Prof Geoffrey Hackett

Good Hope Hospital Sutton Coldfield

Testosterone Deficiency Syndrome –

Time for Proper Personalised Care

University of Bedfordshire

NHS

HEART of ENGLAND NHS Foundation Trust

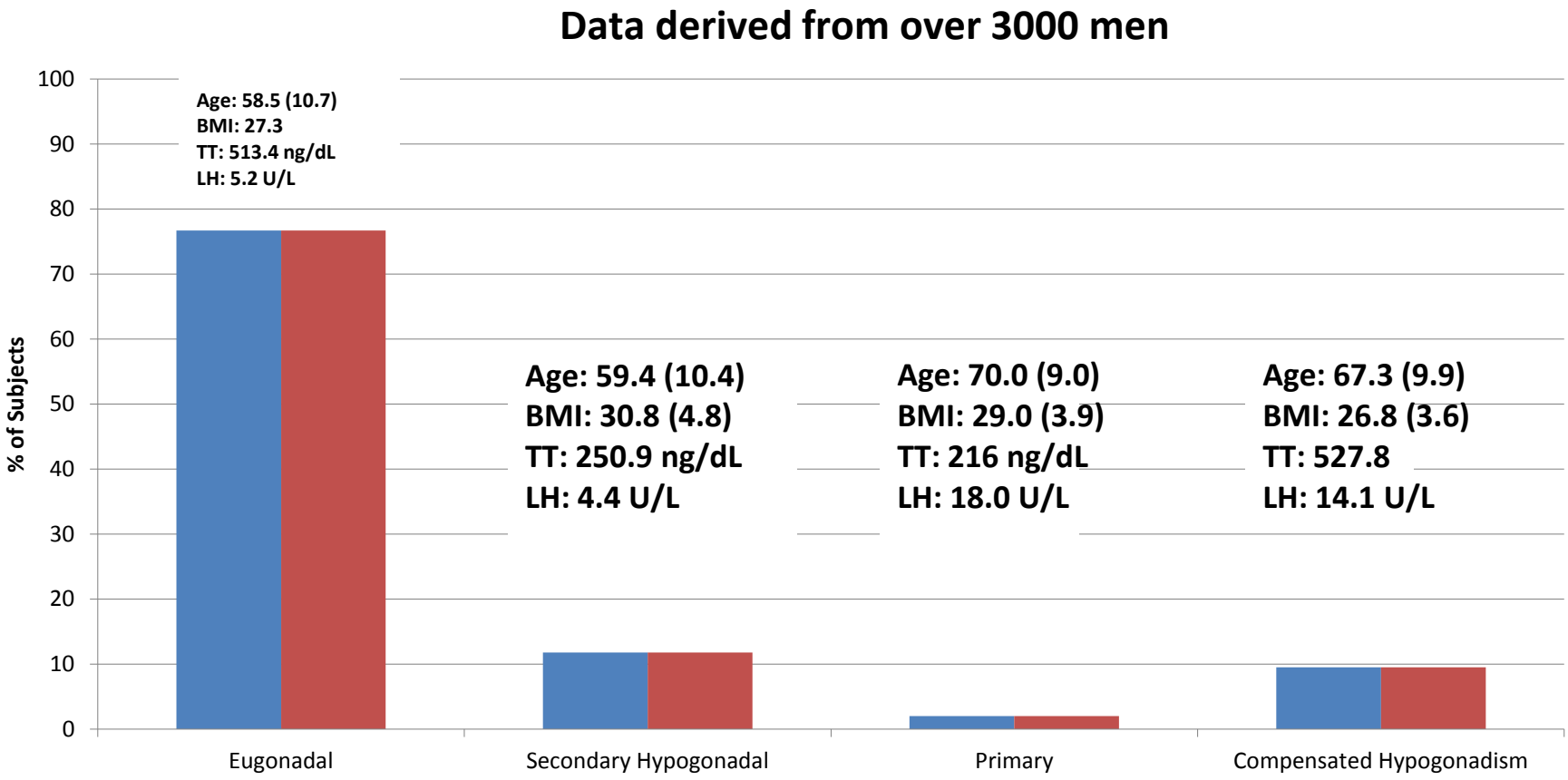
BSSM Testosterone Guidelines 2017

www.bssm.org.uk

Recommendations –Diagnosis		
Restrict the diagnosis of TD to men with persistent symptoms suggesting TD and confirmed low testosterone	3	C
Measure fasting testosterone levels in the morning before 11am, acknowledging that, in normal life, non-fasting levels may be up to 30% lower	2	A
Repeat total testosterone on at least 2 occasions by a reliable method. In addition, measure free testosterone in men with levels close to the lower normal range (8-12nmol/l) or those with suspected or known abnormal SHBG	1	A
Measure LH serum levels to differentiate between primary and secondary TD	2	A
Base decisions on therapy on published action levels rather than laboratory reference ranges	4	B

European Male Aging Study

Distribution and Selected Characteristics of Men Ages 40-70 (Tajar et al)



Cheryl suggests Shane attend for age 40 health check

- Diminished energy
- Reduced vitality /well-being
- Increased fatigue
- Depressed mood
- Impaired cognition
- Diminished muscle mass and strength
- Falling asleep in the evening
- BUT NOT MENTIONED AND NOT ASKED
- DIMINISHED SEXUAL DESIRE
- ED

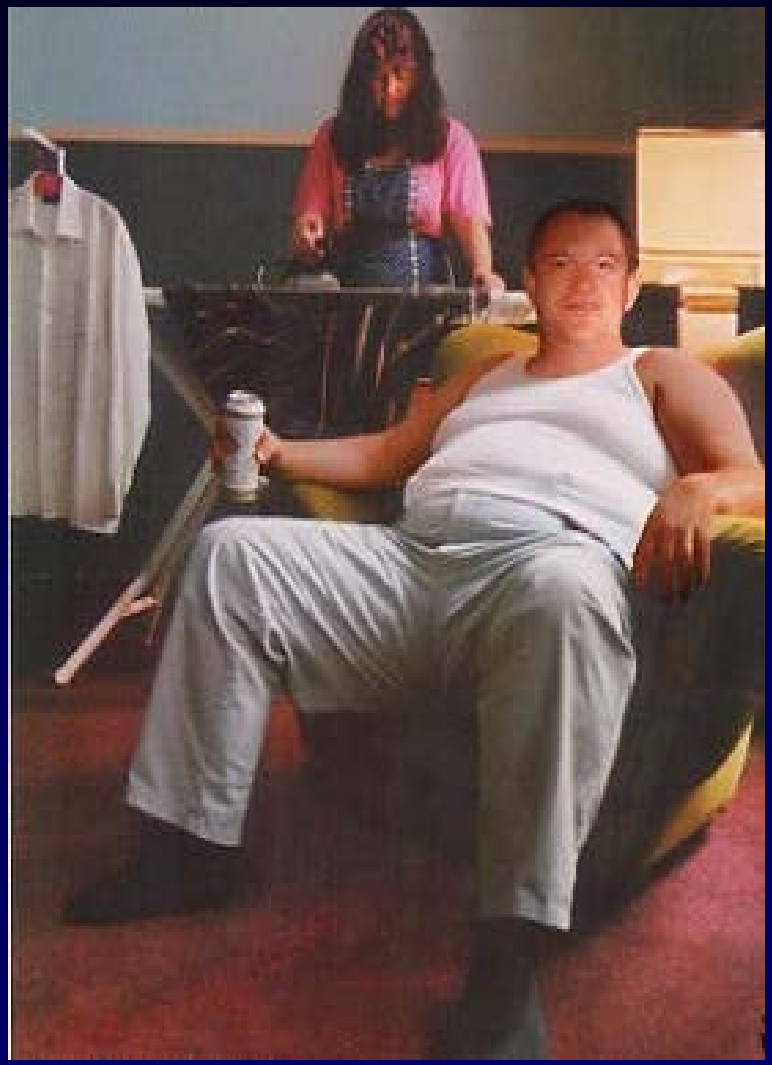
LOSS OF MORNING ERECTIONS

He works as a lorry driver and pulls over for sleep in the afternoon.

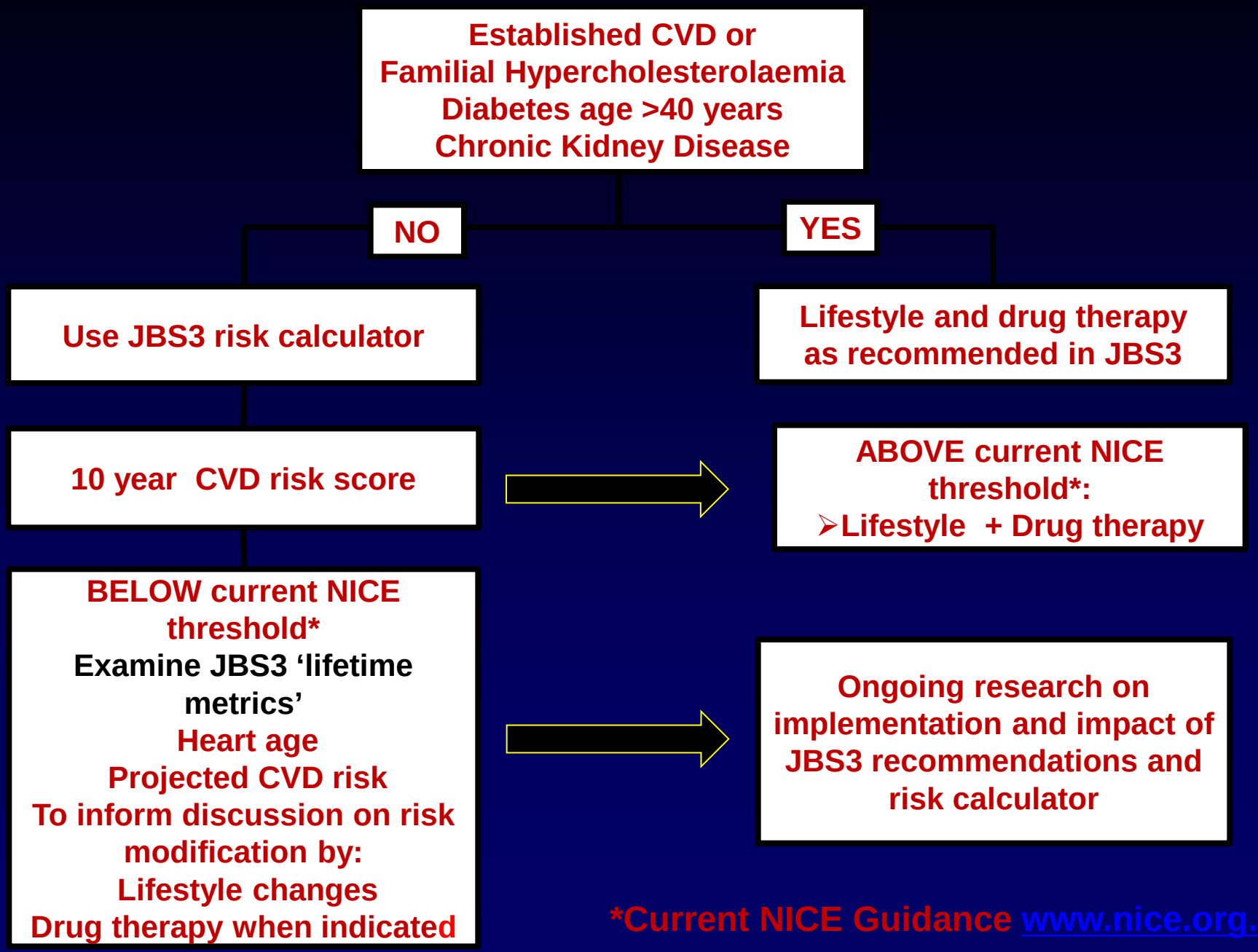
Shane and Cheryl have not had sex since Aston Villa last won away in the premier league – Aug 8th 2015

CONSIDER THE EFFECTIVENESS OF

THIS MAN AT WORK and play!



JBS3 CVD Risk Approach



*Current NICE Guidance www.nice.org.uk

Shane Visits his GP for a 40 plus check

- Weight 106 Kg, BMI 30. WC 104 cm.
- BP 145/90.
- TC 6.2 LDL 5.1 HDL 0.95 TGs 2.8. IFCC 46. HbA1c 6.3. PSA 0.525. Haematocrit 39%

- Heart age 50. 4.7% 10 year risk.

- He leaves with extensive lifestyle modification advice – most of which he already knew.

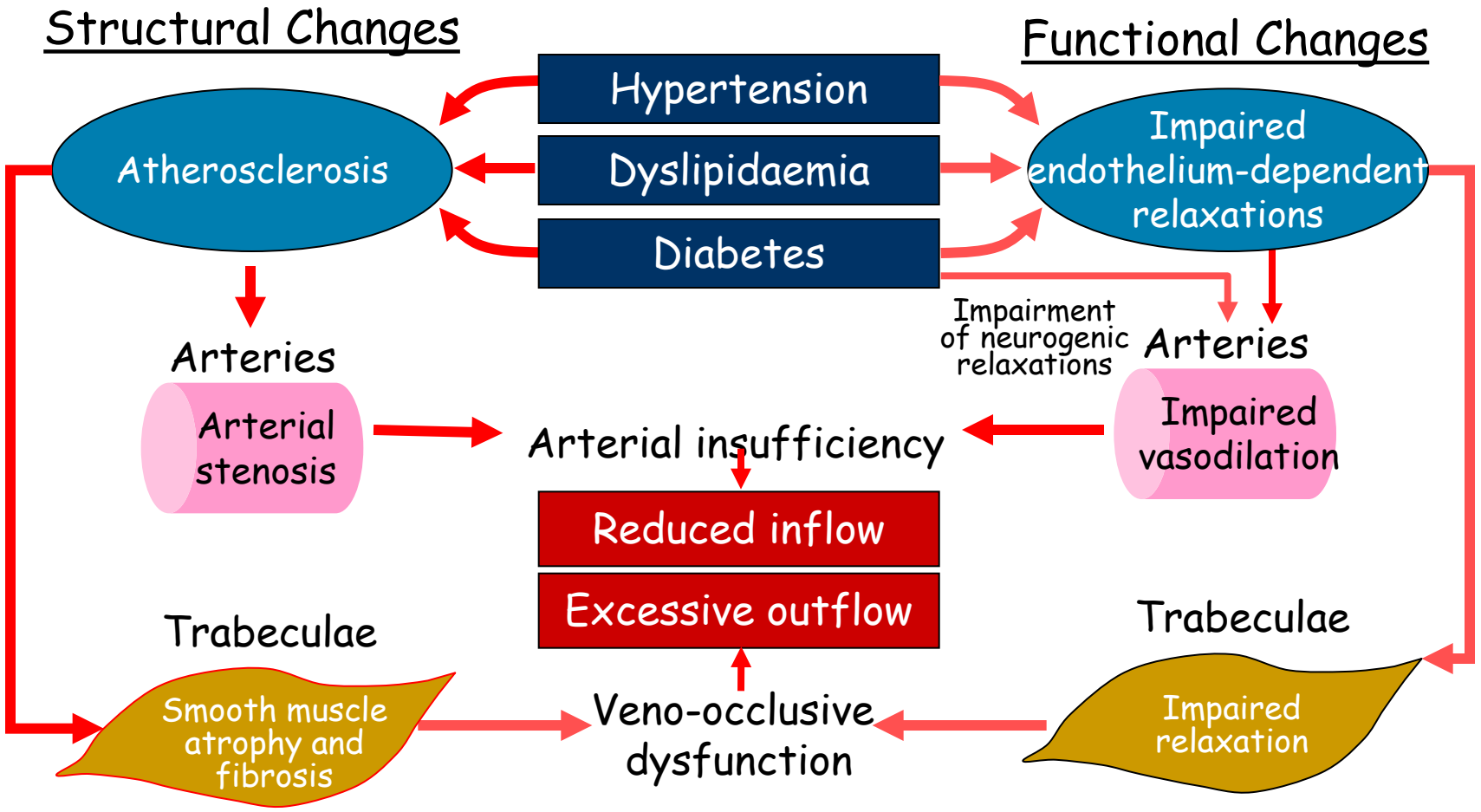
Back to Shane

- On arrival home, he delivers the earth shattering news to his wife that "he is obese and unhealthy".
- Is maximal longevity what he was seeking?
- Was he perhaps wanting to feel less tired at work and be better in the bedroom?
- Does he really want to give up all his pleasures in exchange for a Spartan life?
- Did the consultation address Shane's agenda or the doctors?
- Is Shane receiving personalised health care?
- Shane DECIDES NOT TO ATTEND FOLLOW-UP

Shane – The impact of a single question!

