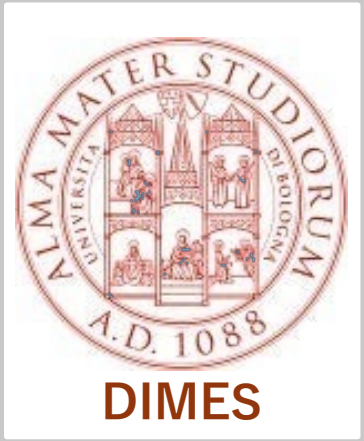
# Management of pulmonary arterial hypertension

**Fabio Dardi, MD**

**Alma Mater Studiorum, University of Bologna**





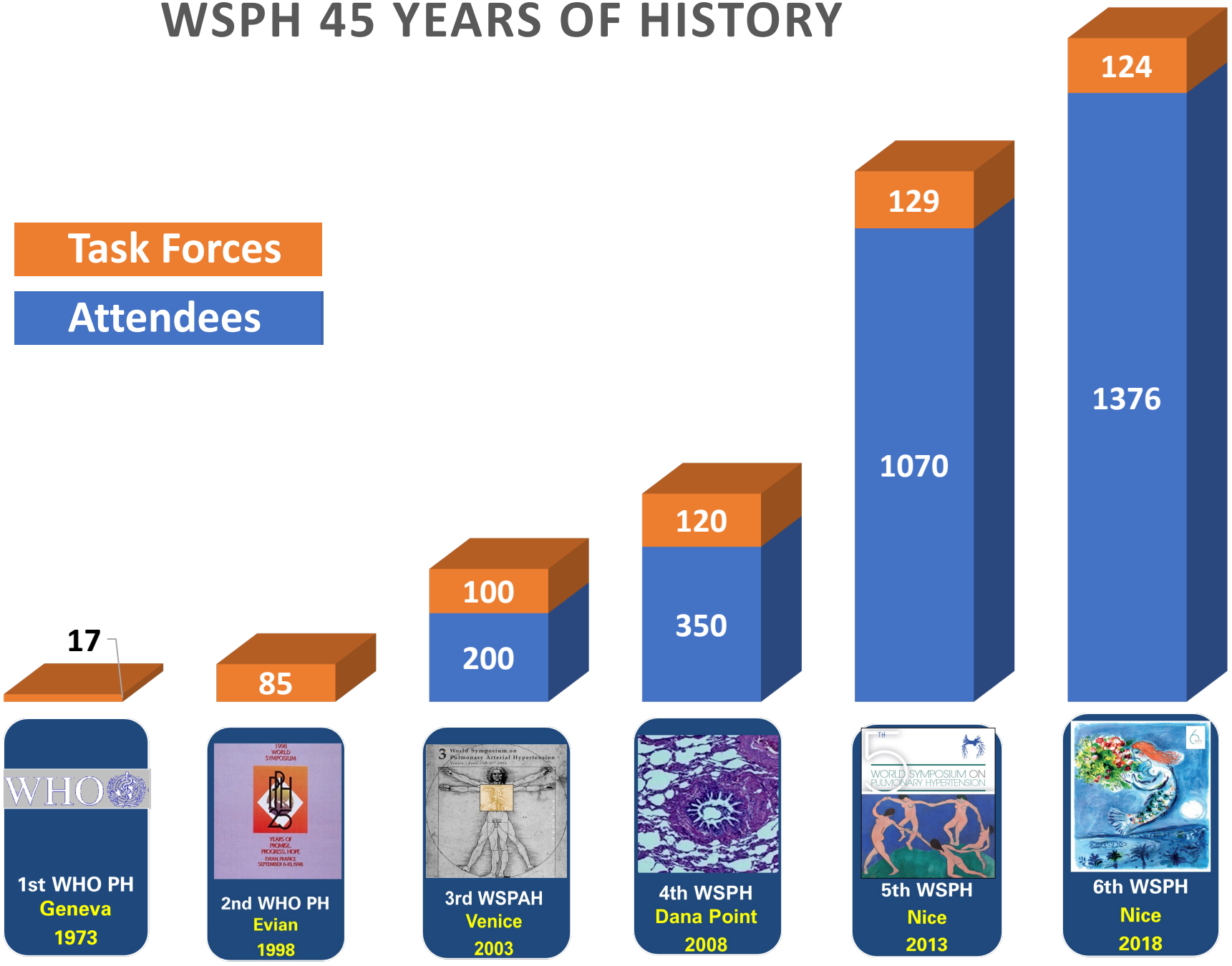
fabio.dardi2@unibo.it

# Disclosures

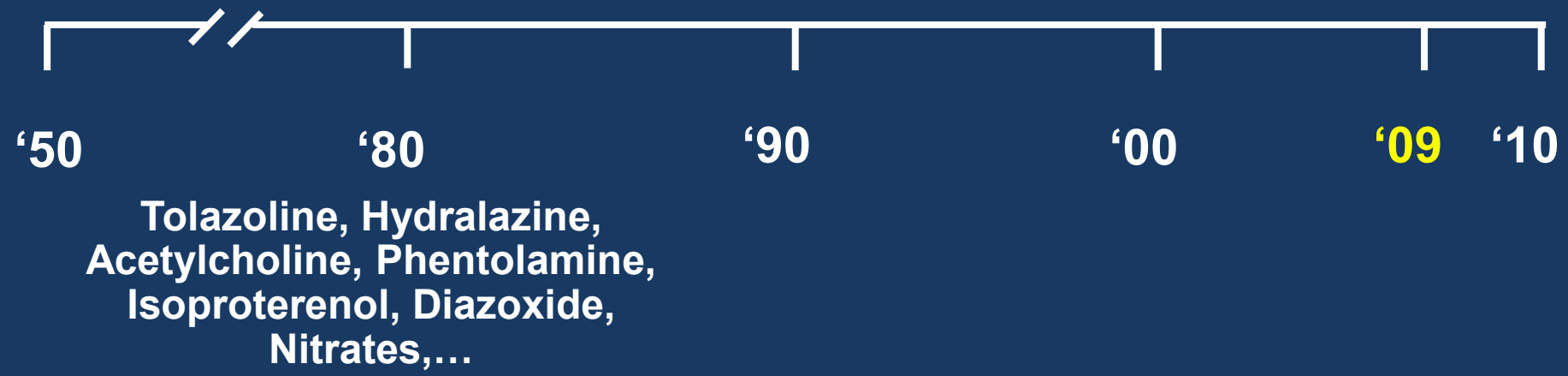
Nothing to disclose

# Historical Perspective

# WSPH 45 YEARS OF HISTORY



# Early time course

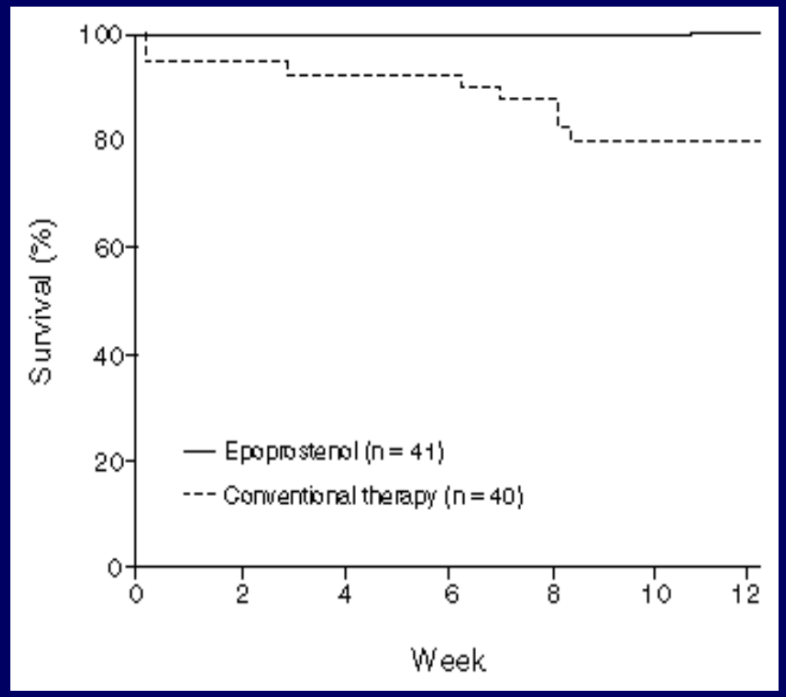


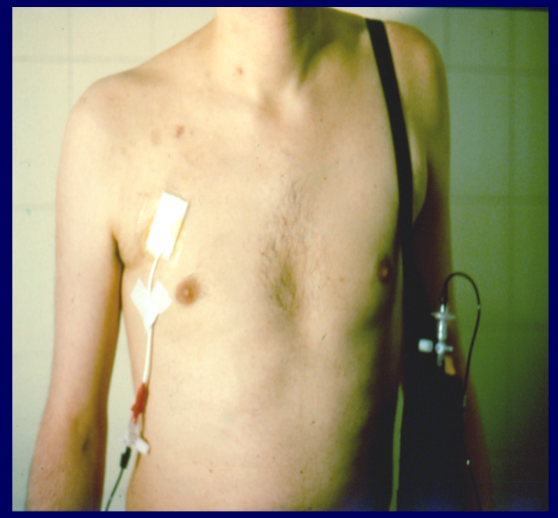
# Treatment Algorithm 1995

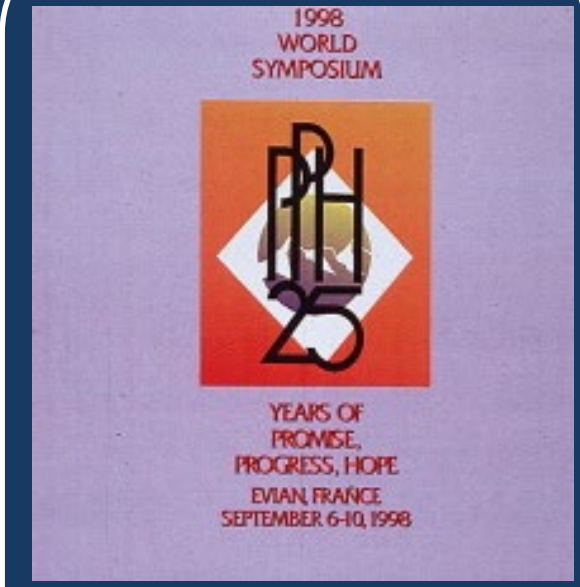
## A COMPARISON OF CONTINUOUS INTRAVENOUS EPOPROSTENOL (PROSTACYCLIN) WITH CONVENTIONAL THERAPY FOR PRIMARY PULMONARY HYPERTENSION

ROBYN J. BARST, M.D., LEWIS J. RUBIN, M.D., WALKER A. LONG, M.D., MICHAEL D. MCGOON, M.D., STUART RICH, M.D., DAVID B. BADESCH, M.D., BERTRON M. GROVES, M.D., VICTOR F. TAPSON, M.D., ROBERT C. BOURGE, M.D., BRUCE H. BRUNDAGE, M.D., SPENCER K. KOERNER, M.D., DAVID LANGLEBEN, M.D., CESAR A. KELLER, M.D., SRINIVAS MURALI, M.D., BARRY F. URETSKY, M.D., LINDA M. CLAYTON, PHARM.D., MARIA M. JÖBSIS, B.A., SHELMER D. BLACKBURN, JR., B.A., DENISE SHORTINO, M.S., JAMES W. CROW, PH.D., FOR THE PRIMARY PULMONARY HYPERTENSION STUDY GROUP*

