

Diabete e Sessualita'

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**DALLA MEDICINA DELLE PATOLOGIE
ALLA SFIDA DELLE COMPLESSITÀ:**

evoluzione e prospettive nella gestione della malattia

sabato 18 MAGGIO 2019

DALLA MEDICINA DELLE PATOLOGIE ALLA SFIDA DELLE COMPLESSITA': evoluzione e prospettive nella gestione della malattia diabetica

Monte Porzio Catone, 18 maggio 2019

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World Health Organization

*Nel 1972 e nel 1974,
l'Organizzazione Mondiale
della Sanità dichiara che:*

- ◆◆ **LA SALUTE SESSUALE È
PARTE INTEGRANTE
DELLA SALUTE
DELL'INDIVIDUO**



*“Il sesso è uno
dei nove motivi
per
reincarnarsi...
gli altri otto
sono
ininfluenti.”*

Henry Miller





Diabetes and Sexuality

Fuat Kizilay, MD,¹ Helena Elizabeth Gali, BA,² and Ege Can Serefoglu, MD, FECSM³

ABSTRACT

Introduction: Deterioration in sexual functioning is one of the major and serious complications of diabetes. This common metabolic disorder not only affects sexuality through microvascular and nerve damage but also has psychological aspects. In men, the primary complications are erectile dysfunction, ejaculatory dysfunction, and loss of libido. Women similarly experience sexual problems, including decreased libido and painful intercourse.

Aim: To summarize the effects of diabetes on sexuality, evaluate the impact of diabetes on sexual function, and assess the conventional and novel treatment approaches based on recent studies.

Methods: A literature review of peer-reviewed journal articles and guidelines was performed.

Main Outcome Measures: To assess the effects of diabetes on sexuality and to focus on treatment approaches.

Results: Male and female sexual dysfunctions are a significant complication of diabetes. Tight glycemic control seems to be beneficial in delaying the onset of sexual problems and ameliorating them when they are present. Erectile dysfunction occurs as one of the first problems. The current mainstay of treatment for erectile dysfunction is therapy with phosphodiesterase type 5 inhibitors and then a stepwise approach of management. Men also can experience ejaculation problems and loss of libido. Diabetes also can decrease testosterone levels, which further decreases libido. Hypogonadal men with diabetes might benefit from testosterone replacement therapy. Diabetic women also can have sexual problems. These problems mainly include loss of libido, decrease in arousal and lubrication resulting in painful intercourse, and loss of orgasm. All these challenges require a multidisciplinary approach.

Conclusion: Diabetes has detrimental effects on the sexual function of patients. Diabetologists who primarily care for the patient should not only focus on the glycemic control of their patients but also address their sexual complaints, because these problems can significantly impair their quality of life. Urologists, gynecologists, endocrinologists, and psychiatrists should work in a multidisciplinary manner for the treatment of decreased sexual functioning as a result of diabetes.

Le sessuopatie nel Diabete Mellito

- **MASCHILI**

- *Disfunzione erettile*
- *Patologia Eiaculazione*
- *Desiderio sessuale ipoattivo*
- *Balanopostiti ecc.*
- *M.di La Peyronie*

- **FEMMINILI**

- *Ipolubrificazione*
- *Anorgasmia*
- *Desiderio sessuale ipoattivo*
- *Infezioni vaginali*

Penile Dimensions of Diabetic and Nondiabetic Men With Erectile Dysfunction: A Case–Control Study

Nader Salama

American Journal of Men's Health
1–10
© The Author(s) 2015

Table 4. The Penile Dimensions in the Current and Veale et al. (2015) Studies.

Penile dimension	The current study ($n = 105$, each group)		
	Controls ($M \pm SD$, cm)	Diabetic patients ($M \pm SD$, cm)	Nondiabetic patients ($M \pm SD$, cm)
Total flaccid length	12.88 ± 1.46	11.8 ± 1.94	12.77 ± 1.53
Flaccid circumference	9.14 ± 0.89	8.84 ± 0.82	9.11 ± 0.79
Total erect length	15.04 ± 1.51	13.96 ± 2	14.88 ± 1.48
Erect circumference	11.92 ± 1.06	11.56 ± 1.17	12.06 ± 1.02

In conclusion, diabetic and nondiabetic patients with ED presented, in varying degrees, significant decline in their penile dimensions, and this was more prevalent in diabetic patients.

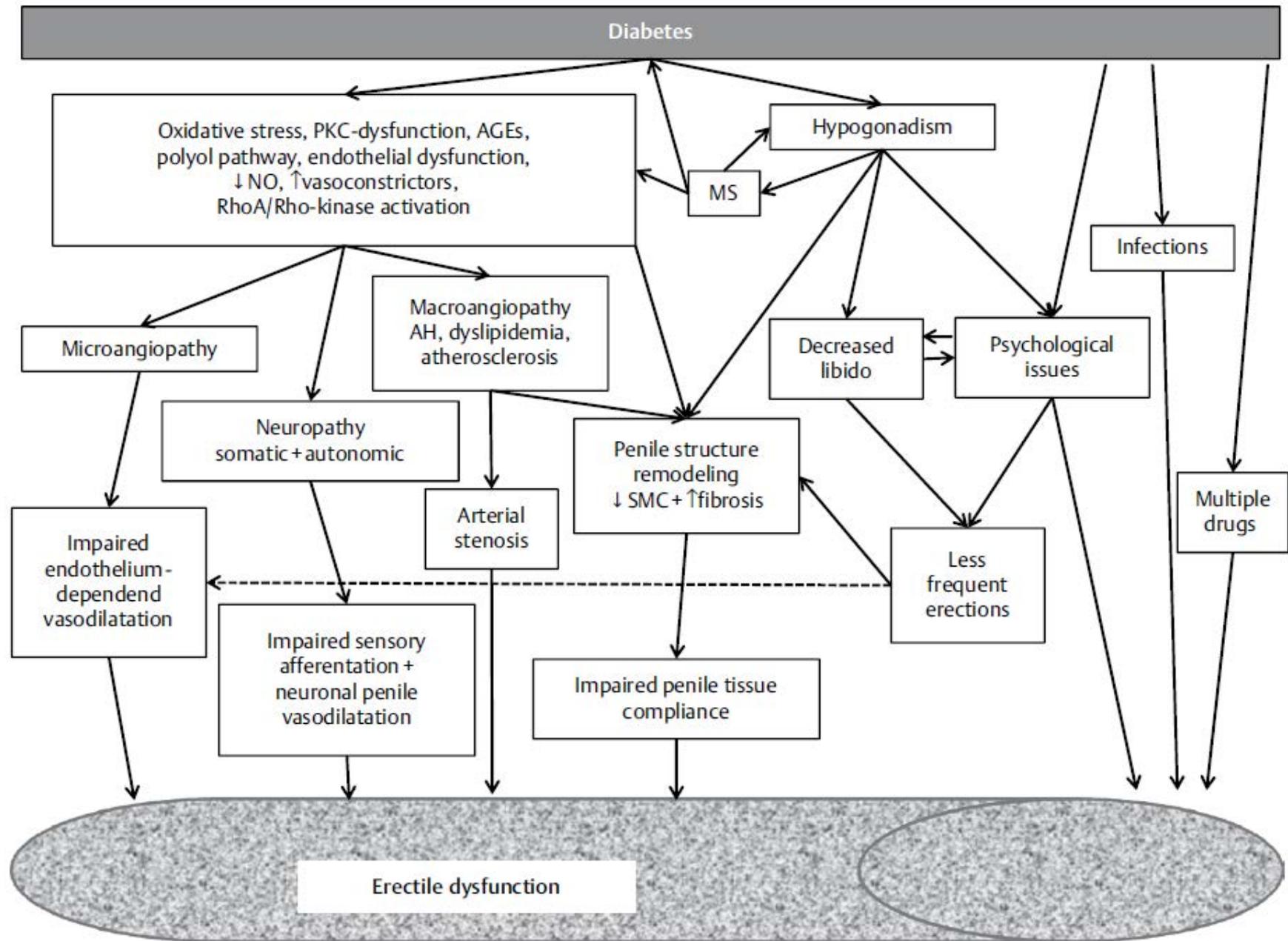


Fig. 3 Pathogenesis of DED. AGEs – advanced glucation end products; PKC – protein kinase C; NO – nitric oxide; MS – metabolic syndrome; SMS – smooth muscle cells; AH – arterial hypertension.

Disfunzione erettile (DE)

- **DSM-IV:** “persistente o ricorrente incapacità di ottenere o mantenere una erezione peniena adeguata per il completamento della attività sessuale”

DSM-IV, American Psychiatric Association, 1994

- **NIH Consensus Development Panel on Impotence:** “incapacità di ottenere e/o mantenere un’ erezione sufficiente a consentire un rapporto sessuale soddisfacente”

NIH Consensus Development Panel on Impotence,

JAMA, 270:83, 1993

FSD

La disfunzione sessuale femminile (FSD) è caratterizzata da disturbi nei cambiamenti psicofisiologici associati con la risposta sessuale nella donna, includendo i disordini del desiderio sessuale, dell'eccitazione, dell'orgasmo e del dolore.

(Basson R. et al 2000 - Fischer 2005)

FSD a seguito di DE ☰

Alcuni autori (es. Fischer, 2005) mettono in evidenza il **forte aumento dei disturbi sessuali femminili DOPO l'insorgenza del DE del partner.**



Fisher, W. A., Rosen, R. C., Eardley, I., Sand, M. and Goldstein, I. (2005), Sexual Experience of Female Partners of Men with Erectile Dysfunction: The Female Experience of Men's Attitudes to Life Events and Sexuality (FEMALES) Study. *Journal of Sexual Medicine*, 2: 675–684

Le partner possono loro stesse creare (anche involontariamente) o mantenere un problema di D.E.

Esiste una correlazione significativa tra disfunzioni sessuali femminili(FSD) e disfunzioni sessuali maschili (56% dei casi)

(Fugl-Meyer 1977)

Anorgasmia 35%

(Greenstein 2006)

Vaginismo

(Pereira 2006)

Prevalenza della disfunzione erettile in 2010 soggetti in Italia

	Età (anni)					
	18–29	30–39	40–49	50–59	60–70	>70
Soggetti (%)	2,1	1,9	4,8	15,7	26.8	48.3

PREVALENZA TOTALE: 12.8 %

Identificazione svolta da 143 medici generici nel periodo gennaio 1996 – febbraio 1997

Prevalenza della disfunzione erettile nei soggetti diabetici in Italia

	Età (anni)				Prevalenza totale
	<45	46–55	56–65	>66	
Tipo 1 (%)	13	43	54	66	51
Tipo 2 (%)	16	29	42	49	37

1383 diabetici tipo 1 e 8373 diabetici tipo 2

The SUBITO-DE study: Sexual dysfunction in newly diagnosed Type 2 diabetes male patients

Without preliminary selection, all male patients recently (<24 months) diagnosed with T2DM were consecutively interviewed by their attending physician at the diabetes care centers and asked whether they had experienced a change in their sexual function or found it unsatisfactory. Those responding positively were then invited to participate in the study.

RESULTS

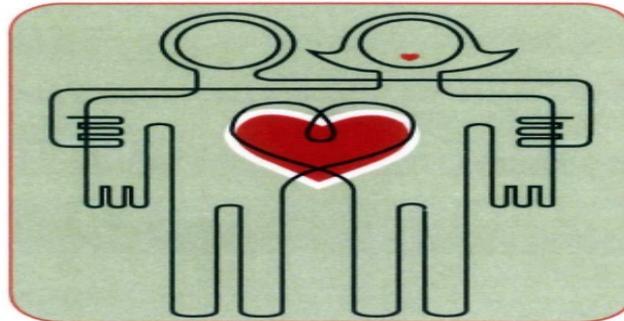
In all, 27 diabetes care centers participated in the study. During the cross-sectional phase, 1503 patients (mean age 58 ± 8.9 yr) were interviewed, of which 666 (43.3%) reported ED. Of these 666 patients, 499 (mean age 58.8 ± 8.8 yr) entered the study, yielding a final enrolment rate of 33.3%.

Use of ED medications

About 20% said they had used ED drugs, 2% reported habitual use and less than 10% occasional use. About 50% said they had abandoned therapy because it was either ineffective or costly.

Indagine Conoscitiva sulla **“Disfunzione Erettile”**

Sindrome delle Basse Vie Urinarie e Ipogonadismo
Regione Lazio



A Cura del
“Gruppo di Lavoro *Diabete e Andrologia*”
AMD - Lazio

Questionario IIEF 5

L'International Index of Erectile Function - 5 (IIEF-5) è stato creato allo scopo di fornire un questionario sensibile e specifico per valutare la funzione erettiva. Nel rispondere si deve tener conto dell'attività sessuale relativa agli ultimi 6 mesi.

