

Slovenská
zdravotnícka
univerzita



Národný ústav
srdcovocievnych
chorôb

Inovativní postupy v léčbě CTEPH

Farmakoterapia CTEPH:
evidencia z klinických štúdií a
skúsenosti s liečbou v reálnej praxi

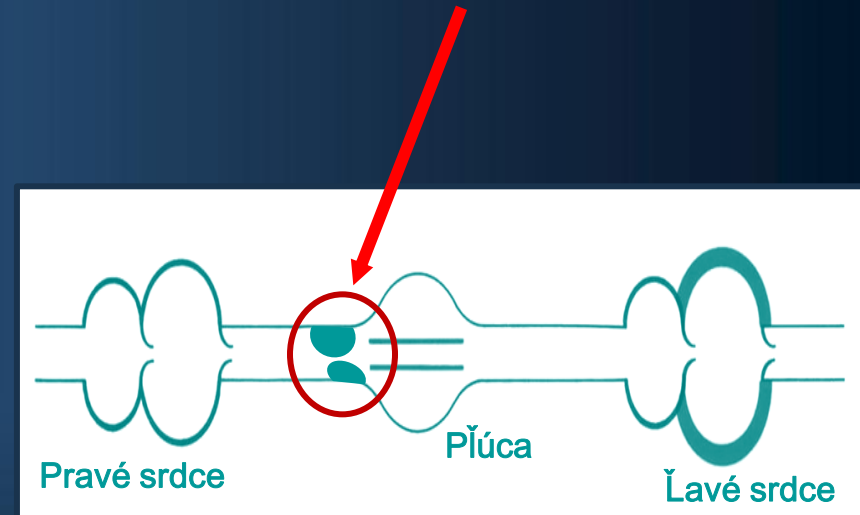
Iveta Šimková

Klinika kardiológie a angiológie LF SZU a NÚSCH a.s.

CTEPH je samostatným typom PH

v klasifikácii pľúcnej hypertenzie
WHO Nice 2013, Odporúčania ESC 2015

1. Pľúcna artériová hypertenzia - PAH
2. Pľúcna venózna hypertenzia
3. Pľúcna hypertenzia asoc. s respiračnými chorobami
4. Chronická tromboembolická pľúcna hypertenzia
5. Pľúcna hypertenzia s nejasným mechanizmom



- symptomatická PH
- prekapilárna PH >25 mmHg+3W.j.
- perzistencia perfúzných defektov pri 3-6mesačnej účinnej AK th

Chronická tromboembolická PH

prekonaná pľúcna embólia
organizácia embolov
pľúcna hypertenzia



2 patomechanizmy
obštrukcie pľúcneho riečiska a PH

organizácia
tromboembolov

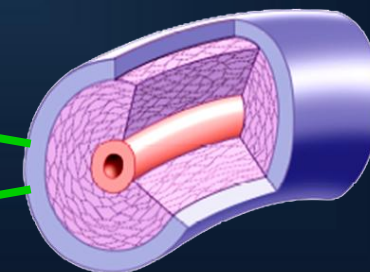
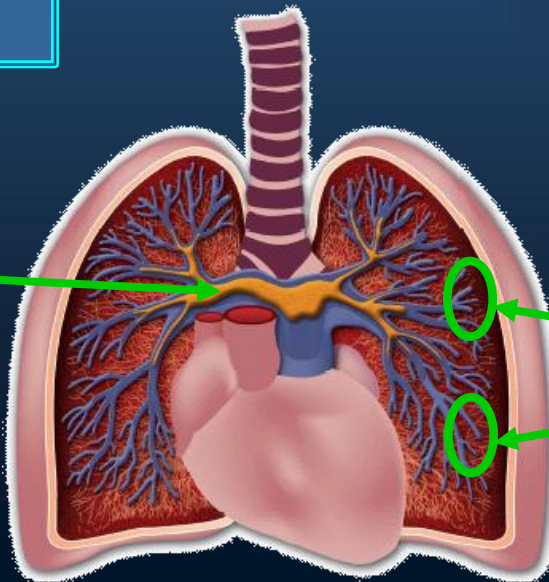
obštrukcia elastických PA

periférna artériopatia

remodelácia
malých muskulárnych PA



mechanický komponent



funkčný komponent



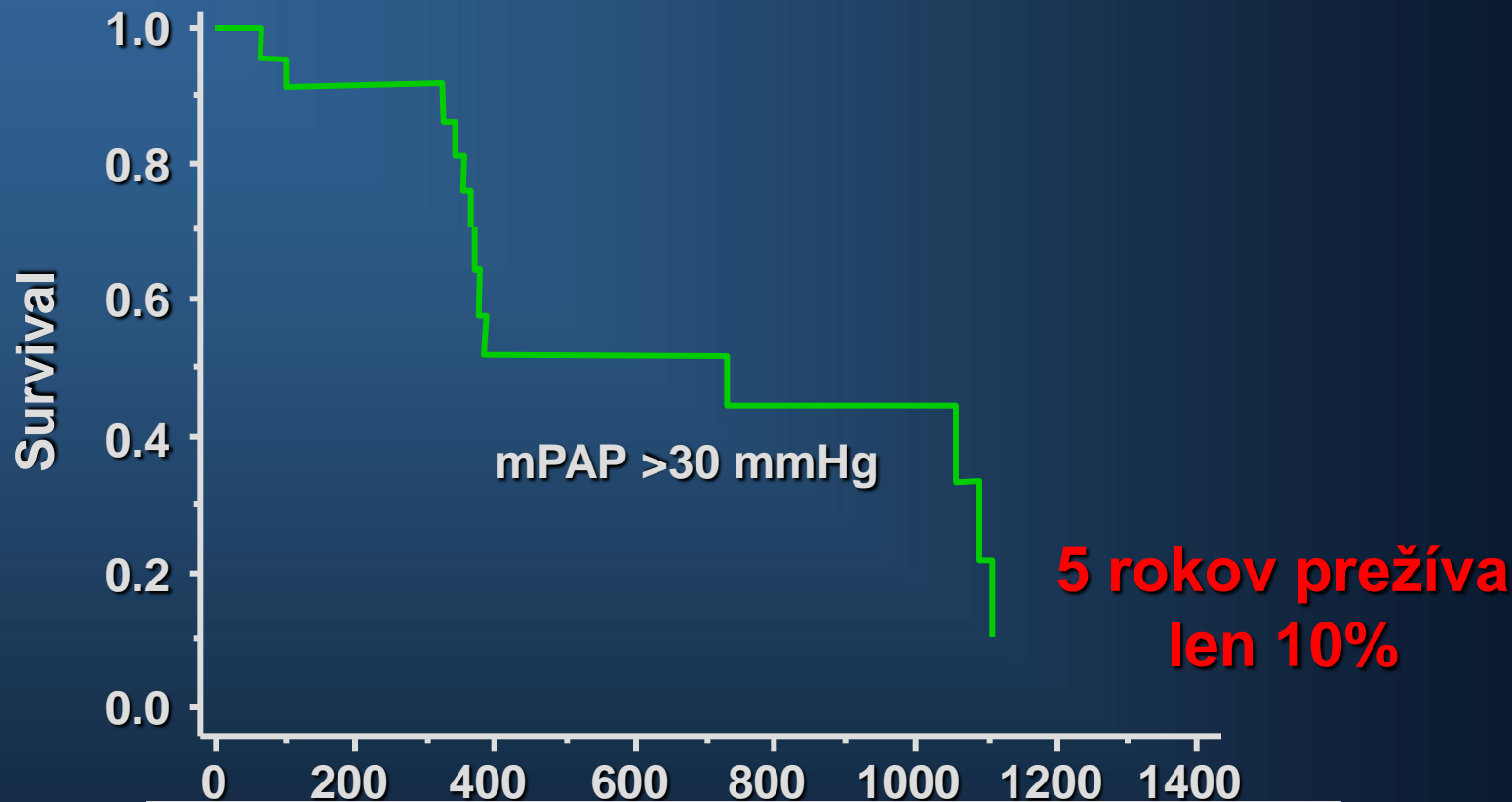
Máme diagnózu CTEPH



rýchlo progredujúca choroba,
invalidizujúca a smrtiaca
pod obrazom zlyhávajúcej pravej komory

ak je neliečená

Neliečená CTEPH má hrozivú prognózu



Aké sú liečebné možnosti?

