SIMPOSIO

IPERTENSIONE ARTERIOSA POLMONARE: DALLA NOVITÀ DELLE LINEE GUIDA ESC ALLA REALTÀ CLINICA

Quando è necessario essere aggressivi nel paziente con ipertensione polmonare per cercare di migliorare la prognosi

Il ruolo del clinico nella gestione del paziente con ipertensione arteriosa polmonare: la diagnosi, la terapia medica, i controlli nel tempo

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2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension – web addenda

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- Group 1, pulmonary arterial hypertension (PAH): pathological changes predominantly affect the distal pulmonary arteries (<500 μm) with medial hypertrophy, intimal proliferative and fibrotic changes, adventitial thickening with mild to moderate perivascular inflammatory infiltrates and lymphoid neogenesis, complex lesions (plexiform, dilated lesions) and thrombotic lesions.

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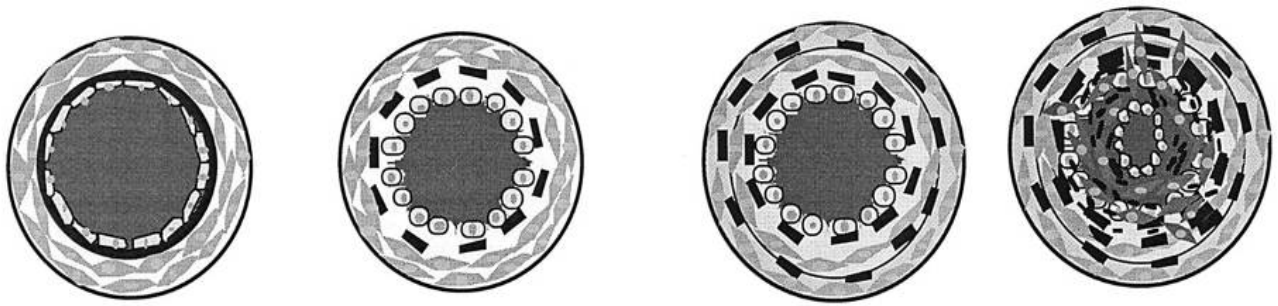
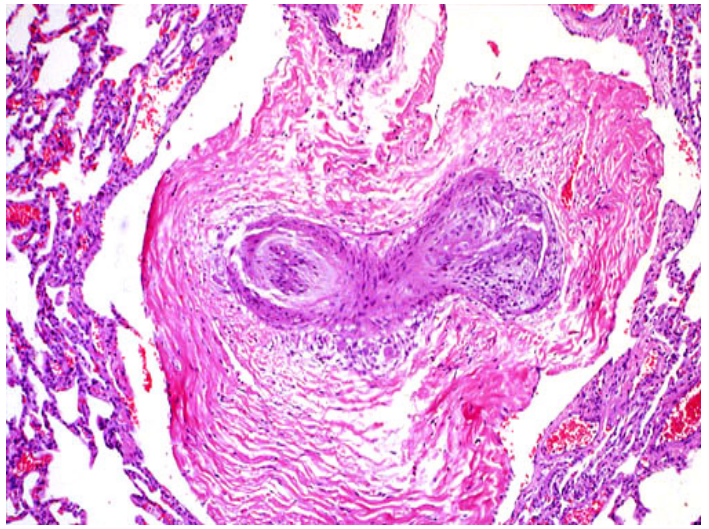
European Heart Journal 2016;37:67–119





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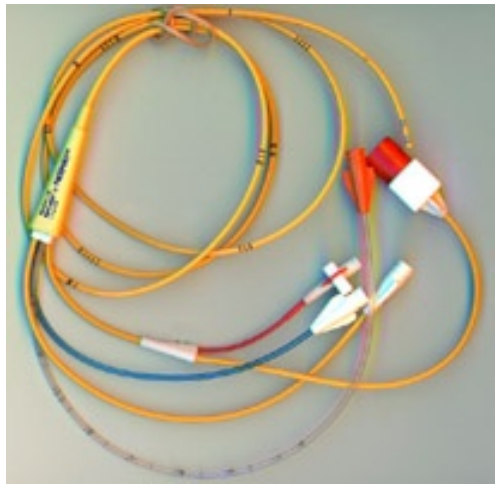

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3. Definitions and classifications

The term PAH describes a group of PH patients characterized haemodynamically by the presence of pre-capillary PH, defined by a pulmonary artery wedge pressure (PAWP) ≤15 mmHg and a PVR >3 Wood units (WU) in the absence of other causes of pre-capillary PH such as PH due to lung diseases, CTEPH or other rare diseases.[1]

European Heart Journal 2016;37:67–119

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

RISK FACTORS AND ASSOCIATED CONDITIONS

Connective Tissue Disease
Congenital Heart Disease
Portal Hypertension
HIV Infection
Drugs and Toxins
Pregnancy

SUSCEPTIBILITY
Abnormal BMPR2 Gene
Other Genetic Factors

VASCULAR INJURY

Endothelial Dysfunction

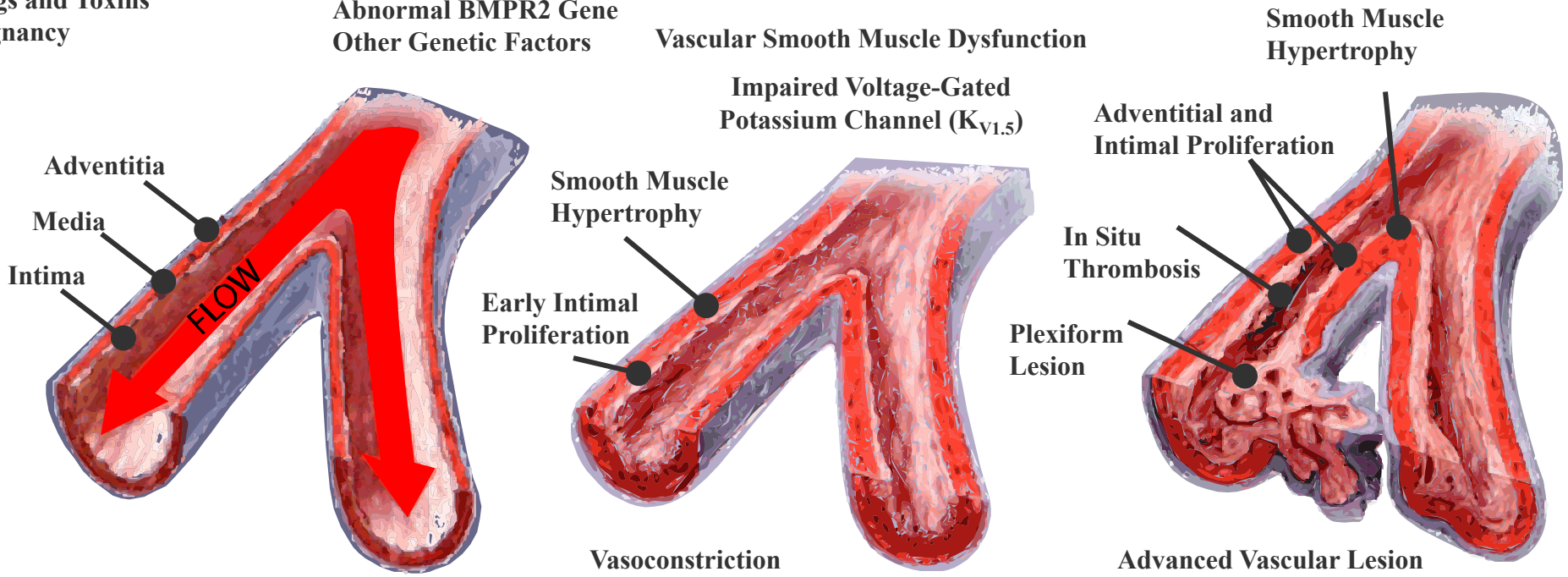
↓Nitric Oxide Synthase
↓Prostacyclin Production
↑Thromboxane Production
↑Endothelin 1 Production

Vascular Smooth Muscle Dysfunction

Impaired Voltage-Gated Potassium Channel ($K_{V1.5}$)

DISEASE PROGRESSION

Loss of Response to Short-Acting Vasodilator Trial



NORMAL — REVERSIBLE DISEASE — IRREVERSIBLE DISEASE

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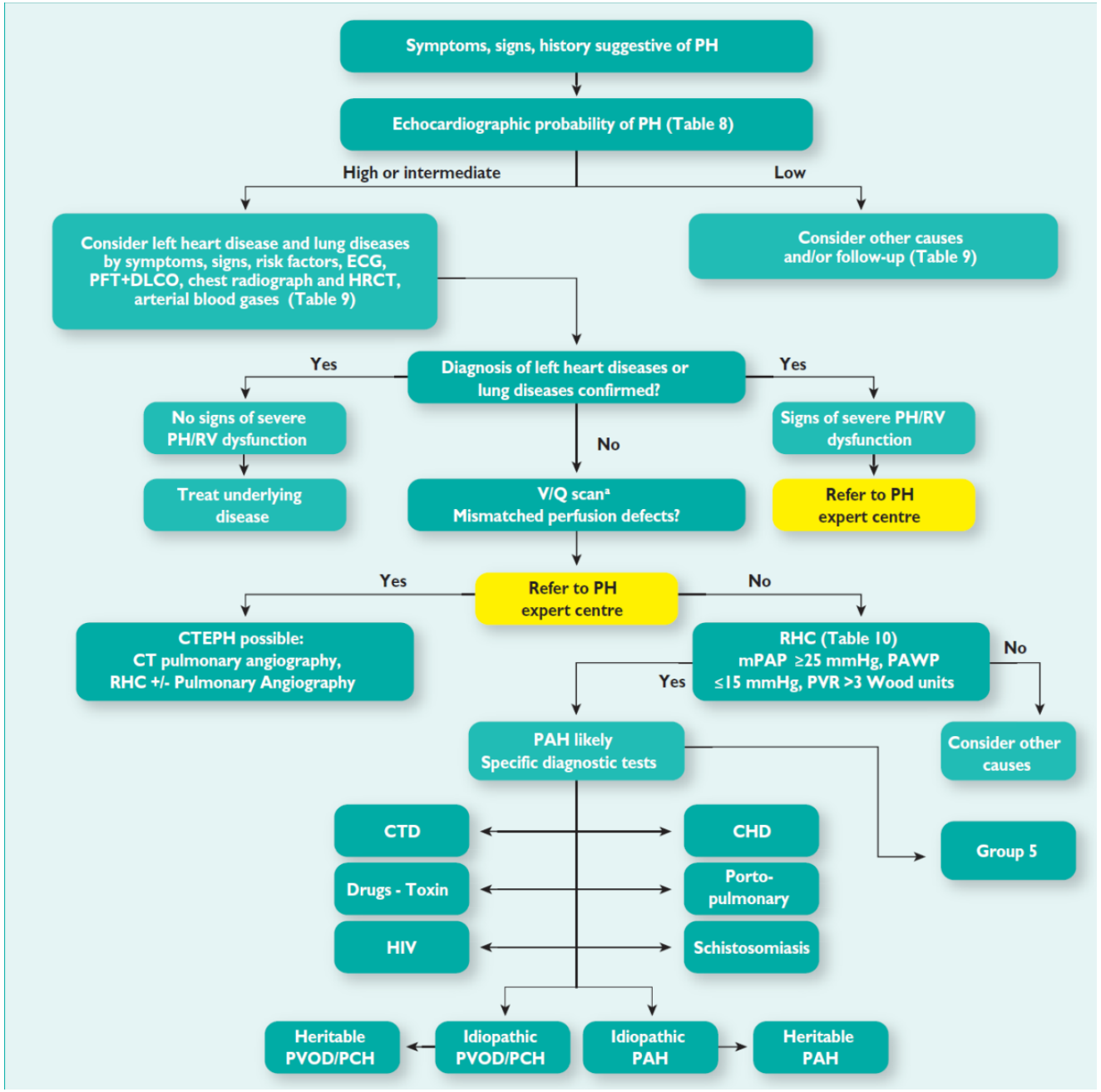

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Table 4 Comprehensive clinical classification of pulmonary hypertension (updated from Simonneau *et al.*[5])

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
5.4 Others: pulmonary tumoral thrombotic microangiopathy, fibrosing mediastinitis, chronic renal failure (with/without dialysis), segmental pulmonary hypertension

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3.2 Classifications

The clinical classification of PH is intended to categorize multiple clinical conditions into five groups according to their similar clinical presentation, pathological findings, haemodynamic characteristics and treatment strategy.[5]

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5. Pulmonary hypertension diagnosis

5.1 Diagnosis

The diagnosis of PH requires a clinical suspicion based on symptoms and physical examination

Peak tricuspid regurgitation velocity (m/s)	Presence of other echo 'PH signs'[a]	Echocardiographic probability of pulmonary hypertension
≤2.8 or not measurable	No	Low
≤2.8 or not measurable	Yes	Intermediate
2.9–3.4	No	
2.9–3.4	Yes	High
>3.4	Not required	

A: The ventricles[a]	B: Pulmonary artery[a]	C: Inferior vena cava and right atrium[a]
Right ventricle/ left ventricle basal diameter ratio >1.0	Right ventricular outflow Doppler acceleration time <105 msec and/or midsystolic notching	Inferior cava diameter >21 mm with decreased inspiratory collapse (<50 % with a sniff or <20 % with quiet inspiration)
Flattening of the interventricular septum (left ventricular eccentricity index >1.1 in systole and/or diastole)	Early diastolic pulmonary regurgitation velocity >2.2 m/sec	Right atrial area (end-systole) >18 cm^2
	PA diameter >25 mm.	

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5. Pulmonary hypertension diagnosis

5.1 Diagnosis

The diagnosis of PH requires a comprehensive set of investigations to confirm that haemodynamic criteria are met and to describe the aetiology and the functional and haemodynamic severity of the condition. The interpretation of these investigations requires, at the very least, expertise in cardiology, imaging and respiratory medicine and may best be discussed at a multidisciplinary team meeting.

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12. Definition of a pulmonary hypertension referral centre

- The importance of expert referral centres in the management of PH patients has been highlighted in both the diagnostic and treatment algorithms.

Recommendations	Class[a]	Level[b]
It is recommended for referral centres to provide care by a multiprofessional team (cardiology and respiratory medicine physicians, clinical nurse specialist, radiologists, psychological and social work support, appropriate on-call expertise)	I	C
It is recommended for referral centres to have direct links and quick referral patterns to other services (such as CTD, family planning, PEA, lung transplantation, adult congenital heart disease)	I	C
It should be considered that a referral centre follow at least 50 patients with PAH or CTEPH and should receive at least two new referrals per month with documented PAH or CTEPH	IIa	C
It should be considered that a referral centre perform at least 20 vasoreactivity tests in IPAH, HPAH or DPAH patients per year	IIa	C
Referral centres should participate in collaborative clinical research in PAH, including phase II and phase III clinical trials	IIa	C

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Table 4 Comprehensive clinical classification of pulmonary hypertension (updated from Simonneau et *al.*[5])

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1'.4 Associated with:
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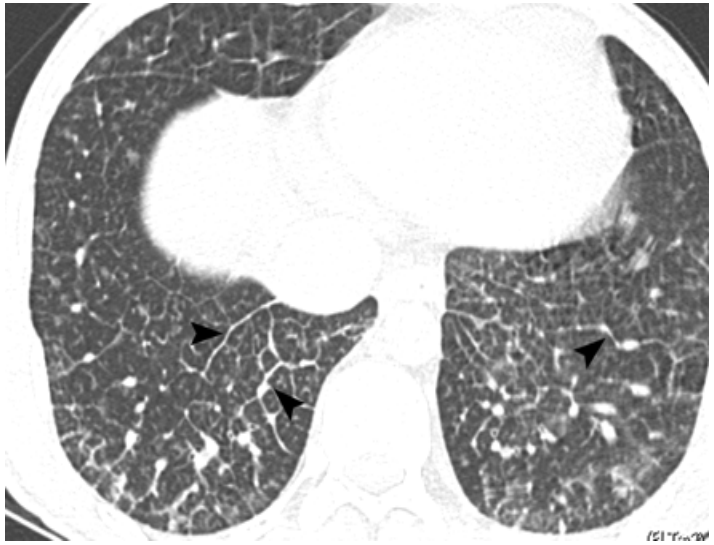
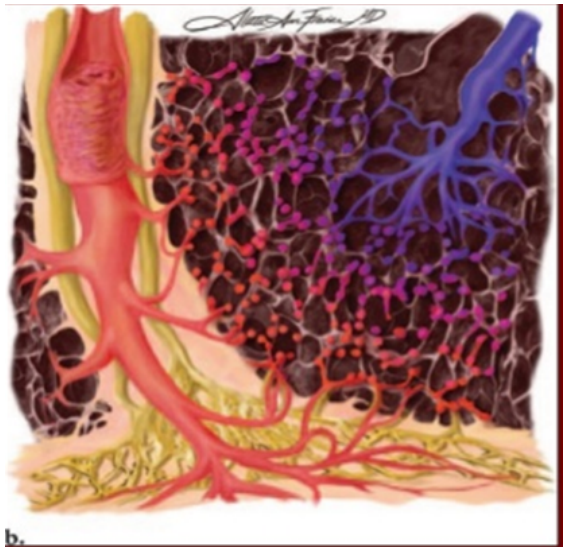
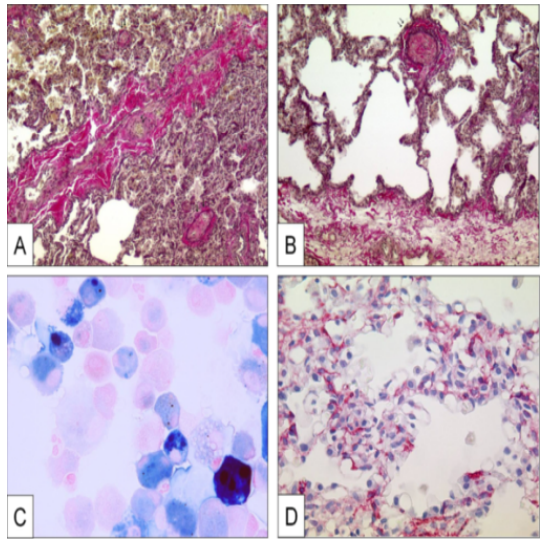
1'.4.2 HIV infection