A) Negli ultimi 6 mesi come è stata la sua capacità di raggiungere e mantenere l'erezione?

0 - Praticamente inesistente

1 - Molto bassa

2 - Bassa

3 - Moderata

4 - Alta

5 - Molto alta

B) Negli ultimi 6 mesi dopo la stimolazione sessuale quanto spesso hai raggiunto un'erezione sufficiente alla penetrazione?

0 - Non ho avuto alcuna attività sessuale

1 - Quasi mai o mai

2 - Poche volte (molto meno della metà delle volte)

3 - Qualche volta (circa la metà delle volte)

4 - La maggior parte delle volte (più della metà delle volte)

5 - Quasi sempre o sempre

C) Negli ultimi 6 mesi, durante il rapporto sessuale, quanto spesso è riuscito a mantenere l'erezione dopo la penetrazione?

0 - Non ho avuto alcuna attività sessuale

1 - Quasi mai o mai

2 - Poche volte (molto meno della metà delle volte)

3 - Qualche volta (circa la metà delle volte)

4 - La maggior parte delle volte (più della metà delle volte)

5 - Quasi sempre o sempre

D) Negli ultimi 6 mesi, durante il rapporto sessuale quanto è stato difficile mantenere l'erezione fino alla fine del rapporto?

0 - Non ho tentato di avere rapporti sessuali

1 - Estremamente difficile

2 - Molto difficile

3 - Difficile

4 - Abbastanza difficile

5 - Facile

E) Negli ultimi 6 mesi, quando ha avuto un rapporto sessuale, quanto spesso ha provato piacere?

0 - Non ho avuto alcuna attività sessuale

1 - Quasi mai o mai

2 - Poche volte (molto meno della metà delle volte)

3 - Qualche volta (circa la metà delle volte)

4 - La maggior parte delle volte (più della metà delle volte)

5 - Quasi sempre o sempre

Sommando i punteggi ottenuti (indicati a fianco della risposta scelta), si ottiene il risultato finale.

Da **22 a 25** - l'attività sessuale è da considerarsi **normale**

Da **17 a 21** - disfunzione erettiva **lieve**

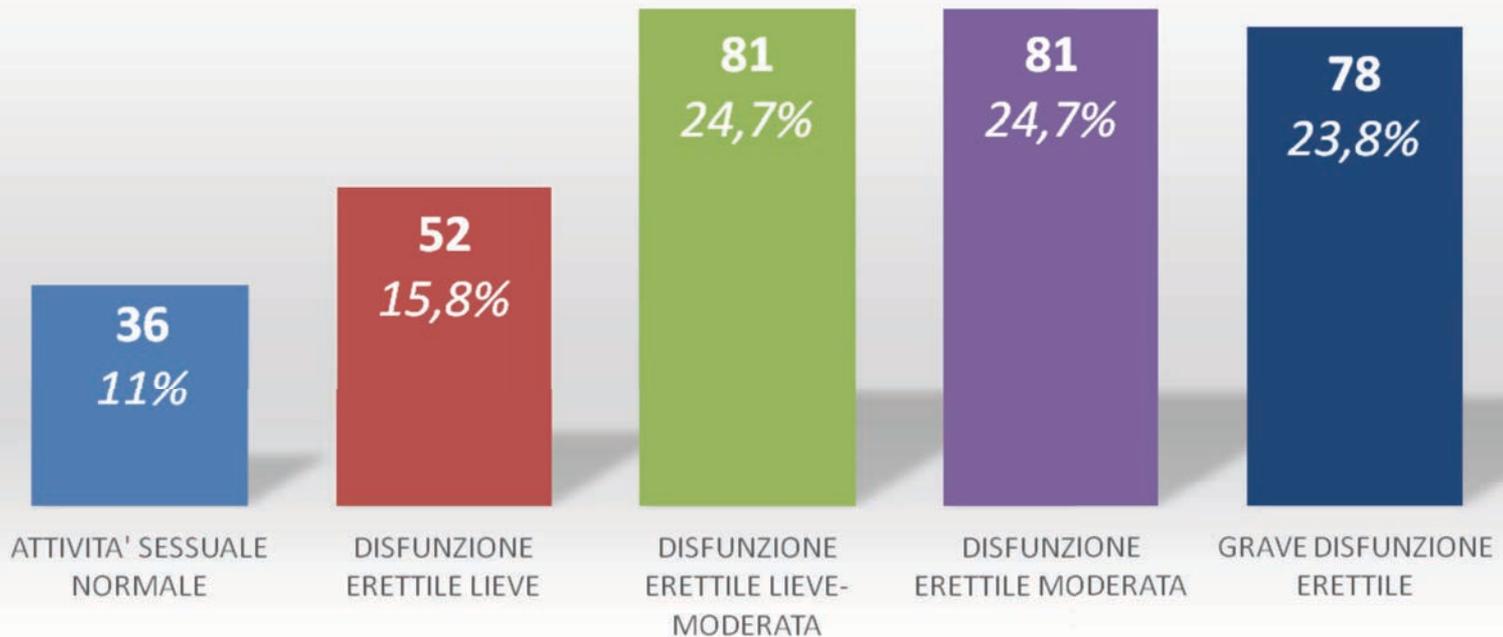
Da **12 a 16** - disfunzione erettiva **lieve - moderata**

Da **8 a 11** - disfunzione erettiva **moderata**

Da **5 a 7** - **grave** disfunzione erettile

Questionario IIEF 5

VALUTAZIONE DELLA FUNZIONE ERETTILE NEGLI ULTIMI 6 MESI



Assessing Female Sexual Dysfunction

Inventory	Discriminant	Divergent	Sensitivity to Change
BISF-W	Functional / dysfunctional women	–	Yes †
CSFQ	Depressed / non-depressed females & males	–	No
DISF	Functional / dysfunctional males	–	Yes ‡
FSFI	FSAD / controls ; FOD / controls; HSDD / controls	MA (Locke-Wallace)	Yes †
GRISS	Functional / dysfunctional couples	–	Yes ‡
HSDD Screener	HSDD / women with no sexual difficulties	–	No
MSFQ	Pre / post menopausal women; oral contraceptive users vs nonusers	–	Yes (pre- to post-menopause; placebo vs estrogen)
SIDI-F	HSDD / FOD / functional women	MA (Locke-Wallace – modified version)	No
SQOL-F	Functional / dysfunctional women; spinal cord-injured women	–	No
SSS-W	Functional / dysfunctional women	MA (Locke-Wallace)	Yes ‡

Female Sexual Function Index (FSFI)



Number of Items	Administration Time/Modality	Domains
19	<ul style="list-style-type: none">• 10-15 minutes• Self-report• Female only	<ul style="list-style-type: none">• Desire• Arousal• Lubrication• Orgasm• Satisfaction• Pain

Rosen R, et al. J Sex Marital Ther. 2000;26:191-208.

Female Sexual Function Index (FSFI)



- 1. quanto spesso ha avvertito desiderio sessuale o interesse per il sesso?*
- 2. come valuta il suo livello di desiderio sessuale o interesse per il sesso?*
- 3. spesso ha provato eccitazione durante i rapporti sessuali?*
- 4. come valuta il suo livello di eccitazione durante i rapporti sessuali?*
- 5. quanto era sicura dell'arrivo dell'eccitazione durante i rapporti sessuali?*
- 6. quanto spesso era soddisfatta della sua eccitazione durante i rapporti sessuali?*
- 7. quanto spesso è stata lubrificata durante i rapporti sessuali?*
- 8. quanto è stato difficile lubrificarsi durante l'attività o i rapporti sessuali?*
- 9. quanto spesso ha mantenuto la lubrificazione fino al completamento dell'attività o dei rapporti sessuali?*
- 10. quanto è stato difficile mantenere la lubrificazione fino al completamento dell'attività o dei rapporti sessuali?*
- 11. quando ha avuto una stimolazione sessuale o un rapporto, quanto spesso ha raggiunto l'orgasmo?*
- 12. quando ha avuto una stimolazione sessuale o un rapporto, quanto spesso ha raggiunto l'orgasmo?*
- 13. quanto è stata soddisfatta della sua capacità di raggiungere l'orgasmo durante l'attività o i rapporti sessuali?*
- 14. quanto è stata soddisfatta del grado di intimità raggiunta col suo partner durante l'attività sessuale?*
- 15. quanto è stata soddisfatta della sua relazione sessuale con il suo partner?*
- 16. quanto è stata complessivamente soddisfatta della sua vita sessuale?*
- 17. quanto spesso ha provato disagio fisico o dolore durante la penetrazione vaginale?*
- 18. quanto spesso ha provato disagio fisico o dolore successivamente alla penetrazione vaginale?*
- 19. come valuta il suo livello di disagio fisico o dolore dovuto alla penetrazione vaginale?*

INDICE DI FUNZIONE SESSUALE FEMMINILE FSFI

desiderio eccitazione
lubrificazione orgasmo
soddisfazione sessuale dolore



**FUNZIONE
SESSUALE**

**BUO
NA
≥30**

**DISFUNZIONE
≤23**

Rosen R e al J Sex Marital Ther
26: 191-208; 2000

Development and Validation of a 6-Item Version of the Female Sexual Function Index (FSFI) as a Diagnostic Tool for Female Sexual Dysfunction



- 1. Nelle ultime 4 settimane, come valuta il suo livello di desiderio sessuale o interesse per il sesso?***
- 2. Nelle ultime 4 settimane, come valuta il suo livello di eccitazione durante i rapporti sessuali?***
- 3. Nelle ultime 4 settimane, quanto spesso è stata lubrificata durante i rapporti sessuali?***
- 4. Nelle ultime 4 settimane, quando ha avuto una stimolazione sessuale o un rapporto, quanto spesso ha raggiunto l'orgasmo?***
- 5. Nelle ultime 4 settimane, quanto è stata complessivamente soddisfatta della sua vita sessuale?***
- 6. Nelle ultime 4 settimane, quanto spesso ha provato disagio fisico o dolore durante la penetrazione?***



Did men with erectile dysfunction discuss their condition with partner and physicians? A survey of men attending a free call information service

V Mirone¹, V Gentile², G Zizzo³, M Terry³, N Longo¹, F Fusco¹ and F Parazzini^{4*}

Erectile dysfunction duration

	<6 m	6m-1y	1-3y	>3y
Discussion with partner				
No %	52.1	39.6	37.6	40.2
Yes %	47.9	60.4	62.4	59.9
Discussion with physician				
No %	66.4	51.7	42.6	42.1
Yes %	33.6	48.3	57.4	57.9

Sexual dysfunction and diabetes

G. JACKSON

Int J Clin Pract, April 2004, **58**, 4, 358–362

Patients reluctant to talk to their doctors about Erectile dysfunction (ED) – why?

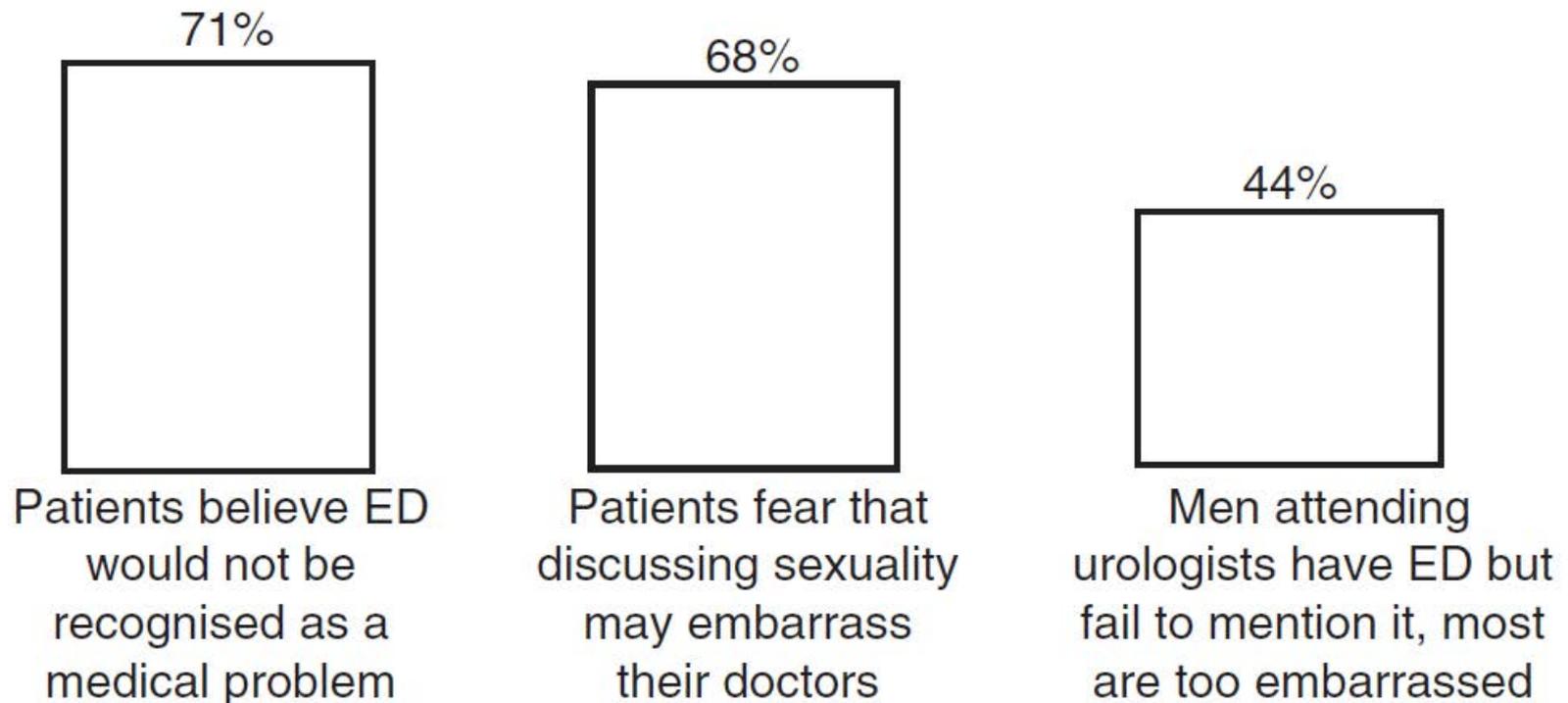


Figure 2 Men fail to volunteer their erectile dysfunction even in the enlightened 'post-Viagra' era (3)

