Disclosures

- **Current Grant Funding**
  - Becker Family Foundation, Principal Investigator
  - A Double-blinded, placebo-controlled pilot study of DMF in pulmonary arterial hypertension (PAH) associated with systemic sclerosis (SSc-PAH): The effect of DMF on clinical disease and biomarkers of oxidative stress, NIH. Sub-investigator.
  - National Jewish Health Chronic Respiratory Disease-Associated Pulmonary Hypertension Registry: CaRDInAl PH Registry, Actelion Investigator-Initiated Grant, Principal Investigator.

- **Industry**
  - Opsumit Users Registry, Actelion
  - A Multicenter, Randomized, Double-Blinded, Placebo-Controlled Trial to Evaluate the Safety and Efficacy of Inhaled Treprostinil in Subjects with Pulmonary Hypertension due to Parenchymal Lung Disease, United Therapeutics Sub-investigator.
  - A Phase 2 Multicenter, Double-Blind, Placebo Controlled, Efficacy, Safety, and Pharmacokinetic Study of 2 Doses of CXA-10, Complexa.
  - A Study eVALuAtiNg the EffiCacy and Safety of Ralin Epag To Improve Treatment OUTCOMES in PAH Patients, Arena.
Disclosures

- **Industry**
  - I serve as a speaker and give non-promotional talks for Actelion, Bayer and Gilead.
Learning Objectives

- Review the classification and epidemiology of pulmonary hypertension, including Pulmonary Arterial Hypertension (PAH) and associated diseases.

- Discuss current and emerging therapies for the management of pulmonary hypertension.
Brief history of Pulmonary Hypertension 1950-1999

1951
- Dresdale makes 1st hemodynamic classification of PH

1973
- Menocil, Apiquel, aminoxaphen, aminoxafen, McN-742 -> PAH epidemic
- World Health Organization organizes 1st WSPH in Geneva: Early classification, NIH registry

1981
- 1st Heart-Lung Transplant by Shumway, Wallwork and Reitz in a patient with PAH

1990
- 1st prostacyclin (epoprostenol) significantly improves survival in PAH

1997
- Phen/Fen taken off the market

1998
- 2nd WSPH in Evian, France: Classification into 5 groups of PH
Pulmonary Hypertension 2000-2010

2002  ■ First endothelin receptor antagonist (bosentan) improves exercise capacity, WHO FC, time to clinical worsening

2003  ■ 3rd WSPH in Venice, Italy: Classification evolved to 5 groups; Refined classification, Treatment Algorithm Proposed, BMPR2 gene mutation in familial PAH

2005  ■ First PDE-5 inhibitor (sildenafil) improves exercise capacity, WHO FC, and hemodynamics

2007  ■ Combination sildenafil + epoprostenol improves exercise capacity

2008  ■ 4th WSPH in Dana Point, California: New treatment strategies: Treating mildly symptomatic patients, combination and goal-directed treatment strategies; Needs for RCTs: Time to clinical worsening
Pulmonary Hypertension 2011-now

2013
- 1\textsuperscript{st} guanylate cyclase stimulator (riociguat) introduced in treatment of PAH and CTEPH
- 5\textsuperscript{th} WSPH in Nice: 12 task forces; development of risk stratification concepts

2015
- AMBITION trial shows dual upfront combination therapy with ambrisentan and tadalafil lowers risk of clinical failure
- 1\textsuperscript{st} oral prostacyclin IP receptor (selexipag) agonist effective as primary or add-on therapy in lowering risk of death or complication of PH

2018
- 6\textsuperscript{th} WSPH in Nice: 13 task forces, including patient perspectives; New definition of PH; Refine diagnostic algorithm
- 14 FDA Approved Medications for PAH by end of 2018
In 25 years 41 RCTs have advanced therapies in PAH

