ΕΛΛΗΝΙΚΗ ΕΤΑΙΡΕΙΑ ΜΕΛΕΤΗΣ ΤΗΣ ΠΝΕΥΜΟΝΙΚΗΣ ΥΠΕΡΤΑΣΗΣ

1ο ΠΑΝΕΛΛΗΝΙΟ ΣΥΝΕΔΡΙΟ ΠΝΕΥΜΟΝΙΚΗΣ ΥΠΕΡΤΑΣΗΣ

Πνευμονική υπέρταση
Γκρίζες ζώνες στις Κατευθυντήριες Οδηγίες του 2015

Γεωργία Γ. Πίτσιου
Πνευμονολόγος- Εντατικολόγος
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Γ.Ν. "Γ.Παπανικολάου"

Conflict of interest

The speaker has received

Honoraria for lectures and/or consultancy for Actelion, Bayer, ELPEN, GSK and MSD.

- “Without data, you are just another person with an opinion”

W. Edwards Deming

National Academy of Sciences

1956

European Heart Journal Advance Access published August 29, 2015

European Heart Journal
doi:10.1093/eurheartj/ehv317

ESC/ERS GUIDELINES

2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS)

Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT)

Authors/Task Force Members: Nazzareno Galiè* (ESC Chairperson) (Italy), Marc Humbert*[a] (ERS Chairperson) (France), Jean-Luc Vachiery[c] (Belgium), Simon Gibbs (UK), Irene Lang (Austria), Adam Torbicki (Poland), Gérald Simonneau[a] (France), Andrew Peacock[a] (UK), Anton Vonk Noordegraaf[a] (The Netherlands), Maurice Beghetti[b] (Switzerland), Ardeschir Ghofrani[a] (Germany), Miguel Angel Gomez Sanchez (Spain), Georg Hansmann[b] (Germany), Walter Klepetko[c] (Austria), Patrizio Lancellotti (Belgium), Marco Matucci[d] (Italy), Theresa McDonagh (UK), Luc A. Pierard (Belgium), Pedro T. Trindade (Switzerland), Maurizio Zompatori[e] (Italy) and Marius Hoeper[a] (Germany)

2015 PH guidelines :

1. PH is defined only at rest. Exercise only to assess functional severity.

Definition	Characteristics[a]	Clinical group(s)[b]
PH	PAPm ≥25 mmHg	All
Pre-capillary PH	PAPm ≥25 mmHg PAWP ≤15 mmHg	1. Pulmonary arterial hypertension 3. PH due to lung diseases 4. Chronic thromboembolic PH 5. PH with unclear and/or multifactorial mechanisms
Post-capillary PH	PAPm ≥25 mmHg PAWP >15 mmHg	2. PH due to left heart disease 5. PH with unclear and/or multifactorial mechanisms
Isolated post-capillary PH (Ipc-PH)	DPG <7 mmHg and/or PVR ≤3 WU[c]	
Combined post-capillary and pre-capillary PH (Cpc-PH)	DPG ≥7 mmHg and/or PVR >3 WU[c]	

NO more definition for « Exercise PH » and « Out of proportion PH » (lack of evidence)

Eur Heart J 2015 doi:10.1093/eurheartj/ehv317, Eur Respir J, 2015

1. Definition: Exercise-induced PH

The limits of normal of the pulmonary circulation during exercise

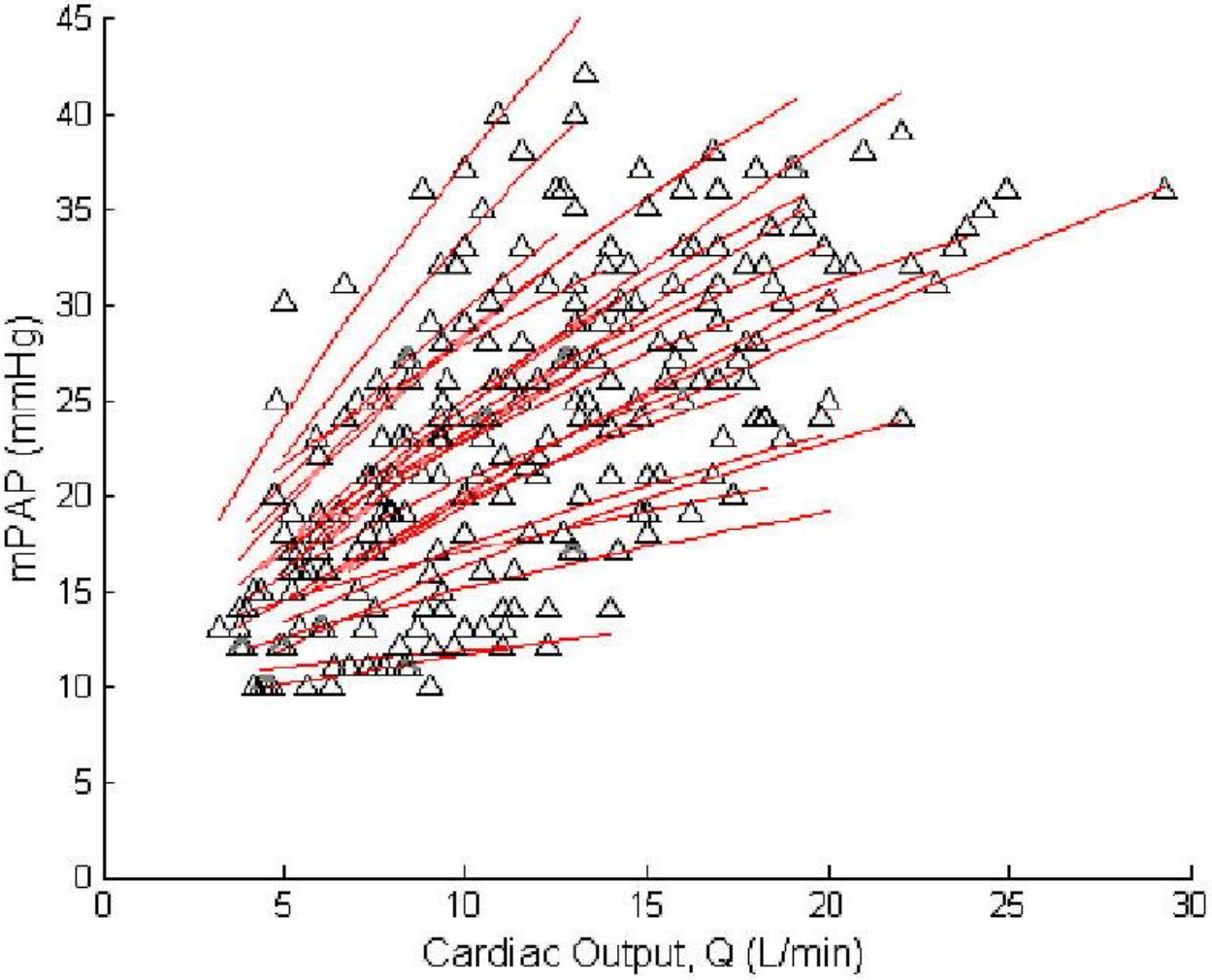
Review of 220 exercise RHC

- Mean PAP from 14±3 to 26±6, up to 45mmHg
- PAWP from 6±3 to 15±8, up to 35mmHg
- CO from 7.5±2 to 20±4, up to 30-35 L/min

Large variability of changes as a function of exercise modality (resistive, dynamic, during or after), workload or cardiac output, few data in older subjects

Kovacs et al. ERJ 2009, Naeije R et al. AJRCCM 2013

Variability of pulmonary artery pressure response to flow during exercise



Mean pulmonary artery pressure (mPAP) and cardiac output (Q) measurements at rest and at progressively increased workload in 25 healthy subjects. By best fit to a simple model of pulmonary vascular distensibility, a slight curvilinearity with convexity to the pressure axis can be seen in mPAP-Q relationships.

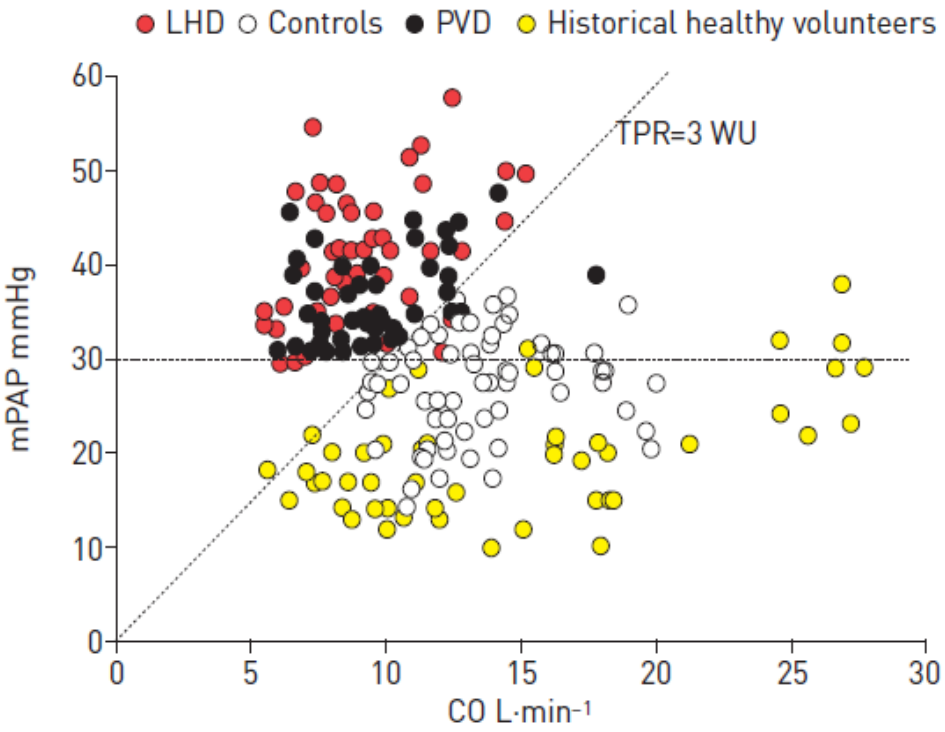
Argiento P. et al. ERJ 2010

1. Definition: Exercise-induced PH

Criteria for diagnosis of exercise pulmonary hypertension

Philippe Herve[1,2,3], Edmund M. Lau[2,4], Olivier Sitbon[2,3,5], Laurent Savale[2,3], David Montani[2,3,5], Laurent Godinas[2,3], Frederic Lador[2], Xavier Jaïs[2,3], Florence Parent[2,3], Sven Günther[2,3], Marc Humbert[2,3,5], Gerald Simonneau[2,3,5] and Denis Chemla[2,5]

Retrospective study n=169 pts
Compare the haemodynamic response during dynamic supine exercise in three groups of subjects



Pts with resting mPAP<20 mmHg

- *mPAP>30mmHg*
- *TPRmax=mPAP/CO>3mmHg.min.L^{-1}*

Naeije R et al. AJRCCM 2013, Herve P et al. ERJ 2015

1. Definition: Exercise-induced PH

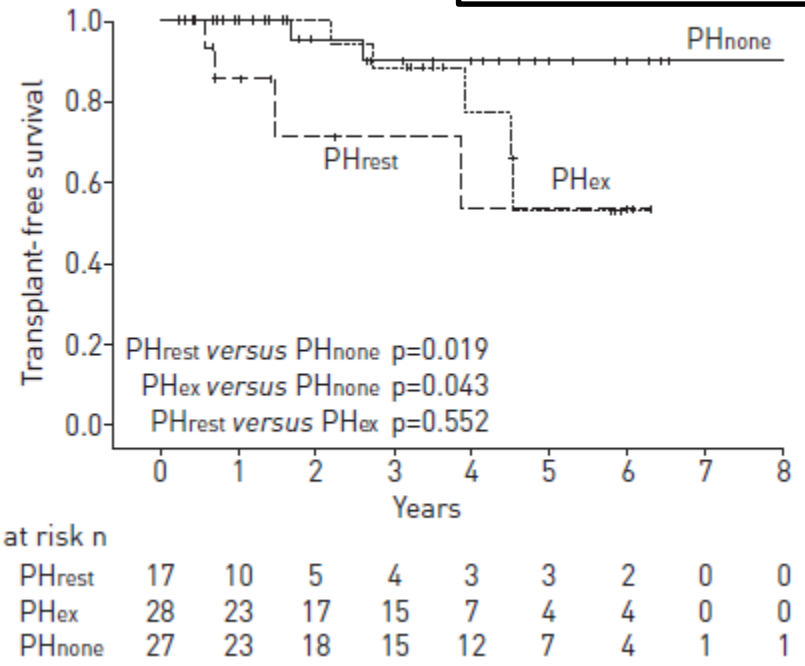
Exercise pulmonary haemodynamics predict outcome in patients with systemic sclerosis

