Pulmonary Hypertension
A simple approach to diagnosis and management

Michael Connelly
Faculty Presenter Disclosure

Cardiology for the Non-Cardiologist
Faculty: Michael Connelly

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- Consulting Fees: None related to PH
- Patents: None
- Other: None
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Potential Conflicts of Interest:
None related to PH
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• Information on specific products will be presented in the context of an unbiased overview of all products related to treating patients.

• All scientific research related to, reported or used in this CME activity in support or justification of patient care recommendations conforms to the generally accepted standards.

• Clinical medicine is based in evidence that is accepted within the profession.
Pulmonary Hypertension
Pulmonary Hypertension

- Classification
- Definition
- Diagnosis
- Pathobiology
- Treatment
Pulmonary Hypertension Classification

1. Pulmonary arterial hypertension
2. Pulmonary hypertension due to left heart disease
3. Pulmonary hypertension due to lung diseases and/or hypoxemia
4. Chronic thromboembolic pulmonary hypertension
5. PH with unclear or multifactorial mechanisms
Pulmonary Hypertension

1. Pulmonary arterial hypertension

2. Pulmonary hypertension due to left heart disease

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

4. Chronic thromboembolic pulmonary hypertension

5. PH with unclear or multifactorial mechanisms
Clinical classification

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

1’. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis
   1’.1 Idiopathic
   1’.2 Heritable
      1’.2.1 EIF2AK4 mutation
      1’.2.2 Other mutations
   1’.3 Drugs, toxins and radiation induced
   1’.4 Associated with:
      1’.4.1 Connective tissue disease
      1’.4.2 HIV infection

1”. Persistent pulmonary hypertension of the newborn
### 2. Pulmonary hypertension due to left heart disease

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

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

- 3.1 Chronic obstructive pulmonary disease
- 3.2 Interstitial lung disease
- 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
- 3.4 Sleep-disordered breathing
- 3.5 Alveolar hypoventilation disorders
- 3.6 Chronic exposure to high altitude
- 3.7 Developmental lung diseases
### 4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions

| 4.1 Chronic thromboembolic pulmonary hypertension |
| 4.2 Other pulmonary artery obstructions          |
| 4.2.1 Angiosarcoma                              |
| 4.2.2 Other intravascular tumours               |
| 4.2.3 Arteritis                                 |
| 4.2.4 Congenital pulmonary artery stenosis      |
| 4.2.5 Parasites (hydatidosis)                   |

### 5. Pulmonary hypertension with unclear and/or multifactorial mechanisms

| 5.1 Haematological disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy |
| 5.2 Systemic disorders, sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis            |
| 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders             |
| 5.4 Others: pulmonary tumoral thrombotic microangiopathy, fibrosing mediastinitis, chronic renal failure (with/without dialysis), segmental pulmonary hypertension |
# Haemodynamic definitions of PH

<table>
<thead>
<tr>
<th>Definition</th>
<th>Characteristics&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Clinical group(s)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>PH</td>
<td>PAP&lt;sub&gt;m&lt;/sub&gt; ≥ 25 mmHg</td>
<td>All</td>
</tr>
</tbody>
</table>
|            | PAWP ≤ 15 mmHg              | 1. Pulmonary arterial hypertension  
            |                               | 3. PH due to lung diseases    
            |                               | 4. Chronic thromboembolic PH  
            |                               | 5. PH with unclear and/or multifactorial mechanisms |
| Pre-capillary PH | PAP<sub>m</sub> ≥ 25 mmHg | 2. PH due to left heart disease  
|            | PAWP > 15 mmHg               | 5. PH with unclear and/or multifactorial mechanisms |
|            | DPG < 7 mmHg and/or PVR ≥ 3 WU |  |
|            | DPG ≥ 7 mmHg and/or PVR ≤ 3 WU |  |

<sup>a</sup> All values measured at rest.

<sup>b</sup> According to the clinical classification of PH.

<sup>c</sup> Wood Units are preferred to dynes.s.cm<sup>-5</sup>.
# Haemodynamic definitions of PH

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<th>Clinical group(s)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>PH</td>
<td>PAPm ≥ 25 mmHg</td>
<td>All</td>
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</tbody>
</table>

<sup>a</sup> All values measured at rest.

