A 50 years old female with HFpEF and pulmonary hypertension

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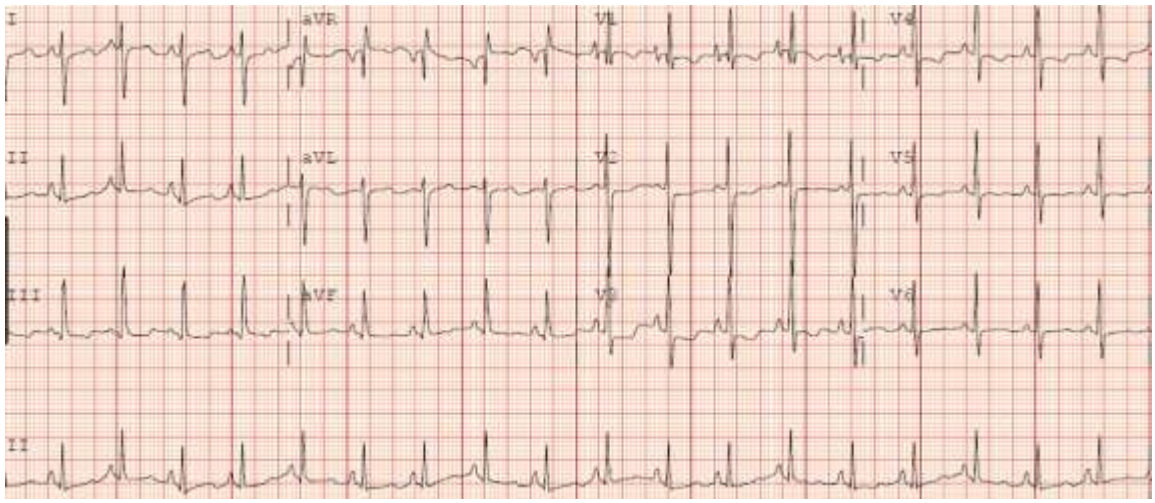
Case Presentation

- Mrs. HN is a 50 year old female.
- Hypertensive for 5 years.
- Presenting with progressive shortness of breath.
- Ankle edema.

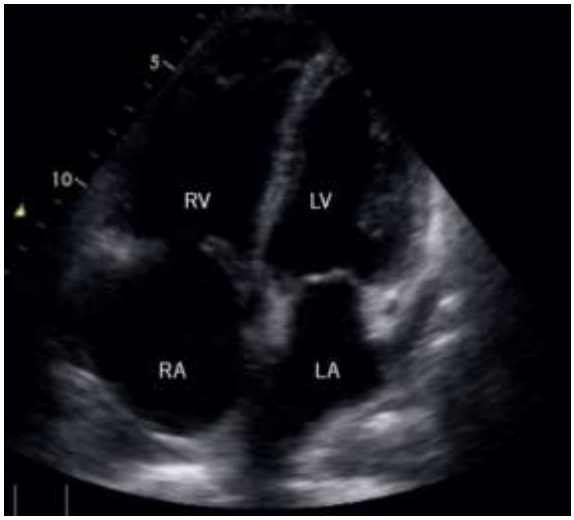
Examination

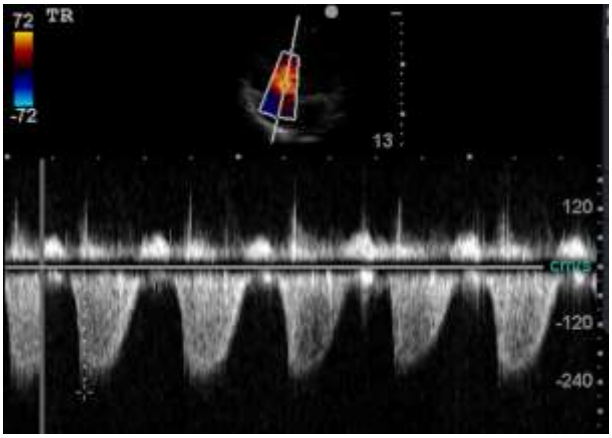
- BP 150/100 mmHg
- HR 105 bpm
- Accentuated S2
- Systolic murmur over the lower sternal border

