Controversies in Pulmonary Hypertension

Hap Farber
Director, Pulmonary Hypertension Center
Boston University School of Medicine
Disclosures

1) Honoria: Actelion, Gilead, Bayer
2) Consultant: Actelion, Gilead, United Therapeutics, Bayer, Bellerephon
3) Research Grants: United Therapeutics, Gilead
Things to discuss today

1) ECHO vs. right heart catheterization (RHC)
2) Accuracy of diagnosis: PAH vs. PH (especially HFpEF/HFrEF or COPD/ILD)
3) CCB for treatment of PAH
4) Choice of treatment for PAH
5) Warfarin (NAC)
Classification of Pulmonary Hypertension (Nice, 2013)

1. Pulmonary arterial hypertension
   
   1.1 Idiopathic PAH
   1.2 Heritable PAH
      1.2.1 BMPR2
      1.2.2 ALK-1, 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 (PPHN)
Classification of Pulmonary Hypertension (Nice, 2013)

2. Pulmonary hypertension due to left heart disease

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

3. Pulmonary hypertension owing to lung diseases and/or hypoxia

   3.1 Chronic obstructive pulmonary disease
   3.2 Interstitial lung disease
   3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
   3.4 Sleep-disordered breathing
   3.5 Alveolar hypoventilation disorders
   3.6 Chronic exposure to high altitude
   3.7 Developmental lung disorders
Classification of Pulmonary Hypertension (Nice, 2013)

4. Chronic thromboembolic pulmonary hypertension (CTEPH)

5. Pulmonary hypertension with unclear multifactorial mechanisms

  5.1 Hematological disorders: chronic hemolytic anemias, myeloproliferative disorders, splenectomy
  5.2 Systemic disorders: sarcoidosis, pulmonary Langerhan’s cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
  5.3 Metabolic disorders: glycogen storage disease, Gaucher’s disease, thyroid disease
  5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH
Definition of Pulmonary Arterial Hypertension (PAH; Nice, 2013)

1) Mean PAP ≥25mm Hg at rest; PCWP or LVEDP ≤15mm Hg; PVR 240 (3 Wood units).

2) Exercise PAH

3) Volume loading?

4) What about mPAP 21-24?
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Echocardiographic Estimation of PH in Clinical Practice

1) ACC/ AHA expert consensus recommends further evaluation of patients with dyspnea and an estimated RVSP >40 mm Hg

2) ECHO-estimated measurements of PH are NOT diagnostic (for anything) and should NEVER be the basis for the prescription of PAH specific agents

3) Estimates >60 and/or right ventricular enlargement/dysfunction are cause for significant concern and expedited evaluation by an expert team

PAH: Echocardiography

1) Semi-subjective (objectivity)
2) Mathematical assumptions for chamber size, shape, and flow
3) Numerous studies demonstrate lack of correlation with hemodynamics
4) Compared to RHC: false negative rate? false positive rate?
5) Reliability as follow-up?
PAH: Echocardiography

ECHO compared to right heart catheterization:

- False negative rate: <1%
- False positive rate: 30-40%
PAH: Echocardiography

Reliability of ECHO as follow-up

Congestive Heart Failure 2011; 17:56–63

1) Good correlation in PAsp between ECHO and RHC at baseline.
2) In contrast, little correlation of serial measurements between ECHO and RHC.
3) Repeat ECHO measurements alone not sufficient to monitor change in PAsp or progression of PAH
Complementary Roles of ECHO and RHC in Clinical Practice

1) ECHO is non-invasive, widely available, and more acceptable to patients
2) RA estimates can be problematic and are often a source of error
3) ECHO provides valuable information about RV size/function and highlights the common aspects of left heart disease (AV/MV function; LVH; LAE)
4) ECHO can over-estimate RVSP in a clinically significant way
5) Done correctly, RHC most accurate information about left heart filling pressures and also measures mixed venous saturation and/or CO (TD)
6) ECHO estimates of left heart pressures and CO are contrived and prone to error

7) **Most patients** with an ECHO-estimate of PH in the community do not have PAH
8) **Most patients** with PH at RHC have elevated left heart filling pressures as the etiology
Things to discuss today

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2) Accuracy of diagnosis: PAH vs. PH (especially HFP EF/HFrEF or COPD/ILD)
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4) Choice of treatment for PAH
5) Warfarin (NAC)
Prevalence of PH and PAH in Large Community Survey

N=926 patients with PH from 10,314 individuals undergoing 15,633 echo studies. PH defined as PASP>40 mm Hg.

