PH due to Left Heart Disease (Group 2) Diagnosis and Current Management

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Agenda : PH-LHD

- Introduction
  - Definition, Epidemiology, Pathophysiology
- Clinical significance of PH in LHD
- Diagnosis
- Treatment principles

Pulmonary hypertension associated with left heart disease (PH-LHD)

- Pulmonary Hypertension (PH) mPAP >20 mmHg
- Post-capillary PH PAWP >15 mmHg
  - IpcPH (isolated post-capillary PH) PVR ⩽2 WU
  - CpcPH (combined post- and pre-capillary PH) PVR >2 WU

cf) Group 1 PAH, pre-capillary PH

- mPAP >20 mmHg, **PAWP ≤15 mmHg**, PVR >2 WU

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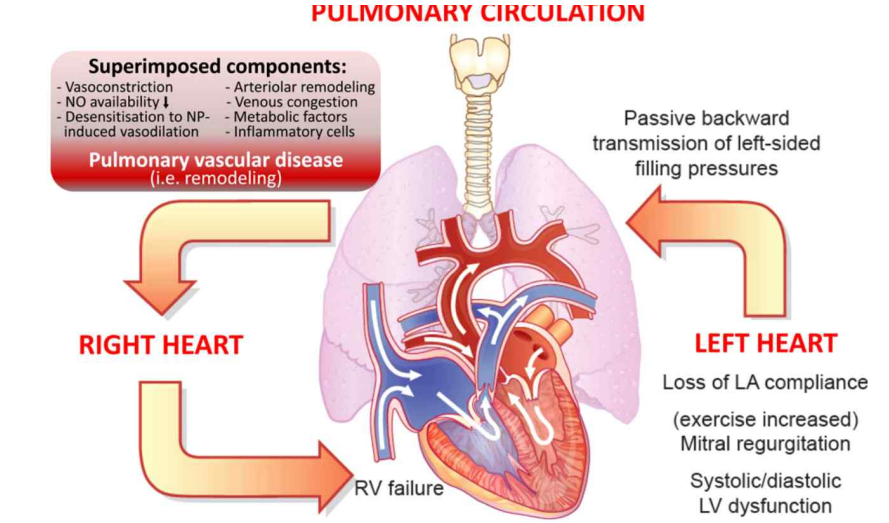
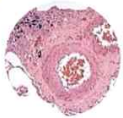
Pathophysiology of PH-LHD



European Heart Journal (2016) 37, 942–954

Pulmonary arterial hypertension (PAH)	PH associated with left heart disease	PH associated with lung disease	PH associated with pulmonary artery obstructions	PH with unclear and/or multifactorial mechanisms
				
• Idiopathic/heritable • Associated conditions	• IpcPH • CpcPH	• Non-severe PH • Severe PH	• CTEPH • Other pulmonary obstructions	• Haematologic disorders • Systemic disorders
PREVALENCE	**65-80%**			
Rare	Very common	Common	Rare	Rare

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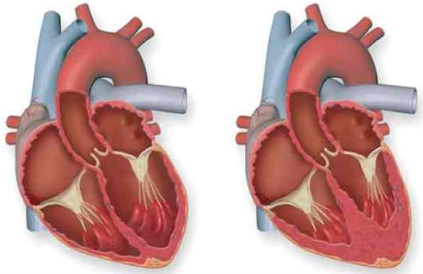
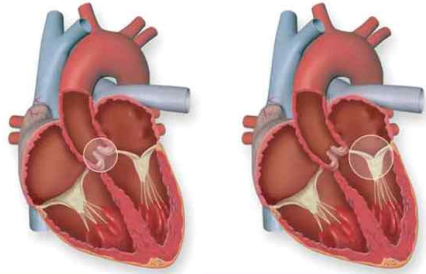
Heart failure/cardiomyopathy



HFrEF	HFmrEF	HFpEF
EF ≤40%	EF 41–49%	EF ≥50%

Valvular heart disease



Aortic valve Mitral valve

Stenosis/Regurgitation

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Pulmonary vascular resistance and clinical outcomes in patients with pulmonary hypertension: a retrospective cohort study

Primary cohort: n=40082, US Veterans Affairs health-care system (2007.10–2016.9)
Validation cohort: n=3699, Vanderbilt University Medical Center (1998.9–2016.6)

Median follow-up: p – 3.2 yrs (1153 days [IQR 570–1971]), v – 4.8 yrs (1752 days [IQR 1281-2999])

