REGISTROVANÁ a NEREGISTROVANÁ FARMAKOLOGICKÁ LÉČBA u CTEPH

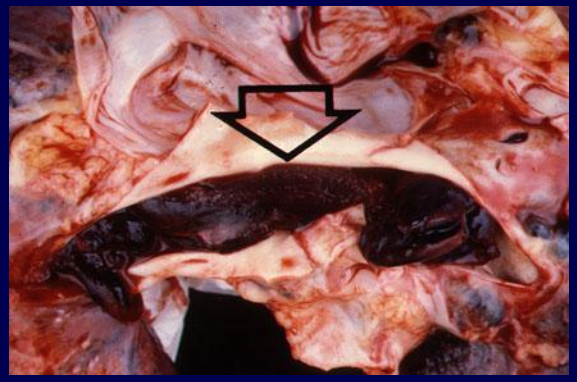
Michael Aschermann,
II. interní klinika 1. LF UK a VFN Praha

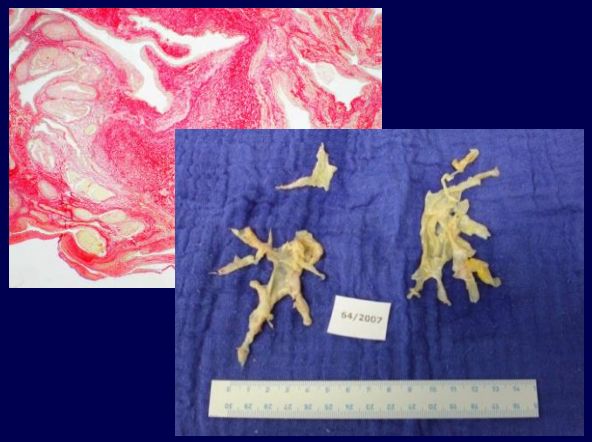
Charakteristika CTEPH

- chronické progresivní onemocnění
- neléčené má velmi špatnou prognózu

- léčba – endarterektomie AP
- až 40% inop. formy – farmaka, PBA

PATOGENETICKÉ MECHANISMY CTEPH





Akutní plicní embolie

↓

Nekompletní rezoluce trombů

↓

Obstrukce plicních cév

↓

Plicní hypertenze

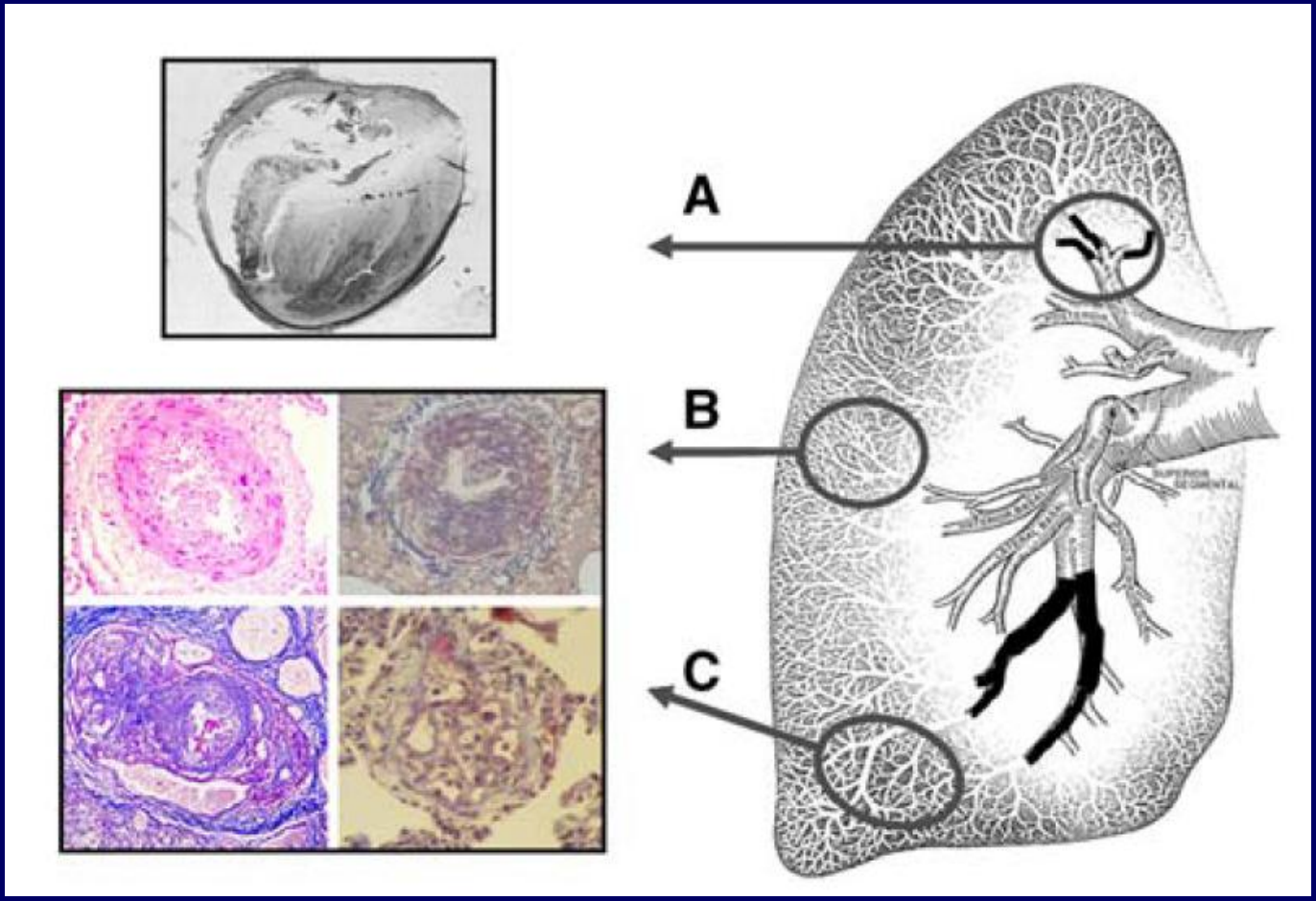
↓

Periferní arteriopatie

↓

Progrese plicní hypertenze

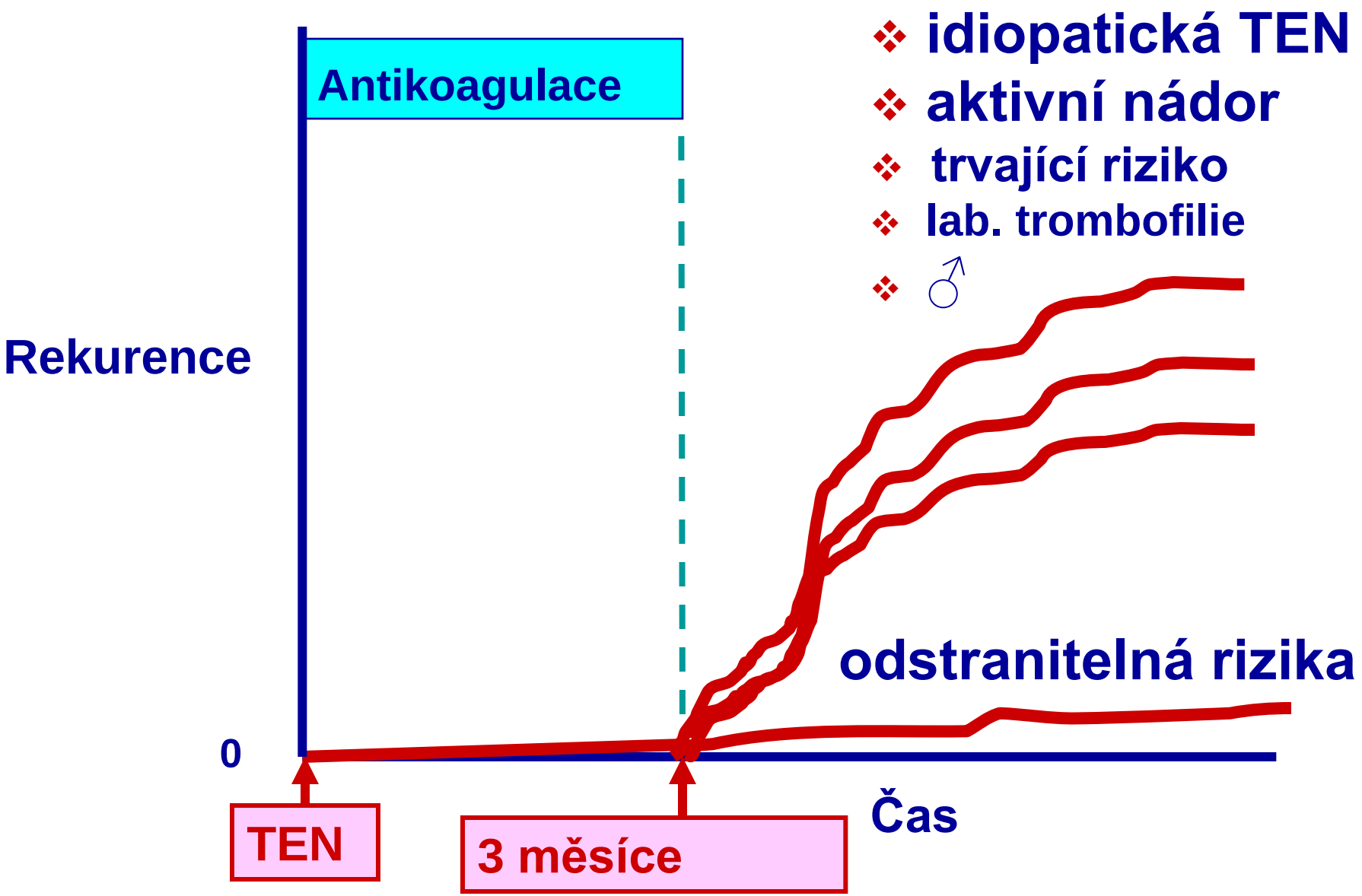
MIKROVASKULÁRNÍ POSTIŽENÍ U CTEPH



Galie, Kim: *Proc Am Thorac Soc*, 2006

KONVENČNÍ LÉČBA

DÉLKA ANTIKOAGULAČNÍ LÉČBY

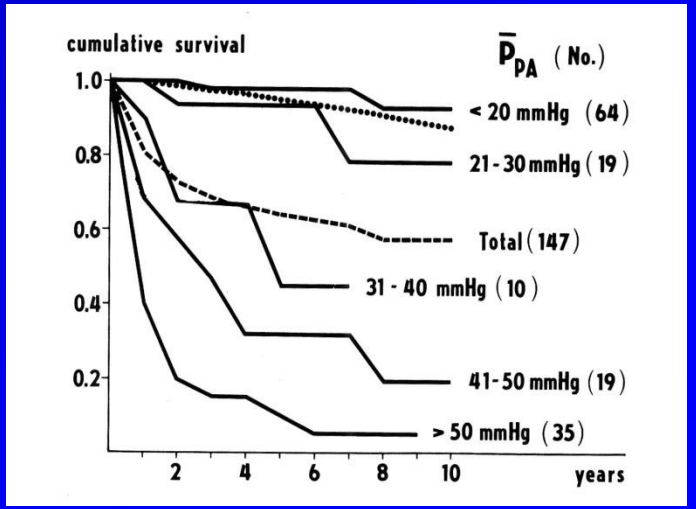


PROGNÓZA PŘI KONVENČNÍ LÉČBĚ

n=76
sledování 1-15 let
plicní hypertenze jediný indikátor prognózy

PAMP < 30 mmHg	90%
PAMP 31-40 mmHg	50%
PAMP 41-50 mmHg	35%
PAMP > 50 mmHg	10%

není souvislost s
- počtem epizod
- lokalizací
- věkem
- léčbou



Riedel M, Stanek V, Widimsky J, Prerovsky I, *Chest* 1982, 81: 151-8

SPECIFICKÁ LÉČBA

FARMAKOTERAPIE PAH

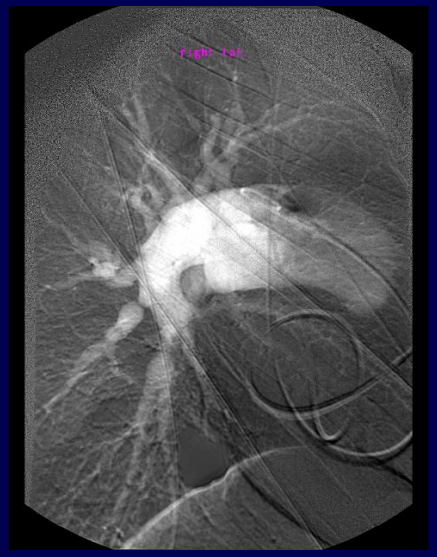
EPOPROSTENOL
TREPROSTINIL
ILOPROST
BERAPROST
VELETRI
SELEXIPAG

SILDENAFIL
TADALAFIL
RIOCIGUAT

BOSENTAN
AMBRISENTAN
MACITENTAN

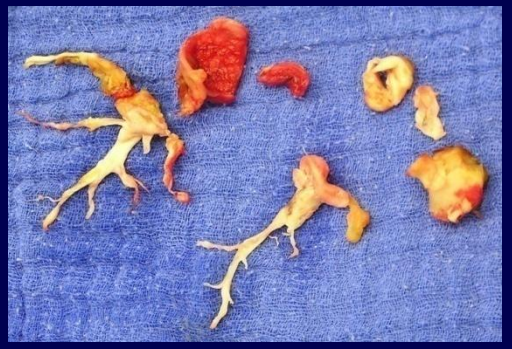
INHIBITORY TYROSIN KINÁZY
INHIBITORY SEROT. RECEPTORU
VASOAKT. INTESTINÁLNÍ PEPTID
ADRENOMEDULIN
SIGNÁLNÍ CESTA Rho kinázy

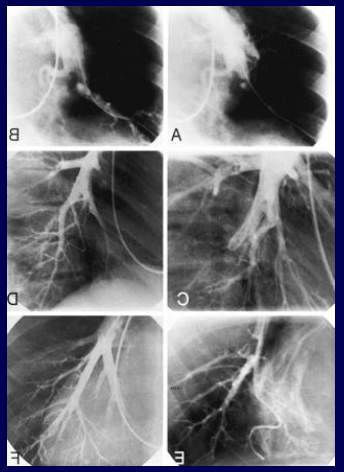
SPECIFICKÁ LÉČBA CTEPH