ECG



Echocardiogram





Symptoms and Signs of Heart Failure

Symptoms	Signs
Typical	**More specific**
Breathlessness Orthopnoea Paroxysmal nocturnal dyspnoea Reduced exercise tolerance Fatigue, tiredness, increased time to recover after exercise Ankle swelling	Elevated jugular venous pressure Hepatojugular reflux Third heart sound (gallop rhythm) Laterally displaced apical impulse
Less typical	**Less specific**
Nocturnal cough Wheezing Bloated feeling Loss of appetite Confusion (especially in the elderly) Depression Palpitations Dizziness Syncope Bendopnea[13]	Weight gain (>2 kg/week) Weight loss (in advanced HF) Tissue wasting (cachexia) Cardiac murmur Peripheral oedema (ankle, sacral, scrotal) Pulmonary crepitations Reduced air entry and dullness to percussion at lung bases (pleural effusion) Tachycardia Irregular pulse Tachypnoea Cheyne Stokes respiration Hepatomegaly Ascites Cold extremities Oliguria Narrow pulse pressure

Table 3.1 Definition of heart failure with preserved (HFpEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF)

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF <40%	LVEF 40–49%	LVEF ≥50%
	3	–	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).

BNP = B-type natriuretic peptide; HF = heart failure; HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LAE = left atrial enlargement; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; NT-proBNP = N-terminal pro-B-type natriuretic peptide.
[a]Signs may not be present in the early stages of HF (especially in HFpEF) and in patients treated with diuretics.
[b]BNP > 35 pg/ml and/or NT-proBNP > 125 pg/mL.

Introduction

- Heart failure (HF) with preserved ejection fraction (HFpEF) is a common disease affecting the elderly in particular.
- Up to 80% of these patients develop pulmonary hypertension (PH), which is associated with worse symptoms and increased mortality.
- It is a matter of concern that drugs approved for pulmonary arterial hypertension (PAH) are sometimes used in such patients despite insufficient data for their safety and efficacy.
- The impact of PH and right ventricular (RV) dysfunction on morbidity and mortality in HFpEF call for proper attention both at the clinical and scientific level.

Epidemiology, natural history, and diagnosis of HFpEF

- HFpEF is currently the dominant form of HF in aging societies globally.
- Epidemiologic trends over the past two decades showed that HFpEF increased relative to HF with reduced ejection fraction (HFrEF).
- Overall mortality does not improve over time, with more than 50% dead in 5 years from diagnosis.
- Differences between epidemiologic and trial populations of HFpEF reflect potential selection bias and lack of uniformity of diagnostic criteria.
- Epidemiologic studies utilize the most widely applicable definition of HFpEF:
- (i) clinically diagnosed HF (e.g. by Framingham criteria) and
- (ii) preserved EF (e.g.≥50%).

The dilemma of HFpEF

- Definitions are rarely specific enough for clinical trials since the accurate diagnosis relies on symptoms and signs of HFpEF, both non-discriminating particularly in elderly patients with multiple comorbidities.
- Yet, the diagnosis of HFpEF remains difficult as many presumably healthy elderly patients fulfil at least some of these echocardiographic criteria.
- Invasive demonstration of increased pulmonary arterial wedge pressure (PAWP) or LV end-diastolic pressure (LVEDP), abnormal LV relaxation, and increased LV diastolic stiffness support the diagnosis.

