Management of PAH

21.8.15 and 11.9.15
Seminar outline

• Definition and classification
• Treatment
  – Specific therapies for PAH
  – Role of combination therapy
  – Status of emerging therapies
• PAH 2° to lung disease (Group 3)
• CTEPH (Group 4)
• Prognosis and prognosis assessment tools
PAH

• Pulmonary arterial hypertension (PAH) remains a highly morbid disease with high mortality.

• Despite a recent growth in therapeutic options, clinicians and their patients continue to struggle with questions regarding pharmacologic treatments and major uncertainties persist in the management of PAH.
Definition & Classification
Old definition

- Pulmonary arterial hypertension (PAH) was defined by
  - Mean PAP >25 mmHg at rest or >30 mmHg with exercise
  - PAWP ≤15 mmHg and
  - PVR >3 mmHg/L/min (Wood units) or >240 dyn·s/cm$^5$

New definition

Pulmonary hypertension (PH) is defined as a resting mPAP $\geq 25$ mmHg at right heart catheterization (RHC)

PAH is defined as a subgroup of PH with:

- PAWP $\leq 15$ mmHg (Pre-capillary PH) with PVR $\leq 3$ Wood units
- Normal or reduced cardiac output
- Absence of other causes of pre-capillary PH (PH due to lung diseases, CTEPH, or other rare diseases)

Why this cut-off?

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

mPAP 21-24 mmHg: Borderline PAH?

Why was exercise cut-off (>30mmHg) eliminated?

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

# Table 1

Updated Classification of Pulmonary Hypertension*

1. **Pulmonary arterial hypertension**
   1.1 Idiopathic PAH
   1.2 Heritable PAH
     1.2.1 BMPR2
     1.2.2 ALK1, ENG, SMAD9, CAV1, KCNK3
     1.2.3 Unknown
   1.3 Drug and toxin induced
   1.4 Associated with:
     1.4.1 Connective tissue disease
     1.4.2 HIV infection
     1.4.3 Portal hypertension
     1.4.4 Congenital heart diseases
     1.4.5 Schistosomiasis

1’ Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis

1”. Persistent pulmonary hypertension of the newborn

2. **Pulmonary hypertension due to left heart disease**
   2.1 Left ventricular systolic dysfunction
   2.2 Left ventricular diastolic dysfunction
   2.3 Valvular disease
   2.4 Congenital/acquired left heart inflow/outflow congenital cardiomyopathies

3. **Pulmonary hypertension due to lung diseases**
   3.1 Chronic obstructive pulmonary disease
   3.2 Interstitial lung disease
   3.3 Other pulmonary diseases with mixed rest and exercise hypoxemia
   3.4 Sleep-disordered breathing
   3.5 Alveolar hypoventilation disorders
   3.6 Chronic exposure to high altitude
   3.7 Developmental lung diseases

4. **Chronic thromboembolic pulmonary hypertension**

5. **Pulmonary hypertension with unclear multifactorial causes**
   5.1 Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
   5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
   5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
   5.4 Others: tumor obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

6. **Persistent pulmonary hypertension of the newborn**

1’ Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)
Disease burden

• Prevalence: 15–50 patients per million population

• Annual incidence: 2-7 cases per million population

• No systematic data on prevalence/incidence from India

Therapies for PAH

Therapy without RCT data
- CCBs
- Warfarin
- Oxygen
- Exercise
- Diuretics

Targeted Therapies
- Prostanoids
- Endothelin receptor antagonists
- PDE-5 inhibitors
- Prostanoids
- Riociguat
- Emerging therapies

Monotherapy vs Combination therapy?
The molecular targets of approved PH therapies

STIMULATION:
Restores cAMP or cGMP

Vasodilation and antiproliferation
PKG

sGC

cGMP

PDE5

Vasoconstriction and proliferation

INHIBITION:
Blocks effects of endothelin or PDE5

sGC stimulator

NO

PDE5 inhibitor

Prostacyclin

Pro-endothelin

Endothelin

ETRα

ETRβ

Prostanoid/IP receptor agonist

IP receptor

Smooth muscle

Fibrosis

Proliferation

RV HYPERTROPHY AND FAILURE

Inflammation

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 180-240 mg/d
  - Diltiazem 720-960 mg/d
  - Amlodipine 20-30 mg/d

