Relevantní cíle současné léčby PAH
Ovlivnění hemodynamiky

Vladimír Dytrych

Podpořeno firmou AOP

VŠEOBECNÁ FAKULTNÍ NEMOCNICE V PRAZE

1. LÉKAŘSKÁ FAKULTA Univerzita Karlova

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

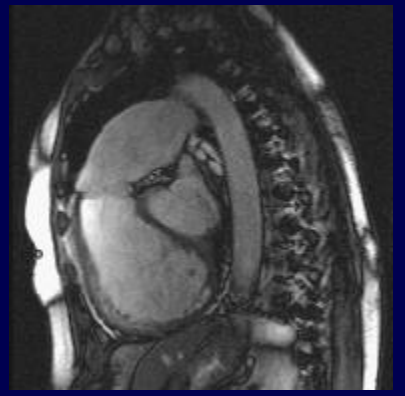
Úvod

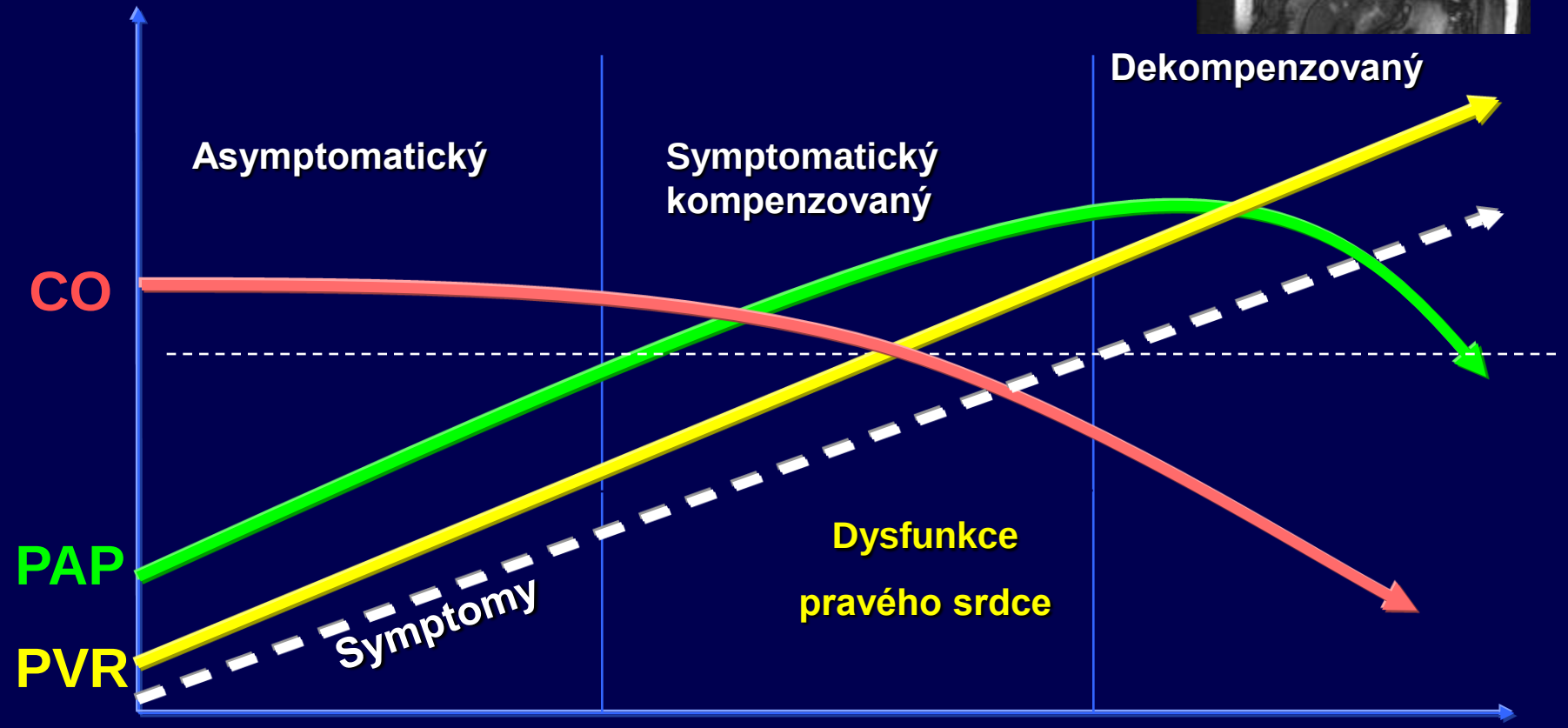
- Definice PAH je hemodynamická
- Ná základě hemodynamických parametrů stanovujeme diagnózu a indikujeme specifickou léčbu
- Cílem léčby PAH je dosažení a udržení nízkorizikového profilu *(ESC guidelines 2022)*
- Hemodynamické parametry nejsou většinou primárním end-pointem klinických studií 3. fáze, jsou end-pointem studií 2. fáze k ověření, zda je lék biologicky aktivní a dostatečně bezpečný

Riziková stratifikace PAH

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%

ESC guidelines, 2022





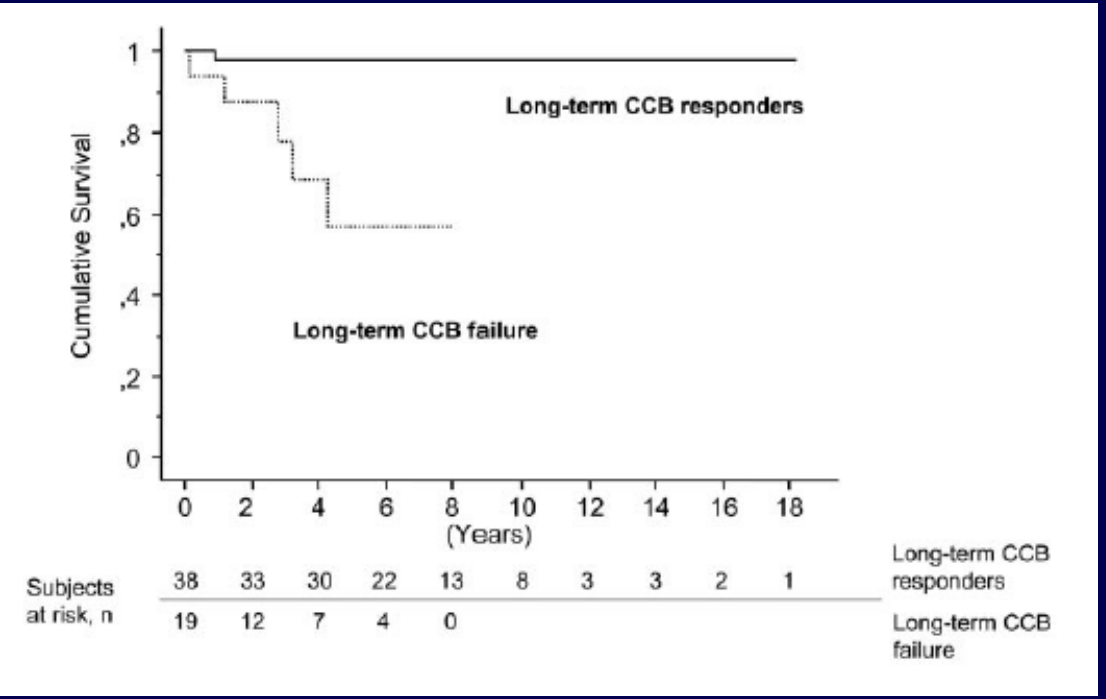
Rich et al. In: Harrison's Principles of Internal Medicine. 15th ed. 2001:1506-1507.

Long-Term Response to Calcium Channel Blockers in Idiopathic Pulmonary Arterial Hypertension

Olivier Sitbon, MD; Marc Humbert, MD, PhD; Xavier Jaïs, MD; Vincent Ioos, MD; Abdul M. Hamid, MD; Steeve Provencher, MD; Gilles Garcia, MD; Florence Parent, MD; Philippe Hervé, MD; Gérald Simonneau, MD

iPAH, n=557, vasoreaktivita: 17 (26%) – i.v. epo, NO

70 akutní respondeři (12.6%), 38 dlouhodobí respondeři (6.8%)



Circulation. 2005;111:3105-3111

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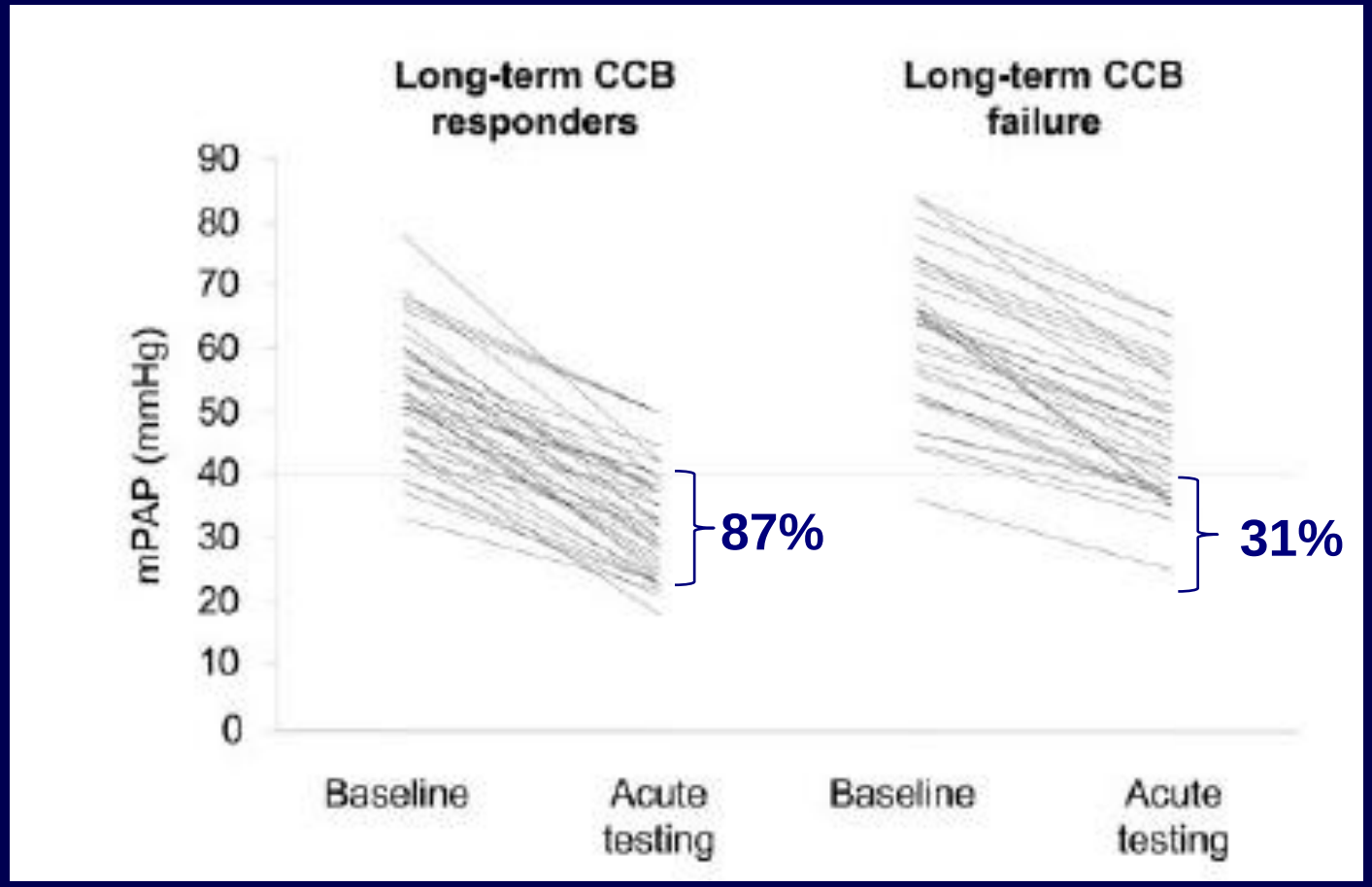