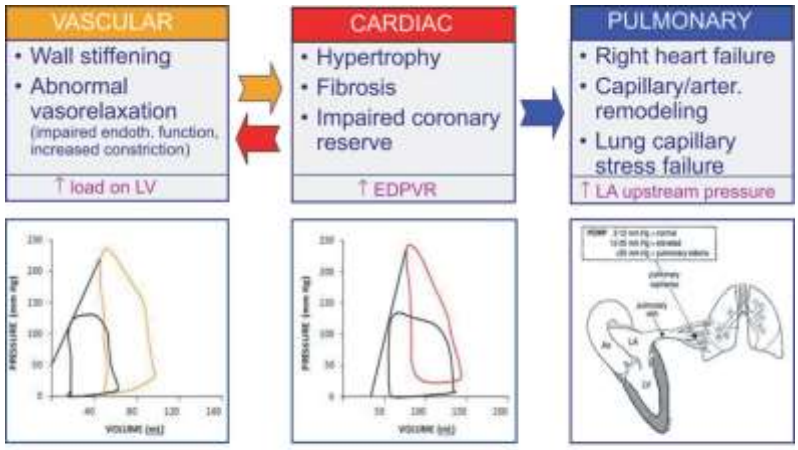
Pulmonary hypertension

- An elevation of left ventricular diastolic and pulmonary venous pressure is typical of HF regardless of LVEF.
- Normal left ventricular diastolic function keeps PCWP low (<12 mm Hg), although some increase may be observed during stress conditions, such as volume overload[1] and exercise.
- When these changes occur within a range of transient periods and in a normal heart, they are well tolerated because of the pulmonary vasculature ability to recruit and distend the capillary network.

Patho-physiological changes

- HFpEF presents with an impaired relaxation and stiffened myocardium, which is in part consequence of an increased load to the left ventricle attributable to the stiff arterial system and resulting in a well-defined ventricular-vascular uncoupling.
- These main hemodynamic alterations expose the lung vasculature to pressure-induced challenges whose most immediate acute threat is pulmonary edema.
- In the long term, the sustained backward hemodynamic transmission, along with the potential contribution of mitral insufficiency, increases the pulsatile loading on the right ventricle (RV) and triggers pulmonary hypertension (PH) development and symptom exacerbation.
- Thus, as a consequence of hemodynamic and functional perturbations, PH-HFpEF develops as a result of diastolic HF, leading to abnormal phenotypes of the lung microcirculation, the arterial system, and right heart function.

From heart failure with preserved ejection fraction (HFpEF) to pulmonary hypertension (PH)
HFpEF: hemodynamic components and pathophysiological correlates.



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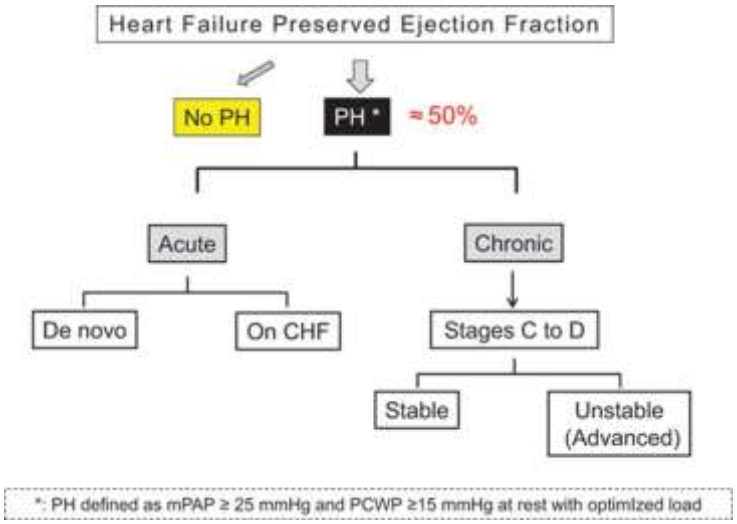
PH in HFpEF

- Post-capillary PH is defined by a mean pulmonary artery pressure (PAPm)≥ 25mmHg and a PAWP > 15mmHg and is further subdivided into isolated post-capillary PH (IpcPH) and combined post- and pre-capillary PH (CpcPH).
- The current PH guidelines base the distinction between IpcPH and CpcPH on a diastolic pressure gradient (DPG, the gradient between diastolic pulmonary artery pressure and PAWP)≥7mmHg and/or a pulmonary vascular resistance (PVR) >3 Wood units.
- Currently, the evidence remains conflicting, and further research is needed to determine whether PVR, DPG, or other variables such as pulmonary artery capacitance are most suitable to identify a clinically relevant pre-capillary component in patients with post-capillary PH due to left heart disease.