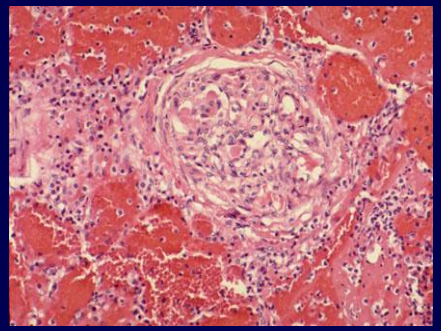


Endarterektomie

Angioplastika







Farmakoterapie

periferní léze

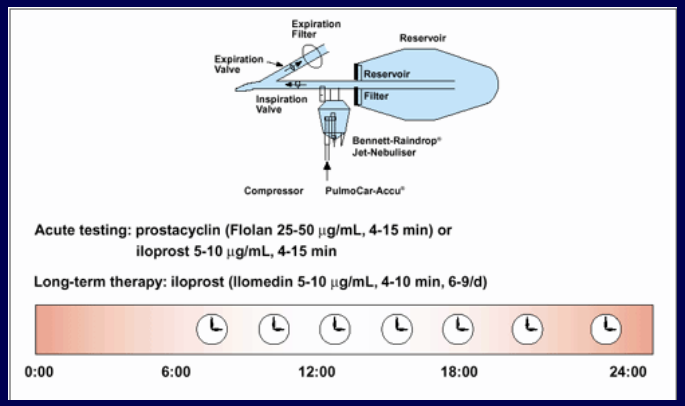
reziduální PH po PEA

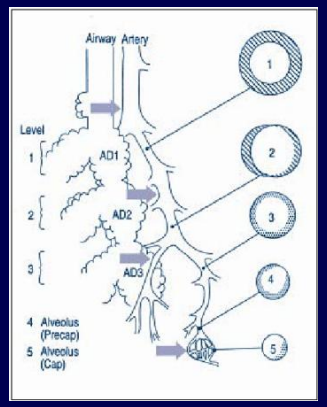
polymorbidní

příprava před PEA

SPECIFICKÁ LÉČBA NEREGISTROVANÝMI PŘÍPRAVKY

ILOPROST





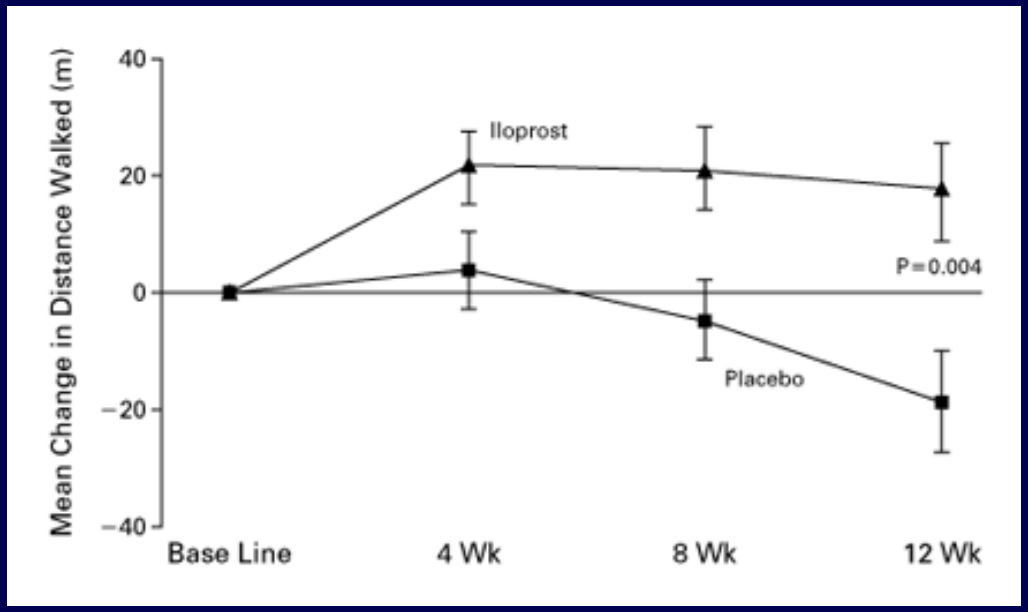


TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	ILOPROST GROUP (N=101)	PLACEBO GROUP (N=102)
Age — yr	51.2±13.2	52.8±12.0
Weight — kg	71.3±14.6	72.6±13.9
Sex — %		
Male	31.7	33.3
Female	68.3	66.7
Underlying disease — no. (%)		
Primary pulmonary hypertension	51 (50.5)	51 (50.0)
Nonprimary pulmonary hypertension	50 (49.5)	51 (50.0)
Appetite suppressants	4 (4.0)	5 (4.9)
Collagen vascular disease	13 (12.9)	22 (21.6)
Chronic thromboembolic pulmonary hypertension	33 (32.7)	24 (23.5)
Oral vasodilator therapy — no. (%)	52 (51.5)	58 (56.9)
NYHA functional class — no. (%)		
III	60 (59.4)	59 (57.8)
IV	41 (40.6)	43 (42.2)
Mahler Dyspnea Index†	4.14±1.8	4.27±1.8
6-Minute walk distance — m	332±93	315±96
Hemodynamic variables‡		
Pulmonary-artery pressure — mm Hg	52.8±11.5	53.8±14.1
Cardiac output — liters/min	3.8±1.1	3.8±0.9
Pulmonary vascular resistance — dyn·sec·cm^{-5}	1029±390	1041±493
Systemic vascular resistance — dyn·sec·cm^{-5}	1872±673	1827±503
Central venous pressure — mm Hg	9.2±5.3	8.2±5.0
Pulmonary-artery wedge pressure — mm Hg	7.5±3.3	7.6±3.9
Arterial oxygen saturation — %	92.6±4.4	92.2±5.0
Mixed venous oxygen saturation — %	60.4±7.5	60.5±8.2
Heart rate — beats/min	83.9±12.2	81.8±15.4

