FAKULTNÍ NEMOCNICE® OLOMOUC

Lékařská fakulta
Univerzita Palackého v Olomouci

KOMPLEXNÍ KARDIOVASKULÁRNÍ CENTRUM
FAKULTNÍ NEMOCNICE OLOMOUC

Plicní arteriální hypertenze

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6. sjezd České asociace ambulantní kardiologie

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ESC/ERS GUIDELINES

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

Developed by the task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS).

Endorsed by the International Society for Heart and Lung Transplantation (ISHLT) and the European Reference Network on rare respiratory diseases (ERN-LUNG).

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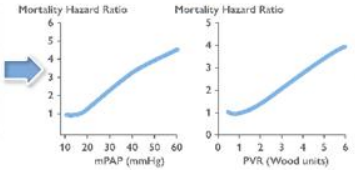
Pulmonary Hypertension

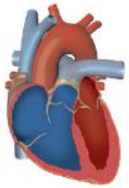
Prevalence

1% Global population

Pulmonary congestion in post-capillary PH

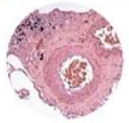
Pulmonary vascular disease / obstruction in pre-capillary PH





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 • Associated conditions	• IpcPH • CpcPH	• Non-severe PH • Severe PH	• CTEPH • Other pulmonary obstructions	• Haematological disorders • Systemic disorders