- "Many men with these health issues have problems getting and maintaining an erection – could this be a problem for you?"
- A positive response would change the direction of the consultation
- SHIM 8, AMS 62
- TT 7.2 nmol/l SHBG 19. LH 2.0
- He therefore has metabolic syndrome, testosterone deficiency and ED, which increases risk by 50%.
- He returns with a prescription for a daily PDE5 inhibitor and testosterone gel. He attends 6 weeks later for follow-up – on his way home from the gym.

CV Risk Factors, Endothelial Dysfunction and ED



Adapted from Saenz de Tejada I et al. 2000:65-102.

Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study

Julia Hippisley-Cox *professor of clinical epidemiology and general practice*[1], Carol Coupland *professor of medical statistics in primary care*[1], Peter Brindle *evaluation and implementation theme lead, NIHR CLAHRC West*[2]

[1]Division of Primary Care, University Park, Nottingham NG2 7RD, UK; [2]Bristol Primary Clinical Commissioning Group and The National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care West (NIHR CLAHRC West) at University Hospitals Bristol NHS Foundation Trust, UK, UK

We showed that erectile dysfunction is likely to be an independent risk factor for cardiovascular disease and was associated with a 25% increased risk of cardiovascular disease (at the mean age), which is compatible with the findings of a meta-analysis that examined the association between erectile dysfunction and cardiovascular disease risk in 13 studies.[23]

ages, except for erectile dysfunction in men, where hazard ratios were highest for men aged around age 45 and then declined gradually with increasing age.

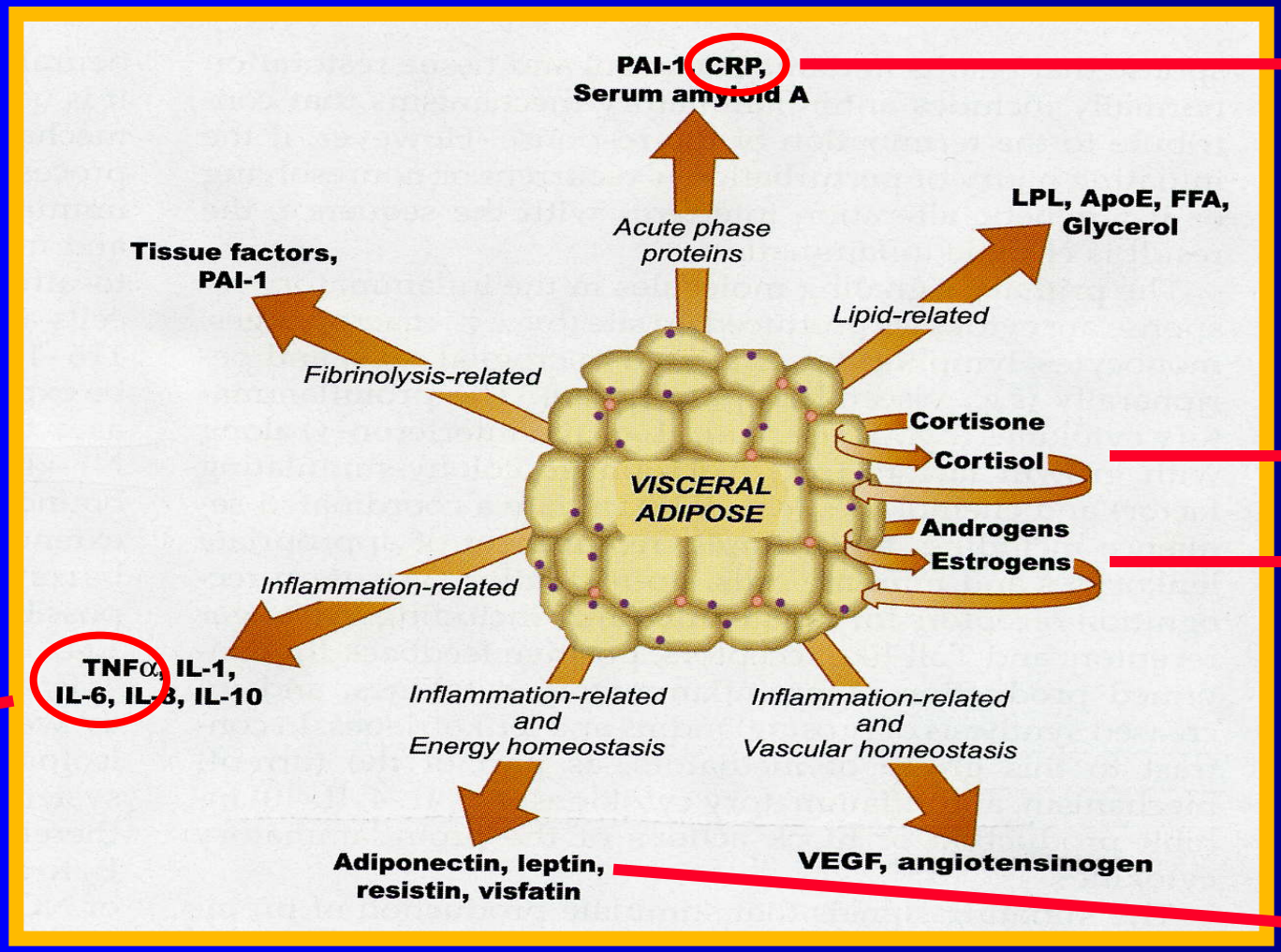
BMJ 2017;357:j2099 doi: 10.1136/bmj.j2099 (Published 24 May 2017)

ED in T2DM

Related to Duration, Control and Number of Complications

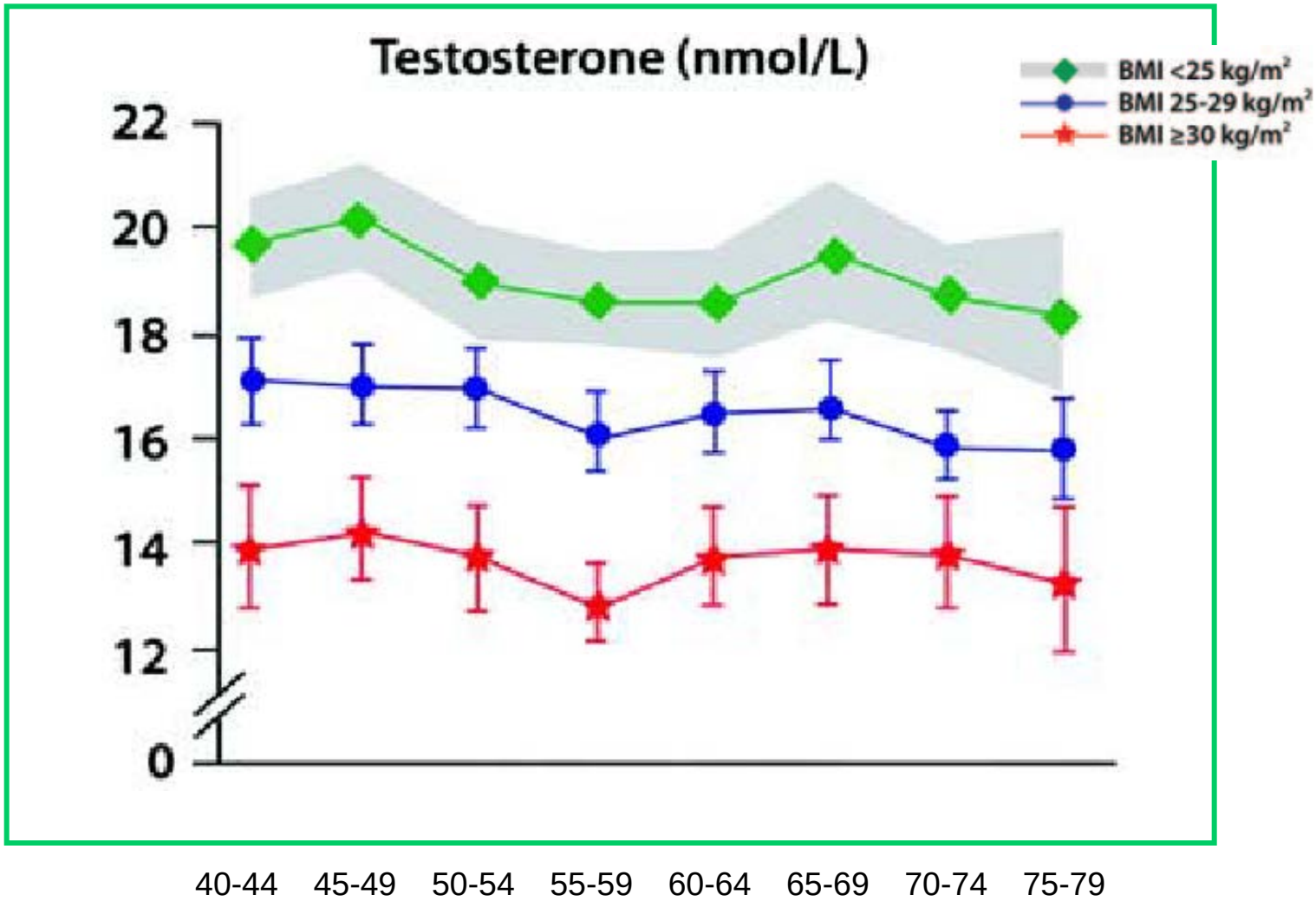
- Autonomic neuropathy
- Peripheral neuropathy
- Hypertension
- Peripheral vascular disease
- Dyslipidaemia
- Drug side effects
- Cavernosal smooth muscle disorder
- Depression
- **Hypogonadism (double risk)**
- Psychological Factors
- Plus Ejaculatory disorders. Retrograde /Anejaculation
- Reduced Sensation

Visceral Fat: T2DM and Hypogonadism



Lyon CJ et al. Endocrinol 144: 2195–2200 (2003), Trayhurn P et al. Br J Nutr 92: 347–355 (2004), Eckel RH et al. Lancet 365: 1415–1428 (2005)

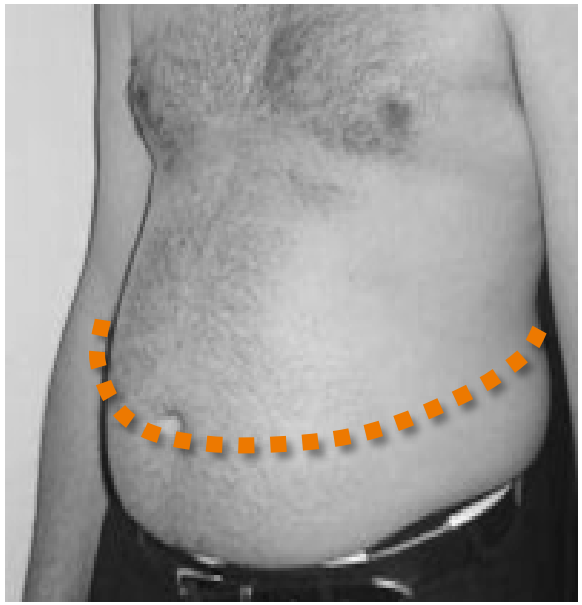
European Male Aging Study (EMAS)
relation between age and testosterone (40-79), n=3174



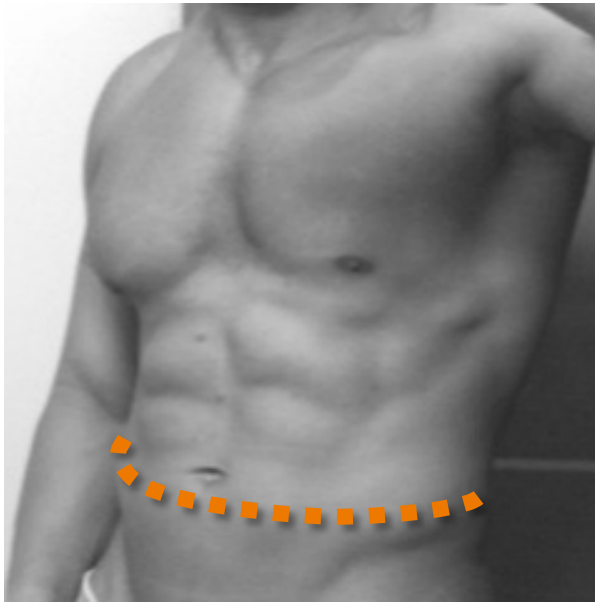
Wu FCW et al. J Clin Endocrin Metab 93(7): 2737-2745 (2008)

BMI and BMI are not the same...
the role of visceral fat tissue

189 cm, 93 kg = BMI 26



190 cm, 94 kg = BMI 26



Waist circumference	**>**	**Waist circumference**
Testosterone	**<**	**Testosterone**

AACE/ACE Guidelines

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY COMPREHENSIVE CLINICAL PRACTICE GUIDELINES FOR MEDICAL CARE OF PATIENTS WITH OBESITY

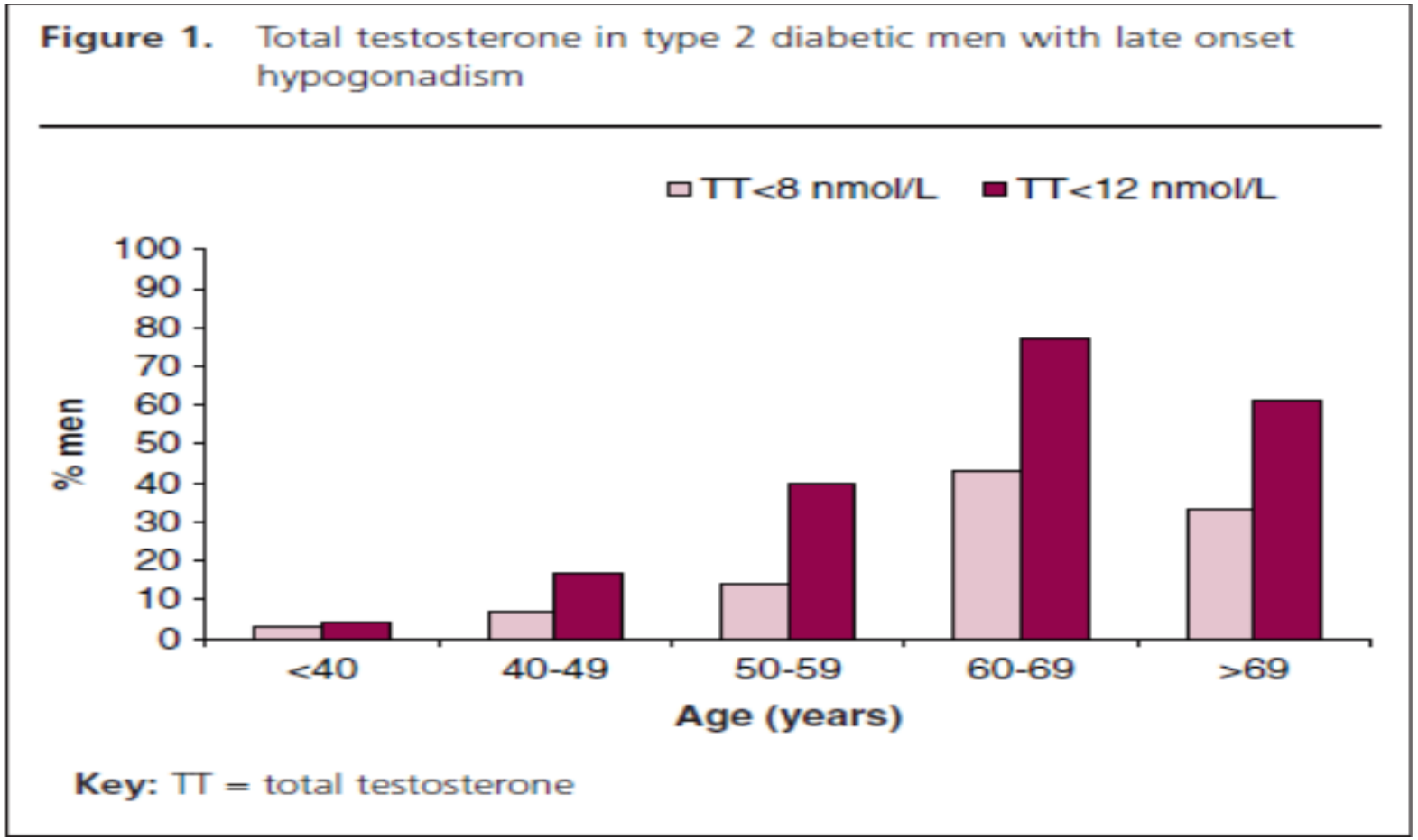
*W. Timothy Garvey, MD, FACE[1]; Jeffrey I. Mechanick, MD, FACP, FACE, FACN, ECNU[2]; Elise M. Brett, MD, FACE, CNSC, ECNU[3]; Alan J. Garber, MD, PhD, FACE[4]; Daniel L. Hurley, MD, FACE[5]; Ania M. Jastreboff, MD, PhD[6]; Karl Nadolsky, DO[7]; Rachel Pessah-Pollack, MD[8]; Raymond Plodkowski, MD[9]; and Reviewers of the AACE/ACE Obesity Clinical Practice Guidelines**

- *Q.3.9. Male hypogonadism*
  - **R19.** All men who have an increased waist circumference or who have obesity should be assessed for hypogonadism by history and physical examination and be tested for testosterone deficiency if indicated; all male patients with hypogonadism should be evaluated for the presence of overweight or obesity (**Grade B; BEL 2**).