1. Taichman, Ornelas et al. CHEST 2014
Vasoreactivity testing

• Done with short acting agent: Inhaled nitric oxide (iNO) is drug of choice
  – IV epoprostenol, acetylcholine, adenosine or tolazoline also used: may have systemic vasodilator effects
  – Inhaled iloprost has emerged as newer alternative

• Fall in mPAP > 10 mmHg to value < 40 mmHg cutoff for selecting patients for CCBs

1. Taichman, Ornelas et al. CHEST 2014
2. Galie et al. Journal of the American College of Cardiology 2013
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·min⁻¹·m⁻²</td>
<td>≥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>≥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>≥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>≥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 $\rightarrow$ RV ischaemia
- Increasing CCB doses in patients who are not vasoreactive may be fatal
- As 93% patients are not likely to respond $\rightarrow$
  Should not be used without vasoreactivity testing

Taichman, Ornelas et al. CHEST 2014
Prostanoids

• Prostacyclin (PGI₂) – 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.

Richa Agarwal et al. AHJ 2011
Prostanoids - Mechanism of Action

• Primary target of prostacyclin → IP receptor on vascular smooth-muscle cells.
• Prostacyclin binds target receptors on smooth-muscle cells, intracellular signaling leads to adenylate cyclase activation and increase in cAMP levels.
• Results in smooth-muscle relaxation with vasodilation.
• Also believed to target pathologic vascular remodeling observed in PAH.
• Additional prostanoid effects include anti-proliferative, inhibition of platelet aggregation, anti-inflammatory, and augmentation of ventricular inotropy
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 – Dosing and administration

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

*Not to be exposed to direct sunlight*
<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> 10 mcg/ml = 2.5 mcg 20 mcg/ml = 5 mcg</td>
<td>No dilution required</td>
<td>Oral inhalation via ultrasonic nebuliser</td>
<td>2.5-5 mcg per dose 6 to 9 times/day</td>
</tr>
<tr>
<td><strong>Treprostenil – Inhaled (TYVASO)</strong> 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>
<td>3-9 breaths per session (18-54 mcg) 4 times/day</td>
</tr>
<tr>
<td><strong>Treprostenil - IV/SC (REMODULIN)</strong></td>
<td>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</td>
<td>Continuous IV/SC infusion with ambulatory infusion pump</td>
<td>1.25 ng/kg/min and titrate upward *Dosage of 40ng/kg/min a/w improved survival</td>
</tr>
<tr>
<td><strong>Treprostenil – Oral (ORENITRAM)</strong></td>
<td>-</td>
<td>-</td>
<td>0.25 mg bd and increase 3-4 days *Mean dose 3.4 mg bd</td>
</tr>
</tbody>
</table>
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
## Comparison of RCTs in Epoprostenol

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Population</th>
<th>6MWD Improvement (compared to placebo)</th>
<th>Survival</th>
<th>Dyspnea</th>
<th>FC change</th>
<th>QoL</th>
<th>Hemodynamics</th>
<th>Serious Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rubin 1990 Barst 1994</td>
<td>25</td>
<td>IPAH</td>
<td>106 m at 6 mon 144 m at 18 mon</td>
<td>At 3 yrs 63% v 40% (p=.045)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Y</td>
<td>2 deaths d/t catheter complication s 7 episodes of sepsis</td>
</tr>
<tr>
<td>Barst 1996</td>
<td>81</td>
<td>IPAH</td>
<td>60 m at 12 wks</td>
<td>8 vs 0 deaths (p =.003)</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>4 sepsis, 1 paradoxical embolism. No deaths.</td>
</tr>
<tr>
<td>Badesc h 2000</td>
<td>11</td>
<td>SSc</td>
<td>108 m at 12 wks</td>
<td>5 vs 4 deaths (p=NS)</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>2 sepsis, 2 cellulitis, 2 pneumothorax, 2 hemorrhage</td>
</tr>
</tbody>
</table>
## Mantel-Haenszel Analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>OR (95% CI)</th>
<th>Events Treatment</th>
<th>Events Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rubin (1990)</td>
<td>0.30 (0.03, 3.43)</td>
<td>1/11</td>
<td>3/12</td>
</tr>
<tr>
<td>Barst (1995)</td>
<td>0.05 (0.00, 0.83)</td>
<td>0/41</td>
<td>8/40</td>
</tr>
<tr>
<td>Badesch (2000)</td>
<td>0.77 (0.20, 3.03)</td>
<td>4/56</td>
<td>5/55</td>
</tr>
<tr>
<td>Overall (I-squared = 41.4%, p = 0.182)</td>
<td>0.30 (0.11, 0.82)</td>
<td>5/108</td>
<td>16/107</td>
</tr>
</tbody>
</table>

