Αριστοτέλειο Πανεπιστήμιο Θεσσαλονίκης
Α΄ Καρδιολογική Κλινική ΑΧΕΠΑ
Ιατρείο Πνευμονικής Υπέρτασης

Σύγχρονες προκλήσεις στην αντιμετώπιση περιστατικών με PH κατηγορίας 2

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Conflicts of interest

- Travel grants by Actelion Pharmaceuticals Ltd

VT

- 78 yo female patient
- DoB: 02/03/1938

Background

- 2000
  - COPD
- 2006
  - Pulmonary embolism (provoked- total hip replacement)
- 2010
  - Atrial fibrillation
  - Arterial hypertension
  - Diabetes mellitus
  - Hypothyreoidism
- 2012
  - Breast Ca (resected – considered cured)
- 2016
  - Heart failure with preserved ejection fraction

Background

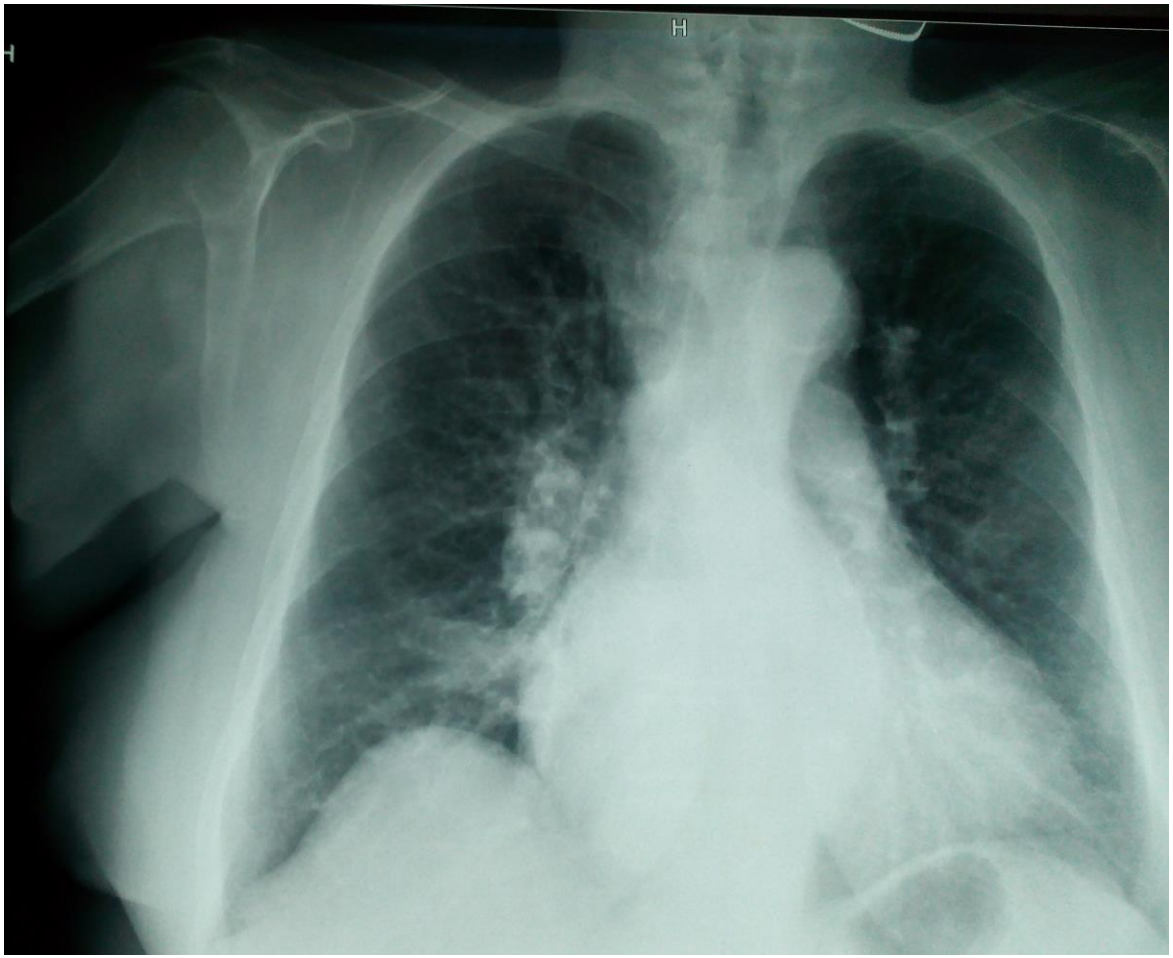
Treatment

- Quinapril 10mg od
- Furosemide 120mg od
- Diltiazem 90 bid
- Apixaban 5 bid
- Spironolactone 25mg od
- Letrozole 2,5mg od
- Vildagliptin 50mg od
- Levothyroxine 50 od
- Inh Budesonide + Formeterol

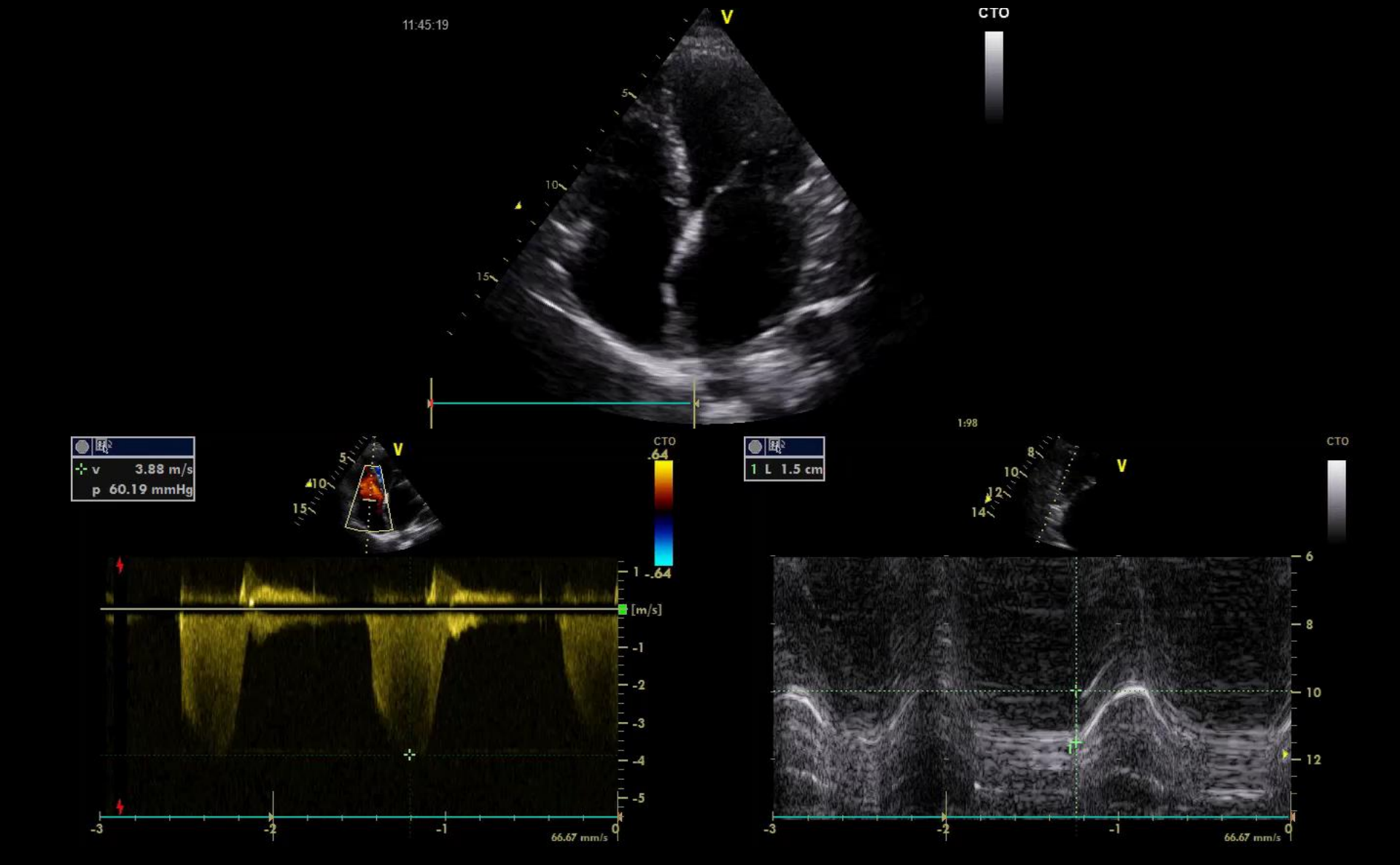
Current condition

- Dyspnea in mild exertion since 1y
- WHO III
- 6MWT: 216m
- BMI 38kg/cm2
- BP 140/80mmHg
- HR 72 bpm, irregular heart sounds
- SpO2 95% (room air)
- Lower leg edema
- Increased JVP
- Pansystolic murmur, 2/6 apical sternum
- Lung auscultation: crackles in bases

