PH asociovaná s onemocněním levého srdce a plic. Léčba PH ve specifických situacích

VLADIMÍR DYTRYCH

KOMPLEXNÍ KARDIO VASKULÁRNÍ CENTRUM VFN Praha

European Reference Network
for rare or low prevalence complex diseases

Network Respiratory Diseases (ERN-LUNG)

Member General University Hospital in Prague — Czechia

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 P

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* 2

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

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

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

Správná metodologie měření PCWP

- Dříve navženo měření v endexpiriu a endiastole, což nejlépe vyjadřuje endiastolický tlak LK
- Měření v endiastole však minimalizuje vliv V vlny, která odráží patologii mitrální chlopně a levé síně na tlak v plicnici, proto průměrný PCWP by měl být více relevantní při kalkulaci PVR
- Vzhledem k dependenci na volumové náplni krevního řečiště je stanovení horní hranice PCWP obtížné, i vzhledem k evidenci z klinických studií ponechána hodnota 15 mmHg
- PCWP 12-15 (18) mmHg je bráno jako rozhraní nejistoty, kontextualizace hemodynamiky s rizikovými faktory nebo onemocněním LK

Maron BA, Bortman G, De Marco T, et al. Pulmonary hypertension associated with left heart disease. Eur Respir J 2024

Fenotypizace PH-LHD

- **PH u mitrální stenózy** – ve světě jedna z nejčastějších PH-LHD, až ve 40 % nedojde k normalizaci PVR po intervenci na chlopni, není dostatečná evidence, jak léčit, časnější intervence ?
- **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
- **Vzrůstá počet pacientů s jinými PH (CTEPH), kteří mají vyšší PCWP**

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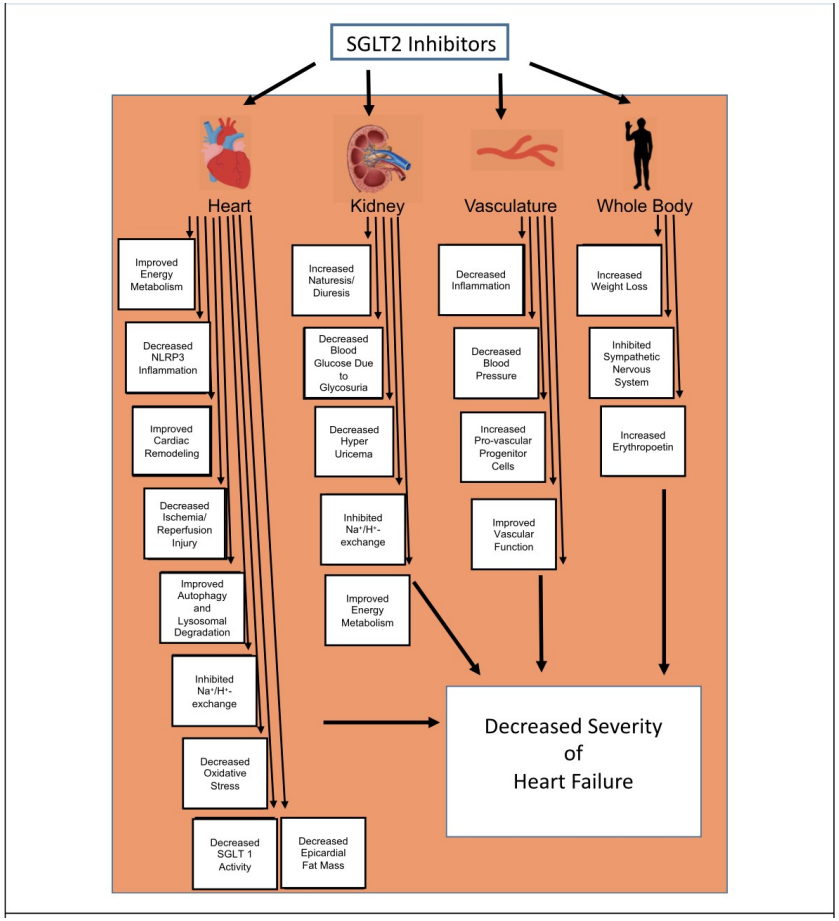
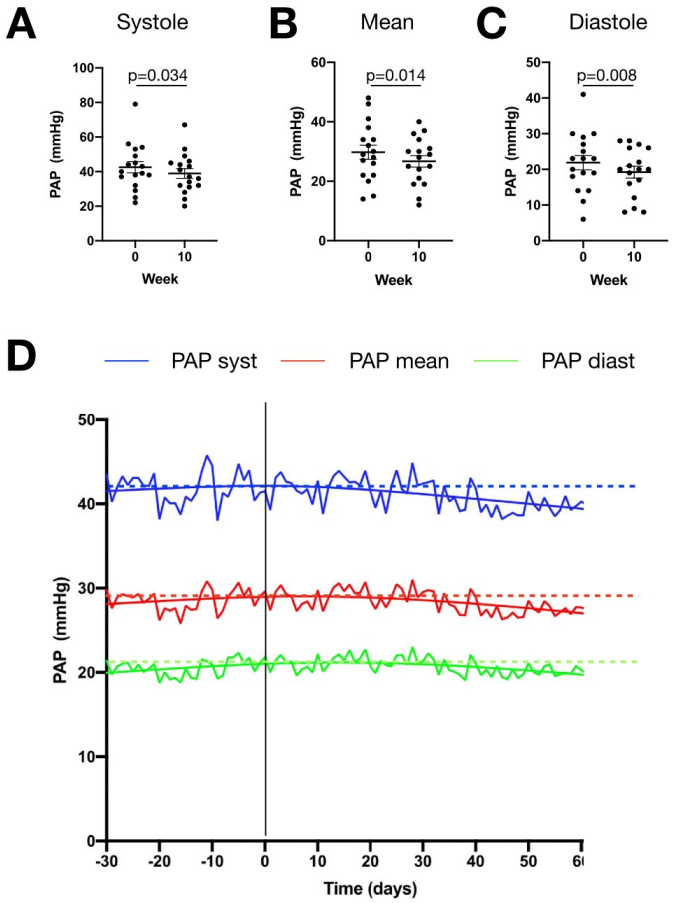
SGLT2 inhibitory a PH-LHD