<sup>b</sup> According to the clinical classification of PH.

<sup>c</sup> Wood Units are preferred to dynes.s.cm<sup>-5</sup>.
## Haemodynamic definitions of PH

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<td>PAP&lt;sub&gt;m&lt;/sub&gt; ≥ 25 mmHg</td>
<td>All</td>
</tr>
</tbody>
</table>
| Pre-capillary PH    | PAP<sub>m</sub> ≥ 25 mmHg, PAWP ≤ 15 mmHg                  | 1. Pulmonary arterial hypertension  
2. PH due to left heart disease  
3. PH due to lung diseases  
4. Chronic thromboembolic PH  
5. PH with unclear and/or multifactorial mechanisms |

<sup>a</sup> All values measured at rest.

<sup>b</sup> According to the clinical classification of PH.

<sup>c</sup> Wood Units are preferred to dynes.s.cm⁻⁵.
## Haemodynamic definitions of PH

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

\(^a\)All values measured at rest. \(^b\)According to the clinical classification of PH. \(^c\)Wood Units are preferred to dynes.s.cm\(^5\).
Diagnostic algorithm

1. Symptoms, signs, history
   - Consider other causes and/or follow-up
   - Echocardiographic probability of PH
   - Signs of severe PH/RV dysfunction
   - Diagnosis of LHD or lung disease confirmed?
      - V/Q scan
         - Mismatched perfusion defects?
            - No
            - Consider other causes
            - CTEPH possible: CT pulmonary angiography, RHC

2. Group 5
   - No signs of severe PH/RV dysfunction
   - RHC: mPAP ≥ 25 mmHg, PAWP ≤ 15 mmHg, PVR > 3 Wood units

3. Heritable
   - PVOD/PCH
   - PAH
   - Heritable PVOD/PCH
   - Heritable PAH

4. Idiopathic
   - PVOD/PCH
   - PAH
   - Idiopathic PVOD/PCH
   - Idiopathic PAH

5. PAH likely
   - Specific diagnostic tests
     - CHD
     - CTD
     - Drugs
     - -toxin
     - Porto-pulmonary
     - HIV
     - Schistosomiasis

6. Refer to PH expert centre

a. CT pulmonary angiography alone may miss diagnosis of CTEPH
Diagnostic algorithm

1. Symptoms, signs, history
2. Echocardiographic probability of PH
   - Yes
   - No
   - Low
   - Intermediate or high
     - Refer to PH expert centre
     - No
   - Consider other causes and/or follow-up

3. Signs of severe PH/RV dysfunction

4. Diagnosis of LHD or lung disease confirmed?
   - V/Q scan
   - Mismatched perfusion defects?
   - No
   - Consider other causes

5. CTEPH possible: CT pulmonary angiography, RHC +/- Pulmonary Angiography

6. Consider LHD and lung diseases by symptoms, signs, risk factors, ECG, PFT+DLCO, chest radiograph and HRCT, arterial blood gases

7. Heritable
   - PVOD/PCH
   - PAH

8. Idiopathic
   - PVOD/PCH
   - PAH

9. PAH likely
   - Specific diagnostic tests

10. CHD
11. CTD
12. Drugs
toxin
Porto
HIV
Schistosomiasis

13. Refer to PH expert centre

14. a CT pulmonary angiography alone may miss diagnosis of CTEPH
### Echocardiographic probability of PH in symptomatic patients

<table>
<thead>
<tr>
<th>Peak tricuspid regurgitation velocity (m/s)</th>
<th>Presence of other echo ‘PH signs’&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Echocardiographic probability of PH</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 2.8 or not measurable</td>
<td>No</td>
<td>Low</td>
</tr>
<tr>
<td>≤ 2.8 or not measurable</td>
<td>Yes</td>
<td>Intermediate</td>
</tr>
<tr>
<td>2.9 – 3.4</td>
<td>No</td>
<td>Intermediate</td>
</tr>
<tr>
<td>2.9 – 3.4</td>
<td>Yes</td>
<td>High</td>
</tr>
<tr>
<td>&gt; 3.4</td>
<td>Not required</td>
<td>High</td>
</tr>
</tbody>
</table>

