Risk-based management pacientů s PAH v Centru pro léčbu PH FN Olomouc

12. sympozium
Pracovní skupiny Plicní cirkulace ČKS

Martin Hutyra

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Podpořeno firmou Actelion

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	Nemám konflikt zájmů	Mám konflikt zájmů	Specifikace konfliktu (vyjmenujte subjekty, firmy či institutce, se kterými Vaše spolupráce může vést ke konfliktu zájmů
Zaměstnanecký poměr	☑	☐	
Vlastník / akcionář	☑	☐	
Konzultant	☑	☐	
Přednášková činnost	☐	☑	AOP Orphan, Actelion, Pfizer, GSK
Člen poradních sborů (advisory boards)	☑	☐	
Podpora výzkumu / granty	☐	☑	IGA Ministerstva zdravotnictví ČR
Jiné honoráře (např. za klinické studie či registry)	☐	☑	Actelion, Pfizer, ICON

European Heart Journal (2014) 35, 3033–3080
doi:10.1093/eurheartj/ehu283

ESC GUIDELINES

2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism

The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC)

Endorsed by the European Respiratory Society (ERS)

Authors/Task Force Members: Stavros V. Konstantinides* (Chairperson) (Germany/Greece), Adam Torbicki* (Co-chairperson) (Poland), Giancarlo Agnelli (Italy), Nicolas Danchin (France), David Fitzmaurice (UK), Nazzareno Galiè (Italy), J. Simon R. Gibbs (UK), Menno V. Huisman (The Netherlands), Marc Humbert† (France), Nils Kucher (Switzerland), Irene Lang (Austria), Mareike Lankeit (Germany), John Lekakis (Greece), Christoph Maack (Germany), Eckhard Mayer (Germany), Nicolas Meneveau (France), Arnaud Perrier (Switzerland), Piotr Pruszczyk (Poland), Lars H. Rasmussen (Denmark), Thomas H. Schindler (USA), Pavel Svitil (Czech Republic), Anton Vonk Noordegraaf (The Netherlands), Jose Luis Zamorano (Spain), Maurizio Zompatori (Italy)

Doporučení pro… | Guidelines

Doporučené postupy Evropské kardiologické společnosti/Evropské respirační společnosti pro diagnostiku a léčbu plicní hypertenze, verze 2015.

Stručný přehled vypracovaný Českou kardiologickou společností

ČESKÁ KARDIOLOGICKÁ SPOLEČNOST
THE CZECH SOCIETY OF CARDIOLOGY

(2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Summary document prepared by the Czech Society of Cardiology)

Michael Aschermann[a], Pavel Jansa[a], Martin Hutyra[b]

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European Heart Journal Advance Access published September 15, 2015

European Heart Journal
doi:10.1093/eurheartj/ehv317

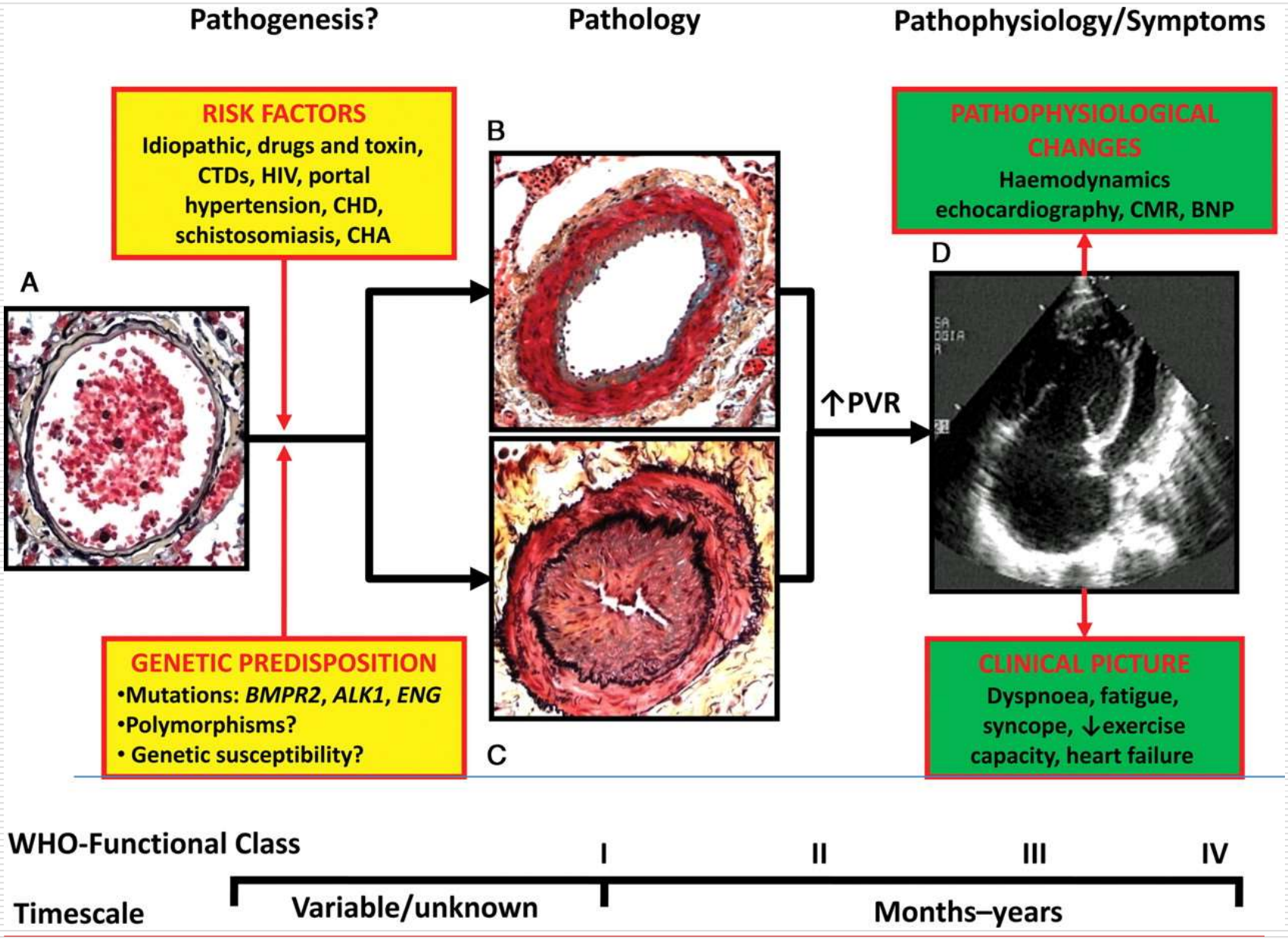
ESC/ERS GUIDELINES

2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS)

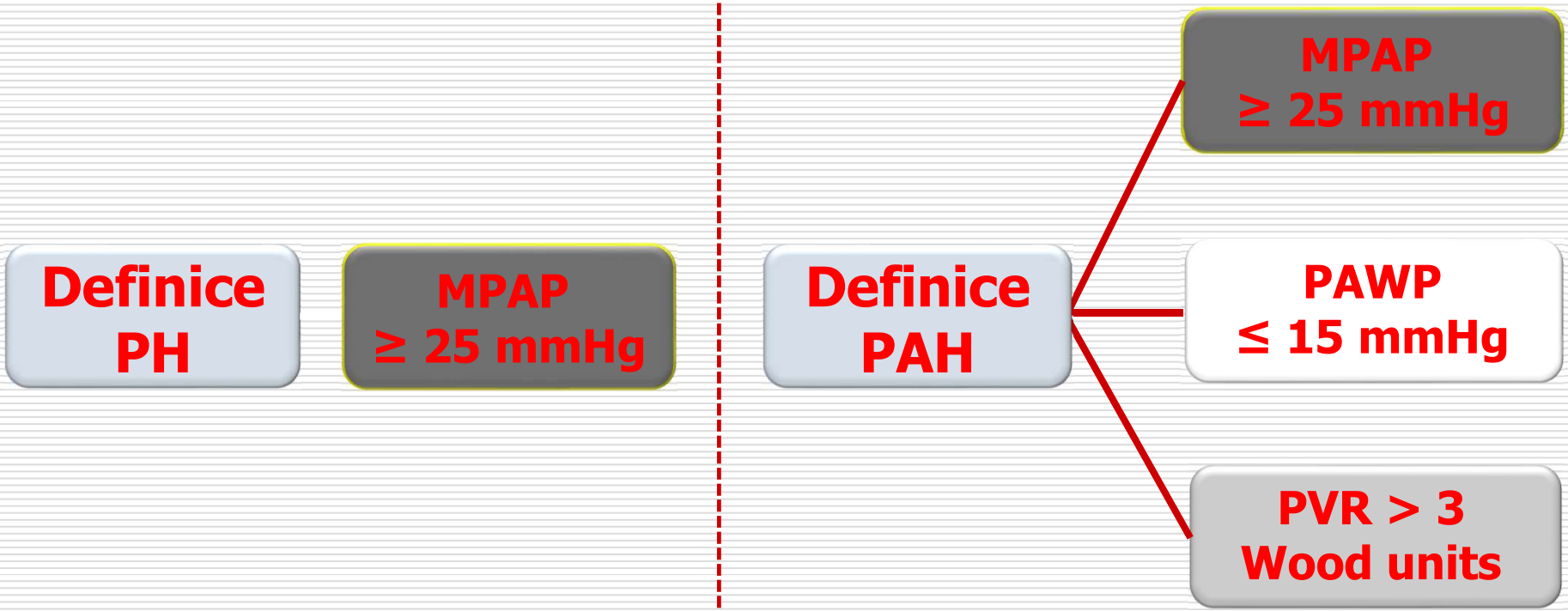
Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT)

I. INTERNÍ KLINIKA
KARDIOLOGIE
FAKULTNÍ NEMOCNICE OLOMOUC



Galiè N et al. Eur Heart J 2010;31:2080-2086

Hemodynamická definice plicní hypertenze



PAP: pulmonary arterial pressure; PAWP: pulmonary artery wedge pressure; PVR: pulmonary vascular resistance

Hoeper MM, *et al. J Am Coll Cardiol* 2013; 62:D42-50.

EPIDEMIOLOGIE A KLASIFIKACE

I. INTERNÍ KLINIKA
KARDIOLOGIE
FAKULTNÍ NEMOCNICE OLOMOUC

Plicní hypertenze - definice a klasifikace

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Updated Clinical Classification of Pulmonary Hypertension

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David Celermajer, MD, PHD,§ Chris Denton, MD, PHD,‖ Ardeschir Ghofrani, MD,¶
Miguel Angel Gomez Sanchez, MD,# R. Krishna Kumar, MD,** Michael Landzberg, MD,††
Roberto F. Machado, MD,‡‡ Horst Olschewski, MD,§§ Ivan M. Robbins, MD,‖‖
Rogiero Souza, MD, PHD¶¶

Definition	Characteristics	Clinical group(s)[b]
Pulmonary hypertension (PH)	Mean PAP ≥25 mmHg	All
Pre-capillary PH	Mean PAP ≥25 mmHg PWP ≤15 mmHg CO normal or reduced[c]	1. Pulmonary arterial hypertension 3. PH due to lung diseases 4. Chronic thromboembolic PH 5. PH with unclear and/or multifactorial mechanisms
Post-capillary PH	Mean PAP ≥25 mmHg PWP >15 mmHg CO normal or reduced[c]	2. PH due to left heart disease
Passive	TPG ≤12 mmHg	
Reactive (out of proportion)	TPG >12 mmHg	

Prevalence of PAH in the general population
15–50 cases per million (0.0015–0.0050%)

Prevalence of PAH in at risk populations
CHD: 4–15%
Systemic sclerosis: 8–10%
Portal hypertension: 0.5–10%
HIV: 0.5%
Sickle cell disease: 2%
BMPR2 mutation carriers: 20%

1. Pulmonary arterial hypertension
   1.1 Idiopathic PAH
   1.2 Heritable PAH
   1.2.1 BMPR2
   1.2.2 ALK-1, ENG, SMAD9, CAV1, KCNK3
   1.2.3 Unknown
   1.3 Drug and toxin induced
   1.4 Associated with:
   1.4.1 Connective tissue disease
   1.4.2 HIV infection
   1.4.3 Portal hypertension
   1.4.4 Congenital heart diseases
   1.4.5 Schistosomiasis

1′ Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
1″. Persistent pulmonary hypertension of the newborn (PPHN)

2. Pulmonary hypertension due to left heart disease
   2.1 Left ventricular systolic dysfunction
   2.2 Left ventricular diastolic dysfunction
   2.3 Valvular disease
   2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