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 pati with chronic heart failure-further evidence for improved hemodynamics by continuous pressure monitoring. Clin F Cardiol 2022

Dif. dg. PAH a PH-LHD

- Vzhledem ke komorbiditám někdy obtížná
- První krok stanovení předtestové pravděpodobnosti LHD
- K potvrzení diagnózy nutná PSK
- Podíl vetrikulární interdependence při PAH a dilataci PK na elevaci PCWP méně pravděpodobný při kardiální kompenzaci a měl by být snadno identifikovaný pokud je RAP větší nebo rovno PCWP
- Zátěžové testy dříve doporučeny při PCWP 13-15 mmHg, dle novějších prací by měly být zváženy i při nižším PCWP a vysoké pravděpodobnosti LHD
- Overlap syndromy (systémová sklerodermie)

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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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Provokační testy

Volume loading				
Agrawal, 2019 [80]	178	In selected patients with mPAP >25 mmHg and PAWP ≤15 mmHg Infusion of 500 mL or 10–15 mL·kg^{-1} of 0.9% sodium chloride over 5 min *via* central venous access	Early diastolic mitral-inflow velocity was higher and ratio of E velocity to average mitral annular tissue Doppler velocity was higher in patients with occult diastolic dysfunction unmasked by saline challenge or resting diastolic dysfunction	Identify noninvasive measures that correlate with degree of pulmonary vascular disease measured by haemodynamics Clarify "abnormal" response following fluid challenge, and if ULN is age-dependent
Exercise provocation				
Gorter, 2018 [93]	161	Supine recumbent bicycle: initial measures when supine, feet on pedals and unloaded then serial measurements with an increase workload by 10–20 W every 3 min until exhaustion	Greater increase in PAWP/CO, reduced PAC, higher PVR with exercise	Define what defines an abnormal RV response to exercise Distinguish exercise haemodynamic parameters that indicate a favourable response to different therapies such as PDEi, SGLT2i, GLP-1
Müller, 2023 [85]	121	Semi-supine exercise on cycle ergometer with stepwise incremental protocol (increase by 10–20 W every 3 min)	PAH and CTEPH patients ≥50 years had significantly higher PAWP/CO slope than patients <50 years without exceeding PAWP 25 mmHg during exercise	Clarify the population in which iCPET testing is useful clinically Characterise the association between underlying lung disease (or spirometry abnormalities) on pulmonary vascular and RV responses to exercise
Caravita, 2023 [89]	86	Passive leg raise (feet on the pedals) and invasive cycle cardiopulmonary exercise testing	Few HFpEF patients have latent PVD	

