MAYO CLINIC

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

Simmoneau G. J Am Coll Cardiol 2013;62:D34-41.

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)

Simonneau G, et al. *J Am Coll Cardiol*. 2013; 62:D34-41

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)

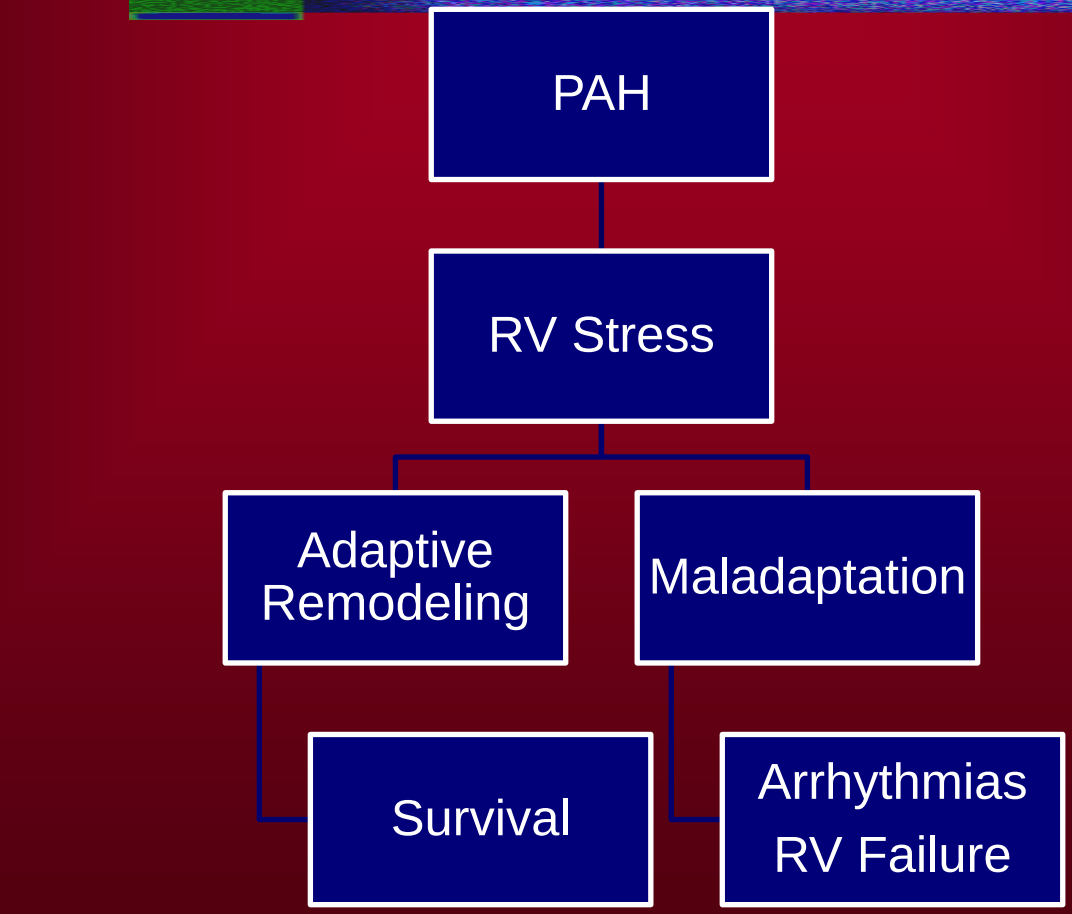
Other Classification Updates

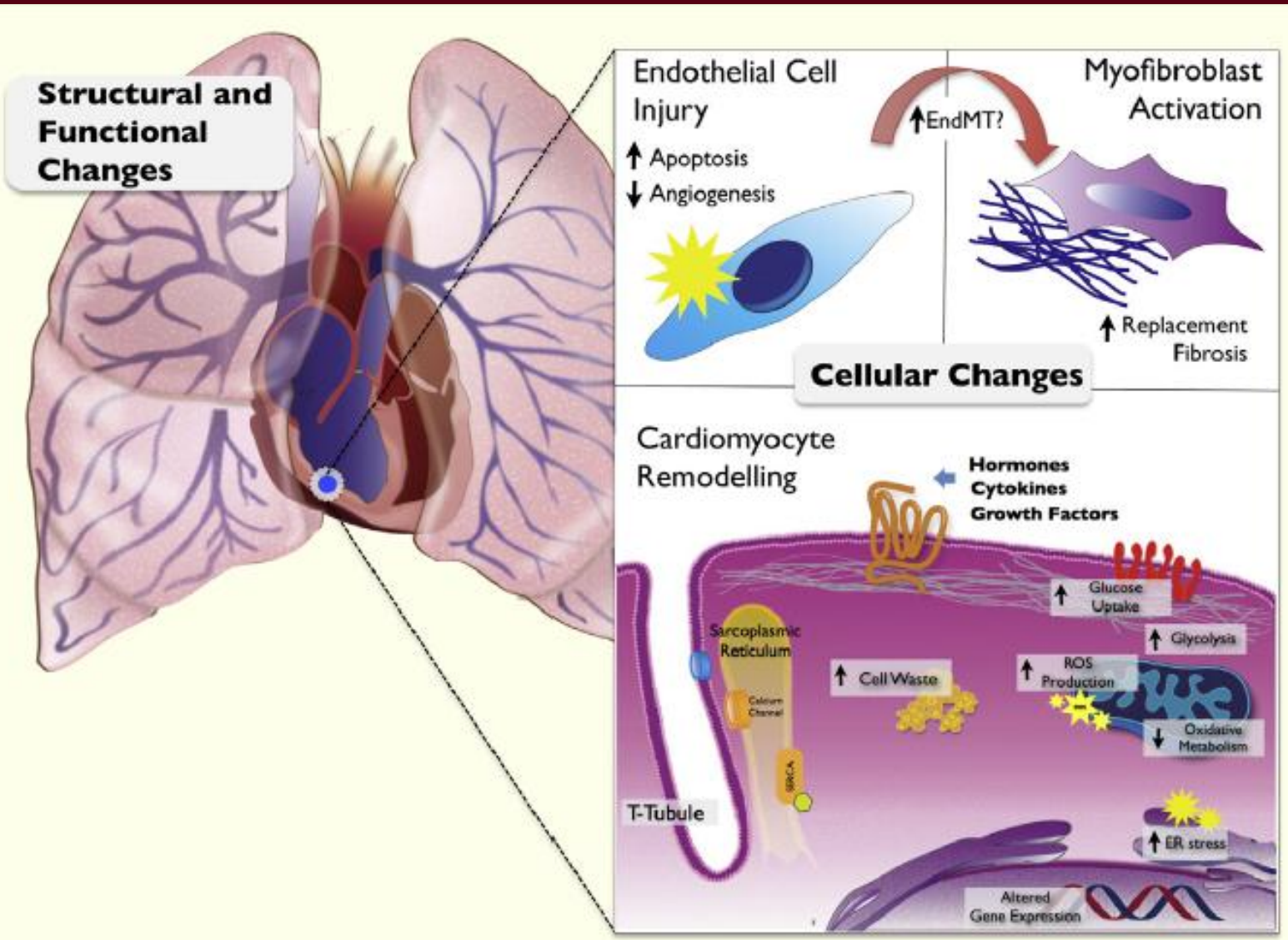
- Chronic Hemolytic Anemias moved "back" to group 5
  - Lower prevalence than thought
  - Often Gp 2 or high CO HD profile
- PPHN added as Group 1"
- Drug and Toxins: e.g. benfluorex
- CHD clarified for clinicians

PATHOBIOLOGY

- New gene locus KCNK3, alters K channel
- Similarities with neoplasia
- Metabolic derangements
- Inflammation

RV is KEY


PAH
RV Stress
Adaptive Remodeling
Maladaptation
Survival
Arrhythmias RV Failure



Vonk-Noordegraaf JACC 2013; 62:D26

DIAGNOSIS

- Requires RHC
- Definition:
  - MPAP ≥ 25 mmHg
  - PAWP ≤ 15 mmHg
  - PVR > 3 Wood units

Hoeper MM et al. Definitions and diagnosis PH. JACC 2013; 62:D42-50.