**Mantel-Haenszel**

- \( z = 2.35 \) \( p = 0.019 \)
- Heterogeneity \( p = 0.182 \)
- RR = 70%

The analysis included 215 patients in 3 trials. The figure shows the cumulative relative risk (RR) estimate of death in active treatment groups when compared with control groups. An overall reduction of the risk of mortality of 70% \( (p = 0.019) \) and 68% \( (p = 0.012) \) is shown with Mantel–Haenszel and Peto methods, respectively. CI = confidence interval; OR = odds ratio.
## RCTs with iloprost/treprostenil

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Population</th>
<th>6MWD Improvement (compared to placebo)</th>
<th>Survival</th>
<th>Dyspnea</th>
<th>FC change</th>
<th>QoL</th>
<th>Hemodynamics</th>
<th>Serious Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olschewski 2002 (AIR-Double blind RCT)</td>
<td>203</td>
<td>IPAH, CTEPH NYH 3 or 4</td>
<td>36 m at 12 wk (p=.004) (59 in IPAH, 12 in CTEPH p=NS)</td>
<td>4 vs 1 (p=NS)</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Increased syncope, flushing, cough</td>
</tr>
<tr>
<td>Simmonneau 2002</td>
<td>470</td>
<td>Grp 1 PAH NYH 2/3/4</td>
<td>16 m at 12 wks (p=.006)</td>
<td>7 vs 7</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>3 GI bleed</td>
<td></td>
</tr>
<tr>
<td>Jing 2013 Freedom-M</td>
<td>349</td>
<td>Grp 1 PAH</td>
<td>26 m at 12 wks (p=.012) (p=NS)</td>
<td>10 vs 6 (p=NS)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>-</td>
<td>2 syncope, 2 pul edema</td>
</tr>
</tbody>
</table>
Selexipag

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

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

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 → pro-ET
- Endothelial cells
- Endothelin-1 (ET-1)
  - Vasoconstriction
  - 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

Richa Agarwal 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>Bosentan</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>BOSENTAN/ LUPIBOSE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rs 110: 62.5 mg</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Ambrisentan</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>AMBRICAN/ ENDOBLOC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rs 140: 5mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Rs 230: 10mg</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Macitentan</td>
<td>10 mg od</td>
<td>Non-selective</td>
<td>do</td>
<td>do</td>
<td>do</td>
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<tr>
<td>Sitaxsentan</td>
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</tbody>
</table>
## RCTs with ERA monotherapy

<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>Dyspnea</th>
<th>FC change</th>
<th>QoL</th>
<th>Hemodynamics</th>
<th>Serious Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Channik 2001</td>
<td>32</td>
<td>Grp 1 PAH NYH 3</td>
<td>76 m at 12 wks (p=.021)</td>
<td>No deaths (CW p=.03)</td>
<td>Y</td>
<td>Y</td>
<td>-</td>
<td>Y</td>
<td>Nil</td>
</tr>
<tr>
<td>Rubin 2002 (BREATHE-1)</td>
<td>213</td>
<td>NYHA -4 also</td>
<td>44 m at 12 wks (p=.001), 250 mg better, IPAH group better</td>
<td>CW (p=.004)</td>
<td>Y</td>
<td>Y</td>
<td>-</td>
<td>Y</td>
<td>Transaminitis in 9%, dose dependent</td>
</tr>
<tr>
<td>Galie 2006 (BREATHE-5)</td>
<td>51</td>
<td>Eisenmengers</td>
<td>53 m at 16 wks (p=.008)</td>
<td>-</td>
<td>-</td>
<td>Y</td>
<td>-</td>
<td>Y</td>
<td>Chest pain, palpitation, edema</td>
</tr>
<tr>
<td>Galie 2008 ARIES-1 and ARIES-2 (Ambrisentan)</td>
<td>202 (5 vs 10 mg)</td>
<td>Grp 1 PAH, 6MW D 150-450m</td>
<td>10mg=51m 5mg=31 m at 12 wks</td>
<td>No diff death or CW</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Cath not done, NT-BNP improved</td>
<td>Nasal congestion, edema do</td>
</tr>
<tr>
<td></td>
<td>192</td>
<td>(2.5 vs 5 mg)</td>
<td>5mg=59 2.5mg=32 m at 12 wks</td>
<td>CW (p&lt;0.05 in both doses)</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td></td>
<td>do</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

