EUROPEAN HEART HOUSE
Pulmonary Hypertension:
Challenging The 2015 PH Guidelines and annual G6 meeting
Friday 14 – Saturday 15 October 2016

Pulmonary Circulation and Right Ventricular Function
ESC Working Group
EUROPEAN SOCIETY OF CARDIOLOGY®

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Pulmonary hypertension due to left heart diseases

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PH-LHD: From Nice 2013…to Nice 2016
Key questions

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- Size of the problem – prevalence and clinical relevance of PH-LHD ?
- Haemodynamic definition – which variable for which purpose ?
- Therapy for PH-LHD – hello from the other side

PH in left heart diseases: Some characteristics...

- Underlying condition as a trigger to the increase in PAP, through elevated left atrial pressure
- Wide range in prevalence (25 to 100%), as a ‘symptom’ of the underlying disorder (HF with or without preserved EF and valvular heart disease)
- Only a small subset of patients present with **significant pulmonary vascular disease** (< 15%)
- Has an impact on symptoms, including exercise limitations, and outcome (hospitalization and mortality)
- High prevalence of associated comorbidities (SAS, COPD…) also causes of PH

Vachiéry JL et al. J Am Coll Cardiol 2013;62:D100–8. Galiè N et al. Eur Respir J 2015; 46: 903-75. Eur Heart J 2016;37:67-119

Prevalence of PH-LHD in the community

Author	n	Design	RHC	HF definition	Ejection Fraction (EF)	% estimated PH
Damy 2010	1380	Consecutive referral to HF clinic	-	Clinical	≥ 45% in 26%	26% with LVD 40% no LVD
Adhyapak 2010	147	Consecutive echo series	-	Framigham criteria	Mean 39%	100%
Khush 2009	171	Substudy of ESCAPE trial	**Yes**	Clinical	Mean 30%	100%
Kjaergaard 2007	1,022	Substudy of ECHOS study	-	Clinical	≥ 50% in 24%	38%
Grigioni 2006	196	Echocardiographic series	**Yes**	Clinical	Mean 27%	100%
Ghio 2001	377	Consecutive referral to HF clinic	**Yes**	Clinical	Only < 35%	100%
Lam 2009	244	Community HF patients	-	Framingham criteria	Only ≥ 50%	83%
Shalaby 2008	270	Echocardiographic series HF undergoing CRT	-	Clinical	NA (likely < 35%)	79%

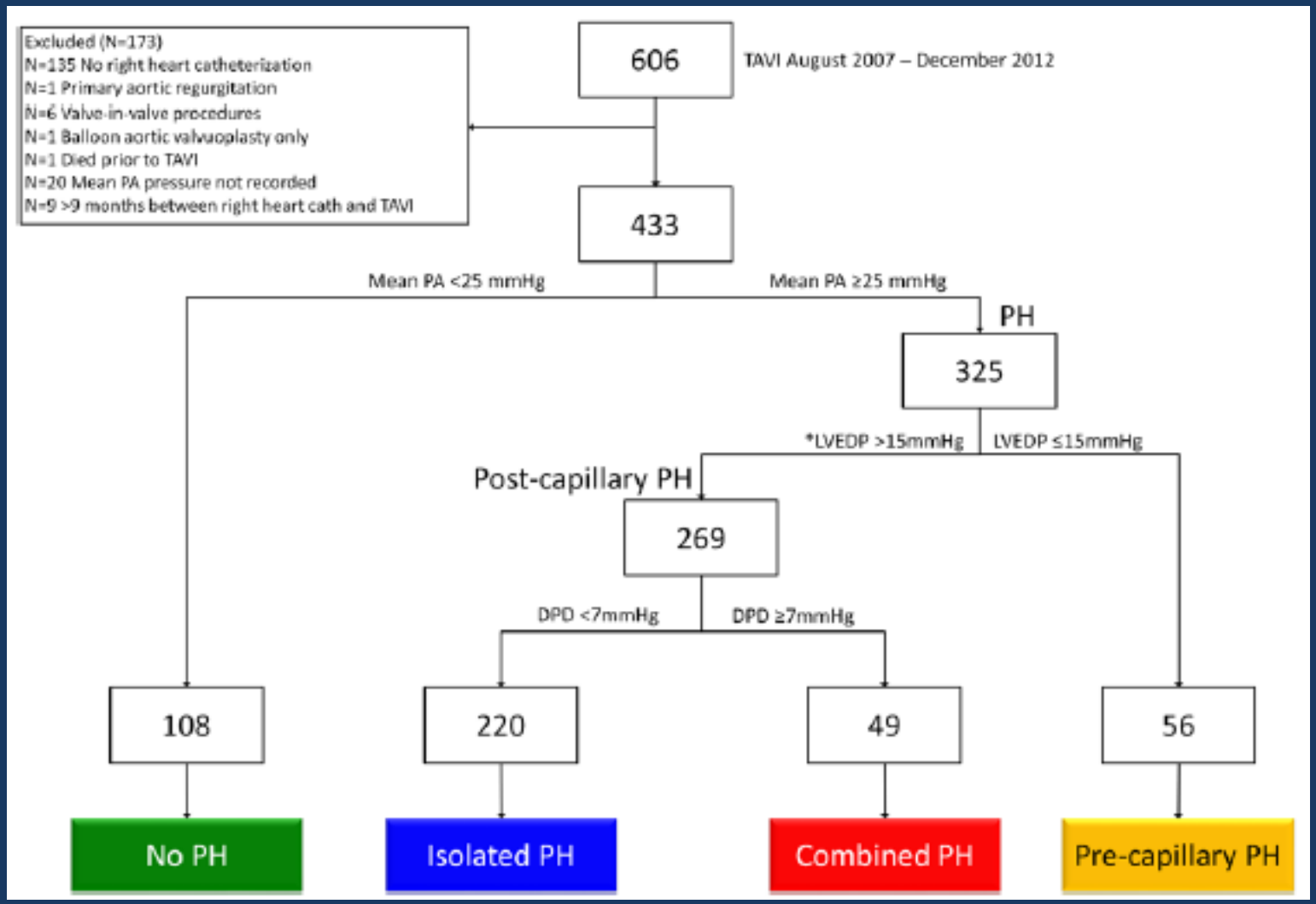
- > 3,000 patients studied, roughly 28% with preserved EF
- ADHF (Khush) to community (Lam) studies ➔ wide range
- Only 3 studies with RHC confirmation

LVD, left ventricle dysfunction; PAWP, pulmonary arterial wedge pressure; RHC, right heart catheterization; TR, tricuspid regurgitation.