Chest X-ray



Echo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V
CTO
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v 3.88 m/s
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.64
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1
-1
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-3
-4
-5
-3
-2
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1 L 1.5 cm
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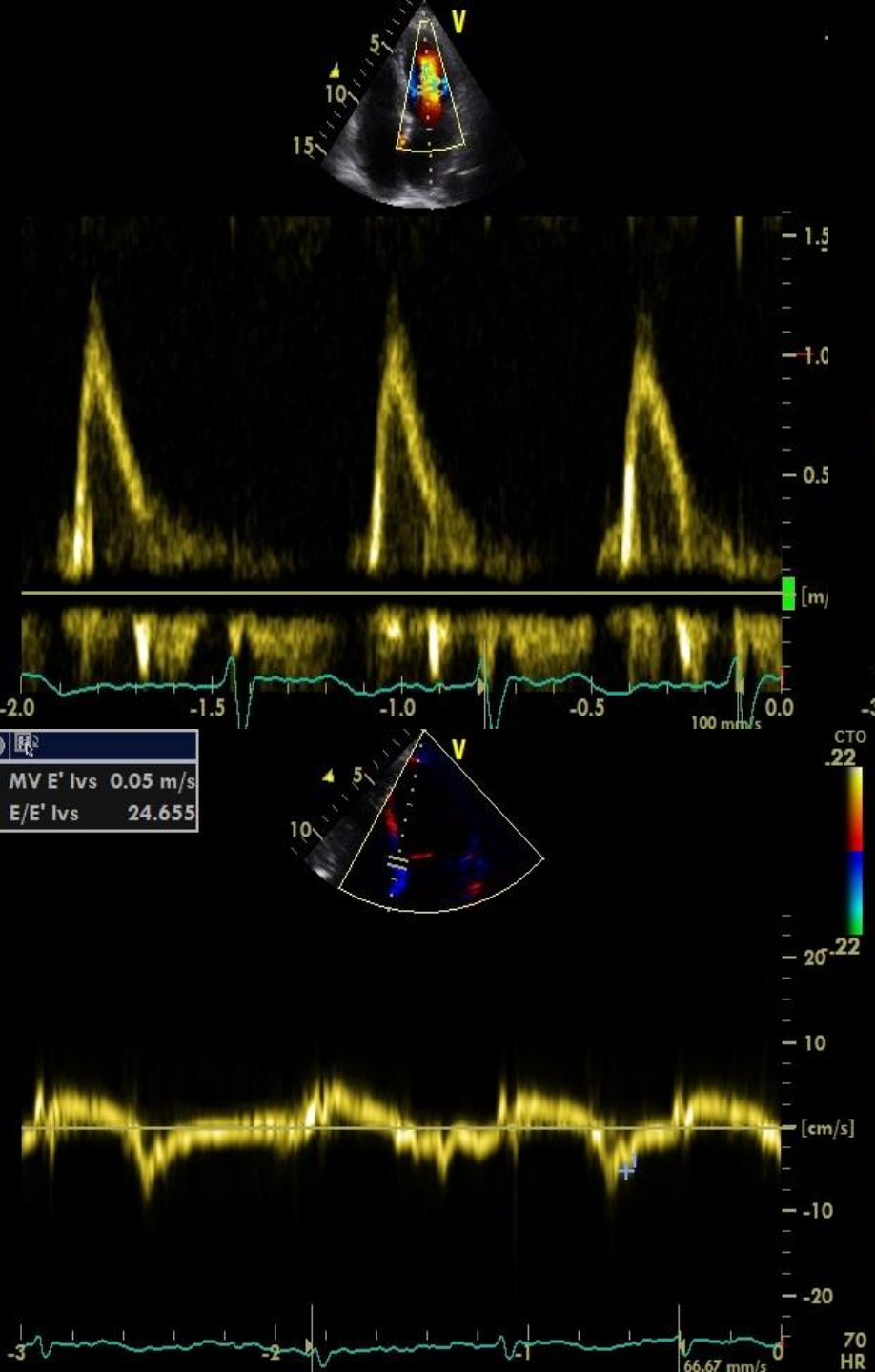


- E= 1.25 m/s
- E septal= 0.05 m/s
- E lateral= 0.14m/s

Diagnostic workup

- Normal thyroid function
- Normal immunologic blood tests
- NT pro-BNP 1346 pg/ml
- CT
  - No pulmonary thrombus
  - No interstitial lung disease
  - No tumors
  - Main pulmonary artery dilatation (35 mm)
- SPECT
  - No CTEPH

- LFT
  - FVC 64,9%
  - FEV1 67,2%
  - TLC 69%
  - DLCO 68,3%

RHC

BSA: 1.9, Hb: 10.2mg/dl, HR 80bpm, SpO_2 98%		
	Pressure (mmHg)	**SAT (%)**
RA	9	
RV	66/1	
PAP	70/23/m42	61.9
PAWP	13	
PVR (Wood)	4.2	
PVRi (W*m²)	8.0	
CO (l/min)	5.5	
CI (l/min/m²)	2.9	

Challenge N# 1 - Diagnosis

- precapillary PH? → idiopathic
  → due to COPD

What about left heart?

Table 3 Haemodynamic definitions of pulmonary hypertension

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]	

CO = cardiac output; DPG = diastolic pressure gradient (diastolic PAP – mean PAWP); mPAP = mean pulmonary arterial pressure; PAWP = pulmonary arterial wedge pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; WU = Wood units.
[a]All values measured at rest; see also section 8.0.
[b]According to *Table 4*.
[c]Wood Units are preferred to dynes.s.cm^{-5}.

Galie et al, Eur Heart J 2015

Importance of "phenotyping"
Examples of key factors suggestive of Group 2 PH

Clinical presentation	Echocardiography	Other features
Age >65 years	Structural left heart abnormality • Disease of left heart valves • LA enlargement (>4.2 cm) • Bowing of the IAS to the right • LV dysfunction • Concentric LV hypertrophy and/or increased LV mass	ECG • LVH and/or LAH • AF/Afib • LBBB • Presence of Q waves
Symptoms of left heart failure	Doppler indices of increased filling pressures • Increased E/e' • >Type 2–3 mitral flow abnormality	Other imaging • Kerley B lines • Pleural effusion • Pulmonary oedema • LA enlargement
Features of metabolic syndrome	Absence of • RV dysfunction • Mid systolic notching of the PA flow • Pericardial effusion	
History of heart disease (past or current)		
Persistent atrial fibrillation		

Eur Heart J, 2015 doi: 10.1093/eurheartj/ehv317
Eur Respir J, 2015 doi: 10.1183/ 13993003.01032-2015

RHC

BSA: 1.9, Hb: 10.2mg/dl, HR 80bpm, SpO_2 98%			
	Pressure (mmHg)	**SAT (%)**	**Fluid challenge** (500ml NaCl 0.9% in 30')
RA	9		
RV	66/1		
PAP	70/23/m42	61.9	
PAWP	13		19
DPG	10		4
TPG	29		23
PVR (Wood)	4.2		
PVRi ($W*m^2$)	8.0		
CO (l/min)	5.5		
CI ($l/min/m^2$)	2.9		

Diagnosis

- HFpEF
- Post-capillary PH

Definition – Classification

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]	

Galie et al. Eur Heart J 2015

How to define pulmonary hypertension due to left heart disease

To the Editor:

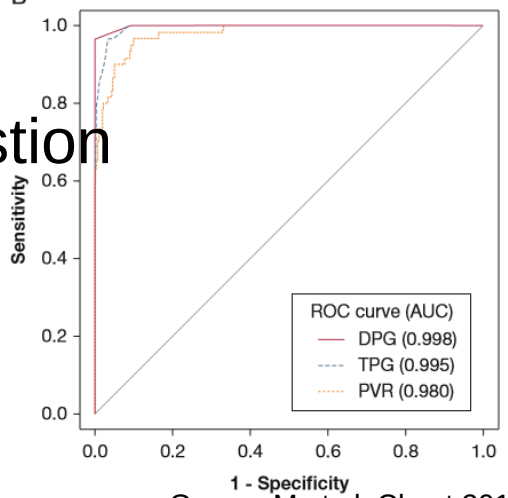
Current 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS diagnosis and treatment of pulmonary hypertension (PH) [1, 2] have adopted ne understanding of PH due to left heart disease (PH

The new guidelines present two subsets of PH-L labelled as "passive" PH-LHD, defined by a mea pulmonary artery wedge pressure (PAWP) >15 r (DPG) <7 mmHg and/or pulmonary vascular res post- and pre-capillary PH (Cpc-PH), previously defined by a mean PAP ⩾25 mmHg, mean PAWP

However, the previous definition of PH-LHD and

Gerge

DPG or PVR?
Here is the question



Gerges M,et al, Chest 2016

TABLE 1 Hazard of Death in DPG, TPG, or PVR

	Hazard Ratio (95% CI) per Unit Increase	p
DPG		
Unadjusted	1.02 (1.00-1.05)	
Adjusted	1.02 (1.00-1.05)	
TPG		
Unadjusted	1.03 (1.00-1.05)	
Adjusted	1.02 (1.00-1.05)	
PVR		
Unadjusted	1.13 (1.06-1.20)	
Adjusted	1.11 (1.04-1.19)	

Adjusted model accounts for age, gender, race, and body mass
CI = confidence interval; DPG = diastolic pulmonary gra
TPG = transpulmonary gradient.

