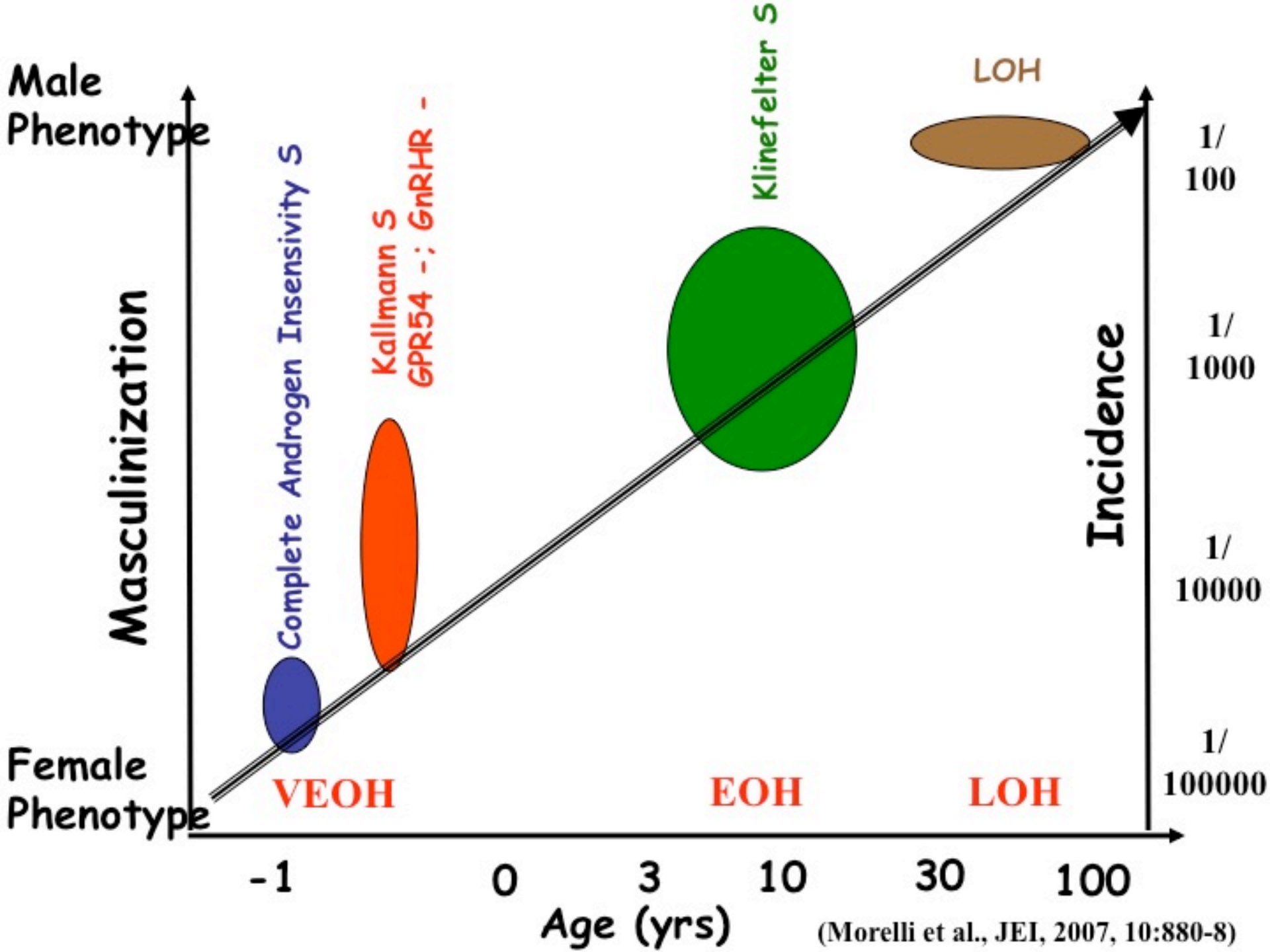
UTILIZZO NON CONVENZIONALE DEL TESTOSTERONE

VA GIAGULLI, PD, PhD
UO TERRITORIALE DI ENDOCRINOLOGIA E
MALATTIE METABOLICHE
OSPEDALE "F JAIA" ASL BARI

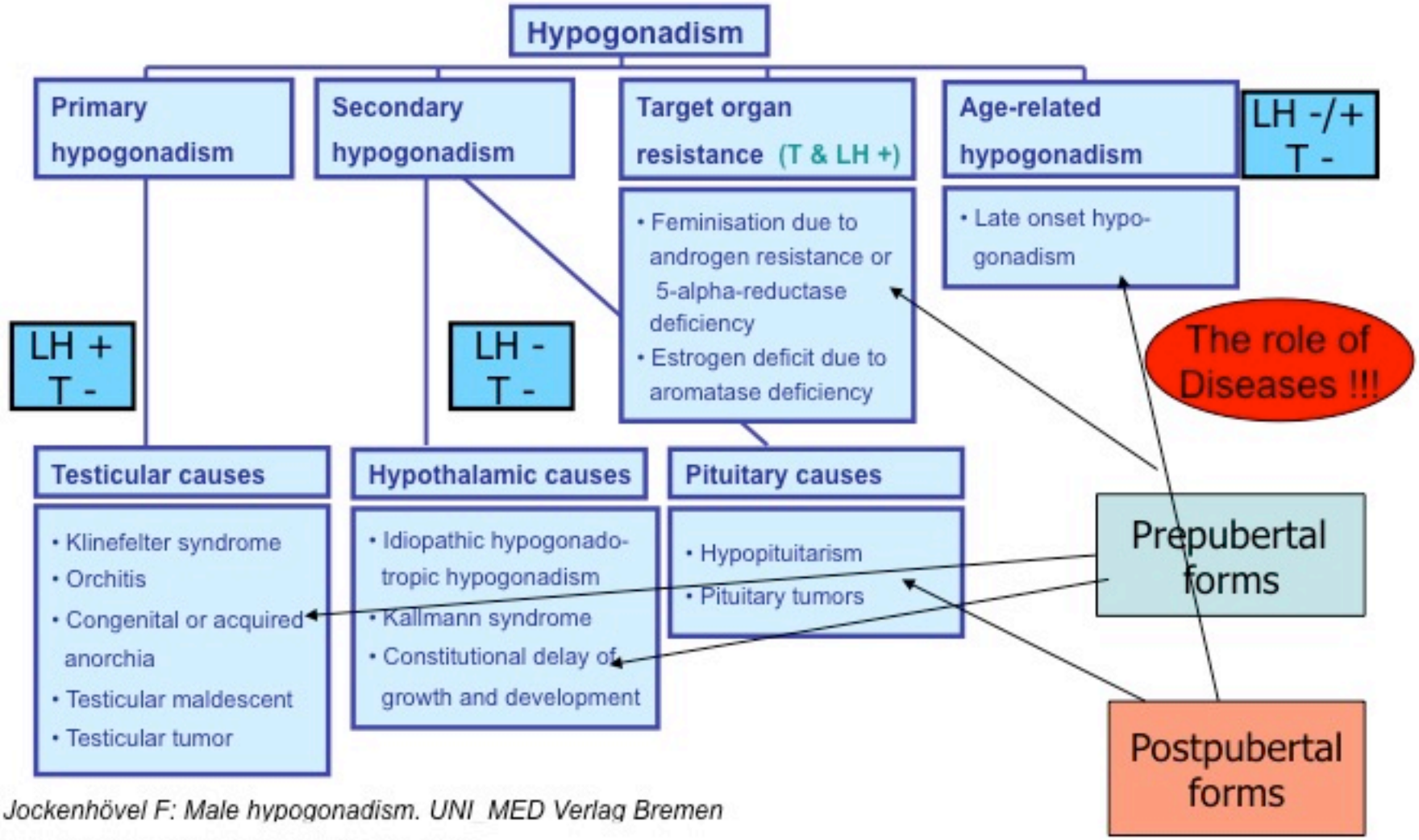
Unconventional use of Testosterone treatment

(i.e. there have been no guidelines so far)

- Micropenis
- Puberty induction
- Cognitive dysfunction/depression
- Metabolic effects (Obesity, Metabolic Syndrome, Type 2 Diabetes Mellitus and Cardiovascular diseases)
- Late-onset hypogonadism/Ageing


Male Phenotype
Female Phenotype
Masculinization
Complete Androgen Insensivity S
Kallmann S
GPR54 -; GnRHR -
Klinefelter S
LOH
Incidence
1/ 100
1/ 1000
1/ 10000
1/ 100000
VEOH
EOH
LOH
-1
0
3
10
30
100
Age (yrs)
(Morelli et al., JEI, 2007, 10:880-8)

Male hypogonadism - classification



Jockenhövel F: Male hypogonadism. UNI MED Verlag Bremen

VA Giagulli et al Curr. Pharm. Des, 2011

Co-morbidity prevalence with low serum T levels in aldult end elderly men

(Mulligan T et al, Int J Clin Prac, 2006)

AACE, 2002	ISA, ISSAM, EAU, EAA and ASA	EMAS
TT<7 nmol/L	TT<8 nmol/L and FT<225 pmol/L	TT<11nmol/L and FT<220 pmol/L
• Low libido • Erectile dysfunction • Decreased muscle mass • Menopausal-type hot flushes (with acute onset of hypogonadism) • Slow growth of body hair • Poor ability to concentrate • Oligospermia and azoospermia	• Low libido • Erectile dysfunction • Decreased muscle mass and strength • Increased body fat • Decreased body mineral density and osteoporosis • Decreased vitality • Depressed mood	• Low libido • Erectile dysfunction • Decreased frequency of morning erection

Condition			5% CI)
Hyperte			93)
Hyperli			58)
Diabete			22)
Obesity			72)
Prostati			76)
Chronic			01)
Insomni			86)
Asthma			62)
Headaches (within the last 2 weeks)	70 (8.4)	125 (9.4)	0.405
Rheumatoid arthritis	28 (3.3)	29 (2.2)	0.101
Osteoporosis	15 (1.8)	15 (1.1)	0.199
Not reported	0 (0.0)	4 (0.3)	nr

Prostatic disease/disorder	41.9 (36.4–46.2)	1.29 (1.03–1.62)
Chronic pain	38.8 (33.7–44.0)	1.13 (0.89–1.44)
Headaches (within last 2 weeks)	32.1 (25.3–38.8)	0.81 (0.58–1.11)

CI, confidence interval; COPD, chronic obstructive pulmonary disease.