Comuni fattori di rischio per la disfunzione erettile

❑ Fattori psicologici

❑ Età

❑ Sport

❑ Farmaci

❑ Consumo di tabacco

❑ Consumo di alcol

❑ Consumo di droghe

❑ Dislipidemie

❑ Traumi

❑ Chirurgia pelvica

❑ Malattie cardiovascolari

❑ **Diabete mellito**

❑ Epatopatie

❑ Nefropatie

❑ Disordini neurologici

❑ Disordini ormonali

DE - Fattori di rischio

Stile di vita

- Consumo di alcool
- Un consumo >600ml a settimana è associato con una aumentata probabilità di DE minima da 17 a 29%

Feldman HA et al, J Urol, 151:54, 1994



DISFUNZIONE ERETTILE

“Marker” di patologie sistemiche?

CARDIOPATIA ISCHEMICA

IPERTENSIONE

DIABETE MELLITO

DISLIPIDEMIA

SINDROME METABOLICA

Diabete Mellito

- **DE multifattoriale (vascolare, neurologica, endocrina, psicologica)**
- **i soggetti diabetici hanno una probabilità tre volte maggiore di sviluppare la DE rispetto agli uomini non diabetici**
- **i diabetici sono inoltre affetti da DE in età più giovane rispetto ai non diabetici**
- **negli uomini in cui il diabete non sia ancora stato diagnosticato, la DE può essere il sintomo di esordio della malattia**
- **fattori di rischio ulteriori sono fumo, alcool, scarso controllo glicemico, durata della malattia, ecc.**

**Come valutare un paziente
con disfunzione erettile?**

Figure. Mechanism of Erection and Sites of Action of Various Treatment Modalities for Erectile Dysfunction

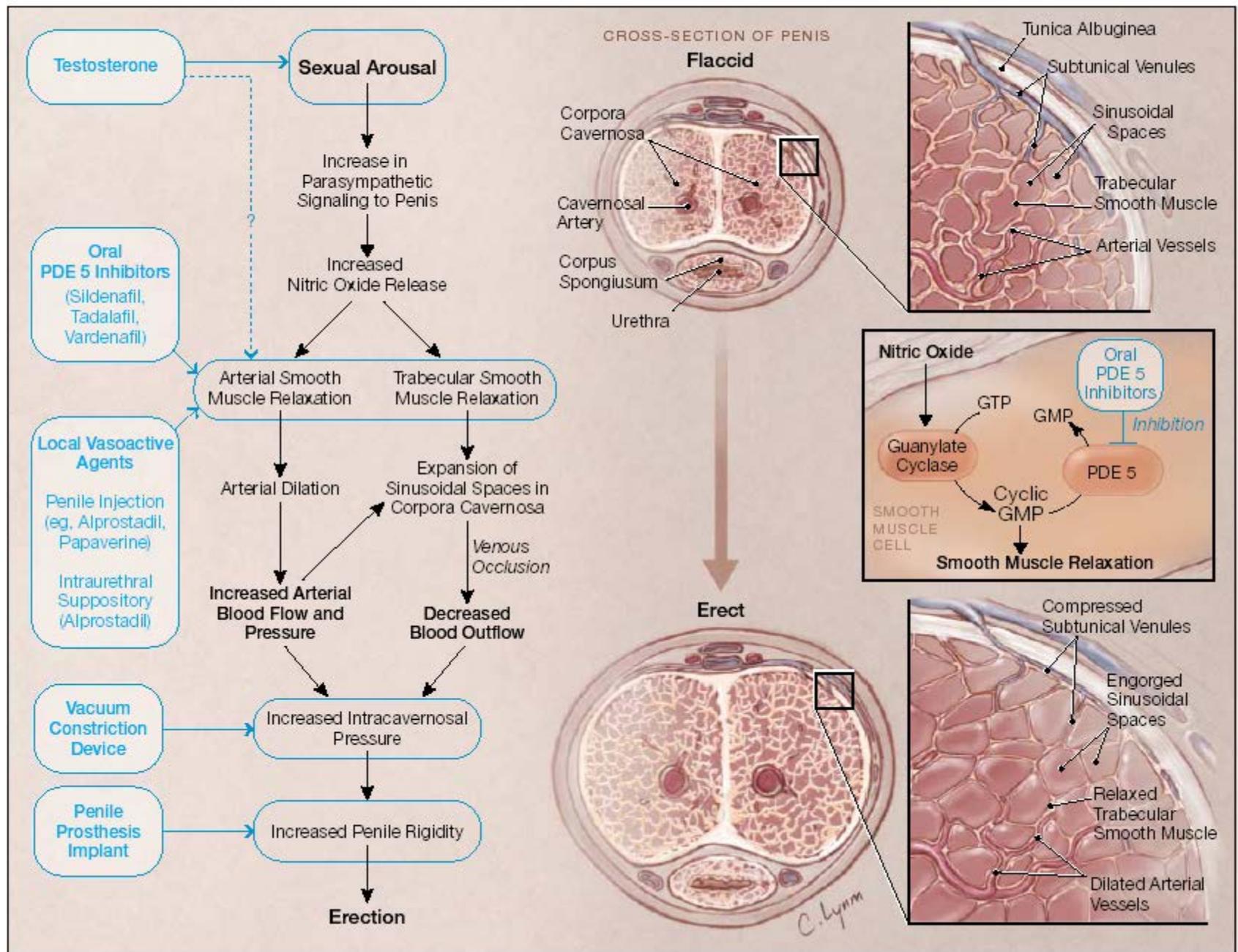


Diagramma di flusso per la valutazione iniziale

- **Anamnesi**
 - **Medica**
 - **Sessuale**
 - **Psicosociale**
- **Esame clinico**
- **Questionari**
- **Esami diagnostici**
- **Educazione del paziente**
- **Trattamento - consulenza specialistica**

Trattamento polifarmacologico nei pazienti diabetici

- ipertensione; →
- insufficienza cardiaca;
- dislipidemia; →

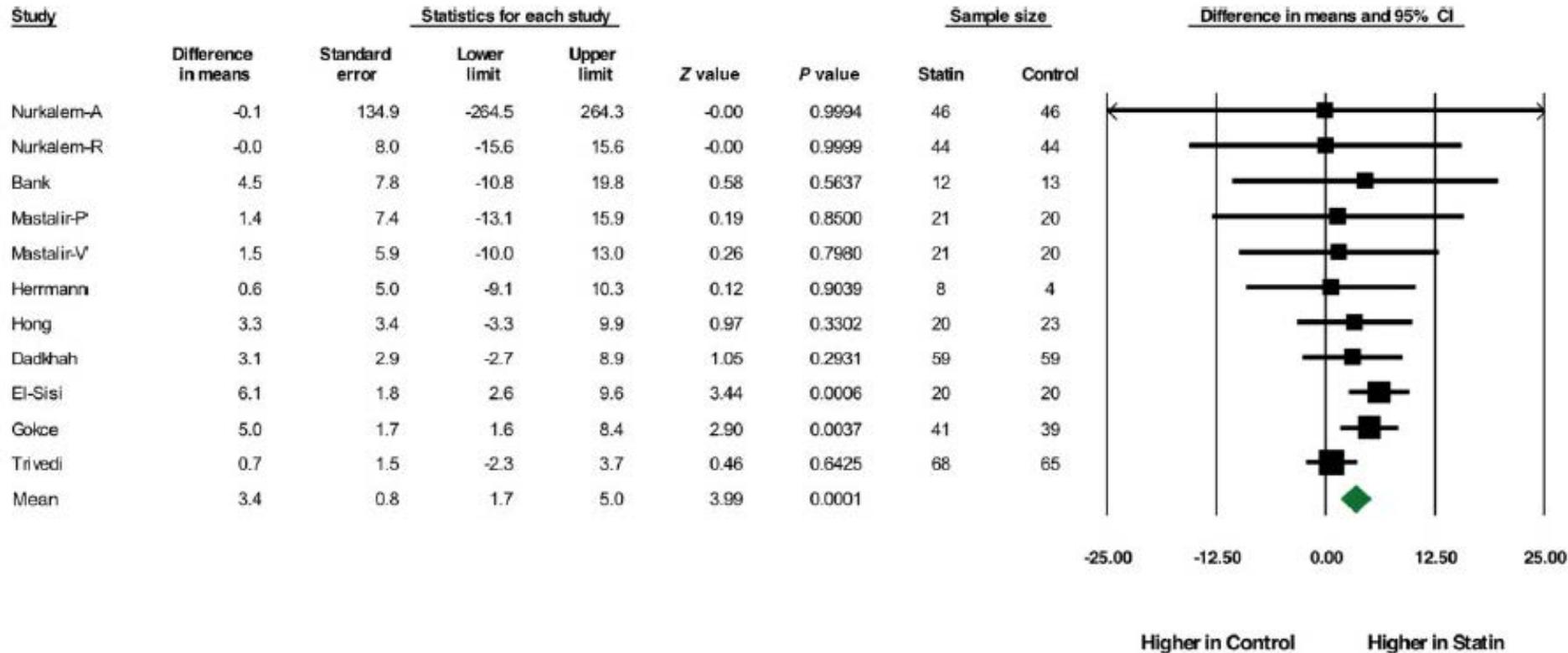
Table 7 Drugs that may contribute to ED [23,25]

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 Methotrexate Roferon-A
Anticholinergics	Disopyramide Anticonvulsants

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

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

J Sex Med 2014;11:1626–1635.



