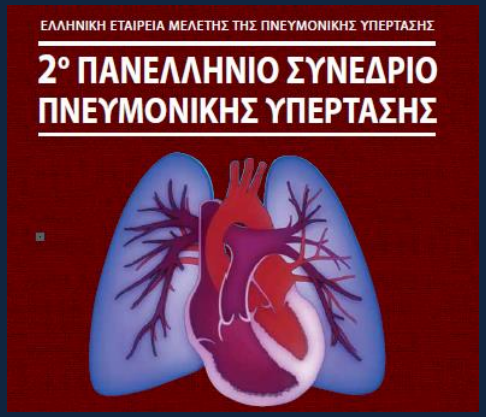
Από το 1ο στο 6ο Παγκόσμιο Συνέδριο Πνευμονικής Υπέρτασης

Αναστασία Ανθη

Β΄ Κλινική Εντατικής Θεραπείας & Διακλινικό Ιατρείο Πνευμονικής Υπέρτασης
Π.Γ.Ν. «ΑΤΤΙΚΟΝ»



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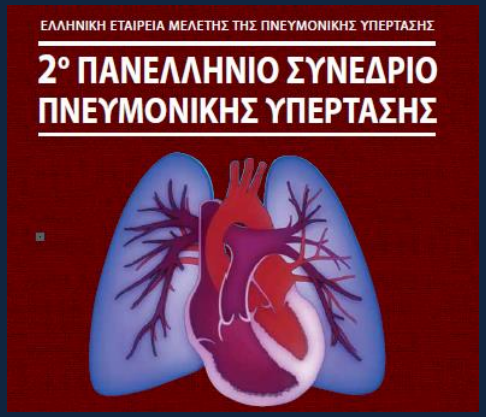


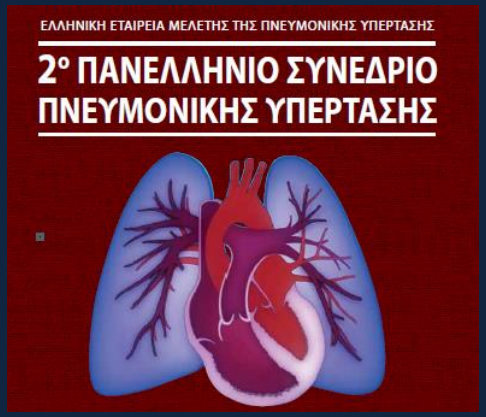
Από το 1ο στο 6ο Παγκόσμιο Συνέδριο Πνευμονικής Υπέρτασης

1865: Julius Klob, a pathologist from Austria, described the "endarteriitis pulmonalis deformans" as

"a disease that is characterized by an increase in mass of the inner vessel skin which grows out to form a pseudomembraneous connective tissue"

&

"this entity was occasionally–but not always–associated with inflammation".

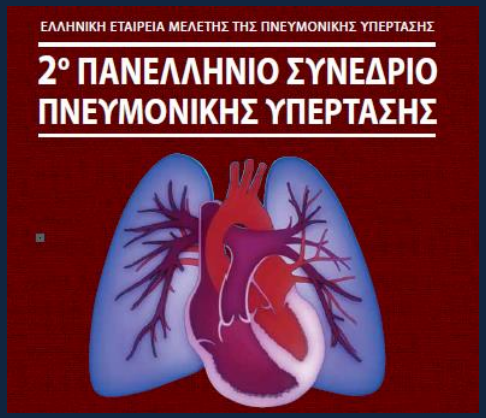


Από το 1ο στο 6ο Παγκόσμιο Συνέδριο Πνευμονικής Υπέρτασης

1891: the first description of pulmonary vascular disorders by Ernst von Romberg

"On sclerosis of pulmonary arteries"

Romberg E. Ueber sklerose der lungen arterie. Dtsch Archiv Klin Med 1891;48:197–206.



Από το 1ο στο 6ο Παγκόσμιο Συνέδριο Πνευμονικής Υπέρτασης

“primary pulmonary vascular sclerosis”

“right ventricular hypertrophy of obscure origin”

“idiopathic pulmonary hypertension”

Primary Pulmonary Hypertension*

I. Clinical and Hemodynamic Study

DAVID T. DRESDALE, M.D., MARTIN SCHULTZ, M.D. *and* ROBERT J. MICHTOM, M.D.

Brooklyn, New York

PULMONARY hypertension is known to occur in association with left heart failure, chronic pulmonary disease, certain types of congenital heart disease (especially those with increased pulmonary blood flow), diffuse pulmonary embolism, kyphoscoliotic heart disease and specific affections of the pulmonary vascular bed. There is also a primary form of pulmonary hypertension, which is defined as that condition in which an elevated pulmonary artery pressure exists without demonstrable cause. We believe that primary pulmonary hypertension, which has emerged as a distinct entity since the advent of right heart catheterization,[1] is the cause of isolated right ventricular hypertrophy[2–10] whether or not associated with pulmonary vascular sclerosis.

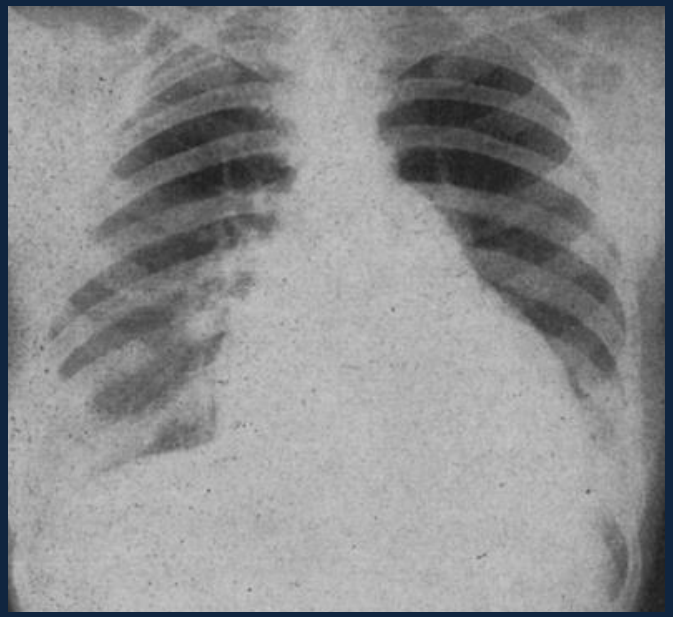
Hypertrophy of the right ventricle in the absence of the previously mentioned disorders was reported by Romberg[24] in 1891. There has been considerable speculation concerning the primary role of pulmonary hypertension[12,16–19] in this condition. Since pulmonary vascular sclerosis was not constantly found, doubt was cast on hypertension in the lesser circulation as the cause of the right ventricular hypertrophy. De Navasquez et al.,[17] for example, preferred to designate their cases as "idiopathic right ventricular hypertrophy" rather than introduce the concept of pulmonary hypertension since no significant changes were found in the pulmonary blood vessels in their cases at necropsy.

Autopsied cases which we consider to fall into the category of primary pulmonary hypertension have been reported under various titles, such as "primary pulmonary vascular sclerosis,"[12,18,21] "right ventricular hypertrophy of unknown origin: so-called pulmonary hypertension,"[17] "isolated hypertrophy of the right ventricle of the heart of unknown cause."[20] These titles stressed different facets of the pathophysiologic features of this disease. All cases showed marked right ventricular hypertrophy, but the nature, distribution and severity of the pulmonary vascular changes proximal to the capillaries showed considerable variation. The predominant changes were atheromatous lesions of the stem and large elastic arteries, alone or in conjunction with fibrous intimal thickening and narrowing of the smaller arteries and arterioles. Medial hypertrophy was occasionally noted. In about half of the reported cases occlusive lesions of the smaller arteries and arterioles were described. Most of these changes have been ascribed to intimal sclerosis and some to thrombi in various stages of organization. A small group remains in which the pathogenesis of the occlusive lesions cannot be definitely established and may conceivably represent organized pulmonary emboli or healed inflammatory lesions. The last group, of course, would not fit into the category of primary pulmonary hypertension. Whether the obliterative sclerosis or thrombosis, when seen, is the cause or the effect of the hypertension has evoked considerable difference of opinion. Arguments against the primary role of the vascular changes are (1) the absence of these findings in some cases of isolated right ventricular hypertrophy,[8,13,14,16,17,20,22] one of which was proven to have pulmonary hypertension by heart catheterization,[22] and (2) the finding of pulmonary arteriosclerosis unassociated with right ventricular hypertrophy.[13]

Ten[21,25–27] catheterized cases of pulmonary hypertension without demonstrable cause have been mentioned in the literature. Although Nellen[28] reported two cases with hemodynamic studies as "idiopathic pulmonary hypertension," they are not included because of extensive thromboses involving the major pulmonary

* From the Medical Service, Maimonides Hospital of Brooklyn and the Department of Medicine, State University of New York at New York City, College of Medicine. This investigation was supported in part by a research grant from the National Heart Institute of the National Institutes of Health, Public Health Service.

Am J Med 1951;11:686–705



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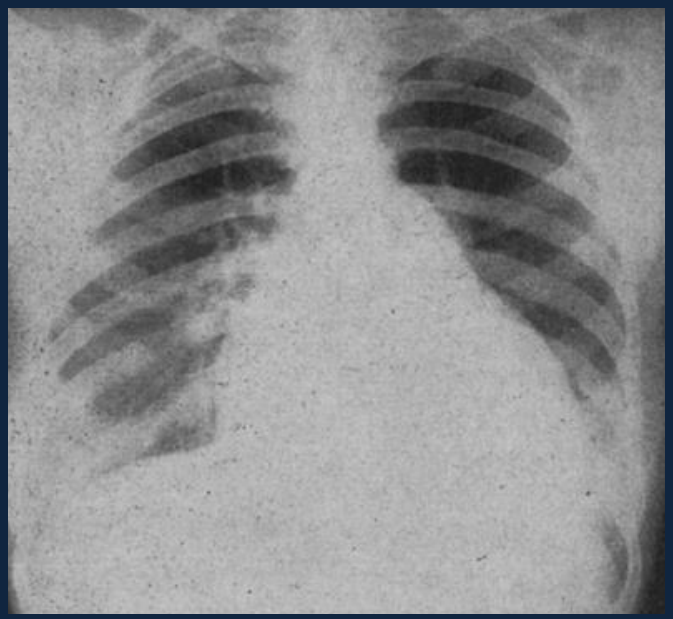

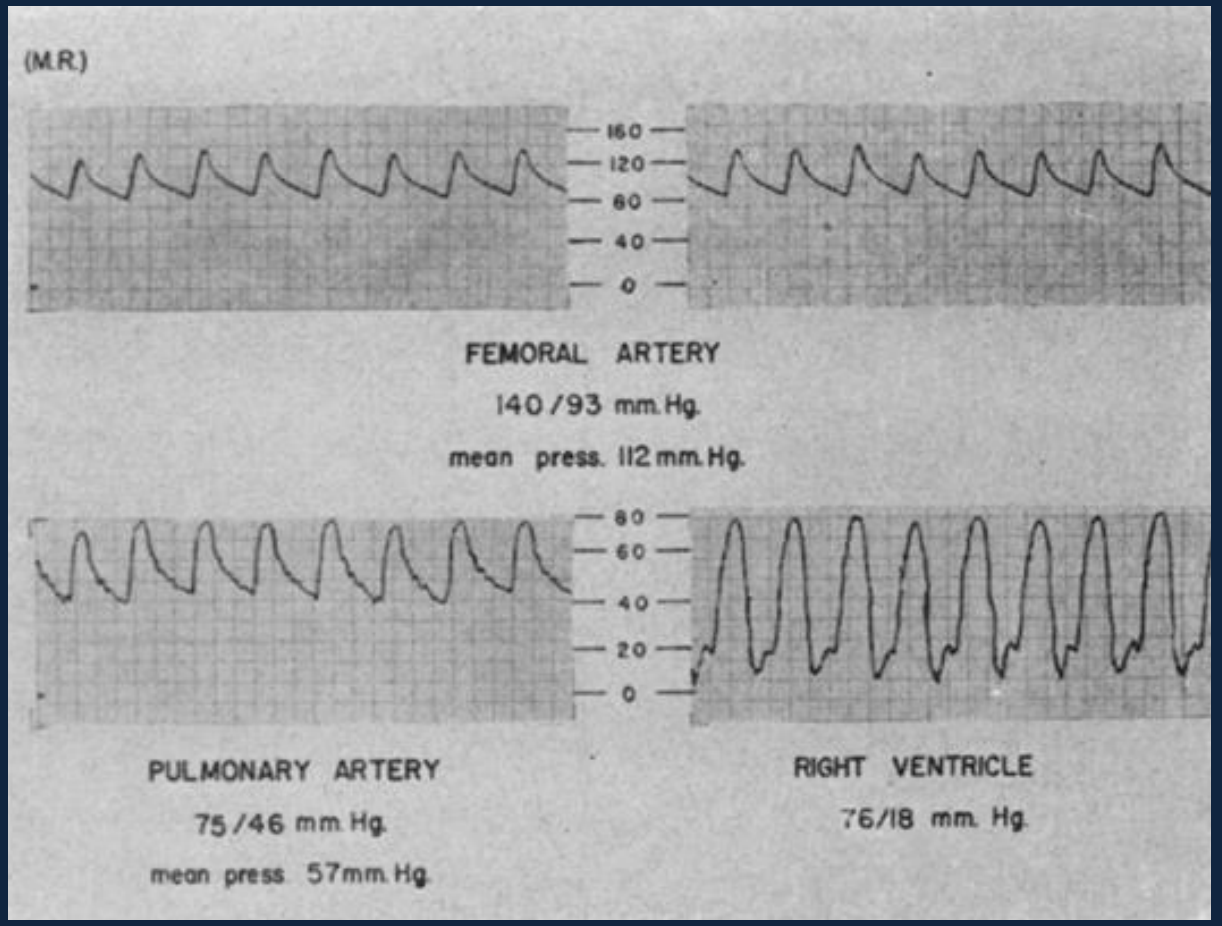

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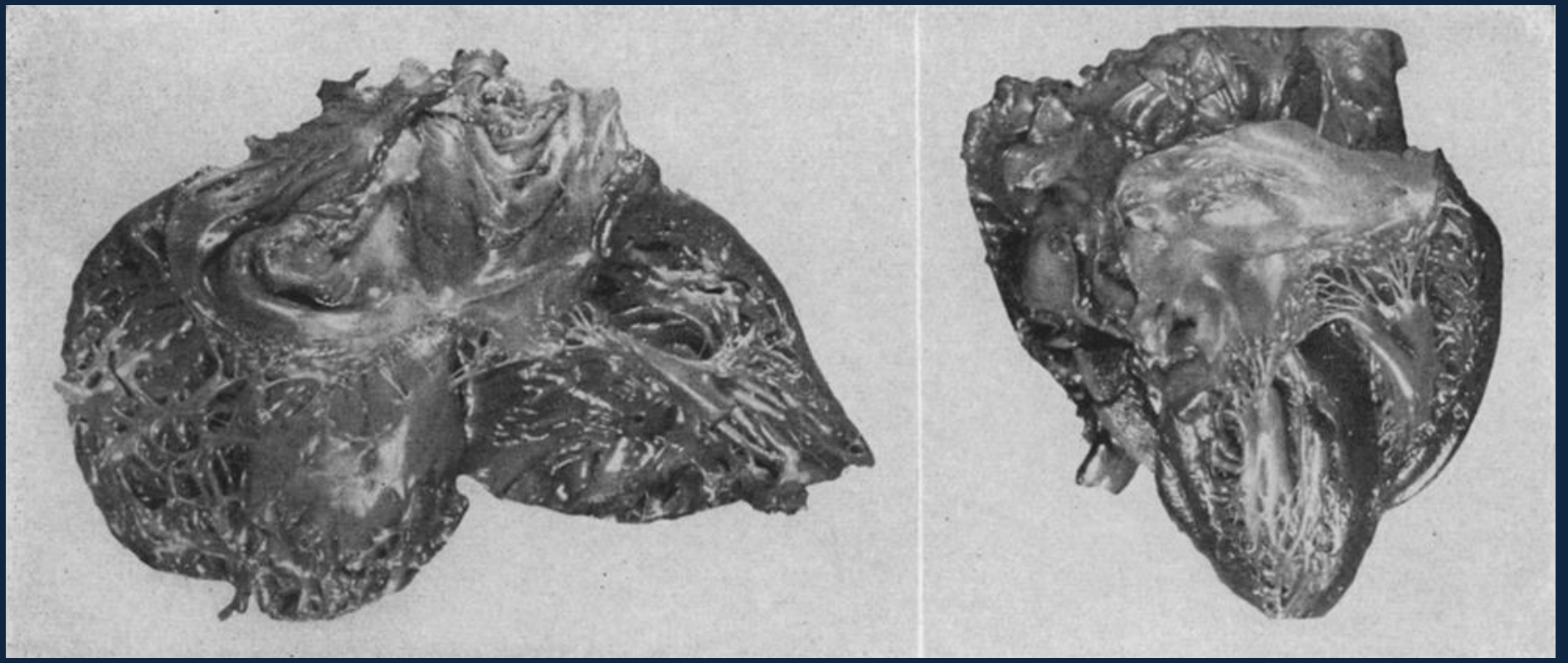

