Πνευμονική «αρτηριακή» υπέρταση -Θεραπεία-

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Διευθύντρια ΕΣΥ
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Γ.Ν.Γ. Παπανικολάου
Θεσ/νικη
The pulmonary circulation is often considered a no-man's land, falling between the domains of the respirologist and the cardiologist and understood only by the physiologist.

W. MacNee, Am J Respir Crit Care Med 1994

Risk-benefit analysis in chest medicine

The Kingdom of the Near-Dead

The Shortened Unnatural Life History of Primary Pulmonary Hypertension


Πορεία στο χρόνο: 1973-2019 εν αρχή: τα ανορεξιογόνα

Pulmonary arterial hypertension: from the kingdom of the near-dead to multiple clinical trial meta-analyses

Θέματα-Key points

- Πότε θεραπεύουμε: ποιούς και σε ποιό στάδιο?
  ορισμός-γκρίζες ζώνες-νέα ταξινόμηση
  (διαφωνίες στις ομοφωνίες)

- Θεραπευτικά διλήμματα:
  - Μονοθεραπεία //vs// Συνδυασμένη θεραπεία
  - up front //vs// add on //vs// switch

- ........ και άλλα νέα φάρμακα

Αναθεώρηση στόχων-καταληκτικών σημείων RCTs
αλλά βελτιώσαμε τελικά την επιβίωση?
1) Αυξημένη μέση πίεση πνευμονικής αρτηρίας
mPAP > 25 mm Hg + end-expiratory PAWP ≤ 15 mmHg + zero point

Όχι borderline - όχι άσκηση-πότε δοκιμασία αγγειοδιαστολής?

2) Παθολογικά αυξημένες πνευμονικές αγγειακές αντιστάσεις
PVR > 3 Wood units - Όχι μέτρηση σε dyn.sec.cm-5

3) Απόδειξη προτριχοειδικής ανατομικά εντόπισης

Out of proportion TPG>12mmHg ΑΚΥΡΟ
PAWP>15 DPG<7 isolated post (Ipc-PH)
DPG>7 combined (Cpc-PH)

Heart failure with preserved ejection fraction:
LVEDP>15mmHg - fluid challenge
isolated postcapillary PH (Ipc-PH)
1, diastolic pulmonary pressure gradient (diastolic PAP minus mean PAWP) < 7 mm Hg,
2, transpulmonary pressure gradient (mean PAP minus mean PAWP) < 12 mm Hg, and
3, pulmonary vascular resistance ≤ 3 Wood units (WU).

combined post- and precapillary PH (Cpc-PH)
postcapillary PH with elevated vascular gradients and pulmonary vascular resistance
Cpc-PH bears similarities to pulmonary arterial hypertension, amenable to therapies
targeting the pulmonary circulation?

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Hemodynamic Classification of Pulmonary Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mPAP</td>
</tr>
<tr>
<td>No PH</td>
<td>&lt;25 mm Hg</td>
</tr>
<tr>
<td>PCPH</td>
<td>≥25 mm Hg</td>
</tr>
<tr>
<td>PAH*</td>
<td>≥25 mm Hg</td>
</tr>
<tr>
<td>Ipc-PH</td>
<td>≥25 mm Hg</td>
</tr>
<tr>
<td>Cpc-PH</td>
<td>≥25 mm Hg</td>
</tr>
</tbody>
</table>

In-depth haemodynamic phenotyping of pulmonary hypertension due to left heart disease
Christian Gerges, Mario Gerges, Johannes Jakowitsch, David S. Celermajer, Irene M. Lang
European Respiratory Journal 2018
Hemodynamic Phenotyping of Pulmonary Hypertension in Left Heart Failure.
Naeije R et al Circ Heart Fail. 2017 Sep;10(9)
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Hemodynamic Phenotyping of Pulmonary Hypertension in Left Heart Failure.
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The difficult diagnosis of pulmonary vascular disease in heart failure
Central Illustration: Pulmonary Hypertension in Typical PAH, Atypical PAH, and HFP EF

- "Typical IPAH"
- "Atypical IPAH"
- PH-HFP EF

Declining Precapillary Component of PH: TPG, DPG, PVR ....

