# Management of PH in patients with HFrEF and HFpEF

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**Cardiology Department**

# Pulmonary hypertension

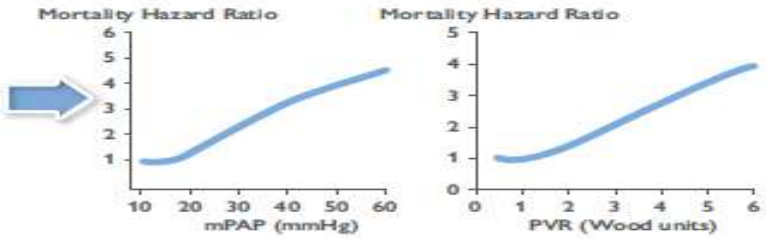
Prevalence

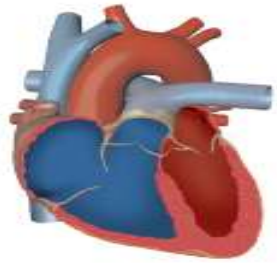
1%

Global population

Pulmonary congestion in post-capillary PH

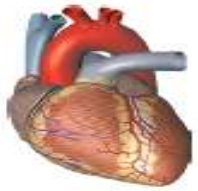
Pulmonary vascular disease / obstruction in pre-capillary PH



Right heart failure

## Clinical Classification

| 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<br>• Associated conditions | • IpcPH<br>• CpcPH | • Non-severe PH<br>• Severe PH | • CTEPH<br>• Other pulmonary obstructions | • Haematologic disorders<br>• Systemic disorders |

## Prevalence

| Rare | Very common | Common | Rare | Rare |
|---|---|---|---|---|
|  |  |  |  |  |

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

From a hemodynamic standpoint, pulmonary pressure can increase from the action of three mechanisms:

- increased cardiac output,
- increased left atrial pressure
- constriction and/or remodeling and/or thrombosis and/or embolism of pulmonary arteries.

# HFrEF and HFpEF: elevated LAP is the primary factor of the increased mPAP

# The pathophysiology of PH-LHD

1. An initial passive increase in LV filling pressures and

backward transmission into the pulmonary circulation

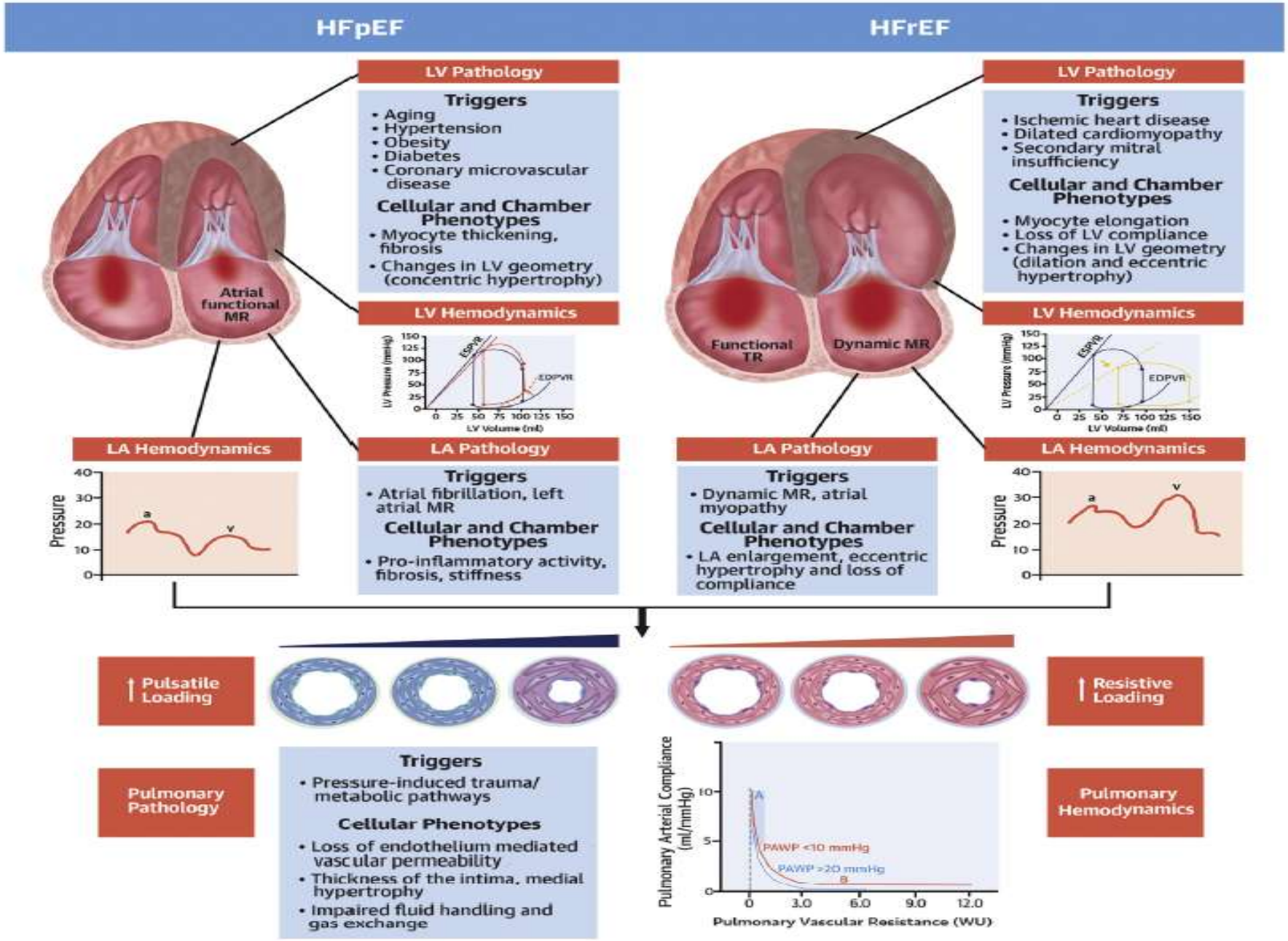
2. PA endothelial dysfunction (including vasoconstriction)

3. Vascular remodelling (which may occur in both venules and/or arterioles)

4. RV dilatation/dysfunction and functional TR

5. Altered RV–PA coupling

PH in HFrEF
40%-72%
PH in HFpEF
36%-83%




Guazzi, M. et al. J Am Coll Cardiol. 2020;76(9):1102-11.

# PH-LHD: mPAP > 20 mmHg ,PAWP >15 mmHg

**PVR ≤ 2 WU**

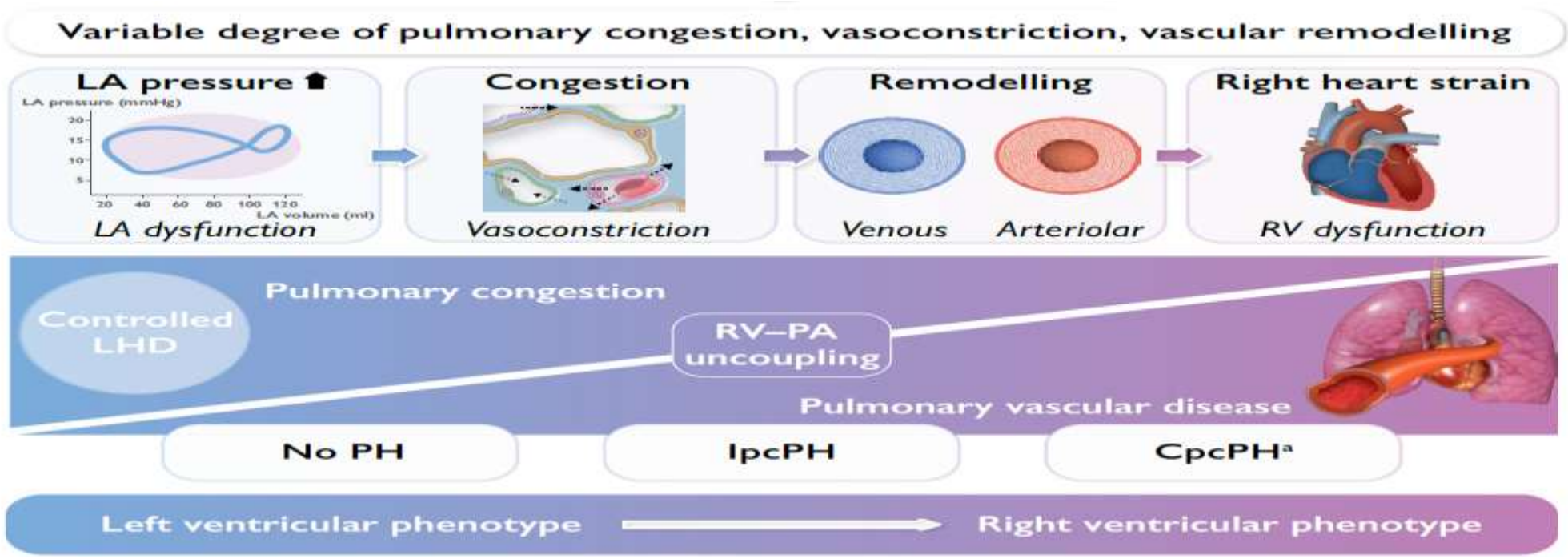
**isolated post-capillary pulmonary hypertension(IpcPH)**

PH results from the passive backwards transmission of elevated LAP

**PVR > 2 WU**

**combined post- and pre-capillary pulmonary hypertension (CpcPH)**

The addition of pulmonary vascular constriction or remodeling to passive PH



# Diagnosis of PH-LHD

1. Diagnosis and control of the underlying LHD
2. Evaluation for PH and patient phenotyping
3. Invasive haemodynamic evaluation, when indicated

