PH asociovaná s onemocněním levého srdce a plic

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Network Respiratory Diseases (ERN-LUNG)

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Klasifikace PH

GROUP 2 PH associated with left heart disease

- 2.1 Heart failure:
  - 2.1.1 with preserved ejection fraction
  - 2.1.2 with reduced or mildly reduced ejection fraction[b]
- 2.2 Valvular heart disease
- 2.3 Congenital/acquired cardiovascular conditions leading to post-capillary PH

GROUP 3 PH associated with lung diseases and/or hypoxia

- 3.1 Obstructive lung disease or emphysema
- 3.2 Restrictive lung disease
- 3.3 Lung disease with mixed restrictive/obstructive pattern
- 3.4 Hypoventilation syndromes
- 3.5 Hypoxia without lung disease (e.g. high altitude)
- 3.6 Developmental lung disorders

Group 2: PH associated with left heart disease

- 2.1 Heart failure:
  - 2.1.1 with preserved ejection fraction
  - 2.1.2 with reduced or mildly reduced ejection fraction
  - 2.1.3 cardiomyopathies with specific aetiologies[¶]
- 2.2 Valvular heart disease:
  - 2.2.1 aortic valve disease
  - 2.2.2 mitral valve disease
  - 2.2.3 mixed valvular disease
- 2.3 Congenital/acquired cardiovascular conditions leading to post-capillary PH

Group 3: PH associated with lung diseases and/or hypoxia

- 3.1 COPD and/or emphysema
- 3.2 Interstitial lung disease
- 3.3 Combined pulmonary fibrosis and emphysema
- 3.4 Other parenchymal lung diseases[+]
- 3.5 Nonparenchymal restrictive diseases:
  - 3.5.1 hypoventilation syndromes
  - 3.5.2 pneumonectomy
- 3.6 Hypoxia without lung disease (*e.g.* high altitude)
- 3.7 Developmental lung diseases

Humbert M et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension, *EHJ* 2022, *ERJ* 2022

Kovacs G, Bartolome S, Denton CP, et al. Definition, classification and diagnosis of pulmonary hypertension. Eur Respir J 2024

Hemodynamická definice PH

	Haemodynamic characteristics
PH	mPAP >20 mmHg
Pre-capillary PH	mPAP >20 mmHg PAWP ⩽15 mmHg PVR >2 WU
Isolated post-capillary PH (ipcPH)	mPAP >20 mmHg PAWP >15 mmHg PVR ⩽2 WU
Combined post- and pre-capillary PH (cpcPH)	mPAP >20 mmHg PAWP >15 mmHg PVR >2 WU
Exercise PH	mPAP/CO slope >3 mmHg/L/min between rest and exercise

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Správná metodologie měření PCWP

- Dříve navrženo měření v endiastole - nejlépe vyjadřuje endiastolický tlak LK
- Měření v endiastole minimalizuje vliv V vlny, která odráží patologii mitrální chlopně a levé síně. Průměrný PCWP by měl být více relevantní při kalkulaci PVR
- PCWP 12-15 (18) mmHg bráno jako rozhraní nejistoty
- Kontextualizace hemodynamiky s rizikovými faktory nebo onemocněním LK

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Fenotypizace PH-LHD

- **PH u aortální stenózy**
  - před intervencí se nedoporučuje léčit spec. léčbou
  - reziduální PH po intervenci zhoršuje dlouhodobý outcome
  - není evidence k léčbě reziduální PH po intervenci

- **Overlap fenotypy** – více jak 75 % pacientů má dvě a více komorbidit, 57 % 2-3 overlap

