Medscape EDUCATION

theheart.org from WebMD

Evaluating Emerging Evidence in PAH

Implications for Practicing Physicians

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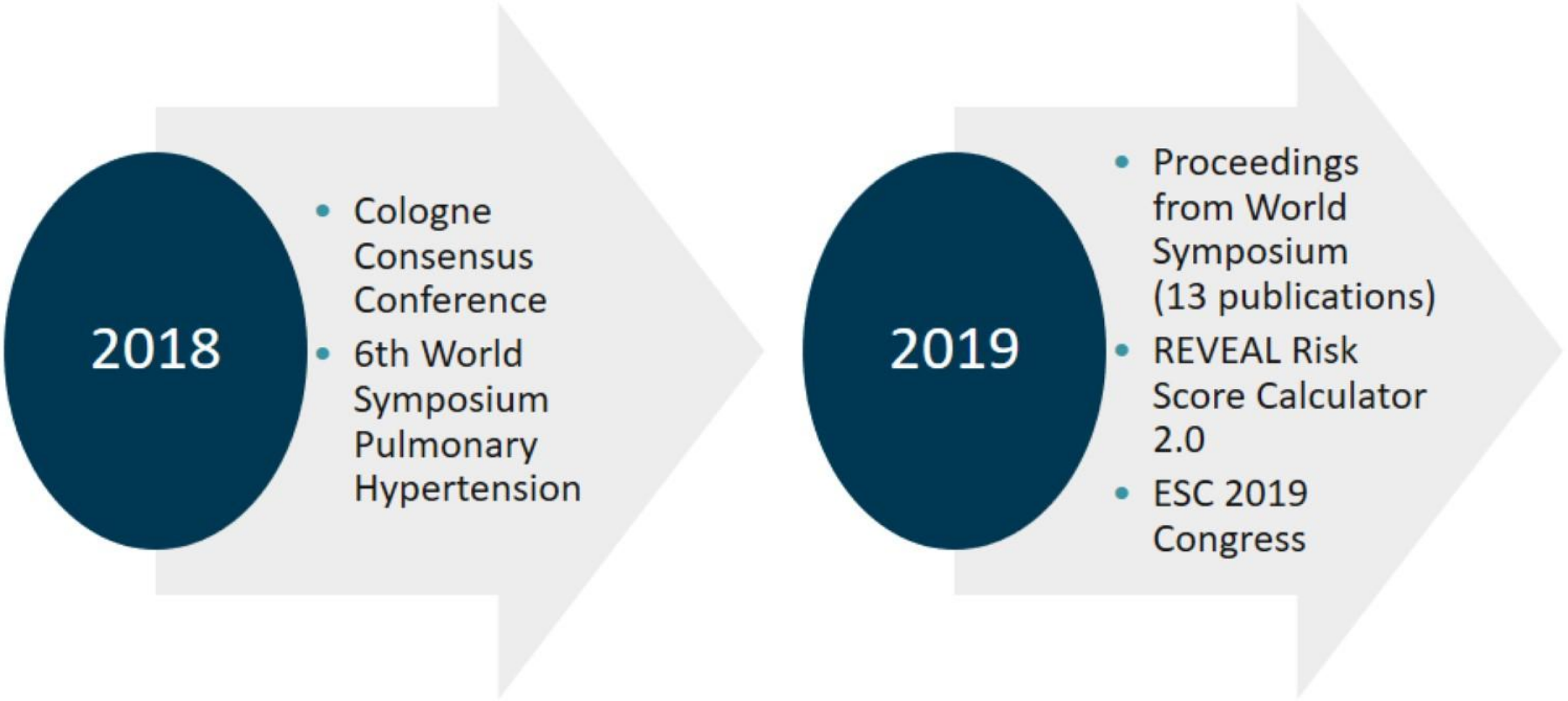
Introduction

- Risk assessment for PAH
- Treating patients with PAH to achieve low-risk status
- Prognostic factors and data available on hospitalizations
- Recommendations and consensus statements
- Team approach to caring for patients with PAH

