What pulmonologist need to know about PAH-targeted therapy

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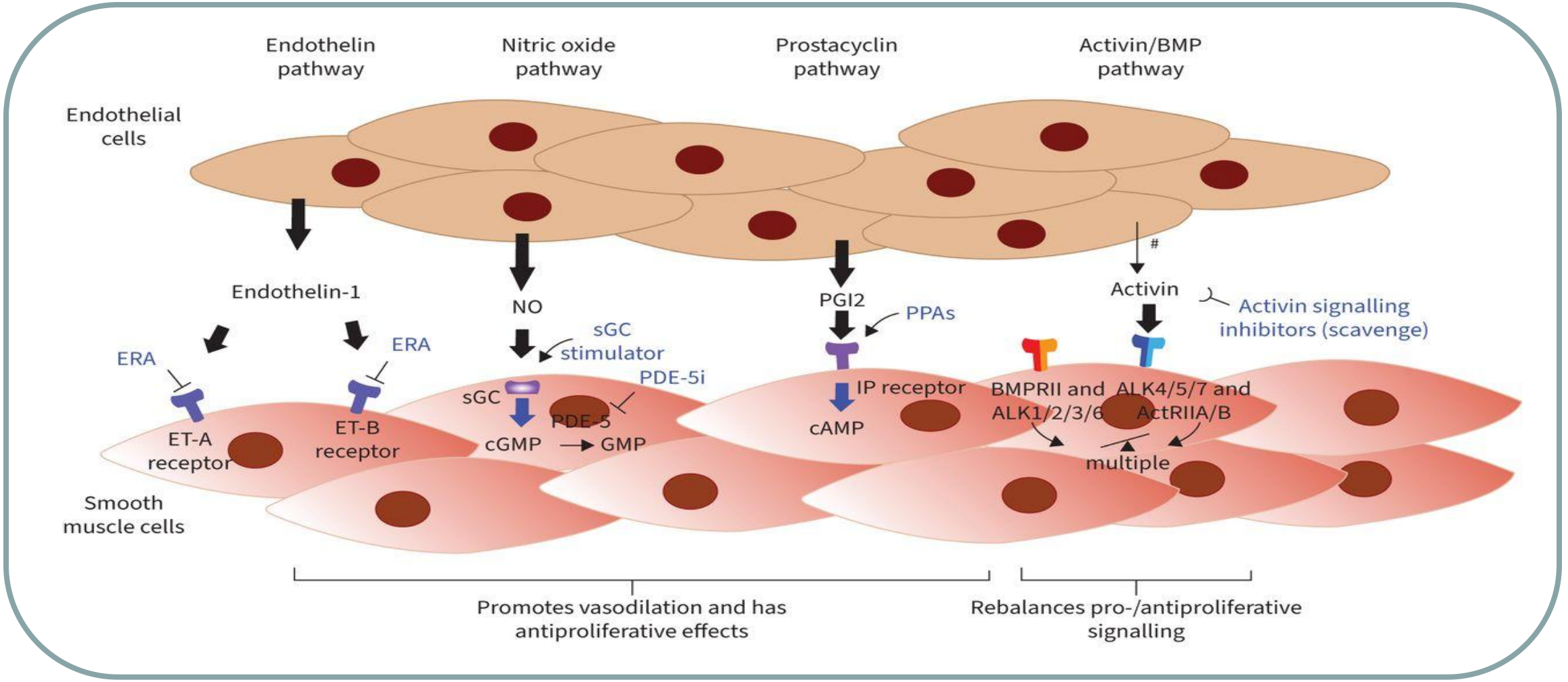
4-pathway drugs for PAH



Chin KM, et al. Eur Respir J 2024; in press: 2401325

Evolving PAH treatment strategy

1995
First Targeted Therapy Approved

Key Drug:
Epoprostenol (IV)

Milestone:
Marked the transition from a hopeless prognosis (<3 years of survival) to a manageable disease.

Mechanism:
Acted as a potent vasodilator via the prostacyclin pathway, significantly improving survival rates despite requiring a continuous injection setup.

2001–2005
First Oral Therapy Era

Key Drugs:
- Bosentan (2001, first oral ERA)
- Sildenafil (2005, first PDE5i)

Milestone:
Shifted the treatment paradigm toward patient convenience with the introduction of oral pills.

Clinical Focus:
Maintained vasodilation through oral routes but required alertness regarding potential side effects (e.g., liver function for Bosentan).

2007–2013
Next-Generation Agents

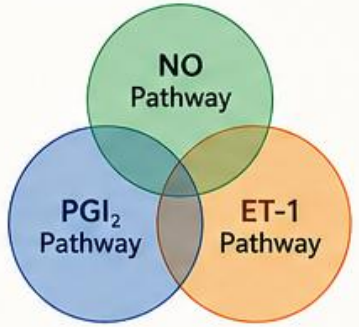
Key Drugs:
- Ambrisentan (2007)
- Macitentan (2013)
- Riociguat (2013)

Milestone:
Optimization of efficacy and safety.

Advancements:
- Introduction of one-a-day dosing (Ambrisentan) and powerful tissue penetration (Macitentan).
- Riociguat expanded treatment to multiple types of pulmonary hypertension (including CTEPH) by directly stimulating the sGC receptor.

2015
Paradigm Shift to Combination Therapy

Key Concept:
Initial Combination Therapy (The AMBITION Trial)



Milestone:
Moving away from **sequential monotherapy.**

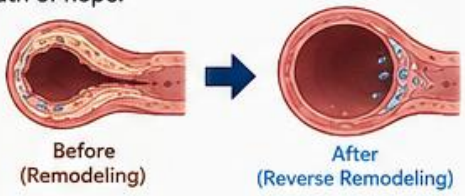
Strategy:
Attacking multiple biological pathways simultaneously (NO, PGI_2, and ET-1) right from the time of diagnosis, which proved to drastically reduce clinical worsening.

2024
The Era of Disease Modification & Reverse Remodeling

Key Drugs:
- Sotatercept (Winrevair)
- Opsynvi (Macitentan/ Tadalafil FDC)

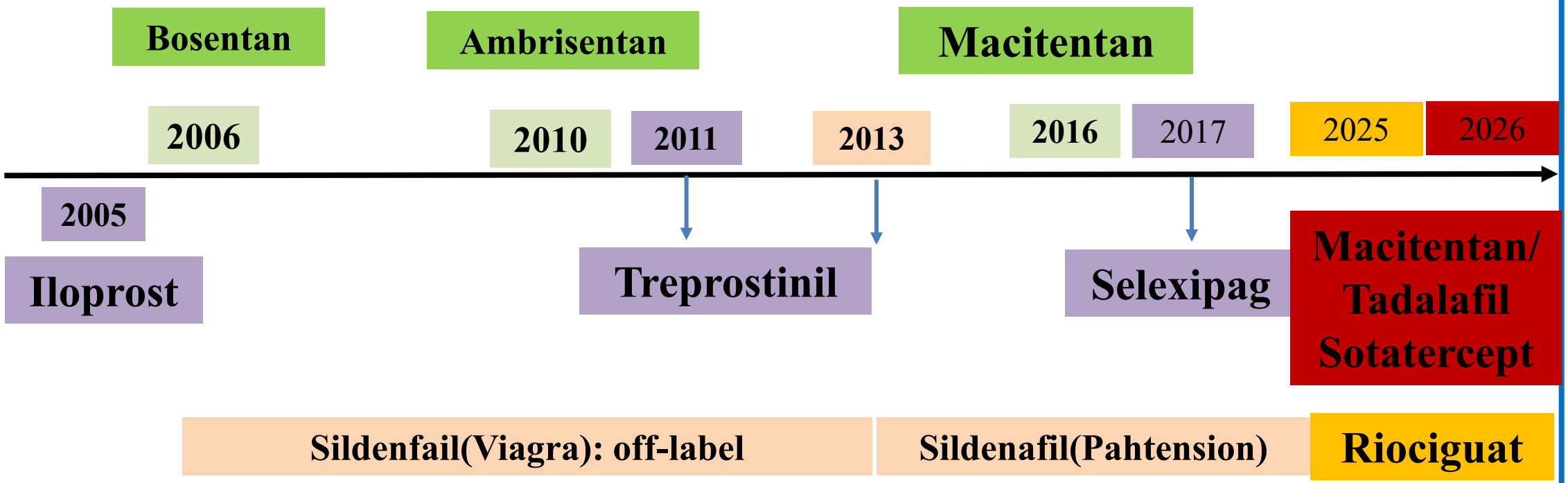
Milestone:
Shifting from just dilating vessels to reversing the disease pathology.

Breakthrough:
Sotatercept actually inhibits the hyperproliferation of vascular cells, effectively **reversing** vascular remodeling and offering a new path of hope.

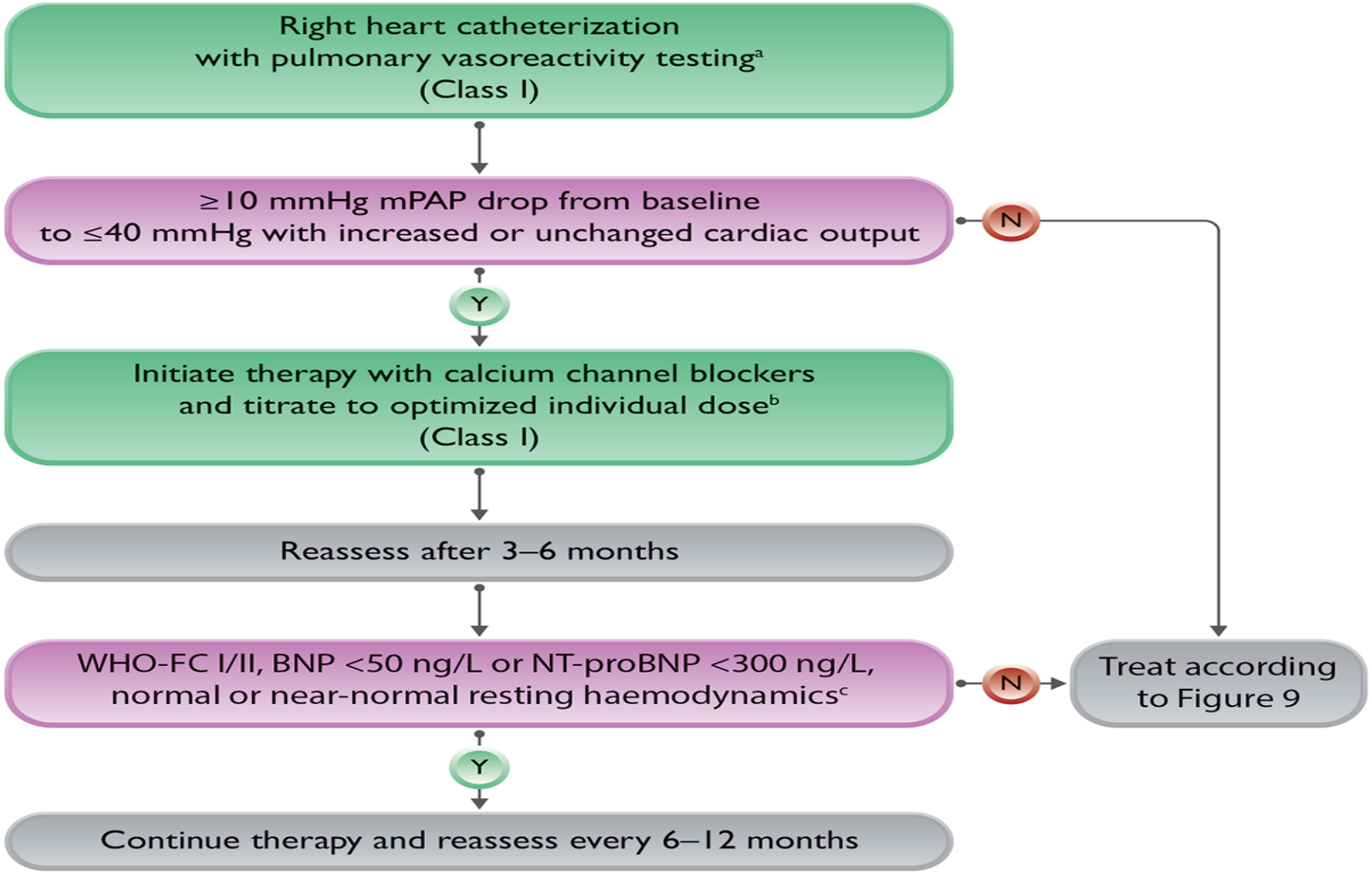


Concurrently, Opsynvi maximized **convenience** as a **Fixed-Dose** Combination (FDC) pill for dual-pathway therapy.

국내 폐동맥고혈압 표적치료제



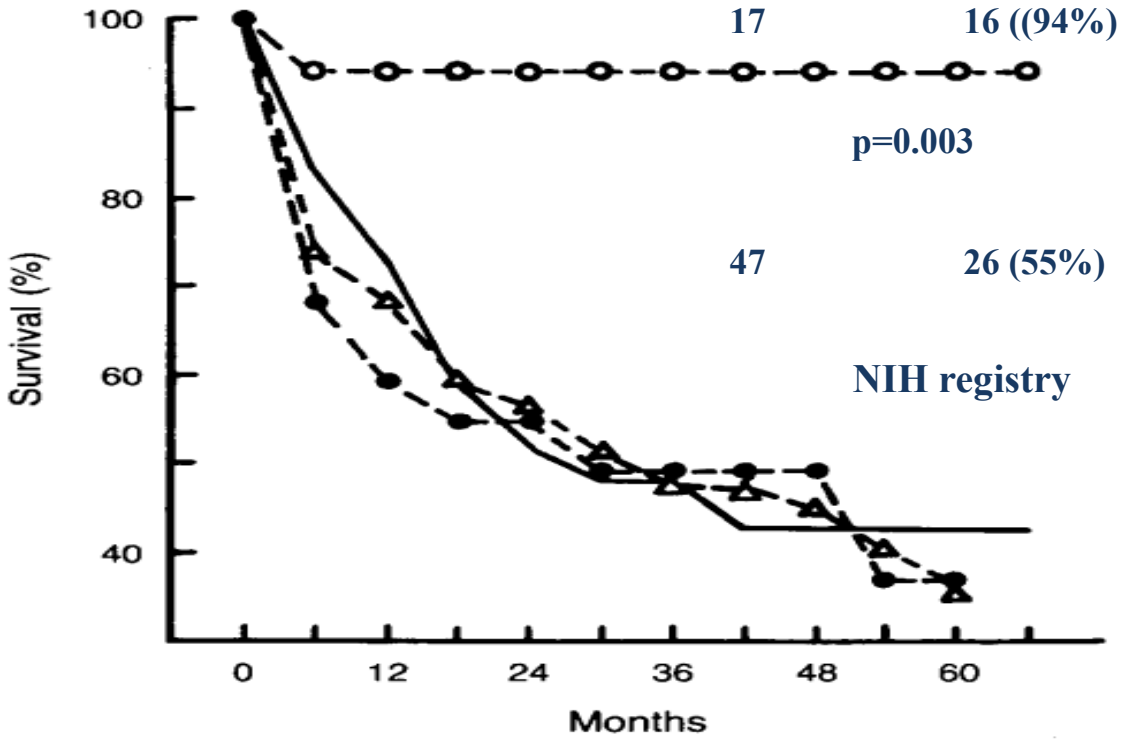
Vasoreactivity testing algorithm in patients with I/H/D-PAH



ESC ERS

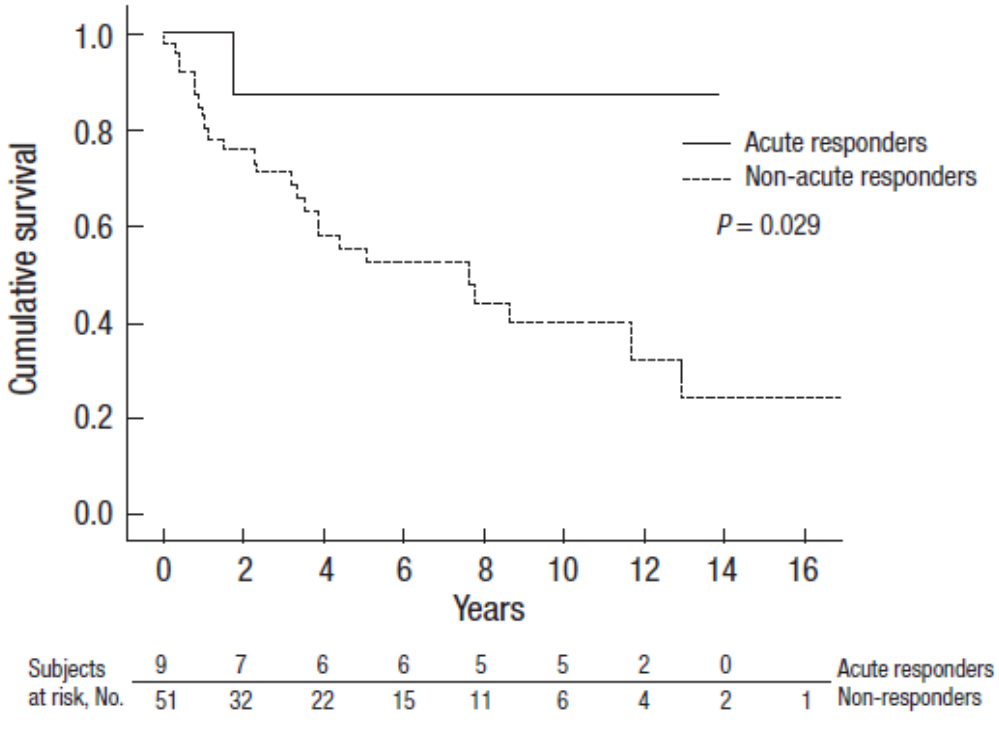
Calcium channel blockers on survival in PPH