  - **R20.** All male patients with T2DM should be evaluated to exclude testosterone deficiency (**Grade B; BEL 2**).

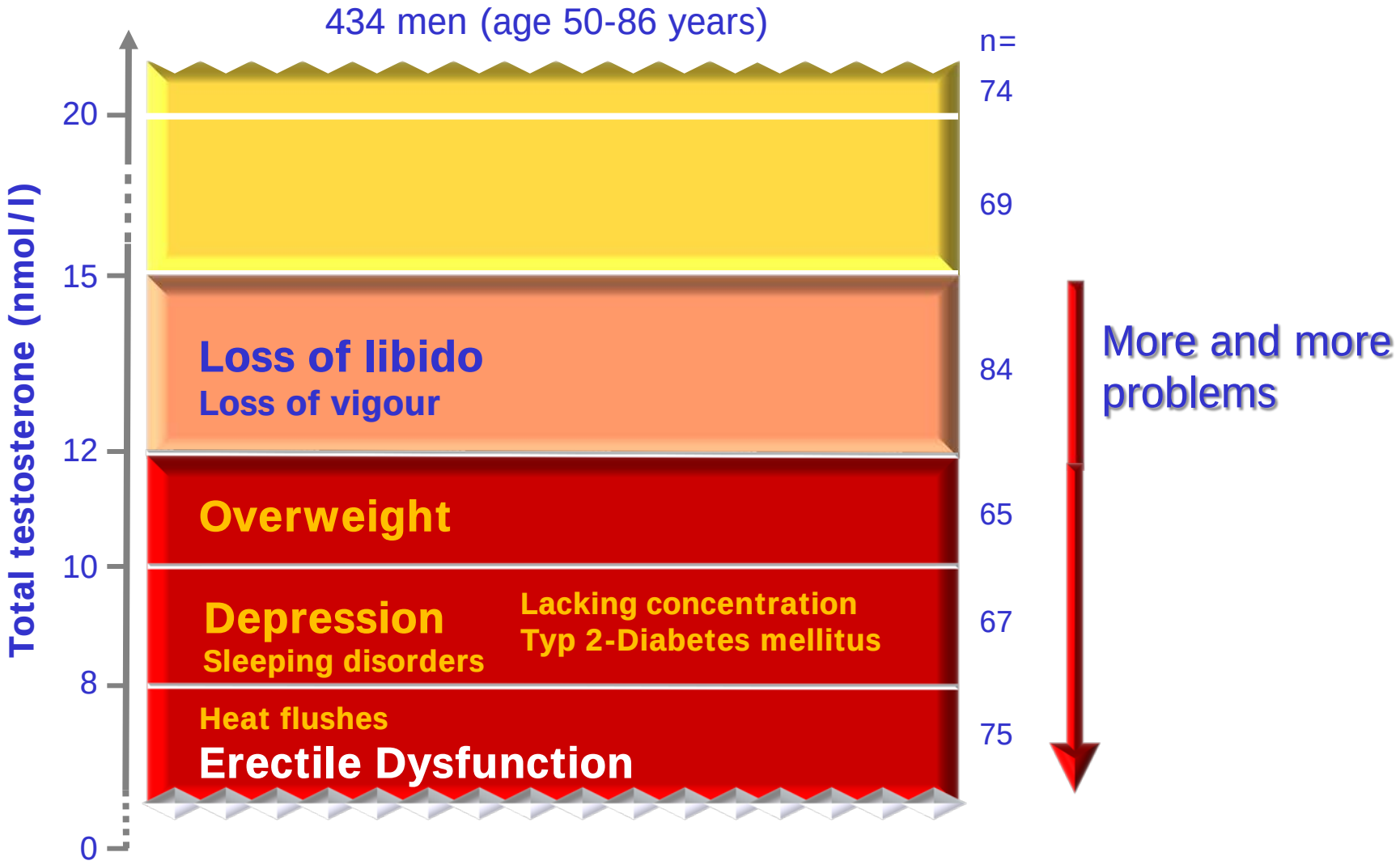
  - **R54.** Men with true hypogonadism and obesity who are not seeking fertility should be considered for testosterone therapy in addition to lifestyle intervention because testosterone in these patients results in weight loss, decreased waist circumference, and improvements in metabolic parameters (glucose, A1C, lipids, and blood pressure) (**Grade A; BEL 1**).

Total Testosterone in men with Type 2 Diabetes



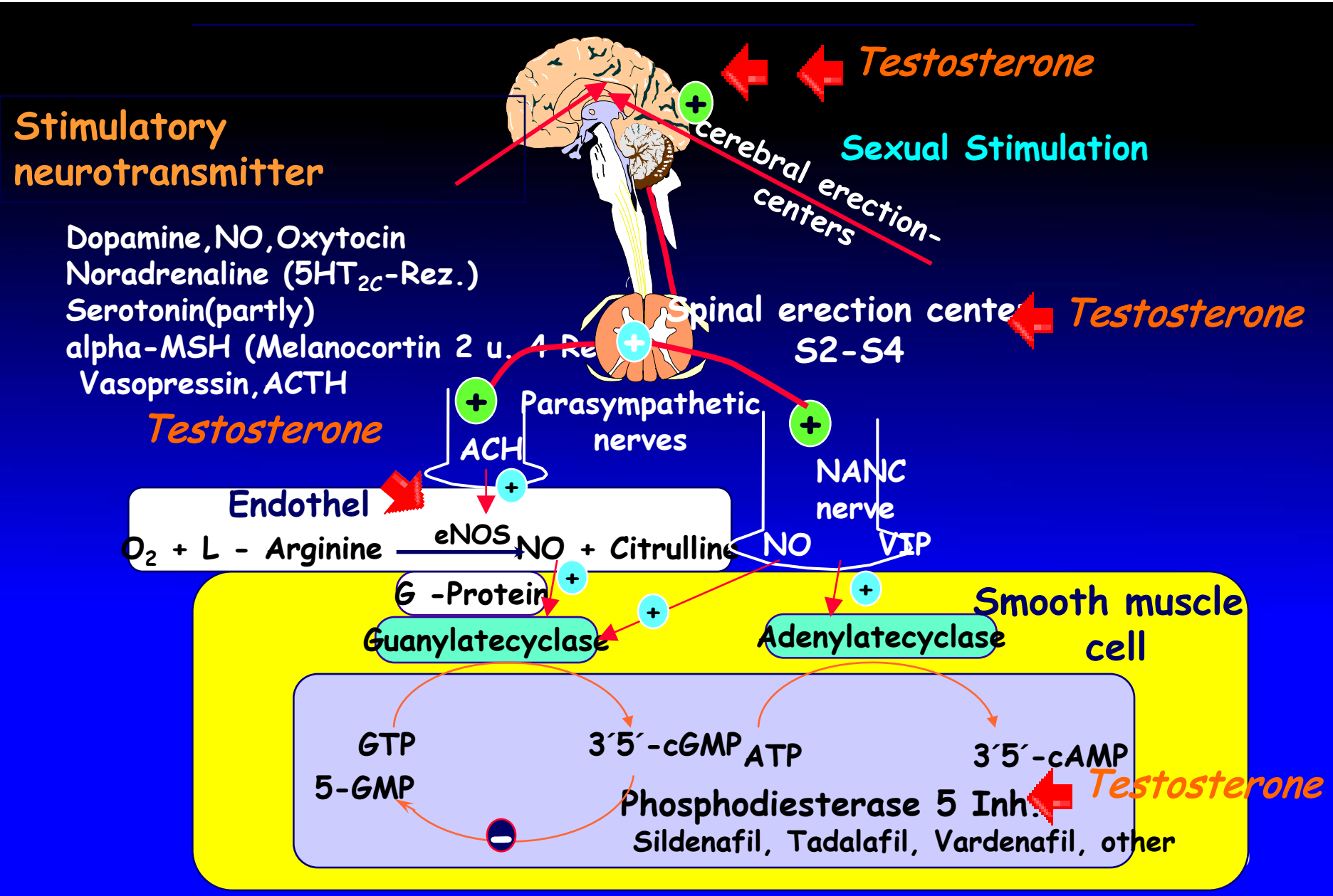
550 men from 5 practices – Hackett et al BJDVD 2009

Testosterone levels and symptoms



Zitzmann et al. J Clin Endocrinol Metab 2006; 91(11): 4335-4343

How Testosterone Influences Erection



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 18, 2016 VOL. 374 NO. 7

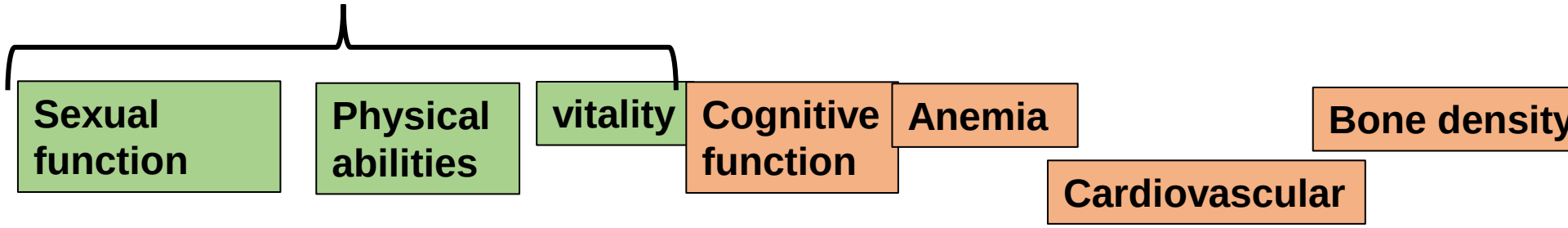
Effects of Testosterone Treatment in Older Men

P.J. Snyder, S. Bhasin, G.R. Cunningham, A.M. Matsumoto, A.J. Stephens-Shields, J.A. Cauley, T.M. Gill, E. Barrett-Connor, R.S. Swerdloff, C. Wang, K.E. Ensrud, C.E. Lewis, J.T. Farrar, D. Cella, R.C. Rosen, M. Pahor, J.P. Crandall, M.E. Molitch, D. Cifelli, D. Dougar, L. Fluharty, S.M. Resnick, T.W. Storer, S. Anton, S. Basaria, S.J. Diem, X. Hou, E.R. Mohler III, J.K. Parsons, N.K. Wenger, B. Zeldow, J.R. Landis, and S.S. Ellenberg, for the Testosterone Trials Investigators*

Coordinated, 7 overlapping trials

(principally one trial)

Published in NEJM



1. **Aim: to show whether TRT works in older men**
2. **Intervention: Testosterone-Gel vs Placebo-Gel**
3. **Duration: 1 year**
4. **Prospective, randomized, placebo-controlled double-blind**

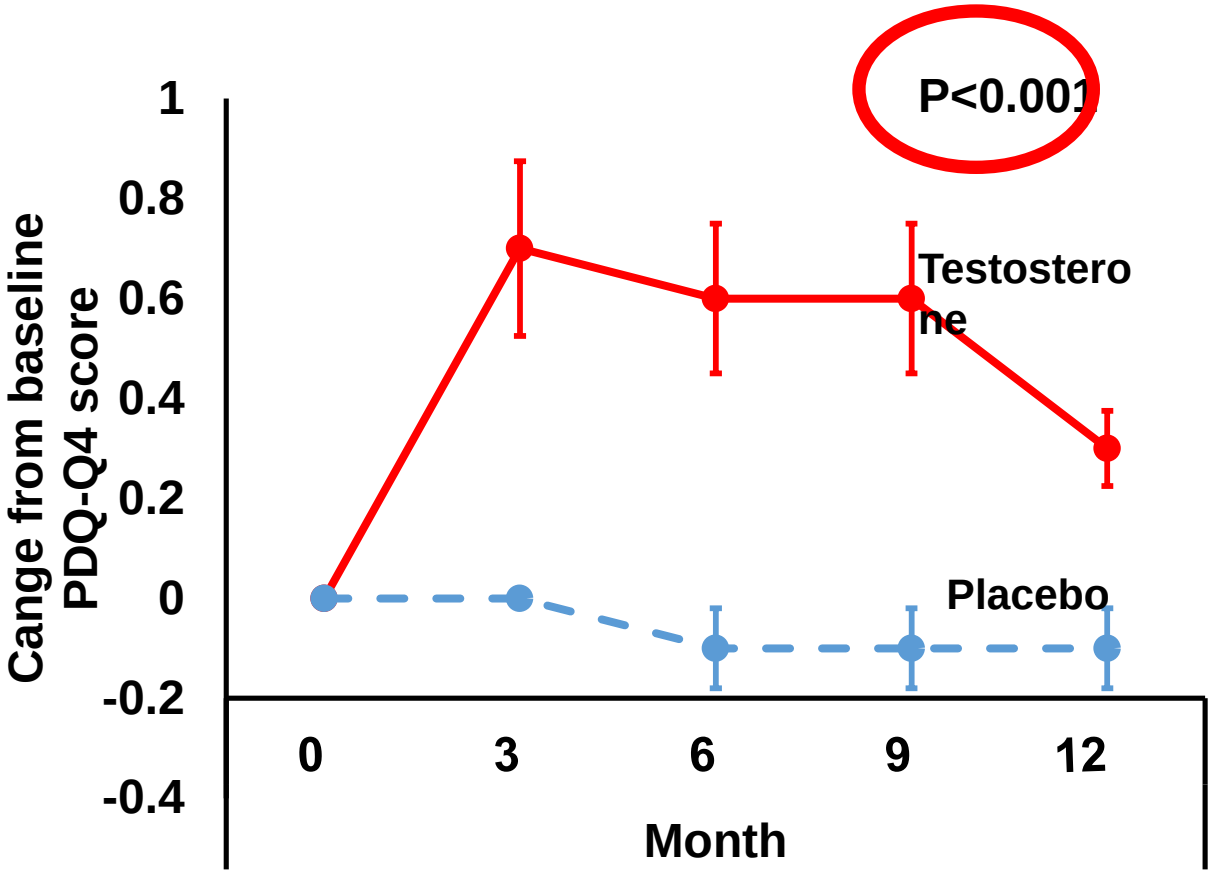
N Engl J Med
2016;374:611

Sexual functions

primary	**Sexual interest and sexual activity**	**Treatment effect: 0.58** **(95% CI):** 0.38–0.78 ***P* <0.001**
secondary	**DISF-M-II interview to score sexual desire.**	**Treatment effect**: **2.93** **(95% CI):** 2.13–3.74 ***P* < 0.001**
	IIEF-5 : Erectile Function	**Treatment effect**: 2.64 **(95% CI):** 1.68–3.61 ***P* = 0.001**