Liečba CTEPH

- doživotná antikoagulačná liečba
- prevencia recidívy PE a prevencia trombóz in situ
-
- definícia CTEPH založená na 3 mesačnej účinnej AK th
- antagonisty vit. K s cieľovou INR 2,5 – 3,0
-
- zlepšenie hemodynamiky a funkčnej zdatnosti
- žiadna regresia PH a žiadne ovplyvnenie prognózy



Recommendations for chronic thromboembolic pulmonary hypertension

Recommendations	Class ^a	Level ^b	Ref ^c
In PE survivors with persistent dyspnoea, diagnostic evaluation for CTEPH should be considered.	IIa	C	414
Screening for CTEPH in asymptomatic survivors of PE is currently not recommended.	III	C	381
It is recommended that, in all patients with CTEPH, the assessment of operability and decisions regarding other treatment strategies be made by a multidisciplinary team of experts.	I	C	391, 398, 403, 412
Life-long anticoagulation is recommended in all patients with CTEPH.	I	C	412
Surgical PEA is recommended for patients with CTEPH.	I	C	412
Riociguat is recommended in symptomatic patients who have been classified as having inoperable CTEPH by a CTEPH team including at least one experienced PEA surgeon, or have persistent/recurrent CTEPH after surgical treatment.	I	B	411, 412
Off-label use of drugs approved for PAH may be considered in symptomatic patients who have been classified as having inoperable CTEPH by a CTEPH team including at least one experienced PEA surgeon.	IIb	B	412

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Liečba CTEPH

zlatý štandard **AK th**

a

chirurgická IC

pľúcna endarterektómia

- pri chirurgicky dosiahnuteľných léziách

mechanická zložka

medikamentózna špecifická

mechanická

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CTEPH = chronic thromboembolic pulmonary hypertension; PE = pulmonary embolism; PEA = pulmonary endarterectomy.

^aClass of recommendation.

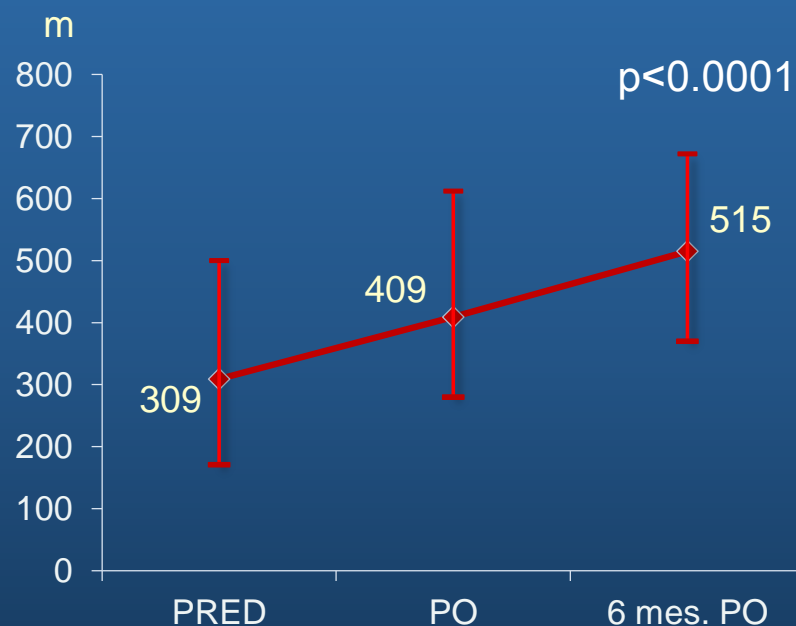
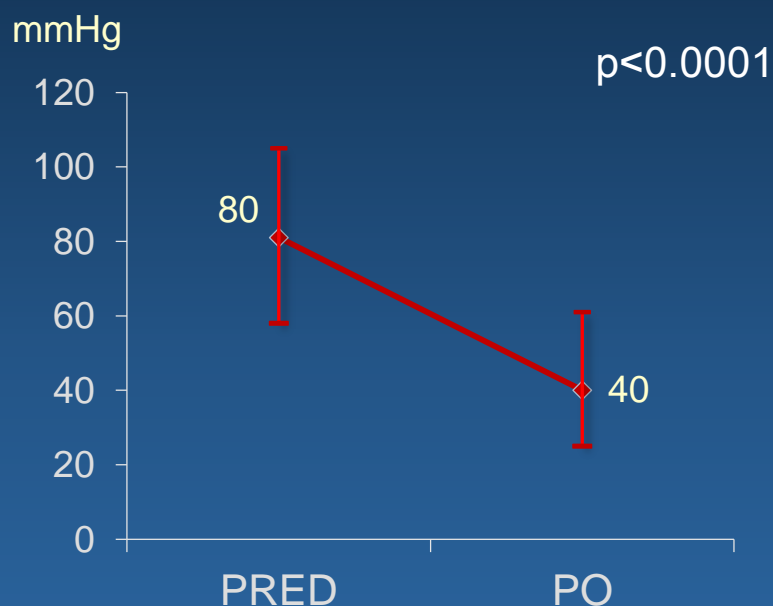
^bLevel of evidence.

^cReferences.

PEA zlepšuje hemodynamiku a symptomatológiu

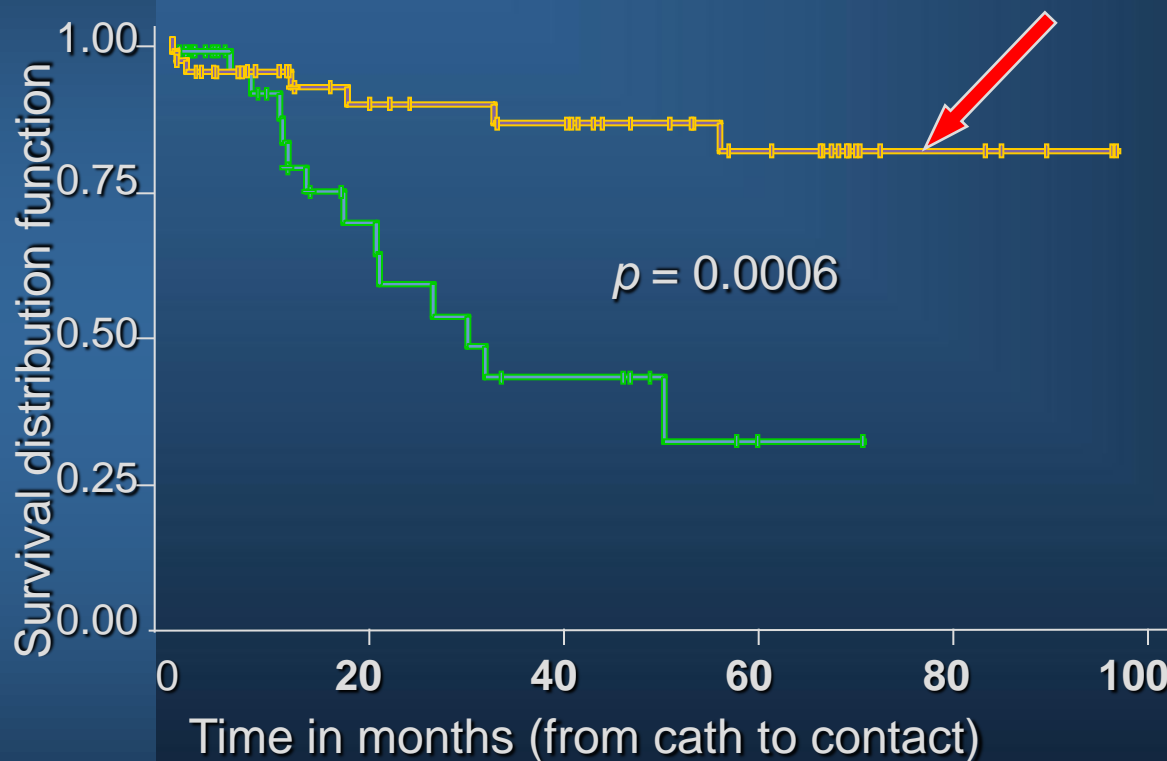
PAP po PEA

Zát'azová kapacita po PEA



Signifikantná regresia veľkosti PK, šírky AP, zlepšenie funkcie PK, NYHA 3,4 → 1,6

