Why diabetologists should screen for Testosterone Deficiency in men with T2DM and improve clinical outcomes and mortality

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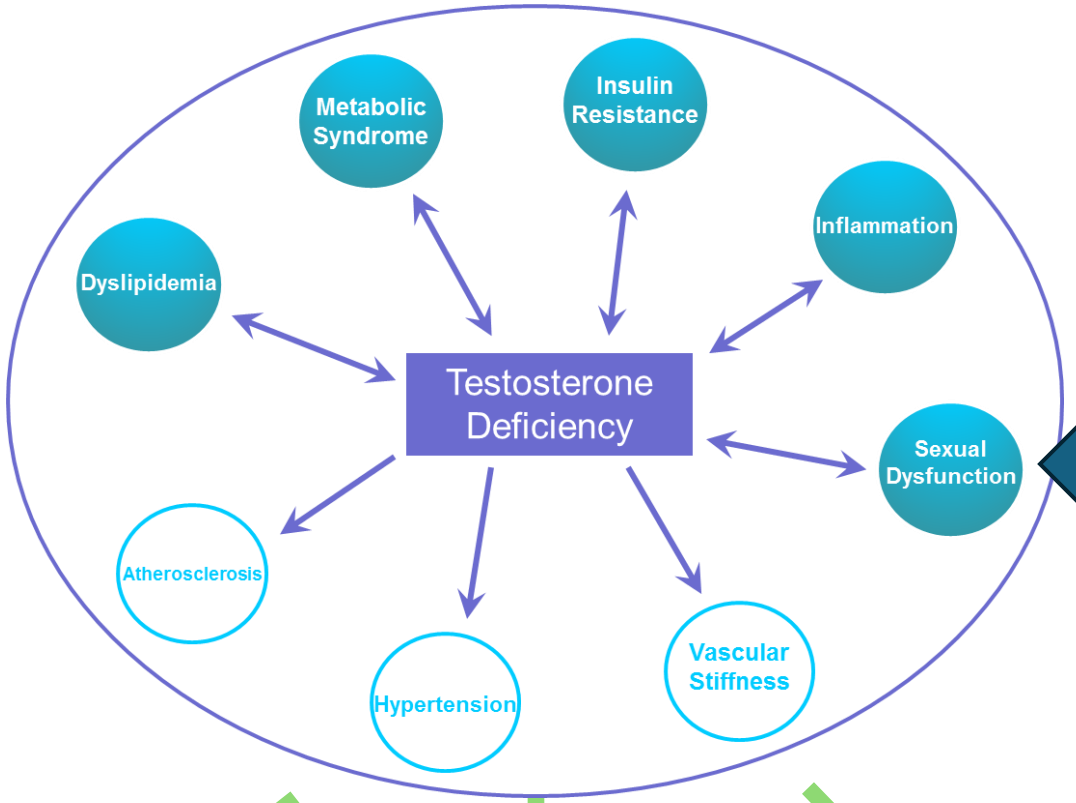
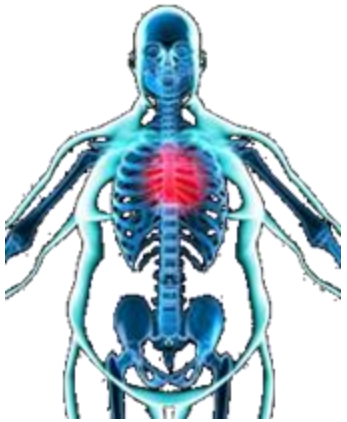
DECLARATIONS

- Besins Healthcare - Research Grant, Educational Lectures, Advisory Boards
- Grunenthal UK - Travel Grant
- Advanz - Consultancy
- Simple Pharma/Androlabs - Advisory Boards

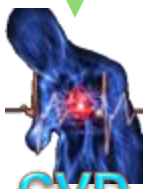
Adverse effects of testosterone deficiency on men's health



PORTAL TO MENS HEALTH



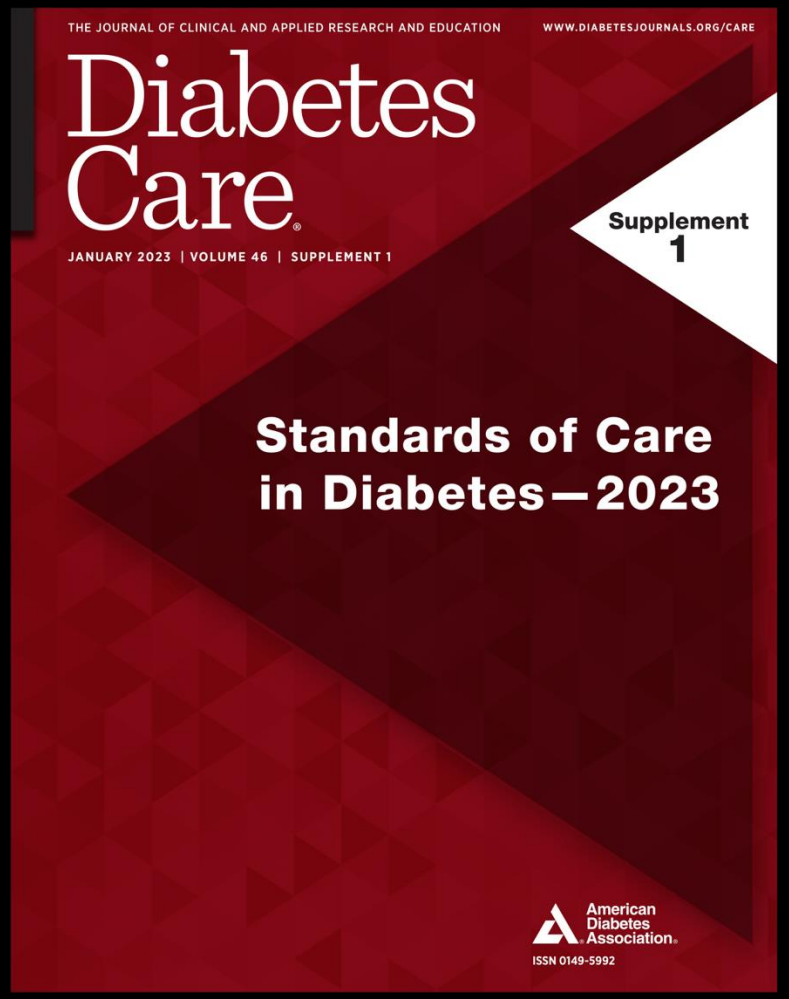
Obesity



CVD

Mortality

Type 2 Diabetes



American Diabetes Association®

4. Comprehensive Medical Evaluation and Assessment of Comorbidities: Standards of Care in Diabetes—2023

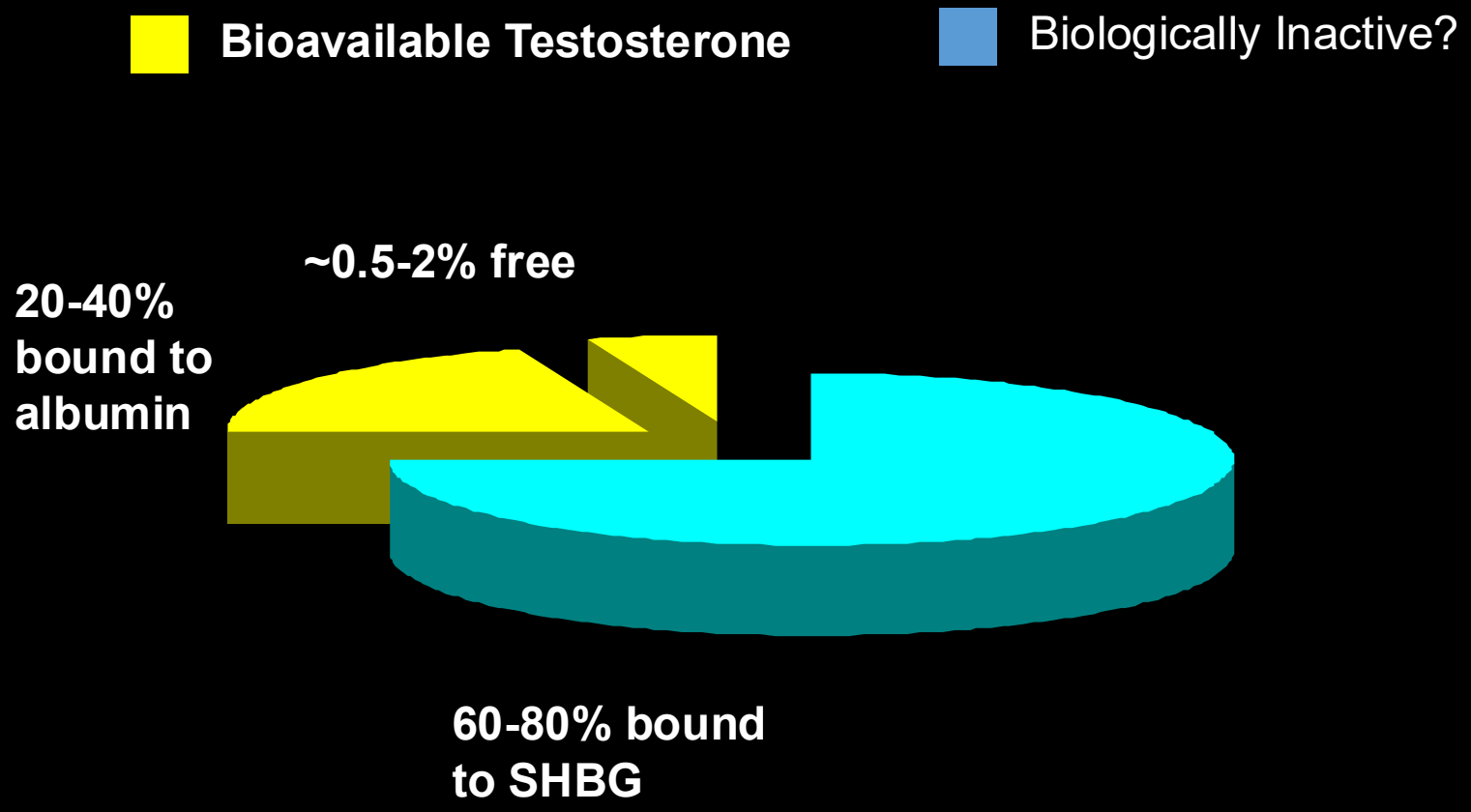
Low Testosterone in Men

Recommendation

4.10 In men with diabetes who have symptoms or signs of hypogonadism, such as decreased sexual desire (libido) or activity, or erectile dysfunction, consider screening with a morning serum testosterone level. B

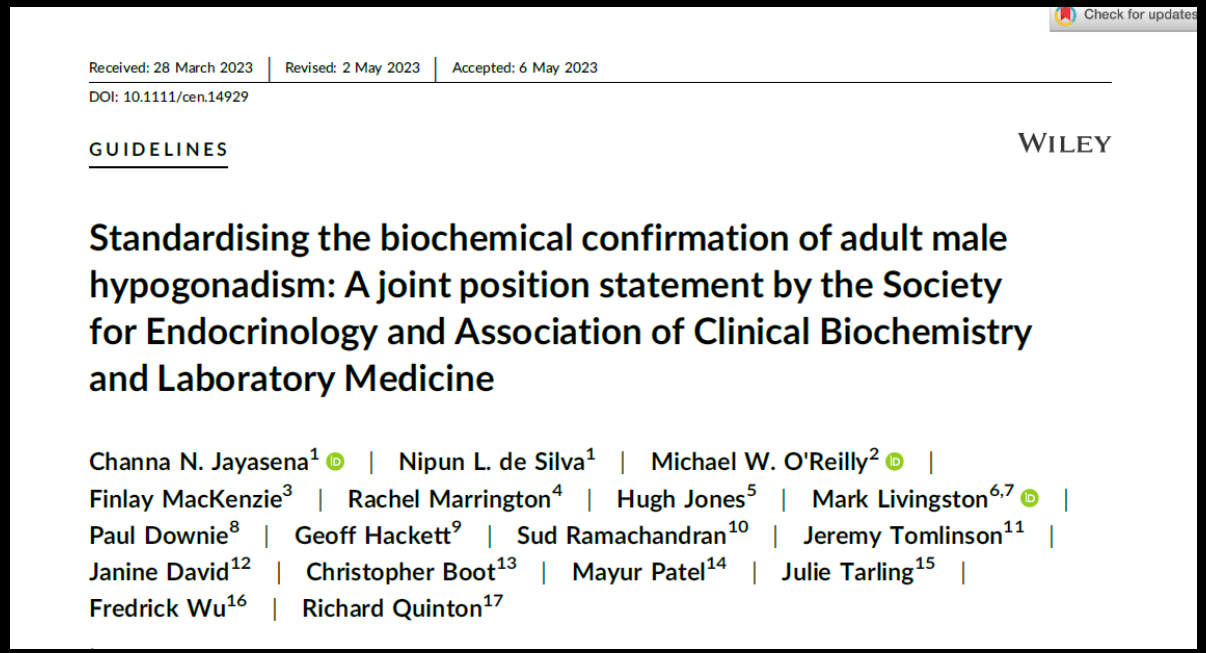
Testosterone replacement in men with symptomatic hypogonadism may have benefits including improved sexual function, well-being, muscle mass and strength, and bone density (81).

Serum Testosterone



STANDARDISING BIOCHEMICAL DIAGNOSIS OF MALE HYPOGONADISM

Society for Endocrinology



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DOI: 10.1111/cen.14929

GUIDELINES

WILEY

Standardising the biochemical confirmation of adult male hypogonadism: A joint position statement by the Society for Endocrinology and Association of Clinical Biochemistry and Laboratory Medicine

Channa N. Jayasena[1] | Nipun L. de Silva[1] | Michael W. O'Reilly[2] | Finlay MacKenzie[3] | Rachel Marrington[4] | Hugh Jones[5] | Mark Livingston[6,7] | Paul Downie[8] | Geoff Hackett[9] | Sud Ramachandran[10] | Jeremy Tomlinson[11] | Janine David[12] | Christopher Boot[13] | Mayur Patel[14] | Julie Tarling[15] | Fredrick Wu[16] | Richard Quinton[17]

Association of Clinical Biochemistry and Laboratory Medicine

Best Practice

The Association for Clinical Biochemistry & Laboratory Medicine
Better Science, Better Testing, Better Care

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Standardising the biochemical confirmation of adult male hypogonadism; a joint position statement by the Society for Endocrinology and Association of Clinical Biochemistry and Laboratory Medicine*

Channa N Jayasena[1], Nipun Lakshitha de Silva[1], Michael W O'Reilly[2], Finlay MacKenzie[3], Rachel Marrington[4], Hugh Jones[5], Mark Livingston[6,7], Paul Downie[8], Geoff Hackett[9], Sud Ramachandran[10], Jeremy Tomlinson[11], Janine David[12], Christopher Boot[13], Mayur Patel[14], Julie Tarling[15], Fredrick Wu[16] and Richard Quinton[17]

UK NEQAS
International Quality Expertise

Jayasena CN et al. Clin Endocrinol 2023:101;531-534
Jayasena CN et al. Annals Clin Biochem 2023:60;223-227

Biochemical Assessment

No generally accepted lower limit of normal but general agreement that:-

TT < 8nmol/l require TRT

TT > 12nmol/l does not require TRT

TT 8-12nmol/l with symptoms can be considered provided other causes have for symptoms have been excluded

GUIDELINES

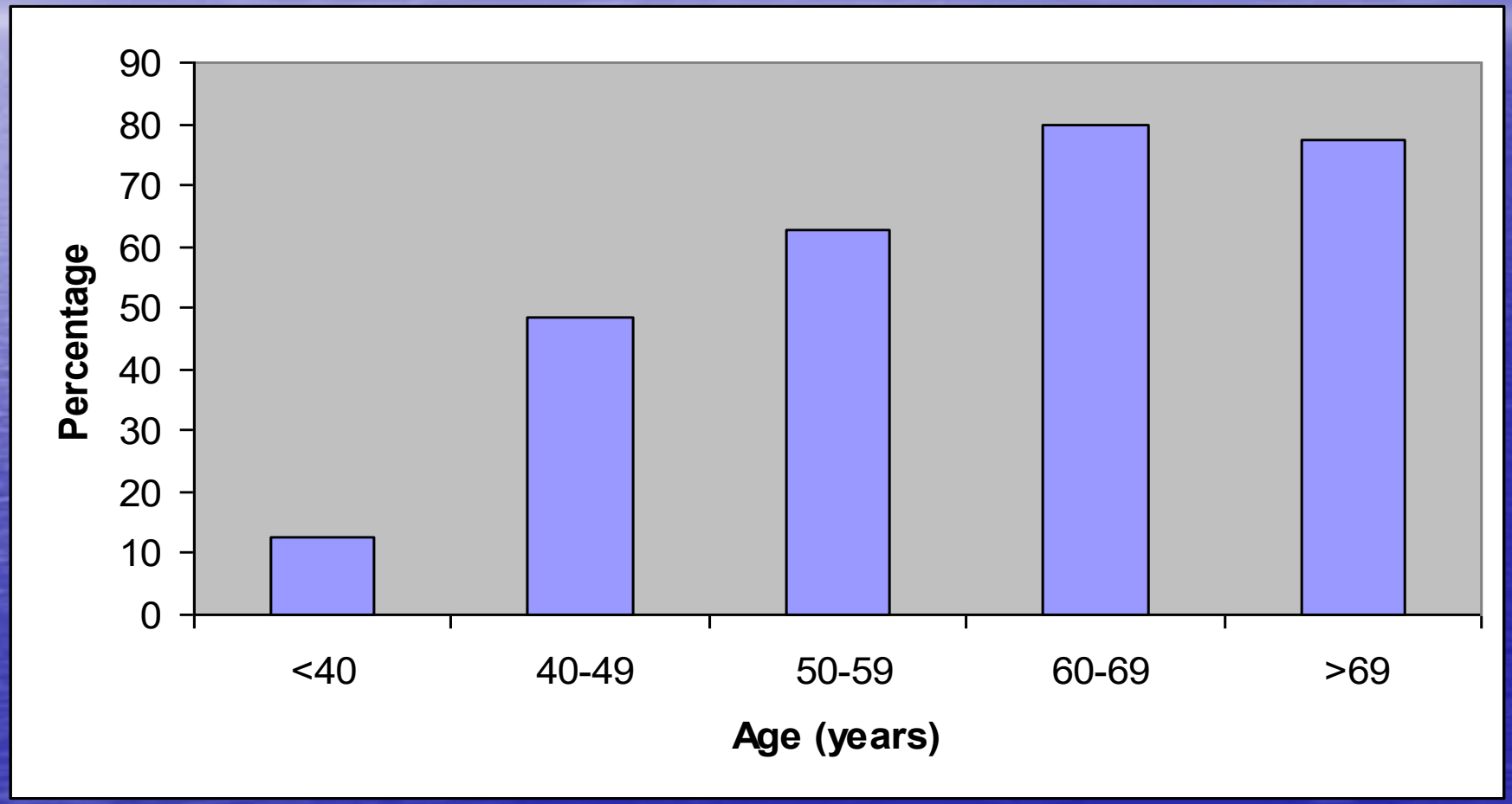
BSSM – Hackett G. et al. World J Mens Health 2023;41:508-37