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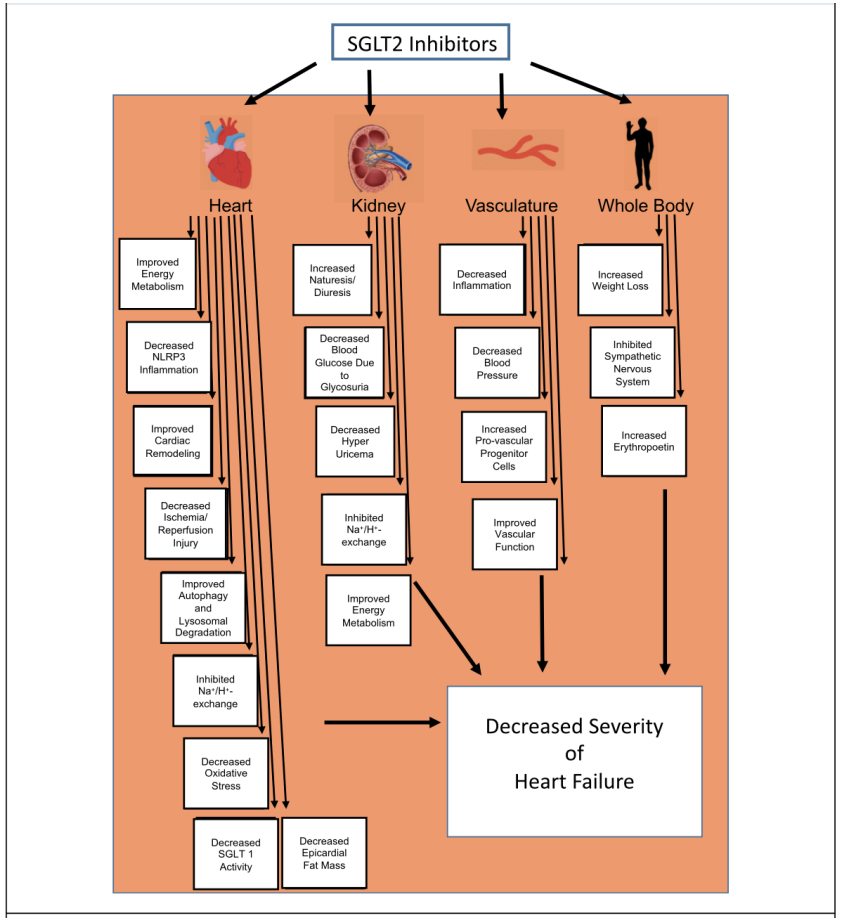
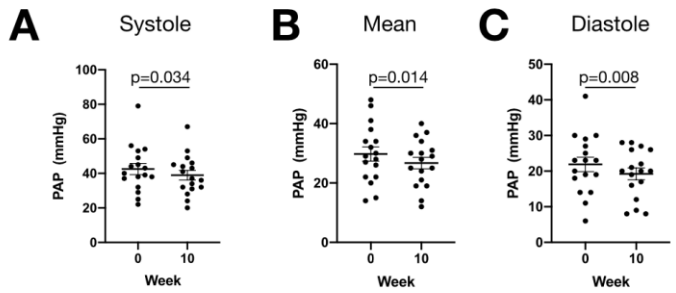
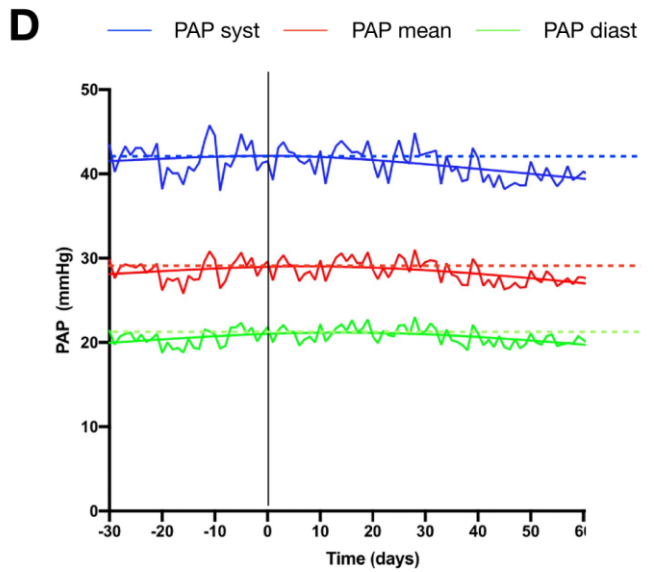
SGLT2 inhibitory a PH-LHD







Lopaschuk GD, Verma S. Mechanisms of cardiovascular benefits of sodium glucose co-transporter 2 (SGLT2) inhibitors: a state-of-the art review. JACC Basic Transl Sci 2020