RISK ASSESSMENT

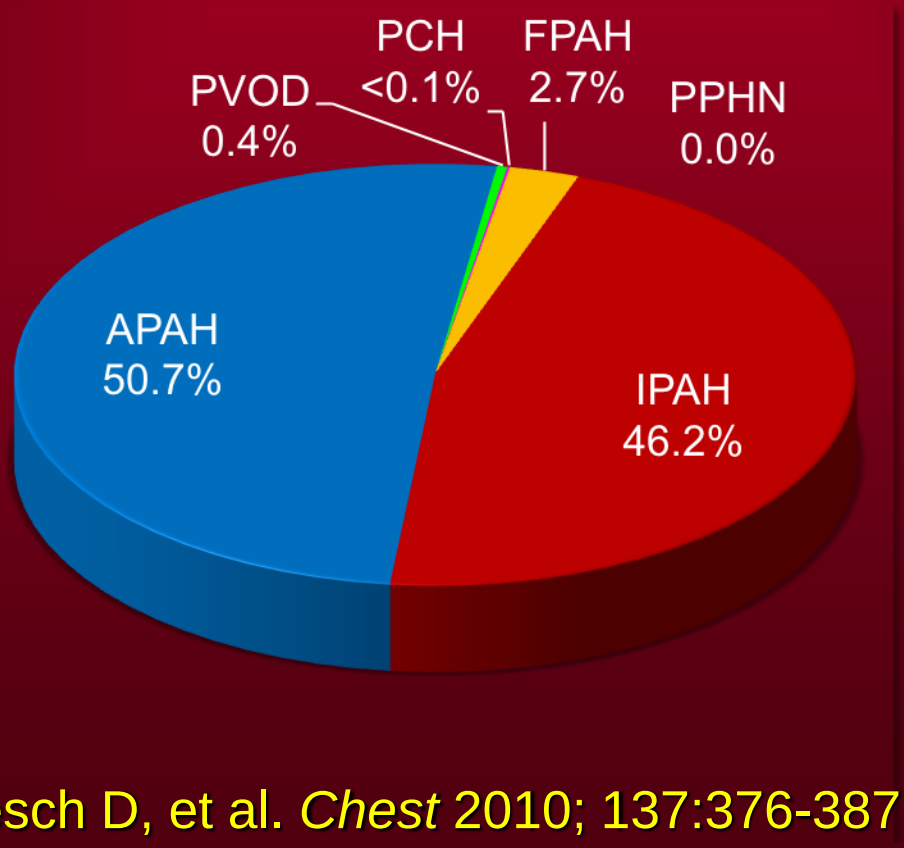
- Risk factors identified in history and physical may lead to ECHO then RHC

