# CONNECTIVE TISSUE DISEASE AND PAH:

# MULTIDISCIPLINARY COORDINATION OF CARE TO OPTIMIZE OUTCOMES

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# FACULTY DISCLOSURES

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Research Grants - Acceleron, Actelion, Aerovate, Altavant, Bellarophon, Bayer, Gossamer, Liquidia, Pfizer, Phase Bio, Reata, and United Therapeutics

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Data Safety Monitoring Board – Pfizer, and United Therapeutics

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# FACULTY DISCLOSURES

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Has no real or apparent conflicts of interest to report

# LEARNING OBJECTIVES

- Review the epidemiology and pathophysiology of CTD, and how it places patients at high risk for secondary PAH
- Discuss how to use appropriate screening and diagnostic criteria to identify patients with CTDs who may have PAH
- Describe how to determine if patients should be referred for cardiac catheterization and definitively diagnose PAH
- Outline how to integrate guideline recommendations and efficacy and safety data of PAH pharmacotherapies for treatment of patients with CTD-PAH
- Describe how to apply a collaborative approach across multidisciplinary experts to optimize outcomes for patients with CTD-PAH

# OUR PROGRAM TODAY WILL INCLUDE THE FOLLOWING TOPICS:

- An overview of the epidemiology and pathophysiology of PAH
- A discussion of various emerging agents targeting PAH and their potential utility in the clinical practice setting
- An interactive pathophysiology puzzle game designed to improve your understanding of PAH pathophysiology.
- Various practitioner and patient resource and support tools

# EPIDEMIOLOGY & PATHOPHYSIOLOGY

# EPIDEMIOLOGY OF PAH

## All PAH

- Current US estimates are unclear
- Canada: estimated incidence from **~2.4 to 3.0 cases/million**
- EU: historical estimated incidence from **2.5 to 7.1 cases/million;** estimated prevalence from **5 to 52/million**

## PAH subtypes

- IPAH or HPAH: **~50%**
- PAH associated with other conditions: **~50%**
  - CTD-PAH most common, followed by CHD-PAH
  - SSc-PAH most common CTD-PAH

## Sex

- Female predominance estimates from **1.7:1 to 4.8:1***

## Race/ethnicity

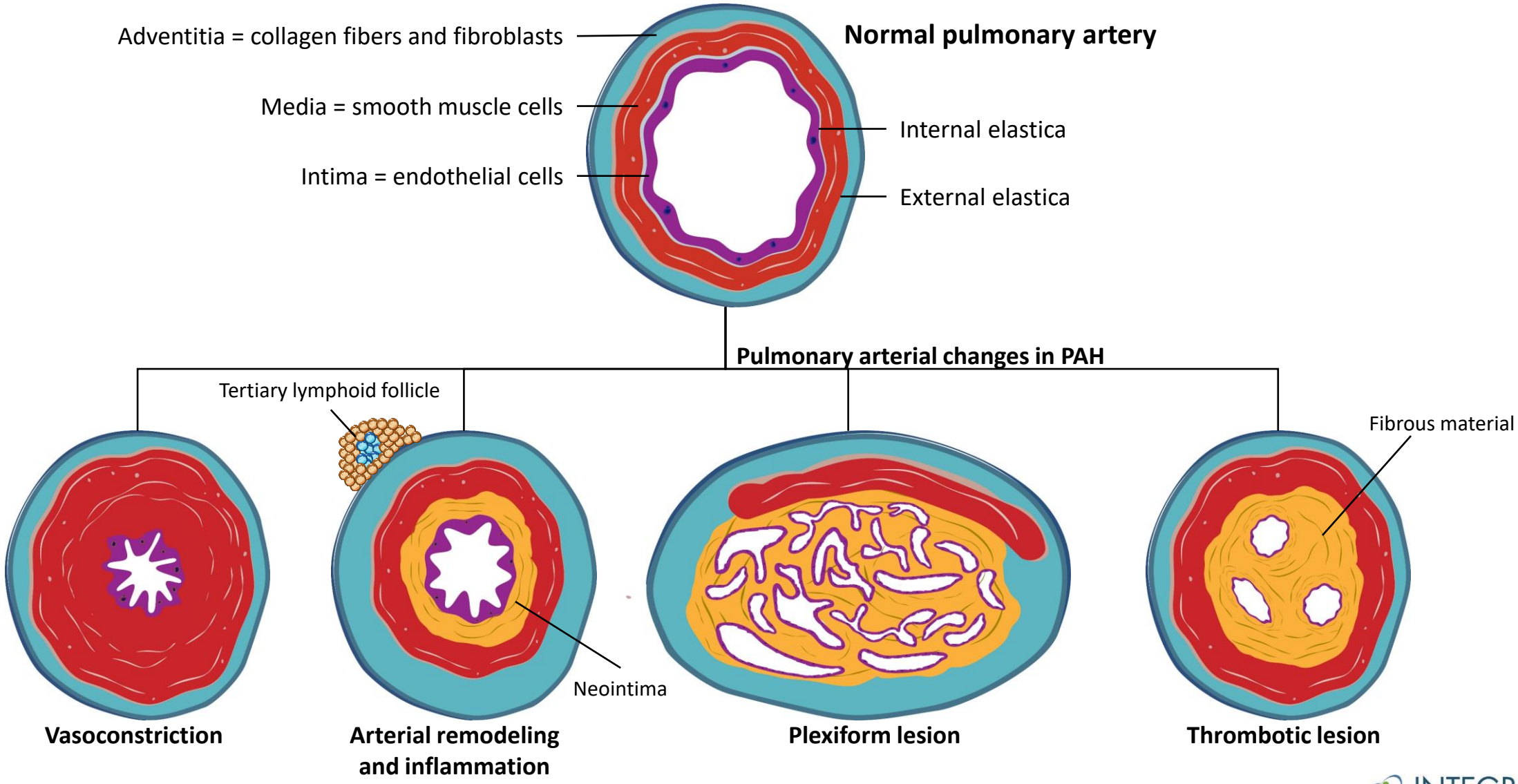
- REVEAL registry:
  - Caucasians: **72.8%**
  - African Americans: **12.2%**
  - Hispanics: **8.9%**,
  - Asians or Pacific Islanders: **3.3%**
  - Other or unknown: **2.8%**

*Based on NIH, PHC, REVEAL, and Mayo registries

CHD, congenital heart disease; IPAH, idiopathic PAH; HPAH, hereditary PAH

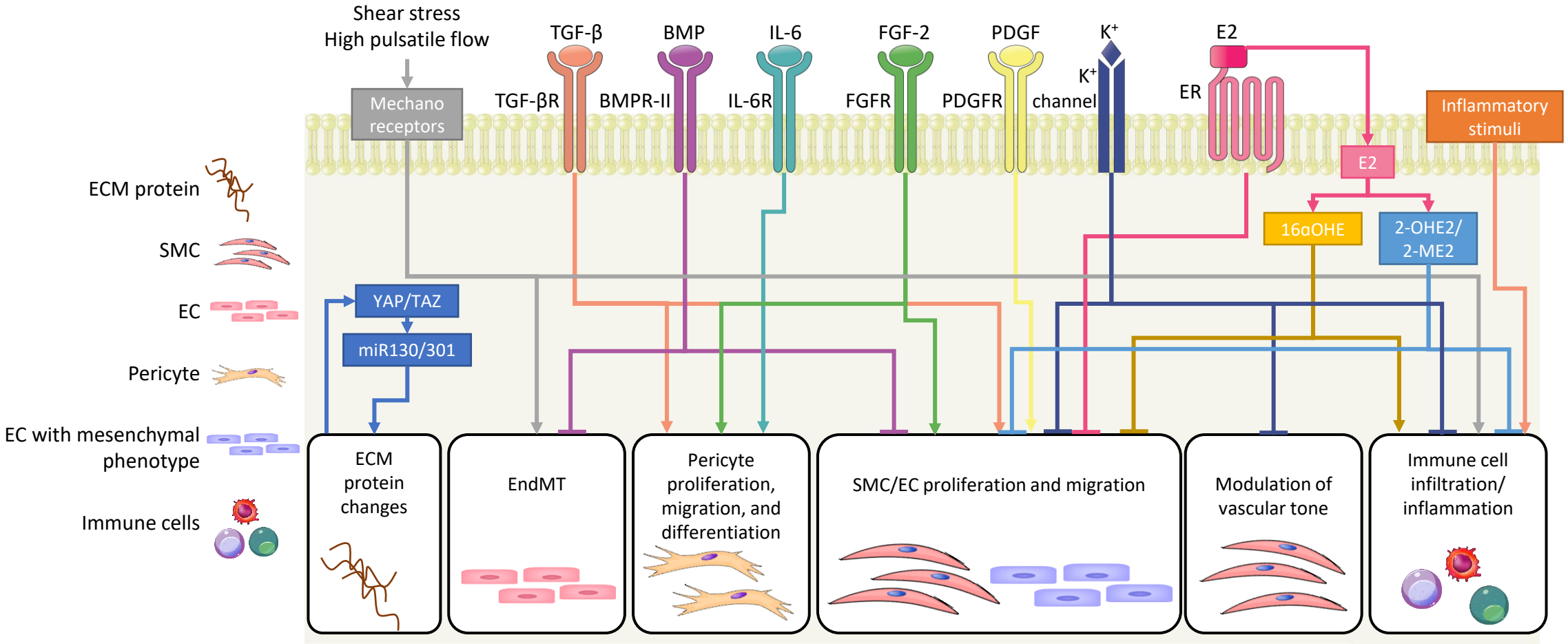
Reviewed in: Prins et al. *Cardiol Clin*. 2016;34:363-74;Peacock et al. *Eur Respir J*. 2007;30:104-9; Humbert et al. *Am J Respir Crit Care Med*. 2006;173:1023-30; Wijeratne et al. *Circ Cardiovasc Qual Outcomes*. 2018;11:e003973.

# PATHOBIOLOGY OF PAH




McLaughlin et al. *J Am Coll Cardiol*. 2015;65:1976-1997.

# DIVERSE CELLULAR PROCESSES AND SIGNALING PATHWAYS THAT CONTRIBUTE TO PAH PATHOGENESIS




EC: endothelial cell; SMC: smooth muscle cell; ECM: extracellular matrix; EndMT: endothelial-to-mesenchymal transition; TGF-β: transforming growth factor-β; TGF-βR: TGF-β receptor; BMP: bone morphogenetic protein; BMPR-II: BMP receptor type 2; IL-6: interleukin-6; IL-6R: IL-6 receptor; FGF-2: fibroblast growth factor-2; FGFR: FGF receptor; PDGF: platelet-derived growth factor; PDGFR: PDGF receptor; E2: oestradiol; ER: oestrogen receptor; YAP/TAZ: Yes-associated protein/transcriptional coactivator with PDZ-binding motif; 16αOHE: 16α-hydroxyoestrone; 2-OHE2: 2-hydroxyoestradiol; 2-ME2: 2-methoxyoestradiol; miR130/301: microRNA-130/301 family

Hemnes et al. *European Respiratory Review*. 2017;26:170093.

# PH, PAH, & CTD-PAH: DEFINITIONS AND CLASSIFICATION

# DEFINITION OF PH AND PAH

**PH**

- An increase in mPAP >20 mmHg at rest as assessed by RHC

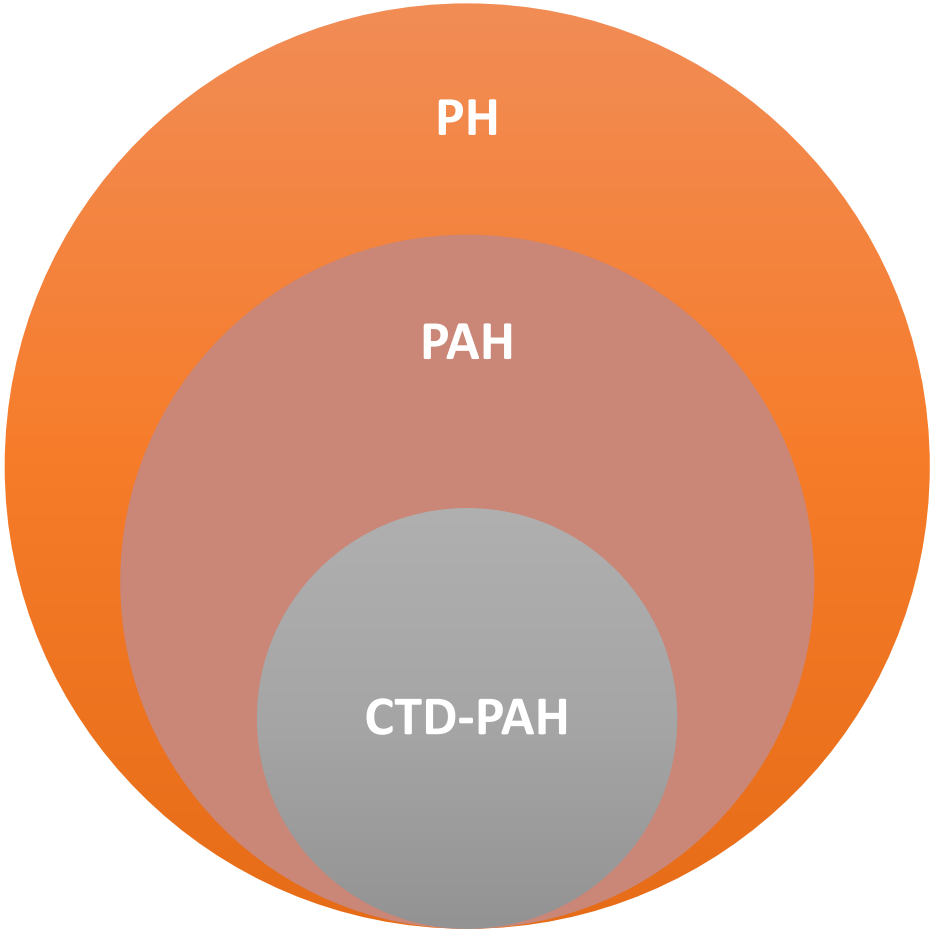
**PAH**

- PH characterized hemodynamically by the presence of pre-capillary PH, defined by PAWP ≤15 mmHg and PVR >3 WU in the absence of other causes of precapillary PH (eg, PH due to lung diseases, CTEPH or other rare diseases)

CTEPH, chronic thromboembolic pulmonary hypertension; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary artery wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RHC, right heart catheterization; WU, Wood units.