Kirschbaum K, Vasa-Nicotera M, Zeiher AM, et al. SGLT2 inhibitor therapy and pulmonary artery pressure in patients with chronic heart failure-further evidence for improved hemodynamics by continuous pressure monitoring. Clin Res Cardiol 2022

Dif. dg. PAH a PH-LHD

- První krok stanovení předtestové pravděpodobnosti LHD
- K potvrzení diagnózy nutná PSK
- Provokační testy dříve doporučeny při PCWP 13-15 mmHg. Nově i při nižším PCWP a vysoké pravděpodobnosti LHD
- Podíl vetrikulární interdependence při PAH a dilataci PK na elevaci PCWP nepravděpodobný při kardiální kompenzaci. Snadno identifikovatelný pokud je RAP větší nebo rovno PCWP

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Běžné komorbidity a rizikové faktory LHD

Common LHD comorbidities	Common LHD risk factors
Obesity	Hypercholesterolaemia
Systemic hypertension	Tobacco use and second-hand smoke exposure
Coronary artery disease	Sedentary lifestyle
Diabetes	Illicit drug use
Valvular heart disease	Chronic alcohol use
Arrhythmia	Infectious exposures in endemic regions
Mild reduction in left ventricular systolic function	
Peripheral artery disease	

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Staging LHD komorbidit a pravděpodobnost LHD

	Mild	Moderate	Severe	Low	Intermediate	High
Obesity	30–35 kg·m^{-2}	35–40 kg·m^{-2}	>40 kg·m^{-2}			
Systemic hypertension	Treated ⩽2 drugs	Treated >3 drugs	Uncontrolled			
Diabetes	Insulin resistance/ pre-diabetes	Type 2 diabetes	Type 2 diabetes with vascular complications			
Coronary artery disease	Single vessel disease	NSTEMI Multiple vessels disease Multiple percutaneous interventions Single episode of SCA	CABG (any time) Repeated SCA STEMI Symptomatic Persistent ischaemia Diffuse disease			
Arrhythmia	Single episode of atrial arrhythmia Absence of AF at diagnosis	Repeated episodes of Afl/AF ⩾1 treatment for arrhythmia	Permanent Afl/ AF Ventricular arrhythmias Repeated ablation Implantation of pacemaker/ ICD CRT			
PAD	Asymptomatic large vessels atheromatosis	Nonsignificant stenosis (carotid, femoral) Previous single percutaneous intervention	Previous surgery for large vessels disease Stage 2b PAD			
Combined LHD comorbidities				⩾1 mild-stage LHD comorbidity	>1 moderate-stage LHD comorbidity or ⩾3 mild-stage LHD comorbidities	>1 severe-stage LHD comorbidity

