Management of PAH

Puneet Saxena
Introduction

• Early identification and treatment
• Advanced disease may be less responsive to therapy
• Principles of management of PAH cannot be extrapolated to other forms of PH
Outline

- Definition and Classification
- Diagnosis
- Vasoreactivity Testing
- Assessment of severity
- Treatment
  - General measures
  - Supportive therapy
  - Advanced therapy
- Recent advances
Definition & Classification
Diagnostic Criteria

- PH is defined as an increase in mean pulmonary arterial pressure (PAPm) $\geq 25$ mmHg at rest as assessed by right heart catheterization (RHC).

- PAH is defined as a subgroup of PH with:
  - PAWP $\leq 15$ mmHg with PVR $> 3$ Wood units
  - Chronic lung diseases and other causes of hypoxemia are mild or absent
  - Venous thromboembolic disease is absent
  - Certain miscellaneous disorders are absent, including systemic disorders (eg, sarcoidosis), hematologic disorders (eg, myeloproliferative diseases), and metabolic disorders (eg, glycogen storage disease).

Borderline PAH?

• Systematic review of 47 studies describing 72 healthy populations (1187 patients)
  – Normal resting PAPm: $14 \pm 3.3$ mmHg
  – Upper limit of normal (ULN = Mean + 2SD): $20.6$ mmHg

PH on exercise?

Age 18–30 yrs = Unshaded
Age 30–50 yrs = Light shade
Age ≥50 yrs = Dark shade

\( \bar{P}_{pa} \text{ mmHg} \)

Group 1. PAH

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 CTD
   1.4.2 HIV
   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 CTD
      1’.4.2 HIV

1”. Persistent pulmonary hypertension of the newborn

ESC/ERS Guidelines 2016
Diagnosis of PAH
<table>
<thead>
<tr>
<th>Registry</th>
<th>Age, yrs</th>
<th>Female, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PAH</td>
<td>IPAH</td>
</tr>
<tr>
<td>U.S. PHC (2010)</td>
<td>48 ± 14</td>
<td>45 ± 14</td>
</tr>
<tr>
<td>Scottish-SMR (2007)</td>
<td>52 ± 12</td>
<td>49 ± 11</td>
</tr>
<tr>
<td>Chinese (2007)</td>
<td>NA</td>
<td>36 ± 12</td>
</tr>
<tr>
<td>U.S. REVEAL (2006-9)</td>
<td>50 ± 14</td>
<td>50 ± 15</td>
</tr>
<tr>
<td>Spanish (2012)</td>
<td>45 ± 17</td>
<td>46 ± 18</td>
</tr>
<tr>
<td>UK (2012)</td>
<td>NA</td>
<td>50 ± 17</td>
</tr>
<tr>
<td>New Chinese registry (2011-12)</td>
<td>36 ± 13</td>
<td>38 ± 13</td>
</tr>
<tr>
<td>Mayo (2011)</td>
<td>52 ± 15</td>
<td>52 ± 15</td>
</tr>
<tr>
<td>Compera (2013)</td>
<td>NA</td>
<td>65 ± 15</td>
</tr>
</tbody>
</table>
Diagnosis of PAH

Rule out Gp 2-5

RHC - mPAP 25 mmHg, PAWP≤ 15 mmHg, PVR >3 Wood units
ECG

- Normal ECG does not exclude the diagnosis
- Abnormal ECG is more likely in severe rather than mild PH
- P pulmonale, RAD, RVH, RV strain, RBBB and QTc prolongation
- Prolongation of the QRS complex and QTc suggest severe disease. *(Int J Cardiol. 2013)*

• Data from 251 patients referred for suspicion of pre-capillary PH
• Noninvasive diagnostic decision tree.
• Prospectively collected data set of 121 consecutive patients for temporal validation.
CXR

- Abnormal in 90% pts at diagnosis
- May suggest Gp 3/2
- May distinguish arterial and venous PH
- degree of PH does not correlate with the extent of radiographic abnormalities

Milne EN. Forgotten gold in diagnosing pulmonary hypertension: the plain chest radiograph. Radiographics 2012
PFT and ABG

- Usually mild to moderate reduction of lung volumes
- Most have reduced DLCO
  - <45% predicted associated with a poor outcome
- Although obstruction is unusual, peripheral airway obstruction can be detected
- PaO2 remains normal or is only slightly lower
- PaCO2 is decreased
  - independent marker of mortality

Prognostic value of blood gas analyses in patients with idiopathic pulmonary arterial hypertension

M.M. Hoeper, M.W. Pletz, H. Golpon and T. Welte

• 12-yr retrospective analysis assessing blood gases, haemodynamics, exercise variables and survival in 101 patients with IPAH

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>6MWD</td>
<td>1.007 (1.003–1.011)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RAP</td>
<td>0.873 (0.805–0.947)</td>
<td>0.001</td>
</tr>
<tr>
<td>mPAP</td>
<td>0.984 (0.954–1.014)</td>
<td>0.292</td>
</tr>
<tr>
<td>Cardiac index</td>
<td>2.591 (1.075–6.241)</td>
<td>0.034</td>
</tr>
<tr>
<td>PVR</td>
<td>0.999 (0.998–1.000)</td>
<td>0.040</td>
</tr>
<tr>
<td>SV,\textsubscript{O₂}</td>
<td>1.057 (1.007–1.109)</td>
<td>0.025</td>
</tr>
<tr>
<td>Pa,\textsubscript{O₂}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At baseline</td>
<td>1.025 (0.996–1.056)</td>
<td>0.097</td>
</tr>
<tr>
<td>At 3 months</td>
<td>1.020 (0.991–1.049)</td>
<td>0.176</td>
</tr>
<tr>
<td>Pa,\textsubscript{CO₂}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At baseline</td>
<td>1.191 (1.058–1.341)</td>
<td>0.004</td>
</tr>
<tr>
<td>At 3 months</td>
<td>1.449 (1.242–1.690)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
ECHO

Echocardiographic probability of pulmonary hypertension in symptomatic patients with a suspicion of pulmonary hypertension

<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>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>

ESC guidelines 2015
Echocardiographic signs in addition to TR velocity measurement

<table>
<thead>
<tr>
<th>Ventricles</th>
<th>Pulmonary artery</th>
<th>IVC and right atrium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right ventricle/ left ventricle basal diameter ratio &gt;1.0</td>
<td>Right ventricular outflow doppler acceleration time &lt;105 msec and/or midsystolic notching</td>
<td>Inferior cava diameter &gt;21 mm with decreased inspiratory collapse (&lt;50% with a sniff or &lt;20% with quiet inspiration)</td>
</tr>
<tr>
<td>Flattening of the Interventricular septum (left ventricular eccentricity index &gt;1.1 in systole and/or diastole)</td>
<td>Early diastolic pulmonary regurgitation velocity &gt;2.2m/sec</td>
<td>Right atrial area (end-systole) &gt;18 cm²</td>
</tr>
<tr>
<td></td>
<td>PA diameter &gt;25 mm</td>
<td></td>
</tr>
</tbody>
</table>

Echocardiographic signs from at least two different categories from the list should be present to alter the level of echocardiographic probability of pulmonary hypertension.
CTPA

- Increased PA diameter (≥29 mm)
  - Sens 0.79, sp 0.83
- Pulm:ascending aorta diameter ratio ≥1.0
  - Sens 0.74, sp 0.81
- Segmental artery:bronchus >1 : 1 in 3-4 lobes

- May give clues for alternative diagnosis

Right heart catheterization

- Morbidity -1.1% and mortality -0.055%
- LHC may be done simultaneously when left heart disease is suspected
- Pressure measurements should be made in the PA, PA wedge position, RV and RA
- Blood samples for oximetry should be taken from the high superior vena cava, IVC and PA
- CO should be measured using thermodilution or the direct Fick method
- Derived variables should include transpulmonary pressure gradient (TPG) and PVR
## Recommendations

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class(^a)</th>
<th>Level(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RHC is recommended to confirm the diagnosis of pulmonary arterial hypertension (group 1) and to support treatment decisions</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>In patients with PH, it is recommended to perform RHC in expert centres (see section 12) as it is technically demanding and may be associated with serious complications</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>RHC should be considered in pulmonary arterial hypertension (group 1) to assess the treatment effect of drugs (Table 16)</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>RHC is recommended in patients with congenital cardiac shunts to support decisions on correction (Table 24)</td>
<td>I</td>
<td>C</td>
</tr>
</tbody>
</table>

## Recommendations

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class(^a)</th>
<th>Level(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RHC is recommended in patients with PH due to left heart disease (group 2) or lung disease (group 3) if organ transplantation is considered</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>When measurement of PAWP is unreliable, left heart catheterization should be considered to measure LVEDP</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>RHC may be considered in patients with suspected PH and left heart disease or lung disease to assist in the differential diagnosis and support treatment decisions</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>RHC is indicated in patients with CTEPH (group 4) to confirm the diagnosis and support treatment decisions</td>
<td>I</td>
<td>C</td>
</tr>
</tbody>
</table>
Vasoreactivity testing

- IPAH, HPAH or drug-induced PAH
- Vasodilator - Inhaled nitric oxide (NO) at 10–20 parts per million (ppm)
  - i.v. epoprostenol
  - i.v. Adenosine
  - inhaled iloprost

- Positive acute response - a reduction of the mPAP $\geq$10 mmHg to reach an absolute value of mPAP $\leq$40 mmHg with an increased or unchanged CO

- 10% of patients with IPAH will meet these criteria
Assessment of severity

• **WHO-FC** - one of the most powerful predictors of survival

• **Echo** – vital follow-up tool
  – Estimated PAPs at rest is usually not prognostic and not relevant for therapeutic decision making
  – Speckle tracking improves the quantification of RV function
  – Echo during exercise provides additional information on RV function

• **RHC** – Important prognostic information
  – RA pressure, CI and SvO2 are the most robust indicators
  – PAPm provides little prognostic information
  – uncertainties around the optimal timing of follow-up RHC
CMR

- More accurate for the assessment of RV morphology and function than echo
- Also allows measurement of stroke volume and CO
- CMR prognostic markers
  - increased RV volume
  - reduced LV volume
  - reduced RV ejection fraction
  - reduced stroke volume
- Follow-up CMR studies may have utility in the long-term management of PAH by identifying RV failure prior to the development of clinical features

Exercise Capacity

• 6MWT most widely used
  – Absolute values, but not changes in 6MWD, provide prognostic information
  – No single threshold that is applicable for all patients
  – Peripheral O2 measurements and heart rate response, BORG scale await confirmation

