CONGRESSO REGIONALE

AMD-SID LAZIO

Il DIABETE OGGI:

UNA MALATTIA SEMPRE PIÙ COMPLESSA

ROMA - 7/8 OTTOBRE 2022 - HOTEL QUIRINALE

V SESSIONE

Disfunzione erettile nel diabete: una complicanza dimenticata

Moderatori: **Renato Giordano, Vincenza Spallone**

10:00 Controllo glicemico e DE **Marzia Bongiovanni**

10:15 Diagnosi e Terapia della DE nel diabete **Giuseppe Defeudis**

10:30 Discussione

DIAGNOSI E TERAPIA DELLA DE NEL DIABETE

Giuseppe Defeudis, M.D., Ph.D.

g.defeudis@policlinicocampus.it

Università Campus Bio-Medico di Roma

DISCLOSURES

Il dr. Giuseppe Defeudis dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- Roche
- Biosys
- Ibsa

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

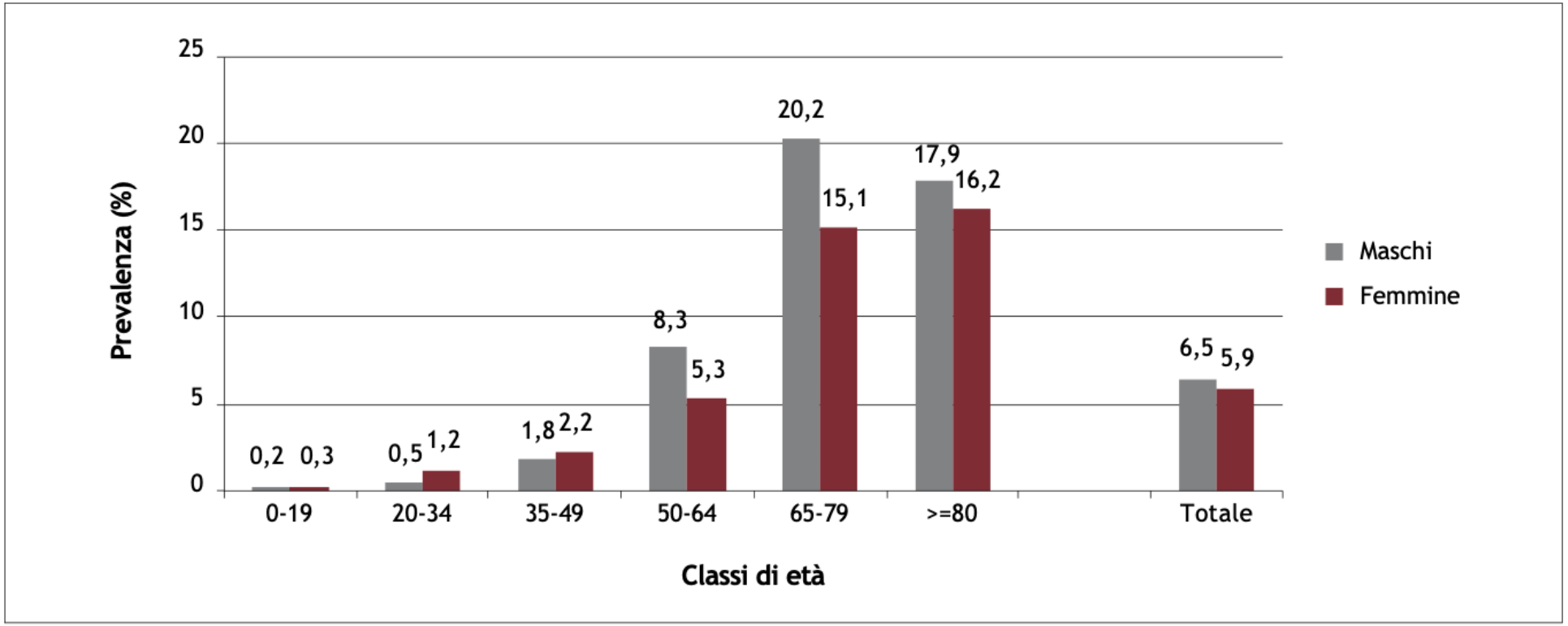
AGENDA

- Epidemiological data/Background
- Diagnosis
- Therapy
- Conclusions/Hints and practical tips

Epidemiological data/Background

Osservatorio ARNO Diabete
Rapporto 2019
Volume XXXI
Collana Rapporti Arno

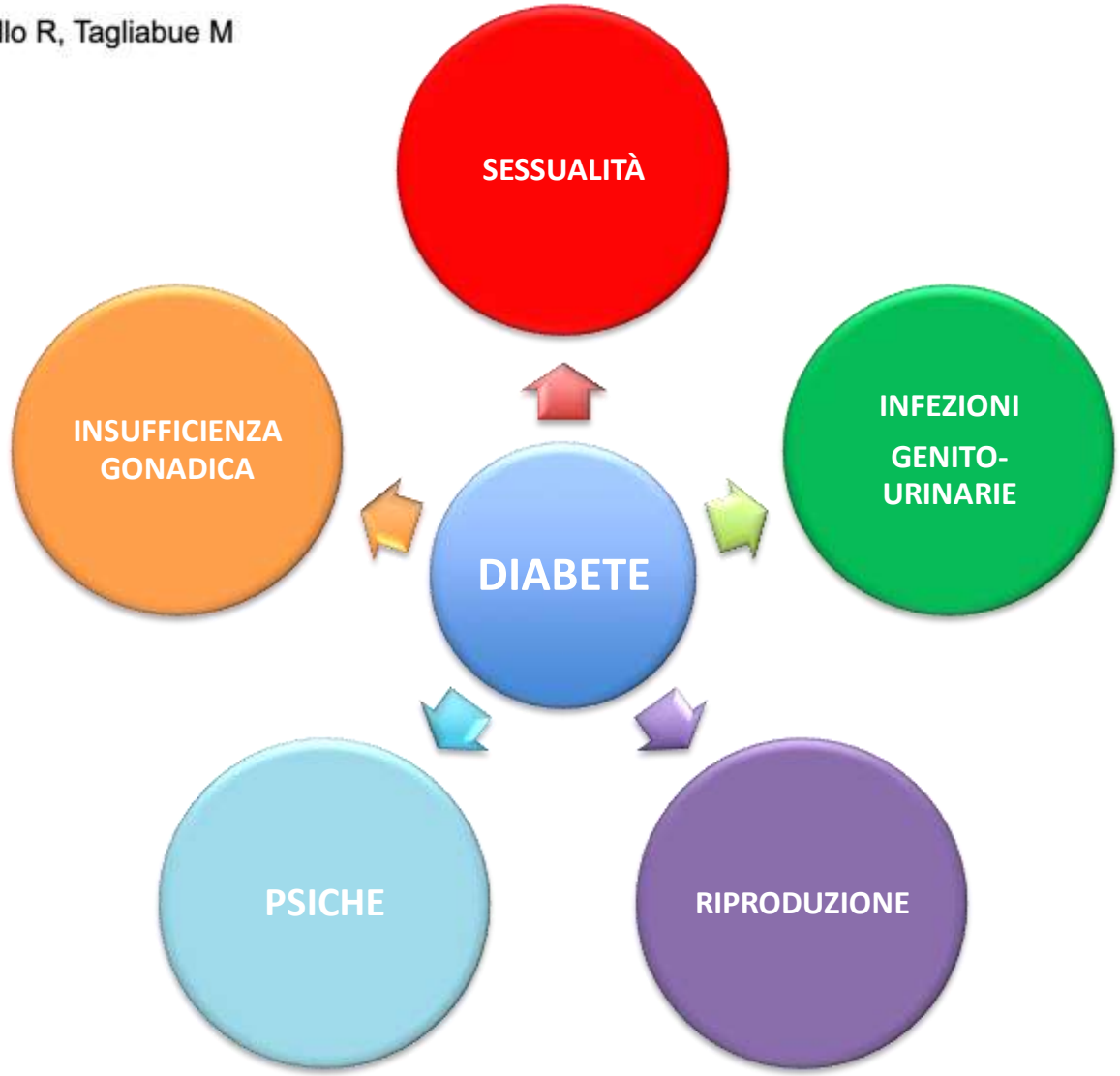
Prevalenza del diabete in funzione del sesso e dell'età[2]



