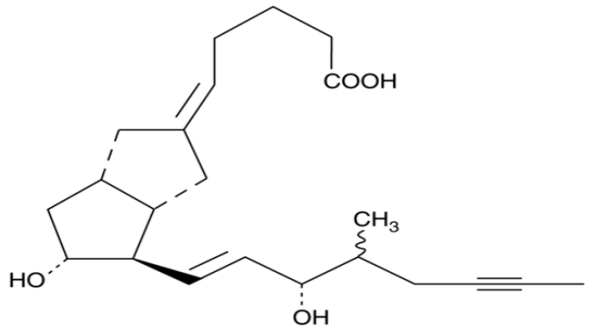
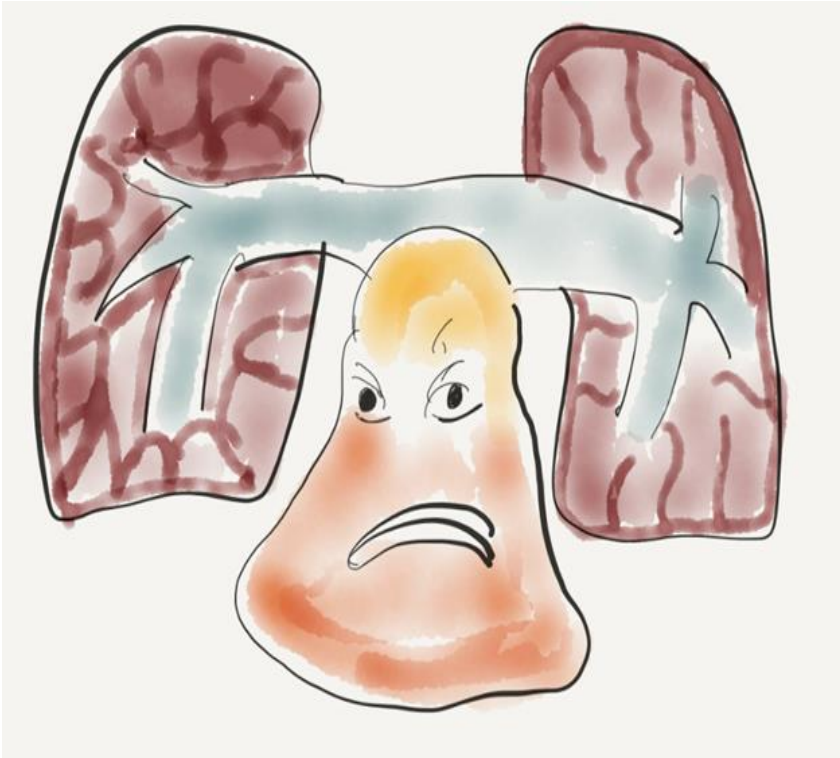
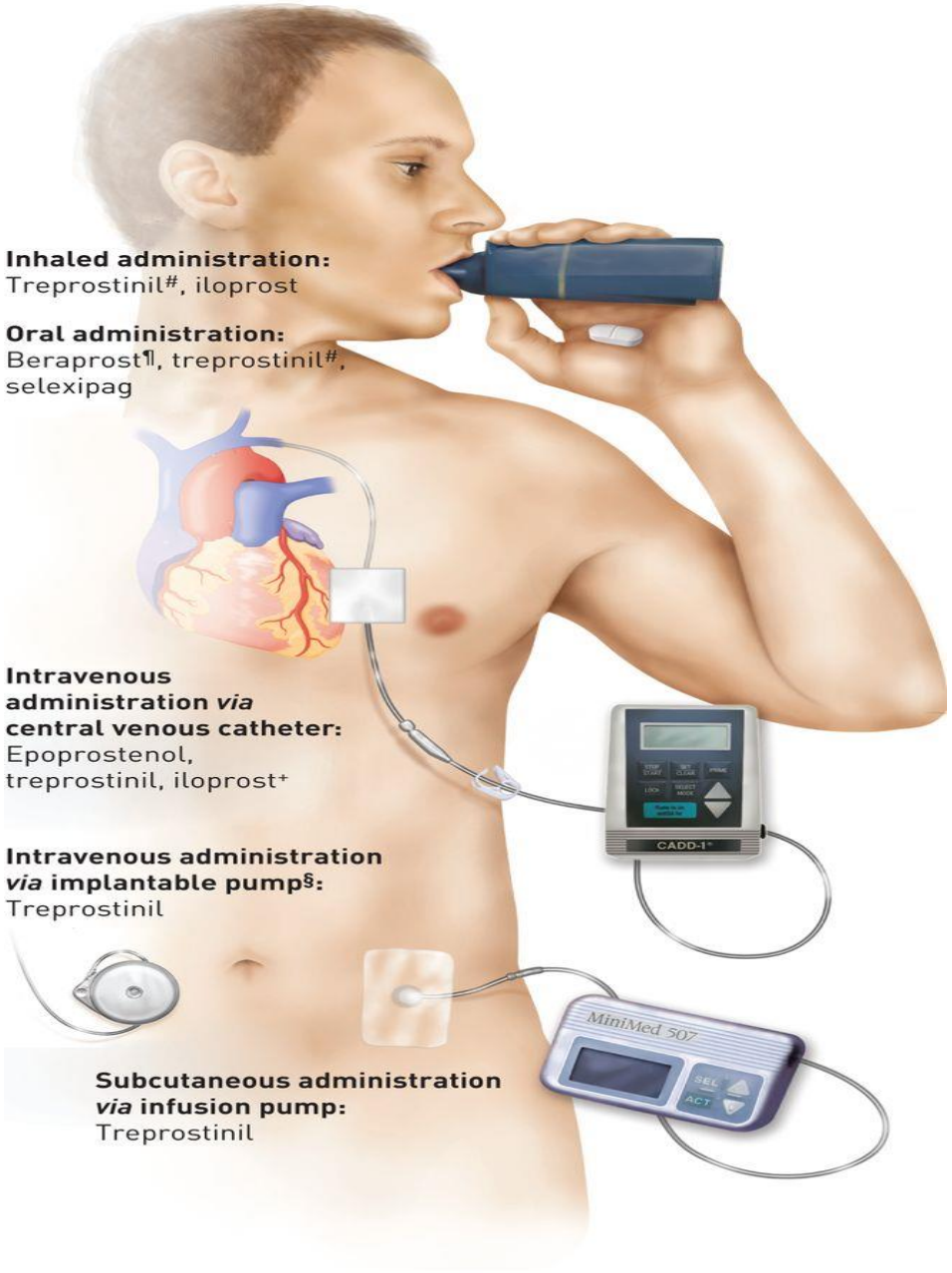


Prostanoid therapy for PAH and PH-ILD

인제의대 해운대백병원
장항제





Prostacycline 계열 약물 장점!

다양한 route 로 투여가 가능하다

Adverse effect - simple, predictable

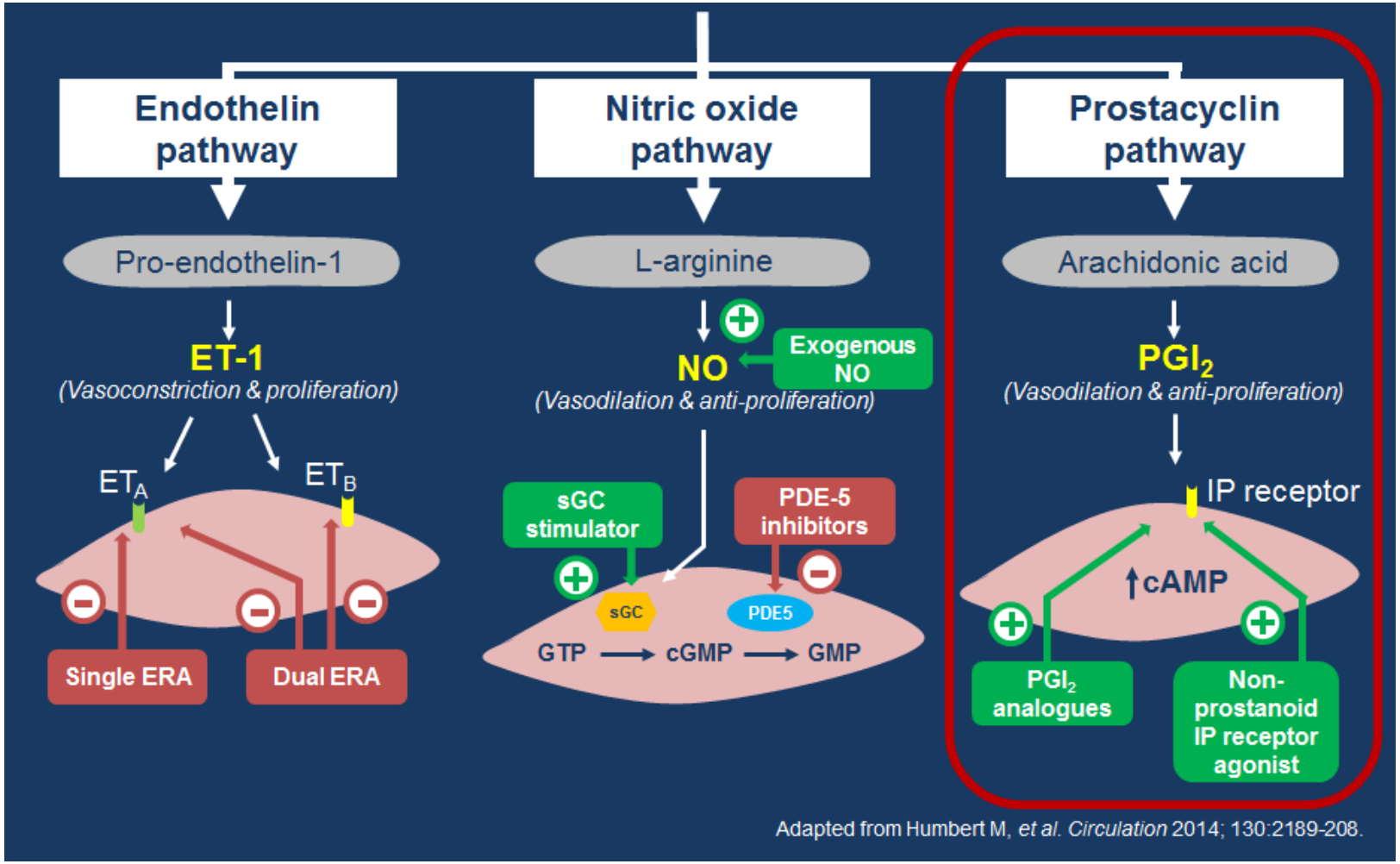
Harrison W. Farber, and Wendy Gin-Sing Eur Respir Rev 2016;25:418-430

Prostacycline pathway

- Prostanoid
- Prostacycline (PGI2)
- Prostacycline analogue

- Prostacycline receptor agonist
  = **IP** receptor agonist - Selexipag

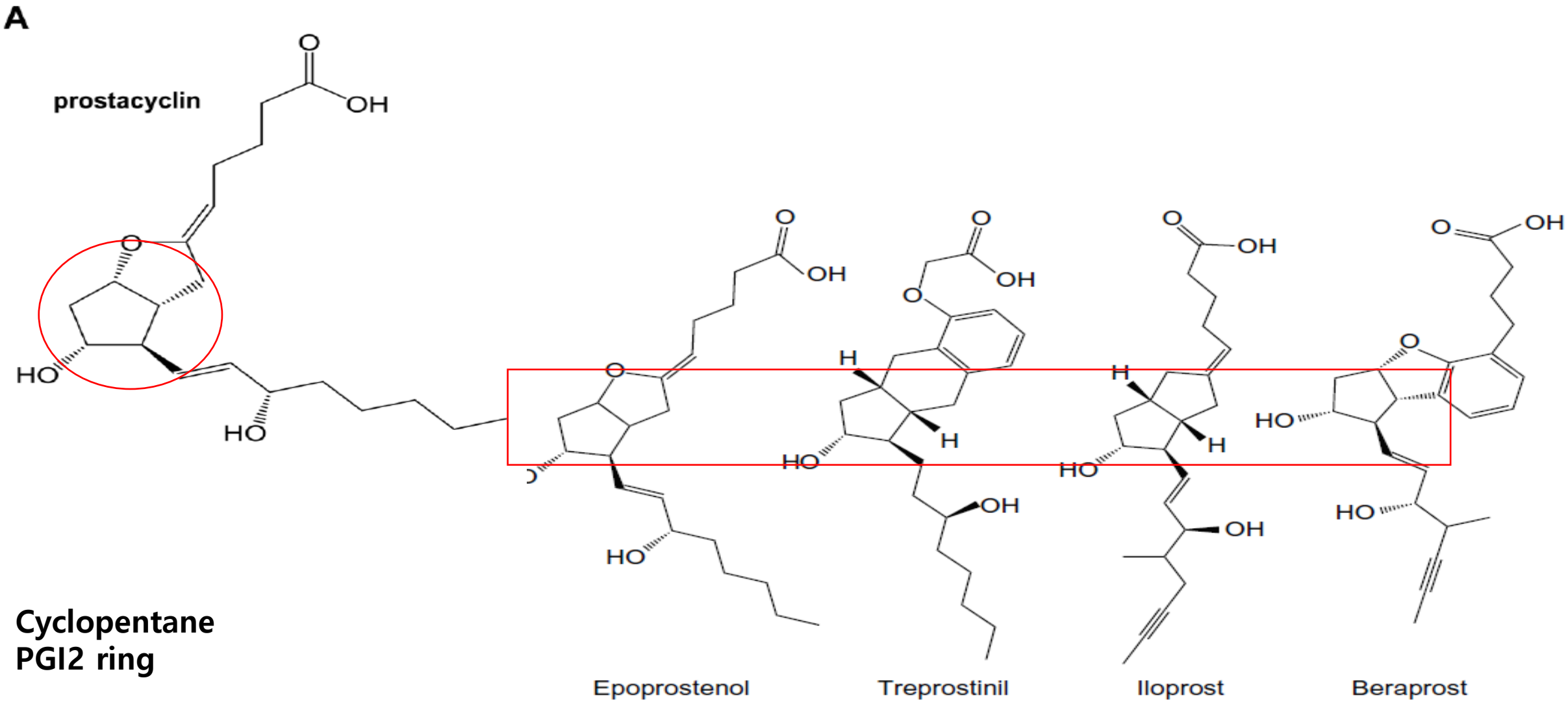
Prostacycline pathway



potent **vasodilation,**
inhibit platelet aggregation
cytoprotective
anti-proliferative activities

m/c adverse effect related to systemic vasodilation
headache, flushing, jaw pain, diarrhea