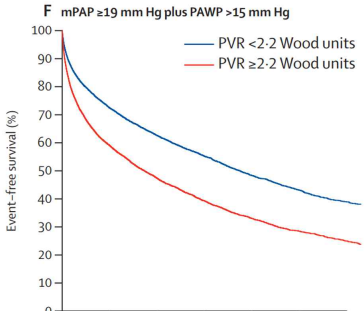
Hx. of HF 57.9%, COPD 33.3% (p)

mPAP ≥19 mmHg and PVR of ≥2.2 WU

	All-cause mortality in the primary cohort (N=32 275)			Heart failure hospitalisation in the primary cohort (N=32 275)			Composite outcome in the primary cohort (N=32 275)			All-cause mortality in the validation cohort (N=2870)		
	Adjusted HR (95% CI)	χ^2	p value	Adjusted HR (95% CI)	χ^2	p value	Adjusted HR (95% CI)	χ^2	p value	Adjusted HR (95% CI)	χ^2	p value
All PAWP	1·47 (1·42–1·53)	379·6	<0·0001	1·17 (1·11–1·24)	32·7	<0·0001	1·37 (1·32–1·42)	308·4	p<0·0001	1·58 (1·31–1·91)	22·6	<0·0001
PAWP >15 mm Hg	1·36 (1·29–1·42)	163·7	<0·0001	1·15 (1·08–1·23)	19·7	<0·0001	1·27 (1·22–1·32)	123·7	p<0·0001	1·44 (1·12–1·83)	8·4	0·0037
PAWP ≤15 mm Hg	1·71 (1·59–1·84)	214·0	<0·0001	1·27 (1·13–1·43)	16·2	0·0001	1·62 (1·52–1·73)	202·5	p<0·0001	1·81 (1·33–2·47)	14·0	0·0002

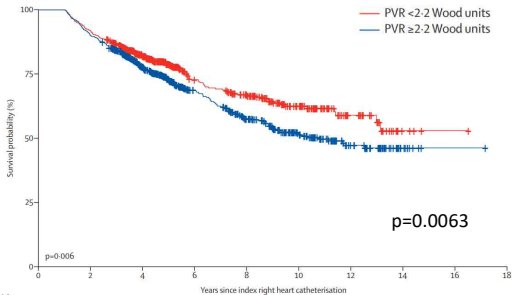
Lancet Respir Med 2020;8: 873–84

unadjusted mortality and HF hospitalization (primary cohort)



Number at risk (number censored)							
PVR<2·2 Wood units	11 040	7495	4897	3216	1946	1014	380
	(0)	(532)	(2222)	(3400)	(4329)	(5096)	(5657)
PVR ≥2·2 Wood units	9612	5322	3239	1971	1162	592	244
	(0)	(378)	(1523)	(2310)	(2846)	(3287)	(3583)

unadjusted mortality (validation cohort)



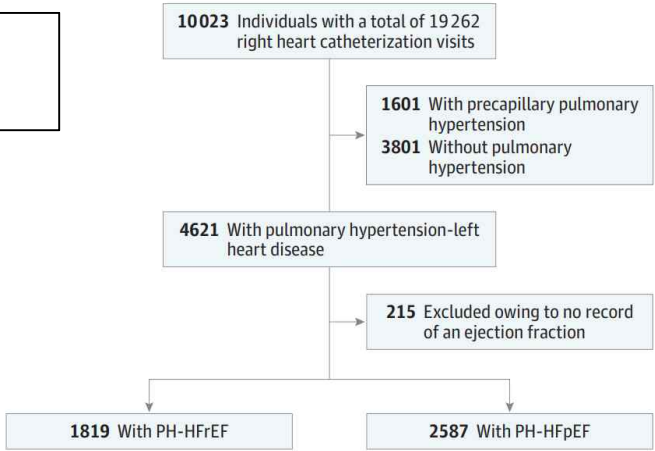
Number at risk (number censored)									
PVR<2·2 Wood units	581 (0)	534 (0)	370 (111)	180 (272)	145 (293)	85 (345)	33 (394)	4 (421)	1 (424)	0 (425)
PVR ≥2·2 Wood units	749 (0)	674 (0)	466 (124)	241 (305)	175 (333)	106 (387)	48 (438)	9 (476)	1 (484)	0 (485)

Lancet Respir Med 2020;8: 873–84

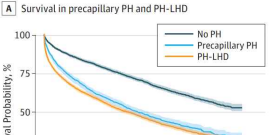
PH-LHD

Patients: n=10023
RHC from 2005.1-2012.9

Median follow-up: 4.3yrs (1.5-6.9)

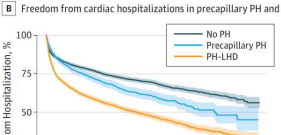


JAMA Cardiol. 2018;3(4):298-306



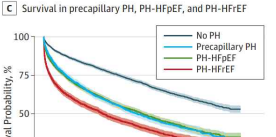
No. at risk

No PH	3792	3176	2569	1608	908	252
Precapillary PH	1595	1088	768	416	194	56
PH-LHD	4603	2909	2059	1237	571	121