- Epoprostenol SSc
  - 1990
- Epoprostenol IPAH
  - 1996
- Bosentan
  - 2000
- Beraprost-US
  - 2001
- Treprostinil
  - 2002
- AIR
  - 2003
- BREATHE-1
  - 2004
- ALPHABET
  - 2005
- Sastry
  - 2006
- BREATHE-2
  - 2009
- STRIDE-1
  - 2010
- STEP
  - 2011
- Singh
  - 2012
- STRIDE-2
  - 2013
- COMBI
  - 2014
- BREATHE-5
  - 2015

RCTs on monotherapy versus placebo or versus monotherapy (n=21)
RCTs on monotherapy and/or sequential combination versus placebo (n=18)
RCTs on initial combination versus monotherapy (n=2)
Despite advances in therapy and 1-yr survival, PH is a chronic and progressive disease

Pre-treatment (NIH 1991)
1-year survival 68%
3-year survival 34%
And PH is often misdiagnosed

- Patients have symptoms on median of 44 months (3.7 yrs) until they are diagnosed with PAH

- Median survival in untreated PH = 2.8 yrs

- Can look like: “out of shape,” asthma, COPD, obesity, hypertension, sleep apnea

At the time of diagnosis, their NYHA/WHO functional class has progressed
Patient M

- 41 yo man from Gunnison (7700 feet), enjoyed backpacking
- 3 yrs ago - winded walking from parking lot to work at 9300 feet (One year prior he could run up 2 flights of stairs)
- Over past 2 years he has had to pace himself, sometimes faking looking at his email on his phone while walking because he could not keep up with colleagues
- He also could not go backpacking as he would lose his appetite and feel sick after the hike in
- He passed out once at a party when he went to chase someone
- Dyspneic on exertion, “struggles to get deep breaths in”
- On exam: Loud P2, no RV heave. 1+ edema, JVP at 7 cmH2O

What symptoms and signs are associated with pulmonary hypertension?
Symptoms of PAH – NIH Registry

- Leg edema
- Palpitations
- Syncope
- Near syncope
- Chest pain
- Fatigue
- Dyspnea

Symptoms at enrollment
Initial symptoms

## Signs and Symptoms

### Symptoms:
- dyspnea on exertion
- chest pain
- fatigue
- dry cough
- dizziness
- presyncope/syncope
- edema, increased abdominal girth
- Raynaud’s phenomenon (10%)
- Indolent

### Signs:
- accentuated P2
- right ventricular S4 gallop
- RV Heave and palpable bulge at LUSB
- elevated JVP
- Graham-Steell murmur (diastolic murmur at LUSB)
- right heart failure
  - Right ventricular S3
  - Hepatomegaly
  - Hepatojugular reflex
  - Peripheral edema
How do we define pulmonary hypertension?

- Pulmonary hypertension = \( \text{mPAP} \geq 20 \text{ mmHg} \) at rest measured by right heart catheterization
- Can be found in multiple conditions
- World Health Organization Classification Scheme (WHO Groups)
  - Diseases grouped by similar pathology/pathophysiology
  - Different groups lead to different treatment paradigms

Simonneau G et al. JACC 2013
Simonneau G et al. ERJ 2018
Clinical classification of PH (Nice 2018)

1. **Pulmonary arterial hypertension**
   1. Idiopathic PAH
   2. Heritable PAH (BMPR2, ALK1)
   3. Drug and Toxin induced
   4. PAH associated with:
      - Connective tissue disease
      - HIV infection
      - Portal hypertension
      - Congenital heart disease
      - Schistosomiasis
   5. PAH long-term responders to CCB
   6. PAH with overt features of venous/capillaries (PVOD/PCH) involvement
   7. Persistent PH of the newborn

3. **PH with lung diseases/hypoxaemia**
   - Obstructive lung disease
   - Restrictive lung disease
   - Other lung disease with mixed obstructive/restrictive pattern
   - Hypoxia without lung disease
   - Developmental lung disorders

4. **PH due to pulmonary artery obstructions**
   - CTEPH
   - Other pulmonary artery obstructions

