Πνευμονική Υπέρταση: Τι άλλαξε στο 6ο Παγκόσμιο Συνέδριο στη Θεραπεία της ΡΑΗ

Σ. Ορφανός

Β' Κλινική Εντατικής Θεραπείας ΕΚΠΑ

&

Διακλινικό Ιατρείο Πνευμονικής Υπέρτασης

Π.Γ.Ν ΑΤΤΙΚΟΝ

Disclosures

Funding, or sponsoring to attend scientific meetings, or honoraria from:

- **Actelion**
- **Bayer**
- **ELPEN**
- **Ferrer**
- **Galenica**
- **GSK**
- **MSD**
- **Pharmaserve Lilly**
- **PharmaSwiss**
- **Pfizer**
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5TH

WORLD SYMPOSIUM ON PULMONARY HYPERTENSION

NICE ACROPOLIS, Nice February 27-28 / March 1, 2013

European Heart Journal Advance Access published September 15, 2015

European Heart Journal
doi:10.1093/eurheartj/ehv317

ESC/ERS GUIDELINES

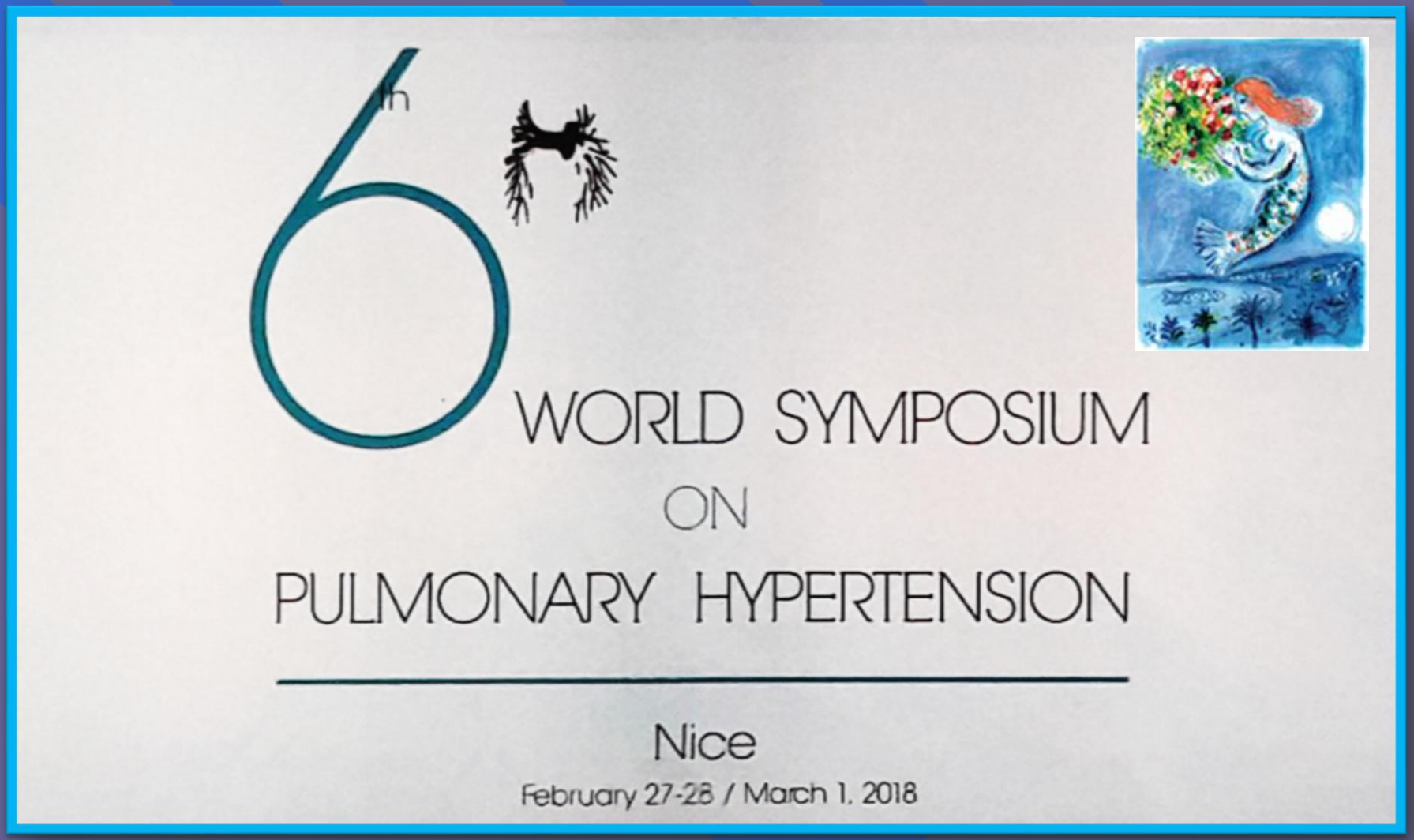
2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS)

Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT)

Authors/Task Force Members: Nazzareno Galiè* (ESC Chairperson) (Italy), Marc Humbert*[a] (ERS Chairperson) (France), Jean-Luc Vachiery[c] (Belgium), Simon Gibbs (UK), Irene Lang (Austria), Adam Torbicki (Poland), Gérald Simonneau[a] (France), Andrew Peacock[a] (UK), Anton Vonk Noordegraaf[a] (The Netherlands), Maurice Beghetti[b] (Switzerland), Ardeschir Ghofrani[a] (Germany), Miguel Angel Gomez Sanchez (Spain), Georg Hansmann[b] (Germany), Walter Klepetko[c] (Austria), Patrizio Lancellotti (Belgium), Marco Matucci[d] (Italy), Theresa McDonagh (UK), Luc A. Pierard (Belgium), Pedro T. Trindade (Switzerland), Maurizio Zompatori[e] (Italy) and Marius Hoeper[a] (Germany)

EHJ & ERJ, 2015



Τα Statement Papers δημοσιεύθηκαν τον ΔΕΚ 2018 στο ERJ

ERJ Express. Published on December 13, 2018 as doi: 10.1183/13993003.01913-2018

Haemodynamic definitions and updated clinical classification of pulmonary hypertension

Gérald Simonneau[1,2], David Montani[1,2], David S. Celermajer[3], Christopher P. Denton[4], Michael A. Gatzoulis[5], Michael Krowka[6], Paul G. Williams[7] and Rogerio Souza[8]

Number 4 in the series
"Proceedings of the 6th World Symposium on Pulmonary Hypertension"
Edited by N. Galiè, V.V. McLaughlin, L.J. Rubin and G. Simonneau

Affiliations: [1]Université Paris-Sud, AP-HP, Centre de Référence de l'Hypertension Pulmonaire, Service de Pneumologie, Département Hospitalo-Universitaire (DHU) Thorax Innovation (TORINO), Hôpital de Bicêtre, Le Kremlin-Bicêtre, France. [2]INSERM UMR_S999, LabEx LERMIT, Hôpital Marie Lannelongue, Le Plessis-Robinson, France. [3]Faculty of Medicine and Health, The University of Sydney, Sydney, Australia. [4]Centre for Rheumatology, Royal Free Campus, University College London, London, UK. [5]Adult Congenital Heart Centre and National Centre for Pulmonary Hypertension, Royal Brompton and Harefield NHS Trust, and the National Heart and Lung Institute, Imperial College London, London, UK. [6]Transplant Center, Mayo Clinic, Rochester, MN, USA. [7]Center of Chest Disease and Critical Care, Milpark Hospital, Johannesburg, South Africa. [8]Pulmonary Circulation Unit, Pulmonary Division, Heart Institute (InCor), Hospital das Clinicas da Faculdade de Medicina da Universidade de Sao Paulo, Sao Paulo, Brazil.

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@ERSpublications
State of the art and research perspectives of haemodynamic definitions and clinical classification of pulmonary hypertension http://ow.ly/TJeR30mgWKj

Cite this article as: Simonneau G, Montani D, Celermajer DS, *et al.* Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J* 2018; in press [https://doi.org/10.1183/13993003.01913-2018].

PULMONARY HYPERTENSION

WHAT IS IT in 2019?

