# State-of-the-Art Management of Pulmonary Hypertension Monitoring and Approach of the Three Main Etiopathogenesis L-Sided Failure, Pulmonary Arterial Hypertension, Thromboembolic

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Co-Director of the Clinical Trials Unit
Inova Heart and Vascular Institute
Professor of Medicine
VCU School of Medicine

# Nice 2013 Classification

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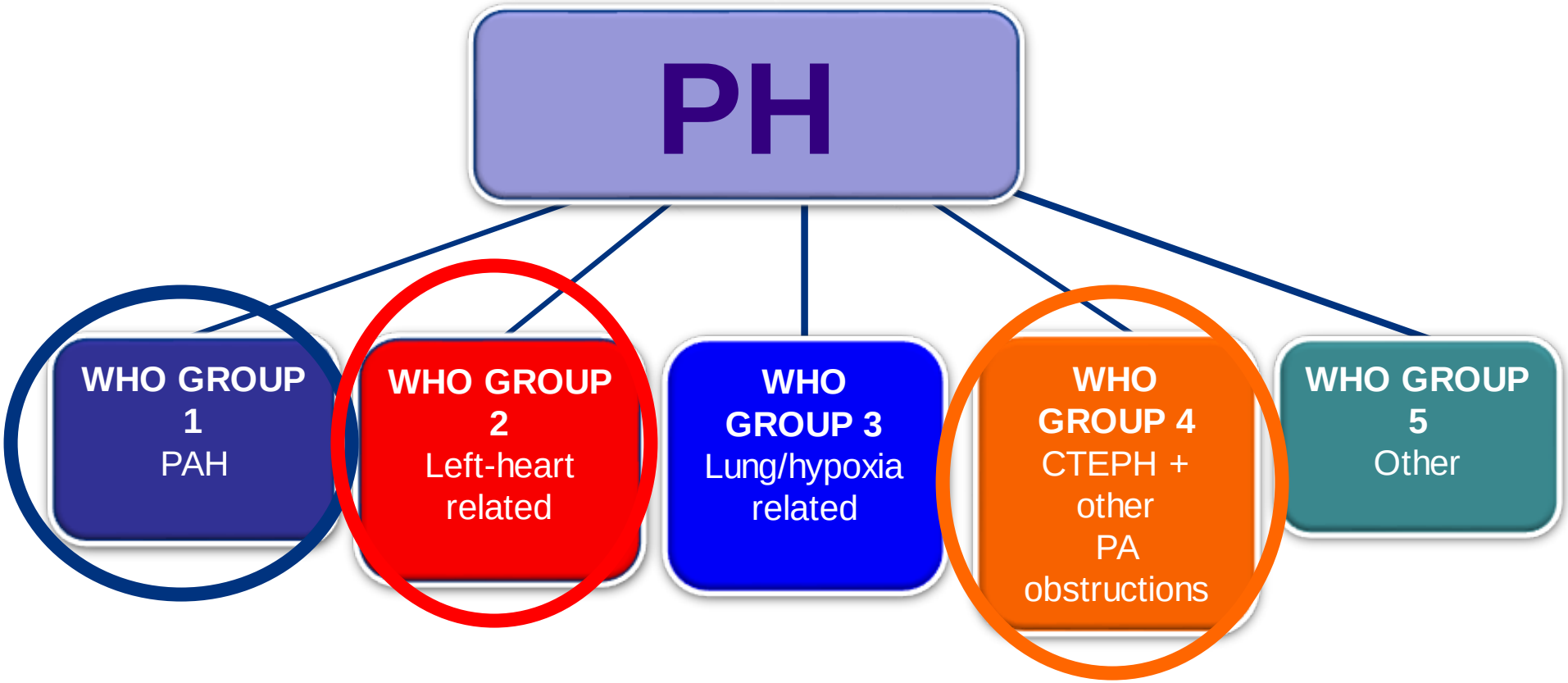
= mean PAP ≥25 mm Hg at rest during RHC




PA, pulmonary artery; WHO, World Health Organization.
Galiè N *et al. Eur Heart J* 2016;37:67–119.

# Group 1: Pulmonary Arterial Hypertension
# Timeline of medical therapies in PAH

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## My PH timeline

**1950s**
- **No Rx**

**1970s**
- $O_2$
- diuretics
- digoxin

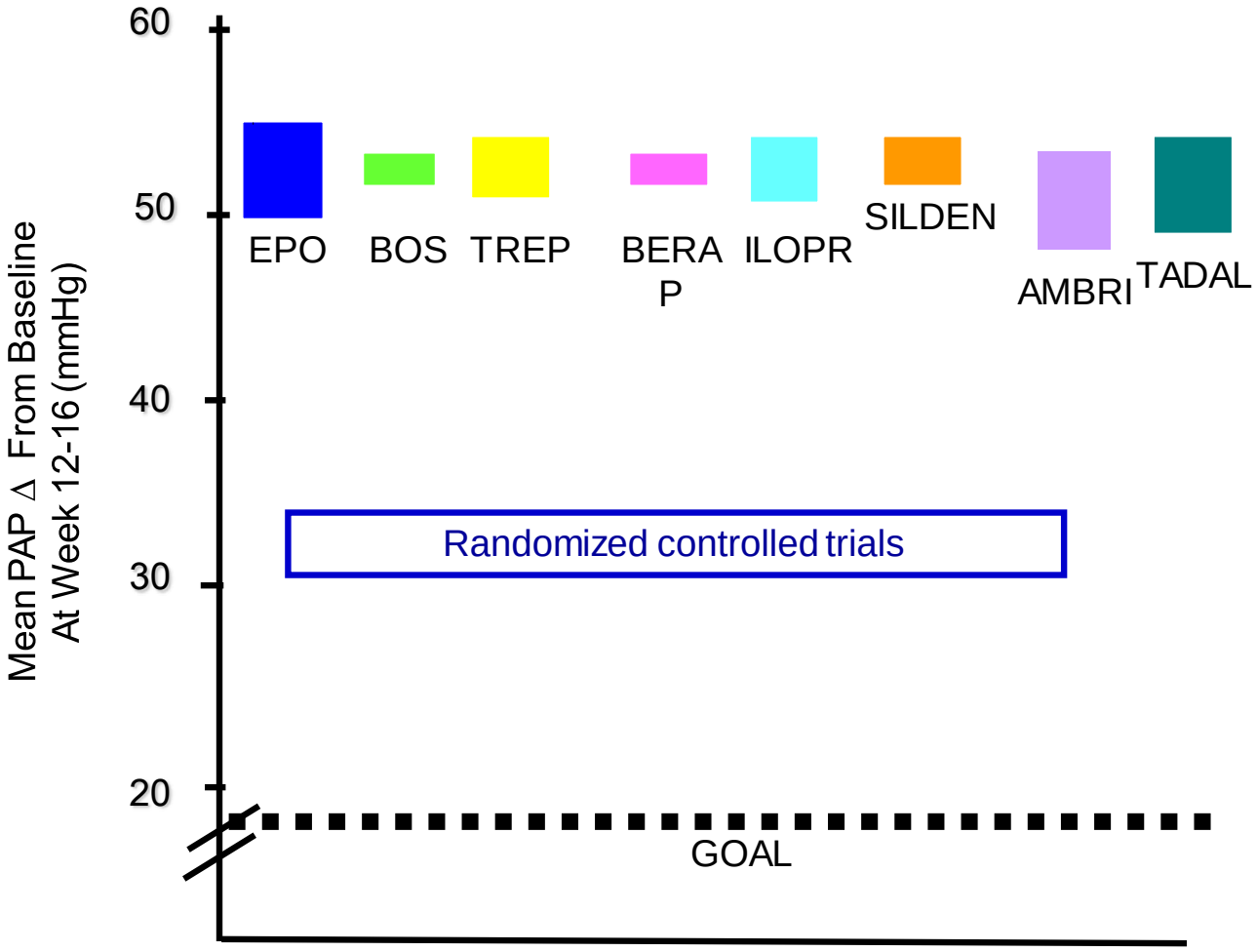
**1980s**
- Epoprostenol

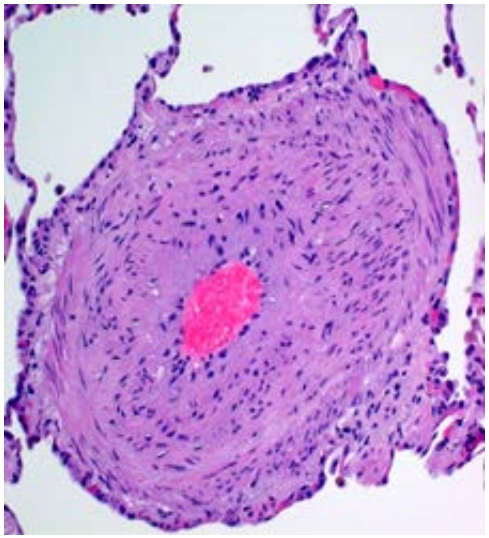
**1992**
- Epoprostenol
- CCBs

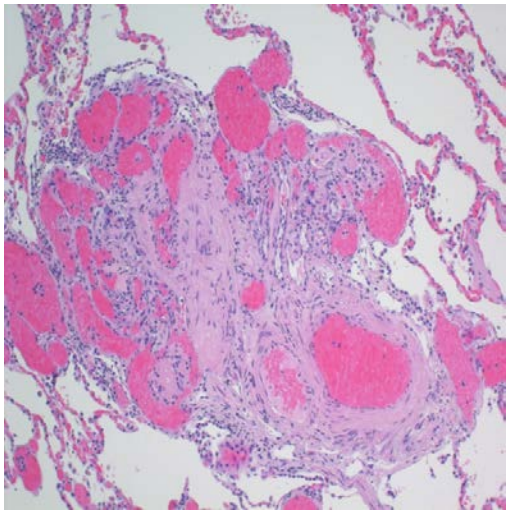
**2003**
- Epoprostenol
- CCBs
- Bosentan
- Treprostinil

**2016**
- Epoprostenol
- CCBs
- Bosentan
- Treprostinil
- Sildenafil
- Ambrisentan
- Tadalafil
- Iloprost
- Macitentan
- Riociguat
- Selexipag

# Improvements on Monotherapy Do Not Restore Normal PAP:
# PAH Patient who lived 20 yrs on epoprostenol

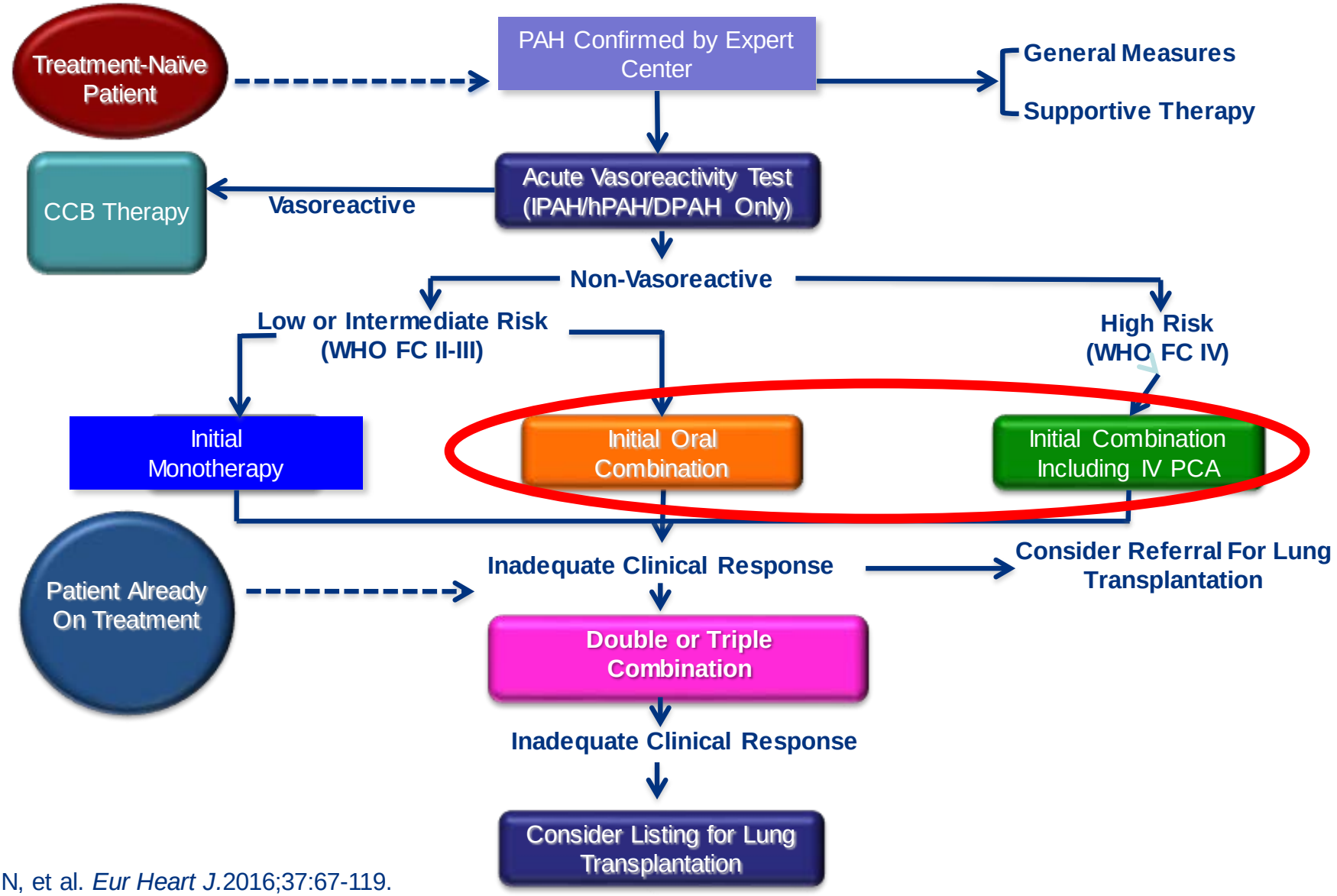




Barst 1996; 2003, 2003; Rubin 2002; Simmoneau 2002; Galie 2002, 2005; Ghofrani 2004, Galie 2005, Galie 2008; Galie 2009. Rich S…….. Gomberg-Maitland, Archer SL. *Chest.* 2010 Nov;138(5):1234-