N Engl J Med

Sexual activity

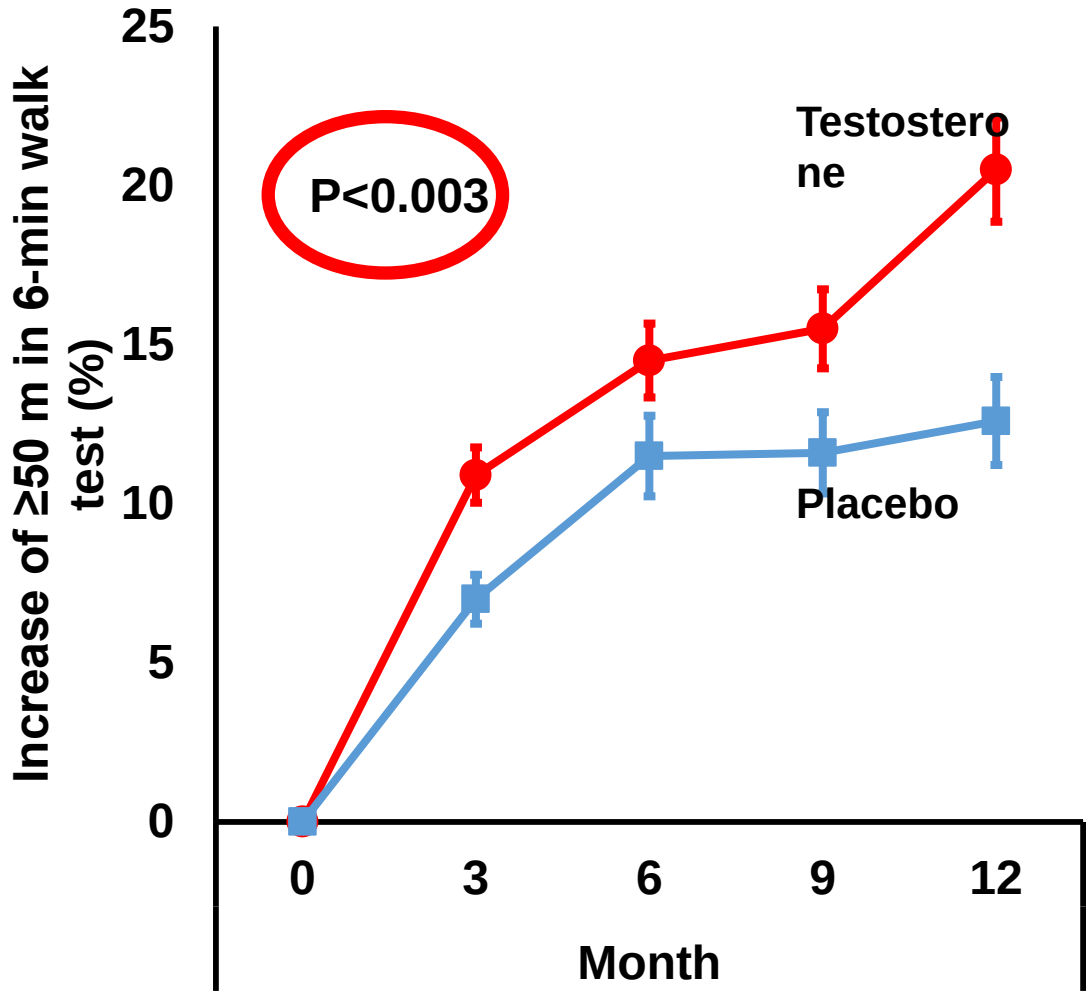


Testosterone
n=387
Placebo n=384

N Engl J Med
2016;374:611

Walking distance increased

Testosterone
n=392
Placebo n=389



N Engl J Med

Vitality

primary	**% of men, whose vitality score increased by at least 4 points**	**Treatment effect:**1.23 **(95% CI)** 0.89-1.7 **P =**0.22
secondary	**Change in fatigue score**	**Treatment effect**:1.27 **(95% CI):** 1.37-2.16 ***P* =** 0.006
	SF-36 Vitality-Score	**Treatment effect**:2.41 **(95% CI):** 1.31- 4.50 ***P* =** 0.03
	PANAS Positive affect score	**Treatment effect**:0.47 **(95% CI):** 0.02-0.92 ***P* =** 0.04
	PANAS Negative affect score	**Treatment effect**:-0.49 **(95% CI):-**079—0.19 ***P* <**0.001
	PHQ-9 Depression-Score	**Treatment effect**:-.72 **(95% CI):** -1.20—0.23 ***P*=** 0.004

N Engl J Med 2016;374:611

T Trials part 1: Take home messages

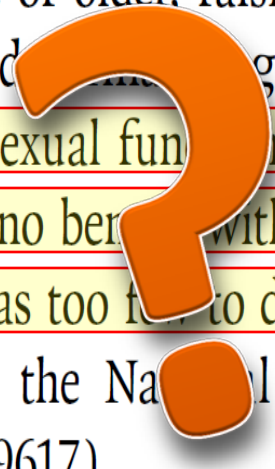
TRT in older men with functional hypogonadism and symptoms is effective

- **Significant improvement of all sexual functions**
- **Good and marked improvement of physical functions**
- **Increase of good mood and energy**
- **Decrease of bad mood and depressive mood**
- **Safe compared to placebo:**
  - ✓ **Prostate-Ca**
  - ✓ **CVD**
- **Increase of**
  - ✓ **Hematocrit**
  - ✓ **PSA**

T Trials part 1

CONCLUSIONS

In symptomatic men 65 years of age or older, raising testosterone concentrations for 1 year from moderately low to the mid[illegible]ge for men 19 to 40 years of age had a moderate benefit with respect to sexual fun[illegible] and some benefit with respect to mood and depressive symptoms but no ben[illegible]with respect to vitality or walking distance. The number of participants was too f[illegible]to draw conclusions about the risks of testosterone treatment. (Funded by the Na[illegible]l Institutes of Health and others; ClinicalTrials.gov number, NCT00799617.)



BJUI
BJU International

Testosterone undecanoate improves sexual function in men with type 2 diabetes and severe hypogonadism: results from a 30-week randomized placebo-controlled study

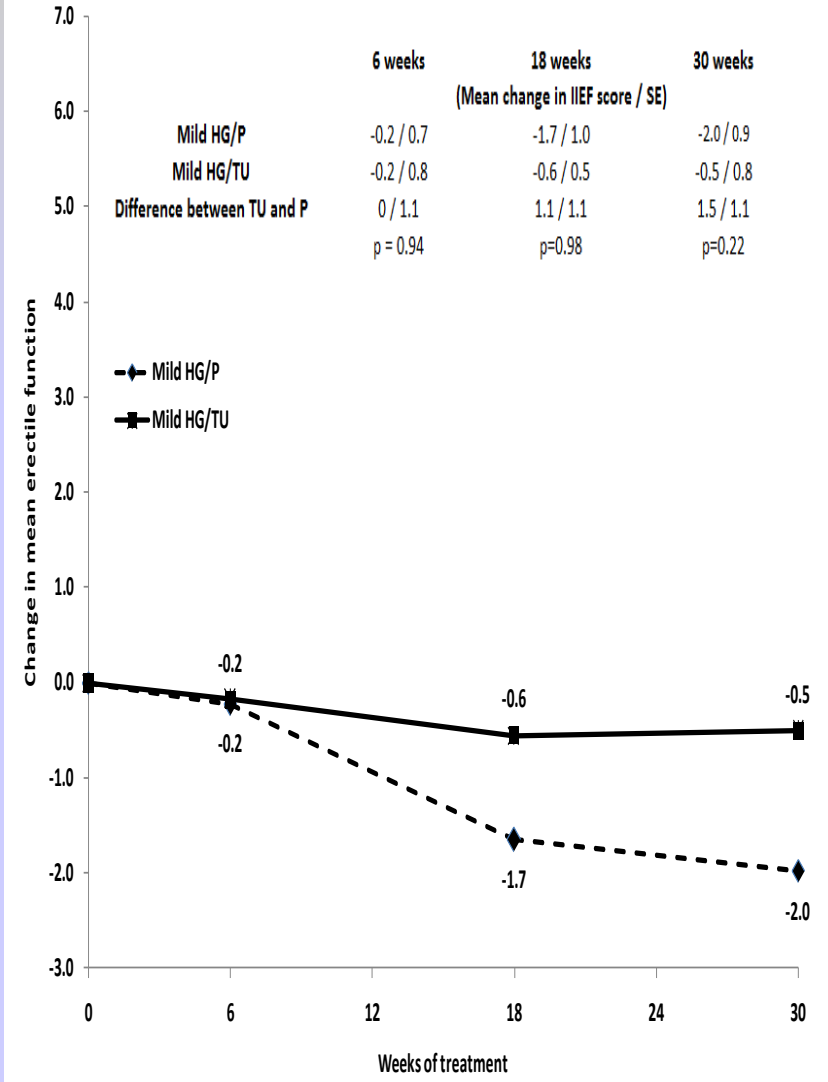
Geoffrey Hackett*, Nigel Cole*, Atif Saghir†, Peter Jones‡, Richards C. Strange‡ and Sudarshan Ramachandran*§¶

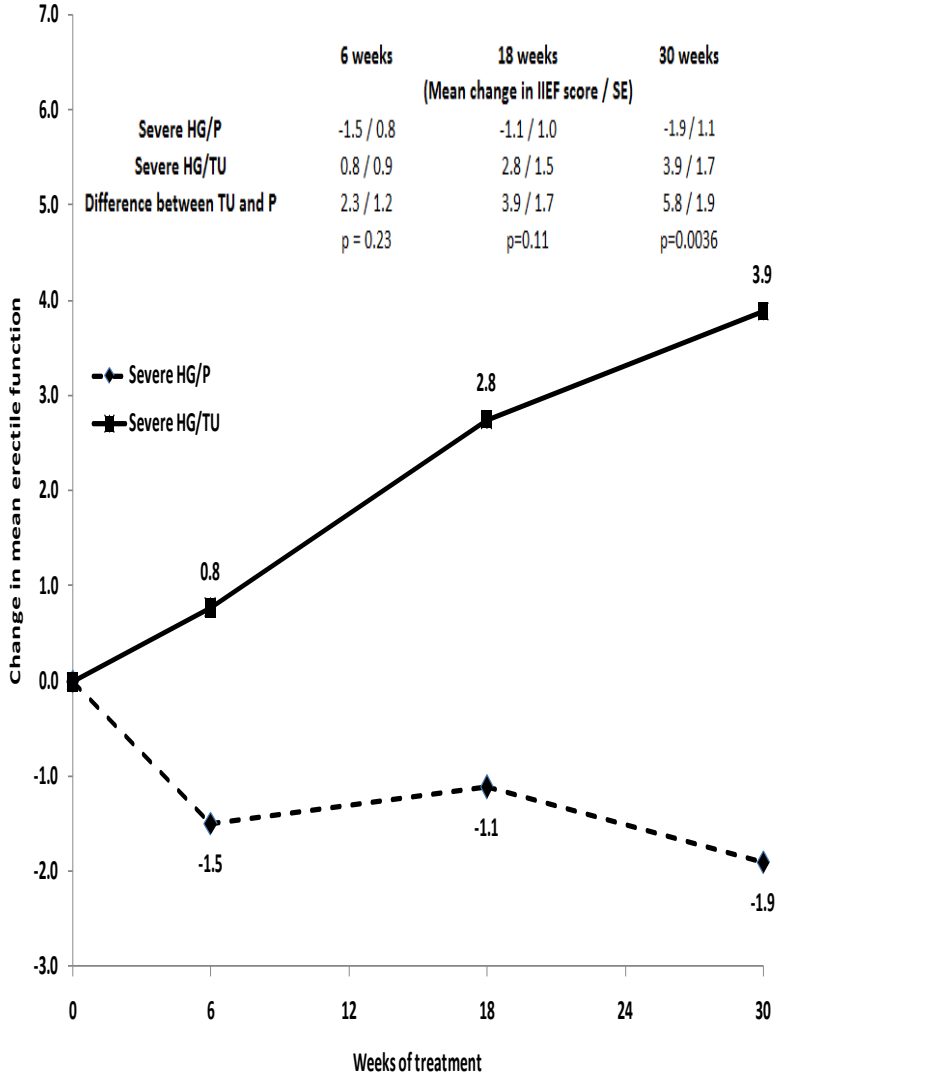
*Heart of England Foundation NHS Trust, Sutton Coldfield, †University of Birmingham, Edgbaston, Birmingham, ‡Institute for Science and Technology in Medicine, Keele University Medical School, Keele, §Department of Clinical Biochemistry, University Hospitals of North Midlands, Keele, and ¶Faculty of Health Sciences, Staffordshire University, Keele, Staffordshire, UK

Conclusions

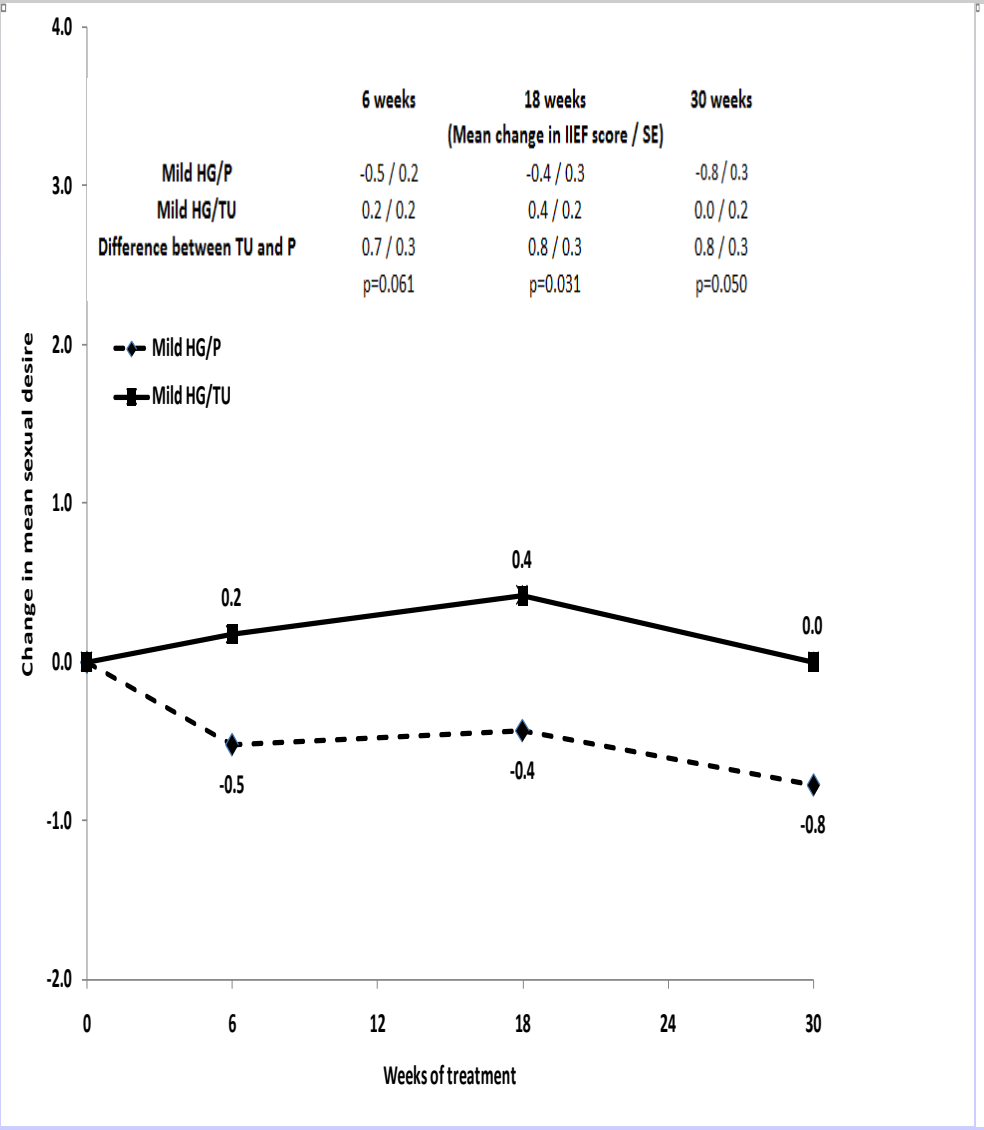
The present study suggests that benefit in sexual symptoms after TU treatment is evident principally in patients with HG with TT levels ≤8 nmol/L and FT levels ≤0.18 nmol/L. We also suggest that 30 weeks of treatment is necessary before evaluating improvement in erectile function.