Prevalence

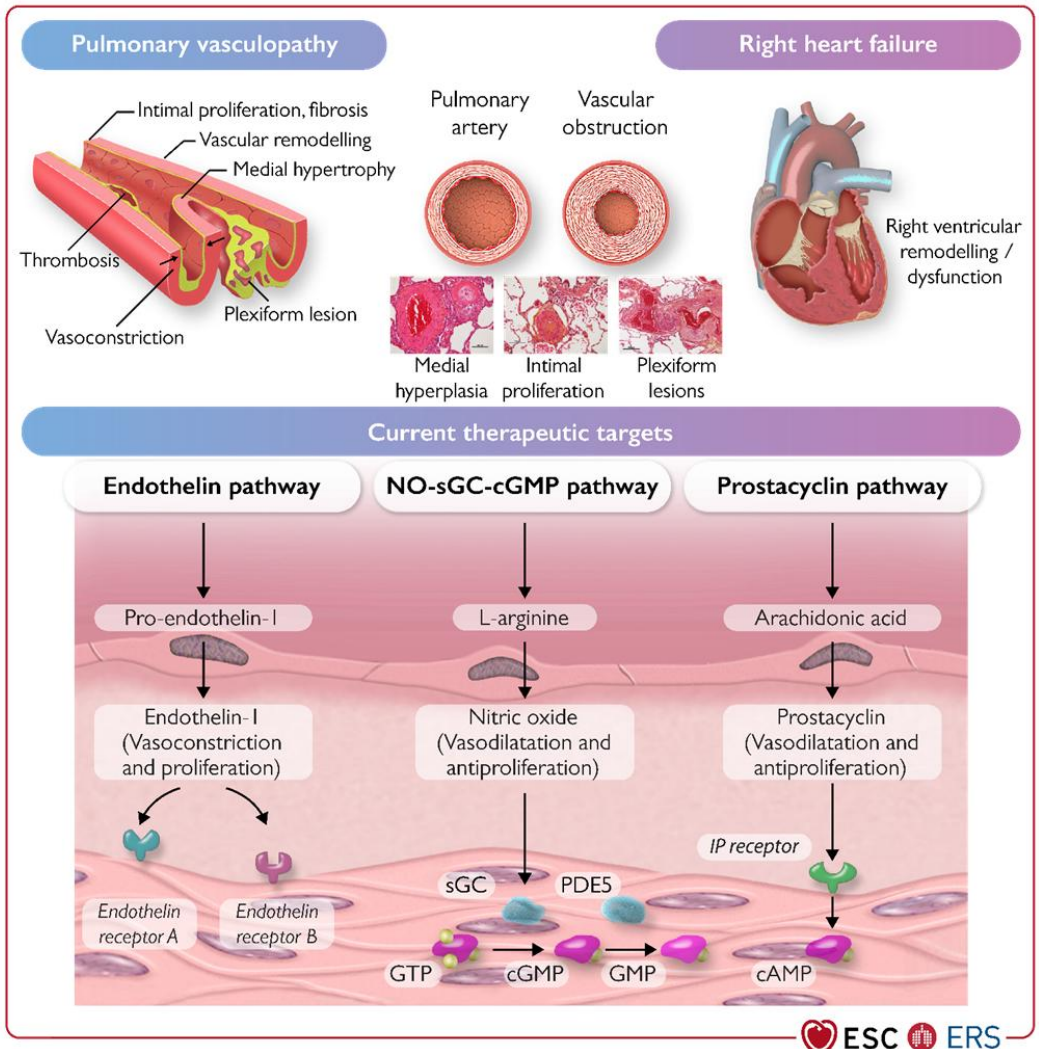
Rare	Very common	Common	Rare	Rare
				

Therapeutic Strategies

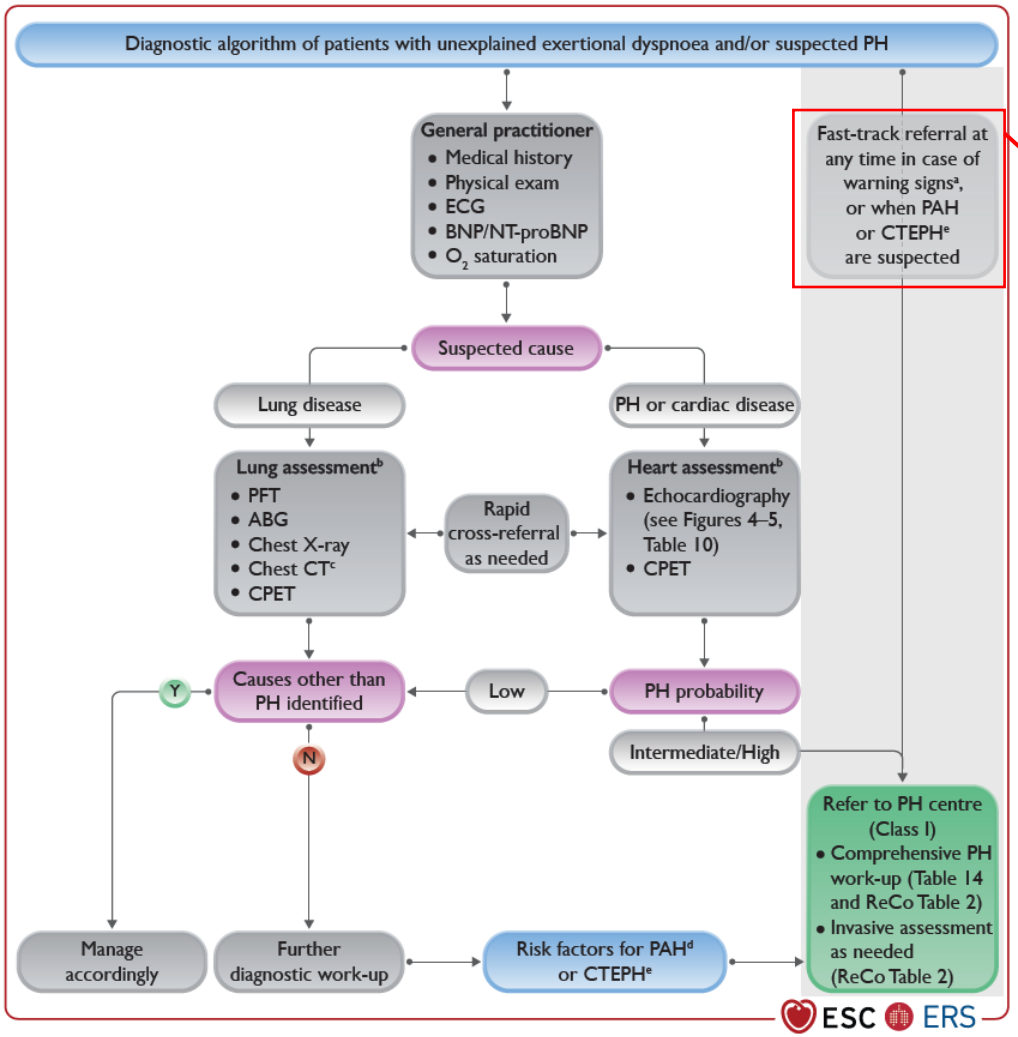
Medical therapy • PAH drugs • CCB in responders **Lung transplantation**	**IpcPH:** • Treatment of LHD [a] **CpcPH:** • Treatment of LHD [a] • Potentially: PAH drugs (trials)	**PH-lung disease:** • Optimized care of underlying lung disease **Severe PH:** • Potentially: PAH drugs (trials)	**Surgical therapy:** • PEA **Interventional:** • BPA **Medical therapy:** • PH drugs	**Optimized treatment of underlying disease** • Potentially: PAH drugs (trials)

ESC ERS

Plicní arteriální hypertenze (PAH)



Dg. algoritmus



Warning signs:

- rapid progression of symptoms
- severely reduced exercise capacity
- pre-syncope or syncope on mild exertion
- signs of right heart failure

Pravostranná katetrizace

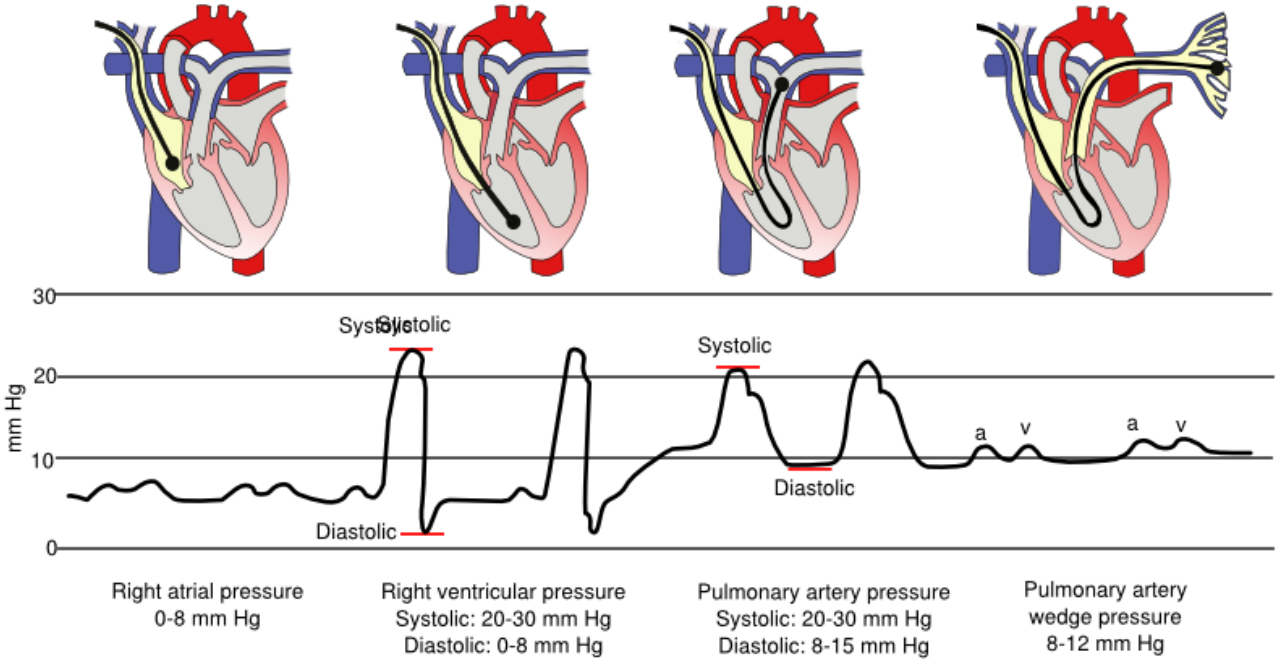


Table 12 **Route of administration, half-life, dosages, and duration of administration of the recommended test compounds for vasoreactivity testing in pulmonary arterial hypertension**

Compound	Route	Half-life	Dosage	Duration
Nitric oxide[129]	inh	15–30 s	10–20 p.p.m.	5–10 min[a]
Iloprost[130,131]	inh	30 min	5–10 μg[b]	10–15 min[c]
Epoprostenol[129]	i.v.	3 min	2–12 ng/kg/min	10 min[d]

Inh, inhaled; i.v., intravenous.
[a]Measurement as a single step within the dose range.
[b]At mouth piece.
[c]Measurement as a single step, temporize full effect.
[d]Incremental increase in 2 ng/kg/min intervals, duration of 10 min at each step.