# Diagnosis of PH-LHD

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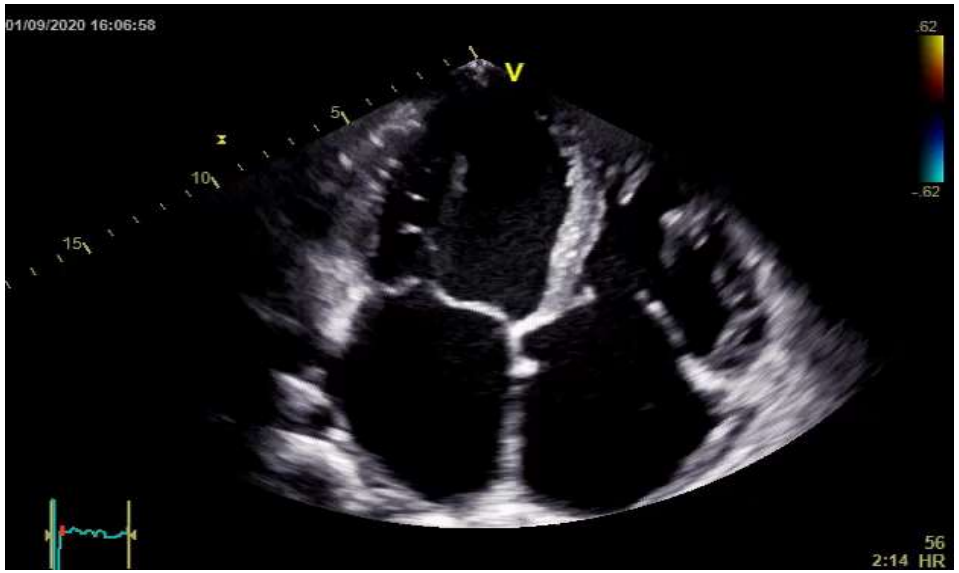
# HFrEF-PH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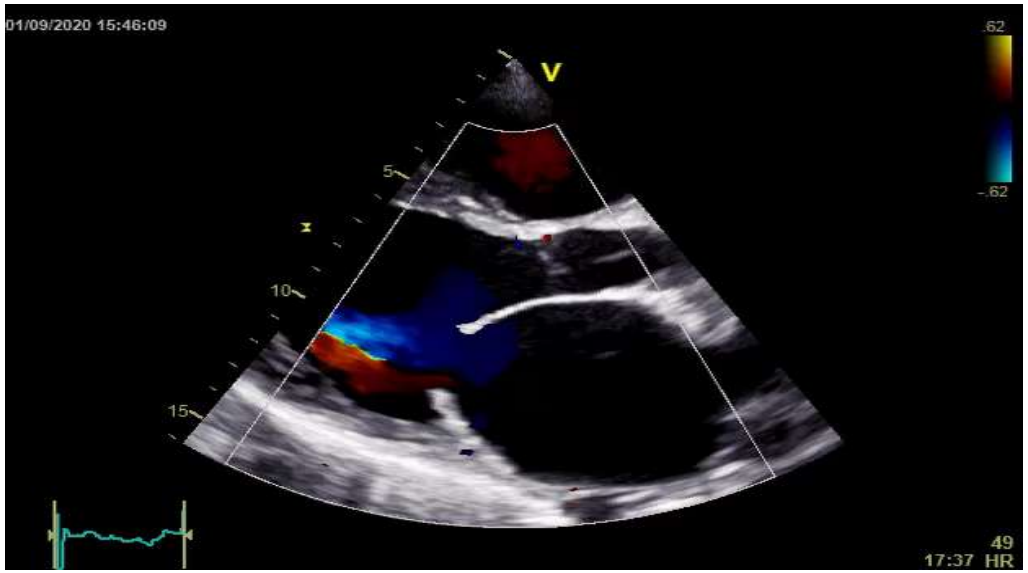
56
2:14 HR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49
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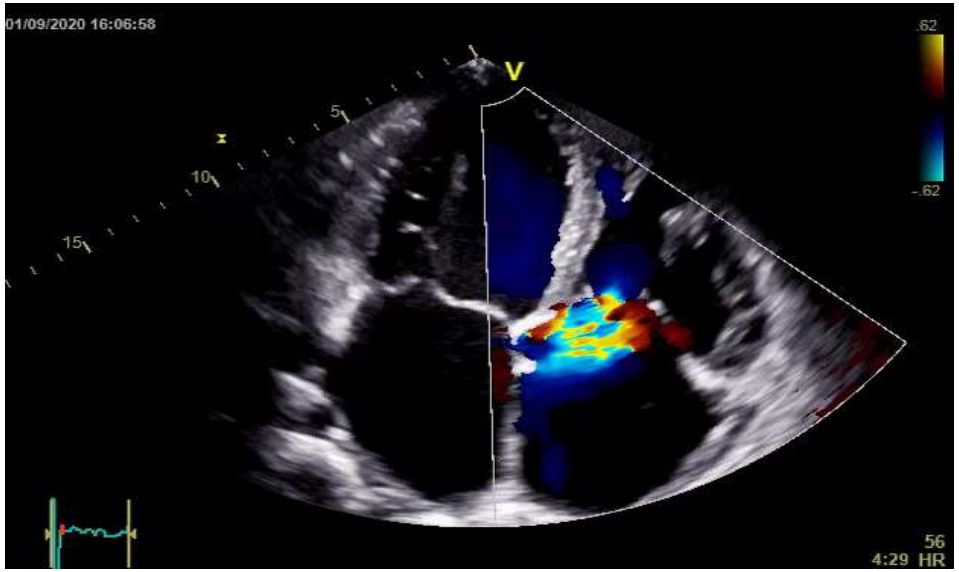
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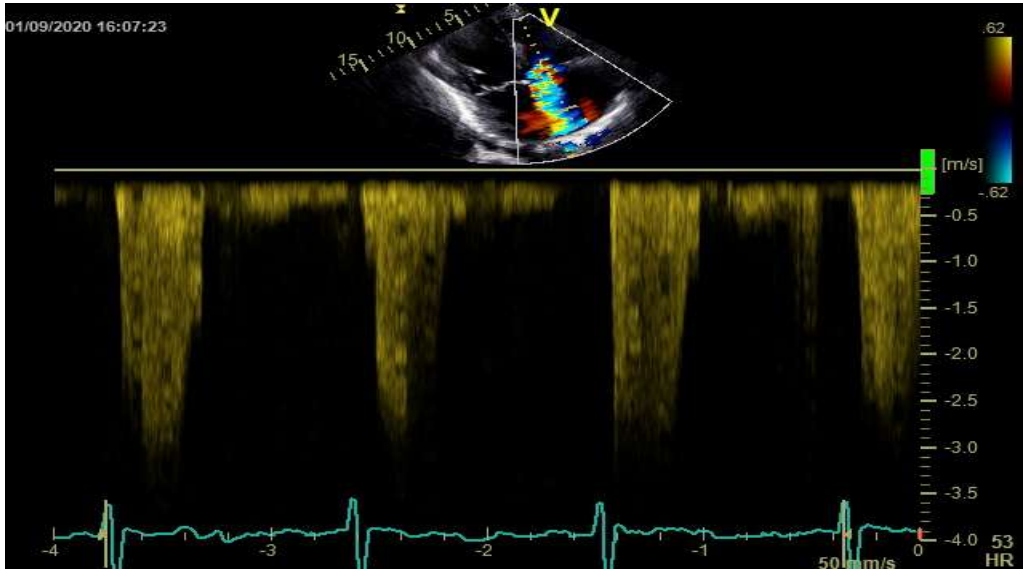
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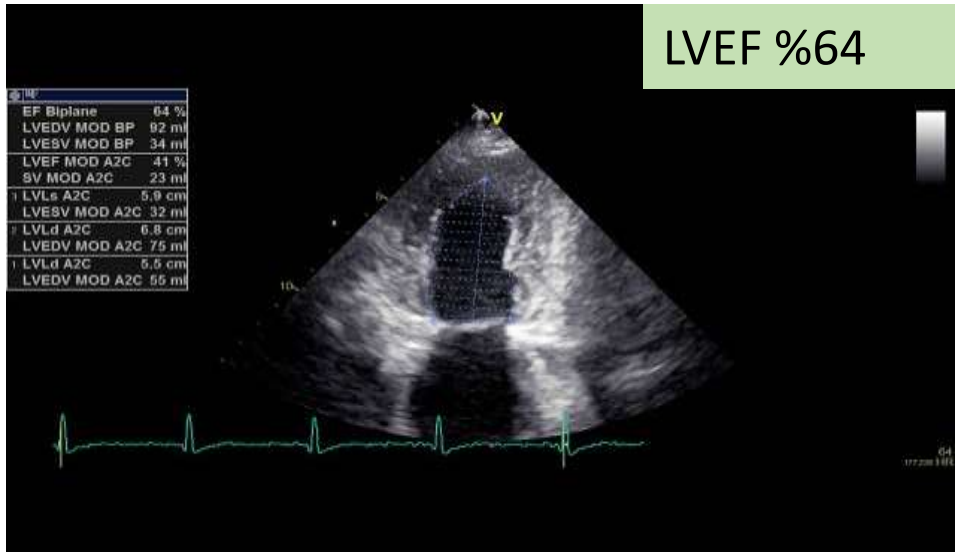
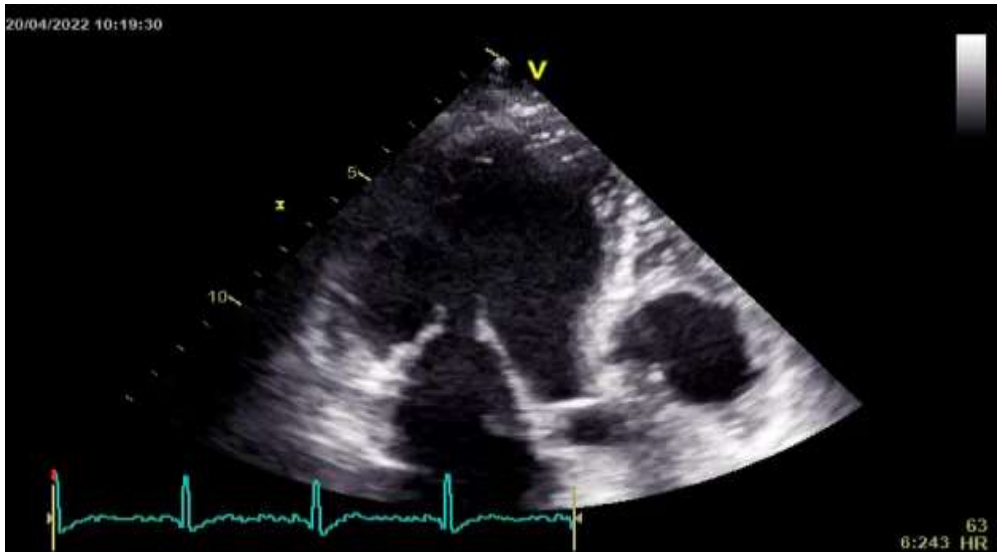
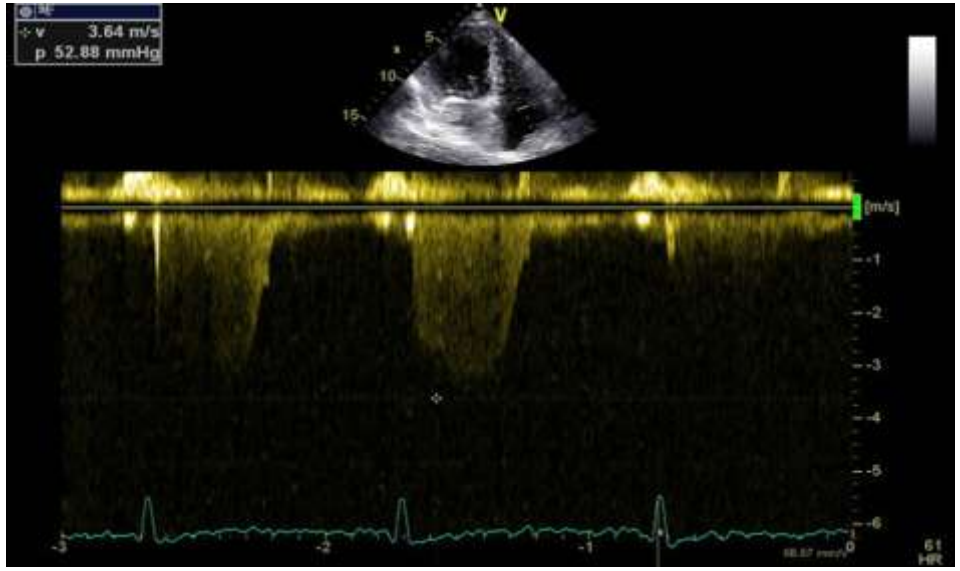
.62
[m/s]
-.62
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
-3.5
-4.0
53
HR

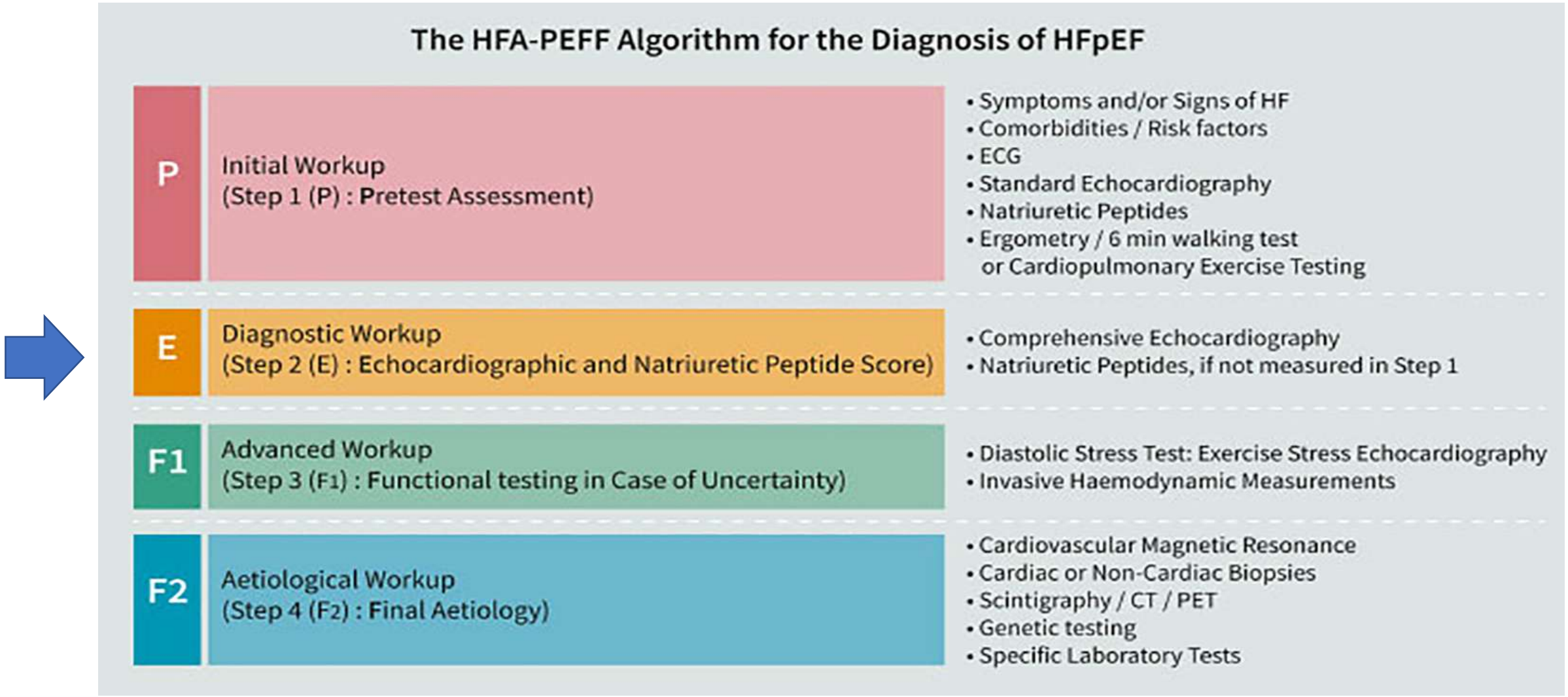
# HFpEF




TY vel: 3,6 m/s, PSAP: 55 mmHg




HFA-PEFF: Heart Failure Association-Preserved Ejection Fraction Failure

Pieske B, et al. European Journal of Heart Failure (2020) 22, 391–412

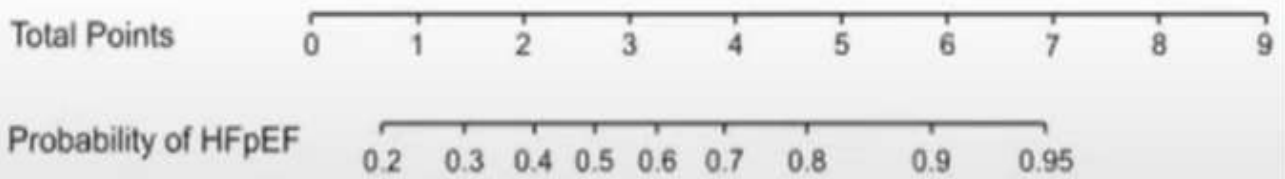
**HFA–PEFF skoru**

| | Functional | Morphological | Biomarker (SR) | Biomarker (AF) |
|---|---|---|---|---|
| Major | septal e' < 7 cm/s or lateral e' < 10 cm/s<br>or<br>Average E/e' ≥ 15<br>or<br>TR velocity > 2.8 m/s (PASP > 35 mmHg) | LAVI > 34 ml/m²<br>or<br>LVMI ≥ 149/122 g/m² (m/w) and RWT > 0,42 # | NT-proBNP > 220 pg/ml<br>or<br>BNP > 80 pg/ml | NT-proBNP > 660 pg/ml<br>or<br>BNP > 240 pg/ml |
| Minor | Average E/e' 9 -14<br>or<br>GLS < 16 % | LAVI 29-34 ml/m²<br>or<br>LVMI > 115/95 g/m² (m/w)<br>or<br>RWT > 0,42<br>or<br>LV wall thickness ≥ 12 mm | NT-proBNP 125-220 pg/ml<br>or<br>BNP 35-80 pg/ml | NT-proBNP 365-660 pg/ml<br>or<br>BNP 105-240 pg/ml |

| | |
|---|---|
| Major Criteria: 2 points | ≥ 5 points: HFpEF |
| Minor Criteria: 1 point | 2-4 points: Diastolic Stress Test or Invasive Haemodynamic Measurements |