Declining Efficacy of Targeted PAH-therapy

Increasing Risk Factor Profile: Age, Obesity, Hypertension, Diabetes, CAD, AF, .....
Pulmonary hypertension and pulmonary arterial hypertension: a clarification is needed

N. Galiè, M. Palazzini and A. Manes

In a survey performed in an echocardiography laboratory [15], the prevalence of PH (defined as a pulmonary artery (PA) systolic pressure >40 mmHg) among 4,579 patients was 10.5%. Among the 483 cases with PH, 78.7% had left heart disease (group 2), 9.7% had lung diseases and hypoxaemia (group 3), 4.2% had PAH (group 1), 0.6% had CTEPH (group 4), and in 6.8% it was not possible to define a diagnosis.

Gabbay E, Yeow W, Playford D. Pulmonary arterial hypertension (PAH) is an uncommon cause of pulmonary hypertension (PH) in an unselected population: the Armadale echocardiography study. Am J Respir Crit Care Med 2007; 175: A713.
Pulmonary hypertension and pulmonary arterial hypertension: a clarification is needed

N. Galiè, M. Palazzini and A. Manes

Recent registries have described the epidemiology of PAH [16, 17]. The lowest estimate of the prevalence of PAH and idiopathic PAH are 15 cases and 5.9 cases per million adult population, respectively. The lowest estimate of PAH incidence is 2.4 cases per million adult population per year. Recent data from Scotland and other countries have confirmed that PAH prevalence is in the range of 15–50 subjects per million population in Europe [17].

In the French registry, 39.2% of patients had idiopathic PAH and 3.9% heritable PAH. In the subgroup of associated PAH, 15.3% had connective tissue diseases (mainly systemic sclerosis), 11.3% had congenital heart diseases, 10.4% had portal hypertension, 9.5% had anorexigen-associated PAH and 6.2% had HIV infection [16].
ΠΝΕΥΜΟΝΙΚΗ ΥΠΕΡΤΑΣΗ

WHO GROUP 1
PAH
- Idiopathic (IPAH)
- Heritable
- Drug- and toxin-induced
- Associated with other conditions (APAH)

WHO Group 1'
- Pulmonary veno-occlusive disease
- Pulmonary capillary hemangiomatosis

WHO Group 1"
- Persistent pulmonary hypertension of the newborn (PPHN)

WHO GROUP 2
Left-heart related
- Systolic dysfunction
- Diastolic dysfunction
- Valvular disease
- Congenital/acquired left heart inflow/outflow tract obstruction

WHO GROUP 3
Lung/hypoxia related
- Chronic obstructive pulmonary disease (COPD)
- Interstitial lung disease (ILD)
- Other pulmonary diseases with mixed restrictive and obstructive pattern
- Sleep-disordered breathing
- Alveolar hypoventilation disorders
- Chronic exposure to high altitude
- Developmental abnormalities

WHO GROUP 4
CTEPH
- Chronic thromboembolic pulmonary hypertension

WHO GROUP 5
Other
- PH with unclear multifactorial mechanisms

ΧΑΠ
Διάμεσες πνευμονοπάθειες
Δρχ αναπνοής στον ύπνο
Κυψελιδικός υποαερισμός
Χρόνια έκθεση σε μεγάλο υψόμετρο

2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension
Guidance for PAH
Πνευμονική Υπέρταση σε Νοσήματα Συνδετικού Ιστού

<table>
<thead>
<tr>
<th></th>
<th>Χωρίς ΠΑΥ</th>
<th>Με ΠΑΥ</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>N</td>
<td>32</td>
<td>18</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Ηλικία (έτη)</td>
<td>57.3(9.2)</td>
<td>65.8(8)</td>
<td>&lt;0.01</td>
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<tr>
<td>Διάμ. Πνευμ/Θεια (n)</td>
<td>16/32(50%)</td>
<td>15/18(83.3%)</td>
<td></td>
</tr>
<tr>
<td>Φαιν. Raynaud (n)</td>
<td>13/32(40.6%)</td>
<td>13/18(72.2%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>PO2 (mmHg)</td>
<td>70(12)</td>
<td>65(10)</td>
<td></td>
</tr>
<tr>
<td>FVC (%pred)</td>
<td>70(10)</td>
<td>64(9)</td>
<td>NS</td>
</tr>
<tr>
<td>DLCO (%pred)</td>
<td>55(17)</td>
<td>45(8)</td>
<td>NS</td>
</tr>
<tr>
<td>6MWD (m)</td>
<td>470(100)</td>
<td>380(110)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Διάρκεια Νόσου (μήνες)</td>
<td>60(25)</td>
<td>55(10)</td>
<td>NS</td>
</tr>
</tbody>
</table>

