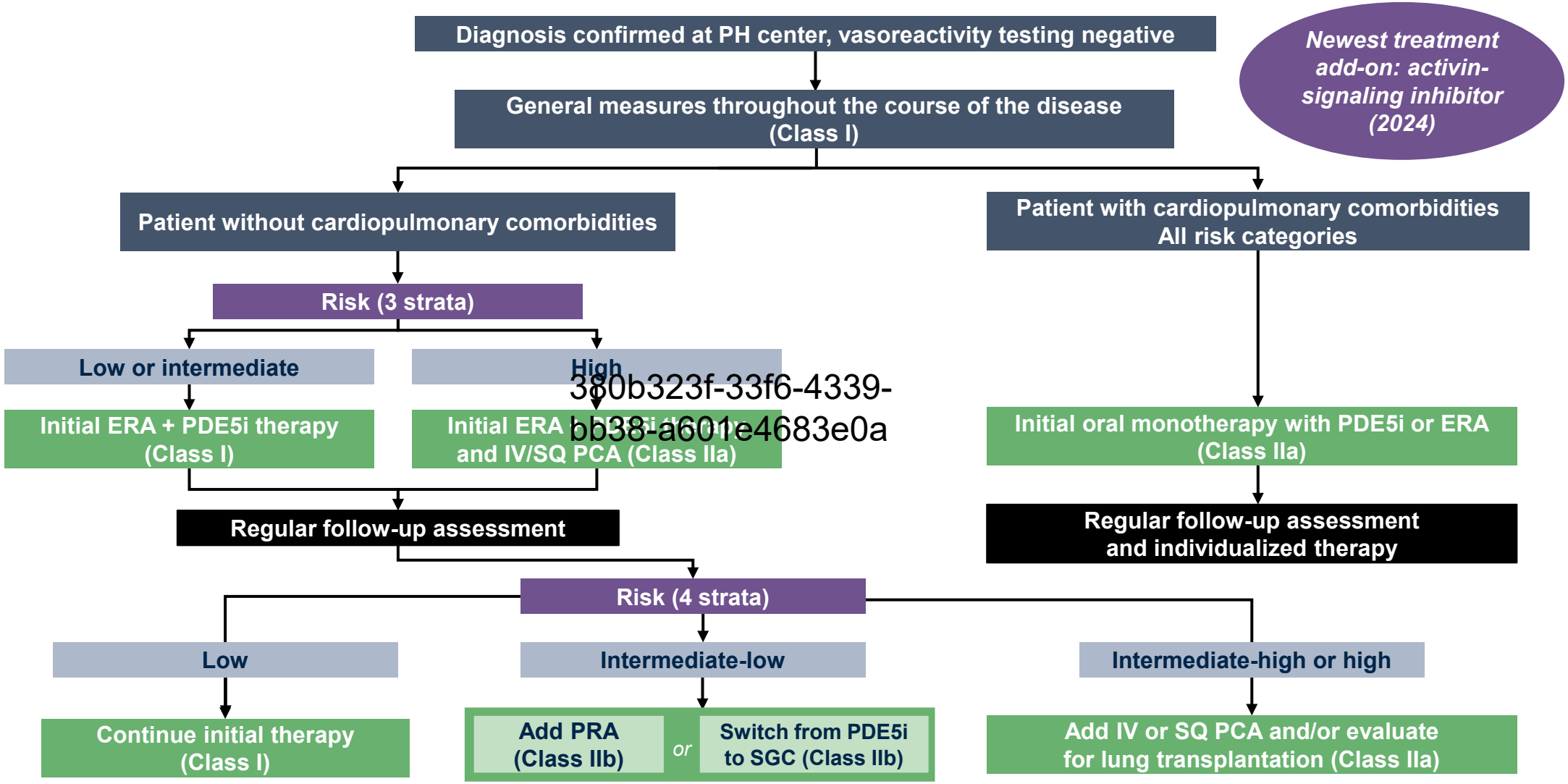
New and Emerging PAH Therapies and Approaches:
A Mixture of Hope and Complexity

