DISFUNZIONE ERETTILE

Terapia farmacologica

SISTEMICA: ENDOCRINA

NON ENDOCRINA

LOCALE: INTRACAVERNOSA

INTRAURETRALE

TRANSDERMICA

DISFUNZIONE ERETTILE

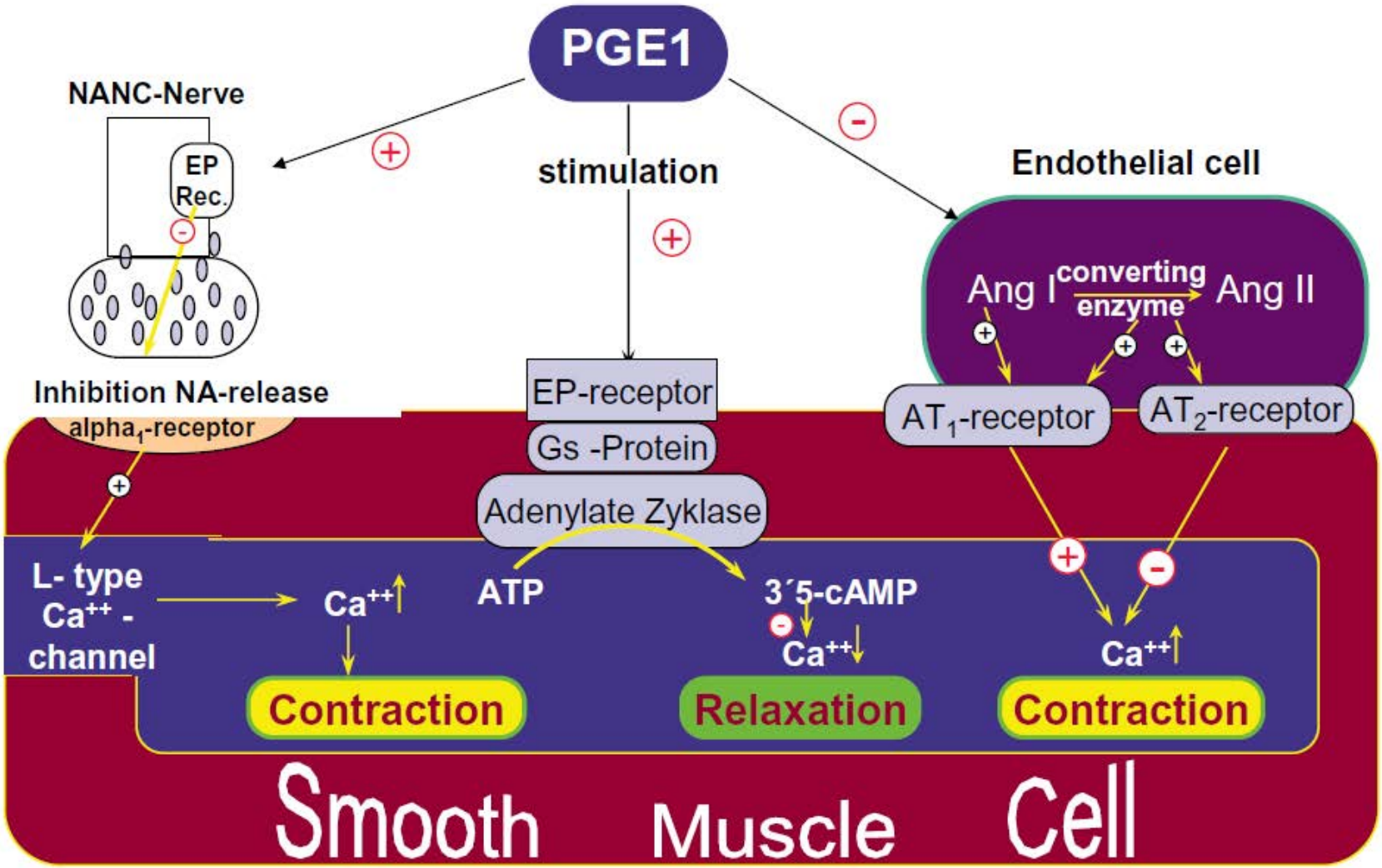
Terapia farmacologica locale

INTRACAVERNOSA	INTRAURETRALE	TRANSDERMICA
PGE-1	PGE-1	PGE-1
Papaverina	Papaverina	Papaverina
Fentolamina	Prazosin	Nitroglicerina
Linsidomina		Minoxidil
Moxisylyte		
VIP		
Altre		

SOP Conservative (Medical and Mechanical) Treatment of Erectile Dysfunction

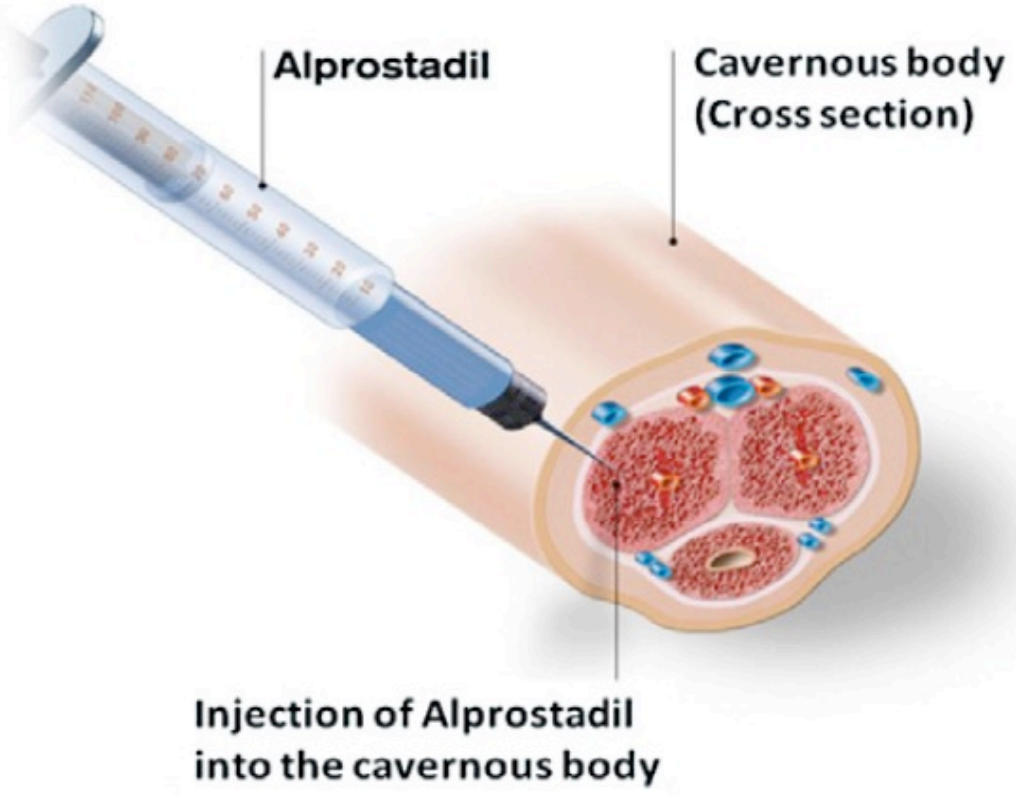
Porst ISSM Standards Committee for Sexual Medicine J Sex Med 2013;10:130

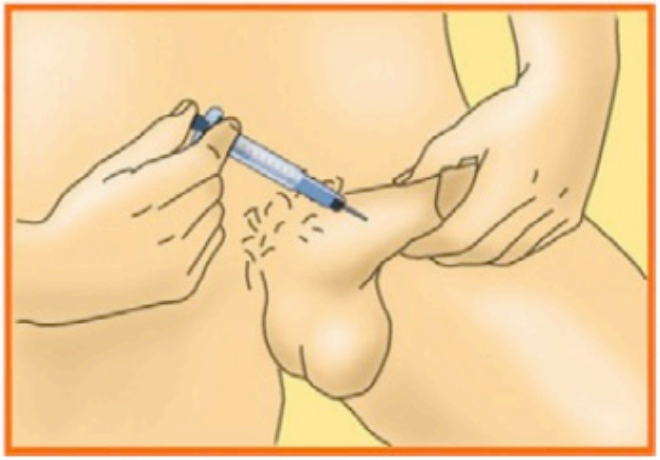
The Impact of PGE1 (Alprostadil) on Erectile Function



SOP Conservative (Medical and Mechanical) Treatment of Erectile Dysfunction

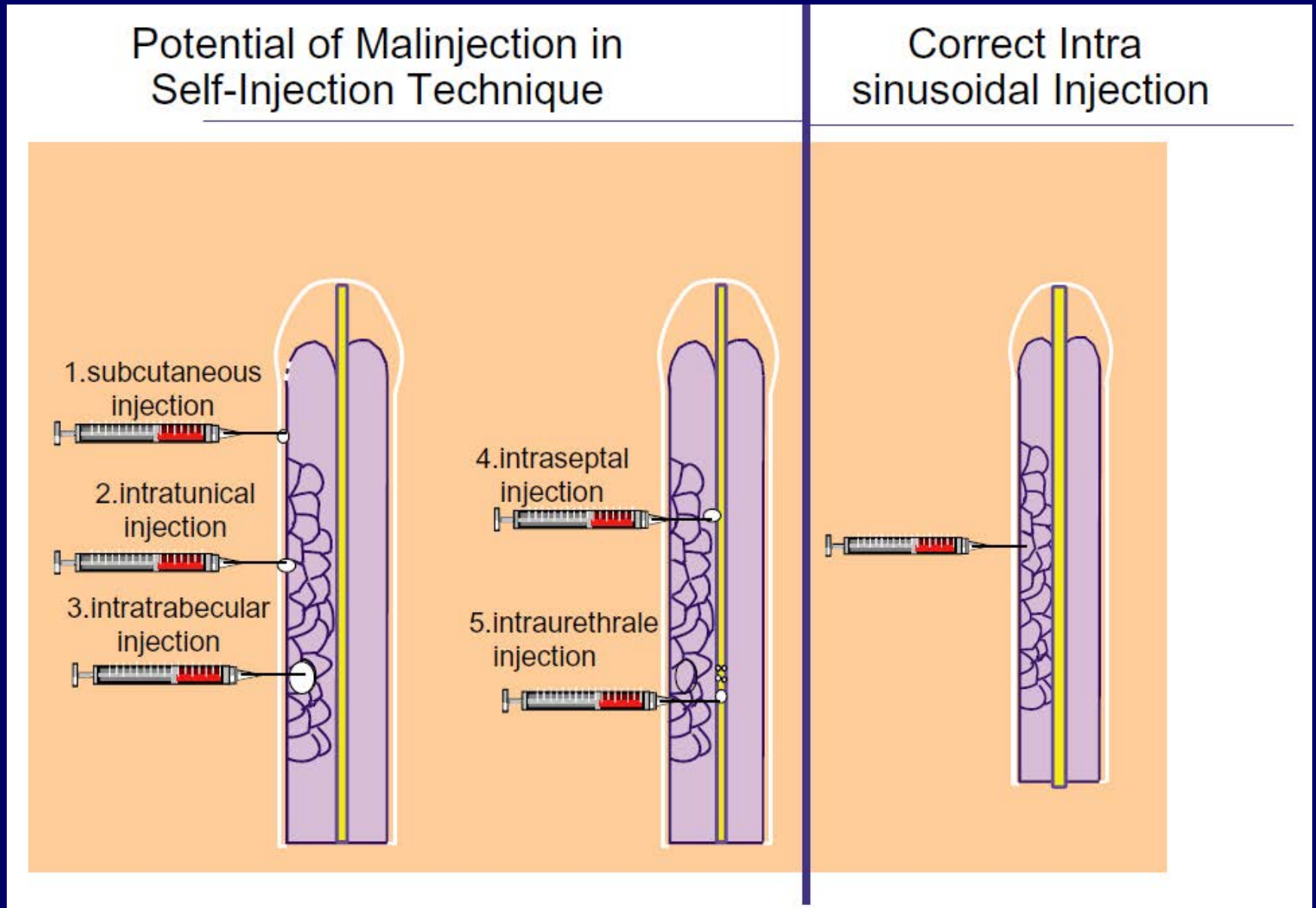
Porst ISSM Standards Committee for Sexual Medicine J Sex Med 2013;10:130





SOP Conservative (Medical and Mechanical) Treatment of Erectile Dysfunction

Porst ISSM Standards Committee for Sexual Medicine J Sex Med 2013;10:130



Anthony J. Bella and Gerald B. Brock

Endocrine, *vol. 23, nos. 2–3, 149–155, March–April 2004*

Table 1
Ideal Candidates for Intracavernous Injection Therapy

Failure of first-line oral therapy
Patient use of nitrates or potential use of nitrates
Neural injury from pelvic surgery, trauma, or radiation
Diabetic patients or severe vasculopaths (often after failed first-line therapy)
Patient desire for rapid onset of erection
Patient desire for greater rigidity and duration of erection than achievable with oral agents

Table 2
Absolute and Relative
Contraindications for Intracavernous Injection Therapy

History of priapism with vasoactive drug use
Severe penile fibrosis
Use of MAOIs (monoamine oxidase inhibitors) which would limit use of phenylephrine for potential priapism
Poor visual acuity limiting needle delivery

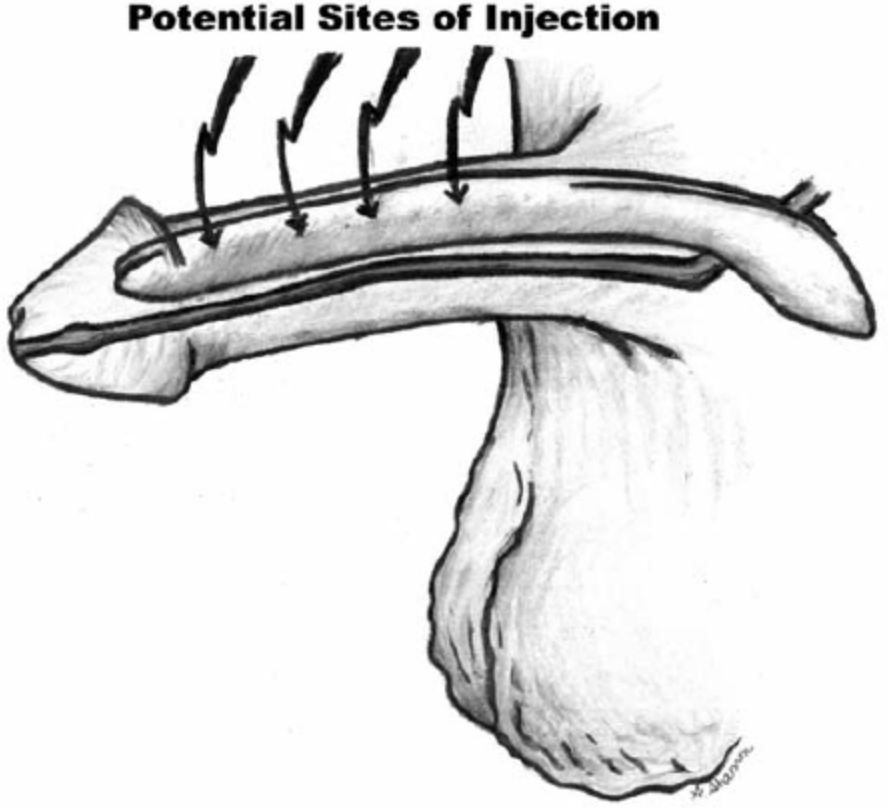


Fig. 2. Sites for intracavernous injection therapy.

Table 3
Strategies to Optimize Intracavernous Injection Therapy

Direct injection into proximal corpora
Gentle local pressure applied to injection site (2–3 min)
Comfortable, stress-free environment
Sexual stimulation following injection
Incremental dose increases if unsuccessful, until recommended dose maximum achieved (minimum 24 h between attempts)
Patient information and support

Endocrine, *vol. 23, nos. 2–3, 149–155, March–April 2004* 0969–711X/04/23:149–155/$25.00

Intracavernous Pharmacotherapy for Erectile Dysfunction

Anthony J. Bella and Gerald B. Brock

Table 4
Inadequate Response
to Intracavernous Injection Therapy: Common Causes

Inadequate dose
Misdirected injection into wrong location (subcutaneous or trabecular)
Leakage of vasoactive agent prior to injection
Inadequate sexual stimulation
Premature ejaculation

Table 5
Common Steps
to Correct Inadequate Therapeutic Response

Reassess dose and increase until therapeutic response achieved
Review of injection technique
Evaluate timing with regards to injection and sexual stimulation
Change to more potent vasoactive agent or combination therapy if at maximum recommended dose
Use combination therapy if pain is limiting factor
Involve partner and reassure

Table 6
Comparison of Single Agent Vs Combination Intracavernous Injection Therapy

Drug	Dose	Efficacy (%)	Priapism > 6 hours (%)	Fibrosis (%)	Drop-out rate (%)
Prostaglandin E-1	12–15 mg (range 5–40 mg)	70–75	1	1–3	40–60
Papaverine	20–80 mg (range 5–160 mg)	55	1–6	6–12	35–50
Phentolamine/papaverine	10 mg/1.25 mg–60 mg/2 mg	70	7	6–12	30–45
Trimix (PGE-1, papaverine, phentolamine)	10 mg/8 mg/0.2 mg–20 mg/20 mg/0.5 mg	75–85	1–3	2–5	25

International Journal of Impotence Research (2016) 28, 88–95

www.nature.com/ijir

REVIEW

What is the current role of intracavernosal injection in management of erectile dysfunction?

AI El-Sakka

The emerging of intracavernosal injection (ICI) of vasoactive materials was a major breakthrough in the treatment of erectile dysfunction (ED). However, the current state and future direction of ICI role in the armamentarium of diagnosis, prevention and treatment of ED are not well defined. The aim of this study was to address the current place of ICI in the armamentarium of ED diagnosis and treatment. An English-language MEDLINE review for the utilization of 'intracavernosal injection & erectile dysfunction' was performed from 1990 to present time. Four hundred forty-eight articles were analyzed and classified according to the current utilization of ICI in the following conditions; diagnosis of ED, phosphodiesterase-5 inhibitor (PDE5I) non-responders, diabetes, post radical prostatectomy (RP), stem cells and gene therapy, new intracavernosal drugs, adverse effects and couple satisfaction. This paper is not a standard systematic review; it is eventually a literature review of original peer-reviewed manuscripts and clinical trials reported in Medline. The comprehensive analyses of all the reviewed data were not possible as the level of evidence for utility of ICI in each topic was not available. Current date have established the role of ICI of vasoactive materials as a very common alternative domain in treatment of severe ED particularly in diabetic patients, post-RP, PDE5I non-responders. Further, new studies have denoted the potential future role of intracavernosal treatment for ED in the era of stem cells and gene therapy. ICI of vasoactive material continues to be a highly effective and safe treatment tool for men with wide varieties of ED etiologies. Several experimental and clinical studies are currently investigating new ICI materials. Hopefully in the near future, we might witness evolved molecules and innovative strategies that could help to treat ED patients with different etiologies.

International Journal of Impotence Research (2016) **28,** 88–95; doi:10.1038/ijir.2016.14; published online 14 April 2016

Long-term treatment with intracavernosal injections in diabetic men with erectile dysfunction

Asian J Androl 2006; 8 (2): 219–224

P. Perimenis, A. Konstantinopoulos, P. P. Perimeni, K. Gyftopoulos, G. Kartsanis, E. Liatsikos, A. Athanasopoulos

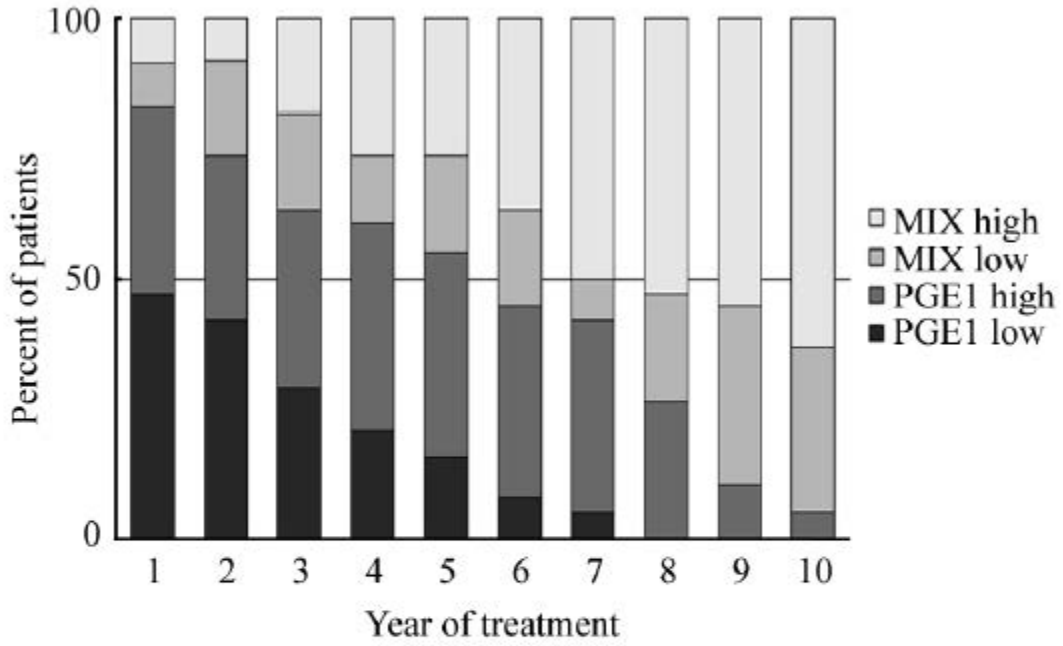
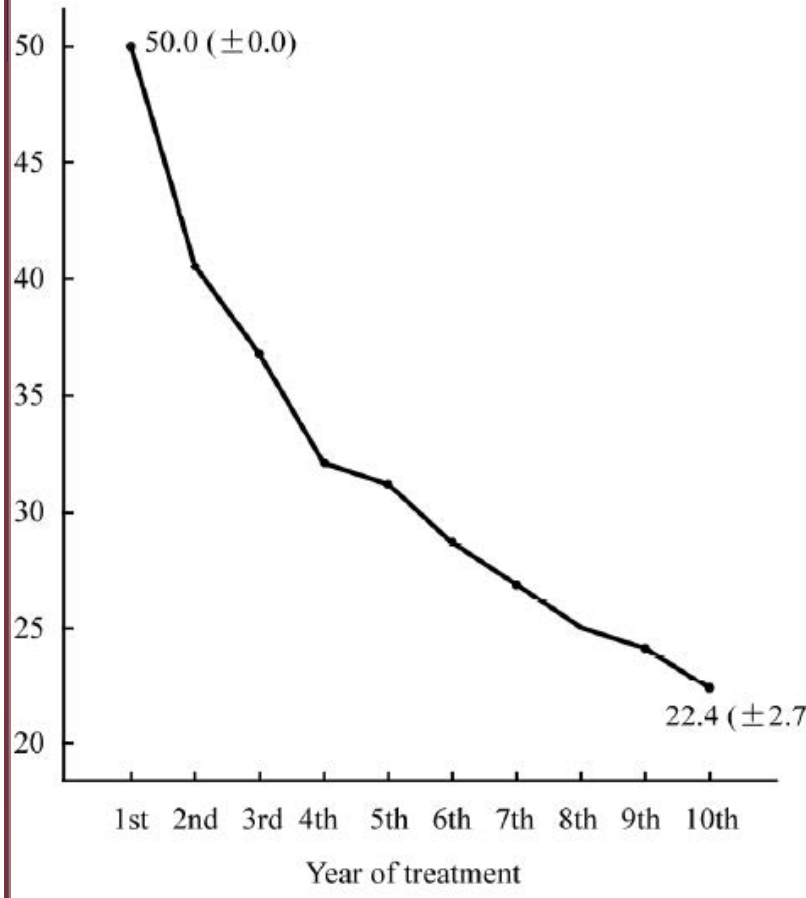


Figure 2. Treatment methods over 10 years applied to the whole study group of 38 diabetic men with erectile dysfunction (ED). prostaglandin E1 (PGE1) low, 5–10 μg PGE1; PGE1 high, 15–20 μg PGE1; MIX low, 20 μg PGE1 + 8–16 mg papaverine (PAP); MIX high, 20 μg PGE1 + > 16 mg PAP.



re 3. Mean number (±SD) of self-injections of vasoactive d

Type I diabetic men were standardized to a level of treatment as early as 5 years after the initiation of treatment. That level was finally reached by type II patients after another 4-5 years.

