Penile Rehabilitation after Radical Prostatectomy

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Post-Radical Prostatectomy Sexual Dysfunctions

- Erectile dysfunction (ED)
- Anejaculation
- Anorgasmia
- Dysorgasmia (painful ejaculation)
- Orgasm associated urine leak (climacturia)
- Penile length alterations
- Penile curvature

Sexual Dysfunction After Radical Prostatectomy

- Despite nerve-sparing surgery RP leaves 25 to 75% of patients with ED (Hollenbeck et al. 2003; Cooperberg et al. 2003; Schover et al. 2002; Meyer et al. 2003; Hu et al. 2004; Penson et al. 2005)
- Meta-analysis: 54 long-term studies found 75% with ED at least 2 years post-RP (Robinson et al. 2002)
- Stanford Study (n=1291): 40% to 55% of bilateral NS patients experienced ED at 18 mos (Stanford et al. 2000)
- Penson Study (n=1288): found 72% with ED at least 5 years post-RP (Penson et al. 2005)
    - Long-term ED post RP: ***40% to 75%*** (Matthew et al. 2005)

Risk Factors of Post-Prostatectomy ED: Patient Factors

- **Age more than 60 years**
- **Vascular diseases**
- **Diabetes**
- **Dyslipidemia**
- **Smoking**
- **High stage of disease**
- **Non-motivated partner**
- **PDE_5-I user**
- **Obesity**

Assessment of a patient's preoperative erectile function is essential.

Using a validated questionnaire, e.g. International Index of Erectile Function (IIEF) may help diagnose and determine the severity of erectile dysfunction

Is it a 'real' Problem: Distress specific to Sexual Dysfunction Post-RP

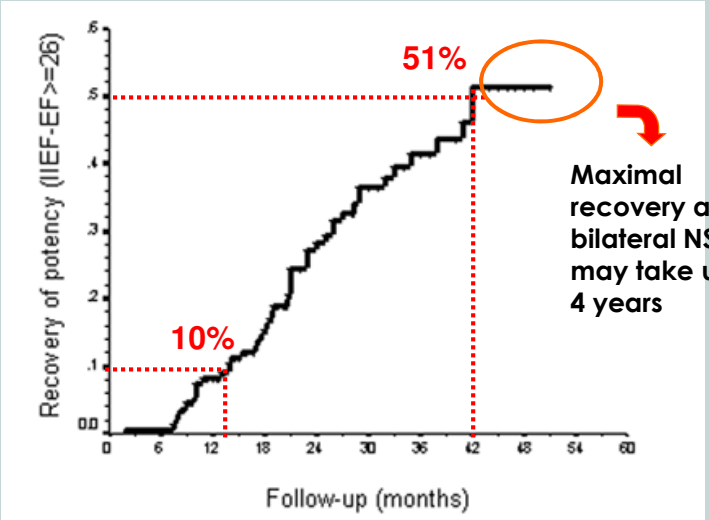
- Distress re SD: *60%* of patients reported moderate to severe distress (Stanford et al. 2000; Cooperberg et al. 2003; Schover et al. 2002)
- In a quality of life study on 1-year post-surgery patients:
  - only 12% reported fear of cancer recurrence
  - 40% reported sexual dysfunction concerns (Heathcote et al. 1998)
- Distress is especially elevated in younger men (Cooperberg et al. 2003; Stanford et al. 2000)
- Partners experience greater distress (Neese, L. E., 2003)

Potency Recovery after Surgery Memorial Sloan Kettering

- N=200 potent men
- Bilateral NSRRP (July 1998 - April 2002)
- Completed follow-up IIEF up to 51 months
- 49% used PDE5 inhibitors post-op
- Actuarial rates of recovery of potency to 4 years

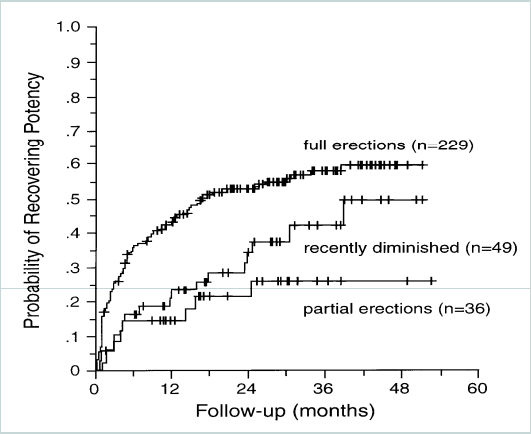
Rabbani et al., AUA 2004

Potency Recovery after Surgery



Rabbani et al., AUA 2004

Recovery of Erections According to Preoperative Sexual Functioning



Rabbani F, et al. *J Urol*. 2000;164:1929-1934.

Agents/Devices…solution??