FVC (%pred) 65(10) 60(9) 72(8) 70 62 (9) 6 (6)
PO2 (mmHg) 67(10) 65(11) 70(9) 76 60 (5) 7 (7)
DLCO (%pred) 50(10) 45(9) 58 (11) 57 45 (9) 8 (8)
6MWD (m) 450 (150) 390 (180) 500 (100) 590 (80) 380 (70)
SPAP (mmHg) 48(10) 58(19) 30 (10) 28 (8) 40 (7)
ΠΑΥ(n) 18/50 (36%) 10/25 (40%) 3/12 (25%) 2/8 25% 3/5 60%

Serasli E, Karvounis C et al ERS 2014
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Συγγενείς καρδιοπαθείες
HIV
Πυλαία υπέρταση
Νοσήματα συνδετικού ιστού...

ΧΑΠ
Διάμεσες πνευμονοπάθειες
Δρχ αναπνοής στον ύπνο
Κυψελικός υποαερισμός
Χρόνια έκθεση σε μεγάλο υψόμετρο

2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension
Guidance for PAH
Suspect → Clinical, functional or imaging results suggestive of concomitant PH
Support → Echocardiogram
Confirm → Right heart catheterisation
Stratify → Group 1 versus group 3 PH

Limited CLD

Obstructive LD: FEV₁ >60% Restrictive LD: FVC >70%
Minimal parenchymal CT changes
Group 1 (PAH)/classification unclear
Treatment algorithm for PAH

Physiological severity
Obstructive LD: FEV₁ <60% Restrictive LD: FVC <70%
Extensive parenchymal CT changes
Group 3 PH

Refer to expert PH and LD centre

Severe CLD

Mild-to-moderate PH
- Registries and RCTs required
- Consider exercise training
- No PAH therapy

Severe PH
- Individualised care
ΠΝΕΥΜΟΝΙΚΗ ΥΠΕΡΤΑΣΗ

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2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension
Guidance for PAH
GROUP 1: Pulmonary Arterial Hypertension (PAH)
- Idiopathic PAH
- Heritable PAH: BMPR2, ALK-1, ENG, SMAD9, CAV1, KCNK3, Unknown
- Drug- and toxin-induced
- Associated with: CTD, HIV infection, Portal HTN, CHD, Schistosomiasis
  - 1st: Pulmonary veno-occlusive disease
  - and/or pulmonary capillary
  - hemangiomatosis
  - 1st*: Persistent PH of the newborn (PPHN)

GROUP 2: PH Due to Left Heart Disease
- LV Systolic dysfunction
- LV Diastolic dysfunction
- Valvular disease
- Congenital/acquired left heart inflow/outflow tract obstruction
- Congenital cardiomyopathies

GROUP 3: PH Due to Lung Diseases and/or Hypoxia
- Chronic obstructive pulmonary disease
- Interstitial lung disease
- Other pulmonary diseases with mixed restrictive and obstructive pattern
  - Sleep-disordered breathing
  - Alveolar hypoventilation disorders
  - Chronic exposure to high altitude
  - Developmental lung abnormalities

GROUP 4: Chronic Thromboembolic PH (CTEPH)
- Thromboembolic obstruction of the pulmonary arteries

GROUP 5: PH With Unclear or Multifactorial Mechanisms
- Hematologic disorders
- Systemic disorders
- Metabolic disorders
- Other disorders
Θέματα - Key points

- Θεραπευτικά διλήμματα:
  - Μονοθεραπεία // vs // Συνδυασμένη θεραπεία
  - up front // vs // add on // vs // switch
- .......... και άλλα νέα φάρμακα

Αναθεώρηση στόχων-καταληκτικών σημείων RCTs
αλλά βελτιώσαμε τελικά την επιβίωση?
Θεραπευτικά μονοπάτια

Endothelin-1 (ET-1)

- Pre-pro-ET → pro-ET
  - ET<sub>A</sub>
  - ET<sub>B</sub>
  - Vasodilatation
  - Anti-proliferation
  - ET-1 clearance

ETRAs
- Bosentan
- Macitentan
- Ambrisentan

Nitric Oxide (NO)

- L-arginine → L-citrulline
  - NO
  - cGMP
  - Vasodilatation
  - Anti-proliferation

Prostacyclin (PGI<sub>2</sub>)

- Arachidonic acid → PGI<sub>2</sub>
  - PGI<sub>2</sub> analogues
  - Iloprost
  - Epoprostanol
  - Treprostinil
  - Selexipag (!!)