Most patients did not have confirmatory RHC (only those with PAH or CTEPH dx)

Diagnostic Findings of PH/PAH Among Patients Referred to Pulmonary Hypertension Specialty Center

Final Diagnosis

- No PH: 7%
- Pre-capillary PH: 53%
- Postcapillary PH: 40%

N=152 consecutive patients referred to PH center over 1y undergoing ECHO and RHC within 1h

# Misdiagnosis of PH and PAH is Common

<table>
<thead>
<tr>
<th>Pre-referral diagnosis</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Group 5</th>
<th>No PH</th>
<th>Unk.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>73%</td>
<td>5%</td>
<td>7%</td>
<td>0</td>
<td>0</td>
<td>12%</td>
<td>18%</td>
</tr>
<tr>
<td>Group 2</td>
<td>0</td>
<td>61%</td>
<td>8%</td>
<td>0</td>
<td>0</td>
<td>31%</td>
<td>0</td>
</tr>
<tr>
<td>Group 3</td>
<td>18%</td>
<td>14%</td>
<td>59%</td>
<td>0</td>
<td>0</td>
<td>9%</td>
<td>0</td>
</tr>
<tr>
<td>Group 4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>75%</td>
<td>0</td>
<td>25%</td>
<td>0</td>
</tr>
<tr>
<td>Group 5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>50%</td>
<td>50%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Unknown</td>
<td>12 (29%)</td>
<td>13 (31%)</td>
<td>1 (2%)</td>
<td>14 (33%)</td>
<td>2 (5%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- = Correct pre-referral diagnosis  
- = Incorrect pre-referral diagnosis

N=141 consecutive patients referred over a 10-month period for PH evaluation. 39% of patients were initiated on PAH-specific mediation prior to referral who did not have Group I PAH.

ECHO-PH and HFpEF

1) Many patients with HFpEF have ECHO-estimated PH
2) Not all patients with HFpEF have classic features like LAE, LVH; in fact, some patients with HFpEF have ECHO-estimated PH as only abnormality
3) More detailed studies on diastolic filling are challenging and often not part of routine ECHOs

What is significance of ECHO-estimated PH in HFpEF?
TOPCAT: Not all Patients with HFpEF have LVH or LAE

N=935 (of 3445) patients with HFpEF enrolled in TOPCAT trial (EF >45%); core lab analyzed;

Initial enrollment based upon: CHF hospitalization in past 12 months or BNP >100, NT-pro >360

Patients were: 90% hypertensive; 57% CAD; 38% AF; 42% CKD; 40% DM

In core lab: Average EF 59%; only 13% with EF < 50%

LAE in 80% if defined by volume (more sensitive than area)

Diastolic dysfunction graded by mitral E/A ratio, tissue doppler E', and mitral deceleration time

Treating HFpEF: More Experience than Data

1) Loop diuretics are under-utilized: burden of increased frequency or higher doses needed in treatment resistant patients
2) High dose ACE-I and ARBs II may limit diuretic efficacy by reducing glomerular filtration
3) Beta-blockers, especially combined alpha & beta blockers, may limit diuretic efficacy by lowering blood pressure
4) Dihydropyridine CCB often contribute to edema

5) Medications approved for PAH generally ineffective in this population
6) Approved PAH medications may be harmful in left-sided heart disease (preserved or reduced ejection fraction)
1) RHC necessary before initiating therapy with PAH-specific medications
2) Vasoreactivity testing recommended for suspected IPAH
3) Testing in centers with established expertise in PAH is optimal when feasible
4) Empiric therapy for suspected PAH is NEVER appropriate
5) Patients with PAH likely to benefit from early referral/treatment at specialty center
5) Managing comorbidities and volume status critical for optimal outcomes

Summary and Conclusions

1) ECHO is a valuable diagnostic tool in the evaluation of dyspnea
2) Increasingly good visualization of RV structure and function
3) HFpEF very common, under-recognized, and clinically important cause of ECHO-estimated PH. ECHO-estimated PH may be ECHO finding in HFpEF patient
4) HFpEF patients should not be treated with PAH therapy outside specialized centers/clinical research studies
5) RVE and IVS flattening are ECHO findings that should prompt early referral to a specialty PH center
6) RHC always necessary for PAH diagnosis and treatment
Things to discuss today

