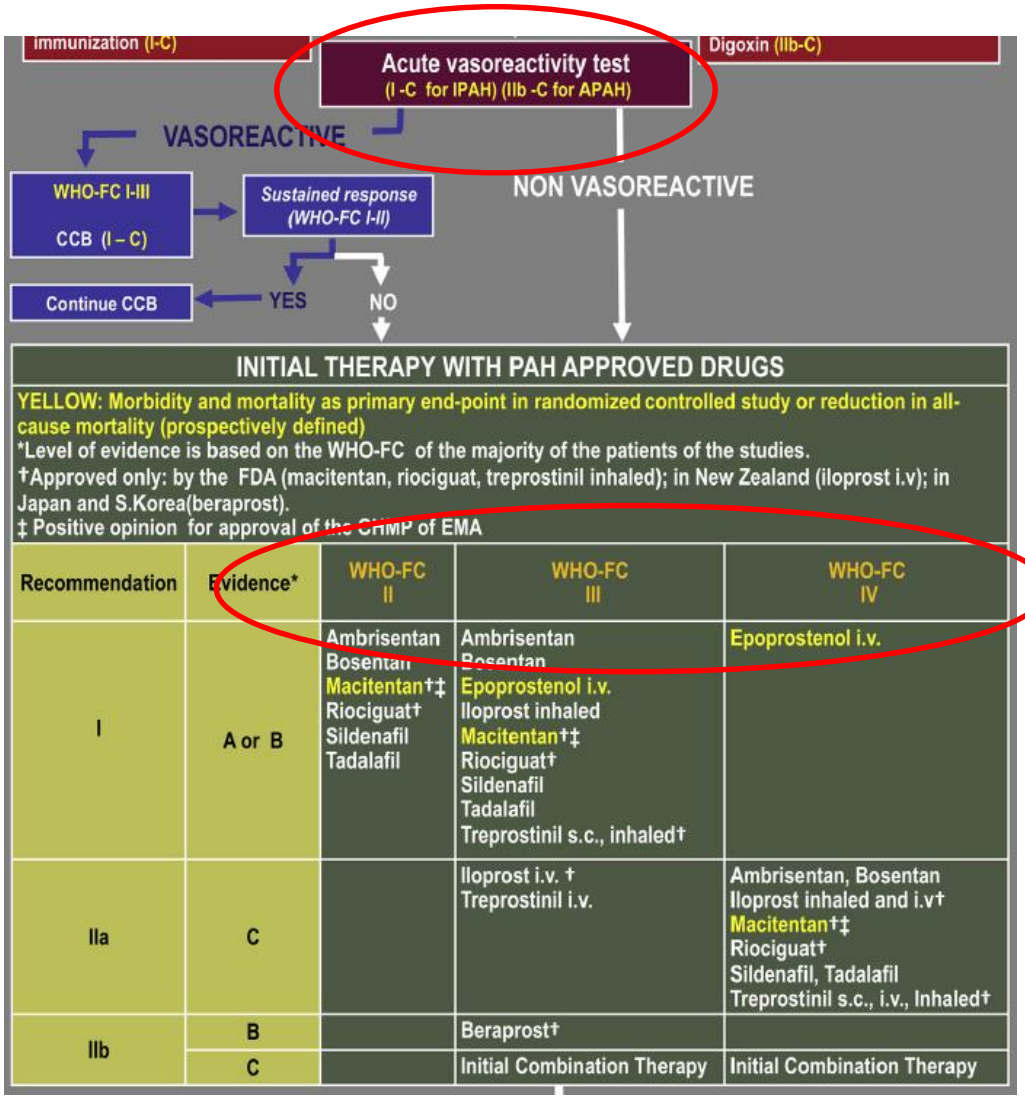
4th World Symposium on PH in Dana Point, 2008

5th World Symposium on PH in Nice, 2013

General measure & Supportive therapy



Evidence-Based Treatment Algorithm



INITIAL THERAPY WITH PAH APPROVED DRUGS

YELLOW: Morbidity and mortality as primary end-point in randomized controlled study or reduction in all-cause mortality (prospectively defined)

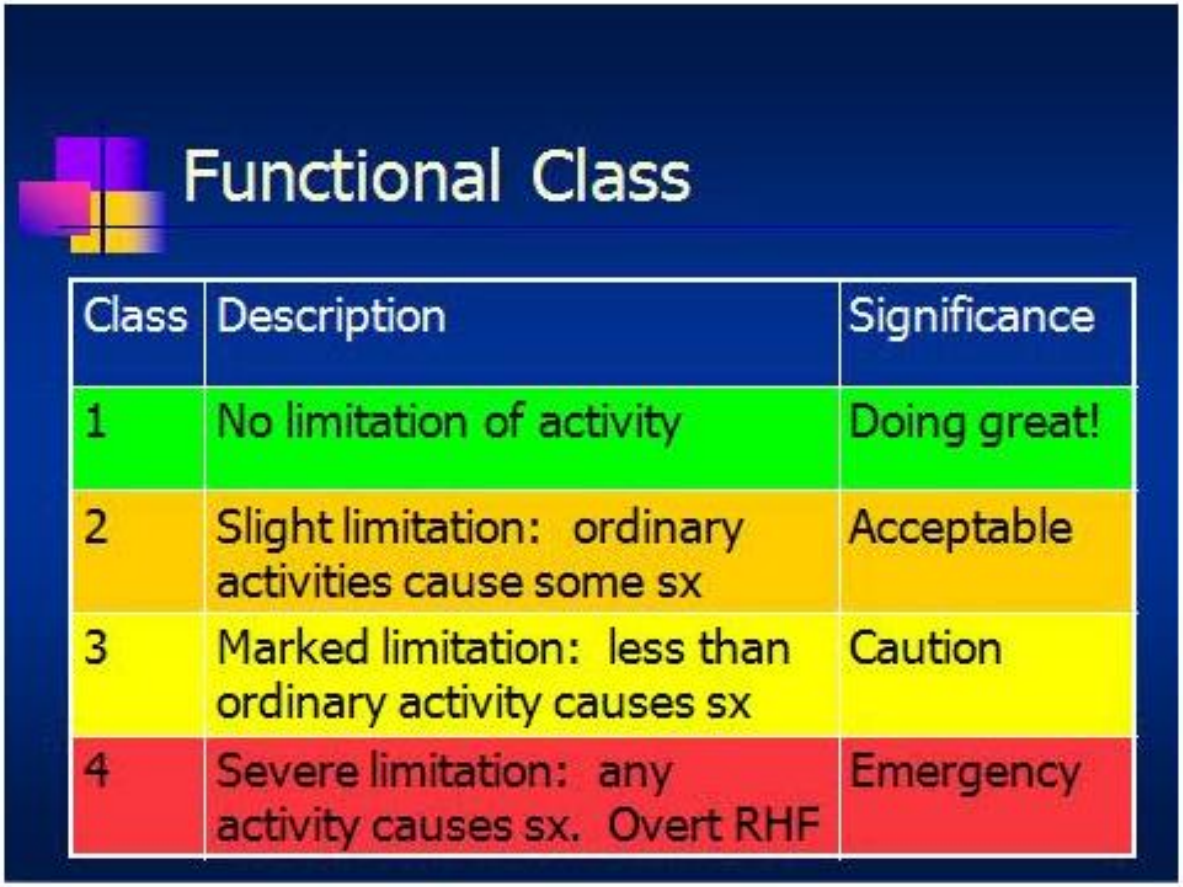
*Level of evidence is based on the WHO-FC of the majority of the patients of the studies.

†Approved only: by the FDA (macitentan, riociguat, treprostinil inhaled); in New Zealand (iloprost i.v); in Japan and S.Korea(beraprost).

‡ Positive opinion for approval of the CHMP of EMA

Recommendation	Evidence*	WHO-FC II	WHO-FC III	WHO-FC IV
I	A or B	Ambrisentan Bosentan Macitentan†‡ Riociguat† Sildenafil Tadalafil	Ambrisentan Bosentan Epoprostenol i.v. Iloprost inhaled Macitentan†‡ Riociguat† Sildenafil Tadalafil Treprostinil s.c., inhaled†	Epoprostenol i.v.
IIa	C		Iloprost i.v. † Treprostinil i.v.	Ambrisentan, Bosentan Iloprost inhaled and i.v† Macitentan†‡ Riociguat† Sildenafil, Tadalafil Treprostinil s.c., i.v., Inhaled†
IIb	B		Beraprost†	
	C		Initial Combination Therapy	Initial Combination Therapy