SOP Conservative (Medical and Mechanical) Treatment of Erectile Dysfunction

Porst ISSM Standards Committee for Sexual Medicine J Sex Med 2013;10:130

MUSE (= **M**edical **U**rethral **S**ystem for **E**rection):
Einmalsystem zur Verabreichung von Alprostadil (PGE1) in die Harnröhre

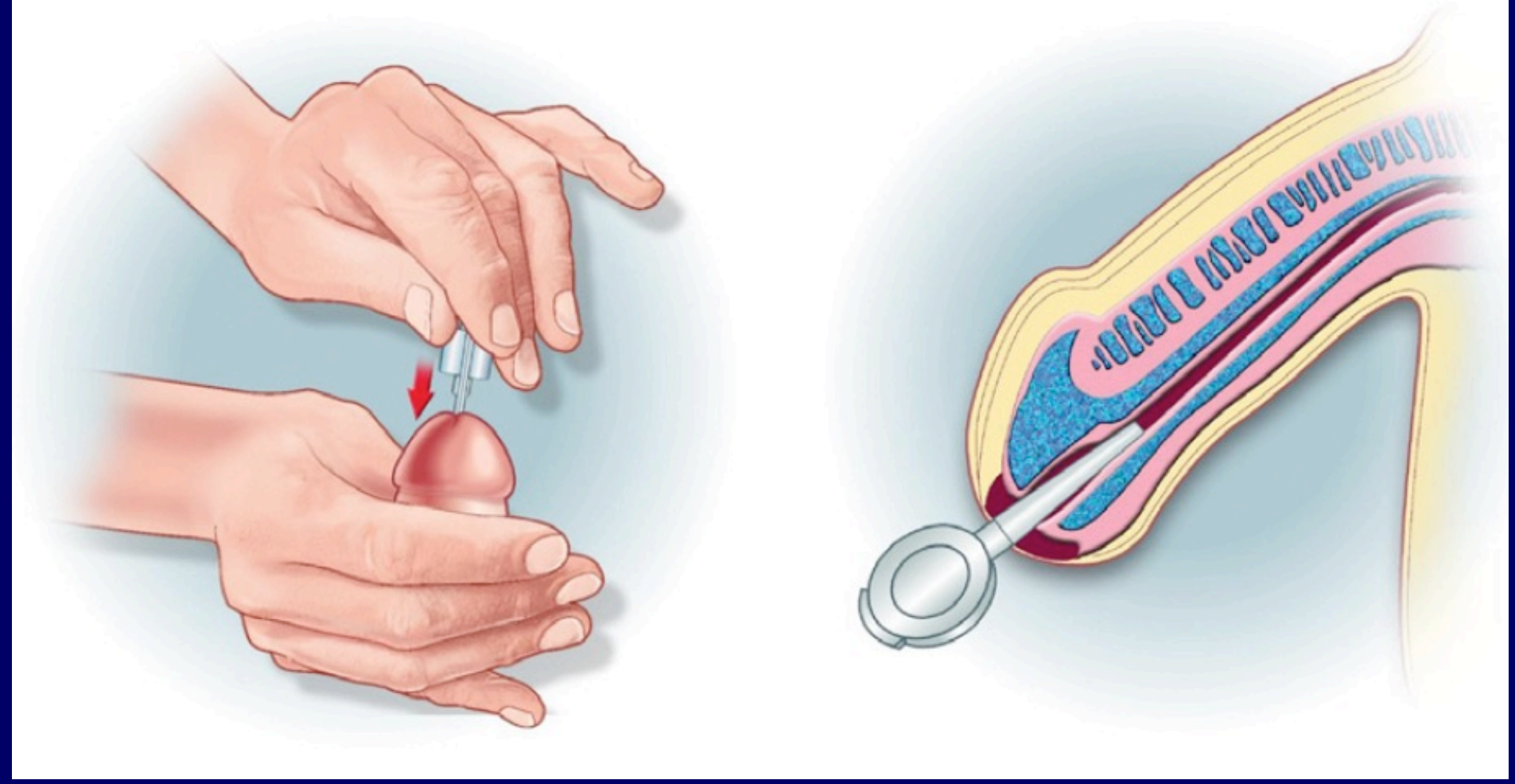


Table 23 Review of the literature: efficacy rates of transurethral alprostadil (MUSE®) vs. self-injection therapy with alprostadil (Caverject®, Viridal®, and Edex®) (from Porst and Adaikan [123])

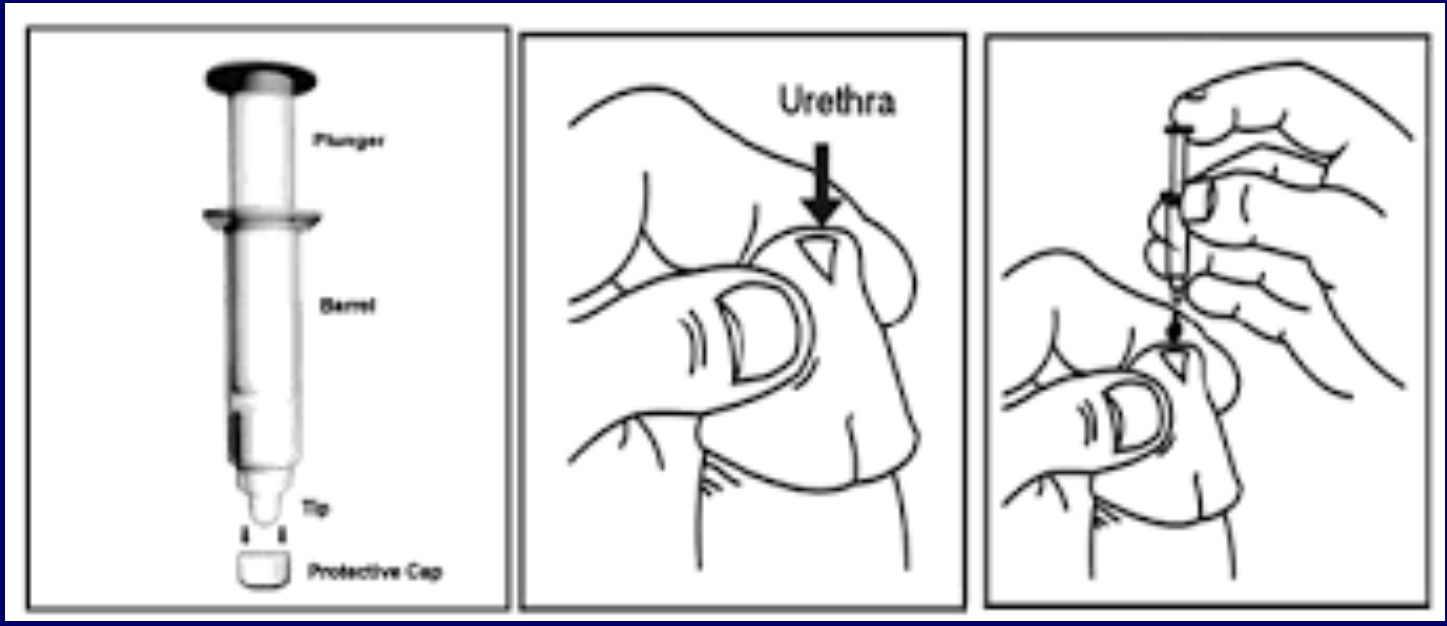
Author	No. of patients	MUSE®	i.c. alprostadil
Ghazi, 1998 [124]	125	48% (61)	79% (98)
Werthman, 1997 [125]	100	37%	89%
Porst, 1997 [126]	103	43% (44)	70% (72)
Shabsigh, 1998 [127]	106	27%	66% (buckling test)
Shabsigh, 2000 [128]	68	53%	83% (at home use)
Flynn, 1998 [129]	Literature review	45%	>70%

MUSE = Medicated Urethral System for Erection

ALPROSTADIL crema

Disponibile in due dosaggi da 200 e 300 microgrammi di alprostadil in 100 mg di crema.

Non applicare più di 2-3 volte alla settimana e non più di una volta nell'arco delle 24 ore. L'effetto compare 5-30 minuti dopo la somministrazione. La durata dell'effetto è di circa 1- 2 ore
Effetti collaterali: dolore locale da lieve a moderato, bruciore o dolore e arrossamento del pene, rash cutaneo,edema del pene,balanite, ecc.



DISFUNZIONE ERETTILE

Terapia farmacologica sistemica

TERAPIA ENDOCRINA

Testosterone
hCG
GnRH
DHT
DHEA
Naltrexone
Dopaminoagonisti
Androstenedione
Antiestrogeni

TERAPIA NON ENDOCRINA

PDE5 inibitori →

Sildenafil
Vardenafil
Tadalafil
Avanafil

Apomorfina
Yohimbina
Trazodone
Fentolamina
Arginina

Clinical efficacy of Apomorphine SL in erectile dysfunction of diabetic men

International Journal of Impotence Research (2005) 17, 80–85

P Gontero[1]*, R D'Antonio[2], G Pretti[1], F Fontana[1], M Panella[3], E Kocjancic[1], G Allochis[2] and B Frea[1]

Table 2 Mean IIEF EF domain score changes before and after treatment in the two arms

	Placebo arm			*Apomorphine arm*		
Parameter	*Baseline*	*Treatment*	P-*value*	Baseline	*Treatment*	P-*value*
IIEF EF domain, mean (s.d.)	12.82 (5.72)	13.24 (6.22)	0.70	13.08 (5.77)	13.81 (6.33)	0.52
IIEF Q3, mean (s.d.)	1.83 (0.87)	2.05 (1.04)	0.20	1.93 (1.02)	2.12 (1.07)	0.33
IIEF Q4, mean (s.d.)	1.89 (0.97)	2.05 (1.12)	0.39	1.93 (0.99)	2.14 (1.09)	0.28

Table 3 Distribution of variables related to diabetes and ED among responders and nonresponders for both arms

	Placebo			*Apomorphine*		
Variable	*Responders*	*Nonresponders*	P-*value*	Responders	*Nonresponders*	P-*value*
Age (y), mean (s.d.)	51.67 (13.77)	56.81 (8.70)	0.15	50.91 (10.79)	57.87 (9.78)	0.04
HB1Ac (%), mean (s.d.)	7.08 (1.55)	7.95 (1.66)	0.06	7.08 (10.57)	8.08 (2.05)	0.04
Total testosterone (ng/dl), mean (s.d.)	290 (120)	306 (97)	0.38	307 (94)	288 (102)	0.40
Time from diagnosis of diabetes (y), mean (s.d.)	12.44 (5.94)	10.98 (7.73)	0.26	15.55 (12.80)	10.60 (7.49)	0.12
Duration of ED (months), mean (s.d.)	18.0 (12.11)	24.19 (20.25)	0.11	19.82 (33.73)	25.75 (23.65)	0.30
IIEF erection domain at baseline, mean (s.d.)	13.10 (5.24)	12.71 (5.72)	0.42	13.42 (5.57)	12.85 (5.90)	0.38
Maximum PSV (cm/s), mean (s.d.)	39.98 (7.46)	34.31 (13.46)	0.04	40.87 (20.01)	32.11 (14.02)	0.10
Minimum EDV (cm/s), mean (s.d.)	2.46 (2.67)	5.10 (3.81)	0.01	2.49 (3.01)	5.08 (3.71)	0.01
Erection grade ≥ 3 (%)	66.67	38.46	0.11	72.72	39.58	0.049
Comorbidities (one or more) (%)	55.56	44.23	0.57	45.46	47.92	0.88

SOP Conservative (Medical and Mechanical) Treatment of Erectile Dysfunction

Porst ISSM Standards Committee for Sexual Medicine J Sex Med 2013;10:130

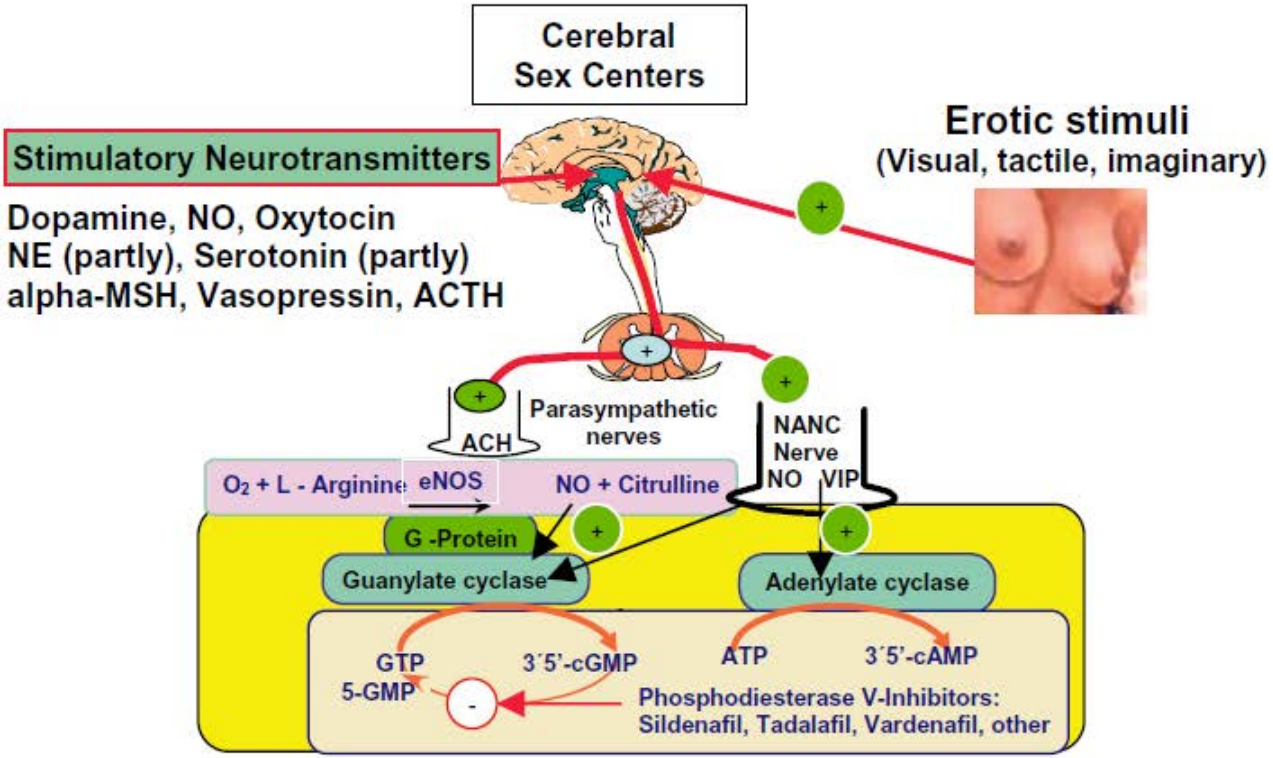
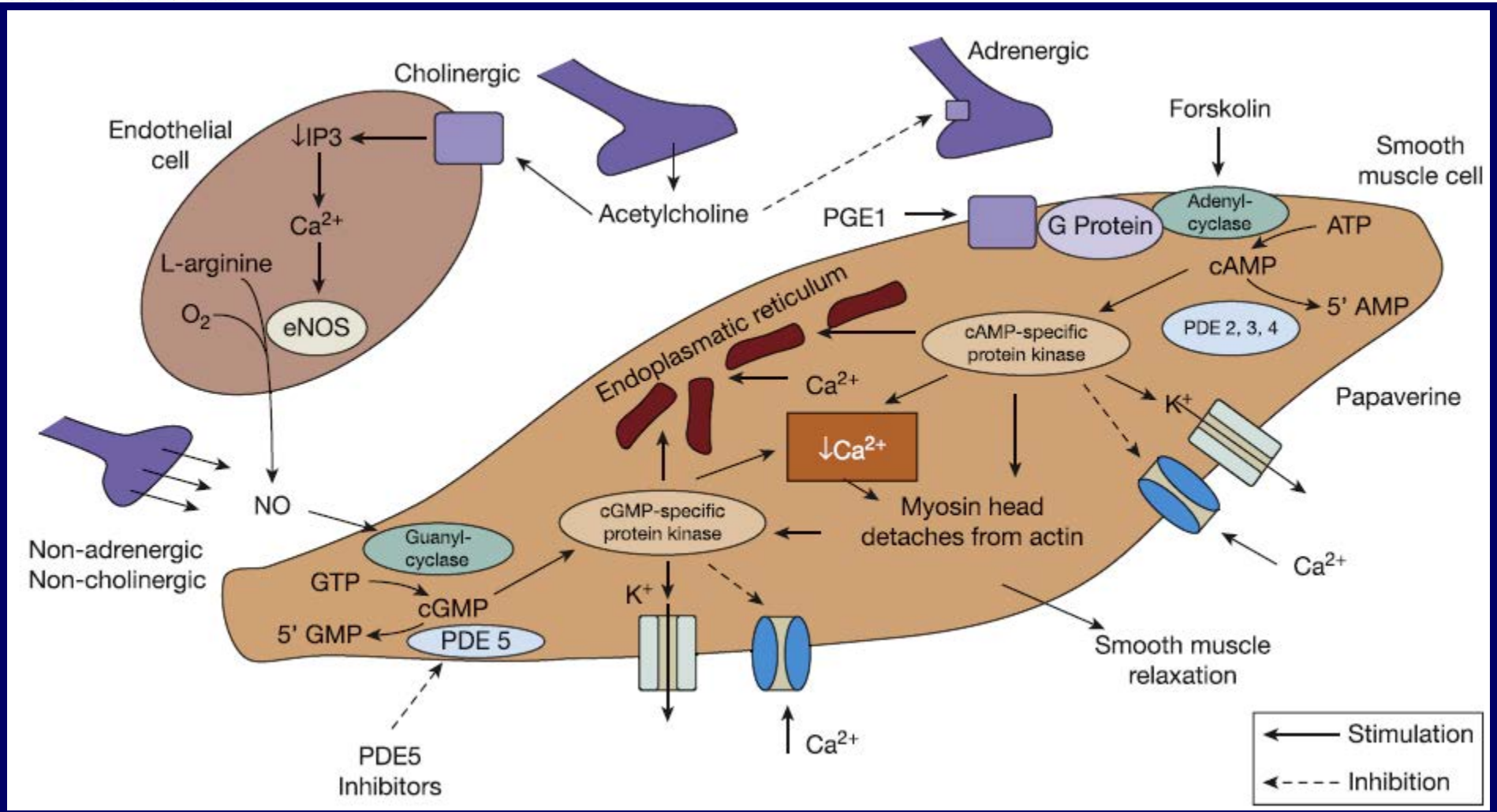


Figure 6 Physiology of erection and impact of PDE5 inhibitors on erection (from [23]). ACH = Acetylcholine; ACTH = Adrenocorticotropic hormone; ATP = Adenosine triphosphate; 3′5′-cAMP = cyclic adenosine monophosphate; 3′5′-cGMP = cyclic guanosine monophosphate; eNOS = endothelial nitric oxide synthase; GTP = Guanosine triphphosphate; MSH = Melanocyte stimulating hormone; NANC = non adrenergic, non cholinergic; NE = Norepinephrine; NO = Nitric oxide; VIP = Vasoactive intestinal polypeptide

Pharmacotherapy for Erectile Dysfunction: Recommendations From the Fourth International Consultation for Sexual Medicine (ICSM 2015)

Konstantinos Hatzimouratidis, MD,[1] Andrea Salonia, MD,[2] Ganesan Adaikan, MD,[3] Jacques Buvat, MD,[4] Serge Carrier, MD,[5] Amr El-Meliegy, MD,[6] Andrew McCullough, MD,[7] Luiz Otavio Torres, MD,[8] and Mohit Khera, MD[9]

J Sex Med 2016;13:465–488.



DISFUNZIONE ERETTILE
Terapia farmacologica con PDE5i

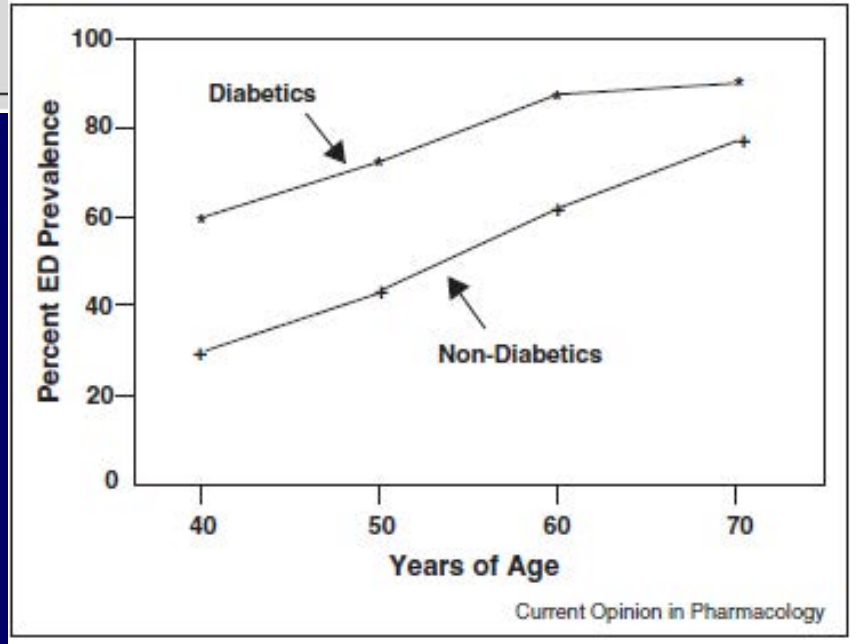
PDE5 inhibitors: targeting erectile dysfunction in diabetics
Sharron H Francis and Jackie D Corbin

Table 1

Emerging and established approaches to improve responsiveness of diabetes-induced erectile dysfunction to PDE5 inhibitor therapy.

- Higher dosing of PDE5 inhibitors and use of different inhibitors
- Education about most effective protocol for use of PDE5 inhibitors
- Increasing PDE5 inhibitor effectiveness by improvement in overall health (decreasing adiposity, improving cardiorespiratory fitness, and controlling hyperglycemia and dyslipidemia)
- Enhancing PDE5 inhibitor effect by normalizing testosterone level
- Chronic daily treatment with PDE5 inhibitors
- Combining PDE5 inhibitor therapy with other therapies

Nei diabetici la prevalenza di DE è maggiore rispetto ai non diabetici.
L'utilizzo corretto dei farmaci a disposizione è fondamentale



Graphic depiction of the frequency and age of onset of erectile dysfunction in type II diabetics and non-diabetics. (Figure was redrawn from that kindly provided by Dr. Culley C. Carson, University of North Carolina at Chapel Hill).

SAPIENZA
UNIVERSITÀ DI ROMA

Table 5: Summary of the key pharmacokinetic data for the four PDE5 inhibitors currently EMA-approved to treat ED*

Parameter	Sildenafil, 100 mg	Tadalafil, 20 mg	Vardenafil, 20 mg	Avanafil 200mg
C_{max}	560 µg/L	378 µg/L	18.7 µg/L	5.2 µg/L
T_{max} (median)	0.8-1 h	2 h	0.9 h	0.5-0.75 h
T1/2	2.6-3.7 h	17.5 h	3.9 h	6 – 17 h
AUC	1685 µg.h/L	8066 µg.h/L	56.8 µg.h/L	11.6 µg.h/L
Protein binding	96%	94%	94%	99%
Bioavailability	41%	NA	15%	8-10%

C_{max}: maximal concentration, T_{max}: time-to-maximum plasma concentration; T1/2: plasma elimination halftime; AUC: area under curve or serum concentration time curve.

** Fasted state, higher recommended dose. Data adapted from EMA statements on product characteristics.*

Table 6: Common adverse events of the four PDE5 inhibitors currently EMA-approved to treat ED*

Adverse event	Sildenafil	Tadalafil	Vardenafil	Avanafil 200mg
Headache	12.8%	14.5%	16%	9.3%
Flushing	10.4%	4.1%	12%	3.7%
Dyspepsia	4.6%	12.3%	4%	uncommon
Nasal congestion	1.1%	4.3%	10%	1.9%
Dizziness	1.2%	2.3%	2%	0.6%
Abnormal vision	1.9%		< 2%	none
Back pain		6.5%		< 2%
Myalgia		5.7%		< 2%

** Adapted from EMA statements on product characteristics.*

Korean Society for Sexual Medicine and Andrology (KSSMA) Guideline on Erectile Dysfunction

World J Mens Health Vol. 31, No. 2, August 2013

Ji Kan Ryu[1], Kang Su Cho[2], Su Jin Kim[3], Kyung Jin Oh[4], Sung Chul Kam[5], Kyung Keun Seo[6], Hong Seok Shin[7], Soo Woong Kim[8]

Table 2. Pharmacokinetic data for the five PDE5 inhibitors used to treat erectile dysfunction in Korea

Parameter	PDE5 inhibitors					
	Sildenafil (100 mg)	Tadalafil (20 mg)	Vardenafil (20 mg)	Udenafil (200 mg)	Mirodenafil (100 mg)	Avanafil (200 mg)
T_{max} (h)	0.8~1	2	0.9	1.5	1	0.5
$T_{1/2}$ (h)	2.6~3.7	17.5	3.9	9.88	2.5	10.6
Action duration (h)	0.5~4	1~36	0.5~5	0.5~12	0.5~4	6
C_{max} (μg/L)	560	378	18.7	1,138	NA	5,161
AUC (μg/h/L)	1,685	8,066	56.8	7,898	NA	10,867
Protein binding (%)	96	94	94	NA	NA	99
Bioavailability (%)	41	NA	15	NA	24~43	NA

PDE5: phosphodiesterase type 5, T_{max}: time to maximum plasma concentration, $T_{1/2}$: terminal half-life, C_{max}: maximum plasma concentration, AUC: area under the curve, NA: not available.