• ELEVATED PULMONARY ARTERIAL PRESSURE
(>20 mm Hg mean, at rest)

PULMONARY ARTERIAL HYPERTENSION

RESULTS FROM

• ABNORMAL PULMONARY VASCULAR RESISTANCE

(PVR ≥ 3 WU)
DUE TO

• PULMONARY VASCULAR REMODELLING AND CONSTRICTION

Left Heart Disease excluded: PAWP ≤ 15 mm Hg

TABLE 2 Updated clinical classification of pulmonary hypertension (PH)

1 PAH
- 1.1 Idiopathic PAH
- 1.2 Heritable PAH
- 1.3 Drug- and toxin-induced PAH (table 3)
- 1.4 PAH associated with:
  - 1.4.1 Connective tissue disease
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  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease
  - 1.4.5 Schistosomiasis
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- 1.6 PAH with overt features of venous/capillaries (PVOD/PCH) involvement (table 5)
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- 5.3 Others
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PAH: pulmonary arterial hypertension; PVOD: pulmonary veno-occlusive disease; PCH: pulmonary capillary haemangiomatosis; LVEF: left ventricular ejection fraction.

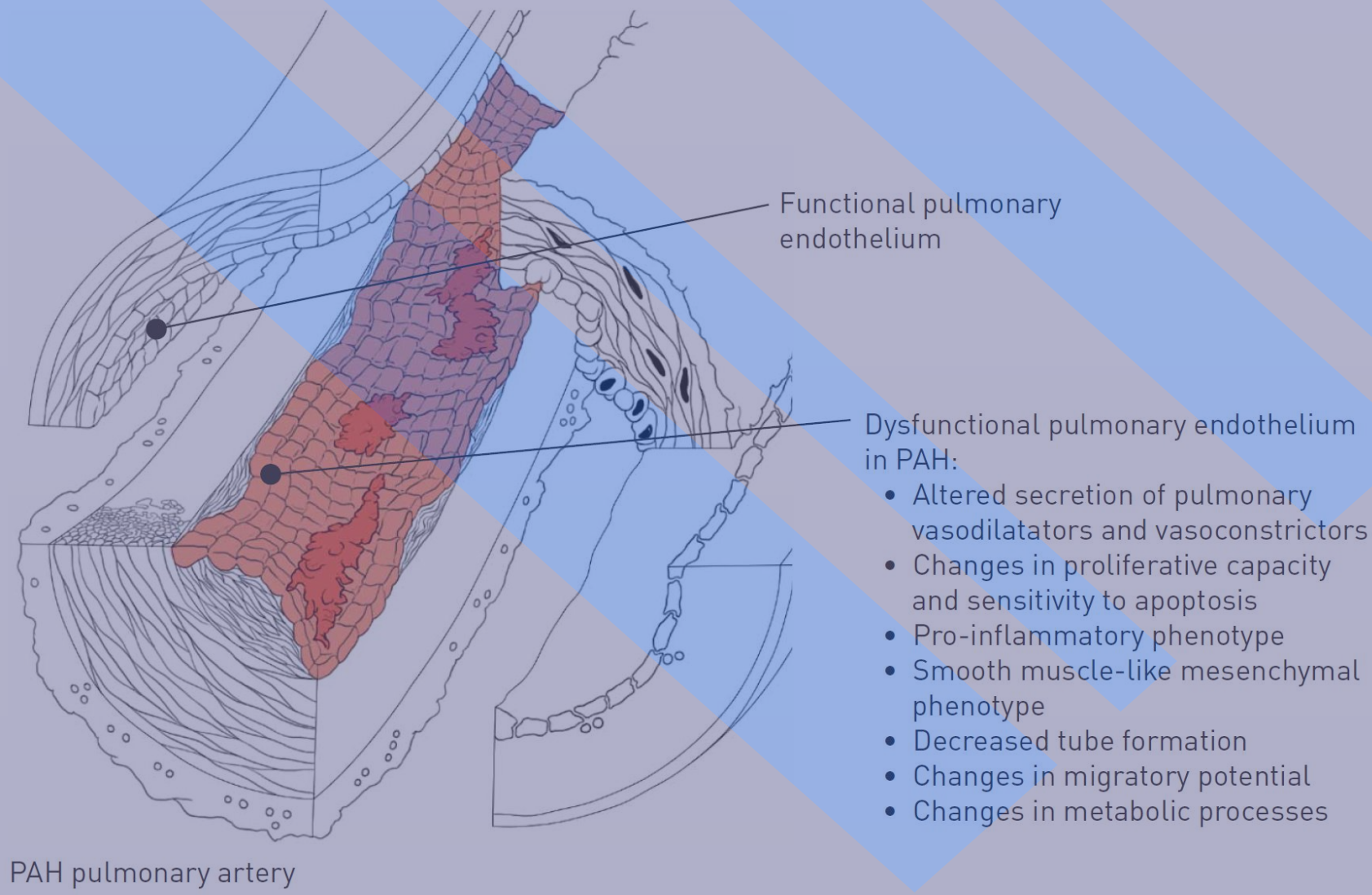
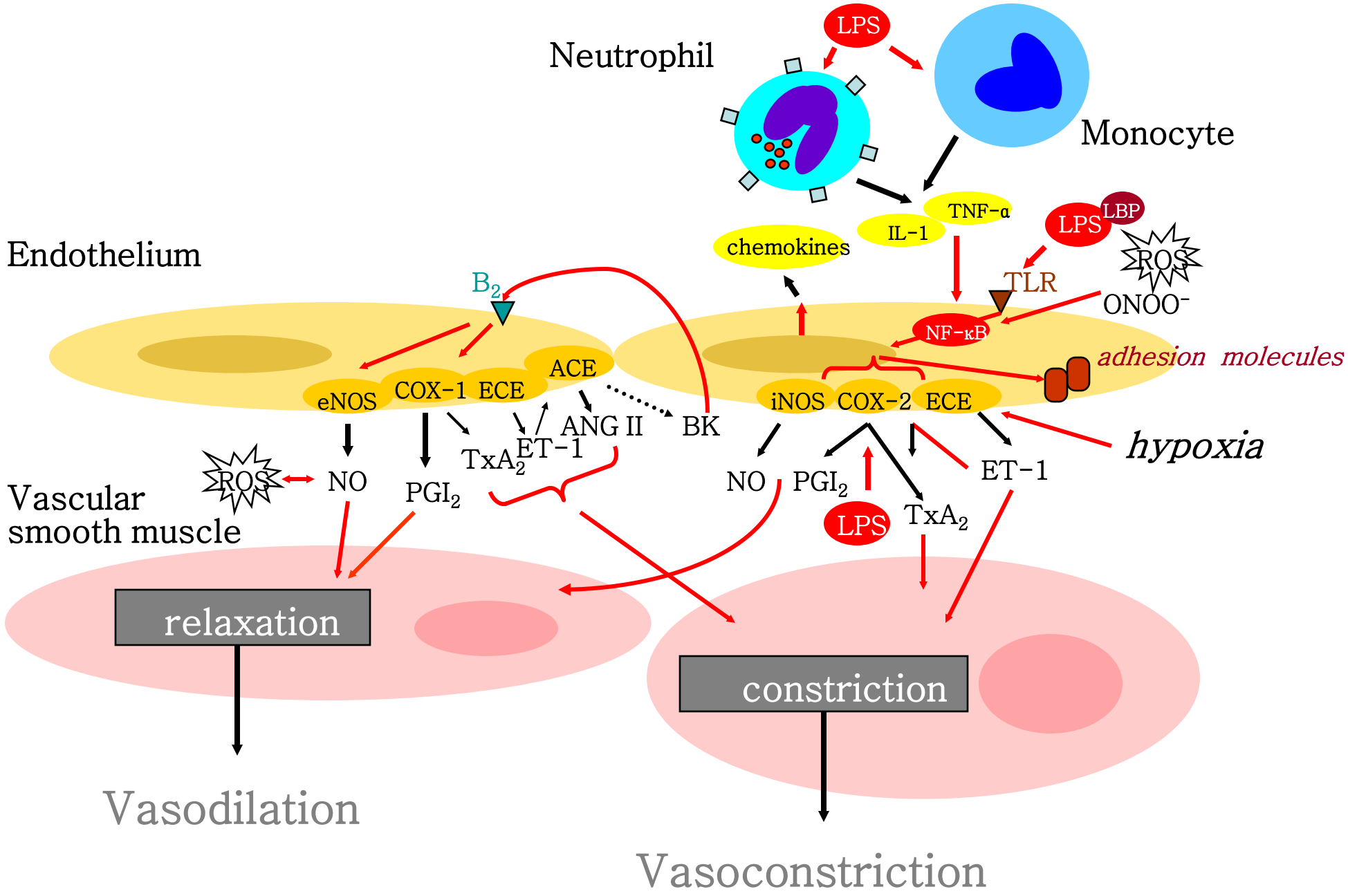