# $H_2$FPEF score

| | Clinical Variable | Values | Points |
|---|---|---|---|
| $H_2$ | Heavy | Body mass index > 30 kg/m$^2$ | 2 |
| | Hypertensive | 2 or more antihypertensive medicines | 1 |
| F | Atrial Fibrillation | Paroxysmal or Persistent | 3 |
| P | Pulmonary Hypertension | Doppler Echocardiographic estimated Pulmonary Artery Systolic Pressure > 35 mmHg | 1 |
| E | Elder | Age > 60 years | 1 |
| F | Filling Pressure | Doppler Echocardiographic E/e' > 9 | 1 |
| | $H_2$FPEF score | | Sum (0-9) |




- Dyspnea on exertion, normal EF
- HFpEF vs. non-cardiac dyspnea?
- Intermediate pre-test probability

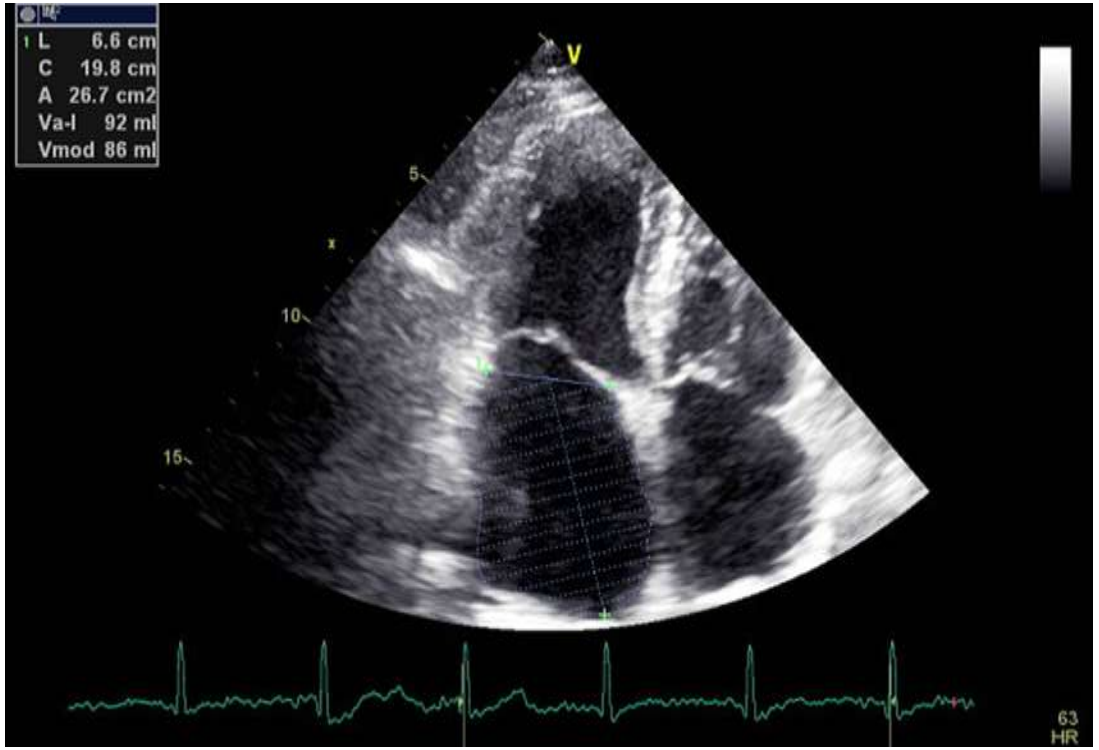
Nomogram below table for probability of HFpEF based on score:

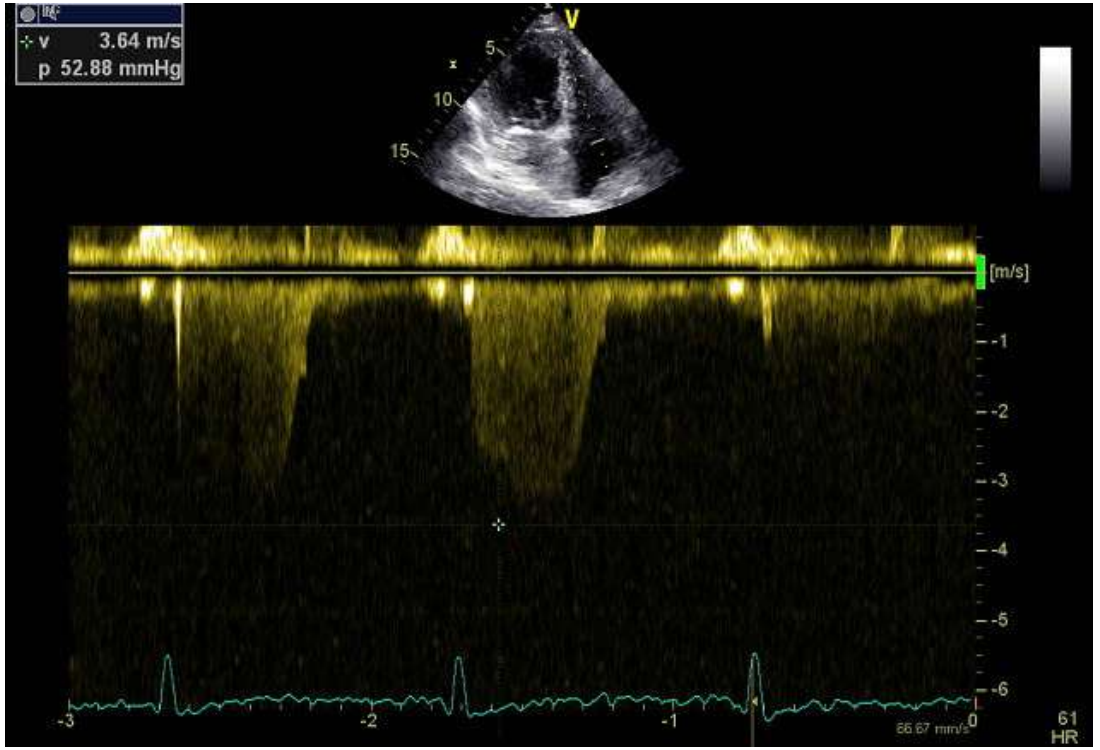
- A score of 4 or higher = 70% probability of HFpEF
- A score of 5 or higher = >80% probability of HFpEF
- A score of 7 or higher = >95% probability of HFpEF