Pharmacotherapy for Erectile Dysfunction: Recommendations From the Fourth

Konstant , MD,[4]
Serge Ca d
Mohit Kh 5–488.

Table 1. Pharmacokinetics of PDE5 Inhibitors (Mean Values in Fasted State)

PDE5 inhibitor	T_{max} (h)	$t_{1/2}$ (h)	C_{max} (ng/mL)	AUC (ng · h/mL)
Avanafil 200 mg[16]	0.75	5.1	2,920	8,490
Lodenafil 160 mg[15]	1.2	2.4	157	530
Mirodenafil 100 mg[12]	1.4	2.5	2,989	7,907
Sildenafil 100 mg[17]	0.95	3.98	514	1,670
Tadalafil 20 mg[18]	2	17.5	378	8,066
Vardenafil FCT 20 mg[13]	0.66	3.9	20.9	74.5
Vardenafil ODT 10 mg[19]	1.5	4.23	7.34	30.39
Udenafil 200 mg[14]	0.76	9.88	1,136.6	7,898

AUC = area under the curve; C_{max} = maximum plasma concentration; FCT = film-coated tablet; ODT = oro-dispersible tablet; PDE5 = phosphodiesterase type 5; $t_{1/2}$ = time required for elimination of one half of the inhibitor from plasma; T_{max} = time required for attaining maximum plasma concentration.

PDE5 inhibitors: considerations for preference and long-term adherence

Int J Clin Pract, August 2013, **67**, 8, 768–780

W. B. Smith II, I. R. McCaslin, A. Gokce, S. H. Mandava, L. Trost, W. J. Hellstrom

Table 1 Pharmacokinetic properties of currently approved phosphodiesterase type 5 inhibitor

	Sildenafil (100 mg)	Vardenafil (20 mg)	Vardenafil orodispersible tablet (10 mg) (78)	Tadalafil (20 mg)	Avanafil (100 mg)
IC50 (nmol/l)	3.9	0.1–0.7		0.94	5.2
C_{max} (ng/ml)	327 ± 236	20.9 ± 1.83	13.43	378	871
T_{max} (h)	1.16 ± 0.99	0.660	1.5 (0.5–2.5)	2.0	0.555
Bioavailability (%)	38–41	15		≥ 36	–
Duration of Action (h)	4–6	5–7		24–36	0.25–6
1/2 (h)	3.82 ± 0.84	3.94 ± 1.31	5.387	17.5	1.23
% Bound	96	95		94	–
Recommended dose time prior to intercourse (h)	1	0.5–1	1	2	0.5

In summary, PDE5i are a safe and effective treatment for ED in adult men. There are multiple drug options from which the provider and patient may choose to optimise the likelihood of long-term treatment success. While all approved drugs display efficacy, initial drug choice should depend on acomprehensive discussion between provider and patient.

Clinical Practice Guidelines

Can J Diabetes 37 (2013) S150–S152

Erectile Dysfunction

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

The initial draft of this chapter was prepared by Gerald Brock MD, FRCSC, William Harper MD, FRCPC

RECOMMENDATIONS

1. All adult men with diabetes should be regularly screened for ED with a sexual function history [Grade D, Consensus].

2. Men with diabetes and ED should be investigated for hypogonadism [Grade D, Level 4 (16,31,32,34)].

3. A PDE5 inhibitor, if there are no contraindications to its use, should be offered as first-line therapy to men with diabetes and ED in either an on-demand [Grade A, Level 1A (47-53)] or scheduled-use [Grade B, Level 2 (53,54)] dosing regimen.

4. Referral to a specialist in ED should be considered for eugonadal men who do not respond to PDE5 inhibitors or for whom the use of PDE5 inhibitors is contraindicated [Grade D, Consensus].

5. Men with diabetes and ejaculatory dysfunction who are interested in fertility should be referred to a healthcare professional experienced in the treatment of ejaculatory dysfunction [Grade D, Consensus].

Men with diabetes may require more aggressive treatment for erectile dysfunction

International Journal of Impotence Research (2013) 26, 112–115

TJ Walsh, JM Hotaling, A Smith, C Saigal and H Wessells the Urologic Diseases in America Project

Table 2. Treatment of erectile dysfunction (n) by second- and third-line therapies among men with and without diabetes mellitus

Patient status	N	n	*(%)*	*Odds ratio*	*(95% CI)*
Second-line therapies					
No diabetes	117 070	2134	1.82	1	(ref)
Diabetes	19 236	538	2.80	1.55	(1.408, 1.706)
Third-line therapies					
No diabetes	117 070	437	0.37	1	(ref)
Diabetes	19 236	152	0.79	2.13	(1.77, 2.56)
Second- and third-line combined					
No diabetes	117 070	68	0.06	1	(ref)
Diabetes	19 236	25	0.13	2.24	(1.416, 3.544)

Among a large populationbased cohort of men with ED, those with DM are more likely to require more aggressive treatments. These data suggest that ED among men with diabetes may be less responsive to first-line treatments (oral agents), worsen more rapidly, or both

How to Treat Erectile Dysfunction in Men with Diabetes: from Pathophysiology to Treatment

Konstantinos Hatzimouratidis · Dimitrios Hatzichristou

Curr Diab Rep (2014) 14:545

Table 1 Efficacy of PDE5i in diabetic men (updated from [9])

Study	Drug	Diabetes type	Outcome measure	Efficacy (%)
Rendell et al., 1999 [58]	Sildenafil (25–100 mg)	Type 1 (n=50) and type 2 (n=136)	IIEF Q4	Placebo 1.6 Sildenafil 2.7 (mean scores, p<0.001)
Boulton et al., 2001 [59]	Sildenafil (25–100 mg)	Type 2 (n=110)	IIEF Q4	Placebo 1.84 Sildenafil 3.35 (mean scores, p<0.0001)
Stuckey et al., 2003 [60]	Sildenafil (25–100 mg)	Type 1 (n=188)	IIEF Q4	Placebo 2.19 Sildenafil 3.25 (mean scores, $p\leq$0.001)
Goldstein et al., 2003 [61]	Vardenafil (10 and 20 mg)	Type 1 (n=51) and type 2 (n=387)	SEP3	Placebo 23 % Vardenafil 10 mg 49 % Vardenafil 20 mg 54 % (p<0.0001 for both 10 and 20 mg)
Safarinejad, 2004 [62]	Sildenafil (100 mg)	Type 1 (n=48) and type 2 (n=234)	IIEF Q4	Placebo 2.9 Sildenafil 2 (mean scores, p<0.002)
Fonseca et al., 2004 [63]	Tadalafil (10 and 20 mg)	Type 1 (n=210) and type 2 (n=427)	SEP3	Placebo 21.5 % Tadalafil 10 mg 48.6 % Tadalafil 20 mg 52.8 % (p<0.001 for both 10 and 20 mg)
Ziegler et al., 2006 [64]	Vardenafil (5–20 mg)	Type 1 (n=154)	SEP3	Placebo 28 % Vardenafil 50 % (p<0.0001)

How to Treat Erectile Dysfunction in Men with Diabetes: from Pathophysiology to Treatment

Konstantinos Hatzimouratidis · Dimitrios Hatzichristou

Curr Diab Rep (2014) 14:545

Table 1 Efficacy of PDE5i in diabetic men (updated from [9])

Study	Drug	Diabetes type	Outcome measure	Efficacy (%)
Hatzichristou et al., 2008 [65]	Tadalafil (2.5 and 5 mg)	Type 1 (n=33) and type 2 (n=265)	SEP3	Placebo 28.2 % Tadalafil 2.5 mg 46 % Tadalafil 5 mg 41.1 % ($p \leq 0.005$ for both 2.5 and 5 mg)
Park et al., 2010 [66]	Mirodenafil 100 mg	Type 1 and type 2 (n=55 for both types, stratification not reported)	SEP3	Placebo 22.3 % Mirodenafil 69 % ($p<0.0001$)
Moon du et al., 2011 [67]	Udenafil (100 and 200 mg)	Type 1 and type 2 (n=174 for both types, stratification not reported)	SEP3	Placebo 22.6 % Udenafil 100 mg 53.13 % Udenafil 200 mg 63 % ($p<0.0001$ for both 100 and 200 mg)
Goldstein et al., 2012 [68]	Avanafil (100 and 200 mg)	Type 1 (n=11) and type 2 (n=349)	SEP3	Placebo 20 % Avanafil 100 mg 34 % Avanafil 200 mg 40 % ($p<0.002$ for 100 mg and $p<0.001$ for 200 mg)

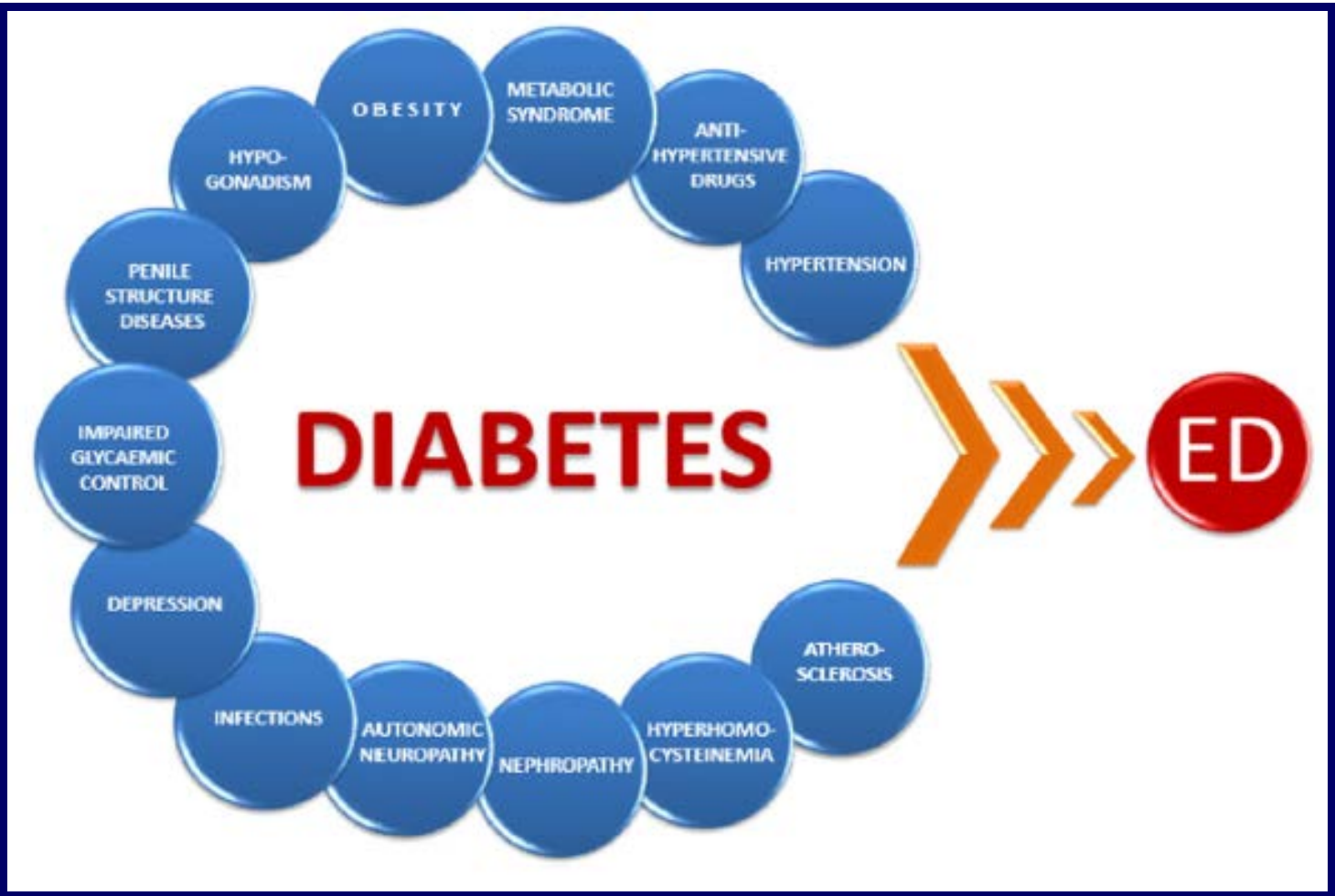
IIEF Q4 International Index for Erectile Function Question 4 (During sexual intercourse, how often were you able to maintain your erection to completion of intercourse? Scale 0–5), *SEP3* Sexual Encounter Profile question 3 (Did your erection last long enough for you to have successful intercourse?)

($p<0.0001$)

Erectile dysfunction and its management in patients with diabetes mellitus

Rev Endocr Metab Disord (2015) 16:213–231

Giuseppe Defeudis[1,2] · Daniele Gianfrilli[2] · Chiara Di Emidio[1] · Riccardo Pofi[2] · Dario Tuccinardi[1] · Andrea Palermo[1] · Andrea Lenzi[2] · Paolo Pozzilli[1]



Sildenafil: Study of a Novel Oral Treatment for Erectile Dysfunction in Diabetic Men

Diabet. Med. 15: 821–825 (1998)

D.E. Price[1], J.C. Gingell[2], S. Gepi-Attee[2], K. Wareham[1], P. Yates[3], M. Boolell*[3]

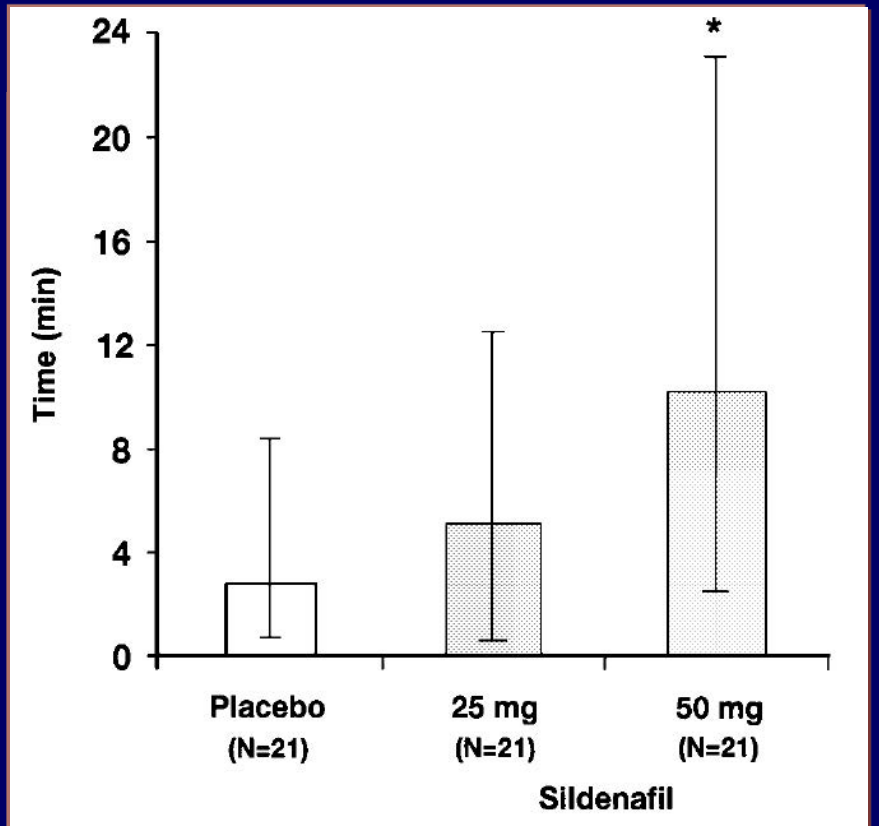
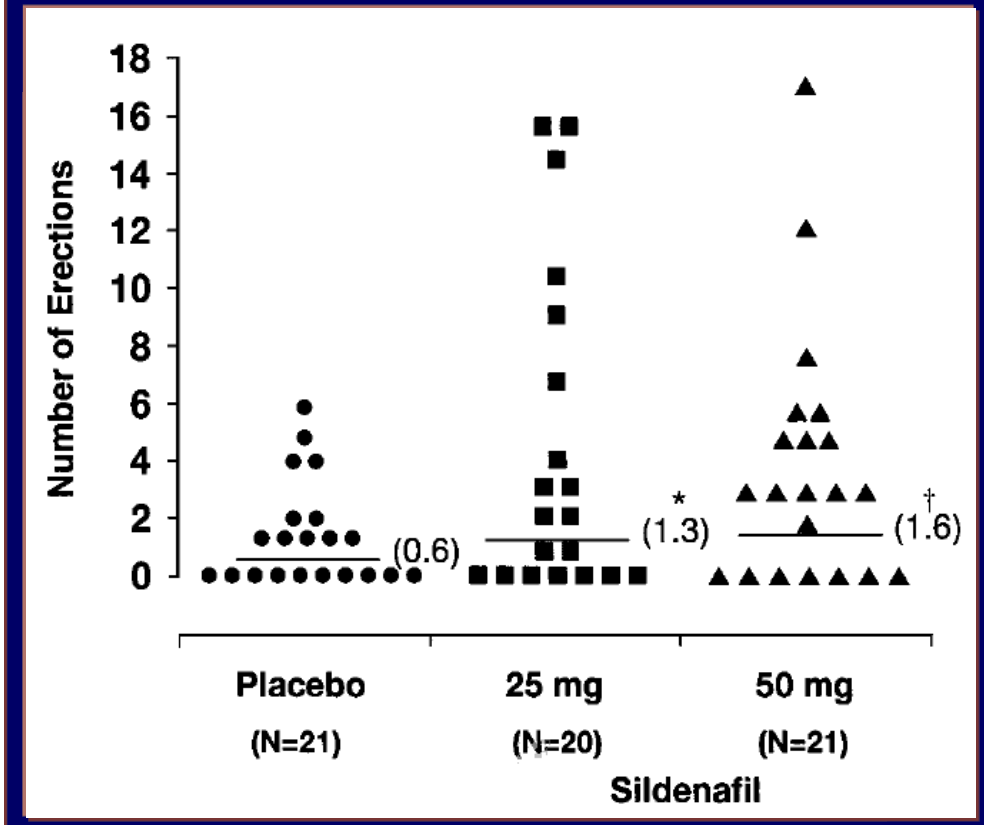


Figure 1. Duration (min) of penile rigidity >60 % at the base of the penis during visual sexual stimulation. Bars and vertical



Sildenafil for Treatment of Erectile Dysfunction in Men With Diabetes

A Randomized Controlled Trial

Marc S. Rendell, MD

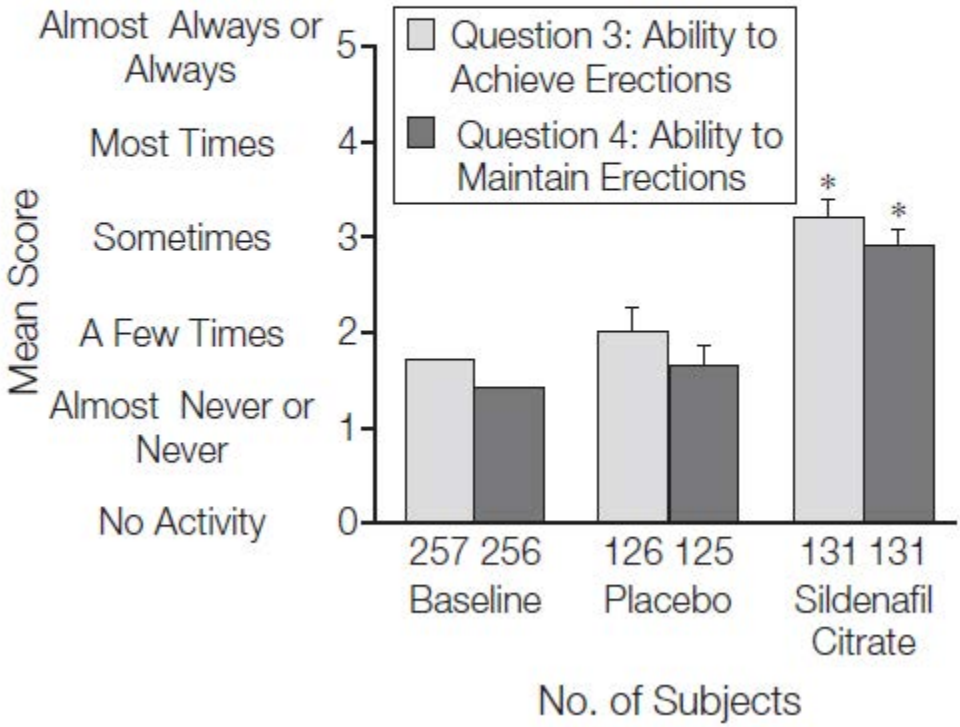
JAMA. 1999;281:421-426

Results Two hundred fifty-two patients (94%) completed the study (131/136 in the sildenafil group, 121/132 in the placebo group). By intention-to-treat analysis, at 12 weeks, 74 (56%) of 131 patients in the sildenafil group reported improved erections compared with 13 (10%) of 127 patients in the placebo group ($P<.001$). The proportion of men with at least 1 successful attempt at sexual intercourse was 61% (71/117) for the sildenafil group vs 22% (25/114) for the placebo group ($P<.001$). Adverse events related to treatment were reported for 22 (16%) of 136 patients taking sildenafil and 1 (1%) of 132 patients receiving placebo. The most common adverse events were headache (11% sildenafil, 2% placebo), dyspepsia (9% sildenafil, 0% placebo), and respiratory tract disorder (6% sildenafil, 2% placebo), predominantly sinus congestion or drainage. The incidence of cardiovascular adverse events was comparable for both groups (3% sildenafil, 5% placebo).