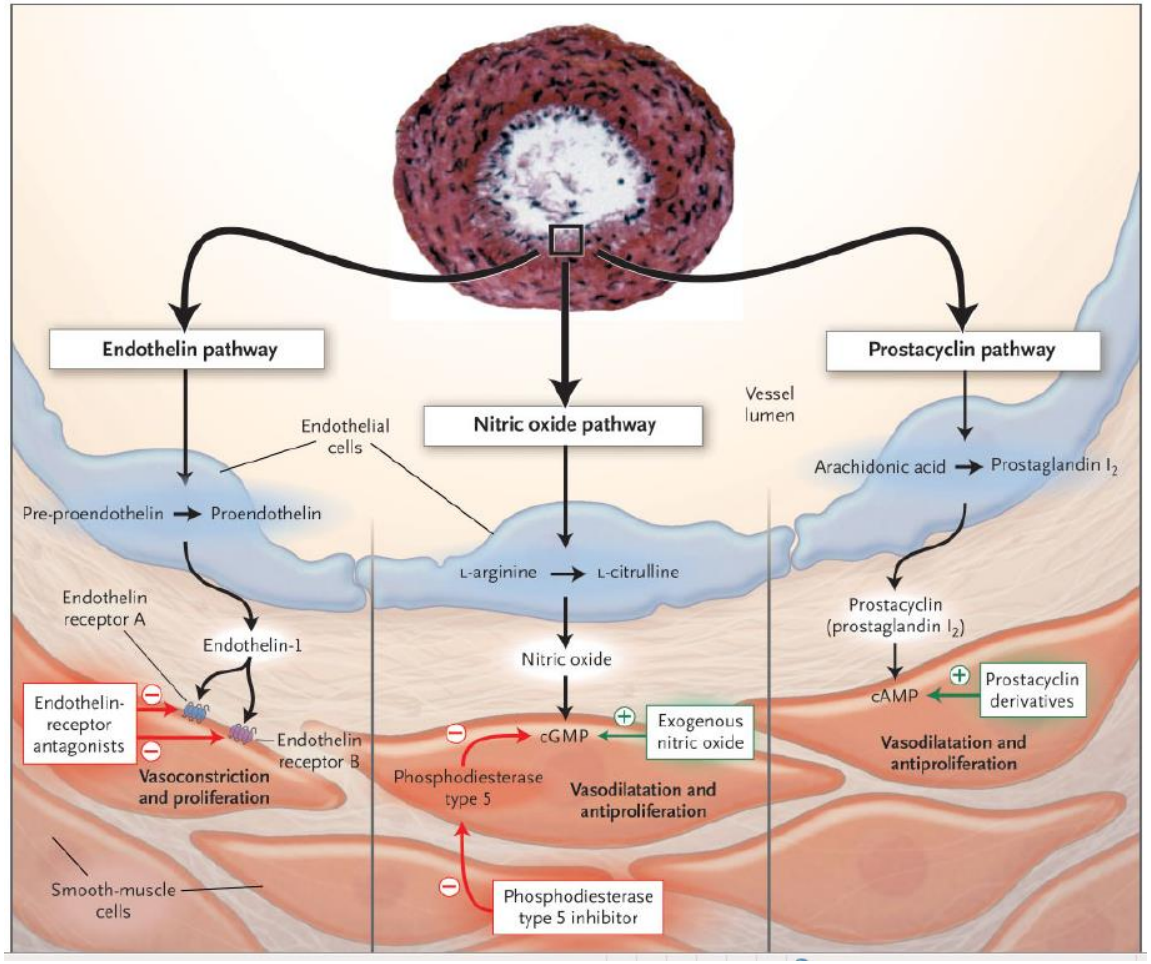
WHO functional class



Functional Class

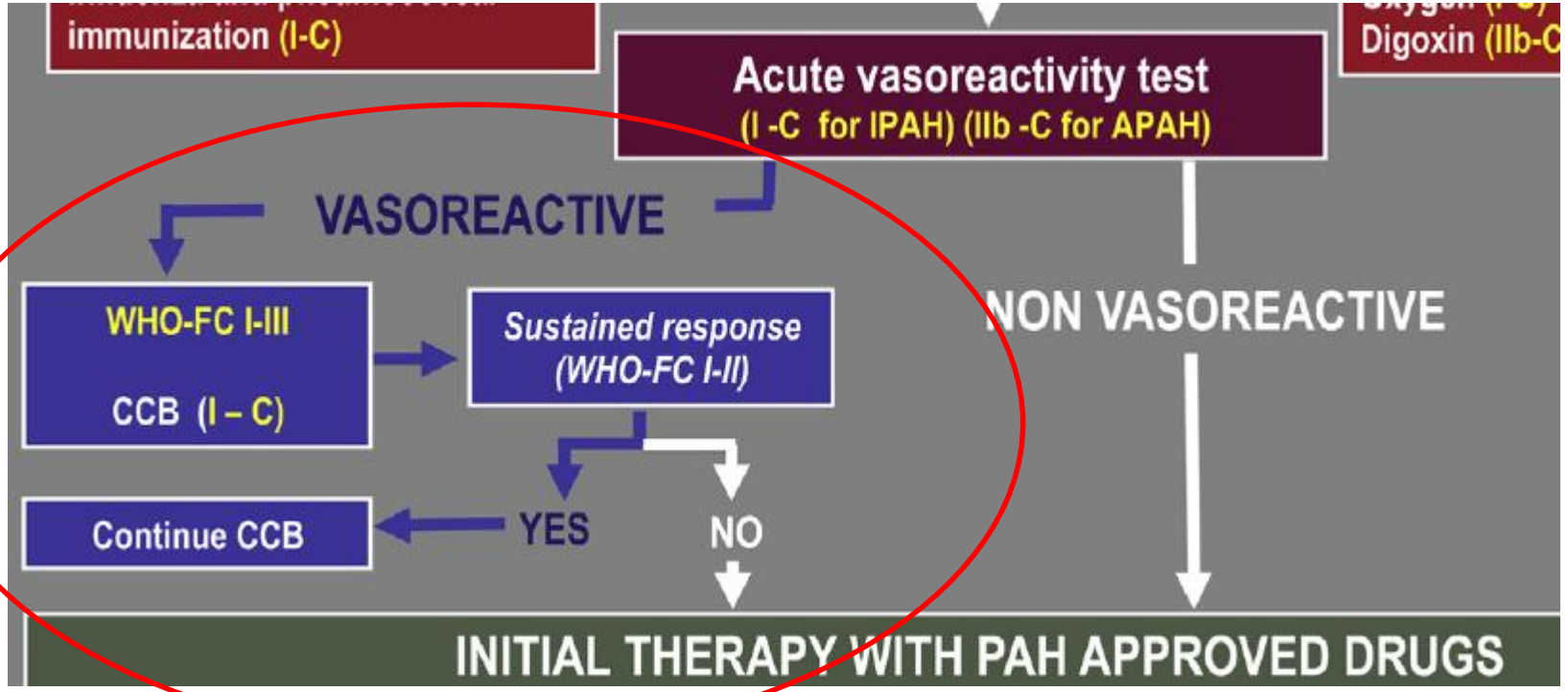
Class	Description	Significance
1	No limitation of activity	Doing great!
2	Slight limitation: ordinary activities cause some sx	Acceptable
3	Marked limitation: less than ordinary activity causes sx	Caution
4	Severe limitation: any activity causes sx. Overt RHF	Emergency

Pathogenesis & Target of Therapeutic drugs

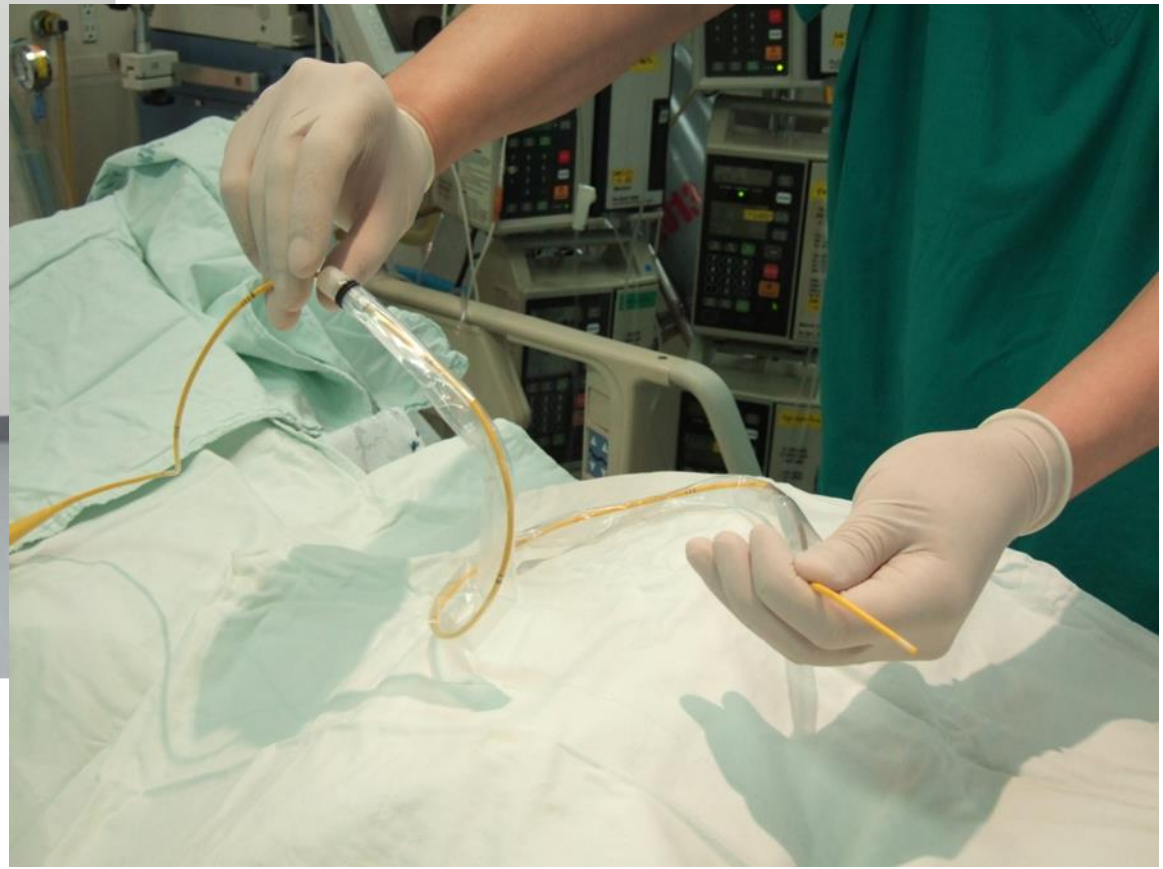


N Engl J Med 2004;351:1425-36.