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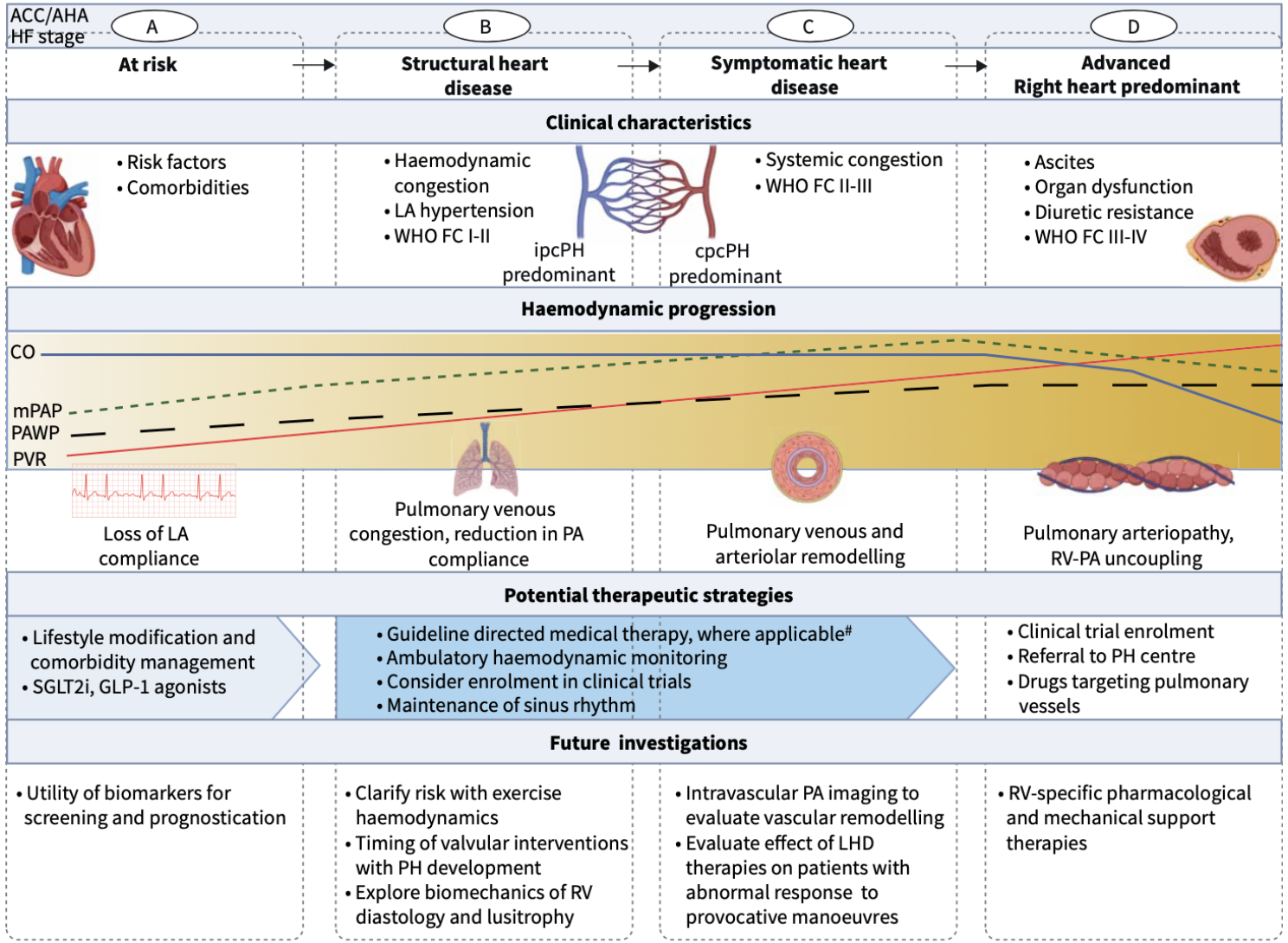
Klinická stádia PH-LHD



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Studie z poslední doby posílily evidenci proti používaní specifické léčby u PH-LHD

Study [reference]	Study drug	Dose	Subjects n	Duration	Population	Primary outcome	Result
DYNAMIC (phase 2B) [114]	Riociguat	1.5 mg three times daily	114	26 weeks	LVEF ⩾50%, mPAP ⩾25 mmHg and PAWP ⩾15 mmHg WHO FC II–IV	Change in CO	Increase in CO (LS mean difference 0.54 (0.112–0.971) $L \cdot min^{-1}$ No change in NT-proBNP, WHO FC, exercise capacity or QoL Higher dropout rates in riociguat group
PASSION (phase 3) [117]	Tadalafil	40 mg daily	372 (125 patients enrolled)	24 weeks and individual end of study	LVEF ⩾50%, elevated BNP or NT-proBNP, and one additional HFpEF criteria mPAP ⩾25 mmHg, PAWP >15 mmHg, PVR >3 WU	Event-free survival (adjudicated HF-related hospitalisation or any cause death)	Terminated early (disruption in study medication supply) No change in primary end-point Increase in all-cause mortality No difference in other secondary end-points
SERENADE (phase 2B) [116]	Macitentan	10 mg daily	300 (142 enrolled)	52 weeks (shortened to 24 weeks)	HFpEF (LVEF ⩾40%) with structural echo abnormalities, diuretic use, NYHA FC II–III Elevated NT-proBNP or BNP PVD or RVD	% change from baseline in NT-proBNP at week 24	Terminated early No difference in primary end-point High run-in failure rate due to fluid retention Not published