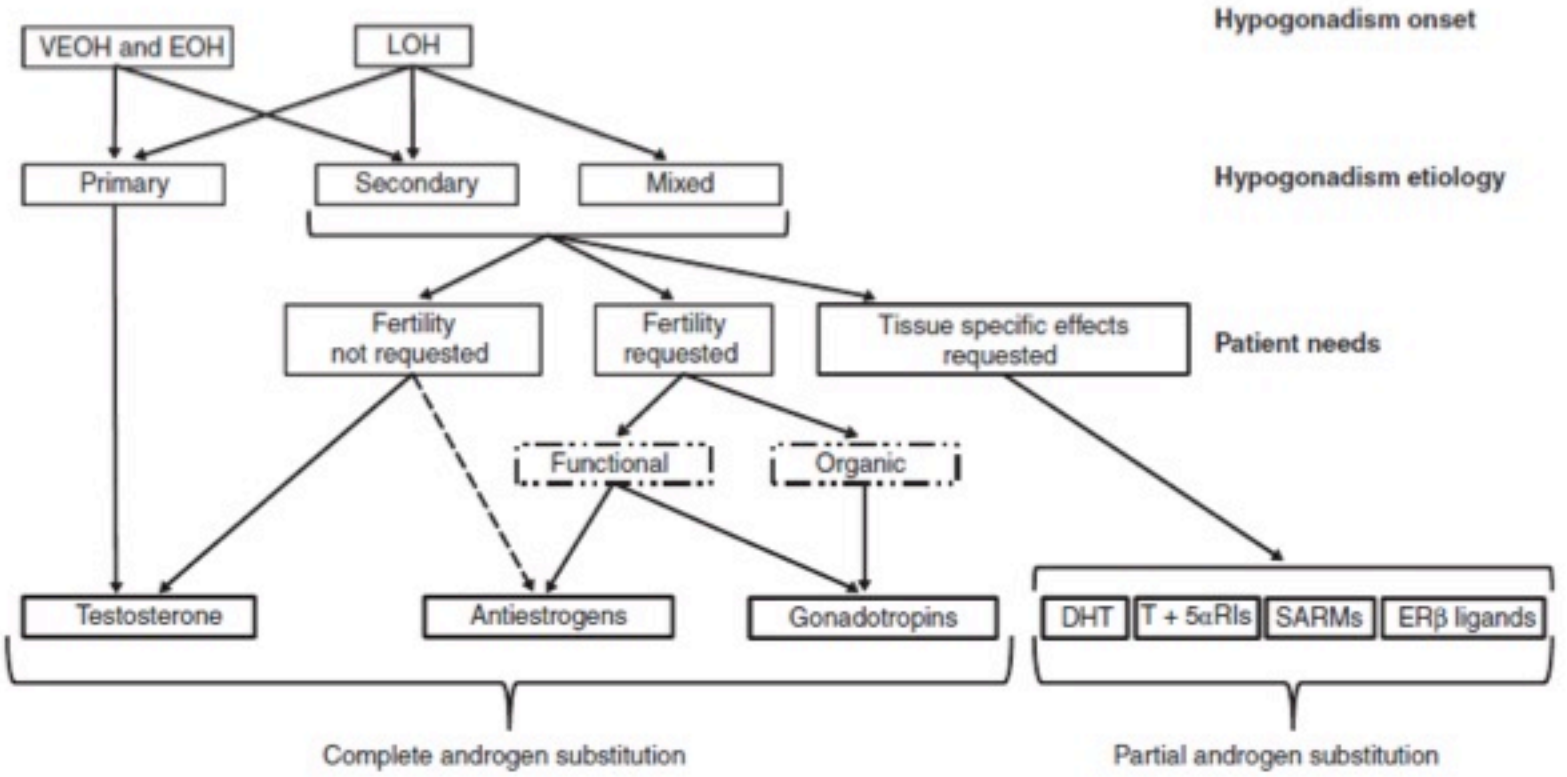


Figure 3. Suggested approach to male hypogonadism according to the age onset and etiology of the problem and patient needs.

Corona et al Exp Opin Emergin Drug, 2012

Current Testosterone Formulations on Market

	Generic name	Commercial name	Doses
INJECTABLE	*Testosterone propionate*	Testovis®	100 mg every 2-4 weeks
	Testosterone enantate	Testoviron® Dep.	200-400 mg every 2-4 weeks
	Testosterone undecanoate	Nebid®	1000 mg every 10-14 weeks
ORAL	*Testosterone undecanoate*	Andriol®	120-240 mg /day
TRANS-DERMAL	*Testosterone patch*	Androderm® Testopatch®	2.5-5 mg/day 1.8-2.4 mg/day
	Testosterone gel	Testogel® Androgel® Testim®	50-100 mg/day
		Tostrex®	60-80 mg/day
BUCCAL	*Buccal Testosterone*	~~Striant®~~	30 mg 2 times a day

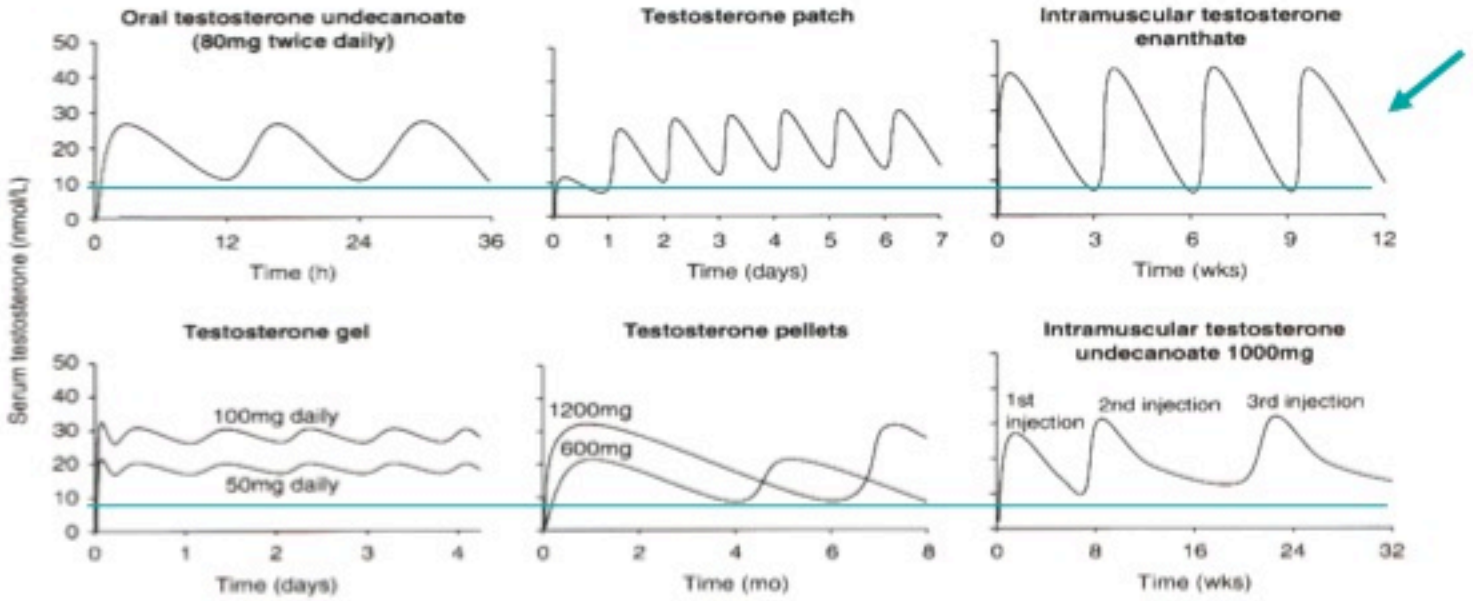
?

?

Testosterone Pellets ???

Giagulli et al Curr.Pharm.Design,2011

Serum T in different forms of T application



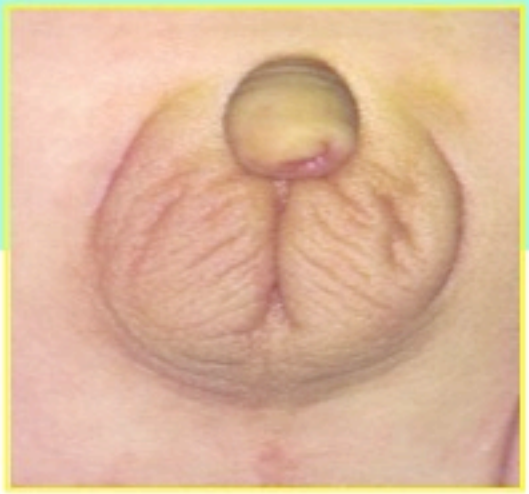
L J.G.Gooren and M.C.M. Bunck
Drugs 64,2004

MICROPENIS

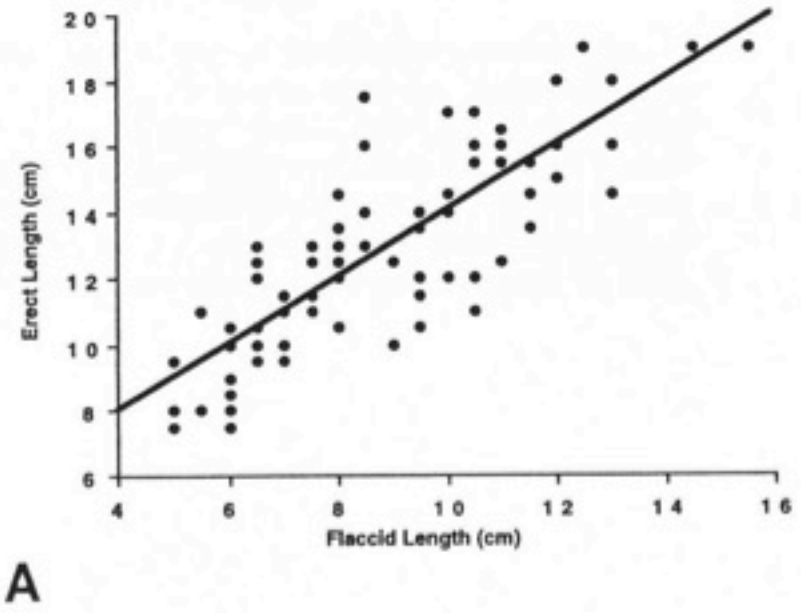
·Normal mophology with < 2 DS of the mean penis length compared with normal childern

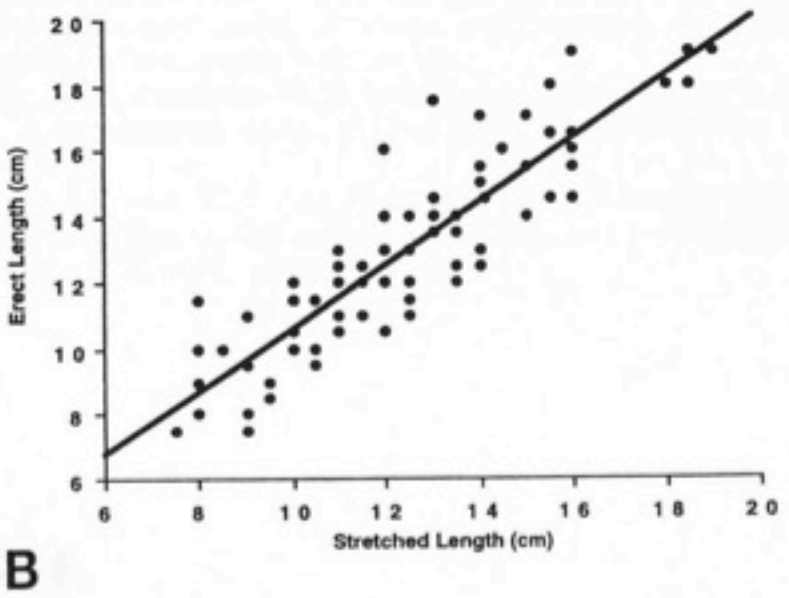
·Reduction of androgen secretion in 2th and 3th trimester of pregnancy

·It is associated with chromosome abnormalities (Klinefelter S, 8,13,18 chromosomes traslocation, X polysomy) and/or gondal disgenetic and/or androgen insensivity (PAIS)