ΠΔΕ5 αναστολή
Sildenafil - Tadalafil
Διέγερση γουανυλικής κυκλάσης

PGI<sub>2</sub> αναστολή
Evidence based treatment algorithm for pulmonary arterial hypertension patients (for group 1 patients only)

CCB = calcium channel blockers; DPAH = drug-induced PAH; HPAH = heritable PAH; IPAH = idiopathic PAH; LA = intravenous; PAH = pulmonary arterial hypertension; PCA = prostacyclin analogues; WHO-FC = World Health Organization functional class.

*Some WHO-FC III patients may be considered high risk (see Table 13).

*Initial combination with ambrisentan plus tadalafil has proven to be superior to initial monotherapy with ambrisentan or tadalafil in delaying clinical failure.

*Intravenous epoprostenol should be prioritised as it has reduced the 3 months rate for mortality in high risk PAH patients also as monotherapy.

*Consider also balloon atrial septostomy.
<table>
<thead>
<tr>
<th>Measure/treatment</th>
<th>Class^a-Level^b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>WHO-FC II</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td></td>
</tr>
<tr>
<td>Endothelin receptor antagonists</td>
<td></td>
</tr>
<tr>
<td>Ambrisentan</td>
<td>I</td>
</tr>
<tr>
<td>Bosentan</td>
<td>I</td>
</tr>
<tr>
<td>Macitentan</td>
<td>I</td>
</tr>
<tr>
<td>Phosphodiesterase type 5 inhibitors</td>
<td></td>
</tr>
<tr>
<td>Sildenafil</td>
<td>I</td>
</tr>
<tr>
<td>Tadalafil</td>
<td>I</td>
</tr>
<tr>
<td>Vardenafil</td>
<td>IIb</td>
</tr>
<tr>
<td>Guanylate cyclase stimulators</td>
<td></td>
</tr>
<tr>
<td>Riociguat</td>
<td>I</td>
</tr>
<tr>
<td>Prostacyclin analogues</td>
<td></td>
</tr>
<tr>
<td>Epoprostenol Intravenous^e</td>
<td>-</td>
</tr>
<tr>
<td>Iloprost Inhaled</td>
<td>-</td>
</tr>
<tr>
<td>Intravenous^e</td>
<td>-</td>
</tr>
<tr>
<td>Treprostinil Subcutaneous</td>
<td>-</td>
</tr>
<tr>
<td>Inhaled^g</td>
<td>-</td>
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<tr>
<td>Intravenous^f</td>
<td>-</td>
</tr>
<tr>
<td>Oral^g</td>
<td>-</td>
</tr>
<tr>
<td>Beraprost^g</td>
<td>-</td>
</tr>
<tr>
<td>Selexipag (oral)^g</td>
<td>I</td>
</tr>
</tbody>
</table>

^a Class: 1: Occasional, 2: Optional, 3: Consider, 4: Recommended, 5: Strongly recommended
^b Level: A: Evidence-based, B: Expert opinion, C: Clinical experience
Το σκεπτικό
tης συνδυασμένης θεραπείας

- Πολλαπλοί παθογενετικοί μηχανισμοί
- Malignant nature: Κακοήθης νόσος
- Επιτυχής εφαρμογή σε
  - Καρδιακή ανεπάρκεια ¹
  - HIV²
  - Cancer³

2. DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents 2006.
Reveal Registry

The combined therapy is a common practice.

PAH-specific medication use at enrolment among previously diagnosed patients:

- **ERA:**
  - 478 (19%)
  - 315 (13%)
  - 244 (10%)

- **PDE5i:**
  - 397 (16%)
  - 345 (14%)

- **Prostaglandin:**
  - 300 (12%)

- **37% on dual combination PAH-specific therapy**
- **9% on triple combination PAH-specific therapy**

*184 (7%) of patients were not on a prostaglandin, PDE5i, or ERA. Of these, 88 were on CCBs.*
Από την αρχή (up front) ή σε ανεπαρκή κλινική ανταπόκριση

<table>
<thead>
<tr>
<th>Recommendation/Evidence&lt;sup&gt;a&lt;/sup&gt;</th>
<th>WHO-FC II</th>
<th>WHO-FC III</th>
<th>WHO-FC IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIb/C</td>
<td>Initial combination tx</td>
<td>Initial combination tx</td>
<td></td>
</tr>
</tbody>
</table>

**INADEQUATE CLINICAL RESPONSE**

Sequential combination therapy (I-A)

ERAs

+ [Prostanoids] + PDE5i or sGCS

---

<sup>a</sup> Level of evidence is based on the WHO-FC of the majority of the patients of the studies.
Σενάρια....