64 patients with PPH



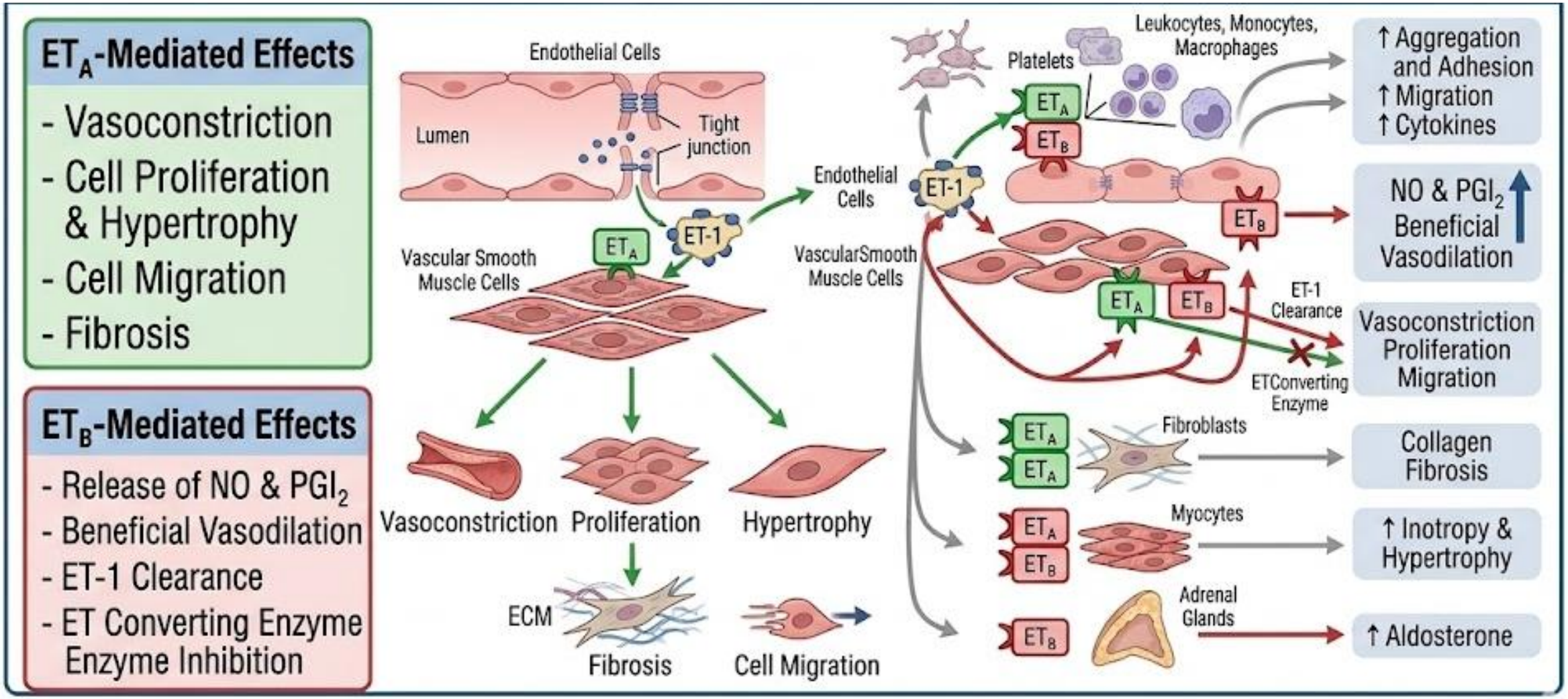
Rich et al. N Engl J Med 1992;327:76-81

60 patients with PPH in AMC



Ahh JH et al. Korean Med Sci 2014; 29: 1665-1671

Effects of endothelin



bosentan vs ambrisentan

	Bosentan	Ambrisentan
FC label indication	II/III/IV	II/III
Receptor selectivity	Dual (E_TA and E_TB)	Selective (E_TA)
Metabolism	Hepatic via **CYP2C9** and **CYP3A4**	Hepatic via **CYP3A4**, **CYP2C19**, and UGTs
Drug interaction	**High** **Significantly decreases levels of Sildenafil, Warfarin**	**Low** **No interaction with sildenafil or warfarin**
Hepatotoxicity	**High (10%)**	**Low (2%)**
Peripheral edema	**moderate**	**High**
Hb decrease	+	+

Macitentan: Dual ERA

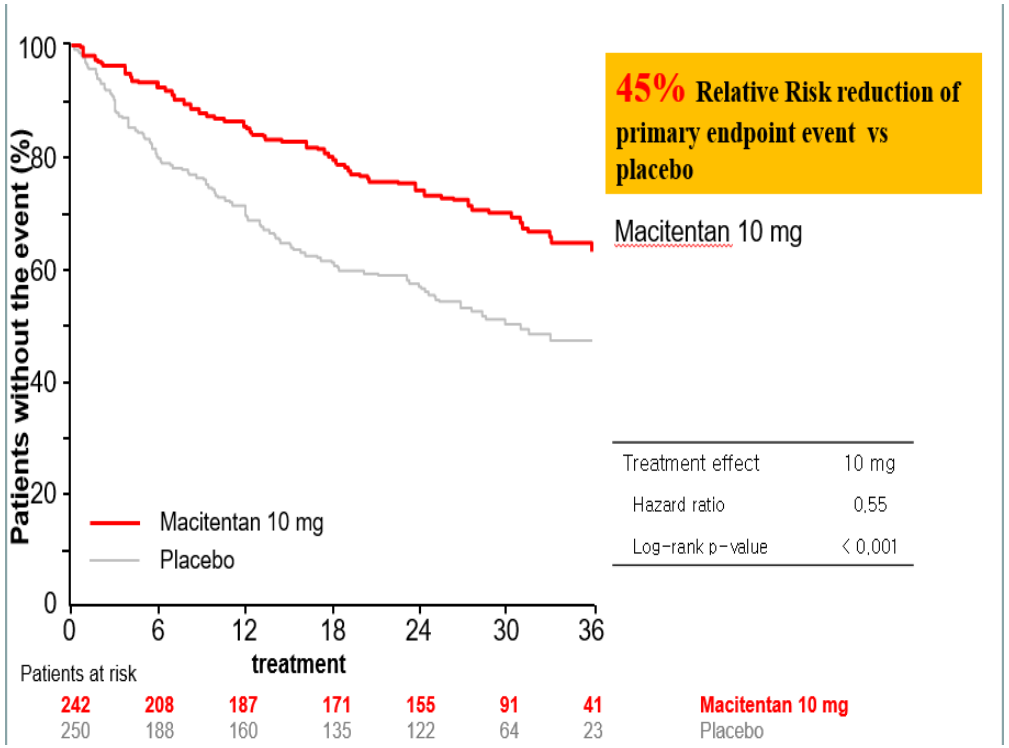
Bosentan Macitentan

- **Optimized physicochemical properties to achieve high affinity for tissue targeting**
- **Enhanced pharmacological activity, longer-lasting receptor occupancy**
- **Higher efficacy compared with other ERAs**
- **Safety profile for liver toxicity**

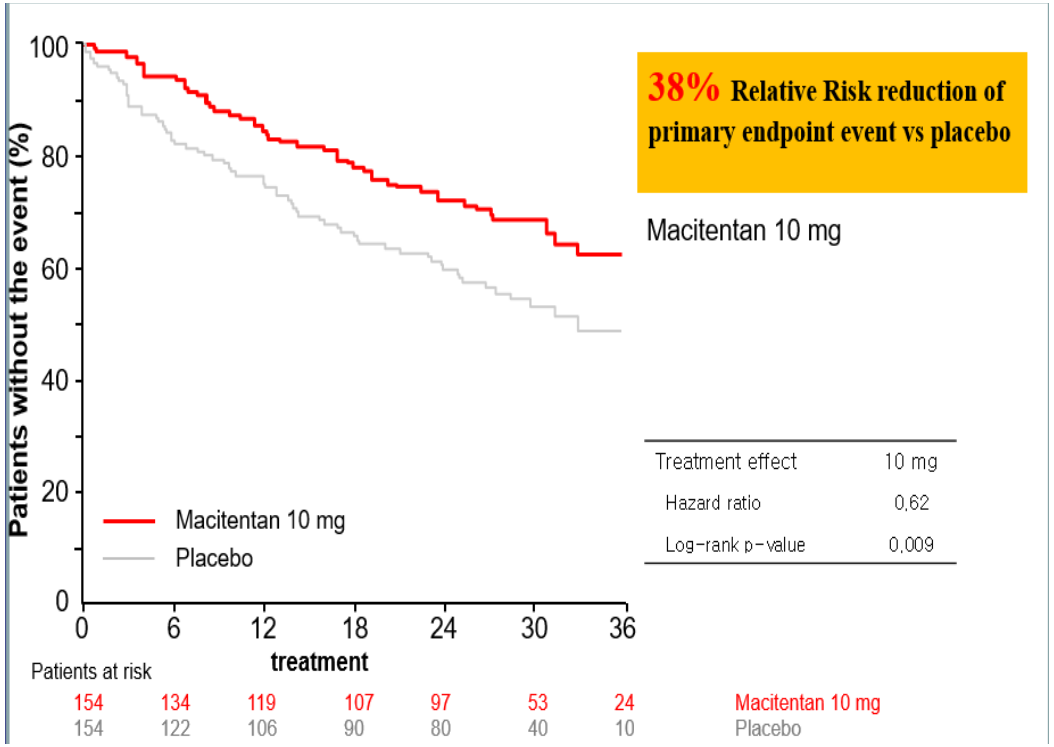
[2]J Pharmacol Exp Ther 2008;327:736–745 [3]PLoS ONE 2012;7(10):e47662;
[4]Am J Respir Crit Care Med 183;2011:A6445; [5]Eur Respir J 2012;717s P3903-P3906
[6]Curr Opin Investig Drugs 2010;11(9):1066-73; [7]AAPS J 2012;14:68-78

Sequential combination therapy : macitentan to PDE5i

All patients



Patients with background Therapy



N Engl J Med 2013;369:809-18

Initial (Upfront) combination therapy: Ambrisentan+Tadalafil

STUDY DESIGN

Study Type
Phase 3, Randomized, Double-blind, Parallel-group, Event-driven

Objective
To evaluate whether initial combination therapy with ambrisentan + tadalafil reduces the risk of clinical failure compared with monotherapy in PAH

Population
Adults with WHO Group 1 PAH
WHO Functional Class II–III
Background therapy: treatment-naïve or ≤ 3 months of single therapy allowed

Patients (N) 500 patients randomized

Arms (1:1:1)

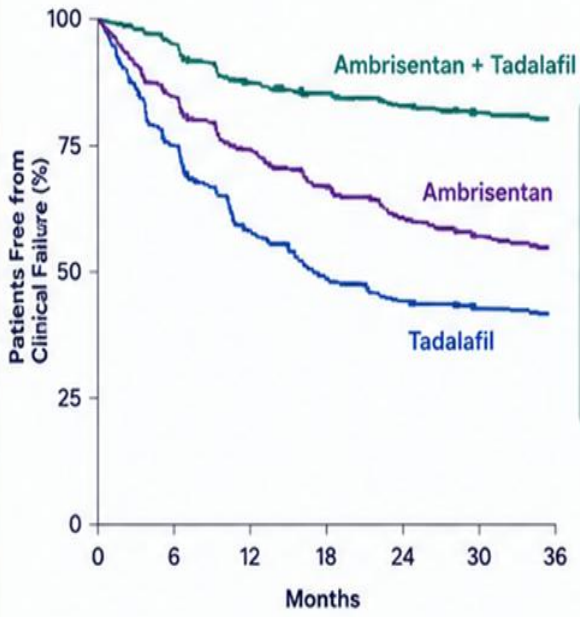
Ambrisentan + Tadalafil (Combination) n=166	Ambrisentan (Monotherapy) n=167	Tadalafil (Monotherapy) n=167

Ambrisentan 10 mg once daily
Tadalafil 40 mg once daily

Duration (Event-driven) Median follow-up: 2.0 years

PRIMARY ENDPOINT RESULT

Time to First Clinical Failure Event
(Composite Endpoint)



50%
Risk Reduction vs Monotherapy
(HR 0.50)
P < 0.001

Upfront combination therapy with ambrisentan + tadalafil significantly reduced the risk of clinical failure by 50% compared with either monotherapy.

KEY SECONDARY OUTCOMES

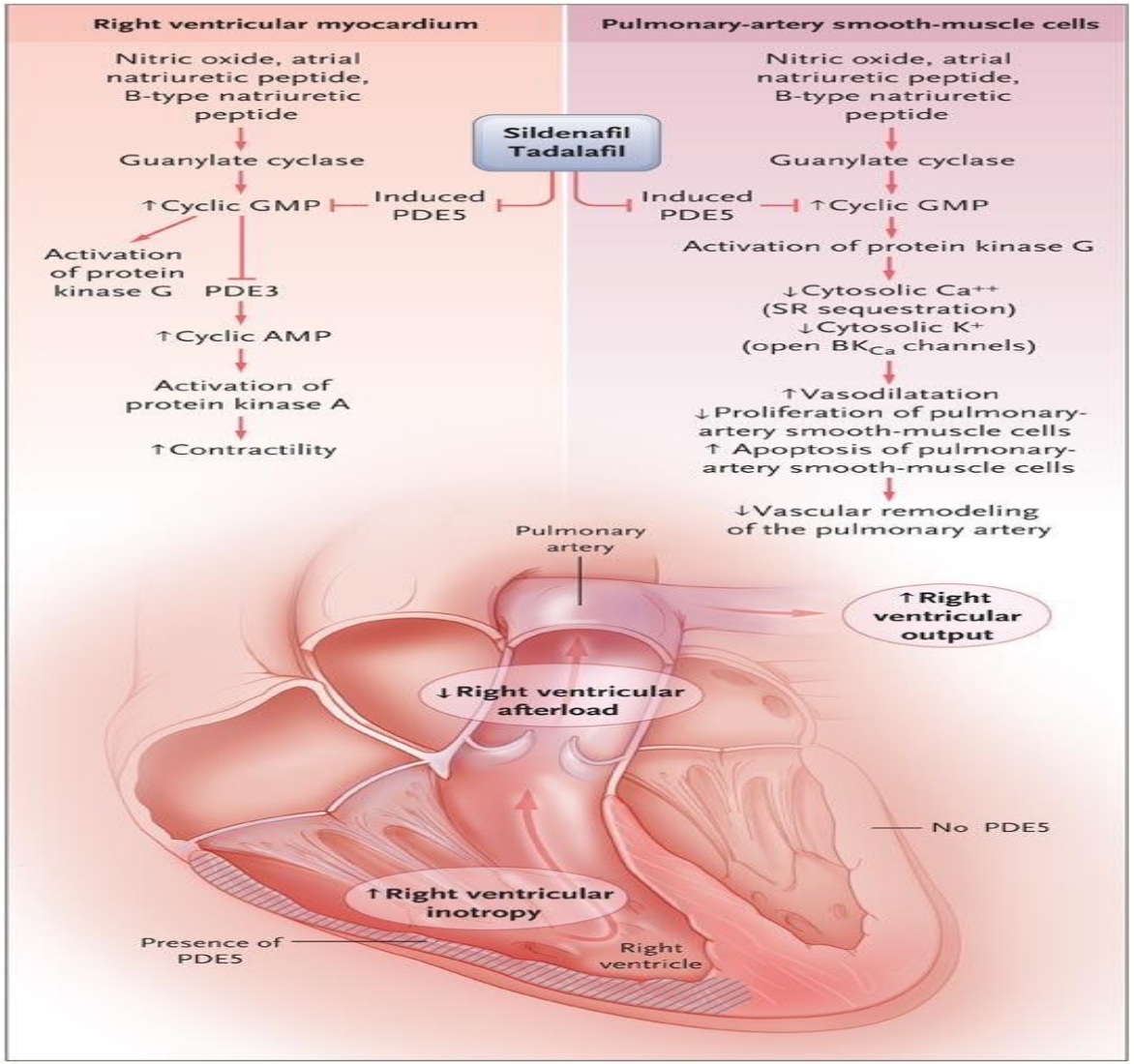
	Ambrisentan + Tadalafil vs Monotherapy	
6-Minute Walk Distance (6MWD)	+32.6 m (vs Ambrisentan) P = 0.002	+36.1 m (vs Tadalafil) P < 0.001
Pulmonary Vascular Resistance (PVR)	Greater reduction vs both monotherapies P < 0.001	
NT-proBNP	Greater reduction vs both monotherapies P < 0.001	
WHO Functional Class	Greater improvement vs both monotherapies P < 0.001	
Time to PAH Hospitalization	Reduced vs both monotherapies P < 0.001	
REVEAL 2.0 Risk Score	Greater improvement vs both monotherapies P < 0.001	