PAH – akutní vazoreaktivita

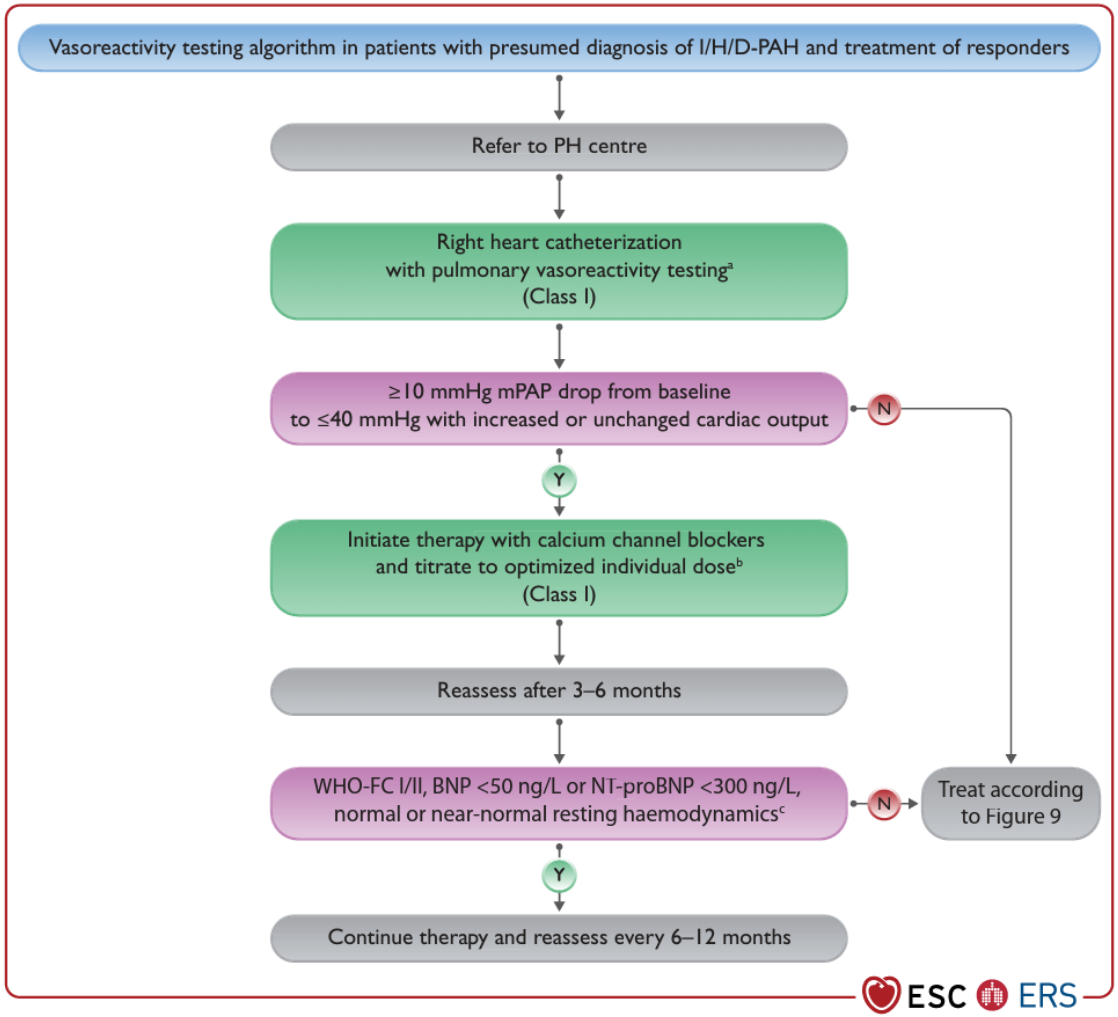
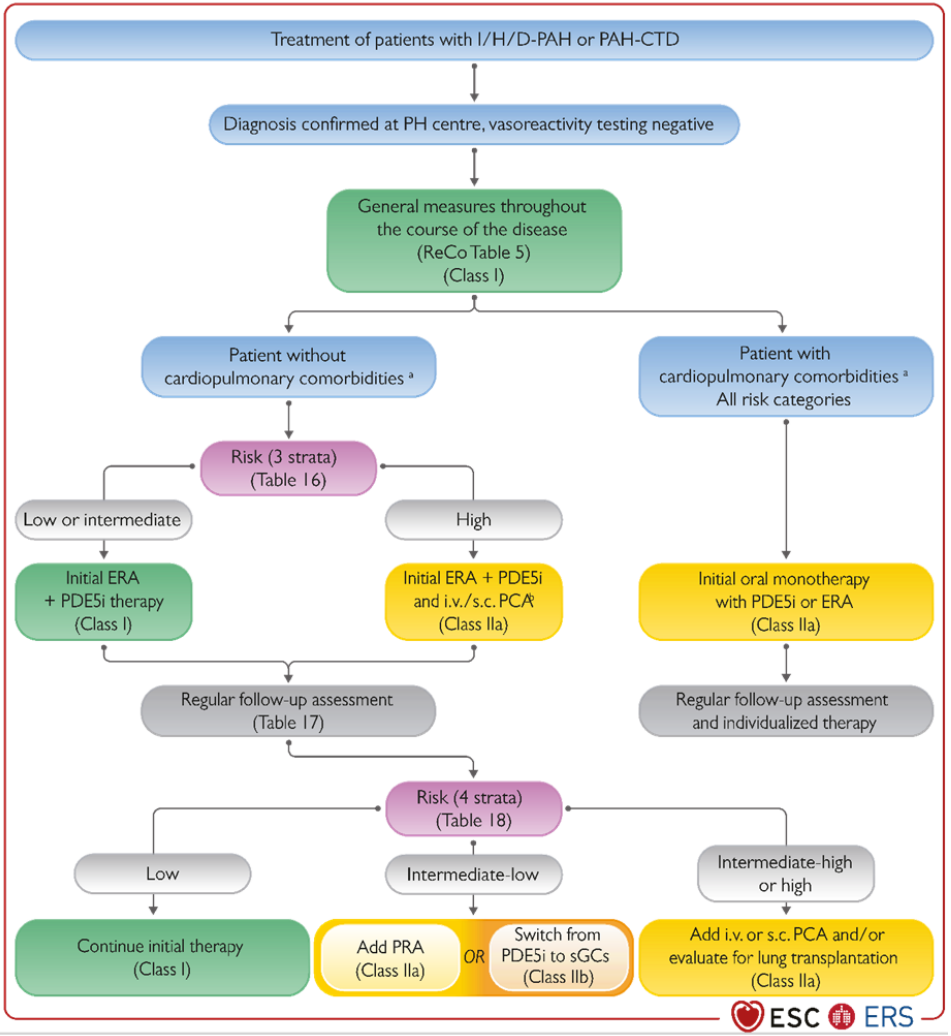