Recent Events and Publications in PAH



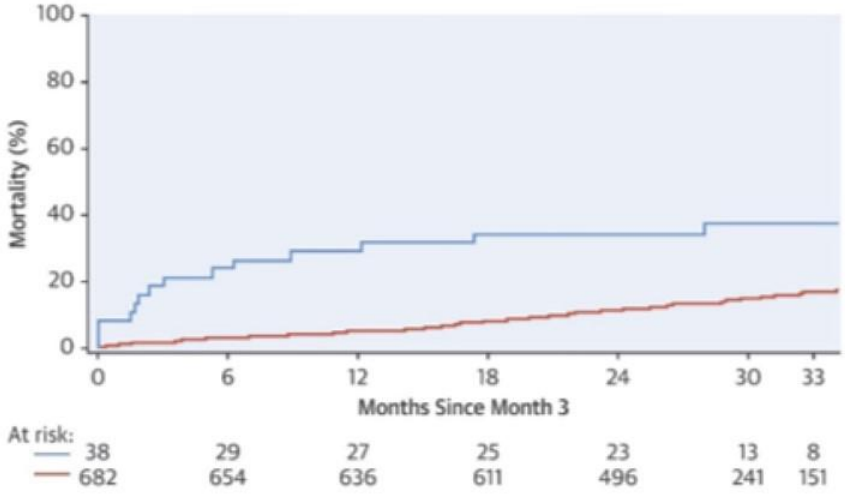
PAH-Related Events Associated With Clinical Outcomes and Mortality

Landmark Analysis

- Morbidity event within 3 to 12 months of initial PAH-related event is prognostic for mortality and subsequent clinical worsening events (eg, hospitalization)

SERAPHIN (Macitentan vs Placebo)

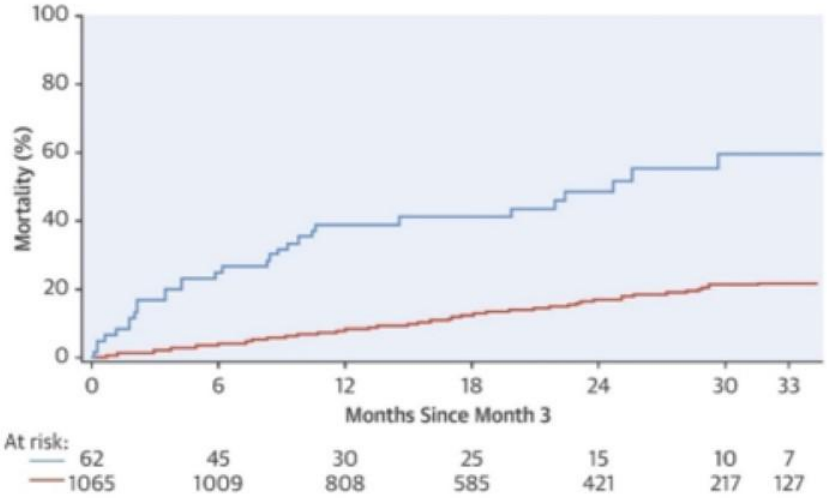
	Risk of death* HR (95% CI)
Main analysis	3.39 (1.94, 5.92)
Sensitivity analysis†	2.29 (1.30, 4.05)



Median follow-up: 27 months

GRIPHON (Selexipag vs Placebo)

	Risk of death* HR (95% CI)
Main analysis	4.48 (2.98, 6.73)
Sensitivity analysis†	3.05 (2.01, 4.61)



