Αριστοτέλειο Πανεπιστήμιο Θεσσαλονίκης
Α΄ Καρδιολογική Κλινική ΑΧΕΠΑ
Ιατρείο Πνευμονικής Υπέρτασης

Πνευμονική υπέρταση στην αριστερή καρδιακή νόσο

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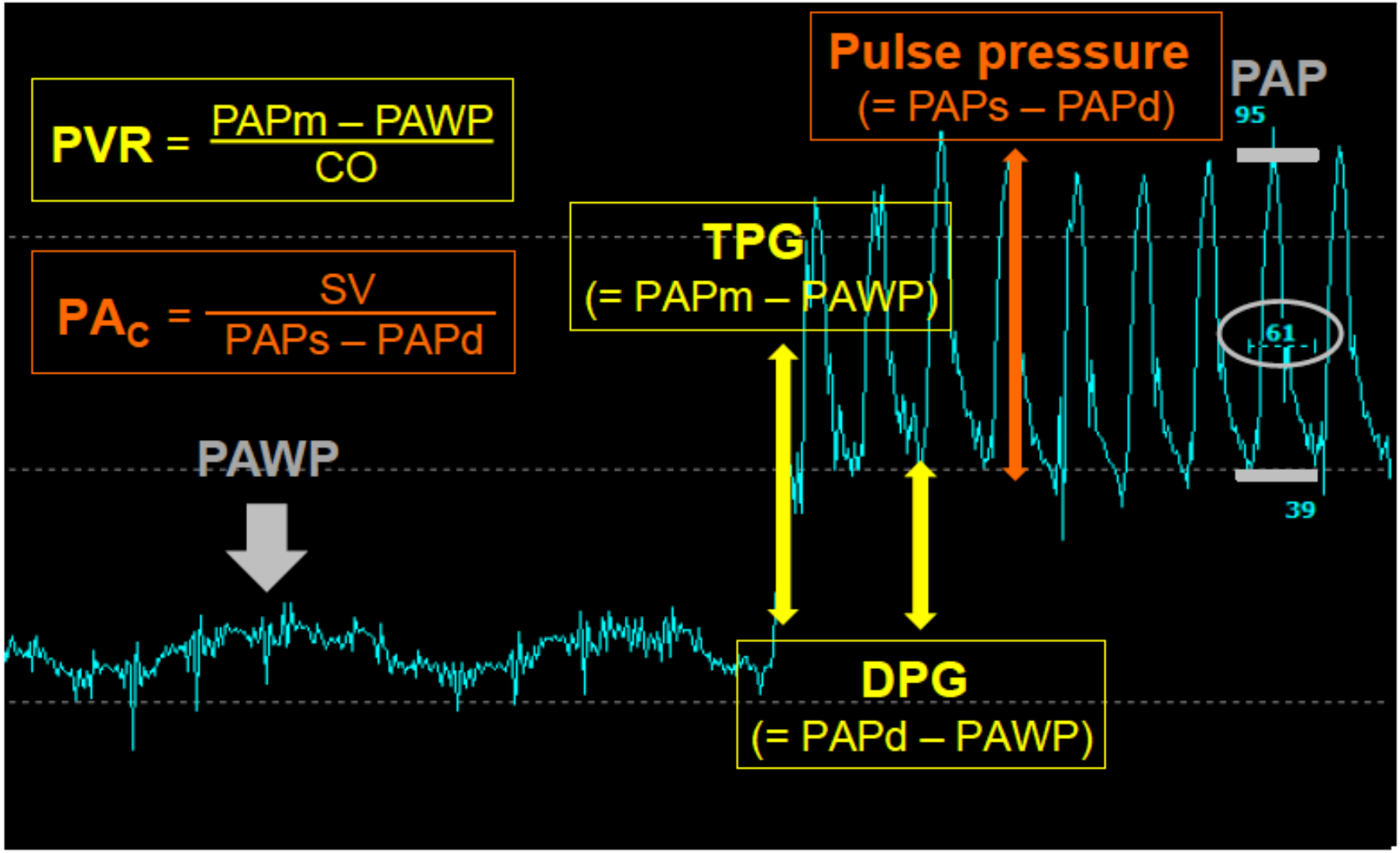
Conflicts of interest

- Honoraria for lectures or Advisory boards: MSD, GlaxoSmithKline, Actelion Pharmaceuticals Ltd, Bayer Healthcare, Servier, Pfizer, Lilly, ELPEN, Novartis, United Therapeutics

Calculated parameters



Haemodynamic definitions of group 2 PH: Isolated post capillary vs combined post and precapillary

Debate and controversy on which variable would be best

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

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

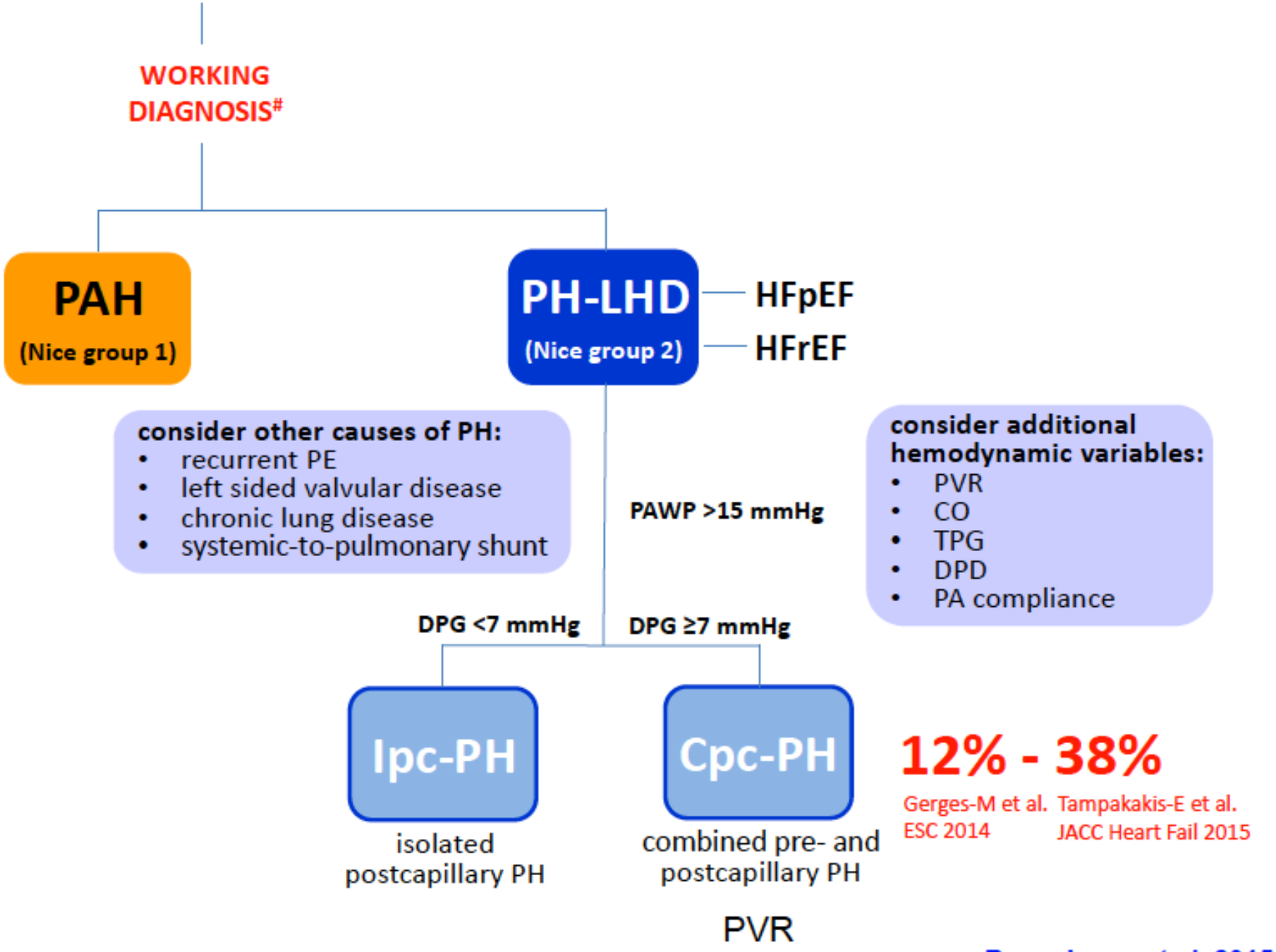
CO = cardiac output; DPG = diastolic pressure gradient (diastolic PAP – mean PAWP); mPAP = mean pulmonary arterial pressure; PAWP = pulmonary arterial wedge pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; WU = Wood units.

[a]All values measured at rest; see also section 7.

[b]According to Table 4.

[c]Wood Units are preferred to dynes.s.cm^{-5}.

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


WORKING DIAGNOSIS#
PAH
(Nice group 1)
PH-LHD
(Nice group 2)
HFpEF
HFrEF
consider other causes of PH:
• recurrent PE
• left sided valvular disease
• chronic lung disease
• systemic-to-pulmonary shunt
PAWP >15 mmHg
consider additional hemodynamic variables:
• PVR
• CO
• TPG
• DPD
• PA compliance
DPG <7 mmHg
DPG ≥7 mmHg
Ipc-PH
isolated postcapillary PH
Cpc-PH
combined pre- and postcapillary PH
PVR
12% - 38%
Gerges-M et al. ESC 2014
Tampakakis-E et al. JACC Heart Fail 2015
Rosenkranz et al. 2015

ESC/ERS 2015: Hemodynamic 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}.

Galiè et al. ESC/ERS Guidelines on PH. *Eur Heart J* 2016; 37: 67-119

ESC/ERS 2015: Hemodynamic Definitions of Pulmonary Hypertension

- Patients with PH-LHD from a tertiary center
- n=1506; PAPm ≥25 mmHg, PAWP >15 mmHg
- Stratified by DPG (< / ≥ 7 mmHg) and PVR (≤ / > 3 WU)

	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)[¶]

➤ Based on the combination of DPG and PVR, **432/1506 patients (28.7%)** were **non-classifiable** as Ipc-PH or Cpc-PH using the current definition in the 2015 ESC/ERS Pulmonary Hypertension guidelines

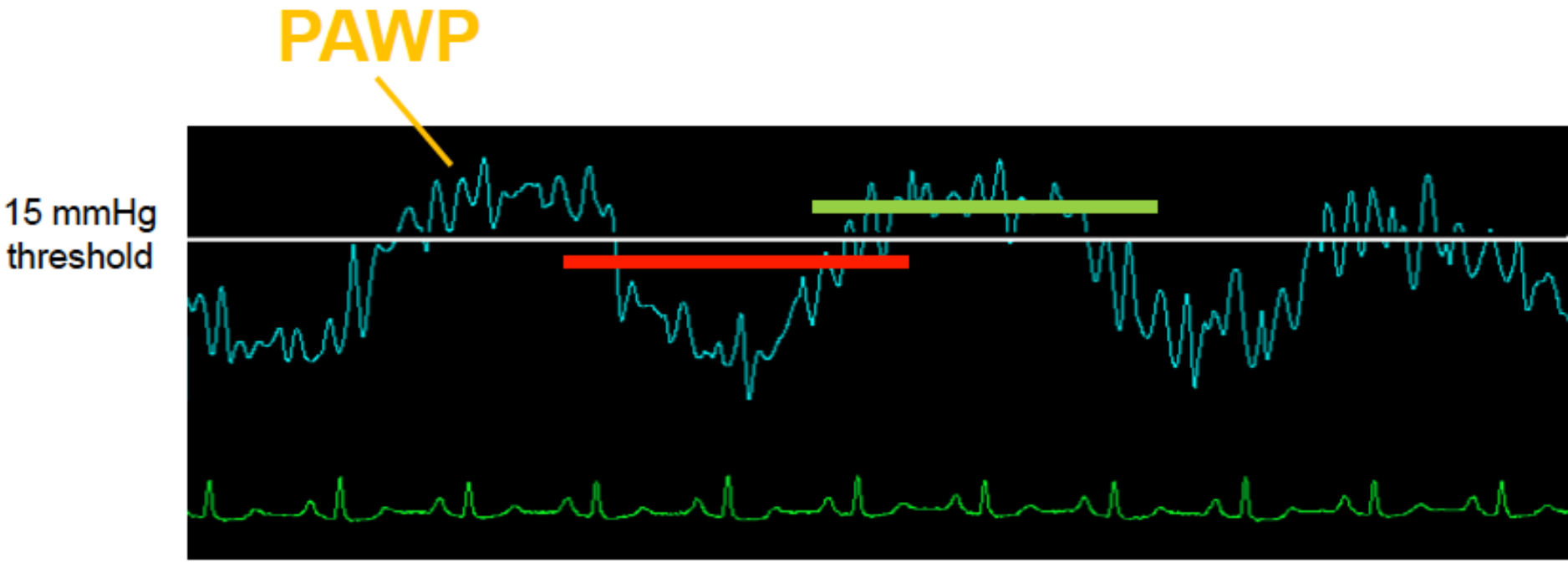
➤ **RV/PA coupling:**

• DPG <7 mmHg, PVR > 3 WU	n=76	Ees/Ea = 1.4±0.3
• DPG ≥ 7 mmHg, PVR > 3 WU	n=41	Ees/Ea = 1.1±0.3 (p<0.001)

Gerges et al. *Eur Respir J* 2016; published on-line first May 12, 2016

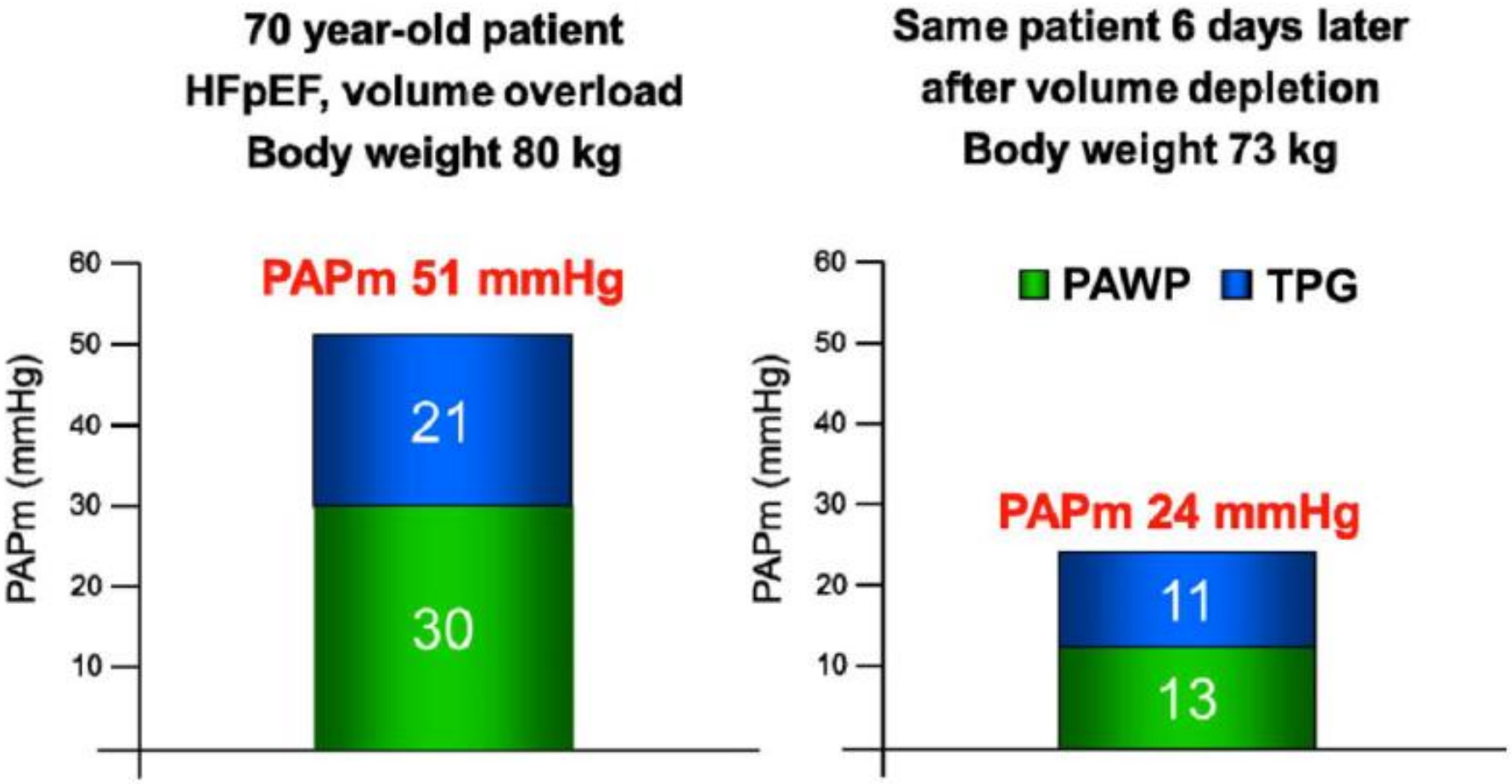
Hemodynamic assessment
Gaps in evidence / standardization

Where to read PAPm and PAWP?