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2) Accuracy of diagnosis: PAH vs. PH (especially HFpEF/HFrEF or COPD/ILD)
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4) Choice of treatment for PAH
5) Warfarin (NAC)
Calcium Channel Blockers

1) Small subset (<<10%) of patients with IPAH have favorable long-term response to high-dose CCB
2) Potential patients identified by reduction in mPAP ≥10 with absolute mPAP <40 and increased or unchanged CO
3) Vasoreactivity testing only performed with short-acting pulmonary vasodilators (iNO currently agent of choice)
4) Slow up-titration with CCB required with high level maintenance doses (Diltiazem, 240–720mg; nifedipine, 120–240mg)
5) Patients without sustained hemodynamic response to NYHA FCI or II require other PAH therapy

Things to discuss today

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4) Choice of treatment for PAH
5) Warfarin (NAC)
Treatment Issues in PAH

1) One, two, or three drugs?
   - Monotherapy
   - Dual combination therapy
   - Triple combination therapy

2) When?
   - Upfront
   - Add-on (stable vs. failing)

3) Which drugs and in what order?
48% of patients were receiving monotherapy at the time of study enrollment.

N = 2438. Treatment reported at time of enrollment in REVEAL

Use of Parenteral Prostanoids at Time of Death in the REVEAL Registry

N=909. All-cause mortality.
REVEAL: Under-use of Parental Prostannoids in Functional Class IV PAH

IV Prostacyclin Use 1 Day Prior to Designation as FC IV

- PGI Monotherapy: 5.8%
- PGI Combination Therapy: 51.0%
- No PGI: 43.2%

IV/SC Prostacyclin Use 90 Days After Designation as FC IV

- PGI Therapy: 48.0%
- No PGI: 52.0%

N=294 patients worsening to FC IV.
PAH Long-term **Monotherapy** Trials: Caveats

1) Most long-term data come from open-label extensions of placebo-controlled trials without a comparator arm.

2) These trials allowed add-on therapy after initial blinded treatment phase; thus, some or all of the efficacy seen in open-label phase could be due to add-on therapy, not “primary” study medication.

3) Some trials defined add-on therapy as a clinical endpoint, but others did not.

4) Results **cannot** be compared across studies because each trial was unique, with fundamental protocol differences (study size, FC, outcomes definitions, use of additional medications without reaching trial endpoint, etc.).
PAH Long-term **Combination** Therapy Trials: Caveats

1) Only AMBITION prospectively studied the question of monotherapy versus *de novo* combination therapy
2) All other currently reported trials featured “add-on” protocols
3) Relative contribution of individual agents to treatment success difficult to assess
4) Combination therapy trials often have only a short-term component, with no long-term follow-up
AMBITION: Ambrisentan-Tadalafil Combination Therapy. Primary Study Endpoint: Time To Clinical Worsening

<table>
<thead>
<tr>
<th>Time (weeks)</th>
<th>Combination Therapy</th>
<th>Pooled Monotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>253</td>
<td>247</td>
</tr>
<tr>
<td>24</td>
<td>229</td>
<td>209</td>
</tr>
<tr>
<td>48</td>
<td>186</td>
<td>155</td>
</tr>
<tr>
<td>72</td>
<td>145</td>
<td>108</td>
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<td>96</td>
<td>106</td>
<td>77</td>
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<tr>
<td>120</td>
<td>71</td>
<td>49</td>
</tr>
<tr>
<td>144</td>
<td>36</td>
<td>25</td>
</tr>
<tr>
<td>168</td>
<td>36</td>
<td>25</td>
</tr>
<tr>
<td>192</td>
<td>36</td>
<td>25</td>
</tr>
</tbody>
</table>