June 18, 2025
12:00 PM - 01:00 PM EDT



TOTAL CME

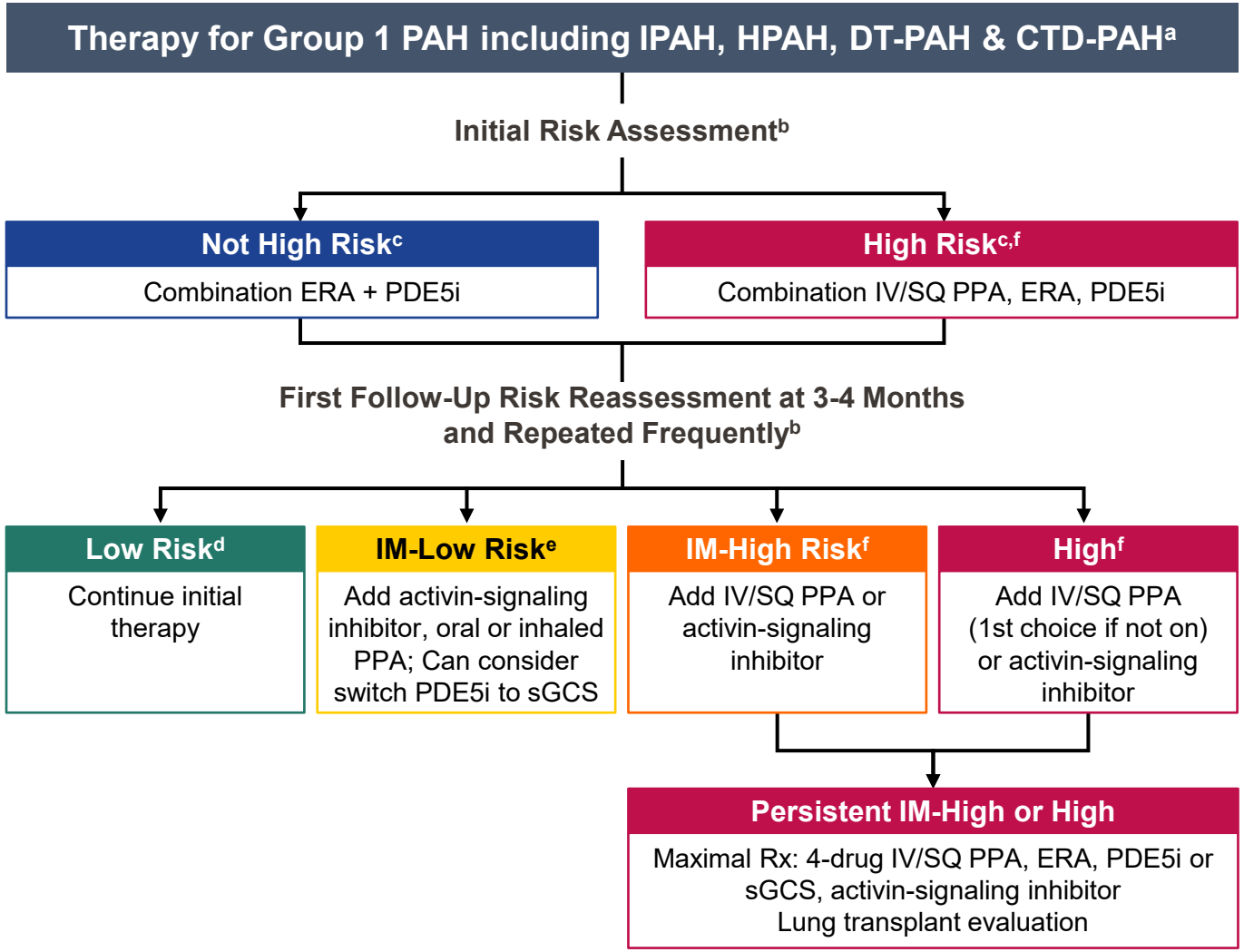
ESC/ERS: Treatment of Patients With I/H/D PAH or PAH-CTD



CTD, connective tissue disease; ERA, endothelin receptor antagonist; ERS, European Respiratory Society; ESC, European Society of Cardiology; I/H/D, idiopathic/heritable/drug-associated; IV, intravenous; PAH, pulmonary arterial hypertension; PCA, prostacyclin analog; PDE5i, phosphodiesterase-5 inhibitor; PH, pulmonary hypertension; PRA, prostacyclin receptor agonist; SGC, soluble guanylate cyclase stimulator; SQ, subcutaneous.

Humbert M, et al. *Eur Heart J*. 2022;43(38):3618-3731. Humbert M, et al. *Eur Respir J*. 2023;61(1):2200879.

7th WSPH Treatment Algorithm



Treatment Algorithm Key Points

a. 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). Treatment nuances 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. Hemodynamics, RV imaging, and other measures should be used to supplement risk assessment.

c. Initial triple therapy with an IV/SQ PPA is recommended in high-risk patients and may be considered in non-high risk with severe hemodynamics and/or poor RV function.

d. Most ***low risk*** at follow-up patients should continue initial therapy.

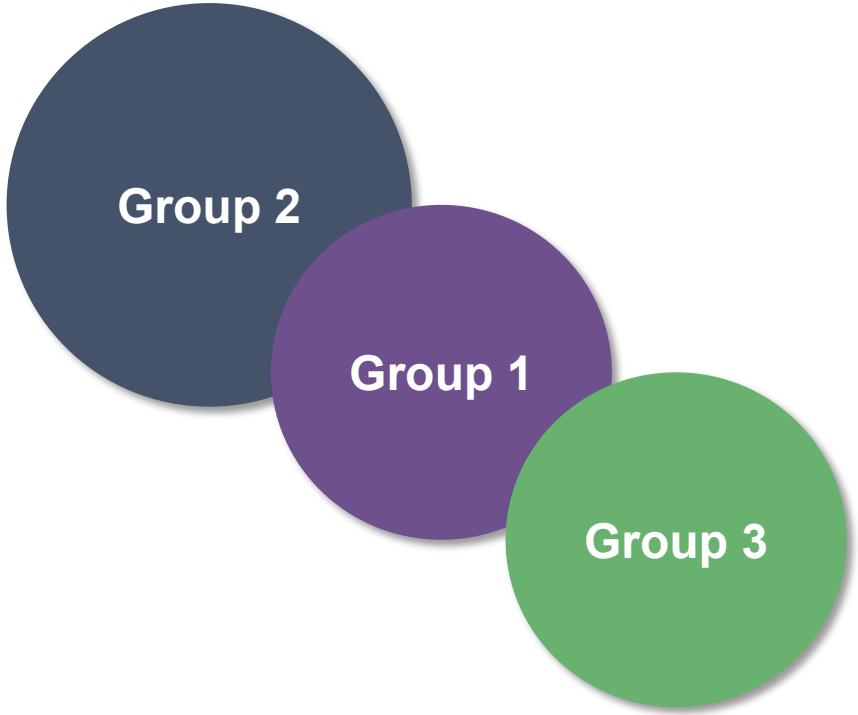
e. Clinical trials with oral and inhaled treprostinil included ***only patients on monotherapy***, while studies of selexipag and sotatercept included patients on combination therapy.

f. Transplant referral should be considered for select high-risk patients **at diagnosis**, and for IM-high and high-risk patients at ***first*** or subsequent follow-up.