5. **PH with unclear/multifactorial mechanisms**
   - Hematologic disorders
   - Systemic and metabolic disorders
   - Renal disease +/- hemodialysis
   - Complex congenital heart disease

Simonneau G et al. ERJ 2018
Pulmonary Arterial Hypertension

- Pulmonary arterial hypertension (PAH, group 1) is characterized by
  - Pre-capillary PH (PAWP ≤ 15 mmHg)
  - Pulmonary vascular resistance ≥ 3 Wood Units
  - In the absence of other causes of pre-capillary PH such as PH due to lung diseases, CTEPH, or other rare diseases

Group 1 – PAH
Group 2 – PH due to LHD
Group 3 – PH due to lung disease
Group 4 – CTEPH
Group 5 – PH due to rare diseases

Simonneau G et al. ERJ 2018
Pulmonary Arterial Hypertension
is a rare disease

PAH
- 15/million
- IPAH 5.9/million
- IPAH ~40% cases of PAH

- APAH majority of the rest
  APAH-Scleroderma. 8-26.7%
  PoPH 1-6% of patients with portal hypertension
  HIV 0.5%
  CTEPH 0.8% after first PE, 3.8% at 2 years post PE
  Schistosomiasis 11.8% (200 million people infected worldwide)

Badesch et al. JACC 2009
McLaughlin et al. JACC 2009
IPAH is the most common WHO Group 1 disease

- 54 centers -> incident and prevalent - 2525 pts
- 1 yr survival model cohort = 91%
- 1 yr survival incident cohort = 84.6%
- 55.5 % Class III/IV at entry

Pathogenesis of PAH

1. **RISK FACTORS AND ASSOCIATED CONDITIONS**
   - Collagen Vascular Disease
   - Congenital Heart Disease
   - Portal Hypertension
   - HIV Infection
   - Drugs and Toxins
   - Pregnancy

2. **VASCULAR INJURY**
   - Endothelial Dysfunction
     - ↓ Nitric Oxide Synthase
     - ↓ Prostacyclin Production
     - ↑ Thromboxane Production
     - ↑ Endothelin 1 Production
   - Vascular Smooth Muscle Dysfunction
     - Impaired Voltage-Gated Potassium Channel (Kv1.5)

3. **DISEASE PROGRESSION**
   - Loss of Response to Short-Acting Vasodilator Trial
     - Adventitial and Intimal Proliferation
     - Plexiform Lesion
     - In situ Thrombosis
     - Advanced Vascular Lesion

**Susceptibility**
- Abnormal BMPR2 Gene
- Other Genetic Factors
Idiopathic PAH

- Young although age of diagnosis getting older
- Female predominance 2:1
- Endothelial dysfunction and smooth muscle proliferation, **plexiform arteriopathy** on path
- High index of suspicion is key
- Average time to diagnosis: 3.7 yrs
- Median survival without treatment... 3.8 yrs

Simonneau G et al. JACC 2013
Hoeper MM, Gibbs JSR. Eur Regis Rev 2014; 23
Plexiform lesion is from a systemic vascular plexus

“Plexiform lesions represent anastomosing structures between bronchial microvessels and pulmonary arteries and veins.”

Humbert M et al. ERJ 2018
Other types of PAH

Heritable PAH

• BMPR2 gene found in 80% of families with HPAH
• Inherited in an autosomal dominant manner with incomplete penetrance (not all obligate carriers of genetic susceptibility develop the disease)
• Other mutations: ALK1, endoglin, Cav-1, Smad9, KCNK3
• Do we do regular genetic screening? Only at specialized centers.

Drug-induced PAH

Definite
Menocil, Apiquel, aminoxaphen, aminoxafen, McN-742
Fenfluramine
Dexfenfluramine
Methamphetamines
Dasitinib
Toxic Rapeseed Oil

Probable
Cocaine
Phenylpropanolamine
St. John’s Wort
Alkylating agents
Bosutinib
Lentiviral agents vs HCV
Leflunomide
Indirubin (Chinese herb Quing Dai)
APAH-Scleroderma

- Scleroderma is a rare disease
  - 138-286 cases per million
- More likely in patients with CREST (limited cutaneous scleroderma)
- Poorer response to therapy, worse long-term survival
- 1-year mortality is twice that of IPAH

Mr. M. Next step in diagnosis?