Assistive aids vary in invasiveness and effectiveness:

1) *Oral Medications* (PDE-5 inhibitors)

- effectiveness in post-RP patients *30-60%* (Brock 2003, Montorsi 2004, Cavallini 2005, Montorsi 2008)

2) *Intracavernous Injections*

- effectiveness in post-RP patients *85%* (Hanash 1997)

3) *Micro-suppositories*

- effectiveness in post-RP patients *57%* (Costabile et al. 1998)

4) *Vacuum device*

- effectiveness in post-RP patients *80%* (Raina et al. 2002)

5) *Penile implant*

- satisfaction rates of *85%* (Carson et al. 2000)

Low rates of ongoing use

- The high success rates assistive aids are offset by low rates of ongoing use
- Only *20-40%* of men remain sexually active at 1-5 yrs. post-RP despite access or attempted use of pro-erectile aids/devices (in many cases 2 or more aids) (Hanash 1997; Althof 2002; Hu et al. 2004; Penson 2005)

Post-RP ED Mechanisms

- Neurogenic
  - Degree/type of trauma required for neuropraxia?
  - Anatomic vs functional integrity
  - Neural trauma leads to structural changes in erectile tissue
  - Denervation apoptosis
- Arteriogenic
  - Arterial injury (accessory pudendal arteries)
- Venogenic
  - Cavernosal hypoxia-induced fibrosis with venous leak
- Psychogenic
  - Impact of cancer diagnosis on erectile function
  - Impact of anxiety centered on re-initiation of intimacy

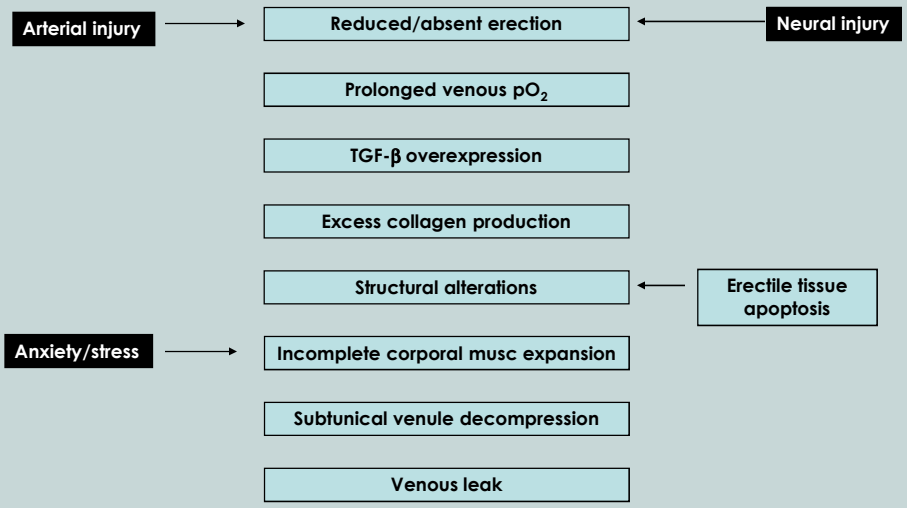
Mulhall JP, et al. *Int J Impot Res*. 1996;8:91-94. Rodriguez-Vela L. Actas *Urol Esp*. 1997;21:909-921. Aboseif S. *Br J Urol*. 1994;73:75-82. User H, et al. *J Urol*. 2001;165:531-533.

Cavernosal Oxygenation

Flaccid	Erect
Flaccid	Penile erection
↓	↓
pO_2 = 35 mm Hg	pO_2 > 70 mm Hg
↓	↓
Increased TGF secretion	Increased PGE secretion
↓	↓
Collagen production	Decreased collagen production

PGE=prostaglandin E.
TGF=transforming growth factor.

Postprostatectomy ED: Proposed Mechanism



What is penile rehabilitation?

- Penile rehabilitation is performed with the aim of achieving better and/or earlier spontaneous erectile recovery compared with no rehabilitation by:
  - Preservation of penile smooth muscle
  - Preservation of endothelial function
  - Optimization of cavernous nerve recovery

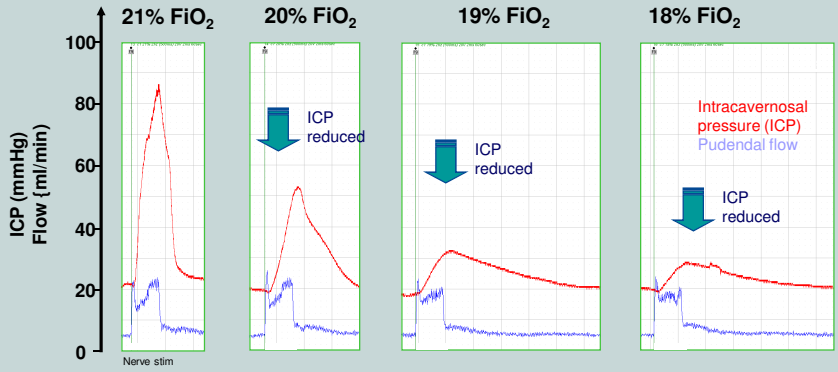
Penile Rehabilitation

Central to the argument supporting Rehab:

1. Apoptosis (nerve injury)
2. Loss of NPT (oxygen)
3. Compensation by early therapy
   - Endothelial benefits
   - Enhanced nerve regeneration
   - Preservation of cavernous smooth muscle

Systemic Hypoxia
Reduced Erection Hardness (ICP)