Tampakakis et al, J

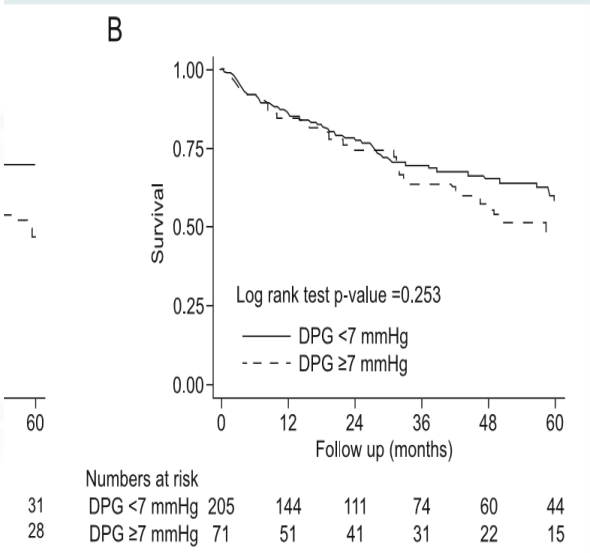
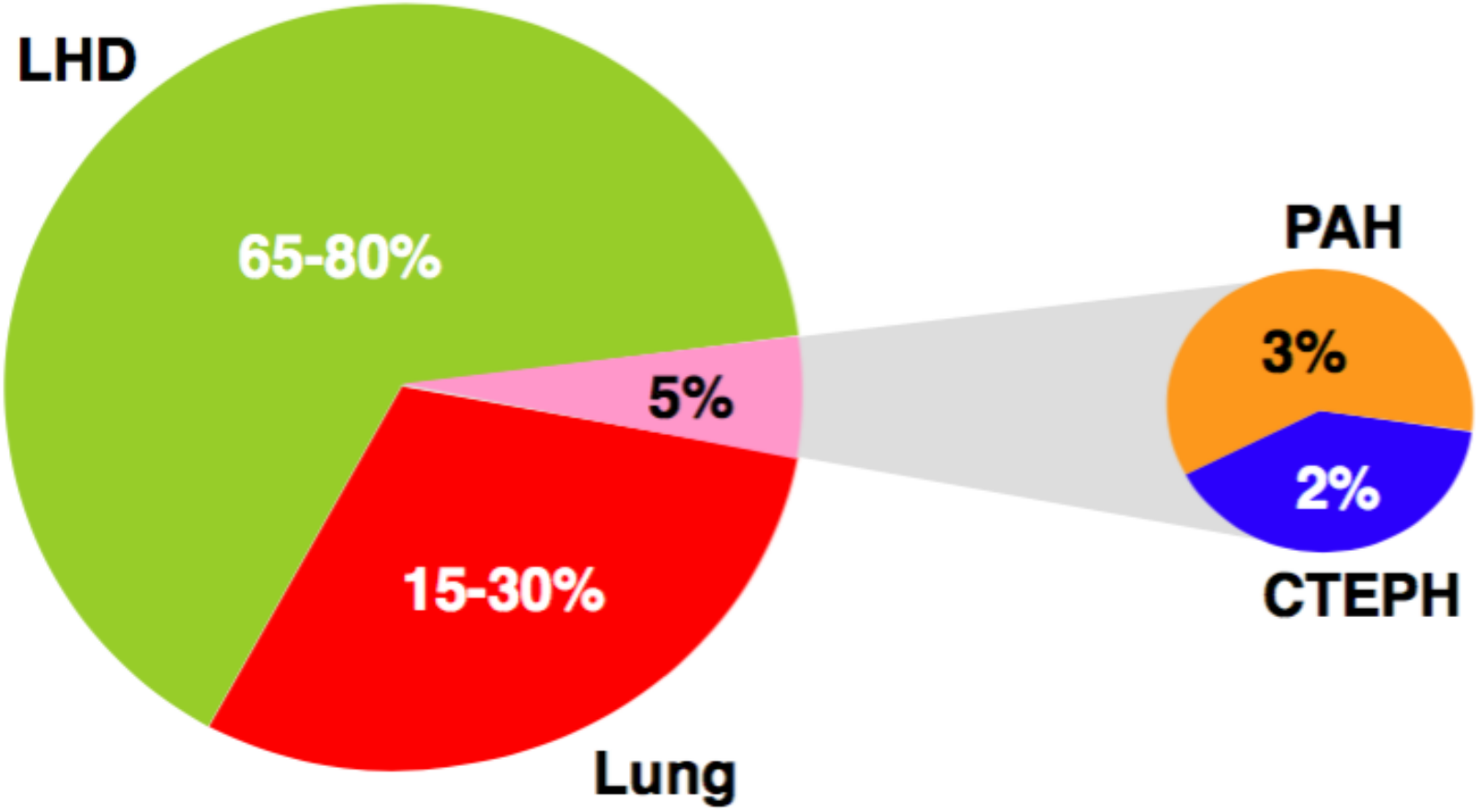


Figure 3 Survival of 276 patients with pulmonary hypertension due to left heart disease according to pulmonary vascular resistance (PVR; *A*) or diastolic pressure gradient (DPG; *B*) values. WU, Wood units.

Palazzini et al, Eur Heart J Heart Fail

Most Common Forms of Pulmonary Hypertension



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

A Pathophysiological Continuum

TABLE 1 Baseline Characteristics

	All Patients (N = 786)	Typical IPAH (n = 421)	Atypical IPAH (n = 139)	Typical vs. Atypical IPAH p Value	PH-HFpEF (n = 226)	Typical IPAH vs. PH-HFpEF p Value	Atypical IPAH vs. PH-HFpEF p Value
Age, yrs	66.6 ± 15.0	61.5 ± 17.3	71.3 ± 9.2	<0.001	73.2 ± 8.3	<0.001	0.434
Female	467 (59.4)	250 (59.4)	77 (55.4%)	1.000	140 (61.9)	1.000	0.686
BMI, kg/m^2	28.1 (24.5-32.6)	26.0 (23.3-29.8)	32.2 (28.3-36.0)	<0.001	29.6 (25.7-34.0)	<0.001	0.002
WHO-FC				0.089		<0.001	0.315
I/II	91 (11.8)	71 (17.4)	12 (8.8)		8 (3.6)		
III	540 (70.3)	275 (67.6)	96 (70.6)		169 (75.1)		
IV	137 (17.8)	61 (15.0)	28 (20.6)		48 (21.3)		
6MWD, m	289.5 ± 121.8	319.0 ± 123.5	250.5 ± 104.2	<0.001	260.0 ± 115.0	<0.001	0.787
RAP, mm Hg	9.8 ± 5.4	8.5 ± 5.2	8.9 ± 4.8	0.615	12.9 ± 4.8	<0.001	<0.001
PAPm, mm Hg	46.0 ± 11.9	46.9 ± 13.3	43.9 ± 10.7	0.025	45.7 ± 9.4	0.437	0.326
PAWP, mm Hg	12.5 ± 6.0	9.3 ± 3.4	10.0 ± 3.6	0.186	19.9 ± 4.4	<0.001	<0.001
TPG, mm Hg	33.5 ± 13.1	37.6 ± 13.6	33.9 ± 11.1	0.006	25.8 ± 9.1	<0.001	<0.001
Cardiac index, l/min/m^2	2.2 ± 0.8	2.3 ± 0.8	2.2 ± 0.8	0.629	2.2 ± 0.7	0.653	0.988
PVR, Wood Units	9.6 ± 6.7	10.8 ± 6.0	9.8 ± 10.6	0.309	7.0 ± 3.4	<0.001	<0.001
SvO_2, %	62.2 ± 9.0	62.1 ± 9.9	62.7 ± 9.0	0.804	62.1 ± 6.9	0.999	0.863
BNP, pg/ml	269 (127-541)	287 (119-543)	200 (115-469)	1.000	310 (186-638)	0.963	0.312
NT-proBNP, pg/ml	1,738 (621-3,891)	1,435 (541-3,888)	1,683 (478-2,815)	1.000	2,196 (1,125-4,285)	0.021	0.066
Arterial hypertension	66.5	43.2	98.6	<0.001	91.9	<0.001	0.021
CAD	32.0	15.7	59.7	<0.001	46.4	<0.001	0.049
Diabetes mellitus	30.6	10.7	74.8	<0.001	41.2	<0.001	<0.001
AF	28.9	10.7	42.4	<0.001	54.4	<0.001	0.187
BMI >30 kg/m^2	37.6	23.5	65.2	<0.001	47.1	<0.001	0.002

Challenge N# 2 - Treatment

Management of pulmonary hypertension in left heart disease

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 importance and role of vasoreactivity testing is not established in PH-LHD, except in patients who are candidates for heart transplantation and/or LV assist device implantation.	III	C
The use of PAH approved therapies is not recommended in PH-LHD.	III	C

Eur Heart J, 2015 doi: 10.1093/eurheartj/ehv317
Eur Respir J, 2015 doi: 10.1183/ 13993003.01032-2015

TABLE 3 Completed and ongoing trials of pulmonary arterial hypertension (PAH)-specific therapies in patients with suspected pulmonary hypertension associated with left heart disease (PH-LHD)