Simmoneau et al. *Eur Respir J.* 2019 24;53(1):1801913.

# PH, PAH, AND CTD-PAH




**PH**

- Progressive increases in PVR, RV failure, possible mortality
- Complication of multiple chronic diseases
- Affects up to 10% of the general population

**PAH**

- PH subtype
- Leading cause of morbidity and mortality in CTD

**CTD-PAH**

- 25% of PAH cases
  - 2nd-most common form of PAH (after IPAH)
- Differs from IPAH
  - Less favorable outcomes
  - Cardiovascular involvement (LV involvement)
  - Need for immunosuppression (for SLE)

PH, pulmonary hypertension; PAH, pulmonary arterial hypertension; CTD-PAH, connective tissue disease-associated PAH; RV, right ventricular.

Galiè N, et al. *Eur Heart J*. 2016;37(1):67-119 ; Vonk M. *Eur Cardiovasc Dis*. 2007;3(2):69–73.

INTEGRITY CONTINUING EDUCATION

# RISK FACTORS FOR CTD-PAH

## SSc-PAH

- Temporal risk factors
  - Older age at scleroderma onset
  - Long-standing disease
- Comorbidities
  - Limited cutaneous SSc
  - Cutaneous telangiectasias
  - Severe digital ischemia
  - Severe Raynaud's phenomenon
- Serologic biomarkers
  - Nucleolar pattern of ANA
  - ACAs
- Lung function
  - Declining or isolated low Dlco

## SLE-PAH

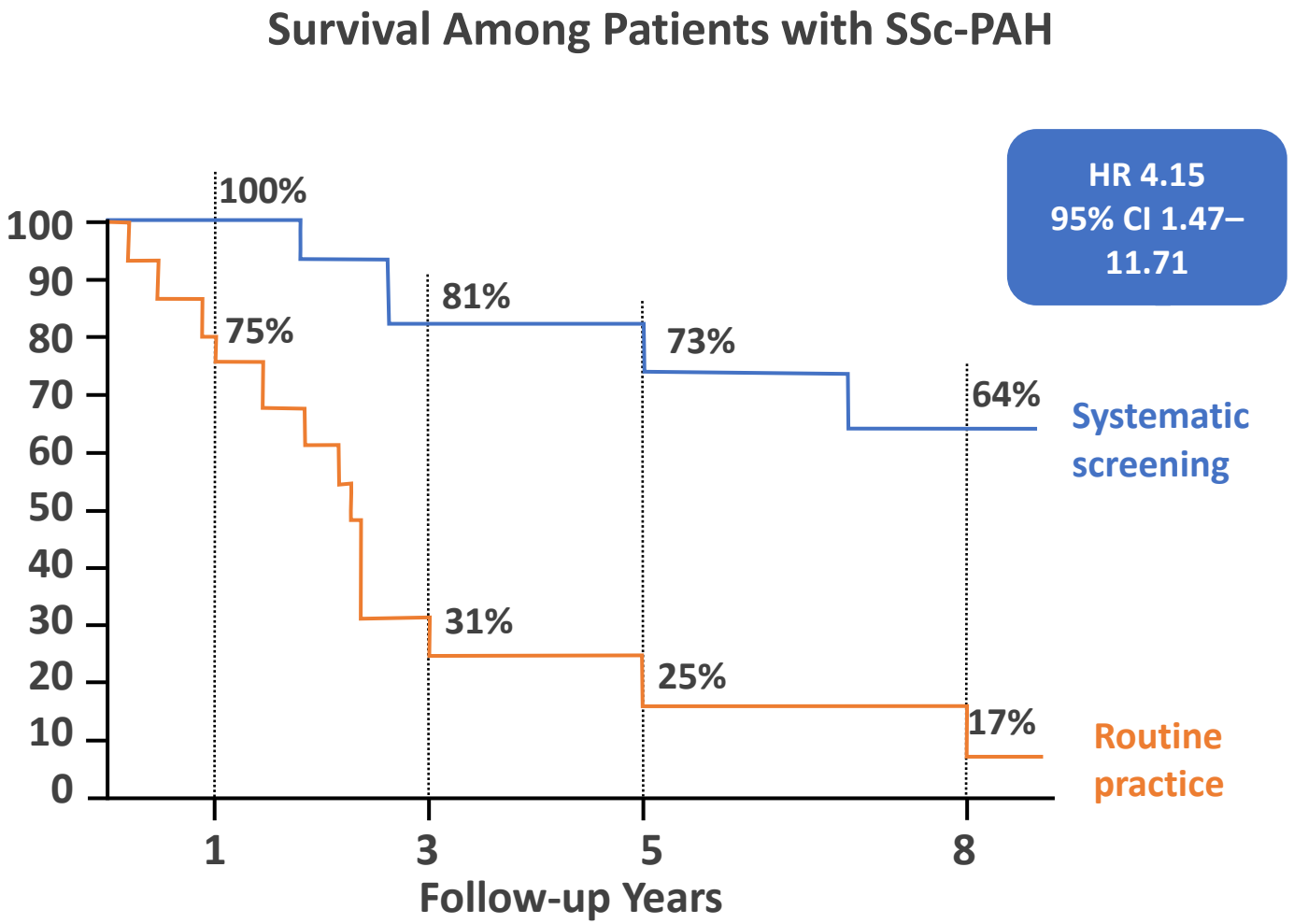
- Temporal risk factors
  - Long-standing disease
- Comorbidities
  - Raynaud's phenomenon
- Serologic biomarkers
  - Anti-phospholipid antibody
  - Anti-RNP antibody
  - Anti-endothelial cell antibody
  - Anti-SSA antibody
- Other risk factors
  - Serositis
  - Pericardial effusion

ACAs, anticardiolipin antibodies; ANA, antinuclear antibodies; DLCO, diffusing capacity of the lung for carbon monoxide; RNP; ribonucleoprotein; SLE, systemic lupus erythematosus.

Jiang et al. *Autoimmun Rev*. 2020;19:10260; Ninagawa et al. *Rheumatol Int*. 2019;39:1883-1887; Huang et al. *Medicine (Baltimore)*. 2016;95:e2761; Wang et al. *Lupus*. 2017;26:1390-1400.

# CTD-PAH SCREENING AND DIAGNOSIS

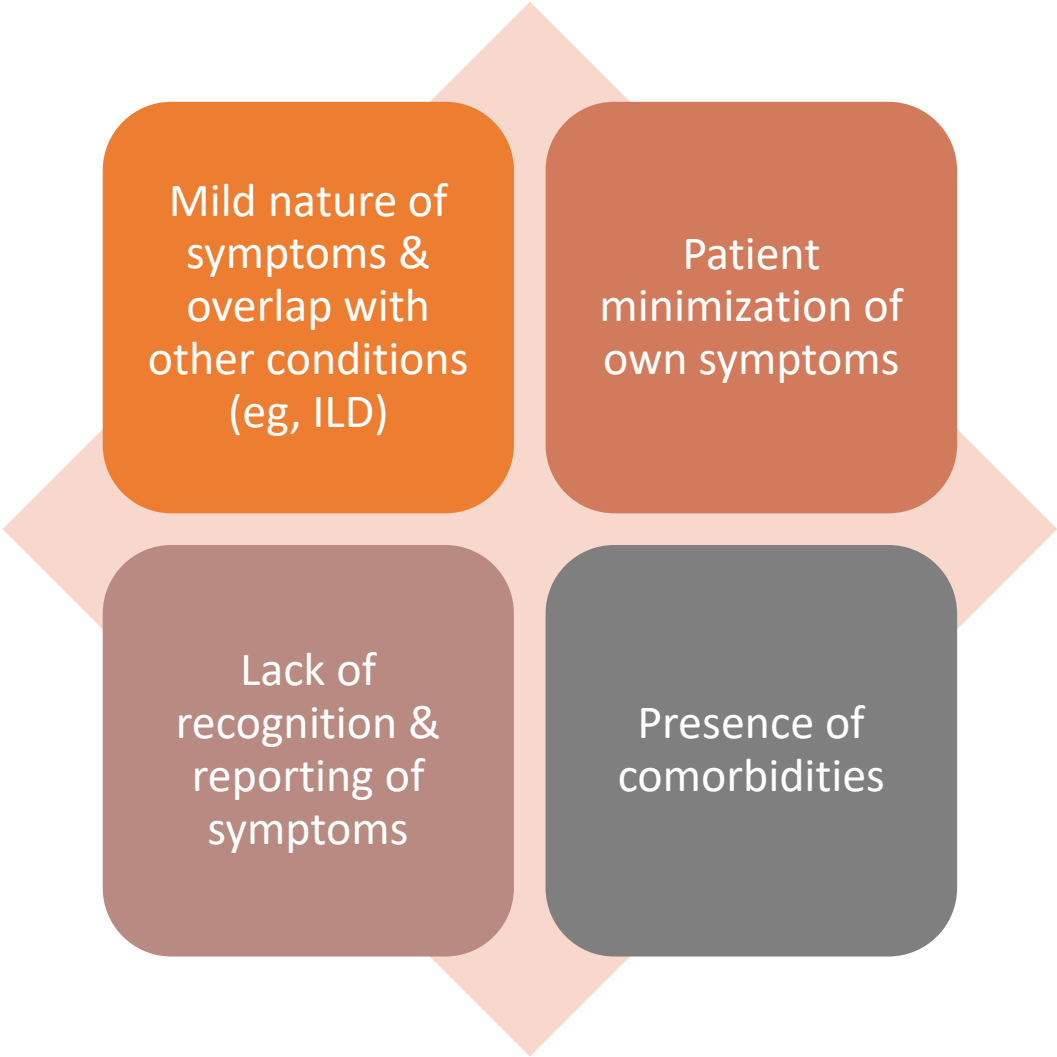
# THE IMPORTANCE OF EARLY RECOGNITION OF CTD-PAH: IMPACT OF SYSTEMATIC SCREENING ON SURVIVAL




APAH, associated PAH; CHD, congenital heart disease; CI, confidence interval; CTD, connective tissue disease; HPAH, hereditary PAH; HR, hazard ratio; IPAH, idiopathic PAH; PAH, pulmonary arterial hypertension; SSc, systemic sclerosis.

Rådegran G, et al. Scand Cardiovasc J. 2016;50(4):243-250.; Humbert M, et al. Arthritis Rheum. 2011;63(11):3522-30.

# BARRIERS TO EARLY DETECTION OF CTD-PAH




ILD, interstitial lung disease.

# CLINICAL MANIFESTATIONS OF PH

## Initial symptoms
(non-specific, induced by exertion)

**Common**:

- Dyspnea
- Fatigue
- Weakness
- Angina
- Syncope

**Less common**:

- Dry cough
- Exercise-induced nausea and vomiting

## Advanced symptoms
(progressing RV failure, occur at rest)

- Abdominal distension
- Ankle edema

## Symptoms specific to underlying/associated diseases or comorbidities

- Hemoptysis
- Hoarseness
- Wheeze
- Angina
- Telangiectasia, digital ulceration, & sclerodactyly (SSc)
- Inspiratory crackles (ILD)
- Spider naevi, testicular atrophy, & palmar erythema (liver disease)
- Digital clubbing (PVOD, cyanotic CHD, ILD, or liver disease)

PVOD, pulmonary venoocclusive disease.

Galie N, et al. *Eur Heart J*. 2016;37(1):67-119.

# PHYSICAL EXAM FINDINGS OF PH

**May be present initially**

- Left parasternal lift
- Accentuated pulmonary component of the second heart sound
- RV third heart sound
- Pansystolic murmur of tricuspid regurgitation
- Diastolic murmur of pulmonary regurgitation

**More common in advanced disease**

- Elevated JVP
- Hepatomegaly
- Ascites
- Peripheral edema
- Cool extremities

**Not usually present**

- Wheezes
- Crackles

Galie N, et al. *Eur Heart J*. 2016;37(1):67-119.