πρώτης γραμμής ΣΘ

Επιδείνωση σε μονοθεραπεία
αποτυχία μονοθεραπείας
### <up front> συνδυασμένη θεραπεία

<table>
<thead>
<tr>
<th>Measure/treatment</th>
<th>Class$^a$-Level$^b$</th>
<th>WHO-FC II</th>
<th>WHO-FC III</th>
<th>WHO-FC IV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ambrisentan + tadalafil</strong></td>
<td>I</td>
<td>B</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Other ERA + PDE-5i</td>
<td>IIa</td>
<td>C</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Bosentan + sildenafil + i.v. epoprostenol</td>
<td>-</td>
<td>-</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Bosentan + i.v. epoprostenol</td>
<td>-</td>
<td>-</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Other ERA or PDE-5i + s.c. treprostinil</td>
<td>IIb</td>
<td>C</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>Other ERA or PDE-5i + other i.v. prostacyclin analogues</td>
<td>IIb</td>
<td>C</td>
<td>IIb</td>
<td>C</td>
</tr>
</tbody>
</table>
### Inadequate clinical response for patients who were initially in WHO-FC II or III:

1. Resulting clinical status defined as stable and not satisfactory*
2. Resulting clinical status defined as unstable and deteriorating*

### Inadequate clinical response for patients who were initially in WHO-FC IV:

1. No rapid improvement to WHO-FC III or better
2. Resulting clinical status defined as stable and not satisfactory*
Πότε και ποιος συνδυασμός?

Ghofrani HA Eur Respir Rev 2014
<table>
<thead>
<tr>
<th>Measure/treatment</th>
<th>Class\textsuperscript{a,Level\textsuperscript{b}}</th>
<th>Ref.\textsuperscript{c}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macitentan added to sildenafil\textsuperscript{d}</td>
<td>I \textsuperscript{II} B \textsuperscript{III}</td>
<td>I B I B Ila C</td>
</tr>
<tr>
<td>Riociguat added to bosentan</td>
<td>I B</td>
<td>Ila C</td>
</tr>
<tr>
<td>Selexipag\textsuperscript{e} added to ERA and/or PDE-5i\textsuperscript{d}</td>
<td>I B</td>
<td>Ila C</td>
</tr>
<tr>
<td>Sildenafil added to epoprostenol</td>
<td>– –</td>
<td>I B Ila B</td>
</tr>
<tr>
<td>Treprostinil inhaled added to sildenafil or bosentan</td>
<td>Ila B</td>
<td>Ila B Ila C</td>
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<tr>
<td>Iloprost inhaled added to bosentan</td>
<td>Ila B</td>
<td>Ila B Ila B</td>
</tr>
<tr>
<td>Tadalafil added to bosentan</td>
<td>Ila C</td>
<td>Ila C Ila C</td>
</tr>
<tr>
<td>Ambrisentan added to sildenafil</td>
<td>Ila C</td>
<td>Ila C Ila C</td>
</tr>
<tr>
<td>Bosentan added to epoprostenol</td>
<td>– –</td>
<td>Ila C Ila C</td>
</tr>
<tr>
<td>Bosentan added to sildenafil</td>
<td>Ila C</td>
<td>Ila C Ila C</td>
</tr>
<tr>
<td>Sildenafil added to bosentan</td>
<td>Ila C</td>
<td>Ila C Ila C</td>
</tr>
<tr>
<td>Other double combinations</td>
<td>Ila C</td>
<td>Ila C –</td>
</tr>
<tr>
<td>Other triple combinations</td>
<td>Ila C</td>
<td>Ila C –</td>
</tr>
<tr>
<td>Riociguat added to sildenafil or other PDE-5i</td>
<td>III B</td>
<td>III B III B</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Class of evidence: I: high, II: moderate, III: low