### AMBITION: Subgroup Analysis

#### Table

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Combination Therapy</th>
<th></th>
<th>Pooled Monotherapy</th>
<th></th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Events</td>
<td>n</td>
<td>Events</td>
<td></td>
</tr>
<tr>
<td>IPAH/HPAH</td>
<td>134</td>
<td>25 (19%)</td>
<td>145</td>
<td>46 (32%)</td>
<td>0.535 (0.329-0.871)</td>
</tr>
<tr>
<td>APAH</td>
<td>119</td>
<td>21 (18%)</td>
<td>102</td>
<td>31 (30%)</td>
<td>0.453 (0.259-0.790)</td>
</tr>
<tr>
<td>WHO FC II</td>
<td>76</td>
<td>4 (5%)</td>
<td>79</td>
<td>17 (22%)</td>
<td>0.211 (0.071-0.629)</td>
</tr>
<tr>
<td>WHO FC III</td>
<td>177</td>
<td>42 (24%)</td>
<td>168</td>
<td>60 (36%)</td>
<td>0.576 (0.388-0.855)</td>
</tr>
<tr>
<td>Age &lt;57 years</td>
<td>124</td>
<td>13 (10%)</td>
<td>120</td>
<td>31 (26%)</td>
<td>0.367 (0.192-0.701)</td>
</tr>
<tr>
<td>Age ≥57 years</td>
<td>129</td>
<td>33 (26%)</td>
<td>127</td>
<td>46 (36%)</td>
<td>0.581 (0.371-0.910)</td>
</tr>
<tr>
<td>BL 6MWD &lt;363.7 m</td>
<td>129</td>
<td>35 (27%)</td>
<td>121</td>
<td>51 (42%)</td>
<td>0.537 (0.349-0.827)</td>
</tr>
<tr>
<td>BL 6MWD ≥363.7 m</td>
<td>124</td>
<td>11 (9%)</td>
<td>126</td>
<td>26 (21%)</td>
<td>0.380 (0.187-0.769)</td>
</tr>
<tr>
<td>North America</td>
<td>116</td>
<td>22 (19%)</td>
<td>112</td>
<td>34 (30%)</td>
<td>0.505 (0.295-0.866)</td>
</tr>
<tr>
<td>Rest of world</td>
<td>137</td>
<td>24 (18%)</td>
<td>135</td>
<td>43 (32%)</td>
<td>0.506 (0.307-0.834)</td>
</tr>
<tr>
<td>Female</td>
<td>188</td>
<td>32 (17%)</td>
<td>200</td>
<td>61 (31%)</td>
<td>0.473 (0.308-0.726)</td>
</tr>
<tr>
<td>Male</td>
<td>65</td>
<td>14 (22%)</td>
<td>47</td>
<td>16 (34%)</td>
<td>0.581 (0.283-1.194)</td>
</tr>
</tbody>
</table>

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AMBITON: Comparison of Initial Combination Therapy in WHO FC II and WHO FC III Patients

Primary Endpoint – Clinical Failure Events

FC II Combination: 5%
FC II Pooled Monotherapy: 22%
FC III Combination: 24%
FC III Pooled Monotherapy: 36%

COMPASS-2: No Benefit of Bosentan Added to Stable Sildenafil

Primary Endpoint: Time to First Morbidity or Mortality Event

N=334. Randomized placebo-controlled event-driven trial of bosentan added to stable sildenafil.

Upfront triple combination therapy in PAH: a pilot study

Summary: Long-term Management of Patients With PAH

1) Availability of oral, inhaled, and parenteral PAH therapies provides multiple treatment strategies for patients with PAH

2) Long-term data on choice of initial medical therapy, de novo combination therapy, or therapy sequencing are still incomplete

3) Considerations for initial therapy selection and for combining therapies should take into account consensus recommendation/guidelines, long-term efficacy and safety data, second-line choices, and patient characteristics, with an individualized approach for each patient

4) In patients with severe disease or in those failing medical therapy, early referral to PAH centers for advanced therapy important
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2) Accuracy of diagnosis: PAH vs. PH (especially HFpEF/HFrEF or COPD/ILD)
3) CCB for treatment of PAH
4) Choice of treatment for PAH
5) Warfarin (NAC)
Anticoagulation

1) Anticoagulation recommended in PAH with vitamin K antagonist (INR of 1.5-2.5, unless contraindicated)

2) Small observational studies support survival benefit of anticoagulation in IPAH

3) Improvement in survival not observed in other forms of APAH (such as SSc)

4) Survival benefit recently suggested by COMPERA trial in EU

5) Anticoagulation warranted to minimize catheter-related thrombosis in those receiving continuous intravenous prostanoid therapy

“That's all Folks!”