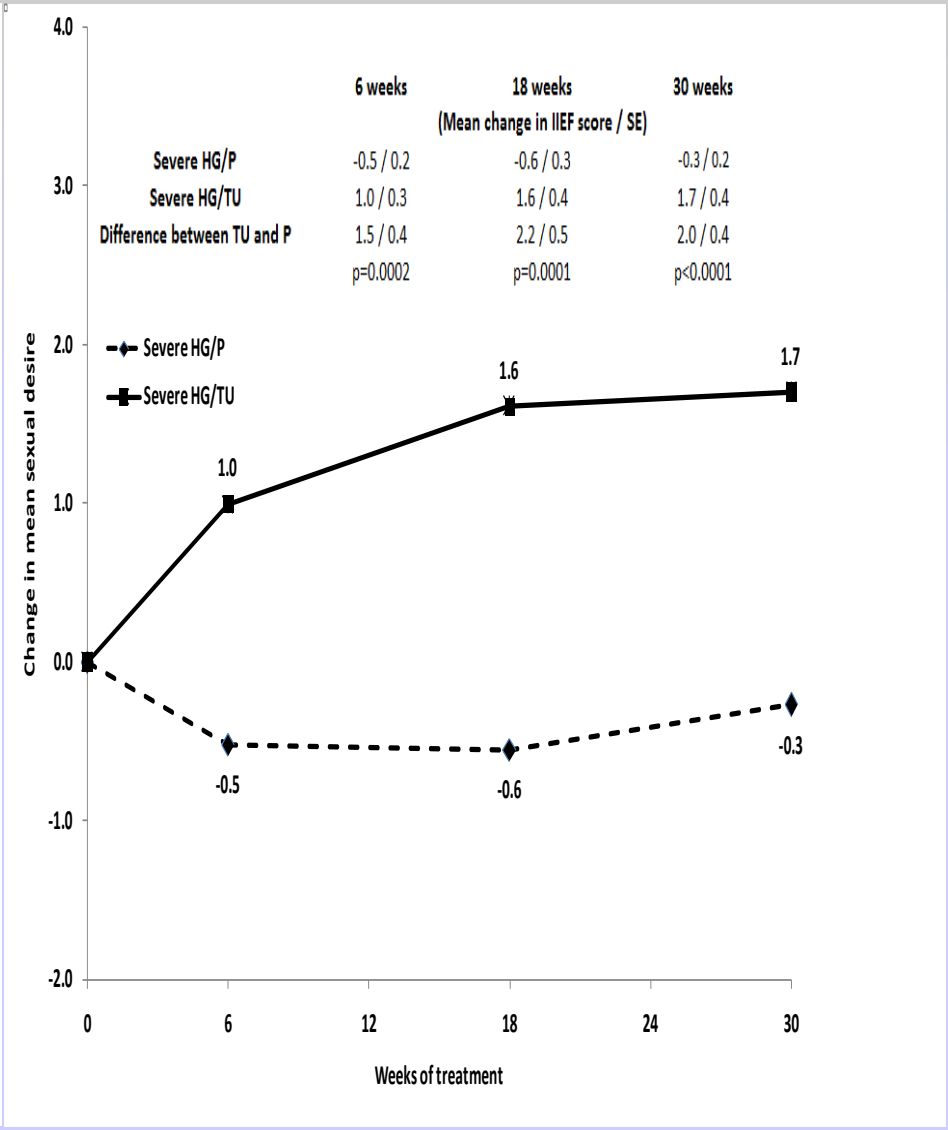
BLAST –IIEF -EF Changes from Baseline in Mild (8-12nmol/l) and Severe HG (<8nmol/l)





BLAST – IIEF – Sexual Desire. Changes from Baseline in Mild (8-12) and Severe HG (<8)





ORIGINAL PAPER

THE INTERNATIONAL JOURNAL OF CLINICAL PRACTICE

The response to testosterone undecanoate in men with type 2 diabetes is dependent on achieving threshold serum levels (the BLAST study)

G. Hackett,[1] N. Cole,[1] M. Bhartia,[1] D. Kennedy,[1] J. Raju,[1] P. Wilkinson,[2] A. Saghir,[3]
For the BLAST STUDY GROUP

	HbA1c (%) >7.5	Weight (kg)	BMI Kg/m2	WC (cm)	TC mmol/l	EF (IIEF)	AMS (pts)	HADS-D	GEQ (% imp)
30 weeks	-0.41	-0.7	-0.3	-2.5	-0.25	+3.0	-5.3	-1.01	46
P value	**0.007**	0.13	**0.01**	**0.012**	**0.025**	**0.006**	0.095	0.64	**<0.001**
82 weeks	-0.87	-2.7	-1.00	-4.2	-0.19	+4.31 +9.57 PDE5I	-8.1	-2.18	67-70
P value	**0.009**	**0.016**	**0.019**	**<0.001**	**0.035**	**0.003**	**0.001**	**0.001**	**0.0001**

Ng Tang Fui *et al. BMC Medicine* (2016) 14:153
DOI 10.1186/s12916-016-0700-9

BMC Medicine

RESEARCH ARTICLE Open Access

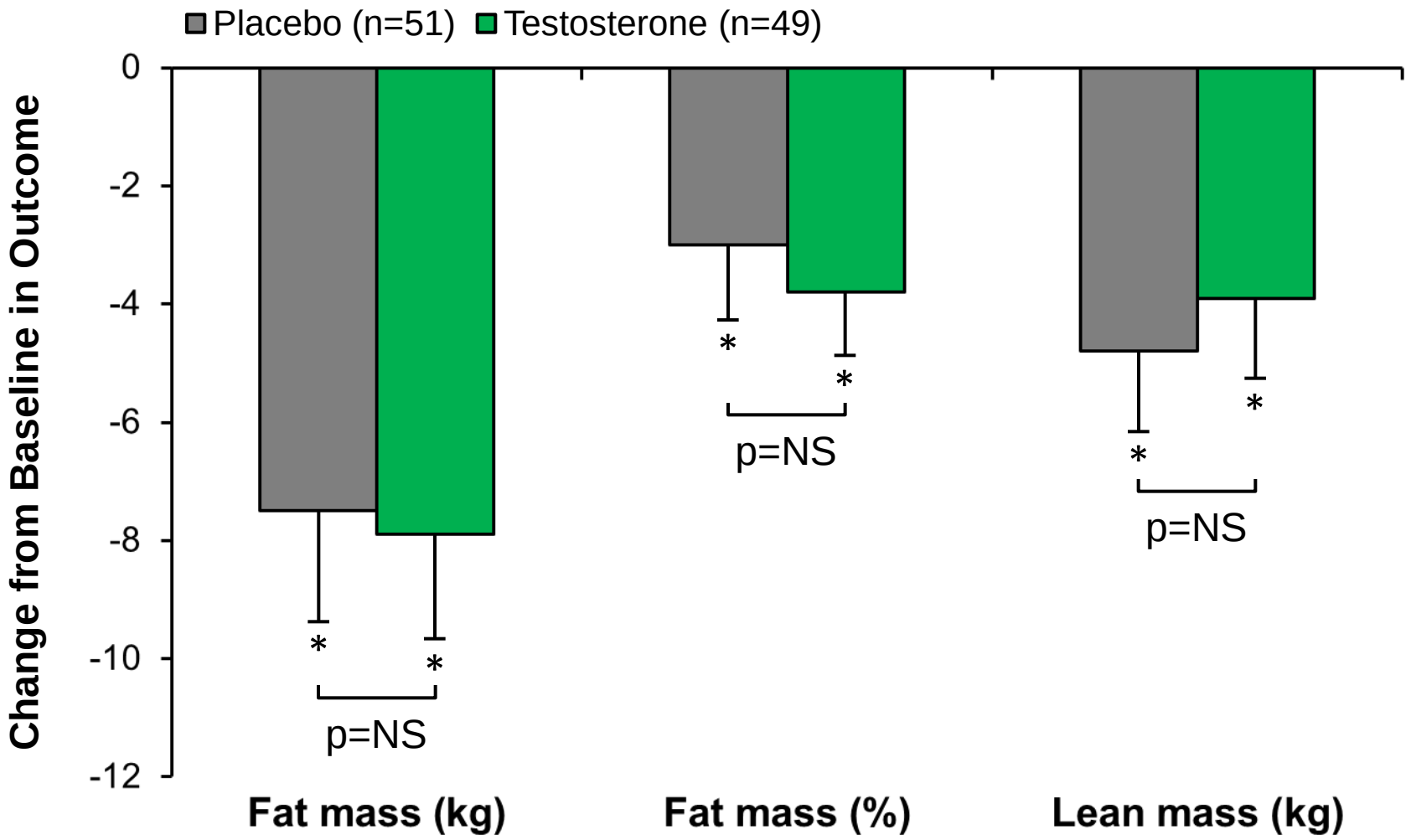
Effects of testosterone treatment on body fat and lean mass in obese men on a hypocaloric diet: a randomised controlled trial

Mark Ng Tang Fui[1,2], Luke A. Prendergast[1,3], Philippe Dupuis[1,2], Manjri Raval[2], Boyd J. Strauss[4], Jeffrey D. Zajac[1,2] and Mathis Grossmann[1,2*]

Methods: We conducted a randomised double-blind, parallel, placebo controlled trial at a tertiary referral centre. A total of 100 obese men (body mass index ≥ 30 kg/m^2) with a total testosterone level of or below 12 nmol/L and a median age of 53 years (interquartile range 47–60) receiving 10 weeks of a very low energy diet (VLED) followed by 46 weeks of weight maintenance were randomly assigned at baseline to 56 weeks of 10-weekly intramuscular testosterone undecanoate ($n = 49$, cases) or matching placebo ($n = 51$, controls). The main outcome measures were the between-group difference in fat and lean mass by dual-energy X-ray absorptiometry, and visceral fat area (computed tomography).

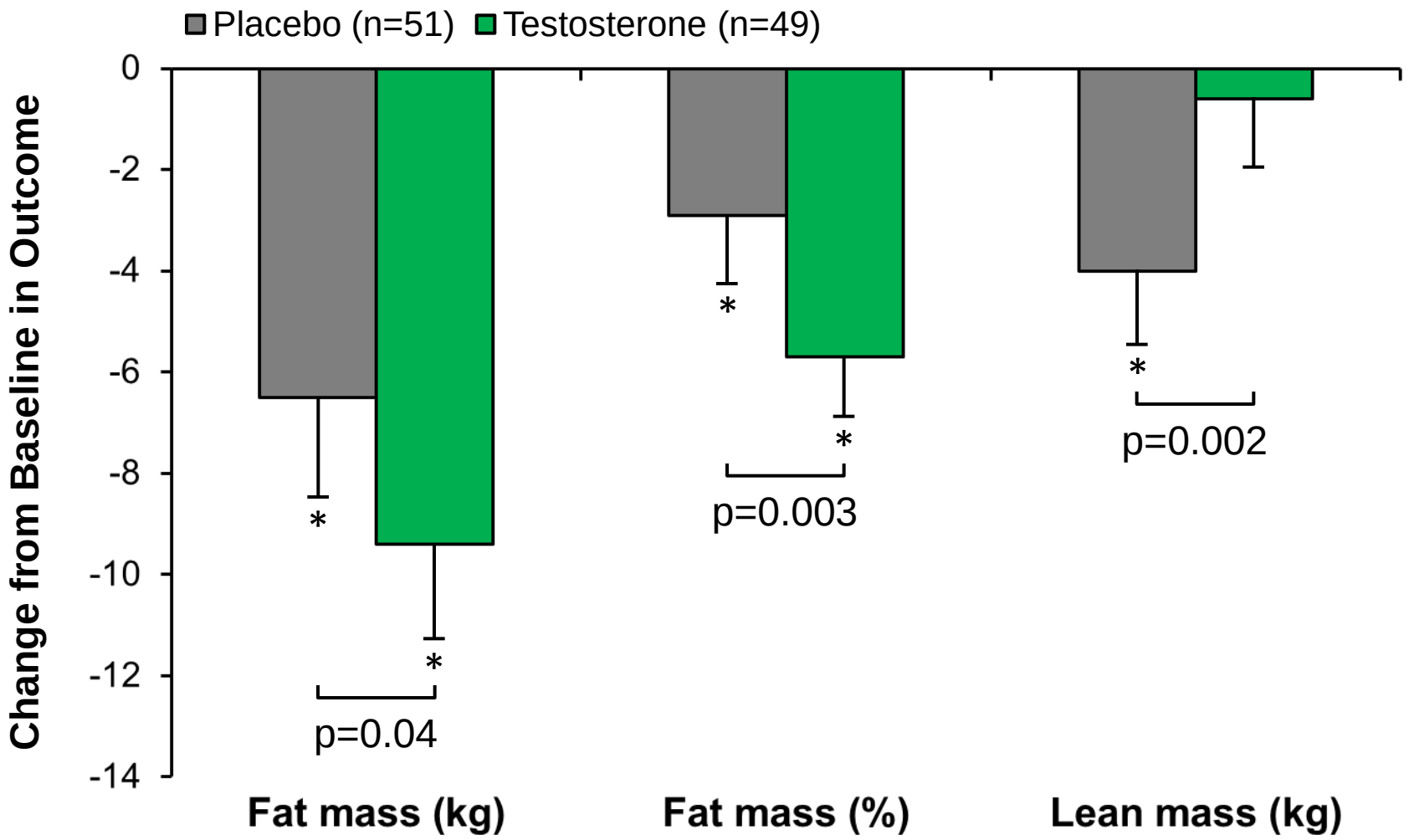
Conclusions: While dieting men receiving placebo lost both fat and lean mass, the weight loss with testosterone treatment was almost exclusively due to loss of body fat.