Drug, year [ref.]	Study acronym/ identifier#	Subjects n	Patient characteristics	Design	Primary end-point	Key results
Epoprostenol 1996 [51]	FIRST	471	Severe heart failure, WHO FC IIIb–IV	1:1 randomisation Event-driven Mean dose 4 ng·kg^{-1}·min^{-1}	Survival	Early termination (trend to decreased survival in treated group)
Bosentan 2002 [50]	ENABLE	1613	Severe heart failure, WHO FC IIIb–IV	1:1 randomisation 18-month duration 125 mg twice daily	Mortality and hospital stays	No effect Early risk of worsening heart failure necessitating hospitalisation due to fluid retention with treatment
Bosentan 2005 [49]	REACH-1	370	Severe heart failure, WHO FC IIIb–IV	1:1:1 randomisation 26-week duration 500 mg twice daily *via* rapid or slow infusion	Change in clinical status	No effect Early termination (safety concerns)
Darusentan 2002 [56]	HEAT	179	Chronic heart failure, WHO FC III	1:1:1:1 randomisation 3-week duration Doses of 30, 100 and 300 mg daily	Haemodynamics (change in PAWP/cardiac index)	Increased cardiac index No change in PAWP
Darusentan 2004 [52]	EARTH	642	Chronic heart failure, WHO FC II–IV	1:1:1:1:1 randomisation 6-month duration Doses of 10, 25, 50, 100 and 300 mg daily	LVESV changes by MRI and clinical events	No effect
Sildenafil 2007 [53]	NCT00309816	13	Heart failure, WHO FC III	Nonrandomised, open-label 50 mg single dose	Exercise capacity and haemodynamics after 60 min	Significant reduction in resting PAP, SVR and PVR, and increased resting and exercise cardiac index ($p<0.05$)
Sildenafil 2007 [55]	NCT00309790	34	Heart failure, WHO FC II–IV	1:1 randomisation 12-week duration 25–75 mg three times daily	Haemodynamics (change in peak $V'o_2$)	Significantly greater increase in $V'o_2$ ($p=0.02$)
Sildenafil 2007 [54]	NCT00407446	46	Chronic heart failure, WHO FC II–III	1:1 randomisation 6-month duration 50 mg twice daily	Exercise performance, ventilation efficiency, symptoms	Significant increases at 3 and 6 months ($p<0.01$)
Sildenafil 2013 [59]	RELAX	216	Heart failure, WHO FC II–IV	1:1 randomisation 24-week duration 20 mg three times daily for 12 weeks, then 60 mg three times daily for 12 weeks	Haemodynamics (change in peak $V'o_2$)	No effect
Riociguat 2013 [48]	LEPHT	201	Heart failure, WHO FC II–IV	2:1:1:2 randomisation 16-week duration 0.5 mg, 1 mg or 2 mg three times daily	Change in mPAP	No effect
Riociguat 2014 [61]	DILATE-1	39	HFpEF	1:1:1:1 randomisation 0.5 mg, 1 mg or 2 mg single dose	Largest mPAP change from baseline ⩽6 h after drug administration	No effect
Tadalafil 2015 [58]	PITCH-HF	23	Heart failure, NYHA FC II–IV	2:1 randomisation ⩽3-year duration 40 mg daily	Cardiovascular mortality or hospitalisation due to heart failure	Trial terminated early
Macitentan 2015 [57]	MELODY-1	Estimated enrolment=60	CpcPH due to left ventricular dysfunction	1:1 randomisation 12-week duration 10 mg once daily	Safety and tolerability	Estimated completion quarter 4 2015

Farber HW, Gibbs S, Eur Reapir Rev 2015

TABLE 2 Targeted PH Therapies

	All Patients	Typical IPAH	Atypical IPAH	Typical vs. Atypical IPAH p Value	PH-HFpEF	Typical IPAH vs. PH-HFpEF p Value	Atypical IPAH vs. PH-HFpEF p Value
PH treatment initiated within first 3 months							
n	786	421	139		226		
ERA	22.6	31.4	22.3	0.157	6.6	<0.001	<0.001
PDE5i	82.4	76.7	81.3	0.870	93.8	<0.001	0.001
PCA	1.7	2.6	0.7	0.931	0.4	0.197	1.000
2 or more PH drugs	11.7	17.8	7.9	0.013	2.7	<0.001	0.112
Anticoagulation	63.0	56.3	69.8	0.016	71.2	0.001	1.000
PH treatment at 1 year							
n	396	207	81		108		
ERA	36.4	48.3	35.8	0.195	13.9	<0.001	0.002
PDE5i	80.6	83.6	75.3	0.391	78.7	0.857	1.000
PCA	4.5	5.8	4.9	1.000	1.9	0.452	1.000
2 or more PH drugs	30.6	44.4	25.9	0.014	7.4	<0.001	0.003
Anticoagulation	67.5	62.8	71.6	0.513	73.4	0.184	1.000

Opitz et al. J Am Coll Cardiol 2016

TABLE 3 Discontinuations of PH Therapies

	All Patients (N = 786)	Typical IPAH (n = 421)	Atypical IPAH (n = 139)	Typical vs. Atypical IPAH p Value	PH-HFpEF (n = 226)	Typical IPAH vs. PH-HFpEF p Value	Atypical IPAH vs. PH-HFpEF p Value
PDE5i ever	696 (88.5)	359 (85.3)	120 (86.3)	1.000	217 (96.0)	<0.001	0.003
Patients with follow-up	618	306	106		206		
PDE5i discontinuations	79 (12.8)	27 (8.8)	14 (13.2)	0.578	38 (18.4)	0.005	0.795
Side effects	23 (3.7)	8 (2.6)	4 (3.8)	1.000	11 (5.3)	0.454	1.000
Efficacy failure	33 (5.3)	9 (2.9)	3 (2.8)	1.000	21 (10.2)	0.003	0.071
Other*	25 (4.0)	11 (3.6)	7 (6.6)	0.801	7 (3.4)	1.000	0.745
ERA ever	322 (41.0)	225 (53.4)	61 (43.9)	0.188	36 (15.9)	<0.001	<0.001
Patients with follow-up	281	190	56		35		
ERA discontinuations	56 (19.9)	28 (14.7)	13 (23.2)	0. 462	15 (42.9)	0.001	0.188
Side effects	36 (12.8)	18 (9.5)	10 (17.9)	0.286	8 (22.9)	0.117	1.000
Efficacy failure	9 (3.2)	4 (2.1)	1 (1.8)	1.000	4 (11.4)	0.066	0.210
Other†	11 (3.9)	6 (3.2)	2 (3.6)	1.000	3 (8.6)	0.447	1.000

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Treatment

- Apixaban 5mg BiD
- Furocemide 80mg BiD
- Metoprolol 50mg BiD
- Ramipril 5mg OD
- Sildenafil 20mg TiD

Challenge N# 3 – Treatment evaluation

- Clinical?
- Hemodynamic?
- Natriuretic peptides?
- Morbidity/mortality?

TABLE 4 Response to Targeted PH Therapy

	Typical IPAH	Atypical IPAH	Typical vs. Atypical IPAH p Value	PH-HFpEF	Typical IPAH vs. PH-HFpEF p Value	Atypical IPAH vs. PH-HFpEF p Value
6MWD, m						
Baseline	320 (234 to 417)	250 (175 to 332)	<0.001	270 (165 to 345)	<0.001	1.000
12 months	414 (324 to 460)	310 (240 to 379)	<0.001	330 (194 to 380)	<0.001	1.000
Change from baseline in 6MWD, m						
Mean ± SD	52 ± 101	58 ± 84	1.000	33 ± 82	0.453	0.904
Median (IQR)	50 (1 to 00)	60 (10 to 75)		29 (−10 to 74)		
WHO-FC I/II						
Baseline	17.4	8.8	0.056	3.6	<0.001	0.164
12 months	39.5	26.2	0.208	23.0	0.026	1.000
Improvement of WHO-FC	34.5	36.9	1.000	36.8	1.000	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	−13.7 (−40.6 to 32.2)	0.031	0.248

Opitz et al. J Am Coll Cardiol 2016

Follow-up

	Baseline	6 month FU
WHO FC	III	III
6MWD (m)	216	264
NT pro – BNP (pg/ml)	1346	960
RHC RA PAP (mmHg) TPG (mmHg) DPG (mmHg) PVR (Woods) CO/CI SVO_2	 9 70/23/m42 29 10 4.2 5.5/2.9 61.9	 8 61/20/m35 15 0 2.5 5.1/2.5 64.7
Minimum leg edema		

Future challenges in LHD - PH therapy

- Implementation of a proper primary endpoint in RCTs
- Patient selection based on careful phenotyping plays an important role in determining which patients may respond to PH-targeted therapies
- Generalised optimization of volume status is important
- Search for the right dose of drugs

