Challenging the 2015 PH Guidelines

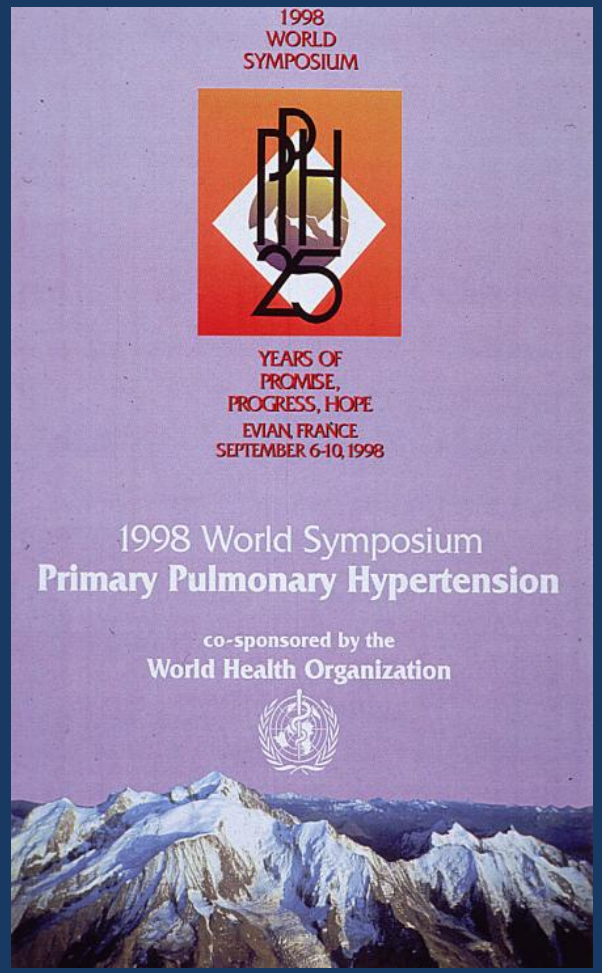
Pulmonary Hypertension

Definitions and Diagnosis

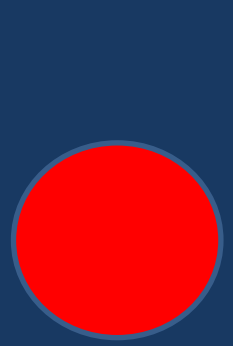
Comments and Proposals

Professor Sean Gaine
Mater Misericordiae University Hospital
Dublin, Ireland

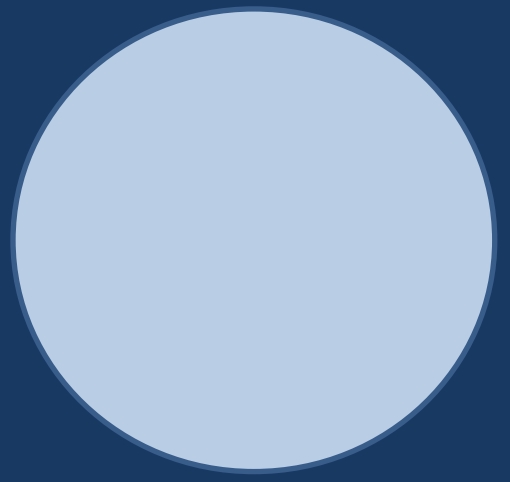
Definitions and Diagnosis:
Evolution in our Definitions and Diagnosis



Pre-1998 World Symposium Evian, France



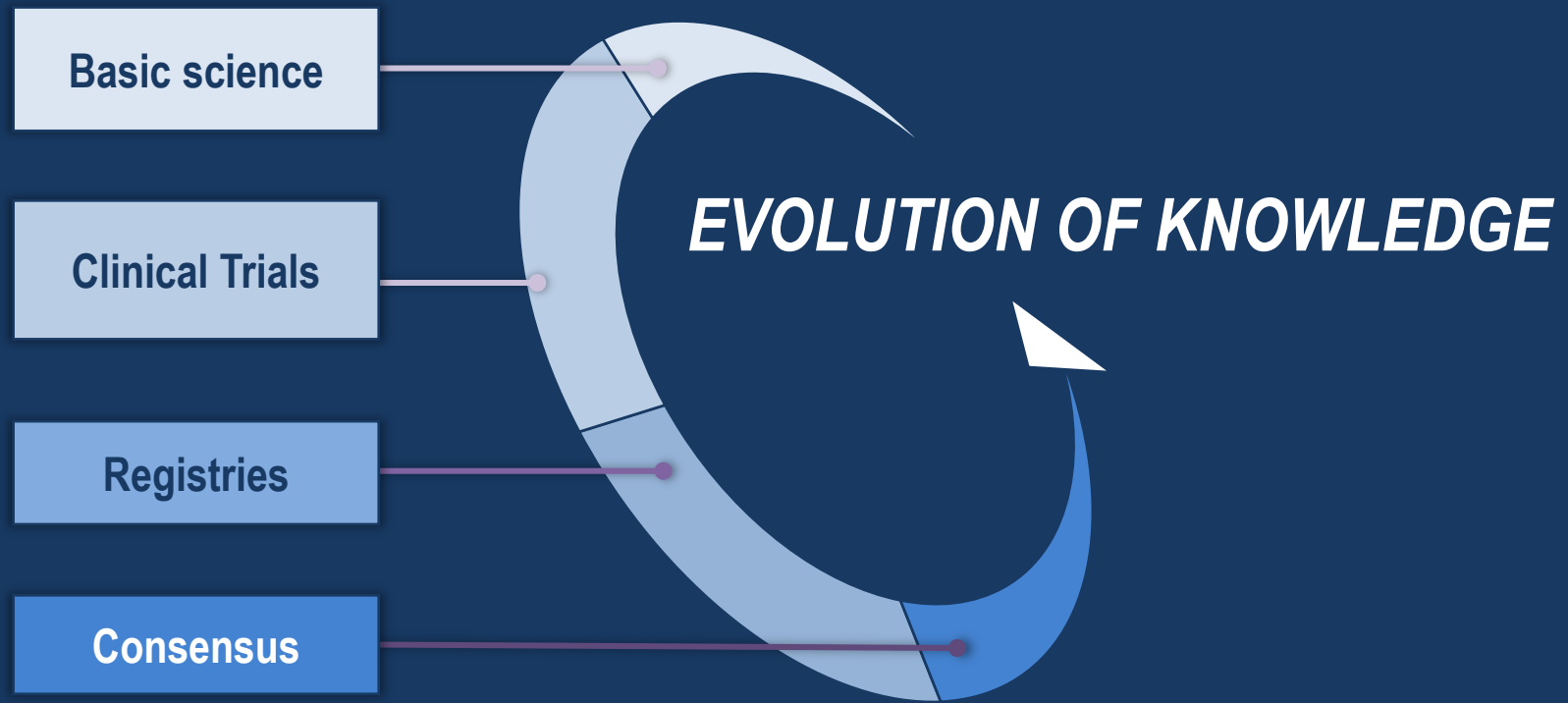
‘PPH’



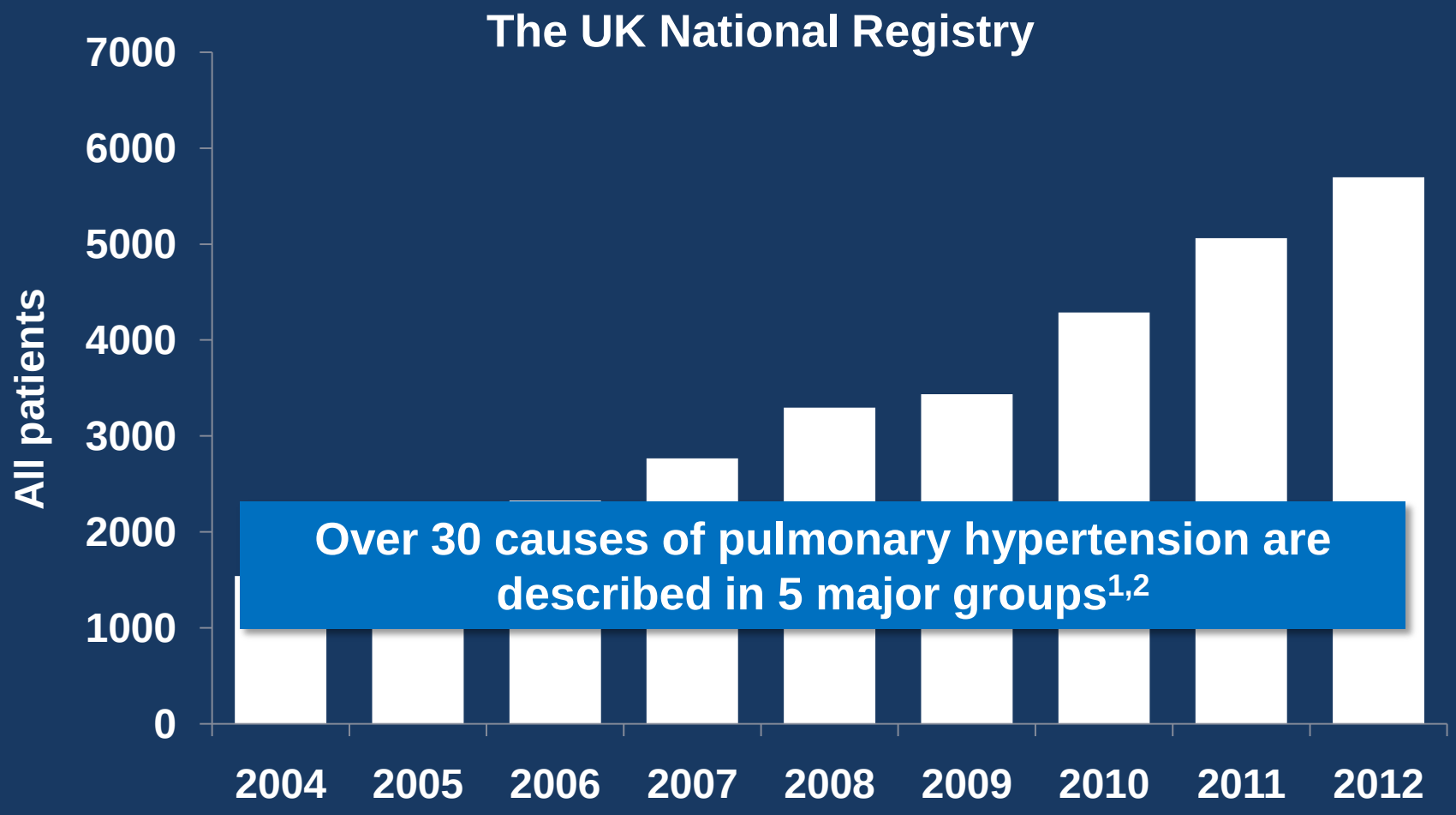
‘Secondary’ Pulmonary Hypertension

Guidelines build on our evolution of knowledge and by constructive comments and proposals over time

Increasing understanding of PAH from 2015-2020



Pulmonary Hypertension is continuing to evolve: The burden of PH is growing as awareness increases



(Groups 1-5) National Audit of Pulmonary Hypertension 2013, NHS Information Centre.