**New Engl J Med 1996; 334:296-301**



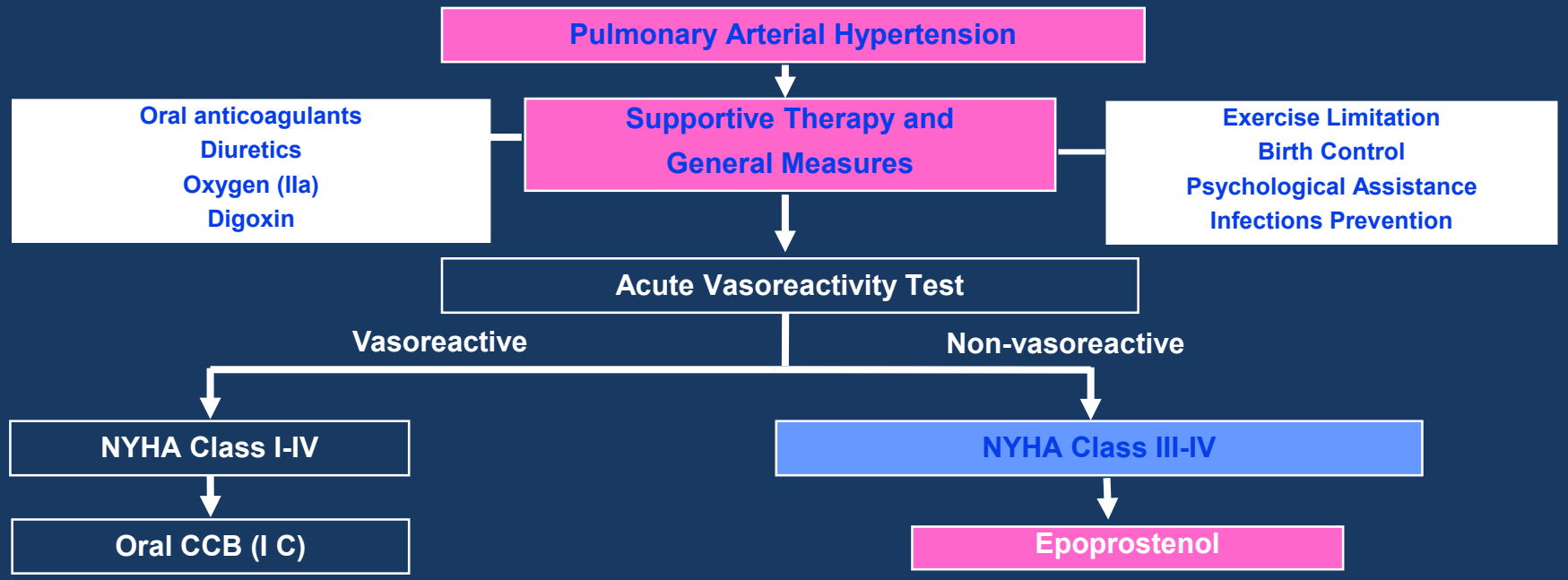


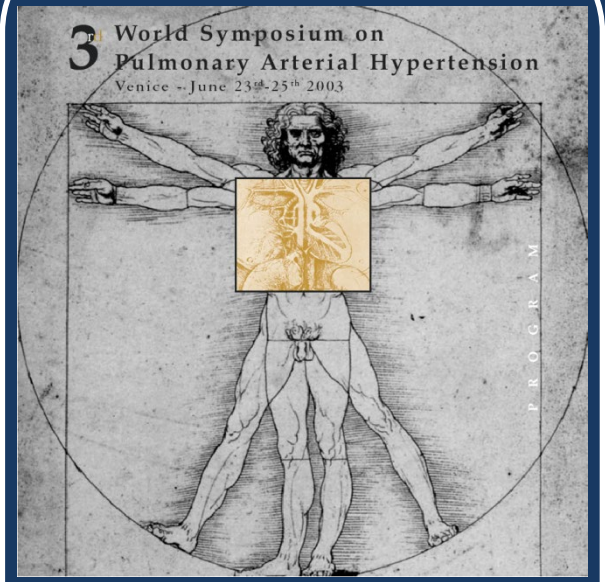

# 2nd WHO PH

## Evian

## 1998

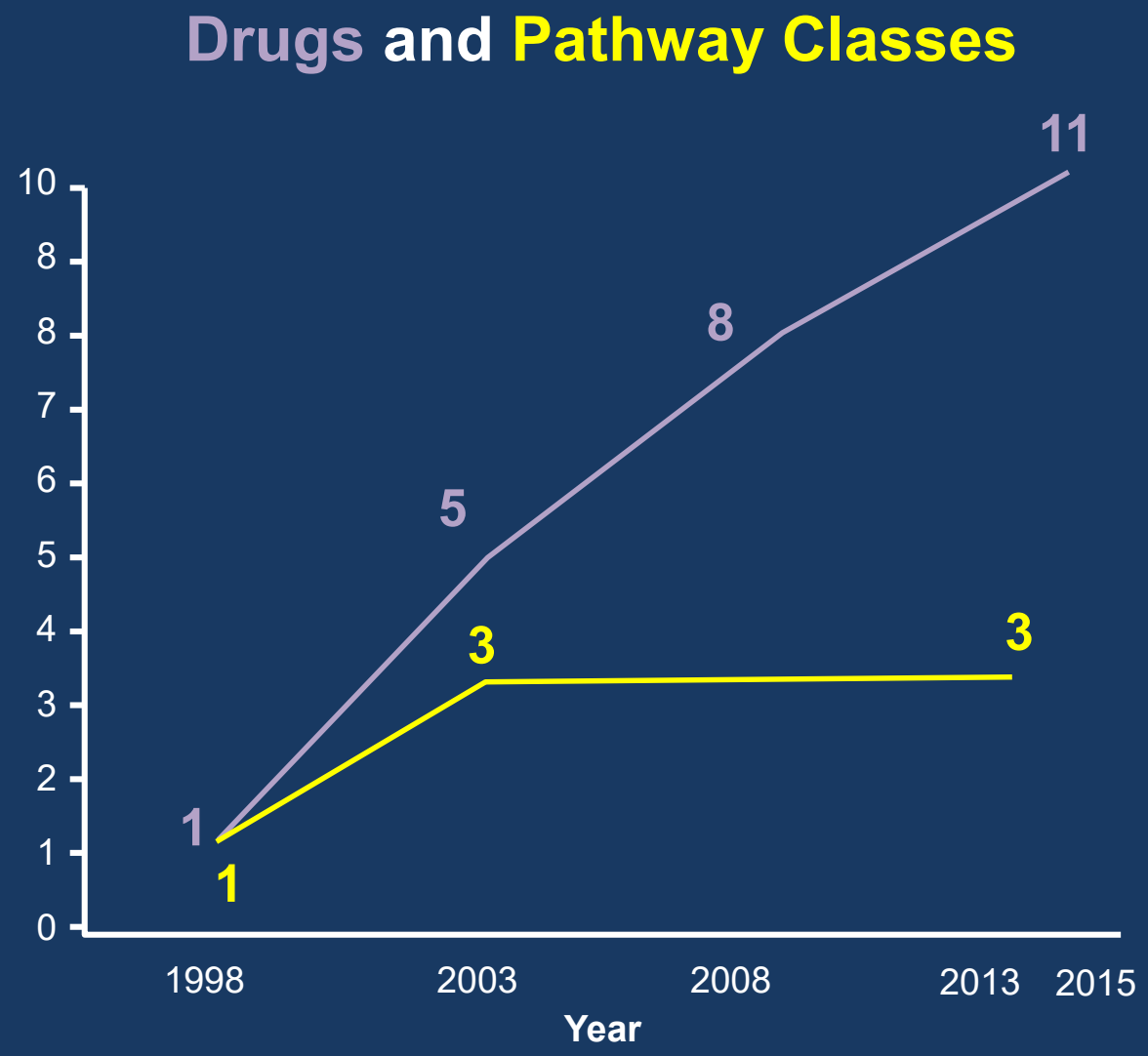
# Treatment Algorithm 1998 - 2003





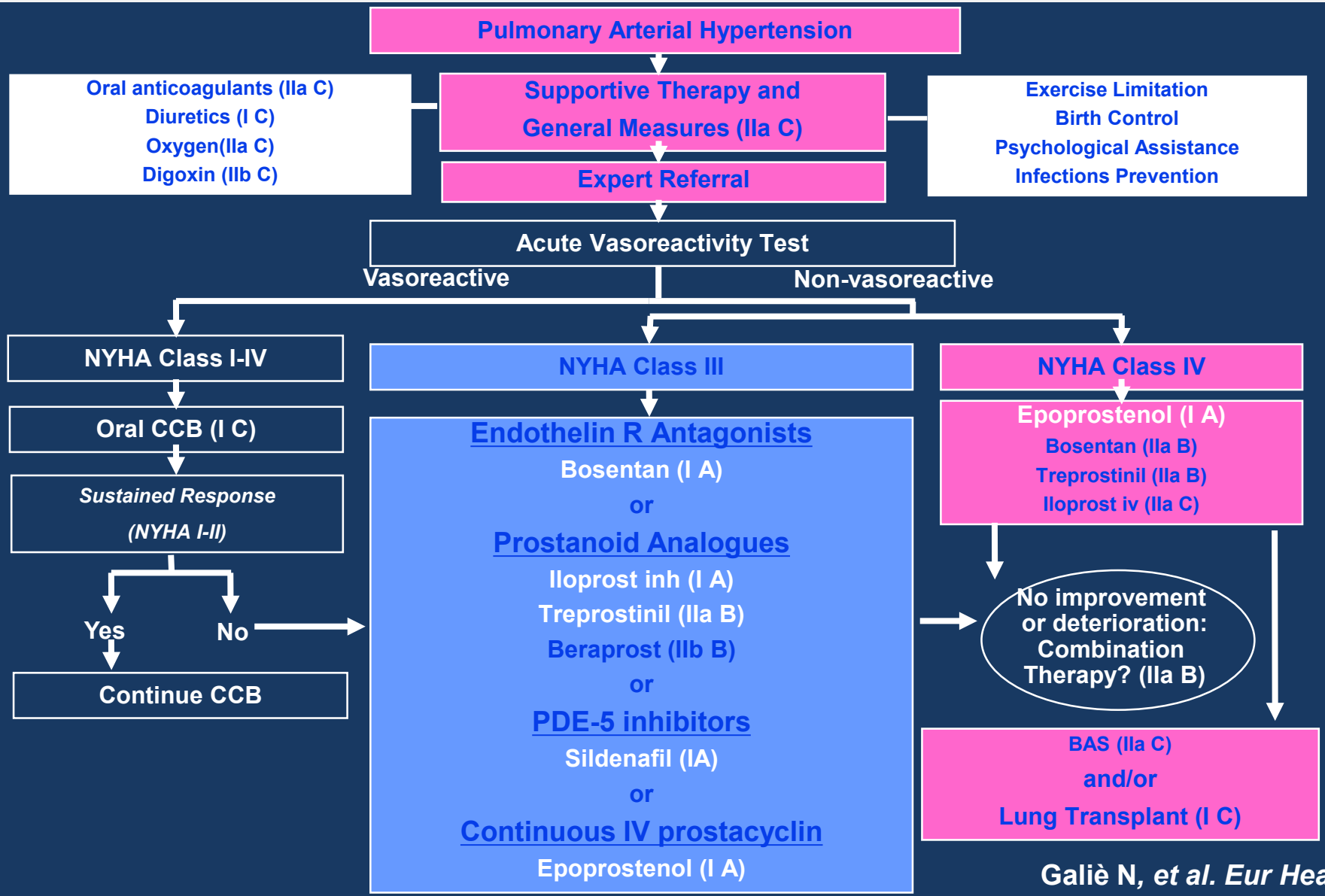

# 3rd WSPAH
# Venice
# 2003

# Approved PAH drugs & pathways/classes

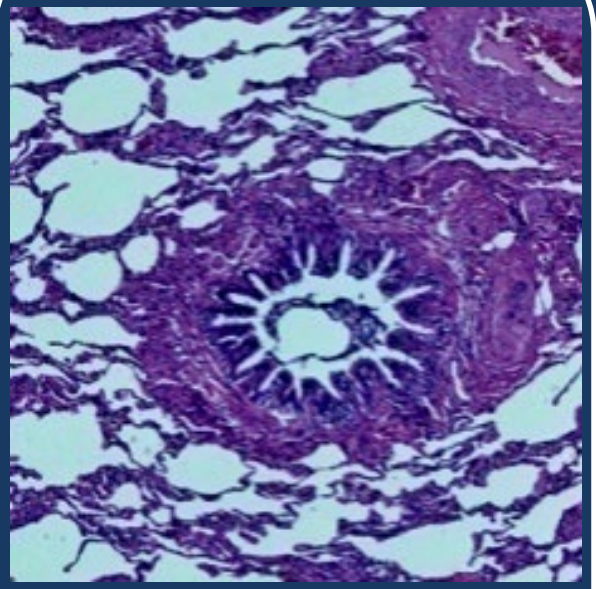



| | |
|---|---|
| Prostacyclin | PCA |
| | IPr-a |
| Endothelin | ERA |
| Nitric Oxide | PDE-5i |
| | GC-s |

# Treatment Algorithm 2004

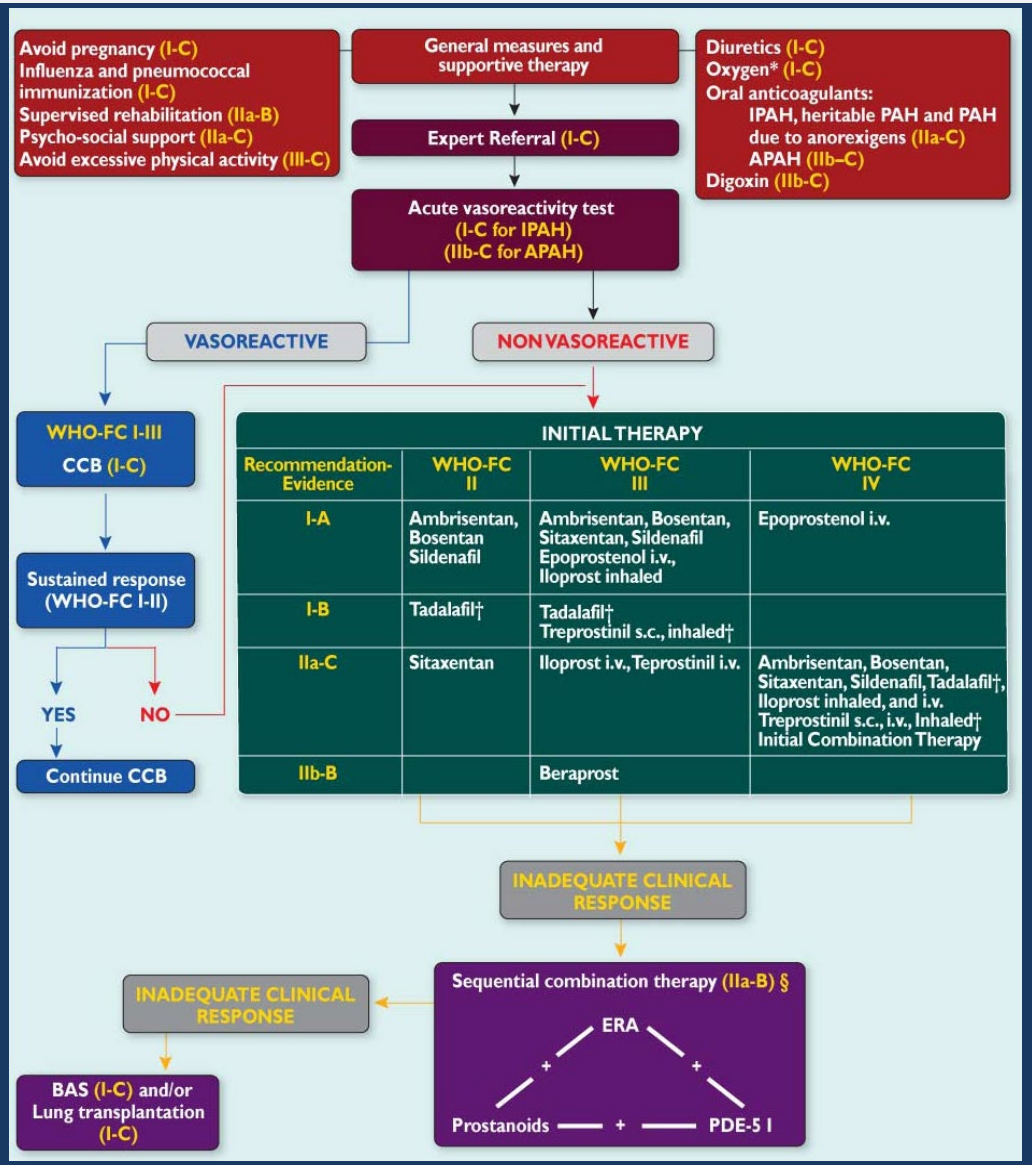



Galiè N, *et al. Eur Heart J* 2004; 25:2243-2278.