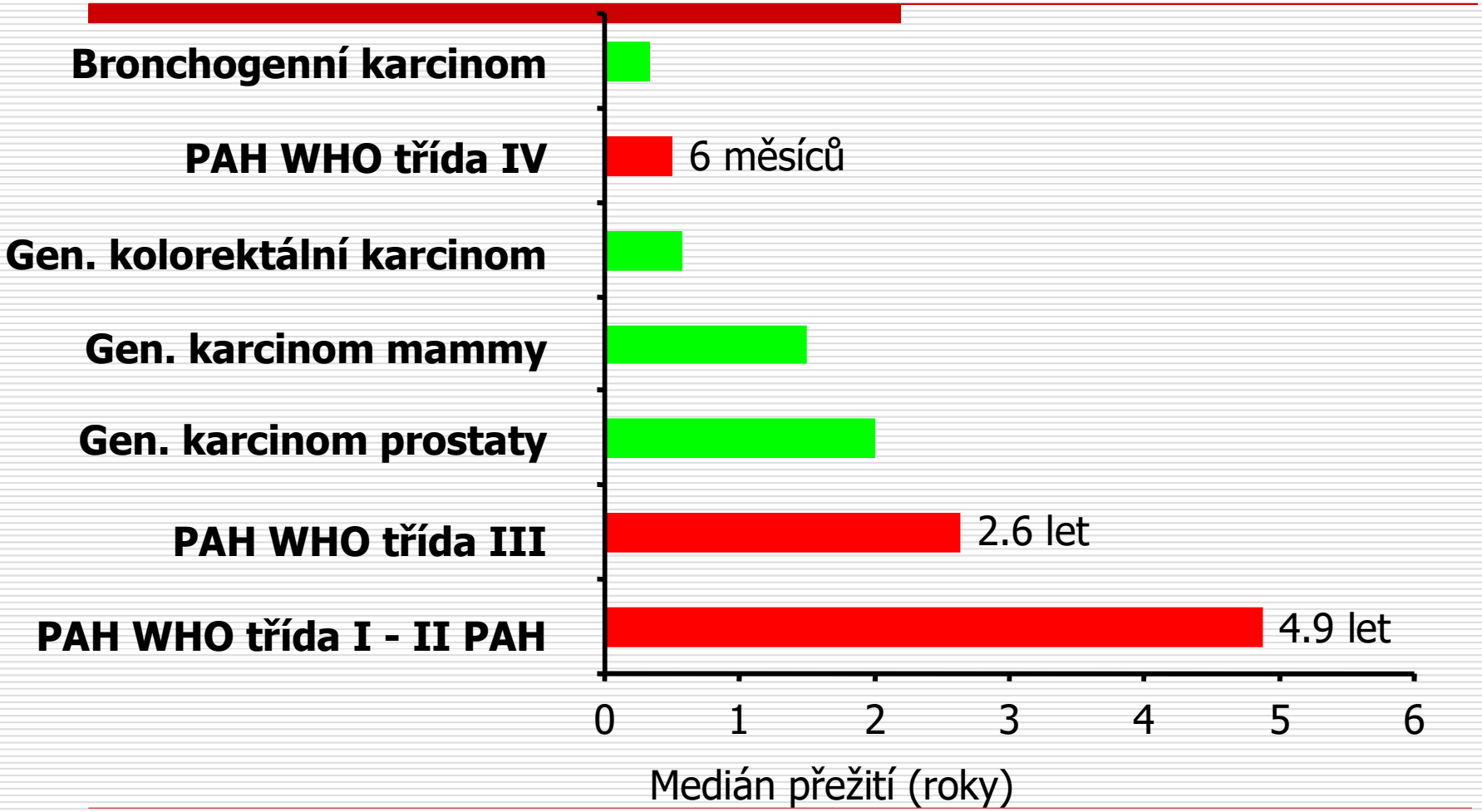
3. Pulmonary hypertension due to lung diseases and/or hypoxia
   3.1 Chronic obstructive pulmonary disease
   3.2 Interstitial lung disease
   3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
   3.4 Sleep-disordered breathing
   3.5 Alveolar hypoventilation disorders
   3.6 Chronic exposure to high altitude
   3.7 Developmental lung diseases

4. Chronic thromboembolic pulmonary hypertension (CTEPH)

5. Pulmonary hypertension with unclear multifactorial mechanisms
   5.1 Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
   5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
   5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
   5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

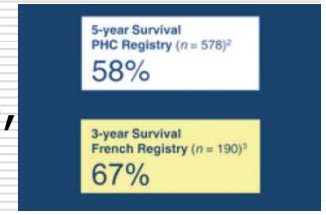
PRŮBĚH ONEMOCNĚNÍ

PAH – prognóza neléčeného onemocnění



D'Alonzo et al. Ann Internal Med 1991; Kato et al. Cancer 2001

Podle registru NIH bylo mediánové přežití pacientů s PAH 2,8 roku s 1, 3, 5-letým přežitím 68%, 48% a 34%.



CHEST Original Research
PULMONARY VASCULAR DISEASE

An Evaluation of Long-term Survival From Time of Diagnosis in Pulmonary Arterial Hypertension From the REVEAL Registry

Raymond L. Benza, MD; Dave P. Miller, MS; Robyn J. Barst, MD, FCCP; David B. Badesch, MD, FCCP; Adaani E. Frost, MD, FCCP; and Michael D. McGoon, MD, FCCP

CHEST 2012; 142(2):448–456

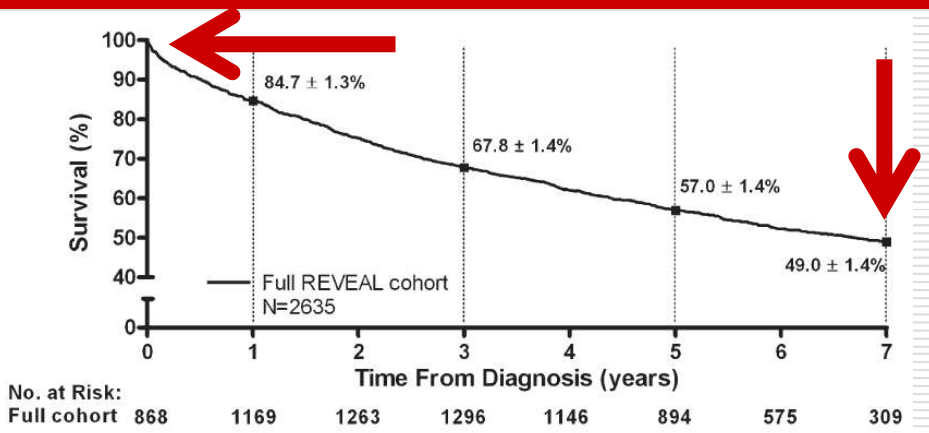


FIGURE 2. Seven-year survival from time of diagnostic right-sided heart catheterization for full REVEAL Registry cohort, using left truncation methods. ■ = estimated survival estimate ± SE at each particular time point. See Figure 1 legend for expansion of abbreviation.

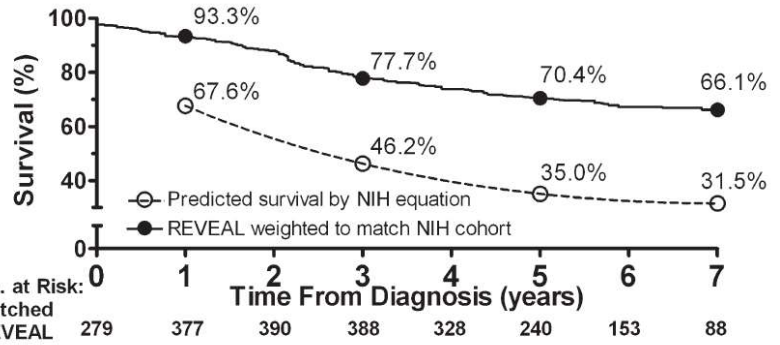
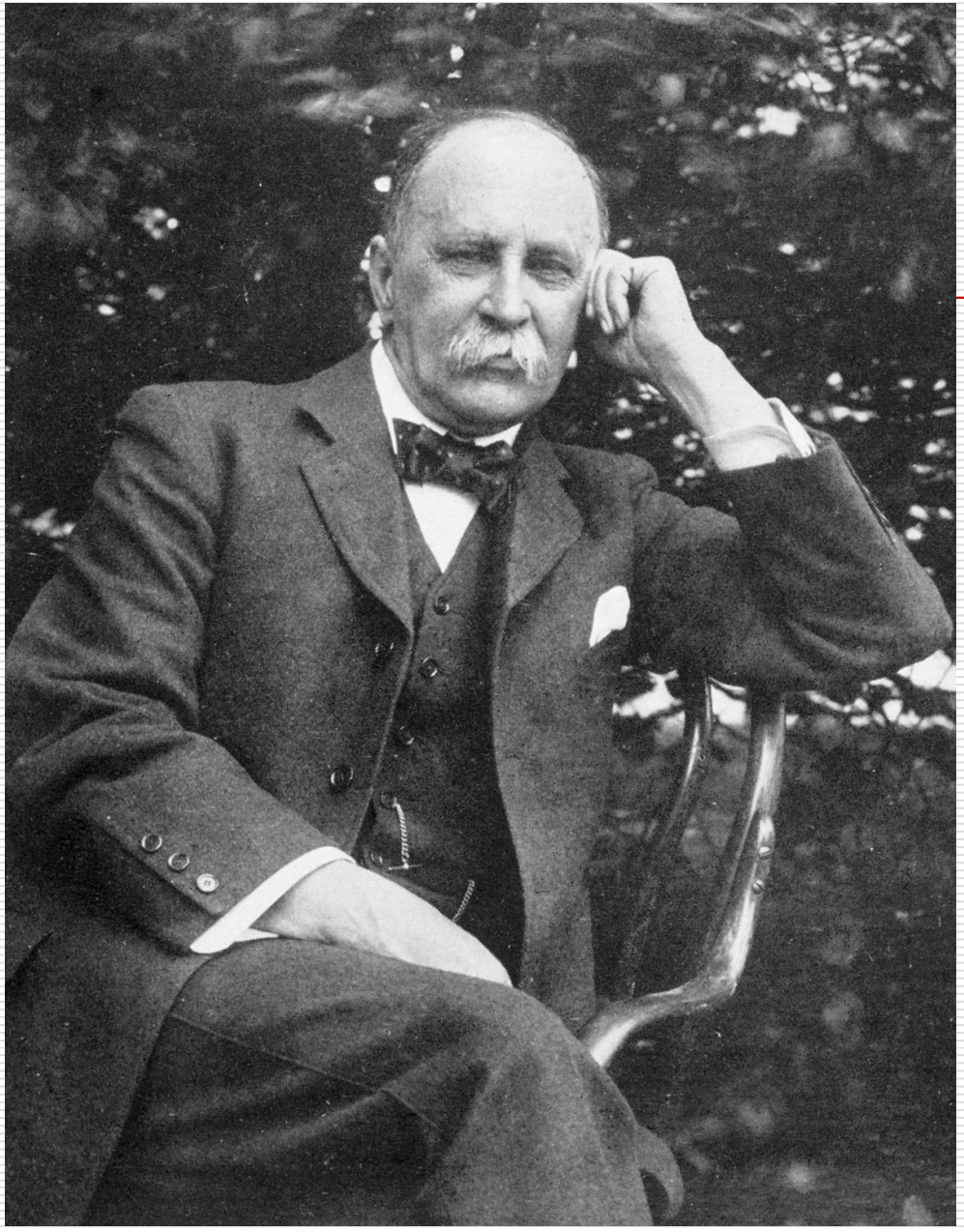


FIGURE 5. Seven-year survival from time of diagnostic RHC of REVEAL Registry cohort weighted to match age, sex, and mean pulmonary artery pressure distribution of NIH cohort. This cohort consisted of patients who met the NIH criteria (ie, had IPAH or FPAH and a pulmonary capillary wedge pressure of ≤12 mm Hg), and initiated an endothelin receptor antagonist, phosphodiesterase-5 inhibitor, or prostacyclin analogue within 6 months of diagnostic RHC. See Figure 1 and 4 legends for expansion of abbreviations.

NIH: Incidence 2/1 mil./1 rok, 187 pacientů (průměrný věk 36 let, Ž/M 2:1) sledovaných přes 7 let, mPAP 60 mmHg, CI 2.3 l/min, PVR 26 WU (Rich, Ann Intern Med, 1987)

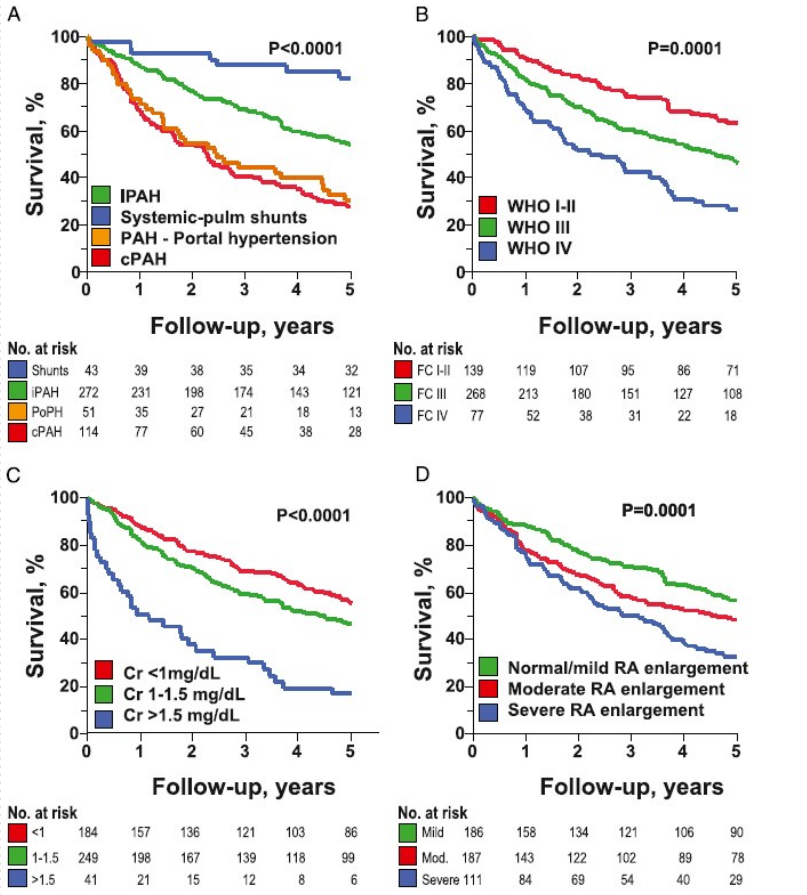
Characteristic	REVEAL Registry Patients "Traditional Definition" Diagnosed After November 2001 (N = 2,635)	NIH Cohort (N = 187)	Unweighted Comparison Cohort[a] (n = 755)	Weighted Comparison Cohort[b] (n = 755)
Female sex, %	77	63	77	62
Age, y	50 ± 17	36 ± 15	47 ± 18	34 ± 16
mPAP, mm Hg	50 ± 14	60 ± 18	53 ± 13	60 ± 15
mRAP, mm Hg	9.4 ± 6.0	9.7 ± 6.0	9.8 ± 6.0	9.9 ± 5.0
Cardiac index, L/min/m²	2.3 ± 0.9	2.3 ± 0.9	2.2 ± 0.9	2.3 ± 1.1