Gruppo di lavoro intersocietario SID – SIE – SIAMS- in progress

Calogero A, Defeudis G, Esposito K, Foresta C, Jannini E, Lombardo F, Maggi M, Pivonello R, Tagliabue M

i disordini andrologici devono considerarsi a pieno titolo nel novero delle complicanze del diabete



Disfunzione Erettile

SESSUALITÀ

Journal of Diabetes and its Complications
Volume 31, Issue 5, May 2017, Pages 785-786

Sexual dysfunctions in diabetes: a gender issue

Maria Ida Maiorino, Giuseppe Bellastella, Katherine Esposito

Erectile dysfunction (ED) has long been recognized as a neuro-vascular complication which occurs in 35% to 90% of diabetic men, manifesting 10 to 15 years earlier than in men without diabetes.

Prevalence

35% *McCulloch et al. 1980*

35.8% *Fedele et al. 1996*

63.6% *Siu et al. 2001*

86.1% *El Sakka et al. 2003*

71% *Giuliano et al. 2004*

90% (T2D) *Sasaki et al. 2005*

58% (T2D) *De Berardis et al. 2006*

65.4% *Cho et al. 2006*

73.1% *Malavige et al. 2008*

81% Defeudis et al. 2018(priv. data)

Incidence

T1D 45/1000 pts /year

T2D 74/1000 pts /year

Duration of DM

1-5 ys: 47/1000 pts

6-10 ys: 55/1000 pts

>11 ys: 77/1000 pts

Fedele et al. J.Urol. 2001

Diabet. Med. 34, 1185–1192 (2017)

DIABETICMedicine

DOI: 10.1111/dme.13403

Systematic Review or Meta-analysis

High prevalence of erectile dysfunction in diabetes: a systematic review and meta-analysis of 145 studies

Y. Kouidrat[1,2,*], D. Pizzol[3,*], T. Cosco[4,5], T. Thompson[6], M. Carnaghi[3], A. Bertoldo[7], M. Solmi[8,9], B. Stubbs[10,11,12,†] and N. Veronese[9,13,†]

145 studi 88577 soggetti (età: 55.8±7.9 anni)

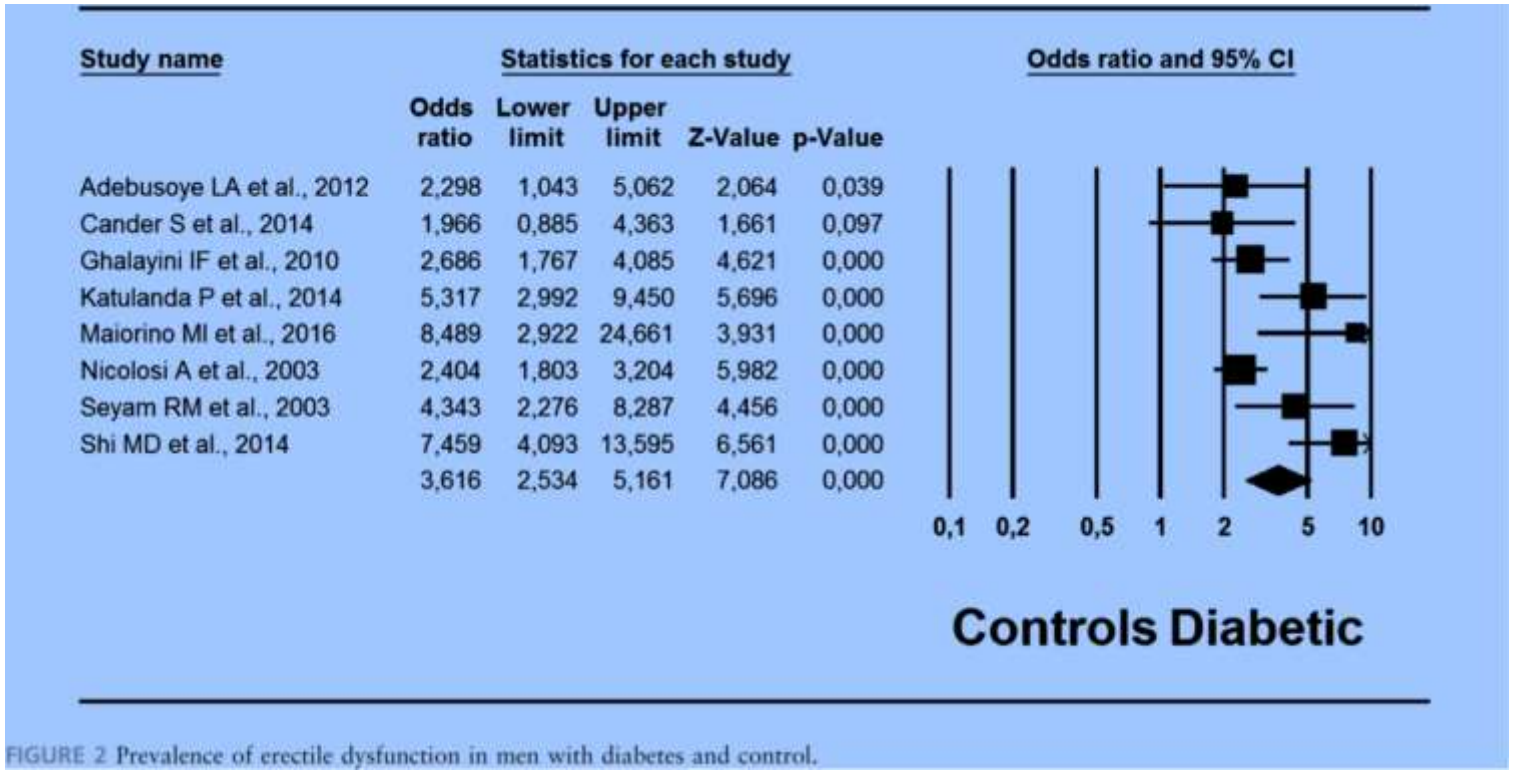
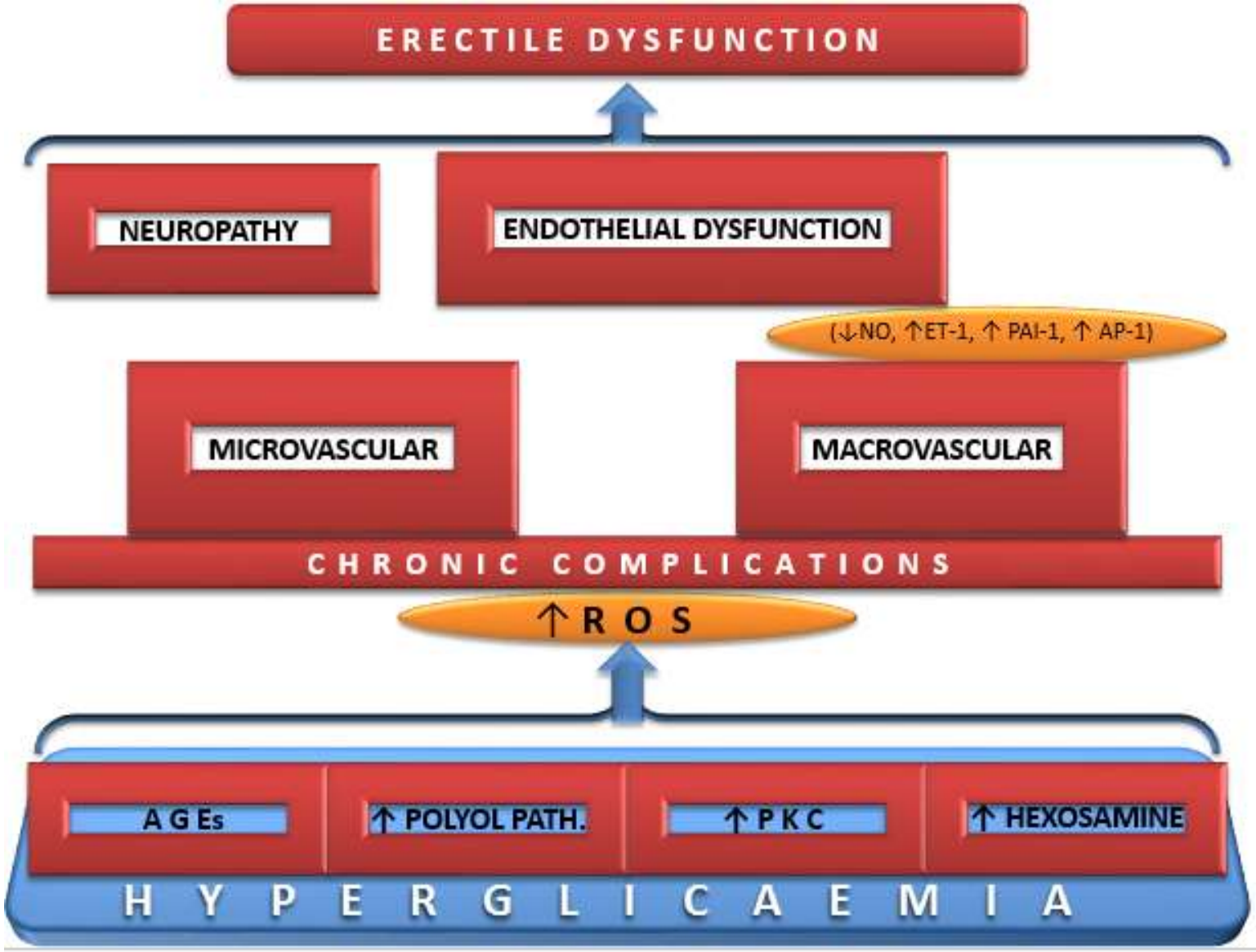