CORRATION BETWEEN FLACCID LENGTH AND STRETCHED LENGTH

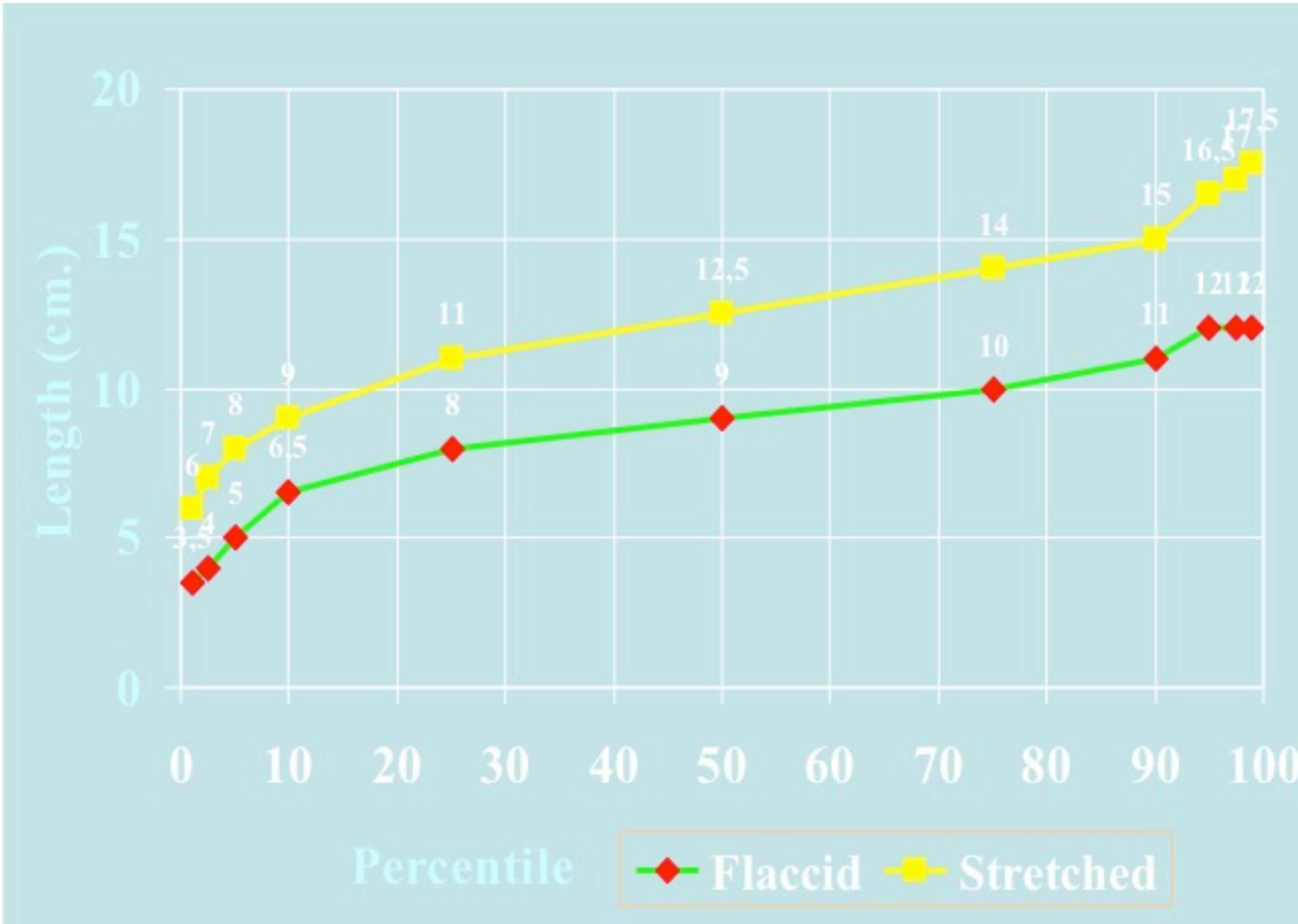




Wessells H J.Urol. 1996 (156): 995-7

Chen J Int J Impot Res 2000 12(6):328-33

Mondaini N. Natali A. et al IJIR 2002



Therapy of micropenis

- Topical DHT (gel 2,5) = 3 mg/kg/day in case of hyponadal men and those patients with AR resistance
- Testosterone enanatato 100 fl i.m. = 25 mg/ month for a three-months course and at puberty up to 100 mg /month for 3 months
- FSH and LH treatment in case of hypogonadal hypogonadism subjects and criptorchidism

Puberty induction

Differentation between costitutional delay of growth and puberty and hypogonadism hypogonadotropic in men

(Rohayem J et al Andrology, 2015)

- Testis volume by Prader orchidometer (> 4 ml)
- Serum inhibin B (> 30 pg/ml)
- Serum AMH (> 20 ng/ml)
- Serum LH and T are not reliable parameters
- T therapy for 3-6 months

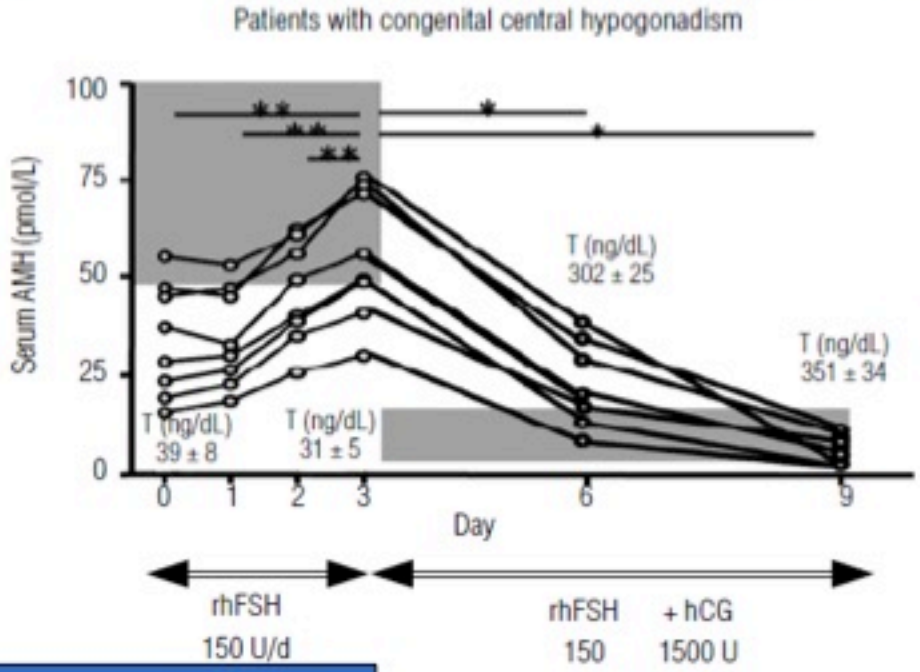
Table 3 - *Serum testosterone (T) and inhibin B (IB) in basal condition and after human chorionic Gn (hCG) (5000 IU/week) alone and human reconbinant FSH (rhFSH) (75 IU three times/week) alone or combined Gn therapy in 6 hypogonadotropic hypogonadism (HH) group.*

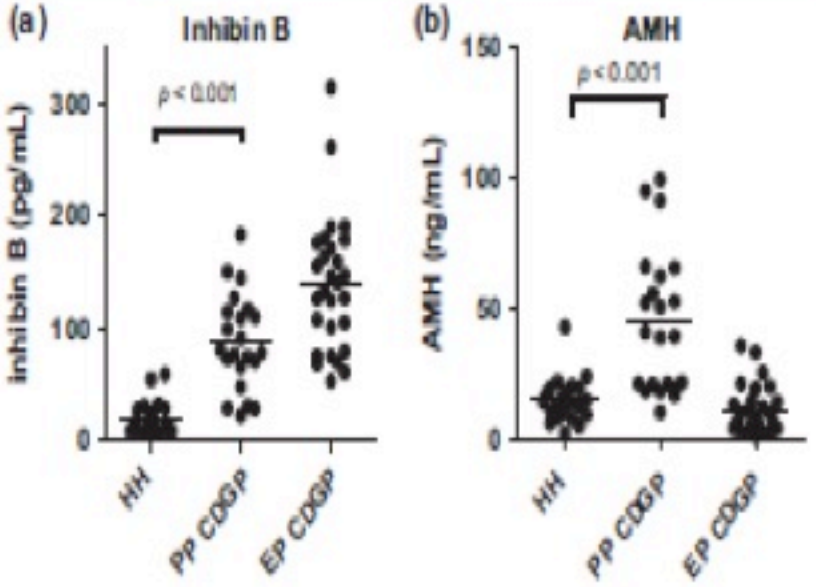
	A	B	C	D	E	F
T (ng/dl)	52.5±18.5*	274.4±89[c]	67.4±15.2	434.5±36.7[c]	483.6±43.4[c,d]	553.2±42[c,f,h]
IB (pg/ml)	46.3±11	53.3±9.3	55±9	90.8±5.4[c]	102.3±14[c]	130.5±28.8[c,d,g]

A: basal condition; B: 3 months hCG therapy alone; C: 3 months rhFSH therapy alone; D: 9 months hCG plus rhFSH therapy: 15 months hCG plus rhFSH therapy; F: 24 months hCG plus rhFSH therapy; *: mean±SD; analysis of variance (ANOVA) test: [a]: $p<0.05$, [b]: $p<0.01$, [c]: $p<0.001$ vs A, [d]: $p<0.05$, [e]: $p<0.01$, [f]: $p<0.001$ vs D, [g]: $p<0.05$, [h]: $p<0.01$ vs E. Conversion to SI U, Tx3.467 (nmol/l).

Giagulli & Carbone,2006

Incremento del volume testicolare





Gripson R et al,201

Schema terapeutico con T per l'induzione della pubertà

Induction of puberty in boys using testosterone esters

Increasing dose schedule every 6 months:

25 mg/m^2 per 2 weeks i.m.

However, there have been no guidelines in Literature until now !

Main warning: growth velocity, while testis size remains stable.

Delmarre et al, 2008

The Role of Long-Acting Parenteral Testosterone Undecanoate Compound in the Induction of Secondary Sexual Characteristics in Males with Hypogonadotropic Hypogonadism

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Table 1 Clinical characteristics, hormonal levels, and number of CAG repeats of patients and controls

Groups	Diagnosis	Case no.	Age (years)	BMI (kg/m²)	Testis (volume)	Penis length (cm)	CAG no.	FSH (IU/L)	LH (IU/L)	T (ng/dL)	SHBG (nm/L)	FT (ng/dL)	BioT (ng/dL)
CG	Normospermic men	15	19.5 ± 1.0	23.9 ± 1.1	22.3 ± 1.5	12.7 ± 2.0	19.8 ± 1.0	6.6 ± 2.5	7.5 ± 2.5	645.5 ± 79.5	41.8 ± 3.8	12.5 ± 1.9	275 ± 61
HHG	Idiopathic	1	18	23	4	4.5	19	1.5	1.0	120	60	1.49	35.1
	Idiopathic	2	17	24	4	4.5	25	1.8	1.2	100	59	1.25	29.3
	Idiopathic	3	17	26	6	5.5	21	0.9	1.7	130	56	1.71	40.2
	Idiopathic	4	17	23	6	4.8	20	1.6	1.1	89	53	1.21	28.4
	Idiopathic	5	19	24	4	3.8	27	2.1	0.9	92	49	1.31	31.1
	Idiopathic	6	17	25	4	4.8	22	1.8	0.9	132	50	1.88	44.1
	Intermediate BT	7	20	24	8	3.5	25	2.2	1.5	141	54	1.91	44.9
	Major BT	8	21	25	6	4.5	20	2.4	1.1	180	59	2.31	54.1
	Major BT	9	20	24	10	5.8	18	1.50	1.2	160	52	2.23	53.4
			18.50 ± 1.50	24.22 ± 1.31	5.78 ± 2.71**	4.7 ± 0.7**	21.89 ± 2.92	1.78 ± 0.43**	1.19 ± 0.27**	127.2 ± 29.2**	53.7 ± 3.8**	1.7 ± 0.39**	40.01 ± 9.27**

*$P < 0.01$; **$P < 0.001$ (Mann–Whitney U-test).
BT = β-thalassemia; BioT = biologically active testosterone; BMI = body mass index; CAG = cytosine-adenine-guanine; CG = control group; FSH = follicle-stimulating hormone; FT = testosterone-free fraction; HHG = hypogonadotropic hypogonadic group; LH = luteinizing hormone; SHBG = sex hormone binding globulin; T = total testosterone.

Table 2 Height, centile, and midparent target height in hypogonadal subjects in basal condition and after 1 and 2 years of parenteral testosterone undecanoate therapy

Diagnosis	Case no. (age [years])	Basal height (cm)	Centile	Height (cm) at 1 year	Centile	Height (cm) at 2 years	Centile	MPTH (cm)
Idiopathic	1 (18)	168.5	20	172	35	174	50	170
Idiopathic	2 (17)	170	25	174	50	176.5	60	172
Idiopathic	3 (17)	173	50	177	75	180	80	182
Idiopathic	4 (17)	170.5	25	174	50	177	60	169
Idiopathic	5 (19)	174	50	178.5	75	182	80	183
Idiopathic	6 (17)	177	70	181.5	80	183	85	185
Intermediate β-thalassemia	7 (20)	168	20	169.5	<50	171	<50	174
Major β-thalassemia	8 (21)	166	10	168	<50	169.5	<50	172
Major β-thalassemia	9 (20)	166.5	10	168	<50	169	<50	174

Calculated centile according to Italian cross-sectional growth charts.
MPTH = Midparental target height.