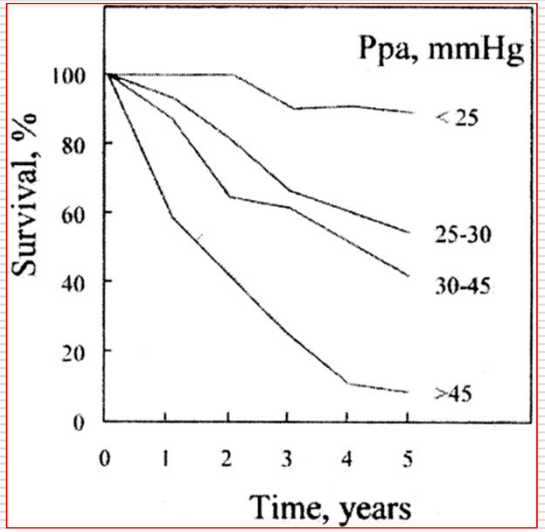
PROGNÓZA

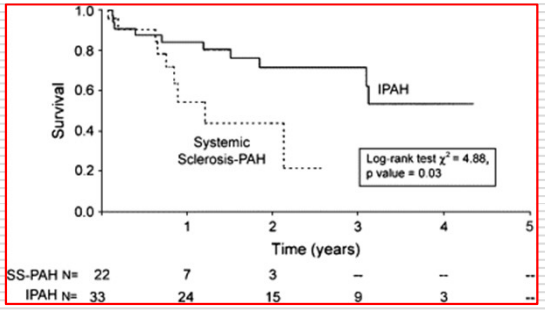


"Man is as old as his arteries"

Plicní hypertenze - prognóza







I. INTERNÍ KLINIKA
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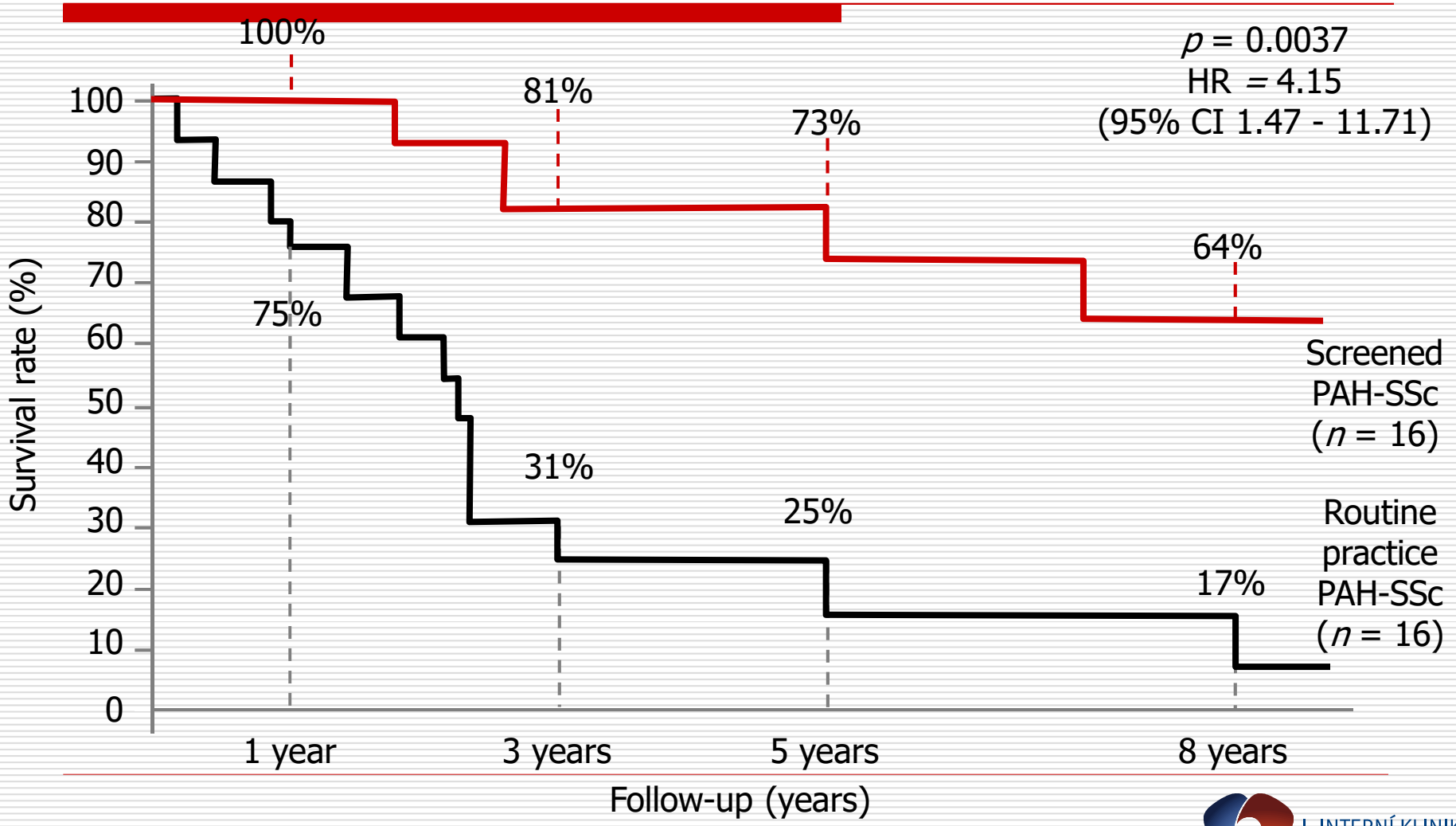
Screening PH u pacientů se SSc



CI: Confidence interval; HR: Hazard ratio; SSc: Systemic Sclerosis

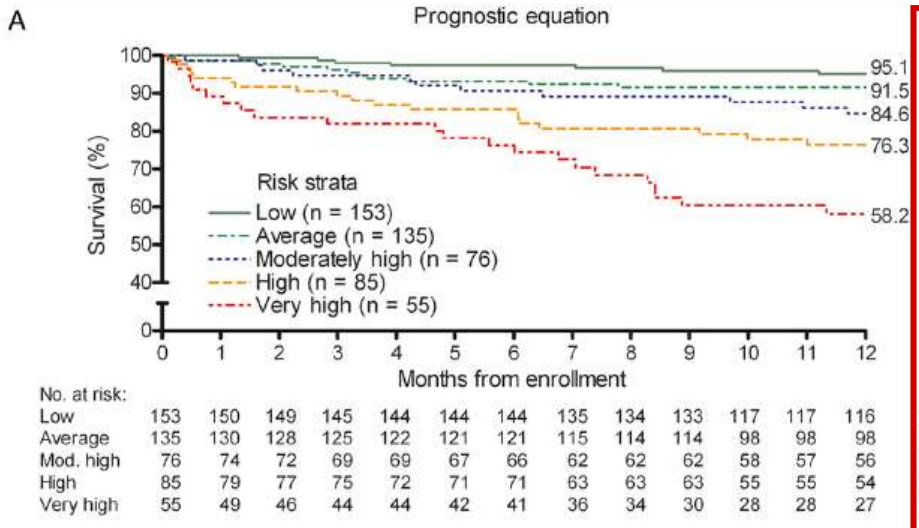
Humbert M, *et al. Arthritis Rheum* 2011; 63:3522-30.

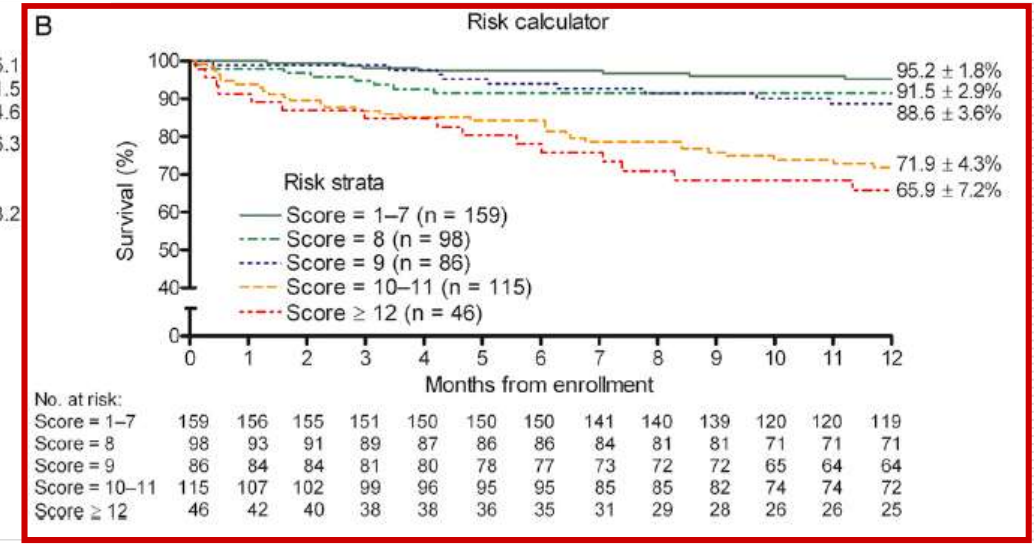
I. INTERNÍ KLINIKA KARDIOLOGIE
FAKULTNÍ NEMOCNICE OLOMOUC

CHEST Original Research
PULMONARY VASCULAR DISEASE

The REVEAL Registry Risk Score Calculator in Patients Newly Diagnosed With Pulmonary Arterial Hypertension

Raymond L. Benza, MD; Mardi Gomberg-Maitland, MD, FCCP; Dave P. Miller, MS; Adaani Frost, MD, FCCP; Robert P. Frantz, MD; Aimee J. Foreman, MA; David B. Badesch, MD, FCCP; and Michael D. McGoon, MD, FCCP





Patient: _____ Date: _____

WHO Group I Subgroup	APAH-CTD +1	APAH-PoPH +2	FPAH +2	
Demographics & Comorbidities	Renal insufficiency +1	Male age >60 yrs +2		
NYHA/WHO Functional Class	I -2	III +1	IV +2	
Vital Signs	SBP <110 mm Hg +1	HR >92 BPM +1		
6-Minute Walk Test	≥440 m -1	<165 m +1		
BNP	<50 pg/mL -2	>180 pg/mL +1		
Echocardiogram	Pericardial effusion +1			
Pulmonary Function Test	% pred. DLco ≥80 -1	% pred. DLco ≤32 +1		
Right-heart Catheterization	mRAP >20 mm Hg within 1 yr +1	PVR >32 Wood units +2		

APAH=associated PAH; BNP=brain natriuretic peptide; BPM=beats per minute; CTD=connective tissue disease; DLco=carbon monoxide diffusing capacity; FPAH=familial PAH; HR=heart rate; mRAP=mean right atrial pressure; NYHA=New York Heart Association; PAH=pulmonary arterial hypertension; PoPH=portopulmonary hypertension; PVR=pulmonary vascular resistance; SBP=systolic blood pressure; WHO=World Health Organization.

SUM OF ABOVE	
(Starting Score)	+ 6
= RISK SCORE	

Risk scores range from 0 (lowest risk) to 22 (highest risk)

	LOW RISK	AVERAGE RISK	MODERATE HIGH RISK	HIGH RISK	VERY HIGH RISK
RISK SCORE	1–7	8	9	10–11	≥12
PREDICTED 1-YEAR SURVIVAL	95%–100%	90%–<95%	85%–<90%	70%–<85%	<70%

United Therapeutics EUROPE LIMITED

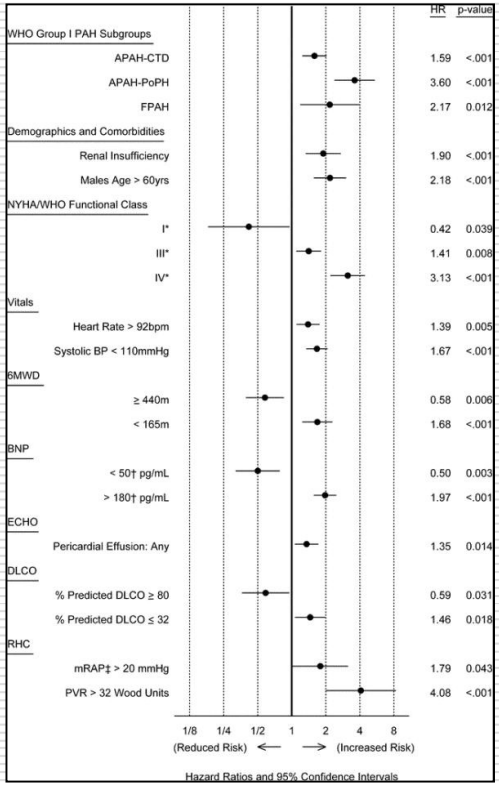
EU/REM/JUL12/248(1). Date of preparation: July 2013.