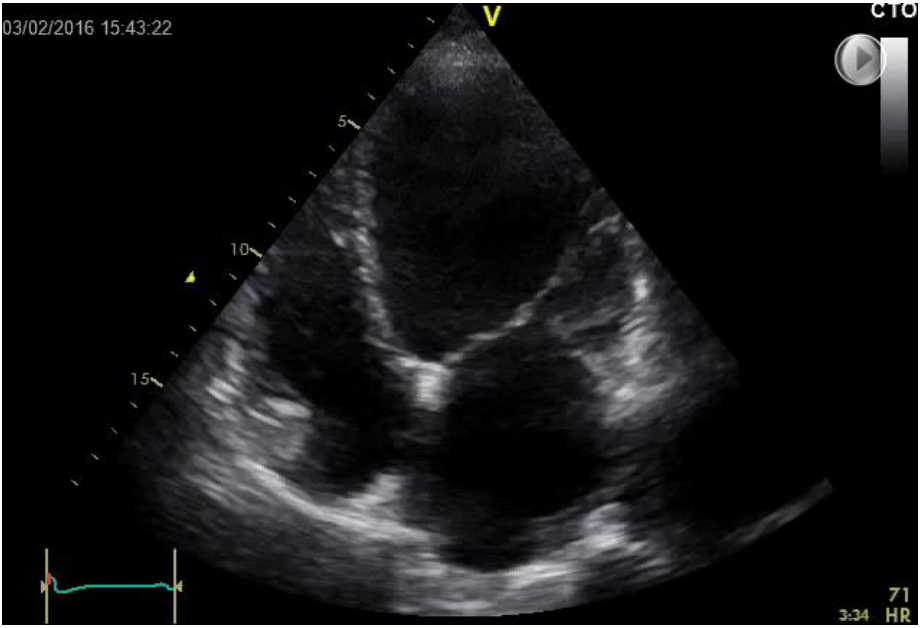
The same patient – PH referral **center A**: PAH
PH referral **center B**: PH-LHD

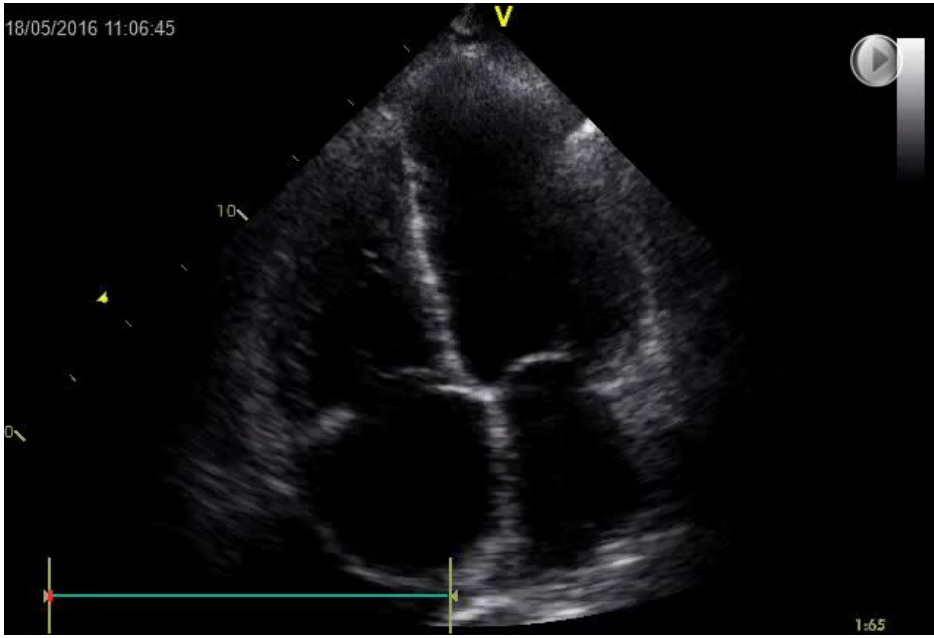
Differentiating between pre- and post-capillary PH: The impact of diuretics……



Rosenkranz et al. *Eur Heart J* 2016; 37: 942-954

HFrEF





Independent and Additive Prognostic Value of Right Ventricular Systolic Function and Pulmonary Artery Pressure in Patients With Chronic Heart Failure

Stefano Ghio, MD, FESC,* Antonello Gavazzi, MD, FESC,* Carlo Campana, MD,* Corinna Inserra, MD,* Catherine Klersy, MD,† Roberta Sebastiani, MD,* Eloisa Arbustini, MD,‡ Franco Recusani, MD,* Luigi Tavazzi, MD, FESC, FACC*

Pavia, Italy

(J Am Coll Cardiol 2001;37:183–8)

- Patients candidates to heart transplantation
- Large population
- Extensive diagnostic work-up
  - Hemodynamic
  - Right ventricular function

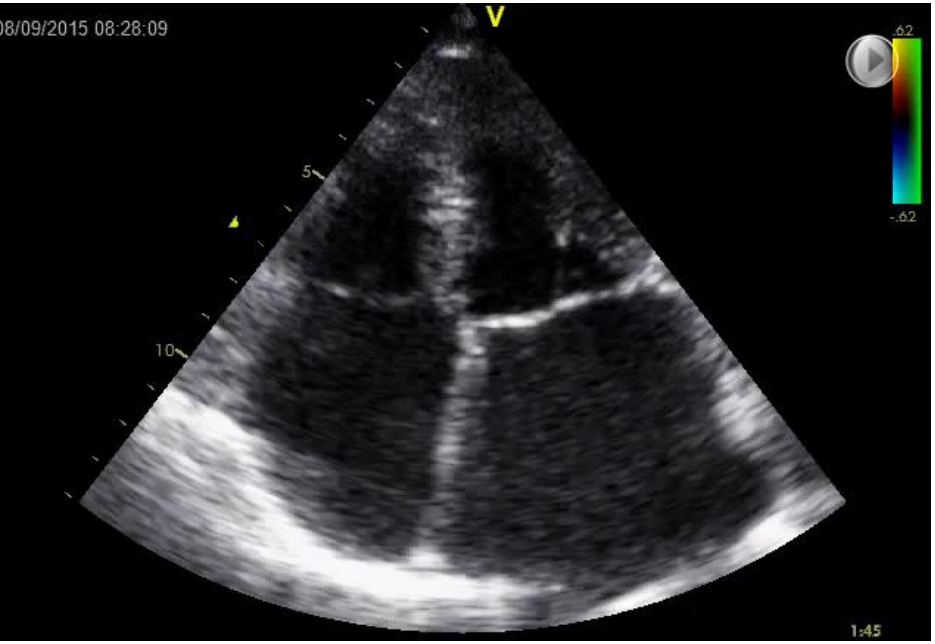
Ghio S. JACC 2001;37:183-8

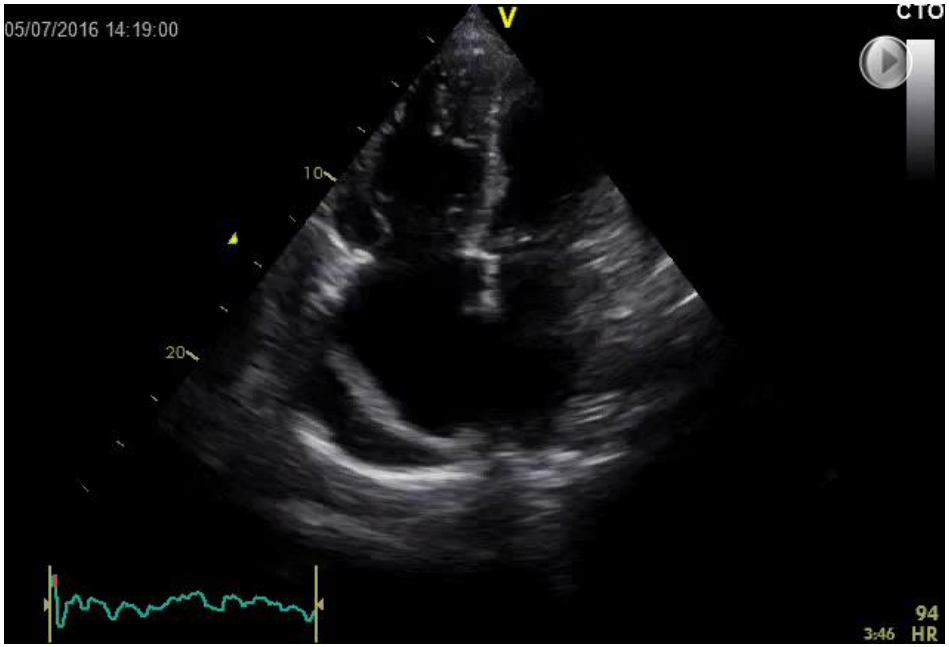
Prognostic determinants of survival

Variable	Hazards Ratio	95% Confidence Interval	p Value
RVEF (per each 5-U decrement)	1.26	1.10–1.46	0.001
NYHA functional class (III or IV vs. II)	2.7	1.4–5.1	0.003
LVESDI (per each 5-mm increment)	1.20	1.04–1.40	0.013
Mean PAP (per each 5-mm Hg increment)	1.10	1.0–1.21	0.047

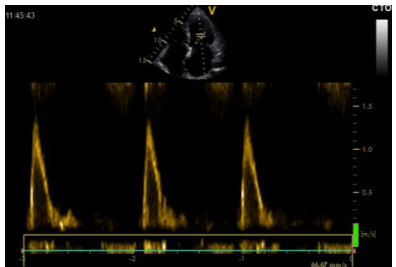
Ghio S. JACC 2001;37:183-8

HFpEF





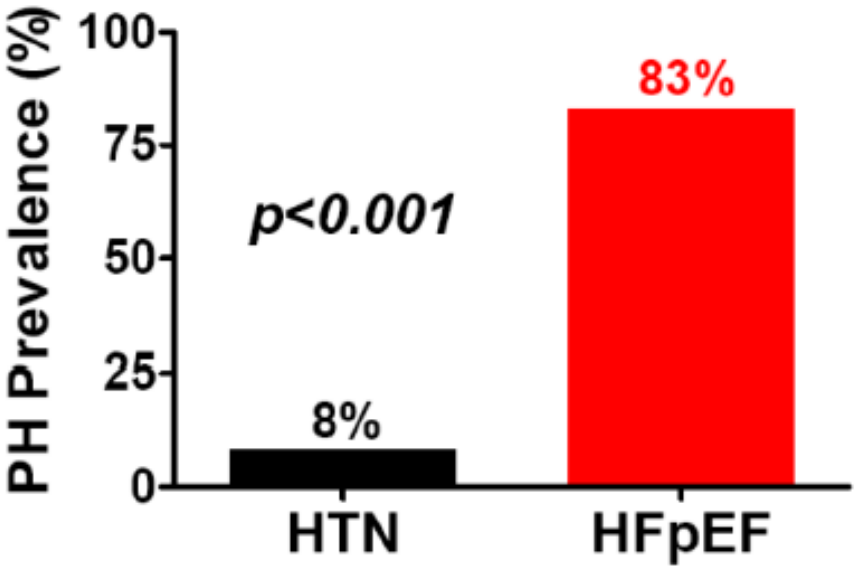
74 year-old lady with chronic Afib
RVSP=38mmHg



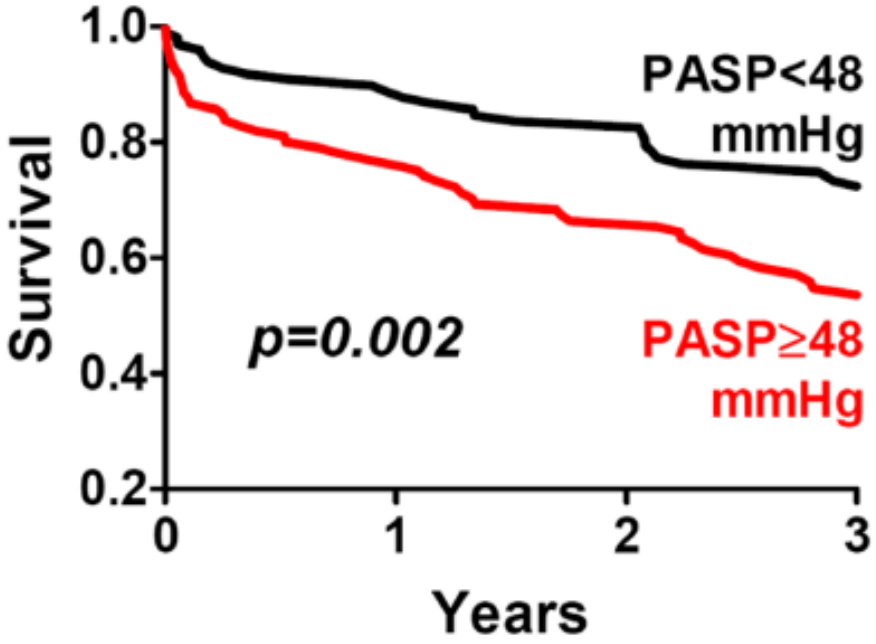
62 year-old lady with chronic Afib
RVSP=78mmHg
Negative V/Q scan
Normal lung function