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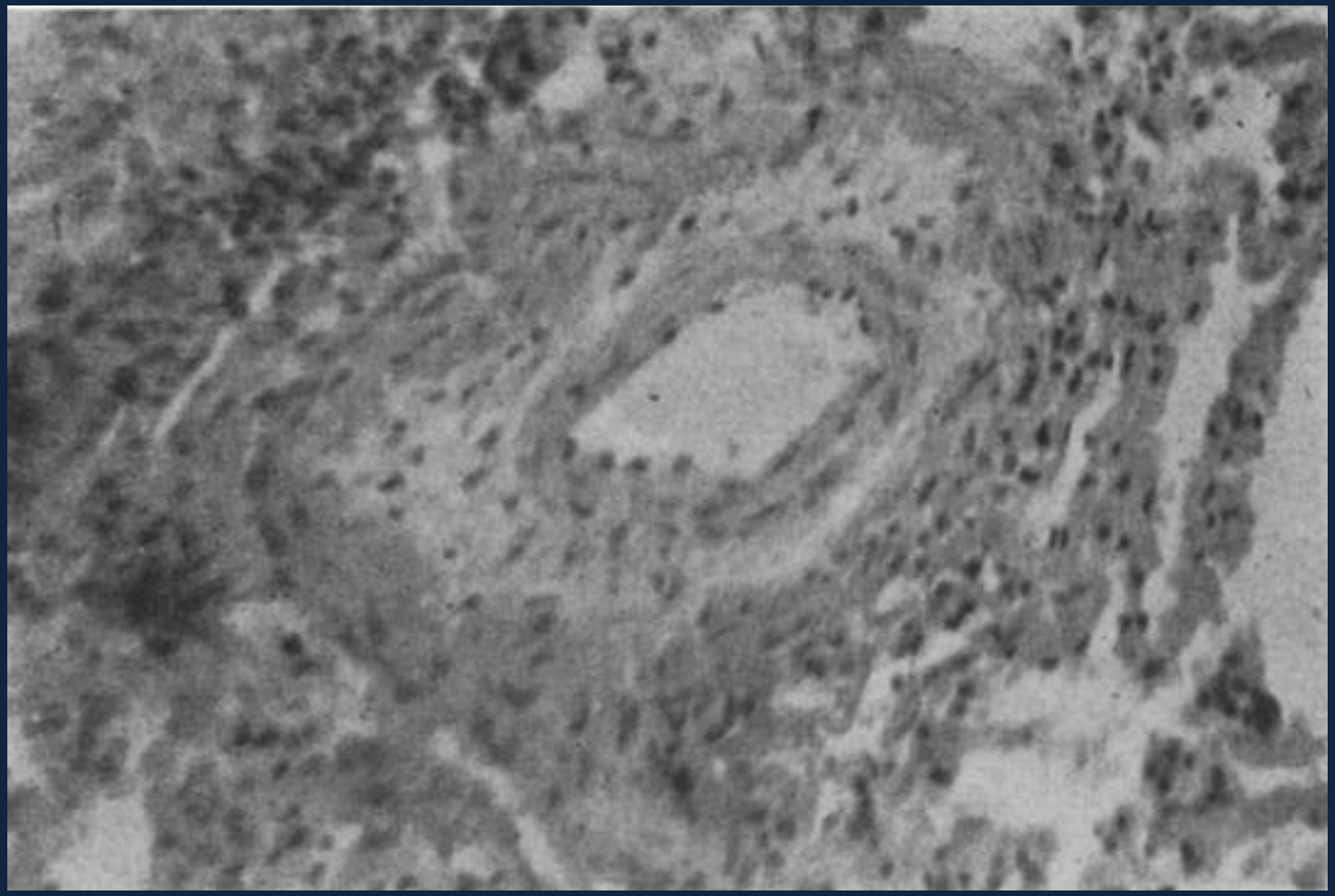

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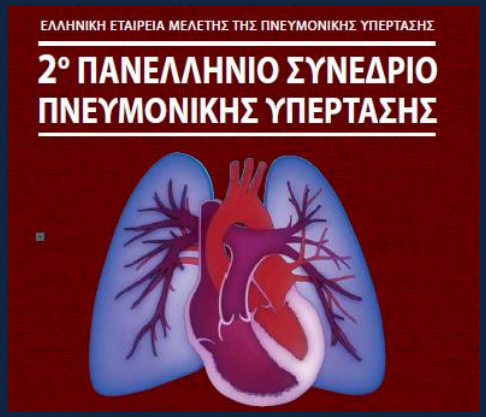
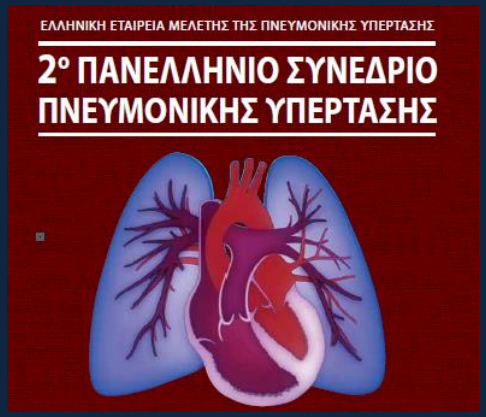


Από το 1ο στο 6ο Παγκόσμιο Συνέδριο Πνευμονικής Υπέρτασης

1960: the first WHO meeting on pulmonary circulation
an expert committee on chronic cor pulmonale

chronic cor pulmonale classification:
diseases primary affecting

- **air passages of the lung and the alveoli**
- **the pulmonary vasculature**



Από το 1ο στο 6ο Παγκόσμιο Συνέδριο Πνευμονικής Υπέρτασης

- **Geneva, 1973:** ***1st world symposium on PH***
  primary/ secondary pulmonary hypertension

PRIMARY PULMONARY HYPERTENSION

Report on a WHO meeting
Geneva, 15–17 October 1973

Edited by

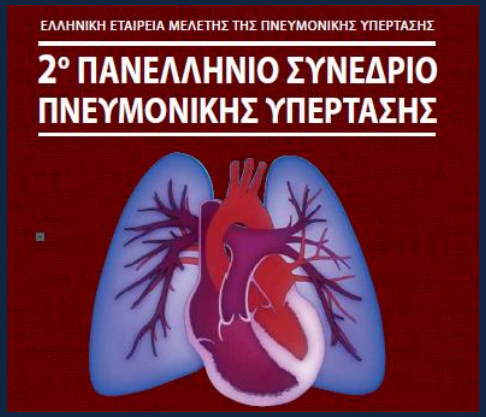
SHUICHI HATANO

and

TOMA STRASSER

Cardiovascular Diseases,
World Health Organization,
Geneva, Switzerland

WORLD HEALTH ORGANIZATION
GENEVA
1975



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- **Geneva**, 1973: *1st world symposium on PH*
  primary/ secondary pulmonary hypertension
- **Evian**, 1998: *2nd world symposium on PH*
  5 groups

Evian, 1998
2nd WSPH

Table 1. The Evian Clinical Classification

1. Pulmonary arterial hypertension
   - 1.1 Primary pulmonary hypertension
     - (a) Sporadic
     - (b) Familial
   - 1.2 Related to
     - (a) Collagen vascular disease
     - (b) Congenital systemic-to-pulmonary shunts
     - (c) Portal hypertension
     - (d) Human immunodeficiency virus infection
     - (e) Drugs/toxins
       - (1) Anorexigens
       - (2) Other
     - (f) Persistent pulmonary hypertension of the newborn
     - (g) Other
2. Pulmonary venous hypertension
   - 2.1 Left-sided atrial or ventricular heart disease
   - 2.2 Left-sided valvular heart disease
   - 2.3 Extrinsic compression of central pulmonary veins
     - (a) Fibrosing mediastinitis
     - (b) Adenopathy/tumors
   - 2.4 Pulmonary veno-occlusive disease
   - 2.5 Other
3. Pulmonary hypertension associated with disorders of the respiratory system or hypoxemia
   - 3.1 Chronic obstructive pulmonary disease
   - 3.2 Interstitial lung disease
   - 3.3 Sleep-disordered breathing
   - 3.4 Alveolar hypoventilation disorders
   - 3.5 Chronic exposure to high altitude
   - 3.6 Neonatal lung disease
   - 3.7 Alveolar-capillary dysplasia
   - 3.8 Other
4. Pulmonary hypertension caused by chronic thrombotic or embolic disease
   - 4.1 Thromboembolic obstruction of proximal pulmonary arteries
   - 4.2 Obstruction of distal pulmonary arteries
     - (a) Pulmonary embolism (thrombus, tumor, ova, or parasites, foreign material)
     - (b) In situ thrombosis
     - (c) Sickle-cell disease
5. Pulmonary hypertension caused by disorders directly affecting the pulmonary vasculature
   - 5.1 Inflammatory
     - (a) Schistosomiasis
     - (b) Sarcoidosis
     - (c) Other
   - 5.2 Pulmonary capillary hemangiomatosis

Evian, 1998
2nd WSPH

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~~secondary pulmonary hypertension~~

Evian, 1998
2nd WSPH

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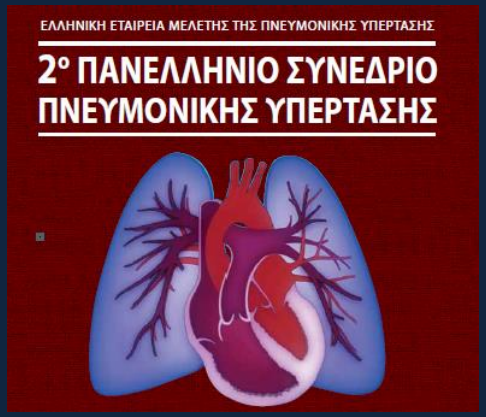

Από το 1ο στο 6ο Παγκόσμιο Συνέδριο Πνευμονικής Υπέρτασης

- **Geneva**, 1973: *1st world symposium on PH*
  primary/ secondary pulmonary hypertension
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  5 groups
- **Venice**, 2003: *3rd world symposium on PH* »

Venice, 2003
3rd WSPH

Table 3. Revised Clinical Classification of Pulmonary Hypertension (Venice 2003)

1. Pulmonary arterial hypertension (PAH)
   - 1.1. **Idiopathic** (IPAH)
   - 1.2. Familial (FPAH)
   - 1.3. Associated with (APAH):
     - 1.3.1. Collagen vascular disease
     - 1.3.2. Congenital systemic-to-pulmonary shunts**
     - 1.3.3. Portal hypertension
     - 1.3.4. HIV infection
     - 1.3.5. Drugs and toxins
     - 1.3.6. **Other** (thyroid disorders, glycogen storage disease, Gaucher disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders, splenectomy)
   - 1.4. **Associated with significant venous or capillary involvement**
     - 1.4.1. Pulmonary veno-occlusive disease (PVOD)
     - 1.4.2. Pulmonary capillary hemangiomatosis (PCH)
   - 1.5. Persistent pulmonary hypertension of the newborn
2. Pulmonary hypertension with left heart disease
   - 2.1. Left-sided atrial or ventricular heart disease
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3. Pulmonary hypertension associated with lung diseases and/or hypoxemia
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   - 3.3. Sleep-disordered breathing
   - 3.4. Alveolar hypoventilation disorders
   - 3.5. Chronic exposure to high altitude
   - 3.6. Developmental abnormalities
4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease
   - 4.1. Thromboembolic obstruction of proximal pulmonary arteries
   - 4.2. Thromboembolic obstruction of distal pulmonary arteries
   - 4.3. Non-thrombotic pulmonary embolism (tumor, parasites, foreign material)
5. **Miscellaneous**

   Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

Venice, 2003
3rd WSPH

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~~primary pulmonary hypertension~~

Venice, 2003
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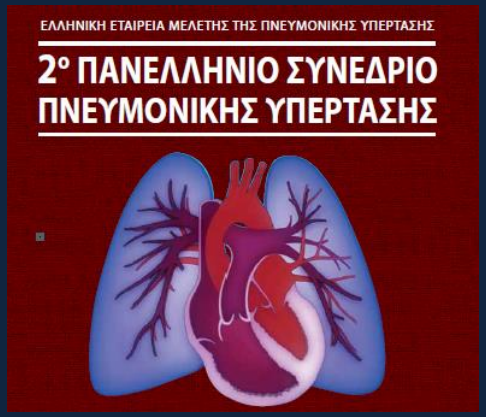

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  5 groups
- **Venice**, 2003: *3rd world symposium on PH* *»*
- **Dana Point**, 2008: *4th world symposium on PH* *»*

Dana Point, 2008
4rd WSPH

Table 2 Updated Clinical Classification of Pulmonary Hypertension (Dana Point, 2008)

1. Pulmonary arterial hypertension (PAH)
1.1. Idiopathic PAH
1.2. **Heritable**
1.2.1. **BMPR2**
1.2.2. **ALK1, endoglin (with or without hereditary hemorrhagic telangiectasia)**
1.2.3. **Unknown**
1.3. Drug- and toxin-induced
1.4. Associated with
1.4.1. Connective tissue diseases
1.4.2. HIV infection
1.4.3. Portal hypertension
1.4.4. Congenital heart diseases
1.4.5. **Schistosomiasis**
1.4.6. **Chronic hemolytic anemia**
1.5 Persistent pulmonary hypertension of the newborn

1'. **Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)**

2. Pulmonary hypertension owing to left heart disease
2.1. **Systolic dysfunction**
2.2. **Diastolic dysfunction**
2.3. Valvular disease

3. Pulmonary hypertension owing to lung diseases and/or hypoxia
3.1. Chronic obstructive pulmonary disease
3.2. Interstitial lung disease
3.3. **Other pulmonary diseases with mixed restrictive and obstructive pattern**
3.4. Sleep-disordered breathing
3.5. Alveolar hypoventilation disorders
3.6. Chronic exposure to high altitude
3.7. Developmental abnormalities

4. **Chronic thromboembolic pulmonary hypertension (CTEPH)**

5. **Pulmonary hypertension with unclear multifactorial mechanisms**
5.1. **Hematologic disorders: myeloproliferative disorders, splenectomy**
5.2. **Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis:** lymphangioleiomyomatosis, neurofibromatosis, vasculitis
5.3. **Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders**
5.4. **Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis**

Main modifications to the previous Venice classification are in **bold**.

ALK1 = activin receptor-like kinase type 1; BMPR2 = bone morphogenetic protein receptor type 2; HIV = human immunodeficiency virus.

Dana Point, 2008
4rd WSPH

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   - 5.2. **Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis:** lymphangioleiomyomatosis, neurofibromatosis, vasculitis
   - 5.3. **Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders**
   - 5.4. **Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis**

Main modifications to the previous Venice classification are in **bold**.

ALK1 = activin receptor-like kinase type 1; BMPR2 = bone morphogenetic protein receptor type 2; HIV = human immunodeficiency virus.