# ESC/ERS 2015: Evidence-based Treatment Algorithm for PAH Patients (Group 1 Patients)



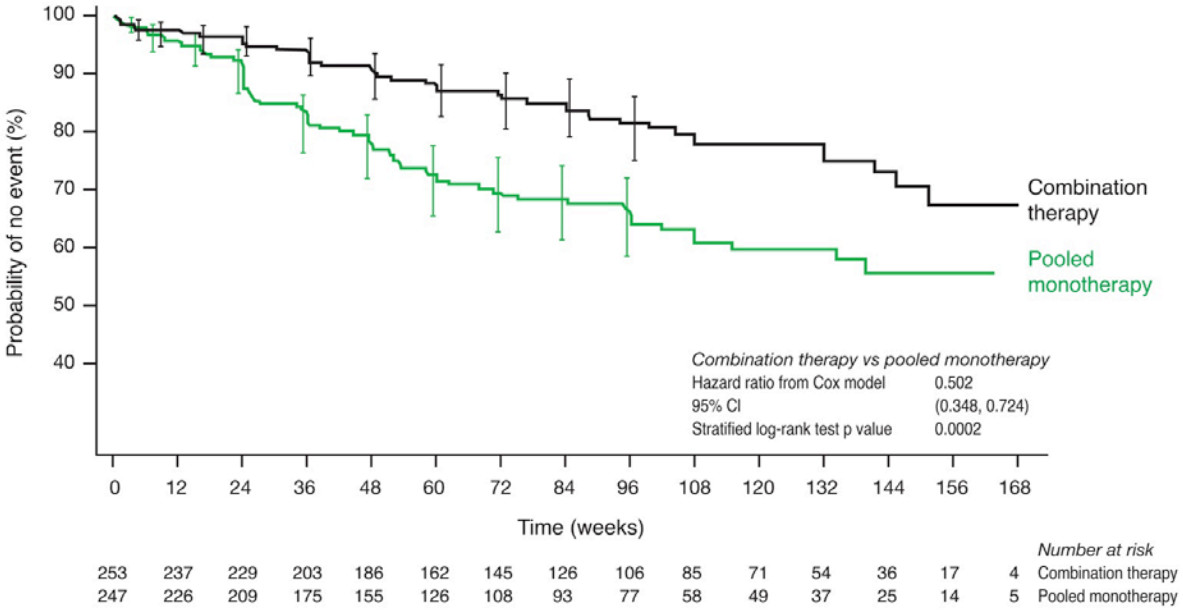

Galiè N, et al. *Eur Heart J.*2016;37:67-119.
Courtesy of Dr I Preston

# Initial Combination is better than monotherapy

- Aimed to answer the question:
  - Is initial treatment with combination therapy superior to initial treatment with monotherapy?

- Novel clinical endpoint: Time to Clinical Failure:
  - TTCF= death, hospitalization for worsening PAH or disease progression, or unsatisfactory clinical response at 6 months (drop 6mwd from BL, remained FC III)

## Combination vs pooled monotherapy




Combination decreased clinical failure event rate vs. monotherapy by **50% (p=0.00002)**

Secondary endpoints **ALL in favor of combination:**
- ΔNT-proBNP
- % achieving satisfactory clinical response,
- 6MWD

95% CIs (using log-log transform method) are presented for each treatment group at weeks 4, 8, 16, 24, and then every 12 weeks up to week 96.

Galiè N. *N Engl J Med*. 2015 Aug 27;373(9):834-844.

# Upfront triple therapy in sick patients
# "Hit them hard and early": Phase 3 study enrolling

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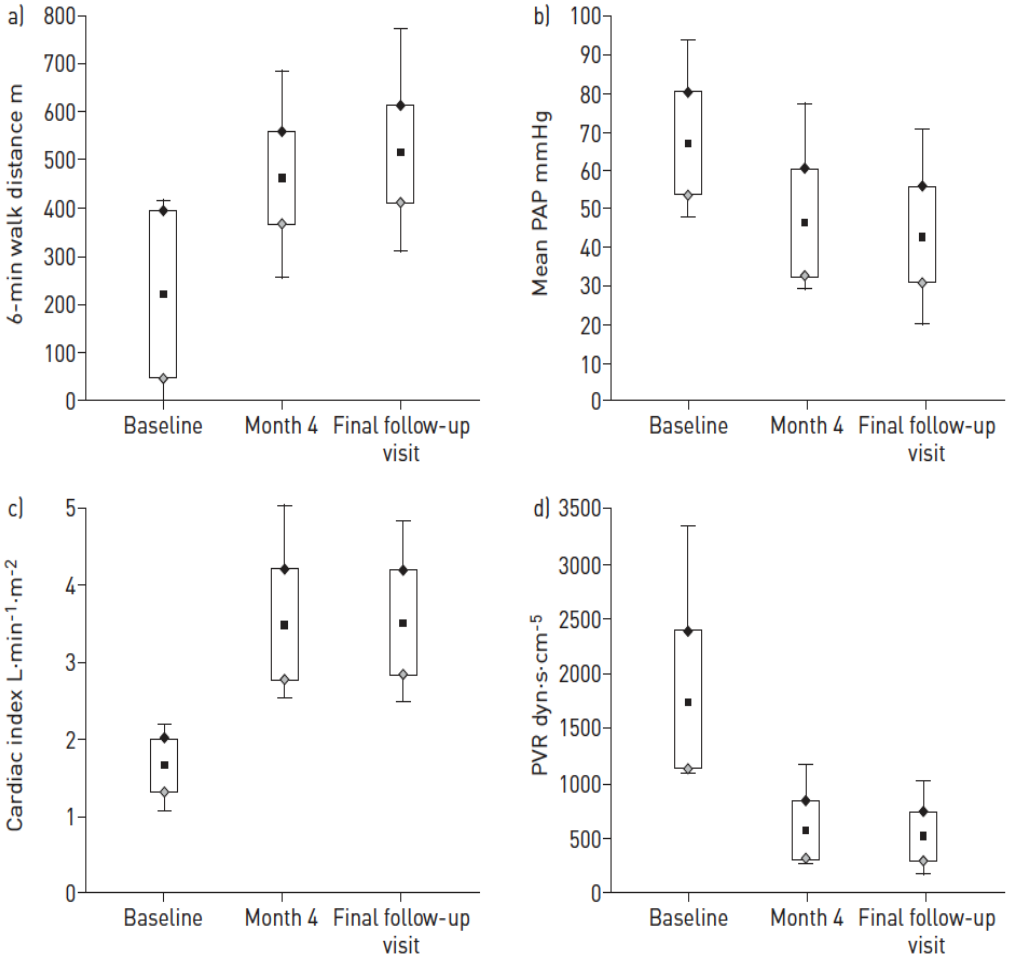
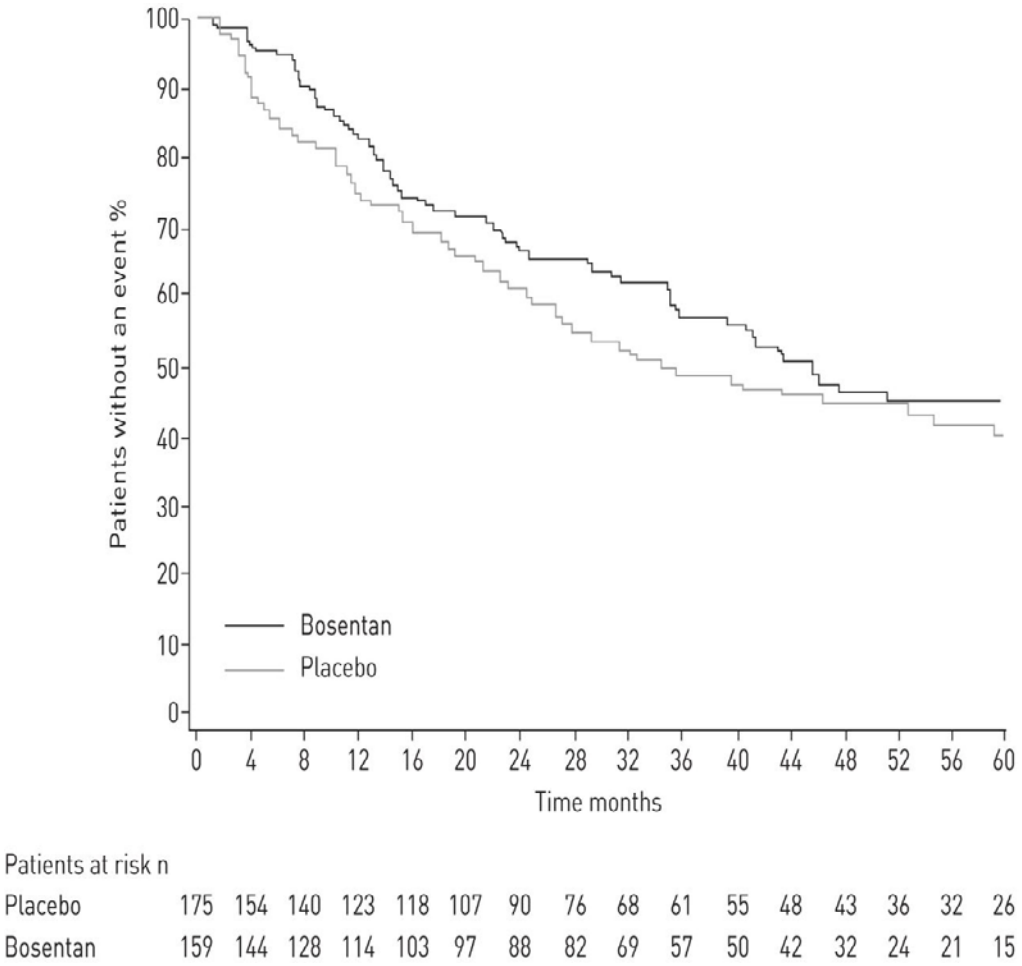
- Small cohort all given aggressive therapy
- Class III/IV, CI<2.0 L/min/m2, +/or mRAP>20 mmHg, +/or PVR≥12.5 Units
- No CTD, HIV, CHD, portal HTN
- Epo 1ng/kg/min q12h up to 10ng/kg/min + bosentan 62.5mg bid
  + sildenafil 20 mg tid day 5
- Max Epo 16ng/kg/min, bosentan 125mg bid, sildenafil 20 mg tid




Sitbon O. *Eur Respir J* 2014; 43: 1691-1697/

# Combination Therapy: The answer or the question?

## Are all combinations the same? Is it a class effect?




The ideal combination of agents is still unknown

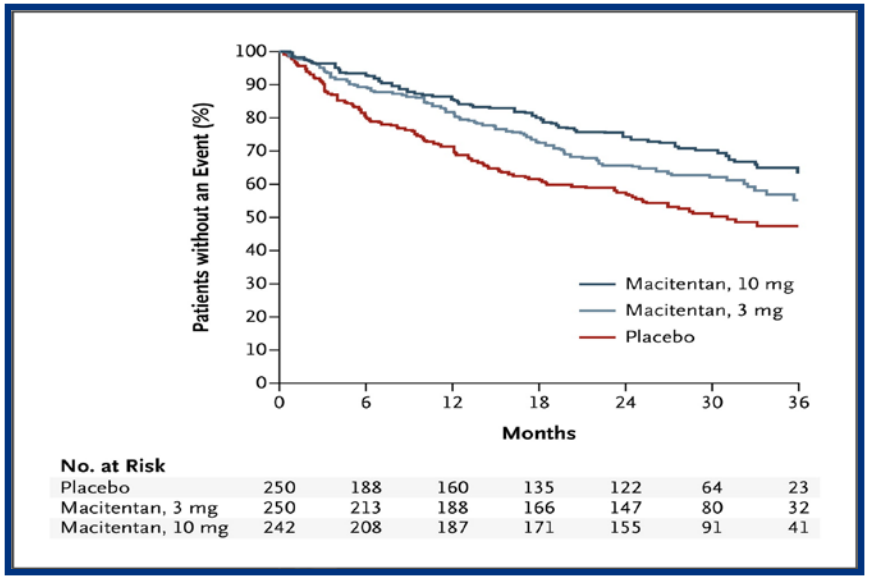
- It is unclear if there are "class" effects
- More drugs available= more uncertainty
- Costs/expenditures; third-party hurdles, approvals, country specific regulations