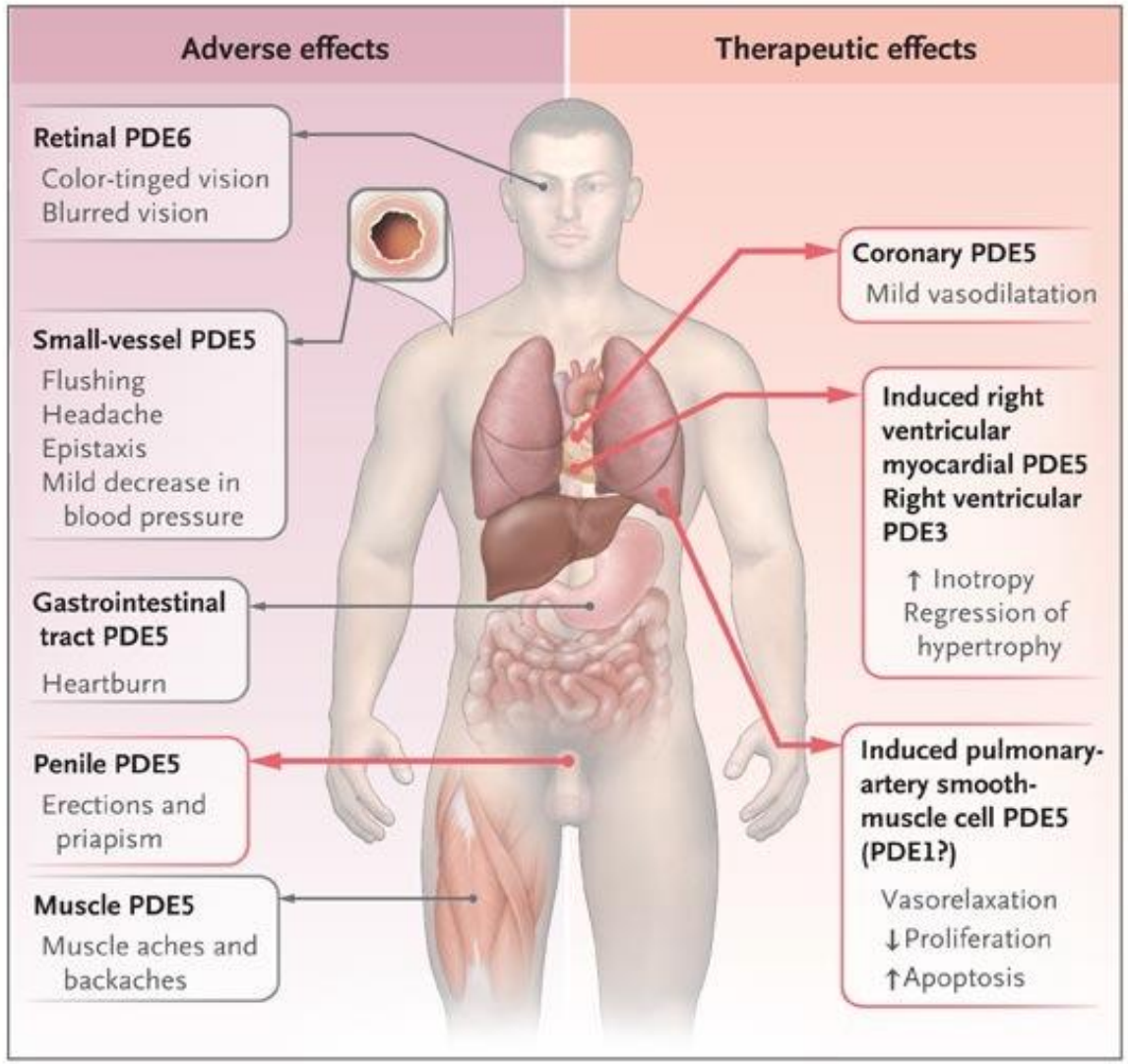
KEY TAKE-HOME MESSAGE

✓ Upfront dual oral combination therapy with ambrisentan + tadalafil significantly improved outcomes across multiple domains.

Galie N et al. N Engl J Med 2015;373:834-44

Phosphodiesterase (PDE)-5 Inhibitors for PAH

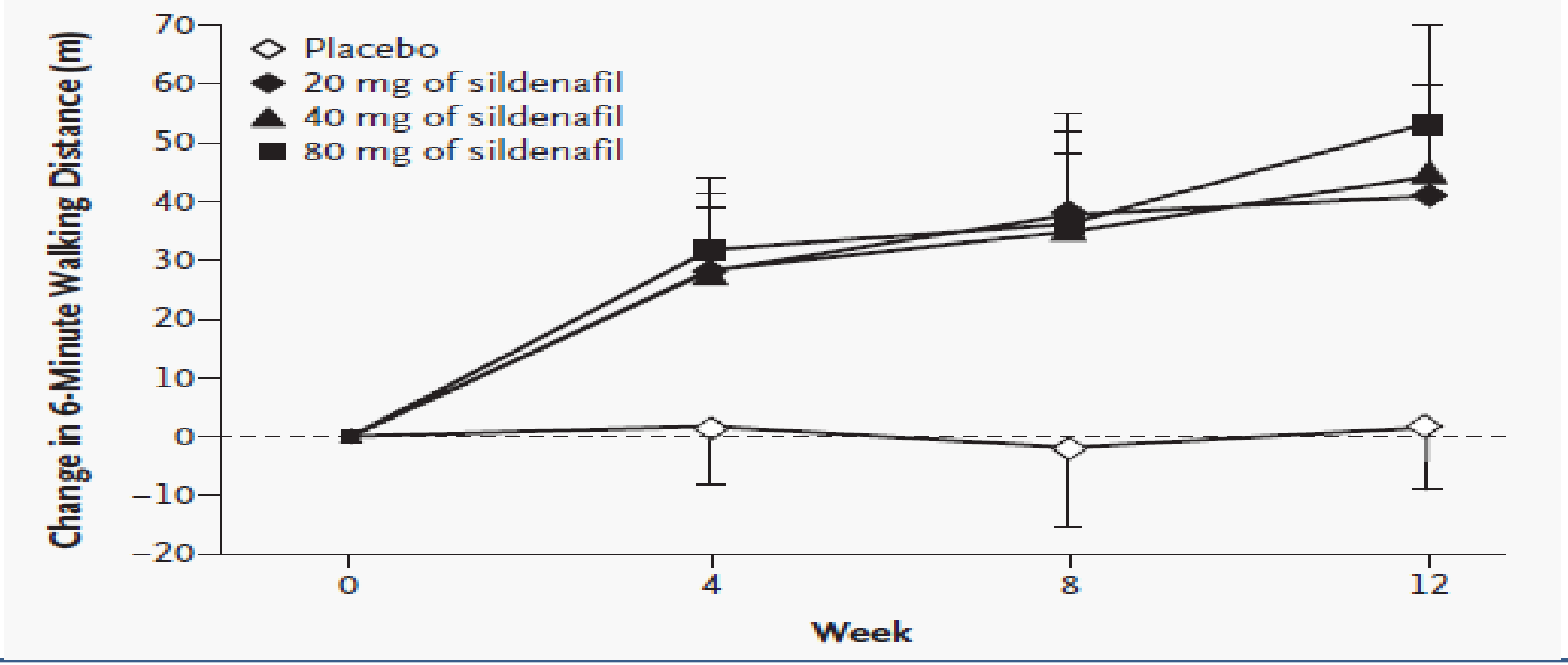




Archer SL, et al. N Engl J Med 2009;361:1864-71

Sildenafil for PAH: SUPER study

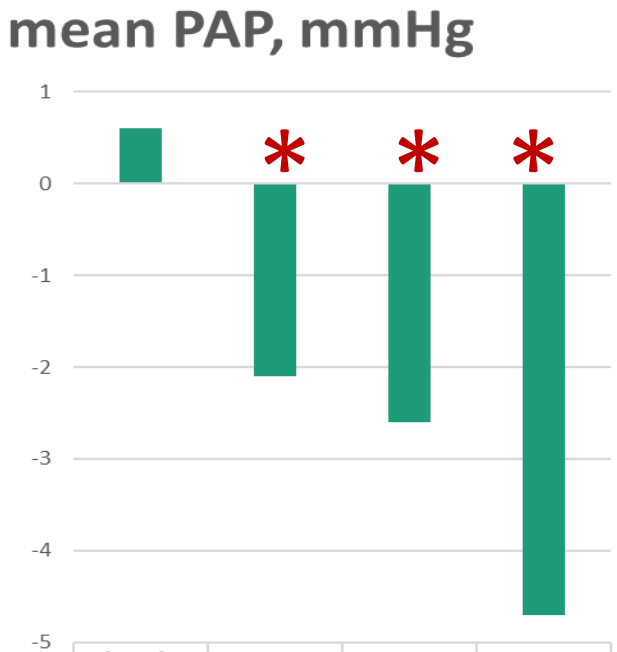
- **12 week, double-blind,** prospective, randomized, multicenter trial
- **PAH(IPAH 63%, CTD-PAH 30%, CHD-PAH 7%), FC II (39%), III (58%)**



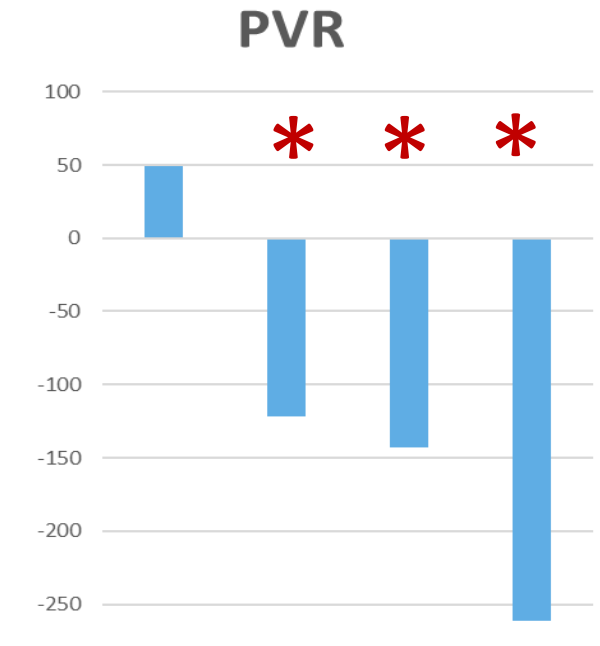
50
46
45

Galie N, et al. N Engl J Med 2005;353:2148-57.

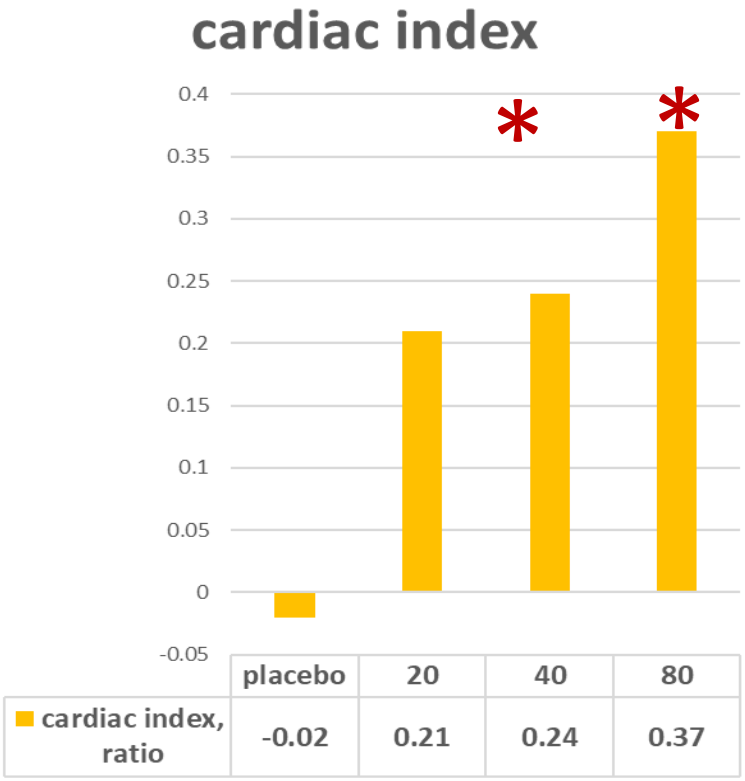
Sildenafil for PAH: SUPER study



	placebo	20	40	80
mean PAP, mmHg	0.6	-2.1	-2.6	-4.7



	placebo	20	40	80
PVR	49	-122	-143	-261

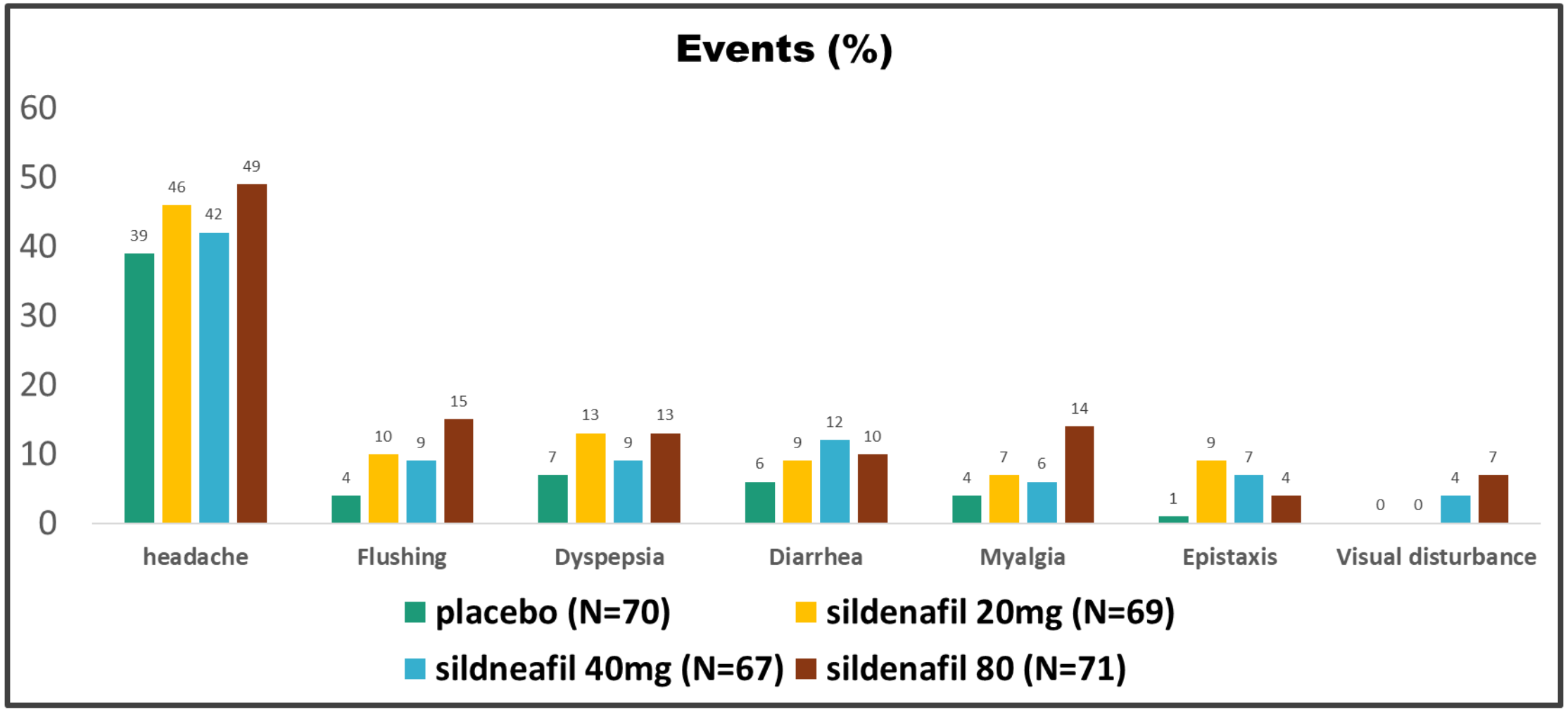


	placebo	20	40	80
cardiac index, ratio	-0.02	0.21	0.24	0.37

US FDA recommend 20 mg TID, and **allows dose titration up to 80 mg TID, if needed**.

Galie N, et al. N Engl J Med 2005;353:2148-57.

Adverse event: SUPER study

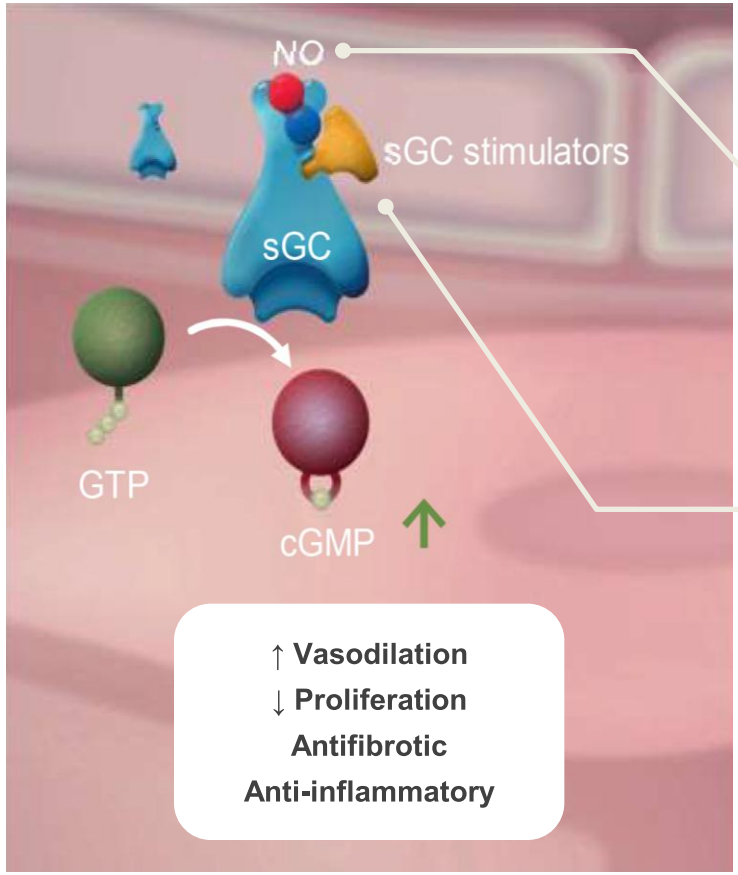


Galie N, et al. N Engl J Med 2005;353:2148-57.

