ΕΛΛΗΝΙΚΗ ΠΝΕΥΜΟΝΟΛΟΓΙΚΗ ΕΤΑΙΡΕΙΑ

9ο Εκπαιδευτικό Φροντιστήριο

Βόλος, 13.5.2012

Πνευμονική υπέρταση

Ηρακλής Τσαγκάρης,

Επίκουρος Καθηγητής Εντατικής Θεραπείας

Β’ Κλινική Εντατικής Θεραπείας και Διακλινικό Ιατρείο Πνευμονικής Υπέρτασης

Αττικό Νοσοκομείο

Ορισμοί

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	
Reactive (out of proportion)	TPG >12 mmHg	

ESC/ERS GUIDELINES

Etiologic classification of pulmonary hypertension

- **MPA - PCWP = CO * PVR**
- **MPA = CO * PVR + PCWP**

Pulmonary Hypertension: Define Lesion

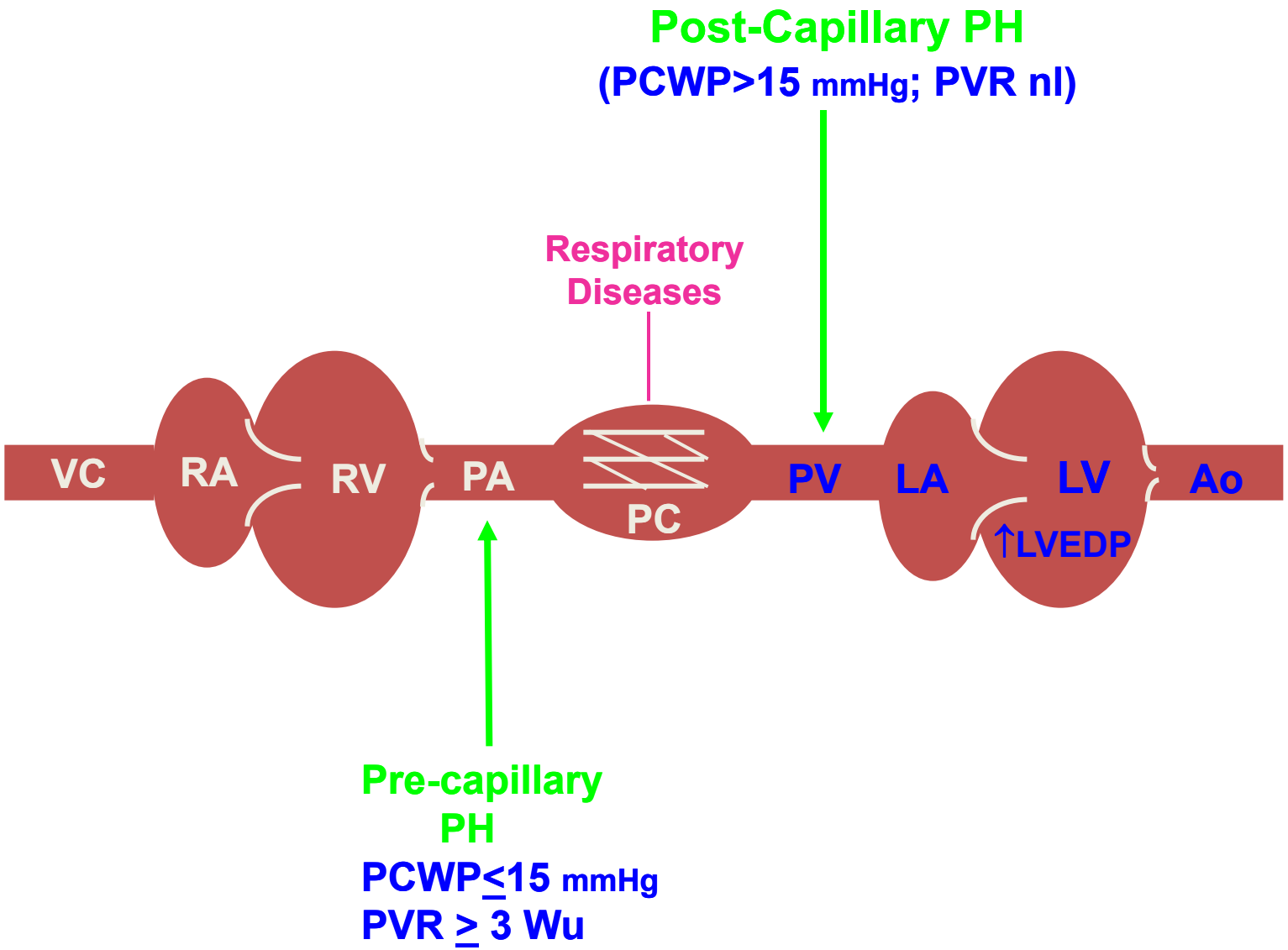

Table 1 Venice Clinical Classification of Pulmonary Hypertension (2003)

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
2.2. Left-sided valvular heart disease

3. Pulmonary hypertension associated with lung diseases and/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. Developmental abnormalities

4. Pulmonary hypertension owing 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. Nonthrombotic pulmonary embolism (tumor, parasites, foreign material)

5. Miscellaneous

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

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

1. Pulmonary arterial hypertension (PAH)
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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)**

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Πνευμονοπάθεια και ΡΗ: Μηχανισμοί

- ✓ Υποξική αγγειοσύσπαση
- ✓ Μείωση της πνευμονικής αγγειακής κοίτης
- ✓ Αύξηση της καρδιακής παροχής και της γλοιότητας του αίματος

5. **Pulmonary hypertension with unclear multifactorial mechanisms**

5.1. **Hematologic disorders: myeloproliferative disorders, splenectomy**

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Venice, 2004

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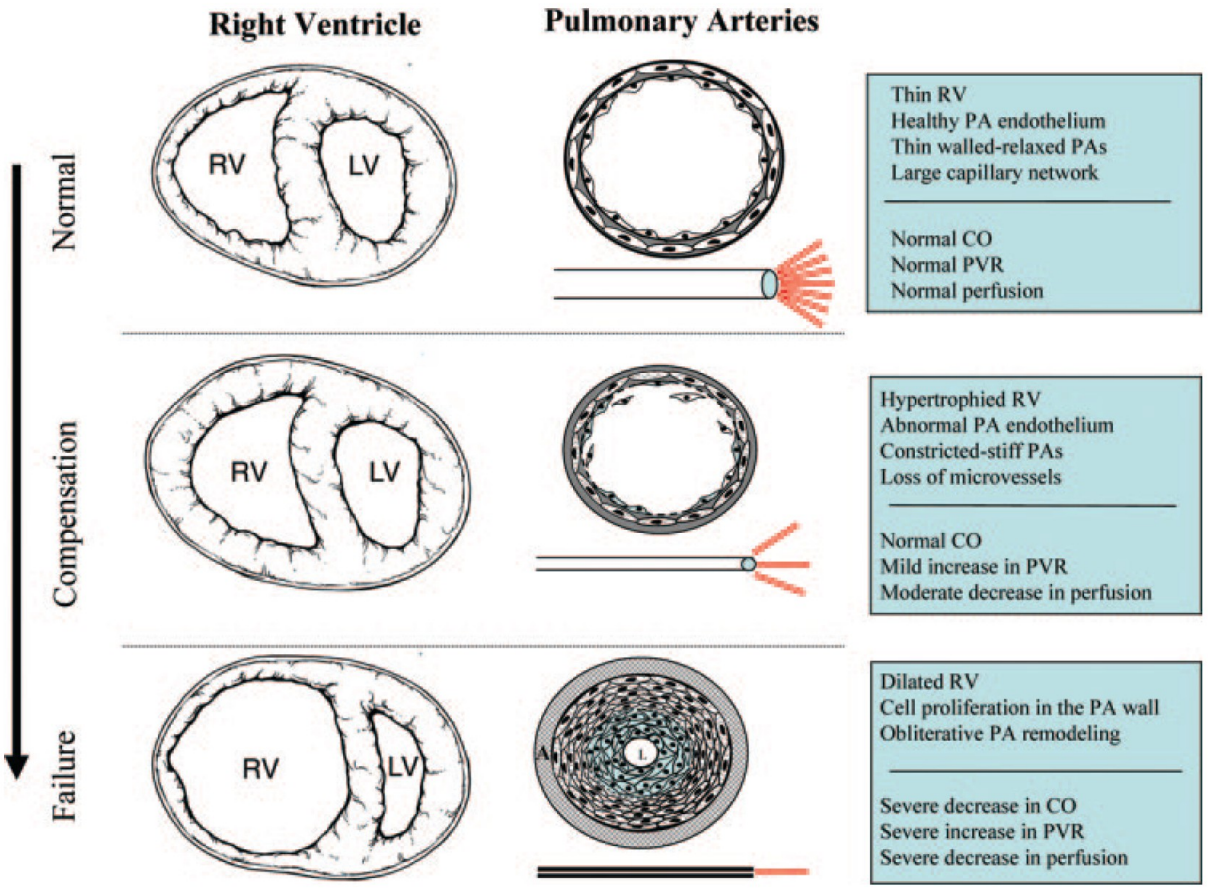
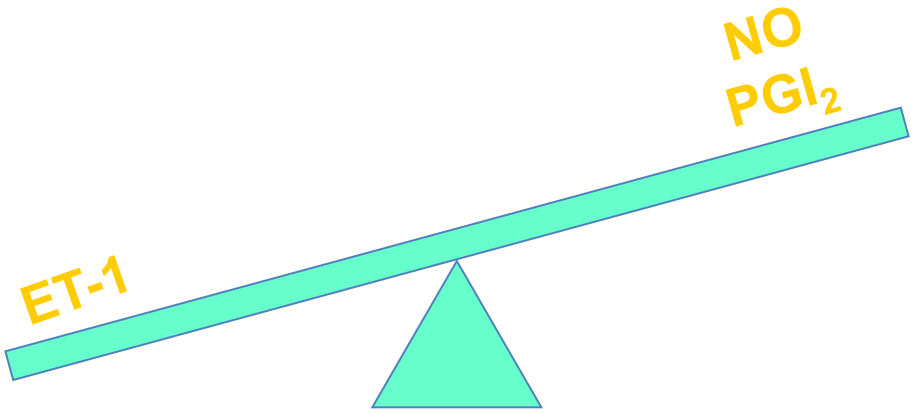
Progression of vascular disease



Hunter C. Champion, Evangelos D. Michelakis and Paul M. Hassoun

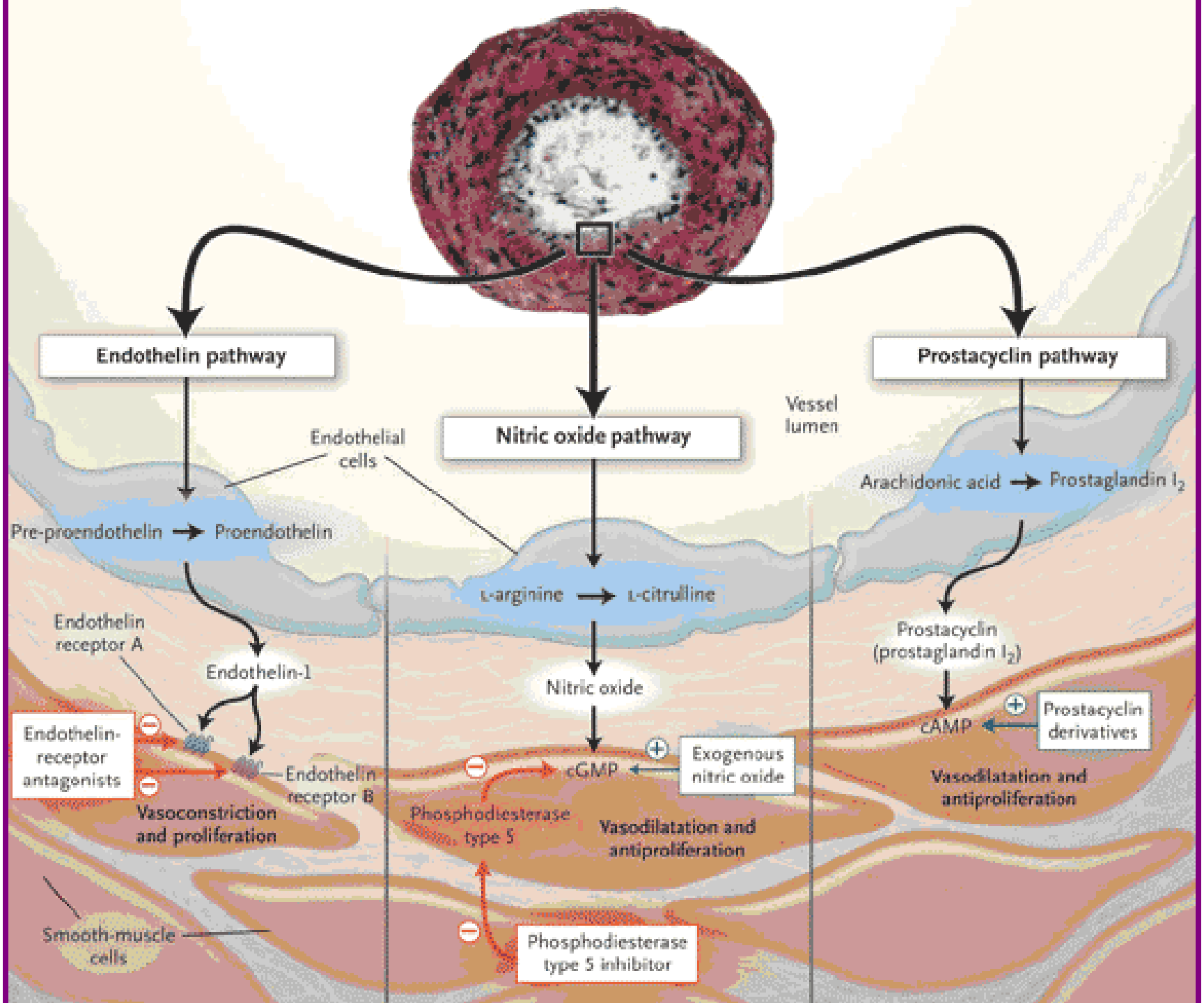
Circulation 2009;120;992-1007

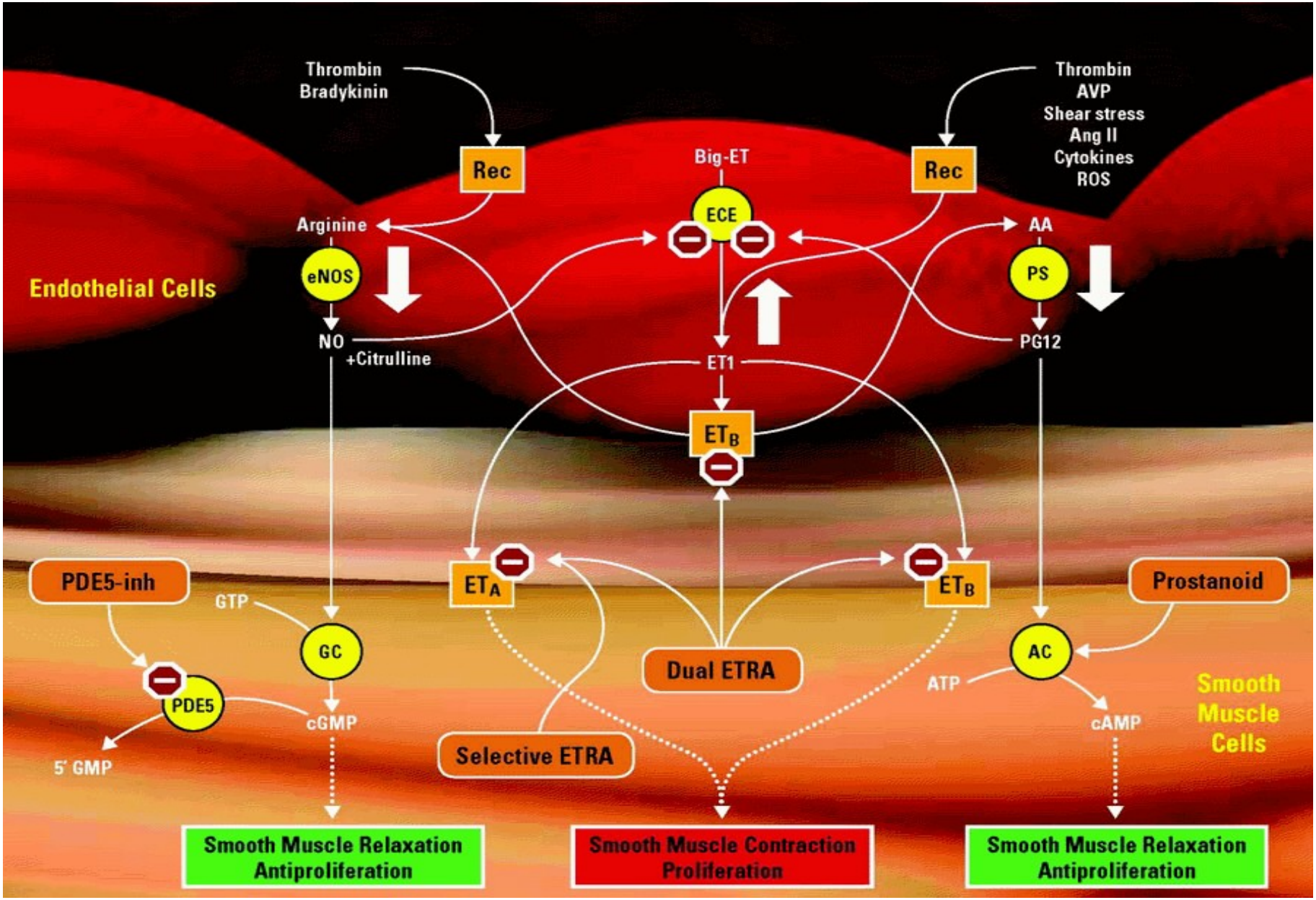
Endothelial Cell Dysfunction in PAH



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

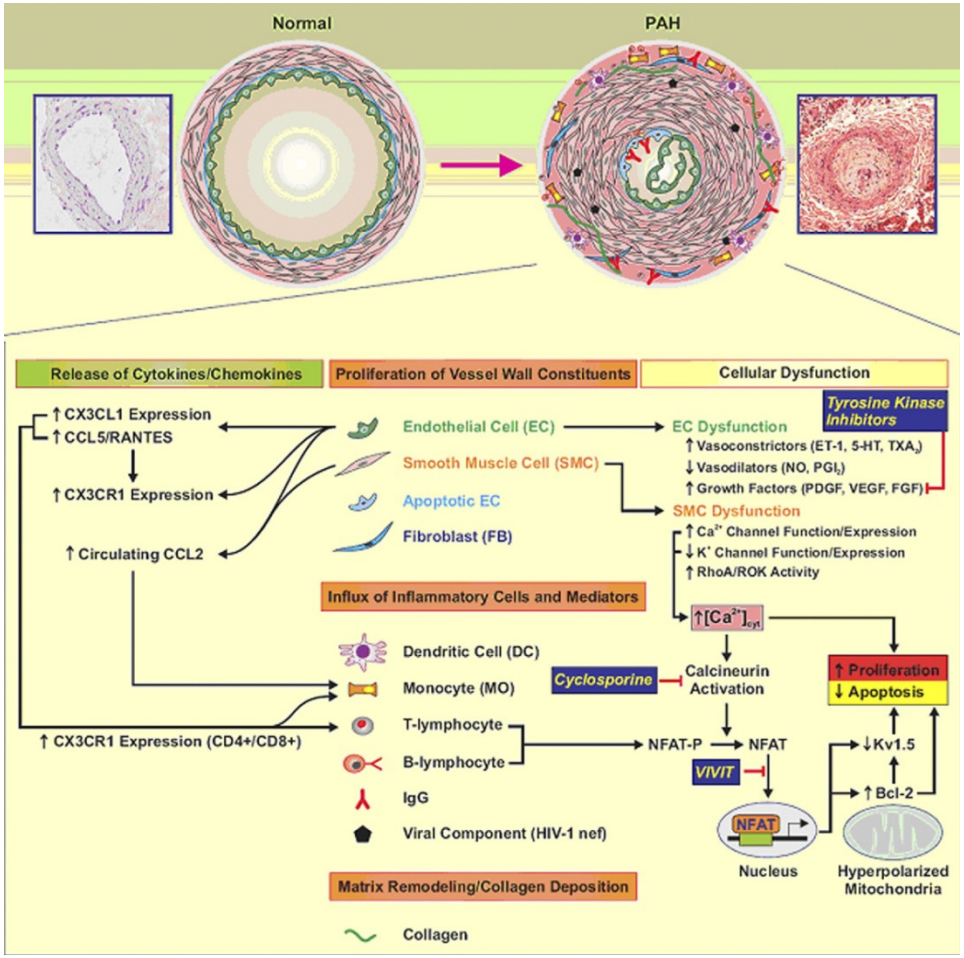
Spieker LE et al. J Am Coll Cardiol. 2001;37:1493-1505.
Luscher TF and Barton M. Circulation. 2000;102:2434-2440.
Albrecht EW et al. J Pathol. 2003;199:8-17.
Hankins SR and Horn EM. Curr Cardiol Rep. 2000;2:244-251.


