# The impact of novel therapeutics on the treatment algorithm of PH

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Pulmonary Vascular Research Institute

# Disclosures

- Consultant & Advisor: United Therapeutics, Janssen, Gossamer Bio, Liquidia, Keros, Pulmovant, MERCK, ATXA and Morphic
- Institutional Clinical trial support from United Therapeutics, Gossamer Bio, Liquidia, Keros, MERCK, Pulmovant
- Participation in DSMB as chair and/or member in NIH studies
- PH program at HMH has philanthropic support from the Diane and Charles Chapman PH fund

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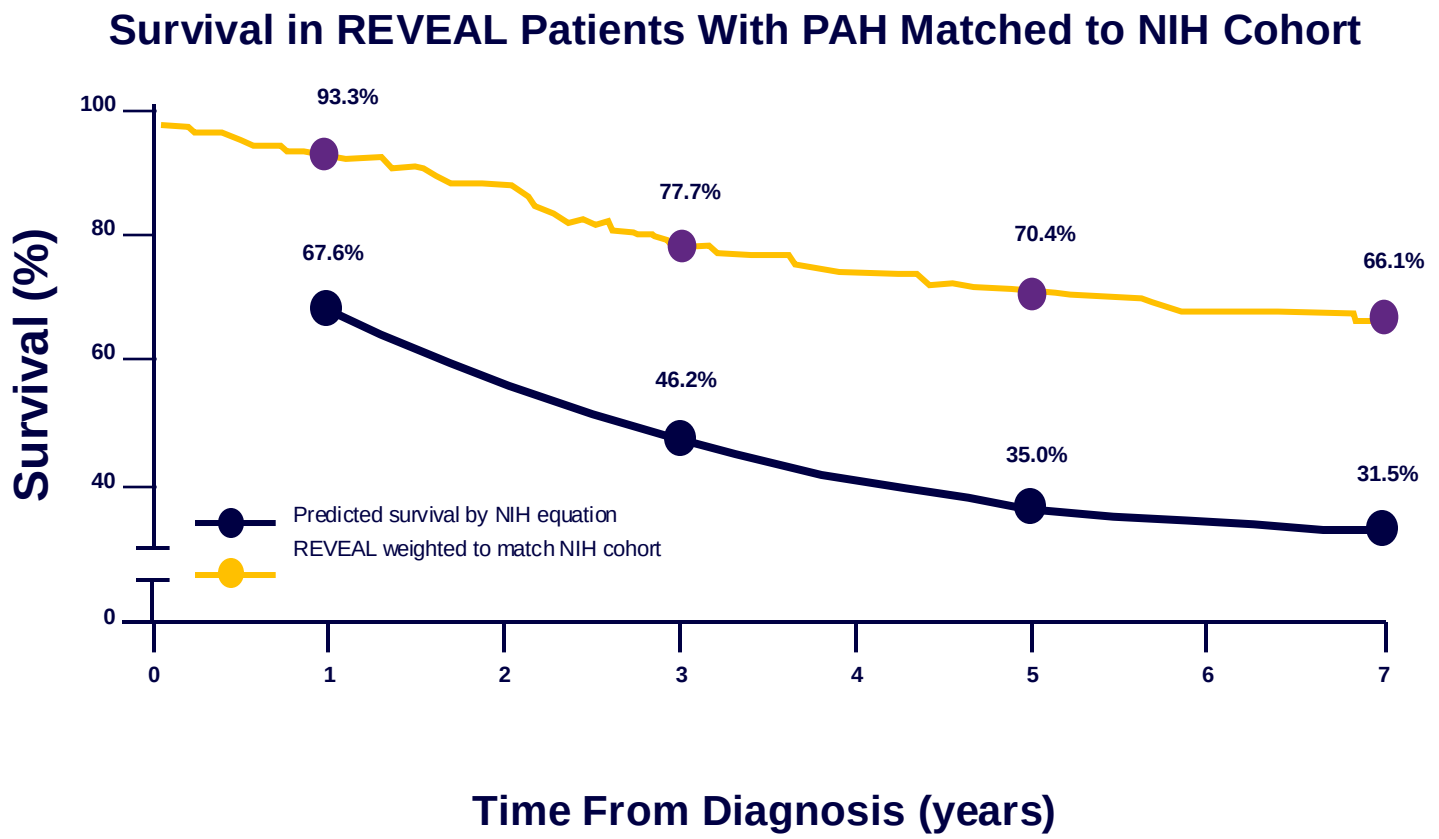
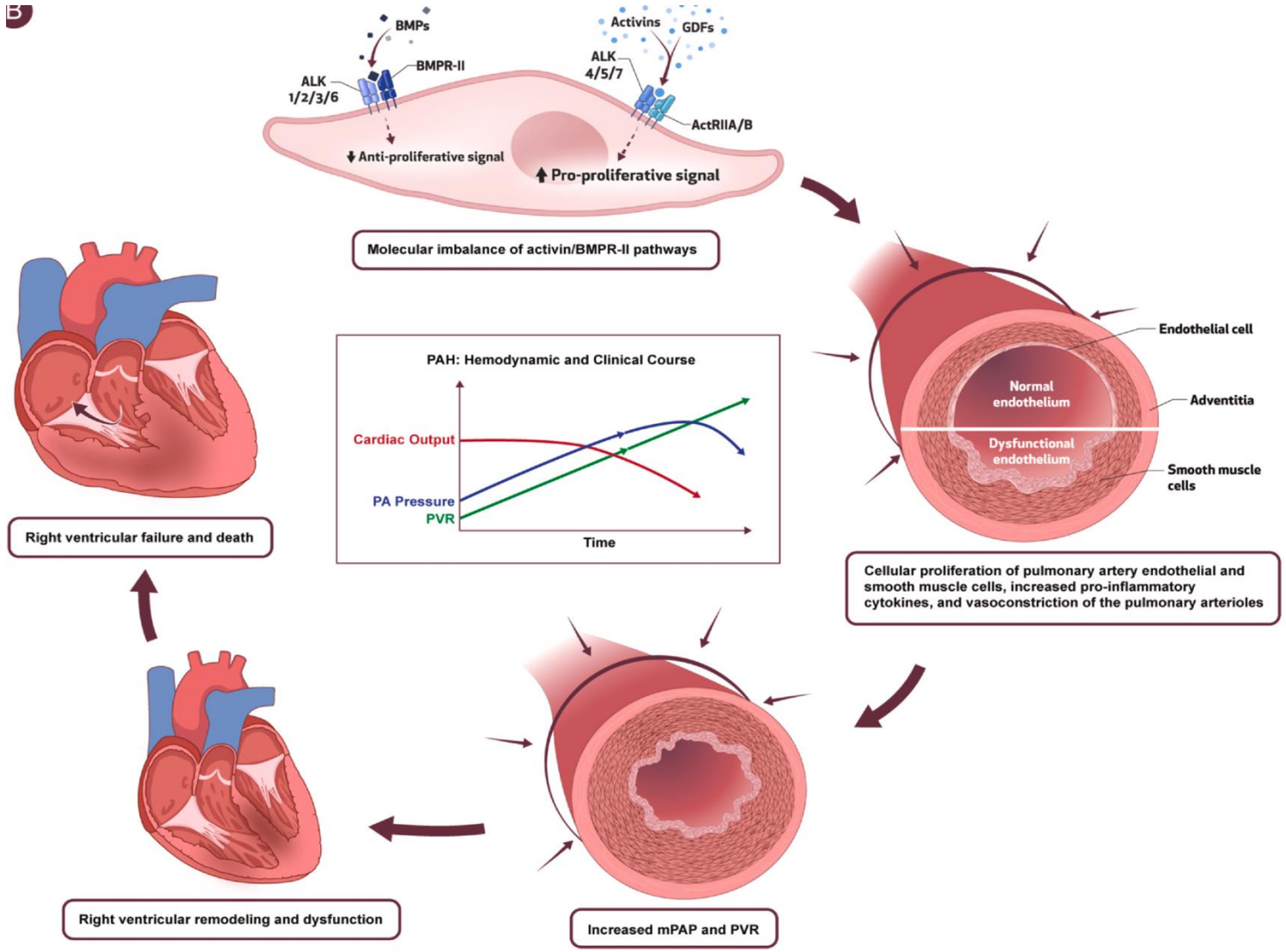
# Management of PAH