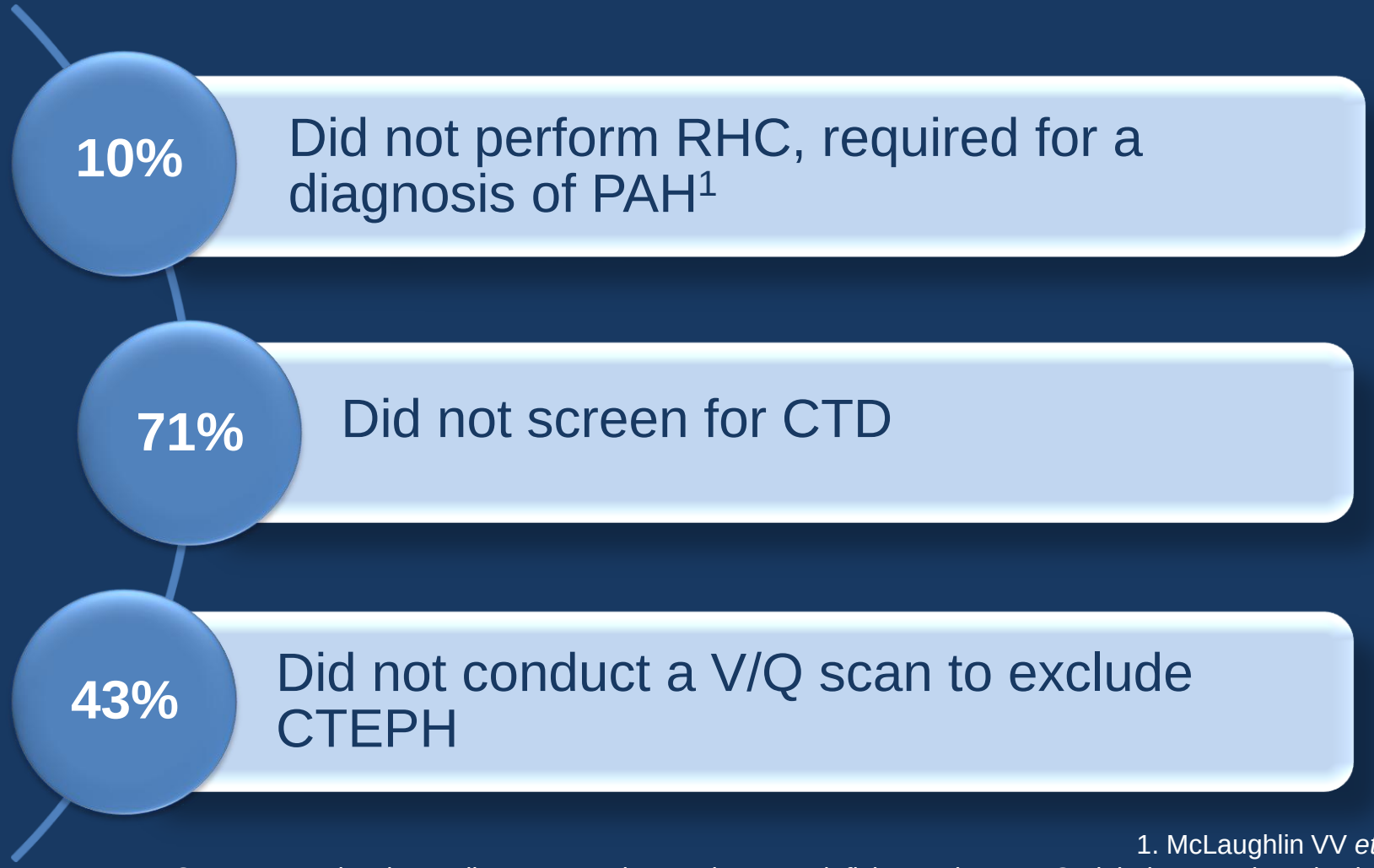
IPAH is diagnosed increasingly in older patients and raises questions about Definitions and Diagnosis

Registry	Time period	Age, years (mean ± SD)
NIH registry[1]	1981–1985	36 ± 15
French registry[2]	2002–2003	50 ± 15
US REVEAL[3-5]	2006–2009	50 ± 14
UK and Ireland registry[6]	2001–2009	50 ± 17
UK National Audit[7]	2012–2013	57*
COMPERA[8]	2007–2011	65 ± 15

1. Rich S *et al. Ann Intern Med* 1987;107:216–23. 2. Humbert M *et al. Am J Respir Crit Care Med* 2006;173:1023–30. 3. Frost AE *et al. Chest* 2011; 139:128–37. 4. Benza RL *et al*. *Circulation* 2010;122:164–72. 5. Barst RJ *et al. Circulation* 2012;125:113–22. 6. Ling Y *et al. Am J Respir Crit Care Med* 2012;186:790–6. 7. UK National Audit on Pulmonary Hypertension, 2013, The NHS Information Centre. 8. Hoeper MM *et al*. *Int J Cardiol* 2013; 168:871–80.

Certain essential and recommended diagnostic tests appear to be underused

The PAH-Quality Enhancement Research Initiative (PAH-QuERI)



1. McLaughlin VV *et al. Chest* 2013;143:324–32.

CTD, connective tissue disease; HIV, human immune deficiency virus; RHC, right heart catheterization; V/Q, ventilation/perfusion.

Definitions and Diagnosis: Comments

- 1: Who are the Guidelines intended for?
  - Expert Centres or the broader medical public?
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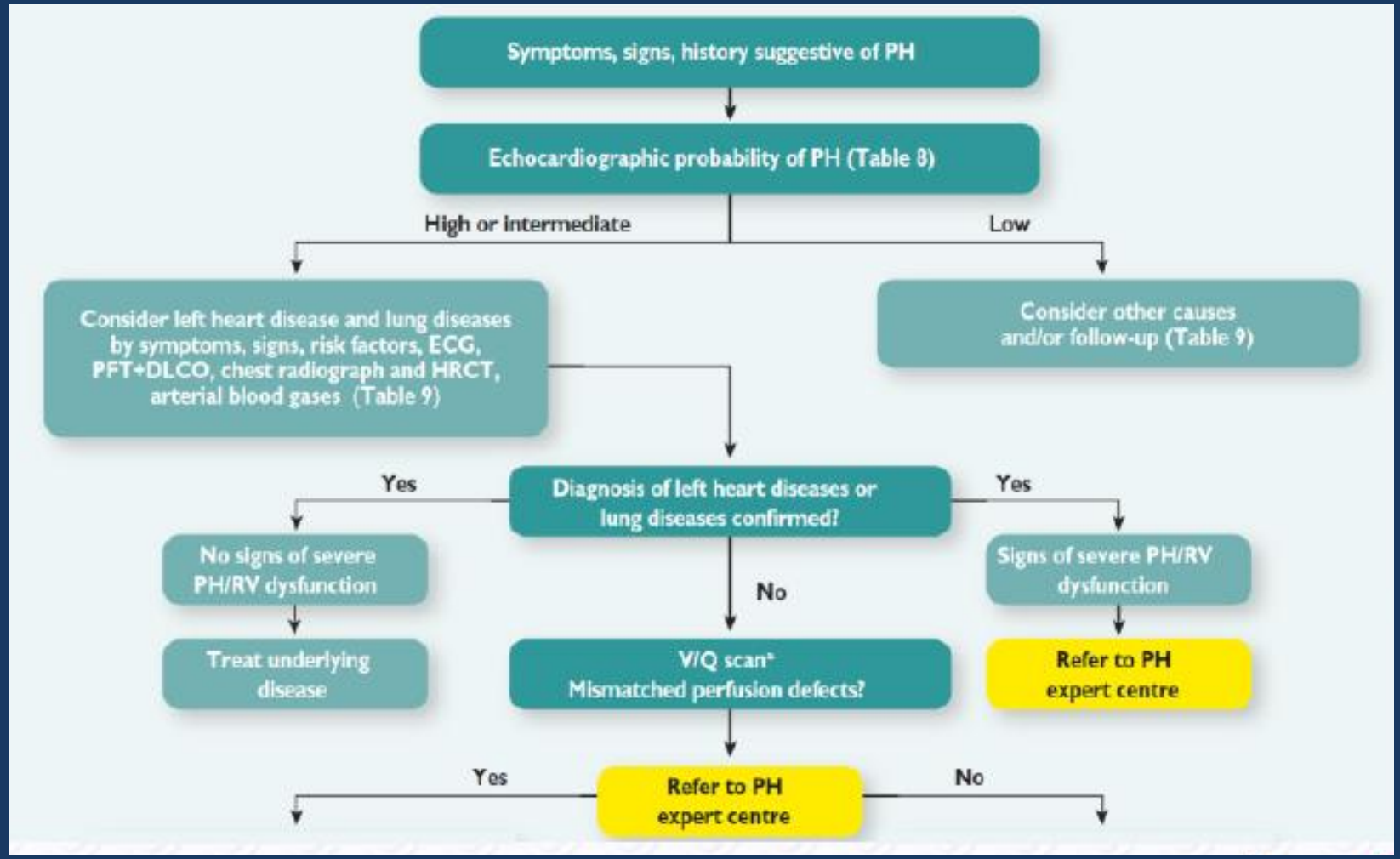
  - Do we want to err on the side of under diagnosis or over diagnosis?
- 3: Does the Classification of PH need to be changed in light of the evolving phenotype and treatment responses?
- 4: Is the ‘Gold Standard’ RHC is in need of some polishing?