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Staging PH-LHD u HFpEF

	A At risk	B Structural heart disease	C Symptomatic heart disease	D Right heart predominant
Clinical profile	Risk factors for HFpEF-PH BMI >30 kg·m^{-2} Systemic hypertension Glucose intolerance/ diabetes Atrial fibrillation Sleep apnoea?	±Risk factors for HFpEF-PH	±Risk factors for HFpEF-PH	±Risk factors for HFpEF-PH
Symptom burden	None	WHO FC I–II	WHO FC II–III	WHO FC IV
Exercise capacity	Normal	V'_{O_2peak} >80% predicted. V'_E/V'_{CO_2} slope <30	V'_{O_2peak} 50–80% predicted with RER >1.05 V'_E/V'_{CO_2} slope 30–37	V'_{O_2peak} <50% predicted with RER >1.05 V'_E/V'_{CO_2} slope >37
Typical echo findings	No abnormalities	Mildly elevated pTRV Mildly enlarged LAVI Grade 1–2 diastolic dysfunction ±Valvular disease Normal RV function	Mild–moderately elevated pTRV Mild–moderately enlarged LAVI Grade 2 diastolic function Mild–moderate valvular disease Mild–moderate RV dysfunction	Severely elevated pTRV Severe enlarged LAVI Grade >2 diastolic dysfunction Severe valvular disease Severe RV dysfunction
Typical haemodynamics		mPAP 19–24 mmHg PAC <3.0 mL·mmHg^{-1}	mPAP 25–35 mmHg PVR >2.0–3.0 WU with PAWP >15 mmHg ±PVR <2.0 with after diuresis ±RAP elevation	mPAP >35 mmHg PVR >5.0 WU with PAWP >15 mmHg PVR >3.0 WU after diuresis Cardiac index <2.2 L·min^{-1}·m^{-2} Significantly elevated RAP Low PAPi
NT-proBNP	Normal	Normal or mildly elevated	Pre-diuresis: >>ULN Post-diuresis: <ULN or >ULN	>>>ULN even after diuresis
PH management approach	Treat comorbidities Risk factor modification Dietary modification	Treat comorbidities Risk factor modification Dietary modification Optimise GDMT Annual echo Clinical trial enrolment (including studying PAH medications)	Risk factor modification Dietary modification Optimise GDMT Biannual follow-up with functional test and echo Treat comorbidities Clinical trial enrolment (including studying PAH medications) Consider PAP monitoring device Consider referral to PH centre	Risk factor modification Dietary modification Optimise GDMT Treat comorbidities Bi-annual follow-up with functional test and echo Clinical trial enrolment Consider PAP monitoring device Clinical trial enrolment (including studying PAH medications) Referral to PH centre for individualised therapy Referral to PH/HF centre for individualised management