Prostacyclin analogues



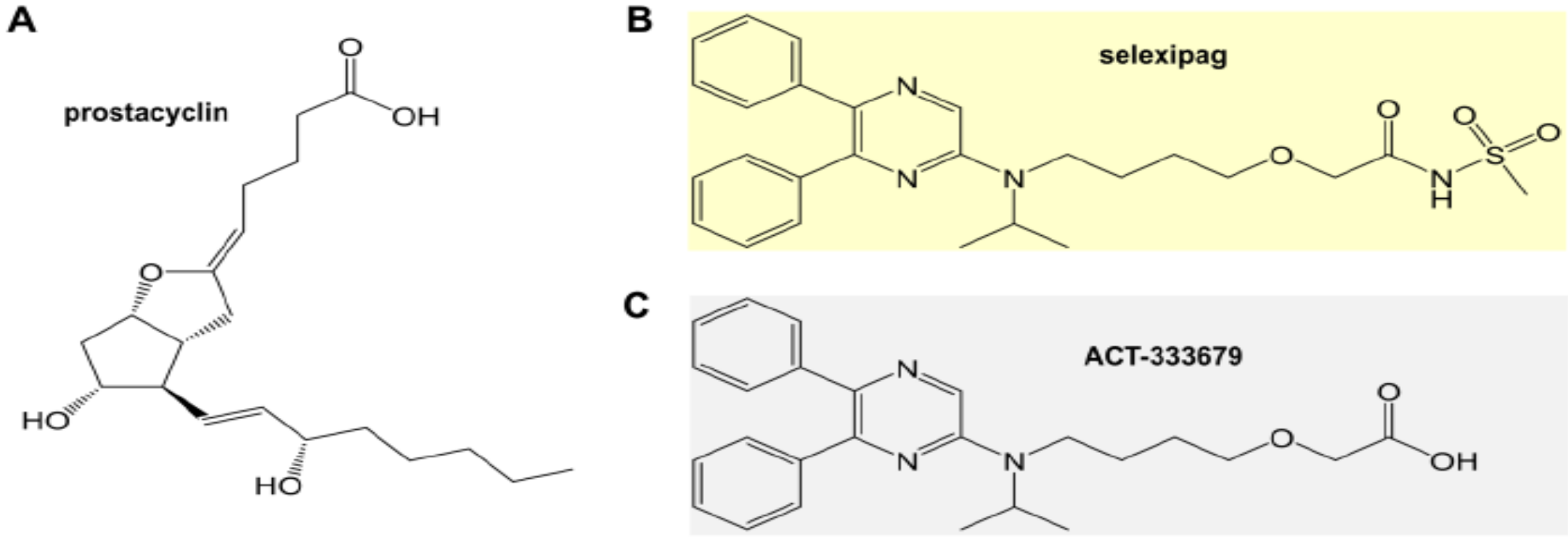
Cyclopentane
PGI2 ring

History of **Prostacyclin pathway**Agonists in Korea

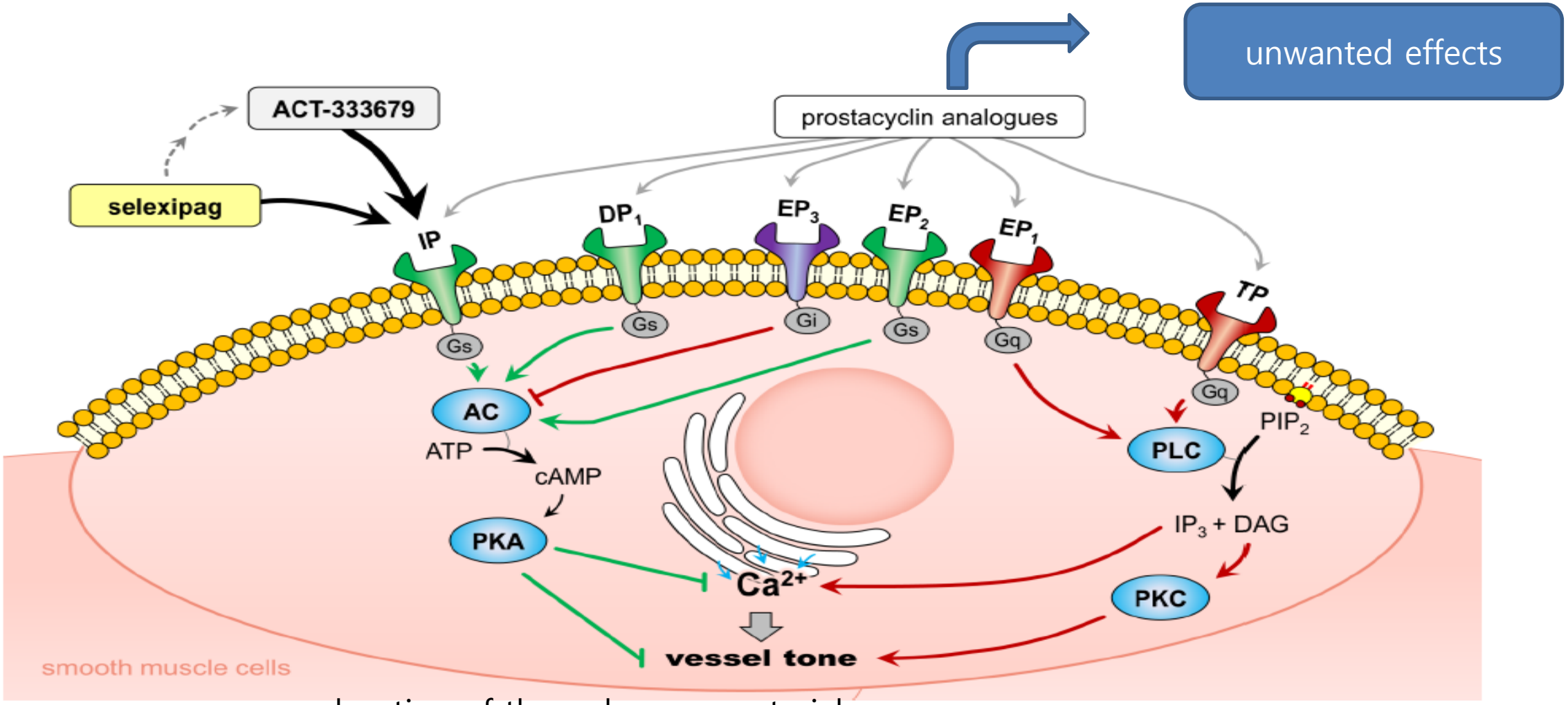
- **Beraprost (berasil) oral** **1997~**
- **Epoprostenol IV →** **아직 도입 안됨**
- **Inhaled Iloprost (Ventavis)** **2005~**
- **Treprostinil (Remodulin) IV,SC** **2010~**
- **Selexipag (Uptravi) oral** **2017~**

- **Inhaled Treprostinil (Tyvaso)** **2025 ?**

Selexipag is chemically distinct from PGI_2 and PGI_2 analogues



Adopted from
Louise Marqvard Sørensen et al, A Special Focus on Selexipag - Treatment of Pulmonary Arterial Hypertension *Current Pharmaceutical Design,* 2017, *23,* 1-9

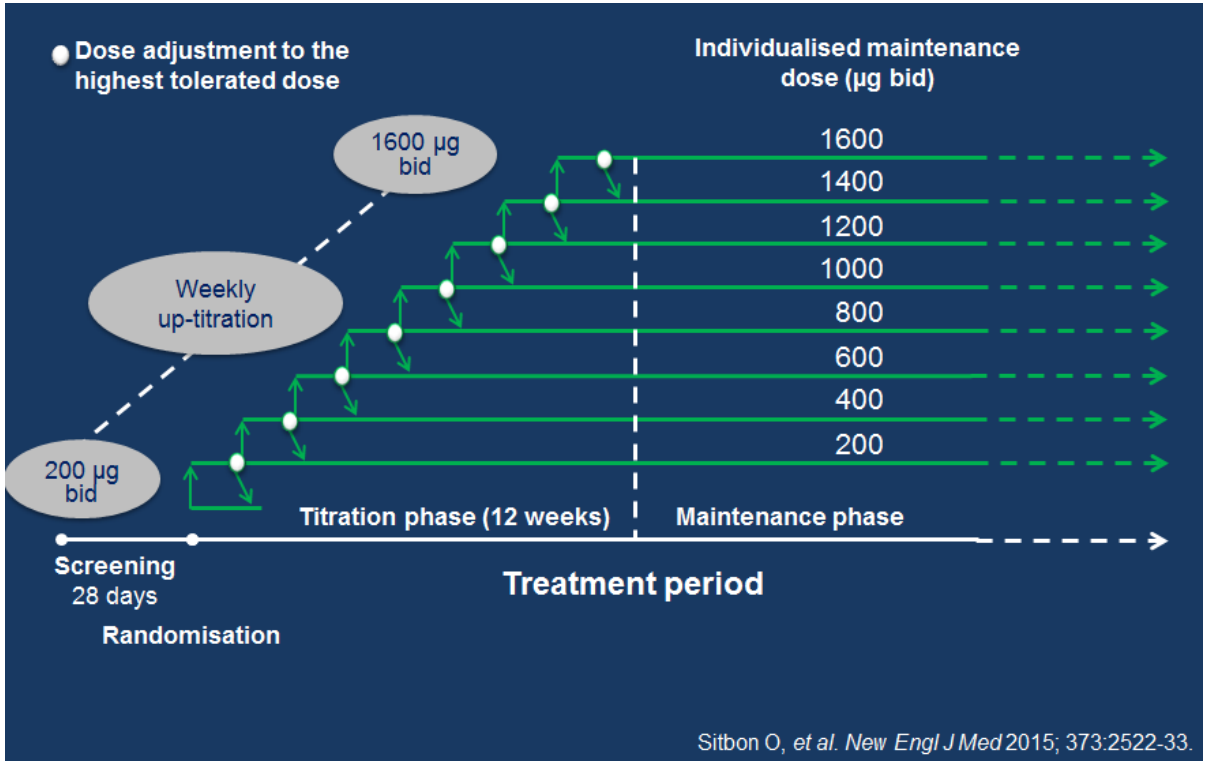


relaxation of the pulmonary arterial smooth muscle cells, vasodilation
reduced proliferative activity

Adopted from
Louise Marqvard Sørensen et al, A Special Focus on Selexipag - Treatment of Pulmonary Arterial Hypertension *Current Pharmaceutical Design,* 2017, *23,* 1-9

Selexipag(Uptravi®) : oral, selective IP prostacyclin receptor agonist

- **Highly selective IP receptor agonist**
- **Not a PGI_2 derivative**

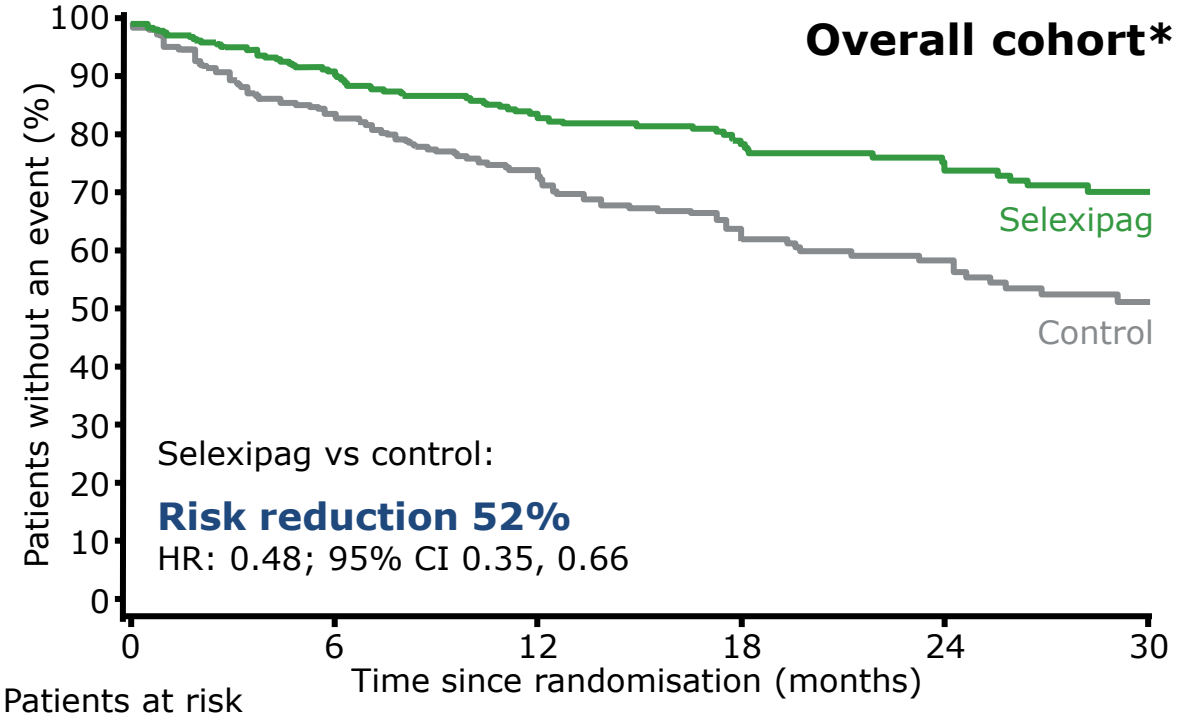


- **Phamacokinetic**

- After oral administration: Tmax 1 hour
- **Half life: 6.2 to 13.5 hours**
- Metabolism in the **liver**

Time to disease progression

Post-hoc analysis of pooled TRITON and GRIPHON data

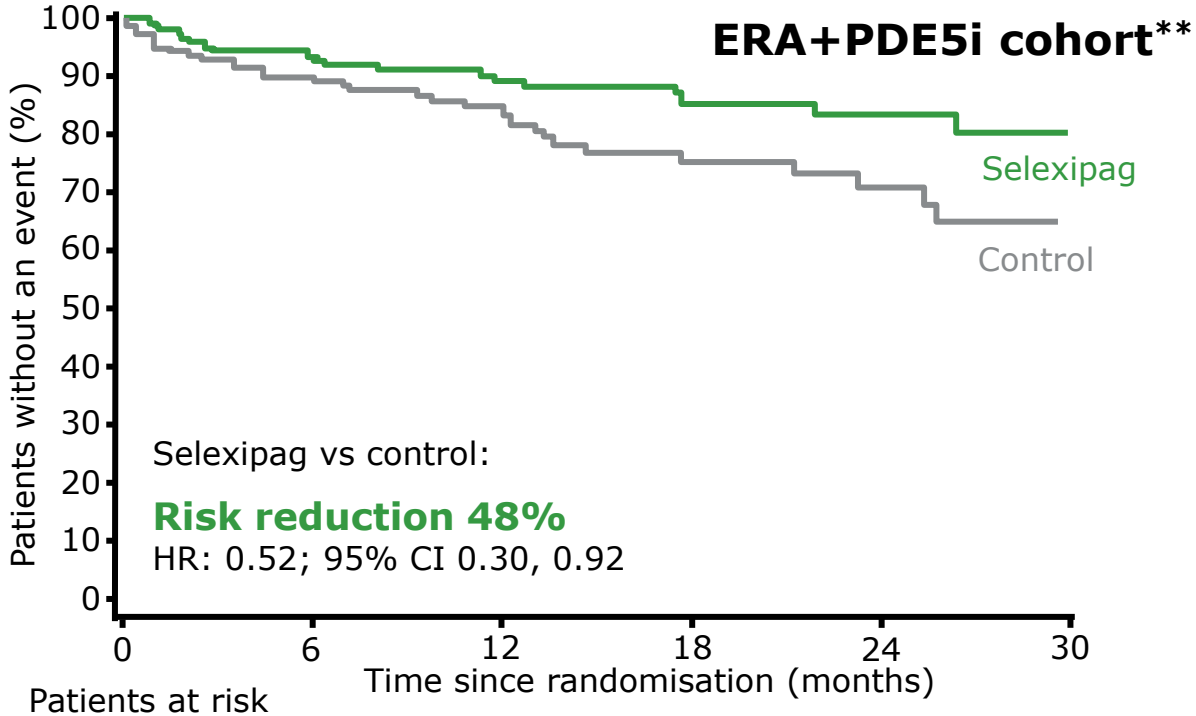


Patients at risk

329	264	205	144	95	43
320	245	177	104	61	34

Number of events

0	25	46	55	63	67
0	48	78	98	104	111



Patients at risk

145	120	87	60	35	16
140	120	81	46	25	13

Number of events

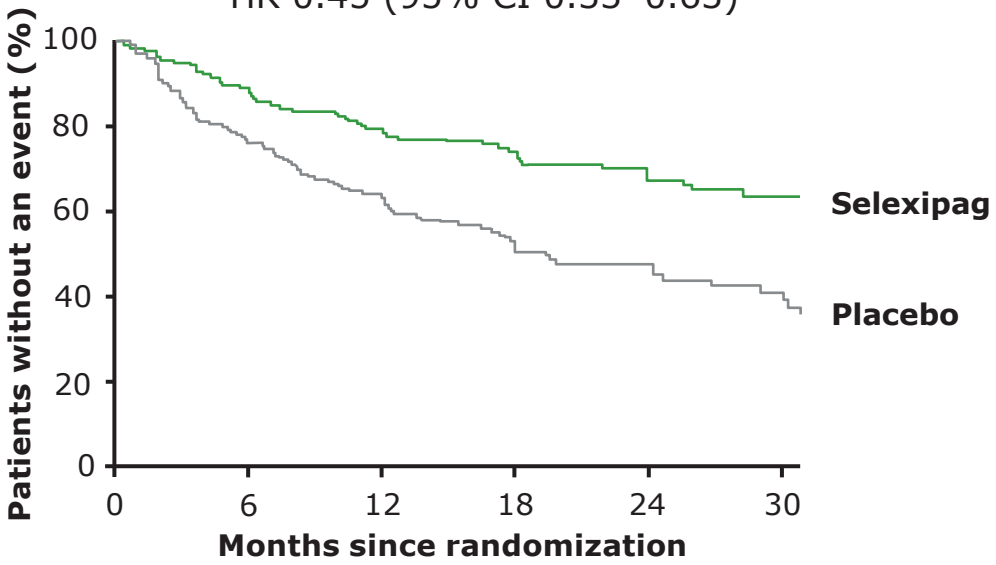
0	9	14	17	18	19
0	14	22	28	30	32

*Cox model included treatment, age, sex, race, aetiology, region, WHO FC, 6MWD, N-terminal pro-brain natriuretic peptide, and study as covariates. Median (range) exposure in days: selexipag: 510 (4-1280); control: 409 (3-1318) days. **Includes TRITON patients and GRIPHON patients receiving ERA + PDE5i background therapy. Cox model included treatment, region, WHO FC, and study as covariates.