Acknowledgements

AHEPA University Hospital

Pulmonary Hypertension Unit

Thank you

CHEST

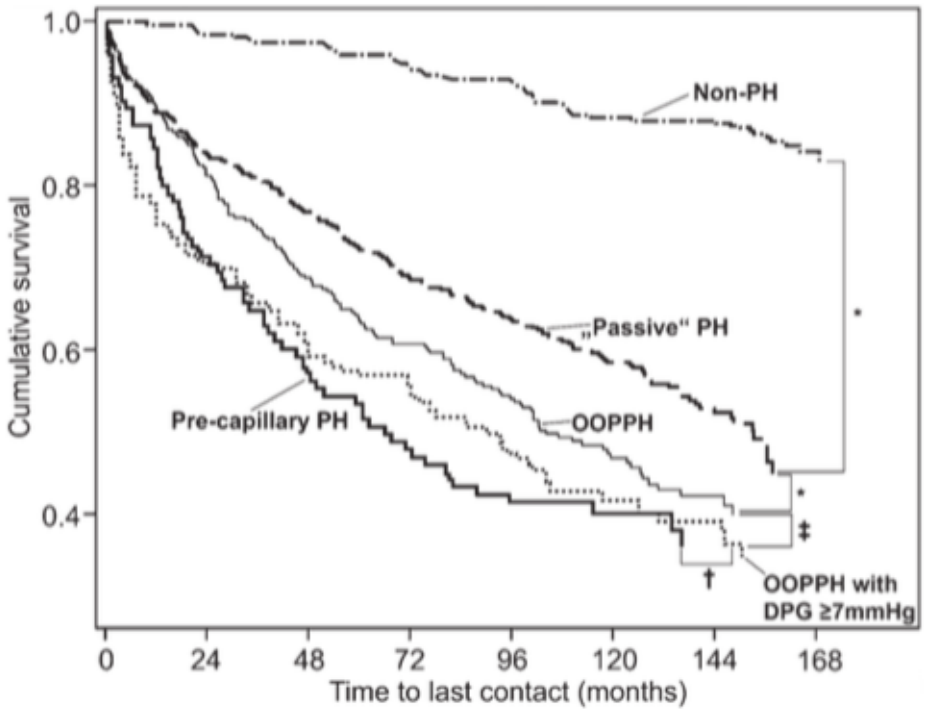
Original Research

PULMONARY VASCULAR DISEASE

Diastolic Pulmonary Vascular Pressure Gradient

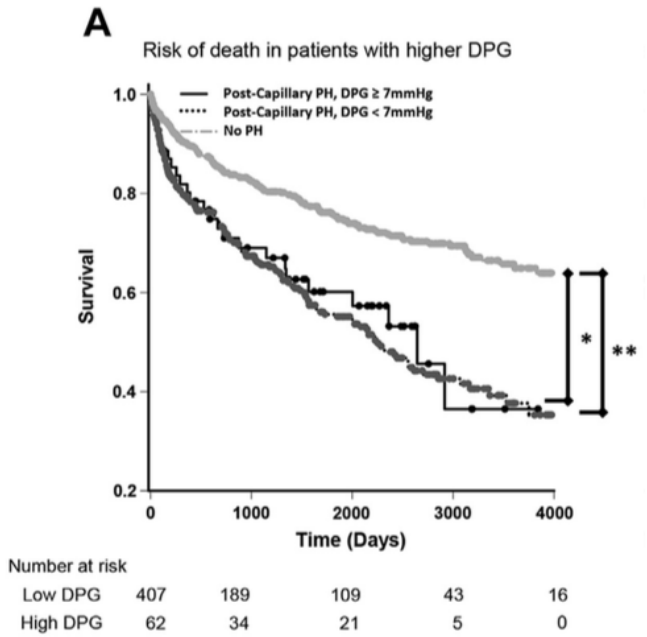
A Predictor of Prognosis in "Out-of-Proportion" Pulmonary Hypertension

Christian Gerges; Mario Gerges, MD; Marie B. Lang; Yuhui Zhang, MD; Johannes Jakowitsch, PhD; Peter Probst, MD; Gerald Maurer, MD; and Irene M. Lang, MD



The Diastolic Pulmonary Gradient Does Not Predict Survival in Patients With Pulmonary Hypertension Due to Left Heart Disease

Emmanouil Tampakakis, MD,* Peter J. Leary, MD, MS,† Van N. Selby, MD,‡ Teresa De Marco, MD,‡ Thomas P. Cappola, MD, ScM,§ G. Michael Felker, MD, MHS,|| Stuart D. Russell, MD,* Edward K. Kasper, MD,* Ryan J. Tedford, MD*



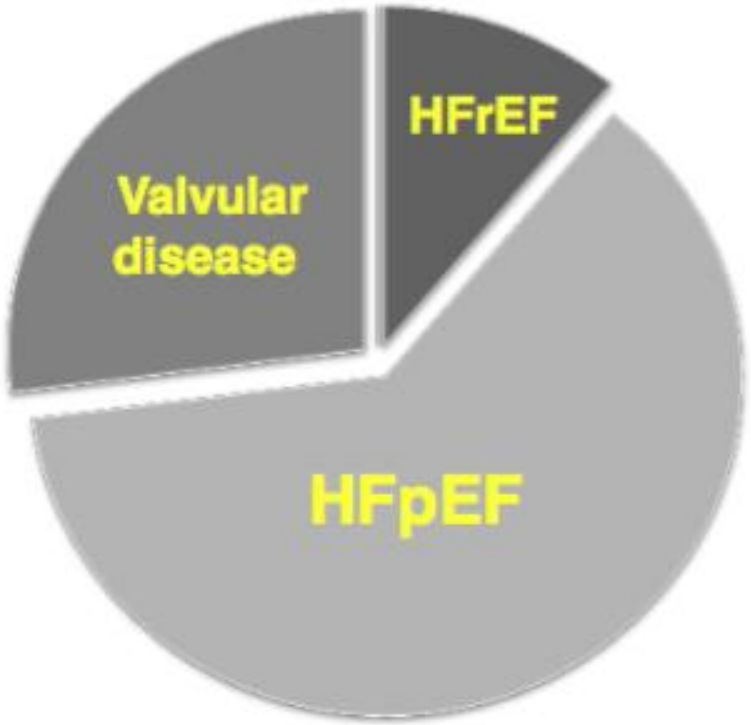
J Am Coll Cardiol HF 2015

Spectrum of group 2 PH. ASPIRE registry

1344 consecutive PAH and PH treatment-naive cases diagnosed between 2001-2010

157 patients with Group 2 PH

	HFrEF	HFpEF	Valv. Dis.
PCWP, mmHg	24	22	26*§
mean PAP, mmHg	43	37	48*
mean RAP, mmHg	17	15	14



Hurdman J et al. Eur Resp J 2012

PDE5 Inhibition To Improve Clinical Status And Exercise Capacity In Diastolic Heart Failure

- Multicenter, double-blind, placebo-controlled, parallel-group, randomized clinical trial of 216 stable outpatients with HF, LVEF >50%, NYHA class II-III, elevated NT-proBNP or elevated invasively measured filling pressures, and reduced exercise capacity
- Sildenafil 20mg tid increased to 60mg tid vs placebo
- Primary end point - change in peak oxygen consumption at 24 weeks
- No benefit in change in peak VO_2, CV or renal hospitalization, indices of LV remodeling and diastolic function, PAP, or QOL
- Sildenafil group - greater increase SCr, cystatin C, NT-proBNP, uric acid, and endothelin-1
- Changes in aldosterone and NT-procollagen III were not significantly different between groups

Redfield et al. JAMA. 2013;309(12):1268-1277

PDE5 inhibition in HFpEF

52 pts with HFpEF, mPAP > 25 mmHg; PCWP > 15 mmHg

Placebo vs sildenafil 60mg tid for 12 weeks

Primary endpoint:

- change in mPAP

Secondary endpoints:

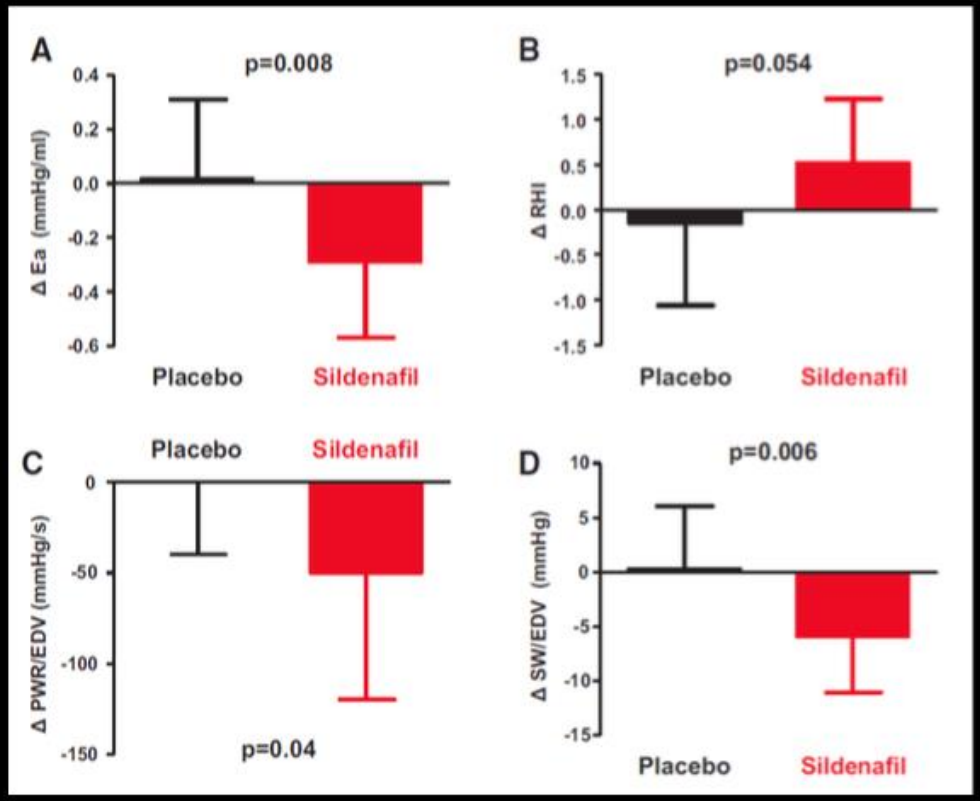
- change in mean PCWP; CO;
- Peak VO2

Table 3 Effect of sildenafil on primary and secondary end points

	Sildenafil	Placebo	P
Mean PAP (mmHg)			
Baseline	35.0 ± 9.5	35.0 ± 7.1	1.00
Week 12	32.3 ± 8.3	29.7 ± 5.6	0.23
Treatment effect	−2.4 (95% CI −4.5 to −0.3)	−4.7 (95% CI −7.1 to −2.3)	0.14
Mean PAWP (mmHg)			
Baseline	19.9 ± 3.2	20.8 ± 4.2	0.38
Week 12	19.2 ± 4.6	17.1 ± 4.0	0.13
Treatment effect	−0.5 (95% CI −1.9 to 1.0)	−3.5 (95% CI −5.2 to −1.8)	0.008
Cardiac output (L/min)			
Baseline	5.3 ± 1.3	5.5 ± 1.2	0.48
Week 12	5.1 ± 1.2	5.3 ± 1.2	0.49
Treatment effect	−0.4 (95% CI −0.9 to 0.1)	−0.2 (95% CI −0.5 to 0.1)	0.37
Peak VO_2 (mL/min/kg)			
Baseline	11.7 ± 3.3	11.1 ± 2.5	0.47
Week 12	12.8 ± 3.1	12.2 ± 2.6	0.55
Treatment effect	0.2 (95% CI −0.9 to 1.4)	0.7 (95% CI −0.3 to 1.6)	0.51

European Heart Journal (2015) 36, 2565–2573

PDE5 Inhibition To Improve Clinical Status And Exercise Capacity In Diastolic Heart Failure Subgroup



48 pts had arterial elastance, endothelial function, LV contractility and SW index assessed

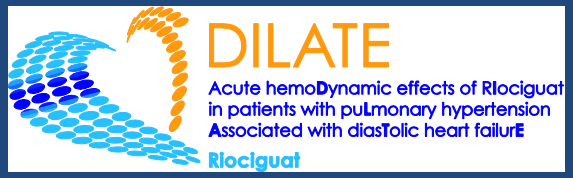
Lack of benefit from sildenafil may due to:

Benefit seen from PDE 5 inh on the systemic vasculature and endothelium was limited

or

Potential negative effects on LV function counteracted the vascular effects

Borlaug et al Circ Heart Fail 2015;8:533

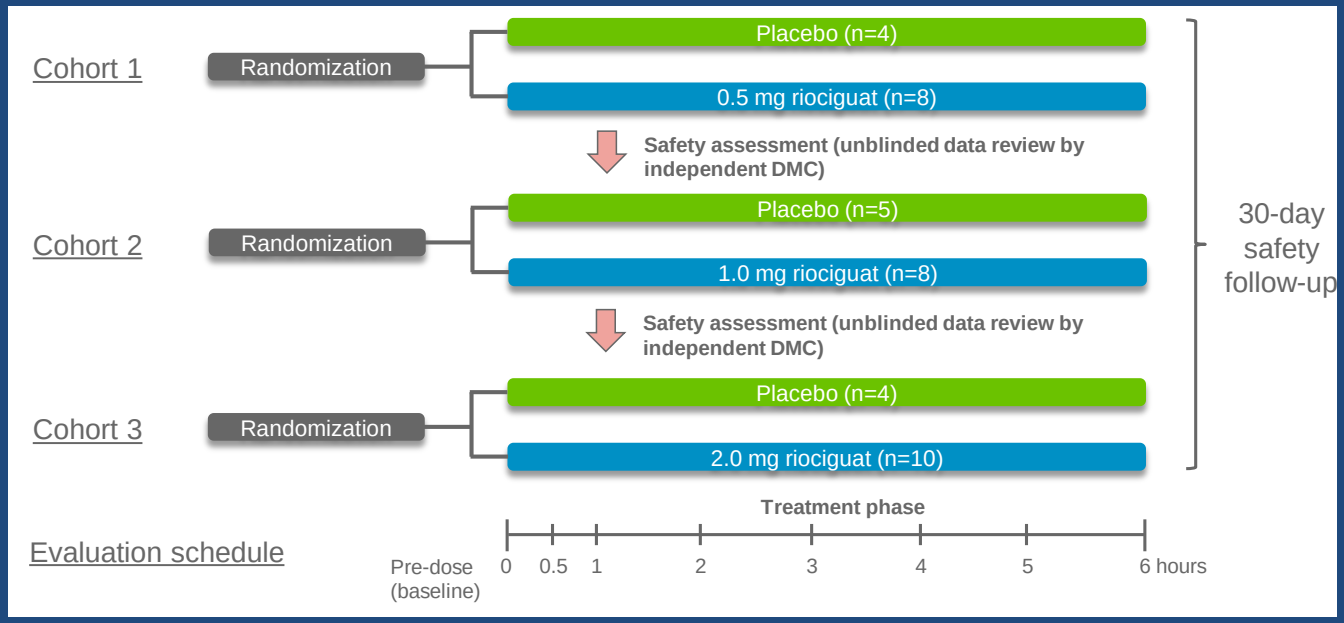


Acute hemodynamic effects of riociguat in patients with pulmonary hypertension associated with diastolic heart failure (DILATE-1): A randomized, double-blind, placebo-controlled, single-dose study

D. Bonderman1, I. Pretsch2, R. Steringer-Mascherbauer3, S. Rosenkranz4, C. Tufaro1, R. Frey5, M. Ochan Kilama6, S. Unger7, L. Roessig8, I. M. Lang1

DILATE: Study design

DILATE
Acute hemoDynamic effects of RIociguat in patients with puLmonary hypertension Associated with diasTolic heart failurE
Riociguat

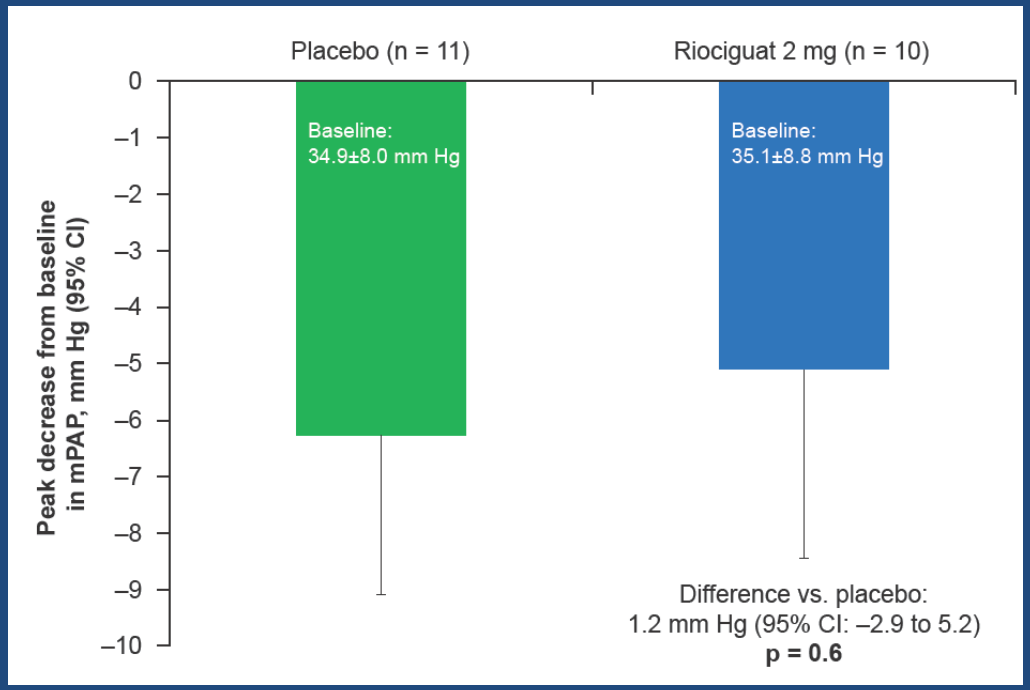


Study design of the DILATE-1 study. Study medication was administered orally as a single dose of a film-coated tablet of riociguat (0.5 mg, 1 mg, or 2 mg) or matching placebo.

Bonderman D *et al. Chest* 2014;146(5):1274–85.

