Pulmonary Hypertension Guidelines
5th World Symposium

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Professor of Medicine
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Disclosures

Industry-sponsored, multi-center clinical studies in patients with pulmonary hypertension

Actelion Pharmaceuticals, Inc; Gilead Sciences; United Therapeutics
Objectives

- Provide risk factor assessment for pulmonary hypertension (PH)
- Utilize guideline-based recommendations for accurate and timely diagnosis
- Employ guideline algorithm for treatment selection for PH patients
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

Subgroups for Group 1 PAH

- Idiopathic PAH (1.1)
- Heritable (1.2)
- PAH Related to:
  - Drugs and Toxins (1.3)
  - Collagen vascular disease (1.4.1)
  - HIV (1.4.2)
  - Portal hypertension (1.4.3)
  - Congenital heart disease (1.4.4)

Group 2 PVH

- LV Systolic Dysfunction (2.1)
- LV Diastolic Dysfunction (2.2): aka HFpEF
- Valvular Disease (2.3)
- Congenital/Acquired outflow tract obstruction or cardiomyopathy (2.4)
Group 3

- COPD (3.1)
- ILD (3.2)
- Mixed OLD and ILD (3.3)
- SDB (3.4)
- Alveolar Hypoventilation (3.5)
Other Classification Updates

- Chronic Hemolytic Anemias moved “back” to group 5
  - Lower prevalence than thought
  - Often Gp 2 or high CO HD profile
- PPHN added as Group 1”
- Drug and Toxins: e.g. benfluorex
- CHD clarified for clinicians
New gene locus KCNK3, alters K channel

Similarities with neoplasia

Metabolic derangements

Inflammation
RV is KEY

PAH

RV Stress

Adaptive Remodeling
Survival

Maladaptation
Arrhythmias RV Failure
DIAGNOSIS

Requires RHC

Definition:

- MPAP ≥ 25 mmHg
- PAWP ≤ 15 mmHg
- PVR > 3 Wood units

RISK ASSESSMENT

Risk factors identified in history and physical may lead to ECHO then RHC

ALTERNATIVELY

Diagnosis may be made by RHC, then proper diagnostic group explored
Badesch D, et al. *Chest* 2010; 137:376-387. n = 2,525
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**

RISK GROUPS

- Heritable
- Drug use such as anorexigens
- CVD, particularly scleroderma
- HIV/AIDS
- Liver disease with portal HTN
- CHD
Genetics

- **BMPR2**
  - 15-20% IPAH patients are carriers
  - 25% patients develop PAH
  - Women 3:1

- **New Gene**
  - KCNK3 or TASK-1
  - Chromosome 18
  - Alters K channel
  - Risk of PAH doubled
Positive ANA

AUC 0.91, LR 48 (p<0.001), PPV 91%
HIV Screening at MCF

BOTTOM LINE:

Consider pre-test probability
Order HIV **ONLY** if risk factor by history
# Thyroid Disease and PH

<table>
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<th>Group of patients</th>
<th>N</th>
<th>Women (%)</th>
<th>Thyroid disease (%)</th>
<th>Men with thyroid disease (% of males)</th>
<th>Women with thyroid disease (% of females)</th>
<th>Estimated OR (95% CI)</th>
<th>P value*</th>
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<td>36 (25)</td>
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Thyroid Disease and PH

**BOTTOM LINE:**

Control 15%

PH 24% (OR = 2)

IPAH was 30% (OR 2.5)
Mean Pulmonary Artery Pressure

Submaximal Exercise

ETCO2 vs mPAP

DIAGNOSIS

Requires RHC

Definition:

- MPAP ≥ 25 mmHg
- PAWP ≤ 15 mmHg
- PVR > 3 Wood units

TREATMENT

- AHA/ACC Guidelines JACC 2009
- WSPH Recommendations JACC 2013
INITIAL THERAPY

Supervised exercise training (I-A)
Psycho-social support (I-C)
Avoid strenuous physical activity (I-C)
Avoid pregnancy (I-C)
Influenza and pneumococcal immunization (I-C)

General measures and supportive therapy

Expert Referral (I-C)

Acute vasoreactivity test
(I-C for iPAH) (IIb-C for APAH)

Oral anticoagulants:
IPAH, heritable PAH and PAH
due to anorexigen (IIa-C)
APAHA (IIb-C)
Diuretics (I-C)
Oxygen (I-C)
Digoxin (IIb-C)