The Guidelines are for Practicing Clinicians and PH Expert Centres



Galie, N et al Eur Heart J 2016: 37;67-119

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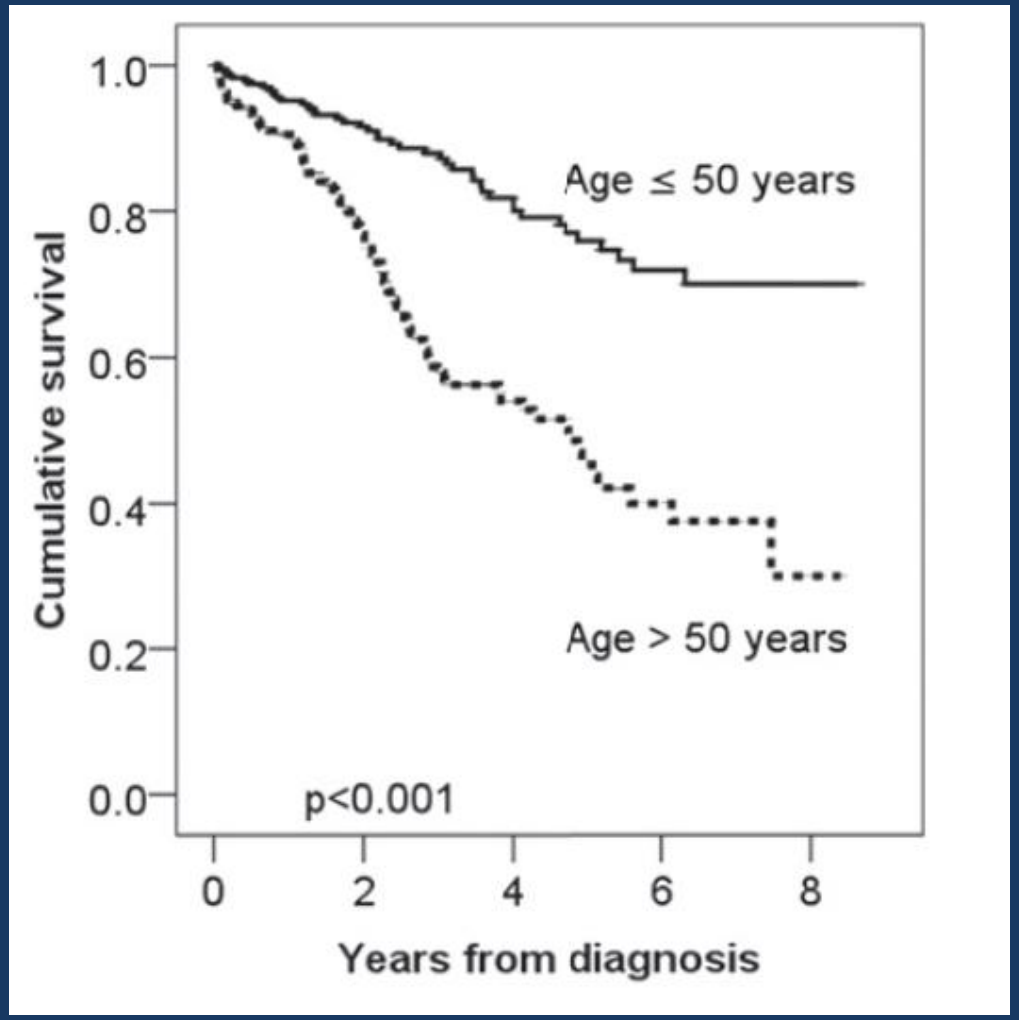
Older patients experience more comorbidities compared with younger patients

Comorbidities (*n*=455)	Age ≤50 years	Age >50 years	*p* value
Ischaemic heart disease	1%	24%	<0.001
Hypertension	11%	42%	<0.001
Atrial fibrillation	0%	11%	<0.001
Diabetes	5%	23%	<0.001
Hypothyroidism	8%	16%	0.005

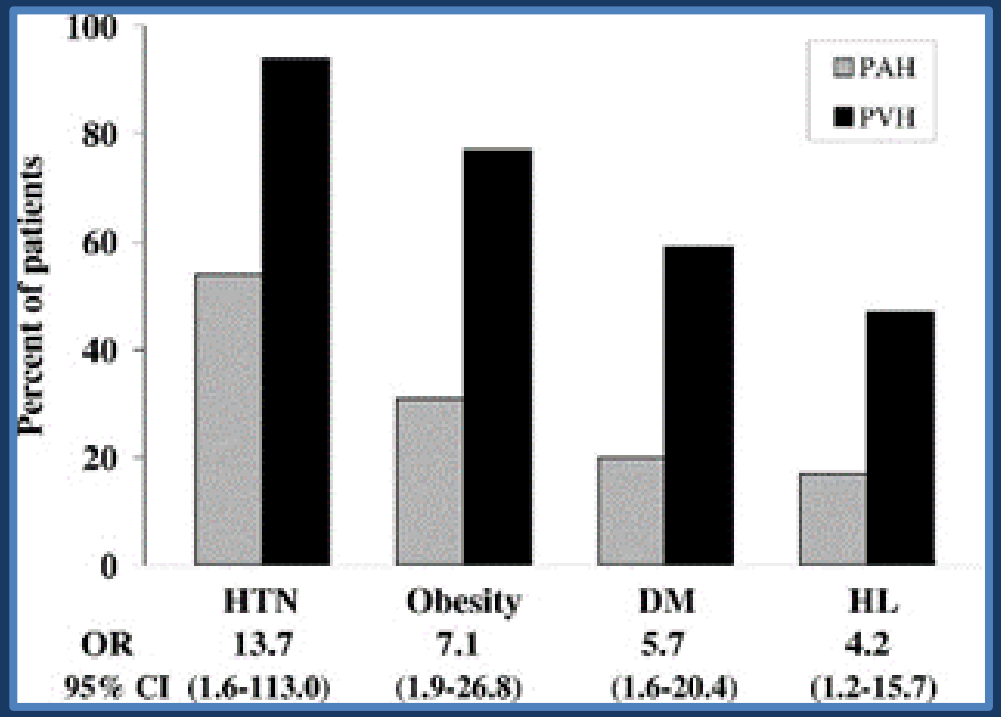
Ling Y *et al. Am J Respir Crit Care Med* 2012;186:790–6.

Older patients have a worse outcome compared with younger patients



Ling Y *et al. Am J Respir Crit Care Med* 2012;186:790–6.

Patients with Group 1 PAH and Group 2 PVH have distinct clinical phenotypes

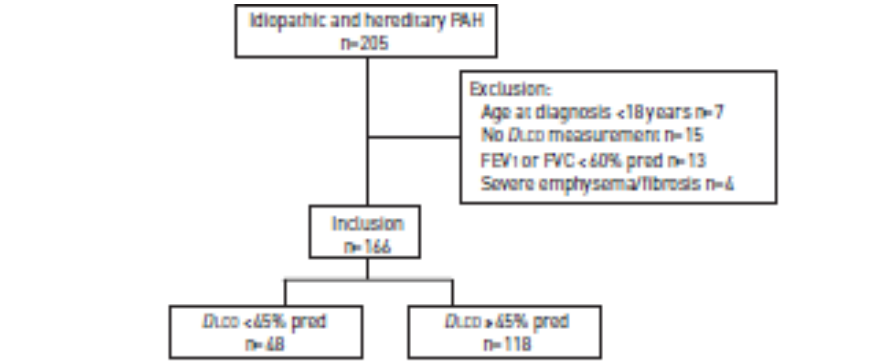


PVH due to HFpEF was a frequent cause of PH evaluated at a larger referral centre.
> 90% of these pts have multiple features of the Metabolic Syndrome.

Bar graph demonstrating the percentage of patients with PAH and PVH with each of the four clinical features of the MS, p = 0.004 for hypertension, p = 0.002 for obesity, p = 0.005 for diabetes mellitus, and p = 0.023 for hyperlipidemia. The odds ratio with 95% CI for PVH with each factor is presented below the graph. DM = diabetes mellitus; HL = hyperlipidemia; HTN = hypertension.

Robbins IM, et al. Chest. 2009;136:31-36.

The diffusion capacity and PAH: Distinct phenotypes



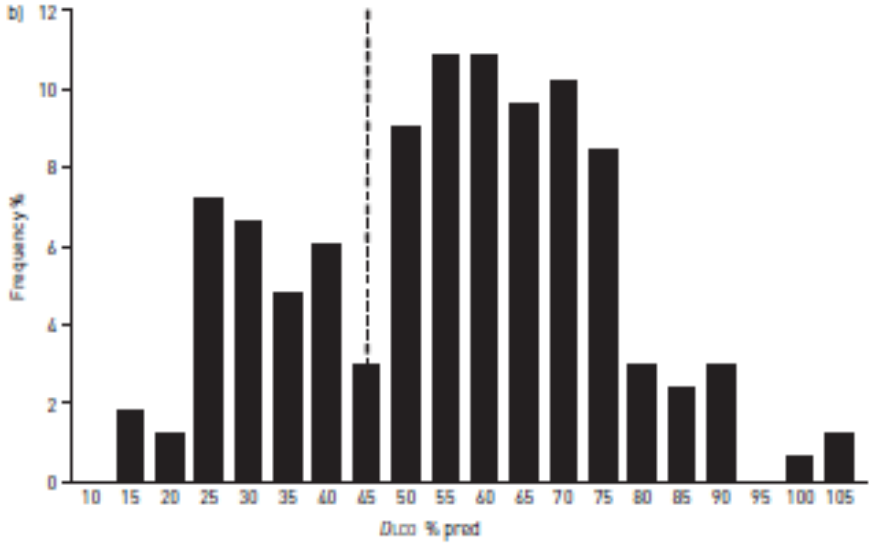
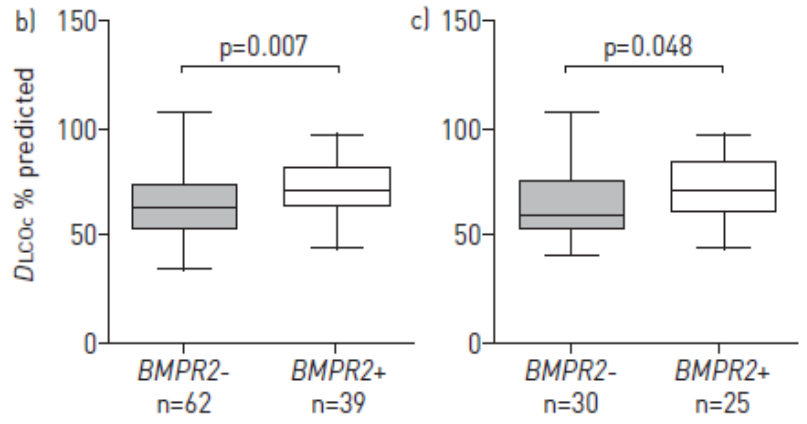