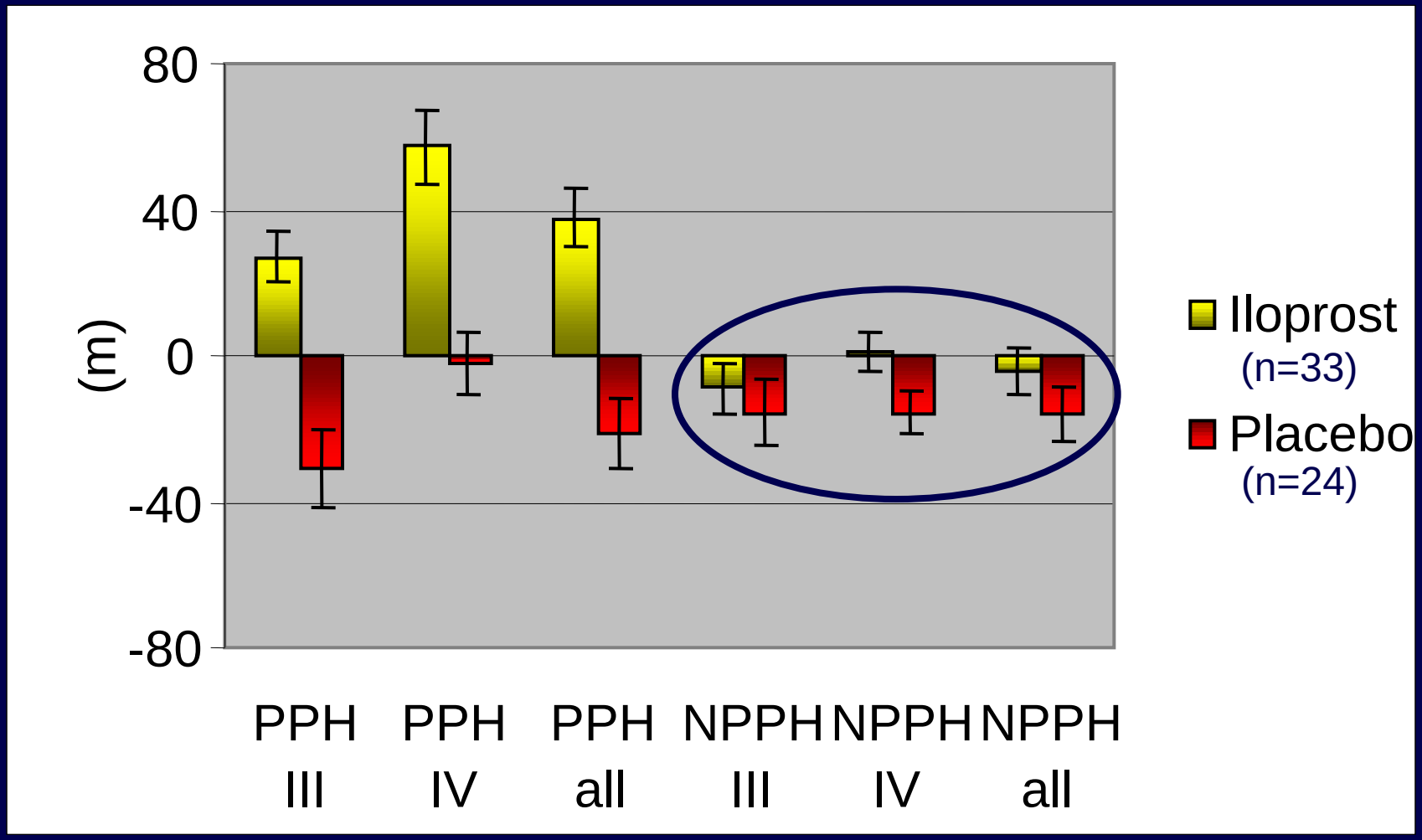
*Plus–minus values are means ±SD. NYHA denotes New York Heart Association. There were no significant differences between the iloprost and the placebo groups. Data on all variables were available for all patients except in the following categories: pulmonary-artery pressure, 1 patient in each group; cardiac output, 1 patient in the iloprost group and 6 in the placebo group; pulmonary vascular resistance, 10 and 6, respectively; systemic vascular resistance, 11 and 14; central venous pressure, 5 and 7; pulmonary-artery wedge pressure, 8 and 3; arterial oxygen saturation, 35 and 31; mixed venous oxygen saturation, 16 and 18; and heart rate, 2 and 3.

†On this 12-point scale, higher scores indicate less dyspnea.

‡Patients who were receiving long-term oxygen therapy received nasal oxygen during the measurement of base-line hemodynamic variables.

Olschewski H et al., *N Engl J Med* 2002, 347: 322-329

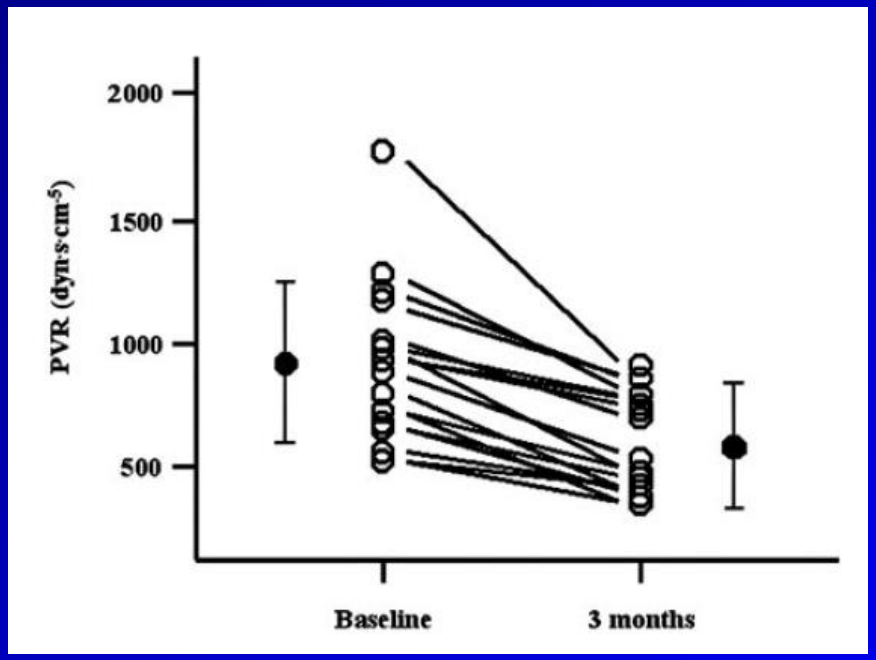
ILOPROST

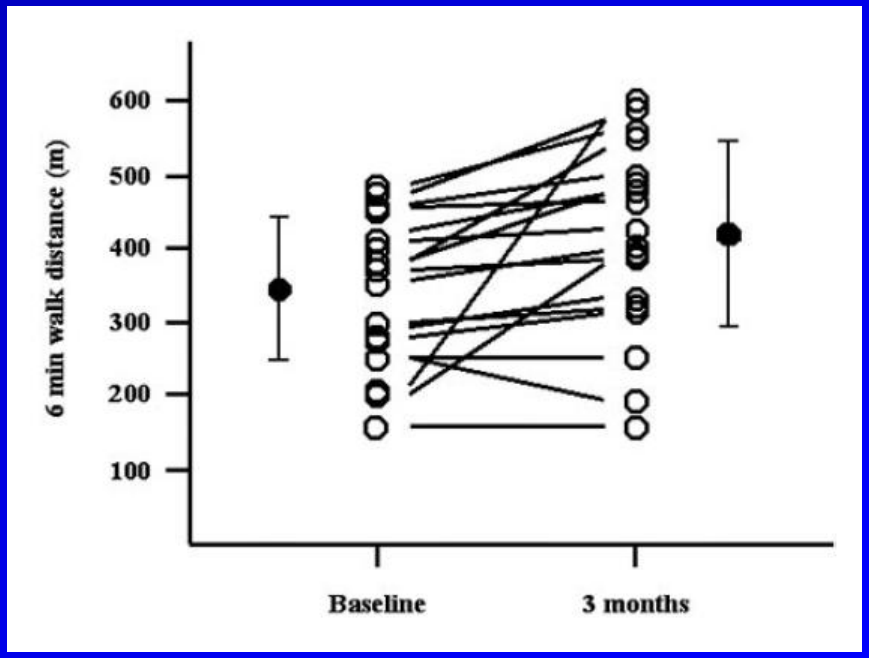


Olschewski H, *et al. N Engl J Med* 2002.

BOSENTAN

- Zlepšení NYHA, prodloužení 6MWD o 92 m, pokles BNP
- Bez výzmané hepatopatie
- RCT BENEFIT