Initial Therapy With PAH-Approved Drugs



Vasoreactivity testing & Calcium channel blocker (CCB)



Vasoreactivity testing

- Inhaled Nitric oxide

10 – 20 – 40 ppm

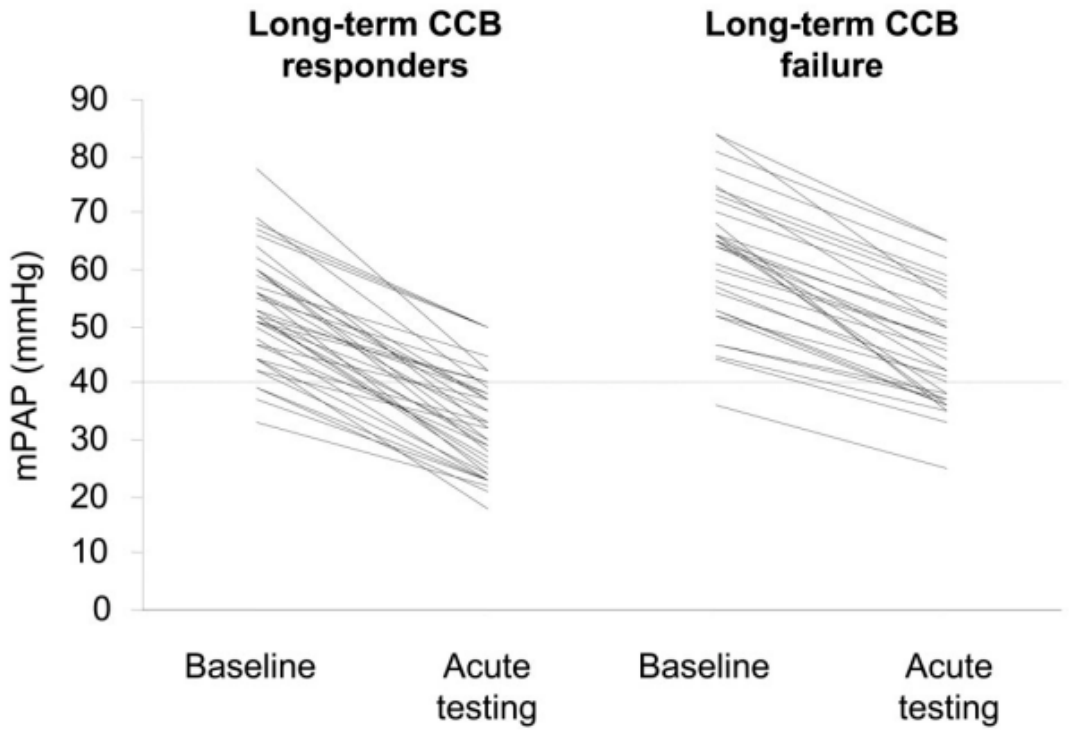
- Iloprost , Adenosine

- *Responder Criteria*

Reduction of mPAP >10 mmHg

Absolute mPAP < 40 mmHg

Based on Acute vasodilator test,
About **10–15%** of the patients receive CCB
but only half of them will have a **sustained response**
- Sitbon et al., 2003 -



Sitbon et al., Circulation. 2005;111:3105-3111

Use of **CCBs**

- **Indication**

- Significant vasodilator response
- Adequate systemic blood pressure
- Fc I, II or III stable over previous few months

- **Not indicated**

- Too low systemic blood pressure
  (systolic < 90-100 mmHg)
- Fc III~IV

1st line oral agent in Fc II

Recommendation	Evidence*	WHO-FC II
I	A or B	Ambrisentan Bosentan Macitentan†‡ Riociguat† Sildenafil Tadalafil

Letter to the Editor

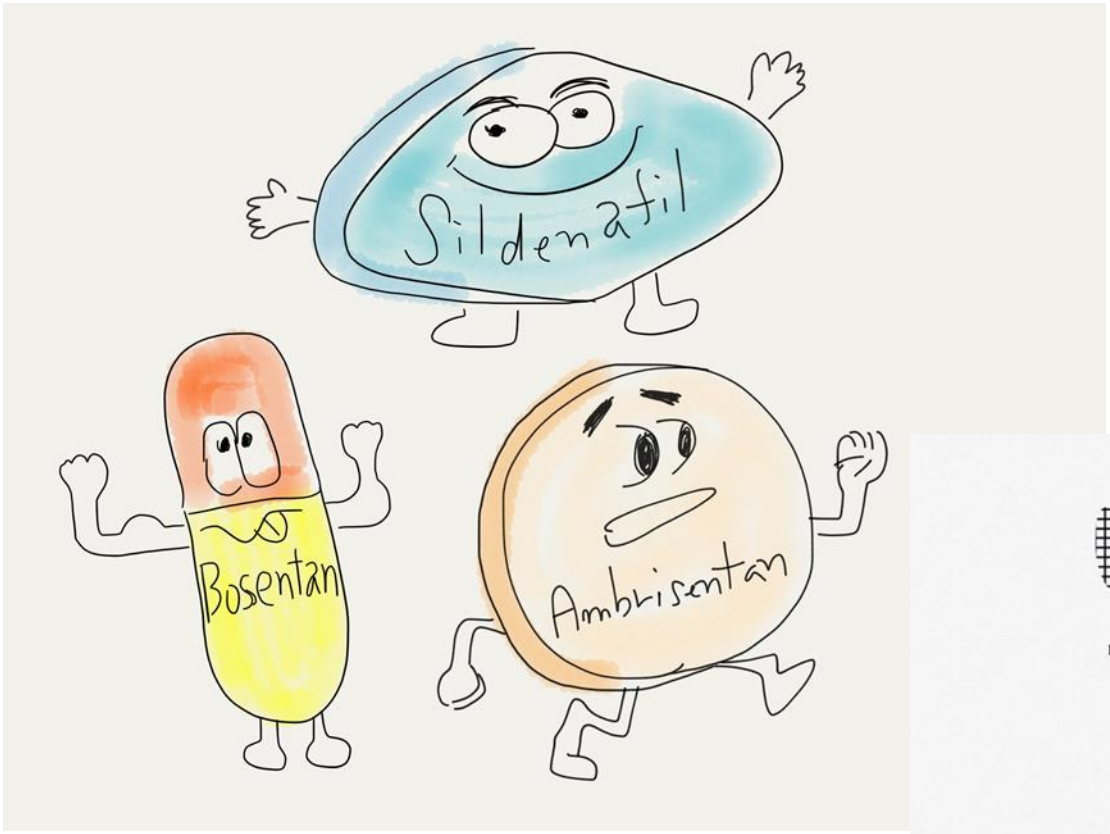
Choosing the best first line oral drug agent in patients with pulmonary hypertension: Evidence from a network meta-analysis

Giuseppe Biondi-Zoccai[b, e], Fabrizio D'Ascenzo[a, e], Margherita Cannillo[a], Nicky J. Welton[f], Walter Grosso Marra[a], Pierluigi Omedè[a], Daniela Libertucci[c], Enrico Fusaro[d], Michele Capriolo[a], Jacopo Perversi[a], Francesco Fedele[b], Giacomo Frati[b], Massimo Mancone[b], James J. DiNicolantonio[g], Carmine Dario Vizza[b], Claudio Moretti[a, e], Fiorenzo Gaita[a]

Odds ratio (95% credible interval) Treatment comparison	Death	Clinical improvement	Clinical worsening
Assuming each drug has its own independent effect relative to placebo			
Bosentan vs. placebo	0.64 (0.04, 2.71)	**1.81** (**1.17**, **2.71**)	**0.25** (**0.11**, **0.48**)
Sildenafil vs. placebo	7.34 (0.14, 37.82)	**9.64** (**3.31**, **25.22**)	0.54 (0.17, 1.33)
Beraprost vs. placebo	0.96 (0.07, 4.09)	1.06 (0.54, 1.89)	0.74 (0.31, 1.48)
Ambrisentan vs. placebo	0.50 (0.09, 1.58)		**0.28** (**0.12**, **0.56**)
Sildenafil vs. bosentan	37.97 (0.17, 174.90)	**5.57** (**1.70**, **15.20**)	2.47 (0.56, 7.23)
Beraprost vs. bosentan	4.70 (0.09, 26.90)	0.61 (0.27, 1.20)	**3.40** (**1.01**, **8.53**)
Ambrisentan vs. bosentan	2.38 (0.09, 12.60)		1.31 (0.39, 3.29)
Beraprost vs. Sildenafil	1.45 (0.01, 9.01)	0.14 (0.03, 0.38)	1.82 (0.40, 5.33)
Ambrisentan vs. sildenafil	0.74 (0.01, 4.09)		0.70 (0.15, 2.02)
Ambrisentan vs. beraprost	1.58 (0.06, 8.51)		0.45 (0.13, 1.15)

Int J Cardiol. 2013 Oct 9;168(4):4336-8

Initial monotherapy, Choice?