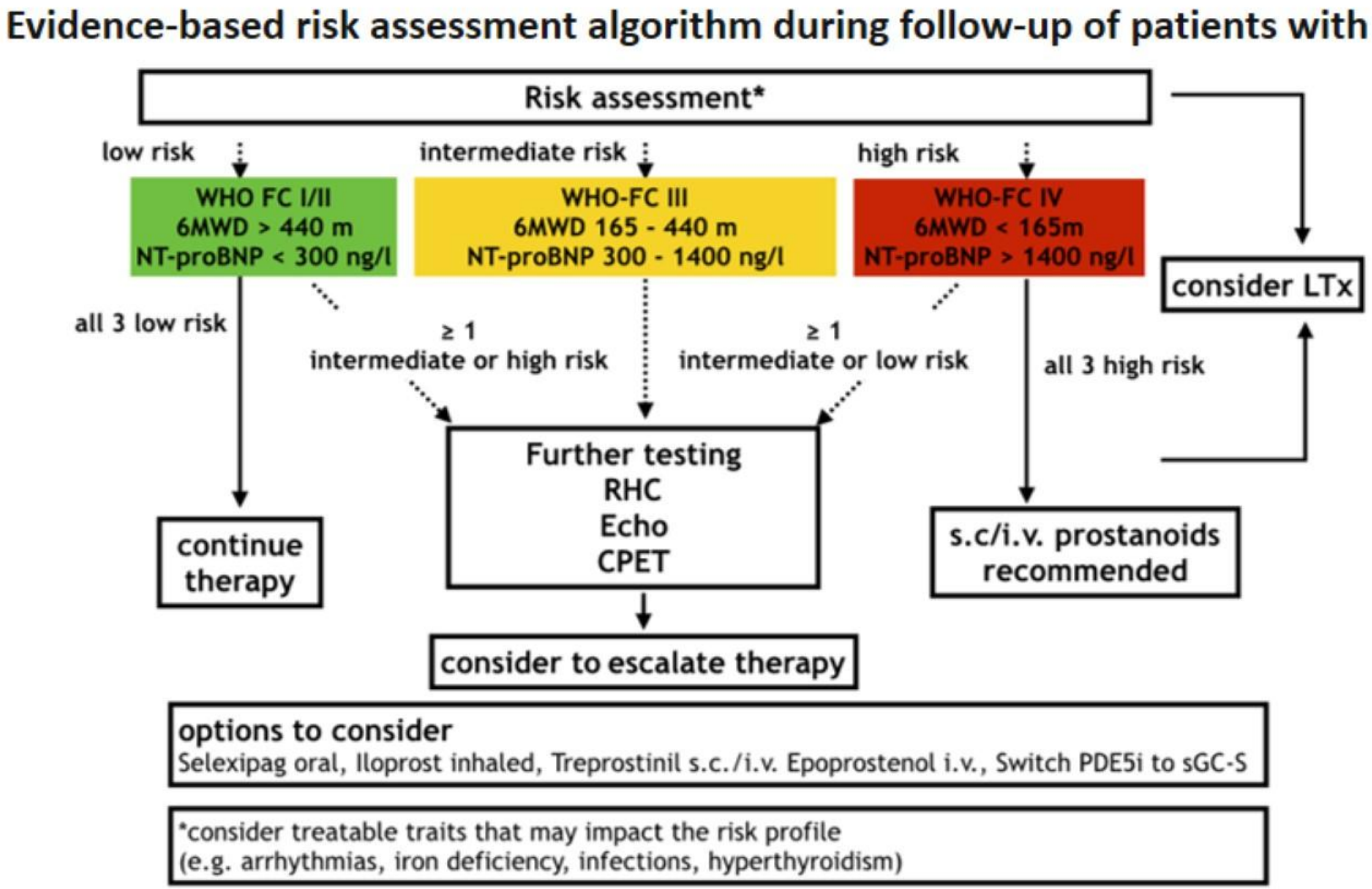
Median follow-up: 20 months

Morbidity Event Prior to Month 3 — No Morbidity Event Prior to Month 3

*Morbidity event vs no prior morbidity event. †Adjusted for baseline WHO FC and 6MWD.

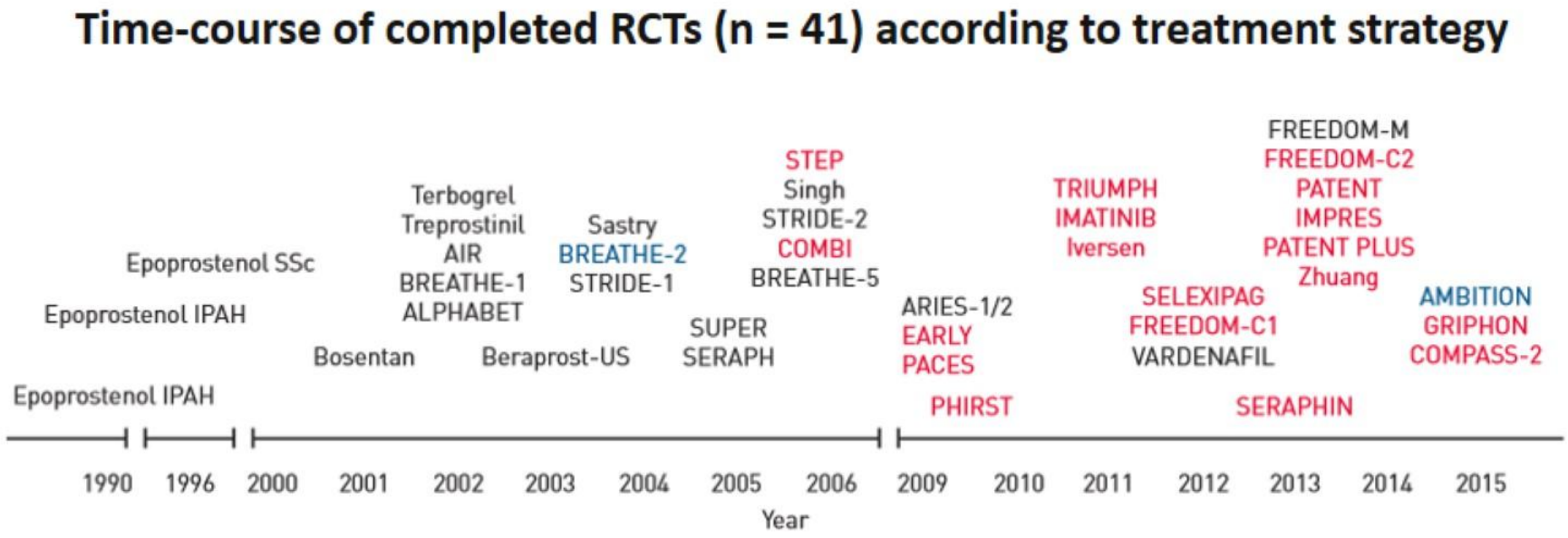
McLaughlin VV, et al. *J Am Coll Cardiol*. 2018;71:752-763.