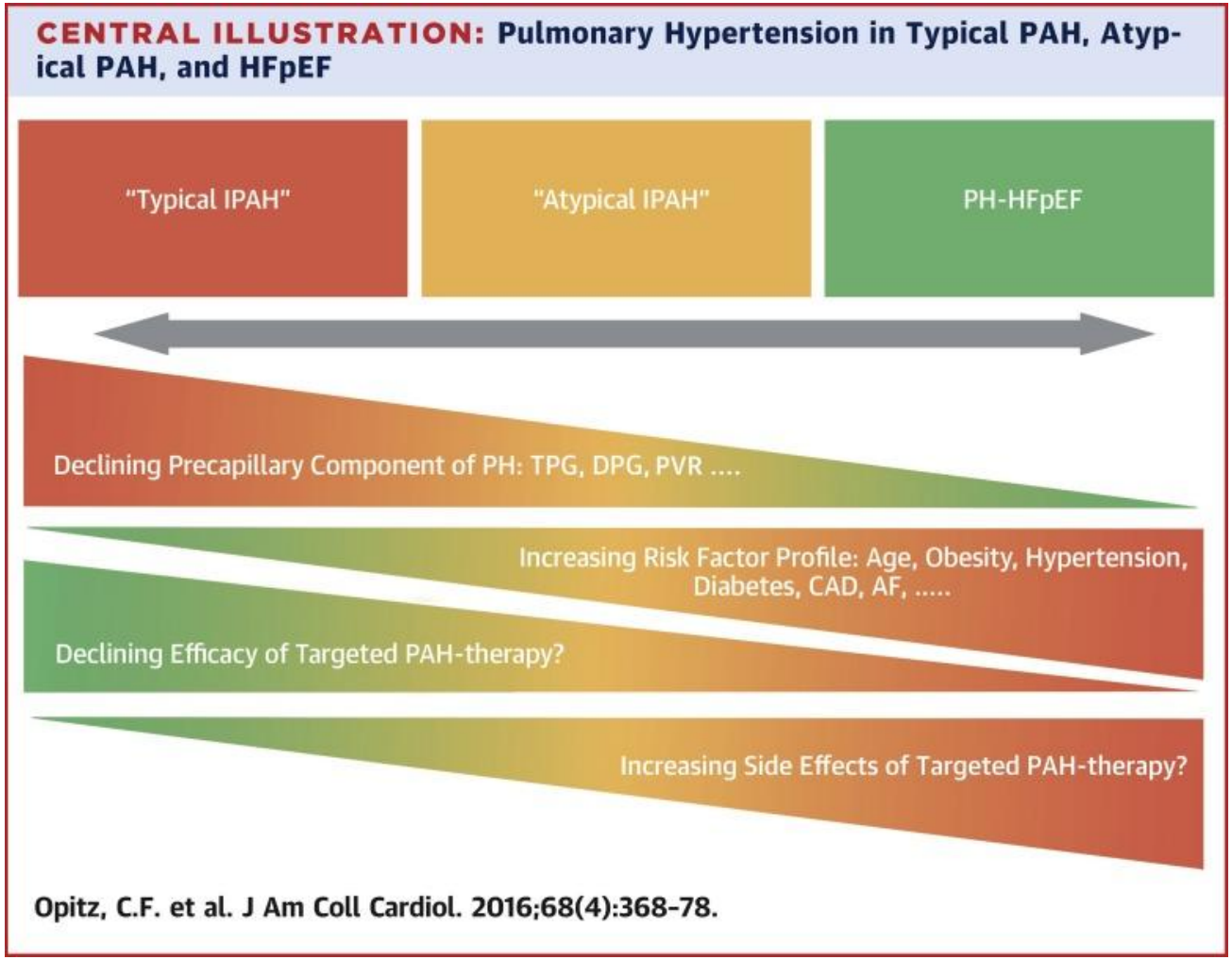
Table 19 **Dosing of pulmonary arterial hypertension medication in adults**

	Starting dose	Target dose
Calcium channel blockers		
Amlodipine	5 mg o.d.	15–30 mg o.d.[a]
Diltiazem	60 mg b.i.d.[b]	120–360 mg b.i.d.[b]
Felodipine	5 mg o.d.	15–30 mg o.d.[a]

PAH – léčebný algoritmus



Klinické fenotypy PAH – role komorbidit



PAH – benefit z časné eskalace léčby

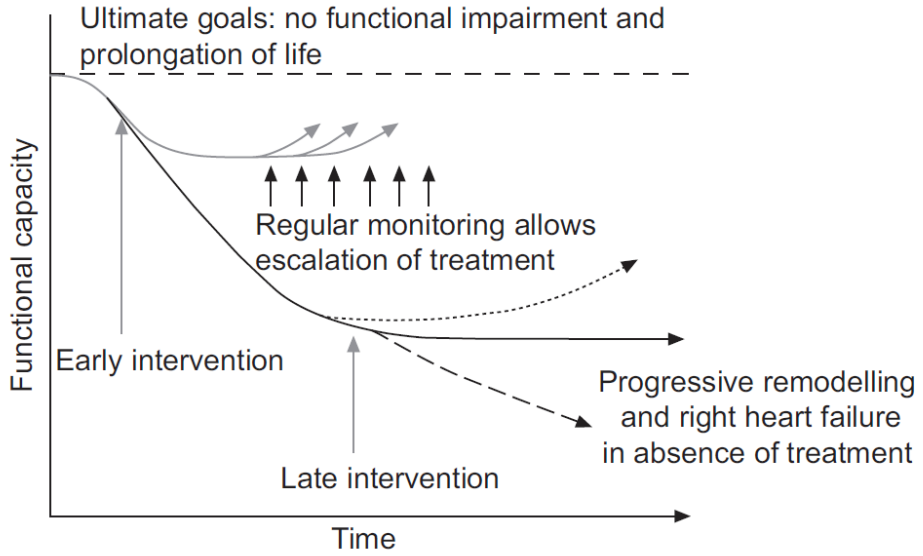


FIGURE 1. Schematic diagram showing the ideal approach to pulmonary arterial hypertension management, which involves regular monitoring and early intervention.