- History, symptoms, signs and/or laboratory tests suggestive of PH
  - Echocardiographic probability of PH#
    - Low
    - High or intermediate
      - Consider V/Q scan to screen for CTEPH
      - Consider left heart disease (assess pre-test probability) and lung disease
      - No clinically significant left heart disease or lung disease
        - Refer to PH expert centre
      - Fast-track referral of selected patients
    - Consider other causes and/or follow-up

- Assess probability of PH
- Identify high-risk patients
- Diagnose common causes of PH
- Diagnose rare causes of PH
Next step in diagnosis: Echo

Initial echo

- LVEF 70-75%
- Moderately increased LV wall thickness
- RV volume and pressure overload
- Mild RAE 6.3 cm
- Severe RVE 5.9 cm
- RVSP 79 mmHg, TRV 4.0 m/s
- Reduced RV systolic function
  TAPSE 1.1 cm
- Negative bubble study
How do we define PH on echo?

- First screening test in patients with symptoms, signs c/w PH
- PASP > 40 mmHg usually warrants further investigation
- Guidelines recommend use of TRV instead of PASP as PASP requires an estimate of RAP, which is variable
- Can identify cardiac conditions that may cause PH (congenital, valve defects, shunt)
- TAPSE < 1.8 associated with worse survival

---

<table>
<thead>
<tr>
<th>Peak tricuspid regurgitation velocity (m/s)</th>
<th>Presence of other echo ‘PH signs’</th>
<th>Echocardiographic probability of pulmonary hypertension</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>High</td>
</tr>
<tr>
<td>&gt;3.4</td>
<td>Not required</td>
<td></td>
</tr>
</tbody>
</table>

---

A: The ventricles

- Right ventricle/ left ventricle basal diameter ratio >1.0

B: Pulmonary artery

- Right ventricular outflow Doppler acceleration time <105 msec and/or mid systolic notching

C: Inferior vena cava and right atrium

- Inferior vena cava diameter >21 mm with decreased inspiratory collapse (<50% with a sniff or <20% with quiet inspiration)
- Flattening of the interventricular septum (left ventricular eccentricity index >1.1 in systole and/or diastole)
- Early diastolic pulmonary regurgitation velocity >2.2 m/sec
- Right atrial area (end-systole) >18 cm²
- PA diameter >25 mm.

---

Hoeper M et al. JACC 2013
Forfia PR et al, AJRCCM 2006
2015 ESC/ERS Guidelines Eur Heart J 2015
Tricuspid Annular Plane Systolic Excursion

1. S-I RAd
2. L-M RAd
3. T.A
4. Basal RVd
5. Medial RVd
6. Major RVd

The marked point with yellow color shows the reference site for TAPSE measurement.

A Overall cohort

TAPSE ≥ 1.8 cm
TAPSE < 1.8 cm

Log rank \( \chi^2 = 10.0 \)
P-value = 0.002

B PAH only

TAPSE ≥ 1.8 cm
TAPSE < 1.8 cm

Log rank \( \chi^2 = 6.8 \)
P-value = 0.009

Guzmán-Sanchez CM et al. Rev Mex Cardiol 2017
Forfia P et al, AJRCCM 2009
Mr. M – Additional testing...

- PFTs: FEV1/FVC 77%, FEV1 3.19L, 76% pred, FVC 4.17L, 79% pred. TLC 6.71L 97% pred, DLCO 43.91 mL/min/mmHg (114% predicted).
- HRCT Chest: Mild bronchial wall thickening, air trapping. No ILD
- Sleep Study: Rec CPAP 15 cm H2O
- V/Q Scan: Low probability for PE
- ECG: Sinus tachycardia, possible RA enlargement, incomplete RBBB, RVH
For whom do you need to get a right heart catheterization?