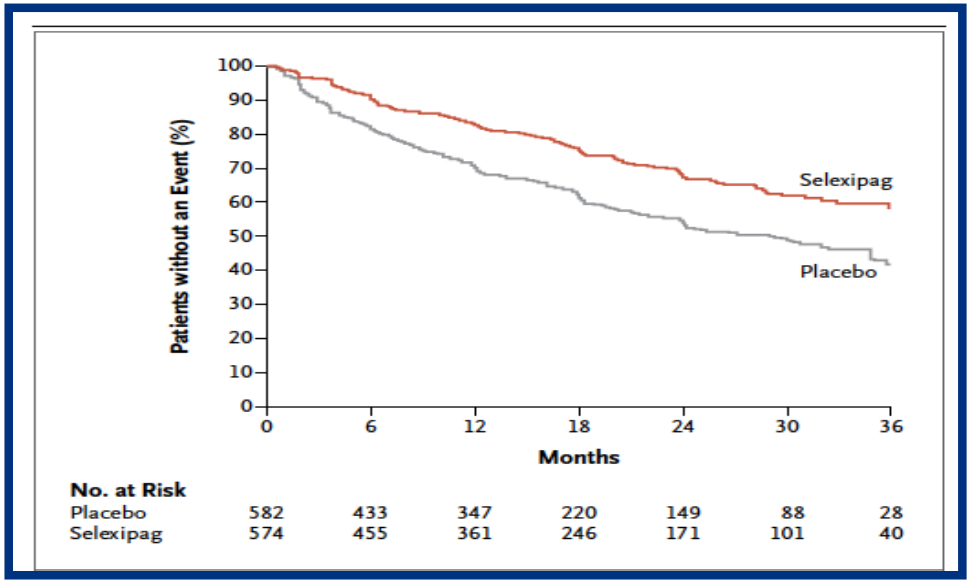
- More questions than answers

McLaughlin V. *Eur Respir J* 2015;46: 405-13

# New treatment Approaches and Endpoints: Event Driven Trials

| Drug tested | Study | Background | Primary endpoint | No. of patients |
|---|---|---|---|---|
| Macitentan | SERAPHIN | None, PDE5i or inhaled iloprost | Morbidity and mortality | 742 |
| Selexipag | GRIPHON | 1 or 2 background therapies not PG | Morbidity and mortality | 1156 |

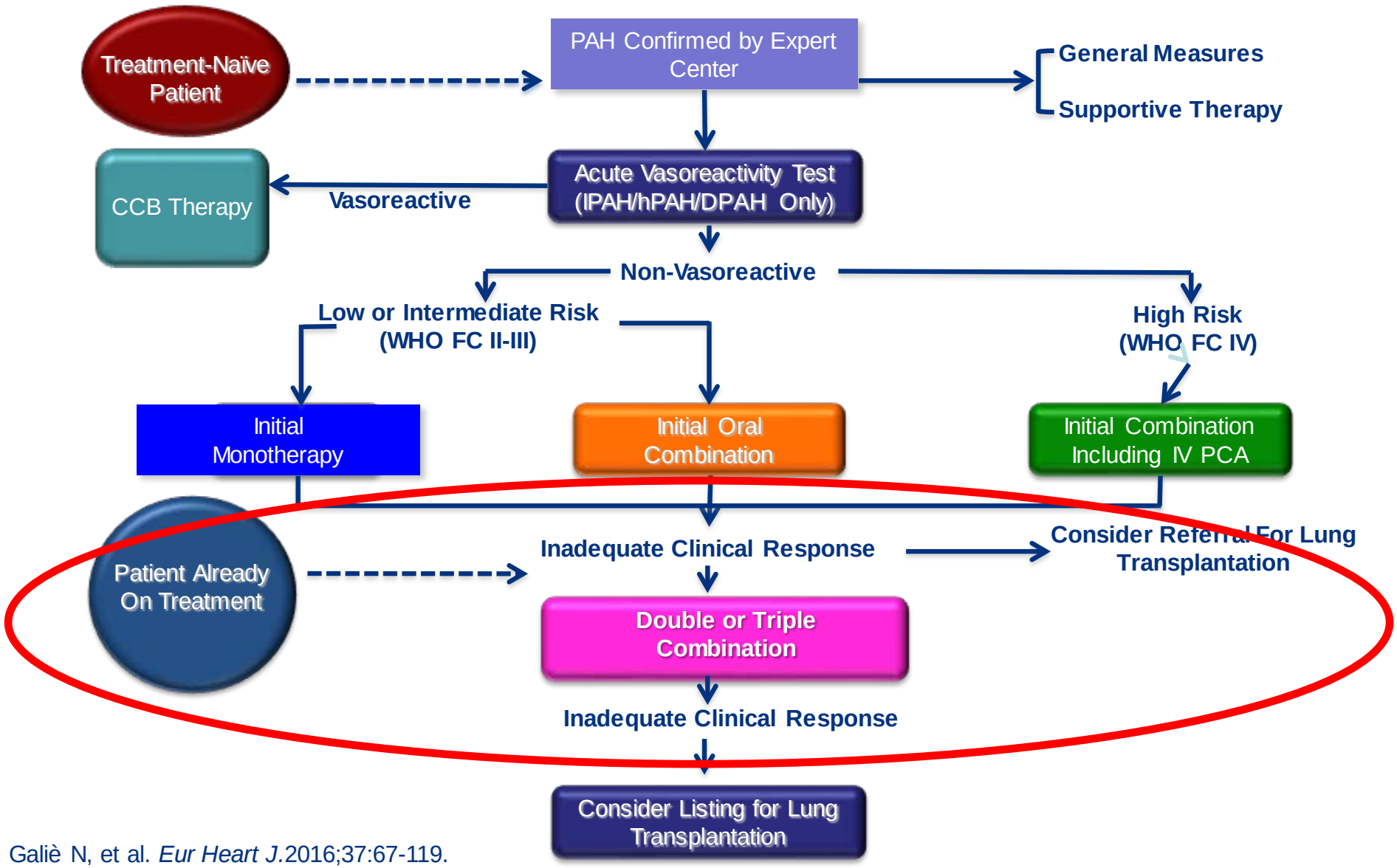



95% CIs (using log-log transform method) are presented for each treatment group at weeks 4, 8, 16, 24, and then every 12 weeks up to week 96.

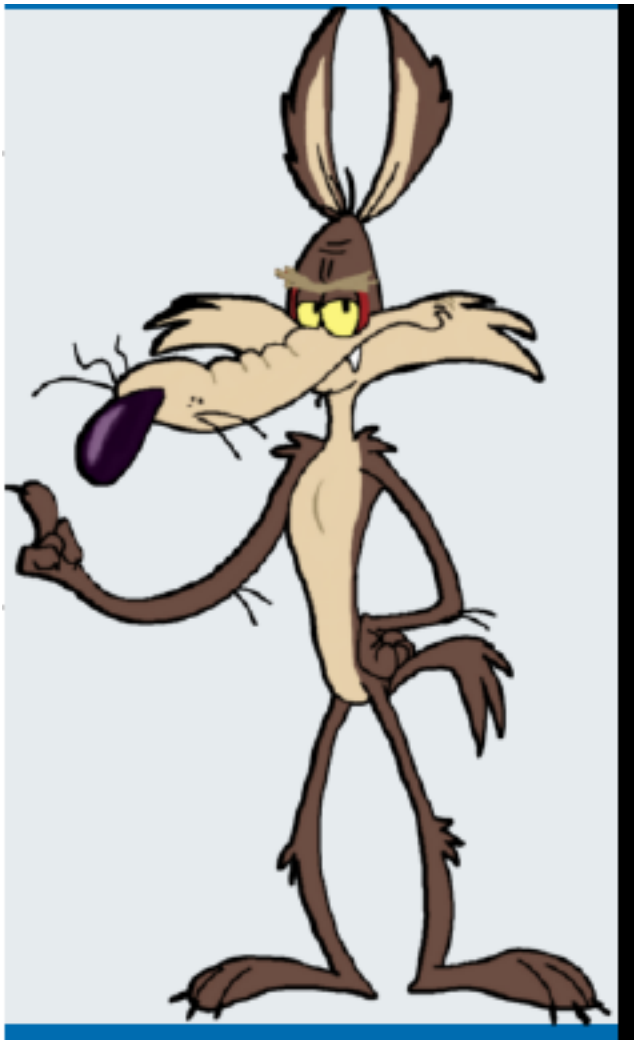
Raja. *Curr Opin Investig Drugs*.2010; 11(9):1066-73. Pulido T. *NEJM*. 2013; 369: 809-818. Sitbon O. *NEJM*. 2015; 373(26):2522-33.

# ERS 2015: Evidence-based Treatment Algorithm for PAH Patients (Group 1 Patients)




Galiè N, et al. *Eur Heart J.*2016;37:67-119.
Courtesy of Dr I Preston

# Patient on therapy presents to clinic on Friday 4PM



NO NO NO!!!!!
LET’S RETHINK THIS.....

# Goal-Oriented Therapeutic approach is **not** new in 2017

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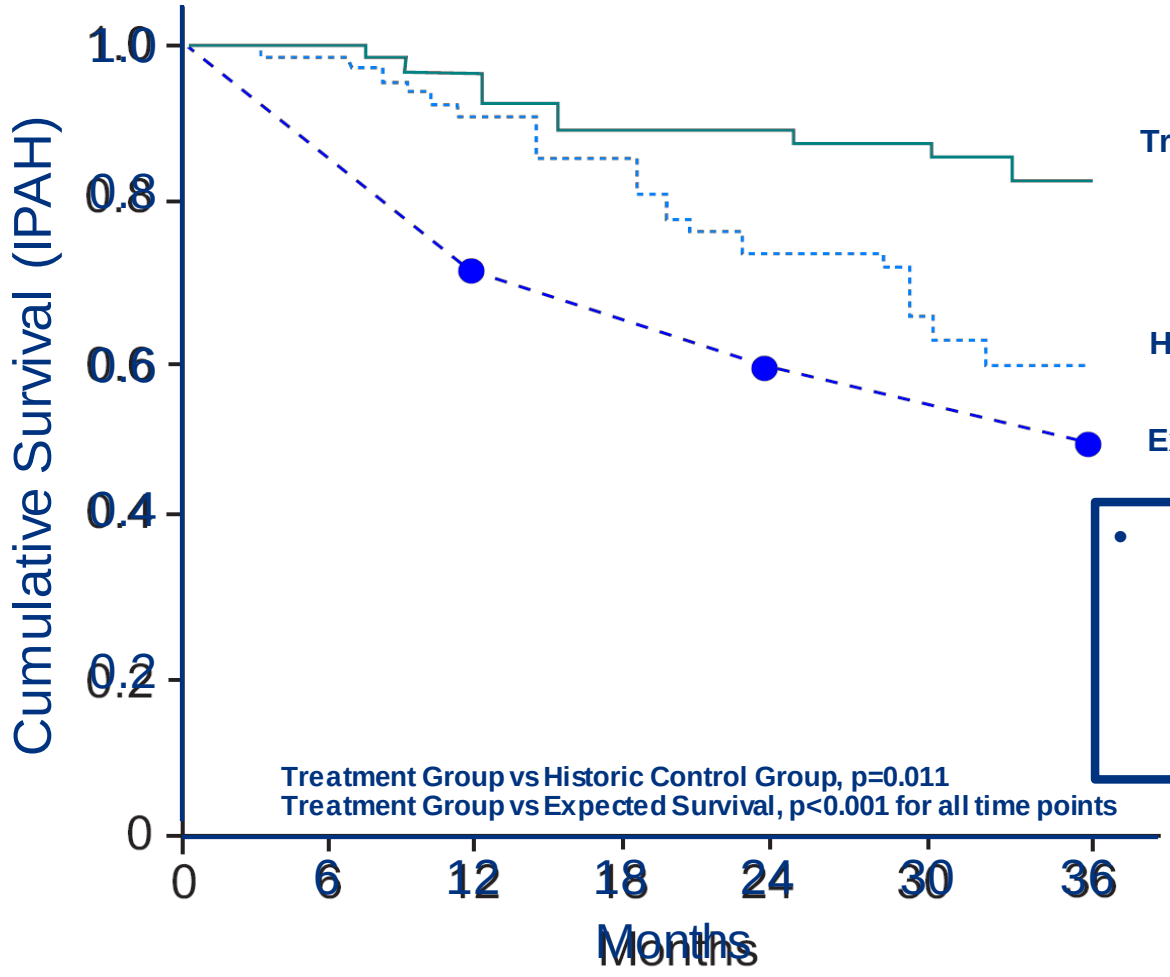


- We want the best results for each patient to translate to better:
  - QoL physical
  - QoL emotional
  - Survival

Hoeper MM et al. *ERJ* 2005; 26:858-63.