Change from Baseline in Body Composition After 10 Weeks of a VLED and Treatment with Intramuscular Testosterone Undecanoate or Placebo



*p<0.05 versus baseline within group; data are mean + 95% confidence interval
NS, not significant; VLED, very low energy diet
Fui MNT et al. BMC Med 14(1):153 (2016)

Change from Baseline in Body Composition After 56 Weeks of Treatment with Intramuscular Testosterone Undecanoate or Placebo



*p<0.05 versus baseline within group; data are mean + 95% confidence interval
NS, not significant
Fui MNT et al. BMC Med 14(1):153 (2016)

International Journal of Obesity (2017), 1–7

www.nature.com/ijo

ORIGINAL ARTICLE

Symptomatic response to testosterone treatment in dieting obese men with low testosterone levels in a randomized, placebo-controlled clinical trial

M Ng Tang Fui[1,2], R Hoermann[1], LA Prendergast[1,3], JD Zajac[1,2] and M Grossmann[1,2]

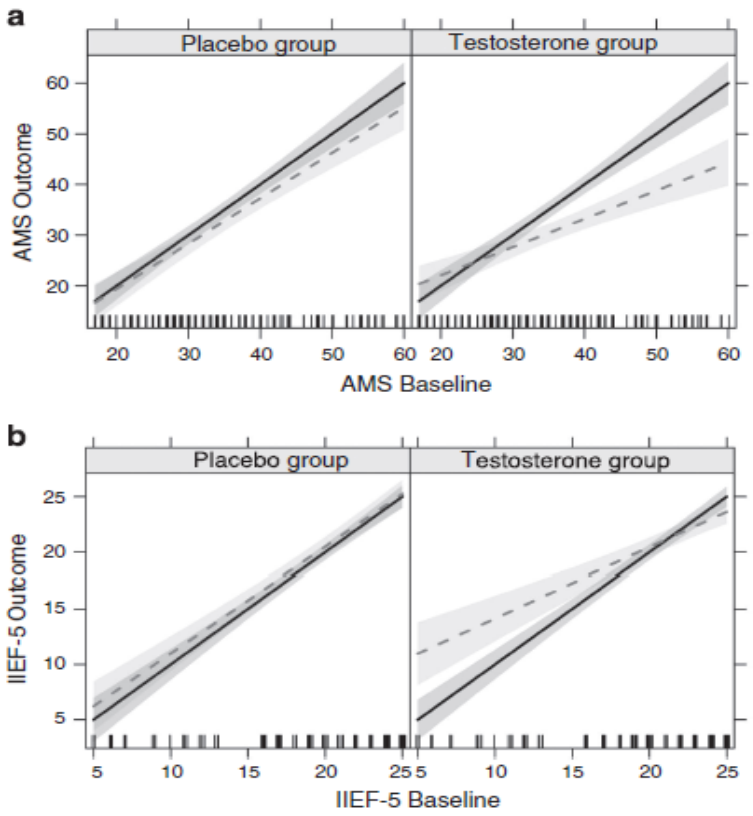


Figure 2. Three-way interaction between mean adjusted differences between the groups and baseline symptom severity. **(a)** Interaction

In conclusion, among relatively healthy middle-aged obese men with a lowered testosterone level, testosterone treatment over 56 weeks improved symptoms of androgen deficiency above and beyond what was achieved with weight loss alone. In conjunction with the metabolically favorable effects on body composition reported elsewhere,[10] this study identifies a subgroup of men with lowered testosterone levels in whom the long-term benefits and risks of testosterone treatment should, in combination with lifestyle measures, be further assessed in larger longer-term clinical trials.

N=100

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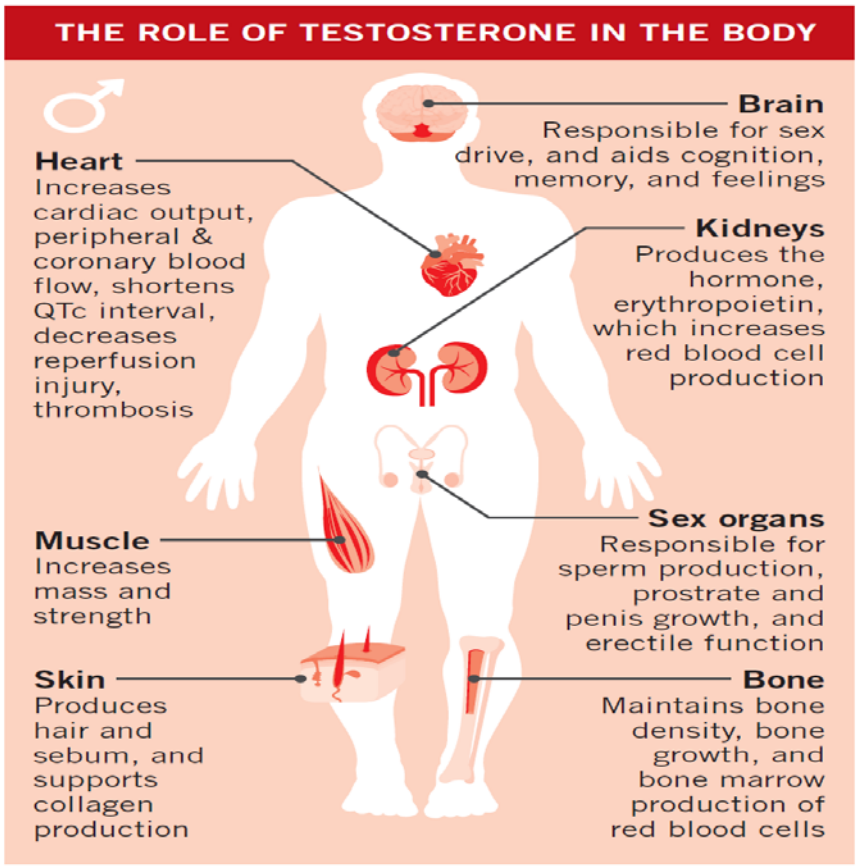
THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Testosterone and Cardiovascular Disease

Robert A. Kloner, MD, PhD,[a,b] Culley Carson III, MD,[c] Adrian Dobs, MD,[d] Stephen Kopecky, MD,[e] Emile R. Mohler III, MD[f]

Testosterone Has Multiple Effects on the Body



Kloner, R.A. et al. J Am Coll Cardiol. 2016; 67(5):545–57.

TABLE 1 Testosterone's Role in Therapy of True Symptomatic Hypogonadism in Young and Older Men

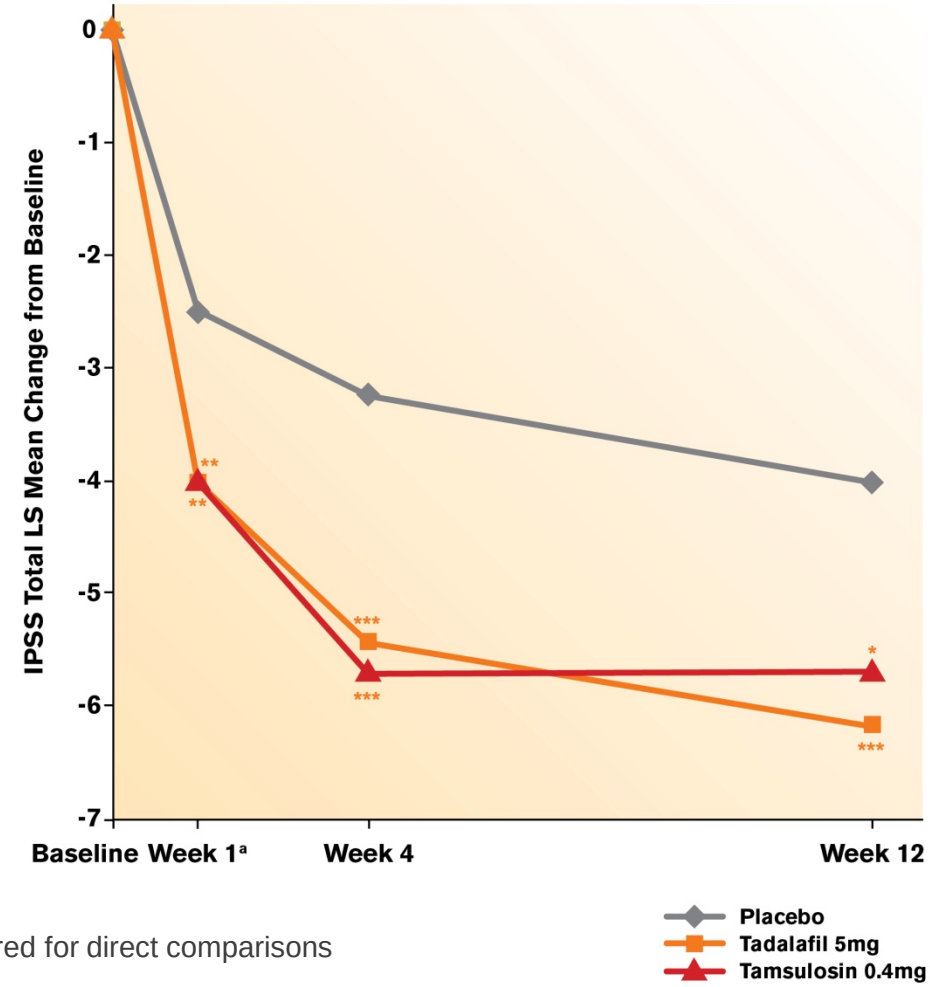
Organ	Young Men	Older Men	Ref. #
Libido	++	++	33–38
Erectile function	++	++	33–38
Cardiovascular	+	+	69–71
Mood	+	+	42,43
Cognition	+	+	47,48
Energy	+	+	49,50
Bone mineral density	++	++	58–63
Fat mass	++	++	54
Hematopoiesis	++	++	69,71
Muscle mass	++	++	53–55
Muscle strength	++	++	54–56
Insulin sensitivity	+	+	67
Sperm count	– –	– –	121

++ = strong evidence of positive effect; + = weak evidence of positive effect; – – = strong evidence of negative effect; – = weak evidence of negative effect.

Comparison Tadalafil and Tamsulosin
Effect on IPSS

Treatment	Baseline Mean (SD)	12-week Endpoint LS Mean Change (ANCOVA, LOCF)
Placebo	17.4 (6.0)	-4.2
Tadalafil 5mg	17.2 (4.9)	-6.3***
Tamsulosin 0.4mg	16.8 (5.3)	-5.7*

*p<.05, **p<.01, ***p≤.001 compared to placebo
[a]Values for week 1 are based on mIPSS



Please note that tamsulosin is an active control. This study was powered for direct comparisons between tadalafil and placebo and between tamsulosin and placebo.

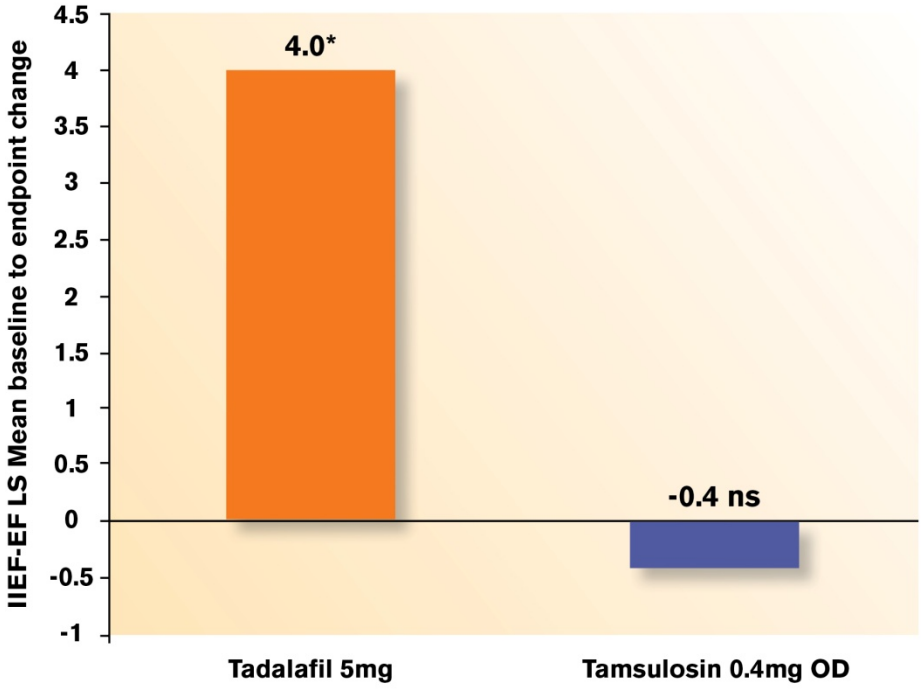
Oelke et al. *Eur Urol* 2012;61: 917 - 925

Comparison Tadalafil and Tamsulosin

Effect on IIEF

Treatment	ED History N (%)	Sexually Active with a Female Partner N (%)
Placebo	120 (69.8)	145 (84.3)
Tadalafil 5mg	121 (70.8)	143 (83.6)
Tamsulosin 0.4mg	116 (69.0)	139 (82.7)

*<0.001 vs. placebo
ns p=0.699 vs. placebo



IIEF-EF domain baseline to end point LS mean change compared with placebo in men with ED who were also sexually active (60% of patients in the trial).

ns = not significant

Oelke et al. *Eur Urol* 2012;61: 917 - 925

World Journal of Diabetes

Submit a Manuscript: http://www.wjgnet.com/esps/

World J Diabetes 2017 March 15; 8(3): 104-111

DOI: 10.4239/wjd.v8.i3.104

ISSN 1948-9358 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

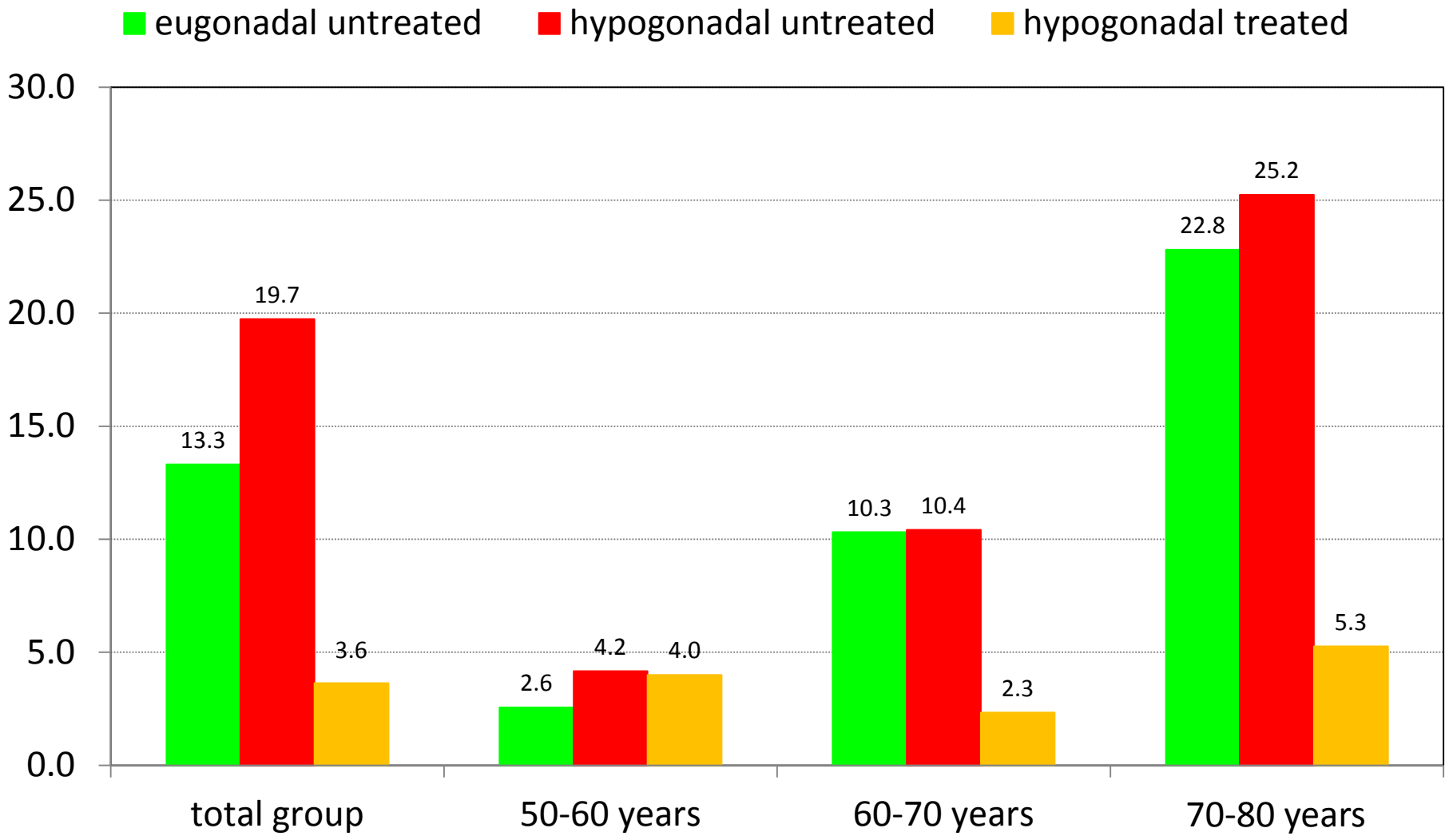
Statin, testosterone and phosphodiesterase 5-inhibitor treatments and age related mortality in diabetes