• CPET
  – low end-tidal partial pressure of carbon dioxide (pCO2)
  – High ventilator equivalents for carbon dioxide (VE/VCO2)
  – low oxygen pulse (VO2/HR)
  – low peak oxygen uptake (peak VO2)
  – peak VO₂ is most widely used for therapeutic decision making
Biochemical markers

- markers of vascular dysfunction
  - asymmetric dimethylarginine (ADMA), endothelin-1, angiopoietins, von Willebrand factor
- markers of inflammation
  - C-reactive protein, interleukin 6, chemokines
- markers of myocardial stress
  - ANP, BNP/NT-proBNP, troponins
- markers of low CO and/or tissue hypoxia
  - pCO2, uric acid, growth differentiation factor 15 (GDF15), osteopontin
- markers of secondary organ damage
  - Creatinine, bilirubin
BNP

• BNP appears to have a slightly tighter correlation with pulmonary haemodynamics and is less affected by kidney function

• NT-proBNP seems to be a stronger predictor of prognosis

## Risk assessment in PAH

<table>
<thead>
<tr>
<th>Determinants of prognosis(^a) (estimated 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(^b)</td>
<td>Repeated syncope(^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>
</tbody>
</table>
| Cardiopulmonary exercise testing                            | Peak\(VO_2\) >1.5 ml/min/kg (>65% pred.)  
YE/VCO\(_2\) slope <36 | Peak\(VO_2\) 11–15 ml/min/kg (35–65% pred.)  
YE/VCO\(_2\) slope 36–44.9 | Peak\(VO_2\) <1.1 ml/min/kg (<35% pred.)  
YE/VCO\(_2\) slope ≥45 |
| NT-proBNP plasma levels                                     | BNP <50 ng/l  
NT-proBNP <300 ng/l | BNP 50–300 ng/l  
NT-proBNP 300–1400 ng/l | BNP >300 ng/l  
NT-proBNP >1400 ng/l |
| Imaging (echocardiography, CMR imaging)                     | RA area <18 cm\(^2\)  
No pericardial effusion | RA area 18–26 cm\(^2\)  
No or minimal, pericardial effusion | RA area >26 cm\(^2\)  
Pericardial effusion |
| Haemodynamics                                               | RAP <8 mmHg  
CI ≥2.5 l/min/m\(^2\)  
\(SvO_2\) >65% | RAP 8–14 mmHg  
CI 2.0–2.4 l/min/m\(^2\)  
\(SvO_2\) 60–65% | RAP >14 mmHg  
CI <2.0 l/min/m\(^2\)  
\(SvO_2\) <60% |

Achievement/maintenance of a low-risk profile is recommended as an adequate treatment response for patients with PAH.

*ESC/ERS 2015*
Suggested assessment and timing for the follow-up of patients with PAH

<table>
<thead>
<tr>
<th>Medical assessment and determination of functional class</th>
<th>At baseline</th>
<th>Every 3–6 months&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Every 6–12 months&lt;sup&gt;a&lt;/sup&gt;</th>
<th>3–6 months after changes in therapy&lt;sup&gt;a&lt;/sup&gt;</th>
<th>In case of clinical worsening</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECG</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>6MWT/Borg dyspnoea score</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CPET</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
<td>+&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Echo</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Basic lab&lt;sup&gt;b&lt;/sup&gt;</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Extended lab&lt;sup&gt;c&lt;/sup&gt;</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Blood gas analysis&lt;sup&gt;d&lt;/sup&gt;</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Right heart catheterization</td>
<td>+</td>
<td></td>
<td>+&lt;sup&gt;f&lt;/sup&gt;</td>
<td>+&lt;sup&gt;e&lt;/sup&gt;</td>
<td>+&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

ESC/ERS 2015
Treatment of PAH - Initial approach

• General measures
  – Physical activity and supervised rehabilitation
  – Pregnancy, birth control and post-menopausal hormonal therapy
  – Infection prevention
  – Psychosocial support
  – Adherence to treatments
  – Genetic counselling

• Supportive therapy (oral anticoagulants, diuretics, O2, digoxin)

• Referral to expert centres

• Acute vasoreactivity testing for the indication of chronic CCB therapy
Treatment of PAH – Advanced therapy

- High-dose CCB in vasoreactive patients
- Drugs approved for PAH in non-vasoreactive patients according to the prognostic risk

Assess response to the initial treatment strategy

- inadequate response?
  - Combination therapy
  - Transplantation
## General Measures

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAH patients should avoid pregnancy</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Immunization against influenza and pneumococcal infection</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Psychosocial support</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Supervised exercise training should be considered in physically deconditioned PAH patients under medical therapy</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>In-flight O2 administration should be considered for patients in WHO-FC III and IV and those with PaO2 consistently &lt;60 mmHg</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>In elective surgery, epidural rather than general anaesthesia should be preferred whenever possible</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Excessive physical activity that leads to distressing symptoms is not recommended</td>
<td>III</td>
<td>C</td>
</tr>
</tbody>
</table>
Physical activity and supervised rehabilitation

- Prospective randomized study to evaluate the effects of exercise and respiratory training in patients with severe symptomatic PH
- 30 patients with PH
  - 21 women; mean age, 50 yrs; PAPm, 50mm Hg; mean WHOclass, 2.9; PAH, n23; CTEPH, n7
- On stable disease-targeted medication
- Randomly assigned to a control (n15) and a primary training (n15) group
- Primary end points
  - changes from baseline to wk 15 in 6MWD
  - Scores of the Short Form Health Survey quality-of-life questionnaire

• At wk 15, patients in the primary and secondary training groups had an improved 6MWD
  – mean difference between the control and the primary training group was 111 m (95% CI, 65 to 139 m; *P < 0.001*)
• Exercise training was well tolerated and improved scores of quality of life, WHO functional class, peak oxygen consumption, oxygen consumption at the anaerobic threshold, and achieved workload.
• PAPs at rest did not change significantly after 15 weeks of exercise and respiratory training (from 61±18 to 54±18 mm Hg) within the training group.
Effects of exercise training in patients with iPAH

• 19 clinically stable iPAH patients (NYHA II-III) underwent a supervised exercise training programme for the duration of 12 weeks.
• Maximal capacity, endurance capacity and quadriceps function were assessed at baseline and after 12 weeks.
• In 12 patients, serial quadriceps muscle biopsies were obtained.

*de Man FS et al. Eur Respir J. 2009;34(3):669-75*
red: cell membrane of the quadriceps myocytes; yellow: capillaries

Exercise training improves peak oxygen consumption and haemodynamics in patients with severe PAH and inoperable CTEPH: a prospective, RCT

- 87 patients (54% female, 56 ± 15 years, 84% WHO-FC III/IV, 53% combination therapy) on stable disease-targeted medication were randomly assigned to a control and training group.
- Non-invasive assessments and right heart catheterization at rest and during exercise were performed at baseline and after 15 weeks.
- Primary endpoint was the change in peak VO$_2$/kg. Secondary endpoints included changes in haemodynamics.

Exercise-based rehabilitation programmes for pulmonary hypertension (Review)

- 6 RCTs, pooled data from 5
- Study duration ranged from 3 to 15 weeks
- Both inpatient- and outpatient based rehabilitation that incorporated both upper and lower limb exercise

- Mean 6MWD following exercise training 60.12 m higher
  - n = 165, 5 RCTs, low-quality evidence; minimal important difference 30 m
- Mean peak VO$_2$ 2.4 ml/kg/minute higher
  - n = 145, 4 RCTs, low quality evidence
- Mean peak power 16.4 W higher
  - n = 145, 4 RCTs, low quality evidence
- Mean change in HRQoL (SF-36 physical component) 4.63 points higher
  - n = 33, 2 RCTs, low-quality evidence
- SF-36 mental component 4.17 points higher
  - n = 33; 2 RCTs, low-quality evidence

Exercise-based rehabilitation programmes for pulmonary hypertension (Review)

- Supervised exercise-based rehabilitation is likely to be safe for people with PH who are stable on medical therapy
- Can lead to meaningful improvements in exercise capacity
- Clinical importance of improvements in HRQoL is less clear

Lacunae

- Optimal method of exercise rehabilitation
- Intensity and duration of the training
- Characteristics of the supervision
- Mechanisms for the improvement of symptoms, exercise and functional capacity
- Effects on prognosis and survival
Pregnancy, birth control and post-menopausal hormonal therapy

• Pregnancy remains associated with a substantial mortality rate in PAH (upto 56%)
• Barrier contraceptives – unpredictable effect
• Progesterone-only pill preferable
  – ERAs can reduce the efficacy of OCPs
• Intra-uterine coils may cause vaso-vagal rxn
• Safety of post-menopausal HRT - unclear

Pregnancy outcomes in pulmonary arterial hypertension in the modern management era

- Multinational, prospective registry to examine the contemporary outcome of pregnancies in patients with PAH
- 3-yr period; 13 participating centres; 26 pregnancies
- 3 (12%) females died (had uncontrolled PAH)
- 1 (4%) developed right heart failure requiring urgent heart–lung transplantation
- 8 eight abortions; 2 spontaneous and 6 induced
- 16 (62%) pregnancies were successful
  - These females had well controlled PAH
  - 8 were long-term responders to CCBs

Supportive therapies

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretic treatment is recommended in PAH patients with signs of RV failure and fluid retention</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Continuous LTOT is recommended in PAH patients when PaO2 is consistently &lt;60 mmHg</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Oral anticoagulant treatment may be considered in patients with IPAH, HPAH and PAH due to use of Anorexigens</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>Correction of anaemia and/or iron status may be considered in PAH patients</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>The use of ACEI/ARB/beta-blockers and ivabradine is not recommended in patients with PAH unless required by co-morbidities (i.e. HTN, CAD or left HF)</td>
<td>III</td>
<td>C</td>
</tr>
</tbody>
</table>
Diuretics

• No good study investigating choice of diuretics in PAH patients
• Many experts add an aldosterone antagonists such as spironolactone
• Torsemide may be better than Frusemide – more consistent results

Oral Anticoagulants

- High prevalence of vascular thrombotic lesions at postmortem examination in patients with IPAH (Fuster V. Circulation 1984)
- Non-specific factors - heart failure and immobility
- Used in 50-85% patients in US/European registries

Warfarin in PAH – meta-analysis

- No RCTs found
- 9 cohort studies were selected (2 prospective)
- 31% mortality risk reduction with warfarin (HR = 0.69, CI 0.57-0.82)
- “Pooled results from cohort studies suggest a survival benefit, but the moderate study quality, the high risk of publication bias, and the methodological limitations inherent in the analysis of observational studies preclude a definite conclusion.”
- Need for quality RCT

Caldeira et al. Canadian Journal of Cardiology 30 (2014)
Recommendations on Warfarin

- Recommended in all patients with IPAH, HPAH and PAH due to anorexigens
- However should be used with caution in patients with hemoptysis or bleeding
- Also interactions with other PAH specific drugs must be kept in mind
- DOAs are not yet validated
  - Risk of bio-accumulation
    
Oxygen therapy

- Oxygen: sO2< 90% or pO2<60 should receive supplemental oxygen
- Demonstrated to reduce the PVR in patients with PAH
- No randomised data to suggest that LTOT is beneficial
- Data extrapolated from evidence in COPD
NOT in Eisenmenger Syndrome

- Kaplan-Meier survival estimates for patients with Eisenmenger Syndrome receiving nocturnal oxygen therapy (open circles) and for those in the control group (closed squares).
- Mean survival estimates are 20.73 mo (95% confidence intervals [CI] 17.48 to 23.97) and 20.77 months (95% CI 16.69 to 24.85), respectively (chi-square log-rank 0.08, p = NS).