Circulation. 2005;111:3105-3111

Barst criteria, 1986:

pokles mPAP o ≥20%, nezměněnný nebo zvýšený srdeční index, a snížený nebo nezměněnný poměr PVR a SVR (PVR/SVR)

Rich criteria, 1992:

pokles v mPAP a PVR o ≥20%

Sitbon criteria, 2005:

pokles v mPAP o ≥10 mm Hg a dosažení mPAP ≤40 mm Hg a zvýšený nebo nezměněnný srdeční výdej

N Engl J Med 1992;327:76–81
Chest 1986;89:497–503
Circulation 2005;111:3105–11
Eur Respir J 2015, 46(4):903-75

Initial dual oral combination therapy in pulmonary arterial hypertension

N=97, kombinace ERA a inhibitorů PDE5, retrospektivní analýza

	Baseline	First follow-up visit#	p-value
NYHA FC I/II/III/IV n	0/15/70/12	4/57/31/5	<0.001
Clinical signs of RHF n (%)	49 (51)	25 (26)	<0.001
6-min walk distance m	324±132	395±114	<0.000 01
Borg dyspnoea index	4.3±2.0	3.1±1.9	<0.000 01
BNP¶ ng·L^{-1} median (IQR)	372 (115–710)	62 (34–274)	<0.000 01
Haemodynamics			
RAP mmHg	9.5±5.7	6.7±4.5	<0.000 01
mPAP mmHg	53.9±10.4	45.1±10.9	<0.000 01
PAWP mmHg	8.8±3.5	8.7±3.3	0.82
Cardiac output L·min^{-1}	3.94±1.17	5.65±1.62	<0.000 01
Cardiac index L·min^{-1}·m^{-2}	2.14±0.51	3.13±0.79	<0.000 01
PVR dyn·s·cm^{-5}	1021±357	565±252	<0.000 01
Mean BP mmHg	97±18	87±13	<0.000 01
Heart rate beats per min	85±15	81±12	<0.011
S_{vO_2} %	59±8	67±8	<0.000 01

Sitbon et al 2016

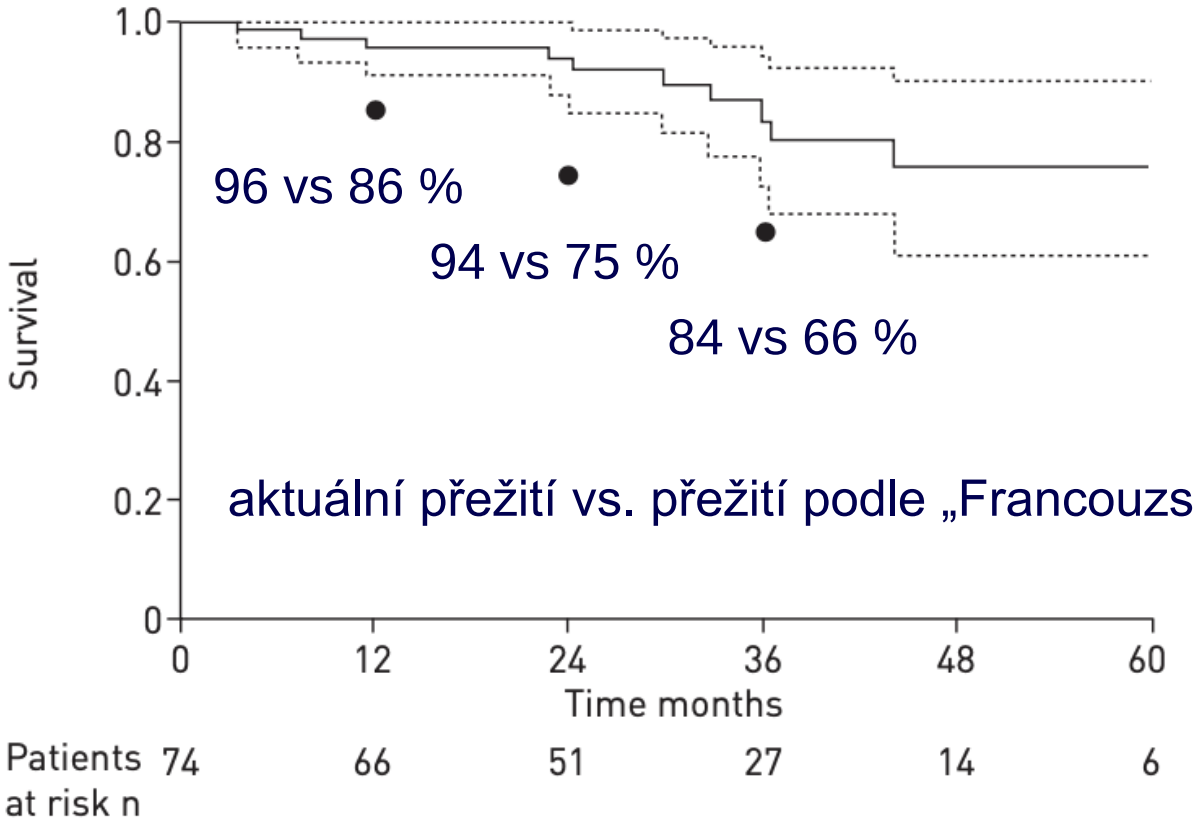
Initial dual oral combination therapy in pulmonary arterial hypertension

First follow-up visit medián 4,1 měsíce, last follow-up visit medián 24,6 měsíců, n=77

	Baseline	First follow-up visit[#]	Last follow-up visit[¶]	p-value
NYHA FC I/II/III/IV n	0/11/57/9	4/49/22/2	10/37/26/4	<0.00001
Clinical signs of RHF n (%)	35 (45)	15 (19)	16 (21)	<0.0004
6-min walk distance m	354±127	427±107**	438±117**	<0.00001
Borg dyspnoea index	4.4±2.1	3.0±2.0**	3.2±1.9**	<0.0003
Haemodynamics				
RAP mmHg	9.1±6.0	6.1±3.9**	7.7±4.5	<0.00008
mPAP mmHg	54.2±11.1	44.6±11.3**	47.4±13.3**	<0.00001
PAWP mmHg	8.9±3.6	8.8±3.5	9.2±3.8	0.67
Cardiac output $L \cdot min^{-1}$	3.93±1.09	5.74±1.75**	5.71±2.00**	<0.00001
Cardiac index $L \cdot min^{-1} \cdot m^{-2}$	2.14±0.49	3.14±0.85**	3.07±0.91**	<0.00001
PVR $dyn \cdot s \cdot cm^{-5}$	978±304	536±215**	618±332**	<0.00001
Mean BP mmHg	94±17	87±14**	89±14**	<0.0003
Heart rate beats per min	86±15	79±12**	79±12**	<0.0006
Sv_{O_2} %	61±9	70±5**	69±7**	<0.00001

Sitbon et al 2016

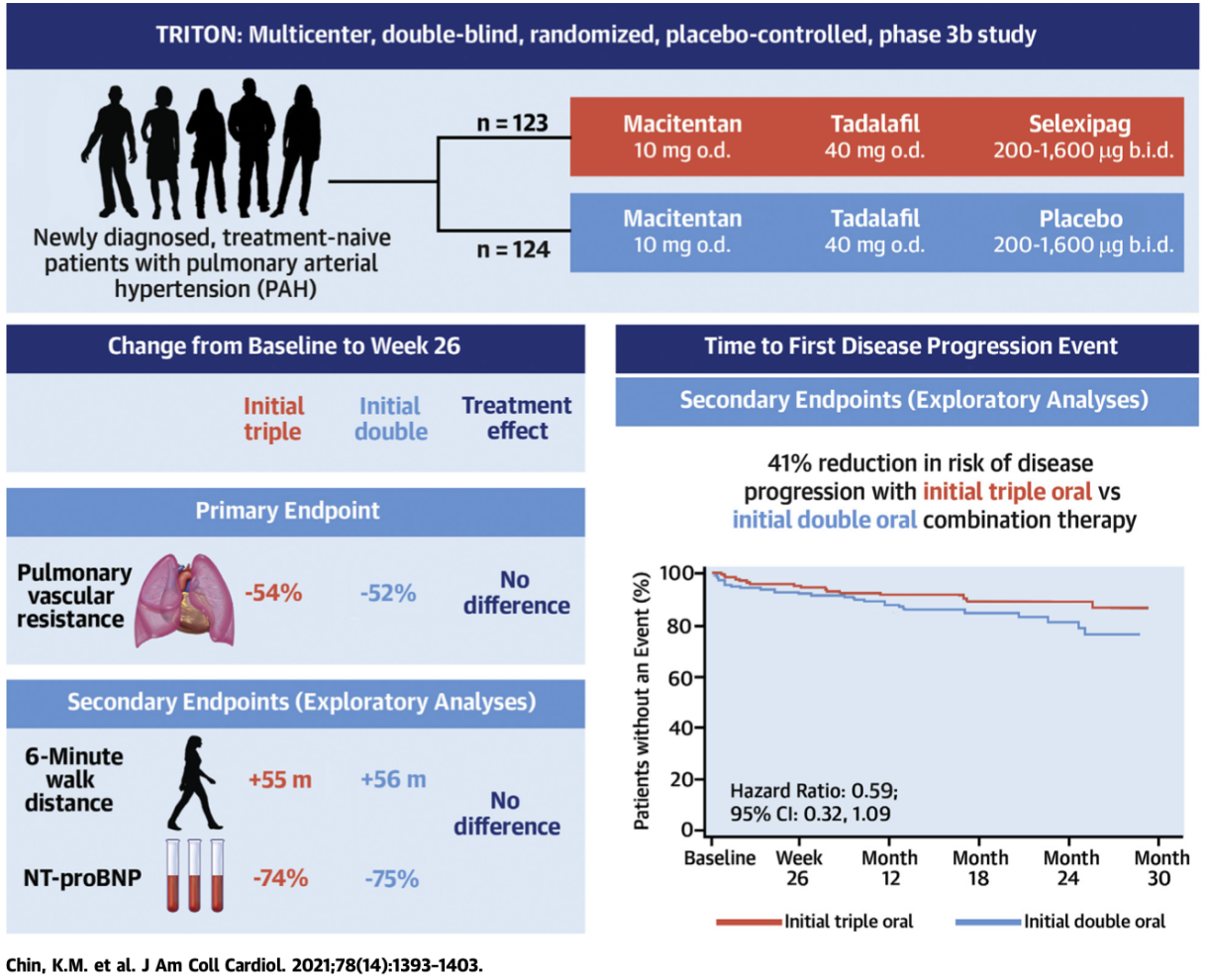
Initial dual oral combination therapy in pulmonary arterial hypertension



aktuální přežití vs. přežití podle „Francouzské rovnice predikce přežití“

Sitbon et al 2016

Iniciální double versus triple terapie (studie TRITON)