Adriana Stamm[1], Stéphanie Saxer[1], Mona Lichtblau[1], Elisabeth D. Hasler[1], Suzana Jordan[2], Lars C. Huber[1], Konrad E. Bloch[3], Oliver Distler[2] and Silvia Ulrich[3]

72 SSc pts
- PH-rest n=17
- Exercise PH n=28
- No-PH n=27

TABLE 2 Haemodynamics of systemic sclerosis patients according to their haemodynamic classification into resting pulmonary hypertension (PH_{rest}), pulmonary hypertension during exercise (PH_{ex}) and without pulmonary hypertension (PH_{none})

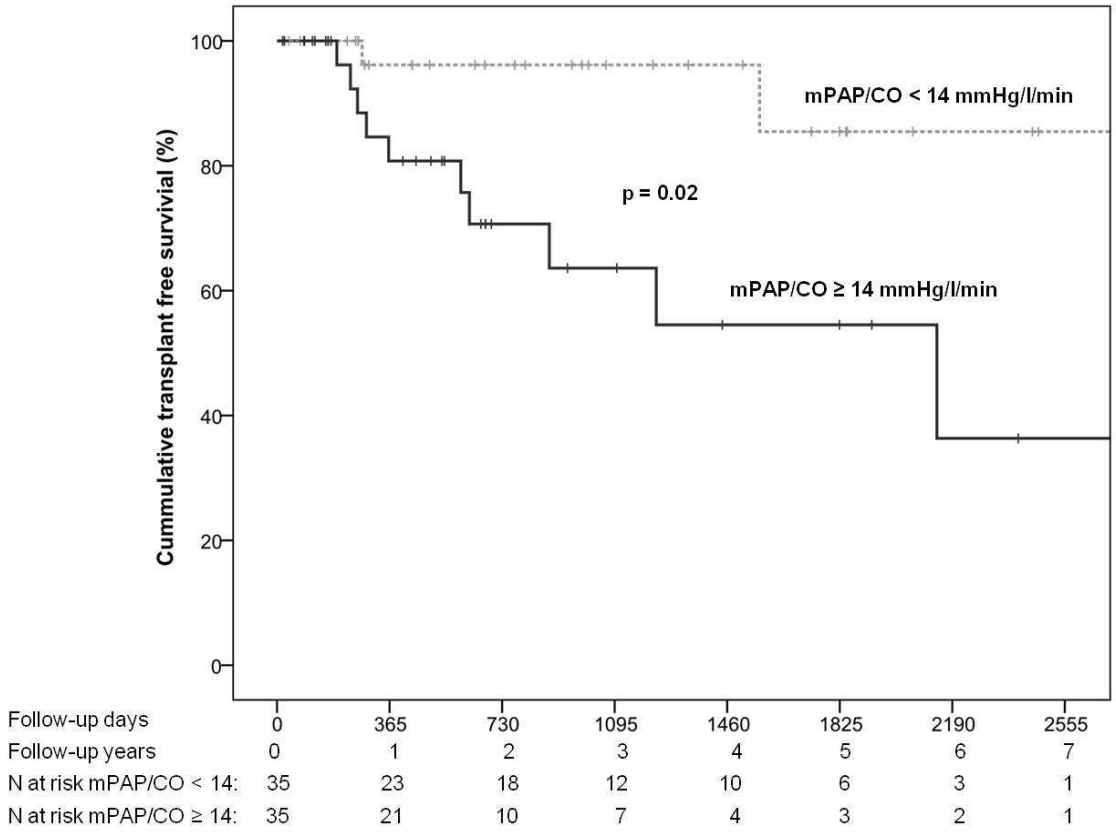
Variable	Patient groups		
	PH_{rest}	PH_{ex}	PH_{none}
Resting haemodynamics			
HR beats·min^{-1}	79 (69–93)	72 (63–78)	75 (68–81)
mBP mmHg	101 (89–113)*,#	89 (81–105)	89 (82–99)
mPAP mmHg	30 (26–43)**,##	20 (17–21)¶¶	16 (14–18)
PAWP mmHg	12 (10–13)*,#	10 (8–12)	9 (7–11)
RAP mmHg	8 (5–9)*,#	8 (4–8)	5 (4–8)
TPG mmHg	20 (16–25)**,##	9 (8–12)¶	7 (6–8)
CI L·min^{-1}·m^{-2}	2.9 (2.3–3.6)	3.3 (2.7–3.9)	3.2 (2.8–3.6)
CO L·min^{-1}	5.1 (3.7–6.4)	5.6 (4.4–6.9)	5.3 (4.4–6.7)
PVR WU	3.6 (2.9–6.1)***,##	1.6 (1.3–2.2)¶	1.3 (0.9–1.7)
Sa_{O_2} %	91 (89–94)**,#	95 (92–95)	95 (93–96)
Sv_{O_2} %	68 (62–70)*,#	71 (67–72)	71 (69–74)
Exercise haemodynamics			
Maximal workload W	20 (15–30)*	30 (20–40)	30 (30–40)
Maximal HR beats·min^{-1}	111 (101–126)	111 (99–123)	104 (100–120)
Maximal mBP mmHg	110 (99–127)*	111 (97–118)¶	99 (89–109)
Maximal mPAP mmHg	50 (45–62)**,##	33 (31–36)¶¶	24 (21–25)
Maximal PAWP mmHg	15 (11–17)*	16 (14–19)¶¶	11 (7–14)
Maximal RAP mmHg	10 (8–18)**,#	8 (5–10)¶	5 (2–6)
Maximal TPG mmHg	34 (26–44)**,##	19 (16–21)¶¶	12 (10–16)
Maximal CI L·min^{-1}·m^{-2}	3.5 (2.6–4.3)	4.2 (3.6–4.8)	3.9 (3.5–4.8)
Maximal CO L·min^{-1}	6.2 (4.1–7.4)#	7.1 (6.6–8.1)	6.9 (5.8–8.9)
Maximal PVR WU	5.4 (3.8–10)**,##	2.7 (2–3.1)¶	1.7 (1.0–2.1)
Maximal Sa_{O_2} %	91 (84–95)**,#	95 (89–96)	96 (95–97)
Maximal Sv_{O_2} %	62 (36–54)	67 (62–74)	69 (66–75)
ΔmPAP/ΔCO mmHg·min·L^{-1}	24 (15–81)**,#	9.4 (6–27)¶¶	3.7 (2–7)
Increase of mPAP with exercise mmHg	18 (12–24)**	14 (13–16)¶¶	7 (5–9)
Increase mPAP per Watt mmHg·W^{-1}	0.8 (0.5–1.2)**,#	0.6 (0.3–0.8)¶¶	0.2 (0.1–0.3)
Distensibility index α %·mmHg^{-1}	0.5 (0.2–0.6)**,##	0.7 (0.6–0.8)¶¶	1.2 (0.9–1.6)



Stamm A et al. ERJ 2016

1. Definition: Exercise-induced PH

Pressure-flow during exercise catheterization predicts survival in PH



- Higher NT-proBNP
- Lower 6MWT
- Worse WHO-FC
- Worse PROs

Retrospective study, n=70pts (PAH & CTEPH)

Pressure-flow-relationship during exercise predicted transplant-free-survival and correlated with established markers of disease severity and prognosis.

Hasler ED et al. Chest 2016

2. How to define PH due to left heart disease?

The diagnosis of pulmonary vascular disease in patients with LHD is more than just a new game of acronyms for dedicated experts

TABLE 1 Patients with pulmonary hypertension (PH) due to left heart disease (n=1506, mean pulmonary artery pressure ⩾25 mmHg, and mean pulmonary artery wedge pressure >15 mmHg) stratified by diastolic pulmonary vascular pressure gradient (DPG) and pulmonary vascular resistance (PVR)

	DPG <7 mmHg	DPG ⩾7 mmHg
PVR ⩽3 WU n (%)	858 (57.0)[#]	**44 (2.9)**
PVR >3 WU n (%)	**388 (25.8)**	216 (14.3)[¶]

Numbers in bold indicate the number of patients (432 (28.7%)) with DPG/PVR combinations that are unclassifiable using the current definition of the 2015 European Society of Cardiology and the European Respiratory Society guidelines [1, 2]. WU: wood units. [#]: isolated post- and pre-capillary PH with DPG <7 mmHg and/or PVR ⩽3 WU; [¶]: combined post- and pre-capillary PH with DPG ⩾7 mmHg and/or PVR >3 WU.

- *Ipc-PH: DPG <7 mmHg and/or PVR≤3 WU*
- *Cpc-PH : DPG≥7 mmHg **and** PVR>3 WU*

Post-capillary PH	PAPm ≥25 mmHg PAWP >15 mmHg
Isolated post-capillary PH (Ipc-PH)	DPG <7 mmHg and/or PVR ≤3 WU[c]
Combined post-capillary and pre-capillary PH (Cpc-PH)	DPG ≥7 mmHg and/or PVR >3 WU[c]

European Journal of Heart Failure (2017)
doi:10.1002/ejhf.860

Pulmonary hypertension due to left heart disease: analysis of survival according to the haemodynamic classification of the 2015 ESC/ERS guidelines and insights for future changes

Massimiliano Palazzini†, Fabio Dardi†, Alessandra Manes, Maria L. Bacchi Reggiani, Enrico Gotti, Andrea Rinaldi, Alessandra Albini, Enrico Monti, and Nazzareno Galiè*

Gerges M, Gerges C, Lang IM. ERJ 2016,
Palazzini et al. Eur J Heart Failure 2017

PAH Challenges
High-Risk Populations

Patients with PAPm values between 21 and 24 mm Hg should be carefully followed, in particular when they are at risk for developing PAH

- *SSc*
- *Family members of pts with heritable PAH*

ESC/ERS guidelines 2015

3. Borderline PH: what is the outcome?

ARTHRITIS & RHEUMATISM
Vol. 65, No. 4, April 2013, pp 1074–1084
DOI 10.1002/art.37838

Borderline Mean Pulmonary Artery Pressure in Patients With Systemic Sclerosis

Transpulmonary Gradient Predicts Risk of Developing Pulmonary Hypertension

Christopher J. Valerio, Benjamin E. Schreiber, Clive E. Handler, Christopher P. Denton, and John G. Coghlan

Chest

Volume 146, Issue 6, December 2014, Pages 1486–1493

Original Research: Pulmonary Vascular Disease

Characterization of Patients With Borderline Pulmonary Arterial Pressure

Gabor Kovacs, MD[a], Alexander Avian, PhD[b], Maria Tscherner, MD[a], Vasile Foris, MD[a], Gerhard Bachmaier, PhD[c], Andrea Olschewski, MD[d], Horst Olschewski, MD, FCCP[a]

Show more

Visovatti *et al. Arthritis Research & Therapy* (2014) 16:493
DOI 10.1186/s13075-014-0493-1

arthritis research&therapy

RESEARCH ARTICLE Open Access

Borderline pulmonary arterial pressure in systemic sclerosis patients: a post-hoc analysis of the DETECT study

Scott H Visovatti[1], Oliver Distler[2], J Gerry Coghlan[3], Christopher P Denton[4], Ekkehard Grünig[5], Diana Bonderman[6], Ulf Müller-Ladner[7], Janet E Pope[8], Madelon C Vonk[9], James R Seibold[10], Juan-Vicente Torres-Martin[11], Martin Doelberg[11], Harbajan Chadha-Boreham[11], Daniel M Rosenberg[11], Vallerie V McLaughlin[1] and Dinesh Khanna[12,13*]

Kovacs and Olschewski *Arthritis Research & Therapy* (2015) 17:123
DOI 10.1186/s13075-015-0649-7

arthritis research&therapy

EDITORIAL Open Access

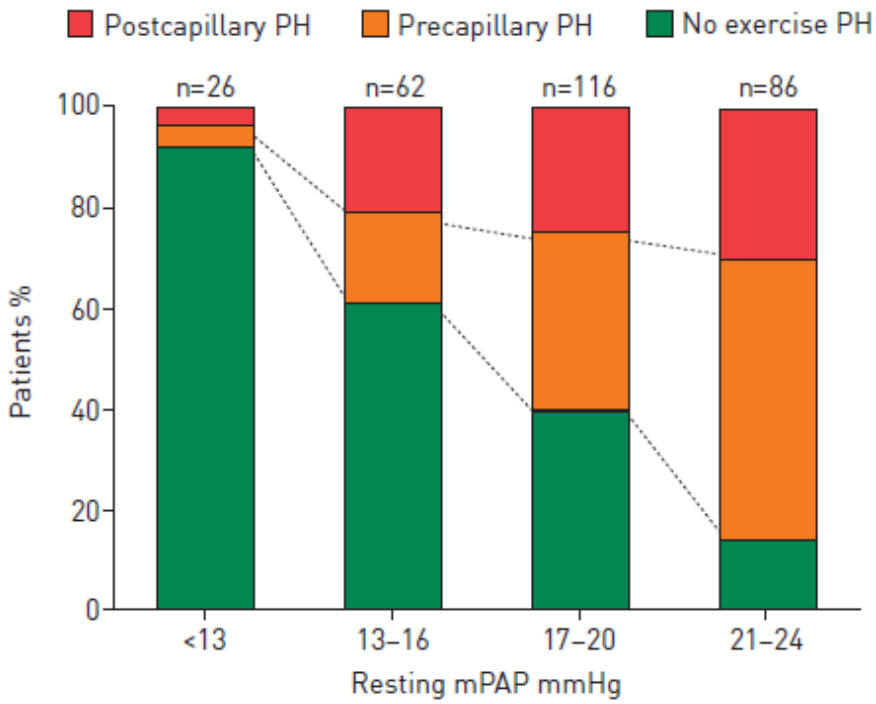
Borderline pulmonary pressures in scleroderma - a 'pre-pulmonary arterial hypertension' condition?