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# WHO FUNCTIONAL CLASSIFICATION OF PH*

## Class I

- No limitation of physical activity
- Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope

## Class II

- Slight limitation of physical activity
- Comfortable at rest
- Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope

## Class III

- Marked limitation of physical activity
- Comfortable at rest
- Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope

## Class IV

- Unable to carry out any physical activity without symptoms
- Manifest signs of right HF
- Dyspnea and/or fatigue may even be present at rest
- Discomfort increased by any physical activity

*Functional classification of pulmonary hypertension modified after the New York Heart Association functional classification according to the WHO 1998.
HF, heart failure.
Galiè N, et al. *Eur Heart J*. 2009;30(20):2493-537.

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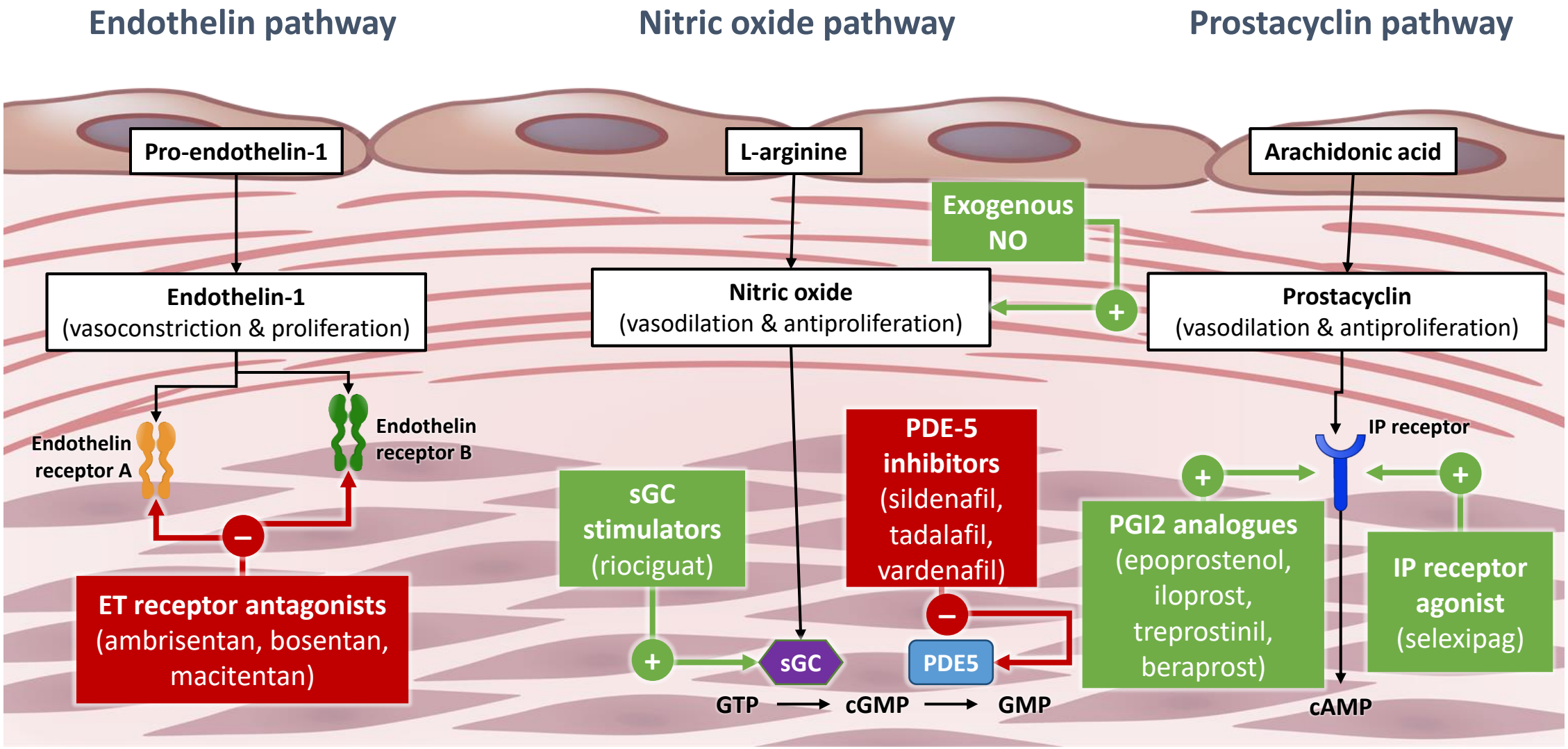
# PAH MECHANISMS OF ACTION & TREATMENT OPTIONS

# THERAPEUTIC TARGETS OF APPROVED AND INVESTIGATIONAL PAH TREATMENTS




cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; ET, endothelin; GTP, guanosine triphosphate; IP, prostacyclin receptor; NO, nitric oxide; PDE-5, phosphodiesterase-5, PGI2, prostacyclin; sGC, soluble guanylate cyclase.

Yerly et al. *Swiss Med Wkly*. 2016;146:w14305. Zhang et al. *Metabolism.* 2017;73:9-21.

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# PATIENT CASE STUDY: PAH SCREENING ALGORITHM

# CASE PATIENT: CELIA

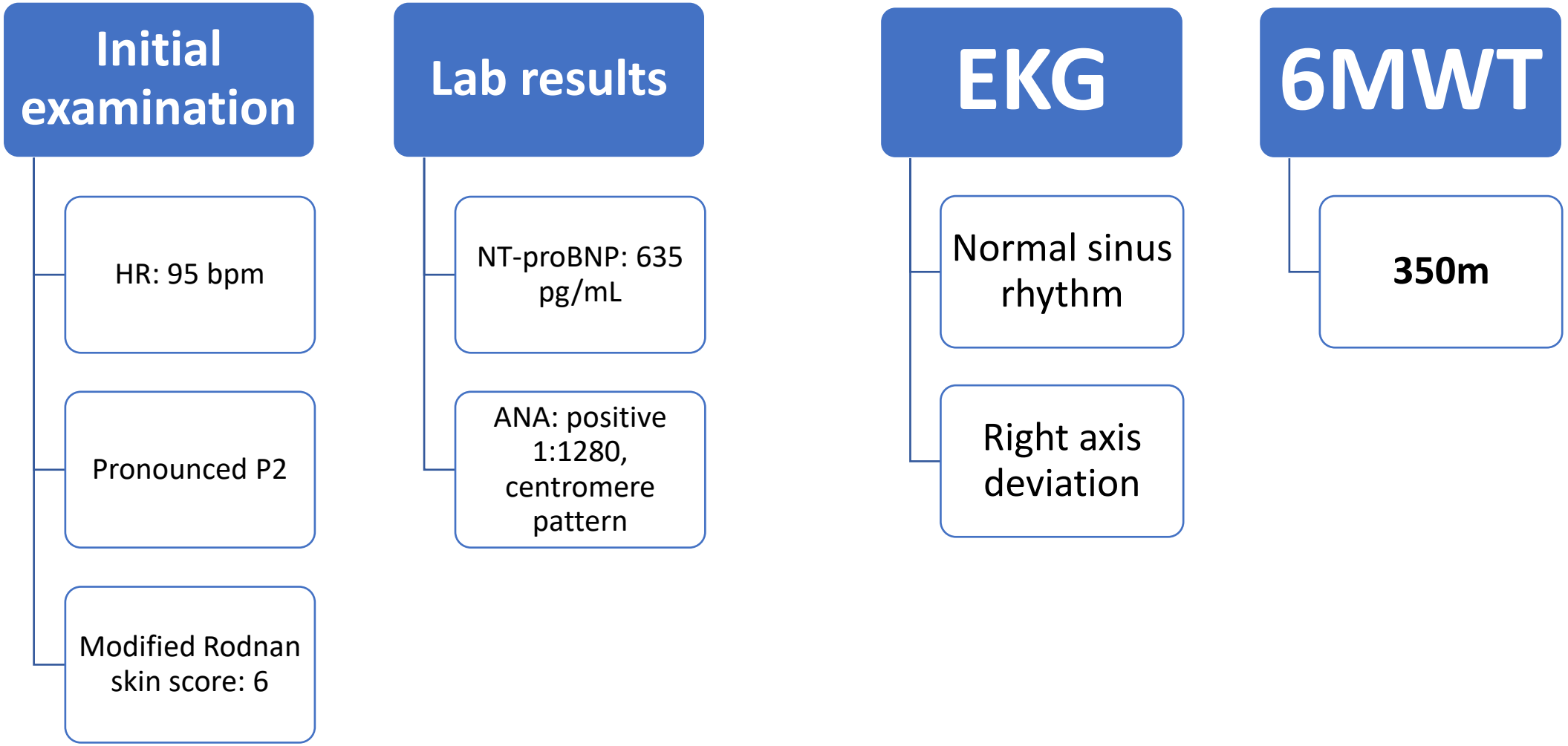
## Background

- 48-year-old woman with limited SSc
  - Raynaud's
  - Telangiectasias
  - Esophageal dysmotility

## Presentation at routine visit

- 3-month history of mild exertional dyspnea
- Is generally comfortable at rest
- Becomes extremely tired after climbing one flight of stairs

# INITIAL PATIENT ASSESSMENTS




6MWT, 6-minute walk test; ANA, antinuclear antibody; bpm, beats per minute; EKG, electrocardiogram; HR, heart rate; NT-proBNP, N-terminal pro-brain natriuretic peptide.

# ESC/ERS 2015 RECOMMENDATIONS FOR PAH SCREENING: KEY RECOMMENDATIONS FOR CTD-PAH WORK-UP

**Grade I**

- **RECOMMENDED**:
  - Resting echocardiography screening asymptomatic patients with SSc (B)

**Grade IIa**

- **CONSIDER** combined approach (biomarkers, PFTs, & echocardiography) to predict PH in SSc (B)

**Grade IIb**

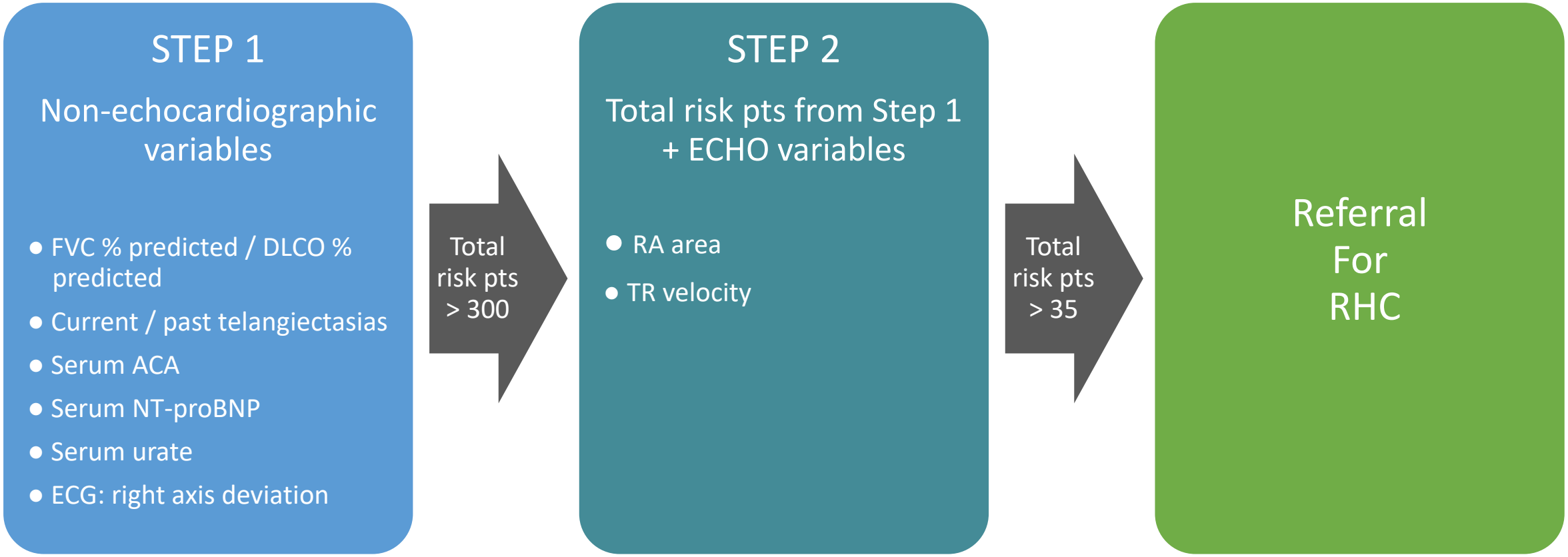
- **MAY BE CONSIDERED**:
  - Initial DETECT algorithm screening in adult SSc patients with >3y disease duration & DLCO <60% predicted (B)
  - Annual screening with echocardiography, PFTs, & biomarkers in patients with SSc (B)

**Grade III**

- Exercise echocardiography is **NOT RECOMMENDED** to predict PH in high-risk population (C)

Note: Level of evidence for the recommendation is denoted in parentheses.
DLCO = diffusing capacity of the lung for carbon monoxide; HPAH = heritable PAH; PFTs = pulmonary function tests; PoPH = portopulmonary hypertension.
Adapted from: https://orbi.uliege.be/bitstream/2268/188918/1/Web_Addenda_ESC-ERS_PH_Guidelines_ERJ-2015.pdf

# THE DETECT ALGORITHM FOR PAH SCREENING




**DETECT recommended RHC in 62% of patients (referral rate) and missed only 4% of PAH patients (false negatives).**

RHC, right heart catheterization.