EAU – Salonia A. et al. Eur Urol. 2021;80:333-57

SfE - Jayasena C. et al. Clin Endocrinol 2022;96:200-19

SEXUAL DYSFUNCTION

Prevalence of Erectile Dysfunction in Men with Type 2 Diabetes



Kapoor D et al, Int J Androl 2007:30;500-507

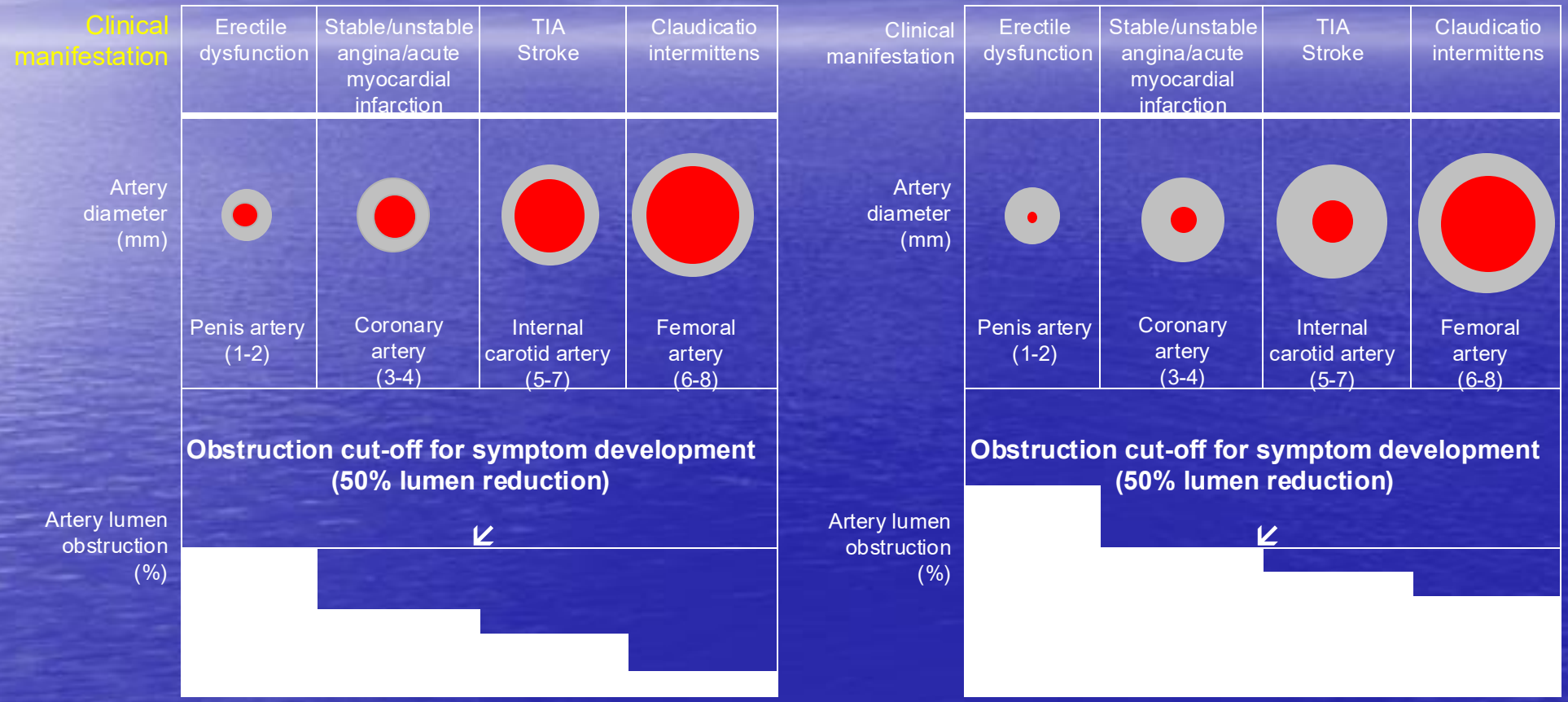
Effect of ED on Quality of Life in Men with Type 2 Diabetes

Domain	R Value	P Value
Total SF-36 Score	0.491	0.003**
Physical health	0.500	0.003**
Physical limitations	0.350	0.031*
Social	0.445	0.022*
Vitality	0.383	0.025*
Pain	0.428	0.012*
General health	0.408	0.001**

Table 6.8 - IIEF Scores versus SF-36 domains after adjusting for covariates. Only the domains that correlated significantly with IIEF scores are presented in this table. (*$p<0.05$, **$p<0.01$).

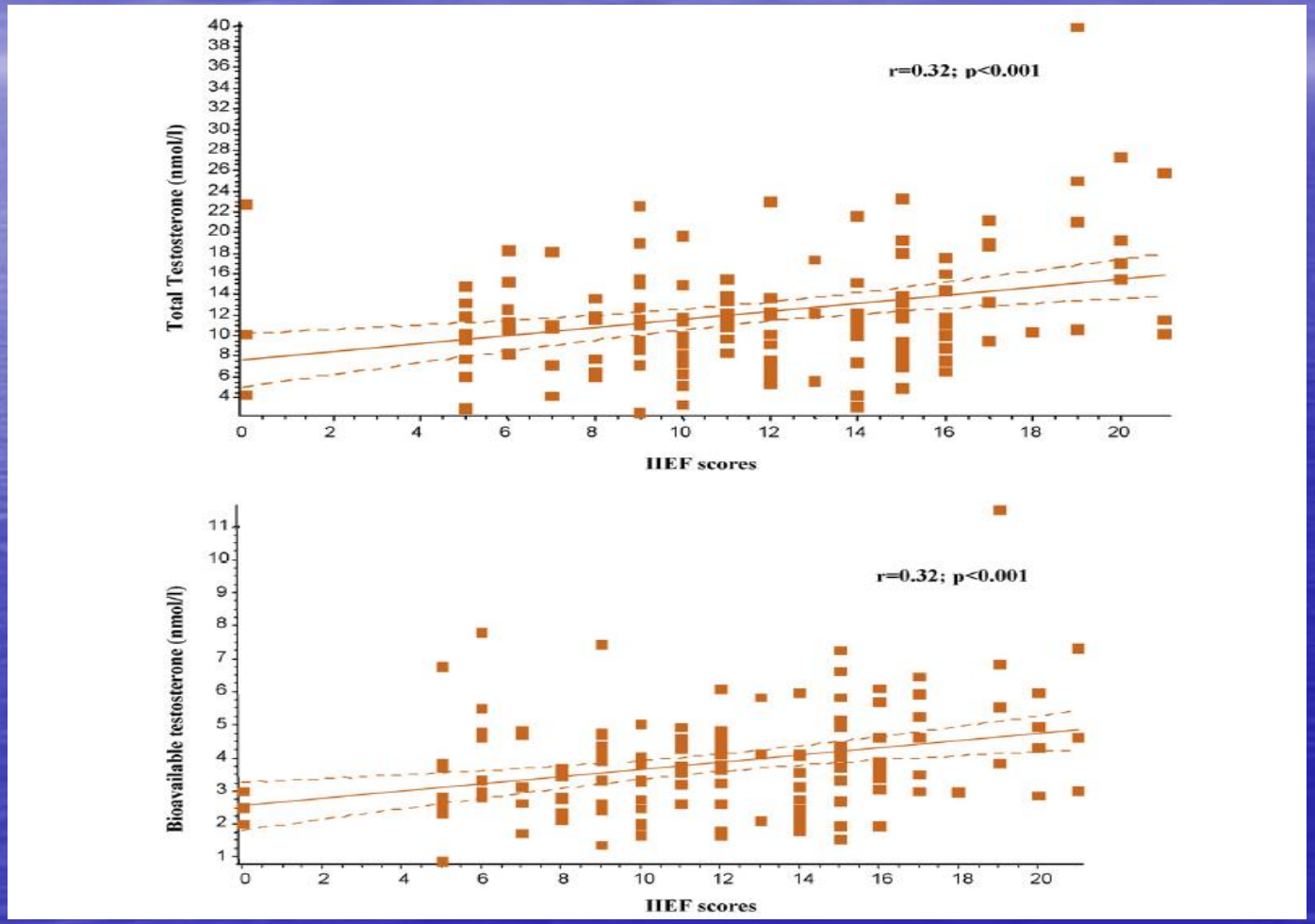
Brooke J et al. Andrology 2014;2:205-211

Common Grounds for Erectile Dysfunction and Coronary Artery Disease – Early and Late Steps of the Atherosclerotic Process



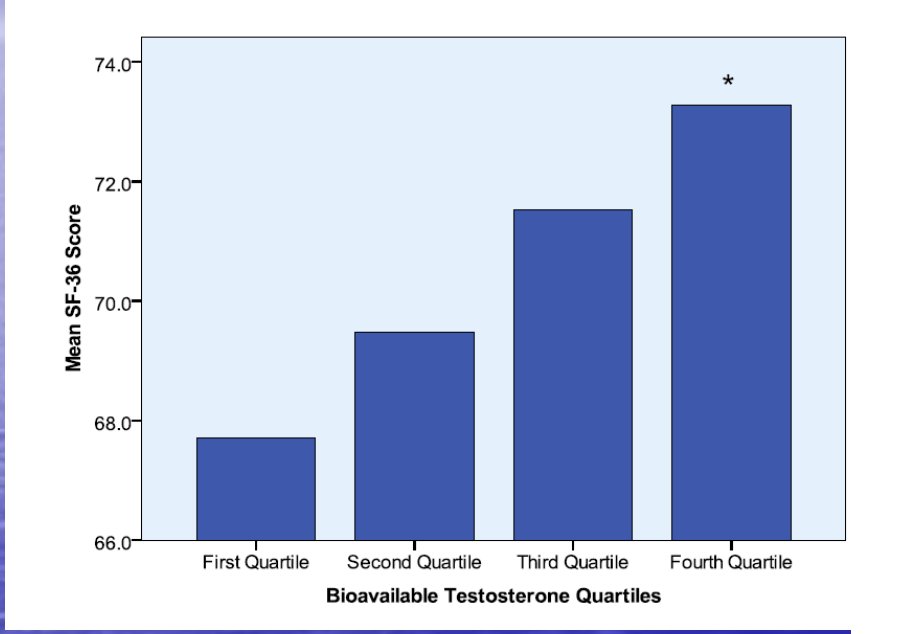
Montorsi P et al. Curr Opin Urol 14: 361-365 (2004)

Association of Testosterone Levels with IIEF Scores in Men with Type 2 Diabetes



Kapoor et al, Int J Androl 2007;30:500-507

Effect of Testosterone Level on Quality of Life in Men (SF-36) with Type 2 Diabetes n=355

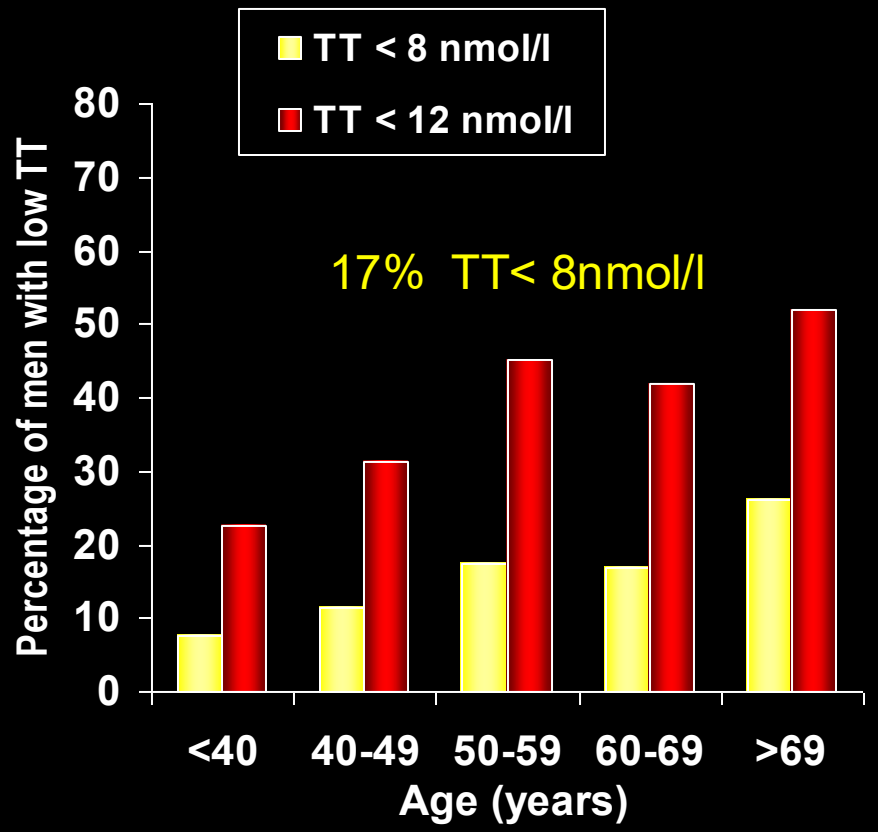


Domain	R Value	P Value
Total SF-36 Score	0.353	0.044*
Social Health	0.318	0.045*
Vitality	0.310	0.037*
Change in Health	0.251	0.006**

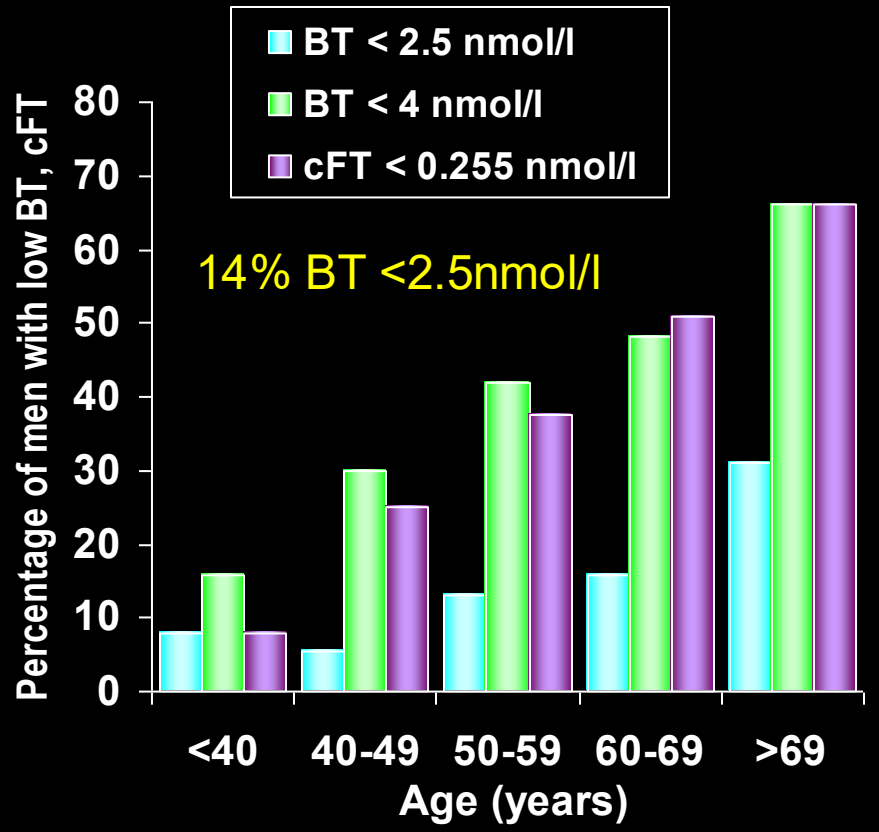
Brooke J et al. Andrology 2014;2:205-211

Prevalence of Symptomatic Hypogonadism in Men with Type 2 Diabetes

Total testosterone (TT)



Bioavailable testosterone (BT) and calculated free testosterone (cFT)



Total T nmol/l 12.72 + 0.29 (2.9 – 39) NR 8.3-41
SHBG nmol/l 32.48 + 1.06 (5.14-129) NR 15-100

N=355 - Included Klinefelters, Pituitary disorders.