# Long-term Survival in PAH From Time of Diagnosis of PAH in the REVEAL Registry



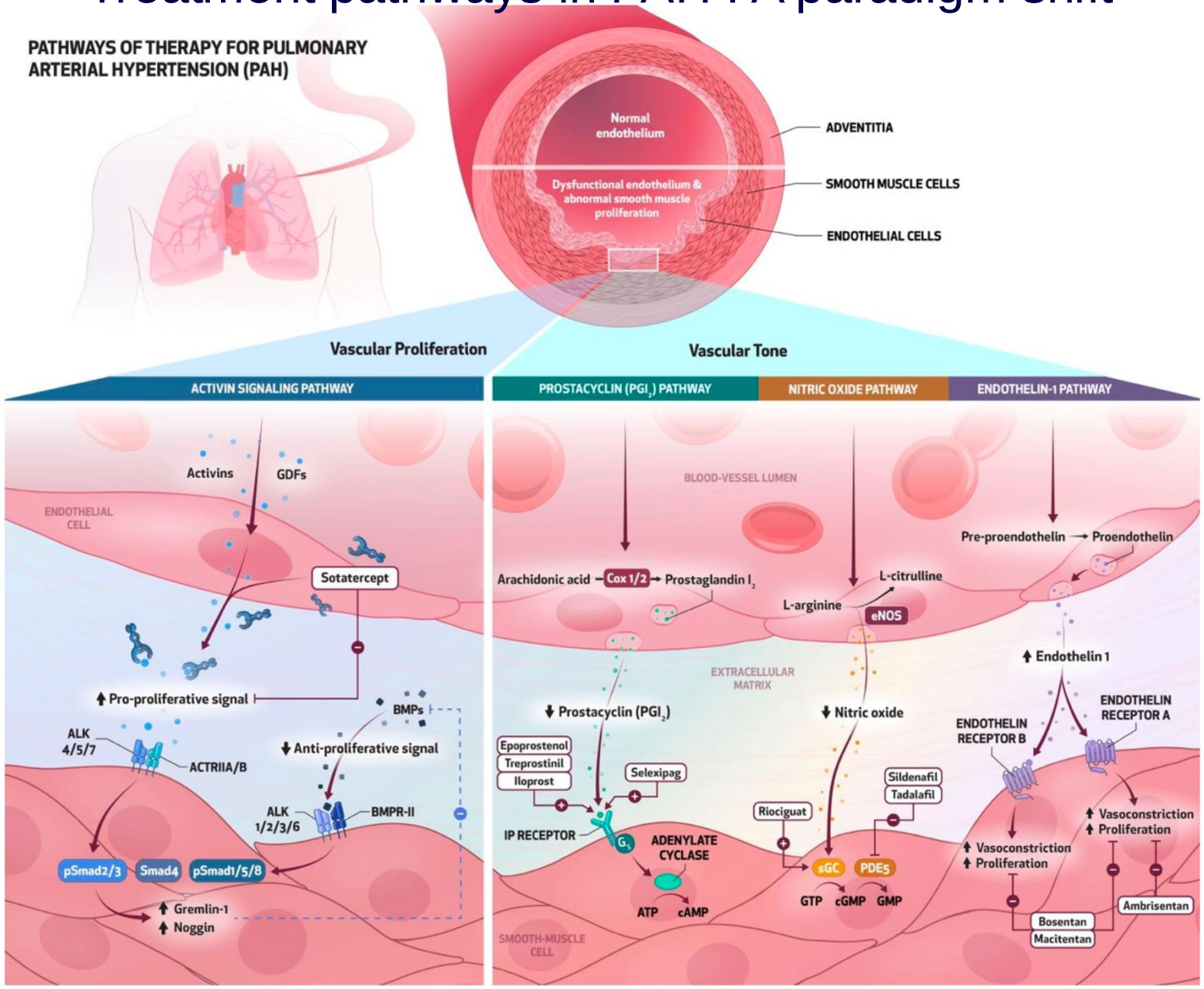

Benza RL, et al. *Chest*. 2012;142:448-456.

# Progression of disease in PAH



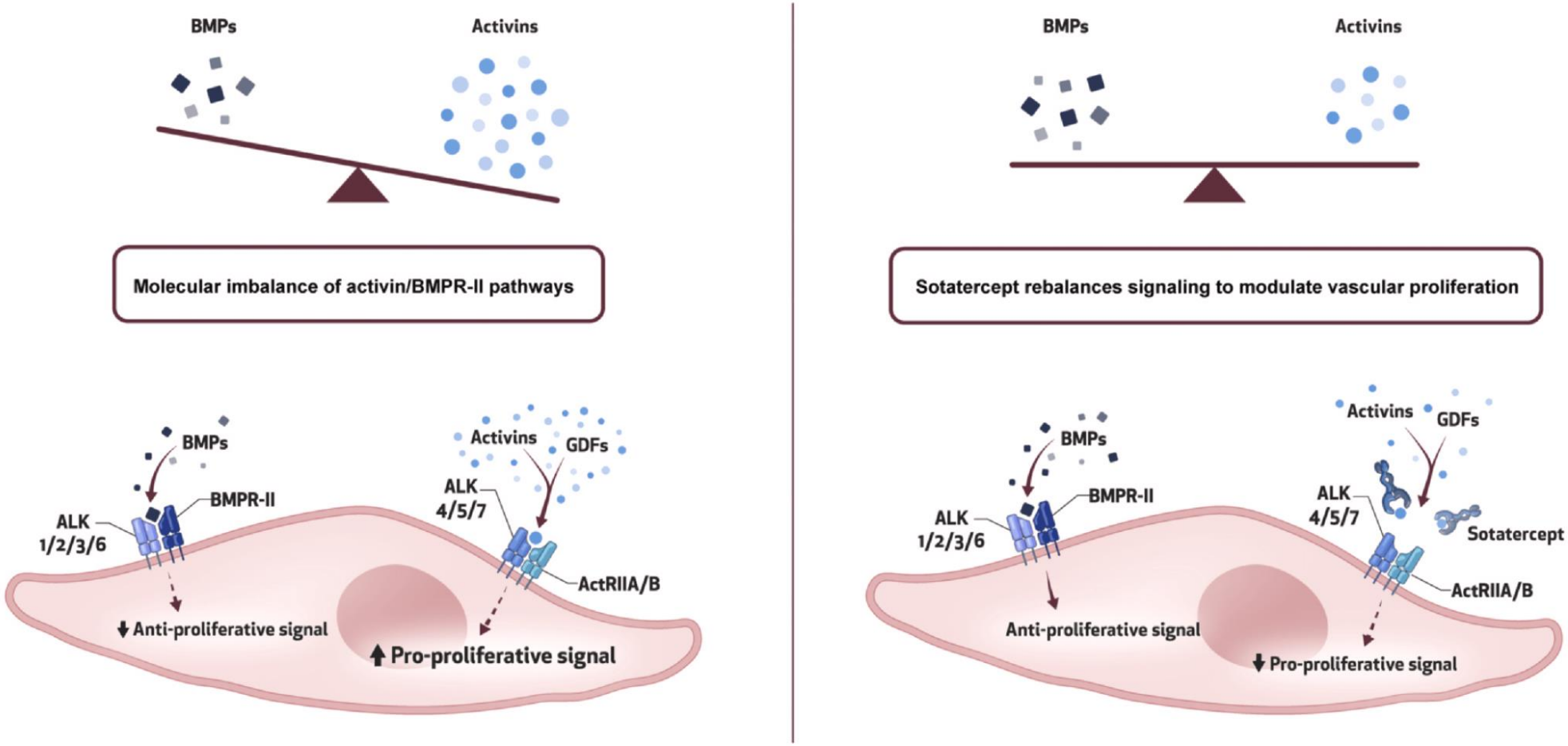

Cascino TM, et al. J Heart Lung Transplant. 2024 Oct 5:S1053-2498(24)01874-6.

# Treatment pathways in PAH : A paradigm shift




Sahay S, et al. Contemporary Treatment of Pulmonary Arterial Hypertension: A US Perspective. *AJRCCM.* 2024

## Proposed Mechanism of Sotatercept to Rebalance Pulmonary Vascular Remodeling




Cascino TM, et al. J Heart Lung Transplant. 2024 Oct 5:S1053-2498(24)01874-6.

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Phase 3 Trial of Sotatercept for Treatment of Pulmonary Arterial Hypertension

M.M. Hoeper, D.B. Badesch, H.A. Ghofrani, J.S.R. Gibbs, M. Gomberg-Maitland, V.V. McLaughlin, I.R. Preston, R. Souza, A.B. Waxman, E. Grünig, G. Kopeć, G. Meyer, K.M. Olsson, S. Rosenkranz, Y. Xu, B. Miller, M. Fowler, J. Butler, J. Koglin, J. de Oliveira Pena, and M. Humbert, for the STELLAR Trial Investigators*

## ABSTRACT

N Engl J Med 2023;388:1478-90.