Vachiéry JL *et al. J Am Coll Cardiol* 2013;62:D100–8.

Prevalence of PH (by RHC) in patients with aortic stenosis

O'Sullivan C et al. Circ Cardiovasc Interv. 2015;8:e002358



17.8 % **36.3%** **8%** **9%**

Prevalence of PH-LHD in (single) PH centers

- Chicago : out of 622 patients, 16% of PH in HF pEF[1]
- Vienna : n=3107 first RHC + 800 prospective cases, 34 % all HF have PH (13% due to HF pEF)[2]
- Ongoing initiative from the French Society of Cardiology to establish the true prevalence

1. Thenappan T et al. Circ Heart Fail 2011;4:257–65.
2. Gerges M et al. Am J Respir Crit Care Med. 2015;192:1234-46

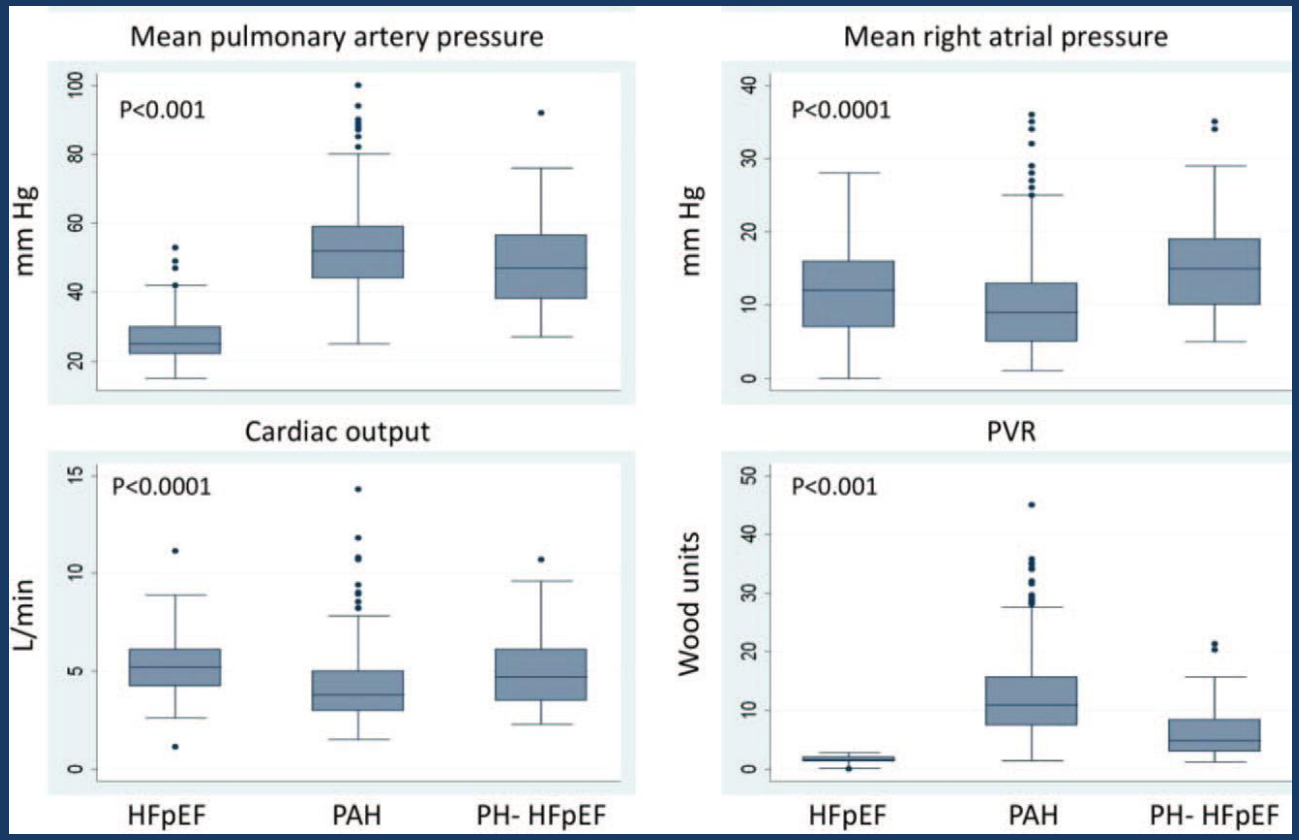
Clinical characteristics from population-based studies of HFpEF

Characteristics	Olmsted Co, MN[40]	Olmsted Co, MN (2006)[40]	Ontario, CA[4]	Framingham[41]	OPTIMIZE[29]	ADHERE[30]	Baltimore, MD[13]	NY HF Consortium[31]	Chicago, IL[33]	China[38]
Sample size, n	244	2167	880	220	10072	26322	37	619	419	132
Age, y	76	74.4±14.4	75.4±11.5	80	75.6±13.1	73.9±13.2	65±10	71.7±14.1	65±13	72.3
Women, %	55	55.7	65.7	65	68	62	84	72.5	62	55.3
Black, %					15	17	76	30	39	
LVEF, %	62±6	61±7	62.4	≥45	62±7	≥40	72±11	60	≥50*	≥45
Outcomes										
% 1-y survival		71	78	80†	65†				86 (1.5 y)	
Comorbidities										
Hypertension, %	96	62.7	55.1		77	77	100	78.2	77	57
CAD, %	53	52.9	35.5	37	32	50	42	43.1	48	39
Diabetes mellitus, %	37	33.1	31.7	22	41	45	61	45.9	33	35
Chronic kidney disease, %						26		9.5	33	9 (end-stage renal disease)
Atrial fibrillation, %		41.3	31.8	29	32	21		23.4	26	
SBP, mm Hg	132±23		156	145±24	150±33	153±33	143±25	160±36	125±20	
DBP, mm Hg	67±14			76±13	75±19	79±21	69±14	84±20	70±12	
BMI, kg/m^2	32±21	30±8		27±5			37±8	31±9	33±9	
Laboratory values										
Hemoglobin, g/dL		11.8±2.1		12.4±2.2				11.8±2.2	11.9±1.9	
Serum creatinine, mg/dL		1.6±1.1		1.5±0.9	1.2	1.7±1.5	1.4±0.7		1.6±1.5	

Sharma K and Kass D.Circ Res. 2014;115:79-96

Clinical characteristics of patients with PH in HF-pEF

- Single center study HF-pEF (n=45) vs PAH (n=522) vs PH HF-pEF (n=100)



- PH HF-pEF was more frequent in the presence of old age, hypertension, coronary artery disease and female gender

Thenappan T et al. Circ Heart Fail 2011;4:257–65.