Recommendations From the Cologne Consensus Conference 2018



Reprinted from *International Journal of Cardiology*, Vol 272/ Leuchte Hanno H, et al., Risk stratification strategy and assessment of disease progression in patients with pulmonary arterial hypertension: Updated Recommendations from the Cologne Consensus Conference 2018. /20-29, Copyright 2018, with permission from Elsevier.

Treatment Strategy and Evolution of Combination Therapy

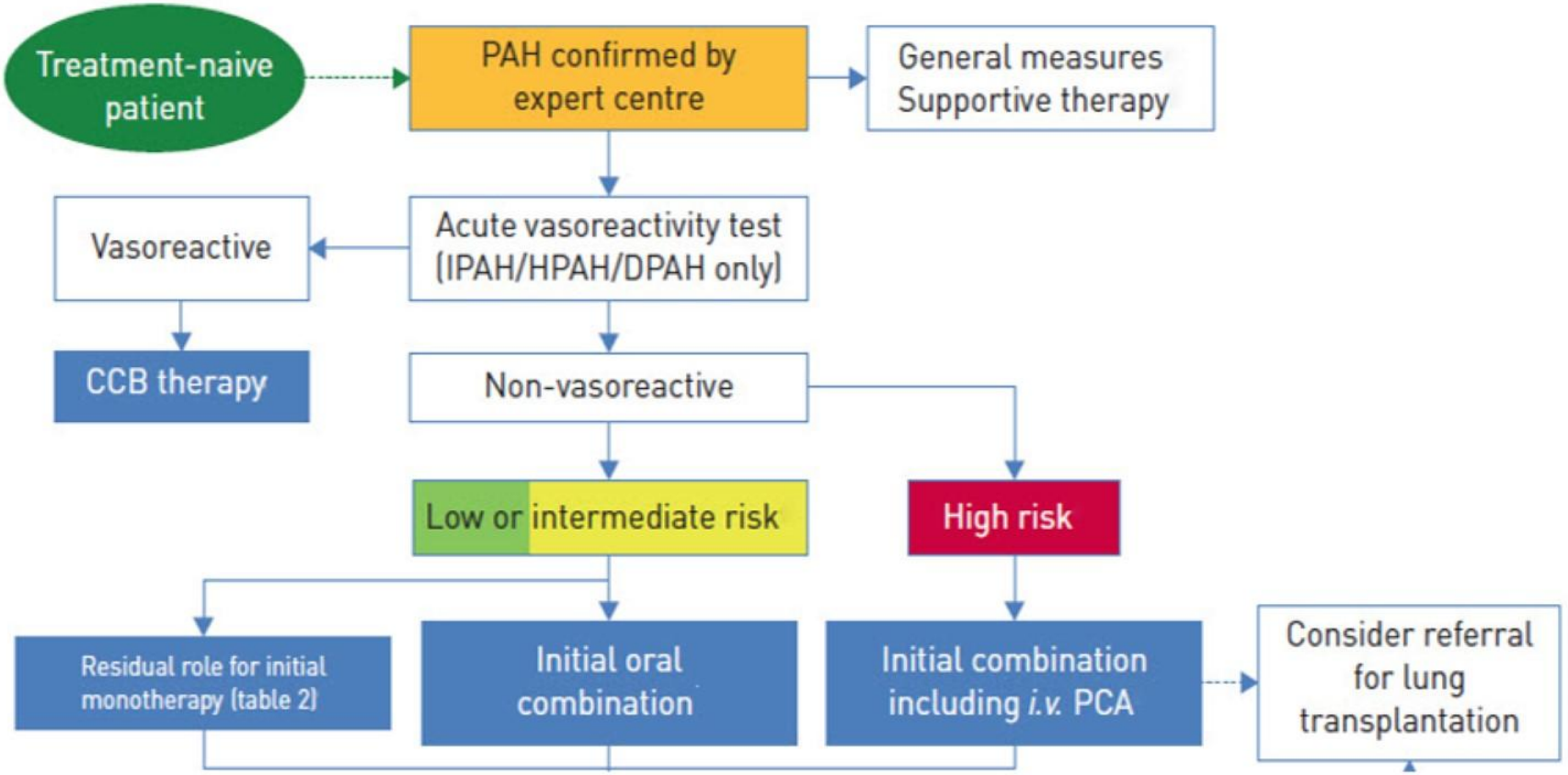


- Monotherapy vs placebo or vs monotherapy (n = 21)
- Monotherapy and/or sequential combination vs placebo (n = 18)
- Initial combination vs monotherapy (n = 2)

Treatment Algorithm for PAH

Treatment-Naive

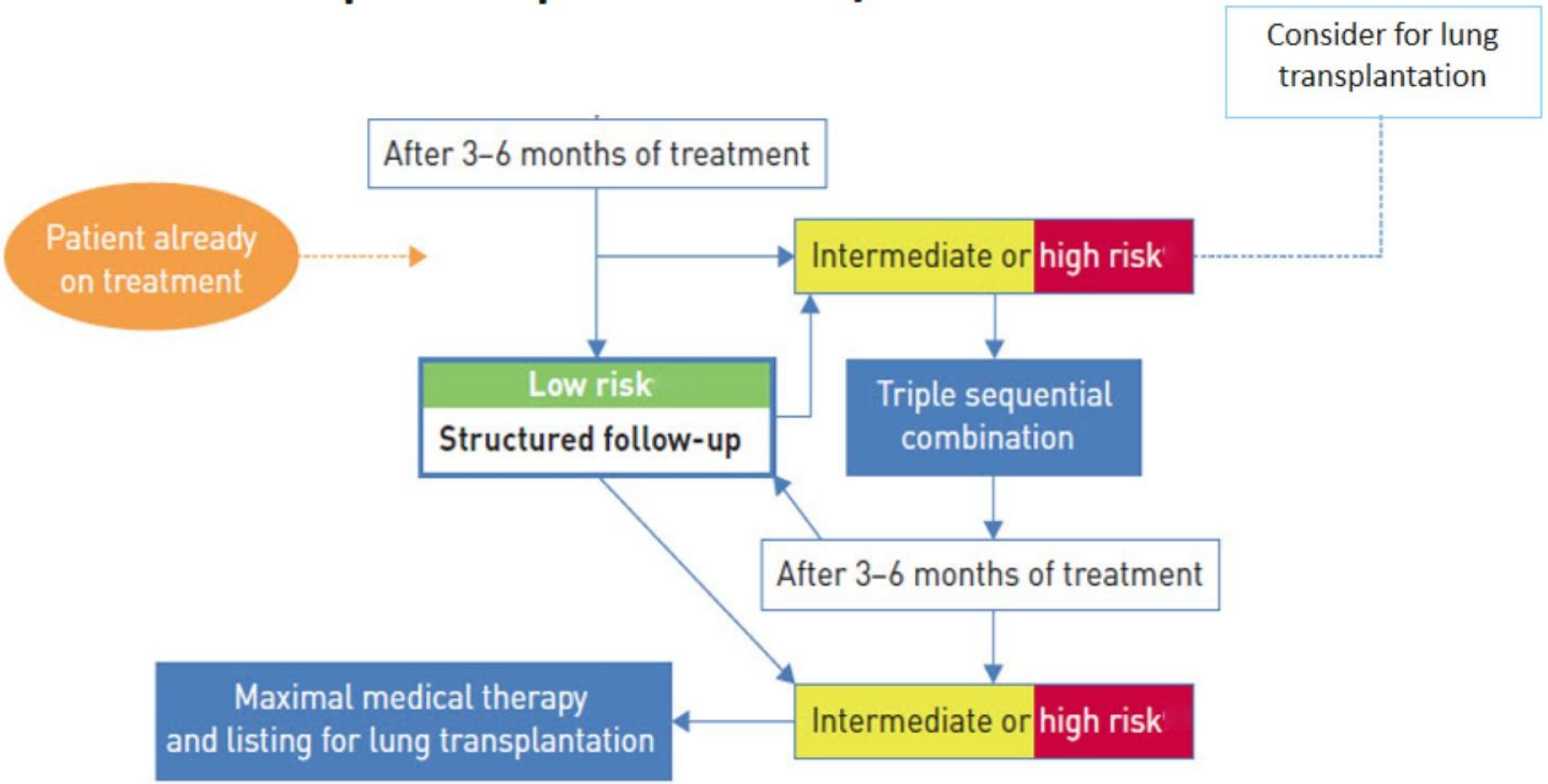
6th World Symposium Proceedings Expands Upon 2015 ESC/ERS Guidelines*