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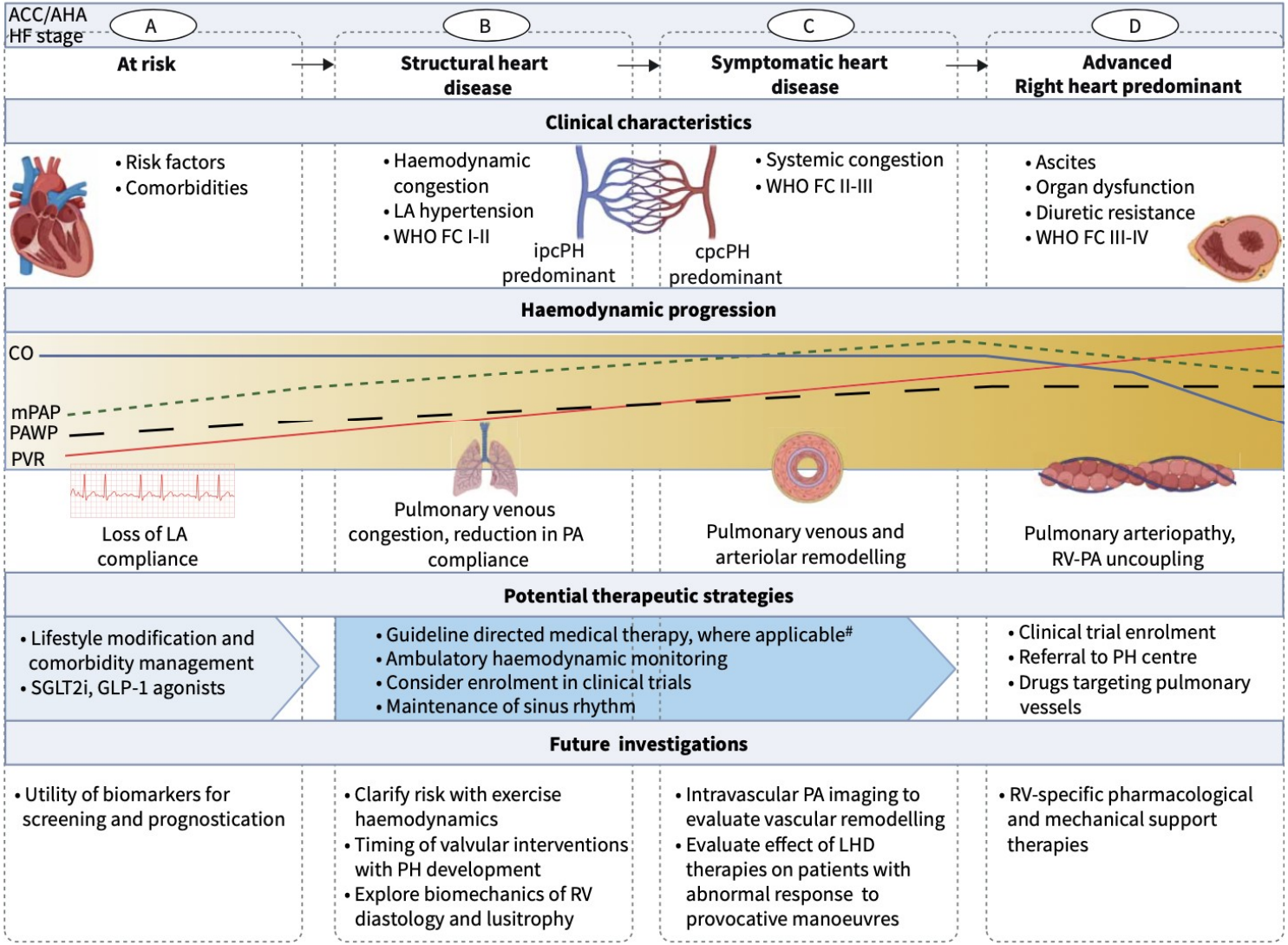
Klinická stádia PH-LHD