Other supportive therapies

• Digoxin - shown to improve CO acutely in IPAH, although its efficacy is unknown when administered chronically *(Rich S, Chest 1998)*

• ACEI/ARB, β-blockers, ivabradine – No evidence

• Iron supplementation
  – May be associated with reduced exercise capacity, and higher mortality, independent of the presence or severity of anaemia *(Broberg CS. J Am Coll Cardiol 2006, Rhodes CJ. J Am Coll Cardiol 2011)*
  – Fe supplementation may improve exercise capacity and QoL *(Viethen T. Int J Cardiol 2014)*
Advanced/Targeted Therapy
CCBs

• Nifedipine and Diltiazem MC used > Amlodipine
• Verapamil avoided d/t negative inotropic effect
• HR > 100 → Diltiazem
• HR < 100 → Nifedipine/Amlodipine
• High dose CCBs required:
  – Nifedipine 120-240 mg/d
  – Diltiazem 240-720 mg/d
  – Amlodipine upto 20 mg/d

Taichman, Ornelas et al. CHEST 2014
McLaughlin, Archer et al. Circulation 2009
CCBs

Rich et al. NEJM 1992
• 17/64 patients (26%) had acute pulmonary vasoreactivity (20% decrease in mPAP and PVR)
• Responders received CCBs: At 5 yrs CCB group had 94% survival compared with 55% in non-responders (p=0.003)

• Retrospective study: 70/557 (12.6%) showed vasoreactivity and got CCB
• Only 38/70 (7% of total) had response to CCB
• CCB responders had better baseline NYHA Class, longer 6MWD and hemodynamic variables
• Also showed significant survival benefit (98% v 48%)

CCB responder group had reached a lower mPAP (<40 mmHg) and lower PVR on vasodilator testing when compared to CCB non-responder group
Figure 4. Breakdown of long-term responders to calcium channel blocker (CCB) monotherapy amongst those who are acutely vasoreactive, by type of PAH (data adopted from Sitbon et al. (2004))
### Factors predicting response to CCBs

#### Table 5: Odds Ratios for Variables Associated With Treatment Success on Long-Term CCB for Acute Responders (Univariate Analysis)

<table>
<thead>
<tr>
<th></th>
<th>Dichotomy/Median</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline clinical variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>&lt;42.8</td>
<td>2.18</td>
<td>0.83–5.75</td>
<td>0.115</td>
</tr>
<tr>
<td>History of RHF</td>
<td>No</td>
<td>3.48</td>
<td>0.95–12.68</td>
<td>0.059</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td>II/III-IV</td>
<td>3.02</td>
<td>1.13–8.13</td>
<td>0.028</td>
</tr>
<tr>
<td><strong>Hemodynamic variables measured at baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean RAP, mm Hg</td>
<td>&lt;7</td>
<td>2.36</td>
<td>0.89–6.21</td>
<td>0.083</td>
</tr>
<tr>
<td>Mean PAP, mm Hg</td>
<td>&lt;56</td>
<td>3.02</td>
<td>1.13–8.13</td>
<td>0.028</td>
</tr>
<tr>
<td>Cardiac index, L \cdot min^{-1} \cdot m^{-2}</td>
<td>&gt;2.5</td>
<td>3.21</td>
<td>1.20–8.54</td>
<td>0.015</td>
</tr>
<tr>
<td>PVR, Wood units</td>
<td>&lt;11.5</td>
<td>4.24</td>
<td>1.55–11.49</td>
<td>0.005</td>
</tr>
<tr>
<td>Svo2, %</td>
<td>&gt;65</td>
<td>19.18</td>
<td>5.73–64.25</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Variables achieved during acute vasodilator testing</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean PAP, mm Hg</td>
<td>&lt;37</td>
<td>6.13</td>
<td>2.11–17.86</td>
<td>0.0009</td>
</tr>
<tr>
<td>Fall in mean PAP, %</td>
<td>&gt;31</td>
<td>7.35</td>
<td>2.54–21.28</td>
<td>0.0002</td>
</tr>
<tr>
<td>PVR, Wood units</td>
<td>&lt;6.7</td>
<td>7.35</td>
<td>2.54–21.28</td>
<td>0.0002</td>
</tr>
<tr>
<td>Fall in PVR, %</td>
<td>&gt;45</td>
<td>3.27</td>
<td>1.22–8.77</td>
<td>0.018</td>
</tr>
</tbody>
</table>

RHF indicates right heart failure; RAP, right atrial pressure.

CCBs: Use with Caution!

- Start with low dose and titrate upwards
- Edema
- Hypotension
- Reflex tachycardia → RV ischaemia
- Increasing CCB doses in patients who are not vasoreactive may be fatal
- As 93% patients are not likely to respond → Should not be used without vasoreactivity testing

Taichman, Ornelas et al. CHEST 2014
ESC 2015 recommendations

• High doses of CCBs are recommended in patients with IPAH, HPAH and DPAH who are responders to acute vasoreactivity testing (1C)
• Close follow-up with complete reassessment after 3–4 months of therapy (including RHC) (1C)
• Continuation recommended in patients in WHO-FC I or II with marked haemodynamic improvement (near normalization) (1C)
Specific PAH Therapy
6R-BH4 = sapropterin dihydrochloride, tetrahydrobiopterin
AC = adenylyl cyclase
BH2 = dihydrobiopterin
BH4 = tetrahydrobiopterin

Gladwin MT. Am J Respir Crit Care Med; 195(1):1–16
Prostanoids

- Prostacyclin (PGI$_2$) – endogenous eicosanoid produced by endothelial cells.
- Epoprostenol is the synthetic equivalent of prostacyclin, and treprostinil and iloprost are both stable synthetic analogs.
- Deficiency of prostacyclin activity identified as an important part of the pathobiology of PAH.
- Loss of expression of prostacyclin synthase also been observed in lung tissue of PAH patients.

Agarwal R et al. AHJ 2011
Prostacyclin pathway

Arachidonic acid → PGI₂

Endothelial cells

Prostacyclin (PGI₂)

→ Vasodilatation

↓ SMC proliferation

Receptors

IP

→ cAMP

Smooth muscle cells (SMC)

PGI₂ derivatives and agonists of PGI₂ receptors (IP)

Epoprostenol
Treprostenil
Iloprost
Beraprost
Selexipag

Perrin et al. Expert Opin. Pharmacother. 2015
Prostanoids - Mechanism of Action

• Results in smooth-muscle relaxation with vasodilation

• Targets pathologic vascular remodeling observed in PAH

• Anti-proliferative, inhibition of platelet aggregation, anti-inflammatory, and augmentation of ventricular inotropy
Prostanoids – Dosing and administration

<table>
<thead>
<tr>
<th>Drug</th>
<th>Preparation</th>
<th>Administration</th>
<th>Dosage</th>
</tr>
</thead>
</table>
| **Epoprostenol GM (glycine-mannitol FLOLAN)** 0.5 mg 1.5 mg lyophilised powder | Reconstituted solutions stable for up to 8 hrs. May be stored for up to 40 hrs refrigerated at 2°C to 8°C. | Continuous IV infusion via central line with ambulatory infusion pump | Start at 2 ng/kg/min (titrate upward 3-7 days)  
Mean dose:  
12 wks = 11 ng/kg/min  
1 yr = 21 ng/kg/min  
1 ½ yr = 35 ng/kg/min                                                                 |
| **Epoprostenol AS (arginine-sucrose VELETRI)** 0.5 mg 1.5 mg lyophilised powder | Reconstituted solutions stable for up to 48 hrs. May be stored for up to 8 days refrigerated at 2°C to 8°C. | do                                                   | do                                                                                               |

Not to be exposed to direct sunlight
# Prostanoids – Dosing and administration (contd)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Preparation</th>
<th>Administration</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Iloprost – Inhaled (VENTAVIS)</strong></td>
<td>10 mcg/ml = 2.5 mcg  20 mcg/ml = 5 mcg</td>
<td>No dilution required</td>
<td>Oral inhalation via ultrasonic nebuliser</td>
</tr>
<tr>
<td><strong>Treprostenil – Inhaled (TYVASO)</strong></td>
<td>1.74 mg/2.9 ml</td>
<td>No dilution required. One ampoule to be changed every 24 hrs.</td>
<td>Oral inhalation via Tyvaso Inhalational System</td>
</tr>
</tbody>
</table>
| **Treprostenil - IV/SC (REMODULIN)** | With sterile water: storage upto 4 hrs at room temp and 24 hrs refrigerated. With diluent: Maybe stored upto 14 days. Administer within 48 hrs | Continuous IV/SC infusion with ambulatory infusion pump | 1.25 ng/kg/min and titrate upward  
*Dosage of 40ng/kg/min a/w improved survival | |
| **Treprostenil – Oral (ORENITRAM)** | - | - | 0.25 mg bd and increase 3-4 days  
*Mean dose 3.4 mg bd | |
Epoprostenol – Landmark Trial

• 12 week prospective randomized open label trial (epoprostenol vs standard care)
• IPAH, NYHA Class III/IV, n = 81 (41 Epoprostenol)
• 1º outcome: mean 6MWD increased by 32 m in epoprostenol group (decrease by 25 m in std Rx)
• Other statistically significant outcomes:
  – Only randomised PAH trial to show improved survival
  – Improvement in hemodynamic parameters, FC, QoL and dyspnea scores

