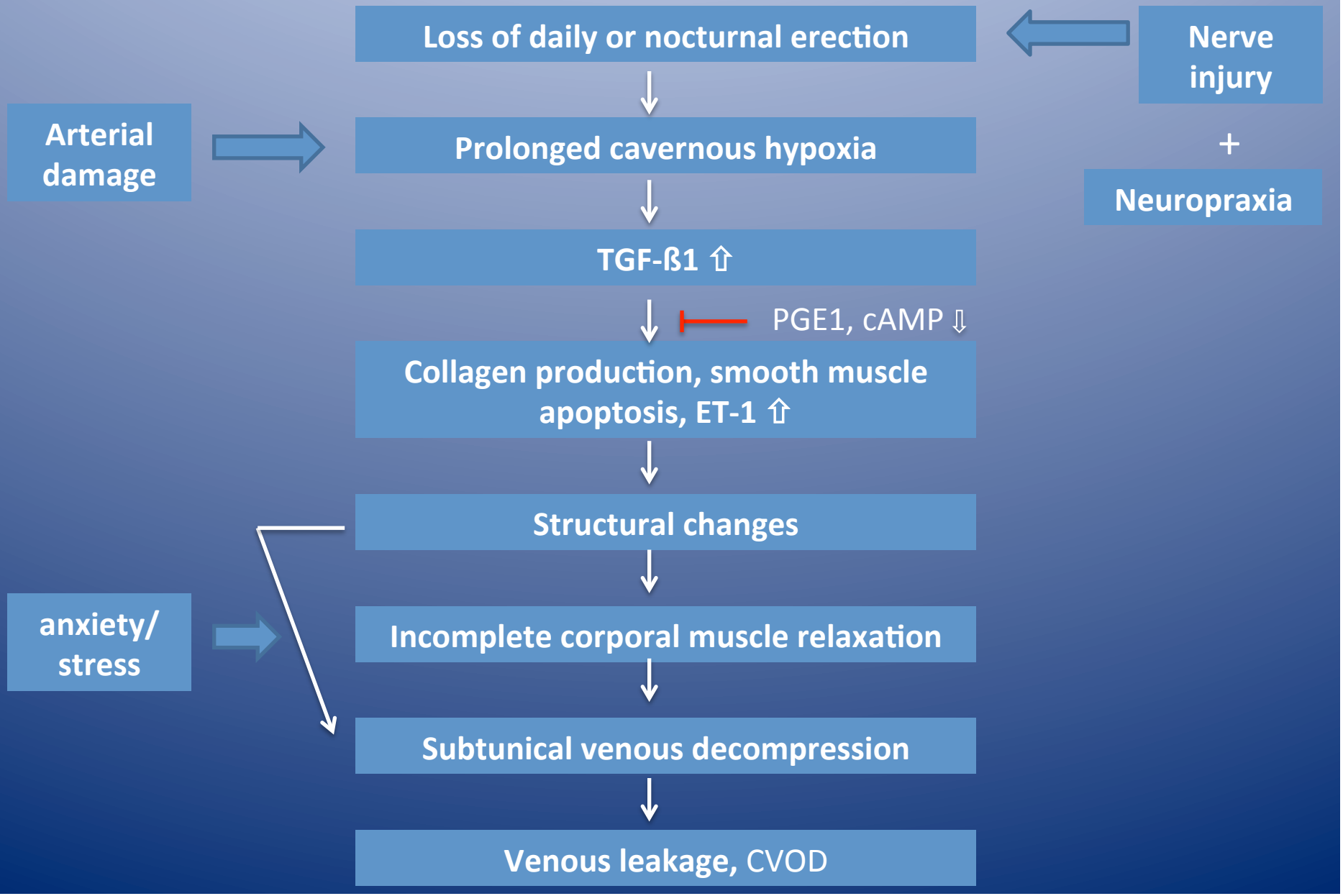
Early oral PDE5I treatment rationale & possibilities

Béla Kovács
Budapest, Hungary

Post-RP ED

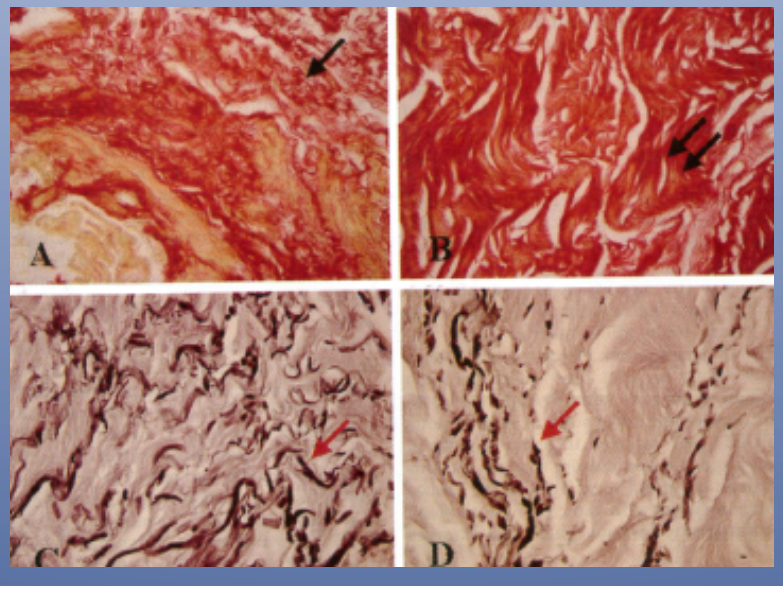
- 25 - 75% of men experience postoperative ED

ED following RP: mechanism



Hystologic changes in the „erectile" tissue

Pre-op.