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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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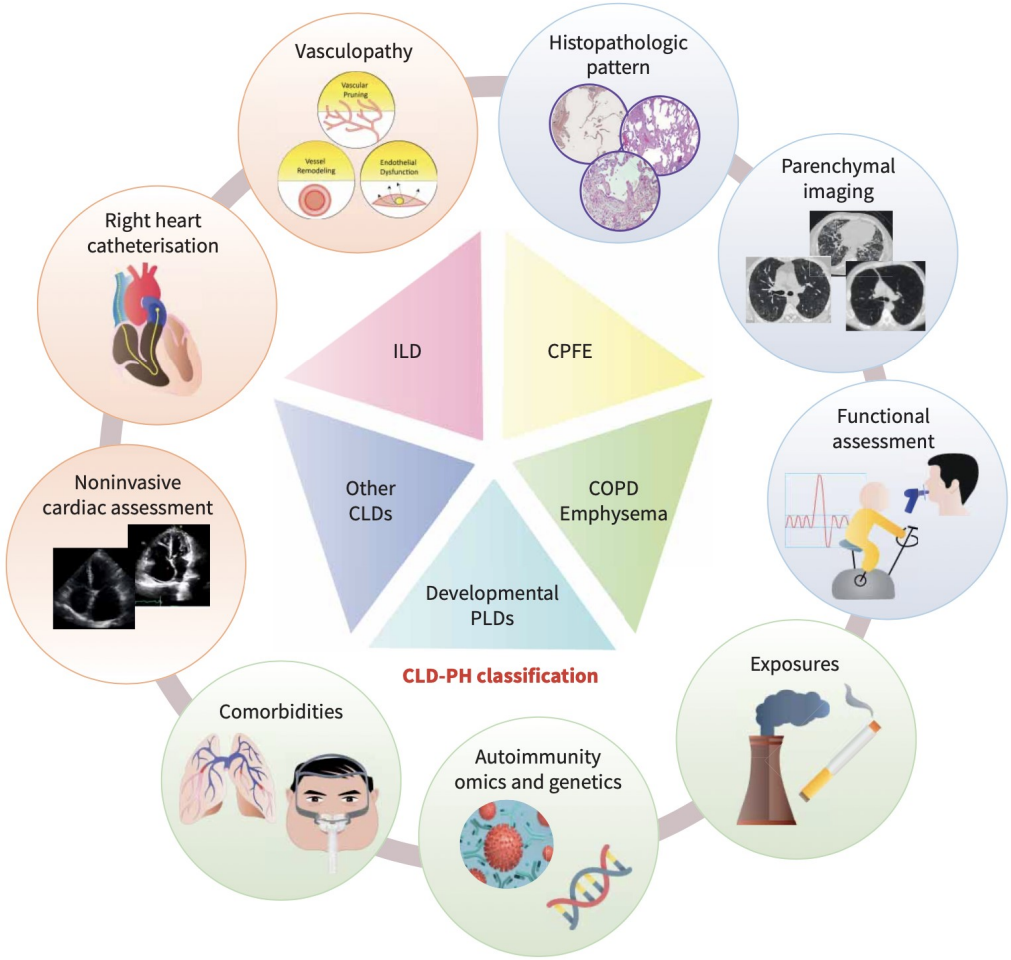
PH-CLD - fenotypizace

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



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PH-COPD - fenotypy

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

HOPN s postkapilární PH – nejčastěji kombinace s HEpEF, 23 % pacientů má ipcPH ebo cpcPH

H s mírnou CHOPN (GOLD 1 nebo 2, FEV1 > 60 (70) % nál.h.) – plicní vaskulární notyp, často DLCO < 45%, v registru COMPERA 52 % pacientů s PAH, až 50 % těchto acientů má středně závažné až závažné parenchymové změny na CT → PH skupiny 3

H se středně závažnou až závažnou CHOPN (GOLD 2 nebo 3)

H se závažnou CHOPN (GOLD 4 a/nebo těžké parenchymové změny), FEV1 < 30 %

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PH-ILD - fenotypy

H-ILD hemodynamika – odklon od cut-off hodnoty 5 W.j., doporučeno hodnocení tíže
ko kontinuum, snaha odlišit prognostické markery od parametrů s indikací k léčbě

H-CTD related ILD – existují práce, které ukazují lepší výsledky se spec. léčbou než
ostatních PH-ILD

H u pacientů s lehkou ILD – často diagnostikována jako PAH, má horší prognózu než PAH bez
D

H-ILD s predominantně postkapilární PH – 5-20% pacientů s PH-ILD, má lepší prognózu

PFE associated PH – často u kuřáku, ale i u CTD, profes. expozic, špatná prognóza