Table 4. Incidence of Adverse Events*

Adverse Event	Placebo	Sildenafil Citrate
Headache	2 (2)	15 (11)
Dyspepsia	0 (0)	12 (9)
Respiratory tract disorder	2 (2)	8 (6)
Flushing	0 (0)	6 (4)
Rhinitis	0 (0)	5 (4)
Abnormal vision†	1 (1)	5 (4)

Figure 2. Scores on Questions 3 and 4 of the International Index of Erectile Function



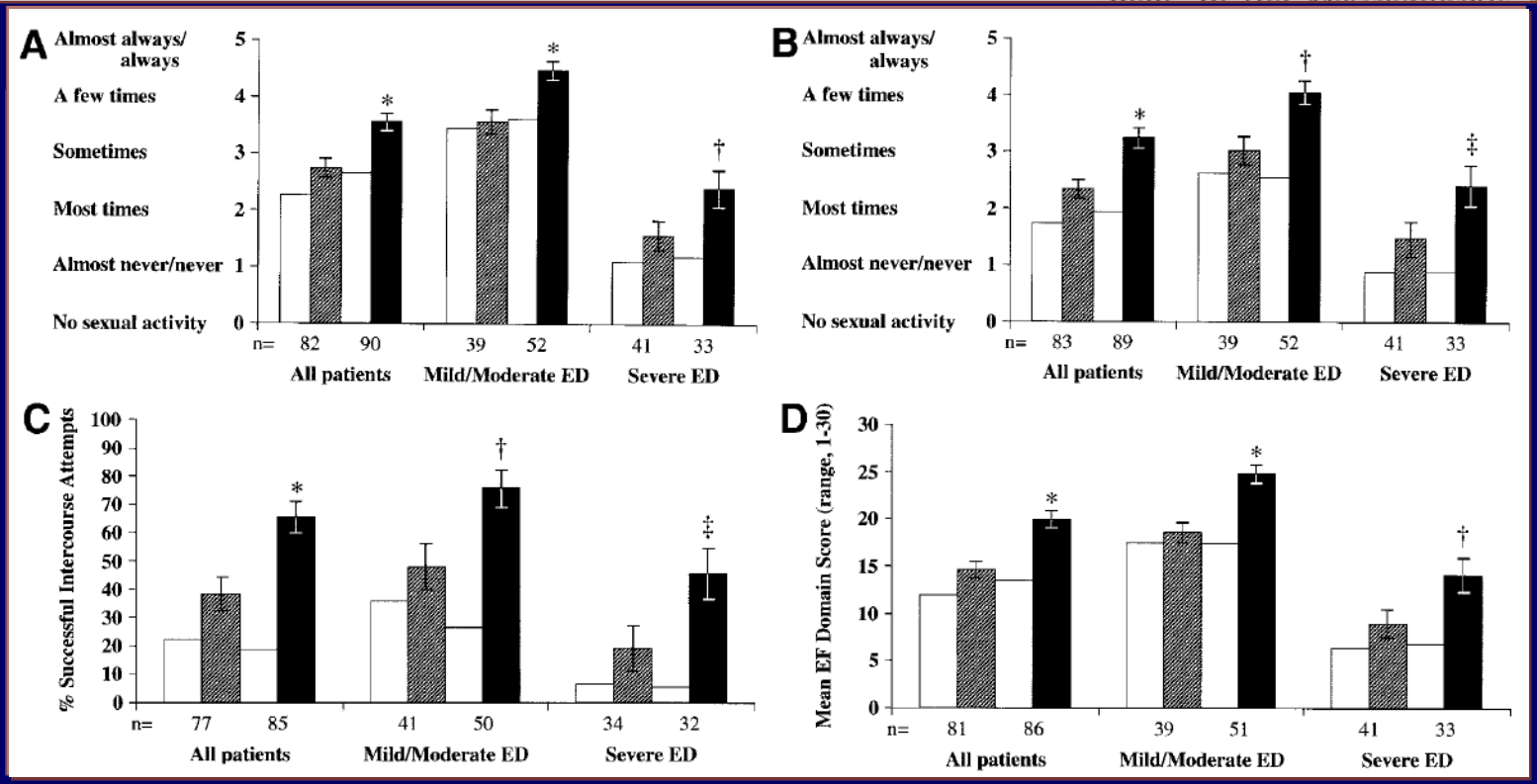
Sildenafil Citrate for Treatment of Erectile Dysfunction in Men With Type 1 Diabetes

Diabetes Care 26:279–284, 2003

Results of a randomized controlled trial

BRONWYN G.A. STUCKEY, MD[1]
MAURICIO N. JADZINSKY, MD[2]
LIAM J. MURPHY, MD[3]
FRANCESCO MONTORSI, MD[4]
ATES KADIOGLU, MD[5]
FADLO FRAIGE, MD[6]
PILAR MANZANO, MD[7]
CHAICHARN DEEROCHANAWONG, MD[8]

is erectile dysfunction (ED), with an estimated prevalence of 20–85% (ranging from mild to complete ED) (3), which occurs at an earlier age than in nondiabetic



Oral sildenafil in the treatment of erectile dysfunction in diabetic men
A randomized double-blind and placebo-controlled study

Mohammad R. Safarinejad*

Department of Urology, Military University of Medical Sciences, P.O. Box 19395-1849, Tehran, Iran

Journal of Diabetes and Its Complications 18 (2004) 205–210

Table 4
Mean scores to Questions 1, 2, and 5 through 15 of the IIEF at baseline and after 16 weeks of treatment with sildenafil or placebo

	Mean score						
	Sildenafil citrate (n = 144)			Placebo (n = 138)			Overall treatment
Question	Baseline	Final[a]	P value	Baseline	Final[a]	P value[b]	P value[c]
1. How often were you able to get an erection during sexual activity?	2.1	3.0 (0.2)	<.002	2.0	2.0 (0.2)	.10	<.002
2. When you had erection with sexual stimulation, how were your erections hard enough for penetration?	1.8	2.9 (0.2)	<.002	1.7	1.9 (0.2)	.82	<.002
5. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	1.4	2.6 (0.2)	<.002	1.3	1.6 (0.2)	.20	<.002
6. How many times have you attempted sexual intercourse?	2.0	3.2 (0.2)	<.001	1.9	2.8 (0.2)	<.001	<.001
7. When you attempted sexual intercourse, how often was it satisfactory for you?	1.7	3.0 (0.3)	<.001	1.6	1.7 (0.3)	.31	<.001
8. How much have you enjoyed sexual intercourse?	1.7	2.7 (0.2)	<.001	1.6	1.8 (0.2)	.53	<.001
9. When you had sexual intercourse, how often did you ejaculate?	2.7	3.7 (0.2)	<.002	2.8	3.3 (0.2)	.50	<.002
10. When you had sexual intercourse, how often did you have the feeling of orgasm or climax?	2.8	3.8 (0.2)	<.002	2.7	3.1 (0.3)	.44	<.003
11. How often have you felt sexual desire?	3.6	3.6 (0.2)	.97	3.5	3.6 (0.2)	.50	.75
12. How would you rate your level of sexual desire?	3.3	3.4 (0.1)	.09	3.3	3.4 (0.1)	.92	.20
13. How satisfied have you been with your overall sex life?	1.8	2.8 (0.2)	<.001	1.8	2.2 (0.2)	.003	<.001
14. How satisfied have you been with your sexual relationship?	2.4	3.2 (0.2)	<.001	2.5	2.8 (0.2)	.03	.002
15. How do you rate your confidence that you could get and keep an erection?	1.7	2.6 (0.2)	<.001	1.6	1.7 (0.2)	.07	<.001

[a] Least squares mean (S.E.) scores.
[b] P values for comparison between baseline and final scores.
[c] P values for overall treatment effect.

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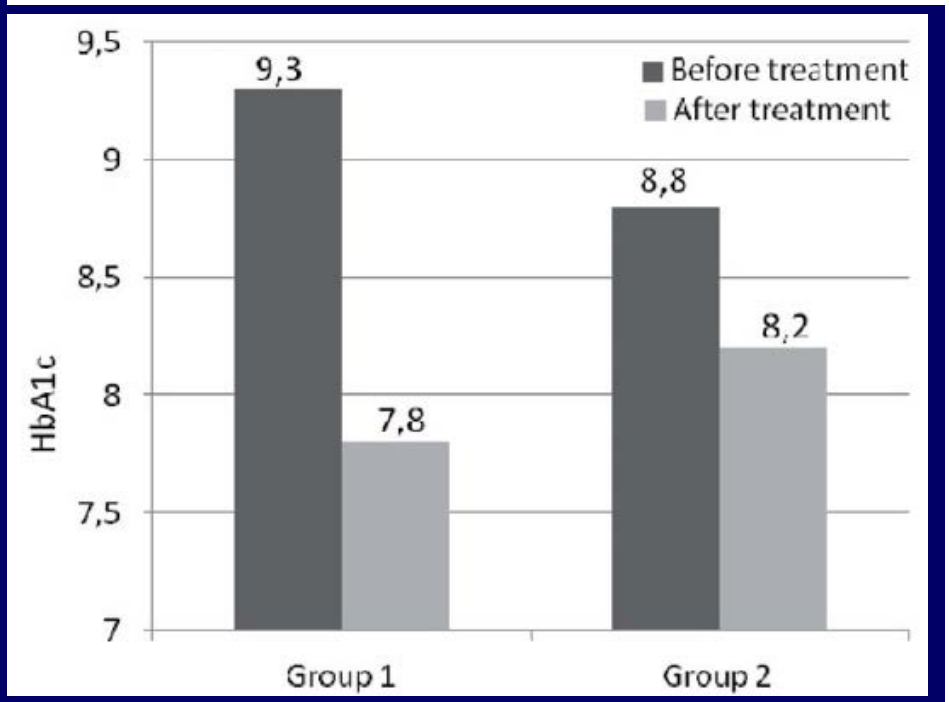
Il sildenafil, attualmente ancora l'unico PDE5i in formulazione generica, ha un ottimo sulla funzionalità erettile nei pazienti diabetici

The effect of lifestyle modification and glycemic control on the efficiency of sildenafil citrate in patients with erectile dysfunction due to type-2 diabetes mellitus

Aging Male, 2015; 18(4): 244–248

Utku Kirilmaz, Ozer Guzel, Yilmaz Aslan, Melih Balci, Altug Tuncel & Ali Atan



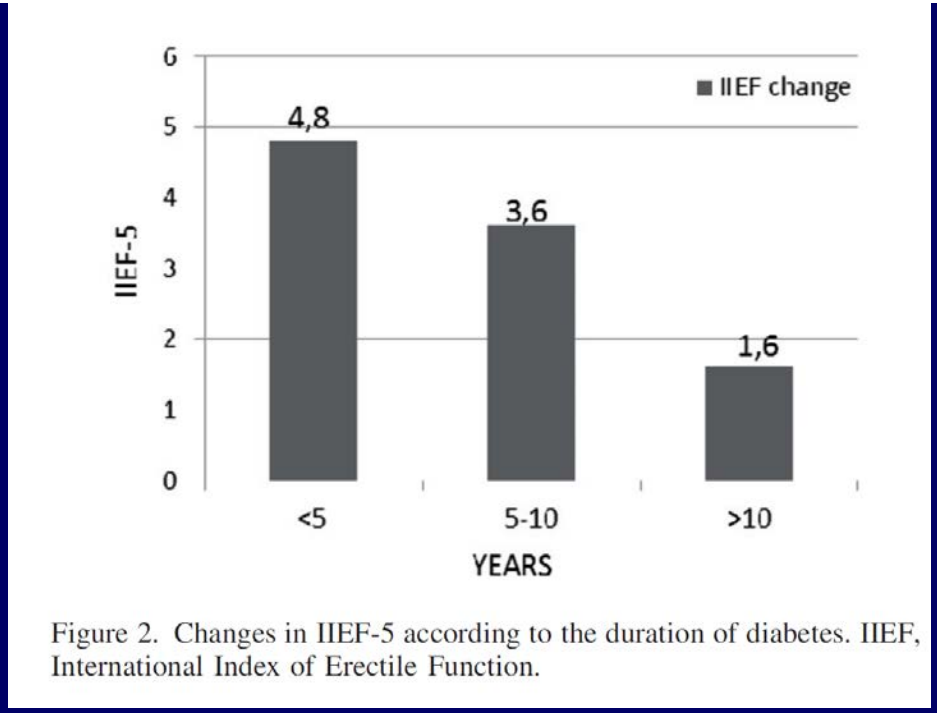


Figure 2. Changes in IIEF-5 according to the duration of diabetes. IIEF, International Index of Erectile Function.

Six months of daily treatment with vardenafil improves parameters of endothelial inflammation and of hypogonadism in male patients with type 2 diabetes and erectile dysfunction: a randomized, double-blind, prospective trial

Daniele Santi[1,2], Antonio R M Granata[2], Alessandro Guidi[2], Elisa Pignatti[1,3], Tommaso Trenti[4], Laura Roli[4], Roberto Bozic[5], Stefano Zaza[6], Chiara Pacchioni[7], Stefania Romano[7], Jerzy Roch Nofer[8], Vincenzo Rochira[1,2], Cesare Carani[1] and Manuela Simoni[1,2,3]

Un trattamento cronico con vardenafil 10 mg bid per 24 settimane ha avuto effetti benefici sull'IIEF-15 e sull'IL6
Possibile effetto antinfiammatorio endoteliale con trattamento cronico?

Table 1 Endothelial health-related parameters in the 54 patients enrolled in the study. Values are expressed as mean ± S.D. and Mann–Whitney test was performed for comparison.

	Vardenafil	Placebo	*P* value
Number of patients	26	28	–
IIEF-15 – erectile function domain			
Baseline	16.62 ± 7.90	17.68 ± 7.51	0.614
End of treatment	26.00 ± 4.59	17.92 ± 8.38	**< 0.001**
End of follow-up	14.38 ± 5.73	14.04 ± 6.39	0.853
P value	**< 0.001**	**< 0.001**	
Fibrinogen (mg/dl; NR: 150–450)			
Baseline	267.24 ± 107.59	312.71 ± 51.45	0.215
End of treatment	272.50 ± 85.77	299.72 ± 46.27	0.187
End of follow-up	270.35 ± 67.28	286.12 ± 53.23	0.385
P value	0.468	0.282	
FMD (%; NR: >7)			
Baseline	6.83 ± 3.89	7.87 ± 5.09	0.308
End of treatment	8.57 ± 2.84	6.41 ± 2.77	**0.040**
End of follow-up	7.07 ± 4.66	6.22 ± 3.49	0.488
P value	0.295	0.194	
Hs-CRP (mg/dl; NR: <0.5)			
Baseline	0.22 ± 0.35	0.29 ± 0.50	0.510
End of treatment	0.23 ± 0.46	0.19 ± 0.19	0.378
End of follow-up	0.15 ± 0.17	0.21 ± 0.18	0.237
P value	0.890	0.926	
IL6 (pg/ml)			
Baseline	4.24 ± 1.81	4.01 ± 1.29	0.144
End of treatment	2.67 ± 0.99	3.79 ± 1.81	**0.017**
End of follow-up	2.69 ± 0.90	2.95 ± 1.11	0.871
P value	**< 0.001**	0.181	
ET-1 (pg/ml; NR: 0.47–2.00)			
Baseline	1.43 ± 0.37	1.41 ± 0.38	0.819
End of treatment	1.34 ± 0.38	1.42 ± 0.40	0.457
End of follow-up	1.25 ± 0.35	1.37 ± 0.45	0.350
P value	0.727	0.962	
ICAM-1 (ng/ml)			
Baseline	9.93 ± 1.87	1.30 ± 2.21	0.410
End of treatment	7.12 ± 1.77	1.32 ± 2.01	0.664
End of follow-up	7.42 ± 1.82	1.24 ± 2.01	0.689
P value	0.514	0.825	
VCAM-1 (ng/ml)			
Baseline	8.0 ± 3.2	7.8 ± 2.9	0.887
End of treatment	7.54 ± 3.2	7.09 ± 2.64	0.837
End of follow-up	7.96 ± 4.49	7.07 ± 2.34	0.999
P value	0.934	0.374	

NR, normal range.

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Vardenafil, a New Phosphodiesterase Type 5 Inhibitor, in the Treatment of Erectile Dysfunction in Men With Diabetes

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JAY M. YOUNG, MD[2]
JEROME FISCHER, MD[3]
KEITH BANGERTER, PHD[4]
THOMAS SEGERSON, MD[4]
TERRY TAYLOR, MD[4]
THE VARDENAFIL DIABETES STUDY GROUP

Diabetes Care 26:777–783, 2003

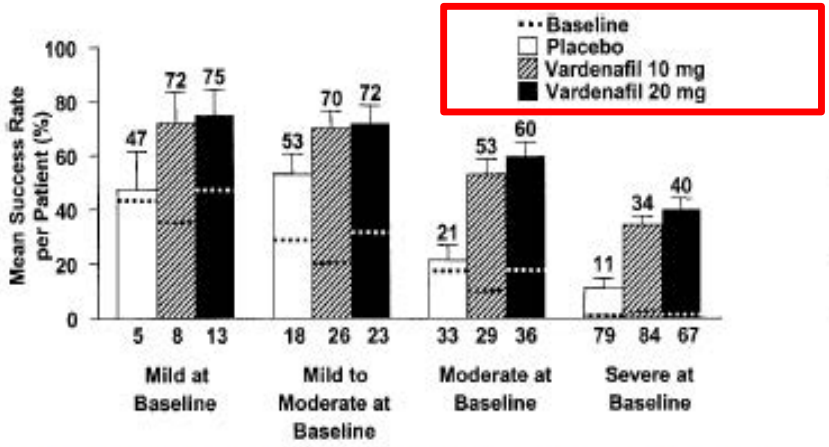

Figure 2—*Efficacy by baseline severity of ED. Rate of successful intercourse ("Did your erection last long enough for you to have successful intercourse?") was determined based on patient baseline ED severity (EF domain scores: mild 22–25, mild to moderate 17–21, moderate 16–11, severe <11) (14). Results presented are the mean (least square) success rates per patient calculated for all attempts over the course of treatment.*

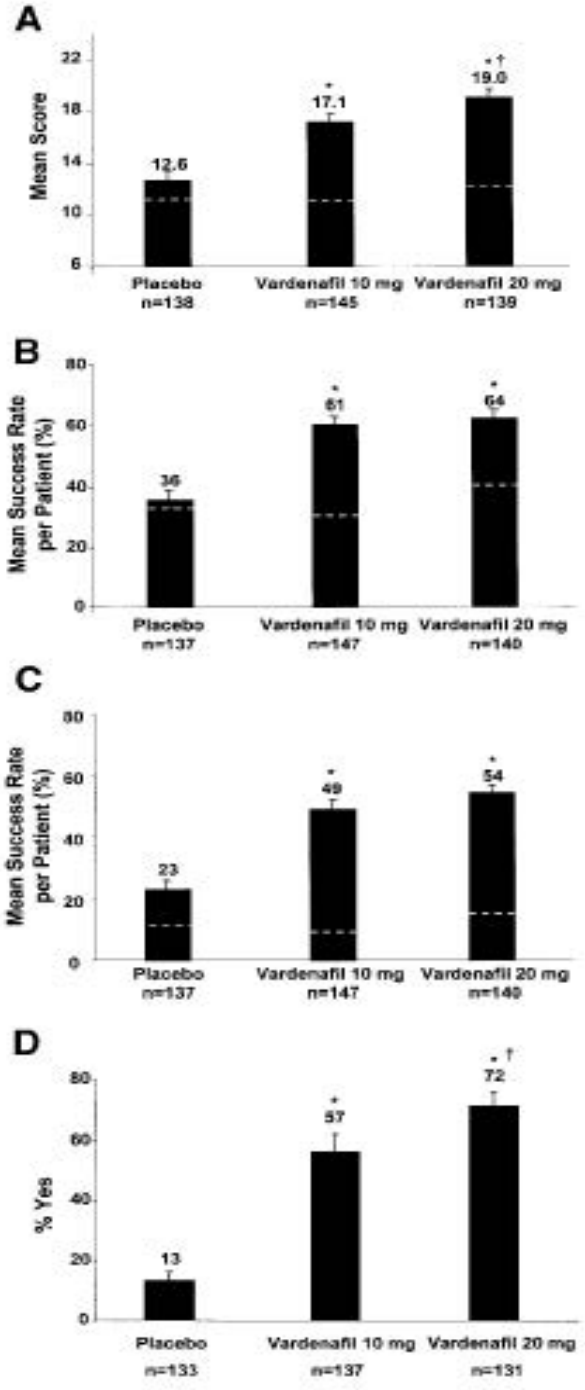

Figure 1—*Primary and secondary efficacy variables. A: EF domain of the IIEF: mean scores (least square) at 12 weeks (LOCF). A score <11 is severe, 11–17 is moderate, 18–25 is mild, and ≥26 is normal. B: Sexual encounter profile (SEP) 2: "Were you able to insert your penis in your partner's vagina?" C: SEP3: "Did your erection last long enough for you to have successful intercourse?" For SEPs, patients recorded their answer ("yes" or "no") in a diary. Results are the mean (least square) per patient value for success rate for all attempts over the course of the 12-week treatment. D: GAQ: "Has the treatment you have been taking over the past 4 weeks improved your erections?" Results are the mean value for patients completing 12 weeks of treatment. Dashed lines represent baseline values. Black bars represent efficacy values after 12 weeks. *P < 0.0001 compared with placebo; †P < 0.03 compared with 10 mg vardenafil.*

Vardenafil 20-mg demonstrated superior efficacy to 10-mg in Japanese men with diabetes mellitus suffering from erectile dysfunction

International Journal of Urology (2006) **13,** 1066–1072

NOBUHISA ISHII,[1] KOICHI NAGAO,[1] KEITA FUJIKAWA,[3] TAKASHI TACHIBANA,[3] YASUHIKO IWAMOTO[2] AND SADAO KAMIDONO[4]

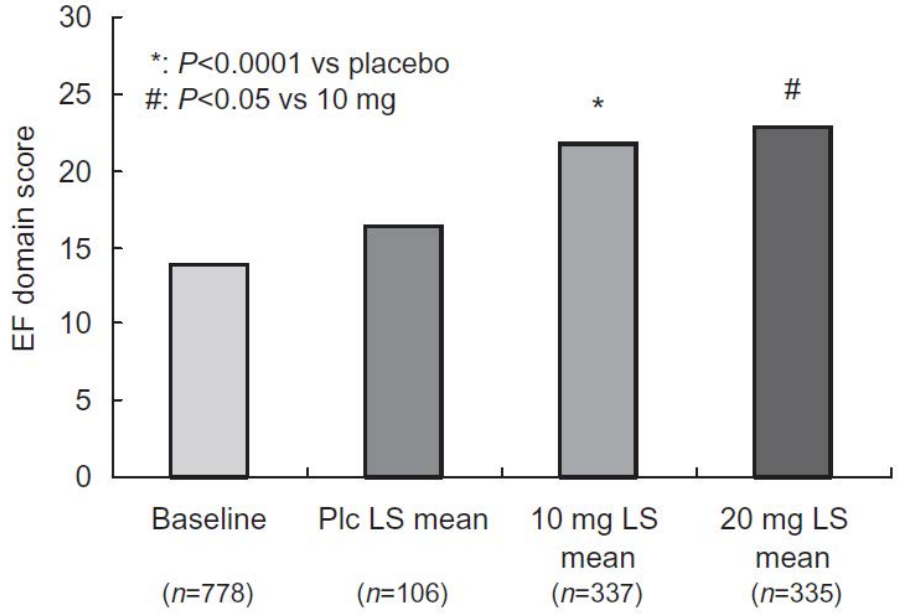

Fig. 2 Vardenafil 10 mg and 20 mg demonstrated significant improvement of IIEF-EF domain score at week 12 (last observation carried forward) compared to placebo. Vardenafil 20 mg demonstrated superior efficacy to 10 mg ($P < 0.05$).

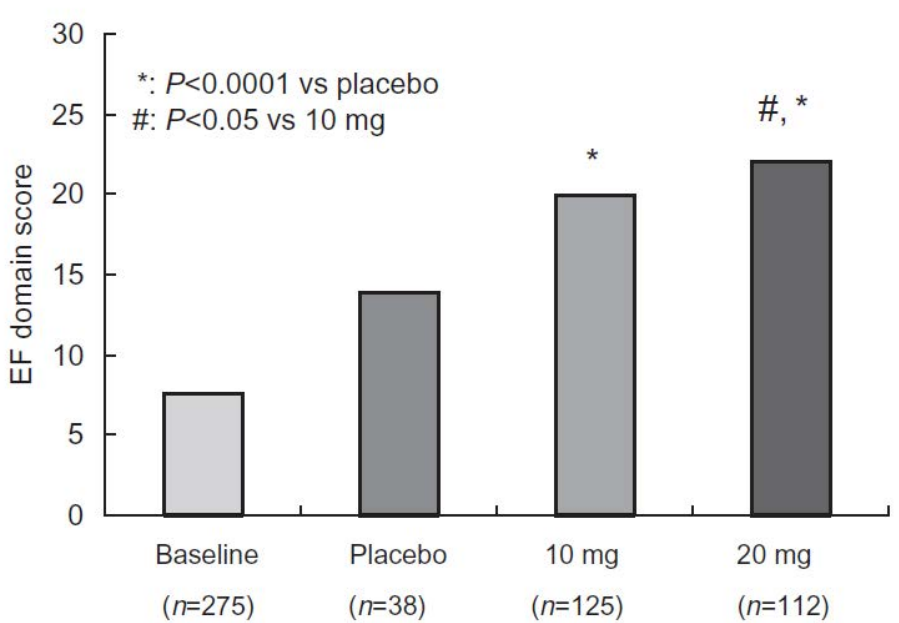

Fig. 3 The difference on efficacy between 10 mg and 20 mg was more evident in severe erectile dysfunction patients (baseline IIEF EF domain score <11).