Coghlan et al. *Ann Rheumatic Dis*. 2014;73:1340.

# PATIENT CASE STUDY: DIAGNOSTIC CRITERIA

# CELIA: ADDITIONAL ASSESSMENTS

## PFTs

| | Actual | % Pred |
|---|---|---|
| $FEV_1$ (liters) | 1.86 | 95% |
| FVC (liters) | 2.38 | 96% |
| $FEV_1$/FVC (%) | 78 | 99% |
| DLCO (mL/min/mmHg) | 11.00 | 54% |
| DLCO [Hb] (mL/min/mmHg) | 10.96 | 54% |

## Echo

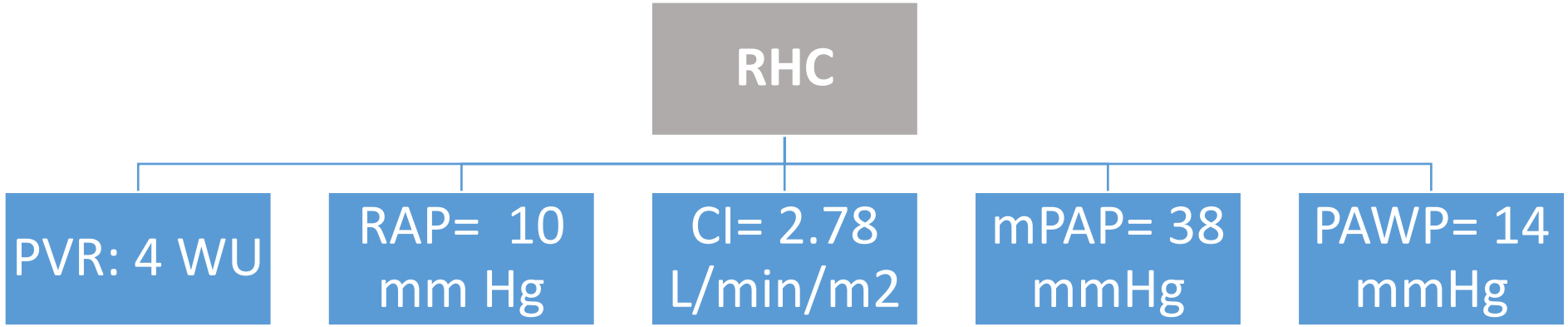
- RV dilation
- Trace pulmonary insufficiency
- Estimated RVSP 58 mmHg

## HRCT

- No cardiomegaly
- No evidence of ILD

Echo, echocardiography; HRCT, high-resolution computed tomography; RV, right ventricular; RVSP, right ventricular systolic pressure.

# CELIA: RHC FINDINGS




RAP, right atrial pressure.

# PATIENT CASE STUDY: RISK ASSESSMENT

# RISK ASSESSMENT OF PATIENTS WITH PAH

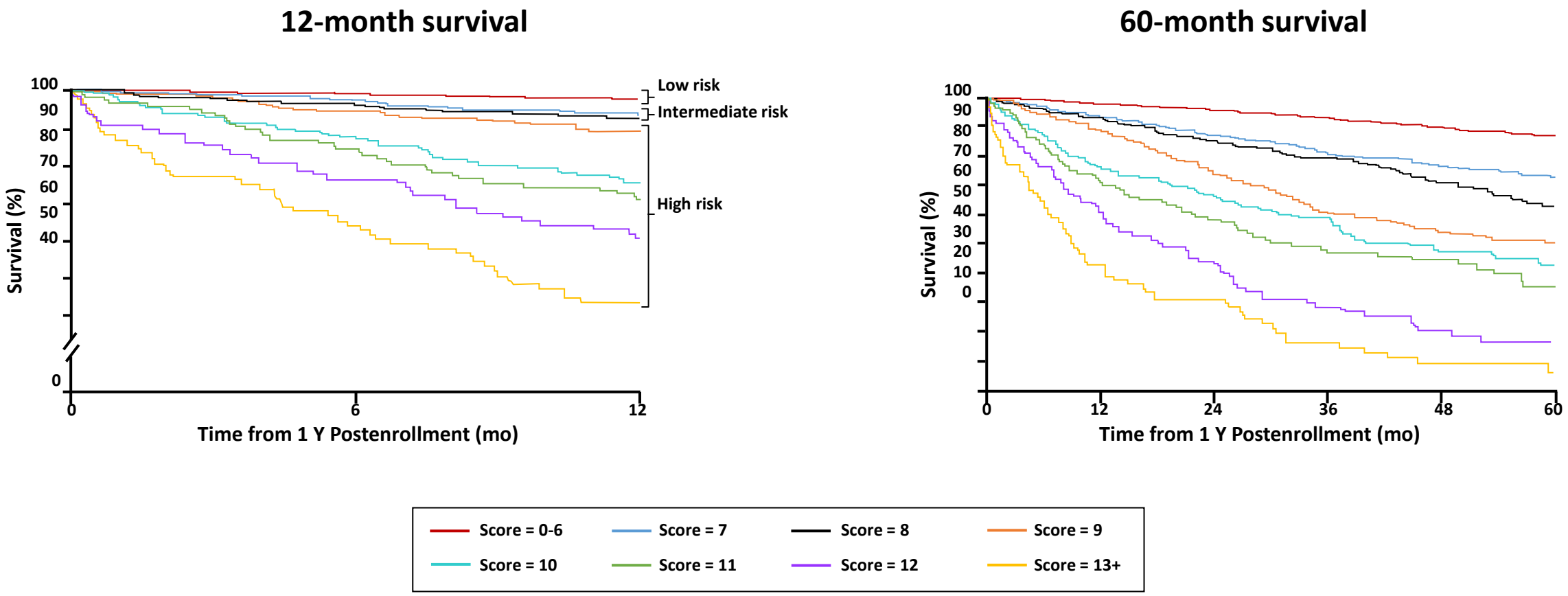
| | Estimated 1-Year Mortality | | |
|---|---|---|---|
| **Determinants of Prognosis*** | **Low Risk (<5%)** | **Intermediate Risk (5%–10%)** | **High Risk (>10%)** |
| **Clinical signs of right heart failure** | Absent | Absent | Present |
| **Symptom progression** | No | Slow | Rapid |
| **Syncope** | No | Occasional syncope | Repeated syncope |
| **WHO FC** | I, II | III | IV |
| **6MWD** | >440 m | 165–440 m | <165 m |
| **Cardiopulmonary exercise testing** | Peak $VO_2$ >15 mL/min/kg (>65% predicted)<br>$VE/VCO_2$ slope <36 | Peak $VO_2$ 11–15 mL/min/kg (35%–65% predicted)<br>$VE/VCO_2$ slope 36–44.9 | Peak $VO_2$ <11 mL/min/kg (<35% predicted)<br>$VE/VCO_2$ slope ≥45 |
| **NT-proBNP plasma levels** | BNP <50 ng/L<br>NT-proBNP <300 ng/L | BNP 50–300 ng/L<br>NT-proBNP 300–1400 ng/L | BNP >300 ng/L<br>NT-proBNP >1400 ng/L |
| **Imaging (echocardiography, cardiac MRI)** | Right atrium area <18 $cm^2$<br>No pericardial effusion | Right atrium area 18–26 $cm^2$<br>No or minimal, pericardial effusion | Right atrium area >26 $cm^2$<br>Pericardial effusion |
| **Hemodynamics** | RAP <8 mmHg<br>Cardiac index ≥2.5 L/min/$m^2$<br>$SvO_2$ >65% | RAP 8–14 mmHg<br>Cardiac index 2.0–2.4 L/min/$m^2$<br>$SvO_2$ 60%–65% | RAP >14 mmHg<br>Cardiac index <2.0 L/min/$m^2$<br>$SvO_2$ <60% |

*Mostly based on expert opinion and validated for IPAH.

$SVO_2$, venous oxygen saturation; $VO_2$, venous oxygen volume; VE, ventilation; WHO FC, World Health Organization functional class.

Galie N, et al. *Eur Heart J*. 2016;37(1):67–119.

# REVEAL 2.0 RISK SCORE CALCULATOR: PREDICTING SURVIVAL IN PAH



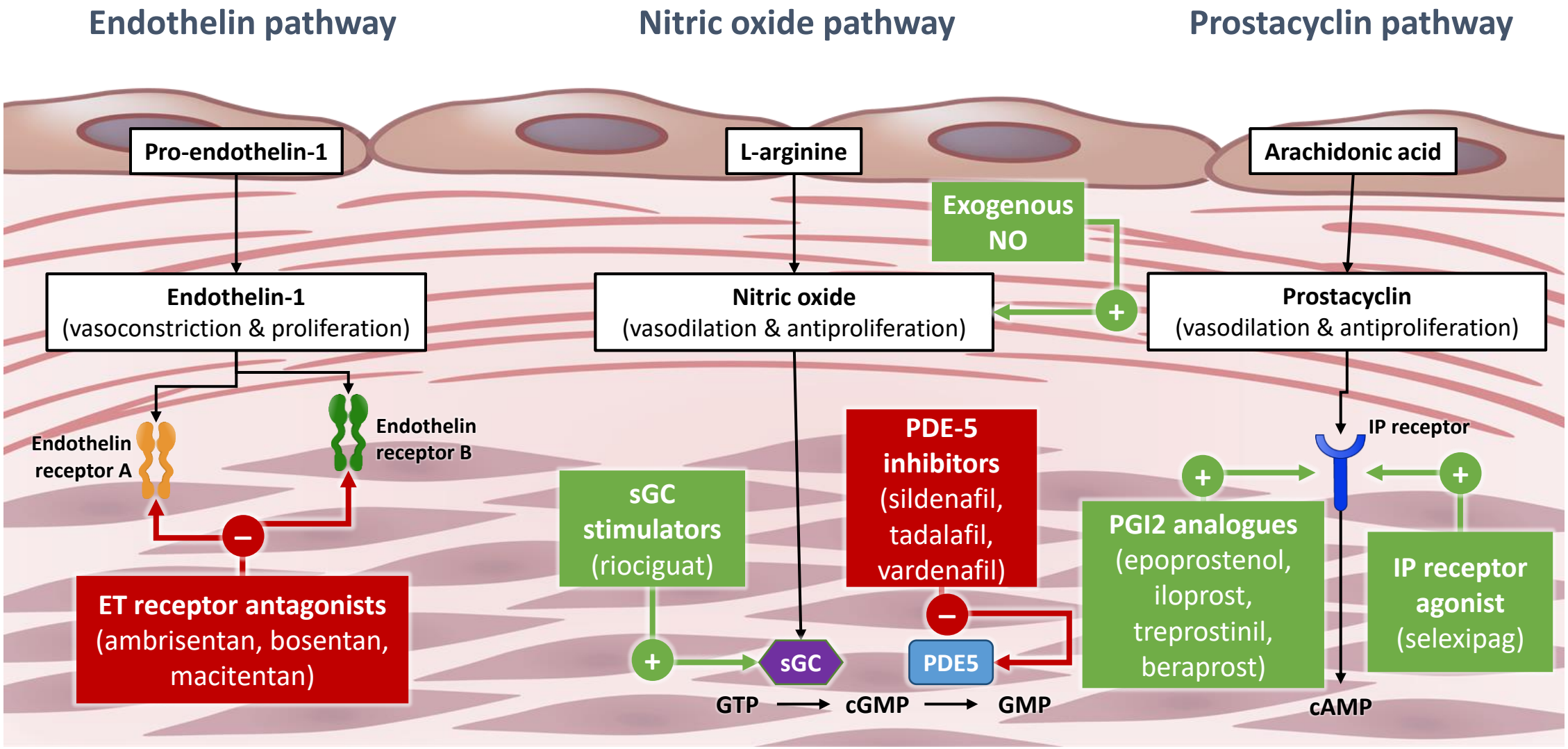

**REVEAL 2.0 provided robust separation of risk among risk categories and predicted 12-month and 60-month survival in patients with PAH.**

Note: REVEAL 2.0 also predicted 12- and 60-month clinical worsening (data not shown).

Benza et al. *Chest*. 2019;156:323-337.

# PAH MECHANISMS OF ACTION: INTERACTIVE ACTIVITY

# THERAPEUTIC TARGETS OF APPROVED AND INVESTIGATIONAL PAH TREATMENTS




Yerly et al. *Swiss medical weekly*. 2016;146:w14305-w14305. Zhang et al. *Metabolism.* 2017;73:9-21.