DT, drug and toxin; FC, Functional Class; HPAH, hereditary PAH; IM, intermediate; IPAH, idiopathic PAH; mPAP, mean pulmonary artery pressure; PPA, prostacyclin pathway agent; PVR, pulmonary vascular resistance; RV, right ventricle; Rx, prescription; sGCS: soluble guanylyl cyclase stimulator; 6MWD, 6-minute walk distance; WSPH, World Symposium on Pulmonary Hypertension.

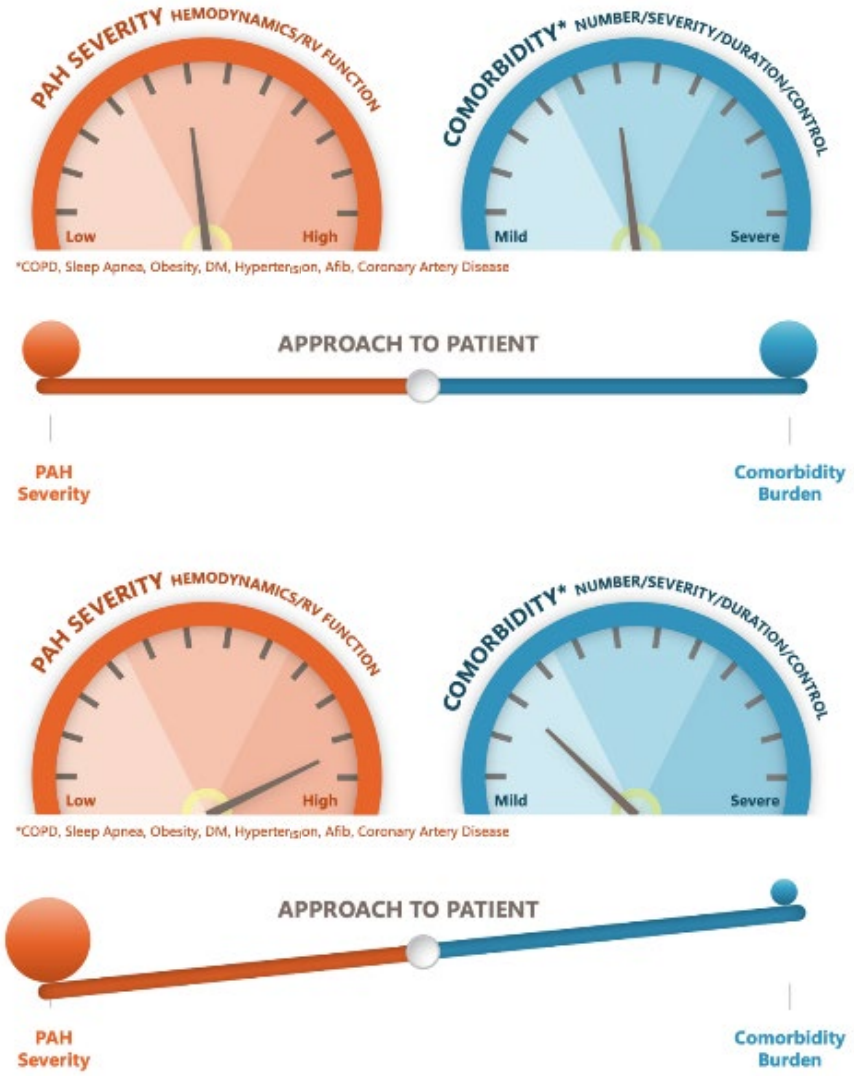
Chin KM, et al. *Eur Respir J*. 2024;64(4):2401325.