# Risk assessment is a composite

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| Determinants of prognosis[a] (estimated 1-year mortality) | Low risk <5% | Intermediate risk 5–10% | High risk >10% |
|---|---|---|---|
| Clinical signs of right heart failure | Absent | Absent | Present |
| Progression of symptoms | No | Slow | Rapid |
| Syncope | No | Occasional syncope[b] | Repeated syncope[c] |
| WHO functional class | I, II | III | IV |
| 6MWD | >440 m | 165–440 m | <165 m |
| Cardiopulmonary exercise testing | Peak $VO_2$ >15ml/min/kg (>65% pred.) $VE/VCO_2$ slope <36 | Peak $VO_2$ 11–15 ml/min/kg (35–65% pred.) $VE/VCO_2$ slope 36–44.9 | Peak $VO_2$ <11 ml/min/kg (<35% pred.) $VE/VCO_2$ slope ⩾45 |
| NT-proBNP plasma levels | BNP <50 ng/l NT-proBNP <300 ng/l | BNP 50–300 ng/l NT-proBNP 300–1400 ng/l | BNP >300 ng/l NT-proBNP >1400 ng/l |
| Imaging (echocardiography, CMR imaging) | RA area <18 $cm^2$ No pericardial effusion | RA area 18–26 $cm^2$ No or minimal, pericardial effusion | RA area >26 $cm^2$ pericardial effusion |
| Haemodynamics | RAP <8 mmHg CI ⩾2.5 l/min/$m^2$ $SvO_2$ >65% | RAP 8–14 mmHg CI 2.0–2.4 l/min/$m^2$ $SvO_2$ 60–65% | RAP >14 mmHg CI <2.0 l/min/$m^2$ $SvO_2$ <60% |

Galiè N, et al. *Eur Heart J.*2016;37:67-119.

# Multiple risk assessment tools:

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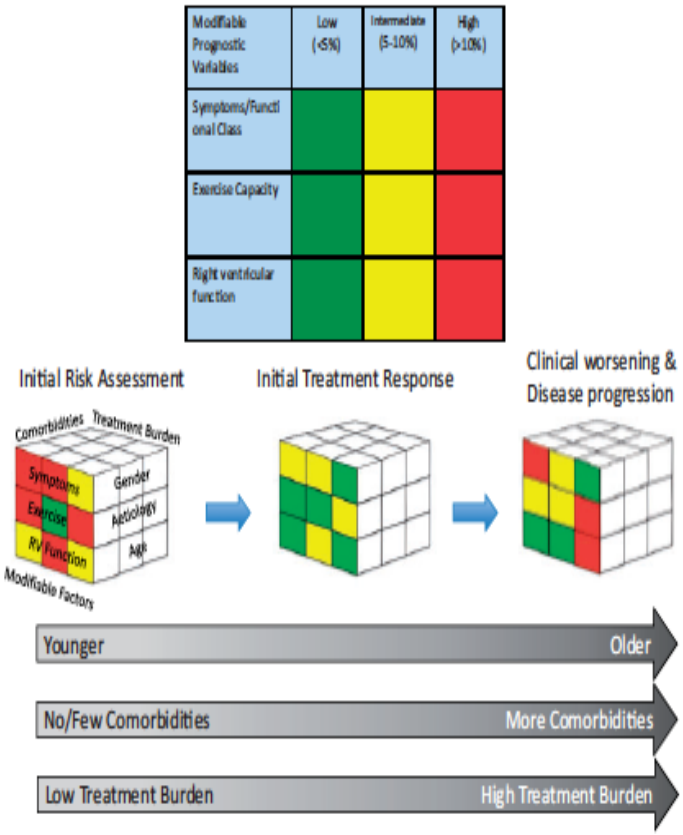
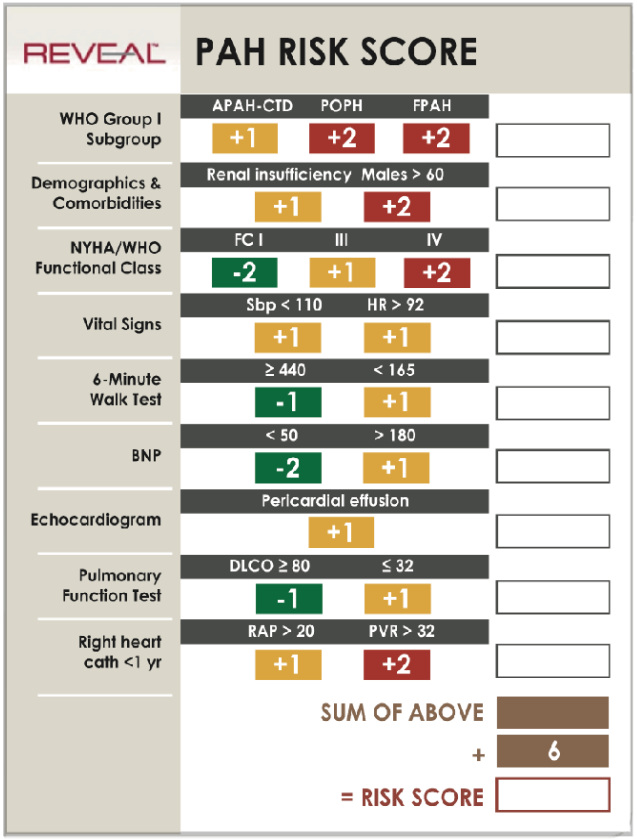
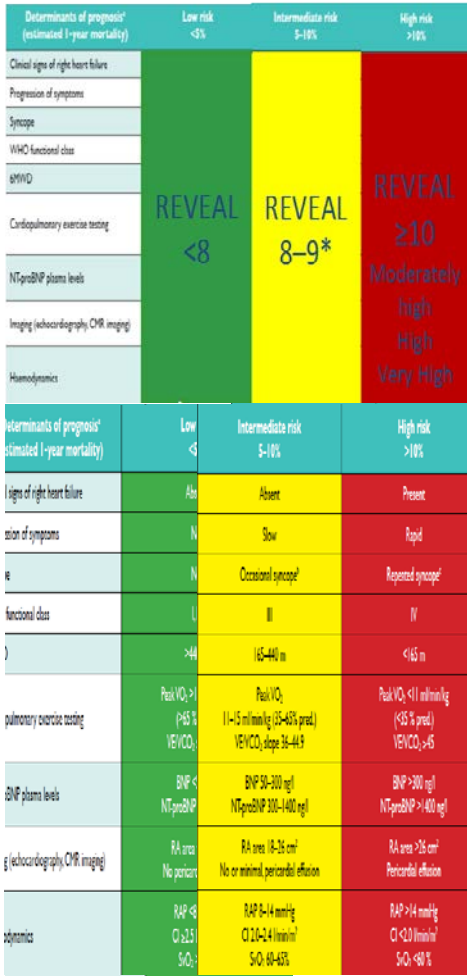
## CUBE vs. CALCULATOR



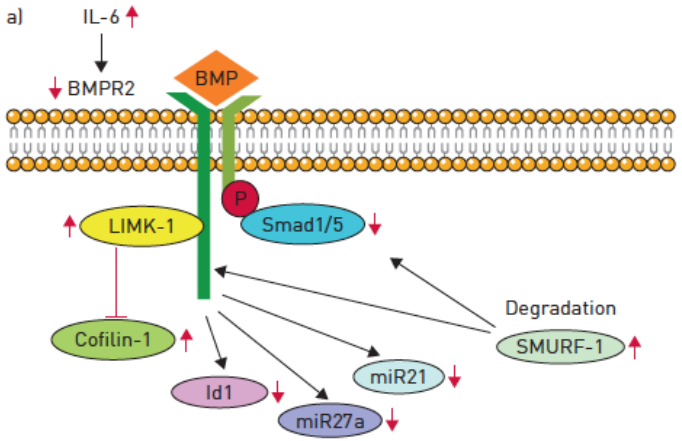



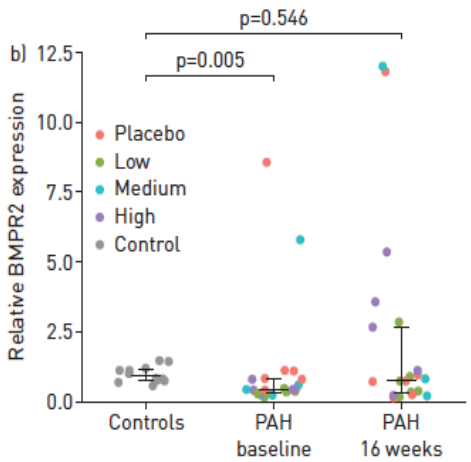



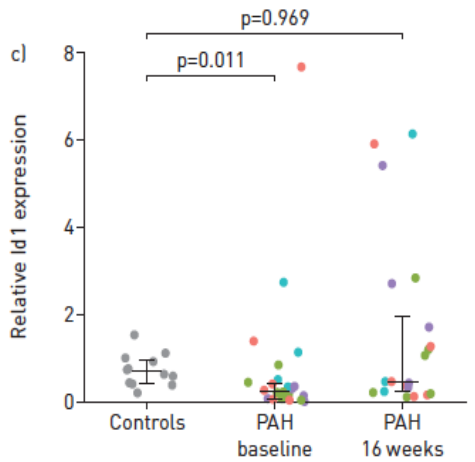

Weatherald J. *Eur Heart J* 2017;0,1-4. Benza RL. *Circ* 2010 Jul 13;122(2):164-72.
Benza RL...Gomberg-Maitland M. *Eur Respir J* 2017 Aug3;50(2);

# New Targets:
# Target signaling linked to genetic mutations

- FK506- tacrolimus
  - BMPR2 mutations associated with heritable PAH known nearly 20 years
  - Powerful modulator of the immune system enhances BMPR2 activity in animal PAH models improving PAH
  - Small case series- 3 patients, low dose FK506
  - 16 week trial, mixed PAH population, short (16 weeks), not at high dosing, BMPR2 mRNA expression attenuated but not related to clinical "responders".
  - Still potential target, needs well-designed proof of concept clinical study

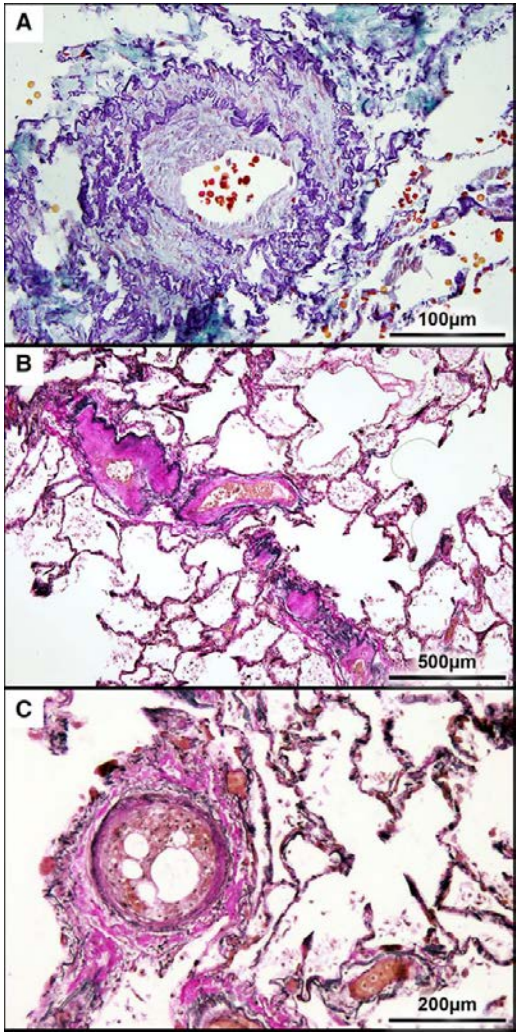



Thompson JR. J Med Genet 2000; Deng Z Am J Hum Geent 200; International PPHC. Nat Genet 2000; Atkinson C. Circ 2002; Spiekerkoetter E. *Am J Respir Crit Care Med*. 2015; Spiekeroetter E. *Eur Respir J* 2017; Sep; Rubin LJ. *Eur Respir J* 2017;Sep

# Group 2 PH: Histopathology & Definitions of PH-LHD




Medial hyperterophy and intimal/ adventitial proliferation small PA[5]

Medial hyperterophy and intimal/ adventitial proliferation small PV[5]

Re-canalized fibrotic thrombus in arterioles[5]