Gabor Kovacs[1,2*] and Horst Olschewski[1,2]

3. Borderline PH

Resting pulmonary artery pressure of 21–24 mmHg predicts abnormal exercise haemodynamics

Edmund M.T. Lau[1,2,3,4,8], Laurent Godinas[2,3,4,5,8], Olivier Sitbon[2,3,4], David Montani[2,3,4], Laurent Savale[2,3,4], Xavier Jaïs[2,3,4], Frederic Lador[3,6], Sven Gunther[2,3,4], David S. Celermajer[1], Gérald Simonneau[2,3,4], Marc Humbert[2,3,4], Denis Chemla[2,4] and Philippe Herve[3,4,7]



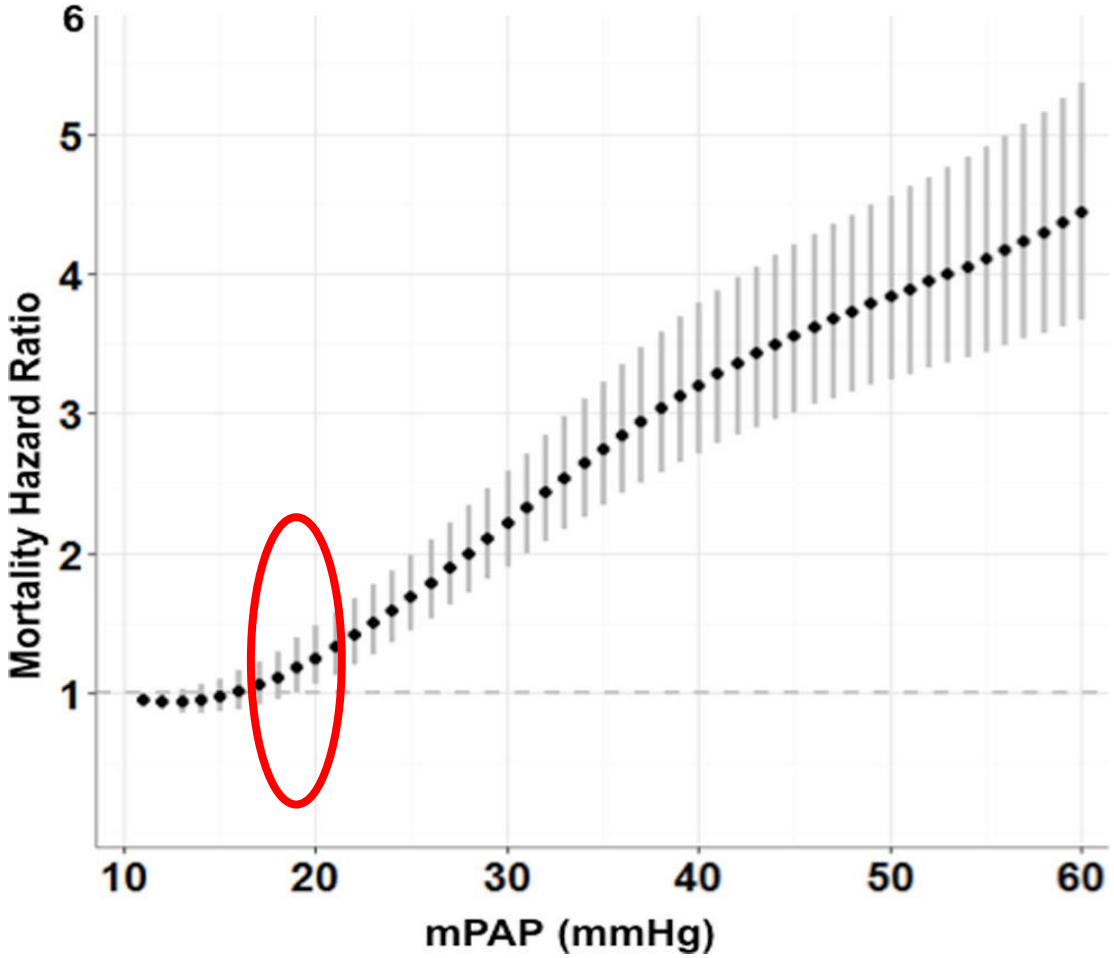
- Retrospective analysis
- Pts (n=290) with resting PH<25mmHg referred for suspected PH or unexplained dyspnea

- Pts with a resting mPAP 21–24 mmHg: high prevalence of an abnormal pulmonary vascular response during exercise, together with reduced exercise capacity and functional status

Lau EMT et al. ERJ 2016

3. Borderline PH

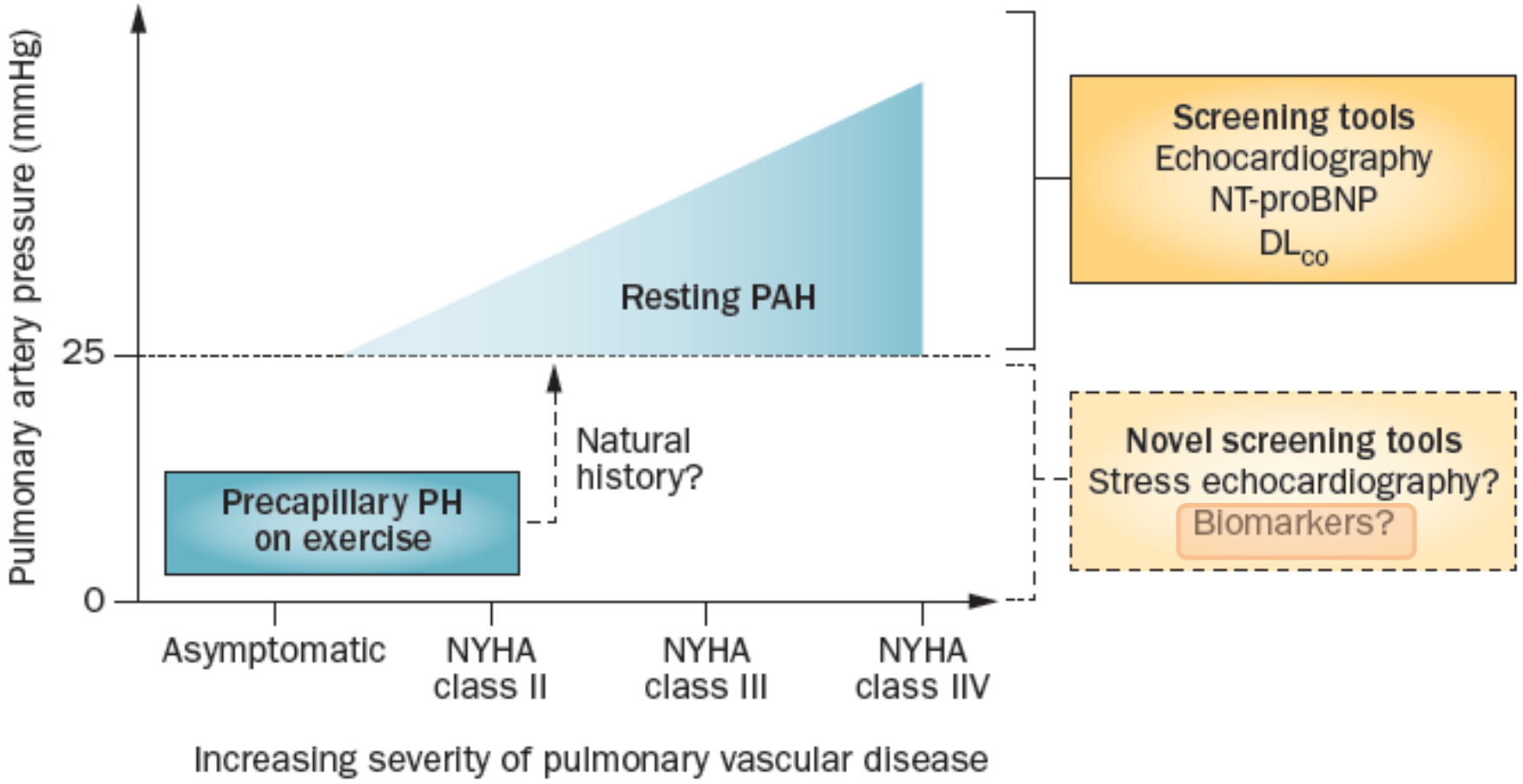
- Mortality is directly proportional to mean Pulmonary Arterial Pressure



- Large VA cohort with RHC data
- Pts with a mean pressure of 19-24mmHg were older and African American
- Pts with a mean pressure of 19-24mmHg had higher prevalence of metabolic disease