Different clinical conditions associated with pulmonary hypertension–heart failure with preserved ejection fraction (PH-HFpEF).



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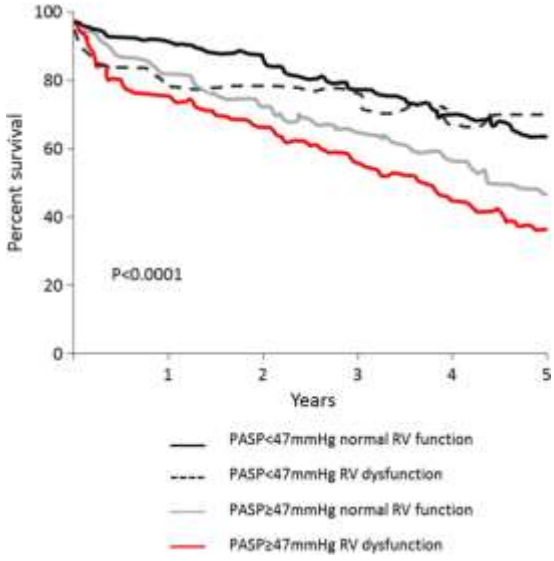
Epidemiology of PH in HFpEF

- PH is common in patients with HFpEF.
- A population-based study of 244 patients with HFpEF reported echocardiographic signs of PH in 83%.
- The estimated systolic PAP was a predictor of mortality (hazard ratio 1.3 per 10mmHg increase; P< 0.001).
- In a catheter based study,18 PH was found in 168 of 219 (77%) prospectively evaluated patients with HFpEF, 26 (12%) of whom had CpcPH (defined as elevated DPG and PVR). Patients with CpcPH, unlike those with IpcPH, had impaired RV to pulmonary vascular coupling and their survival was worse.
- Consistently, a prospective series demonstrated that right HF was the cause of death in 55% of patients dying with PH-HFpEF (Bonderman et al.).
- In a cross-sectional study, HFpEF patients with and without PH had almost identical risk factors, co-morbidities, left-sided echocardiographic findings, and left-sided filling pressures.

Five-year Kaplan–Meier survival curves in heart failure preserved ejection fraction according to pulmonary arterial systolic pressure (PASP) median value distribution (47 mm Hg) and right ventricular (RV) function (normal or systolic dysfunction).



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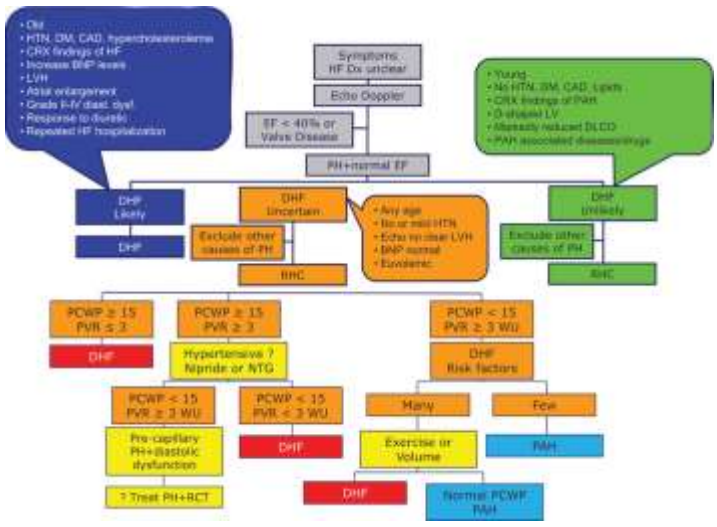
Diagnostic algorithm for pulmonary hypertension–heart failure with preserved ejection fraction (PH-HFpEF) proposed by the working group on non–pulmonary arterial hypertension (PAH)-PH at the 4th World Symposium on PH