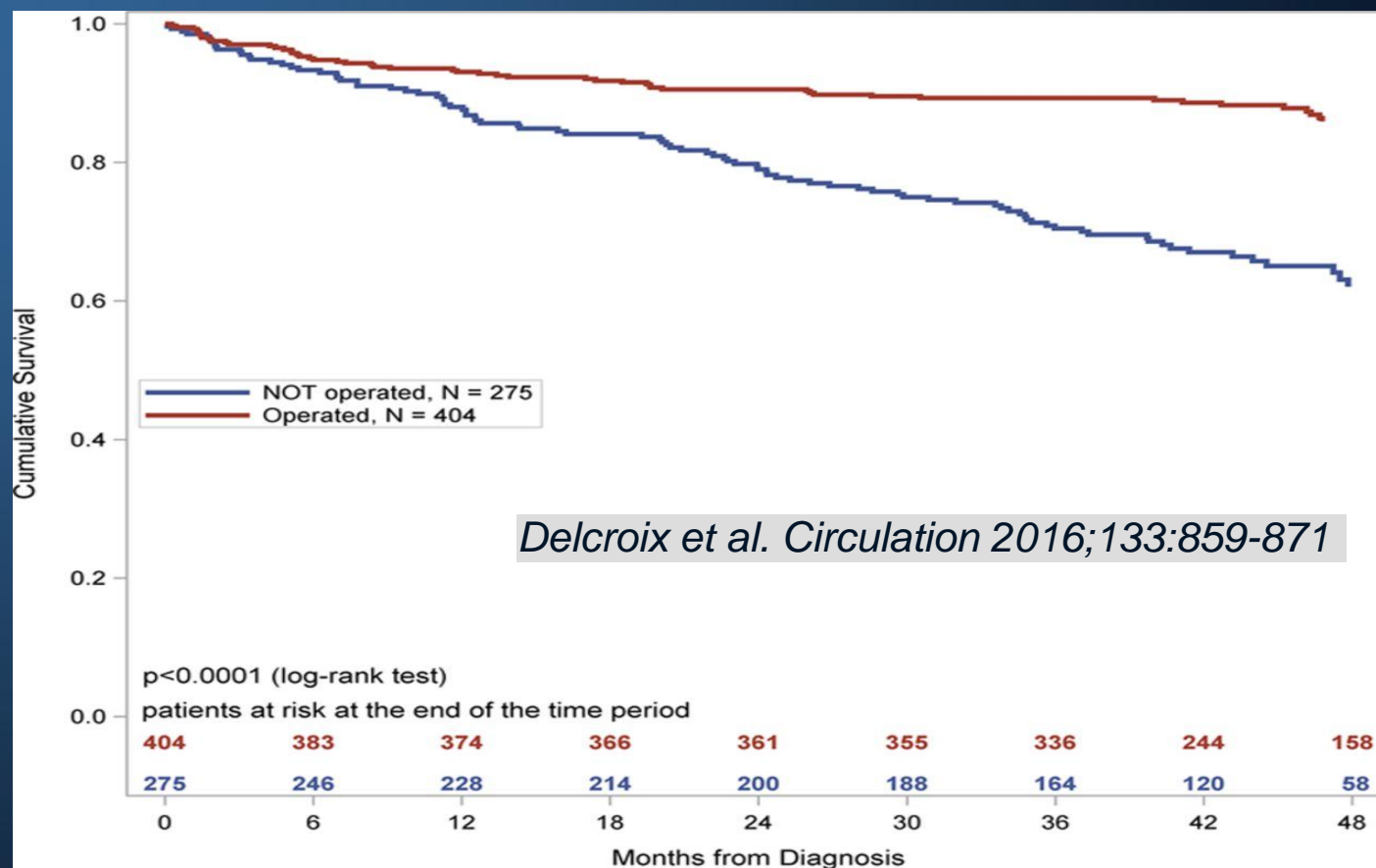
PEA zlepšuje prognózu u CTEPH



N = 308

5r. prežívání v 75%

Prežívanie operovaných a neoperovaných pacientov



Avšak

- 35 – 40% pacientov je nevhodná na PEA distálne lézie, komorbidity
- 5 – 35% pacientov po PEA má perzistujúcu PH

Liečba CTEPH

chirurgická pľúcna endarterektómia

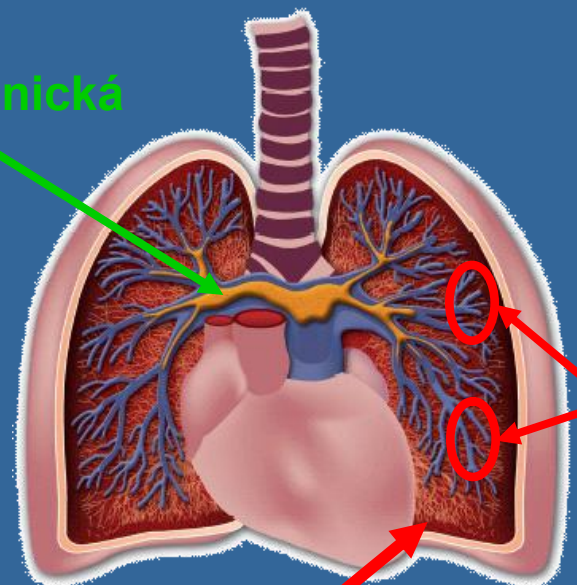
- pri chirurgicky dosiahnuteľných
mechanická zložka

medikamentózna špecifická

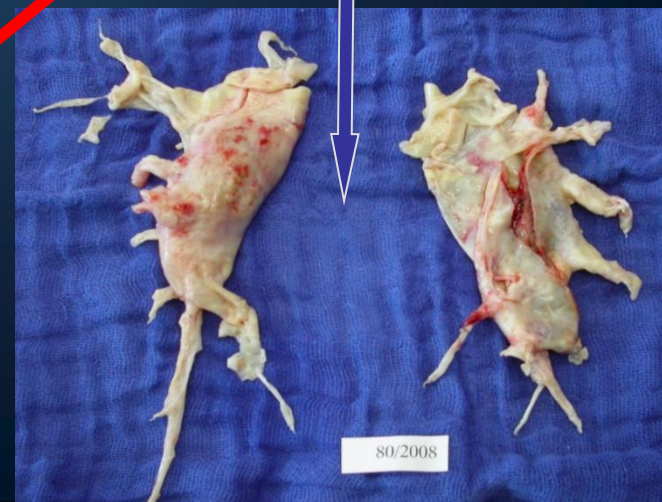
- pri inoperabilnej forme CTEPH
- pri reziduálnej PH po endarterektómii

funkčná zložka

mechanická



funkčná



Moderná koncepcia liečby CTEPH

Všetky triedy pre PAH špecických lieč

per os, subkutánne, i.v., inhalačne



- **ERA** bosentan, ambrisentan, macitenta
- **Analógy prostacyklínov** epoprostenol, treprostinil, iloprost
- **Inhibítory PDE-5** sildenafil, tadalafil
- **stimulátor GC** riociguát EBM → schválený EMA v indikácii CTEPH

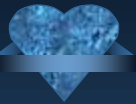
- početné nekontrolované štúdie epoprostenol¹⁻⁴, bosentan⁵⁻⁹, sildenafil¹⁰⁻¹¹, treprostinil¹², riociguat¹³

- 3 RKŠ bosentan¹⁴, sildenafil¹⁵, riociguat¹⁶



hemodynamický a klinický benefit u inoperabilnej CTEPH
alebo perzistentnej PH po PEA

1. Nagaya et al Chest, 2003; 2. Bresser et al ERJ 2006; 3. Scelsi et al. Ital Heart J 2004; 4. Cabrol et al JHLJ 2006; Bondermann et al, Chest 2006; 6. Hoepfer et al Chest 2008; Hughes et al, Thorax 2008; Hughes et al. ERJ 2007; 9. Seyfarth et al. Respiration 2006; 10. Ghofrani et al AJRCCM 2003; Reichenberger et al, ERJ 2007; Skoro-Sayer et al. Thromb Haemostat 2007; 13. Ghofrani et al. ERJ 2010; 14. Jais et al. JAAC 2008; 15. Suntharalingam et al. Chest 2008; 16. Ghofrani et al. NEJM 2013.