Pre-clinical model

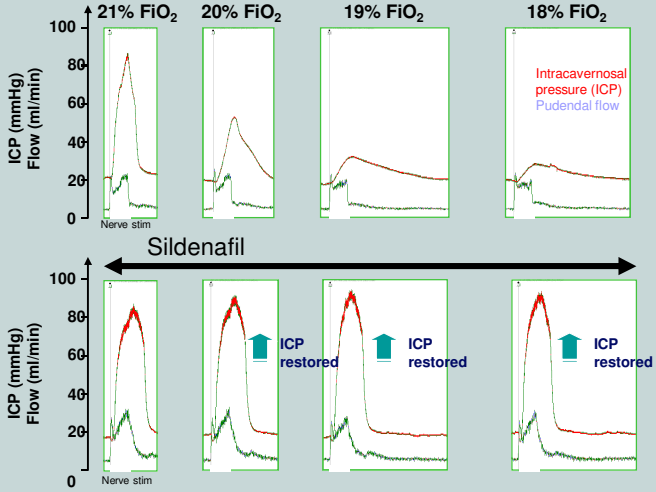


- **Systemic hypoxia reduces ICP**
- **Illustrates importance of sufficient penile oxygenation for effective nitrergic signalling (i.e. induction and maintenance of penile erection)**

Wayman C et al. ESSM. 4-7 Dec 2005. Poster P-01-153.

Sildenafil Overcame Systemic Hypoxia-Induced ED

Pre-clinical model



Wayman C et al. ESSM. 4-7 Dec 2005. Poster P-01-153.

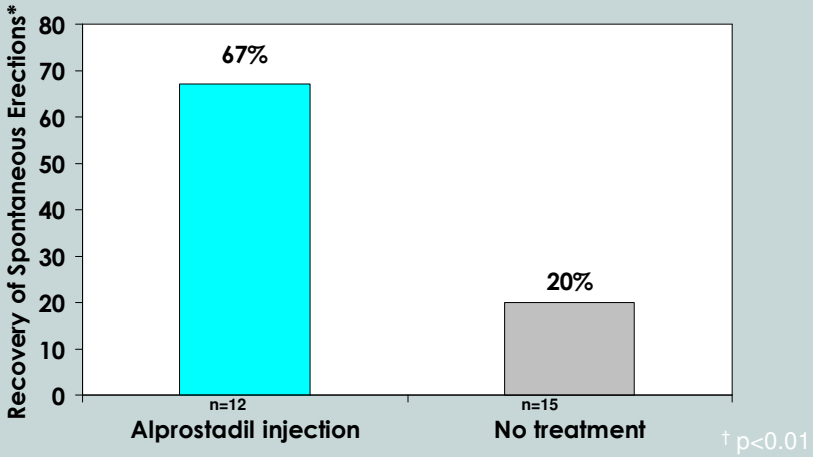
Alprostadil Injection study

Montorsi et al., J Urol 1997; 158: 1408-1410

- 30 patients randomized
- Group 1(n=15): alprostadil injections 3 times/week for 12 weeks
- Group 2 (n=15): observation without erectaids

- Patient-reported recovery of spontaneous erections sufficient for satisfactory sexual intercourse

Alprostadil Injections
Results



Montorsi et al., J Urol 1997; 158: 1408-1410

Hypothesis:
Nightly Post-Operative Sildenafil Dramatically Improves the Return of Spontaneous Erections Following a Bilateral NS-RRP

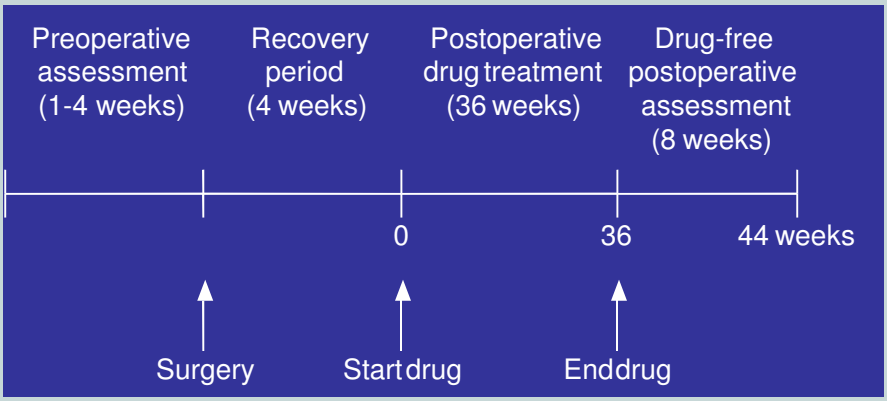
Padma-Nathan H, McCullough A, Giuliano F, et al. AUA 2003, Chicago

Methodology

- Double-blind, placebo controlled, multicentre, randomized clinical trial
- 76 men (≤65 yrs) with ***normal preoperative EF***
- Combined score of ≥8 for IIEF questions 3 &4
- Normal nocturnal penile tumescence (NPT)
- Scheduled to undergo a bilateral NSRRP
- 50 mg, n=23; 100 mg, n=28; Placebo, n=25

Padma-Nathan H et al. AUA 2003, Chicago

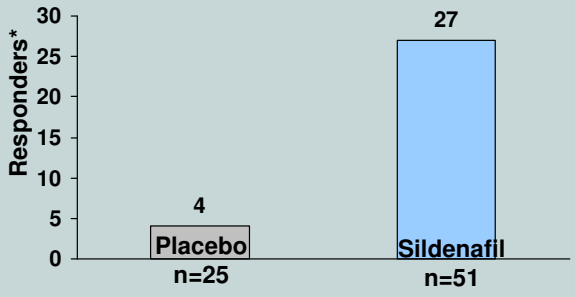
Prevention Study Design



Padma-Nathan H, McCullough A, Giuliano F, et al. AUA 2003, Chicago

Effects of nightly sildenafil treatment on recovery of spontaneous erections: results