Riociguat: sGC stimulator

sGC stimulators target the NO-sGC-cGMP pathway

sGC STIMULATORS



1 **Riociguat sensitizes sGC to any NO that is present in the cells, by stabilizing the NO-sGC binding**

2 **Independently of NO, Riociguat stimulates sGC directly to produce cGMP**

cGMP, cyclic guanosine monophosphate; **GTP,** guanosine triphosphate; **NO,** nitric oxide; **PDE5,** phosphodiesterase 5; **sGC,** soluble guanylate cyclase

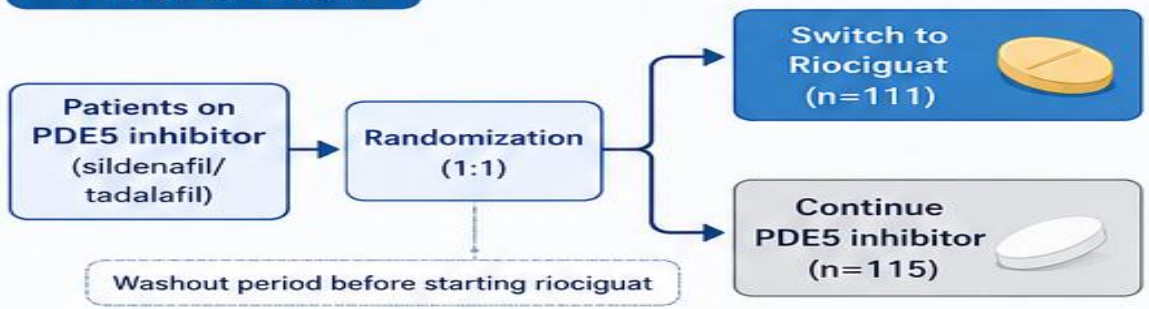
References 1. Stasch JP, Evgenov OV. Handbook of Experimental Pharmacology: Pharmacotherapy of Pulmonary Hypertension. Springer-Verlag, 2013 **2.** Evgenov OV et al. *BMC Pharmacol.* 2011;11(Suppl 1):O9 **3.** Lang M et al. *PLoS One.* 2012;7:e43433 **4.** Hoeper MM et al. *Eur Respir J.* 2017;50:1602425

Riociguat replacing PDE5 inhibitor

STUDY POPULATION

- Adults with PAH (WHO Group 1)
- WHO Functional Class III
- Intermediate-risk status
- On stable PDE5 inhibitor (sildenafil or tadalafil)
- Inadequate clinical response
- Background ERA therapy allowed (bosentan, ambrisentan, macitentan)

STUDY DESIGN



ERA = Endothelin Receptor Antagonist

PRIMARY ENDPOINT (24 Weeks)

Clinical Improvement WITHOUT Clinical Worsening

Achieve ≥2 of the following AND no clinical worsening

≥10% increase in 6MWD

+

≥30% reduction in NT-proBNP

+

Improvement in WHO Functional Class

AND

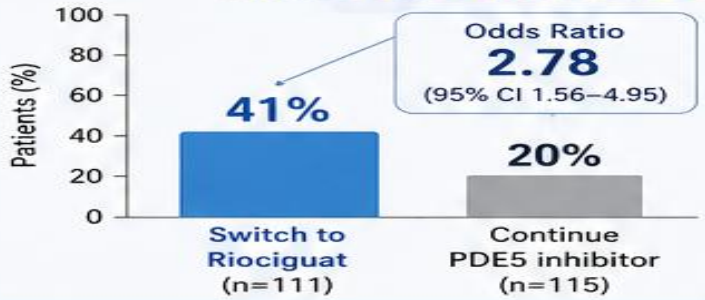
No clinical worsening

CLINICAL WORSENING

- Death
- Lung transplantation
- Hospitalization for PAH
- ≥15% decrease in 6MWD
- Need for parenteral prostacyclin or escalation of PAH therapy

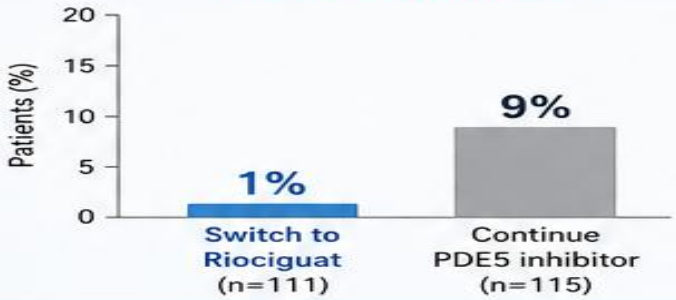
KEY RESULTS

PRIMARY ENDPOINT ACHIEVED



More than **2 times** greater likelihood of clinical improvement

CLINICAL WORSENING



89% relative **reduction** in clinical worsening

Hoeper MM, et al. Lancet Respir Med2021 ;9(6):573-584

Adverse events: riociguat vs PDE5i

Event (%)	Riociguat (n=111)	PED5i (n=114)
Hypotension*	**14%**	**5%**
Headache	**13%**	**7%**
Dyspepsia	**9%**	**0**
Gastroesophageal reflux disease	**7%**	**1%**
Any severe AE	9%	11%
Any serious adverse event	7%	17%
Adverse events leading to death	0	3%

Hoeper MM, et al. Lancet Respir Med2021 ;9(6):573-584

Macitentan/Tadalafil single-table dual combination therapy

STUDY DESIGN (A DUE Trial)

Phase 3, Randomized, Double-blind, Active-controlled

Primary Endpoint
Change in Pulmonary Vascular Resistance (PVR) at Week 16

Population
Adults with WHO Functional Class II–III PAH

Patients (N) 187

Duration 16 weeks

Arms (1:1:1)

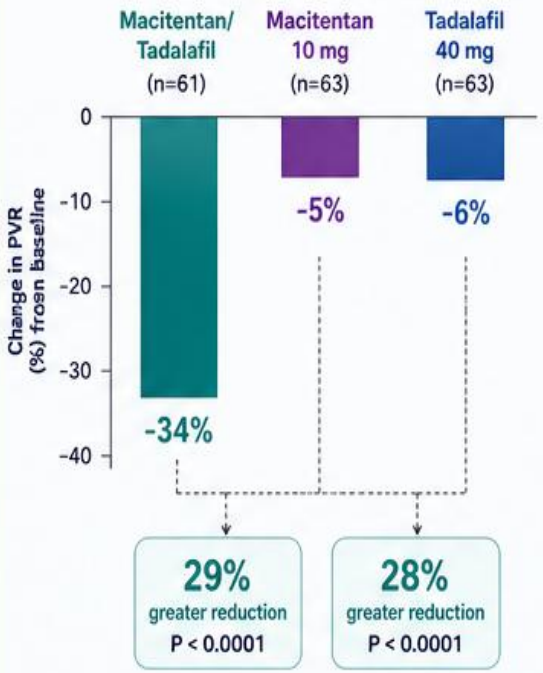
Macitentan/ Tadalafil	Macitentan	Tadalafil
10 mg / 40 mg Once daily (single-tablet)	10 mg Once daily	40 mg Once daily

PRIMARY ENDPOINT MET
Superior PVR reduction vs either monotherapy

EFFICACY RESULTS (Week 16)

Primary Endpoint: Change in PVR

Greater reduction with combination therapy vs either monotherapy



Key Secondary Outcomes

Exercise Capacity (6-Minute Walk Distance)	↑ Improved
NT-proBNP	↓ Reduced
Clinical Risk Profile (incl. WHO FC, risk score)	↑ Improved
Time to Clinical Worsening (exploratory)	↑ Favorable trend

Overall Conclusion
Macitentan/tadalafil single-tablet combination was superior to either monotherapy as initial dual therapy in PAH

SAFETY – ADVERSE EVENTS

Most Common Adverse Events (Combination Arm)	Incidence
Peripheral edema / fluid retention	21%
Anemia	19%
Headache	18%
Abdominal pain	7%
Hypotension	7%
Myalgia	6%
Nasopharyngitis	6%
Nausea	6%
Uterine bleeding	5%
Back pain	5%
Flushing	4%
Palpitations	4%
Epistaxis (nosebleed)	3%

Serious Adverse Events

- SAEs occurred more frequently than with monotherapy
- Treatment discontinuation due to AEs: 8–10%
- Major safety concerns: Anemia, edema, hypotension
- No new safety signals identified
- Overall tolerability acceptable and consistent with individual components

Pharmacologic properties of prostacyclins

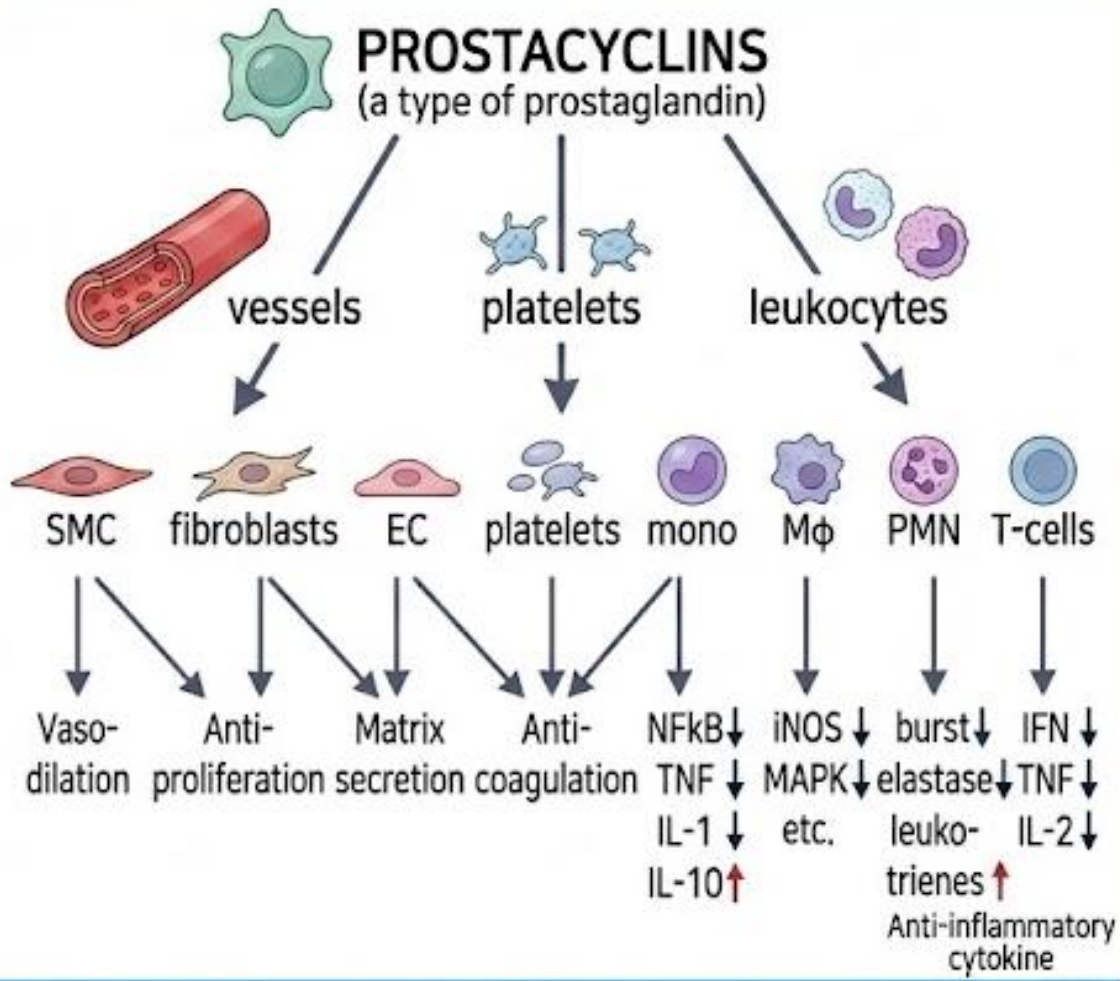
Potent Vasodilator
- 강력한 혈관 확장 효과

Anti-platelet effect
- 항혈소판 효과 (혈전 형성 억제)

Anti-proliferative
- 세포 증식 억제 효과

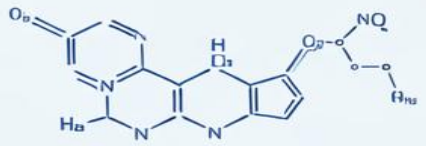
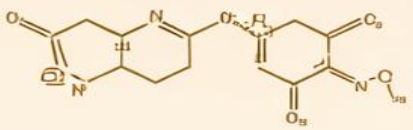
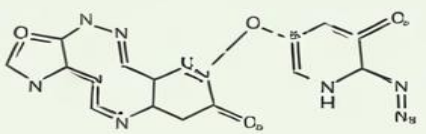
Anti-inflammatory
- 항염증 효과

Inotropic effect
- 심근 수축력 강화 효과

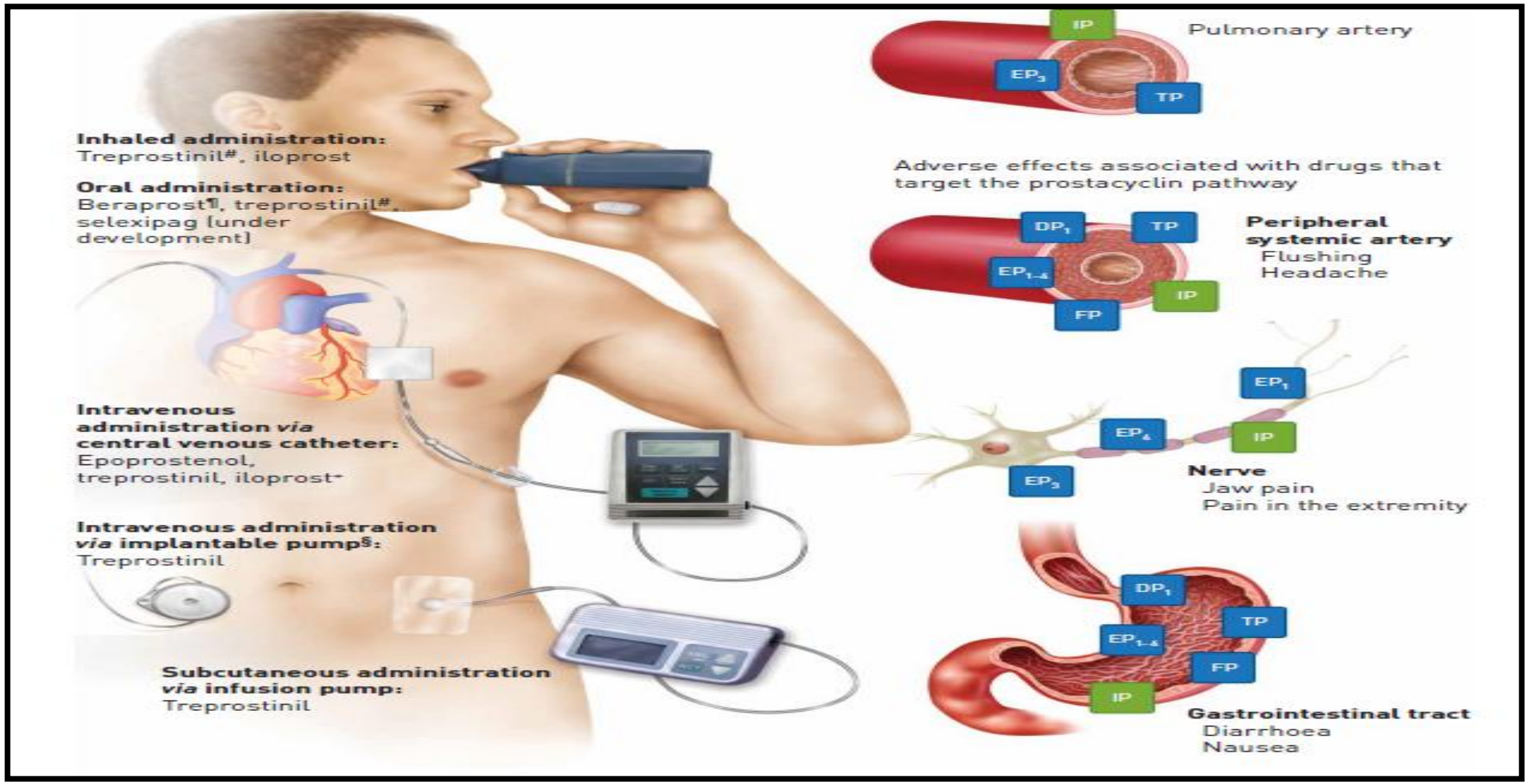


Source: Olszewski H et al., J Lab Clin Med 2001; 138: 287-297

Prostacyclin pathway Agents (PPAs)