# ESC/ERS RECOMMENDATIONS & CLINICAL TRIAL DATA

# ESC/ERS GUIDELINES: INITIAL COMBINATION THERAPY FOR PAH

| Class | Therapy | Indication | | |
|---|---|---|---|---|
| | | WHO-FC II | WHO-FC III | WHO-FC IV |
| **ERA + PDE-5i** | Ambrisentan + tadalafil | ☑ | ☑ | ☑ |
| | Other ERA + PDE-5i | ☑ | ☑ | ☑ |
| **ERA + PDE-5i + prostacyclin analogue** | Bosentan + sildenafil + IV epoprostenol | | ☑ | ☑ |
| **ERA/PDE-5i + prostacyclin analogue** | Bosentan + IV epoprostenol | | ☑ | ☑ |
| | Other ERA or PDE-5i + SC treprostinil | | ☑ | ☑ |
| | Other ERA or PDE-5i + IV prostacyclin analogue | | ☑ | ☑ |

Sequence is by rating. **Therapies/indications highlighted in orange have IB recommendations.**
ERA, endothelin receptor antagonist; IV, intravenous; PDE-5i, phosphodiesterase-5 inhibitor; SC, subcutaneous.
Galie N, et al. Eur Heart J. 2016;37(1):67–119.

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# ESC/ERS GUIDELINES: SEQUENTIAL COMBINATION THERAPY FOR PAH

| Class | Therapy | Indication | | |
|---|---|---|---|---|
| | | WHO-FC II | WHO-FC III | WHO-FC IV |
| PDE-5i + ERA | Macitentan added to sildenafil | ☑ | ☑ | ☑ |
| | Ambrisentan added to sildenafil | ☑ | ☑ | ☑ |
| | Bosentan added to sildenafil | ☑ | ☑ | ☑ |
| ERA + guanylate cyclase stimulator | Riociguat added to bosentan | | ☑ | ☑ |
| ERA and/or PDE-5i + IP receptor agonist | Selexipag added to ERA and/or PDE-5i | ☑ | ☑ | ☑ |
| Prostacyclin analogue + PDE-5i | Sildenafil added to epoprostenol | ☑ | ☑ | ☑ |
| PDE-5i/ERA + prostacyclin analogue | INH treprostinil added to sildenafil/bosentan | ☑ | ☑ | ☑ |
| | INH iloprost added to bosentan | ☑ | ☑ | ☑ |
| ERA + PDE-5i | Tadalafil added to bosentan | | ☑ | ☑ |
| | Sildenafil added to bosentan | ☑ | ☑ | ☑ |
| Prostacyclin analogue + ERA | Bosentan added to epoprostenol | ☑ | ☑ | ☑ |
| Other double combinations | | ☑ | ☑ | ☑ |
| Other triple combinations | | ☑ | ☑ | ☑ |
| PDE-5i + guanylate cyclase stimulator | Riociguat added to sildenafil/other PDE-5i | ☑ | ☑ | ☑ |

Sequence is by rating, class, and alphabetical order. **Therapies/indications highlighted in orange have IB recommendations.**
INH, inhaled; IP, prostacyclin.
Galie N, et al. *Eur Heart J*. 2016;37(1):67–119.

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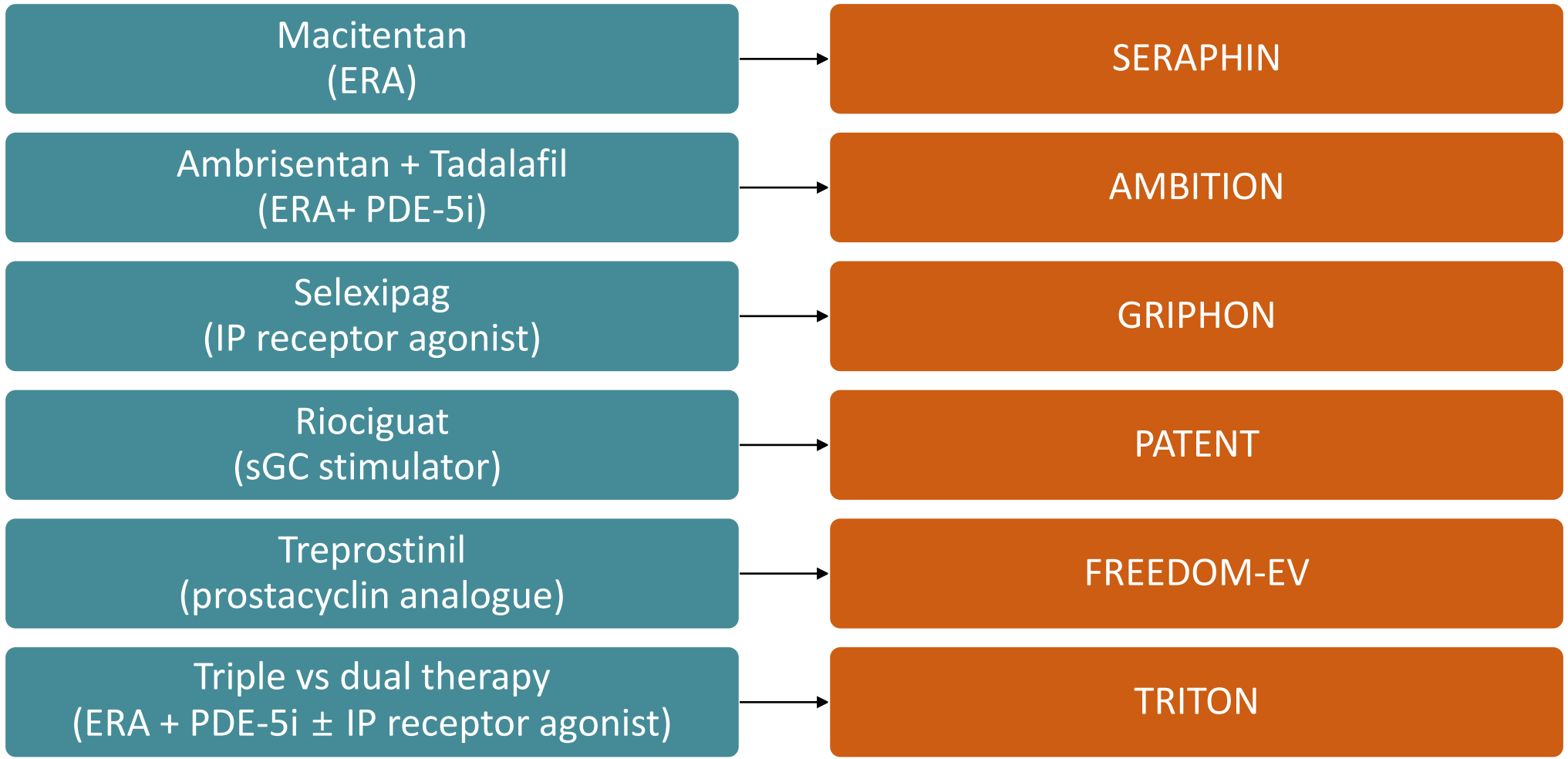
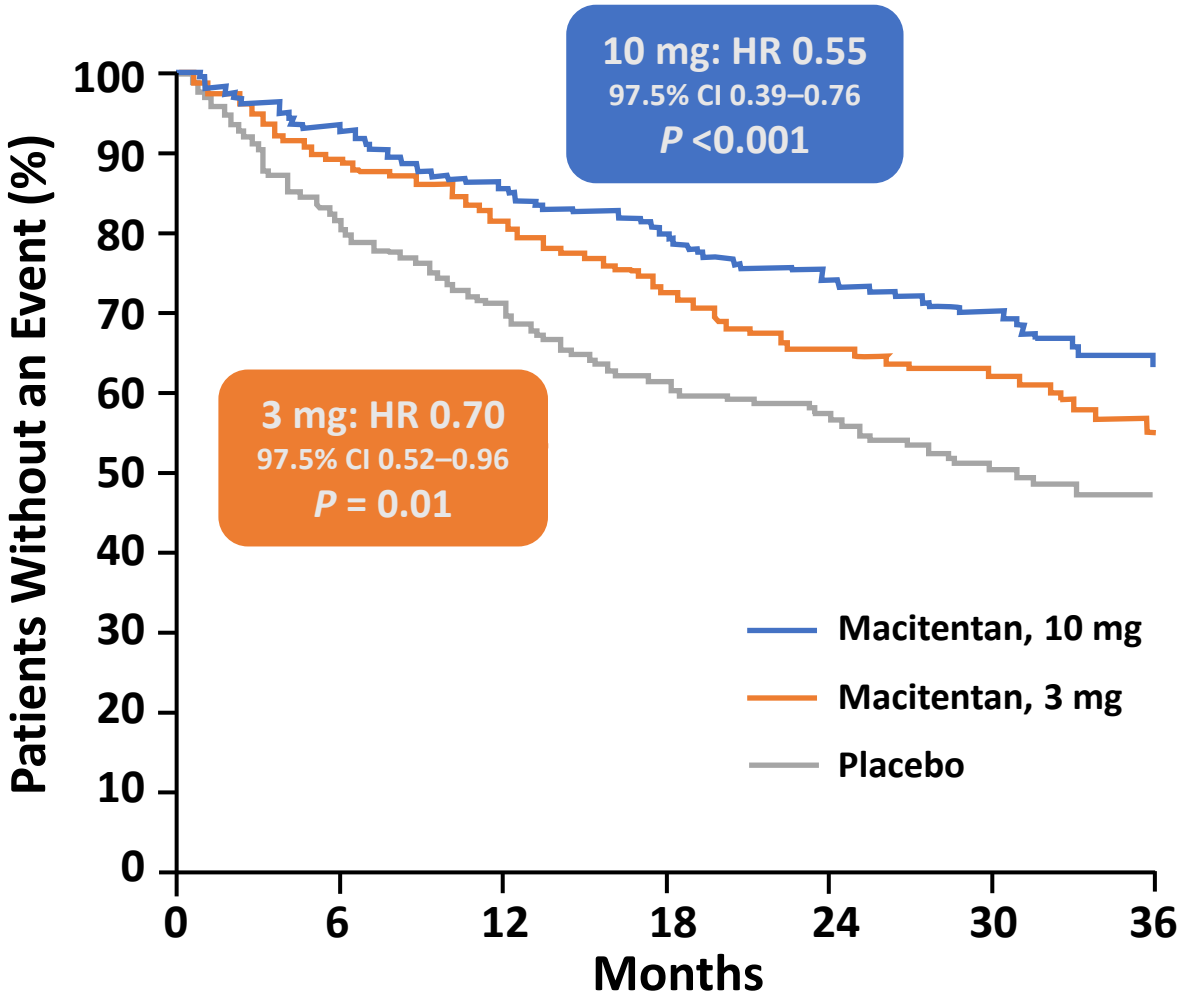
# OVERVIEW OF KEY CLINICAL TRIALS IN PAH




ERA, endothelial receptor antagonist; IP, prostacyclin; PDE-5i, phosphodiesterase-5 inhibitor; sGC, soluble guanylate cyclase.

# EFFICACY AND SAFETY OF MACITENTAN IN PATIENTS WITH PAH

## SERAPHIN Trial




**Study population:**

- Patients with symptomatic PAH

**Treatment**:

- MAC 3 mg (n=250) or 10 mg (n=242), PBO (n=250)

**Composite primary endpoint**:

- Time to first occurrence (death, AS, LTX, IV or SC prostanoid, or PAH worsening)

**Findings**:

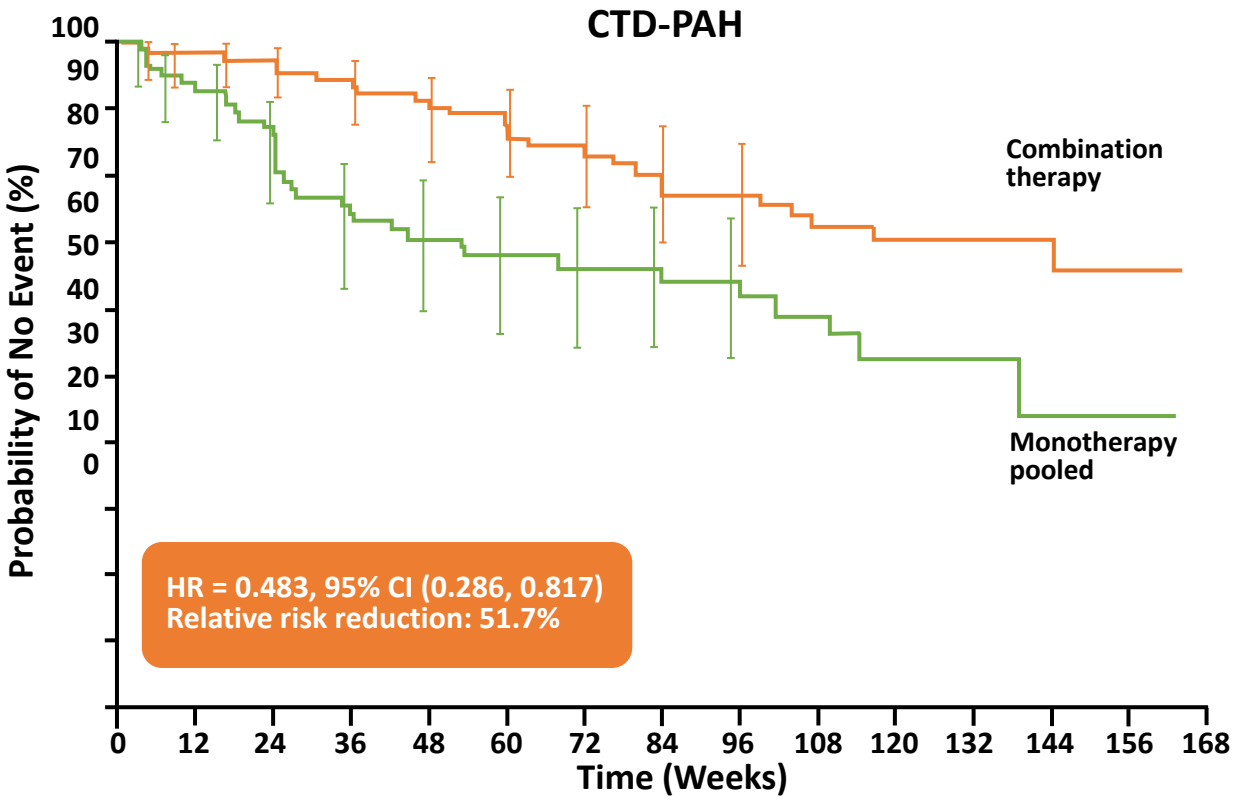
- Risk for worsening was ↓ with 3-mg & 10-mg MAC vs PBO (*graph*)
- AEs more common with MAC vs PBO: headache, nasopharyngitis, & anemia

AEs, adverse events; AS, atrial septostomy; IV, intravenous; LTX, lung transplant; MAC, macitentan; PBO, placebo; SC, subcutaneous.