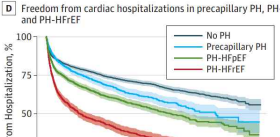
No. at risk

No PH	3807	2007	1225	637	253	
Precapillary PH	1600	650	314	128	32	
PH-LHD	4021	1390	674	301	87	



No. at risk

No PH	3792	3176	2569	1608	908	252
Precapillary PH	1595	1088	768	416	194	56
PH-HFpEF	2577	1735	1226	740	356	79
PH-HFrEF	1813	1028	727	424	176	32

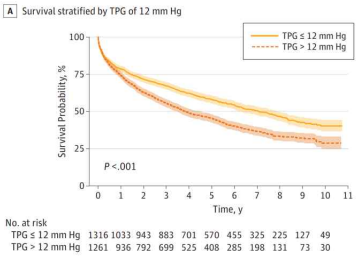


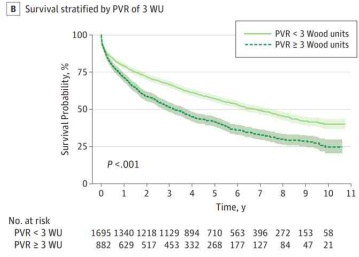
No. at risk

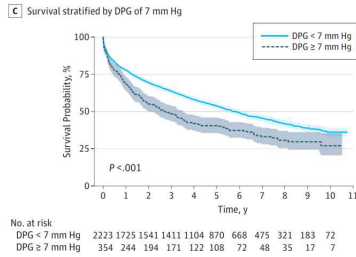
No PH	3807	2007	1225	637	253	
Precapillary PH	1600	650	314	128	32	
PH-HFpEF	2587	939	460	213	68	
PH-HFrEF	1819	390	184	70	14	

JAMA Cardiol. 2018;3(4):298-306

Elevated TPG, PVR, DPG : Increased Mortality in PH-HFpEF





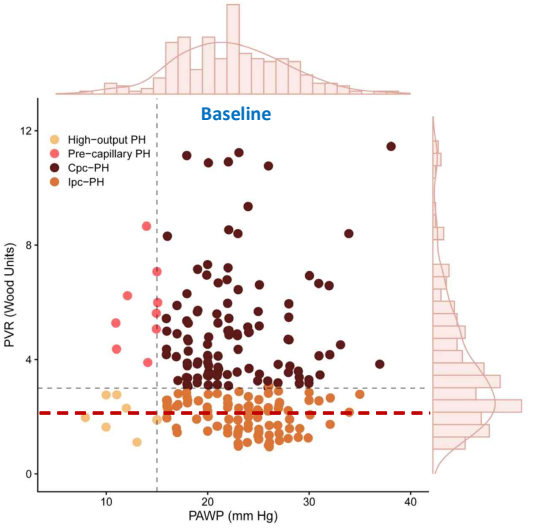


JAMA Cardiol. 2018;3(4):298-306

Persistent PH in Corrected VHD

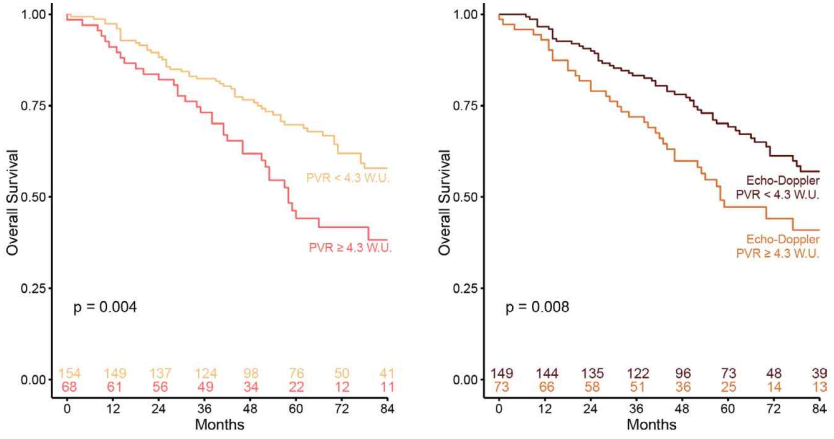
Patients: n=222
PH and VHD successfully corrected at least 1 year before

Median follow-up: 4.5 years



J Am Heart Assoc. 2021;10:e019949

Persistent PH in Corrected VHD



Compared with the Spanish age-matched population
the standardized mortality ratio was 4.21 (95% CI, 3.43–5.17; *P*<0.0001)

