Current Guidelines
Combination Therapy for Pulmonary Arterial Hypertension

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Disclosures

- Industry-sponsored, multi-center clinical studies in patients with pulmonary hypertension: Actelion Pharmaceuticals, Inc; Gilead Sciences; United Therapeutics

- Single-day consulting with Actelion and Gilead
Objectives

- Navigate grading system for guideline development
- Utilize guideline-based recommendations for accurate & timely diagnosis
- Employ a guideline algorithm for treatment selection for PH patients
Grading system:

- Class 1: is recommended, is indicated
- Class 2: 2a should be considered; 2b may be considered
- Class 3: is not recommended

Strength of evidence:

- A: multiple RCT’s or meta-analysis
- B: one RCT or large non-randomized studies
- C: expert opinion
Followed rigorous 2011 IOM methodology for guidelines

Grading system

- Strong recommendation = 1
- Weak recommendation = 2
- Consensus-based rec = CB
CHEST: PAH Treatment

Quality of Evidence

- High = A
- Mod = B
- Low = C

Guidelines have number and letter grade
WHO DIAGNOSTIC GROUPS

- **Group 1**: Pulmonary Arterial Hypertension
- **Group 2**: Pulmonary Venous Hypertension
- **Group 3**: PH in association with hypoxemia
- **Group 4**: PH in association with CTE
- **Group 5**: Miscellaneous

Diagnosis and Group Classification

History – Physical – CXR - ECG

Echocardiography

VQ Scan - ABGs

Overnight Oximetry

HIV – ANA - LFTs

Functional Testing

Right Heart Catheterization

Index of Suspicion – Evaluate for LH & RH disease

CTEPH

OSA

Underlying Causes

Functional Severity

Confirm Diagnosis

Groups 2 and 3

5th World Symposium—No proven RX

ATS and ACCP Choosing Wisely campaign recommend against treatment

- No proven benefit
- May cause harm

Am J Respir Crit Care Med 2014; 189(12):1451-2; Chest 2014; 145:1383-91;
JACC December 2013 supplement 5th WSPH Guidelines
Targets for Current PAH Therapies

Prostacyclin Pathway
- Arachidonic Acid
  - Prostacyclin Synthase
  - Prostacyclin
  - cAMP
  - Prostacyclin Derivatives

Endothelin Pathway
- Big Endothelin
  - Endothelin-converting Enzyme
  - Endothelin-1
  - Endothelin Receptor Antagonists
    - Endothelin Receptor A
    - Endothelin Receptor B

Nitric Oxide Pathway
- Arginine
  - Nitric Oxide Synthase
  - Nitric Oxide
  - cGMP
  - Exogenous Nitric Oxide
  - Phosphodiesterase Type-5
    - Phosphodiesterase Type-5 Inhibitors
  - Riociguat

Vasodilatation and Antiproliferation
Vasoconstriction and Proliferation
Vasodilatation and Antiproliferation

Add-On Inhaled/Oral Therapy Trials

- **STEP**: Inhaled iloprost to stable bosentan
- **TRIUMPH**: Inhaled treprostinil to stable oral rx
- **COMPASS-3**: Sildenafil added to bosentan for patients who did not reach therapeutic target
- **PHIRST**: Tadalafil added to stable bosentan
- **PACES**: Sildenafil added to IV epoprostenol
Combination Trials—Cont’d

**BREATHE-2**: IV epoprostenol plus bosentan vs monotherapy in 33 patients 2:1

**COMBI**: inhaled Iloprost added to bosentan
STEP: Add-on Inhaled Iloprost to Stable Bosentan Monotherapy

N=67. Inhaled iloprost added to stable bosentan monotherapy for a mean of 17.6 to 18.8 months. 94% of patients were NYHA class III at baseline.

Inhaled Treprostinil Added to Stable Oral Therapy: 6MWD Changes at 12 Weeks

N=235 PAH patients receiving either oral sildenafil or bosentan.