Overlap Between PAH Groups



Relationship of Comorbidities With Severity of PAH

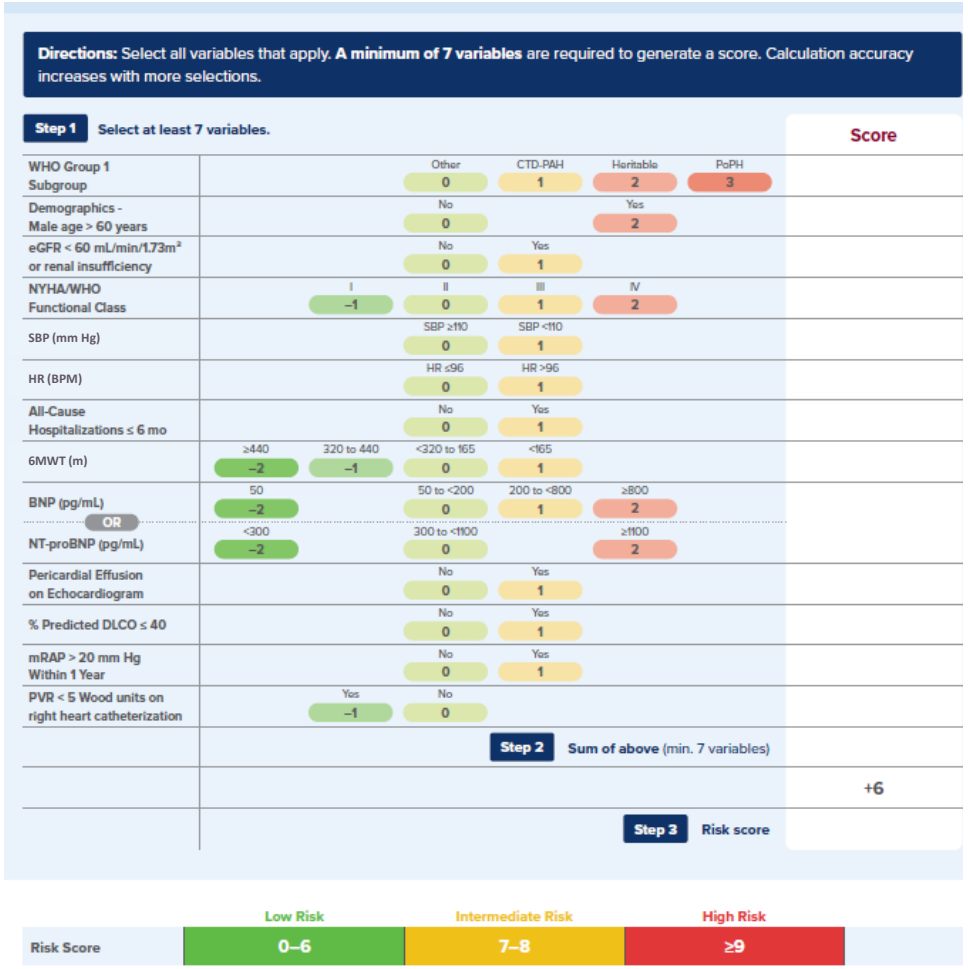
- Approach while evaluating patients with PAH and comorbidities:
  - Consider the severity of the underlying comorbidities
  - Put into perspective with the severity of the PAH, how advanced the hemodynamics are, and how much the right ventricle is affected



Afib, atrial fibrillation; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus.
Sahay S, et al. *Am J Respir Crit Care Med*. 2024;210(5):581-592.

Risk Score Calculators

REVEAL 2.0 Risk Calculator

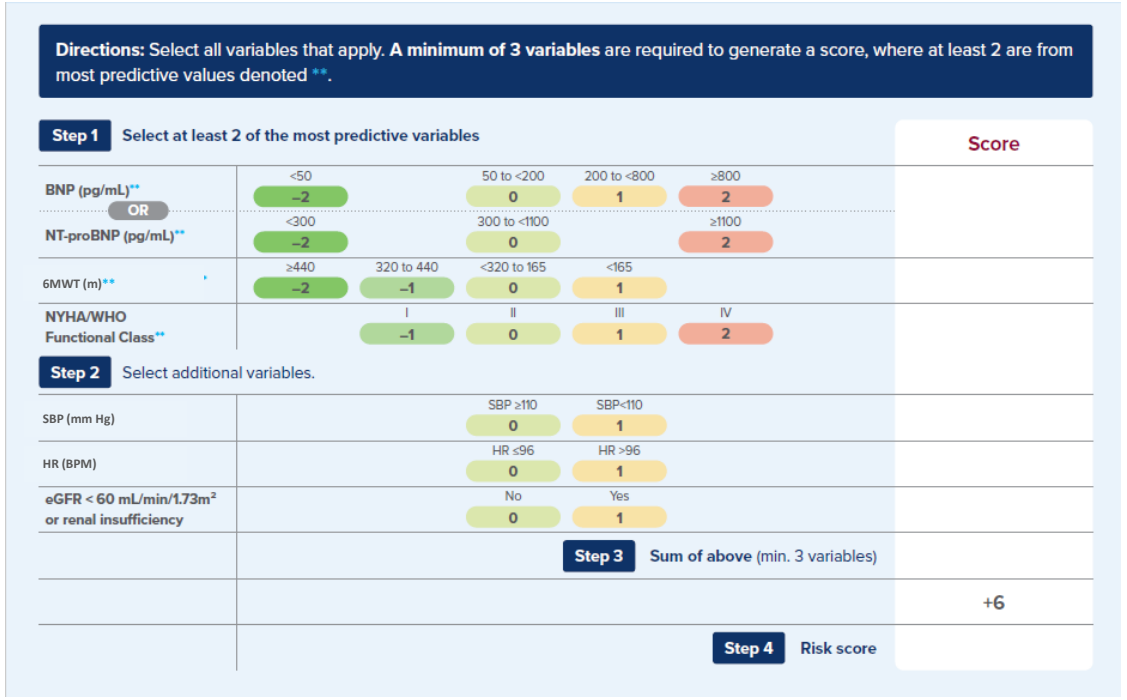


Directions: Select all variables that apply. **A minimum of 7 variables** are required to generate a score. Calculation accuracy increases with more selections.