Epidemiology and Prognostic Impact of PH in Diastolic Heart Failure

Prevalence



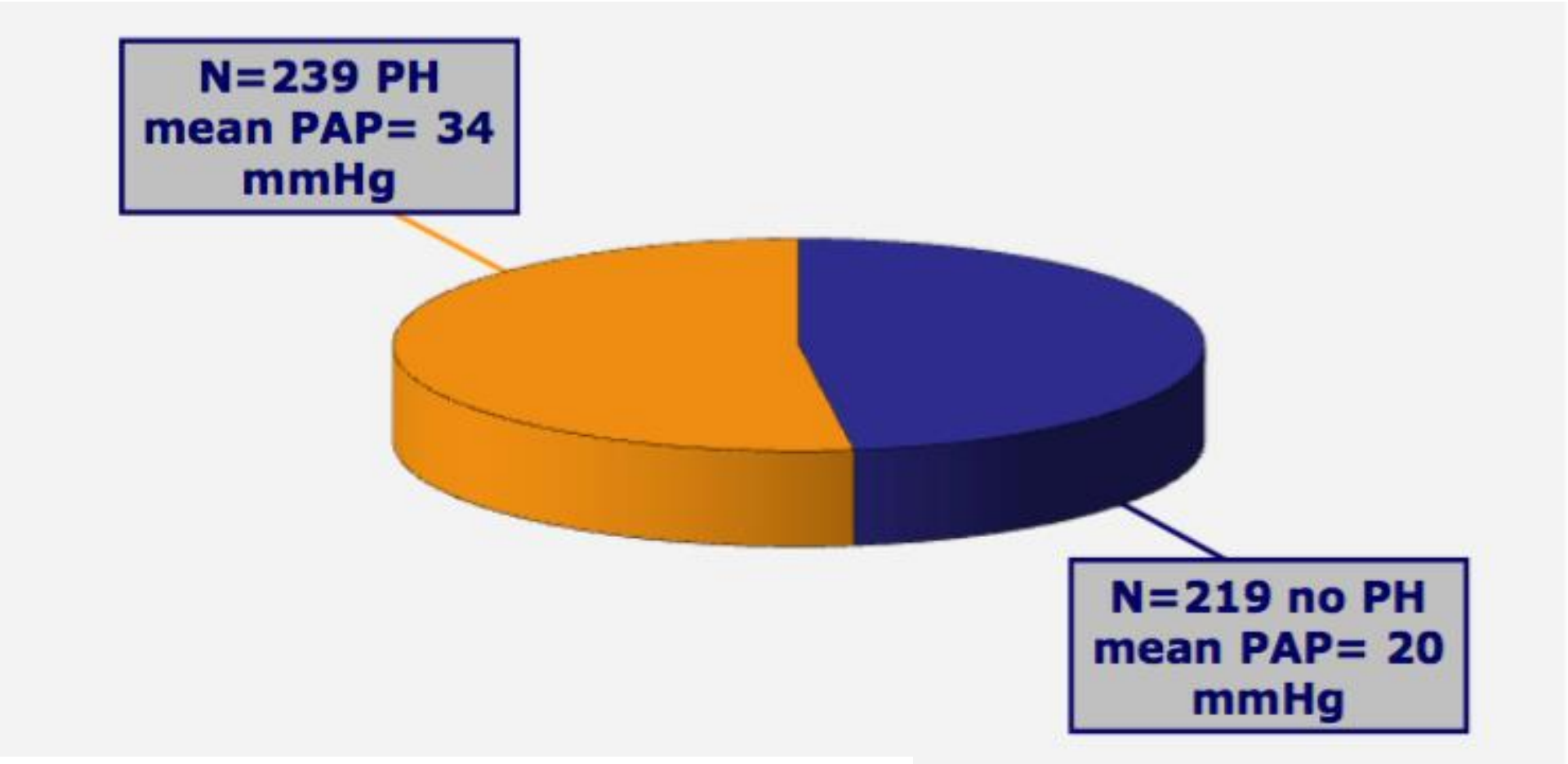
Survival



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

Emerging concepts in PH HFpEF. Prevalence by RHC



- 455 HFpEF patients studied
- mPAP determined by right heart cath.

Leung CC et al. Am J Cardiol 2010

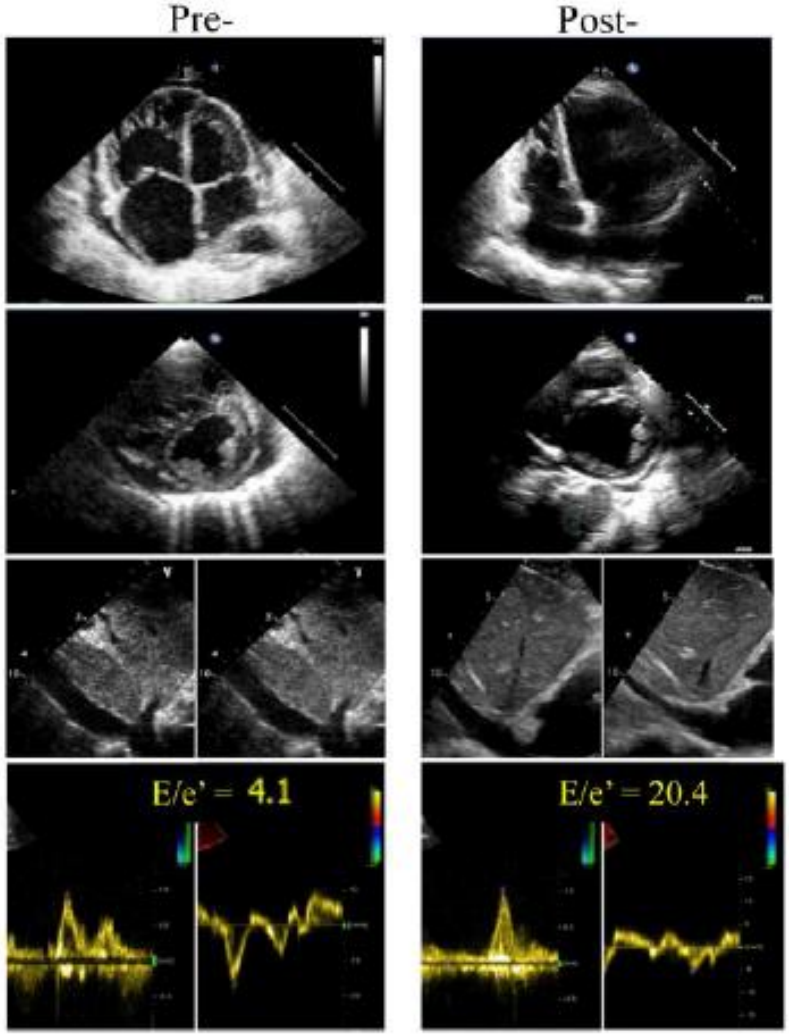
LOOK LEFT
LOOK RIGHT

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		

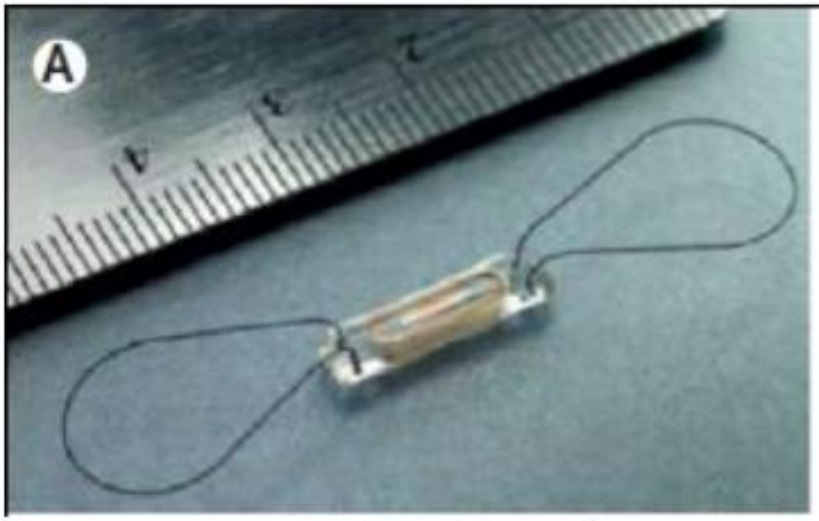
Eur Heart J, 2015 doi: 10.1093/eurheartj/ehv317
Eur Respir J, 2015 doi: 10.1183/ 13993003.01032-2015

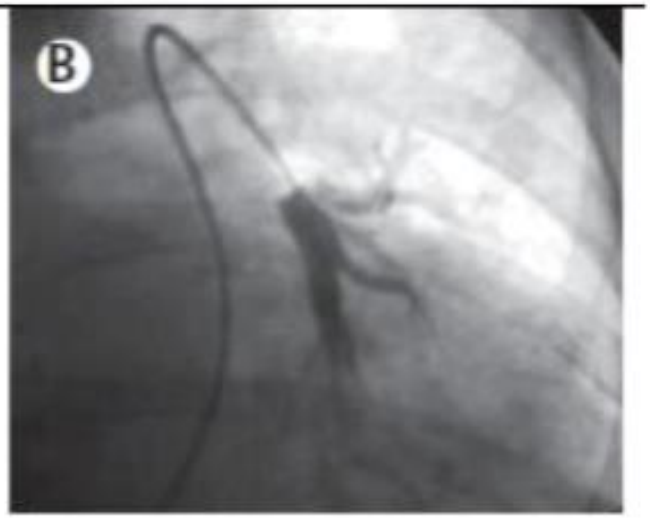
Echocardiographic Prediction of Pre- Versus Postcapillary PH

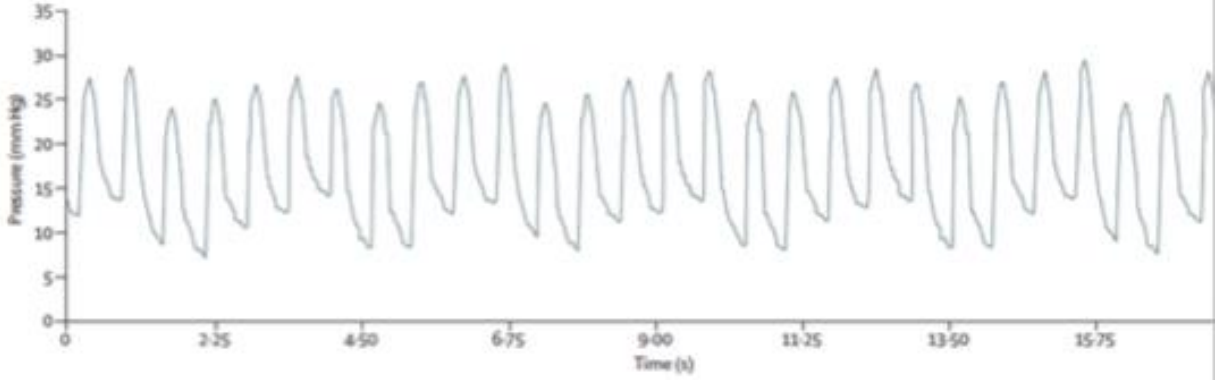


D´Alto-M et al., *J Am Soc Echocardiogr* 2015; 28: 108-115

Wireless pulmonary artery haemodynamic monitoring in CHF: a randomised controlled trial