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

Losartan improves erectile dysfunction in diabetic patients: a clinical trial

International Journal of Impotence Research (2012) 24, 217–220
© 2012 Macmillan Publishers Limited All rights reserved 0955-9930/12
www.nature.com/ijir

Y Chen¹, S Cui¹, H Lin¹, Z Xu¹, W Zhu¹, L Shi¹, R Yang¹, R Wang² and Y Dai¹

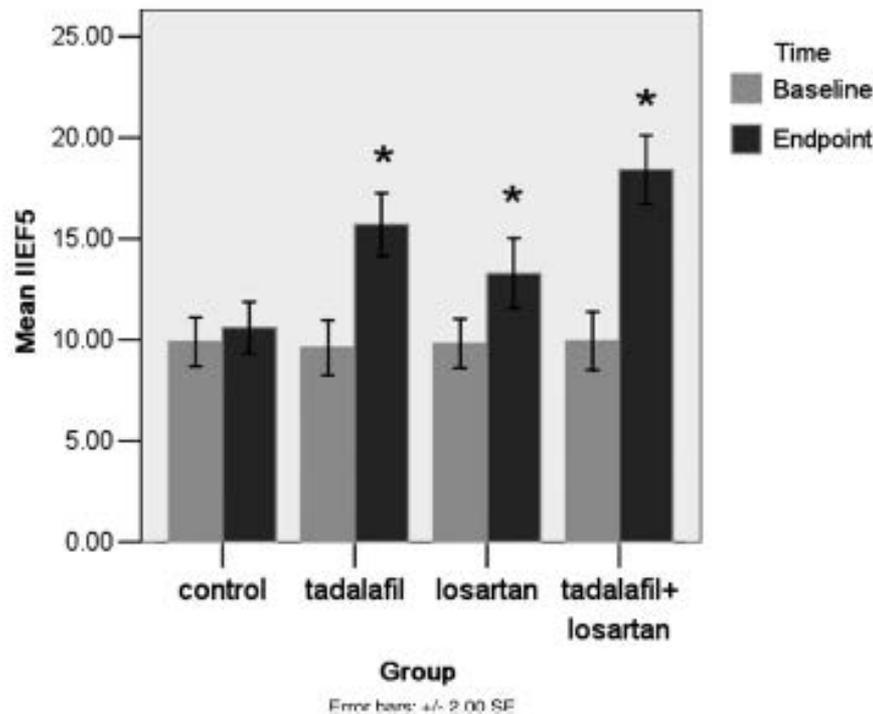


Figure 1. Mean IIEF-5 (International Index of Erectile Function) scores at baseline and endpoint of each group. * $P < 0.05$ for endpoint vs baseline of each group. The treatment of tadalafil, losartan or losartan plus tadalafil were effective on increasing the mean IIEF-5 scores. # $P < 0.05$ for tadalafil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

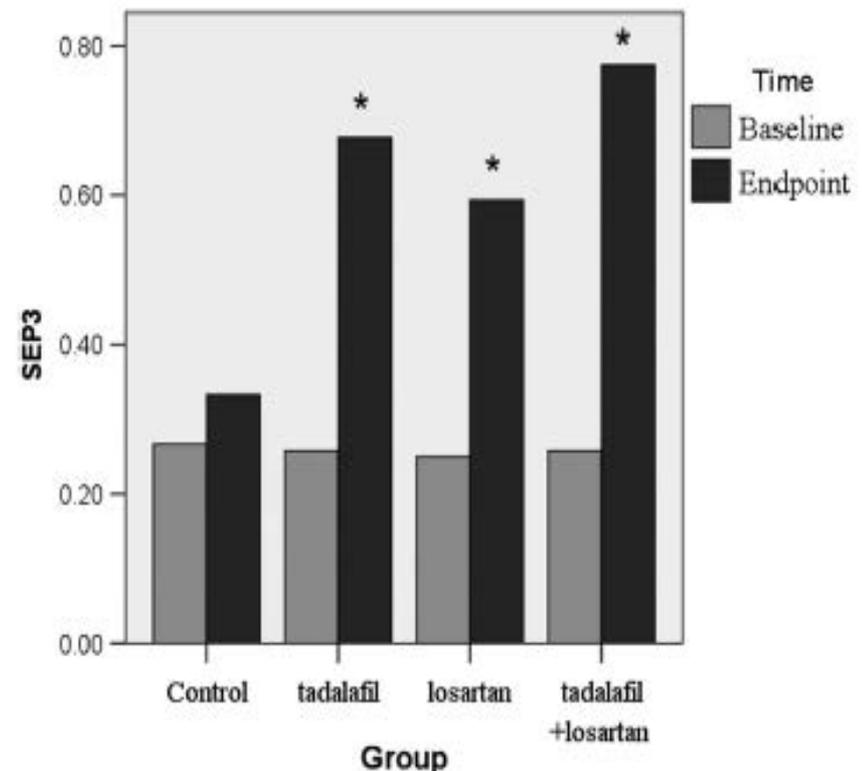


Figure 4. The percentage of positive answers to the sexual encounter profile questions-3 (SEP-3) in diabetic patients with (erectile dysfunction) ED at baseline and following 12 weeks of treatment. * $P < 0.05$ for end point vs baseline.

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

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

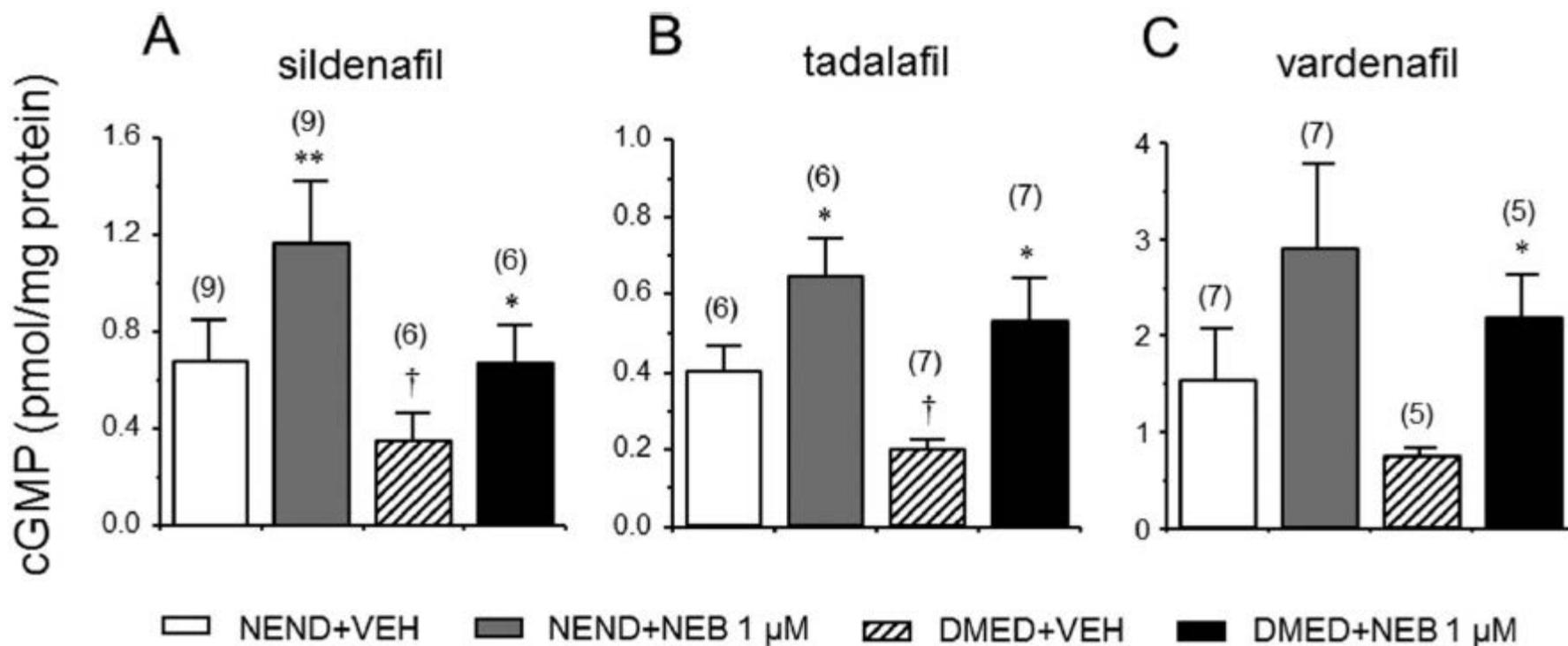


Figure 4 Nebivolol increases cGMP accumulation induced by PDE5 inhibitors in human corpus cavernosum from diabetic patients with ED.

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 cavernosum 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.

Disfunzione erettile

Esami di laboratorio

- Raccomandati glicemia e/o emoglobina glicosilata
assetto lipidico
emocromo, creatinina, esame urine
testosterone, prolattina
- Opzionali PSA, TSH, LH, SHBG, DEAS, estradiolo,
transaminasi, uricemia, folatemia,
25OHcolecalciferolo (vit.D)

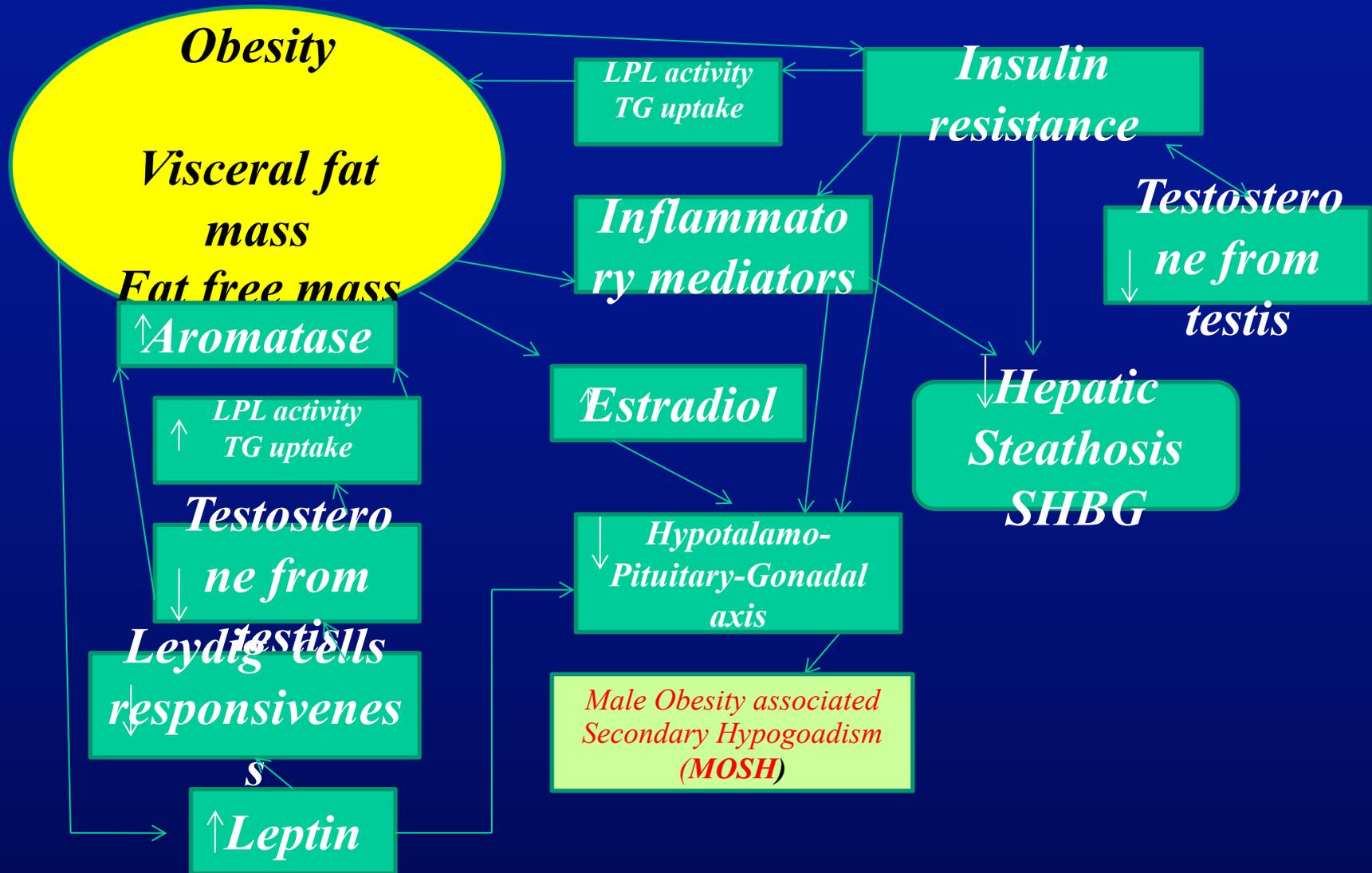
Ipogonadismo

Per la diagnosi di ipogonadismo sono necessari la presenza di sintomi e segni specifici in presenza di valori di testosterone totale (TT) ematici al di sotto di 8 nmol/L (2,3 ng/ml)

Segni e sintomi caratteristici sono:

- Disfunzione erettile;**
 - Riduzione della libido e/o dei pensieri sessuali;**
 - Riduzione delle erezioni mattutine spontanee**
- Laddove il valore ematico di TT sia compreso fra 8 e 12 nmol/L (3,46 ng/ml) si suggerisce l'utilizzo del calcolo del testosterone biologicamente attivo**

Link tra diabete mellito e deficit di testosterone



Erectile Dysfunction as a Predictor of Cardiovascular Events and Death in Diabetic Patients With Angiographically Proven Asymptomatic Coronary Artery Disease

A Potential Protective Role for Statins and 5-Phosphodiesterase Inhibitors

Carmine Gazzaruso, MD, PhD,* Sebastiano B. Solerte, MD,† Arturo Pujia, MD,§
Adriana Coppola, RN, MS,* Monia Vezzoli, MD,* Fabrizio Salvucci, MD,* Cinzia Valentini, MD,*
Andrea Giustina, MD,|| Adriana Garzaniti, MD‡
Vigevano, Pavia, Catanzaro, and Brescia, Italy



DE marker precoce di cardiopatia ischemica silente nel paziente diabetico

DE E RISCHIO CARDIOVASCOLARE

Sexual inquiry of all men

Table 2. Stratification of cardiovascular risk factors according to 'The Second Princeton Consensus Conference' and indications to sexual activity according to low-intermediate or high risk (adapted from [115]).