Testosterone deficit and depression/cognitive dysfunctions

0021-972X/99/$03.00/0
Journal of Clinical Endocrinology and Metabolism

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Bioavailable Testosterone and Depressed Mood in Older Men: The Rancho Bernardo Study

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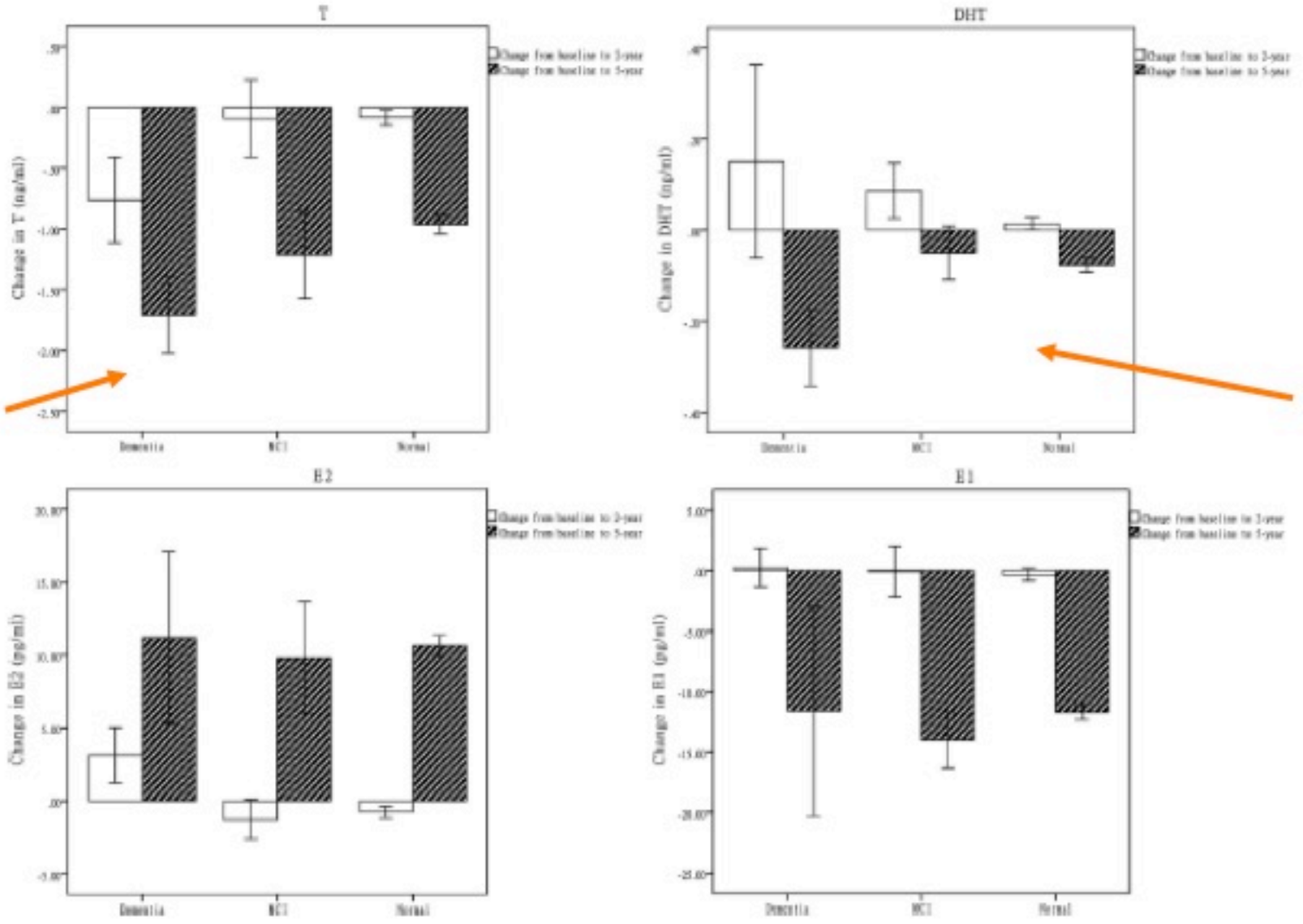
TABLE 4. Linear regression adjusted association between sex hormones and BDI scores among 856 men, The Rancho Bernardo Study

Sex hormone	B	Adjusted[a] SE B	*P*
Testosterone	−0.038	0.03	0.24
Bioavailable testosterone	−0.302	0.11	0.007
Estradiol	−0.003	0.01	0.57
Bioavailable estradiol	−0.006	0.01	0.42
DHT	−0.363	0.18	0.048

[a] Adjusted for age, weight change between visit 1 and visit 4, and regular exercise.



Hsu et al JCEM, 2015

Tab. n.1 Testosterone treatment and cognitive functions: Intervention studies

Study/Author/year	Age (yrs) (m/ range)	Duration (weeks)	Dose	Results	Ref.
Cherrier 2005 (CI or AD)	63-85	6	T 100 mg imweekly	Improved spatial memory and ability, and verbal memory; no differences in verbal fluency or attention	[23]
Janowsky 1994	67.4	12	T (scrotal patch) 15 mg/daily	Improved spatial cognition. No effect on verbal memory, dexterity and cognitive flexibility	[68]
Cherrier 2001	50-80	6	T (im) 100 mg/weekly	Improved spatial memory and ability, and verbal memory; no effect on attention or verbal fluency	[69]
Sih 1997	51-79	52	T (im) 200 mg/2 weekly	No effect on memory, recall or verbal fluency	[70]
Kenny 2002	76.4	52	T 2.5 mg patch daily	No difference in cognitive test results between groups	[71]
Kenny 2004	80	12	T 200 mg im 3 weekly	No difference in cognitive test results between groups	[72]
Cherrier 2002	21-46	8	T (im) 100 mg/weekly + LN 125 mcg oral/day	Decreased performance in tests of verbal memory in LN-treated group, improved selective attention in T + LN group	[73]

Giagulli VA in press

ANNALS OF CLINICAL PSYCHIATRY 2014;26(1):19-32

RESEARCH ARTICLE

Impact of exogenous testosterone on mood: A systematic review and meta-analysis of randomized placebo-controlled trials

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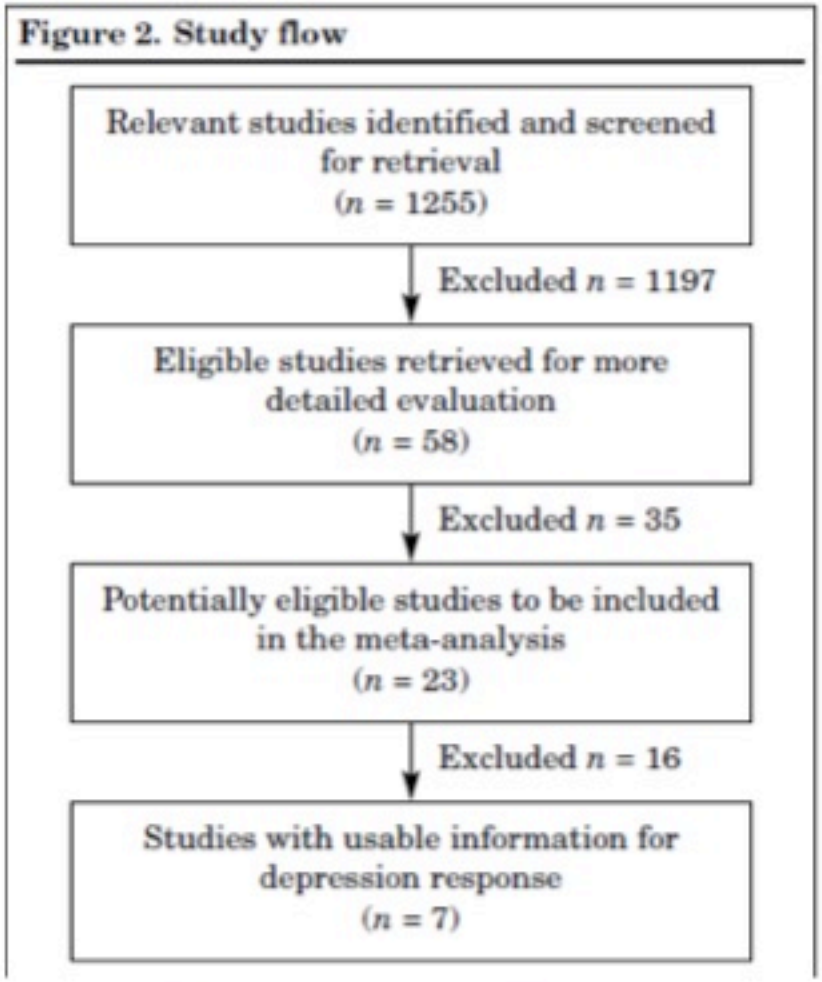
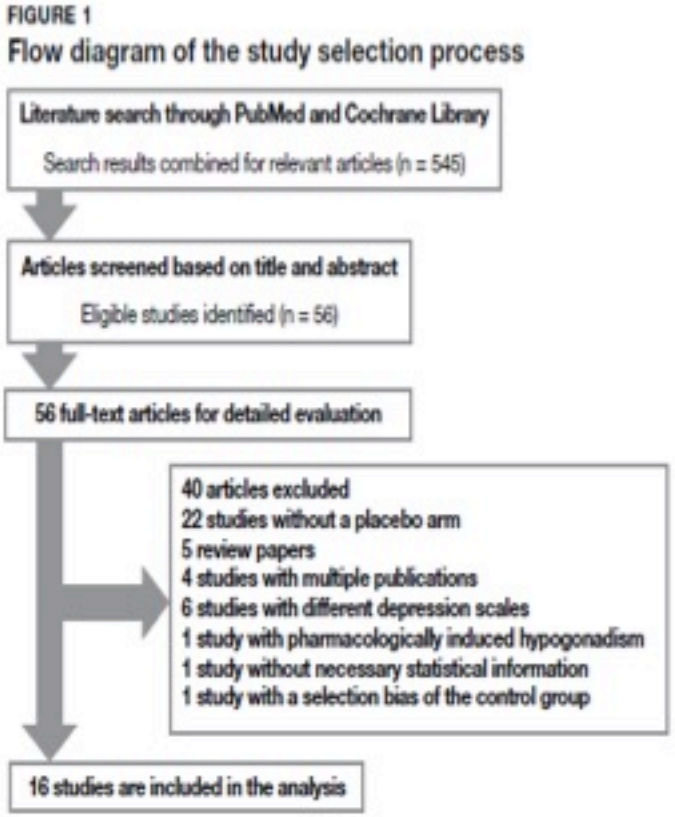
BACKGROUND: In the last decade, there has been a surge of new clinical trials studying the impact of exogenous testosterone on mood. The results of these studies have been inconsistent.

METHODS: Meta-analysis of controlled clinical trials using common depression rating scales was performed.

RESULTS: Sixteen trials with a total of 944 subjects met selection criteria. Meta-analysis of data showed a significant positive impact of testosterone on mood ($z = 4.592$; $P < .0001$). Subgroup analysis showed a significant



N 369 paz



N 964 paz.