<sup>a</sup> Echocardiographic signs from at least two different categories (A/B/C) from the list should be present to alter the level of echocardiographic probability of PH.
Diagnostic algorithm

Symptoms, signs, history

Echocardiographic probability of PH

Intermediate or high

Consider LHD and lung diseases by symptoms, signs, risk factors, ECG, PFT+DLCO, chest radiograph and HRCT, arterial blood gases

Low

Consider other causes and/or follow-up

If PH is confirmed by echocardiography:

- V/Q scan
- Matched perfusion defects
- Mismatched perfusion defects:
  - CTEPH likely
    - CT pulmonary angiography
    - RHC

If PH is ruled out by echocardiography:

- Refer to PH expert centre

If no PH is confirmed by echocardiography:

- Consider other causes
- Follow-up
Diagnostic algorithm

1. Symptoms, signs, history

2. Echocardiographic probability of PH
   - Intermediate or high
     - Consider LHD and lung diseases by symptoms, signs, risk factors, ECG, PFT-DLCO, chest radiograph and HRCT, arterial blood gases
   - Low
     - Consider other causes and/or follow-up

3. Diagnosis of LHD or lung disease confirmed?
   - V/Q scan
     - Mismatched perfusion defects?
       - No
         - Consider other causes
       - Yes
         - CTEPH possible: CT pulmonary angiography, RHC

4. Signs of severe PH/RV dysfunction
   - RHC: mPAP ≥ 25 mmHg, PAWP ≤ 15 mmHg, PVR > 3 Wood units

5. Yes
   - Group 5
   - No signs of severe PH/RV dysfunction
   - Heritable PVOD/PCH
   - Heritable PAH
   - Idiopathic PVOD/PCH
   - Idiopathic PAH

6. PAH likely
   - Specific diagnostic tests
     - CHD
     - CTD
     - Drugs
       - Heroin
       - Tobacco
       - Portocapillary
       - HIV
       - Schistosomiasis

7. Refer to PH expert centre

8. CTEPH alone may miss diagnosis of CTEPH
Diagnostic algorithm

1. Symptoms, signs, history
2. Echocardiographic probability of PH
   - Intermediate or high
   - Low
3. Consider LHD and lung diseases by symptoms, signs, risk factors, ECG, PFT-DLCO, chest radiograph and HRCT, arterial blood gases
4. Diagnosis of LHD or lung disease confirmed?
   - Yes
   - No
5. Signs of severe PH/RV dysfunction
6. Consider other causes and/or follow-up
7. No signs of severe PH/RV dysfunction
8. Consider other causes

Specific diagnostic tests
- CHD
- CTD
- Drugs
- Heritable PVOD/PCH
- Heritable PAH
- Idiopathic PVOD/PCH
- Idiopathic PAH
- PAH likely

Specific causes
- Porto-pulmonary
- HIV
- Schistosomiasis
- CTEPH: pulmonary angiography, RHC
- V/Q scan
- Mismatched perfusion defects? Yes

Additional diagnostic tests
- RHC: mPAP ≥ 25 mmHg, PAWP ≤ 15 mmHg, PVR > 3 Wood units
- Pulmonary Angiography
- CTEPH possible: CT pulmonary angiography, RHC

Additional therapies
- Heritable PVOD/PCH
- Heritable PAH
- Idiopathic PVOD/PCH
- Idiopathic PAH
- PAH likely

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Diagnostic algorithm

1. Symptoms, signs, history
   - Echocardiographic probability of PH
     - Intermediate or high
     - Low

   Consider LHD and lung diseases by symptoms, signs, risk factors, ECG, PFT+DLCO, chest radiograph and HRCT, arterial blood gases

   No signs of severe PH/RV dysfunction
   - Yes: Treat underlying disease
   - No: Diagnosis of LHD or lung disease confirmed?