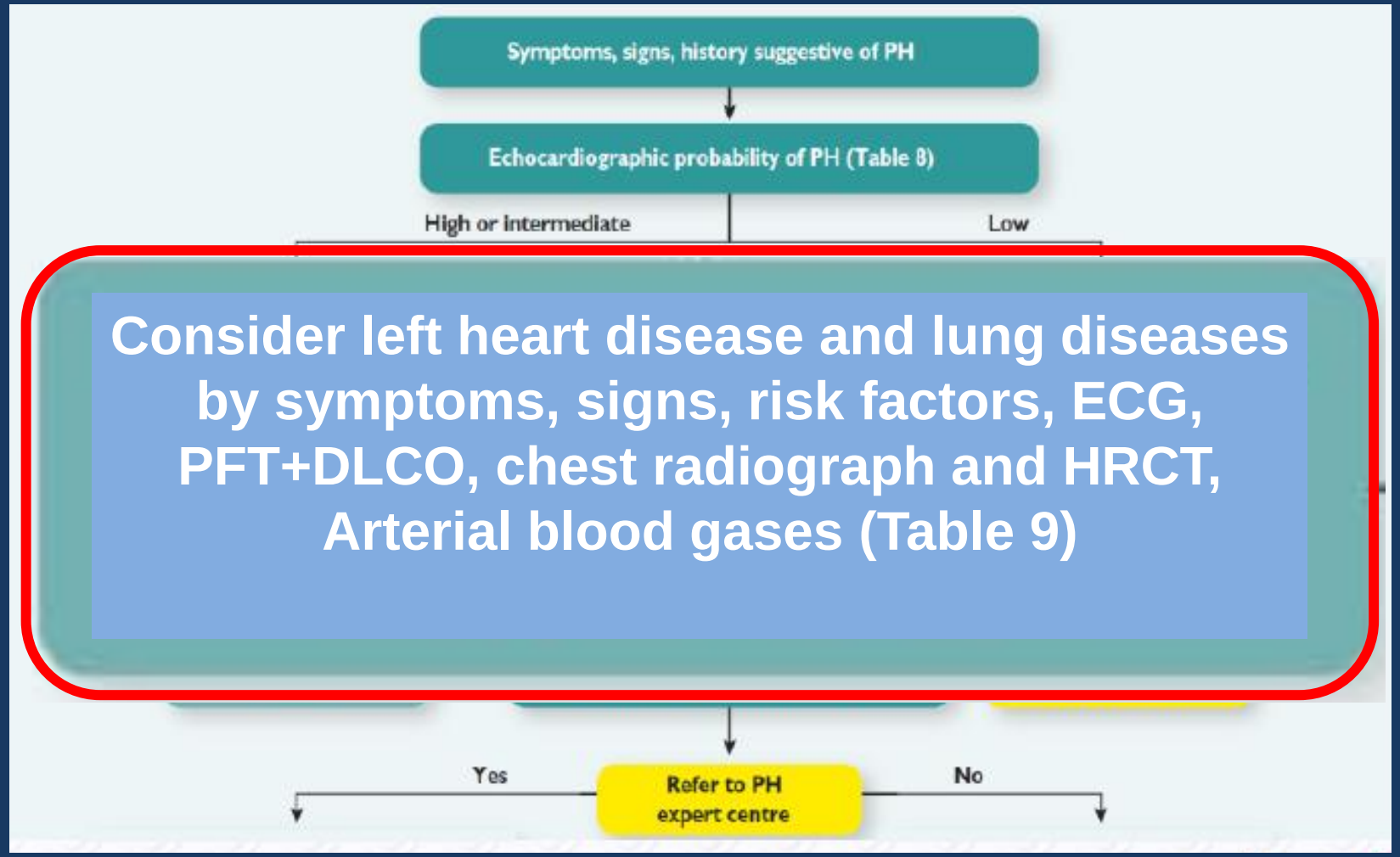
TABLE 5 First-line treatment, treatment response and survival

	DLCO <45% pred	DLCO ≥45% pred	p-value
Survival	**DLCO <45%**	**DLCO >45%**	
1yr	87%	95%	
3yr	54%	86%	
5yr	38%	80%	



Trip P *et al. Eur Respir J* 2013 Dec;42(6):1575–85. Trip P *et al. Eur Respir J* 2014 Apr;43(4):1195–8.

Perhaps we need to give more directions on how to ‘Consider’ left heart and lung diseases?



Galie, N et al Eur Heart J 2016: 37;67-119

The Inclusion and Exclusion Criteria as per the Revised Criteria Amendment in AMBITION. A good place to start?

Inclusion criteria:

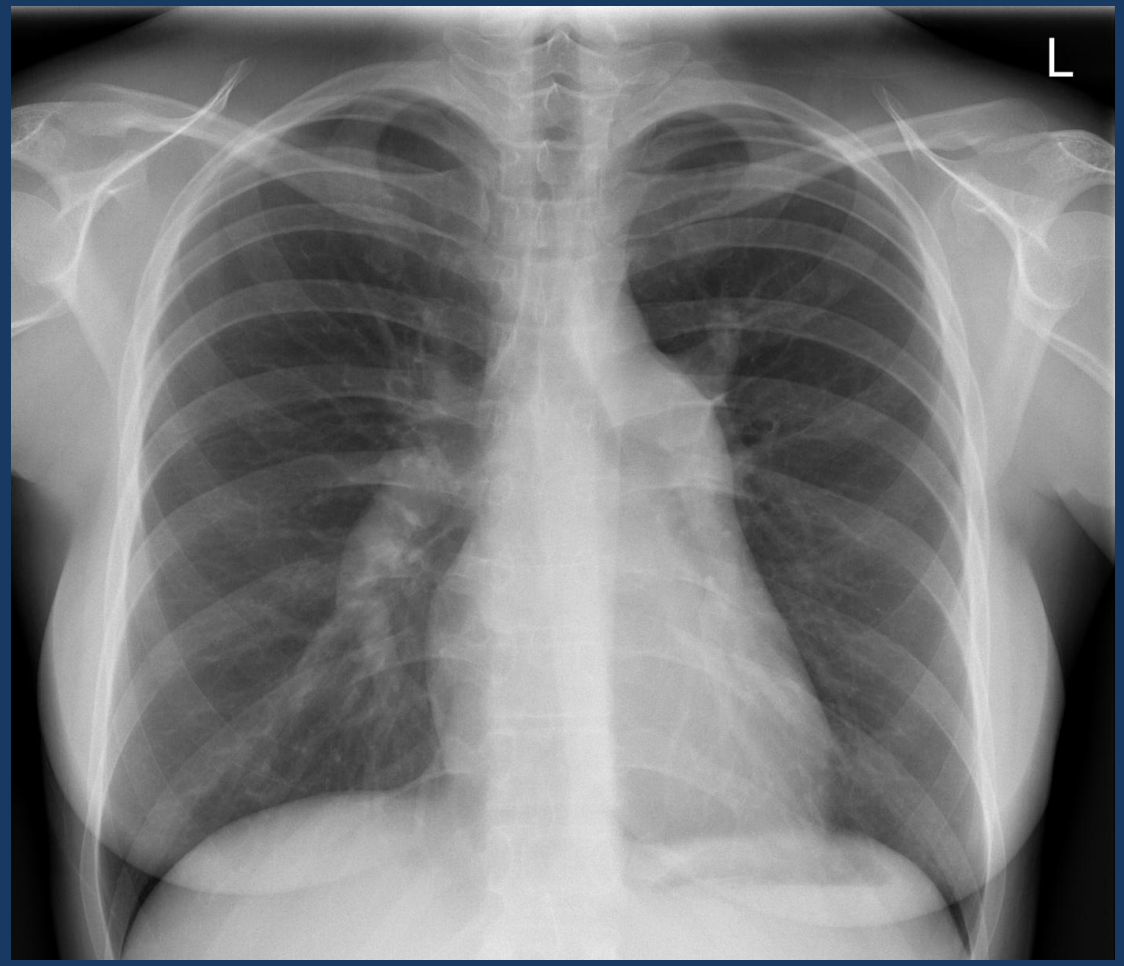
- Confirmed diagnosis of PAH with:*
- - mPAP ≥25 mm Hg
- - PVR ≥300 dyne·sec/cm5 (up from 240)
- - PCWP or LVEDP ≤12 mm Hg if PVR
- ≥300 to <500 dyne·sec/cm5
- - or PCWP or LVEDP ≤15 mm Hg if PVR ≥500 dyne·sec/cm5

Exclusion criteria:

- Participants must not have ≥3 of the following HFpEF risk factors:
- - BMI ≥30 kg/m2
- - History of essential hypertension
- - Diabetes mellitus (any type)
- - Historical evidence of significant CAD established by any of the following:
- - History of MI, History of PCI
- - Angiographic evidence of CAD
- (>50% stenosis in ≥1 vessel)
- - Positive ST
- - Previous CABG
- - Stable angina

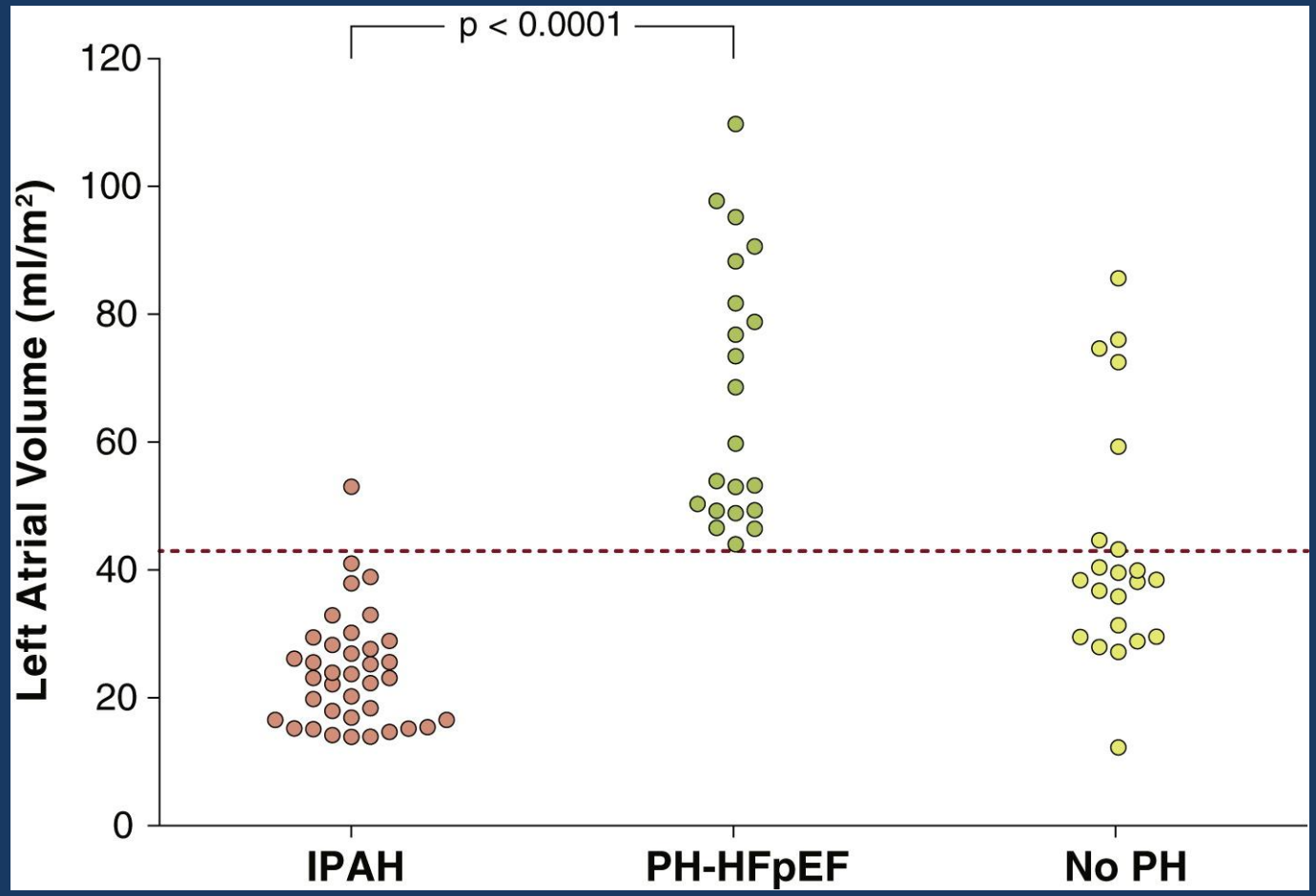
Gailie N et al New Engl J Med 2014

Simple diagnostics remain very helpful



- Group 2
  - Upper lobe diversion, Kerely B lines, effusions, pulmonary oedema
- Group 3:
  - Fibrosis, hyperinflation, increased bronchial wall markings, bullae