Table 4. Meta-analysis of the effects of testosterone vs. placebo on HAM-D response

Study or subgroup	*Testosterone Events*	*N*	*Placebo Events*	*N*	*Odds ratio Weight%*	*M-H, Fixed, 95% CI*
Pope et al. 2003[113]	3	11	0	10	5.1%	0.12 [0.01, 2.56]
Rabkin et al. 2006[93]	43	77	21	68	44.5	0.35 [0.18, 0.70]
Rabkin et al. 2004[94]	23	38	20	39	18.1	0.69 [0.28, 1.70]
Rabkin et al. 2000[95]	11	19	1	7	8.1	0.12 [0.01, 1.21]
Seidman and Roose 2006[111]	5	13	7	17	5.3	1.12 [0.26, 4.91]
Seidman et al. 2005[112]	7	13	3	13	8.6	0.26 [0.05, 1.39]
Shores et al. 2007[114]	8	15	3	15	10.2	0.22 [0.04, 1.11]
Total	**100**	**186**	**55**	**169**	**100.0%**	**0.40 [0.26, 0.63]**

Heterogeneity: $\chi^2 = 5.80$, $df = 6$ ($p = 0.45$); $I^2 = 0\%$
Test for overall effect: $Z = 4.04$ ($p = 0.0001$)
M-H: Mantel-Haenszel test; CI: confidence interval

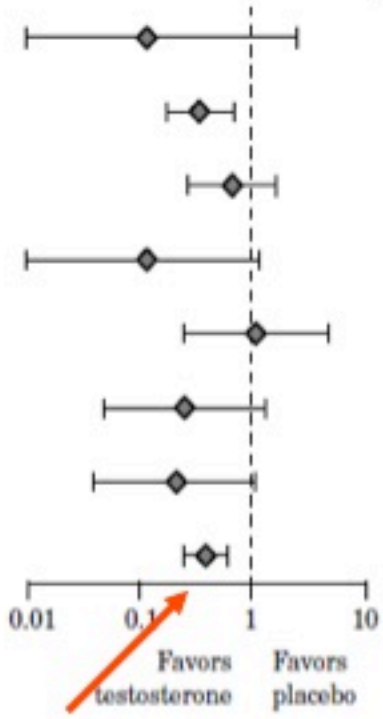


Table 5. Subgroups meta-analysis

Study or subgroup	*Testosterone Events*	*N*	*Placebo Events*	*N*	*Odds ratio Weight%*	*M-H, Fixed, 95% CI*
Hypogonadism						
Pope[113]	3	11	0	10	1.4	0.12 [0.01, 2.56]
Rabkin[93]	43	77	21	68	12.5	0.35 [0.18, 0.70]
Rabkin[95]	11	19	1	7	2.3	0.12 [0.01, 1.21]
Seidman[111]	5	13	7	17	1.5	1.12 [0.26,4.91]
Shores[114]	8	15	3	15	2.9	0.22 [0.04, 1.11]
Total (95%CI)	**70**	**135**	**32**	**117**	**20.6**	**0.35 [0.20, 0.60]**
Heterogeneity: χ^2 = 4.01, df = 4 (p = 0.40); I^2 = 0%; Test for overall effect: Z = 3.84 (p = 0.0001)						
Eugonadism						
Rabkin[94]	23	38	20	39	5.1	0.69 [0.28, 1.70]
Seidman[112]	7	13	3	13	2.4	0.26 [0.05, 1.39]
Total (95%CI)	**30**	**51**	**23**	**52**	**7.5**	**0.55 [0.25, 1.21]**
Heterogeneity: χ^2 = 1.01, df = 1 (p = 0.32); I^2 = 1%; Test for overall effect: Z = 1.49 (p = 0.14)						
HIV/AIDS						
Rabkin[93]	43	77	21	68	12.5	0.35 [0.18, 0.70]
Rabkin[94]	23	38	20	39	5.1	0.69 [0.28, 1.70]
Rabkin[95]	11	19	1	7	2.3	0.12 [0.01, 1.21]
Total (95%CI)	**77**	**134**	**42**	**114**	**19.9**	**0.41 [0.24, 0.69]**
Heterogeneity: χ^2 = 2.50, df = 2 (p = 0.29); I^2 = 20%; Test for overall effect: Z = 3.33 (p = 0.0009)						
No HIV						
Pope[113]	3	11	0	10	1.4	0.12 [0.01, 2.56]
Seidman[111]	5	13	7	17	1.5	1.12 [0.26, 4.91]
Seidman[112]	7	13	3	13	2.4	0.26 [0.05, 1.39]
Shores[114]	8	15	3	15	2.9	0.22 [0.04, 1.11]
Total (95%CI)	**23**	**52**	**13**	**55**	**8.2**	**0.38 [0.16, 0.87]**
Heterogeneity: χ^2 = 3.28 , df = 3 (p = 0.35); I^2 = 8%; Test for overall effect: Z = 2.29 (p = 0.02)						
TT Injections						
Rabkin[94]	23	38	20	39	5.1	0.69 [0.28, 1.70]
Rabkin[95]	11	19	1	7	2.3	0.12 [0.01, 1.21]
Seidman[111]	5	13	7	17	1.5	1.12 [0.26, 4.91]
Seidman[112]	7	13	3	13	2.4	0.26 [0.05, 1.39]
Total (95%CI)	**46**	**83**	**31**	**76**	**11.3**	**0.54 [0.28, 1.03]**
Heterogeneity: χ^2 = 3.57, df= 3 (p = 0.31); I^2 = 16%; Test for overall effect: Z = 1.88 (p = 0.06)						
TT Gel						
Pope[113]	3	11	0	10	1.4	0.12 [0.01, 2.56]
Shores[114]	8	15	3	15	2.9	0.22 [0.04, 1.11]
Total (95%CI)	**11**	**26**	**3**	**25**	**4.3**	**0.18 [0.04, 0.77]**
Heterogeneity: χ^2 = 0.13 , df= 1 (p=0.72); I^2 = 0%; Test for overall effect: Z = 2.32 (p= 0.02)						

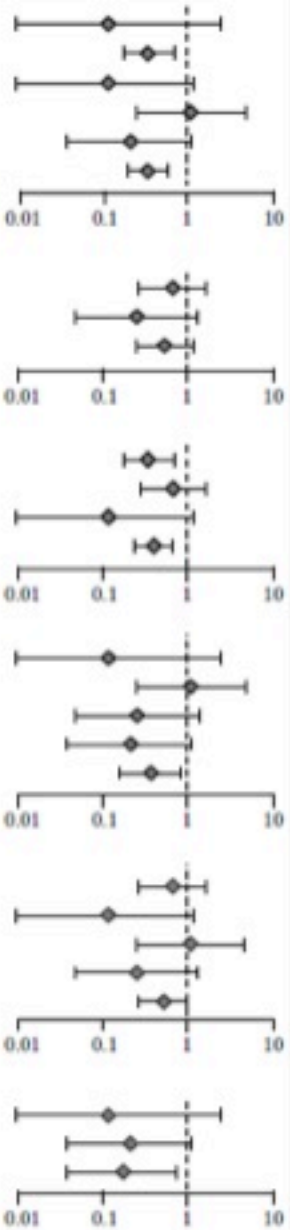


FIGURE 2

Meta-analysis of the impact of testosterone on mood

Study name	Standard error	Std diff in means	Variance	Lower limit	Upper limit	z	P	Relative weight
Pope et al, 2000	0.283	0.039	0.080	−0.516	0.593	0.137	.891	6.65
Pope et al, 2003	0.871	1.189	0.759	−0.519	2.897	1.365	.172	0.70
Pope et al, 2010	0.300	0.484	0.090	−0.104	1.073	1.614	.107	5.90
Rabkin et al, 2000	0.648	1.163	0.420	−0.107	2.434	1.795	.073	1.27
Rabkin et al, 2004	0.286	0.074	0.082	−0.487	0.635	0.259	.795	6.49
Rabkin et al, 2006	0.201	0.673	0.040	0.279	1.066	3.350	.001	13.20
Seidman et al, 2005	0.475	0.749	0.226	−0.183	1.680	1.576	.115	2.36
Seidman and Roose, 2006	0.415	−0.062	0.173	−0.877	0.752	−0.150	.880	3.08
Seidman et al, 2009	0.657	1.296	0.432	0.008	2.584	1.973	.049	1.23
Shores et al, 2009	0.512	1.370	0.262	0.367	2.373	2.678	.007	2.03
Zhang et al, 2012	0.159	0.300	0.025	−0.012	0.611	1.886	.059	21.04
Lu et al, 2006	0.640	0.601	0.409	−0.653	1.855	0.939	.348	1.30
Giltay et al, 2010	0.159	0.336	0.025	0.023	0.648	2.104	.035	20.92
Grinspoon et al, 2000	0.326	0.486	0.106	−0.152	1.125	1.493	.136	5.01
Haren et al, 2005	0.270	−0.565	0.073	−1.095	−0.035	−2.090	.037	7.28
Orengo et al, 2005	0.587	0.211	0.345	-0.939	1.362	0.360	.719	1.54
	0.073	0.335	0.005	0.192	0.478	4.592	.000	

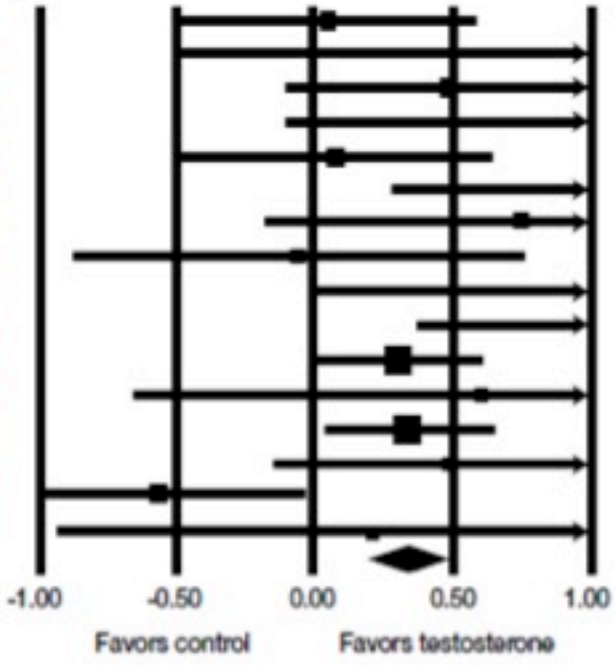


FIGURE 3

Subgroup meta-analysis based on mean age in the selected studies

Group by comparison	Study name	Standard error	Std diff in means	Variance	Lower limit	Upper limit	z	P
<60	Pope et al, 2000	0.283	0.039	0.080	−0.516	0.593	0.137	.891
<60	Pope et al, 2003	0.871	1.189	0.759	−0.519	2.897	1.365	.172
<60	Pope et al, 2010	0.300	0.484	0.090	−0.104	1.073	1.614	.107
<60	Rabkin et al, 2000	0.648	1.163	0.420	−0.107	2.434	1.795	.073
<60	Rabkin et al, 2004	0.286	0.074	0.082	−0.487	0.635	0.259	.795
<60	Rabkin et al, 2006	0.201	0.673	0.040	0.279	1.066	3.350	.001
<60	Seidman et al, 2005	0.475	0.749	0.226	−0.183	1.680	1.576	.115
<60	Seidman and Roose, 2006	0.415	−0.062	0.173	−0.877	0.752	−0.150	.880
<60	Seidman et al, 2009	0.657	1.296	0.432	0.008	2.584	1.973	.049
<60	Shores et al, 2009	0.512	1.370	0.262	0.367	2.373	2.678	.007
<60	Zhang et al, 2012	0.159	0.300	0.025	−0.012	0.611	1.886	.059
<60	Giltay et al, 2010	0.159	0.336	0.025	0.023	0.648	2.104	.035
<60	Grinspoon et al, 2000	0.326	0.486	0.106	−0.152	1.125	1.493	.136
<60		0.077	0.406	0.006	0.255	0.557	5.279	.000
>60	Lu et al, 2006	0.640	0.601	0.409	−0.653	1.855	0.939	.348
>60	Haren et al, 2005	0.270	−0.565	0.073	−1.095	−0.035	−2.090	.037
>60	Orengo et al, 2005	0.587	0.211	0.345	−0.939	1.362	0.360	.719
>60		0.229	−0.297	0.053	−0.746	0.152	−1.296	.195