VASOREACTIVE

WHO-FC I-III
CCB (I-C)
Continue CCB

Sustained response (WHO-FC I-II)

NON VASOREACTIVE

Targets for Current or Emerging Therapies in PAH

**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
      - Exogenous Nitric Oxide
        - cGMP
          - Phosphodiesterase Type-5
            - Phosphodiesterase Type-5 Inhibitors

**Vasodilatation and Antiproliferation**

**Vasoconstriction and Proliferation**

## INITIAL THERAPY WITH PAH APPROVED DRUGS

**YELLOW:** Morbidity and mortality as primary end-point in randomized controlled study or reduction in all-cause mortality (prospectively defined)

*Level of evidence is based on the WHO-FC of the majority of the patients of the studies.

†Approved only: by the FDA (macitentan, riociguat, treprostinil inhaled); in New Zealand (iloprost i.v); in Japan and S.Korea (beraprost).

‡ Positive opinion for approval of the CHMP of EMA

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<td>C</td>
<td>Initial Combination Therapy</td>
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NEW DRUGS

- Macitentan
  - Tissue-specific ERA
  - Group 1 PAH

- Riociguat
  - Guanylate cyclase stimulator
  - Group 1 PAH and CTEPH
MACITENTAN

- 742 pts randomized to 3 groups: PCB, macitentan 3 or 10 mg daily
- Background therapy in 2/3, usually PDE5I
- Primary composite endpoint including death, transplant, IV therapy, or PAH worsening.

MACITENTAN

- Primary endpoint
  - PCB 46%  Maci3 38%  Maci10 31%
- There was a reduction in hospitalization
- Effect more prominent in treatment naïve patients on 10 mg daily

RIOCIGUAT

- Phase 3 studies in Group 1 PAH and CTEPH
- Soluble guanylate cyclase stimulator
- Oral administration in doses up to 2.5 mg TID
- Results in July 25, 2013 *N Engl J Med*

RIOCI GUAT

- 261 patients with inoperable CTEPH
- MCRDBPCT over 16 weeks
- Primary: 6MWD improved 46 meters
- Secondary Outcomes
  - Improved: WHO FC, BNP, PVR
  - Not improved: Time to clinical worsening
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%
BERAPROST

Oral prostacyclin manufactured by Toray a Tokyo-based pharmaceutical

10 year data presented at ATS

75% survival

MCF submitted application to IRB to participate in a MC prospective trial in US
**MONOTHERAPY**

**Modified NYHA FC II-III**
- Both macitentan and riociguat added with I-A rating
- Epoprostenol IV also added to FC III with I-A rating
- Beraprost given IIb-B rating for FC III

**Modified NYHA FC IV**
- Epoprostenol remains only agent with I-B rating
- Macentantan added to multiple other agents with IIa-C rating
SUBSEQUENT THERAPY

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

INADEQUATE CLINICAL RESPONSE

INADEQUATE CLINICAL RESPONSE on MAXIMAL THERAPY

BAS (IIa-C)

Referral for LUNG TRANSPLANTATION (I-C)

CONSIDER ELIGIBILITY FOR LUNG TRANSPLANTATION
COMBINATION THERAPY

Positive studies include PACES, TRIUMPH, PHIRST

Negative: BREATHE-2, COMBI

Upfront Combination Therapy

- BREATHE-2 negative 6MWD and TTCW
- AMBITION results pending

WSPH: I-A for sequential; IIb-C for initial combo Rx
Body Habitus and PH

- Background study at Mayo 207 PAH pts vs 965 controls yielded no difference in BMI > 30 (Williams Open Obesity J 2010)
- REVEAL looked at 2141 PAH patients compared to NHANES controls

William WH et al Open Obesity J 2010;
### REVEAL

<table>
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<th>Entire Group</th>
<th>Control</th>
<th>IPAH</th>
<th>Control</th>
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<tr>
<td><strong>BMI</strong></td>
<td>28.4</td>
<td>28.2</td>
<td>29.1</td>
<td>28.1</td>
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<tr>
<td><strong>P value</strong></td>
<td>NS</td>
<td>NS</td>
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<tr>
<td><strong>OBESE (%)</strong></td>
<td>36.5</td>
<td>33</td>
<td>40</td>
<td>33</td>
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<td><strong>P value</strong></td>
<td>0.004</td>
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SEVERITY

- Change from “WHO Functional Class” to “Modified NYHA Functional Class”

- Benza Risk Score (Chest 2012)
  - Validated in REVEAL
  - Application as prospective tool to influence treatment decisions unclear
GOALS