 ■ Mayo Clin Proc. 2012;87(9):843-852

Avanafil for the Treatment of Erectile Dysfunction: A Multicenter, Randomized, Double-Blind Study in Men With Diabetes Mellitus

Irwin Goldstein, MD; LeRoy A. Jones, MD; Laurence H. Belkoff, DO; Gary S. Karlin, MD; Charles H. Bowden, MD; Craig A. Peterson, MS; Brenda A. Trask, BS; and Wesley W. Day, PhD

L'avanafil sia alla dose di 100 mg che di 200 mg appare essere efficace già nei primi 15 minuti dopo l'assunzione

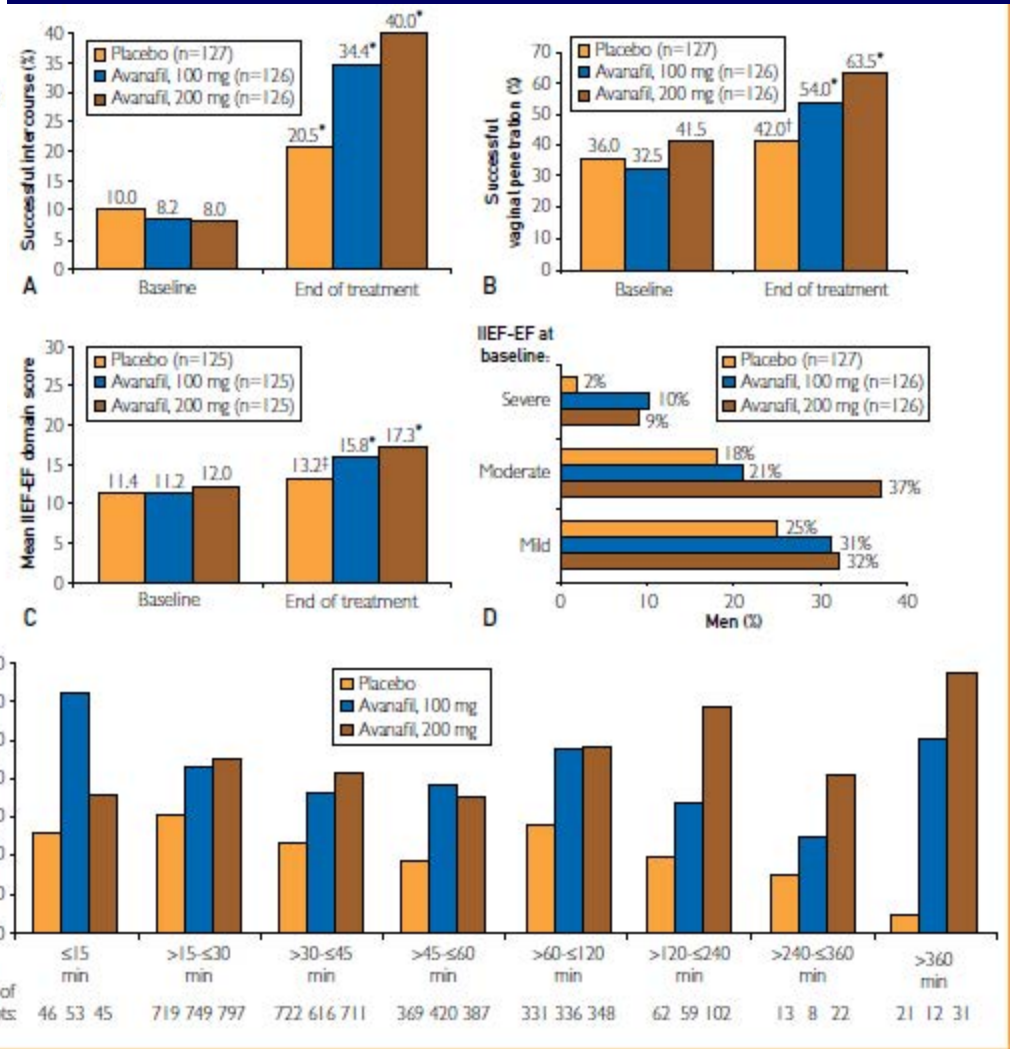

FIGURE 2. Effect of treatment between baseline and the treatment period on Sexual Encounter Profile (SEP) 3 (intent-to-treat [ITT] population) (A) and SEP 2 (ITT population) (B) and from baseline to the end of treatment on International Index of Erectile Function erectile function (IIEF-EF) domain score (ITT population) (C), normalization of IIEF-EF domain score (≥26) (ITT population) (D), and percentage of successful sexual attempts (SEP 3) over time after dosing (ITT last observation carried forward population) (E). *P<.001 vs baseline; †P=.009 vs baseline; ‡P=.007 vs baseline.

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Fra i PDE5i attualmente in commercio l'avanafil sembra avere il più breve onset time of action

Comparison of the efficacy and safety of once-daily dosing and on-demand use of udenafil for type 2 diabetic patients with erectile dysfunction

Asian Journal of Andrology (2015) 17, 143–148

Soon Hyun Park[1], Sung Woo Park[2], Bong Yun Cha[3], Ie Byung Park[4], Kyung Wan Min[5], Yeon Ah Sung[6], Tae Hwa Kim[7], Jae Min Lee[1], Kang Seo Park[1]

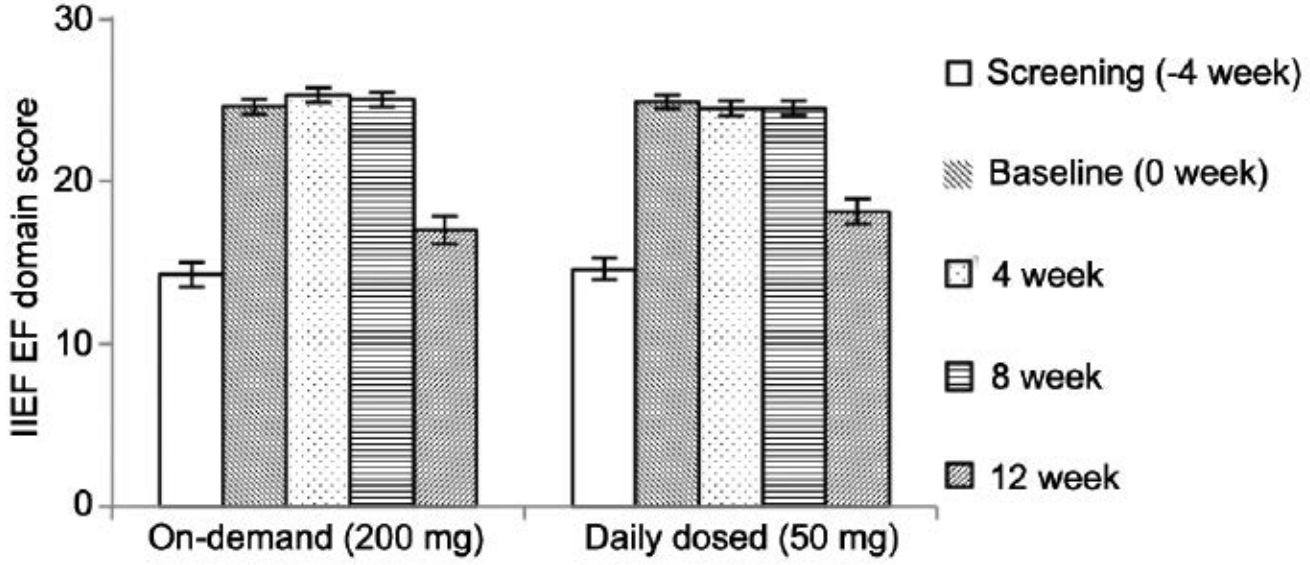

Figure 3: Primary efficacy variable. Erectile function domain score of International Index of Erectile Function in both treatment groups. After 8 weeks of treatment, a significant increase was observed compared with the screening period. After the 4 weeks treatment-free follow-up period, the erectile function domain score decreased significantly in both groups.

Tadalafil in the treatment of erectile dysfunction

Therapeutics and Clinical Risk Management 2008:4(6) 1315–1329

Robert M Coward
Culley C Carson

Division of Urologic Surgery, University of North Carolina, Chapel Hill, NC, USA

Il tadalafil rappresenta un PDE5 inibitore differente rispetto alle altre molecole in commercio:

1. Emivita di 17,5 h negli adulti sani e di 21,6 h negli anziani
2. Finestra terapeutica di circa 36 ore (sono necessarie 48 ore di distanza dall'assunzione di nitrati)
3. Assorbimento non influenzato da pasti grassi e da alcool
4. Possibilità di utilizzo giornaliero (5 mg/die corrispondono ad una concentrazione ematica allo steady state pari ad una somministrazione acuta di 8 mg)
5. T max di 2 h
6. Approvato anche nel trattamento dei disturbi delle vie urinarie inferiori

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Based on these findings, men with diabetes and ED may benefit from daily dosing with PDE5 inhibitors at the onset of treatment, thus leading to an increased therapeutic response with subsequent use. This "priming" phase of therapy could serve to restore or improve endothelial function.

Effects of Tadalafil on Erectile Dysfunction in Men With Diabetes

Iñigo Sáenz de Tejada, MD[1]
Greg Anglin, PhD[2]
James R. Knight, AB, MT (ASCP) SC[3]
Jeffrey T. Emmick, MD, PhD[3]

Diabetes Care 25:2139–2164, 2002

Change in efficacy end points*	Placebo	Tadalafil 10 mg	P†	Tadalafil 20 mg	P‡
n	71	73		72	
ΔIIEF EF domain	0.1	6.4	<0.001	7.3	<0.001
By HbA_{1c} level					0.5068§
Good: <7.0%	−1.0	9.7	—	8.3	
Fair: 7.0–9.5%	−0.9	6.0	—	6.7	
Poor: >9.5%	3.9	3.8	—	8.3	
By concomitant antihypertensive medication use					<0.001‖
Yes	−1.8	3.9	—	9.5	
No	1.1	7.9	—	5.5	
ΔSEP-Q2 (%)	−4.1	22.2	<0.001	22.6	<0.001
By HbA_{1c} level					0.6498§
Good: <7.0%	−13.7	21.0	—	30.6	
Fair: 7.0–9.5%	−3.3	24.1	—	21.0	
Poor: >9.5%	3.7	13.0	—	21.2	
By concomitant antihypertensive medication use					0.004‖
Yes	−4.2	16.4	—	33.8	
No	−4.1	25.8	—	13.4	
ΔSEP-Q3 (%)	1.9	28.4	<0.001	29.1	<0.001
By HbA_{1c} level					0.7939¶
Good: <7.0%	4.4	35.7	—	34.2	
Fair: 7.0–9.5%	−1.7	27.8	—	28.8	
Poor: >9.5%	9.7	21.1	—	26.8	
By concomitant antihypertensive medication use					0.085‖
Yes	−4.5	21.9	—	31.9	
No	5.4	32.5	—	26.9	

Data are % unless otherwise indicated. *Changes from baseline to end point in mean erectile function domain scores (unitless) or in proportions (%) of "yes" responses to SEP-Q2 ("Were you able to insert your penis into your partner's vagina? [yes/no]") or SEP-Q3 ("Did your erection last long enough to have successful intercourse? [yes/no]"). †*P* for comparison of tadalafil 10 mg vs. placebo; ‡*P* for comparison of tadalafil 20 mg vs. placebo; §interaction *P* for difference in response

SAPIENZA
UNIVERSITÀ DI ROMA

Il tadalafil anche alla dose di 10 mg migliora significativamente la funzionalità erettile , in modo più marcato in coloro in quali non utilizzino farmaci per l'ipertensione

Impact of diabetes mellitus on the severity of erectile dysfunction and response to treatment: analysis of data from tadalafil clinical trials

Diabetologia (2004) 47:1914–1923
DOI 10.1007/s00125-004-1549-6

V. Fonseca[1] · A. Seftel[2] · J. Denne[3] · P. Fredlund[4, 5]

[1] Section of Endocrinology and Metabolism, Tulane University Health Sciences Centre, New Orleans, USA
[2] Case Western Reserve University, University Hospitals of Cleveland, Cleveland, Ohio, USA
[3] Lilly Research Laboratories, Indianapolis, Indiana, USA
[4] ICOS Corporation, Bothell, Washington, USA
[5] University of Washington, Seattle, Washington, USA

Table 3. Treatment efficacy

	Diabetic patients			Non-diabetic patients		
	Placebo *n*=201	Tadalafil 10 mg *n*=141	Tadalafil 20 mg *n*=295	Placebo *n*=508	Tadalafil 10 mg *n*=253	Tadalafil 20 mg *n*=920
IIEF erectile function domain						
Mean endpoint score	13.4	19.2	19.9	15.7	21.6	23.9
Change from baseline (mean ± SEM)	0.9±0.6	6.2±0.8[a]	7.4±0.5[a]	0.8±0.3	6.7±0.5[a]	8.9±0.3[a]
SEP diary question 2 (vaginal penetration)						
Mean % success post-baseline	35.8	59.5	64.7	52.8	75.3	82.7
Change from baseline (mean ± SEM)	−0.8±2.5	23.2±3.3[a]	27.0±2.1[a]	3.4±1.2	24.3±2.0[a]	29.9±1.0[a]
SEP diary question 3 (intercourse completion)						
Mean % success post-baseline	21.5	48.6	52.8	33.2	60.9	70.6
Change from baseline (mean ± SEM)	4.1±2.6	29.7±3.4[a]	36.7±2.2[a]	8.8±1.3	34.7±2.3[a]	47.1±1.2[a]
Secondary efficacy measures						
Improved erections (GAQ1)[b]	29.7	60.6[a]	74.5[a]	33.4	72.1[a]	85.8[a]
Return to normal IIEF, %[c]	7.9	35.6[a]	34.3[a]	12.5	40.9[a]	58.1[a]

IIEF evaluable population: diabetic patients: placebo, *n*=194; 10 mg, *n*=137; 20 mg, *n*=283; non-diabetic patients: placebo, *n*=492; 10 mg, *n*=245; 20 mg, *n*=896. SEP evaluable population: diabetic patients: placebo, *n*=194; 10 mg, *n*=139; 20 mg, *n*=286; non-diabetic patients: placebo, *n*=500; 10 mg, *n*=245; 20 mg, *n*=902. [a] $p<0.001$ (pairwise comparison between placebo and treatment). [b] Patients with yes response to GAQ question 1 (percent of the total who answered the question). NB.: Study no. 5 did not administer GAQ. [c] Defined as the percent of patients whose IIEF erectile function domain score improved to ≥26 from a baseline score below 26. IIEF, International Index of Erectile Function; SEP, sexual encounter profile; GAQ, global assessment question

SAPIENZA
UNIVERSITÀ DI ROMA

Il tadalafil migliora significativamente la funzionalità erettile nei pazienti diabetici in modo solo lievemente inferiore ai soggetti sani

Impact of diabetes mellitus on the severity of erectile dysfunction and response to treatment: analysis of data from tadalafil clinical trials

Diabetologia (2004) 47:1914–1923
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[5] University of Washington, Seattle, Washington, USA

Table 4. Treatment efficacy in men with diabetes as a function of diabetes medication

Mean values	No oral agents or insulin			Oral agents only			Insulin		
	Placebo *n*=22	Tadalafil 10 mg *n*=13	Tadalafil 20 mg *n*=28	Placebo *n*=107	Tadalafil 10 mg *n*=80	Tadalafil 20 mg *n*=177	Placebo *n*=72	Tadalafil 10 mg *n*=48	Tadalafil 20 mg *n*=90
IIEF EF domain									
Baseline score	14.2	12.2	15.8	12.9	13.5	12.3	11.4	12.3	12.0
Endpoint score	15.9	23.1	23.3	13.6	19.8	20.6	12.3	17.0	17.4
Change from baseline	1.6	10.9[a]	7.5[a]	0.7	6.3[b]	8.4[b]	0.8	4.7[b]	5.4[a]
SEP Diary question 3									
Baseline % success	21.6	19.7	27.5	18.0	18.9	17.6	15.1	18.5	9.9
Post-baseline % success	26.2	52.0	64.4	25.4	53.7	55.8	14.0	39.0	43.7
Change from baseline	4.6	32.3[a]	36.9[a]	7.4	34.8[b]	38.2[b]	−1.1	20.5[b]	33.8[b]

[a] $p<0.05$ (pairwise comparison between placebo and treatment); [b] $p<0.001$ (pairwise comparison between placebo and treatment).
IIEF, International Index of Erectile Function; SEP, Sexual Encounter Profile

SAPIENZA
UNIVERSITÀ DI ROMA

Il tadalafil migliora significativamente la funzionalità erettile nei pazienti diabetici, anche se in maniera lievemente minori nei soggetti in terapia ipoglicemizzante

Phosphodiesterase inhibitors for erectile dysfunction in patients with diabetes mellitus (Review)

Cochrane Library
Cochrane Database of Systematic Reviews

Vardi M, Nini A *Cochrane Database of Systematic Reviews* 2007, Issue 1. Art. No.: CD002187.

AUTHORS' CONCLUSIONS

Implications for practice

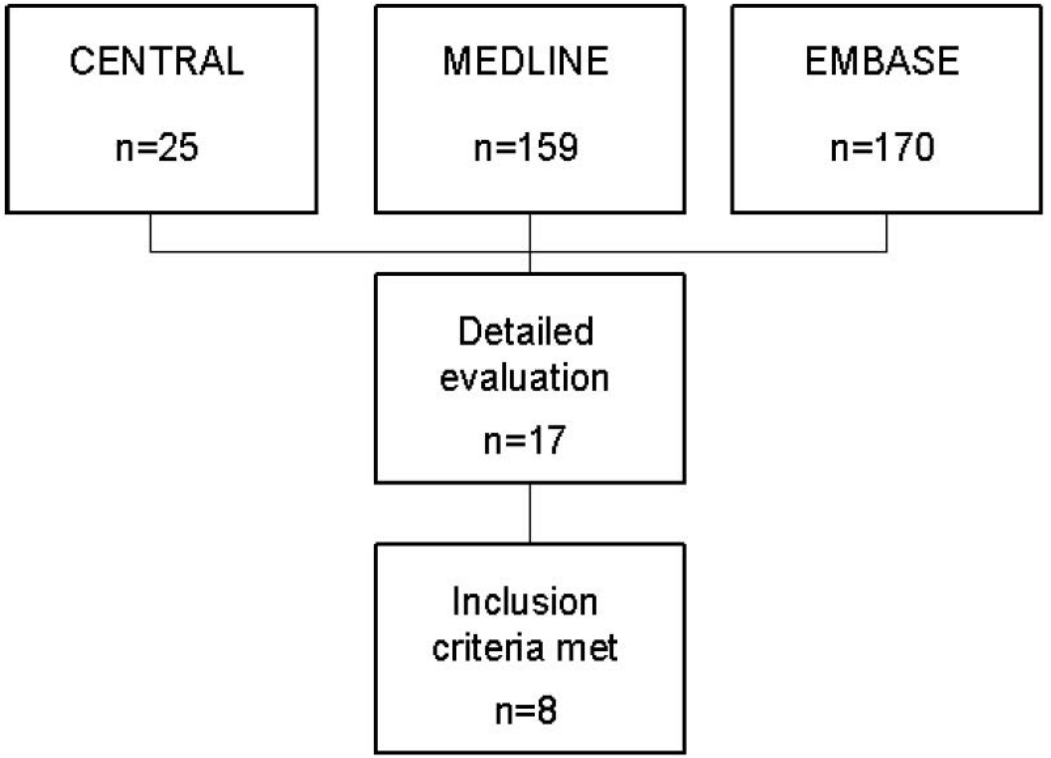
Sufficient evidence exists that phosphodiesterase type 5 (PDE-5) inhibitors form a care that improves erectile dysfunction in diabetic men.

Implications for research

More research is needed in the following areas:

- assessing the effects of PDE-5 inhibitors in uncontrolled diabetic patients with erectile dysfunction;
- assessing the effects of PDE-5 inhibitors in diabetic women with sexual dysfunction;
- further assessment of the effects of PDE-5 inhibitors on the cardiovascular system in diabetic patients who are prone to coronary arterial disease, and may suffer silent ischemia;
- direct comparisons between the three different available PDE-5 inhibitors;
- direct comparisons between PDE-5 inhibitors and other therapeutic options.

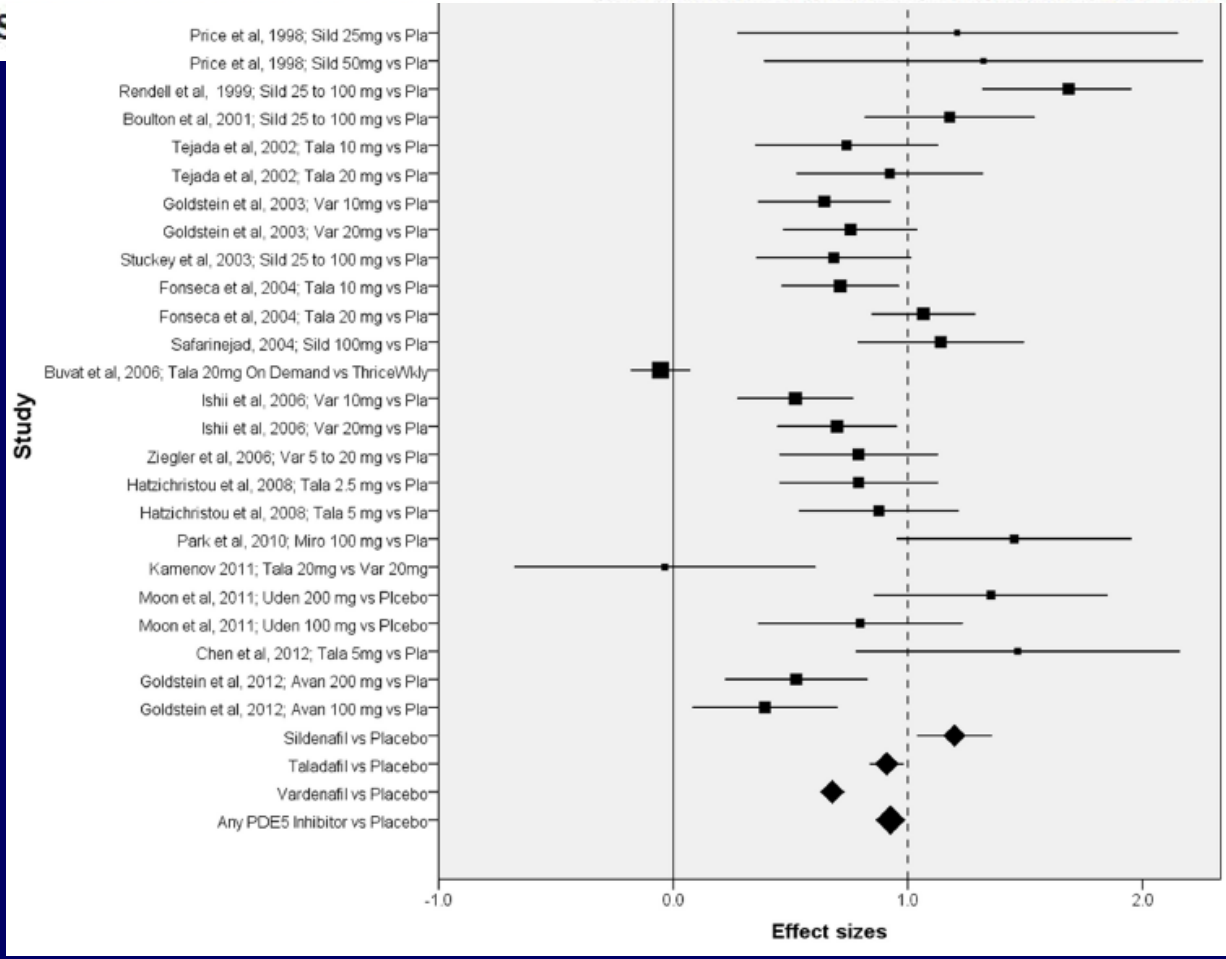
Figure 1.