Nightly sildenafil (50–100 mg) *vs* placebo after 36 weeks of treatment



†p=0.0156

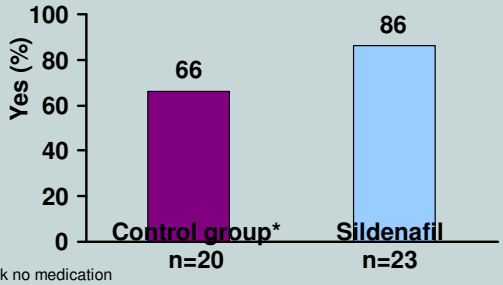
*Responders: patients with combined IIEF Q3/4 score of ≥8 and positive response to question: "Over the past 4 weeks, have your erections been good enough for satisfactory sexual activity?" at 8 weeks after discontinuation of drug

Padma-Nathan et al. AUA 2003, Chicago.

Potency rate following treatment with nightly sildenafil 25 mg (1 year) followed by sildenafil on-demand

43 patients; 95% had nocturnal erections 2 weeks after surgery

Patients able to achieve and maintain an erection long enough for successful intercourse



*Control group took no medication before the on-demand period

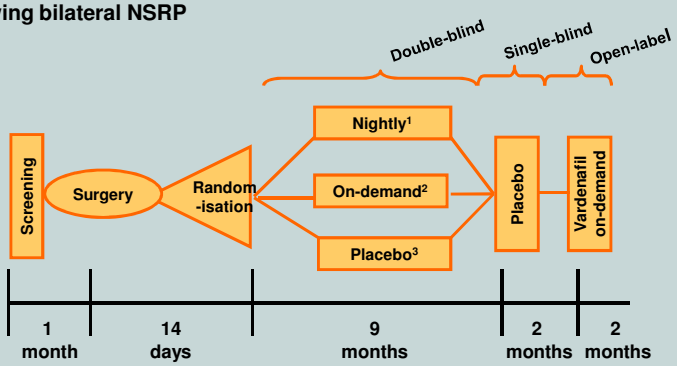
Bannowsky et al. *BJU Int* 2008; 101: 1279–83.

Limitations of existing studies

- Padma-Nathan et al. 2003:
  - Small sample size (N=76)
  - Single centre
  - Did not compare nightly dosing with on-demand use of a PDE-5 inhibitor
- Bannowsky et al. 2008
  - Small sample size (N=43)
  - Single centre of surgical excellence – does not reflect general worldwide urological practice
  - Not placebo-controlled
  - 95% of patients had nocturnal erections following catheter removal – not typical of post-surgical situation in general urological practice

Recovery of erections – intervention with vardenafil early nightly therapy (REINVENT): study design

Randomised, double-blind, double-dummy, multicentre, parallel-group comparison of vardenafil nightly or on-demand *vs* placebo in men immediately (within 14 days) following bilateral NSRP



1) 10 mg nightly vardenafil (which could be decreased to 5 mg if required) plus on-demand placebo;
2) flexible-dose on-demand vardenafil (starting at 10 mg with option to titrate to 5 mg or 20 mg) plus nightly placebo;
3) nightly placebo plus on-demand placebo

Montorsi et al. *Eur Urol. 54:924;* 2008

REINVENT: study endpoints

Primary endpoint:

- % of subjects with IIEF-EF domain score ≥22 after 9 months of double-blind treatment plus 1–2 months of single-blind treatment

Secondary endpoints:

- Measures of erectile function
  - Mean per-patient success rates from diary questions (SEP2 and SEP3)
  - IIEF-EF domain score of ≥17, ≥22, ≥26
  - IIEF domain total scores
  - RigiScan at select sites
- Quality of life measures
  - Center for Epidemiologic Studies Depression Scale (CES-D)
  - Duke Health Questionnaire
- Other measures
  - Vascular biomarkers
  - Flaccid and stretched penile length

Montorsi et al. *Eur Urol. 54:924;* 2008

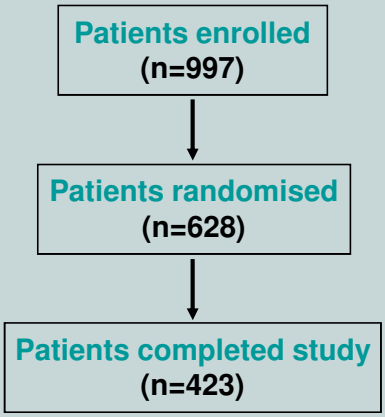
REINVENT: Centers (88) and Countries (15)

Country	Centers	Patients*
Austria	2	34
Belgium	6	62
Canada	11	90
Switzerland	1	3
Germany	12	184
Spain	7	64
Finland	3	68
France	5	88
UK	6	21
Italy	8	140
Netherlands	3	8
Norway	2	24
Sweden	6	65
USA	11	101
South Africa	5	45