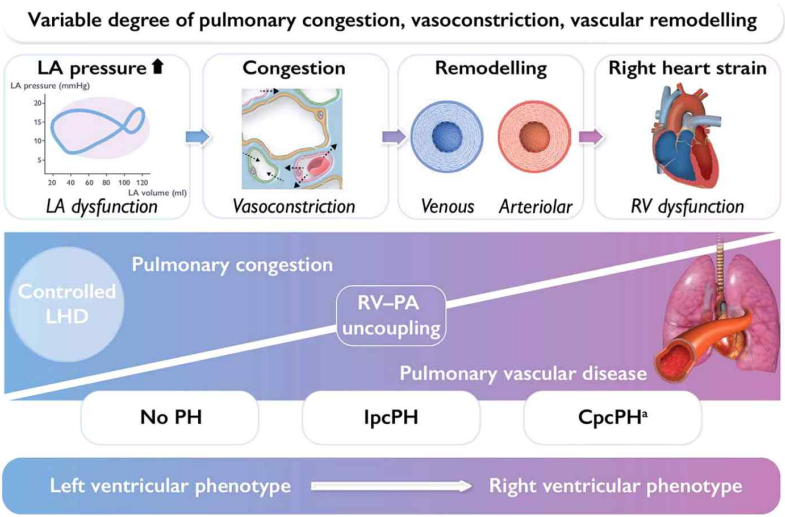
J Am Heart Assoc. 2021;10:e019949

Clinical significance of PH in HF

- RV is susceptible to pressure overload compared to LV
- PH : related with poor prognosis
- High PVR: consistent marker for poor prognosis

J Am Heart Assoc. 2021;10:e019949

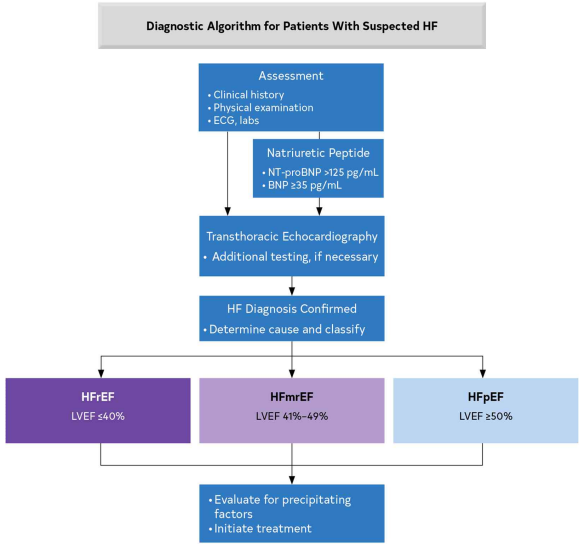
Pathophysiology of PH-LHD



2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

Diagnosis of PH-LHD

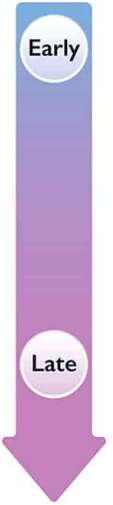
- Symptom: Non-specific
- Sign: Non-specific
- EKG
- Laboratory tests including BNP
- Echocardiography
- Right heart catheterization



2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension
2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure

Diagnosis of PH-LHD

- Symptom: Non-specific



Symptoms

- Dyspnoea on exertion (WHO-FC)
- Fatigue and rapid exhaustion
- Dyspnoea when bending forward (bendopnoea)
- Palpitations
- Haemoptysis
- Exercise-induced abdominal distension and nausea
- Weight gain due to fluid retention
- Syncope (during or shortly after physical exertion)

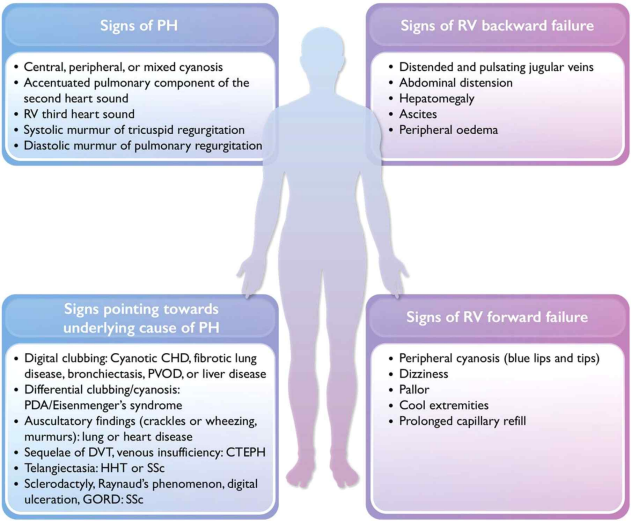
Rare symptoms due to pulmonary artery dilation[a]

- Exertional chest pain:
  dynamic compression of the left main coronary artery
- Hoarseness (dysphonia):
  compression of the left laryngeal recurrent nerve (cardiovocal or Ortner´s syndrome)
- Shortness of breath, wheezing, cough, lower respiratory tract infection, atelectasis:
  compression of the bronchi