Kapoor D et al. Diabetes Care 30: 911–917 (2007)

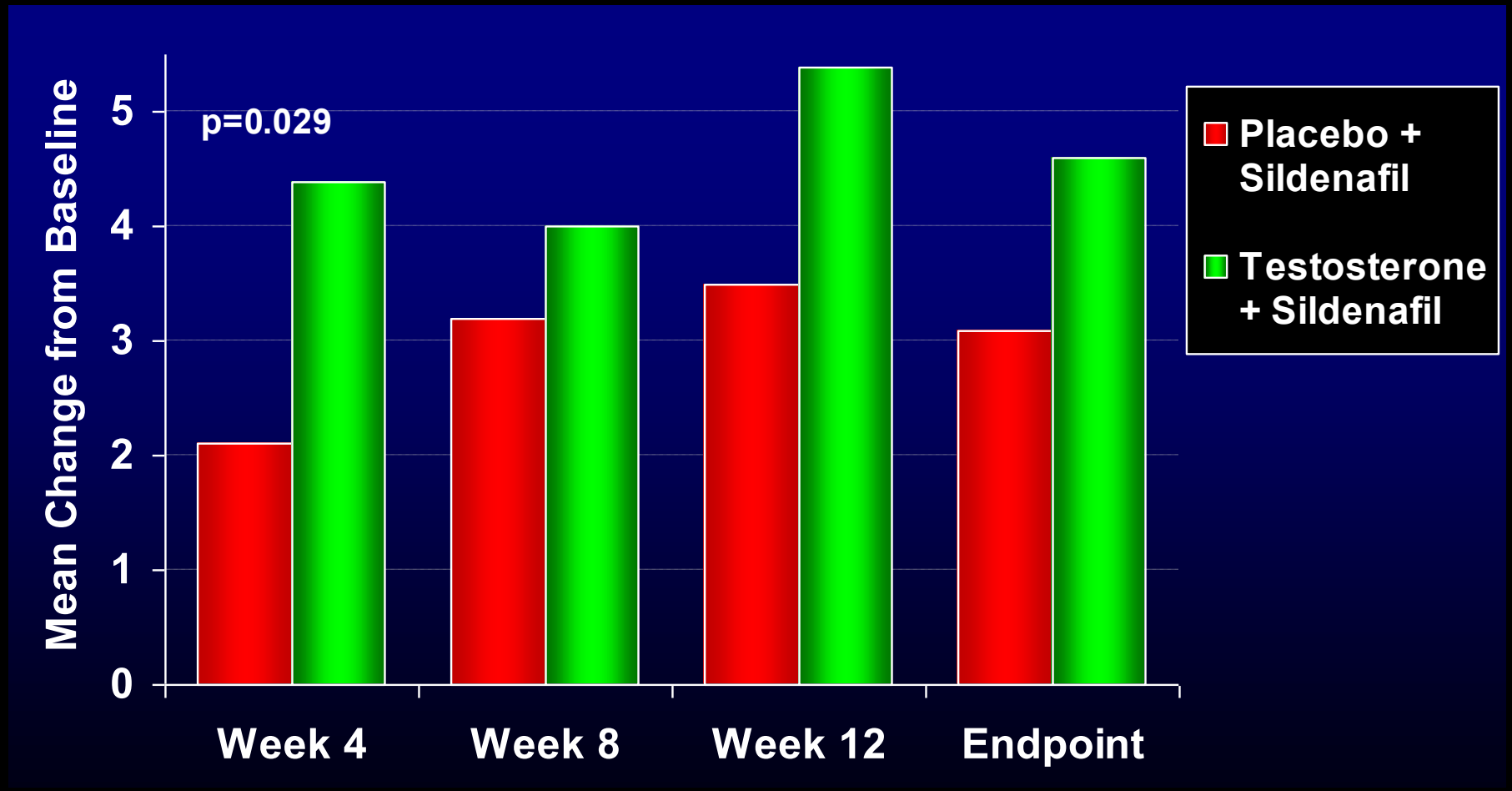
Different Testosterone Levels in Diabetic Responders and Non-Responders to PDE5 Inh.

	PDE5i nonresponders n = 120	PDE5i responders n = 100	
	Mean ± SD	Mean ± SD	p value
Total testosterone (nmol/L)	**6.9 ± 1.3**	**18.6 ± 1.2**	**< 0.001**
	(4.5 - 9.6)	(14.3 - 29.1)	

Kalinchenko S et al. Aging Male 6: 94-99 (2003)

12 wk Testosterone Therapy Converts Sildenafil 100 mg Non-Responders to Responders in Men with Hypogonadism (tT<14 nmol/L) and Erectile Dysfunction

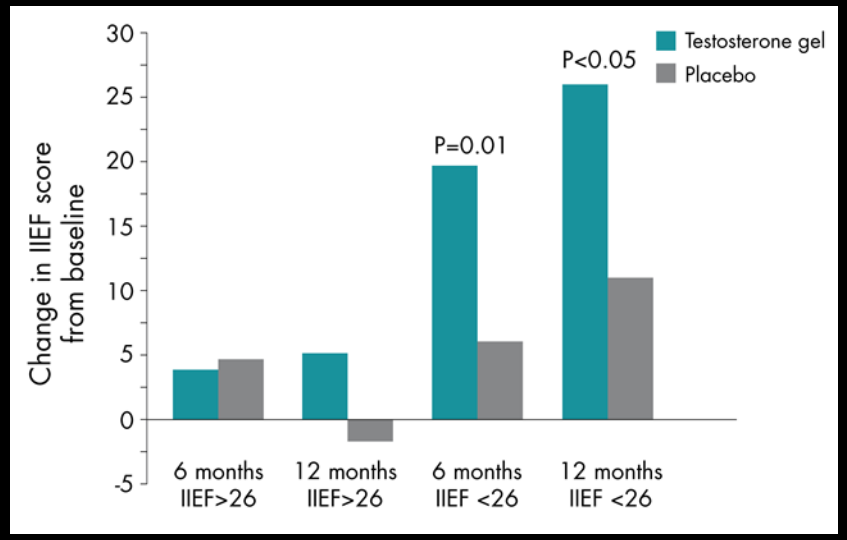
IIEF Erectile Function Domain

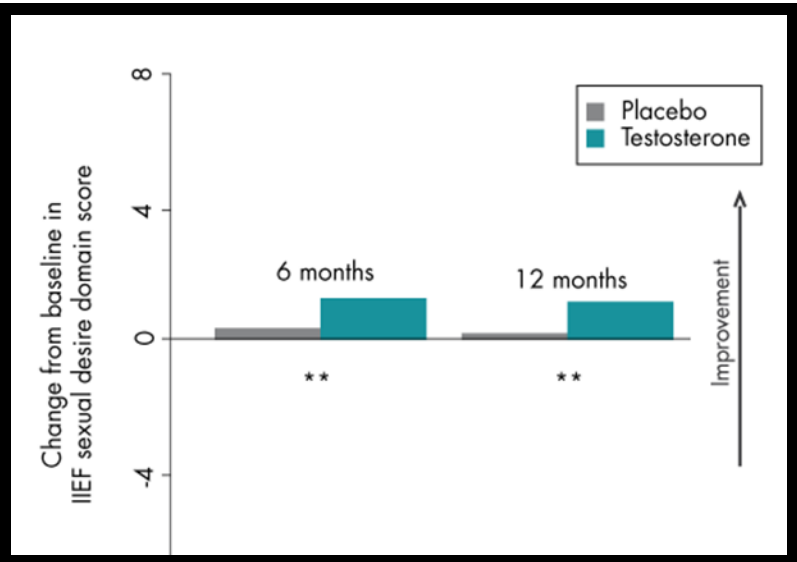


Shabsigh R et al. J Urol 172: 658-663 (2004)

Effect of TRT on Sexual Function (IIEF) in Type 2 Diabetes

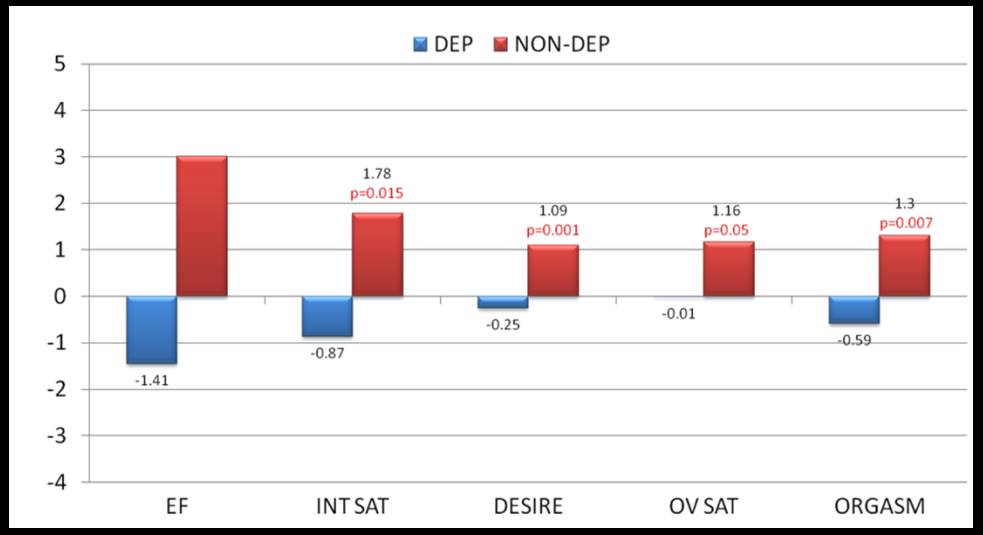
TIMES2 12 months Testosterone Gel

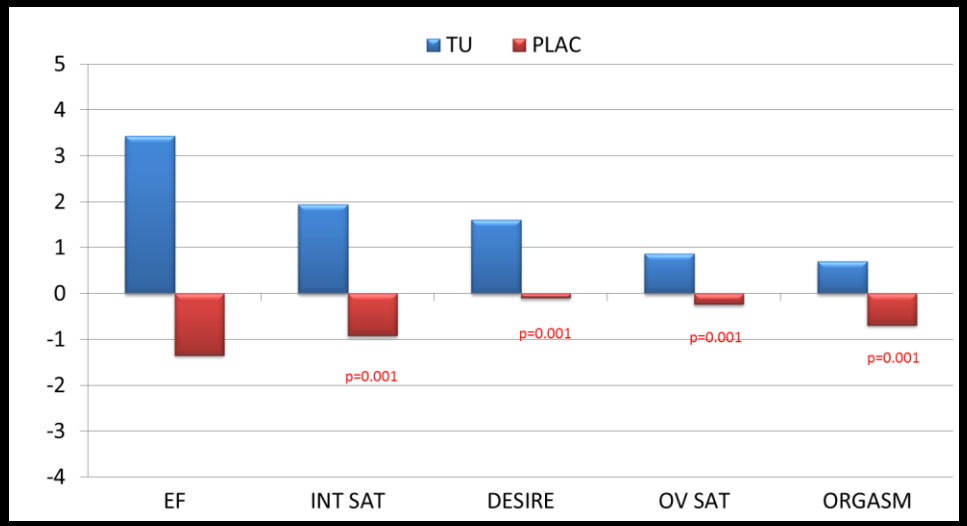




Other domains at 12 months:-
Erectile Function
p= 0.089
Intercourse satisfaction
p= 0.004
Orgasmic Function
p= 0.176
Overall sexual satisfaction
p= 0.045

BLAST 30weeks Testosterone Undeconoate i/m



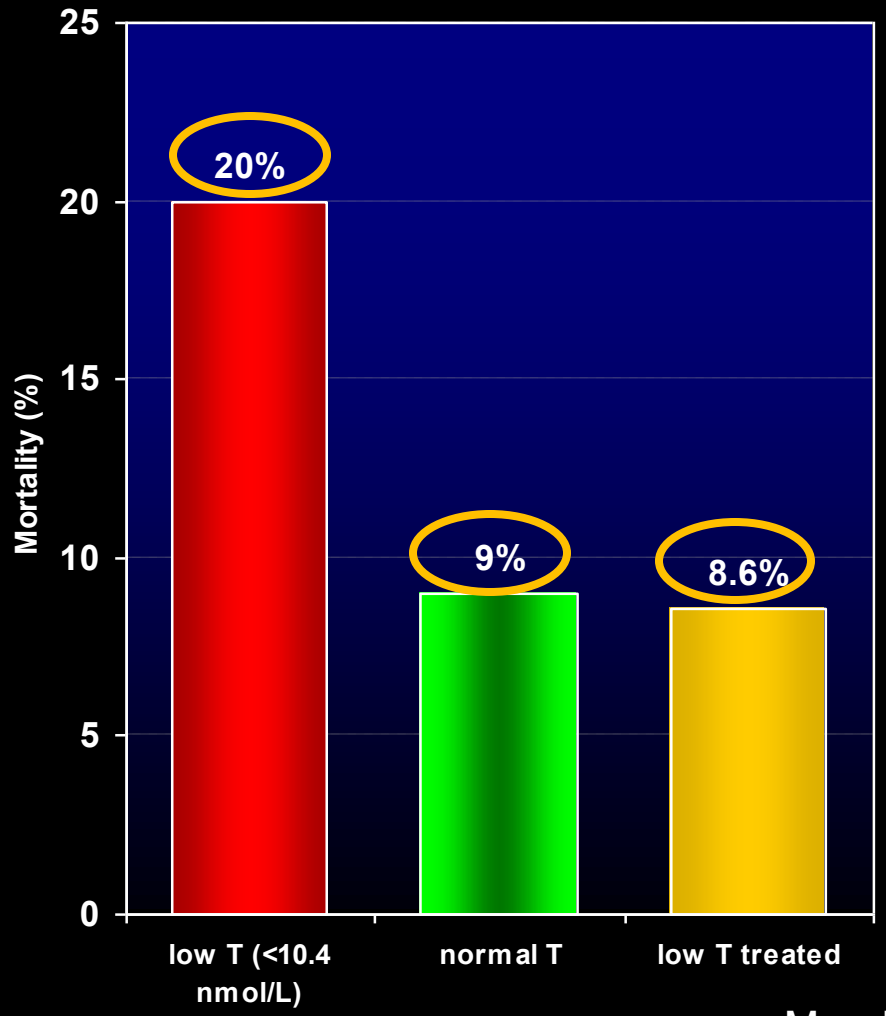


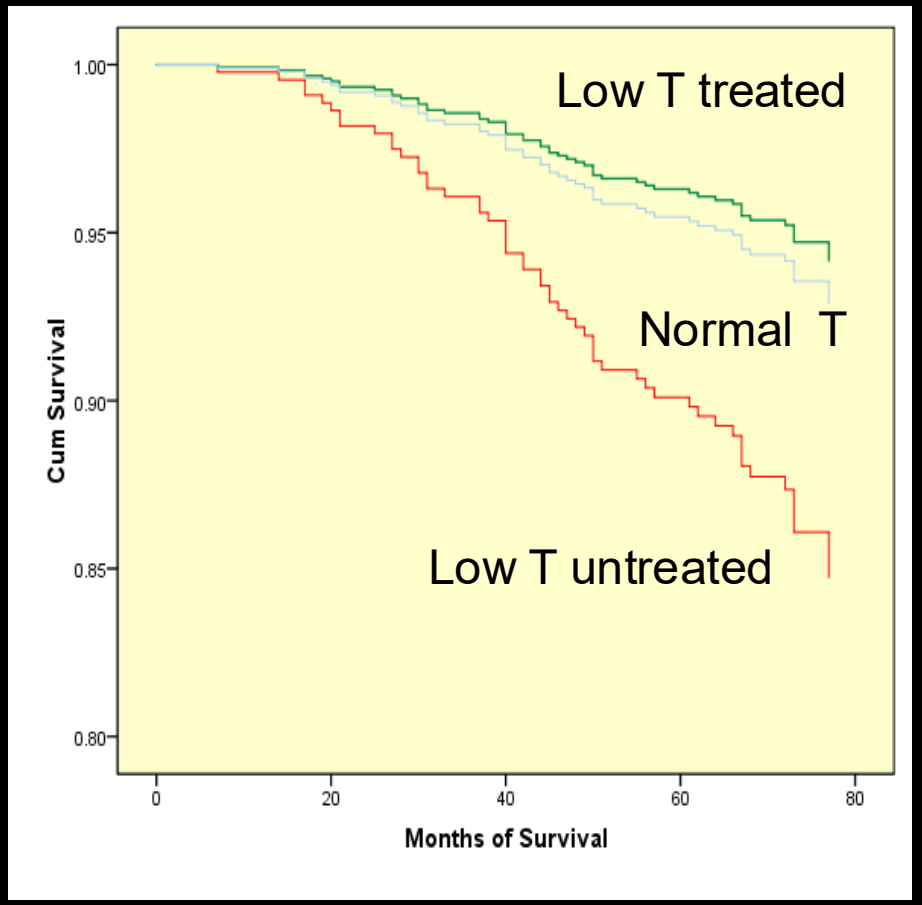
Jones TH et al. Diabetes Care 2011;34:828

Hackett G et al. J Sex Med 2013;16:12, Hackett G et al. BJU Int 2016;118:804

MORTALITY

Low Testosterone Predicts Increased Mortality and Testosterone Therapy Improves Survival in Men with Type 2 Diabetes (mean Follow-up: 5.8 years, n=587)