Barst et al. NEJM 1996
<table>
<thead>
<tr>
<th>Drug(s) tested</th>
<th>Study</th>
<th>N</th>
<th>Weeks</th>
<th>Background therapy</th>
<th>Primary endpoint</th>
<th>Main Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beraprost</td>
<td>ALPHABET</td>
<td>130</td>
<td>12</td>
<td>No</td>
<td>6MWD</td>
<td>6MWD improved Haemodynamics not improved</td>
</tr>
<tr>
<td></td>
<td>Barst</td>
<td>116</td>
<td>52</td>
<td>No</td>
<td>CW</td>
<td>CW not improved</td>
</tr>
<tr>
<td>Epoprostenol</td>
<td>Rubin</td>
<td>23</td>
<td>12</td>
<td>No</td>
<td>6MWD</td>
<td>6MWD improved Haemodynamics improved</td>
</tr>
<tr>
<td></td>
<td>Barst</td>
<td>81</td>
<td>12</td>
<td>No</td>
<td>6MWD</td>
<td>6MWD improved Haemodynamics improved Survival improved</td>
</tr>
<tr>
<td></td>
<td>Badesch</td>
<td>111</td>
<td>12</td>
<td>No</td>
<td>6MWD</td>
<td>6MWD improved</td>
</tr>
<tr>
<td>Inhaled Iloprost</td>
<td>AIR</td>
<td>203</td>
<td>12</td>
<td>No</td>
<td>6MWD &amp; FC</td>
<td>6MWD &amp; WHO-FC improved Haemodynamics improved at peak</td>
</tr>
<tr>
<td></td>
<td>STEP</td>
<td>67</td>
<td>12</td>
<td>Bosentan</td>
<td>6MWD</td>
<td>6MWD improved (P = 0.051) TTCW improved</td>
</tr>
<tr>
<td></td>
<td>COMBI</td>
<td>40</td>
<td>12</td>
<td>Bosentan</td>
<td>6MWD</td>
<td>Terminated for futility 6MWD not improved No clinical improvement</td>
</tr>
<tr>
<td>Drug(s) tested</td>
<td>Study</td>
<td>N</td>
<td>Weeks</td>
<td>Background therapy</td>
<td>Primary endpoint</td>
<td>Main Results</td>
</tr>
<tr>
<td>---------------</td>
<td>----------------</td>
<td>-----</td>
<td>-------</td>
<td>--------------------</td>
<td>------------------</td>
<td>----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Treprostini</td>
<td>SC-Pivotal</td>
<td>470</td>
<td>12</td>
<td>No</td>
<td>6MWD</td>
<td>6MWD improved Haemodynamics improved Pain at infusion site</td>
</tr>
<tr>
<td></td>
<td>TRICUMPH</td>
<td>235</td>
<td>12</td>
<td>No</td>
<td>6MWD</td>
<td>6MWD improvement (+20 m at peak, +12 m at trough) TTCW not improved</td>
</tr>
<tr>
<td></td>
<td>PO-Freedom</td>
<td>185</td>
<td>16</td>
<td>No</td>
<td>6MWD</td>
<td>6MWD improvement (+26 m at peak, +17 m at trough) TTCW not improved</td>
</tr>
<tr>
<td></td>
<td>PO-Freedom</td>
<td>354</td>
<td>16</td>
<td>ERA and/or PDE-5i</td>
<td>6MWD</td>
<td>6MWD not improved TTCW not improved</td>
</tr>
<tr>
<td></td>
<td>PO-Freedom</td>
<td>310</td>
<td>16</td>
<td>ERA and/or PDE-5i</td>
<td>6MWD</td>
<td>6MWD not improved TTCW not improved</td>
</tr>
<tr>
<td></td>
<td>Phase-2</td>
<td>43</td>
<td>17</td>
<td>ERA and/or PDE-5i</td>
<td>PVR</td>
<td>PVR improved 6MWD not improved</td>
</tr>
<tr>
<td>Selexipag</td>
<td>GRIPHON</td>
<td>115</td>
<td>74</td>
<td>ERA and/or PDE-5i</td>
<td>Composite</td>
<td>TTCW improved</td>
</tr>
</tbody>
</table>

- 130 patients with PAH
- Randomized to the maximal tolerated dose of beraprost (median dose 80 μg qid) or to placebo for 12 wks
- Primary end point – 6MWD
- Difference between groups in the mean change of 6MWD - 25.1 m (95% CI: 1.8 to 48.3, p = 0.036)

Barst RJ et al. J Am Coll Cardiol 2003

- 116 patients
- Randomized to the maximal tolerated dose of beraprost (median dose 120 μg qid) or to placebo for 12 months
- Primary end point was disease progression; i.e., death, transplantation, epoprostenol rescue, or >25% decrease in peak oxygen consumption (VO₂)
- Benefecial effects observed at 6 months but attenuated by 12 months
Selexipag

-33.0% (95% CI -47.0 to -15.2)
p=0.0022

+24.2 m (95% CI -23.7 to 72.2)

Griphon Study

• Event-driven, phase 3, randomized, double-blind, placebo-controlled trial
• 1156 patients; individualised doses
• Background therapy allowed
• Primary end point- composite of death from any cause or a complication related to PAH
• Risk of the primary composite end point significantly lower with selexipag than with placebo (by 40%)

Adverse events with prostacyclins

Drug Related
- Flushing
- Headache
- Diarrhea
- Nausea/Vomiting
- Jaw pain
- Flu-like symptoms
- Syncope/hypotension
- Cough (with inhaled)

Catheter Related
- Sepsis
- Thrombosis
- Bleeding
- Drug interruption and rebound PAH
- Paradoxical embolism
Endothelin pathway

Pre-pro-ET $\rightarrow$ pro-ET

Endothelial cells

Endothelin-1 (ET-1)
$\rightarrow$ Vasoconstriction
$\rightarrow$ SMC proliferation

Receptors

ETA
ETB

Smooth muscle cells (SMC)

ET-1 receptors agonists

Perrin et al. Expert Opin. Pharmacother. 2015
Endothelin receptor antagonists

- ET-1 → potent vasoconstrictor that promotes smooth muscle proliferation and contributes to disease progression in PAH.
- ET-1 levels increased in PAH, levels correlate with PVR in IPAH.
- 2 receptors, endothelin-A (ETA) and endothelin-B (ETB).
- ETA receptors, found on smooth muscle cells only, induce vasoconstriction and cellular proliferation.
- ETB receptors on smooth muscle cells, when activated, also stimulate vasoconstriction; however, ETB receptors on endothelial cells have the counter-effect of vasodilation and clearance of ET-1.
- Whether selective ETA receptor antagonism offers greater benefit in PAH? – Inconclusive data

Agarwal R et al. AHJ 2011
## Comparison of ERAs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Selectivity</th>
<th>Main Adverse Affects</th>
<th>Interactions</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bosentan</strong></td>
<td>Initially 62.5 mg bd, If LFT normal increase to 125 mg bd</td>
<td>Non-selective</td>
<td>Transaminitis, Teratogenic, Edema, Anemia</td>
<td>Glyburide, Cyclosporine, CYP450 inhibitors/inducers</td>
<td>Monthly LFT, Monthly pregnancy testing</td>
</tr>
<tr>
<td><strong>BOSENTAS/LUPIBOSE</strong></td>
<td>Rs 110: 62.5 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ambrisentan</strong></td>
<td>5 mg to 10 mg od</td>
<td>ET-A</td>
<td>&lt;Transaminitis, Teratogenic, Nasal congestion, edema, Anemia</td>
<td>Cyclosporine, CYP450 inhibitors/inducers</td>
<td>Monthly pregnancy testing</td>
</tr>
<tr>
<td><strong>AMBRICAN/ENDOBLOC</strong></td>
<td>Rs 140: 5mg Rs 230: 10mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Macitentan</strong></td>
<td>10 mg od</td>
<td>Non-selective</td>
<td>do</td>
<td>do</td>
<td></td>
</tr>
</tbody>
</table>

Sitaxsentan withdrawn after reports of ALF
<table>
<thead>
<tr>
<th>Drug(s) tested</th>
<th>Study</th>
<th>No of pts</th>
<th>Duration (weeks)</th>
<th>Background therapy</th>
<th>Primary endpoint</th>
<th>Main Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambrisentan</td>
<td>ARIES-1</td>
<td>202</td>
<td>12</td>
<td>No</td>
<td>6MWD</td>
<td>6MWD improved, TTCW not improved</td>
</tr>
<tr>
<td></td>
<td>ARIES-2</td>
<td>192</td>
<td>12</td>
<td>No</td>
<td>6MWD</td>
<td>6MWD improved, TTCW improved</td>
</tr>
<tr>
<td>Bosentan</td>
<td>Study-351</td>
<td>32</td>
<td>12</td>
<td>No</td>
<td>6MWD</td>
<td>6MWD improved, TTCW improved</td>
</tr>
<tr>
<td></td>
<td>Breathe-1</td>
<td>213</td>
<td>16</td>
<td>No</td>
<td>6MWD</td>
<td>6MWD improved, TTCW improved</td>
</tr>
<tr>
<td></td>
<td>Early</td>
<td>185</td>
<td>24</td>
<td>No or CCB(41%)</td>
<td>PVR, 6MWD</td>
<td>PVR improved, TTCW improved, 6MWD not improved</td>
</tr>
<tr>
<td></td>
<td>BREATHE-5</td>
<td>54</td>
<td>12</td>
<td>No</td>
<td>SaO2, PVR</td>
<td>PVR improved, 6MWD improved</td>
</tr>
<tr>
<td></td>
<td>Compass-2</td>
<td>334</td>
<td>99</td>
<td>Sildenafil</td>
<td>TTCW</td>
<td>TTCW not improved, 6MWD improved, NT-proBNP improved</td>
</tr>
<tr>
<td>Macitentan</td>
<td>Seraphin</td>
<td>742</td>
<td>115</td>
<td>No, or Sildenafil or Inh Iloprost</td>
<td>TTCW</td>
<td>TTCW improved in monotherapy and combination</td>
</tr>
</tbody>
</table>
ARIES 1 & 2: Ambrisentan

All WHO FC included, but consisted predominantly of WHO FC II, III
Dyspnea scores improved in 5mg & 10 mg, Survival better when compared with NIH registry

EARLY: Bosentan in WHO FC II

Δ6MWD = 19 m, p=ns
✓ FC improvement
✓ Time to CW improved
✓ nT-BNP

N = 185

Macitentan – SERAPHIN trial

- Multicentre, double blind RCT, n=742
- 250 = placebo, 250 = 3 mg, 242 = 10 mg
- Group 1, NYHA class II or III
- 61% PDE-5, 5% prostanoids as additional Rx
- Follow-up for 2 yrs
- Primary outcome = composite of mortality and morbidity
Treatment effect maintained across subgroups including those receiving background therapy
Other outcomes and status

- 6MWD (vs placebo): 3 mg-16.8m, 10 mg-22m
- Significant change in FC (20 and 22% resp)
- Better cardiac hemodynamics at 6 months
- ADR: Headache, anemia (4.3% in 10mg arm), nasal congestion
- 10 mg received FDA approval in October 2013
Macitentan Improves Health-Related Quality of Life for Patients With Pulmonary Arterial Hypertension
Results From the Randomized Controlled SERAPHIN Trial

• To evaluate the effect of macitentan on
• HRQoL
• SF-36 at baseline, at month 6 and month 12, and at the end of treatment (EOT)
• Time to a clinically meaningful deterioration in the PCS and MCS scores
• Associations between baseline PCS/MCS scores and time to morbidity/mortality events

CHEST 2017; 151(1):106-118
At month 6, macitentan 10 mg significantly improved seven of eight SF-36 domains and the PCS and MCS scores vs placebo.