2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

Diagnosis of PH-LHD

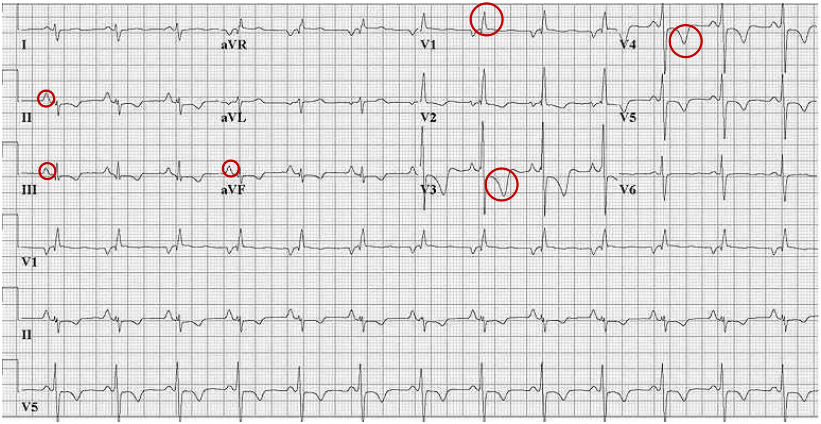
- Sign: Non-specific



2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

Diagnosis of PH-LHD

- ECG: Right axis deviation, P pulmonale, RV strain , RBBB



2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

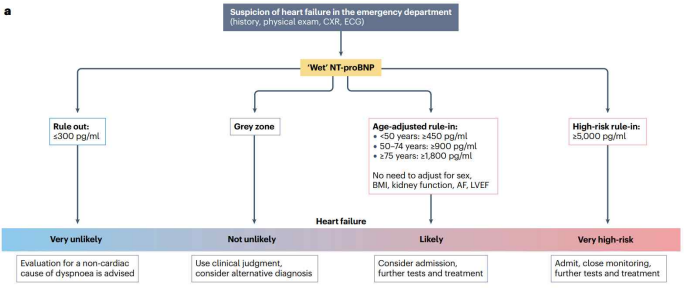
Diagnosis of PH-LHD

- Laboratory tests
  - CBC, UA, electrolytes, BUN, Creatinine, glucose, lipid profile, LFT, iron studies, TSH
  - BNP/NT-proBNP

Table 6. Selected Potential Causes of Elevated Natriuretic Peptide Levels[50–53]

Cardiac
HF, including RV HF syndromes
ACS
Heart muscle disease, including LVH
VHD
Pericardial disease
AF
Myocarditis
Cardiac surgery
Cardioversion
Toxic-metabolic myocardial insults, including cancer chemotherapy
Noncardiac
Advancing age
Anemia
Renal failure
Pulmonary: Obstructive sleep apnea, severe pneumonia
Pulmonary embolism, pulmonary arterial hypertension
Critical illness
Bacterial sepsis
Severe burns

2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure



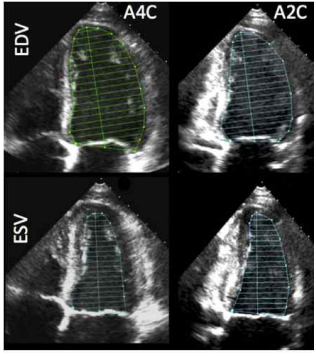
Nature Reviews Disease Primers volume 10, Article number: 55 (2024)

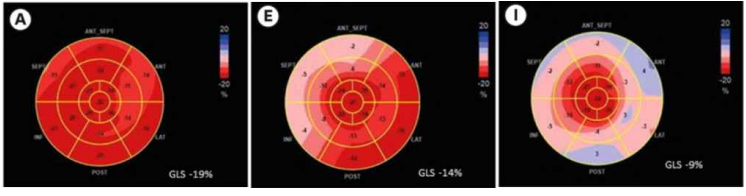
Diagnosis of PH-LHD : Echocardiography

- Left heart disease (LHD)
  - Chamber size and systolic function
  - LV diastolic function
  - Cardiomyopathy
- Valvular Heart Disease (VHD)
- Pulmonary hypertension : TR maximal velocity
- Rt. heart assessment : RA, RV, function

Diagnosis of PH-LHD : Echocardiography

- Left heart disease (LHD)
  - Chamber size
  - LV EF: HFrEF, HFmrEF, HFpEF
  - LV strain: peak GLS > 20% in healthy person
  - LV diastolic function
  - Cardiomyopathy