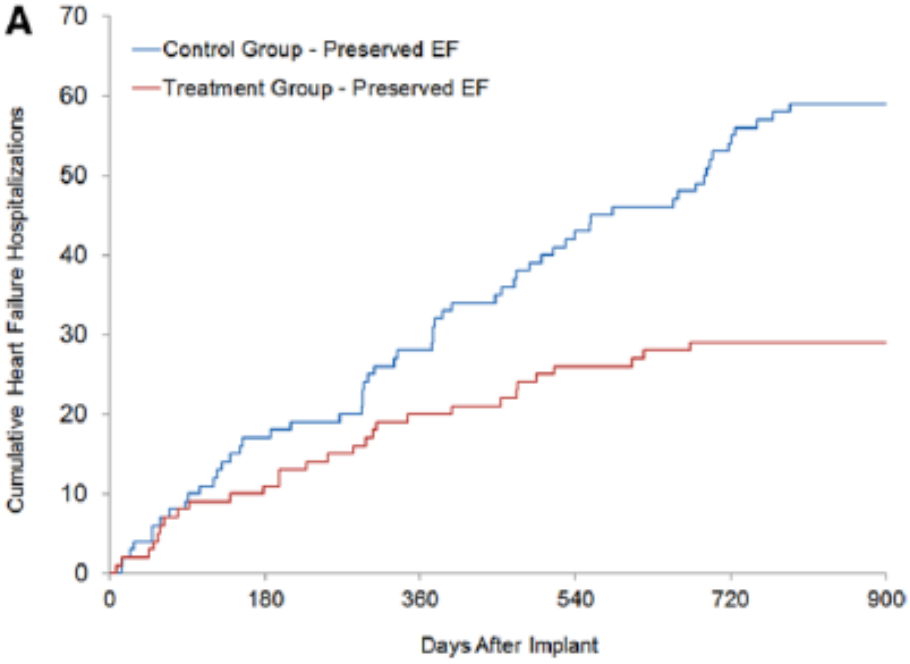


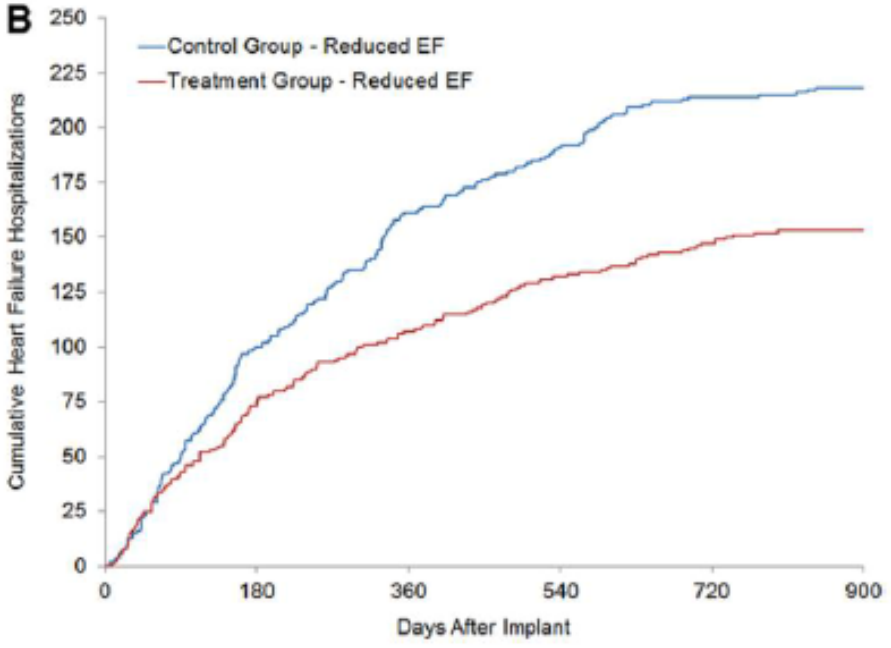


Abraham, Lancet 2011

Wireless PAP Monitoring in HFpEF: Guidance to Reduce Decompensation

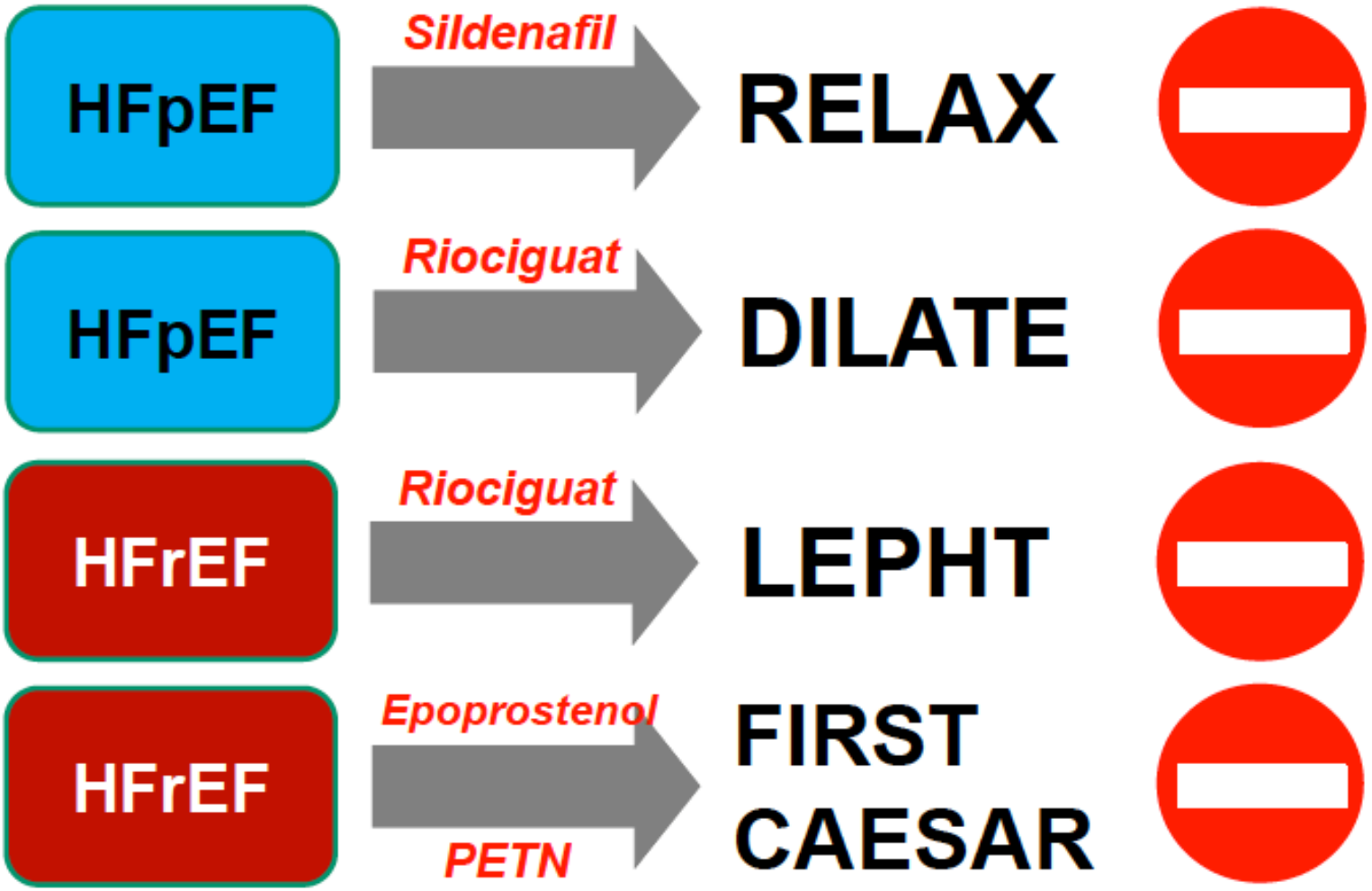
- CardioMEMS Heart Sensor
- Hemodynamically guided HF management vs. standard of care
- HFpEF patients: Hospitalizations 50% lower after 17.6 months
- Response to elevated PAP: more diuretics and vasodilator therapies





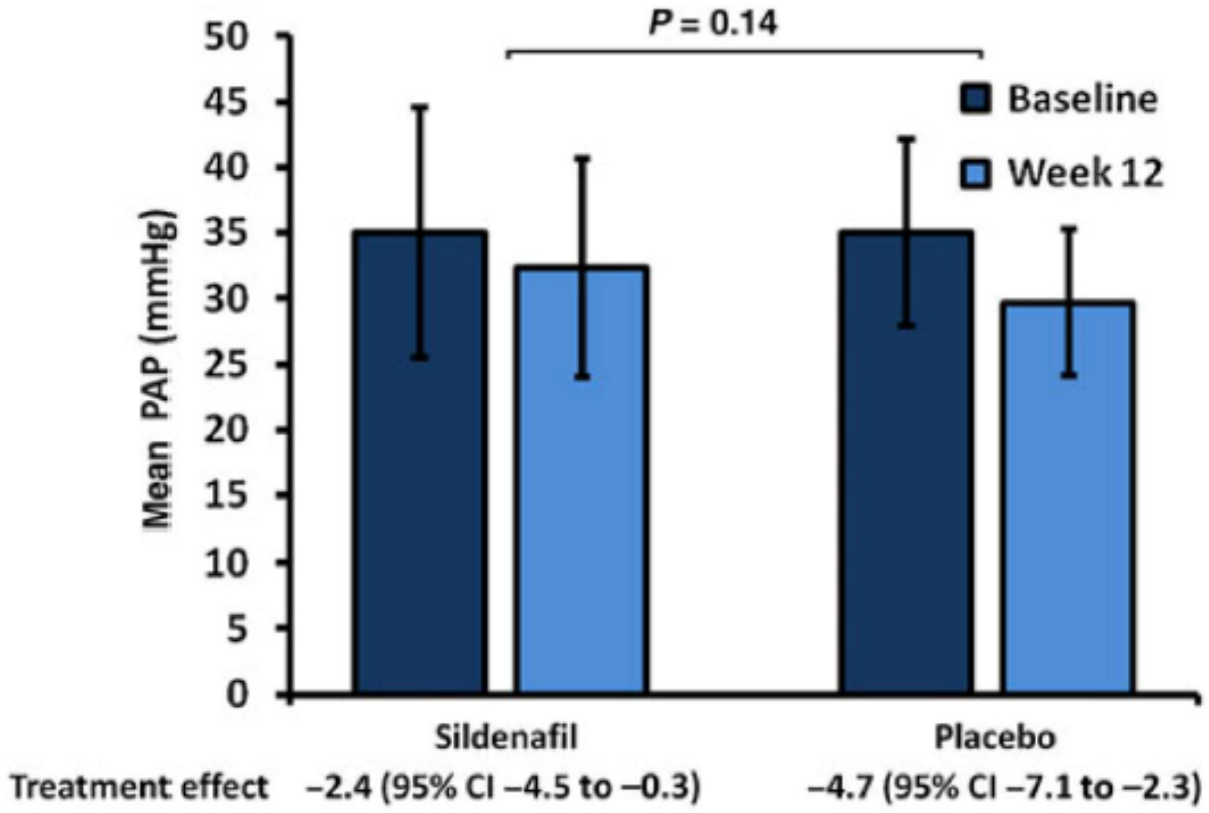
Adamson PB et al. *Circ Heart Fail* 2014; 7: 935-944

Recent Trials in Heart Failure and PH



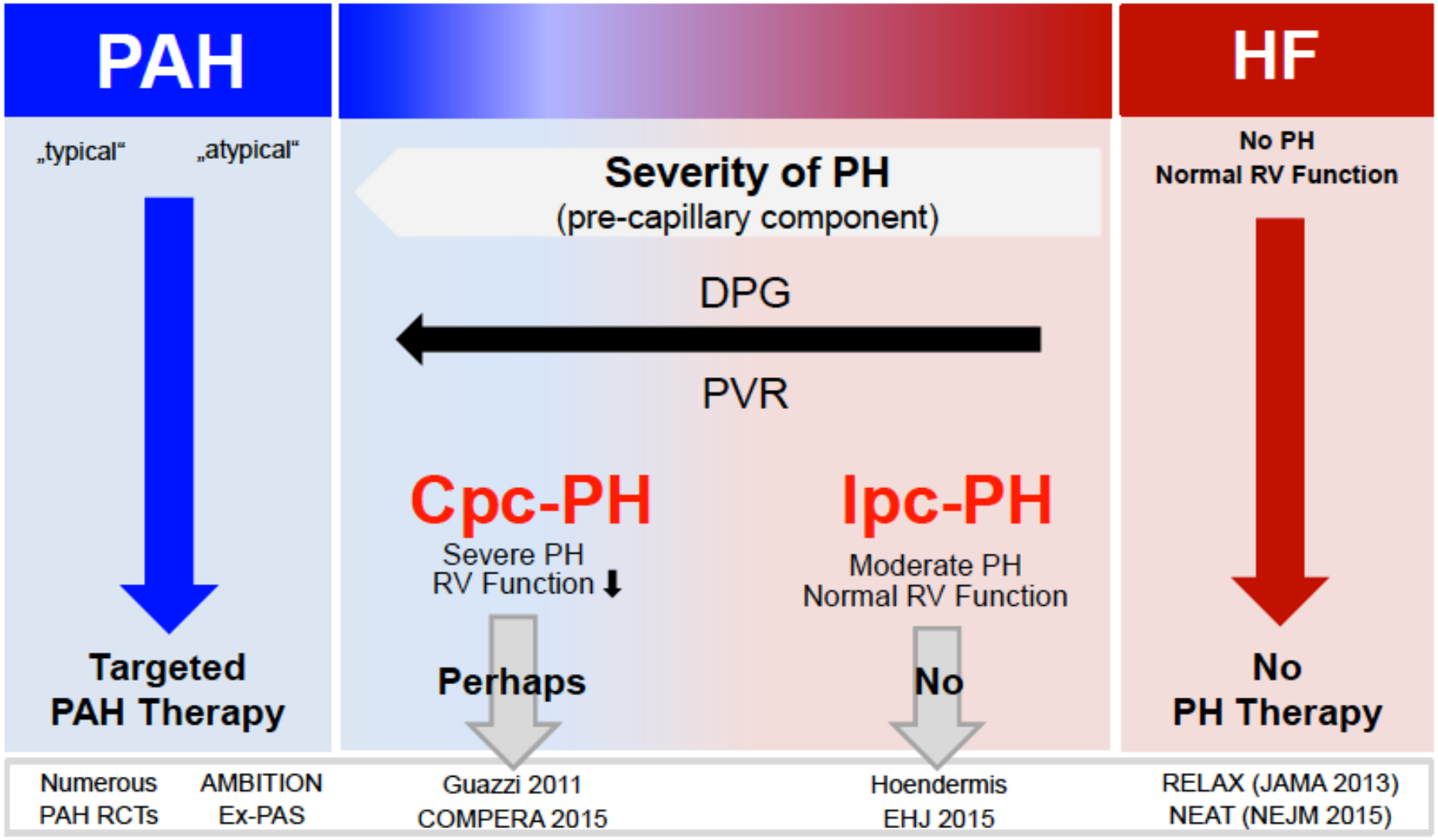
Sildenafil in Patients with HFpEF and Ipc-PH

A double-blind, randomized controlled Study (n=52)
(HFpEF, PH, mean PAPm 35 mHg, mean DPG 1 mmHg, mean PVR 2.4 WU)



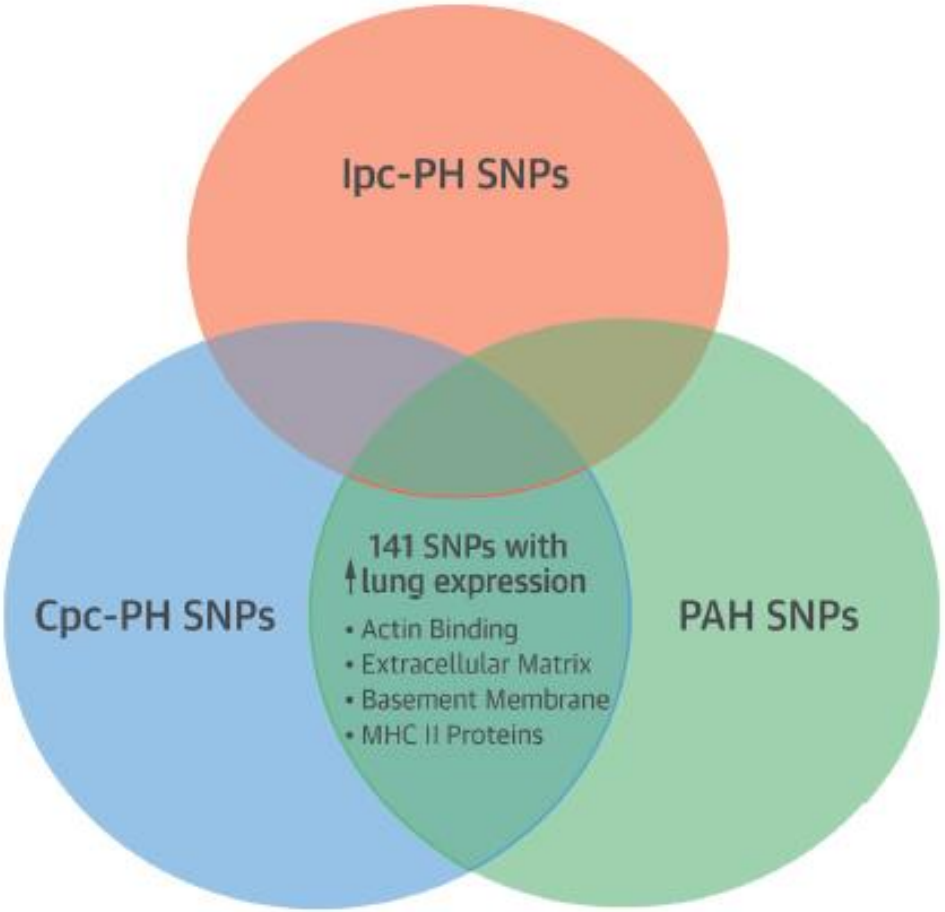
Hoendermis-ES et al., *Eur Heart J* 2015; 36: 2565-2573

PAH vs. PH in Heart Failure: Spectrum of Phenotypes and Therapeutic Consequences



Cpc-PH: Combined post- and pre-capillary PH
Ipc-PH: Isolated post-capillary PH

Genetic similarities



Assad et al. J Am Coll Cardiol 2016

Macitentan in pulmonary hypertension due to left ventricular dysfunction

	Macitentan	Placebo	Total
Subjects n	31	32	63
NYHA functional class n (%)			
II	5 (16.1)	10 (31.3)	15 (23.8)
III	26 (83.9)	22 (68.8)	48 (76.2)
Median (IQR) 6MWD m	300 (216–435)	305 (207–380)	300 (215–410)
Median (IQR) NT-proBNP pg·mL^{-1}	1458 (830–2700)	1756 (992–3503)	1515 (959–2921)
Median (IQR) pulse rate# beats·min^{-1}	80.0 (71.0–84.0)	74.5 (62.0–82.0)	77.0 (67.0–84.0)
Median (IQR) blood pressure¶ mmHg			
Systolic blood pressure	129.0 (120.0–138.0)	133.0 (119.0–147.5)	130.0 (120.0–140.0)
Diastolic blood pressure	77.0 (70.0–87.0)	72.0 (69.0–80.0)	75.0 (70.0–83.0)
Median (IQR) haemodynamic parameters			
PVR dyn·s·cm^{-5}	450.0 (296.0–590.0)	483.5 (362.0–738.5)	462.0 (341.0–695.0)
mPAP mmHg	44.0 (40.0–54.0)	48.5 (38.5–53.5)	47.0 (40.0–54.0)
mRAP mmHg	13.0 (10.0–17.0)	12.5 (10.0–16.5)	13.0 (10.0–17.0)
PAWP mmHg	20.0 (18.0–21.0)	20.0 (16.0–23.0)	20.0 (17.0–22.0)
TPR dyn·s·cm^{-5}	762.0 (571.0–1143.0)	882.5 (664.5–1191.0)	813.0 (591.0–1158.0)
Cardiac index L·min^{-1}·m^{-2}	2.40 (2.10–3.00)	2.20 (1.90–2.60)	2.35 (1.90–2.70)
Cardiac output L·min^{-1}	4.90 (3.70–5.80)	4.15 (3.80–5.05)	4.60 (3.70–5.60)
TPG mmHg	27.0 (21.0–33.0)	27.5 (21.5–33.5)	27.0 (21.0–33.0)
DPG mmHg	10.0 (8.0–15.0)	10.0 (8.0–13.5)	10.0 (8.0–14.0)
Mixed venous oxygen saturation %	72.0 (61.0–73.0)	61.0 (49.0–65.0)	64.5 (59.0–72.0)