	Epoprostenol	Treprostinil	Iloprost
Pharmacologic nature			
Half-life	Synthetic form identical to endogenous PGI_2	Chemically stable PGI_2 derivative	Chemically stable PGI_2 analogue
Half-life	**Very short** (<6 minutes)	Relatively long (2-4 hours)	Intermediate (20-30 minutes)
Administration	Continuous IV infusion	IV, SC, Inhaled, Oral	Inhaled (nebulizer)
Dosing Frequency	24-hour continuous	Continuous (IV/SC) or 4x/day (Inhaled)	6–9 times daily
Primary Drawbacks	Catheter-related infection; rebound effect if stopped)	Significant injection site pain (with SC delivery)	Frequent admistration burden

Drugs that target the prostacyclin pathway



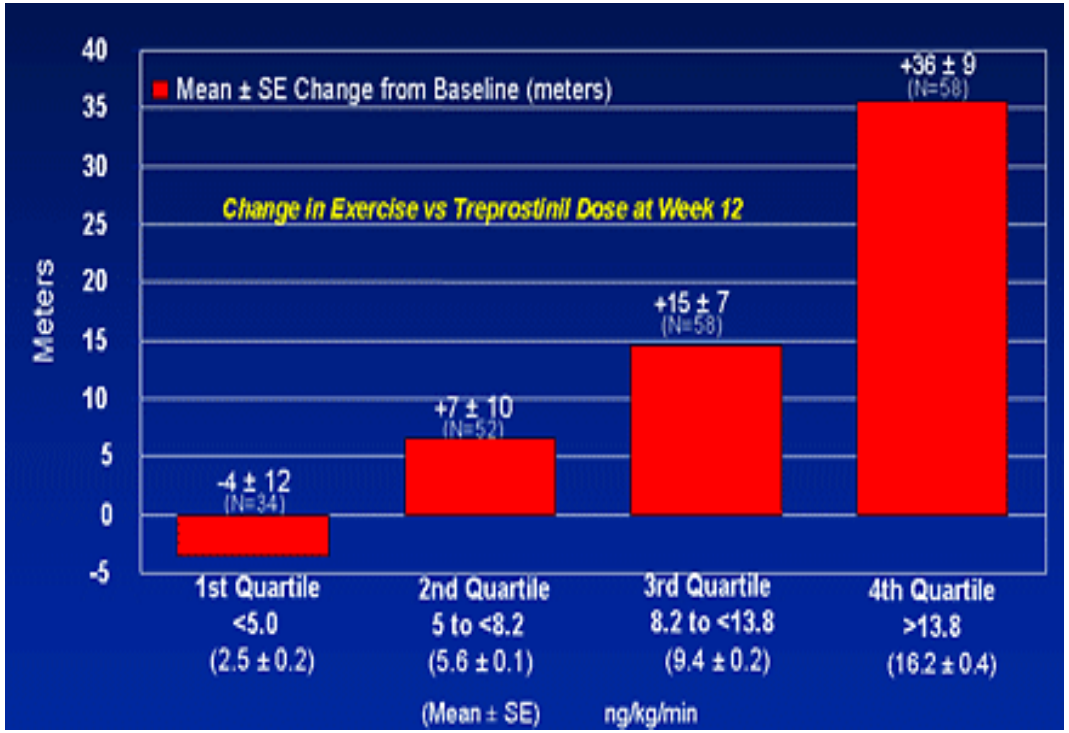
Irene M. Lang & Sean P. Gaine Eur Respir Rev 2015; 24: 630–641

Continuous SC treprositnil in PAH

Inclusion: PPH (134/136), PH with CTD (41/49) or CHD (58/51)
FC II (25/28), III (190/192), IV (18/16)
Design: 12 weeks, double-blind, placebo-controlled multicenter

Exercise capacity
; Δ6MWD 16 m (p=0.006)

Greater in the sicker
and dose-related.



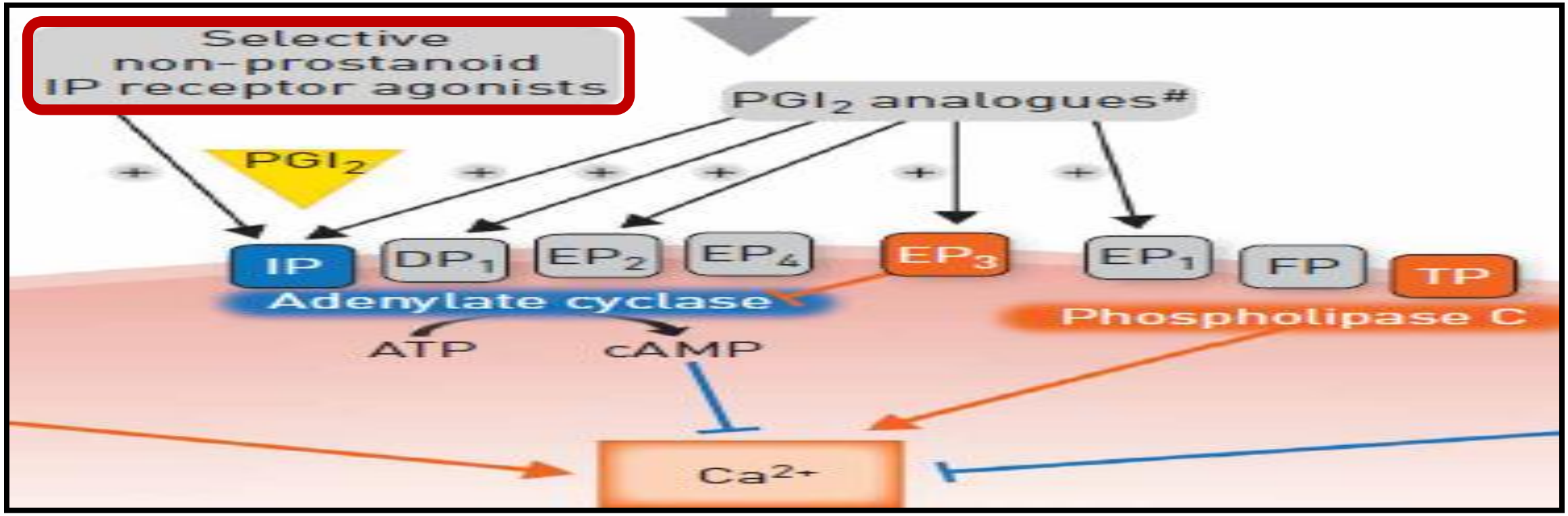
Am J Respir Crit Care Med Vol 2002; 165: 800–804,

Infusion site pain in SC treprostinil

- **Up to 5-23% of patients discontinue due to site pain.**
- Typically reaches an apex 2 to 5 days after starting new infusion site, usually subsides 5 to 7 days.
- Mechanism: vasodilatation and pain stimulation, inflammation

- **Recommendations for reducing site pain**
  - **rapid dose titration**
  - **pretreatment with anti-inflammatory agents**
  - **dry catheter pre-placement**

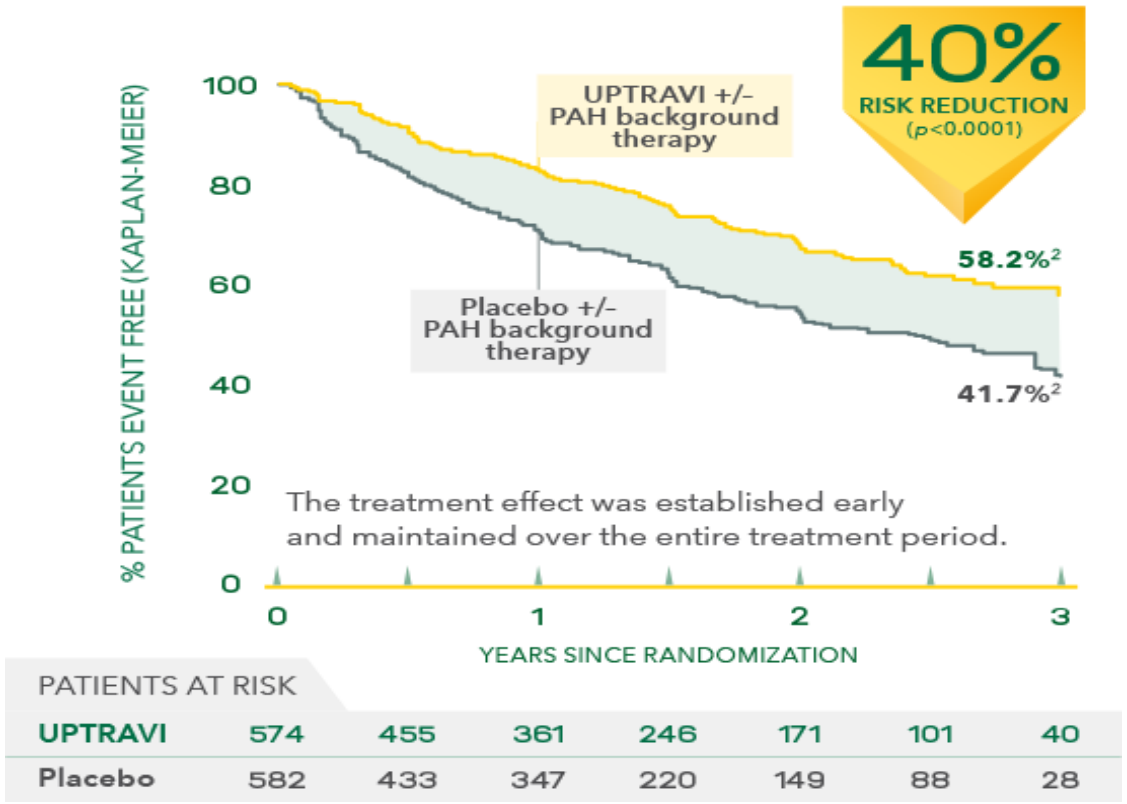
Selexipag : selective IP receptor agonists

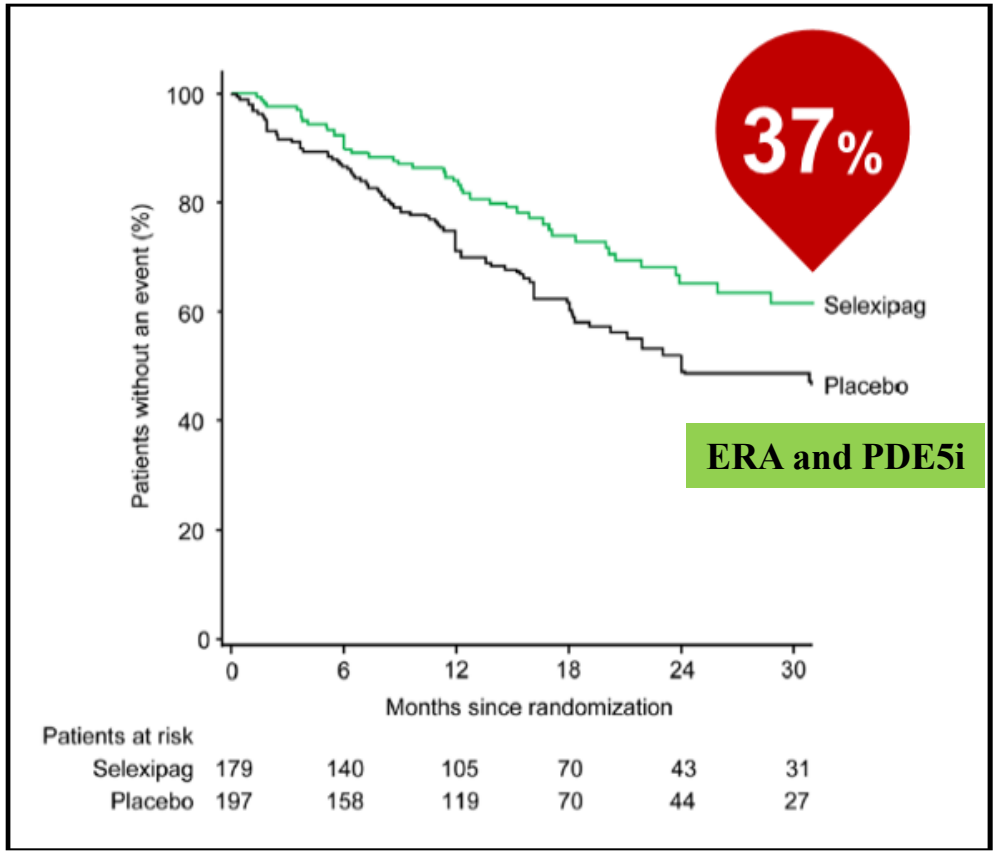


In animal models, selectivity for the IP receptor has been shown to avoid activation of other prostanoid receptor subtypes **(e.g., EP3) which can cause vasoconstriction and gastrointestinal side effects as shown by other prostacyclin analogs** in vitro and in vivo (beraprost, treprostinil, iloprost)

Sitbon O, et al N Engl J Med 2015;373:2522-2533

Triple combination therapy: selexipag to ERA and PDE5i

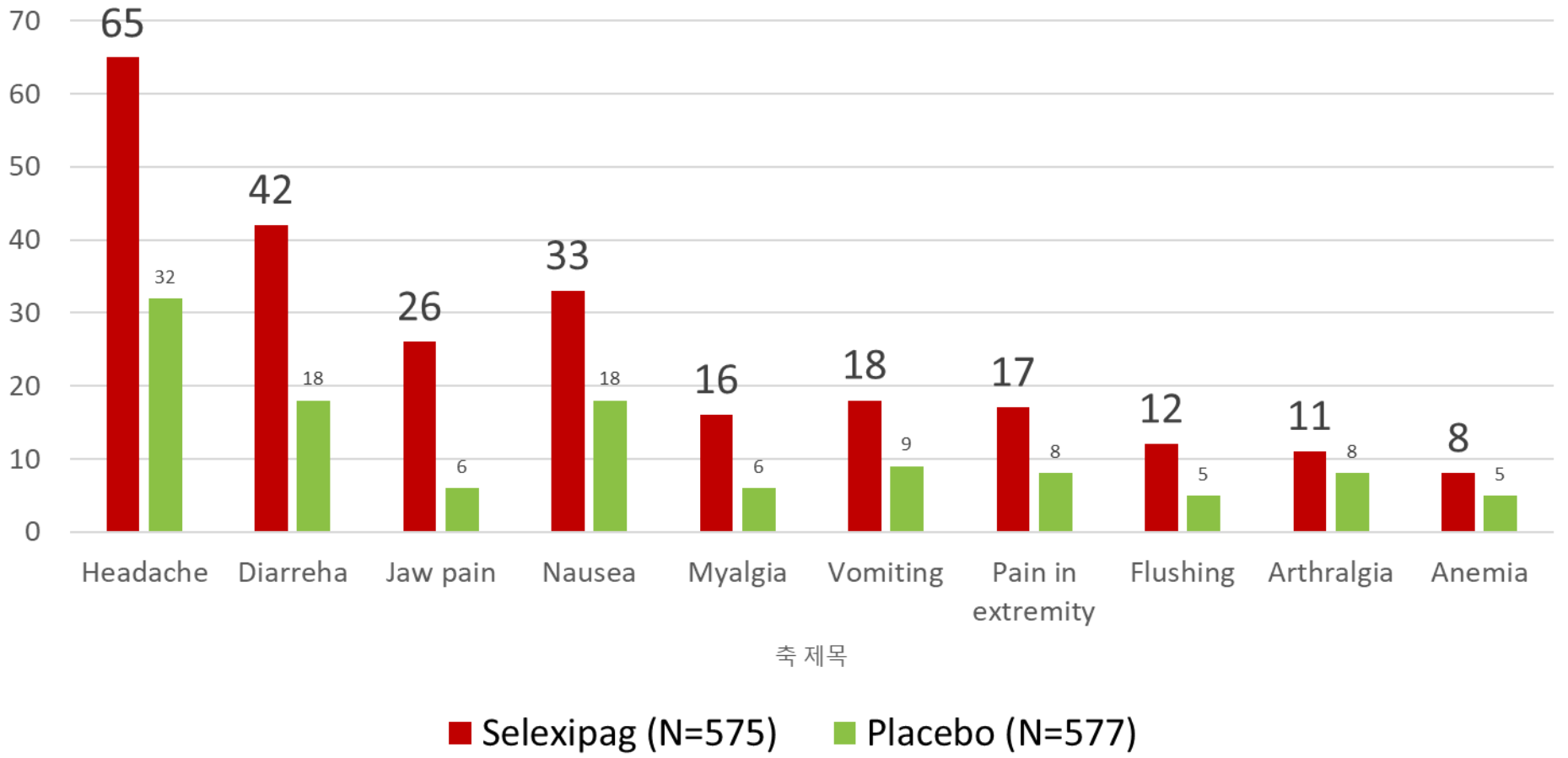




Sitbon O, et al N Engl J Med 2015;373:2522-2533

J. Gerry Coghlan , et al. Am J Cardiovasc Drugs 2018, 18;37-47

Adverse events



Overall, 41 patients (7.1%) in the placebo group and **82 patients (14.3%) in the selexipag group discontinued their study regimen prematurely.**

Sitbon O, et al. N Engl J Med. 2015 Dec 24;373(26):2522-33

Why Consider Upfront Triple Combination Therapy in Intermediate-Risk PAH?