Eur Respir Rev 2010; 19: 118, 272–278
DOI: 10.1183/09059180.00008210

REVIEW

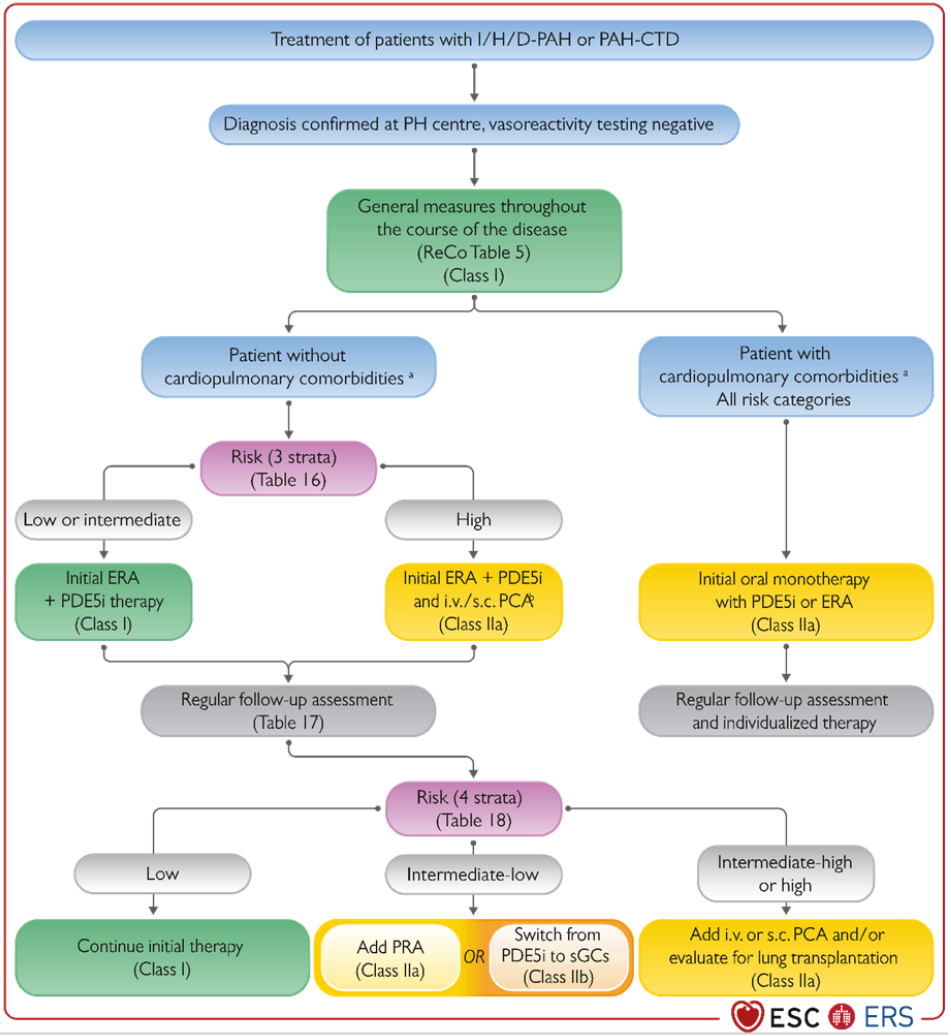
Treat-to-target strategies in pulmonary arterial hypertension: the importance of using multiple goals

O. Sitbon* and N. Galiè#

- Častější výskyt akutních příhod a progrese onemocnění vedou k častým hospitalizacím a zvýšenému riziku úmrtnosti
- S každou akutní příhodou může poškození myokardu přispívat k progresivní dysfunkci

Sitbon O et al. Eur Respir Rev 2010 Dec;19(118):272-8

PAH – léčebný algoritmus



Riziková stratifikace pacientů

Table 16 Comprehensive risk assessment in pulmonary arterial hypertension (three-strata model)

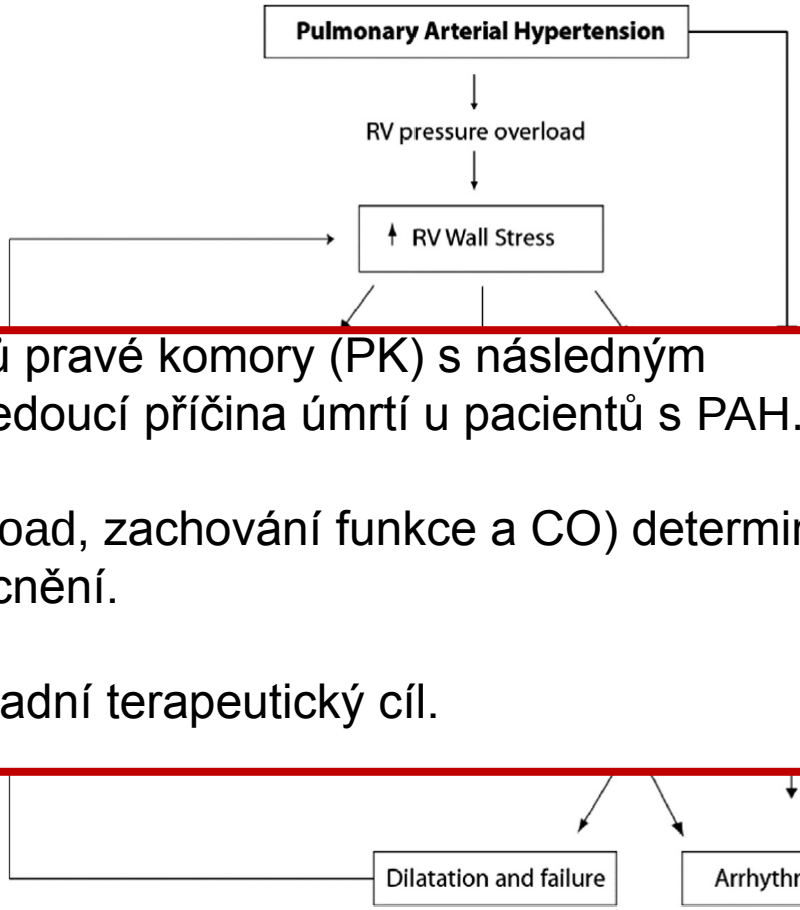
Determinants of prognosis (estimated 1-year mortality)	Low risk (<5%)	Intermediate risk (5–20%)	High risk (>20%)
Clinical observations and modifiable variables			
Signs of right HF	Absent	Absent	Present
Progression of symptoms and clinical manifestations	No	Slow	Rapid
Syncope	No	Occasional syncope[a]	Repeated syncope[b]
WHO-FC	I, II	III	IV
6MWD[c]	>440 m	165–440 m	<165 m
CPET	Peak VO_2 >15 mL/min/kg (>65% pred.) VE/VCO_2 slope <36	Peak VO_2 11–15 mL/min/kg (35–65% pred.) VE/VCO_2 slope 36–44	Peak VO_2 <11 mL/min/kg (<35% pred.) VE/VCO_2 slope >44
Biomarkers: BNP or NT-proBNP[d]	BNP <50 ng/L NT-proBNP <300 ng/L	BNP 50–800 ng/L NT-proBNP 300–1100 ng/L	BNP >800 ng/L NT-proBNP >1100 ng/L
Echocardiography	RA area <18 cm^2 TAPSE/sPAP >0.32 mm/mmHg No pericardial effusion	RA area 18–26 cm^2 TAPSE/sPAP 0.19–0.32 mm/mmHg Minimal pericardial effusion	RA area >26 cm^2 TAPSE/sPAP <0.19 mm/mmHg Moderate or large pericardial effusion
cMRI[e]	RVEF >54% SVI >40 mL/m^2 RVESVI <42 mL/m^2	RVEF 37–54% SVI 26–40 mL/m^2 RVESVI 42–54 mL/m^2	RVEF <37% SVI <26 mL/m^2 RVESVI >54 mL/m^2
Haemodynamics	RAP <8 mmHg CI ≥2.5 L/min/m^2 SVI >38 mL/m^2 SvO_2 >65%	RAP 8–14 mmHg CI 2.0–2.4 L/min/m^2 SVI 31–38 mL/m^2 SvO_2 60–65%	RAP >14 mmHg CI <2.0 L/min/m^2 SVI <31 mL/m^2 SvO_2 <60%