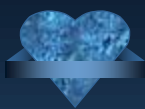
RKŠ

liečba	N	trvanie štúdie	primárny endpoint	sekundárne endpointy
BENEFIT <i>bosentan</i> vs placebo	157 inOP	16 týždňov	Δ PVR -24% (p=0,0001) Δ 6MWD +2,2m (p=0,54)	pozit: PVR; CI; Borg Δ NT-proBNP negat: FC; TTCW QoL (SF 36)
SILDENAFIL <i>sildenafil</i> vs placebo	19 10 inOP 9 perzist.	12 týždňov	Δ 6MWD +17,5m (p=0,38)	pozit: FC (p=0,025) PVR (p=0,044) negat: Borg QoL (CAMPHOR) Δ NT-proBNP
CHEST-1 <i>riociguat</i> vs placebo	261 189 inOP 72 perzist.	16 týždňov	Δ 6MWD + 46m (p=0,0001)	pozit: PVR, NT-proBNP, Borg, FC QoL (ED-Q5) negat: TTCW

RKŠ

Sumár hemodynamického efektu

		N	baseline PVR	Δ PVR 12.-16.týž.	zmena v % 12.-16.týž.
BENEFIT	<i>bosentan</i>	66	778 \pm 323	-146	-19%
SILDENAFIL	<i>sildenafil</i>	9	814 \pm 385	- 179 \pm 245	- 22%
CHEST-1	<i>riociguat</i>	151	791 \pm 432	-226 \pm 248	- 29%



~ 60% pacientov s CTEPH operabilní, inoperabilní, ako bridging
 ~ 25% kombinačná th

Table 33 Recommendations for chronic thromboembolic pulmonary hypertension

Statement	Class ^a	Level ^b
The diagnosis of CTEPH is based on the presence of pre-capillary PH (mean PAP \geq 25 mmHg, PWP \leq 15 mmHg, PVR $>$ 2 Wood units) in patients with multiple chronic/organized occlusive thrombi/emboli in the elastic pulmonary arteries (main, lobar, segmental, subsegmental)	I	C
In patients with CTEPH lifelong anticoagulation is indicated	I	C
Surgical pulmonary endarterectomy is the recommended treatment for patients with CTEPH	I	C
Once perfusion scanning and/or CT angiography show signs compatible with CTEPH, the patient should be referred to a centre with expertise in surgical pulmonary endarterectomy	IIa	C
The selection of patients for surgery should be based on the extent and location of the organized thrombi, on the degree of PH, and on the presence of co-morbidities	IIa	C
PAH-specific drug therapy may be indicated in selected CTEPH patients such as patients not candidates for surgery or patients with residual PH after pulmonary endarterectomy	IIb	C

^aClass of recommendation.
^bLevel of evidence.

European Heart Journal
 doi:10.1093/eurheartj/ehu101
do roku 2014 ESC/EAS GUIDELINES

Guidelines for the diagnosis and treatment of pulmonary hypertension

The Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT)

Off label 
EMB – štúdia CHEST
riociguát

Štúdia CHEST

Ghofrani et al. Riociguat for the treatment of CTEPH. N Engl J Med 2013;369:319-29

CHEST-1

dvojito-zaslepená, randomizovaná, multicentrická štúdia

261 pacientov

CTEPH inOP / perzistentná po PEA

riociguat vs placebo:

- ↑ **6MWD**
- ↓ **funkčnú triedu WHO**
- ↓ **PVR** a ↑ **CI**
- ↓ **NT-proBNP**

CHEST-2: extenzia štúdie

- **d'alšie zlepšenie 6MWD**

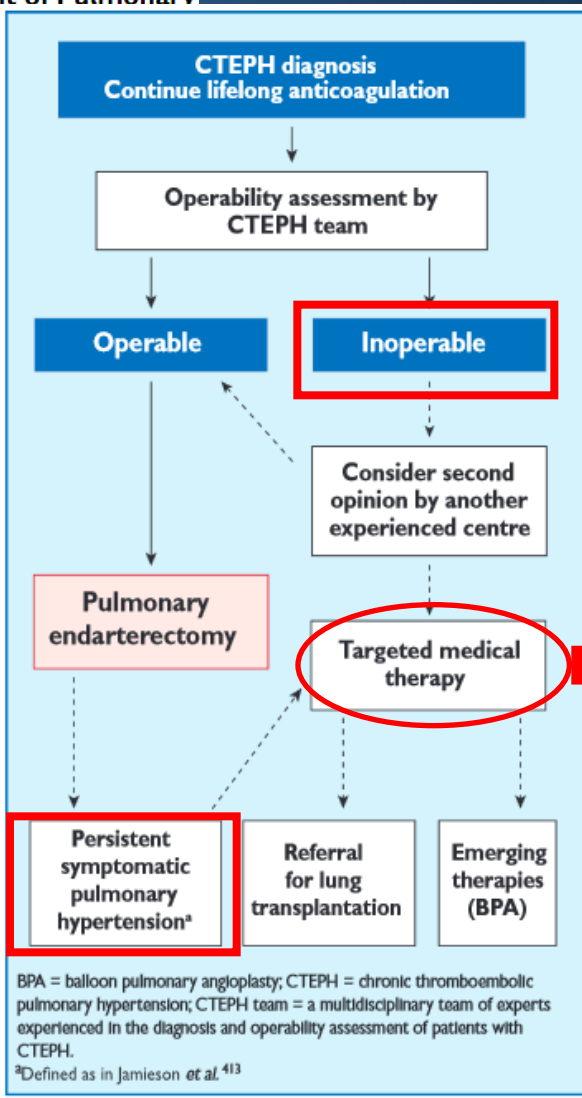
2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

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

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

The Task Force for the Diagnosis and Management of Pulmonary Embolism of the European Society of Cardiology

Guidelines reviewers: ...Iveta Simkova (Slovakia)



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Jediná schválená farmakoterapia Trieda I B

Surgical PEA is recommended for patients with CTEPH.	I	C	412
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^bLevel of evidence.

^cReferences.

Iniciálna kombinačná terapia inOP CTEPH

Observačná, multicentrická, retrospektívna analýza inOP CTEPH

Bosentan + sildenafil 76%

Ambrisentan + sildenafil 5%

Bosentan + tadalafil 16%

Ambrisentan + tadalafil 2%

N=73	iniciálne	po 4.3 M	p	
NYHA II/III/IV	12/47/11	28/40/2	0.0046	
6MWD	309±15	352±125	0.0002	
hemodynamika				
RAP	9.5±5.7	7.8 ±4.9	0.0067	
mPAP	50.6±10.5	44 ±9.7	0.00001	
CI	2.0±0.4	2.7±0.7	0.00001	
PVR	12.7±5.2	9.7±3.5	0.00001	- 38%

Iniciálna kombinačná terapia inOP CTEPH

Observačná, multicentrická, retrospektívna analýza inOP CTEPH

Bosentan + sildenafil 76%

Ambrisentan + sildenafil 5%

Bosentan + tadalafil 16%

Ambrisentan + tadalafil 2%

Iniciálne kombinačná terapia ERA + PDE₅i :

- zlepšila zát'azovú kapacitu a hemodynamiku
- zlepšenie pri duálnej liečbe pretrvávalo **28.8 mesiaci**
- prežívanie 1, 2 a 3 ročné: 90.4%, 82.7% a 80.7%
- prežívanie bez príhody 80.8%, 67.9% a 60.7%

BPA vs medikamentózna liečba u inOP CTEPH

RACE Riociguat vs ballon pulmonary angioplasty in non-operable CTEPH

randomizovaná, multicentrická, open-label štúdia

20 PH centier vo Francúzsku

62 novodiagnostikovaných pacientov v každej skupine

Primárny cieľ: zmena PVR v % po 26 týždňoch


RACE: extenzia štúdie

Pri perzistentnej PH dať vice verza liečebnú metódu BPA resp. riociguat

Manažment CTEPH na Slovensku

Komplexný manažment CTEPH

- diagnostika CTEPH
- Indikácia PEA v kooperácii so zahraničnými expertnými centrami
- špecifická liečba
- dispenzarizácia