\textsuperscript{b} Level of recommendation: A: strong, B: moderate, C: weak

\textsuperscript{c} Reference numbers

\textsuperscript{d} FDA approved for PAH

\textsuperscript{e} FDA approved for peripheral vascular disease

\textsuperscript{f} FDA approved for both indications
Therapy for Pulmonary Arterial Hypertension in Adults 2018

- Treatment naive PAH patients with WHO FC III without evidence of rapid disease progression or poor prognosis
  - Is the patient willing and able to tolerate combination therapy?
    - Yes
    - No
    - Combination therapy with ambrisentan and tadalafil (Recommendation 10; weak recommendation, moderate quality evidence)
  - Monotherapy with either bosentan, macitentan, ambrisentan, riociguat, sildenafil, or tadalafil (See Box 2)

- PAH patients with WHO FC III with evidence of rapid disease progression or poor prognosis
  - Is the patient willing and able to manage parenteral prostanoids?
    - Yes
    - Continuous IV epoprostenol, IV treprostinil, or SC treprostinil (See Box 3)
    - No
    - Consider addition of inhaled or oral prostanoid **

- PAH patients with WHO FC IV
  - Is the patient willing and able to manage parenteral prostanoids?
    - Yes
    - Continuous IV epoprostenol, IV treprostinil, or SC treprostinil (See Box 4)
    - No
    - Inhaled prostanoid in combination with an oral PDE-5 inhibitor and an oral endothelin receptor antagonist (Recommendation 59; ungraded consensus-based)

- Patients with inadequate response to initial therapy
  - For WHO FC III or IV PAH patients with unacceptable clinical status despite established PAH-specific monotherapy
    - Addition of a second class of PAH therapy (See Box 5)
  - For WHO FC III or IV PAH patients with unacceptable or deteriorating clinical status despite established PAH-specific therapy with two classes of PAH pharmacotherapy
    - Addition of a third class of PAH therapy (Recommendation 70; ungraded consensus-based)

- FC III and IV Patients with inadequate response to maximal pharmacotherapy
  - Is the patient a candidate for lung transplant?
    - Yes
    - List for lung transplantation ***
    - No
    - Incorporate palliative care services in the management of PAH patients (Recommendation 72; ungraded consensus-based statement)

* Combination therapy carries with it costs as well as multiple medications, including the potential for increased adverse events that may be undesirable for some patients. In these situations, patients are unwilling or unable to tolerate combination therapy and the panel suggests monotherapy.

** No data available for the use of oral or inhaled prostanoids in patients in whom parenteral prostanoids are indicated, but patient is unable to comply. Thus, we do not have a specific recommendation for this population.

*** Lung transplantation is outside the scope of this guideline, which focuses on pharmacotherapy for patients with PAH. Thus, the evidence-based for lung transplants in patients with PAH has not been evaluated by this panel.

James R. Klinger et al DOI: 10.1016/j.chest.2018.11.030
Παρακολούθηση θεραπευτικού αποτελέσματος

<table>
<thead>
<tr>
<th></th>
<th>At baseline (prior to therapy)</th>
<th>Every 3-6 months*</th>
<th>3-4 months after initiation or changes in therapy</th>
<th>In case of clinical worsening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical assessment</td>
<td><img src="#" alt="checkmark" /></td>
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<td>WHO-FC ECG</td>
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<td><img src="#" alt="checkmark" /></td>
<td><img src="#" alt="checkmark" /></td>
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<tr>
<td>6MWT†</td>
<td><img src="#" alt="checkmark" /></td>
<td><img src="#" alt="checkmark" /></td>
<td><img src="#" alt="checkmark" /></td>
<td><img src="#" alt="checkmark" /></td>
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<tr>
<td>Cardio-pulmonary exercise testing†</td>
<td><img src="#" alt="checkmark" /></td>
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<td><img src="#" alt="checkmark" /></td>
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<tr>
<td>BNP/NT-proBNP</td>
<td><img src="#" alt="checkmark" /></td>
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<td><img src="#" alt="checkmark" /></td>
<td><img src="#" alt="checkmark" /></td>
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<tr>
<td>Echocardiography</td>
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Κλινική ανταπόκριση—πως εκτιμάται?