ALTERNATIVELY

- Diagnosis may be made by RHC, then proper diagnostic group explored

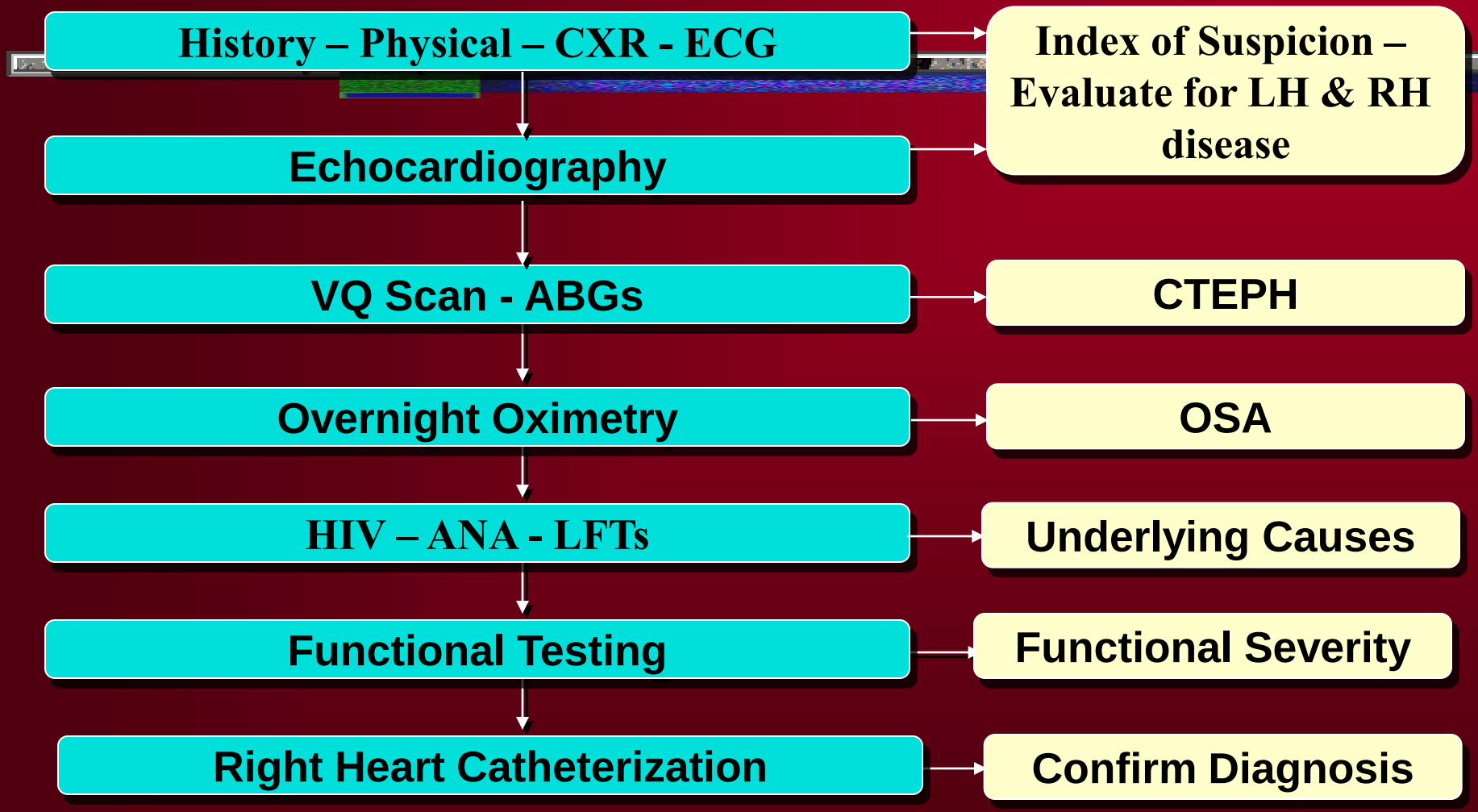
WHO Diagnostic Group 1

REVEAL



Badesch D, et al. *Chest* 2010; 137:376-387. n = 2,525

Diagnosis and Group Classification



McLaughlin VV, et al. *Circulation.* 2009;119(16):2250-2294

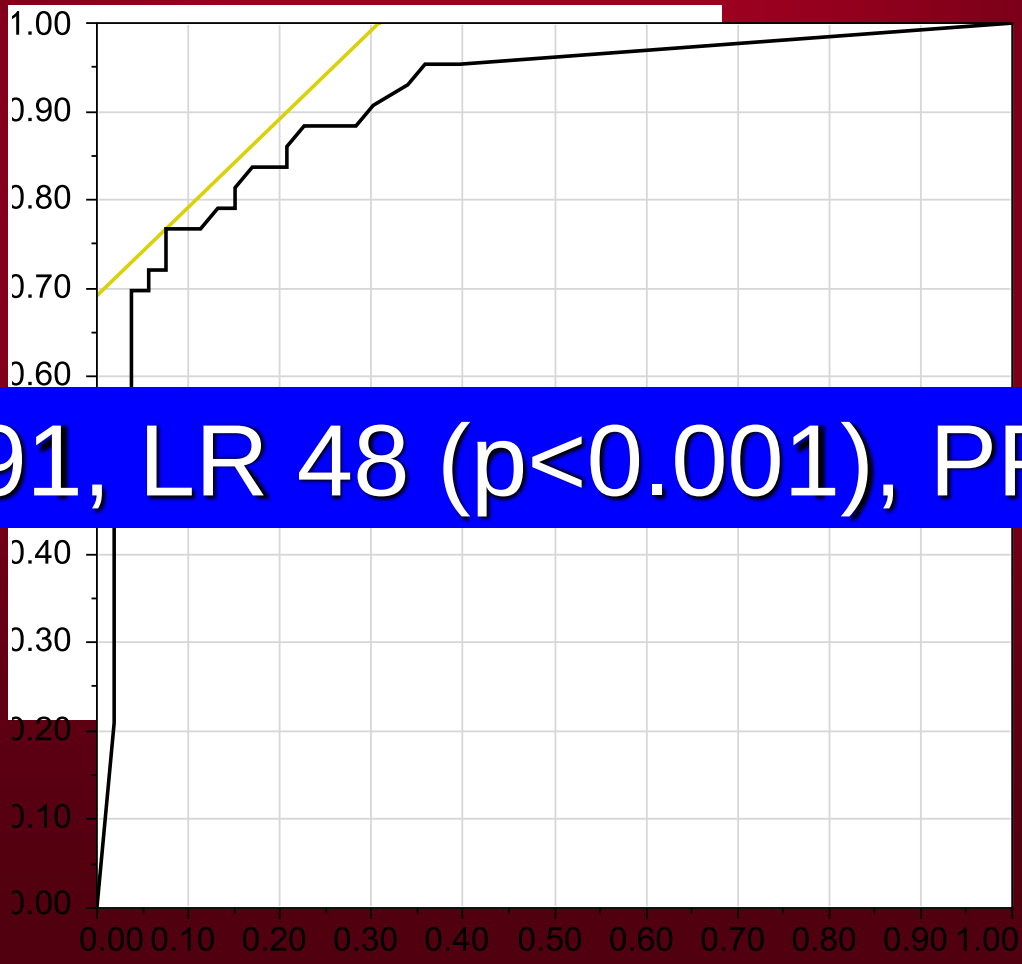
RISK GROUPS

- 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

Group of patients	N	Women (%)	Thyroid disease (%)	Men with thyroid disease (% of males)	Women with thyroid disease (% of females)	Estimated OR (95% CI)	P value*
Controls	698	453 (65)	107 (15)	13 (5)	94 (21)	1.00 (baseline)	…
All PH patients	356	230 (65)	85 (24)	14 (11)	71 (31)	2.00 (1.43-2.80)	<.001
WHO diagnostic group†							
1	196	141 (72)	48 (24)	6 (11)	42 (30)	2.10 (1.38-3.18)	<.001
1, with RHC	142	99 (70)	36 (25)	4 (9)	32 (32)	2.53 (1.55-4.08)	<.001
1, IPAH	91	69 (76)	27 (30)	2 (9)	25 (36)	2.50 (1.46-4.21)	<.001
1, associated groups	105	72 (69)	21 (20)	4 (12)	17 (24)	1.79 (1.00-3.11)	.04
2	53	34 (64)	20 (38)	5 (26)	15 (44)		
3	84	41 (49)	12 (14)	9 (21)	3 (7)	1.85 (1.18-2.88)	.007
4	23	14 (61)	5 (21)	5 (55)	0 (0)		

Thyroid Disease and PH

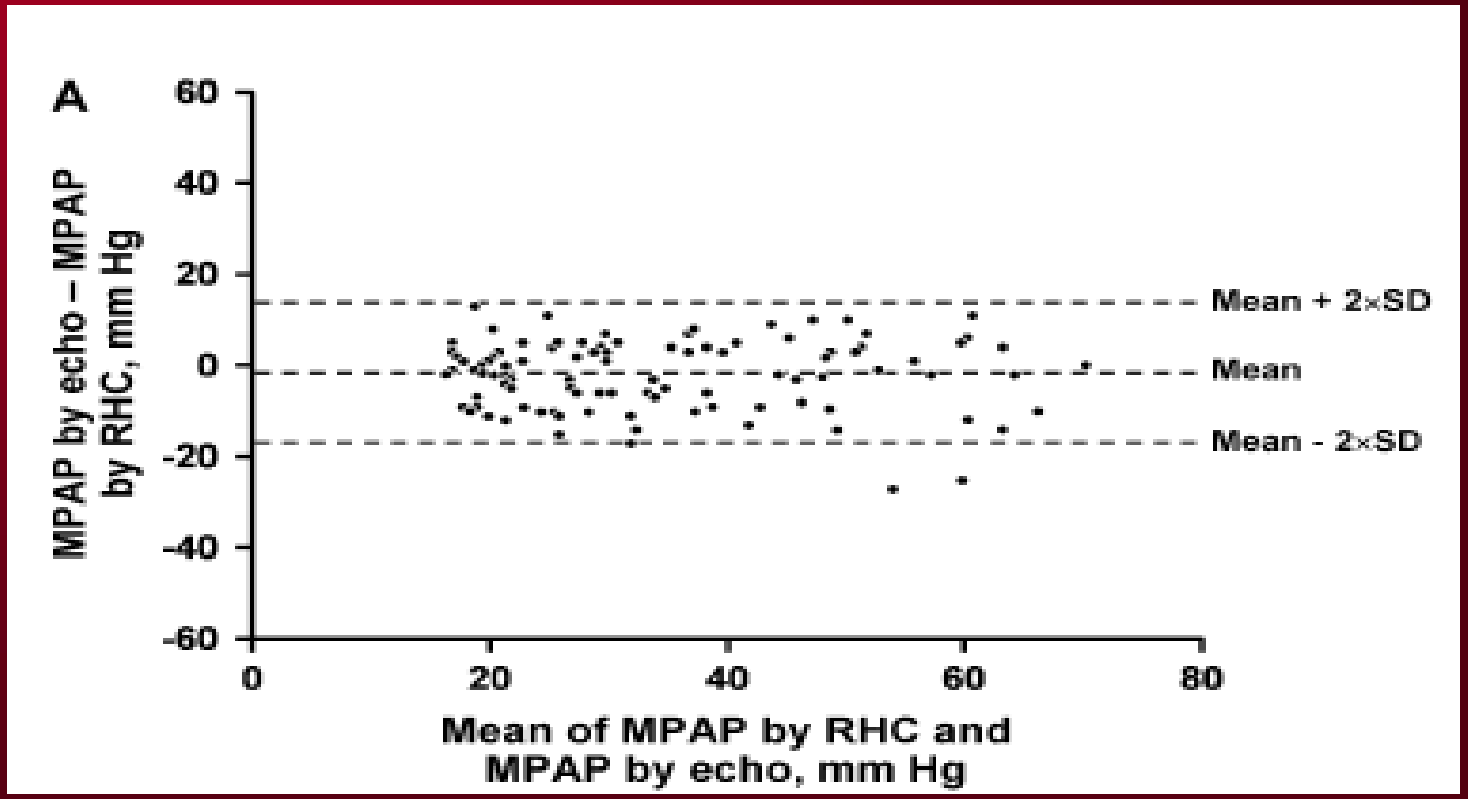
BOTTOM LINE:

Control 15%

PH 24% (OR = 2)

IPAH was 30% (OR 2.5)

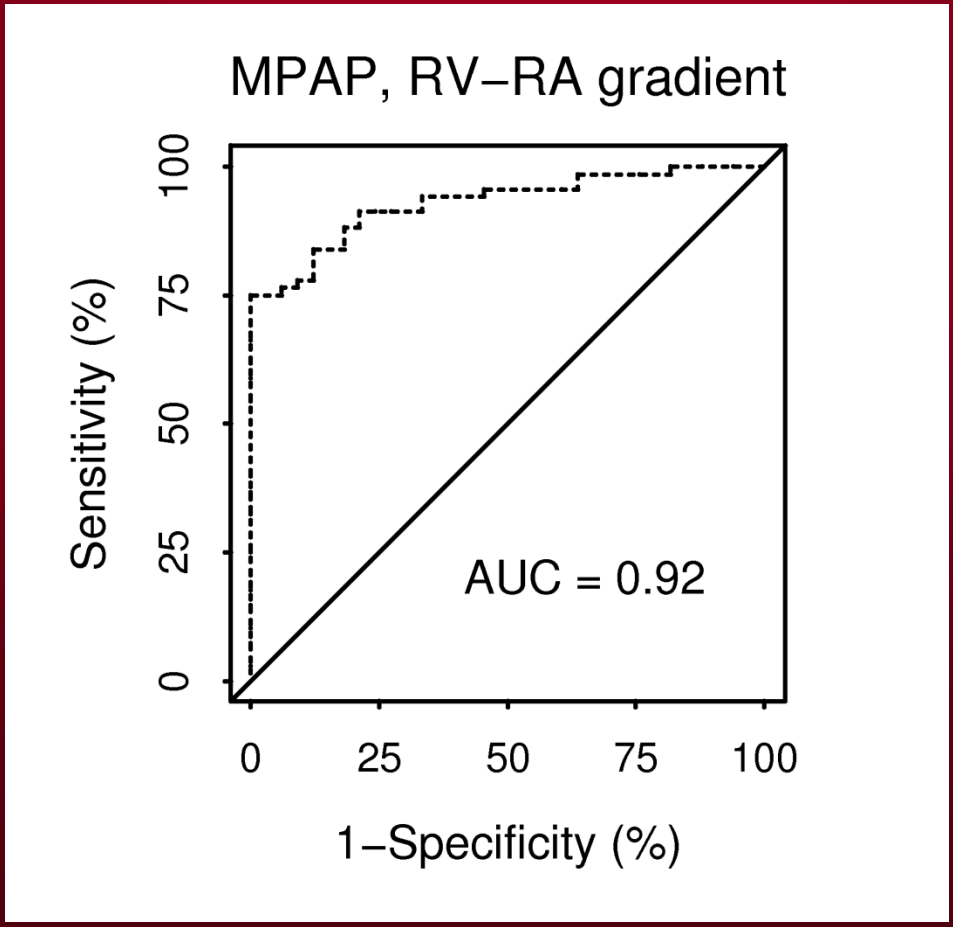
Mean Pulmonary Artery Pressure



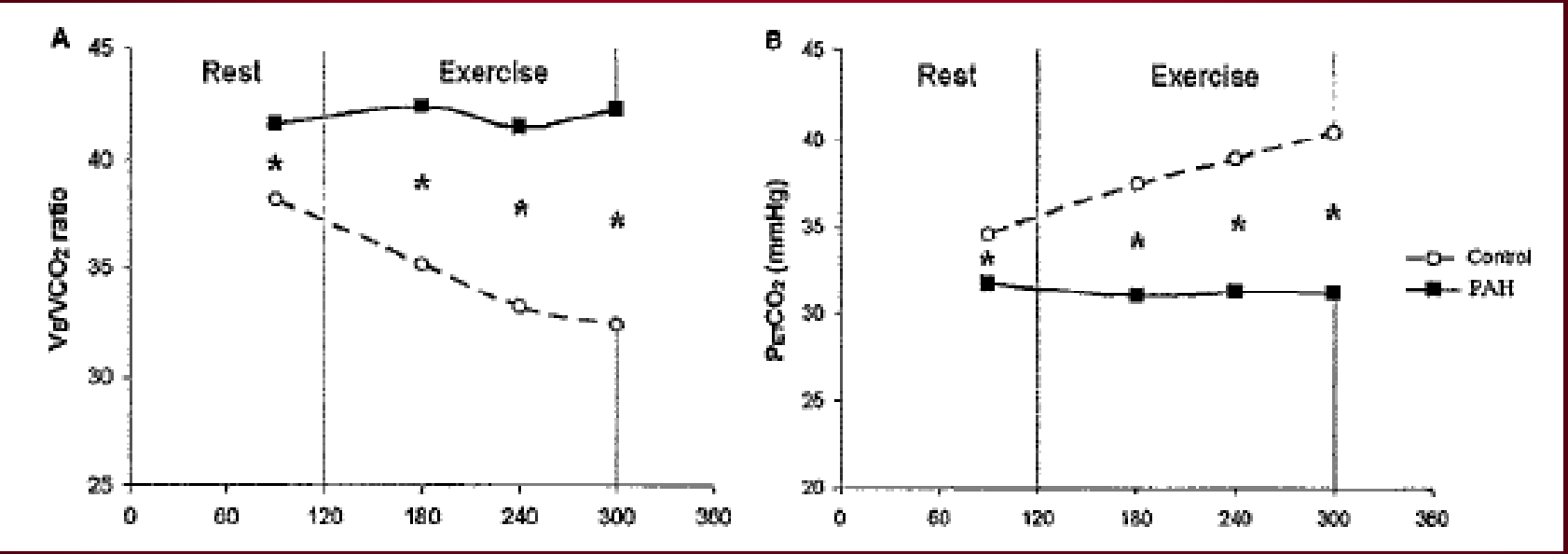
Aduen JF …Burger CD. JASE 2009; 22:814-19.