   Yes: Consider other causes and/or follow-up
   No: Signs of severe PH/RV dysfunction

   - Yes: Refer to PH expert centre
   - No: Consider other causes

2. V/Q scan mismatched perfusion defects?
   - No: Consider other causes
   - Yes: CTEPH possible: CT pulmonary angiography, RHC +/-
Pulmonary Angiography

3. Diagnosis of LHD or lung disease confirmed?
   - Yes: Consider LHD and lung diseases by symptoms, signs, risk factors, ECG, PFT+DLCO, chest radiograph and HRCT, arterial blood gases
   - No: Heritable PVOD/PCH
   - Yes: Heritable PAH

4. RHC: mPAP ≥ 25 mmHg, PAWP ≤ 15 mmHg, PVR > 3 Wood units
   - Yes: Specific diagnostic tests
   - No: CHD, CTD, Drugs - toxin, Porto-pulmonary, HIV, Schistosomiasis

Pulmonary Angiography alone may miss diagnosis of CTEPH
Diagnostic algorithm

1. Symptoms, signs, history

2. Echocardiographic probability of PH
   - Intermediate or high
   - Low

3. Consider LHD and lung diseases by symptoms, signs, risk factors, ECG, PFT+DLCO, chest radiograph and HRCT, arterial blood gases

4. No signs of severe PH/RV dysfunction
   - Treat underlying disease

5. Diagnosis of LHD or lung disease confirmed?
   - Yes
   - No

6. Signs of severe PH/RV dysfunction
   - Refer to PH expert centre

7. Consider other causes and/or follow-up

8. Heritable
   - PVOD/PCH
   - PAH

9. Idiopathic
   - PVOD/PCH
   - PAH

10. PAH likely
    - Specific diagnostic tests

11. CHD
12. CTD
13. Drugs
   - toxin
   - Porto-pulmonary
   - HIV
   - Schistosomiasis
Diagnostic algorithm

1. Symptoms, signs, history

2. Echocardiographic probability of PH
   - Intermediate or high
   - Low

3. Consider LHD and lung diseases by symptoms, signs, risk factors, ECG, PFT-DLCO, chest radiograph and HRCT, arterial blood gases

4. No signs of severe PH/RV dysfunction
   - Yes: Treat underlying disease
   - No: Diagnosis of LHD or lung disease confirmed?

5. No: V/Q scan\(^a\) Mismatched perfusion defects?
   - Yes: Signs of severe PH/RV dysfunction
   - No: Consider other causes and/or follow-up

6. Yes: Consider other causes and/or follow-up

\(a\) CT pulmonary angiography alone may miss diagnosis of CTEPH.
Diagnostic algorithm

Symptoms, signs, history

Echocardiographic probability of PH

Intermediate or high

Low

Consider LHD and lung diseases by symptoms, signs, risk factors, ECG, PFT+DLCO, chest radiograph and HRCT, arterial blood gases

Yes

No signs of severe PH/RV dysfunction

Treat underlying disease

Consider other causes and/or follow-up

Low

Consider other causes

Yes

Signs of severe PH/RV dysfunction

Diagnosis of LHD or lung disease confirmed?

No

Yes

V/Q scan

Mismatched perfusion defects?

Refer to PH expert centre

Refer to PH expert centre

Group 5

No signs of severe PH/RV dysfunction

RHC: mPAP ≥ 25 mmHg, PAWP ≤ 15 mmHg, PVR > 3 Wood units

Heritable PVOD/PCH

Heritable PAH

Idiopathic PVOD/PCH

Idiopathic PAH

PAH likely

Specific diagnostic tests

CHD

CTD

Drugs

- toxin

Porto-pulmonary

HIV

Schistosomiasis

Refer to PH expert centre

CT pulmonary angiography alone may miss diagnosis of CTEPH
Diagnostic algorithm

1. Symptoms, signs, history
   - Echocardiographic probability of PH
     - Intermediate or high
     - Low

2. Consider LHD and lung diseases by symptoms, signs, risk factors, ECG, PFT+DLCO, chest radiograph and HRCT, arterial blood gases
   - No signs of severe PH/RV dysfunction
     - Treat underlying disease
     - CTEPH possible: CT pulmonary angiography, RHC +/- Pulmonary Angiography
   - Diagnosis of LHD or lung disease confirmed?
     - Yes
     - No