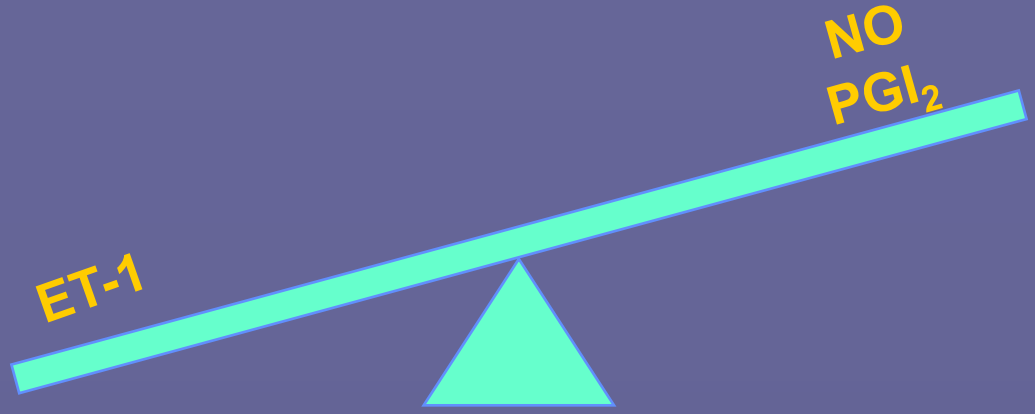
FIGURE 4 Phenotypic signature of dysfunctional pulmonary vascular endothelium in pulmonary arterial hypertension (PAH).

Humbert M, Guignabert C, Bonnet S, *et al.* *Eur Respir J* 2018; in press



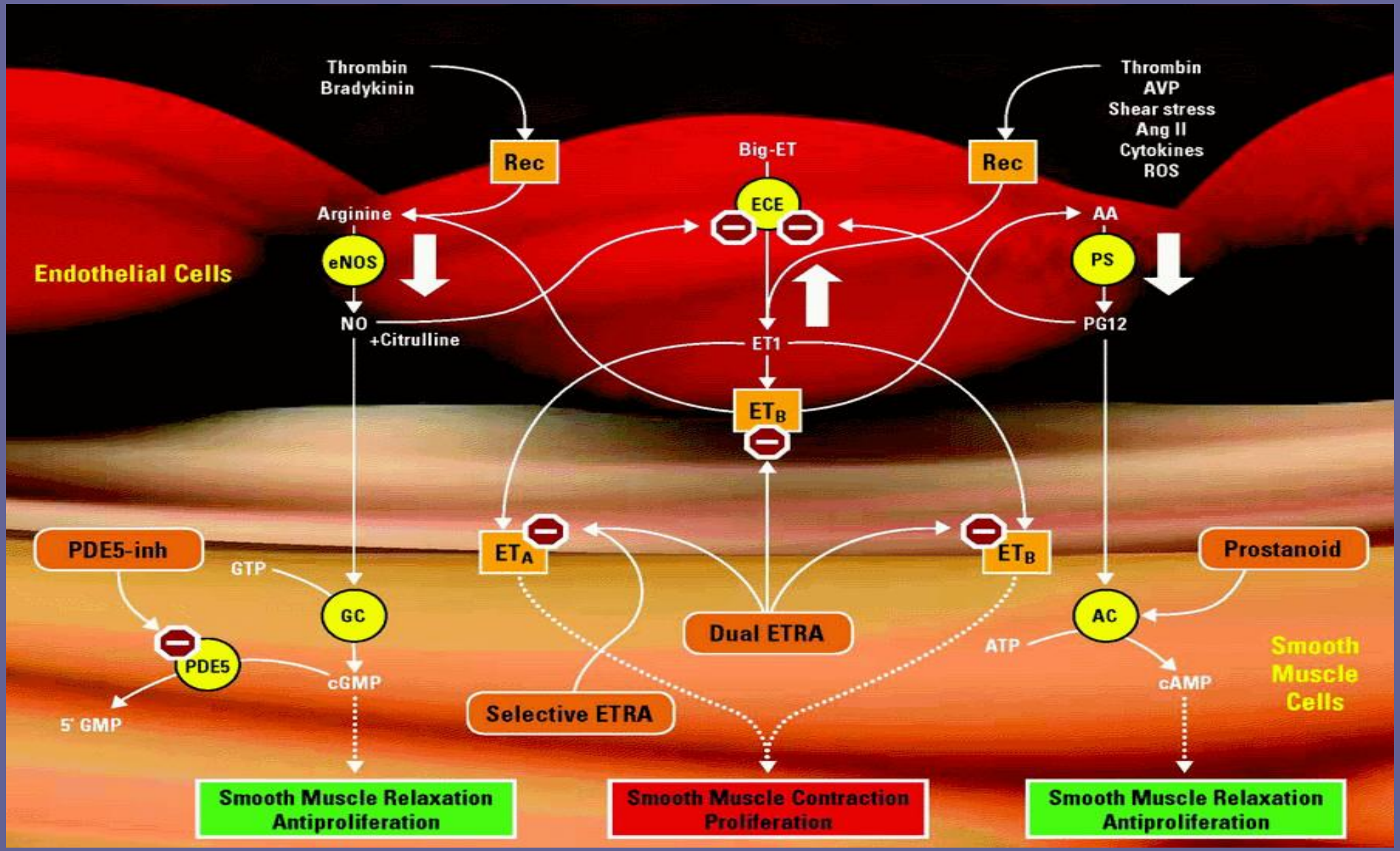
Intensive Care Med 2004; 30:1702-14

Ενδοθηλιακή Δυσλειτουργία επί ΠΑΥ



- **ET-1 is elevated (+)**
  - Vasoconstriction
  - Cell proliferation / Hypertrophy
- **NO and PGI_2 are reduced (-)**
  - Vasodilation
  - Anti-proliferation
  - Anti-inflammation

Spieker LE et al. J Am Coll Cardiol. 2001;37:1493-1505.
Luscher TF and Barton M. Circulation. 2000;102:2434-2440.
Albrecht EW et al. J Pathol. 2003;199:8-17.
Hankins SR and Horn EM. Curr Cardiol Rep. 2000;2:244-251.



McLaughlin & McGoon *Circulation* 2006, 114:1417-1431

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EHJ & *ERJ*, 2015

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%
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Progression of symptoms	No	Slow	Rapid
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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 slope ≥45
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 (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%

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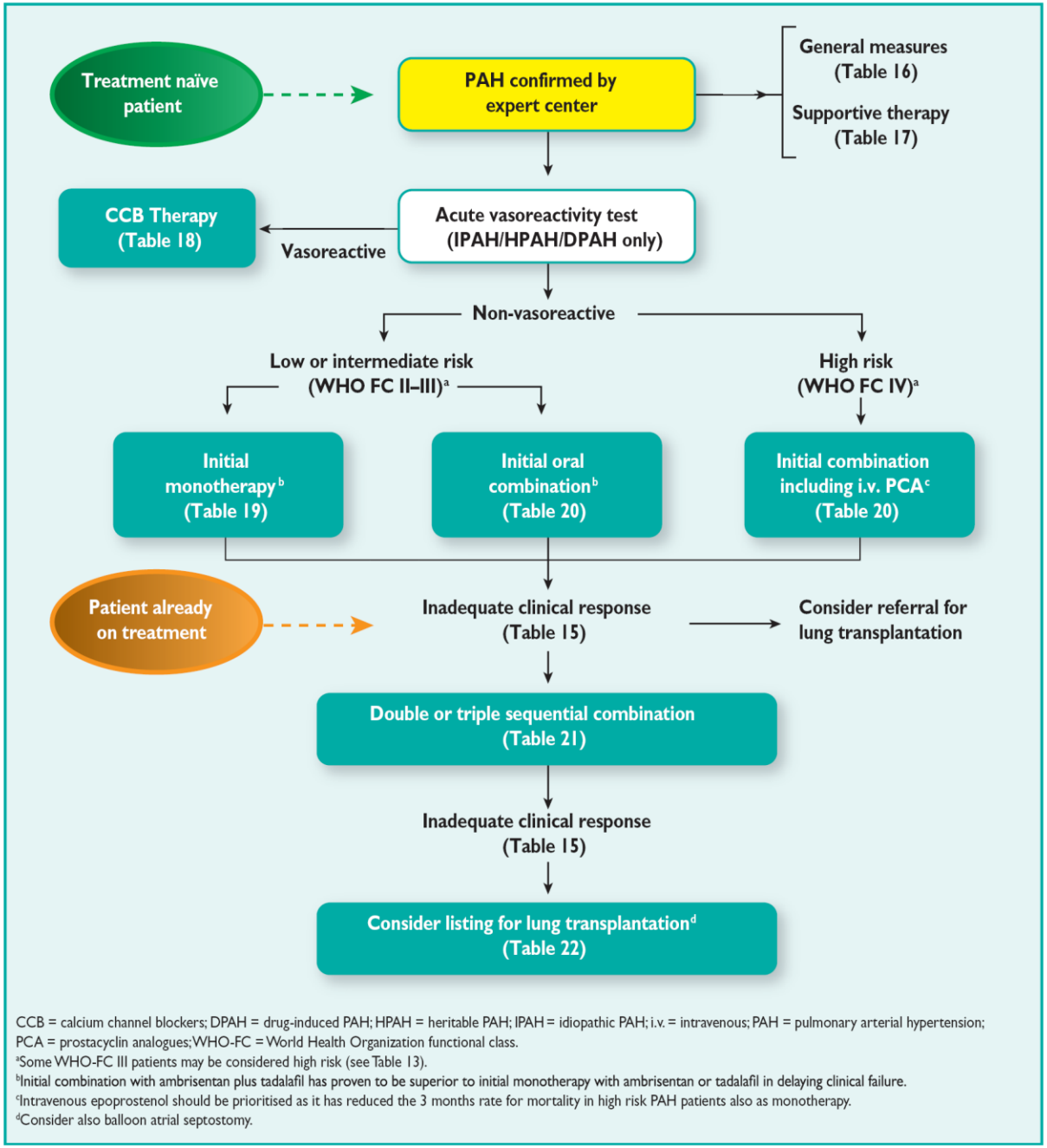