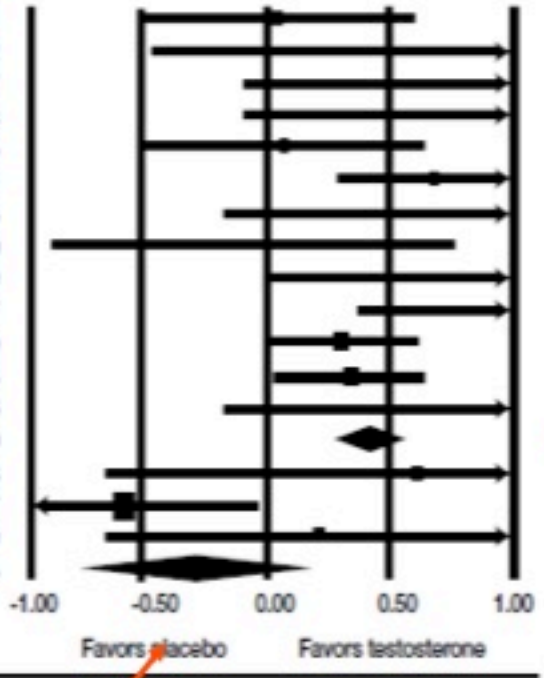
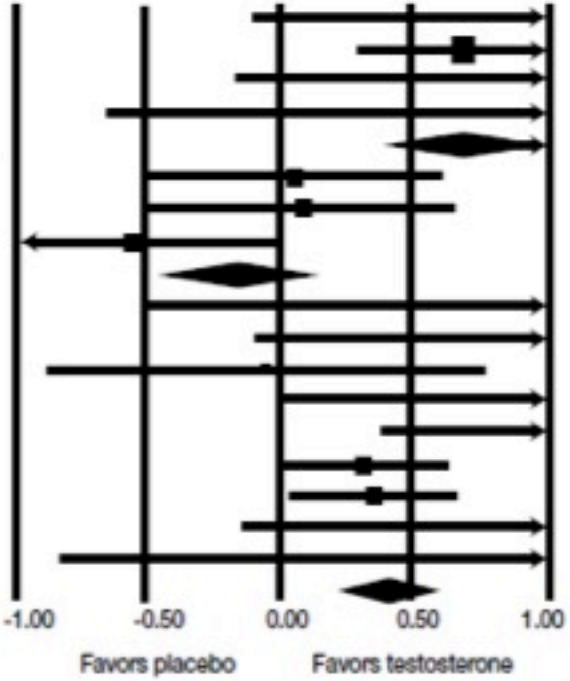


FIGURE 4

Subgroup meta-analysis in hypogonadal vs eugonadal subjects

Group by comparison	Study name	Standard error	Std diff in means	Variance	Lower limit	Upper limit	z	P
Both	Rabkin et al, 2000	0.648	1.163	0.420	–0.107	2.434	1.795	.073
Both	Rabkin et al, 2006	0.201	0.673	0.040	0.279	1.066	3.350	.001
Both	Seidman et al, 2005	0.475	0.749	0.226	–0.183	1.680	1.576	.115
Both	Lu et al, 2006	0.640	0.601	0.409	–0.653	1.855	0.939	.348
Both		0.171	0.712	0.029	0.376	1.047	4.153	.000
Eugonadal	Pope et al, 2000	0.283	0.039	0.080	–0.516	0.593	0.137	.891
Eugonadal	Rabkin et al, 2004	0.286	0.074	0.082	–0.487	0.635	0.259	.795
Eugonadal	Haren et al, 2005	0.270	–0.565	0.073	–1.095	–0.035	–2.090	.037
Eugonadal		0.161	–0.165	0.026	–0.482	0.151	–1.024	.306
Hypogonadal	Pope et al, 2003	0.871	1.189	0.759	–0.519	2.897	1.365	.172
Hypogonadal	Pope et al, 2010	0.300	0.484	0.090	–0.104	1.073	1.614	.107
Hypogonadal	Seidman and Roose, 2006	0.415	–0.062	0.173	–0.877	0.752	–0.150	.880
Hypogonadal	Seidman et al, 2009	0.657	1.296	0.432	0.008	2.584	1.973	.049
Hypogonadal	Shores et al, 2009	0.512	1.370	0.262	0.367	2.373	2.678	.007
Hypogonadal	Zhang et al, 2012	0.159	0.300	0.025	–0.012	0.611	1.886	.059
Hypogonadal	Giltay et al, 2010	0.159	0.336	0.025	0.023	0.648	2.104	.035
Hypogonadal	Grinspoon et al, 2000	0.326	0.486	0.106	–0.152	1.125	1.493	.136
Hypogonadal	Orengo et al, 2005	0.587	0.211	0.345	–0.939	1.362	0.360	.719
Hypogonadal		0.093	0.390	0.009	0.208	0.572	4.192	.000

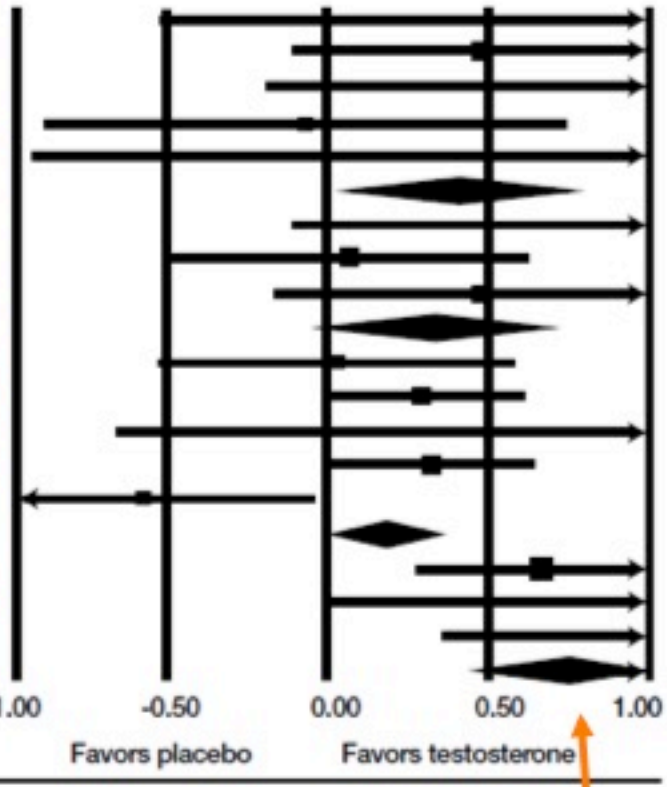


Both: trials with both hypogonadal and eugonadal subjects.

FIGURE 5

Subgroup meta-analysis based on level of depression

Group by comparison	Study name	Standard error	Std diff in means	Variance	Lower limit	Upper limit	z	P
MDD	Pope et al, 2003	0.871	1.189	0.759	–0.519	2.897	1.365	.172
MDD	Pope et al, 2010	0.300	0.484	0.090	–0.104	1.073	1.614	.107
MDD	Seidman et al, 2005	0.475	0.749	0.226	–0.183	1.680	1.576	.115
MDD	Seidman and Roose, 2006	0.415	–0.062	0.173	–0.877	0.752	–0.150	.880
MDD	Orengo et al, 2005	0.587	0.211	0.345	–0.939	1.362	0.360	.719
MDD		0.198	0.411	0.039	0.024	0.799	2.080	.038
Mixed	Rabkin et al, 2000	0.648	1.163	0.420	–0.107	2.434	1.795	.073
Mixed	Rabkin et al, 2004	0.286	0.074	0.082	–0.487	0.635	0.259	.795
Mixed	Grinspoon et al, 2000	0.326	0.486	0.106	–0.152	1.125	1.493	.136
Mixed		0.204	0.344	0.042	–0.056	0.744	1.685	.092
NA	Pope et al, 2000	0.283	0.039	0.080	–0.516	0.593	0.137	.891
NA	Zhang et al, 2012	0.159	0.300	0.025	–0.012	0.611	1.886	.059
NA	Lu et al, 2006	0.640	0.601	0.409	–0.653	1.855	0.939	.348
NA	Giltay et al 2010	0.159	0.336	0.025	0.023	0.648	2.104	.035
NA	Haren et al, 2005	0.270	–0.565	0.073	–1.095	–0.035	–2.090	.037
NA		0.096	0.179	0.009	–0.010	0.368	1.859	.063
SD	Rabkin et al, 2006	0.201	0.673	0.040	0.279	1.066	3.350	.001
SD	Seidman et al, 2009	0.657	1.296	0.432	0.008	2.584	1.973	.049
SD	Shores et al, 2009	0.512	1.370	0.262	0.367	2.373	2.678	.007
SD		0.180	0.805	0.032	0.453	1.158	4.480	.000

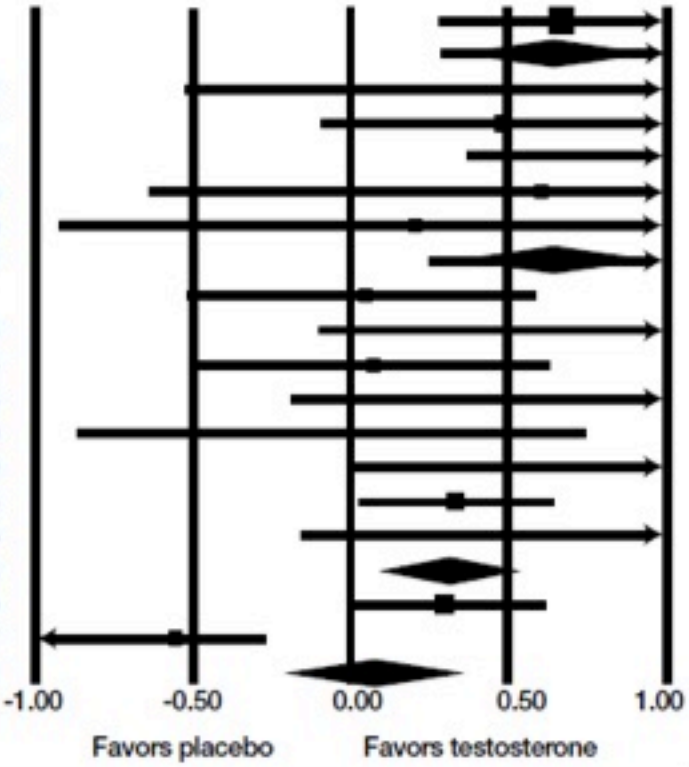


MDD: major depressive disorder; Mixed: trials with a mixture of participants from MDD to SD; NA: trials without enough data describing the diagnosed depression rate among participants or trials studying testosterone on subjects without any diagnosed depression; SD: subthreshold depression, including dysthymia and minor depression.

FIGURE 8

Subgroup meta-analysis based on route of administration

Group by comparison	Study name	Standard error	Std diff in means	Variance	Lower limit	Upper limit	z	P
DHEA	Rabkin et al, 2006	0.201	0.673	0.040	0.279	1.066	3.350	.001
DHEA		0.201	0.673	0.040	0.279	1.066	3.350	.001
Gel	Pope et al, 2003	0.871	1.189	0.759	–0.519	2.897	1.365	.172
Gel	Pope et al, 2010	0.300	0.484	0.090	–0.104	1.073	1.614	.107
Gel	Shores et al, 2009	0.512	1.370	0.262	0.367	2.373	2.678	.007
Gel	Lu et al, 2006	0.640	0.601	0.409	–0.653	1.855	0.939	.348
Gel	Orengo et al, 2005	0.587	0.211	0.345	–0.939	1.362	0.360	.719
Gel		0.215	0.661	0.046	0.239	1.083	3.069	.002
IM	Pope et al, 2000	0.283	0.039	0.080	–0.516	0.593	0.137	.891
IM	Rabkin et al, 2000	0.648	1.163	0.420	–0.107	2.434	1.795	.073
IM	Rabkin et al, 2004	0.286	0.074	0.082	–0.487	0.635	0.259	.795
IM	Seidman et al, 2005	0.475	0.749	0.226	–0.183	1.680	1.576	.115
IM	Seidman and Roose, 2006	0.415	–0.062	0.173	–0.877	0.752	–0.150	.880
IM	Seidman et al, 2009	0.657	1.296	0.432	0.008	2.584	1.973	.049
IM	Giltay et al, 2010	0.159	0.336	0.025	0.023	0.648	2.104	.035
IM	Grinspoon et al, 2000	0.326	0.486	0.106	–0.152	1.125	1.493	.136
IM		0.106	0.316	0.011	0.107	0.524	2.967	.003
Oral	Zhang et al, 2012	0.159	0.300	0.025	–0.012	0.611	1.886	.059
Oral	Haren et al, 2005	0.270	–0.565	0.073	–1.095	–0.035	–2.090	.037
Oral		0.137	0.077	0.019	–0.191	0.346	0.565	.572



DHEA: oral dehydroepiandrosterone; Gel: transdermal gel testosterone; IM: intramuscular testosterone; Oral: oral testosterone.

J Endocrinol Invest (2015) 38:103–112
DOI 10.1007/s40618-014-0155-9

CONSENSUS STATEMENT

Outcomes of androgen replacement therapy in adult male hypogonadism: recommendations from the Italian society of endocrinology

A. M. Isidori · G. Balercia · A. E. Calogero · G. Corona · A. Ferlin · S. Francavilla · D. Santi · M. Maggi

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Other outcomes

15. We suggest that clinicians offer TS to HG men with depression to improve depressive symptoms (2 ØØOO), in addition to the established therapies for depression.