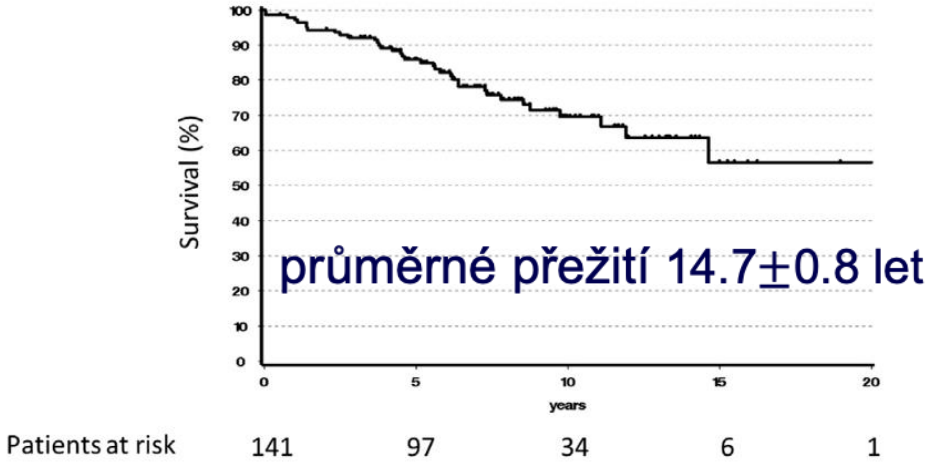


Chin, K.M. et al. J Am Coll Cardiol. 2021;78(14):1393-1403.

Chin et al 2021

Survival of Japanese Patients With Idiopathic/Heritable Pulmonary Arterial Hypertension

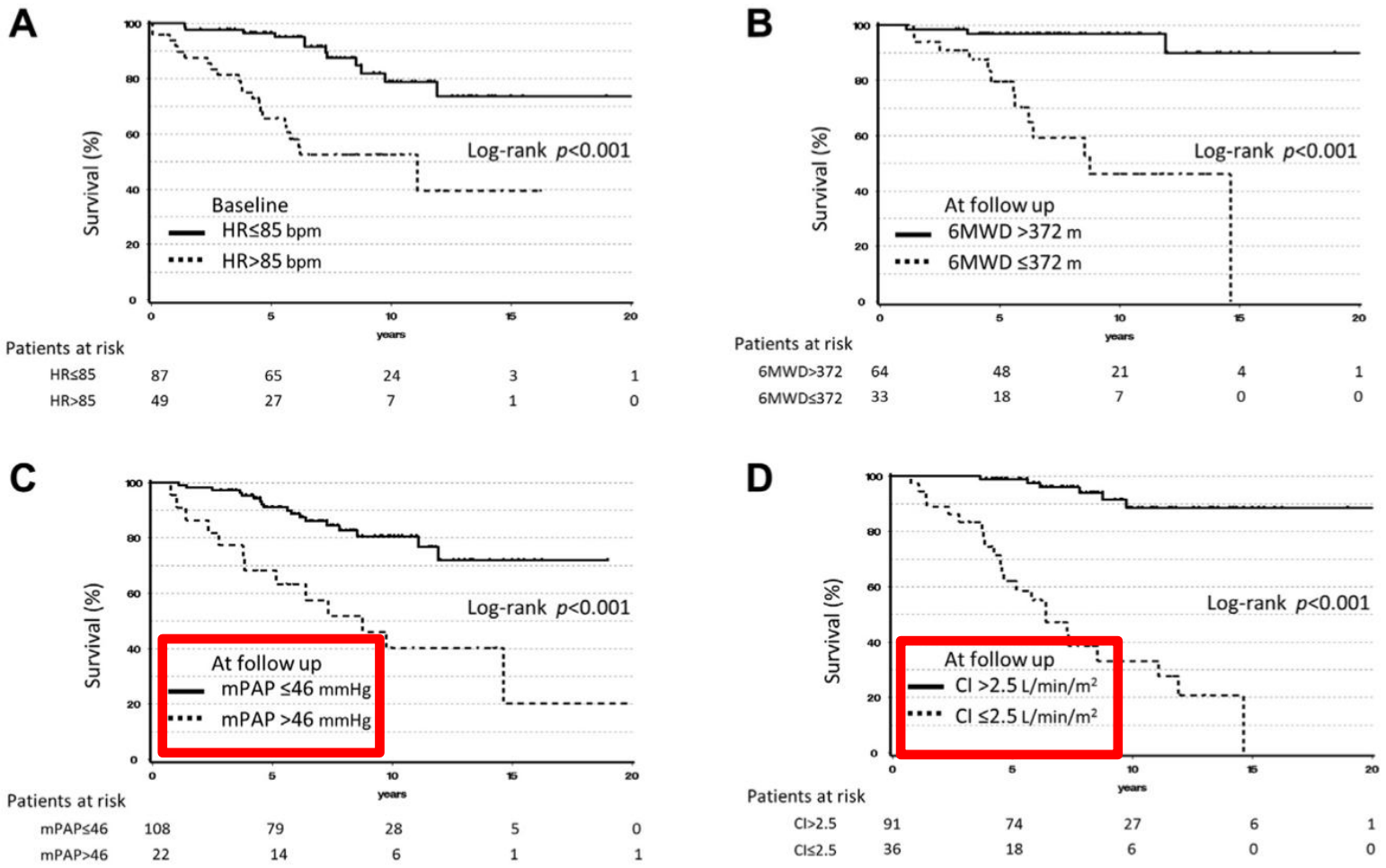
Variable	Baseline (n=141)	Follow-up (n=130)	*P* Value
Male	37 (26.2%)		
Age at diagnosis (years)	33.3±14.4		
Heritable pulmonary arterial hypertension	12 (8.5%)		
Time between baseline and follow-up, (years) median (min−max)		3.3 (0.2−14.4)	
WHO functional class (I/II/III/IV), n	1/18/91/31	10/83/34/3	<.001
6-minute walk distance (meters)	267.1±154.4	407.9±106.6	<.001
Brain natriuretic peptide (pg/mL)	326.2±348.1	74.1±172.2	<.001
Heart rate (bpm)	78.9±15.7	79.0±15.6	.385
Oxygen saturation (%)	95.2±4.2	96.1±3.5	.037
Mean pulmonary artery pressure (mm Hg)	60.3±14.7	37.6±11.4	<.001
Cardiac index (L/min/m^2)	2.1±0.9	3.2±1.1	<.001
Mixed venous oxygen saturation (%)	63.2±9.9	74.0±7.0	<.001
Pulmonary vascular resistance (dyn•s/cm^5)	1522.7±799.5	591.6±426.3	<.001



- retrospektivní analýza (1992-2012)
- 78 % léčeno epoprostenolem

Ogawa et al, 2017

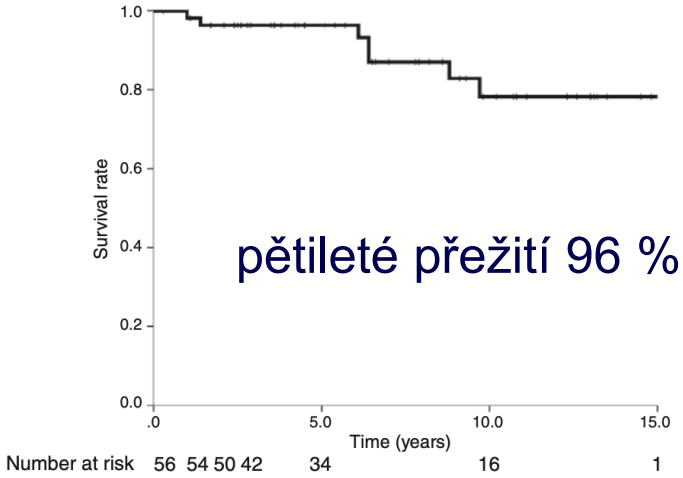
Survival of Japanese Patients With Idiopathic/Heritable Pulmonary Arterial Hypertension



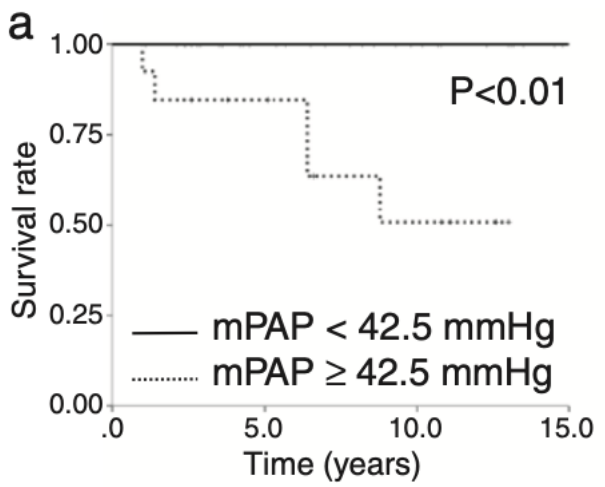
Ogawa et al, 2017

Long-term patient survival with idiopathic/heritable pulmonary arterial hypertension treated at a single center in Japan

	Survivor ($n = 49$)	Non-survivor ($n = 7$)	P
Age, years	33 ± 18	25 ± 10	0.26
Male, *n* (%)	14 (29)	1 (14)	0.43
HPAH, *n* (%)	10 (20)	0 (0)	0.41
WHO functional class (I/II/III/IV)	3 (0/2/34/13)	4 (0/0/2/5)	<0.01
6MWD (m)	257 ± 166	103 ± 179	<0.05
BNP (pg/mL)	260 ± 307	705 ± 556	<0.01
Uric acid (mg/dL)	6.3 ± 2.0	6.7 ± 1.0	0.66
mPAP (mm Hg)	61 ± 17	62 ± 14	0.95
RAP (mm Hg)	8 ± 4	13 ± 9	<0.05
PCWP (mm Hg)	9 ± 3	10 ± 5	0.82
SvO_2 (%)	66.1 ± 8.7	65.4 ± 10.1	0.86
Cardiac index (L/min/m^2)	2.4 ± 0.9	2.4 ± 0.9	0.82
PVR (dyn·s/cm^5)	1391 ± 615	1375 ± 537	0.96
Heart rate (bpm)	74 ± 16	86 ± 15	0.07
SpO_2 (%)	97 ± 3	95 ± 3	0.08
Treatment			
Oral PGI_2	9 (18)	0 (0)	0.22
IV PGI_2	37 (76)	6 (86)	0.55
Dose of epoprostenol (ng/kg/min)	79.6 ± 43.2	54.0 ± 47.8	0.19
ERA	34 (69)	4 (57)	0.52
PDE5 inhibitor	28 (57)	1 (14)	<0.05
Monotherapy	10 (20)	3 (43)	0.24
Combination therapy	38 (78)	4 (57)	0.24
Number of PAH-targeted drugs: 2	16 (33)	4 (57)	0.21
Number of PAH-targeted drugs: 3	22 (45)	0 (0)	<0.05
Warfarin	11 (22)	2 (29)	0.72
Oxygen therapy	46 (94)	7 (100)	0.50