CCB = calcium channel blockers; DPAH = drug-induced PAH; HPAH = heritable PAH; IPAH = idiopathic PAH; i.v. = intravenous; PAH = pulmonary arterial hypertension; PCA = prostacyclin analogues; WHO-FC = World Health Organization functional class.
[a]Some WHO-FC III patients may be considered high risk (see Table 13).
[b]Initial combination with ambrisentan plus tadalafil has proven to be superior to initial monotherapy with ambrisentan or tadalafil in delaying clinical failure.
[c]Intravenous epoprostenol should be prioritised as it has reduced the 3 months rate for mortality in high risk PAH patients also as monotherapy.
[d]Consider also balloon atrial septostomy.

Figure 2 Evidence based treatment algorithm for pulmonary arterial hypertension patients (for group 1 patients only; see description in the text).

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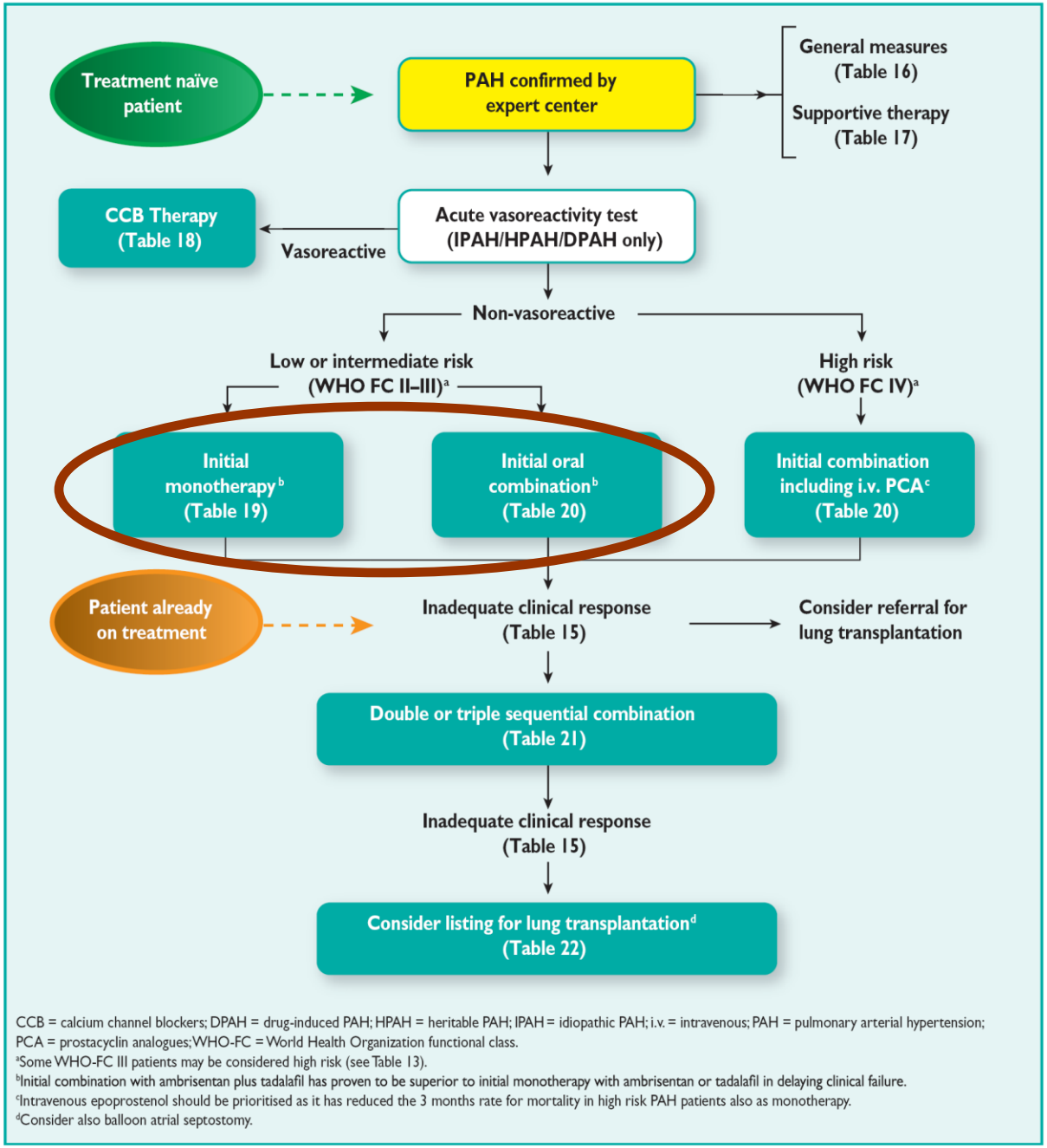
EHJ & ERJ, 2015



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EHJ & ERJ, 2015

ERJ Express. Published on December 13, 2018 as doi: 10.1183/13993003.01889-2018

SERIES
WORLD SYMPOSIUM ON PULMONARY HYPERTENSION

Risk stratification and medical therapy of pulmonary arterial hypertension

Nazzareno Galiè[1], Richard N. Channick[2], Robert P. Frantz[3], Ekkehard Grünig[4], Zhi Cheng Jing[5], Olga Moiseeva[6], Ioana R. Preston[7], Tomas Pulido[8], Zeenat Safdar[9], Yuichi Tamura[10] and Vallerie V. McLaughlin[11]

Number 6 in the series
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Edited by N. Galiè, V.V. McLaughlin, L.J. Rubin and G. Simonneau

Affiliations: [1]Dept of Experimental, Diagnostic and Specialty Medicine (DIMES), Alma Mater Studiorum, University of Bologna, Bologna, Italy. [2]Pulmonary and Critical Care Division, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA. [3]Dept of Cardiovascular Diseases, Mayo Clinic, Rochester, MN, USA. [4]Pulmonary Hypertension Center, Thoraxklinic at Heidelberg University Hospital, Heidelberg, Germany. [5]State Key Lab of Cardiovascular Disease, FuWai Hospital and Key Lab of Pulmonary Vascular Medicine, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China. [6]Non-Coronary Heart Disease Dept, Almazov National Medical Research Centre, St Petersburg, Russian Federation. [7]Tufts University School of Medicine, Pulmonary, Critical Care and Sleep Division, Tufts Medical Center, Boston, MA, USA. [8]Cardiopulmonary Dept, National Heart Institute, La Salle University, Mexico City, Mexico. [9]Pulmonary, Critical Care Division, Houston Methodist Hospital, Weill Cornell College of Medicine, Houston, TX, USA. [10]Dept of Cardiology, International University of Health and Welfare School of Medicine, Tokyo, Japan. [11]Cardiovascular Medicine, The University of Michigan, Ann Arbor, MI, USA.

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State of the art and research perspectives on medical therapy of pulmonary arterial hypertension, including treatment algorithm http://ow.ly/4UkJ30md5GS

Cite this article as: Galiè N, Channick RN, Frantz RP, *et al*. Risk stratification and medical therapy of pulmonary arterial hypertension. *Eur Respir J* 2018; in press [https://doi.org/10.1183/13993003.01889-2018].