Selexipag treatment effect on disease progression was more pronounced in newly diagnosed patients

Time from diagnosis ≤ 6 months

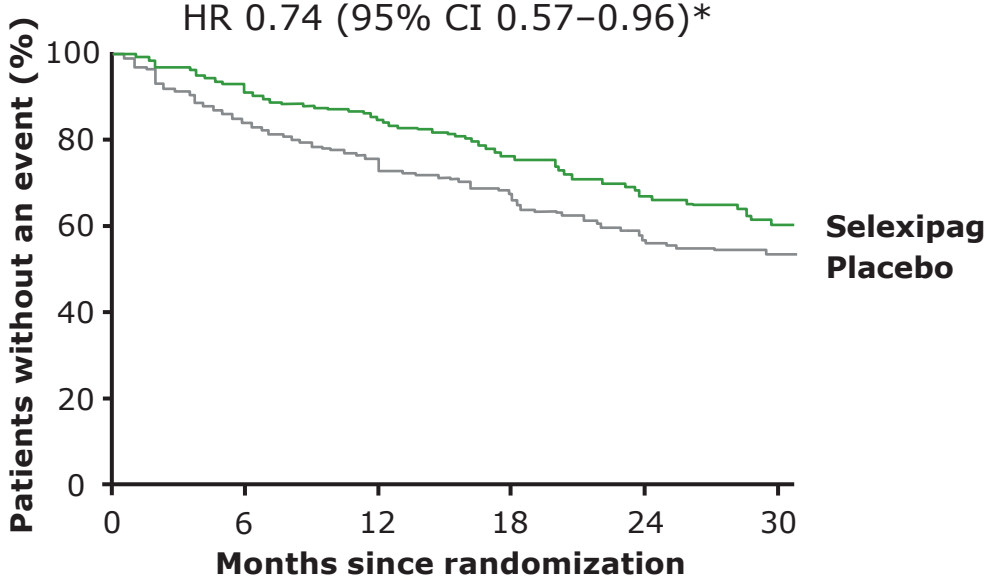
Selexipag vs placebo: Risk reduction 55%
HR 0.45 (95% CI 0.33–0.63)*



Number at risk						
Selexipag	207	161	133	95	68	32
Placebo	197	138	108	63	39	23

Time from diagnosis > 6 months

Selexipag vs placebo: Risk reduction 26%
HR 0.74 (95% CI 0.57–0.96)*



Selexipag	367	294	228	151	103	69
Placebo	385	295	239	157	110	65

*HRs determined by adjusted Cox models.

Gaine S. et al. Chest. 2021 Jul;160(1):277-286

2022 급여 인정 기준 변경

[일반원칙] 폐동맥고혈압 약제

구 분	세부인정기준 및 방법	
	현 행	개 정(안)
	1개와 ⑤~⑨항 중 최소 1개를 모두 만족), 기존 사용 약제에 Selexipag경구제의 순차적 병용투여(sequential combination)를 인정함 - 다 음 -	소 1개와 ⑤~⑨항 중 최소 1개를 모두 만족), 2제 요법에서 사용되지 않은 작용 기전이 다른 약제※ 1종을 추가한 순차적 병용투여(sequential combination)를 인정함. - 다 음 -

지표	기준	지표	기준
① 우심실부전의 임상적 증거(clinical evidence of RV failure)	있음	① 우심실부전의 임상적 증거(clinical evidence of RV failure)	있음
② 증상진행의 속도(Rate of progression of symptoms)	빠름	② 증상진행의 속도(Rate of progression of symptoms)	빠름
③ 실신(Syncope)	있음	③ 실신(Syncope)	있음
④ WHO 기능분류(WHO-FC)	**IV단계**	④ WHO 기능분류(WHO-FC)	**III단계 이상**
⑤ 6분 보행거리(6MWT)	**300m 미만**	⑤ 6분 보행거리(6MWT)	**440m 이하**
⑥ 운동부하심폐검사 (Cardio-pulmonary exercise testing)	**Peak O_2 consumption<12mL /min/kg**	⑥ 운동부하심폐검사 (Cardio-pulmonary exercise testing)	**Peak O_2 consumption≤15mL /min/kg**
⑦ BNP/NT-proBNP plasma levels	**300/1800 이상**	⑦ BNP/NT-proBNP plasma levels	**50/300 이상**
⑧ 심초음파검사소견 (Echocardiographic findings)	Pericardial effusion 또는 TAPSE<1.5cm	⑧ 심초음파검사소견 (Echocardiographic findings)	Pericardial effusion 또는 TAPSE<1.5cm
⑨ 혈류역학검사지표(Hemodynamics)	**RAP>15mmHg 또는 CI≤2.0L/mim/m^2**	⑨ 혈류역학검사지표(Hemodynamics)	**RAP≥8mmHg 또는 CI<2.5L/mim/m^2**

계열이 다른 약제라면 3제까지 순차적 병용 요법 급여 가능

- ✓ WHO FC: IV→**III**
- ✓ 6MWD: 300m→**440m**
- ✓ BNP/NT-proBNP: 300/1800→**50/300**
- ✓ RAP 15 mmHg→**8mmHg** / CI≤2.0 L/min/m^2→**2.5L/min/m^2**

Intermediate-low 에서도 병용요법 가능

20220120 요양급여의 적용기준 및 방법에 관한 세부사항 일부개정고사(안)

Selexipag for COPD or ILD ??

Role of Selexipag in Chronic Obstructive Pulmonary Disease (COPD) Patients With Out-of-Proportion Pulmonary Hypertension

Sherif T. Abuserewa [1], Ahmed Selim [2], Amr Youssef [2], Ronald Zolty [2]

Retrospective single-center case series observational study
Resting mean PAP of **≥ 35 mmHg**
Relatively preserved lung function **FEV1 > 50%**

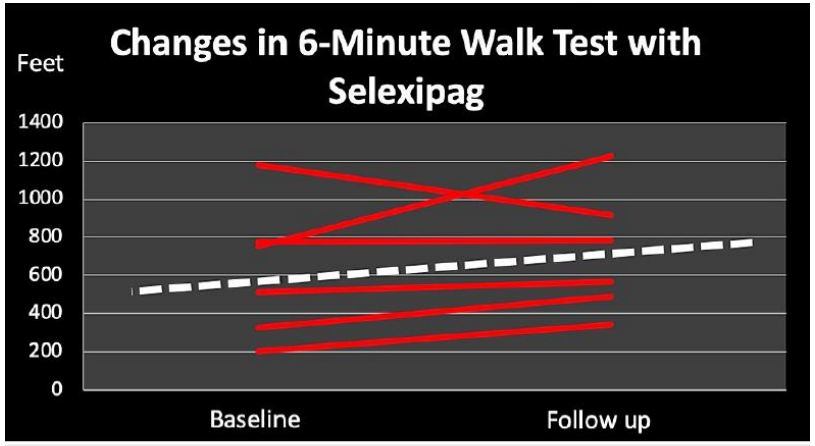


FIGURE 1: Changes in six-minute walk test over six months of selexipag treatment

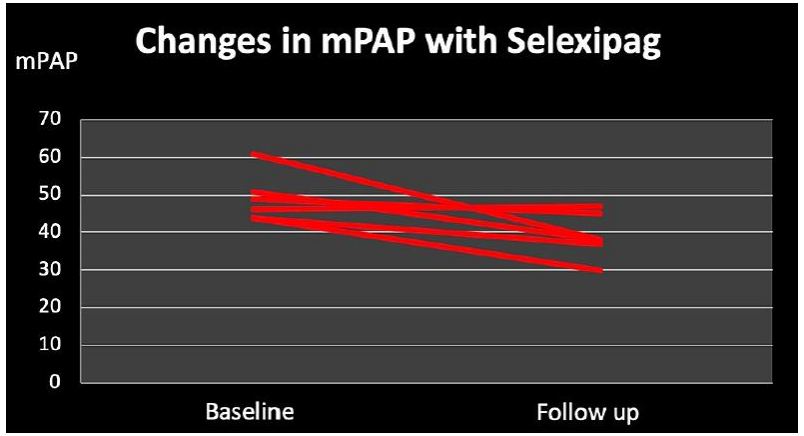
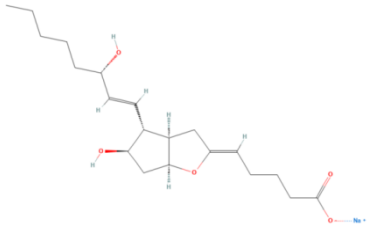
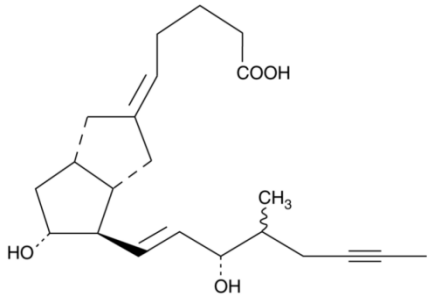


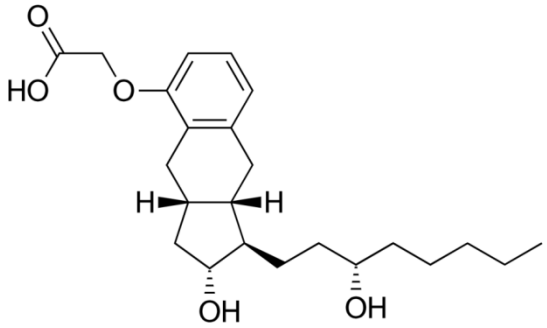
FIGURE 2: Changes in mean pulmonary artery pressure (mPAP) with selexipag treatment over six months

Cureus. 2021 Jul 20;13(7):e16520.

Prostanoids – for **inhalation**







2024.7.5 국내 품목허가 취득
진료상 필수약제로 보험약가 신청

IPF 산정특례 대상으로 추진 예정

Epoprostenol Sodium

Iloprost
현재 국내사용중

Treprostinil

환율계산기 (매매기준율 기준)

미국 달러 USD		대한민국 원 KRW
200,000 $	=	275,180,000.00 ₩

Inhaled Treprostinil in PH due to Interstitial Lung Disease

INCREASE trial *N Engl J Med* 2021; 384:325-334

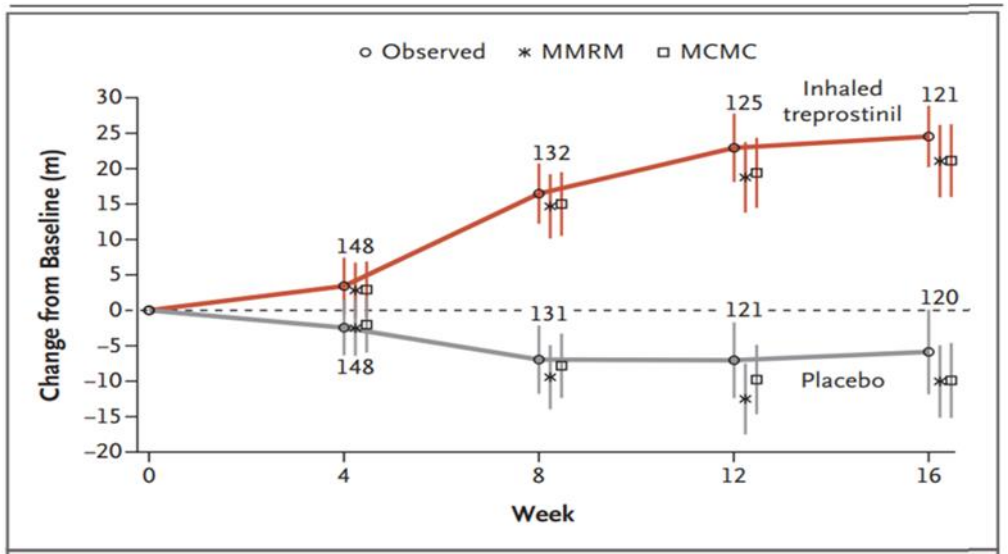
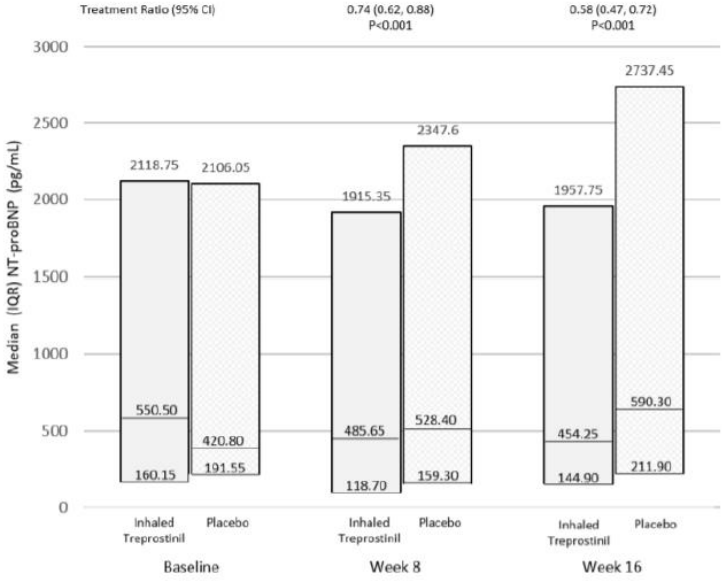
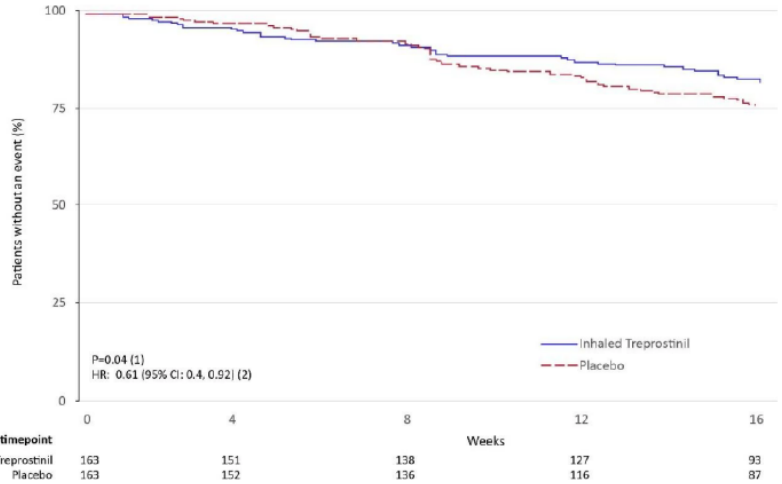


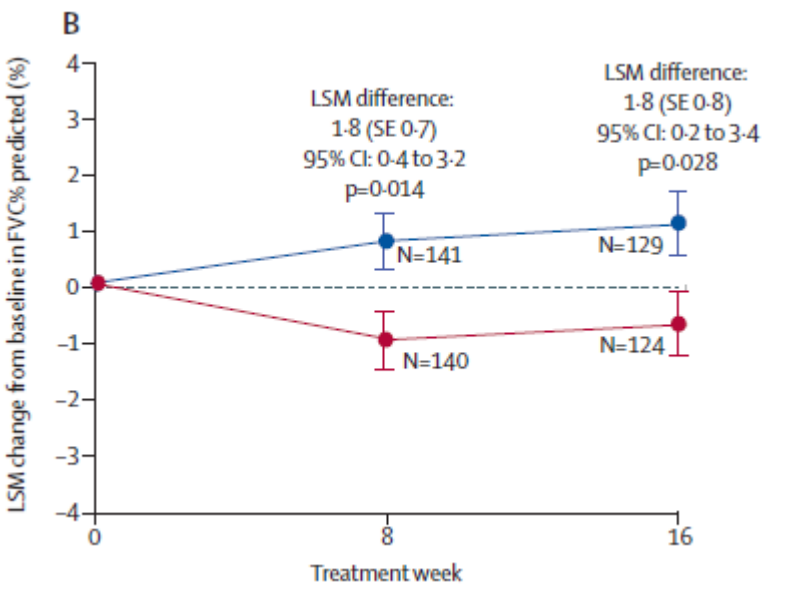
Figure 2. Mean Change from Baseline in Peak 6-Minute Walk Distance through Week 16.