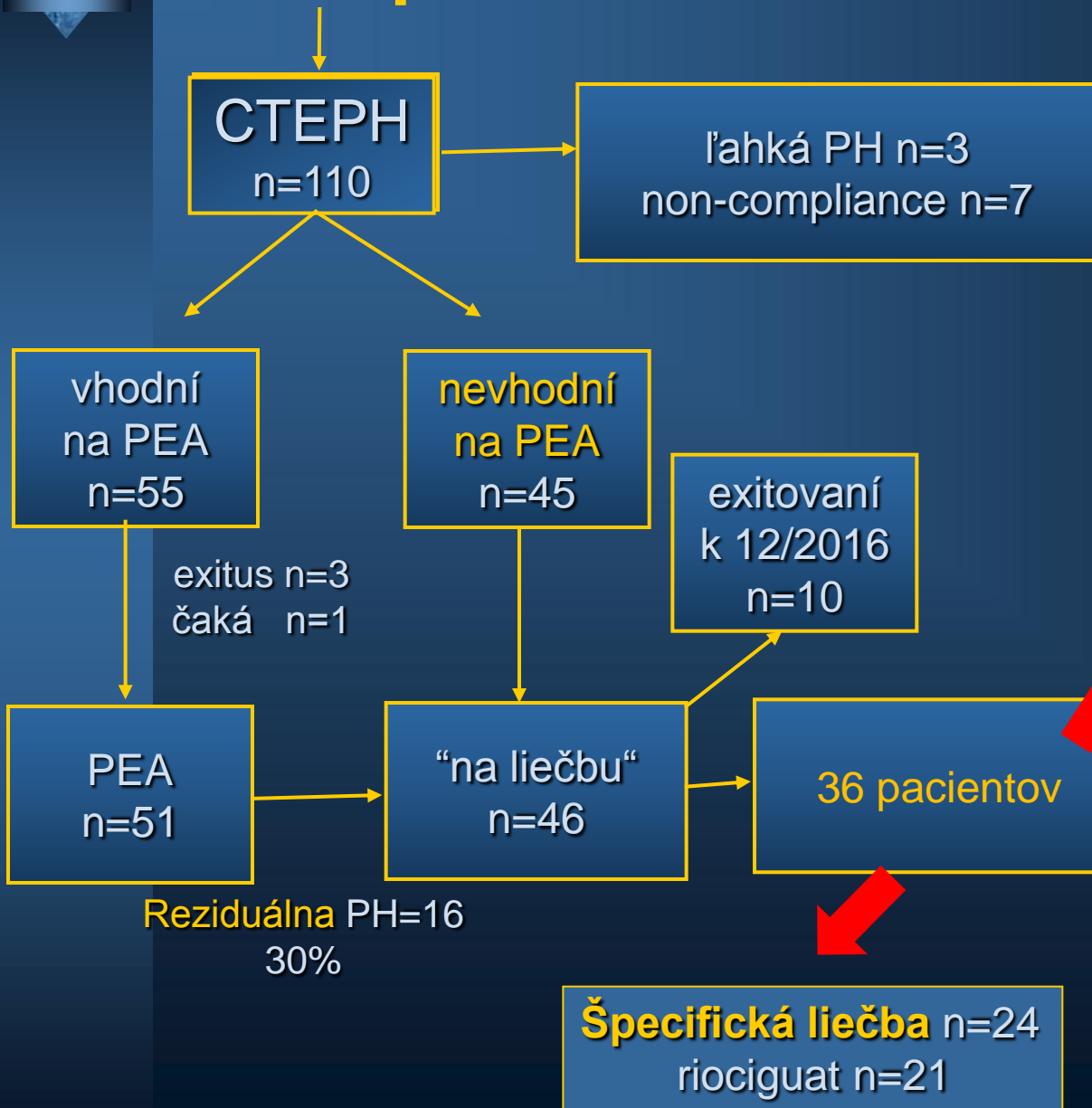


Klinika kardiológie a
angiológie LF SZU a
NÚSCH Bratislava



podľa Odporúčaní ESC na pôde špecializovaného pracoviska, v našej starostlivosti 110 pacientov s diagnózou CTEPH

Naši pacienti so CTEPH



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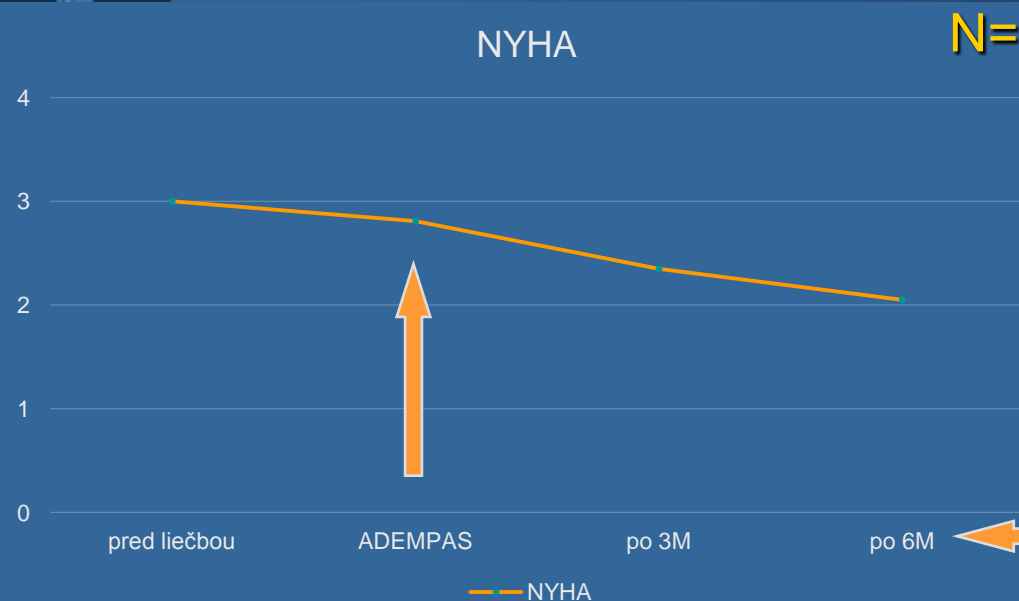
^aClass of recommendation.

^bLevel of evidence.

^cReferences.