*Treatment algorithm for PAH, IPAH, HPAH, DPAH.

Treatment Algorithm for PAH
Patient Already on Treatment

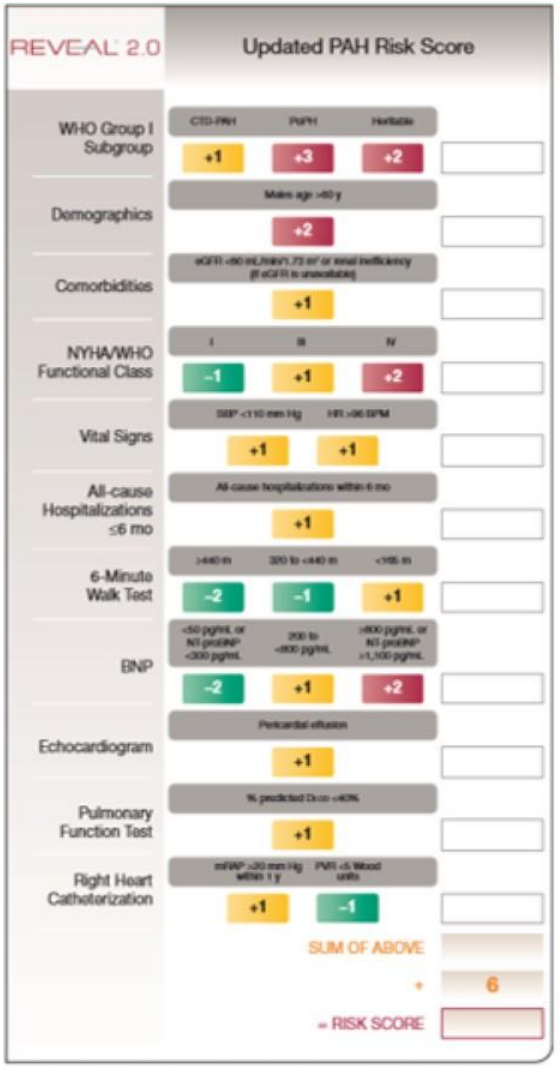
6th World Symposium Proceedings Expands Upon 2015 ESC/ERS Guidelines*



*Treatment algorithm for PAH, IPAH, HPAH, DPAH.

REVEAL Risk Score Calculator 2.0

- Refinement of the original REVEAL calculator
- Classifies patients into low-, intermediate-, and high-risk
- Greater discrimination (c-statistic = .76) than other assessment strategies
  - COMPERA (c-statistic = .62) and French Registry (c-statistic = .64)
- Includes all-cause hospitalizations within previous 6 months and renal insufficiency



REVEAL Risk Score Calculator 2.0
What Has Changed?

Existing variables with unchanged risk points/cut points	• PAH associated with connective tissue disease • Heritable PAH • Renal insufficiency • Males age > 60 years • SBP < 110 mm Hg • Pericardial effusion • mRAP ≥ 20 mm Hg within 1 year
Existing variables with revised risk points/cut points	• BNP/NT-proBNP • Heart rate • 6MWD • Pulmonary vascular resistance • PAH associated with portopulmonary hypertension • Percent predicted DLCO • NYHA/WHO FC
New/revised variables	• Hospitalizations within the last 6 months • eGFR < 60 mL/min/1.73m^2 or renal insufficiency if missing eGFR