15 negativních prediktorů

4 protektivní faktory

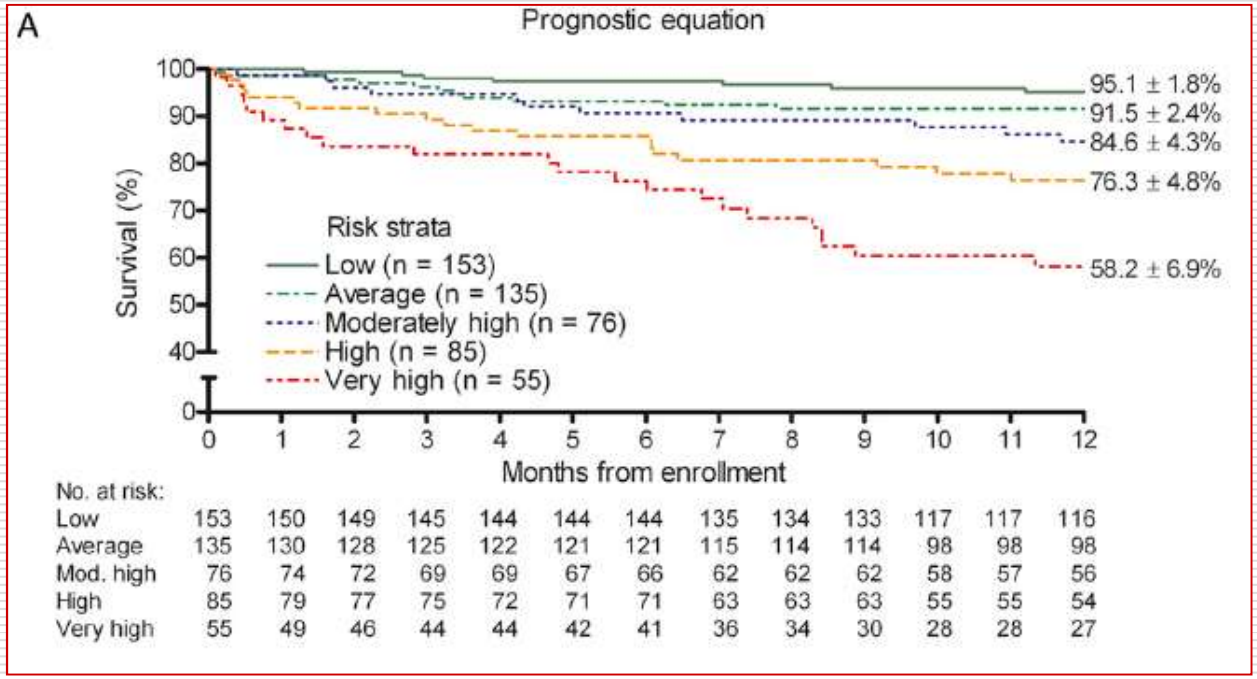
Kalk. rizikové skóre 0-22

Průměrné REVEAL skóre 7.4



Benza RL; Miller DP; Gomberg-Maitland M; Frantz RP; et al. Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). Circulation. 122(2):164-72, 2010 Jul 13.

1-leté přežívání v rámci skupin rizikové stratifikace pacientů v registru REVEAL



Riziko	1-leté přežívání
Nízké	> 95%
Střední	90-95%
Vyšší	85-90%
Vysoké	70-85%
Velmi vysoké	<70%

Benza RL; Miller DP; Gomberg-Maitland M; Frantz RP; et al. Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). Circulation. 122(2):164-72, 2010 Jul 13.

European Heart Journal Advance Access published September 15, 2015

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Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT)

- V klinických studiích a registrech bylo identifikováno množství prognostických faktorů.

- Faktory predikující přežití u pacientů s PAH jsou důležité pro jejich klinický management.

- Jsou založeny na hodnocení demografických, funkčních, laboratorních a hemodynamických parametrů.

Determinants of prognosis[a] (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope[b]	Repeated syncope[c]
WHO functional class	I, II	III	IV
6MWD	>440 m	165–440 m	<165 m
Cardiopulmonary exercise testing	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 36–44.9	Peak VO_2 <11 ml/min/kg (<35% pred.) VE/VCO_2 slope ≥45
NT-proBNP plasma levels	BNP <50 ng/l NT-proBNP <300 ng/l	BNP 50–300 ng/l NT-proBNP 300–1400 ng/l	BNP >300 ng/l NT-proBNP >1400 ng/l
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2 No pericardial effusion	RA area 18–26 cm^2 No or minimal, pericardial effusion	RA area >26 cm^2 Pericardial effusion
Haemodynamics	RAP <8 mmHg CI ≥2.5 l/min/m^2 SvO_2 >65%	RAP 8–14 mmHg CI 2.0–2.4 l/min/m^2 SvO_2 60–65%	RAP >14 mmHg CI <2.0 l/min/m^2 SvO_2 <60%

Galiè N, *et al. Eur Heart J* 2016; 37:67-119.

Demografie, klinický stav a symptomy

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NT-proBNP plasma levels	BNP <50 ng/l NT-proBNP <300 ng/l	BNP 50–300 ng/l NT-proBNP 300–1400 ng/l	BNP >300 ng/l NT-proBNP >1400 ng/l
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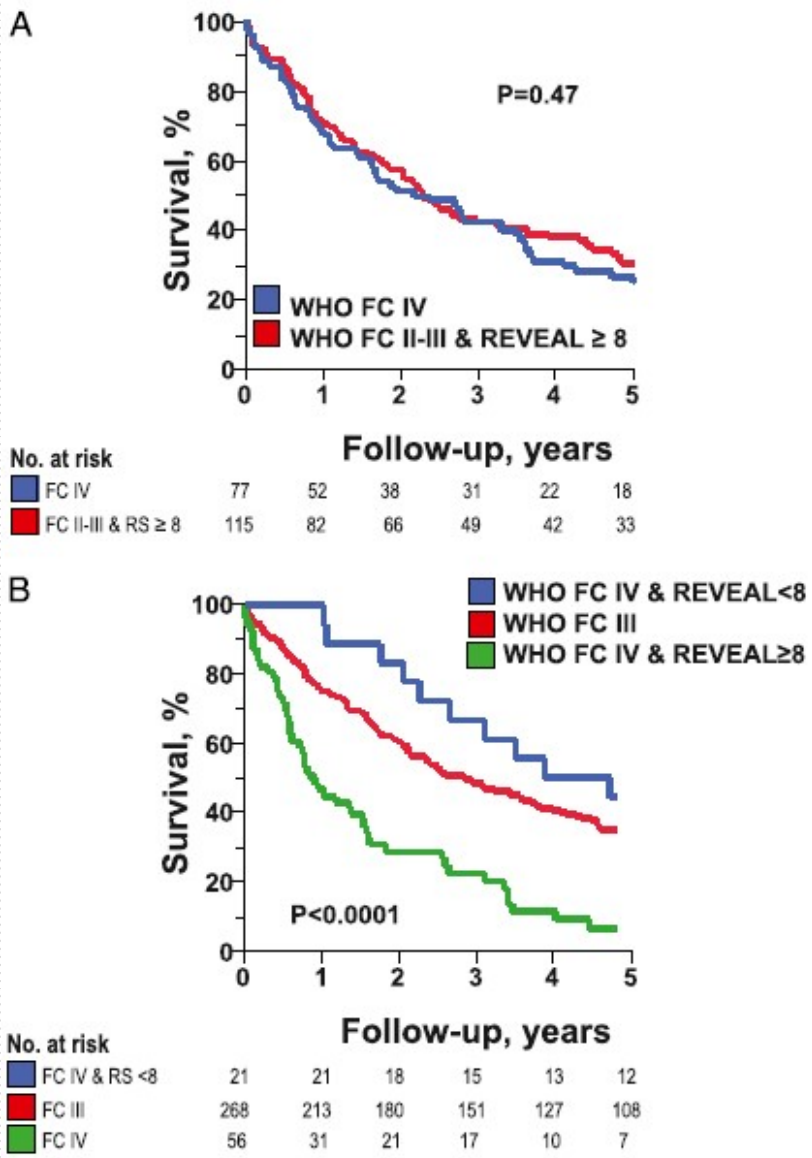
[a]Estimated 1-year mortality. [b]Occasional syncope during brisk or heavy exercise, or occasional orthostatic syncope in an otherwise stable patient.
[c]Repeated episodes of syncope, even with little or regular physical activity

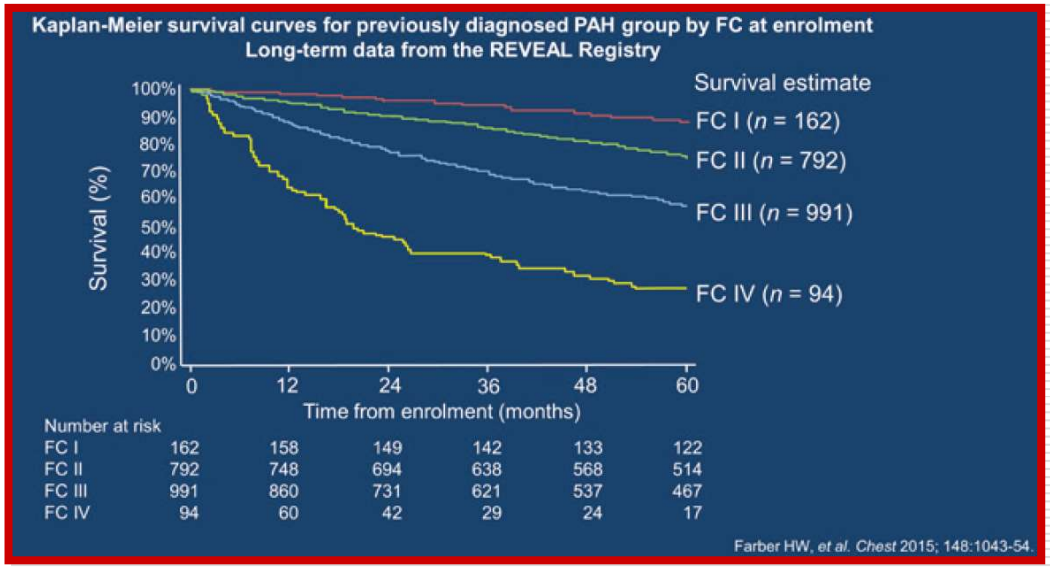
Galiè N, *et al. Eur Heart J* 2016; 37:67-119.



CHEST Original Research
PULMONARY VASCULAR DISEASE

Integration of Clinical and Hemodynamic Parameters in the Prediction of Long-term Survival in Patients With Pulmonary Arterial Hypertension

Garvan C. Kane, MD, PhD, FCCP; Hilal Maradit-Kremers, MD; Josh P. Slusser, BS; Chris G. Scott, MS; Robert P. Frantz, MD; and Michael D. McGoon, MD, FCCP



Demografie, klinický stav a symptomy

- Pokročilý věk a mužské pohlaví jsou často uváděny jako faktory, které jsou spojeny s horším přežíváním. Důvody pro to nejsou známy, ale předpokládá se, že je způsoben rozdíly v kardiopulmonální hemodynamice v závislosti na věku a pohlaví.
- Kromě toho horší prognóza u starších pacientů může odrážet přítomnost multifaktoriálních onemocnění nebo přítomnost komorbidit, které mají vliv na přežití.
- Registry z UK pacientů s PAH diagnostikovanou v období 2001-2009 prokázal, že ve srovnání s pacienty mladšími 50 let měly osoby nad 50 let horší přežití v 1 roce (90 vs. 95%), 3 roky (76 vs. 91%), 5 let (57 vs. 87 %) a 7 let (44 vs. 75%).
- Z dat registru REVEAL vyplývá, že u jedinců s PAH, kteří byli starší 60 let, měli muži horší přežití po 2 letech než ženy (64 vs. 78%, poměr rizik 1,67, 95% CI 1,3-2,2).
- Na rozdíl od toho nebyl prokázán žádný rozdíl v přežití mezi muži a ženami s PAH, kteří byli mladší 60 let (84 vs. 86%).

Hyduk A, Croft JB, Ayala C, et al. Pulmonary hypertension surveillance--United States, 1980-2002. MMWR Surveill Summ 2005; 54:1.
Gall H, Felix JF, Schneck FK, et al. The Giessen Pulmonary Hypertension Registry: Survival in pulmonary hypertension subgroups. J Heart Lung Transplant 2017; 36:957.
Benza RL, Miller DP, Barst RJ, et al. An evaluation of long-term survival from time of diagnosis in pulmonary arterial hypertension from the REVEAL Registry. Chest 2012; 142:448
McLaughlin VV, Shillington A, Rich S. Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. Circulation 2002; 106:1477.
Ventetuolo CE, Praestgaard A, Palevsky HI, et al. Sex and haemodynamics in pulmonary arterial hypertension. Eur Respir J 2014; 43:523.
Jacobs W, van de Veerdonk MC, Trip P, et al. The right ventricle explains sex differences in survival in idiopathic pulmonary arterial hypertension. Chest 2014; 145:1230.