Phosphodiesterase-5 inhibitors for erectile dysfunction in patients with diabetes mellitus: A systematic review and meta-analysis of randomized controlled trials

2015 Indian Journal of Endocrinology and Metabolism

Yatan Pal Singh Balhara, S



Phosphodiesterase-5 inhibitors for erectile dysfunction in patients with diabetes mellitus: A systematic review and meta-analysis of randomized controlled trials

2015 Indian Journal of Endocrinology and Metabolism

Yatan Pal Singh Balhara, Siddharth Sarkar[1], Rishab Gupta

Table 4: Adverse events with PDE5 inhibitors

Author, year	Comparison	Adverse event rate (%)	Adverse event ratio	Adverse events which were more common than the comparator
Price *et al.*, 1998[25]	Sildenafil 25 mg versus placebo	15 versus 5	3.0	Headache, nausea, dyspepsia
Price *et al.*, 1998[25]	Sildenafil 50 mg versus placebo	23.8 versus 5	4.8	Headache, dyspepsia
Rendell *et al.*, 1999[26]	Sildenafil 25-100 mg versus placebo	16.2 versus 0.8	21.4	Headache, dyspepsia, respiratory tract disorder, flushing, rhinitis, abnormal vision
Boulton *et al.*, 2001[27]	Sildenafil 25-100 mg versus placebo	37.3 versus 6.4	5.8	Headache, flushing, dyspepsia, abnormal vision
Tejada *et al.*, 2002[28]	Tadalafil 10 mg versus placebo	39.7 versus 31.0	1.3	Dyspepsia, headache, myalgia
Tejada *et al.*, 2002[28]	Tadalafil 20 mg versus placebo	44.4 versus 31.0	1.4	Dyspepsia, headache, myalgia, back pain
Goldstein *et al.*, 2003[29]	Vardenafil versus placebo	13 versus 7	1.9	Hot flush, rhinitis, headache
Stuckey *et al.*, 2003[30]	Sildenafil 25-100 mg versus placebo	35.8 versus 14.0	2.6	Headache, flushing, dyspepsia
Safarinejad, 2004[32]	Sildenafil 100 mg versus placebo	22.2 versus 2.9	7.7	Headache, flushing, dyspnea, rhinitis, cardiovascular side effects
Buvat *et al.*, 2006[33]	Tadalafil 20 mg versus thrice weekly	NA	NA	Dyspepsia, headache, flushing, back pain, myalgia
Ishii *et al.*, 2006[34]	Vardenafil 10 mg versus placebo	49 versus 28	1.8	Hot flush, nasal congestion, nasopharyngitis, headache, palpitations
Ishii *et al.*, 2006[34]	Vardenafil 20 mg versus placebo	46 versus 28	1.6	Hot flush, nasal congestion, headache
Ziegler *et al.*, 2006[35]	Vardenafil 5-20 mg versus placebo	29.4 versus 20.6	1.4	Headache, flushing
Hatzichristou *et al.*, 2008[36]	Tadalafil 5 mg versus 2.5 mg versus placebo	NA		Back pain more in 5 mg group than 2.5 mg group
Park *et al.*, 2010[37]	Mirodenafil 100 mg versus placebo	19.6 versus 7.1	2.8	Flushing, nausea, headache, arthralgia
Chen *et al.*, 2012[40]	Tadalafil 5 mg versus placebo	6.7	NA	Flushing, rhinorrhea
Goldstein *et al.*, 2012[41]	Avanafil 100 mg versus placebo	35.4 versus 23.8	1.5	Headache, flushing, sinusitis, influenza
Goldstein *et al.*, 2012[41]	Avanafil 200 mg versus placebo	32.1 versus 23.8	1.3	Headache, flushing, sinus congestion, dyspepsia

Quali possibilità di trattamento della DE?

a) Utilizzo di un PDE5i orale a breve emivita *on demand;*

b) Utilizzo di tadalafil *on demand;*

c) Utilizzo di tadalafil in cronico (come terapia per la disfunzione endoteliale);

d) Utilizzo di tadalafil in cronico + PDEi a breve emivita *on demand ?!?!*

e) Utilizzo di alprostadil intraureterale (Vitaros ™) o per uso intracavernoso (Caverject ™)

Attualmente sono disponibili diverse opzioni farmacologiche per la DE; al clinico va la capacità di operare le scelte più opportune

Quali possibilità di trattamento della DE?

a) Sildenafil (disponibile come farmaco generico) 50 mg e 100 mg; 50 mg Viagra ™ ORO (orosolubile)
b) Vardenafil (Levitra ™)5mg, 10 mg e 20 mg (10 mg anche in versione orosolubile)
c) Avanafil (Spedra ™) 100 mg e 200 mg
d) Tadalafil (Cialis ™) 5mg (approvato per uso cronico), 10 mg e 20 mg
e) Alprostadil intrauretrale (Vitaros ™) 2 mg/g e 3 mg/g
f) Alprostadil intracavernoso (Caverject ™) 10 mcg e 20 mcg

Nella primavera del 2018 sarà disponibilie in formulazione generica anche il tadalafil

Nuova formulazione di sildenafil in film orodispersibile (ODF's) brevettata da IBSA Farmaceutici

Disponibili in 4 dosaggi: 25mg-50mg-75mg-100mg
Saranno disponibili 3 confezioni: da 2,4 e 8 film In commercio da metà Maggio.
Vantaggi della nuova formulazione:
-Migliore aderenza terapeutica
-Comodità e discrezione nell'assunzione, facilmente trasportabile
-Assunzione senz'acqua
-Dissoluzione rapida in pochi secondi
-Dosaggio preciso e uniforme
-Pochi eccipienti (e allergeni): polimero filmante idrosolubile(maltodestrine), plasticizzante, colorante ed aroma
Primi dati di utilizzo suggeriscono una maggiore biodisponibilità se assunto a livello sublinguale limitando al tempo stesso gli effetti indesiderati rispetto alle formulazioni in uso attualmente (compresse e compresse orodispersibili).

Sexual Dysfunction in Type 2 Diabetes at Diagnosis: Progression over Time and Drug and Non-Drug Correlated Factors

Giovanni Corona[1]*, Carlo B. Giorda[2], Domenico Cucinotta[3], Piero Guida[4], Elisa Nada[5], SUBITO-DE Study Group[¶]

PLOS ONE | DOI:10.1371/journal.pone.0157915 October 5, 2016

Table 2. Prevalence of erectile dysfunction (ED) severity based on the International Index of Erectile Function (IIEF) short version score (No ED >21; Mild ED 17–21, Mild-moderate ED 12–16, Moderate ED 8–11, severe ED <8) at baseline (phase 1) and follow-up assessment (phase 2) in the whole study population and after excluding subjects who reported no sexual activity.

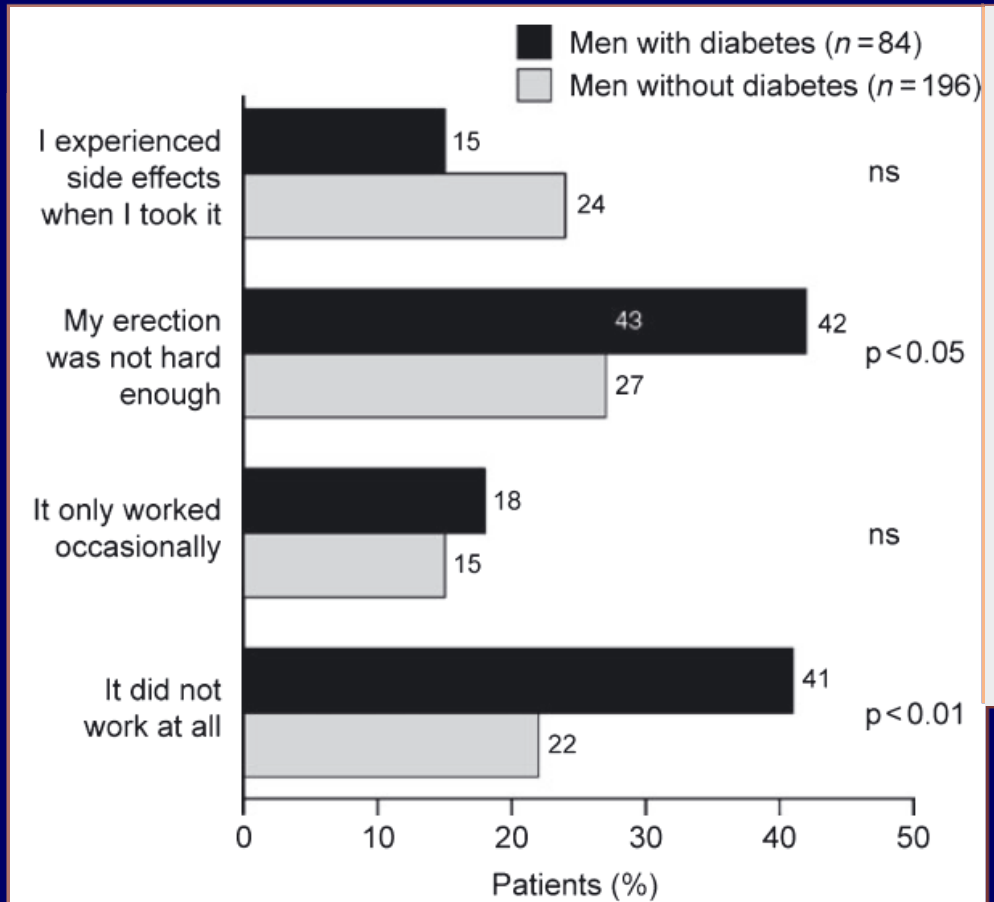
Whole study population	Phase 1 n (%)	Phase 2 n (%)
No sexual activity	82 (18.2)	65 (14.4)
Severe ED	20 (4.4)	14 (3.1)
Moderate ED	41 (9.1)	33 (7.3)
Mild-Moderate ED	68 (15.1)	55 (12.2)
Mild ED	89 (19.8)	87 (19.3)
No ED	150 (33.3)	196 (43.6)
Total	450	450
Excluding subjects who reported no sexual activity	**Phase 1 n (%)**	**Phase 2 n (%)**
Severe ED	18 (5.2)	11 (3.2)
Moderate ED	39 (11.2)	29 (8.3)
Mild-Moderate ED	64 (18.3)	51 (14.6)
Mild ED	84 (24.1)	77 (22.1)
No ED	144 (41.3)	181 (51.9)
Overall ED improvement	-	102 (29.2)*
Overall ED worsening	-	58 (14.9)
Total	349	349

…sexual function is a major concern for men with T2DM. The SUBITO-DE study provides evidence that, when combined with adequate counseling and a tailored PDE5i therapy, an integrated approach to helping men with recently diagnosedT2DM achieve their metabolic targets may also improve sexual function and depressive symptoms.

The multinational Men's Attitudes to Life Events and Sexuality study: the influence of diabetes on self-reported erectile function, attitudes and treatment-seeking patterns in men with erectile dysfunction

Int J Clin Pract, September 2007, **61**, 9, 1446-

I. Eardley,[1] W. Fisher,[2] R. C. Rosen,[3] C. Niederberger,[4] A. Nadel,[5] M. Sand[6]



What's new

The prevalence of ED is greater in men with diabetes compared with those without. The cardiovascular associations of ED are confirmed. Men with diabetes are more likely to consider their ED as severe and permanent, more likely to discuss their condition with a healthcare professional, and more likely to have filled a prescription for an oral PDE5 inhibitor. Discontinuation rates are high, however, because of a perceived lack of efficacy.

Time for one-person trials

Precision medicine requires a different type of clinical trial that focuses on individual, not average, responses to therapy, says **Nicholas J. Schork**.

Muammer Kendirci Curr Opin Urol 16:449–459. © 2006

Table 1 Success and failure rates of sildenafil therapy in men with erectile dysfunction and concomitant risk factors

Risk factors	Per cent success (more than 75% of attempts)	Per cent failure
Neurological disease	85	15
Hypogonadism with testosterone replacement therapy (TRT)	85	15
Alcohol abuse	85	15
Hypogonadism without TRT	75	9
Hypertension	83	17
Smoking	80	20
Multiple medications	77	23
Asthma	76	24
Penile fibrosis	75	25
Asymptomatic coronary artery disease	71	29
Hypertension with diabetes	65	35
Diabetes	63	37
Peripheral vascular disease	63	37
Transurethral resection of the prostate	60	40
Diabetes with neuropathy	50	50
Uncontrolled diabetes	44	56
Postradical prostatectomy	43	57

REVIEW N Mehrotra[1], M Gupta[2], A Kovar[3] and B Meibohm[1]

The role of pharmacokinetics and pharmacodynamics in phosphodiesterase-5 inhibitor therapy

International Journal of Impotence Research (2007) 19, 253–264

Table 3 Contraindications and dose adjustments for PDE5 inhibitors[15,42]

Pharmacodynamic interactions

Contraindications

- *Nitrates*: concomitant use of PDE5 inhibitors with nitrates is absolutely contraindicated as they potentiate the hypotensive effects of nitrates

REVIEW N Mehrotra[1], M Gupta[2], A Kovar[3] and B Meibohm[1]

The role of pharmacokinetics and pharmacodynamics in phosphodiesterase-5 inhibitor therapy

International Journal of Impotence Research (2007) 19, 253–264

Pharmacokinetic interactions

Concomitant medications potentially requiring lower doses of PDE5 inhibitors or administering them with caution

- Ketoconazole
- Itraconazole
- Erythromycin
- Clarithromycin
- HIV protease inhibitors (ritonavir, saquinavir and indinavir): Ritonavir has an unusually high effect on systemic exposure of vardenafil, and 50% dose reduction is warranted
- Grapefruit juice
- Cimetidine
- Antacids: tadalafil's rate of absorption decreased by 30%; no interaction with sildenafil or vardenafil

Concomitant medications potentially requiring higher doses of PDE5 inhibitors

- Rifampin
- Phenobarbital
- Phenytoin
- Carbamazepin

European Association of Urology 2015

MALE SEXUAL DYSFUNCTION - UPDATE MARCH 2015

3A.4.5.1.7.4 α-Blocker interactions

All PDE5Is show some interaction with α-blockers, which under some conditions may result in orthostatic hypotension.

- Sildenafil labelling advises that 50 or 100 mg sildenafil should be used with caution in patients taking an α-blocker (especially doxazosin). Hypotension is more likely to occur within 4 h following treatment with an α-blocker. A starting dose of 25 mg is recommended [99].
- Concomitant treatment with vardenafil should only be initiated if the patient has been stabilised on his α-blocker therapy. Co-administration of vardenafil with tamsulosin is not associated with clinically significant hypotension [102-104].
- Tadalafil is not recommended in patients taking doxazosin, but this is not the case for tamsulosin [101, 118].
- Avanafil labelling currently reports that patients should be stable on α-blocker therapy prior to initiating avanafil. In these patients, avanafil should be initiated at the lowest dose of 50 mg. Conversely, in those patients already taking an optimised dose of avanafil, α-blocker therapy should be initiated at the lowest dose.

Koji Mita

Women's perception of male erectile dysfunction drugs in the general population

Hiroshima, Japan

Maturitas 56 (2007) 216–222

***1262 women*, 20-77 yrs old ,participated.**

83.3% were aware of the existence of ED drugs, but only 12.0% showed some interest in them,

46.4% and 43.2% of the participants claimed to have an unfavorable image of ED drugs, and of men using ED drugs, respectively.

45.2% stated that if their partners suffered from ED at present or in the future, they would not desire their partners to use ED drugs, and 25.5% stated that they would not accept it.

Assessing satisfaction in men and their female partners after treatment with phosphodiesterase type 5 inhibitors for erectile dysfunction

S-T Huang[1,2] and B-P Jiann[3,4]

International Journal of Impotence Research (2013), 1–5

Table 3. Comparison between patients and female partners' treatment satisfaction for ED with PDE5 inhibitors in 111 couples

Variables	*EDITS (n = 111)*	*EDITS Partner (n = 111)*	P-*value*
Index score, mean[a]	79.6 ± 15.0	57.2 ± 27.0	<0.001
Degree of treatment satisfaction (range of Index score)[b] (*n*)			<0.001
Very satisfied (75–100)	73.0% (81)	33.3% (37)	
Satisfied (50–74)	22.5% (25)	27.9% (31)	
Dissatisfied (25–49)	3.6% (4)	29.7% (33)	
Very dissatisfied (0–24)	0.9% (1)	9.0% (10)	

Abbreviations: ED, erectile dysfunction; EDITS, Erectile Dysfunction Inventory of Treatment Satisfaction; PDE5, phosphodiesterase 5.
[a]Paired-samples *t*-test. [b]χ^2 test.

J Sex Med 2012;9:2652–2663

The HelpED Study: Agreement and Impact of the Erection Hardness Score on Sexual Function and Psychosocial Outcomes in Men with Erectile Dysfunction and Their Partners

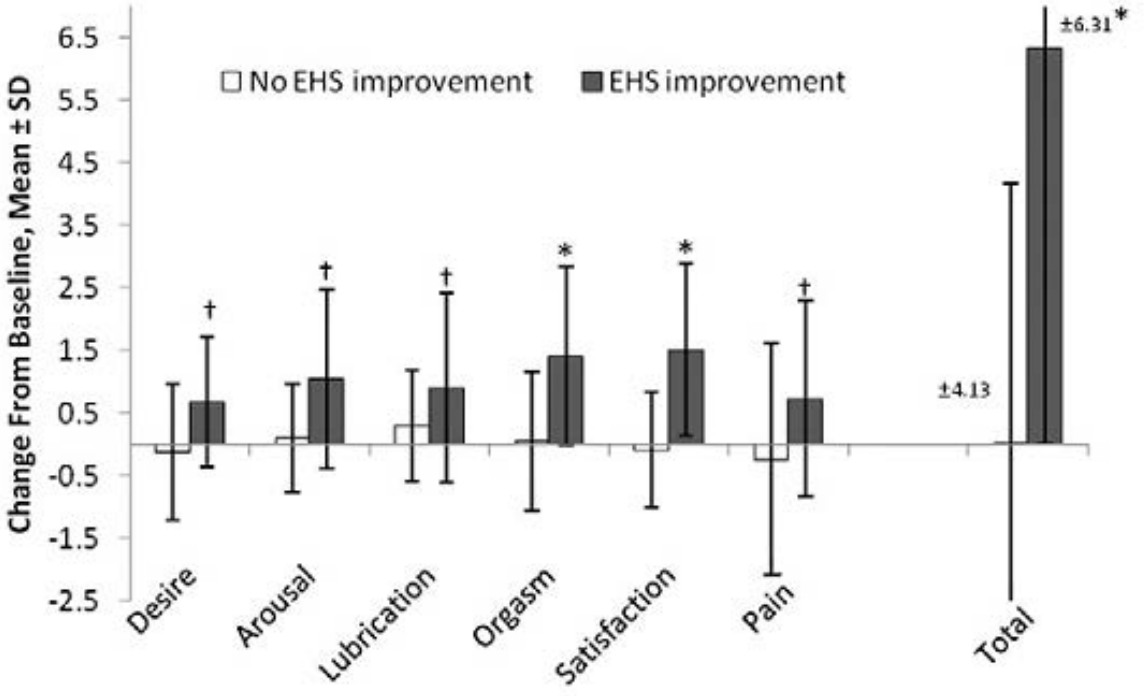


Figure 3 Mean ± SD changes in partners' sexual function (Female Sexual Function Index scores) between partners of patients with (N = 96) and without (N = 29) improvement in EHS assessed by the partner. EHS = Erection Hardness Score. $^{*}P < 0.0001$; $^{\dagger}P < 0.05$ (EHS improvement vs. no EHS improvement).

SOP Conservative (Medical and Mechanical) Treatment of Erectile Dysfunction

Porst ISSM Standards Committee for Sexual Medicine J Sex Med 2013;10:130

Table 6 Pharmacodynamic characteristics of the three PDE5 inhibitors (source: U.S. labels for Cialis®, Levitra®, and Viagra® as of July 2005)

Parameter/condition	Sildenafil	Tadalafil	Vardenafil
CYP 3A4 inhibitors*	Start dose 25 mg	Max. dose 10 mg/72 hours	Max. 2.5 mg/day
CYP 3A4 inhibitors†	Start dose 25 mg Max. dose 25 mg/day	Max dose 10 mg/72 hours	Max. dose: 2.5 mg/72 hours
Age > 65 years	Start dose 25 mg	No dose adjustment	Start dose 5 mg
Severe renal failure (creat. clearance < 30 mL/minutes)	Start dose 25 mg	Max. dose 5 mg	No dose adjustment
Mild/mod. hepatic failure (Child Pugh A/B)	Start dose 25 mg	Max. dose 10 mg	Start dose 5 mg Max. dose 10 mg
Blood pressure drop syst./diast.	8.4/5.5 mm Hg	1.6/0.8 mm Hg	7/8 mm Hg
Alpha blockers	Interval of 4 hours recommended	Stable alpha-blocker therapy recommended. Start dose 5 mg	Stable alpha-blocker therapy recommend. Start dose 10 mg
Antihypertensives (all drug classes)	No interactions of clinical relevance	No interactions of clinical relevance	No interactions of clinical relevance
Alcohol intake (0.5–0.6 g/kg)	No additional hypotensive effect	No additional hypotensive effect	No additional hypotensive effect
Contraindications	Nitrates and NO donors‡	Nitrates and NO donors	Nitrates and NO donors
Safe interval for nitrate medication in emergencies	24 hours	48 hours	24 hours

**CYP 3A4 inhibitors:* erythromycin, ketoconazole, itraconazole: up to 3- to 10-fold increases of the plasma concentrations of the respective PDE5 inhibitors, cimetidine (56% increase of sildenafil plasma concentrations, not valid for vardenafil, tadalafil not reported)

†*CYP 3A4 inhibitors:* protease inhibitors ritonavir, indinavir, saquinavir: increase of plasma concentrations of the respective PDE5 inhibitors between onefold and fivefold for tadalafil and 16-fold for vardenafil

CYP 3A4 inducers: rifampin: decrease of PDE5 inhibitor plasma levels up to 88% (reported for tadalafil)

Treatment Strategy for Non-Responders to PDE5 Inhibitors

Nam Cheol Park[1,2], Tae Nam Kim[1,2], Hyun Jun Park[1,2]

World J Mens Health 2013 April 31(1): 31-35

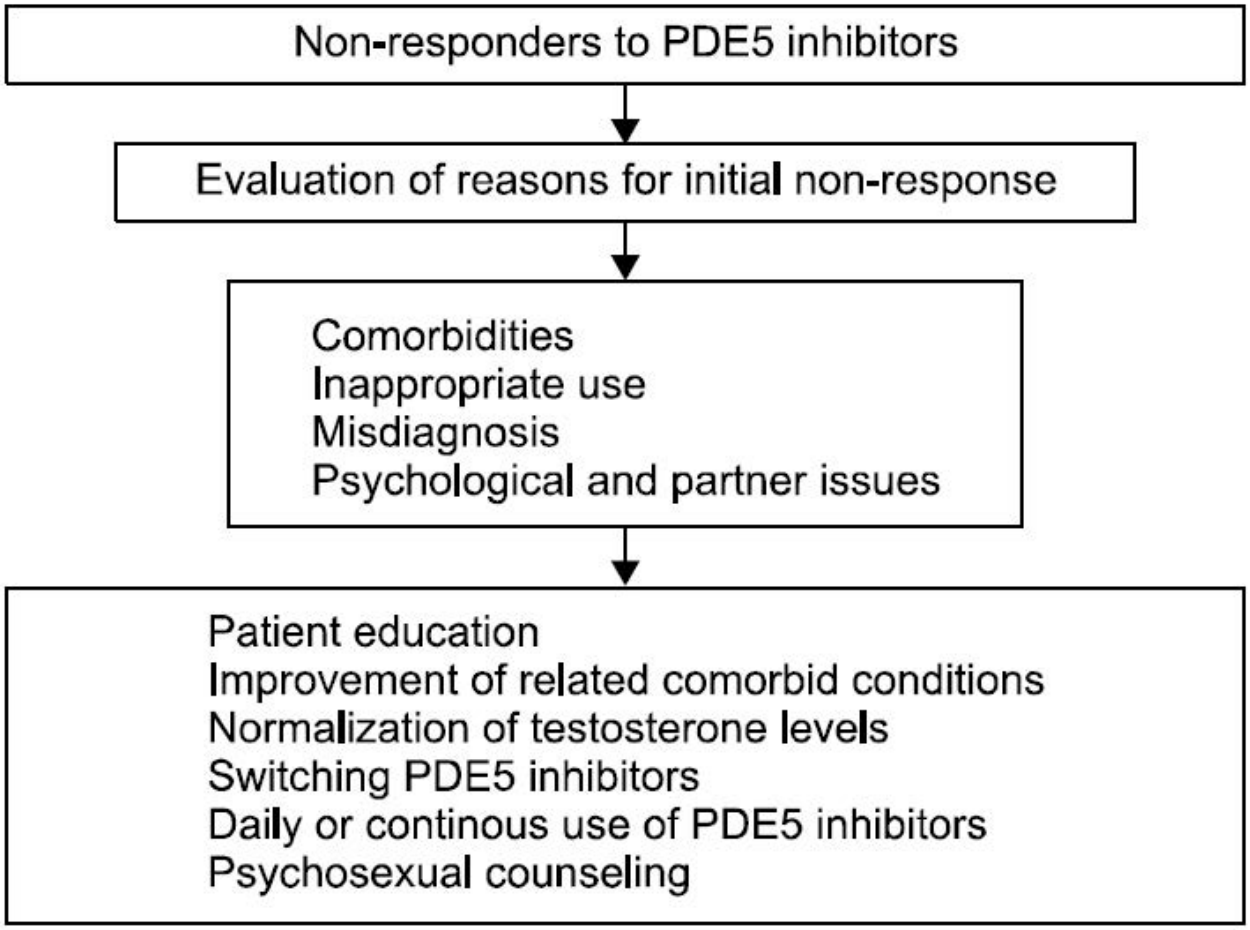


Fig. 1. Treatment strategy for non-responders to PDE5 inhibitors.
PDE: phosphodiesterase.

“COUNSELING”

STRATEGIE ALTERNATIVE

Modificazione fattori di rischio

Correzione ipogonadismo

Trattamento continuativo

Switch terapeutico

Evaluation of Current Errors Within the Administration of Phosphodiesterase-5 Inhibitors After More Than 10 Years of Use

UROLOGY 83: 1334–1338, 2014.

Otero

Table 2. Percentage of patients presenting deviation in the semistructured interview covering 6 main topics related to PDE5i poor response

Question	Percentage
1. Did you have adequate sexual stimulation?	3.2
2. Did you try at least six different days?	32.8
3. Did you reach the maximum dose at which the drug can be administered?	30.8
4. Did you have an empty stomach and/or had ingested alcohol prior to the intake of the drug (except for tadalafil)?	21.6
5. Did you wait at least 1 hour if taking sildenafil or vardenafil and 2 hours in case of tadalafil before initiating the sexual relationship?	17.2
6. Have you tried at least two different types of PDE5i?	40.8

Why Don't Healthcare Professionals Talk About Sex? A Systematic Review of Recent Qualitative Studies Conducted in the United Kingdom

Kerry Dyer

J Sex Med 2013;10:2658

Nineteen interconnected themes emerged relating to healthcare professionals' experience of discussing sexuality with service users, including fear about "opening up a can of worms," lack of time, resources, and training, concern about knowledge and abilities, worry about causing offense, personal discomfort, and a lack of awareness about sexual issues.

The majority of healthcare professionals do not proactively discuss sexuality issues with service users.

Management of Erectile Dysfunction in General Practice

Giorgia De Berardis J Sex Med 2009;6:1127–1134.