Geoffrey Hackett, Peter W Jones, Richard C Strange, Sudarshan Ramachandran

CONCLUSION

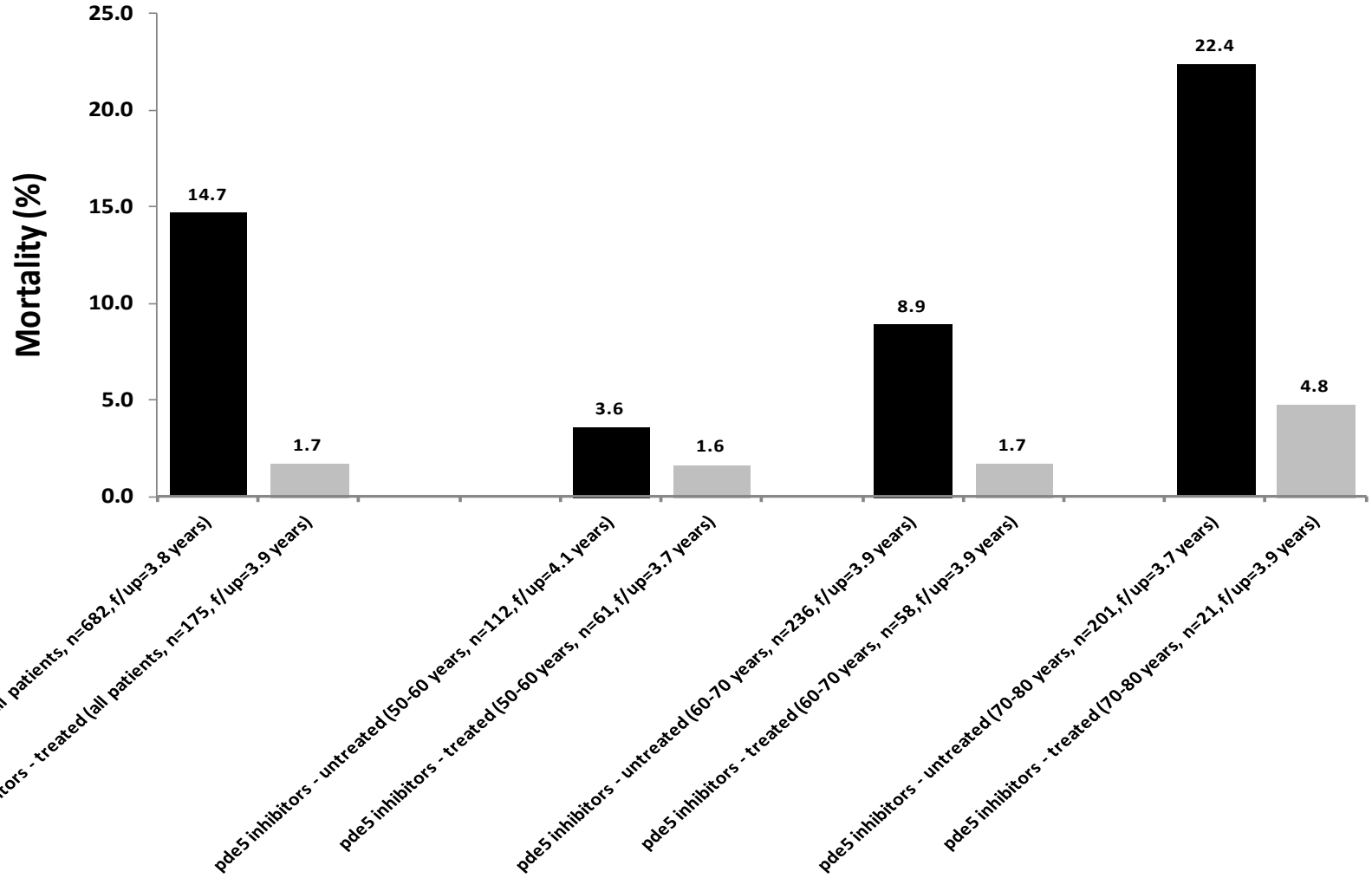
We show that statins, PDE5I and TRT reduce mortality in diabetes. PDE5I, alone and with the other treatments significantly alter age related mortality in diabetic men.

Mortality Data of Men with Type 2 Diabetes mellitus not receiving PDE5 Inhibitors followed for approximately 4 Years (n= 682)



Hackett G et al. Int J Clin Pract 70(3): 244-253 (2016)

Long Term Mortality Data in Diabetes – The BLAST LONG TERM STUDY (2016) (n=857)



ORIGINAL ARTICLE

Phosphodiesterase type-5 inhibitor use in type 2 diabetes is associated with a reduction in all-cause mortality

Simon G Anderson,[1,2] David C Hutchings,[1] Mark Woodward,[2,3] Kazem Rahimi,[2] Martin K Rutter,[4,5] Mike Kirby,[6] Geoff Hackett,[7] Andrew W Trafford,[1] Adrian H Heald[8,9]

What might this study add?

We undertook a retrospective analysis of mortality in a cohort of patients with type 2 diabetes mellitus (T2DM) and therefore high-attendant cardiovascular risk. Our findings demonstrated that, for the first time, PDE5 inhibitor use is associated with significantly reduced mortality in patients with T2DM, an effect which remained after multiple adjustments for known confounding factors.

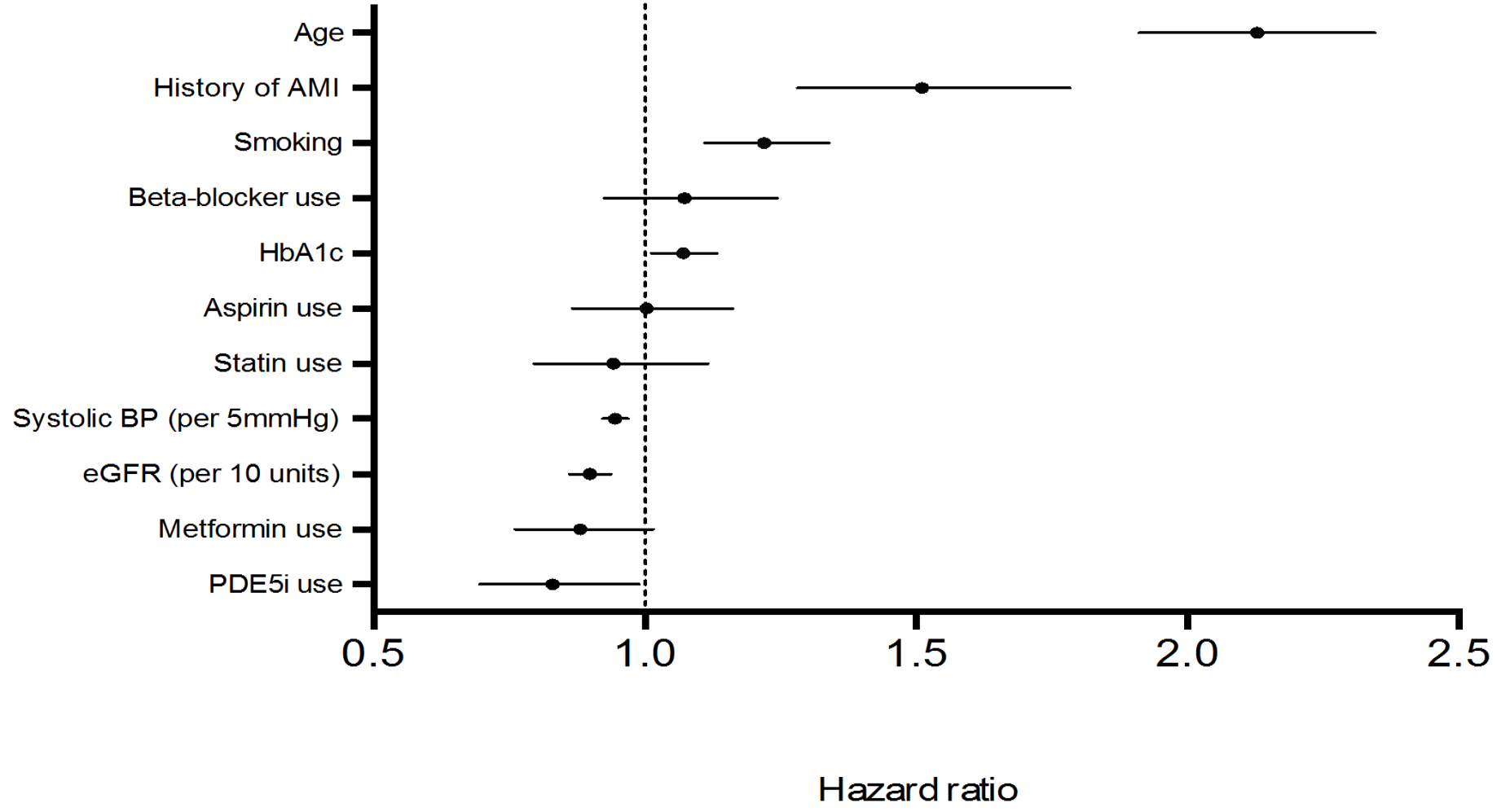
How might this impact on clinical practice?

Our findings provide strong evidence for PDE5 inhibitors acting to reduce mortality in T2DM. Further evidence is required to elucidate the role of PDE5is in cardioprotection.

Anderson et al Heart 2016

Multivariate Regression model for risk of mortality (N=7860):

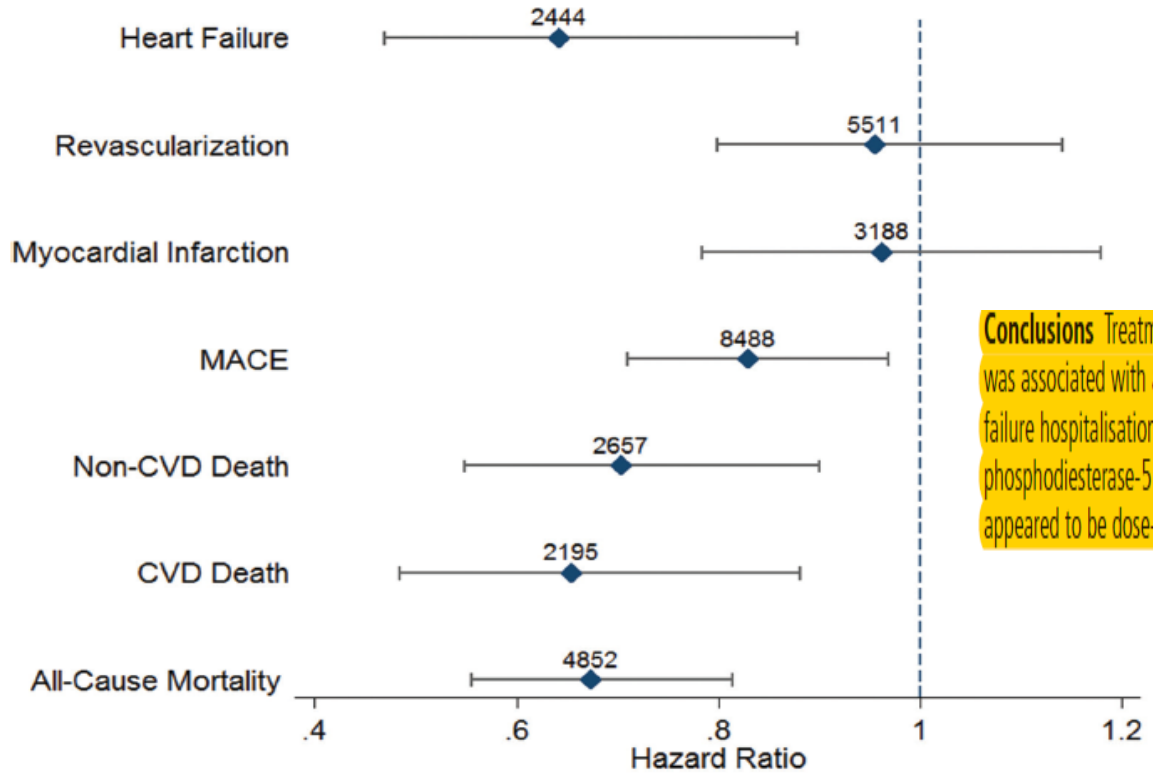
(Anderson, Heald, Hackett, Heart 2016 –press)



Association between treatment for erectile dysfunction and death or cardiovascular outcomes after myocardial infarction

Daniel P Andersson,[1] Ylva Trolle Lagerros,[2] Alessandra Grotta,[3] Rino Bellocco,[3,4] Mikael Lehtihet,[1] Martin J Holzmann[5,6]

Andersson DP, *et al. Heart* 2017;**0**:1–7. doi:10.1136/heartjnl-2016-310746



Conclusions Treatment for ED after a first MI was associated with a reduced mortality and heart failure hospitalisation. Only men treated with phosphodiesterase-5 inhibitors had a reduced risk, which appeared to be dose-dependent.

Figure 2 Adjusted HRs and 95% CI for the association between treatment for erectile dysfunction, compared with no treatment for erectile dysfunction, and outcomes after a first myocardial infarction in 43 145 men. Number of events are depicted above the point estimate for each outcome. MACE, major adverse cardiac event; CVD, cardiovascular disease.