Distinguishing clinical features between groups

Characteristic	HFpEF	PH-HFpEF	PAH
Age	Older	Older	Younger
Comorbidities	Frequent	More frequent	Rare
RA enlargement	Absent	Less frequent	More frequent
LA enlargement	Frequent	Frequent	Absent
Systolic aortic pressure	Elevated	Elevated	Normak
RAP	Normal	↑	↑
CO	Normal	Normal	↓↓
PVR	Normal	↑	↑↑(↑)

Thenappan T *et al. Circ Heart Fail* 2011;4:257–65.

Interim conclusion 1

- The true prevalence of PH in LHD is by large unknown, but likely high (>50%)
- PH-LHD is heterogeneous (population studied, definition of PH) and few studies report PH established by RHC.
- Patients with HF pEF and PH HF pEF have a similar profile, consistently different with PAH, although profiles may overlap
- Differentiating PAH, PAH with comorbidities and from PH due to HF with preserved EF is challenging.
- PH complicating HF-pEF should be studied as a separate entity

PH-LHD: From Nice 2013…to Nice 2016
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Haemodynamic definitions of pulmonary hypertension

Definition	Characteristics[a]	Clinical group(s)[b]
PH	PAPm ≥25 mmHg	All

Debate and controversy on which variable would be best

1. As a marker of pulmonary vascular disease and
2. To predict outcome

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]	

Galiè N, Humbert M, Vachiéry JL et al. Eur Heart J, 2016;37:67-119 ; Eur Respir J 2015; 46: 903-75

WSPH Nice 2013: aims of the TF 11
How to define 'out-of-proportion' PH in LHD?

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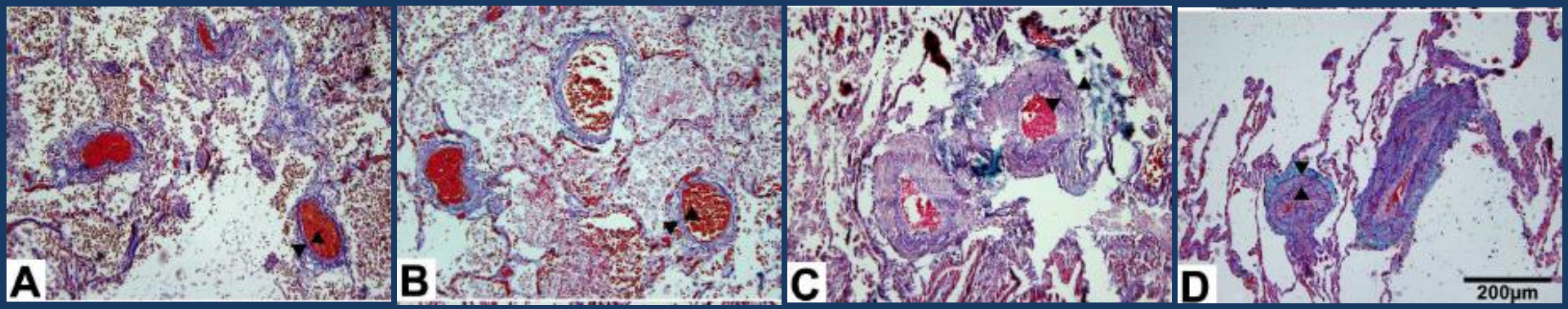
- Move towards a unified terminology for PH-LHD
- Define « pulmonary vascular disease » in LHD, i.e. the precapillary component, by an easily measurable HD criteria (similar to the definition of PH, based on mPAP)
- Candidates identified (alone or in combination?)

1. Pulmonary vascular resistance
2. Transpulmonary gradient (PAPm – PAWP)
3. Diastolic pulmonary gradient (PAPd – PAWP)

4. Compliance (SV/PP) ?

Vachiéry JL, et al. *J Am Coll Cardiol* 2013;62:D100–8

Histology of PH-LHD



IpcPH TPG = 3 mmHg

IpcPH DPG 5 mmHg
TPG 13 mmHg

CpcPH DPG 13 mmHg
TPG 30 mmHg

iPAH

Vessel morphology (semi quantitatve)	iPAH (n=10)	IpcPH (n=9)	CpcPH (n=9)
Medial hypertrophy	63 %	35 %	84 %
Intimal fibrosis	60 %	14 %	68 %
Adventitial fibrosis	64 %	13 %	25 %
Occluded	44 %	7 %	26 %
Plexiform lesions (%)	1 (10%)	0 (0%)	1 (11%)

Gerges C. et al. *Chest* 2013; 143:758–766.