FIGURE 2 Prevalence of erectile dysfunction in men with diabetes and control.

DM quasi quadruplica il rischio di DE

The diabetic erectile dysfunction wall

AGEs advanced
glycation end-products, POLYOL
PATH. polyol pathway,
PKC protein kinase C,
ROS reactive oxygen species,
NO nitric oxide,
ET-1 endothelin-1,
PAI-1 Plasminogen
activator inhibitor-1,
AP-1 activator protein 1

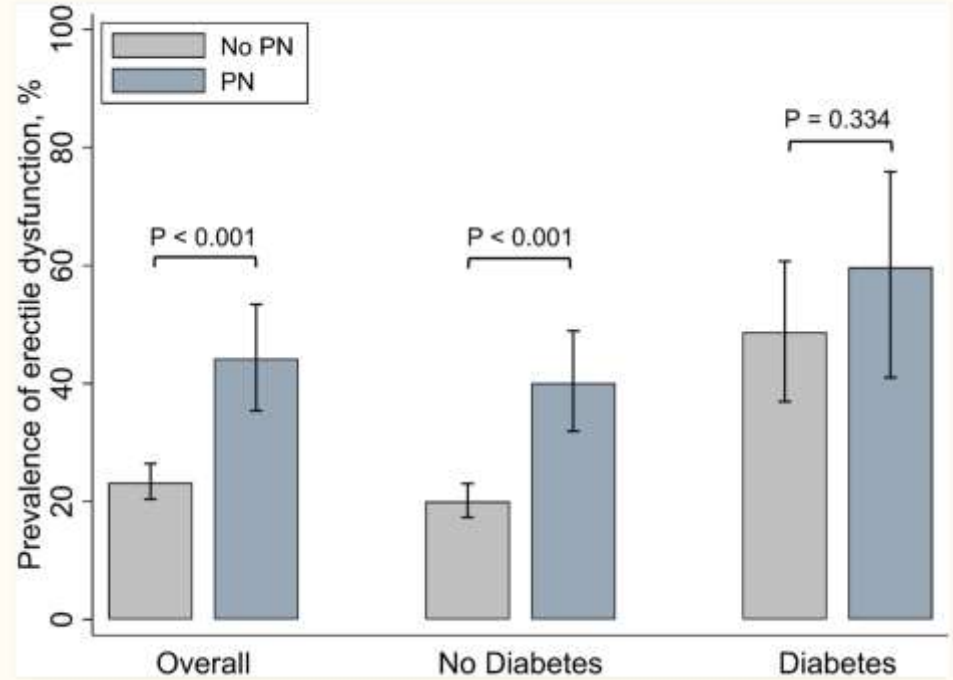


Defeudis G, Gianfrilli D. et al, Rev Endocr and Metab Disord, 2015

Published in final edited form as:
Am J Med. 2021 February ; 134(2): 282–284. doi:10.1016/j.amjmed.2020.07.015.