Riziková stratifikace - změny

Determinants of prognosis (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–20%	High risk >20%
Biomarkers: BNP or NT-proBNP	BNP <50 ng/L NT-proBNP <300 ng/L	BNP 50–**800** ng/L NT-proBNP 300–**1100** ng/L	BNP >**800** ng/L NT-proBNP >**1100** ng/L
Echocardiography	RA area <18 cm^2 **TAPSE/sPAP** **>0.32 mm/mmHg** No pericardial effusion	RA area 18–26 cm^2 **TAPSE/sPAP** **0.19–0.32 mm/mmHg** Minimal pericardial effusion	RA area >26 cm^2 **TAPSE/sPAP** **<0.19 mm/mmHg** Moderate or large pericardial effusion
cMRI	**RVEF >54%** **SVI >40 mL/m^2** **RVESVI <42 mL/m^2**	**RVEF 37–54%** **SVI 26–40 mL/m^2** **RVESVI 42–54 mL/m^2**	**RVEF <37%** **SVI <26 mL/m^2** **RVESVI >54 mL/m^2**
Haemodynamics	RAP <8 mmHg CI ≥2.5 L/min/m2 **SVI >38 mL/m^2** SvO2 >65%	RAP 8–14 mmHg CI 2.0–2.4 L/min/m2 **SVI 31–38 mL/m^2** SvO2 60–65%	RAP >14 mmHg CI <2.0 L/min/m2 **SVI <31 mL/m^2** SvO2 <60%

Pravá komora u PAH

- An **afterload mismatch** - increased RV afterload, driven by increased PVR, leads to right heart failure.
- At an early stage, the RV adapts to the increased afterload to preserve stroke volume



- Vyčerpání kompenzačních mechanismů pravé komory (PK) s následným pravostranným srdečním selháním je vedoucí příčina úmrtí u pacientů s PAH.
- Funkce PK (adaptace na zvýšený afterload, zachování funkce a CO) determinuje funkční status a klinický průběh onemocnění.
- Zachování/zlepšení funkce PK jako zásadní terapeutický cíl.

adapted to the pulmonary vascular load so that energy transfer is most efficient.

- In contrast, *maladapted ventricles* usually are characterized by **uncoupling of the RV to the pulmonary circulation**

Figure 1 Pathophysiology of RV Dysfunction in PAH

Increased right ventricular (RV) wall stress, neurohormonal activation, inflammation, and altered bioenergetics contribute to RV remodeling in pulmonary arterial hypertension (PAH). Adaptive remodeling is associated with minimally altered ventriculoarterial coupling. Progressive RV dilation with maladaptive remodeling further contributes to RV stress. Adapted, with permission, from Champion et al. (5), Benza et al. (8), and Rudski et al. (99).

TAPSE/PASP ratio

- significant marker of **ventriuloarterial coupling**
  - index of in vivo RV shortening in the longitudinal axis versus developed force in patients with heart failure
  - non-invasive, indirect measurement of RV contractile function and RV-pulmonary arterial (PA) coupling
  - validated against the ratio of end-systolic to arterial elastances (Ees/Ea)
  - directly compared with pressure–volume loop measures of ventriculoarterial coupling (invasively measured)
- validated as an important **clinical and prognostic parameter** in patients
  - *with **heart failure with and without pulmonary hypertension***
  - *with **combined post- and pre-capillary PH*** (even after adjusting for other echocardiographic or hemodynamic prognostic indicators)

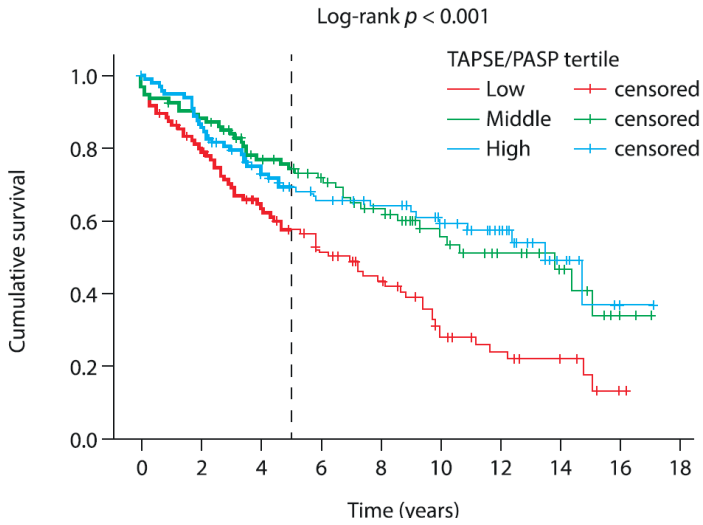
- promising echocardiographic parameter derived from **routinely measured indices**, fully applicable on the **daily basis routine**
  - variation coefficient for intra and interobserver agreements is about 1%
- **Cut-off value:**
  - 0.55 mm/mmHg - probability of PH
  - 0.32 mm/mmHg - low-risk status in patients with PAH
  - 0.19 mm/mmHg - high mortality risk in patients with PAH

Tello K et al. Int J Cardiol . 2018 Sep 1;266:229-235.

TAPSE/PASP ratio

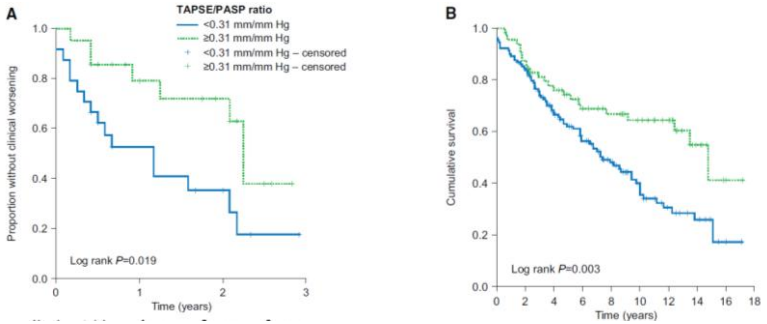
- *Tello K et al. Int J Cardiol 2018*
  - 290 patients with PAH
  - associated with hemodynamics and functional class
  - independently associated with overal mortality (even after adjusting for other echocardiographic or hemodynamic prognostic indicators)