The goal: Achieve and maintain low-risk status early to improve long-term outcomes

1 Limited Success with Initial Oral Dual Therapy

Only **30–40%** of intermediate-risk patients achieve low-risk status with upfront oral combination therapy.

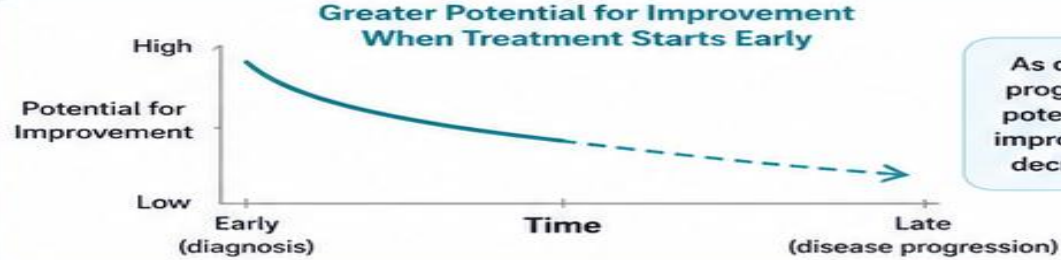
30–40% reach low-risk

60–70% do not reach low-risk

Many patients remain at intermediate or high risk.

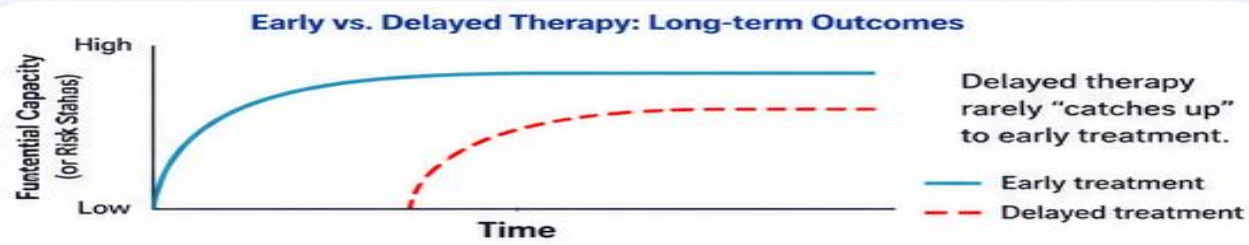
2 Earlier Treatment Works Better

PAH therapies are generally **more effective when initiated early,** before irreversible vascular remodeling develops.



3 Delayed Escalation Loses Opportunity

Patients who receive PAH-targeted therapies later often **do not fully recover the benefits** lost during the delay.

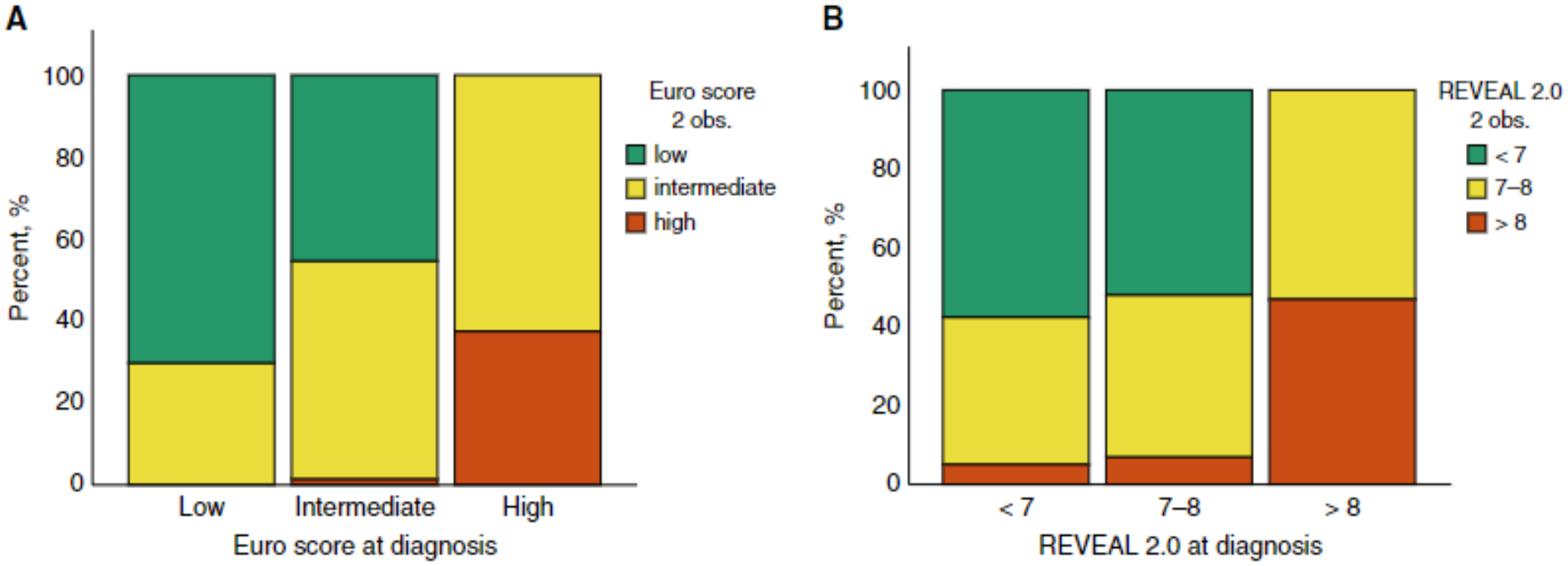


4 Clinical Worsening Carries Prognostic Consequences

Waiting for clinical deterioration before intensifying treatment may expose patients to events associated with **higher mortality risk**.

Risk reduction with initial combination therapy with ERA and PED5-inhibitors

- 181 treatment-naive patients with PAH (81% idiopathic) with a follow-up right heart catheterization at 6 months



Badagliacca R, et al. Am J Respir Crit Care Med 2021; 203 ;484–49

Initial triple versus dual oral combination therapy in PAH

TRITON: Multicenter, double-blind, randomized, placebo-controlled, phase 3b study

Newly diagnosed, treatment-naive patients with pulmonary arterial hypertension (PAH)

n = 123	Macitentan 10 mg o.d.	Tadalafil 40 mg o.d.	Selexipag 200-1,600 µg b.i.d.
n = 124	Macitentan 10 mg o.d.	Tadalafil 40 mg o.d.	Placebo 200-1,600 µg b.i.d.

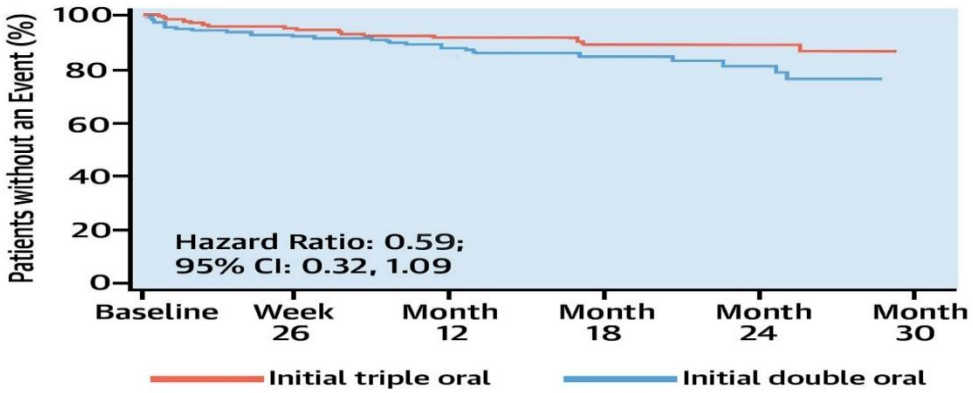
Change from Baseline to Week 26

	Initial triple	Initial double	Treatment effect
Primary Endpoint			
Pulmonary vascular resistance	-54%	-52%	No difference
Secondary Endpoints (Exploratory Analyses)			
6-Minute walk distance	+55 m	+56 m	No difference
NT-proBNP	-74%	-75%	

Time to First Disease Progression Event

Secondary Endpoints (Exploratory Analyses)

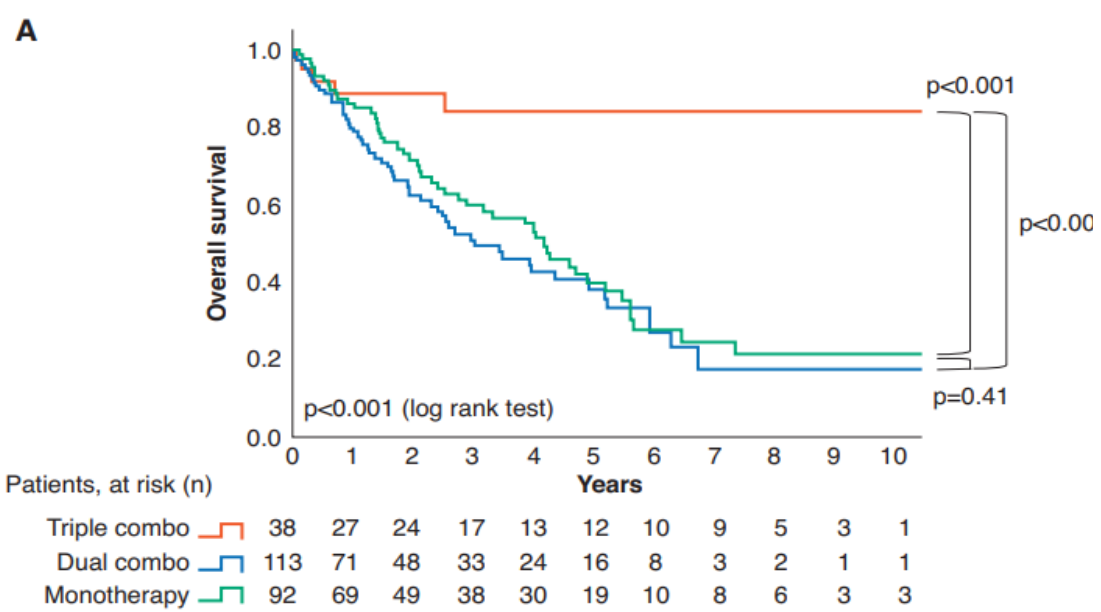
41% reduction in risk of disease progression with initial triple oral vs initial double oral combination therapy



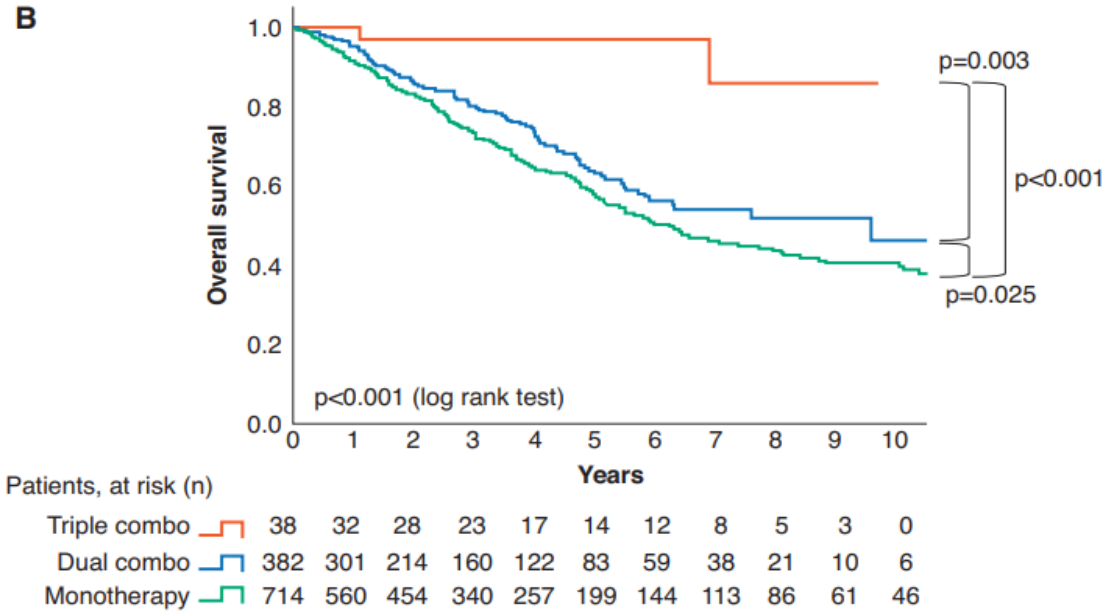
Chin, K.M. et al. J Am Coll Cardiol. 2021;78(14):1393–1403.

Initial triple-combination therapy with parenteral prostacyclin

- A retrospective analysis of incident patients with idiopathic, heritable, or anorexigen-induced PAH enrolled in **the French Pulmonary Hypertension Registry**



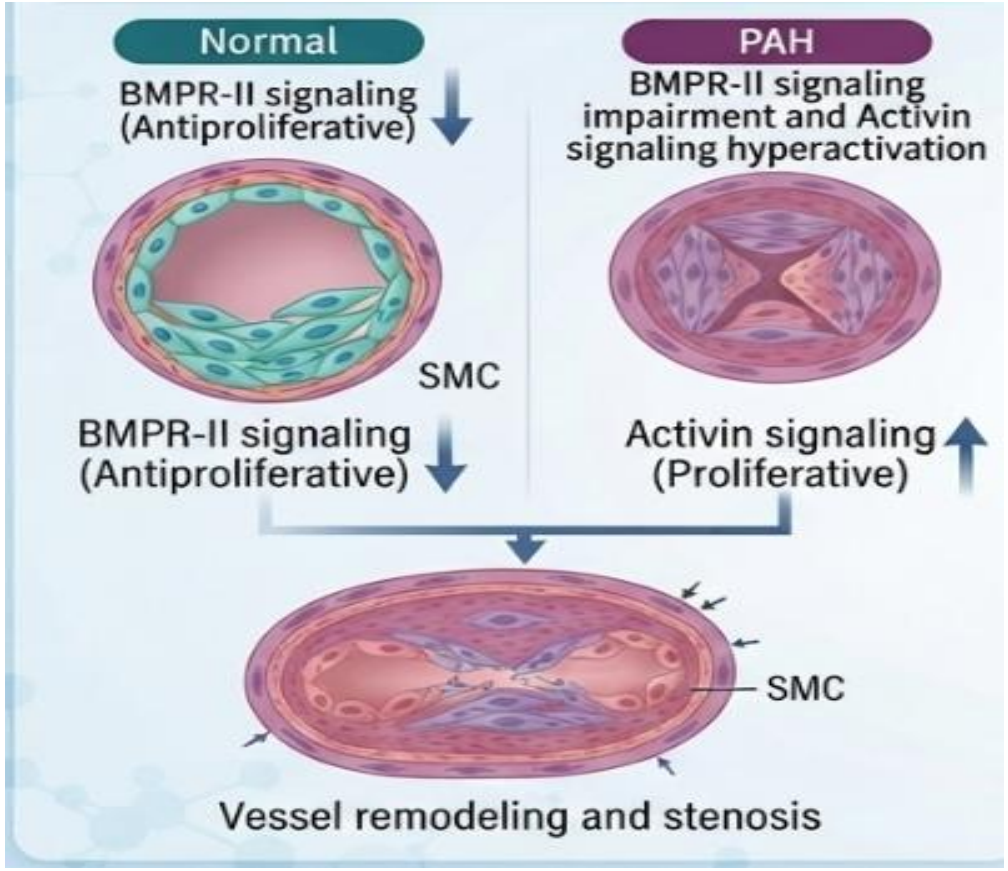
A) Patients with a high-risk status

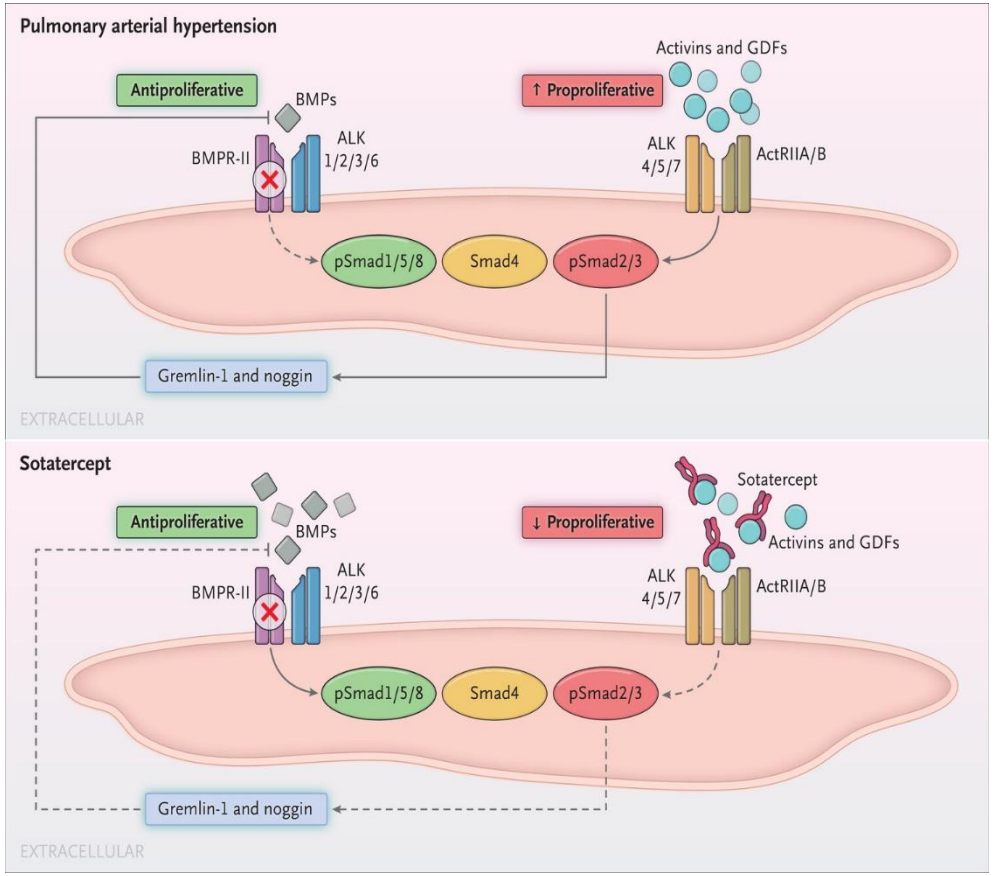


(B) patients with an intermediate-risk status

Boucly A, et al. Am J Respir Crit Care Med. 2021;204-842-54

Sotatercept: a first-in-class activin signaling inhibitor targeting vascular remodeling