Low Risk	Intermediate/indeterminate risk	High risk
Asymptomatic, < 3 risk factors*	Asymptomatic, ≥ 3 risk factors	Unstable or refractory angina
Controlled hypertension	Moderate, stable angina pectoris	Uncontrolled hypertension
Mild, stable angina pectoris	MI > 2 weeks but < 6 weeks	CHF (NYHA class III, IV)
Post revascularisation and without significant residual ischaemia	LVD/CHF (NYHA class II)	Recent MI (< 2 weeks)
Post MI (> 6 – 8 weeks) but asymptomatic and without ETT-induced ischaemia	Noncardiac atherosclerotic sequelae	High-risk arrhythmias
Mild valvular disease		Obstructive hypertrophic cardiomyopathies
LVD (NYHA class I)		Moderate-to-severe valve disease

those with known cardiovascular disease. *Sexual activity is equivalent to walking 1 mile on the flat in 20 minutes or briskly climbing 2 flights of stairs in 10 seconds.

^bSexual activity is equivalent to 4 minutes of the Bruce treadmill protocol.



CME¹

Cardiometabolic Risk and Female Sexual Health: The Princeton III Summary

□ Martin Miner, MD,* Katherine Esposito, **,† Andre Guay, MD,‡ Piero Montorsi, **,§ and Irwin Goldstein, MD[¶]

- *Is FSD Associated with the Full Range of Risk Factors for CVD? Hypertension, Dyslipidemia/Hyperlipemia, Smoking, Diabetes, Metabolic Syndrome/Obesity*
- *Is FSD More Prevalent in Women with CVD?*
- *Is FSD a Predictor of Future CV Events?*
- *Can Treatment of Associated Risk Factors Modify FSD Incidence?*
- *Which Treatment Is Indicated for FSD?*



Continuing Medical Education

J Sex Med 2012;9:641–651

CME

Cardiometabolic Risk and Female Sexual Health: The Princeton III Summary

Is FSD Associated with the Full Range of Risk Factors for CVD?

- *Risposta: SI!*
- *Impatto del fattore di rischio sulla vita sessuale (il fattore danneggia l'integrità vascolare del tratto genitale)*
- *Impatto della FSD sul fattore (ridotta soddisfazione sessuale può generare stili di vita distorti che si associano a incremento ponderale e/ o ridotta attività fisica)*
- *Meccanismo comune per entrambi (insulin resistance as suggested for erectile dysfunction)*



Continuing Medical Education

J Sex Med 2012;9:641–651

CME

Cardiometabolic Risk and Female Sexual Health: The Princeton III Summary

Is FSD a Predictor of Future CV Events ?

***•Risposta
No!! (Forse)***

I risultati si basano principalmente su uno studio prospettico (Women's Health Initiative) che mostra i dati di 46525 donne seguite per 8--12 anni: essere non soddisfatta sessualmente aumentava del 44% il rischio di malattia arteriosa periferica ma non di altri eventi (angina, infarto, ictus, scompenso cardiaco)

Valutazione dello stato vascolare

Test di farmaco infusione intracavernosa (FIC test)

Ecocolordoppler penieno basale e dopo test farmacologico

- **Pazienti giovani**
- **Pazienti con DE primaria**
- **Pazienti con DE post traumatica**
- **Pazienti che vogliono essere informati**

Arteriografia dell'arteria pudenda

Pazienti con disfunzione erettile su sospetta base arteriosa all'ecocolordoppler penieno

Cavernosometria - Cavernosografia Farmacologica

- **Pazienti con disfunzione erettile su sospetta base venosa all'ecocolordoppler penieno**

Dynamic PCDU: PSV and CV risk

Male Sexuality and Cardiovascular Risk. A Cohort Study in Patients with Erectile Dysfunction

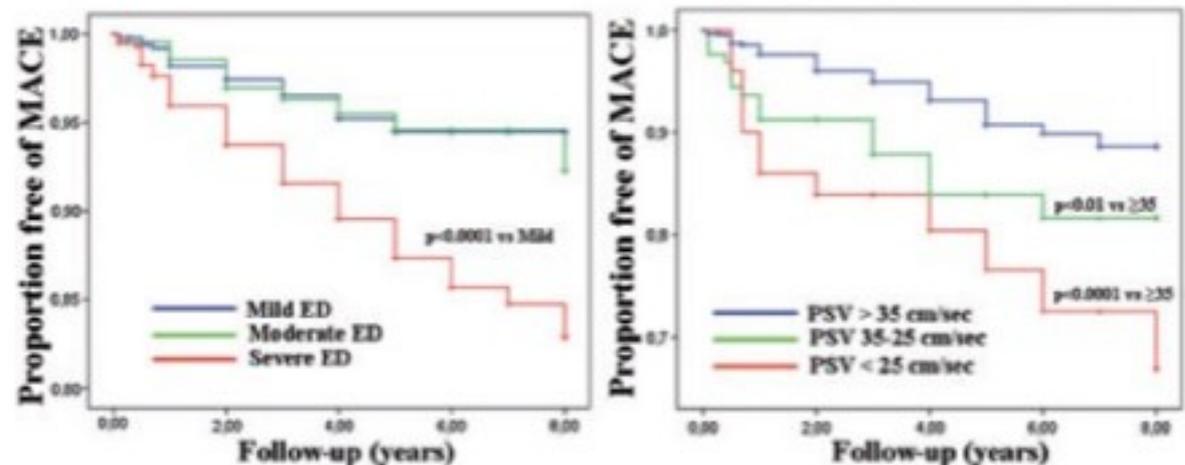
J Sex Med 2010;7:1918–1927

Giovanni Corona, MD,^{§§} Matteo Monami, MD,^{††} Valentina Boddi,^{*} Michela Cameron-Smith, MD,^{*} Francesco Lotti, MD,^{*} Giulia de Vita, MD,^{*} Cecilia Melani, MD,[‡] Daniela Balzi, MD,^{*} Alessandra Sforza, MD,[§] Gianni Forti, MD,^{*} Edoardo Mannucci, MD,[†] and Mario Maggi, MD^{*}

N = 1687 consulting for ED (age 52.9 ± 12.8 years)

During a mean follow-up of 4.3 ± 2.6 years, 139 MACE observed, 15 of which were fatal

Figure 4 Risk of incident major cardiovascular events (MACE) as derived from Kaplan Mayer curves, according to erectile dysfunction (ED) severity (difficulties in achieving an erection sufficient for penetration in <50%, mild ED; 50–75%, moderate ED, and >75%, severe ED; see ref. [1]) or to different degrees of penile vascular insufficiency (dynamic peak systolic velocity PSV, >35, 35–25 or < 25 cm/second).



Veno-occlusive dysfunction

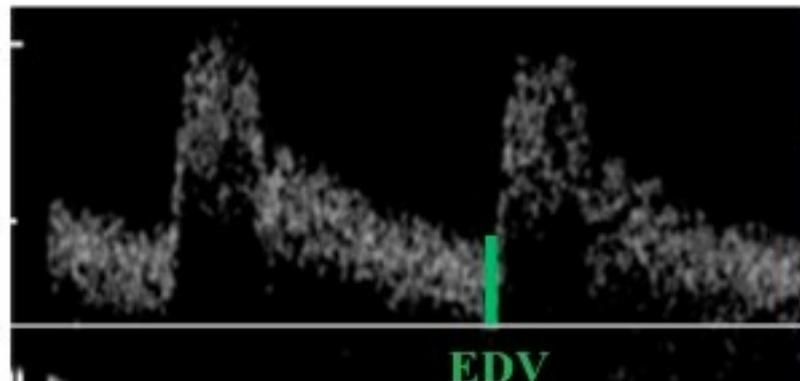
Failure of adequate venous occlusion

End diastolic velocity (EDV) > 5 cm/s

Limitation: lack of specificity for venous leakage in presence of arterial insufficiency

Causes:

- Tunica albuginea degenerative changes (Peyronie's disease, diabetes, old age)
- Traumatic injury (penile fracture)
- Structural alterations in the fibroelastic components of the trabeculae, cavernous smooth muscle, and endothelium
- Acquired venous shunts (correction of priapism)
- Anxiety



NIH Public Access

Author Manuscript

Urol Clin North Am. Author manuscript; available in PMC 2006 January 25.

Published in final edited form as:

Urol Clin North Am. 2005 November ; 32(4): 379-v.

Physiology of Penile Erection and Pathophysiology of Erectile Dysfunction

Robert C. Dean, MD^a and Tom F. Lue, MD^b

Basal PCDU: PSV and CV risk

Penile Doppler Ultrasound in Patients with Erectile Dysfunction (ED): Role of Peak Systolic Velocity Measured in the Flaccid State in Predicting Arteriogenic ED and Silent Coronary Artery Disease

J Sex Med 2008;5:2623–2634

Giovanni Corona, MD,^{1*} Giorgio Fagioli, MD,² Edoardo Mannucci, MD,³ Annadina Romeo, MD,² Massimiliano Rossi, MD,² Francesco Lotti, MD,⁴ Alessandra Sforza, MD,¹ Stefano Morittu, MD,¹ Valerio Chiarini, MD,¹ Gianni Casella, MD,¹ Giuseppe Di Pasquale, MD,⁵ Elisa Bandini, MD,⁶ Gianni Forti, PhD,⁷ and Mario Maggi, PhD⁸

A subset of 20 subjects with uncomplicated type 2 diabetes underwent diagnostic testing for silent coronary heart disease by means of “adenosine stress myocardial perfusion scintigraphy” (SPECT).

When the **threshold of <13 cm/s** was chosen, PSV before SPECT was **predictive of impaired coronary flow reserve with an accuracy of 80%** (area under the ROC curve = 0.798 ± 0.10 ; $p < 0.05$).

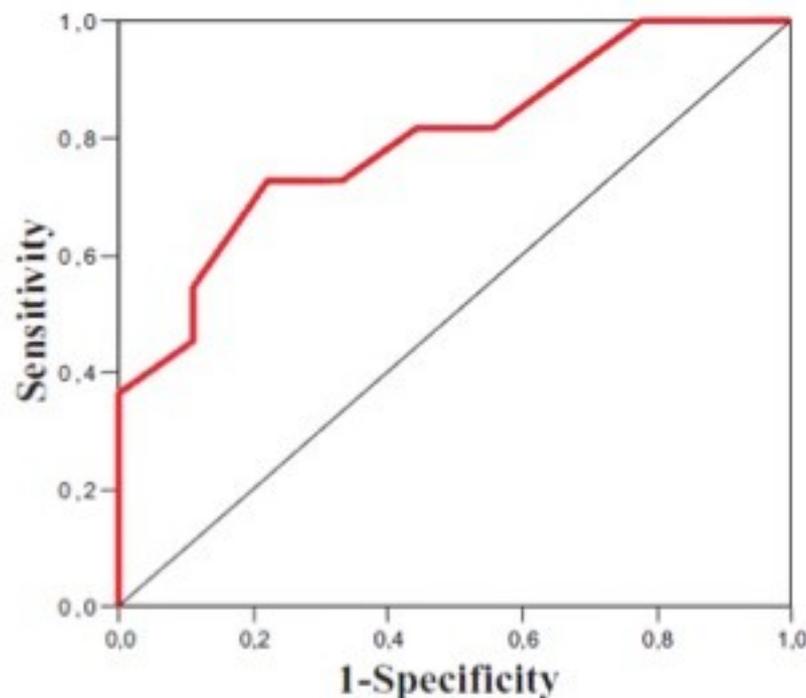


Figure 5 Receiver operating characteristic curve for impaired coronary flow reserve at myocardial perfusion scintigraphy in relation to peak systolic velocity at penile Doppler ultrasound measured before adenosine administration.

DISFUNZIONE ERETTILE: TERAPIA



Can lifestyle modification affect men's erectile function?