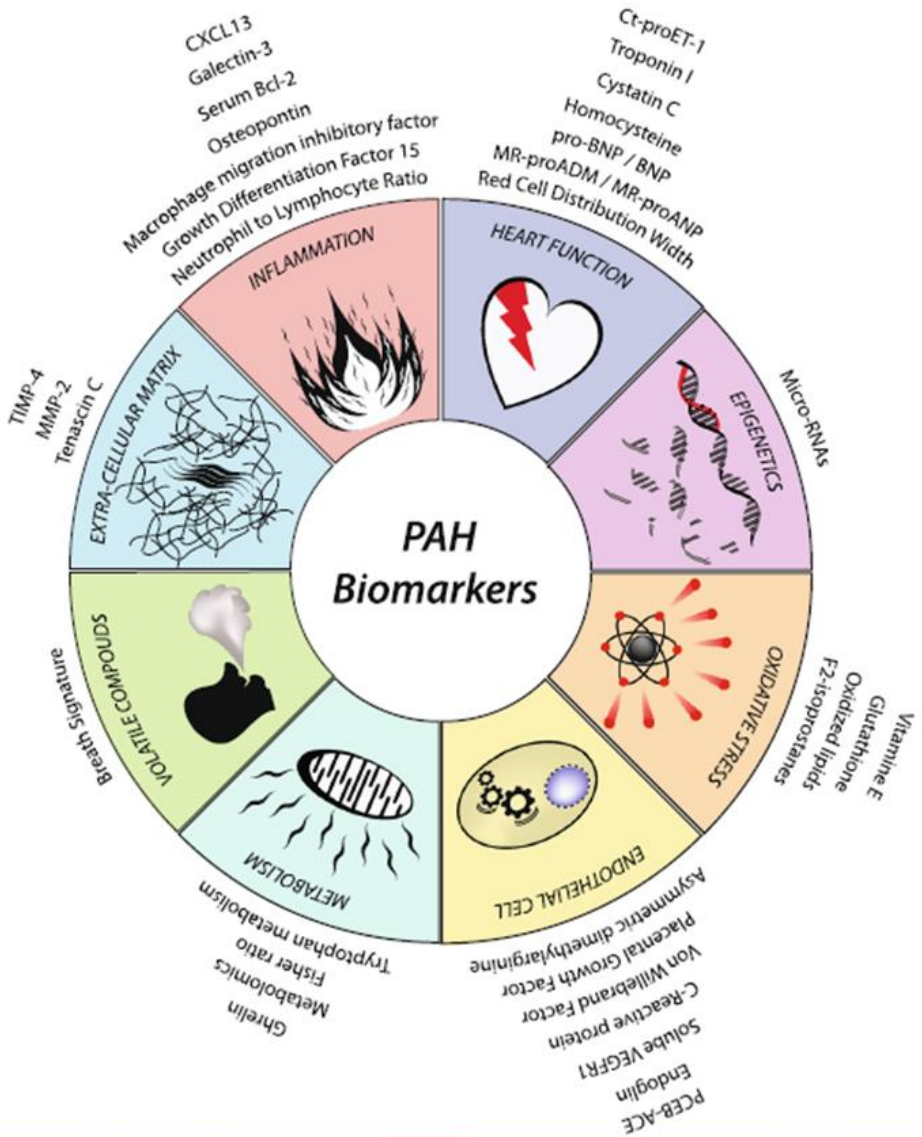
Maron BA et al. Circulation 2016

4. Screening-Early diagnosis



Humbert et al, Circulation. 2014;130:2189-2208

Screening: Biomarkers in PAH



- Predictive biomarkers
- Prognostic biomarkers

Anwar et al. Respiratory Research (2016) 17:88

Screening- Monitor: Biomarkers in PAH

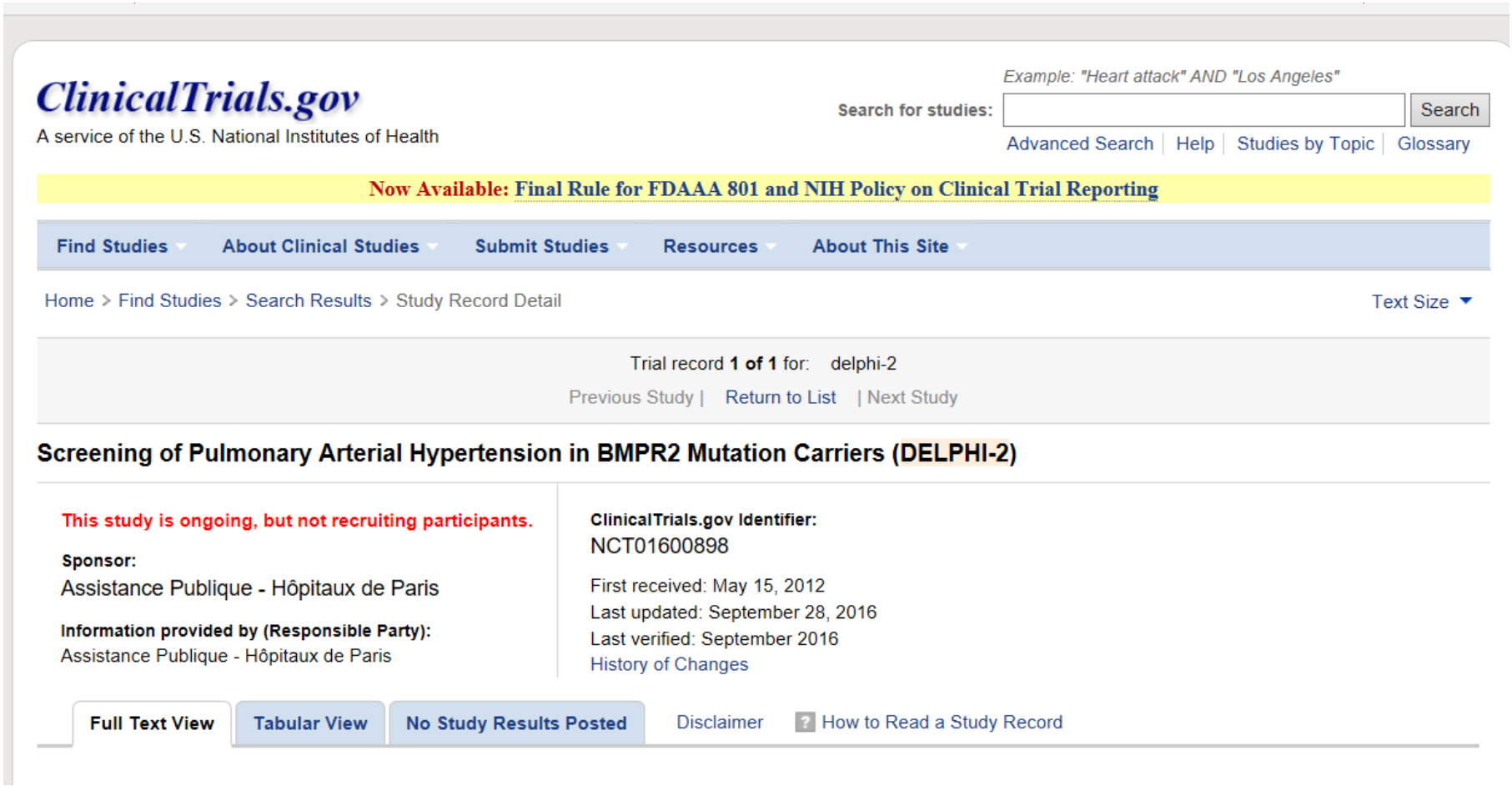
Table 10 Comparison Among Main Features of Biomarkers That May Influence Their Use in Clinical Practice

Biomarker	Availability	Cost	Specificity for disease	Immediacy of access to information	Prognostic impact
BNP	+++	+	–	+	+
NT-proBNP	+++	+	–	+	+
Endothelin-1	+	++	–	–	+
Adrenomedullin	+	++	–	–	+
Copeptin	+	++	–	–	+
Troponins	+++	+	– –	+	+
Markers of inflammation	+++	+	– –	+	+
Markers of oxidative stress	+	++	– –	–	+
Angiopoietin-2	+	++	–	–	+
Osteopontin	+	++	–	–	+
GDF-15	+	++	–	–	+
Exhaled nitric oxide	+	++	–	–	+
ADMA	+	++	–	–	+
Serotonin	+	++	–	–	
Microparticles	+	++	–	–	NA
Plasma von Willebrand factor	+	++	–	–	+
CD40 ligand	+	++	–	–	NA
D-dimer	+++	–	–	+	+
Renal function	+++	–	–	+	+
Hyponatremia	+++	–	–	+	+
Uric acid	+++	–	-	+	+
Liver function	+++	–	–	+	+
Micro RNA	+	+++	+	–	NA
PIM-1	–	+++	+	–	+
Genomics and proteomics biomarkers	–	+++	+	–	NA

ADMA, asymmetric dimethylarginine; BNP, brain natriuretic peptide; GDF-15, growth differentiation factor-15; NA, not assessed; PIM-1, provirus integration site for Moloney murine leukemia virus.

Pezzuto B et al. J Heart Lung Transplant 2015

Screening: Exercise hemodynamics in BMPR2 Carriers



ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Example: "Heart attack" AND "Los Angeles"
Search for studies: Search
Advanced Search | Help | Studies by Topic | Glossary

Now Available: Final Rule for FDAAA 801 and NIH Policy on Clinical Trial Reporting

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Text Size

Trial record 1 of 1 for: delphi-2
Previous Study | Return to List | Next Study

Screening of Pulmonary Arterial Hypertension in BMPR2 Mutation Carriers (DELPHI-2)

This study is ongoing, but not recruiting participants.

Sponsor:
Assistance Publique - Hôpitaux de Paris

Information provided by (Responsible Party):
Assistance Publique - Hôpitaux de Paris

ClinicalTrials.gov Identifier:
NCT01600898

First received: May 15, 2012
Last updated: September 28, 2016
Last verified: September 2016
History of Changes

Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read a Study Record

5. Fluid challenge

Fluid challenge may be useful in identifying patients with occult HFpEF, but this technique requires meticulous evaluation and standardization before its use in clinical practice can be recommended.

- *Agreement is emerging about 500 ml of saline given over 5 to 10 min and a PAWP of 18 mmHg as an upper limit of a normal response*

Invasive Assessment of Pulmonary Hypertension

Time for a More Fluid Approach?

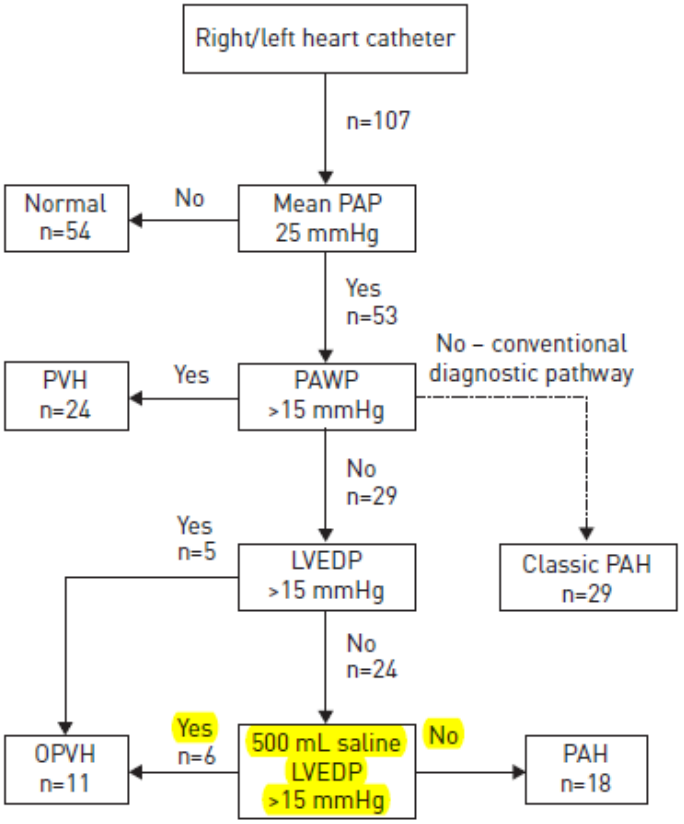
Barry A. Borlaug, MD

D'Alto M et al. Chest 2017, Fujimoto N et al. Circulation 2013
Borlaug BA et al. Circ Heart Fail. 2014

High prevalence of occult left heart disease in scleroderma-pulmonary hypertension

Benjamin D. Fox[1,2], Avi Shimony[1], David Langleben[1], Andrew Hirsch[1], Lawrence Rudski[1], Robert Schlesinger[1], Mark J. Eisenberg[1], Dominique Joyal[1], Marie Hudson[1], Kim Boutet[3], Alexandrina Serban[3], Ariel Masetto[4] and Murray Baron[1]

Eur Respir J 2013; 42: 1083–1091

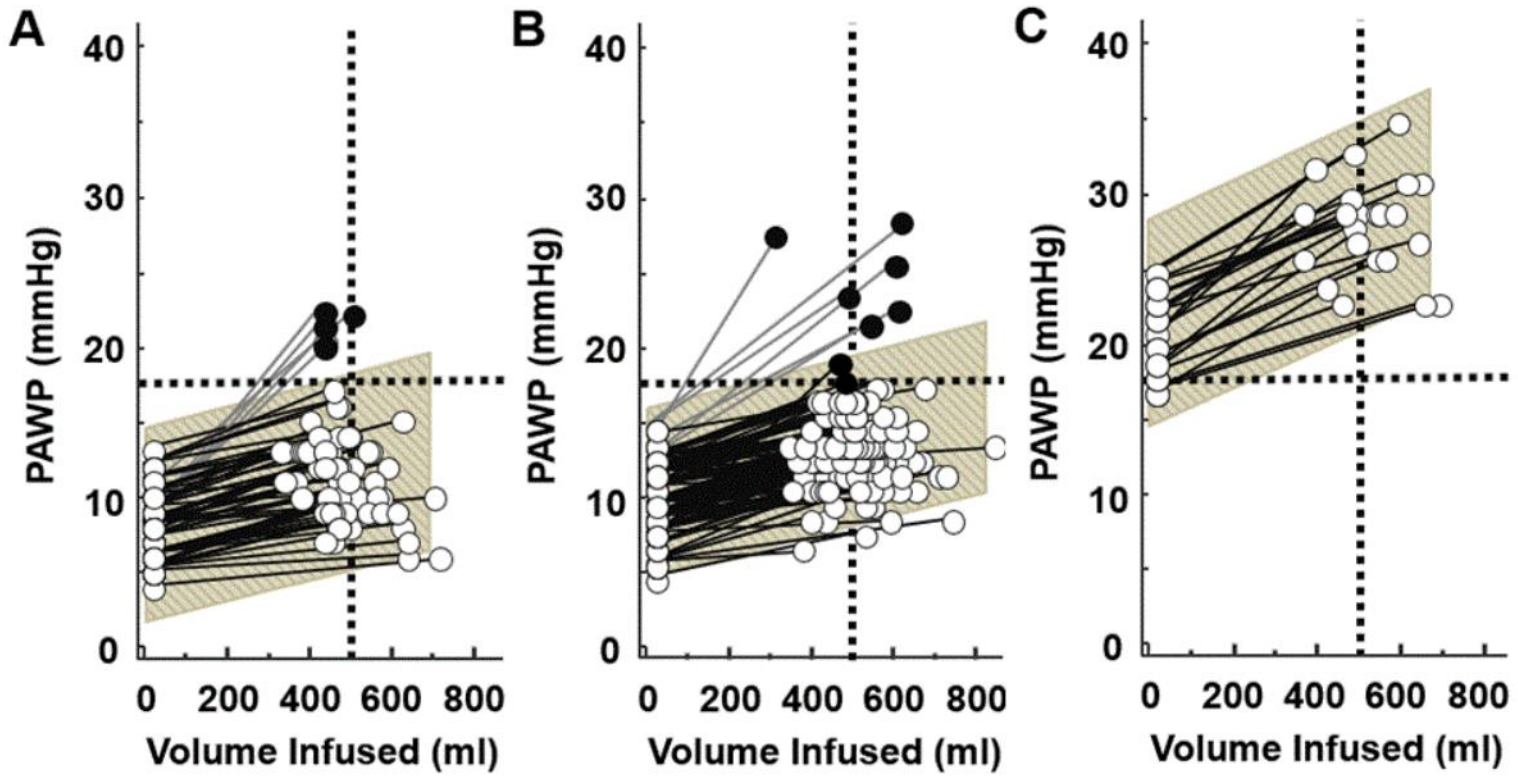


- Retrospective review of 107 SSc patients
- Right and left catheterization data (LVEDP pre-/post-fluid challenge)