ABSTRACT Pulmonary arterial hypertension (PAH) remains a severe clinical condition despite the availability over the past 15 years of multiple drugs interfering with the endothelin, nitric oxide and prostacyclin pathways. The recent progress observed in medical therapy of PAH is not, therefore, related to the discovery of new pathways, but to the development of new strategies for combination therapy and on escalation of treatments based on systematic assessment of clinical response. The current treatment strategy is based on the severity of the newly diagnosed PAH patient as assessed by a multiparametric risk stratification approach. Clinical, exercise, right ventricular function and haemodynamic parameters are combined to define a low-, intermediate- or high-risk status according to the expected 1-year mortality. The current treatment algorithm provides the most appropriate initial strategy, including monotherapy, or double or triple combination therapy. Further treatment escalation is required in case low-risk status is not achieved in planned follow-up assessments. Lung transplantation may be required in most advanced cases on maximal medical therapy.

6 WSPH

Simplified Risk stratification in PAH

	Prognostic Criteria	Low risk variables	Intermediate risk variables	High risk variables
A.	WHO functional class	I, II	III	IV
B.	6MWD	> 440 m	165–440 m	< 165 m
C.	NT-proBNP/BNP plasma levels OR RAP	BNP < 50 ng/l NTproBNP < 300 ng/ml OR RAP < 8 mmHg	BNP 50–300 ng/l NT-proBNP 300–1400 ng/l OR RAP 8–14 mmHg	BNP > 300 ng/l NT-proBNP > 1400 ng/l OR RAP > 14 mmHg
D.	CI OR SvO2	CI ≥ 2.5 l/min/m² OR SvO_2 > 65%	CI 2.0–2.4 l/min/m² OR SvO_2 60–65%	CI < 2.0 l/min/m² OR SvO_2 < 60%

Ανεπίσημα δεδομένα από το 6ο WSPH

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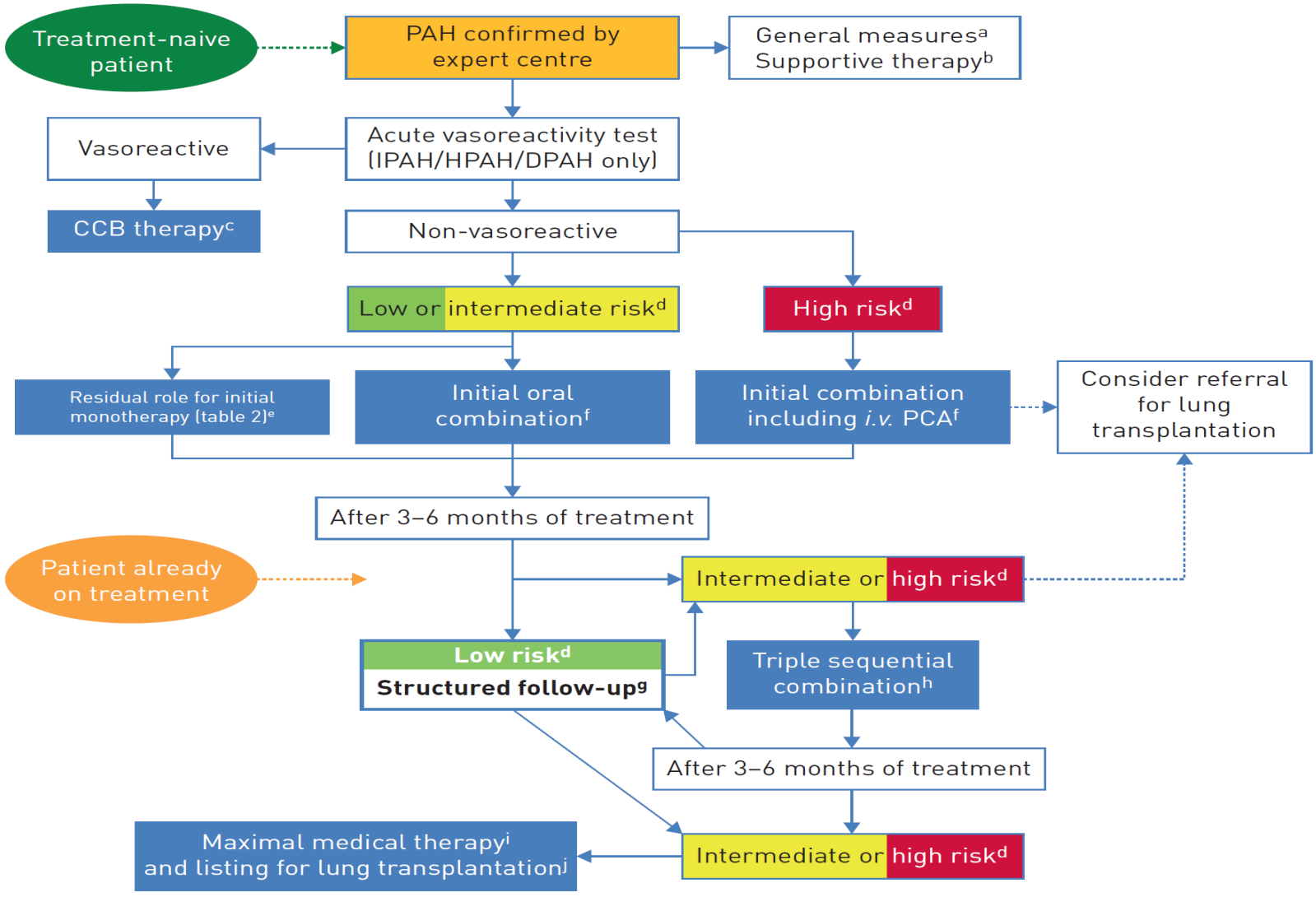

FIGURE 2 Treatment algorithm. PAH: pulmonary arterial hypertension; IPAH: idiopathic PAH; HPAH: heritable PAH; DPAH: drug-induced PAH; CCB: calcium channel blocker; PCA: prostacyclin analogue; PH: pulmonary hypertension. [a]: 2015 ESC/ERS PH guidelines *Table 16*; [b]: 2015 ESC/ERS PH guidelines *Table 17*; [c]: 2015 ESC/ERS PH guidelines *Table 18*; [d]: 2015 ESC/ERS PH guidelines *Table 13*; [e]: 2015 ESC/ERS PH guidelines *Table 19*; [f]: 2015 ESC/ERS PH guidelines *Table 20*; [g]: 2015 ESC/ERS PH guidelines *Table 14*; [h]: 2015 ESC/ERS PH guidelines *Table 21*; [i]: maximal medical therapy is considered triple combination therapy including a *s.c.* or an *i.v.* PCA (*i.v.* preferred in high-risk status); [j]: 2015 ESC/ERS PH guidelines *Table 22*.

TABLE 2 Updated clinical classification of pulmonary hypertension (PH)

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- 1.3 Drug- and toxin-induced PAH (table 3)
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- 5.3 Others
- 5.4 Complex congenital heart disease

PAH: pulmonary arterial hypertension; PVOD: pulmonary veno-occlusive disease; PCH: pulmonary capillary haemangiomatosis; LVEF: left ventricular ejection fraction.

TABLE 4 Definitions of acute and long-term response

Acute pulmonary vasoreactivity[#] for patients with idiopathic, hereditable or drug-induced PAH	Reduction of mPAP ⩾10 mmHg to reach an absolute value of mPAP ⩽40 mmHg Increased or unchanged cardiac output
Long-term response to CCBs	New York Heart Association Functional Class I/II With sustained haemodynamic improvement (same or better than achieved in the acute test) after at least 1 year on CCBs only

PAH: pulmonary arterial hypertension; mPAP: mean pulmonary arterial pressure; CCB: calcium channel blocker. [#]: nitric oxide (10–20 ppm) is recommended for performing vasoreactivity testing, but *i.v.* epoprostenol, *i.v.* adenosine or inhaled iloprost can be used as alternatives.