Marah C. Hehemann¹, James A. Kashanian²

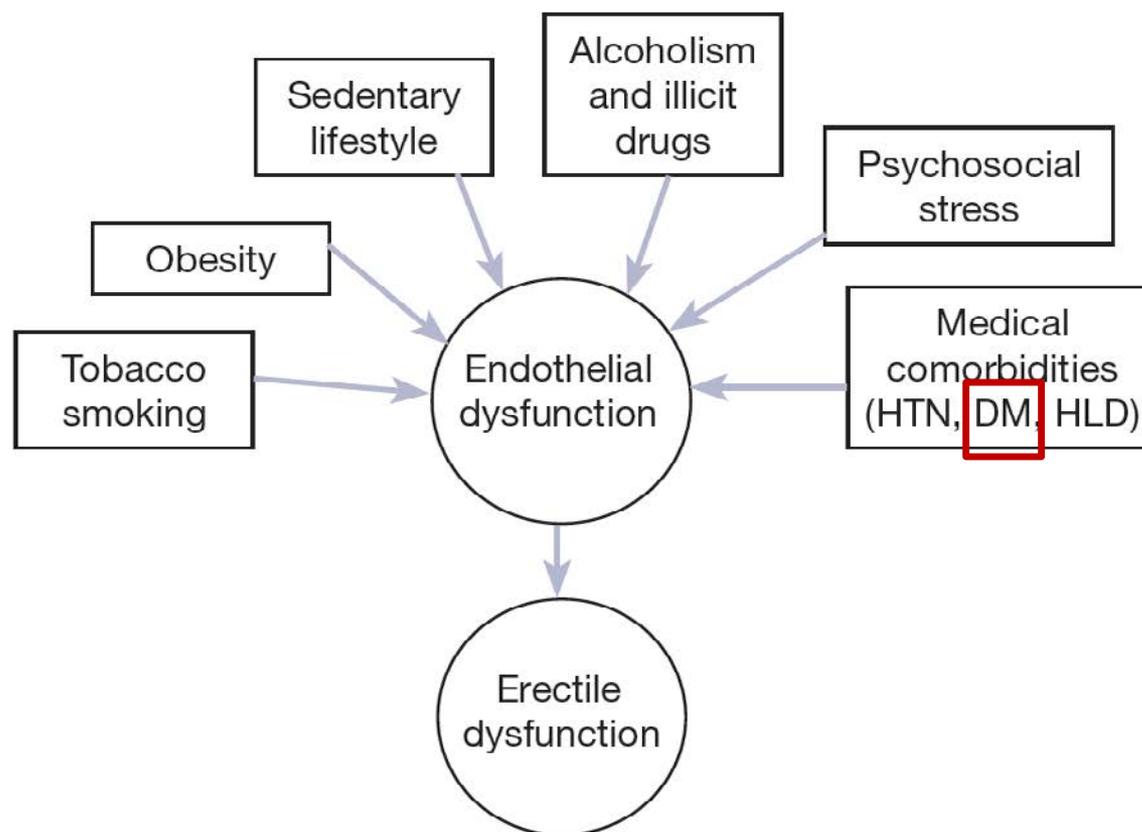


Figure 1 Relationship of modifiable risk factors and erectile dysfunction.

Effects of Mediterranean diet on sexual function in people with newly diagnosed type 2 diabetes: The MÈDITA trial

Maria Ida Maiorino ^{a,*}, Giuseppe Bellastella ^a, Mariangela Caputo ^a, Filomena Castaldo ^a, Maria Rosaria Improta ^a, Dario Giugliano ^a, Katherine Esposito ^b

Journal of Diabetes and Its Complications 30 (2016) 1519–1524

Table 3
Outcomes at the end of trial^a.

	EOT	Change (95% CI)	EOT	Change (95% CI)	Difference (95% CI) between-group comparison of change	P value of comparison
	Men (Med diet)		Men (low-fat diet)			
IIEF	20.8 (2.2)	1.22 (0.80–1.64)	19.6 (2.9)	2.23 (1.6–2.82)	–1.16 (–2.16 to –0.15)	0.024
Weight (kg)	85.6 (9.8)	–3.7 (2.4)	86.9 (10.1)	–2.9 (2.3)	–0.82 (–1.5 to –0.1)	0.046
Waist (cm)	100 (11)	–3.2 (2.0)	101 (11)	–2.2 (2.1)	–1.0 (–2.0 to 0.0)	0.051
HbA1c (%)	6.91 (0.5)	–0.71 (0.31)	7.29 (0.41)	–0.41 (0.27)	–0.30 (–0.61 to –0.01)	0.048
TC (mg/dL)	215 (27)	–10 (9)	208 (25)	–5 (5)	–5 (–10 to 1)	0.064
SBP (mm Hg)	138 (12)	–2.5 (2.9)	140 (13)	–0.7 (0.8)	–1.8 (–3.3 to –0.2)	0.039
CRP (mg/L)	2.2 (1.7–3.4)	0.31 (0.08–0.62)	2.35 (1.9–3.1)	0.03 (–0.21 to 0.26)	0.30 (0.02–0.58)	0.041
	Women (Med diet)		Women (low-fat diet)			
FSFI	25.1 (2.8)	1.13 (0.29–2.16)	23.9 (3.4)	2.25 (1.62–2.9)	–1.18 (–2.16 to –0.18)	0.019
Weight (kg)	78.9 (10)	–3.5 (2.6)	80.3 (11)	–2.7 (2.5)	–0.80 (–1.69 to –0.10)	0.048
Waist (cm)	92 (11)	–3.0 (2.4)	93 (11)	–2.5 (2.2)	–0.6 (–1.3 to 0.1)	0.065
HbA1c (%)	6.87 (0.4)	–0.69 (0.29)	7.30 (0.38)	–0.39 (0.25)	–0.30 (–0.060 to –0.01)	0.049
TC (mg/dL)	205 (29)	–9 (10)	210 (30)	–5 (4)	–5 (–12 to 2)	0.088
SBP (mm Hg)	136 (11)	–2.3 (2.5)	138 (12)	–0.6 (0.6)	–1.7 (–3.2 to –0.2)	0.045
CRP (mg/L)	2.45 (1.8–3.0)	0.41 (0.21–0.62)	2.8 (1.7–3.3)	0.1 (–0.1 to 0.28)	0.24 (–0.75 to 0.26)	0.348

MED = Mediterranean; EOT = end of trial; IIEF = International Index of Erectile Function; CRP = C-reactive protein; FSFI = Female Sexual Function Index; TC = total cholesterol; SBP = systolic blood pressure.

In conclusion, compared with low-fat diet, Mediterranean diet conferred benefit on sexual function deterioration in both men and women with newly diagnosed type 2 diabetes.

Physical activity and exercise for erectile dysfunction: systematic review and meta-analysis

André B Silva,¹ Nelson Sousa,^{1,2} Luís F Azevedo,^{3,4} Carlos Martins¹

Summary box

- ▶ A systematic review and meta-analysis of seven randomised controlled trials of patients with erectile dysfunction.
- ▶ Different physical activity and exercise interventions increase short-term and long-term patient-reported erectile function in different patient population and treatment scenarios.
- ▶ The pooled evidence supports the need to review current recommendations for prescribing physical activity and exercise to patients with erectile dysfunction.

Vasculogenesis and Diabetic Erectile Dysfunction: How Relevant Is Glycemic Control?

Journal of Cellular Biochemistry 118:82–91 (2017)

Angela Castela,^{1,2,3} Pedro Gomes,⁴ Ricardo Silvestre,^{5,6} Luísa Guardão,⁷ Liliana Leite,⁷ Rui Chilro,⁸ Ilda Rodrigues,¹ Pedro Vendeira,⁹ Ronald Virag,¹⁰ and Carla Costa^{1,3*}

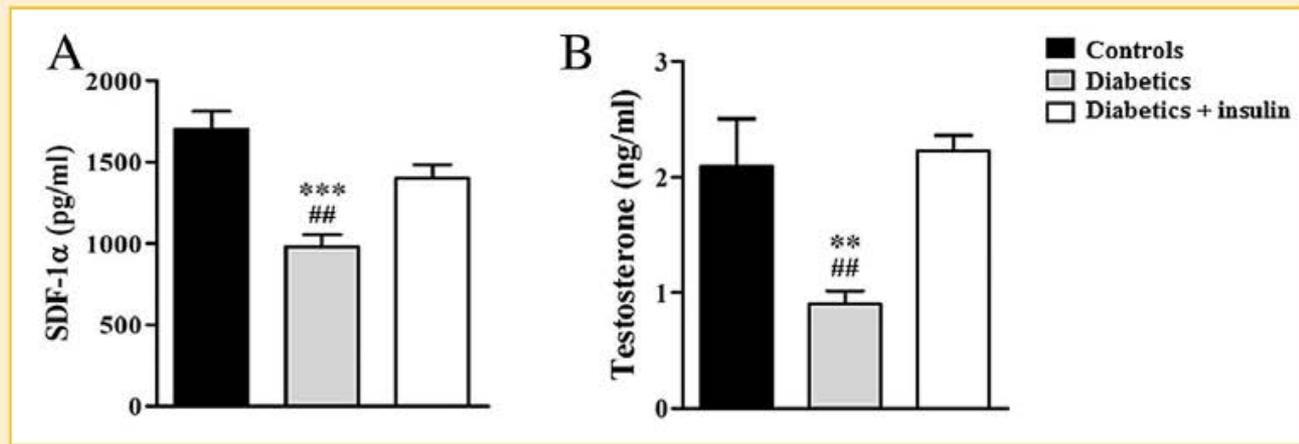


Fig. 3. Plasmatic quantification of SDF-1 α and testosterone. (A) Diabetic animals presented a significant reduction in systemic SDF-1 α and (B) testosterone. Insulin therapy prevented the effects of diabetes, increasing SDF-1 α and testosterone levels. Data presented as Mean \pm SE. ** $P < 0.01$, *** $P < 0.001$ diabetics compared to control group; ## $P < 0.01$ diabetic group compared to insulin-treated diabetics.

Insulin administration rescued the effects of diabetes on BM function, CECs levels, testosterone, and plasmatic/penile SDF-1a protein expression. This emphasizes the importance of glycemic control in the prevention of diabetes-induced systemic and penile EDys, by the amelioration of endothelial damage, and increase in protective pathways

DISFUNZIONE ERETTILE

Terapie.....nel passato!

NOCE MOSCATA

PINNA DI PESCECANE

PEPE ROSSO

CERVELLO DI UCCELLO

OSTRICHE

CORNO DI RINOCERONTE

AGLIO – PORRO

ZUPPA DI LUCERTOLA

CIPOLLA

CORNO DI RENNA

European Association of Urology 2015

MALE SEXUAL DYSFUNCTION - UPDATE MARCH 2015

3A.4.8 *Recommendations for the treatment of ED*

	LE	GR
Lifestyle changes and risk factor modification must precede or accompany ED treatment.	1a	A
Pro-erectile treatments have to be given at the earliest opportunity after RP.	1b	A
When a curable cause of ED is found, it must be treated first.	1b	B
PDE5Is are first-line therapy.	1a	A
Inadequate/incorrect prescription and poor patient education are the main causes of a lack of response to PDE5Is.	3	B
A VED can be used in patients with a stable relationship.	4	C
Intracavernous injection is second-line therapy.	1b	B
Penile implant is third-line therapy.	4	C

ED = erectile dysfunction; RP = radical prostatectomy; VED = vacuum erection devices; PDE5I = phosphodiesterase type 5 [inhibitors].

CLINICAL PERSPECTIVES

Erectile dysfunction

C. G. McMahon

Australian Centre for Sexual Health,

Table 3 Guidelines for prescribing ED treatment in patients with cardiac disease

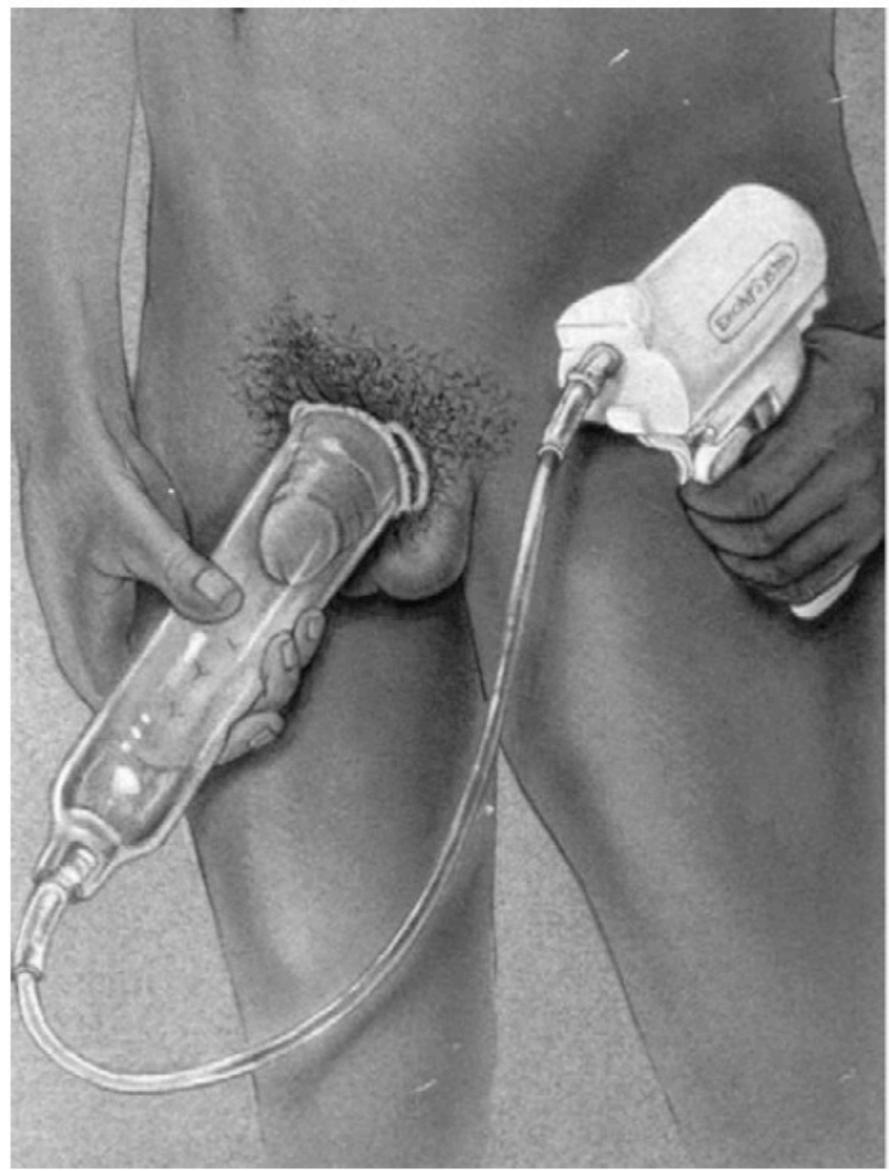
Risk	Cardiac status	Management
Low	<ul style="list-style-type: none">• Controlled hypertension• Mild valvular disease• Mild stable angina• Post-revascularisation	Manage in primary care
Moderate	<ul style="list-style-type: none">• Recent MI or cerebrovascular accident (6 weeks)• Congestive heart failure• Murmur of unknown cause• Moderate stable angina	Specialised evaluation recommended
High	<ul style="list-style-type: none">• Uncontrolled angina• Uncontrolled hypertension• Severe heart failure• Recent MI or cerebrovascular accident (2 weeks)• High-risk arrhythmia• Hypertrophic cardiomyopathy• Moderate/severe valve disease	Refer for cardiac opinion