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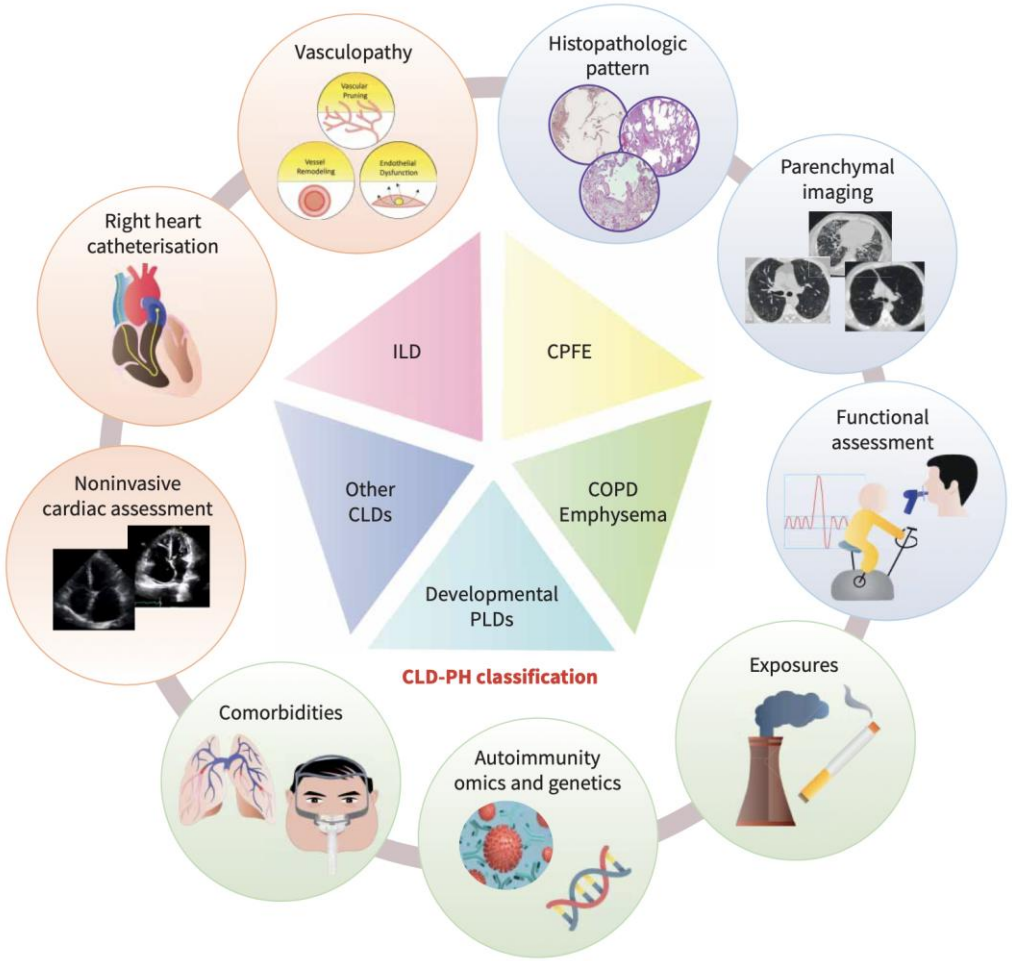
PH-CLD

- **Nová hemodynamická definice PH - prevalence PH u ILD (47.6 % → 73.6 %) , u CHOPN (52.4 % → 82.4 %)**



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PH-COPD - fenotypy

- **Těžká (disproporcionální) PH-COPD –** PVR > 5 W.j.

- **PH s mírnou CHOPN (GOLD 1 nebo 2, FEV1 > 60 (70) % nál.h.)**

  - v registru COMPERA 52 % pacientů s PAH, často DLCO < 45 %

  - až 50 % středně závažné až závažné parenchymové změny na CT → PH skupiny 3?