<table>
<thead>
<tr>
<th>Table 2</th>
<th>Variables Used in Clinical Practice to Determine Response to Therapy and Prognosis in Patients With Pulmonary Arterial Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exercise tolerance</strong></td>
<td></td>
</tr>
<tr>
<td>NYHA FC</td>
<td>(2,4,9,10)</td>
</tr>
<tr>
<td>6MWD</td>
<td>(2-4,10,61)</td>
</tr>
<tr>
<td>Peak VO₂</td>
<td>(24)</td>
</tr>
<tr>
<td><strong>Hemodynamics</strong></td>
<td></td>
</tr>
<tr>
<td>RAP</td>
<td>(2,9,10,24,40,50,61,62)</td>
</tr>
<tr>
<td>PAPm</td>
<td>(1,4)</td>
</tr>
<tr>
<td>PVR</td>
<td>(24)</td>
</tr>
<tr>
<td>CO/Cl</td>
<td>(2,3,9,24,40,50,61)</td>
</tr>
<tr>
<td>SvO₂</td>
<td>(2,24,64)</td>
</tr>
</tbody>
</table>

**Prognostic Implications at Baseline (Ref. #)**

- TAPSE
- RV strain
- RA area
- Pericardial effusion

**Prognostic Implications at Follow-Up (Ref. #)**

- BNP/NT-proBNP
- Troponin
- Uric acid
- CRP
- PaCO₂

**Echocardiographic variables**

- Time to clinical worsening
- Morbidity (ν)
- Mortality (Θ)

Δομή και όγκοι

*Ceiling effect*
Θέτουμε υψηλότερους στόχους...

<table>
<thead>
<tr>
<th>Measure</th>
<th>Current Treatment Goal</th>
<th>New Treatment Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified NYHA FC</td>
<td>I or II</td>
<td>I or II</td>
</tr>
<tr>
<td>6MWD</td>
<td>&gt;380 m</td>
<td>380 to 440 m&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cardiopulmonary exercise testing</td>
<td>Peak VO&lt;sub&gt;2&lt;/sub&gt; &gt;15 mL/min/kg</td>
<td>Peak VO&lt;sub&gt;2&lt;/sub&gt; &gt;15 mL/min/kg EqCO&lt;sub&gt;2&lt;/sub&gt; &lt;45 L/min/L/min</td>
</tr>
<tr>
<td>Echocardiography</td>
<td>Normalisation of RV size and function</td>
<td>Normal/near-normal RV size and function</td>
</tr>
<tr>
<td>BNP</td>
<td>Decreasing or normalisation</td>
<td>Normal</td>
</tr>
<tr>
<td>Haemodynamics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Right atrial pressure</td>
<td>&lt;8 mm Hg</td>
<td>&lt;8 mm Hg</td>
</tr>
<tr>
<td>• Cardiac index</td>
<td>&gt;2.5 mg/kg/min&lt;sup&gt;2&lt;/sup&gt;</td>
<td>&gt;2.5 to 3.0 L/min/m&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

RCTs για συνδυασμένη θεραπεία

Combination Therapy

- ERA + Prostanoids
  - BREATHE-2
  - COMBI
  - STEP
  - TRIUMPH-I
- ERA + PDE5i
  - PHIRST-1
- PDE5i + Prostanoids
  - PACES
  - TRIUMPH-I

- Significant improvement of combination not shown
- Low number of patients (<70)
- Short-term endpoint(s)

- Generally, these trials are evaluating escalation/sequential combination therapy, not upfront (initial) combination therapy

- A meta-analysis of these trials showed a modest improvement in exercise capacity, but no significant improvement in mortality, or combined clinical worsening with combination therapy

Meta-analysis of monotherapy versus combination therapy for pulmonary arterial hypertension. Fox et al Am J Cardiol 2011
The role of combination therapy in managing pulmonary arterial hypertension. Humbert M et al Eur Respir Review 2014
Combination therapy targeting PAH may confer preferable therapeutic efficacy compared with monotherapy in patients with CTD-PAH as evidenced by a more remarkable reduction in the risk of clinical worsening and a probable improvement of exercise capacity in these patients.


Overall, we recommend EAP as the optimal choice for patients with PAH in clinical practice and PAE as suboptimal in view of their desirable performance in efficacy. Most of the combination therapies performed better than monotherapies.