Zátěžová kapacita

Determinants of prognosis[a] (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope[b]	Repeated syncope[c]
WHO functional class	I, II	III	IV
6MWD	>440 m	165–440 m	<165 m
Cardiopulmonary exercise testing	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 36–44.9	Peak VO_2 <11 ml/min/kg (<35% pred.) VE/VCO_2 slope ≥45
NT-proBNP plasma levels	BNP <50 ng/l NT-proBNP <300 ng/l	BNP 50–300 ng/l NT-proBNP 300–1400 ng/l	BNP >300 ng/l NT-proBNP >1400 ng/l
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2 No pericardial effusion	RA area 18–26 cm^2 No or minimal, pericardial effusion	RA area >26 cm^2 Pericardial effusion
Haemodynamics	RAP <8 mmHg CI ≥2.5 l/min/m^2 SvO_2 >65%	RAP 8–14 mmHg CI 2.0–2.4 l/min/m^2 SvO_2 60–65%	RAP >14 mmHg CI <2.0 l/min/m^2 SvO_2 <60%

[a]Estimated 1-year mortality. [b]Occasional syncope during brisk or heavy exercise, or occasional orthostatic syncope in an otherwise stable patient.
[c]Repeated episodes of syncope, even with little or regular physical activity

Galiè N, *et al. Eur Heart J* 2016; 37:67-119.

Zátěžová kapacita

- Vzdálenost dosažená v 6MWT je široce používaný parametr pro hodnocení prognózy při stanovení dg. a hodnocení efektu léčby při následném sledování.
- Existuje však mnoho limitací 6MWT, včetně učebního efektu, cirkadiánních změn a dopadu demografických charakteristik/komorbidit.
- Metaanalýza Savarese a kol. hodnotila výsledky u 3112 pacientů ze 22 klinických studií a dospěla k závěru, že farmakologická specifická léčba PAH vedla k významnému snížení celkové mortality, hospitalizací pro PAH, transplantací plic, zahájení rescue terapie, ale příznivé účinky na klinické příhody nebylo predikováno změnami v 6MWT.
- Změna v 6MWD ve statistické analýze reflektovala pouze 22,1% účinku léčby; průměrný rozdíl 6MWD v průběhu sledování byl 22,4 m a významný prahový efekt byl vypočítán na 41,8 m.
- Studie tedy dospěla k závěru, že změna v 6MWD nepredukeje významně klinický efekt léčby.

Savarese G, et al. Do changes of 6-minute walk distance predict clinical events in patients with pulmonary arterial hypertension?: a meta-analysis of 22 randomized trials. J Am Coll Cardiol 2012;60:1192–201.

Zátěžová kapacita

- Absolutní hodnota 6MWD, která je spojena se zlepšeným přežíváním PAH > 380 m (Sitbon), nebo> 440 m, (REVEAL).
- Měly by být zhodnoceny demografické charakteristiky a komorbidity pacienta, které mají vliv na výsledek 6MWD (věk, pohlaví, výška…).

- Bylo prokázáno, že vrcholová spotřeba kyslíku predikuje přežití pacientů s PAH, přičemž 3 studie definují cut-off hodnoty 10,4 ml/min/kg, 11,5 ml/min/ kg a 13,2 ml/min/kg, predikující mortalitu.
- Vrcholová spotřeba kyslíku jako cíl terapie s <10 ml/min/kg naznačuje rizikový profil pacienta a potřebu eskalace léčby. Naopak VO2max > 15 ml/min/kg naznačuje lepší prognózu.

Benza RL, Miller DP, Gomberg-Maitland M, et al. Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). Circulation 2010;122:164–72.
Sitbon O, Humbert M, Nunes H, et al. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. J Am Coll Cardiol 2002;40:780–8.
Lee WT, Peacock AJ, Johnson MK. The role of percent predicted 6-min walk distance in pulmonary arterial hypertension. Eur Respir J 2010;36:1294–301.
Deboeck G, Scoditti C, Huez S, et al. Exercise testing to predict outcome in idiopathic versus associated pulmonary arterial hypertension. Eur Respir J 2012;40:1410–9.
GroepenhoffH, Vonk-Noordegraaf A, BoonstraA, SpreeuwenbergMD, Postmus PE, Bogaard HJ. Exercise testing to estimate survival in pulmonary hypertension. Med Sci Sports Exerc 2008;40:1725–32

Laboratorní vyšetření

Determinants of prognosis[a] (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk >10%
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[a]Estimated 1-year mortality. [b]Occasional syncope during brisk or heavy exercise, or occasional orthostatic syncope in an otherwise stable patient.
[c]Repeated episodes of syncope, even with little or regular physical activity

Galiè N, *et al. Eur Heart J* 2016; 37:67-119.

Laboratorní vyšetření

Current guidelines suggest a "normal" BNP level as a potential treatment goal. Therefore, it has to be taken into account that both BNP and N-terminal pro–B-type natriuretic peptide (NT-proBNP) are age- and sex-dependent, leading to higher normal values (especially with age).
Individual normal values are given by the manufacturer. An attempt to individualize BNP values has been suggested by dividing the measured BNP values by the age- and sexspecific normal values. This BNP ratio would be increased whenever >1.
BNP levels have been shown to parallel hemodynamic and functional responses to PAH therapies in most clinical trials. Recent data support the hypothesis that the change in NT-proBNP levels carries prognostic information.
Independently of baseline values, follow-up NT-proBNP levels <1,800 pg/ml indicated better survival in a cohort of 84 PAH patients in the current treatment era.

Benza RL, Miller DP, Gomberg-Maitland M, et al. Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). Circulation 2010;122:164–72.
Leuchte HH, El Nounou M, Tuerpe JC, et al. N-terminal pro-brain natriuretic peptide and renal insufficiency as predictors of mortality in pulmonary hypertension. Chest 2007;131:402–9.
Leuchte HH, Baumgartner RA, Nounou ME, et al. Brain natriuretic peptide is a prognostic parameter in chronic lung disease. Am J Respir Crit Care Med 2006;173:744–50.

Zobrazovací metody

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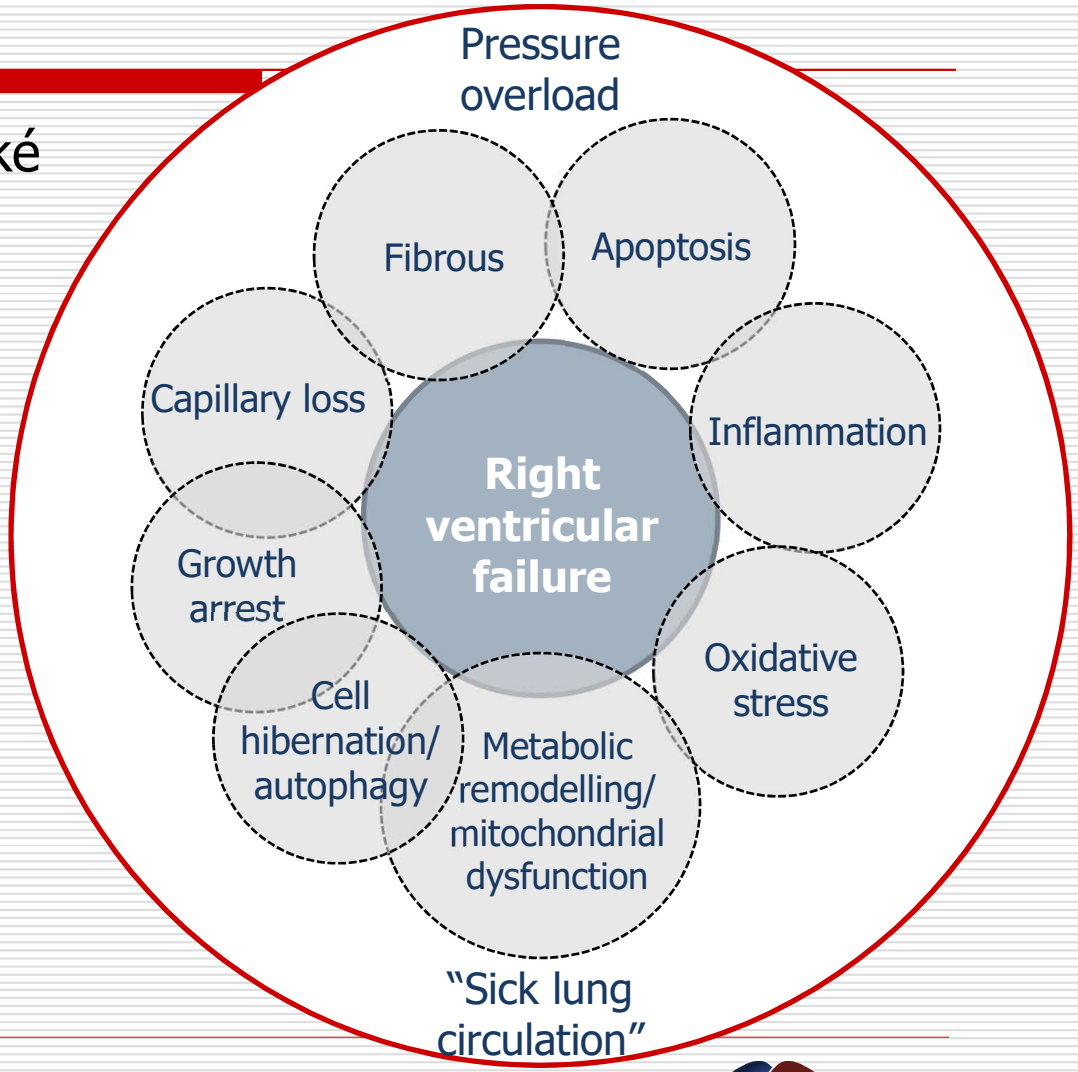
Jaké informace poskytuje echokardiografie?

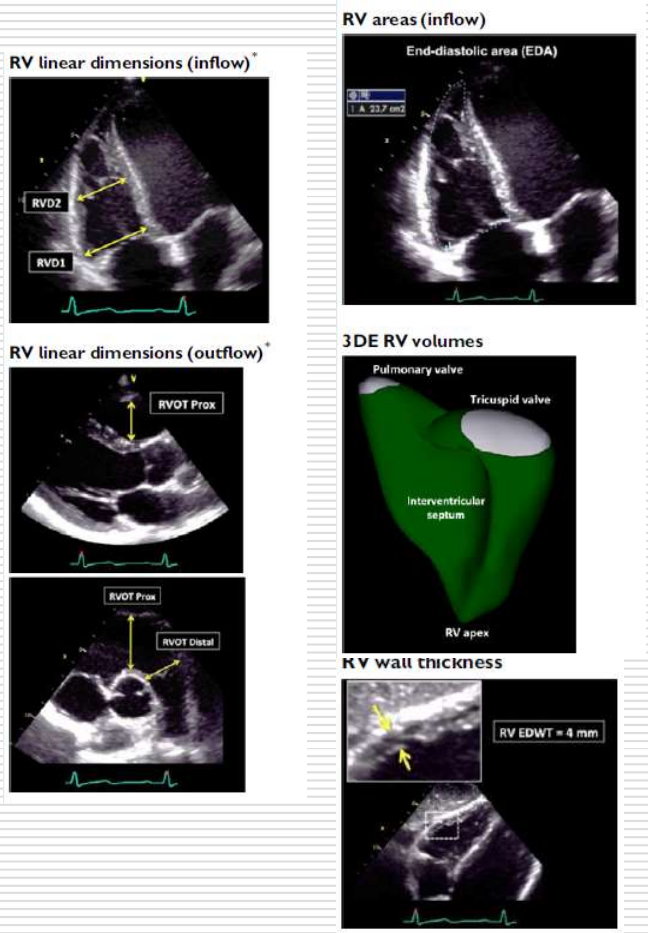
- Screeningové a diagnostické
- Prognostické
- Indikační



Naeije R, *et al. Eur Respir Rev* 2014; 23:476-87.

CHAMBER SIZE AND WALL THICKNESS

Given the complex and multifaceted configuration of the RV, all available echocardiographic views should be reviewed to obtain a comprehensive assessment, and quantitative measures of RV and right atrium (RA) size and function should be reported as part of a comprehensive echocardiographic assessment



European Heart Journal – Cardiovascular Imaging (2015) **16**, 233–271
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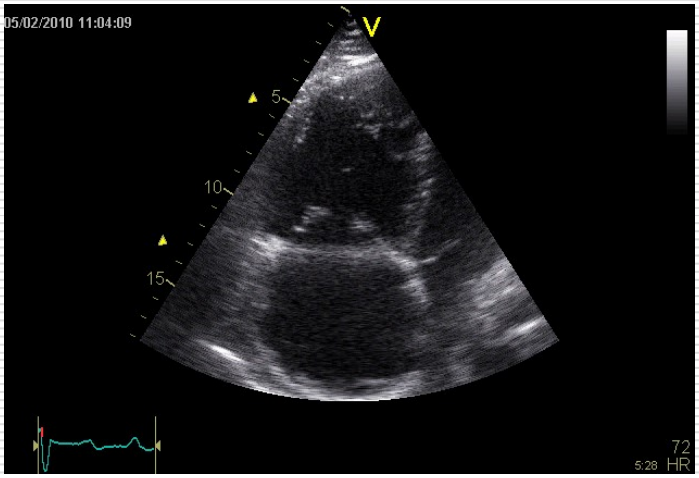
POSITION PAPER

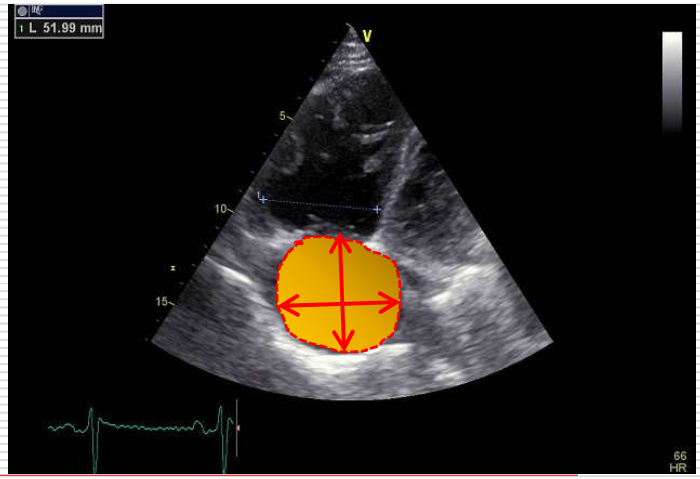
Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging

Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015;28(1):1.