2 Mo postop

Elastic and collagen fibers in 19 patients before, and 2 and 12 months after radical prostatectomy

	Mean Fibers ± SD	
	Elastic/High Power Field	Collagen/% Biopsy Area
Before	129.32 ± 13.13	44.80 ± 5.73
After 2 mos	80.80 ± 23.26	55.05 ± 5.29
After 12 mos	44.20 ± 11.58	73.10 ± 7.85

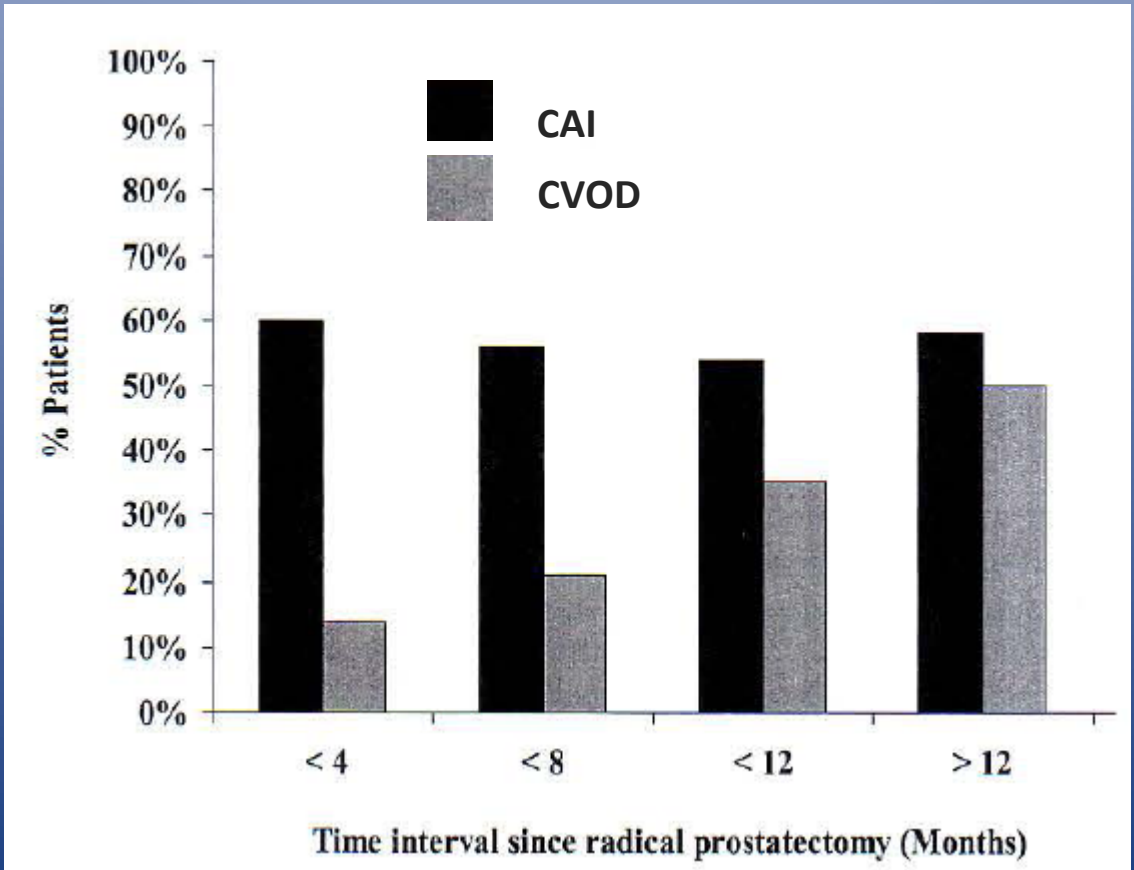
Before vs after 2 and 12 months, and after 2 vs 12 months $p < 0.0003$.

Iacono F et al. J Urol. 163:1673-76. 2005

ERECTILE DYSFUNCTION AFTER RADICAL PROSTATECTOMY: HEMODYNAMIC PROFILES AND THEIR CORRELATION WITH THE RECOVERY OF ERECTILE FUNCTION

JOHN P. MULHALL, RON SLOVICK, JAMES HOTALING, NADID AVIV, ROLANDO VALENZUELA, W. BEDFORD WATERS AND ROBERT C. FLANIGAN

From the Department of Urology, Loyola University Medical Center, Stritch School of Medicine, Maywood, Illinois



Postop ED treatment

≠

Penile rehabilitation

Preserve the functional smooth-muscle content during the neuropraxia period

Rehabilitation

Possible ?

Yes

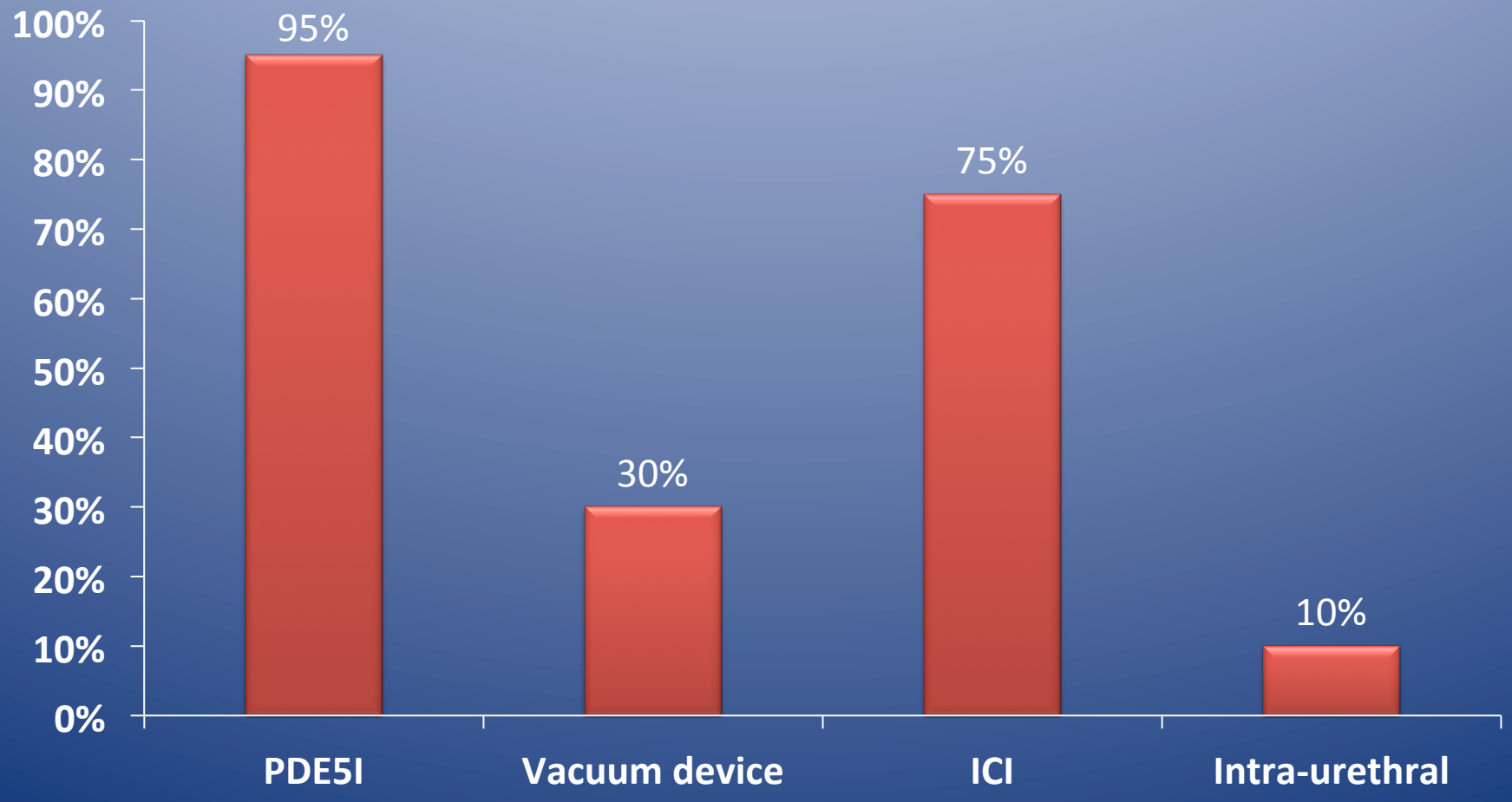
When ?