Classification of Pulmonary Hypertension

- **Geneva, 1973:** primary/ secondary pulmonary hypertension
  1st world symposium on PH

- **Evian, 1998:**
  2nd world symposium on PH *5 groups*

- **Venice, 2003:**
  3rd world symposium on PH »

- **Dana Point, 2008:**
  4th world symposium on PH »

- **Nice, 2013:**
  5th world symposium on PH »

Clinical classification of Pulmonary Hypertension (ESC/ERS guidelines 2015)

1. Pulmonary arterial hypertension

- 1.1 Idiopathic
- 1.2 Heritable
  - 1.2.1 BMPR2 mutation
  - 1.2.2 Other mutations
- 1.3 Drugs and toxins induced
- 1.4 Associated with:
  - 1.4.1 Connective tissue disease
  - 1.4.2 Human immunodeficiency virus (HIV) infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease (Table 6)
  - 1.4.5 Schistosomiasis

1'. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis

- 1'.1 Idiopathic
- 1'.2 Heritable
  - 1'.2.1 EIF2AK4 mutation
  - 1'.2.2 Other mutations
- 1'.3 Drugs, toxins and radiation induced
- 1'.4 Associated with:
  - 1'.4.1 Connective tissue disease
  - 1'.4.2 HIV infection

1''. Persistent pulmonary hypertension of the newborn

2. Pulmonary hypertension due to left heart disease

- 2.1 Left ventricular systolic dysfunction
- 2.2 Left ventricular diastolic dysfunction
- 2.3 Valvular disease
- 2.4 Congenital / acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
- 2.5 Congenital /acquired pulmonary veins stenosis

3. Pulmonary hypertension due to lung diseases and/or hypoxia

- 3.1 Chronic obstructive pulmonary disease
- 3.2 Interstitial lung disease
- 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
- 3.4 Sleep-disordered breathing
- 3.5 Alveolar hypoventilation disorders
- 3.6 Chronic exposure to high altitude
- 3.7 Developmental lung diseases (Web Table III)

4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions

- 4.1 Chronic thromboembolic pulmonary hypertension
- 4.2 Other pulmonary artery obstructions
  - 4.2.1 Angiosarcoma
  - 4.2.2 Other intravascular tumors
  - 4.2.3 Arteritis
  - 4.2.4 Congenital pulmonary arteries stenoses
  - 4.2.5 Parasites (hydatidosis)

5. Pulmonary hypertension with unclear and/or multifactorial mechanisms

- 5.1 Haematological disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy
- 5.2 Systemic disorders, sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
- 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
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Nice
February 27-28 / March 1, 2018

6TH WORLD SYMPOSIUM ON PULMONARY HYPERTENSION

A global view of pulmonary hypertension

Pulmonary hypertension
is becoming an increasing common
global health issue

Pulmonary arterial hypertension,
especially the idiopathic form
- is a rare disease - incidence of 2–5 per million adults
- is increasingly being diagnosed in elderly people

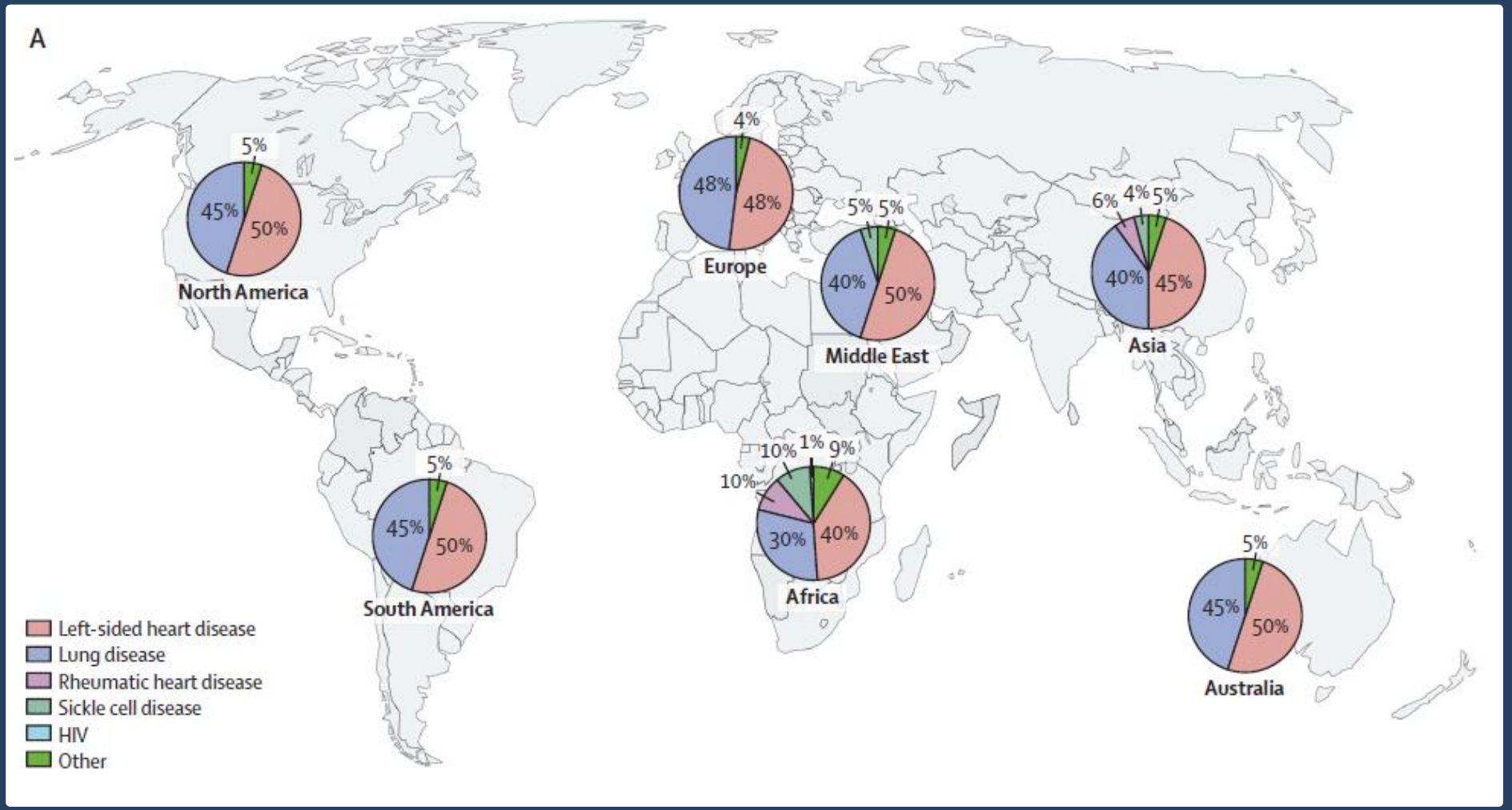
A global view of pulmonary hypertension

- **Left-sided heart failure**, particularly HFpEF,
  is becoming a **leading cause** of PH,
  affecting 5–10% of individuals aged 65 years or older

- **Lung disease**, especially COPD,
  is another **leading cause** of PH

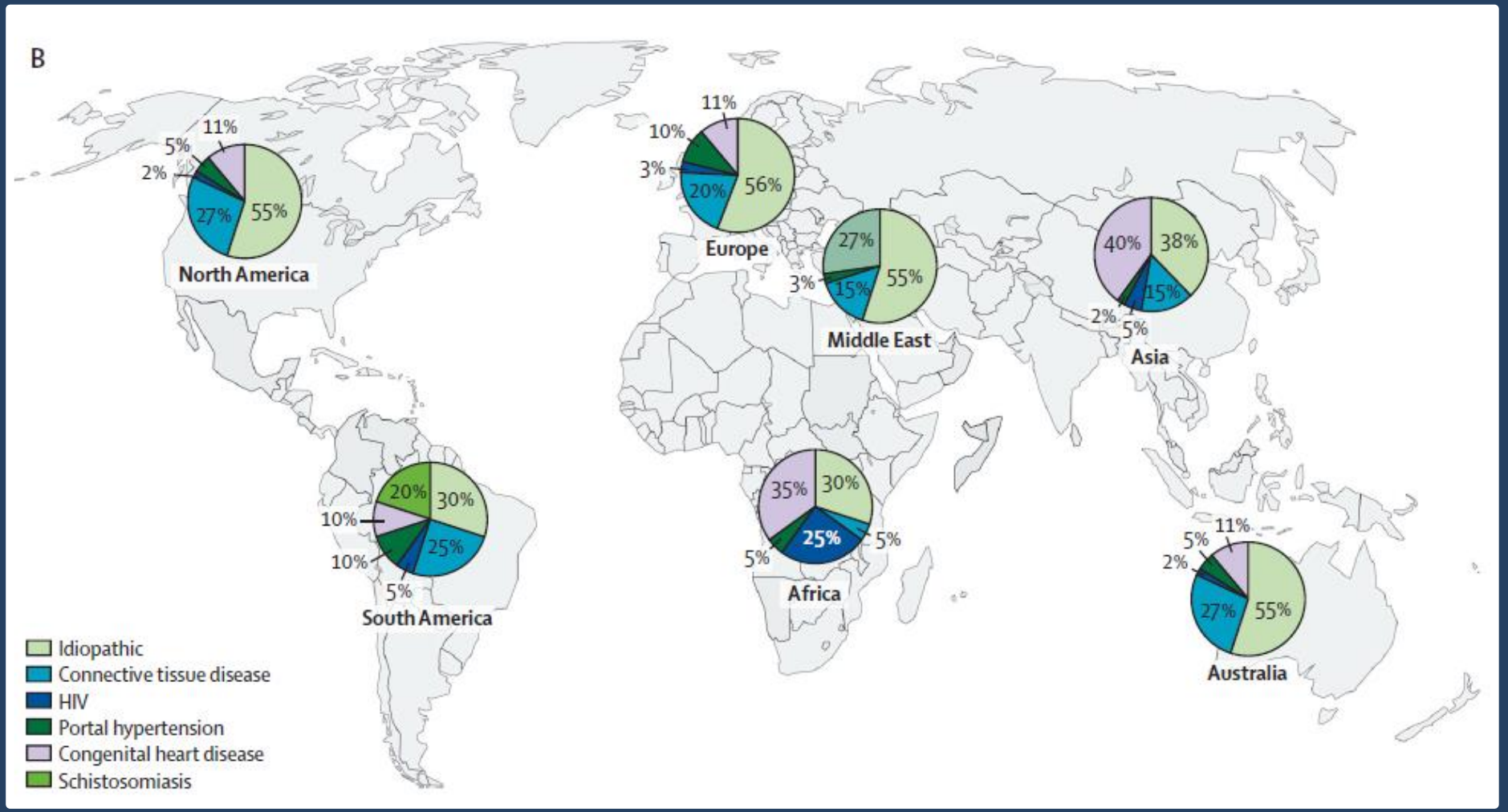
- **Schistosomiasis**,
  HIV infection,
  post-streptococcal rheumatic heart disease,
  & **sickle cell disease**
  are **frequent causes** of pulmonary hypertension in countries where *these diseases are still en*demic

Estimated global distribution of the most prevalent forms of pulmonary hypertension



Lancet Respir Med 2016; 4: 306–322

Estimated global distribution of the most prevalent forms of pulmonary arterial hypertension



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Haemodynamic definition of Pulmonary Hypertension

Definition	Characteristics[a]	Clinical group(s)[b]
PH	PAPm ≥25 mmHg	All
Pre-capillary PH	PAPm ≥25 mmHg PAWP ≤15 mmHg	1. Pulmonary arterial hypertension 3. PH due to lung diseases 4. Chronic thromboembolic PH 5. PH with unclear and/or multifactorial mechanisms
Post-capillary PH	PAPm ≥25 mmHg PAWP >15 mmHg	2. PH due to left heart disease 5. PH with unclear and/or multifactorial mechanisms
Isolated post-capillary PH (Ipc-PH)	DPG <7 mmHg and/or PVR ≤3 WU[c]	
Combined post-capillary and pre-capillary PH (Cpc-PH)	DPG ≥7 mmHg and/or PVR >3 WU[c]	

PH guidelines 2015

Haemodynamic definition of Pulmonary Hypertension

Definition	Characteristics[a]	Clinical group(s)[b]
PH	PAPm ≥25 mmHg	All
Pre-capillary PH	PAPm ≥ 25 mm Hg PAWP ≤ 15 mm Hg **PVR > 3 Wood Units**	**Pulmonary Arterial Hypertension**
Post-capillary PH	PAPm ≥25 mmHg PAWP >15 mmHg	2. PH due to left heart disease 5. PH with unclear and/or multifactorial mechanisms
Isolated post-capillary PH (Ipc-PH)	DPG <7 mmHg and/or PVR ≤3 WU[c]	
Combined post-capillary and pre-capillary PH (Cpc-PH)	DPG ≥7 mmHg and/or PVR >3 WU[c]	

PH guidelines 2015

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PH guidelines 2015

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Combined post-capillary and pre-capillary PH (Cpc-PH)	DPG ≥7 mmHg and/or PVR >3 WU[c]	

DPG

PH guidelines 2015

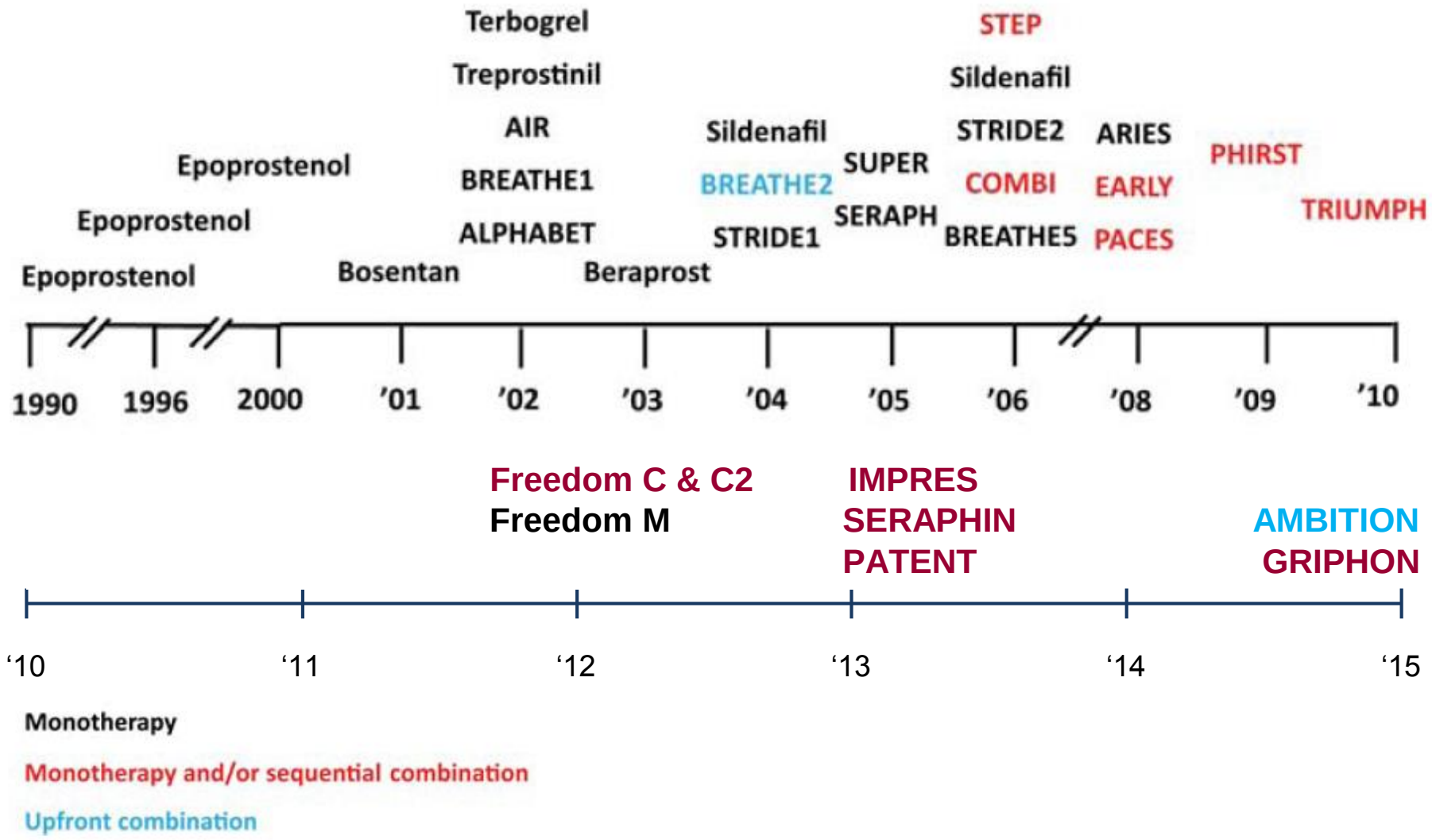
Table 3 Haemodynamic definitions of pulmonary hypertension[a]