*number of patients enrolled

Montorsi et al. *Eur Urol. 54:924;* 2008

REINVENT: patient disposition



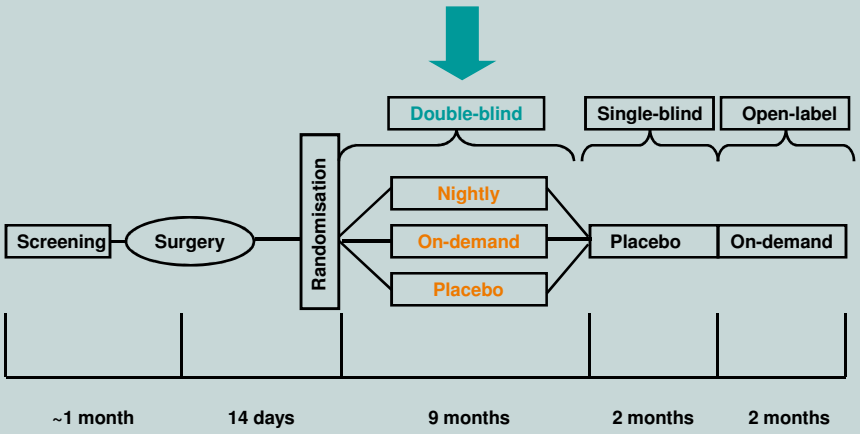
Montorsi et al. *Eur Urol. 54:924;* 2008

REINVENT: patient baseline characteristics (mITT population)

Mean values	Total N=445
Age (years)	57.1
BMI (kg/m^2)	26.9
Baseline IIEF-EF score*	28.5
Marital status (%):	
Married	91
Divorced	5
Widowed	2
Never married	2

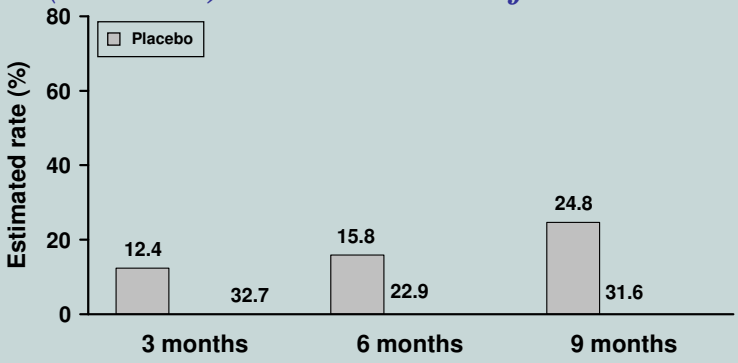
*Pre-surgery baseline measurement
mITT population (patients with at least one IIEF-EF measurement during the single-blind placebo washout period)

REINVENT: results from double-blind treatment period



Montorsi et al. *Eur Urol. 54:924;* 2008

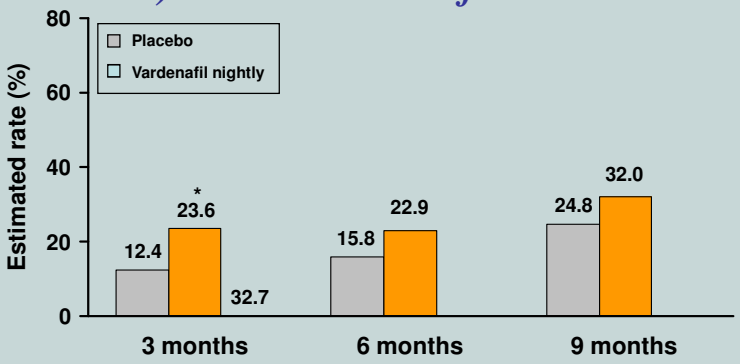
REINVENT: IIEF-EF domain score ≥22 (mild ED) over 9 months of treatment



mITT population (at least one IIEF-EF measurement during the single-blind placebo washout period)

Montorsi et al. *Eur Urol* 2008; in press.

REINVENT: IIEF-EF domain score ≥22 (mild ED) over 9 months of treatment

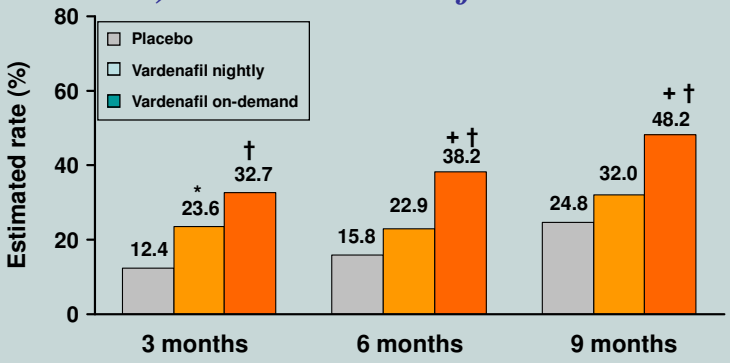


*p=0.0144 for comparison of vardenafil nightly *vs* placebo
(For all secondary variables, p<0.05 considered to be nominally significant)

mITT population

Montorsi et al. *Eur Urol* 2008; in press.