	Macitentan	Placebo	Treatment effect % (95% CI)#	p-value¶
Subjects n	31	32		
Significant fluid retention or worsening in NYHA functional class from baseline+	7 (22.6)	4 (12.5)	10.08 (−15.07 to 33.26)	0.34
Significant fluid retention	7 (22.6)	3 (9.4)	13.21 (−11.96 to 36.21)	0.18
Increased body weight from baseline by ⩾5% or ⩾5 kg due to fluid overload	3 (9.7)	0 (0)		
Parenteral administration of diuretics	5 (16.1)	3 (9.4)		
Worsening in NYHA functional class from baseline§	1 (3.2)	2 (6.3)		

Vachiéry JL et al. Eur Respir J. 2018

Pulmonary Hypertension Phenotypes: „Typical“ and „atypical“ IPAH versus CpcPH-HFpEF

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

A Pathophysiological Continuum

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Opitz et al., COMPERA Investigators, *J Am Coll Cardiol* 2016; 68: 368-378

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

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

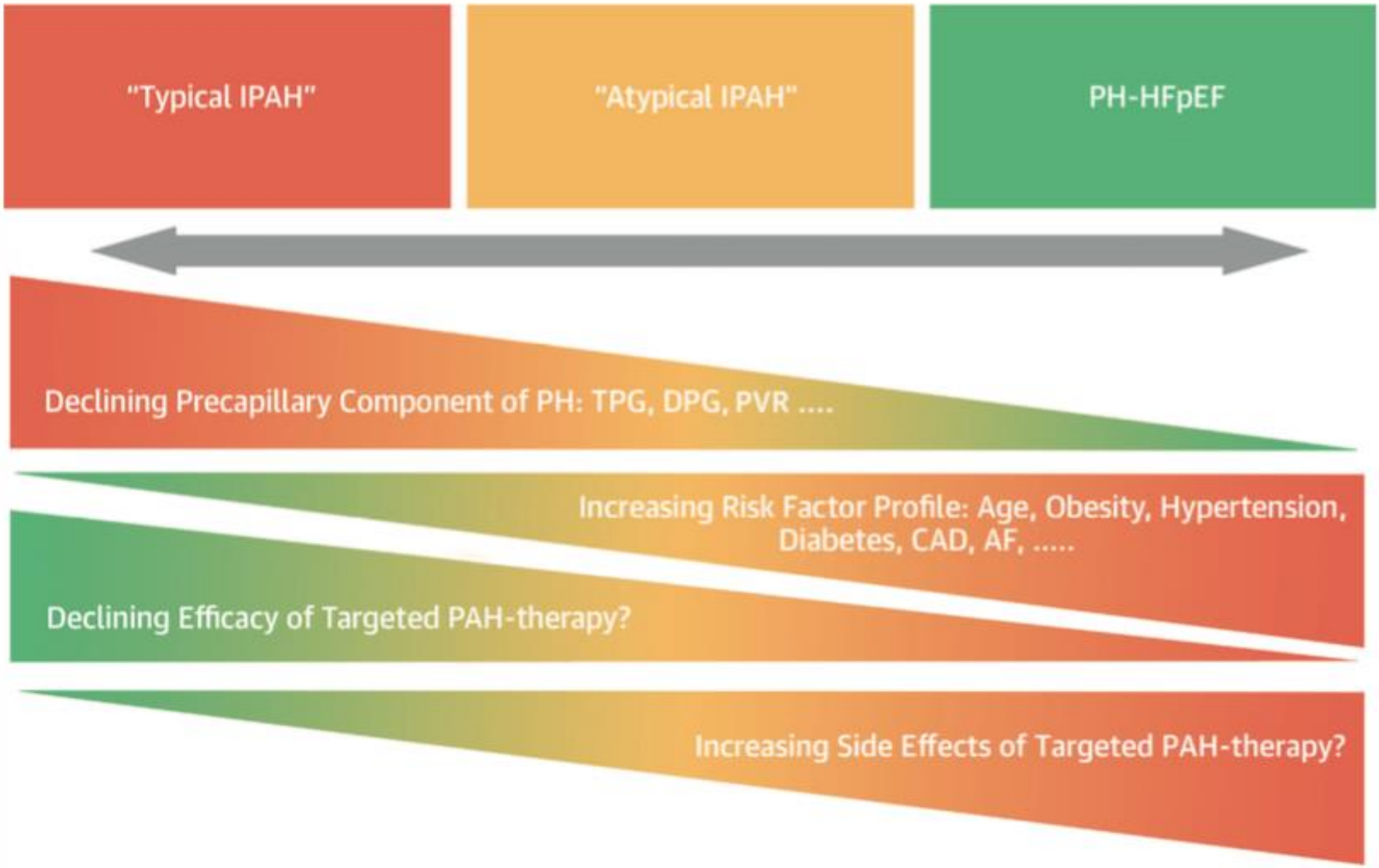
Opitz et al. J Am Coll Cardiol 2016

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

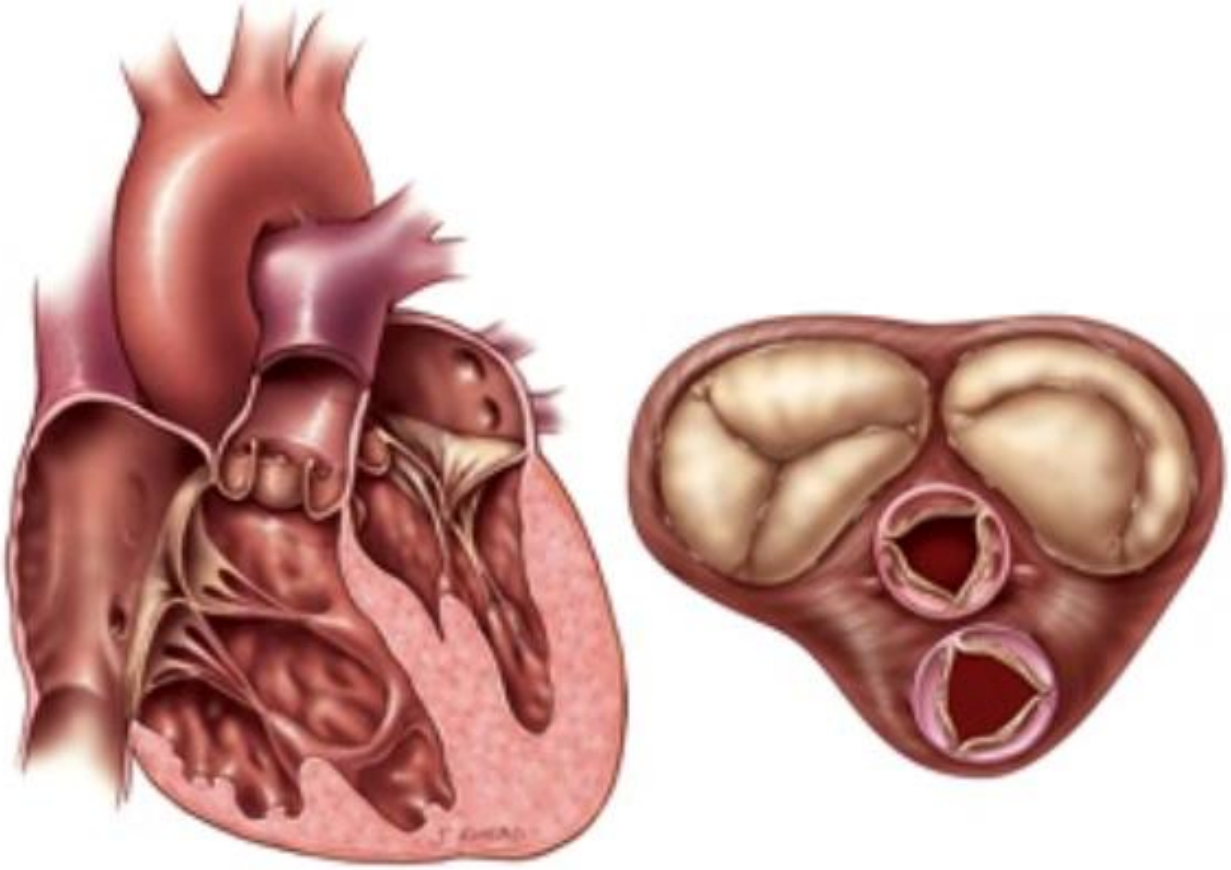
Opitz et al. J Am Coll Cardiol 2016

CENTRAL ILLUSTRATION Pulmonary Hypertension in Typical PAH, Atypical PAH, and HFpEF



Opitz, C.F. et al. J Am Coll Cardiol. 2016;68(4):368–78.

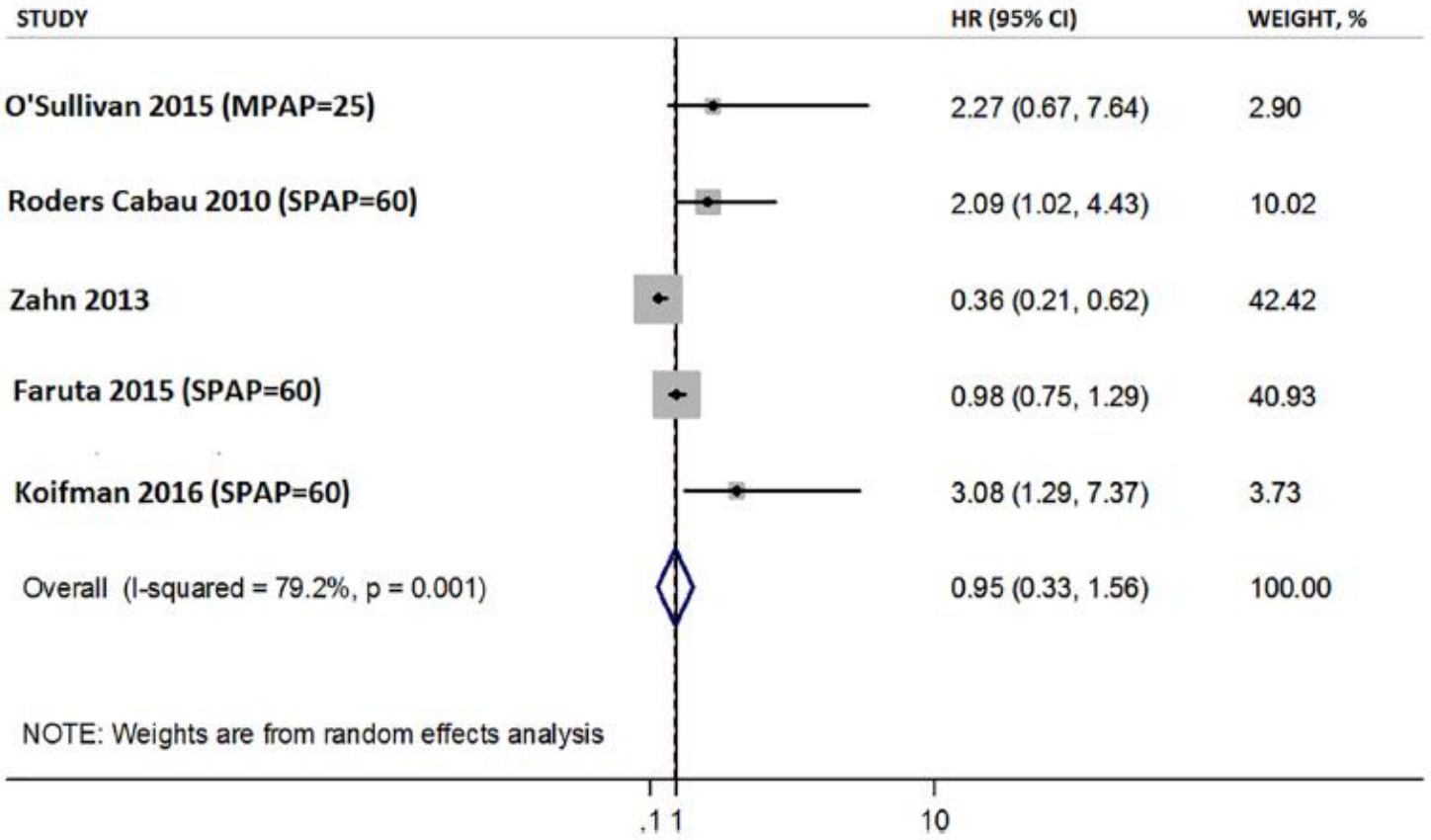
VALVULAR HEART DISEASE



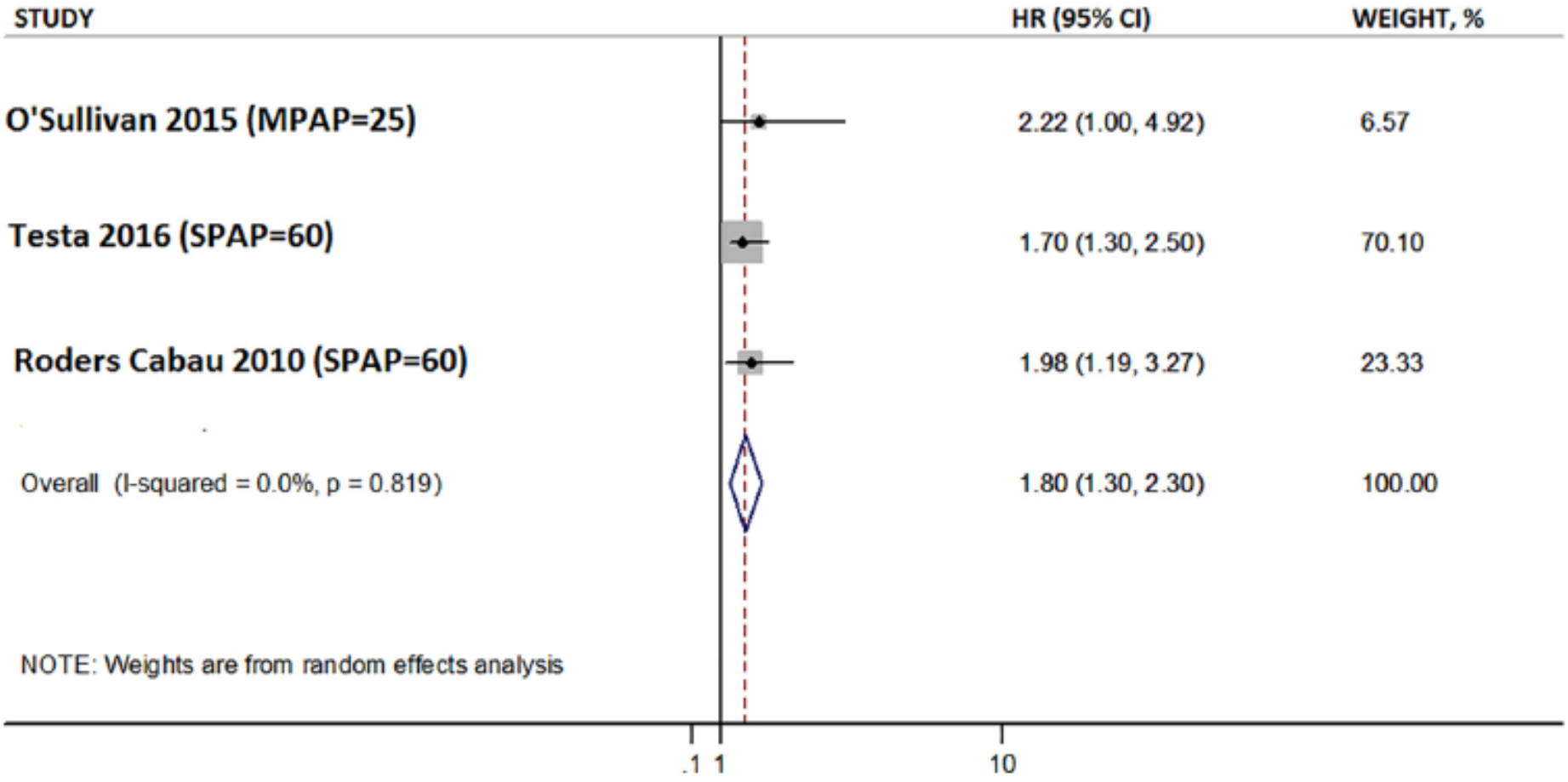
The predictive value of baseline pulmonary hypertension in early and long term cardiac and all-cause mortality after transcatheter aortic valve implantation for patients with severe aortic valve stenosis: A systematic review and meta-analysis ☆,☆☆