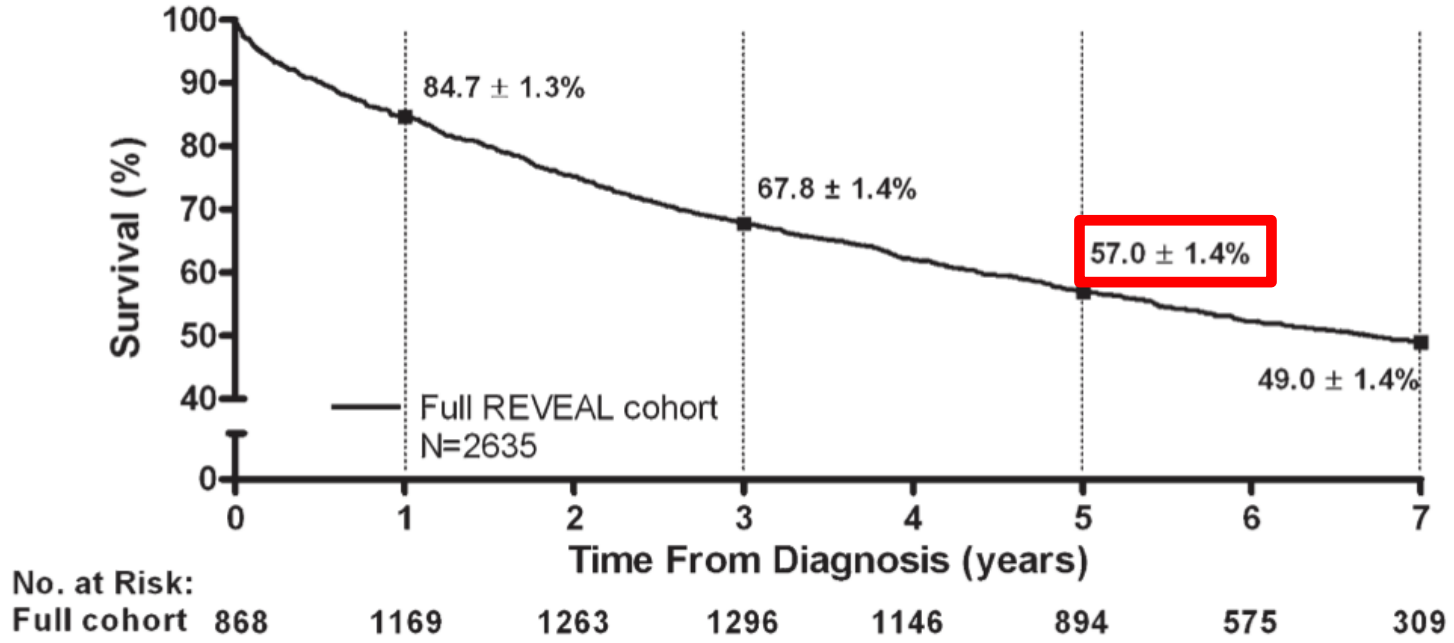
pětileté přežití 96 %



Ogawa et al, 2014

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

N=2635, 2006-2009, PH centra v USA



Benza et al, 2012

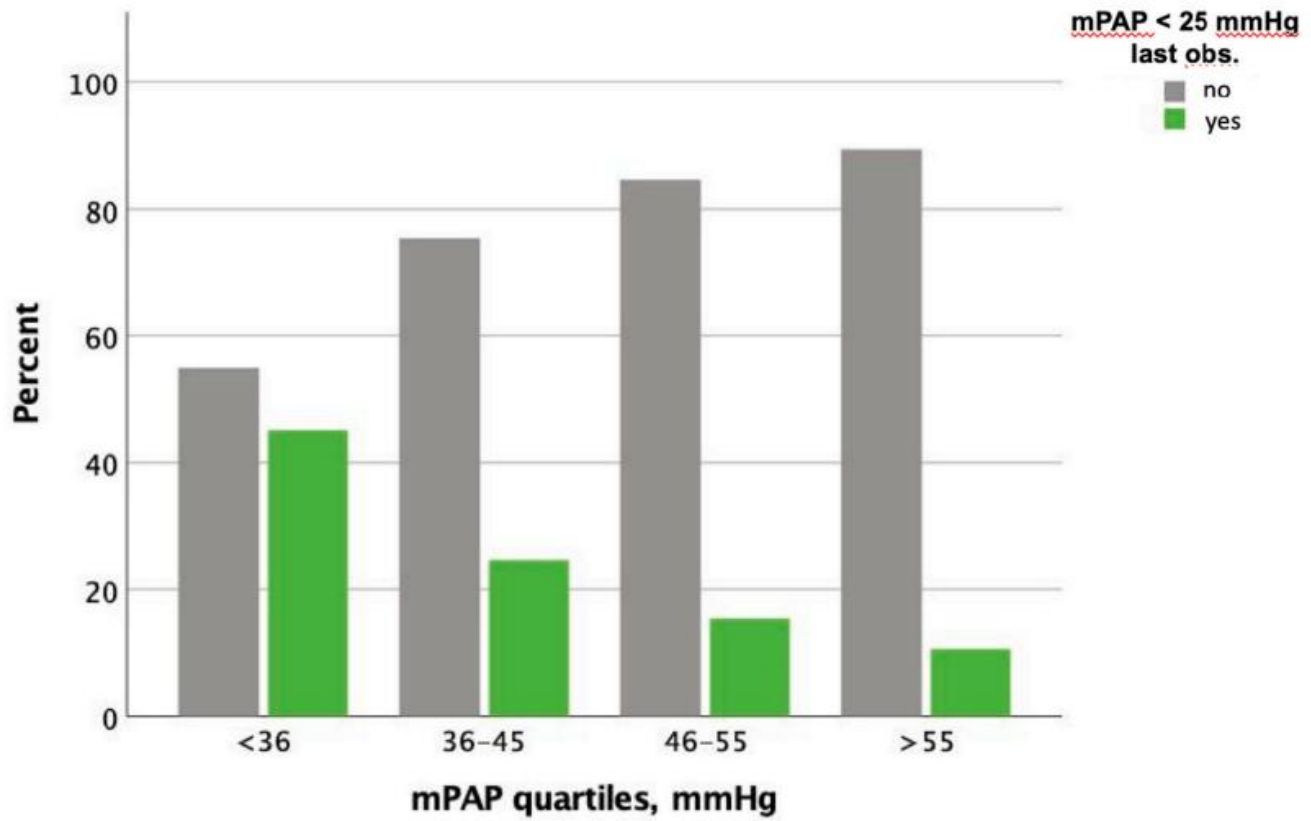
Pulmonary pressure recovery in idiopathic, hereditary and drug and toxin-induced pulmonary arterial hypertension: determinants and clinical impact

	Total	Europe	Japan	p
Baseline				
Age, years	46 (19)	51 (18)	33 (16)	<0.001
Gender, F	165 (62%)	119 (59.5%)	46 (68.6%)	0.11
Weight, Kg	67 (18)	70 (17)	55 (18)	<0.001
Height, cm	161 (24)	163 (26)	156 (14)	<0.001
WHO, class	2.8 (0,6)	2.7 (0.6)	3.1 (0.6)	<0.001
I-II	80 (30%)	73 (36%)	7 (11%)	
III	159 (60%)	117 (58%)	42 (62%)	
IV	28 (10%)	10 (5%)	18 (27%)	
6MWT, m	367 (131)	397 (102)	275 (162)	<0.001
Hemodynamics				
HR, beat/min	78 (14)	79 (13)	78 (16)	0.655
mPAP, mmHg	52.5 (15.4)	50.6 (14.9)	58.3 (15.8)	<0.001
RAP, mmHg	8.6 (4.7)	8.8 (4.8)	8.14 (4.4)	0.332
CI, l/min/m^2	2.33 (0.75)	2.31 (0.73)	2.37 (0.84)	0.537
PAWP, mmHg	9.7 (3.8)	10.0 (3.8)	8.7 (3.6)	0.02
PVR, WU	12.3 (6.6)	11.2 (5.9)	15.5 (7.4)	<0.001
ESC Risk estimate				0.03
Low	54 (20.2%)	27 (23.5%)	7 (10.4%)	
Intermediate	189 (70.8%)	138 (69%)	51 (76.1%)	
High	24 (9%)	15 (7.5%)	9 (13.4%)	

N=267
Konsekutivní pacienti 1999-2016
Terapeutický cíl mPAP < 25 mmHg
Multicentrická studie – Japonsko, Rakousko, Itálie

Badagliacca et al, 2022

Pulmonary pressure recovery in idiopathic, hereditary and drug and toxin-induced pulmonary arterial hypertension: determinants and clinical impact



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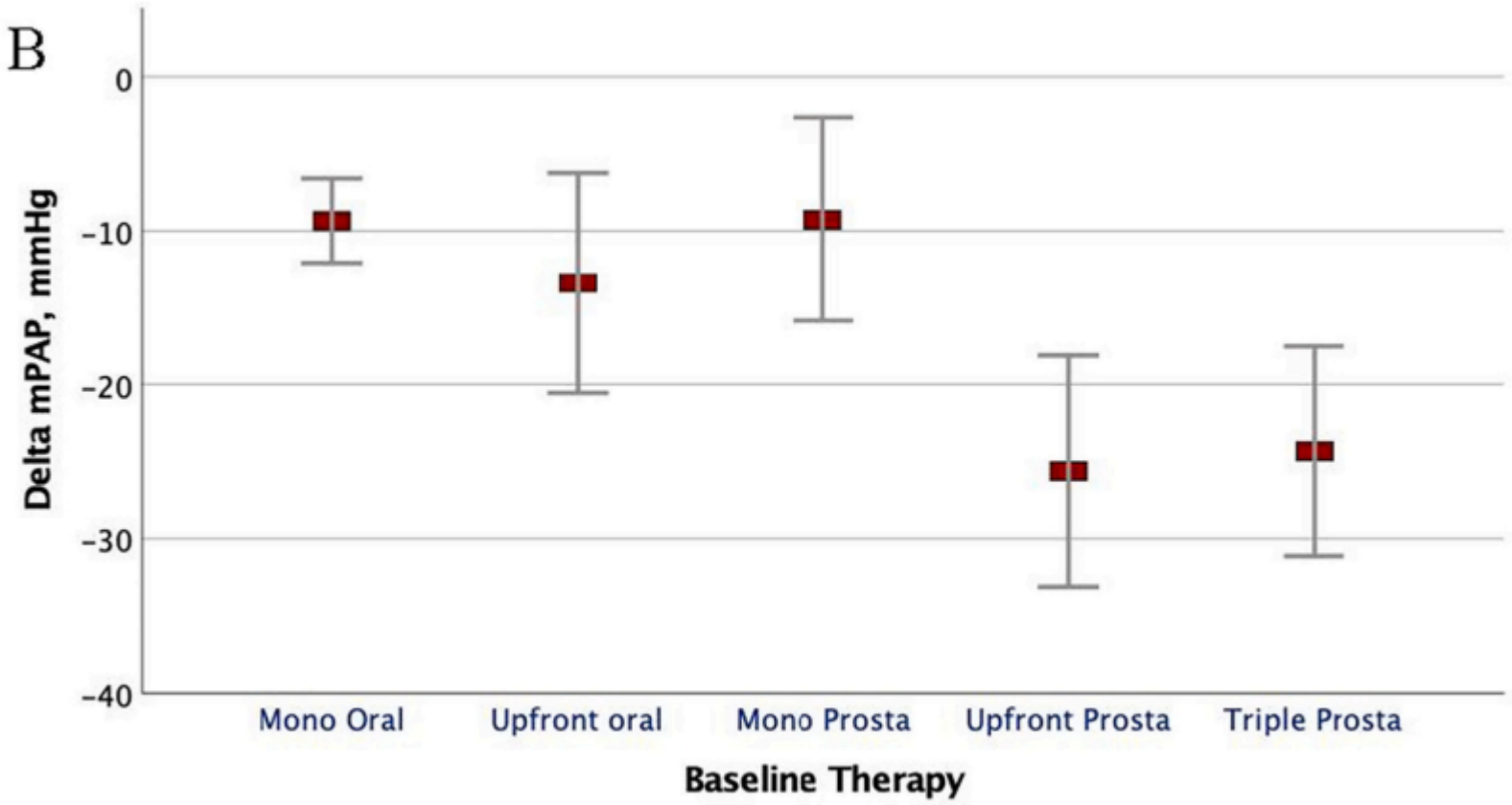