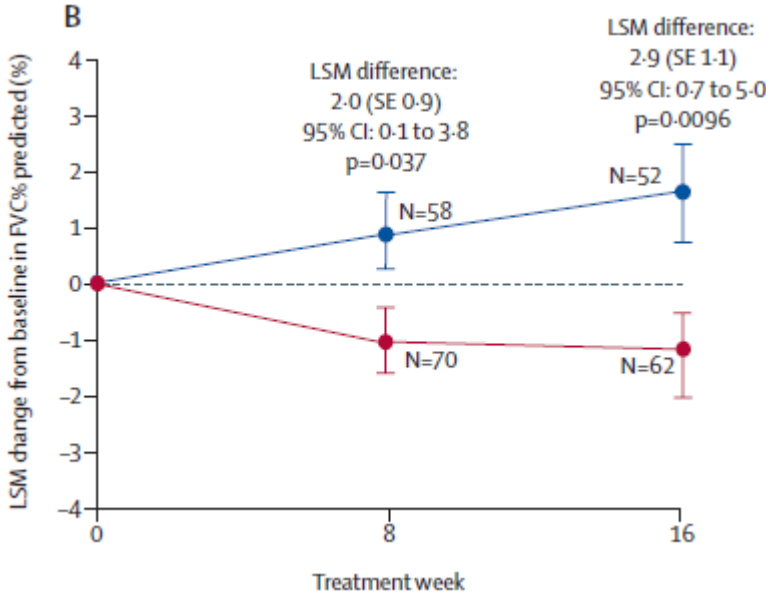
6MWT – exercise capacity ↑
NT-proBNP ↓
Risk of clinical worsening ↓



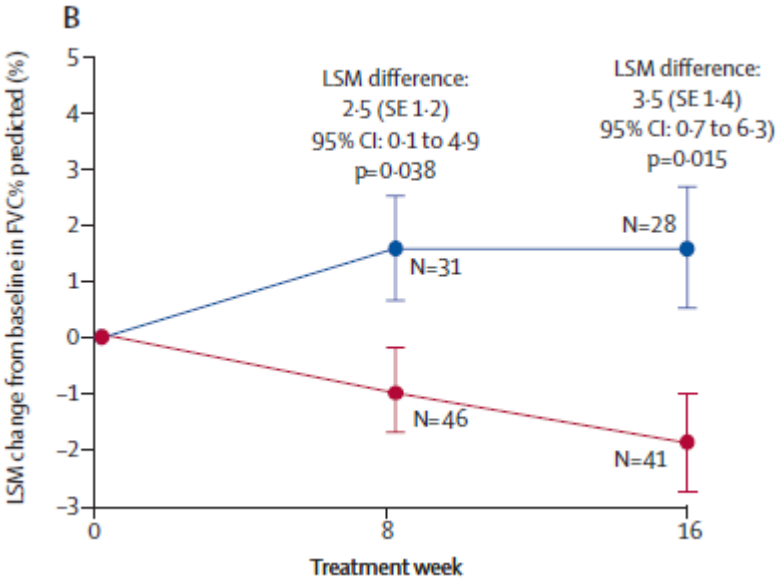
A post-hoc analysis of the INCREASE study
Change of Lung function FVC % predicted



Overall population



subgroup **IIP**



subgroup **IPF**

N Engl J Med 2021; 384:325-334

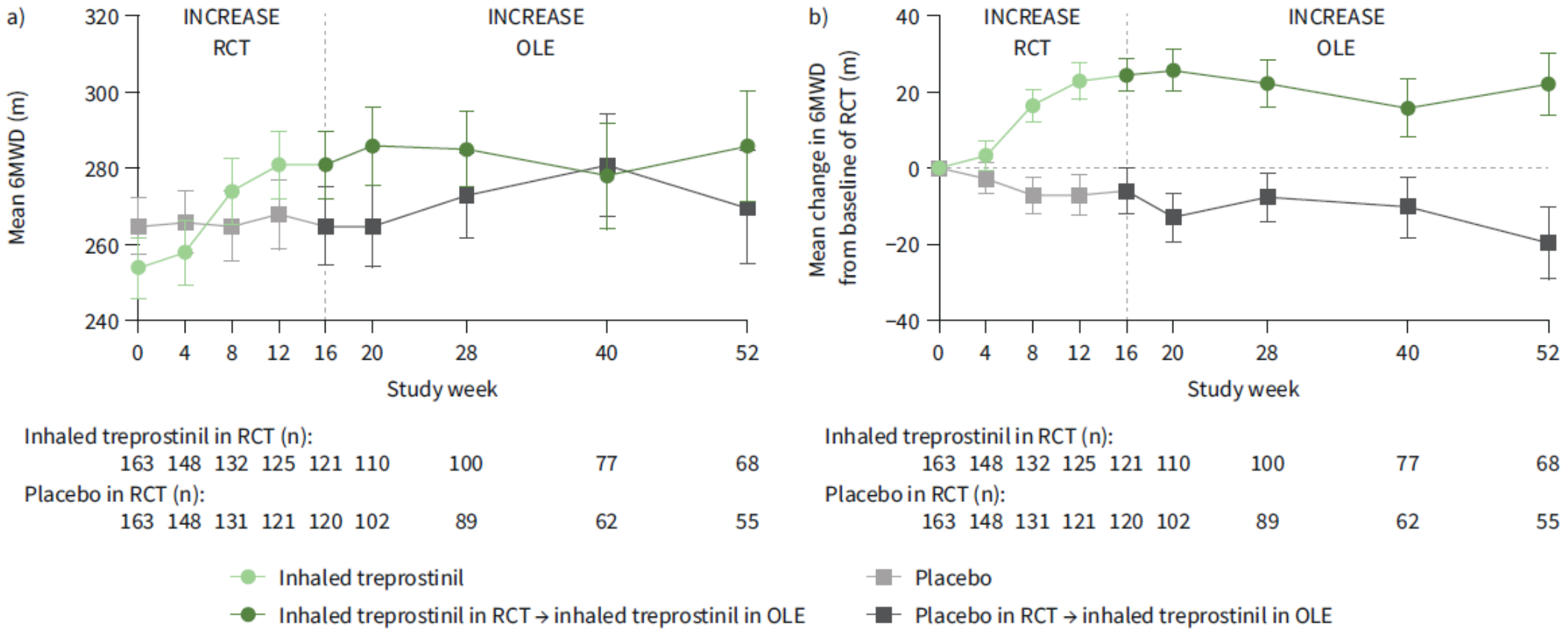
INCREASE trial
Greater treatment effect in higher **PVR** & **NT-proBNP**

	Inhaled treprostinil (n)	Placebo (n)	Placebo-corrected difference in week-16 FVC, mL	p value
Pulmonary vascular resistance, Wood units				
<5·275	64	75	−1·6 (47·9; −95·9 to 92·8)	0·97
≥5·275	65	49	112·5 (52·6; 9·0 to 215·9)	0·033
NT-proBNP, pg/mL				
<503·85	62	75	19·9 (53·7; −86·3 to 126·1)	0·71
≥503·85	63	47	94·4 (47·4; 0·7 to 188·2)	0·048

Placebo-corrected difference in week-16 FVC stratified by median baseline clinical characteristics

Long-term Inhaled Treprostinil for PH-ILD:

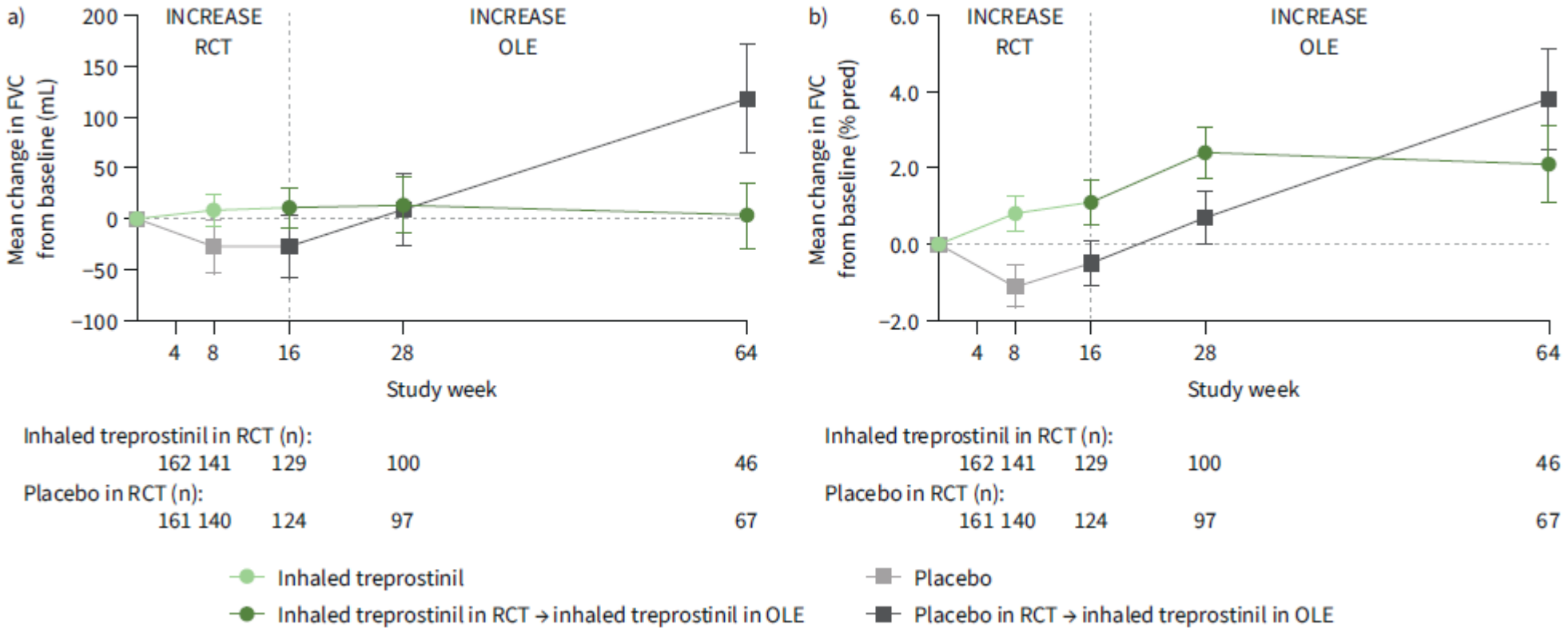
INCREASE Open-Label Extension Study : 6MWT change



A. Waxman, et al Eur Respir J 2023; 61: 2202414

Long-term Inhaled Treprostinil for PH-ILD:

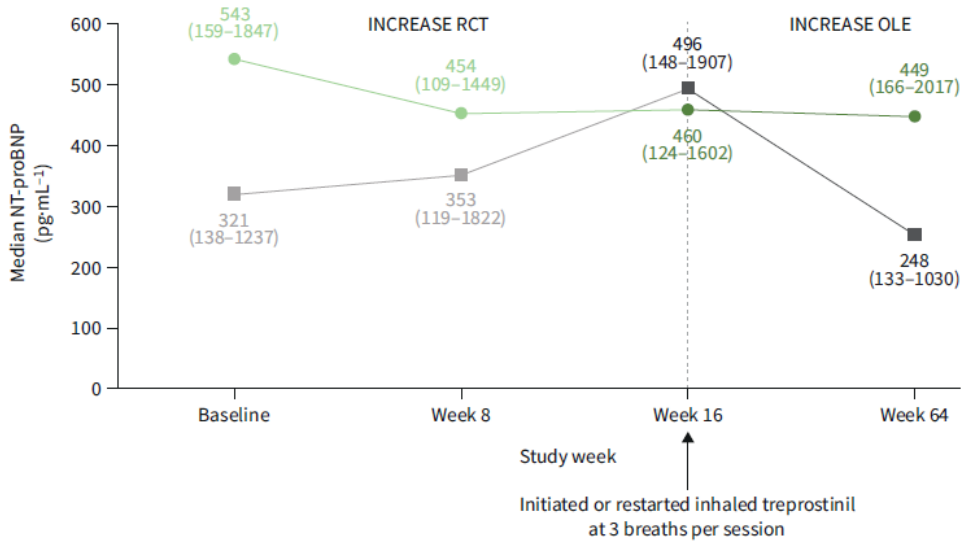
INCREASE Open-Label Extension Study : FVC% change

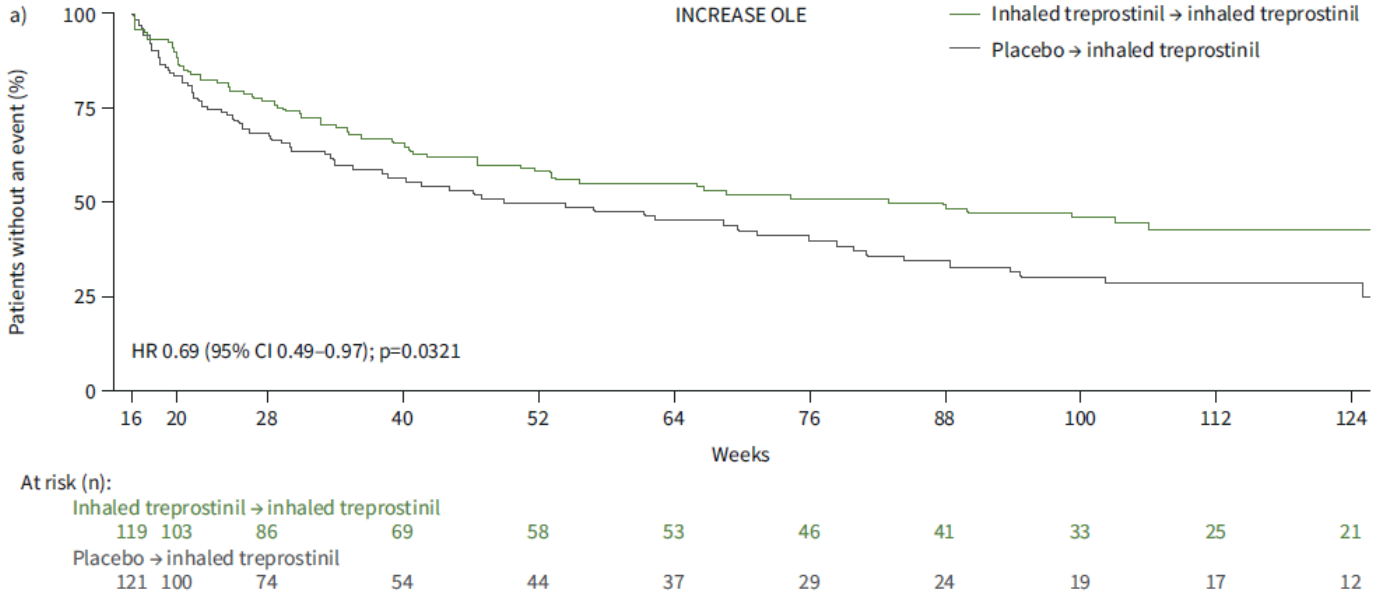


A. Waxman, et al Eur Respir J 2023; 61: 2202414

Long-term Inhaled Treprostinil for PH-ILD:

INCREASE Open-Label Extension Study : NT-proBNP & time to exacerbation





A. Waxman, et al Eur Respir J 2023; 61: 2202414

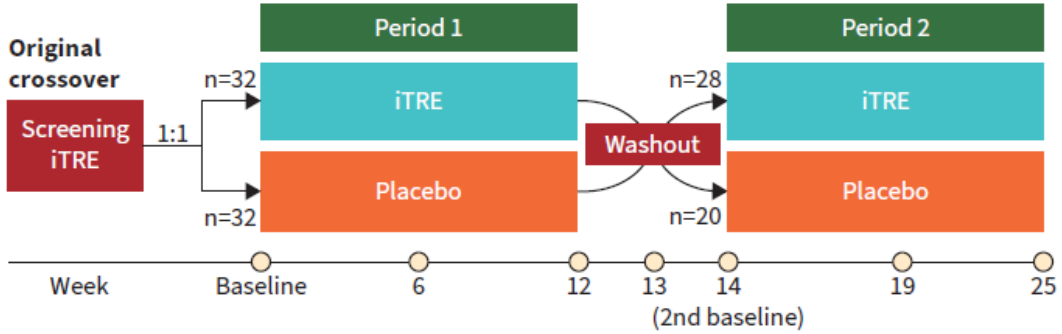
Pulmonary Function Test Results : **DLCO %**

Long-term Inhaled Treprostinil for PH-ILD: INCREASE Open-Label Extension Study

	Received Inhaled Treprostinil in INCREASE RCT (n=119)				**Received Placebo in INCREASE RCT (n=121)**			
DLCO % Predicted, %								
Week 16[a]	112	28.8 (11.6)	-	-	106	26.9 (11.1)	-	-
Week 28	97	29.2 (13.0)	92	-1.0 (5.2)	90	28.5 (12.3)	85	0.2 (6.4)
Week 64	65	29.5 (12.4)	63	-0.8 (7.2)	42	31.8 (12.1)	39	0.4 (9.2)

S.D. Nathan et al,
Eur Respir J. 2024 Jun 6;63(6)

Inhaled treprostinil in pulmonary hypertension associated with COPD: PERFECT study results



76 patients (FVC 74.8±17.6, FEV1 42.6±18.4 Dlco 30.4±12.5)
moderate to severe PH
based on RHC : mPAP ⩾30 mmHg, PVR ⩾4 WU
Resting spO2 ⩾90%

The study was terminated early
increased the risk of serious adverse events
suggestive evidence of an increased risk of mortality.
The change in 6MWD was numerically worse

S.D. Nathan et al,
Eur Respir J. 2024 Jun 6;63(6)

Inhaled treprostinil in pulmonary hypertension associated with COPD: PERFECT study results

SAE inhaled TRE vs. placebo → 25.8% vs 10.3%
dyspnea 28.8% vs 15.5%
fatigue 10.6% vs 3.4%

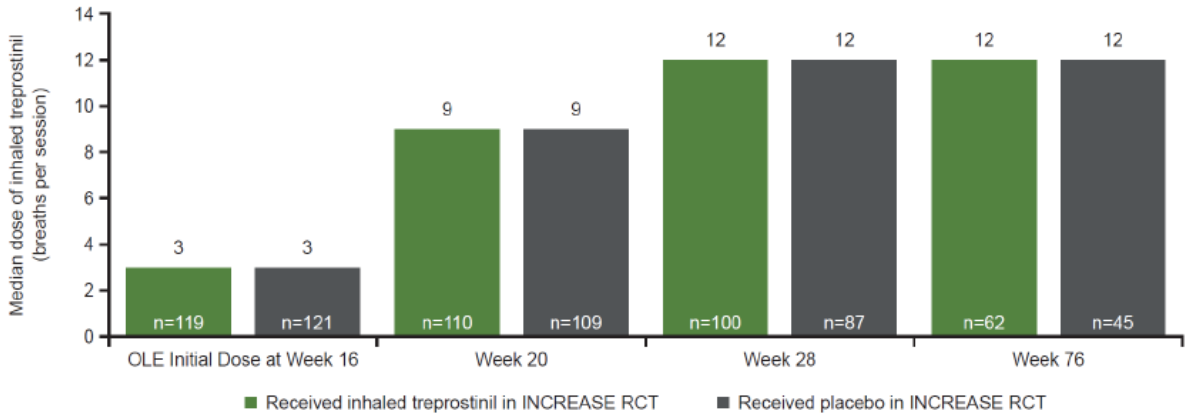
Patients with **DLCO <25%** predicted have a reduced likelihood of benefit and are at greater risk of mortality which may or may not be related to the PH therapy

Those PH-COPD patients with **FEV1>40% + mPAP >40 mmHg** might be more likely to demonstrate benefit.

Inhalation 에 따른 부작용은 ? Compliance ?

- Prostacycline 구조상 short- half life
- 하루 4번 nebulized 투여
- Upper,lower airway irritation symptom

- Cough, dyspnea, chest tightness
- Dose escalation



Inhalation 에 따른 부작용은 ? Compliance ?

- 47/163 (25%) patients in the inhaled treprostinil group
- 38/163 (23%) patients in the placebo group discontinued study drug prematurely in INCREASE study (ILD)

- SAE inhaled TRE vs. placebo **25.8% vs 10.3%** in PERFECT study (COPD)

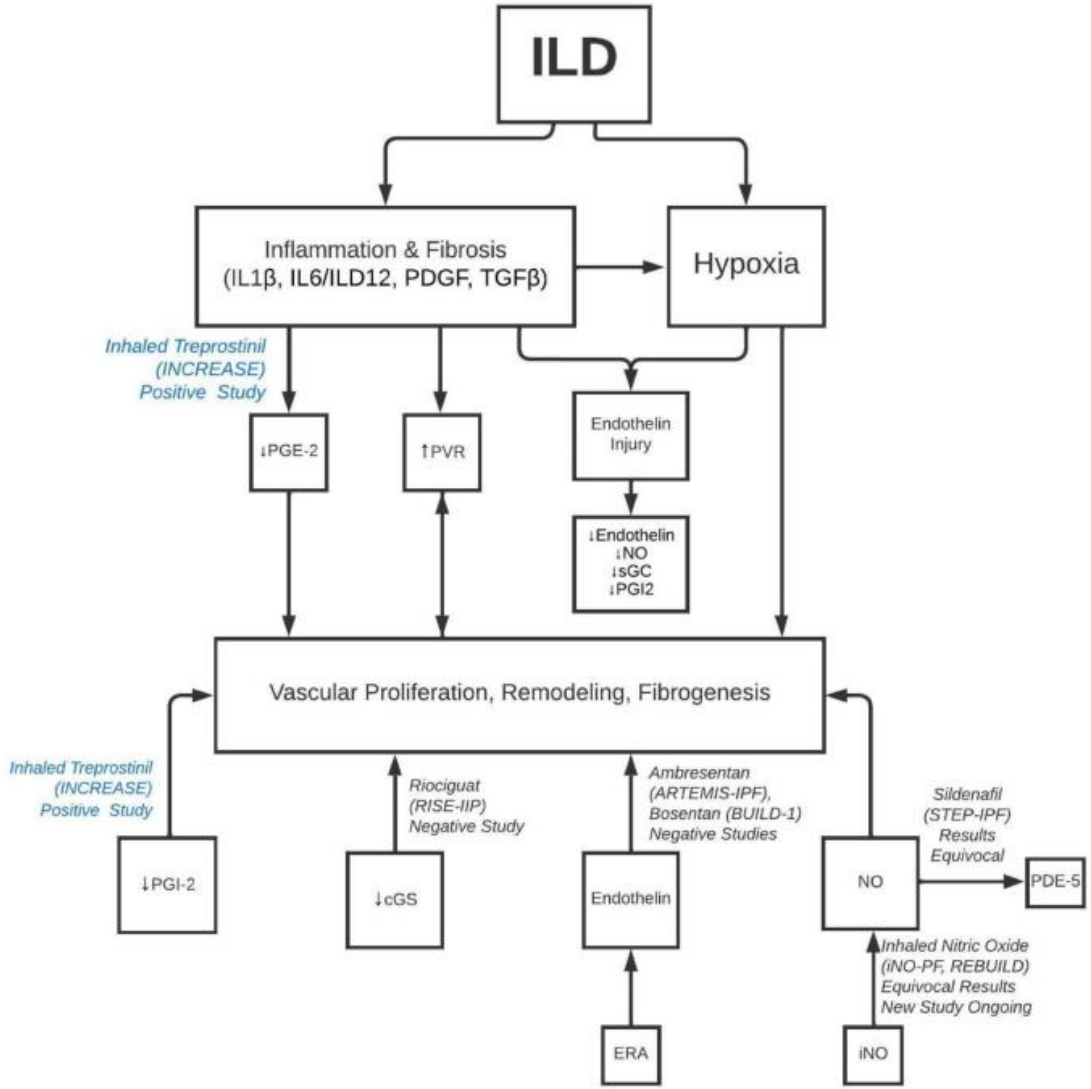
dyspnea 28.8% vs 15.5%

fatigue 10.6% vs 3.4%

INCREASE (ILD-PH) vs. PERFECT (COPD-PH)

positive vs. negative Why ??

- COPD 는 Airway disease 라서 inhalation adverse effect가 심하다?
- Drug delivery efficacy 문제 ?
- COPD vs. ILD airway structure?
- Effect on Pathogenesis of ILD



A. Arslan Front Med 2024 Jan 17:1

Treprostinil (Tyvaso) – inhalation powder DPI 가 도입되면

COPD 에도 효과적일까?

Formulation	Dosing	Key Trials	FDA Approval
Treprostinil nebulizer (Tyvaso)	3 breaths (18 mcg) four times daily, increasing by 3 breaths every 1–2 weeks to target dose of 9–12 breaths four times daily	Inhaled treprostinil in pulmonary hypertension due to interstitial lung disease (INCREASE)[7]	WHO Group I (PAH) (October 2017) WHO Group III (PH-ILD) (April 2021)
Treprostinil dry powder inhaler (Tyvaso DPI)	1 breath four times daily Cartridges available in 18, 32, and 64 mcg; 80 mcg dosing uses two cartridges (64 + 18 mcg)	BREEZE: Open-label clinical study to evaluate the safety and tolerability of treprostinil inhalation powder as Tyvaso DPI™ in patients with pulmonary arterial hypertension[31]	WHO Group I (PAH) WHO Group III (PH-ILD) (both May 2022)

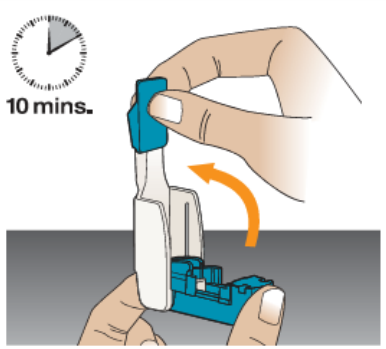


Figure N

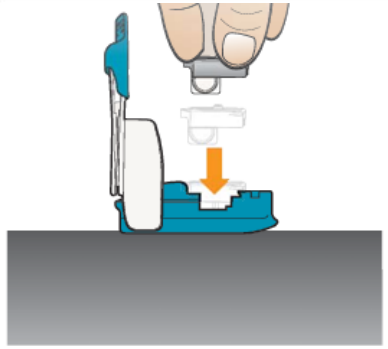


Figure O

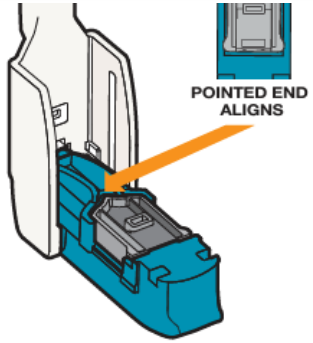
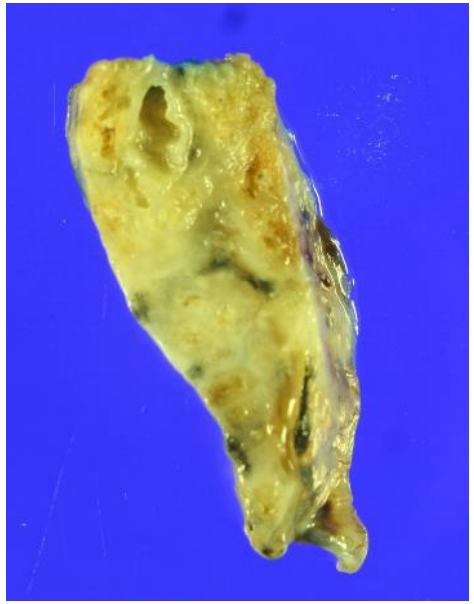


Figure P

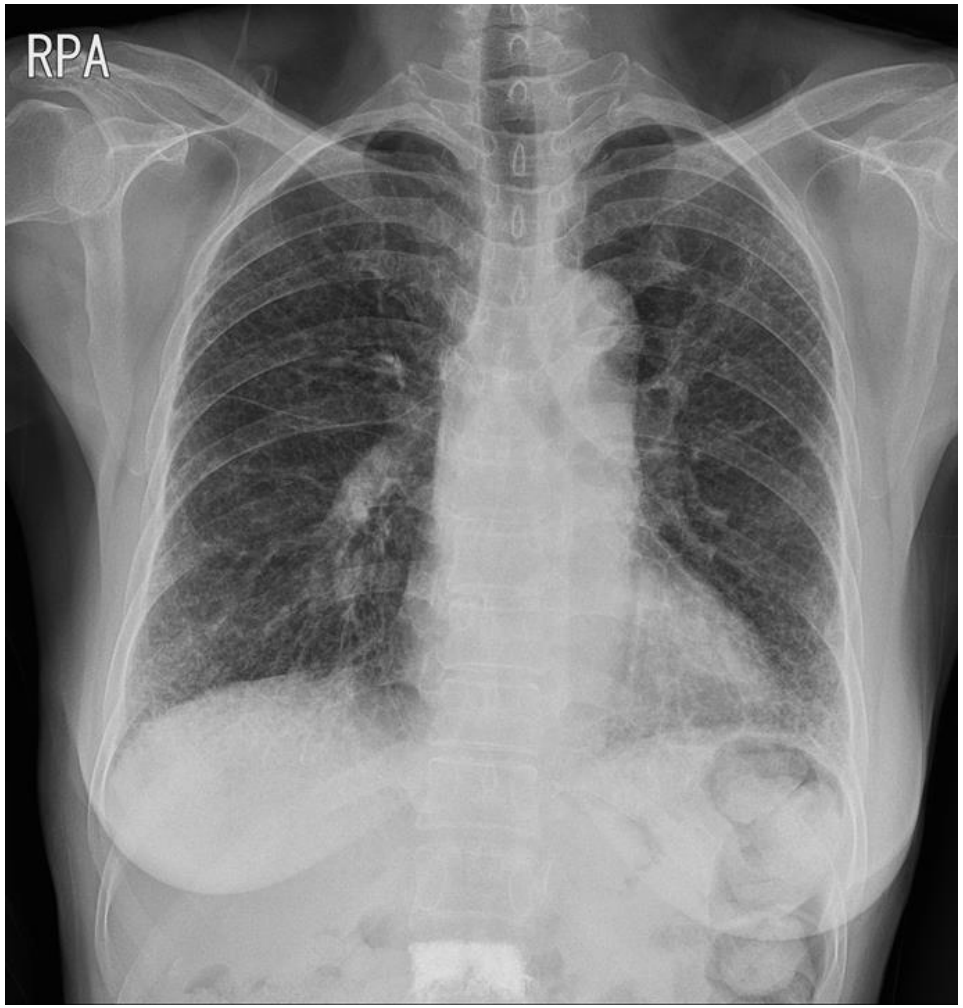
69/F, Worsening exertional dyspnea : NYHA Fc III