Initial bosentan monotherapy; sildenafil added if clinical threshold objectives not reached at 16 weeks. 84% of patients added sildenafil at 16 weeks.
PHIRST: Tadalafil Added To Stable Bosentan Therapy Compared With Tadalafil Monotherapy

N=405, patients receiving either background bosentan or tadalafil monotherapy (treatment naïve) in PHIRST Study.

PACES: Sildenafil Added to Epoprostenol: Change from Baseline in 6-Minute Walk Distance

N=267; *P<0.0009 versus placebo (ITT population).

COMBINATION THERAPY

Positive studies include PACES, TRIUMPH, PHIRST

Negative: BREATHE-2, COMBI

Upfront Combination Therapy

- BREATHE-2 negative 6MWD and TTCW
- AMBITION and COMPASS 2 were not complete prior to current guidelines

WSPH Guideline next slides

5th WSPH Recommendations: Inadequate Clinical Response to Initial PAH Therapy

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

Inadequate Clinical Response

Consider Eligibility for Lung Transplantation

Referral for Lung Transplantation (I-C)

GUIDELINES

2013 5\textsuperscript{TH} World Symposium on PH. \textit{J Am Coll Cardiol} 2013; 62:D [December 2013 suppl].

Recommendation:

- I-A for sequential
- IIb-C for initial combo Rx

Recommendations to follow
CHEST: FC III worse on Rx

WHO FC III & disease progression despite oral therapy, initiate treatment with a parenteral prostanoid.

- IV epoprostenol to improve FC (CB)
- IV epo or IV/SQ treprostinil to increase 6MWD (CB) AND improve hemodynamics

CHEST: COMBO Treatment

- Add inhaled treprostinil to either ERA or PDE5 for increased 6MWD(2C)
- Add inhaled iloprost to either ERA or PDE5 for improved FC (CB) and delay TTCW (CB).
What’s the Latest?

Since 5th WSPH
- Macitentan
- Riociguat
- Oral treprostinil
- Combination Rx

Since CHEST
- AMBITION
- COMPASS II
- GRIPPHON
MACITENTAN

742 pts randomized to 3 groups: PCB, macitentan 3 or 10 mg daily

Background therapy in 60+%, usually PDE5I

Primary composite endpoint including death, transplant, IV therapy, or PAH worsening.

Primary endpoint

- PCB 47%  Maci3 38%  Maci10 31%

There was a reduction in hospitalization

Effect more prominent in treatment naïve patients on 10 mg daily

Time To Clinical Worsening or Death

Mean change from baseline in 6 MWD (m)

- Macitentan 10 mg: (n=242)
- Macitentan 3 mg: (n=250)
- Placebo (n=250)

61% of patient population were on background PDE-5 inhibitor therapy at study enrollment. 5% were receiving oral/inhaled prostanoids.

- Macitentan 10 mg: Hazard ratio=0.55; log rank $P<0.001$
- Macitentan 3 mg: Hazard ratio=0.70; log-rank $P=0.01$

10 mg on All-cause Hospitalization

*P=0.0378. †P=0.0005.
RIOCI GUAT

- 443 patients for Group 1 PAH
- MCRDBPCT over 12 weeks
- Primary: 6MWD improved 36 meters
- Secondary Outcomes
  - Improved: FC, BNP, TTCW, and PVR
  - SE: HA 27%, Dyspepsia 19%, Edema 17%
N=445. Double-blind, placebo-controlled Phase III trial. Placebo-corrected treatment effect = 36 m (95% CI: 20-52 m; P<0.0001). 50% of patients were on stable background PAH therapy with ERAs (43%) or prostacyclin (7%).

Oral Treprostinil In Combination With Oral ERAs or PDE-5 Inhibitors

Between Treatment Median Difference From Baseline

N=310. Double-blind, placebo-controlled multicenter study. All patients were receiving concomitant ERA or PDE5i therapy.