Pulido et al. NEJM 2013
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
- India - NA
PDE-5 inhibitors - mechanism

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.
- Also, increased myocardial PDE-5 expression, facilitated by pressure-overloaded myocytes, occurs in the hypertrophied RV but not in normal hearts.
- PDE5 inhibitors may directly target RV function and acutely improve contractility in RV failure patients who express elevated PDE5 levels.

Richa Agarwal 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), Cy450 inhibitors</td>
<td>MI in past 3 mon, 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>Study</td>
<td>n</td>
<td>Population</td>
<td>6MWD Improvement (compared to placebo)</td>
<td>Death/Clinical Worsening</td>
</tr>
<tr>
<td>------------------------</td>
<td>------------</td>
<td>------------------</td>
<td>----------------------------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>Galie 2005 SUPER (Sildenafil)</td>
<td>278</td>
<td>Grp 1 PAH, NYH II or III</td>
<td>45, 46 and 50 m for the 3 doses at 12 wks (p&lt;.001)</td>
<td>P= NS</td>
</tr>
<tr>
<td>Galie 2009 PHIRST (Tadalafil)</td>
<td>405</td>
<td>Grp 1 PAH, NYH II or III, 53% on bosentan</td>
<td>33 m at 16 wks (p=.01) Sig benefit seen in 40 mg &amp; bosentan naïve</td>
<td>CW (p=.04 for 40 mg)</td>
</tr>
<tr>
<td>Galie 2012 PHIRST Extn (Tadalafil)</td>
<td>357</td>
<td>Effect maintained at 52 wks, but no improvement in dose escalated patients</td>
<td>No diff in 20 or 40 mg,</td>
<td>N</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 ½ = 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></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</td>
<td></td>
<td>(Dyspnea scores also improved)</td>
</tr>
<tr>
<td>Ghofrani 2015</td>
<td>22</td>
<td>COPD with PAH, GOLD II-IV, FEV1&lt;70, pO2&gt;50</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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 (eg 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

Emerging concept

- Mortality and Morbidity similar to many rheumatologic and oncologic disorders
- Multi-mechanistic approach from the start, in which physicians use several drug combinations to effectively treat the disease and gain disease remission.
- Several large trials testing the upfront multi-drug combination therapy are ongoing, AMBITION trial recently published
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 cardio-pulmonary 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.

Baseline

Week 16
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

Ruled bars: Background sildenafil
Dotted bars: Background bosentan
Solid bars: Entire population

N = 235
NYHA III/IV

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 20 mg TAD
5 mg ABS 40 mg TAD
10 mg ABS 40 mg TAD
N=302

5 mg ABS PBO TAD
Sham (PBO) up-filtration
N=152

40 mg TAD PBO ABS
Sham (PBO) up-filtration
N=151

20 mg TAD PBO ABS

Evaluation of secondary efficacy endpoints
105 clinical failure events: primary endpoint

FAV: final assessment visit
EOS: end of study

(~28 days after 105 clinical failure events reached)
(~4 weeks after first db lock)
## Results