Vasodilator responsiveness in idiopathic pulmonary arterial hypertension: identifying a distinct phenotype with distinct physiology and distinct prognosis

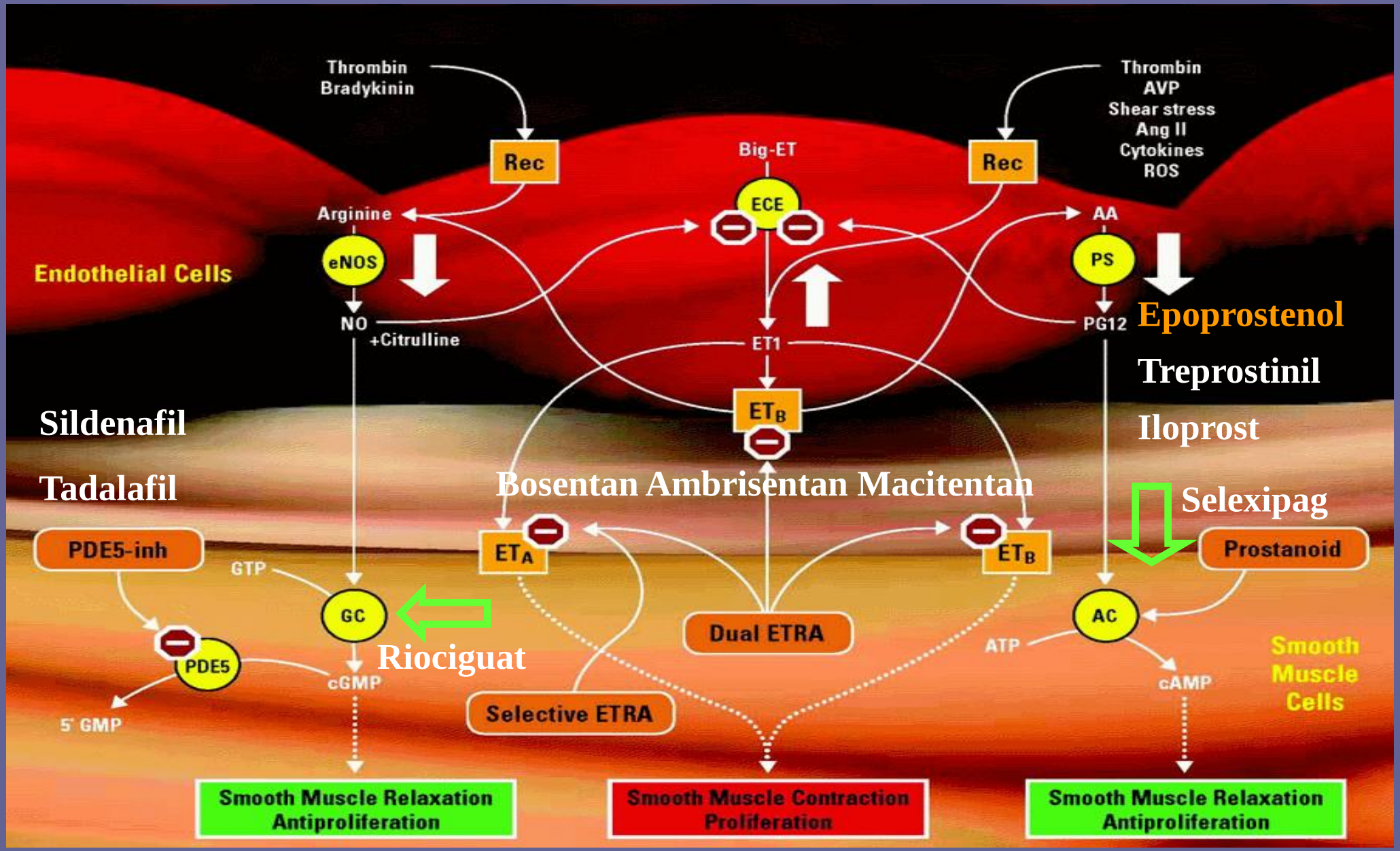
David Langleben[1],* and Stylianos Orfanos[2],*

[1]Center for Pulmonary Vascular Disease, Division of Cardiology, Jewish General Hospital, McGill University, Montreal, Quebec Canada; [2]Pulmonary Hypertension Clinic, Department of Critical Care, Attikon Hospital, National and Kapodistirian University of Athens, Athens, Greece

Abstract

Within the cohort of patients suffering from idiopathic pulmonary arterial hypertension (IPAH) is a group that responds dramatically (VR-PAH) to an acute vasodilator challenge and that has excellent long-term hemodynamic improvement and prognosis on high dose calcium channel blockers compared with vasodilator non-responders (VN-PAH). For the purposes of diagnosing VR-PAH, there is to date no test to replace the acute vasodilator challenge. However, recent studies have identified markers that may aid in the identification of VR-PAH, including peripheral blood lymphocyte RNA expression levels of desmogelin-2 and Ras homolog gene family member Q, and plasma levels of provirus integration site for Moloney murine leukemia virus. Genome wide-array studies of peripheral blood DNA have demonstrated differences in disease specific genetic variants between VR-PAH and NR-PAH, with particular convergence on cytoskeletal function pathways and Wnt signaling pathways. These studies offer hope for future non-invasive identification of VR-PAH, and insights into pathogenesis that may lead to novel therapies. Examination of the degree of pulmonary microvascular perfusion in PAH has offered additional insights. During the acute vasodilator challenge, VR-PAH patients demonstrate true vasodilation with recruitment and increased perfusion of the capillary bed, while VN-PAH patients are unable to recruit vasculature. In the very few reports of lung histology, VR-PAH has more medial thickening in the precapillary arterioles, while VN-PAH has the classic histology of PAH, including intimal thickening. VR-PAH is a disorder with a phenotype distinct from VN-PAH and other types of PAH, and should be considered separately in the classification of PAH.

Pulmonary Circulation 2017; 7(3) 1–10



McLaughlin & McGoon *Circulation* 2006, 114:1417-1431

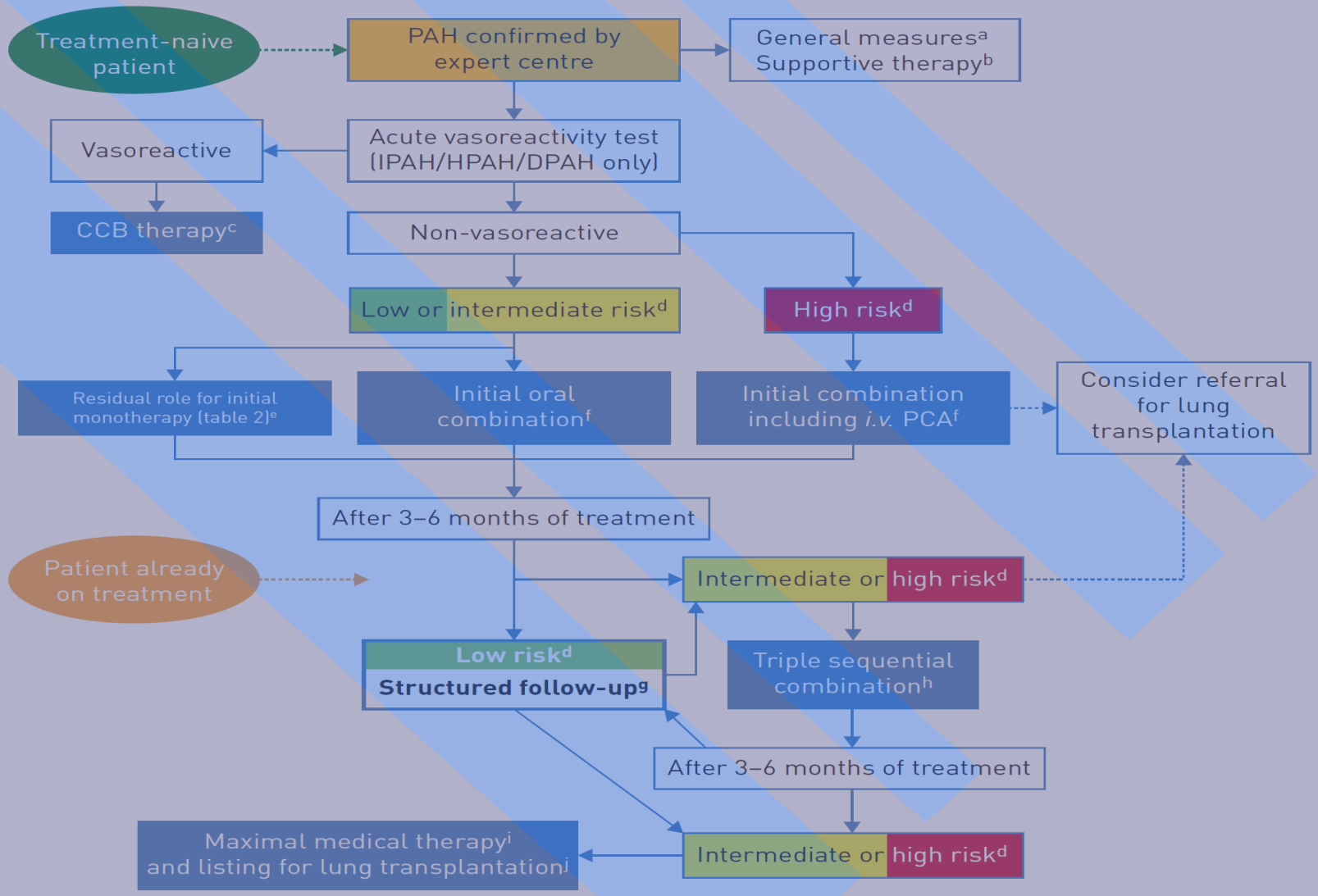


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TABLE 2 Potential role for initial monotherapy in specific pulmonary arterial hypertension (PAH) subsets