Endothelin pathway
Nitric oxide pathway
Prostacyclin pathway
Vessel lumen
Endothelial cells
Pre-proendothelin
Proendothelin
Arachidonic acid
Prostaglandin I2
L-arginine
L-citrulline
Endothelin receptor A
Endothelin-1
Endothelin-receptor antagonists
Endothelin receptor B
Vasoconstriction and proliferation
Nitric oxide
Prostacyclin (prostaglandin I2)
cAMP
Prostacyclin derivatives
Vasodilatation and antiproliferation
cGMP
Exogenous nitric oxide
Phosphodiesterase type 5
Vasodilatation and antiproliferation
Smooth-muscle cells
Phosphodiesterase type 5 inhibitor



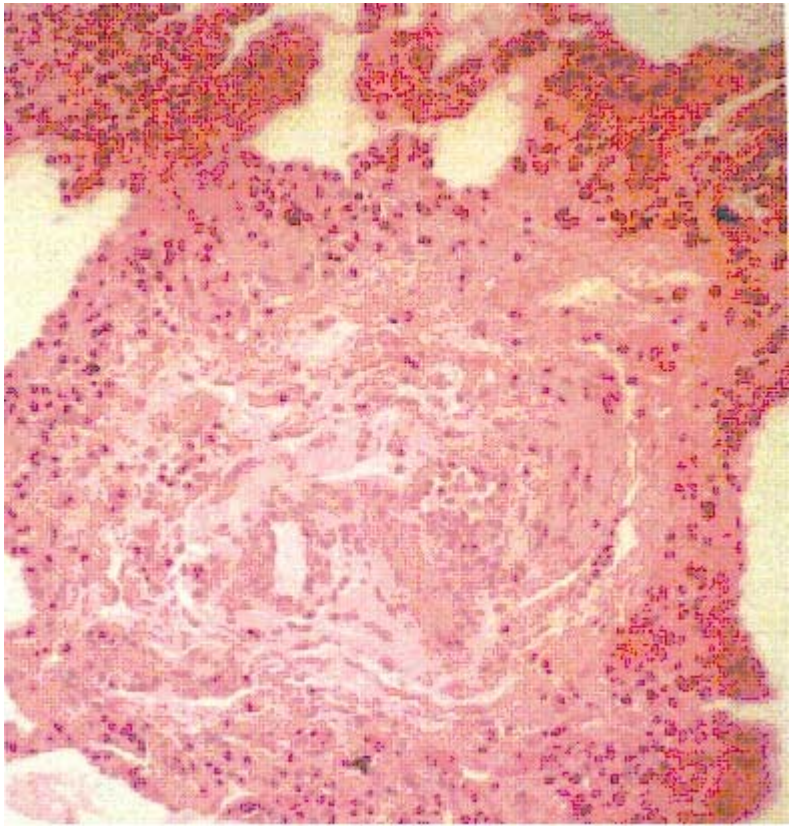
McLaughlin & McGoon *Circulation* 2006, 114:1417-143

Mechanisms of Inflammation-Mediated Remodeling

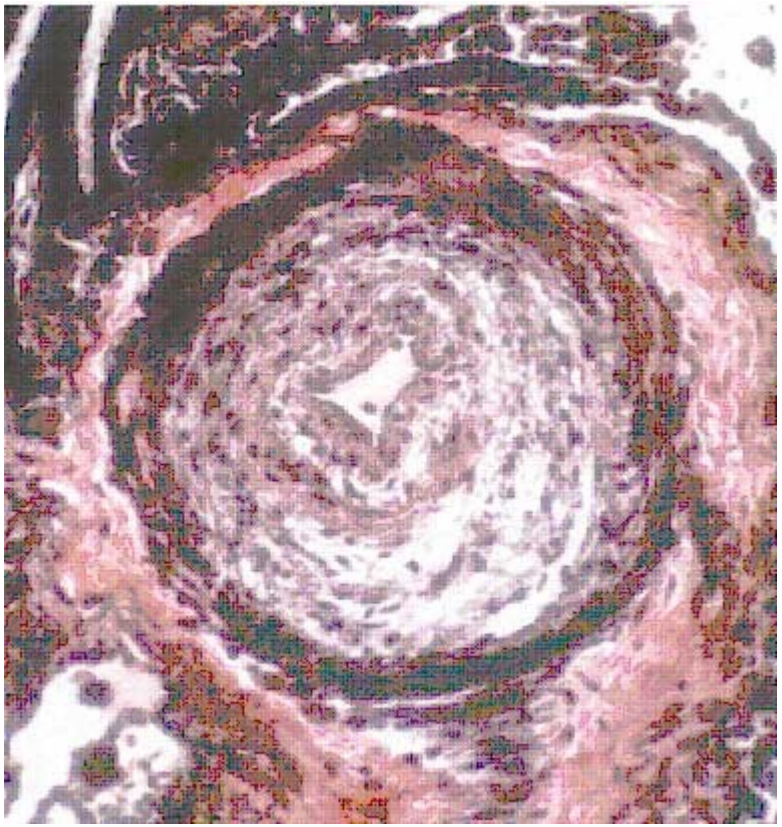


ΠΑΥ: νόσος υπερπλασίας και απόφραξης

Plexiform lesion



Occlusion of pulmonary artery



Fishman. Physiol Res 2000

Severe Pulmonary Arterial Hypertension

A Forme Fruste of Cancer?

At first examination, pulmonary arterial hypertension is not cancer. The vascular lesions of severe pulmonary arterial hypertension exhibit only some of the classic characteristics of malignancy. As cancer-like processes, these lesions are angiogenic, apoptotic cells are rarely found, and antiapoptotic proteins are overexpressed. However, some major characteristics of cancer are missing, most importantly tissue invasion and metastasis.

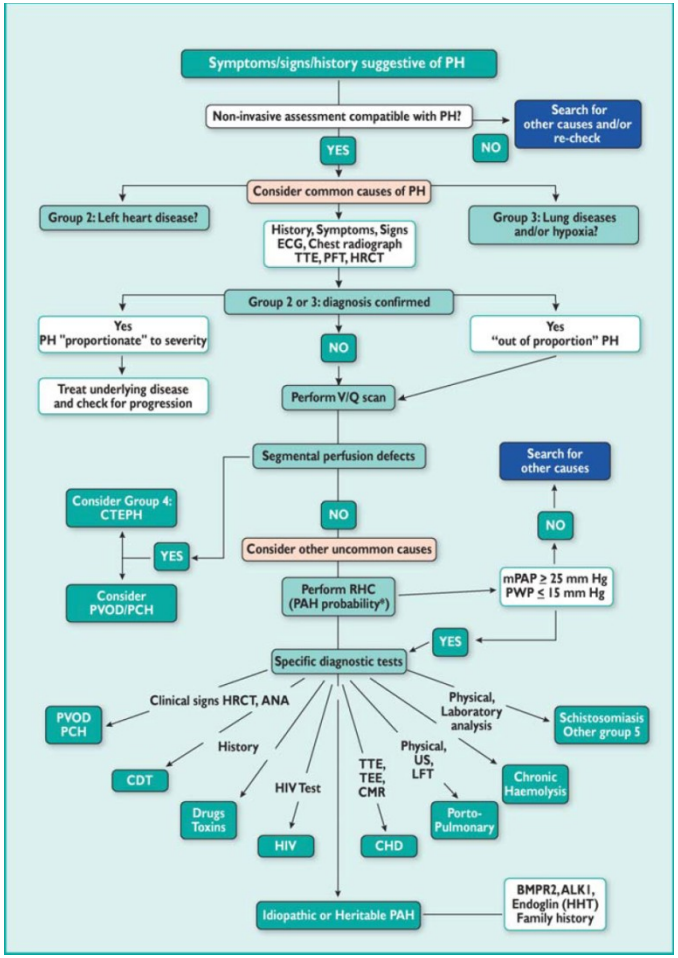
- As stated by the authors, the lesions characteristic of pulmonary arterial hypertension are not cancerous in the true meaning of word, but they show many features of neoplastic proliferation in that there is a process of abnormal and uncontrolled cell growth.

Humbert and Hoeper
Am J Respir Crit Care Med Vol 178. pp 551–557, 2008

Διαγνωστική προσέγγιση

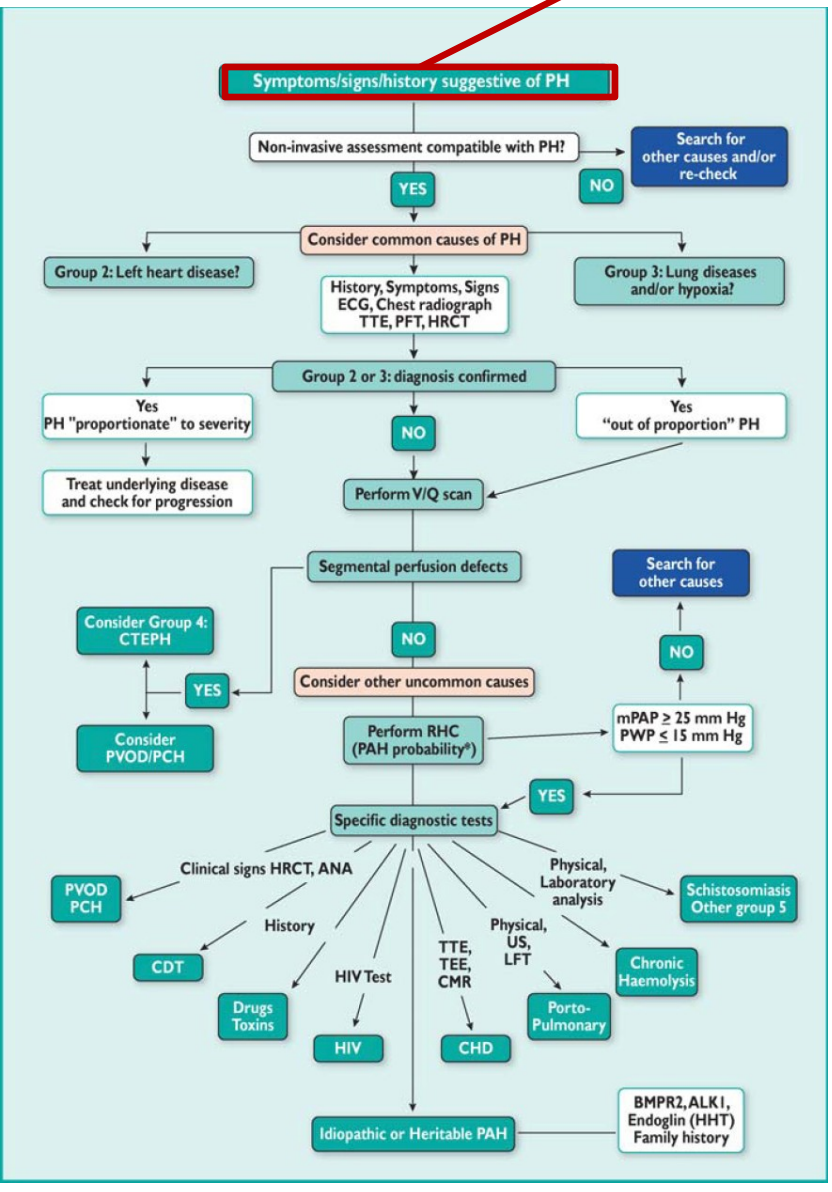
- Υποψία (suspicion)
- Ανίχνευση (detection)
- Ταυτοποίηση (identification)
- Αξιολόγηση-κατάταξη

Διαγνωστικός αλγόριθμος



ESC/ERS GUIDELINES

Συμπτώματα/σημεία/ιστορικό

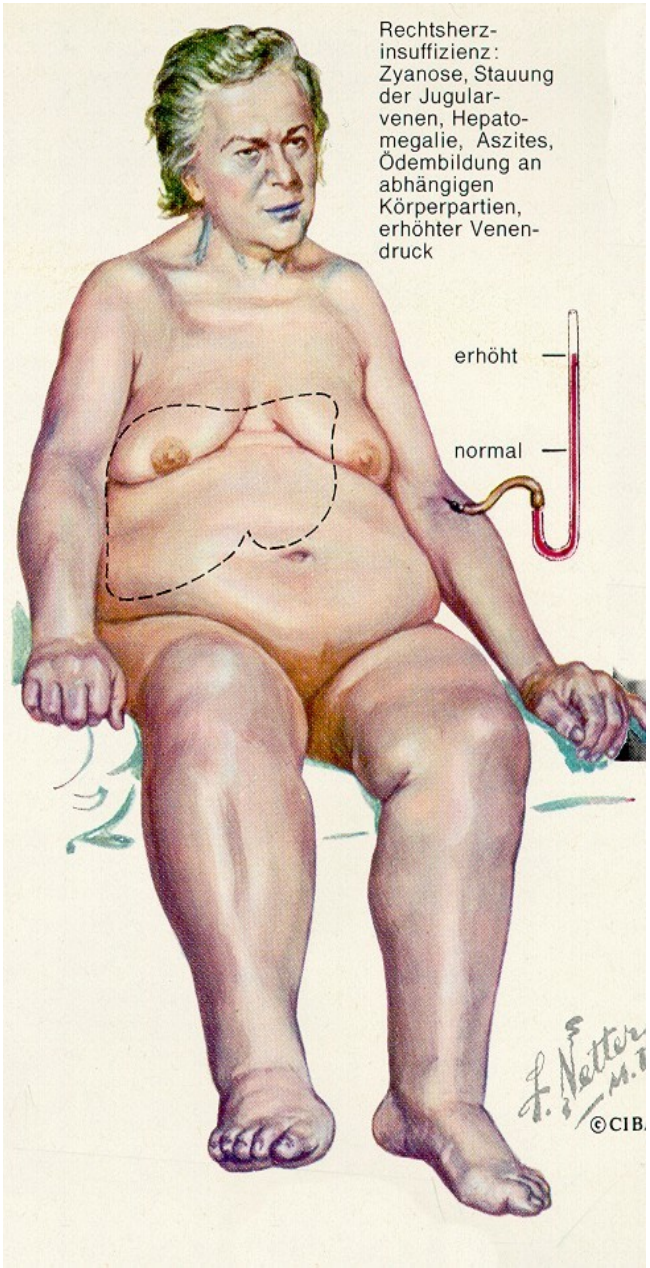


- Δύσπνοια
- Στηθάγχη
- Συγκοπτικό επεισόδιο
- Οίδημα
- Raynaud

ESC/ERS GUIDELINES

Right heart failure

Dyspnea
Palpitations
Fatigue
Chest pain
Nausea
Edemas
Ascites
Stasis liver (“cardiac liver”)
Impaired digestion



Clinical picture: Symptoms

- first clinical symptoms inconspicuous and not specific
- often misinterpretation of symptoms
- incidence higher in younger persons (3.-4. decade)

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- first clinical symptoms inconspicuous and not specific
- often misinterpretation of symptoms
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2 χρόνια καθυστέρηση

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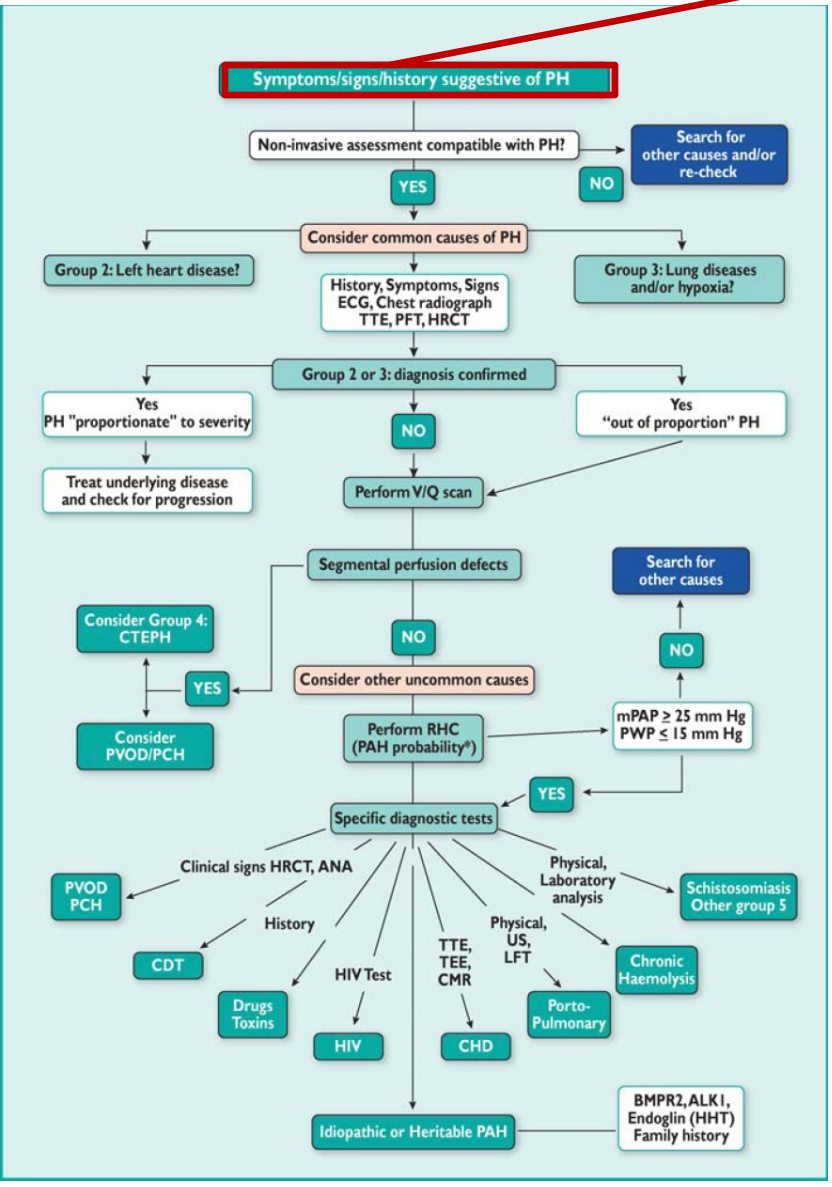

- Κλινική εξέταση
- Ακτινογραφία
- ΗΚΓ

ESC/ERS GUIDELINES

Υπάρχει λόγος υποψίας PAH?

Ιστορικό (συμπτώματα, παράγοντες κινδύνου, οικογενειακό Hx)

κλινική εξέταση, ακτινογραφία, ΗΚΓ

PH	RHF
Έντονος P2	Διάταση σφαγιτίδων με V
Ώση RV	RV S3
Συστολικό φύσημα (TR)	Ηπατομεγαλία
Διαστολικό φύσημα (PR)	Οίδημα
RV S4	Ασκίτης

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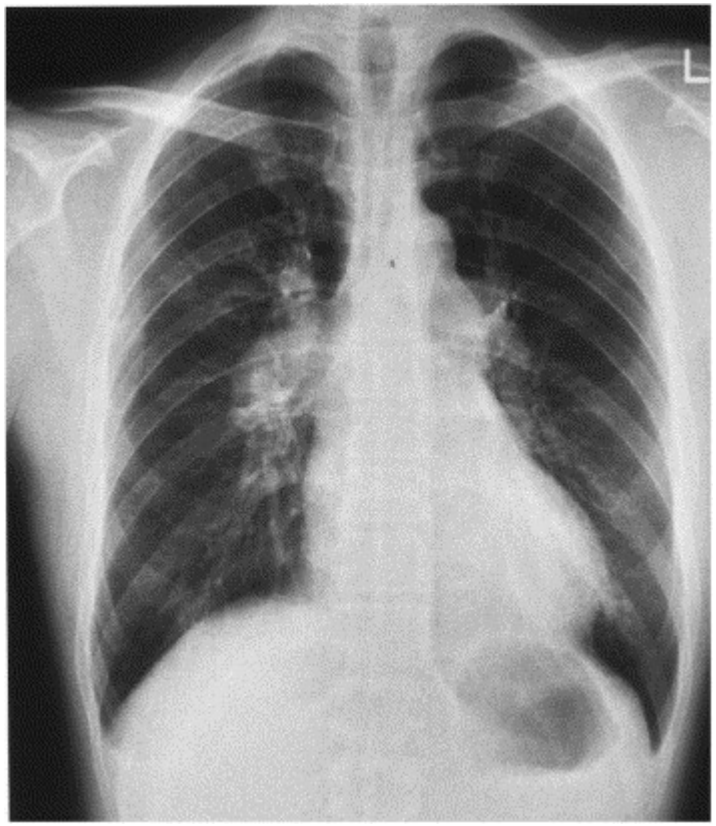
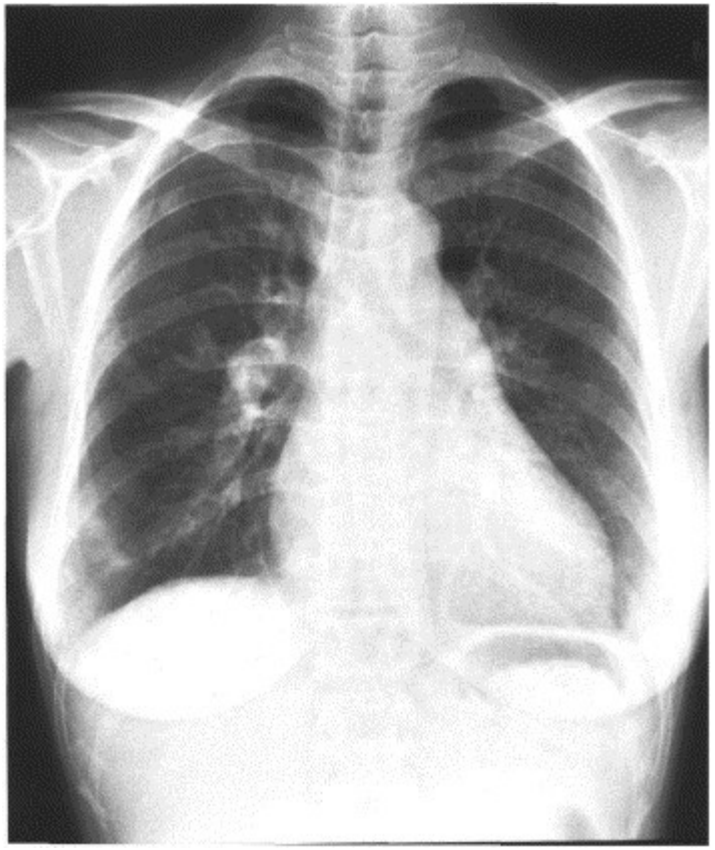