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PH-ILD - fenotypy

- **PH-CTD related ILD –** lepší výsledky se spec. léčbou než u ostatních PH-ILD

- **CPFE associated PH –** často u kuřáku, ale i u CTD, profes. expozic

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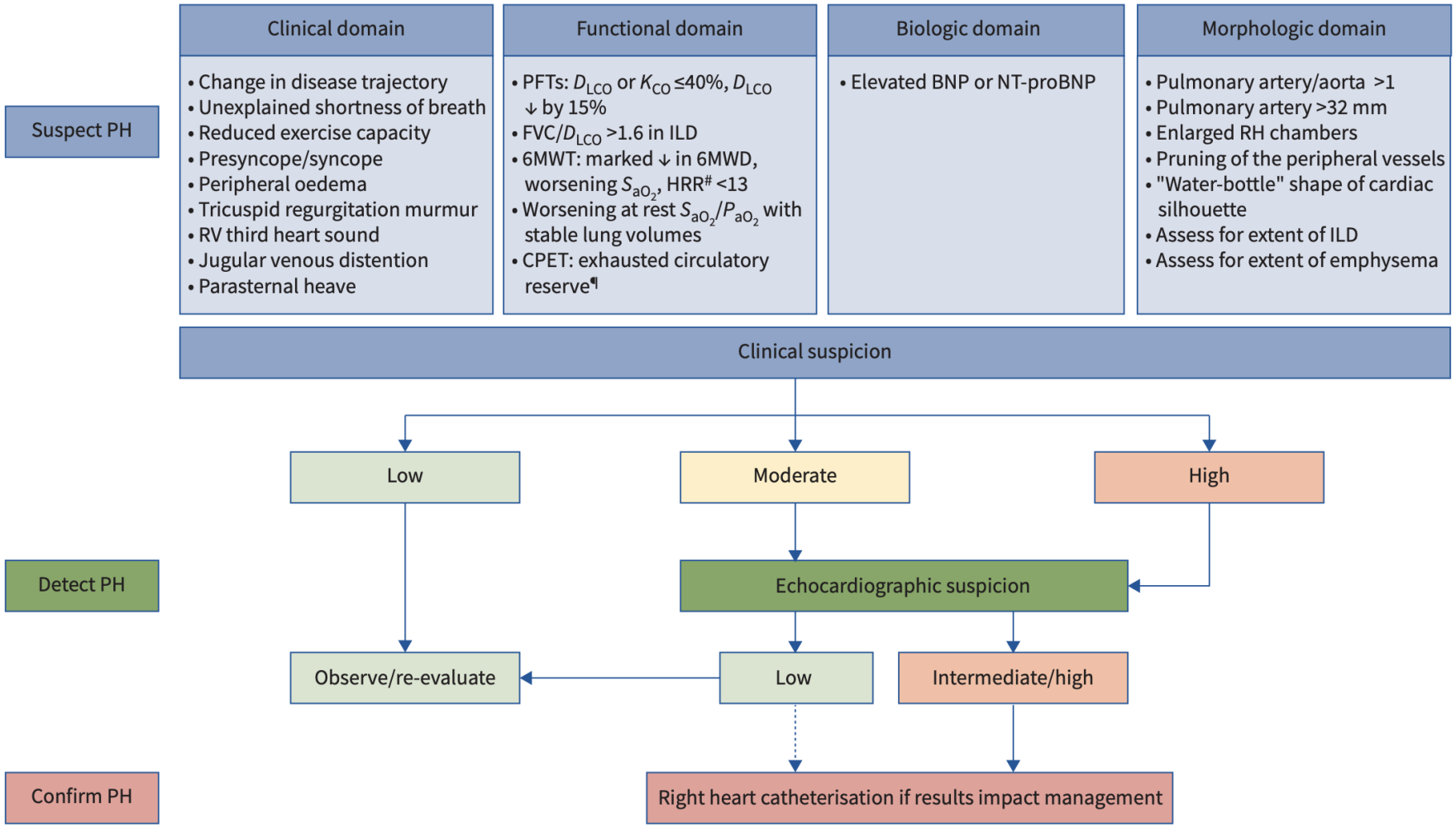
Diagnostika PH-CLD