Prostanoid

- **Beraprost**

- 1st orally active prostacyclin analogue
- RCT : ALPHABET in Europe and USA

  Improvement in exercise capacity

  but persists only up to 3~6 months

  No hemodynamic benefits

- Flushing, jaw pain
- Approved in Japan, Korea

Prostanoid

- **Epoprostenol**
- Short half life (3~5 min)
- Continuous IV infusion
- Currently not available in Korea

Recommendation	Evidence*	WHO-FC II	WHO-FC III	WHO-FC IV
I	A or B	Ambrisentan Bosentan Macitentan†‡ Riociguat† Sildenafil Tadalafil	Ambrisentan Bosentan Epoprostenol i.v. Iloprost inhaled Macitentan†‡ Riociguat† Sildenafil Tadalafil Treprostinil s.c., inhaled†	Epoprostenol i.v.
IIa	C		Iloprost i.v. † Treprostinil i.v.	Ambrisentan, Bosentan Iloprost inhaled and i.v† Macitentan†‡ Riociguat† Sildenafil, Tadalafil Treprostinil s.c., i.v., Inhaled†
IIb	B		Beraprost†	
	C		Initial Combination Therapy	Initial Combination Therapy

Prostanoid

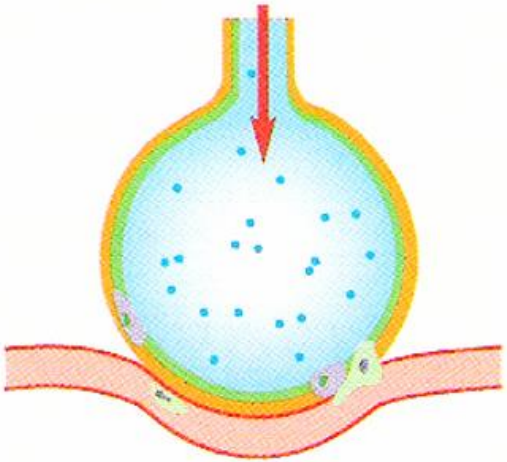
- **Iloprost (Ventabis®)**

- Prostacyclin analogue (IV, oral, **inhaled**)
- Well tolerated
- Inhalation frequency: **6** times a day
- Useful in hypoxemic patients
- Rapid action
- ICU situation ?

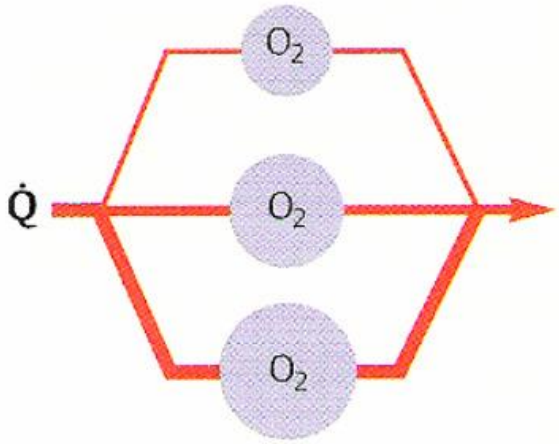
Iloprost

Ventilation/perfusion ratio

Pulmonary selectivity



Intrapulmonary selectivity



Anti-remodelling

Treatment with Inhaled Iloprost,

- **Usage & Dosage**
  - Fill a nebulizer with 1 ampoule (2ml)
  - Inhalation frequency: 6 times a day
  - Daily Dosage : 3 ampoules a day
  - Required time for one inhalation : 5~10 min.

Prostanoid

- **Treprostinil (Remodulin®)**

- a tricyclic benzidine analogue of epoprostenol
- IV, SQ
- Oral : recently approved by FDA
- IV site pain
- Functional class IV

→ Useful in ICU setting

Endothelin receptor antagonists (ERA)

- **Bosentan**

- dual endothelin A & B receptor antagonist
- abnormal LFT 10%
- dose-dependent and reversible after dose reduction or discontinuation

- **Ambrisentan**

- selective for the endothelin-A receptor
- The incidence of abnormal LFT range from 0.8% to 3%.
- monthly liver function assessment is not mandated in the United States

Endothelin receptor antagonists (ERA)

- **Macitentan**

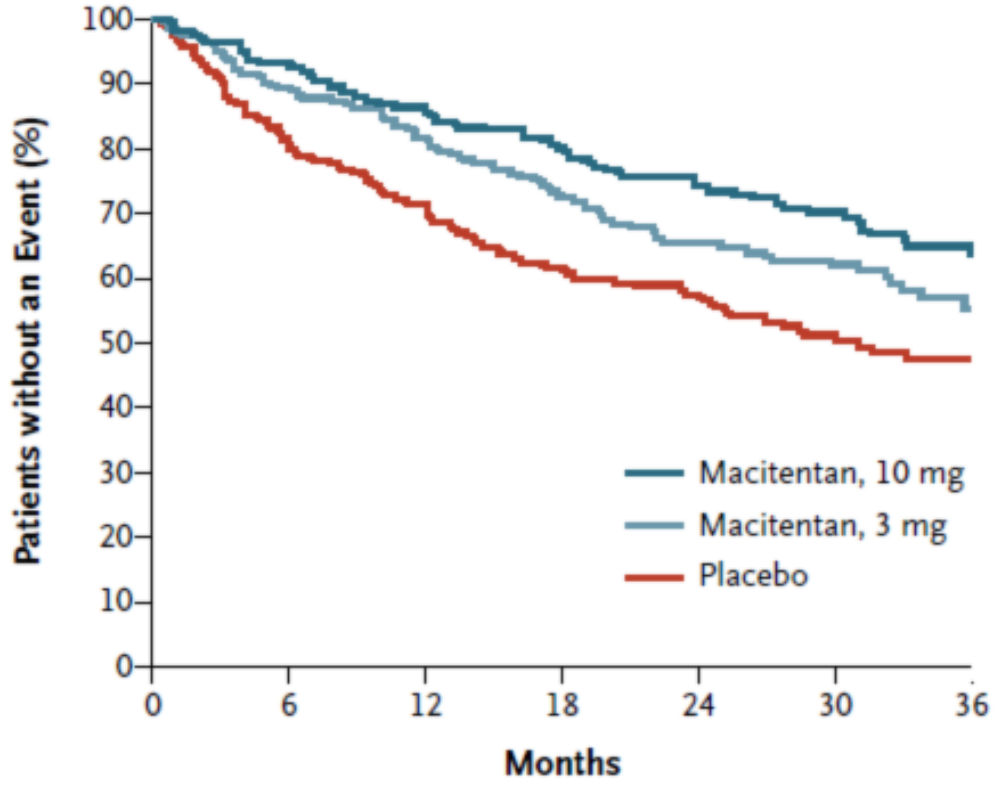
- dual ERA
- modifying the structure of bosentan to increase efficacy and safety
- sustained receptor binding and enhanced tissue penetration

Macitentan and Morbidity and Mortality in PAH

- Study with an Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve Clinical Outcome (**SERAPHIN**)
- Multicenter, double blind, randomized, placebo-controlled, event driven, **phase 3 trial**
- **The composite primary end point**

  : the time from the initiation of treatment to the first event related to PAH (worsening of PAH, initiation of treatment with intravenous or subcutaneous prostanoids, lung transplantation, or atrial septostomy) or death from any cause up to the end of treatment
- Median follow-up, **129 weeks**

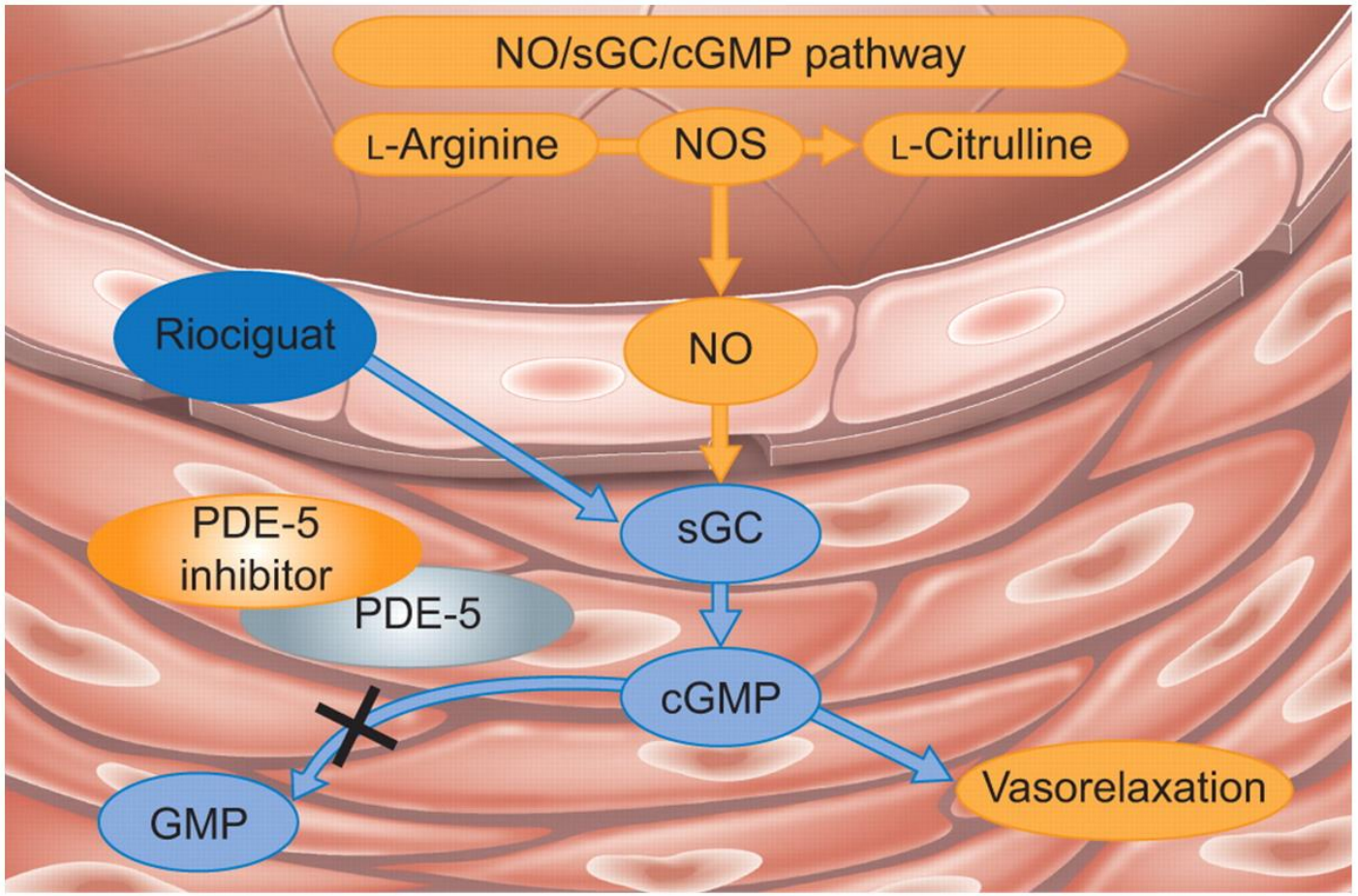
Macitentan and Morbidity and Mortality in PAH