# Demographics : ***STELLAR trial***

| Characteristic | Sotatercept (N=163) | Placebo (N=160) | Total (N=323) |
|---|---|---|---|
| Female sex — no. (%) | 129 (79.1) | 127 (79.4) | 256 (79.3) |
| Age — yr | 47.6±14.1 | 48.3±15.5 | 47.9±14.8 |
| Geographic region — no. (%) | | | |
| North America | 49 (30.1) | 56 (35.0) | 105 (32.5) |
| South America | 13 (8.0) | 15 (9.4) | 28 (8.7) |
| Europe | 91 (55.8) | 77 (48.1) | 168 (52.0) |
| Asia–Pacific | 10 (6.1) | 12 (7.5) | 22 (6.8) |
| Race — no. (%)† | | | |
| White | 147 (90.2) | 141 (88.1) | 288 (89.2) |
| Black | 2 (1.2) | 5 (3.1) | 7 (2.2) |
| Asian | 1 (0.6) | 6 (3.8) | 7 (2.2) |
| Other | 7 (4.3) | 6 (3.8) | 13 (4.0) |
| Missing | 6 (3.7) | 2 (1.2) | 8 (2.5) |
| Body-mass index‡ | 26.1±5.7 | 26.6±6.1 | 26.4±5.9 |
| Body-mass index ≥30 — no. (%)‡ | 36 (22.1) | 38 (23.8) | 74 (22.9) |
| Time since diagnosis of pulmonary arterial hypertension — yr§ | 9.2±7.3 | 8.3±6.7 | 8.8±7.0 |
| Classification of pulmonary arterial hypertension — no. (%) | | | |
| Idiopathic | 83 (50.9) | 106 (66.2) | 189 (58.5) |
| Heritable | 35 (21.5) | 24 (15.0) | 59 (18.3) |
| Associated with connective-tissue disease | 29 (17.8) | 19 (11.9) | 48 (14.9) |
| Drug-induced or toxin-induced | 7 (4.3) | 4 (2.5) | 11 (3.4) |
| Associated with corrected congenital shunts | 9 (5.5) | 7 (4.4) | 16 (5.0) |
| WHO functional class — no. (%)¶ | | | |
| II | 79 (48.5) | 78 (48.8) | 157 (48.6) |
| III | 84 (51.5) | 82 (51.2) | 166 (51.4) |
| Background therapy for pulmonary arterial hypertension — no. (%)‖ | | | |
| Prostacyclin infusion therapy** | 65 (39.9) | 64 (40.0) | 129 (39.9) |
| Monotherapy | 9 (5.5) | 4 (2.5) | 13 (4.0) |
| Double therapy | 56 (34.4) | 56 (35.0) | 112 (34.7) |
| Triple therapy | 98 (60.1) | 100 (62.5) | 198 (61.3) |

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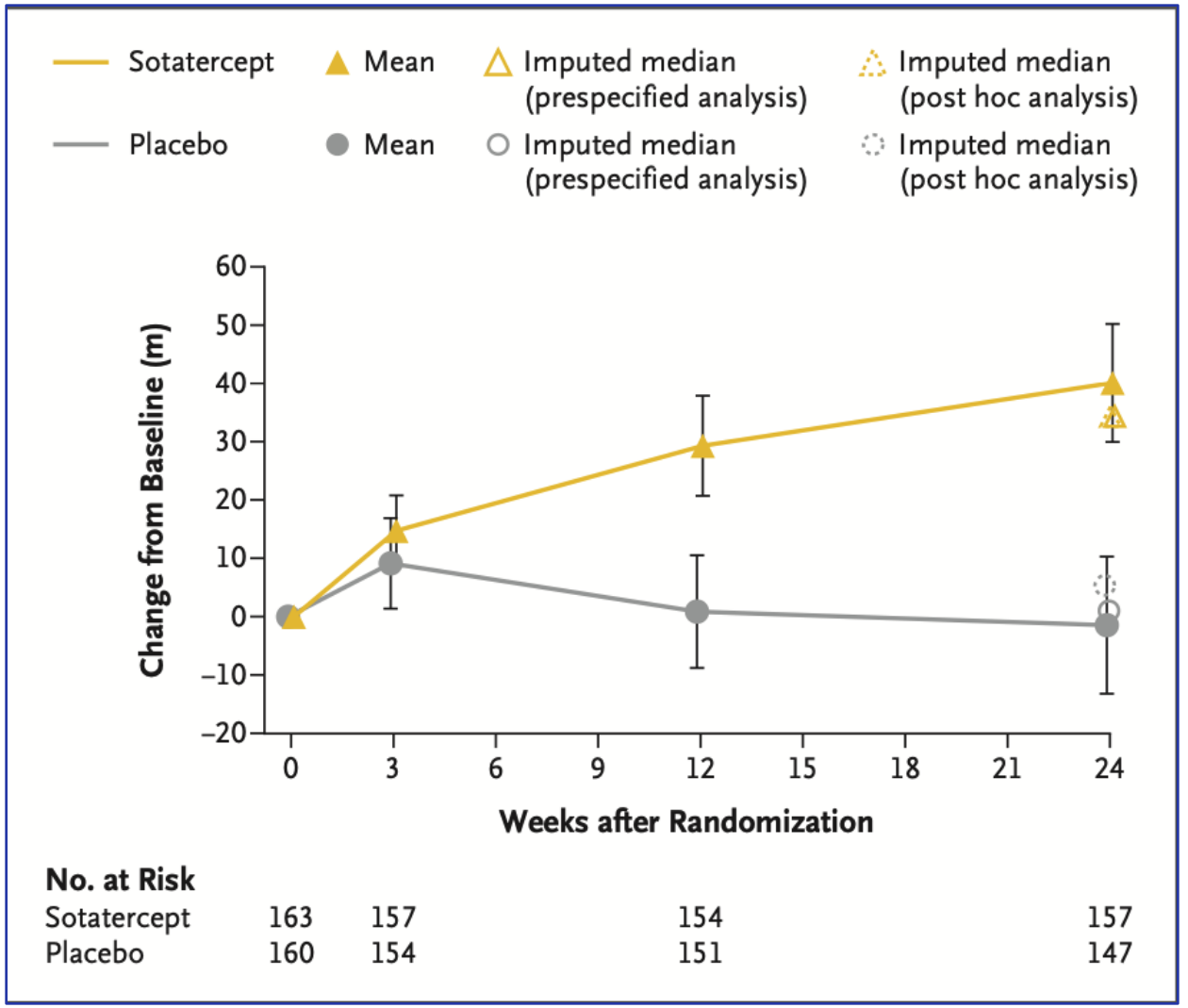
N Engl J Med 2023;388:1478-90.

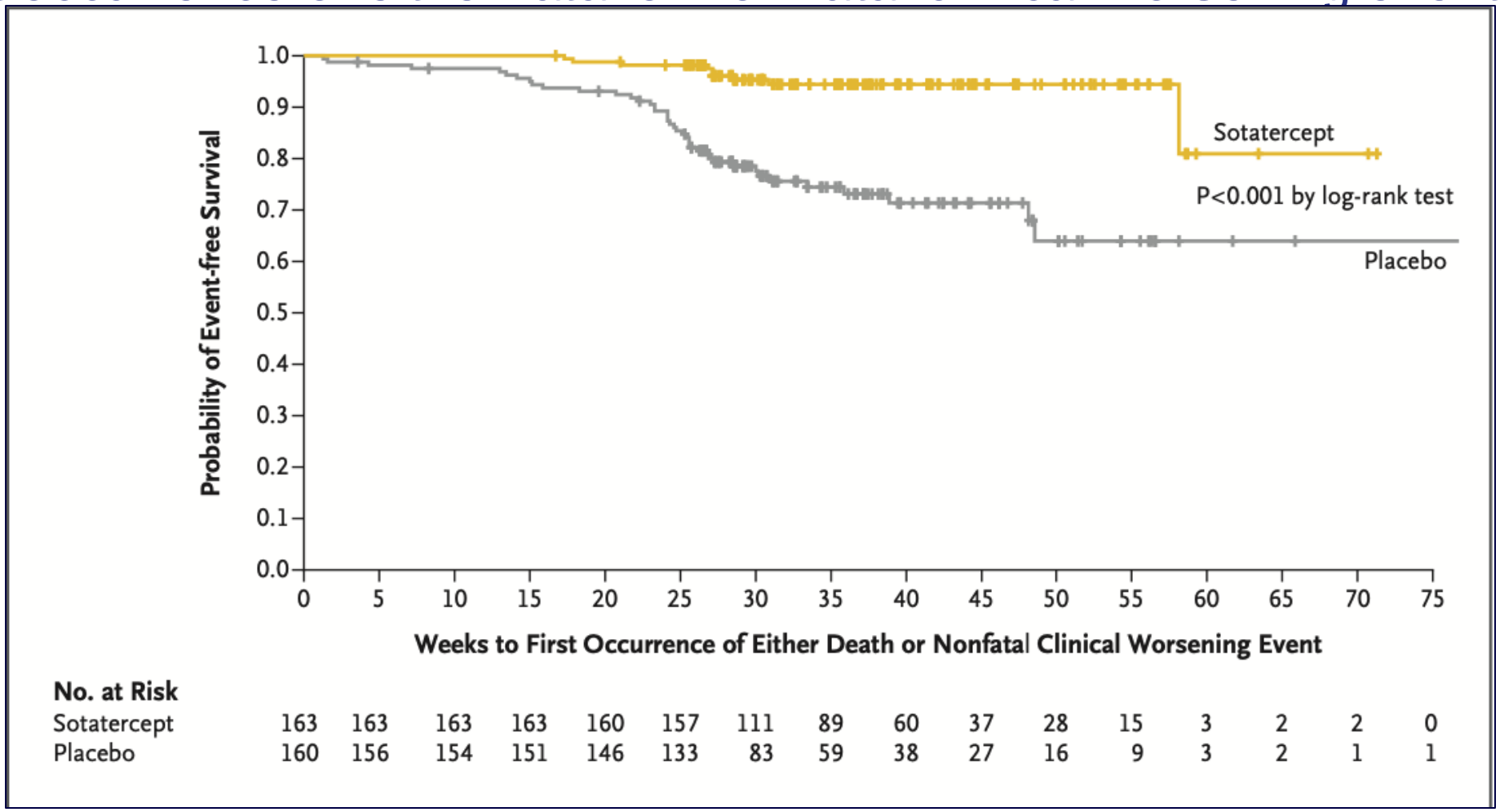
# STELLAR Study :Change in 6MWD




N Engl J Med 2023;388:1478-90.