Badagliacca et al, 2022

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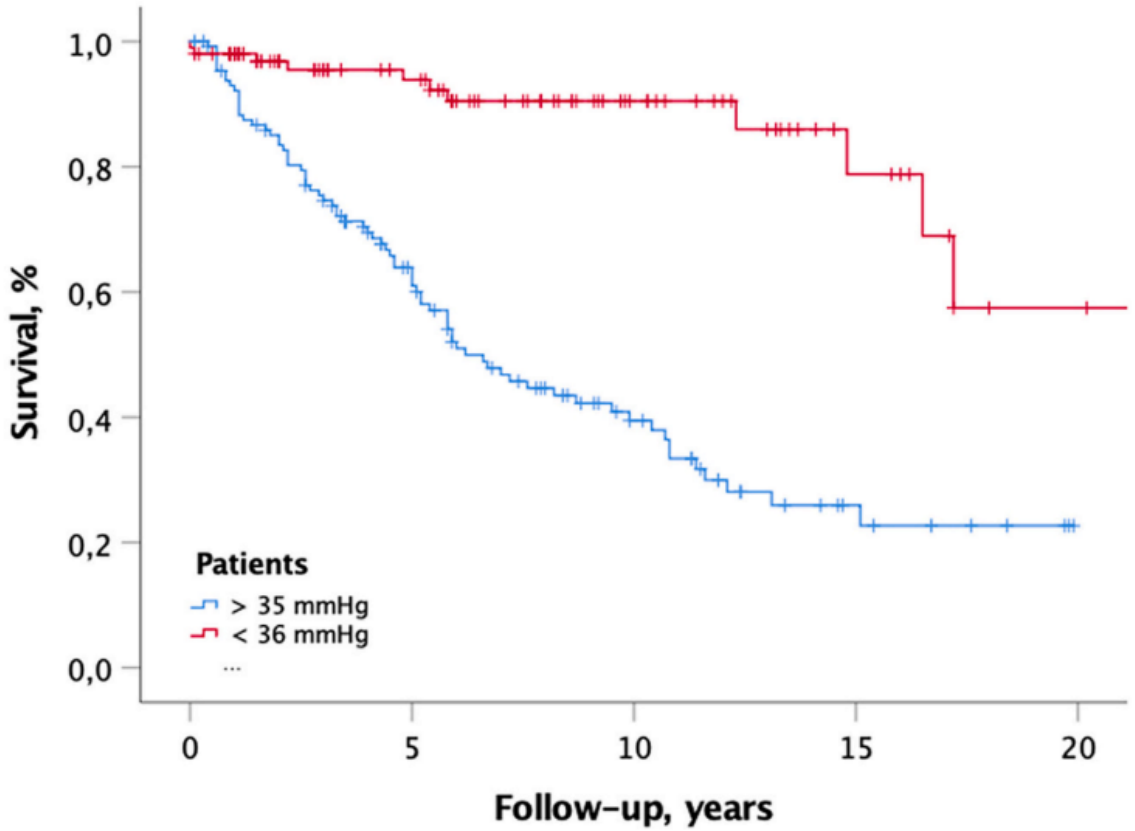
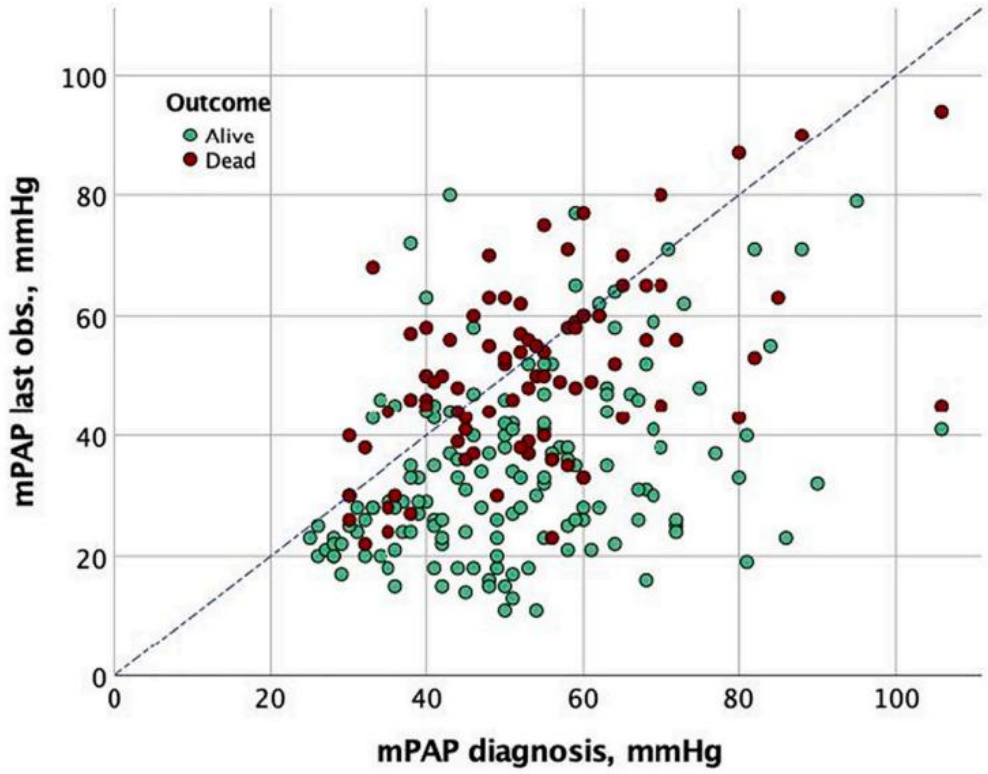
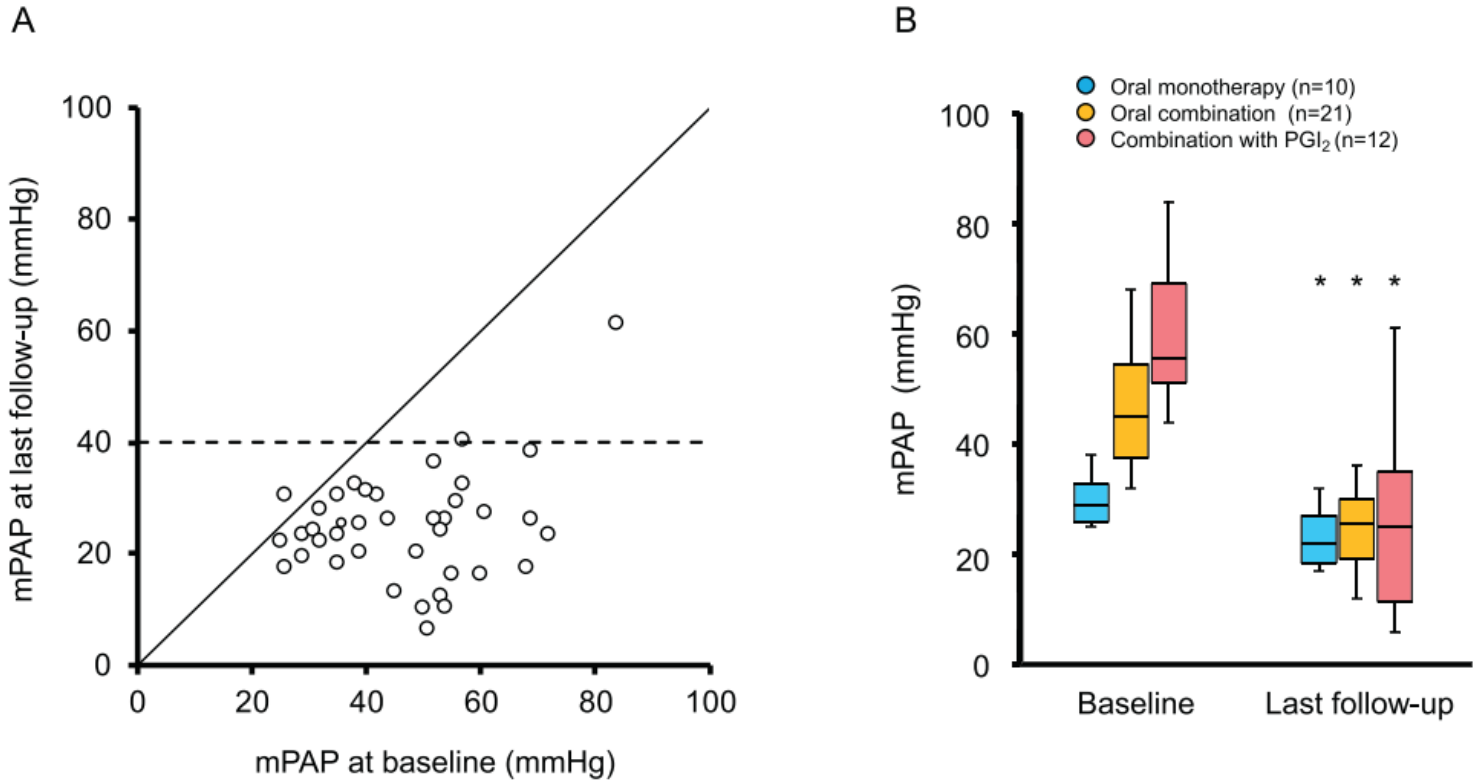