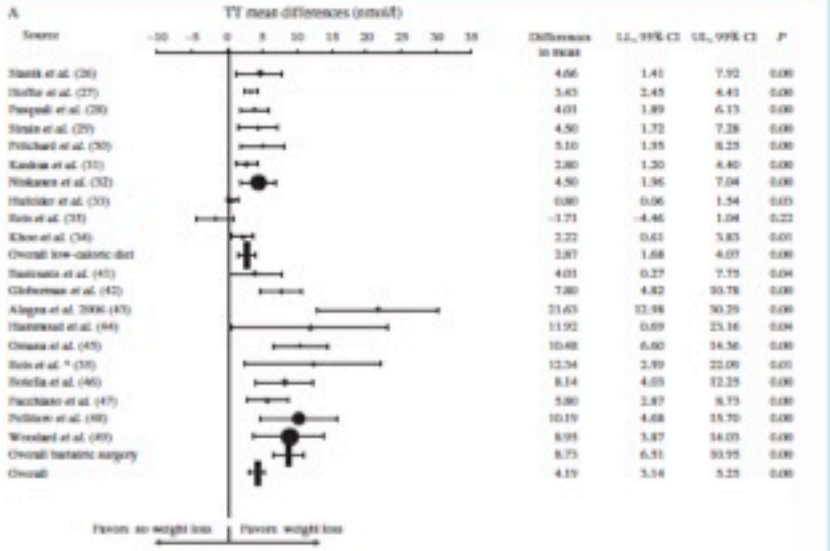
Body composition, metabolic and cardiovascular diseases

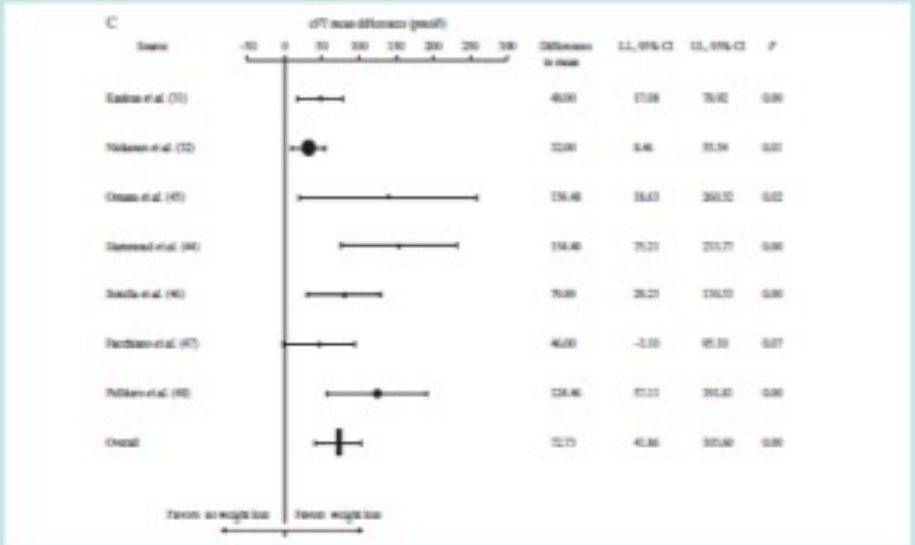
European Journal of Endocrinology (2013) 168 1–16 ISSN 0804-4643

CLINICAL STUDY

Body weight loss reverts obesity-associated hypogonadotropic hypogonadism: a systematic review and meta-analysis

Giovanni Corona[1,2], Giulia Rastrelli[1], Matteo Monami[3], Farid Saad[4], Michaela Luconi[5], Marcello Lucchese[6], Enrico Facchiano[6], Alessandra Sforza[2], Gianni Forti[5], Edoardo Mannucci[3] and Mario Maggi[1]





This meta-analysis meets the Endocrine Society Guidelines (Bhasin et al , 2010)

THERAPY OF ENDOCRINE DISEASE

Testosterone supplementation and body composition: results from a meta-analysis study

Giovanni Corona, Vito A Giagulli[1], Elisa Maseroli[2], Linda Vignozzi[2], Antonio Aversa[3], Michael Zitzmann[4], Farid Saad[5,6], Edoardo Mannucci[7] and Mario Maggi[2]

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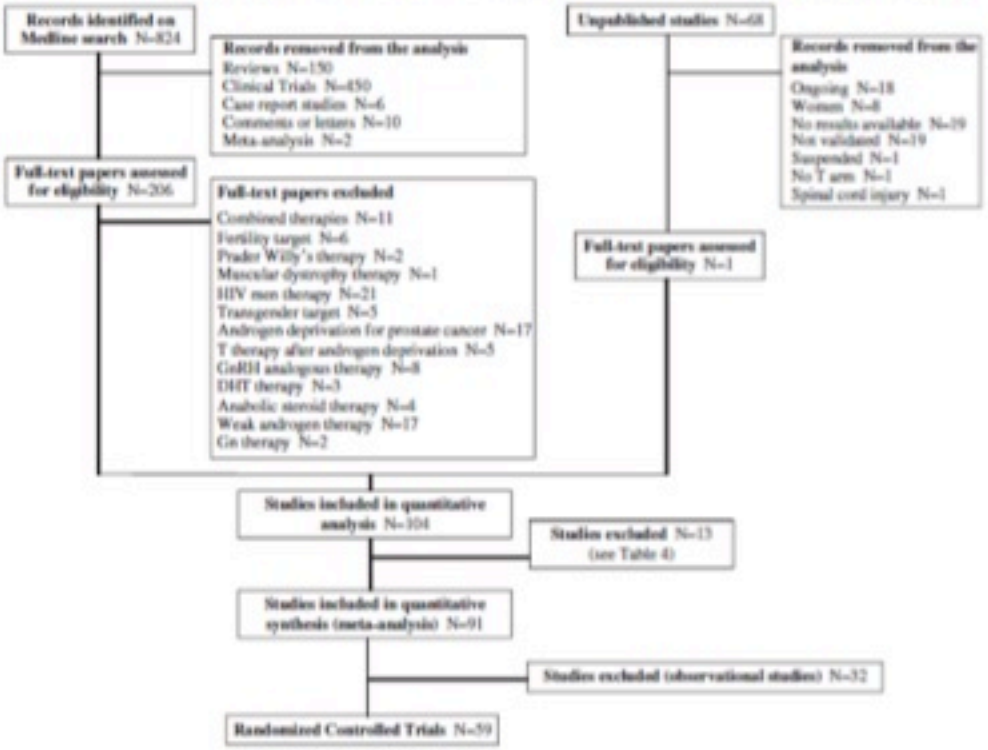
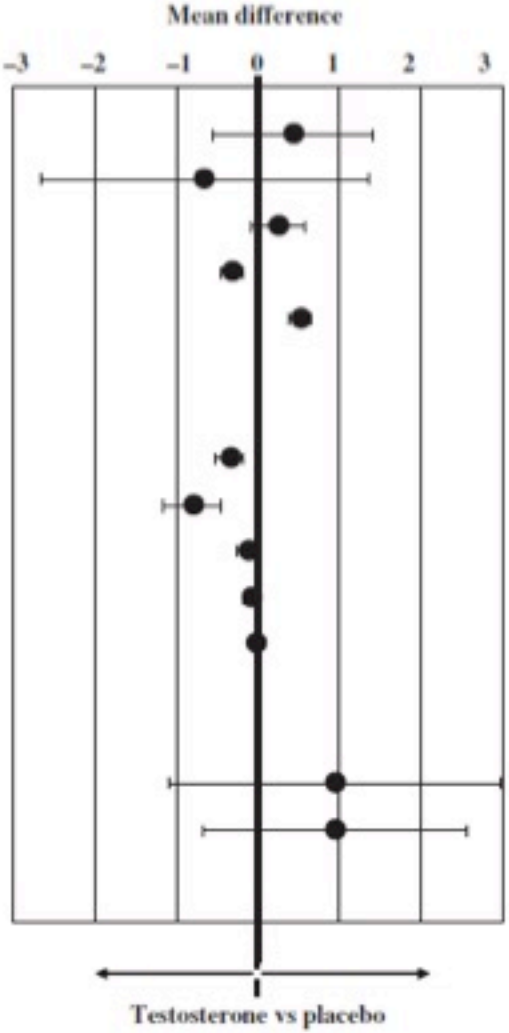


Source	Number of trials	Diff in mean	LL	UL	P	I^2
Body composition						
Weight (kg)	32	0.43	–0.54	1.39	0.39	35.85
Waist circumference (cm)	17	–0.66	–2.66	1.35	0.52	76.05
BMI (kg/m^2)	29	0.25	–0.09	0.58	0.15	68.86
Fat mass*	42	–0.32	–0.44	–0.19	0.00	68.20
Lean mass*	40	0.51	0.37	0.66	0.00	74.68
Glyco-metabolic profile						
Fasting glycemia (mM)	23	–0.34	–0.51	–0.17	0.00	56.49
HOMA index	16	–0.80	–1.16	–0.45	0.00	59.25
Total cholesterol (mM)	42	–0.12	–0.25	0.01	0.08	73.59
Triglycerides (mM)	33	–0.08	–0.18	0.01	0.09	66.80
HDL (mM)	40	–0.03	–0.08	0.01	0.18	93.17
Blood pressure						
SBP (mmHg)	17	0.94	–1.08	2.96	0.36	53.81
DBP (mmHg)	16	0.95	–0.66	2.54	0.25	70.42



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ANDROLOGY

ORIGINAL ARTICLE

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Keywords:
erectile dysfunction, glucagon-like peptide-1 agonist, hypogonadism, obesity, testosterone replacement therapy, type 2 diabetes mellitus

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Adding liraglutide to lifestyle changes, metformin and testosterone therapy boosts erectile function in diabetic obese men with overt hypogonadism

[1,2]V. A. Giagulli, [3]M. D. Carbone, [1]M. I. Ramunni, [2]B. Licchelli, [4]G. De Pergola, [5]C. Sabbà, [2]E. Guastamacchia and [2]V. Triggiani

Prepubertal onset hypogonadism men with obesity and T2DM

G2 N (n = 10)	T1	T2	p1 (p)	T3	p2 (p)
Age (years)	50.0 ± 4.7	–	–	–	–
Duration of diabetes (years)	3.2 ± 0.8	–	–	–	–
Height (cm)	172.9 ± 2.5	–	–	–	–
Weight (kg)	105.3 ± 9.8	102.5 ± 7.1	**<0.05**	98.0 ± 8.3	**<0.01**
BMI (kg/m^2)	34.8 ± 2.6	33.5 ± 2.0	**<0.05**	32.5 ± 2.3	**<0.05**
WC (cm)	106.8 ± 11.0	104.5 ± 9.9	**<0.05**	99.2 ± 9.8	**<0.001**
SBP (mmHg)	151.5 ± 8.8	147.5 ± 8.3	**<0.05**	142.0 ± 8.6	**<0.01**
DBP (mmHg)	89.5 ± 4.4	87.7 ± 2.6	<0.06	85.9 ± 4.1	**<0.05**
Gly (mg/dL)	211.4 ± 25.7	169.9 ± 15.3	**<0.01**	133.9 ± 12.8	**<0.01**
HbA1c (%)	8.8 ± 0.8	8.2 ± 0.3	**<0.04**	7.4 ± 0.6	**<0.01**
TC (mg/dL)	189.9 ± 12.4	176.5 ± 25.7	**<0.01**	175.8 ± 19.0	<0.15
TG (mg/dL)	319.1 ± 152.7	270.3 ± 104.9	**<0.01**	226.0 ± 48.7	**<0.001**
HDL (mg/dL)	35.7 ± 3.7	37.1 ± 3.0	<0.34	37.9 ± 3.5	<0.12
LDL (mg/dL)	105.6 ± 12.4	94.3 ± 19.5	**<0.05**	92.4 ± 18.9	**<0.05**
T (ng/dL)	304.8 ± 30.4	395.5 ± 40.0	**<0.01**	420.0 ± 27.5	**<0.01**
SHBG (nmol/L)	37.1 ± 2.6	38.4 ± 2.0	**<0.02**	40.8 ± 1.5	**<0.02**
FT (ng/dL)	5.6 ± 0.7	7.2 ± 0.8	**<0.01**	7.6 ± 0.6	<0.16
BioT (ng/dL)	132.8 ± 16.2	170.7 ± 18.0	**<0.01**	178.4 ± 13.6	<0.18
IIEF (score)	14.2 ± 1.8	16.5 ± 1.6	**<0.01**	19.9 ± 1.1	**<0.001**

Statistically significant p values are in bold. p1, significance T2 vs. T1; p2, significance T3 vs. T2; Met, metformin; TU, testosterone undecanoate; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; Gly, glycaemia; HbA1c, glycosylated haemoglobin; TC, total cholesterol; TG, triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein; T, testosterone; SHBG, sex hormone binding globulin; FT, free T; BioT, bioavailable T; IIEF, International Index of Erectile Function.