# STELLAR Study:

## Time to first occurrence of either fatal or non-fatal clinical worsening event

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N Engl J Med 2023;388:1478-90.

# STELLAR Study:

# Adverse Events

| Variable | Sotatercept (N=163) | Placebo (N=160) | Difference† |
|---|---|---|---|
| | *number (percent)* | | *percentage points* |
| Adverse events | | | |
| Any | 138 (84.7) | 140 (87.5) | −2.8 (−10.5 to 4.8) |
| Related to sotatercept or placebo‡ | 67 (41.1) | 41 (25.6) | 15.5 (5.2 to 25.5) |
| Leading to discontinuation of sotatercept or placebo | 3 (1.8) | 10 (6.2) | −4.4 (−9.5 to −0.1) |
| Leading to withdrawal from the trial | 3 (1.8) | 5 (3.1) | −1.3 (−5.5 to 2.5) |
| Leading to death | 0 | 6 (3.8) | −3.8 (−7.9 to −1.4) |
| Severe adverse event§ | 13 (8.0) | 21 (13.1) | −5.1 (−12.2 to 1.6) |
| Serious adverse events¶ | | | |
| Any | 23 (14.1) | 36 (22.5) | −8.4 (−16.9 to 0.1) |
| Related to sotatercept or placebo‡ | 2 (1.2) | 2 (1.2) | −0.0 (NR) |
| Leading to discontinuation of sotatercept or placebo | 1 (0.6) | 8 (5.0) | −4.4 (−9.0 to −1.0) |
| Leading to withdrawal from the trial | 1 (0.6) | 5 (3.1) | −2.5 (−6.6 to 0.6) |
| Adverse events of interest or special interest‖ | | | |
| Increased hemoglobin level: increased hematocrit or increased red-cell count | 9 (5.5) | 0 | 5.5 (2.9 to 10.2) |
| Thrombocytopenia | 10 (6.1) | 4 (2.5) | 3.6 (−0.9 to 8.8) |
| Bleeding events | 35 (21.5) | 20 (12.5) | 9.0 (0.8 to 17.2) |
| Increased blood pressure | 6 (3.7) | 1 (0.6) | 3.1 (−0.2 to 7.3) |
| Telangiectasia | 17 (10.4) | 5 (3.1) | 7.3 (2.0 to 13.3) |
| Adverse events reported in ≥10% of patients in either group | 138 (84.7) | 140 (87.5) | −2.8 (−10.5 to 4.8) |
| Headache | 33 (20.2) | 24 (15.0) | 5.2 (−3.1 to 13.6) |
| Covid-19 | 24 (14.7) | 21 (13.1) | 1.6 (−6.1 to 9.3) |
| Nausea | 16 (9.8) | 18 (11.2) | −1.4 (−8.4 to 5.4) |
| Diarrhea | 20 (12.3) | 12 (7.5) | 4.8 (−1.8 to 11.6) |
| Fatigue | 17 (10.4) | 12 (7.5) | 2.9 (−3.5 to 9.5) |
| Epistaxis | 20 (12.3) | 3 (1.9) | 10.4 (5.2 to 16.6) |
| Telangiectasia | 17 (10.4) | 5 (3.1) | 7.3 (2.0 to 13.3) |
| Dizziness | 17 (10.4) | 3 (1.9) | 8.6 (3.6 to 14.4) |

N Engl J Med 2023;388:1478-90.

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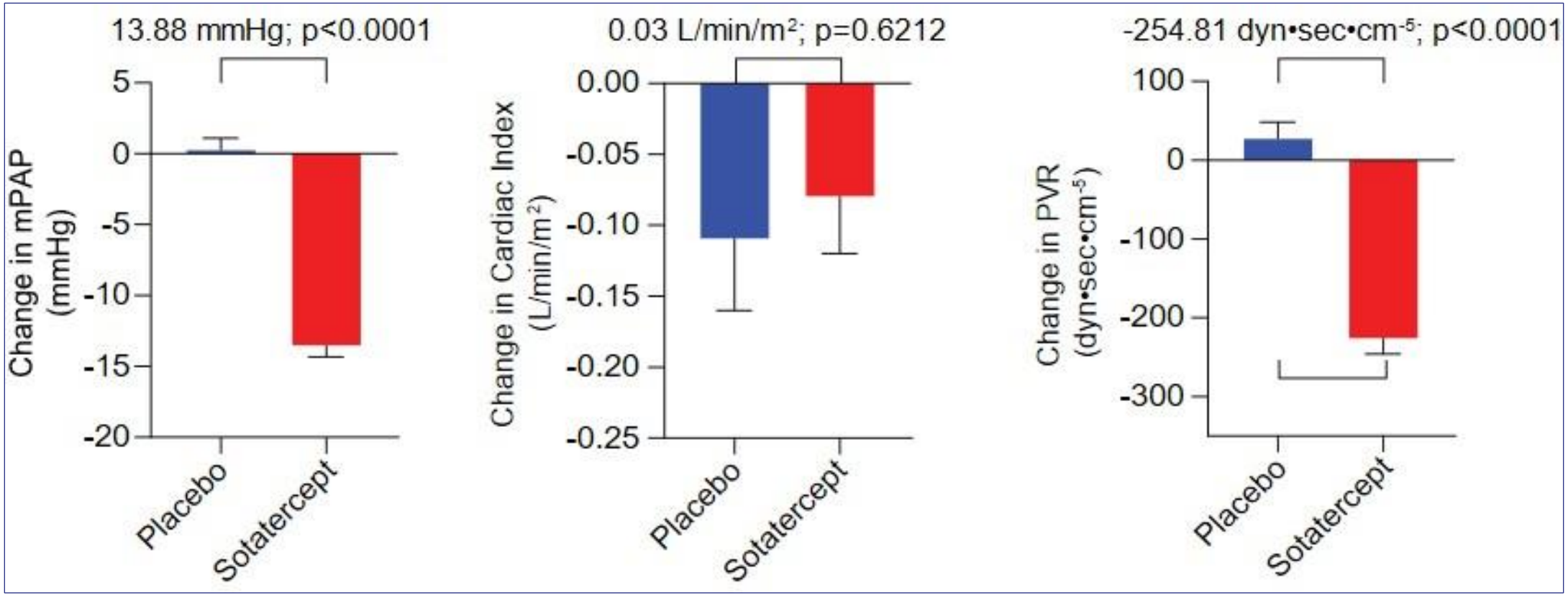
# STELLAR: Impact on hemodynamics




LS mean change (± SE) from baseline in mPAP, CI, and PVR at week 24

Cardiac index = cardiac output/body surface area; PVR = (mPAP – pulmonary artery wedge pressure)/cardiac output.
LS, least-squares; mPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance; SE, standard error.
Souza R, et al. *Eur Resp J*. 2023.

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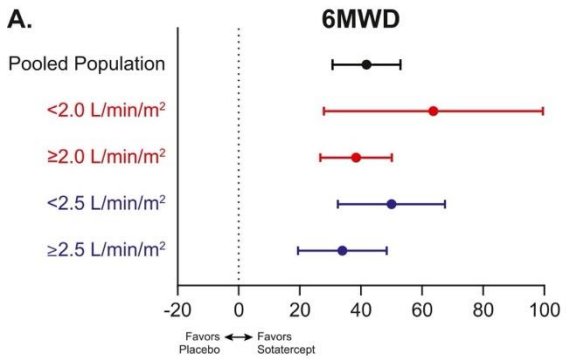
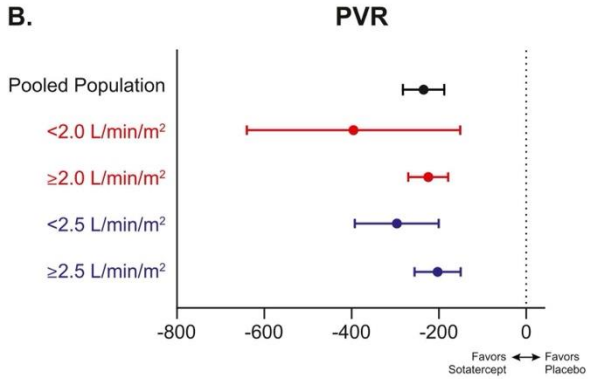
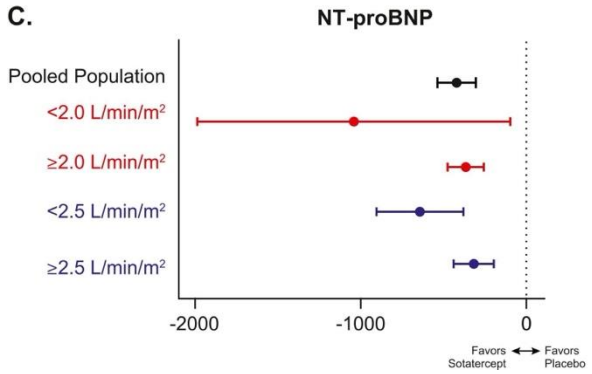
# Pooled analysis across CI subgroups: A Pooled Analysis of PULSAR and STELLAR