- It depends on echo severity and risk factors...

<table>
<thead>
<tr>
<th>Echocardiographic probability of PH</th>
<th>Without risk factors or associated condition for PAH or CTEPH&lt;sup&gt;d&lt;/sup&gt;</th>
<th>Class&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Level&lt;sup&gt;b&lt;/sup&gt;</th>
<th>With risk factors or associated conditions for PAH or CTEPH&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Class&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Level&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Ref&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Alternative diagnosis should be considered</td>
<td>IIa</td>
<td>C</td>
<td>Echo follow-up should be considered</td>
<td>IIa</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>Alternative diagnosis, echo follow-up, should be considered</td>
<td>IIa</td>
<td>C</td>
<td>Further assessment of PH including RHC should be considered</td>
<td>IIa</td>
<td>B</td>
<td>45, 46</td>
</tr>
<tr>
<td></td>
<td>Further investigation of PH may be considered</td>
<td>IIb</td>
<td>C</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>Further investigation of PH (including RHC&lt;sup&gt;3&lt;/sup&gt;) is recommended</td>
<td>I</td>
<td>C</td>
<td>Further investigation of PH&lt;sup&gt;4&lt;/sup&gt; including RHC is recommended</td>
<td>I</td>
<td>C</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Peak tricuspid regurgitation velocity (m/s)</th>
<th>Presence of other echo ‘PH signs’&lt;sup&gt;1a&lt;/sup&gt;</th>
<th>Echocardiographic probability of pulmonary hypertension</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></td>
</tr>
</tbody>
</table>

2015 ESC/ERS Guidelines Eur Heart J 2015
DK – Next step in diagnosis?

History, symptoms, signs and/or laboratory tests suggestive of PH

- Assess probability of PH
- Identify high-risk patients
- Diagnose common causes of PH
- Diagnose rare causes of PH

Echocardiographic probability of PH

- High or intermediate: Consider V/Q scan to screen for CTEPH
- Low: Consider other causes and/or follow-up

V/Q scan abnormal

- Consider left heart disease (assess pre-test probability) and lung disease
- No clinically significant left heart disease or lung disease

Refer to PH expert centre
Don’t forget about CTEPH screening!

- V/Q scan = most sensitive test for CTEPH
  - Sensitivity of V/Q > 96% versus 54% CTPA
  - Specificity of V/Q 95% versus 99% CTPA
  - Reliance on CTPA alone may miss diffuse diffuse disease of the distal segmental/subsegmental pulmonary arteries
- Yet not used in all patients, even at PH centers
- Often patients diagnosed with CTEPH will have no history of symptomatic PE (2/3-3/4 of patients!)
- Approx 3.8% of patients with PE go on to develop CTEPH at 2 years (Pengo et al, 2004)
Next step: Right Heart Cath
Confirming the diagnosis: Right Heart Catheterization

- **Gold standard in diagnosis of PAH**
  - Pulmonary arterial hypertension = pre-capillary PH
  - mPAP > 20 mmHg, PAWP < 15 mmHg and PVR > 3 WU
  - Every RHC should have comprehensive hemodynamics including cardiac output

- **When to perform vasodilator testing?**
  - In all patients with newly diagnosed IPAH
  - In all other forms of PH and PAH, not recommended because the number of responders is small and results can be misleading.
    - Inhaled NO at 10 to 20 parts per million is the gold standard
    - Positive: Decrease in mPAP by at least 10 mmHg to < 40 mmHg and no decrease in CO

Simonneau G et al, ERJ 2018
Hoeper et al. JACC 2013
Mr. M : Right Heart Cath

RHC results

- RA 23
- RV 94/29
- PA 94/54 (70)
- PAWP 16
- TD CO 3.03 L/min
- TD CI 1.22 L/m/kg
- Fick CO 4.66 L/min
- Fick CI 1.88 L/m/kg
- PVR 12.9 - 17.8 WU
- No response to NO

Cardiac Output (Fick) in L/min =
(135 ml O2/min/m2*BSA)/(13*Hgb*(SaO2-SvO2))

So what next for our patient?