Badagliacca et al, 2022

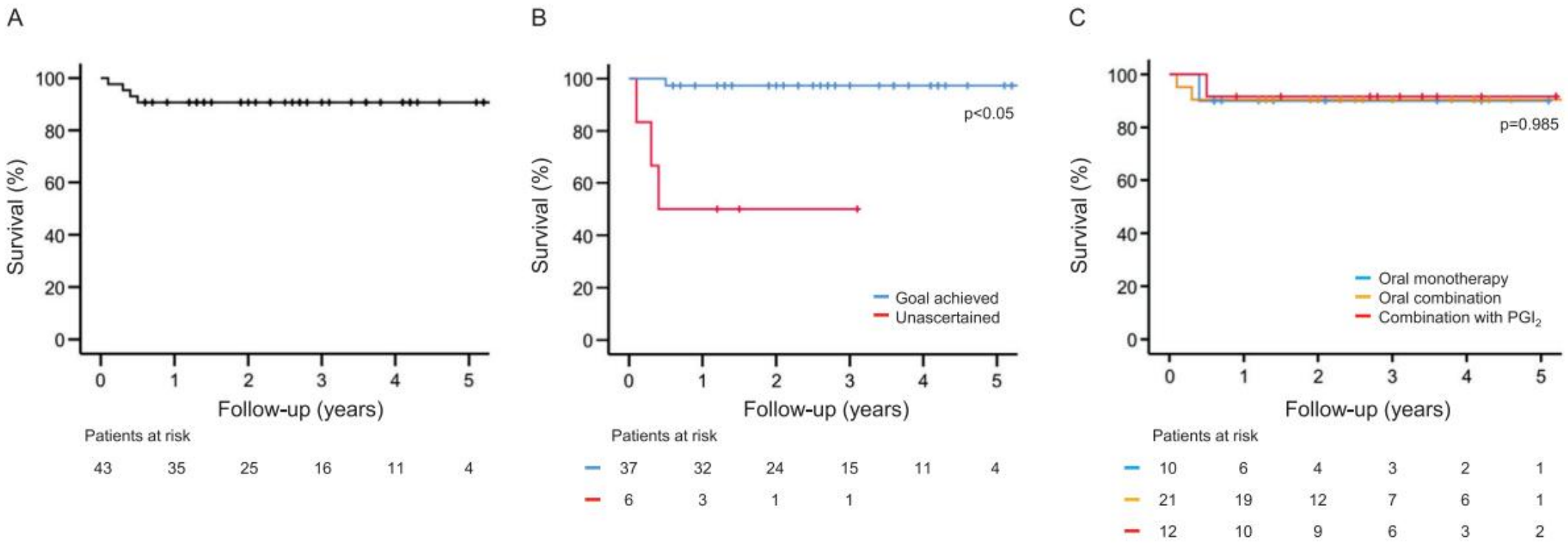
Outcome of mean pulmonary arterial pressure-based intensive treatment for patients with pulmonary arterial hypertension

N=43, konsekutivní pacienti 2014- 2019, terapeutický cíl mPAP < 40 mmHg



Sugiyama et al, 2022

Outcome of mean pulmonary arterial pressure-based intensive treatment for patients with pulmonary arterial hypertension

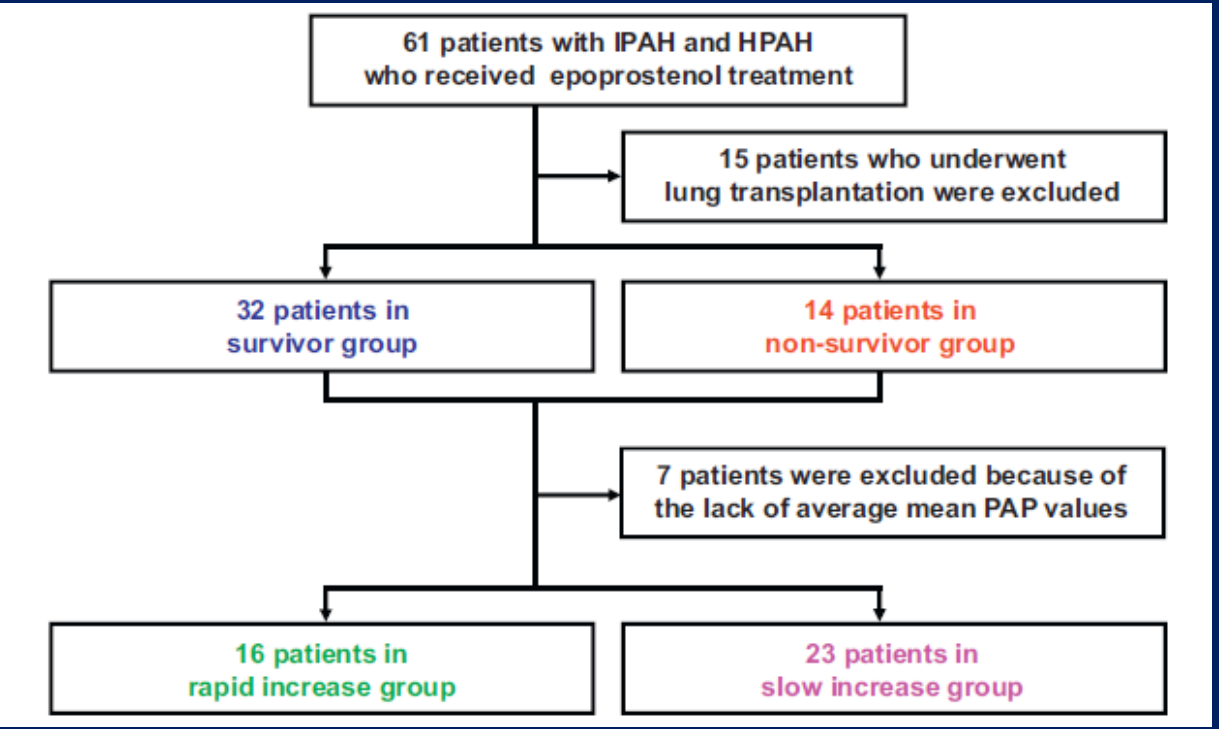


Sugiyama et al, 2022

Rapid and high-dose titration of epoprostenol improves pulmonary hemodynamics and clinical outcomes in patients with idiopathic and heritable pulmonary arterial hypertension

Naoto Tokunaga (MD)[a,b,c], Aiko Ogawa (MD, PhD)[b], Hiroshi Ito (MD, PhD, FJCC)[c], Hiromi Matsubara (MD, PhD)[a,b,*]

N=46, IPAH, HPAH, NYHA III + NYHA IV
rapid increase: ≥ 20 ng/kg/min at 3 months and ≥ 45 ng/kg/min at 1 year



Journal of Cardiology 68 (2016) 542–547

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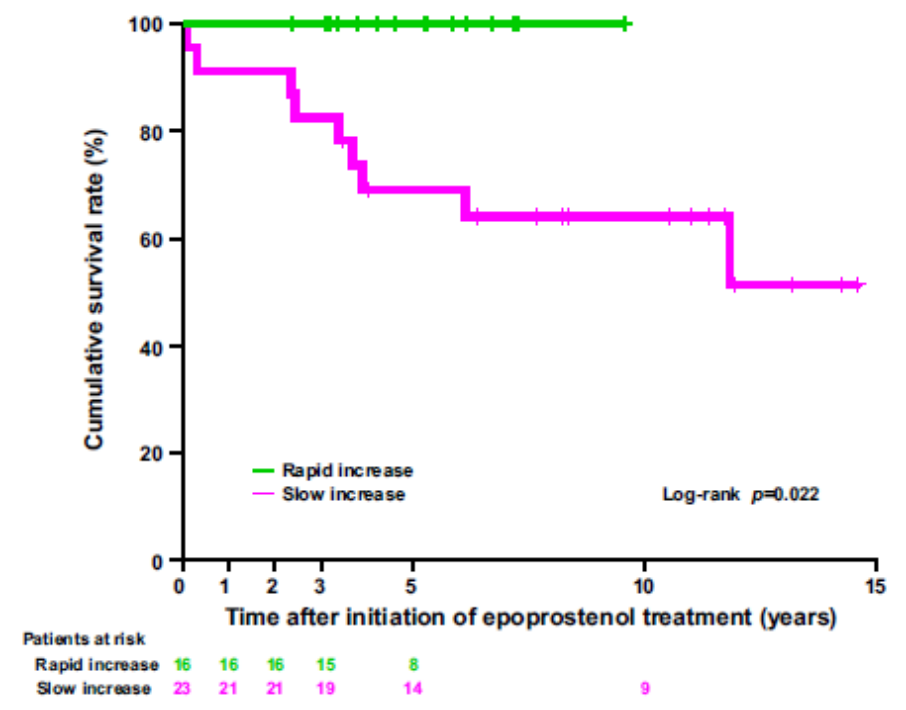