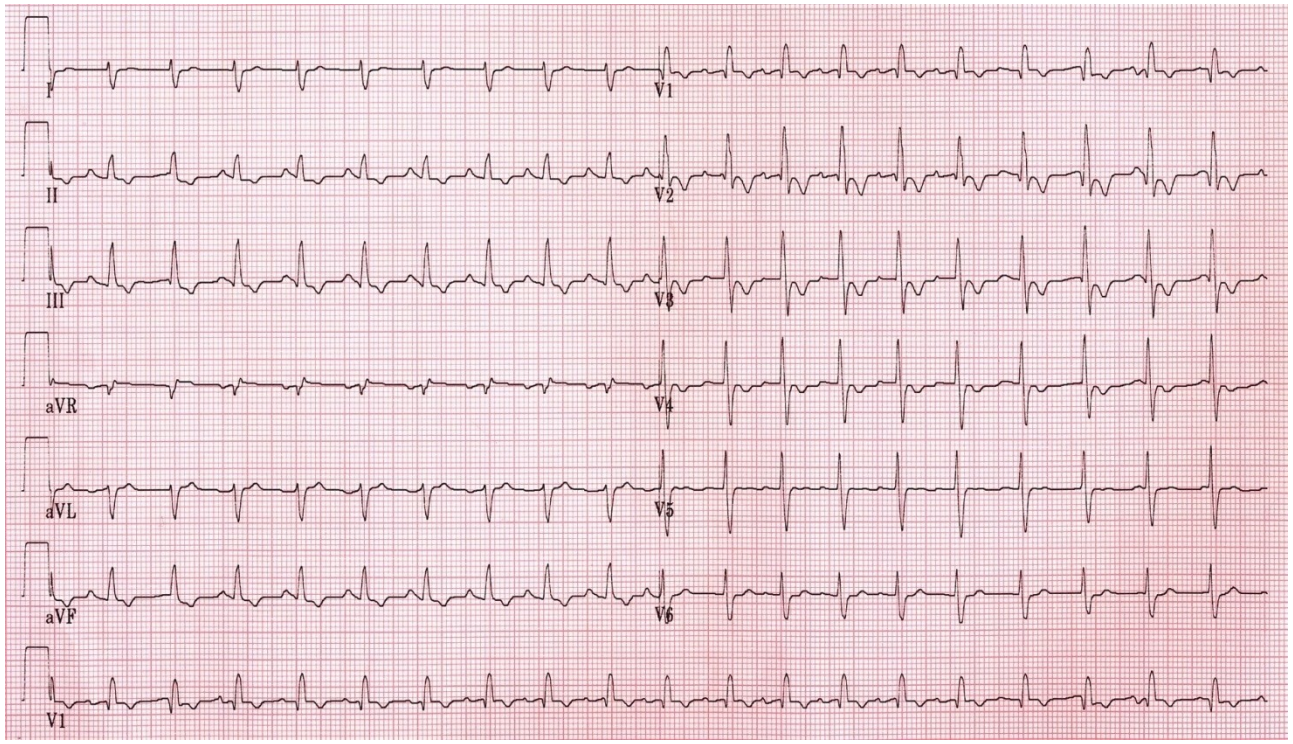


ECG

Often misinterpreted

Normal in one third of the patients

Does not parallel hemodynamics



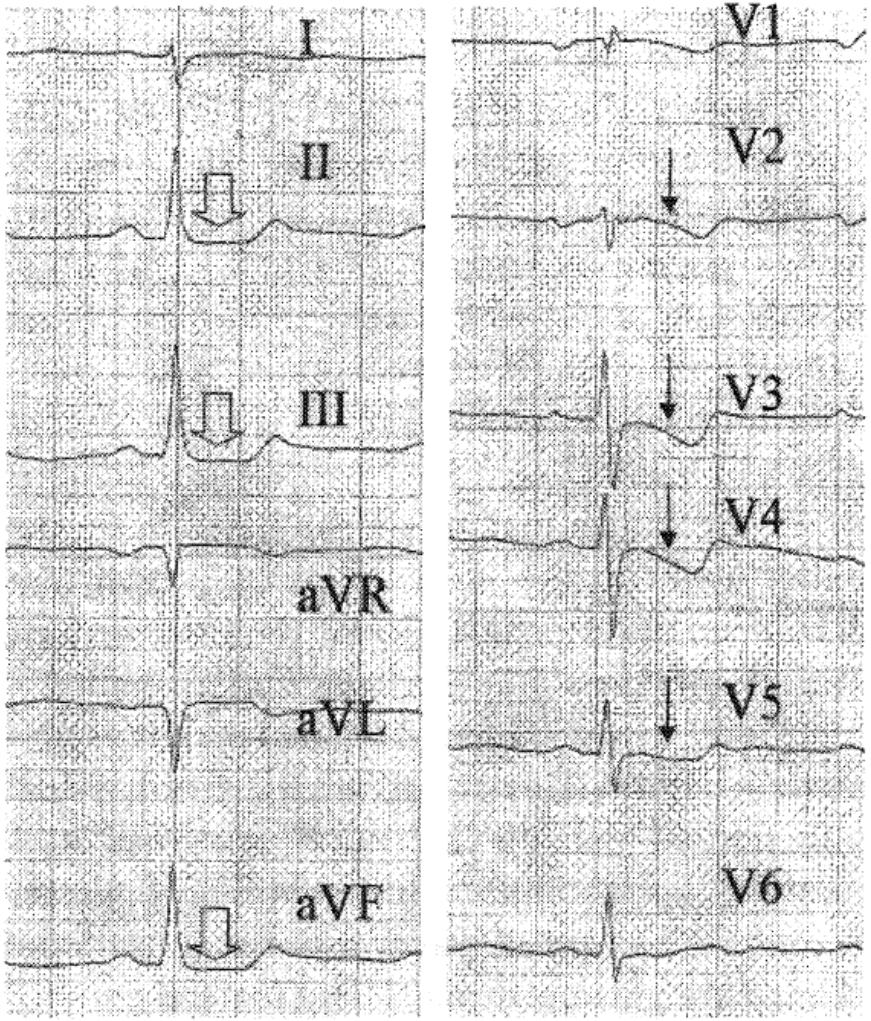
With permission of Prof. Ewert

ECG

- **In early stages:** ~50% of patients with PHT have an inconspicuous ECG at rest

- **In late stages:** typical ECG signs of right heart overload may appear:

    - Upright/right type, sagittal type
    - Positive Sokolow sign for right heart hypertrophy
    - Right bundle block
    - Convex ST-segment depression
    - Biphasic to pre-terminal inverted T in V1 – V3
      Pulmonal P-wave



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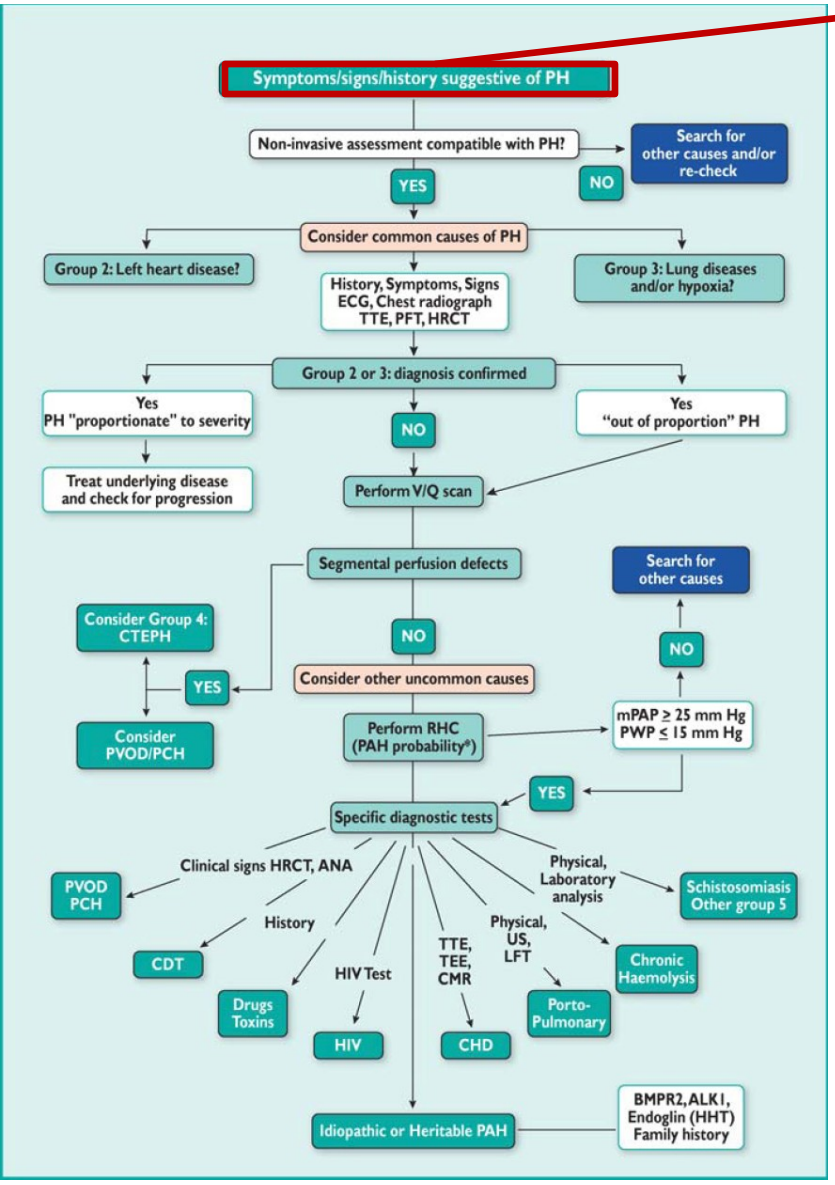

- Οικογενειακό ιστορικό
- Νόσος συνδετικού ιστού
- Συγγενής καρδιοπάθεια
- Πυλαία υπέρταση
- Φλεβική θρόμβωση/ εμβολή
- Πνευμονικ
- Χρήση ανορεξιογόνων
- HIV

Υπάρχει λόγος υποψίας PAH?

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κλινική εξέταση, ακτινογραφία, ΗΚΓ

- 6-12% ασθενών με iPAH έχουν heritable PH (familial)
- Χρωμόσωμα 2/Αυτοσωματικό επικρατές
- Κωδικοποιεί τον bone morphogenetic protein receptor II (BMPR-II)
- Χαμηλή διεισδυτικότητα (10-20%)

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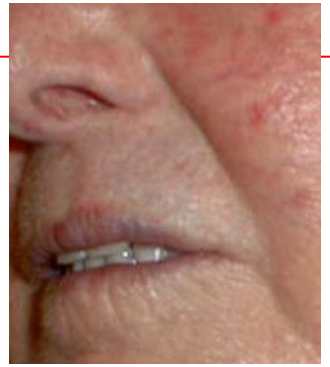
- Χρήση ανορεξιογόνων
- HIV

Υπάρχει λόγος υποψίας ΡΑΗ?

Ιστορικό (συμπτώματα, παράγοντες κινδύνου, οικογενειακό Ηx)

κλινική εξέταση, ακτινογραφία, ΗΚΓ

- CREST- περιορισμένο σκληρό-δερμα 30-50%
- Διάχυτο σκληρόδερμα έως 33%
- ΣΕΛ 4-14%
- ΡΑ έως 21% (ήπια)



- Οικογενειακό ιστορικό
- Νόσος συνδετικού ιστού
- Συγγενής καρδιοπάθεια
- Πυλαία υπέρταση
- Φλεβική θρόμβωση/ΠΕ
- Χρήση ανορεξιογόνων
- HIV

Υπάρχει λόγος υποψίας PAH?

Ιστορικό (συμπτώματα, παράγοντες κινδύνου, οικογενειακό Hx)

κλινική εξέταση, ακτινογραφία, ΗΚΓ

- 10-21% RVSP 30-50mmHg
- 4-15% RHC
- OLT:↑ θνητότητα όταν mPAP>35mmHg
- 4% OLT

- Οικογενειακό ιστορικό
- Νόσος συνδετικού ιστού
- Συγγενής καρδιοπάθεια
- Πυλαία υπέρταση
- Φλεβική θρόμβωση/ΠΕ
- Χρήση ανορεξιογόνων
- HIV

Υπάρχει λόγος υποψίας PAH?

Ιστορικό (συμπτώματα, παράγοντες κινδύνου, οικογενειακό Hx)

κλινική εξέταση, ακτινογραφία, ΗΚΓ

0,1% ασθενών με ΠΕ

- Οικογενειακό ιστορικό
- Νόσος συνδετικού ιστού
- Συγγενής καρδιοπάθεια
- Πυλαία υπέρταση
- Φλεβική θρόμβωση/ΠΕ
- Χρήση ανορεξιογόνων
- HIV

Definite

- Aminorex
- Fenfluramine
- Dexfenfluramine
- Toxic rapeseed oil
- Benfluorex

Possible

- Cocaine
- Phenylpropanolamine
- St John's Wort
- Chemotherapeutic agents
- Selective serotonin reuptake inhibitors
- Pergolide

Likely

- Amphetamines
- L-tryptophan
- Methamphetamines

Unlikely

- Oral contraceptives
- Oestrogen
- Cigarette smoking

Υπάρχει λόγος υποψίας PAH?

Ιστορικό (συμπτώματα, παράγοντες κινδύνου, οικογενειακό Hx)

κλινική εξέταση, ακτινογραφία, ΗΚΓ

- Οικογενειακό ιστορικό
- Νόσος συνδετικού ιστού
- Συγγενής καρδιοπάθεια
- Πυλαία υπέρταση
- Φλεβική θρόμβωση/ΠΕ
- Χρήση ανορεξιογόνων
- HIV

1/200 HIV

Υπάρχει λόγος υποψίας PAH

Echo

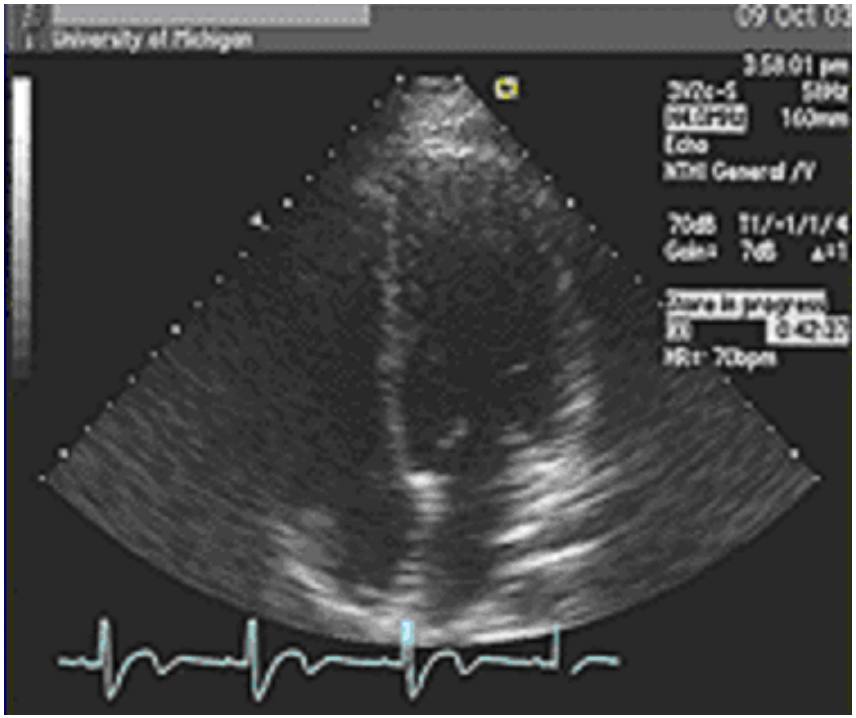
Εκτίμηση δεξιάς καρδιάς

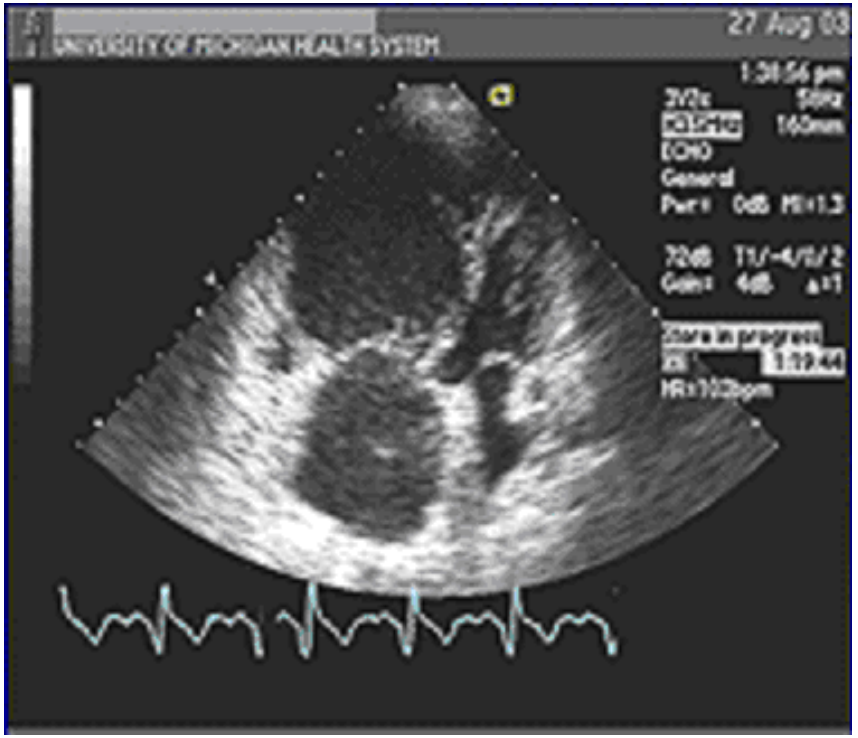
- Ταχύτητα TR>>>RVSP
- RAE, RVE, δυσλειτουργία RV