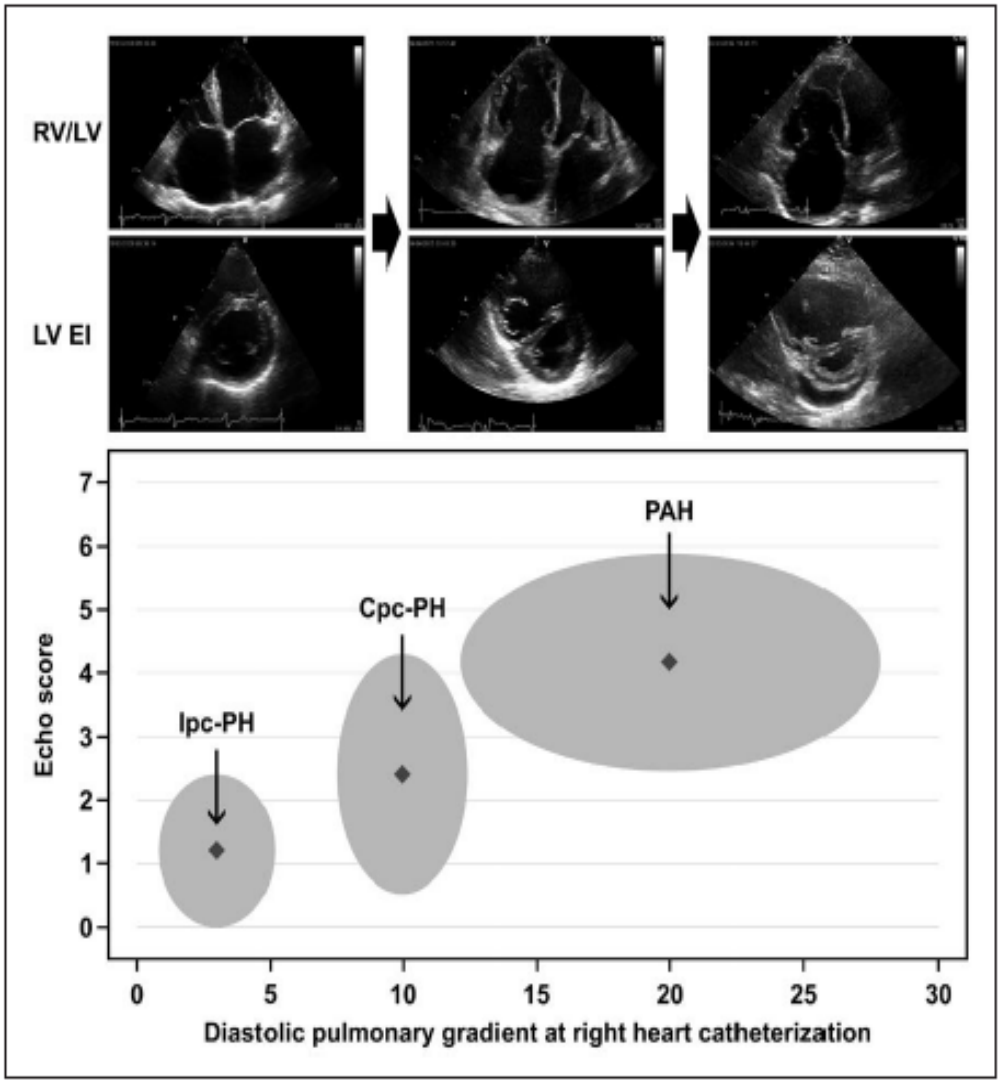
## Diastolic Pulmonary Gradient: PAPd-PAWP

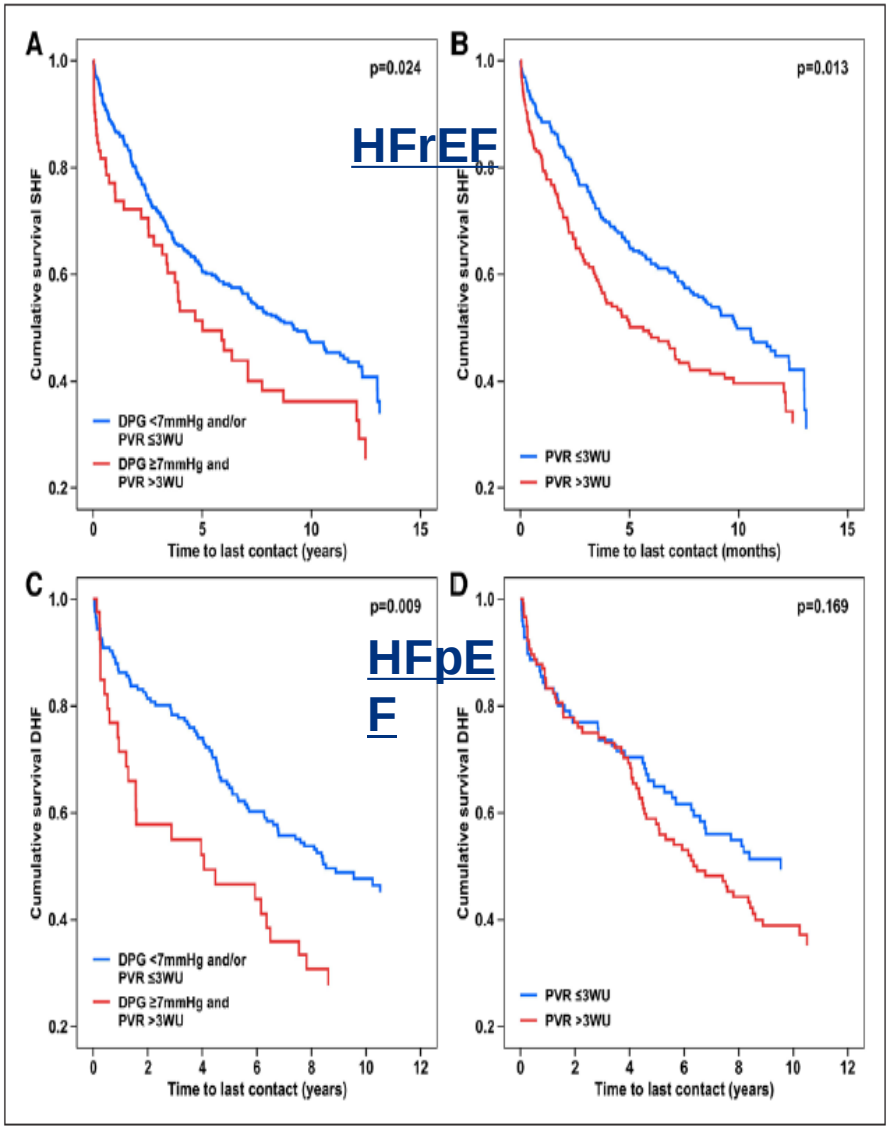
- Normal value: 1 – 2 mmHg[1-3]
- Abnormal level: > 5 mmHg[2,3]
- Prognostic marker: ≥ 7 mmHg[4]
- Pre-capillary PH: ≥ 10 mmHg

| Terminology | PAWP | DPG PAPd-PAWP |
|---|---|---|
| Isolated post capillary PH | > 15 mmHg | < 7 mmHg |
| Combined post capillary & pre-capillary PH | > 15 mmHg Normalized | ≥ 7 mmHg |

1. Harvey R et al. *CHEST* 1971. 2. Buchbinder N. *Anesthesiology* 1976; 45(2): 146-55 R. Naeije R . *Eur Resp J* 2013; 41(1): 217-223. August 30, 2012. 4. Gerges C et al. *CHEST 2013*. 143(3):758-766; 5. Naeije R. *Circ Heart Fail 2017*;Sep

# Group 2 PH: Phenotypes using DPG




Naeije R. *Circ Heart Fail* 2017;Sep; Gerges M. *Am J Respir Crit Care Med*. 2015;192:1234-1246 (survival derived from)

# Sildenafil for Improving Outcomes after Valvular Correction (SIOVAC) Trial 200 patients

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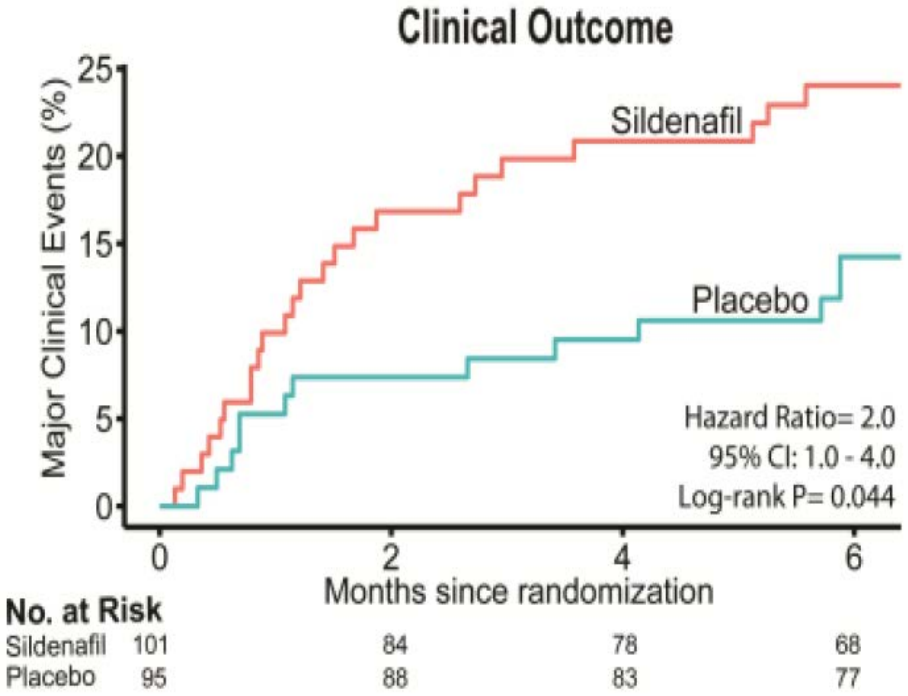
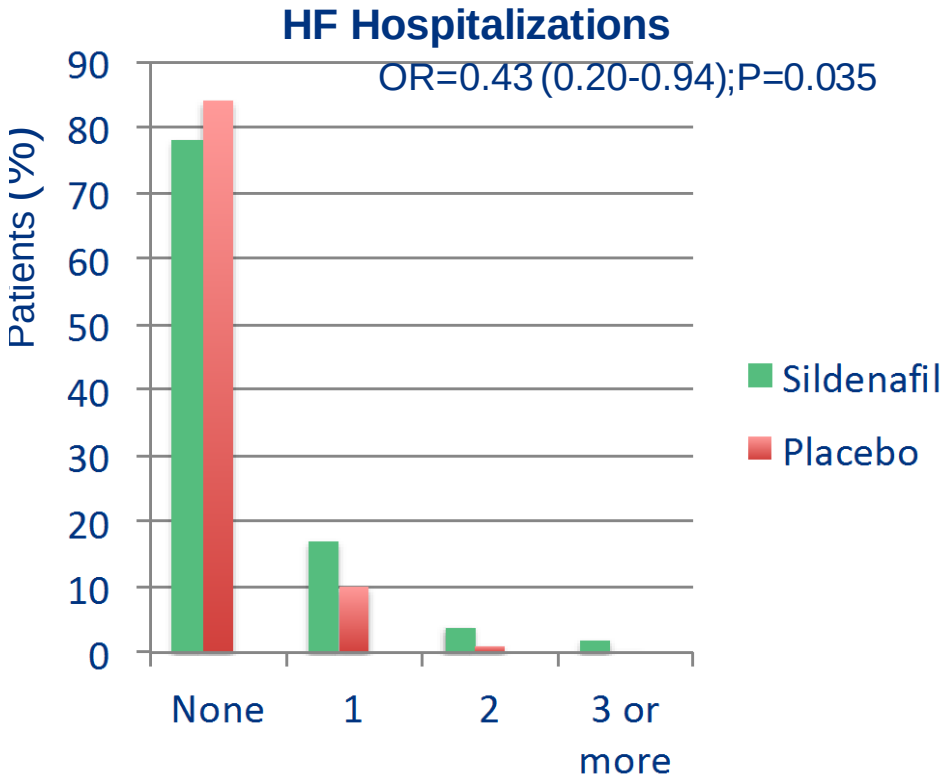
Corrected Valvular Heart Disease>1 yr ; RHC <1 mo mPAP≥30 mmHg/ echo PASP>50 mmHg and cath=mPAP≥30 mmHg

- **Sildenafil should NOT be given to these patients**




Bermejo, J on behalf of SIOVAC investigators; ESC 2017, Milan, Italy.
http://www.clinicaltrialresults.org/Slides/ESC2017/SIOVAC_Bermejo.pdf

# Current Recommendations for PHTN-LHD

| Recommendations | Class[a] | Level[b] |
|---|---|---|
| Optimization of the treatment of the underlying condition is recommended before considering assessment of PH-LHD (i.e. treating structural heart disease). | I | C |
| It is recommended to identify other causes of PH (i.e. COPD, SAS, PE, CTEPH) and to treat them when appropriate before considering assessment of PH-LHD. | I | C |
| It is recommended to perform invasive assessment of PH in patients on optimized volume status. | I | C |
| Patients with PH-LHD and a severe pre-capillary component as indicated by a high DPG and/or high PVR should be referred to an expert PH center for a complete diagnostic work-up and an individual treatment decision. | IIa | C |
| The use of PAH approved therapies is not recommended in PH-LHD. | III | C |