Reddy YN…Borlaug BA. *Circulation* 2018

Hastanın LAVI: 42,4 mL/m2

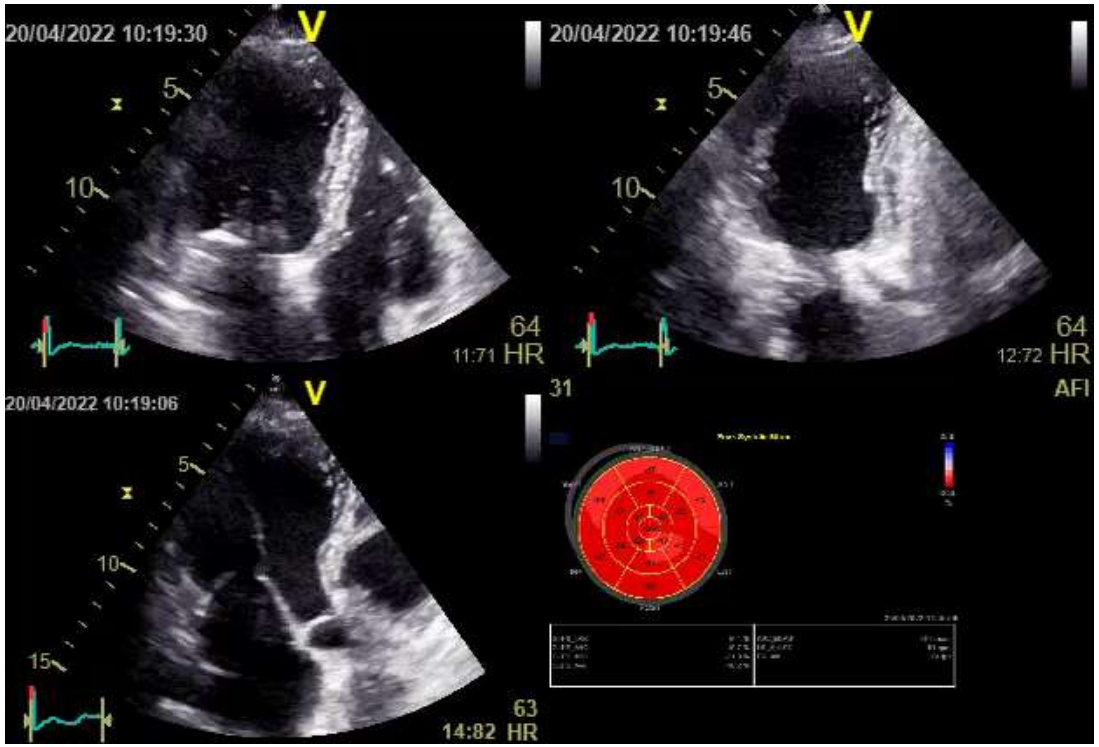
Hastanın TY vel: 3,6 m/s,
PSAB: 55 mmHg

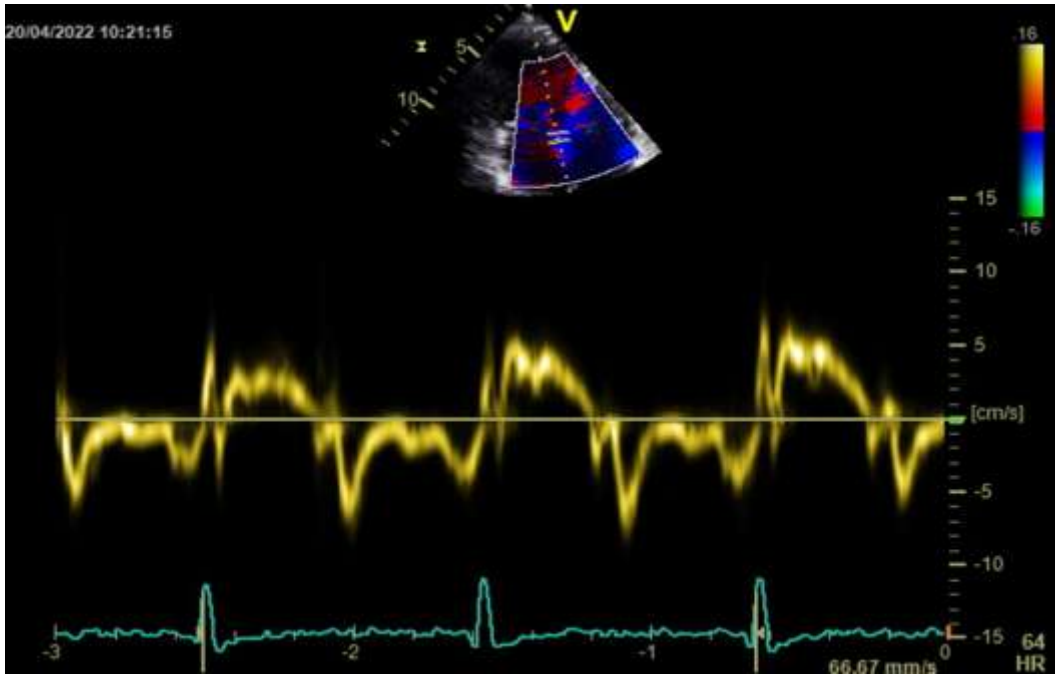


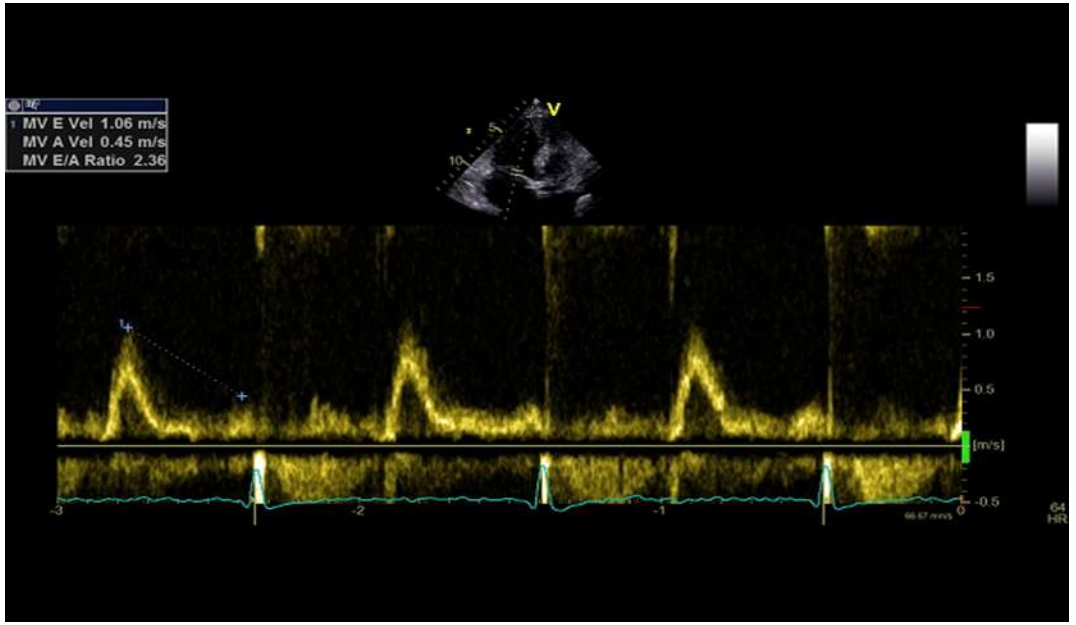



Hastanın sol ventrikül GLS: -%16

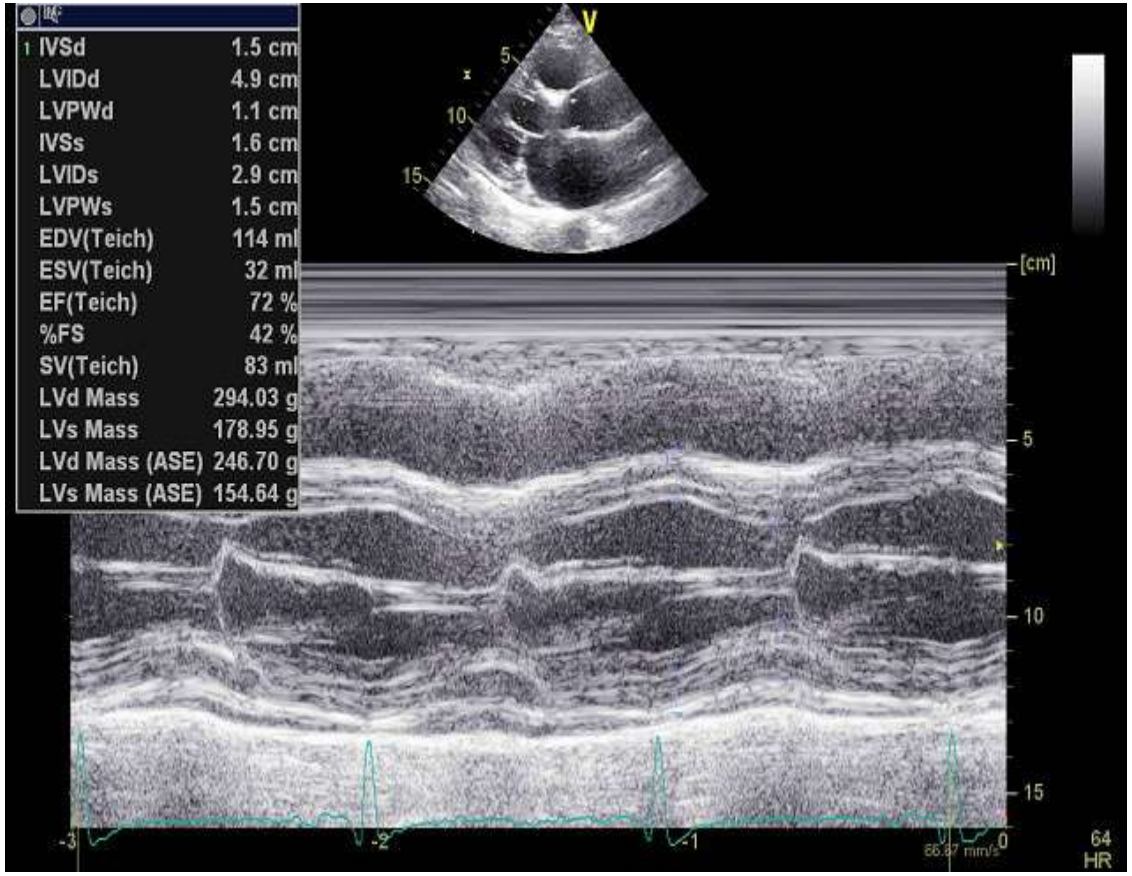
E/e’ oranı: 15



Hastanın LVMI : 121 g/m2, RWT: 0,44




Hastanın pro-BNP: 1078 pg/ml

**HFA–PEFF skoru**

E/e' oranı: 15

Hastanın TY vel: 3,6 m/s, PSAB: 55 mmHg

Hastanın sol ventrikül GLS: -%16

Hastanın LAVI: 42,4 mL/m2

Hastanın LVMI : 121 g/m2, RWT: 0,44

Hastanın pro-BNP: 1078 pg/ml

**Hastanın HFA-PEFF skoru: 6**

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# Diagnosis of PH-LHD

1. Diagnosis and control of the underlying LHD
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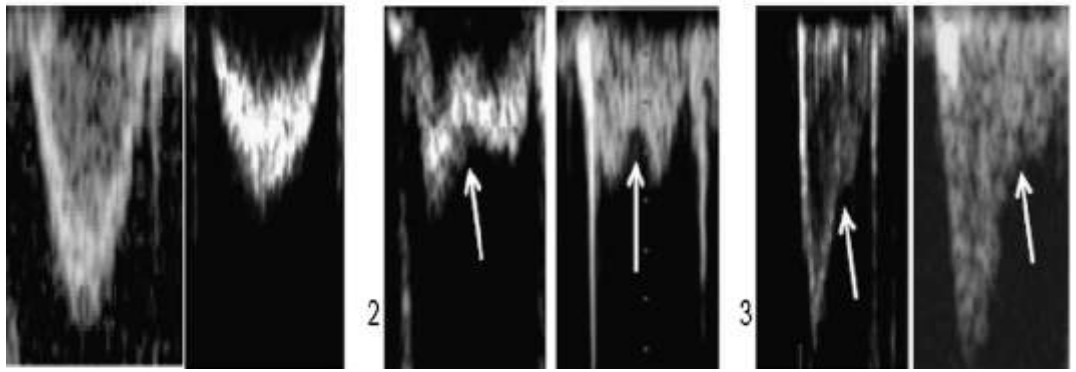
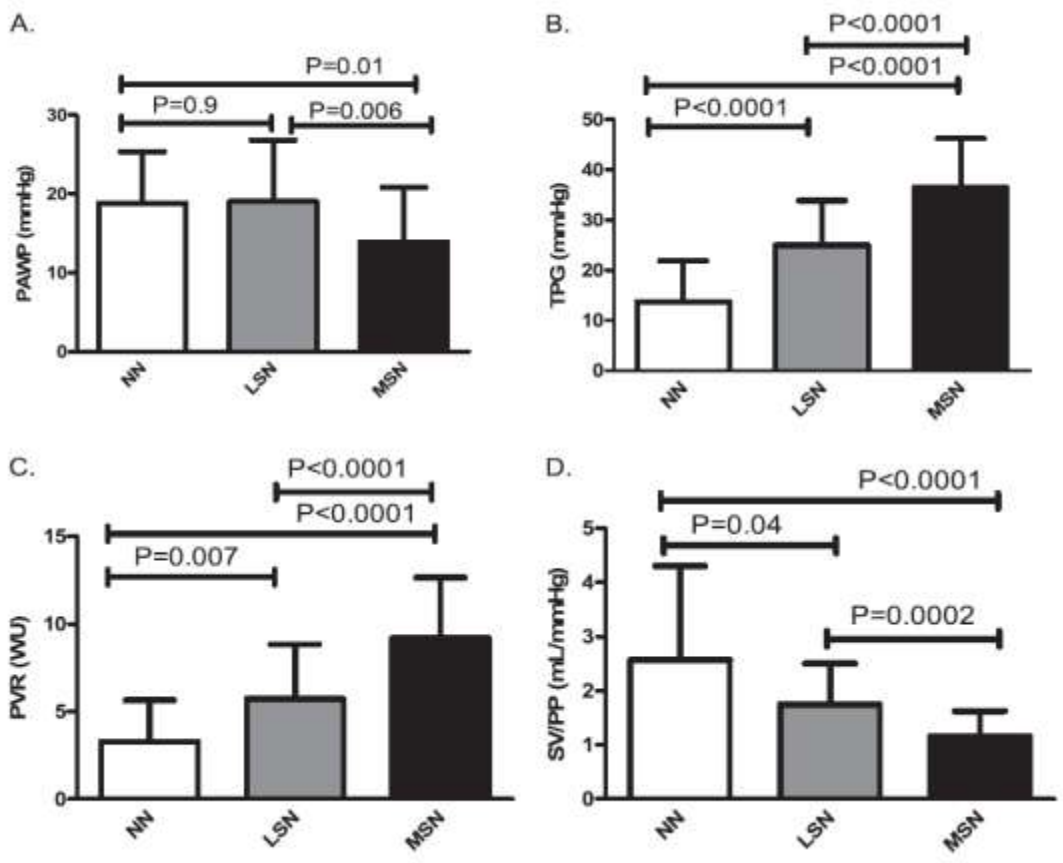
# Shape of the Right Ventricular Doppler Envelope Predicts Hemodynamics and Right Heart Function in PH

no notch  mid-systolic notch  late-systolic notch




- 88 pt (28 pts group I, 22 pts group II, 30 pts group III, 4 group V)
- A notched RVDE was highly associated with PH and a PVR > 3 WU, whereas its absence (NN) predicted PH with a PVR ≤ 3 WU and a PAWP > 15 mm Hg



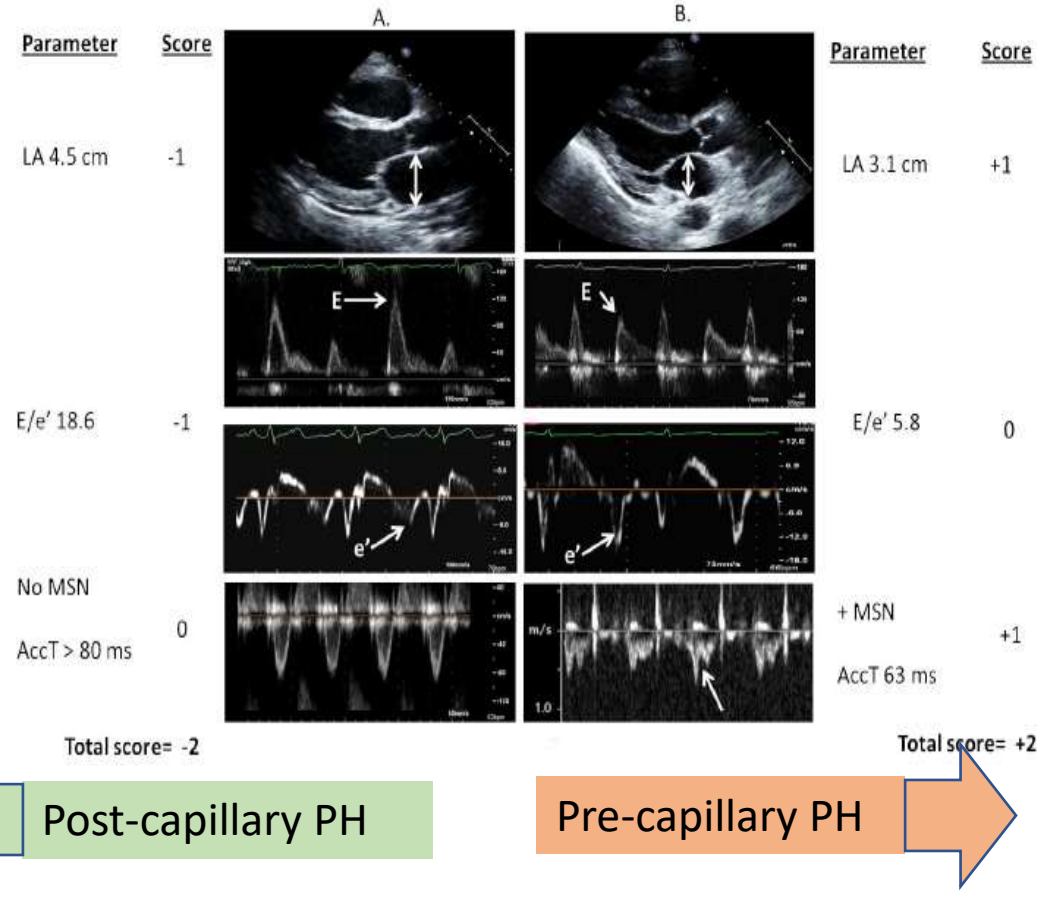

Arkles J.S. Et al; Am J Resp Crit Care Med, 2011

# Opotowsky Score

The Echocardiographic Score

| Echocardiographic Parameter | If Present |
|---|---|
| E:e′ >10 | −1 |
| Left atrial AP dimension>4.2cm | −1 |
| Left atrial AP dimension<3.2cm | +1 |
| RVOT PW Doppler mid-systolic notch or acceleration time<80msec | +1 |