Selexipag

- Non-prostanoid IP receptor agonist
- Active metabolite $t_{1/2}$ 8 hours
- Phase II trial 43 pts randomized 3:1 to selexipag vs PCB demonstrated 30% reduction in PVR at 17 weeks ($p=0.0001$). All patients on background therapy

GRIPHON

Inclusion

- Adults with group 1 PAH
- PAH profile and PVR ≥ 5 Wood units
- Background therapy permitted
- Randomized 1156 patients 1:1
Primary Endpoint, Time to first event

- Death, PAH hosp, transplant, septostomy, add O2, clinical worsening

- Time to death

Goal 378 primary events
GRIPHON

Secondary Endpoints

- 6MWD, Borg dyspnea index
- Absence of worsening FC
- Camphor QOL
- Time to death
Results

Background therapy

- 20% treatment naïve
- 80% on PDE5i or ERA or Both
Results

- 39% reduction in primary events ($p<0.0001$)
- Positive effect consistent across subgroups
  - Age, Sex
  - WHO Group and FC
  - Background therapy
    - PDE5i, ERA, or Both
Results

Side Effects:

- HA, nausea, diarrhea, jaw pain

DC rate

- Selexipag 14%
- PCB 7%
AMBITION

- First PRPCT of upfront combination therapy compared to monotherapy
- Ambrisentan and tadalafil combo versus each as monotherapy
AMBITION

N = 605 in intent-to-treat

Admendmt 2 to reduce mixed cause PH

Next 500 classified as Primary Analysis Set (PAH)
## Forest Plot of TTCF

### AMBITION Study – Ambrisentan-Tadalafil Initial Combination

### Subgroup

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Combination Therapy</th>
<th>Pooled Monotherapy</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Events</td>
<td>N</td>
</tr>
<tr>
<td>IPAH/HPAH</td>
<td>134</td>
<td>25 (19%)</td>
<td>145</td>
</tr>
<tr>
<td>APAH</td>
<td>119</td>
<td>21 (18%)</td>
<td>102</td>
</tr>
<tr>
<td>WHO FC II</td>
<td>76</td>
<td>4 (5%)</td>
<td>79</td>
</tr>
<tr>
<td>WHO FC III</td>
<td>177</td>
<td>42 (24%)</td>
<td>168</td>
</tr>
<tr>
<td>Age&lt;57years</td>
<td>124</td>
<td>13 (10%)</td>
<td>120</td>
</tr>
<tr>
<td>Age&gt;=57years</td>
<td>129</td>
<td>33 (26%)</td>
<td>127</td>
</tr>
<tr>
<td>BL 6MWD &lt;363.7m</td>
<td>129</td>
<td>35 (27%)</td>
<td>121</td>
</tr>
<tr>
<td>BL 6MWD&gt;=363.7m</td>
<td>124</td>
<td>11 (9%)</td>
<td>126</td>
</tr>
<tr>
<td>North America</td>
<td>116</td>
<td>22 (19%)</td>
<td>112</td>
</tr>
<tr>
<td>Rest of world</td>
<td>137</td>
<td>24 (18%)</td>
<td>135</td>
</tr>
<tr>
<td>Female</td>
<td>188</td>
<td>32 (17%)</td>
<td>200</td>
</tr>
<tr>
<td>Male</td>
<td>65</td>
<td>14 (22%)</td>
<td>47</td>
</tr>
</tbody>
</table>

COMPASS II

- Bosentan or PCB added sequentially to sildenafil or tadalafil
- Negative Study
  - HR 0.831  p value 0.25
  - Powered for 43% reduction
COMPASS II

8 year study

Consent withdrawal:

- Bos + PDE5i 20%
- PCB + PDE5i 15%

Exploratory 2º endpoints BNP & 6MWD
SUBSEQUENT THERAPY
MCF* Guideline

- **Mild PH**—Single drug, then sequential rx

- **Moderate PAH insufficiently severe for infusion prostanoid**—Upfront combo rx
  - ERA/PDE5i/riociguat plus oral/inhaled prostanoid