Association of Peripheral Neuropathy with Erectile Dysfunction in US Men

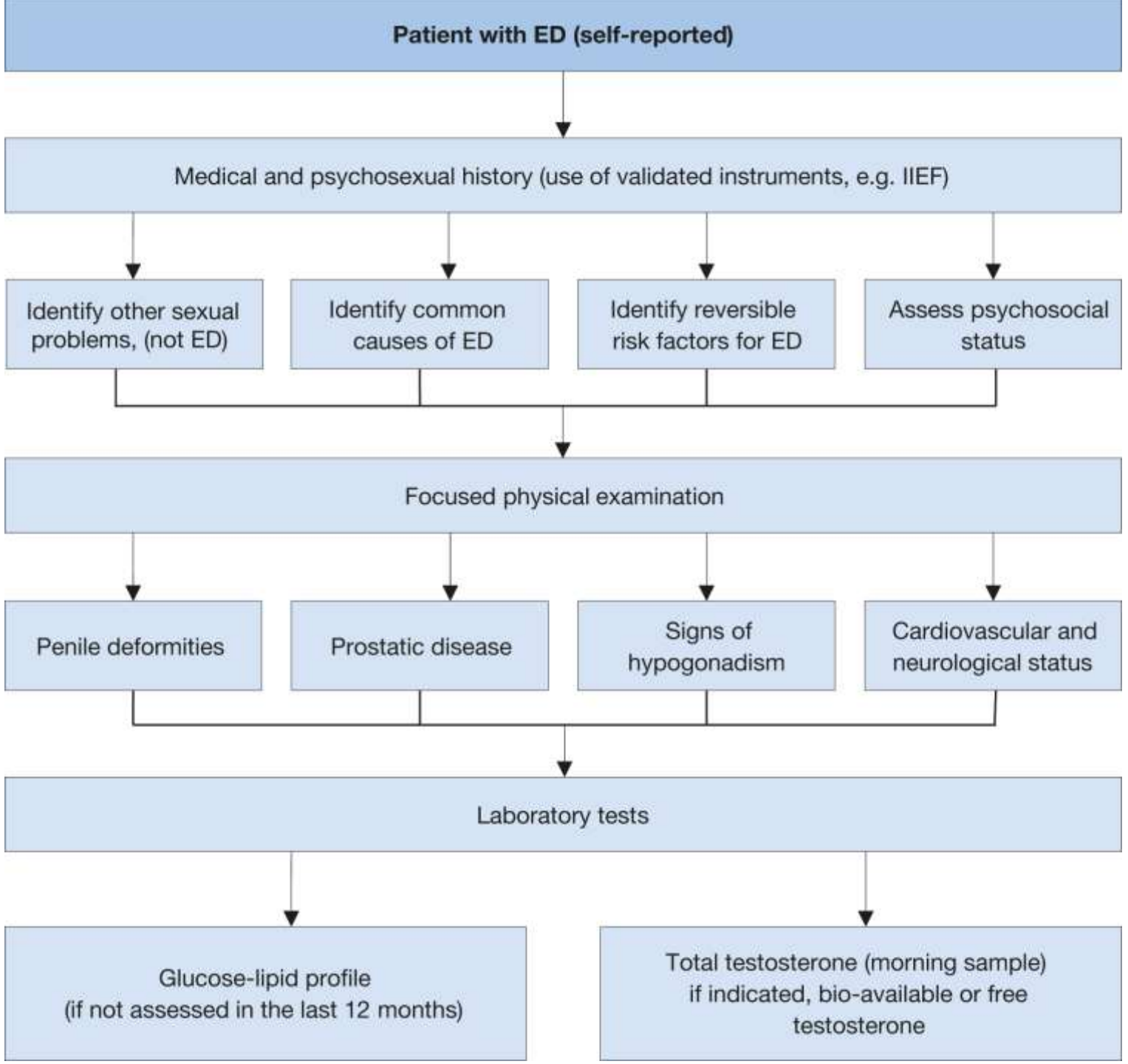
Caitlin W. Hicks, MD MS, MS[1], Dan Wang, MS[2], B. Gwen Windham, MD MHS[3], Elizabeth Selvin, PhD, MPH[2]



Clinical Significance

- Peripheral neuropathy (decreased lower extremity sensation) is common even in the absence of diabetes
- There is a significant independent association of peripheral neuropathy with erectile dysfunction in US men aged ≥40 years
- The association of peripheral neuropathy with erectile function is more pronounced in men without diabetes
- Peripheral neuropathy is a novel risk factor for erectile dysfunction

Diagnosis



EAU Guidelines on Sexual and Reproductive Health

A. Salonia (Chair), C. Bettocchi, J. Carvalho, G. Corona, T.H. Jones, A. Kadioğlu, J.I. Martinez-Salamanca, S. Minhas (Vice-chair), E.C. Serefoğlu, P. Verze
Guidelines Associates: L. Boeri, P. Capogrosso, A. Cocci, K. Dimitropoulos, M. Gül, G. Hatzichristodoulou, A. Kalkanli, L.A. Morgado, V. Modgil, U. Milenkovic, G. Russo, T. Tharakan
Guidelines Office: J.A. Darraugh

Therapy

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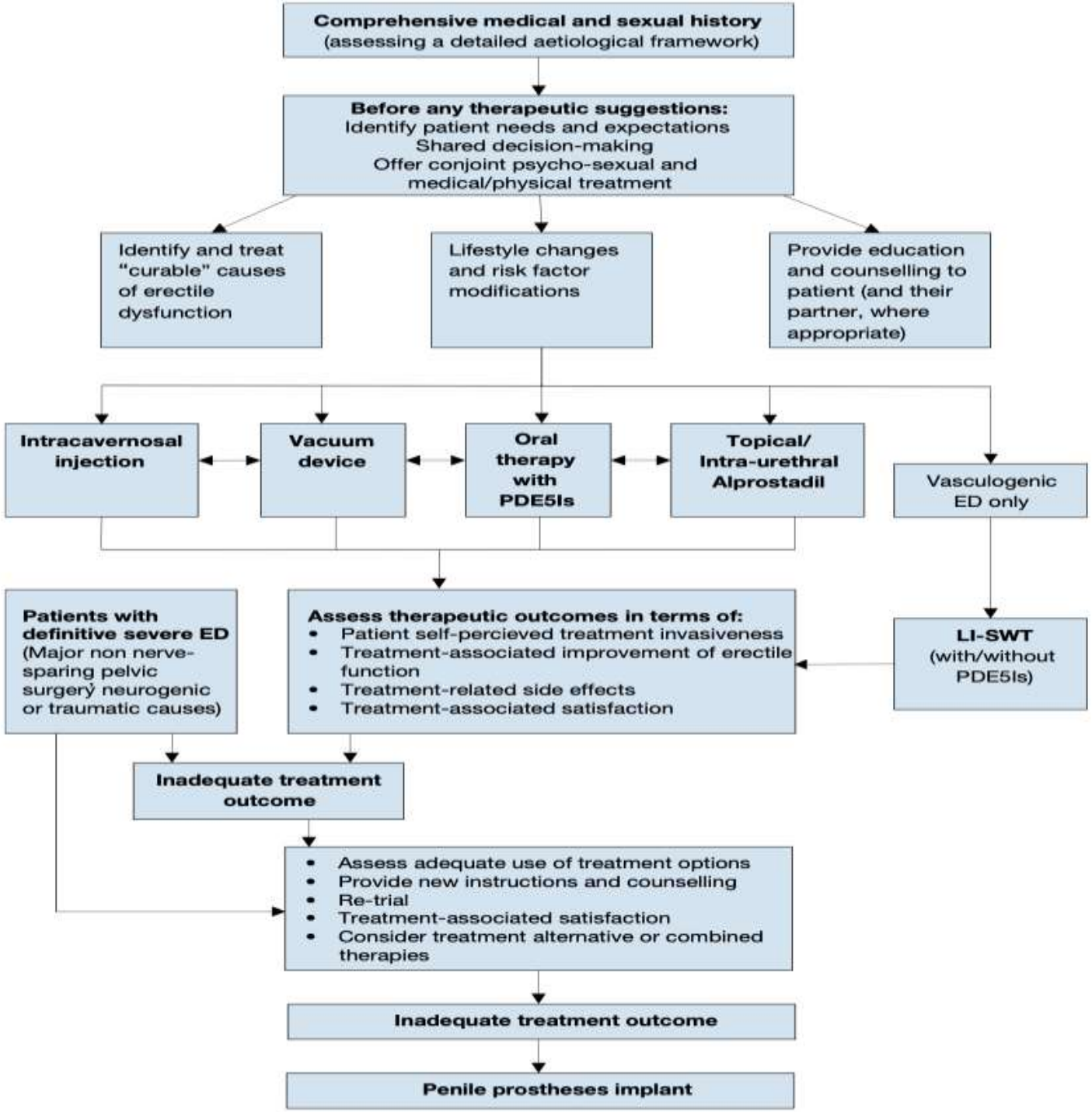