Mean Pulmonary Artery Pressure

Aduen J et al. JASE 2009; 22:814-19

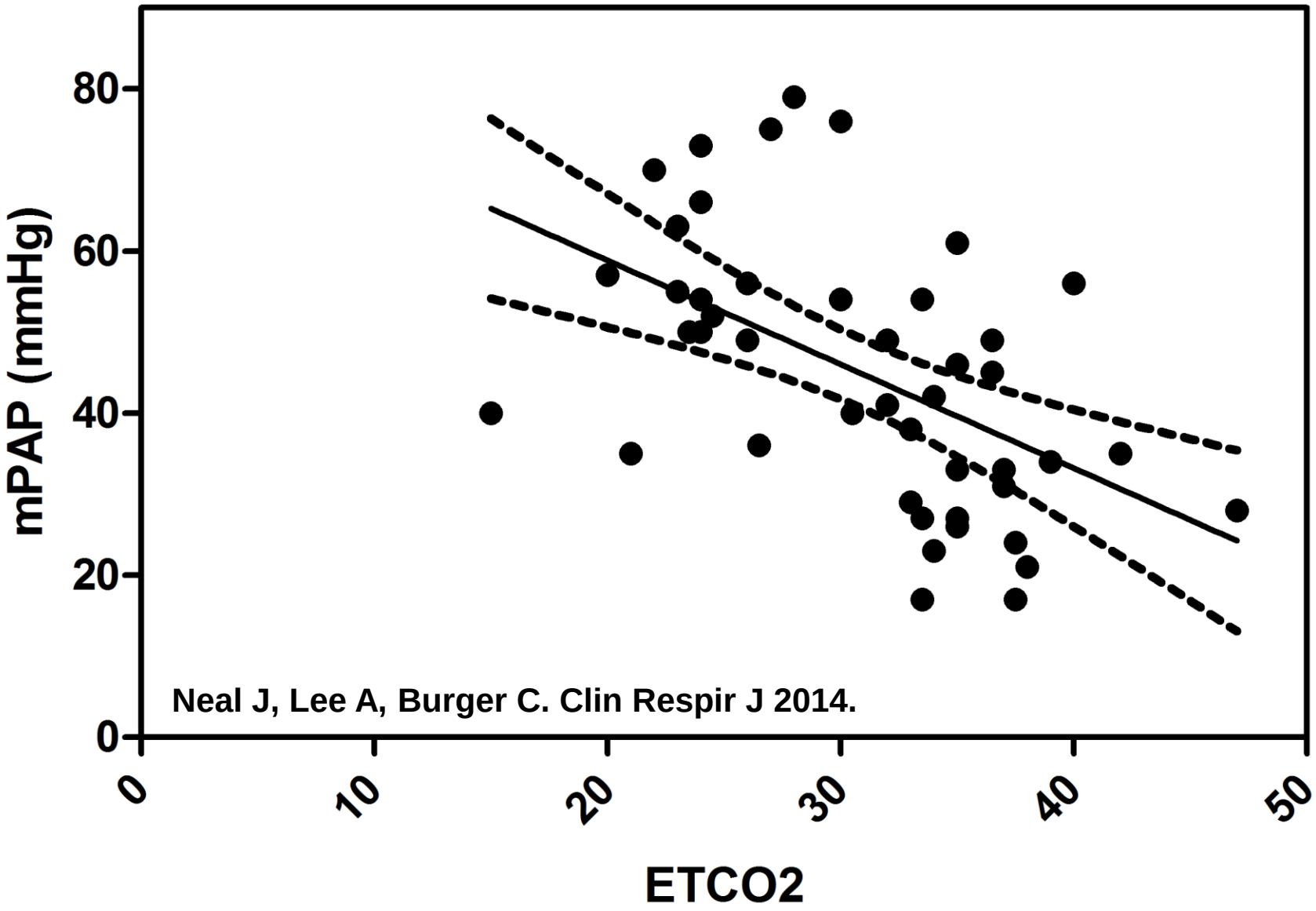


Submaximal Exercise



Woods PR et al. J Heart Lung Transplant 2011;30:1133-42

ETCO2 vs mPAP



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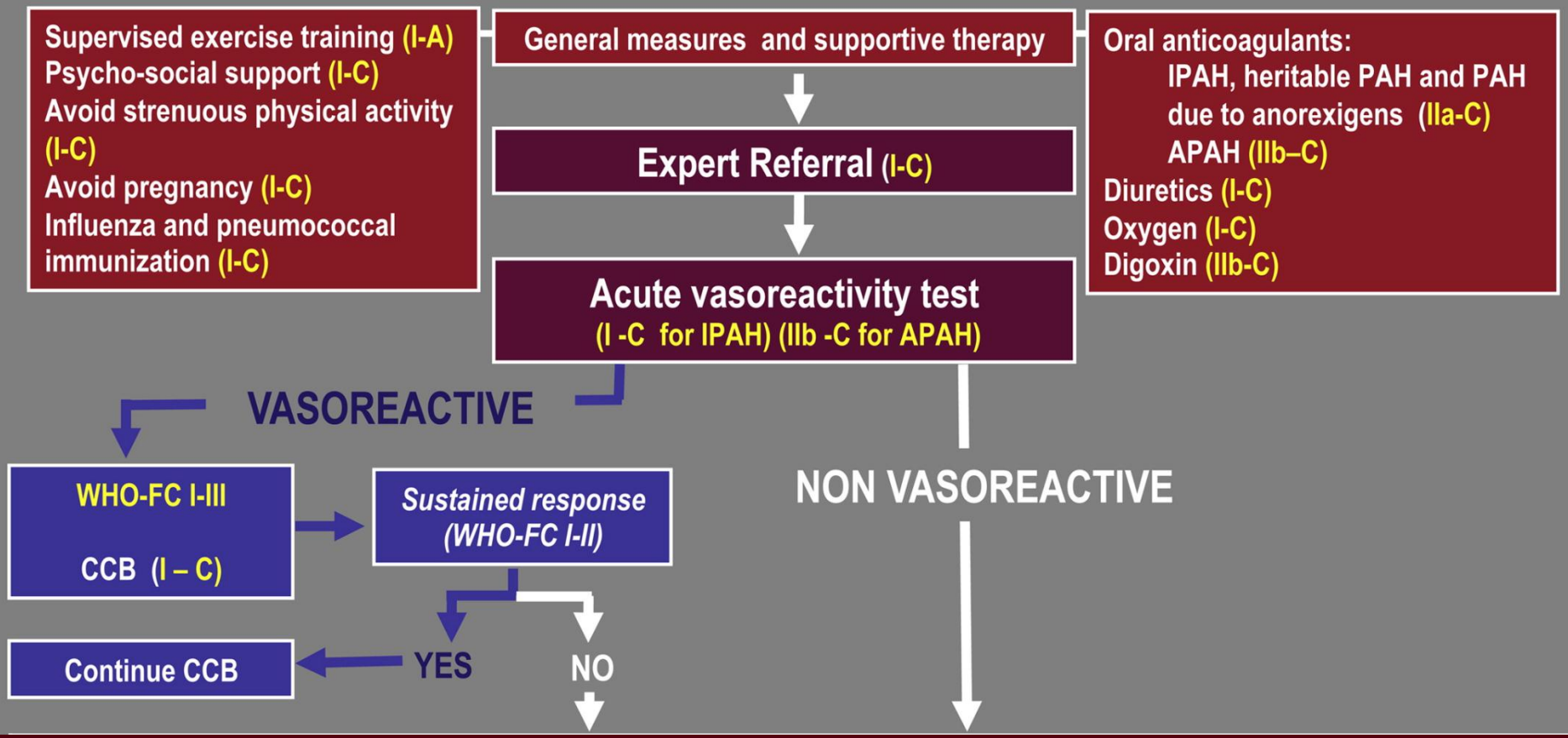
TREATMENT