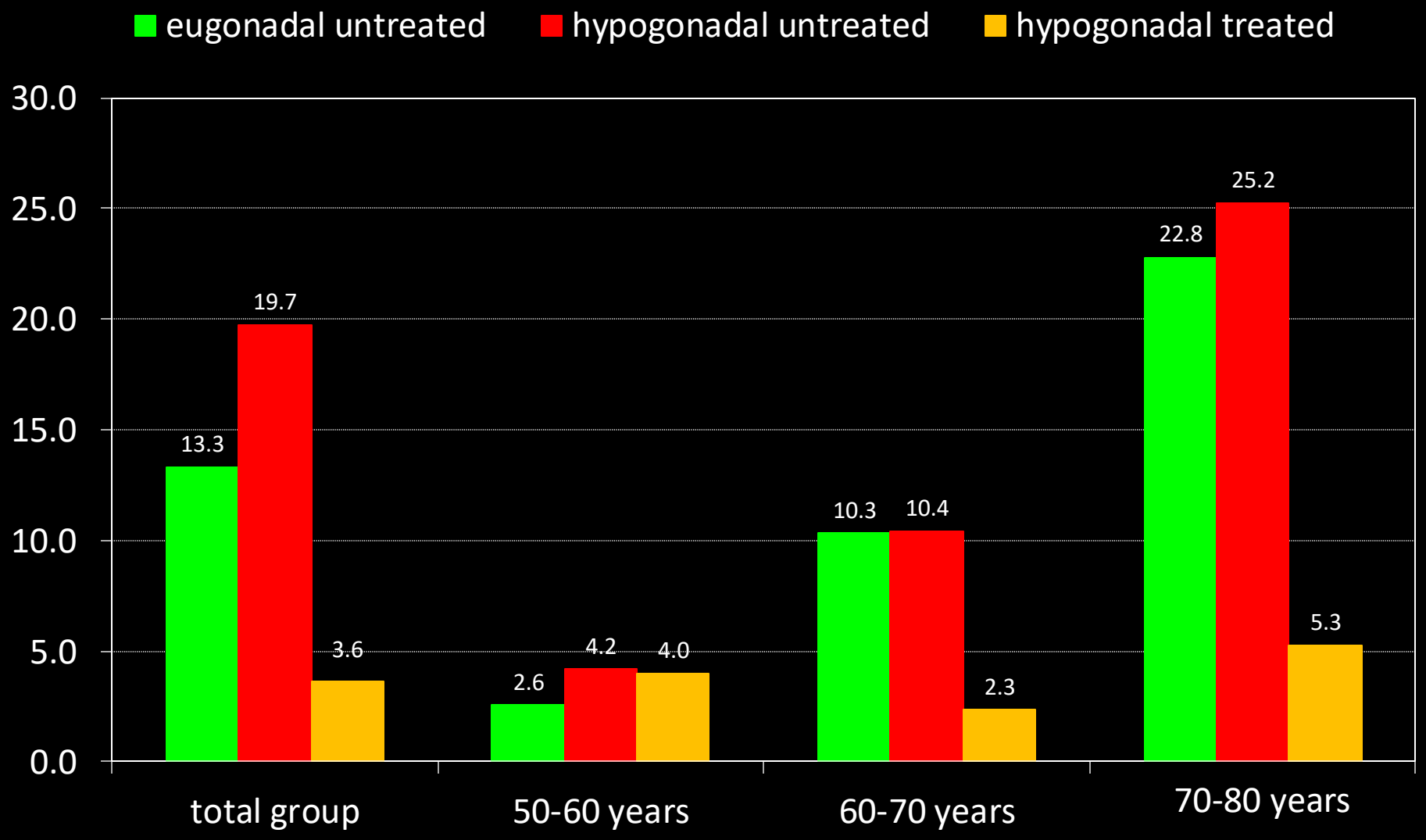
Cardiovascular Mortality Sub-Analysis
TT<8.4nmol/l HR 2.5 (p=0.02)

Multivariate-adjusted survival curves

BMI
HbA1c
Smoking
Statin Therapy
ACEI/ARB Rx
Pre-existing CVD

Muraleedharan V et al. Eur J Endocrinol 169;6 2013

Mortality Data of Patients with Type 2 Diabetes mellitus not Receiving PDE5 Inhibitors Followed for Approximately 4 Years



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

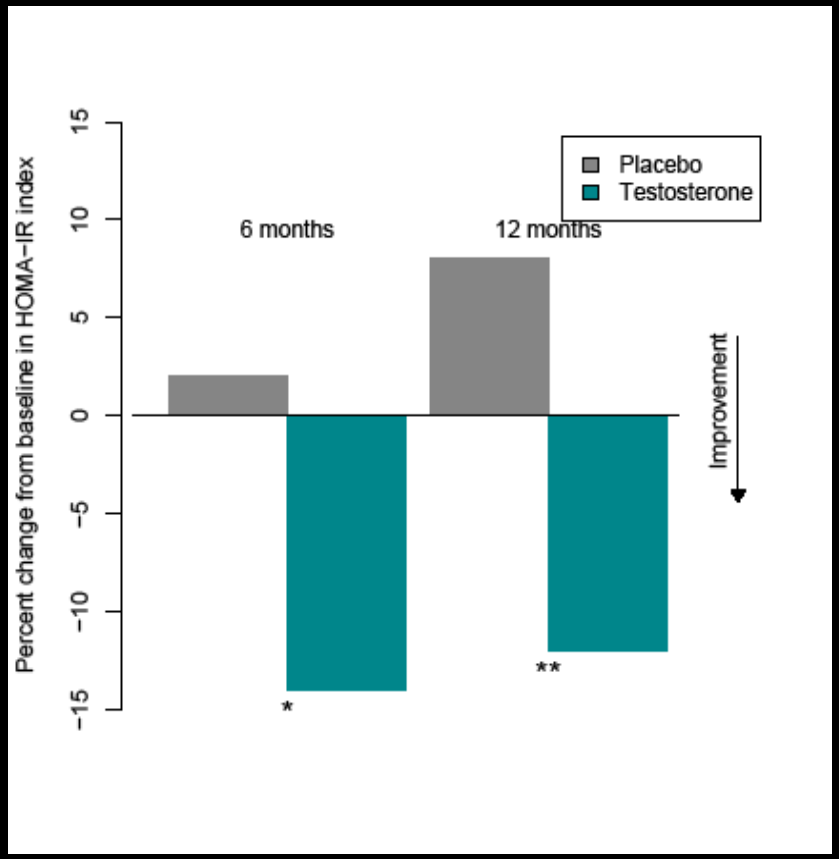
INSULIN RESISTANCE AND GLYCAEMIC CONTROL

Testosterone replacement In hypogonadal men with Metabolic Syndrome and/or type 2 diabetes – the TIMES2 Study (Placebo controlled RCT)

Percentage mean change from baseline in HOMA-IR for patients with T2D (with or without MS) (LOCF)

RCT
Testosterone Gel v Placebo
12 months
n=220

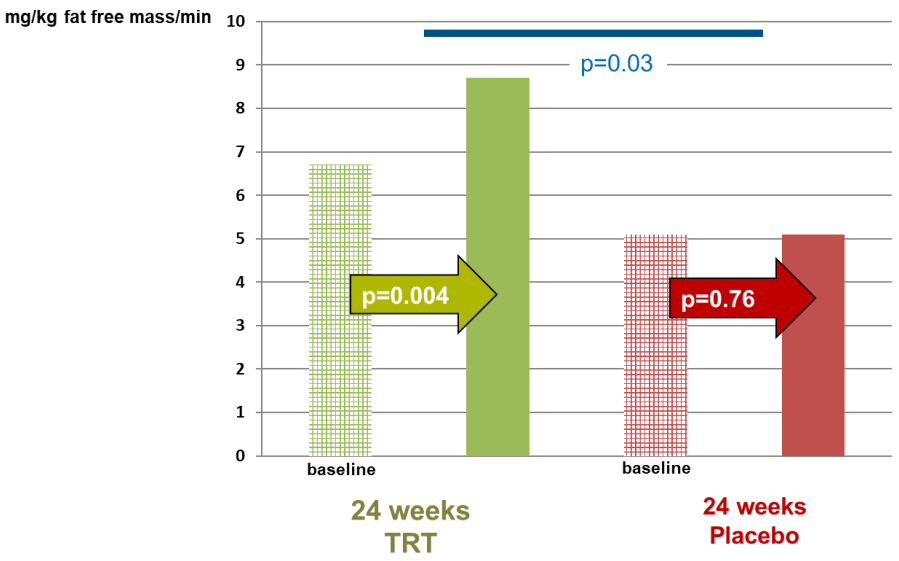
2% Testosterone Gel 50mg od v Placebo



Jones TH et al. Diabetes Care 2011;34:828-37

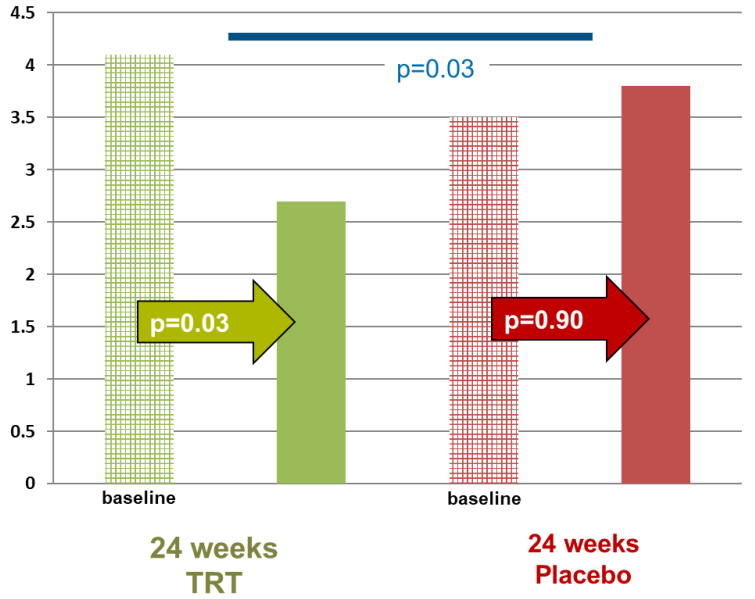
Effect of Testosterone Testosterone Undeconoate i/m on Insulin Sensitivity and Resistance

Insulin Resistance
HOMA-IR



Dhindsa et al Diabetes Care 2016 39:1-10

Insulin Sensitivity
Clamp Trial - Glucose Infusion Rate (GIR)



Dhindsa et al Diabetes Care 2016 39:1-10

EFFECT of TRT on HOMA-ir and HbA1c

TIMES2 Study

ALL

TYPE 2 DIABETES

METABOLIC SYNDROME

INSULIN RESISTANCE

HbA1C

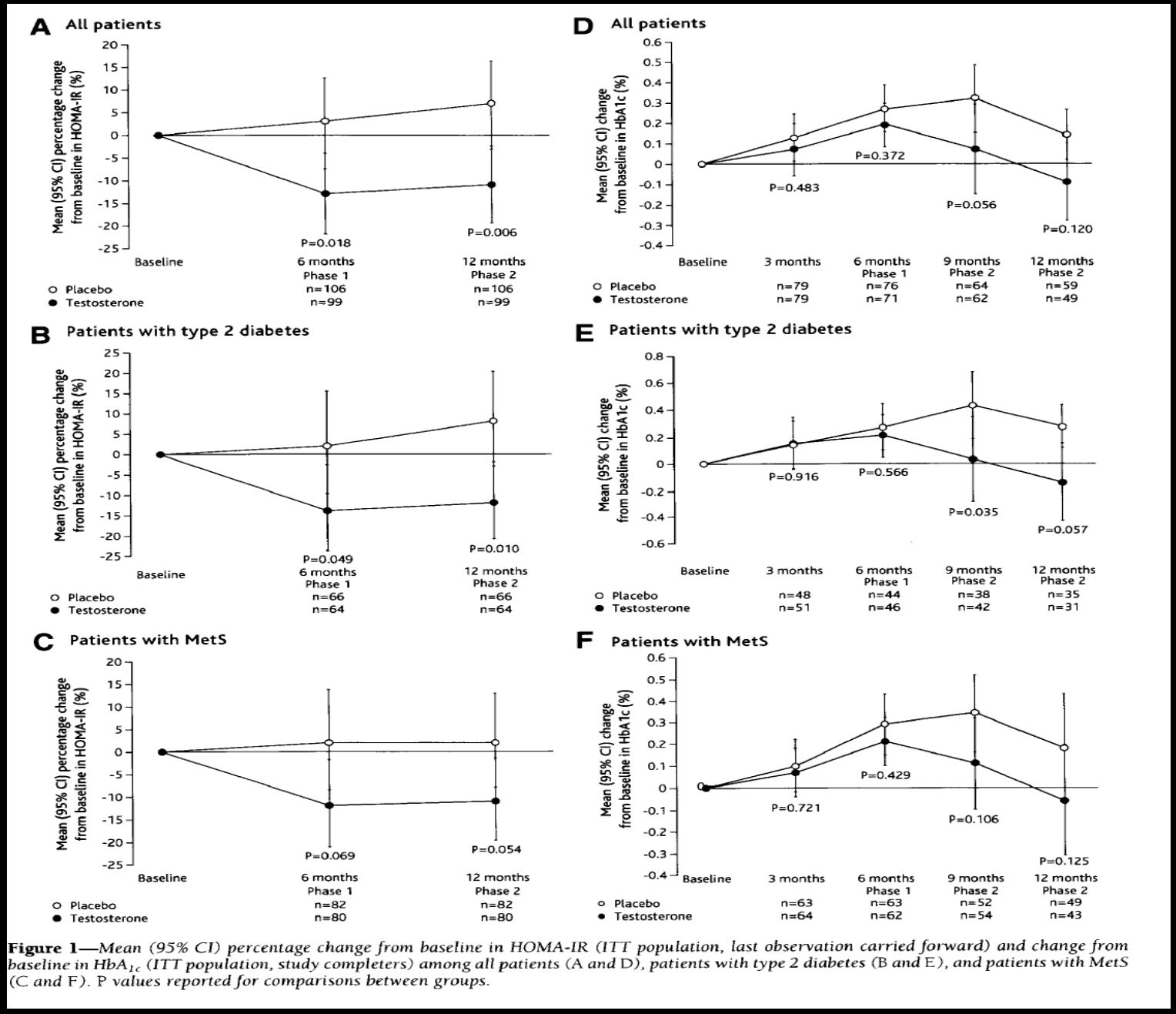


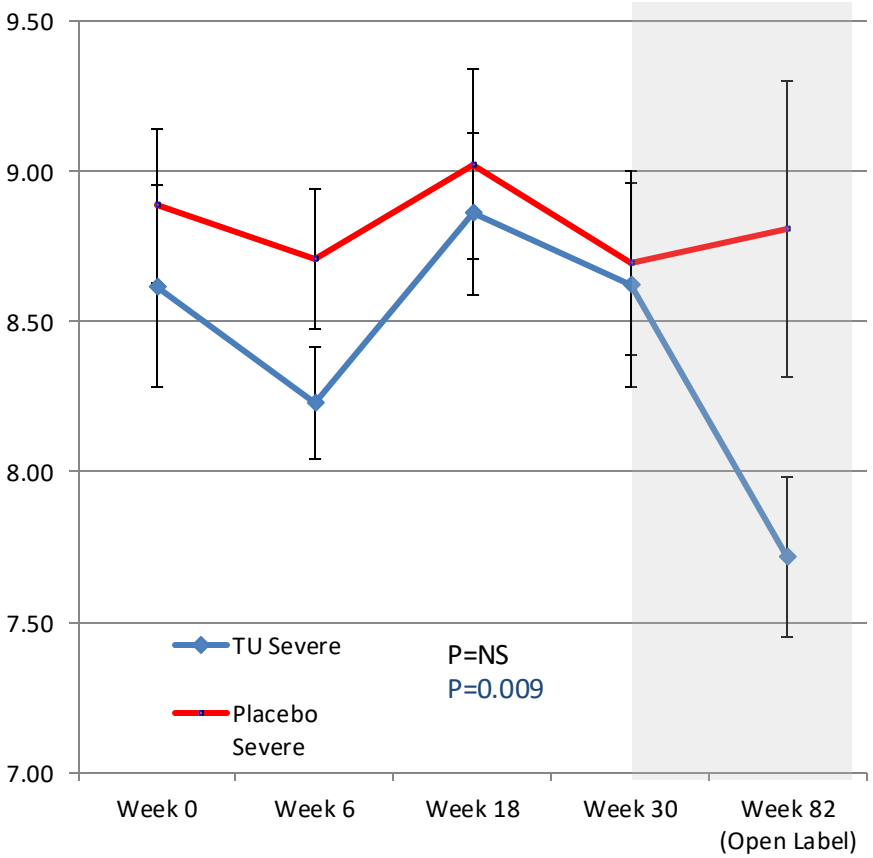
Figure 1—*Mean (95% CI) percentage change from baseline in HOMA-IR (ITT population, last observation carried forward) and change from baseline in HbA_{1c} (ITT population, study completers) among all patients (A and D), patients with type 2 diabetes (B and E), and patients with MetS (C and F). P values reported for comparisons between groups.*

Jones TH et al. Diabetes Care 2011;34:828-37

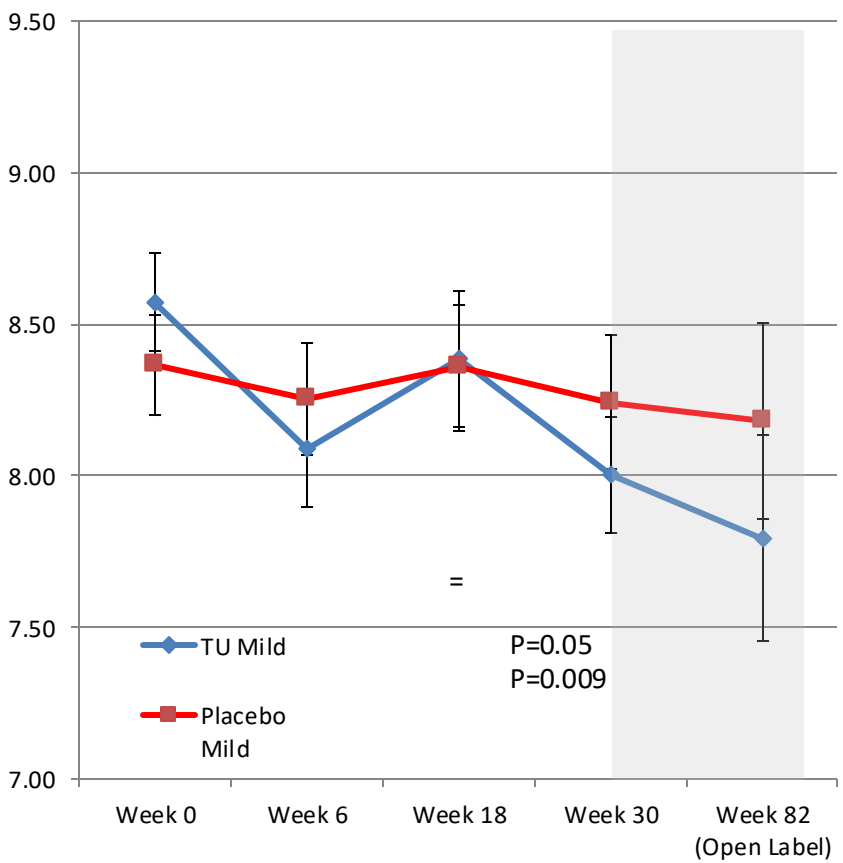
Treatment Effect in BLAST on HbA1c (Poor control HbA1c>7.5 (N=84)