- PH: 53/107
- PAH: 18/53 (33%)
- PVH: 24/53 + OPVH:11/53 (66%)
- 11 PAH patients were reclassified as occult PVH (OPVH)

Pulmonary venous hypertension has high prevalence in SSc-PH population

5. Fluid challenge



No PH controls | Pre-capillary PH | Post-capillary PH

- Administration of 7 ml/kg of saline given in 5 to 10 minutes
- A PAWP > 18 mmHg after fluid challenge indeed allowed to reclassify 6 % of pre-capillary PH and 8 % of no-PH patients as having post capillary PH

D'alto M et al. Chest 2017

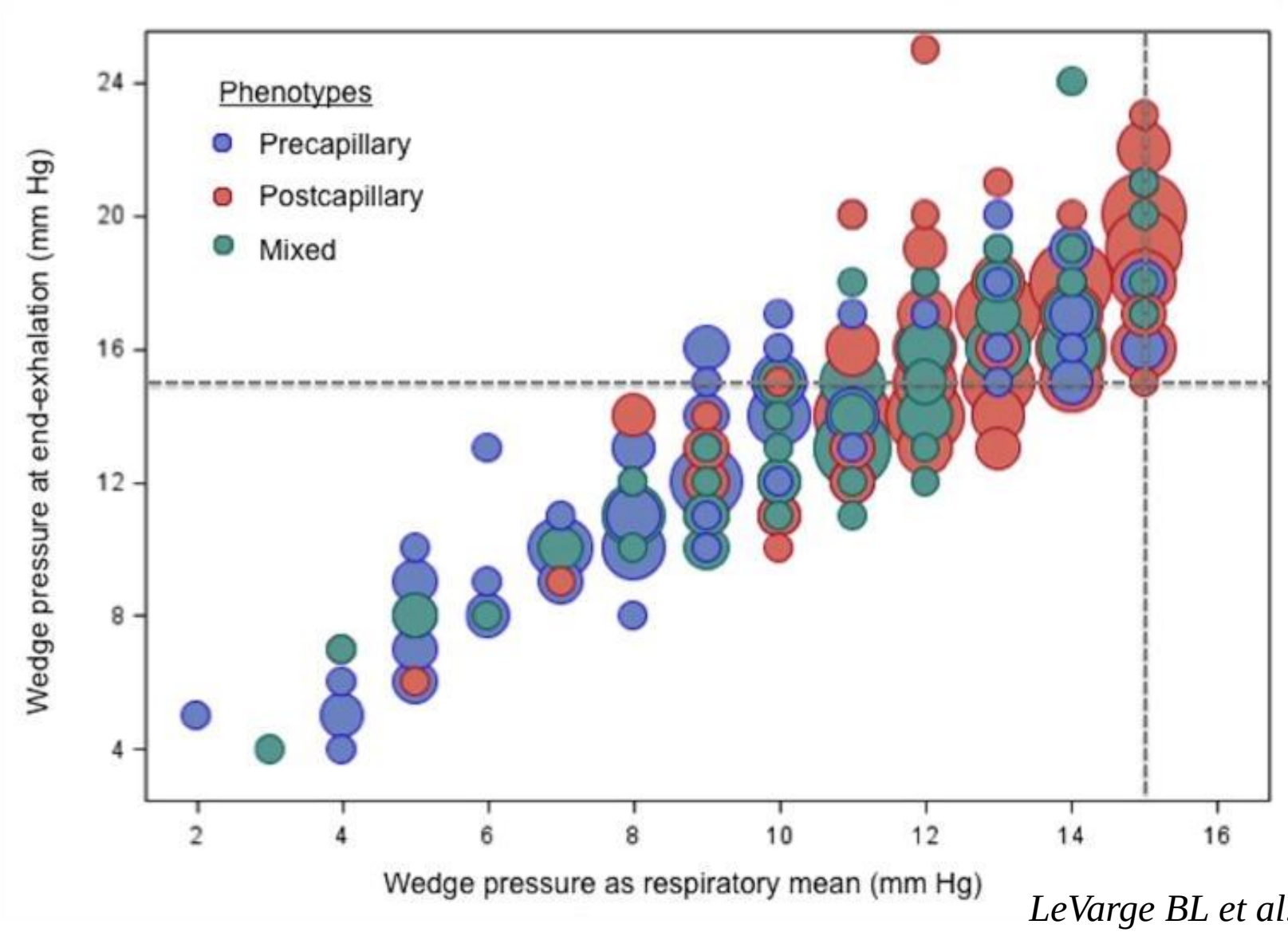
2015 PH guidelines :

1. PH is defined only at rest.
2. Ultrasound assessment of PH
3. **Right heart catheterization**

Recommendations	Class[a]	Level[b]	Ref.[c]
RHC is recommended to confirm the diagnosis of pulmonary arterial hypertension (group 1) and to support treatment decisions	I	C	
In patients with PH, it is recommended to perform RHC in expert centres (see section 12) as it is technically demanding and may be associated with serious complications	I	B	69
RHC should be considered in pulmonary arterial hypertension (group 1) to assess the treatment effect of drugs (Table 16)	IIa	C	

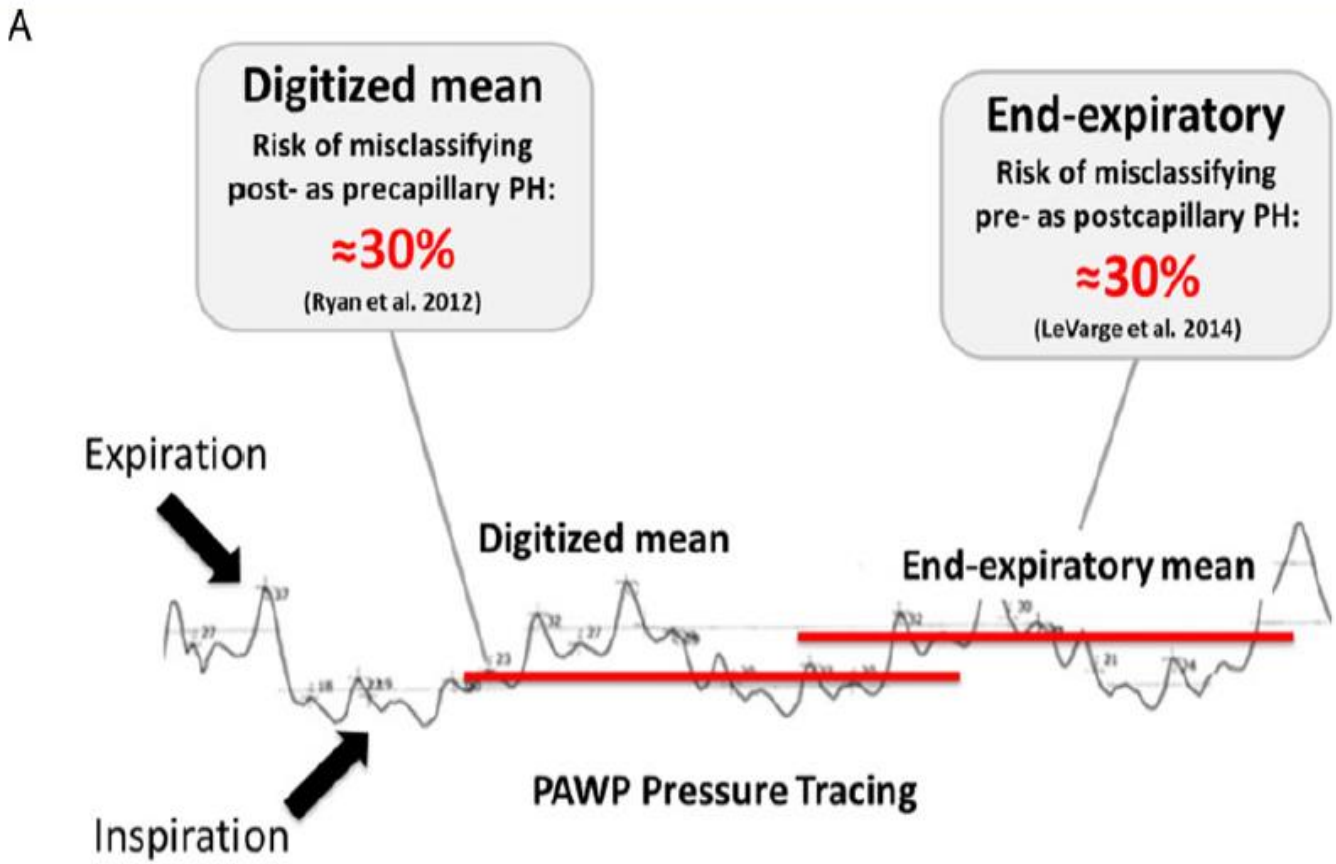
Eur Heart J 2015 doi:10.1093/eurheartj/ehv317,
Eur Respir J, 2015

6. Right heart catheterization:
The dilemma of PAWP measurements



LeVarge BL et al. ERJ 2014

6. Right heart catheterization:
The dilemma of PAWP measurements



Potential misclassifications between pre- and post-capillary pulmonary hypertension depending on the method of PAWP reading

S. Rosenkranz et al. Eur Heart J 2015

7. Phenotyping PH

Registries: The Changing Phenotype of PAH

- Elderly patients, mean age at diagnosis 50-65 years
- Comorbidities
- Female predominance is quite variable

Table 1 General Information of PAH Registries From Different Countries and Time Periods