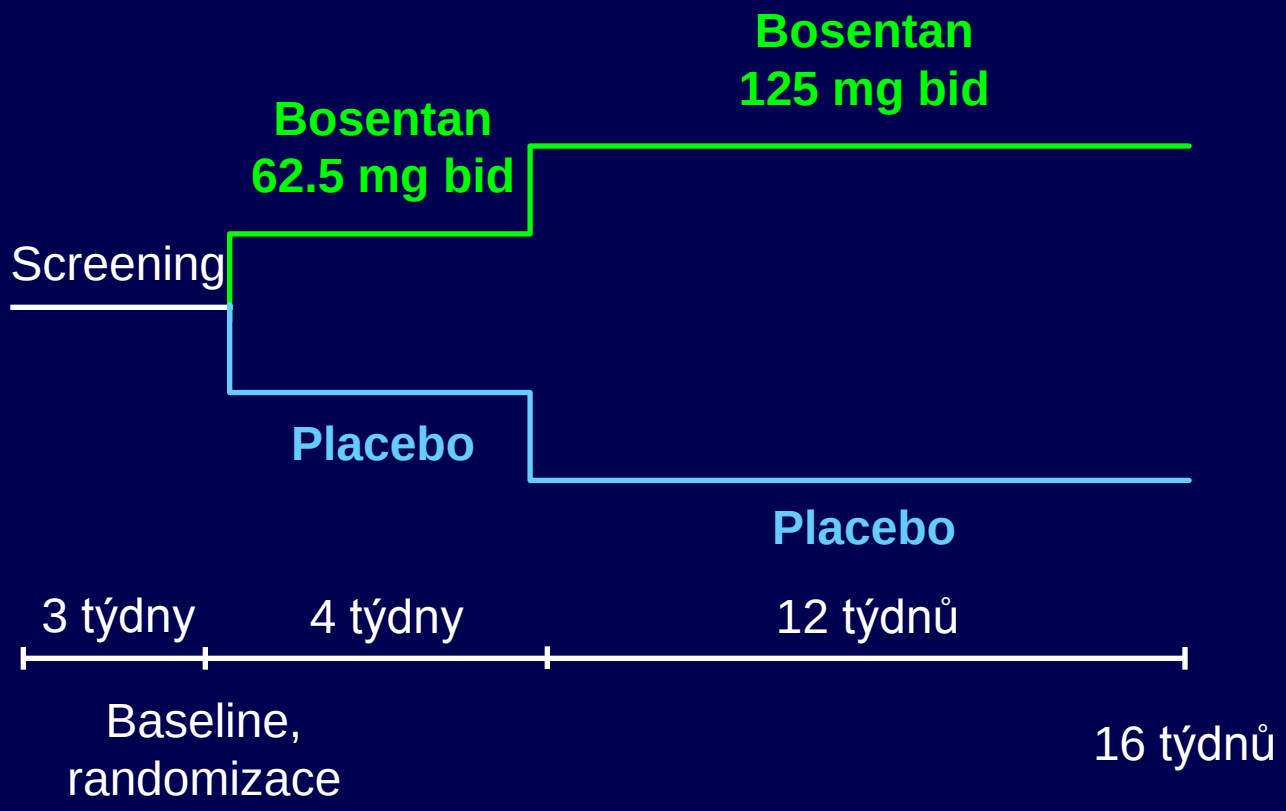


Hoeper, *Chest* 2005: 128: 502-508
Bonderman, *Chest* 2005: 128: 2599-2603

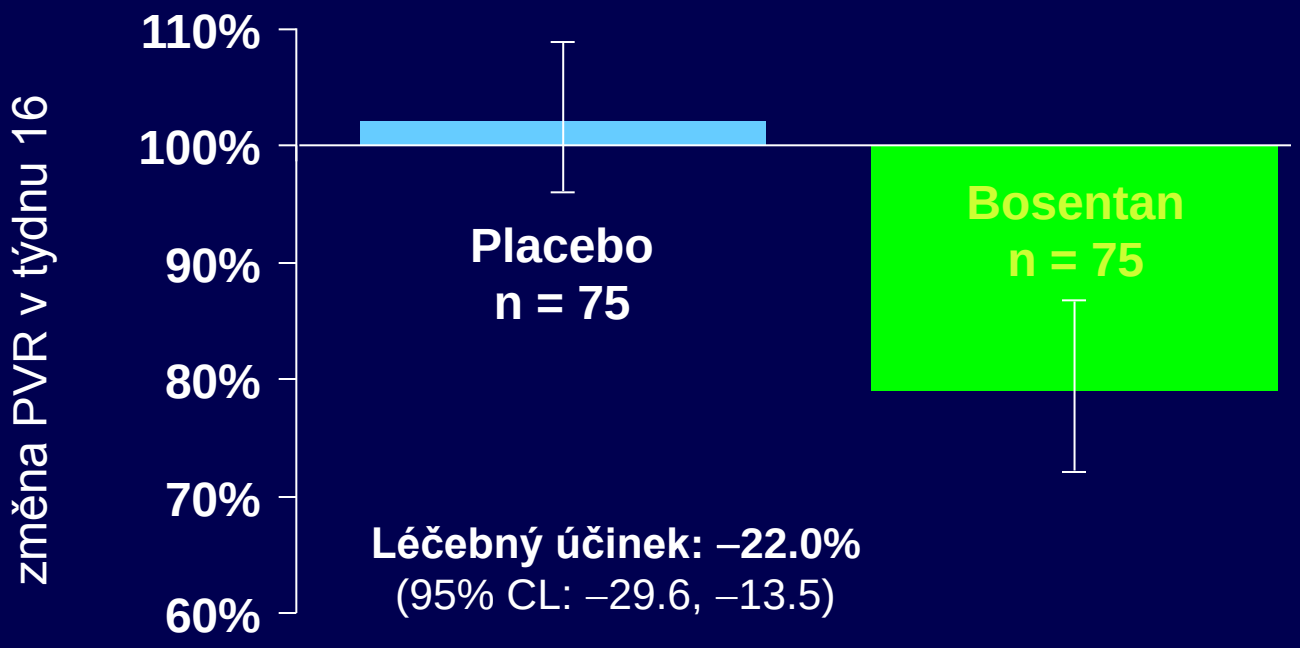
BENEFIT

Bosentan Effects in Inoperable Forms of Chronic Thromboembolic Pulmonary Hypertension

Prospektivní, dvojitě slepá, randomizovaná, placebem kontrolovaná multicentrická klinická studie