TU: Long Acting I/M RCT 30WEEKS then Open Label (Week 30-82)

SEVERE HYPOGONADISM

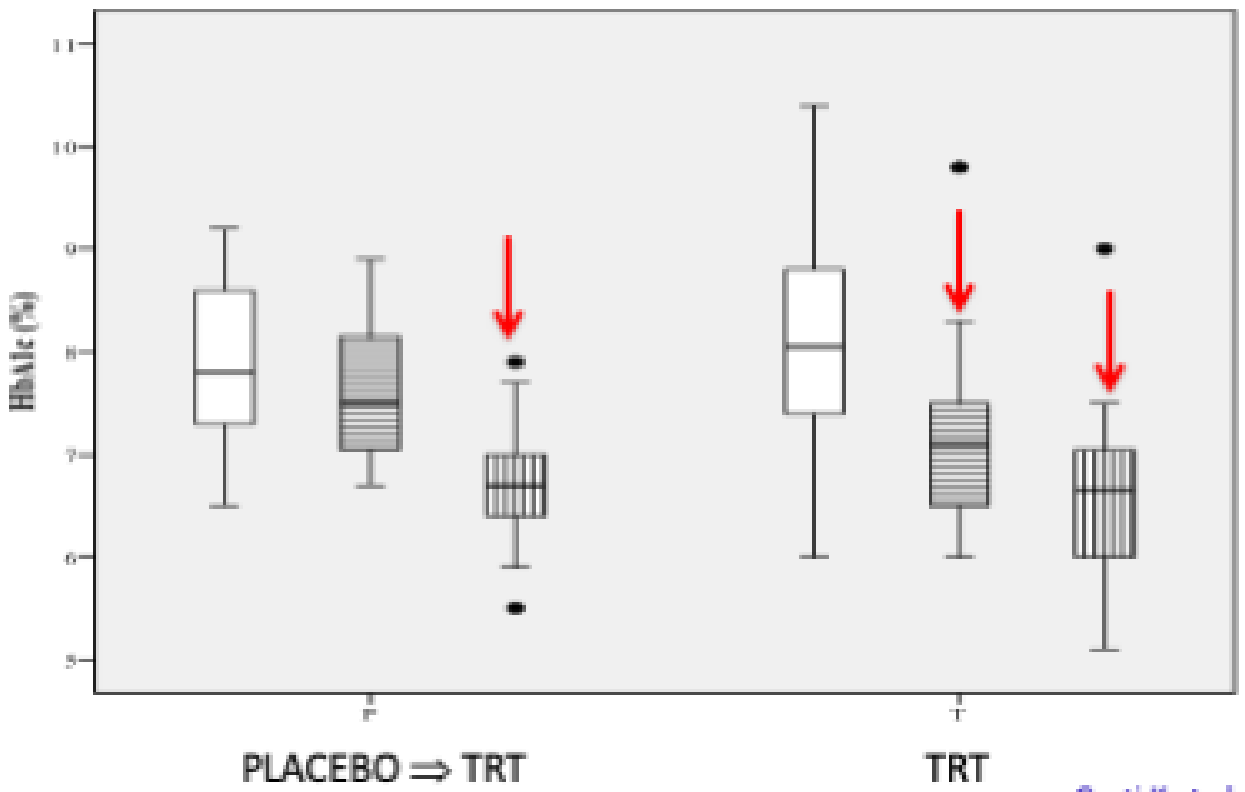


MILD HYPOGONADISM



Hackett G. et al. J Sex Med 2014;11:840-856

Impact of TRT on HbA1c



In group **T** at **1y** by
– 0 .94 ± 0.88 %
(p <0.001)

In group **P** at **2y** by
– 0.97 ± 0,54 %
(p <0.001)

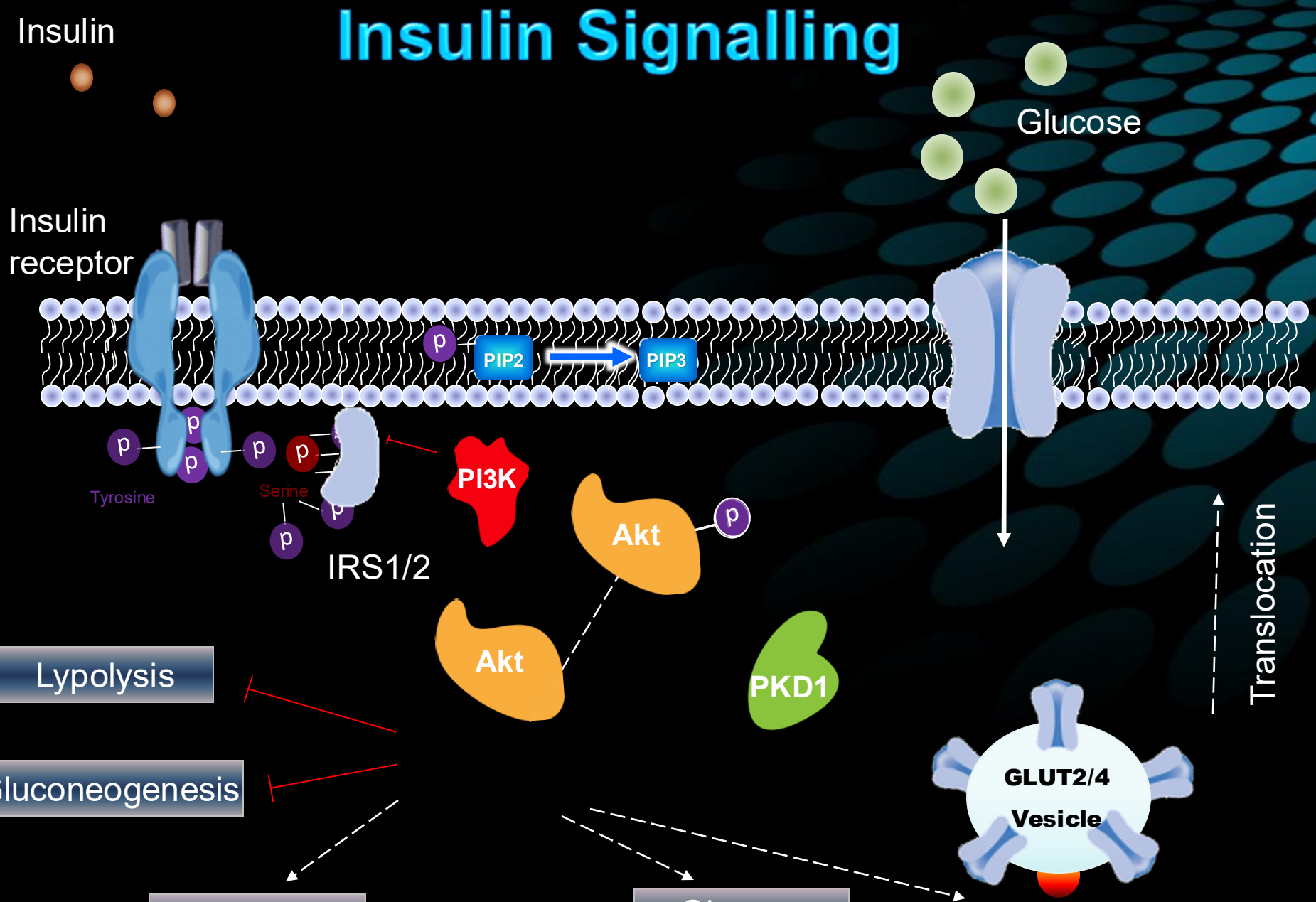
In group **T** at **2y**
additional
– 0.57 ± 0.33 %
(p <0.001)

Groti K et al. Aging Male 2018

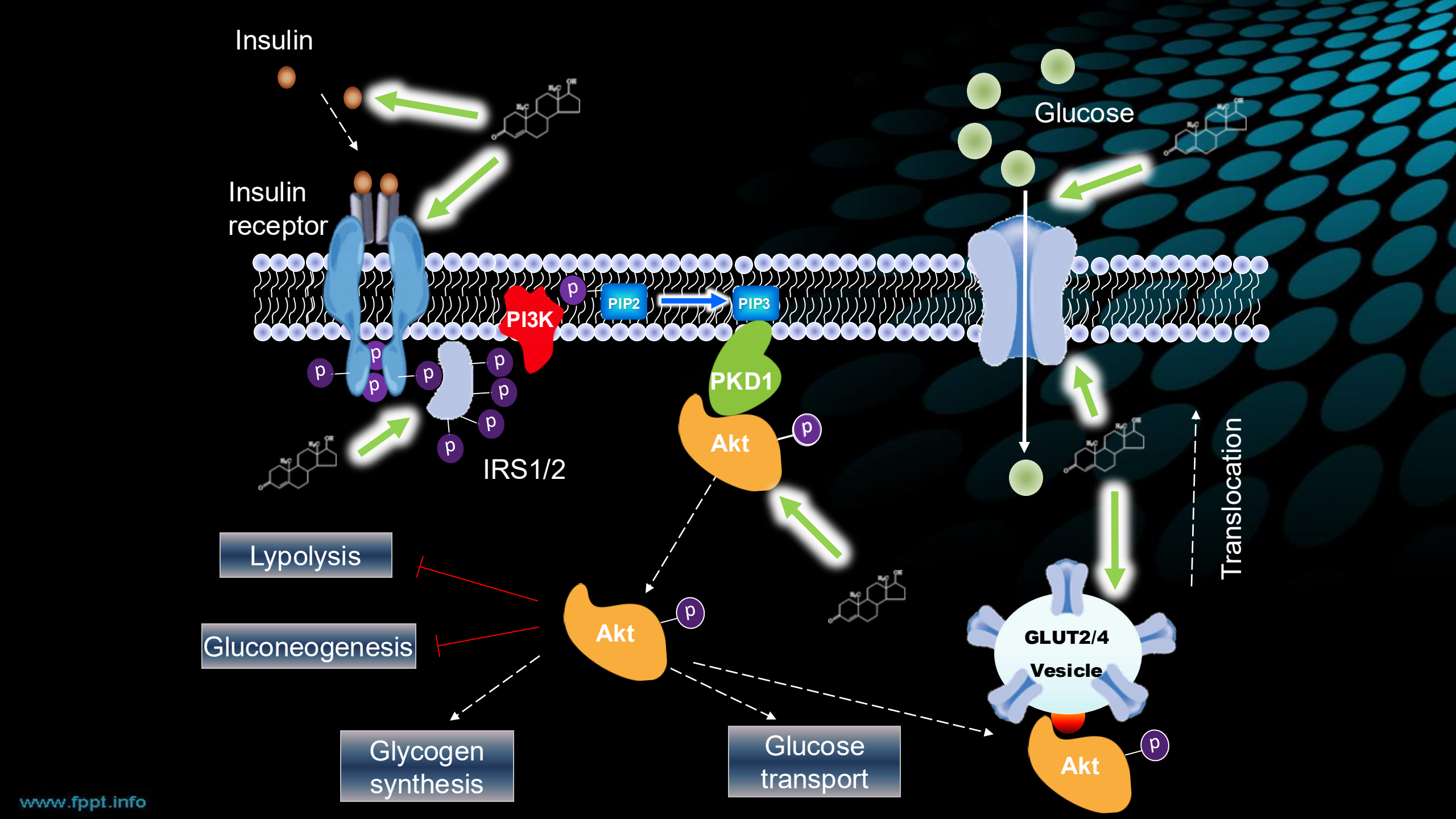
Groti K.et al. Aging Male 2018;21:158-169

Slide: courtesy Dr. M Pfeifer

Insulin Signalling



www.fppt.info

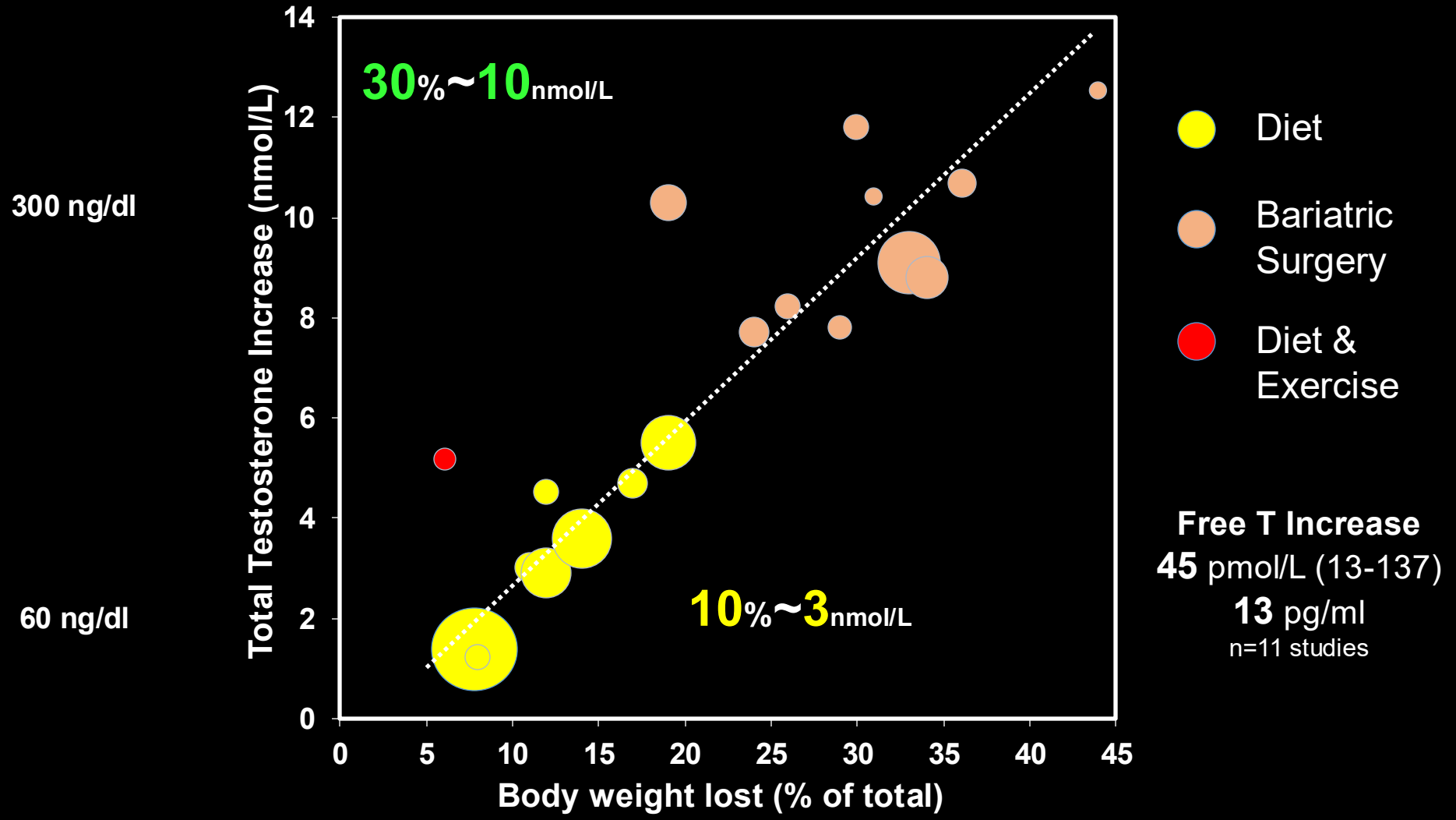


www.fppt.info

Weight Loss Increases Testosterone Concentrations

Baseline median (range): Age **44**y (21-62), BMI **46** kg/m^2 (26-56),Total T **11.4** nmol/L (10.6-14.1) **328** ng/dl

Number of men per study: 24 (10-891). RCTs = 6, controlled = 1, uncontrolled =12



Each data point refers to an individual study, and the size of the data point is proportional to the size of the study