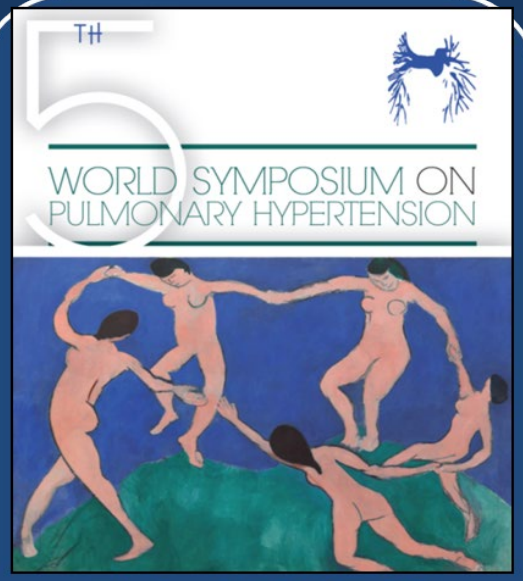


# 4th WSPH
# Dana Point
# 2008

# Treatment Algorithm 2009




*Galiè.N et al Eur Heart J and Eur Respir J, 2009*




# 5th WSPH

## Nice

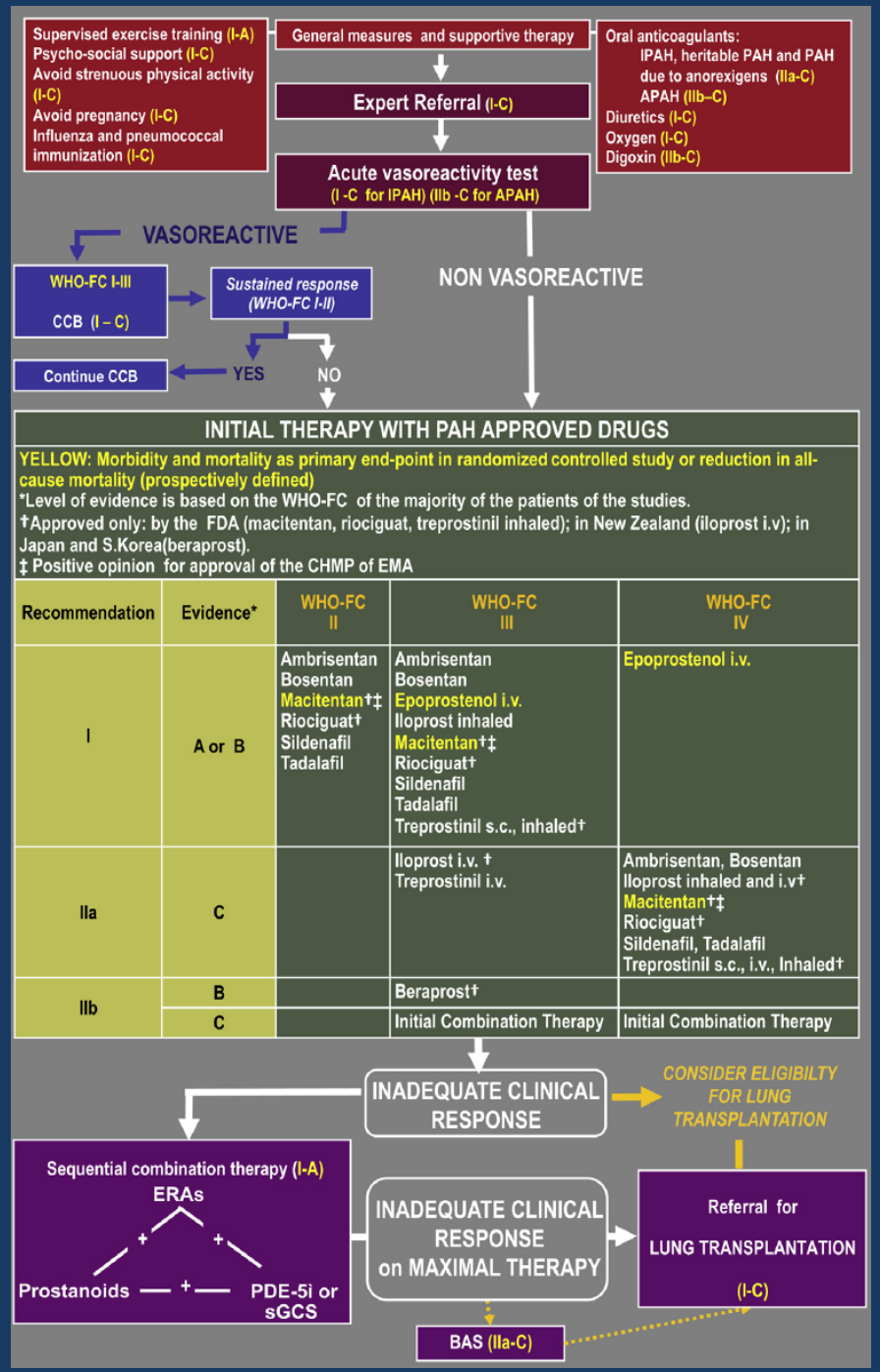
## 2013

# Updated Treatment Algorithm of Pulmonary Arterial Hypertension

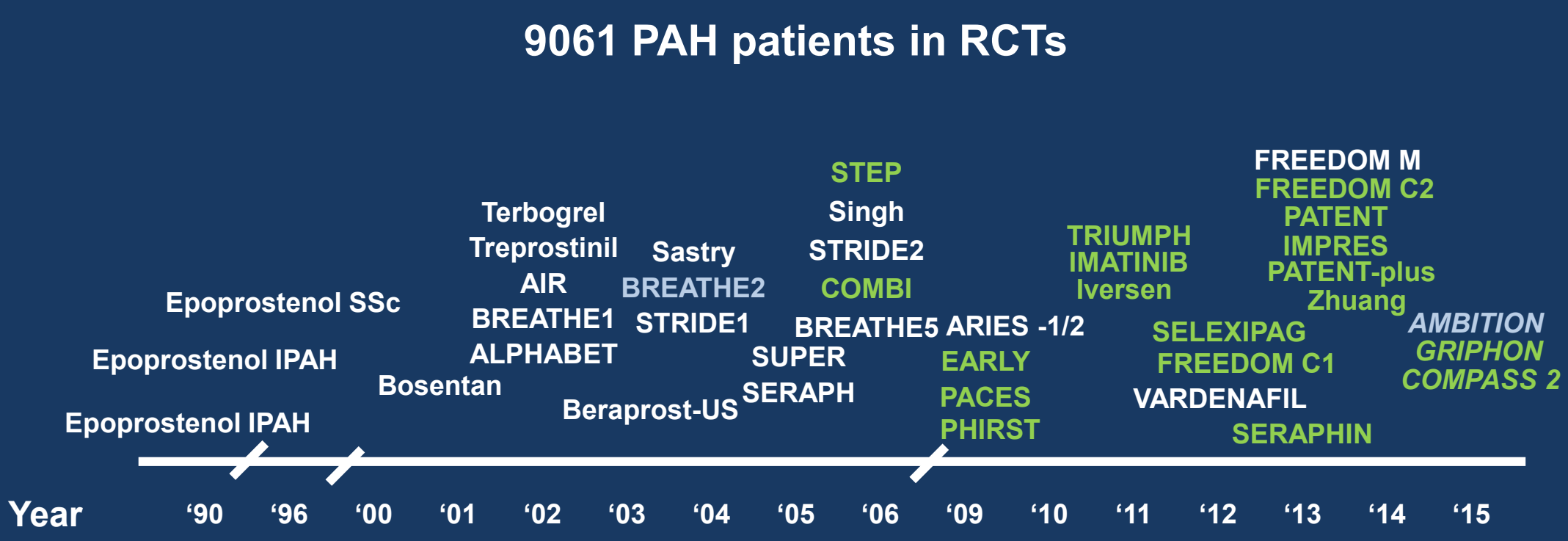
## Updated Treatment Algorithm of Pulmonary Arterial Hypertension

Nazzareno Galiè, MD,* Paul A. Corris, MD,† Adaani Frost, MD,‡ Reda E. Girgis, MD,§ John Granton, MD,‖ Zhi Cheng Jing, MD,¶ Walter Klepetko, MD,# Michael D. McGoon, MD,** Vallerie V. McLaughlin, MD,†† Ioana R. Preston, MD,‡‡ Lewis J. Rubin, MD,§§ Julio Sandoval, MD,‖‖ Werner Seeger, MD,¶¶ Anne Keogh, MD##

(J Am Coll Cardiol 2013;62:D60–72)



# Time-course of completed and published RCTs in PAH (41) – Therapy strategy




RCTs on monotherapy vs placebo or vs monotherapy (21)

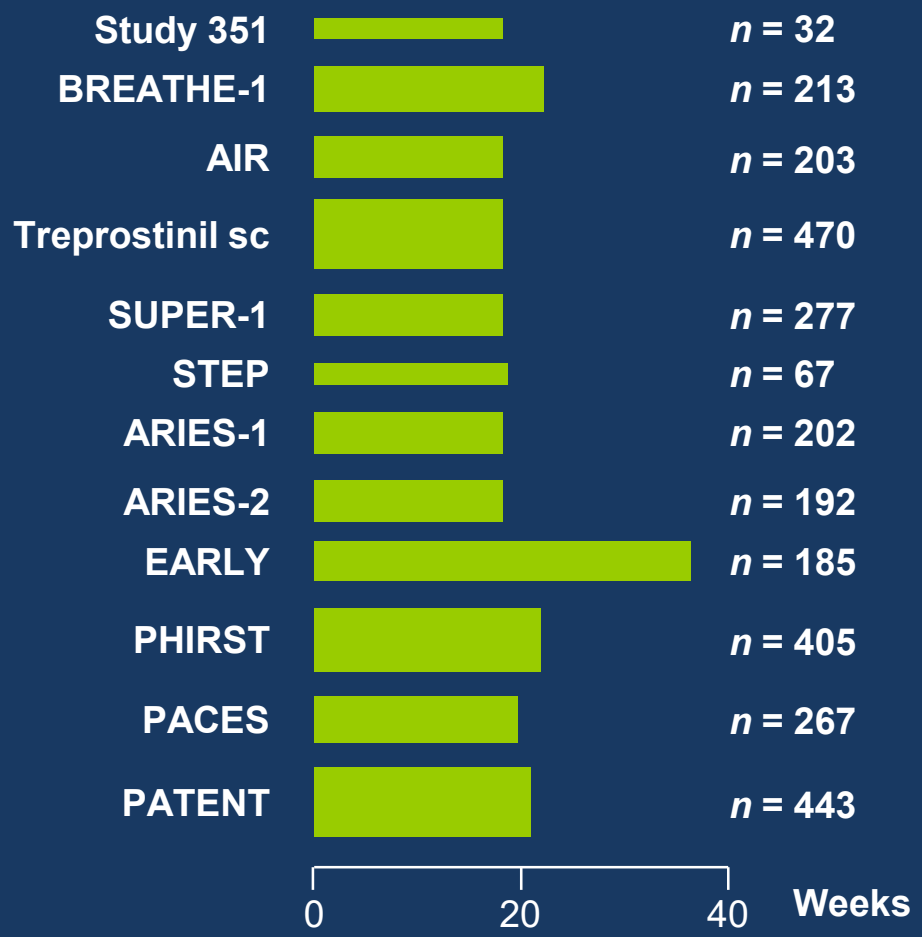
RCTs on monotherapy and/or sequential combination vs placebo (18)

RCTs on initial combination vs monotherapy (2)

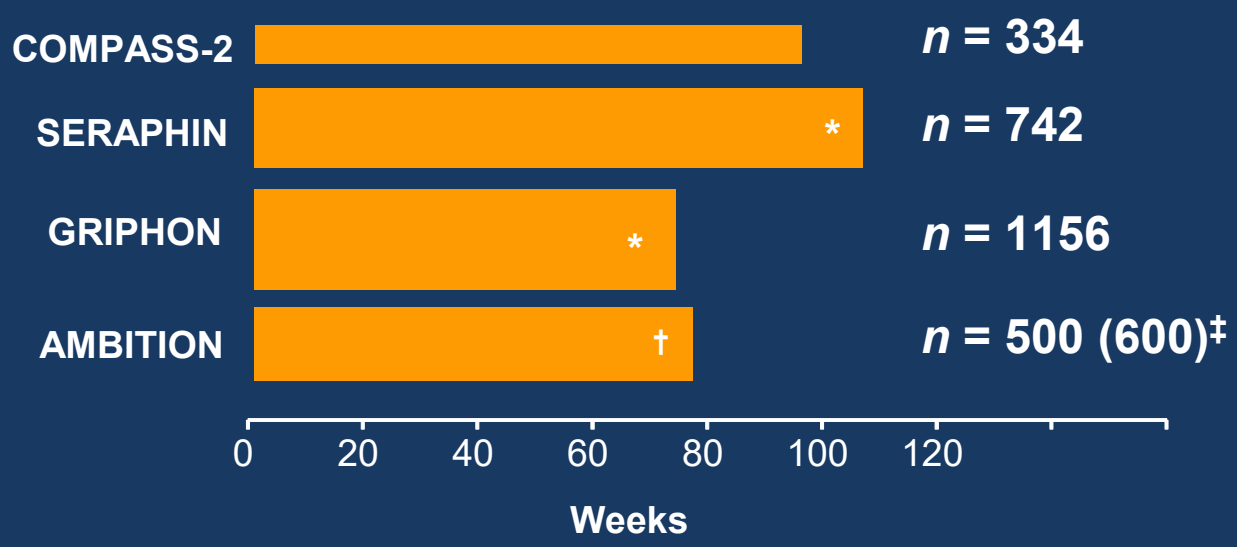
Modified from Galiè N, *et al. Eur Heart J* 2010; 31:2080-6.