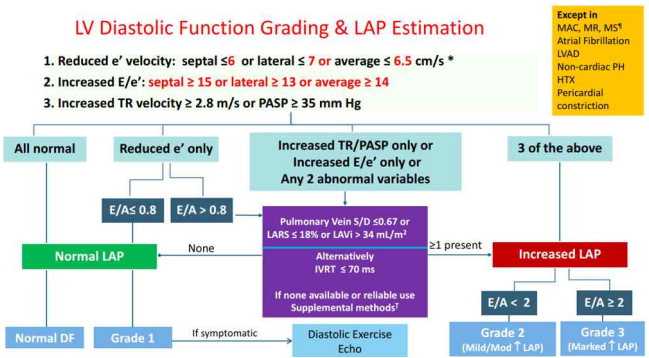


Diagnosis of PH-LHD : Echocardiography

- LHD - LV diastolic function
  - E, A, e', pulmonary vein flow
  - LA volume index
  - LA strain
  - LVH
  - PH - peak TR velocity

Table 6 Mitral annular e' velocity values for diagnosis of impaired LV relaxation

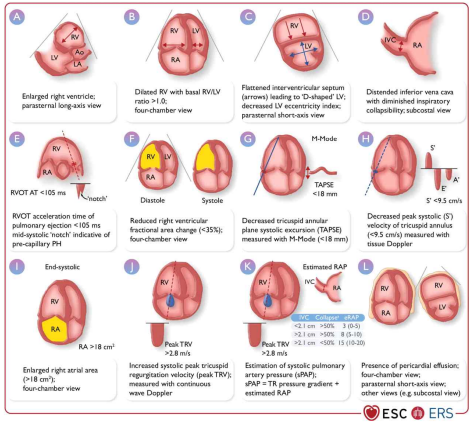
	20-39 y	40-65 y	>65 y
1. Septal e', cm/s	<7	<6	<6
2. Lateral e', cm/s	<10	<8	<7
3. Average e', cm/s	<9	<7	<6.5



2025 ASE Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography and for HFpEF Diagnosis

Diagnosis of PH-LHD : Echocardiography

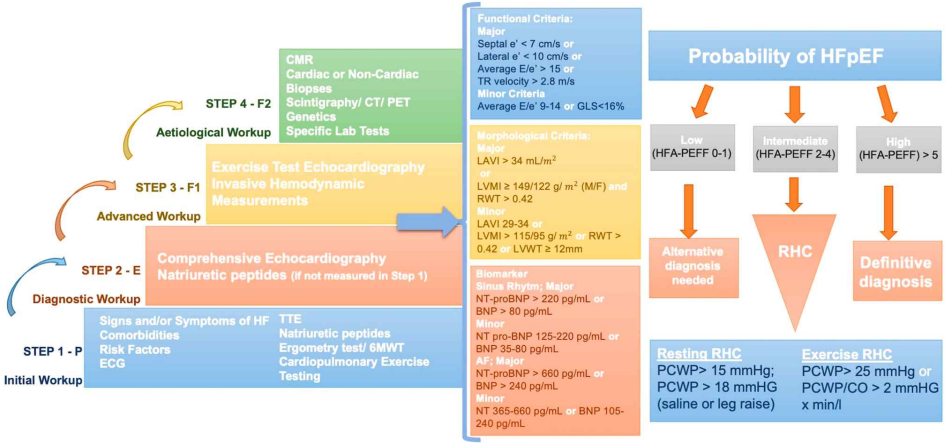
- Valvular heart disease (VHD)
- Pulmonary hypertension
  - Elevated sPAP
  - Rt. heart assessment



2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

Diagnosis of PH-LHD : HFpEF scores

- HFA-PEFF



European Heart Journal, Volume 40, Issue 40, 21 October 2019, Pages 3297–3317, Diagnostics 2024, 14(2), 136

Diagnosis of PH-LHD : HFpEF scores

- H2FPEF

	Clinical Variable	Values	Points
H_2	**H**eavy	Body mass index > 30 kg/m^2	2
	Hypertensive	2 or more antihypertensive medicines	1
F	Atrial **F**ibrillation	Paroxysmal or Persistent	3
P	**P**ulmonary Hypertension	Doppler Echocardiographic estimated Pulmonary Artery Systolic Pressure > 35 mmHg	1
E	**E**lder	Age > 60 years	1
F	**F**illing Pressure	Doppler Echocardiographic E/e' > 9	1
H_2FPEF score			Sum (0-9)

Circulation. 2018;138:861–870.

Feature	PH-LHD unlikely	Intermediate probability	PH-LHD likely
Age	<60 years	60–70 years	>70 years
Obesity, hypertension, dyslipidaemia, glucose intolerance/diabetes	No factors	1–2 factors	>2 factors
Presence of known LHD	No	Yes	Yes
Previous cardiac intervention	No	No	Yes
Atrial fibrillation	No	Paroxysmal	Permanent/persistent
Structural LHD	No	No	Present
ECG	Normal or signs of RV strain	Mild LVH	LBBB or LVH
Echocardiography	No LA dilation E/e' <13	No LA dilation Grade <2 mitral flow	LA dilation (LAVI >34 mL/m^2) LVH Grade >2 mitral flow
CPET	High VE/VCO_2 slope No EOV	Elevated VE/VCO_2 slope EOV	Mildly elevated VE/VCO_2 slope EOV
cMRI	No left-heart abnormalities		LVH LA dilation (strain or LA/RA >1)