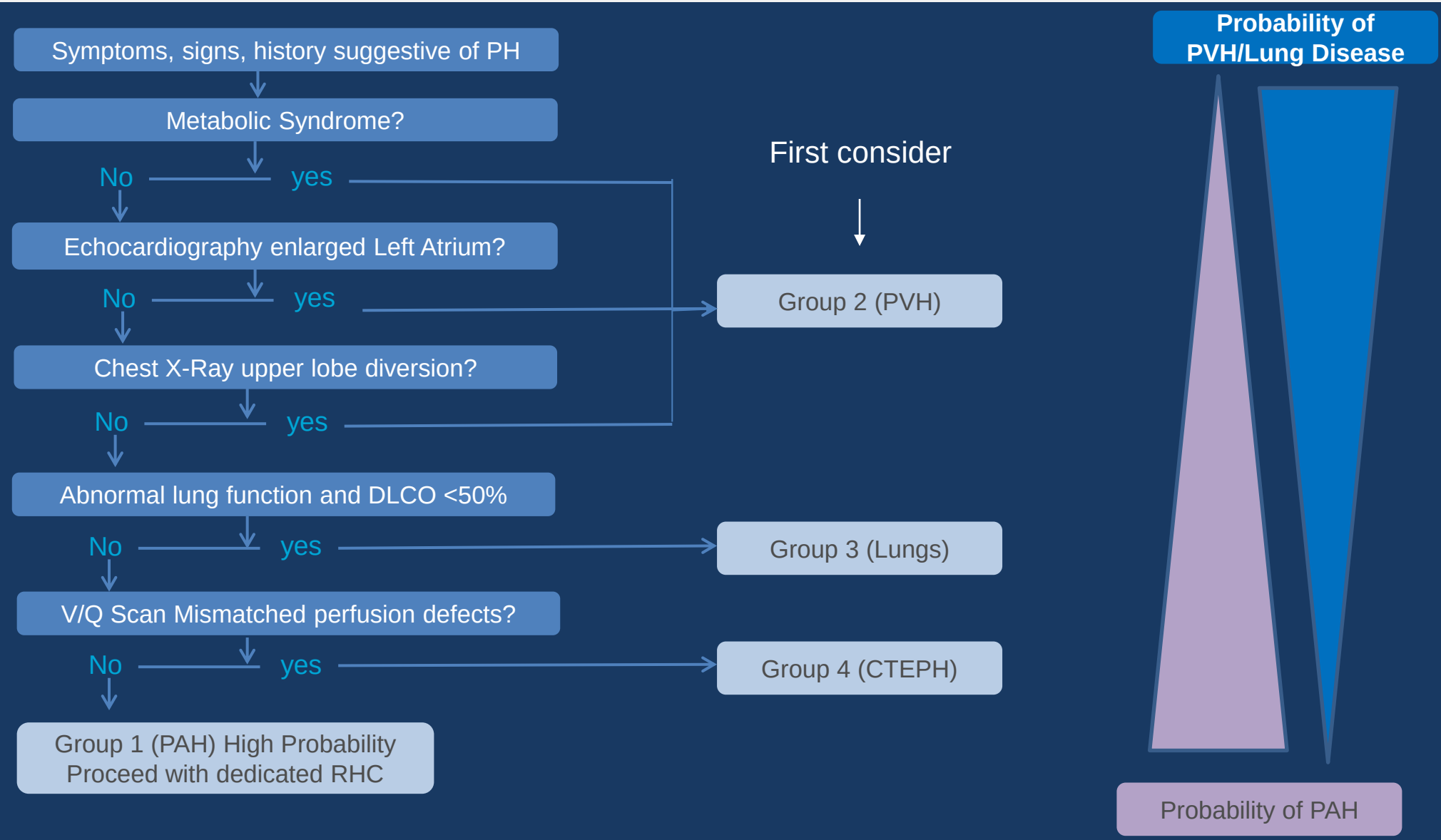
LA volume by CMR distinguishes idiopathic from pulmonary hypertension due to HFpEF



Crawley SF *et al. JACC Cardiovasc Imaging* 2013;6:1120–1.

CMR, cardiovascular magnetic resonance imaging; HFpEF, heart failure with preserved ejection fraction; IPAH, idiopathic PAH; LA, left atrial.

Diagnostic algorithm for PAH: Improving the Pre-test Probability of PAH



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Pulmonary hypertension is a severe manifestation of many connective tissue diseases

- Systemic sclerosis (SSc)[1]
- Systemic lupus erythematosus (SLE)[2]
- SSc-SLE overlap syndrome[3]
- Mixed connective tissue disease (MCTD)[4]
- Inflammatory myositides (dermatomyositis and polymyositis)[5]
- Sjögren's syndrome[6]
- Rheumatoid arthritis[7]

1. Steen VD, et al. Ann Rheum Dis 2007;
2. Tanaka E, et al J Rheumatol 2002; 29: 282–287.
3. Pope J. Lupus 2008; 17: 274–277.
4. Dahl M, et al. J Rheumatol 1992; 19: 1807–1809.
5. Minai OA Lupus 2009; 18: 1006–1010.
6. Launay D, et al Medicine (Baltimore) 2007; 86: 299–315.
7. Dawson JK, et al. Rheumatology (Oxford) 2000; 39: 1320–1325.

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- Sjögren's syn
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<u>3-yr survival rate in the UK</u>
75% SLE-PAH
47% SSc-PAH (p=0.01).

Condliffe R, et al. Am J Respir Crit Care Med 2009; 179: 151–157.

1. Steen VD, et al. Ann Rheum Dis 2007;
2. Tanaka E, et al J Rheumatol 2002; 29: 282–287.
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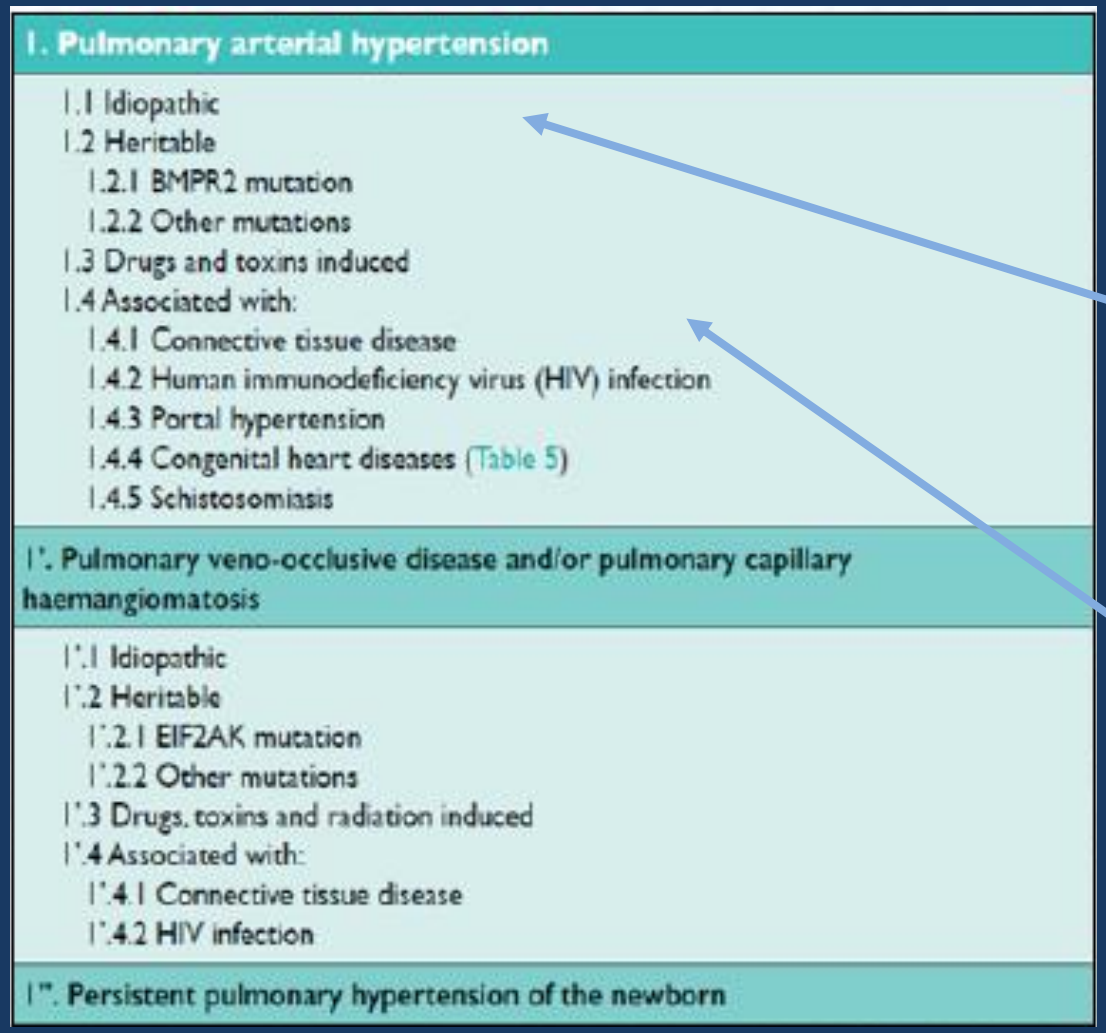
Heterogeneous conditions under the heading of Group I PAH



1. Pulmonary arterial hypertension

- 1.1 Idiopathic
- 1.2 Heritable
  - 1.2.1 BMPR2 mutation
  - 1.2.2 Other mutations
- 1.3 Drugs and toxins induced
- 1.4 Associated with:
  - 1.4.1 Connective tissue disease
  - 1.4.2 Human immunodeficiency virus (HIV) infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart diseases (Table 5)
  - 1.4.5 Schistosomiasis