Step 1 Select at least 7 variables.						Score
WHO Group 1 Subgroup			Other 0	CTD-PAH 1	Heritable 2	PoPH 3	
Demographics - Male age > 60 years			No 0		Yes 2		
eGFR < 60 mL/min/1.73m² or renal insufficiency			No 0	Yes 1			
NYHA/WHO Functional Class		I –1	II 0	III 1	IV 2		
SBP (mm Hg)			SBP ≥110 0	SBP <110 1			
HR (BPM)			HR ≤96 0	HR >96 1			
All-Cause Hospitalizations ≤ 6 mo			No 0	Yes 1			
6MWT (m)	≥440 –2	320 to 440 –1	<320 to 165 0	<165 1			
BNP (pg/mL)	50 –2		50 to <200 0	200 to <800 1	≥800 2		
OR							
NT-proBNP (pg/mL)	<300 –2		300 to <1100 0		≥1100 2		
Pericardial Effusion on Echocardiogram			No 0	Yes 1			
% Predicted DLCO ≤ 40			No 0	Yes 1			
mRAP > 20 mm Hg Within 1 Year			No 0	Yes 1			
PVR < 5 Wood units on right heart catheterization		Yes –1	No 0				
			Step 2 Sum of above (min. 7 variables)				
							+6
						Step 3 Risk score	

Risk Score	Low Risk	Intermediate Risk	High Risk
	0–6	7–8	≥9

REVEAL Lite 2 Risk Calculator



Directions: Select all variables that apply. **A minimum of 3 variables** are required to generate a score, where at least 2 are from most predictive values denoted **.

Step 1 Select at least 2 of the most predictive variables						Score
BNP (pg/mL)**	<50 –2		50 to <200 0	200 to <800 1	≥800 2	
OR						
NT-proBNP (pg/mL)**	<300 –2		300 to <1100 0		≥1100 2	
6MWT (m)**	≥440 –2	320 to 440 –1	<320 to 165 0	<165 1		
NYHA/WHO Functional Class**		I –1	II 0	III 1	IV 2	
Step 2 Select additional variables.						
SBP (mm Hg)			SBP ≥110 0	SBP<110 1		
HR (BPM)			HR ≤96 0	HR >96 1		
eGFR < 60 mL/min/1.73m² or renal insufficiency			No 0	Yes 1		
			Step 3 Sum of above (min. 3 variables)			
						+6
					Step 4 Risk score	

Risk Score	Low Risk	Intermediate Risk	High Risk
	≤5	6–7	≥8

BNP, B-type natriuretic peptide; BPM, beats per minute; DLCO, diffusing capacity of the lungs for carbon monoxide; eGFR, estimated glomerular filtration rate; HR, heart rate; mRAP, mean right atrial pressure; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; PoPH, portopulmonary hypertension; REVEAL, Registry to Evaluate Early and Long-Term PAH Disease Management; RHC, right heart catheterization; SBP, systolic BP; 6MWT, 6-minute walk test; WHO, World Health Organization.

Benza RL, et al. *Chest*. 2021;159(1):337-346.

Risk Stratification Models
ESC/ERS

3-strata risk score

Comprehensive risk assessment in pulmonary arterial hypertension (three-strata model)

Determinants of prognosis (estimated 1-year mortality)	Low risk (<5%)	Intermediate risk (5–20%)	High risk (>20%)
Clinical observations and modifiable variables			
Signs of right HF	Absent	Absent	Present
Progression of symptoms and clinical manifestations	No	Slow	Rapid
Syncope	No	Occasional syncope[a]	Repeated syncope[b]
WHO-FC	I, II	III	IV
6MWD[c]	>440 m	165–440 m	<165 m
CPET	Peak VO_2 >15 mL/min/kg (>65% pred.) VE/VCO_2 slope <36	Peak VO_2 11–15 mL/min/kg (35–65% pred.) VE/VCO_2 slope 36–44	Peak VO_2 <11 mL/min/kg (<35% pred.) VE/VCO_2 slope >44
Biomarkers: BNP or NT-proBNP[d]	BNP <50 ng/L NT-proBNP <300 ng/L	BNP 50–800 ng/L NT-proBNP 300–1100 ng/L	BNP >800 ng/L NT-proBNP >1100 ng/L
Echocardiography	RA area <18 cm^2 TAPSE/sPAP >0.32 mm/mmHg No pericardial effusion	RA area 18–26 cm^2 TAPSE/sPAP 0.19–0.32 mm/mmHg Minimal pericardial effusion	RA area >26 cm^2 TAPSE/sPAP <0.19 mm/mmHg Moderate or large pericardial effusion
cMRI[e]	RVEF >54% SVI >40 mL/m^2 RVESVI <42 mL/m^2	RVEF 37–54% SVI 26–40 mL/m^2 RVESVI 42–54 mL/m^2	RVEF <37% SVI <26 mL/m^2 RVESVI >54 mL/m^2
Haemodynamics	RAP <8 mmHg CI ⩾2.5 $L/min/m^2$ SVI >38 mL/m^2 SvO_2 >65%	RAP 8–14 mmHg CI 2.0–2.4 $L/min/m^2$ SVI 31–38 mL/m^2 SvO_2 60–65%	RAP >14 mmHg CI <2.0 $L/min/m^2$ SVI <31 mL/m^2 SvO_2 <60%