Only 9.6% of the GPs reported routinely inquiring about ED of men older than 40 years of age,

45.2% did investigate the presence of ED in patients with identifiable risk factors;

45.2% of the respondents reported inquiring about ED only when the patient raised the problem.

General Practitioners' Procedures for Sexual History Taking and Treating Sexual Dysfunction in Primary Care

J Sex Med 2014;11:386–393

Sofia Ribeiro, MD,* Violeta Alarcão, D. Sociol.,* Rui Simões, MSc,* Filipe Leão Miranda, MA,* Mário Carreira, MD,* and Alberto Galvão-Teles, PhD*†

Results. Of the 50 participants (73.5% response rate), 15.5% actively ask their patients about SD. The main reasons for asking patients about their sexuality are diabetes (84.0%), prescription of medication with adverse effects on sexuality (78.0%), and family planning (72.0%), the latter being a significantly more frequent reason for GPs with 20 or less years of practice. Routine sexual history taking (22.0%) appears as one of the least mentioned motives. The percentage of appointments with active exploration of SD was positively associated with guidelines' consultation, as well as considering the specialty as a good source of information and having longer appointments when SD is mentioned. However, 76.0% report not having consulted any guidelines in the previous year. Lack of time (31.6%) and low accessibility (25.0%) were referred to as the main reasons for not consulting guidelines.

Conclusions. Routine sexual history taking and consultation of guidelines about SD are not yet a generalized practice in primary care.
Data should be interpreted with caution as they are self-reported.
Further objective measurement such as direct observation or clinical files consultation should be implemented.

Trattamento polifarmacologico nei pazienti diabetici

Buona parte dei pazienti diabetici affetti da disfunzione erettile assume diversi altri farmaci per condizioni patologiche interconnesse alla patologia diabetica quali, ad esempio, ipertensione, cardiopatia, dislipidemia, ecc

I farmaci assunti per tale patologie possono avere effetti positivi o negativi sulla DE. Al curante spetta pertanto la scelta corretta in tal senso

Trattamento polifarmacologico nei pazienti diabetici

- *ipertensione;*
- *insufficienza cardiaca;*
- *dislipidemia;*

Table 7 Drugs that may contribute to ED [23,25]

Class	Individual agents
Diuretics	Thiazides
	Spironolactone
Antihypertensives	Methyldopa
	Clonidine
	Reserpine
	Beta-blockers
	Guanethidine
	Verapamil
Cardiac/circulatory	Clofibrate
	Gemfibrozil
	Digoxin
Tranquilizers	Phenothiazines
	Butyrophenones
Antidepressants	Tricyclic antidepressants
	MAOIs
	Lithium
	SSRIs
H_2 antagonists	Cimetidine
	Ranitidine
Hormones	Estrogens/progesterone
	Corticosteroids
	Cyproterone acetate
	5-alpha reductase inhibitors
	LHRH agonists
Cytotoxic agents	Cyclophosphamide
	Methotraxate
	Roferon-A
Anticholinergics	Disopyramide
	Anticonvulsants

ED = erectile dysfunction; MAOIs = monoamine oxidase inhibitor; SSRIs = selective serotonin reuptake inhibitor.

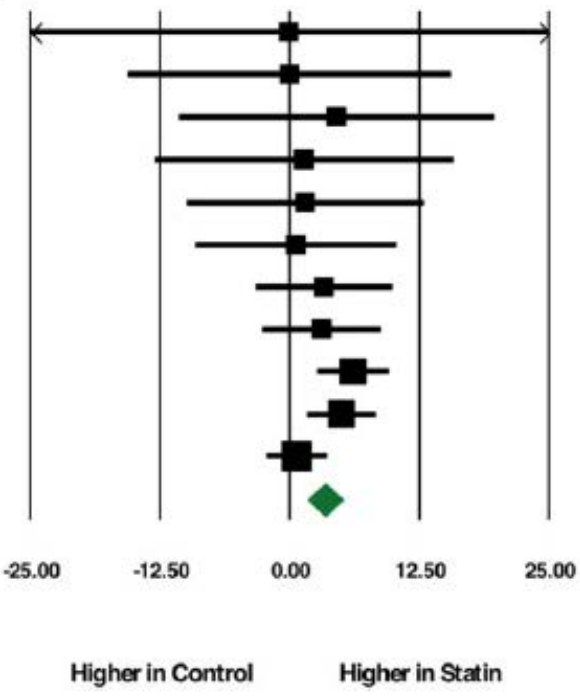
REVIEW

John B. Kostis, MD and Jeanne M. Dobrzynski, BA

The Effect of Statins on Erectile Dysfunction: A Meta-Analysis of Randomized Trials

J Sex Med 2014;11:1626–1635.

Study	Statistics for each study						Sample size	
	Difference in means	Standard error	Lower limit	Upper limit	Z value	P value	Statin	Control
Nurkalem-A	-0.1	134.9	-264.5	264.3	-0.00	0.9994	46	46
Nurkalem-R	-0.0	8.0	-15.6	15.6	-0.00	0.9999	44	44
Bank	4.5	7.8	-10.8	19.8	0.58	0.5637	12	13
Mastalir-P	1.4	7.4	-13.1	15.9	0.19	0.8500	21	20
Mastalir-V	1.5	5.9	-10.0	13.0	0.26	0.7980	21	20
Herrmann	0.6	5.0	-9.1	10.3	0.12	0.9039	8	4
Hong	3.3	3.4	-3.3	9.9	0.97	0.3302	20	23
Dadkhah	3.1	2.9	-2.7	8.9	1.05	0.2931	59	59
El-Sisi	6.1	1.8	2.6	9.6	3.44	0.0006	20	20
Gokce	5.0	1.7	1.6	8.4	2.90	0.0037	41	39
Trivedi	0.7	1.5	-2.3	3.7	0.46	0.6425	68	65
Mean	3.4	0.8	1.7	5.0	3.99	0.0001		



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This meta-analysis indicates that statins are associated with better erectile function as measured by the subjective measure of IIEF score.

The Effect of Statin Therapy on Testosterone Levels in Subjects Consulting for Erectile Dysfunction

Giovanni Corona, MD,*† Valentina Boddi, MD,* Giancarlo Balercia, MD,‡ Giulia Rastrelli, MD,* Giulia De Vita, MD,* Alessandra Sforza, MD,† Gianni Forti, MD,* Edoardo Mannucci, MD,§ and Mario Maggi, MD*

*Andrology Unit, Department of Clinical Physiopathology, University of Florence, Florence Italy; †Endocrinology Unit, Medical Department, Azienda Usl, Maggiore-Bellaria Hospital, Bologna, Italy; ‡Endocrinology Unit, Polytechnic University of Marche, Ancona, Italy; §Diabetes Section Geriatric Unit, Department of Critical Care, University of Florence, Florence, Italy

Le statine possono migliorare la funzionalità endoteliale, ma allo stesso tempo ridurre il livello sierico di testosterone

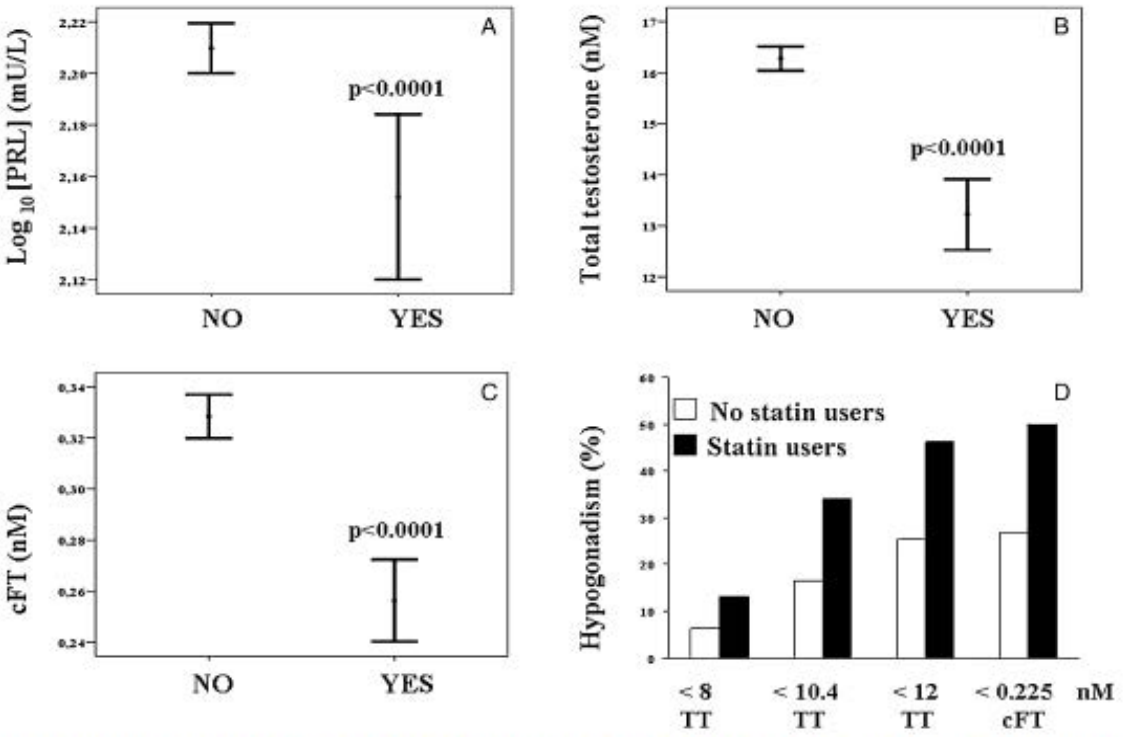

Figure 1 (A–C) Hormonal parameters in patients treated (YES) or not (NO) with statin therapy. Data are expressed as mean [95% confidence interval]. (D) Prevalence of hypogonadism considering different thresholds of TT and cFT, in patients treated or not with statin therapy; all $P < 0.001$. PRL = prolactin; TT = total testosterone; cFT = calculated free testosterone according to Vermeulen formula [28].

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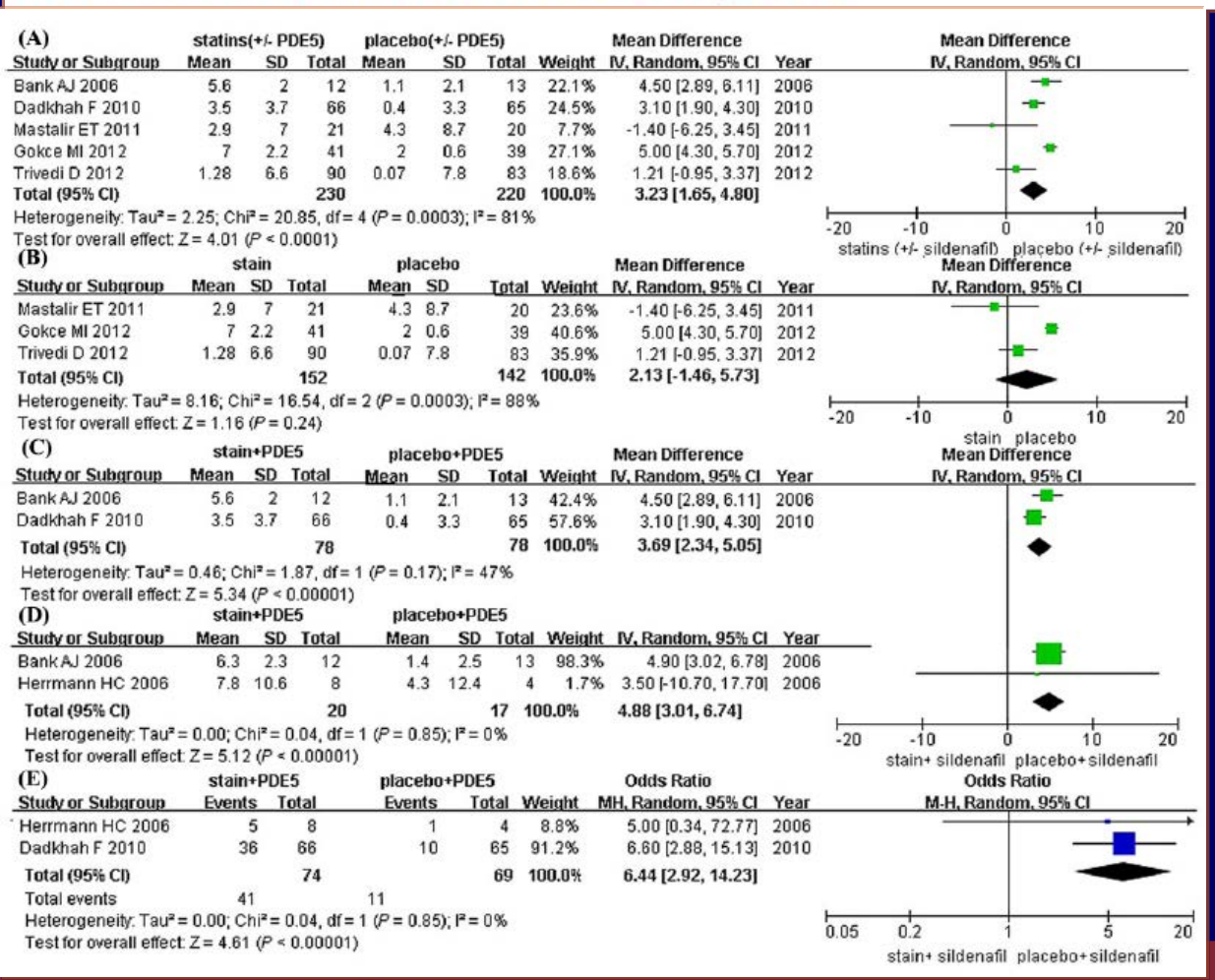
Attenzione alle statine! Double edged sword??????

Yuanshan Cui, MD, Huantao Zong, MD, Huilei Yan, MD, and Yong Zhang, PhD

The Effect of Statins on Erectile Dysfunction: A Systematic Review and Meta-Analysis



J Sex Med 2014;11:1367–1375

This meta-analysis indicates that statins (+/– sildenafil) may improve ED compared with placebo (+/– sildenafil)

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L'effetto antinfiammatorio endoteliale delle statine può migliorare la funzionalità erettile

ORIGINAL ARTICLE

Atorvastatin improves the response to sildenafil in hypercholesterolemic men with erectile dysfunction not initially responsive to sildenafil

International Journal of Impotence Research (2010) 22, 51–60

0955-9930/10 $32.00
www.nature.com/ijir

F Dadkhah[1], MR Safarinejad[2], MA Asgari[1], SY Hosseini[1], A Lashay[1] and E Amini[1]

[1]*Department of Urology, Shahid Modarress Hospital, Shahid Beheshti University (MC), Tehran, Iran and*
[2]*Urology and Nephrology Research Center, Shahid Beheshti University (MC), Tehran, Iran*

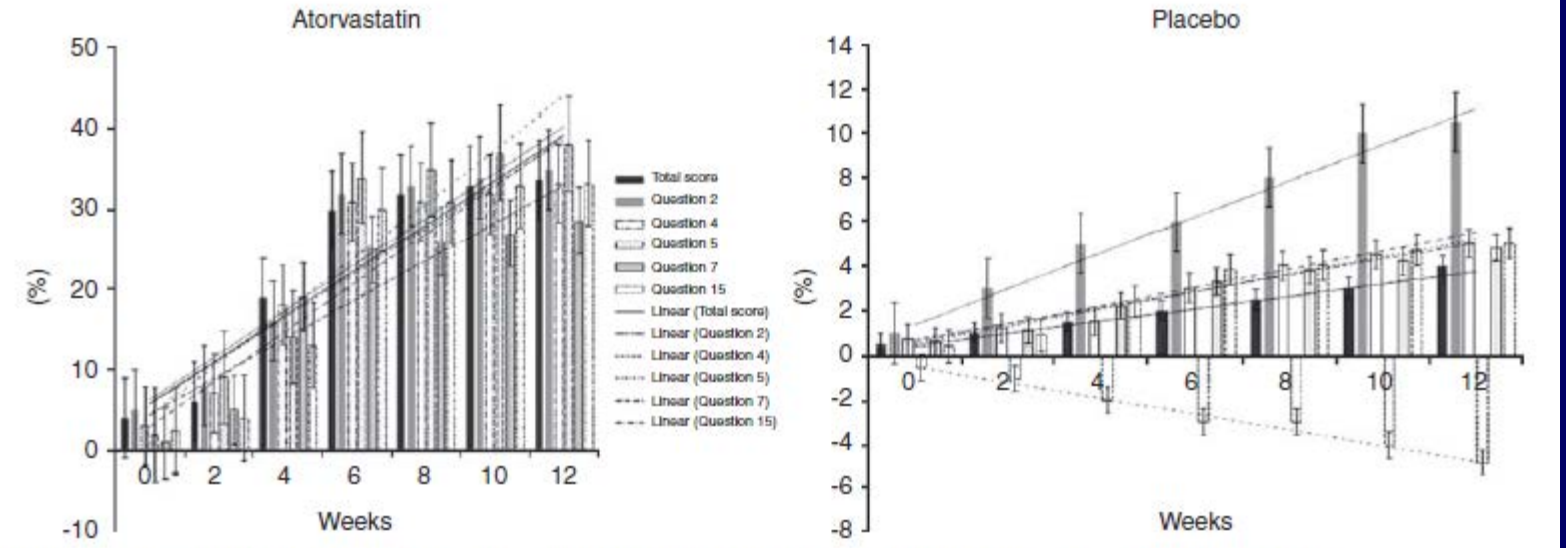

Figure 2 Percentage change in IIEF-5 scores through the study period. IIEF, International Index of Erectile Function.

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L'effetto antinfiammatorio endoteliale delle statine può migliorare la funzionalità erettile

Losartan improves erectile dysfunction in diabetic patients: a clinical trial

International Journal of Impotence Research (2012) 24, 217–220

www.nature.com/ijir

Y Chen[1], S Cui[1], H Lin[1], Z Xu[1], W Zhu[1], L Shi[1], R Yang[1], R Wang[2] and Y Dai[1]

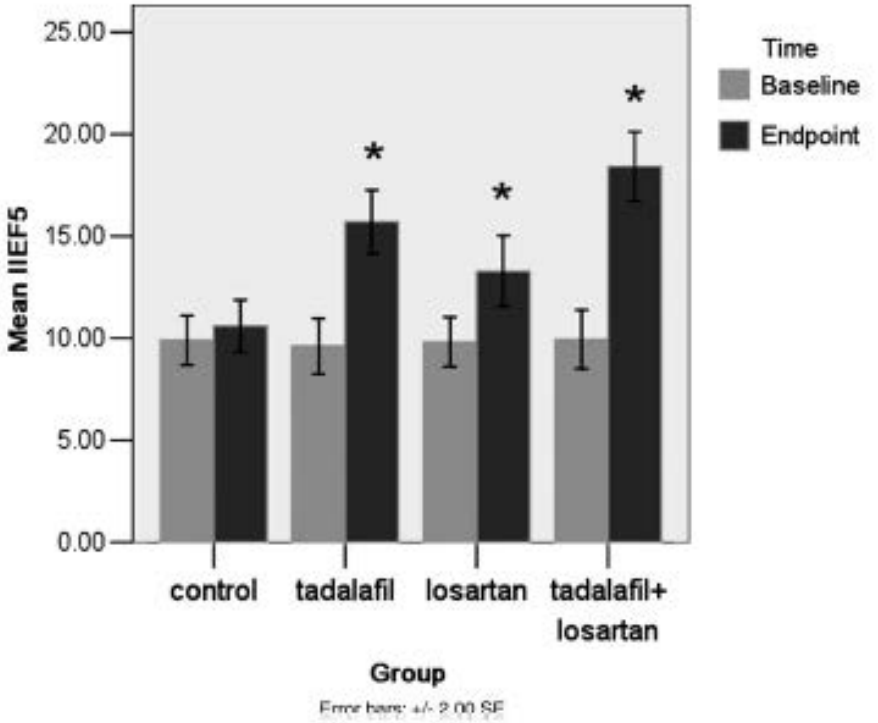

Figure 1. Mean IIEF-5 (International Index of Erectile Function) scores at baseline and endpoint of each group. *$P<0.05$ for end point vs baseline of each group. The treatment of tadalafil, losartan or losartan plus tadalafil were effective on increasing the mean IIEF-5 scores. #$P<0.05$ for tadalafil or losartan vs losartan plus tadalafil at end point. The treatment of the combination of losartan and tadalafil were more effective than single-use.

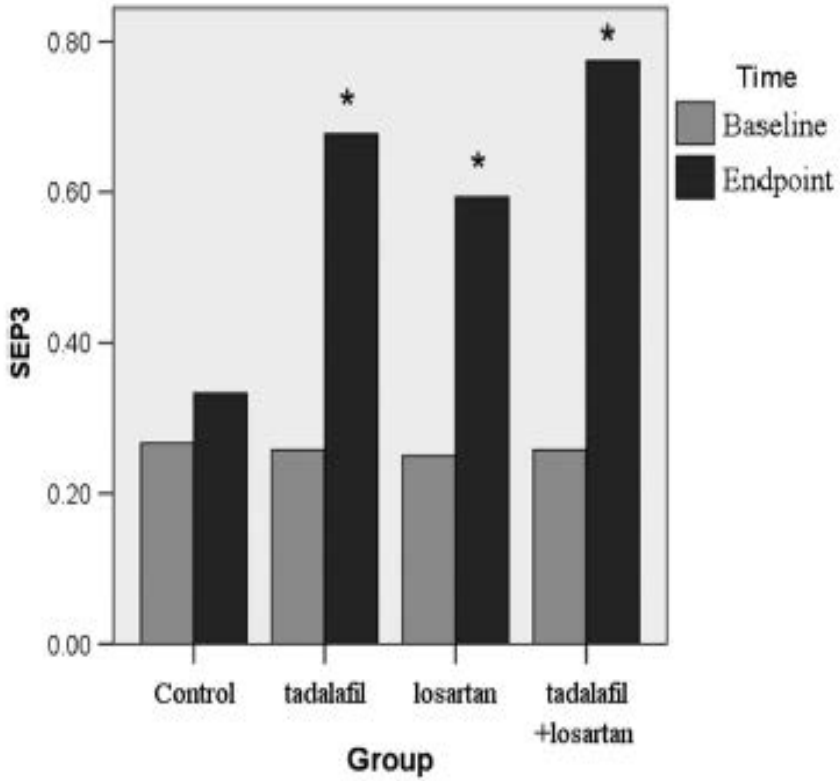

Figure 4. The percentage of positive answers to the sexual encounter profile questions-3 (SEP-3) in diabetic patients with (erectile dysfunction) ED at baseline and following 12 weeks of treatment. *$P<0.05$ for end point vs baseline.

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Losartan, antagonista del recettore AT-1 (ARB), sembra mostrare effetti positivi sulla funzionalità erettile

Pathophysiological role of the renin–angiotensin system on erectile dysfunction

Rodrigo A. Fraga-Silva*, Fabrizio Montecucco†,‡, François Mach†, Robson A. S. Santos§ and Nikos Stergiopulos*

*Institute of Bioengineering, Ecole Polytechnique Fédérale de Lausanne, Lausanne, Switzerland, †Division of Cardiology, Faculty of Medicine, Foundation for Medical Researches, Geneva University Hospitals,Geneva, Switzerland, ‡First Clinic of Internal Medicine, Department of Internal Medicine, University of Genoa, Genoa, Italy, §Department of Physiology and Biophysics, Biological Science Institute, Federal University of Minas Gerais, Belo Horizonte, Minas Gerais, Brazil

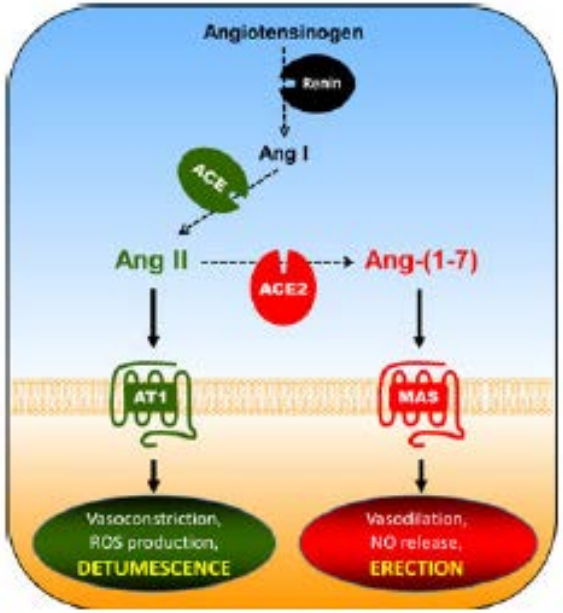

Figure 1 Schematic representation of the renin–angiotensin system (RAS) cascade and its role on erectile function. Focus on the two major axes of the RAS and its major effects on erectile tissues. Ang I, angiotensin I; Ang II, angiotensin II; Ang-(1-7), angiotensin-(1-7); ACE, angiotensin-converting enzyme; ACE2, angiotensin-converting enzyme 2; AT1, angiotensin II type 1 receptor; Mas, Mas receptor.