Damianos G. Kokkinidis [a,b,*], Christos A. Papanastasiou [c], Anil Kumar Jonnalagadda [d], Evangelos K. Oikonomou [e], Christina A. Theochari [e], Leonidas Palaiodimos [a], Haralambos I. Karvounis [c], Ehrin J. Armstrong [b], Robert T. Faillace [a], George Giannakoulas [c]

Early mortality after TAVI

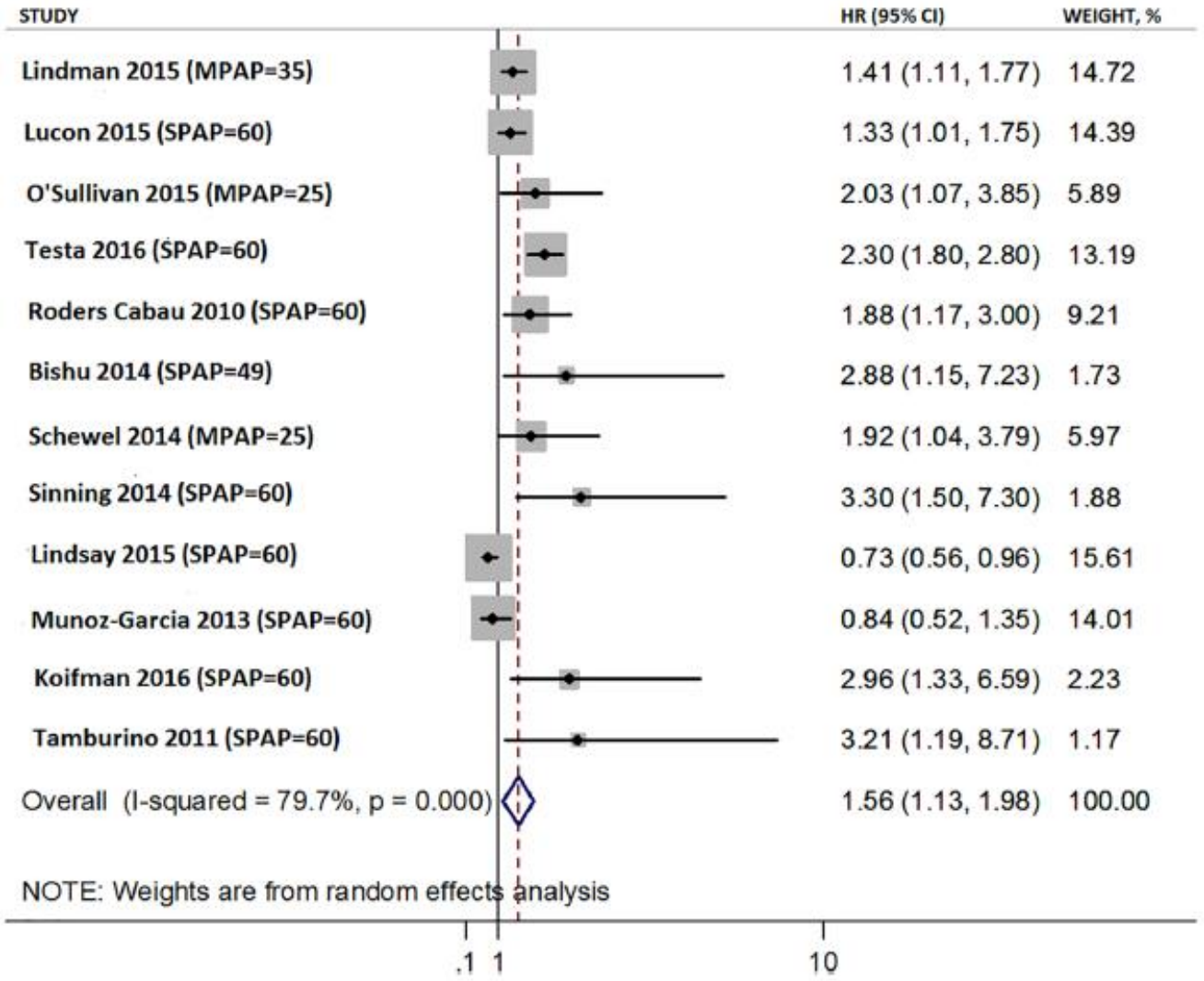


Late cardiac mortality after TAVI



Kokkinidis et al. Cardiovasc Revasc Med 2018

Late overall mortality after TAVI



Kokkinidis et al. Cardiovasc Revasc Med 2018

Hospital General Universitario Gregorio Marañón

SaludMadrid

Comunidad de Madrid

cibercv

Effect of Sildenafil on Clinical Outcomes in Patients with Corrected Valvular Heart Disease and Residual Pulmonary Hypertension.

The **S**ildenafil for **I**mproving **O**utcomes after **Va**lvular **C**orrection (SIOVAC) Trial.

Javier Bermejo, on behalf of the SIOVAC investigators

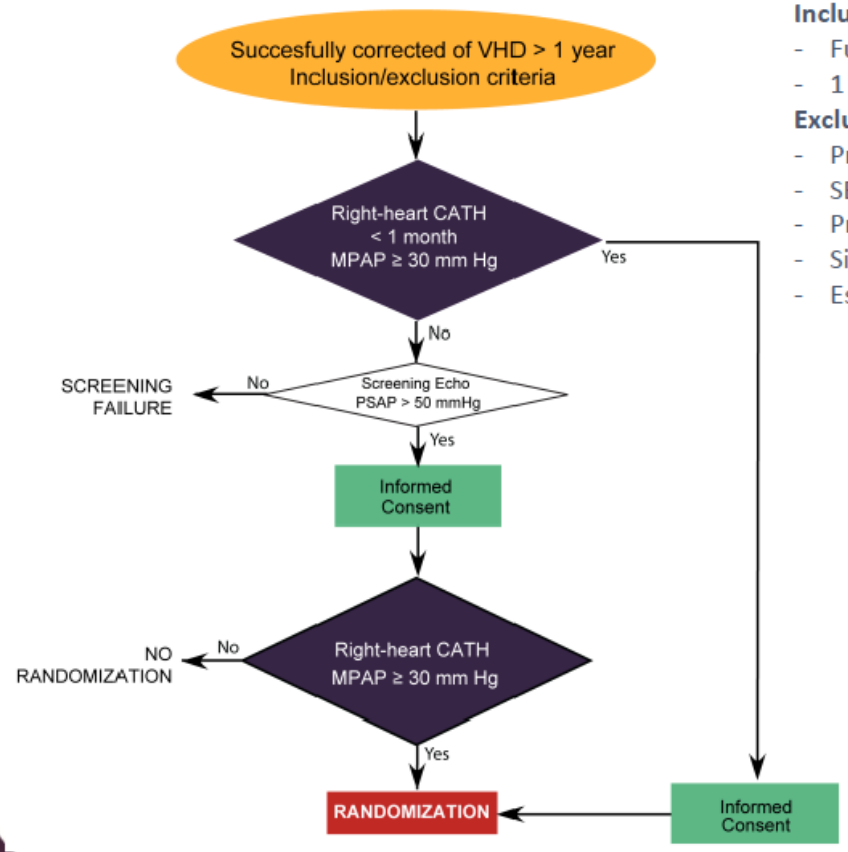
Hospital General Universitario Gregorio Marañón

SaludMadrid

Comunidad de Madrid

The SIOVAC Design

ciber cv

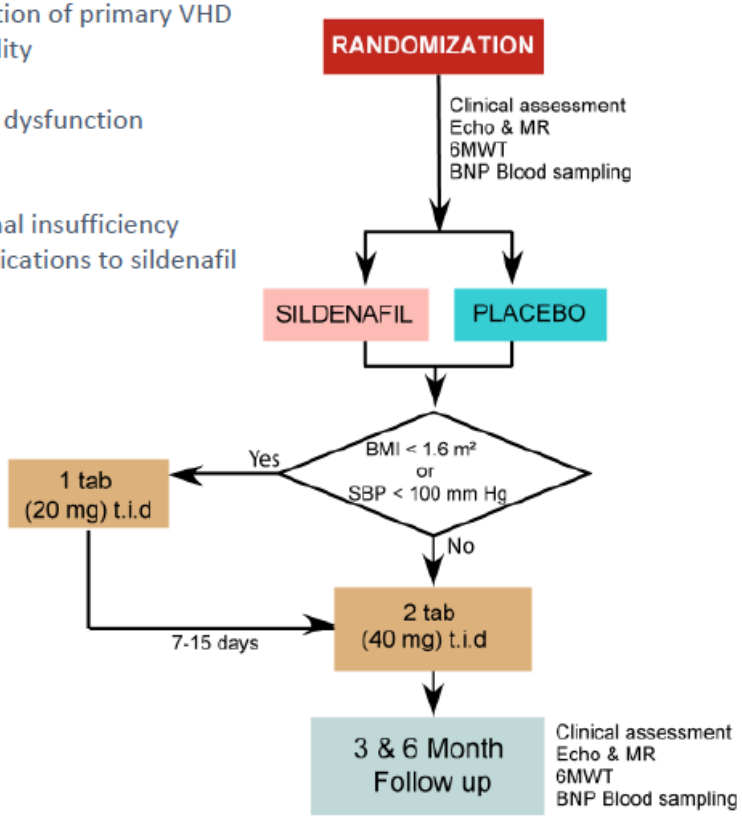


Inclusion Criteria:

- Full successful correction of primary VHD
- 1 month clinical stability

Exclusion Criteria:

- Prosthesis or valvular dysfunction
- SBP < 90 mmHg
- Previous MI or stroke
- Significant liver or renal insufficiency
- Established contraindications to sildenafil

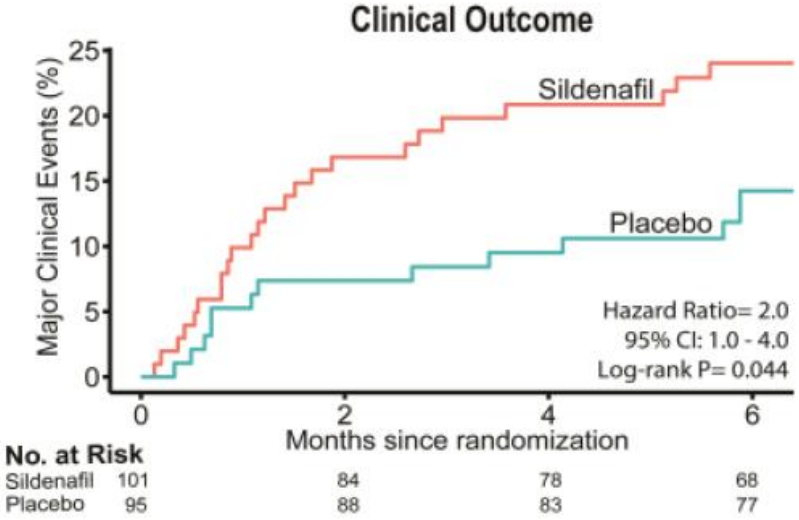


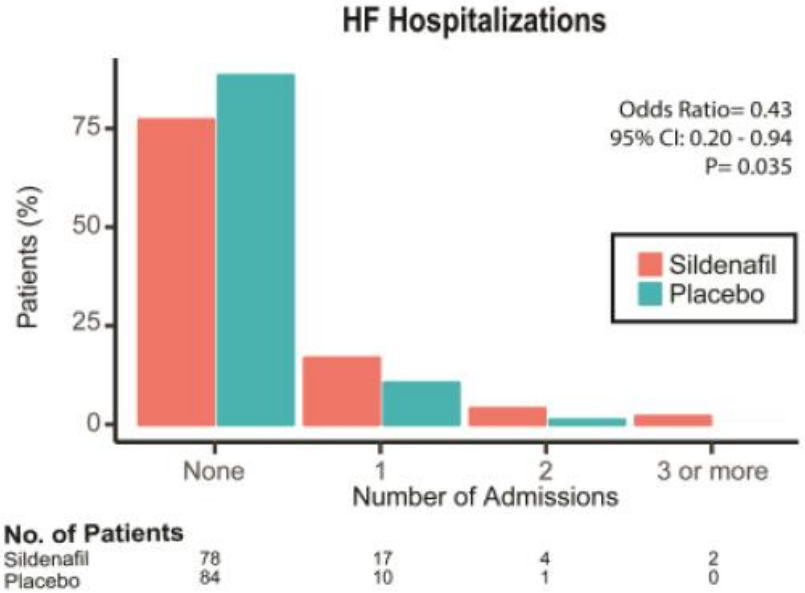
Key Catheterization Data

	SILDENAFIL (N= 104)	PLACEBO (N= 96)	TOTAL (N= 200)
Mean Pulmonary Artery Pressure (mm Hg)	40 (34, 46)	37 (34, 44)	38 (34, 44)
Mean Wedge Pulmonary Pressure (mm Hg)	23 (19, 26)	22 (19, 26)	22 (19, 26)
Cardiac Index ($L \cdot min^{-1} \cdot m^{-2}$)	2.8 (2.4, 3.2)	2.8 (2.3, 3.4)	2.8 (2.4, 3.3)
Transpulmonary Pressure Gradient (mm Hg)	16.0 (13.0, 22.0)	15.0 (12.0, 20.0)	16.0 (12.0, 21.2)
Diastolic Transpulmonary Pressure Gradient (mm Hg)	2.0 (0.0, 6.0)	3.0 (0.0, 7.0)	3.0 (0.0, 6.2)
Pulmonary Vascular Resistance (Wood Units)	3.4 (2.4, 4.6)	3.1 (2.2, 4.9)	3.3 (2.3, 4.9)