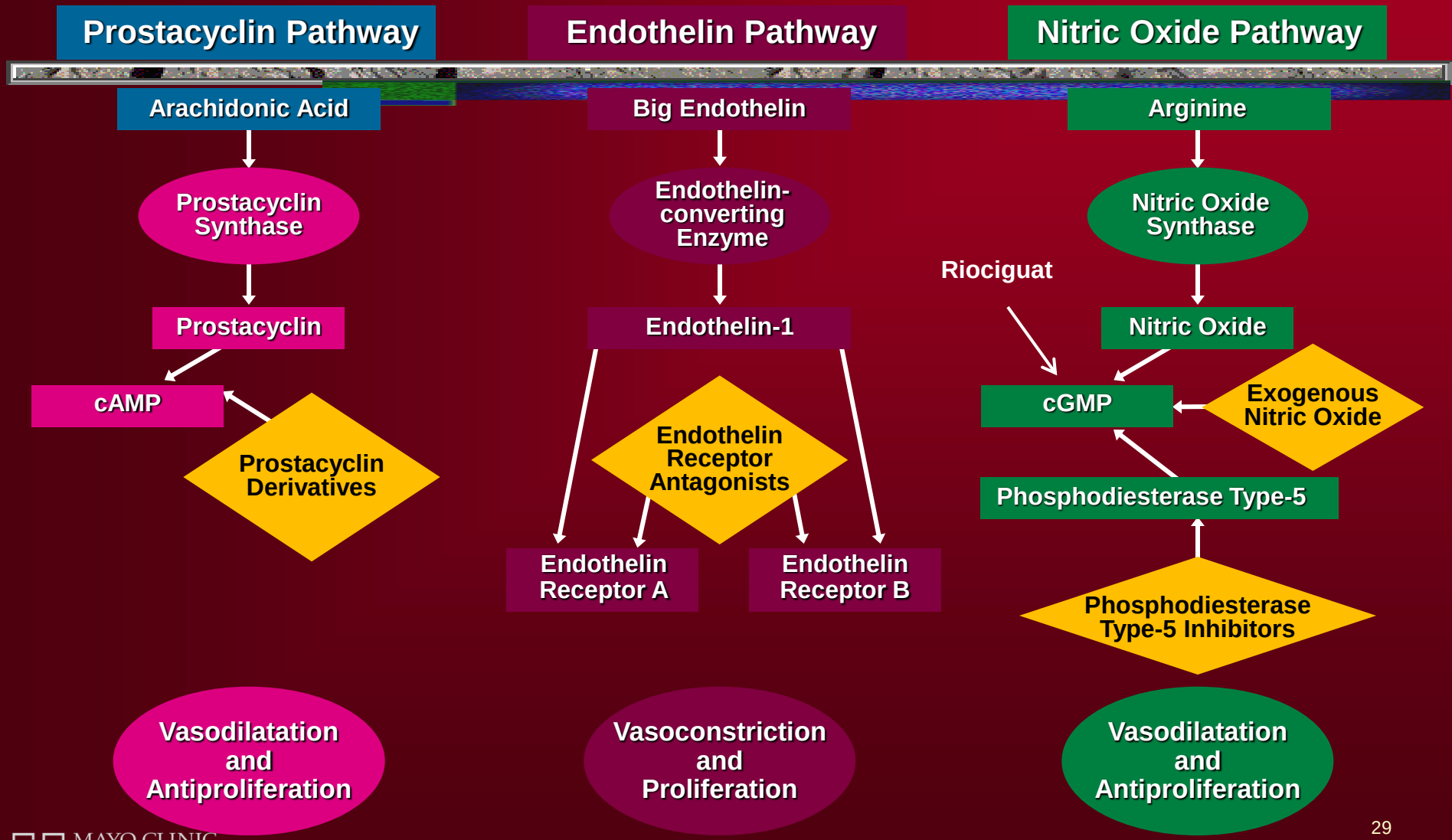
- AHA/ACC Guidelines JACC 2009
- WSPH Recommendations JACC 2013

INITIAL THERAPY



Galie N et al. Updated Treatment Algorithm of Pulmonary Arterial Hypertension. J Am Coll Cardiol 2013; 62:D60-72.

Targets for Current or Emerging Therapies in PAH



Humbert M et al. *N Engl J Med.* 2004;351:1425-1436.

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

Recommendation	Evidence*	WHO-FC II	WHO-FC III	WHO-FC IV
I	A or B	Ambrisentan Bosentan Macitentan†‡ Riociguat† Sildenafil Tadalafil	Ambrisentan Bosentan Epoprostenol i.v. Iloprost inhaled Macitentan†‡ Riociguat† Sildenafil Tadalafil Treprostinil s.c., inhaled†	Epoprostenol i.v.
IIa	C		Iloprost i.v. † Treprostinil i.v.	Ambrisentan, Bosentan Iloprost inhaled and i.v† Macitentan†‡ Riociguat† Sildenafil, Tadalafil Treprostinil s.c., i.v., Inhaled†
IIb	B		Beraprost†	
	C		Initial Combination Therapy	Initial Combination Therapy

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.

Pulido T et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. N Engl J Med 2013; 369:809-18.

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

Pulido T et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. N Engl J Med 2013; 369:809-18.

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*

Ghofrani H et al. N Engl J Med 2013; 369:319-29.

RIOCIGUAT

- 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

RIOCIGUAT

- 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%

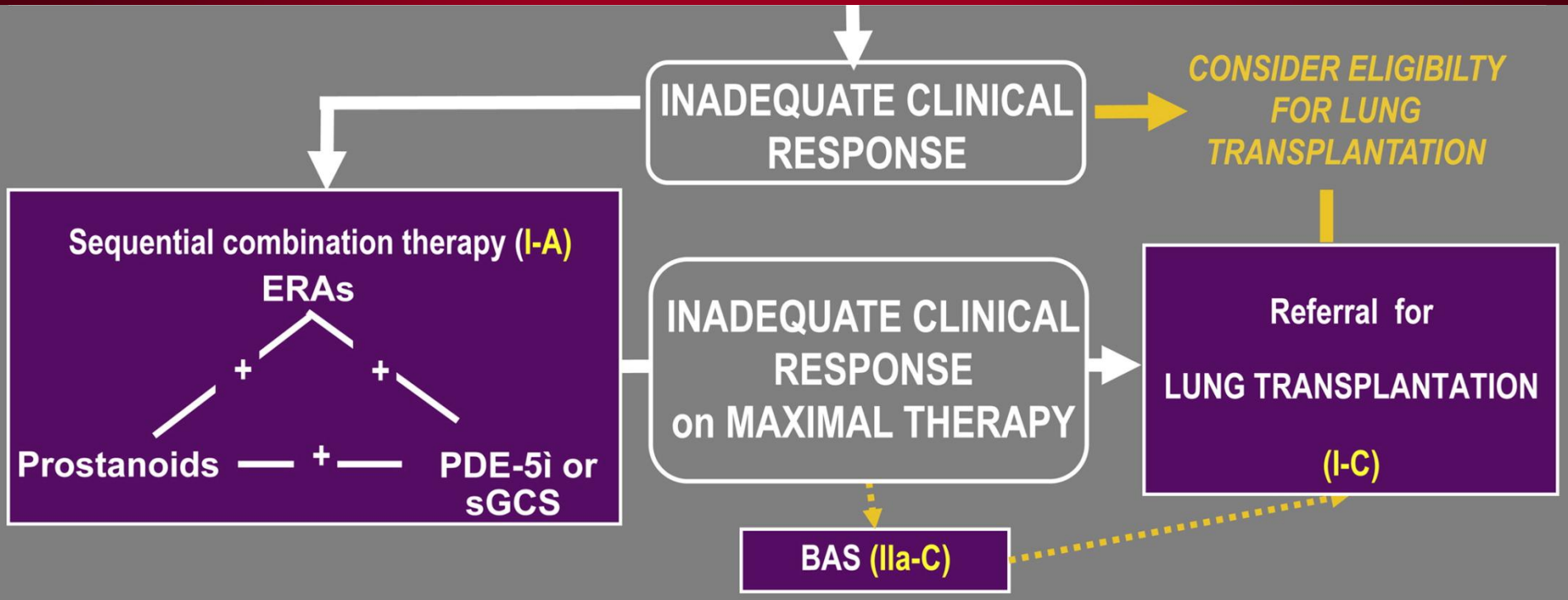
BERAPROST

- 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
  - Macentanten added to multiple other agents with IIa-C rating

SUBSEQUENT THERAPY



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;

Burger CD et al Mayo Clin Proc 2011.