I sartani permettono la fisiologica produzione dell'eptapeptide Ang (1-7) che attiivando il recettore MAS svolge positivi effetti sulla funzionalità eretile tramite le azioni di:

-Antipertensivo;

--Antifibrotico;

--Antitrombotico;

--Antiossidante;

--Aumento della produzione di NO

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The effects of quinapril and atorvastatin on the responsiveness to sildenafil in men with erectile dysfunction

Alan J Bank[a,b], Aaron S Kelly[a,b], Daniel R Kaiser[a,b], William W Crawford[a], Benjamin Waxman[c], Douglas A Schow[d] and Kevin L Billups[b,e]

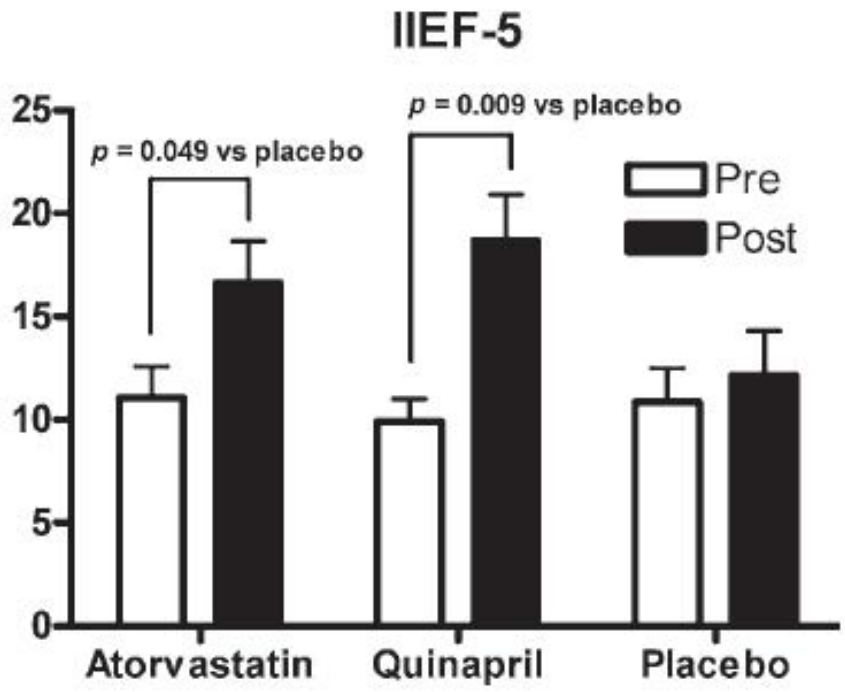

Figure 1 Effects of atorvastatin and quinapril on the IIEF-5 score in men with erectile dysfunction. (IIEF-5 = International Index of Erectile Function-5.)

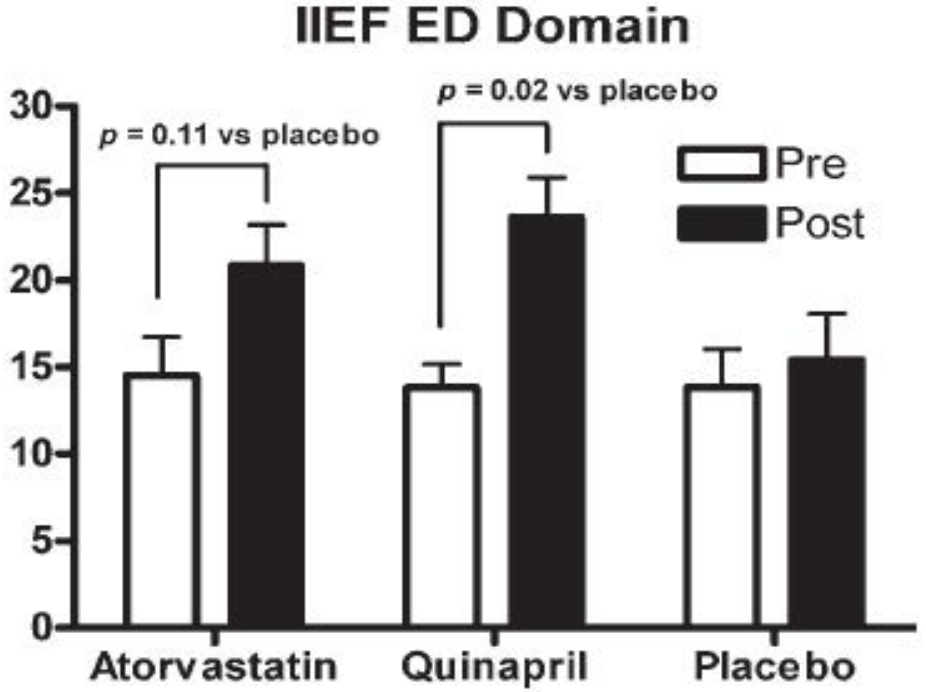

Figure 2 Effects of atorvastatin and quinapril on the IIEF ED Domain score in men with erectile dysfunction. (IIEF ED Domain = International Index of Erectile Function Erectile Dysfunction Domain.)

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Quinapril e atorvastatina sembrano avere positivi sulla DE, in particolar modo il Quinapril

Erectile dysfunction and endothelial disfunction = ED^2

Asian Journal of Andrology (2014) 16, 902–906

A new potential risk factor in patients with erectile dysfunction and premature ejaculation: folate deficiency

Wen-Jie Yan*, Nan Yu*, Tai-Lang Yin, Yu-Jie Zou, Jing Yang

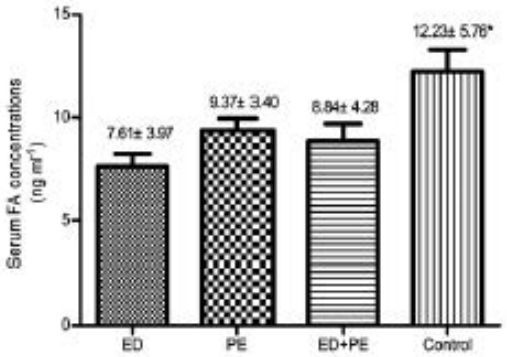

Figure 1: Serum folic acid (FA) concentrations in patients with sexual dysfunctions and in control participants. The bars show the average serum FA concentration in each group. *Significantly higher FA levels.

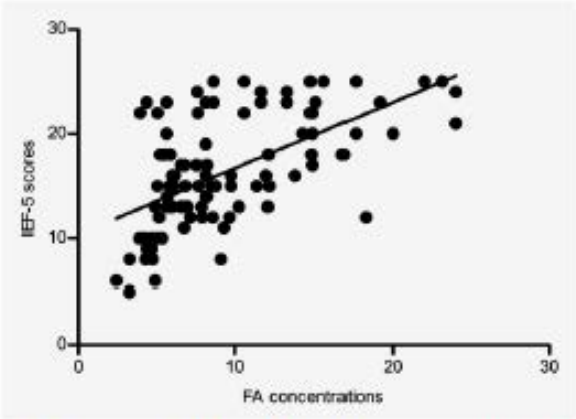

Figure 2: Correlation between International Index of Erectile Function-5 scores and folic acid concentrations. The scatter diagram shows that the correlation coefficient (r) is 0.589, $P < 0.01$.

A role for folate?

Table 2: Correlation coefficients of FA concentrations with clinical parameters

	FA (r)	*P*
Age	0.096	0.271
BMI	–0.142	0.104
LH	0.052	0.551
FSH	–0.110	0.209
Total T	0.134	0.124
IELT	0.445	<0.01
Hcys	–0.508	<0.01
CIPE score	0.530	<0.01
IIEF-5 score	0.589	<0.01

BMI: body mass index; FSH: follicle-stimulating hormone; LH: luteinizing hormone; Total T: total testosterone; Hcys: homocysteine; IELT: intravaginal ejaculation latency time; CIPE: Chinese Index of Premature Ejaculation; IIEF-5: International Index of Erectile Function-5; FA: folic acid

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Assessment of the Efficacy of Combination Therapy with Folic Acid and Tadalafil for the Management of Erectile Dysfunction in Men with Type 2 Diabetes Mellitus

J Sex Med 2013;10:1146–1150

Ali Hamidi Madani, MD, Ahmad Asadolahzade, MD, Gholamreza Mokhtari, MD, Reza Shahrokhi Damavand, MD, Alireza Farzan, MD, and Samaneh Esmaeili, BS

Department of Urology, Urology Research Center, Guilan University of Medical Sciences, Rasht, Iran

Table 2 Comparison of IIEF score before and after treatment in 2 groups

	Group (A)	Group (B)	*P* value
IIEF-score before treatment	11.65 ± 2.67	12.70 ± 2.31	0.066
IIEF-score after treatment	16.80 ± 4.03	14.37 ± 2.17	0.002
P value	0.001	0.001	

Table 3 The changes of IIEF-score in 2 groups

	Group (A)	Group (B)	*P* value
IIEF-score changes	*5.14 ± 3.84	*1.68 ± 0.99	0.001†

*Wilcoxon
†Mann–Whitney

Gruppo A: tadalafil 10 mg a giorni alterni ed acido folico 5 mg per 3 mesi
Gruppo B: tadalafil 10 mg a giorni alterni per 3 mesi

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A role for folate?

Nebivolol Potentiates the Efficacy of PDE5 Inhibitors to Relax Corpus Cavernosum and Penile Arteries from Diabetic Patients by Enhancing the NO/cGMP Pathway

Martínez-Salamanca et al. J Sex Med 2014;11:1182-

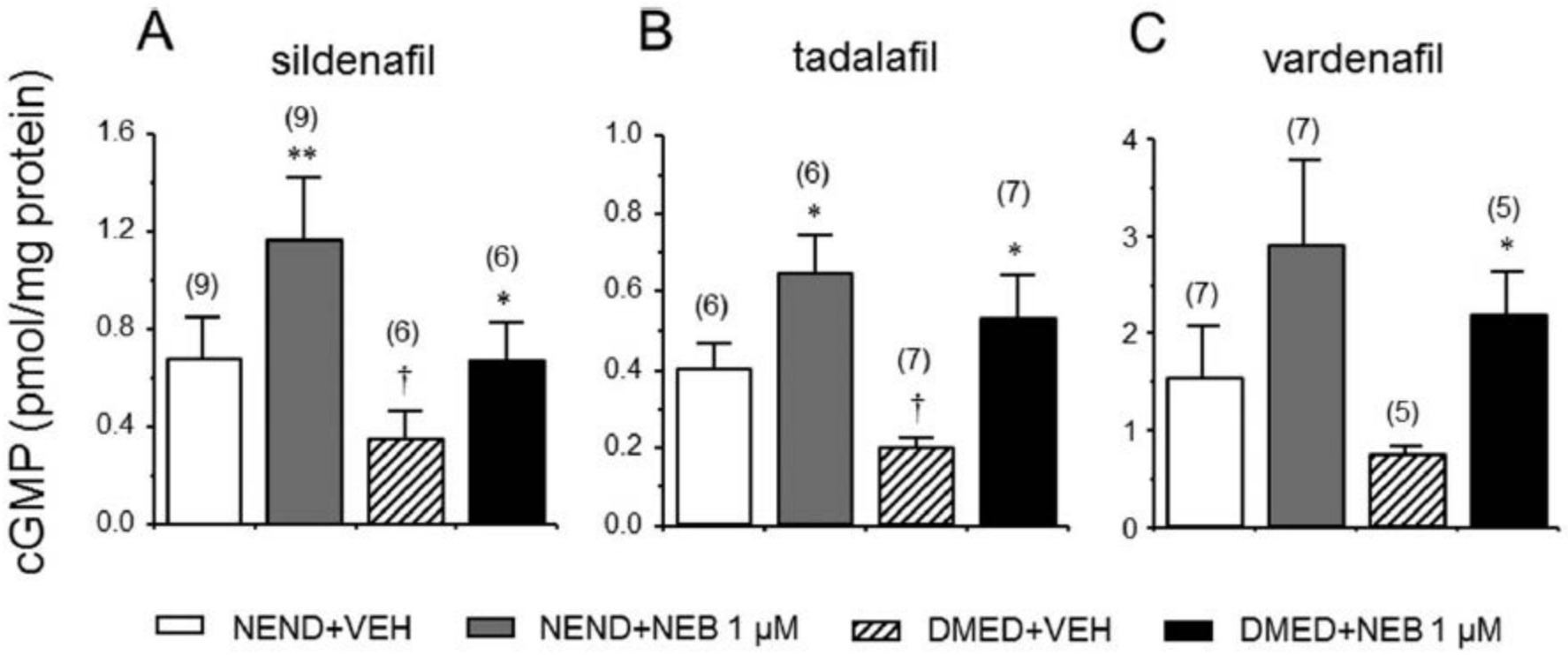
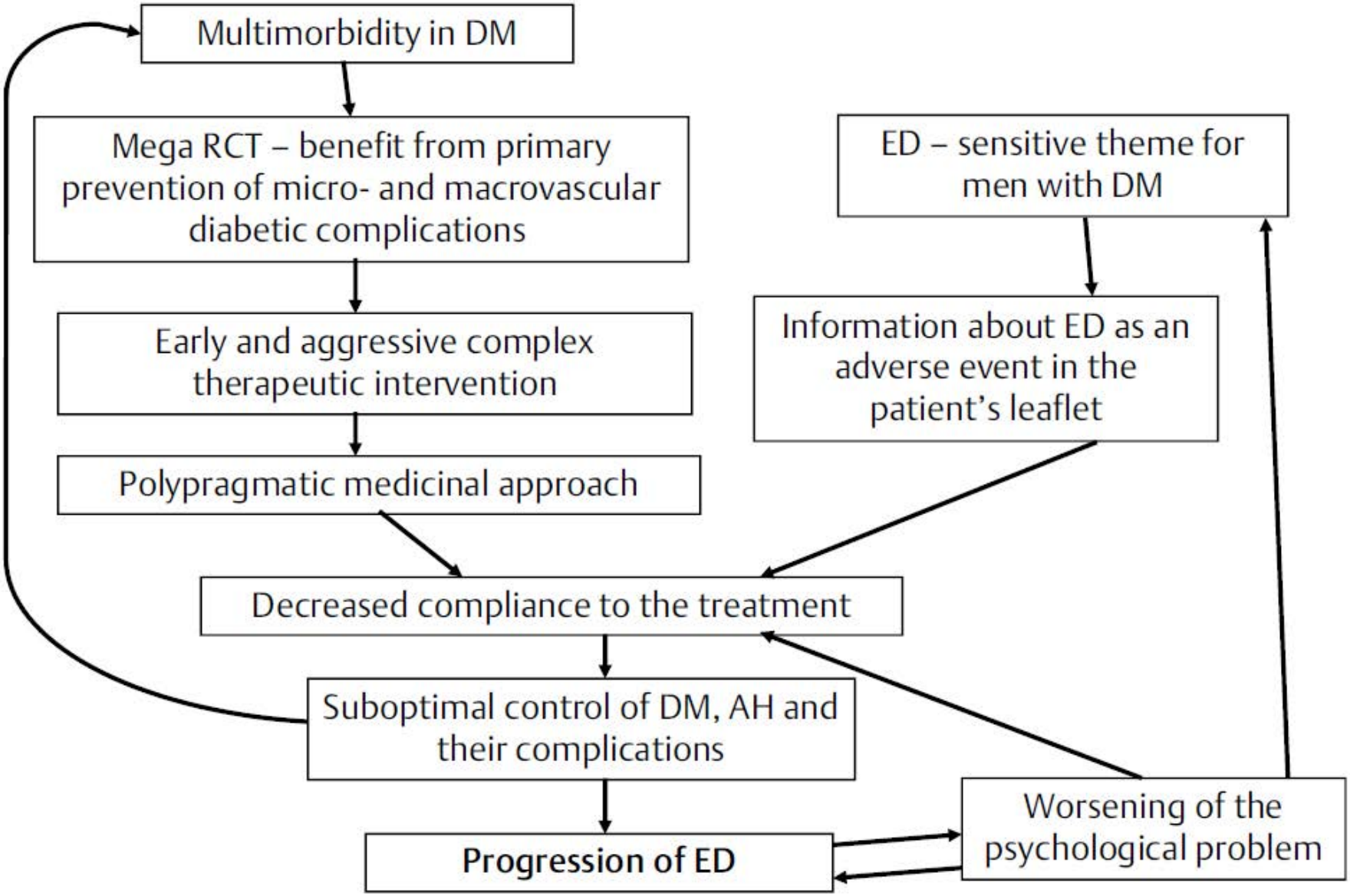


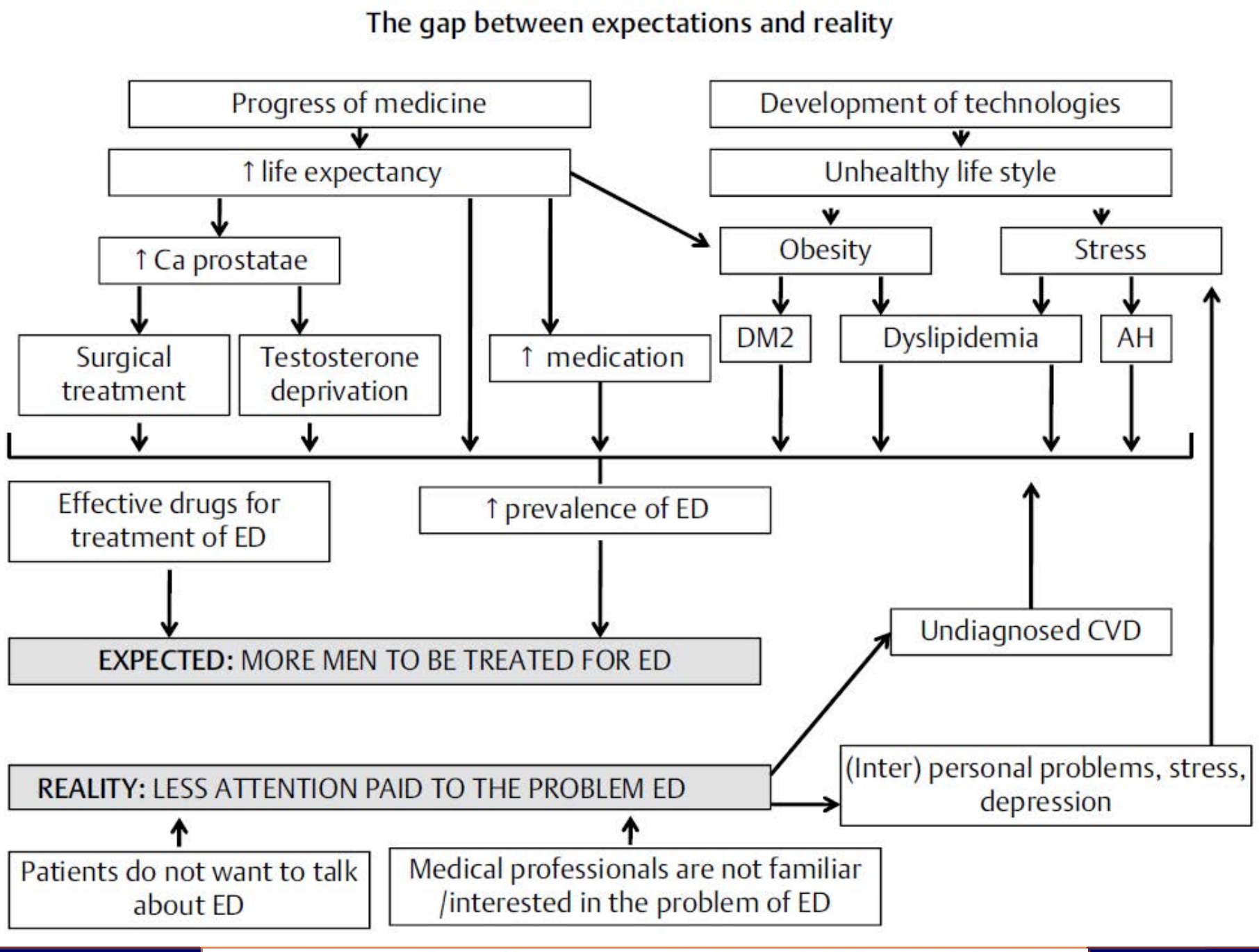
Figure 4 Nebivolol increases cGMP accumulation induced by PDE5 inhibitors in human corpus cavernosum from diabetic patients with ED.

Effects of nebivolol (NEB; 1 μM) or vehicle (VEH; 0.01% DMSO) on cGMP accumulation induced by the PDE5 inhibitors (10 μM), sildenafil (A), tadalafil (B), and vardenafil (C), in human corpus cavernousm from organ donors without a history of diabetes or ED (NEND) and from diabetic patients with ED (DMED). Data are expressed as mean±SEM of pmoles of cGMP per milligram of tissue protein. n indicates the number of patients from whom the tissues were collected. $^{*}P < 0.05$, $^{**}P < 0.01$ vs. vehicle, †$P < 0.05$ vs. NEND by one-factor ANOVA followed by Student-Newmann-Keuls test.

The problem of multiple drugs and the subjective factor in DM



Kamenov ZA. A Comprehensive Review of… Exp Clin Endocrinol Diabetes 2015; 123: 141–158

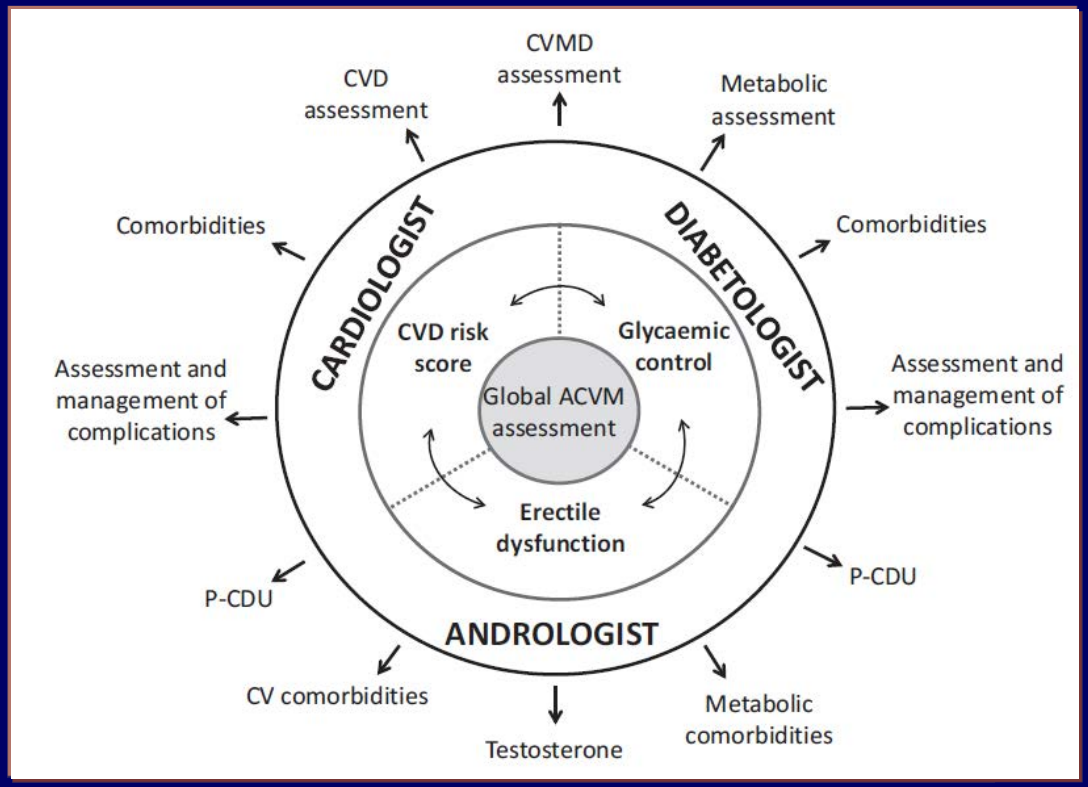


Kamenov ZA. A Comprehensive Review of… Exp Clin Endocrinol Diabetes 2015; 123: 141–158

The great opportunity of the andrological patient: cardiovascular and metabolic risk assessment and prevention

[1]C. Foresta, [1]A. Ferlin, [2]A. Lenzi, [3]P. Montorsi and *Italian Study Group on Cardiometabolic Andrology

Andrology, 1–6



“Parlare è un po' come il sesso quando si invecchia: cominciare diventa ogni giorno un po' più difficile, ma quando hai cominciato non vorresti mai finire.”

Stephen King

Francesco Romanelli

Endocrinologo e Andrologo

Azienda Policlinico Umberto I

Università di Roma "La Sapienza"

Ambulatorio Tel. 06-49972738 e 06-4822430 (IM)

Ufficio (per colleghi) Tel. e fax 06-49970724

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