‚Pro-erectile treatments have to be given at the earliest opportunity after RP.' LE 1b

How to ??

Rehabilitation strategies

ESSM



Rationale of phosphodiesterase type 5i

- Animal research

Animal research

NERVE INJURY

FIBROSIS

HYPOXIA

APOPTOSIS

- Muller A et al. [illegible] and structural consequences of cavernous nerve injury ameliorated by sildenafil citrate. J Sex Med. 2008
- Kovanecz I et al. Long-term continuous sildenafil treatment ameliorates CVOD induced by cavernosal nerve resection in rats. IJIR. 2008: 20:202
- Ferrini M et al. Vardenafil prevents fibrosis of smooth muscle after bilateral cavernosal nerve resection in rat. [illegible]gy, 2006: 68.428
- Vignozzi L et al. Effect of tadalafil administration on penile hypoxia induced by cavernosal dissection in the rat. J. Sex Med, 2006. 3:419
- Kovanecz I et al. Chronic daily tadalafil prevents the corporal fibrosis and venocclusive dysfunction that occurs after cavernosal nerve resection. BJUI; 2008, 101.203
- Lysiak JJ et al. Tadalafil increases AKT and extracellular [illegible]related kinase ½ activation and prevents apoptotic cell death in the penis following denervation. J Urol. 2008; 179:779

Animal research – PDE5i

- ⇧ smooth-muscle to collagen ratio
- ⇧ smooth-muscle replication
- ⇩ apoptotic index
- ≅ endothelial integrity
  - preserving platelet endothelial cell adhesion molecule-1 [CD31] and eNOS expression
- ⇧ GPX levels (an antioxidant enzyme)
- ⇩ nitrotyrosine (NT) levels (an oxidative stress marker)
- ⇧ iNOS

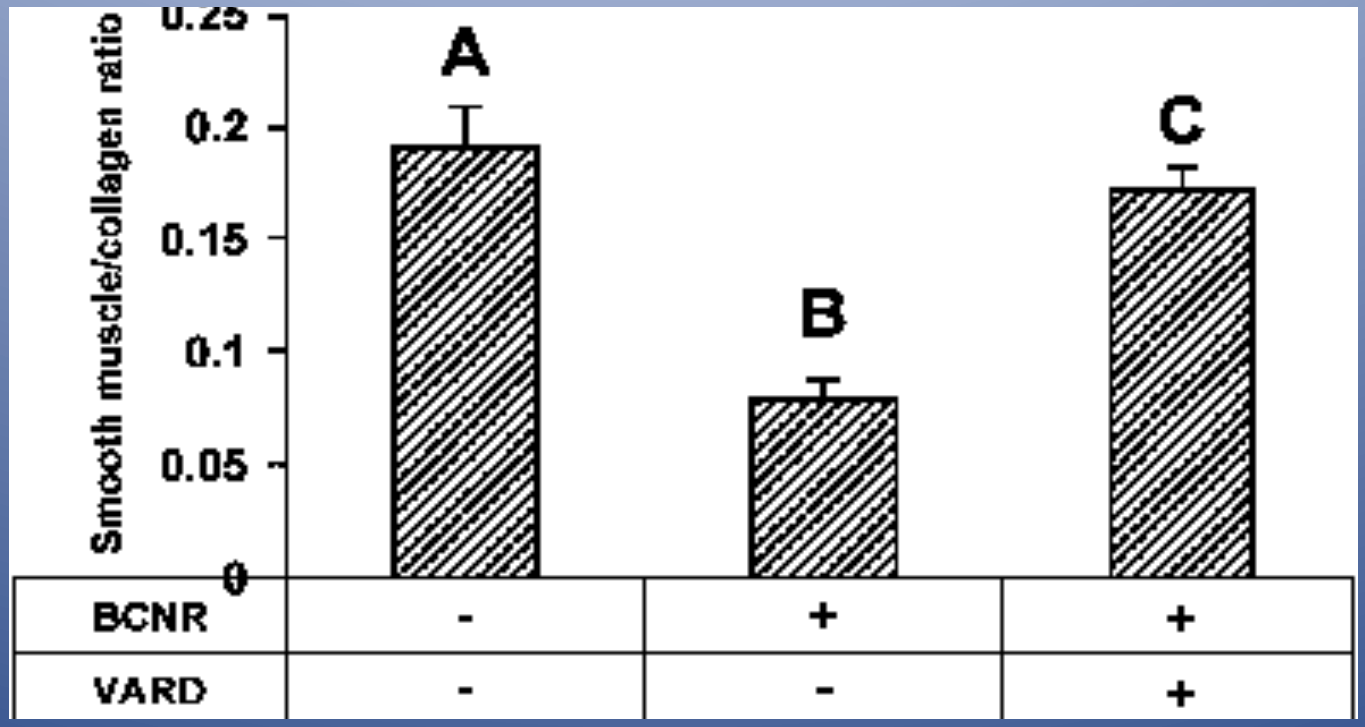
Animal research

- Based on cavernosal nerve resection or crush
- Prostate and ves. sem in place

Can be applied to humans ?