VÝSLEDKY I

N=21 liečených 6 mesiacov riociguátom
N=7 postPEA

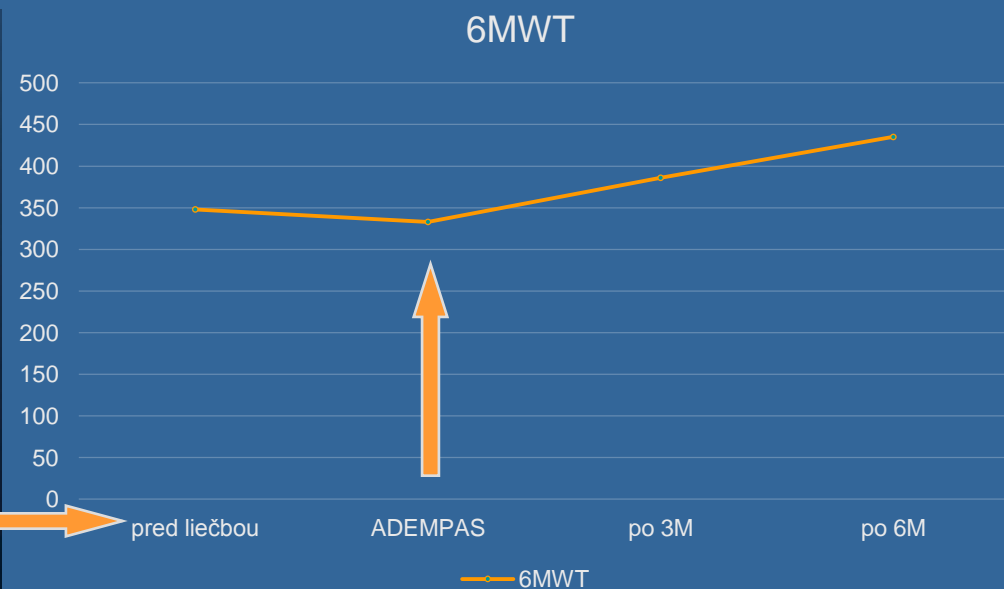


zlepšenie funkčnej triedy
NYHA/WHO

3 → 2 → 1,5

zlepšenie záťažovej kapacity
6MWD

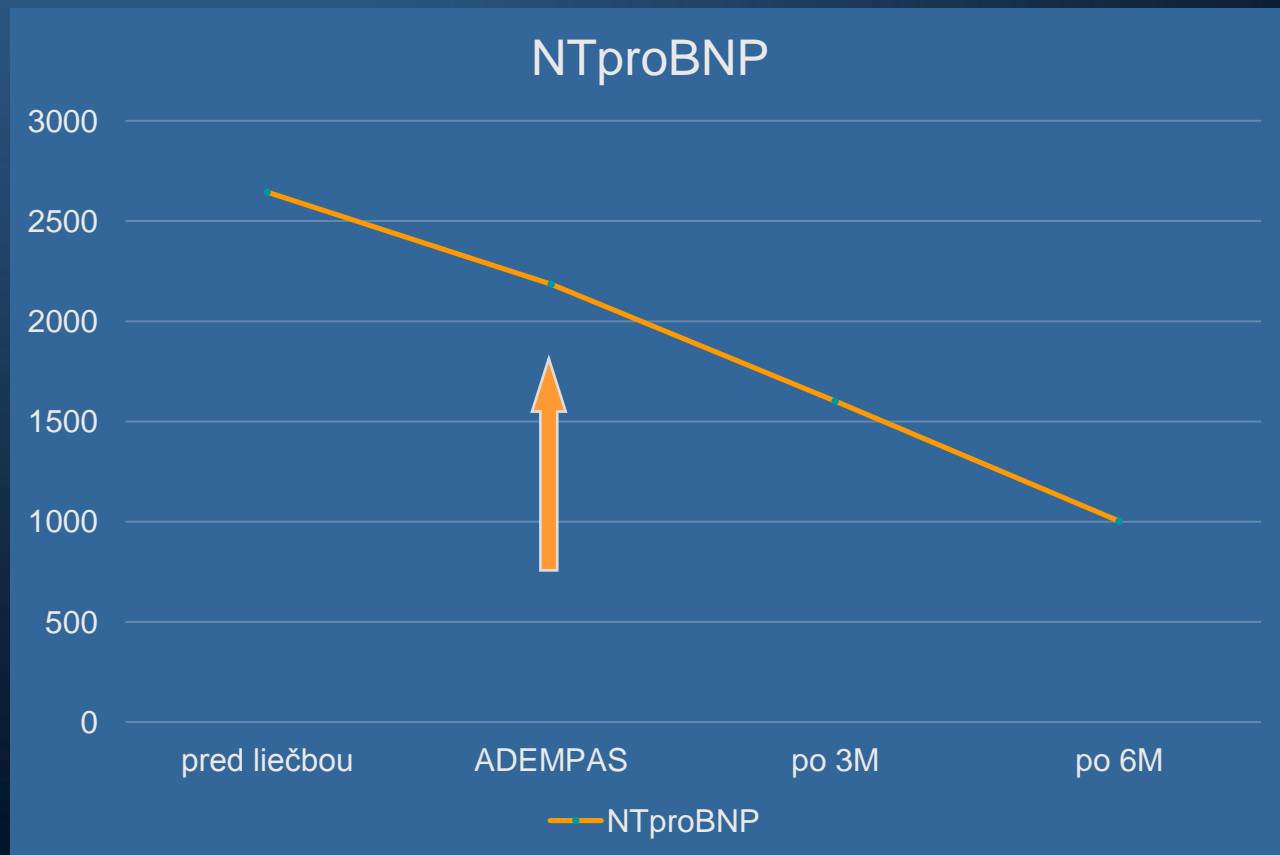
333 → 435 → 599



VÝSLEDKY II

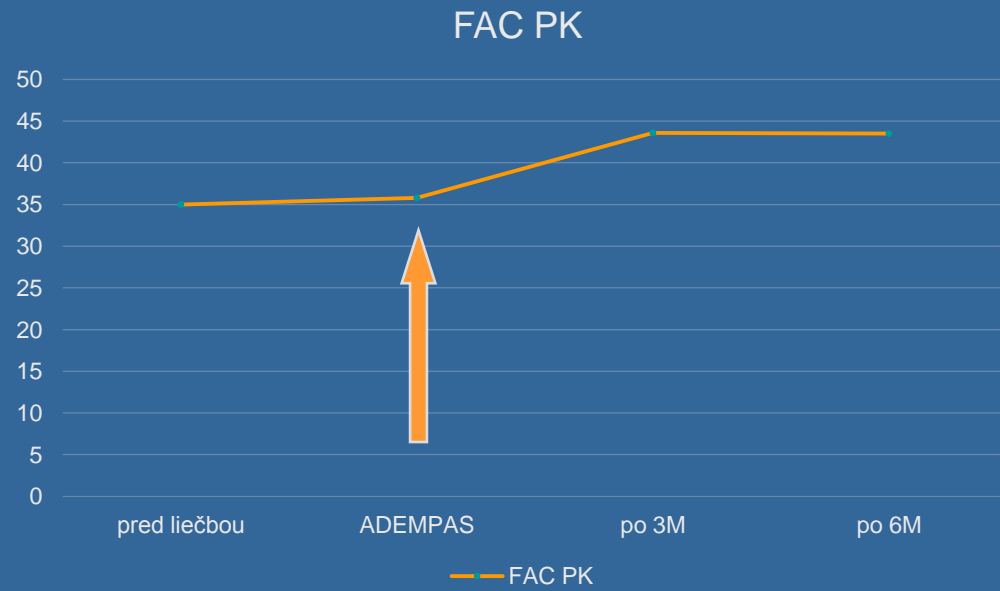
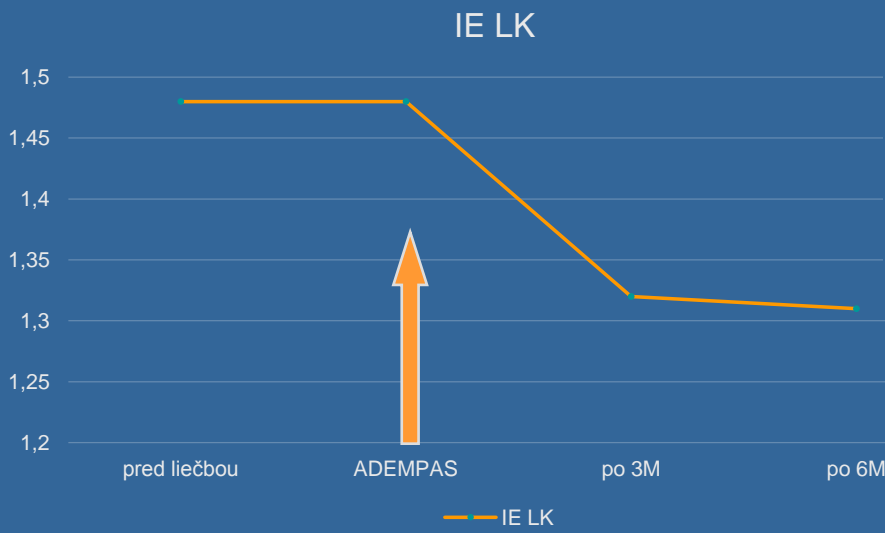
významný pokles
NT-proBNP

2185 → 1602 → **1003 ng/l**





VÝSLEDKY III:

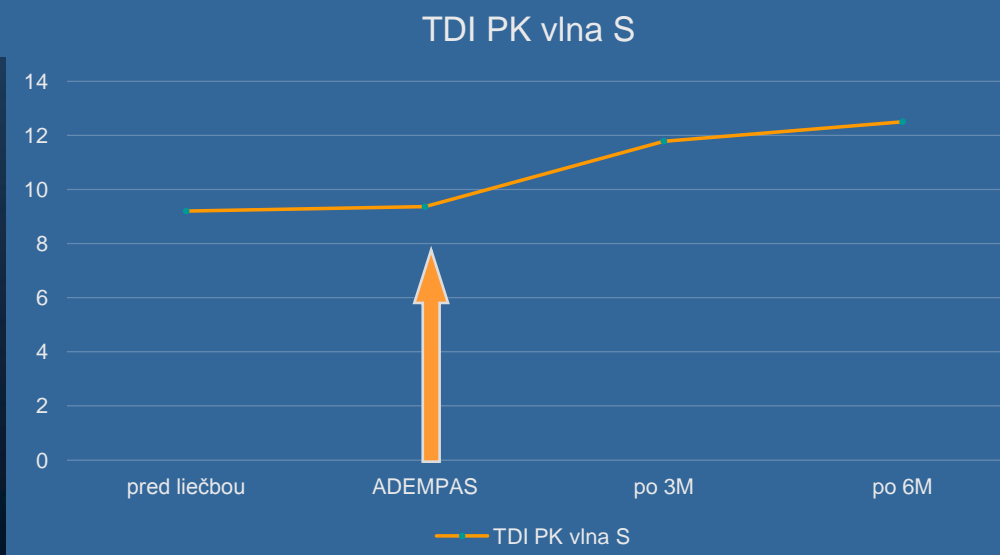


zlepšenie funkcie PK

- FAC 35 → 44%
- vlna S 9,2 → 12,5 cm/s

zlepšenie indexu excentricity
IE LK

1,48 → 1,32 → 1,31





Špecifická liečba CTEPH

- Riociguat je jedinou účinnou liečbou inoperabilnej a reziduálnej/rekurentnej CTEPH v triede IB
- V súlade s výsledkami štúdie CHEST v našom súbore ku významnému zlepšeniu:

- výkonnosti:

trieda NYHA, 6MWD

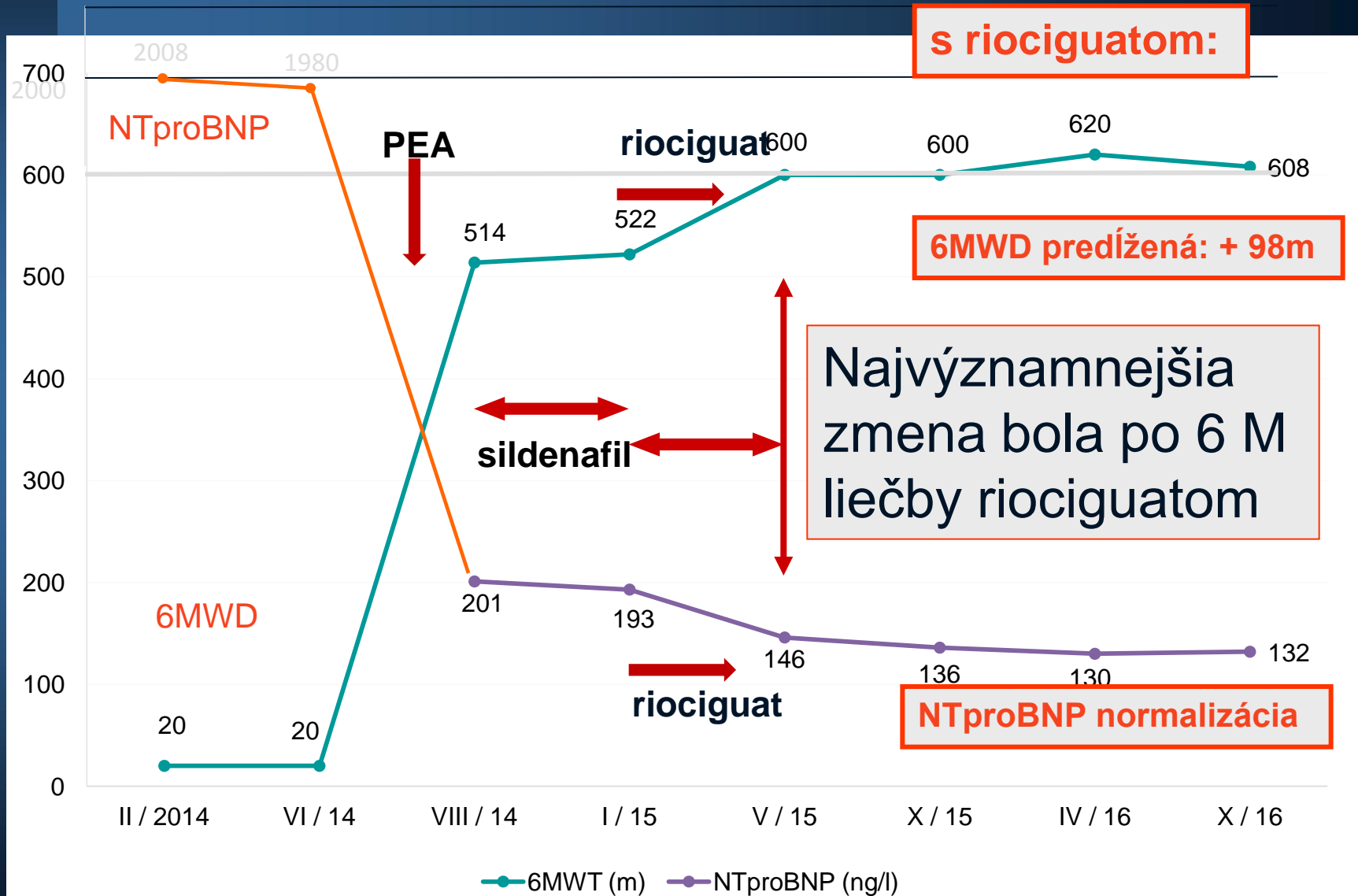
- laboratórnych aj

echokg markerov

Efekt 6M špecifickej liečby:

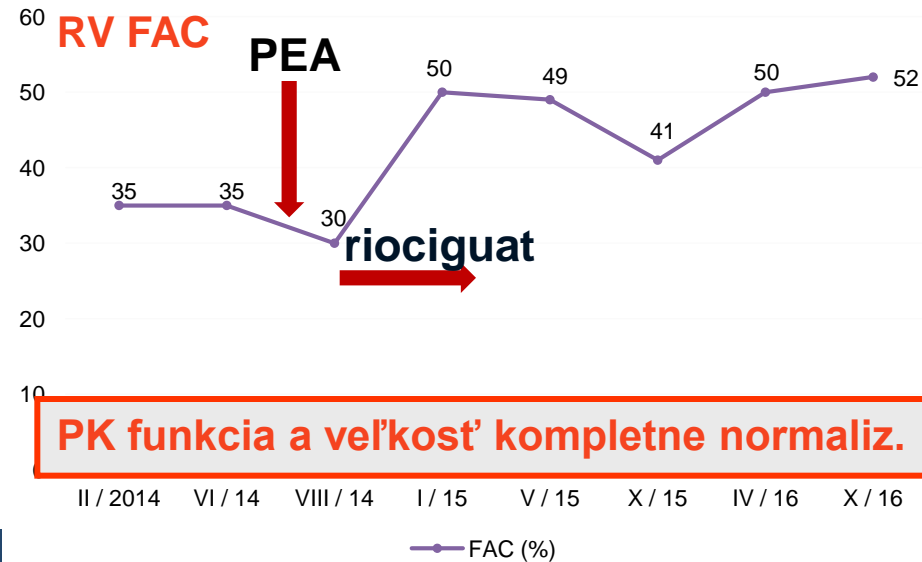
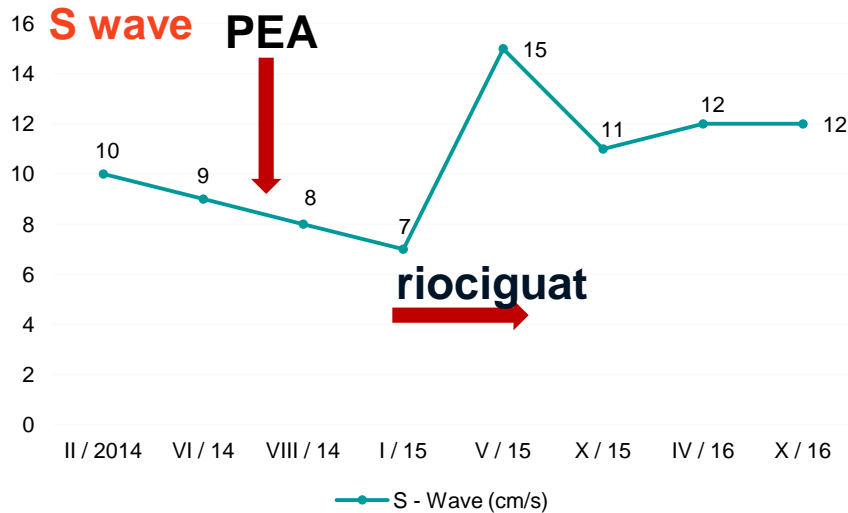
- zlepšenie 6MWD: 333→599m
- zlepšenie NYHA/WHO: 3,0→1,5
- pokles NTproBNP: 2185→1003 ng/l
- pokles IE LK: 1,5→1,3
- zlepšenie funkcie PK:
 - FAC 35 → 44%
 - vlna S 9,2 → 12,5 cm/s
- klesol reg. Tr grad: 85→76mmHg