*Eur Heart J*, 2015
*Eur Respir J*, 2015

# Novel studies of PAH therapies in PH-HFpEF

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## Southpaw Study:
## Oral Treprostinil in Subjects with pulmonary hypertension and HFpEF

**Adaptive Study Design:**
- Interim safety reviews at N=10, 30, 60, 100, + 200 pts
- Start with low dose with increased max dose following each review
- Initiate trial at select centers to allow for highest likelihood of success

**Target RV:**
- Echo: RV dysfunction
- LVEF>50%
- PVR>4U (TD),
- PCWP>15 but <30 mmHg
- mPAP≥ 25 mmHg
- 6MWD>200 m

- N=314
- Randomize 1:1
- 24-week treatment period
- 75 PH clinical sites

Orenitram

Placebo

**Primary endpoint:** placebo-correct change in 6MWD at week 24

**Key Secondary endpoints:**
- N-terminal pro-BNP
- QoL
- Clinical worsening
- Safety

## Serenade Study:
## Oral Macitentan in Subjects HFpEF and pulmonary vascular disease

**Multicenter Phase 2b**
- Stratified by: NTproBNP <1000 and ≥ 1000 pg/ml
- Screening up to 30 days
- Single blind placebo run-in 4 weeks followed by single blind macitentan run-in

**Targeting RV**
- Cath within 6 mo, Echo: (1) LAV, LAVI, LA area, LA diameter, LV septal thickness, NTproBNP/BNP ≥ 250/75 pg / ml in NSR, or ≥ 1000/300 pg / ml in AF
- PV disease: (1), DPG>5mmHg, PVR>3U, mPAP>40mmHg, peak TR >2.8 m/s TAPSE<17, RVFAC<35%m RV tissue doppler s'<9.5 cm/s

- N=300
- Randomize 1:1
- 24-week treatment period
- 100 clinical sites
- 15 countries

Macitentan

Placebo

**Primary endpoint:**
Reduces NTproBNP vs. placebo

**Key Secondary endpoints:**
- Daily physical activity
- QoL
- Worsening of HF

# Goal/Premise: Monitoring catches change early

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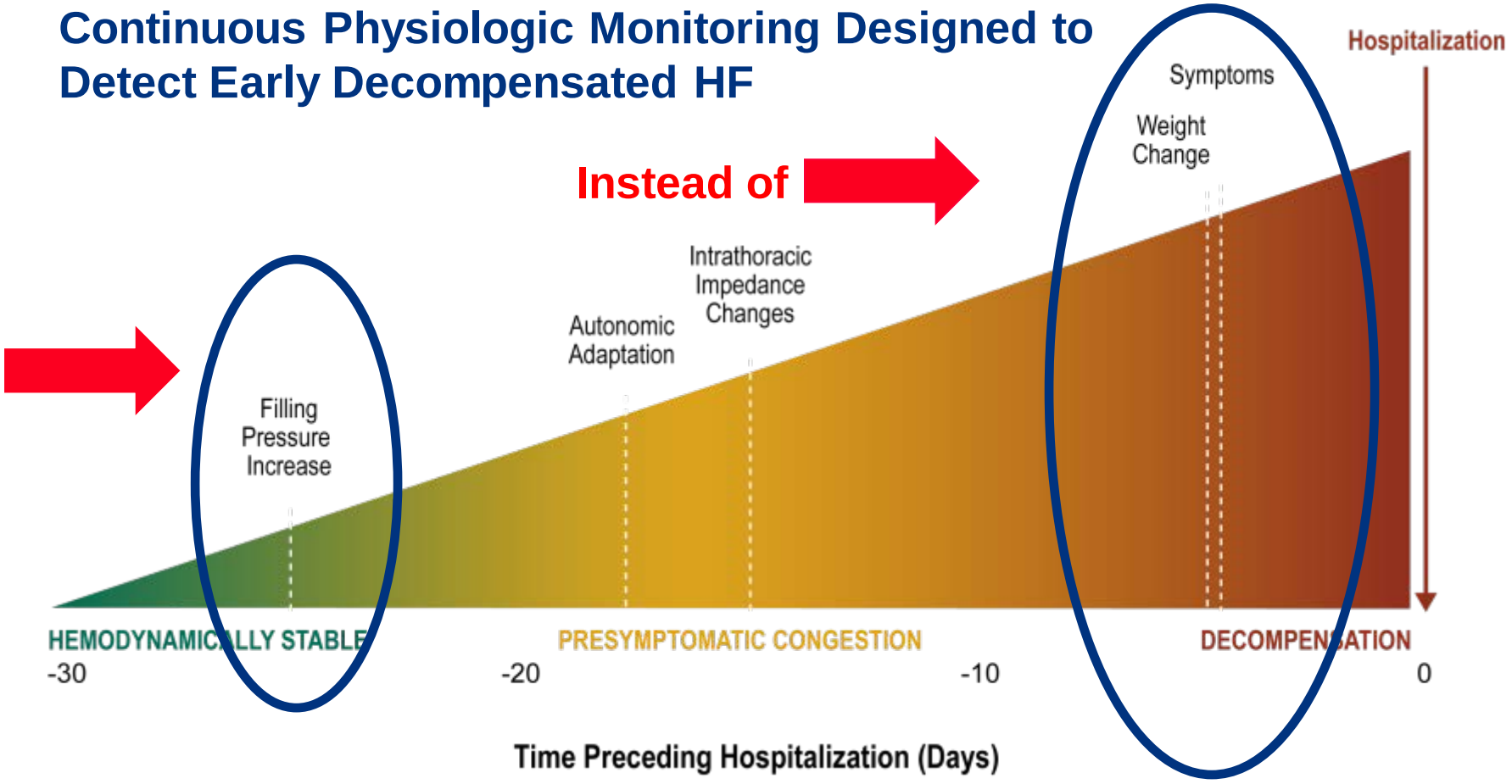
## Continuous Physiologic Monitoring Designed to Detect Early Decompensated HF




Graph adapted by St. Jude Medical from Adamson PB, et al. *Curr Heart Fail Reports*, 2009.
Slide adapted from Dr. RL. Benza

# Monitoring in PH-LHD: So what? Why?

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## Individual Benefit:

- Monitoring may detect early decompensation✔
- Monitoring may help personalize response to therapy✔

## Society Benefit:

- Monitoring can increase access to care✔
- Monitoring might decrease
  - MD visit✔
  - hospitalizations ✔
  - and overall medical cost✔✔

# PH Cohort in CHAMPION:

## HF Hospitalization Rates Improved with Monitoring (Treatment vs. Control)

**Table 5** Heart Failure Hospitalization (hosp) Rates in Subgroups of Pulmonary Hypertension Patients

| | Treatment | | | Control | | | | |
|---|---|---|---|---|---|---|---|---|
| HF hosp rates | *n* | HF hosp | HF hosp rate (annualized) | *n* | HF hosp | HF hosp rate (annualized) | RRR | Andersen–Gill model |
| Mean PAP >25 mm Hg | 151 | 113 | 0.60 | 163 | 186 | 0.94 | 36% | HR = 0.64, CI 0.51–0.81, $p = 0.0002$ |
| PVR ≥3 | 75 | 63 | 0.74 | 76 | 104 | 1.11 | 33% | HR = 0.66, CI 0.48–0.90, $p = 0.0094$ |
| PVR <3 | 76 | 50 | 0.48 | 87 | 82 | 0.79 | 39% | HR = 0.63, CI 0.45–0.90, $p = 0.0113$ |
| Transpulmonary gradient >15 | 56 | 49 | 0.69 | 45 | 55 | 0.99 | 30% | HR = 0.71, CI 0.48–1.04, $p = 0.0801$ |
| Transpulmonary gradient ≤15 | 95 | 64 | 0.54 | 118 | 131 | 0.92 | 41% | HR = 0.59, CI 0.44–0.80, $p = 0.0006$ |



Benza et al. *J Heart Lung Transplant* 2015;34:329-337

# Cardiomems: General use trends are better than trial cohort with greater drop in mPAP

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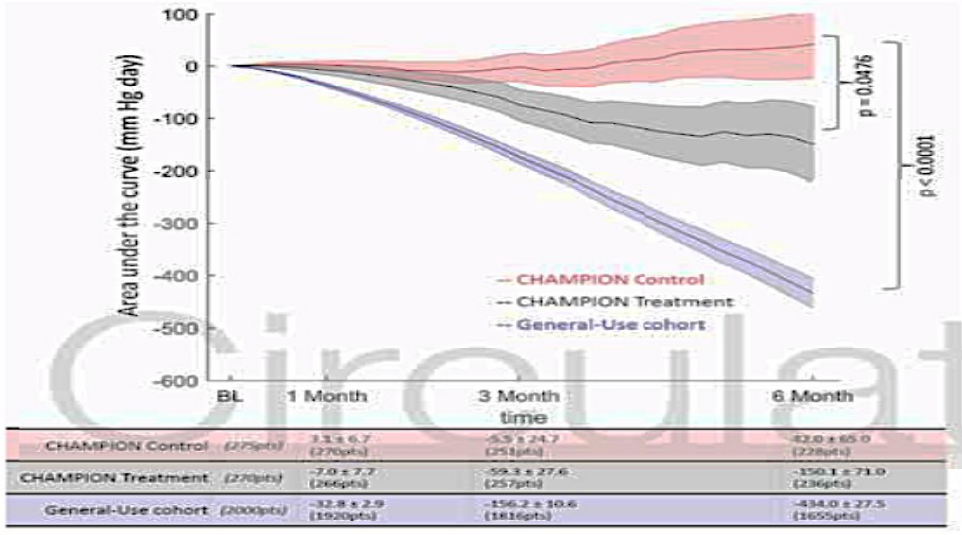
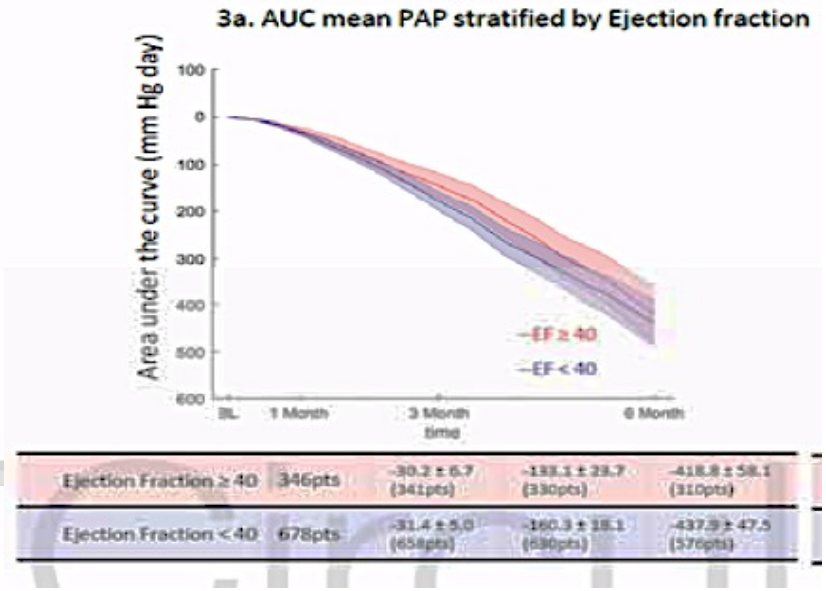
Analysis of first **2000 patients** in US implanted with cardiomems- de-identified data from Merlin.net remote monitoring with 6 mo f/u:

- PA trends compared with historic CHAMPION trial
- General use patients higher mPAP vs CHAMPION pts (active + control groups): 34.9 ±10.2 mmHg
- Pressure information transmitted with a median 1.27 days between transmissions
- **Monitoring lowered PAP over time more than CHAMPION**
- **PAP dropped most in patients with higher mPAP; similar HFrEF-PH and HFpEF-PH**






Heywood et al. *Circulation*. 2017;135(16):1509-1517.