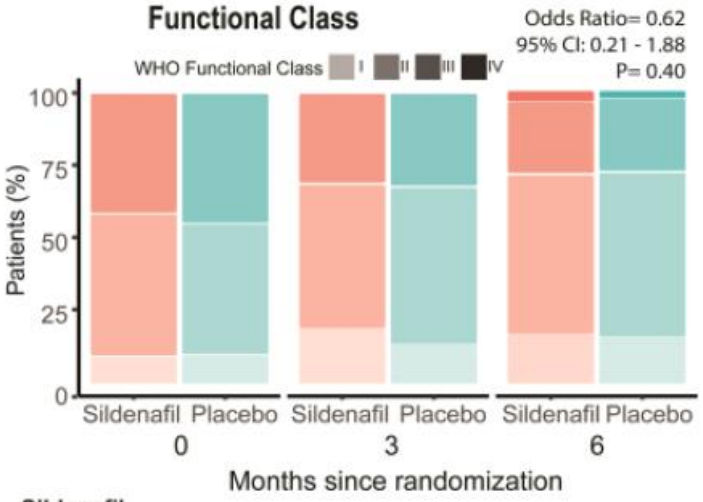
Median (IQR)

Key Secondary Endpoints

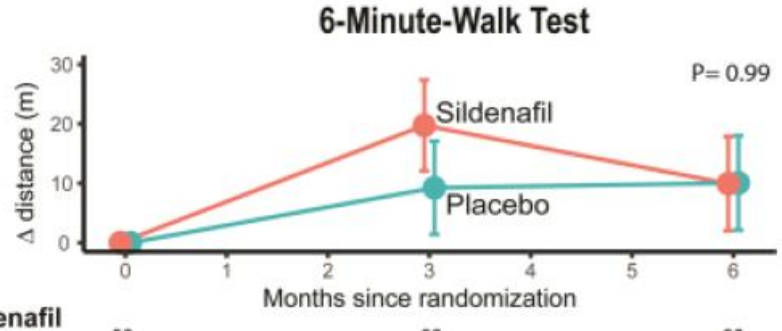




Key Secondary Endpoints



Sildenafil			
OMS Functional Class I	8	17	14
II	51	48	50
III	42	29	22
IV	0	0	2
Placebo			
OMS Functional Class I	8	11	13
II	44	51	51
III	43	29	22
IV	0	0	1



Sildenafil			
No. of pts.	99	88	80
LS Mean Distance (m)	346 ± 11	367 ± 11	357 ± 11
Placebo			
No. of pts.	93	84	81
LS Mean Distance (m)	331 ± 11	340 ± 11	341 ± 11

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

Πνευμονική υπέρταση στην αριστερή καρδιακή νόσο

Thank you!

Acknowledgements

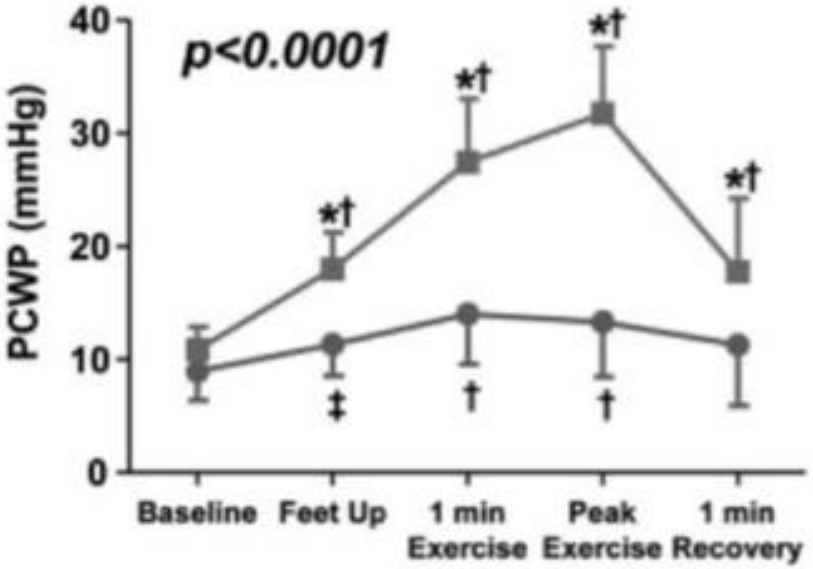
Aristotle University of Thessaloniki

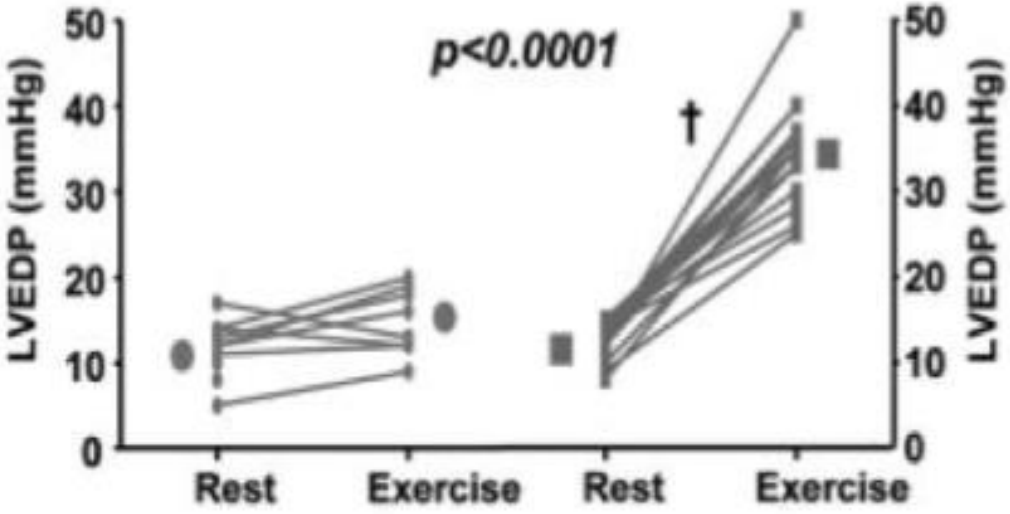
Pulmonary Hypertension Unit, AHEPA Hospital

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

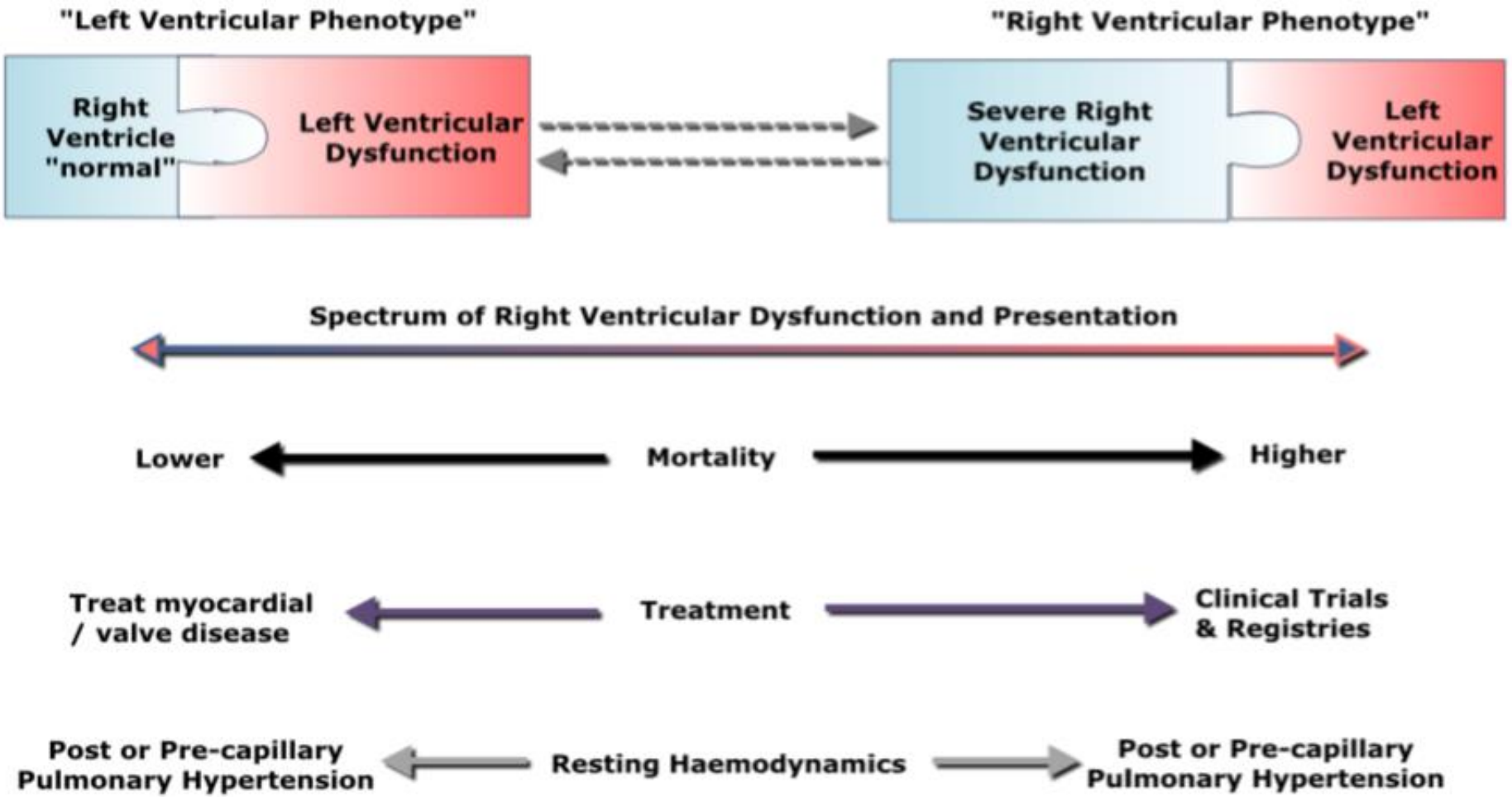
RIGHT and LEFT HEART catheterisation during supine exercise





Borlaug B et al. Circ Heart Fail 2010

Heart Failure:
Left vs. Right Ventricular Phenotype



Rosenkranz et al. Eur Heart J 2016

Many thanks

TPG versus DPG

CHEST

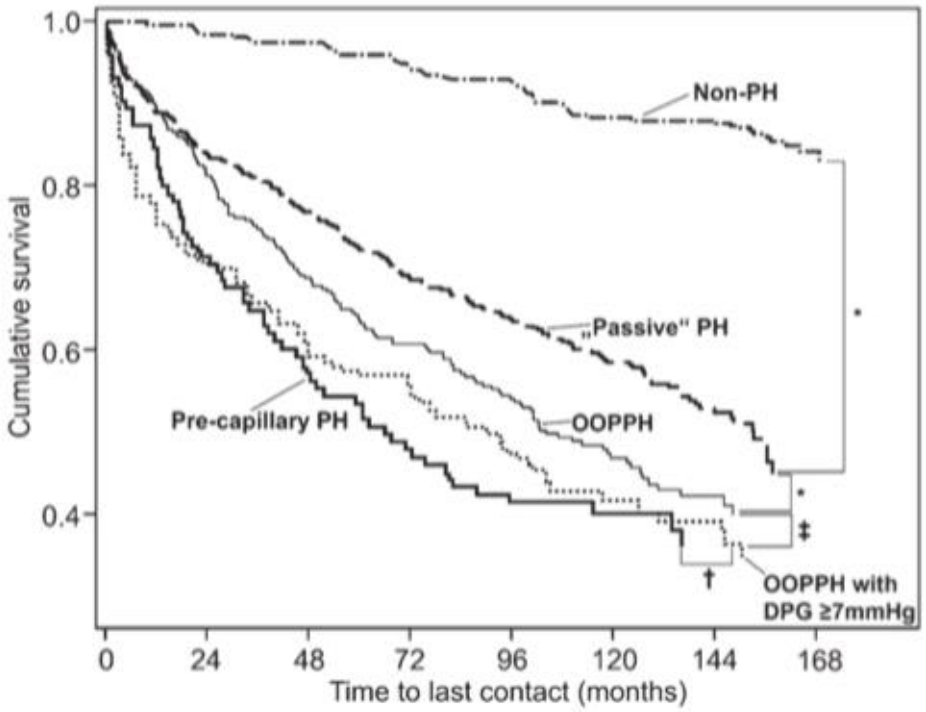
Original Research

PULMONARY VASCULAR DISEASE

Diastolic Pulmonary Vascular Pressure Gradient

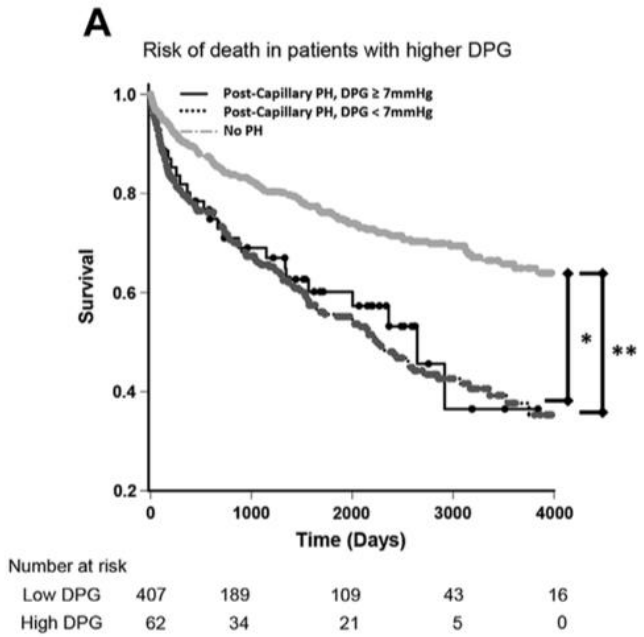
A Predictor of Prognosis in "Out-of-Proportion" Pulmonary Hypertension