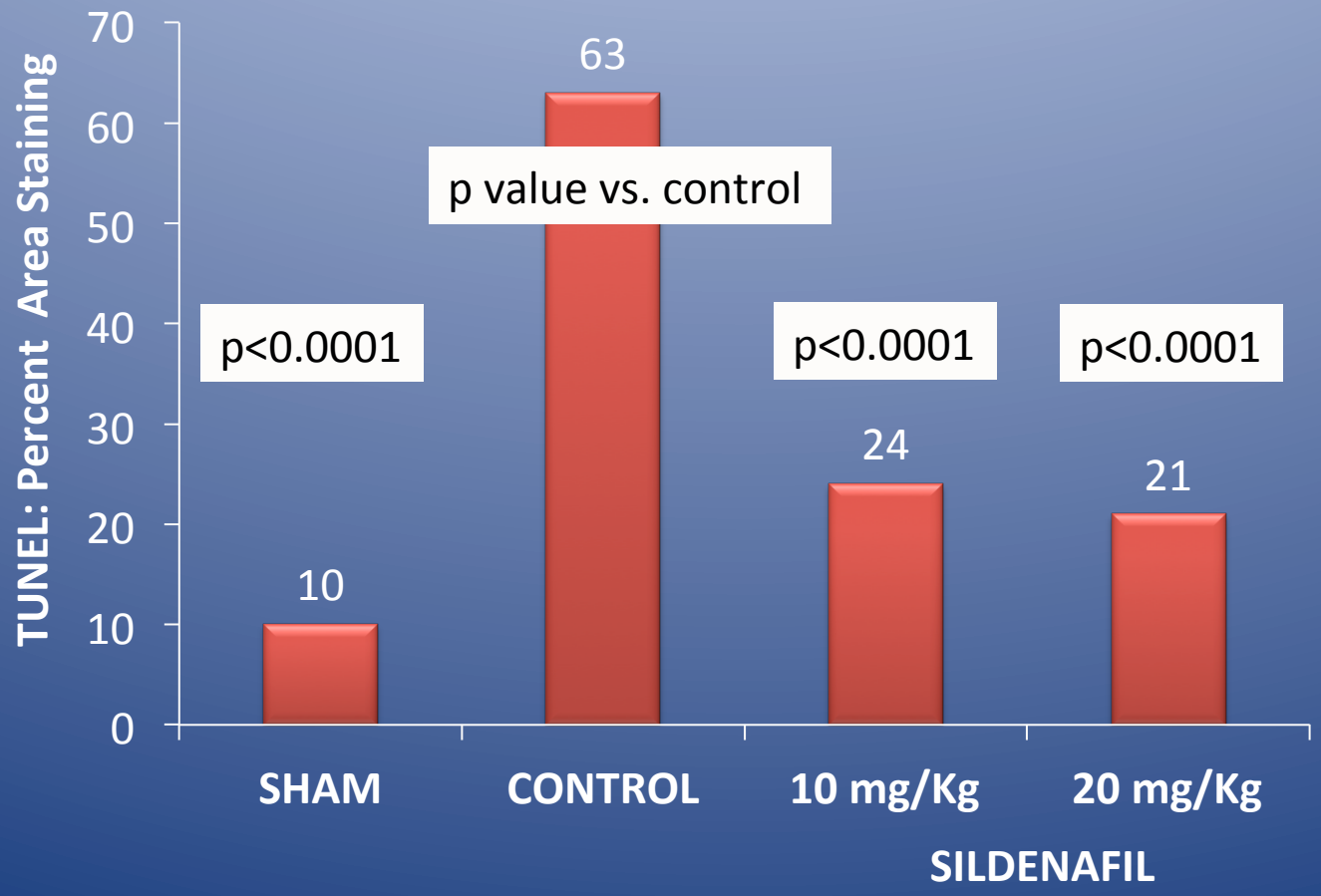
We don’t know…

Vardenafil prevents fibrosis



Ferrini et al, Urology. 2006

Corporal smooth muscle apoptosis: Effect of Sildenafil



Recommended rehabilitation strategy

- PDE5i
  - Endothel structure preservation[1,2]
  - Smooth muscle structure preservation[3]
  - Smooth muscle relaxation defense[4]
  - Neuroregeneration[5,6]
  - Erection indpendent cavernosal oxigenization?[7]

1. Rosano et al. Eur Urol 2004; 2. Desousa et al. Diabetes Care. 2002; 3. Schwartz et al J. urol. 2007; 4. Waxman et al. ESSM 2006; 5. Zhang et al. Stroke 2002; 6. Zhang et al. Brain Resaarch 2008; 7. Ghofrani et al. JACC 2004.

Erectile Function (EF) recovery

- Preoperative potency is a major factor
- Cavernosal nerves must be preserved
- Role of vascular insufficiency