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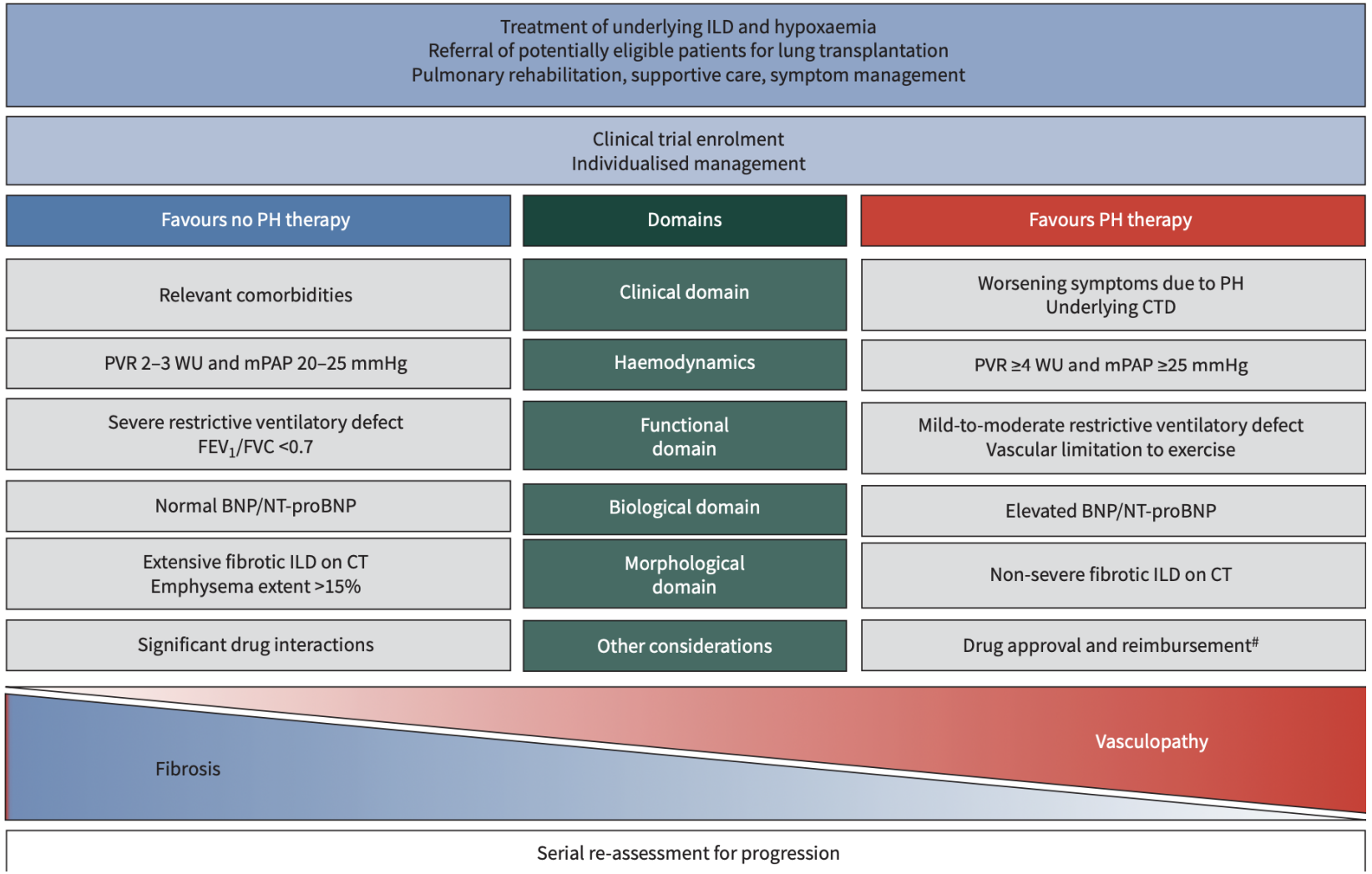
Managemenet PH-ILD



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PH-CLD – PSK

- **Indikace:**
  - perioperační management
  - fenotypizace choroby a úvaha o léčbě PH
  - klinické studie
  - před Tx plic
  - před volum redukčními výkony
- **Provádět měření ve stabilizovaném stavu**

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PH-CLD – léčba (holistický přístup)

- **Léčba plicního onemocnění**
- Obecná opatření (léčba komorbidit, zanechání kouření, vakcinace, DDOT, RHB..)
- Léčba specifickou léčbou PAH ?