| | placebo n | sotatercept n | H-L shift estimates (95% Confidence Interval) | *P* value |
|---|---|---|---|---|
| Pooled Population | 192 | 237 | 41.8 (30.7, 52.9) | <0.001 |
| <2.0 L/min/m² | 21 | 30 | 63.7 (27.9, 99.6) | <0.001 |
| ≥2.0 L/min/m² | 171 | 207 | 38.4 (26.7, 50.1) | <0.001 |
| <2.5 L/min/m² | 84 | 95 | 50.0 (32.5, 67.5) | <0.001 |
| ≥2.5 L/min/m² | 108 | 142 | 33.9 (19.4, 48.4) | <0.001 |




| | placebo n | sotatercept n | H-L shift estimates (95% Confidence Interval) | *P* value |
|---|---|---|---|---|
| Pooled Population | 192 | 237 | -234.8 (-282.2, -187.4) | <0.001 |
| <2.0 L/min/m² | 21 | 30 | -395.4 (-639.9, -151.0) | 0.002 |
| ≥2.0 L/min/m² | 171 | 207 | -224.2 (-270.0, -178.5) | <0.001 |
| <2.5 L/min/m² | 84 | 95 | -296.3 (-392.3, -200.4) | <0.001 |
| ≥2.5 L/min/m² | 108 | 142 | -202.8 (-255.5, -150.0) | <0.001 |




| | placebo n | sotatercept n | H-L shift estimates (95% Confidence Interval) | *P* value |
|---|---|---|---|---|
| Pooled Population | 192 | 237 | -420.7 (-536.9, -304.6) | <0.001 |
| <2.0 L/min/m² | 21 | 30 | -1041.2 (-1986.8, -95.6) | <0.001 |
| ≥2.0 L/min/m² | 171 | 207 | -365.7 (-474.6, -256.8) | <0.001 |
| <2.5 L/min/m² | 84 | 95 | -642.2 (-904.2, -380.1) | <0.001 |
| ≥2.5 L/min/m² | 108 | 142 | -317.3 (-439.0, -195.7) | <0.001 |

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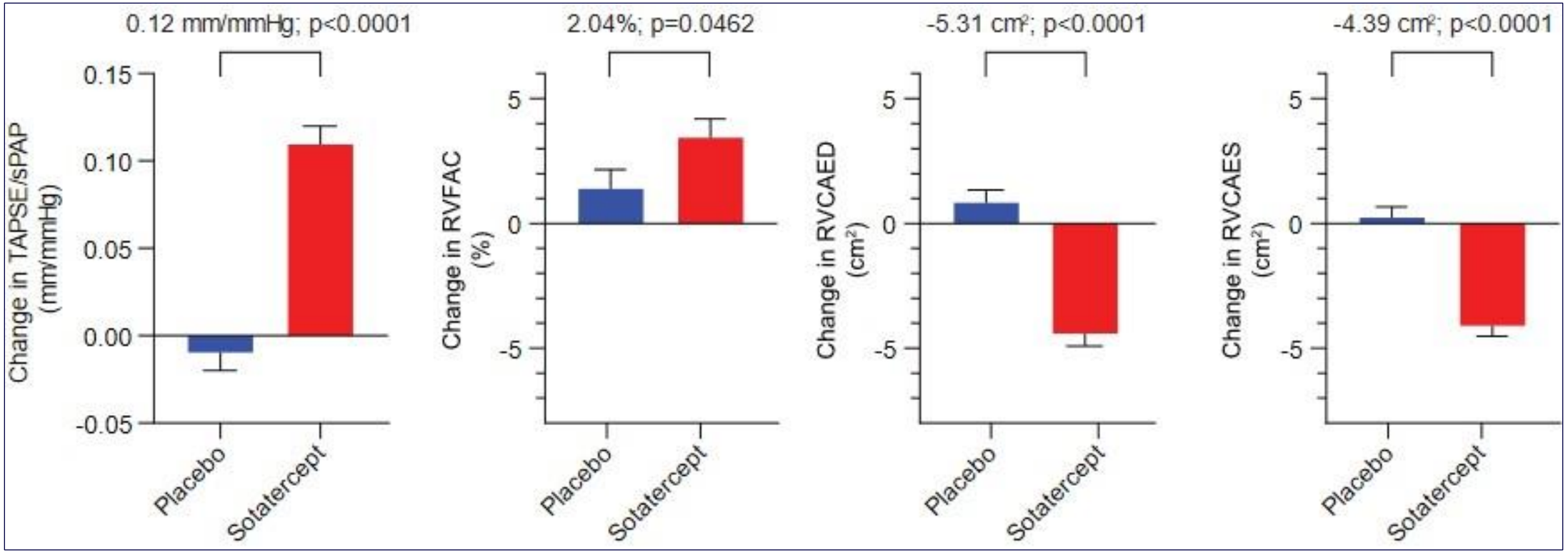
Gomberg-Maitland M, et al. J Heart Lung Transplant. 2024 Dec 5:S1053-2498(24)02009-6. doi: 10.1016/j.healun.2024.11.037.

# STELLAR: Changes in the echocardiographic parameters




LS mean change (± SE) from baseline in echocardiographic parameters at week 24

RVFAC = (RVAED – RVAES)/RVAED.
LS, least-squares; sPAP, systolic pulmonary artery pressure; RVAED, right ventricular area in end-diastole; RVAES, right ventricular area in end-systole; RVFAC, right ventricular fractional area change; SE, standard error; TAPSE, tricuspid annular plane systolic excursion.
Souza R, et al. *Eur Resp J*. 2023.

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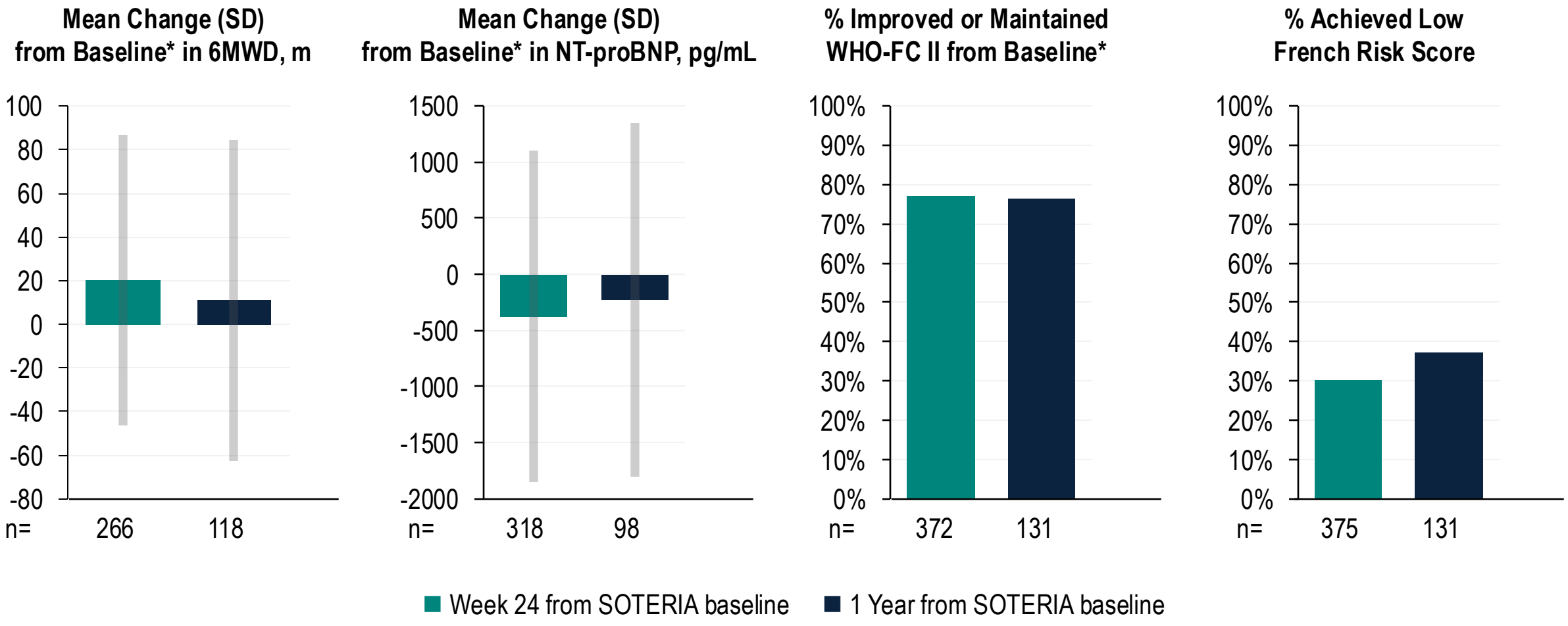
# SOTERIA Study: Long Term Use of Sotatercept