For individual references see Grossmann, JCEM 2011 & JCEM 2017

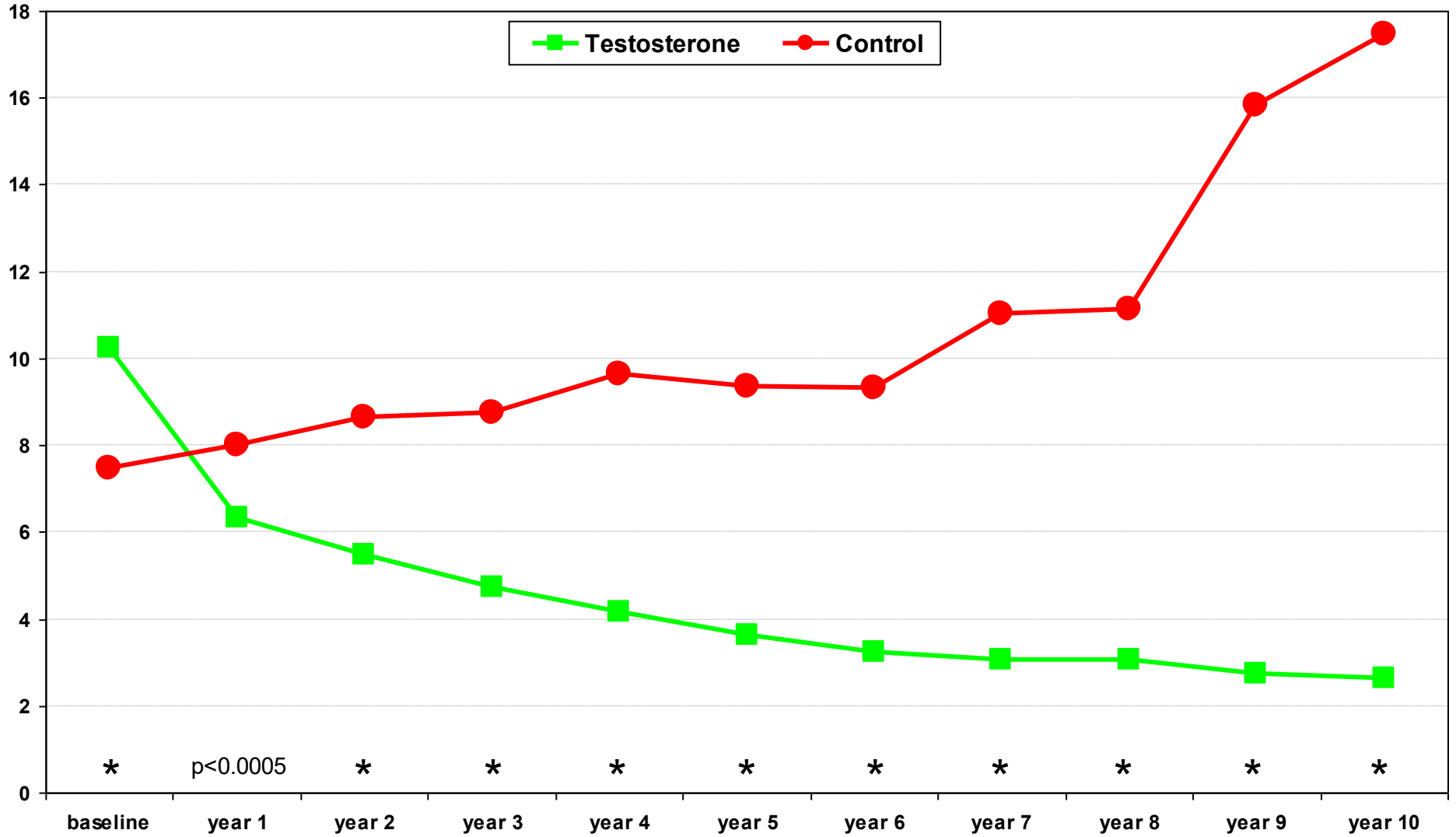
Improvement of Type 2 Diabetes (T2DM) in Hypogonadal Men with Long-Term Testosterone Therapy (TTh) is Sustained for up to 10 Years Compared to Untreated Controls

U Wissinger[1], A Haider[2], KS Haider[2], G Doros[3], A Traish[2], F Saad[1,5]

[1]Medical Affairs, Bayer AG, Berlin, Germany
[2]Private Urology Practice, Bremerhaven, Germany
[3]Department of Epidemiology and Statistics, Boston University School of Public Health, Boston, MA, USA
[4]Department of Biochemistry and Department of Urology, Boston University School of Medicine, Boston, MA, USA
[5]Gulf Medical University School of Medicine, Ajman, UAE

Wissinger U et al. Diabetologia 61 (Suppl. 1): S328 (2018)

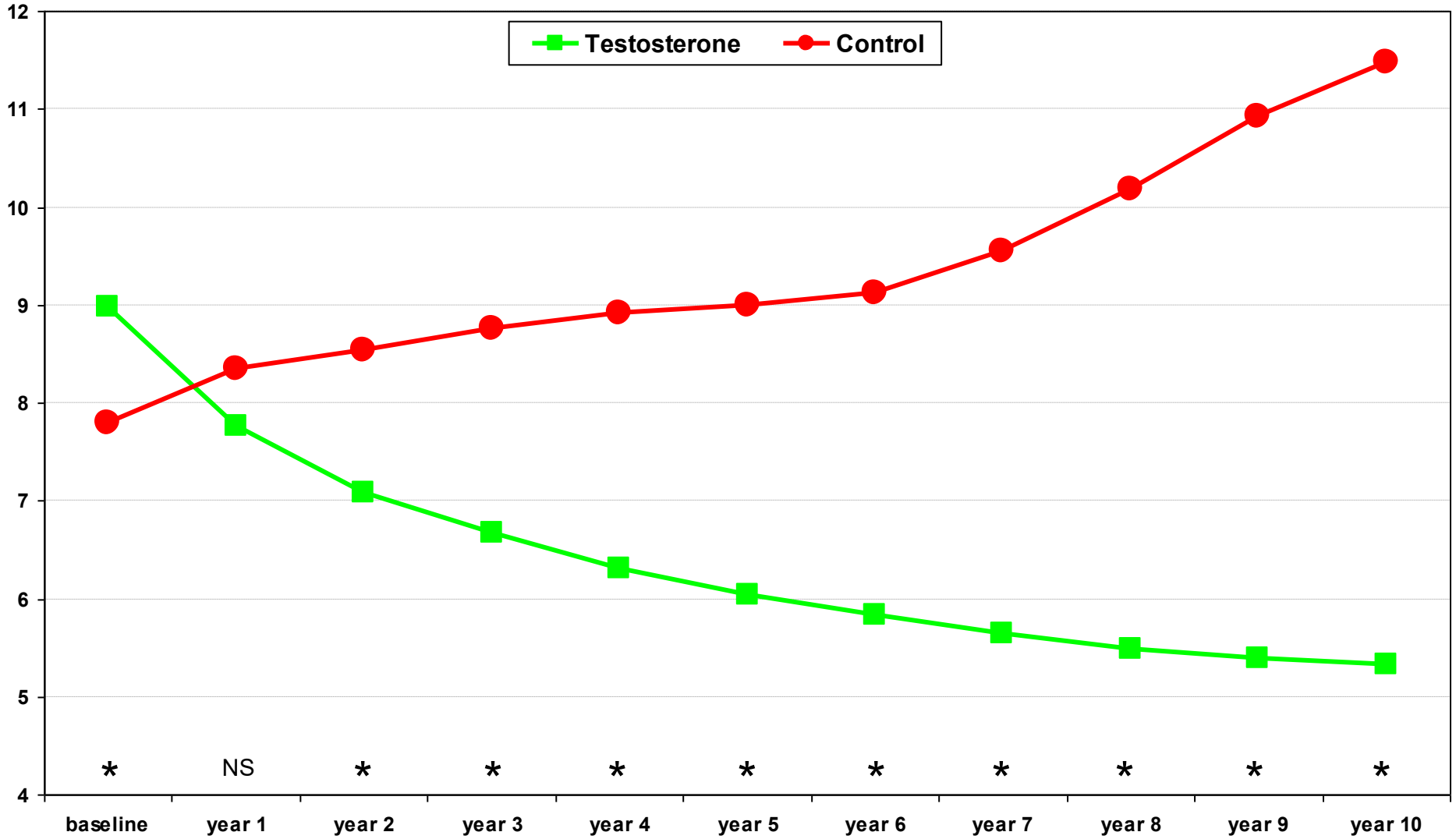
HOMA-IR in 141 hypogonadal men with T2DM on long-term treatment with testosterone undecanoate and 170 untreated hypogonadal controls



Data are shown as least squares means after adjustment for waist circumference, weight, fasting glucose, systolic and diastolic blood pressure, total cholesterol, HDL, LDL, triglycerides, QoL scale Aging Males Symptoms. *p<0.0001 between groups

Wissinger U et al. Diabetologia 61 (Suppl. 1): S328 (2018)

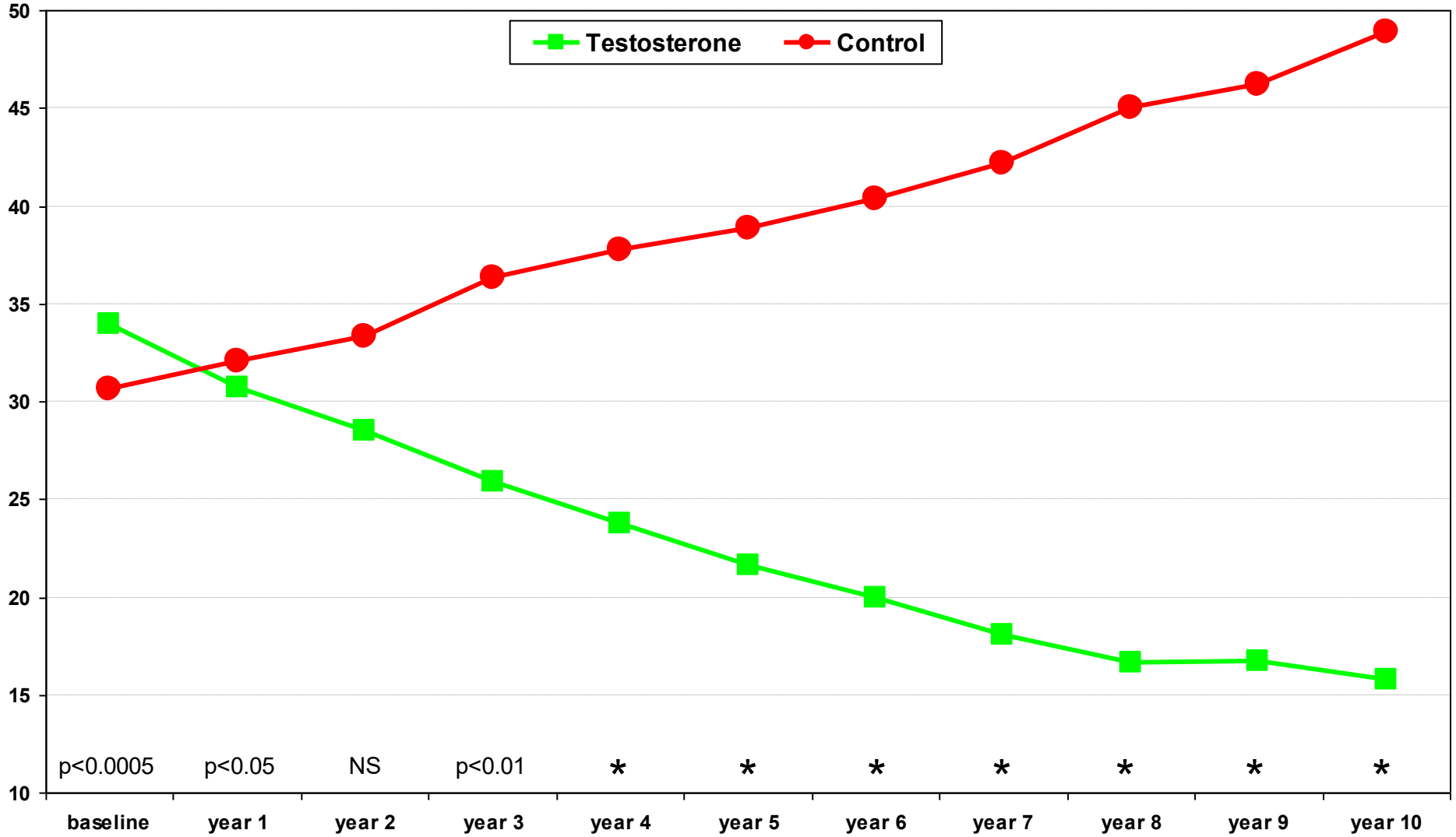
HbA_{1c} (%) in 141 hypogonadal men with T2DM on long-term treatment with testosterone undecanoate and 170 untreated hypogonadal controls



Data are shown as least squares means after adjustment for waist circumference, weight, fasting glucose, systolic and diastolic blood pressure, total cholesterol, HDL, LDL, triglycerides, QoL scale Aging Males Symptoms. NS=non-significant; *p<0.0001 between groups

Wissinger U et al. Diabetologia 61 (Suppl. 1): S328 (2018)

Insulin dose (U/d) in 61 hypogonadal men with T2DM on long-term treatment with testosterone undecanoate and 63 untreated hypogonadal controls



Data are shown as least squares means after adjustment for waist circumference, weight, fasting glucose, systolic and diastolic blood pressure, total cholesterol, HDL, LDL, triglycerides, QoL scale Aging Males Symptoms. NS=non-significant; *p<0.0001 between groups

Wissinger U et al. Diabetologia 61 (Suppl. 1): S328 (2018)

Remission of type 2 diabetes with Testosterone Therapy in Hypogonadal Men: 12-Year Data from a Registry Study

- 152 hypogonadal men with type 2 diabetes and total testosterone ≤12.1 nmol/L
- Mean follow-up was 8 years, maximum 12 years.
- 51 patients (34%) were in remission at the last measurement. Remission was defined as HbA1c <6.5% and not taking anti-hyperglycemic agents.
- Seventeen of these patients had been on insulin at baseline.
- The average time to discontinuation of diabetes medication was 9 years. How long have they been in remission on average? Any relapses?

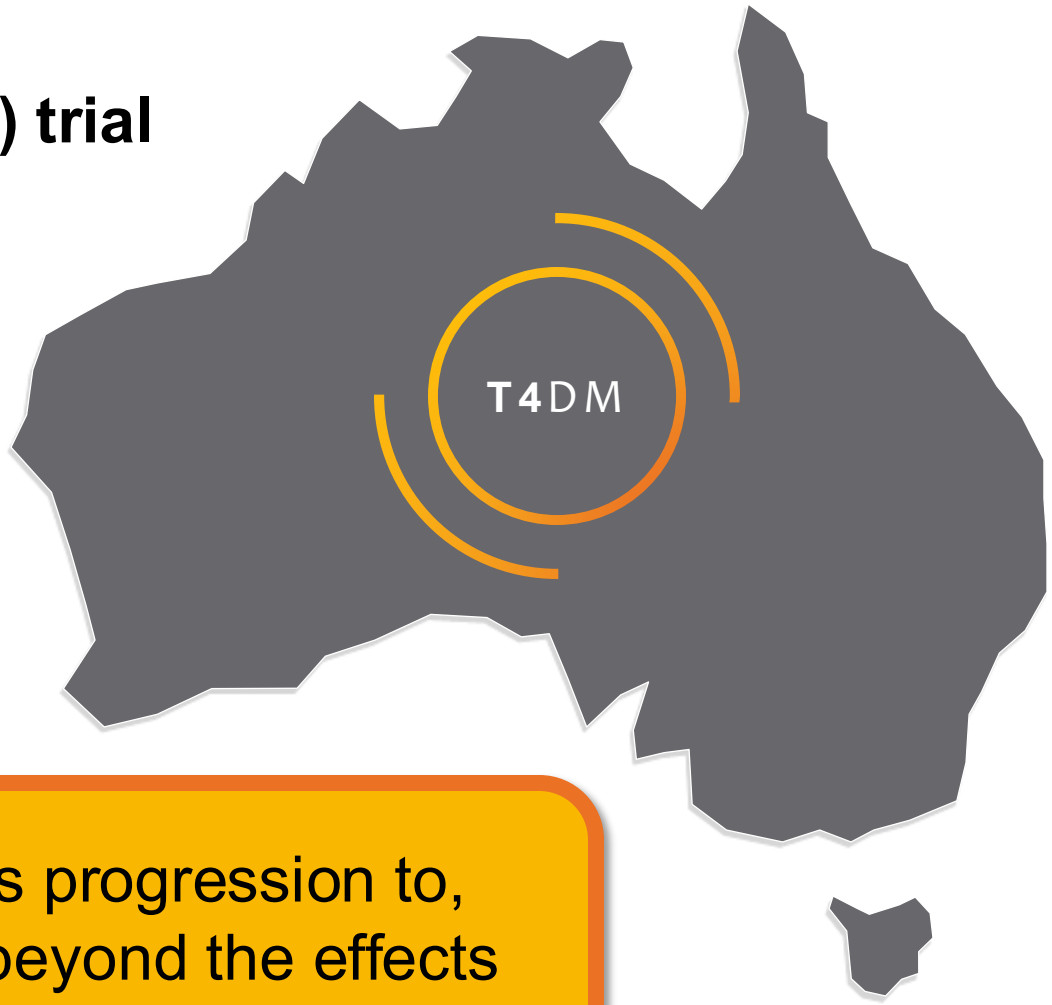
51 patients	baseline	End of follow-up
Hemoglobin A1c	8.6±1.0 %	5.5±0.2%
Weight (kg)	113±13	90±7
Waist circumference	111±8	98±5
HOMA-IR	9.8±2.7	2.0±0.5

Haider, Saad et al, Abstract, *American Diabetes Association* 2019

T4DM study: overview

The Testosterone for Diabetes Mellitus (T4DM) trial

- Randomized, double-blind, placebo-controlled, **2-year**, phase 3b trial
- Involved 6 Australian tertiary care centres
- Enrolled men with low testosterone levels (hypogonadism) and abdominal obesity



Aim

To determine whether TTh prevents progression to, or reverses early type 2 diabetes, beyond the effects of a community-based, standardized lifestyle program

TTh, testosterone therapy

Wittert G et al. Lancet Diabetes Endocrinol. 2021;9(1):32–45.