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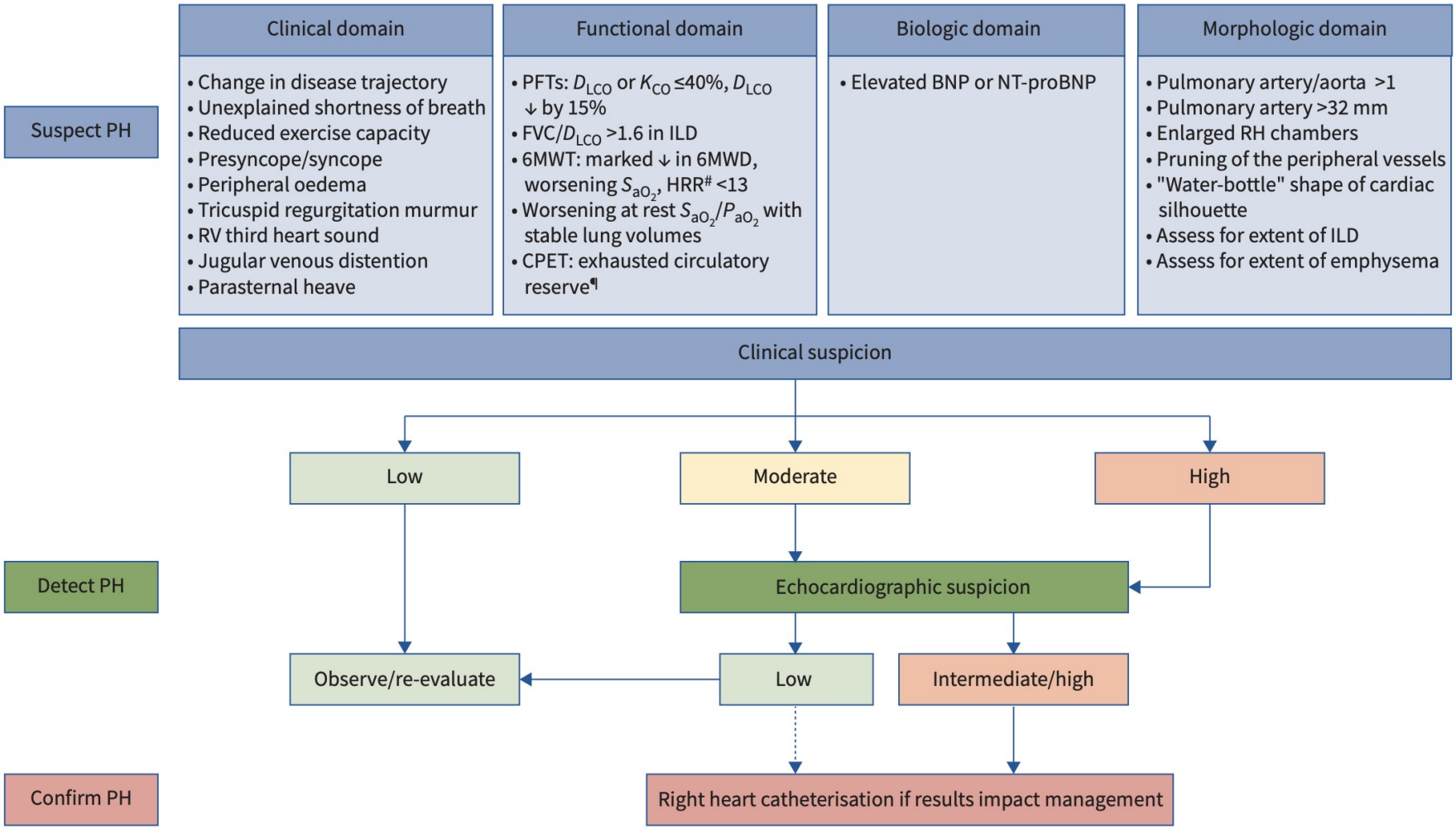
Diagnostika PH-CLD



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PH-CLD – PSK

ndikace:

- perioperační management
- fenotypizace choroby a úvaha o léčbě PH
- klinické studie
- před Tx plic
- před volum redukčními výkony

rovádět měření ve stabilizovaném stavu

zhledem k velkým změnám během respirace (zejména CHOPN a bézní) spíše průměrné hodnoty všech tlakových měření z několika espiračních cyklů než měření v end-expiriu

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PH-CLD – léčba (holistický přístup)

- éčba plicního onemocnění
- Obecná opatření (léčba komorbidit, zanechání kouření, vakcinace, DOT, RHB..)
- éčba 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