# CTEPH Pathophysiology: Known as Dual Vascular Disease

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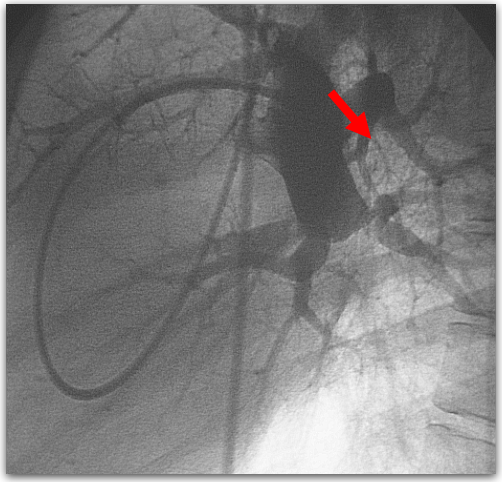
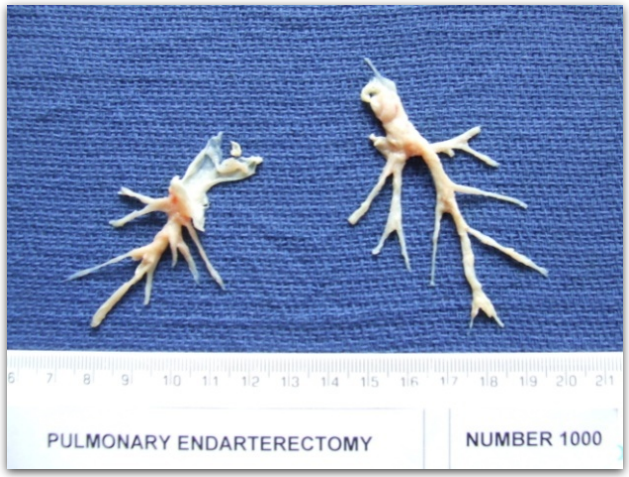
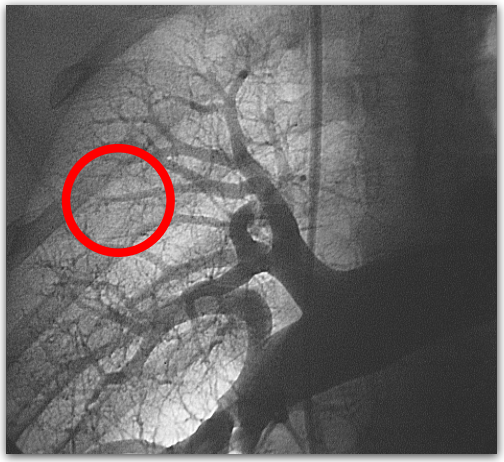
## Group 4: Chronic Thromboembolic Pulmonary Hypertension



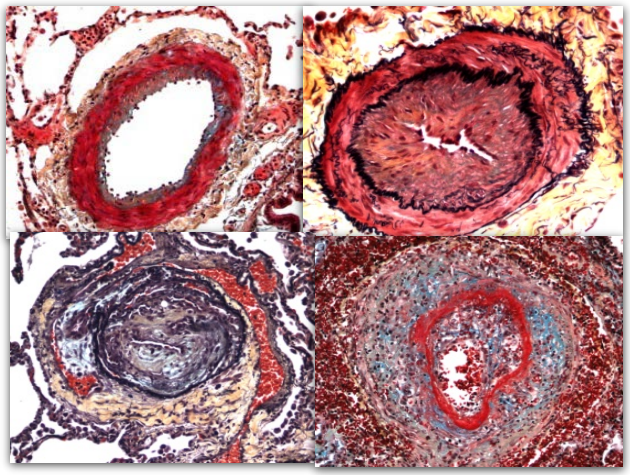
**OCCLUDED**

**Organized thromboemboli**



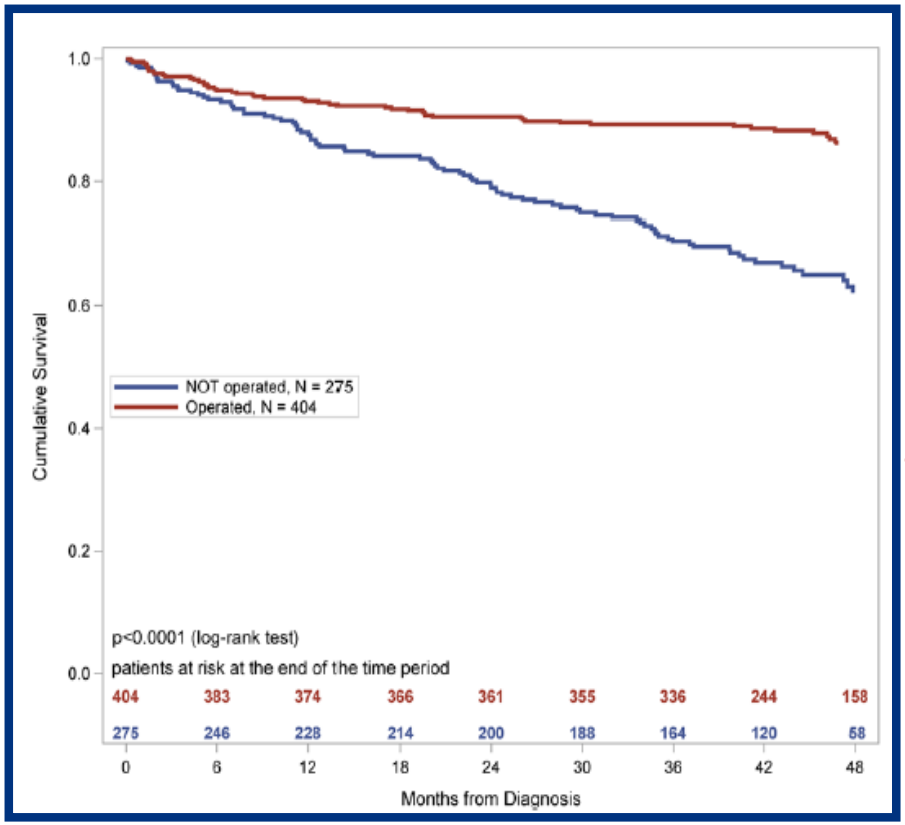
**Changes are similar to those seen in PAH**

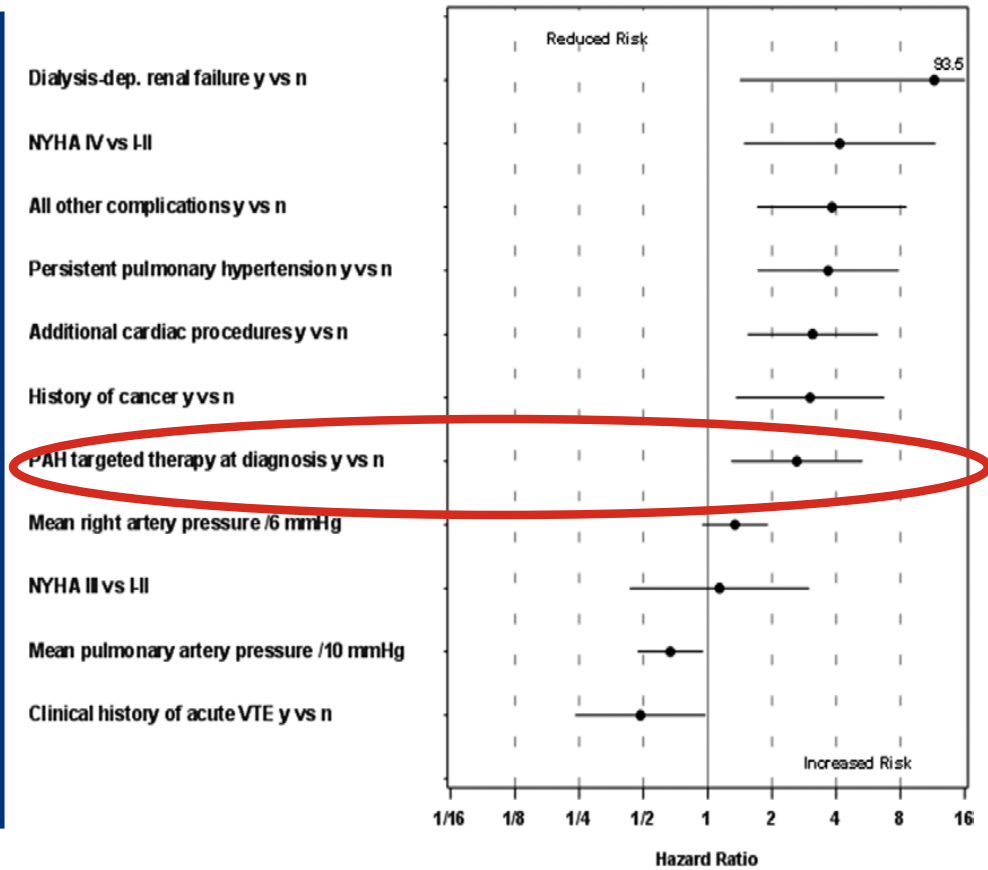


Angiogram and PEA specimen images are speaker's own.

# Group 4 PH: Chronic thromboembolic disease
# Long-term outcome from International Registry

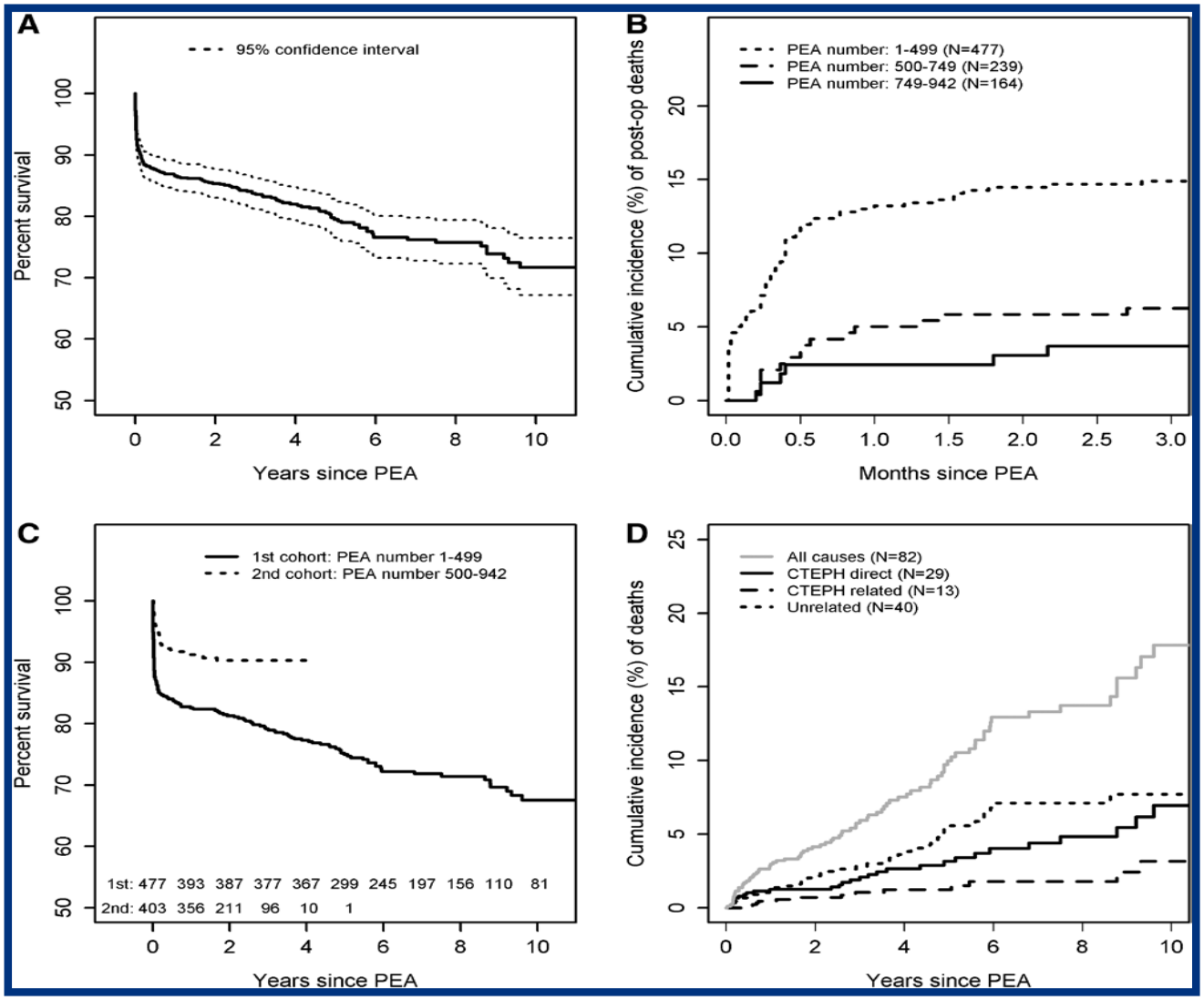
- 27 centers: operated vs non-operated CTEPH patients
- 629 patients prospectively enrolled over 24 months: Operated >survival
- Bridging with PAH therapy increased risk of death in operated patients; PAH therapy given to sicker patients in non-operated group, unclear benefit
- IVC filter did not improve mortality




Delcroix M. *Circulation* 2016:133:859-71.