DILATE: Peak decrease in mPAP

DILATE
Acute hemoDynamic effects of RIociguat in patients with puLmonary hypertension Associated with diasTolic heart failurE
Riociguat

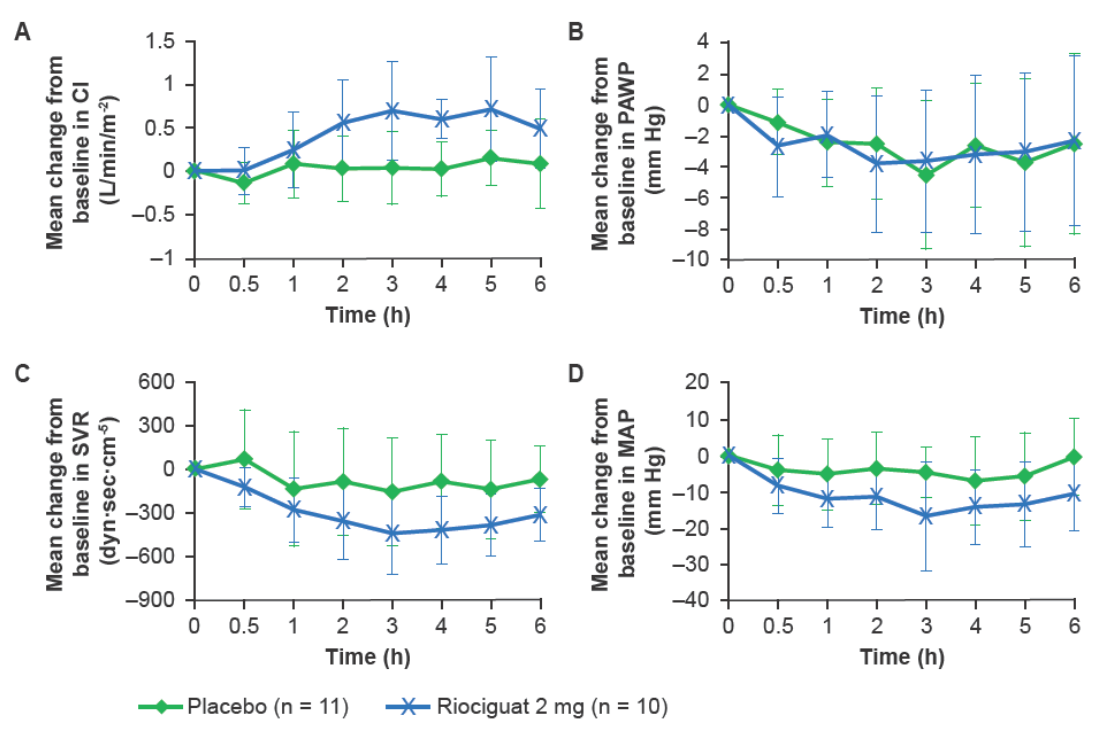


Peak decrease in mean pulmonary artery pressure (mPAP) from baseline up to 6 h after administration of study drug in the riociguat 2 mg group vs. placebo (primary endpoint). The difference between treatment groups was analyzed by a two-group, two-sided t-test. The treatment difference (95% confidence interval) and p-value are also shown

Bonderman D *et al. Chest* 2014;146(5):1274–85.

DILATE: Hemodynamics

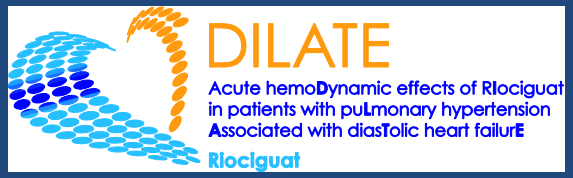
DILATE
Acute hemoDynamic effects of RIociguat in patients with puLmonary hypertension Associated with diasTolic heart failurE
Riociguat



Mean change from baseline in selected hemodynamic parameters in the 6 h following administration of study drug. (A) cardiac index (CI); (B) pulmonary arterial wedge pressure (PAWP); (C) systemic vascular resistance (SVR); and (D) mean arterial pressure (MAP)

Bonderman D *et al. Chest* 2014;146(5):1274–85.

DILATE: Results III



Echocardiography

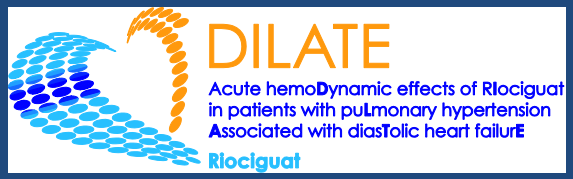
•Compared with placebo, riociguat 2 mg decreased left atrial area, with a trend towards statistical significance (P=0.06), and significantly decreased right ventricular end-diastolic (RVED) area (P=0.04) .

Exploratory biomarkers

•Plasma levels of NT-proBNP, asymmetric dimethylarginine, ST2, and Galectin-3 revealed significant variability and no significant changes vs. placebo.

Bonderman D *et al. Chest* 2014;146(5):1274–85.

DILATE: Conclusions



- Single doses of riociguat were well-tolerated and showed favorable hemodynamic and echocardiographic effects in patients with HFpEF and PH.
- The ventricular filling required to establish an increased SV was not accompanied by increased PAWP, indicating that riociguat might improve diastolic function via a change in relaxation and/or distensibility of the LV.
- Chronic, large-scale, placebo-controlled studies are required to further assess the long-term clinical safety and efficacy of riociguat started at lower doses and carefully up-titrated in this population.

Bonderman D *et al. Chest* 2014;146(5):1274–85.

Challenges in performing a RHC

- Catheter motion artifacts
- Inaccurate wedging (overestimation of PAWP)
- Recording of averaged PAWP pressures throughout the respiratory cycle, rather than those measured at end-expiration (underestimation of PAWP)
- Recording of end-expiration PAWP pressures, rather than average measured throughout the respiratory cycle in COPD (overestimation of PAWP)
- DPG has been shown to increase with heart rate in a linear fashion
- HFpEF patients may have a normal PAWP after diuresis or overnight fast (fluid challenge is mandatory)

Ramu et al. Curr Heart Fail Rep 2016

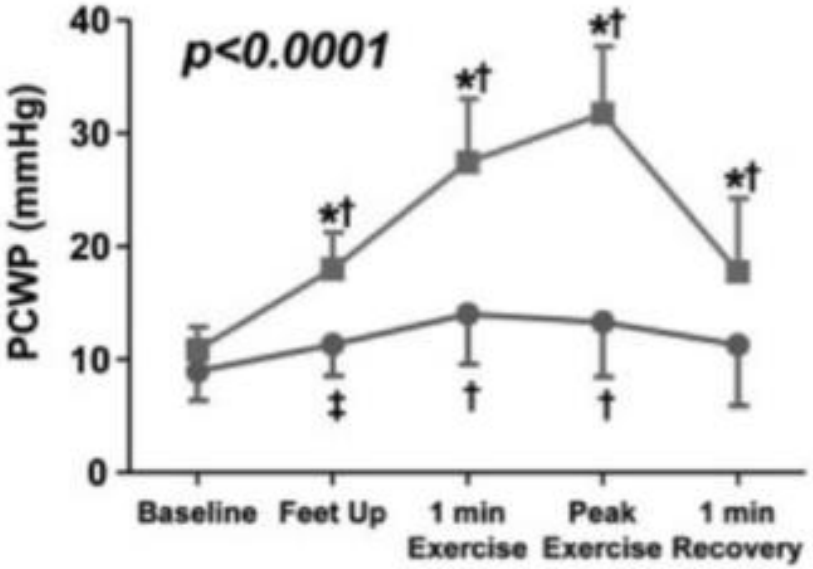
The RV in CHF

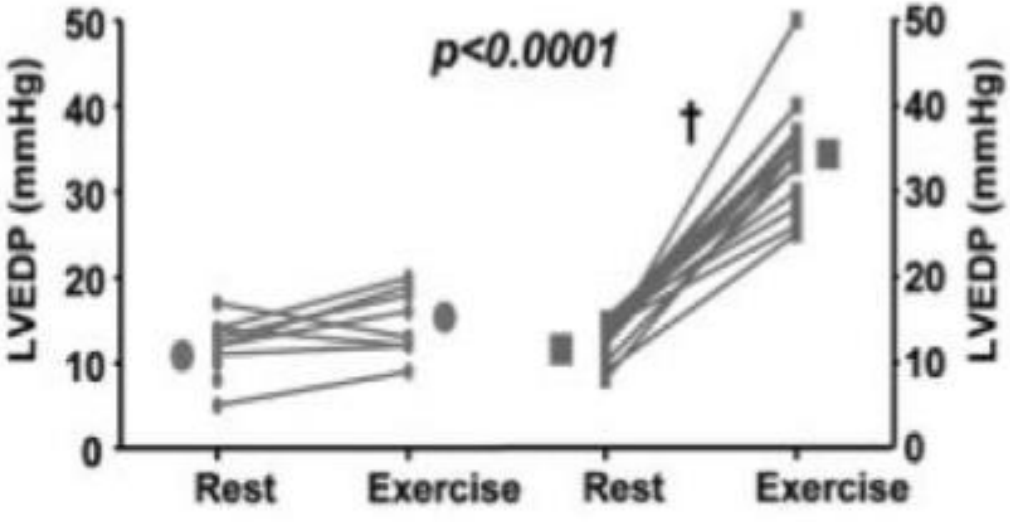
- LV dysfunction frequently induces PH
- PH is a negative prognostic sign in CHF
- RV dysfunction and dilatation indicate impaired survival
- Both reduce functional capacity
- PH can precede overt heart failure

PH diagnosis by exercise hemodynamics in HFpEF

- 55 patients with exercise dyspnoea, normal BNP assay; normal resting haemodynamics and euvolemic
- PCWP > 25 mmHg at peak exercise as main criteria for PH diagnosis