Εκτίμηση αριστερής καρδιάς

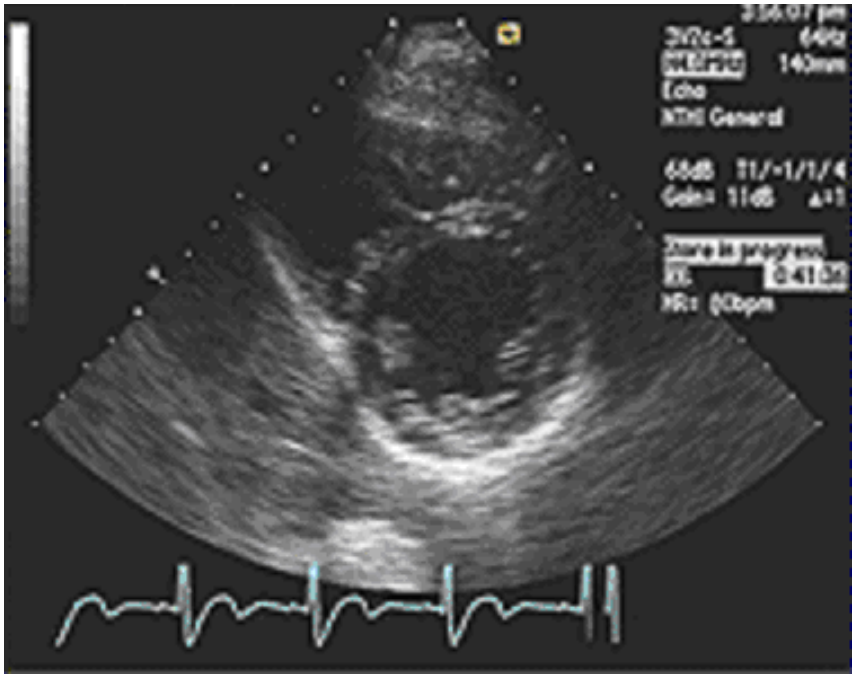
R/o συγγενείς καρδιοπάθειες

Apical 4-chamber

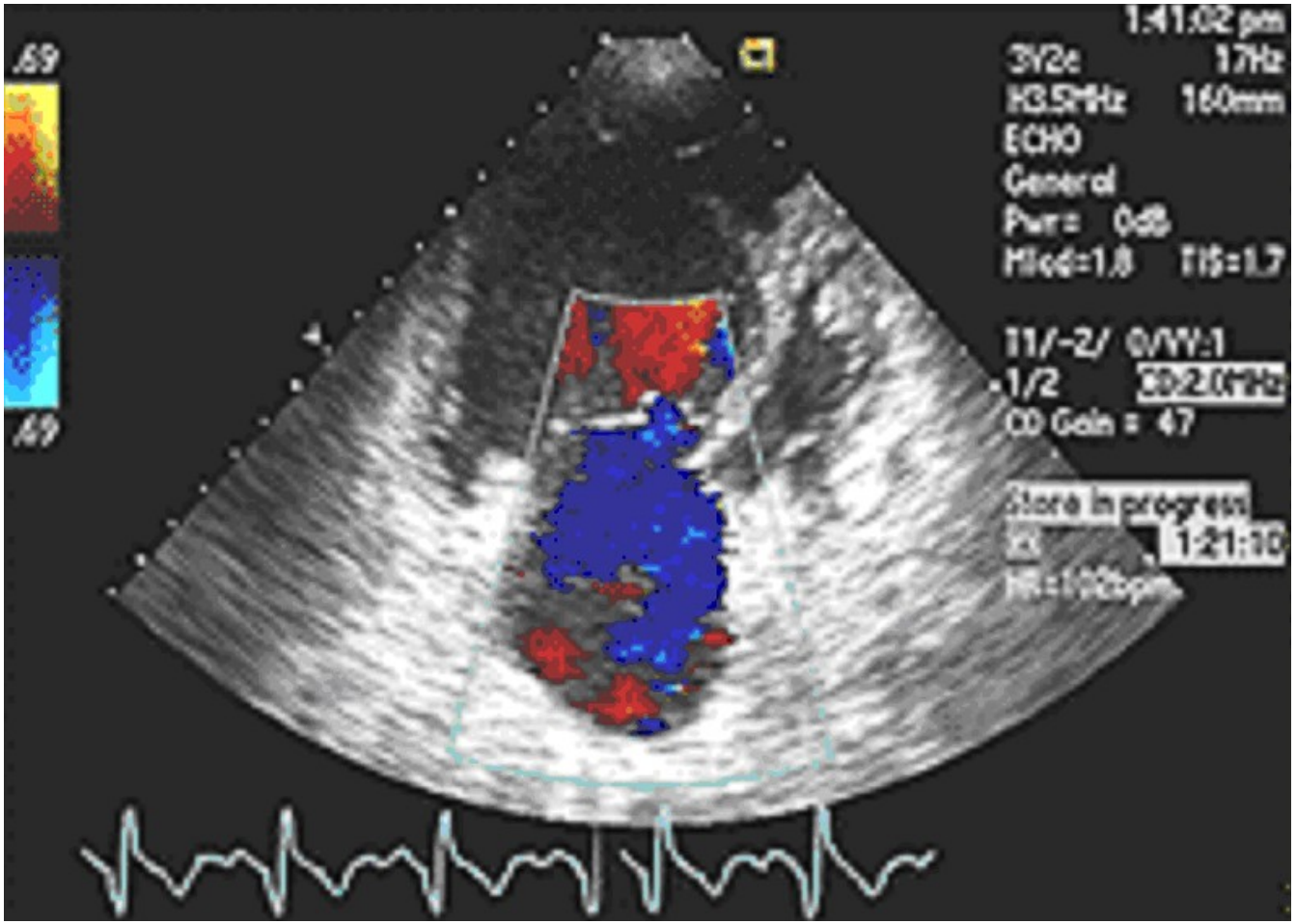


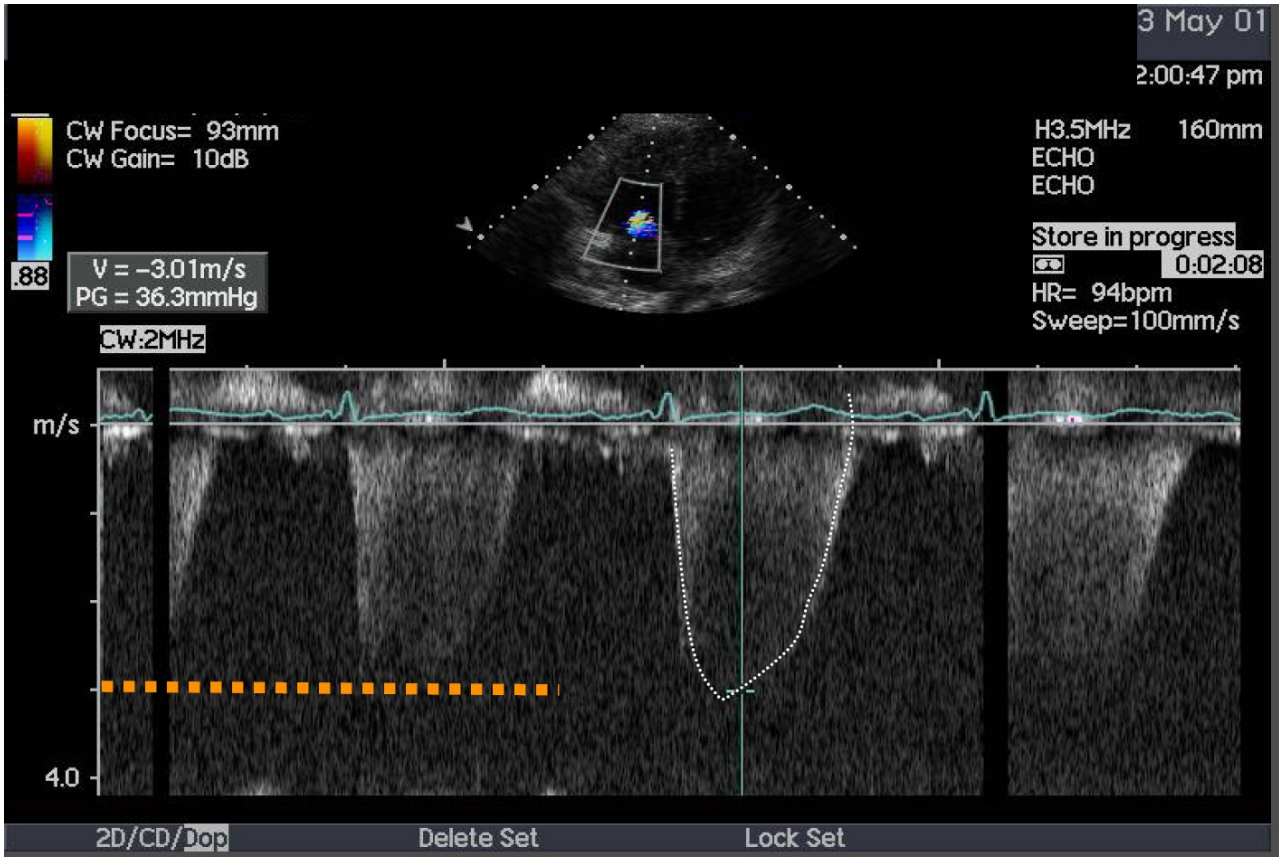


Parasternal short axis



Tricuspid Regurgitation





Tricuspid insufficiency Vmax

TI Pressure Gradient = 4 $Vmax^2$

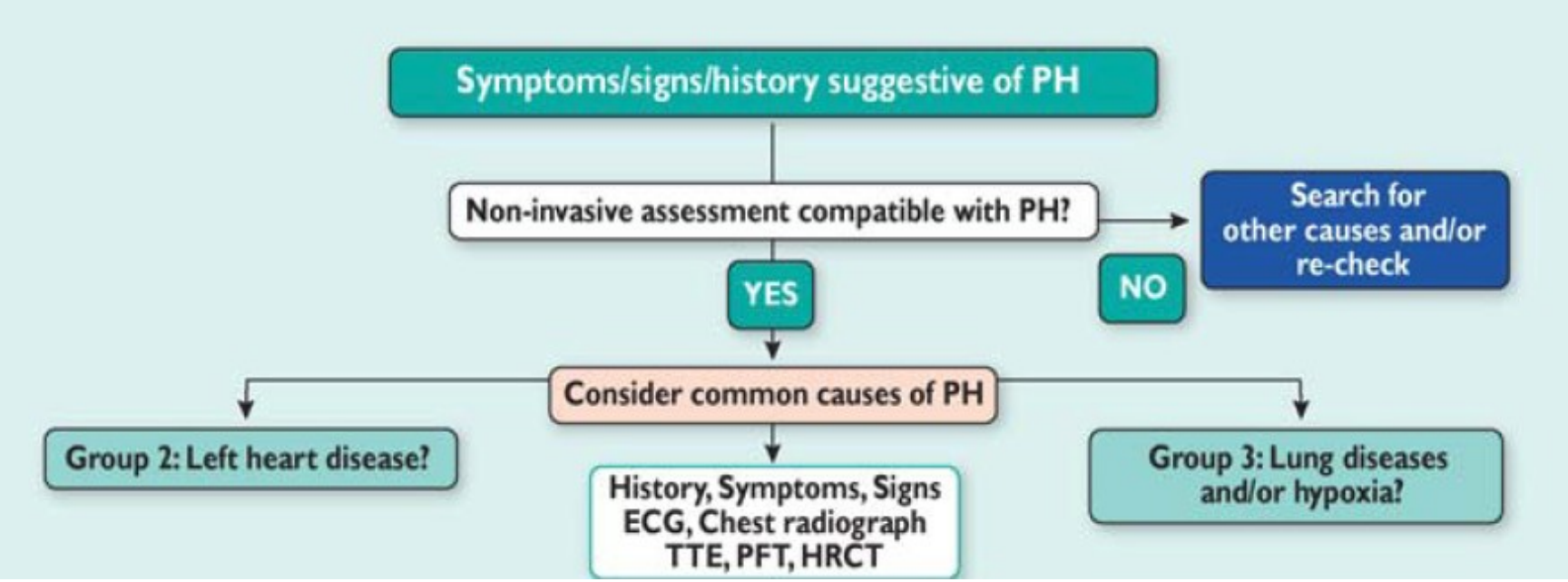
PASP = 4 x $Vmax^2$ + RAP*(est)*

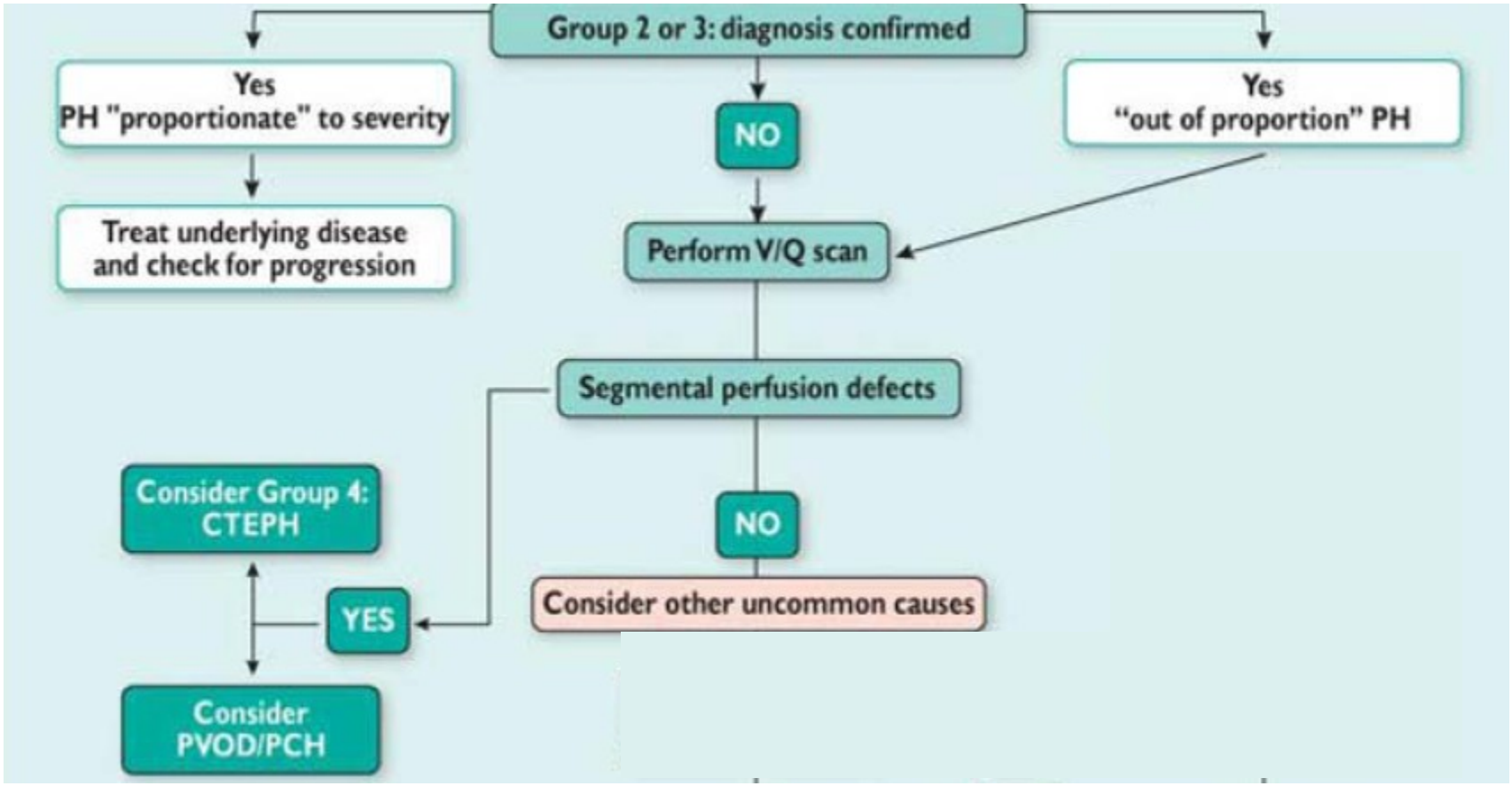
Pulmonary

mPAP:

at rest >

exercise > 3

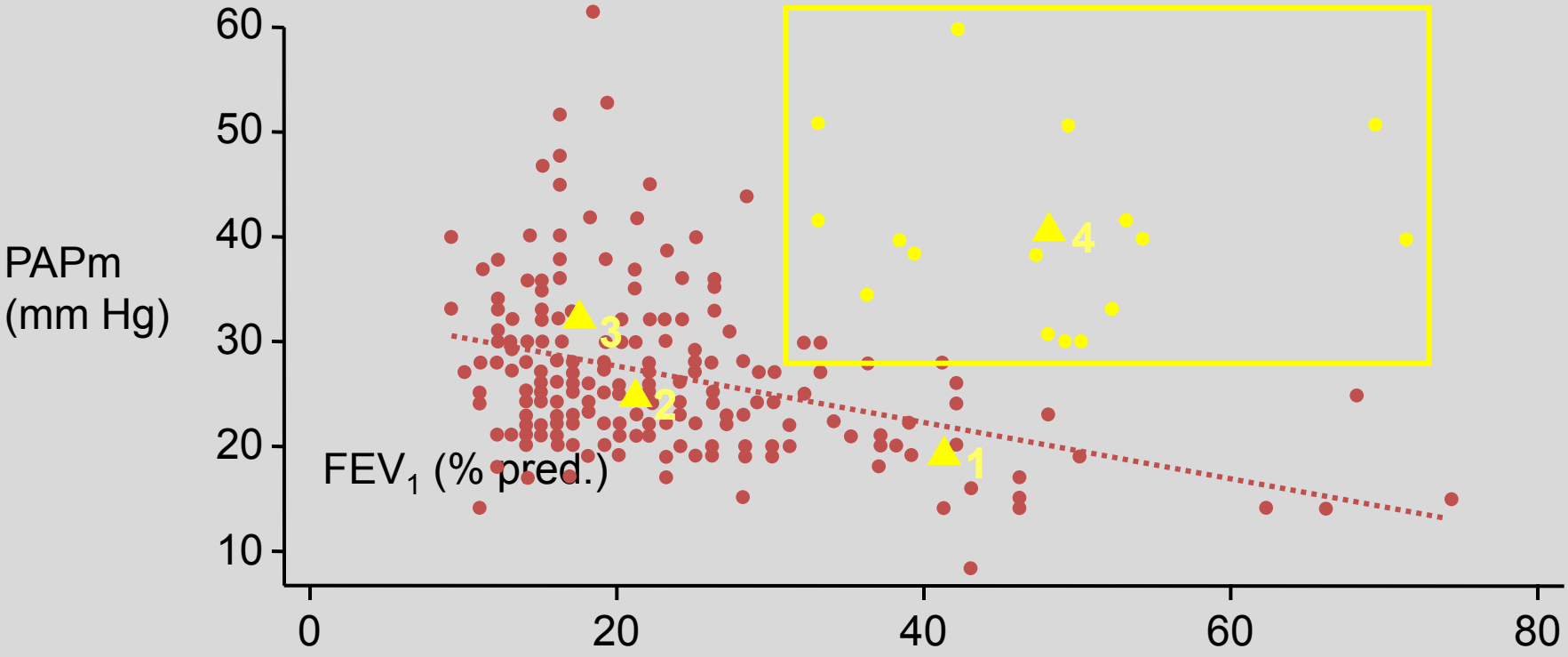

Symptoms/signs/history suggestive of PH
Non-invasive assessment compatible with PH?
Search for other causes and/or re-check
NO
YES
Consider common causes of PH
Group 2: Left heart disease?
History, Symptoms, Signs
ECG, Chest radiograph
TTE, PFT, HRCT
Group 3: Lung diseases and/or hypoxia?


Group 2 or 3: diagnosis confirmed
Yes
PH "proportionate" to severity
Treat underlying disease and check for progression
NO
Yes
"out of proportion" PH
Perform V/Q scan
Segmental perfusion defects
Consider Group 4: CTEPH
YES
Consider PVOD/PCH
NO
Consider other uncommon causes

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	
→ Reactive (out of proportion)	TPG >12 mmHg	

COPD and Pulmonary Hypertension

- **Retrospective study of 215 COPD patients**
- **7.4% of patients with pulmonary hypertension "out of proportion"**



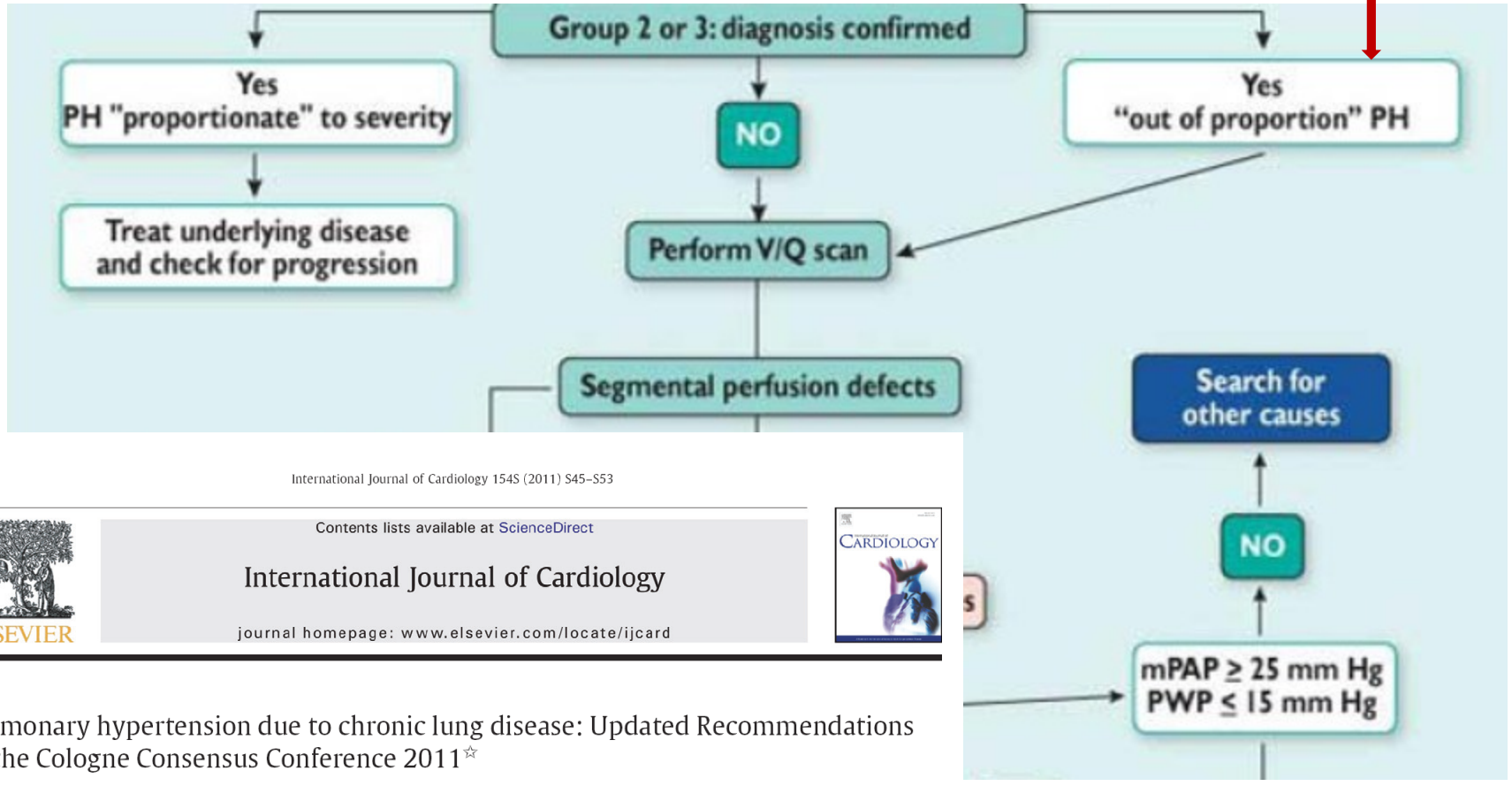
Thabut G et al. *Chest.* 2005;127:1531-1536.

Criteria for the presence of severe pulmonary hypertension in patients with chronic lung disease*.

At least 2 of the following criteria must be met:

1. Mean PA pressure (PAPm) >35 mmHg
2. PAPm ≥25 mmHg with limited cardiac output (CI <2.0 l/min/m^2)
3. Pulmonary vascular resistance (PVR) >480 dyn s cm^{-5}

*As a rule, these criteria only apply if other causes of PH (e.g. chronic thromboembolic PH or left ventricular failure) have been excluded.