2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

Diagnosis of PH-LHD

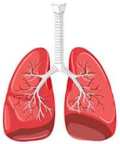
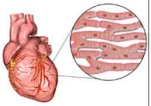
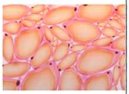
Invasive assessment of hemodynamics - RHC

- Indications for RHC in LHD
  - Suspected PAH or CTEPH
  - Suspected CpcPH with a severe pre-capillary component, where further information will aid phenotyping and treatment decisions
  - Advanced HF and evaluation for heart transplantation
  - LHD with a high likelihood of PH-LHD and normal resting PAWP
    - Exercise testing and fluid challenge

Treatment of PH-LHD

- The primary strategy
  - Treat the underlying cardiac disease
- Optimize GDMT
  - HFrEF: ARNI/ACEi (ARB), beta-blocker, MRA, SGLT2i
  - HFpEF: Tx. underlying disease, SGLT2i
- Correct structural lesions: MR, AS
- Manage comorbidities: HTN, AF, obesity (GLP1 receptor agonist)
- Diuretics : in the presence of fluid retention, ↓PAP and RV afterload

Treatment of PH-LHD

		Pulmonary vasculature	Miocardium	Adipose tissue	Kidney
	Mechanism of action				
SGLT2 inhibitors	Reduce renal tubular glucose reabsorption, producing a reduction in blood glucose without stimulating insulin release	Reduce PA pressure and adverse remodelling	Reduce right ventricle systolic and diastolic pressures and adverse remodelling	Improve insulin sensitivity	Enhance diuresis
GLP1 agonists	Mimic the action of GLP-1	Reduce inflammation, fibrosis and adverse remodelling	Improve RV function, reduce inflammation, reduce adverse remodelling	Improve insulin sensitivity, weight loss and brown fat thermogenesis	
ANRI	Inhibit the RAAS and promotes the functioning of natriuretic peptides	Reduce PA pressure and adverse remodelling	Reduce RV pressure and adverse remodelling	Might improve insulin sensitivity	Enhance natriuresis and diuresis

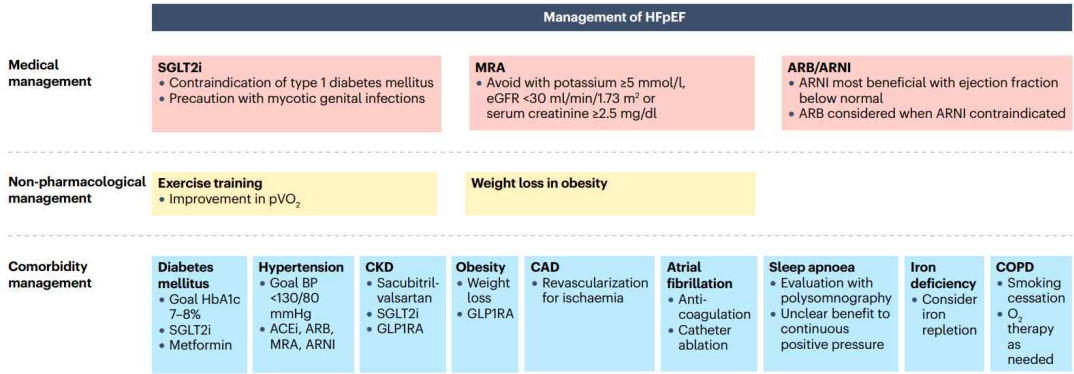
European Journal of Internal Medicine 129 (2024) 1–15

Treatment of PH-LHD

- ESC Guidelines recommendations on GLP-1 receptor agonist (GLP-1RA)
  - Overweight or obese patients with T2DM to reduce weight (Class IIa)
- GLP-1 RAs with proven CV benefit
  - liraglutide, semaglutide s.c., dulaglutide, efpeglenatide
  - recommended in T2DM and ASCVD to reduce CV events
  - independent of baseline or target HbA1c (Class I)
- GLP-1 RA semaglutide
  - in overweight (BMI >27 kg/m^2) or obese chronic coronary syndrome patients without diabetes to reduce CV mortality, MI, or stroke. (Class IIa)

2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes

Treatment of PH-LHD



Nature Reviews Disease Primers volume 10, Article number: 55 (2024)

Treatment of PH-LHD

- PH contributes to RV dysfunction and HF symptoms
- PAH-targeted drugs tested (PDE5i, ERAs, prostacyclins)
- Key trials
  - RELAX (sildenafil in HFpEF): no benefit
  - PASSION (tadalafil in HFpEF + PH): early stop, no benefit
  - ENABLE (bosentan in HFrEF): no benefit, safety concerns
- Risks: systemic hypotension, pulmonary edema
- Current stance: Do not use PAH drugs in Group 2 PH