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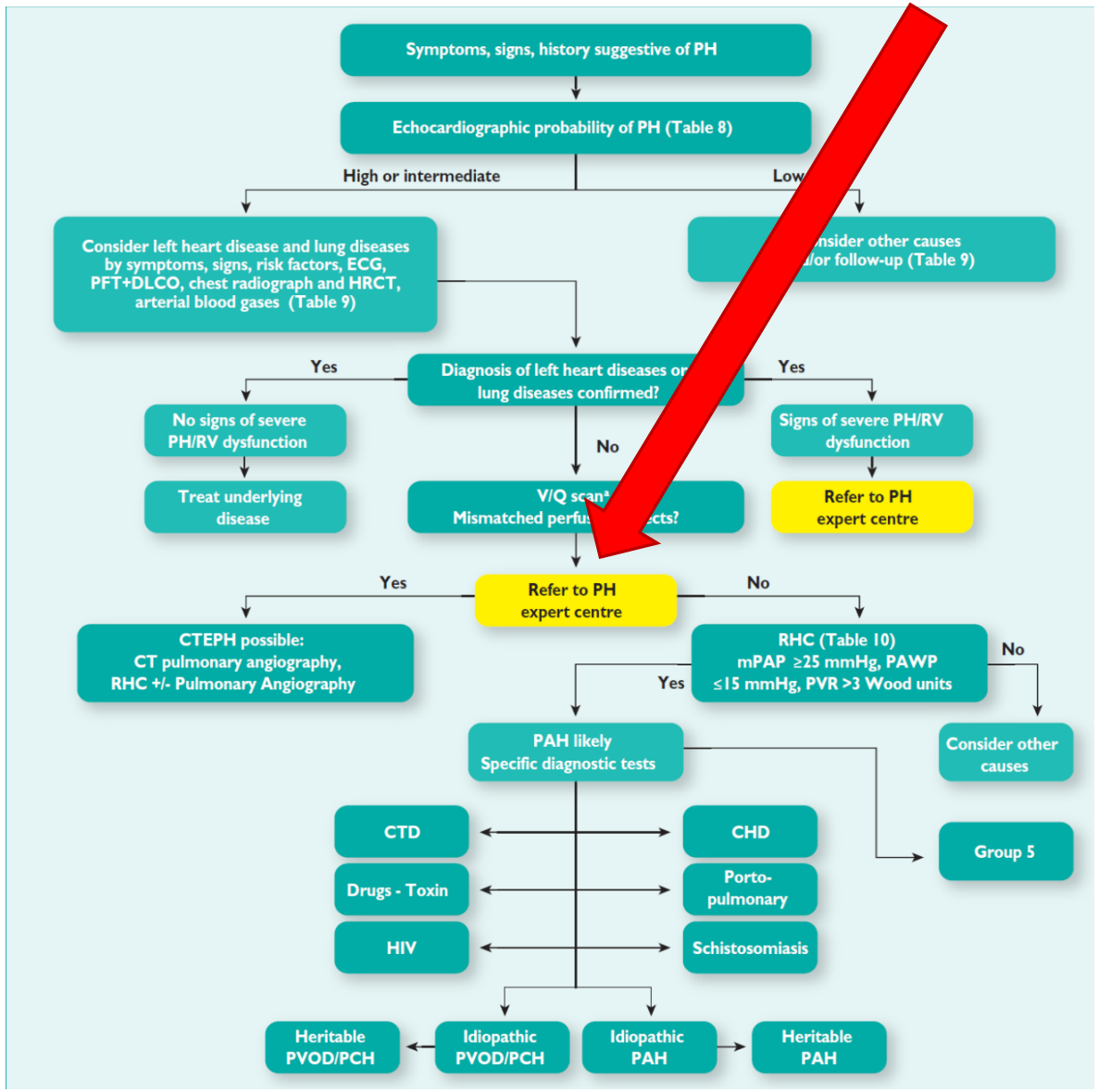

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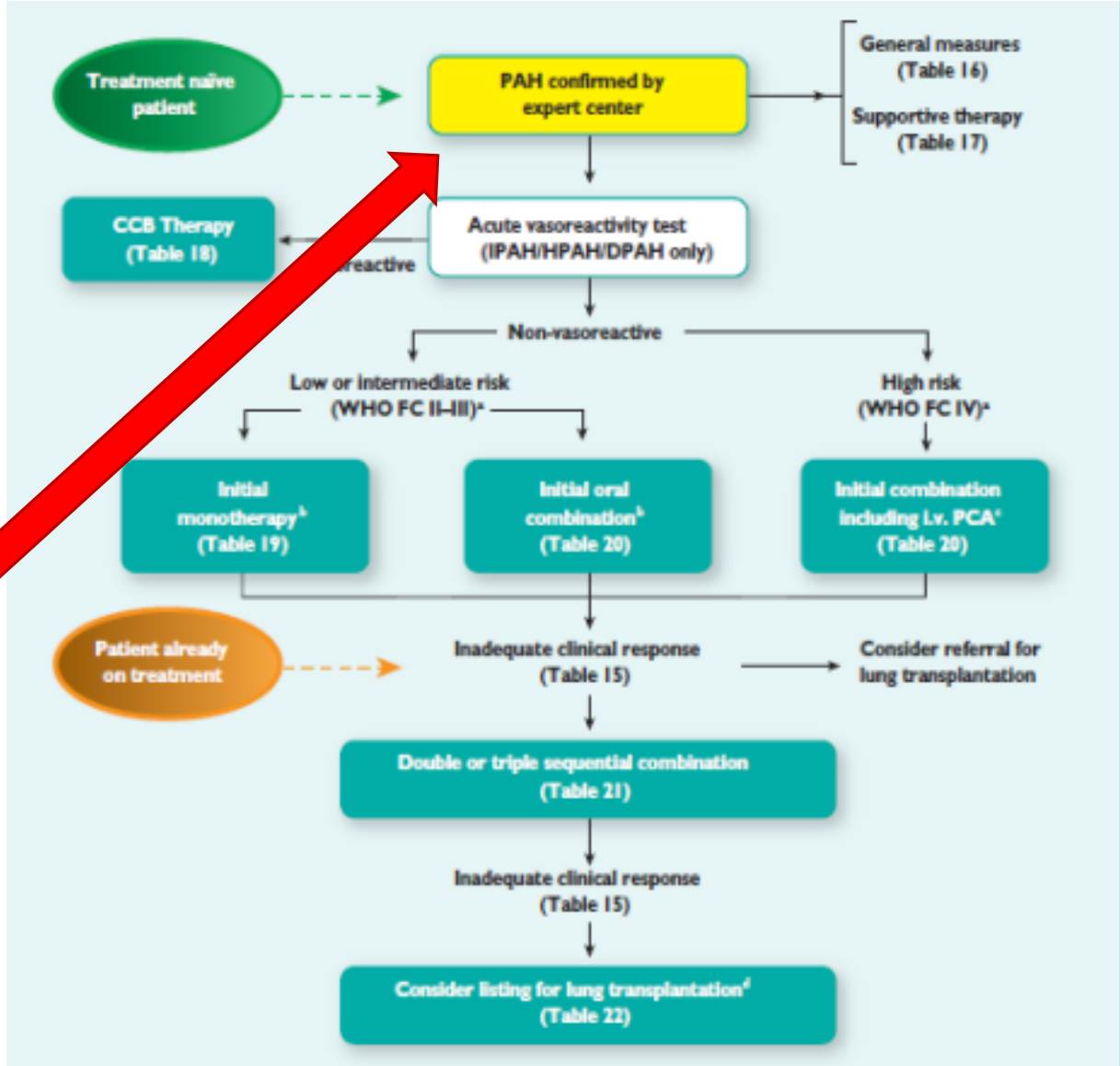

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1. Pulmonary arterial hypertension

1.1 Idiopathic

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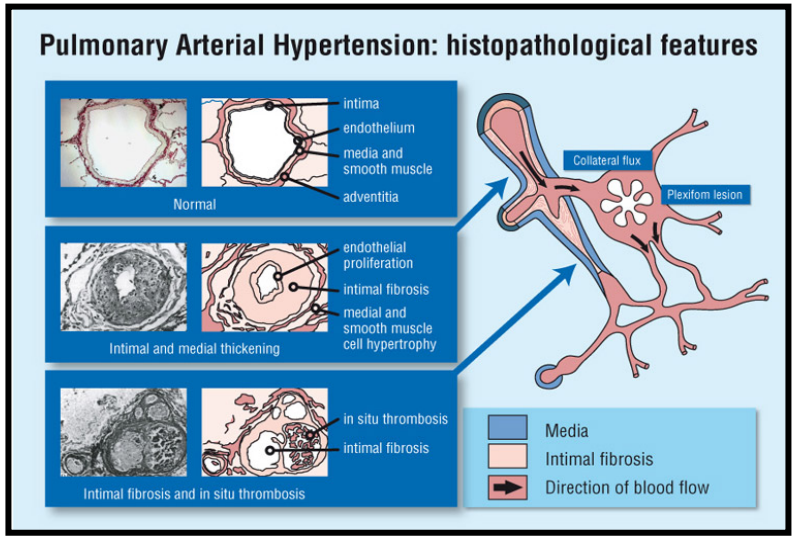

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4. Epidemiology and genetics of pulmonary hypertension

5.1.12 Genetic testing

Genetic counselling and *BMPR2* mutation screening (point mutations and large rearrangements) should be offered by referral centres to patients with IPAH considered to be sporadic or induced by anorexigens and to patients with a family history of PAH.

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4.2 Genetics

- Group 1 (PAH): Heterozygous *BMPR2* mutations account for approximately 75% of familial PAH and up to 25% of apparently sporadic PAH cases.[26] *BMPR2* encodes a type 2 receptor for bone morphogenetic proteins involved in the control of vascular cell proliferation.

When no *BMPR2* mutations are identified in familial PAH patients or in IPAH patients <40 years old, or when PAH occurs in patients with a personal or familial history of hereditary haemorrhagic telangiectasia, screening of the *ACVRL1* and *ENG* genes may be performed. If no mutations in the *BMPR2*, *ACVRL1* and *ENG* genes are identified, screening of rare mutations may be considered (*KCNK3*, *CAV1*, etc.).

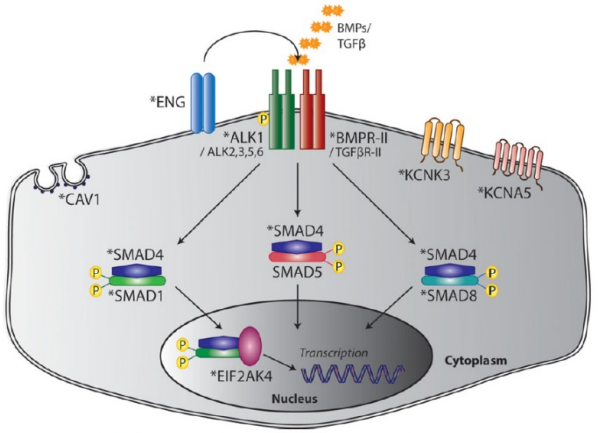

Figure 1. Schematic of canonical BMP signaling and additional pathways implicated in PAH pathogenesis by conventional and next-generation sequence analysis. Causal genes are indicated by the asterisks.

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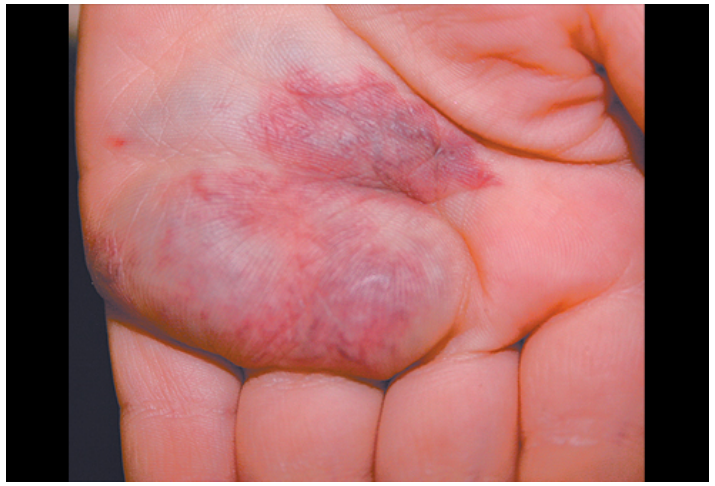

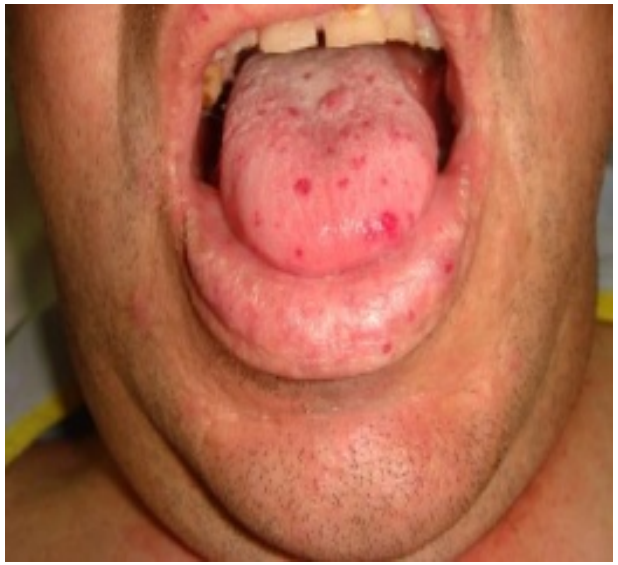

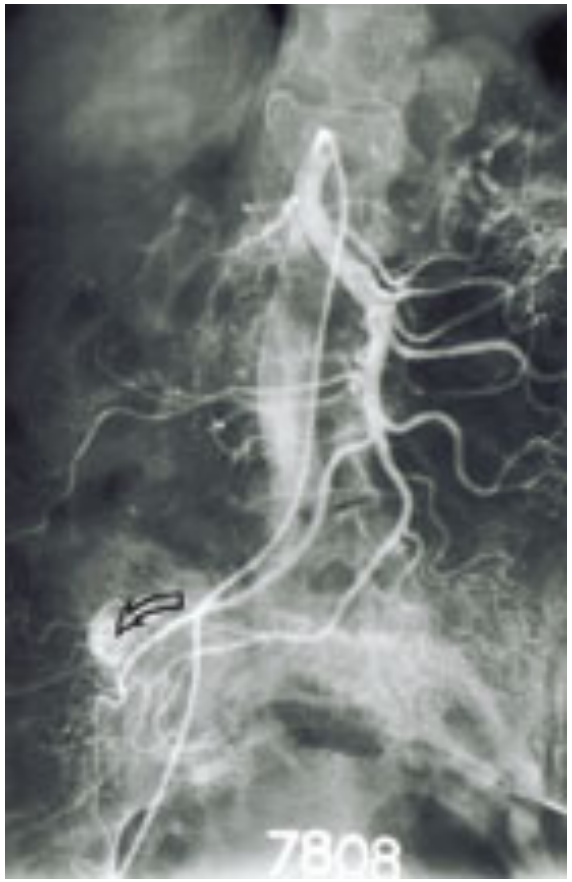
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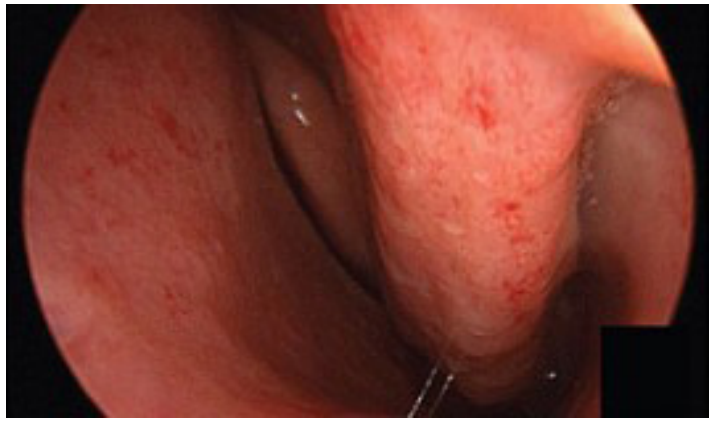

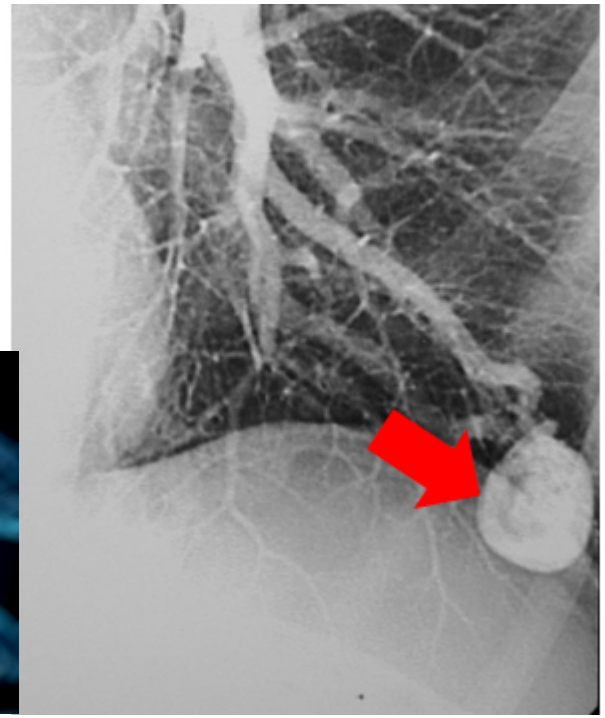

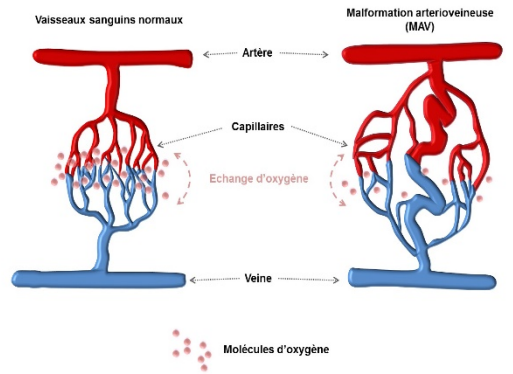
Vaisseaux sanguins normaux
Malformation arterioveineuse (MAV)
Artère
Capillaires
Echange d'oxygène
Veine
Molécules d'oxygène