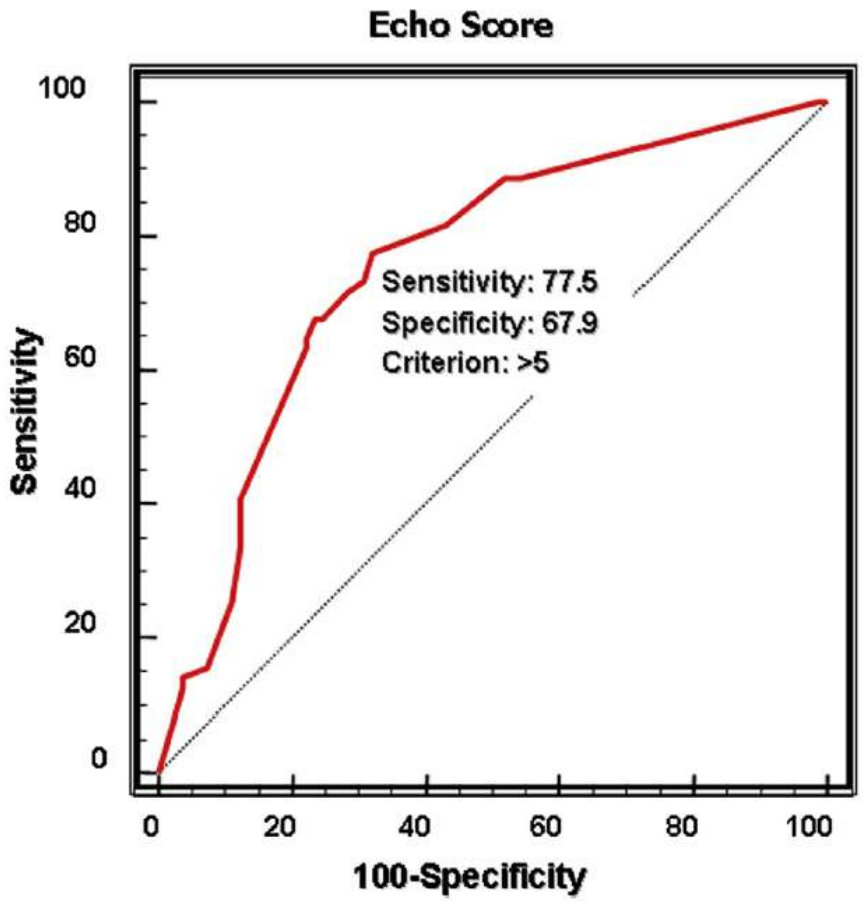
152 patients

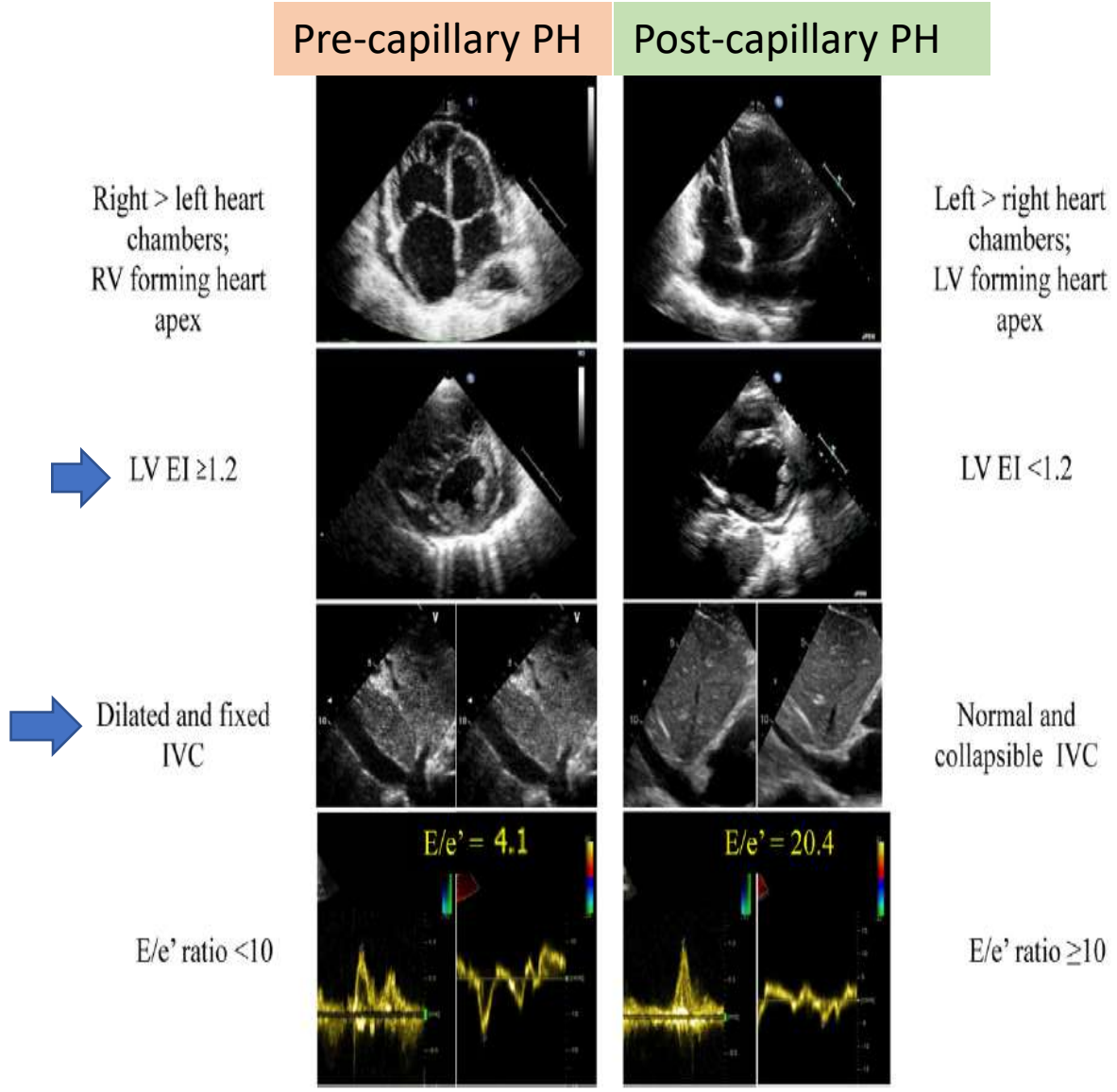



Opotowsky A.R. et al; Circ Cardiovasc Imaging. 2012; 5: 765–775

# D'Alto Score

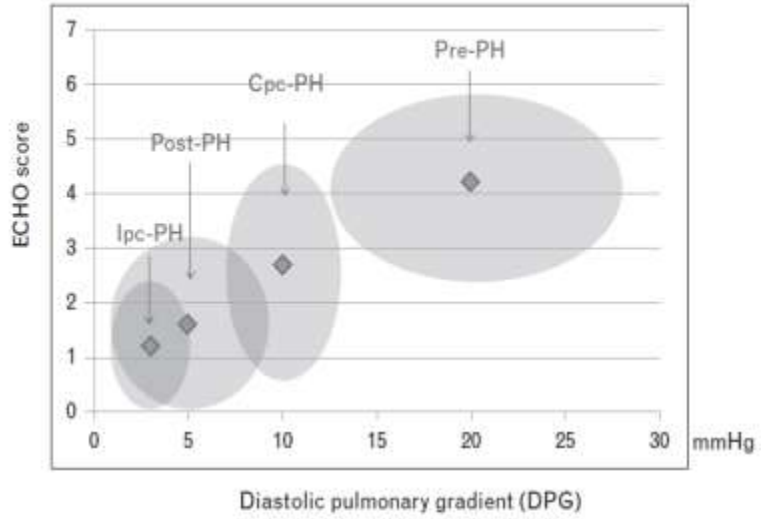
## For precapillary PH



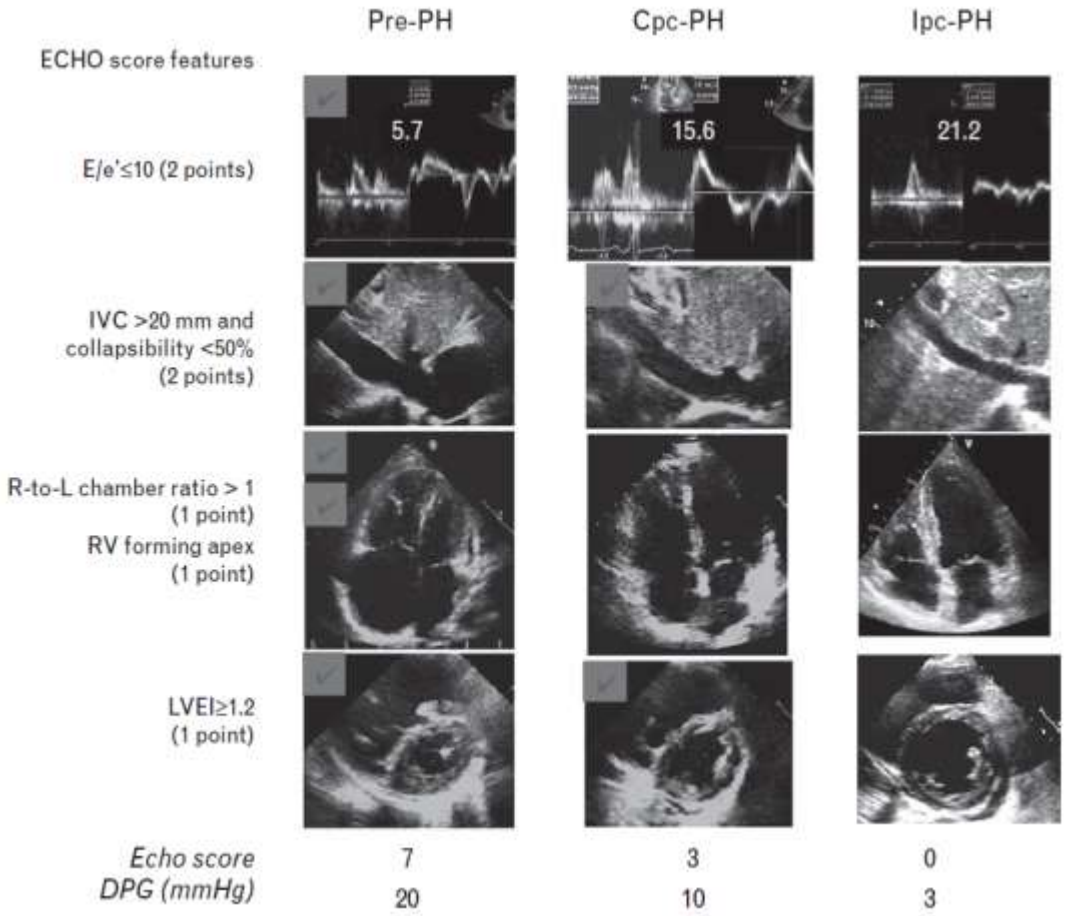




D'Alto M, et al; Am Soc Echocardiogr 2015;28:108-15.

# New simplified D'Alto score




| | Total ($n$ = 230) | Pre-PH ($n$ = 160) | Post-PH ($n$ = 70) | Ipc-PH ($n$ = 51) | Cpc-PH ($n$ = 19) | P (Pre-vs post-PH) | P (Ipc-PH vs Cpc-PH) |
|---|---|---|---|---|---|---|---|
| DPG | 15±10 | 20±8 | 5±4 | 3±2 | 10±3 | <0.000001 | <0.000001 |
| Echo-score | 3.4±2.1 | 4.2±1.7 | 1.6±1.7 | 1.2±1.3 | 2.7±2.1 | <0.000001 | 0.0004 |




The sensitivity and specificity of the echo score at least 2 for precapillary pulmonary hypertension were 99 and 54%, respectively

D'alto M.et al; J Cardiovasc Med 2017, 18:237–243

# Echocardiographic distinction between precapillary and postcapillary PH

| Pre-capillary PH | PH-LHD |
|---|---|
| Normal sized or small LV cavity | Normal sized or dilated LV cavity |
| No LV hypertrophy | LV hypertrophy |
| Preserved LVEF | Variable LVEF |
| Normal sized or small left atrium | Dilated left atrium |
| Grade I LV diastolic dysfunction or normal LV diastolic function | ≥ Grade II LV diastolic dysfunction |
| Presence of mid-systolic notching | Absence of mid-systolic notching |
| RV/LV ratio > 1 | RV/LV ratio < 1 |
| PASP > 70 mmHg | Typically PASP < 70 mmHg |
| Pericardial effusion | No pericardial effusion |
| No mitral and/or aortic valve disease | Mitral and/or aortic valve disease |

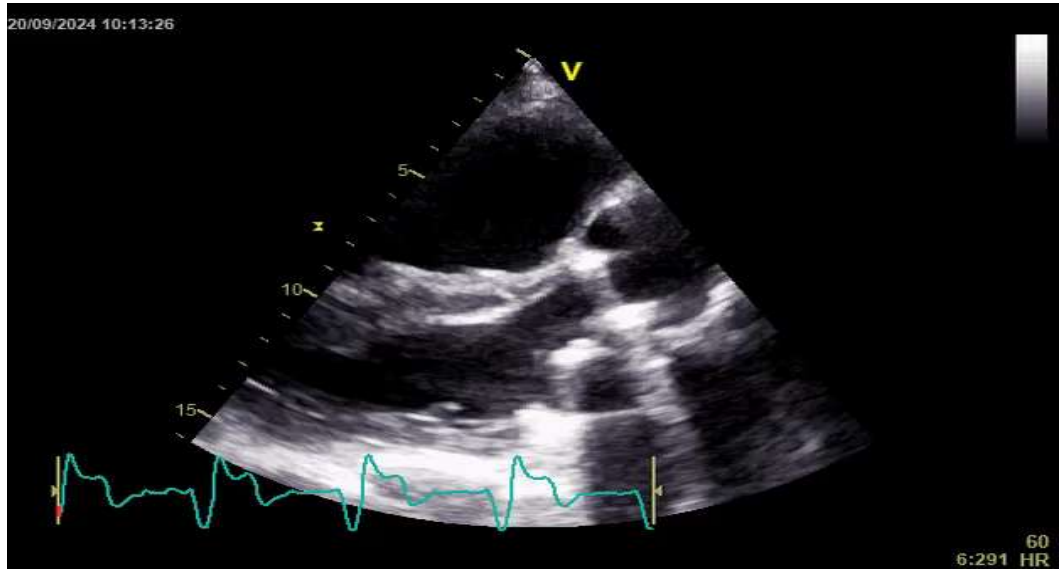
Charalampopoulos A, Frontiers in Medicine, 2018;5
D'Alto M. Et al; Heart Failure Clin, 2018;14:353–360