CPET: ventilatory efficiency in CpcPh in between PAH and IpcPH

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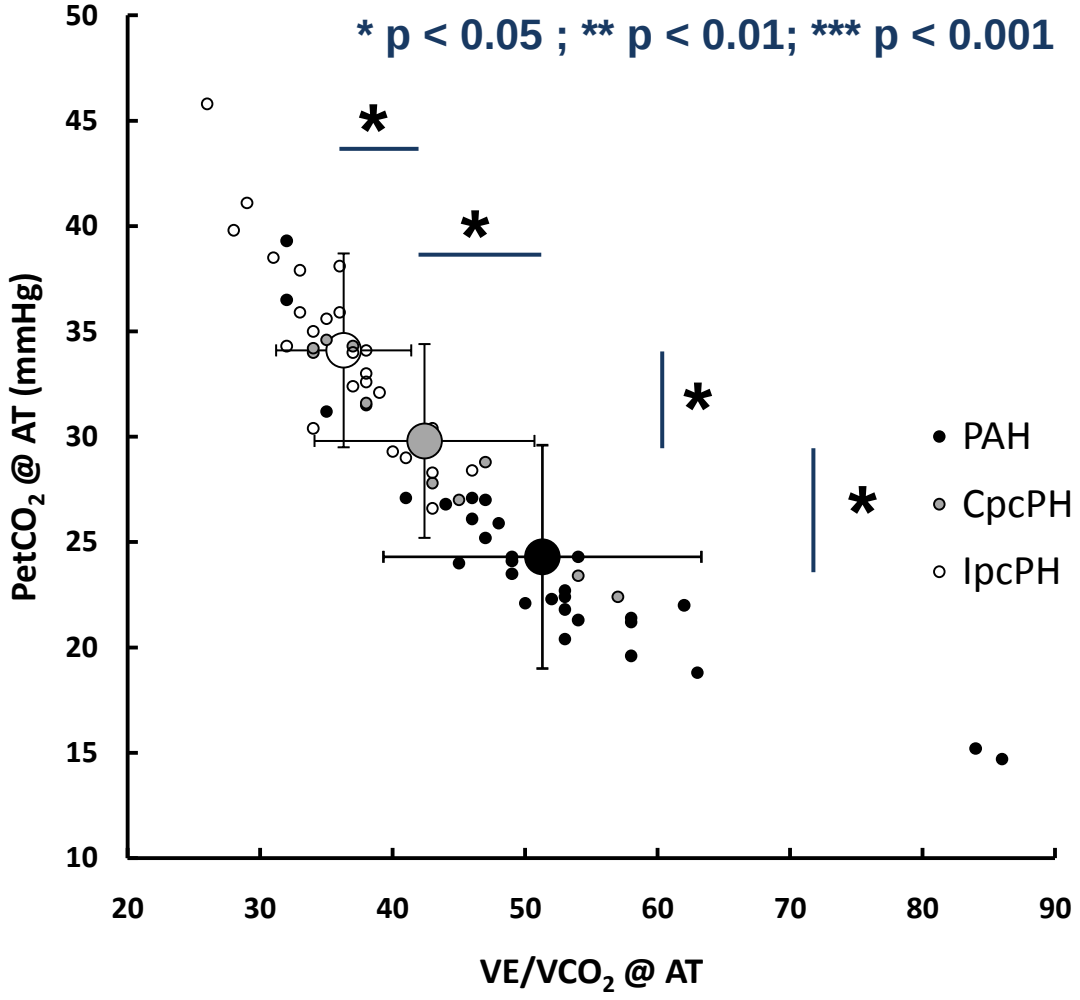
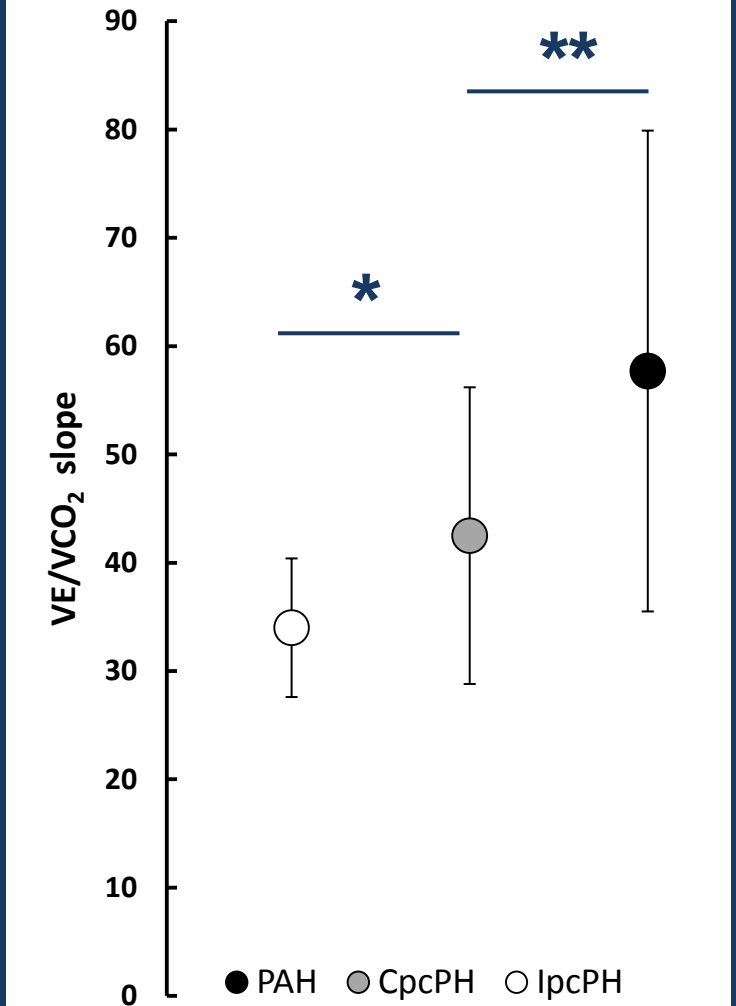


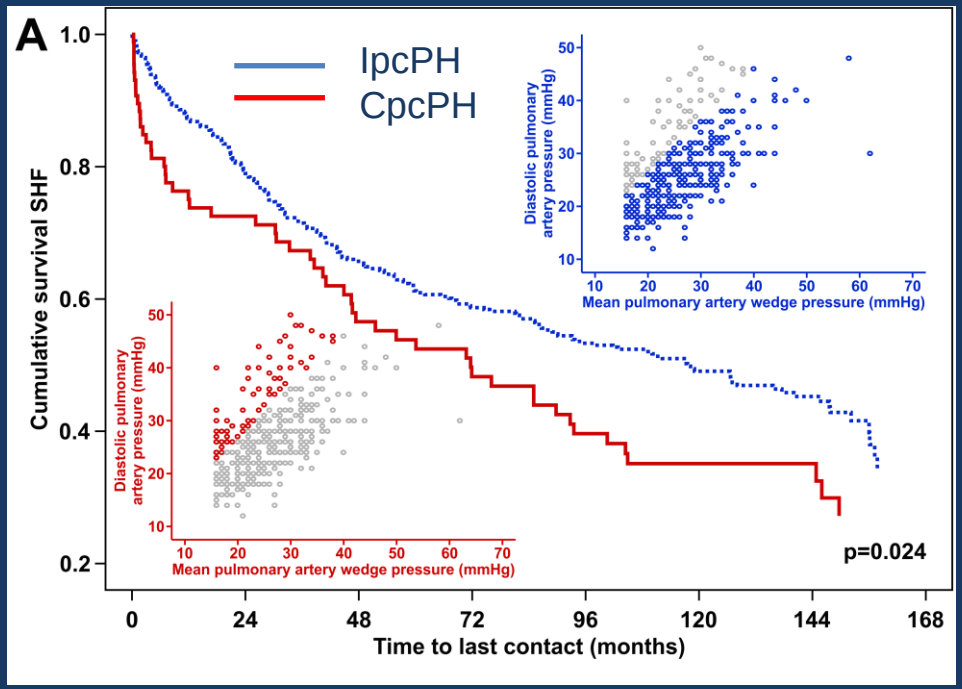


Caravita S et al. J Heart Lung Transplantation (under review)