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1. Pulmonary arterial hypertension

1.1 Idiopathic
1.2 Heritable
1.2.1 BMPR2 mutation
1.2.2 Other mutations
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1.4 Associated with:
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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

European Heart Journal 2016;37:67–119

Early detection and management of pulmonary arterial hypertension

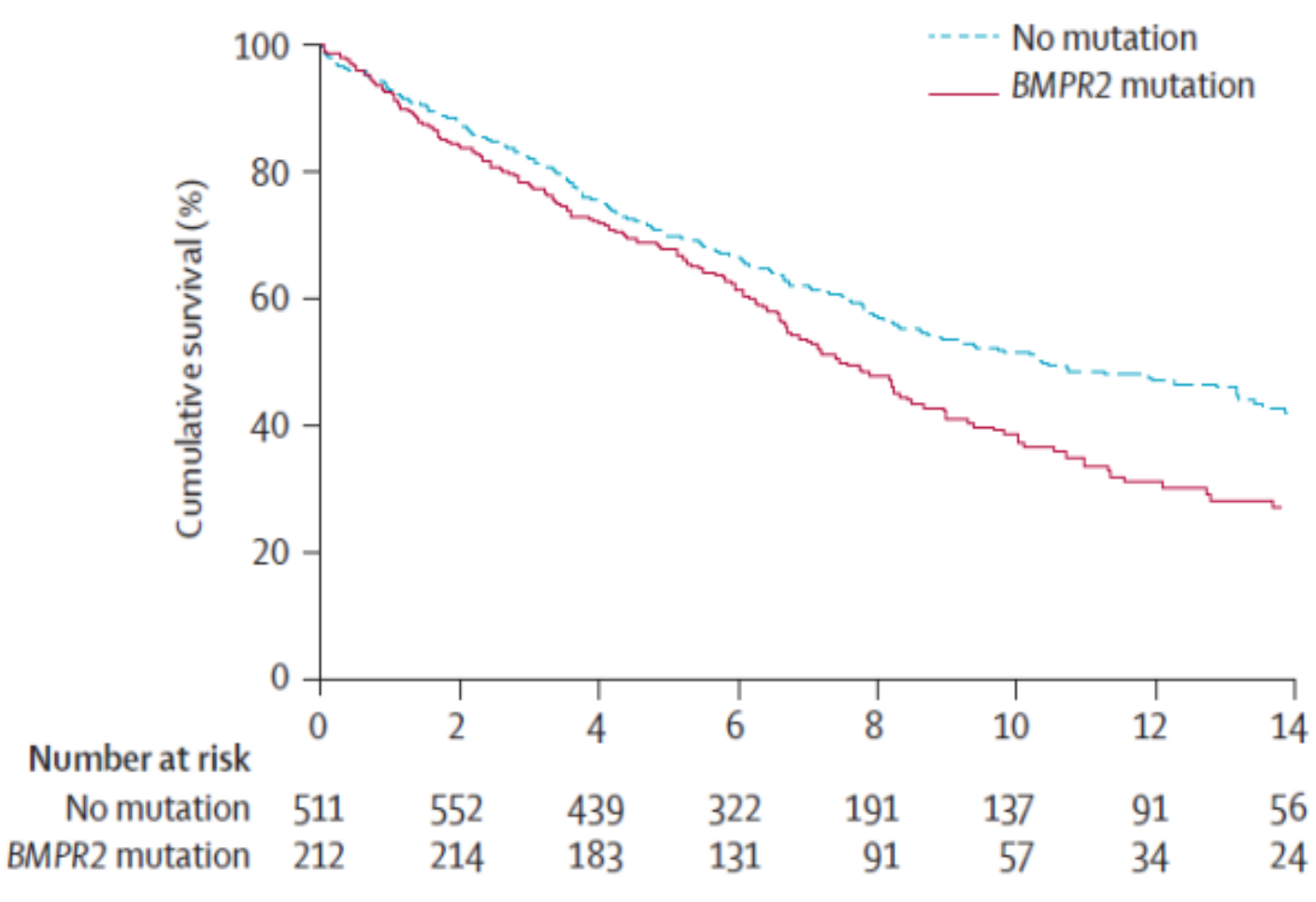
Marc Humbert*, J. Gerry Coghlan# and Dinesh Khanna¶

Screening is defined as the systematic testing of asymptomatic individuals for pre-clinical disease

Web Table X Recommendations for pulmonary arterial hypertension screening

Recommendations	Class [a]	Level [b]
Resting echocardiography is recommended as a screening test in asymptomatic patients with systemic sclerosis.	I	B
Resting echocardiography is recommended as a screening test in *BMPR2* mutation carriers or first-degree relatives of patients with HPAH and in patients with PoPH referred for liver transplantation.	I	C
A combined approach (including biomarkers, PFTs and echocardiography) should be considered to predict PH in systemic sclerosis.	IIa	B
Systemic sclerosis patients with a mean PAP ranging from 21 to 24 mmHg should be closely monitored, because of a higher risk of PAH.	IIa	B
Initial screening using the stepwise DETECT algorithm may be considered in adult systemic sclerosis patients with >3 years' disease duration and a DLCO <60% predicted.	IIb	B
Annual screening with echocardiography, PFTs and biomarkers may be considered in patients with systemic sclerosis.	IIb	B
In individuals who test positive for PAH-causing mutations and first-degree relatives of HPAH cases may be considered to have an annual screening echocardiogram.	IIb	C
Exercise echocardiography is not recommended to predict PH in high risk population.	III	C

BMPR2 mutations and survival in pulmonary arterial hypertension: an individual participant data meta-analysis



Implications of all the available evidence

Patients with PAH with underlying *BMPR2* mutations are younger at diagnosis, have more severe disease, and have a worse prognosis than patients without *BMPR2* mutations.

Lancet Respir Med 2016;4:129–37

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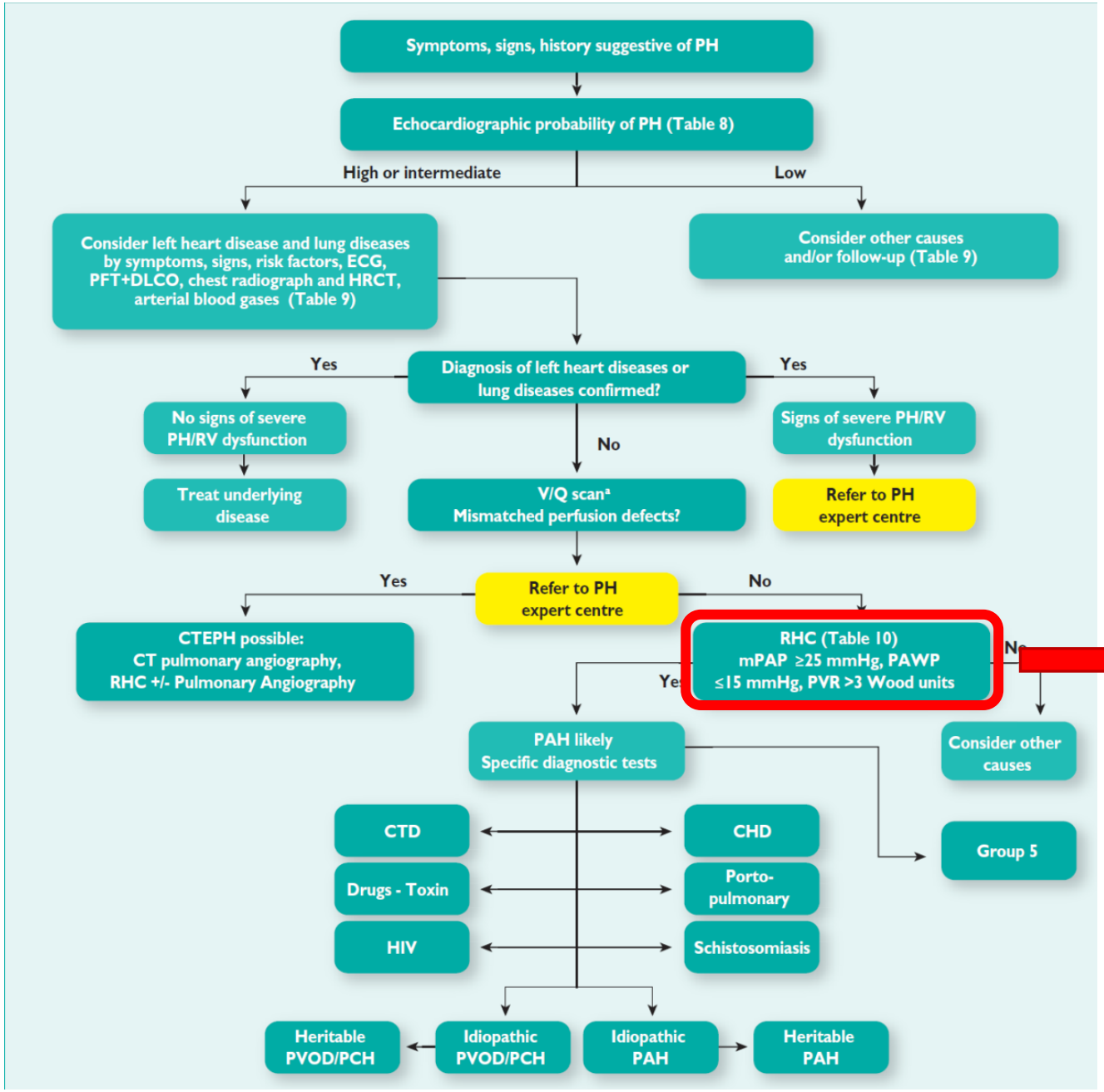
European Heart Journal 2016;37:67–119



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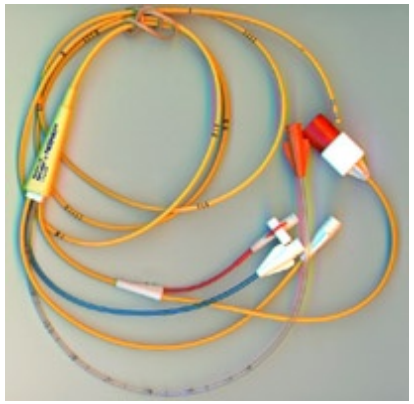
5.1.11 Right heart catheterization and vasoreactivity



RHC is required to confirm the diagnosis of PAH and CTEPH, to assess the severity of haemodynamic impairment and to undertake vasoreactivity testing of the pulmonary circulation in selected patients

Table 3 Haemodynamic definitions of pulmonary hypertension[a]

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]	

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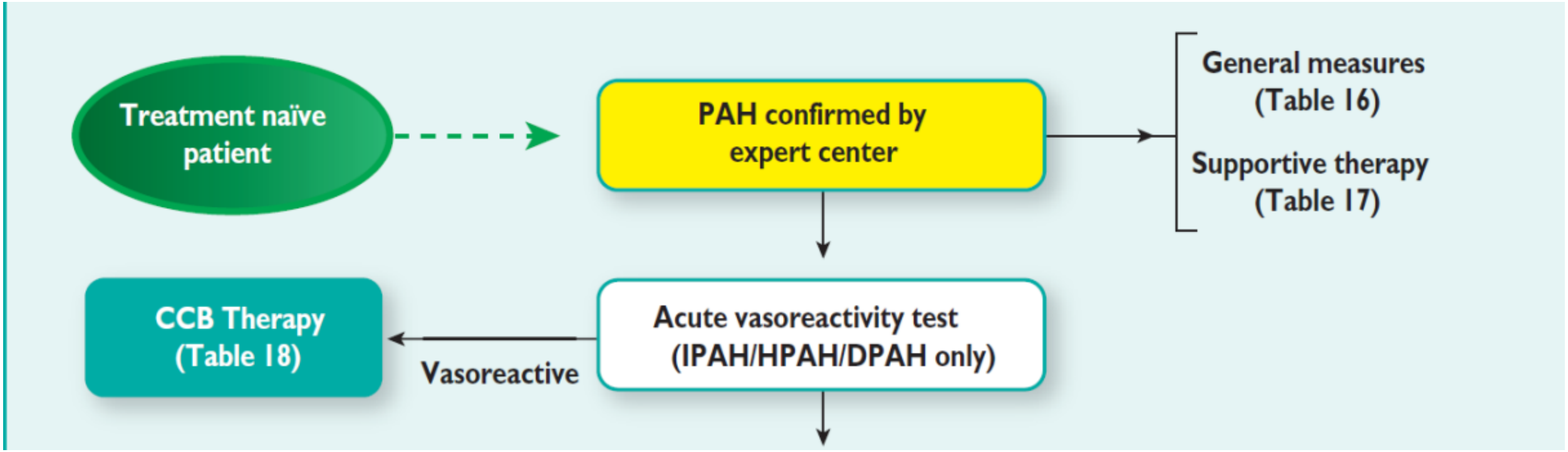

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Web Table IV Route of administration, half-life, dose ranges, increments, and duration of administration of the most commonly used agents for pulmonary vasoreactivity tests

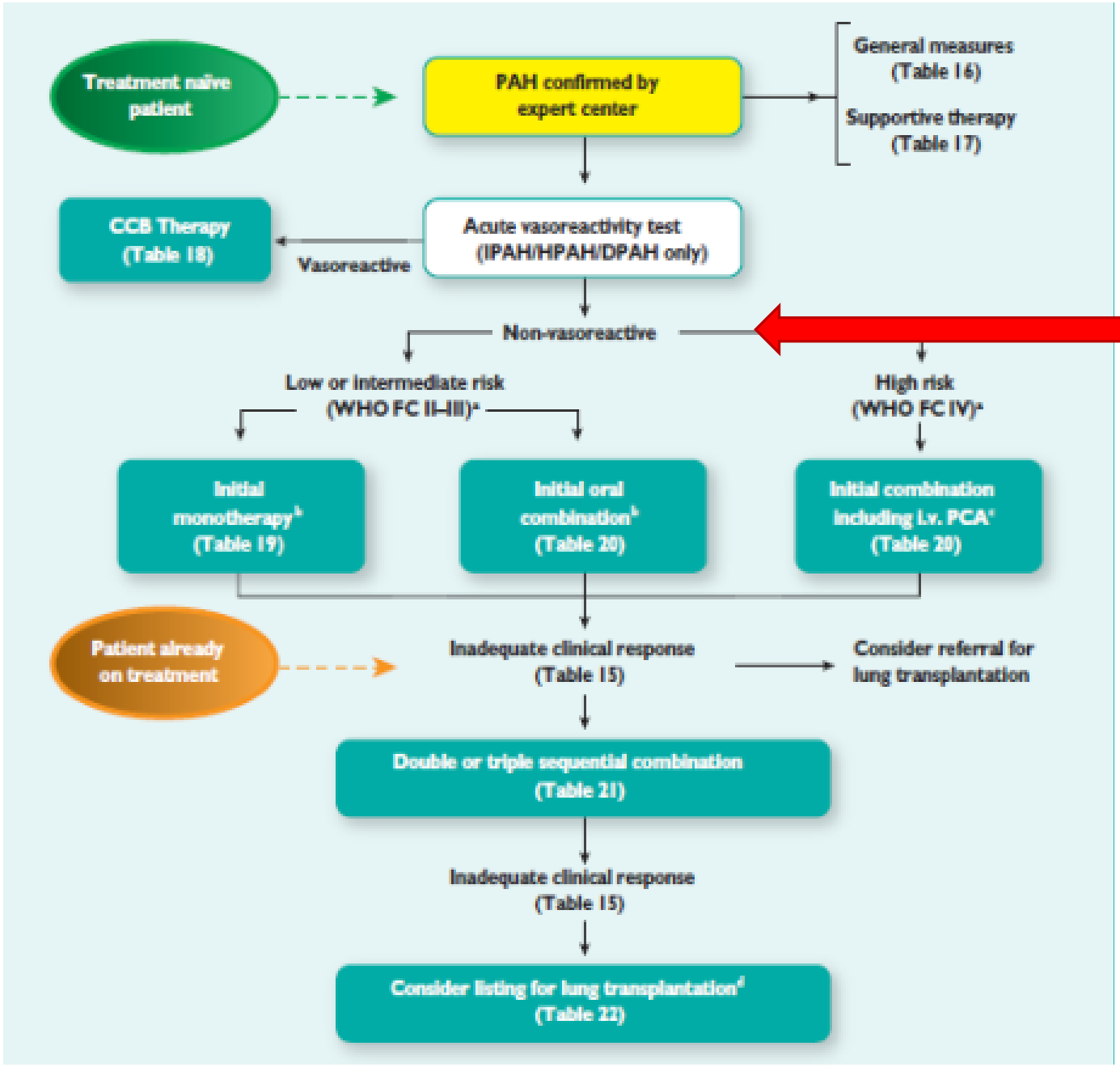
Drug	Route	Half-life	Dose range[d]	Increments[e]	Duration[f]	Class[a]	Level[b]	Ref[c]
Nitric oxide	Inh	15–30 sec	10–20 ppm	-	5 min[g]	I	C	4, 5
Epoprostenol	i.v.	3 min	2–12 ng/kg/min	2 ng/kg/min	10 min	I	C	4, 6
Adenosine	i.v.	5–10 sec	50–350 μg/kg/min	50 μg/kg/min	2 min	IIa	C	7
Iloprost	Inh	30 min	5–20 μg	-	15 min	IIb	C	8

"Responder" ↓ PAPm di almeno 10 mmHg (> 20%) fino a raggiungere PAPm ≤ 40 mmHg in assenza di una riduzione dell'indice cardiaco (↑ o ↔)

→ Solo i pazienti *responders* sono candidati alla terapia con calcio-antagonisti