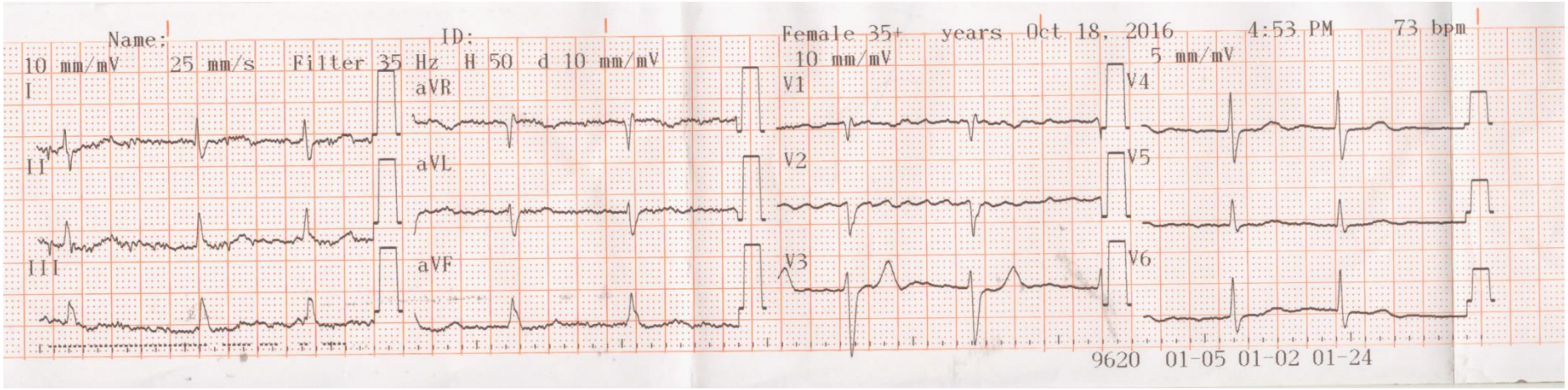
RIGHT and LEFT HEART catheterisation during supine exercise





Borlaug B et al. Circ Heart Fail 2010

ECG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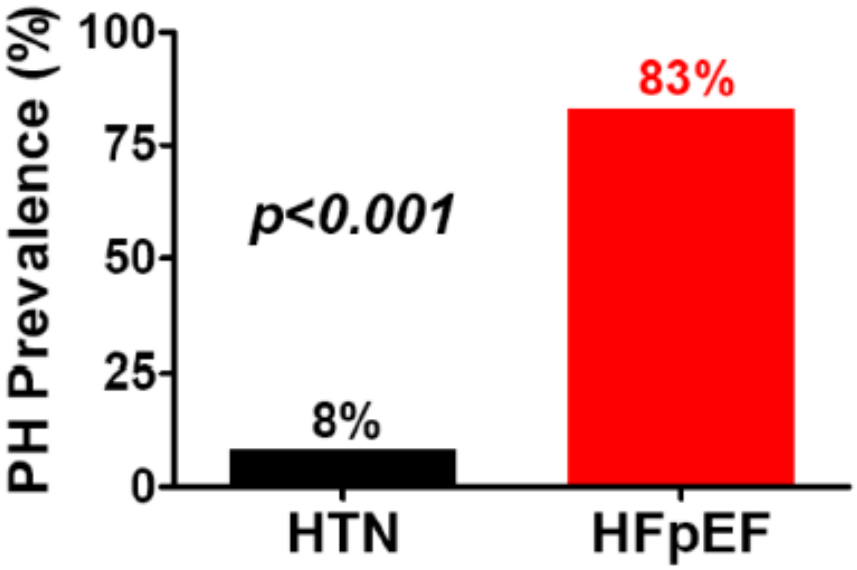
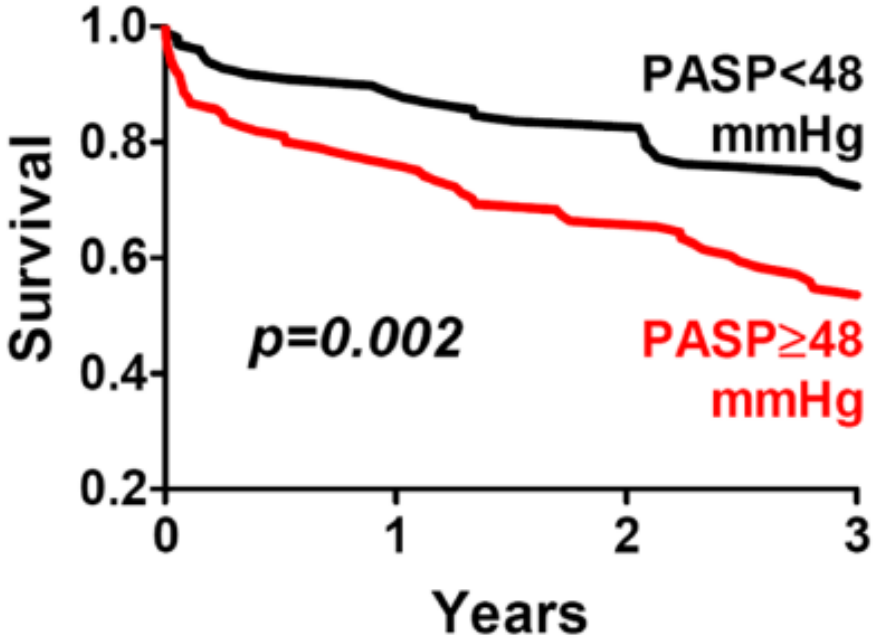
Epidemiology and Prognostic Impact of PH in Diastolic Heart Failure

Prevalence



Survival



HFpEF: PASP > 35 mmHg present in 83% (median PASP 48 mmHg)
PVH does not fully account for the severity of PH in HFpEF

Lam et al., *JACC* 2009; 53: 1119-1126

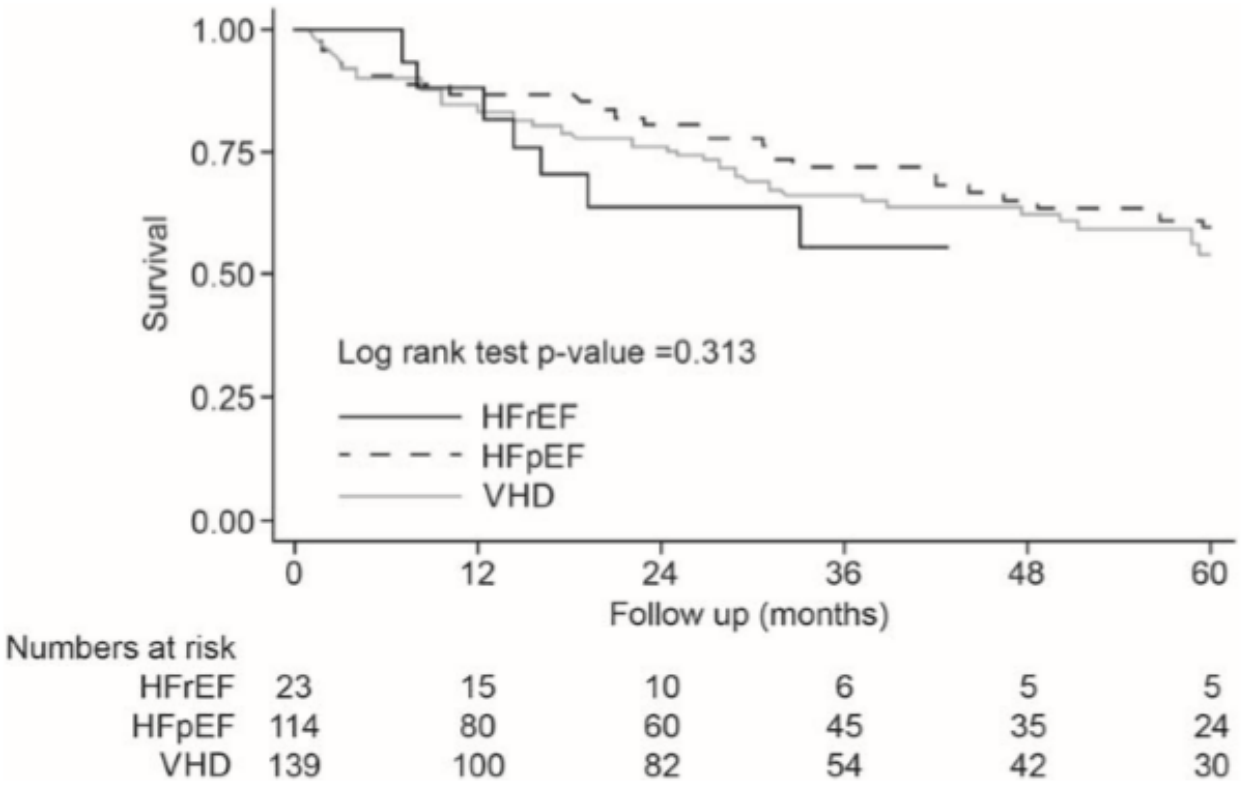


Figure 4 Survival of 276 patients with pulmonary hypertension due to left heart disease according to the aetiology. Overall log-rank test $P = 0.313$. HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; VHD, valvular heart disease.

Palazzini et al, Eur Heart J Heart Fail 2017