Most Frequent Adverse Events and Laboratory Abnormalities

Adverse event — no. of patients (%)†			
Worsening of pulmonary arterial hypertension‡	87 (34.9)	75 (30.0)	53 (21.9)
Upper respiratory tract infection	33 (13.3)	50 (20.0)	37 (15.3)
Peripheral edema	45 (18.1)	40 (16.0)	44 (18.2)
Nasopharyngitis	26 (10.4)	37 (14.8)	34 (14.0)
Right ventricular failure‡	56 (22.5)	37 (14.8)	32 (13.2)
Headache	22 (8.8)	33 (13.2)	33 (13.6)
Anemia	8 (3.2)	22 (8.8)	32 (13.2)
Dizziness	27 (10.8)	24 (9.6)	26 (10.7)
Bronchitis	14 (5.6)	20 (8.0)	28 (11.6)
Dyspnea	22 (8.8)	26 (10.4)	18 (7.4)
Cough	30 (12.0)	20 (8.0)	21 (8.7)
Laboratory abnormality — no. of patients/total no. (%)			
Alanine aminotransferase or aspartate amino-transferase >3× ULN	11/244 (4.5)	9/247 (3.6)	8/236 (3.4)
Alanine aminotransferase or aspartate amino-transferase >3× ULN and bilirubin >2× ULN	4/237 (1.7)	5/241 (2.1)	4/230 (1.7)
Hemoglobin ≤8 g/dl	1/237 (0.4)	4/241 (1.7)	10/230 (4.3)

Nitric oxide pathway



Nitric oxide pathway

- **PDE-5 inhibitor**

Sildenafil

Tadalafil

Vardenafil

- **Soluble guanylate cyclase stimulator**

Riociguat

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Riociguat for the Treatment of Pulmonary Arterial Hypertension

Hossein-Ardeschir Ghofrani, M.D., Nazzareno Galiè, M.D., Friedrich Grimminger, M.D., Ekkehard Grünig, M.D., Marc Humbert, M.D., Zhi-Cheng Jing, M.D., Anne M. Keogh, M.D., David Langleben, M.D., Michael Ochan Kilama, M.D., Arno Fritsch, Ph.D., Dieter Neuser, M.D., and Lewis J. Rubin, M.D., for the PATENT-1 Study Group*

- a soluble guanylate cyclase stimulator
- Dual mode of action:
  - Synergy with endogenous NO
  - Directly stimulating soluble-GC

Riociguat

- Phase 3, double-blind study
- Randomly assigned 443 patients

No other treatment

receiving ERA or non-IV prostanoid

- 12 weeks
- **Primary end point**

Change of 6MWT

- **Secondary end point**

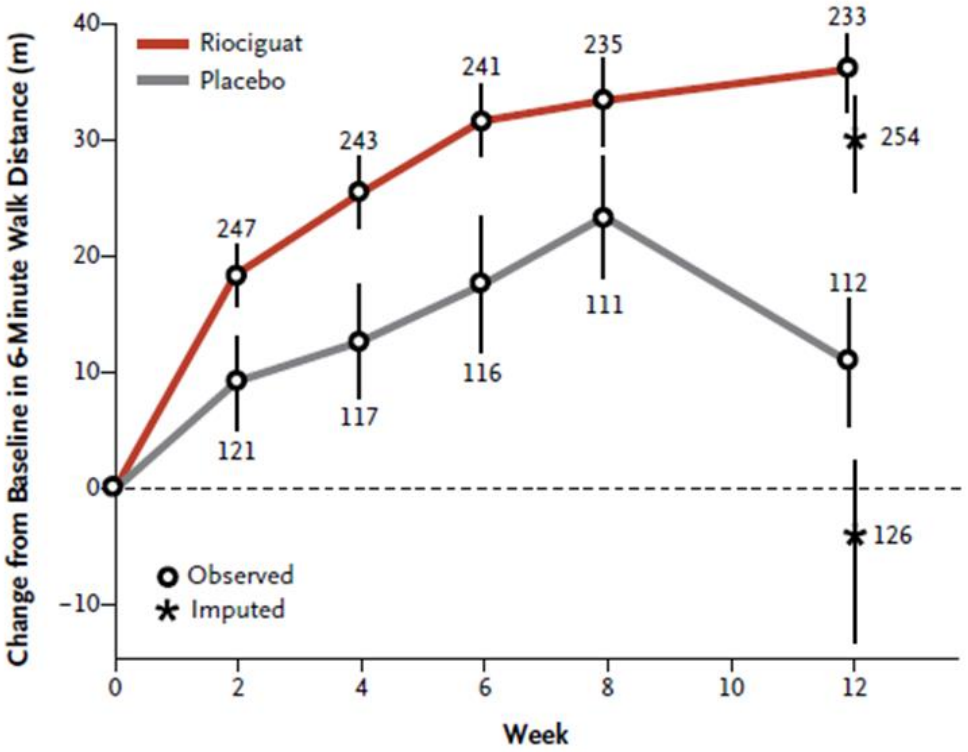
PVR, NT-proBNP, WHO Fc

Time to clinical worsening

6MWT

Mean **30 m** ↑ in 2.5 mg maximum group
6 m ↓ in placebo group

(least-squares mean difference, 36 m; 95% confidence interval, 20 to 52; P<0.001)



Riociguat

- Secondary end point

significant improvements
pulmonary vascular resistance (P<0.001),
NT-proBNP levels (P<0.001),
WHO functional class (P = 0.003),
time to clinical worsening(P = 0.005)
Borg dyspnea score (P = 0.002)

- Most common serious adverse event

  syncope (4% and 1%, respectively).

Treatment of CTEPH

ORIGINAL ARTICLE

Riociguat for the Treatment of Chronic Thromboembolic Pulmonary Hypertension

Hossein-Ardeschir Ghofrani, M.D., Andrea M. D'Armini, M.D., Friedrich Grimminger, M.D., Marius M. Hoeper, M.D., Pavel Jansa, M.D., Nick H. Kim, M.D., Eckhard Mayer, M.D., Gerald Simonneau, M.D., Martin R. Wilkins, M.D., Arno Fritsch, Ph.D., Dieter Neuser, M.D., Gerrit Weimann, M.D., and Chen Wang, M.D., for the CHEST-1 Study Group*