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



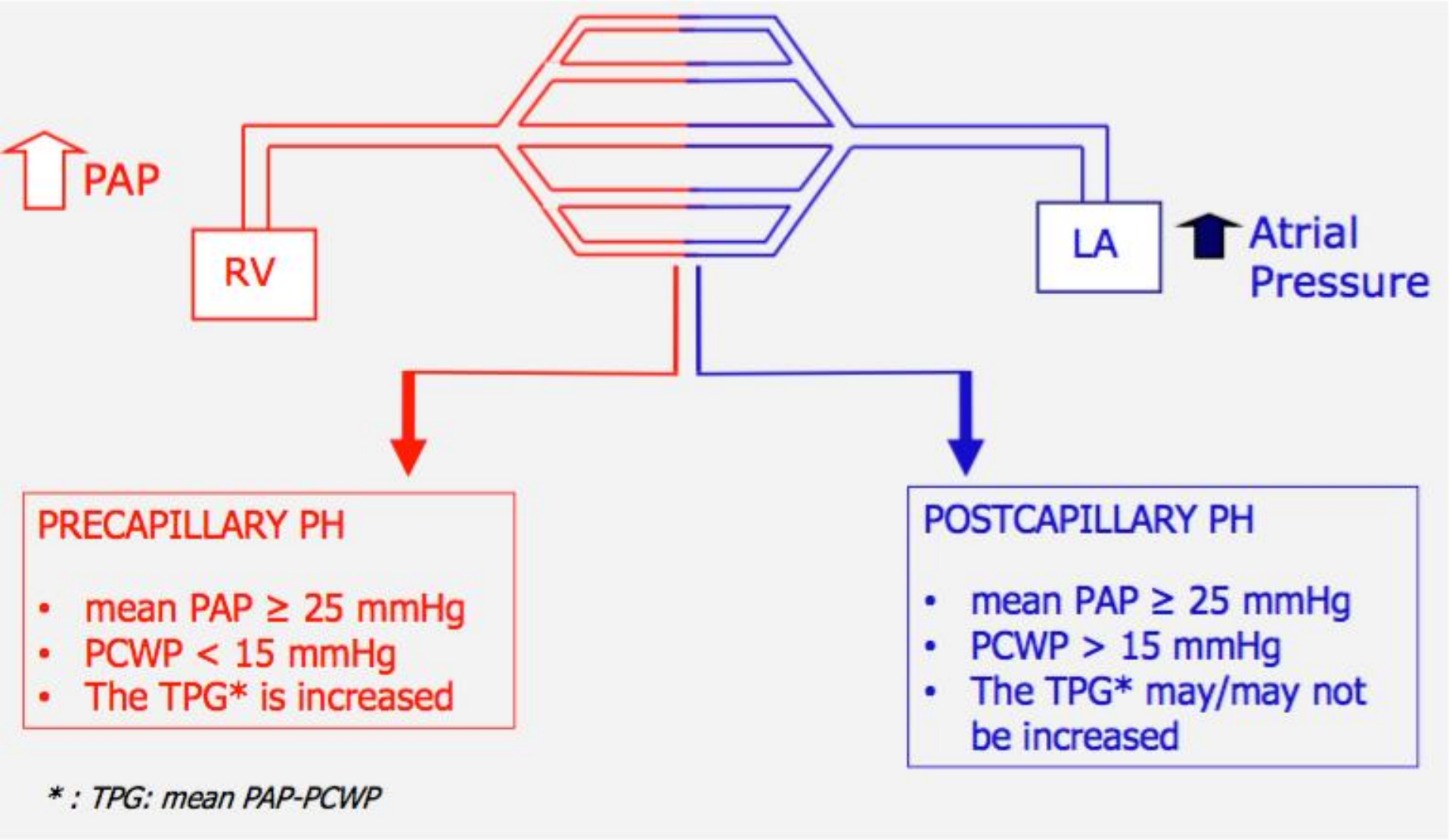
The Diastolic Pulmonary Gradient Does Not Predict Survival in Patients With Pulmonary Hypertension Due to Left Heart Disease

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

PH due to left heart disease (group 2)

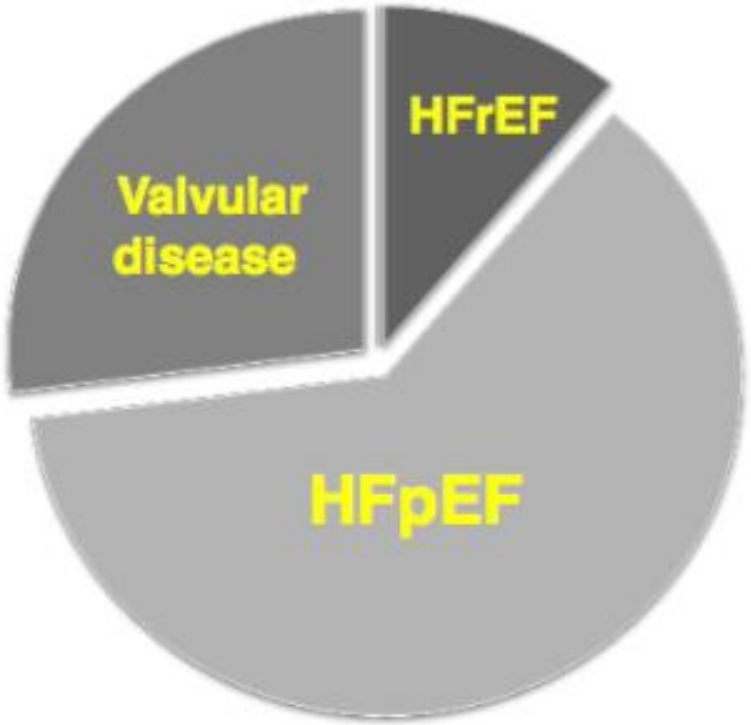


Spectrum of group 2 PH. ASPIRE registry

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

157 patients with Group 2 PH

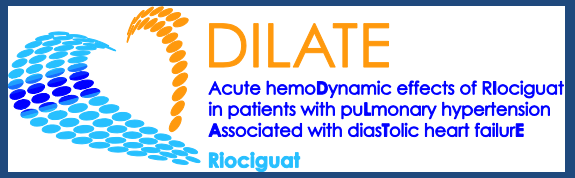
	HFrEF	HFpEF	Valv. Dis.
PCWP, mmHg	24	22	26*§
mean PAP, mmHg	43	37	48*
mean RAP, mmHg	17	15	14



Hurdman J et al. Eur Resp J 2012

Left ventricular systolic dysfunction associated with pulmonary hypertension riociguat trial (LEPHT)

Dr Diana Bonderman (Medical University of Vienna), Dr Stefano Ghio (University Hospital, Pavia), Prof. Stephan B. Felix (Ernst-Moritz-Arndt-University of Greifswald), Prof. Hossein A. Ghofrani (Justus Liebig University Giessen), Prof. Evangelos D. Michelakis (University of Alberta), Prof. Veselin Mitrovic (Kerckhoff-Klinik Forschungsgesellschaft mbH), Prof. Ronald J. Oudiz (Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center), Dr Francis Boateng (Bayer Healthcare Pharmaceuticals), Dr Andrea-Viviana Scalise (Bayer Hispania), Dr Lothar Roessig (Bayer Pharma AG), Dr Marc J. Semigran (Massachusetts General Hospital and Harvard Medical School)

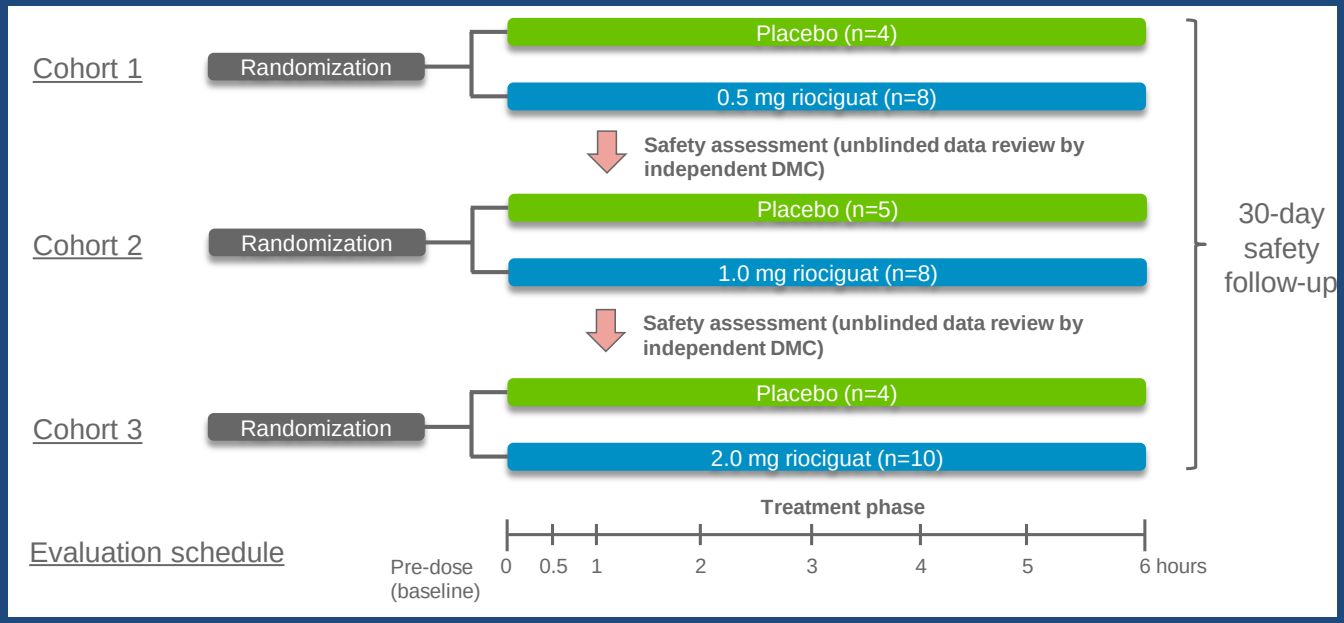


Acute hemodynamic effects of riociguat in patients with pulmonary hypertension associated with diastolic heart failure (DILATE-1): A randomized, double-blind, placebo-controlled, single-dose study

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

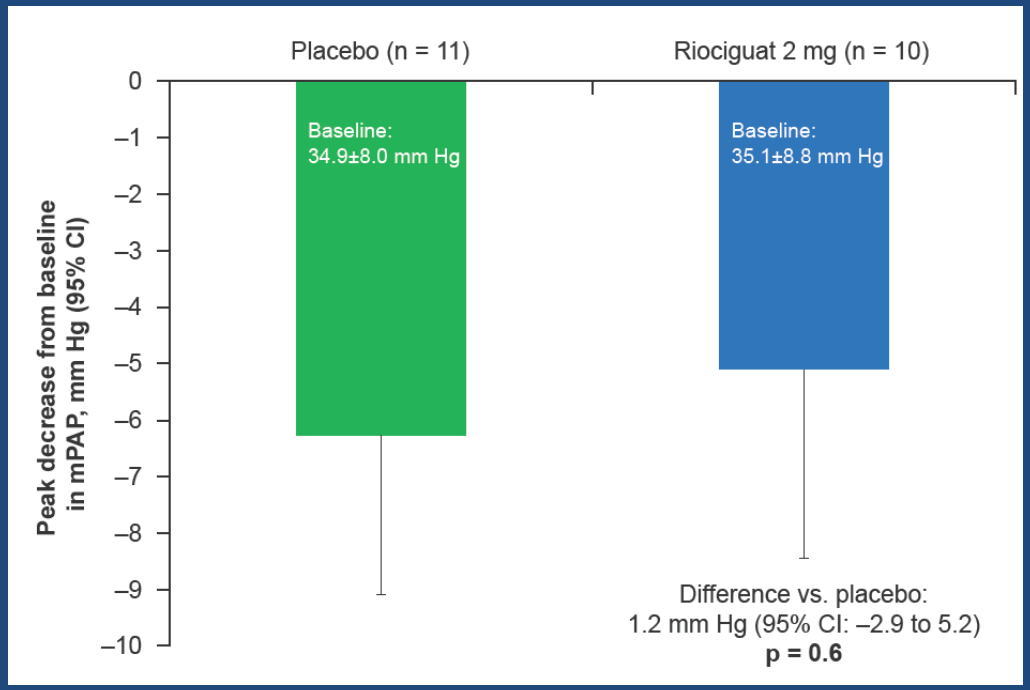


Study design of the DILATE-1 study. Study medication was administered orally as a single dose of a film-coated tablet of riociguat (0.5 mg, 1 mg, or 2 mg) or matching placebo.

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

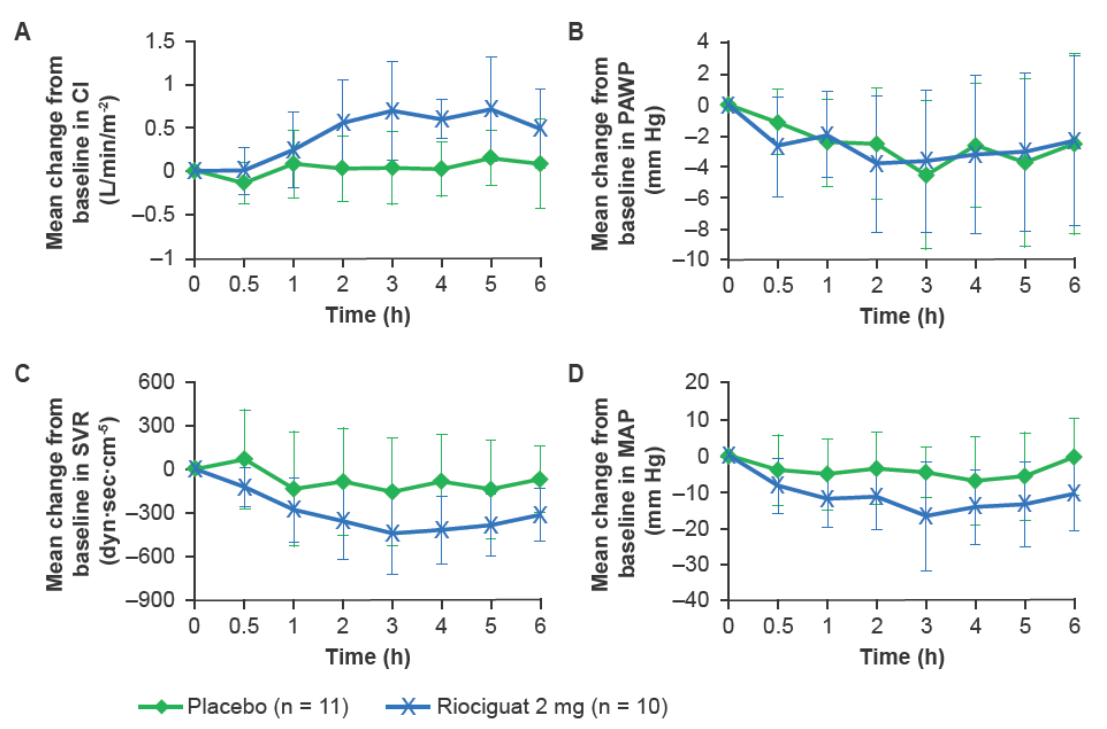


Peak decrease in mean pulmonary artery pressure (mPAP) from baseline up to 6 h after administration of study drug in the riociguat 2 mg group vs. placebo (primary endpoint). The difference between treatment groups was analyzed by a two-group, two-sided t-test. The treatment difference (95% confidence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

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

DILATE: Hemodynamics

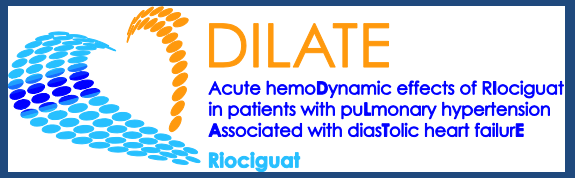
DILATE
Acute hemoDynamic effects of RIociguat in patients with puLmonary hypertension Associated with diasTolic heart failurE
Riociguat



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

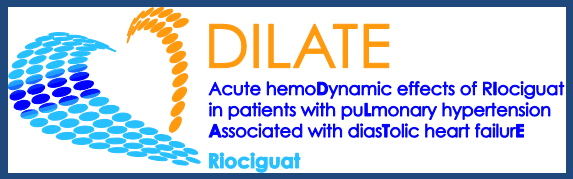
•Compared with placebo, riociguat 2 mg decreased left atrial area, with a trend towards statistical significance (P=0.06), and significantly decreased right ventricular end-diastolic (RVED) area (P=0.04) .

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.