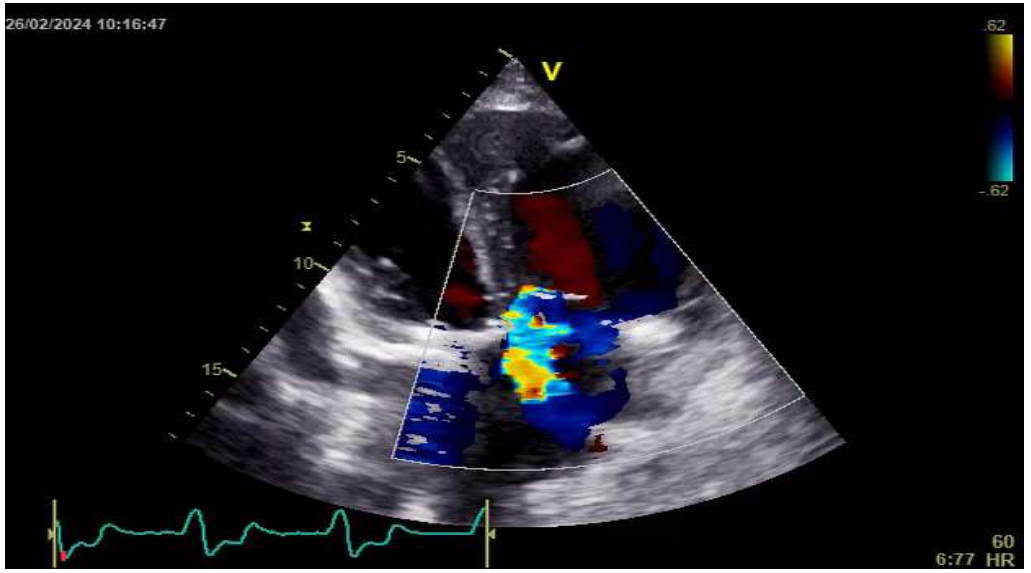
# Patient phenotyping and likelihood for LHD as cause of PH

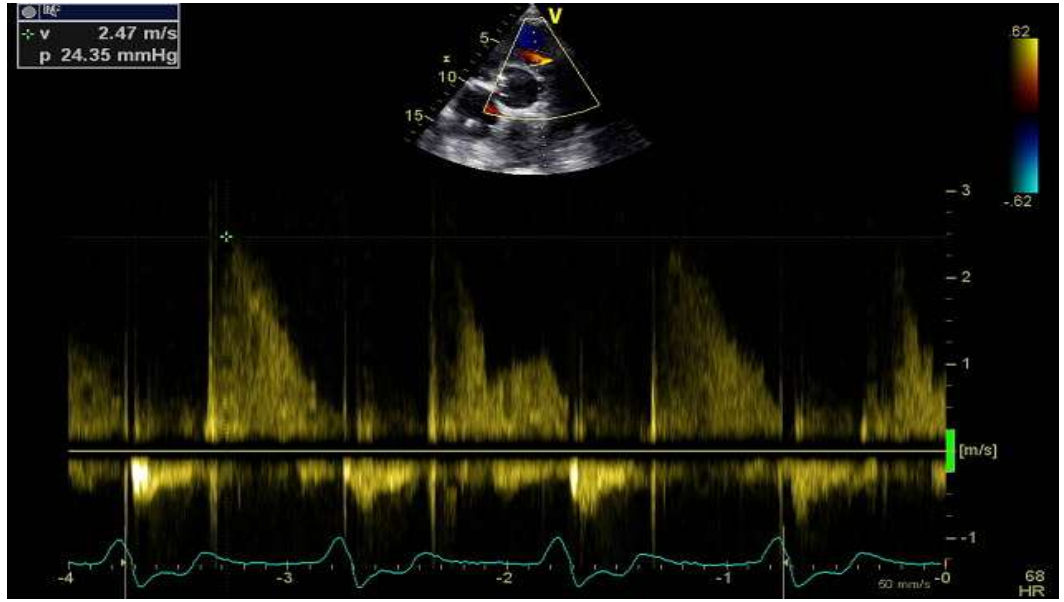
| Feature | PH-LHD unlikely | Intermediate probability | PH-LHD likely |
|---|---|---|---|
| Age | <60 years | 60–70 years | >70 years |
| Obesity, hypertension, dyslipidaemia, glucose intolerance/ diabetes | No factors | 1–2 factors | >2 factors |
| Presence of known LHD | No | Yes | Yes |
| Previous 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<br>E/e′ <13 | No LA dilation<br>Grade <2 mitral flow | LA dilation (LAVI >34 mL/ $m^2$)<br>LVH<br>Grade >2 mitral flow |

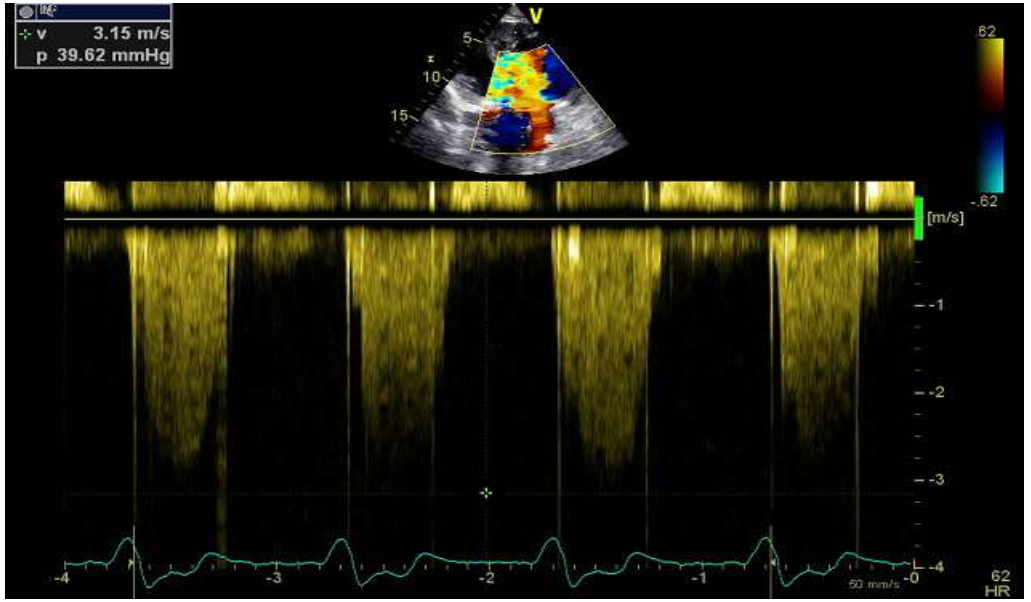
2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

# Group 1 or group 2 ?



# Diagnosis of PH-LHD

1. Diagnosis and control of the underlying LHD
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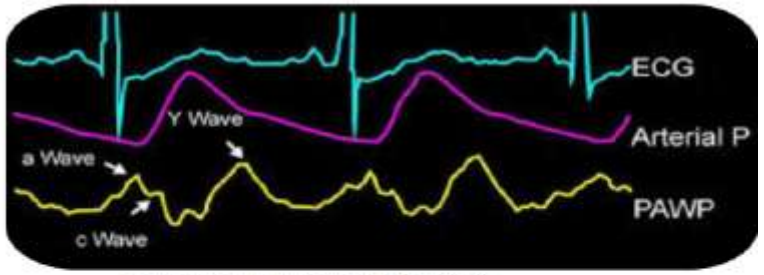
3. **Invasive haemodynamic evaluation, when indicated**

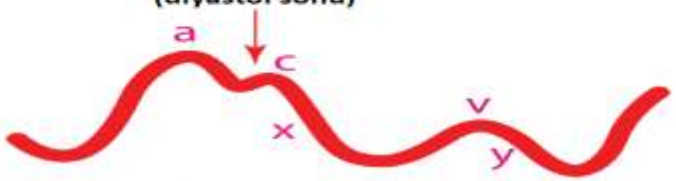
# Indications for RHC in LHD

1. suspected PAH or CTEPH
2. suspected CpcPH with a severe pre-capillary component
3. advanced HF and evaluation for heart transplantation

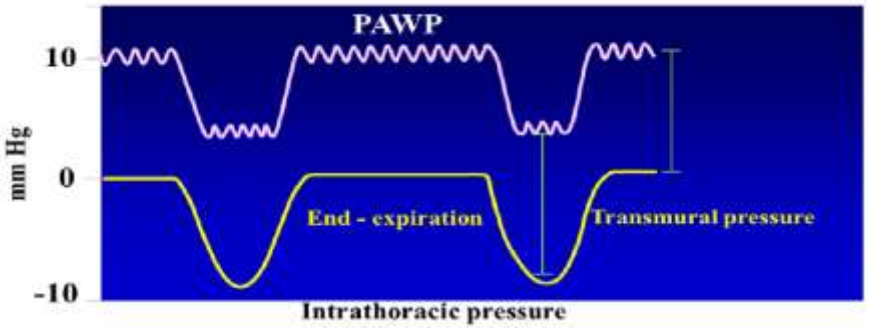
# A strict methodology for PAWP measurement is mandatory for accurate diagnosis



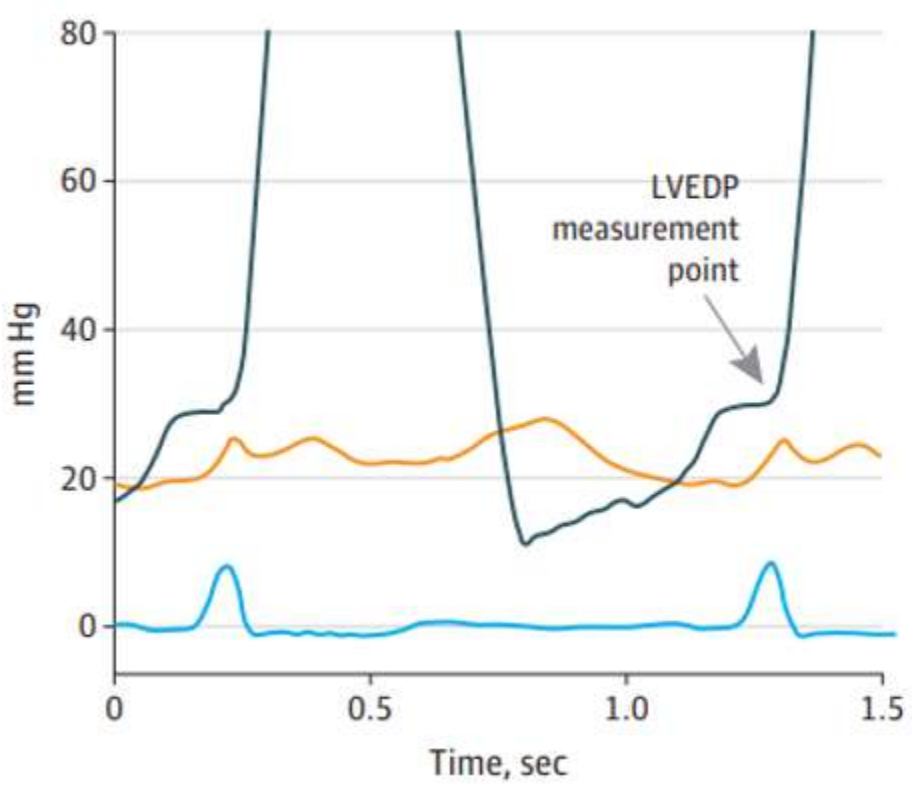

C dalgasının hemen öncesi
(diyastol sonu)

