PULMONARY HYPERTENSION

RESPIRATORY & CRITICAL CARE CONFERENCE
APRIL 21, 2016
LAURA G. HOOPER
OUTLINE

- Brief review of WHO Group Classification Scheme

- Subgroups we’ll focus on:
  - WHO Group I – Pulmonary Arterial Hypertension
  - WHO Group II – PH secondary to Left Heart Disease

- Interpreting right-heart catheterization hemodynamics
- Overview of pharmacologic therapies
WHO CLASSIFICATION

1) Pulmonary Arterial HTN
   - Idiopathic PAH
   - Heritable
   - Drug/Toxin Induced
     - Methamphetamines
     - Anorexigens
   - Connective Tissue Disease
   - HIV
   - Portal Hypertension
   - Congenital Heart Disease
   - Schistosomiasis
   - PVOD

2) (PH due to Left Heart Disease)
   - HFrEF
   - HFpEF
   - Valvular disease

3) Lung Disease/Chronic Hypoxia
   - COPD
   - ILD
   - OSA/OHS
   - Chronic High Altitude Exposure
   - CPFE

4) Chronic Thromboembolic PH (CTEPH)

5) Uncertain/Multifactorial Mechanisms
   - Hematologic disorders
   - Sarcoidosis
   - Pulmonary histiocytosis
   - LAM
   - Metabolic Disorders
   - Other: CKD, fibrosing mediastinitis
Correctly classifying is critical
- Entities within groups are similar in regards to pathophysiology, clinical course, and response to therapy
- Therapeutic management varies widely between groups

Especially important to distinguish PAH (Group 1) from PH due to Left Heart Disease (Group 2) from CTEPH (Group 3)
- More to come...
<table>
<thead>
<tr>
<th>Pivotal Tests</th>
<th>Contingent Tests</th>
<th>Contribute to Assessment of</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td>TEE</td>
<td>Index of suspicion of PH</td>
</tr>
<tr>
<td>Exam</td>
<td>Exercise Echo</td>
<td>RVE, RAE, RVSP, RV Function</td>
</tr>
<tr>
<td>CXR</td>
<td>Pulmonary Angiography</td>
<td>Left Heart Disease</td>
</tr>
<tr>
<td>ECG</td>
<td>Chest CT Angiogram</td>
<td>VHD, CHD</td>
</tr>
<tr>
<td>Echocardiogram</td>
<td>Coagulopathy Profile</td>
<td>Chronic PE</td>
</tr>
<tr>
<td>VQ Scan</td>
<td>ABGs</td>
<td>Ventilatory Function</td>
</tr>
<tr>
<td>PFTs</td>
<td>Polysomnography</td>
<td>Gas Exchange</td>
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<tr>
<td>Overnight Oximetry</td>
<td></td>
<td>Sleep Disorder</td>
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<tr>
<td>HIV</td>
<td>Other CTD Serologies</td>
<td>HIV Infection</td>
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<tr>
<td>ANA</td>
<td></td>
<td>Scleroderma, SLE, RA</td>
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<tr>
<td>LFTs</td>
<td></td>
<td>Portopulmonary Htn</td>
</tr>
<tr>
<td>Functional Test (6MWT, CPET)</td>
<td>Vasodilator Test</td>
<td>Establish Baseline</td>
</tr>
<tr>
<td>RH Cath</td>
<td>Exercise RH Cath</td>
<td>Confirmation of PAH</td>
</tr>
<tr>
<td></td>
<td>Volume Loading</td>
<td>Haemodynamic Profile</td>
</tr>
<tr>
<td></td>
<td>Left Heart Cath</td>
<td>Vasodilator Response</td>
</tr>
</tbody>
</table>

6MWT, 6-minute walk test; ABGs, arterial blood gases; ANA, antinuclear antibodies; CHD, congenital heart disease; CPET, cardiopulmonary exercise test; CT, computerised tomography; CTD, connective tissue disease; CXR, chest x-ray; ECG, electrocardiogram; HIV, human immunodeficiency virus screening; HTN, hypertension; LFT, liver function test; PE, pulmonary embolism; PFT, pulmonary function test; PH, pulmonary hypertension; RA, rheumatoid arthritis; RAE, right atrial enlargement; RH Cath, right heart catheterisation; RVE, right ventricular enlargement; RVSP, right ventricular systolic pressure; SLE, systemic lupus erythematosus; TEE, transoesophageal echocardiography; VHD, valvular heart disease; VQ Scan, ventilation-perfusion scintigram.
RIGHT-HEART CATHETERIZATION