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

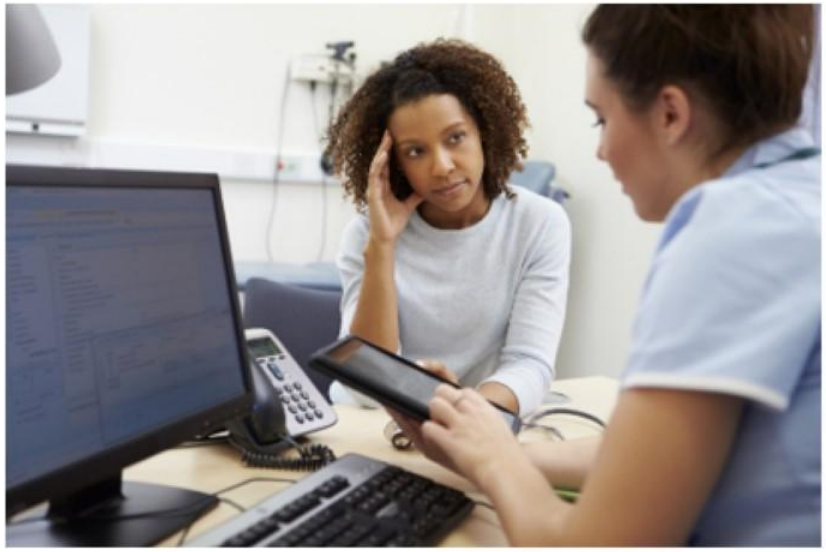
Achieving Low-Risk Status

- Important to achieve, regardless of score or method used
  - Need to be confident that you are bringing the patient's PAH under control
  - Upfront combination therapy considerations
  - Maximize triple therapy if necessary
  - Refer for lung transplantation consideration, if necessary

What if the patient doesn't fit into one of the status/risk categories?

Patient Case: Idiopathic PAH

- 29-year-old woman
- Placed on a dual oral combination therapy at time of diagnosis
- Did not tolerate ERA → switched to combination selexipag plus PDE5i
- Did well for 2 years, but then markers got worse
  - BNP went up
  - RV on echo became more enlarged
- Symptoms and 6MWD test were the same
  - All other noninvasive assessments were stable



Is this patient getting worse?
Or is this just variability during the disease course and the disease is still under control?

How Do We Detect Deterioration?

- Patients with idiopathic PAH can show unexpected clinical deterioration due to progressive RV failure
- Retrospective analysis of 22 patients with idiopathic PAH who were clinically stable for 5 years
- Total follow-up period of 10 years
  - 12 remained clinically stable; 10 showed late clinical disease progression
  - Baseline hemodynamics were comparable in both groups and remained unchanged
  - Late-progressive patients had:
    - Higher baseline RVESV and lower RVEF
    - Gradually increased RV end-diastolic volume and RVESV
    - Decline in RVEF
  - Long-term-stable patients did not show any RV changes

Monitoring RV volumes can anticipate clinical worsening, even at a time of apparent clinical stability

van de Veerdonk MC, et al. *Chest*. 2015;147:1063-1071.

How Important Is Cardiopulmonary Exercise Testing?

- Assessed added value of CPET during follow-up in patients with stable PAH
  - Investigated the prognostic relevance of CPET variables added to clinical and hemodynamic assessment
  - Patients without clinical worsening for 1 year after diagnosis and treatment initiation were prospectively followed
    - Derivation (n = 80) and validation (n = 80) cohorts enrolled at an interval of 6 years and followed for 3 years
  - Results
    - With addition of CPET variables, VO_2 peak and changes in cardiac index independently improved the power of the prognostic model

CPET can be an important addition to right heart catheterization when assessing clinically improved, stabilized patients

Badagliacca R, et al. *J Heart Lung Transplant*. 2019;38:306-314.

Implementation Strategies

- Routinely perform risk assessment and repeat at follow-up
- Exercise assessment with CPET
  - 6MWD may not always be predictive or discriminatory in detecting slight or preclinical worsening of disease
- Use and record risk scores and follow-up assessments
- Employ multiple parameters to evaluate disease severity

Continual Reassessment of Risk Status

2015 ESC/ERS Guidelines: PAH Baseline and Follow-up Assessments

At baseline	•Medical assessment and determination of functional class •ECG •6MWT/Borg dyspnea score •CPET •Echo	•Basic lab† •Extended lab‡ •Blood gas analysis§ •Right heart catheterization
Every 3–6 months*	•Medical assessment and determination of functional class •ECG •6MWT/Borg dyspnea score •Basic lab†	
Every 6–12 months*	•Medical assessment and determination of functional class •ECG •6MWT/Borg dyspnea •CPET •Echo	•Basic lab† •Extended lab‡ •Blood gas analysis§ •Right heart catheterization‖
3–6 months after changes in therapy*	•Medical assessment and determination of functional class •ECG •6MWT/Borg dyspnea score •Echo	•Basic lab† •Blood gas analysis§ •Right heart catheterization¶
In case of clinical worsening	•Medical assessment and determination of functional class •ECG •6MWT/Borg dyspnea score •CPET¶ •Echo	•Basic lab† •Extended lab‡ •Blood gas analysis§ •Right heart catheterization¶