Therapy

ED TREATMENTS

- Lifestyle changes
- PDE5is
- (T2D treatments)
- PGE (i.c., transuretral)
- Hormonal treatments (i.e. hypogonadism, etc.)
- Shockwave therapy
- Vacuum devices
- Penile Prosthesis
- Psycosexual approach

ED TREATMENTS in diabetes
- Lifestyle changes
- PDE5is
- (T2D treatments)
- PGE (i.c., transuretral)
- Hormonal treatments (i.e. hypogonadism, etc.)
- Vacuum devices
- Penile Prosthesis
- Psycosexual approach

LIFESTYLE CHANGES

Authors	Diet	Diet assessment	Study design	Erectile dysfunction assessment	Cases	Type	Effect
Cassidy et al. 2016	habitual diet	food-frequency questionnaires	prospective cohort study	5-point scale	25096	healthy men	higher habitual intake of specific flavonoid-rich foods is associated with reduced ED incidence
Bauer et al. 2020	habitual diet	food-frequency questionnaires	prospective cohort study	5-point scale	21469	healthy men	adherence to healthy dietary patterns was associated with a lower risk for erectile dysfunction
liu et al 2016	habitual diet	food-frequency questionnaires	prospective cohort study	IIEF-5	1564	elderly men	fruit and vegetable consumption had no significant association with the score change of ED
Wang et al. 2013	habitual diet	food-frequency questionnaires	cross-sectional study	single question y/n	1466	men with T2D	10% risk reduction of ED was found with each additional daily serving of fruit/vegetable consumed
Chen et al. 2016	habitual diet	food-frequency questionnaires	cross-sectional study	IIEF-5	4208	men >50 years old	vegetable intake (p=0.001), and milk and dairy product intake (p=0.001) decreased the IIEF-5
Farnas et al. 2020	habitual diet	2-day food diary	cross-sectional study	5-point scale	4027	men 18-85	no association between specific diets (low fat, med, unrestricted) and EF
Lu et al. 2021	habitual diet	food-frequency questionnaires	cross-sectional study	IIEF-5	116	young healthy men <45	plant-based diet was not associated with ED
Carto et al. 2022	habitual diet	food-frequency questionnaires	cross-sectional study	5-point scale	2549	men 20-70 years	healthful plant-based diet is associated with less chance of having erectile dysfunction
Huynh et al. 2020	habitual diet	dichotomic questionnaire	cross-sectional study	IIEF-5	271	men accessing a men's health clinic	men with ED less likely to report an organic diet or intermittent fasting
Giugliano et al. 2010	habitual diet	food-frequency questionnaires	cross-sectional study	IIEF-5	555	men 35-70 with T2D	greater adherence to Mediterranean diet is associated with a lower prevalence of ED
Angelis et al. 2020	habitual diet	food-frequency questionnaires	cross-sectional study	Sexual Health Inventory for Men-5 (SHIM-5)	150	men with stable heart failure	The SHIM-5 score was positively correlated with the MedDietScore (p = 0.006)
Della camera et al. 2017	habitual diet	questionnaire adherence to med diet	case-control	IIEF-15	141	healthy men aged 50-72	patients with ED have lower Med-Diet scores
Esposito et al. 2006	habitual diet	food-frequency questionnaires	case-control	IIEF-5	200	healthy men with and without ED	intake of fruits and nuts, and the ratio of monounsaturated lipids to saturated lipids
Mykoniatis et al. 2018	habitual diet	food-frequency questionnaires	case-control	IIEF-15	350	healthy young men	Increased intake of fruits, vegetables, and flavonoids decreases the risk of ED in young men
Lu et al. 2021	habitual diet	food-frequency questionnaires	case-control	IIEF-5	184	without ED (older) including T2D	was associated with a reduced presence of ED and less severe ED
Talib et al. 2015	intermittent fasting (ramadam)	not monitored	observational study	IIEF (1to5-11-12-15)	45	men observing ramadam	No statistically significant differences were found on EF
Ramirez et al. 2016	habitual diet	14-item food questionnaire	observational study	IIEF-15	440	men over 40 non diabetic with or without ED	consumption of nuts (> twice a week) (OR 0.41 (95% CI 0.25 to 0.67) and vegetables (≥ once a day) (OR 0.47 (95% CI 0.28-0,77)), were inversely related to ED
Khoo et al. 2011	VLCD vs high protein low fat low carb diet higher in calories	daily food diaries	RCT	IIEF-5	31	men with obesity and T2D	similar results for both diet despite different degree of weight loss
Khoo et al. 2010	VLCD vs control	daily food diaries	controlled clinical trial	IIEF-5	68	obese men with or without T2D	The degree of weight loss was significantly associated with improvements in EF (r=−0.26)
Moran et al. 2016	higher protein low fat vs higher carbohydrate low fat diet	3-day food diaries	RCT	IIEF-15	118	men with obesity or overweight	no improvement in either group despite significant weight loss

ANDROLOGY

REVIEW ARTICLE | Free Access

Effects of Diet and Antihyperglycemic Drugs on Erectile Dysfunction: A Systematic Review

Giuseppe Defeudis, Rossella Mazzilli, Alfonso Maria Di Tommaso, Virginia Zamponi, Francesco Carlomagno, Dario Tuccinardi, Mikiko Watanabe, Antongiulio Faggiano, Daniele Gianfrilli

First published: 29 April 2022 | https://doi.org/10.1111/andr.13192

Esposito et al. 2004	hypocaloric diet vs control	3-day food diaries	RCT	IIEF-5	110	men with obesity and ED	weight loss and physical activity associated with improvement
Wing et al. 2010	hypocaloric diet vs control	daily food diaries	RCT	IIEF-15	306	overweight obese men with T2D	weight loss intervention was mildly helpful in maintaining EF
Collins et al. 2013	hypocaloric diet vs control	follow ups and weight loss monitoring	RCT	IIEF-5	145	overweight or obese men	weight loss associated with improvement
Esposito et al. 2006	Mediterranean diet vs control	3-day food diaries	controlled clinical trial	IIEF-5	65	men with MS and ED	consumption of a Mediterranean-style diet in men with the metabolic syndrome and ED at baseline produced significant improvement of EF