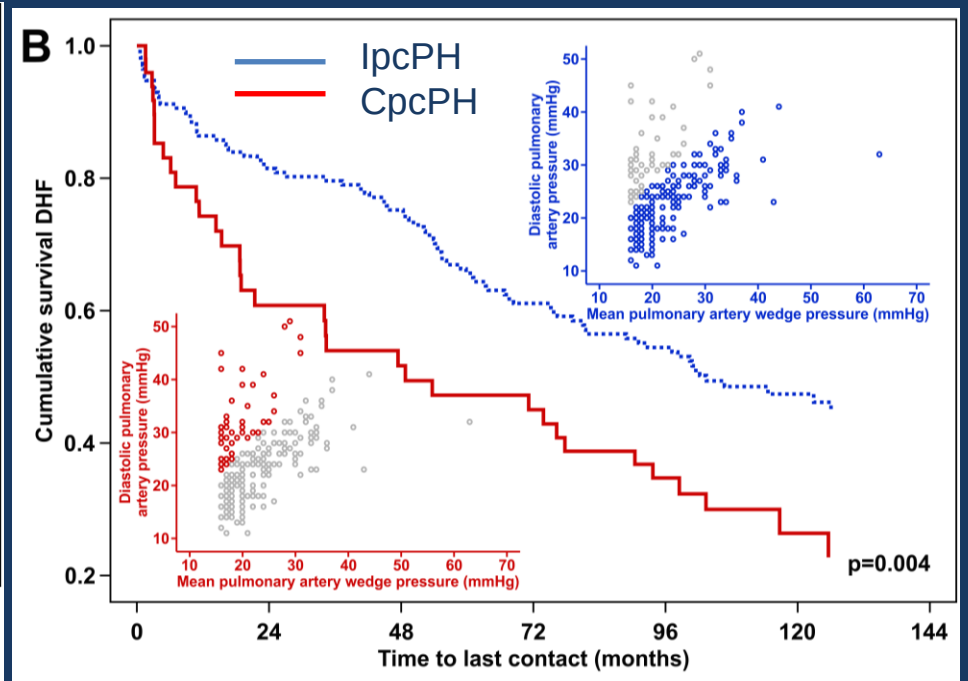
Pulmonary hypertension in heart failure: epidemiology, right ventricular function and survival

- N=3107 stable patients with first diagnostic RHC + n=800 prospective
- 34% HF (21% HF-rEF and 13% HF-pEF)
- Cpc-PH in 14% (HF-rEF) and 12% (HF-pEF)

HF systolic dysfunction

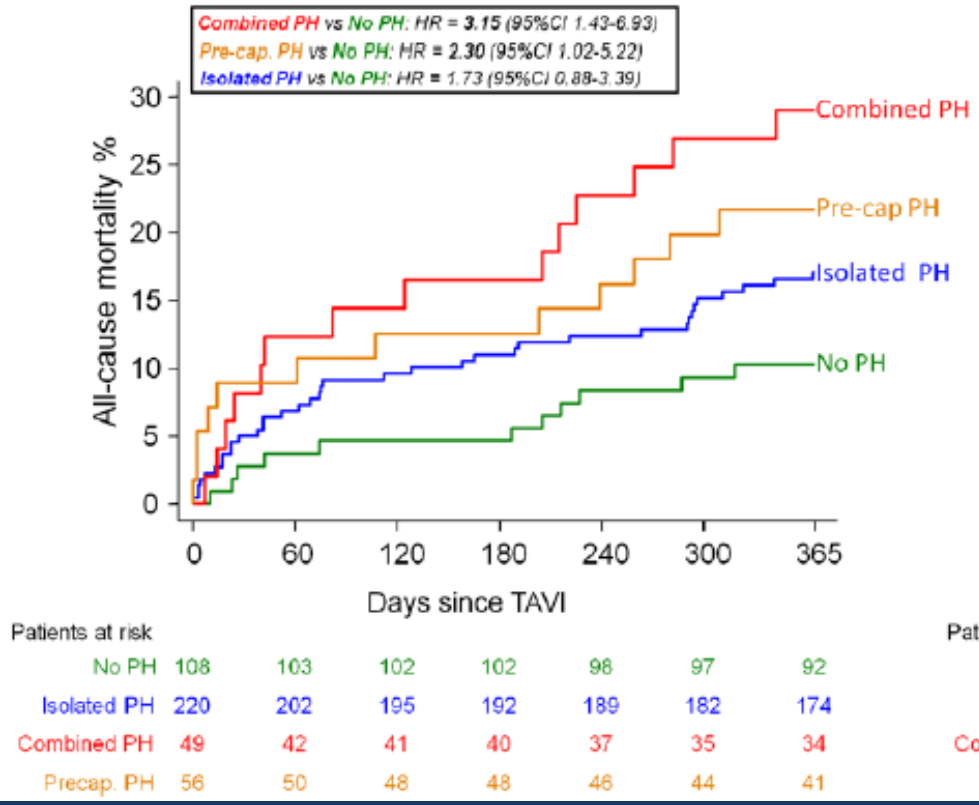


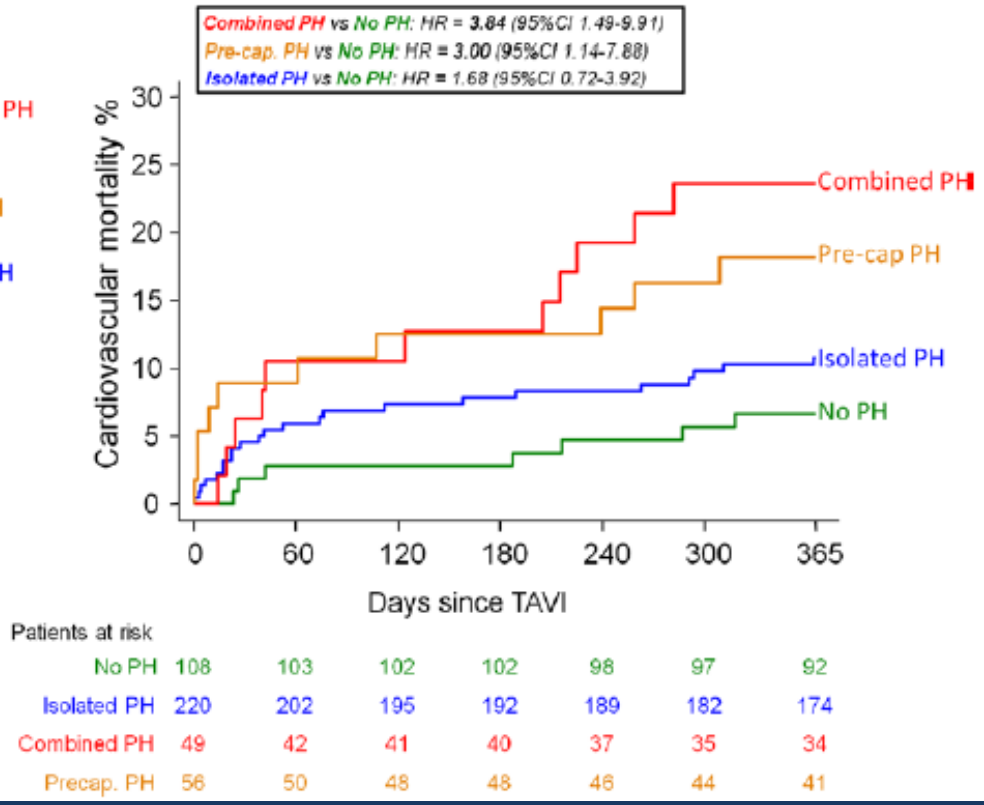
HF diastolic dysfunction



Gerges M et al. Am J Respir Crit Care Med. 2015;192:1234-46

Retrospective analysis of outcome in 600 patients with aortic stenosis





O'Sullivan C et al. Circ Cardiovasc Interv. 2015;8:e002358

Controversial issues: an abnormal DPG does not consistently predict outcome in PH-LHD