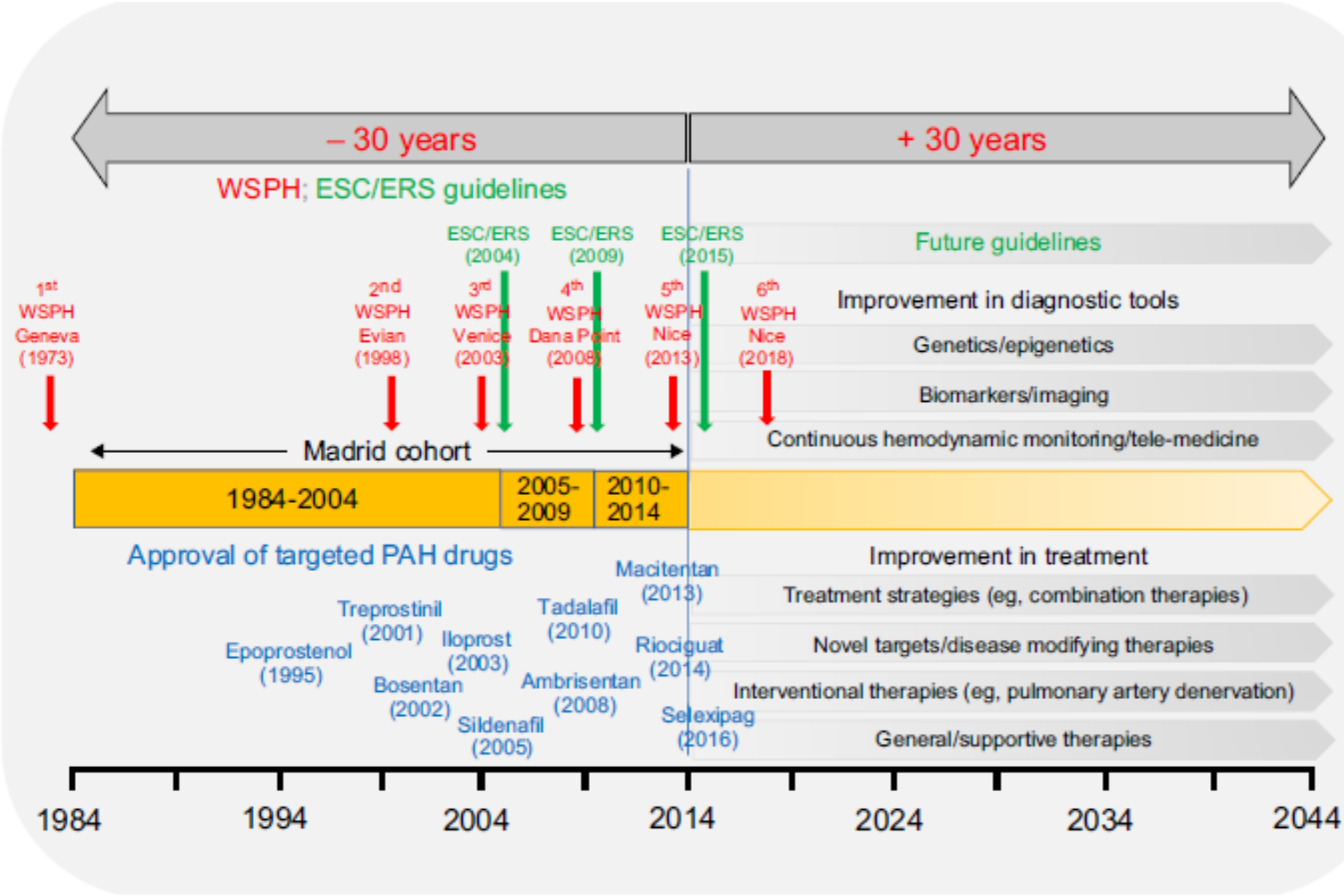
Definition	Characteristics	Clinical group(s)[b]
Pulmonary hypertension (PH)	Mean PAP ≥25 mmHg	All
Pre-capillary PH	Mean PAP ≥25 mmHg PWP ≤15 mmHg CO normal or reduced[c]	1. Pulmonary arterial hypertension 3. PH due to lung diseases 4. Chronic thromboembolic PH 5. PH with unclear and/or multifactorial mechanisms
Post-capillary PH	Mean PAP ≥25 mmHg PWP >15 mmHg CO normal or reduced[c]	2. PH due to left heart disease
Passive	TPG ≤12 mmHg	TPG
Reactive (out of proportion)	TPG >12 mmHg	

[a]All values measured at rest.
[b]According to *Table 4*.
[c]High CO can be present in cases of hyperkinetic conditions such as systemic-to-pulmonary shunts (only in the pulmonary circulation), anaemia, hyperthyroidism, etc.
CO = cardiac output; PAP = pulmonary arterial pressure; PH = pulmonary hypertension; PWP = pulmonary wedge pressure; TPG = transpulmonary pressure gradient (mean PAP − mean PWP).

ESC/ ERS guidelines 2009

Clinical trials in PAH




– 30 years
+ 30 years
WSPH; ESC/ERS guidelines
ESC/ERS (2004)
ESC/ERS (2009)
ESC/ERS (2015)
Future guidelines
1st WSPH Geneva (1973)
2nd WSPH Evian (1998)
3rd WSPH Venice (2003)
4th WSPH Dana Point (2008)
5th WSPH Nice (2013)
6th WSPH Nice (2018)
Improvement in diagnostic tools
Genetics/epigenetics
Biomarkers/imaging
Continuous hemodynamic monitoring/tele-medicine
Madrid cohort
1984-2004
2005-2009
2010-2014
Approval of targeted PAH drugs
Improvement in treatment
Macitentan (2013)
Treprostinil (2001)
Tadalafil (2010)
Treatment strategies (eg, combination therapies)
Epoprostenol (1995)
Iloprost (2003)
Riociguat (2014)
Novel targets/disease modifying therapies
Bosentan (2002)
Ambrisentan (2008)
Interventional therapies (eg, pulmonary artery denervation)
Sildenafil (2005)
Selexipag (2016)
General/supportive therapies
1984
1994
2004
2014
2024
2034
2044

PAH Evidence-Based Algorithm

Oral anticoagulants (E/B) – IPAH/HPAH
Diuretics (E/A)
Oxygen* (E/A)
Digoxin (E/C)
Supervised rehabilitation (E/B)

Supportive therapy and general measures

Avoid excessive physical exertion (E/A)
Birth control (E/A)
Psychological and social support (E/C)
Infection prevention (E/A)

Expert referral (E/A)

Acute vasoreactivity test (A for IPAH)
(E/C for APAH)

ACUTE RESPONDER

NON-RESPONDER

WHO Class I-IV
Amlodipine, diltiazem, nifedipine (B)

Sustained response (WHO I-II)

YES

NO

Amlodipine, diltiazem, nifedipine (B)

Strength of Recommendation	WHO Class II	WHO Class III	WHO Class IV
A	Ambrisentan, Bosentan, Sildenafil	Ambrisentan, Bosentan, Epoprostenol IV, Iloprost inh, Sildenafil	Epoprostenol IV
B	Sitaxsentan, Tadalafil	Sitaxsentan, Tadalafil, Treprostinil SC	Iloprost inh
C		Beraprost	Treprostinil SC
E/B		Iloprost IV, Treprostinil IV	Iloprost IV, Treprostinil IV Initial combination therapy (see below)
E/C			Ambrisentan, Bosentan, Sildenafil, Sitaxsentan, Tadalafil
Not approved		Treprostinil inh+	Treprostinil inh+

INADEQUATE CLINICAL RESPONSE

Sequential combination therapy

Prostanoids
+ (B)
+ (B)
PDE-5 I
+ (B)
ERA

INADEQUATE CLINICAL RESPONSE

Atrial septostomy (E/B) and/or lung transplant (E/A)

JACC, June 2009

PAH Evidence-Based Algorithm

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Diuretics (E/A)
Oxygen* (E/A)
Digoxin (E/C)
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Supportive therapy and general measures

Avoid excessive physical exertion (E/A)
Birth control (E/A)
Psychological and social support (E/C)
Infection prevention (E/A)

Expert referral (E/A)

Acute vasoreactivity test (A for IPAH)
(E/C for APAH)

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NON-RESPONDER

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Amlodipine, diltiazem, nifedipine (B)

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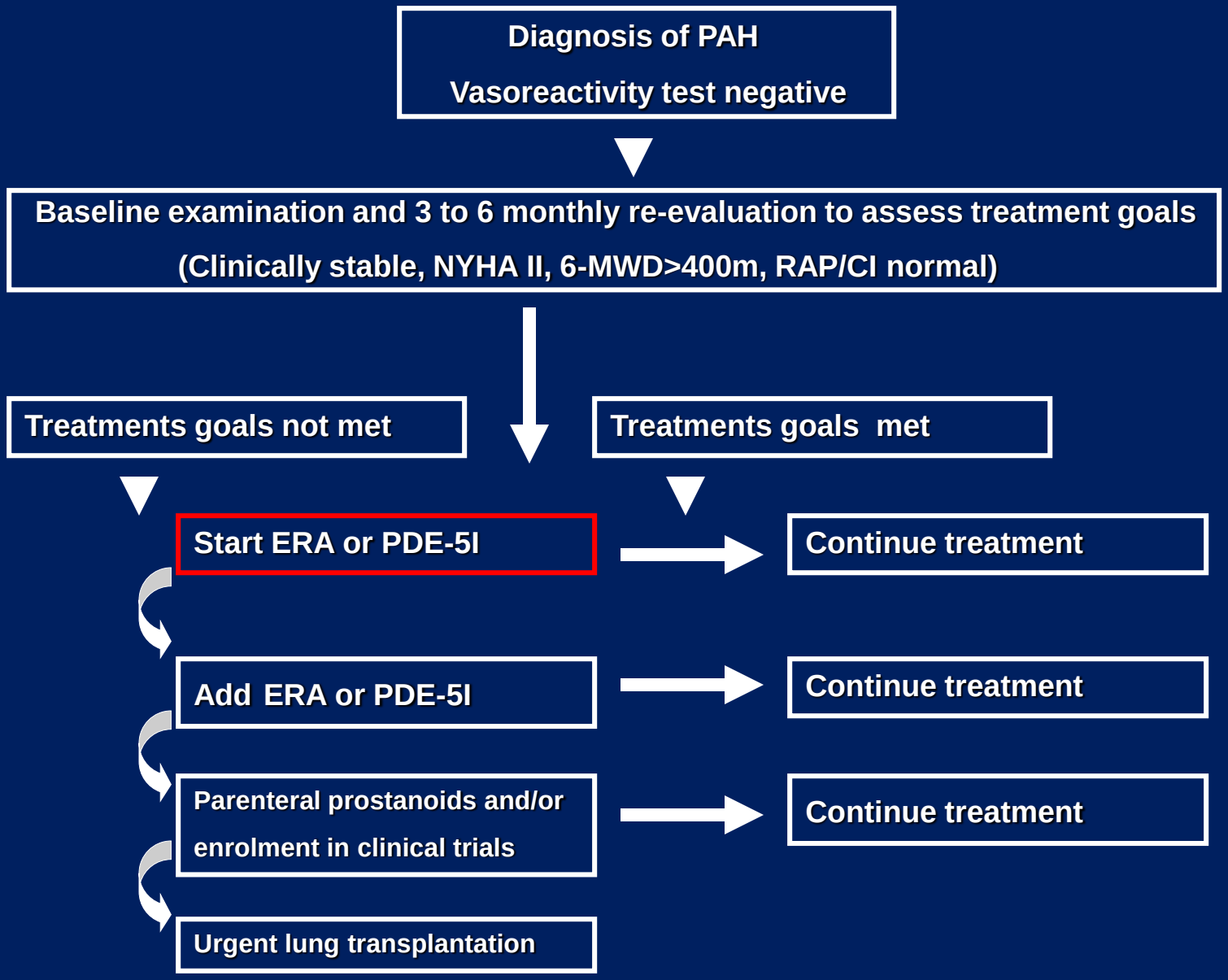
JACC, June 2009