N Engl J Med 2013;369:319-29.
DOI: 10.1056/NEJMoa1209657

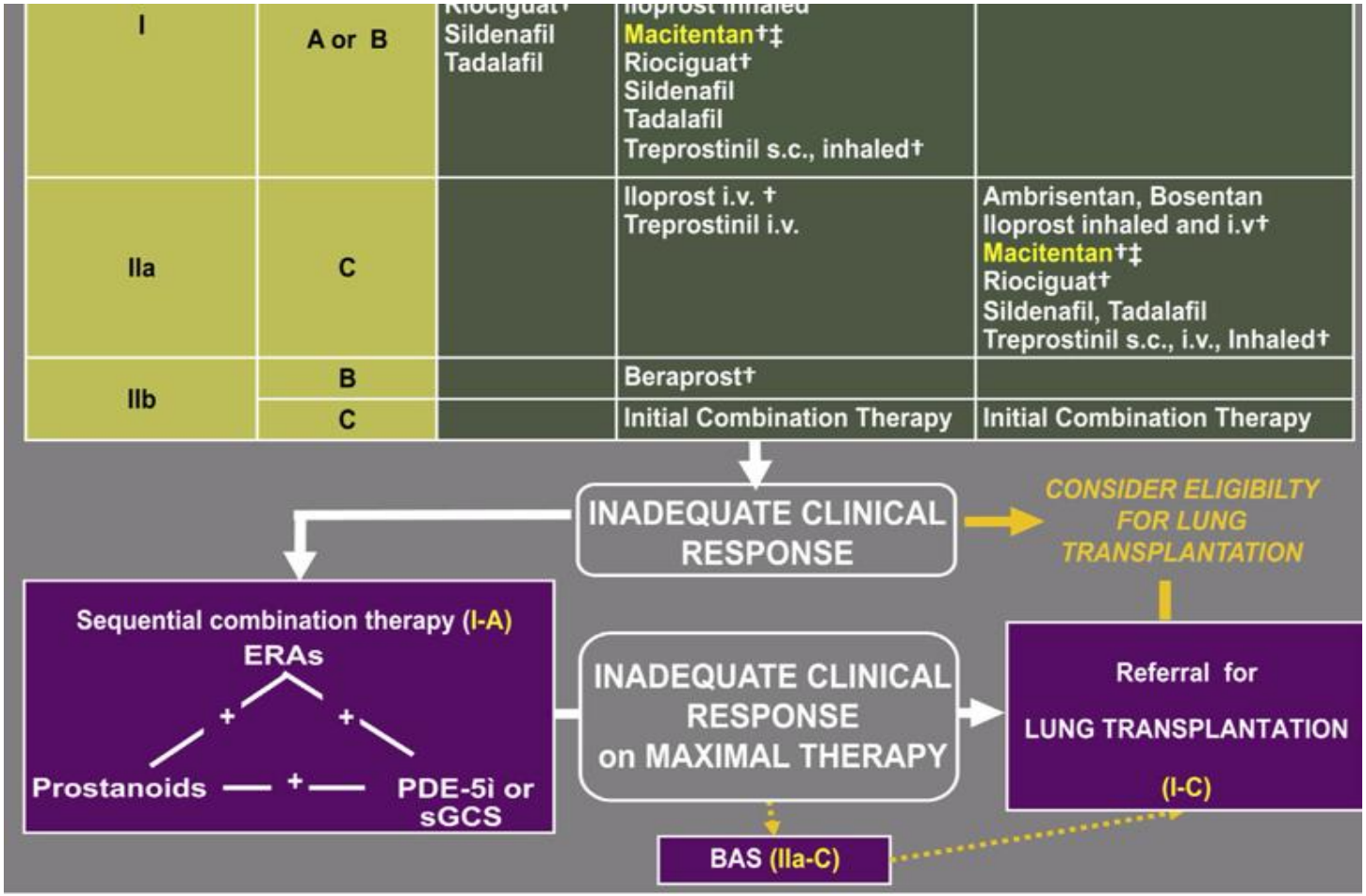
Rationale – Combination Tx

- Sequential combination
- Initial combination

"Add on" treatment protocol in many studies

Progressive fatal disease

Combination Chemotherapy in cancer


I
A or B
Riociguat†
Sildenafil
Tadalafil
Macitentan†‡
Riociguat†
Sildenafil
Tadalafil
Treprostinil s.c., inhaled†
IIa
C
Iloprost i.v. †
Treprostinil i.v.
Ambrisentan, Bosentan
Iloprost inhaled and i.v†
Macitentan†‡
Riociguat†
Sildenafil, Tadalafil
Treprostinil s.c., i.v., Inhaled†
IIb
B
Beraprost†
C
Initial Combination Therapy
Initial Combination Therapy
INADEQUATE CLINICAL RESPONSE
CONSIDER ELIGIBILTY FOR LUNG TRANSPLANTATION
Sequential combination therapy (I-A)
ERAs
+
+
Prostanoids
+
PDE-5i or sGCS
INADEQUATE CLINICAL RESPONSE on MAXIMAL THERAPY
Referral for LUNG TRANSPLANTATION (I-C)
BAS (IIa-C)

In Meta-analysis

TABLE 1. Main Features of Included Studies

Studies	Publication Year	Patients Included	Mean Age, Mean (SD)		Baseline Therapy	Add-on Drugs	Follow-up (wks)
			MT	CT			
Humbert et al[10] (BREATHE-2)	2004	33	47 (19)	45 (17)	Epoprostenol IV	Bosentan 125 mg, 2/day	16
McLaughlin et al[11] (STEP)	2006	67	49 (15)	51 (14)	Bosentan PO	Inhaled iloprost 5 μg, 6–9/day	12
Hoeper et al[12] (COMBI)	2006	40	56 (13)	48 (14)	Bosentan PO	Inhaled iloprost 5 μg, 6/day	12
Simonneau et al[13] (PACES)	2008	267	48 (13)	48 (13)	Epoprostenol IV	Sildenafil 20–80 mg, 3/day	16
Galie et al[14] (PHIRST-1)	2011	87	52 (16)	50 (13)	Bosentan PO	Tadalafil 40 mg/day	16
McLaughlin et al[16] (TRIUMPH I)	2010	235	52 (18–75)*	55 (20–75)	Bosentan (70%) or sidenafil (30%) PO	Inhaled treprostinil 18–54 μg, 4/day	12
Iversen et al[15]	2010	39	42 (22–68)*	42 (22–68)	Bosentan PO	Sildenafil 50 mg, 3/day	12

*Data is reported as median (range).
CT, combination therapy; MT, monotherapy; IV, intravenously; PO, orally; SD, standard difference.

J Cardiovasc Pharmacol Volume 60, Number 4, October 2012

In Meta-analysis

- Increased 6MWD by **21.59 meters**
  (weighted mean difference 21.59 m, 95% CI of 13.25–29.93; P , 0.001)
- Reduced the risk of clinical worsening
  (risk ratio: 0.43, 95% CI: 0.26–0.72, P = 0.001)

J Cardiovasc Pharmacol Volume 60, Number 4, October 2012

Case 처방실례

- 40/F
- Idiopathic PH
- WHO functional class II

Case

Cardiac Catheterization & acute vasodilator test

	Base-Line	NO 10ppm	NO 20ppm	NO 40ppm		Nif10	Nif20	Nif30	Nif40
BP	101/61	100/57	114/67	114/68		111/67	109/65	108/65	107/64
mean PAP	65	41	39	42		59	55	54	52
PCWP	14	14	13	13					
C.I	3.0	2.9	2.84	2.83					
HR	84	77	67	65					
PVRI	1358.3	743.9	731.5	818.8					

*No evidence of intra-cardiac shunt

Drop in mPAP
=26 mmHg(40%)

Responder Criteria
Reduction of mPAP >10 mmHg
Absolute mPAP < 40 mmHg

CCBs OK?

- WHO Fc II
- Slowly progression

Medication>>

Nifedipine 10mg tid → 20mg tid → 60mg SR
Beraprost 0.02mg tid → 0.04mg tid

→ "Tolerable"

Discharged and OPD follow-up

Case

- If WHO Fc III ?
  or recent worsening ?