- **Severe**: Infusion prostanoid with sequential or upfront oral therapy
Treatment Goals

- Reduce symptom burden
- Avoid hospitalization
- Minimized treatment burden
- Improve survival
GOALS

Single-center goal directed study

- FC ≤ II
- BNP normal
- 6MWD >380 to 440 m
- Normalize RV function
- Exercise: VO2 > 15 mL/kg/min; VE/VCO2 < 45

Characterization of First Hospitalization Following PAH Diagnosis

REVEAL population
(N=3515; data download February 4, 2013)

Newly diagnosed
(n=960)

Not newly diagnosed
(n=2555)

Newly diagnosed; PCWP ≤15 mm Hg (n=865)

Not meeting hemodynamics criteria (n=95)

At risk for on-study hospitalizations (n=862)

Died in hospital at enrollment (n=3)

≥1 hospitalization admission post-enrollment (n=490, 56.8%)

PAH-related hospitalization (n=257, 52.4%)

PAH-unrelated hospitalization (n=214, 43.7%)

Indeterminate hospitalization (n=19, 3.9%)

No hospitalization admissions post-enrollment (n=372, 43.2%)

## PAH-Related Admits (n=257)

<table>
<thead>
<tr>
<th>DISCHARGE DIAGNOSIS</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td>81 (32)</td>
</tr>
<tr>
<td>Placement or removal of CVC</td>
<td>63 (25)</td>
</tr>
<tr>
<td>Initial CVC line insertion</td>
<td>30 (12)</td>
</tr>
<tr>
<td>Escalation in PAH treatment</td>
<td>23 (9)</td>
</tr>
<tr>
<td>Catheter infection</td>
<td>21 (8)</td>
</tr>
<tr>
<td>Syncope</td>
<td>12 (5)</td>
</tr>
<tr>
<td>Conversion of CVC line</td>
<td>7 (3)</td>
</tr>
<tr>
<td>PH medication-related adverse event</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Transplant</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Right heart catheterization</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Atrial septostomy</td>
<td>0 (0)</td>
</tr>
<tr>
<td>PAH-related but uncharacterized</td>
<td>42 (16)</td>
</tr>
</tbody>
</table>

## NonPAH-Related Admits (n=214)

<table>
<thead>
<tr>
<th>DISCHARGE DIAGNOSIS</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAH-unrelated infections (not pneumonia)</td>
<td>38 (21)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>34 (16)</td>
</tr>
<tr>
<td>Surgery/procedure</td>
<td>24 (11)</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>19 (9)</td>
</tr>
<tr>
<td>Gastrointestinal disorder (not hemorrhage or infection)</td>
<td>12 (6)</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>11 (5)</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>11 (5)</td>
</tr>
<tr>
<td>Anemia</td>
<td>10 (5)</td>
</tr>
<tr>
<td>Non-cardiac chest pain</td>
<td>7 (3)</td>
</tr>
<tr>
<td>Respiratory disorder (not pneumonia or respiratory failure)</td>
<td>7 (3)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>7 (3)</td>
</tr>
<tr>
<td>Trauma/fracture</td>
<td>7 (3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DISCHARGE DIAGNOSIS</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrolyte abnormality</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Neurologic disorder (not stroke)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Acute coronary syndrome†</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Hepatic failure</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Pain (not chest pain)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Psychiatric disorder</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Other</td>
<td>15 (7)</td>
</tr>
</tbody>
</table>

Survival

PAH=pulmonary arterial hypertension.

SEVERITY

REVEAL Risk Score (Benza R. Chest 2012)

- Validated in REVEAL
- Application as prospective tool to influence treatment decisions unclear


GUIDELINE REFERENCES


ADDITIONAL REFERENCES