- Essential for definitive diagnosis of pulmonary HTN
- Provides necessary hemodynamic measurements to differentiate between pre-capillary and post-capillary PH
GROUP 1
PULMONARY ARTERIAL HYPERTENSION

Pathophysiology

- Muscularization of small-medium arterioles
- Cellular neointimal proliferation
- Plexiform lesions
PAH
DIAGNOSTIC CRITERIA

Diagnostic Criteria:
• Mean PAP $\geq$ 25 mmHg
• PCWP $\leq$ 15 mmHg
• Pulmonary Vascular Resistance $>$ 3 Woods Units

For Review…

\[
\text{TPG} = \text{mPAP} - \text{PCWP}
\]
\[
\text{PVR} = \frac{(\text{mPAP} - \text{PCWP})}{\text{CO}}
\]
PAH
AREAS OF CONTROVERSY

- Vasoreactivity testing for CCB responders
  - Only for IPAH (~10%), including familial & drug-associated
  - Not recommended for other PAH or PH forms
    - “responders” are extremely rare in these groups
  - (+) Test: ↓ mPAP by 10 to mPAP < 40mmHg and stable/increased CO

- “Borderline PH” (mPAP 21-24 mmHg): not a distinct entity
  - BUT, indicates pts who should be followed very closely

- Exercise-induced PH: currently lacks consensus definition
  - Not a recognized entity
Considerations for all PH patients:

- Diuretics
- Oxygen for those with PH + hypoxemia
  - Goal saturation > 90%
- Formal exercise training
  - Improved 6MWD that exceeds benefits seen in all pharmacologic intervention trials
- Vaccinations (influenza, pneumonia)
- Identify & treat co-existent conditions (i.e. OSA)
# PAH Therapeutics

## Step 1: Determine disease severity

<table>
<thead>
<tr>
<th>WHO Functional Class</th>
<th>NYHA Functional Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 No Sxs with ordinary activity</td>
<td>1 No Sxs with ordinary activity</td>
</tr>
<tr>
<td>2 Sxs with ordinary activity</td>
<td>2 Sxs with ordinary activity</td>
</tr>
<tr>
<td>→ dyspnea, CP, near-syncope</td>
<td>→ Slight limitation of activity</td>
</tr>
<tr>
<td>3 Sxs with &lt; ordinary activity</td>
<td>3 Sxs with &lt; ordinary activity</td>
</tr>
<tr>
<td>→ Comfortable at rest</td>
<td>→ Marked limitation</td>
</tr>
<tr>
<td>4 Sxs with any activity</td>
<td>4 Sxs with any activity</td>
</tr>
<tr>
<td>→ Sxs at rest</td>
<td>→ Sxs at rest</td>
</tr>
<tr>
<td>→ Signs of right-heart failure</td>
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</tr>
</tbody>
</table>

Although not in WHO classification scheme, clinical importance of syncope is highlighted...should prompt consideration of Class 4 designation.
PAH THERAPEUTICS
PAH
ADVANCED THERAPIES

**Endothelin Receptor Antagonists**
- Bosentan (Tracleer)
- Ambrisentan (Letairis)
- Macitentan (Opsumit)

**PDE-5 Inhibitors**
- Sildenafil (Revatio)
- Tadalafil (Adcirca, Cialis)

**Prostanoids**
- Epoprostenol (Flolan)
- Treprostinil (Remodulin)

**Guanylate Cyclase Stimulator**
- Riociguat (Adempas)

**Selective Prostaglandin Receptor Agonist**
- Selexipag (Uptravi)
PAH
INITIATING ADVANCED THERAPIES

Determine Functional Class

Conventional Therapies (Oxygen, Diuretics, etc.)