REINVENT: IIEF-EF domain score ≥22 (mild ED) over 9 months of treatment

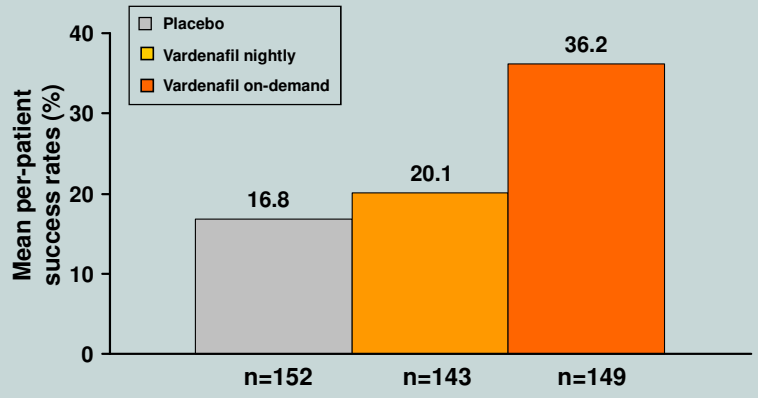


*p=0.0144 for comparison of vardenafil nightly *vs* placebo
†p≤0.0001 for comparison of vardenafil on-demand *vs* placebo
+p<0.01 for comparison of vardenafil on-demand *vs* nightly
(For all secondary variables, p<0.05 considered to be nominally significant)

mITT population

Montorsi et al. *Eur Urol* 2008; in press.

*REINVENT: IIEF-EF domain score ≥26 (normal EF) over 9 months of treatment**



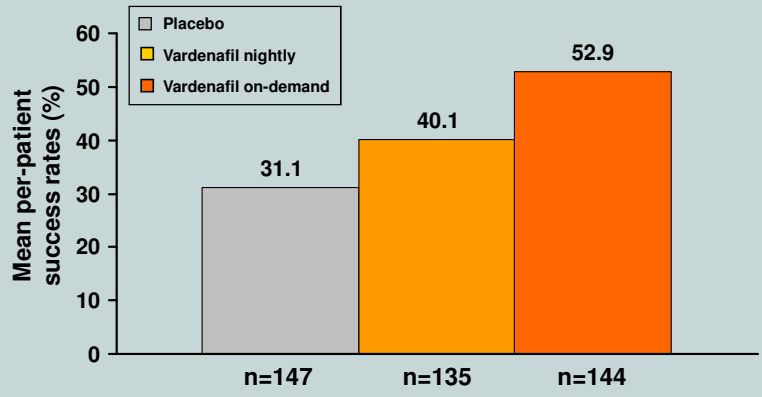
p<0.0003 for the comparison of on-demand *vs* placebo
p=0.479 for the comparison of nightly *vs* placebo

*Observed at last observation carried forward (LOCF)

mITT population

Montorsi et al. *Eur Urol. 54:924;* 2008

*REINVENT: SEP3 success rates after 9 months of treatment at LOCF**



p<0.0001 for the comparison of on-demand *vs* placebo
p=0.0753 for the comparison of nightly *vs* placebo

*Observed at last observation carried forward (LOCF)

mITT population

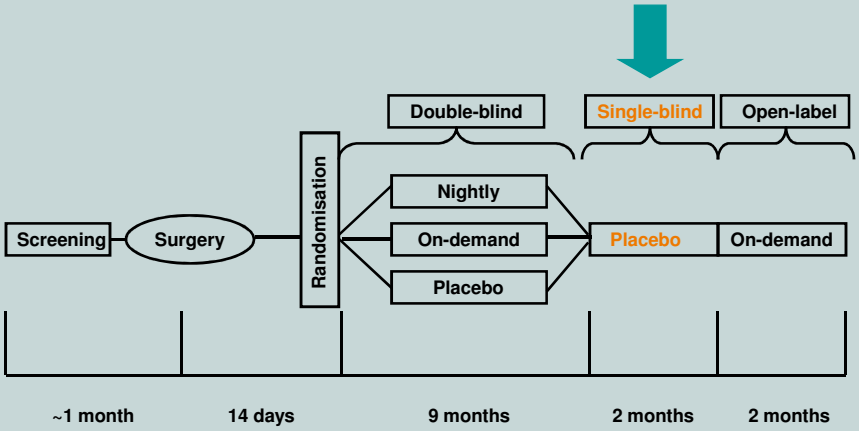
Montorsi et al. *Eur Urol. 54:924;* 2008

REINVENT: summary of results from double-blind treatment period

- At all double-blind visits, a significantly greater proportion of patients in the vardenafil on-demand group had IIEF-EF scores ≥22 compared with the placebo group (p≤0.0001)
  - At double-blind LOCF, a significantly greater proportion of patients in the vardenafil on-demand group had IIEF-EF scores ≥22 compared with the placebo group (p=0.0001)
  - The proportion of patients in the vardenafil on-demand group with IIEF-EF scores ≥22 was significantly greater than the vardenafil nightly group at several visits and at double-blind LOCF (p=0.0065)
- Over the entire double-blind treatment period:
  - Significantly greater mean per-patient SEP3 success rates were observed with vardenafil on-demand compared with placebo (p<0.0001)
  - Significantly greater mean per-patient SEP3 success rates were observed with vardenafil nightly compared with placebo (p=0.0344)