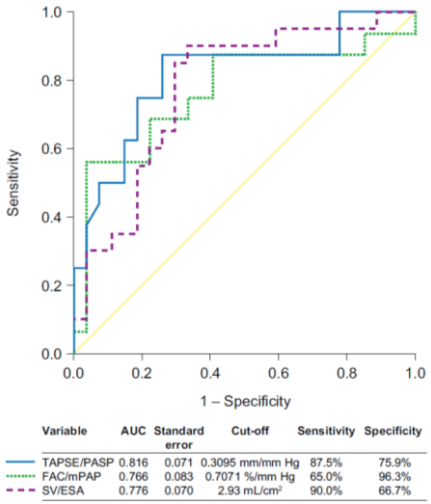
	Overall mortality	
Variables	HR [95% CI]	*p*
TAPSE/PASP ratio, mm/mmHg	4.13 [2.02–8.48]	<0.001



TAPSE/PASP tertile (mm/mmHg)		
Low (<0.19)	Middle (0.19–0.32)	High (>0.32)

- *Tello K et al. Circ Cardiovasc Imaging 2019*
  - 52 patients with PAH and CTEPH
  - TAPSE/PASP correlated with Ees/Ea and end-diastolic elastance
  - TAPSE/PASP <0.31 mm/mm Hg
    - significantly worse prognosis
    - discriminated RV-arterial uncoupling (Ees/Ea <0.805) - sensitivity: 87.5%; specificity: 75.9%

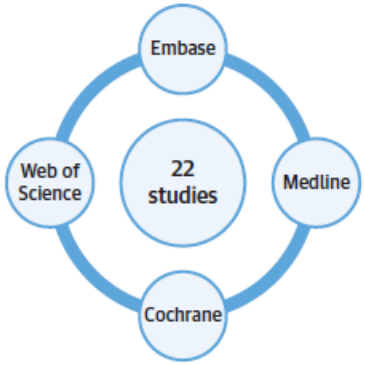


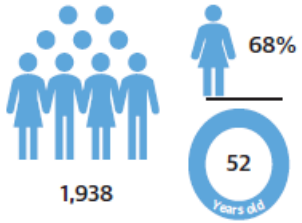


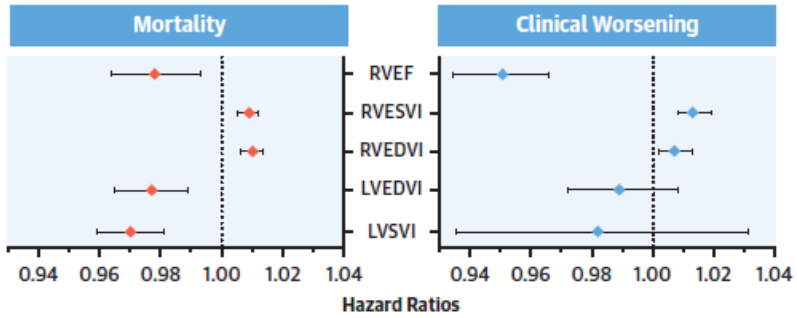
Tello K et al. Int J Cardiol . 2018 Sep 1;266:229-235.
Tello K et al. Circ Cardiovasc Imaging. 2019 Sep;12(9):e009047.

MR a predikce mortality a klin. zhoršení u PAH

CENTRAL ILLUSTRATION Cardiac Magnetic Resonance Imaging for Prediction of Clinical Worsening and Mortality in Pulmonary Arterial Hypertension







Results	Increment	Mortality Risk (Over 54 Months)	Clinical Worsening (Over 22 Months)
RVEF	per 1% decrease	2.1% increase	4.9% increase
RVESVI	per 1 ml/m² increase	0.9% increase	1.3% increase
RVEDVI	per 1 ml/m² increase	0.6% increase	1% increase
LVEDVI	per 1 ml/m² decrease	1.8% increase	Not significant
LVSVI	per 1 ml/m² decrease	2.5% increase	Not significant

Alabed, S. et al. J Am Coll Cardiol Img. 2021;14(5):931–42.

Pooled results for mortality and clinical worsening are presented in the forest plots and described in the table underneath for various factors. The literature search details and demographic characteristics of the meta-analysis cohort are shown on the left. LVEDVI = left ventricular end-diastolic volume index; LVESVI = left ventricular end-systolic volume index; LVSVI = left ventricular stroke volume index; RVEDVI = right ventricular end-diastolic volume index; RVEF = right ventricular ejection fraction; RVESVI = right ventricular end-systolic volume index.

Alabed S et al. J Am Coll Cardiol Img. 2021;14(5):931-42

Riziková stratifikace ESC/ERS 2022 – simplifikovaná verze pro hodnocení průběhu léčby (4 kategorie)

Table 18 **Variables used to calculate the simplified four-strata risk-assessment tool**

Determinants of prognosis	Low risk	Intermediate–low risk	Intermediate–high risk	High risk
Points assigned	1	2	3	4
WHO-FC	I or II[a]	-	III	IV
6MWD, m	>440	320–440	165–319	<165
BNP or NT-proBNP,[a] ng/L	<50 <300	50–199 300–649	200–800 650–1100	>800 >1100

6MWD, 6-minute walking distance; BNP, brain natriuretic peptide; NT-proBNP, N-terminal pro-brain natriuretic peptide; WHO-FC, World Health Organization functional class.
Risk is calculated by dividing the sum of all grades by the number of variables and rounding to the next integer.
[a]WHO-FC I and II are assigned 1 point as both are associated with good long-term survival.

ESC/ERS Guidelines

At follow-up, the four-strata model (*Table 18*) is recommended as a basic risk-stratification tool, but additional variables should be considered as needed, especially right heart imaging and haemodynamics. At any stage, individual factors such as age, sex, disease type, comorbidities, and kidney function should also be considered.

Humbert M et al. Eur Hear J 2022, DOI: 10.1093/eurheartj/ehac237

Kontrolní vyšetření

	At baseline	3–6 months after changes in therapy	Every 3–6 months in stable patients	In case of clinical worsening
Medical assessment (including WHO-FC)	Class I	Class I	Class I	Class I
6MWT	Class I	Class I	Class I	Class I
Blood test (including NT-proBNP)	Class I	Class I	Class I	Class I
ECG	Class I	Class I	Class I	Class I
Echocardiography or cMRI	Class I	Class I	Class IIb	Class I
ABG or pulse oximetry	Class I	Class I	Class I	Class I
Disease-specific HR-QoL	Class IIb	Class IIb	Class IIb	Class IIb
CPET	Class IIb	Class IIb	Class IIb	Class IIb
RHC	Class I	Class IIa	Class IIb	Class IIa

Humbert M et al. Eur Hear J 2022, DOI: 10.1093/eurheartj/ehac237

PAH - léčba

6.3. Therapy

According to the revised haemodynamic definition, PAH may be diagnosed in patients with mPAP >20 mmHg and PVR >2 WU. Yet, the efficacy of drugs approved for PAH has only been demonstrated in patients with mPAP ≥25 mmHg and PVR >3 WU (see Supplementary Data, *Table S1*). No data are available for the efficacy of drugs approved for PAH in patients whose mPAP is <25 mmHg and whose PVR is <3 WU. Hence, for such patients, the efficacy of drugs approved for PAH has not been established. The same is true for patients with exercise PH, who, by definition, do not fulfil the diagnostic criteria for PAH. Patients at high risk of developing PAH, for instance patients with SSc or family members of patients with HPAH, should be referred to a PH centre for individual decision-making.