- Preoperative vascular risk factors
- BMI
- Patient's age

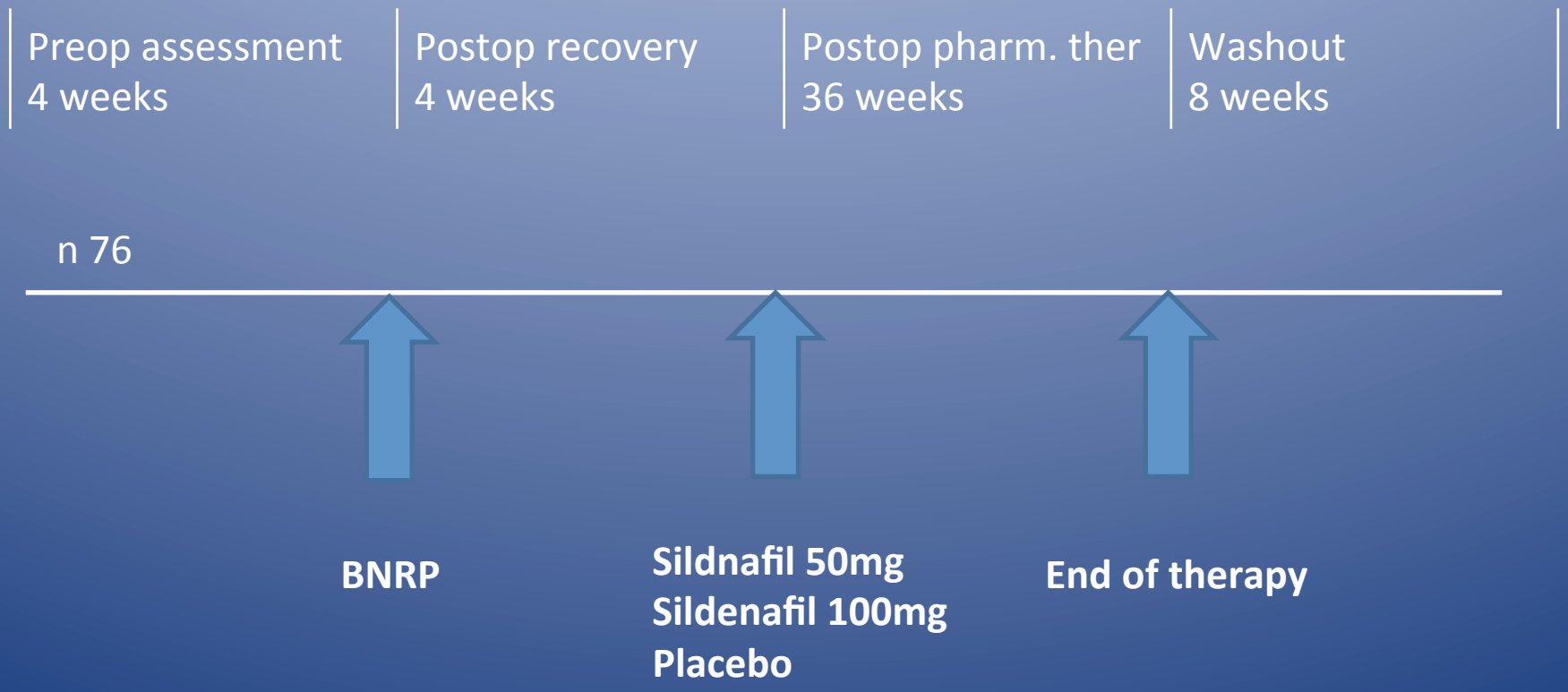
Use of PDE5I for post-RP ED

- Higher rates of erectile function recovery
- Any drug (therapeutic or prophylactic)
- Advantages:
  - demonstrated efficacy
  - ease of use
  - good tolerability
  - excellent safety
  - positive impact on QoL

BUT

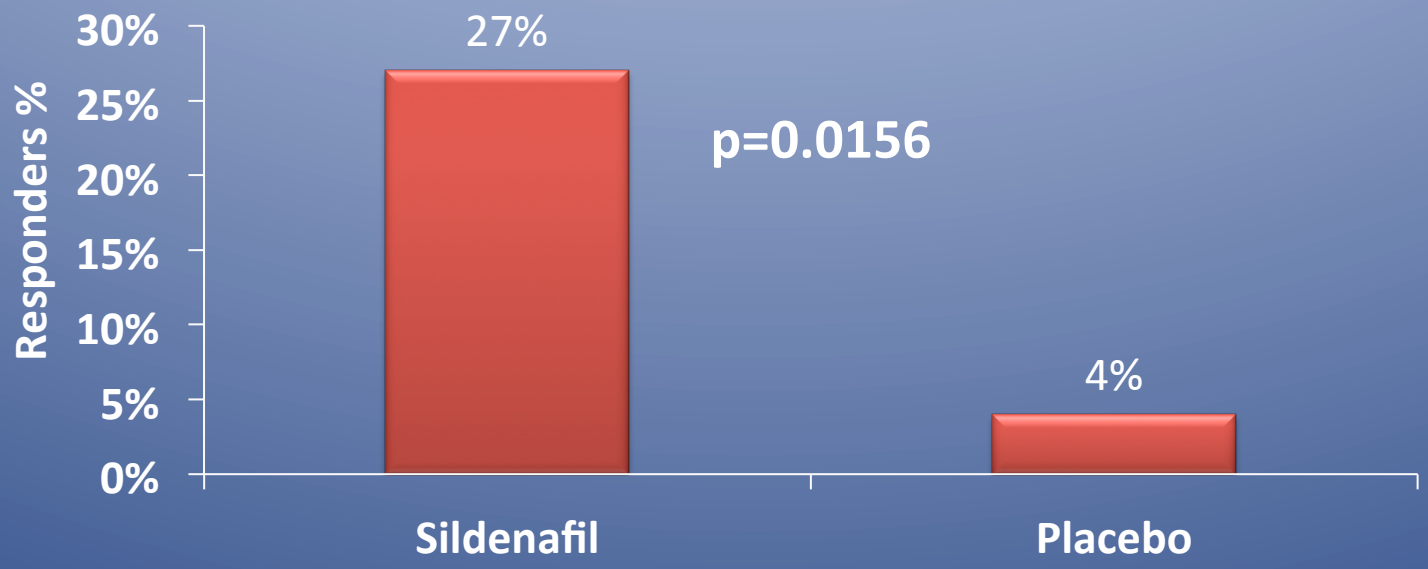
- post-RP ED patients are poor responders to PDE5Is

Randomized, double-blind, placebo-controlled study of postoperative nightly sildenafil citrate for the prevention of erectile dysfunction after BNRP