OPZIONI TERAPEUTICHE

- **Terapia farmacologica sistemica e locale**
- **Vacuum device (Meccanismi di pompa a vuoto)**
- **Dispositivi di costrizione venosa**
- **Psicoterapia, Terapia sessuologica**
- **Impianto di protesi peniene**
- **Interventi di rivascolarizzazione arteriosa**
- **Interventi di legatura venosa**

SOP Conservative (Medical and Mechanical) Treatment of Erectile Dysfunction

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



DISFUNZIONE ERETTILE

Terapia farmacologica

SISTEMICA: ENDOCRINA

NON ENDOCRINA

LOCALE: INTRACAVERNOSA

INTRAURETRALE

TRANSDERMICA

TESTOSTERONE E DE

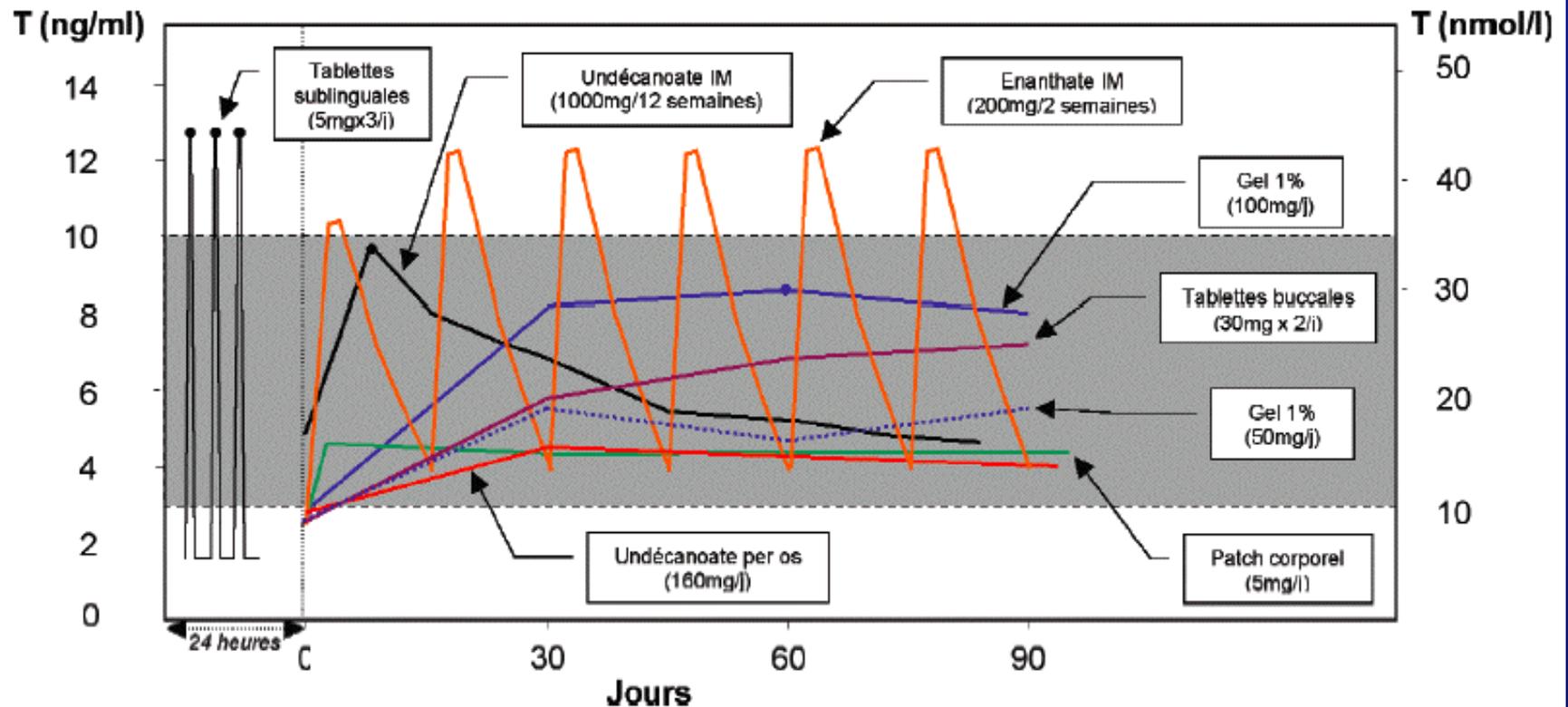


Figure 2 : Profils pharmacocinétiques des principales préparations de testostérone Données tirées des références [169] (tablettes sublinguales, courbe noire maigre), [218] (tablettes buccales, courbe mauve), [209] (undécanoate de testostérone IM, courbe noire grasse), [26, 69] (éнанthate de testostérone, courbe orange), [197] (gel 1%, courbes bleues, et patch corporel, courbe verte), [157] (undécanoate de testostérone per os, courbe rouge). La zone grisée et les lignes discontinues représentent la fourchette des valeurs normales.

DISFUNZIONE ERETTILE

Terapia farmacologica locale

INTRACAVERNOSA

PGE-1

Papaverina

Fentolamina

Linsidomina

Moxisylyte

VIP

Altre

INTRAURETRALE

PGE-1

Papaverina

Prazosin

TRANSDERMICA

PGE-1

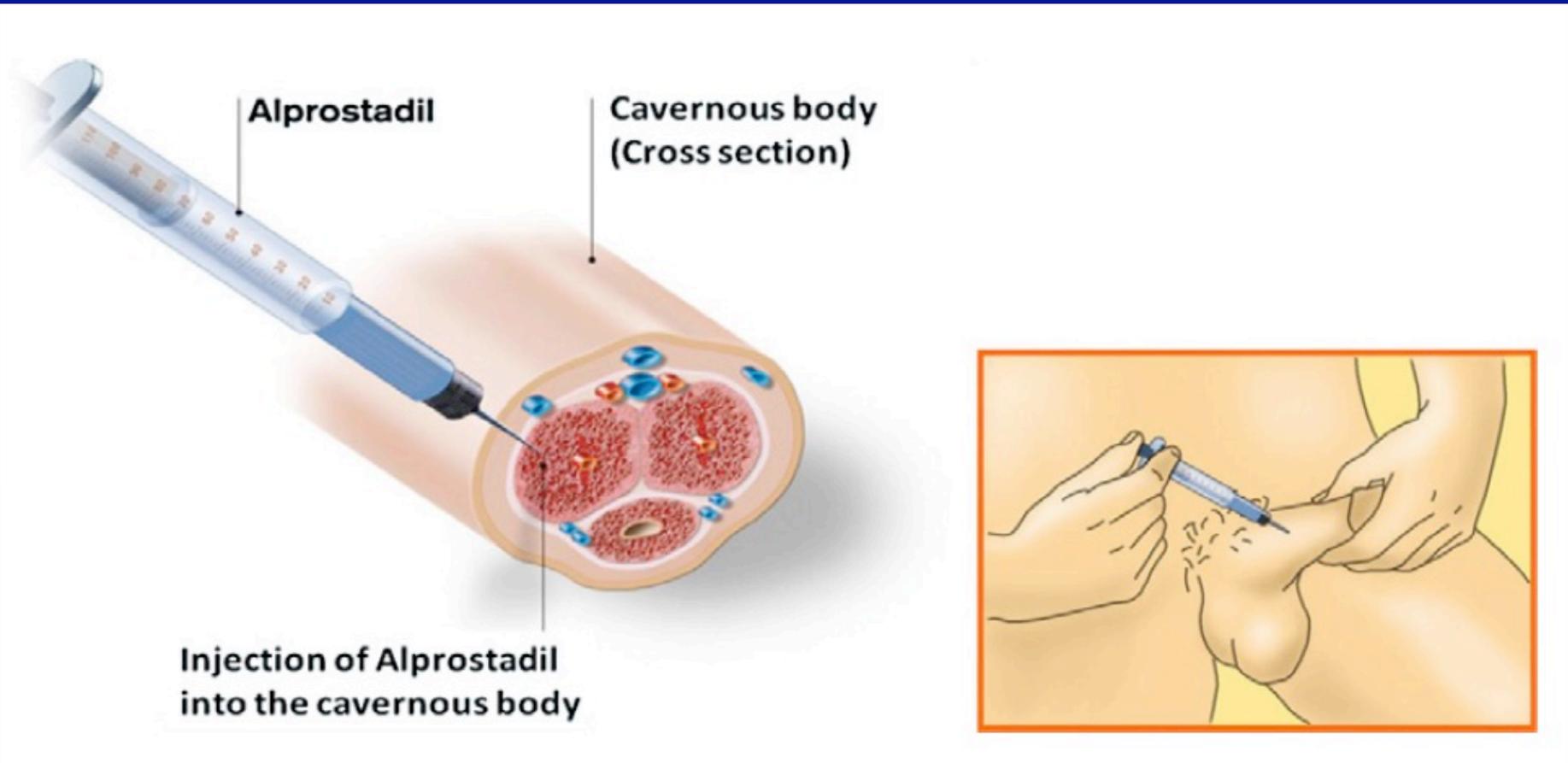
Papaverina

Nitroglicerina

Minoxidil

SOP Conservative (Medical and Mechanical) Treatment of Erectile Dysfunction

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

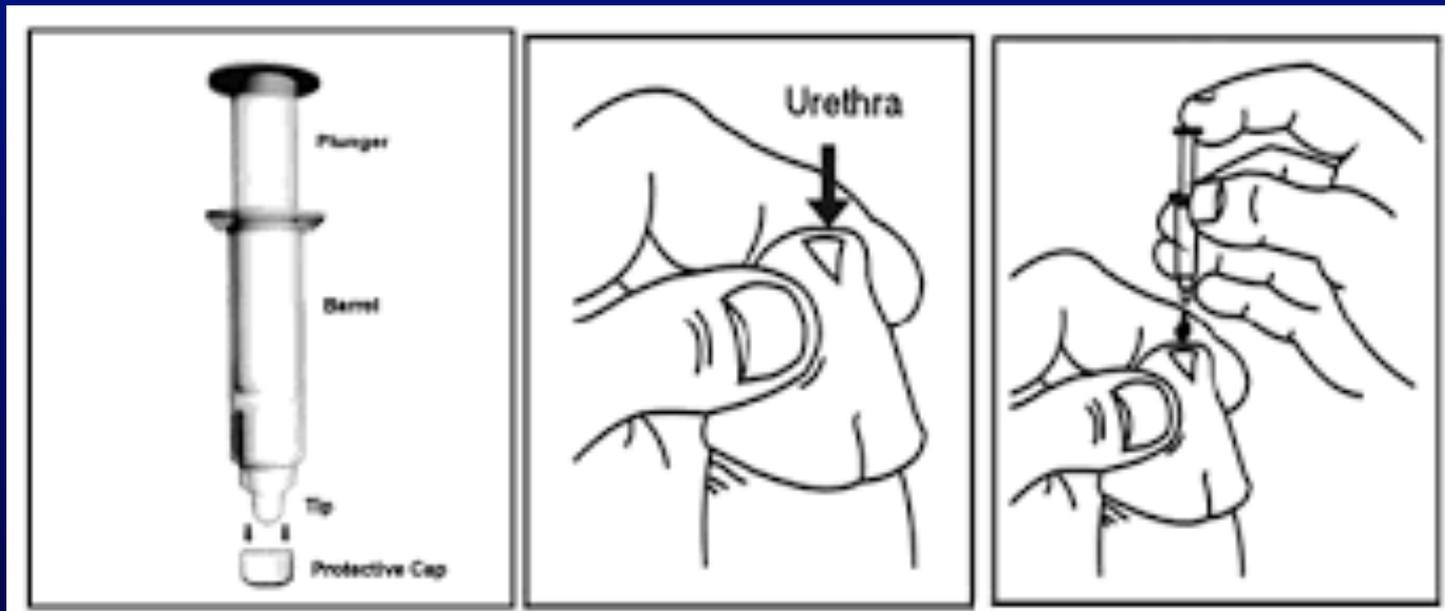


ALPROSTADIL crema

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

TERAPIA NON ENDOCRINA

Testosterone

hCG

GnRH

DHT

DHEA

Naltrexone

Dopaminoagonisti

Androstenedione

Antiestrogeni

*PDE5
inibitori*



Sildenafil

Vardenafil

Tadalafil

Avanafil

Apomorfina

Yohimbina

Trazodone

Fentolamina

Arginina

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, MD⁹
J Sex Med 2016;13:465–488.