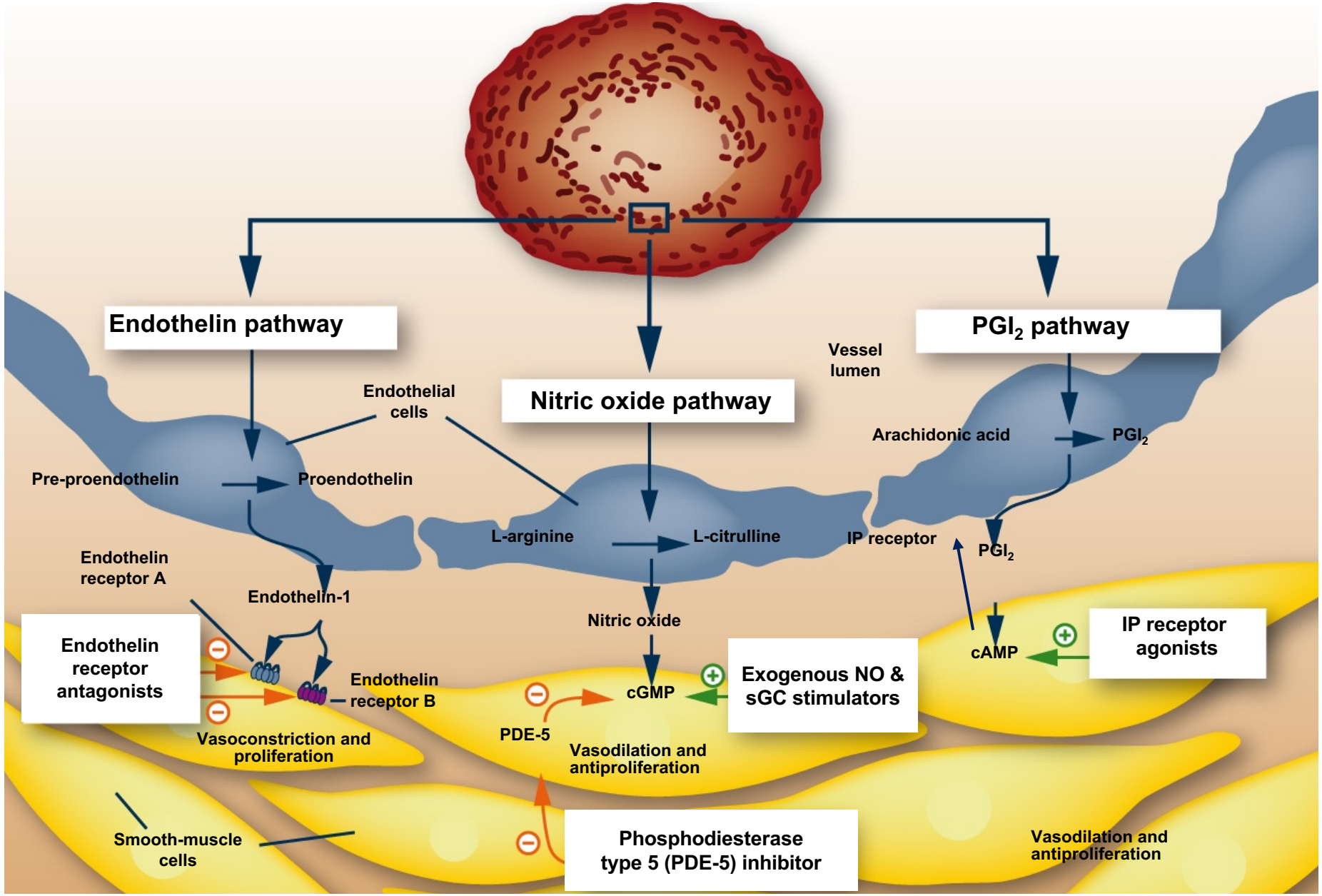
2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

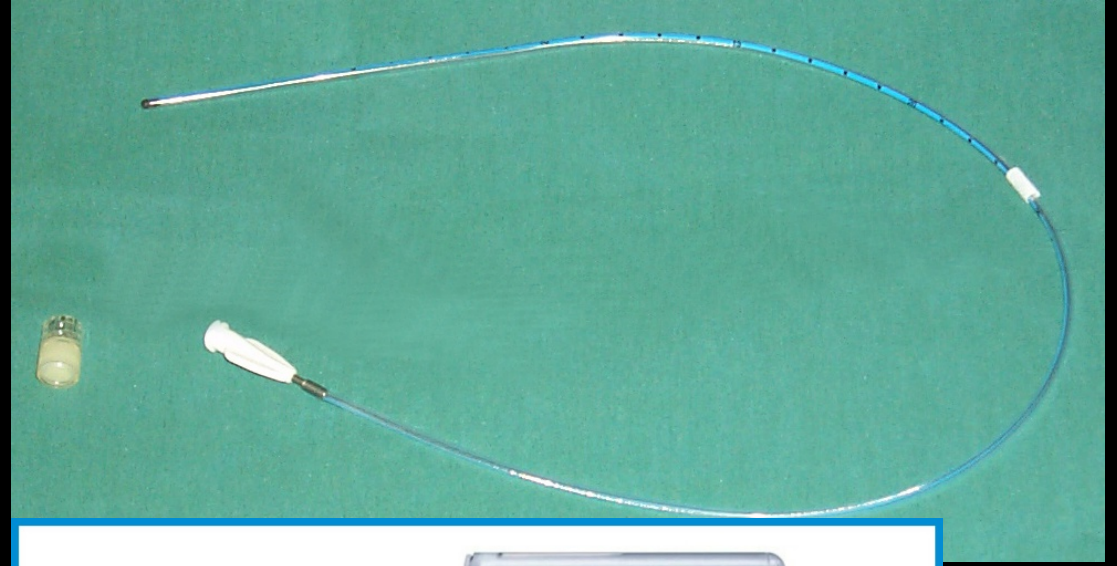
European Heart Journal 2016;37:67–119



ESC/ERS GUIDELINES

EUROPEAN SOCIETY OF CARDIOLOGY


Endothelin pathway
Nitric oxide pathway
PGI2 pathway
Vessel lumen
Endothelial cells
Pre-proendothelin
Proendothelin
Endothelin receptor A
Endothelin-1
L-arginine
L-citrulline
Nitric oxide
Arachidonic acid
PGI2
IP receptor
PGI2
Endothelin receptor antagonists
Endothelin receptor B
Vasoconstriction and proliferation
cGMP
PDE-5
Exogenous NO & sGC stimulators
Vasodilation and antiproliferation
cAMP
IP receptor agonists
Smooth-muscle cells
Phosphodiesterase type 5 (PDE-5) inhibitor
Vasodilation and antiproliferation




réservoir
Medtronic
1.0ml
2.0ml
3.0ml
Medtronic
1.8 ml
tubulure
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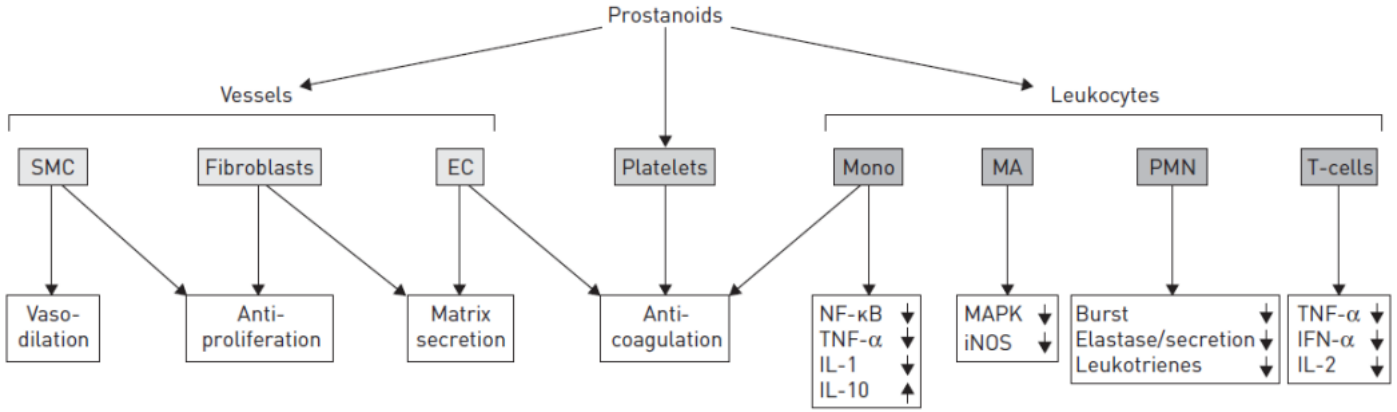
réservoir
Medtronic
MINIMED
PARADIGM
ACT


I-neb
50

Epoprostenol and pulmonary arterial hypertension: 20 years of clinical experience

REVIEW
PULMONARY ARTERIAL HYPERTENSION

Olivier Sitbon[1,2,3] and Anton Vonk Noordegraaf[4]



Conclusion

Epoprostenol has been an important treatment for PAH for two decades and its place in patient management continues to evolve. As the first disease-specific treatment for PAH, and the first therapy shown in an RCT to improve patient survival, epoprostenol transformed PAH management and opened the door to a new era of scientific and clinical study of PAH. With a wealth of clinical data supporting the efficacy and tolerability profile of epoprostenol, this agent remains a key treatment option in PAH, and the development of new, more convenient formulations of this therapy looks set to ensure a continuing role for epoprostenol within the management of patients with PAH.

Eur Respir Rev 2017; 26: 160055

Upfront triple combination therapy in pulmonary arterial hypertension: a pilot study

Olivier Sitbon[1,2,3], Xavier Jaïs[1,2,3], Laurent Savale[1,2,3], Vincent Cottin[4], Emmanuel Bergot[5], Elise Artaud Macari[1,2,3], Hélène Bouvaist[6], Claire Dauphin[7], François Picard[8], Sophie Bulifon[1,2,3], David Montani[1,2,3], Marc Humbert[1,2,3] and Gérald Simonneau[1,2,3]

ABSTRACT Patients with severe pulmonary arterial hypertension (PAH) in New York Heart Association (NYHA) functional class (FC) III/IV have a poor prognosis, despite survival benefits being demonstrated with intravenous epoprostenol. In this pilot study, the efficacy and safety of a triple combination therapy regimen in patients with severe PAH was investigated.

Data from newly diagnosed NYHA FC III/IV PAH patients (n=19) initiated on upfront triple combination therapy (intravenous epoprostenol, bosentan and sildenafil) were collected retrospectively from a prospective registry.

Survival analysis

All patients initiated with upfront triple combination therapy were still alive after a mean follow up of 41.2±13.4 months. Overall survival estimates were 100%, 100% and 100% at 1, 2 and 3 years, and respective transplant-free survival estimates were 94%, 94% and 94%. Expected survival calculated from the French equation was 75% (95% CI 68–82%), 60% (95% CI 50–70%) and 49% (95% CI 38–60%) at 1, 2 and 3 years, respectively.

2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

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6.3 Therapy

The treatment process of PAH patients cannot be considered as a mere prescription of drugs, but is characterised by a complex strategy that includes the initial evaluation of severity and the subsequent response to treatment.

European Heart Journal 2016;37:67–119

2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

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European Heart Journal 2016

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Table 19 Recommendations for efficacy of drug monotherapy for pulmonary arterial hypertension (group 1) according to World Health Organization functional class. The sequence is by pharmacological group, by rating and by alphabetical order

Measure/treatment			Class[a]-Level[b]						Ref.[c]
			WHO-FC II		WHO-FC III		WHO-FC IV		
Calcium channel blockers			I	C[d]	I	C[d]	-	-	84,85
Endothelin receptor antagonists	Ambrisentan		I	A	I	A	IIb	C	194
	Bosentan		I	A	I	A	IIb	C	196–200
	Macitentan[e]		I	B	I	B	IIb	C	201
Phosphodiesterase type 5 inhibitors	Sildenafil		I	A	I	A	IIb	C	205–208
	Tadalafil		I	B	I	B	IIb	C	211
	Vardenafil[g]		IIb	B	IIb	B	IIb	C	212
Guanylate cyclase stimulators	Riociguat		I	B	I	B	IIb	C	214
Prostacyclin analogues	Epoprostenol	Intravenous[e]	-	-	I	A	I	A	220–222
	Iloprost	Inhaled	-	-	I	B	IIb	C	229–231
		Intravenous[g]	-	-	IIa	C	IIb	C	232
	Treprostinil	Subcutaneous	-	-	I	B	IIb	C	233
		Inhaled[g]	-	-	I	B	IIb	C	237
		Intravenous[f]	-	-	IIa	C	IIb	C	234
		Oral[g]	-	-	IIb	B	-	-	238–240
	Beraprost[g]		-	-	IIb	B	-	-	218
IP receptor agonists	Selexipag (oral)[g]		I	B	I	B	-	-	241,248

Table 21 Recommendations for efficacy of sequential drug combination therapy for pulmonary arterial hypertension (group 1) according to World Health Organization functional class. Sequence is by rating and by alphabetical order

Measure/treatment	Class[a]-Level[b]						Ref.[c]
	WHO-FC II		WHO-FC III		WHO-FC IV		
Macitentan added to sildenafil[d]	I	B	I	B	IIa	C	201
Riociguat added to bosentan	I	B	I	B	IIa	C	214
Selexipag[e]	I	B	I	B	IIa	C	241, 248
	-	-	I	B	IIa	B	209
	IIa	B	IIa	B	IIa	C	237
	IIb	B	IIb	B	IIb	C	230, 231
	IIa	C	IIa	C	IIa	C	211
	IIb	C	IIb	C	IIb	C	249
	-	-	IIb	C	IIb	C	250
	IIb	C	IIb	C	IIb	C	251, 252
	IIb	C	IIb	C	IIb	C	252
	IIb	C	IIb	C	IIb	C	-
	IIb	C	IIb	C	IIb	C	-
	III	B	III	B	III	B	215

Table 20 Recommendations for efficacy of initial drug combination therapy for pulmonary arterial hypertension (group 1) according to World Health Organization functional class. Sequence is by rating

Measure/treatment	Class[a]-Level[b]						Ref.[c]
	WHO-FC I		WHO-FC III		WHO-FC IV		
Ambrisentan + tadalafil[d]	I	B	I	B	IIb	C	247
Other ERA + PDE-5i	IIa	C	IIa	C	IIb	C	-
Bosentan + sildenafil + i.v. epoprostenol	-	-	IIa	C	IIa	C	246
Bosentan + i.v. epoprostenol	-	-	IIa	C	IIa	C	198, 245
Other ERA or PDE-5i + s.c. treprostinil			IIb	C	IIb	C	-
Other ERA or PDE-5i + other i.v. prostacyclin analogues			IIb	C	IIb	C	-

Table 17 Recommendations for evaluation of severity and follow-up

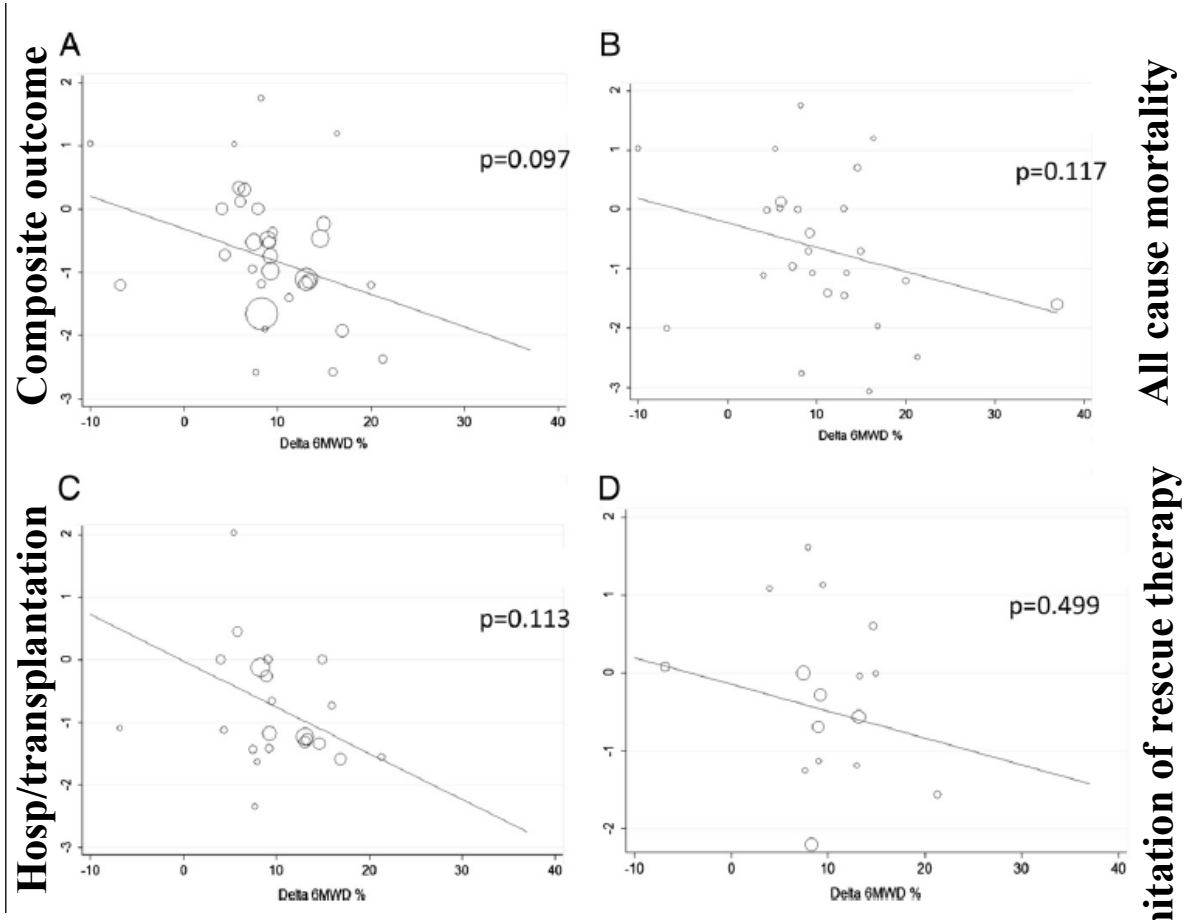
Statement	Class[a]	Level[b]
It is recommended to evaluate the severity of PAH	I	C
It is recommended to perform regular follow-up every 3–6 months (*Table 16*) also in stable patients with PAH	I	C
A goal-oriented treatment strategy is recommended in patients with PAH	I	C

A goal-oriented treatment strategy is recommended in patients with PAH

European Heart Journal 2009;30:2493-2537

Do Changes of 6-Minute Walk Distance Predict Clinical Events in Patients With Pulmonary Arterial Hypertension?