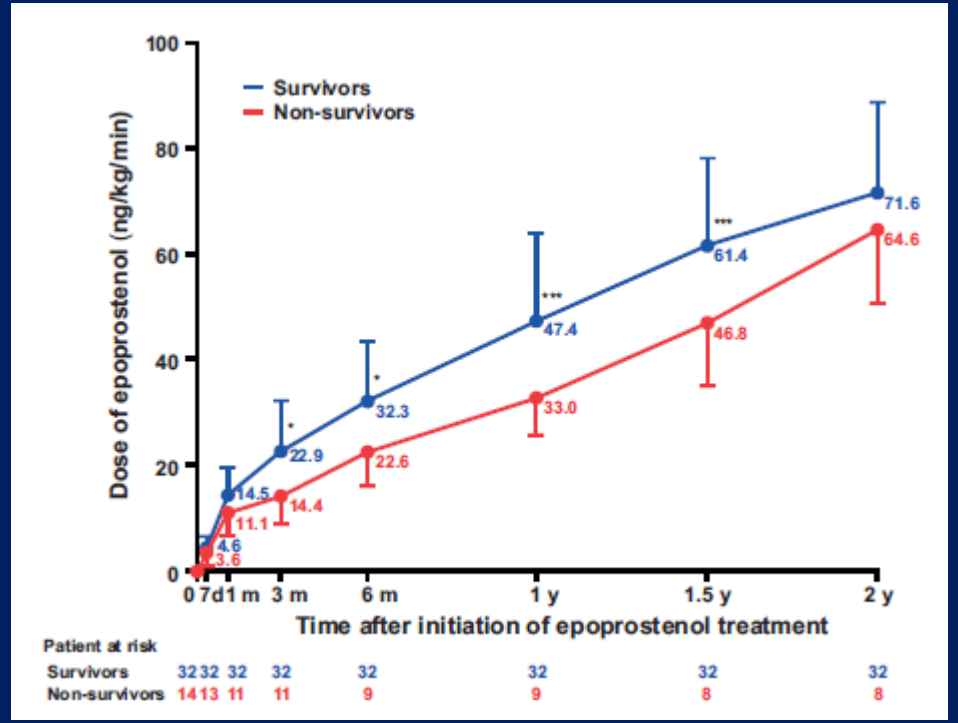

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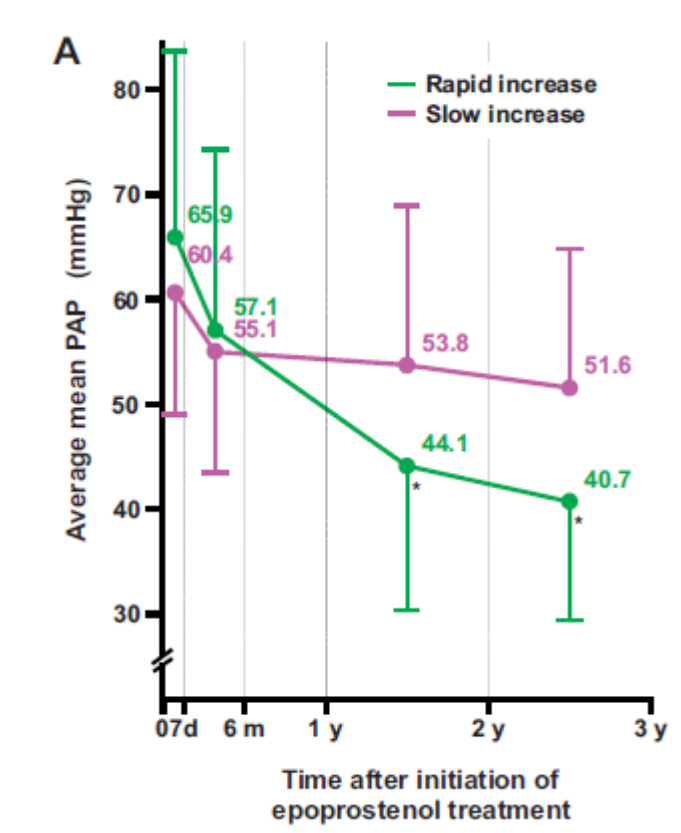
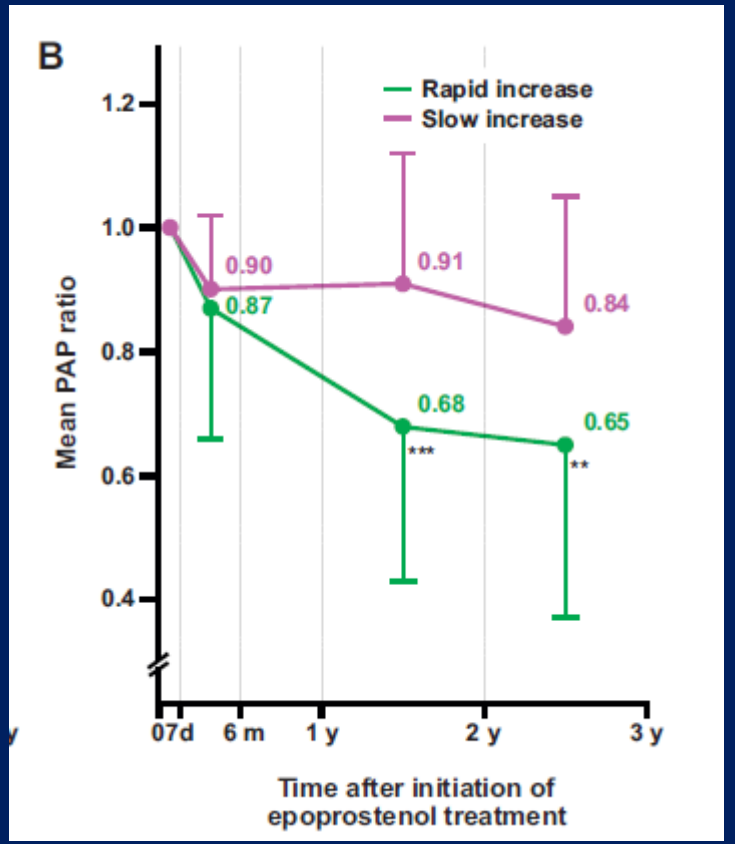
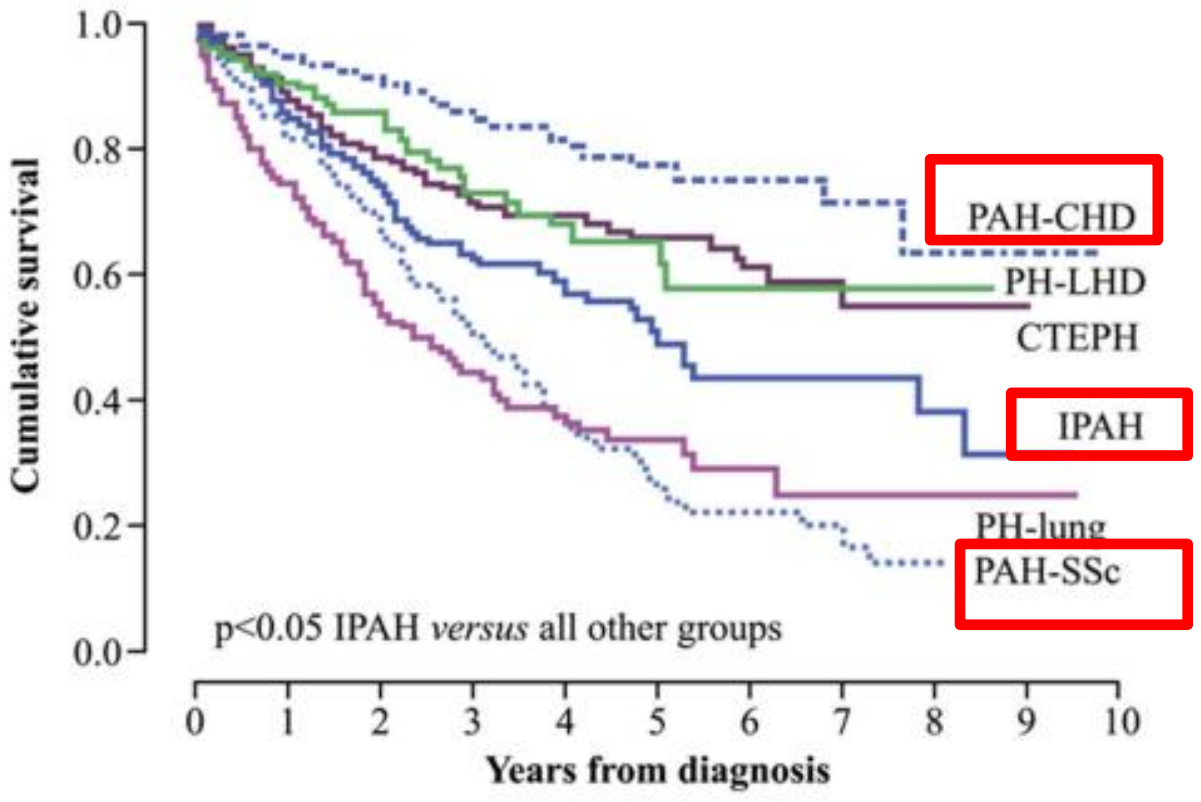




Journal of Cardiology 68 (2016) 542–547

Je redukce mPAP stejně účinná u všech forem PAH?

Adaptabilita pravé komory na zvýšený afterload



Condlife et al, 2020

Je redukce mPAP bezpečná a možná u všech typů PH ?

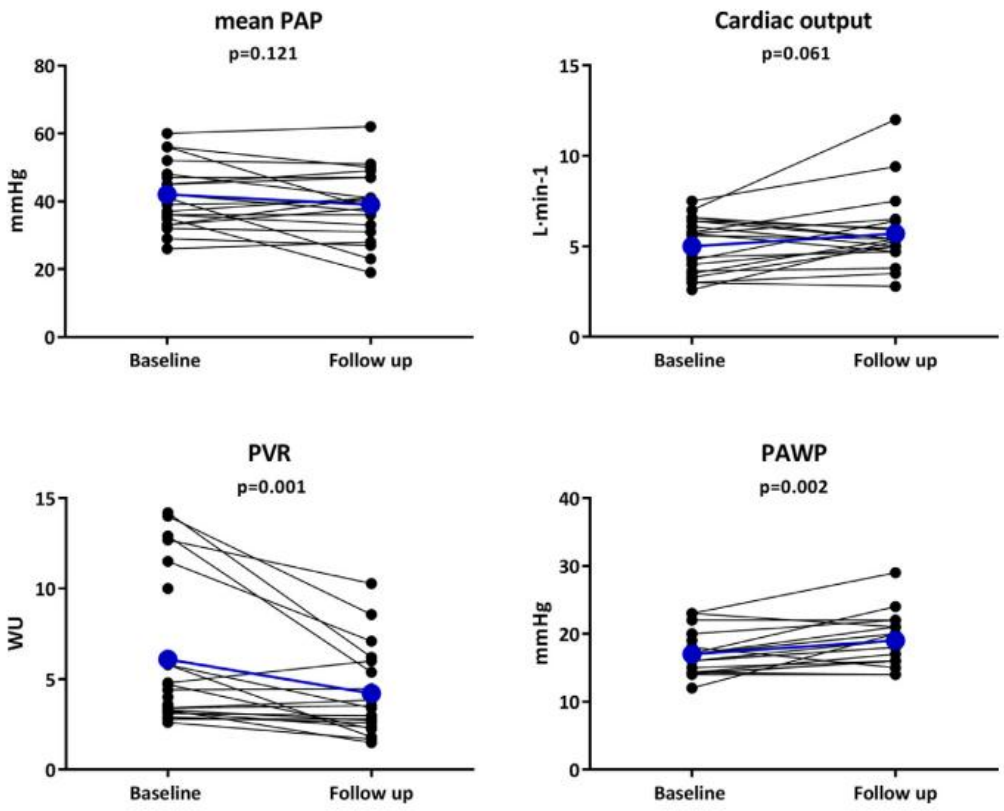
Epidemiology and treatment of pulmonary arterial hypertension

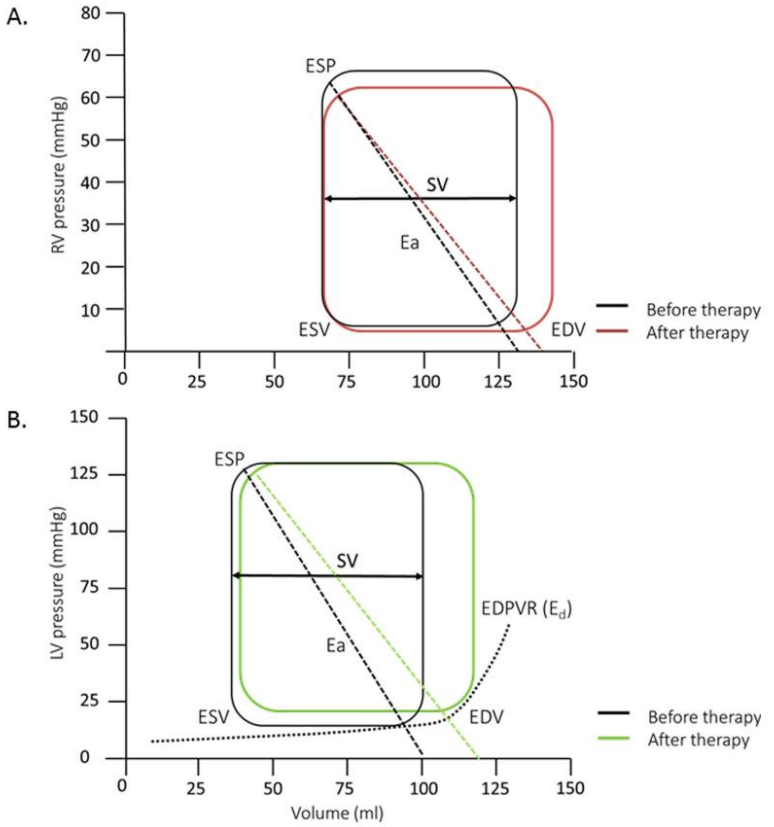
Průměrný věk pacientů s PAH se zvyšuje a s tím přibývají komorbidity