International Journal of Cardiology 154S (2011) S45–S53

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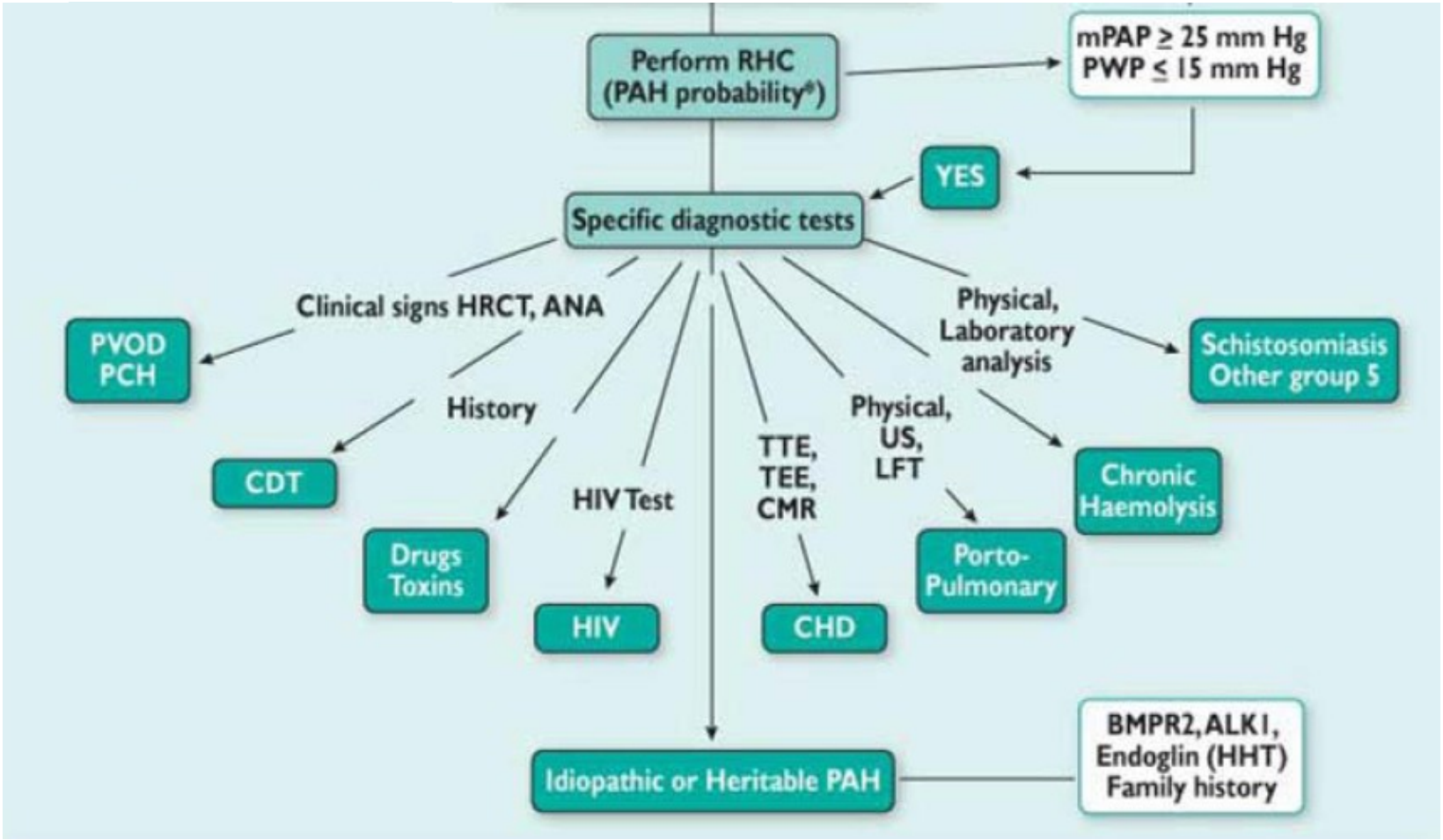
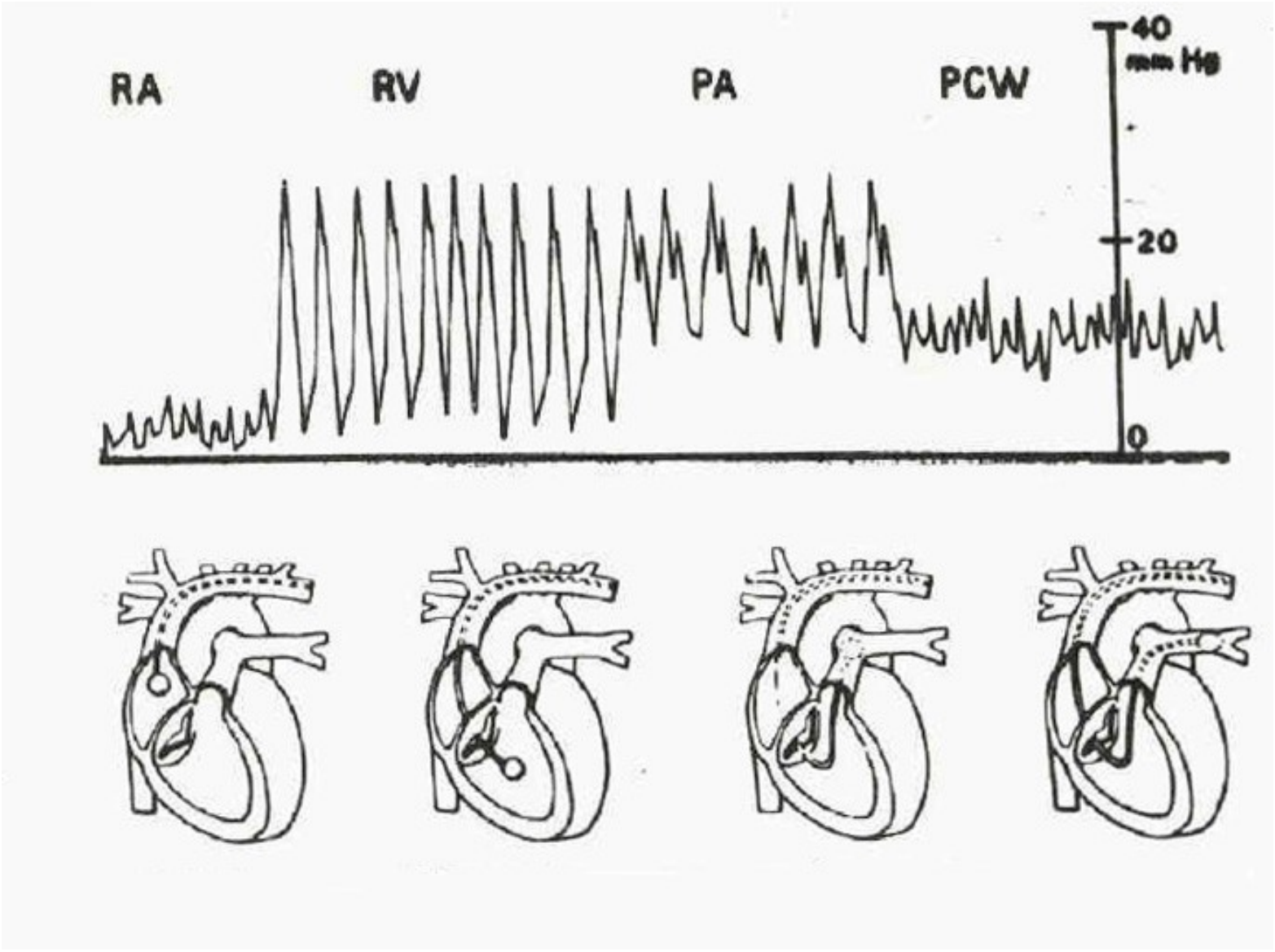
journal homepage: www.elsevier.com/locate/ijcard

Pulmonary hypertension due to chronic lung disease: Updated Recommendations of the Cologne Consensus Conference 2011☆

Διαγνωστικός αλγόριθμος



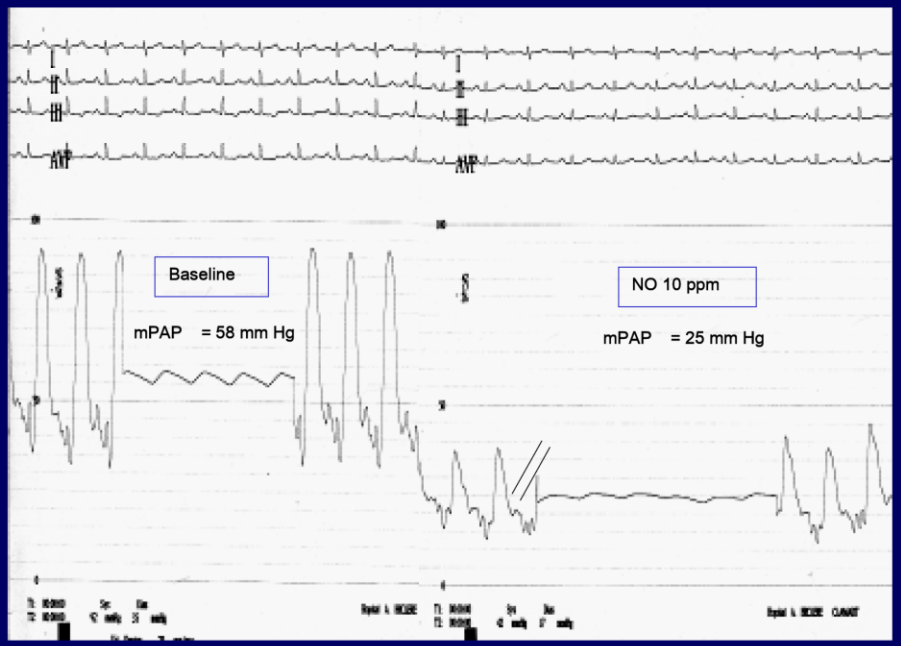
Δεξιός καρδιακός καθετηριασμός



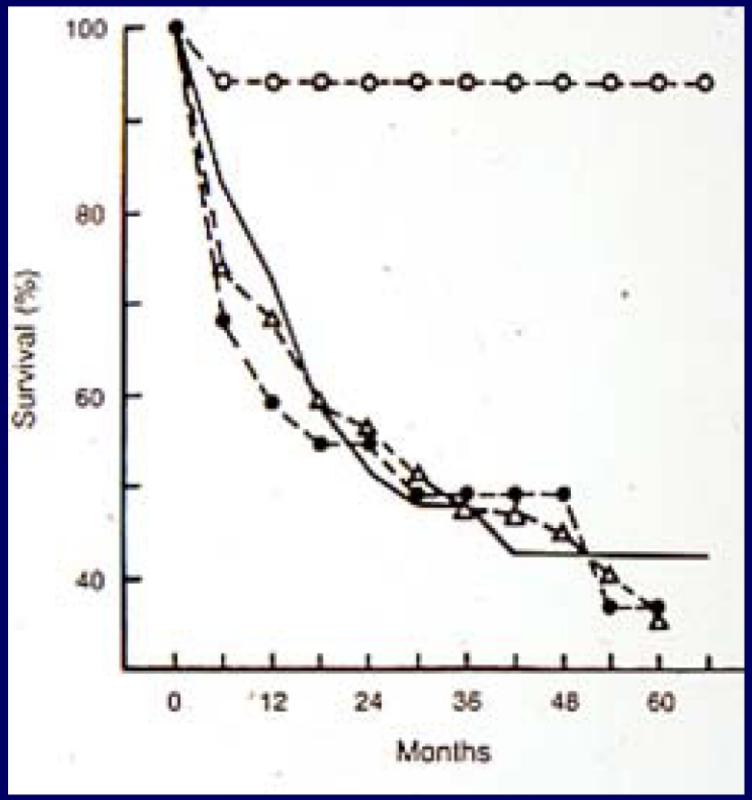
Vasoreactivity – NO test

Definition

↓ mPAP > 10, < 40 mmHg abs; CO =/↑

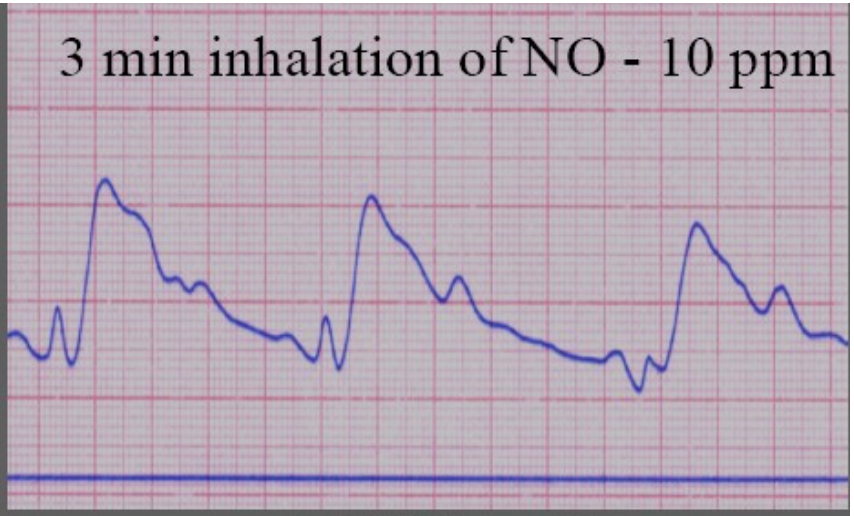


~ 10%



Rich S et al. N Engl J Med 1992, 32:76-81

mPAP 51 mmHg
CO 5,14 l / min
PVR 8,75jW



mPAP 25 mmHg
CO 5,33 l / min
PVR 3,5 j. W.

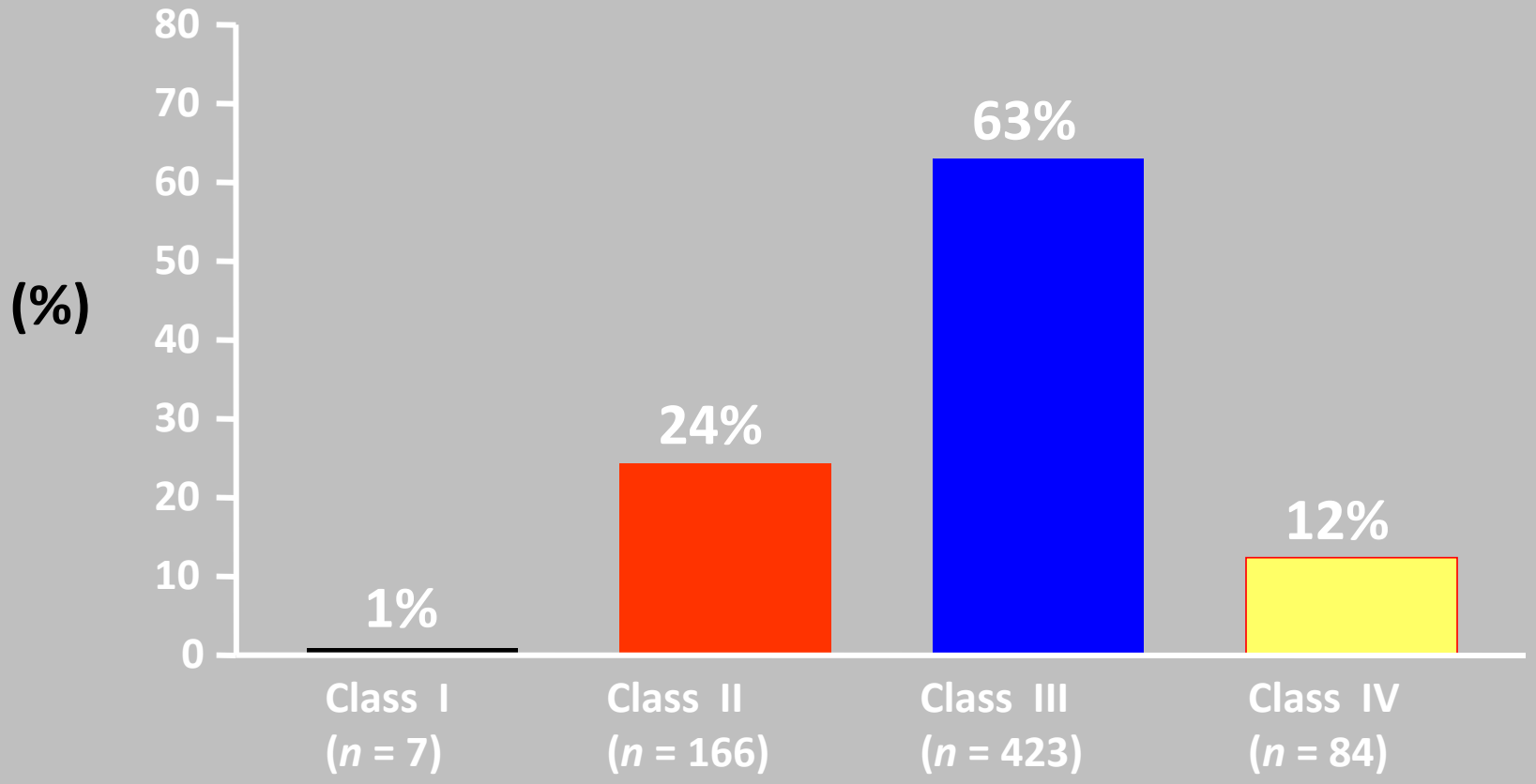
Διαγνωστική προσέγγιση

- Υποψία (suspicion)
- Ανίχνευση (detection)
- Ταυτοποίηση (identification)
- Αξιολόγηση-κατάταξη

NYHA Functional Class

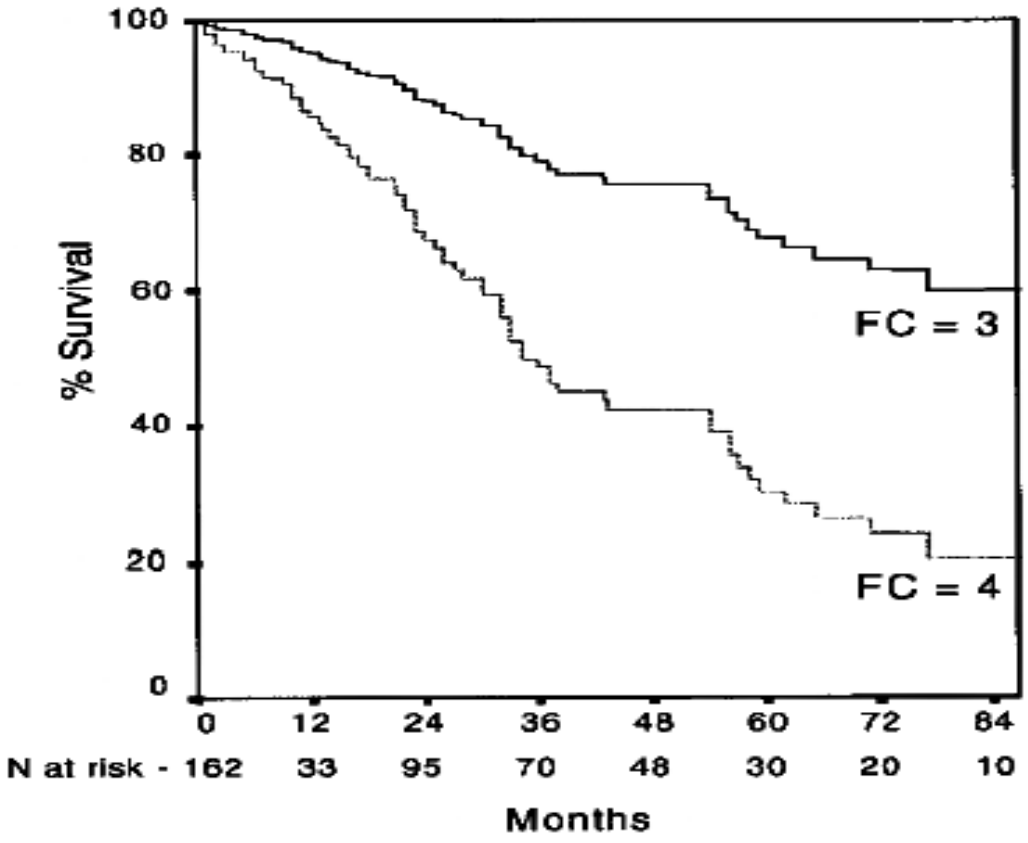
Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue symptoms
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, ordinary physical activity results in symptoms.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms.
Class IV (Severe)	Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

NYHA functional class at diagnosis



Humbert M, et al. Am J Respir Crit Care Med 2006; 173:1023-30.

Severity of PAH: NYHA Functional Class (Predictor of survival in PAH)



McLaughlin, Circulation 2002

The kingdom of the near-dead. The shortened unnatural life history of primary pulmonary hypertension.

Robin ED

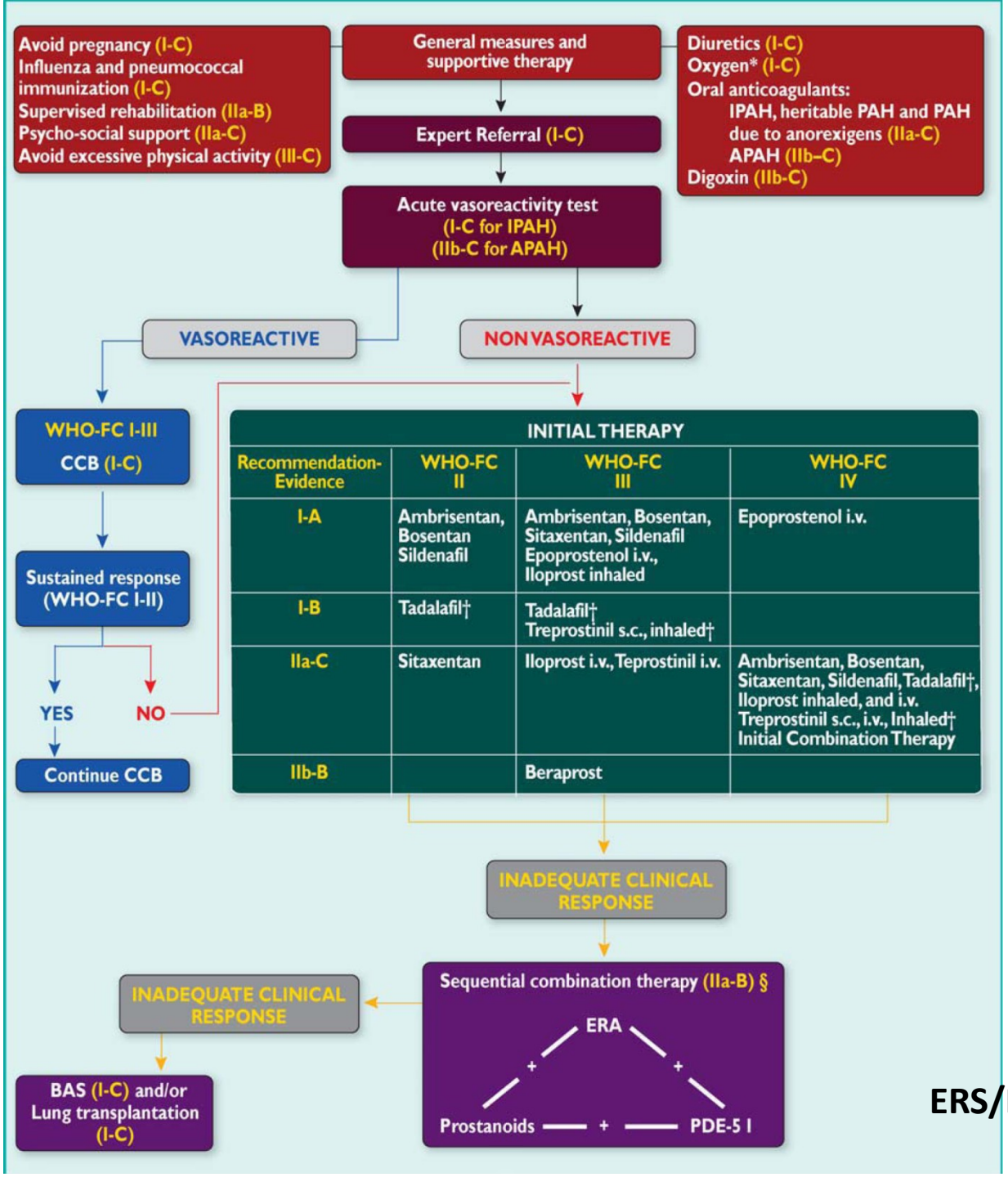
Chest 1987;92(2): 330-4

Recommendations for the efficacy of specific PAH drug therapy, balloon atrial septostomy, and lung transplantation for PAH (group 1) according to WHO functional class [1,2]#.