4-strata risk score

Variables used to calculate the simplified four-strata risk-assessment tool

Determinants of prognosis	Low risk	Intermediate–low risk	Intermediate–high risk	High risk
Points assigned	1	2	3	4
WHO-FC	I or II[a]	-	III	IV
6MWD, m	>440	320–440	165–319	<165
BNP or NT-proBNP, ng/L	<50 <300	50–199 300–649	200–800 650–1100	>800 >1100

CI, cardiac index; cMRI, cardiac magnetic resonance imaging; CPET, cardiopulmonary exercise test; HF, heart failure; RA, right atrium; RAP, right atrial pressure; RVEF, right ventricular ejection fraction; RVESVI, right ventricular end-systolic volume index; sPAP, systolic pulmonary arterial pressure; SVI, stroke volume index; SVO_2, venous oxygen saturation;TAPSE, tricuspid annular plane systolic excursion; VE/VCO_2, ventilatory equivalent for carbon dioxide; VO_2, oxygen uptake.

Benza RL, et al. *Chest*. 2021;159(1):337-346.

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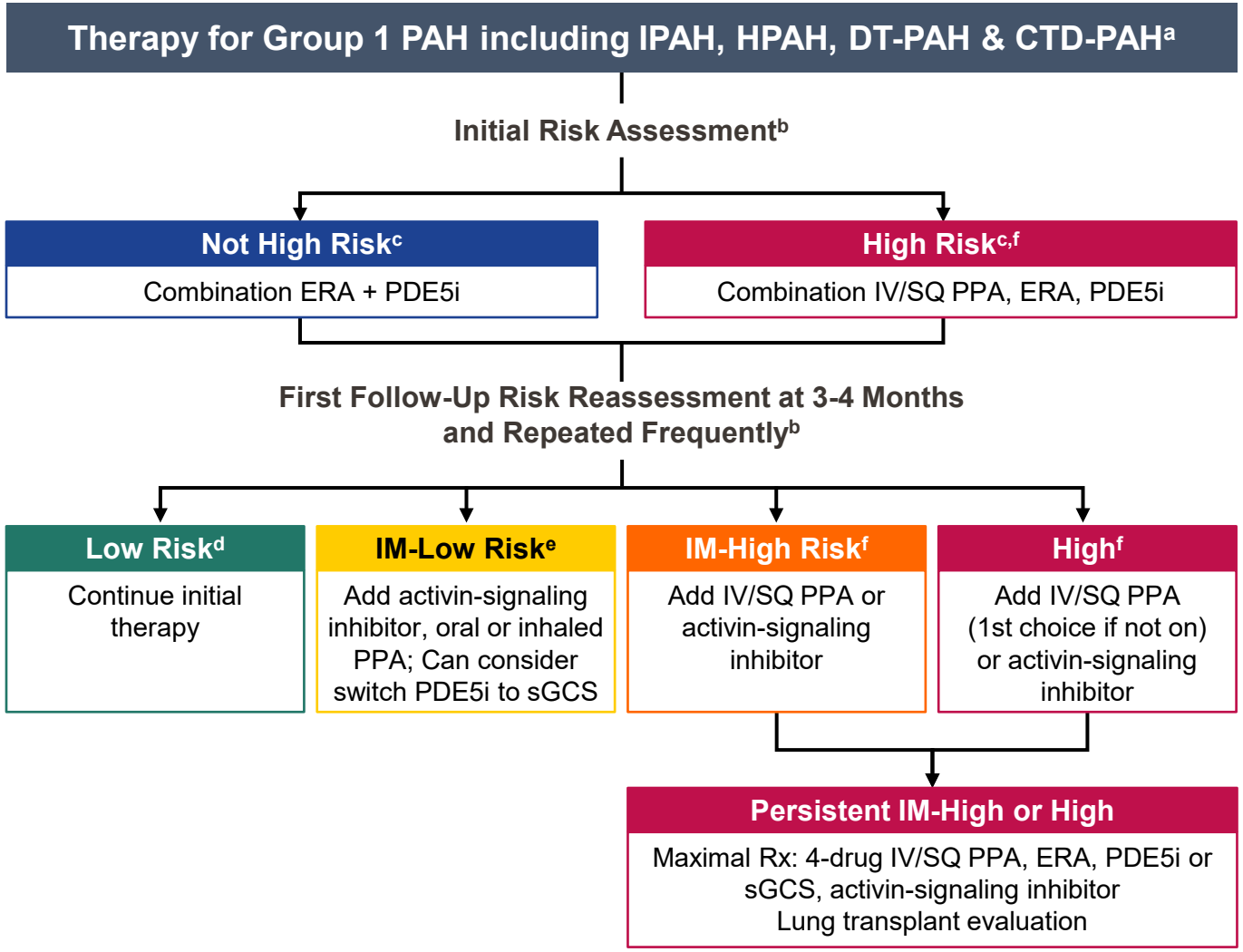