- 2018년 VATS lung Biopsy
→UIP



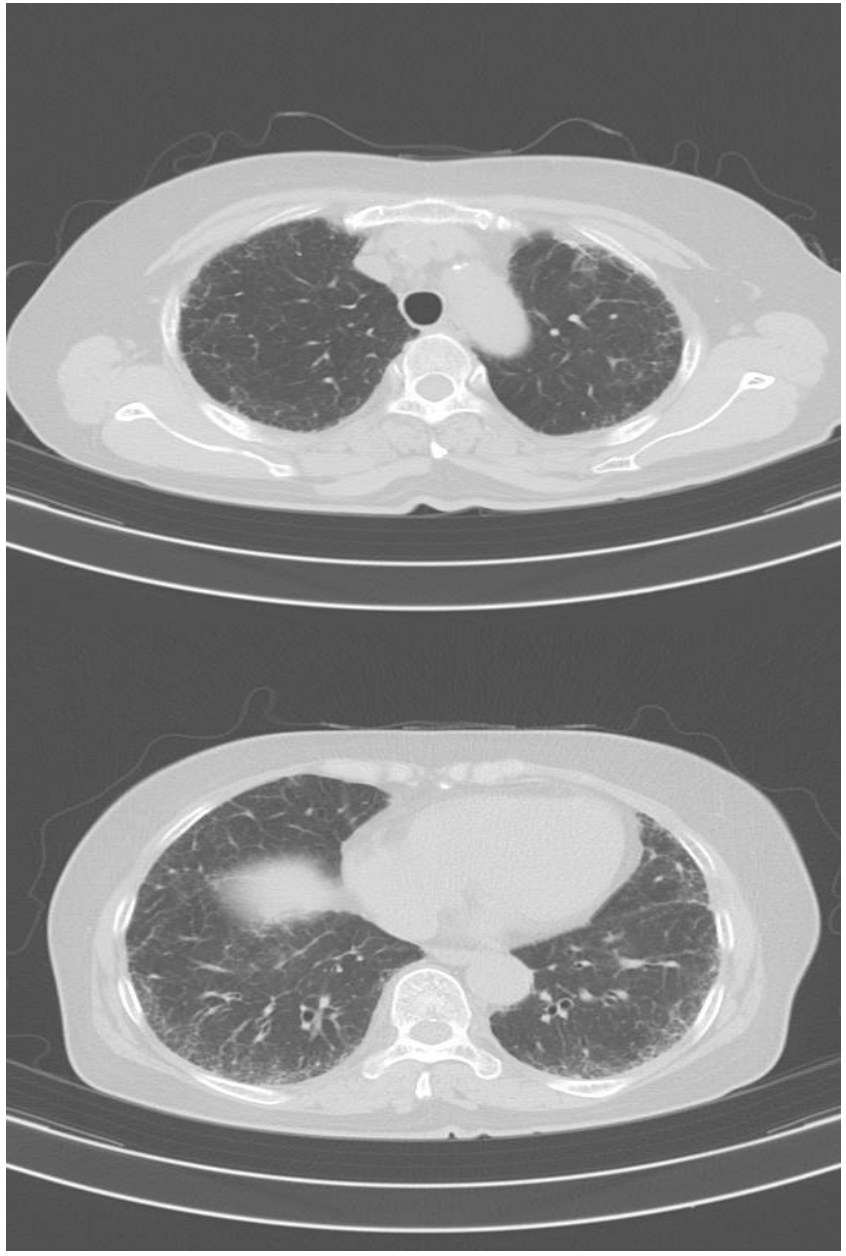
Pirfenidone 복용중

- DM
- Hypertension
- CAOD s/p stent
- Major depression disorder

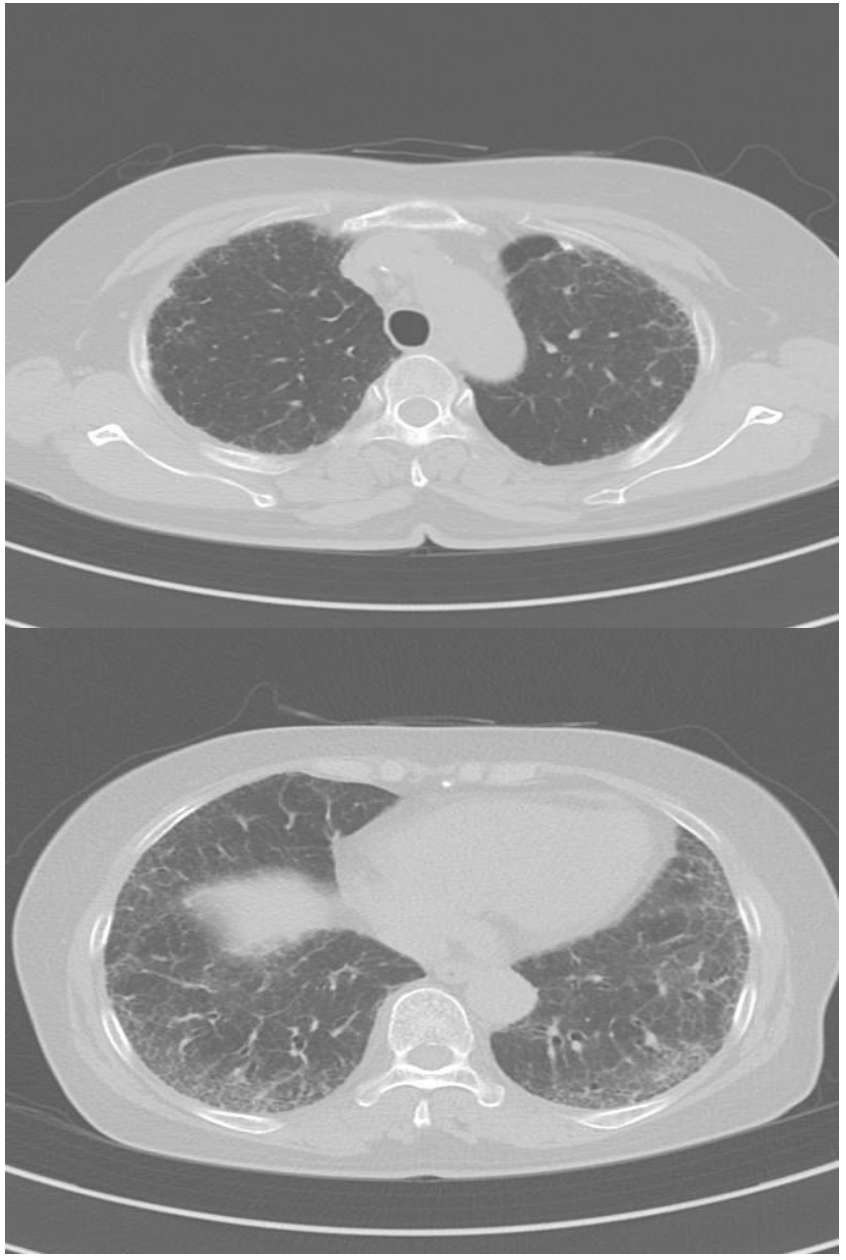


Changes of Radiologic findings

2021.3.16

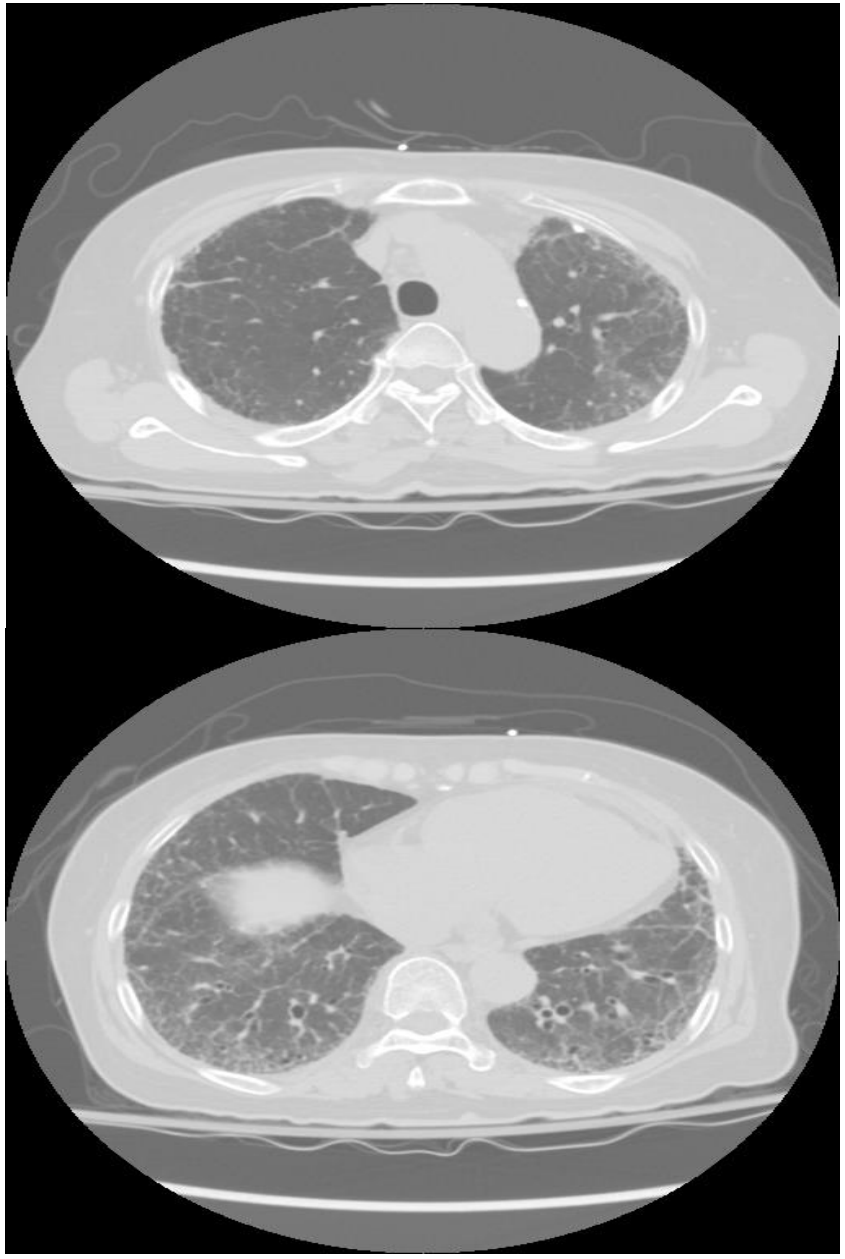


2022.10.6

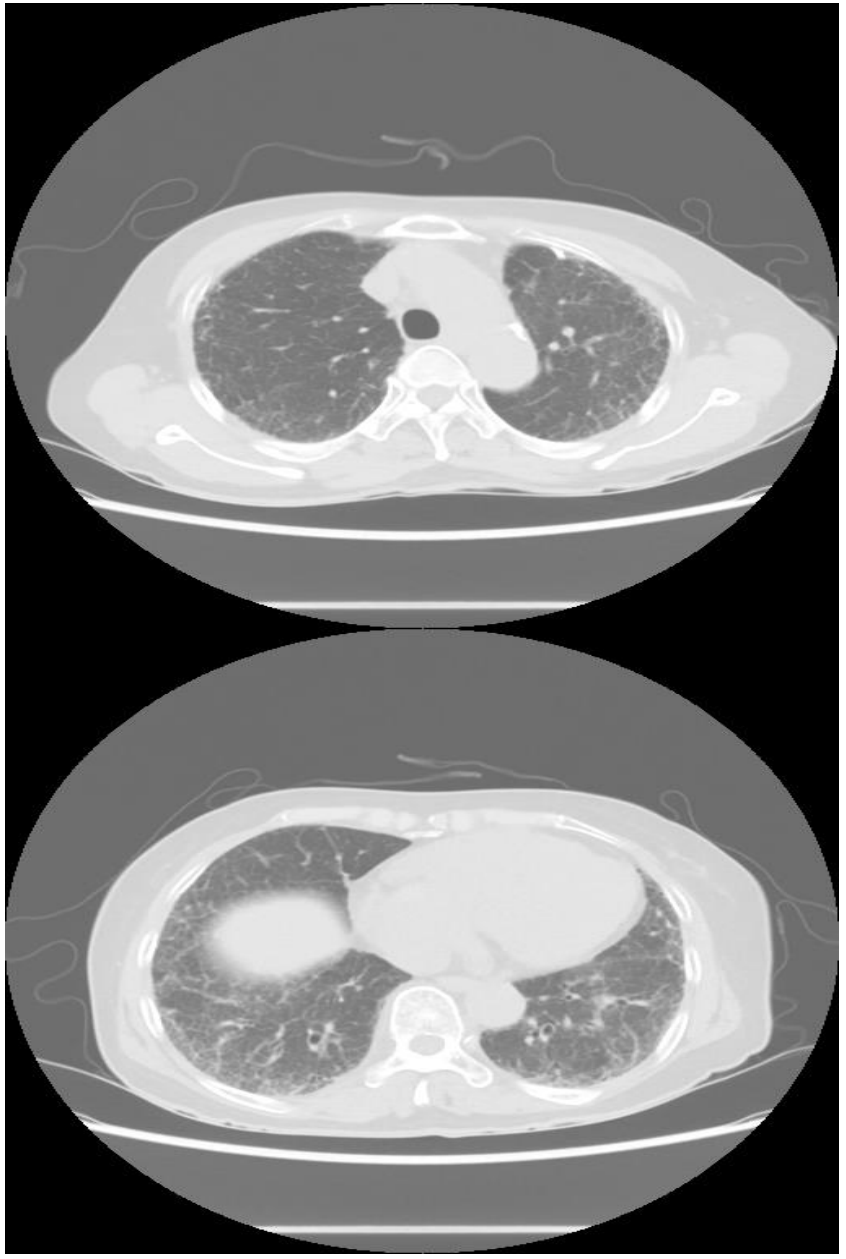


Recent annual CT follow up reveals no significant interval change

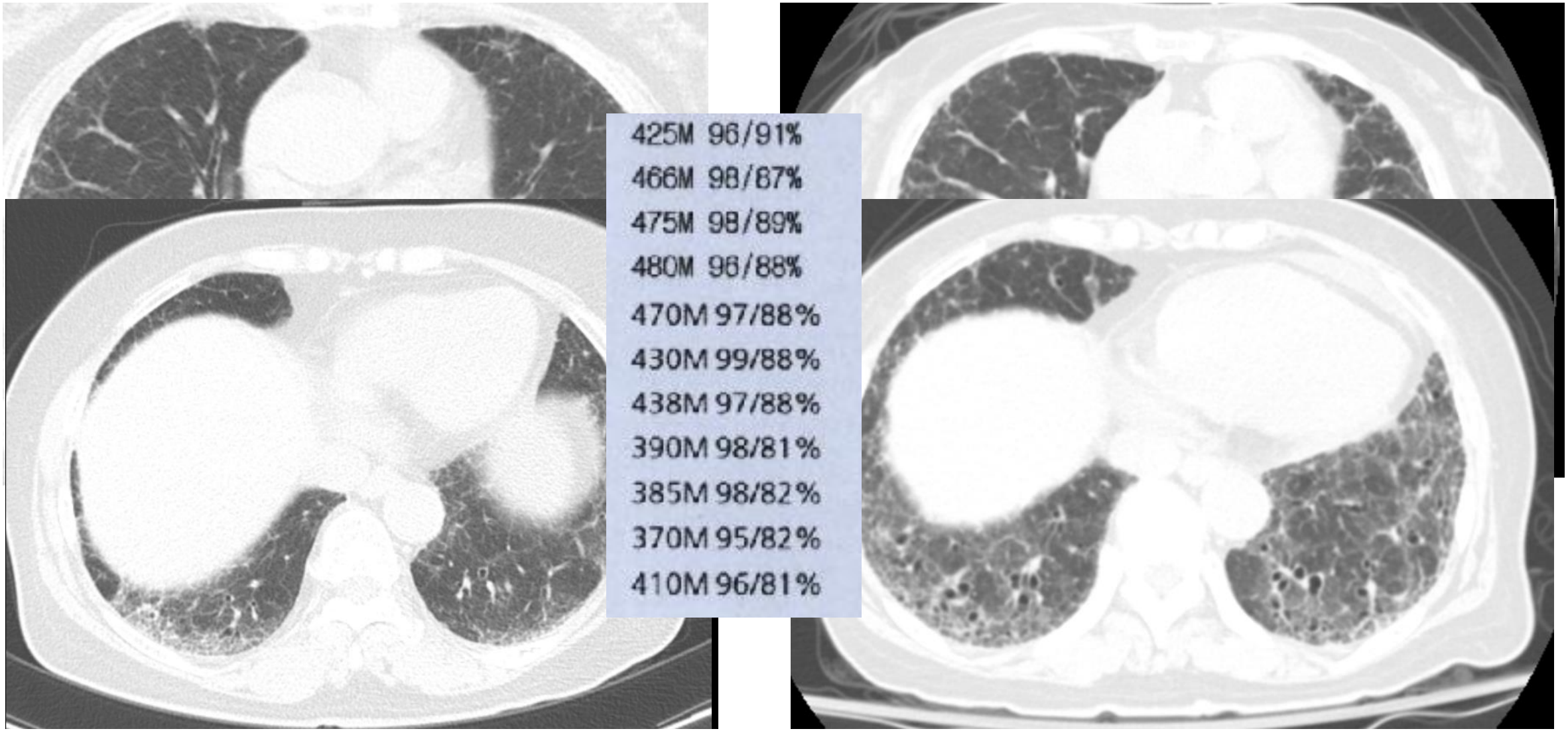
2023.3.27



2023.10.17



2018 at diagnosis → 5years→ 2023



leg edema, exertional dyspnea, desaturation 악화

- Suspicious Rt heart failure
- Echo F/U sPAP 75 mmHg
- RV, RA enalrgent
- RHC

RHC	2023.3.16
mean PAP, mmHg	43
PCWP, mmHg	8
RAP, mmHg	11
CO, L/min	2.12
PVR	17
Svo2 %	45

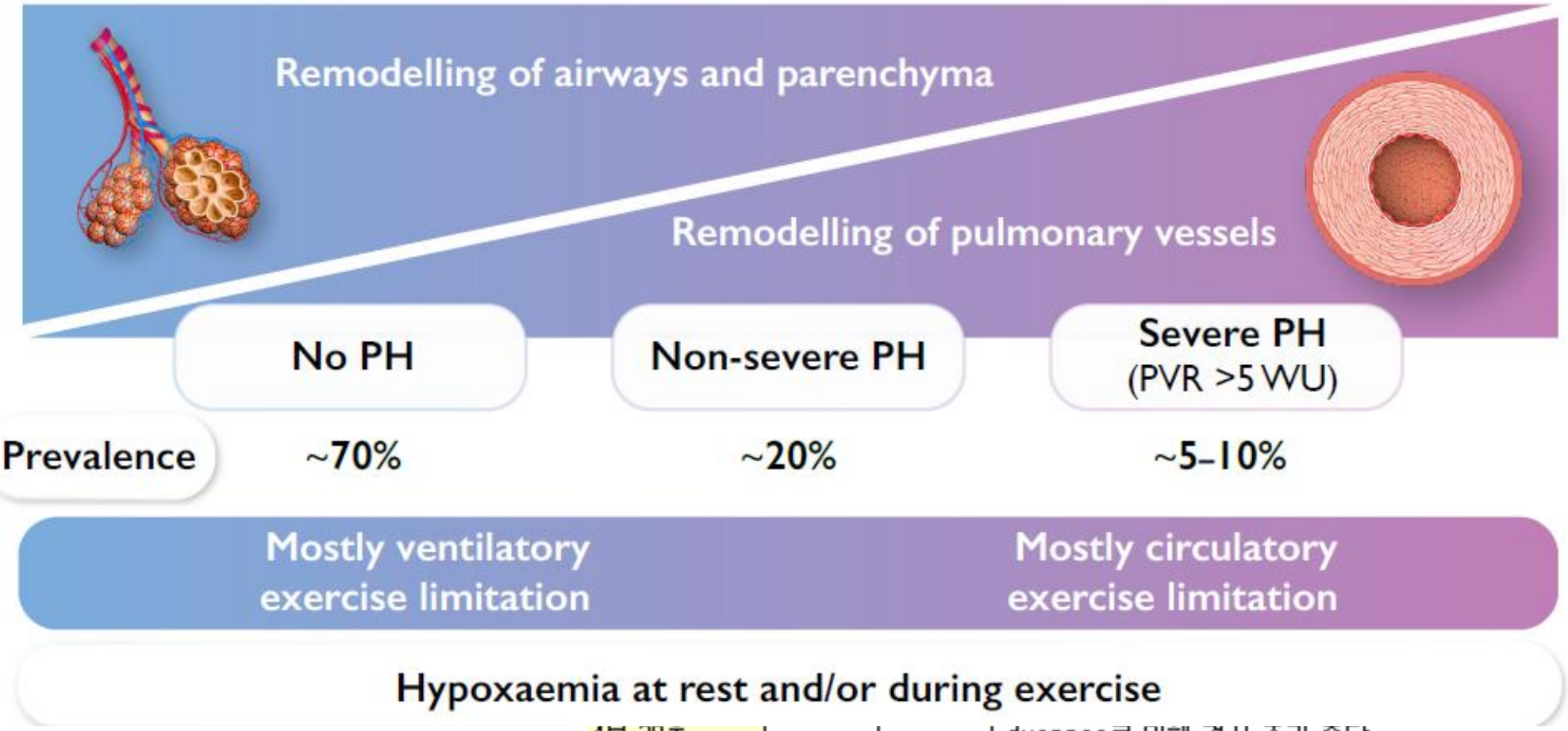
- **Sildenafil 12.5mg tid start**

폐기능검사 vs. DLco

FVC

FEV

pC



4분 30초			dyspnea로 인해 검사 조기 중단
5분			dyspnea로 인해 검사 조기 중단
5분 30초			dyspnea로 인해 검사 조기 중단
6분			dyspnea로 인해 검사 조기 중단

Assessment

- **IPF/UIP** slowly progression in terms of CT image, FVC
- **Worsenig Hypoxemia at rest and/or during exercise**
- Worsening pulmonary hypertension, RV function
  → Signs of RVF

No improvement despite sildenafil for 7 months

- NYHA functional class **III**
- 집안에서만 활동가능