A Meta-Analysis of 22 Randomized Trials



Savarese G. JACC 2012;60:1192-201

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

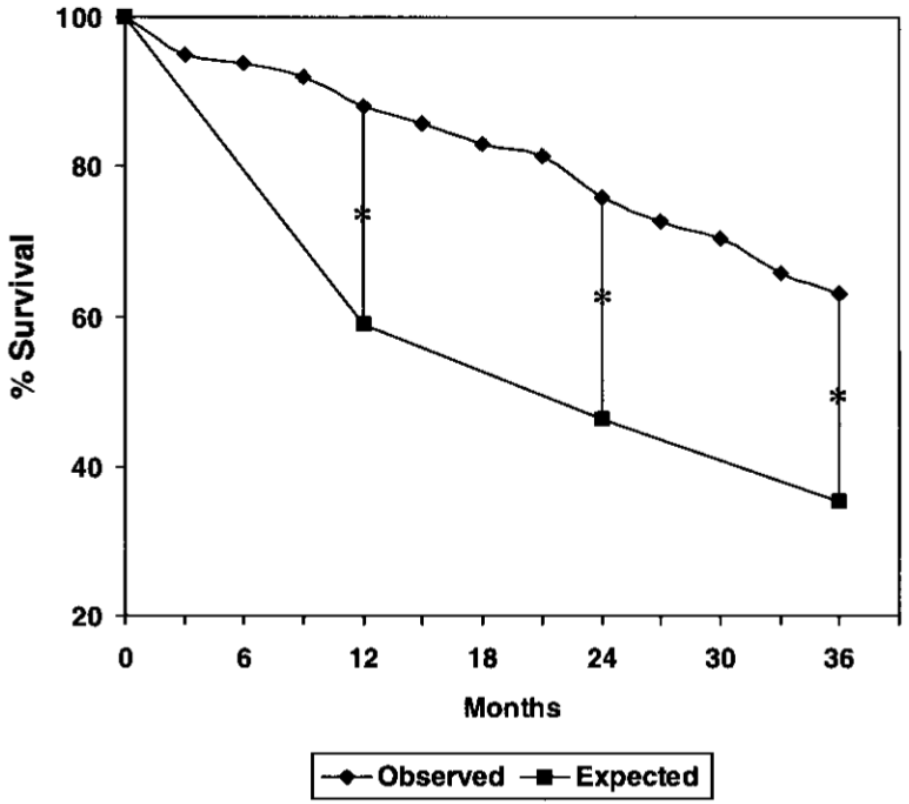
American Heart Association

Survival in Primary Pulmonary Hypertension: The Impact of Epoprostenol Therapy

Vallerie V. McLaughlin, Alicia Shillington and Stuart Rich

Circulation. 2002;106:1477-1482; originally published online August 26, 2002;
doi: 10.1161/01.CIR.0000029100.82385.58
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539



Treat-to-target approach in pulmonary arterial hypertension: a consensus-based proposal

Eur Respir Rev 2012;21(125):259-262

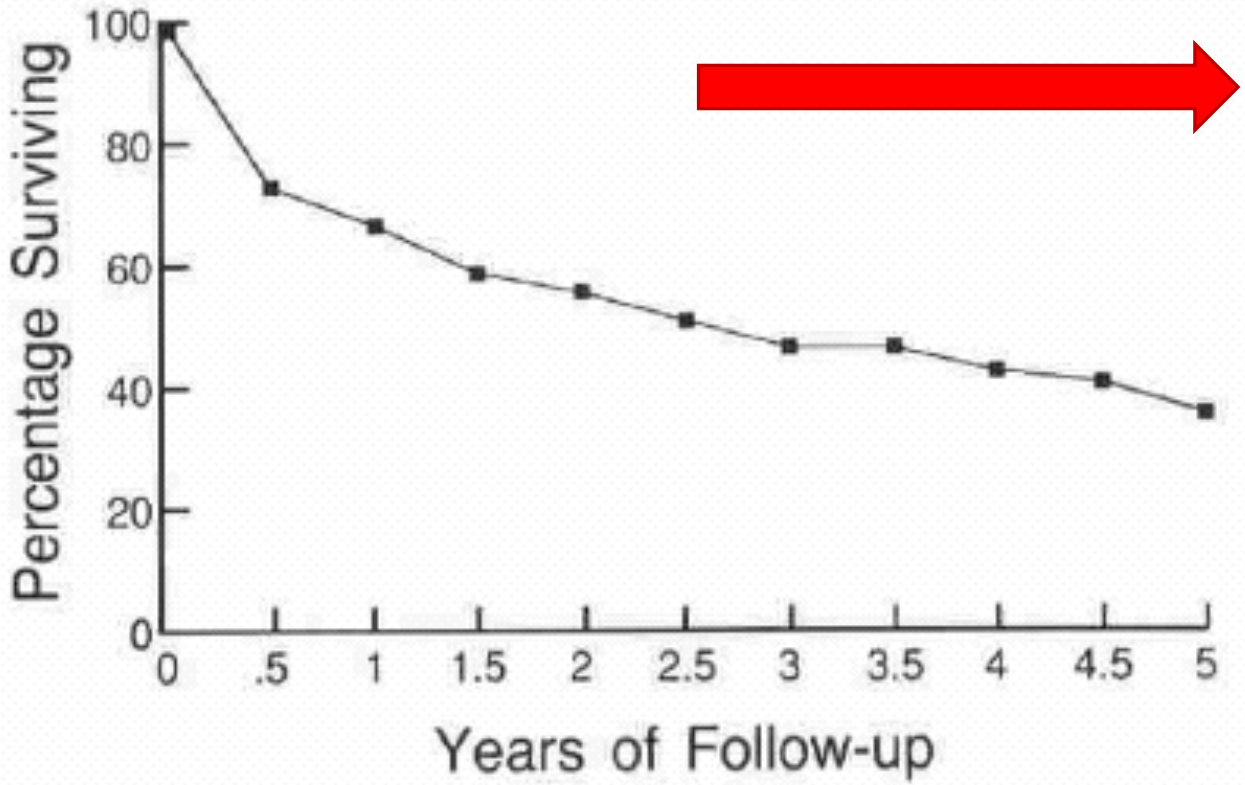
Table 1 Variables Used in Clinical Practice to Determine Response to Therapy and Prognosis in Patients With PAH

Functional class	
	I or II
Echocardiography/CMR	
	Normal/near-normal RV size and function
Hemodynamics	
	Normalization of RV function (RAP <8 mm Hg and CI >2.5 to 3.0 l/min/m^2)
6-min walk distance	
	>380 to 440 m; may not be aggressive enough in young individuals
Cardiopulmonary exercise testing	
	Peak VO_2 >15 ml/min/kg and $EqCO_2$ <45 l/min/l/min
B-type natriuretic peptide level	
	Normal

JACC 2013;62:D73-81

Survival in Patients with Primary Pulmonary Hypertension

Results from a National Prospective Registry



a 1 anno sopravvivenza del 68%

a 3 anni sopravvivenza del 48%

a 5 anni sopravvivenza del 34%

Annals of Internal Medicine;1991:115

Predicting Survival in Pulmonary Arterial Hypertension

Insights From the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL)

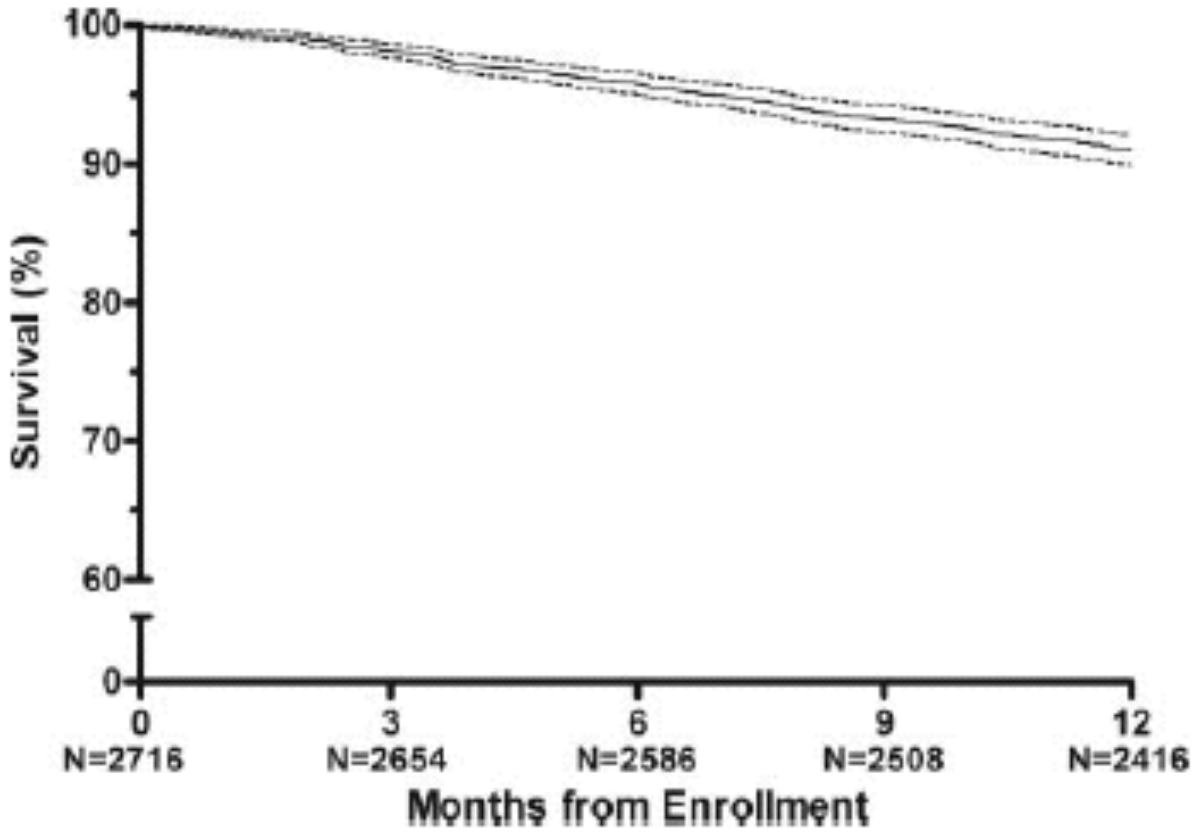
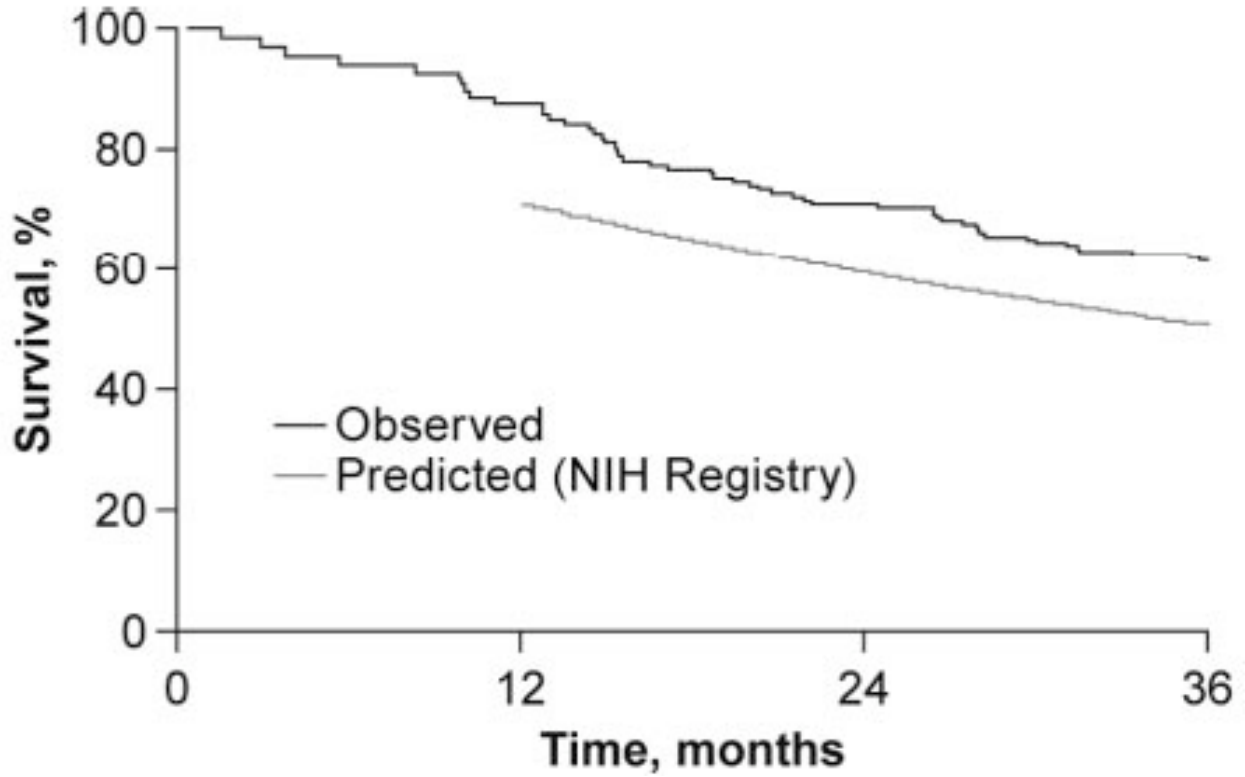


Figure 1. Kaplan-Meier estimates of 1-year survival from time of enrollment. Dashed lines represent the 95% CI for the Kaplan-Meier estimates.

Circulation 2010;122:164-172

Survival in Patients With Idiopathic, Familial, and Anorexigen-Associated Pulmonary Arterial Hypertension in the Modern Management Era



Humbert M. Circulation 2010;122:156-163

The NEW ENGLAND JOURNAL of MEDICINE

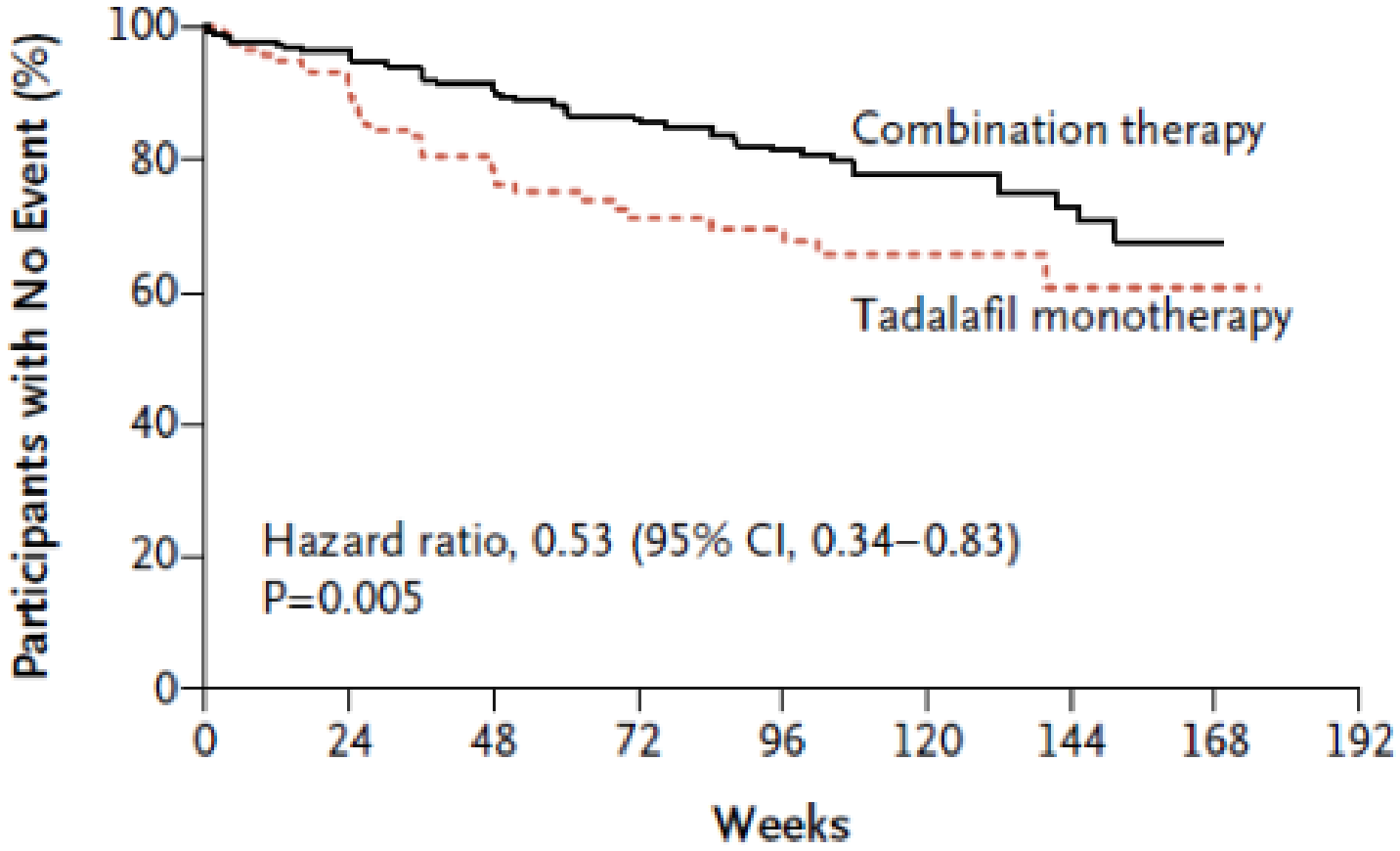
ORIGINAL ARTICLE

Initial Use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension

N. Galiè, J.A. Barberà, A.E. Frost, H.-A. Ghofrani, M.M. Hoeper, V.V. McLaughlin, A.J. Peacock, G. Simonneau, J.-L. Vachiery, E. Grünig, R.J. Oudiz, A. Vonk-Noordegraaf, R.J. White, C. Blair, H. Gillies, K.L. Miller, J.H.N. Harris, J. Langley, and L.J. Rubin, for the AMBITION Investigators*