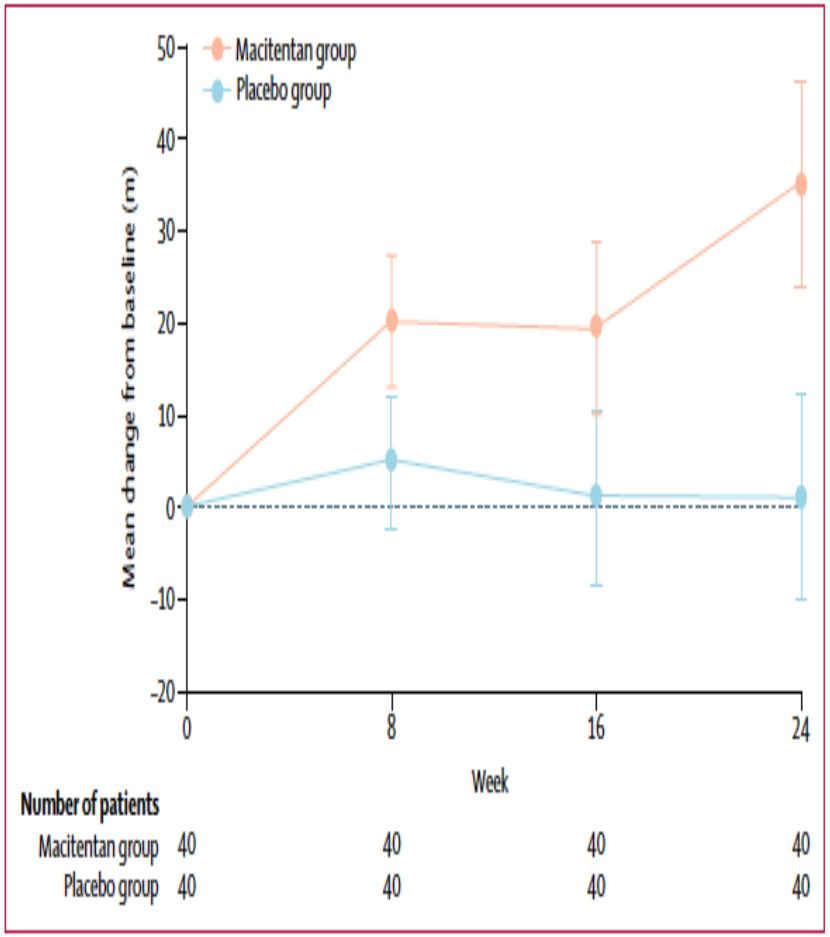
# Group 4 PH: Chronic thromboembolic disease Long-term outcome From UK National Cohort

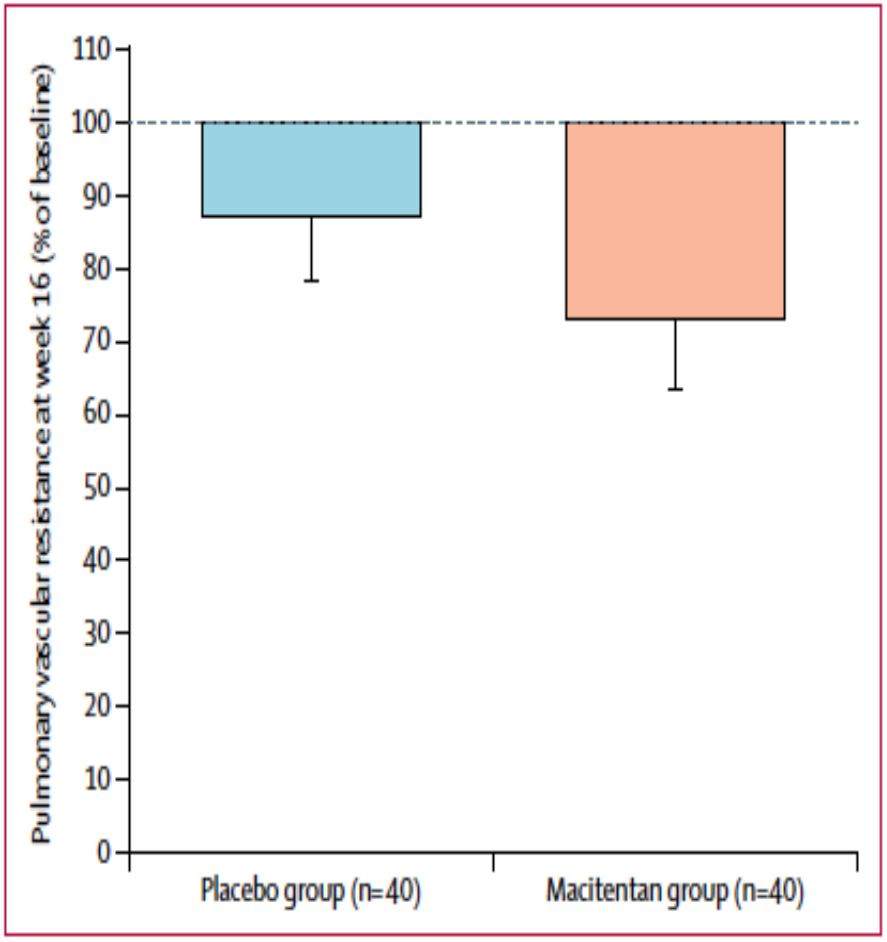



- 880 patients prospectively enrolled: RHC and non-invasive tests 3-6, +12 months after OR (1997-2012)
- Higher center experience= higher overall survival
- Worse mPAP≥38mmHg
- 51% mPAP>25 mmHg at 3-6 mo. Irrespective of immediate post-op HD

Cannon JE . *Circulation* 2016;133:1761-1771.

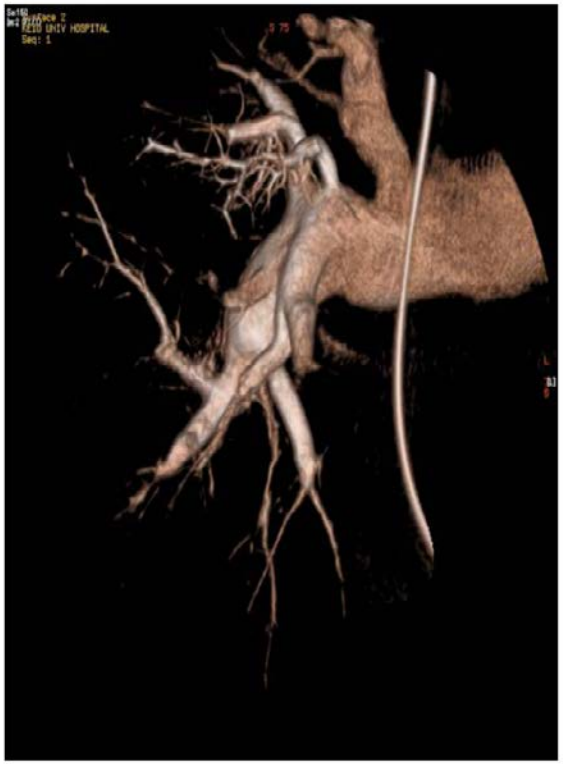
# MERIT-1: Macitentan in CTEPH Phase 2



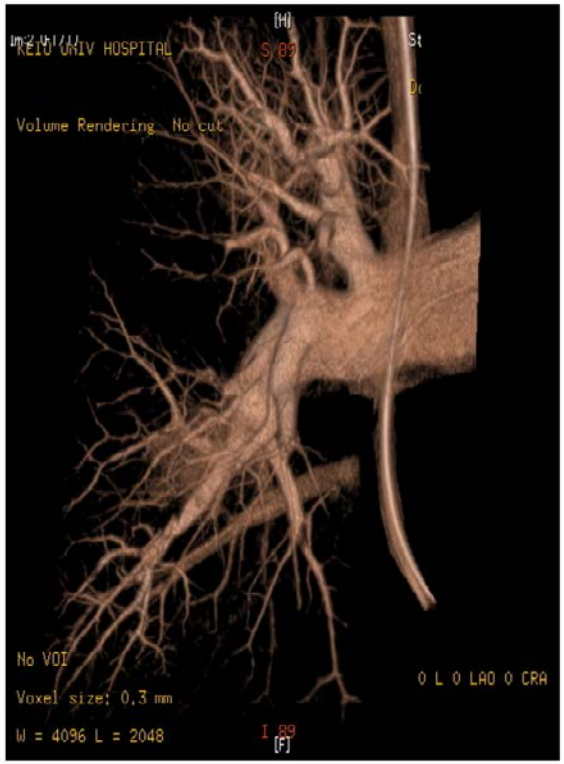




Ghofrani. *Lancet Resp Med* 2017 (online 9/11/17)

# Balloon pulmonary angioplasty (BPA) for CTEPH



Baseline




Follow-up

**Brief Rapid Communications**

## Balloon Pulmonary Angioplasty for Treatment of Chronic Thromboembolic Pulmonary Hypertension

Jeffrey A. Feinstein, MD, MPH; Samuel Z. Goldhaber, MD; James E. Lock, MD; Susan M. Ferndandes, PA-C; Michael J. Landzberg, MD

*Background*—Although pulmonary throm… nary hyp… cause of c… ategy of balloon pulmonary angioplasty (BPA).

*Methods and Results*—Eighteen patients (mean age, 51.8 years; range, 14 to 75 years) with CTEPH underwent BPA; they averaged 2.6 procedures (range, 1 to 5) and 6 dilations (range, 1 to 12). Selection of pulmonary artery segments for dilation required (1) complete occlusion, (2) filling defects, or (3) signs of intravascular webs. After an average of 36 months of follow-up (range, 0.5 to 66 months), the average New York Heart Association class improved from 3.3 to 1.8 ($P<0.001$), and 6-minute walking distances increased from 209 to 497 yards ($P<0.0001$). Pulmonary artery mean pressures decreased from 43.0… pulmonary edema; 3 required me…

*Conclusions*—BPA reduces pulmo… improvement in New York Heart Association class and … walking distances. BPA is a promising interventional technique that warrants randomized comparison with medical therapy in CTEPH patients who are not surgical candidates. (*Circulation*. 2001;103:10-13.)

Key Words: balloon ■ angioplasty ■ embolism ■ thrombus ■ pulmonary heart disease

**n=18**

**6WMD 209 =>497 yards**

**Reperfusion edema, n=11 (Mechanical ventilation, n=3)**

Kataoka M et al. *Circ Cardiovasc Interv* 2012;5:756-62
Feinstein JA. *Circulation* 2000;113:10-13.

# BPA German Experience

- 56 pts 266 BPA (median 5/pt), cath baseline and 24 weeks post BPA
- BPA improved 6mwd (+33m) RV function, hemodynamics (mPAP 18%, PVR 26%)
- Most common complication: pulmonary vascular injury & pulmonary bleeding- why?
- Undersize balloon, longer prevalence disease

| | Total | Hannover | Bad Nauheim |
|---|---|---|---|
| Interventions[#] n | 266 | 155 | 111 |
| Pulmonary arterial dissection without bleeding | 2 (0.8) | 1 (0.6) | 1 (0.9) |
| Vascular lesions with pulmonary bleeding but without haemoptysis | 3 (1.1) | 1 (0.6) | 2 (1.8)[¶] |
| Vascular lesions with haemoptysis | 15 (5.6) | 5 (3.2) | 10 (9) |
| Reperfusion oedema | 2 (0.8) | 0 (0) | 2 (1.8)[+] |
| Others | 3 (1.1) | 2 (1.3) | 1 (0.9) |
| Total | 25 (9.4) | 9 (5.8) | 16 (14.4) |

Data are presented as n (%), unless otherwise stated. [#]: others were groyne haematoma (n=1), peripheral arteriovenous fistula (n=1), induction of atrial fibrillation, self-limiting (n=1); [¶]: one event was fatal, see text for details; [+]: both patients recovered after noninvasive ventilation.

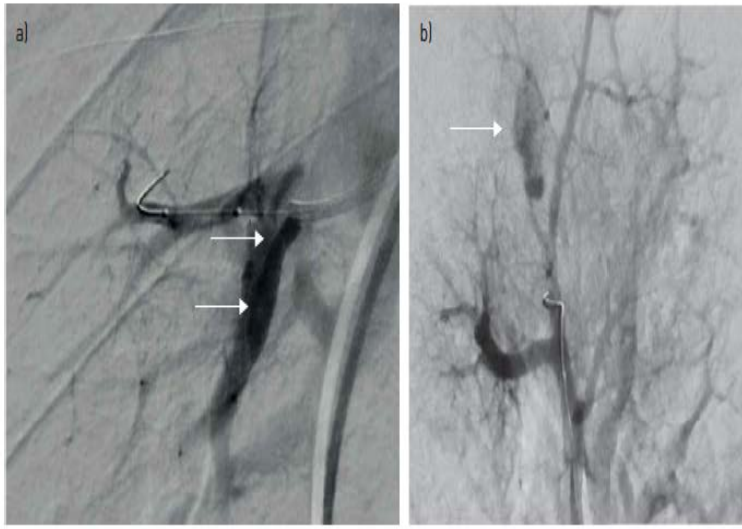



FIGURE 1 a) Digital subtraction angiography of the middle lobe arteries in a 63-year-old man with inoperabl chronic thromboembolic pulmonary hypertension (CTEPH) showing a pulmonary artery dissection (arrow after manipulation with the guiding catheter. b) Digital subtraction angiography of the right upper lob arteries in a 72-year-old woman with inoperable CTEPH showing pulmonary haemorrhage (arrow) after guid wire perforation.

Olsson KM. *Eur Respir J* 2017;49: Kataoka M et al. *Circ Cardiovasc Interv* 2012;5:756-62

# PH in 2017

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**In summary:**

- Group 1 PAH: New treatments, approaches, and risk assessment
- Group 2 PH-LHD: Better phenotyping, monitoring and targeted treatment trials
- Group IV CTEPH: Improved understanding of the epidemiology, surgical, medical, and interventional care