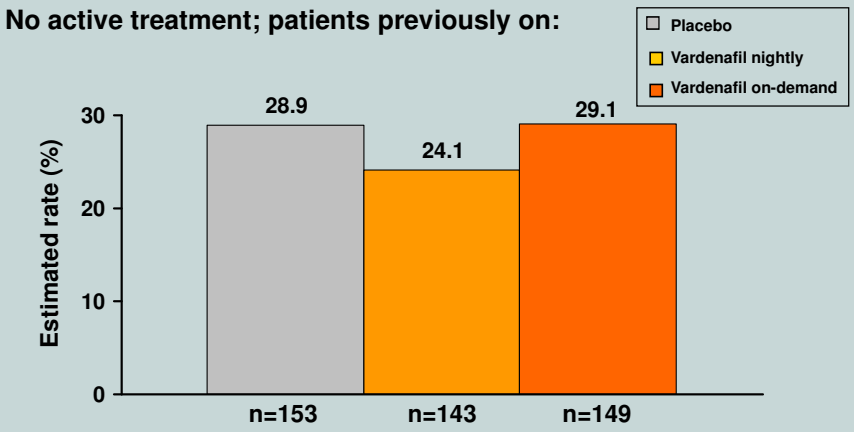
Montorsi et al. *Eur Urol. 54:924;* 2008

REINVENT: results from single-blind placebo washout period



Montorsi et al. *Eur Urol. 54:924;* 2008

*REINVENT: IIEF-EF domain score ≥22 (mild ED) after 2 months of washout (primary efficacy variable)**

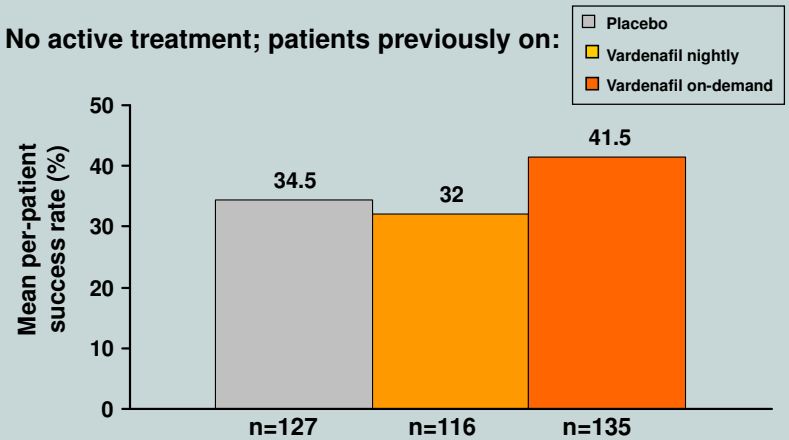


All between group comparisons non-significant
mITT population

*Observed at LOCF

Montorsi et al. *Eur Urol. 54:924;* 2008

*REINVENT: SEP3 success rates after 2 months of washout**



All between group comparisons non-significant
mITT population

*Observed at overall single-blind time point

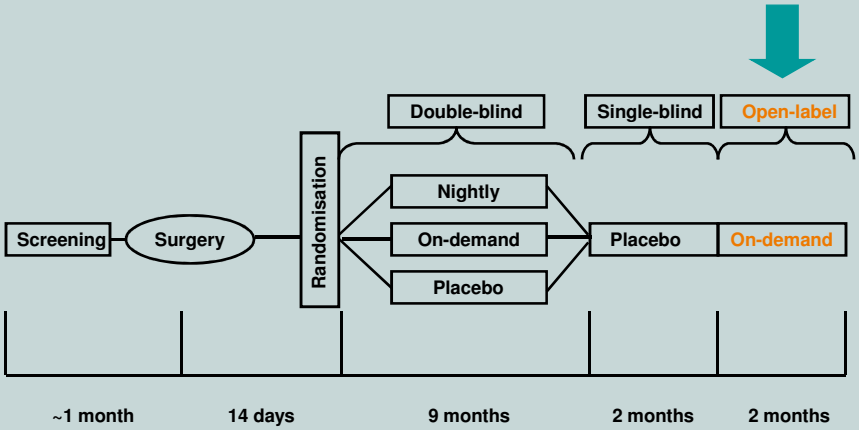
Montorsi et al. *Eur Urol. 54:924;* 2008

REINVENT: summary of results from single-blind washout period

- The primary efficacy variable was not met:
  - No statistically significant differences between treatment groups in the percentage of patients with IIEF-EF scores ≥22 at end of 2-month washout period (LOCF)
- No significant differences between treatment groups in the proportions of patients with IIEF-EF scores ≥17 or ≥26
- No significant differences between treatment groups in SEP3 mean per-patient success rates

Montorsi et al. *Eur Urol. 54:924;* 2008

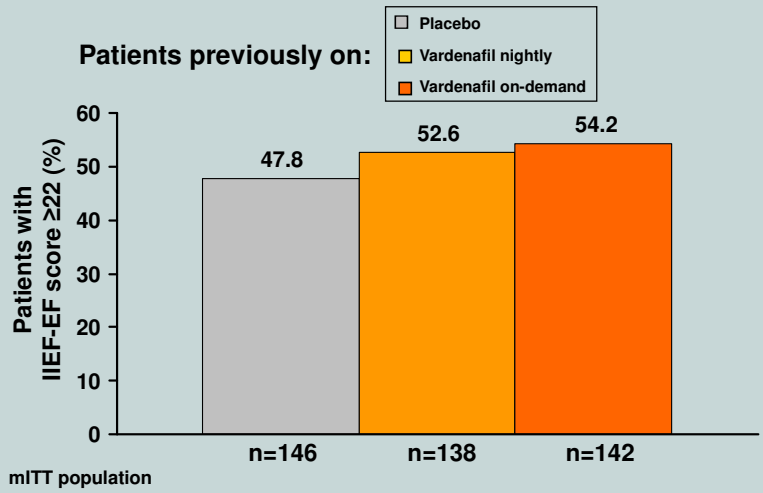
REINVENT: results from open-label period



*vardenafil on-demand at a starting dose of 10 mg for 1 month, after which the dose could be adjusted to either 5 or 20 mg.