Macitentan 10 mg significantly reduced the risk of a three-point or greater deterioration in

- PCS (hazard ratio [HR], 0.60; 95% CI, 0.47-0.76; P < .0001)
- MCS scores (HR, 0.76; 95% CI, 0.61-0.95; P = .0173)
PDE-5 inhibitors - mechanism

No-cGMP pathway

$O_2 + L$-arginine $\rightarrow$ L-citrulline

No synthase

Endothelial cells

Nitric oxide (NO)

$\uparrow$ Vasodilatation

$\downarrow$ SMC proliferation

sGC stimulators

GCs

GMPc $\rightarrow$ GMP

Smooth muscle cells (SMC)

PDE-5 inhibitors

Perrin et al. Expert Opin. Pharmacother. 2015
PDE-5 inhibitors - mechanism

• NO \(\rightarrow\) vasodilator, antiproliferative, and antithrombotic.
• Its activity is mediated by second messenger, cGMP.
• cGMP rapidly degraded by PDE-5 isoenzyme.
• PDE-5 inhibition thus acts to enhance cGMP levels and prolong its vasodilating effects.
• Increased myocardial PDE-5 expression, facilitated by pressure-overloaded myocytes, in the hypertrophied RV
• PDE5 inhibitors may directly target RV function and acutely improve contractility in RV failure patients who express elevated PDE5 levels.

Agarwal R et al. AHJ 2011
# Comparison of PDE-5 inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Main Adverse Affects</th>
<th>Interactions</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sildenafil</td>
<td>Only 20 mg TDS FDA approved (higher doses used off-label)</td>
<td>Flushing, dyspepsia, myalgia, visual changes, epistaxis, nasal congestion, headache</td>
<td>Concomitant nitrates avoided (hypotension), Cyp450 inhibitors</td>
<td>MI in past 3 months, hypotension, AION</td>
</tr>
<tr>
<td>Tadalafil</td>
<td>40 mg OD</td>
<td>do</td>
<td>do</td>
<td>do</td>
</tr>
<tr>
<td>Vardenafil</td>
<td>5mg BD</td>
<td>do</td>
<td>do</td>
<td>do</td>
</tr>
<tr>
<td>Drug(s) tested</td>
<td>Study</td>
<td>N</td>
<td>Weeks</td>
<td>Background therapy</td>
</tr>
<tr>
<td>---------------</td>
<td>-----------</td>
<td>----</td>
<td>-------</td>
<td>-------------------------------------</td>
</tr>
<tr>
<td></td>
<td>PATENT</td>
<td>443</td>
<td>12</td>
<td>No, or bosentan, or prostanoids</td>
</tr>
<tr>
<td></td>
<td>PATENT PLUS</td>
<td>30</td>
<td>18</td>
<td>Sildenafil</td>
</tr>
<tr>
<td>Riociguat</td>
<td>SUPER-I</td>
<td>277</td>
<td>12</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Sastry</td>
<td>22</td>
<td>12</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Singh</td>
<td>20</td>
<td>6</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>PACES</td>
<td>264</td>
<td>16</td>
<td>Epoprostenol</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>Iversen</td>
<td>20</td>
<td>12</td>
<td>Bosentan</td>
</tr>
<tr>
<td></td>
<td>Pfizer study</td>
<td>103</td>
<td>12</td>
<td>Bosentan</td>
</tr>
<tr>
<td>Tadalafil</td>
<td>PHIRST</td>
<td>405</td>
<td>16</td>
<td>No, or Bosentan (54%)</td>
</tr>
<tr>
<td>Vardenafil</td>
<td>EVALUATION</td>
<td>66</td>
<td>12</td>
<td>No</td>
</tr>
</tbody>
</table>
Guanylyl cyclase activator - Riociguat

Perrin et al. Expert Opin. Pharmacother. 2015
Guanylyl cyclase activator - Riociguat

- Soluble guanylyl cyclase stimulator → increases cGMP levels → Vasodilation
- Pyrimidine derivative
- First-in-its class drug
- Good oral bioavailability
- $T\frac{1}{2} = 5-10$ hrs
- Dose = 1-2.5 mg tds

- MC adverse effects: Hypotension, syncope, transaminitis, supraventricular tachycardia, edema, headache, nasal congestion, neck pain
- Dose to be reduced by 0.5-1 mg in case of ADR

Meis et al. Expert Opin. Pharmacother. 2015
# RCTs with Riociguat

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Population</th>
<th>6MWD Improvement (compared to placebo)</th>
<th>Death/Clinical Worsening</th>
<th>FC change</th>
<th>QoL</th>
<th>Hemodynamics</th>
<th>Serious Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ghofrani 2013 (PATENT)</td>
<td>443</td>
<td>Grp 1 PAH, NYHA II,III&gt;IV</td>
<td>36m at 12 wks, 55m at 24 wks (p=.001), NYHA III/IV had more benefit</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Hypotension (10%, p=.005))</td>
</tr>
<tr>
<td>Ghofrani 2013 (CHEST-1)</td>
<td>261</td>
<td>CTEPH, NYH II or III</td>
<td>46m at 12 wks, (p=.001)</td>
<td>N</td>
<td>Y</td>
<td>Y (Dyspnea scores also improved)</td>
<td>Y</td>
<td>do</td>
</tr>
</tbody>
</table>
Guanylate cyclase stimulators for pulmonary hypertension (Cochrane review)

- 5 trials involving 962 participants are included
- short duration (< 16 weeks)
- Mean difference increase in 6MWD of 30.13 metres (95% CI 5.29 to 54.96; participants = 659; studies = 3)
  - On subgroup analysis, for PAH there was no effect noted (6MWD; MD 11.91 metres, 95% CI -44.92 to 68.75; participants = 398; studies = 2)
  - when participants receiving PDE5i were excluded, sGC stimulators increased 6MWD by a MD of 36 m

PATENT 2

- Long term extension arm – open labelled
- 396 patients
  - 197 riociguat monotherapy
  - 199 combination therapy
- Significant association between overall survival with
  - 6MWD - p=0.0006
  - NT-proBNP concentration – p= 0.0225
  - WHO FC p= 0.0191
- Riociguat well tolerated; improvement in parameters persisted at 2 yrs

*Eur Respir J. 2015 May;45(5):1303-13. Epub 2015 Jan 22*
Summary of RCTs Testing the Effect of Prostacyclin Replacement Therapy, PDE5i, and ERAs on Mortality in PAH

Maron et al. doi:10.1001/jamacardio.2016.4471
New drugs

- Inhaled VIP
- TKIs (PDGF inhibitors)
- Serotonin antagonists
- Rho kinase inhibitors
- VEGFR inhibitors
- Angiopoietin-1 inhibitors
- Elastase inhibitors
- Mitochondrial modulators

Other modalities

• Gene therapy

• Stem-cell therapy
  – effective in the monocrotaline rat model

• PA denervation by a radiofrequency ablation catheter

PADN1 Study

- 21 patients with IPAH
  - 13 patients received the PADN procedure
  - 8 control group
- PADN was performed at the bifurcation of the main PA, and at the ostial right and left PA
- Primary endpoints - change of PAP, TEI, and 6MWT at 3 months
- Results
  - PAPm (from 55±5 mm Hg to 36±5 mm Hg, p < 0.01)
  - 6MWT (from 324±21 m to 491±38 m, p < 0.006)
  - Tei index (from 0.7±0.04 to 0.50±0.04, p < 0.001)

Combination therapy for PAH

- Strong rationale for combining drugs as different drugs act on different pathways
- Beyond a simple additive effect, certain combinations may also have a synergistic action (e.g., Sildenafil and prostanoid/Selective ETRA)
- REVEAL registry – 52% pts on combination Rx
- The general treatment paradigm has been to add drugs sequentially
- In an early open-label trial using a step-wise goal-directed approach, sildenafil and iloprost added sequentially after 1st line therapy with bosentan (n=123) showed significant benefit

Sequential vs. upfront combination

- Retrospective analysis of 97 patients with newly diagnosed PAH (86% FC class III-IV)
- Explored initial dual oral combination treatment with
  - bosentan plus sildenafil (n=61)
  - bosentan plus tadalafil (n=17)
  - ambrisentan plus tadalafil (n=11)
  - ambrisentan plus sildenafil (n=8)
- Significant improvements in FC, exercise capacity, dyspnoea and haemodynamic indices after 4 months
- Overall survival rates were 97%, 94% and 83% at 1, 2 and 3 years, respectively

<table>
<thead>
<tr>
<th>Drug(s) tested</th>
<th>Study</th>
<th>No of pts</th>
<th>Duration (weeks)</th>
<th>Background therapy</th>
<th>Primary endpoint</th>
<th>Main Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epoprostenol vs epoprostenol + bosentan</td>
<td><strong>BREATHE-2</strong></td>
<td>33</td>
<td>12</td>
<td>No</td>
<td>PVR</td>
<td>PVR not improved</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6MWD not improved</td>
</tr>
<tr>
<td>Ambrisentan or Tadalafil vs ambrisentan + tadalafil</td>
<td><strong>AMBITIO\N</strong></td>
<td>500</td>
<td>78</td>
<td>No</td>
<td>TTCW</td>
<td>TTCF improved</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6MWD improved</td>
</tr>
</tbody>
</table>
ABSTRACT: The efficacy and safety of combining bosentan, an orally active dual endothelin receptor antagonist and epoprostenol, a continuously infused prostaglandin, in the treatment of pulmonary arterial hypertension (PAH) was investigated.