1'. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis

- 1'.1 Idiopathic
- 1'.2 Heritable
  - 1'.2.1 EIF2AK mutation
  - 1'.2.2 Other mutations
- 1'.3 Drugs, toxins and radiation induced
- 1'.4 Associated with:
  - 1'.4.1 Connective tissue disease
  - 1'.4.2 HIV infection

1". Persistent pulmonary hypertension of the newborn

Towards a molecular classification of PAH*

1.1. Idiopathic
- **1.1.1. Acute vasodilator responsive**
- **1.1.2. Classical IPAH**
- **1.1.3. Atypical IPAH**

1.4.1. CTD
- **1.4.1.1. Scleroderma**
- **1.4.1.2 SLE**
- **1.4.1.3. CTD Other**

*Stefan Graf and Nicholas Morrell: Eur Respir J 2016 48:987-989

Definitions and Diagnosis: Comments

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  - Is the increase in age a reflection of a failure in our guidelines?
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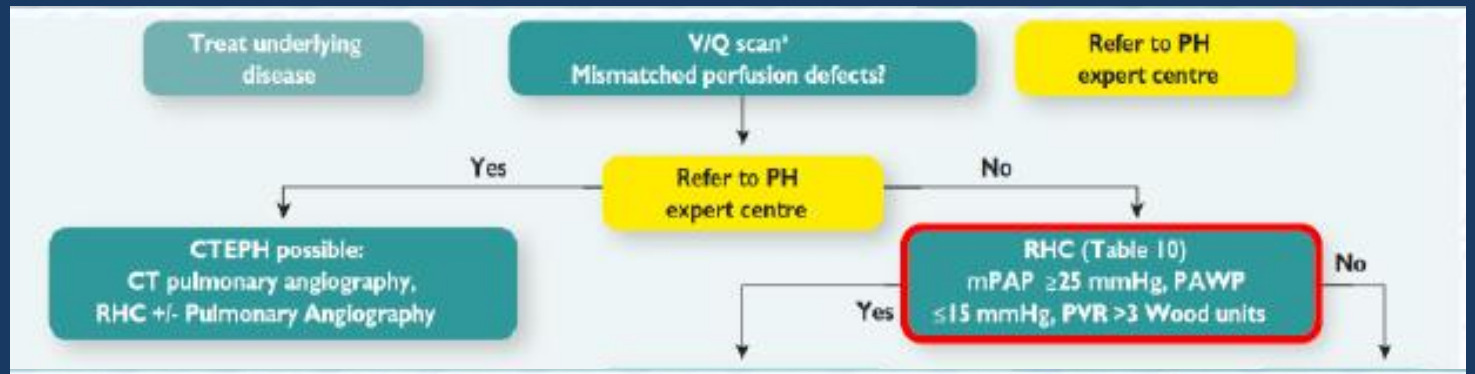
The ESC Guidelines allow for Expert Centres to complete the PAH work up with the RHC

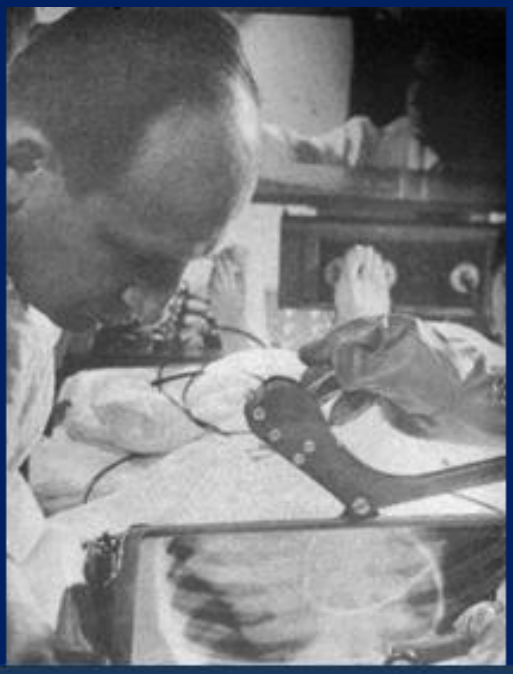


Recommendations	Class[a]	Level[b]
RHC is recommended to confirm the diagnosis of pulmonary arterial hypertension (Group 1) and to support treatment decisions.	I	C
In patients with PH, it is recommended to perform RHC in expert centres (Table 34) as it is technically demanding and may be associated with serious complications.	I	B
RHC should be considered in pulmonary arterial hypertension (Group 1) to assess treatment effect of drugs (Table 12).	IIa	C

Galie, N et al Eur Heart J 2016: 37;67-119

Limitations and controversies in right heart catheterization

- Data acquisition during RHC requires resting and supine patients.
  - There is no standard operating procedure for capturing hemodynamic changes with an upright posture or with physical activity[1].
- Ongoing debate about definitions surrounding PH and Left Heart Disease and the DPG[2,5]
  - Ipc-PH (Isolated) DPG < 7mmHg
  - Cpc-PH (Combined) DPG >7mmHg
- Proposed role for DPG and a PVR of >3 WU[3,4]
  - Review if large database[4]



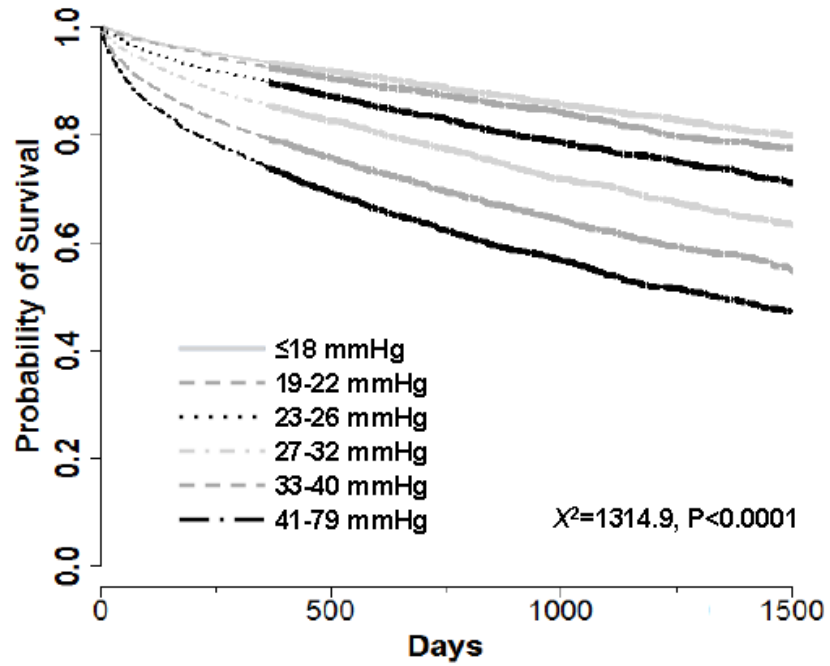
Dr. David Dresdale
1950's

1. Hoeper MM, et al. J Am Coll Cardiol 2006;48:2546-52.
2. Galie N et al Eur Respir J 2016;48:311-314
3. Naeije R and Hemnes A Eur Respir J 2016 48;308-310
4. Gerges M et al Eur Respir J 2016; 48; 553-555
5. PROGNOSIS: Tampakakis E et al JACC Heart Fail 2015;3;424

Time to look at ‘Borderline PAH’ again?

Association of Borderline Pulmonary Hypertension With Mortality and Hospitalization in a Large Patient Cohort: Insights From the VA-CART Program

Running title: *Maron et al.; Borderline pulmonary hypertension increases mortality*



NEWS & VIEWS

HYPERTENSION

Definition of pulmonary hypertension challenged?

Adam Torbicki

The current definition of pulmonary hypertension (PH) is based on resting mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg; however, analysis of long-term follow-up data now reveals increased mortality even with mPAP ≥ 19 mmHg. Do we need to modify the definition of PH, and what are the implications for clinical practice?

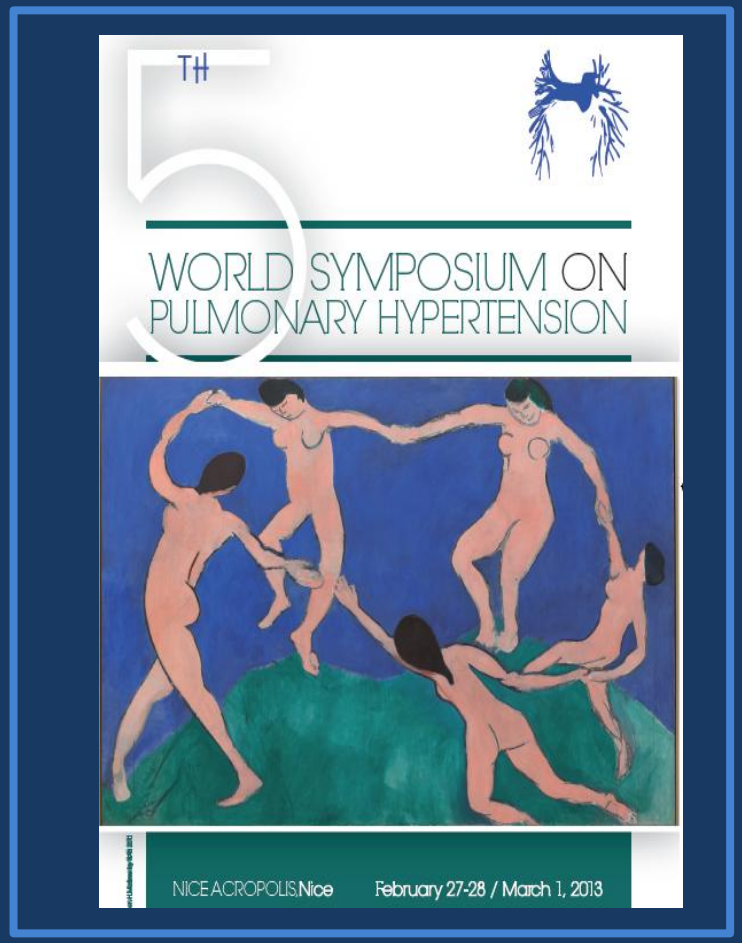
prognostic factor is the cause of the increased right ventricular afterload, and the risk of its rapid progression. These factors are dramatically different between the two groups of PH, as identified in the current PH classification[1]. In the analysis by Maron and colleagues, most of the cohort had common causes of PH: left ventricular dysfunction and chronic lung disease[2]. The dominant role of left ventricular dysfunction is suggested by the parallel increases in pulmonary artery wedge pressure (PAWP) and mPAP across normal, borderline PH, and diagnosed PH subgroups (FIGURE 1).

In the study population, borderline PH seems to be a marker of underlying disease — predominantly left ventricular dysfunction and, in some patients, probably also chronic lung disease. Specific anti-PH treatments targeting pulmonary arterioles are of occurs

Maron et al.; Borderline pulmonary hypertension increases mortality Circulation 2016
Torbicki A Nature Reviews Cardiol 2016

Should fluid or exercise challenge distinguish PAH from Group 2 PH?