IPAH, HPAH and drug-induced PAH patient responders to acute vasoreactivity tests and with WHO FC I/II and sustained haemodynamic improvement (same or better than achieved in the acute test) after at least 1 year on CCBs only
Long-term-treated historical PAH patients with monotherapy (>5–10 years) stable with low-risk profile
IPAH patients >75 years old with multiple risk factors for heart failure with preserved LVEF (high blood pressure, diabetes mellitus, coronary artery disease, atrial fibrillation, obesity)
PAH patients with suspicion or high probability of pulmonary veno-occlusive disease or pulmonary capillary haemangiomatosis
Patients with PAH associated with HIV infection or portal hypertension or uncorrected congenital heart disease, as they were not included in RCTs of initial combination therapy
PAH patients with very mild disease (*e.g.* WHO FC I, PVR 3–4 WU, mPAP <30 mmHg, normal right ventricle at echocardiography)
Combination therapy unavailable or contraindicated (*e.g.* severe liver disease)

IPAH: idiopathic PAH; HPAH: heritable PAH; CCB: calcium channel blocker; PAP: pulmonary arterial pressure; PVR: pulmonary vascular resistance; LVEF: left ventricular ejection fraction; RCT: randomised controlled trial; WHO: World Health Organization; FC: Functional Class; WU: Wood Units; mPAP: mean PAP.

Galiè N, Channick RN, Frantz RP, *et al.*

Eur Respir J 2018; in press

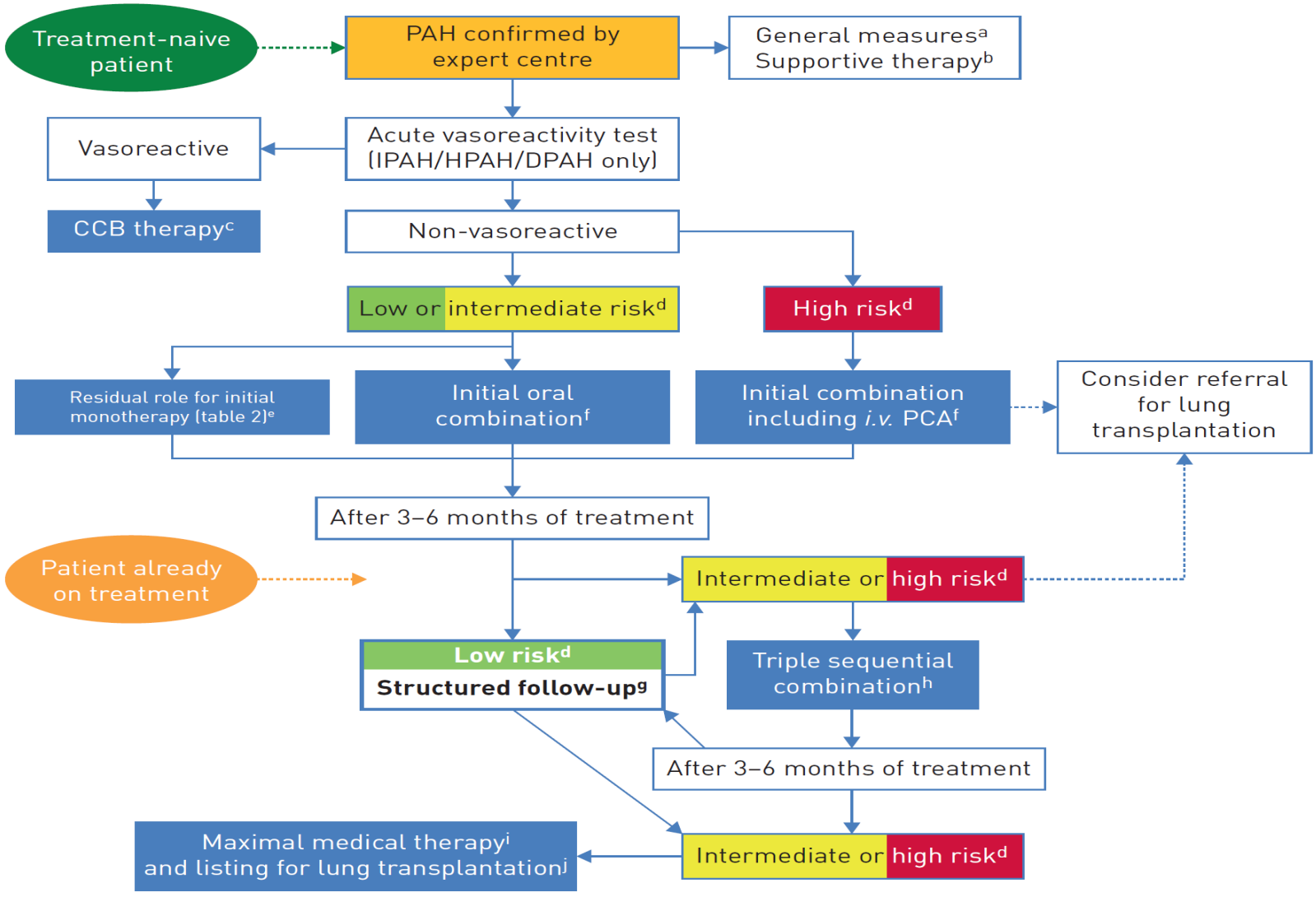

FIGURE 2 Treatment algorithm. PAH: pulmonary arterial hypertension; IPAH: idiopathic PAH; HPAH: heritable PAH; DPAH: drug-induced PAH; CCB: calcium channel blocker; PCA: prostacyclin analogue; PH: pulmonary hypertension. [a]: 2015 ESC/ERS PH guidelines *Table 16*; [b]: 2015 ESC/ERS PH guidelines *Table 17*; [c]: 2015 ESC/ERS PH guidelines *Table 18*; [d]: 2015 ESC/ERS PH guidelines *Table 13*; [e]: 2015 ESC/ERS PH guidelines *Table 19*; [f]: 2015 ESC/ERS PH guidelines *Table 20*; [g]: 2015 ESC/ERS PH guidelines *Table 14*; [h]: 2015 ESC/ERS PH guidelines *Table 21*; [i]: maximal medical therapy is considered triple combination therapy including a *s.c.* or an *i.v.* PCA (*i.v.* preferred in high-risk status); [j]: 2015 ESC/ERS PH guidelines *Table 22*.

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 II		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	-

ERA = endothelin receptor antagonist; i.v. = intravenous; PDE-5i = phosphodiesterase type 5 inhibitor; RCT = randomized controlled trial; s.c. = subcutaneous; WHO-FC = World Health Organization functional class.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.
[d]Time to clinical failure as primary endpoint in RCTs or drugs with demonstrated reduction in all-cause mortality (prospectively defined).

European Heart Journal
doi:10.1093/eurheartj/ehv317

OPTIMA study

Initial Combination Therapy With Macitentan And Tadalafil In Newly Diagnosed Patients With Pulmonary Arterial Hypertension: Results From The Optima Trial

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For the OPTIMA Investigators