In this double-blind, placebo-controlled prospective study, 33 patients with PAH started epoprostenol treatment (2 ng·kg⁻¹·min⁻¹ starting dose, up to 14±2 ng·kg⁻¹·min⁻¹ at week 16) and were randomised for 16 weeks in a 2:1 ratio to bosentan (62.5 mg b.i.d for 4 weeks then 125 mg b.i.d) or placebo.

Haemodynamics, exercise capacity and functional class improved in both groups at week 16. In the combination treatment group, there was a trend for a greater (although nonsignificant) improvement in all measured haemodynamic parameters. There were four withdrawals in the bosentan/epoprostenol group (two deaths due to cardiopulmonary failure, one clinical worsening, and one adverse event) and one withdrawal in the placebo/epoprostenol group (adverse event).

This study showed a trend but no statistical significance towards haemodynamics or clinical improvement due to the combination of bosentan and epoprostenol therapy in patients with pulmonary arterial hypertension. Several cases of early and late major complications were reported. Additional information is needed to evaluate the risk/benefit ratio of combined bosentan-epoprostenol therapy in pulmonary arterial hypertension.

BREATHE-2: Bosentan + IV epoprostenol

a) Placebo/epoprostenol
   Bosentan/epoprostenol
   Baseline

b) Placebo/epoprostenol
   Bosentan/epoprostenol
   Week 16

6MWD m
-40 0 40 80 120
COMBI Trial: Iloprost + Bosentan

ABSTRACT: Addition of inhaled iloprost to bosentan may have beneficial effects in patients with idiopathic pulmonary arterial hypertension (IPAH). A multicentre, open, randomised, controlled trial was performed to assess the safety and efficacy of inhaled iloprost in patients with IPAH who had already been treated with bosentan.

The trial was terminated early after a futility analysis predicted failure with respect to the predetermined sample size. At that time, 40 patients were randomised to receive either bosentan alone (control group) or bosentan plus inhaled iloprost (combination group) for a 12-week period.

The primary end-point, change in 6-min walking distance, was not met (mean changes +1 m and -9 m in the control and combination group, respectively). These results may have been skewed by three outliers in the iloprost group who presented with severe clinical worsening. None of the secondary end-points including functional class, peak oxygen uptake, and time to clinical worsening differed significantly between groups.

The current study failed to show a positive effect of adding inhaled iloprost to bosentan in idiopathic pulmonary arterial hypertension patients. Further studies involving larger sample sizes and long-term follow-up are needed to determine the efficacy of adding inhaled iloprost to bosentan in patients with idiopathic pulmonary arterial hypertension.

Hoeper et al. Eur Respir J 2006
STEP trial: Addition of Inhaled Iloprost to Bosentan

- 6MWD = 26 m (p=0.051)
  - FC Improvement
  - Time to CW
  - Hemodynamics

N = 67
12 weeks
WHO FC II, III, IV (Mainly III)

McLaughlin et al Am J Respir Crit Care Med. 2006
PACES: Addition of sildenafil to epoprostenol

6MWD = 29 m (p=0.01)
- QoL improvement
- Time to CW
- Hemodynamics

N = 265
16 weeks

All WHO FC included, but predominantly II, III

TRIUMPH I: Addition of inhaled treprostinil to oral therapy

Improvement in 6MWD and QoL
No differences in the TTCW, dyspnea, or WHO FC

Tadalafil + Bosentan in PHIRST: 6MWD

Figure 1. Placebo-adjusted treatment differences in 6-min walk distance (meters) from baseline to week 16 by bosentan use.
Tadalafil + Bosentan in PHIRST: clinical worsening

Figure 2. Clinical worsening by bosentan use and tadalafil treatment subgroup.
**AMBITION trial**

- Multicenter, randomized, double-blind, phase 3 trial, n=500
- 126 pts = Ambrisentan 10 mg monotherapy
- 121 pts = Tadalafil 40 mg monotherapy
- 253 pts = Combination
- Follow-up 517 days
- Group I PAH
- NYHA II (30%), III (70%)

Galie et al. NEJM. Aug 2015
Study Design

Clinic visits every 12 weeks
Safety visits every 4 weeks

PAH participants (n=610)
Randomized 2:1:1 to combination therapy or monotherapy + matching placebo

Visit | Week -4 | Week 0 | Week 4 | Week 8 | Week 16 | Week 24 |
--- | --- | --- | --- | --- | --- | --- |
Randomization | | | | | | |

- 5 mg ABS 40 mg TAD: N=302
- 10 mg ABS 40 mg TAD: N=152
- 40 mg TAD PBO ABS: N=151

Evaluation of secondary efficacy endpoints
105 clinical failure events: primary endpoint
FAV: final assessment visit
EOS: end of study

Ambrisentan (ABS)
Tadalafil (TAD)
Placebo (PBO)
## Results

### Table 4. Primary and Secondary Efficacy End Points.

<table>
<thead>
<tr>
<th>End Point</th>
<th>Combination-Therapy Group (N = 253)</th>
<th>Pooled-Monotherapy Group (N = 247)</th>
<th>Ambrisentan-Monotherapy Group (N = 126)</th>
<th>Tadalafil-Monotherapy Group (N = 121)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First event of clinical failure — no. of participants (%)</td>
<td>46 (18)</td>
<td>77 (31)</td>
<td>43 (34)</td>
<td>34 (28)</td>
</tr>
<tr>
<td>Death</td>
<td>9 (4)</td>
<td>8 (3)</td>
<td>2 (2)</td>
<td>6 (5)</td>
</tr>
<tr>
<td><strong>Hospitalization for worsening pulmonary arterial hypertension</strong></td>
<td>10 (4)</td>
<td>30 (12)</td>
<td>18 (14)</td>
<td>12 (10)</td>
</tr>
<tr>
<td>Disease progression</td>
<td>10 (4)</td>
<td>16 (6)</td>
<td>12 (10)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Unsatisfactory long-term clinical response</td>
<td>17 (7)</td>
<td>23 (9)</td>
<td>11 (9)</td>
<td>12 (10)</td>
</tr>
<tr>
<td>Hazard ratio, combination therapy vs. monotherapy (95% CI)</td>
<td>Reference</td>
<td>0.50 (0.35 to 0.72)</td>
<td>0.48 (0.31 to 0.72)</td>
<td>0.53 (0.34 to 0.83)</td>
</tr>
<tr>
<td>P value</td>
<td>—</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.005</td>
</tr>
<tr>
<td>Group</td>
<td>Events Participants with events / total participants (%)</td>
<td>Hazard Ratio (95% CI)</td>
<td>P Value</td>
<td></td>
</tr>
<tr>
<td>------------------------</td>
<td>-----------------------------------------------------------</td>
<td>-----------------------</td>
<td>---------</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical failure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combination</td>
<td>46 / 253 (18)</td>
<td>0.50 (0.35, 0.72)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Pooled Monotherapy</td>
<td>77 / 247 (31)</td>
<td>0.50 (0.35, 0.72)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>AMB Monotherapy</td>
<td>43 / 126 (34)</td>
<td>0.48 (0.31, 0.72)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>TAD Monotherapy</td>
<td>34 / 121 (28)</td>
<td>0.53 (0.34, 0.83)</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical worsening</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combination</td>
<td>36 / 253 (14)</td>
<td>0.51 (0.34, 0.78)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Pooled Monotherapy</td>
<td>60 / 247 (24)</td>
<td>0.44 (0.28, 0.70)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>AMB Monotherapy</td>
<td>36 / 126 (29)</td>
<td>0.44 (0.28, 0.70)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>TAD Monotherapy</td>
<td>24 / 121 (20)</td>
<td>0.61 (0.36, 1.03)</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combination</td>
<td>13 / 253 (5)</td>
<td>0.64 (0.31, 1.29)</td>
<td>0.21</td>
<td></td>
</tr>
<tr>
<td>Pooled Monotherapy</td>
<td>19 / 247 (8)</td>
<td>0.71 (0.30, 1.67)</td>
<td>0.43</td>
<td></td>
</tr>
<tr>
<td>AMB Monotherapy</td>
<td>9 / 126 (7)</td>
<td>0.57 (0.25, 1.29)</td>
<td>0.32</td>
<td></td>
</tr>
<tr>
<td>TAD Monotherapy</td>
<td>10 / 121 (8)</td>
<td>0.57 (0.25, 1.29)</td>
<td>0.32</td>
<td></td>
</tr>
<tr>
<td><strong>First hospitalization</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combination</td>
<td>19 / 253 (8)</td>
<td>0.37 (0.22, 0.64)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Pooled Monotherapy</td>
<td>44 / 247 (18)</td>
<td>0.32 (0.18, 0.58)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>AMB Monotherapy</td>
<td>27 / 126 (21)</td>
<td>0.44 (0.23, 0.85)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>TAD Monotherapy</td>
<td>17 / 121 (14)</td>
<td>0.44 (0.23, 0.85)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td><strong>First disease progression</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combination</td>
<td>13 / 253 (5)</td>
<td>0.62 (0.31, 1.25)</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>Pooled Monotherapy</td>
<td>19 / 247 (8)</td>
<td>0.44 (0.21, 0.93)</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>AMB Monotherapy</td>
<td>14 / 126 (11)</td>
<td>0.67 (0.32, 1.41)</td>
<td>0.29</td>
<td></td>
</tr>
<tr>
<td>TAD Monotherapy</td>
<td>5 / 121 (4)</td>
<td>1.12 (0.40, 3.15)</td>
<td>0.84</td>
<td></td>
</tr>
<tr>
<td><strong>First ULTGR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combination</td>
<td>17 / 253 (7)</td>
<td>0.61 (0.33, 1.13)</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>Pooled Monotherapy</td>
<td>25 / 247 (10)</td>
<td>0.61 (0.33, 1.13)</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>AMB Monotherapy</td>
<td>12 / 126 (10)</td>
<td>0.67 (0.32, 1.41)</td>
<td>0.29</td>
<td></td>
</tr>
<tr>
<td>TAD Monotherapy</td>
<td>13 / 121 (11)</td>
<td>0.55 (0.27, 1.14)</td>
<td>0.10</td>
<td></td>
</tr>
</tbody>
</table>
Kaplan–Meier Curves for the Probability of a First Adjudicated Primary End-Point Event.