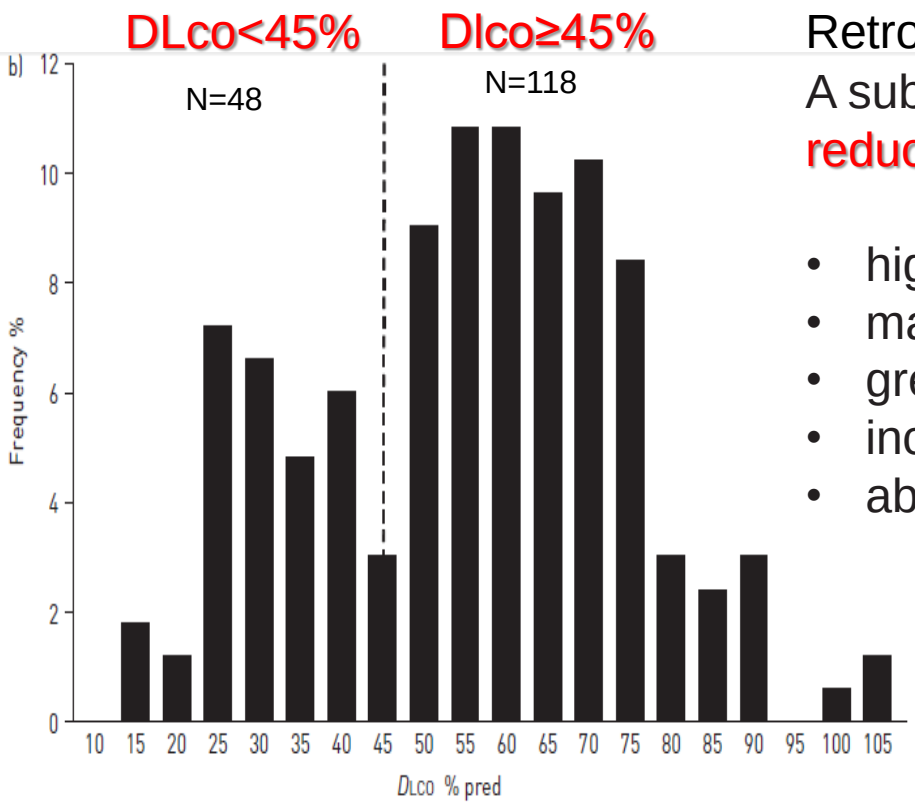
Registry (Ref. #)	Study Cohort	Study Design and Time Period	No. of Centers	No. of Patients	Incidence/Prevalence	Predominant Etiologies of PAH
U.S. NIH (17,18)	IPAH	Prospective, 1981–1985	32	187	NA	NA
U.S. PHC (19)	Group 1 PH, age >18 yrs	Retrospective, 1982–2004; prospective, 2004–2006	3	578	NA	IPAH, 48%; CTD-PAH, 30%; CHD-PAH, 11%
Scottish-SMR (20)	Group 1 PH (IPAH, CHD-PAH, and CTD-PAH), age 16–65 yrs	Retrospective, 1986–2001	NA	374	PAH, 7.6/26 cases/MAI; IPAH, 2.6/9 cases/MAI	IPAH, 47%; CTD-PAH, 30%; CHD-PAH, 23%
French (9,21,22)	Group 1 PH, age >18 yrs	Prospective, 2002–2003	17	674	PAH, 2.4/15 cases/MAI; IPAH, 1.0/5.9 cases/MAI	IPAH, 39%; CTD-PAH, 15% (SSc, 76%); CHD-PAH, 11%
Chinese (23)	IPAH and HPAH	Prospective, 1999–2004	1	72	NA	NA
U.S. REVEAL (8,24–33)	Group 1 PH	Prospective, 2006–2009	55	3,515 (age >3 months)	PAH, 2.0/10.6 cases/MAI IPAH, 0.9 cases/MAI	IPAH, 46%; CTD-PAH, 25% (SSc, 62%); CHD-PAH, 10%
Spanish (34)	Group 1 PH and CTEPH, age >14 yrs	Retrospective, 1998–2006; prospective, 2007–2008	31	PAH, 866; CTEPH, 162	PAH, 3.2/16 cases/MAI; IPAH, 1.2/4.6 cases/MAI	IPAH, 30%; CTD-PAH, 15% (SSc 61%); CHD-PAH, 16%
UK (6,35)	IPAH, HPAH, and anorexigen-associated PAH	Prospective, 2001–2009	8	482	1.1/6.6 cases/MI	NA
New Chinese Registry (36,37)	Group 1 PH, age >18 yrs	Prospective, 2008–2011	9	956	NA	CHD-PAH, 43%; IPAH, 35%; CTD-PAH, 19% (SLE, 51%; SSc, 9%)
Mayo (38)	Group 1 PH	Prospective, 1995–2004	1	484	NA	IPAH, HPAH 56%; CTD-PAH, 24%, other, 20%
Compera (39)	IPAH, age >18 yrs	Prospective, 2007–2011	28	587	NA	IPAH, 100%

CHD = congenital heart disease; CTD = connective tissue disease; CTEPH = chronic thromboembolic pulmonary hypertension; HPAH = heritable pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension; MAI = million adult inhabitants; MI = million inhabitants; NA = not available; NIH = National Institutes of Health; PAH = pulmonary arterial hypertension; PHC = pulmonary hypertension connection; SMR = Scottish morbidity record; SSc = systemic sclerosis.

McGoon et al. JACC 2013

7. Phenotyping PH

The distribution of DLco in IPAH



Retrospective, 166 IPAH patients

A subgroup of IPAH patients with a severely reduced DLco has a distinct clinical profile:

- higher age
- male sex
- greater tobacco exposure,
- increased prevalence of coronary disease
- abnormalities on chest CT scan

- *Worse exercise performance and worse survival rate*

Trip P et al. ERJ 2013

How to explain?

- Unmasked Pulmonary Veno Occlusive Disease?

  Godinas L et al.J Heart Lung Transplant 2016
- Unmasked left heart disease and/or lung disease?
- Different entity?

Further pathological studies are required!

7. Phenotyping PH

Pre-Capillary, Combined, and Post-Capillary Pulmonary Hypertension

A Pathophysiological Continuum

Christian F. Opitz, MD,[a,b] Marius M. Hoeper, MD,[c] J. Simon R. Gibbs, MD,[d] Harald Kaemmerer, MD, VMD,[e] Joanna Pepke-Zaba, MD,[f] J. Gerry Coghlan, MD,[g] Laura Scelsi, MD,[h] Michele D'Alto, MD,[i] Karen M. Olsson, MD,[c] Silvia Ulrich, MD,[j] Werner Scholtz, MD,[k] Uwe Schulz, MD,[l] Ekkehard Grünig, MD,[m] Carmine D. Vizza, MD,[n] Gerd Staehler, MD,[o] Leonhard Bruch, MD,[p] Doerte Huscher, MSc, PhD,[q,r] David Pittrow, MD,[s] Stephan Rosenkranz, MD[t,u]

TABLE 1 Baseline Characteristics

	All Patients (N = 786)	Typical IPAH (n = 421)	Atypical IPAH (n = 139)	Typical vs. Atyp IPAH p Value
Age, yrs	66.6 ± 15.0	61.5 ± 17.3	71.3 ± 9.2	<0.001
Female	467 (59.4)	250 (59.4)	77 (55.4%)	1.000
BMI, kg/m^2	28.1 (24.5-32.6)	26.0 (23.3-29.8)	32.2 (28.3-36.0)	<0.001
WHO-FC				0.089
I/II	91 (11.8)	71 (17.4)	12 (8.8)	
III	540 (70.3)	275 (67.6)	96 (70.6)	
IV	137 (17.8)	61 (15.0)	28 (20.6)	
6MWD, m	289.5 ± 121.8	319.0 ± 123.5	250.5 ± 104.2	<0.001
RAP, mm Hg	9.8 ± 5.4	8.5 ± 5.2	8.9 ± 4.8	0.615
PAPm, mm Hg	46.0 ± 11.9	46.9 ± 13.3	43.9 ± 10.7	0.025
PAWP, mm Hg	12.5 ± 6.0	9.3 ± 3.4	10.0 ± 3.6	0.186
TPG, mm Hg	33.5 ± 13.1	37.6 ± 13.6	33.9 ± 11.1	0.006
Cardiac index, l/min/m^2	2.2 ± 0.8	2.3 ± 0.8	2.2 ± 0.8	0.629
PVR, Wood Units	9.6 ± 6.7	10.8 ± 6.0	9.8 ± 10.6	0.309
SvO_2, %	62.2 ± 9.0	62.1 ± 9.9	62.7 ± 9.0	0.804
BNP, pg/ml	269 (127-541)	287 (119-543)	200 (115-469)	1.000
NT-proBNP, pg/ml	1,738 (621-3,891)	1,435 (541-3,888)	1,683 (478-2,815)	1.000
Arterial hypertension	66.5	43.2	98.6	<0.001
CAD	32.0	15.7	59.7	<0.001
Diabetes mellitus	30.6	10.7	74.8	<0.001
AF	28.9	10.7	42.4	<0.001
BMI >30 kg/m^2	37.6	23.5	65.2	<0.001

TABLE 4 Response to Targeted PH Therapy

	Typical IPAH	Atypical IPAH	Typical vs. Atypical IPAH p Value
6MWD, m			
Baseline	320 (234 to 417)	250 (175 to 332)	<0.001
12 months	414 (324 to 460)	310 (240 to 379)	<0.001
Change from baseline in 6MWD, m			
Mean ± SD	52 ± 101	58 ± 84	1.000
Median (IQR)	50 (1 to 00)	60 (10 to 75)	
WHO-FC I/II			
Baseline	17.4	8.8	0.056
12 months	39.5	26.2	0.208
Improvement of WHO-FC	34.5	36.9	1.000
Change from baseline in NT-proBNP/BNP, %	−42.6 (−77.1 to 17.4)	−35.9 (−69.9 to 13.8)	1.000

Values are median (interquartile range), mean ± SD, or %. Data shown on 6-min walking distance (6MWD) a atypical IPAH, and n = 184 for PH-HFpEF), at 12 months (on the basis of n = 126 for typical IPAH, n = 38 for at (on the basis of n = 111 for typical IPAH, n = 29 for atypical IPAH, and n = 40 for PH-HFpEF); WHO-FC at base IPAH, and n = 225 for PH-HFpEF), at 12 months (on the basis of n = 177 for typical IPAH, n = 65 for atypical IP of n = 174 for typical IPAH, n = 65 for atypical IPAH, and n = 87 for PH-HFpEF); and % changes from baseline (NT-proBNP or BNP, respectively; on the basis of n = 115 for typical IPAH, n = 47 for atypical IPAH, and n =

Abbreviations as in Table 1.