- Confirmed PAH
  - Initial RHC: RA 23, mPAP 70, PCWP 16, CI 1.2, PVR 17.8
  - 6MWT: 402 m
When we start PAH-targeted therapy, our goals are to:

A. Reduce mPAP to normal ≤ 25 mmHg
B. Normalize BNP
C. Improve cardiac index to ≥ 2.5 L/min/m²
D. Improve NYHA/WHO functional class
E. Improve PASP to < 35 mmHg
F. A, B, C, D
G. B, C, D
H. All of the above
How sick is the patient?
WHO Functional Class

• FC 1 - PH but no resulting limitation on activity. Ordinary activity does not cause dyspnea/fatigue, chest pain, near syncope.

• FC 2 - Slight limitation in activity. Comfortable at rest. Ordinary activity causes dyspnea/fatigue, chest pain, near syncope.

• FC 3 - Marked limitation in activity. Comfortable at rest. Less than ordinary activity causes dyspnea/fatigue, chest pain, near syncope.

• FC 4 - Inability to carry out activity without symptoms. Dyspnea/fatigue at rest. Syncope.
Goal-directed therapy: ERS Risk Assessment

<table>
<thead>
<tr>
<th>Determinants of prognosis \n(estimating 1-year mortality)</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>Present</td>
</tr>
<tr>
<td>Progression of symptoms</td>
<td>No</td>
<td>Slow</td>
<td>Rapid</td>
</tr>
<tr>
<td>Syncope</td>
<td>No</td>
<td>Occasional syncope\textsuperscript{b}</td>
<td>Repeated syncope\textsuperscript{c}</td>
</tr>
<tr>
<td>WHO functional class</td>
<td>I, II</td>
<td>III</td>
<td>IV</td>
</tr>
<tr>
<td>6MWD</td>
<td>&gt;440 m</td>
<td>165–440 m</td>
<td>&lt;165 m</td>
</tr>
<tr>
<td>Cardiopulmonary exercise testing</td>
<td>Peak VO\textsubscript{2} &gt;15 ml/min/kg (&gt;65%) pred. (\text{VE/VO}<em>{2}\text{ CO}</em>{2}) slope &lt;36</td>
<td>Peak VO\textsubscript{2} 11–15 ml/min/kg (35–65%) pred. (\text{VE/VO}<em>{2}\text{ CO}</em>{2}) slope 36–44.9</td>
<td>Peak VO\textsubscript{2} &lt;11 ml/min/kg (&lt;35%) pred. (\text{VE/VO}<em>{2}\text{ CO}</em>{2}) slope 45</td>
</tr>
<tr>
<td>NT-proBNP plasma levels</td>
<td>BNP &lt;50 ng/l</td>
<td>BNP 50–300 ng/l</td>
<td>BNP &gt;300 ng/l</td>
</tr>
<tr>
<td></td>
<td>NT-proBNP &lt;300 ng/l</td>
<td>NT-proBNP 300–1400 ng/l</td>
<td></td>
</tr>
<tr>
<td>Imaging (echocardiography, CMR imaging)</td>
<td>RA area &lt;18 cm\textsuperscript{2} No pericardial effusion</td>
<td>RA area 18–26 cm\textsuperscript{2} No or minimal, pericardial effusion</td>
<td>RA area &gt;26 cm\textsuperscript{2} Pericardial effusion</td>
</tr>
<tr>
<td>Haemodynamics</td>
<td>RAP &lt;8 mmHg</td>
<td>RAP 8–14 mmHg</td>
<td>RAP &gt;14 mmHg</td>
</tr>
<tr>
<td></td>
<td>CI (\geq 2.5) l/min/m\textsuperscript{2} SvO\textsubscript{2} &gt;65%</td>
<td>CI 2.0–2.4 l/min/m\textsuperscript{2} SvO\textsubscript{2} 60–65%</td>
<td>CI &lt;2.0 l/min/m\textsuperscript{2} SvO\textsubscript{2} &lt;60%</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Determinants of prognosis: estimated 1-year mortality. 
\textsuperscript{b} Occasional syncope: less than 2–3 episodes per week. 
\textsuperscript{c} Repeated syncope: more than 2–3 episodes per week.
REVEAL Risk Stratification