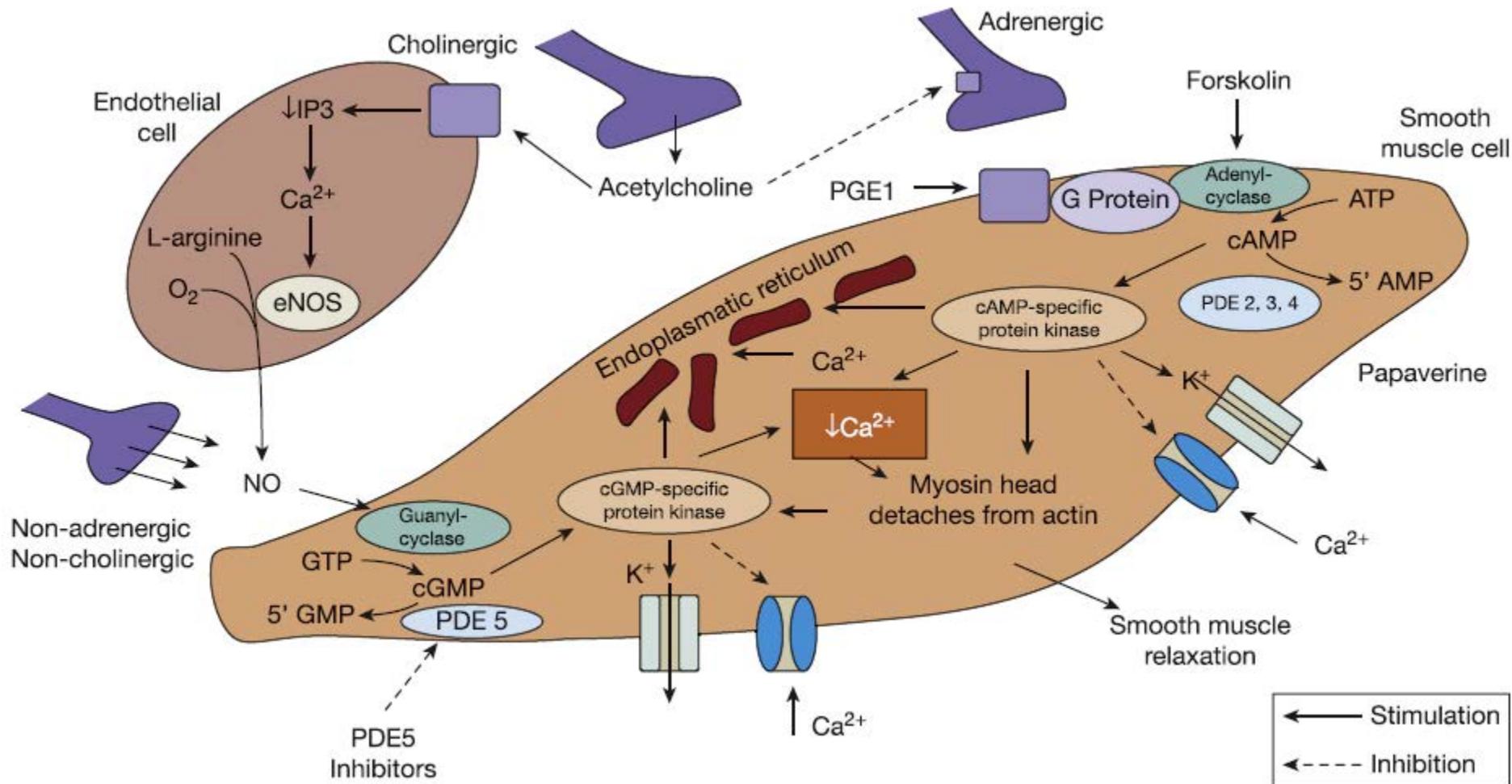


Table 5: Summary of the key pharmacokinetic data for the four PDE5 inhibitors currently EMA-approved to treat ED* European Association of Urology 2015 MALE SEXUAL DYSFUNCTION - UPDATE MARCH 2015

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.

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

<i>Patient status</i>	<i>N</i>	<i>n</i>	<i>(%)</i>	<i>Odds ratio</i>	<i>(95% CI)</i>
<i>Second-line therapies</i>					
No diabetes	117 070	2134	1.82	1	(ref)
Diabetes	19 236	538	2.80	1.55	(1.408, 1.706)
<i>Third-line therapies</i>					
No diabetes	117 070	437	0.37	1	(ref)
Diabetes	19 236	152	0.79	2.13	(1.77, 2.56)
<i>Second- and third-line combined</i>					
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

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

Diabet. Med. 15: 821–825 (1998)

D.E. Price¹, J.C. Gingell², S. Gepi-Attee², K. Wareham¹, P. Yates³, M. Boolell^{*3}

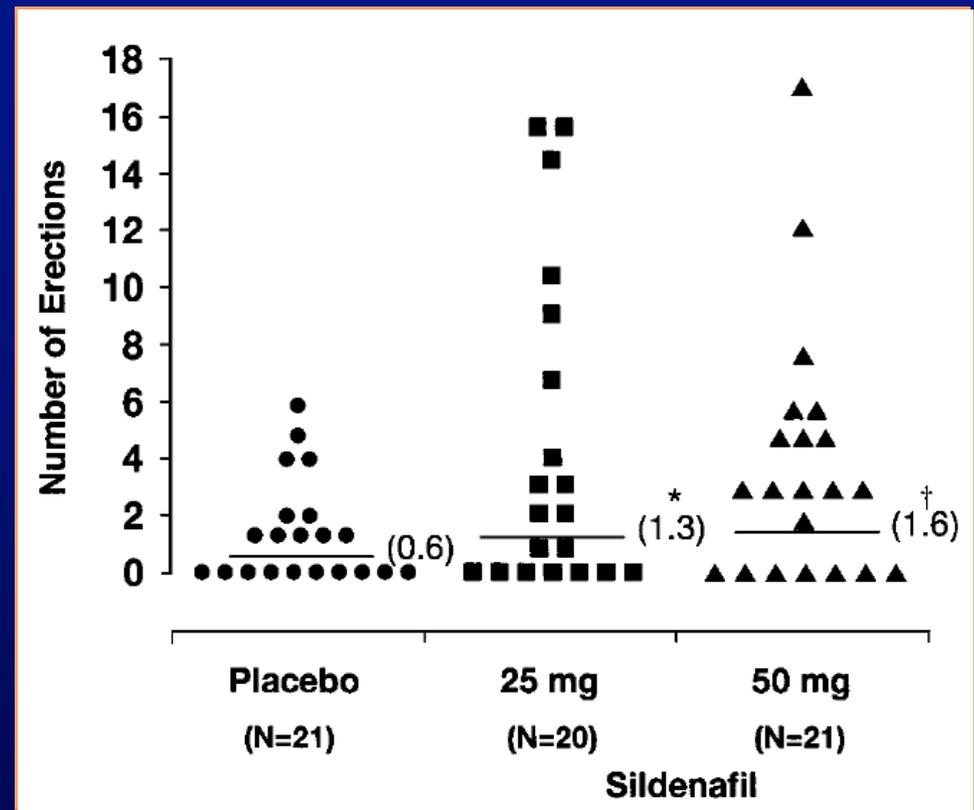
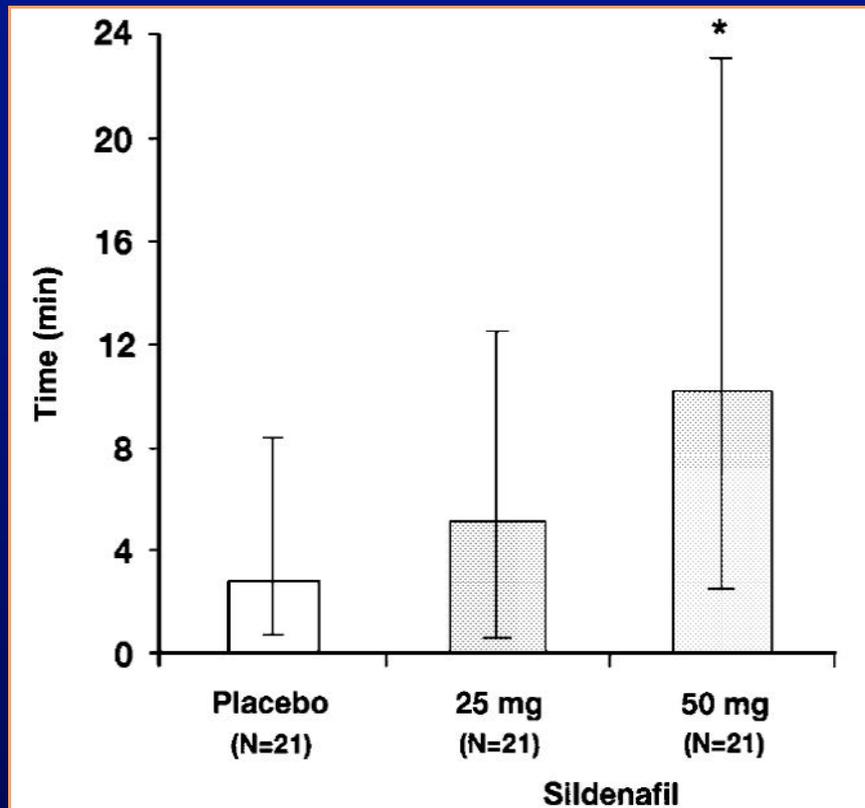


Figure 1. Duration (min) of penile rigidity >60% at the base of the penis during visual sexual stimulation. Bars and vertical

Tadalafil in the treatment of erectile dysfunction

Therapeutics and Clinical Risk Management 2008:4(6) 1315–1329
© 2008 Dove Medical Press Limited. All rights reserved

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

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.

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 TM) o per uso intracavernoso (Caverject TM)

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



AHA Scientific Statement

Sexual Activity and Cardiovascular Disease

A Scientific Statement From the American Heart Association

PDE5 inhibitor use has been explored in females for treatment of arousal disorders and has largely been shown to be no more effective than placebo.

The safety of PDE5 inhibitor use in females with CVD has not been established.

Local and Topical Estrogen Therapy

Recommendation

1. Nonsystemic (local or topical) estrogen use for the treatment of dyspareunia in women with CVD is reasonable

Because systemic absorption with vaginal administration is minimal, and focal vulval application

is expected to be even less, topical estrogen therapy is unlikely to pose any cardiac risk in women with CVD.

BASIC SCIENCE

J Sex Med 2018;

The Favorable Effect of Empagliflozin on Erectile Function in an Experimental Model of Type 2 Diabetes

Rana Assaly, PharmD, PhD,^{1,2} Diane Gorny,^{1,2} Sandrine Compagnie,^{1,2} Eric Mayoux, PhD,³ Jacques Bernabe, PhD,^{1,2} Laurent Alexandre, MD,¹ François Giuliano, MD, PhD,^{1,2,4} and Delphine Behr-Roussel, PharmD, PhD^{1,2}

] , this study showed that empagliflozin preserved the proerectile effect of acute sildenafil in GK rats. This was associated with an improvement in cavernosal nitrenergic relaxation, suggesting a favorable effect of empagliflozin on the attenuation of nerve injury in T2DM.

Thus, it is plausible to suggest that empagliflozin ameliorates NANC-mediated relaxation by attenuating the nerve injury, which could be confirmed by histological examination of nerves and/or major pelvic ganglion.



“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

GG