2009: Goal-oriented therapy for PAH



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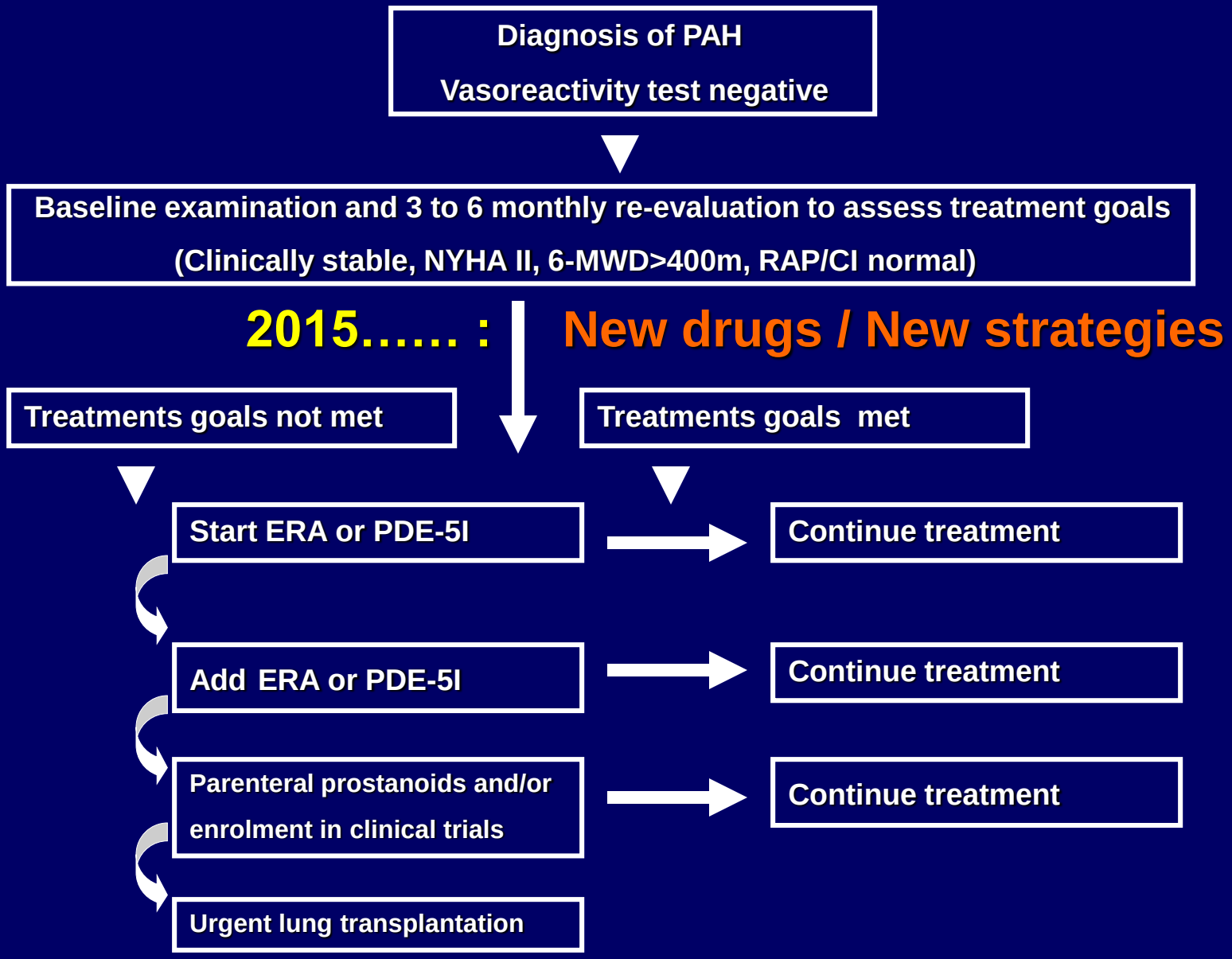
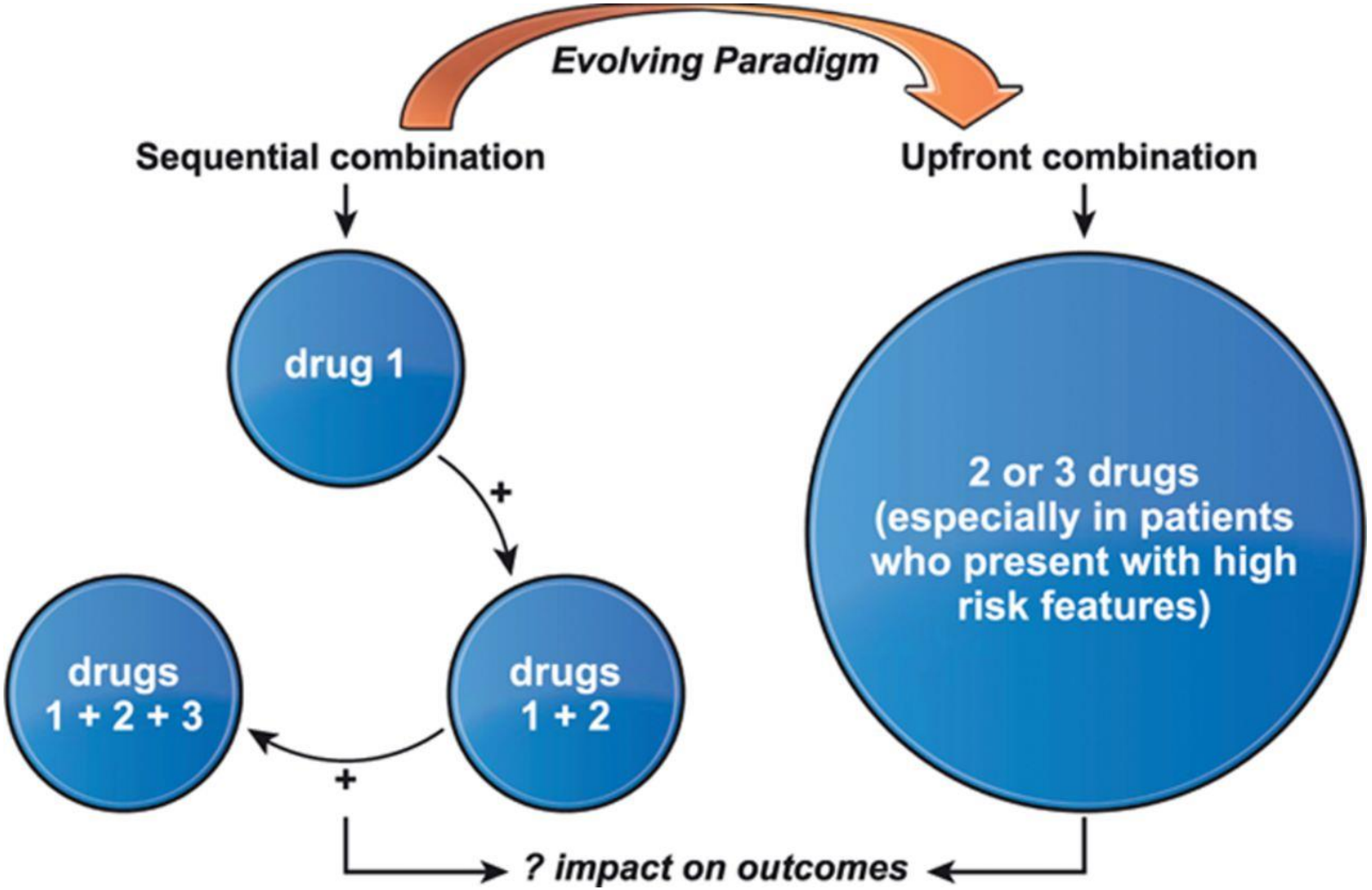
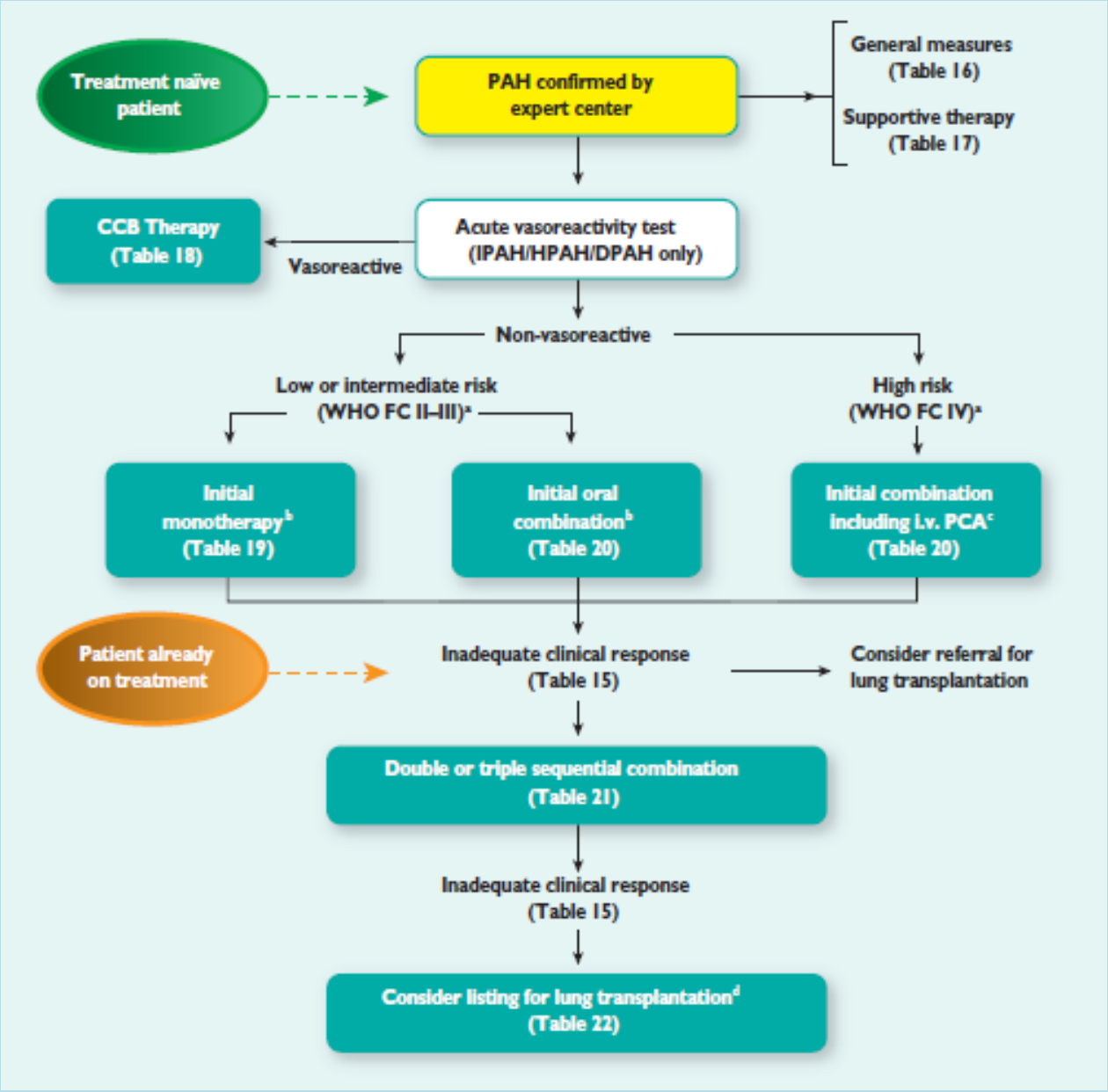


Paradigm of combination therapy in PAH. Combination therapy can be given by either sequentially adding agents if treatment response is unsatisfactory or by upfront combination.



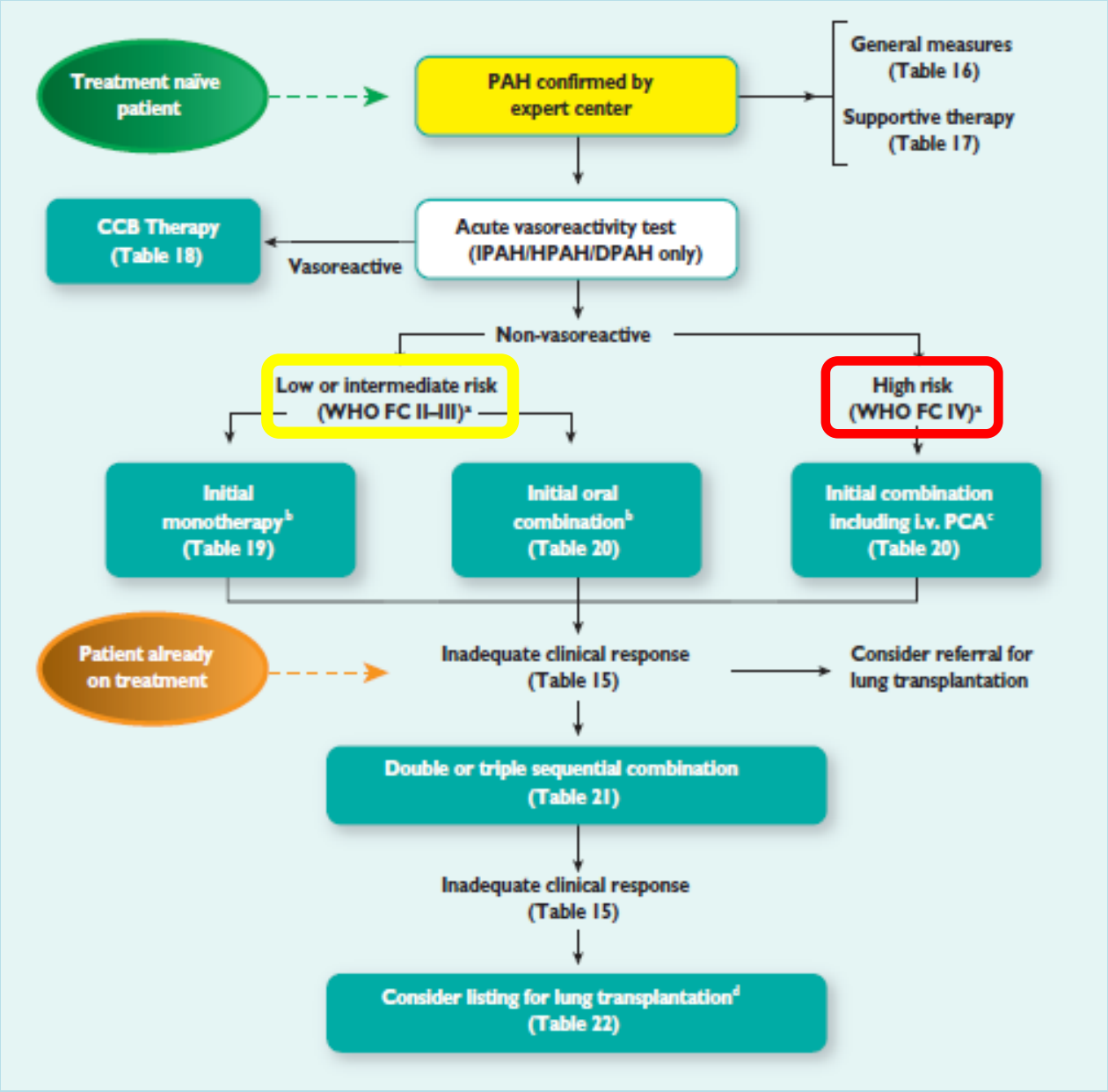
Marc Humbert et al. Circulation. 2014;130:2189-2208

Evidence based treatment algorithm for PAH patients



PH guidelines 2015

Evidence based treatment algorithm for PAH patients



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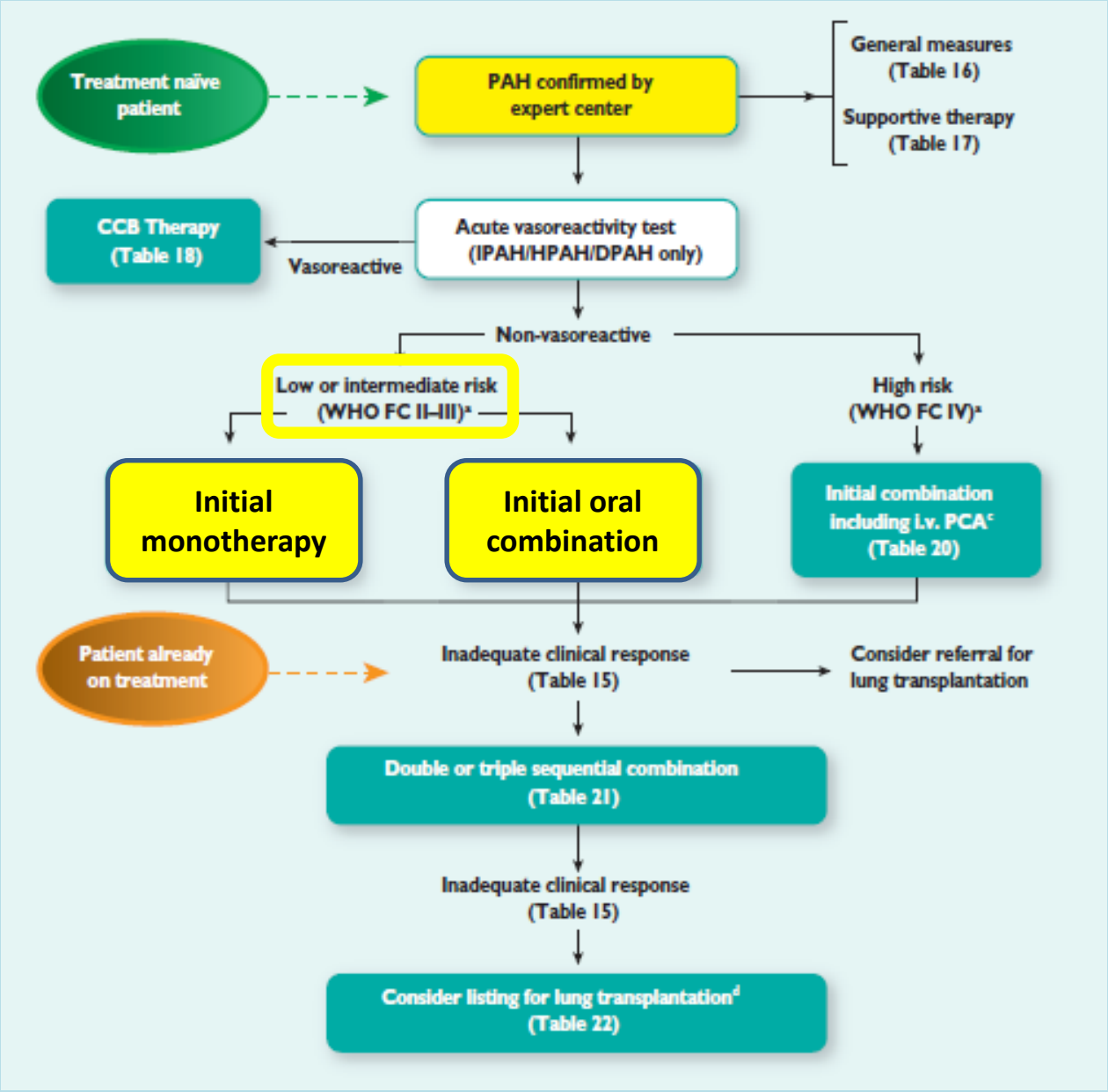