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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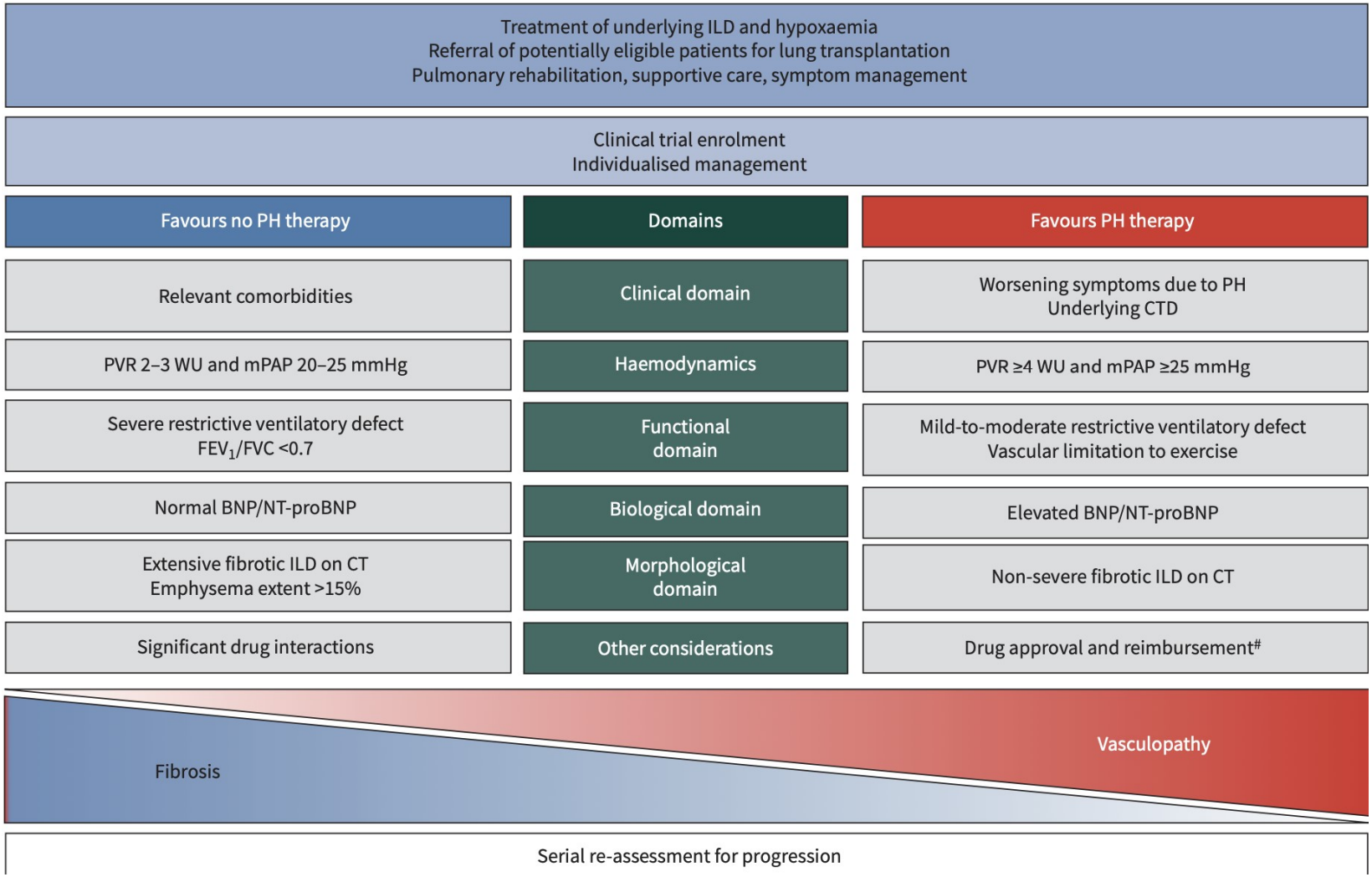
Managemenet PH-ILD



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Léčba PH ve specifických situacích – WSPH 2024