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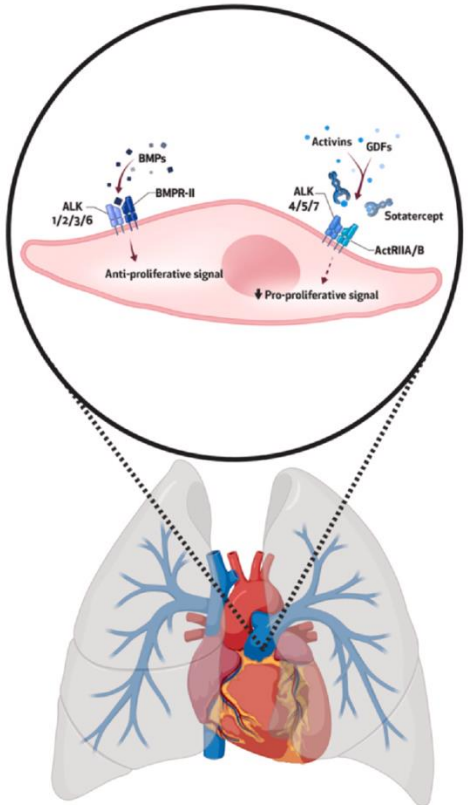
Preston I, et al. Presented at the ERS 2023 Congress

# Sotatercept for the management of pulmonary arterial hypertension

## Benefits

- Increase functional exercise capacity
- Improve WHO functional class
- Decreased mPAP and PVR without a change in CO
- Reduce risk of clinical worsening events
- Improvements in patient-reported health status
- Decreased RV size and mass




## Adverse Events

- 15% erythrocytosis >2 g/dL above ULN
- 3% thrombocytopenia platelets <50,000/mm3
- 36% bleeding event
  22% epistaxis
  4% serious bleeding
- 10% telangiectasia
- 25% headache
  20% rash
  15% diarrhea
  15% dizziness
  14% erythema

## Key Unknowns

- Long-term efficacy and safety
- Impact of development of antidrug antibodies
- May cause fetal harm and infertility

Cascino TM, et al. JHLT. 2024 Oct 5:S1053-2498(24)01874-6.

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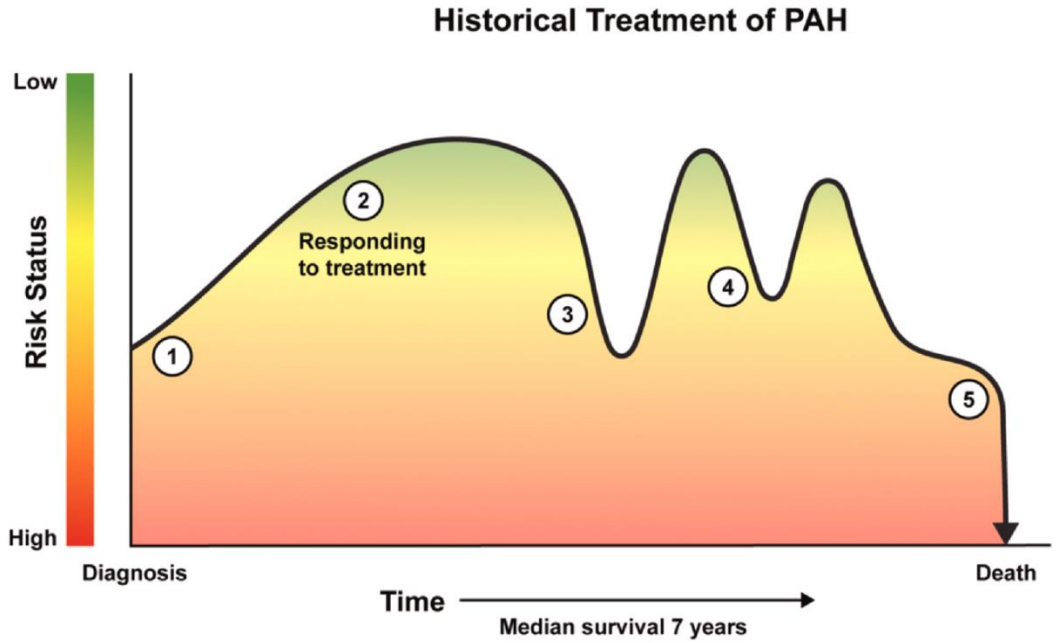
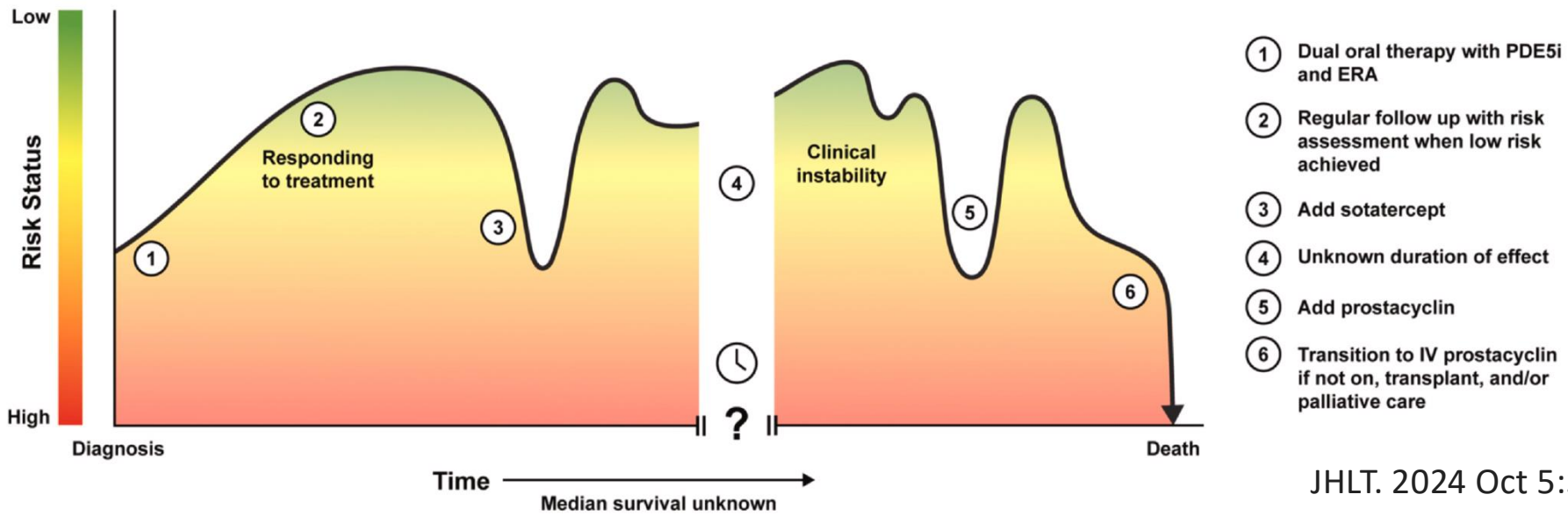



STATE OF ART

## A new day has come: Sotatercept for the treatment of pulmonary arterial hypertension

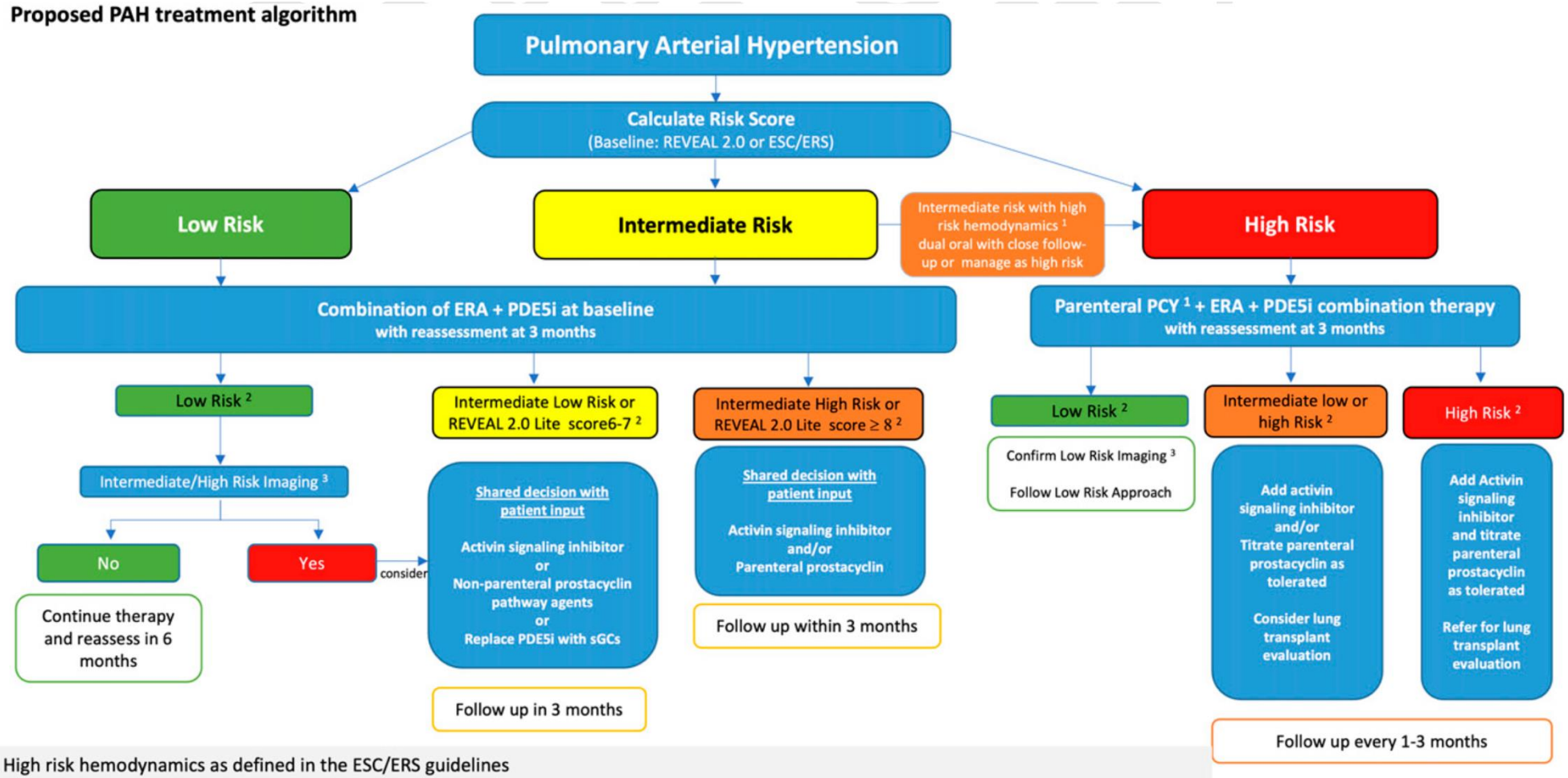
Thomas M. Cascino, MD, MSc,[a] Sandeep Sahay, MSc,[b] Victor M. Moles, MD,[a] and Vallerie V. McLaughlin, MD[a]