ED TREATMENTS in diabetes

- Lifestyle changes
- PDE5is
- (T2D treatments)
- PGE (i.c., transuretral)
- Hormonal treatments (i.e. hypogonadism, etc.)
- Vacuum devices
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- Psycosexual approach

PDE5i

Table 14: Summary of the key pharmacokinetic data for the four PDE5Is currently EMA-approved to treat ED*

Parameter	Sildenafil, 100 mg	Tadalafil, 20 mg	Vardenafil, 20 mg	Avanafil, 200mg
C_{max}	0.8-1 hours	2 hours	0.9 hours	0.5-0.75 hours
T_{max} (median)	2.6-3.7 hours	17.5 hours	3.9 hours	6-17 hours
T1/2	1,685 µg.h/L	8,066 µg.h/L	56.8 µg.h/L	11.6 µg.h/L
AUC	96%	94%	94%	99%
Protein binding	41%	NA	15%	8-10%
Bioavailability	41%	NA	15%	8-10%

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

Table 15: Common adverse events of the four PDE5Is 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.*

NOVEL INDICATIONS FOR USE OF PDE5is IN PATIENTS WITH DIABETES

Table 5 Novel indications for use of PDE5is in patients with diabetes

Author	Type	N°. of patients	Disease	Mean/ range age	Intervention	Methodologies and scale	Results
Aversa et al.	DB PC RCT parallel design	20	T2D	40–75	Sildenafil 100 mg for 3 days - > Sildenafil 25 mg TID for 4 weeks **or** sildenafil 25 mg TID for 4 days - > placebo TID for 3 weeks	Flow-mediated dilatation (FMD), endothelial function (CRP;IL-6; ICAM; VCAM)	Significant improvement in FMD after chronic sildenafil (from 6.8 ± 0.5 to 12.5 ± 0.7 %), Reduced endothelial function biomarkers
Stirban et al.	DB PC RCT cross-over	40	T2D	55.1 ± 1.17	Single dose of 100 mg Sildenafil or placebo	Haemodynamic parameters, FMD, cardiovascular autonomic function tests and spontaneous baroreflex sensitivity (BRS)	Mild increase in heart rate and decrease in BP, Neither acute improvement of FMD nor any adverse effects on orthostatic BP regulation, HRV.
Aversa et al.	Open-label, randomised, crossover study	20	ED	54	Tadalafil 20 mg on alternate days or on demand for 4 weeks	Serum biomarkers of endothelial function (CRP;ET1;VCAM)	ET1, VCAM and CRP decreased after chronic vs. on demand regimes
Grover-Páez F et al.	DB PC RCT	40	T2D	35–50	Sildenafil 50 mg daily or placebo for 30 days	hs-CRP, microalbuminuria, homocysteine, HbA1c	Significant decrease in microalbuminuria and HbA1c concentrations versus baseline and versus placebo
Giannetta et al.	DB PC RCT	59	T2D	60.3 ± 7.4	Sildenafil 100 mg/d or placebo for 3 months	Left ventricular torsion (T), strain (σ), monocyte chemotactic protein-1 (MCP-1), transforming growth factor-β (TGF-β)	Significant improvement compared with placebo in LV T and σ, LV geometry and performance, reduction in MCP-1 and TGF-β
Burnett et al.	DB PC RCT	305	T2D + ED	35–70	Daily sildenafil 50 mg for 1 week and 100 mg for 3 weeks **or** placebo for 4 weeks - > sildenafil 25/50/100 mg on demand for 12 weeks	Serum biomarkers of endothelial function	Serum cyclic guanosine monophosphate levels were increased Serum 8-isoprostane levels were unchanged at 16 weeks
Santi et al.	Meta-analysis	476	T2D	NK	Sildenafil or placebo	FMD Endothelial function	Improvement in FMD and serum pro-inflammatory makers (IL-6)
Rosano et al.	PC RCT	32	ED + increate cardiovascular risk	65.4 ± 6.3	Tadalafil 20 mg on alternate days or placebo for 4 weeks	FMD Serum biomarkers of endothelial function	Improvement in FMD Increase nitrite/nitrate levels and decreased ET

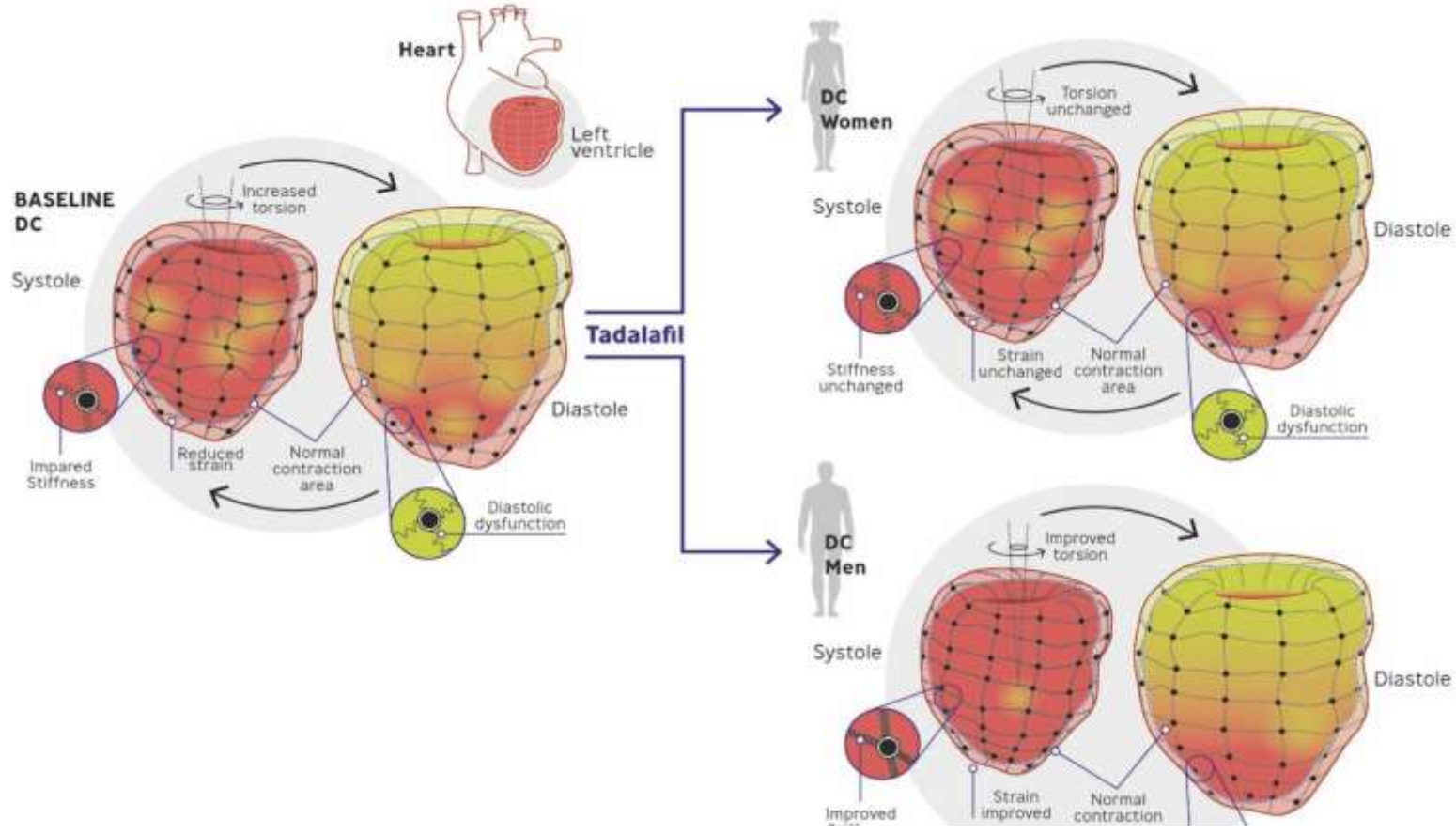
RCT randomed controlled trial, *PC* placebo controlled, *DB* double blind, *TID* three times a day, *T2D* Type 2 Diabetes, *BP* blood pressure, *NK* not known, *ED* erectile dysfunction, *IL-6* interleukin 6, *CRP* c reactive protein, *IIEF* International Index of Erectile Function, *ET* endothelin, *FMD* Flow-mediated dilatation, *ICAM* intercellular Cell Adhesion Molecule, *VCAM* vascular Cell Adhesion Molecule, *HRV* heart rate variability, *TGF* Transforming growth factor