# Evolution from exercise capacity to outcome RCTs

## 6MWD trials (2001 – 2013)



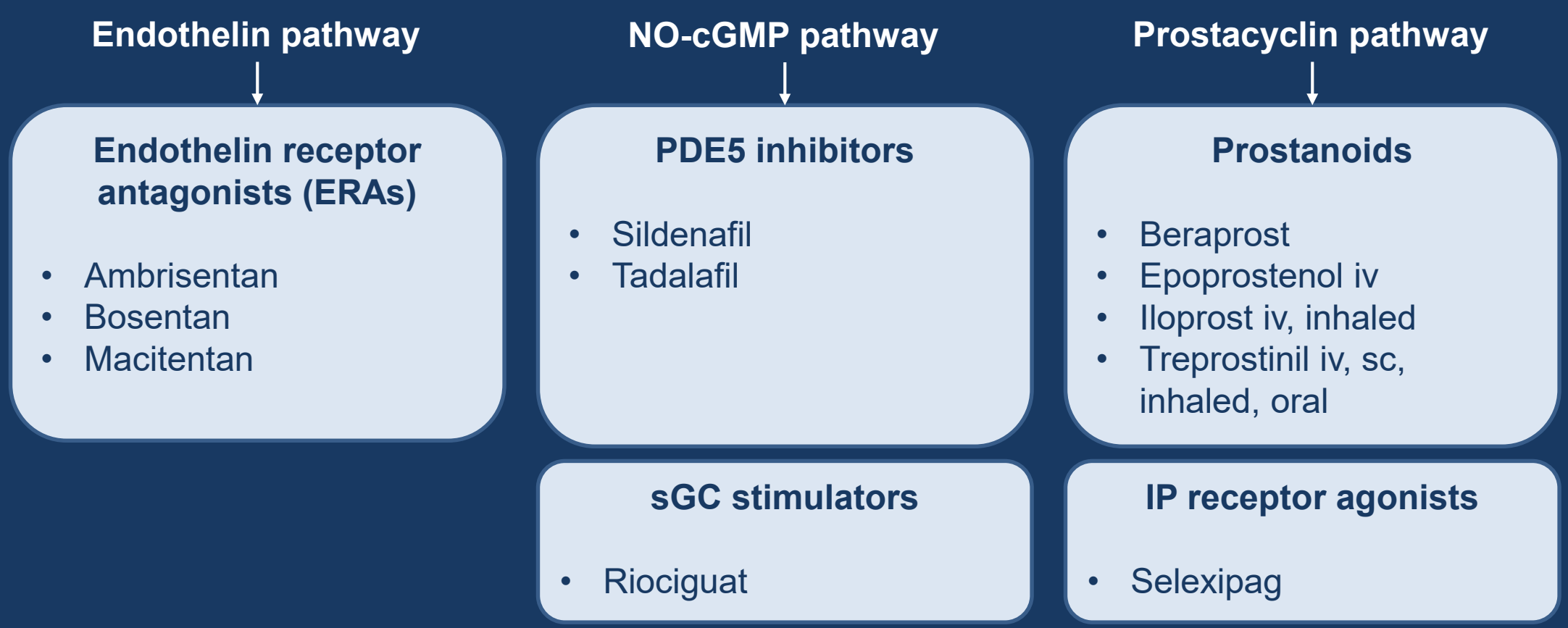

## Outcome trials (2013 – 2015)




*Mean study drug exposure. †Median study drug exposure. ‡Target enrollment.

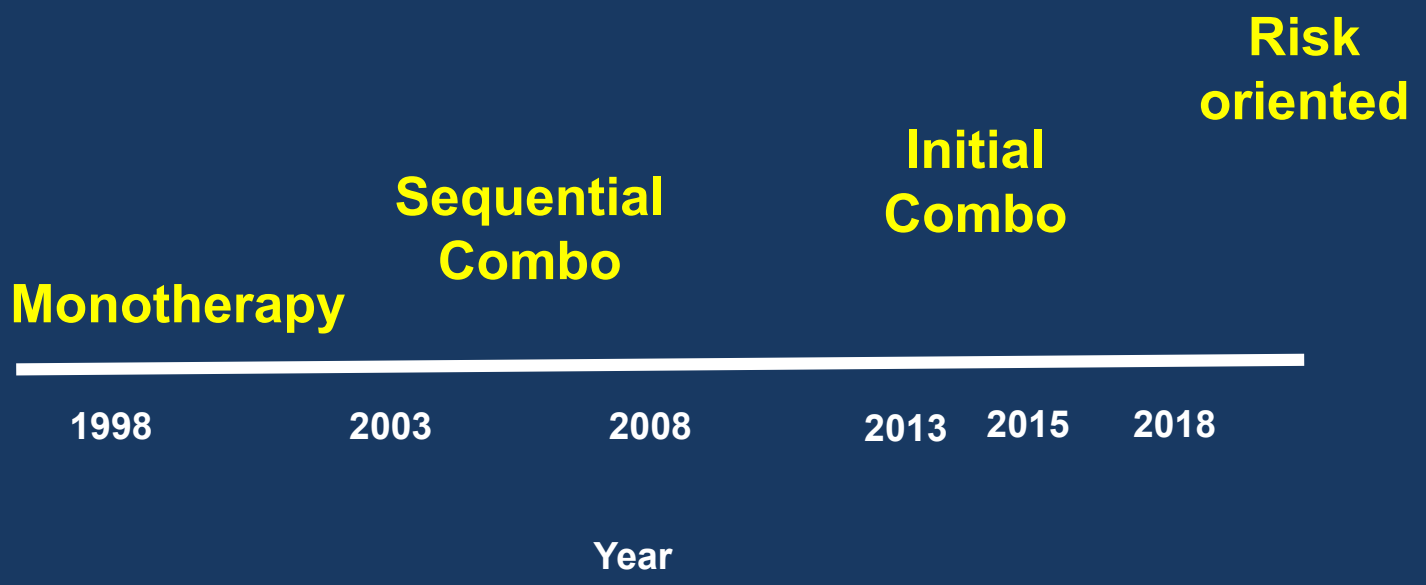

Channick RN, *et al. Lancet* 2001; Rubin LJ, *et al. N Engl J Med* 2002; Galiè N, *et al. Lancet* 2008; Galiè N, *et al. Circulation* 2008; Galiè N, *et al. N Engl J Med* 2005; Simonneau G, *et al. Am J Respir Crit Care Med* 2002; McLaughlin VV, *et al. Am J Respir Crit Care Med* 2006; Galiè N, *et al. Circulation* 2009; Simonneau G, *et al. Ann Intern Med* 2008; Olschewski H, *et al. N Engl J Med* 2002; McLaughlin VV, *et al. Eur Respir J* 2015; Pulido S, *et al. New Engl J Med* 2013; Sitbon O, *et al. Eur Respir J* 2015; Galiè N, *et al. New Engl J Med* 2015.

# Approved drugs by pathway

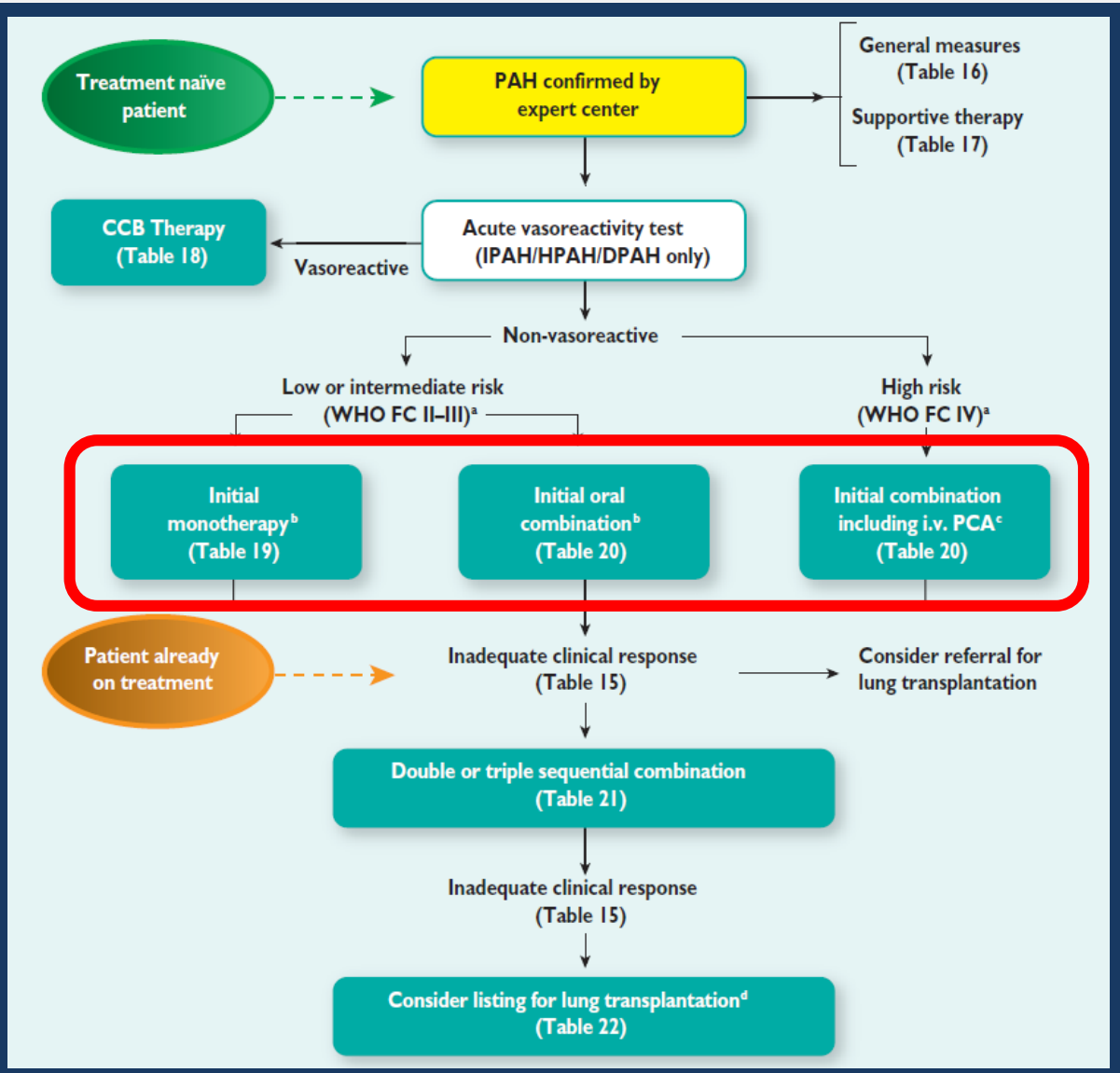



Modified from Galiè N, *et al. J Am Coll Cardiol* 2013; 62:D60-72.