Pulido T, et al. *N Engl J Med*. 2013;369(9):809-818.

# EFFICACY OF COMBINED AMBRISENTAN AND TADALAFIL IN PATIENTS WITH CTD-PAH

## AMBITION Trial




**Study objective:**

- Post hoc analysis of AMBITION mITT subpopulation

**Treatment**:

- AMB + TAD (COMB; n=117) vs AMB or TAD alone (MONO; n=99)

**Primary endpoint**:

- Time to clinical failure

**Findings**:

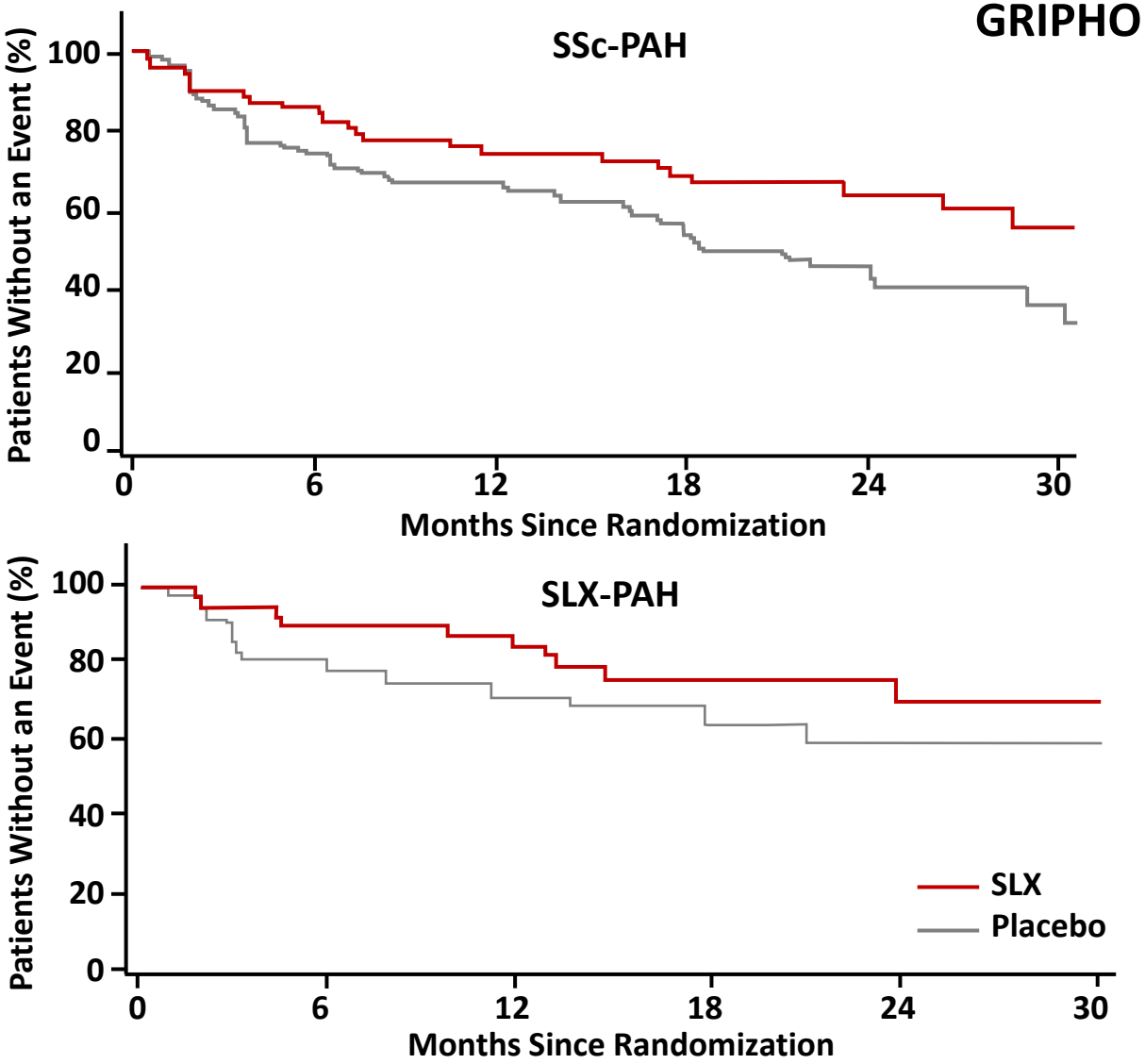
- Clinical failure risk ↓ with COMB vs MONO (risk reduction: CTD-PAH 51.7%, SSc-PAH 53.7%)
- Risk ↓ in patients with low and intermediate risk at baseline, and those with low risk at follow-up
- AEs similar across treatments for both CTD-PAH (*graph*) & SSc-PAH populations (*not shown*)

AMB, ambrisentan; COMB, combination therapy; MONO, monotherapy; TAD, tadalafil.

Kuwana et al. *Ann Rheum Dis*. 2020;79:626.

# SELEXIPAG MONO-, DOUBLE, OR TRIPLE THERAPY FOR THE TREATMENT OF CTD-PAH

## GRIPHON Trial




**Study objective:**

- Post hoc analysis of GRIPHON CTD-PAH subpopulation

**Treatment**:

- SLX (n=167) vs PBO (n=167)

**Primary composite endpoint**:

- Morbidity/mortality

**Findings**:

- SLX ↓ risk in patients with PAH-CTD by 41% (HR 0.59; 95% CI 0.41–0.85)
- ↓ irrespective of baseline therapy or CTD subtype
- AEs & SAEs similar across treatments for PAH-CTD and CTD subtypes

SAEs, serious adverse events; SLX, selexipag.

Gaine et al. *Eur Respir J*. 2017;50:1-9.

INTEGRITY CONTINUING EDUCATION

# EFFICACY AND SAFETY OF RIOCIGUAT TREATMENT OF PATIENTS WITH CTD-PAH

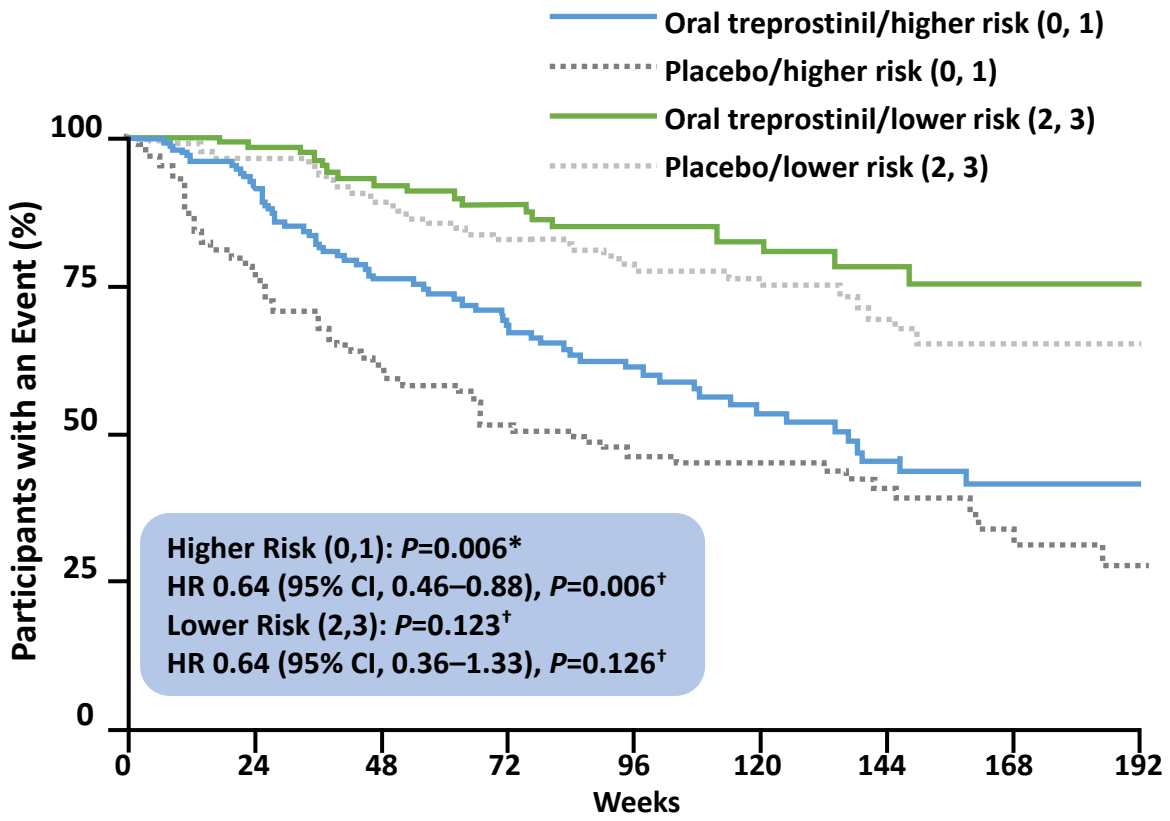
## PATENT Trials

| Study objective | Treatment | Efficacy endpoints | Findings |
|---|---|---|---|
| • Prospective subgroup analysis of patients with CTD-PAH in PATENT 1 & PATENT 2 | • Riociguat vs PBO | • PATENT 1: Change from baseline in 6MWD (primary), hemodynamics, WHO FC<br>  • Long-term extension PATENT-2: Safety and tolerability | • ↑ 6MWD, ↓ WHO FC, ↓ PVR & ↑ cardiac index<br>• 6MWD and WHO FC improvements persisted at 2 years<br>• Safety profile similar to that of overall population in the PAH-CTD subgroup<br>• **6MWD increased by a mean of 30 m in 2.5 mg–max group** and decreased by a mean of 6 m in placebo group (least-squares mean difference, 36 m; 95% CI, 20 to 52; P<0.001)<br>• Improvements in PVR (P<0.001) |

Humbert et al. *Ann Rheum Dis*. 2017;76:422-426.

# EFFICACY AND SAFETY OF TREPROSTINIL TREATMENT IN PATIENTS WITH PAH

## FREEDOM-EV Trial




**Study participants:**

- Patients with PAH (IPAH, heritable PAH, CTD-PAH, HIV-PAH, PAH-CHD, & other)

**Treatment**:

- TRE (n=345) vs PBO (n=345)

**Primary endpoint**:

- Time to first adjudicated clinical worsening event

**Findings**:

- Clinical worsening was decreased with TRE vs PBO (26% vs 36%; HR, 0.74; 95% CI, 0.56-0.97; *P*=0.028)
- Most common AEs with TRE: headache, diarrhea, flushing, nausea, & vomiting

TRE, treprostinil.

White RJ, et al. *Am J Respir Crit Care Med*. 2020;201(6):707-717.

# EFFICACY OF TRIPLE VS DUAL COMBINATION THERAPY

## TRITON Trial

- **Study objective:**
  - Comparison of initial triple vs double therapy (selexipag + macitentan ± tadalafil)
- **Efficacy findings:**

| Outcome | Triple initial therapy (N=123) | Double initial therapy (N=124) | Ratio/ Difference/ HR | 95%CI | P-value |
|---|---|---|---|---|---|
| **Change in PVR at Week 26** | 54% ↓ | 52% ↓ | Ratio: 0.96 | (0.86–1.07) | 0.424 |
| **Change in 6MWD at Week 26** | 55.0 m ↑ | 56.4 m ↑ | LSM difference: −1.4m | (−19.4 to 16.5) | 0.876 |
| **Change in NT-proBNP at Week 26** | 74% ↓ | 75% ↓ | Ratio: 1.03 | (0.77–1.37) | 0.853 |
| **Time to disease progression*** | Not reported | Not reported | HR: 0.59 | (0.32-1.09) | 0.087 |

- **Safety findings:**
  - AEs more frequent with triple vs double therapy: headache, diarrhea, nausea, extremity pain, jaw pain, & vomiting
  - Rate of selexipag/placebo discontinuation due to AEs was similar between groups

*Centrally adjudicated, until end of observation period +7d.