In this highly comprehensive meta-analysis, CT reduces the risk of CCW events in patients with PAH and brings physiological improvement.
Comparative Effectiveness of Pharmacologic Interventions for Pulmonary Arterial Hypertension
A Systematic Review and Network Meta-Analysis

Snigdha Jain, MD; Rohan Khera, MD; Saket Girotra, MD, SM; David Badesch, MD; Zhen Wang, PhD;

Among oral agents, ERA, PDE5i, and their combination are associated with improvement in patient morbidity (both clinical worsening and hospitalization) and functional status. Other approved agents are associated

CHEST 2017; 151(1):90-105
Combination therapy in pulmonary arterial hypertension: recent accomplishments and future challenges

Lajoie AC et al. *Pulm Circ.* 2017
Θέματα-Key points

• Πορεία στο χρόνο: 1973-2019 εν αρχή: τα ανορεξιογόνα

• Πότε θεραπεύουμε: ποιούς και σε ποιό στάδιο?

• Θεραπευτικά διλήμματα:
  – Μονοθεραπεια // vs // Συνδυασμένη θεραπεία
  – up front // vs // add on // vs // switch

• .......... και άλλα νέα φάρμακα

Αναθεώρηση στόχων-καταληκτικών σημείων RCTs αλλά βελτιώσαμε τελικά την επιβίωση?
Review on bosentan, a dual endothelin receptor antagonist for the treatment of pulmonary arterial hypertension.

Serasli E et al. Recent Pat Cardiovasc Drug Discov. 2010 Nov;5(3):184-95
Patients were treated with vasoactive drugs in 61.1% of cases. These data clearly indicate that many patients with SSc do not yet receive sufficient vasoactive therapy.
Pulmonary hypertension and the right ventricle—thinking outside the box

Rich JD. *Pulm Circ.* 2014

Galie N. *Eur Heart J.* 2010 Sep; 31(17): 2080-2086
Προστανοειδή: Δεδομένα Επιβίωσης

**Epoprostenol**


Barst et al. *Eur Respir J* 2006;28:1195-1203


Subgroup IPAH patients n=332

![Cumulative Survival](image)

Survival (patients n=178) 85%, 70%, 63%, 55%, 58%, 43%, 33%, 28%

95% CI

**Iloprost**

Iloprost INH

NIH predicted

Log rank $P = 0.28.$

Survival % (patients n=76)

95% CI

Log rank $P = 0.28.$
Long-term survival and safety with selexipag in patients with pulmonary arterial hypertension: results from the GRIPHON study and its open-label extension.

Targeting the Prostacyclin Pathway with Selexipag in Patients with Pulmonary Arterial Hypertension Receiving Double Combination Therapy: Insights from the Randomized Controlled GRIPHON Study. 
Η επιβίωση εξαρτάται από NYHA FC στη διάγνωση

Cumulative survival

Time from diagnosis (years)

FC I/II ($n = 41$)
FC III ($n = 176$)
FC IV ($n = 42$)

$p < 0.001$
Ένα πρόγραμμα ανίχνευσης PAH μπορεί να βελτιώσει την πρόγνωση

8-year survival of incident PAH patients
(from diagnostic right heart catheterization)

- 'Detected' cohort
  - 100% (95% CI 51-93%)
  - 81% (95% CI 43-89%)
  - 73% (95% CI 33-84%)
  - 64% (95% CI 8-47%)

- 'Routine practice' cohort
  - 75% (95% CI 46-90%)
  - 31% (95% CI 11-54%)
  - 25% (95% CI 3-39%)
  - 17% (95% CI 1.47-11.71)

\( p = 0.0037 \)

Pulmonary arterial hypertension: from the kingdom of the near-dead to multiple clinical trial meta-analyses

Nazzareno Galiè*, Massimiliano Palazzini, and Alessandra Manes

✓ υψηλός δείκτης κλινικής υπόνοιας
✓ έγκαιρη διάγνωση
✓ βήμα προς βήμα στρατηγική θεραπευτική προσέγγιση
Future Perspectives for the Treatment of Pulmonary Arterial Hypertension

Hossein A. Ghofrani, MD,* Robyn J. Barst, MD,† Raymond L. Benza, MD,‡ Hunter C. Champion, MD, PhD,§ Karen A. Fagan, MD,¶ Friedrich Grimminger, MD, PhD,* Marc Humbert, MD, PhD,¶ Gérard Simonneau, MD,¶ Duncan J. Stewart, MD,# Carlo Ventura, MD, PhD,** Lewis J. Rubin, MD††
ευχαριστώ