# Treatment Strategies Evolution



# 2015 ESC/ERS Guidelines – Combination therapy is widely recommended and supported by clinical trial data




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

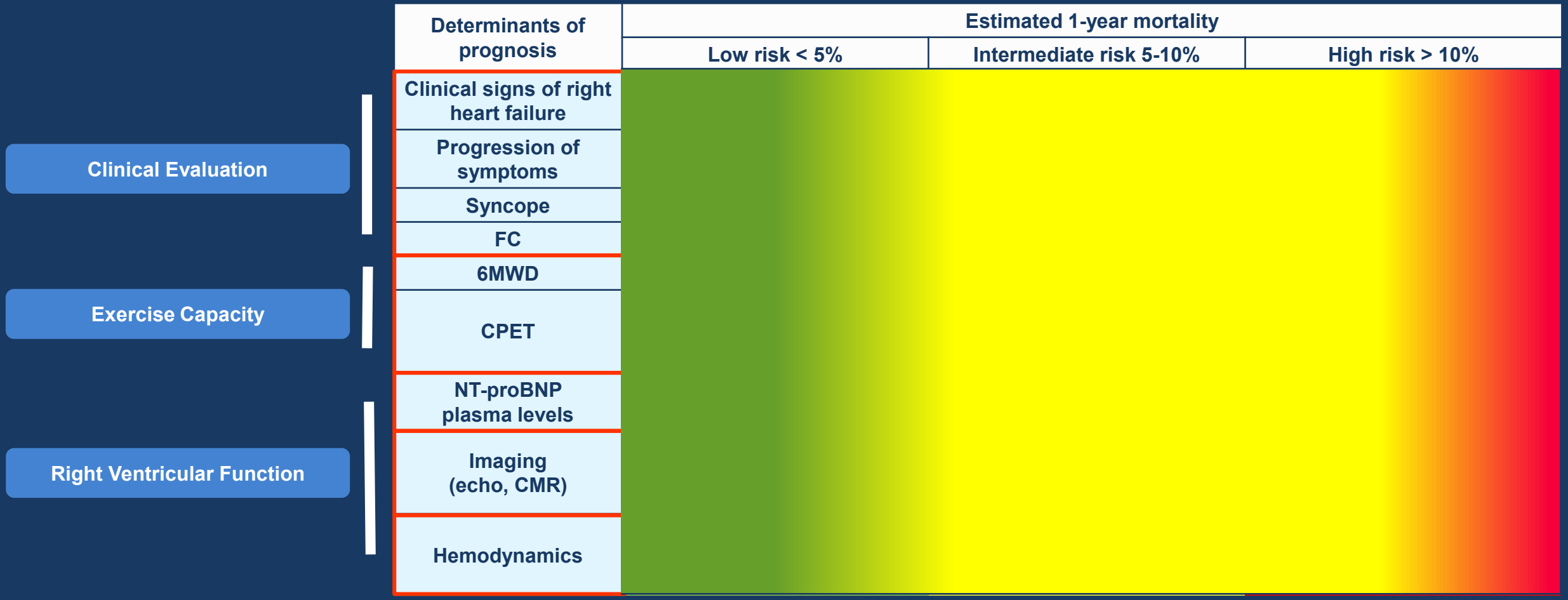
# PAH Patients Risk Stratification

# 2015 ESC/ERS Guidelines – Risk stratification in PAH

| | Determinants of prognosis | Estimated 1-year mortality | | |
|---|---|---|---|---|
| | | Low risk < 5% | Intermediate risk 5-10% | High risk > 10% |
| Clinical Evaluation | Clinical signs of right heart failure | Absent | Absent | Present |
| | Progression of symptoms | No | Slow | Rapid |
| | Syncope | No | Occasional syncope | Repeated syncope |
| | FC | I, II | III | IV |
| Exercise Capacity | 6MWD | > 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 - 44.9 | Peak $VO_2$ < 11ml/min/kg (< 35% pred.) $VE/VCO_2$ slope ≥ 45 |
| Right Ventricular Function | NT-proBNP plasma levels | BNP < 50 ng/l NT-proBNP < 300 ng/l | BNP 50–300 ng/l NT-proBNP 300–1400 ng/l | BNP > 300 ng/l NT-proBNP > 1400 ng/l |
| | Imaging (echo, CMR) | RA area < 18 $cm^2$ No pericardial effusion | RA area 18–26 $cm^2$ No or minimal pericardial effusion | RA area > 26 $cm^2$ Pericardial effusion |
| | Hemodynamics | RAP < 8 mmHg CI ≥ 2.5 l/min/$m^2$ $SvO_2$ > 65% | RAP 8–14 mmHg CI 2.0–2.4 l/min/$m^2$ $SvO_2$ 60–65% | RAP > 14 mmHg CI < 2.0 l/min/$m^2$ $SvO_2$ < 60% |

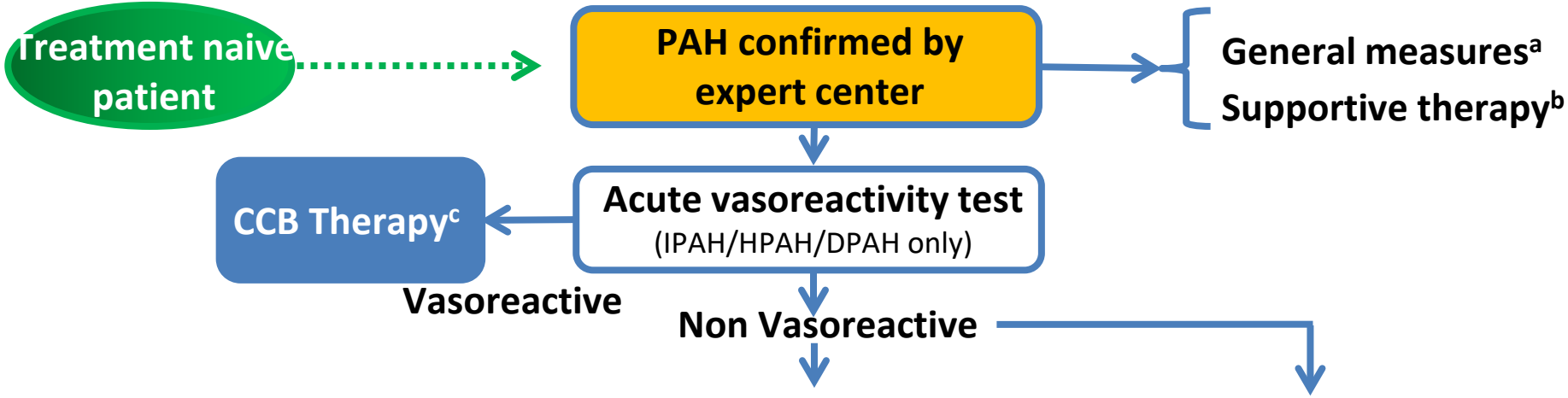
Galiè N, *et al. Eur Heart J* 2016; 37:67-119; Galiè N, *et al. Eur Respir J* 2015; 46:903-75.

# 2015 ESC/ERS Guidelines – Risk stratification in PAH

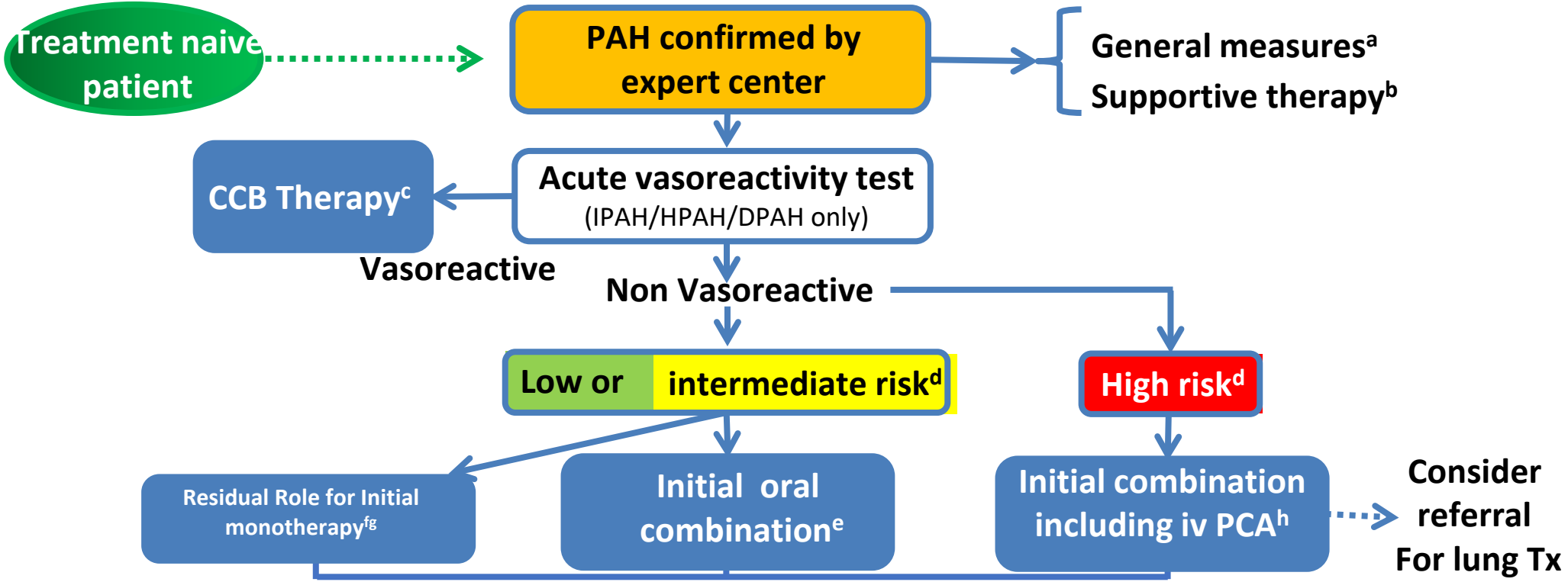



Galiè N, *et al. Eur Heart J* 2016; 37:67-119; Galiè N, *et al. Eur Respir J* 2015; 46:903-75.

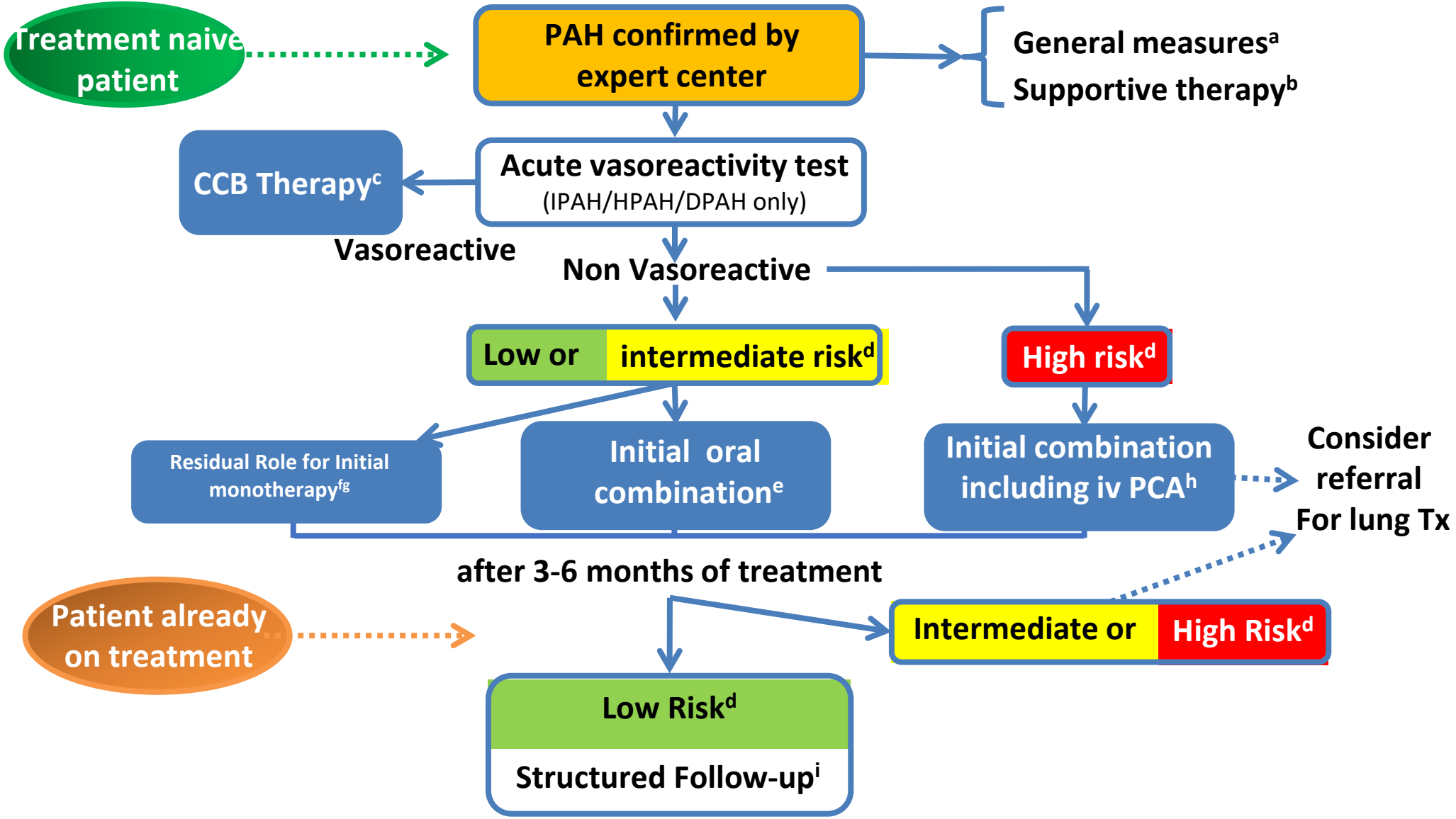
# Risk Stratification, Treatment Strategies and Treatments Algorithm



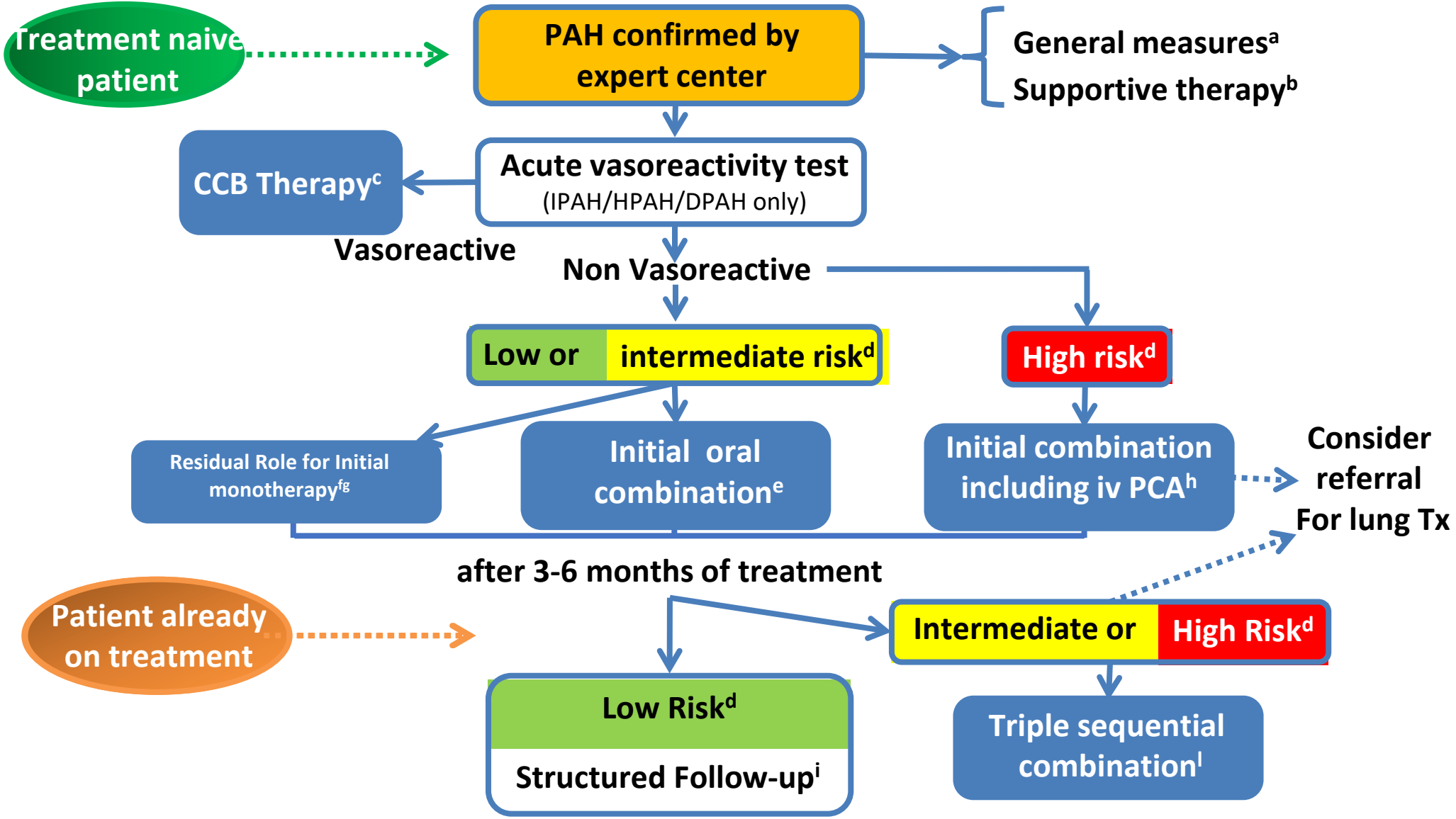

Galiè et al. Eur Respir J. 2019 Jan 24;53(1)