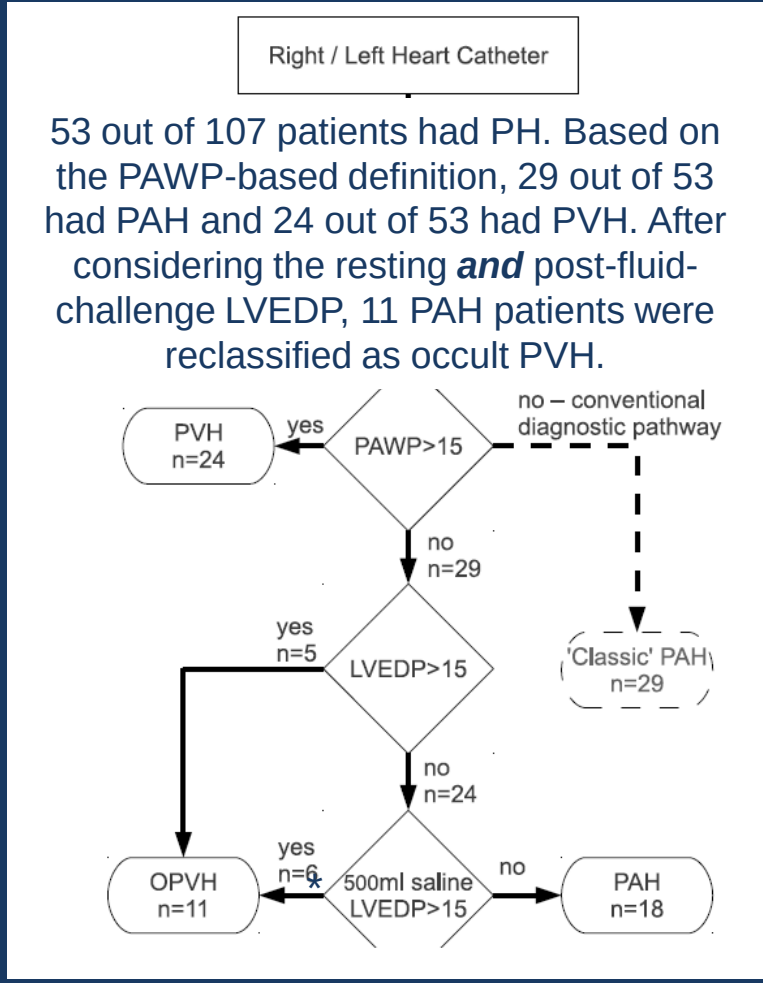
- Fluid challenge and exercise testing may be useful in identifying patients with occult HFpEF.
- ‘However, these technique remain investigational and require meticulous evaluation and standardization before its use in clinical practice can be recommended’.
- Will this still be the case by the time of the next guidelines?



HFpEF, heart failure with preserved ejection fraction; LV, left ventricular.
Hoeper MM *et al. J Am Coll Cardiol* 2013

The role for fluid challenging at right heart catheterisation?

- Used to detect latent pulmonary venous hypertension (Group 2)[1]
- Emerging consensus to infuse 500ml of pre-warmed 0.9% saline solution over 5 - 10 minutes[1,2,3,4]
- Debate about how to standardise and what cut-offs of PAWP to consider but 20mmHg seems like best option[3,4]
- Exercise may be more sensitive way to detect HFpEF[5]



1. Fox, BD et al Eur Respir J. 2012 Dec 20; 2. Coughlan, G Eur Respir J. 2013 Oct;42(4):888-90 EDITORIAL ; 3. Robbins IM et al Circ Heart Fail2014; 7: 116-122; 4. Lau EM and Naije R Eur Respir J 2016; 48; 18-20; 5. Argiento P, Vanderpool RR etc al Chest 2012;590; 4279-4288

Can we agree on criteria for diagnosis of exercise pulmonary hypertension?

ORIGINAL ARTICLE
PULMONARY VASCULAR DISEASES

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]

Proposed standardised protocol of exercise haemodynamic testing

1. Include patients with resting mPAP<25 mmHg
2. Brachial or jugular vein approach
3. Dynamic exercise in supine position on bicycle
4. Number of work step and work increment to reach the maximum within 10–15 min
5. Successive stages: baseline supine, legs on cycle pedal, unloaded pedalling (0 W) and at constant workload increments of 10–30 W depending on estimated exercise capacity (usually 1–3 work load steps)
6. Measurement of mPAP and PAWP averaged over the respiratory cycle and CO in triplicate using thermodilution or direct Fick method
7. Measure mPAP, PAWP and CO at steady state at each step: *i.e.* unchanged mPAP and heart rate; usually during the last 2 min of each exercise step
8. Interpretations
If at submaximal workload, mPAP >30 mmHg with CO <10 L·min^{-1}: (TPR >3 WU) you can stop the test: exercise PH
If not, continue the test until maximum tolerable workload:
If TPR_{max} ≤3 WU with mPAP >30 mmHg: no exercise PH
If TPR_{max} ≤3 WU with mPAP ≤30 mmHg: no exercise PH
If TPR_{max} >3 WU with mPAP ≤30 mmHg: no exercise PH
If TPR_{max} >3 WU with mPAP >30 mmHg: exercise PH

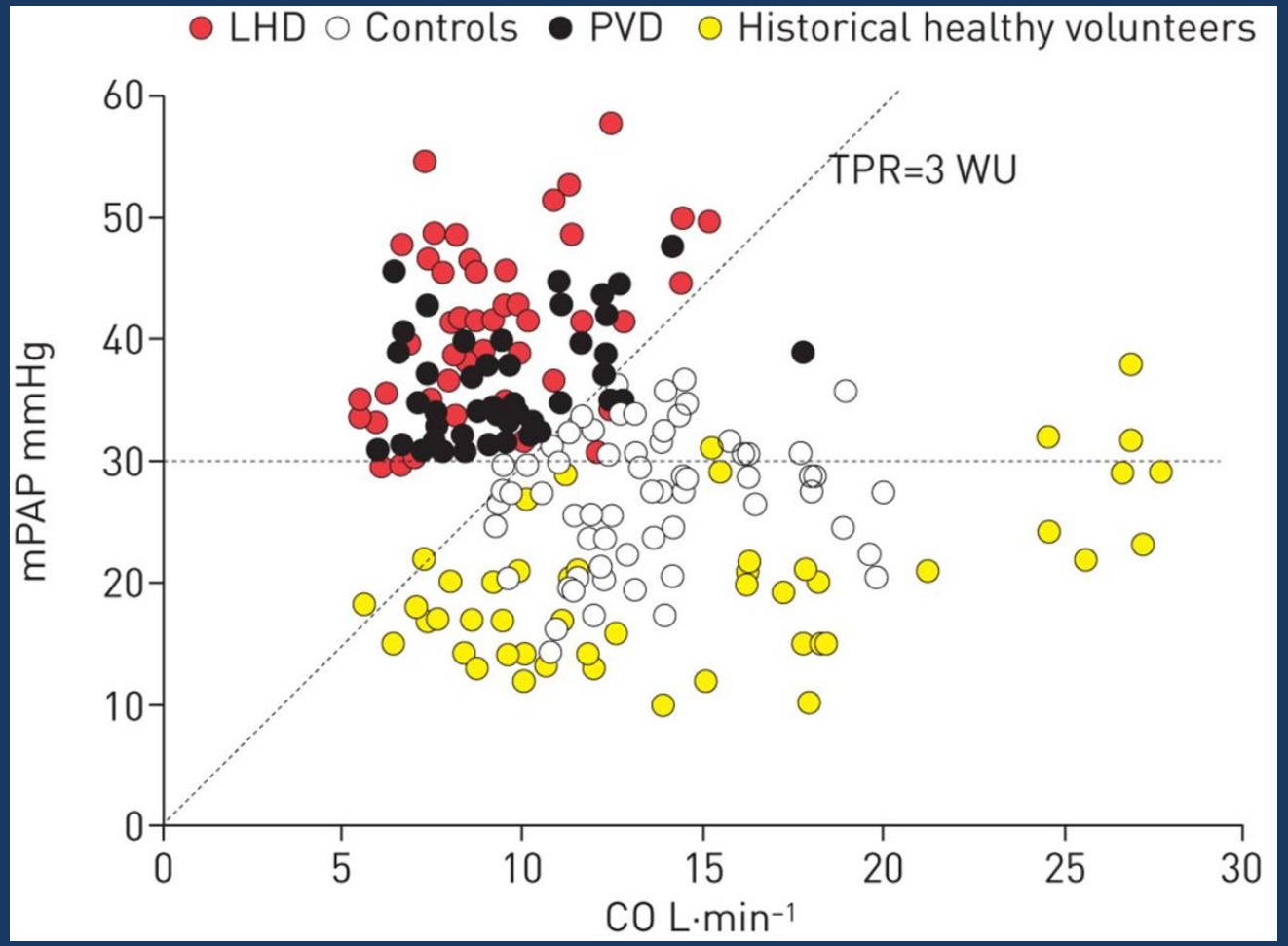
mPAP: mean pulmonary artery pressure; PAWP: pulmonary artery wedge pressure; CO: cardiac output; TPR_{max}: total pulmonary resistance at maximal exercise; PH: pulmonary hypertension.