*Intervals to be adjusted according to patient needs; †Basic lab includes blood count, INR (inpatients receiving vitamin K antagonists), serum creatinine, sodium, potassium, AST/ALT (in patients receiving ERAs), bilirubin and BNP/NT-proBNP; ‡Extended lab includes TSH, troponin, uric acid, iron status (iron, ferritin, soluble transferrin receptor) and other variables according to individual patient needs; §From arterial or arterialized capillary blood; may be replaced by peripheral oxygen saturation in stable patients or if BGA is not available; ‖Some centers perform RHCs at regular intervals during follow-up; ¶Should be considered.

Galiè N et al. *Eur Heart J*. 2016;37:67-119.

Multidisciplinary Team Approach Is Important

- Cardiology
- Pulmonology
- Rheumatology
  - Particularly for patients with scleroderma
  - Current assessment tools may not be as accurate
  - Functional status can be affected by rheumatologic disease
- Pulmonary rehabilitation
- Dietary management
- Social workers

Summary

- Data support structured follow-up and continued risk assessment approach for PAH
  - Essential to evaluate patients
    - Whose disease will worsen?
    - Adjust therapy accordingly
  - REVEAL Risk Score Calculator 2.0
- Goal of achieving low-risk status
  - User-friendly treatment algorithms for clinical practice to assess risk status
- Important to use a multidisciplinary team approach
  - Integrate different specialties to provide full care
- PAH Expert Center listing available
  - Pulmonary Hypertension Association website
  - https://phassociation.org/phcarecenters/accredited-centers/

Abbreviations

AIR = Aerosolized Iloprost Randomized
ALT = alanine aminotransferase
ALPHABET = Arterial Pulmonary Hypertension and Beraprost European Trial
ARIES = Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy
AST = aspartate aminotransferase
BGA = blood gas analysis
BNP = B-type natriuretic peptide
BPM = beats per min
BREATHE = Bosentan Randomized trial of Endothelin Antagonist Therapy for PAH
CCB = calcium channel blocker
CI = cardiac index
CI = confidence interval
COMBI = Combination Therapy of Bosentan and Aerosolised Iloprost in Idiopathic Pulmonary Arterial Hypertension
COMPERA = Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension
CPET = cardiopulmonary exercise test
CTD-PAH = PAH associated with connective tissue disease

Abbreviations (cont)

DLCO = diffusing capacity of the lungs for carbon monoxide
DPAH = drug-induced pulmonary arterial hypertension
ECG = electrocardiogram
echo = echocardiogram
eGFR = estimated glomerular filtration rate
ERA = endothelin receptor antagonist
ERS = European Respiratory Society
ESC = European Society of Cardiology
GRIPHON = Prostacyclin (PGI2) Receptor Agonist In Pulmonary Arterial Hypertension
HPAH = heritable pulmonary arterial hypertension
HR = hazard ratio
HR = heart rate
INR = international normalized ratio
IPAH = idiopathic pulmonary arterial hypertension
iv = intravenous
LTx = lung transplantation
mRAP = mean right atrial pressure
MRI = magnetic resonance imaging
NT-proBNP = N-terminal-pro hormone B-type natriuretic peptide

Abbreviations (cont)

NYHA = New York Heart Association
PAH = pulmonary arterial hypertension
PCA = prostacyclin analogue
PDE5i = phosphodiesterase type 5 inhibitor
PoPH = portopulmonary hypertension
PVR = pulmonary vascular resistance
RAP = right atrial pressure
RCT = randomized controlled trial
REVEAL = Registry to Evaluate Early and Long-Term PAH Disease Management
RHC = right heart catheterization
RV = right ventricle
RVEF = right ventricle ejection fraction
RVESV = right ventricle end-systolic volume
SBP = systolic blood pressure
sc = subcutaneous
SERAPHIN = Study with an Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve Clinical Outcome
sGC-S = soluble guanylyl cyclase stimulator
6MWD = 6-minute walk distance

Abbreviations (cont)

6MWT = 6-minute walk test
SSc = systemic sclerosis
STRIDE = Sitaxsentan To Relieve Impaired Exercise
TSH = thyroid stimulating hormone
VO_2 peak = peak oxygen uptake
WHO FC = World Health Organization functional class