T4DM study: design

Population

- Abdominal obesity*
- Age 50–74 years
- Serum testosterone ≤14 nmol/L (hypogonadism)
- At risk of T2D or newly diagnosed with T2D**

1:1 Randomization

TTh group: 504 men

Lifestyle program§ + ♂ **Testosterone undecanoate 1000 mg** injection every 12 weeks for 2 years

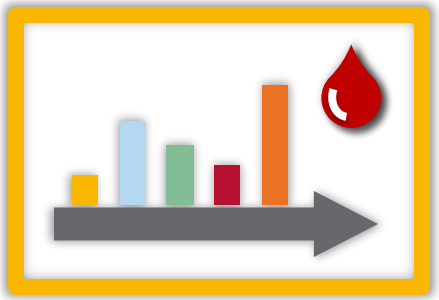
Placebo group: 503 men

Lifestyle program§ + ⊘ **Placebo** injection every 12 weeks for 2 years

*Waist circumference >95 cm; **A 2-h plasma glucose ≥7.8 to <11.1 mmol/L (≥140.4 to <199.8 mg/dL) (at risk) or ≥11.1 to ≤15.0 mmol/L (≥198.0 to ≤270.0 mg/dL) (newly diagnosed) in response to a 75 g oral glucose tolerance test; §Provided by WW (formerly Weight Watchers). T2D, type 2 diabetes; TTh, testosterone therapy

Wittert G et al. Lancet Diabetes Endocrinol. 2021;9(1):32–45; Wittert G et al. Diabetes Obes Metab. 2019;21:772–80.

T4DM study: endpoints



1° Co-primary endpoints

- **OGTT 2-h glucose ≥11.1 mmol/L [199.8 mg/dL]** (Proportion of patients with T2D at 2 years)
- **Mean change in 2-h glucose on OGTT at 2 years *vs* baseline**

2° Key secondary endpoints

- **Normalization of 2-h glucose on OGTT** (OGTT <7.8 mmol/L [140.4 mg/dL])
- **Initiation of pharmacotherapy for T2D**
- **Adherence to the lifestyle program and taking sufficient exercise**
- **Change *vs* baseline at 2 years in:**
  - Fasting glucose
  - HbA_{1c}
  - Bodyweight
  - Waist circumference
  - Body composition
  - Non-dominant hand-grip strength
  - Sexual function
  - LUTS
  - Hormonal profile

HbA_{1c}, glycated hemoglobin; LUTS, lower urinary tract symptoms; OGTT, oral glucose tolerance test; T2D, type 2 diabetes

Wittert G et al. Lancet Diabetes Endocrinol. 2021;9(1):32–45.

Summary

- In men with hypogonadism who were at risk of T2D (prediabetes) or were newly diagnosed with T2D, TTh + lifestyle intervention **reduced the prevalence of T2D after 2 years by 41%** *vs* lifestyle intervention alone (RR 0.59; p<0.001)
- Treatment with TTh + lifestyle intervention for 2 years resulted in **significant improvements in body composition, glucose regulation and physical ability** among men with hypogonadism
- In men with hypogonadism at risk of T2D (prediabetes), the proportion who progressed to T2D was 7.6% (n=355) with TTh + lifestyle intervention and 14.9% (n=329) with placebo + lifestyle intervention

TTh + lifestyle intervention **cut the risk of developing T2D by half** *vs* placebo (RR 0.51, 95% CI: 0.33 to 0.80)

CI, confidence interval; RR, relative risk; T2D, type 2 diabetes; TTh, testosterone therapy

Wittert G et al. Lancet Diabetes Endocrinol. 2021;9(1):32–45.

Summary (2)

- In men with hypogonadism and newly diagnosed T2D, TTh + lifestyle intervention seemingly **reversed T2D in 13.4% more men than with lifestyle intervention alone** (RR 0.70, 95% CI: 0.48 to 1.03)
- The safety profile of TTh was reassuring and in keeping with what is already known about TTh treatment, with no differences observed between groups in incident CV events or prostate events*
- A treatment-limiting increase in hematocrit to ≥54%, a prespecified safety trigger, was flagged in 106 (22%) of 491 participants treated with TTh
  - This proportion is within the range (2.5–40%) seen in other studies of TTh, and this increase in hematocrit led to cessation of treatment for 26 participants (25 [4.9%] in the TTh group)

*Benign prostatic hyperplasia-related hospital admissions and/or prostate cancer.
CI, confidence interval; CV, cardiovascular; RR, relative risk; T2D, type 2 diabetes; TTh, testosterone therapy

Wittert G et al. Lancet Diabetes Endocrinol. 2021;9(1):32–45.

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Wittert G et al. Lancet Diabetes Endocrinol. 2021;9(1):32–45.

TRAVERSE STUDY

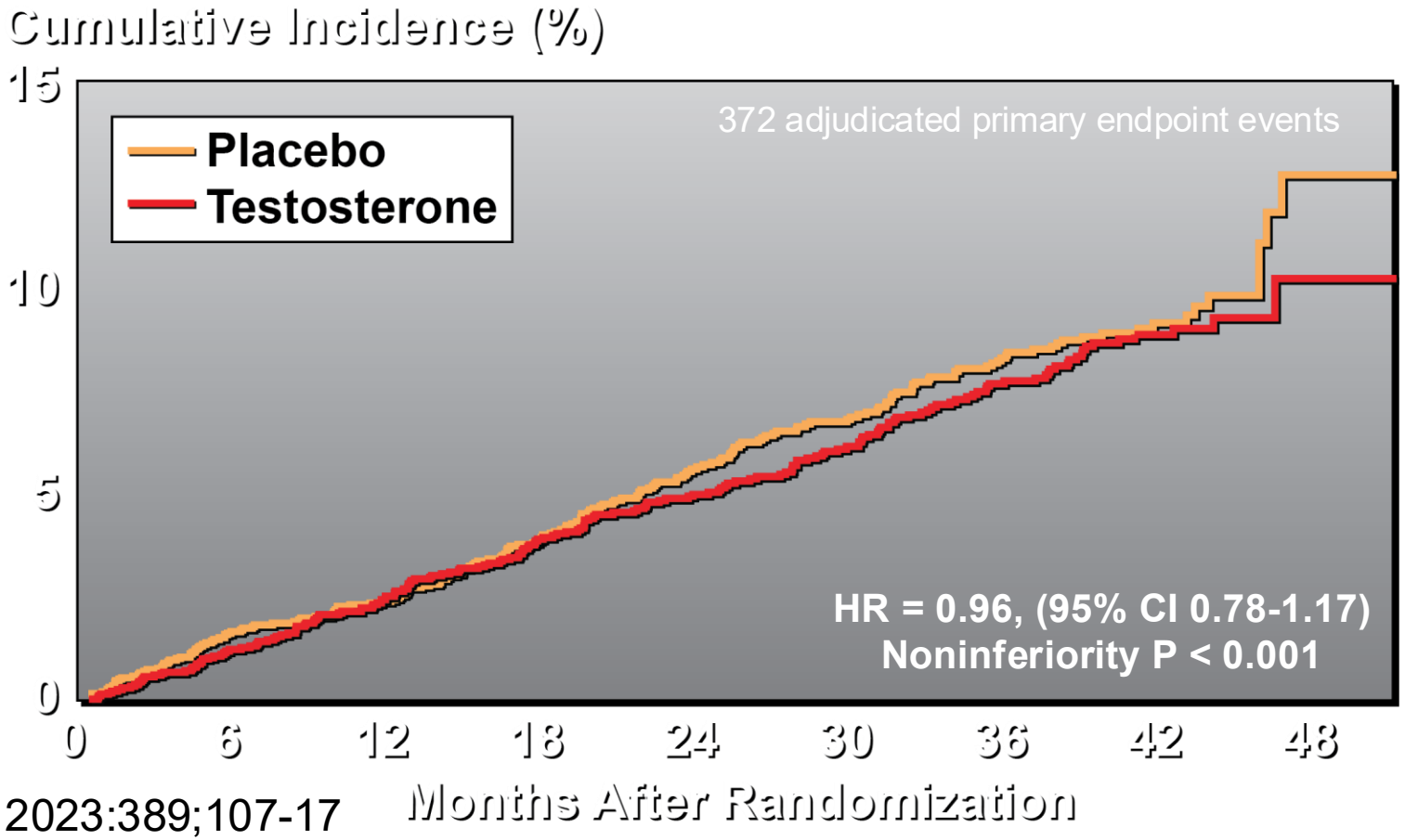
- Randomised Double-Blind T v Placebo Non-inferiority Trial
- Multicentre
- Age 45-80 years with Pre-existing or High Risk of Cardiovascular Disease and Hypogonadism
- n=5246
- Testosterone Gel Dose-adjusted to achieve Testosterone 12.1 -26.0nmol/l
- Mean Duration 21.7±14.1 months
- Mean Follow up 33.0+12.1 months
- Type 1 or Type 2 Diabetes in Study Population:

  T Group 68.7%; Placebo Group 70.8%

Lincoff AM, et al. NEJM 2023:389;107-117
DOI: 10.1056/NEJMoa2215025

TRAVERSE – Primary Cardiovascular Safety Endpoint [CV Death, Non-fatal MI, Non-fatal Stroke]

372 adjudicated primary endpoint events



Lincoff AM et al. NEJM 2023:389;107-17

Research

JAMA Internal Medicine | Original Investigation

Effect of Testosterone on Progression From Prediabetes to Diabetes in Men With Hypogonadism

A Substudy of the TRAVERSE Randomized Clinical Trial

Shalender Bhasin, MB, BS; A. Michael Lincoff, MD; Steven E. Nissen, MD; Kathleen Wannemuehler, PhD; Marie E. McDonnell, MD; Anne L. Peters, MD; Nader Khan, MD; Michael C. Snabes, MD, PhD; Xue Li, PhD; Geng Li, MS; Kevin Buhr, PhD; Karol M. Pencina, PhD; Thomas G. Travison, PhD

PRIMARY – Risk of Progression from Prediabetes to Diabetes defined as HbA1c >6.5%, initiation of diabetes medication or 2 Fasting Glucose > 125mg/dl.

SECONDARY – Glycemic remission in participants with Diabetes at baseline defined as HbA1c <6.5% 0r 2 consecutive FBG <126mg/dl without current use of antidiabetic medication.

JAMA Intern Med. doi:10.1001/jamainternmed.2023.7862
Published online February 5, 2024.

Key Points

Question Does testosterone replacement therapy (TRT) prevent progression from prediabetes to diabetes or induce glycemic remission in middle-aged and older men with hypogonadism?

Findings In this randomized clinical trial of 5204 participants aged 45 to 80 years with hypogonadism and prediabetes (n = 1175) or diabetes (n = 3880), the risk of progression from prediabetes to diabetes did not differ significantly between a group that received TRT and a placebo group and TRT did not improve glycemic control in men with prediabetes or diabetes.

Meaning This study did not provide evidence of TRT's efficacy in preventing progression from prediabetes to diabetes or improving glycemic control in men with hypogonadism.

BUT

- Not all patients had adequate Testosterone Replacement
- Glycemic Analysis not Optimum for Prediabetes OR well controlled Diabetes Subjects (Risk of Progression from Prediabetes to Diabetes defined as HbA1c >6.5%, initiation of diabetes medication or 2 Fasting Glucose > 125mg/dl).
- No evidence of Lifestyle Interventions or Change in Diabetes Drug Therapy
- Diabetes Patient Population is Heterogeneous in responses to Medications and Lifestyle Interventions
- Did not really consider Main Reasons Why we treat men with Testosterone Deficiency

This audit sets out to inform individual clinicians and to determine from several centres the clinical effects of testosterone therapy in men with type 2 diabetes and hypogonadism in real world clinical practise

This audit allows you to analyse the data of your own patients for your own local interest and at the same time the data will automatically be available for international analysis of anonymised data

Association of British Clinical Diabetologists

Association of British Clinical Diabetologists

WORLDWIDE AUDIT OF TESTOSTERONE DEFICIENCY IN MEN WITH TYPE 2 DIABETES

http://www.diabetologists-abcd.org.uk/Testosterone/Testosterone_Deficiency_Diabetes_Nationwide_Audit.htm

'In men with diabetes who have symptoms or signs of hypogonadism such as decreased sexual desire (libido) or activity, or erectile dysfunction, consider screening with a morning serum testosterone level'.

American Diabetes Association Standards of Medical Care in Diabetes 2022

Google "ABCD Testosterone Audit"

Free audit / Open to any HCP who uses testosterone therapy in diabetic patients
Primary and secondary care centres encouraged to participate / All contributors will be acknowledged in all papers and presentations / Biggest contributors will be offered the possibility of being co-authors

Purpose of the ABCD Worldwide Audit on Testosterone and Diabetes

- The audit sets out to help individual clinicians and to determine from several centres the clinical effects and monitoring of testosterone replacement therapy in men with type 2 diabetes and hypogonadism in real world clinical practice in the short and longer term.

- Data can be used from retrospective as well as new treatment prospectively.

- On-line audit tool forms for new and follow up clinic appointments as per routine patient management

- Patient details are encrypted and not visible to anyone else apart from the registered clinician / centre.

Supported Audit by grant from BesinsHealthcare, Grunenthal and Advanz Pharmaeuticals

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Purpose of ABCD Testosterone Audit (2)

- Identify reasons for which patients respond and those who do not in respect of glycemic control
- Risk of Hypoglycemic Episodes on TRT
- Is there a combination of diabetes drugs for glycemic control with testosterone therapy which is best to lower HbA1c
- Check Cardiovascular risk and other conditions
- Is there a difference in response between obese and overweight patients

AUDIT RECRUITMENT

- **40 Centres in 10 Countries** mainly UK but also in Germany, Canada, Brazil, South Africa, New Zealand, Malaysia, Vietnam
- Patients **460** recruited

- Three Year evaluable paired data on HbA1c
- BASELINE DATA (n=196)

  Mean Age **70.76** ± 9.35 years

  Weight **114.24** ± 17.54 kg

  Waist Circumference **104.8** ± 16.8 cm

  Testosterone **9.22** ± 1.74 nmol/l (**266**ng/dl)

  Aging Male Symptom Score (**AMS**) for Hypogonadism of 40.3/ 85 (Hypogonadism >30/85)

Testosterone Formulations – Testosterone Undeconoate (Nebido®) long-acting i/m injection, Testosterone gels (Testogel®, Tostran®).

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Glycaemic control (HbA1c) – 3 Year follow up

* P=<0.001		HbA1c (%)		
		6 Month	12 Month	36 Month
		(n=163)	(n=145)	(n=125)
Time (Months)	0	8.6%	8.6%	8.6%
	6	8.1%*		
	12		7.8%*	
	36			6.9%*

* P=<0.001

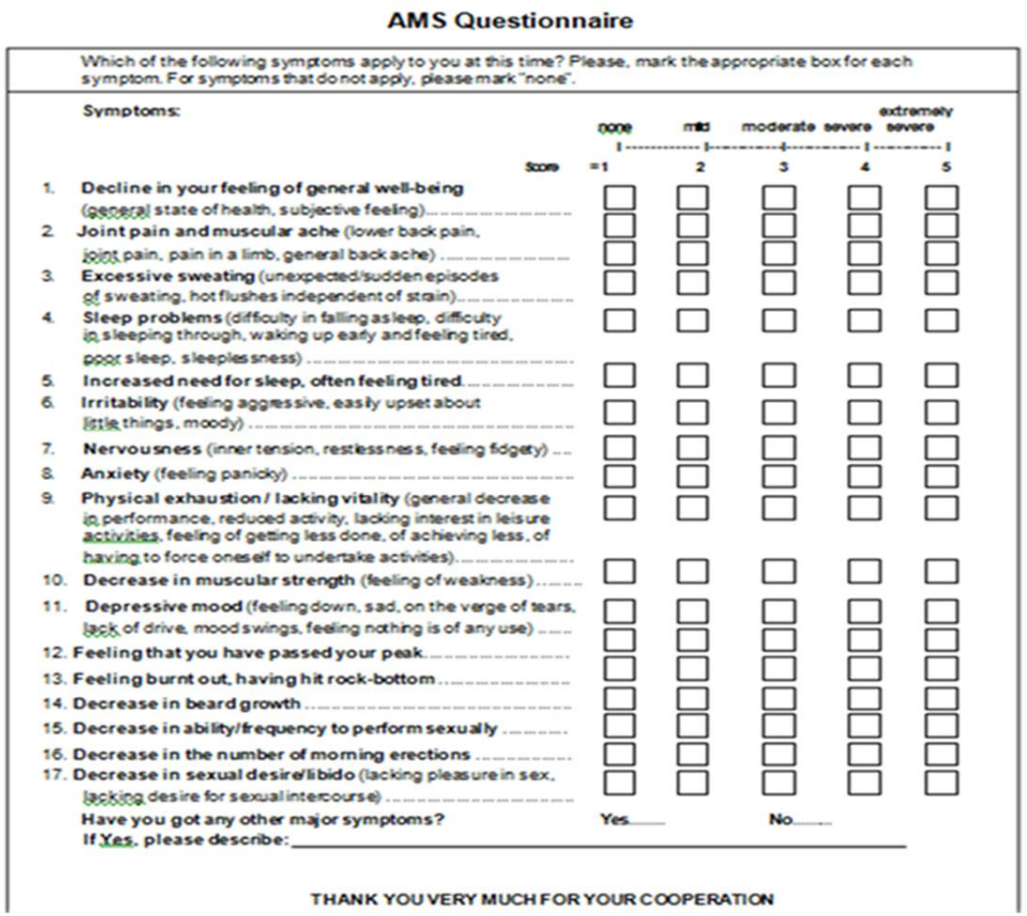
		HbA1c (mmol/mol)		
		6 Month	12 Month	36 Month
		(n=163)	(n=145)	(n=125)
Time (Months)	0	70.51	70.82	70.99
	6	64.96*		
	12		61.6*	
	36			51.7*

Statistical Analysis – t test: Paired two sample means, Pearson Correlation.

"The UK Prospective Diabetes Study (UKPDS) showed a linear relationship between mean HbA1c and T2DM-related endpoints, where for every 1% reduction in HbA1c there was a 21% lower risk of all-cause mortality" 1

1. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;321:405–12.