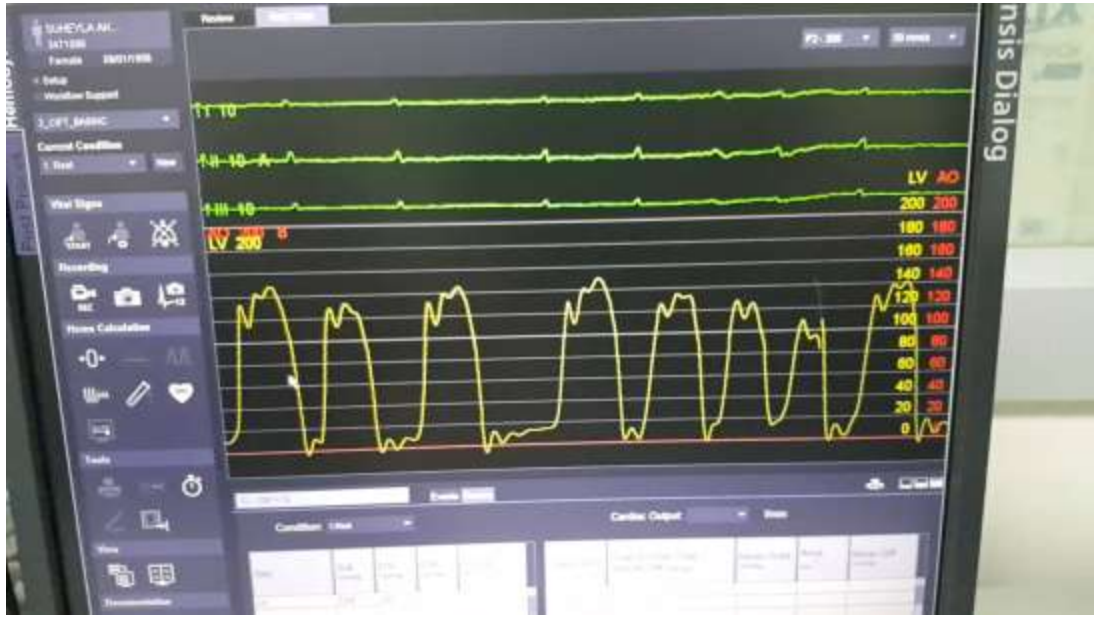



Diyastol sonu PAWP ≈ oPAWP




# LVEDP measurement



Reddy YN, et al. JAMA Cardiology, 2018

# A strict methodology for PAWP measurement is mandatory for accurate diagnosis

## resting PAWP 12–15 mmHg :

May be  a mild form of, post-capillary PH

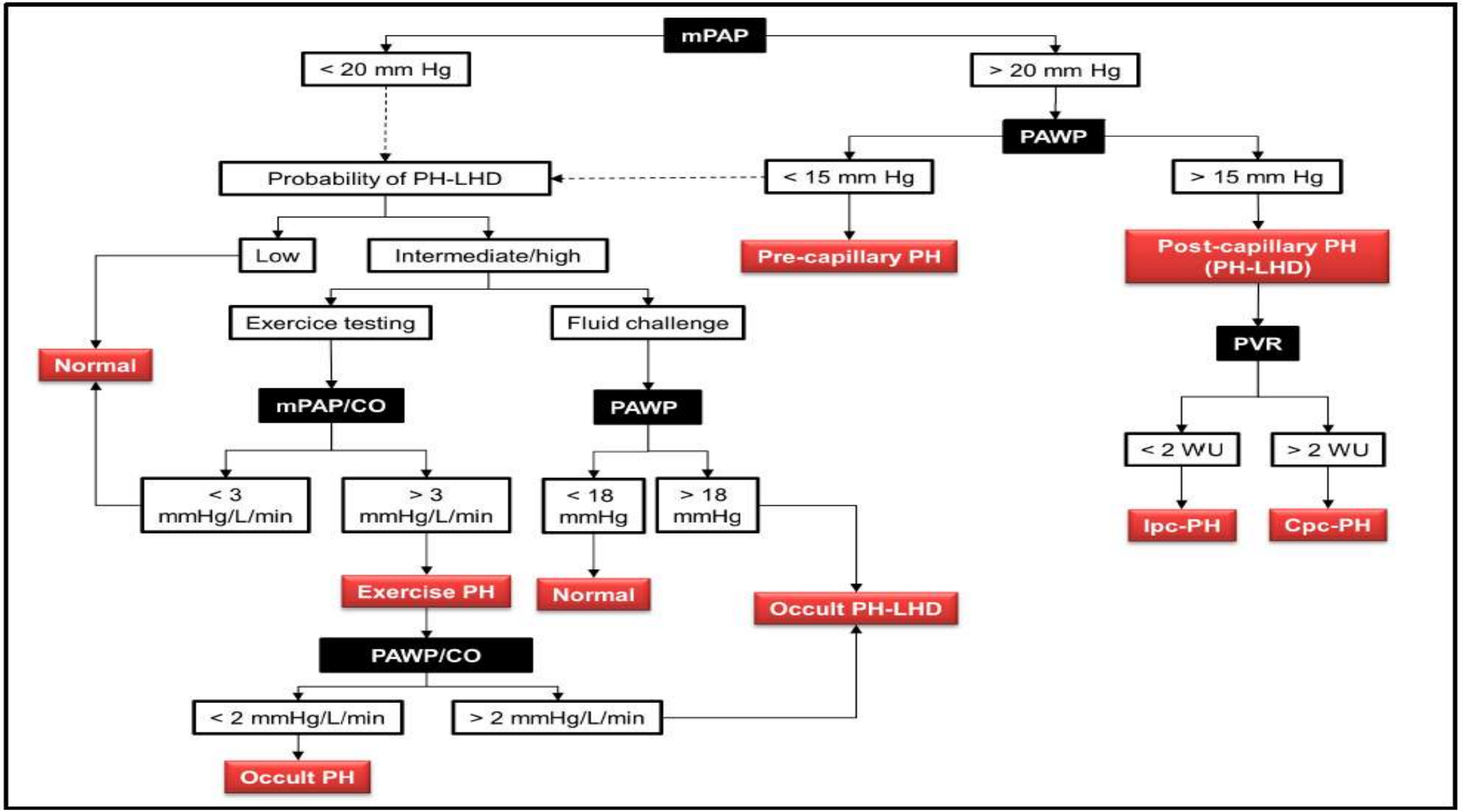
## PAWP 12-(15)-18 mmHg: a zone of PAWP “uncertainty”

- Use all imaging and clinical variables, including pre-test probability of PH-LHD to phenotype and categorise PH patients

# Provocative Testing

| Variable (Provocative Testing) | N | PH-LHD |
|---|---|---|
| 1. Exercise | | |
| mPAP/CO (mm Hg/L/min) | <3 | >3 |
| PAWP/CO (mm Hg/L/min) | <2 | >2 |
| 2. Volume challenge | | |
| PAWP at the end of volume challenge (<5 min) | <18 | >18 |

administer a 7 mL/kg bolus of normal saline over 5 min and to measure PAWP at the end of infusion

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# Therapeutic Management

Aims:

- Decrease PAWP to improve PA compliance and prevent PVD
- Reduce PVR in the case of established PVD,
- Prevent or treat RV-PA uncoupling.

# Optimize the management of the underlying cardiac disease

Guideline-directed medical therapies,
treatment of comorbidities with HFpEF, primarily, diabetes, obesity and hypertension

# Optimize the management of the underlying cardiac disease

Novel drugs used in HF therapy in reducing PAP in patients with PH-LHD, including angiotensin receptor–neprilysin inhibitör (ARNI) and sodium–glucose cotransporter-2 (SGLT-2) inhibitors

# Left Ventricle Assist Device

- In advanced HFrEF, LVAD is a therapeutic option as a bridge to transplantation, bridge to candidacy or as a destination therapy
- Implantation of an LVAD may normalize PAP and PVR in a significant number of, but not in all, patients, and those with persisting pre-capillary PH have reduced survival
- It may be possible that such patients could benefit from PAH tx (SOPRANO : macitentan in patients with LVAD and persisting elevated PVR)

# Drugs Approved for Pulmonary Artery Hypertension

# ERAs- clinical trials in PH-LHD

| Study | N, Patients | PVR (WU) | Intervention | Main Outcome | Results |
|---|---|---|---|---|---|
| ERAs | | | | | |
| Sutsch et al. [129] | 36 HFrEF | 2.6 ± 1.3 | Bosentan 2 w | CO, mPAP, PCWP, RAP | ↗ CO; ↘ mPAP, PCWP, RAP |
| Luscher et al. [130] | 157 HFrEF | 3.1 ± 0.6 | Darusentan 3 w | CI, PCWP, PVR, RAP | ↗ CI; ↔ PCWP, PVR, RAP |
| Anand et al. [131] | 642 HFrEF | NA | Darusentan 24 w | LVESV | ↔ LVESV |
| Packer et al. [132] | 370 HFrEF | NA | Bosentan 26 w | Death, NYHA, HHF | Early stop (liver toxicity) |
| Kaluski et al. [133] | 94 HFrEF | NA | Bosentan 20 w | sPAP, CI | ↔ sPAP, CI<br>↗ SAEs |
| Packer et al. [134] | 1613 HFrEF | NA | Bosentan 9 m | Death, HF admission | ↔ outcome<br>↗ congestion |
| Frantz et al. [135] | 57 LVAD (Cpc-PH) | 4.3 ± 0.9 | Macitentan 12 w | PVR, mPAP, RAP, PCWP | ↘ PVR<br>↔ mPAP, RAP, PCWP |
| Koller et al. [136] | 63 HFpEF | 3.7 ± 2.5 | Bosentan 12 w | 6MWD<br>PASP, RAP, TAPSE | ↔ all variables<br>Early stop (liver toxicity, ↗ HF) |
| Vachiery et al. [137] | 63 mixed<br>76% HFpEF (Cpc-PH) | 5.6 (3.7–7.3) | Macitentan 12 w | CI, NT-proBNP<br>PCWP, PVR, RAP | ↔ PCWP, PVR, RAP, CI; ↗ fluid retention |
| SERENADE NCT03153111 | 300 HFrEF (Cpc-PH) | NA | Macitentan 24 w | Plasma NT-proBNP, worsening heart failure | ↔ all variables<br>Early stop |

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| Luscher | | | | | PCWP, |
| Anand e | | | | | |
| Packer e | | | | | (liver |
| Kaluski | | | | | CI |
| Packer e | | | | | ne tion |
| Frantz et | | | | | RAP, |
| Koller et | | | | | ables (liver ↗ HF) |
| Vachiery | | (Cpc-PH) | | | PVR, ↗ fluid retention |
| SERENADE NCT03153111 | 300 HFrEF (Cpc-PH) | NA | Macitentan 24 w | Plasma NT-proBNP, worsening heart failure | ↔ all variables Early stop |

ERAs do not work in patients with PH-LHD related to HFpEF or HFrEF and may be associated with significant side effects, primarily increased congestion and liver toxicity.

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# PDE5i- clinical trials in PH-LHD

| Study | N, Patients | PVR (WU) | Intervention | Main Outcome | Results |
|---|---|---|---|---|---|
| PDE5i | | | | | |
| Lewis et al. [138] | 34 HFrEF | 4.3 ± 0.5 | Sildenafil 12 w | Peak VO2, PVR, 6MWD, QOL | ↗ VO2, 6MWT, QOL<br>↘ PVR |
| Behling et al. [139] | 19 HFrEF | NA | Sildenafil 4 w | PAPS, exercise capacity (CPET) | ↗ exercise capacity<br>↘ PAPS |
| Guazzi et al. [140] | 45 HFrEF | NA | Sildenafil 12 m | LVEF, LV diastolic function, exercise capacity, QOL | ↗ all variables<br>AE: flushing, headache |
| Guazzi et al. [141] | 32 HFrEF | 4.5 ± 0.7 | Sildenafil 12 m | Exercise capacity, pulmonary hemodynamics | ↗ exercise capacity<br>↘ PCWP, PVR, mPAP |
| Amin et al. [142] | 106 HFrEF | NA | Sildenafil 12 w | MAP, 6MWD, hospitalization | ↔ MAP<br>↗ 6MWD (ns)<br>↘ hospitalization (ns) |
| Cooper et al. [143] | 210 HFrEF | NA | Sildenafil 24 w | Symptoms score, 6MWD, QOL and PASP | 69 pts analyzed<br>↔ all variables<br>↗ temporary withdrawals |
| Guazzi et al. [144] | 44 HFpEF (Cpc-PH+ RV failure) | 3.9 ± 1.4 | Sildenafil 6–12 m | mPAP, PAWP, PVR, TAPSE | ↘ mPAP, PAWP, PVR<br>↗ TAPSE, ↗ CI |
| Redfield et al. [145] | 216 HFpEF (Ipc-PH) | NA | Sildenafil 24 w | Peak VO2, 6MWD | ↔ Peak VO2, 6MWD<br>↗ AEs (ns) |
| Andersen et al. [146] | 70 HFpEF (Ipc-PH) | 2.6 ± 0.9 * | Sildenafil 9 w | PCWP, PAP, CI | ↔ PCWP, PAP<br>↗ CI |
| Hoendermis et al. [147] | 52 HFpEF (65% Ipc-PH) | >3 in 35% pts | Sildenafil 12 w | mPAP, PCWP, CO and peak VO2 | ↔ all variables |
| Bermejo et al. [148] | 200 LVD (57% Cpc-PH) | 3.4 (2.4–4.6) | Sildenafil 24 w, >1 y after valve repair | Composite: death, HF episodes; 6MWD, sPAP, BNP | Clinical worsening<br>↔ 6MWD, BNP, sPAP |
| Belyavskiy et al. [149] | 50 HFpEF (Cpc-PH) | 3.3 ± 0.6 | Sildenafil 24 w | 6MWD, NYHA, PASP, TAPSE | ↗ 6MWD<br>↘ PASP, NYHA<br>↗ TAPSE |

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# PDE5i- clinical trials in PH-LHD

| Study | N, Patients | PVR (WU) | Intervention | Main Outcome | Results |
|---|---|---|---|---|---|
| PDE5i | | | | | |
| Lewis et al. [138] | 34 HFrEF | 4.3 ± 0.5 | Sildenafil 12 w | Peak VO2, PVR, 6MWD, QOL | ↗ VO2, 6MWT, QOL<br>↘ PVR |
| Behling et al. [139] | 19 HFrEF | NA | Sildenafil 4 w | PAPS, exercise | ↗ exercise |
| Guazzi e | | | | | |
| Guazzi e | | | | | R, |
| Amin et | | | | | tion |
| Cooper e | | | | | ed |
| Guazzi e | | | | | VP, CI |
| Redfield | | | | | |
| Andersen et al. [146] | 70 HFpEF (Ipc-PH) | 2.6 ± 0.9 * | Sildenafil 9 w | PCWP, PAP, CI | ↔ PCWP, PAP<br>↗ CI |
| Hoendermis et al. [147] | 52 HFpEF (65% Ipc-PH) | >3 in 35% pts | Sildenafil 12 w | mPAP, PCWP, CO and peak VO2 | ↔ all variables |
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| Belyavskiy et al. [149] | 50 HFpEF (Cpc-PH) | 3.3 ± 0.6 | Sildenafil 24 w | 6MWD, NYHA, PASP, TAPSE | ↗ 6MWD<br>↘ PASP, NYHA<br>↗ TAPSE |

- Current evidence does not support the general use of sildenafil for PH-LHD
- Registry data suggested improvements in exercise capacity with PDE5i in patients with HFpEF-CpcPH and PVR mostly >5 WU.