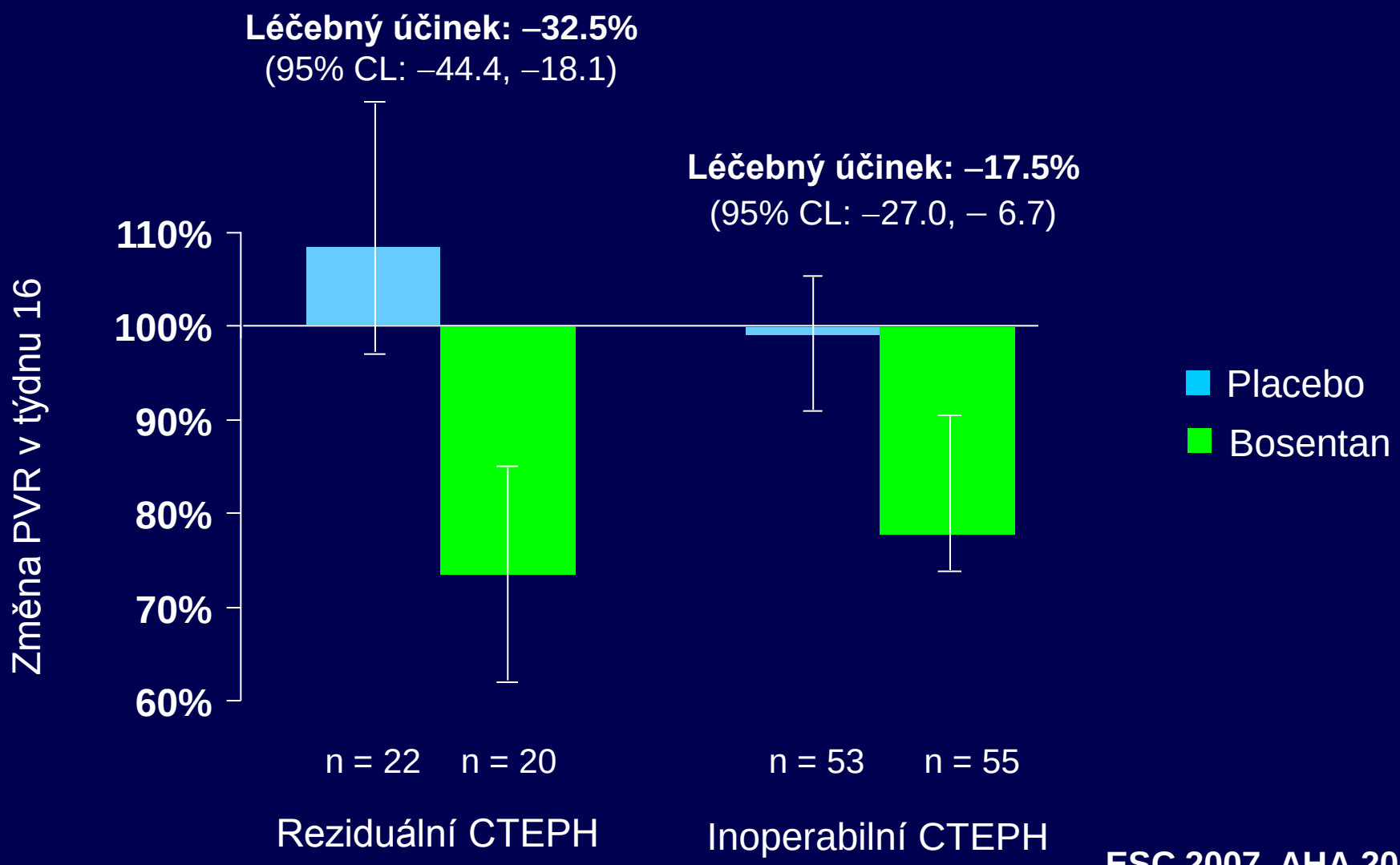
ZMĚNA PVR V LÉČENÉ POPULACI



p<0.0001; Wilcoxon test

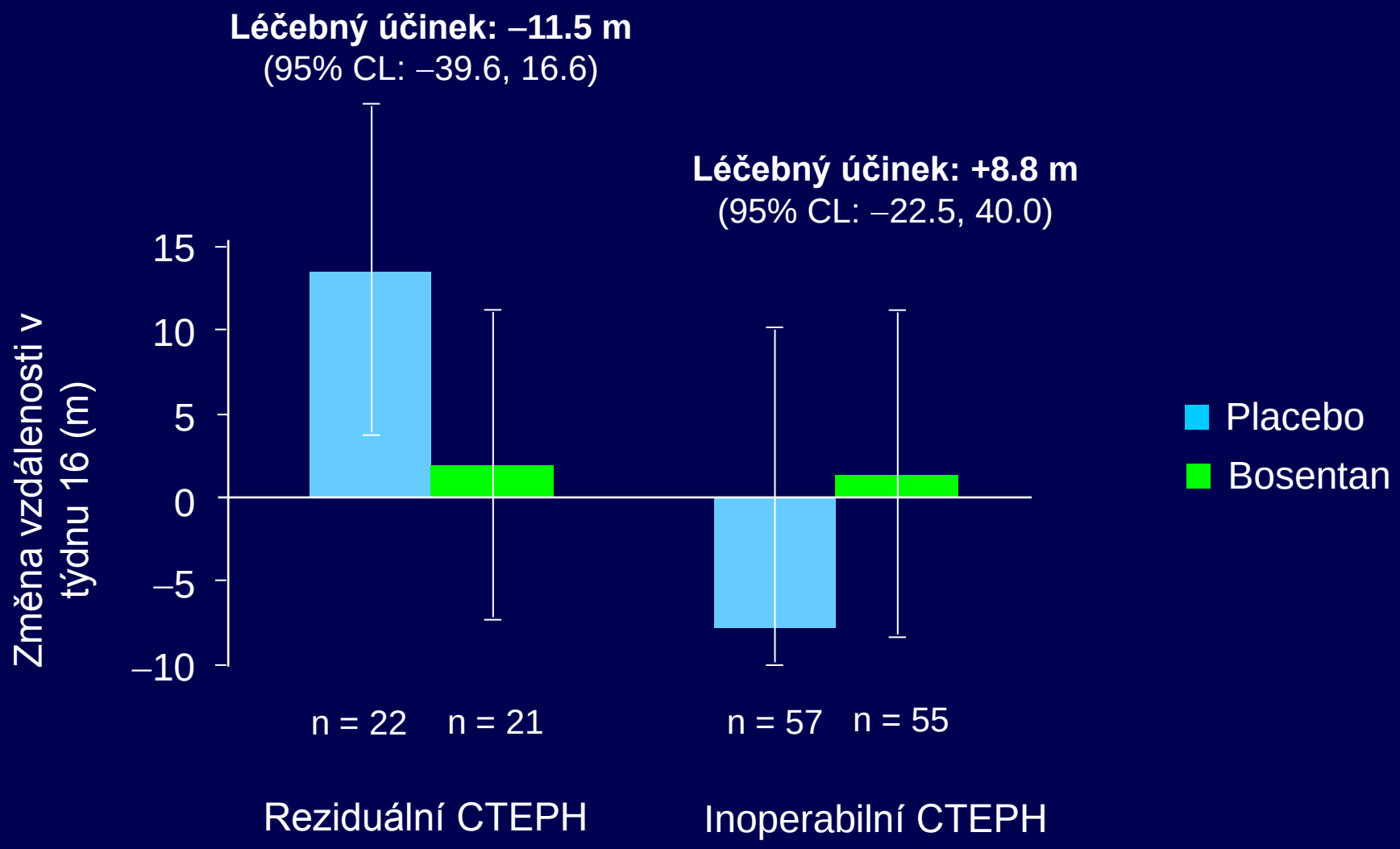
ESC 2007, AHA 2007

ZMĚNA PVR V PODSKUPINÁCH



ESC 2007, AHA 2007

ZMĚNA VZDÁLENOSTI PŘI 6MWT



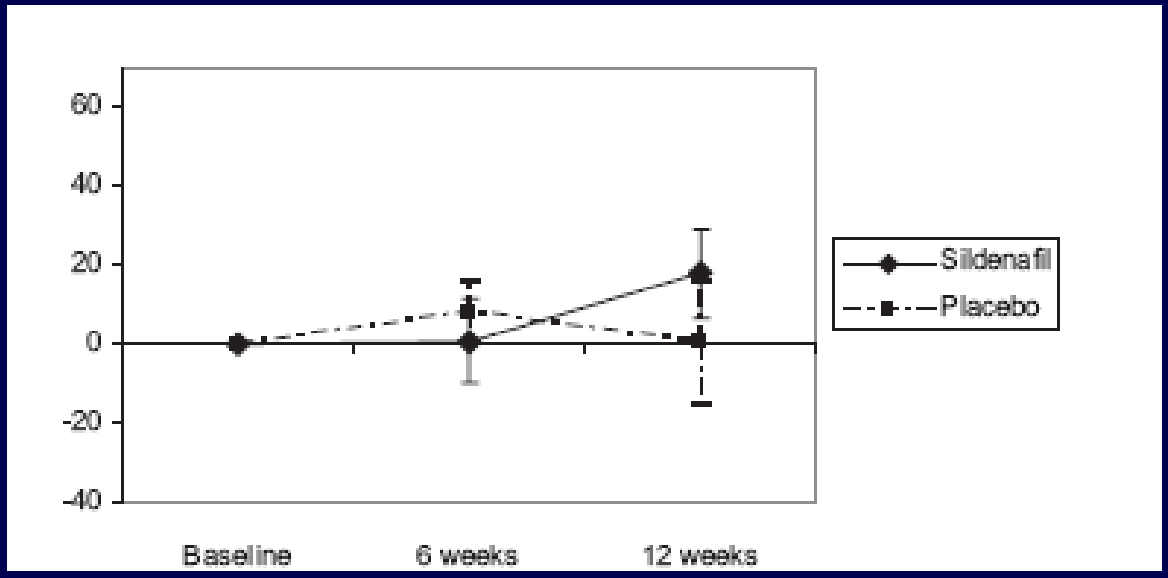
ESC 2007, AHA 2007

Long-term Use of Sildenafil in Inoperable Chronic Thromboembolic Pulmonary Hypertension*

Jay Suntharalingam, MRCP; Carmen M. Treacy, BSc; Natalie J. Doughty, RN; Kimberley Goldsmith, MD; Elaine Soon, MRCP; Mark R. Toshner, MRCP; Karen K. Sheares, MRCP; Rodney Hughes, MRCP; Nicholas W. Morrell, FRCP; and Joanna Pepke-Zaba, FRCP

N=19, inoperabilní CTEPH, 12 týdnů

silde 40 mg 3x denně vs. placebo



Chest 2008

Chronic Thromboembolic Pulmonary Hypertension (CTEPH)

Results From an International Prospective Registry

Joanna Pepke-Zaba, MD; Marion Delcroix, MD; Irene Lang, MD; Eckhard Mayer, MD; Pavel Jansa, MD; David Ambroz, MD; Carmen Treacy, BSc; Andrea M. D'Armini, MD; Marco Morsolini, MD; Repke Snijder, MD; Paul Bresser, MD; Adam Torbicki, MD; Bent Kristensen, MD; Jerzy Lewczuk, MD; Iveta Simkova, MD; Joan A. Barberà, MD; Marc de Perrot, MD; Marius M. Hoeper, MD; Sean Gaine, MD; Rudolf Speich, MD; Miguel A. Gomez-Sanchez, MD; Gabor Kovacs, MD; Abdul Monem Hamid, MD; Xavier Jaïs, MD; Gérald Simonneau, MD

N=679, nově diagnostikovaní pro CTEPH (2007-2009)

16 evropských zemí + Kanada

62.9 % operabilní, 56.8 % operováno

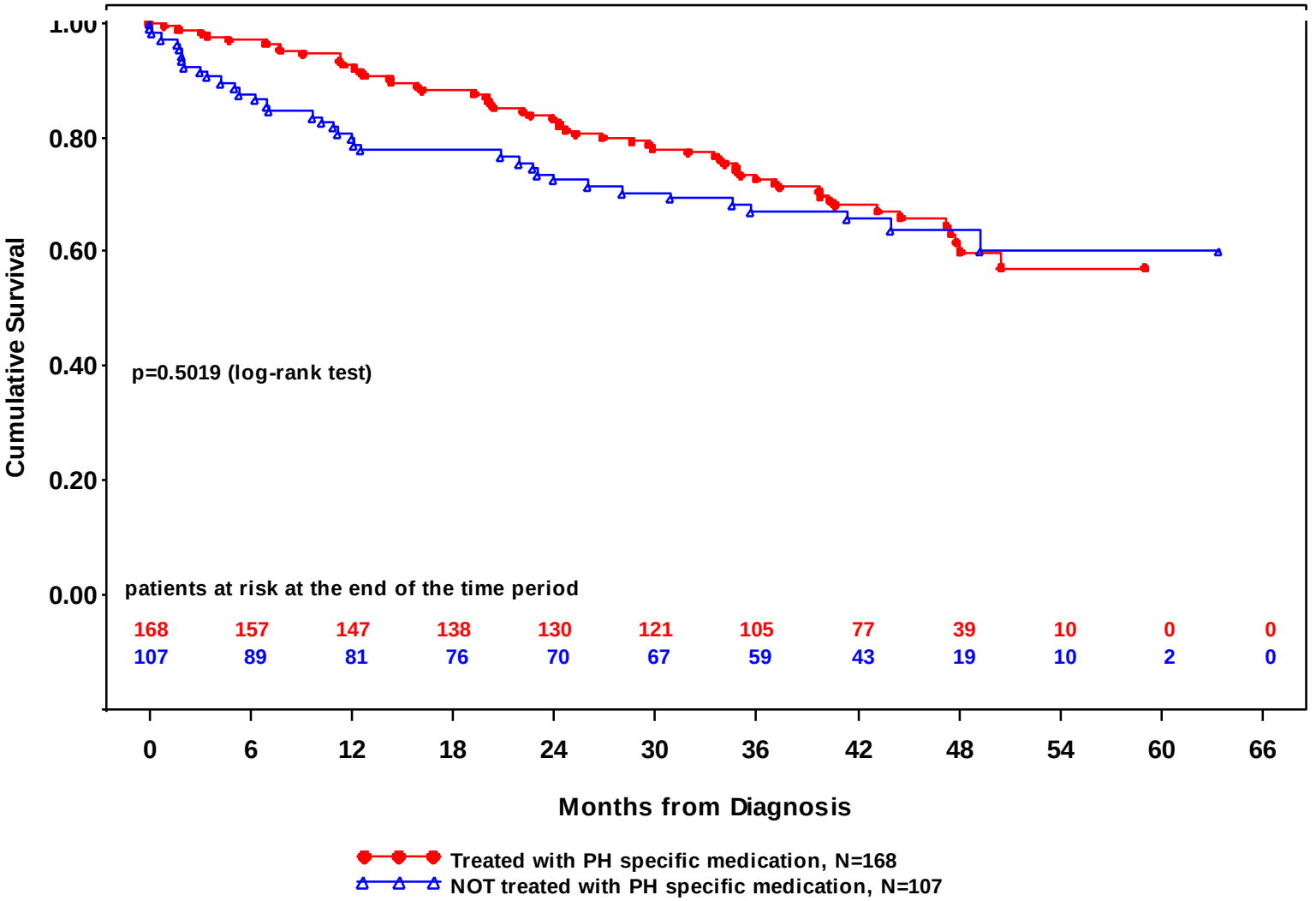
	All Patients (n=679)	Operable Patients* (n=427)	Nonoperable Patients* (n=247)	*P* (Exploratory)
PAH-targeted therapy, % (n)	37.9 (676)	28.3 (427)	53.8 (247)	<0.0001
Phosphodiesterase type V inhibitor, %	17.5	16.2	19.4	0.2923
Endothelin receptor antagonist, %	21.7	12.2	37.7	<0.0001
Prostacyclin analogue, %	2.7	1.6	4.5	0.0443
Combination therapies, %	4.0	1.6	7.7	0.0002

P values from Fisher exact test. (n): patients with assessment. PAH indicates pulmonary arterial hypertension.
*Five patients had no data on operability.

Circulation 2011, 124 (Nov)

INTERNATIONAL EUROPEAN CTEPH REGISTRY

INOPERABILNÍ, FARMAKOLOGICKY LÉČENÍ VS NELÉČENÍ



Simonneau et al, *ATS 2013*

S.C. TREPROSTINIL

- otevřená studie
- N=25, těžká CTEPH, distální léze
- sledování 19 ± 6.3 měs.
- zlepšení
  - 6MWT
  - BNP
  - hemodynamika

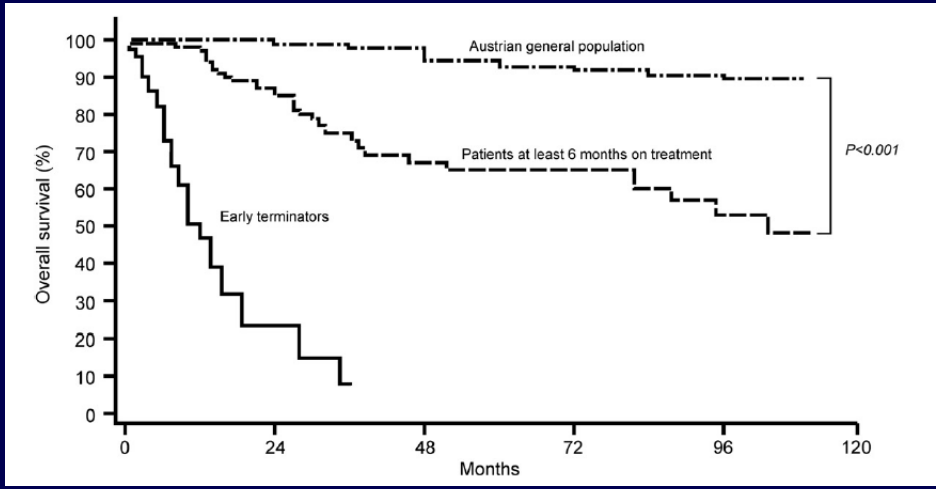
Variable (n = 19)	Change from baseline	P-value
SPAP (mmHg)	−7.8 ± 17	n.s.
DPAP (mmHg)	−0.8 ± 10.2	n.s.
MPAP (mmHg)	−3.5 ± 9.2	n.s.
MRAP (mmHg)	−1.7 ± 3.4	n.s.
CO (L min^{-1})	0.7 ± 1.2	0.007
CI (L min^{-1} m^{-2})	0.3 ± 0.5	0.02
S_vO_2 (%)	3.7 ± 9.1	n.s.
PVR (dynes s cm^{-5})	−116 ± 325	0.01
RVEDP (mmHg)	−3.5 ± 6.6	0.01
HR (beats per min)	−1 ± 0.3	n.s.
SBP (mmHg)	−8.2 ± 3.9	0.03
DBP (mmHg)	−3.5 ± 2.4	0.03