Chin K, et al. *Am J Respir Crit Care Med*. 2020;201:A2928.

# PATIENT CASE STUDY:
# TREATMENT MANAGEMENT APPROACH

# GENERAL MANAGEMENT OF CONFIRMED PAH

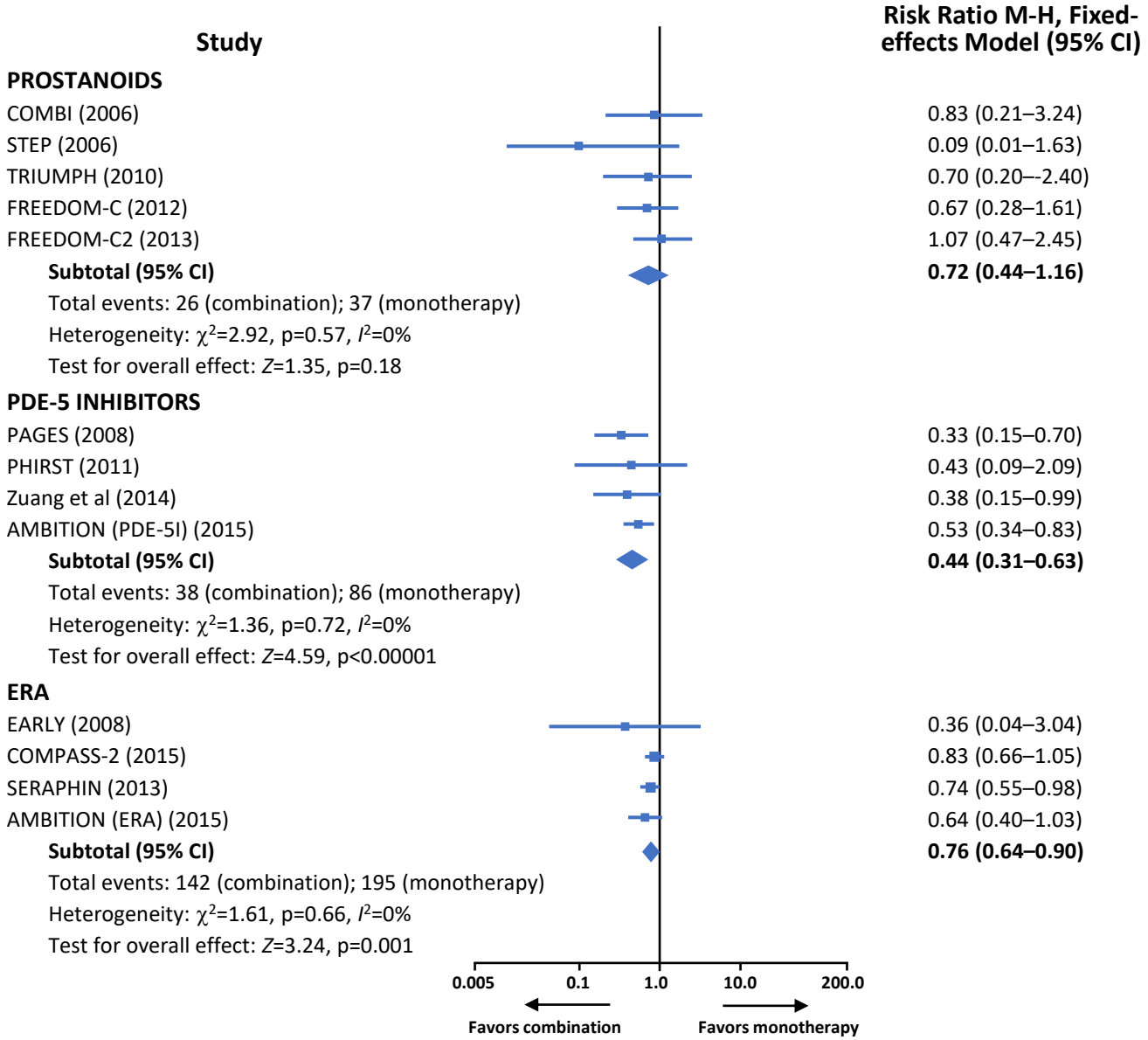
- Evaluate severity in a systematic and consistent manner
- Coordinate care between local physicians and PH centers
- Aggressively treat contributing causes
- Incorporate palliative care services
- Participate in supervised exercise activity
- Maintain current immunizations (influenza pneumococcal pneumonia, and COVID)

**Avoid the following:**

- Pregnancy (if pregnancy does occur, PH center care is suggested)
- High altitude (if exposed to high altitude or air travel, use supplemental $O_2$ as needed to maintain saturations > 91%)
- Non-essential surgery (if surgery is necessary, PH center care is suggested)

Klinger et al. *Chest*. 2019;155:565-586.

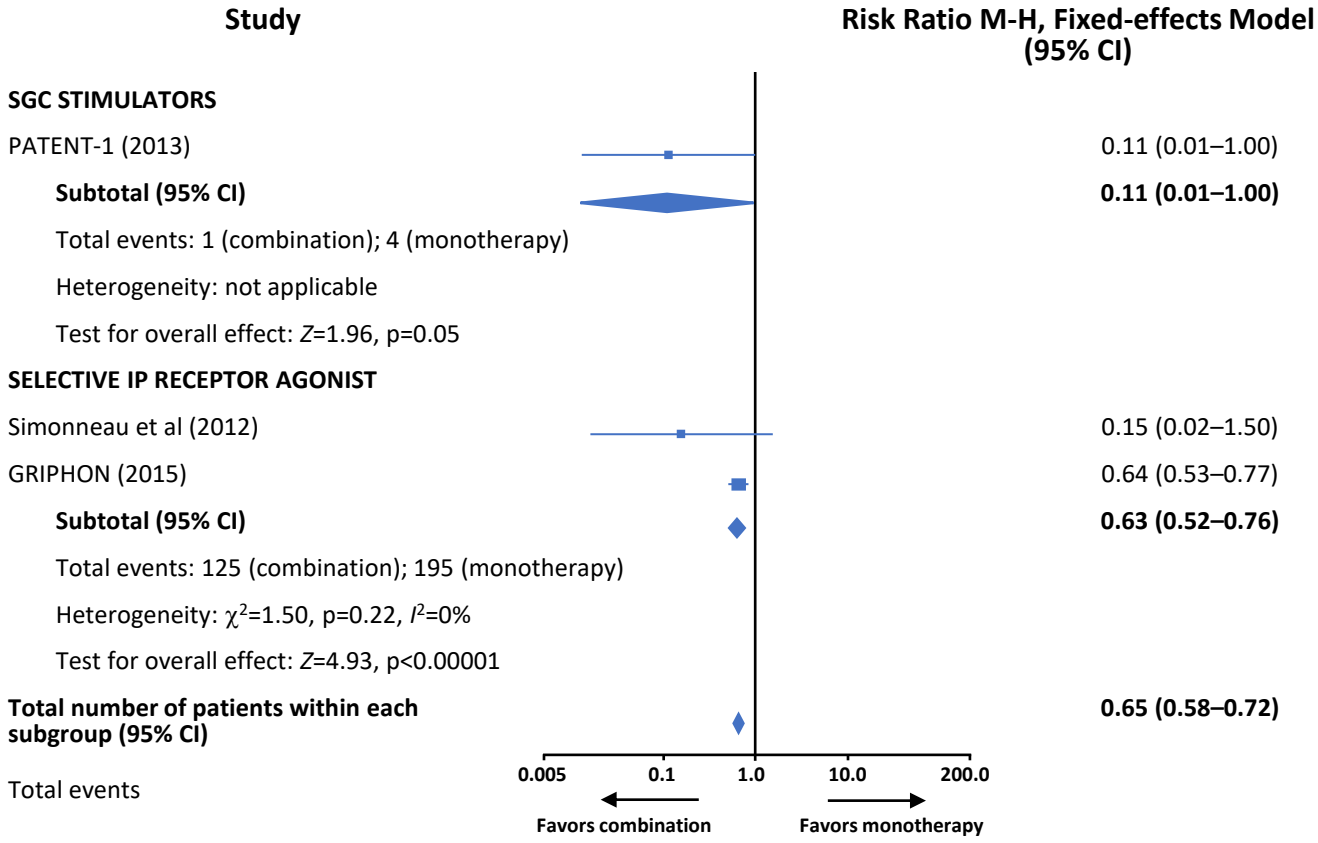
# COMBINATION THERAPY VERSUS MONOTHERAPY FOR PAH




- Meta-analysis of 15 studies (N=3802) of prospective RCTs of combined PAH specific therapies (upfront and sequential add-on) vs background PAH-specific monotherapy
- **Risk for clinical worsening was reduced with combined therapy vs monotherapy [17% vs 28%, respectively; HR 0.65 (95% CI 0.58–0.72); p<0·00001]**

Adapted from: Lajoie et al. *Lancet Respir Med*. 2016;4:291-305.

# COMBINATION THERAPY VERSUS MONOTHERAPY FOR PAH

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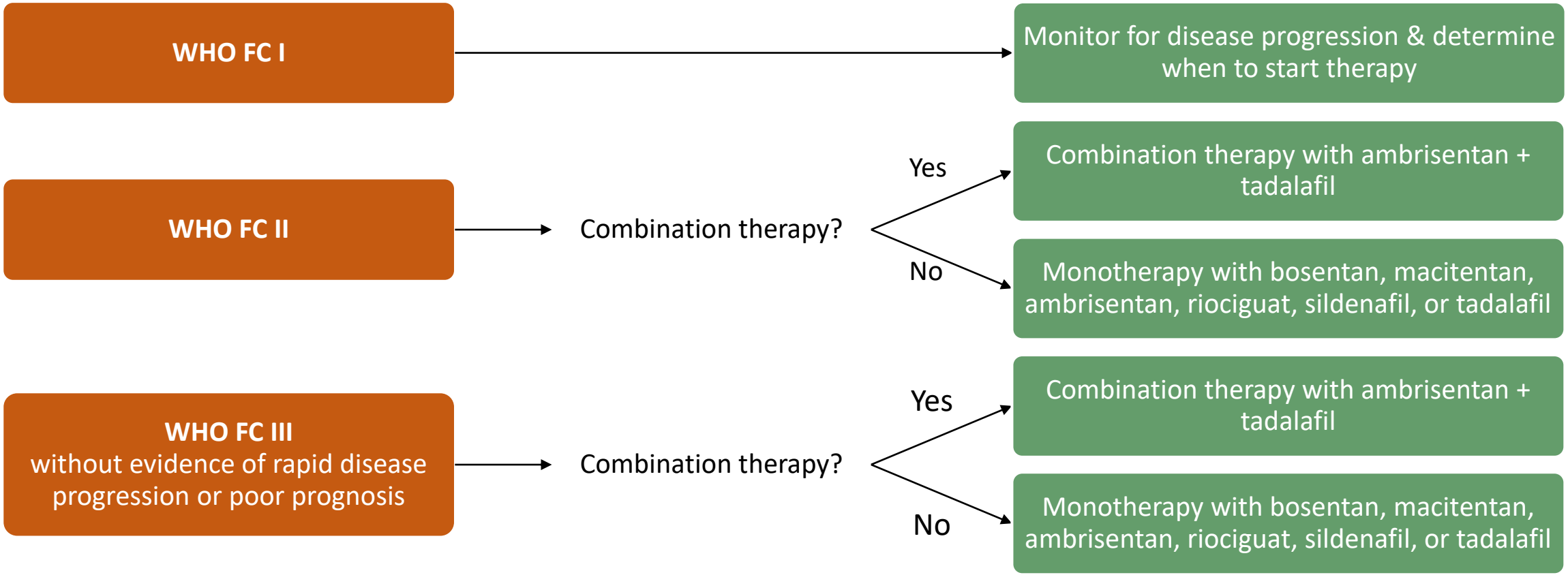
- **Risk for clinical worsening was reduced with combined therapy vs monotherapy [17% vs 28%, respectively; HR 0.65 (95% CI 0.58–0.72); p<0·00001]**

RCTs, randomized, controlled trials.
Adapted from: Lajoie et al. *Lancet Respir Med*. 2016;4:291-305.

# 2019 CHEST GUIDELINES FOR MANAGEMENT OF PAH IN TREATMENT NAÏVE PATIENTS




*Calcium channel blockers are not recommended in patients with CTD-PAH, as long-term efficacy has been confirmed in only 0.6% of patients. (Zanatta 2019).

Klinger et al. Chest. 2019;155:565-586; Zanatta et al. *Exp Biol Med.* 2019; 244:120-131.