→ Choice of other oral agent

Bosentan

Ambrisentan

Sildenafil

처방실례: WHO functional class III-IV

- 48/M
- Idiopathic PAH on beraprost
- Admitted for clinical worsening

- Abdominal distention, edema
  hypotension, dyspnea

처방실례: WHO functional class III-IV

- Dopamine infusion
- IV lasix
- Add sildenafil 25 mg tid 4 days

→Consultation for persistent hypotension and hypoxemia need dopamine and O2

처방실례: WHO functional class III-IV

- Add iloprost inhalation

10 mcg q 4hr

- Tapering dopamine and oxygen

→ WHO Fc II

- Discharge with Iloprost & sildenafil

처방실례: WHO functional class III-IV

- OPD follow-up

WHO Fc I, climbing mountain

Patient complaining of Iloprost inhalation q 4hr

→Order 20 mcg t i d inhalation

→ Still complaining~

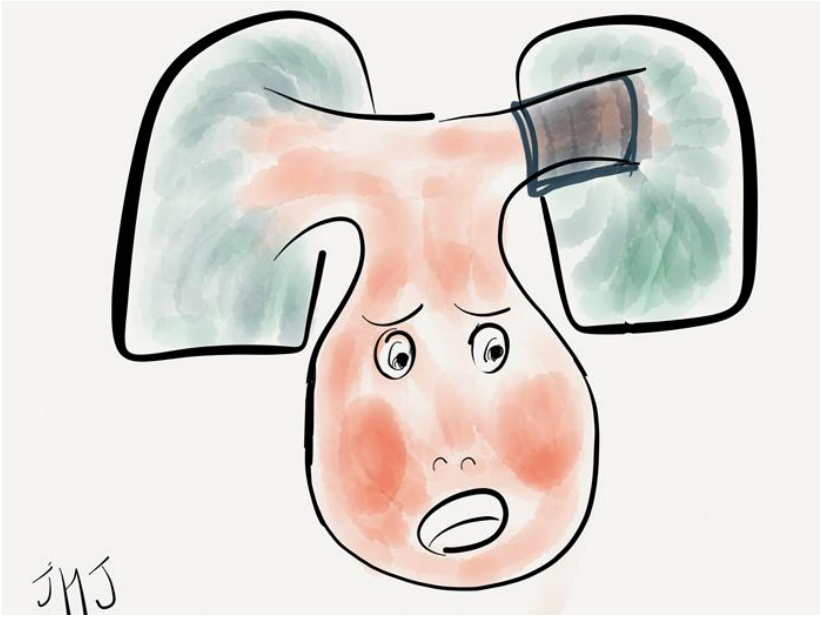
처방실례: WHO functional class III-IV

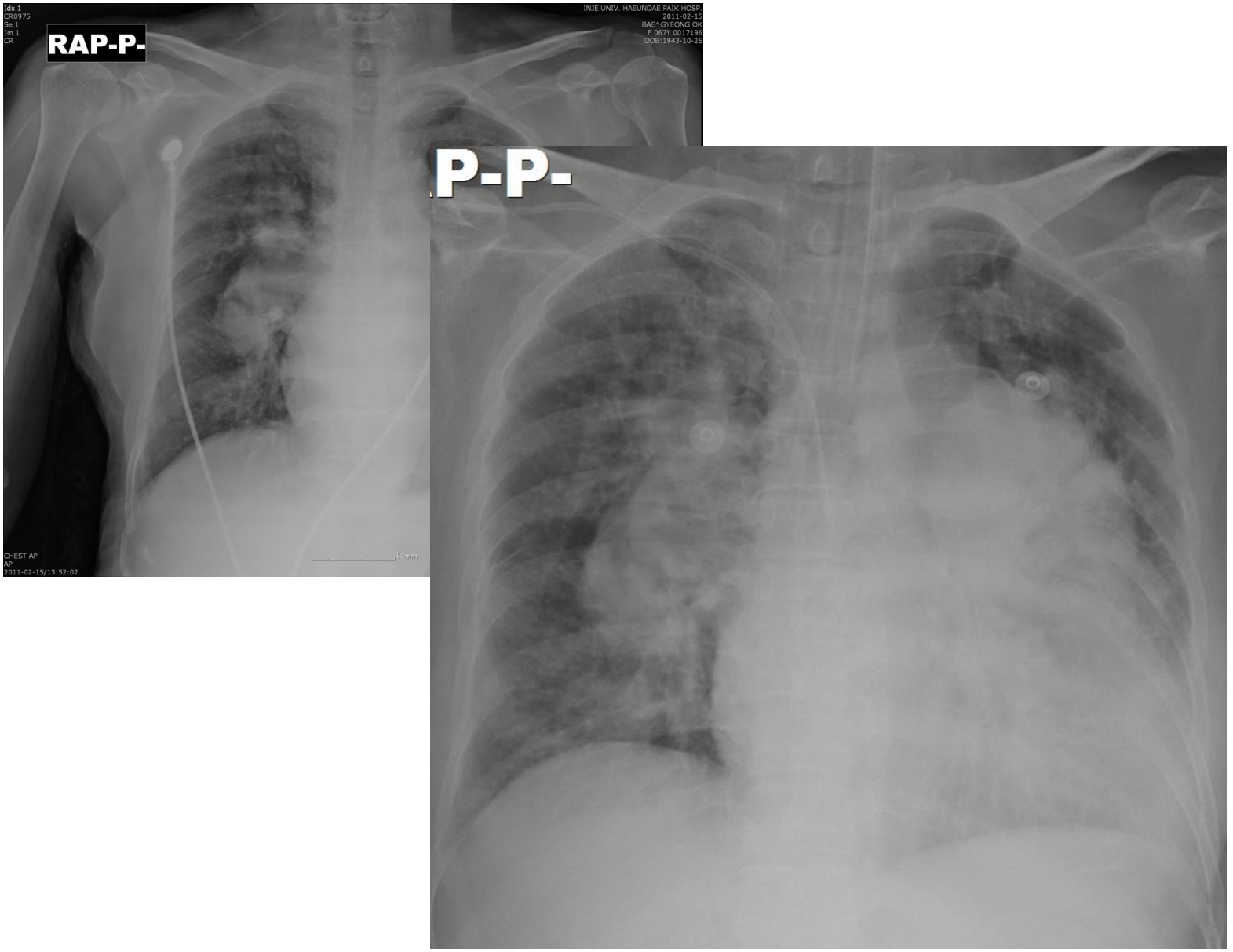
- Add **Ambrisentan**
- Overlap with Iloprost & Sildenafil
- Stop Iloprost after 2 weeks
- WHO Fc I
- Maintaining **Ambrisentan & Sildenafil**

"Patient say Thanks!"

WHO Fc IV

Pulmonary Hypertension Crisis - *Eisenmenger syndrome*




Idx 1
CR0975
Se 1
Im 1
CR
RAP-P-
INJE UNIV. HAEUNDAE PAIK HOSP.
2011-02-15
BAE^GYEONG OK
F 067Y 0017196
DOB:1943-10-25
CHEST AP
AP
2011-02-15/13:52:02
P-P-

Management in ICU

- Intubation and ventilator apply
  : Refractory hypoxemia
    Hemodynamic deterioration
- **Nitric oxide** inhalation
  10 -> 20 -> 40 ppm
- **Iloprost** inhalation via ventilator
- **Treprostinil** continuous IV infusion
- Stand-by **veno-arterial ECMO**

Management in ICU

- Stop **Treprostinil** d/t adverse effect

(chest discomfort, hypotension)

- Continue **Iloprost** inhalation
- Add **Sildenafil** 12.5 mg →25 mg tid
- Tapering and stop **NO gas**
- Ventilator weaning