- No role in the UNOS database[1] (22.6% had TPG > 12 mmHg) and a cardiomyopathy registry[2] (37.9% had PH)
- Predictive in a large PH center[3] (36% had TPG > 12 mmHg, 16% had a DPG $\geq$ 7 mmHg) and a valvular heart disease registry[4]
- A PVR > 3 WU appears to be a better prognosis indicator than TPG in HF rEF
- Most studies focused on HF rEF [1,2,5]
- A PVR > 3 WU appears to have prognostic value over TPG[2]

- A marker of disease is not necessarily a prognostic indicator
- If a consistent definition is considered (DPG > 7 mmHg), $\pm$ 13% of patients with HF do have CpcPH[2,3,6]
- Significant technical and methodological issues may explain why DPG may not always reflect prognosis

1. Tedford et al. J Heart Lung Transplant 2014. 2. Tampatakis et al. J Am Coll Cardiol 2014. 3.Gerges et al. Chest 2013; 143:758–766. 4. O'Sullivan C et al. Circ Cardiovasc Interv. 2015;8:e002358. 5. Chatterjee, N and Lewis G. J Am Coll Cardiol HF 2014. 6. Gerges et al. Am J Respir Crit Care Med 2015. Miller et al. J Am Coll Coll HF 2013

Clinical Features, Hemodynamics, and Outcomes of Pulmonary Hypertension Due to Chronic Heart Failure With Reduced Ejection Fraction

Pulmonary Hypertension and Heart Failure

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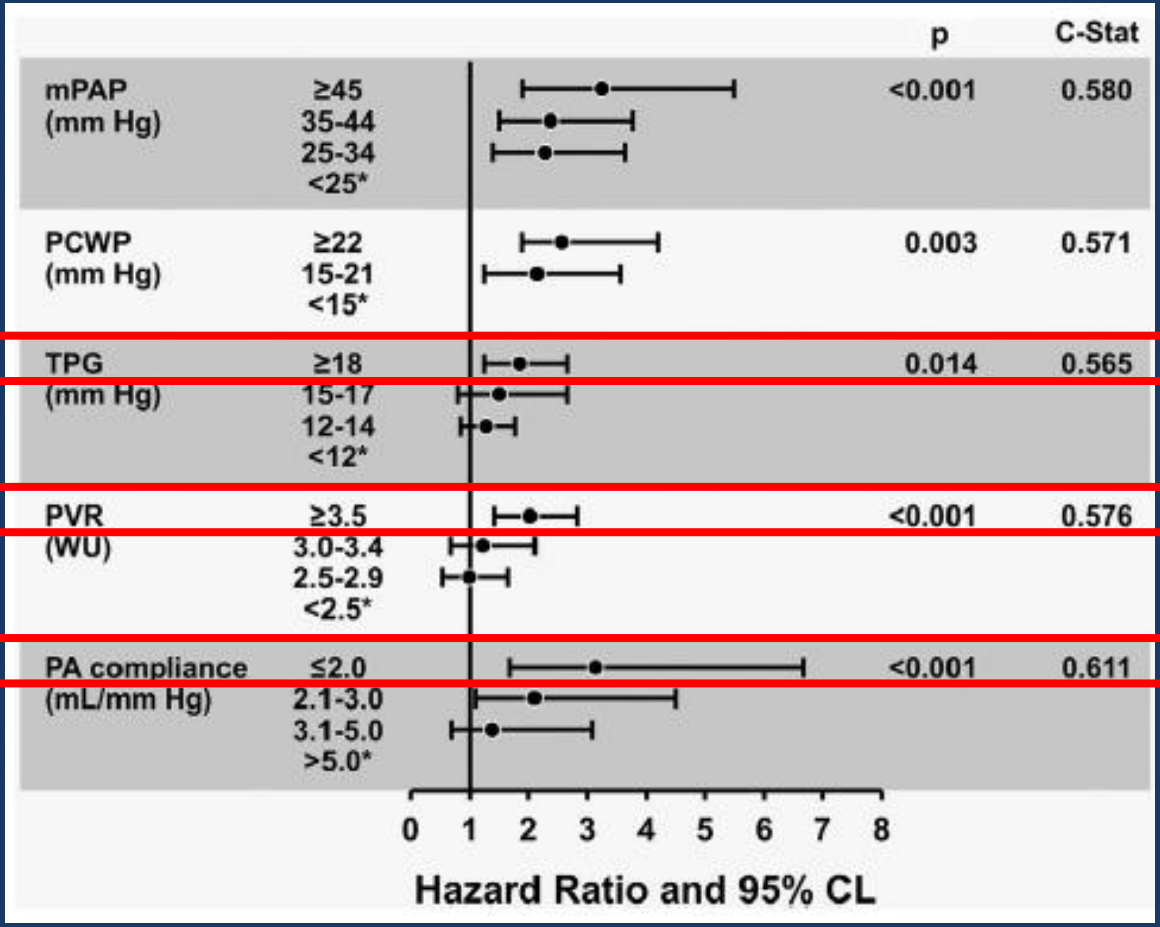
- Forest plot predictors of mortality: role of severe PH



Miller WJ et al. J Am Coll Cardiol HF 2013;1:290–9

Vienna database revisited according to the new classification

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)¶

- IpcPH (DPG < 7 mmHg and/or PVR ≤ 3 WU) = 57 %
- CpcPH (DPG > 7 mmHg and/or PVR > 3 WU) = 14.3 %
- Other (unclassifiable) combination = 28.7 %