28r. pacientka s reziduálnou PH po PEA

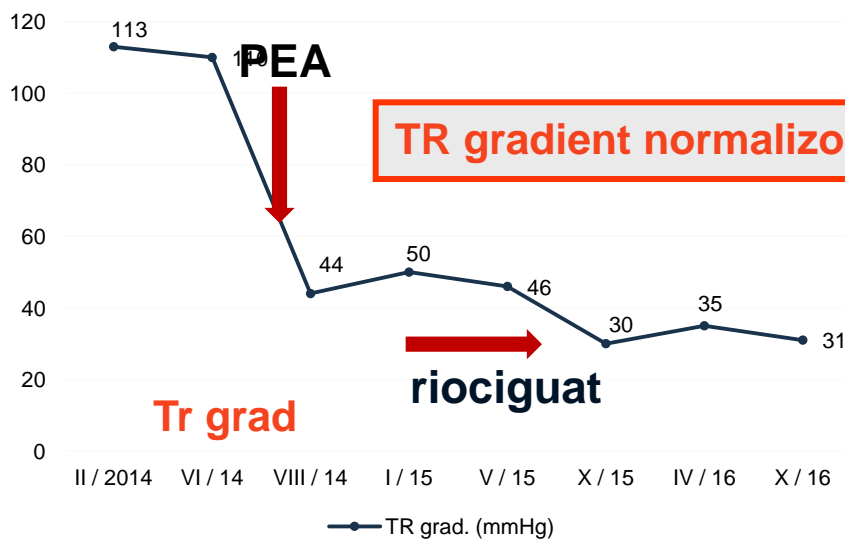


Efekt pretrváva 30 mesiacov

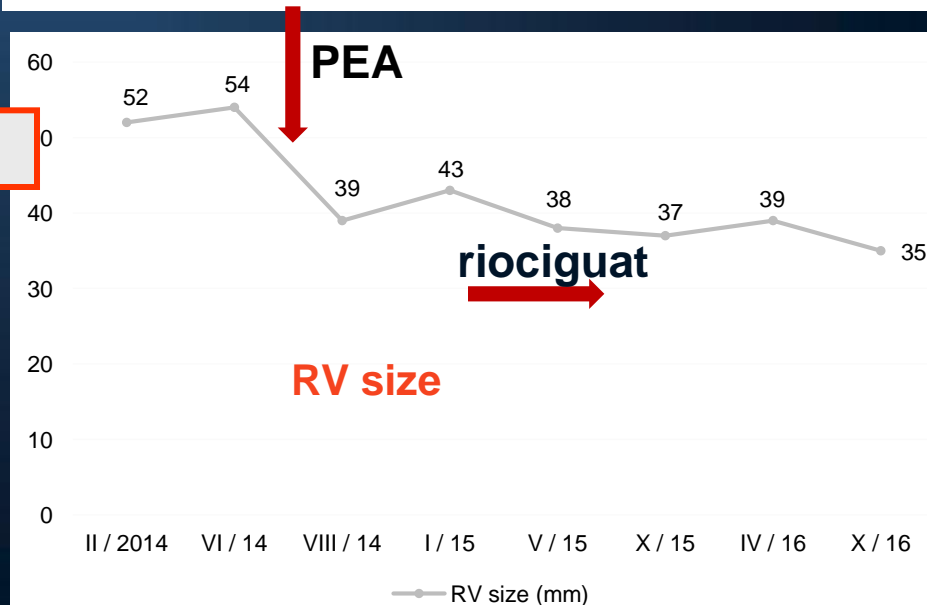
s riociguatom:



PK funkcia a veľkosť kompletne normaliz.

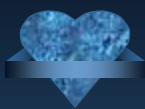


TR gradient normalizov.

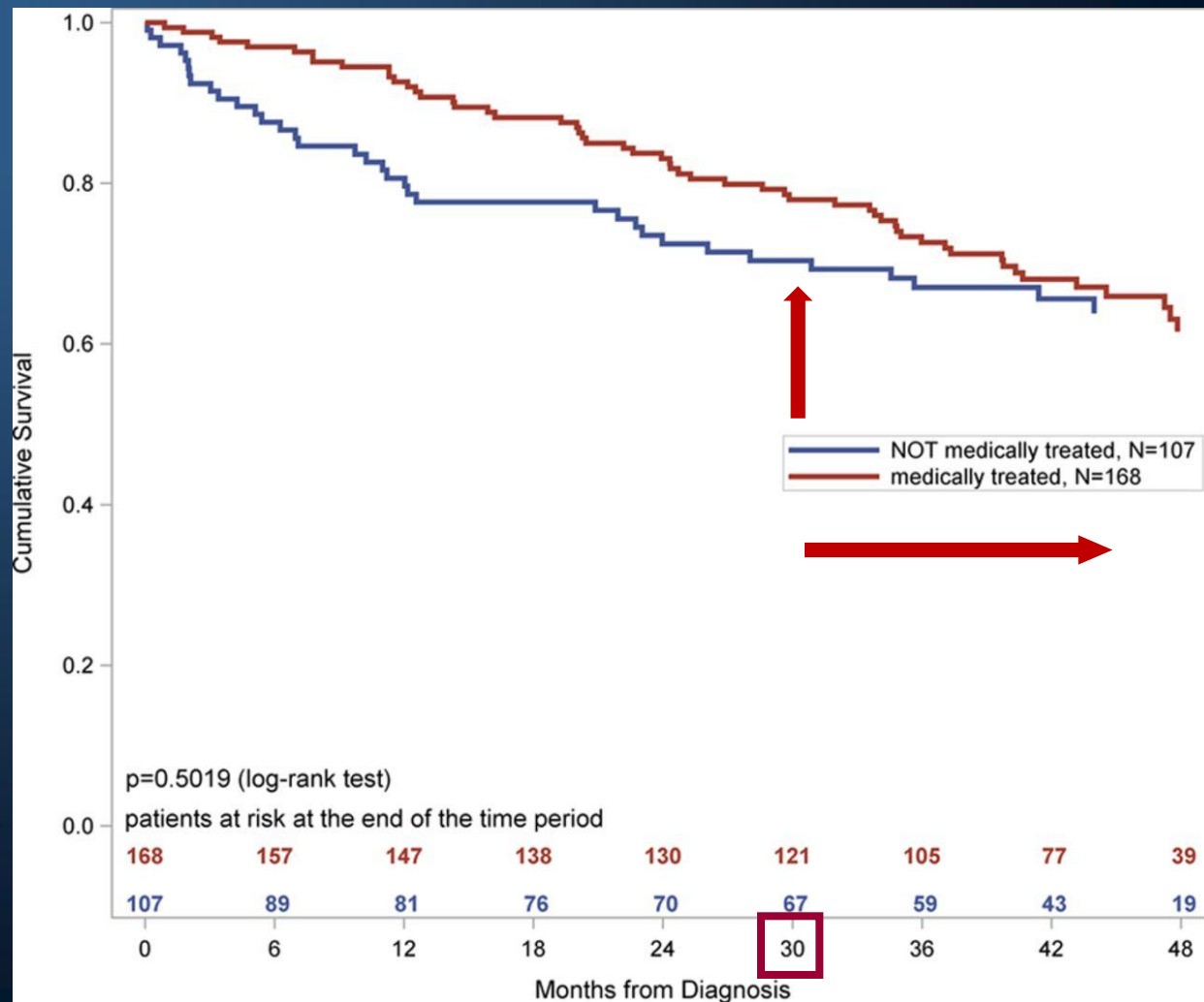


Prežívání neOP CTEPH

medikamentózne liečení vs neliečení



dlhodobá prognóza



PVR

dyn.s.cm-5

Medically treated 778

NOT medically treated 480

Záver

- CTEPH ako možný následok PE je závažná klinická jednotka → významne redukuje kvalitu a dĺžku života
- Dostupnosť kurabilnej chirurgickej liečby a špecifickej liečby → liečiteľnosť
- PEA ostáva nateraz liečbou voľby
- U neoprovateľných pacientov a u perzistentnej PH po PEA má multidisciplinárny konsenzus zväžiť špecifickú liečbu, avšak
- Ovplyvnenie dlhodobého prežívania špecifickou liečbou je otázne
- Chýbajú výsledky EBM na doriešenie postavenia a sledu liečebných modalít: špecifická liečba vs BPA vs iniciálna kombinovaná liečba
- Manažment patrí do rúk expertného centra → exaktná diagnostika a následný manažment up to date