Padma-Nathan et al. Int J Impot Res, 2008

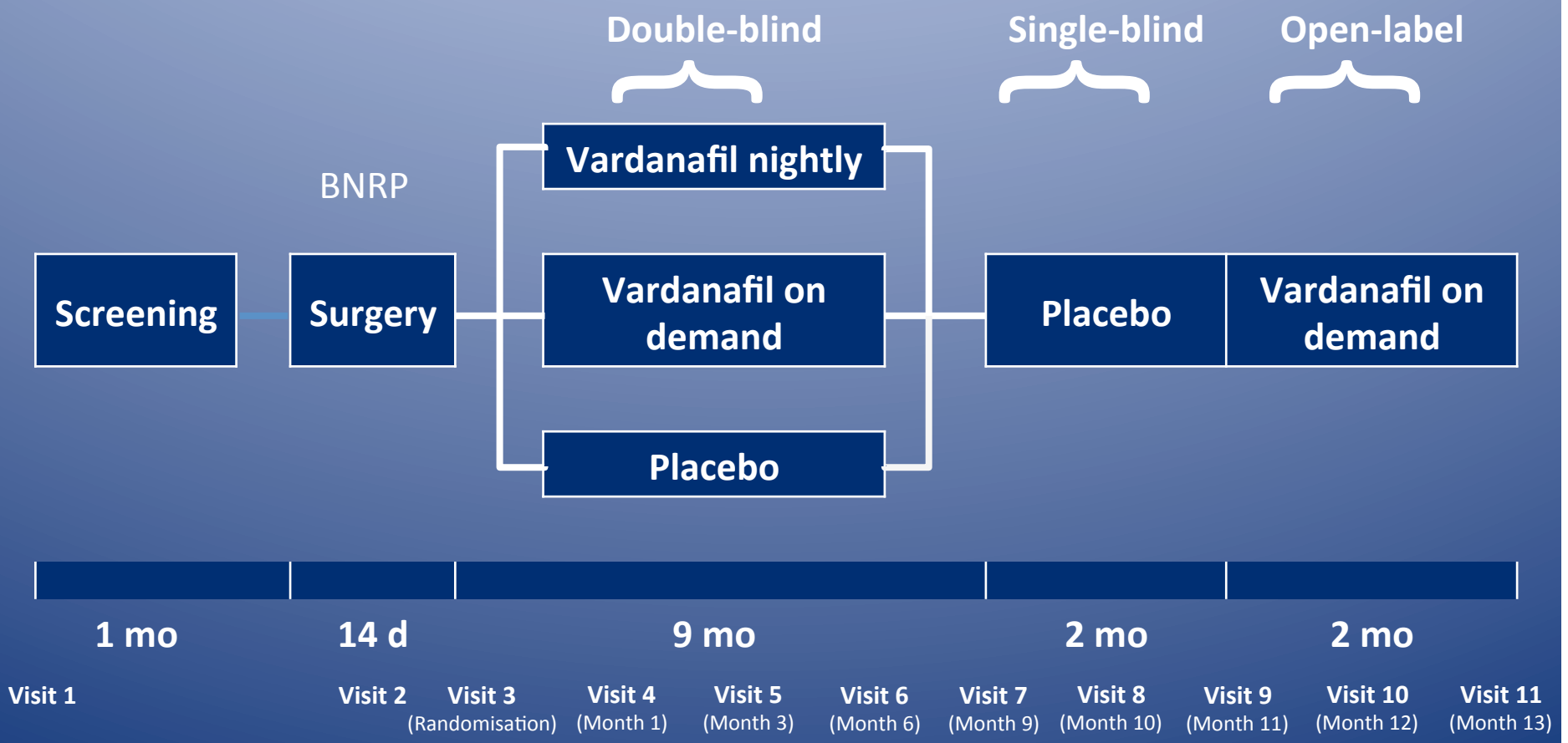
Responders



Responder def: IIEF Q3+4 ≥ 8
GEQ +
after 8 w washout
no erectogenic aids

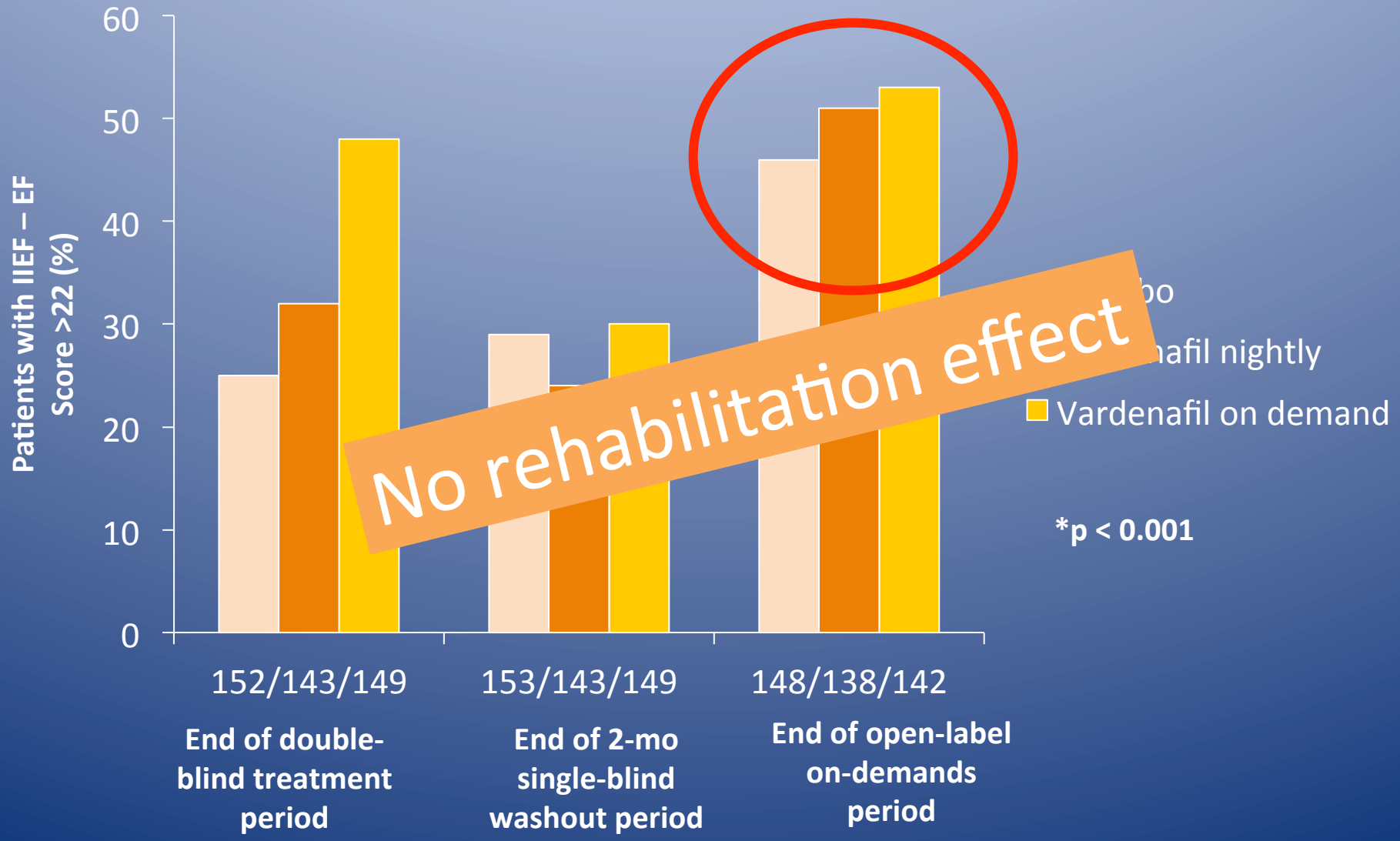
Padma-Nathan et al. Int J Impot Res, 2008

REINVENT (n 423)



Montorsi et al. Eur Urol. 2008

REINVENT



Montorsi et al. Eur Urol. 2008

Choosing the Best Candidates for Penile Rehabilitation after Bilateral Nerve-Sparing Radical Prostatectomy