Restoring cellular rebalancing and reverse remodeling

Humbert M, et al. N Engl J Med 2021;384:1204–1215

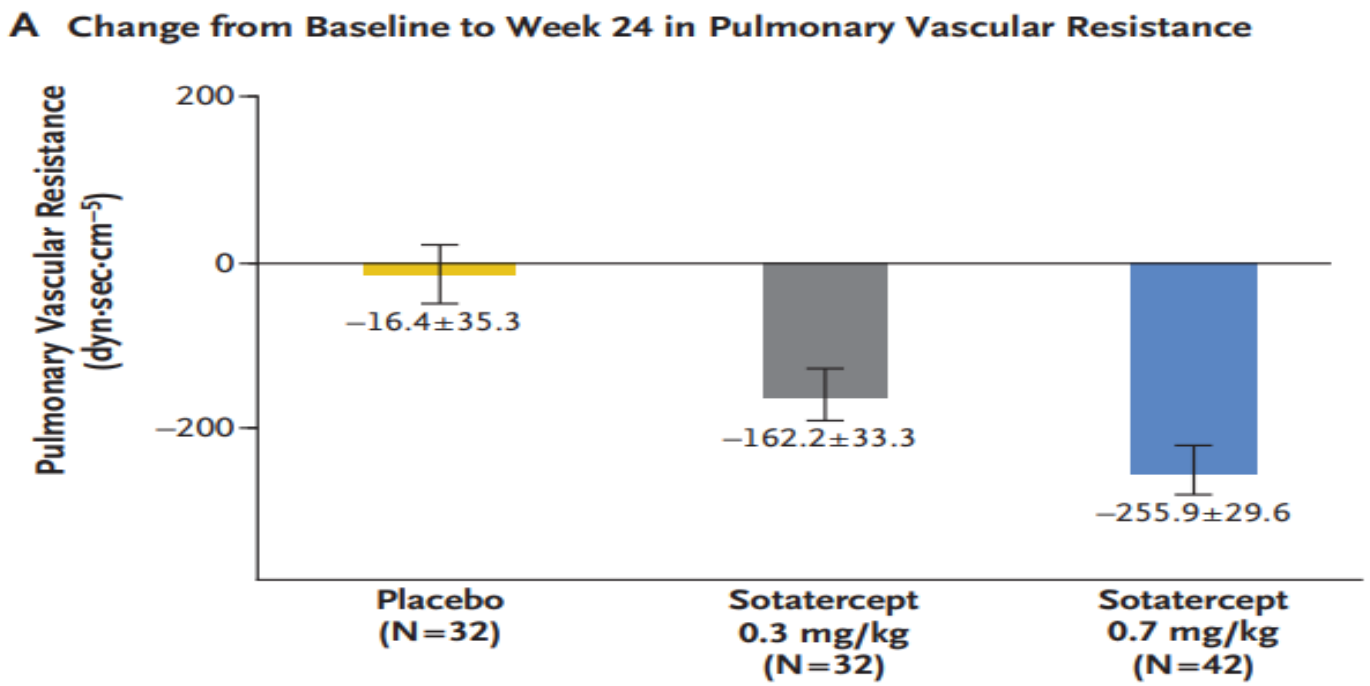
Sotatercept: the PULSAR trial

Inclusion(n=106): **IPAH (58%), Heritable (16%), CTD(17%).** **Drug(7%), CHD (3%)**

FC II (53%), III (47%)

Mono (9%), dual (35%), Triple (56%), IV/SC PCA (37%)

Design: 24 weeks, double-blind, placebo-controlled multicenter



Humbert M, et al. N Engl J Med 2021;384:1204-1215

Sotatercept Phase 3 trials

	STELLAR *Established PAH Population*	HYPERION *Early PAH Population*	ZENITH *Advanced High-Risk PAH*
STUDY DESIGN	Phase 3, Randomized, Double-blind, Placebo-controlled (24 weeks)	Phase 3, Randomized, Double-blind, Placebo-controlled (24 weeks)	Phase 3, Randomized, Double-blind, Placebo-controlled (Event-driven)
PATIENT POPULATION	Stable PAH on therapy	Newly diagnosed PAH	High-risk PAH despite maximal therapy
WHO FC	II–III	II–III	III–IV (predominantly)
BACKGROUND THERAPY	61% on triple therapy ~40% on prostacyclin infusion	Standard-of-care therapy initiated early	Maximal tolerated PAH therapy (mono, dual, triple, ± prostacyclin)
N (Patients)	323 (Sotatercept 163 / Placebo 160)	~320 (Sotatercept ≈160 / Placebo ≈160)	172 (Sotatercept 87 / Placebo 85)
PRIMARY ENDPOINT	**Change in 6-Minute Walk Distance (6MWD) at Week 24**	**Change in Pulmonary Vascular Resistance (PVR) at Week 24**	**Time to First Morbidity/Mortality Event (composite)**

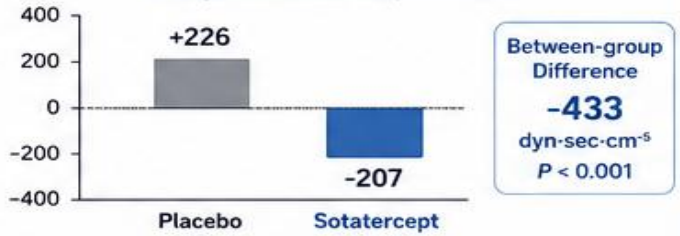
PRIMARY ENDPOINT (6MWD)

PVR ↓ Significant | NT-proBNP ↓ Significant | WHO FC Improved | Clinical Worsening Reduced

All key secondary endpoints met

PRIMARY ENDPOINT (PVR)

Change from Baseline (dyn·sec·cm⁻⁵)

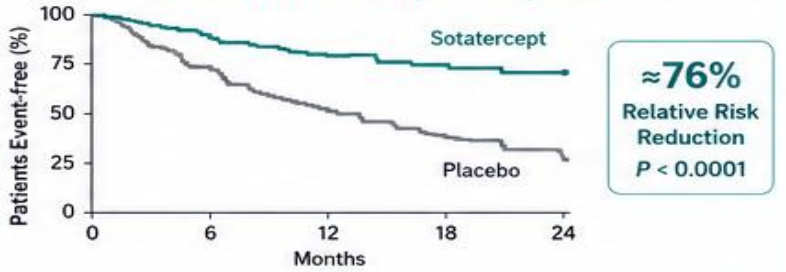


6MWD Improved | NT-proBNP ↓ Significant | WHO FC Improved | Clinical Worsening Reduced (trend)

Supports benefit of earlier intervention

PRIMARY ENDPOINT

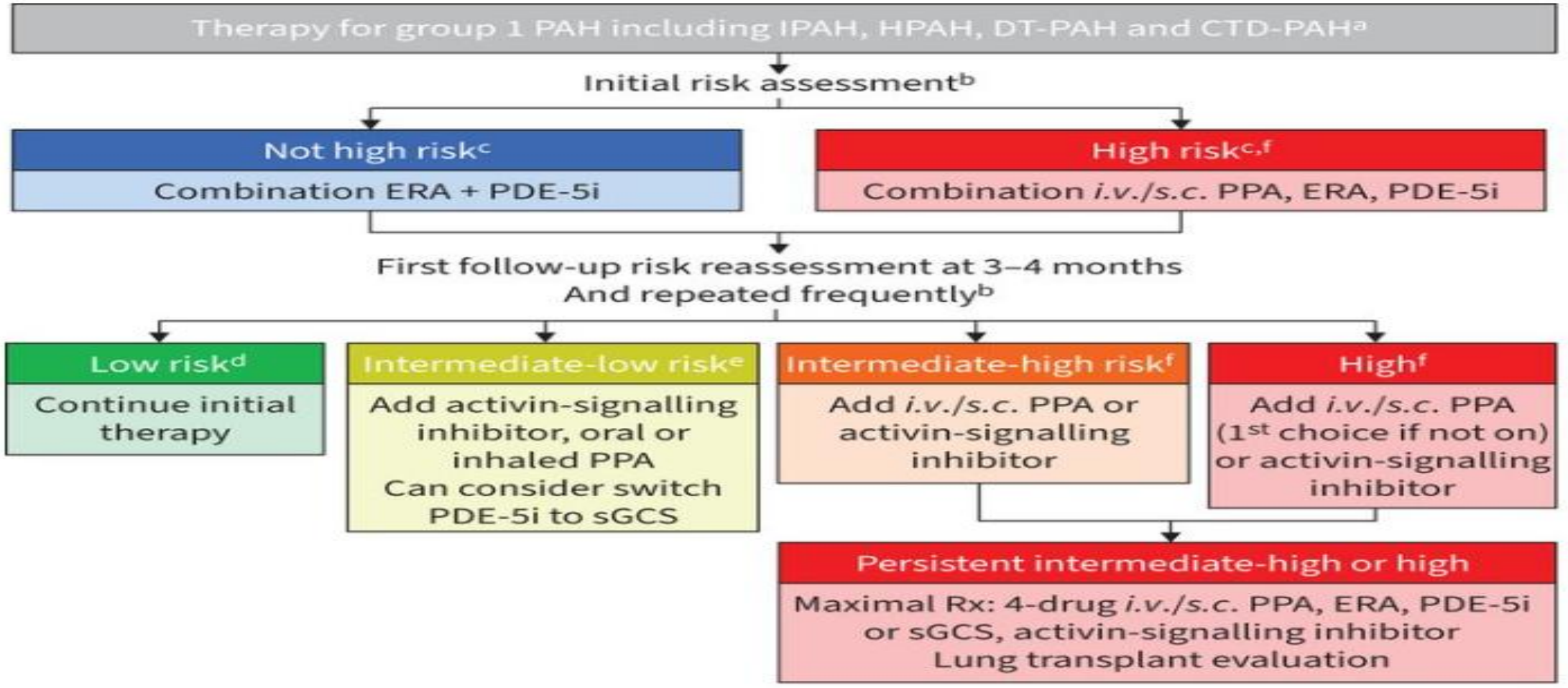
(Time to First Morbidity/Mortality Event)



PVR ↓ Significant | NT-proBNP ↓ Significant | WHO FC Improved | PAH Hospitalization Markedly Reduced

Trial stopped early for overwhelming efficacy

2024 7th World symposium on PH



Chin KM, et al. Eur Respir J 2024; in press: 2401325

Case 34/F IPAH

2020.03 DOE (WHO Fc II)

2020.08 외부병원 echo: **severe PH (sPAP 88mmHg) with mild RV dysfunction**

RHC: **mPAP 57mmHg**, PAWP 11, mRAP 13mmHg -> bosentan

2020.09 AMC WHO Fc II/III

NT pro-BNP 1404 pg/mL

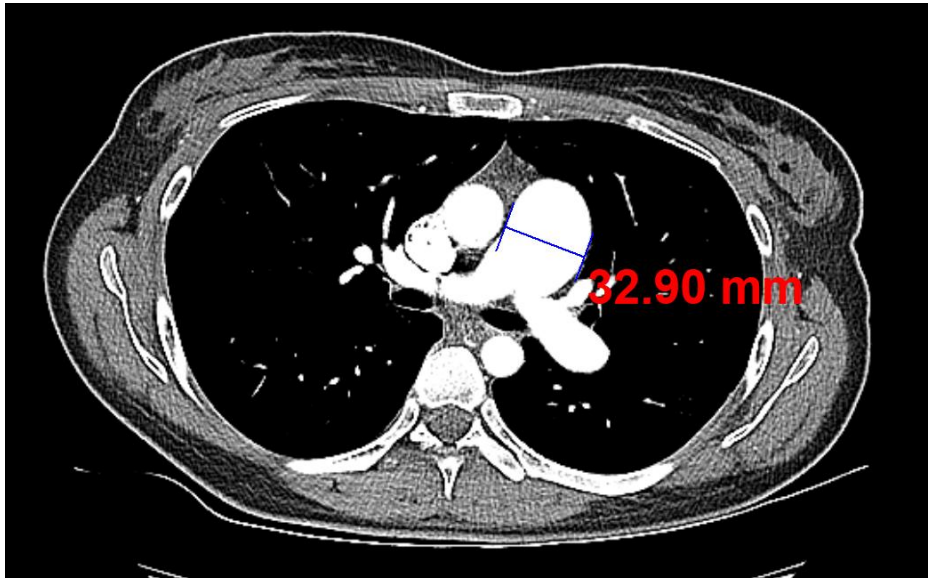
6MWT 484m (HR 113 -> 141, SpO2 99 -> 97%)

CPET: VO2max 15.1 mm/kg/min, 83 watts,

peak HR 156, **O2 pulse 6.2 ml/beat**

macitentan, sildenafil

2020.08



폐동맥고혈압 신속(초기) 병용요법 급여기준

가) 인정 가능 2제 병용 조합 : PDE5i계+ ERA계, Treprostinil 주사제+ ERA계, Treprostinil 주사제+ PDE5i계

나) 대상환자: 우심도자를 통해 폐동맥고혈압이 확진되고, WHO 기능분류 단계 IV에 해당하면서, 아래의 지표 중 한 개 이상을 만족하는 경우

- 환자의 상태로 인해 우심도자 검사가 불가능한 경우, 심초음파 검사 상 'peak tricuspid regurgitation velocity >3.4(m/s)' 등 폐동맥고혈압을 확실히 의심할 수 있는 경우를 포함함

폐동맥고혈압 순차적 병용요법 급여기준

1) 2제 요법

단독요법으로 3개월 이상 투여 후 임상적 반응이 충분하지 않을 때
(다음의 ①~④항 소견 중 최소 1개와 ⑤~⑨항 중 최소 1개를 모두 만족),
작용기전이 다른 약제※ 1종을 추가한 병용요법을 인정함.

2) 3제 요법

상기 1)의 2제 요법으로 3개월 이상 투여 후 임상적 반응이 충분하지 않을 때c),
2제 요법에서 사용되지 않은 작용기전이 다른 약제※ 1종을 추가한 순차적 병용투여(sequential combination)를 인정함.

폐동맥고혈압(PAH) 치료 단계 상향 시 **급여 인정 기준**

단독요법 ➡ 2제 병용요법
2제 병용요법 ➡ 3제 병용요법

! 아래 **두 조건을 동시에** 만족해야 급여가 인정됩니다.