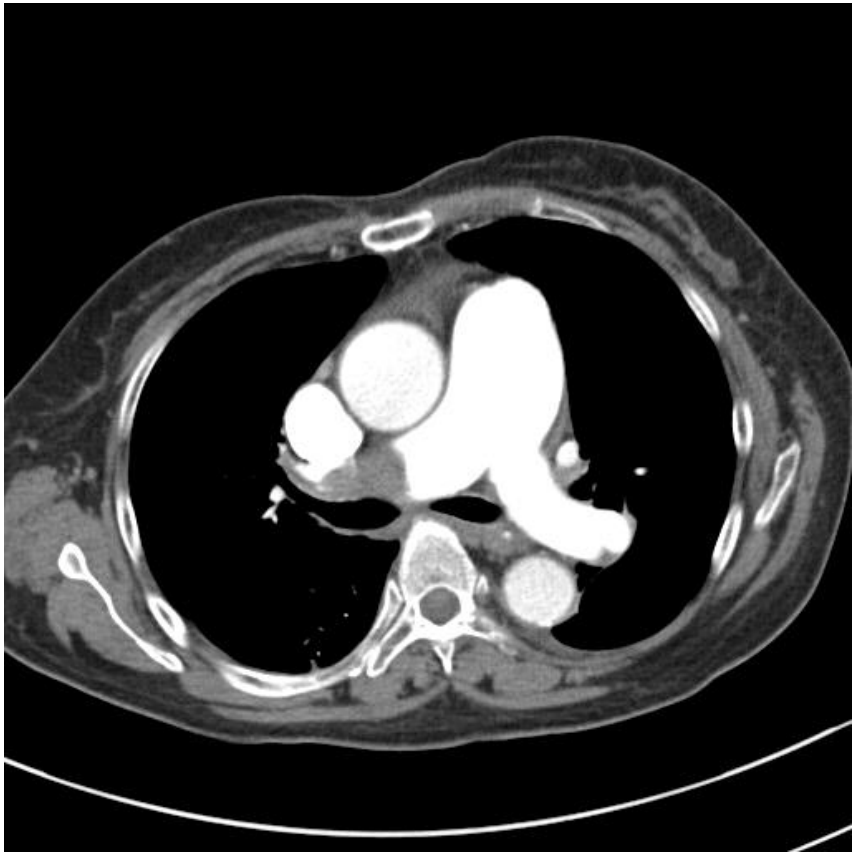
Medical Treatment of CTEPH

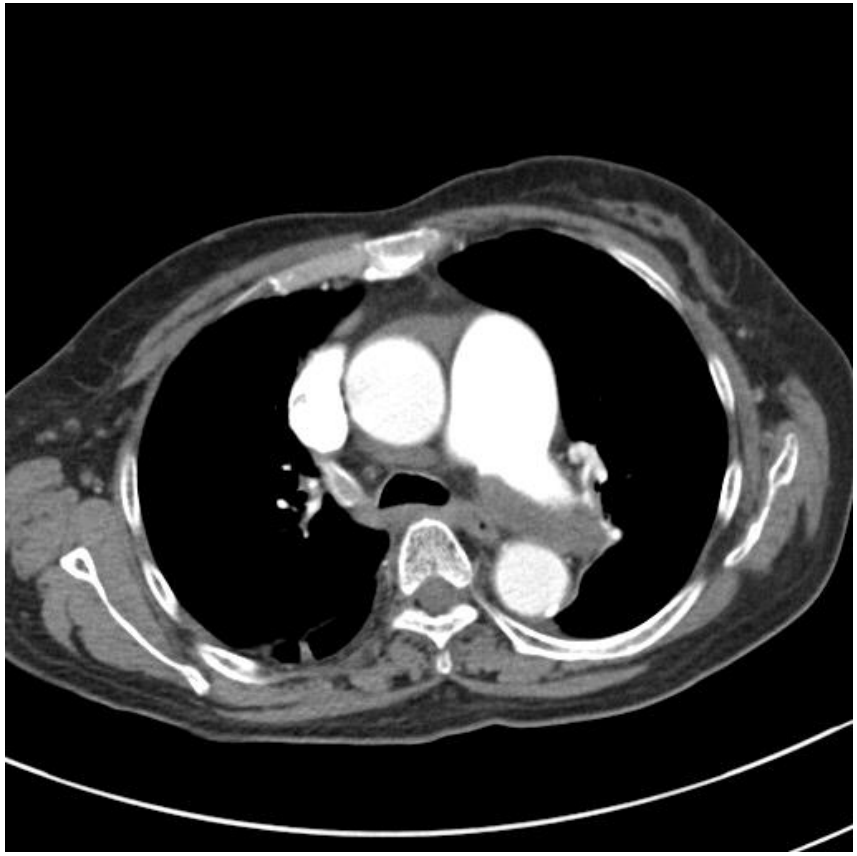
- Rationale

Pathogenesis of Advanced CTEPH is similar to Idiopathic PH

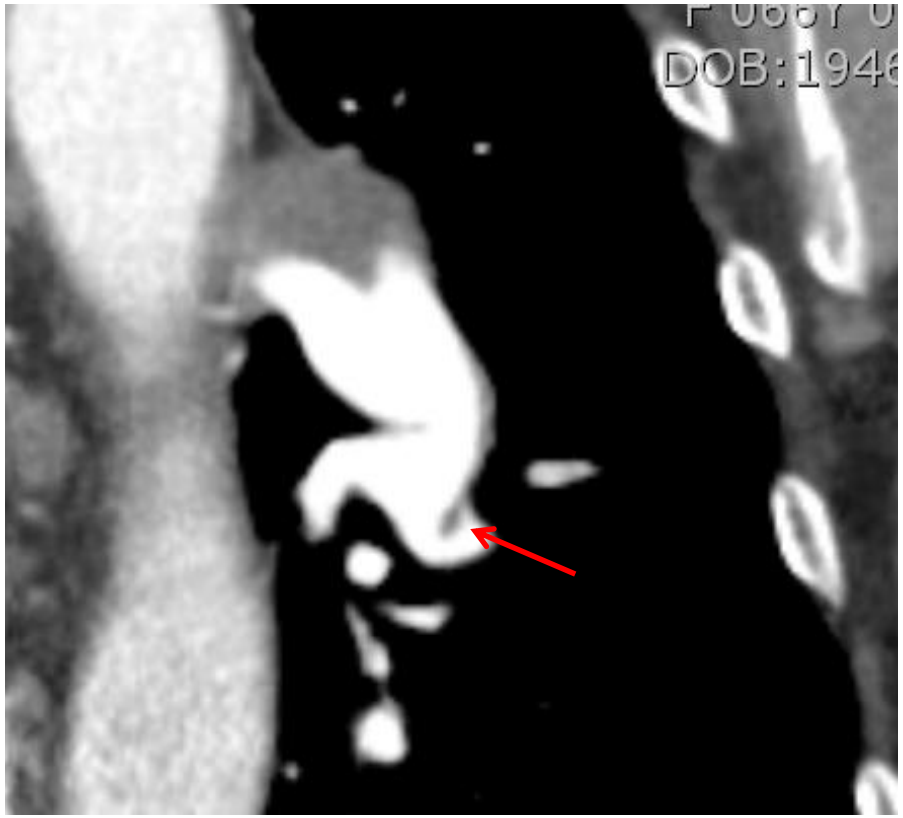
Vascular remodeling

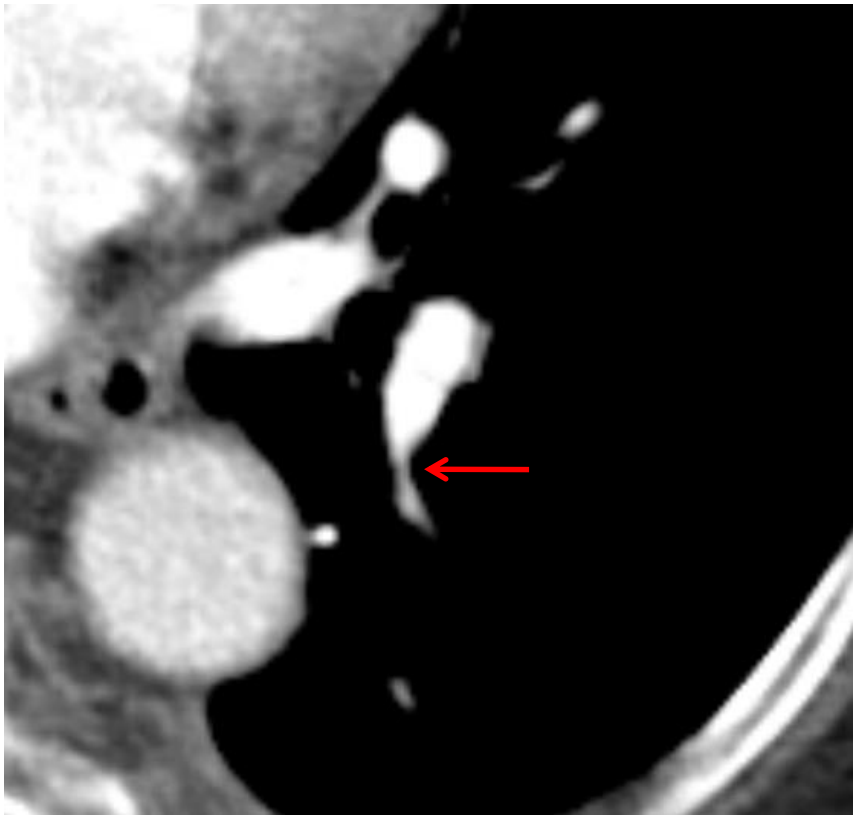
CT - proximal



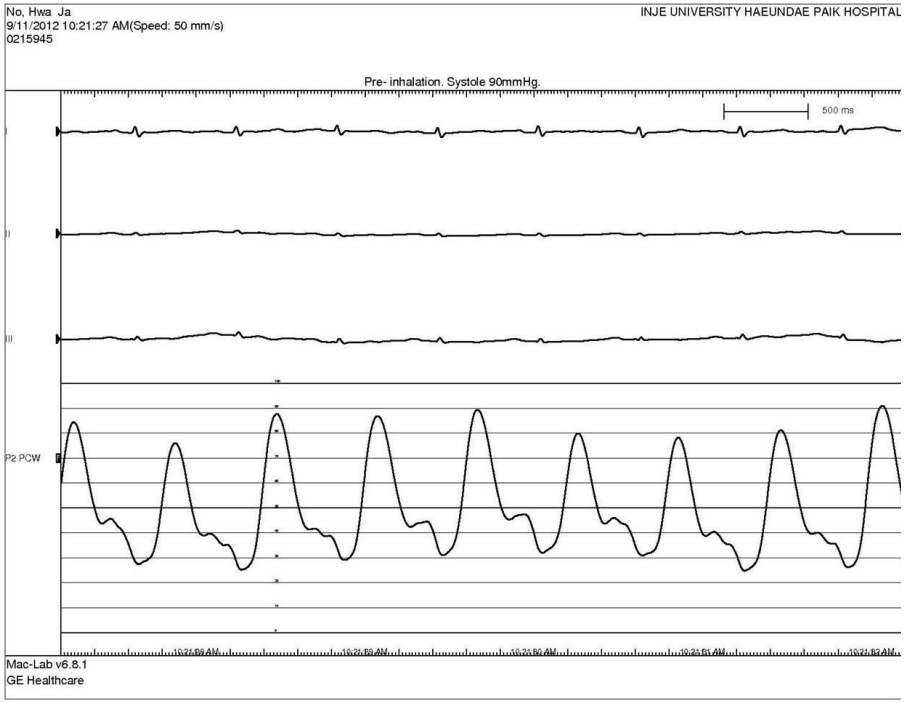


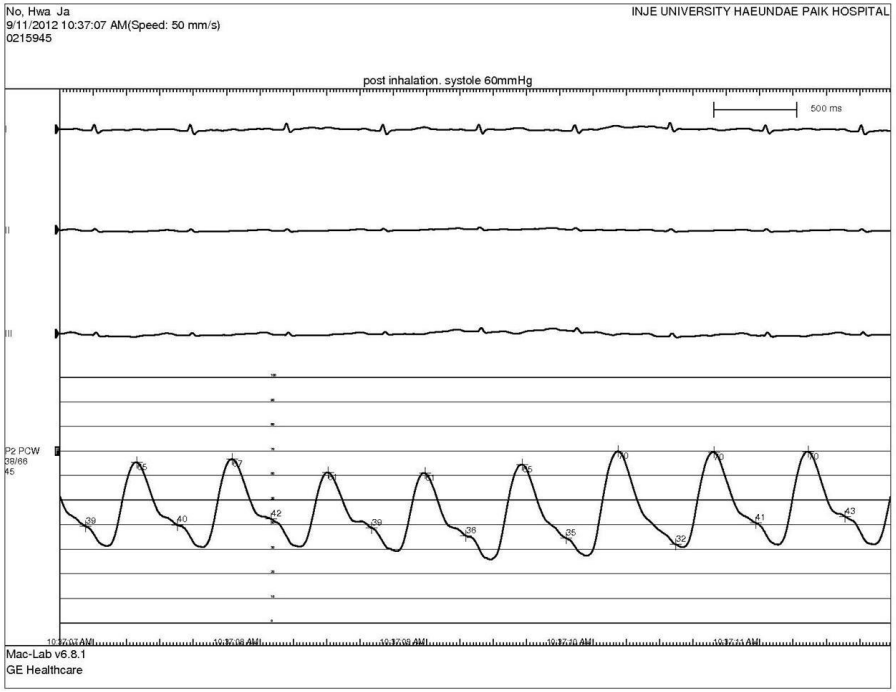
CT - Distal





Rt heart catheterization





Baseline

PAP(mean) **92/28(50)** mmHg

CO 4.4 L/min

PCWP 15 mmHg

PVR **650** dyn*sec/cm5

After Iloprost inhalation

PAP **66/32(43)**

Treatment Goals of Pulmonary Hypertension

- WHO Fc class
- 6MWT
- NT-proBNP
- Echocardiography