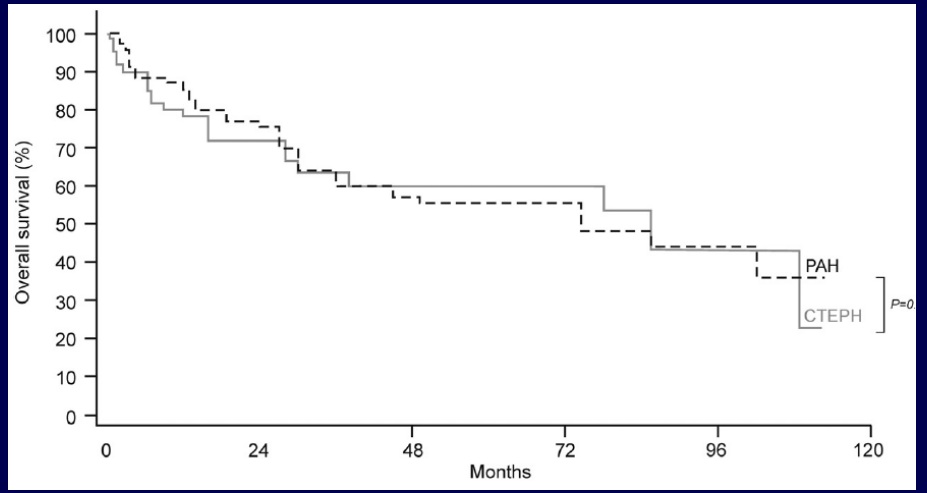
Skoro-Sajer N, *et al. J Thromb Haemost* 2007; 5:483-9.

Long-term treatment, tolerability, and survival with sub-cutaneous treprostinil for severe pulmonary hypertension

Roela Sadushi-Koliçi, MD,[a] Nika Skoro-Sajer, MD,[a] Daniel Zimmer, MD,[a] Diana Bonderman, MD,[a] Michael Schemper, PhD,[b] Walter Klepetko, MD,[c] Jutta Glatz, MSc,[d] Johannes Jakowitsch, PhD,[a] and Irene Lang, MD[a]

111 pacientů s PAH a CTEPH (1999-2010), NYHA III+IV
12 % ukončilo léčbu, 9.9 % Tx, 44.1 % zemřelo





J Heart Lung Transplant 2012

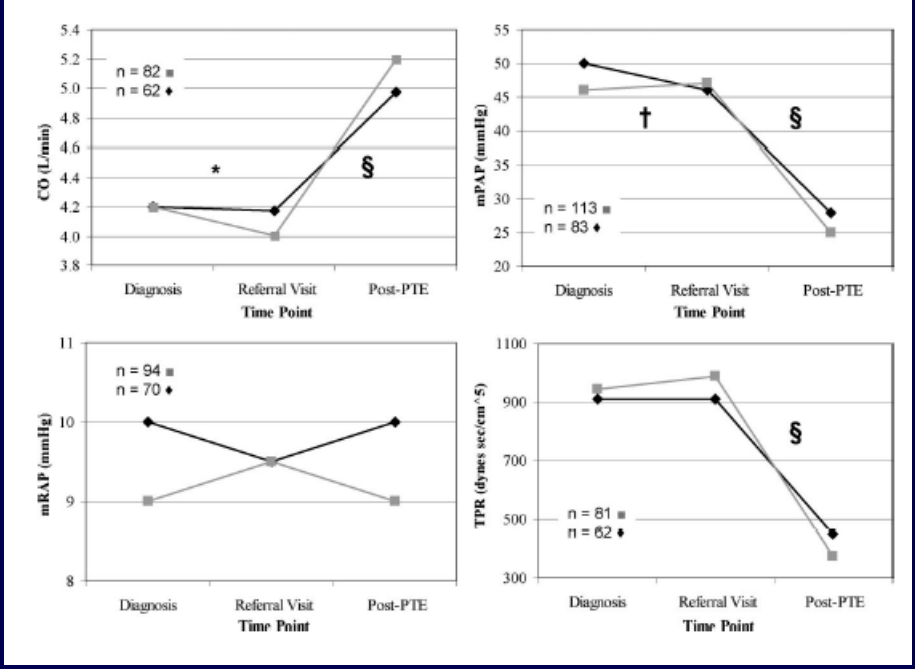
Pulmonary Hypertensive Medical Therapy in Chronic Thromboembolic Pulmonary Hypertension Before Pulmonary Thromboendarterectomy

Kurt W. Jensen, MD; Kim M. Kerr, MD; Peter F. Fedullo, MD; Nick Hyong Kim, MD; Victor J. Test, MD; Ori Ben-Yehuda, MD; William R. Auger, MD

Retrospective analysis, 2005–2007

Medical therapy n=111 (19.9% in 2005…37% in 2007)

Control group n=244



Circulation 2009;120:1248–54

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Retrospective analysis, 2005-2007

Medical therapy n=111 (19.9% in 2005…37 % in 2007)

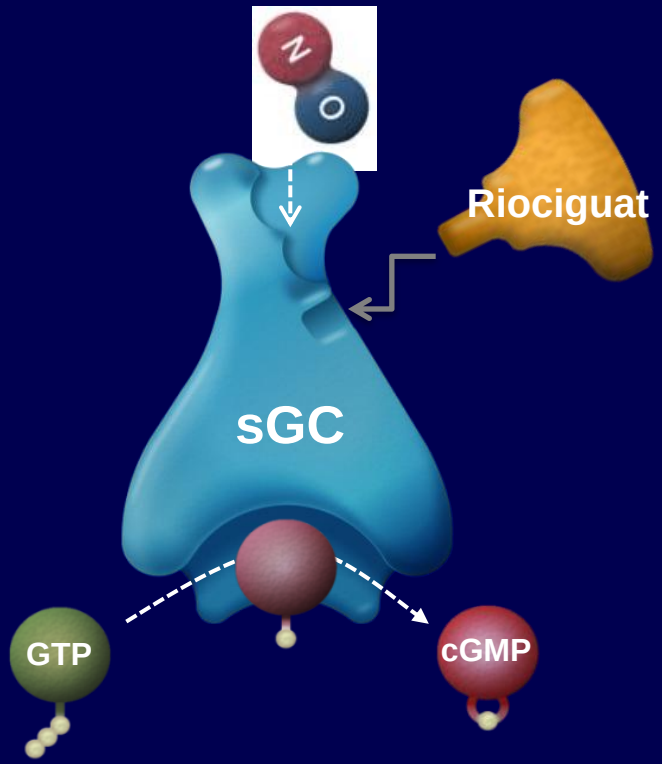
Control group n=244

	PHT Group (n=111)	Control Group (n=244)	*P*
Median age, y (IQR)	51 (39–62.5)	52 (37–64)	0.84
Sex, M/F	52/59	121/123	0.63
Median time to referral, mo (IQR)	8.9 (4–13)	4.4 (2.5–7)	<0.01
Anticoagulation	110 (99.1)	240 (98.4)	0.89
Diuretic	65 (58.6)	114 (46.7)	0.04
Spironolactone	24 (21.6)	18 (7.4)	<0.01
Digoxin	16 (14.4)	15 (6.1)	0.01
Dopamine	3 (2.7)	2 (0.8)	0.16

Values are n (%) unless otherwise indicated.