Right atrial size

Emerging data have suggested that RA enlargement is an important **prognostic marker** for patients with various types of cardiopulmonary disease, which should be routinely measured in the echolab and is an important prognostic marker for patients with various types of cardiopulmonary disease:





1. In a study of 81 patients with **primary pulmonary hypertension** followed for an average of 37 months, RA area indexed to height was one of only two echocardiographic predictors of mortality.
2. In a study of 192 patients with **chronic systolic heart failure** followed for an average of 36 months, RA volume indexed to body surface area (BSA) was found to be predictive of mortality, need for heart transplantation, or hospitalization for heart failure; an association that persisted after adjusting for age, left ventricular ejection fraction, RV systolic function, and BNP.
3. **Atrial fibrillation and flutter** may originate from electrophysiologic perturbations within the RA, and RA enlargement has been shown to be a risk factor for the development of these arrhythmias.

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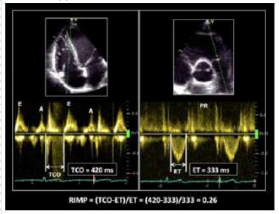
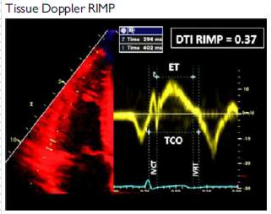
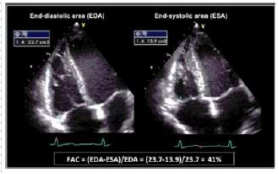
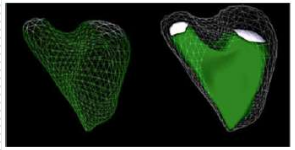
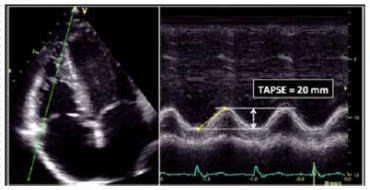
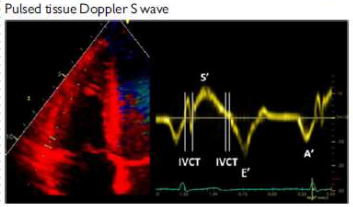
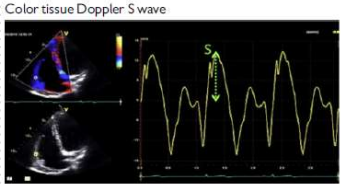
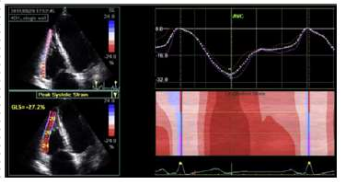
Echocardiographic imaging	Recommended methods	Advantages	Limitations
RV global function Pulsed Doppler RIMP 	RIMP (Tei index) by pulsed Doppler: RIMP = (TCO − ET)/ET	• Prognostic value • Less affected by heart rate	• Requires matching for R-R intervals when measurements are performed on separate recordings • Unreliable when RA pressure is elevated
Tissue Doppler RIMP 	RIMP by tissue Doppler: RIMP = (IVRT + IVCT)/ET = (TCO − ET)/ET	• Less affected by heart rate • Single-beat recording with no need for R-R interval matching	• Unreliable when RA pressure is elevated
RV global systolic function FAC 	RV FAC in RV-focused apical four-chamber view: RV FAC (%) = 100 × (EDA − ESA)/EDA	• Established prognostic value • Reflects both longitudinal and radial components of RV contraction • Correlates with RV EF by CMR	• Neglects the contribution of RV outflow tract to overall systolic function • Only fair inter-observer reproducibility
EF 	Fractional RV volume change by 3D TTE: RV EF (%) = 100 × (EDV − ESV)/EDV	• Includes RV outflow tract contribution to overall function • Correlates with RV EF by CMR	• Dependent on adequate image quality • Load dependency • Requires offline analysis and experience • Prognostic value not established

Echocardiographic imaging	Recommended methods	Advantages	Limitations
RV longitudinal systolic function TAPSE 	• Tricuspid annular longitudinal excursion by M-mode (mm), measured between end-diastole and peak systole • Proper alignment of M-mode cursor with the direction of RV longitudinal excursion should be achieved from the apical approach.	• Established prognostic value • Validated against radionuclide EF	• Angle dependency • Partially representative of RV global function*
Pulsed tissue Doppler S wave 	• Peak systolic velocity of tricuspid annulus by pulsed-wave DTI (cm/sec), obtained from the apical approach, in the view that achieves parallel alignment of Doppler beam with RV free wall longitudinal excursion	• Easy to perform • Reproducible • Validated against radionuclide EF • Established prognostic value	• Angle dependent • Not fully representative of RV global function, particularly after thoracotomy, pulmonary thromboendarterectomy or heart transplantation
Color tissue Doppler S wave 	• Peak systolic velocity of tricuspid annulus by color DTI (cm/sec)	• Sampling is performed after image acquisition • Allows multisite sampling on the same beat	• Angle dependent • Not fully representative of RV global function, particularly after thoracotomy, pulmonary thrombendarterectomy or heart transplantation • Lower absolute values and reference ranges than pulsed DTI S′ wave • Requires offline analysis
GLS 	• Peak value of 2D longitudinal speckle tracking derived strain, averaged over the three segments of the RV free wall in RV-focused apical four-chamber view (%)	• Angle independent • Established prognostic value	• Vendor dependent

I. INTERNÍ KLINIKA
KARDIOLOGIE
FAKULTNÍ NEMOCNICE OLOMOUC

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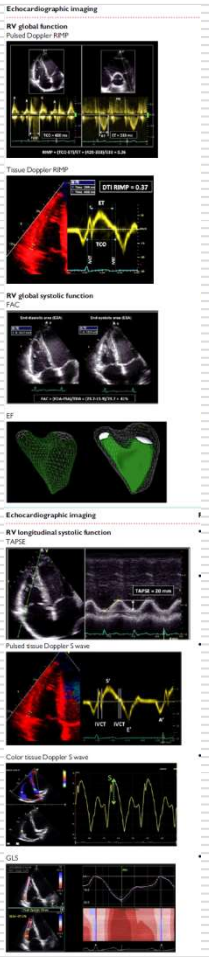
RIGHT VENTRICULAR FUNCTION

Tricuspid annular plane systolic excursion (TAPSE) reflects longitudinal shortening of the RV. TAPSE is measured in the A4C by placing an M-mode cursor on the lateral tricuspid annulus and measuring the peak distance travelled by this reference point during systole. A greater distance travelled during systole implies greater RV systolic function, with the normal reference limit being a TAPSE of ≥1.7 cm.
The primary limitation of TAPSE is that it only represents one component of RV motion within one single segment of RV myocardium. The RV may be frankly dysfunctional despite relatively preserved TAPSE, as in some cases of severe pulmonary arterial hypertension. Alternatively, the RV function may be globally preserved despite significantly reduced TAPSE, as often seen after cardiac surgery. In healthy individuals, TAPSE correlates with RV size.
Two common sources of error with TAPSE are:

1. Not placing the M-mode cursor parallel to the plane of longitudinal motion, which results in angle-dependent underestimation of TAPSE.
2. Incorrectly measuring the magnitude of displacement from the M-mode image.



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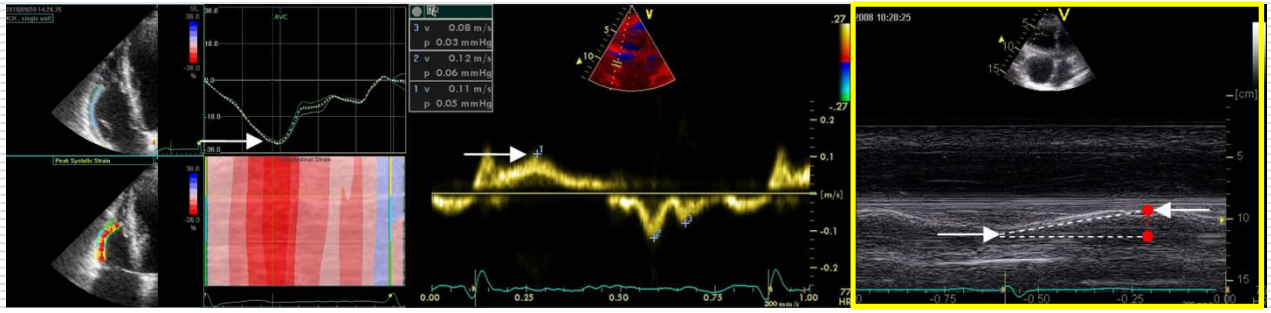
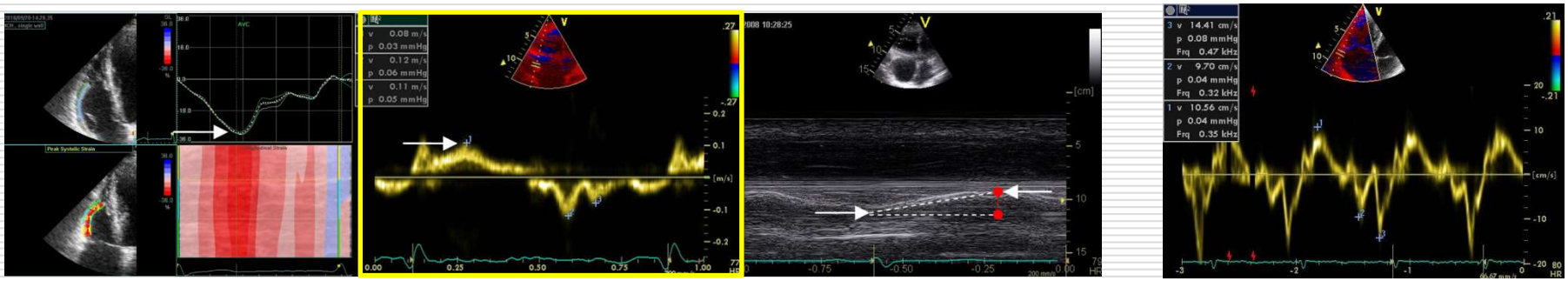
TAPSE remains one of the most widely used measures of RV systolic function since it is easily obtained and has been shown to have robust diagnostic and prognostic value in several disease states.

1. In patients with precapillary **pulmonary hypertension**, TAPSE has been shown to correlate with cardiovascular magnetic resonance (CMR)-derived RV ejection fraction (RVEF) and predict long-term mortality.
2. In patients presenting with **inferior myocardial infarction**, a reduced TAPSE was found to be a rapid and accurate indicator of RV infarction even when no RV regional wall motion abnormalities could be identified.
3. In three separate series of patients with chronic left-sided systolic heart failure, up to 50 percent of patients were found to have a reduced TAPSE, a finding that was associated with a significant increase in long-term mortality.
4. In a meta-analysis of patients undergoing **transcatheter aortic valve replacement**, abnormal TAPSE as well as abnormal tricuspid annular velocity (S') and fractional area change (FAC) were independent risk factors for post-procedural mortality.





Tricuspid annular velocity reflects the longitudinal velocity of the tricuspid annulus during systole.

S' is measured in the A4C by placing a tissue Doppler cursor on the lateral tricuspid annulus and measuring the peak velocity of this reference point during systole. Care should be taken to measure the peak of the ejection waveform and not the earlier isovolumetric contraction waveform.

A greater velocity during systole implies greater RV systolic function, with the **normal reference limit** being an S' of ≥9.5 cm/s. Both pulsed tissue Doppler and color-coded tissue Doppler can be used to measure S', although the color-coded method yields mean velocities that are usually slightly lower.

The **advantages and limitations** are the same as TAPSE:

1. S' is simple to perform and has prognostic data, yet it is angle-dependent and only represents the longitudinal annular component of RV motion.
2. S' has been shown to correlate with CMR-derived RVEF and predicts outcomes in patients with pulmonary hypertension, inferior myocardial infarction, chronic heart failure, and arrhythmogenic RV cardiomyopathy (ARVC).