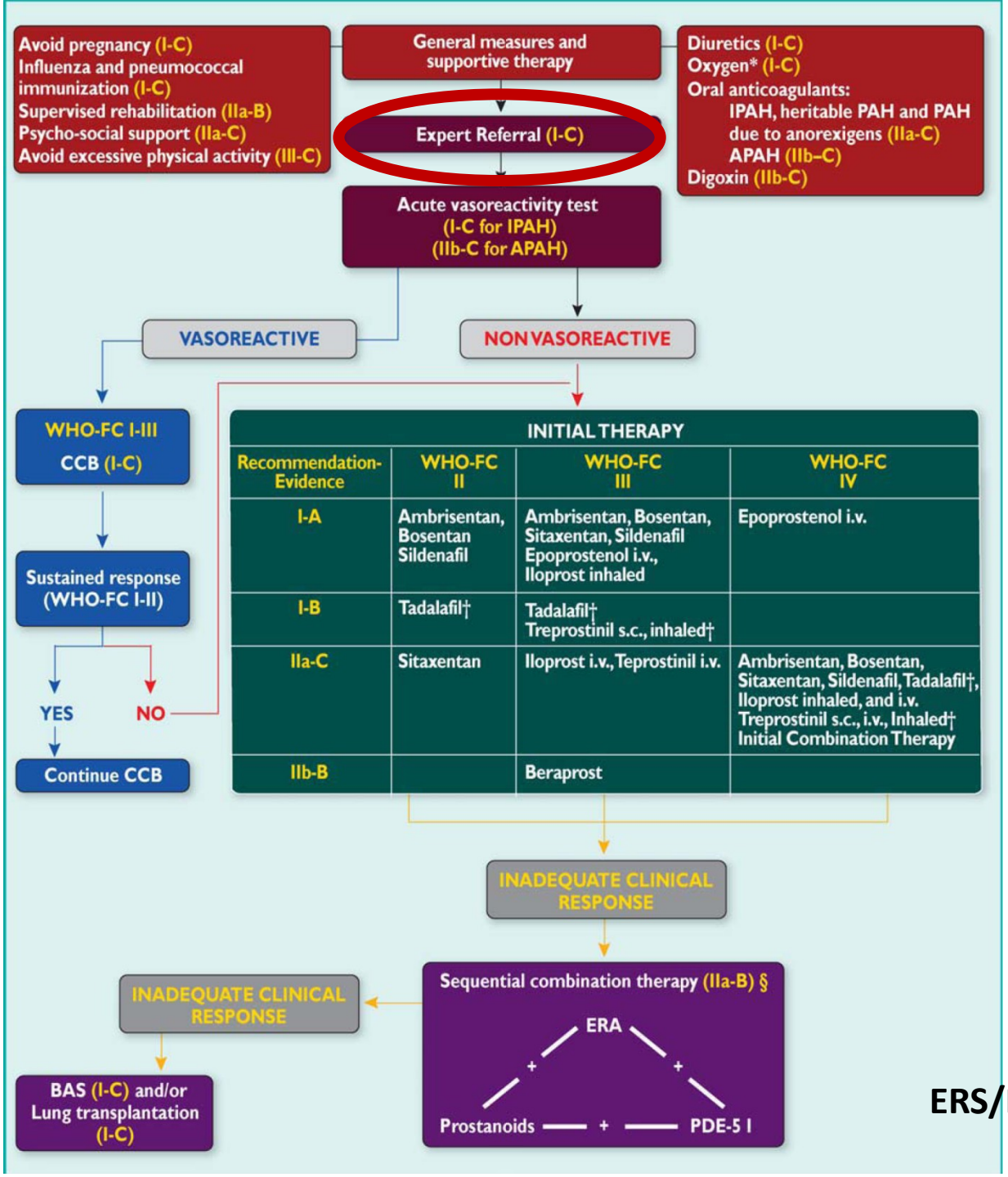
Measure		WHO-FC II	WHO-FC III	WHO-FC IV
Calcium channel blockers		I-C[a]	I-C[a]	–
Endothelin receptor antagonists	Ambrisentan	I-A	I-A	IIa-C
	Bosentan	I-A	I-A	IIa-C
Phosphodiesterase type-5 inhibitors	Sildenafil	I-A	I-A	IIa-C
	Tadalafil	I-B	I-B	IIa-C
Prostanoids	Beraprost	–	IIb-B	–
	Epoprostenol (iv)	–	I-A	I-A
	Iloprost (inhaled)	–	I-A	IIa-C
	Iloprost (iv)	–	IIa-C	IIa-C
	Treprostinil (sc)	–	I-B	IIa-C
	Treprostinil (iv)	–	IIa-C	IIa-C
	Treprostinil (inhaled)[b]	–	I-B	IIa-C
Primary combination therapy		–	–	IIa-C

Country-specific regulatory approval and labeling for PAH-specific drug therapy [1,2] #.

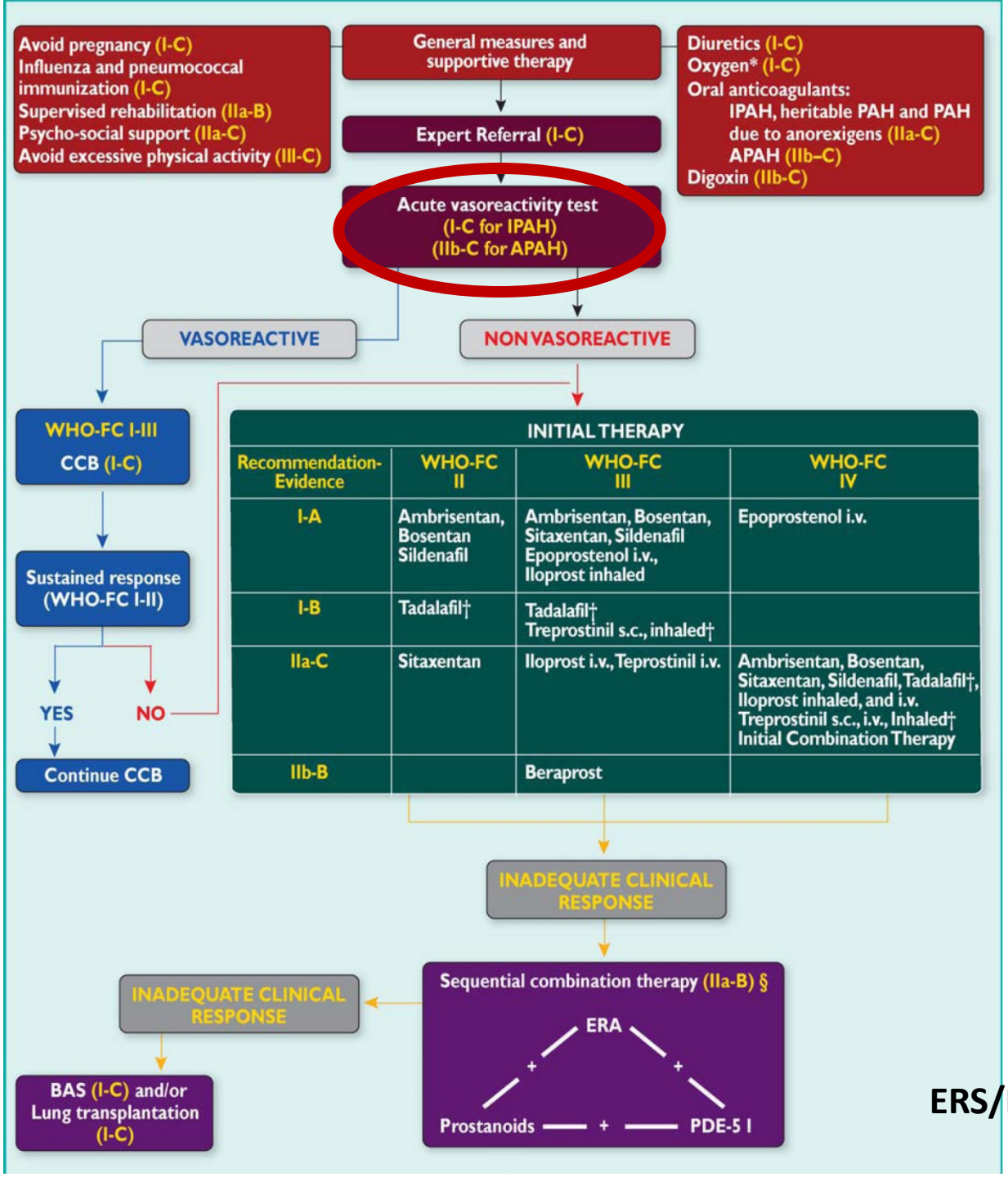
Treatment	Country	Etiology	WHO-FC
Calcium channel blockers	–	–	–
Ambrisentan	USA, Canada, EU	PAH	II–III–IV
Bosentan [a]	EU	PAH	II–III
	USA, Canada	PAH	II–III–IV
Sildenafil	USA, Canada	PAH	II–III–IV
	EU	PAH	II–III
Tadalafil	USA	PAH	II–III–IV
	EU	PAH	II–III
Beraprost [b]	Japan, Korea	PAH	II–III–IV
Epoprostenol (iv) [c]	EU	PAH	III–IV
Iloprost (inhaled)	EU	IPAH	III
	USA	PAH	III–IV
Iloprost (iv)	New Zealand	IPAH, PAH-CTD, CTEPH	III–IV
Treprostinil (sc)	USA	PAH	II–III–IV
	Canada	PAH	III–IV
	EU [d]	IPAH	III
Treprostinil (iv)	USA [e]	PAH	II–III–IV
Treprostinil (inhaled) [b]	USA	PAH	III



ERS/ESC guidelines



ERS/ESC guidelines



ERS/ESC guidelines

Αναστολείς διαύλων ασβεστίου-CCB

- Υψηλές ημερήσιες δόσεις

  120–240 nifedipine

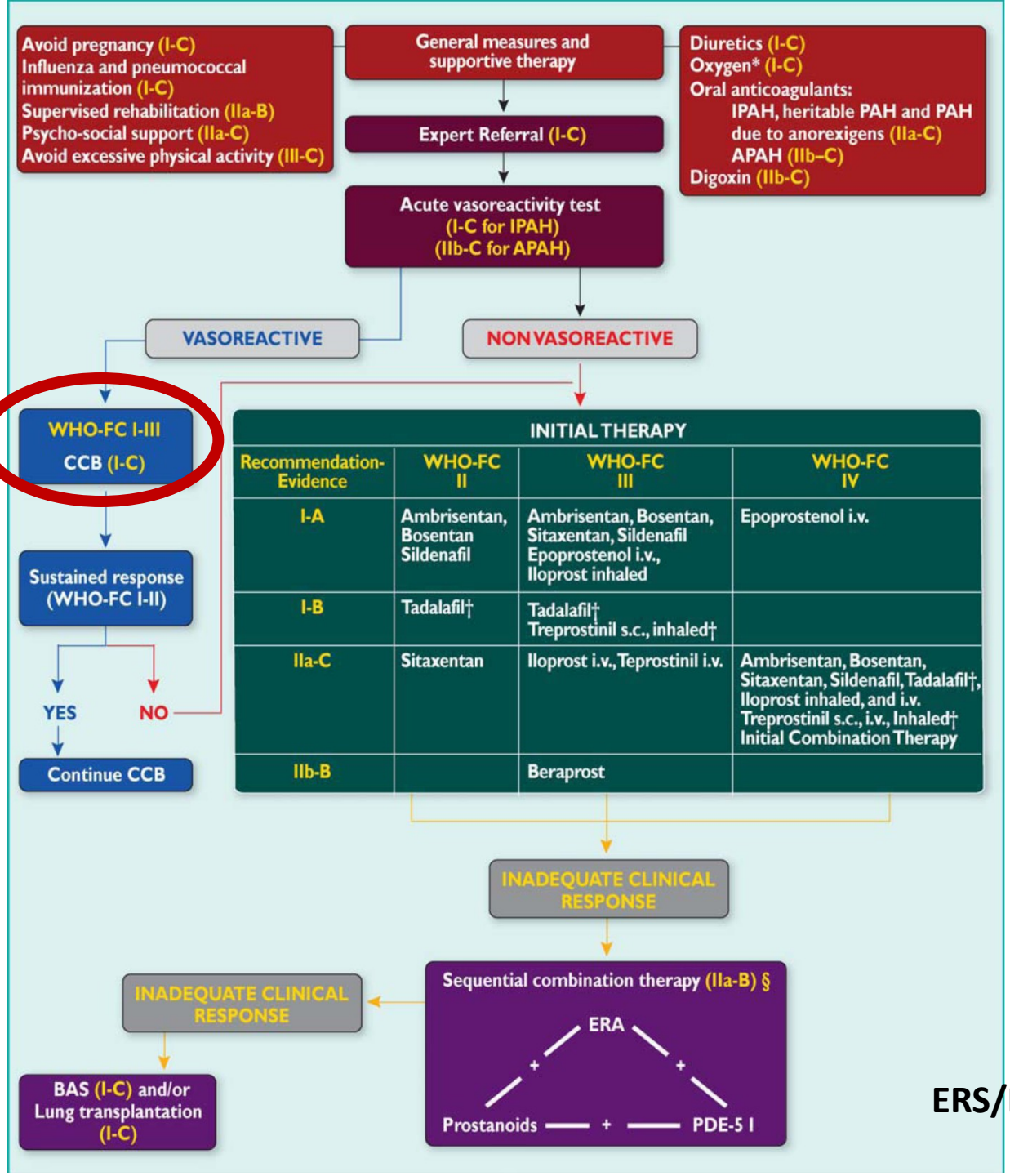
  240–720 diltiazem

  10-20 mg for amlodipine

- Οι CCBs αρχίζουν από χαμηλή δόση και αυξάνονται προσεκτικά στη μέγιστη επιτρεπόμενη δόση
- Περιοριστικοί παράγοντες: συστηματική υπόταση, οιδήματα

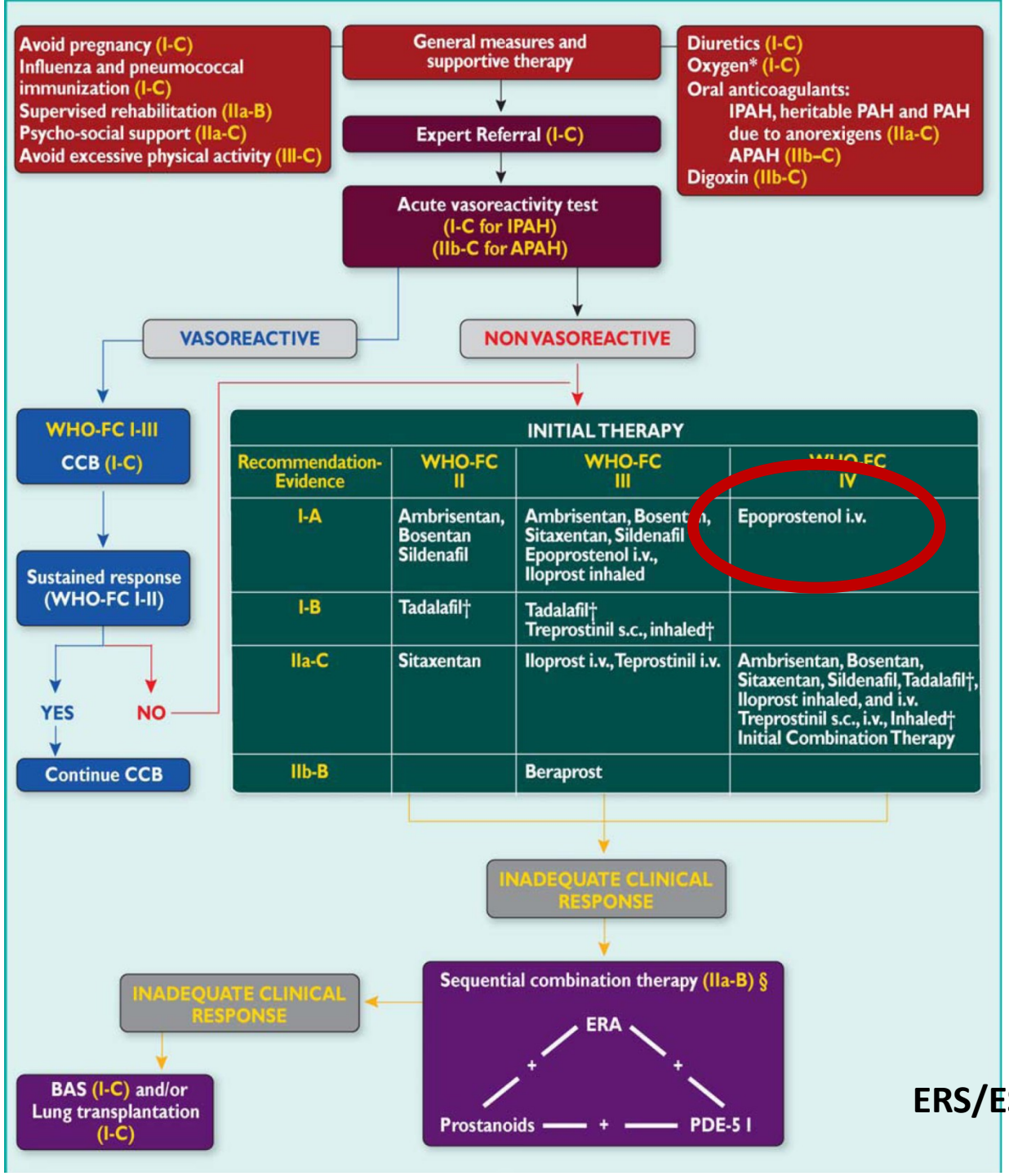
Αναστολείς διαύλων ασβεστίου-CCB

- Προσοχή όταν ο CI<1.5 L/min/m^2



ERS/ESC guidelines

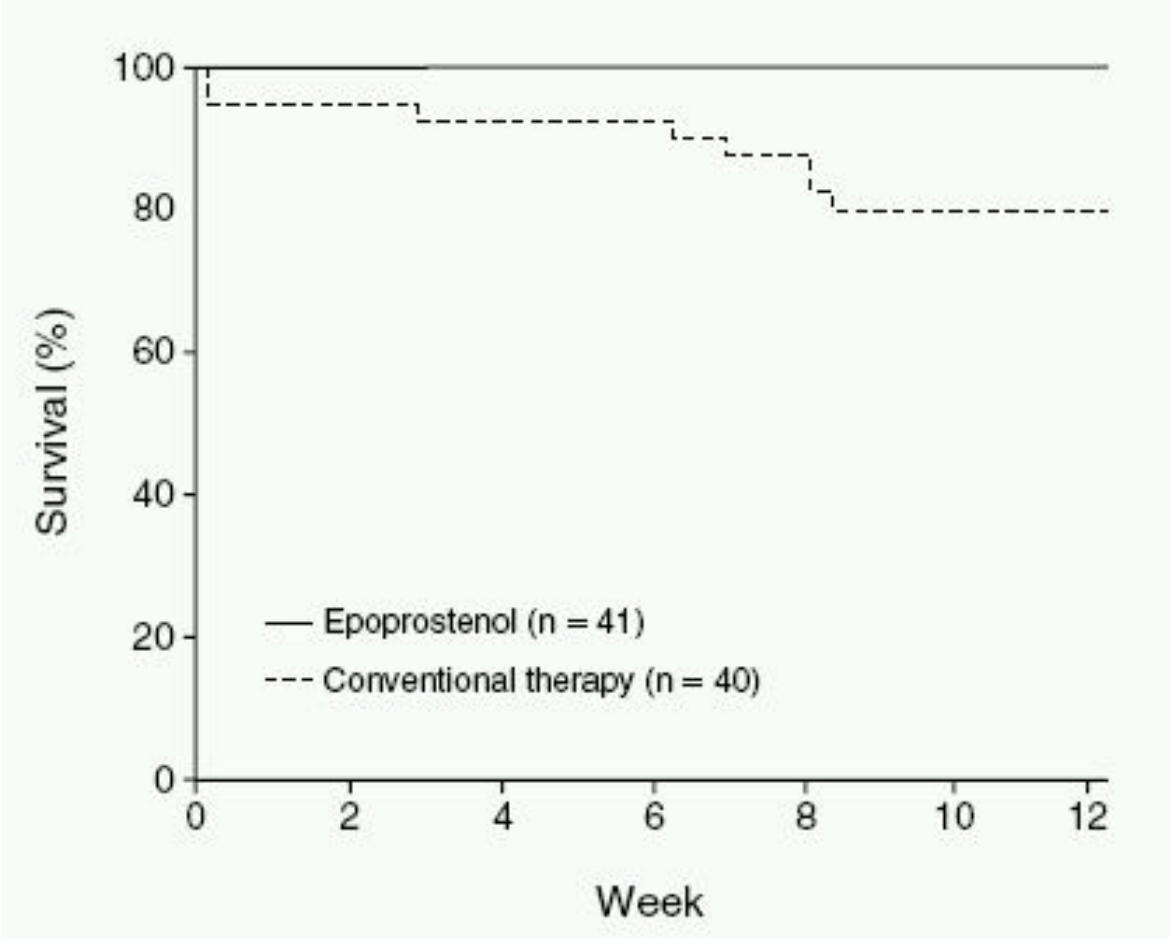
Class IV



ERS/ESC guidelines

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

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



*

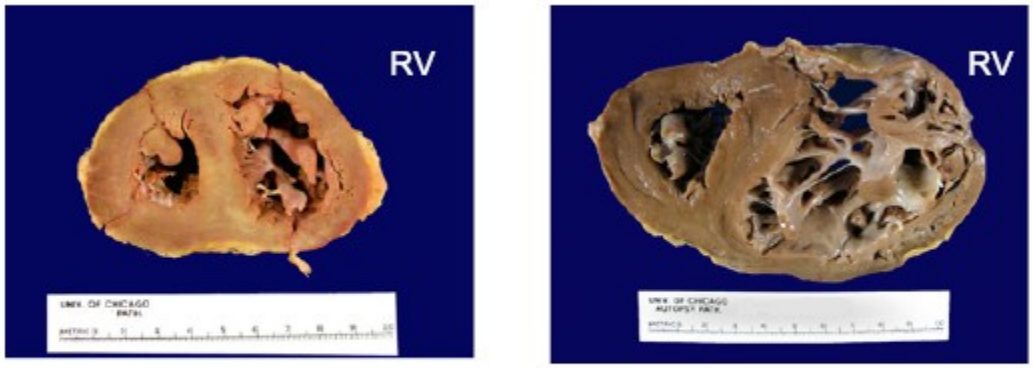
CHEST ONLINE

Long-term Effects of Epoprostenol on the Pulmonary Vasculature in Idiopathic Pulmonary Arterial Hypertension