그룹 A

주관적·임상적 증상

(최소 1개 이상 만족)

1. **우심실 부전 증거**
   임상적 증거 있음

2. **증상 진행 속도**
   빠름

3. **실신 여부**
   있음

4. **WHO 기능분류**
   Ⅲ단계 이상

A + B
동시 만족

두 그룹에서
각각 1개 이상
만족해야
급여 인정

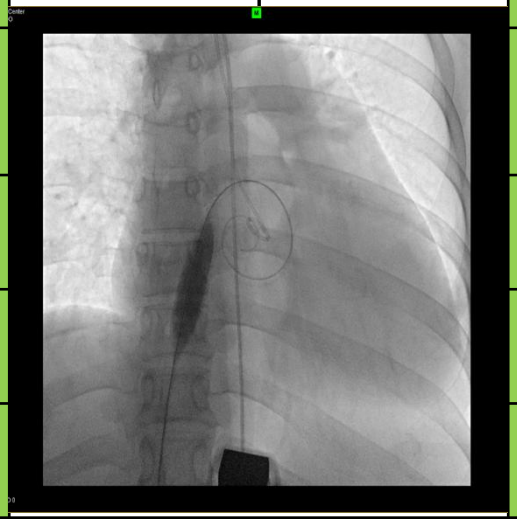
그룹 B

객관적 검사 지표

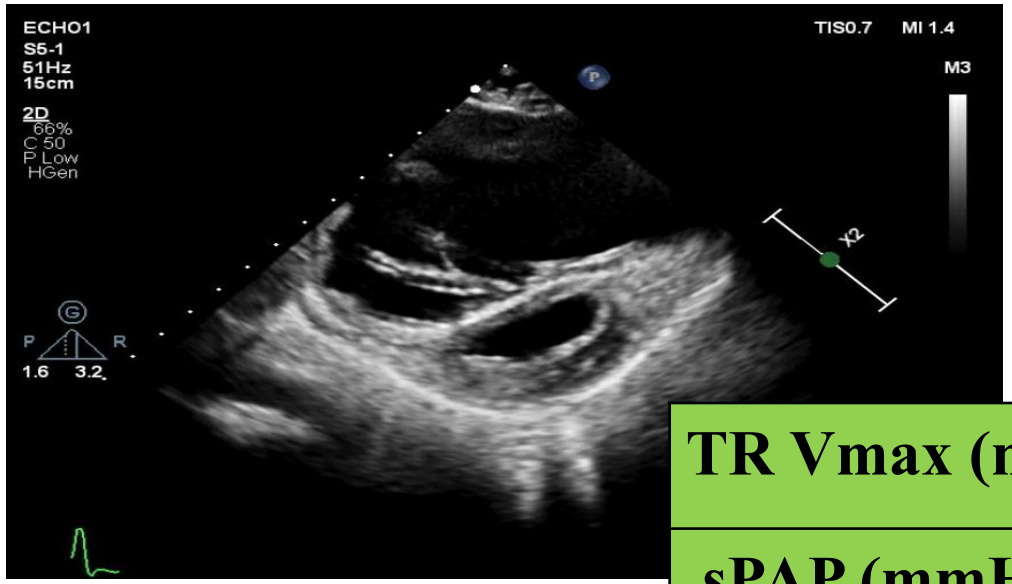
(최소 1개 이상 만족)

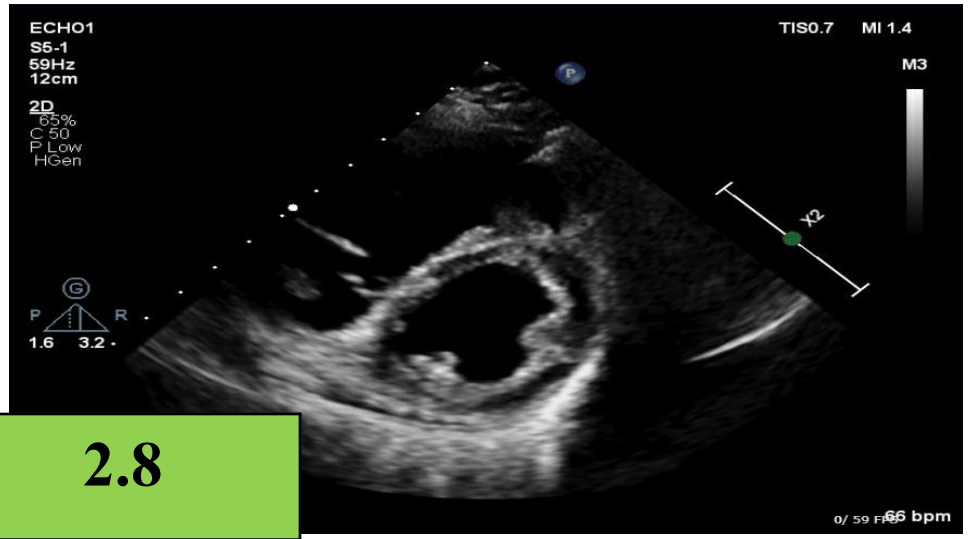
	5 **6분 보행거리 (6MWT)**	**440m 이하**
	6 **운동부하심폐검사 (CPET)**	Peak O_2 consumption ≤ **15 mL/min/kg**
	7 **혈액 검사 (BNP / NT-proBNP)**	**50 / 300 이상** (BNP ≥ 50 pg/mL 또는 NT-proBNP ≥ 300 pg/mL)
	8 **심초음파 검사 소견**	심낭삼출 (Pericardial effusion) 또는 **TAPSE < 1.5cm**
	9 **혈류역학 검사 지표**	**RAP ≥ 8 mmHg** 또는 **CI < 2.5 L/min/m²**

	2020.08		2022.11		2023.11		2025.01
WHO function class	II	Macitentan + sildenafil	III	Macitentan + Sildenafil + selexipag	III	Macitentan + Sildenafil + selexipag	III
Syncope	-		+		+		-
BNP (pg/ml)	160		874		1691		786
6MWT (m)	484		420		325		330
mRAP (mmHg)	13		7		10		3
Mean PAP (mmHg)	57		57		60		60
CO (L/m)			4.4		2.3		2.9
PVR (WU)			8.4		23		17
ScvO2 (%)			69		52		56

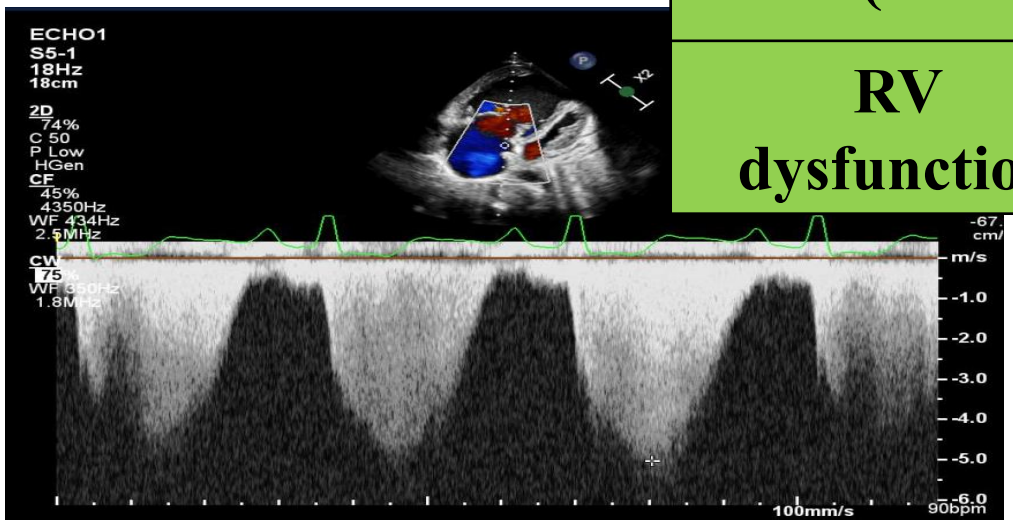


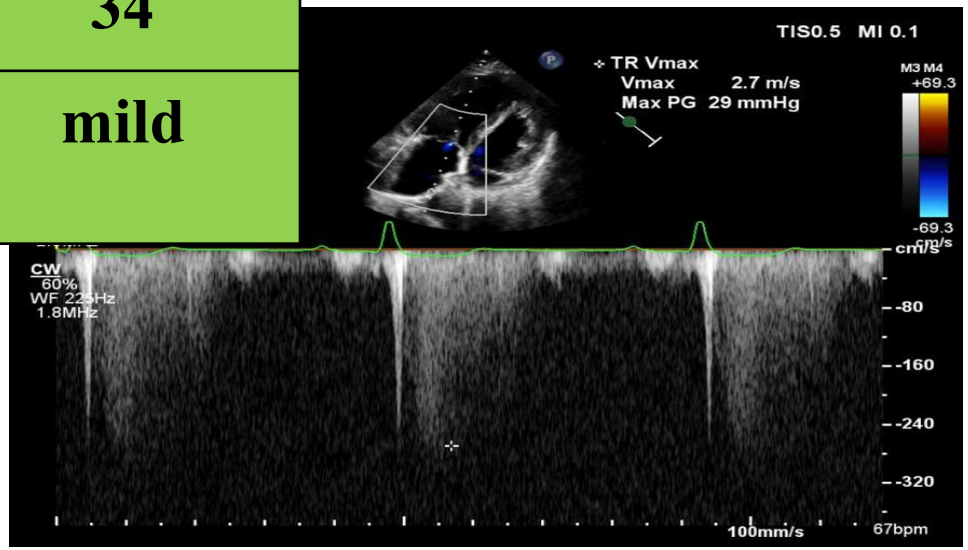
Quadruple Tx with macitentan, sildenafil, selexipag and sotaterpcet



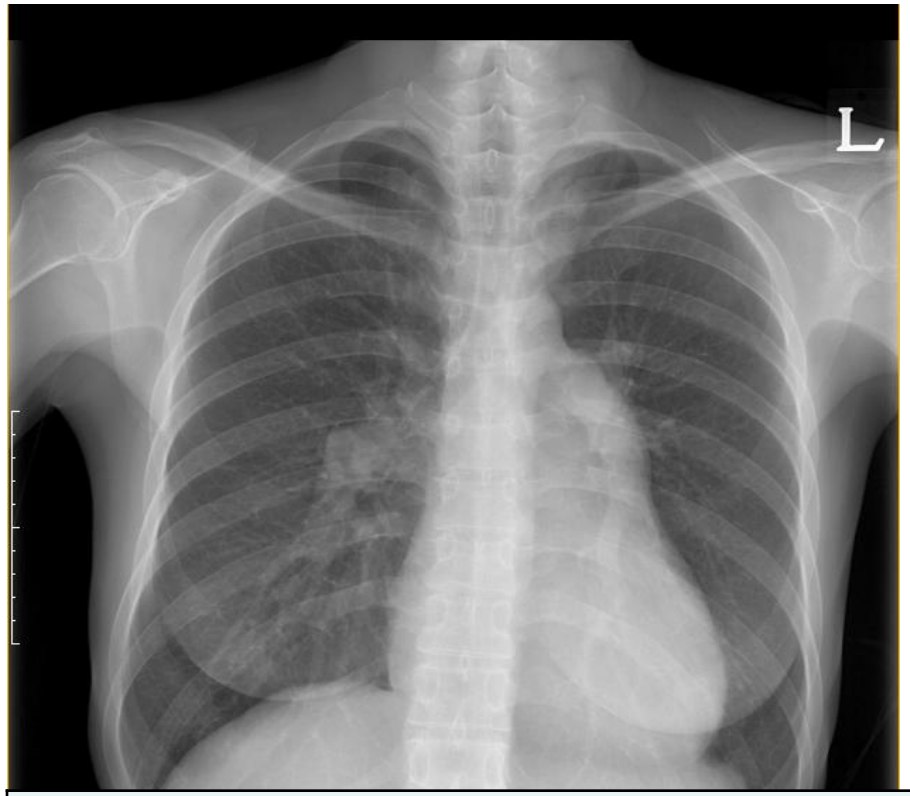


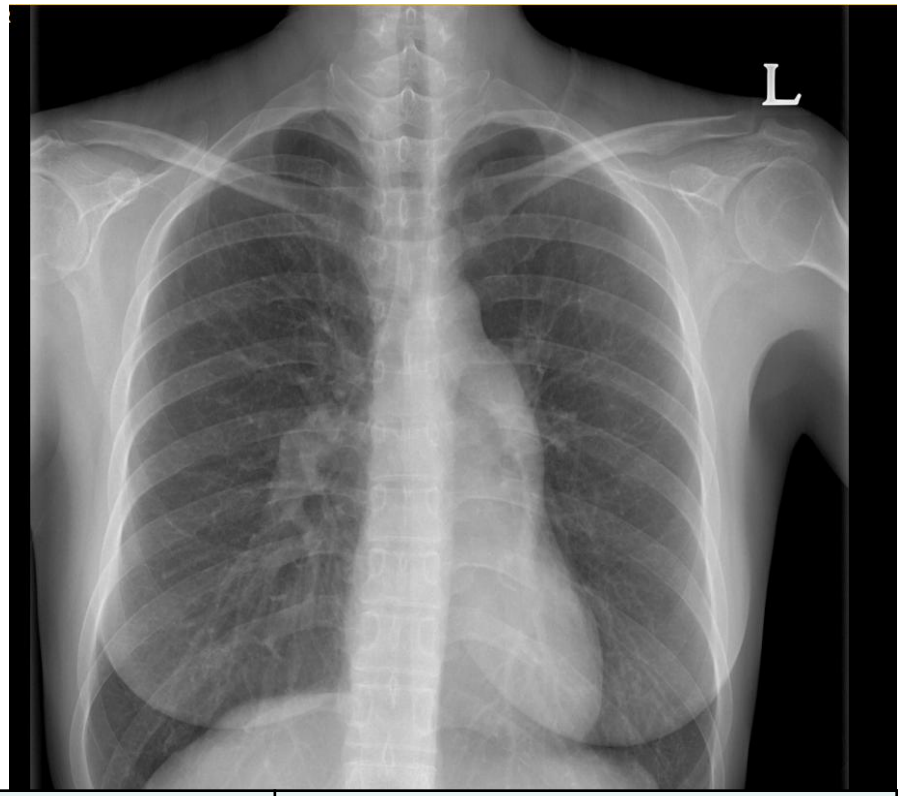
TR Vmax (m/s)	5.0	2.8
sPAP (mmHg)	103	34
RV dysfunction	severe	mild





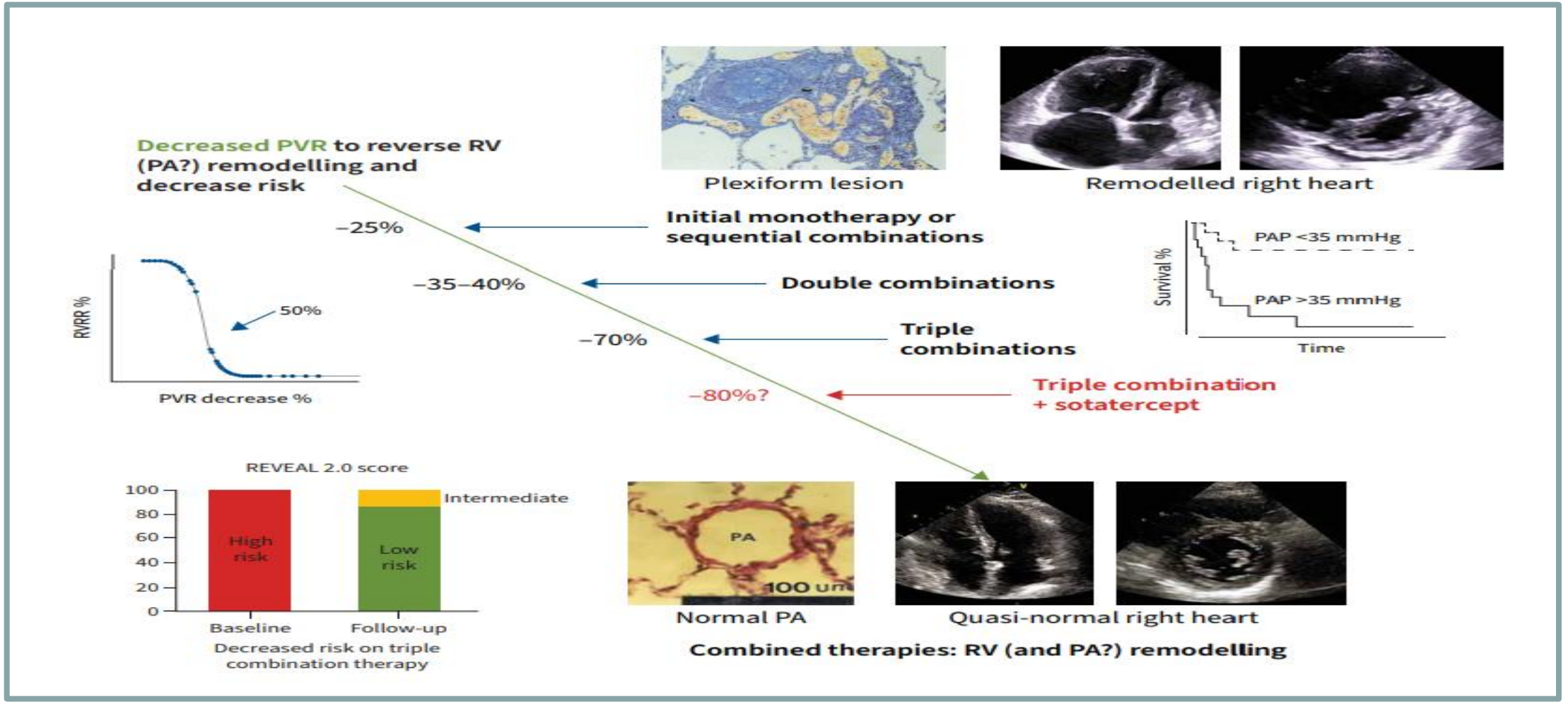
Quadruple Tx with macitentan, sildenafil, selexipag and sotaterpcet





	2025.01	2026.05
WHO function class	III	II
BNP (pg/ml)	786	17
6MWT (m)	330	420

Partial/complete remission of PAH



Rubin LJ, Naeije R.Eur Respir J 2023; 61: 2201972.

Treatment strategies of PH

Clinical Classification

Pulmonary arterial hypertension (PAH)	PH associated with left heart disease	PH associated with lung disease	PH associated with pulmonary artery obstructions	PH with unclear and/or multifactorial mechanisms
• Idiopathic/heritable • Associated conditions	• IpcPH • CpcPH	• Non-severe PH • Severe PH	• CTEPH • Other pulmonary obstructions	• Haematologic disorders • Systemic disorders

Prevalence

Rare	Very common	Common	Rare	Rare

Therapeutic Strategies

Medical therapy • PAH drugs • CCB in responders **Lung transplantation**	**IpcPH:** • Treatment of LHD[a] **CpcPH:** • Treatment of LHD[a] • Potentially: PAH drugs (trials)	**PH-lung disease:** • Optimized care of underlying lung disease **Severe PH:** • Potentially: PAH drugs (trials)	**Surgical therapy:** • PEA **Interventional:** • BPA **Medical therapy:** • PH drugs	**Optimized treatment of underlying disease** • Potentially: PAH drugs (trials)

ESC ERS