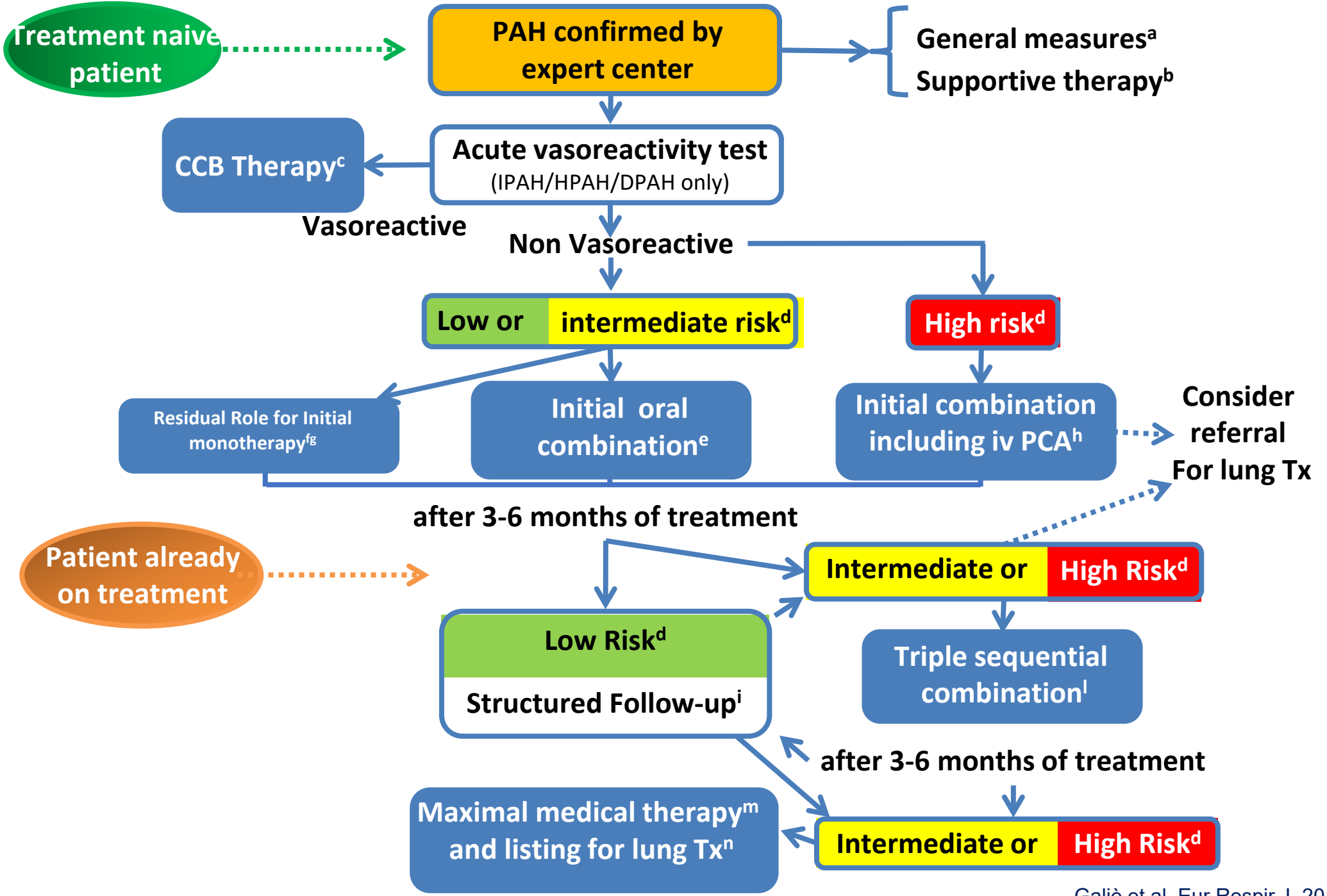

Galiè et al. Eur Respir J. 2019 Jan 24;53(1)



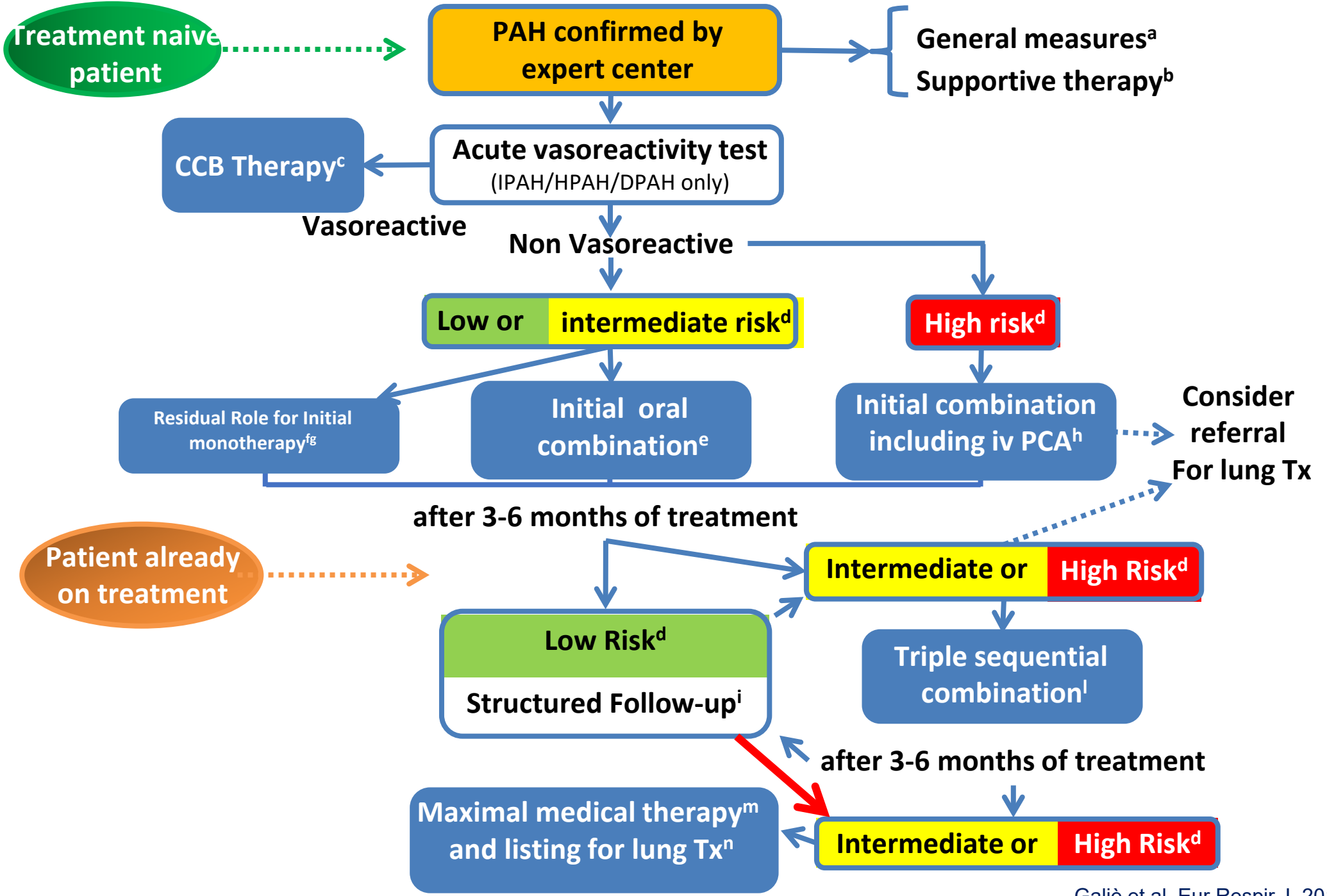

Galiè et al. Eur Respir J. 2019 Jan 24;53(1)




Galiè et al. Eur Respir J. 2019 Jan 24;53(1)




Galiè et al. Eur Respir J. 2019 Jan 24;53(1)




Galiè et al. Eur Respir J. 2019 Jan 24;53(1)

# Table 14: Suggested assessment and timing for the prospective and structured follow-up of patients with PAH

| | At baseline | Every 3–6 months[a] | Every 6–12 months[a] | 3–6 months after changes in therapy[a] | In case of clinical worsening |
|---|---|---|---|---|---|
| Medical assessment and determination of functional class | + | + | + | + | + |
| ECG | + | + | + | + | + |
| 6MWT/Borg dyspnoea score | + | + | + | + | + |
| CPET | + | | + | | +[e] |
| Echo | + | | + | + | + |
| Basic lab[b] | + | + | + | + | + |
| Extended lab[c] | + | | + | | + |
| Blood gas analysis[d] | + | | + | + | + |
| Right heart catheterization | + | | +[f] | +[e] | +[e] |

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

Galiè N, *et al. Eur Respir J* 2015; 46:903-75;
Galiè N, *et al. Eur Heart J* 2016; 37:67-119.

# Residual role of monotherapy

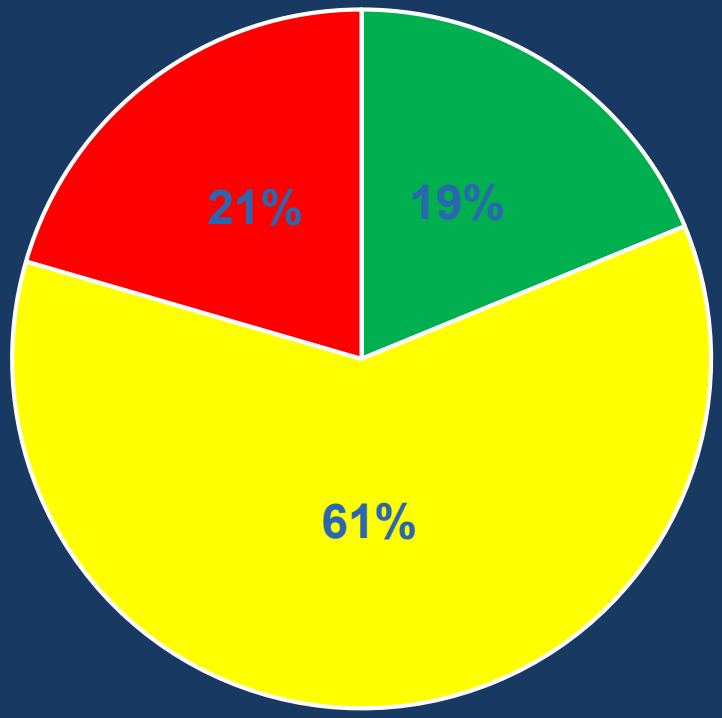
1. IPAH patient responders to acute vasoreactivity tests and with near-normalization of symptoms, exercise capacity, PAP and PVR on high doses of CCBs
2. Historical PAH patients on long-term monotherapy (> 5-10 years) and stable with a low-risk profile
3. PAH patients > 75 years old with multiple risk factors for heart failure with preserved left ventricular ejection fraction (high blood pressure, diabetes mellitus, coronary artery disease, atrial fibrillation, obesity)
4. PAH patients with suspicion or high probability of pulmonary veno-occlusive disease