3. V/Q scan
   - Mismatched perfusion defects?
     - Yes
     - Refer to PH expert centre
     - No

4. Signs of severe PH/RV dysfunction
   - Consider other causes and/or follow-up

5. Consider other causes
   - Refer to PH expert centre

6. Heritable
   - PVOD/PCH
   - PAH

7. Idiopathic
   - PVOD/PCH
   - PAH

8. PAH likely
   - Specific diagnostic tests
   - CHD
   - CTD
   - Drugs
   - -toxin
   - Porto
   - HIV
   - Schistosomiasis

9. Pulmonary Angiography alone may miss diagnosis of CTEPH

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Diagnostic algorithm

1. Symptoms, signs, history

2. Echocardiographic probability of PH
   - Intermediate or high
   - Low

3. Consider LHD and lung diseases by symptoms, signs, risk factors, ECG, PFT+DLCO, chest radiograph and HRCT, arterial blood gases

4. No signs of severe PH/RV dysfunction
   - Yes: Treat underlying disease
   - No: Diagnosis of LHD or lung disease confirmed?

5. Diagnosis of LHD or lung disease confirmed?
   - Yes: Signs of severe PH/RV dysfunction
   - No: V/Q scan? Mismatched perfusion defects?

6. V/Q scan?
   - Yes: Refer to PH expert centre
   - No: RHC: mPAP ≥ 25 mmHg, PAWP ≤ 15 mmHg, PVR > 3 Wood units

7. CTEPH possible: CT pulmonary angiography, RHC +/- Pulmonary Angiography

8. Heritable PVOD/PCH
   - Yes: Heritable PAH
   - No: Idiopathic PVOD/PCH

9. Idiopathic PAH
   - Yes: PAH likely
   - No: Specific diagnostic tests

10. CHD

11. CTD

12. Drugs
   - Toxin
   - Porto-pulmonary
   - HIV
   - Schistosomiasis

13. Refer to PH expert centre

14. CT pulmonary angiography alone may miss diagnosis of CTEPH
Diagnostic algorithm

Symptoms, signs, history

Echocardiographic probability of PH

Intermediate or high

Low

Consider LHD and lung diseases by symptoms, signs, risk factors, ECG, PFT+DLCO, chest radiograph and HRCT, arterial blood gases

No signs of severe PH/RV dysfunction

Treat underlying disease

CTEPH possible: CT pulmonary angiography, RHC +/- Pulmonary Angiography

Yes

Diagnosis of LHD or lung disease confirmed?

Yes

No

V/Q scan

Mismatched perfusion defects?

Yes

Refer to PH expert centre

No

Signs of severe PH/RV dysfunction

Refer to PH expert centre

RHC: mPAP ≥ 25 mmHg, PAWP ≤ 15 mmHg, PVR > 3 Wood units

No

Consider other causes

Consider other causes and/or follow-up
Diagnostic algorithm

1. **Symptoms, signs, history**

2. **Echocardiographic probability of PH**
   - Intermediate or high
   - Low

3. Consider LHD and lung diseases by symptoms, signs, risk factors, ECG, PFT+DLCO, chest radiograph and HRCT; arterial blood gases
   - No signs of severe PH/RV dysfunction
     - Treat underlying disease
   - Diagnosis of LHD or lung disease confirmed?
     - Yes
     - No
   - Signs of severe PH/RV dysfunction
     - Refer to PH expert centre

4. **Groups**
   - Group 5
     - No signs of severe PH/RV dysfunction
     - RHC: mPAP ≥ 25 mmHg, PAWP ≤ 15 mmHg, PVR > 3 Wood units
   - Heritable PVOD/PCH
     - Heritable PAH
   - Idiopathic PVOD/PCH
     - Idiopathic PAH
   - CHD
   - Porto-pulmonary
   - HIV
   - Schistosomiasis

5. **Specific diagnostic tests**
   - CTEPH possible: CT pulmonary angiography, RHC + Pulmonary Angiography

6. **Consider other causes and/or follow-up**
   - V/Q scan
     - Mismatched perfusion defects?
     - Yes
     - No
   - Consider other causes
   - Refer to PH expert centre