<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><strong>Primary end point</strong></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>Hospitalization for worsening pulmonary arterial hypertension</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>
</tbody>
</table>
Kaplan–Meier Curves for the Probability of a First Adjudicated Primary End-Point Event.
<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</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etiology</td>
<td></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>
<td></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>
<td></td>
</tr>
<tr>
<td>Baseline WHO FC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.08</td>
<td></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>
<td></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>
<td></td>
</tr>
<tr>
<td>Age at Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.26</td>
<td></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>
<td></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>
<td></td>
</tr>
<tr>
<td>Baseline 6MWD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.41</td>
<td></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>
<td></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>
<td></td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.92</td>
<td></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>
<td></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>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.68</td>
<td></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>
<td></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>
<td></td>
</tr>
</tbody>
</table>
# 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>P value</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>Odds ratio, combination therapy vs. monotherapy (95% CI)</td>
<td>Reference</td>
<td>1.56 (1.05 to 2.32)</td>
<td>1.42 (0.88 to 2.31)</td>
<td>1.72 (1.05 to 2.83)</td>
</tr>
<tr>
<td>P value</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>P value</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>P value</td>
<td>Reference</td>
<td>0.24</td>
<td>0.30</td>
<td>0.36</td>
</tr>
<tr>
<td></td>
<td>Current therapy</td>
<td>Added therapy</td>
<td>Patients (n)</td>
<td>Study duration</td>
</tr>
<tr>
<td>----------------</td>
<td>-----------------------------------------------</td>
<td>---------------------</td>
<td>--------------</td>
<td>----------------</td>
</tr>
<tr>
<td>FREEDOM-C</td>
<td>Bosentan and/or sildenafil</td>
<td>Treprostinil oral</td>
<td>300</td>
<td>16 weeks</td>
</tr>
<tr>
<td>AMBITION</td>
<td>Ambrisentan/tadalafil/combo</td>
<td>Combo vs mono</td>
<td>300</td>
<td>Event-driven</td>
</tr>
<tr>
<td>Pfizer</td>
<td>Bosentan</td>
<td>Sildenafil</td>
<td>106</td>
<td>12 weeks</td>
</tr>
<tr>
<td>COMPASS-1</td>
<td>Bosentan</td>
<td>Sildenafil</td>
<td>45</td>
<td>Single dose</td>
</tr>
<tr>
<td>COMPASS-2</td>
<td>Sildenafil</td>
<td>Bosentan</td>
<td>250</td>
<td>Event-driven</td>
</tr>
<tr>
<td>COMPASS-3</td>
<td>Bosentan</td>
<td>Sildenafil</td>
<td>100</td>
<td>16 weeks</td>
</tr>
<tr>
<td>ATHENA-1</td>
<td>Sildenafil or tadalafil</td>
<td>Ambrisentan</td>
<td>40</td>
<td>24 weeks</td>
</tr>
<tr>
<td>SERAPHIN</td>
<td>Naive/PDE-5/PGI/combo</td>
<td>Macitentan</td>
<td>742</td>
<td>Event-driven</td>
</tr>
<tr>
<td>PATENT</td>
<td>Naive/PGI/ERA</td>
<td>Riociguat</td>
<td>462</td>
<td>12 weeks</td>
</tr>
<tr>
<td>IMPRES</td>
<td>≥2 current therapies</td>
<td>Imatinib</td>
<td>200</td>
<td>24 weeks</td>
</tr>
<tr>
<td>Gilead</td>
<td>Stable PAH therapy</td>
<td>Cicletinib</td>
<td>160</td>
<td>12 weeks</td>
</tr>
<tr>
<td>ATPAHSS</td>
<td>Ambrisentan/tadalafil/combo</td>
<td>Combo vs mono</td>
<td>63</td>
<td>36 weeks</td>
</tr>
<tr>
<td>GRIPHON</td>
<td>ERA, PDE5 or both</td>
<td>Selexipag</td>
<td>670</td>
<td>Event-driven</td>
</tr>
<tr>
<td>Novartis</td>
<td>Stable PAH therapy</td>
<td>Nilotinib</td>
<td>66</td>
<td>6 months</td>
</tr>
</tbody>
</table>
Warfarin – role in Group 1 PAH

• Retrospective data show benefit, No prospective RCT in modern PAH therapy era
• But used in 50-85% patients in US/European registries
• Rationale for use:
  – Many endothelial cell abnormalities that predispose patients to PAH also predispose thrombosis
  – Microscopic throbi well documented on pathology
  – Heart failure, immobilisation, Central venous lines