A Combination Therapy vs. Pooled Monotherapy

- Participants with No Event (%)
  - Combination therapy
  - Pooled monotherapy

Hazard ratio, 0.50 (95% CI, 0.35–0.72)
P<0.001

No. at Risk
- Combination therapy: 253, 229, 186, 145, 106, 71, 36, 4

Weeks
<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Participants</th>
<th>Combination Therapy</th>
<th>Pooled Monotherapy</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Etiology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPAH/HPAH</td>
<td>279</td>
<td>25 /134 (19)</td>
<td>46 /145 (32)</td>
<td>0.54 (0.33, 0.87)</td>
<td>0.01</td>
</tr>
<tr>
<td>APAH</td>
<td>221</td>
<td>21 /119 (18)</td>
<td>31 /102 (30)</td>
<td>0.45 (0.26, 0.79)</td>
<td>0.005</td>
</tr>
<tr>
<td>Baseline WHO FC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.08</td>
</tr>
<tr>
<td>WHO FC II</td>
<td>155</td>
<td>4 /76 (5)</td>
<td>17 /79 (22)</td>
<td>0.21 (0.07, 0.63)</td>
<td>0.005</td>
</tr>
<tr>
<td>WHO FC III</td>
<td>345</td>
<td>42 /177 (24)</td>
<td>60 /168 (36)</td>
<td>0.58 (0.39, 0.86)</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>Age at Baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.26</td>
</tr>
<tr>
<td>&lt;= 57 years</td>
<td>244</td>
<td>13 /124 (10)</td>
<td>31 /120 (26)</td>
<td>0.37 (0.19, 0.70)</td>
<td>0.002</td>
</tr>
<tr>
<td>&gt;= 57 years</td>
<td>256</td>
<td>33 /129 (26)</td>
<td>46 /127 (36)</td>
<td>0.58 (0.37, 0.91)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Baseline 6MWD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.41</td>
</tr>
<tr>
<td>&lt; 363.7 m</td>
<td>250</td>
<td>35 /129 (27)</td>
<td>51 /121 (42)</td>
<td>0.54 (0.35, 0.83)</td>
<td>0.005</td>
</tr>
<tr>
<td>&gt;= 363.7 m</td>
<td>250</td>
<td>11 /124 (9)</td>
<td>26 /126 (21)</td>
<td>0.38 (0.19, 0.77)</td>
<td>0.007</td>
</tr>
<tr>
<td><strong>Region</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.92</td>
</tr>
<tr>
<td>North America</td>
<td>228</td>
<td>22 /116 (19)</td>
<td>34 /112 (30)</td>
<td>0.51 (0.30, 0.87)</td>
<td>0.01</td>
</tr>
<tr>
<td>Rest of World</td>
<td>272</td>
<td>24 /137 (18)</td>
<td>43 /135 (32)</td>
<td>0.51 (0.31, 0.83)</td>
<td>0.008</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.68</td>
</tr>
<tr>
<td>Female</td>
<td>388</td>
<td>32 /188 (17)</td>
<td>61 /200 (31)</td>
<td>0.47 (0.31, 0.73)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male</td>
<td>112</td>
<td>14 /65 (22)</td>
<td>16 /47 (34)</td>
<td>0.58 (0.28, 1.19)</td>
<td>0.14</td>
</tr>
</tbody>
</table>

The diagram illustrates the comparison of combination therapy versus monotherapy for different subgroups, showing the hazard ratio and 95% CI with corresponding p-values.
## Secondary end points

<table>
<thead>
<tr>
<th>Secondary end points</th>
<th>Combination</th>
<th>Pooled Monotherapy</th>
<th>Ambrisentan</th>
<th>Tadalafil</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NT-proBNP level†</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage change in geometric mean from baseline to week 24</td>
<td>-67.2</td>
<td>-50.4</td>
<td>-56.2</td>
<td>-43.8</td>
</tr>
<tr>
<td><strong>P value</strong></td>
<td>Reference</td>
<td>&lt;0.001</td>
<td>0.01</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Satisfactory clinical response at week 24</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>— no. of participants/total no. (%)‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>91/234 (39)</td>
<td>66/226 (29)</td>
<td>35/113 (31)</td>
<td>31/113 (27)</td>
</tr>
<tr>
<td>No</td>
<td>143/234 (61)</td>
<td>160/226 (71)</td>
<td>78/113 (69)</td>
<td>82/113 (73)</td>
</tr>
<tr>
<td>Unknown</td>
<td>19/253 (8)</td>
<td>21/247 (9)</td>
<td>13/126 (10)</td>
<td>8/121 (7)</td>
</tr>
<tr>
<td><strong>Odds ratio, combination therapy vs. monotherapy (95% CI)</strong></td>
<td>Reference</td>
<td>1.56</td>
<td>1.42</td>
<td>1.72</td>
</tr>
<tr>
<td></td>
<td>(1.05 to 2.32)</td>
<td>(0.88 to 2.31)</td>
<td>(1.05 to 2.83)</td>
<td></td>
</tr>
<tr>
<td><strong>P value</strong></td>
<td>—</td>
<td>0.03</td>
<td>0.15</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>6-Minute walk distance — m§</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR) change from baseline to week 24</td>
<td>48.98 (4.63 to 85.75)</td>
<td>23.80 (-12.25 to 64.53)</td>
<td>27.00 (-14.00 to 63.25)</td>
<td>22.70 (-8.25 to 66.00)</td>
</tr>
<tr>
<td><strong>P value</strong></td>
<td>Reference</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Change in WHO functional class at week 24</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>— no. of participants/total no. (%)§</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved</td>
<td>94/252 (37)</td>
<td>81/244 (33)</td>
<td>42/124 (34)</td>
<td>39/120 (33)</td>
</tr>
<tr>
<td>No change</td>
<td>146/252 (58)</td>
<td>147/244 (60)</td>
<td>73/124 (59)</td>
<td>74/120 (62)</td>
</tr>
<tr>
<td>Deteriorated</td>
<td>12/252 (5)</td>
<td>16/244 (7)</td>
<td>9/124 (7)</td>
<td>7/120 (6)</td>
</tr>
<tr>
<td><strong>P value</strong></td>
<td>Reference</td>
<td>0.24</td>
<td>0.30</td>
<td>0.36</td>
</tr>
</tbody>
</table>
Upfront triple combination therapy in pulmonary arterial hypertension: a pilot study

- Newly diagnosed NYHA FC III/IV PAH patients
- IV epoprostenol, bosentan and sildenafil
- N=19
- Retrospectively from a prospective registry
- Significant improvements in 6MWD and haemodynamics after 4 months in 18 pts (p<0.01)
  - 17 had improved to NYHA FC I or II

Sitbon O et al. Eur Respir J 2014; 43
Comparative Effectiveness of Pharmacologic Interventions for Pulmonary Arterial Hypertension
A Systematic Review and Network Meta-Analysis

• 31 RCTs
  – 29 two-arm trials comparing active intervention to placebo
  – 1 two-arm trial comparing active agents against each other
  – one three-arm trial comparing combination therapy of two active agents against each of the agents as monotherapy

Jain S et al. Chest 2017; 151(1):90-105
<table>
<thead>
<tr>
<th>Efficacy in improving functional status as risk ratio (95% CI)</th>
<th>ERA</th>
<th>1.02 (0.70-1.50)</th>
<th>0.89 (0.48-1.65)</th>
<th>0.31 (0.14-0.70)</th>
<th>1.10 (0.50-2.17)</th>
<th>0.89 (0.55-1.45)</th>
<th>1.01 (0.50-1.82)</th>
<th>1.56 (1.22-2.00)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.37 (0.86-2.18) PDE5i</td>
<td>0.87 (0.45-1.68)</td>
<td>0.30 (0.13-0.71)</td>
<td>1.08 (0.52-2.24)</td>
<td>0.87 (0.53-1.42)</td>
<td>0.98 (0.51-1.88)</td>
<td>1.53 (1.06-2.19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.71 (0.39-1.29) PO/INH Prostanoid</td>
<td>0.52 (0.27-1.00)</td>
<td>0.35 (0.13-0.89)</td>
<td>1.24 (0.52-2.94)</td>
<td>1.01 (0.47-2.15)</td>
<td>1.13 (0.52-2.50)</td>
<td>1.76 (0.99-3.13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.85 (0.66-12.31)</td>
<td>2.09 (0.47-9.20)</td>
<td>4.02 (0.91-17.68)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Riociguat 0.81 (0.36-1.83)</td>
<td>0.91 (0.40-2.09)</td>
</tr>
<tr>
<td>1.98 (1.10-3.59)</td>
<td>1.45 (0.79-2.66)</td>
<td>2.79 (1.26-6.20)</td>
<td>-</td>
<td>0.70 (0.15-3.29)</td>
<td>ERA + PDE5i 1.13 (0.54-2.37)</td>
<td>1.75 (1.05-2.92)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.82 (0.42-1.60)</td>
<td>0.60 (0.29-1.22)</td>
<td>1.15 (0.56-2.35)</td>
<td>-</td>
<td>0.29 (0.00-1.30)</td>
<td>Selexipag 0.41 (0.18-0.97)</td>
<td>1.55 (0.91-2.60)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.53 (0.36-0.78)</td>
<td>0.39 (0.24-0.62)</td>
<td>0.75 (0.47-1.19)</td>
<td>-</td>
<td>0.19 (0.05-0.76)</td>
<td>0.27 (0.14-0.52)</td>
<td>0.65 (0.38-1.12)</td>
<td>Placebo</td>
<td></td>
</tr>
</tbody>
</table>
Results

• Riociguat, ERA, PDE5i, and ERA + PDE5i compared with placebo associated with significant reduction in risk of CW
  – Riociguat had the strongest effect (single study)
• IV/SC prostanoids, ERA, PDE5i, and ERA + PDE5i associated with significant improvement in WHO FC and 6MWD compared with placebo
• ERA + PDE5i associated with a lower likelihood of PAH-related hospitalization (single study)
• none of the studied agents was associated with reduced mortality
• PO/INH prostanoids and selexipag were more likely to be discontinued secondary to adverse events