Class I
- Observation

Class II
- ERA + PDE-5 Inhibitor (Ambrisentan + Tadalafil)
- Other Combinations or Single-Agent therapy
- Prostanoid (IV, SQ, Inh)

Class III
- Other Combinations or Single-Agent therapy
- Prostanoid (IV, SQ, Inh)

Class IV
- IV Prostanoid
  Combination therapy strongly recommended
AMBITION TRIAL

- 500 participants (WHO Group I, Class II or III)
- 2:1:1 random assignment to:
  - Ambrisentan-tadalafil
  - Tadalafil monotherapy
  - Ambrisentan monotherapy
- Composite end-point:
  - Death, disease progression, unsatisfactory long-term response
- Results:
  - HR 0.50 combination vs. pooled-monotherapy


**Graph: A Combination Therapy vs. Pooled Monotherapy**

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

- Hazard ratio, 0.50 (95% CI, 0.35–0.72)
- P<0.001
<table>
<thead>
<tr>
<th></th>
<th><strong>Fixed-effects model</strong></th>
<th><strong>Random-effects model</strong></th>
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<tbody>
<tr>
<td></td>
<td>Combination</td>
<td>Monotherapy</td>
</tr>
<tr>
<td><strong>Prostanoids</strong></td>
<td></td>
<td></td>
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<tr>
<td>COMBI (2006)</td>
<td>3</td>
<td>19</td>
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<tr>
<td>STEP (2006)</td>
<td>0</td>
<td>32</td>
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<tr>
<td>TRIUMPH (2010)</td>
<td>4</td>
<td>115</td>
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<tr>
<td>FREEDOM-C (2012)</td>
<td>8</td>
<td>174</td>
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<tr>
<td>FREEDOM-C2 (2013)</td>
<td>11</td>
<td>157</td>
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<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>497</td>
<td>503</td>
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<tr>
<td>Total events</td>
<td>26</td>
<td>37</td>
</tr>
<tr>
<td>Heterogeneity $\chi^2=2.92, p=0.67, l=0%$ Test for overall effect: $Z=1.35, p=0.18$</td>
<td></td>
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<tr>
<td><strong>Phosphodiesterase type 5 inhibitors</strong></td>
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<td>PAGES (2008)</td>
<td>8</td>
<td>134</td>
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<tr>
<td>PHIRST (2011)</td>
<td>2</td>
<td>42</td>
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<tr>
<td>Zhao et al (2014)</td>
<td>5</td>
<td>60</td>
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<tr>
<td>AMBITION (PDE-5i) (2015)</td>
<td>23</td>
<td>127</td>
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<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>363</td>
<td>366</td>
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<tr>
<td>Total events</td>
<td>38</td>
<td>86</td>
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<td>Heterogeneity $\chi^2=1.36, p=0.72, l=0%$ Test for overall effect: $Z=4.59, p=0.00001$</td>
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<tr>
<td><strong>ERA</strong></td>
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<td>EARLY (2008)</td>
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<td>14</td>
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<tr>
<td>COMPASS-2 (2015)</td>
<td>68</td>
<td>159</td>
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<tr>
<td>SERAPHIN (2013)</td>
<td>50</td>
<td>154</td>
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<tr>
<td>AMBITION (ERA) (2015)</td>
<td>23</td>
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<td><strong>Subtotal (95% CI)</strong></td>
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<td>465</td>
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<tr>
<td>Total events</td>
<td>142</td>
<td>195</td>
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<tr>
<td>Heterogeneity $\chi^2=1.61, p=0.66, l=0%$ Test for overall effect: $Z=3.24, p=0.001$</td>
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<td><strong>SGC stimulators</strong></td>
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<tr>
<td>PATENT-1 (2013)</td>
<td>1</td>
<td>131</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>131</td>
<td>60</td>
</tr>
<tr>
<td>Total events</td>
<td>1</td>
<td>4</td>
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<tr>
<td>Heterogeneity: not applicable Test for overall effect: $Z=3.96, p=0.05$</td>
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<td></td>
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<tr>
<td>Selective prostacyclin receptor agonist</td>
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<tr>
<td>Simonneau et al (2012)</td>
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<td>33</td>
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<tr>
<td>GRIFFIN (2015)</td>
<td>124</td>
<td>462</td>
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<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>495</td>
<td>468</td>
</tr>
<tr>
<td>Total events</td>
<td>125</td>
<td>395</td>
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<tr>
<td>Heterogeneity $\chi^2=1.50, p=0.22, l=0%$ Test for overall effect: $Z=4.93, p=0.00001$</td>
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</tr>
</tbody>
</table>

**Total number of patients within each subgroup (95% CI)**

<table>
<thead>
<tr>
<th></th>
<th>Combination</th>
<th>Monotherapy</th>
<th><strong>Favors Combination</strong></th>
<th>Monotherapy</th>
<th>Favors Monotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number</td>
<td>1940</td>
<td>1862</td>
<td>100% 0.65 (0.58-0.72)</td>
<td>100%</td>
<td>0.65 (0.56-0.76)</td>
</tr>
</tbody>
</table>