- NP 3~4 L/min home O2
- 이동형 O2 착용하고 휠체어

Treatment plan

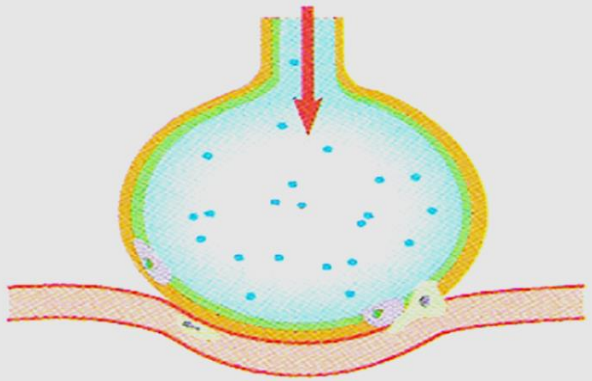
- Re-assessment PH hemodynamic
- Consider other treatment for Pulmonary hypertention

RHC	2023.3.16	2023.10.16
mean PAP, mmHg	43	62
PCWP, mmHg	8	11
RAP, mmHg	11	7
CO, L/min	2.12	3.7
PVR	17	14
Svo2 %	45	42

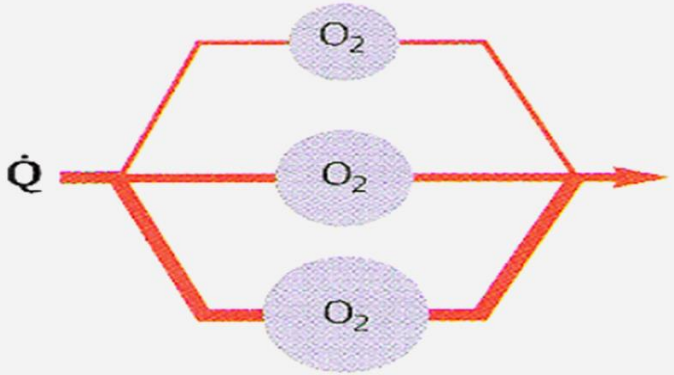
Prostanoid

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

[Ventilation/perfusion ratio]



Pulmonary selectivity



Intrapulmonary selectivity

Anti-remodelling

Baseline and Follow-up Hemodynamic

RHC	2023.3.16	2023.10.16	2024.5.29
mean PAP, mmHg	43	62	**37**
PCWP, mmHg	8	11	**6**
RAP, mmHg	11	7	**7**
CO, L/min	2.12	3.7	**4.0**
PVR	17	14	**8**
Svo2 %	45	42	**66**

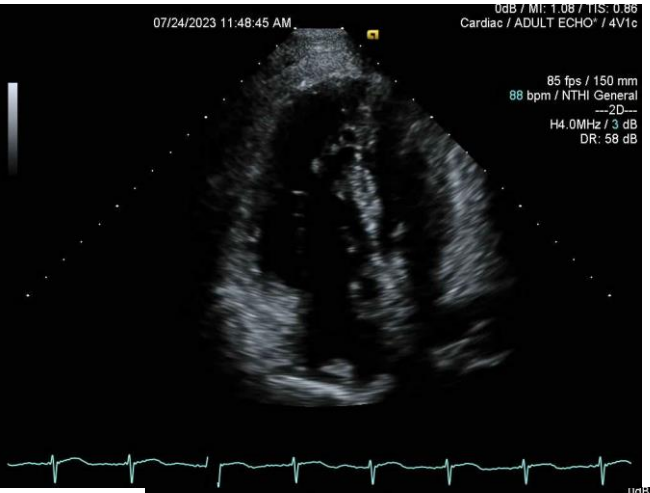
- Functional Class III → II
- Home oxygen supplementation (3~4 L/min) → Everyday life without O_2 supplementation
- 6MWT improvement

	2023.10.17	2023.12.1	2024.5.3
6MWD, m	180	180	342
Nadir SpO_2, %	66	73	73

Iloprost (Ventavis®) inhalation

10 mcg qid start until 4 weeks

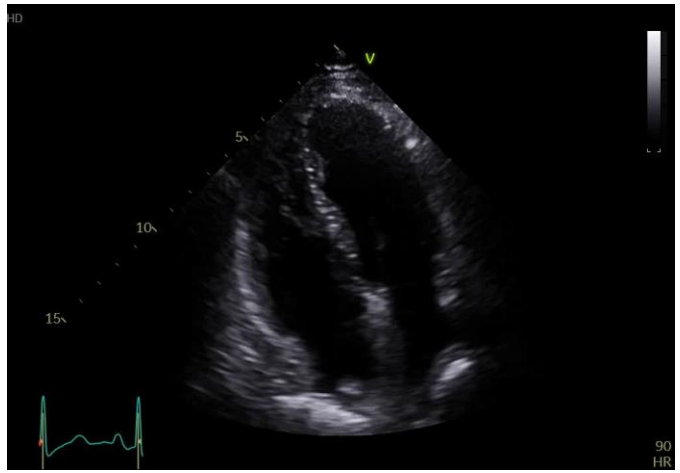
if tolerable → 20 mcg tid

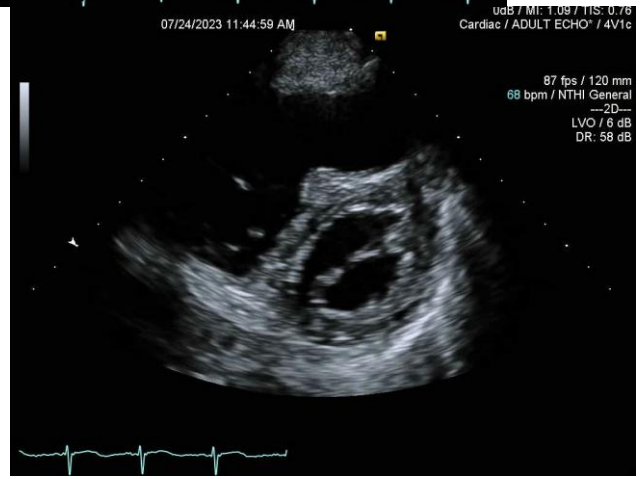


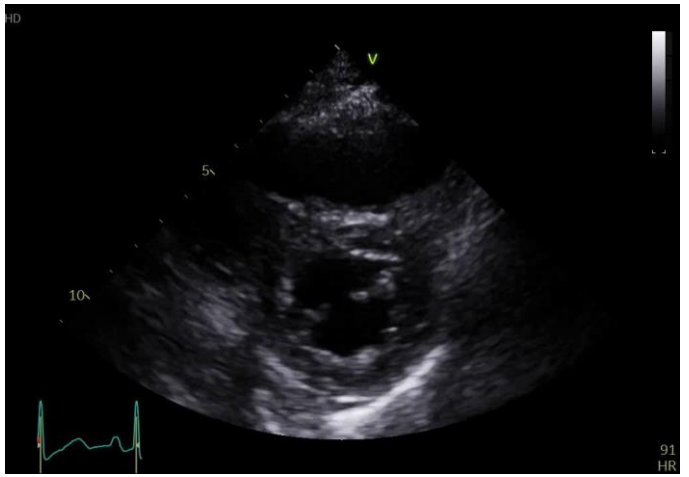
Iloprost start

- Pro-BNP (pg/ml)