# Residual role of monotherapy

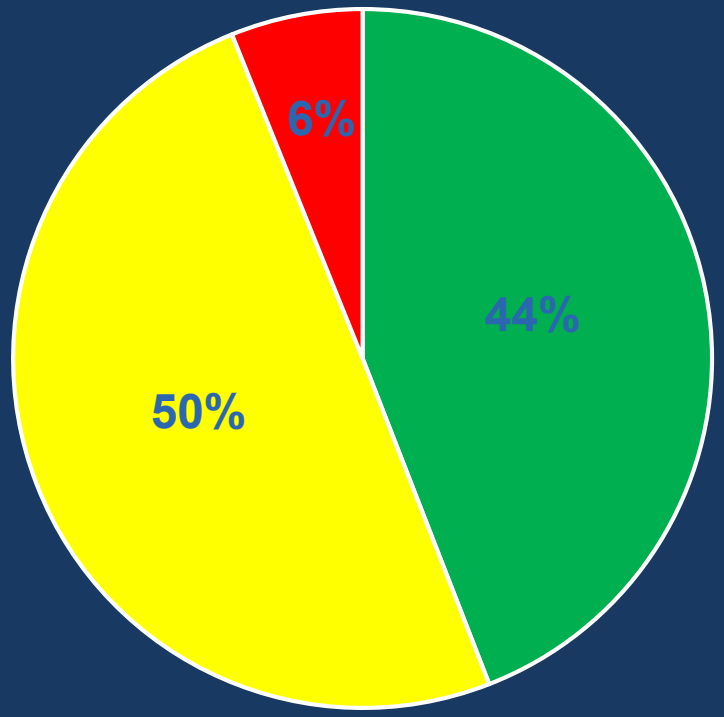
5. Patients with PAH associated with HIV or portal hypertension, stable and with a low-risk profile with monotherapy (no proven efficacy of initial combination)
6. Patients with PAH due to uncorrected CHD and stable on monotherapy (no proven efficacy of initial combination)
7. PAH patients with very mild disease (i.e. WHO FC I, PVR < 4 WU, mPAP < 30 mmHg, near normal RV at echocardiography)
8. Combination therapy unavailable or contraindicated (e.g. severe liver disease)

# Risk stratification at baseline and 1st follow-up (PAH)

## BASELINE EVALUATION




## FIRST FOLLOW-UP (TREATMENT RESPONSE)



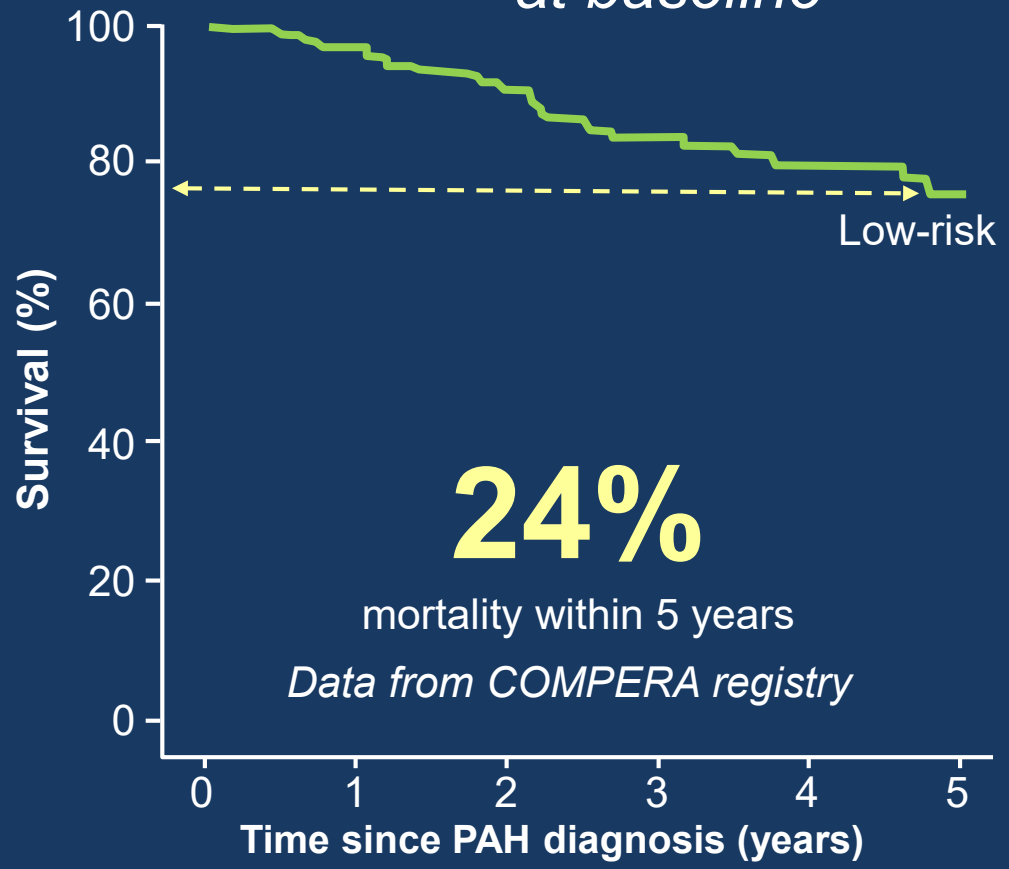

Low Intermediate High

Dardi F, *et al*. European Heart Journal (2018) 39 (Supplement), 924

# Even patients deemed to be low-risk continue to experience disease progression

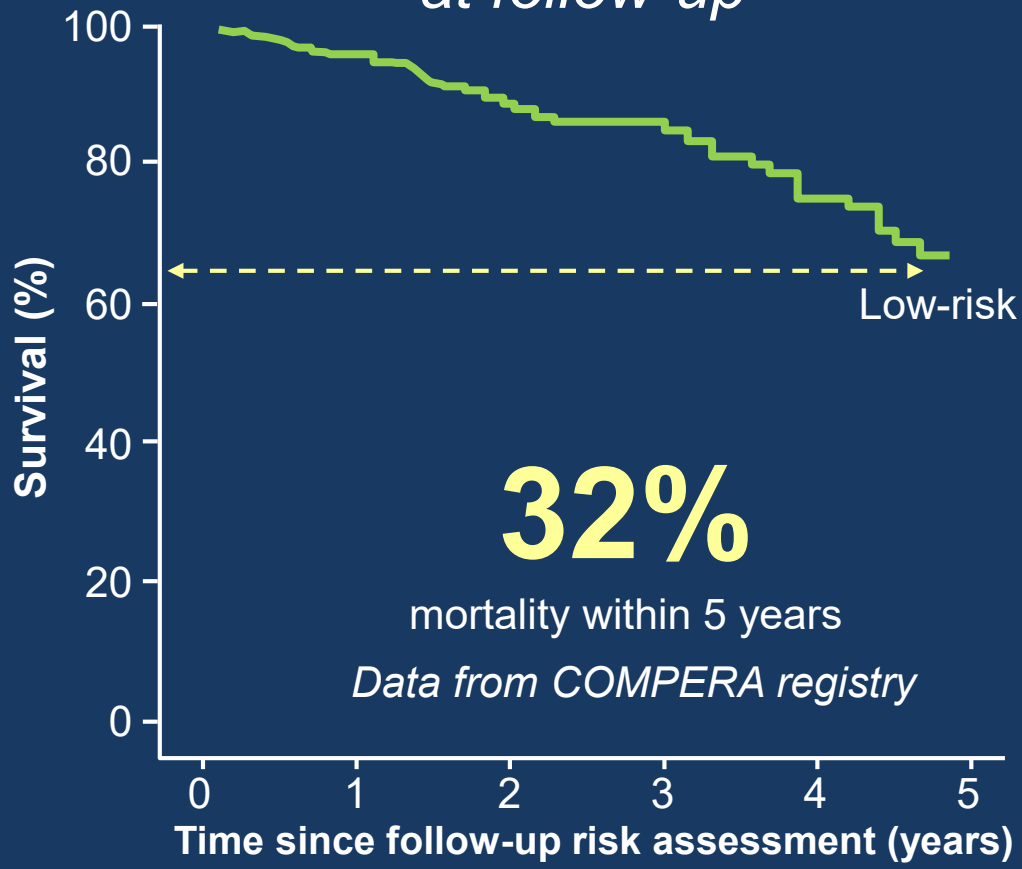
**Mortality** in patients who were categorized as low-risk

*at baseline*




**Patients at risk** 196 156 111 75 47 31

*at follow-up*



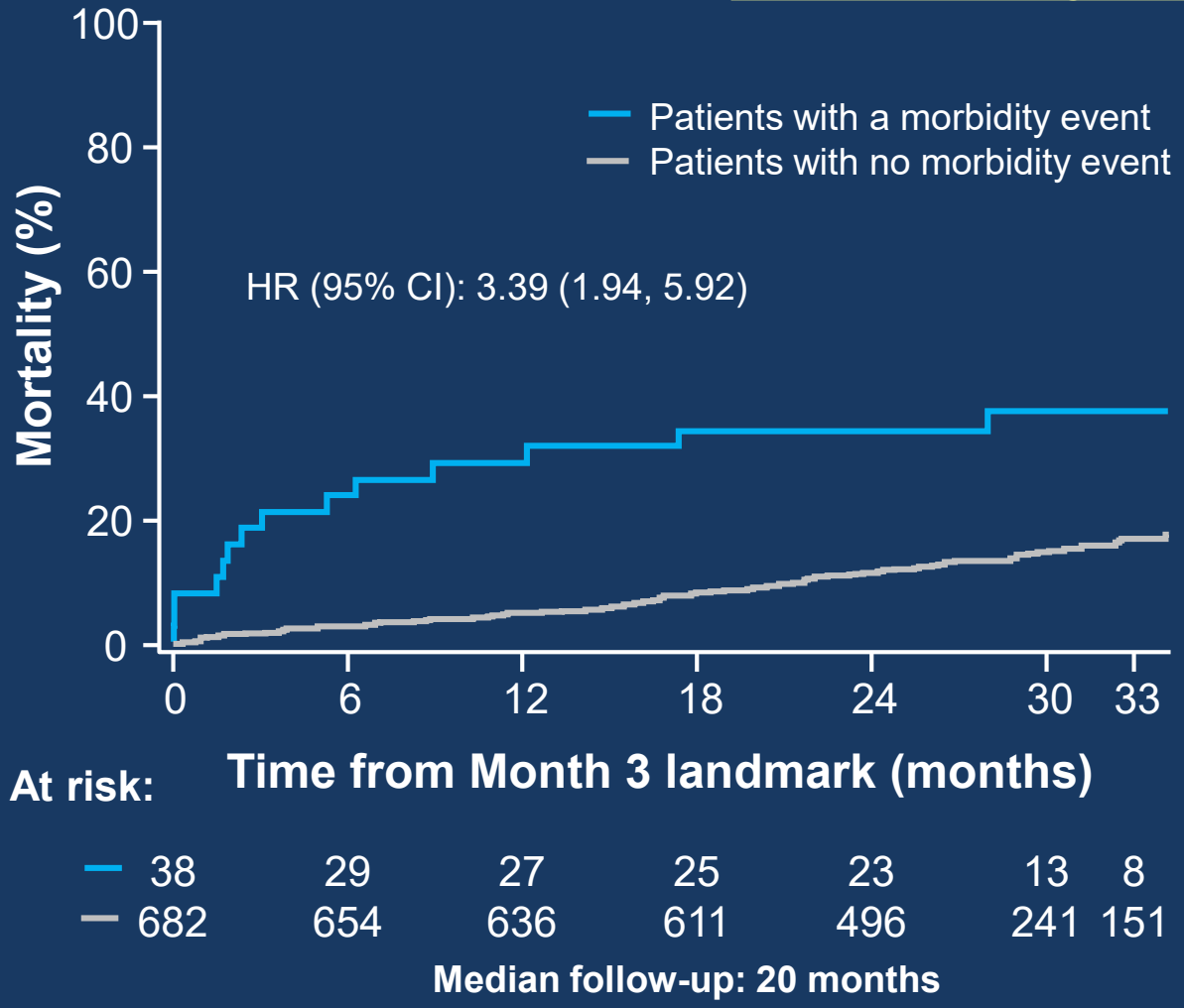

261 203 145 101 67 35

*Follow-up risk assessment between 3 months and 2 years after treatment initiation.

Hoeper MM, *et al. Eur Respir J* 2017; 50:1700740.

# Patients who experience morbidity events have an increased risk of death

## Landmark analyses from SERAPHIN




**Median follow-up: 20 months**

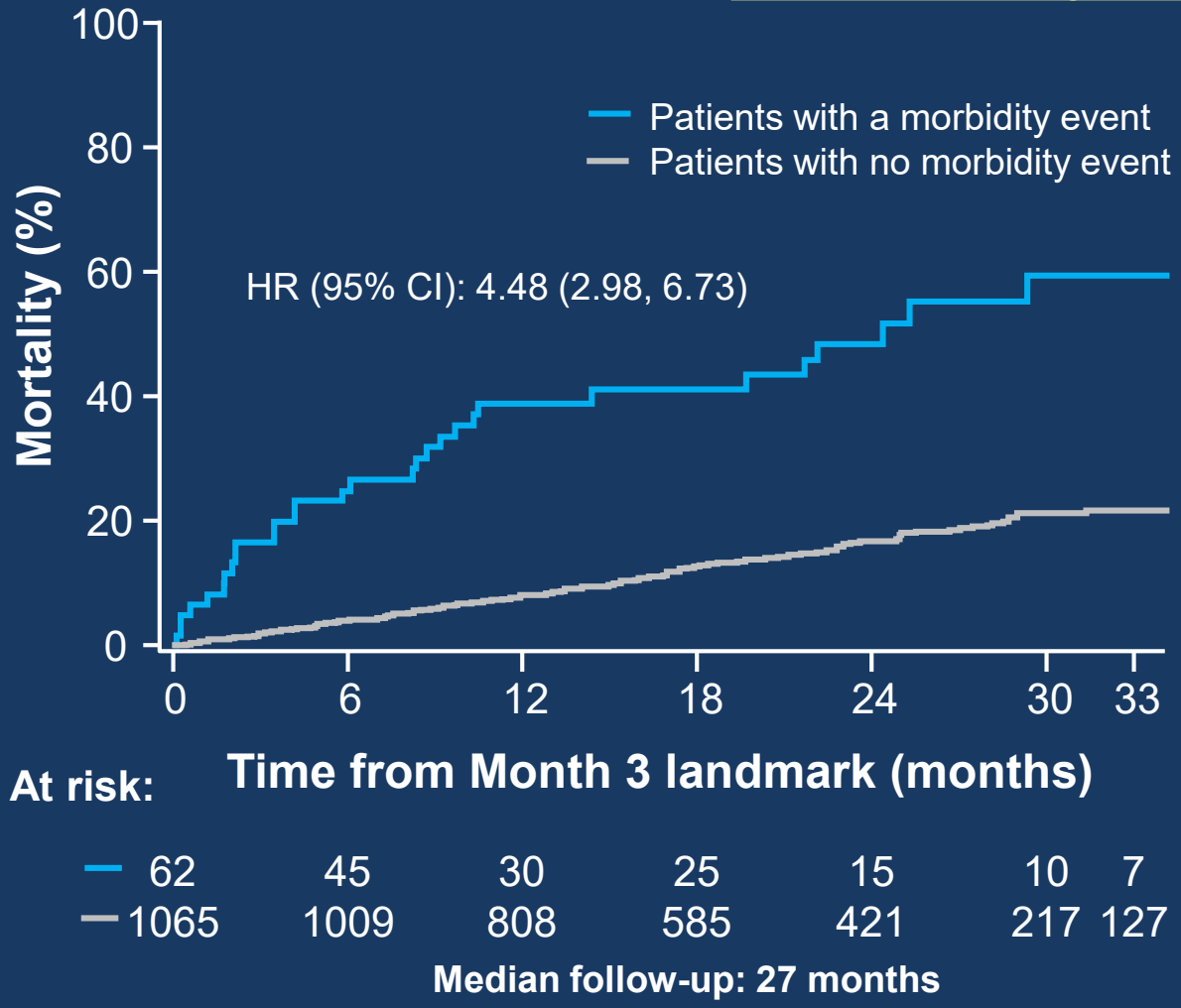
| | Risk of death<br>Morbidity event vs no prior morbidity event<br>HR (95% CI) |
|---|---|
| **Main analysis** | 3.39 (1.94, 5.92) |

Risk of death up to EOS increased ≥ 3 fold for patients who experienced a morbidity event prior to Month 3 landmark, compared with those who did not

McLaughlin V, *et al. J Am Coll Cardiol* 2018; 71:752-63.