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*CT pulmonary angiography alone may miss diagnosis of CTEPH*
Pulmonary arterial hypertension
Early PAH is asymptomatic despite hemodynamic changes

Preclinical: Cardiac output at peak exercise
Symptomatic / stable
Progressive / declining: Pulmonary pressure

Cardiac output at rest

Level

Time

Increasing PVR

Harrison's Principles of Internal Medicine, 14th ed.
Key pathways in the pathophysiology of PAH

Endothelin pathway
- Pro-endotheli-1
- ET-1 (Vasoconstriction & proliferation)
  - Single ERA
  - Dual ERA

Nitric oxide pathway
- L-arginine
- NO (Vasodilation & anti-proliferation)
  - Exogenous NO
  - sGC stimulator
  - PDE-5 inhibitors
  - IP receptor

Prostacyclin pathway
- Arachidonic acid
- PGI₂ (Vasodilation & anti-proliferation)
  - PGI₂ analogues
  - Non-prostanoid IP receptor agonist

cAMP: cyclic adenosine monophosphate; cGMP: cyclic guanosine monophosphate; GTP: guanosine triphosphate; NO: nitric oxide; PDE-5i: phosphodiesterase-5 inhibitor; PGI₂: prostacyclin; sGC: soluble guanylate cyclase

Adapted from Humbert M, et al. Circulation 2014; 130:2189-2208
## Risk assessment in PAH

### Determinants of prognosis

<table>
<thead>
<tr>
<th>Clinical signs of right heart failure</th>
<th>Low risk &lt; 5%</th>
<th>Intermediate risk 5-10%</th>
<th>High risk &gt; 10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression of symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syncope</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO functional class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6MWD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiopulmonary exercise testing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NT-proBNP plasma levels</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imaging (echocardiography, CMR imaging)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemodynamics</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Estimated 1-year mortality.

b Occasional syncope during brisk or heavy exercise, or occasional orthostatic syncope in an otherwise stable patient.

c Repeated episodes of syncope, even with little or regular physical activity.
# Risk assessment in PAH

## Determinants of Prognosis

<table>
<thead>
<tr>
<th>Determinants of Prognosis(^a)</th>
<th>Low risk &lt; 5%</th>
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<th>High risk &gt; 10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical signs of right heart failure</td>
<td>Absent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progression of symptoms</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syncope</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO functional class</td>
<td>I, II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6MWD</td>
<td>&gt; 440 m</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiopulmonary exercise testing</td>
<td>Peak VO(_2) &gt; 15 ml/min/kg (&gt; 65% pred.) VE/VCO(_2) slope &lt; 36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NT-proBNP plasma levels</td>
<td>BNP &lt; 50 ng/l NT-proBNP &lt; 300 ng/ml</td>
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<tr>
<td>Imaging (echocardiography, CMR imaging)</td>
<td>RA area &lt; 18 cm(^2) No pericardial effusion</td>
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<tr>
<td>Haemodynamics</td>
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</tbody>
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\(^a\) Estimated 1-year mortality.

\(^b\) Occasional syncope during brisk or heavy exercise, or occasional orthostatic syncope in an otherwise stable patient.

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## Risk assessment in PAH

<table>
<thead>
<tr>
<th>Determinants of prognosis</th>
<th>Low risk &lt; 5%</th>
<th>Intermediate risk 5-10%</th>
<th>High risk &gt; 10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical signs of right heart failure</td>
<td>Absent</td>
<td>Absent</td>
<td></td>
</tr>
<tr>
<td>Progression of symptoms</td>
<td>No</td>
<td>Slow</td>
<td></td>
</tr>
<tr>
<td>Syncope</td>
<td>No</td>
<td>Occasional syncope&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>WHO functional class</td>
<td>I, II</td>
<td>III</td>
<td></td>
</tr>
<tr>
<td>6MWD</td>
<td>&gt; 440 m</td>
<td>165-440 m</td>
<td></td>
</tr>
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<td>Peak VO&lt;sub&gt;2&lt;/sub&gt; &gt; 15 ml/min/kg (&lt; 65% pred.) VE/VCO&lt;sub&gt;2&lt;/sub&gt; slope &lt; 36</td>
<td>Peak VO&lt;sub&gt;2&lt;/sub&gt; 11-15 ml/min/kg (35-65% pred.) VE/VCO&lt;sub&gt;2&lt;/sub&gt; slope 36–44.9</td>
<td></td>
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<td>NT-proBNP plasma levels</td>
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<td>RAP &lt; 8 mmHg CI ≥ 2.5 l/min/m&lt;sup&gt;2&lt;/sup&gt; SvO&lt;sub&gt;2&lt;/sub&gt; &gt; 65%</td>
<td>RAP 8-14 mmHg CI 2.0-2.4 l/min/m&lt;sup&gt;2&lt;/sup&gt; SvO&lt;sub&gt;2&lt;/sub&gt; 60-65%</td>
<td></td>
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<sup>a</sup> Estimated 1-year mortality.