AMS (Aging Male Symptom) Score for Quality of Life and Symptoms of Testosterone Deficiency



AMS Questionnaire

Which of the following symptoms apply to you at this time? Please, mark the appropriate box for each symptom. For symptoms that do not apply, please mark "none".

Symptoms:	none	mild	moderate	severe	extremely severe
Score	=1	2	3	4	5
1. Decline in your feeling of general well-being (general state of health, subjective feeling)	☐	☐	☐	☐	☐
2. Joint pain and muscular ache (lower back pain, joint pain, pain in a limb, general back ache)	☐	☐	☐	☐	☐
3. Excessive sweating (unexpected/sudden episodes of sweating, hot flushes independent of strain)	☐	☐	☐	☐	☐
4. Sleep problems (difficulty in falling asleep, difficulty in sleeping through, waking up early and feeling tired, poor sleep, sleeplessness)	☐	☐	☐	☐	☐
5. Increased need for sleep, often feeling tired	☐	☐	☐	☐	☐
6. Irritability (feeling aggressive, easily upset about little things, moody)	☐	☐	☐	☐	☐
7. Nervousness (inner tension, restlessness, feeling fidgety)	☐	☐	☐	☐	☐
8. Anxiety (feeling panicky)	☐	☐	☐	☐	☐
9. Physical exhaustion / lacking vitality (general decrease in performance, reduced activity, lacking interest in leisure activities, feeling of getting less done, of achieving less, of having to force oneself to undertake activities)	☐	☐	☐	☐	☐
10. Decrease in muscular strength (feeling of weakness)	☐	☐	☐	☐	☐
11. Depressive mood (feeling down, sad, on the verge of tears, lack of drive, mood swings, feeling nothing is of any use)	☐	☐	☐	☐	☐
12. Feeling that you have passed your peak	☐	☐	☐	☐	☐
13. Feeling burnt out, having hit rock-bottom	☐	☐	☐	☐	☐
14. Decrease in beard growth	☐	☐	☐	☐	☐
15. Decrease in ability/frequency to perform sexually	☐	☐	☐	☐	☐
16. Decrease in the number of morning erections	☐	☐	☐	☐	☐
17. Decrease in sexual desire/libido (lacking pleasure in sex, lacking desire for sexual intercourse)	☐	☐	☐	☐	☐

Have you got any other major symptoms? Yes____ No____

If Yes, please describe: _____

THANK YOU VERY MUCH FOR YOUR COOPERATION

- SCORING of AMS
- 17-26 = Normal/low symptoms,
- 27-36, mild symptoms,
- 37-49, moderate symptoms,
- >50 Severe symptoms

Effect of Testosterone Therapy on Symptoms and Quality of Life

AMS SYMPTOMS TOTAL SCORE

*** P=<0.001**

		AMS TOTAL SCORE			
		3 Month	6 Month	12 Month	24 Month
		(n=168)	(n=202)	(n=174)	(159)
Time (Months)	0	55.86	55.95	54.5	54.12
	3	27.39*			
	6		27.32*		
	12			21.74*	
	24				19.09*

Weight and Waist Circumference

	Baseline	12 months	p value
Weight (kg)	112.6	107.15	0.6
Waist (cm)	116.08	115.12	0.43

Statistical Analysis – t test: Paired two sample means, Pearson Correlation.

CONCLUSIONS

- Early evidence that Testosterone replacement in a population of men with Type 2 Diabetes is associated with a reduction in HbA1c over 3 years.
- Improvement in QoL and Symptoms of Sexual Function.

- The audit with a greater number of patients inputted and longer-term data is likely to provide valuable data on which patients are those which respond and those who may not.

TESTOSTERONE DEFICIENCY IN MEN WITH TYPE 2 DIABETES

- **High prevalence - 40% of men with type 2 diabetes have symptomatic testosterone deficiency.**

- **Testosterone deficiency is associated with an adverse effect on cardiovascular risk factors, osteoporosis, muscular strength (including frailty), anaemia, sexual dysfunction and psychological well-being.**

- **Testosterone replacement therapy (TRT) in T2DM has been shown to:**

  Improves insulin resistance **and in some studies lower HbA1c.**

  Reduce body weight and Waist Circumference.

  Can improve Sexual Function and Quality of Life

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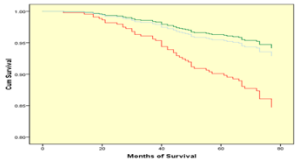
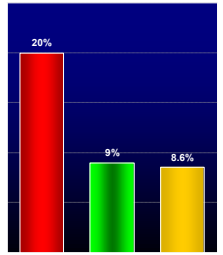
Kapoor D. et al. Eur J Endocrinol 2006:154;899-906. JonesT.H. et al. Diabetes Care 2011:34;828-837. Hackett G et al. J Sex Med 2014:11;840-856. Dhindsa S, et al. 2016:39;82-91. Groti K. et al. Aging Male 2018:21;158-169. Haider KS et al. Diab Obes Metab 202011;2055-68. Rao PM & JonesTH, J Endocrine Society(Suppl 1) 2022:6;A702-A703.

TRT – Mortality, Protection, Remission and CV Safety

- **Testosterone deficiency is also associated with an increased mortality** in type 2 diabetes and independently in cardiovascular disease (n=581, mean follow up 5.8 years). Testosterone therapy Improves reduces mortality by TWO-FOLD.

  Muralheedharan V. et al. Eur J Endocrinol 2013:169;725-733





- T4D RCT - **Testosterone replacement and Lifestyle Intervention reduces the progression of Prediabetes to Overt Diabetes by TWO-FOLD** and can lead to 13% remission of newly diagnosed diabetes compared to Lifestyle alone over 2 years (n=1007).

  Wittert G et al. Lancet Diab Endocrinol 2020:9;32-45

- TRAVERSE STUDY – **Cardiovascular safety study showed no evidence of increased risk of MACE** in Testosterone v Placebo in men with Pre-existing or a High Risk of CV Disease (n=5246). 75% patients in each arm had Type 2 Diabetes.

  Lincoff AM et al. New Eng J Med 2023:DOI: 10.1056/NEJMoa2215052

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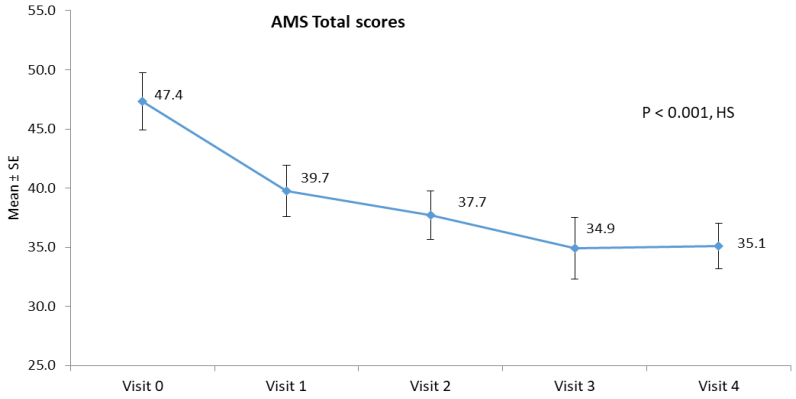
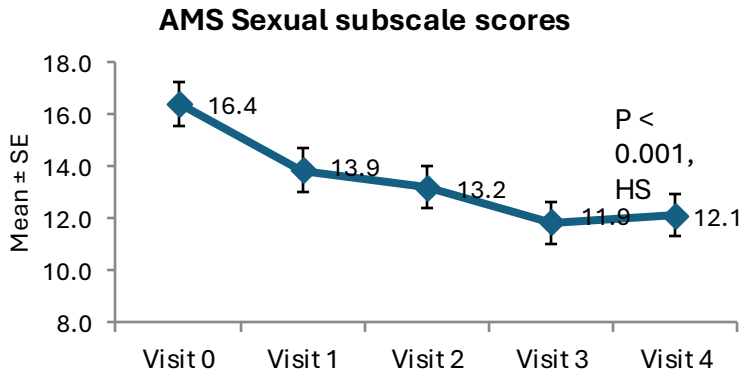
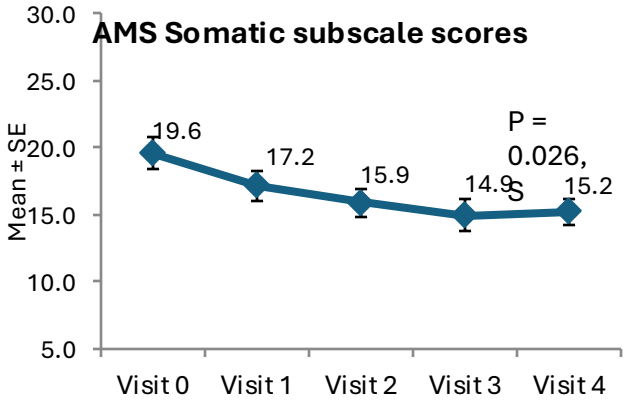
STUDY OF TESTOSTERONE REPLACEMENT IN UNCONTROLLED TYPE 2 DIABETIC HYPOGONADAL MEN- STRIDE Study

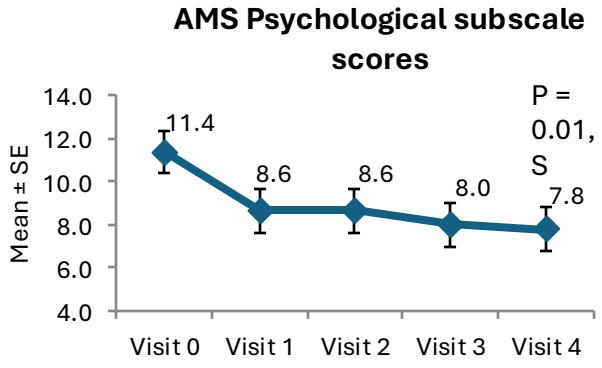
EFFECT ON QUALITY OF LIFE (AMS SCORE)

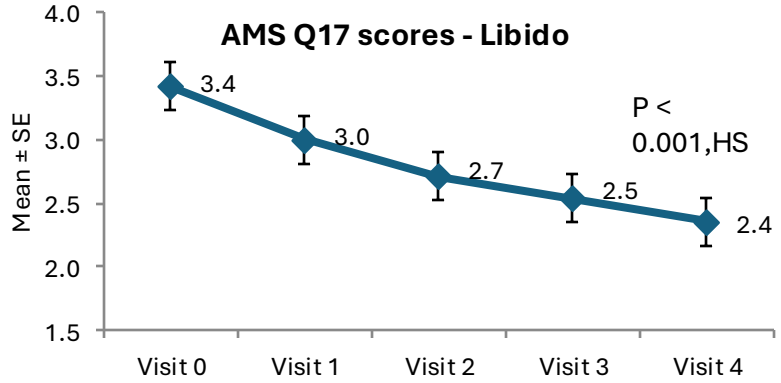
RCT T Undeconoate i/m v
Placebo 6 months
Open-Label to 12 months



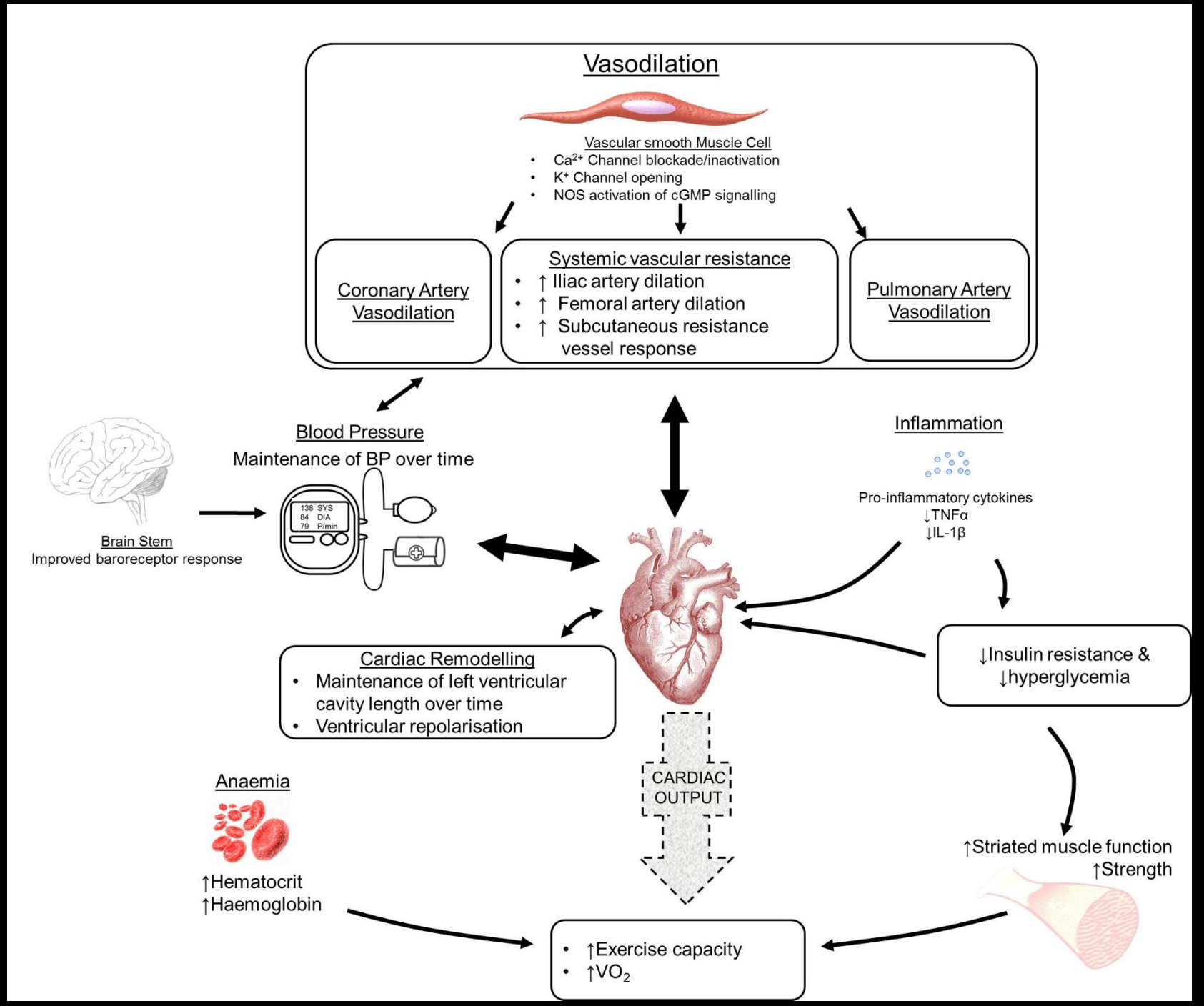








Potential Sites for Beneficial Actions of Testosterone on Cardiac Function in Heart Failure



Historical Basis for Concern

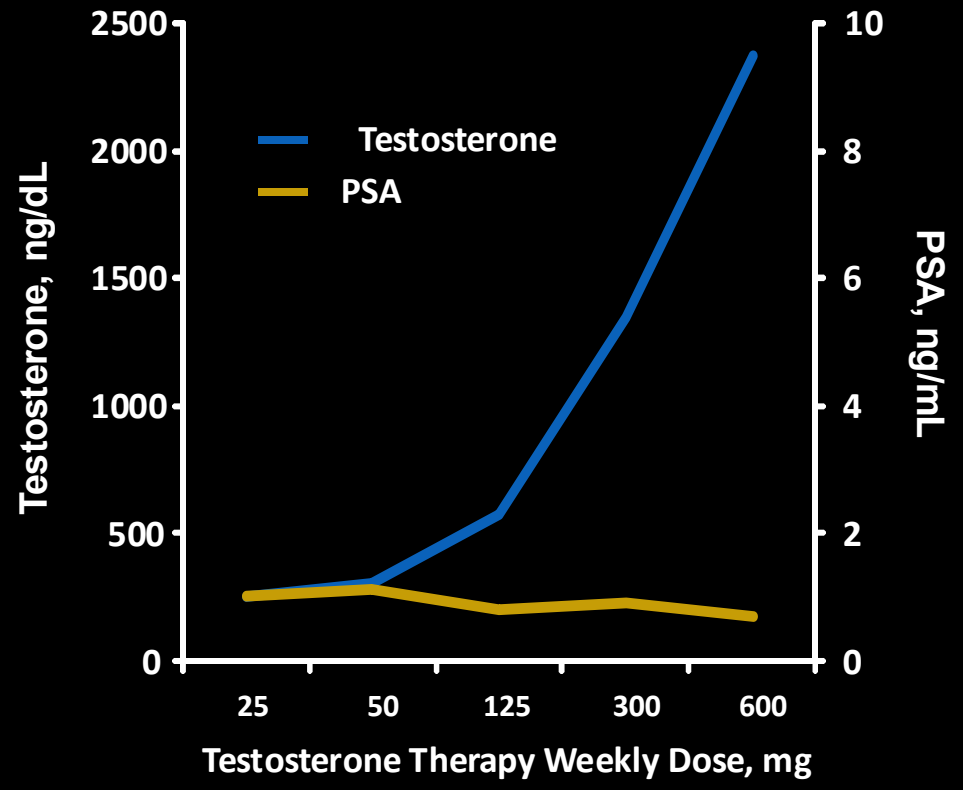
In 1941 – Huggins & Hodges reported:

1. **Reducing T to castrate levels caused prostate cancer to regress**
2. **Administration of exogenous T caused prostate cancer to grow**

(based on a single patient)

PSA at Supraphysiologic Levels of Testosterone

- Testosterone 600 mg or placebo weekly for 10 weeks
- PSA did not change significantly from baseline despite supraphysiologic testosterone levels (>2500 ng/dL)



Bhasin S et al. *N Engl J Med.* 1996;335(1):1-7.