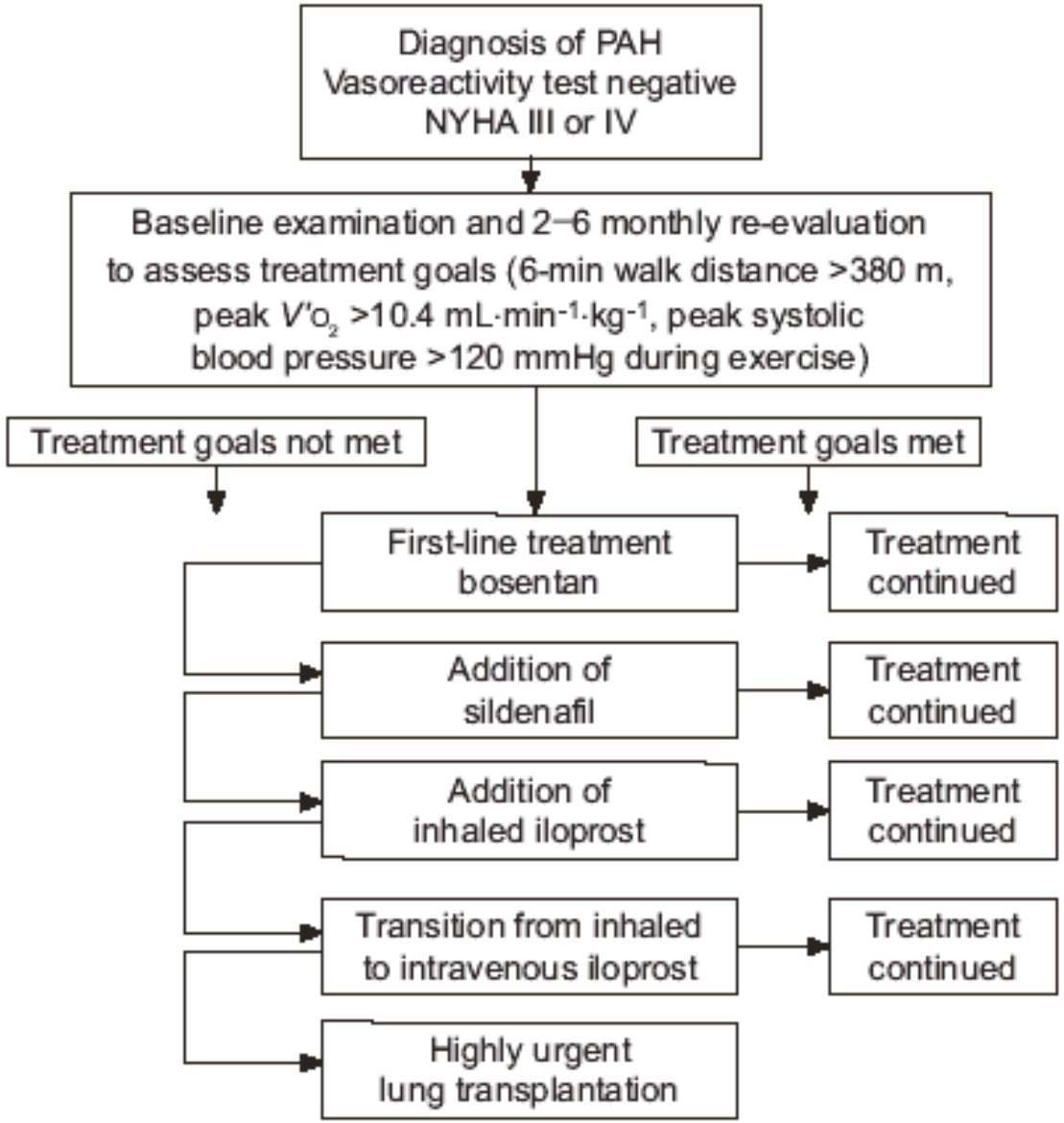
N Engl J Med 2015;373:834-44

C Combination Therapy vs. Tadalafil Monotherapy



No. at Risk

Combination therapy	253	229	186	145	106	71	36	4
Tadalafil monotherapy	121	105	74	51	38	26	11	2

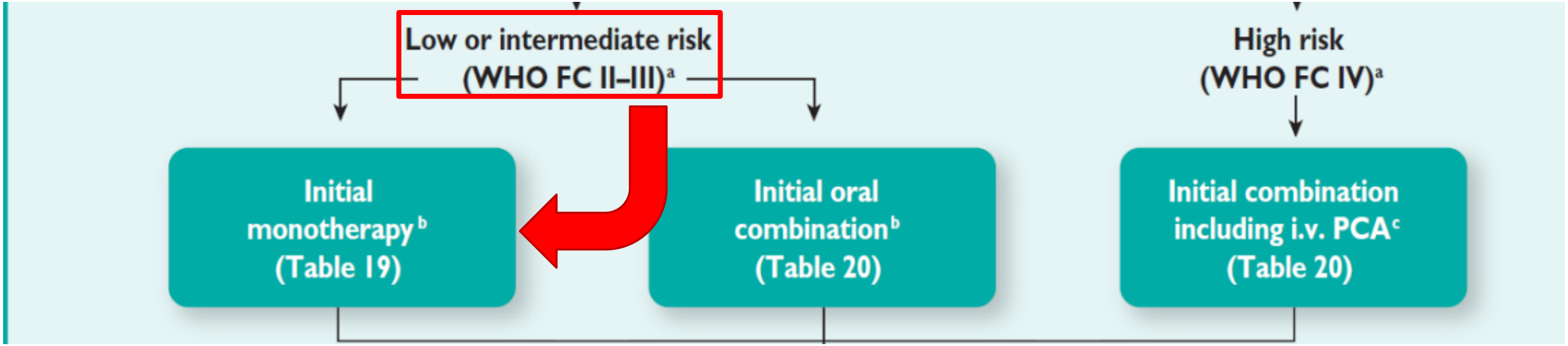


European Heart Journal 2009;30:2493-2537

2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

ESC/ERS GUIDELINES

6.3 Therapy



European Heart Journal 2016;37:67–119

2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

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Table 13 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%

European Heart Journal 2016;37:67–119

Most of the proposed variables and cut-off values are based on expert opinion

They may provide prognostic information and may be used to guide therapeutic decisions, but application to individual patients must be done carefully

One must also note that most of these variables have been validated mostly for IPAH and the cut-off levels used above may not necessarily apply to other forms of PAH

Furthermore, the use of approved therapies and their influence on the variables should be considered in the evaluation of the risk

European Heart Journal 2016;37:67–119

2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

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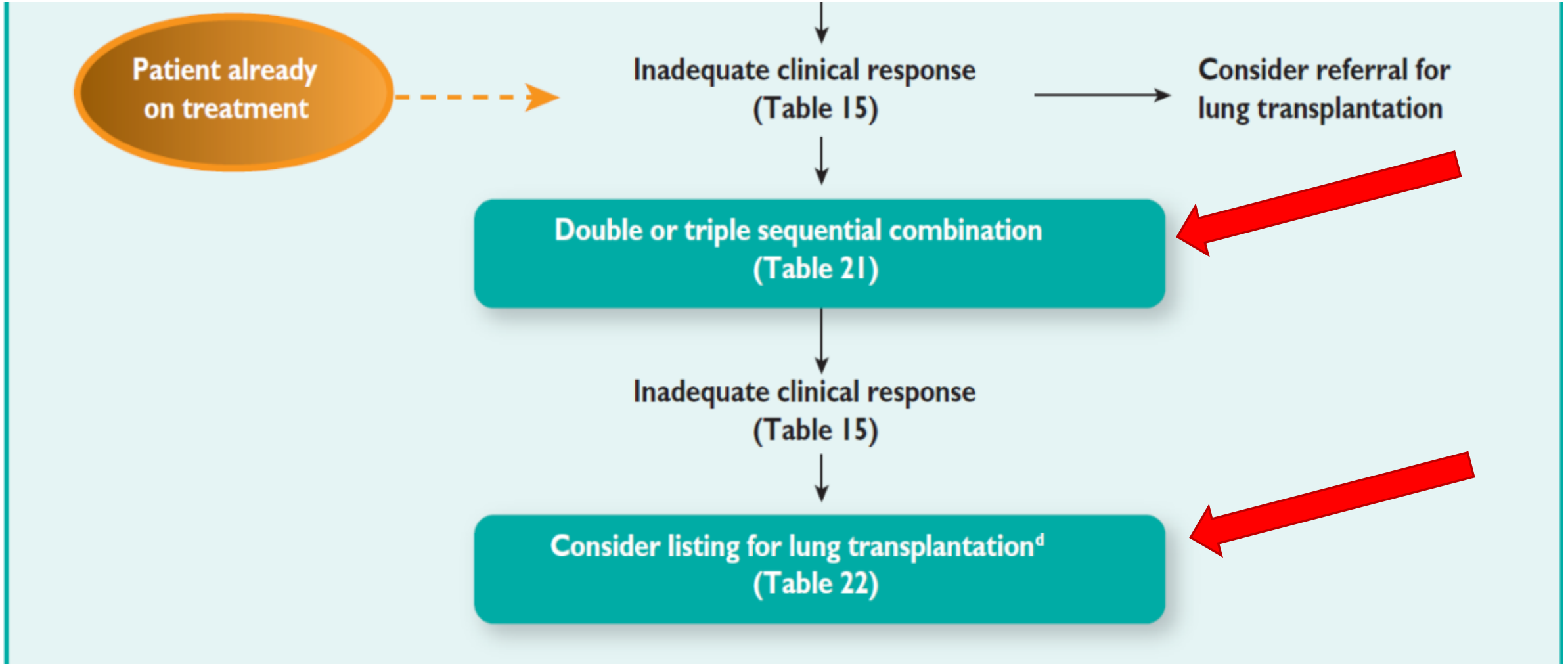

European Heart Journal 2016;37:67–119

Guidelines for the diagnosis and treatment of pulmonary hypertension

ESC/ERS GUIDELINES

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Evaluation of severity

The clinical assessment of the patient has a pivotal role in the choice of the initial treatment, the evaluation of the response to therapy, and the possible escalation of therapy if needed.

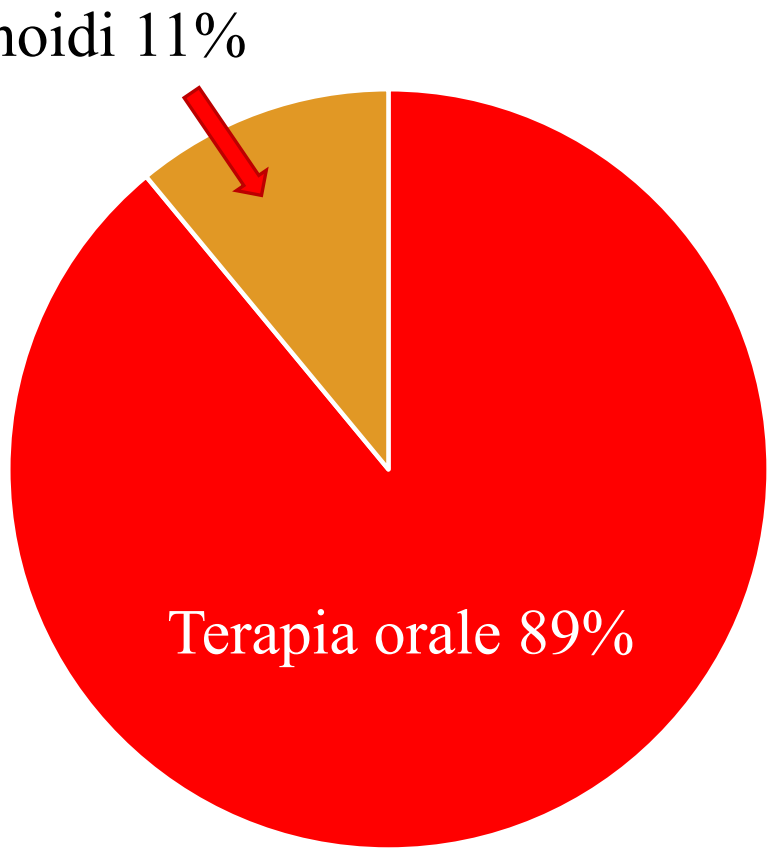
6.2.4 Comprehensive prognostic evaluation and risk assessment

Regular assessment of patients with PAH in expert PH centres is strongly recommended.

European Heart Journal 2016;37:67–119

Accredo Database

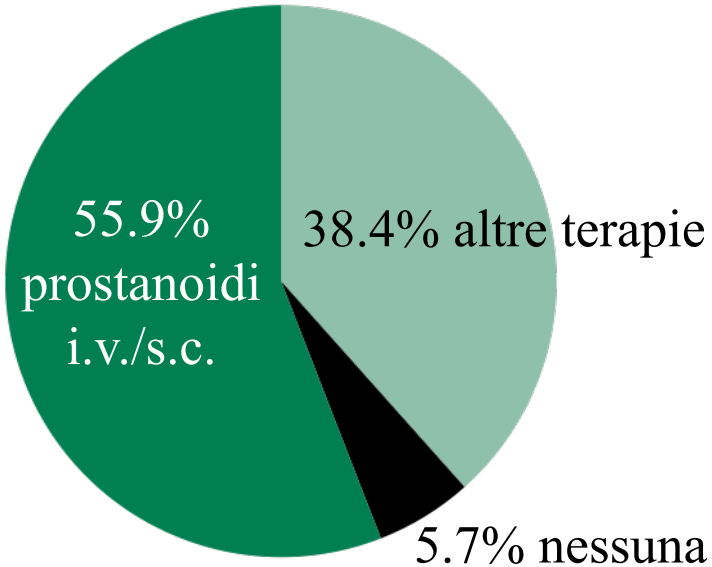
dati raccolti da un provider di farmaci in USA, relativi a 821 pz PAH che iniziavano bosentan



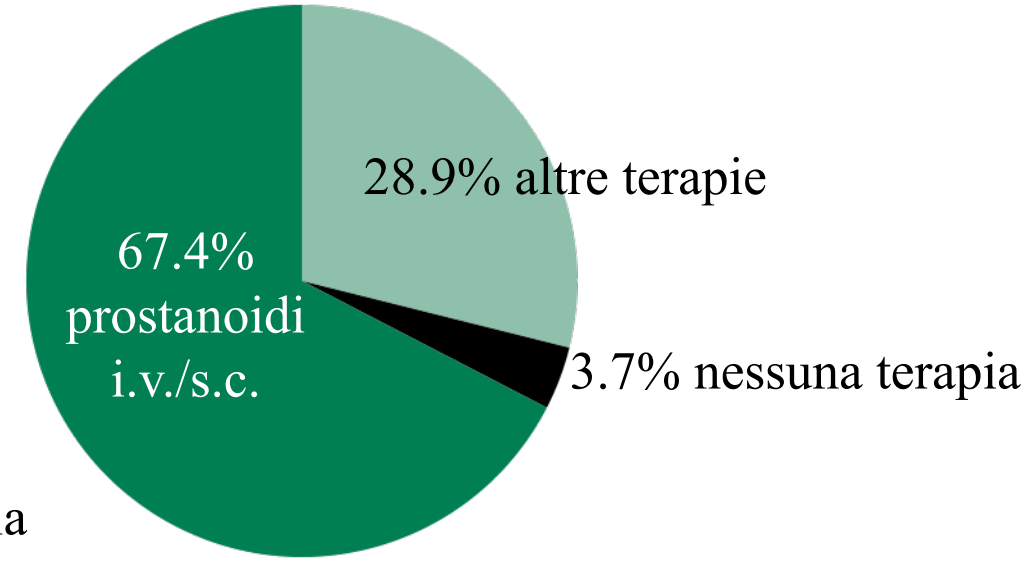
decessi

Trattamento al momento della morte correlata a PAH

Tutti i pazienti (*n* = 487)



Pazienti FC IV* (*n* = 135)



- Quasi la metà dei pazienti (44.1%) non stava ricevendo prostanoidi
- Quasi un terzo dei pazienti (32.6%) FC IV* non stava ricevendo prostanoidi

Tra i pazienti valutati < 6 mesi prima della morte (*n* = 308), 135 (43.8%) erano in FC IV

Farber et al. J Heart Lung Transplant 2013

2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

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Table 14 Suggested assessment and timing for the follow-up of patients with pulmonary arterial hypertension

	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]

European Heart Journal 2016;37:67–119

2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

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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
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European Heart Journal 2016;37:67–119

Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging

European Heart Journal – Cardiovascular Imaging 2015;16: 233–271

III. The Left and Right Atria

GUIDELINES AND STANDARDS

Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging

III. THE LEFT AND RIGHT ATRIA

J Am Soc Echocardiogr 2015;28:1–39

10. Right Atrial measurements

As with the left atrium, RA volumes are likely to be more robust and accurate for determination of RA size compared with linear dimensions.

Recommendations. The recommended parameter to assess RA size is RA volume, calculated using single-plane area-length or disk summation techniques in a dedicated apical four-chamber view.