# Patients who experience morbidity events have an increased risk of death

## Landmark analyses from GRIPHON




| | Risk of death<br>Morbidity event vs no prior morbidity event<br>HR (95% CI) |
|---|---|
| **Main analysis** | 4.48 (2.98, 6.73) |

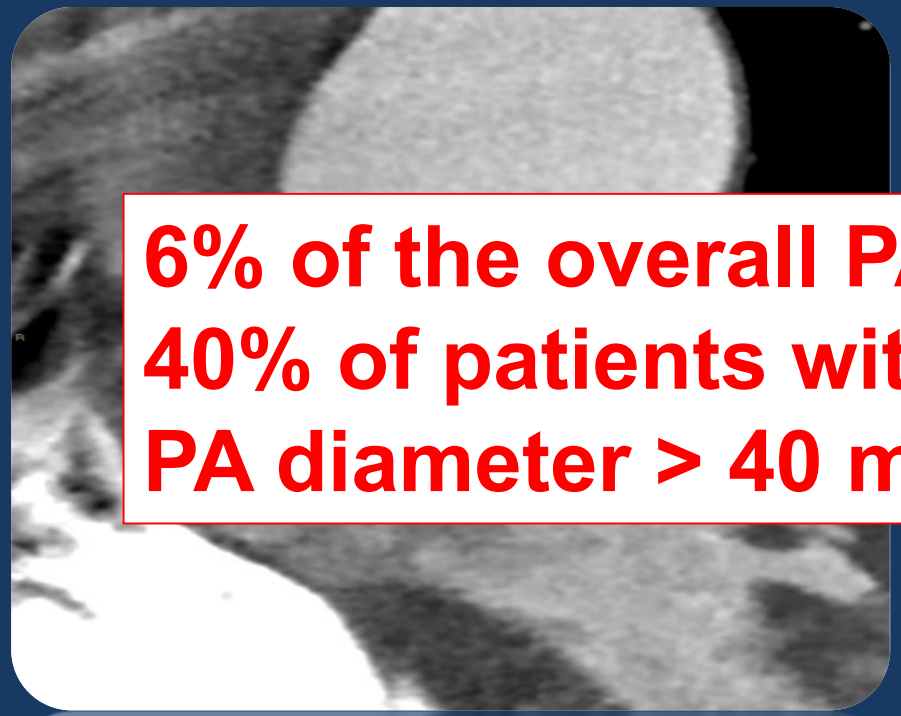
Risk of death up to EOS increased ≥ 4 fold for patients who experienced a morbidity event prior to Month 3 landmark, compared with those who did not

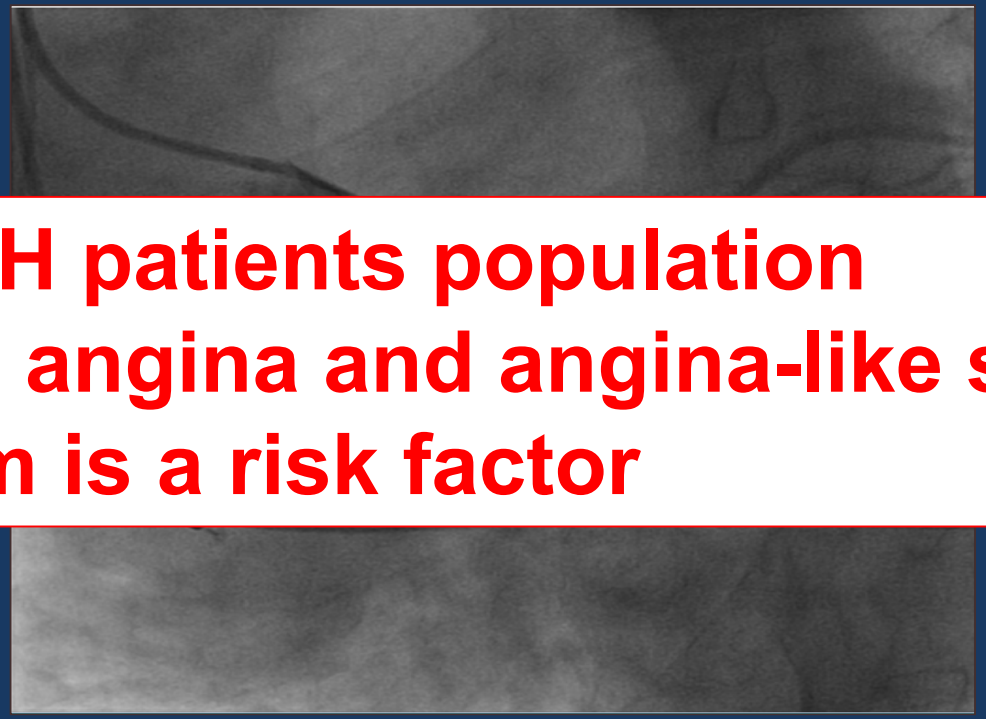
McLaughlin V, *et al. J Am Coll Cardiol* 2018; 71:752-63.

# Complications

# Left Main Coronary Artery Compression in Patients With Pulmonary Arterial Hypertension and Angina

Nazzareno Galiè, MD,[a] Francesco Saia, MD,[b] Massimiliano Palazzini, MD,[a] Alessandra Manes, MD,[b] Vincenzo Russo, MD,[b] Maria Letizia Bacchi Reggiani, PhD,[a] Gianni Dall'Ara, MD,[a] Enrico Monti, MD,[a] Fabio Dardi, MD,[a] Alessandra Albini, MD,[a] Andrea Rinaldi, MD,[a] Enrico Gotti, MD,[a] Nevio Taglieri, MD,[a] Cinzia Marrozzini, MD,[b] Luigi Lovato, MD,[b] Maurizio Zompatori, MD,[a] Antonio Marzocchi, MD[b]

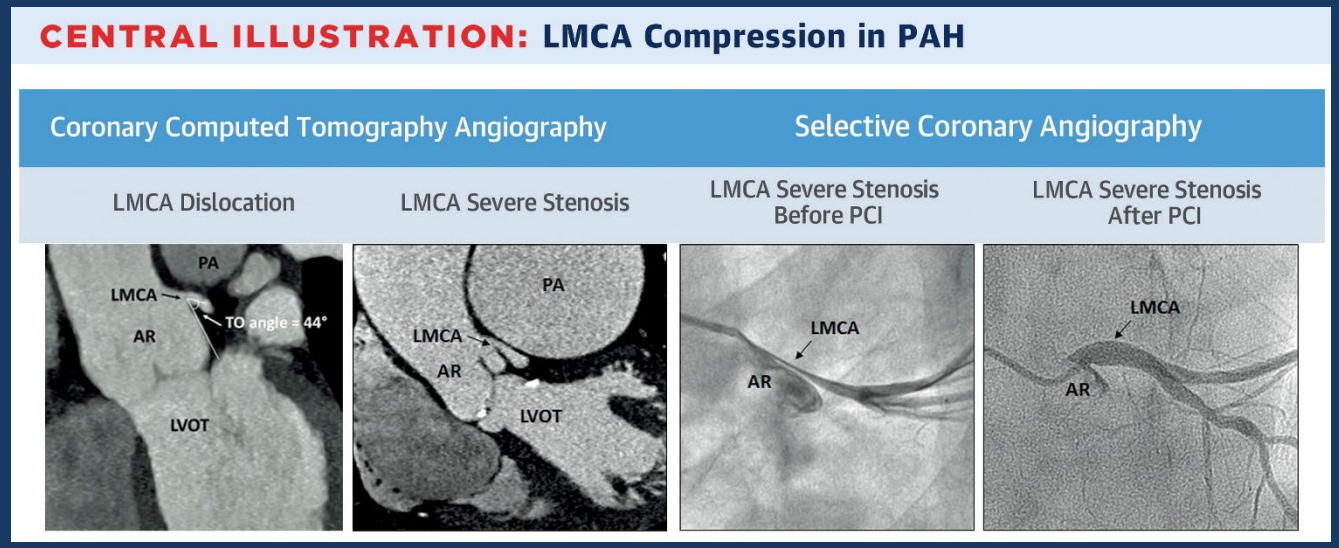


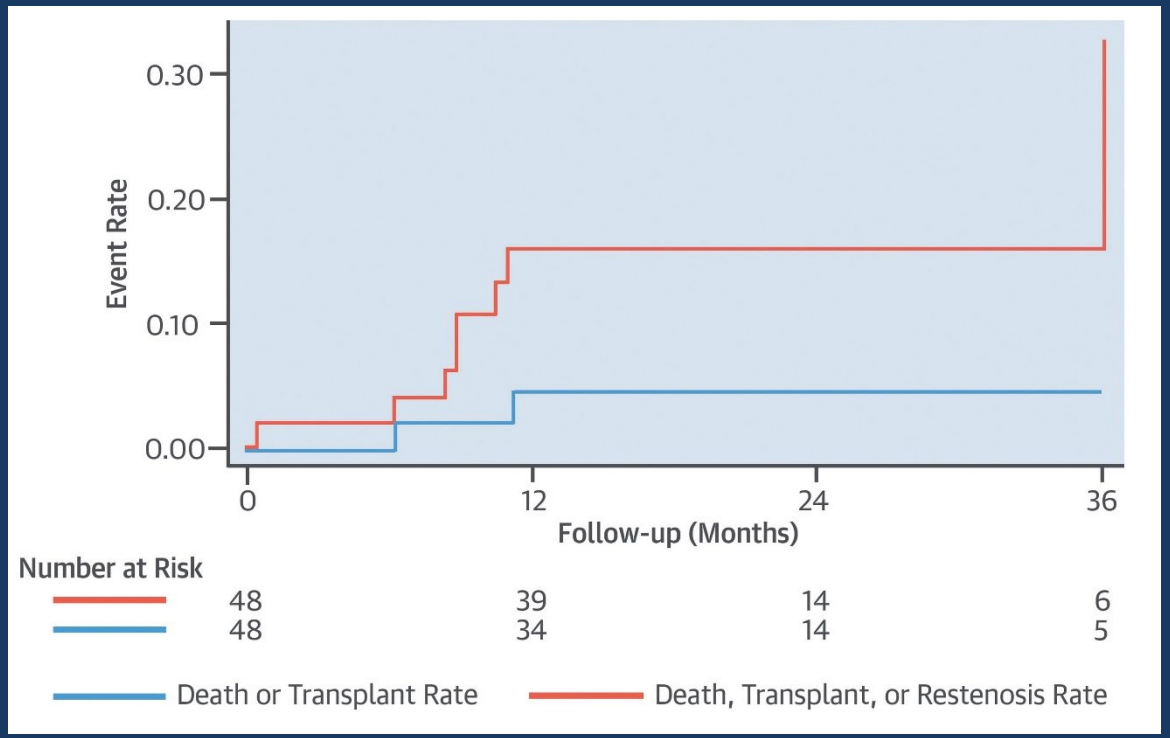


**6% of the overall PAH patients population**
**40% of patients with angina and angina-like symptoms**
**PA diameter > 40 mm is a risk factor**

Galiè N et al. *J Am Coll Cardiol* 2017;69:2808–17.

# PAH and angina or angina-like symptoms

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# Conclusions

- A comprehensive treatment algorithm, including patients phenotyping and risk stratification is required for the appropriate management of patients with PAH
- Risk-oriented initial combination therapy seems to be the better approach in the majority of treatment-naïve patients
- Further treatment escalation is aimed to reach the low-risk status
- Patients in the intermediate or high-risk status despite maximal medical therapy require listing for lung transplantation in absence of contraindications

# Limitations and areas for future developments

- Despite the application of the most evoluted treatment algorithm, the majority of the patients remain in the intermediate-risk status
- Low-risk patients, in particular if treated with maximal medical therapy, may deteriorate over time and require an appropriate follow-up to identify early signs of disease progression
- Mechanical complications may be responsible for sudden deterioration and should be considered in the follow-up


# Thank you!