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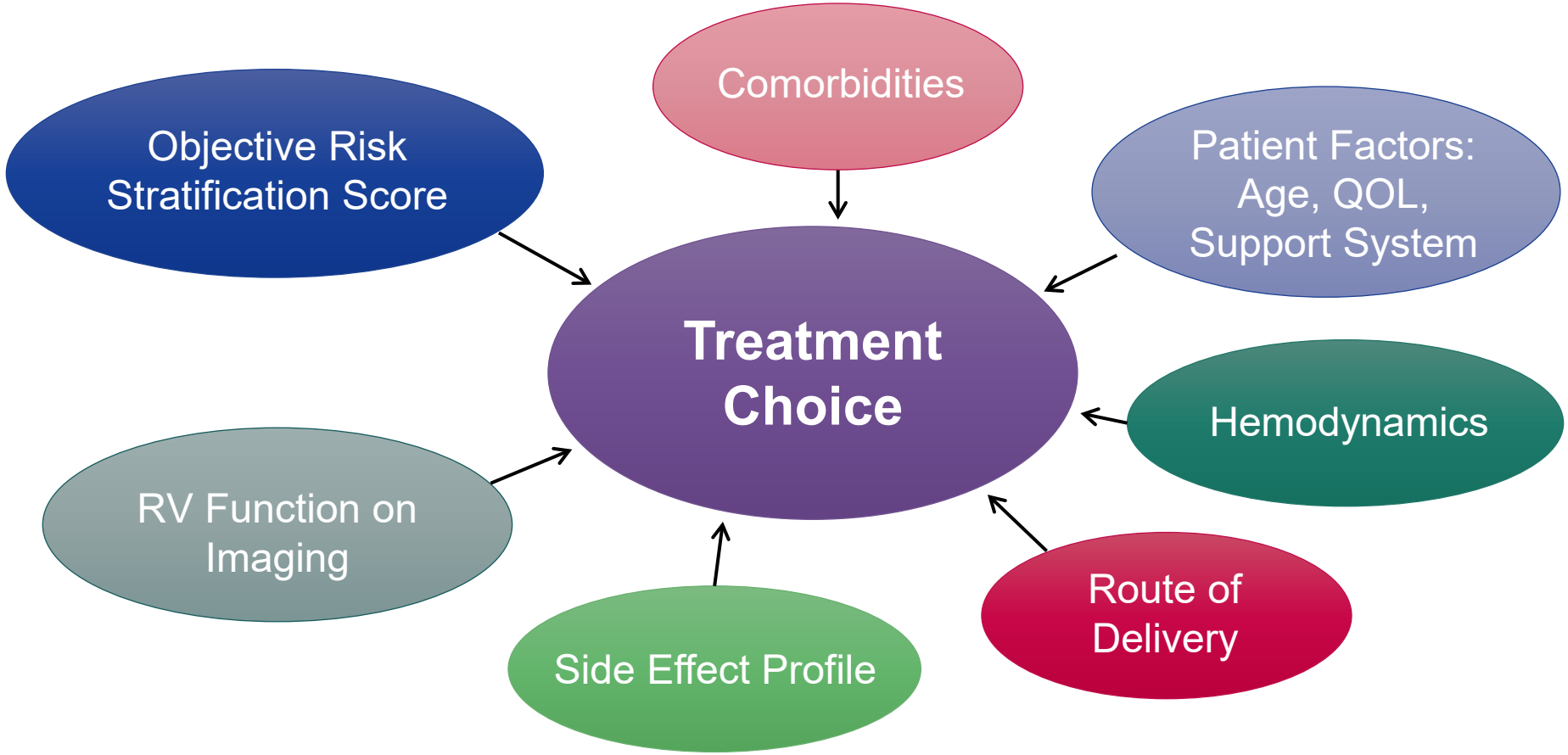
Factors Affecting Treatment Choice



FDA-Approved Treatment Options

ERA	NO-cGMP pathway	PPA	PCA	Activin-signaling inhibitor	Combination NO-cGMP pathway/ERA
Bosentan PO	Sildenafil PO	Epoprostenol IV	Selexipag PO, IV	Sotatercept SQ	Tadalafil/ Macitentan PO
Ambrisentan PO	Tadalafil PO	Treprostinil IV, SQ, PO, Inh			
Macitentan PO	Riociguat PO	Iloprost Inh			

Inh, inhaled; NO-cGMP, nitric oxide-cyclic guanosine monophosphate; PO, by mouth.

Therapy Considerations

- Promoting adherence, compliance, and tolerability
- Potential benefits of combination therapy:
  - May ease pill burden
  - Fewer prior authorizations, refills, and copays