Proposal: CpcPH could be defined by DPG ≥ 7mmHg **AND** PVR > 3 WU

Gerges M et al. Eur Respir J 2016; 48: 553-555

Pros and cons in the choice of the determinant of „PVD“ in HF pEF

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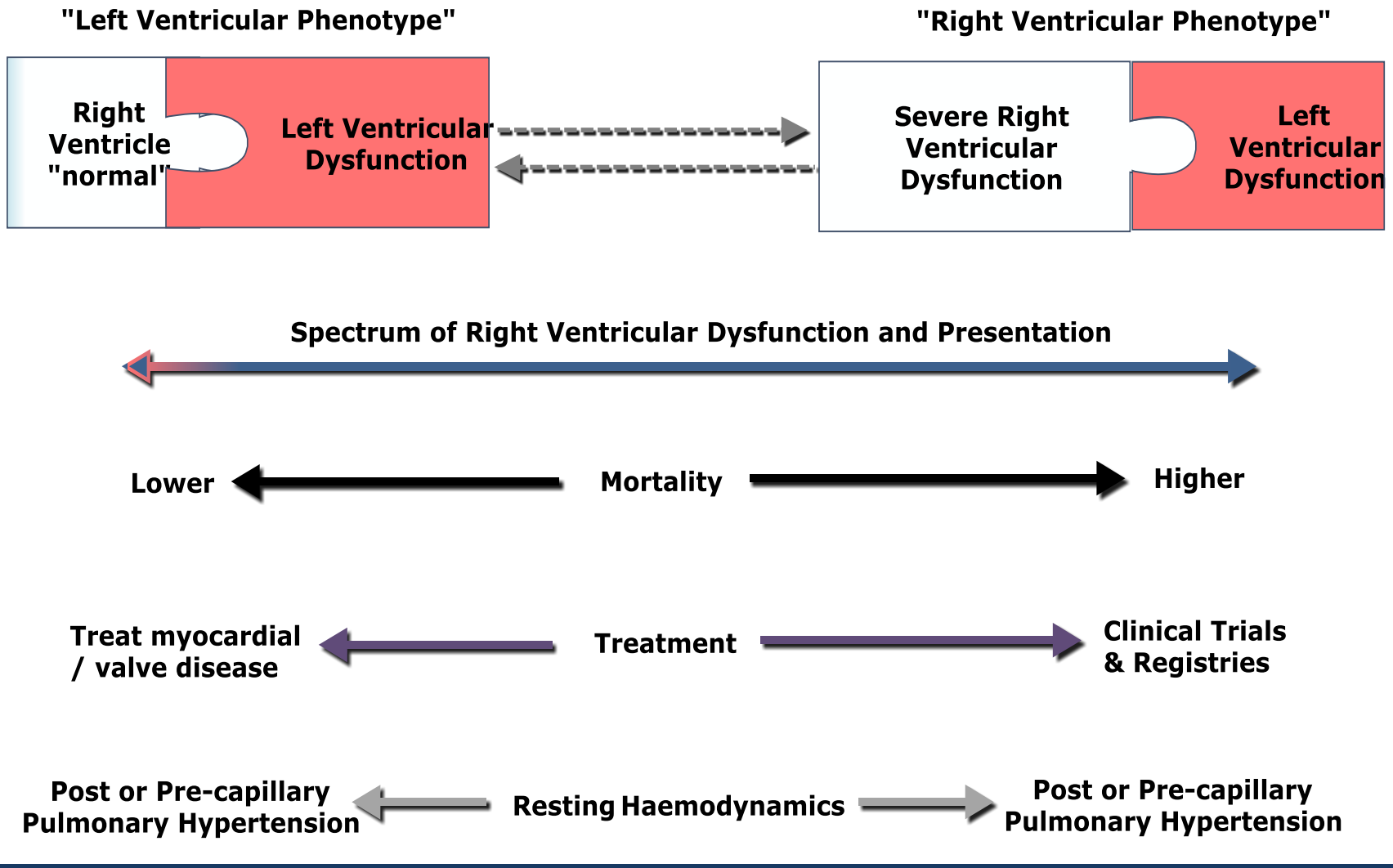
Characteristic	TPG	DPG	PVR	Ca
Physiological rationale	-(+)	+++	+++	+(+)
Independance from flow and filling pressure	-	+	-(+)	-
Marker of disease	+	++	++	+
Marker of prognosis	+	+	++	+
« Historical » variable	+++	+	+++	-
Level of Comfort for clinical use	++	++(+)	+++	-
Level of controversy	++	++++	++	?

Level of controversy is proportionate to the strength of the physiological rationale and inversely correlated with history…

Vachiéry JL. Personal (strong) opinion, unpublished

PH-LHD: looking for different phenotypes, haemodynamic and clinical



Rosenkranz S, Gibbs JS, Wachter R, De Marco T, Vonk-Noordegraaf A, Vachiéry JL. Eur Heart J 2016; 37:942-54

Interim conclusion 2

- The distinction between passive and active changes in the pulmonary circulation makes physiological and clinical sense.
- The current **terminology** is appropriate to identify a distinct haemodynamic phenotype, to underscore the incremental role of PH on outcome
- However, the current controversies on outcome prediction should encourage the use of a combination of variables (i.e. DPG **and** PVR)
- In addition, prognosis is highly likely linked to the degree of RV dysfunction and other factors independent from the degree of pulmonary vascular involvement. A clinical phenotype could complement HD characterization

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Recommendations for treatment of patients with HF-pEF and HF-mrEF

Recommendations	Class [a]	Level [b]	Ref [c]
it is recommended to screen patients with HFpEF or HFmrEF for both cardiovascular and non-cardiovascular comorbidities, which, if present, should be treated provided safe and effective interventions exist to improve symptoms, well-being and/or prognosis.	I	C	
Diuretics are recommended in congested patients with HFpEF or HFmrEF in order to alleviate symptoms and signs.	I	B	178, 179

Why should we treat PH, a complication of an underlying condition with no evidence for therapy ?