Volume.
2D volumetric measurements are usually based on tracings of the blood-tissue interface on the apical four-chamber view. At the tricuspid valve level, the contour is closed by connecting the two opposite sections of the tricuspid ring with a straight line. Volumes can be computed by using either the single plane area-length:

$$\frac{8}{3\pi}\left[\frac{(A)^2}{L}\right]$$

or the disks summation technique. 3D data sets are usually obtained from the apical approach using a full-volume acquisition

2D view

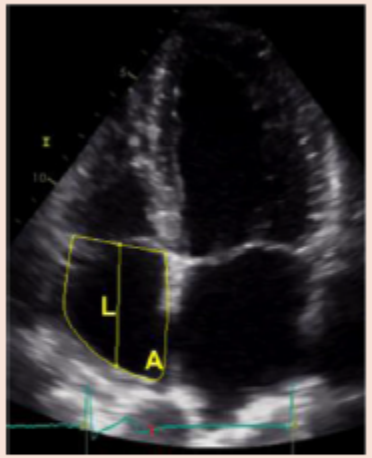


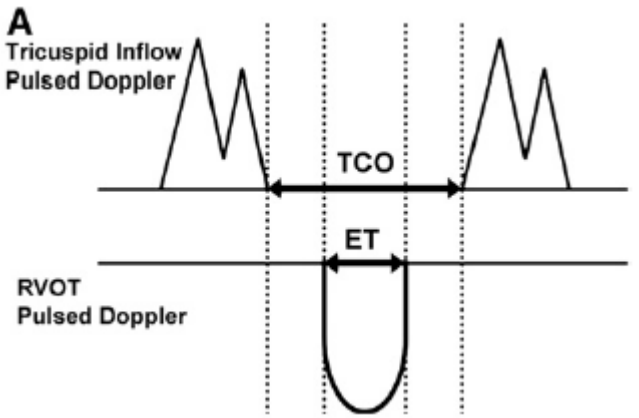
Table 13 Normal RA size obtained from 2D echocardiographic studies

	Women	Men
RA minor axis dimension (cm/m^2)	1.9 ± 0.3	1.9 ± 0.3
RA major axis dimension (cm/m^2)	2.5 ± 0.3	2.4 ± 0.3
2D echocardiographic RA volume (mL/m^2)	21 ± 6	25 ± 7

- More representative of actual RA size than linear dimensions

J Am Soc Echocardiogr 2015;28:1-39

Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging



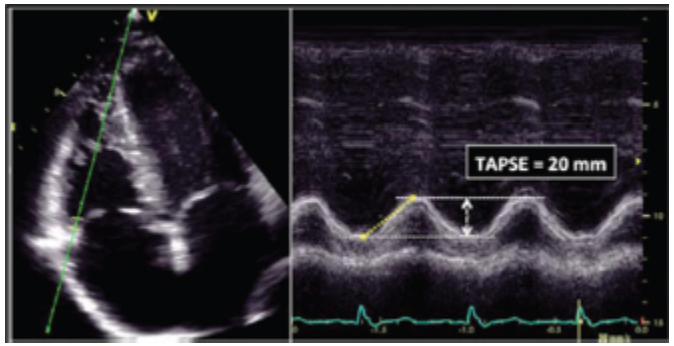
II. The Right Ventricle

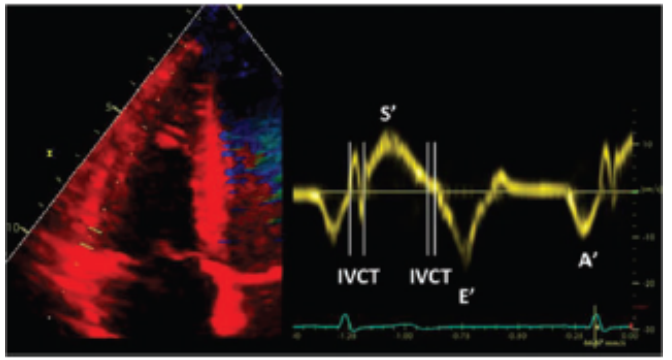
8. RV Systolic Function

RV systolic function has been evaluated using multiple parameters (*Table 9*), including RIMP, TAPSE, 2D FAC, 3DEEF, S′, and longitudinal strain and strain rate by DTI and 2D STE.[25]

Recommendations

Two-dimensional STE-derived strain, particularly of the RV free wall, appears to be reproducible and feasible for clinical use. Because of the need for additional normative data from large studies involving multi-vendor equipment, no definite reference ranges are currently recommended for either global or regional RV strain or strain rate.





European Heart Journal – Cardiovascular Imaging 2015;16: 233–271

2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

ESC/ERS GUIDELINES

Table 13 Risk assessment in pulmonary arterial hypertension

Determinants of prognosis[a] (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Imaging (echocardiography, CMR imaging)	RA area <18 cm² No pericardial effusion	RA area 18–26 cm² No or minimal, pericardial effusion	RA area >26 cm² Pericardial effusion
	No pericardial effusion TAPSE[b] >2.0 cm		Pericardial effusion TAPSE[b] <1.5 cm

6.2 Evaluation of severity

6.2.1 Clinical parameters, imaging and haemodynamics

As RV function is a key determinant of exercise capacity and outcome in patients with PH, echocardiography remains an important follow-up tool.

European Heart Journal 2016;37:67–119

6.2 Evaluation of severity

6.2.1 Clinical parameters, imaging and haemodynamics

A comprehensive echocardiographic assessment includes a description of chamber sizes, particularly of the RA and RV area, the magnitude of tricuspid regurgitation, the LV eccentricity index and RV contractility, which can be determined by several variables, including RV longitudinal systolic strain/strain rate and RV fractional area change, Tei index and tricuspid annular plane systolic excursion (TAPSE).[101–108]

How to detect disease progression in pulmonary arterial hypertension

J-L. Vachiéry, P. Yerly and S. Huez

European Journal of Echocardiography (2010) **11**, 516–522
doi:10.1093/ejechocard/jeq011

New echocardiographic prognostic factors for mortality in pulmonary arterial hypertension†

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REVIEW

Factors that prognosticate mortality in idiopathi pulmonary arterial hypertension: A systematic review of the literature☆

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Received 26 April 2010; accepted 9 August 2010

Doppler Echocardiographic Index for Assessment of Global Right Ventricular Function

Chuwa Tei, MD, Karl S. Dujardin,* MD, David O. Hodge, MS, Kent R. Bailey, PhD, Michael D. McGoon, MD, A. Jamil Tajik, MD, and James B. Seward, MD,
Rochester, Minnesota

Tricuspid Annular Displacement Predicts Survival in Pulmonary Hypertension

Paul R. Forfia, Micah R. Fisher, Stephen C. Mathai, Traci Housten-Harris, Anna R. Hemnes, Barry A. Borlaug, Elzbieta Chamera, Mary C. Corretti, Hunter C. Champion, Theodore P. Abraham, Reda E. Girgis, and Paul M. Hassoun

Eur Respir J 2005; 26: 858–863
DOI: 10.1183/09031936.05.00075305

Goal-oriented treatment and combination therapy for pulmonary arterial hypertension

M.M. Hoeper, I. Markevych, E. Spiekerkoetter, T. Welte and J. Niedermeyer

Pulmonary vascular disease

openheart

Prognostic value of TAPSE after therapy optimisation in patients with pulmonary arterial hypertension is independent of the haemodynamic effects of therapy

Stefano Ghio,[1] Silvia Pica,[1] Catherine Klersy,[2] Eleonora Guzzafame,[1] Laura Scelsi,[1] Claudia Raineri,[1] Annalisa Turco,[1] Sandra Schirinzi,[1] Luigi Oltrona Visconti[1]

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Primary Pulmonary Hypertension

Echocardiographic Predictors of Adverse Outcomes in Primary Pulmonary Hypertension

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Chapel Hill, Research Triangle Park and Durham, North Carolina; Seattle, Washington; Portland, Maine; St. Louis, Missouri; Providence, Rhode Island; and New Orleans, Louisana

2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

ESC/ERS GUIDELINES

6.2 Evaluation of severity

6.2.1 Clinical parameters, imaging and haemodynamics

a marked increase (>30 mmHg) of PAPs during exercise reflects better RV function and is associated with a better long-term outcome than a modest or no increase.[111] This so-called contractile reserve has recently been shown to be an independent prognostic marker in patients with severe PH.[111]

European Heart Journal 2016;37:67–119

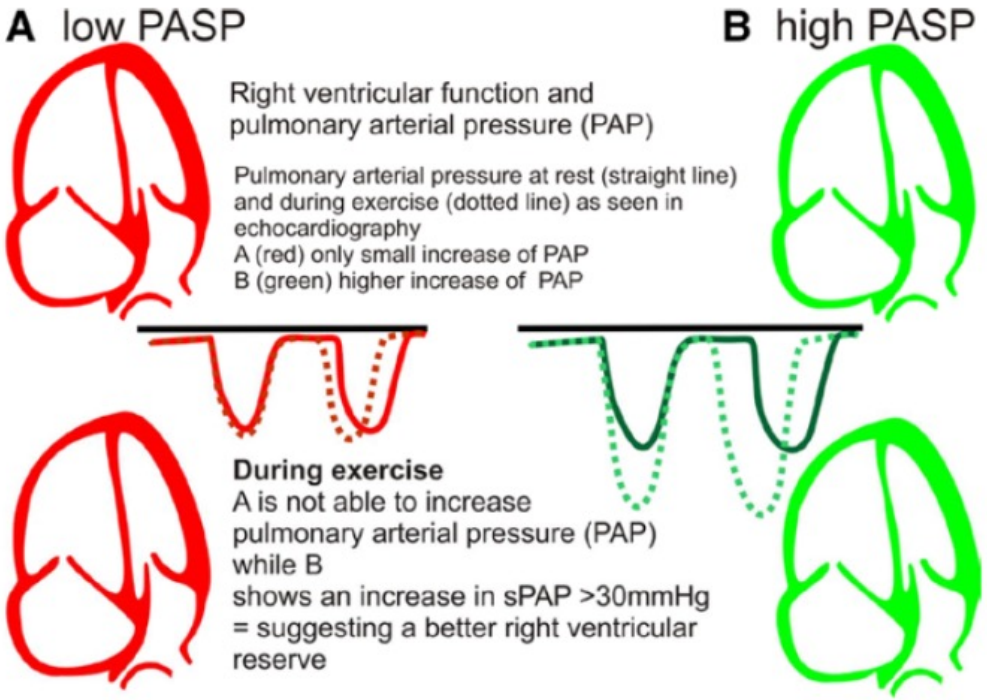
Assessment and Prognostic Relevance of Right Ventricular Contractile Reserve in Patients With Severe Pulmonary Hypertension

Ekkehard Grünig, MD; Henning Tiede, MD, MSc; Esi Otuwa Enyimayew; Nicola Ehlken, BSc; Hans-Jürgen Seyfarth, MD; Eduardo Bossone, MD; Antonello D'Andrea, MD; Robert Naeije, MD; Horst Olschewski, MD; Silvia Ulrich, MD; Christian Nagel, MD; Michael Halank, MD; Christine Fischer, PhD

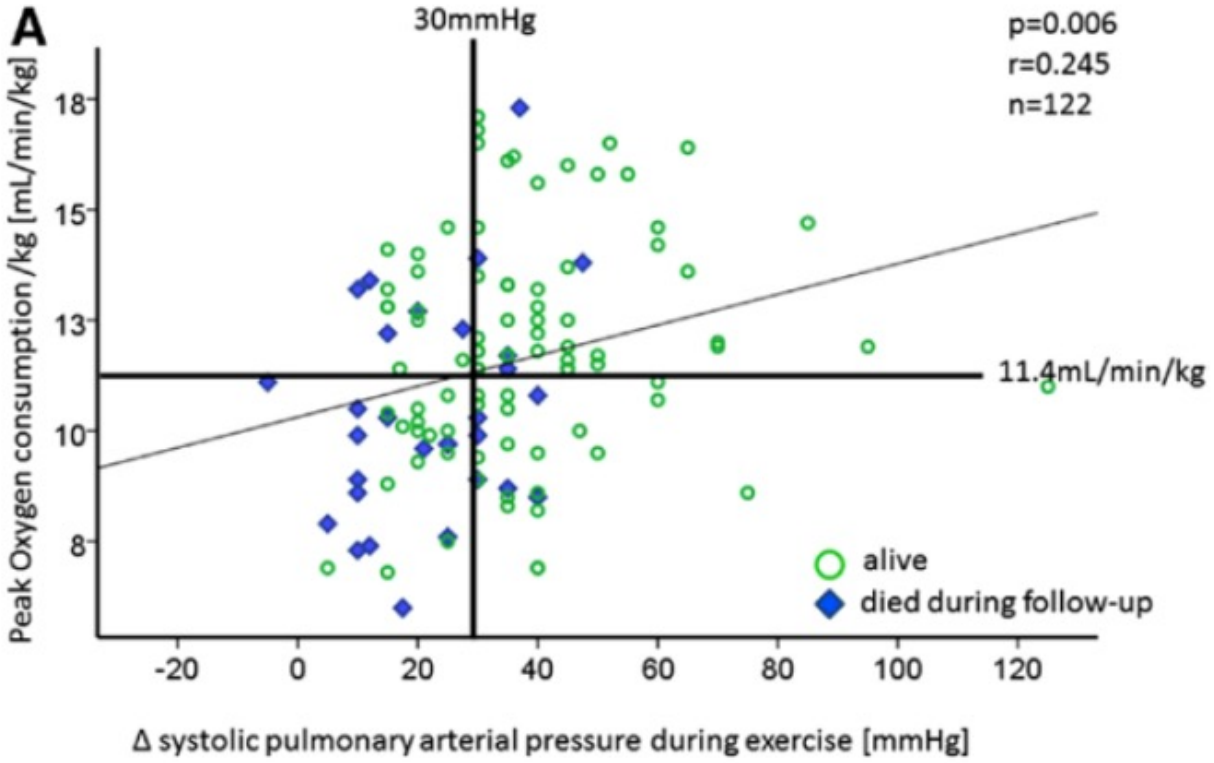
Circulation 2013;128:2005–2015

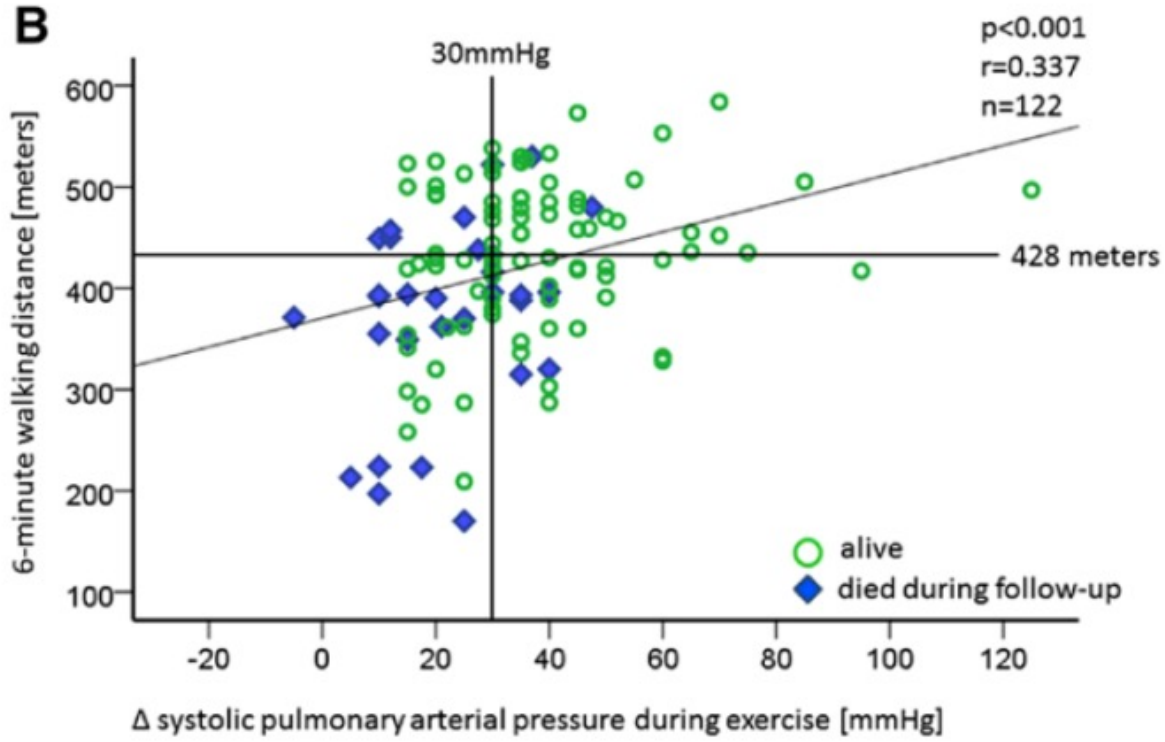
Clinical Implications and Conclusions

Assessment of PASP increase during exercise by stress echocardiography at low workloads may reflect RV contractile reserve and can contribute to follow-up assessment and risk stratification of PAH/CTEPH patients. The combination of stress Doppler echocardiography and cardiopulmonary exercise test revealed the most important independent prognostic factors to be peak $\dot{V}O_2$ and low PASP increase and may be useful for therapeutic decision making by identifying patients of especially high risk and inadequate therapy. Estimation of RV contractile reserve may be even more important than resting hemodynamics measured by echocardiography for the follow-up and therapeutic management of PH patients.