Stuart Rich, Jennifer Pogoriler, Aliya N. Husain, Peter T. Toth, Mardi Gomberg-Maitland and Stephen L. Archer

Chest 2010;138;1234-1239

A

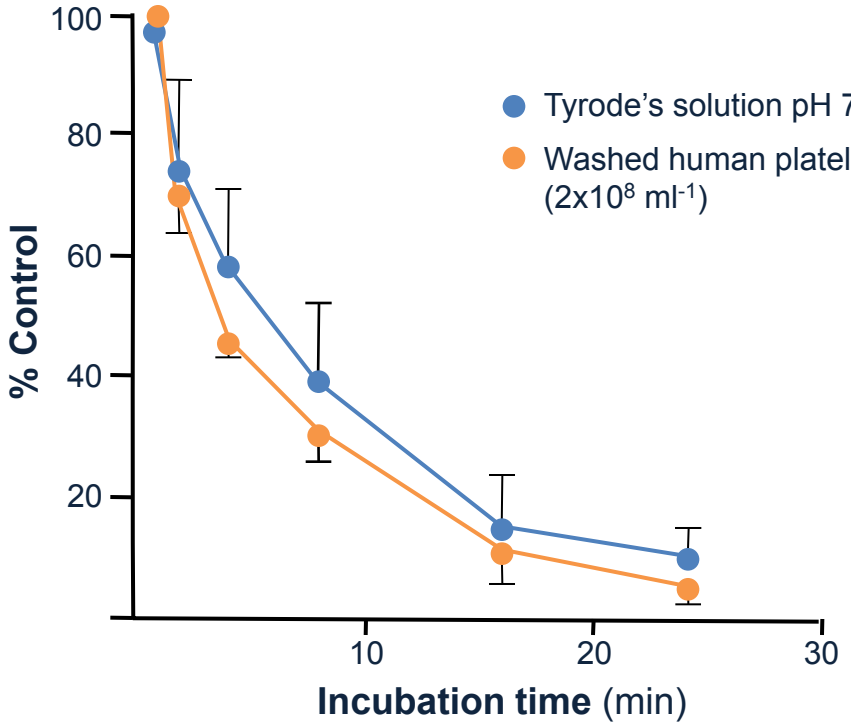


PAH patient
Long survival

PAH patient
Died with RV failure

Date	Drug	RA, mm Hg	PAP (mm Hg)	CO, L/min	PVR, units
July 1987	None	3	74/30 (43)	6.24	6.40
November 1991	None	8	128/54 (72)	3.40	16.7
February 1992	Epoprostenol	5	97/34 (51)	6.64	9.20
March 1998	Epoprostenol	6	90/39 (47)	6.10	6.90
February 2005	Epoprostenol	7	95/54 (63)	7.60	7.84

Instability of epoprostenol



Decay of prostacyclin at 37˚C *in vitro*[1]

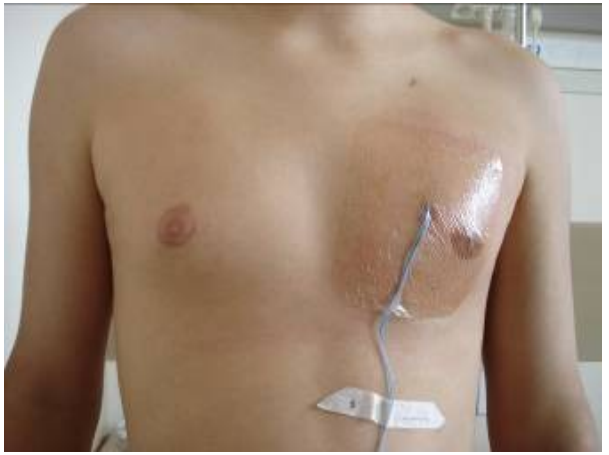
Epoprostenol

- Unstable at physiological temperatures and pH[2]
- Light sensitive[2]
- Hydrolysed to 6-oxo-$PGF_{1\alpha}$[2]
- Elimination half-life of approximately 3 minutes[2]

Data are mean ±standard error
PGF, prostaglandin F

1. Adapted from Whittle BJR; 1983. Actions of prostacyclin and thromboxanes: Products of the arachidonic acid cascade. In: Hormones and cell regulation, Volume 7. Eds Dumont, J.E., Nunez, J., Denton, R.M. Elsevier Biomedical Press; Amsterdam, pp 3-23; 2. Flolan® (epoprostenol sodium) Summary of Product Characteristics, GlaxoSmithKline. March 2006

I.V. Εποπροστενόλη



Adverse events with IV epoprostenol from SmPC

Adverse event(s)[1]	Frequency
Sepsis, septicaemia*	Very common
Headache	Very common
Facial flushing	Very common
Nausea, vomiting	Very common
Jaw pain	Very common
Decreased platelet count	Common
Anxiety, nervousness	Common
Tachycardia (at doses of 5 ng/kg/min and below)	Common
Abdominal colic/abdominal discomfort	Common
Dry mouth	Uncommon
Local infection*, chest pain	Rare
Reddening/pain at the infusion site*, occlusion of the IV catheter*, pain at infusion site*, lassitude, chest tightness	Very rare
Pallor	Very rare

*Associated with the delivery system for epoprostenol

Very common – 10%; common – 1% and <10%; uncommon – 0.1% and <1%; rare – 0.01% and <0.1%; very rare –<0.01%

1. Flolan® Summary of Product Characteristics

What are the facts about practicalities of Flolan administration

Practicalities

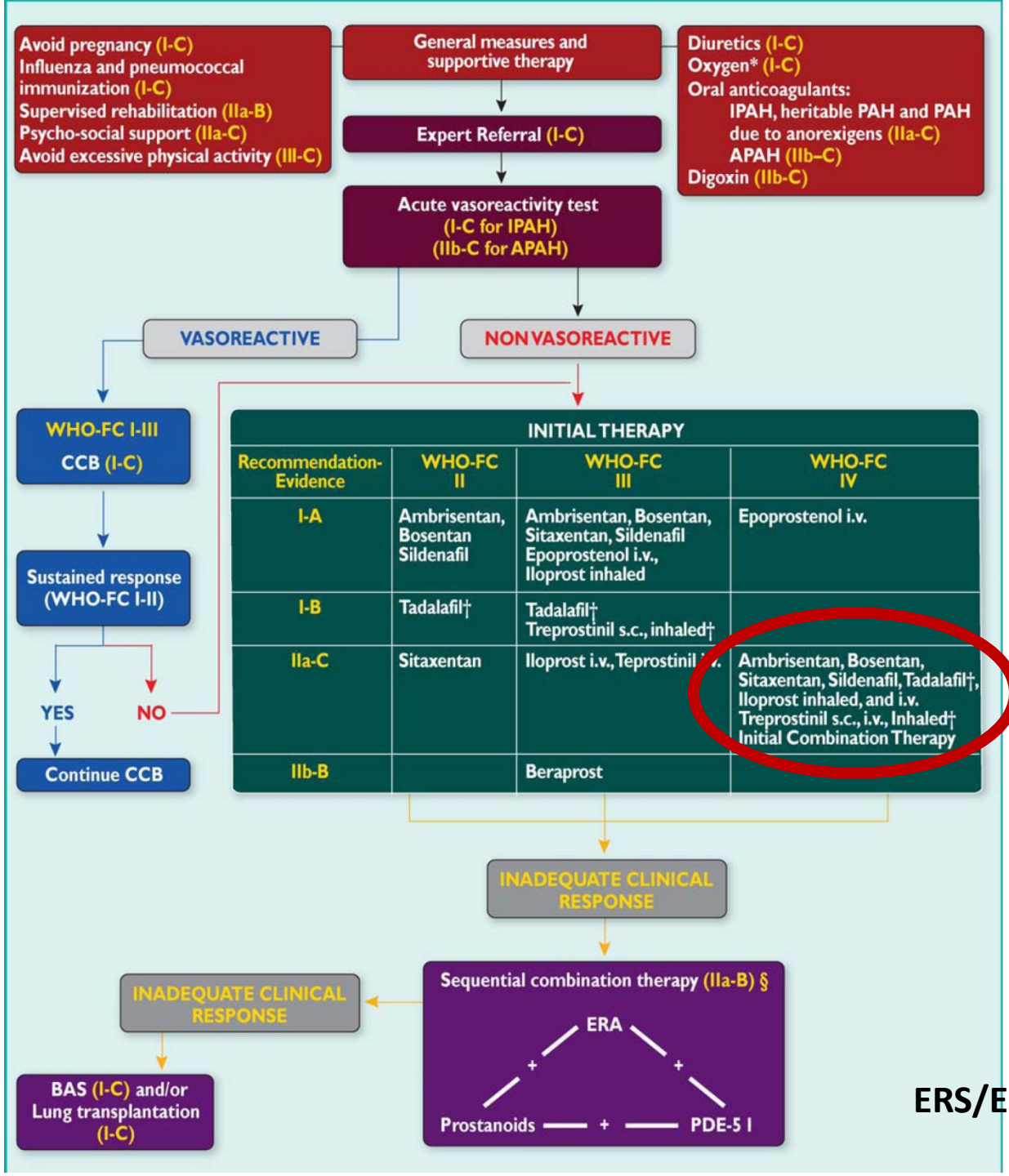
- Short half-life (3-5 minutes)
- Continuous IV infusion - Permanent tunneled subclavian catheter
- Drug preparation and change-over crucial
- Mixed with buffer
- Drug must be stored refrigerated
- Post change flushing
- 12hour dosing un-cooled, 24 hour dosing if cooled
- Continuous infusion
- Patient education / Specialized nurses

Complications

- Total infections: 0.19 patients/year[1]
- Catheter related sepsis: 0.1-0.4 per patient/year[2]

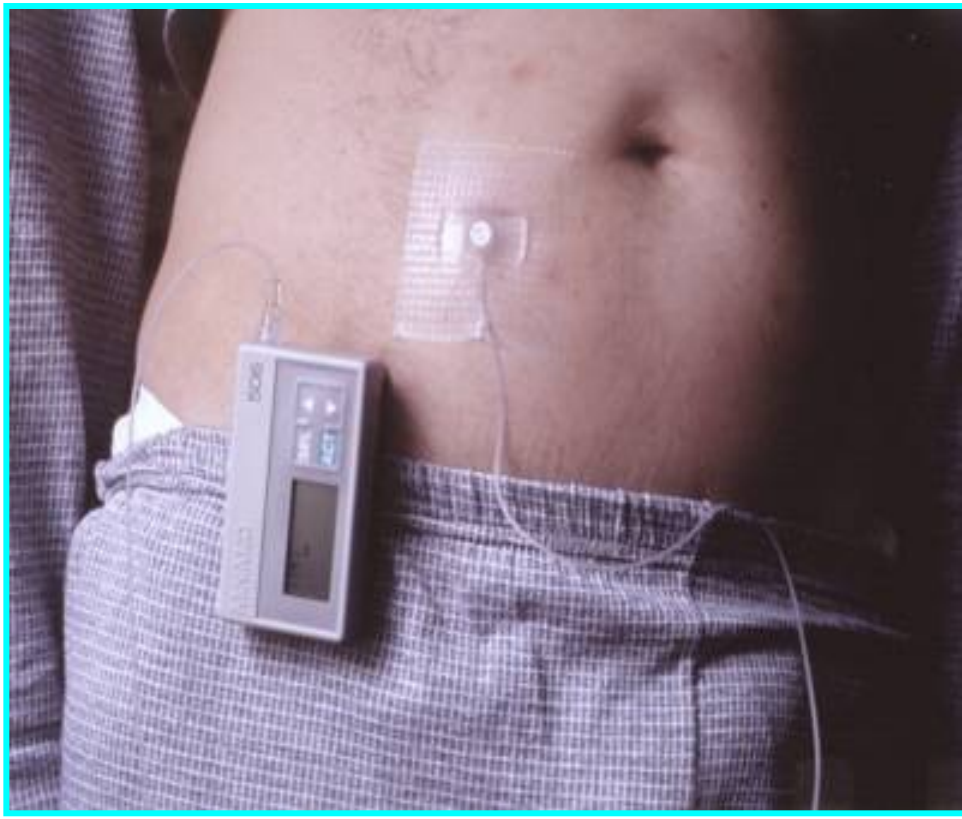
1. **Sitbon et al 2002 JACC 40:7807-88**
2.Hoeper et al, Am J Respir Crit Care Med 165.:209–1216, 2002.

Εναλλακτική λύση?



ERS/ESC guidelines

MiniMed 507
ACT



REMODULIN®

Μορφή / Περιεκτικότητα

Διάλυμα για έγχυση 1 mg/ml (φιαλίδιο 20ml)

Διάλυμα για έγχυση 2.5 mg/ml (φιαλίδιο 20ml)

Διάλυμα για έγχυση 5 mg/ml (φιαλίδιο 20ml)

Διάλυμα για έγχυση 10 mg/ml (φιαλίδιο 20ml)

- **Πολλαπλές συγκεντρώσεις**
- **Tailoring dose /συμπτωματολογία**
- **Εξατομικευμένη χορήγηση**

Infusion pump comparison

	CADD-MS™ 3[1]	CADD-Legacy™[2,3]	Canè Crono Five[4]
Administration	SC and IV use (treprostinil)	IV use (epoprostenol or treprostinil)	SC and IV use (treprostinil)
Reservoir	3 ml syringe	50–100 ml	10–20 ml
Dimensions	80 x 47 x 24 mm	41 x 97 x 112 mm	77 x 47 x 29 mm
Weight	90 g	391 g	115 g

Treprostinil reservoir should be changed at least every 72 hours[5]

Safety profile and tolerability

Event (≥10% in SC treprostinil group)	**SC treprostinil** (n=233; n [%])	**Placebo** (n=236; n [%])	**p value**
Infusion site pain	200 (85)	62 (27)	<0.0001
Infusion site reaction	196 (83)	62 (27)	<0.0001
Infusion site bleeding / bruising	79 (34)	102 (44)	ns
Headache	64 (27)	54 (23)	ns
Diarrhoea	58 (25)	36 (16)	0.009
Nausea	52 (22)	41 (18)	ns
Rash	32 (14)	26 (11)	ns
Jaw pain	31 (13)	11 (5)	0.001
Vasodilatation	25 (11)	11 (5)	0.01

- 18 patients (8%) in treprostinil group discontinued treatment due to intolerable abdominal infusion site pain vs 1 patient in placebo group

ns, non-significant; SC, subcutaneous

Adapted from Simonneau et al. *Am J Respir Crit Care Med*. 2002;165:800-804

Πόνος στο σημείο της έγχυσης

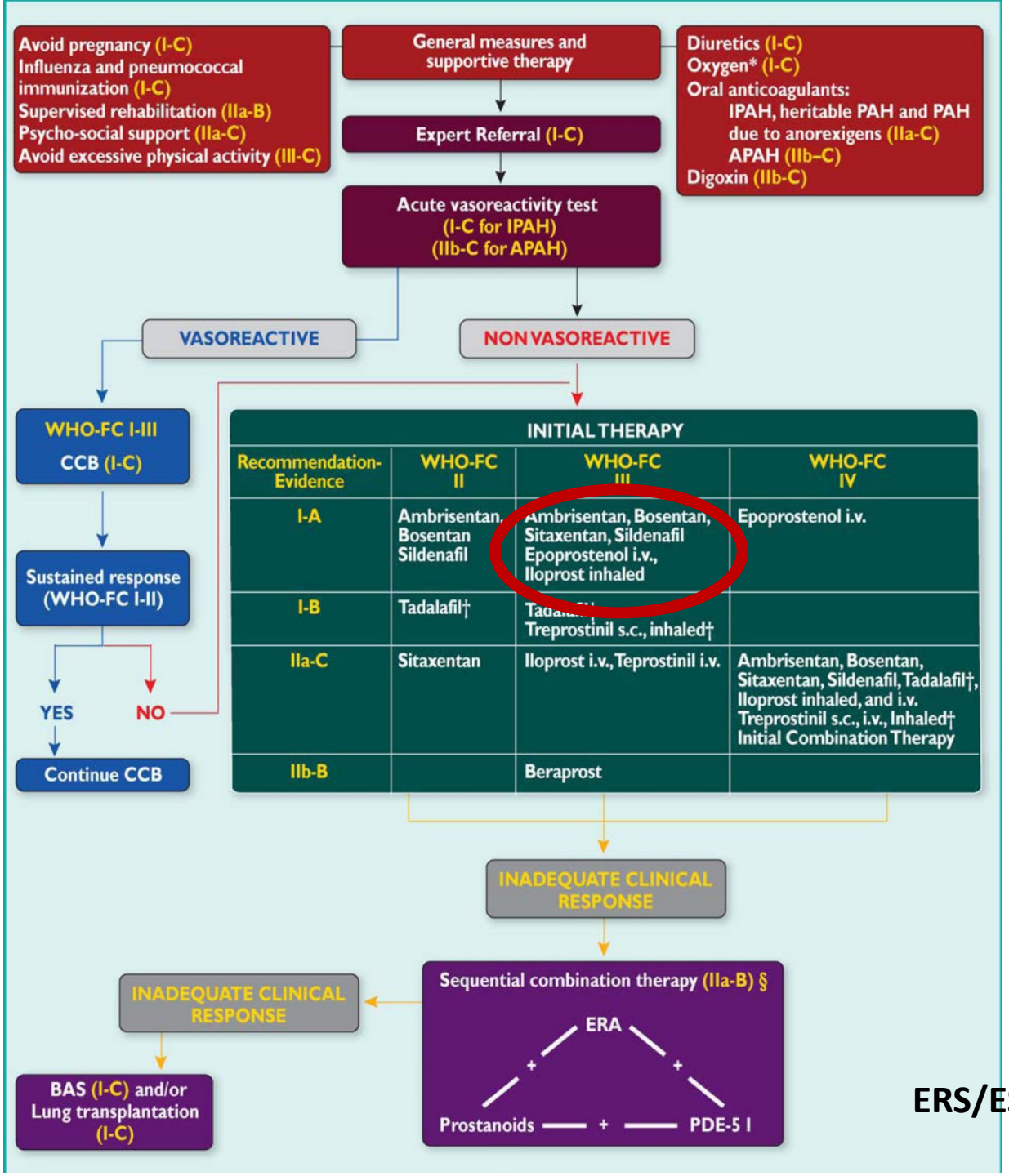
- Συνήθως υποχωρεί μετά από 3-5 ημέρες
- Μπορεί να διαχειριστεί αποτελεσματικά και μπορεί να μειωθεί με τη μακροχρόνια θεραπεία
- Το σημείο της έγχυσης να αλλάζει μια φορά κάθε 3-4 εβδομάδες: *γεγονός το οποίο μπορεί να βοηθήσει στην ελαχιστοποίηση εμφάνισης του πόνου*

Site pain care:
Possible pharmacological approaches

- Hot / cold packs
- Oral and topical analgesics
- Anti-inflammatory creams
- Oral and topical antihistamines
- Corticosteroids
- Anti-depressants
- Systemic analgesics (eg NSAIDs, GABA analogues or opioids)