Registry	Time period	Mean age (years)	Women (%)	NYHA functional class III–IV (%)	6MWD (m)	Estimated survival at 1 year (%)	Estimated survival at 3 years (%)
NIH[12]	1981–1985	36 ± 15	63	75	NA	68	48
PHC[16]	1982–2004	46 ± 14	76	80	NA	91	75
Japanese[23]	1992–2012	33 ± 14	74	87	267 ± 154	98	92
Scottish[29]	2002–2009	49 ± 11	62	NA	NA	NA	NA
French[14]	2002–2003	52 ± 15	62	81	328 ± 112	83	58
UK and Ireland[10]	2001–2009	50 ± 17	70	84	292 ± 123	93	73
REVEAL[18]	2006–2009	53 ± 15	83	55	374 ± 129	91	74
COMPERA[22]	2007–2011	65 ± 15	60	91	293 ± 126	92	74
Spanish[19]	2007–2008	46 ± 18	73	70	382 ± 117	89	77
New Chinese[20]	2008–2011	33 ± 15	70	52	394 ± 114	92	75
Korean[24]	2008–2011	45 ± 16	73	63	398 ± 116	NA	NA

Lau et al, 2017

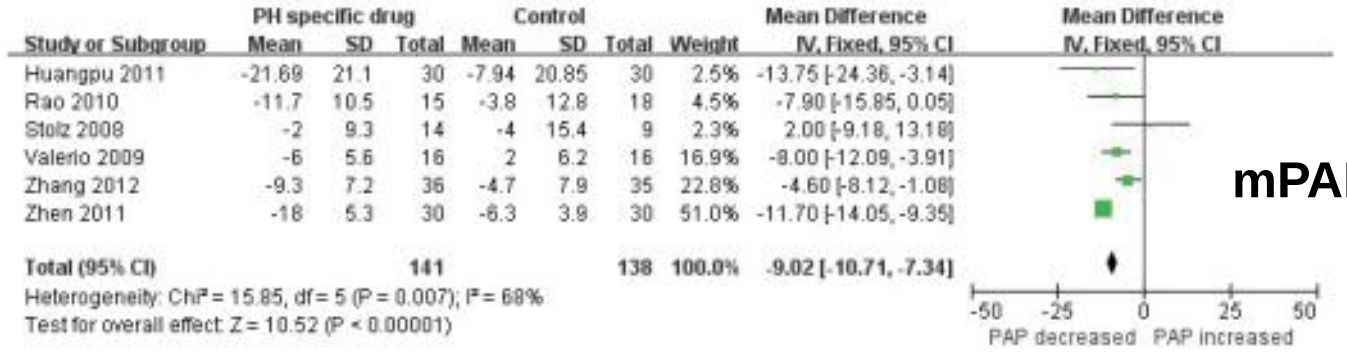
Hemodynamic Effects of Pulmonary Arterial Hypertension-Specific Therapy in Patients With Heart Failure With Preserved Ejection Fraction and With Combined Post- and Precapillay Pulmonary Hypertension



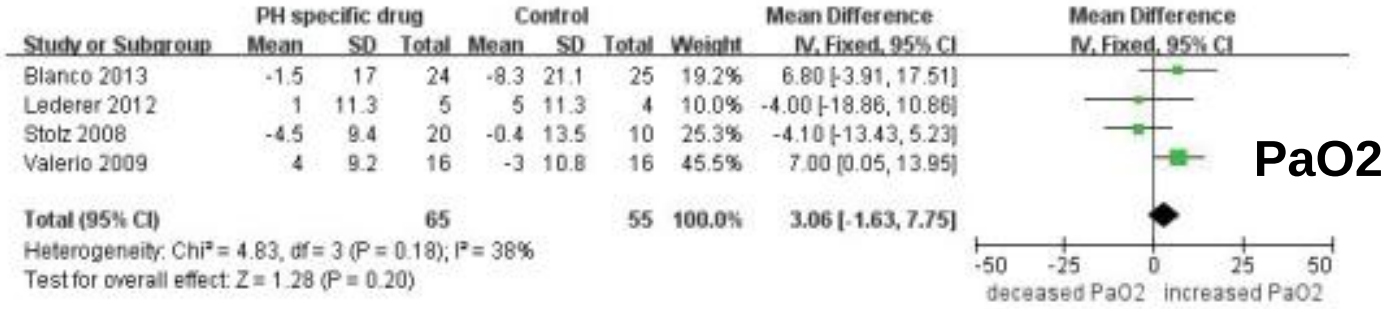


Veld et al, 2020

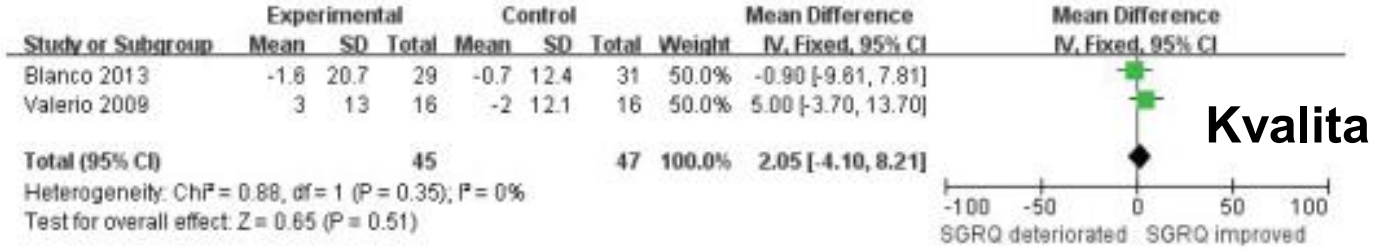
Therapy in stable chronic obstructive pulmonary disease patients with pulmonary hypertension: a systematic review and meta-analysis



mPAP



PaO2

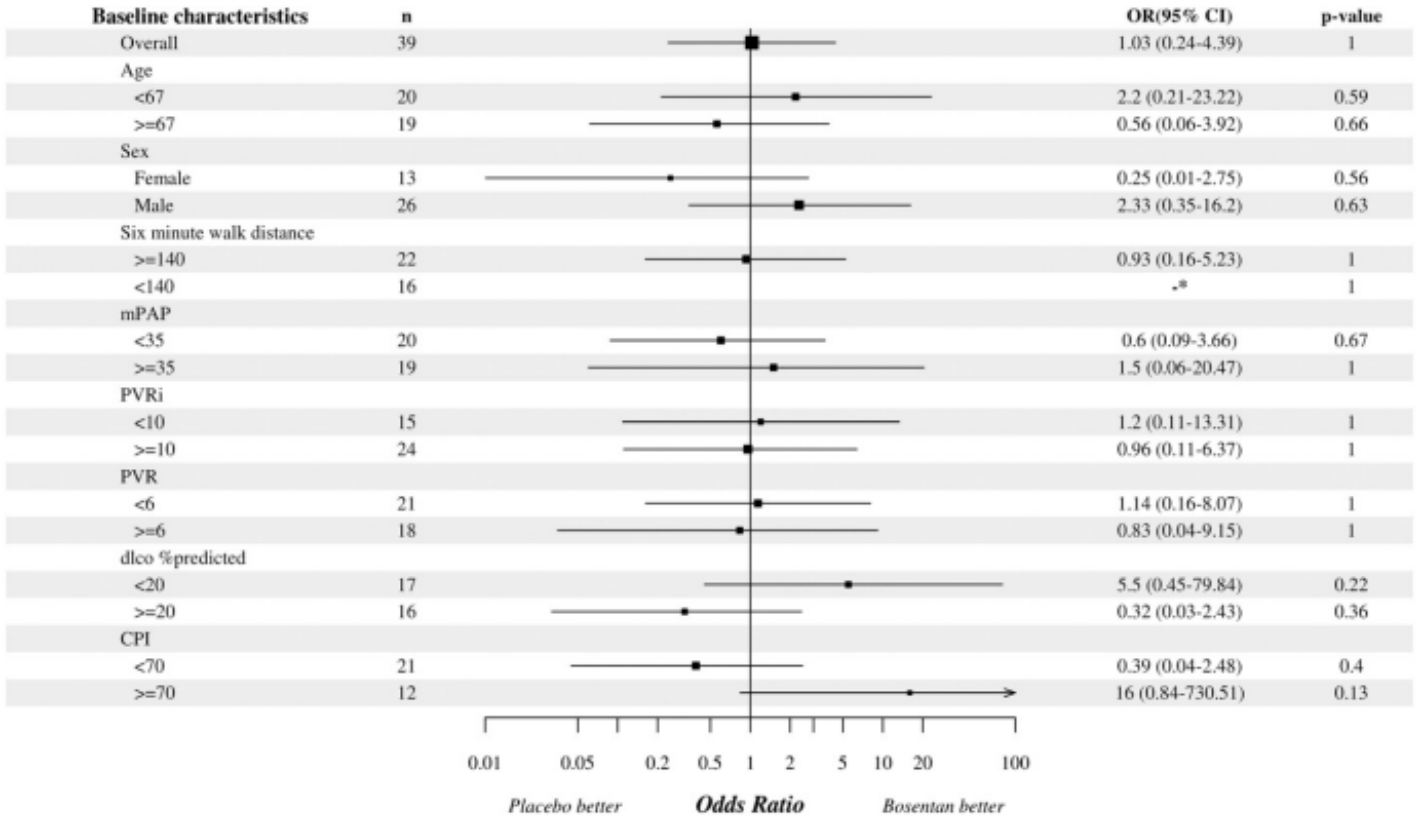


Kvalita života SGRQ u CHOPN

Chen et al, 2014

Bosentan in Pulmonary Hypertension Associated with Fibrotic Idiopathic Interstitial Pneumonia

	Bosentan (*n* = 40)	Placebo (*n* = 20)	*P* Value
Age	66.4 (9.2)	66.9 (9.3)	0.77
Male	27 (67.5%)	15 (75%)	NA
WHO FC II/III/IV	2/17/21	2/9/9	NA
6MWD, m	149.3 (99.6)	170.7 (97.0)	0.39
mPAP, mm Hg	37.2 (9.9)	33.5 (6.1)	0.30
mRAP, mm Hg	7.4 (5.4)	6.1 (5.4)	0.26
PVR, Wood units	7.4 (4.0)	6.0 (2.4)	0.33
PVR index, Wood Units/m^2	13.9 (7.5)	11.4 (4.5)	0.31
Cardiac index, L/min/m^2	2.2 (0.5)	2.2 (0.5)	0.68
D_{LCO}, % predicted	21.3 (9.6)	21.2 (7.5)	0.88
Kco, % predicted	45.1 (21.8)	48.8 (20.5)	0.43
FEV_1, % predicted	58.8 (20.8)	49.8 (19.8)	0.10
FVC%, % predicted	55.7 (19.8)	51.1 (24.0)	0.28
CPI	67.5 (8.6)	68.2 (7.9)	0.79



Corte et al, 2014

Závěr

- Hemodynamická parametry nejsou většinou primárním end-pointem klinických studií 3.fáze se specifickou léčbou u pacientů s PAH
- Efekt specifické léčby PAH na redukci mPAP a PVR lze zhodnostit jen PSK, což není možné při každé návštěvě pacienta
- Řada prací prokázala zejména u mladších pacientů s PAH, kteří nemají významné kardiopulmonální komorbidity signifikantně lepší krátkodobé a dlouhodobé přežívání při výraznější redukci mPAP a PVR
- U pacientů s vyšším mPAP je redukce možná zejmnéna při kombinační terapii včetně parenterálních prostanoidů
- Účinnost redukce mPAP a PVR je závislá na adaptibilitě pravé komory srdeční na zvýšený afterolad (PAH u SSc vs. PAH u vrozených srdečních chorob
- U starších pacientů a u pacientů s kardiopulmonálními komorbiditami pravděpodobně není výraznější redukce mPAP a PVR vždy bezpečná a účinná