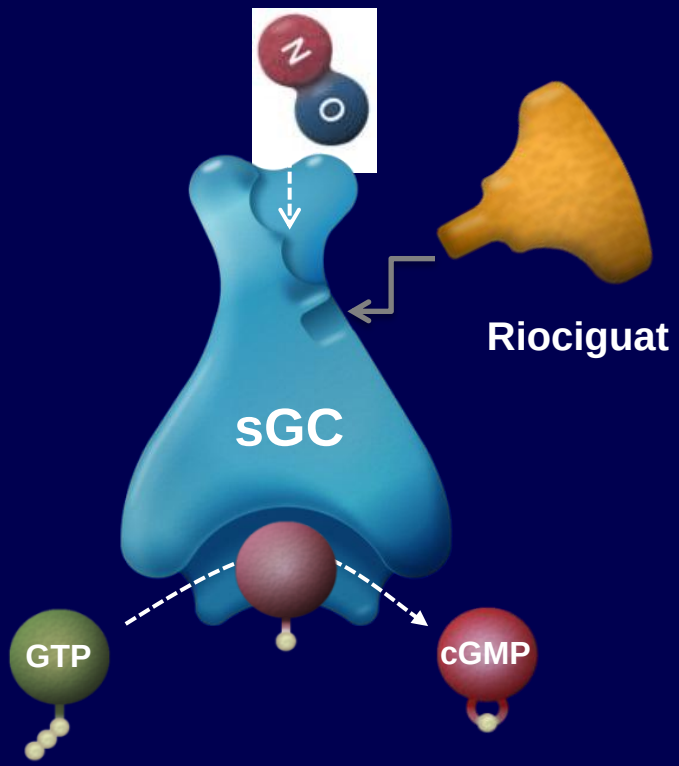
Circulation 2009, 120: 1248-54

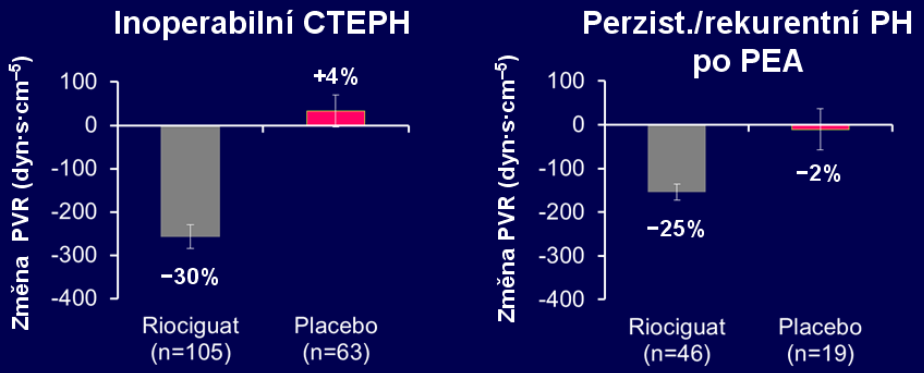
SPECIFICKÁ LÉČBA RIOCIGUATEM

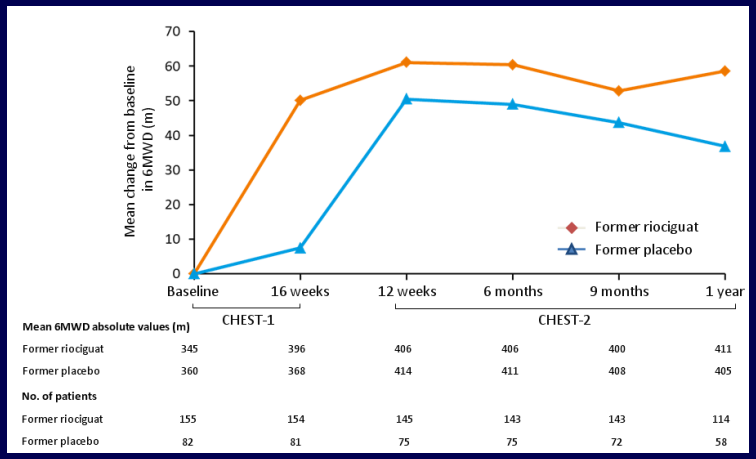

N
O
Riociguat
sGC
GTP
cGMP

Riociguat for the Treatment of Chronic Thromboembolic Pulmonary Hypertension

Hossein-Ardeschir Ghofrani, M.D., Andrea M. D'Armini, M.D., Friedrich Grimminger, M.D., Marius M. Hoeper, M.D., Pavel Jansa, M.D., Nick H. Kim, M.D., Eckhard Mayer, M.D., Gerald Simonneau, M.D., Martin R. Wilkins, M.D., Arno Fritsch, Ph.D., Dieter Neuser, M.D., Gerrit Weimann, M.D., and Chen Wang, M.D., for the CHEST-1 Study Group*



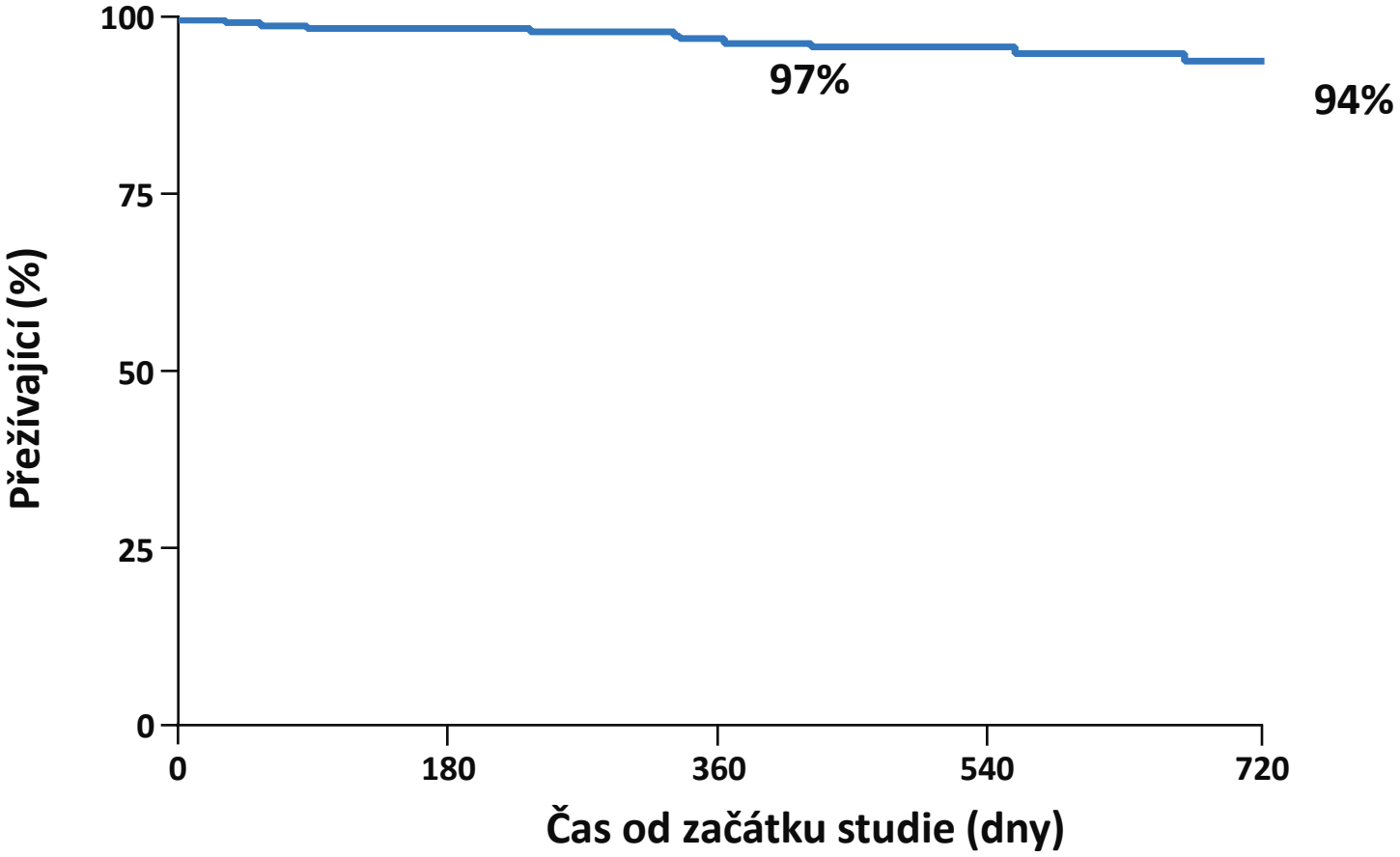




Mean 6MWD absolute values (m)						
Former riociguat	345	396	406	406	400	411
Former placebo	360	368	414	411	408	405
No. of patients						
Former riociguat	155	154	145	143	143	114
Former placebo	82	81	75	75	72	58

NEJM 2013, 369: 319-329

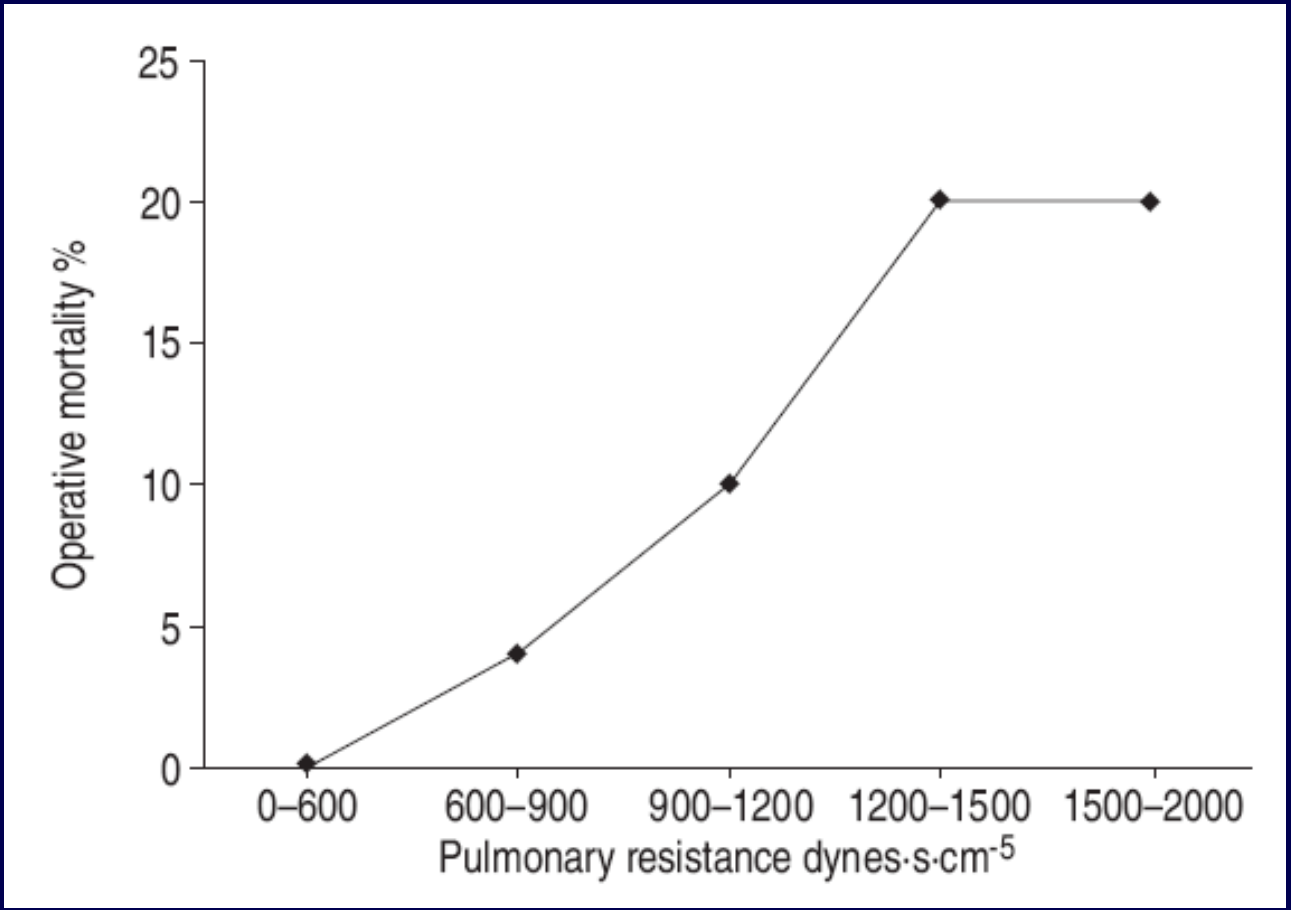
CHEST 2 – CELKOVÉ PŘEŽITÍ



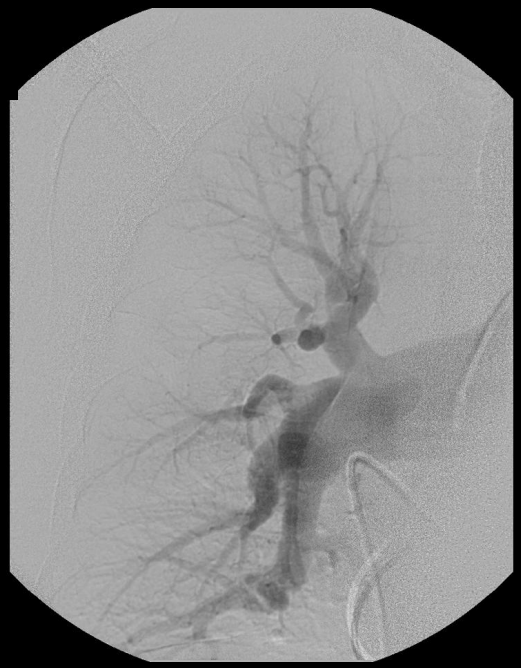
Pacienti v riziku	237	223	166	105	74
Počet úmrtí	0	3	6	8	10