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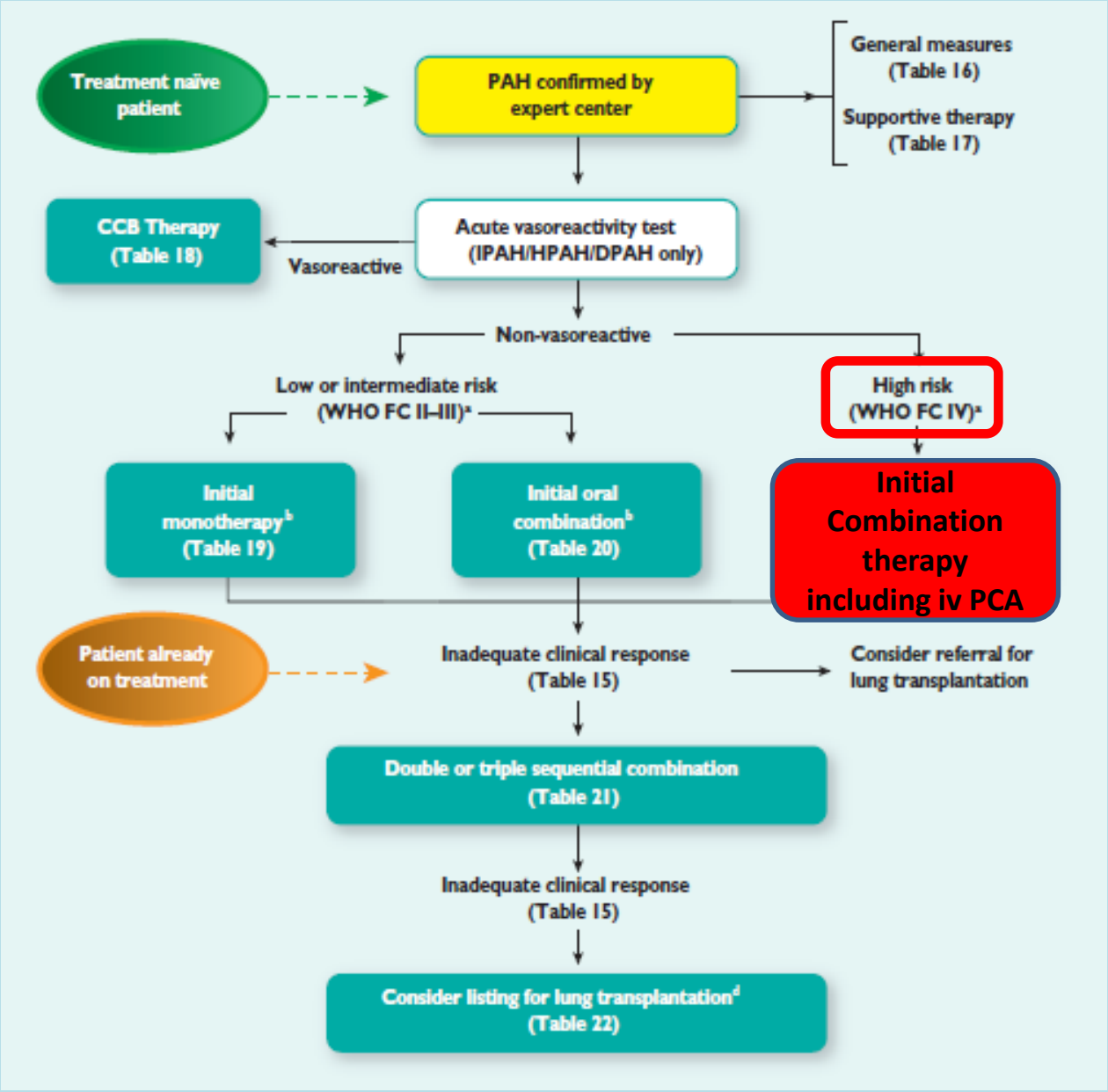

PH guidelines 2015

Risk assessment in pulmonary arterial hypertension

Determinants of prognosis[a] (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope[b]	Repeated syncope[c]
WHO functional class	I, II	III	IV
6MWD	>440 m	165–440 m	<165 m
Cardiopulmonary exercise testing	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 <11 ml/min/kg (<35% pred.) VE/VCO_2 ≥45
NT-proBNP plasma levels	BNP <50 ng/l NT-proBNP <300 ng/ml	BNP 50–300 ng/l NT-proBNP 300–1400 ng/l	BNP >300 ng/l NT-proBNP >1400 ng/l
Imaging (echocardiography, CMR imaging)	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
Haemodynamics	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%

PH guidelines 2015

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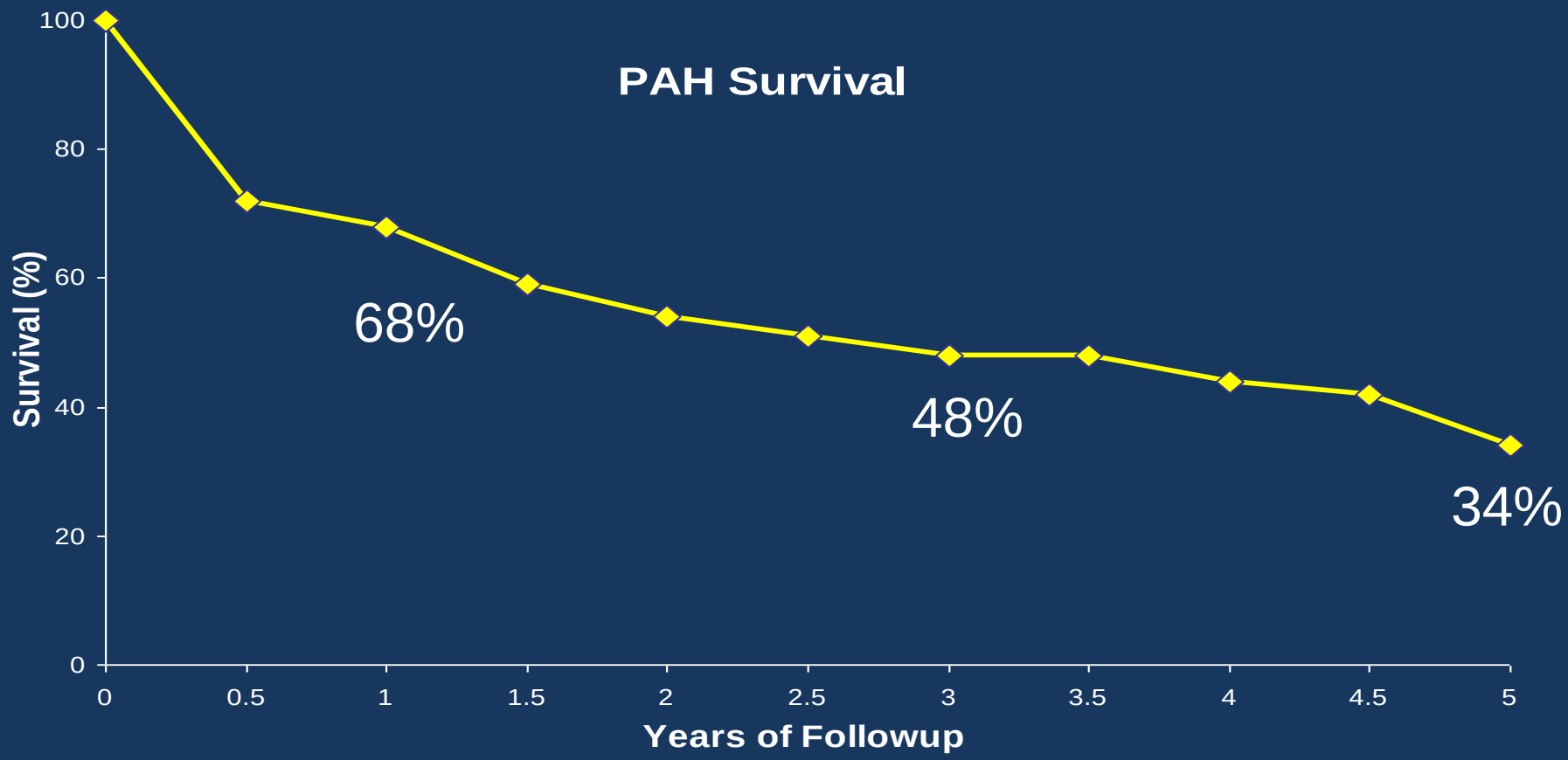
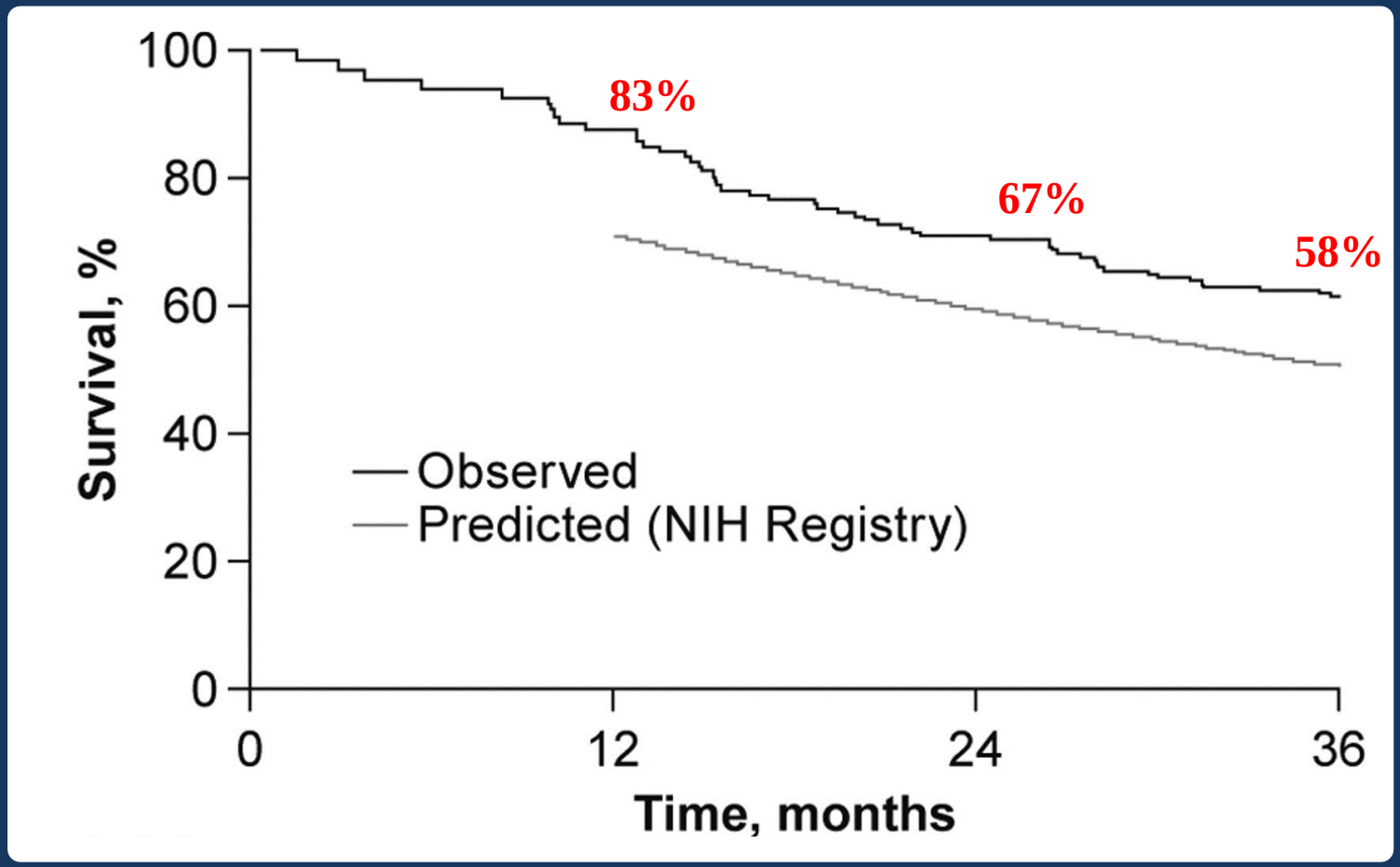
NT-proBNP plasma levels	BNP <50 ng/l NT-proBNP <300 ng/ml	BNP 50–300 ng/l NT-proBNP 300–1400 ng/l	BNP >300 ng/l NT-proBNP >1400 ng/l
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2 No pericardial effusion	RA area 18–26 cm^2 No or minimal, pericardial effusion	RA area >26 cm^2 Pericardial effusion
Haemodynamics	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%