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<td>Present</td>
</tr>
<tr>
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<td>No</td>
<td>Slow</td>
<td>Rapid</td>
</tr>
<tr>
<td>Syncope</td>
<td>No</td>
<td>Occasional syncope(^b)</td>
<td>Repeated syncope(^c)</td>
</tr>
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<td>III</td>
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\(^a\) Estimated 1-year mortality.

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## Recommendations for efficacy of drug monotherapy for PAH (group 1) according to WHO FC

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<td>WHO-FC II</td>
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<tr>
<td>Calcium channel blockers</td>
<td></td>
</tr>
<tr>
<td>ERAs</td>
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<tr>
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<tr>
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<td></td>
</tr>
<tr>
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Only in responders to acute vasoreactivity tests: class I, for IPAH, HPAH and PAH due to drugs; class II\textsuperscript{a}, for conditions associated with PAH; class II\textsuperscript{b}, for all cause mortality; class II\textsuperscript{c}, in patients not tolerating the subcutaneous form; class II\textsuperscript{d}, this drug is not approved by the EMA at the time of publication of these guidelines.
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<tr>
<td>Bosentan</td>
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</tr>
<tr>
<td>Macitentan&lt;sup&gt;d&lt;/sup&gt;</td>
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</tr>
<tr>
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<tr>
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</tr>
<tr>
<td>Vardenafil&lt;sup&gt;f&lt;/sup&gt;</td>
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</tr>
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<td>Treprostinil</td>
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<tr>
<td>Beraprost&lt;sup&gt;f&lt;/sup&gt;</td>
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<sup>d</sup> Only in responders to acute vasoreactivity tests: class I, for IPAH, HPAH and PAH due to drugs; class IIa, for conditions associated with PAH; class IIb, for conditions associated with PAH and sudden death.

<sup>*</sup> Time to clinical worsening as primary endpoint in RCTs or drugs with demonstrated reduction in all-cause mortality.

<sup>f</sup> In patients not tolerating the subcutaneous form.

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<td>Ambrisentan</td>
<td>I A, C&lt;sup&gt;+&lt;/sup&gt;</td>
<td>I A</td>
<td>IIb C</td>
<td></td>
</tr>
<tr>
<td>Bosentan</td>
<td>I A, C&lt;sup&gt;+&lt;/sup&gt;</td>
<td>I A</td>
<td>IIb C</td>
<td></td>
</tr>
<tr>
<td>Macitentan&lt;sup&gt;d&lt;/sup&gt;</td>
<td>I B, C&lt;sup&gt;+&lt;/sup&gt;</td>
<td>I B</td>
<td>IIb C</td>
<td></td>
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<tr>
<td>Vardenafil&lt;sup&gt;f&lt;/sup&gt;</td>
<td>IIb B, C&lt;sup&gt;+&lt;/sup&gt;</td>
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<td>Intravenous&lt;sup&gt;d&lt;/sup&gt;</td>
<td>- -</td>
<td>I A</td>
<td>I A</td>
</tr>
<tr>
<td>Iloprost</td>
<td>Inhaled</td>
<td>- -</td>
<td>I B</td>
<td>IIb C</td>
</tr>
<tr>
<td>Subcutaneous</td>
<td>Intravenous&lt;sup&gt;f&lt;/sup&gt;</td>
<td>- -</td>
<td>IIa C</td>
<td>IIb C</td>
</tr>
<tr>
<td>Inhaled&lt;sup&gt;f&lt;/sup&gt;</td>
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<td>Treprostinil</td>
<td>Intravenous&lt;sup&gt;e&lt;/sup&gt;</td>
<td>- -</td>
<td>IIa C</td>
<td>IIb C</td>
</tr>
<tr>
<td>Oral&lt;sup&gt;f&lt;/sup&gt;</td>
<td>- -</td>
<td>IIb B</td>
<td>- -</td>
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</tr>
<tr>
<td>Selexipag (oral)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>I B</td>
<td>I B</td>
<td>- -</td>
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<sup>a</sup> Only in responders to acute vasoreactivity tests: class I, for IPAH, HPAH and PAH due to drugs; class IIa, for conditions associated with PAH; class IIb, for additional support of PAH in selected patients.  
<sup>b</sup> Time to clinical worsening as primary endpoint in RCTs or drugs with demonstrated reduction in all-cause mortality.  
<sup>c</sup> In patients not tolerating the subcutaneous form;  
<sup>d</sup> This drug is not approved by the EMA at the time of publication of these guidelines.
Improved prognosis following introduction of PAH-specific therapies