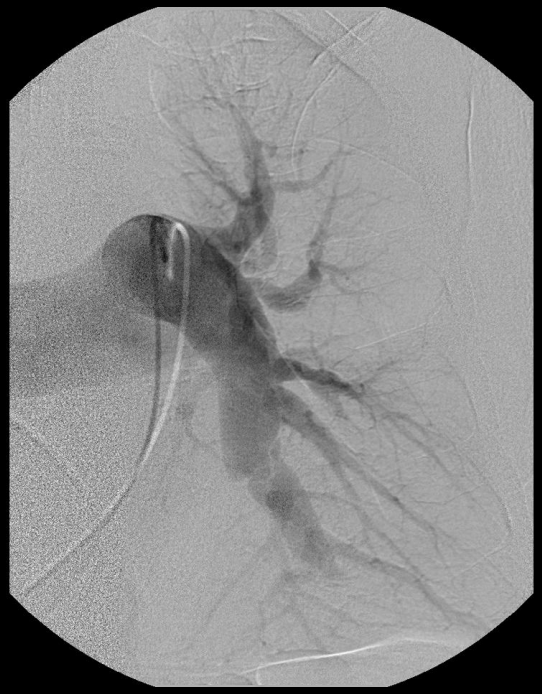
PŘÍPRAVA PŘED PEA

MORTALITA PEA



ERJ 2004, 23: 637-48



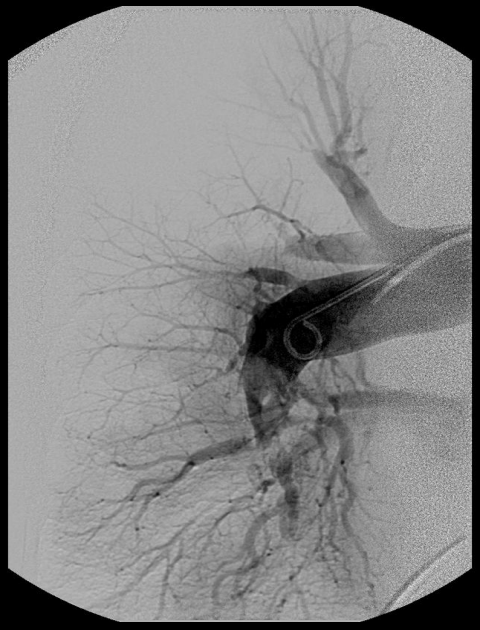


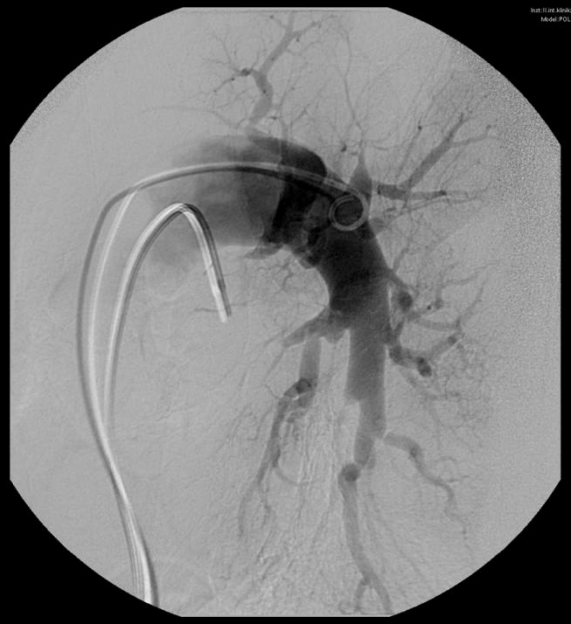
♀ , 76 let

PAP 106/53/73

CO 2.78, CI 1.89

PAR 21.58



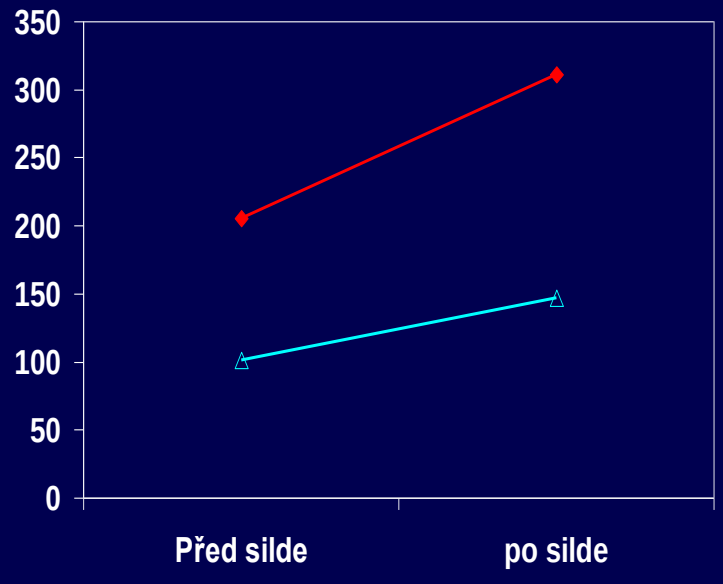


♂ , 67 let

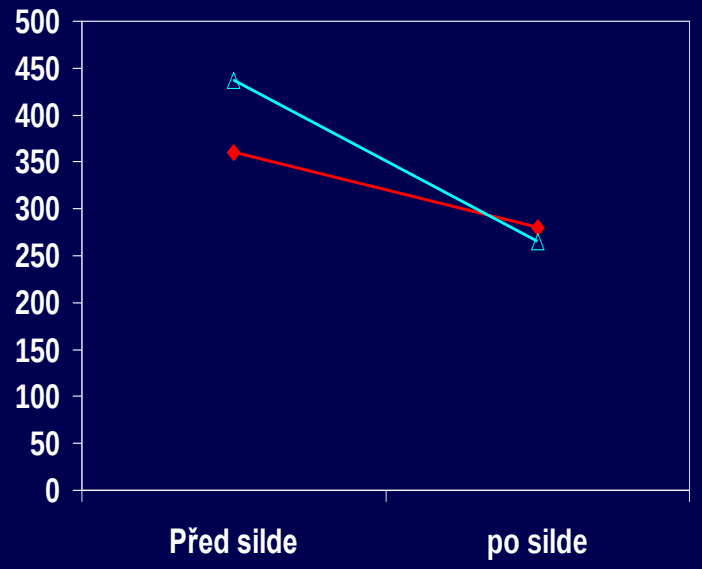
PAP 96/47/66

CO 3.11, CI 1.94

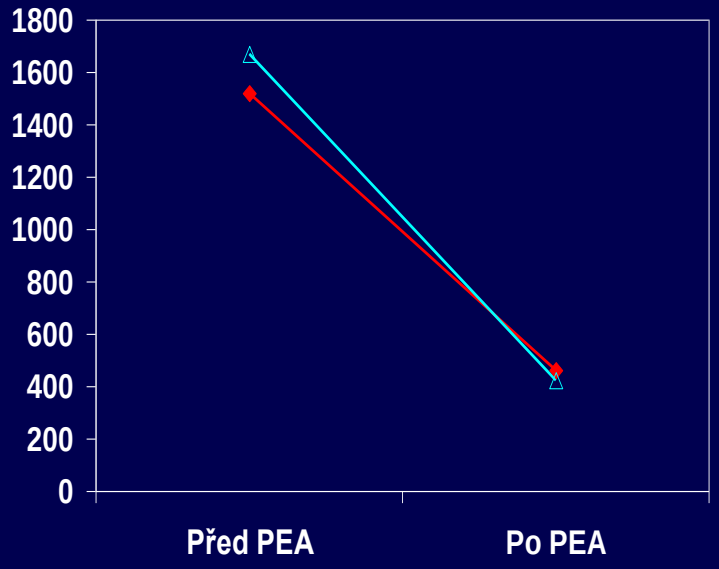
PAR 20.86



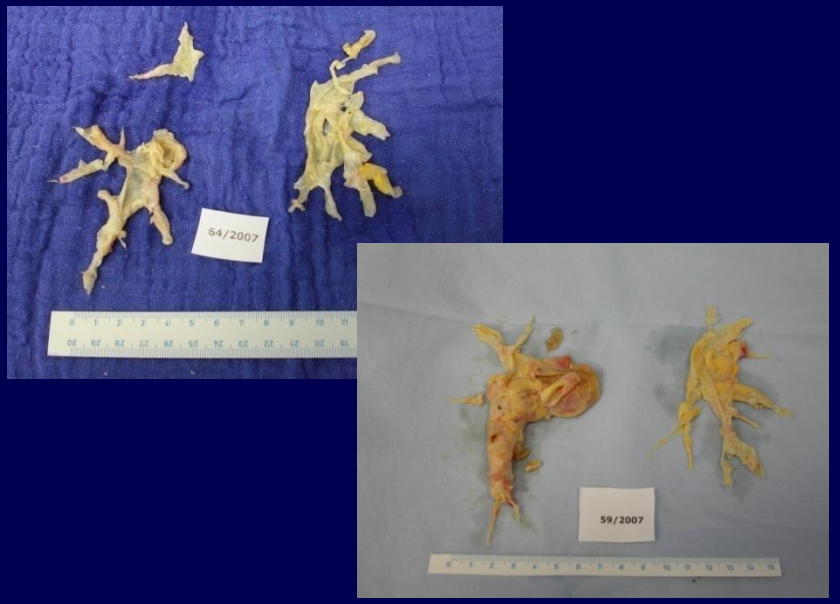
6MWT (m)



BNP (ng/L)



PVR (dyn.s.cm-5)



ZÁVĚRY 1.

- Jedinou indikací k farmakoterapii
  CTEPH je léčba technicky inoperabilní CTEPH
  nebo reziduální PH po PEA (riociguat)

- Pro léčbu jinými přípravky chybí evidence

ZÁVĚRY 2.

- Neindikovaná farmakoterapie operabilní CTEPH prodlužuje dobu do indikace PEA a zvyšuje riziko reziduální PH
- „Neoadjuvantní“ farmakoterapie před PEA je indikována jen v přísně selektovaných případech (PVR > 1000 dyn.s.cm^{-5})