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# sGSs - clinical trials in PH-LHD

| Study<br>SGCs | N, Patients | PVR (WU) | Intervention | Main Outcome | Results |
|---|---|---|---|---|---|
| Bonderman et al. [150] | 201 HFrEF | 3.6 ± 0.3 | Riociguat 16 w | mPAP, CI, SVI, PVR | ↔ mPAP<br>↗ CI, SVI; ↘ PVR |
| Gheorghiade et al. [151] | 351 HFrEF | NA | Vericiguat 12 w | Change in NT-proBNP | ↔ NT-proBNP |
| Armstrong et al. [152] | 5050 HFrEF | NA | Vericiguat 10.8 m | Composite: CV death,<br>first HHF | ↘ primary outcome |
| Bonderman et al. [153] | 39 HFpEF | 2.8 ± 1.3 | Riociguat 6 h | mPAP, PVR, PCWP, TPG, SV, PAS | ↔ mPAP, PVR, PCWP, TPG; ↗ SV, ↘ PAS |
| Pieske et al. [154] | 477 HFpEF | NA | Vericiguat 12 w | NT-proBNP, LA volume, QOL | ↔ NT-proBNP, LA volume; ↗ QOL |
| Udelson et al. [155] | 181 HFpEF | NA | Praliciguat 12 w | Peak VO2, 6MWD | ↔ peak VO2, 6MWD |
| Armstrong et al. [156] | 789 HFpEF | NA | Vericiguat 24 w | Physical limitation score | ↔ score |
| Dachs et al. [157] | 114 HFpEF<br>(Ipc-PH 60%) | 3.2 ± 1.7 | Riociguat 26 w | CO, PVR, PCWP, TPG, SVR | ↗ CO; ↘ PVR, TPG<br>↔ PCWP, SVR<br>5 dropouts |

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# sGSs - clinical trials in PH-LHD

- Riociguat and vericiguat provide favorable hemodynamic effects in both HFrEF and HFpEF patients, with a significant increase in cardiac output and reduction in PVR
- Additional studies specifically in patients with a Cpc-PH should be conducted.
- Vericiguat significantly improves clinical outcomes in HFrEF patients with a recent worsening of HF symptoms

| Study SGCs | N, Patients | PVR (WU) | Intervention | Main Outcome | Results |
|---|---|---|---|---|---|
| Armstrong et al. [156] | 789 HFpEF | NA | Vericiguat 24 w | Physical limitation score | ↔ score |
| Dachs et al. [157] | 114 HFpEF (Ipc-PH 60%) | 3.2 ± 1.7 | Riociguat 26 w | CO, PVR, PCWP, TPG, SVR | ↗ CO; ↘ PVR, TPG ↔ PCWP, SVR 5 dropouts |

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# Prostacylin analogs- clinical trials in PH-LHD

| Study | N, Patients | PVR (WU) | Intervention | Main Outcome | Results |
|---|---|---|---|---|---|
| Prostacyclin analogs | | | | | |
| Sueta et al. [158] | 33 HFrEF | 3.6 ± 0.5 | Epoprostenol 12 w, IV | 6MWD | ↗ 6MWD |
| Califf et al. [159] | 471 HFrEF | NA | Epoprostenol 36 w, IV | Mortality, HF symptoms, 6MWD, QOL | Early stop (↗ mortality) |
| SOUTHPAW NCT03037580 | 84 HFpEF | NA | Treprostinil 24 w | 6MWD, Plasma NT-proBNP, NYHA class | ↔ all variables Early stop (slow enrolment) |
| RECAPTURE NCT04882774 | 30 HFpEF (Cpc-PH) | NA | Treprostinil | PVR, 6MWD | Not started |

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# Prostacylin analogs- clinical trials in PH-LHD

| Study | N, Patients | PVR (WU) | Intervention | Main Outcome | Results |
|---|---|---|---|---|---|
| Prostacyclin analogs | | | | | |
| Sueta | | | | | TD |
| Califf | | | | | op<br>tality) |
| SOUT<br>NCT0 | | | | | riables<br>op (slow<br>nt) |
| RECA<br>NCT0 | | | | | ted |

- Only limited information currently exists regarding prostacyclin analogs for the treatment of PH-LHD.
- Long-term epoprostenol has been associated with detrimental effects in HFrEF.
- In HFpEF, some encouraging experimental data have been produced using treprostinil

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# IASDs- clinical trials in PH-LHD

| Study | N, Patients | PVR (WU) | Intervention | Main Outcome | Results |
|---|---|---|---|---|---|
| Interatrial shunt devices (IASDs) | | | | | |
| Obokata et al. [160] | 79 HFpEF | 1.5 ± 0.8 | IASD up to 6 m | Resting and exercise pulmonary hemodynamics | ↘ PVR, Ea<br>↗ PAC |
| Shah et al. [161] | 626 HFpEF | 1.5 (1.1–2.1) | IASD 12–24 m | CV death, HF events<br>QOL | ↔ all variables |

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# IASDs- clinical trials in PH-LHD

| Study | N, Patients | PVR (WU) | Intervention | Main Outcome | Results |
|---|---|---|---|---|---|
| Interatrial shunt devices (IASDs) | | | | | |

- IASD was associated with worse outcomes in the presence of latent PVD
- HFpEF patients with Ipc-PH and no evidence of latent PVD may benefit from shunt-mediated left atrial unloading

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# Pulmonary artery denervation- in PH-LHD

| Study | N, Patients | PVR (WU) | Intervention | Main Outcome | Results |
|---|---|---|---|---|---|
| Pulmonary artery denervation (PADN) | | | | | |
| Zhang et al. [162] | 98 mixed<br>60% HFrEF<br>(Cpc-PH) | 6.3 ± 3.2 | PADN vs sham procedure 6 m | 6MWD, PVR, clinical worsening | ↗ 6MWD,<br>↘ PVR<br>↘ clinical worsening |

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# Pulmonary artery denervation- in PH-LHD

| Study | N, Patients | PVR (WU) | Intervention | Main Outcome | Results |
|---|---|---|---|---|---|
| Pulmonary artery denervation (PADN) | | | | | |

There is growing evidence that PADN permits significant hemodynamic and clinical benefits in patients with PH of various etiologies, including patients with a Cpc-PH

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# Levosimendan

- calcium sensitizer, potassium ATP (KATP) channel activator and phosphodiesterase-3 inhibitor with inotropic, vasodilatory and cardioproptective activity
- Experimental data showed that Levo could attenuate pulmonary vascular remodeling in an animal model of PH, attributed to antiproliferative and anti-inflammatory effects mediated by KATP channel activation
- In humans, some limited evidence suggests that Levo may reduce PAP and PVR and improve RV function in patients with PAH

# Levosimendan- clinical trials in PH-LHD

| Study | N, Patients | PVR (WU) | Intervention | Main Outcome | Results |
|---|---|---|---|---|---|
| Levosimendan | | | | | |
| Slawsky et al. [112] | 146 HFrEF | NA | Levo 6 h, IV | SV, CI, PCWP, RAP, dyspnea score | ↗ CI, SV<br>↘ PCWP, RAP,<br>↘ dyspnea |
| Parissis et al. [113] | 54 HFrEF | NA | Levo 24 h, IV | RV function, sPAP, Plasma BNP | ↗ RV function<br>↘ sPAP, BNP |
| Burkhoff et al. [115] | 37 HFpEF | $3.3 \pm 2.6$ | Levo 6 w, IV | exercise-PCWP 6MWD, PCWP and CVP | ↔ PCWP<br>↗ 6MWD<br>↘ PCWP, CVP |

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# β3-Adrenoreceptor Agonists

- Mirabegron: a new class of drugs approved for the clinical treatment of overactive bladder,
- promotes NO-dependent signaling and indirectly activates cardiac myocyte Na+/K+-ATPase,
- improved cardiac performance in experimental heart failure and induced the vasodilation of isolated pulmonary vessels from animals and humans
- β3AR agonists could exert some benefits in severe HFrEF, but not in HFpEF  patients

Bungaard H, et al. Circ. Heart Fail. **2022**,15, e009120
Garcia-Alvarez, A.; Eur. J. Heart Fail. **2023**, 25, 373–385.

# β3-Adrenoreceptor Agonists- trials in PH-LHD

| Study | N, Patients | PVR (WU) | Intervention | Main Outcome | Results |
|---|---|---|---|---|---|
| β3AR agonist | | | | | |
| Bundgaard et al. [118] | 22 HFrEF | 3.5 ± 2.5 | Mirabegron 1 w | PVR, SVR, CI, MAP | ↔ MAP, SVR<br>↗ CI; ↘ PVR |
| García-Álvarez et al. [120] | 80 HFpEF (70%) | 4.0 (3.4–4.6) | Mirabegron 16 w | PVR, QOL<br>RV function | ↔ PVR, QOL<br>↗ RV function |

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# Recommendations for pulmonary hypertension associated with left heart disease (2)

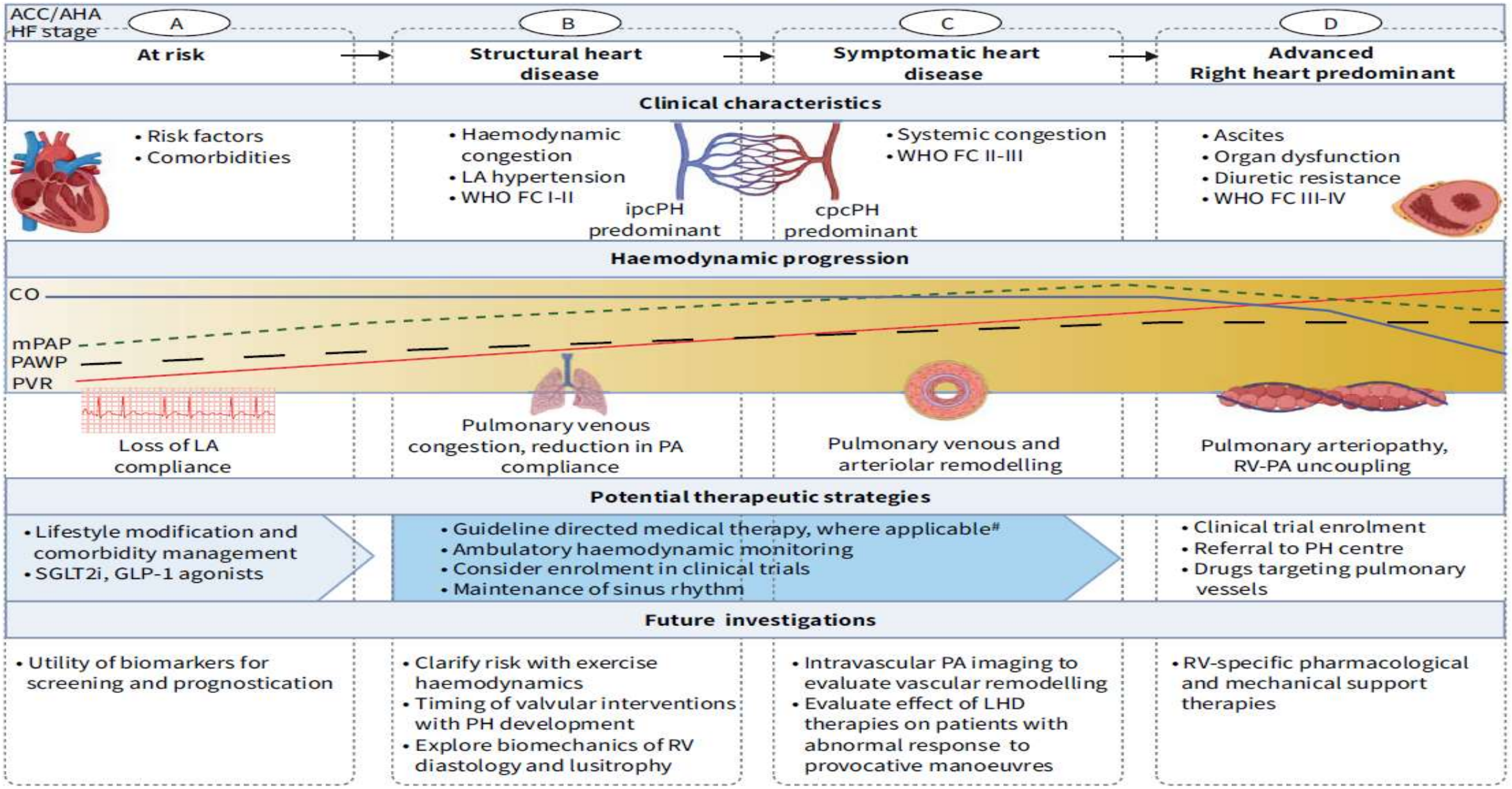
| Recommendations | Class | Level |
|---|---|---|
| In patients with LHD and CpcPH with a severe pre-capillary component (e.g. PVR >5 WU), an individualized approach to treatment is recommended | I | C |
| When patients with PH and multiple risk factors for LHD, who have a normal PAWP at rest but an abnormal response to exercise or fluid challenge, are treated with PAH drugs, close monitoring is recommended | I | C |
| In patients with PH at RHC, a borderline PAWP (13–15 mmHg) and features of HFpEF, additional testing with exercise or fluid challenge may be considered to uncover post-capillary PH | IIb | C |
| Drugs approved for PAH are not recommended in PH-LHD | III | A |





2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension
(*European Heart Journal*; 2022 – doi: 10.1093/eurheartj/ehac237 and *European Respiratory Journal*; 2022 – doi: 10.1183/13993003.00879-2022)

## Clinical stages of PH-LHD



# In conclusion…

- Pulmonary hypertension related to left heart disease represents the most frequent form of PH
- Treatment should aim to reduce congestion and left-sided filling pressures, primarily with diuretics and heart failure tx
- All targeted therapies aiming to reduce PVR have mostly failed in patients with PH-LHD (A noticeable exception is  the vericiguat in patients with advanced heart failure (VICTORIA study).

# In conclusion…

- Studies will need to address the role of pulmonary vasodilators in the context of new heart failure therapies, including angiotensin receptor–neprilysin inhibitors and SGLT2 inhibitors
- Oral Levosimendan is an encouraging development.
- Positive results obtained with pulmonary artery denervation are also of considerable interest
- Based on available data, a PVR >5 WU may indicate a severe pre-capillary component, the presence of which may prompt physicians to refer patients to PH centers.

# Thank you…

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