Opitz CF et al. JACC 2016

Pre-Capillary, Combined, and Post-Capillary Pulmonary Hypertension

A Pathophysiological Continuum

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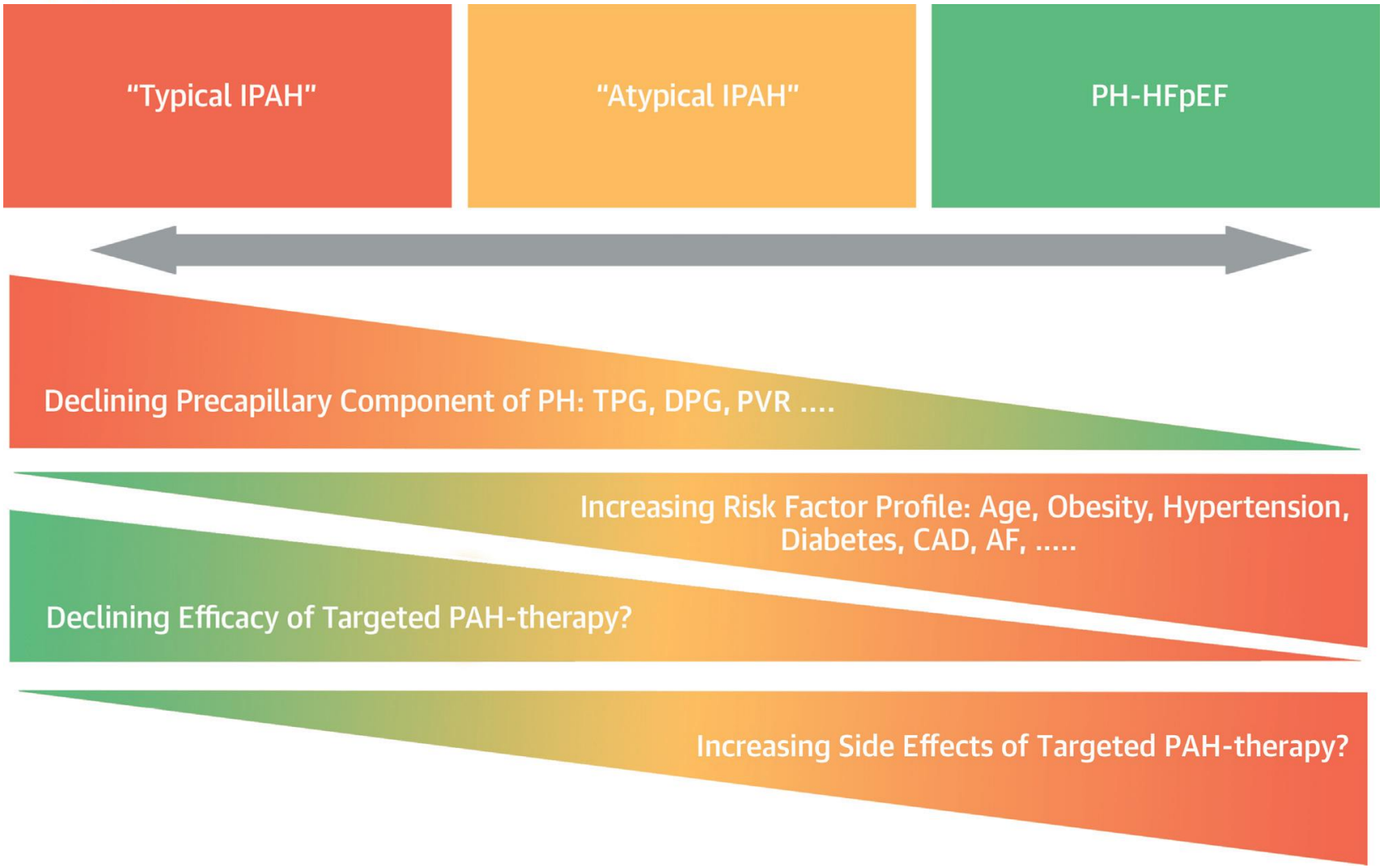
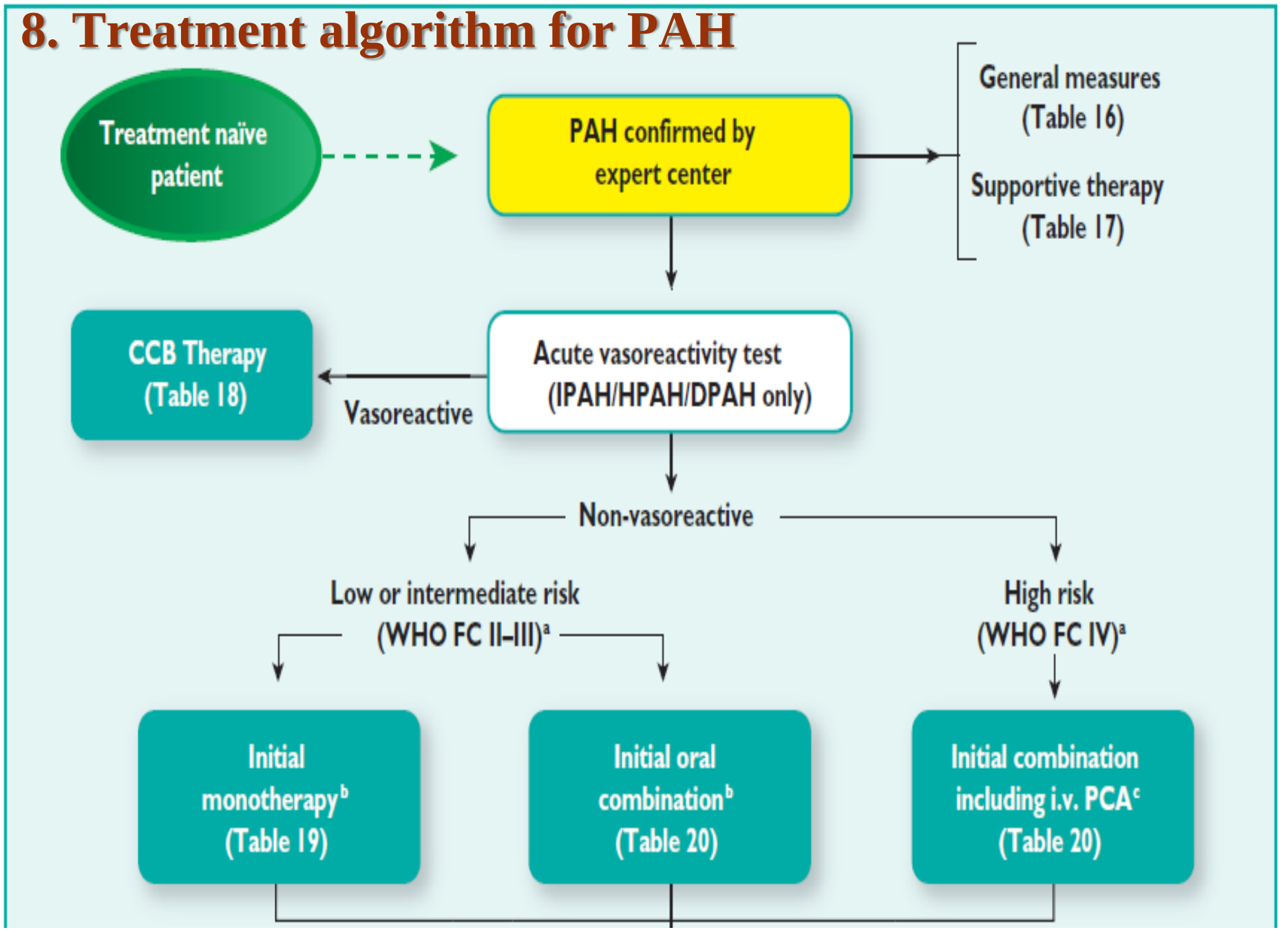


Opitz CF et al. JACC 2016

8. Treatment algorithm for PAH



ESC/ERS guidelines 2015

What We Don't Know

- How to use/combine our numerous options
- Optimal treatment strategy
- Individual variation in response to specific therapies

What About Even Earlier Aggressive Treatment?

One can have goal-directed treatment, which requires aggressive reassessment and goal-oriented therapy

OR

One can treat all patients with aggressive upfront therapy without knowing whether a particular patient is benefiting

Initial Triple Therapy

TRITON

The Efficacy and Safety of Initial Triple Versus Initial Dual Oral Combination Therapy in Patients With Newly Diagnosed Pulmonary Arterial Hypertension: A Multi-Center, Double-Blind, Placebo-Controlled, Phase 3b Study

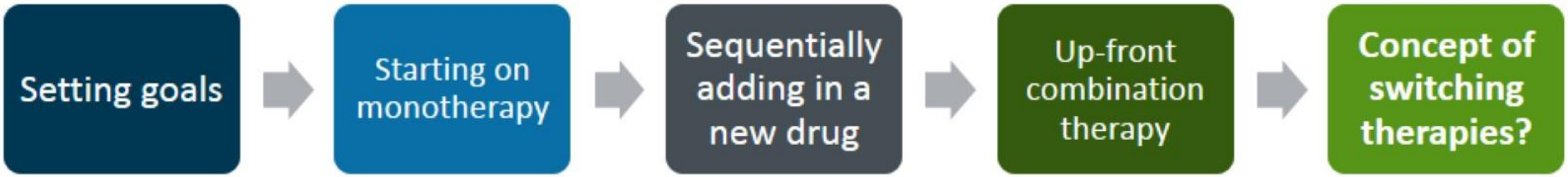
ClinicalTrials.gov. NCT02558231.

Is there a role of Monotherapy for the treatment of PAH?

- Monotherapy will likely continue to have a place in the treatment of patients with PAH
- Patients with PAH are a very heterogeneous group and may be appropriately treated with monotherapy under certain circumstances

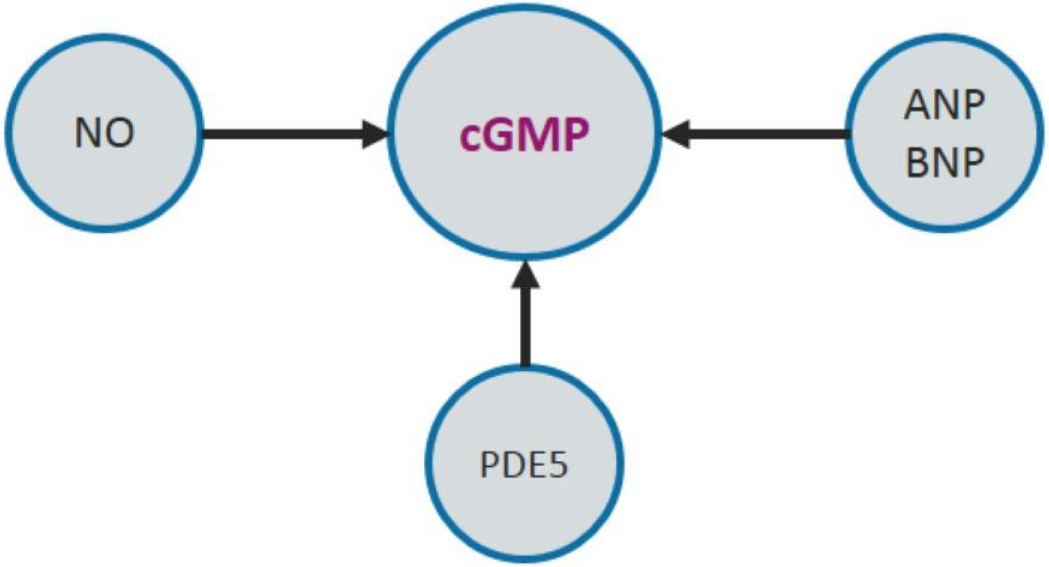
8. Treatment: switching therapies

New Step in the Evolution of Management of PAH?



Does PDE5 (-) = sGC (+)?

- Are some patients more likely to respond to PDE5is?
- Are some patients more likely to respond to sGC stimulators?
- How can we tell?



9. PH due to lung diseases (group 3)

Table 32 Haemodynamic classification of pulmonary hypertension due to lung disease[9]

Terminology	Haemodynamics (right heart catheterization)
COPD/IPF/CPFE without PH	PAPm <25 mmHg
COPD/IPF/CPFE with PH	PAPm ≥25 mmHg
COPD/IPF/CPFE with severe PH	PAPm >35 mmHg, or PAPm ≥25 mmHg in the presence of a low cardiac output (CI <2.5 L/min, not explained by other causes)

CI = cardiac index; COPD = chronic obstructive pulmonary disease; CPFE = combined pulmonary fibrosis and emphysema; IPF = idiopathic pulmonary fibrosis; PAP = pulmonary artery pressure; PAPm = mean pulmonary arterial pressure; PH = pulmonary hypertension.

Recommendations	Class[a]	Level[b]	Ref.[c]
Echocardiography is recommended for the non-invasive diagnostic assessment of suspected PH in patients with lung disease	I	C	403, 405
Referral to an expert centre is recommended[d] in patients with echocardiographic signs of severe PH and/or severe right ventricular dysfunction	I	C	
The optimal treatment of the underlying lung disease, including long-term O_2 therapy in patients with chronic hypoxaemia, is recommended in patients with PH due to lung diseases	I	C	169
Referral to PH expert center should be considered for patients with signs of severe PH/severe RV failure for individual-based treatment	IIa	C	
RHC is not recommended for suspected PH in patients with lung disease, unless therapeutic consequences are to be expected (e.g. lung transplantation, alternative diagnoses such as PAH or CTEPH, potential enrolment in a clinical trial)	III	C	169
The use of drugs approved for PAH is not recommended in patients with PH due to lung diseases	III	C	411–416

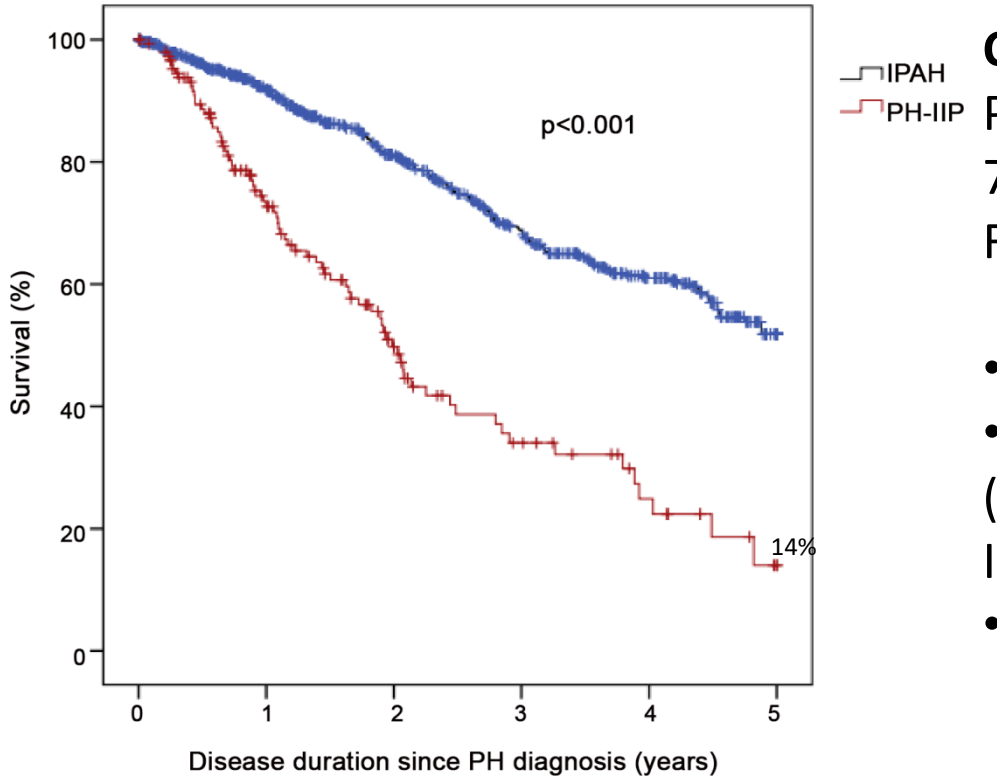
ESC/ERS guidelines 2015

Pulmonary Hypertension in Patients with Chronic Fibrosing Idiopathic Interstitial Pneumonias

Marius M. Hoeper[1]*, Juergen Behr[2], Matthias Held[3], Ekkehard Grunig[4], C. Dario Vizza[5], Anton Vonk-Noordegraaf[6], Tobias J. Lange[7], Martin Claussen[8], Christian Grohé[9], Hans Klose[10], Karen M. Olsson[1], Thomas Zelniker[11], Claus Neurohr[2], Oliver Distler[12], Hubert Wirtz[13], Christian Opitz[14], Doerte Huscher[15], David Pittrow[16], J. Simon R. Gibbs[17]

PLOS ONE

Dec 2015



COMPERA registry

PH-IIP n=151 (IPF: 113, NSIP:38)

79% severe PH (mPAP>35mmmHg)

FVC 62.9±20.0, DLco 28.5±15.8

- 88% PDE5i
- Short-term response to therapy (6MWT & FC) comparable to that of IPAH
- Dismal survival

PH due to lung diseases (group 3)

We urgently need robust trials in which the objectives and the design are adapted to the specific characteristics of these patients

- Reconsider end-points
- Selection of the appropriate patient population

  pts with severe PH and mild or moderate parenchymal lung disease

  cut-off of PH?

  cut-off of FVC?