Alberto Briganti, MD, Ettore Di Trapani, MD, Firas Abdollah, MD, Andrea Gallina, MD, Nazareno Suardi, MD, Umberto Capitanio, MD, Manuela Tutolo, MD, Niccolò Passoni, MD, Andrea Salonia, MD, Valerio DiGirolamo, MD, Renzo Colombo, MD, Giorgio Guazzoni, MD, Patrizio Rigatti, MD, and Francesco Montorsi, MD

Urological Research Institute, Department of Urology, University Vita-Salute San Raffaele, Milan, Italy

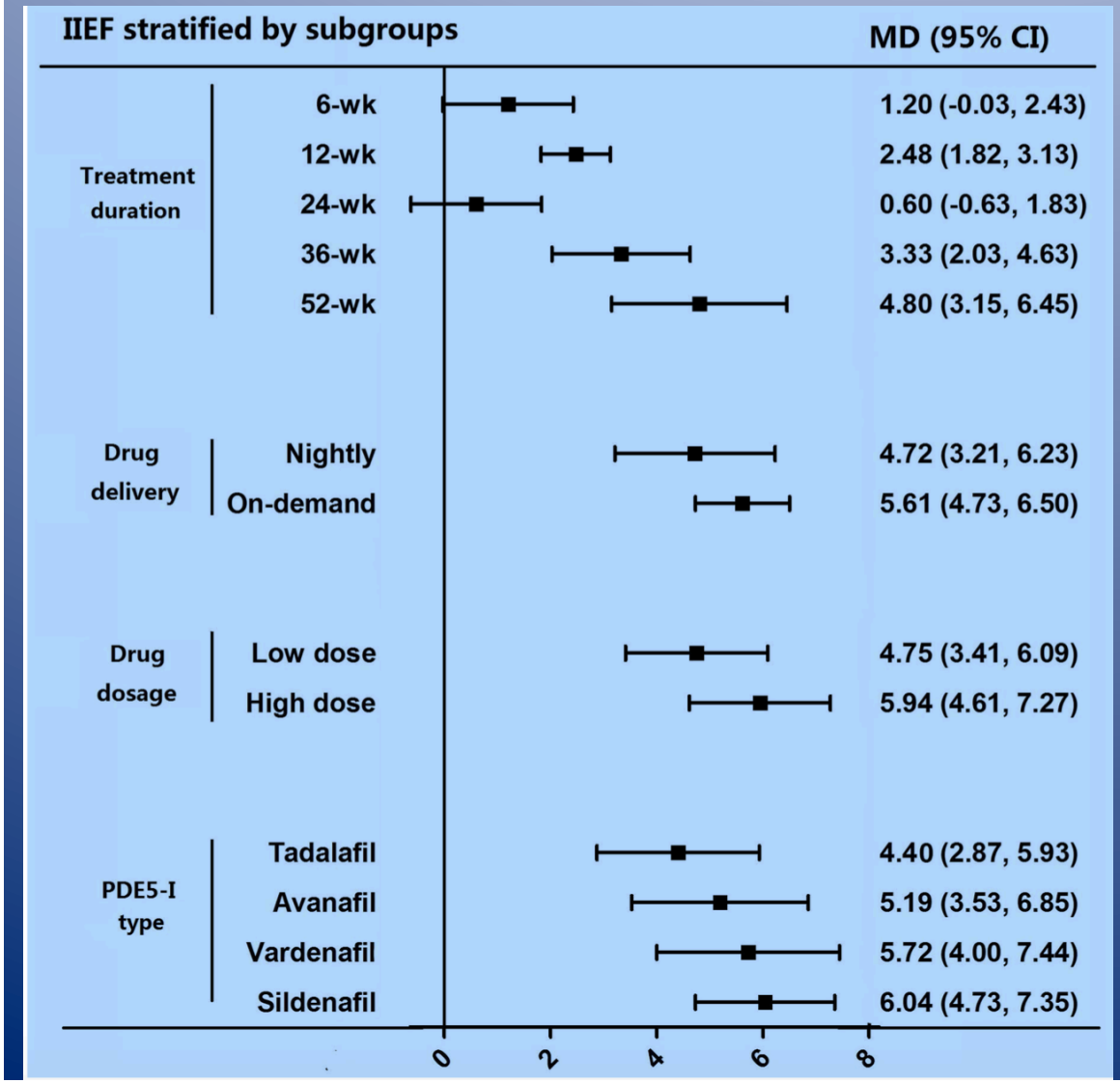
J Sex Med 2012;9:608–617

Patients' risk categorization

- low — age ≤65, IIEF-EF ≥26, CCI ≤1; N = 184
- intermediate — age 66-69 or IIEF-EF 11-25, CCI ≤1; N = 115
- high — age ≥70 or IIEF-EF ≤10 or CCI ≥2; N = 136

Intermediate 3-year EF recovery: 74% vs. 52% Daily vs. On demand

Systematic Review and Meta-Analysis of the Use of Phosphodiesterase Type 5 Inhibitors for Treatment of Erectile Dysfunction following Bilateral Nerve-Sparing Radical Prostatectomy



Xiao Wang et al,
Public Library of Science. 2015

Systematic Review and Meta-Analysis of the Use of Phosphodiesterase Type 5 Inhibitors for Treatment of Erectile Dysfunction following Bilateral Nerve-Sparing Radical Prostatectomy

- PDE5-Is efficacious and well tolerated
- Higher dose, longer course, on demand dosing, mild ED
  = greater responsiveness to PDE5-Is
- Direct comparisons MISSING
  Indirect comparison trend that sildenafil was more effective
- Statistical significance for these trends could not be obtained
- When to initiate, what dosage, duration of treatment, which drug is most efficacious, more clinical trials are required
- ATTENTION TO TRIAL DESIGN !!!