- The previous definition of exercise PH (mPA pressure >30mmHg) was abandoned because healthy individuals can exceed the threshold at high cardiac output (CO).
- Sensitivity 0.99 but Specificity 0.77

- Combining mPA >30mmHg and TPR >3mmHg.min.L^{-1}
- Sensitivity 0.93 and Specificity 1.0

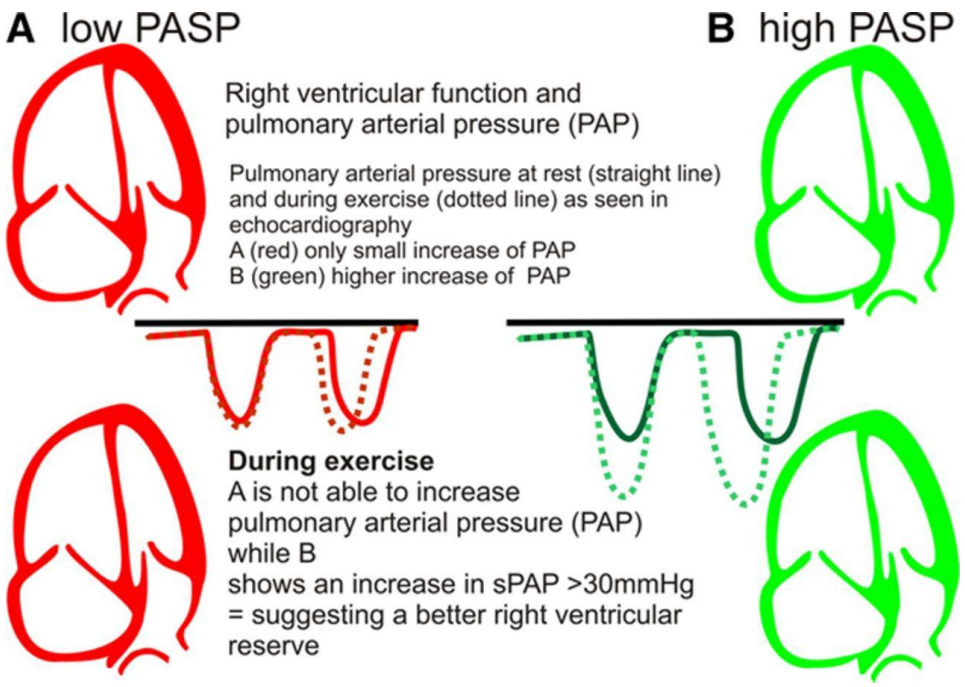
1: Herve P et al Eur Respir J 2015; 46: 728-737
Naeije R, Vonk Noordegraaf, A and Kovacs, G Eur Respir J 2016: 46; 583-586

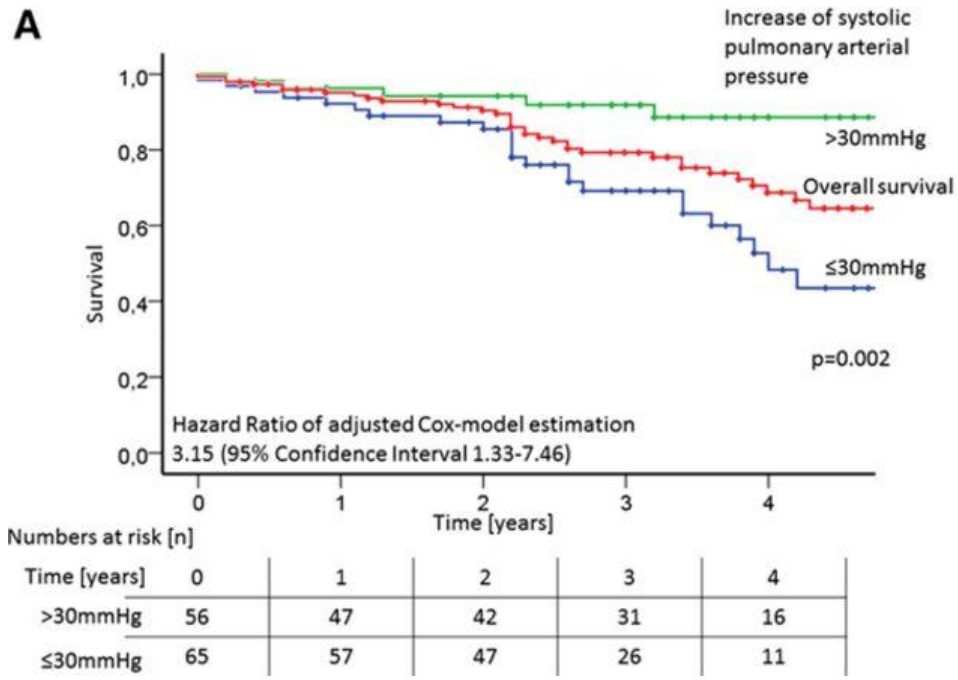
Relationship between exercise mean pulmonary artery pressure (mPAP) and cardiac output (CO).



Herve P et al Eur Respir J 2015; 46: 728-737
Grunig E et al Circulation. 2013 Oct 29;128(18):2005-15

Prognostic Relevance of Right Ventricular Contractile Reserve in Patients With Severe Pulmonary Hypertension



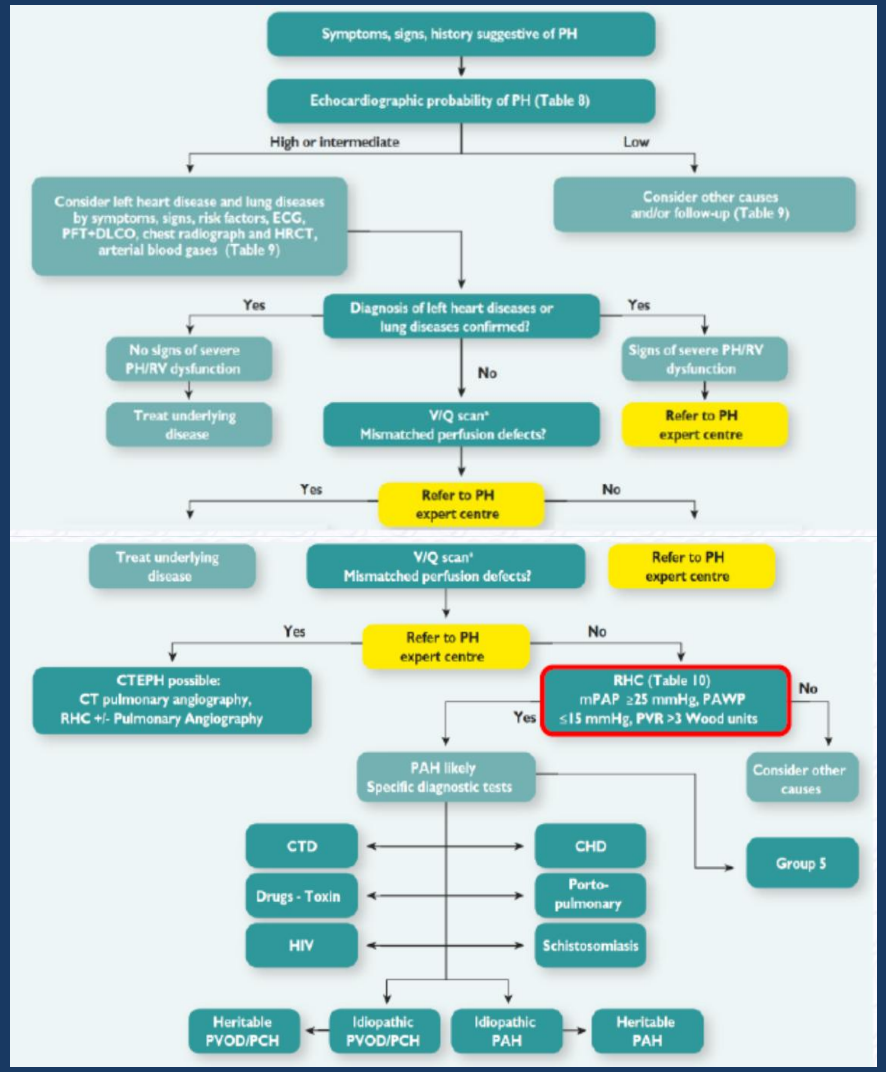


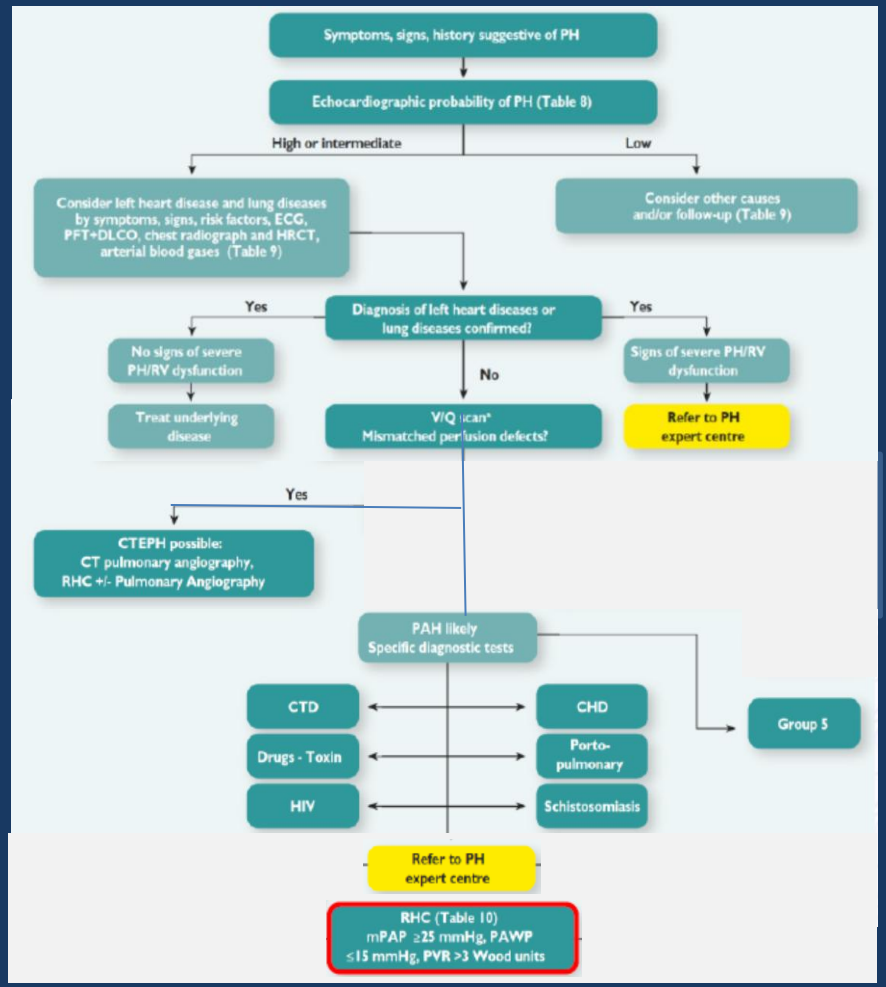
Ekkehard Grünig et al. Circulation. 2013;128:2005-2015

Time to ‘Pimp the Right Heart Cath in PH’?

- Given that the it is recommended that the RHC only be done at the expert centre-can we ‘Pimp’ the test?
- We already do ‘Provocation’ testing with the NO vasodilator trial
  - Should we exercise for diagnosis and/or prognosis?
  - Should we fluid load when ‘atypical’ PAH phenotype?
- Perhaps we should relook at the test as a battery of tests?
  - Fluid challenge– Liver wedge- Exercise - Vasoreactivity - Saturation
  - The ‘FLEVS’ RHC test for PH?

Diagnostic algorithm 2015-2020….





Galie, N et al Eur Heart J 2016: 37;67-119

Definitions and Diagnosis: Proposals and Summary

- 1: Expand the algorithm for clinical evaluation prior to referral to expert centre
  - Increase the role of bedside evaluation
  - Increase the discriminating role of left atrial size and diffusion capacity
- 2: Refresh the Classification of PH
  - Consider dividing IPAH into Classical and atypical..
  - Break up the connective tissue diseases…
  - Review the evidence emerging around ‘Borderline’ PAH
- 3: ‘Pimp’ the Right Heart Catheterisation
  - Provocative Testing (i.e. ‘FLEVS’ testing)…