10. Precision-medicine approach

Table 1 Updated Classification of Pulmonary Hypertension*

1. Pulmonary arterial hypertension
   - 1.1 Idiopathic PAH
   - 1.2 Heritable PAH
   - 1.2.1 BMPR2
   - 1.2.2 ALK-1, ENG, SMAD9, CAV1, KCNK3
   - 1.2.3 Unknown
   - 1.3 Drug and toxin induced
   - 1.4 Associated with:
   - 1.4.1 Connective tissue disease
   - 1.4.2 HIV infection
   - 1.4.3 Portal hypertension
   - 1.4.4 Congenital heart diseases
   - 1.4.5 Schistosomiasis

1′ Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis

1″. Persistent pulmonary hypertension of the newborn (PPHN)

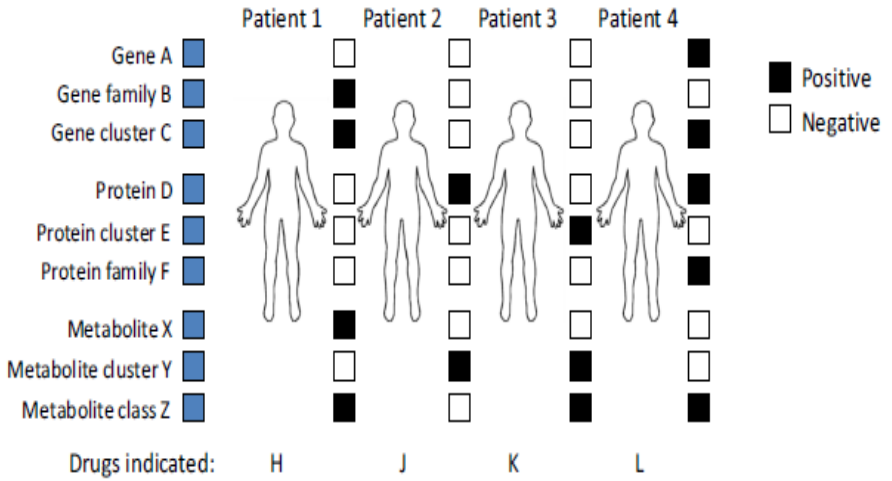
2. Pulmonary hypertension due to left heart disease
   - 2.1 Left ventricular systolic dysfunction
   - 2.2 Left ventricular diastolic dysfunction
   - 2.3 Valvular disease
   - 2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

3. Pulmonary hypertension due to lung diseases and/or hypoxia
   - 3.1 Chronic obstructive pulmonary disease
   - 3.2 Interstitial lung disease
   - 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
   - 3.4 Sleep-disordered breathing
   - 3.5 Alveolar hypoventilation disorders
   - 3.6 Chronic exposure to high altitude
   - 3.7 Developmental lung diseases

4. Chronic thromboembolic pulmonary hypertension (CTEPH)

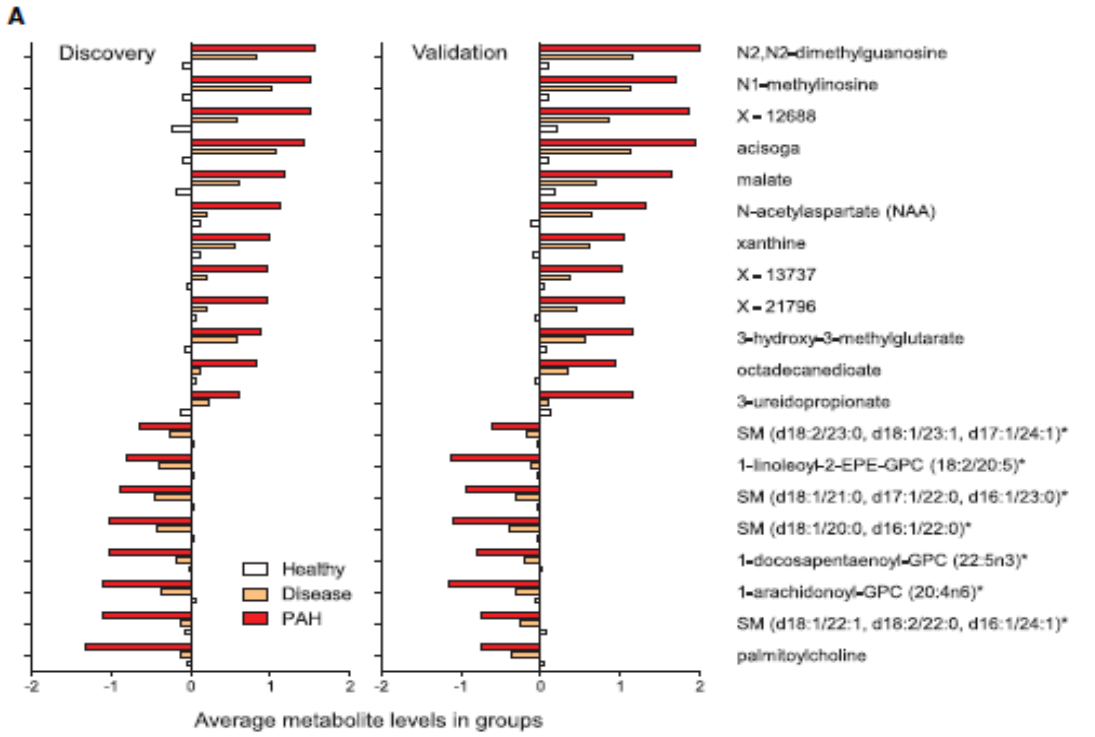
5. Pulmonary hypertension with unclear multifactorial mechanisms
   - 5.1 Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
   - 5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
   - 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
   - 5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

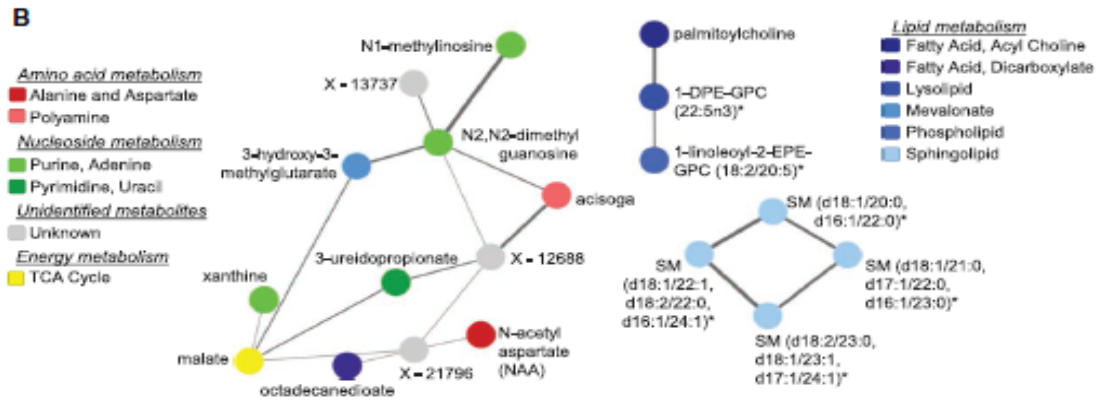
- Current classification is based on a relatively simple combination of patient characteristics and hemodynamics



ESC/ERS guidelines 2015, Ghataorhe et al. JIM 2017

Plasma Metabolomics Implicates Modified Transfer RNAs and Altered Bioenergetics in the Outcomes of Pulmonary Arterial Hypertension

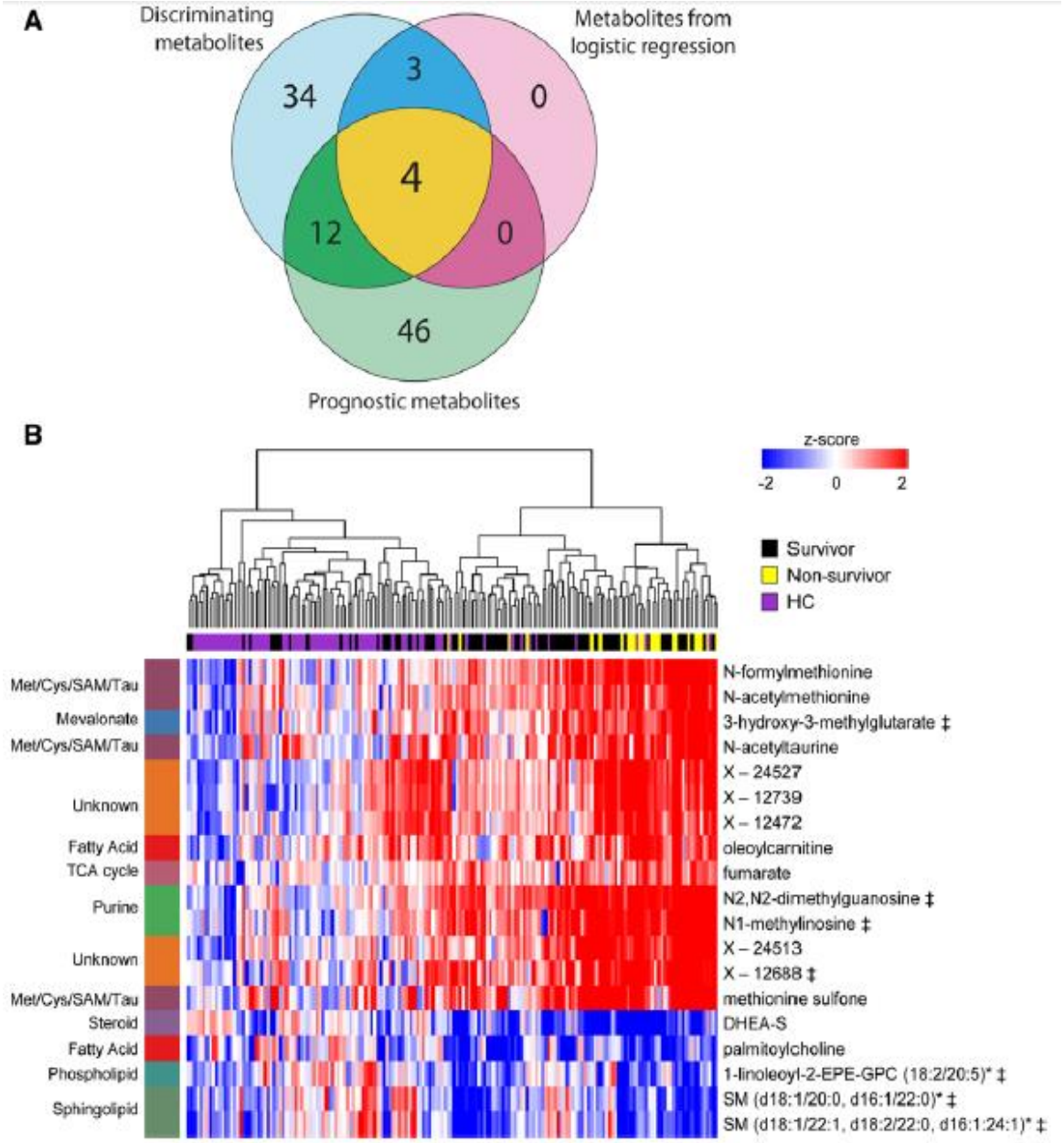




- Large UK consortium
- Performed metabolomics in 365 pts with PAH & controls

➢ Only 20 metabolites needed to differentiate PAH patients from control subjects

Rhodes CJ et al. Circulation 2017



- Metabolites can also predict survival- and reveal potentially important therapeutic targets

Rhodes CJ et al. Circulation 2017

➢ Patients perspective

- Will I feel better?
- Will I function better?
- Will I survive longer?