Assessment and Prognostic Relevance of Right Ventricular Contractile Reserve in Patients With Severe Pulmonary Hypertension





Circulation 2013;128:2005–2015

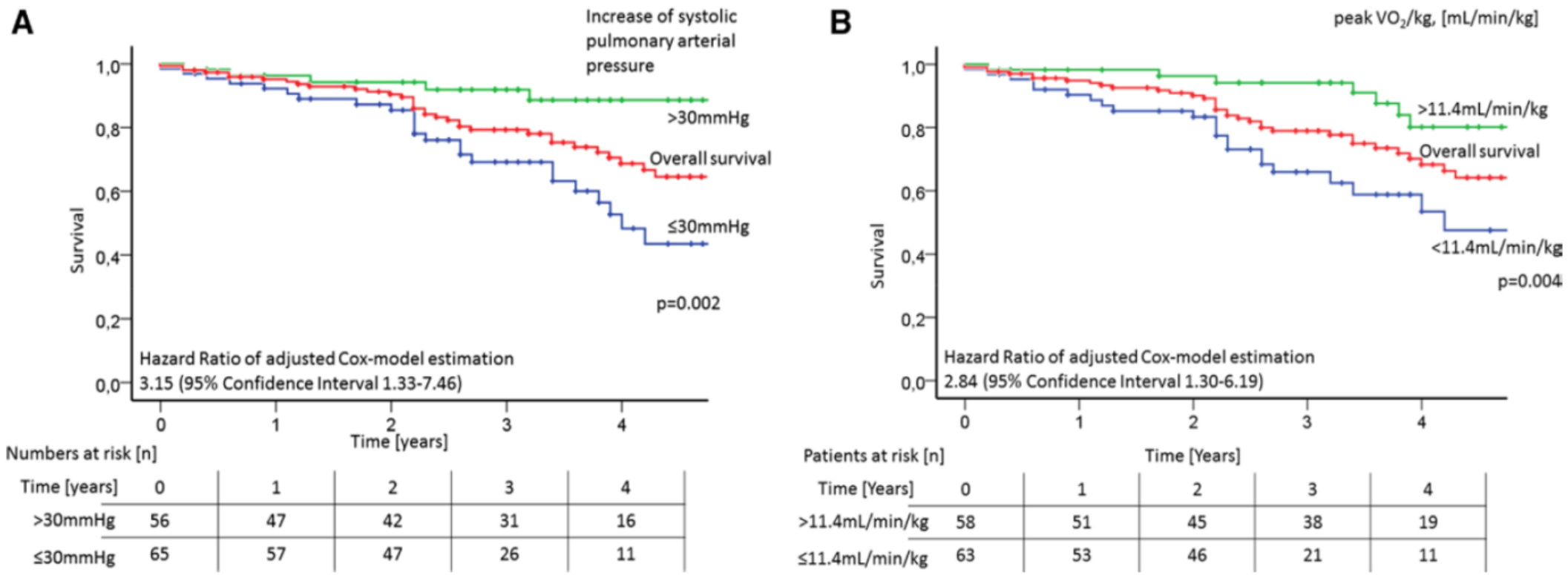
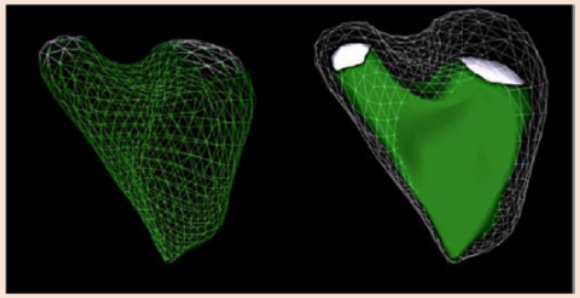


Figure 4. A, Survival rate of pulmonary hypertension patients in relation to right ventricular contractile reserve obtained by pulmonary arterial systolic pressure (PASP) increase during exercise. The 1-, 3-, and 4-year survival rates among the patients with PASP increase ≤30 mm Hg were 92%, 69%, and 48%, respectively, and 96%, 92%, and 89% among group B with high PASP >30 mm Hg. **B**, Survival among patients in relation to peak $\dot{V}O_2$ per kilogram. The median of peak $\dot{V}O_2$ per kilogram (11.4 mL·min^{-1}·kg^{-1}) was used to split the patients into 2 groups. Patients with a peak $\dot{V}O_2$ per kilogram >11.4 mL·min^{-1}·kg^{-1} had significantly higher survival rates (98%, 93%, and 80%) than patients with peak $\dot{V}O_2$ per kilogram ≤11.4 mL·min^{-1}·kg^{-1} (90%, 67% and 56%) at 1, 3, and 4 years.

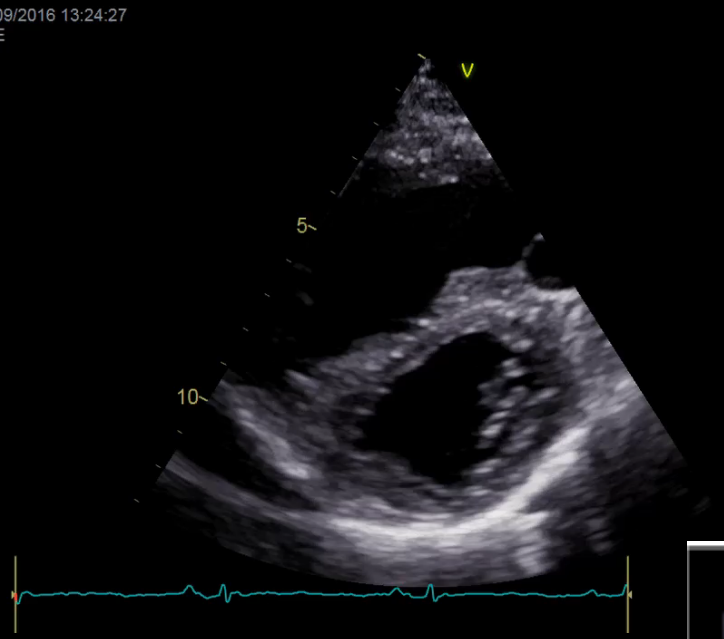
Circulation 2013;128:2005–2015

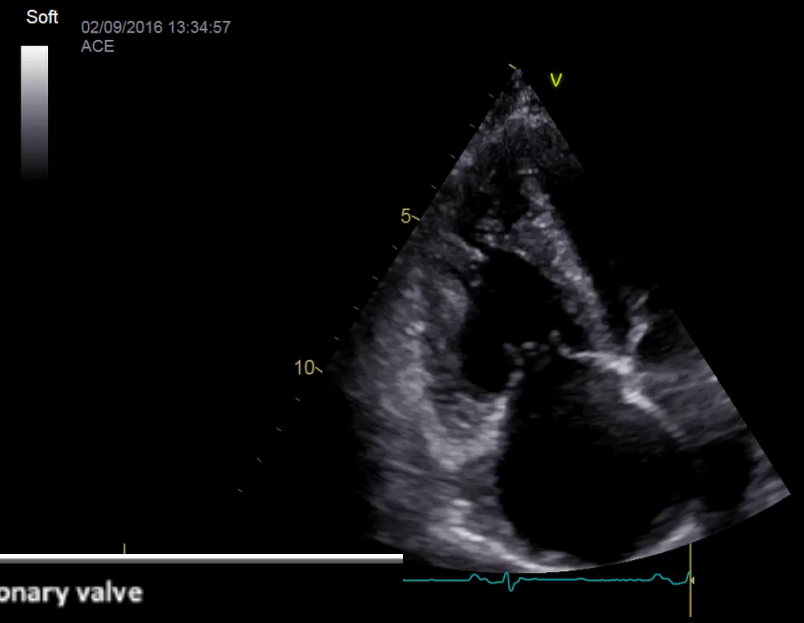
Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging

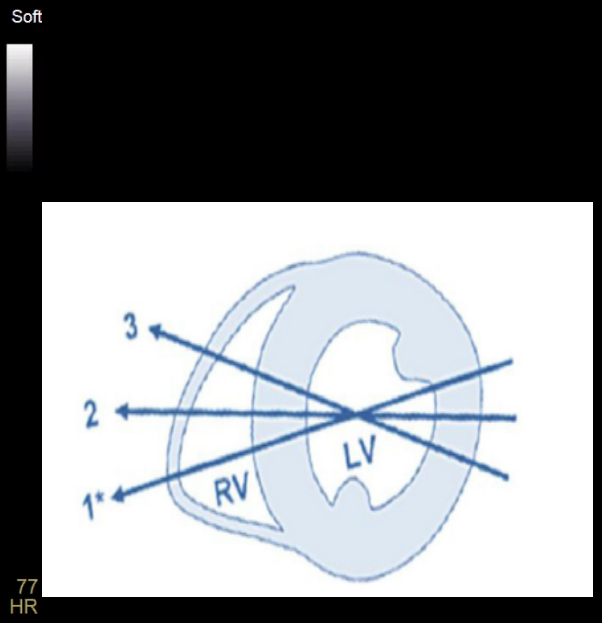
Table 9 Recommendations for the echocardiographic assessment of RV function

Echocardiographic imaging	Recommended methods	Advantages	Limitations
EF 	Fractional RV volume change by 3D TTE: RV EF (%) = 100 × (EDV − ESV)/EDV	• Includes RV outflow tract contribution to overall function • Correlates with RV EF by CMR	• Dependent on adequate image quality • Load dependency • Requires offline analysis and experience • Prognostic value not established

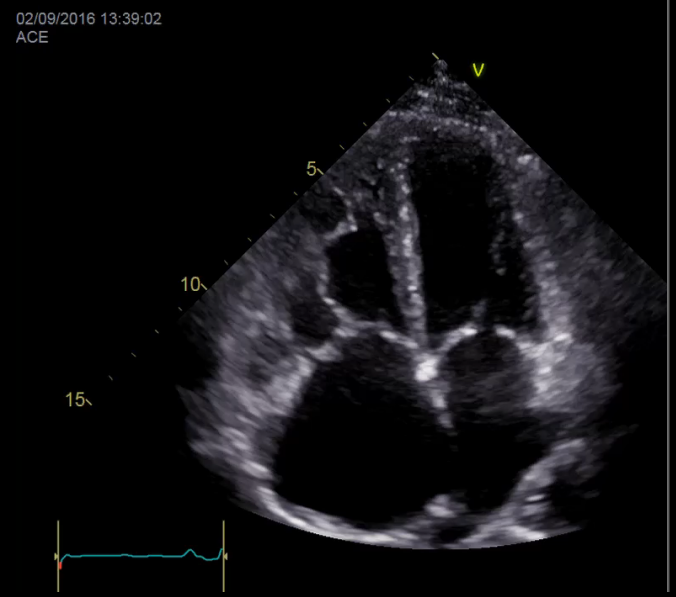
J Am Soc Echocardiogr 2015;28:1-39

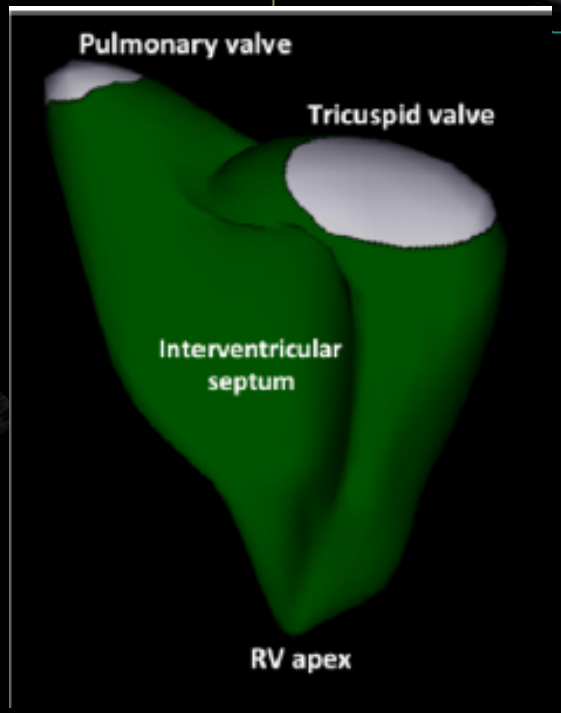

02/09/2016 13:24:27
ACE
V
5
10

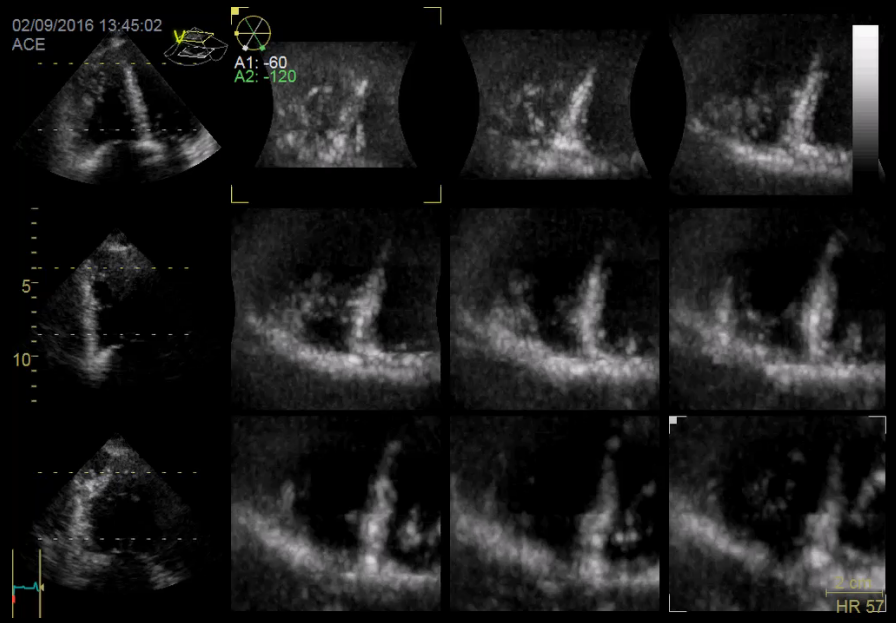

Soft
02/09/2016 13:34:57
ACE
V
5
10


Soft
77
HR

3
2
1*
RV
LV


02/09/2016 13:39:02
ACE
V
5
10
15


Pulmonary valve
Tricuspid valve
Interventricular septum
RV apex


02/09/2016 13:45:02
ACE
A1: -60
A2: -120
5
10
HR 57

Accuracy of Right Ventricular Volumes and Function Determined by Three-Dimensional Echocardiography in Comparison with Magnetic Resonance Imaging: A Meta-Analysis Study

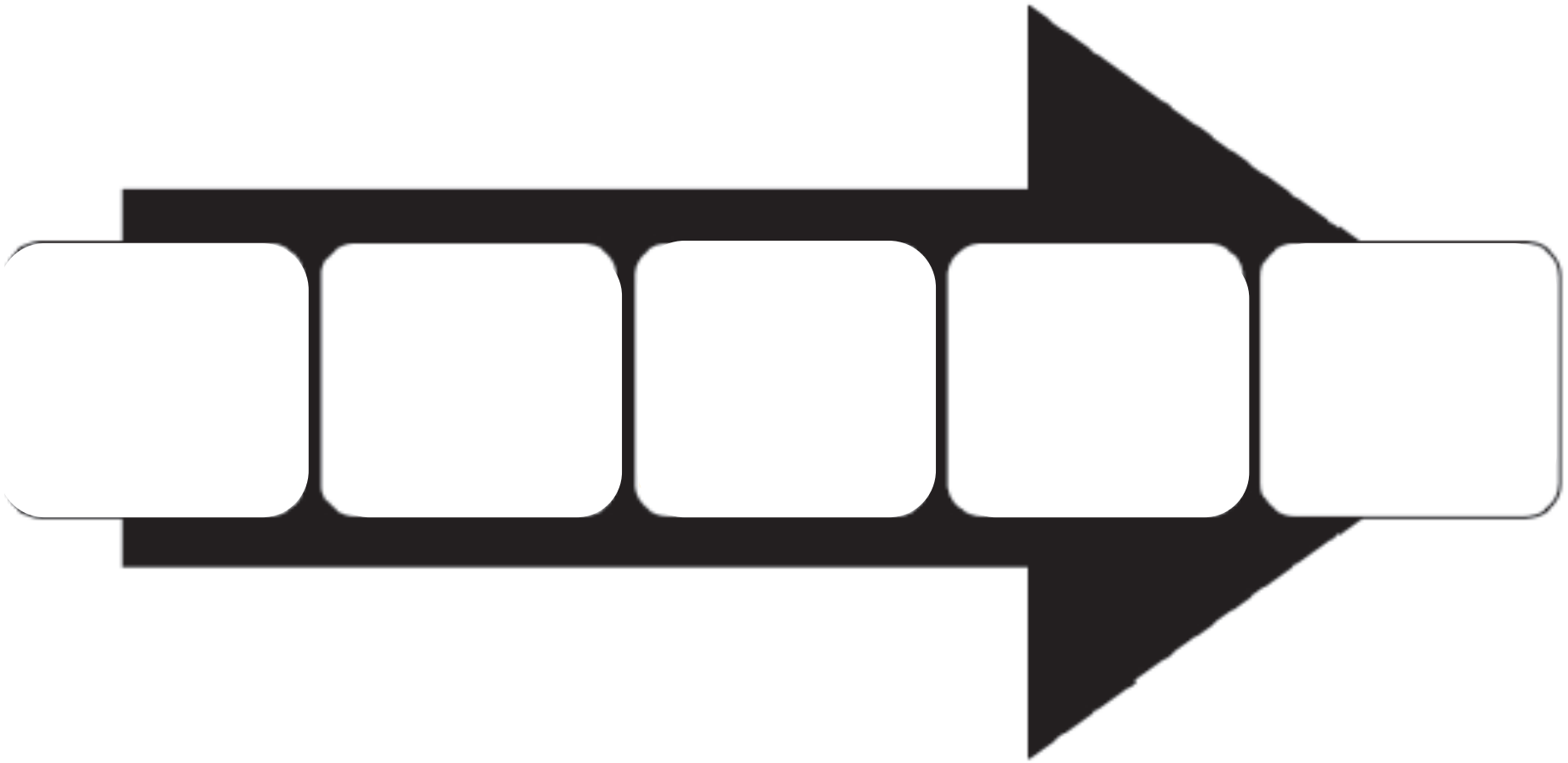
Yuichi J. Shimada, MD, Maiko Shiota, MD, Robert J. Siegel, MD, and
Takahiro Shiota, MD, PhD, FACC, FASE, FAHA, *New York, New York; Los Angeles and Palo Alto, California*

CONCLUSIONS

Only by synthesizing a number of small studies in a meta-analysis could we display an underestimation of RV volumes and EF by 3DE and factors of the systematic bias. Furthermore, semiautomated tracking systems, matrix-array transducers, software for diseased right ventricles, spatial and temporal resolution, and time for obtaining images were identified as targets for development. These data provide a more detailed basis for analyzing and improving the accuracy of 3DE, an indispensable step toward further clinical application in RV assessment.

J Am Soc Echocardiogr 2010;23:943–53

La strategia vincente nell'ipertensione arteriosa polmonare



Humbert M, et al. Eur Respir Rev 2012;21:126,306-312