Jain S et al. Chest 2017; 151(1):90-105
# RECOMMENDATIONS FOR EFFICACY OF INITIAL DRUG COMBINATION THERAPY

<table>
<thead>
<tr>
<th>Measure/treatment</th>
<th>WHO-FC II</th>
<th>WHO-FC III</th>
<th>WHO-FC IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambrisentan + tadalafil</td>
<td>I</td>
<td>B</td>
<td>IIb</td>
</tr>
<tr>
<td>Other ERA + PDE-5i</td>
<td>IIa</td>
<td>C</td>
<td>IIb</td>
</tr>
<tr>
<td>Bosentan + sildenafil + i.v. epoprostenol</td>
<td>-</td>
<td>-</td>
<td>IIa</td>
</tr>
<tr>
<td>Bosentan + i.v. epoprostenol</td>
<td>-</td>
<td>-</td>
<td>IIa</td>
</tr>
<tr>
<td>Other ERA or PDE-5i + s.c. treprostinil</td>
<td>IIb</td>
<td>C</td>
<td>IIb</td>
</tr>
<tr>
<td>Other ERA or PDE-5i + other i.v. prostacyclin analogues</td>
<td>IIb</td>
<td>C</td>
<td>IIb</td>
</tr>
</tbody>
</table>
# RECOMMENDATIONS FOR EFFICACY OF SEQUENTIAL DRUG COMBINATION THERAPY

<table>
<thead>
<tr>
<th>Measure/treatment</th>
<th>WHO-FC II</th>
<th>WHO-FC III</th>
<th>WHO-FC IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macitentan added to sildenafil&lt;sup&gt;d&lt;/sup&gt;</td>
<td>I</td>
<td>B</td>
<td>IIa</td>
</tr>
<tr>
<td>Riociguat added to bosentan</td>
<td>I</td>
<td>B</td>
<td>IIa</td>
</tr>
<tr>
<td>Selexipag added to ERA and/or PDE-5i&lt;sup&gt;d&lt;/sup&gt;</td>
<td>I</td>
<td>B</td>
<td>IIa</td>
</tr>
<tr>
<td>Sildenafil added to epoprostenol</td>
<td>–</td>
<td>–</td>
<td>IIa</td>
</tr>
<tr>
<td>Treprostinil inhaled added to sildenafil or bosentan</td>
<td>IIa</td>
<td>B</td>
<td>IIa</td>
</tr>
<tr>
<td>Iloprost inhaled added to bosentan</td>
<td>IIb</td>
<td>B</td>
<td>IIb</td>
</tr>
<tr>
<td>Tadalafil added to bosentan</td>
<td>IIa</td>
<td>C</td>
<td>IIa</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Measure/treatment</th>
<th>WHO-FC II</th>
<th>WHO-FC III</th>
<th>WHO-FC IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambrisentan added to sildenafil</td>
<td>IIb</td>
<td>C</td>
<td>IIb</td>
</tr>
<tr>
<td>Bosentan added to epoprostenol</td>
<td>–</td>
<td>–</td>
<td>IIb</td>
</tr>
<tr>
<td>Bosentan added to sildenafil</td>
<td>IIb</td>
<td>C</td>
<td>IIb</td>
</tr>
<tr>
<td>Sildenafil added to bosentan</td>
<td>IIb</td>
<td>C</td>
<td>IIb</td>
</tr>
<tr>
<td>Other double combinations</td>
<td>IIb</td>
<td>C</td>
<td>IIb</td>
</tr>
<tr>
<td>Other triple combinations</td>
<td>IIb</td>
<td>C</td>
<td>IIb</td>
</tr>
<tr>
<td>Riociguat added to sildenafil or other PDE-5i</td>
<td>III</td>
<td>B</td>
<td>III</td>
</tr>
</tbody>
</table>
Balloon atrial septostomy

- Inter-atrial R-L shunt can decompress the right heart chambers and increase LV preload and CO
- improves systemic $O_2$ transport
- decreases sympathetic hyperactivity
- benefit in WHO-FC IV with RHF refractory to medical therapy or with severe syncopal symptoms
- Bridge to Lung Tx
- No mortality benefit
Lung Transplantation

- NYHA Class III or IV despite a trial of at least 3 months of combination therapy including prostanoids.
- Cardiac index ≤ 2 liters/min/m².
- Mean right atrial pressure ≥ 15 mm Hg.
- 6-minute walk test ≤ 350 m.
- Development of significant hemoptysis, pericardial effusion, or signs of progressive right heart failure (renal failure, increasing bilirubin, brain natriuretic peptide, or recurrent ascites)
- survival is increased to 52–75% at 5 years and to 45–66% at 10 years

Weill et al. ISHLT consensus guidelines. January 2015
Lung Tx only or Heart-lung Tx?

• Isolated bilateral lung transplantation is associated with comparable or better results than heart-lung transplantation

• Patients with irreversible myocardial dysfunction or congenital defects with irreparable defects of the valves or chambers in conjunction with intrinsic lung disease or severe PAH are considered for heart-lung transplantation

Weill et al. ISHLT consensus guidelines. January 2015
Recommendations for efficacy of ICU management, balloon atrial septostomy and lung transplantation

<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>Hospitalization in ICU is recommended in PH patients with high heart rate (&gt;110 beats/min), low blood pressure (systolic blood pressure &lt;90 mmHg), low urine output and rising lactate levels due or not due to co-morbidities</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

<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>Inotropic support is recommended in hypotensive patients</td>
<td>I</td>
<td>C</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Lung transplantation is recommended soon after inadequate clinical response on maximal medical therapy</td>
<td>-</td>
<td>-</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>BAS may be considered where available after failure of maximal medical therapy</td>
<td>-</td>
<td>-</td>
<td>IIb</td>
<td>C</td>
</tr>
</tbody>
</table>
PAH associated with Adult Congenital Heart Disease

- Better survival than IPAH
- Some patients may have Gp 2 or 3 PAH
- No prospective data available on the usefulness of vasoreactivity testing, closure test or lung biopsy for operability assessment
- Closure contraindicated in Eisenmenger syndrome
- Closure useless in patients with small/coincidential defects
PAH associated with congenital heart disease

1. Eisenmenger’s syndrome
2. 2. PAH associated with prevalent systemic-to-pulmonary shunts
   – Correctable
   – Non-correctable
3. PAH with small/coincidental defects
   VSD <1 cm and ASD<2 cm; closing contraindicated
4. PAH after defect correction

# Recommendations for correction of CHD with prevalent systemic-to-pulmonary shunts

<table>
<thead>
<tr>
<th>PVRi (WU . m²)</th>
<th>PVR (WU)</th>
<th>Correctable</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;4</td>
<td>&lt;2.3</td>
<td>Yes</td>
</tr>
<tr>
<td>&gt;8</td>
<td>&gt;4.6</td>
<td>No</td>
</tr>
<tr>
<td>4-8</td>
<td>2.3-4.6</td>
<td>Individualise</td>
</tr>
</tbody>
</table>
Medical mgt

- Data scarce
- Recommended to avoid strenuous exercise
- Pregnancy discouraged
- LTOT may improve symptoms, but not survival
- Oral anticoagulation – individualise
- CCBs not recommended
- **Bosentan** is recommended in WHO-FC III patients with Eisenmenger syndrome (IB)
- Other ERAs, PDE-5is and prostanoids should be considered in patients with Eisenmenger syndrome
PAH in CTD

• Prevalence of haemodynamically proven precapillary PH in SSc - 5 to 12%
• Prognosis worse than IPAH
• Same treatment algorithm as IPAH
• Resting echocardiography as a screening test in asymptomatic patients with SSc
• Annual screening - echo, DLCO and biomarkers
• RHC in all cases of suspected PAH
• OAC – individualise; CCBs not useful
Porto-pulmonary HTN

- ECHO– symptomatic and Tx candidates
- RHC recommended in all suspected cases
- Higher CI and a lower PVR than IPAH
- Mortality risk at least as high as in IPAH
- Treatment algorithm same
- Anticoagulation not recommended
- Beta-blockers avoided; Bosentan avoided
- Liver Tx in selected patients responding well to PAH therapy; C/I in severe PAH
## PAH associated with HIV

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echocardiographic screening in asymptomatic HIV pts to detect PH is not recommended</td>
<td>III</td>
<td>C</td>
</tr>
<tr>
<td>Same treatment algorithm used for patients with PAH should be considered, taking into consideration co-morbidities and drug–drug interactions</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Anticoagulation is not recommended because of a lack of data on the efficacy:risk ratio</td>
<td>III</td>
<td>C</td>
</tr>
<tr>
<td>CCBs not recommended</td>
<td>III</td>
<td>C</td>
</tr>
</tbody>
</table>
# Prognostic markers in PAH

<table>
<thead>
<tr>
<th>Lower</th>
<th>Determinants of Risk</th>
<th>Higher</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Clinical Evidence of RV Failure</td>
<td>Yes</td>
</tr>
<tr>
<td>Gradual</td>
<td>Progression</td>
<td>Rapid</td>
</tr>
<tr>
<td>II, III</td>
<td>WHO Class</td>
<td>IV</td>
</tr>
<tr>
<td>Longer (&gt;400 m)</td>
<td>6 Minute Walk Distance</td>
<td>Shorter (&lt;300 m)</td>
</tr>
<tr>
<td>Minimally elevated</td>
<td>BNP</td>
<td>Very elevated</td>
</tr>
<tr>
<td>Minimal RV Dysfunction</td>
<td>Echocardiographic Findings</td>
<td>Pericardial Effusion</td>
</tr>
<tr>
<td>Normal/Near normal RAP and CI</td>
<td>Hemodynamics</td>
<td>High RAP, Low CI</td>
</tr>
</tbody>
</table>

Take Home message

• No approved therapy for PAH shown to prevent progression of the underlying pulmonary vascular disease - PAH remains an incurable disease
• Correct diagnosis (PAH and group) and ruling out treatable causes is must
• Stepwise approach to Rx based on WHO FC
• Rational combination therapy maybe helpful in those with progressive disease
• Lung Tx for those symptomatic despite maximal Rx
## Available in India

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambrisentan 5mg</td>
<td>Endobloc 5</td>
<td>145</td>
</tr>
<tr>
<td>Ambrisentan 10mg</td>
<td>Endobloc 10</td>
<td>235</td>
</tr>
<tr>
<td>Bosentan 62.5mg</td>
<td>Bosentas/Lupibose 62.5mg</td>
<td>69</td>
</tr>
<tr>
<td>Bosentan 125mg</td>
<td>Bosentas/ Lupibose 125mg</td>
<td>110</td>
</tr>
<tr>
<td>Sildenafil 20mg</td>
<td>Assurans/Vasosure</td>
<td>15</td>
</tr>
<tr>
<td>Tadalafil 20mg</td>
<td>Pulmopres</td>
<td>25</td>
</tr>
</tbody>
</table>
THANK YOU