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RATIONALE: Combination therapy with an endothelin receptor antagonist and a phosphodiesterase type 5 inhibitor is recommended for the treatment of pulmonary arterial hypertension (PAH).[1] OPTIMA (EudraCT 2015-002078-19) is an ongoing study evaluating the efficacy, safety and tolerability of initial combination therapy with macitentan and tadalafil in newly diagnosed patients with PAH.
METHODS: In this multicenter, prospective, single-arm, open-label Phase IV trial, newly diagnosed PAH patients (18–75 years) in WHO functional class II–III receive macitentan 10 mg once daily and tadalafil 40 mg once daily. Treatment is initiated with macitentan 10 mg and tadalafil 20 mg on the same day; after 1 week the dose of tadalafil is increased to 40 mg. The primary endpoint is pulmonary vascular resistance (PVR) at Week 16, calculated as percent change from baseline (geometric mean ratio) and presented with 95% confidence intervals (CI). Secondary endpoints include the change from baseline to Week 16 in other hemodynamic variables, WHO functional class, 6-minute walk distance and N-terminal pro-brain natriuretic peptide (NT-proBNP). Safety and tolerability are monitored throughout.
RESULTS: By October 2016, 16 patients had completed 16 weeks of treatment. At baseline, the mean (SD) age was 58.4 (15.6) years and 62.5% were female. The population included 9 patients with idiopathic PAH, 5 patients with connective tissue disease-associated PAH, 1 patient with heritable PAH, and 1 patient with HIV-associated PAH . All were receiving the combination of macitentan 10 mg and tadalafil 40 mg 1 week after treatment initiation. No patients prematurely discontinued the combination regimen. At Week 16, PVR decreased by 54% (95% CI 48, 60). Change from baseline in efficacy endpoints are summarized in the table. The most frequent adverse events were peripheral edema or swelling, headache and anemia (3 patients each). No patients experienced hypotension. No increases in aminotransferases greater than 3 times the upper limit of normal were observed; 1 patient experienced a decrease in hemoglobin below 10 g/dL.
CONCLUSION: In the OPTIMA study, initial treatment with macitentan and tadalafil in patients with PAH led to significant improvements in cardiac hemodynamic parameters indicative of right ventricular function. The treatment regimen was well tolerated and allowed patients to receive macitentan in combination with the recommended dose of tadalafil 1 week after treatment initiation.
1. Galiè N, *et al. Eur Heart J* 2016;37:67–119

American Thoracic Society 2017 International Conference, May 19-24, 2017 - Washington, DC

American Journal of Respiratory and Critical Care Medicine®

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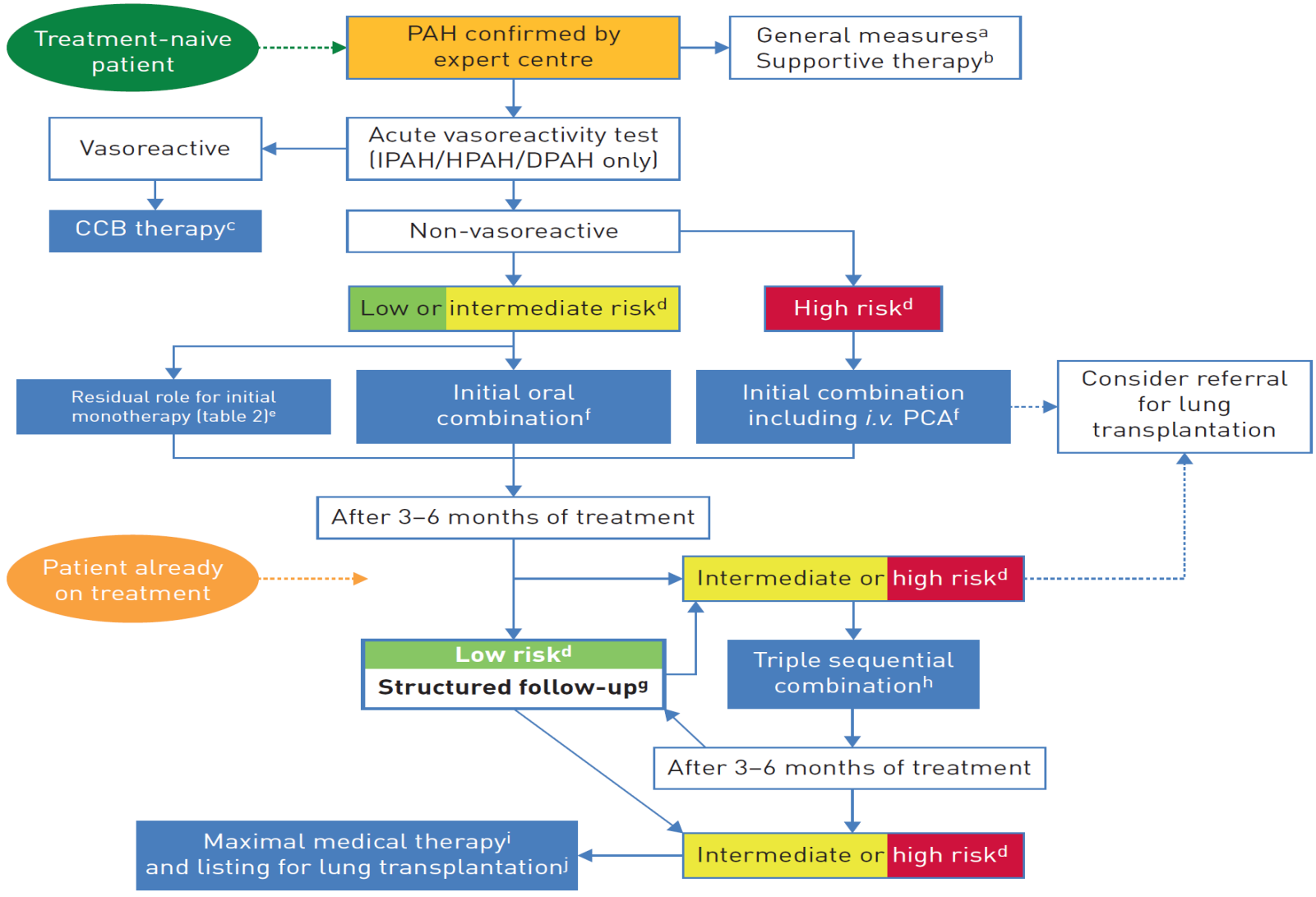

FIGURE 2 Treatment algorithm. PAH: pulmonary arterial hypertension; IPAH: idiopathic PAH; HPAH: heritable PAH; DPAH: drug-induced PAH; CCB: calcium channel blocker; PCA: prostacyclin analogue; PH: pulmonary hypertension. [a]: 2015 ESC/ERS PH guidelines *Table 16*; [b]: 2015 ESC/ERS PH guidelines *Table 17*; [c]: 2015 ESC/ERS PH guidelines *Table 18*; [d]: 2015 ESC/ERS PH guidelines *Table 13*; [e]: 2015 ESC/ERS PH guidelines *Table 19*; [f]: 2015 ESC/ERS PH guidelines *Table 20*; [g]: 2015 ESC/ERS PH guidelines *Table 14*; [h]: 2015 ESC/ERS PH guidelines *Table 21*; [i]: maximal medical therapy is considered triple combination therapy including a *s.c.* or an *i.v.* PCA (*i.v.* preferred in high-risk status); [j]: 2015 ESC/ERS PH guidelines *Table 22*.

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] added to ERA and/or PDE-5i[d]	I	B	I	B	IIa	C	241, 248
Sildenafil added to epoprostenol	–	–	I	B	IIa	B	209
Treprostinil inhaled added to sildenafil or bosentan	IIa	B	IIa	B	IIa	C	237
Iloprost inhaled added to bosentan	IIb	B	IIb	B	IIb	C	230, 231
Tadalafil added to bosentan	IIa	C	IIa	C	IIa	C	211
Ambrisentan added to sildenafil	IIb	C	IIb	C	IIb	C	249
Bosentan added to epoprostenol	–	–	IIb	C	IIb	C	250
Bosentan added to sildenafil	IIb	C	IIb	C	IIb	C	251, 252
Sildenafil added to bosentan	IIb	C	IIb	C	IIb	C	252
Other double combinations	IIb	C	IIb	C	IIb	C	–
Other triple combinations	IIb	C	IIb	C	IIb	C	–
Riociguat added to sildenafil or other PDE-5i	III	B	III	B	III	B	215

EMA = European Medicines Agency; ERA = endothelin receptor antagonist; PAH = pulmonary arterial hypertension; PDE-5i = phosphodiesterase type 5 inhibitor; RCT = randomized controlled trial; WHO-FC = World Health Organization functional class.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.
[d]Time to clinical worsening as primary endpoint in RCTs or drugs with demonstrated reduction in all-cause mortality (prospectively defined).
[e]This drug was not approved by the EMA at the time of publication of these guidelines.

European Heart Journal
doi:10.1093/eurheartj/ehv317

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 slope ≥45
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 (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
doi:10.1093/eurheartj/ehv317

Treatment should not be "lighter" than needed because..!

WHY IS THIS PLANT STILL BEING WATERED?

IT'S EASY TO JUST FOLLOW THE INSTRUCTIONS, BUT TREATING TOO LONG WITHOUT RECOGNIZING FAILURE IS DANGEROUS

- **IRREPLACEABLE TIME IS LOST BEFORE SWITCHING THERAPIES**
- **NEED EXPERIENCED FOLLOWUP**
- ***…και Καλή Συνεργασία με Εξειδικευμένα Κέντρα !!!***

- ***Ευχαριστώ για την υπομονή σας***