- Registry to Evaluate Early and Long-term PAH Disease Management
- 54 US centers
- WHO Group 1 PAH
  - mPAP ≥ 25 mmHg, PAWP < 18 mmHg, PVR ≥ 3 WU
- 2006-2007: 2967 patients enrolled

Badesch, D, et al. CHEST 2010
Benza R et al. CHEST 2012
Clinical worsening predicts worse overall survival

![Graph showing survival rates for patients who did not worsen and those who worsened over time. The graph indicates a significant difference in survival rates between the two groups, with those who worsened having a lower survival rate.](image-url)
Survival is associated with improvement in risk score

Benza R et al. J Heart Lung Transplant 2015
Treatments

NO - sGC - cGMP Pathway
- L-arginine → L-citrulline
- eNOS
- NO Inhalation
- Nitrite / Nitrate
- NO uncoupling
- BH4
- 6R-BH4
- Riociguat
- NO → sGC
- GTP → cGMP
- cGMP → GMP
- PDE5
- sGC
- cGMP
- Vasodilation
- ↓ Proliferation

Prostacyclin Pathway
- Arachidonic acid → Prostaglandins
- COX
- Prostacyclin (PGI2)
- Epoprostenol
- Treprostinil
- Iloprost
- Beraprost
- Selexipag
- IP receptor
- AC
- cAMP
- ATP
- Vasoconstriction
- ↑ Proliferation

Endothelin-1 Pathway
- Big Endothelin-1
- ECEs
- Ambrisentan
- Endothelin-1
- ETA receptor
- ETB receptor
- Bosentan
- Macitentan
- Vasoconstriction
- ↑ Proliferation

Smooth muscle cells
- New therapeutic strategies
- FDA-approved drugs
Which treatment to begin?

<table>
<thead>
<tr>
<th>Measure/treatment</th>
<th>Class&lt;sup&gt;a&lt;/sup&gt;-Level&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Ref.</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>WHO-FC II</td>
<td>WHO-FC III</td>
<td>WHO-FC IV</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endothelin receptor antagonists</td>
<td>Ambrisentan</td>
<td>l</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>Bosentan</td>
<td>l</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>Macitentan</td>
<td>l</td>
<td>B</td>
</tr>
<tr>
<td>Phosphodiesterase type 5 inhibitors</td>
<td>Sildenafil</td>
<td>l</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>Tadalafil</td>
<td>l</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Vardenafil</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>Guanylate cyclase stimulators</td>
<td>Riociguat</td>
<td>l</td>
<td>B</td>
</tr>
<tr>
<td>Prostacyclin analogues</td>
<td>Epoprostenol</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Inhaled</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Intravenous</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Treprostinil</td>
<td>Subcutaneous</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Inhaled</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Intravenous</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Beraprost</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IP receptor agonists</td>
<td>Selexipag (oral)</td>
<td>l</td>
<td>-</td>
</tr>
</tbody>
</table>

2015 ESC/ERS Guidelines Eur Heart J 2015
Treatment depends on the degree of illness at presentation

- **Treatment naive patient**
  - PAH confirmed by expert center
  - General measures (Table 16)
  - Supportive therapy (Table 17)

- **CCB Therapy (Table 18)**
  - Acute vasoreactivity test (IPAH/HPAH/DPAH only)
  - Vasoreactive
    - Low or intermediate risk (WHO FC II–III)
      - Initial monotherapy (Table 19)
      - Patient already on treatment
        - Double or triple sequential combination (Table 21)
      - Inadequate clinical response (Table 15)
        - Consider referral for lung transplantation