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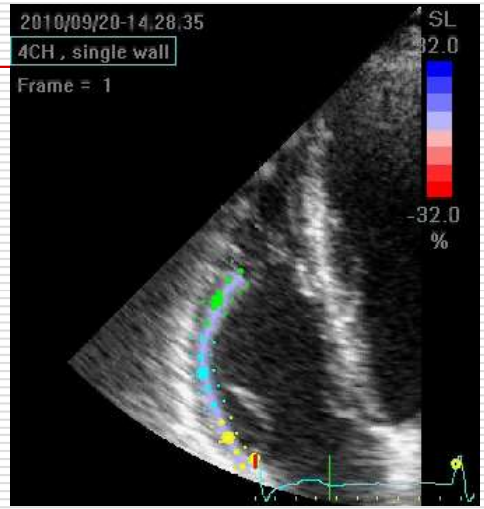
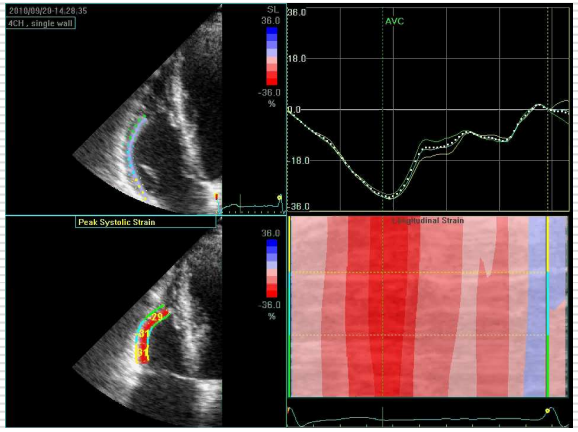


2D strain imaging is defined as the % change in myocardial deformation (RV longitudinal shortening). Strain is currently measured principally by the speckle-tracking (non-angle-dependent) approach.
Potential pitfalls include technical challenges in image acquisition and analysis (need for high frame rates, high signal-to-noise, experienced observers for reproducible measurements). Contemporary speckle-tracking algorithms have enhanced reproducibility and are beginning to yield **clinically relevant** observations:

1. In a large cohort of 575 patients with pulmonary arterial hypertension, free wall longitudinal strain by 2D speckle tracking was predictive of functional capacity and 18-month mortality.
2. In 200 patients with heart failure and seemingly normal RV systolic function (TAPSE >16 mm), a substantial proportion of patients was found to have abnormal RV free wall strain indicative of subclinical RV dysfunction, which was in turn predictive of death and hospitalization.
3. To identify signs of RV infarction in patients presenting with acute myocardial infarction, RV free wall strain was superior to conventional echocardiographic parameters.



The **normal reference limit** for 2DS of the RV free wall is -23%/-20%.

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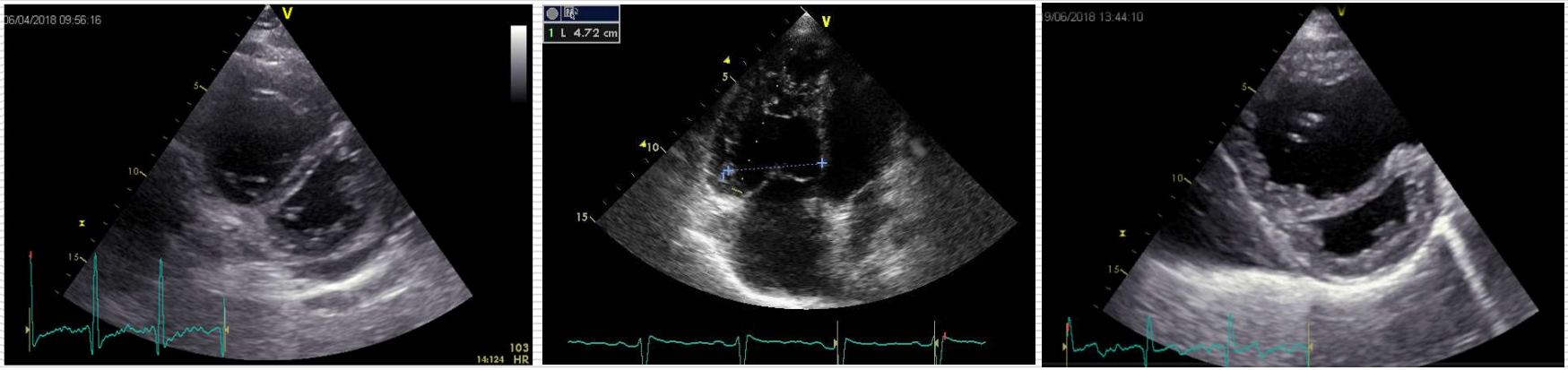
Perikardiální výpotek



Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015;28(1):1.

	Prognostická informace
Echokardiografický parametr:	
TAPSE	+
RV strain	+
RA area	+
Perikardiální výpotek	++

Table indicates the number of studies that have shown prognostic implications for each variable at baseline or follow-up
+ One study
++ Two studies

McLaughlin VV, *et al. J Am Coll Cardiol* 2013; 62:D73-81.

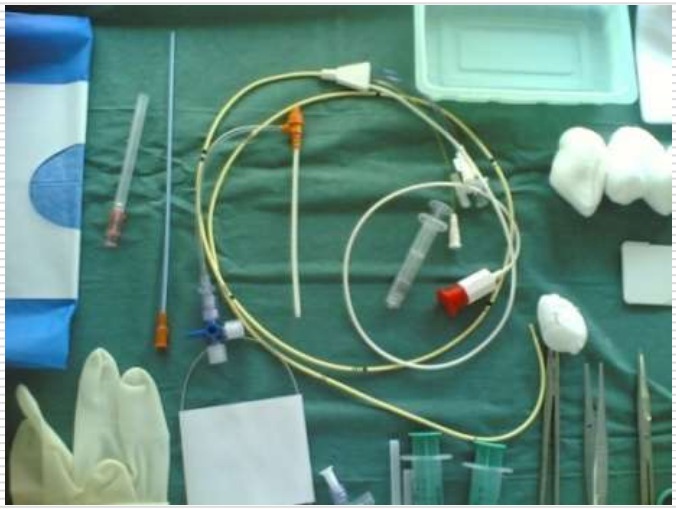
Determinants of prognosis[a] (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope[b]	Repeated syncope[c]
WHO functional class	I, II	III	IV
6MWD	>440 m	165–440 m	<165 m
Cardiopulmonary exercise testing	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 36–44.9	Peak VO_2 <11 ml/min/kg (<35% pred.) VE/VCO_2 slope ≥45
NT-proBNP plasma levels	BNP <50 ng/l NT-proBNP <300 ng/l	BNP 50–300 ng/l NT-proBNP 300–1400 ng/l	BNP >300 ng/l NT-proBNP >1400 ng/l
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2 No pericardial effusion	RA area 18–26 cm^2 No or minimal, pericardial effusion	RA area >26 cm^2 Pericardial effusion
Haemodynamics	RAP <8 mmHg CI ≥2.5 l/min/m^2 SvO_2 >65%	RAP 8–14 mmHg CI 2.0–2.4 l/min/m^2 SvO_2 60–65%	RAP >14 mmHg CI <2.0 l/min/m^2 SvO_2 <60%

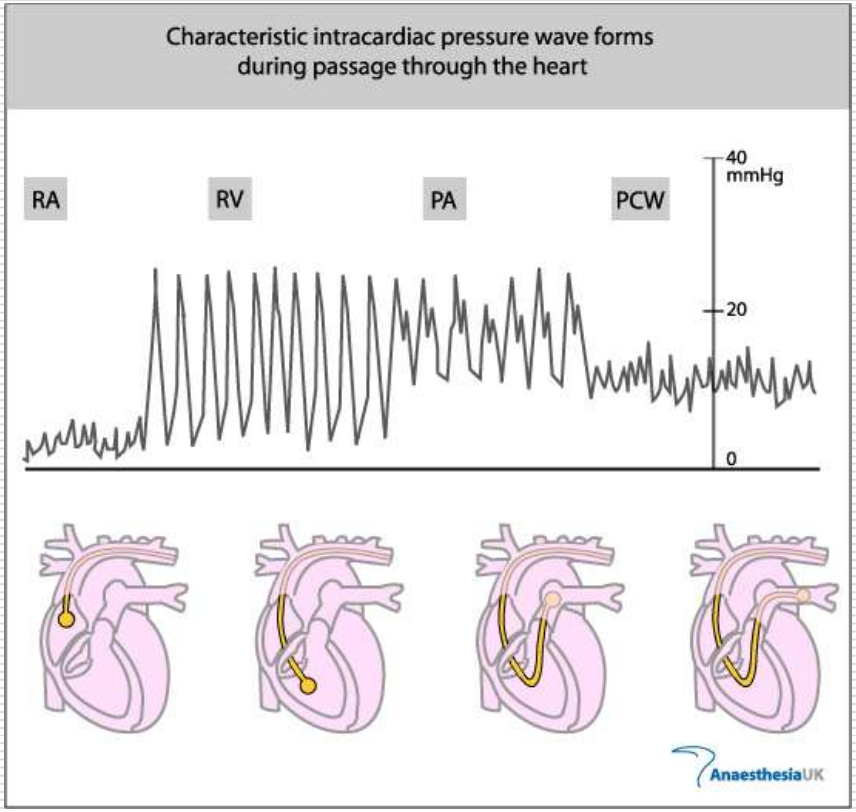
[a]Estimated 1-year mortality. [b]Occasional syncope during brisk or heavy exercise, or occasional orthostatic syncope in an otherwise stable patient.
[c]Repeated episodes of syncope, even with little or regular physical activity

Galiè N, *et al. Eur Heart J* 2016; 37:67-119.

Pravostranná katetrizace - test akutní vazoreaktivity

Přípravek	Iniciální dávka	Max. dávka	Protokol
NO inh. (ppm)	10–20	–	Jednorázová inhalace
Epoprostenol i.v. (ng/kg/min)	2	12	Dávku zvýšit každých 10 min o 2 ng/kg/min
Adenosin i.v. (µg/kg/min)	50	350	Dávku zvýšit každé 2 min o 50 µg/kg/min





ESC guidelines. Eur Heart J 2009;30:2493-2537
Jansa P. Chronicka plicni hypertenze. Cor Vasa 2011;53(3)

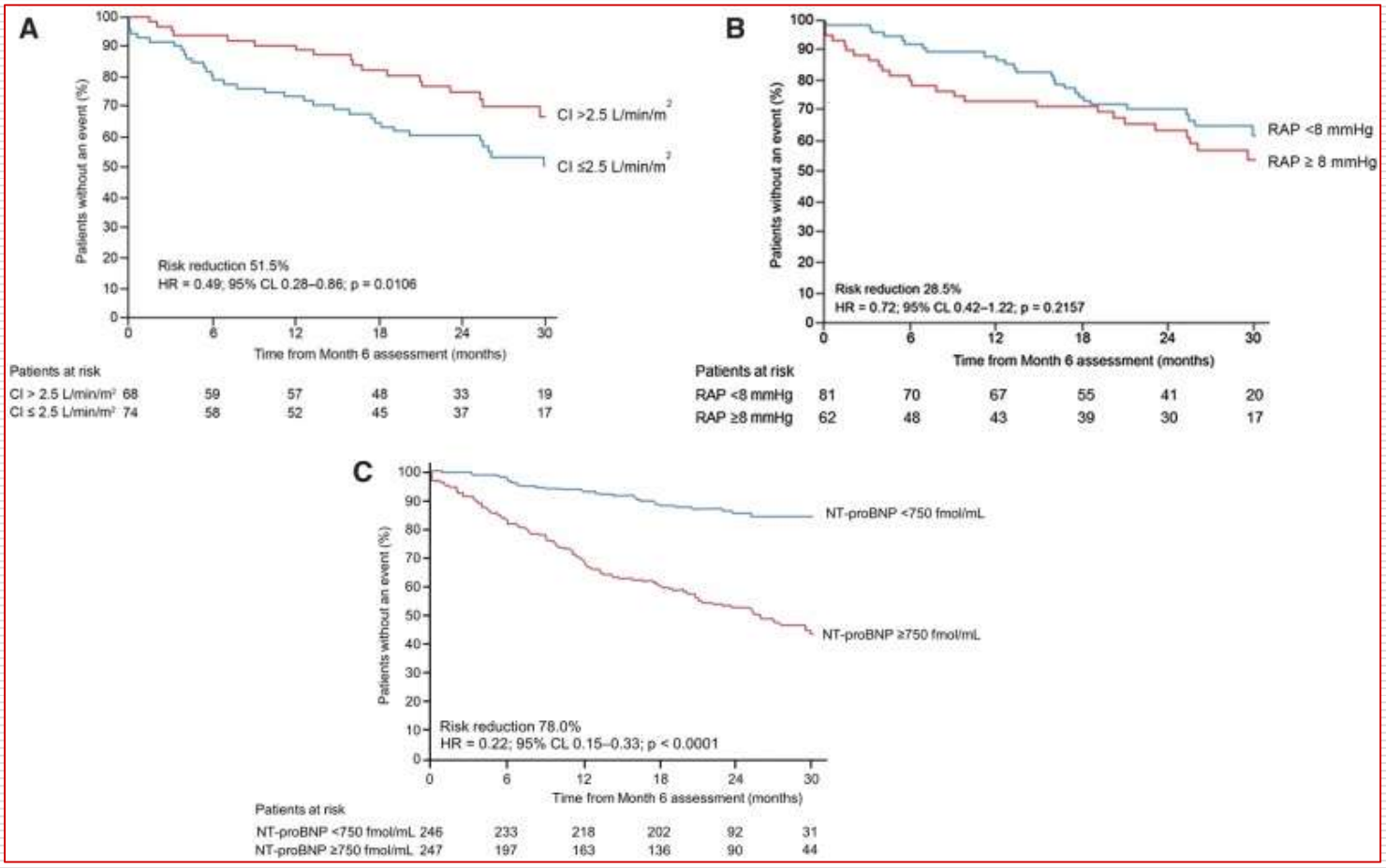
- Klinické zhoršení vztažené k PAH je významným **prediktorem mortality**
- V registru REVEAL byla u 73% pacientů, kteří zemřeli v důsledku PAH, zaznamenáno **klinické zhoršení v předchozích 8 měsících** (hospitalizace)
- Snížení rizika hospitalizací v důsledku PAH je tedy zásadním **terapeutickým cílem** a endpointem klinických studií.
- Data z hemodynamické podstudie SERAPHIN podporují dosažení nízkorizikového profilu jako terapeutického cíle (CI >2,5 L/min/m2 a/nebo NT-proBNP <750 fmol/ml)