Defeudis G. Gianfrilli D. et al. Rev Endocr and Metab Disord. 2015

DIABETIC CARDIOMYOPATHY

Sex-specific effects of daily tadalafil on diabetic heart kinetics in RECOGITO, a randomized, double-blind, placebo-controlled trial

Riccardo Pofi[1]†, Elisa Giannetta[1]†, Tiziana Feola[1,2], Nicola Galea[1], Federica Barbagallo[1], Federica Campolo[1], Roberto Badagliacca[3], Biagio Barbano[4], Federica Ciolina[5], Giuseppe Defeudis[6], Tiziana Filardi[1], Franz Sesti[1], Marianna Minnetti[1], Carmine D. Vizza[3], Patrizio Pasqualetti[7], Pierluigi Caboni[8], Iacopo Carbone[5], Marco Francone[5], Carlo Catalano[5], Paolo Pozzilli[6], Andrea Lenzi[1], Mary Anna Venneri[1], Daniele Gianfrilli[1]*‡, Andrea M. Isidori[1]*‡



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- Psycosexual approach

DM treatments

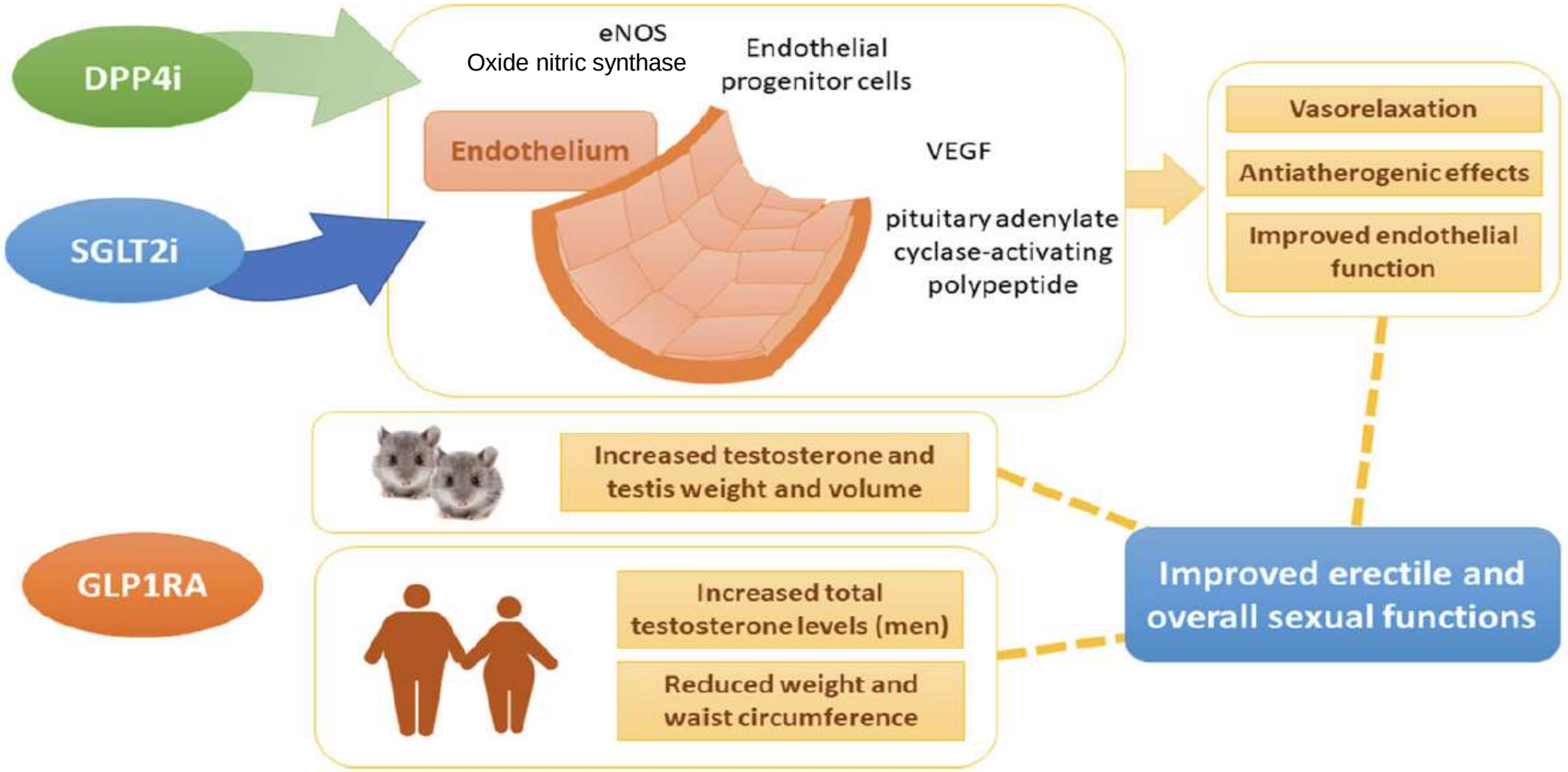
Trials In humans

Class	Drugs	Authors	Study design	Erectile dysfunction assessment	Cases	Effect
Biguanide	Metformin	Rey-Valzacchi GJ et al, 2011	Prospective, randomized, controlled, double-blind placebo study	IIEF-5	30	IIEF score increased after Metformin treatment
Biguanide and sulfonylurea	Metformin vs glibenclamide	Al-Kuraishy HM et al, 2016	Cross-sectional study	SHIM	91	Sulfonylureas have a better effect on EF
Insulin	CSII vs MDI	Maiorino MI et al, 2016	Observational study	IIEF-5	224	Insulin improves EF without statistically significant difference between CSII and MDI
		Kesavadev J et al	Prospective study	IIEF-5	46	At six months, CSII showed increased IIEF-5 ($P = .0037$). More subjects in the CSII than the MDI arm achieved reductions in ED severity
		Intensive insulin treatment vs conventional therapy	Wessels et al, 2011	Cohort study	IIEF	571	Intensive insulin treatment is associated with a decrease incidence of ED in patients with microalbuminuria or non-proliferative retinophaty, wherease no difference was observed between conventional therapy towards intensive in patient in primary prevention
Thiazolidinediones	Pioglitazone	Gholamine B et al, 2008	Prospective, randomized, placebo-controlled, double-blinded trial study	IIEF-6	38	Improved EF and increased sildenafil response