Xiao Wang et al, Public Library of Science. 2015

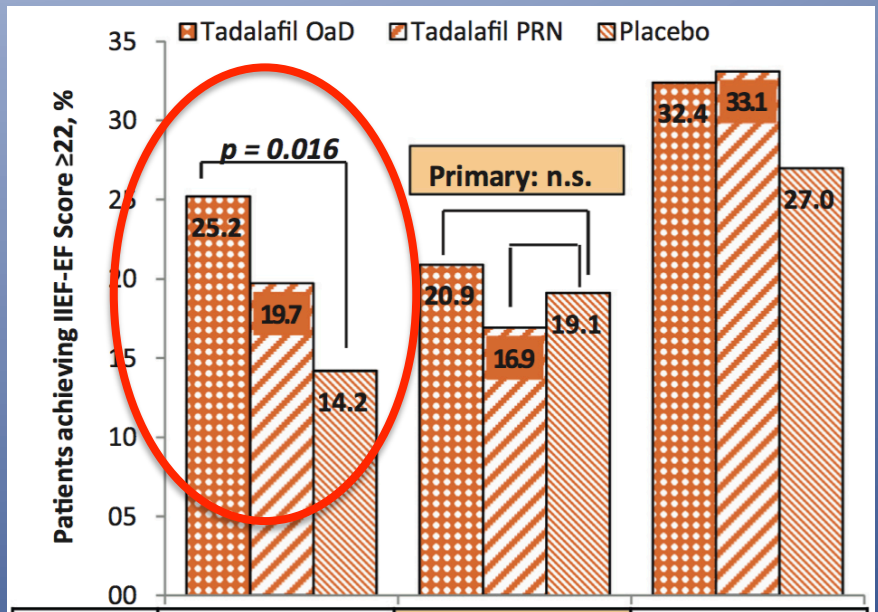
REACTT (n 423)

- Objective: PDE5i rehabilitative effect after BNRPE
- ~50 Center in Eurpe and Canada
- Randomised, double-blind, double-dummy, placebo- controlled trial
- Tadalafil 5mg Once daily vs. 20mg On demand vs Pbo
- 9 Mo Th - 6W Wo – 3 Mo Once daily
- Primary endpoint: IIEF-EF ≥22
- Secondary endpoints: SEP3, Penile length

Montorsi et al, Eur Urol. 2014

REACTT

- Completers: n 305
- IIEFΔ EDT
  - MCID achieved:
    - Once Daily arm
    - On demand arm



	Month 9	Month 10.5	Month 13.5
	OR (95% CI); *p value*		
OaD vs Placebo	**2.15 (1.16–3.99); *0.016***	1.14 (0.63–2.06); *0.675*	1.34 (0.79–2.28); *0.273*
PRN vs Placebo	1.50 (0.79–2.85); *0.210*	0.89 (0.48–1.65); *0.704*	1.35 (0.80–2.29); *0.259*

Montorsi et al, Eur Urol. 2014

REACTT

More effective

- SEP-3: MCID (>23%) Once a Day
- Penile length loss: Once a Day
  (significantly reduced)
- Treatment effect: Once a Day

'Unassisted EF was not improved after cessation of active therapy for 9 mo'

'data suggest a potential role for tadalafil once daily provided early after surgery in contributing to the recovery of EF after prostatectomy and possibly protecting from penile structural changes'

Montorsi et al, Eur Urol. 2014

A comparison of different oral therapies versus no treatment

- 196 NSRPE Bilateral (BP)-Unilateral (UP)
- Arms
  - OD: 100 mg sildenafil, 20 mg tadalafil or vardenafil
  - RR (regimented rehabilitation)
    - 3 days / week 100 mg sildenafil or 20 mg vardenafil or 20 mg tadalafil 2 days/ week
  - NT

Natali et al, J Impot Res. 2015

A comparison of different oral therapies versus no treatment

- EF recovery correlated:
  - surgical technique
    - -BP 68% (61% with no therapy and 71% with PDE5-Is)
    - -UP 44% (29% with no therapy and 51% with PDE5-Is
  - OT when compared to NT (P < 0.02)

- No differences:
  - between OD a… …tocols
    - …ilitation and 70% with OD therapy)
    - …% with rehabilitation and 50% with OD therapy)

Rehabilitation protocol not superior

Natali et al, J Impot Res. 2015

Efficacy and safety of PDE5Is after BNSRPE

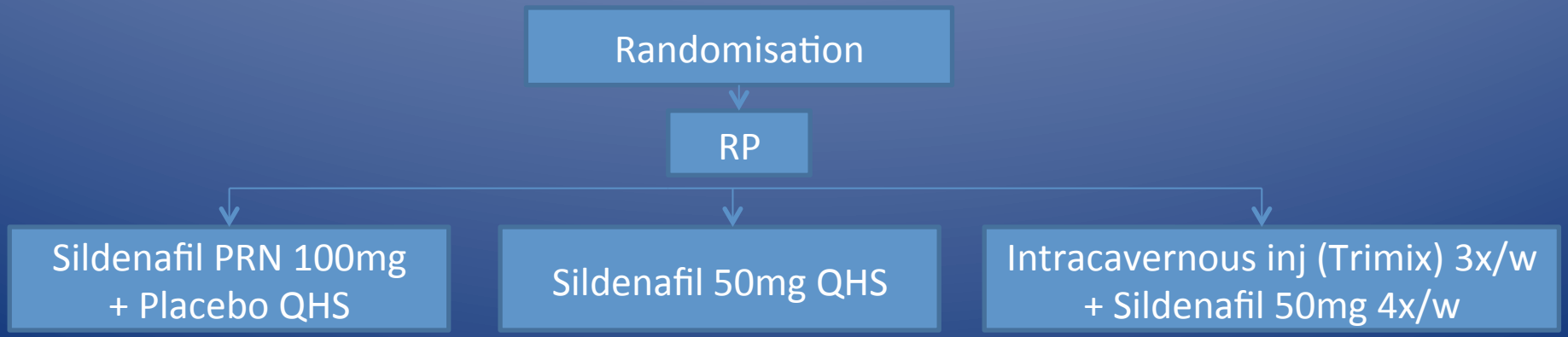
- systematic review and meta-analysis
  - All RCT; MEDLINE, Cochran Controlled Trials Register, EMBASE = 6 RCT
- Primary endpoints
  - IIEF-EF SMD 4.04
  - SEP2
  - SEP3 47
- A[illegible]ne (12.08%), dyspepsia (6.76%) flushing (6.52%)

PDE5I Effective and well tolerated

Cui Y et al Andrologia. 2015 Feb

Pharmacological Penile Rehabilitation in the Preservation of Erectile Function Following Bilateral Nerve-Sparing Radical Prostatectomy /Ongoing TRIAL/

- PI: John P. Mulhall MD MSKCC
- Randomised patients had IIEF-EFD score ≥22
- 12 Mo treatment - 24 Mo follow up
- Primary endmpoint:: ΔIIEF-EFD score



Conclusions

- Effective sexual rehabilitation:
  - Strong evidences in animal research
  - Conflicting / Promising results in human research
- Widely accepted and used PDE5is
- Initiation, dosage, duration, agent not determined
- Expensive

Thank you for your attention