Determinants of prognosis[a] (estimated 1-year mortality)	Low risk <5%
Clinical signs of right heart failure	Absent
Progression of symptoms	No
Syncope	No
WHO functional class	I, II
6MWD	>440 m
Cardiopulmonary exercise testing	Peak VO_2 >15 ml/min/kg (>65% pred.) VE/VCO_2 slope <36
NT-proBNP plasma levels	BNP <50 ng/l NT-proBNP <300 ng/l
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2 No pericardial effusion
Haemodynamics	RAP <8 mmHg CI ≥2.5 l/min/m^2 SvO_2 >65%

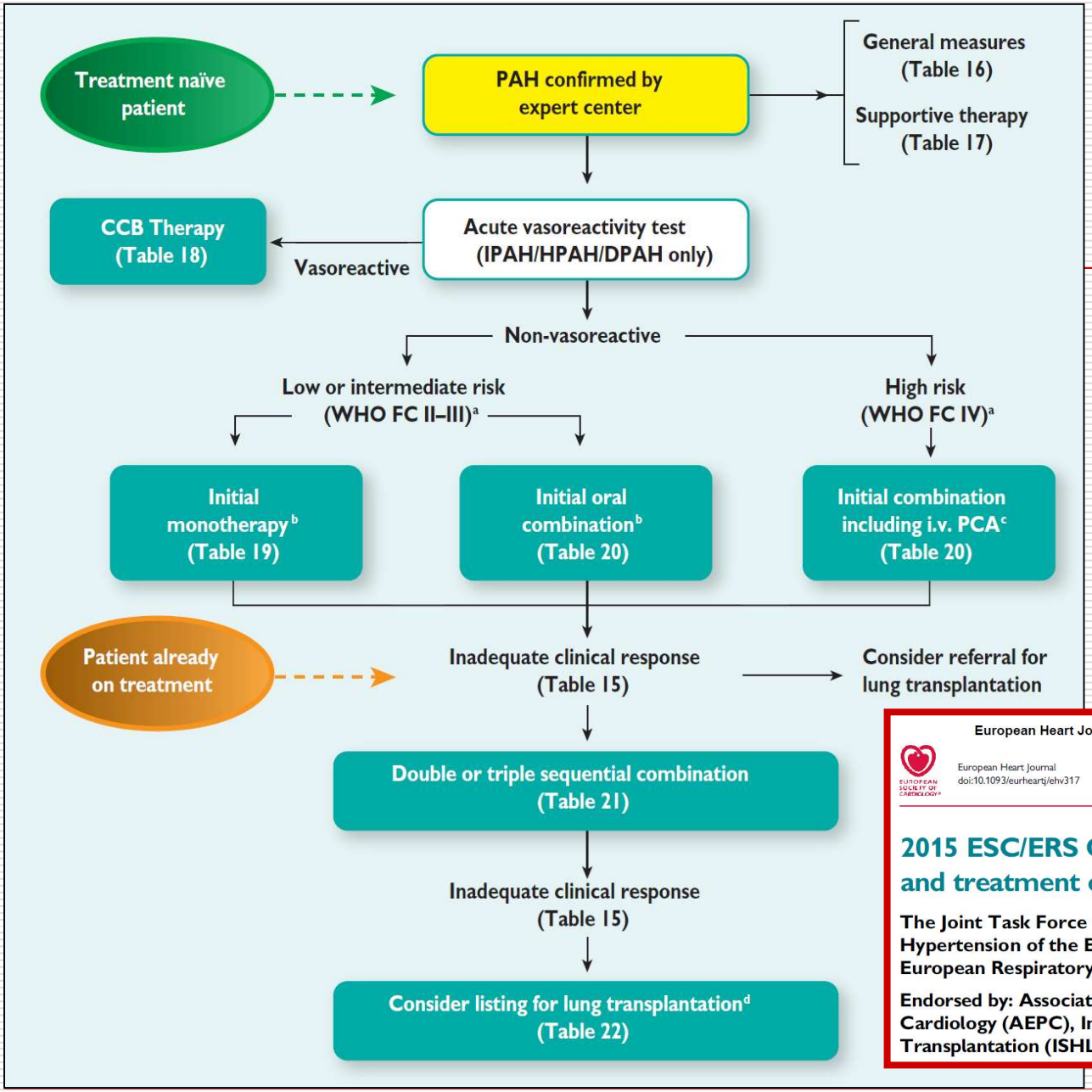
European Heart Journal (2017) 38, 1147–1155
doi:10.1093/eurheartj/ehx025

SERAPHIN haemodynamic substudy: the effect of the dual endothelin receptor antagonist macitentan on haemodynamic parameters and NT-proBNP levels and their association with disease progression in patients with pulmonary arterial hypertension

Nazzareno Galiè[1]*, Pavel Jansa[2], Tomás Pulido[3], Richard N. Channick[4], Marion Delcroix[5], Hossein-Ardeschir Ghofrani[6], Franck-Olivier Le Brun[7], Sanjay Mehta[8], Loïc Perchenet[7], Lewis J. Rubin[9], B.K.S. Sastry[10], Gérald Simonneau[11], Olivier Sitbon[11], Rogério Souza[12], and Adam Torbicki[13]



Galie N. et al. Eur Heart J. 2017 Apr 14; 38(15): 1147–1155.



European Heart Journal Advance Access published September 15, 2015

European Heart Journal
doi:10.1093/eurheartj/ehv317

ESC/ERS GUIDELINES

2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

The Joint 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: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT)

Hodnocení fragility

Frailty criteria	Assessment	Score
Shrinkage	Ask the patient: Have you unintentionally lost ≥10 lbs in the past year? **Yes / No**	*If **Yes**, add 1 point*
Weakness (grip strength)	1. Ask the patient to hold dynamometer in dominant hand with arms parallel to their body without squeezing arms against their body. 2. Adjust the handle to ensure that the middle phalanx rests on the inner handle. 3. Ask the patient to squeeze the handle and record. 4. Perform three trials, and obtain the average value. Record results below: Trial 1: _____ kg force Trial 2: _____ kg force Trial 3: _____ kg force **Average:** _____ kg force	Compare patient's average with the lowest 20th percentile by gender and BMI shown below: **Men** / **Women** **BMI** / **Kg force** / **BMI** / **Kg force** ≤24 / ≤29 / ≤23 / ≤17 24.1 to 26 / ≤30 / 23.1 to 26 / ≤17.3 26.1 to 28 / ≤31 / 26.1 to 29 / ≤18 >28 / ≤32 / >29 / ≤21 *Add 1 point* if the **average** falls within or below the above values
Exhaustion	Ask the patient the following two questions: 1. How often in the last week did you feel that everything you did was an effort? _____ 2. How often in the last week did you feel that you could not get going? _____	**0** / **1** / **2** / **3** Rarely or none of the time (<1 day) / Some or a little of the time (1 to 2 days) / Moderate amount of the time (3 to 4 days) / Most of the time (>4 days) *Add 1 point* for a score of 2 or 3 for EITHER question

Frailty criteria	Assessment	Score
Low physical activity	Ask the patient the following four questions: 1. Can you get out of bed or chair yourself? **Yes / No** 2. Can you dress and bathe yourself? **Yes / No** 3. Can you make your own meals? **Yes / No** 4. Can you do your own shopping? **Yes / No**	*Add 1 point* for any **No** answer
Slowness	1. Ask the patient to stand up and walk toward the tape on the ground. 2. Using a stopwatch, record the time it takes for the patient to walk 15 feet. Record results below: Trial: _____ seconds	**Men** / **Women** **Height** / **Time** / **Height** / **Time** ≤173 cm / ≥7 seconds / ≤159 cm / ≥7 seconds >173 cm / ≥6 seconds / >159 cm / ≥6 seconds *Add 1 point* if the trial time falls higher than the above values

- 0 to 1: Not frail
- 2 to 3: Intermediate (pre-frail)
- 4 to 5: Frail

Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001; 56:M146.
Frailty. In: Geriatrics Evaluation & Management Tools: Clinical Templates to Support Clinicians and Systems that are Caring for Older Adults, American Geriatrics Society, New York 2013

Hodnocení mentálního stavu a kognitivních funkcí

Impairment	None (0)	Questionable (0.5)	Mild (1)	Moderate (2)	Severe (3)
Memory	No memory loss or slight inconstant forgetfulness	Consistent slight forgetfulness; partial recollection of events	Moderate memory loss; more marked for recent events; defect interferes with everyday activities	Severe memory loss; only highly learned material retained; new material rapidly lost	Severe memory loss; only fragments remain
Orientation	Fully oriented	Fully oriented or slight difficulty with time relationships	Moderate difficulty with time relationships; oriented for place at examination; may have geographic disorientation elsewhere	Severe difficulty with time relationships; usually disoriented in time, often to place	Oriented to person only
Judgment and problem	Solves everyday problems and handles business and financial affairs well; judgment good in relation to past performance	Slight impairment to solving problems, similarities, differences	Moderate difficulty in handling problems, similarities, differences; social judgment usually maintained	Severely impaired in handling problems, similarities, differences; social judgment usually impaired	Unable to make judgments or solve problems
Community affairs	Independent function at usual level in job, shopping, volunteer and social groups	Slight impairment in these activities	Unable to function independently at these activities though may still be engaged in some; appears normal to casual inspection	No pretense of independent function outside of home; appears well enough to be taken to functions outside of family home	No pretense of independent function outside of home; appears too ill to be taken to functions outside a family home
Home and hobbies	Life at home, hobbies, intellectual interests well maintained	Life at home, hobbies, intellectual interests slightly impaired	Mild but definite impairment of function at home; more difficult chores abandoned; more complicated hobbies and interests abandoned	Only simple chores preserved; very restricted interests, poorly maintained	No significant function in home
Personal care	Fully capable of self care	Fully capable of self care	Needs prompting	Requires assistance in dressing, hygiene, keeping of personal effects	Requires much help with personal care; frequent incontinence

Oblast hodnocení:	Max.skóre:
1. Orientace: Položte nemocnému 10 otázek. Za každou správnou odpověď započítejte 1 bod. - Který je teď rok? - Které je roční období? - Můžete mi říci dnešní datum? - Který je den v týdnu? - Který je teď měsíc? - Ve kterém jsme státě? - Ve které jsme zemi? - Ve kterém jsme městě? - Jak se jmenuje tato nemocnice?(toto oddělení?,tato ordinace?) - Ve kterém jsme poschodí?(pokoji?)	 1 1 1 1 1 1 1 1 1 1
2. Paměť: Vyšetřující jmenuje 3 libovolné předměty (nejlépe z pokoje pacienta- například židle, okno, tužka)a vyzve pacienta, aby je opakoval. Za každou správnou odpověď je dán 1 bod	3
3. Pozornost a počítání: Nemocný je vyzván, aby odečítal 7 od čísla 100, a to 5 krát po sobě. Za každou správnou odpověď je 1 bod.	5
4. Krátkodobá paměť (=výbavnost): Úkol zopakovat 3 dříve jmenovaných předmětů (viz bod 2.)	3
5. Řeč,komunikace a konstrukční schopnosti: (správná odpověď nebo splnění úkolů = 1 bod) Ukažte nemocnému dva předměty (př.tužka,hodinky) a vyzvěte ho aby je pojmenoval. Vyzvěte nemocného, aby po vás opakoval: - Žádná ale - Jestliže - Kdyby Dejte nemocnému třístupňový příkaz: „*Vezměte* papír do pravé ruky, *přeložte* ho na půl a *položte* jej na podlahu." Dejte nemocnému přečíst papír s nápisem „Zavřete oči". Vyzvěte nemocného, aby napsal smysluplnou větu (obsahující podmět a přísudek), která dává smysl) Vyzvěte nemocného, aby na zvláštní papír nakreslil obrazec podle předlohy. 1 bod jsou-li zachovány všechny úhly a protnutí vytváří čtyřúhelník.	 2 1 3 1 1 1
Hodnocení: 00 – 10 bodů těžká kognitivní porucha 11 – 20 bodů středně těžká kognitivní porucha 21 – 23 bodů lehká kognitivní porucha 24 – 30 bodů pásmo normálu	

Morris JC. The clinical dementia rating (CDR): Current version and scoring rules. Neurology 1993; 43:2412. Copyright © 1993 Lippincott Williams & Wilkins.

ZÁVĚRY

- **Přežívání pacientů** s PAH se zásadním způsobem zlepšilo v souvislosti s dostupností specifické léčby PAH
- V klinických studiích a registrech bylo popsáno mnoho **prognostických faktorů**. Tyto faktory jsou založeny na demografických, funkčních, laboratorních a hemodynamických parametrech.
- Faktory predikující přežití u PAH jsou důležité pro **klinický management** pacientů s PAH.
- Součástí stanovení terapeutického managementu a specifické léčby je stanovení **mentálního stavu pacienta** s ohledem na spolupráci a **hodnocení jeho fragility**.
- Cílem léčby pacientů s PAH je co možná nejrychlejší **dosažení nízkého rizika** a tedy nízké mortality.

Děkuji za pozornost

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