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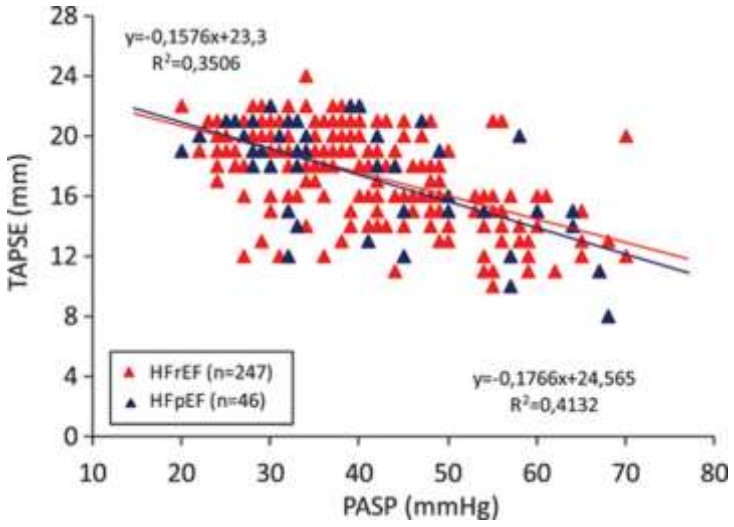
Plot of TAPSE/ PASP relationship according to HFrEF vs HFpEF



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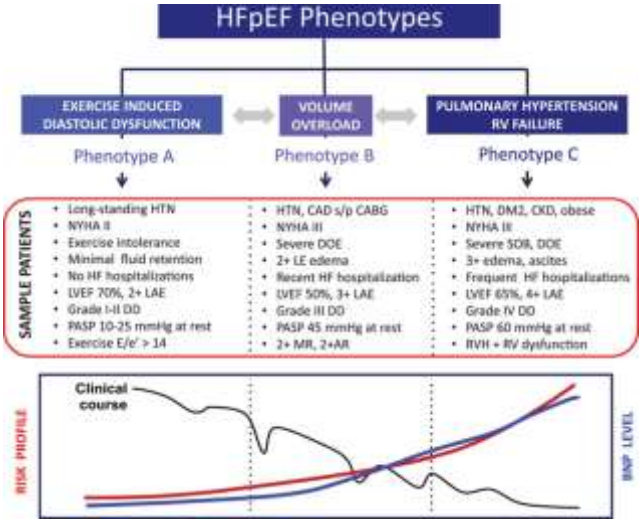
Different HFpEF phenotypes based on clinical sings and symptoms, degree of diastolic dysfunction, and presence or not of pulmonary hypertension (PH) and right heart disease.