Montorsi et al. *Eur Urol. 54:924;* 2008

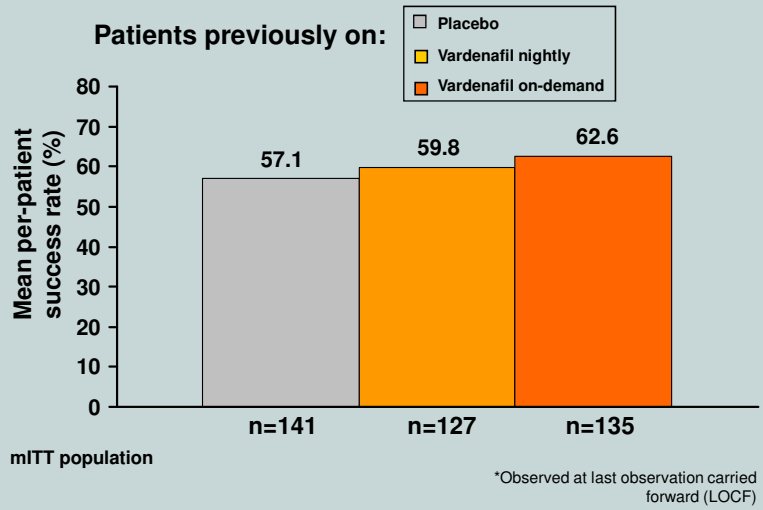
*REINVENT: IIEF-EF domain score ≥22 after 2 months of open-label on-demand vardenafil treatment**



*Observed at LOCF

Montorsi et al. *Eur Urol. 54:924;* 2008

*REINVENT: SEP3 success rates after 2 months of open-label on-demand vardenafil treatment**



*Observed at last observation carried forward (LOCF)

Montorsi et al. *Eur Urol. 54:924;* 2008

REINVENT: summary of results from open-label period

- No significant differences between the proportions of with IIEF-EF scores ≥22 at LOCF, irrespective of original treatment group
- No significant differences between treatment groups in mean SEP3 per-patient success rates
  - Mean SEP3 per-patient success rates of approximately 60% achieved following 2 months of on-demand vardenafil treatment, irrespective of original treatment group

Montorsi et al. *Eur Urol. 54:924;* 2008

REINVENT: adverse events

- A total of 39 patients discontinued the study due to adverse events (AEs)
- No difference between treatment groups in the percentage of patients that discontinued due to AEs (vardenafil nightly 8%; vardenafil on-demand 6%; placebo 5%)
- Most common AEs were headache, flushing and nasopharyngitis

Montorsi et al. *Eur Urol. 54:924;* 2008

REINVENT: Problems

- Conducted over 3 years at 88 centres; only 423 completed (dropout>30%) so mean # pts per centre <5 (?homogeneity of NS technique)
- No documentation of compliance rates in nightly or on-demand groups (Potential confounder:total # of vardenafil pills used in each group?)
- True blinding difficult to achieve in these types of studies (how motivated can these pts be if they stay on 9 months of placebo!)
- Duration of study too short as so many men recover at 18-24 months

Montorsi et al. *Eur Urol. 54:924;* 2008

REINVENT: conclusions

- In this study, the primary efficacy variable was not met:
  - After 9 months of treatment plus 2 months of washout, nightly dosing with vardenafil did not show any effect beyond that of on-demand use on recovery of erectile function.
- Vardenafil on-demand showed good efficacy in this notoriously difficult-to-treat patient population with ED.
- Vardenafil on-demand was observed to work early after NSRP.
- Methodologic problems do not justify the authors conclusions that the data supports a shift to on-demand PDE5i.
- Need to perform more trials of on-demand vs nightly dosing

An Approach to Rehab:
Pre-Radical Prostatectomy

- Manage EXPECTATION
- Awareness of potential changes in sexual response
- Awareness of available ED treatments (trial PDE5i)
- Awareness of rationale for early ED treatment approach

An Approach to Rehab:
Immediate post op

- Early therapy is encouraged
- Based on recent reports we initiate ASAP with low dose PDE5i (sildenafil 25, vardenafil 5-10, tadalafil 5) nightly
- As soon as patient is dry and libido returns, may switch to on-demand dosing
- If rigidity with PDE5i is suboptimal
  - Full dose PDE5i
  - ICI
  - Pump

An Approach to Rehab:
3 to 6 months post-RP

- Sexual Health Psychotherapy
  - Normalize distress
  - Assessment of partner's sexual functioning
  - Intimacy Counselling and Couple Communication
  - Resume Sexual Activity (intercourse or non-intercourse)

An Approach to Rehab:
Beyond 12 months post-RP

- Determine EFFECTIVE ED TREATMENT
- Focus on partner concerns
- Maintenance of INTIMACY and SEXUAL ACTIVITY
- ADAPTATION to changes in sexual response
- ACCEPTANCE of sexual activity (intercourse or non-intercourse)

Improving QOL outcomes after RP