ANTICIPATED TRIALS

• **RESPITE**
  - Riociguat (sGCS) as alternative to PDE-5 inhibitor in pts with insufficient clinical response
  - June 2016

• **TRITON**
  - Macitentan + Tadalafil + Selexipag vs. Macitentan + Tadalafil
    - (ERA + PDE-5 + PCA) vs. (ERA + PDE-5)
    - Starting this year

• **FREEDOM**
  - Oral treprostinil added to background ERA or PDE-5
  - August 2016
ANTICOAGULATION FOR PAH?

- Histopathologic rationale based on in situ thrombosis seen in IPAH

- Conflicting data on benefit in IPAH compared to other types of Group I PAH
  - Suggestion of potential harm in
    - Systemic Sclerosis PAH
    - Portopulmonary hypertension

- Current recommendation:
  - Case-by-case consideration for IPAH only
  - Risk-benefit ratio less favorable in remainder of Group I PAH
QUESTIONS?

A PREGNANT PAUSE
GROUP 2
PH DUE TO LEFT-HEART DISEASE

• Left-heart disease accounts for 65-80% of PH cases
  • By far the most common form of PH

• HFrEF (systolic), HFpEF (diastolic), valvular disease
  • PH common (~40-80% prevalence) in all forms of LHD

• Presents as:
  • Isolated post-capillary PH
  • Post-capillary PH + pre-capillary component (worse survival)

• RV dysfunction resulting in ↓ cardiac output is a critical predictor of poor outcome in PH-LHF
LEFT-HEART DISEASE
PULMONARY HYPERTENSION

Making the Diagnosis:

• Correctly identifying PH-LHD (and not misclassifying as PAH) is critical
  • Inappropriate treatment with PAH drugs may be harmful

• Right-heart catheterization is necessary, but may not be sufficient
  • Multiple limitations of RHC (stay tuned…)
  • Take in context of non-invasive measure (i.e. TTE) & “pre-test working diagnosis”
Right-Heart Catheterization

- Essential to distinguish Pre-Capillary vs Post-Capillary vs Combined Post- and Pre-Capillary PH

<table>
<thead>
<tr>
<th>Pulmonary HTN</th>
<th>mPAP</th>
<th>PCWP</th>
<th>PVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Capillary</td>
<td>↑</td>
<td>≤ 15</td>
<td>&gt; 3</td>
</tr>
<tr>
<td>Post-Capillary</td>
<td>↑</td>
<td>&gt; 15</td>
<td>&lt; 3</td>
</tr>
<tr>
<td>Combined Pre/Post</td>
<td>↑</td>
<td>&gt; 15</td>
<td>&gt; 3</td>
</tr>
</tbody>
</table>

- PCWP is vulnerable to significant variability & risk of miscategorizing PAH as PH-LHD (and vice versa)
PCWP LIMITATIONS

70 year-old patient
HFpEF, volume overload
Body weight 80 kg

PAPm 51 mmHg

PCWP

TPG

PCWP LIMITATIONS

Digitized mean
Risk of misclassifying post- as precapillary PH:
\( \approx 30\% \)
(Ryan et al. 2012)

End-expiratory
Risk of misclassifying pre- as postcapillary PH:
\( \approx 30\% \)
(LeVarge et al. 2014)

Expiration

Inspiration

Digitized mean

End-expiratory mean

PAWP Pressure Tracing

TAKE-HOME MESSAGES ON PCWP

• Be aware of the limitations in regards to volume and respiratory shifts
  • Important in patients with COPD, recent diuresis
• Can be significant variability between cath labs, particularly between community & “expert centers”

• If pre-test suspicion for LHD is high:
  1. Request volume challenge during RHC to potentially “unmask” occult post-capillary hemodynamics
  2. Revisit comprehensive TTE evaluation if concern for LHD remains high with inconclusive RHC
  3. LHC to measure LVEDP if still in doubt
PH-LHD TREATMENT

Are any PAH therapies effective or safe in Group II?