PAH – iniciální léčba (pacienti bez komorbidit)

Recommendations for the treatment of non-vasoreactive patients with idiopathic, heritable, or drug-associated PAH who present without cardiopulmonary comorbidities (initial therapy)

ESC
ERS

Recommendations	Class	Level
For initial therapy		
In patients with IPAH/HPAH/DPAH who present at **high risk** of death, initial combination therapy with a PDE5i, an ERA, and i.v./s.c. prostacyclin analogues should be considered	IIa	C

PICO 1: Should initial oral double-combination therapy vs. monotherapy be used in symptomatic patients with PAH?

	GRADE			
Recommendations	**Quality of evidence**	**Strength of recommendation**	**Class**	**Level**
In patients with IPAH/HPAH/DPAH who present at **low or intermediate risk** of death, initial combination therapy with a PDE5i and an ERA is recommended	Low	Conditional	I	B

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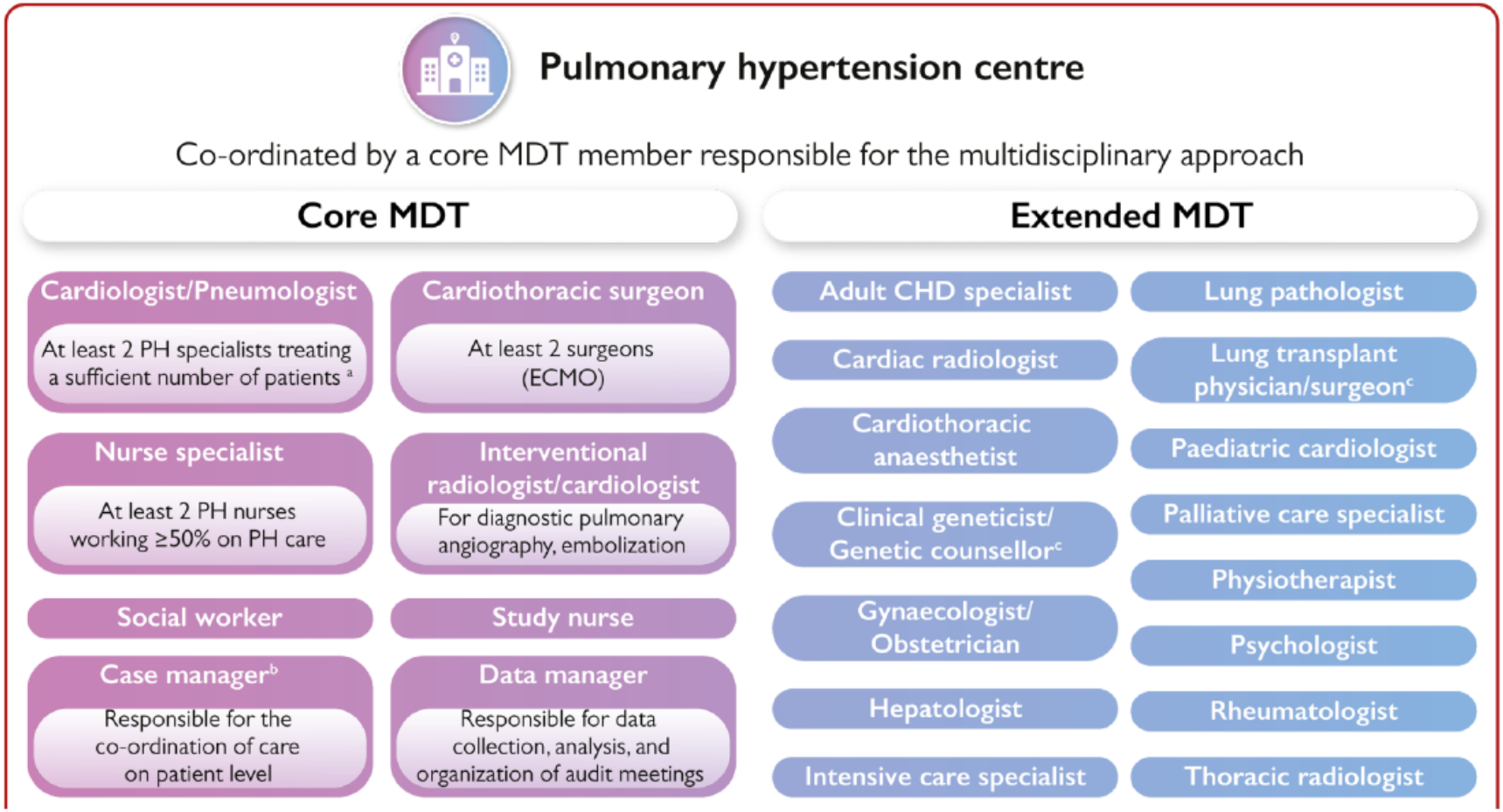
Recommendations	Class	Level
Initial combination therapy with ambrisentan and tadalafil is recommended	I	B
Initial combination therapy with macitentan and tadalafil is recommended	I	B
Initial combination therapy with other ERAs and PDE5is should be considered	IIa	B
Initial combination therapy with macitentan and tadalafil and selexipag is not recommended	III	B

PAH – eskalace léčby (pacienti bez komorbidit)

Recommendations	Class	Level
During follow-up		
In patients with IPAH/HPAH/DPAH who present at intermediate-low risk of death while receiving ERA/PDE5i therapy, **addition of selexipag** should be considered	IIa	B
In patients with IPAH/HPAH/DPAH who present at intermediate-high or high risk of death while receiving ERA/PDE5i therapy, **addition of i.v./s.c. prostacyclin** analogues and **referral for lung transplantation** evaluation should be considered	IIa	C
In patients with IPAH/HPAH/DPAH who present at intermediate-low risk of death while receiving ERA/PDE5i therapy, **switching from PDE5i to riociguat** may be considered	IIb	B

Centrum pro diagnostiku a léčbu PH



DĚKUJEME ZA POZORNOST

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