- Single-center goal directed study but data overall lacking (Hoeper ERJ 2005)
- Committee recommendations, more study needed
  - FC ≤ II
  - BNP normal
  - 6MWD >380 to 440 m
  - Normalize RV function
  - Exercise: VO2 > 15 mL/kg/min; VE/VCO2 < 45
CTEPH

- Surgical disease--PTEA
- Pulmonary angioplasty receiving more attention with a couple of recent studies with benefit over short term

Medical Therapy (37% non-operable in EU)
- Pre-PTEA treatment discouraged
- Bosentan: Decreased PVR 24%, No change 6MWD
- Riociguat: Increased 6MWD 46 m, No change TTCW
HFpEF

- Limited data
- Abandon “Out-of-Proportion” label
- Classification: Committee recommendations
  - PAWP > 15, (PAPd – PAWP) < 7 = Post-cap PVH
  - PAWP > 15, (PAPd – PAWP) > 7 = Mixed disease
- Treatment
  - Lots of negative studies including RELAX
  - Ongoing RCT
  - WSPH did not recommend treatment except in trial
GROUP 3

- COPD and ILD
- Consider PAH as potentially limiting if MPAP > 35
- CPEX may distinguish ventilatory vs vascular deadspace limitation in COPD (Boerrighter Chest 12)
- Failed studies
  - COPD: Sildenafil (Blanco), Bosentan (Stolz 2008)
  - ILD: Sildenafil (STEP-IPF), Bosentan (BUILD 1 and 3), Ambrisentan (ARTEMIS)
- No treatment recommended except in clinical trial
GUIDELINES


Discussion and Questions
New genes put into Group 1: KCNK3, SMAD8, CAV
Move Hemolytic Anemia from Group 1 to Group 5
Expand Group 1 primes
  Group 1’ PVOD, PCH
  Group 1” Persistent PH Newborn
Additional Group 2 subgroup to cover unrepaired CHD and HCOM
Additional Group 3 subgroup to cover developmental lung disease
SSCD
- Prevalence 5 – 10% (not 30% as in NEJM ECHO)
- 50% have elevated PAWP on RHC; MPAP 28
- Sildenafil study terminated due to increased crisis
- Bosentan trial stopped poor recruitment

Drug and Toxin
- Benfluorex metabolized to norfenfluramine
- Other agents may be have “likelihood” designation changed
SUBGROUPS

DEFINITE: Benfluorex and SSRI during pregnancy

LIKELY: Dasatinib

POSSIBLE: Amphetamines and interferons
Mayo Clinic Florida PH Center

n = 1,050: Age 64 ± 14; 64% women
REVEAL Registry

The Registry to Evaluate Early And Long-term PAH Disease Management (REVEAL)

Multicenter, observational, U.S.-based study of patients diagnosed with GROUP 1 PAH.

54 sites in the United States.

Demographic data gathered at the time of enrollment.

REVEAL DEMOGRAPHICS

N = 2,525

Women 80%
Mean age 53 years

RACE

73% Caucasian
12% AA, 9% Hispanic, 3% Asian

### REVEAL Preliminary Analysis
(n = 2,967)

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<tr>
<th>Symptoms</th>
<th>Percentage</th>
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<td>Dyspnea</td>
<td>83%</td>
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<tr>
<td>Fatigue</td>
<td>27%</td>
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<td>Chest pain or LE edema</td>
<td>20%</td>
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<tr>
<td>Syncope/near syncope</td>
<td>17%</td>
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<td>Cough</td>
<td>14%</td>
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Modified NYHA Functional Class

I  No limitation
II  Mild limitation: Sx with ordinary activity
III  Moderate limitation: Sx with low level activity
IV  Severe limitation: Sx at rest, Syncope

Sx = symptoms: dyspnea, chest pain, near-syncope or syncope
REVEAL DEMOGRAPHICS

N = 2,525

- Functional Class I: 8%
- Functional Class II: 37%
- Functional Class III: 50%
- Functional Class IV: 5%

Body Habitus and PH
TREATMENT

- CP Rehab increases VO2

New Therapy

- Drugs
  - Beraprost
  - Macitentan
  - Riociguat

- Recommendation by subcommittee
RELAX TRIAL

- Sildenafil 113 pt vs 103 PCB
- 20 mg tid for 12 wks, then 60 tid for 12
- No difference in:
  - $O_2$ consumption
  - 6MWD
GRADING

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