- **IV Epoprostenol (FIRST Study)**
  - + Hemodynamic improvement
  - No change in 6MWD
  - Trend towards decreased survival (terminated early)

- **Endothelin Receptor Antagonists**
  - No evidence of effect
  - Significant side effects (primarily edema)

- **Riociguat (LEPHT, DILATE)**
  - LEPHT: enrolled HFrEF
    - Did not meet 1° endpoint (mPAP Δ)
    - Improved CO, SV, PVR
  - DILATE: enrolled HFpEF
    - Acute hemodynamic (SV, CI) changes

- **Sildenafil**
  - CONFLICTING RESULTS
    1. Decreased mPAP, PCWP, PVR
    2. RELAX: ∅ change in 6MWD or QoL
    3. ∅ change in mPAP, CO

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2 Hoendermiss ES. Effects of sildenafil on invasive hemodynamics and exercise capacity. Eur Heart J. 2015
LIMITATION

• Current data suffer from:
  • Cohort characterization lacks standardization
    • Mostly UN-selected cohorts
    • Lack of RHC confirmation of PH
  • Hemodynamic, rather than clinical, outcomes
    • FIRST trial highlighted that: improved hemodynamics ≠ improved outcomes
  • Often short-term (<12 weeks)
ANTICIPATED TRIALS

• SOCRATES-PRESERVED
  • RCT of vericiguat (analogue of riociguat)
  • HFpEF
  • Outcomes: NT-proBNP levels, left atrial volume
  • Completion: May 2016

• 2 PDE-5 Trials underway (Sildenafil, Tadalafil)
  • Well-defined PH (by TTE) in HFrEF population

• MELODY
  “Macitentan in subjects with combined pre- and post-capillary pulmonary hypertension due to left ventricular dysfunction”
  • Highly selected cohort (HFpEF, pre + post-capillary PH)
  • Outcomes: safety (edema or worsening functional class)
  • Completion: soon
CURRENT RECOMMENDATIONS

• PDE-5 and Riociguat felt to hold most promise
  • Long-term, **event-driven** trials needed

• Currently, no PAH-approved drugs recommended for PH secondary to left-heart disease
  → Focus on optimizing medical HF management

• Highly selected patients (i.e. combined post- and pre-capillary PH) may be considered for PDE-5 or riociguat therapy
  • (defer to ‘expert center’ consultation)
DON'T BITE OFF MORE THAN YOU CAN CHEW
GROUP 3
PH DUE TO LUNG DISEASE

- 2nd most common cause of PH (after LHD)
  - COPD
  -ILD
  - Combined pulmonary fibrosis & emphysema (CPFE)
  - Sleep disordered breathing
  - Alveolar hypoventilation
- Lung disease typically severe/advanced
  - But not always...
  - Severity of PH tends to trend with degree of hypoxemia

No approved (or recommended) PAH-targeted therapies for Group 3 PH
- RISE-IIP Trial: Riociguat for PH in ILD (expected 2017)
• 1-5% of survivors of PE develop CTEPH

• Preferred diagnostic imaging modality: V/Q Scan
  - More sensitive than CT-PA
  - May underestimate central pulmonary vascular obstruction
    - i.e. recanalized thrombus in central PA

• Treatment
  - Surgical pulmonary artery endarterectomy (preferred)
  - Non-surgical candidates:
    - Interventional balloon pulmonary angioplasty
    - Riociguat (only FDA approved drug for inoperable CTEPH)

TAKE-HOME POINTS

• Correct classification of PH is essential
  • Often requires right-heart catheterization
• PVR (in Woods units) is now part of diagnostic criteria for PAH (in addt’n to mPAP and PCWP)
• Vasoreactivity testing only useful in IPAH
  • Includes heritable and drug-related PAH
  • Vast majority of PAH pts will be non-responders so CCB is rarely indicated
• Initial treatment for PAH w/ Class II/III status:
  • Ambrisentan (ERA) + Tadalafil (PDE-5)
  • Combination therapy favored over monotherapy
• Initial treatment for PAH w/ Class IV status:
  • Parenteral prostacyclin analogue + addt’l agent
• Anticoagulation in PAH is controversial
  • Case-by-case consideration for IPAH only
• Evidence of RH failure is especially poor prognostic sign in PH-LHD
• PCWP can be highly variable
• No PAH-targeted drugs are currently approved for Group II (PH-LHD) or Group III (lung disease)
• Pulmonary artery endarterectomy is curative treatment of choice for CTEPH
  • Riociguat if inoperable
QUESTIONS?