**Survival (%)**

- **Before 1992 Pre-epoprostenol**
- **1992–1999 Pre-ERA**
- **After 2000 Post-ERA**

**Time (months)**

*ERA – Endothelin receptor antagonist*

Evidence based treatment algorithm

PAH confirmed by expert centre

General measures
Supportive therapy

PAH confirmed by expert centre

CCB therapy

Vasoreactive

Non-vasoreactive

Low intermediate risk (WHO FC II-III)¹

Initial monotherapy²

Initial oral combination²

Initial combination including i.v. PCA³

High risk (WHO FC IV)³

Inadequate clinical response

Double or triple sequential combination

Inadequate clinical response

Consider listing for lung transplantation⁴

Treatment naïve patient

Inadequate clinical response

Consider referral for lung transplantation

Some WHO-FC III patients may be considered high risk; ²Initial combination with ambrisentan plus tadalafil has proven to be superior to initial monotherapy with ambrisentan or tadalafil in delaying clinical failure; ³Intravenous epoprostenol should be prioritised as it has reduced the 3 months rate for mortality in high risk PAH patients also as monotherapy; ⁴Consider also balloon septostomy.
Effective PAH management requires regular monitoring and prompt action.
Pulmonary Hypertension – take home messages

1. Pulmonary arterial hypertension

2. Pulmonary hypertension due to left heart disease

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

4. Chronic thromboembolic pulmonary hypertension

5. PH with unclear or multifactorial mechanisms
## Pulmonary Hypertension – take home messages

<table>
<thead>
<tr>
<th>PH diagnosis</th>
<th>Class&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Level&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right heart catheterisation is recommended to confirm the diagnosis of PAH and to support treatment decisions</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Vasoreactivity testing is recommended in patients with IPAH, HPAH and PAH induced by drugs use to detect patients who can be treated with high doses of a calcium channel blocker</td>
<td>I</td>
<td>C</td>
</tr>
</tbody>
</table>

### PAH severity

- It is recommended to evaluate the severity of PAH patients with a panel of data derived from clinical assessment, exercise tests, biochemical markers, and echocardiographic and haemodynamic evaluation and to perform regular follow-up assessments every 3-6 months in stable patients

### PAH general measures

- It is recommended to avoid pregnancy in patients with PAH

<sup>a</sup>Class of recommendation.  <sup>b</sup>Level of evidence.
It is recommended for referral centres to provide care by a multi-professional team (cardiology and respiratory medicine physicians, clinical nurse specialist, radiologists, psychological and social work support, appropriate on-call expertise)

Initial approved drugs monotherapy is recommended in treatment naïve, low or intermediate risk patients with pulmonary arterial hypertension

Initial approved oral drugs combination therapy is recommended in treatment naïve, low or intermediate risk patients with pulmonary arterial hypertension

Sequential drugs combination therapy is recommended in patients with inadequate treatment response to initial monotherapy or to initial double combination therapy

Class of recommendation. Level of evidence.