GABA, gamma-aminobutyric acid; NSAID, nonsteroidal anti-inflammatory drug

Class III



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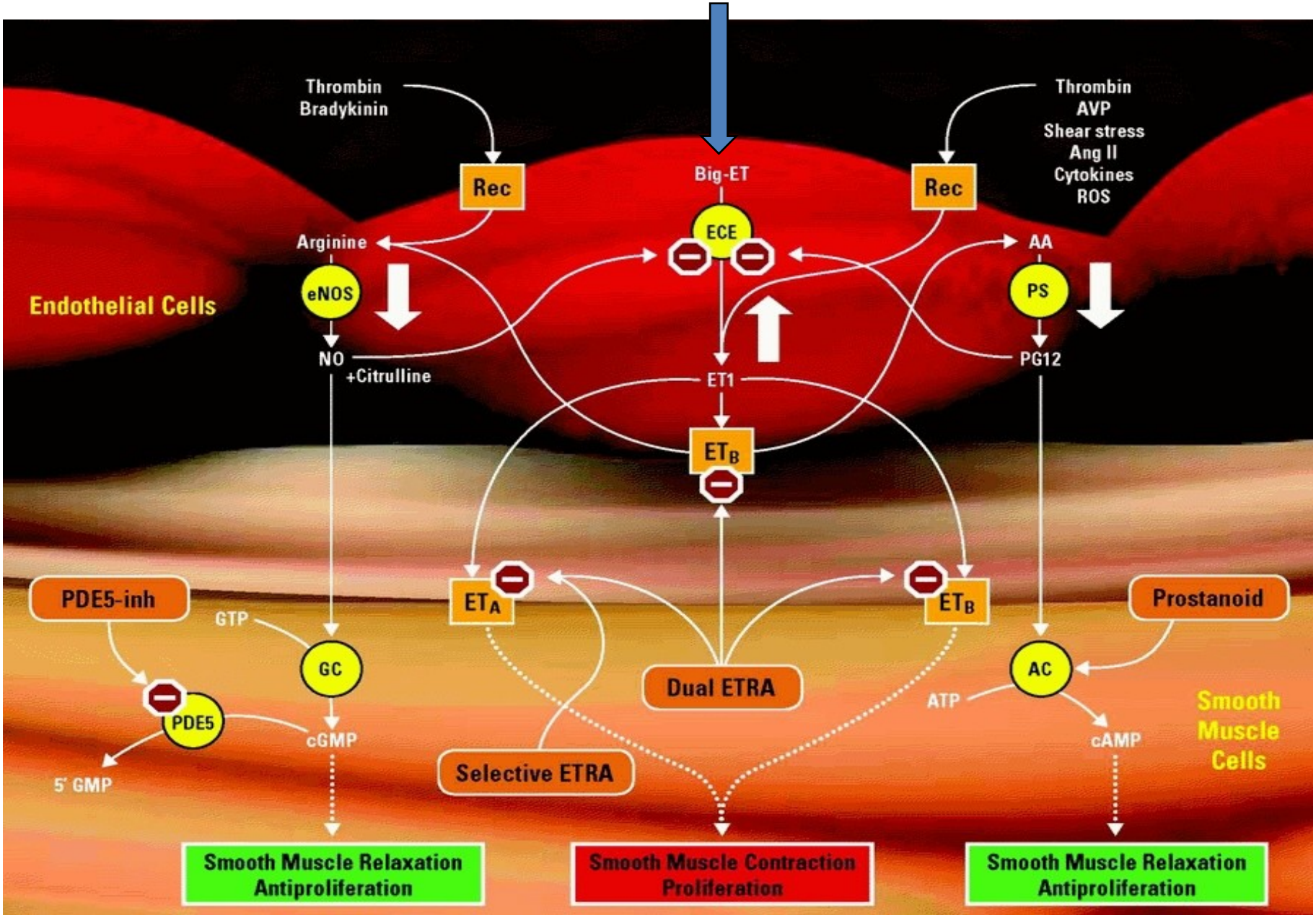
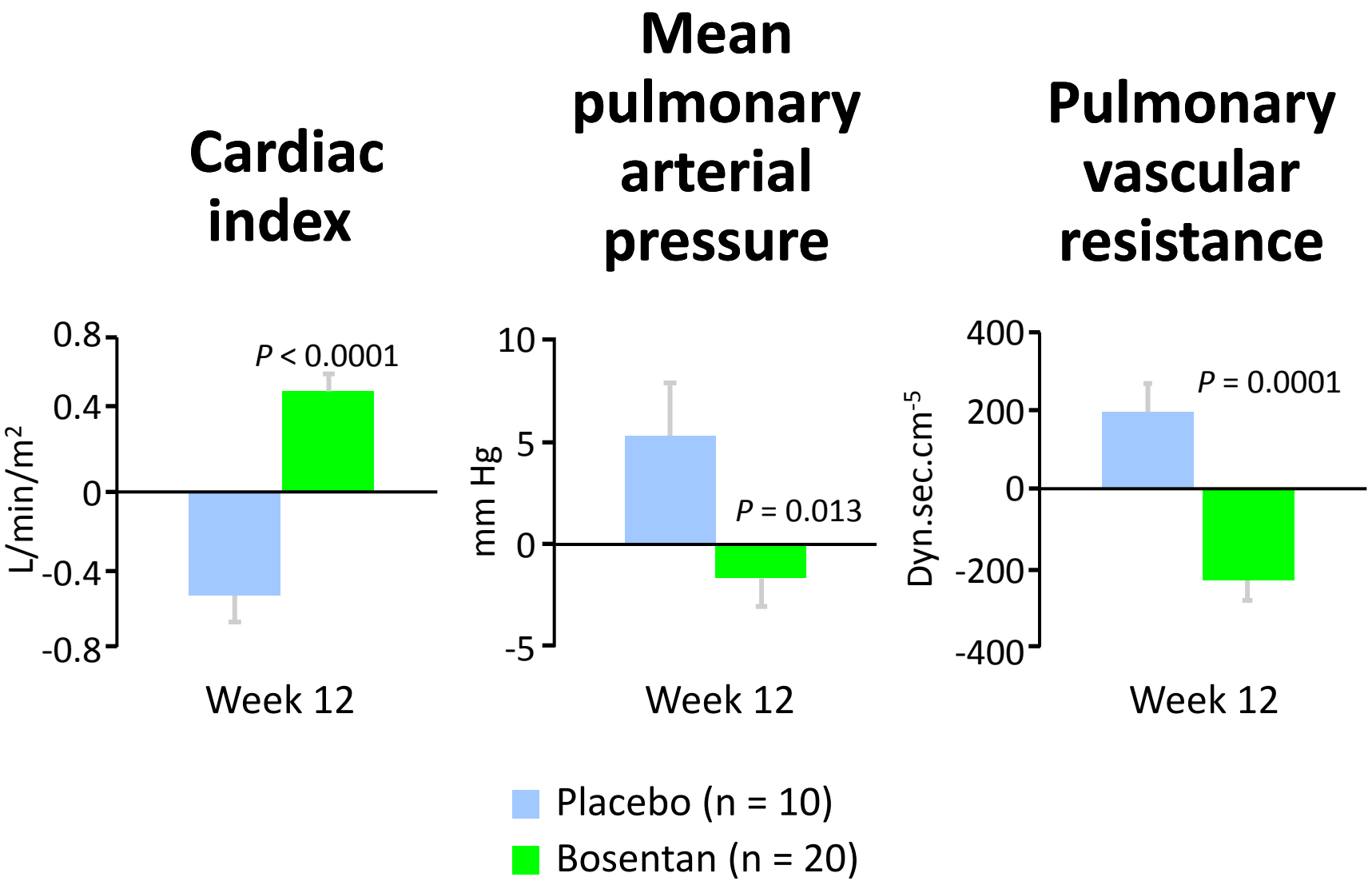


McLaughlin & McGoon *Circulation* 2006, 114:1417-1431

Hemodynamics Change from baseline to week 12

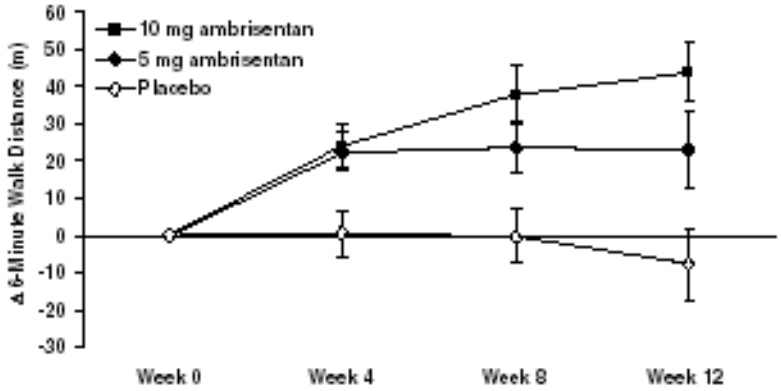


Channick et al. Lancet 2001;358:1119

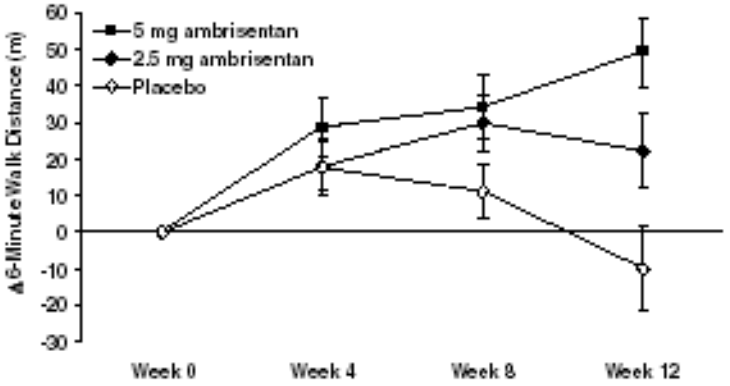
Ambrisentan for the Treatment of Pulmonary Arterial Hypertension

Results of the Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy (ARIES) Study 1 and 2

Nazzareno Galiè, MD; Horst Olschewski, MD; Ronald J. Oudiz, MD; Fernando Torres, MD; Adaani Frost, MD; Hossein A. Ghofrani, MD; David B. Badesch, MD; Michael D. McGoon, MD; Vallerie V. McLaughlin, MD; Ellen B. Roecker, PhD; Michael J. Gerber, MD; Christopher Dufton, PhD; Brian L. Wiens, PhD; Lewis J. Rubin, MD; for the Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy Studies (ARIES) Group



ARIES-1



ARIES-2

Circulation. 2008;117:000-000

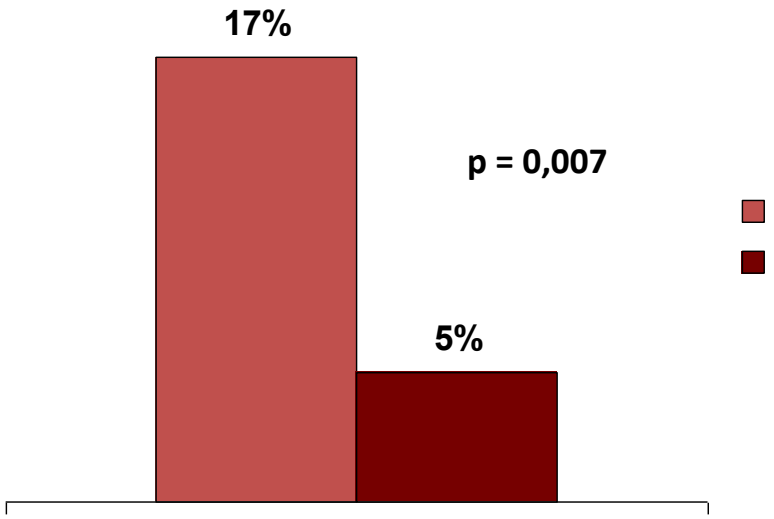
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Sildenafil Citrate Therapy for Pulmonary Arterial Hypertension

Nazzareno Galiè, M.D., Hossein A. Ghofrani, M.D., Adam Torbicki, M.D., Robyn J. Barst, M.D., Lewis J. Rubin, M.D., David Badesch, M.D., Thomas Fleming, Ph.D., Tamiza Parpia, Ph.D., Gary Burgess, M.D., Angelo Branzi, M.D., Friedrich Grimminger, M.D., Marcin Kurzyna, M.D., and Gérald Simonneau, M.D., for the Sildenafil Use in Pulmonary Arterial Hypertension (SUPER) Study Group

AIR-Study Results

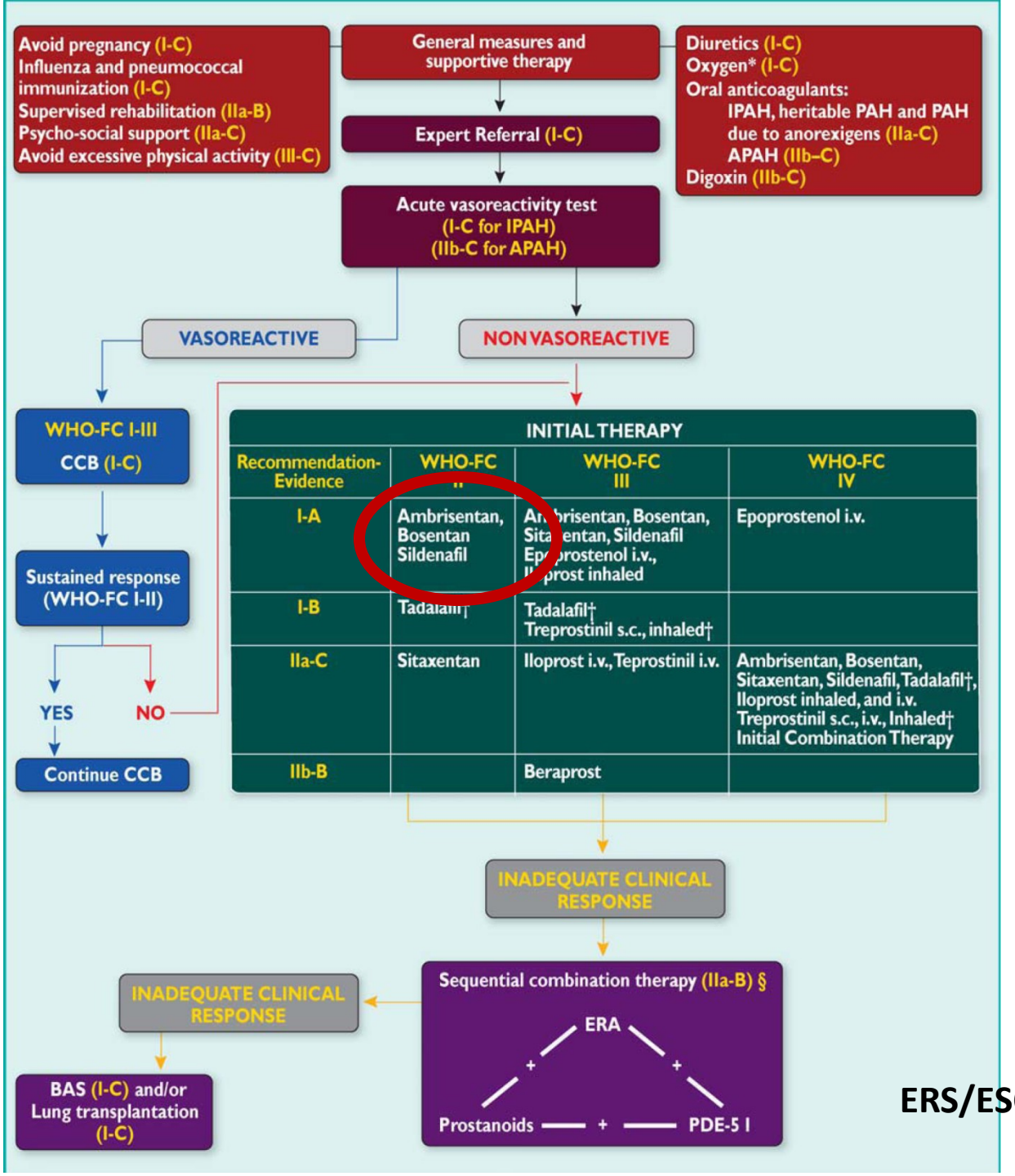


Combined clinical end point:

Improvement in NYHA Stadium (at least one class)
AND improvement of 6 min walk test for at least 10%
AND no deterioration or death

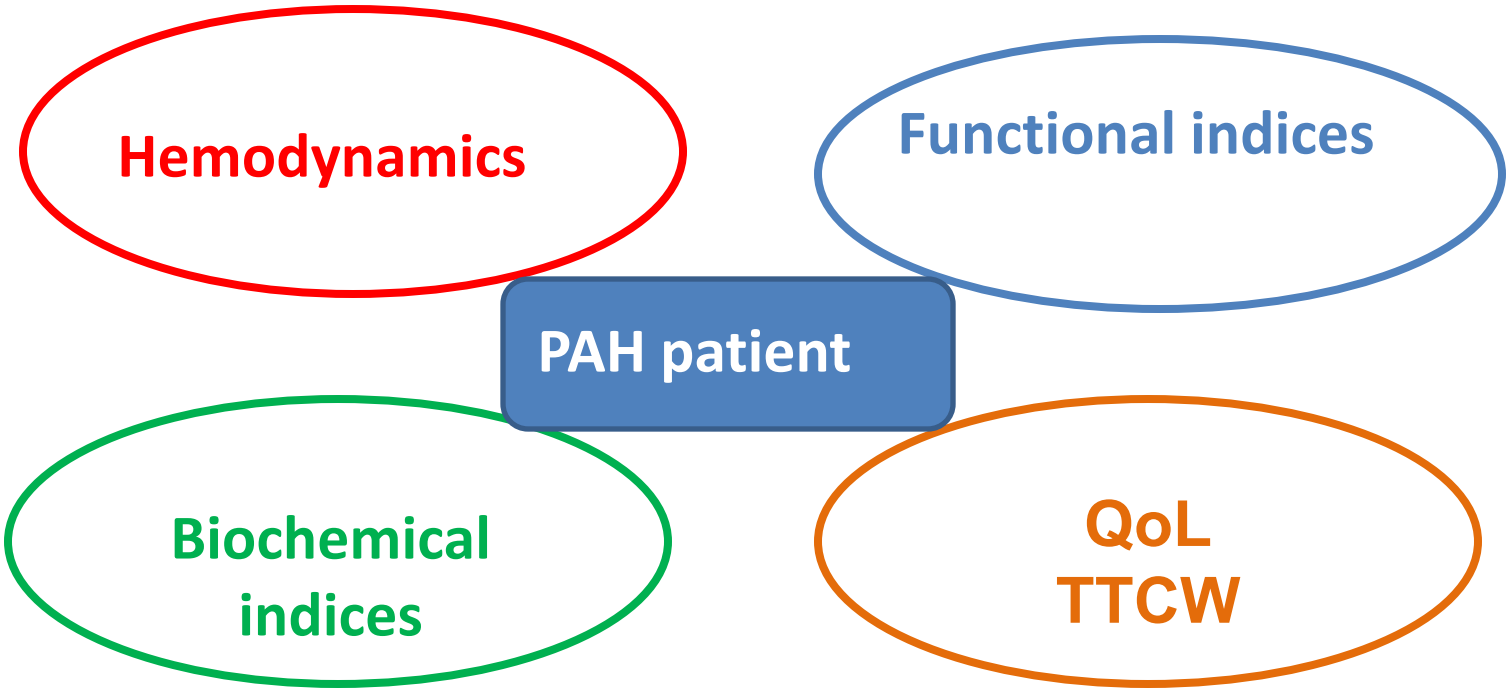
Source: Olschewski et al, New England Journal of Medicine 2002;347:322-9

Class II



ERS/ESC guidelines

Παρακολούθηση



Determinants of prognosis	Better prognosis	Worse prognosis
Clinical evidence of RV failure	No	Yes
Rate of progression of symptoms	Slow	Rapid
Syncope	No	Yes
WHO-FC	I, II	IV
6MWT	Longer (>500 m)[a]	Shorter (<300 m)
Cardio-pulmonary exercise testing	Peak O_2 consumption >15 mL/min/kg	Peak O_2 consumption <12 mL/min/kg
BNP/NT-proBNP plasma levels	Normal or near-normal	Very elevated and rising
Echocardiographic findings[b]	No pericardial effusion TAPSE[b] >2.0 cm	Pericardial effusion TAPSE[b] <1.5 cm
Haemodynamics	RAP <8 mmHg and CI $\geq$2.5 L/min/m^2	RAP >15 mmHg or CI $\leq$2.0 L/min/m^2

McLaughlin and McGoon, 2006

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Clinical status	Stable and satisfactory	Stable and not satisfactory	Unstable and deteriorating

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Clinical response	Adequate	Inadequate

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Clinical status	Stable and satisfactory	Stable and not satisfactory	Unstable and deteriorating

Clinical response	Adequate	Inadequate

Treatment	Continuation	Add on treatment ?

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International Journal of Cardiology

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- *In this context, it is crucial to ensure a proper diagnostic work-up and classification, and to prescribe targeted PAH therapies within the approved indication and meet the requirements of each individual patient.*
- It is the responsibility of PH expert centers to ensure this.

Recommendations of the European guidelines for pulmonary hypertension associated with lung disease and/or hypoxia.

Recommendation	Class of recommendation	Level of evidence
Echocardiography is a recommended screening method for PH due to lung disease	I	C
In patients with PH due to lung disease, RHC is recommended to confirm diagnosis	I	C
The optimization of treatment of patients with PH due to lung disease including long-term oxygen therapy for hypoxemia is recommended	I	C
Patients with out or proportion PH due to lung disease should be enrolled in RCTs for PAH-targeted drugs	IIa	C
The treatment of patients with PH due to lung disease with PAH-targeted drugs is not recommended	III	C

PH, pulmonary hypertension; RCTs, randomized controlled trials; PAH, pulmonary arterial hypertension; RHC, right heart catheterization.