erioperační péče

lanagement těhotenství

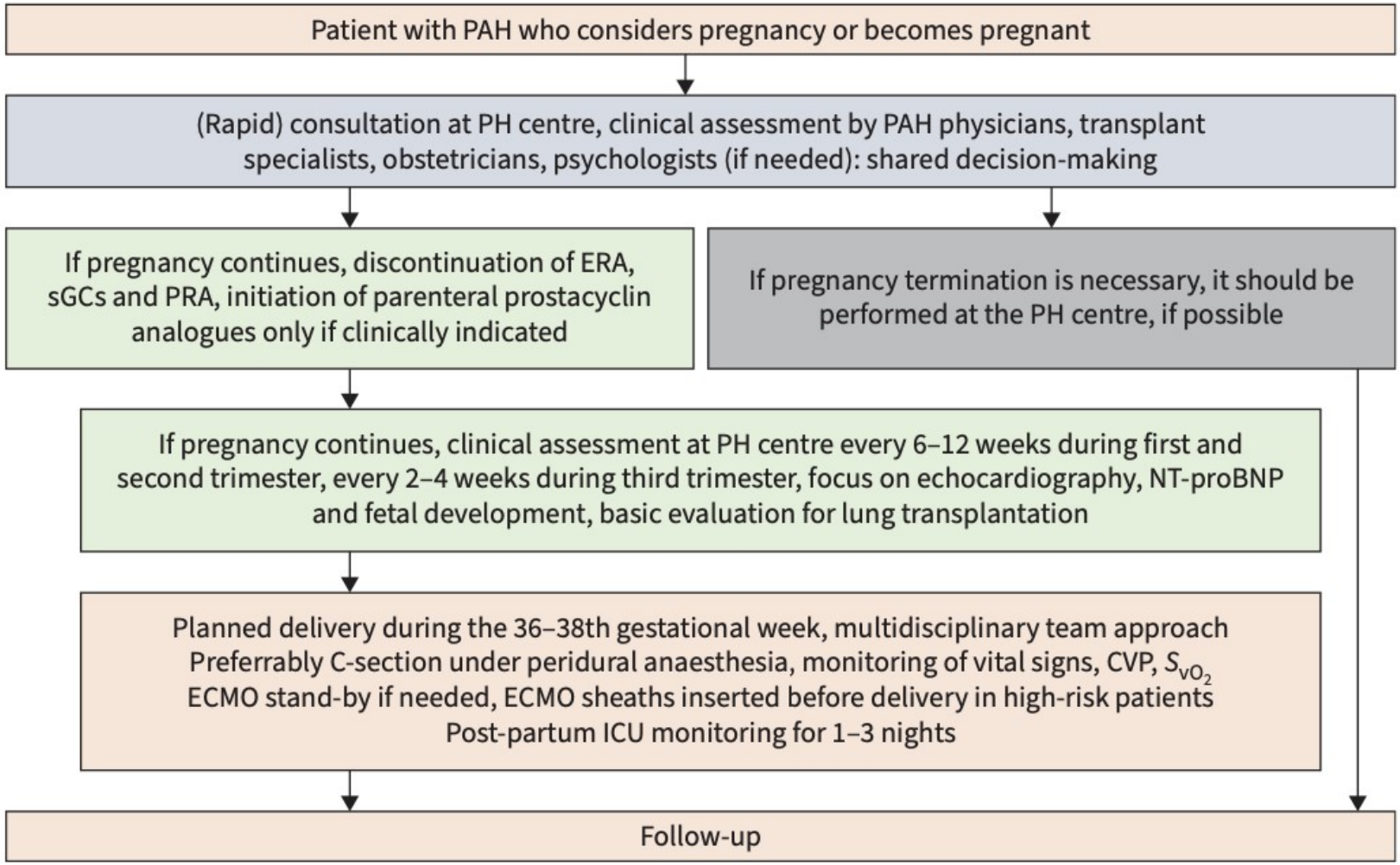
dherence k léčbě

aliativní péče

liv klimatu na PH

Preston IR, Howard LS, Langleben D, et al. Management of pulmonary hypertension in special conditions. Eur Respir J

Léčba PH ve specifických situacích – management těhotenství



Preston IR, Howard LS, Langleben D, et al. Management of pulmonary hypertension in special conditions. Eur Respir J

Závěry

ak u PH-LHD, tak PH-CLD důraz na přesnější fenotypizaci

ůsledná diferenciální diagnostika vzhledem k velmi častému výskytu komorbidit

Dif. dg. PAH a LHD-PH – předtestová pravděpodobnost LHD, PSK a provokační testy

taging PH-LHD, důraz na prevenci u pacientů s lehkou PH a HFpEF

PH-LHD studie z poslední doby (riociguat, tadalafil a macitentan) neprokázaly efekt, naop některých potenc. škodlivý efekt

PH-CLD – tendence ke zlepšení při léčbě sildenafilem, PH-ILD – inhalační treprostinil

PH-CLD – vedle funkčního vyšetření plic důraz na používaní zobrazovacích metod k anovení tíže parenchymového postižení plic

Shlobin OA, Adir Y, Barbera JA, et al. Pulmonary hypertension associated with lung diseases. Eur Respir J 2