REVEAL

	Entire Group	Control	IPAH	Control
BMI	28.4	28.2	29.1	28.1
P value	NS		NS	
OBESE (%)	36.5	33	40	33
P value	0.004		0.001	

Burger CD et al Mayo Clin Proc 2011; 86:105-12.

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: VO_2 > 15 mL/kg/min; VE/VCO_2 < 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

- ACCF/AHA 2009 Expert Consensus Document on Pulmonary Hypertension. *J Am Coll Cardiol* 2009; 53:1573-1619.
- Galiè N et al. Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J* 2009; 30:2493-537.

Discussion and Questions

CLASSIFICATION

- 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

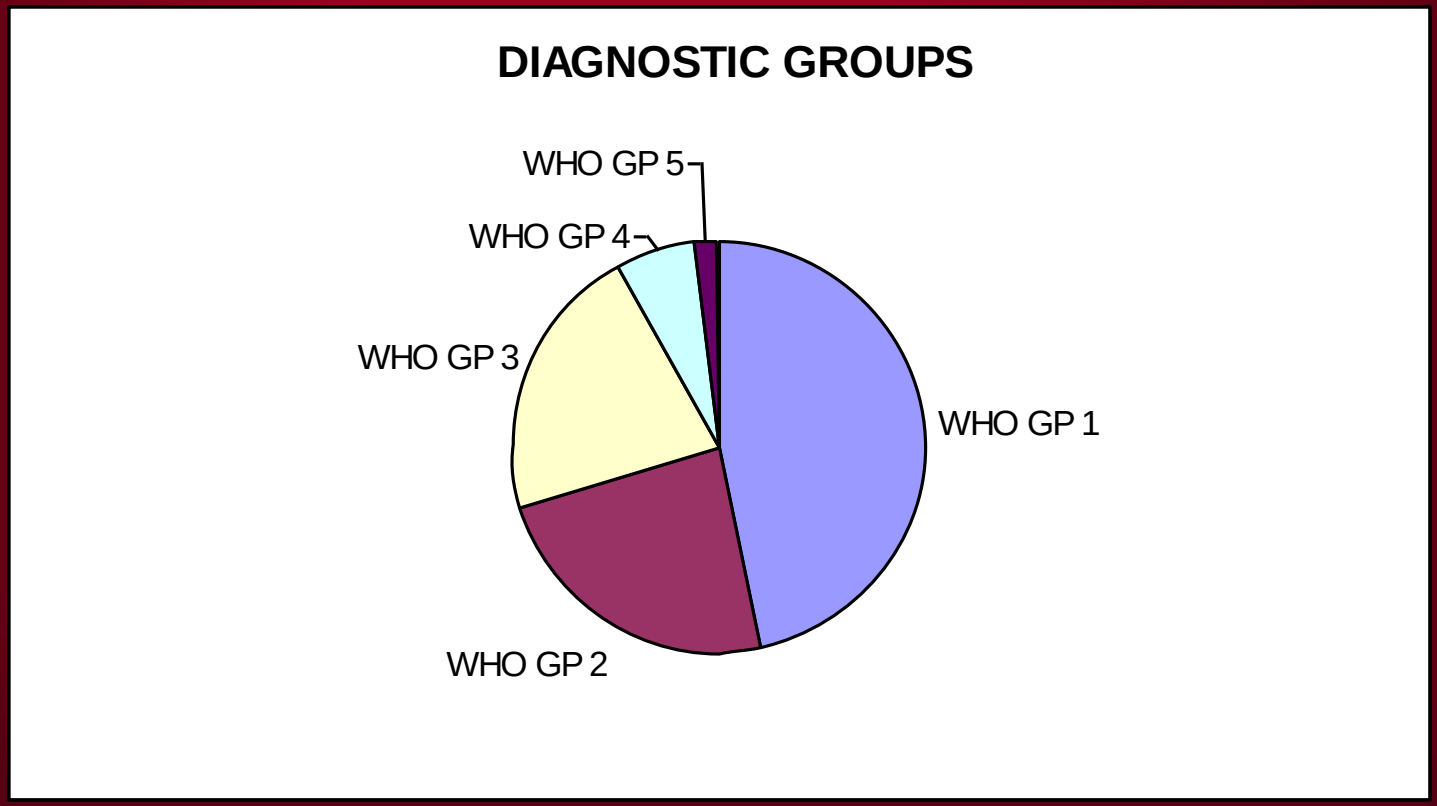
SUBGROUPS

- 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.

McGoon MD et al. *Mayo Clin Proc* 2008; 83:923-931.

REVEAL DEMOGRAPHICS

N = 2,525

- Women 80%
- Mean age 53 years
- RACE
  - 73% Caucasian
  - 12% AA, 9% Hispanic, 3% Asian

Badesch D, et al. *Chest* 2010; 137:376-387

REVEAL Preliminary Analysis (n = 2,967)

- Symptoms
  - Dyspnea 83%
  - Fatigue 27%
  - Chest pain or LE edema 20%
  - Syncope/near syncope 17%
  - Cough 14%