  - Non-vasoreactive
    - High risk (WHO FC IV)
      - Initial combination including i.v. PCA (Table 20)
      - Consider referral for lung transplantation

- **Patient already on treatment**
  - Inadequate clinical response (Table 15)
  - Consider listing for lung transplantation (Table 22)

**ACR active**
- Acute vasoreactivity test (IPAH/HPAH/DPAH only)
- Vasoreactive
  - CCB therapy
  - Low or intermediate risk
  - High risk
- Non-vasoreactive

**ACR plus**
- Acute vasoreactivity test (IPAH/HPAH/DPAH only)
- Vasoreactive
  - CCB therapy
  - Low or intermediate risk
  - High risk
- Non-vasoreactive

**CVR**
- Acute vasoreactivity test (IPAH/HPAH/DPAH only)
- Vasoreactive
  - CCB therapy
  - Low or intermediate risk
  - High risk
- Non-vasoreactive

**Maximal medical therapy and listing for lung transplantation**

---

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

1. Some WHO FC III patients may be considered high risk (see Table 11).
2. Initial combination with ambisentan plus tadalafil has been shown to be superior to initial monotherapy with ambisentan or tadalafil in delaying clinical failure.
3. Intravenous epoprostenol should be prioritised as it has reduced the 3 months rate for mortality in high risk PAH patients also as monotherapy.
4. Consider also balloon aortic septostomy.

---

2015 ESC/ERS Guidelines Eur Heart J 2015
Galiè N et al ERJ 2018
Our patient Mr. M.

- BNP 316 pg/mL
- Initial REVEAL Score: 9 = moderate-high risk
- Exertional presyncope/syncope
- Initiated on IV treprostinil
Our patient Mr. M.

- BNP 316 pg/mL
- Initial REVEAL Score: 9 = moderate-high risk
- Exertional presyncope/syncope
- Initiated on IV treprostinil and macitentan

Follow up cath after 9 days of IV treprostinil and macitentan:
- RAP 13 mmHg
- PAP 113/41 (65)
- PCWP 12 mmHg
- TD CO 7.7 L/min
- TD CI 3.1 L/min/m²
- Fick CO 8.5 L/min
- Fick CI 3.6 L/min/m²
- PVR 6 WU
Follow up echo

Initial echo
- LVEF 70-75%
- Moderately increased LV wall thickness
- RV volume and pressure overload
- Mild RAE 6.3 cm
- Severe RVE 5.9 cm
- RVSP 79 mmHg, TRV 4.0 m/s
- Reduced RV systolic function TAPSE 1.1cm
- Negative bubble study

Approx 1 month on 3-drug therapy
- LVEF > 75%
- Normal LV diastolic function
- RV pressure overload
- Moderate RAE 6.9 cm
- Moderate RVE 5.0 cm
- RVSP 61 mmHg, TRV 3.4 m/s
- Normal RVSF TAPSE 2.30 cm
Serial, close follow up is crucial to make sure they are moving toward low risk status

- Initiate therapy
- Follow up on average every 3 months with 6-minute walk test
- Echo every 6 months
- More frequent initial follow up in sicker patients (i.e., parenteral therapy)
New therapeutic directions

- Genetically determined targets – BMPR2 signaling pathway
- Growth factors, cellular proliferation
- Metabolism, insulin resistance
- Inflammation, immune modulation
- Estrogen signaling
- Oxidative and hypoxic stress
- Serotonin and humoral modulation
- Pulmonary artery denervation
- Stem cells
Summary

- Despite progress over the past 25 years, PH is still a chronic and progressive disease.
- Misdiagnosis/delay in diagnosis affects outcomes.
- It is crucial to have PH on the differential diagnosis in patients with unexplained dyspnea.
- Diagnosis and proper classification and risk stratification are key to determining the best treatment course.
Thank you
CXR Findings in PAH

Prominent Hilar PAS

Peripheral Hypovascularity (Pruning)

RV enlargement into retrosternal clear space
ECG in PAH