Ponikowski P et al. Eur Heart J doi:10.1093/eurheartj/ehw128

Completed RCTs targeting the PDE5i/NO pathway in PH-LHD

Drug	*n*	Duration	Primary endpoint	Secondary endpoints	Results
HF with reduced EF					
Riociguat LEPHT [1]	201	16 weeks	Change in mPAP vs placebo	AEs, PK, PVR, NT-proBNP	• **No change in mPAP** • **Decrease in PVR (CO)**
Tadalafil PITCH2 (NCT01910389)	2102 **(23)**	**Event-driven**	Time to CV death or 1st HF hospitalisation	Biomarkers, exercise, QoL	• **Study terminated in Feb 2014 (funding source)**
HF with preserved EF					
Riociguat DILATE [3]	48	Acute (6 hours)	Change in mPAP vs placebo	AEs, PK, PVR, NT-proBNP	• **No change in mPAP**
Sildenafil Hoendermis[4]	52	12 weeks	Change in mPAP vs placebo	AEs,, PVR, BNP, Peak VO_2	• **No change in mPAP** • **No change 2ary EP**

- None of the above-mentionned studies met the primary endpoint
- < 300 patients included vs > 3,000 in recent RCTs in PAH

1. Bonderman et al. Circulation 2013; 128: 502-511
2. www.clinicaltrials.gov, accessed 11th september 2015
3. Bonderman D et al. Chest. 2014;146(5):1274-85

Comparing the studies:
Heterogeneity of patient demographics

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Parameter	LePHT Study[1] (*n* = 201)	DILATE-1 Study[2] (*n* = 36)	Dutch Study[3] (*n* = 52)
Male sex, %	86	39	29
Mean age, y	58.1	71.0	74.0
Mean LVEF, %	27.8*	62.1	58.0
Atrial fibrillation at baseline, %	12.5*	44.0	62.0
Origin of heart failure, %			
Ischaemic cardiomyopathy	45	-	-
Non-ischaemic cardiomyopathy	54	-	-
Data missing	2	-	-
Median NT-proBNP	-	1152.25 pg/L*	1087 ng/L
Mean 6MWD, m	395.4*	-	-

*Calculated by taking the means of all treatment group mean values including placebo.

1. Bonderman D, *et al. Circulation* 2013; 128:502-11; 2. Bonderman D, *et al. Chest* 2014; 146:1274-85; 3. Hoendermis E, *et al. Eur Heart J* 2015; 36:2565-73.

Comparing the studies:
RHC characteristics are typical of IpcPH

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Parameter*	LePHT Study[1] (*n* = 160†)	DILATE-1 Study[2] (*n* = 36)	Dutch Study[3] (*n* = 52)
Mean PAP, mmHg	37.9	33.3	35.0
Mean PAWP, mmHg	23.9	20.2	20.4
RAP, mmHg	9.6	11.4	9.5
Cardiac output, L/min	-	4.8	5.4
Cardiac index, L/min/m^2	2.3	2.5	2.7
PVR, dynes/s/cm^{-5}	273.6	243	205
TPG, mmHg	14.0	13.1	13
DPG, mmHg	-	2.0**	1

*Calculated by taking the mean or median of all treatment groups.
**Post-hoc analysis.
†Per-Protocol population.

1. Bonderman D, *et al. Circulation* 2013; 128:502-11; 2. Bonderman D, *et al. Chest* 2014; 146:1274-85; 3. Hoendermis E, *et al. Eur Heart J* 2015; 36:2565-73.

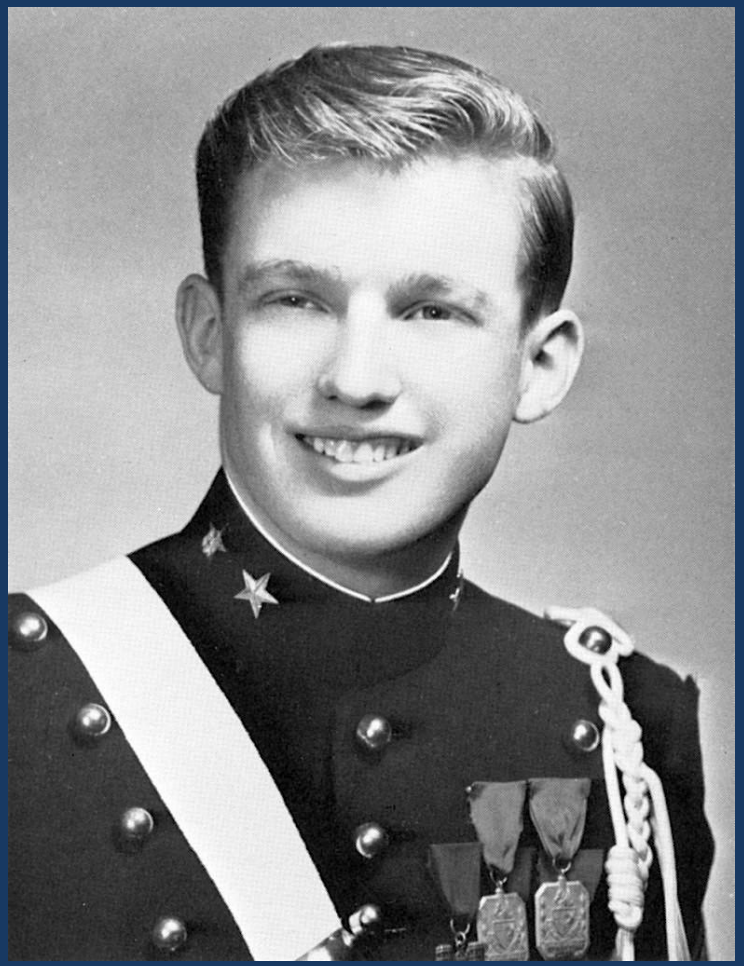
Ongoing RCTs in PH-LHD [1]

Drug	*n*	Start	End	Duration	Primary endpoint	Secondary endpoints
HF with reduced EF						
Sildenafil Sil-HF [1,2] (NCT01616381)	210	9/2012	6/2014	24 weeks	Patient Global Assessment and 6MWD	QoL, Kansas city questionnaire, AEs
HF with EF > 35%						
Macitentan MELODY-1 [2] (NCT02070991)	60	Completed, awaiting results		12 weeks	Safety and tolerability (fluid retention)	PVR, haemodynamics, changes in TPG and DPG, echo (RV function)
HF with EF ≥ 50%						
Riociguat DYNAMIC[3] (NCT02744339)	114	5/2015		26 weeks	Change in CO by RHC	PVR, haemodynamics, changes in TPG and DPG, echo (RV function)

1. www.clinicaltrials.gov, accessed 11th september 2015
2. Cooper JC, *et al. Eur J Heart Fail* 2013; 15:119-22.

Conclusions

- A small proportion of patient with PH-LHD present significant pulmonary vascular disease and a RV “phenotype”. The latter should be defined in complement of the haemodynamic characterization
- The definition of CpcPH may be refined by the combination of DPG **and** PVR, pending validation in multicenter registries
- Therapy should aim at treating the underlying condition and control confounding factors (OSAS, PE, COPD…)
- There is still no convincing evidence supporting the use of any PAH therapies in PH-LHD



« The times they are a-changing »[1]

« The answer, my friend, is blowing in the wind »[2]

1. Bob Dylan 1964
2. Bob Dylan 1063
3. Litterature Nobel Price 2016