PH guidelines 2015

PAH: A Progressive Disease of Poor Survival

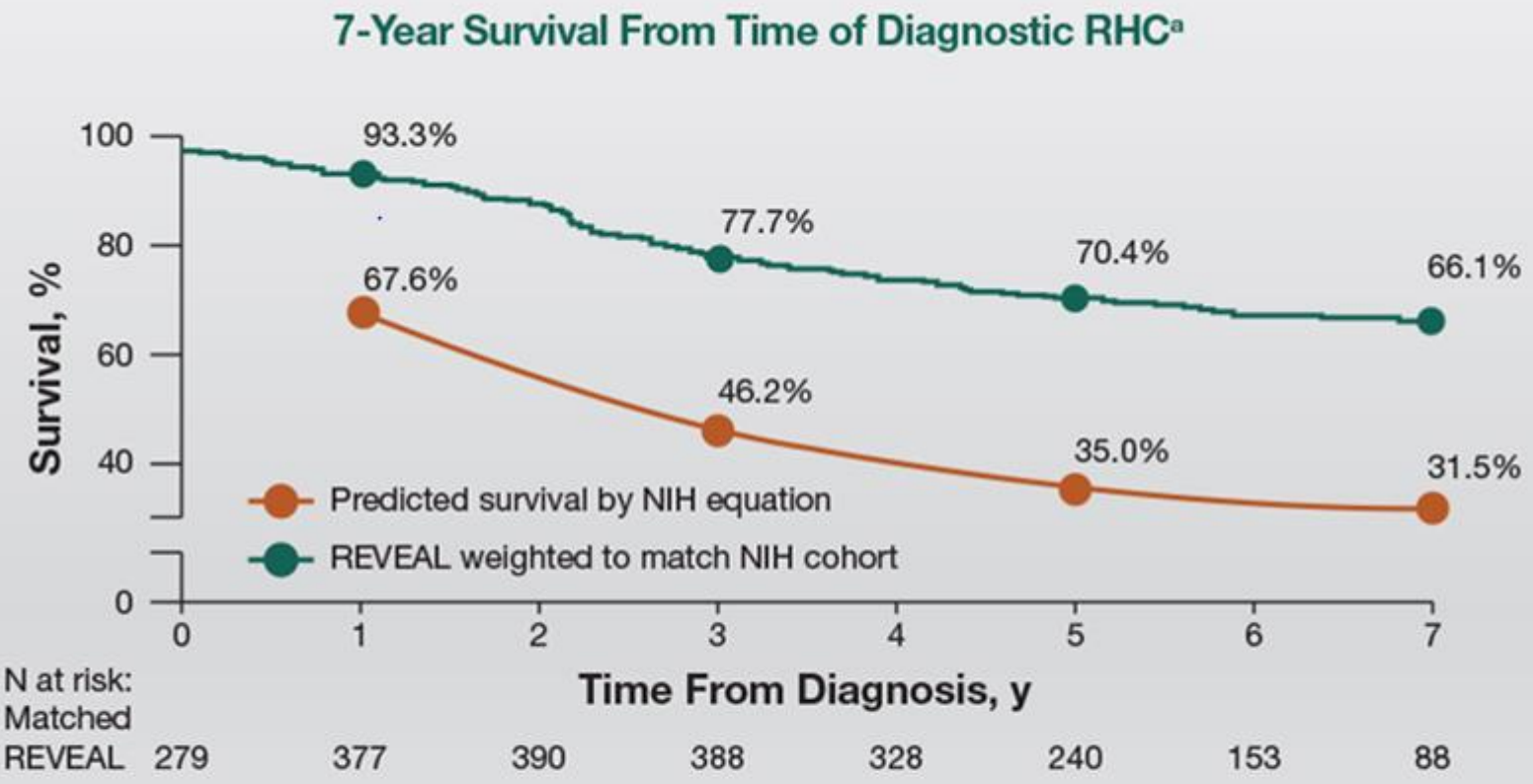


Adapted from: D'Alonzo et al. *Ann Internal Med*. 1991

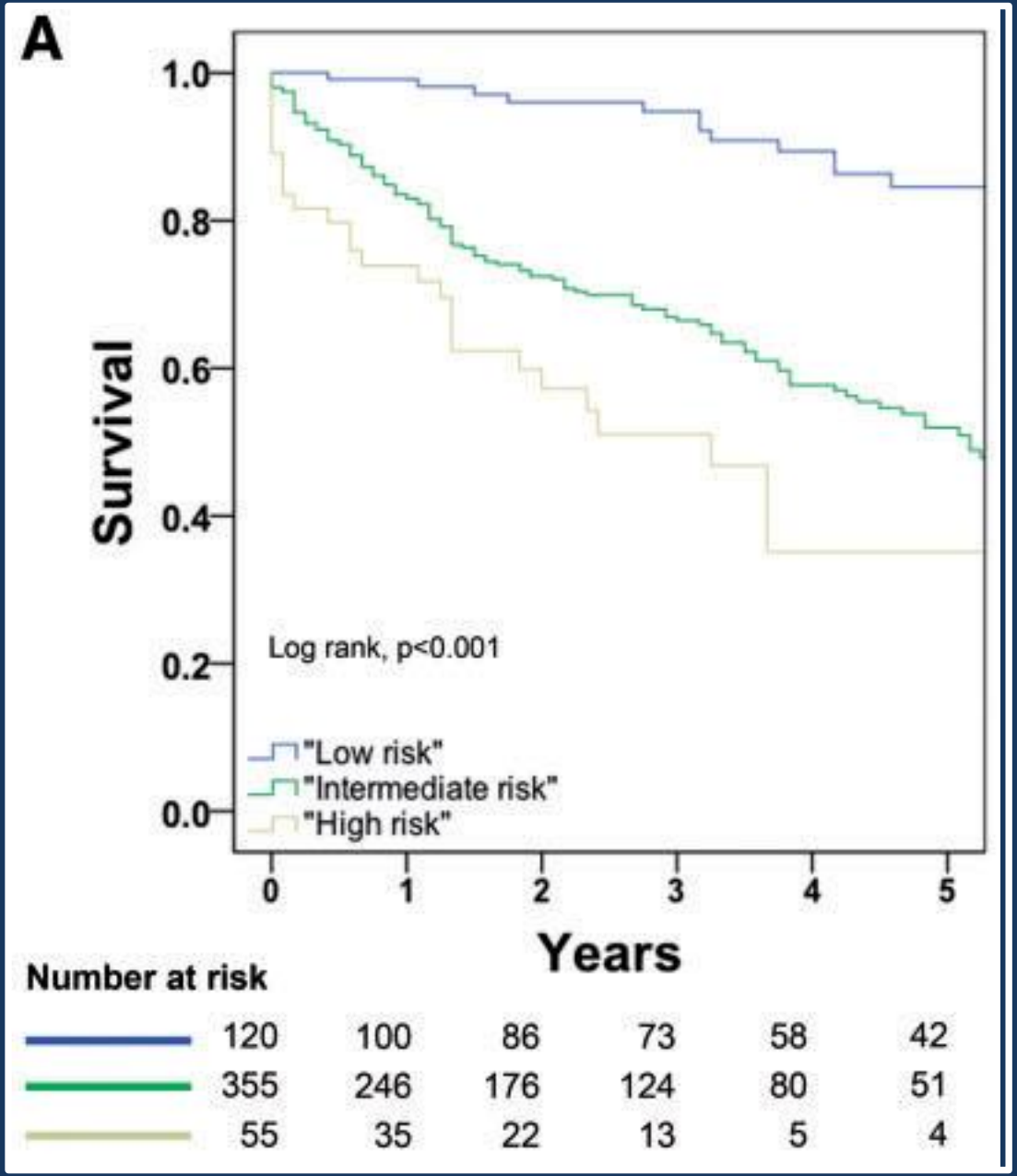


Humbert M et al. Circulation 2010;122:156-163

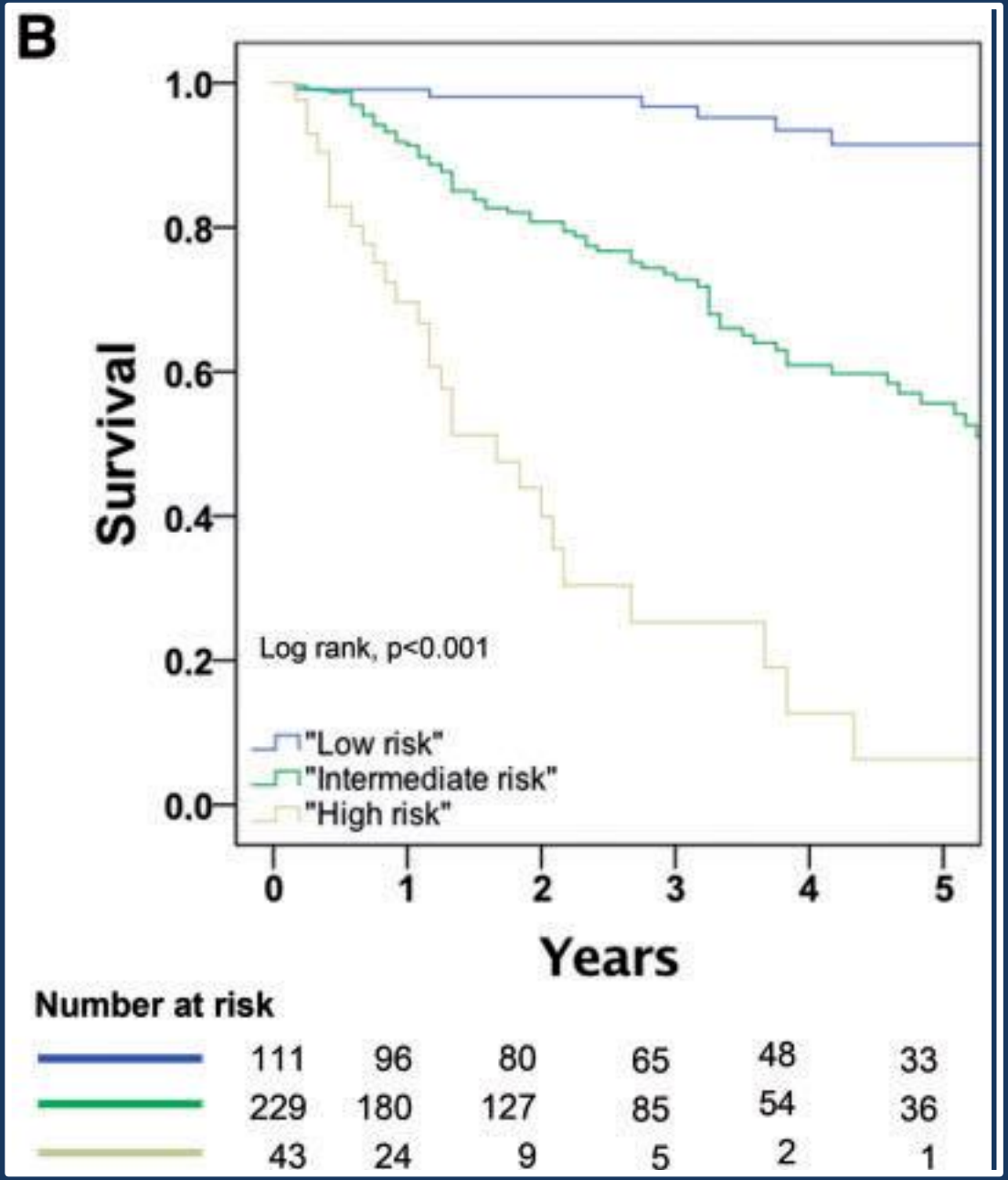
Despite Improvements in Survival
PAH is Still Associated With High Mortality

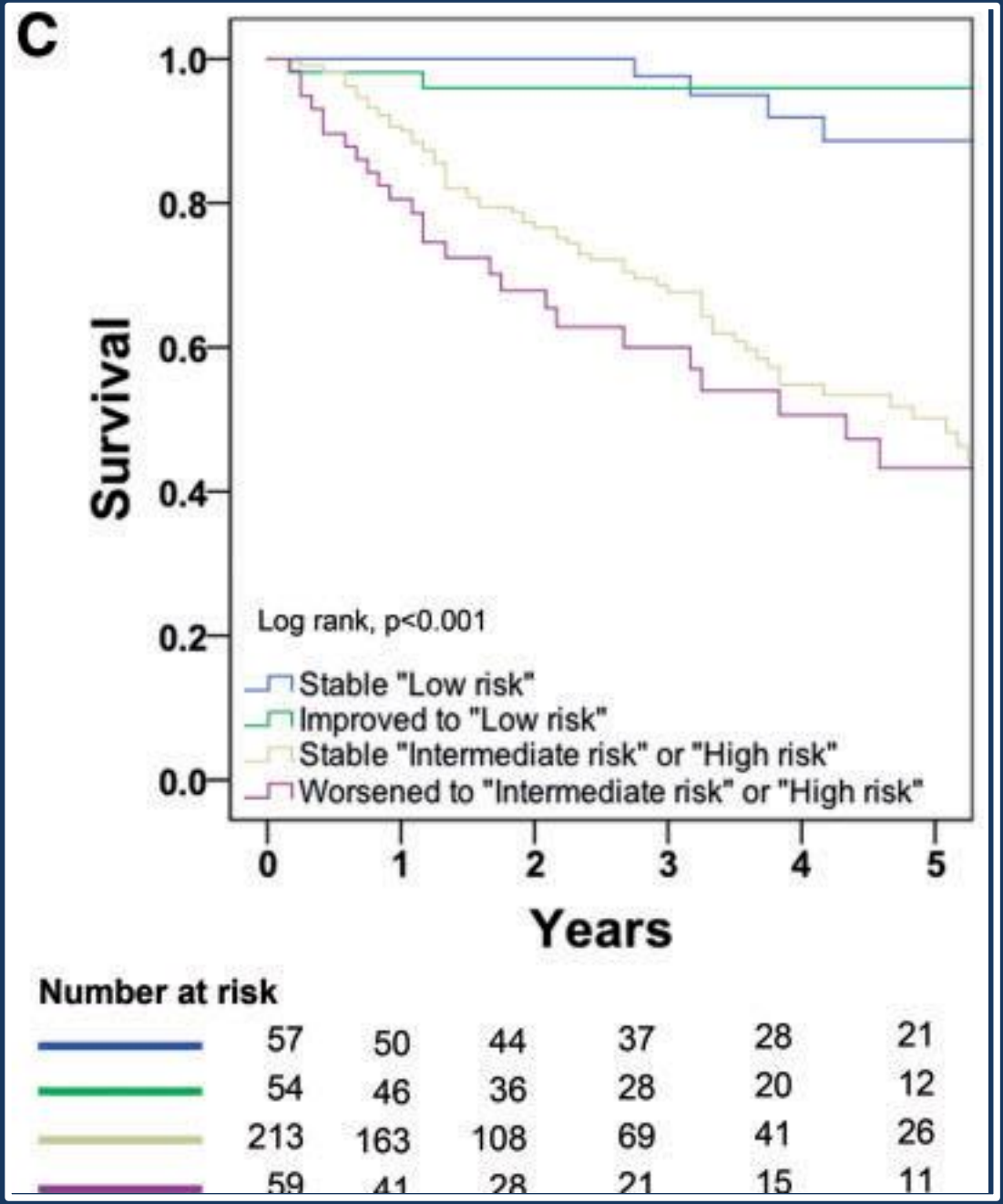


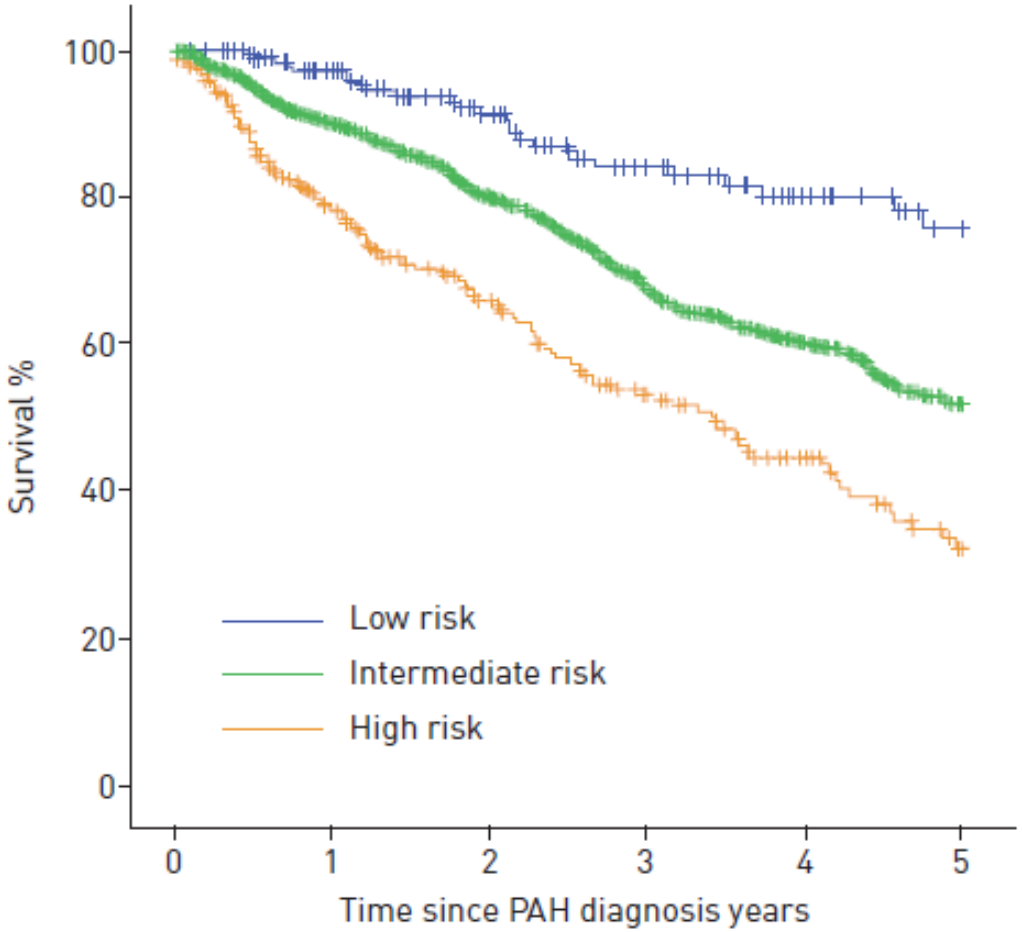
[a] REVEAL registry cohort weighted to match age, sex, and mean pulmonary artery pressure distribution of NIH cohort. Cohort consisted of patients who met the NIH criteria (ie, had iPAH or fPAH and a pulmonary capillary wedge pressure of ≤12 mm Hg), and initiated an ERA, PDE5 inhibitor, or prostacyclin analogue within 6 mo of diagnostic RHC.



D. Kylhammar et al. European Heart Journal (2017)


B
1.0
0.8
0.6
0.4
0.2
0.0
Survival
Log rank, p<0.001
"Low risk"
"Intermediate risk"
"High risk"
0
1
2
3
4
5
Years
Number at risk
111 96 80 65 48 33
229 180 127 85 54 36
43 24 9 5 2 1

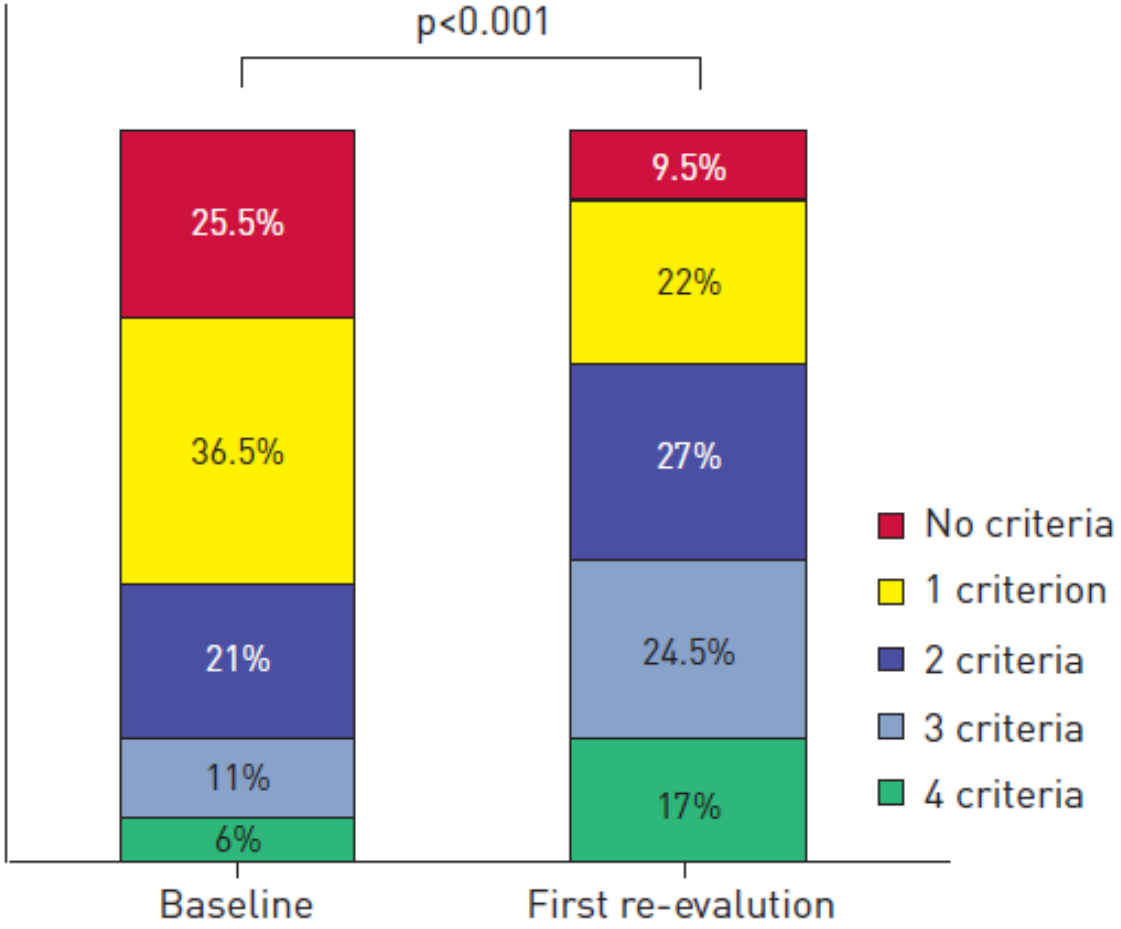

C
1.0
0.8
0.6
0.4
0.2
0.0
Survival
Log rank, p<0.001
Stable "Low risk"
Improved to "Low risk"
Stable "Intermediate risk" or "High risk"
Worsened to "Intermediate risk" or "High risk"
0
1
2
3
4
5
Years
Number at risk
57 50 44 37 28 21
54 46 36 28 20 12
213 163 108 69 41 26
59 41 28 21 15 11