*From the [a]Division of Cardiovascular Medicine, University of Michigan, Ann Arbor, Michigan; and the [b]Division of Pulmonary, Critical Care and Sleep Medicine, Houston Methodist Hospital, Houston, Texas.*




JHLT. 2024 Oct 5:S1053-2498(24)01874-6.

# Treatment algorithm : US perspective

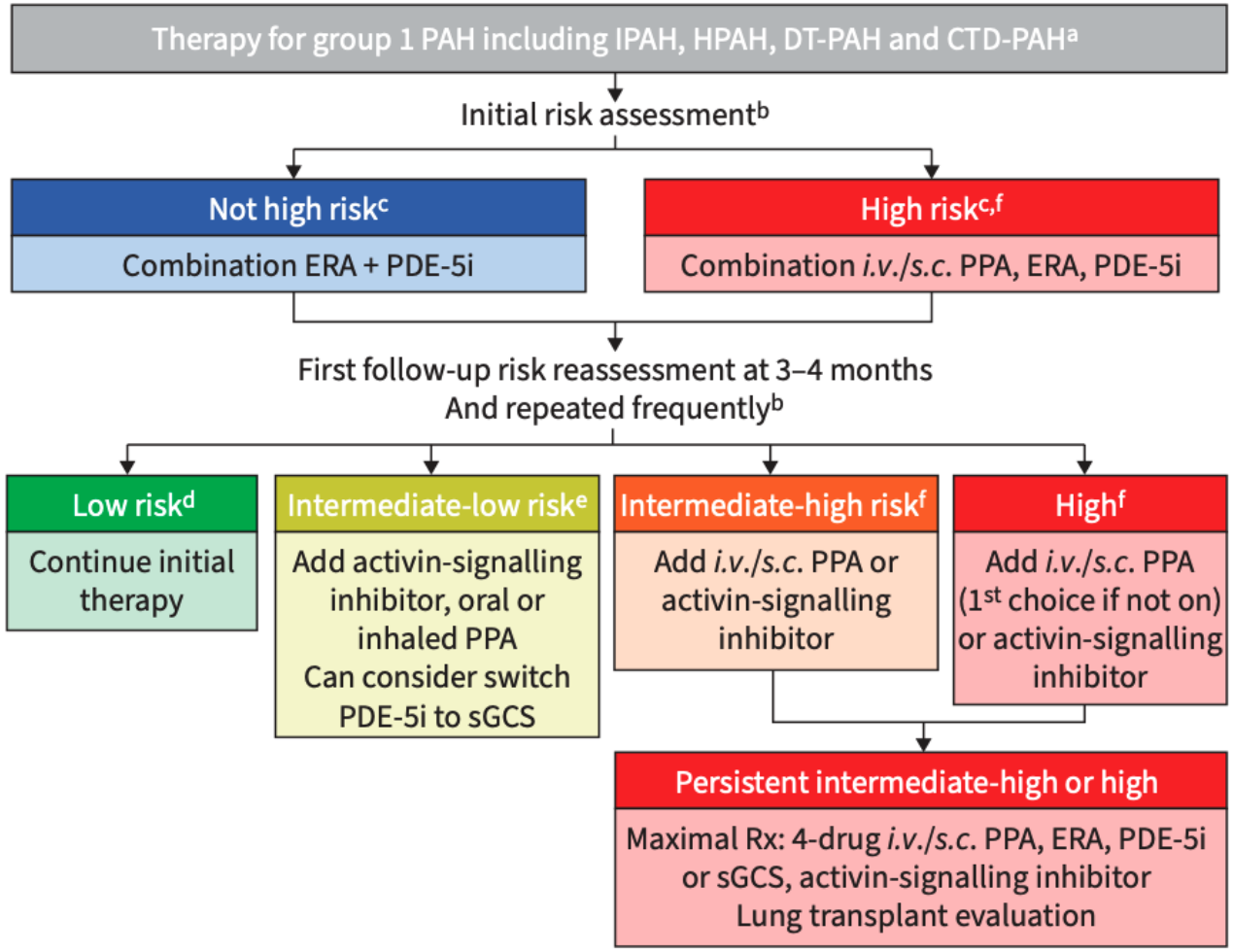



1. High risk hemodynamics as defined in the ESC/ERS guidelines
2. Follow-up risk assessment: REVEAL 2.0 Lite or ESC/ERS 4-strata; Patients with REVEAL lite 2.0 ≥ 8 should be treated as high-risk approach
3. Imaging risk: Suggest referring to the risk table in the 2022 ESC/ERS guidelines. In patients with intermediate and high-risk imaging parameters should be considered for further escalation of therapy (this is based on the expert opinion only )

** Among patients not able to tolerate therapies as indicated above alternative approaches can be adopted as an individualized approach*

Sahay S, et al. Contemporary Treatment of Pulmonary Arterial Hypertension: A US Perspective. *AJRCCM.* 2024

# Risk based treatment recommendations




**Treatment algorithm key points**

a. The treatment algorithm is intended for patients with confirmed group 1 PAH (phenotypically clear-cut, including **mPAP ≥25 mmHg and PVR >3 Wood Units** and no significant response on acute vasoreactivity testing). See text for treatment in PAH with complex phenotypes.
b. ***Risk assessment*** should be performed at baseline, within 3–4 months and periodically thereafter, and using FC, 6MWD and natriuretic peptides as a part of a validated risk calculator. Haemodynamics, RV imaging and other measures should be used to supplement risk assessment.
c. ***Initial triple therapy*** with an *i.v./s.c.* PPA is recommended in high-risk patients and may be considered in non-high risk with severe haemodynamics and/or poor RV function.
d. Most ***low-risk patients*** at follow-up should continue initial therapy.
e. Clinical trials with oral and inhaled treprostinil included ***only patients on monotherapy***, while studies of selexipag and sotarcept included patients on combination therapy.
f. ***Transplant referral*** should be considered for select high-risk patients at diagnosis, and for intermediate-high and high-risk patients at first or subsequent follow-up.

PVRI

Chin KM, et al. Treatment algorithm for pulmonary arterial hypertension. Eur Respir J 2024

# Seralutinib in adults with pulmonary arterial hypertension (TORREY): a randomised, double-blind, placebo-controlled phase 2 trial

*Robert P Frantz, Vallerie V McLaughlin, Sandeep Sahay, Pilar Escribano Subías, Ronald L Zolty, Raymond L Benza, Richard N Channick, Kelly M Chin, Anna R Hemnes, Luke S Howard, Olivier Sitbon, Jean-Luc Vachiéry, Roham T Zamanian, Matt Cravets, Robert F Roscigno, David Mottola, Robin Osterhout, Jean-Marie Bruey, Erin Elman, Cindy-ann Tompkins, Ed Parsley, Richard Aranda, Lawrence S Zisman, Hossein-Ardeschir Ghofrani, on behalf of the TORREY Study Investigators**

## Summary

**Background** Morbidity and mortality in pulmonary arterial hypertension (PAH) remain high. Activation of platelet-derived growth factor receptor, colony stimulating factor 1 receptor, and mast or stem cell growth factor receptor kinases stimulates inflammatory, proliferative, and fibrotic pathways driving pulmonary vascular remodelling in PAH. Seralutinib, an inhaled kinase inhibitor, targets these pathways. We aimed to evaluate the efficacy and safety of seralutinib in patients with PAH receiving standard background therapy.