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

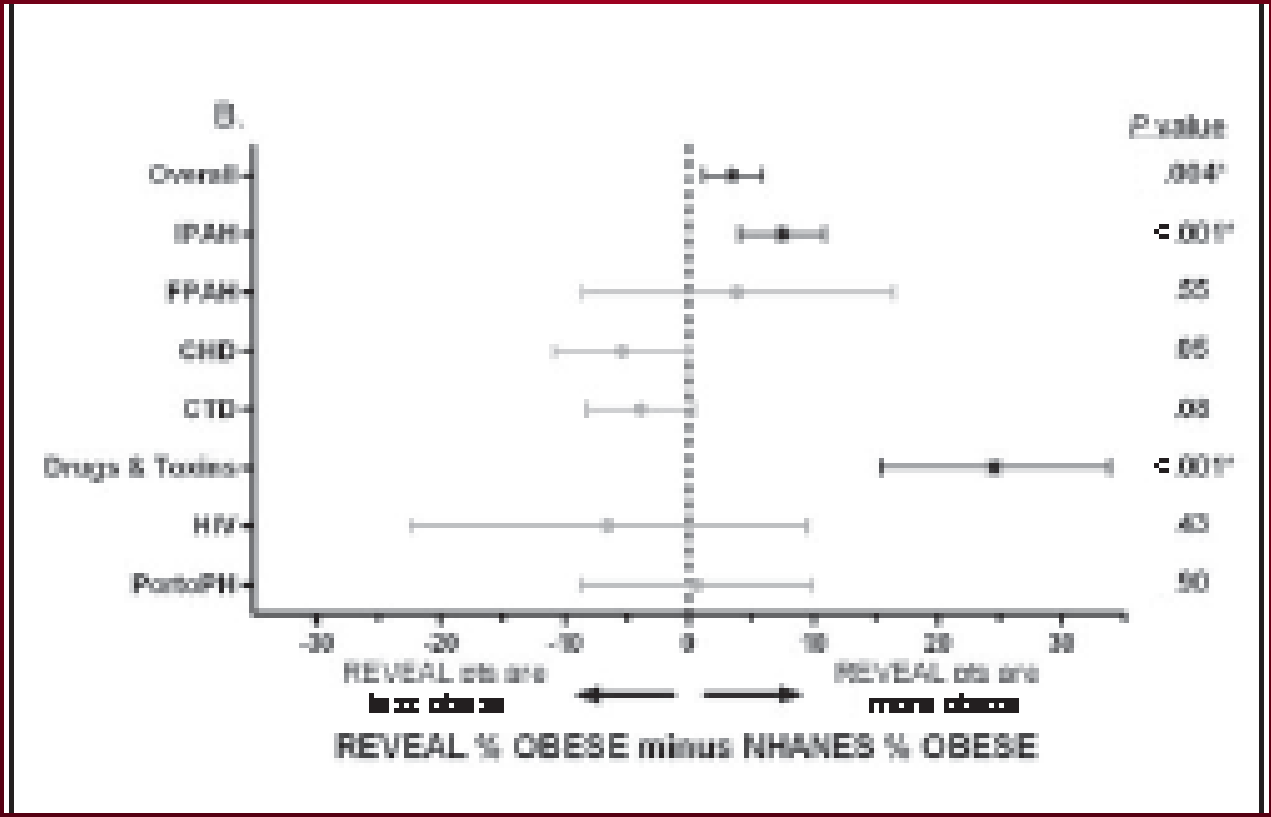
REVEAL DEMOGRAPHICS

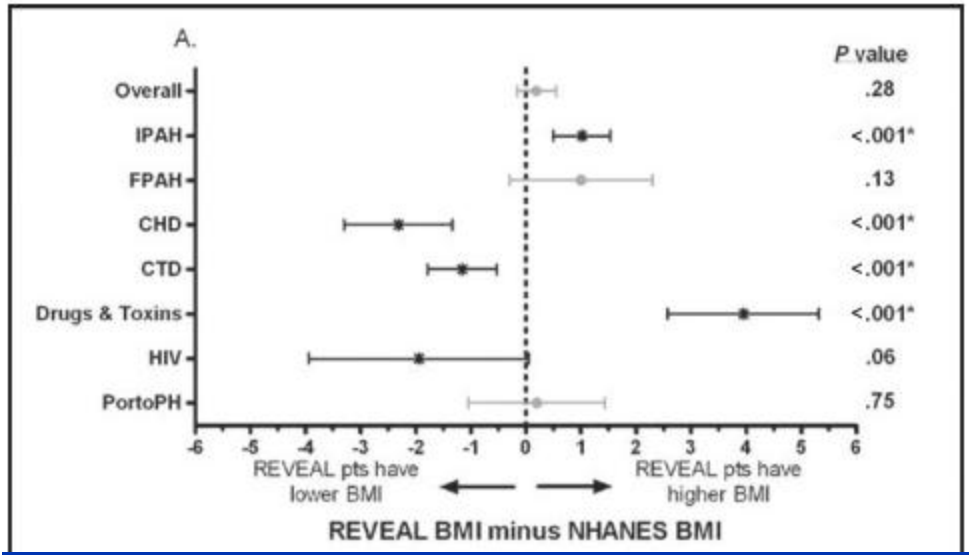
N = 2,525

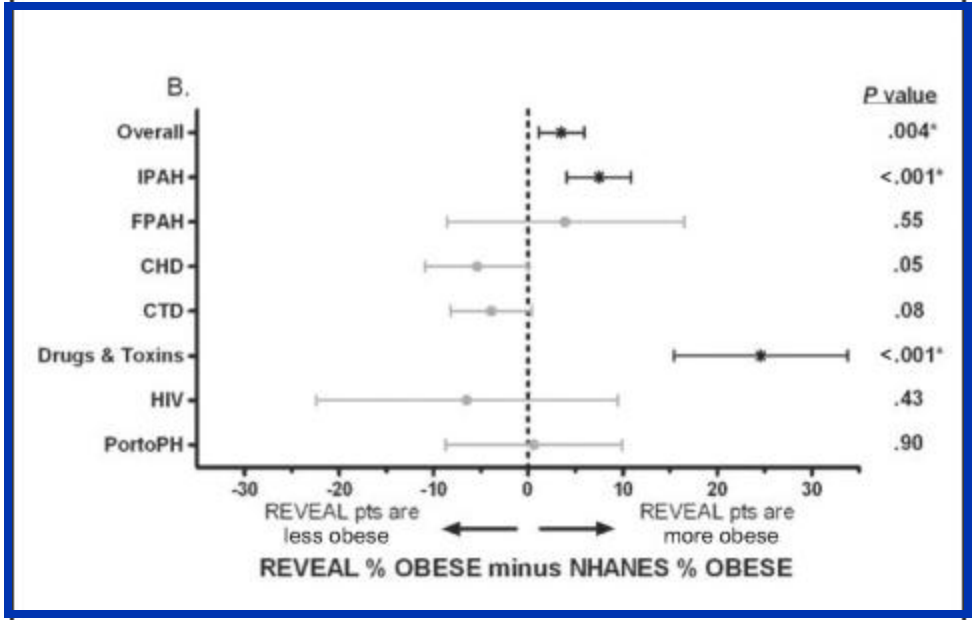
- Functional Class I 8%
- Functional Class II 37%
- Functional Class III 50%
- Functional Class IV 5%

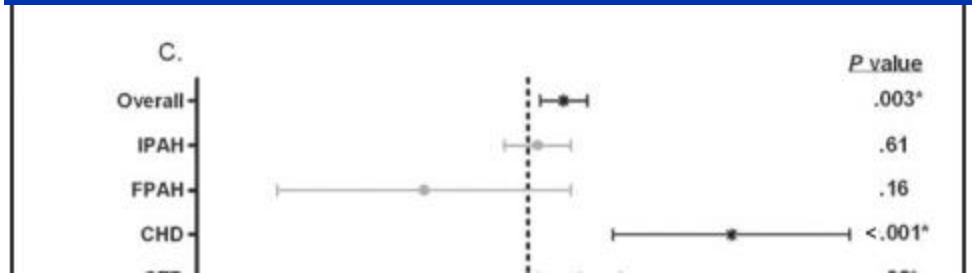
Badesch D, et al. *Chest* 2010; 137:376-387

Body Habitus and PH




A.
P value
Overall
IPAH
FPAH
CHD
CTD
Drugs & Toxins
HIV
PortoPH
.28
<.001*
.13
<.001*
<.001*
<.001*
.06
.75
-6 -5 -4 -3 -2 -1 0 1 2 3 4 5 6
REVEAL pts have lower BMI
REVEAL pts have higher BMI
REVEAL BMI minus NHANES BMI


B.
P value
Overall
IPAH
FPAH
CHD
CTD
Drugs & Toxins
HIV
PortoPH
.004*
<.001*
.55
.05
.08
<.001*
.43
.90
-30 -20 -10 0 10 20 30
REVEAL pts are less obese
REVEAL pts are more obese
REVEAL % OBESE minus NHANES % OBESE


C.
P value
Overall
IPAH
FPAH
CHD
.003*
.61
.16
<.001*

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