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Therapeutic Perspectives

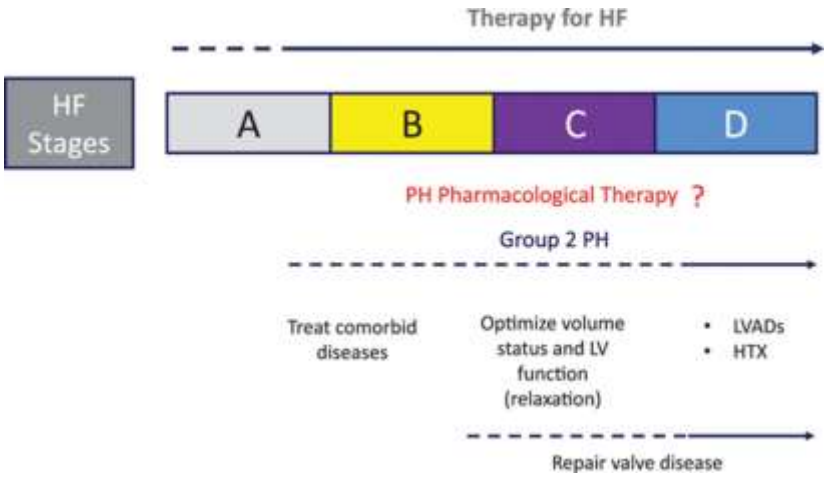
- There are currently no consensus therapeutic strategies and reference algorithms for PH except for advanced stages of the disease, when mechanical pump support and heart transplantation are needed.

- Specifically, no evidence is provided on preventing and reversing early or intermediate stages of PH except for treating comorbid disorders and optimizing volume status and LV relaxation properties.

- There are few evidences available at this time for lung vascular disease treatment in PH-HFpEF.
- An explanation may be that endothelin receptor antagonists (ERAs) and prostanoids, which are effective treatments for PAH, have been shown to be neutral or even harmful in patients with left-sided PH.
- Accordingly, despite their use in cardiac forms of PH being contraindicated, there are 2 provocative ongoing trials aimed at testing the potential significance of ERAs in PH-HFpEF.
- At variance with other pulmonary vasodilators, evidence is accumulating that inhibition of phosphodiesterase-5 (PDE5), the isoenzyme that breaks down cGMP to its inactive form, may be an effective and well-tolerated tool for targeting the pulmonary vasculature and unloading the RV in left-sided PH.
- This is suggested by multiple observations made in patients with left-sided PH of various pathogenesis and severity, with acute and long-term administration of sildenafil.
- The benefits of PDE5 inhibitors compared with other classes of pulmonary vasodilators stand on the pulmonary vascular selectivity of PDE5 expression in lung microvessels.

- The mechanism by which other pulmonary vasodilators increase PCWP whereas PDE5 inhibitors do not, is unclear, but an explanation may be the direct beneficial effects of PDE5 inhibition on LV diastolic stiffness, through cGMP-dependent phosphorylation of titin.
- In parallel with evidence showing PDE5 inhibitor benefits, the Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Heart Failure with Preserved Ejection Fraction (RELAX) trial, involving larger number of patients with HFpEF, has failed to show any benefit by sildenafil administration over 24 weeks.
- Another class of agents that selectively target the downstream intracellular nitric oxide pathway is the soluble guanylate cyclase (sGC) stimulators.
- Riociguat is the first of this class of novel therapeutics that has a dual mode of action: it sensitizes sGC to endogenous nitric oxide and directly stimulates sGC independently of nitric oxide.
- Riociguat is currently undergoing regulatory review for the indications of PAH and inoperable chronic thromboembolic pulmonary hypertension and is being investigated as a treatment for PH-HFpEF in a Phase 2b study (Effects of Riociguat in Patients With Pulmonary Hypertension Associated With Left Ventricular Diastolic Dysfunction, DILATE trial.

Current therapeutic strategies for reversing/treating pulmonary hypertension (PH) in left heart disease.