*Lancet Respir Med* 2024; 12: 523–34

Published Online May 2, 2024 https://doi.org/10.1016/S2213-2600(24)00072-9

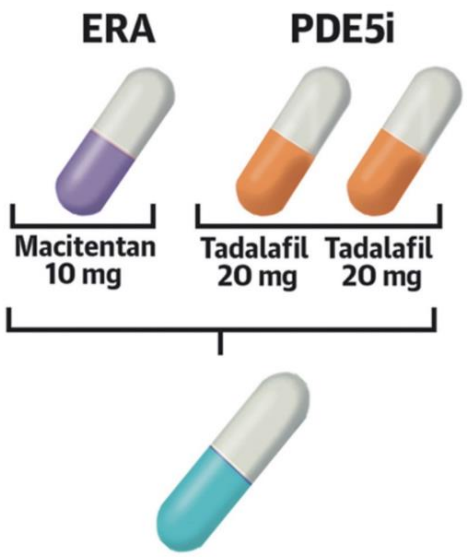
*The TORREY Study

Lancet Respir Med. 2024 Jul;12(7):523-534.

# Single-tablet combination therapy with macitentan and tadalafil vs monotherapy in patients with pulmonary arterial hypertension

## A DUE: Multicenter, randomized, controlled, double-blind, Phase 3, adaptive study

### ERA + PDE5i is the foundation of PAH treatment*




Macitentan/tadalafil fixed-dose combination (M/T FDC)

Simplified treatment approach in a once-daily single tablet

### Study Design

Adults with PAH WHO FC II or III

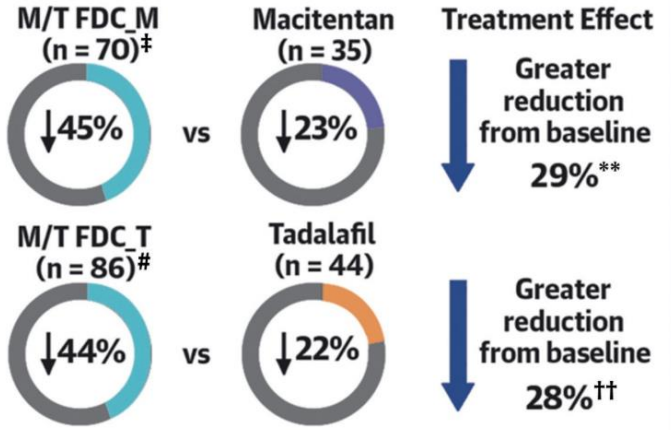
n = 187†

**Study Groups**

| M/T FDC_M | M/T FDC_T |
|---|---|
| naïve or prior ERA-treated vs | naïve or prior PDE5i-treated vs |
| Macitentan monotherapy 10 mg | Tadalafil monotherapy 40 mg |
| naïve or prior ERA-treated | naïve or prior PDE5i-treated |

### Efficacy and Safety Results

**Primary endpoint: Change in PVR from baseline to week 16 (% from baseline, geometric means)**




Marked hemodynamic improvement in the M/T FDC arms

The M/T FDC was well tolerated: safety profile consistent with macitentan and tadalafil

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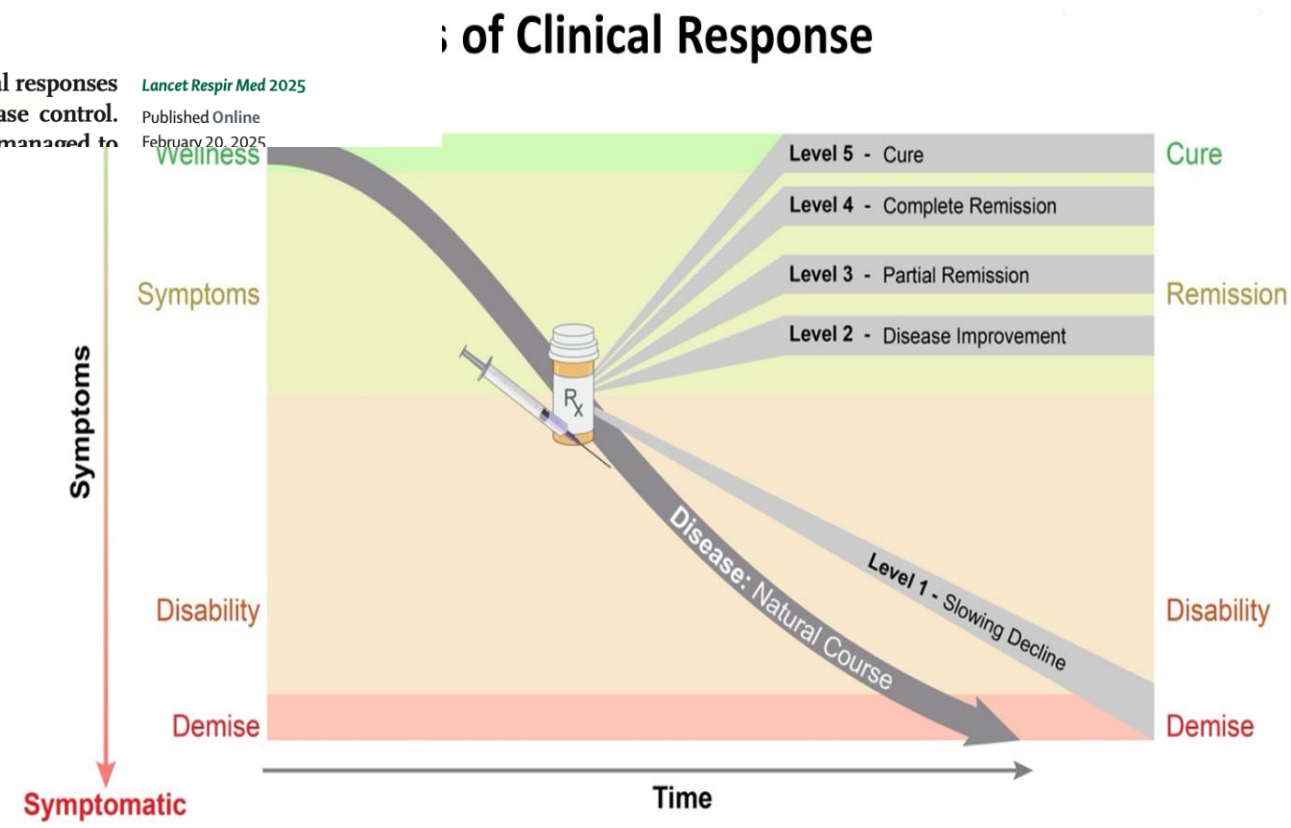
Grünig, E, et al. JACC. 2024 Jan, 83 (4) 473–484.

# Future treatment paradigms in pulmonary arterial hypertension: a personal view from physicians, health authorities, and patients

Franck F Rahaghi, Marc Humbert, Marius M Hoeper, R James White, Robert P Frantz, Paul M Hassoun, Anna R Hemnes, Steven M Kawut, Vallerie V McLaughlin, Gergely Meszaros, Peter G M Mol, Steven D Nathan, Mitchel A Psotka, Farbod N Rahaghi, Olivier Sitbon, Norman Stockbridge, Jason Weatherald, Faiez Zannad, Sandeep Sahay

Novel treatments in pulmonary arterial hypertension (PAH) with significant pathophysiological and clinical responses have generated renewed interest in changing the course of the disease and achieving long-term disease control. Historically, the term disease modification was coined in rheumatological conditions with therapies that managed to

*Lancet Respir Med* 2025
Published Online
February 20, 2025




Lancet Respir Med. 2025 Feb 20:S2213-2600(24)00425-9.
doi: 10.1016/S2213-2600(24)00425-9. PMID: 39987941.

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# Proposed Criteria for Achieving Levels of Disease Modification in Pulmonary Hypertension

| Disease modification | Haemodynamics | Right Heart Functions | Mortality Risk | Symptoms | Function | Disease Course |
|---|---|---|---|---|---|---|
| **Cure (all PAH medications withdrawn)** | mPAP ≤20 mmHg and PVR ≤2 WU at rest | Normal RA/RV Size and function | Low | No PH related symptoms | WHO FC I | Life expectancy no longer affected by PAH |
| **Complete Remission (PAH medication continued)** | mPAP ≤20 mmHg and PVR ≤2 WU at rest | Normal RA/RV Size and function | Low | No PH related symptoms | WHO FC I | Life expectancy no longer affected by PAH |
| **Partial Remission (PAH medication continued)** | Substantial improvement in pulmonary haemodynamics to mPAP ≤35 mmHg, and/or PVR<5 WU | Improvement in RA/RV Size and function | Low | Mild PH related symptoms | WHO FC I-II | Major improvement in progression free survival and/or overall survival |
| **Improvement** | Any decrease (improvement) in mPAP and PVR not fulfilling the partial remission criteria | Improvement in RA/RV Size and Function | Improved risk category | Moderate PH related symptoms | WHO FC II-III | Improvement in progression-free survival possible |
| **Slowing Decline** | Slowing deterioration of mPAP and/or PVR | Slowing deterioration of RA/RV function | Stable risk category | Moderate-to-severe PAH-related symptoms, signs of right heart failure may be present | WHO FC II-III | Improvement in progression-free survival possible |

PVRi

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## Conclusions

- PAH remains incurable, fatal and progressive disease
- Sotatercept, a first-in-class, novel activin signaling inhibitor, appears efficacious and safe.
- the possibility of reverse remodeling??
- durability of effects
- known/unknown future side effects
- Multiple novel pathways are being explored

# Thank you!