McLaughlin et al. ACCF/AHA 2009 Expert Consensus Document on PAH
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)
Guidelines on Warfarin

• Warfarin anticoagulation is recommended in all patients with IPAH.
• Updated guidelines have not changed this recommendation.
• However should be used with caution in patients with hemoptysis or bleeding
• Also interactions with other PAH specific drugs must be kept in mind

McLaughlin et al. ACCF/AHA 2009 Expert Consensus Document on PAH
Other supportive therapy

- Oxygen: sO2< 90% or pO2<60 should receive supplemental oxygen.
- Diuretics
- A sodium restricted diet (<2400 mg per day) advised and is important to manage volume status in patients with RV failure.
- Routine Immunizations (influenza and pneumococcal)
- Avoid:
  - Pregnancy
  - High altitude
  - Heavy exercise (aerobic exercises allowed)
Initial therapy with PAH-approved drugs

Inadequate clinical response

Sequential combination therapy (I–A)
ERAs
+ +
Prostanoids — + — PDE-5i or sGCS

Inadequate clinical response on maximal therapy

BAS (IIa–C)

Consider for eligibility for lung transplantation

Referral for lung transplantation (I–C)

Approach to PAH specific therapy based on NYHA class

• Class I: Wait and watch, assess 6 monthly
• Class II/III/IV: Vasoreactivity testing $\rightarrow$ If positive try CCB
• Class II: Oral monotherapy
  • Riociguat
  • Ambrisentan/bosentan/macitentan
  • Sildenafil/Tadalafil

Add second drug if no response
May consider upfront combination therapy
• Class III: Consider combination oral therapy upfront
  – For Class III with:
    • Poor prognostic markers*
    • Progression despite 2 oral therapies
      Add IV or inhaled prostanoid

• Class IV
  – IV Prostanoid drug of choice
  – Inhaled prostanoid + ETRA in unwilling patients
  – Combination oral therapy if prostanoids NA
# Prognostic markers in PAH

<table>
<thead>
<tr>
<th>Lower</th>
<th>Determinants of Risk</th>
<th>Higher</th>
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</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></td>
<td></td>
<td>Significant RV Dysfunction</td>
</tr>
<tr>
<td>Normal/Near normal RAP and CI</td>
<td>Hemodynamics</td>
<td>High RAP, Low CI</td>
</tr>
</tbody>
</table>

## Follow-up

<table>
<thead>
<tr>
<th></th>
<th>At baseline (prior to therapy)</th>
<th>Every 3–6 months&lt;sup&gt;a&lt;/sup&gt;</th>
<th>3–4 months after initiation or changes in therapy</th>
<th>In case of clinical worsening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical assessment</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
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<td>WHO-FC</td>
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<td>ECG</td>
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<tr>
<td>6MWT&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>✅</td>
<td>✅</td>
<td>✅</td>
</tr>
<tr>
<td>Cardio-pulmonary exercise</td>
<td>✅</td>
<td></td>
<td>✅</td>
<td>✅</td>
</tr>
<tr>
<td>testing&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BNP/NT-proBNP</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
</tr>
<tr>
<td>Echocardiography</td>
<td>✅</td>
<td></td>
<td>✅</td>
<td>✅</td>
</tr>
<tr>
<td>RHC</td>
<td>✅&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td>✅&lt;sup&gt;d&lt;/sup&gt;</td>
<td>✅&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
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)

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

• In most patients with pulmonary hypertension associated with RV failure, isolated bilateral lung transplantation is associated with comparable or better results than heart-lung transplantation.

• Most commonly, 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
CTEPH

- Endarterectomy recommended in all patients who are fit for surgery and show evidence of PAH at rest or exercise
- Warfarin in all
- Those not-operable or those with residual PAH after surgery may be put on PAH specific Rx
PAH secondary to lung disease

• Only short term hemodynamic benefits of PAH specific Rx (ERA, PDE-5) demonstrated in both ILD/COPD
• Long term benefits not seen
• IPF patients with bosentan and ambrisentan showed worse outcomes
• Likely due to worsening hypoxia due to reversal of protective vasoconstriction $\rightarrow$ V/Q mismatch
• Patients with CTD with disproportionate PAH to lung disease may benefit with PAH specific therapy
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