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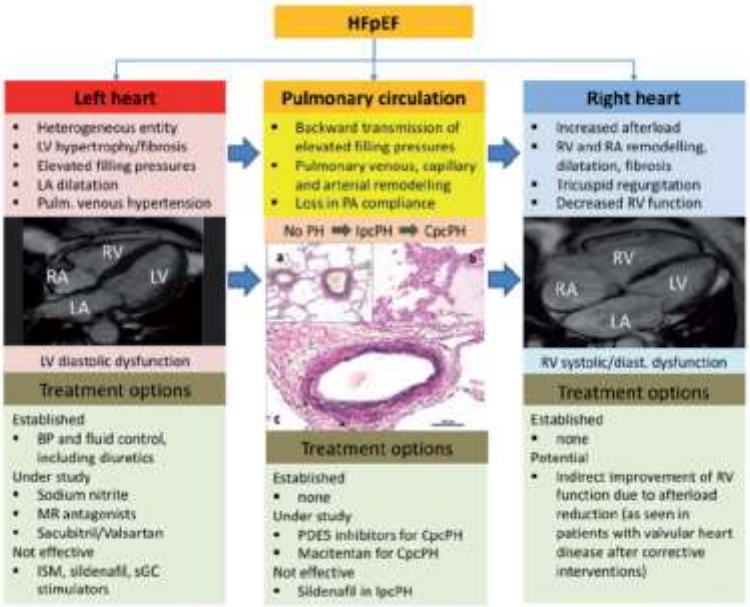
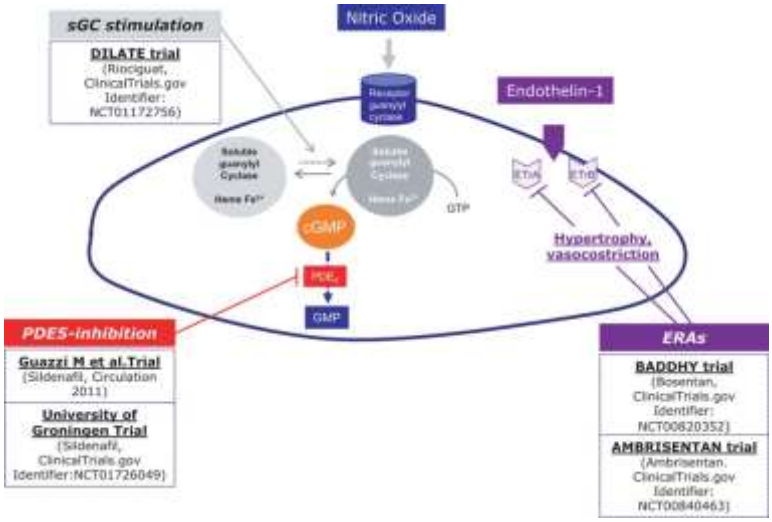
PH-HFpEF, features, and treatment options



Recommendations for the future approach to PH-HFpEF

- The most effective prevention and therapy of PH-HFpEF may be effective treatment of HFpEF.
- No drug approved for PAH has thus far been shown to be safe and effective in PH-HFpEF.
- Patients with CpcPH-HFpEF have a high mortality, and right-sided HF contributes to death. Preliminary data from a single-centre clinical trial suggest that PDE5 inhibitors may be safe and effective in this selected patient population. However, the available evidence is insufficient to make a recommendation to use PDE5 inhibitors or other drugs approved for PAH as treatments for CpcPH-HFpEF.
- Robust evidence on the safety and efficacy of treatments targeting PH requires randomized, controlled, long-term multicentre trials in the subset of patients with CpcPH-HFpEF.

Pathways, pharmacological agents, and published and ongoing trials in pulmonary hypertension–heart failure with preserved ejection fraction.



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Conclusions

- In HFpEF, the development of PH, is now viewed as an important contributor to clinical worsening and increased mortality.
- Patients PH and HFpEF typically present with the same risk factors.
- This recognition is progressively increasing, making therapeutic interventions aimed at targeting elevated pulmonary pressures as an important challenge.
- Out of several classes of pulmonary vasodilators, oral phosphodiesterase-5 inhibitors, because of their strong selectivity for targeting the cGMP pathway in the pulmonary circulation, are increasingly emerging as the most promising ones, in terms of hemodynamic benefits, reverse RV remodeling, and improved functional capacity.
- GC stimulators show similar properties but have not been extensively tested yet in this subset of patients with PH. Future trials will show whether these pharmacological strategies translate into decreased morbidity and mortality in the growing populations of PH-HFpEF.

Thank You