CASE REPORT

doi: 10.1111/j.1742-1241.2006.01087.x

PDE5 inhibitors in diabetic peripheral neuropathy

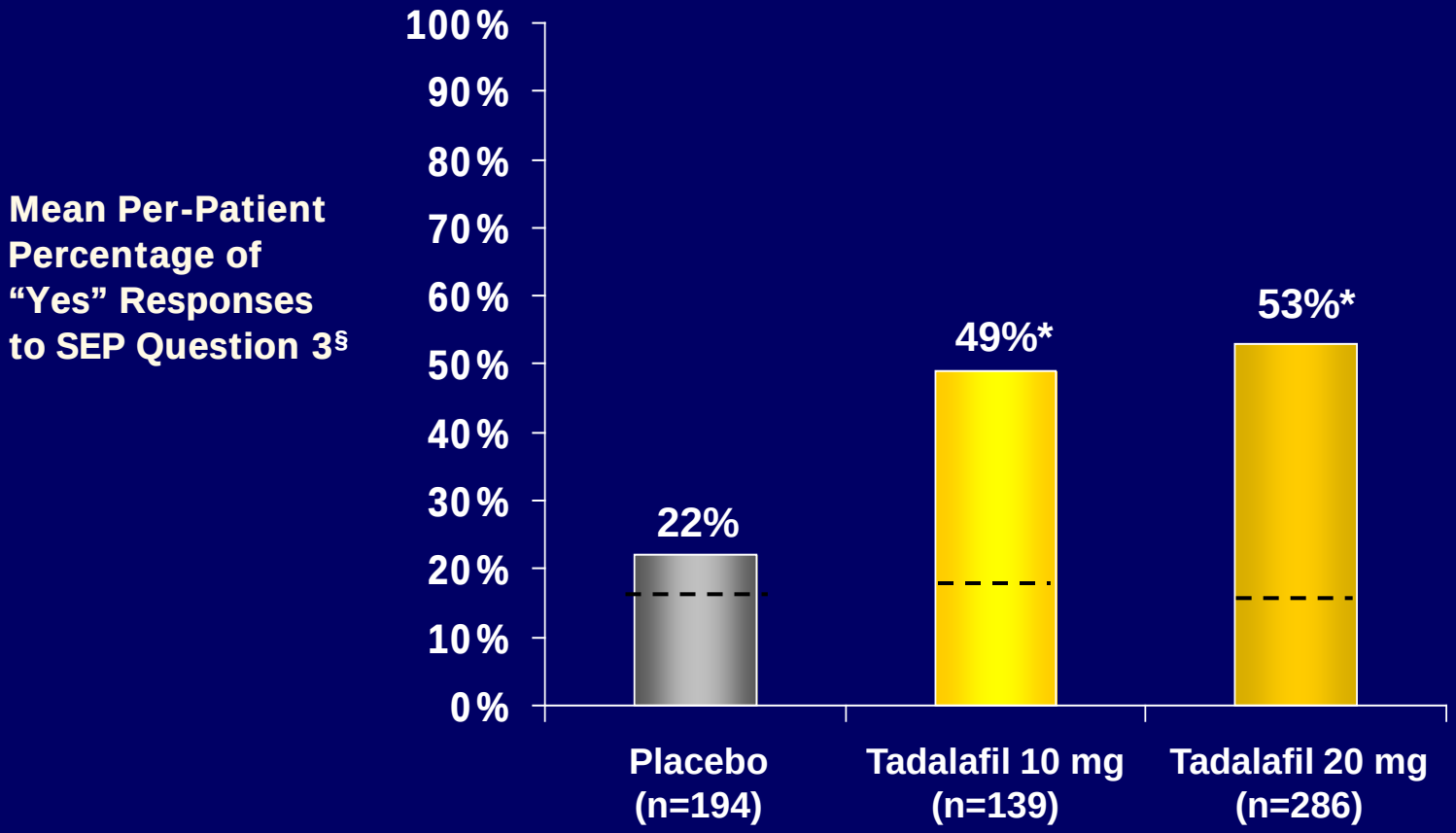
G. HACKETT

Good Hope Hospital, Sutton Coldfield, UK

CONCLUSION

These five cases from clinical practice strongly support the recommendations of other authors that PDE5Is may have an important therapeutic role in peripheral as well as autonomic diabetic neuropathy. Further research is urgently required to investigate this important therapeutic indication. As neuropathy is the commonest complication of diabetes, affecting 50%, and is frequently asymptomatic in the early stages, there may also be a place for early preventive therapy with PDE5Is, especially as 50% of diabetic men will also develop ED.

TADALAFIL - Successful Intercourse in Men With Diabetes (unrestricted medication)



*P<0.001 vs. placebo.

§SEP Question 3: Did your erection last long enough for you to have successful intercourse?

Dashed line within each bar represents baseline SEP3 score (% Yes).

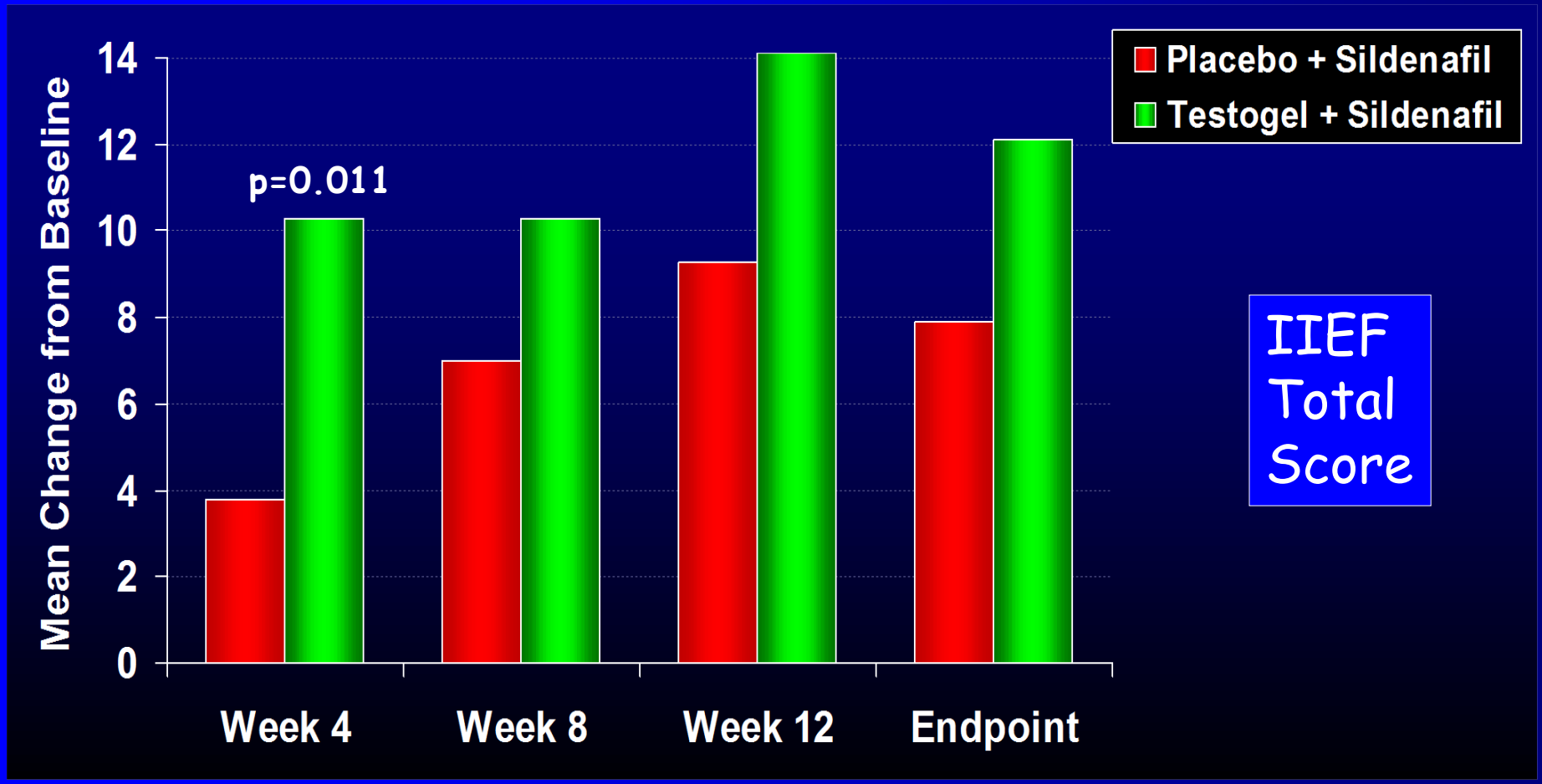
Fonseca V et al. *Diabetologia* 2004;47:1914-1923.

4 **'High-dose' (overdosing) PDE 5 inibitor therapy.** High dose PDE 5 inhibitor therapy, i.e. doubling the maximum dose, resulted in a 24% salvage rate of ED patients (n=54) previously unresponsive to 100 mg Sildenafil [152]. According to the personal experience this may also apply for Vardenafil and Tadalafil in individual patients especially in unresponsive diabetics.

5 **Shifting patients to another PDE 5 inhibitor.** Shifting of real non-responders to Sildenafil to Vardenafil resulted in a rescue-/success rate of 12% [153]. According to the personal experience with more than 8,000 patients on PDE 5 inhibitors only a small minority (5-8%) of real non-responders (vaginal penetration not possible after 4 attempts with the highest dose) on one PDE 5 may be rescued by another one.

6 **Daily dosing of PDE 5 inhibitors.** Daily dosing of PDE 5 inhibitors for several months in patients previously unresponsive to on demand therapy to either Tadalafil (figure 15.10) [154] or Sildenafil [155] at maximum doses, was able to salvage more than 50% of failures. Although that was proven in preliminary small series for Tadalafil and Sildenafil it can be assumed that this concept holds true also for other PDE 5 inhibitors in particular in patients with severe organic ED.

Testosterone Therapy (5g Testogel®/d/12 wk) Converts Sildenafil 100 mg Non-responders to Responders in Men with Hypogonadism (tT<14nmol/l) and ED



Shabsigh R et al. J Urol 169(4) Suppl.: 247 (2003)

THE COMMON SCENARIO FOR TESTOSTERONE THERAPY.

An obese 50 year old man with metabolic syndrome and ED has failed to respond repeated to Sildenafil 100mg and Tadalafil 20mg , His marriage is severely at risk . His TT is 9.0. LH 2.5 SHBG 32 Haematocrit 40% (AM results repeated)

- **OPTION 1**
- Rx Alprostadil (injection or intra-urethral)
- Cost £1040@1 per week or £2040@ twice per week funded by patient (NHS if T2DM).
- Training required
- Adverse events: pain, fibrosis, rarely priapism.
- High discontinuation rate.
- UNHAPPY PATIENTS AND PARTNERS

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- Training required
- Adverse events: pain, fibrosis, rarely priapism.
- High discontinuation rate.
- UNHAPPY COUPLES

OPTION 2.

- **Testosterone gel 50mg daily**
- **Plus DAILY PDE5I**
- Annual Cost £414.40@1/week, £428.80.at twice per week
- ALL FUNDED BY THE NHS,
- PATIENT COST = £0
- Adverse events: Improved desire, mood and energy, loss of visceral fat, improved glycaemic control. Raised haematocrit (rare).
- PATIENT TAKES SECONDS to CHOOSE OPTION 2. – A logical Cost Effective Solution to a Real Problem
- THE ISSUE IS NOT MIDDLE AGED MEN SEARCHING FOR THEIR “MOJO” or “ELIXIR OF YOUTH”..

Should PDE5Is be prescribed routinely for all men with newly diagnosed type 2 diabetes?

GEOFFREY HACKETT

Abstract

Diabetes and erectile dysfunction are closely associated. It is good that there is now more awareness of the issue, especially given the strong link to heightened cardiovascular risk. This article challenges current practice and explores the routine use of phosphodiesterase inhibitors.

Br J Diabetes Vasc Dis 2015;**15**:184-186

Key words: type 2 diabetes, erectile dysfunction, cardiovascular risk, phosphodiesterase type 5 inhibitors, lower urinary tract symptoms

Introduction

I present to my GP as a 53-year-old man with type 2 diabetes (T2DM), HbA_{1c} 6.6 (IFCC 48%), slightly overweight (body mass index 28.5), BP 125/80, total cholesterol 5.1. I am otherwise fit with an excellent marriage. My sex life is OK but not what it used

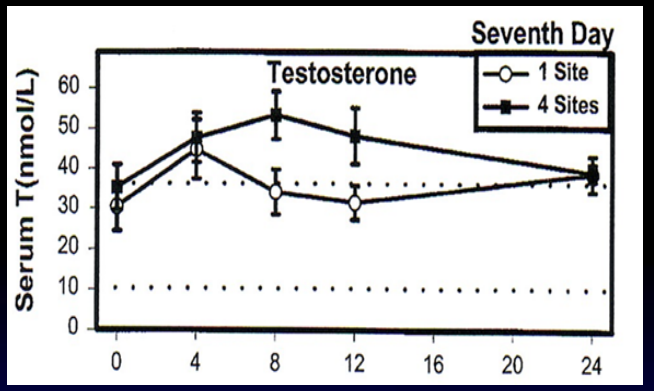
Figure 1. Multifactorial mechanisms associated with ED in diabetes

- Autonomic neuropathy
- Peripheral neuropathy
- Hypertension
- Peripheral vascular disease
- Hyperlipidaemia
- Drug related side effects
- Cavernosal smooth muscle disorder
- Hypogonadism with reduced sexual desire (double risk)
- Psychological factors including depression
- Ejaculatory disorders
- Retrograde/anejaculation
- Reduced sensation

TAKE HOME MESSAGES

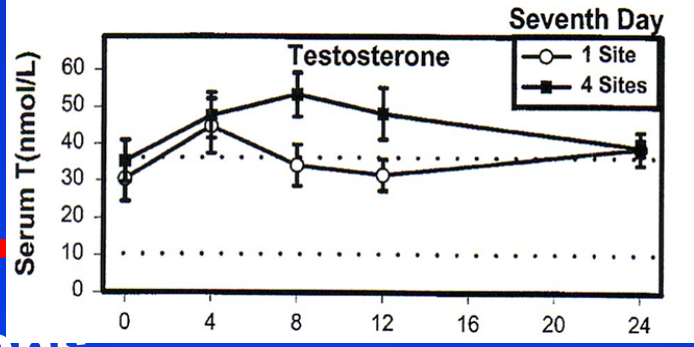
- Measure TT and FT in men with T2DM and MetS.
- Measure TT in all men with ED
- Men with Low T + co-morbidities need TRT + PDE5I.
- Full response to TRT takes at least 6 months.
- Low T is associated with increased mortality
- TRT reduces mortality in hypogonadal men
- TRT does not increase CV or prostate cancer risk
- Daily PDE5Is salvage 50% of on-demand failures.
- Correcting low T salvages PDE5i failures.
- PDE5Is appear to reduce mortality, heart failure and hospital admissions- THEY ARE NOW GENERIC – SHOULD THEIR USED BE RESTRICTED ANY LONGER.

TESTOSTERONE GEL IN HYPOGONADISM



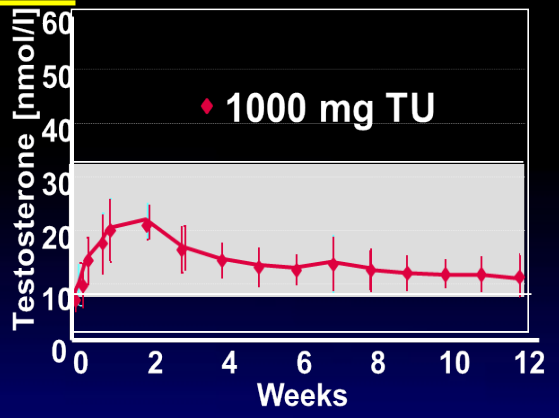
- **BUT**
- **Can be messy**
- **around 30% require more than 50mg**
- **Skin irritation and rashes in 7%**
- **Partner transfer.**
- **Greater conversion to DHT by 5AR in skin.**
- **Patient compliance can be an issue - especially long term**
- **Monitoring more difficult as daily level assessed rather than long term values**
- **Effects on insulin resistance may be more convincing with long acting injections**
- **MONITORING - TT, SHBG, PSA,FBC, haematocrit at 3-6 months, then annually. Bloods 2-4 hours after application. Skin contamination can cause false elevated values**

TESTOSTERONE GEL IN HYPOGONADISM



- Available as 1% and 2% formulations
- Tube, sachet and pump dispenser
- Applied AM after shower or wash
- Needs to be applied long term
- More closely mirrors natural diurnal variation
- Can be stopped abruptly
- Low incidence of raised haematocrit (<5%)
- Higher levels can be achieved /skin contamination
- Generally well tolerated with no interactions with oral drugs
- Active prostate or breast cancer only important contraindications.

TESTOSTERONE INJECTIONS IN HYPOGONADISM



Avoid Cheaper Short Acting preparations as 2-4 weekly unacceptable and not cost effective Mood swings, variable levels, higher rates of raised haematocrit mean it should be replaced by 1000mg/4ml (12 weekly) formulation.

- **Single injection into buttock over 2-3 minutes after WARMING THE AMPOULE**
- **Loading dose, second dose at 6 weeks then 10-12 weekly.**
- **Active prostate and breast cancer only clear contra-indication (PSA and DRE At baseline, 6 months then annually)**
- **Caution with anti-coagulants. Well tolerated**
- **Rapid withdrawal of T levels not possible**
- **Greater certainty patient is compliant.**

Prof Geoffrey Hackett

Good Hope Hospital Sutton Coldfield

There has never been a better time to offer men "Proper Personalised Care!!"

University of Bedfordshire

NHS

HEART of ENGLAND NHS Foundation Trust