941 → 540.2 → 508.3 → 182.0 → 52.7







Iloprost (Ventavis®) inhalation

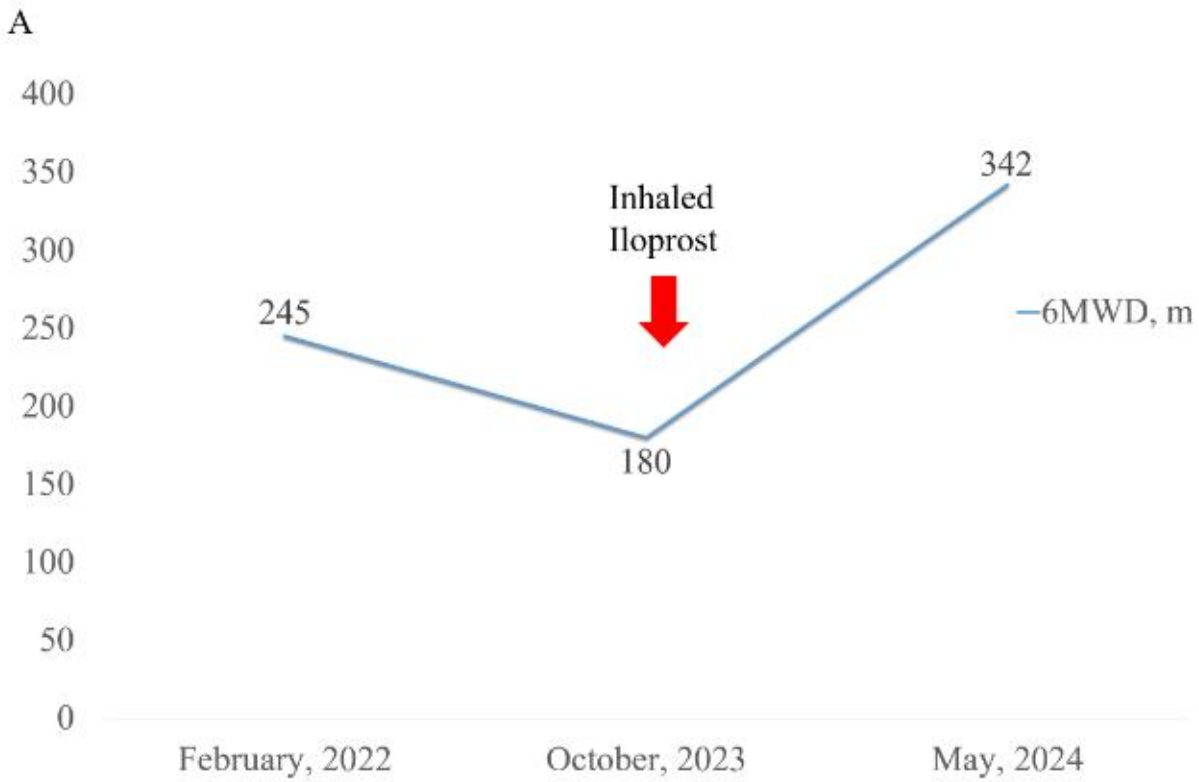
10cmg qid start until 4 weeks
if tolerable → 20 mcg tid

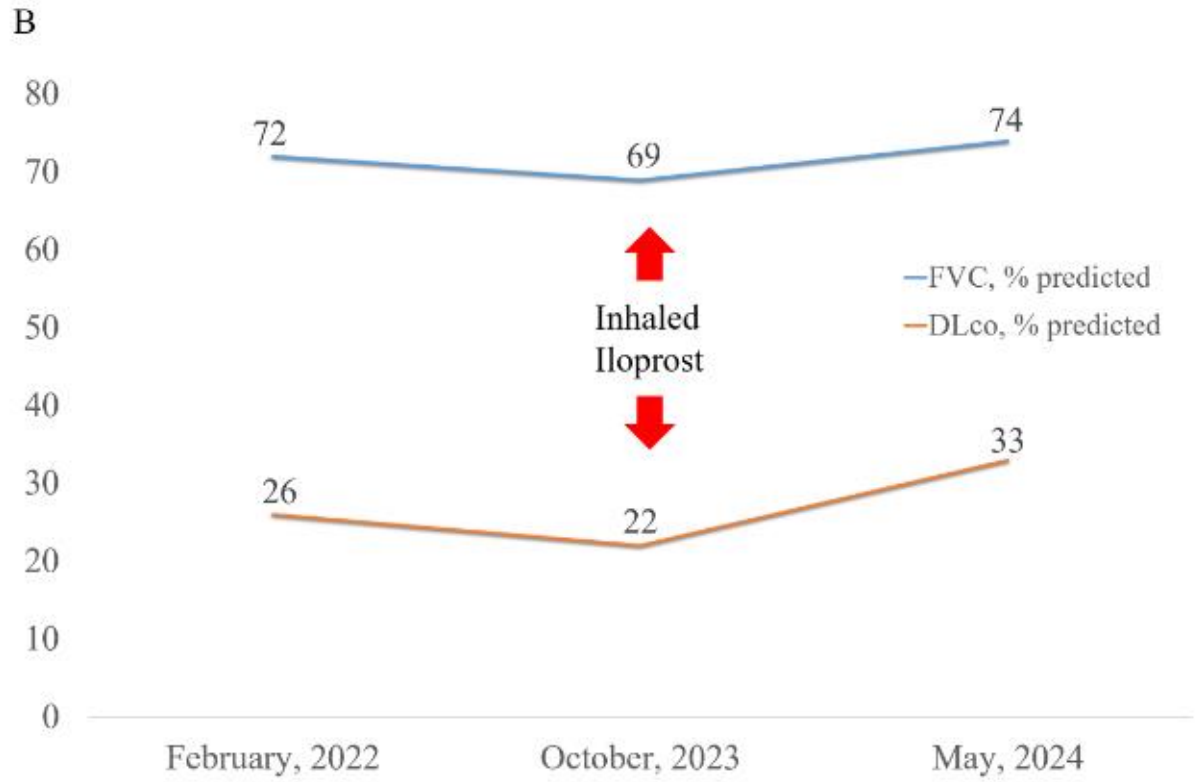
Iloprost start
(2023/10/17)

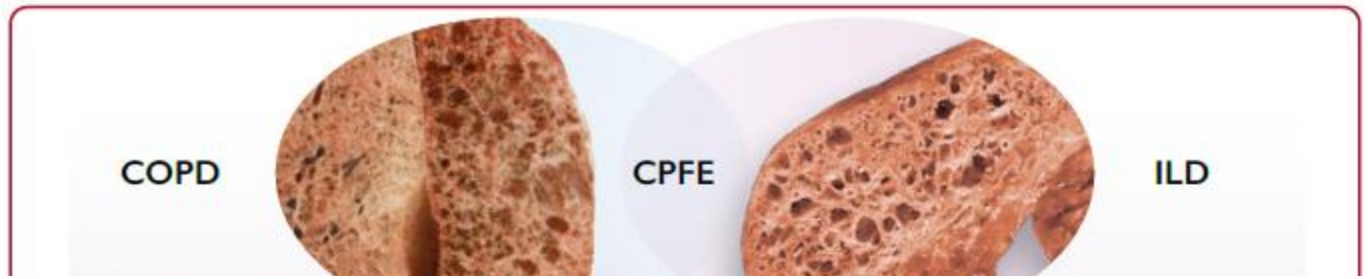
KL-6

1123.4 → 1028.3 → 924.4 → 885.3

(2023/10/16) (2024/1/30) (2024/5/3)

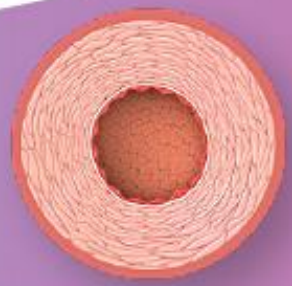

A
400
350
300
250
200
150
100
50
0
245
180
342
Inhaled
Iloprost
6MWD, m
February, 2022
October, 2023
May, 2024


B
80
70
60
50
40
30
20
10
0
72
69
74
26
22
33
Inhaled
Iloprost
FVC, % predicted
DLco, % predicted
February, 2022
October, 2023
May, 2024



Remodelling of airways and parenchyma

Remodelling of pulmonary vessels



	No PH	Non-severe PH	Severe PH (PVR >5 WU)
Prevalence	~70%	~20%	~5–10%

Mostly ventilatory exercise limitation

Mostly circulatory exercise limitation

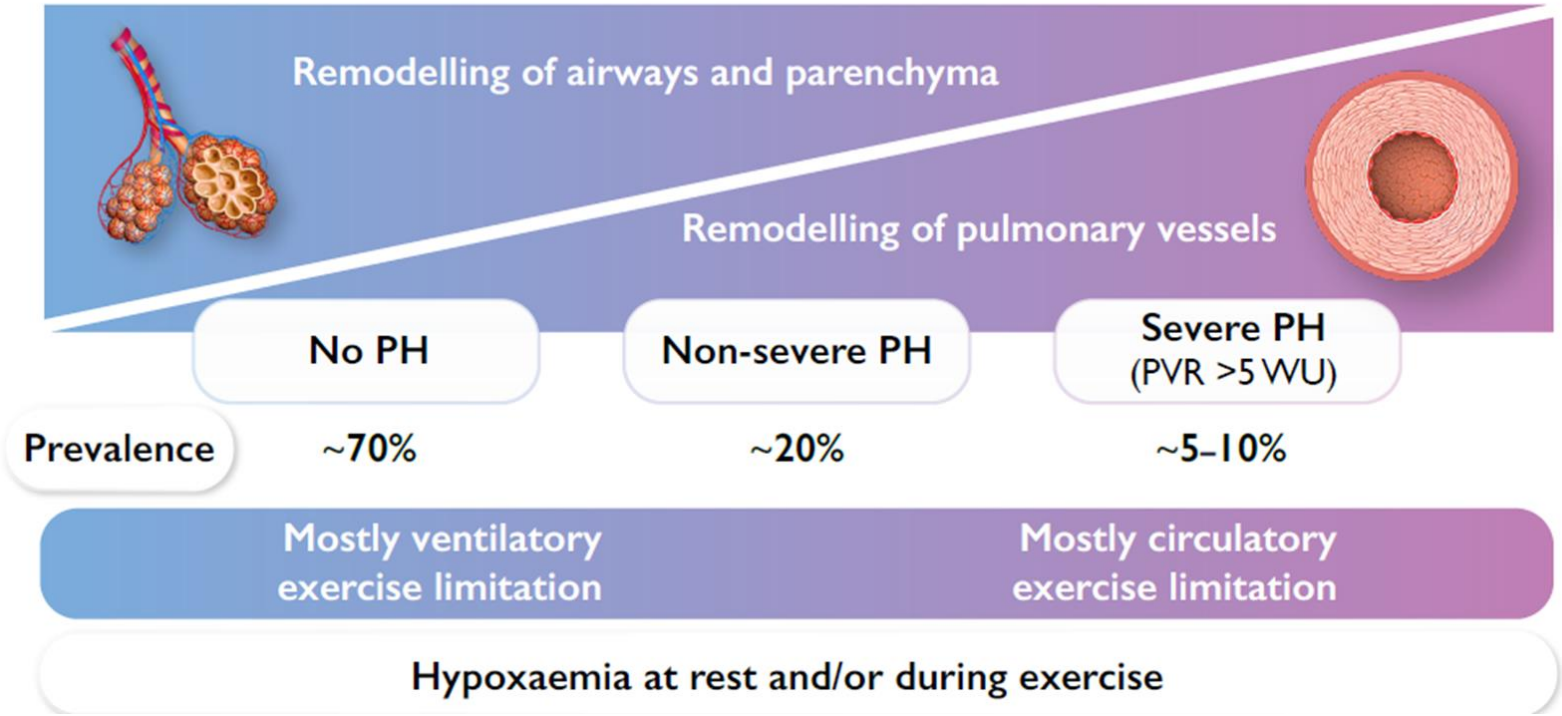
Hypoxaemia at rest and/or during exercise

exercise limitation
exercise limitation
Hypoxaemia at rest and/or during exercise

ESC ERS

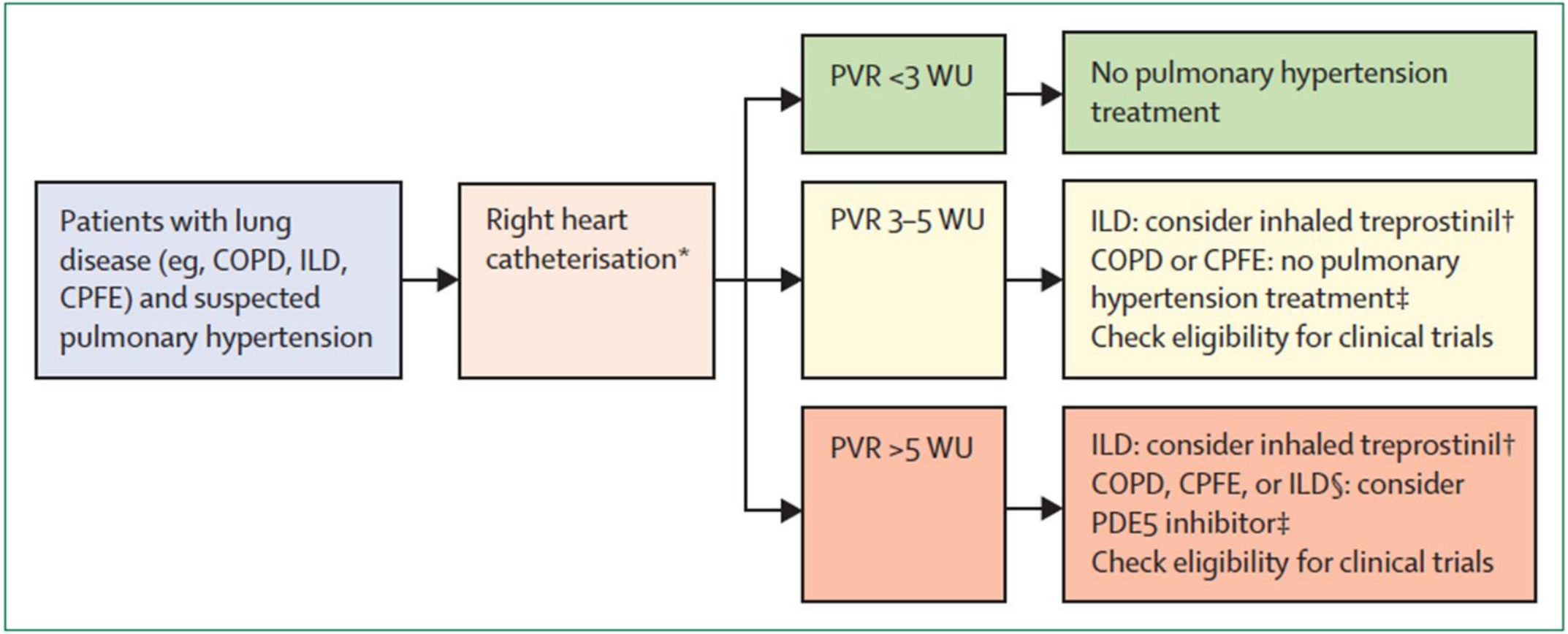
62/F, Exertional dyspnea Fc III

PH	7.35 ~ 7.45
PCO_2	35.0 ~ 45.0
PO_2	75.0 ~ 100.0



city	
	20
	20
	0.95
	33
	0.61
	26

Treatment guidance of PH associated chronic lung disease



Lancet Respir Med 2023;11: 820–35

Criteria favoring group 1 PH vs. group 3 PH or vascular phenotype of chronic lung disease

Criteria favouring group 1 (PAH)	Testing	Criteria favouring group 3 (PH due to lung disease)
	Extent of lung disease	
Normal or mildly impaired: • FEV_1 >60% pred (COPD) • FVC >70% pred (IPF) • Low diffusion capacity in relation to obstructive/restrictive changes	Pulmonary function testing	Moderate to very severely impaired: • FEV_1 <60% pred (COPD) • FVC <70% pred (IPF) • Diffusion capacity "corresponds" to obstructive/restrictive changes
Absence of or only modest airway or parenchymal abnormalities	High-resolution CT scan¶	Characteristic airway and/or parenchymal abnormalities
	Haemodynamic profile	
Moderate-to-severe PH	Right heart catheterisation Echocardiogram	Mild-to-moderate PH
	Ancillary testing	
Present	Further PAH risk factors (*e.g.* HIV, connective tissue disease, *BMPR2* mutations, *etc.*)	Absent
Features of exhausted circulatory reserve: • Preserved breathing reserve • Reduced oxygen pulse • Low $CO/\dot{V}O_2$ slope • Mixed venous oxygen saturation at lower limit • No change or decrease in P_{ACO_2} during exercise	Cardiopulmonary exercise test+ (P_{ACO_2} particularly relevant in COPD)	Features of exhausted ventilatory reserve: • Reduced breathing reserve • Normal oxygen pulse • Normal $CO/\dot{V}O_2$ slope • Mixed venous oxygen saturation above lower limit • Increase in P_{ACO_2} during exercise
Predominant haemodynamic profile		Predominant obstructive/restrictive profile

Nathan et al. Eur Respir J 2019; 53: 1801914

감사합니다!