A-DUE: Single-Tablet Combination Therapy of Macitentan/Tadalafil

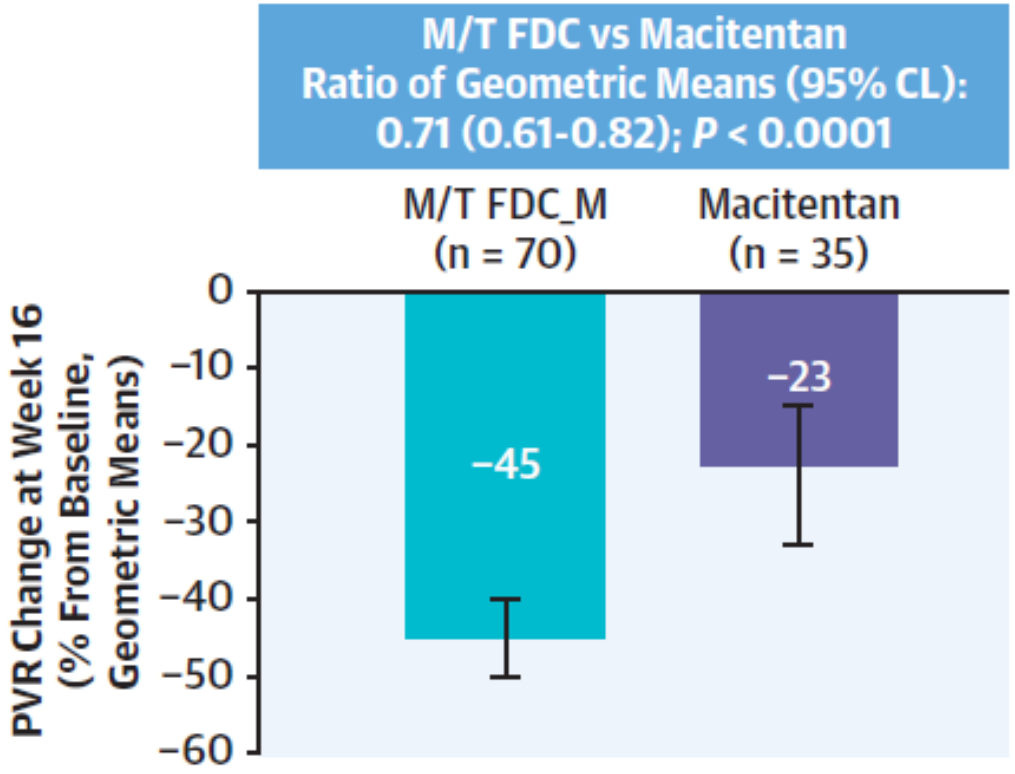
- Safety and efficacy of macitentan/tadalafil (M/T)
- Adults with PAH in WHO FC II or III
  - Treatment naïve
  - On stable dose (≥3 months) of an ERA (prior ERA) or a PDE5i (prior PDE5i)
- Efficacy endpoints at week 16:
  - Primary endpoint: Change in PVR, expressed as ratio of baseline
  - Secondary endpoints (hierarchical order): Change in 6MWD, change in PAH-SYMPACT scores, absence of worsening in WHO FC
  - Treatment effects were calculated for:
    - M/T FDC vs macitentan monotherapy
    - M/T FDC vs tadalafil monotherapy
- Safety and tolerability were monitored throughout the study

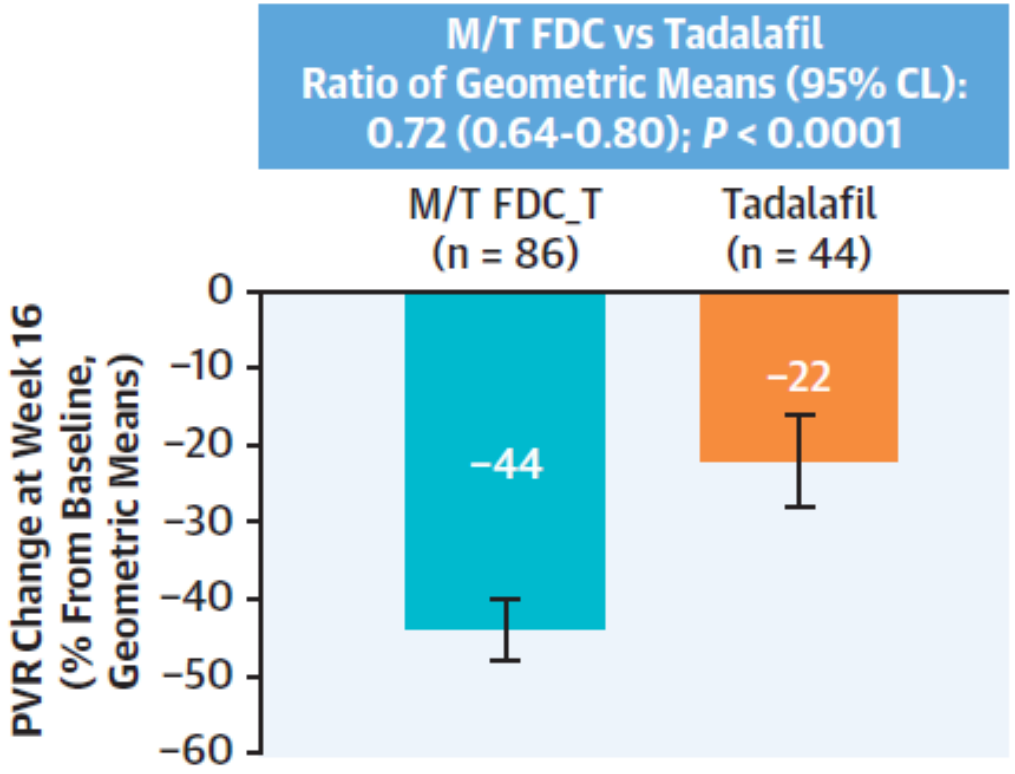
FDC, fixed-dose combination.

Grünig E, et al. *J Am Coll Cardiol*. 2024;83(4):473-484.

A-DUE: Results

Primary endpoint: change in PVR at Week 16





CL, confidence limits.

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Key Takeaways

- Be methodical about the diagnosis
  - Make the right diagnosis
  - Understand what may and may not be attributed to comorbidities
  - Be willing to reevaluate as you go down the treatment pathway
- Be proactive and on the ball
  - Follow the patients on a regular basis, even when they're doing well
  - Ensure that both patient goals and clinical goals are aligned and achieved