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First author, year [reference]	Lung disease	Study design	Subjects n	Therapy	Results	Comments
COPD trials						
Vitulo, 2017 [167]	COPD-PH	RCT	28	Sildenafil (n=18)	Decrease in PVR, improvement in BODE, D_{LCO} and quality of life	No adverse effect on oxygenation
Maron, 2022 [168]	COPD-PH	RCT	42	Tadalafil (n=28)	No change in PVR or mPAP at 6 months Improvement in shortness-of-breath questionnaire	No adverse effect on oxygenation
Nathan, 2024 [169]	COPD-PH	RCT	136	Inhaled treprostinil (n=66)	Decrease in 6MWD at 12 weeks	Study terminated due to increased SAE in the treated group
ILD/IIP/IPF trials						
Kolb, 2018 [170]	IPF	RCT	274	Nintedanib +sildenafil (n=137)	Primary end-point of change in SGRQ was not met	
Behr, 2021 [171]	IPF	RCT	177	Pirfenidone +sildenafil (n=88)	No difference in disease progression (composite end-point)	Composite end-point of decline in 6MWD and hospitalisation or all-cause mortality
Nathan, 2020 [172]	Fibrotic ILD	RCT	45	iNO (n=23)	Improvement in moderate to vigorous and overall activity	Patients on supplemental oxygen
Bellerophon Pulse Technologies [173]	Fibrotic ILD	RCT	145	iNO (n=73)	Did not improve moderate to vigorous activity	Patients on supplemental oxygen
PH associated with ILD/ IIP/IPF trials						
Faria-Urbina, 2018 [174]	ILD-PH	Retrospective	22	Treprostinil (inhaled) (n=22)	Improvement in FC and 6MWD No change in resting oxygen requirements	
Nathan, 2019 [62]	IIP-PH	RCT	147	Riociguat (n=73)	Terminated early for unfavourable risk/benefit profile	*Post hoc* analysis of CT scans suggested that advanced CPFE phenotype with emphysema >> fibrosis may have contributed to the negative signal [87]
Waxman, 2021 [61]	ILD-PH	RCT	326	Treprostinil (inhaled) (n=163)	Improved 6MWD, NT-proBNP, clinical worsening and FVC	
Dawes, 2023 [175]	ILD-PH	Retrospective	60	PDE-5i (n=50) ERAs (n=10)	Patients treated with sildenafil showed longer survival	No effect on V'/Q' matching

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PH-CLD – spec. léčba, probíhající studie

Compound, clinicaltrials.gov identifier [reference]	Pathway/mechanism	Trial	End-points	Company/institution
COPD-PH				
MK-5475-03, NCT05612035 [177]	Daily inhaled sGC	Phase 2a INSIGNIA-PH-COPD	Efficacy (6MWD) and safety	Merck
Tadalafil, NCT05844462 [178]	Daily PDE-5i	Phase 3 ERASE PH-COPD	Efficacy (6MWD) and safety in severe PH	Assistance Publique Hôpitaux de Paris
ILD-PH				
Treprostinil palmitil, NCT05176951 [179]	Daily DPI formulation of inhaled treprostinil (prostanoid) prodrug	Phase 2 extension	Safety and tolerability	Insmed
Treprostinil, NCT06129240 [180]	Four times daily DPI formulation of inhaled prostanoid	Phase 3 ASCENT extension	Safety and tolerability	Liquidia
Inhaled treprostinil, NCT04691154 [181]	Twice daily aerosolised liposomal prostanoid	Phase 2 open label	Safety and tolerability	Liquidia/Pharmosa
Hymecromone, NCT05128929 [182]	Twice daily oral coumarin derivative (inhibitor of hyaluronan synthesis)	Phase 2 SATURN study	Safety and tolerability	Stanford University
Bardoxolone methyl, NCT03068130 [183]	Antioxidant (acts *via* Nrf2 pathway)	Phase 2 LARIAT and RANGER studies	6 IPF-PH, 4 IIP-PH 17 CTD ILD-PH patients 6MWD change of +38 m in the IPF-PH cohort	Reata/Biogen

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Závěry

- **Důraz na přesnější fenotypizaci**
- **Časté overlap syndromy (kombinace více příčin PH)**
- **Dif. dg. PAH a LHD-PH – předtestová pravděpodobnost LHD, PSK a provokační testy**
- **PH-LHD studie z poslední doby (riociguat, tadalafil a macitentan) vyšly negativně**
- **PH-CLD – tendence ke zlepšení u sildenafilu, PH-ILD – inhalační treprostinil**
- **PH-CLD – vedle funkčního vyšetření plic důraz na používaní zobrazovacích metod**

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