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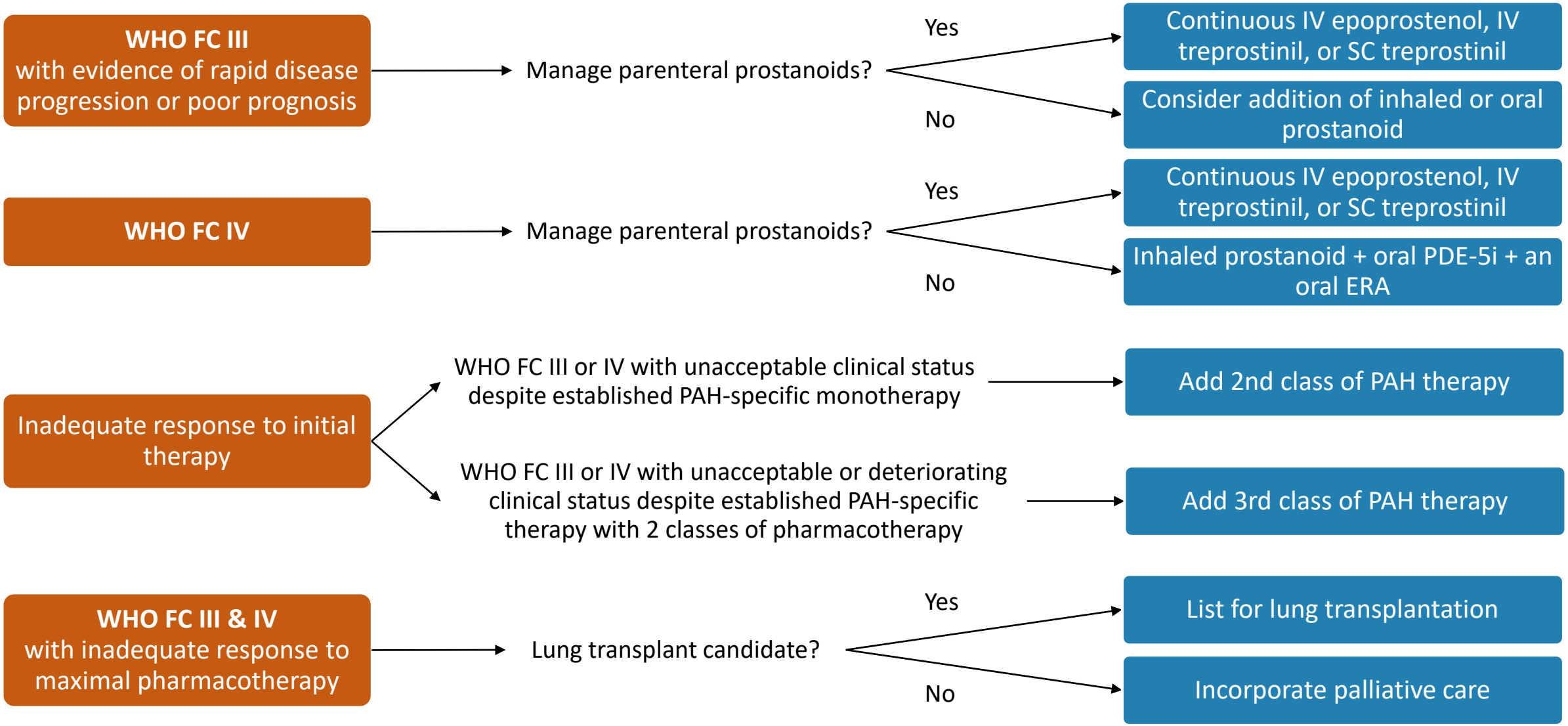
# 2019 CHEST GUIDELINES FOR MANAGEMENT OF PAH




Klinger et al. *Chest*. 2019;155:565-586.

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# REFERRAL FOR TRANSPLANTATION FOR PAH

- ISHLT guidelines recommend early counseling about transplant and early referral to a transplant program to minimize risks of delay of timely listing for transplantation.
- Potential candidates include patients with the following:

- ❑ WHO FC III (with worsening symptoms despite optimal therapy)
- ❑ WHO FC IV symptoms
- ❑ Rapidly progressive disease
- ❑ Use of parenteral PAH therapy regardless of symptoms or FC
- ❑ Known or suspected pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis

ISHLT, International Society for Heart and Lung Transplantation.
Klinger et al. *Chest*. 2019;155:565-586.

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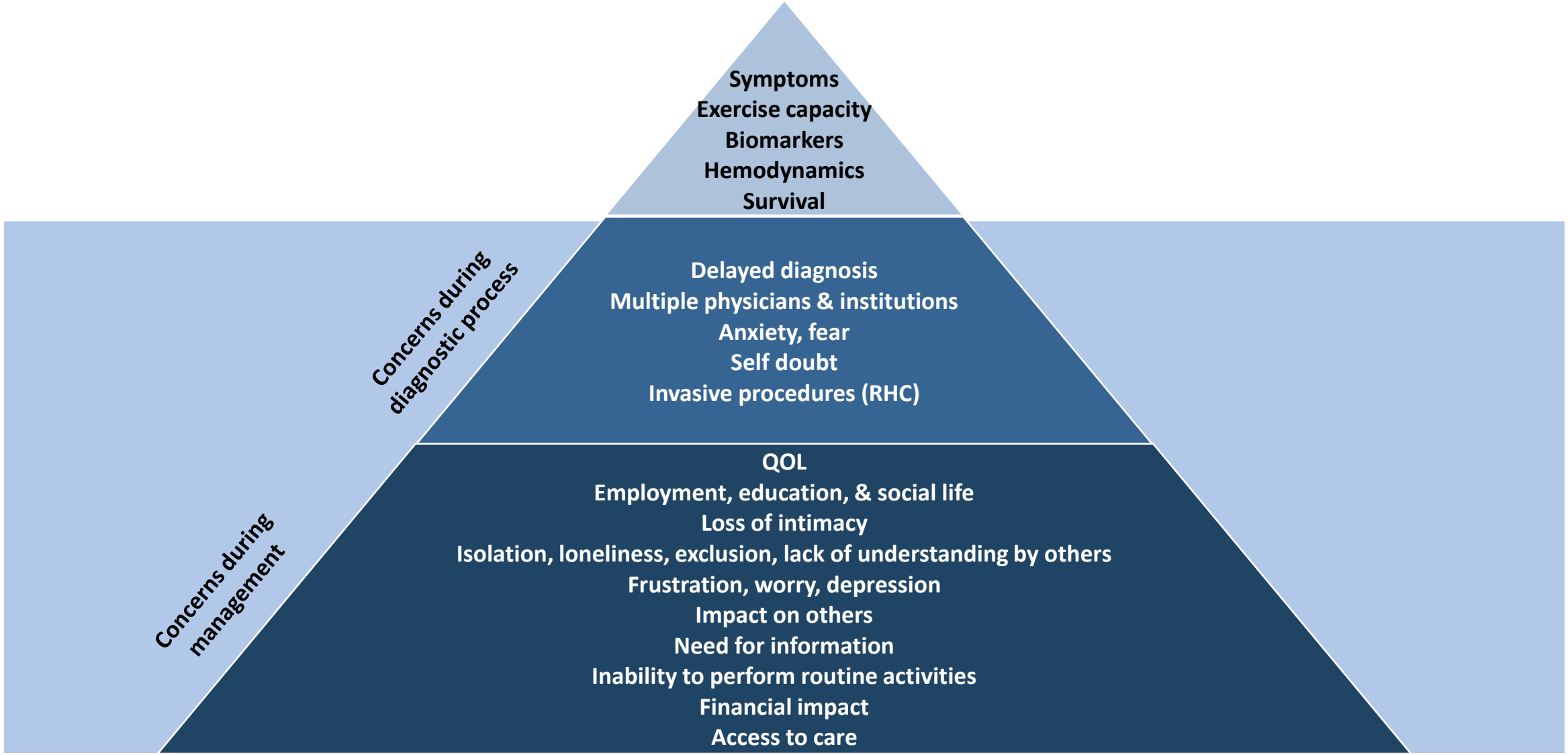
# CONSIDERATIONS FOR OPTIMAL LONG-TERM MANAGEMENT OF PAH

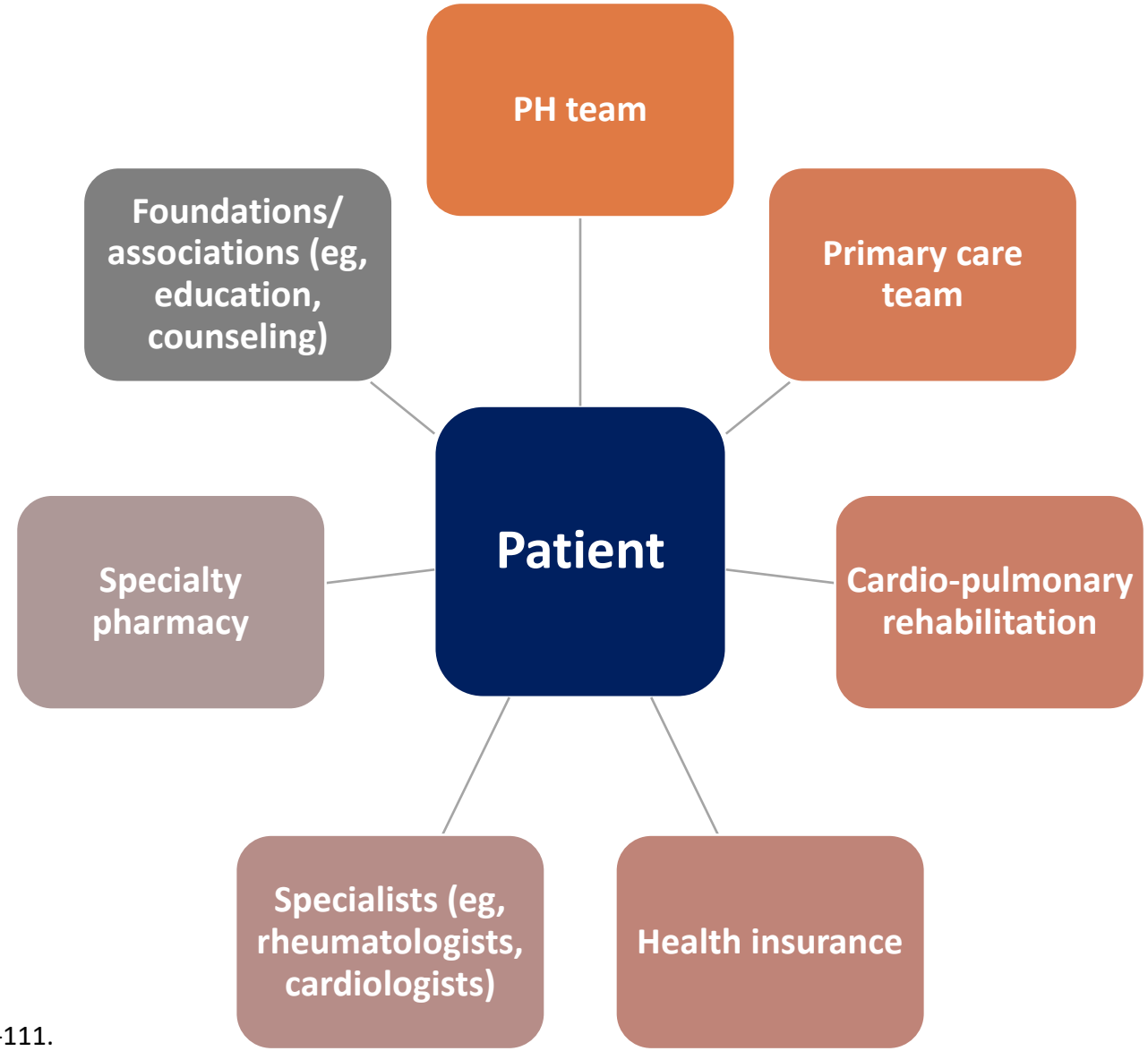
# CONCERNS REGARDING PAH MANAGEMENT: THE PATIENT PERSPECTIVE




McGoon MD, et al. *Eur Respir J*. 2019;53(1):1801919.

INTEGRITY CONTINUING EDUCATION

# COLLABORATIVE CTD-PAH CARE




Stewart et al. *Pulmonary Therapy*. 2017;3:93-111.

# PROGRAM SUMMARY

# PROGRAM SUMMARY

- CTD-PAH is a chronic vascular disease characterized by abnormal thickening of the arterial wall leading to increased pulmonary vascular resistance, right ventricular failure, and eventually heart failure, if left untreated
- Early recognition, accurate diagnosis, and treatment that is appropriately tailored based on patient risk are central to avoiding morbidity and mortality
- Multiple treatments targeting the endothelial, NO, and prostacyclin pathways are approved and have shown good efficacy as monotherapy and/or combination therapy
- Over the course of the disease, regular assessment is important to make sure that any change in risk is promptly detected and that treatment is adjusted accordingly
- Likewise, collaborative management between specialty care centers, patients, and caregivers is needed to ensure optimal disease management over the long-term

NO, nitric oxide.

# THANK YOU!