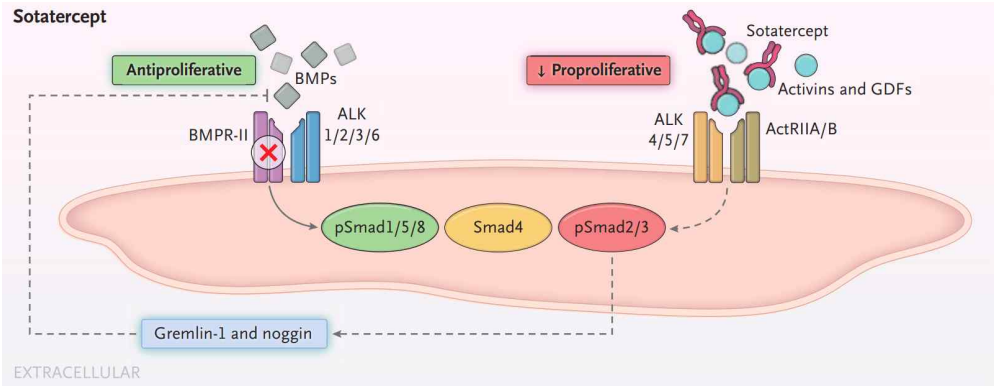
Trials of PDE5 inhibitor in HF

Medication/device	Dose	Duration	Sample size	Inclusion	Primary endpoint	Results
PDE5i						
Sildenafil[32]	50 mg tid	24 weeks	44	HFpEF (LVEF ≥50%)	Pulmonary hemodynamics and RV performance in 1-year	Significant improvements in mPAP and RV function
Sildenafil (RELAX trial)[33]	20 mg tid	12 weeks	216	HFpEF (LVEF ≥50%)	Change in peak oxygen consumption after 24 weeks	No significant improvement
Sildenafil[34]	60 mg tid	12 weeks	52	HFpEF (LVEF ≥45%)	Change in mPAP after 12 weeks	No significant improvement
Sildenafil (SIOVAC trial)[35]	40 mg tid	6 months	200	Persistent PH after surgical correction of VHD	Composite clinical score	Worsening in clinical outcomes
Sildenafil[36]	100 mg daily	68±58 days	6	HTPL candidates with CpcPH	PVR	Sildenafil lowers PVR in HTPL candidates with CpcPH
Sildenafil[37]	75 mg tid	12 to 15 weeks	58 (26 in sildenafil + LVAD; 32 in LVAD control)	Post-LVAD patients with persistent CpcPH	12 to 15 weeks change in PVR and dP/dtmax/IP	Significant decrease in PVR
Sildenafil[38]	140 mg/day	163 days	119	CpcPH patients with scheduled HTPL	mPAP, PVR, and TPG	Improved pulmonary hemodynamics with sildenafil + HTPL compared with HTPL without sildenafil

Inconsistent results across trials

Int J Heart Fail. 2021 Jul;3(3):147-159

Sotatercept



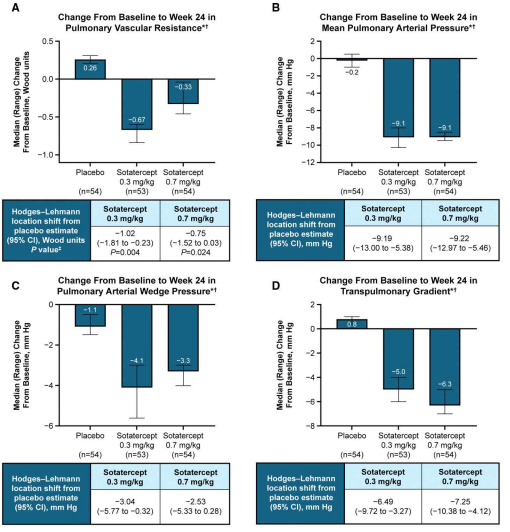
N Engl J Med 2021;384:1204-15

Sotatercept for CpcPH (CADENCE study)

Design: Phase 2, RCT
Patients: n=164

Baseline median
- NTproBNP 1119 pg/mL
- PVR 5.2 WU
- mPAP 43 mmHg
- PAWP 21 mmHg

Median follow-up: 24 weeks



Circulation. 2026 May 12;153(19):1446-1459.

Summary

- PH-LHD
  - PH-LHD is the most common form of PH
  - with or without pulmonary vascular remodeling : IpcPH, CpcPH
- Diagnosis: Comprehensive approach
- Treatment
  - GDMT and comorbidity treatment
  - PAH specific drug for PH-LHD: not proven, could be harmful
  - Further investigation with new therapeutic options i.e.) Sotatercept