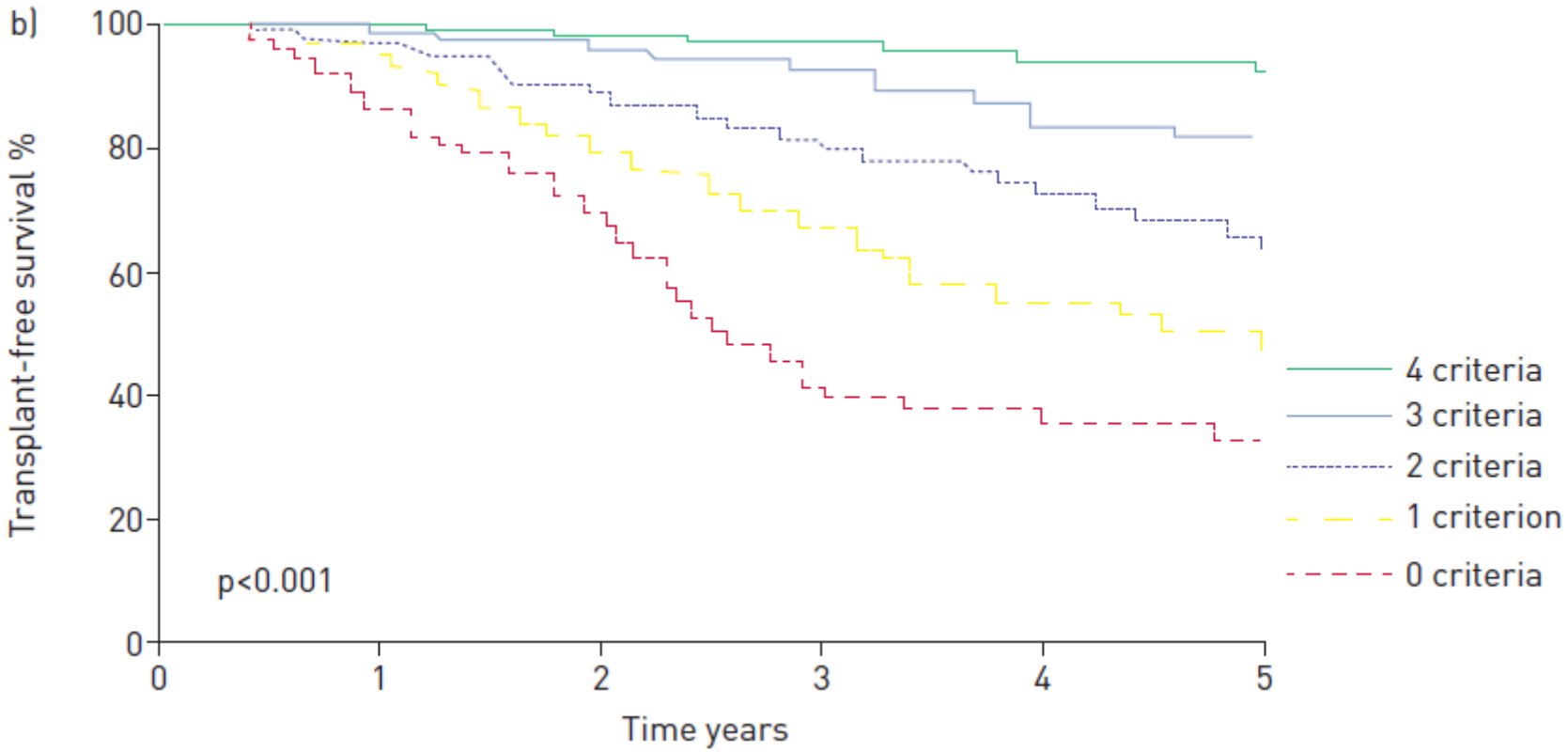
Hoeper M et al Eur Respir J 2017; 50: 1700740

Low-risk criteria achieved within a year

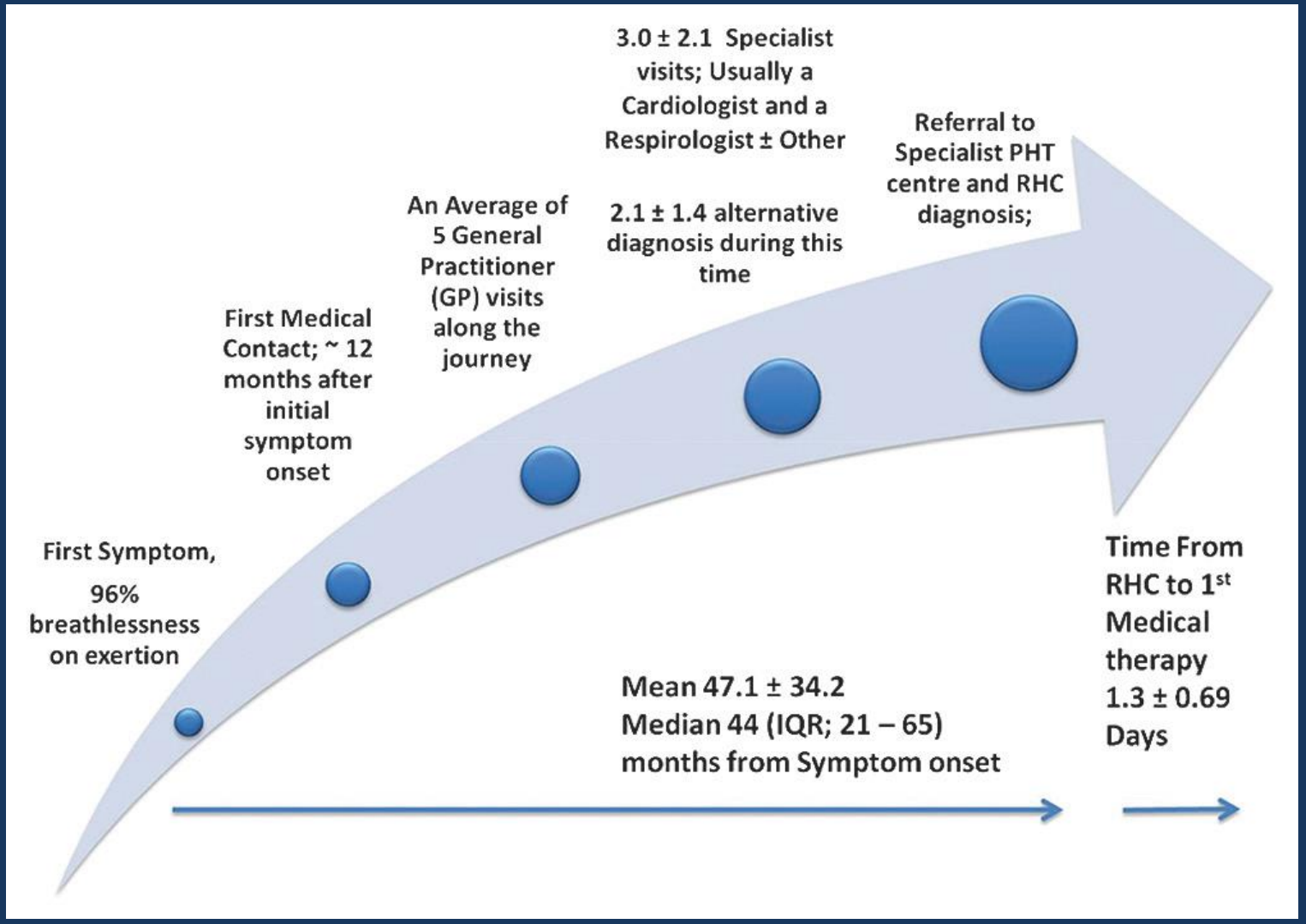
- FC I-II
- 6MWD >440 m
- RAP <8 mmHg
- CI >2.5 L/min/m^2



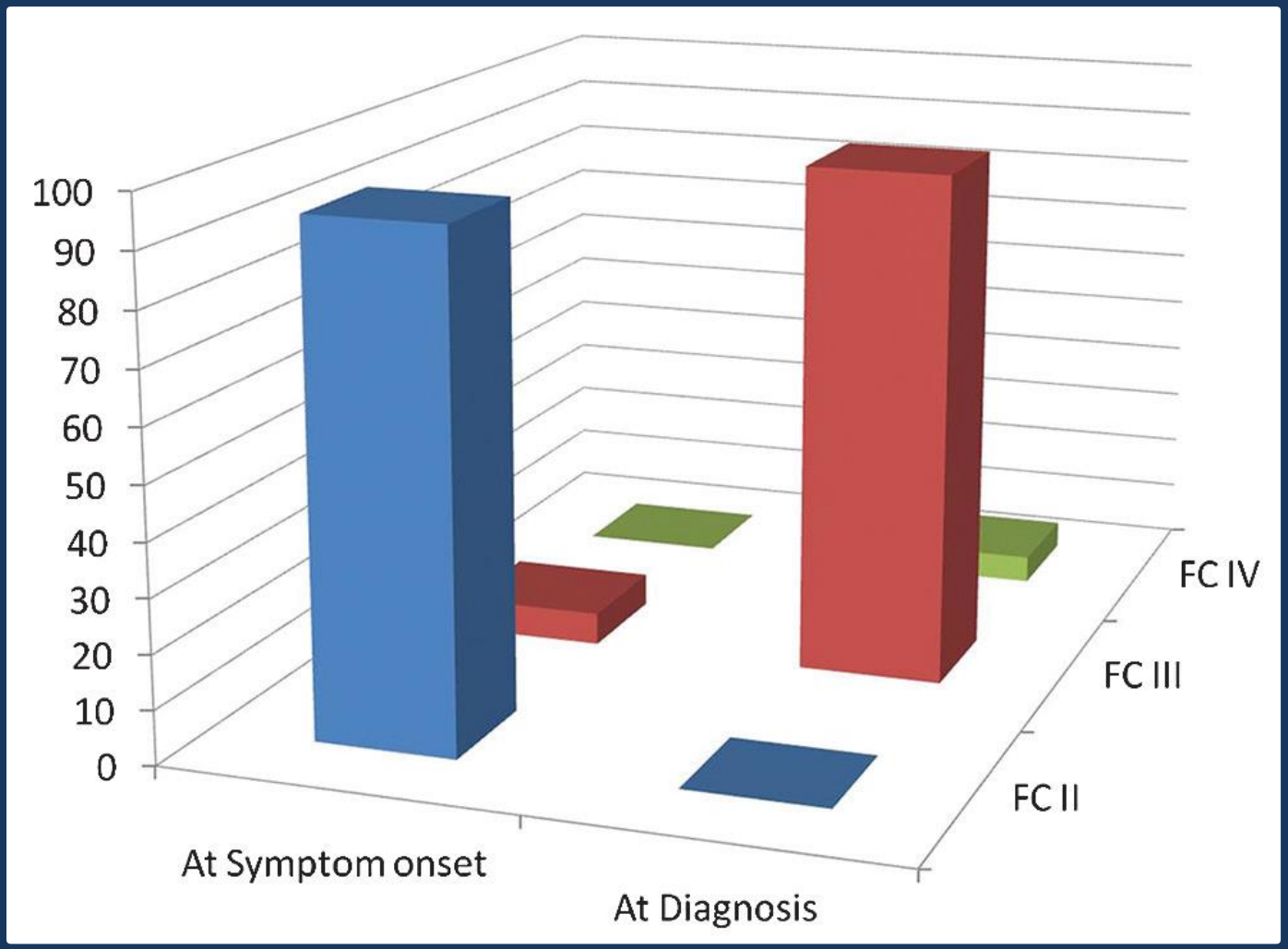
Boucly A et al. Eur Respir J 2017; 50: 1700889



Boucly A et al. Eur Respir J 2017; 50: 1700889

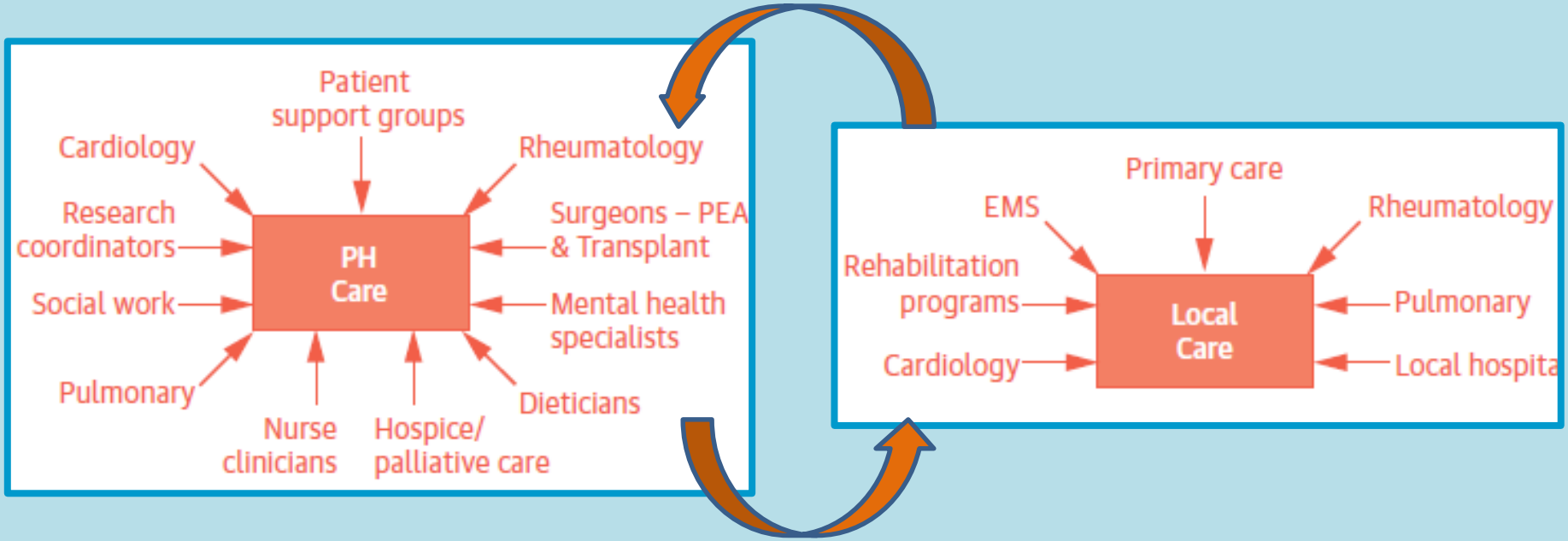


Strange et al.: Pulmonary Circulation, January-March 2013



Strange et al.: Pulmonary Circulation, January-March 2013

Collaboration: PH Care- Local Care



JACC 2015;65:1976–97