DPP-4 Inhibitors	Linagliptin	Mourad S et al, 2019	Prospective study	/	9	Increase Tadalafil plasma concentration.
GLP-1RAs	Liraglutide vs metformin	Giagulli VA et al, 2015	Retrospective observational study	IIEF-15	43	Improve of EF, glycemic control and weight loss
	Dulaglutide	Bajaj HS et al, 2021	Randomized, double blind, placebo-controlled study	IIEF-15	3725	Improve of EF

Reviews in Endocrine and Metabolic Disorders
https://doi.org/10.1007/s11154-019-09535-7

Male and female sexual dysfunction in diabetic subjects: Focus on new antihyperglycemic drugs

Giovanni Corona[1] · Andrea M. Isidori[2] · Antonio Aversa[3] · Marco Bonomi[4,5] · Alberto Ferlin[6] · Carlo Foresta[7] · Sandro La Vignera[8] · Mario Maggi[9] · Rosario Pivonello[10] · Linda Vignozzi[9] · Francesco Lombardo[3]



ED TREATMENTS in diabetes

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Testosterone

CONSENSUS STATEMENT

Adult- and late-onset male hypogonadism: the clinical practice guidelines of the Italian Society of Andrology and Sexual Medicine (SIAMS) and the Italian Society of Endocrinology (SIE)

A. M. Isidori[1] · A. Aversa[2] · A. Calogero[3] · A. Ferlin[4] · S. Francavilla[5] · F. Lanfranco[6] · R. Pivonello[7,8] · V. Rochira[9] · G. Corona[10] · M. Maggi[11]

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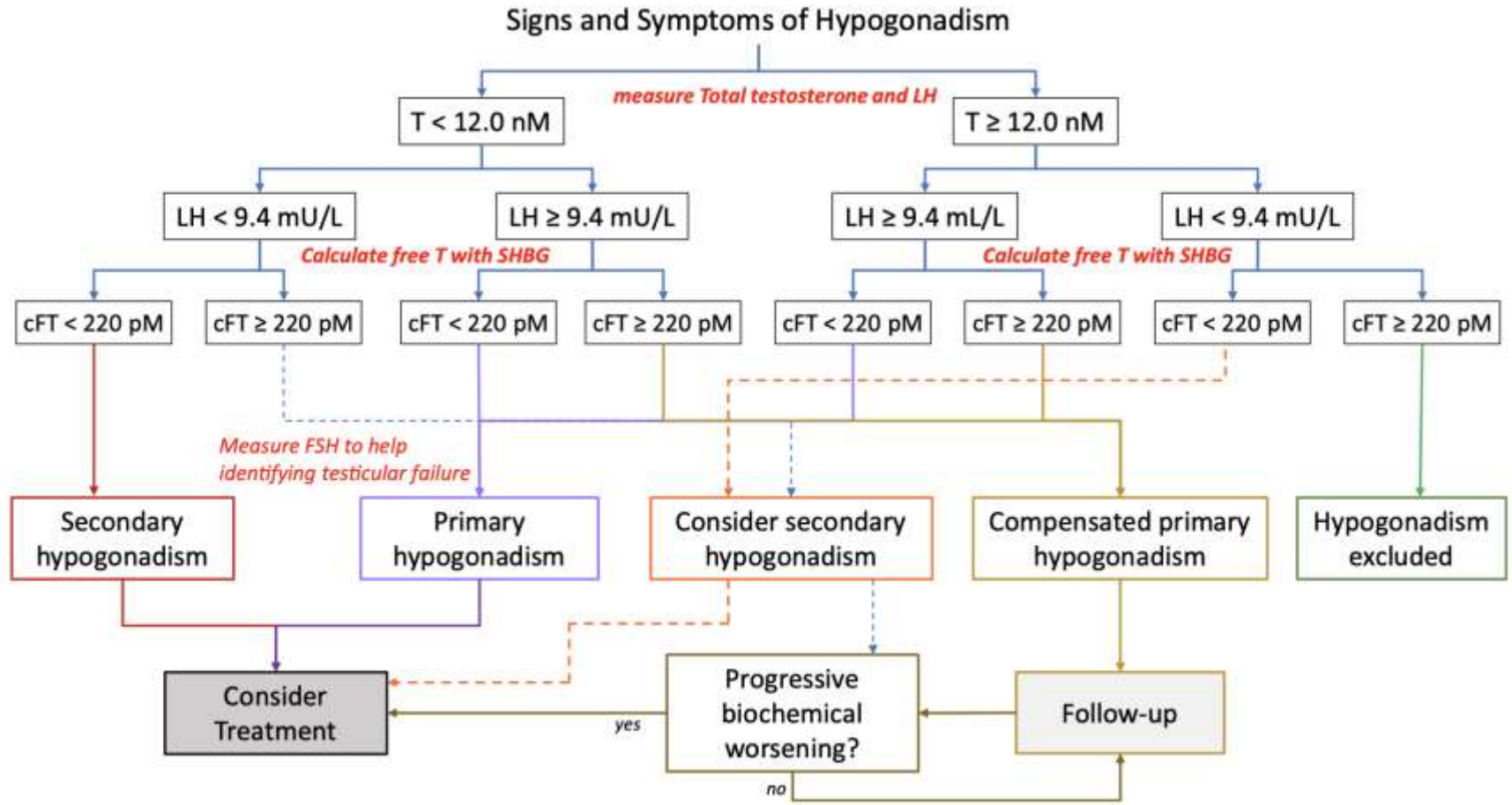

Fig. 2 Proposed flowchart to diagnose and manage adult-onset hypogonadism: *cFT* calculated free, testosterone; *FSH* follicular-stimulating hormone, *LH* luteinizing hormone, *SHBG* sex hormone binding globulin, *T* testosterone. The dashed lines reflects a lower level of evidence

Conclusions/Hints and practical tips

Disordini andrologici chiara complicanza del DM

DE DM: prevalenza variabile ma in crescita

DM quadruplica rischio DE

DE DM e associazione con numerose comorbidità

Diagnosi DE: anamnesi corretta, questionari, valutazione psicosessuologica e quadro ormonale

Terapia DE DM: dallo stile di vita, ai PDE5i, onde d'urto, iniezioni IC e protesi

- Terapia DM in DE
- Novelties su uso PDE5i

GRAZIE !!!

Giuseppe Defeudis, M.D., Ph.D.
g.defeudis@policlinicocampus.it

Università Campus Bio-Medico di Roma