Postpubertal onset Hypogonadal men with obesity and T2DM

G1N (n = 16)	T1	T2	p1 (p)	T3	p2 (p)
Age (years)	52.7 ± 4.5	–	–	–	–
Duration of diabetes (years)	3.8 ± 0.8	–	–	–	–
Height (cm)	171.2 ± 5.7	–	–	–	–
Weight (kg)	102.7 ± 9.1	99.0 ± 7.6	**<0.01**	93.7 ± 6.3	**<0.01**
BMI (kg/m^2)	35.2 ± 2.3	34.0 ± 3.1	**<0.01**	32.6 ± 2.0	**<0.01**
WC (cm)	103.7 ± 7.0	99.1 ± 6.2	**<0.01**	92.5 ± 5.3	**<0.001**
SBP (mmHg)	155.8 ± 13.7	150.1 ± 12.0	**<0.01**	145.7 ± 9.6	**<0.001**
DBP (mmHg)	86.4 ± 4.5	85.5 ± 4.2	<0.07	82.5 ± 2.6	**<0.01**
Gly (mg/dL)	180.4 ± 24.8	155.5 ± 19.7	**<0.001**	130.3 ± 15.6	**<0.001**
HbA1c (%)	9.1 ± 0.4	8.3 ± 0.3	**<0.001**	7.3 ± 0.3	**<0.001**
TC (mg/dL)	226.6 ± 20.8	216.8 ± 16.8	**<0.01**	206.9 ± 10.8	**<0.01**
TG (mg/dL)	202.8 ± 28.6	190.1 ± 27.3	**<0.001**	175.4 ± 19.4	**<0.001**
HDL (mg/dL)	38.6 ± 2.8	39.0 ± 2.6	<0.61	39.6 ± 3.0	<0.07
LDL (mg/dL)	147.3 ± 21.3	133.6 ± 15.4	**<0.001**	125.5 ± 10.7	**<0.001**
T (ng/dL)	285.8 ± 25.0	466.1 ± 63.6	**<0.001**	481.7 ± 57.3	**<0.001**
SHBG (nmol/L)	36.0 ± 3.2	37.1 ± 2.8	**<0.05**	39.1 ± 2.2	**<0.01**
FT (ng/dL)	5.4 ± 0.6	8.7 ± 1.6	**<0.001**	9.0 ± 1.3	<0.13
BioT (ng/dL)	124.6 ± 13.4	204.0 ± 37.1	**<0.001**	211.1 ± 30.0	<0.14
IIEF (score)	12.2 ± 2.2	14.6 ± 1.7	**<0.05**	19.9 ± 2.0	**<0.001**

Statistically significant p values are reported in bold. p1, significance T2 vs. T1; p2, significance T3 vs. T2; Met, metformin; TU, testosterone undecanoate; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; Gly, glycaemia; HbA1c, glycosylated haemoglobin; TC, total cholesterol; TG, triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein; T, testosterone; SHBG, sex hormone binding globulin; FT, free T; BioT, bioavailable T; IIEF, International Index of Erectile Function.

Late-onset hypogonadism and ageing

TRT in elderly Men

(Kaufmann JM & Vermeulen A Endocr Rew.,2005; Buvart J, Maggi M, et al J Sex Med, 2013)

- Only few RCT studies with a short duration and about 600 subjects were treated with T (T i.m T gel)
- Res

1. Se
2. C
3. Sk en trate about fracture
4. Body composi ease in lean mass and a decrese in fat mass
5. No definitive data about mortality

Concerns

There were significant rise in CV side effects in the group of hypogonadal elder men (mean age:74yrs) with CVD treated with T compared with group on placebo (Basaria S et al NJEM, 2010)

Testosterone and mortality

(Muraleedharan V & Jones TH Clin Endocrinol, 2014)

Author, year (study name)	Country	N	Mean Follow-up years	All-cause Mortality HR/OR for TT unless indicated (95% CI)
Pye *et al.*[15] 2014 (EMAS)	Europe	2599	4·3	HR 5·5 (2·7,11·4) (with severe LOH) HR 2·3 (1·2,4·2) (TT <8 nmol/l) HR 3·2
Haring *et al.*[17] 2013 (Framingham Heart Study)	USA	254	At 5 and 10 years	HR (per quartile increment) NS
Hyde *et al.*[18] 2012 (Health in Men Study)	Australia	4249	5·1	HR 1·62 (1·20–2·19)
Haring *et al.*[8] 2010 (SHIP)	Germany	1954	7·2	HR 2·24 (1·41–3·57)
Menke *et al.*[11] 2010 (NHANES III)	USA	1114	At 9 and 18 years	HR – at 9 years FT: 1·43 (1·09, 1·87) TT: NS At 18 years: FT & TT NS
Vikan *et al.*[9] 2009 (Tromsø)	Norway,	1568	11·2	HR FT: 1·24 (1·01–1·54); TT: (NS)
Tivesten *et al.*[10] 2009 (MrOS)	Sweden	5014	4·5	HR 1·63 (1·29–2·12)
Lehtonen *et al.*[14] 2008 (Turku)	Finland	187	10	OR 0·93 (0·87–0·99)
Laughlin *et al.*[7] 2008 (Rancho–Bernardo Study)	USA	794	11·8	HR 1·44 (1·12, 1·84)
Araujo *et al.*[18] 2007 (MMAS)	USA	1686	15·3	RR TT: NS FT: NS
Khaw *et al.*[13] 2007 (EPIC-Norfolk)	UK	2314	7	OR (TT increasing quartiles compared to lowest) 0·75 (0·55–1·00);0·62 (0·45–0·84);0·59 (0·42–0·85)
Shores *et al.*[6] 2006 (Veterans)	USA	858	4·3	HR 1·88 (1·34–2·63)
Smith *et al.*[19] 2005 (Caerphilly)	UK	2512	16·5	HR: NS

EPIC-Norfolk, European Prospective Investigation into Cancer in Norfolk; MMAS, Massachusetts Male Aging Study; MrOS, Swedish Osteoporotic Fractures in Men; NHANES, Third National Health and Nutrition Examination Survey; Mortality StudySHIP, Study of Health in Pomerania; TT, total testosterone; BT, bioavailable testosterone; FT, free testosterone; HR, hazard ratio; OR, odds ratio; NS, not significant; NA, not applicable; CI, confidence interval.

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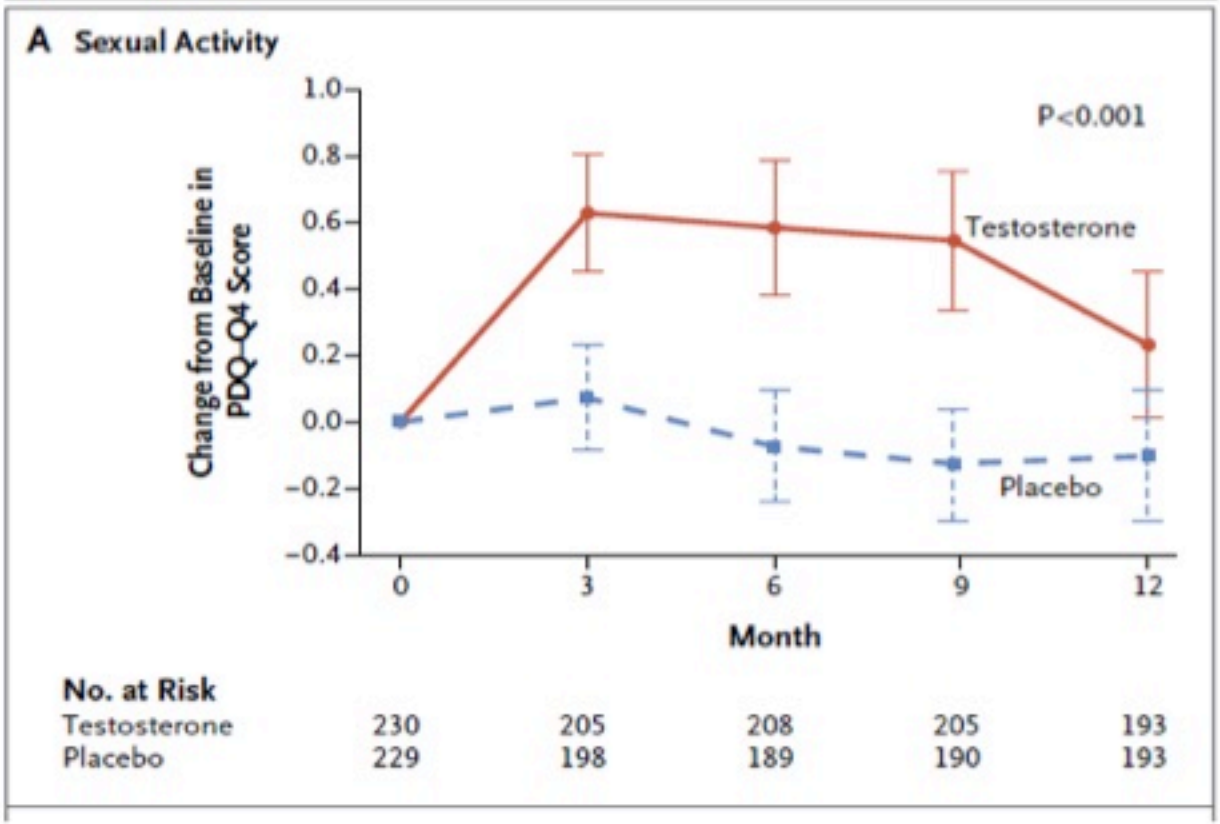
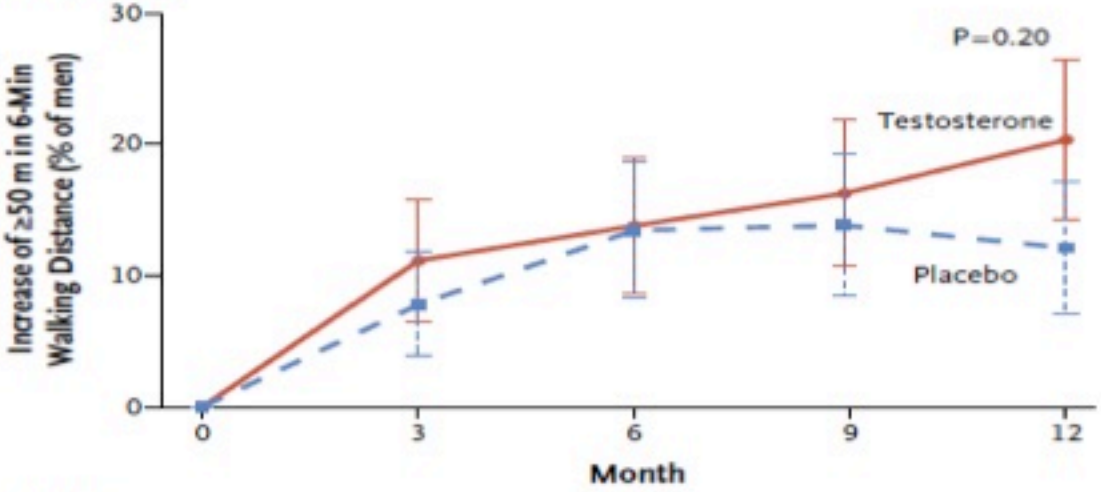
Effects of Testosterone Treatment in Older Men

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*

Hypogonadal Men ≥ 65 yrs

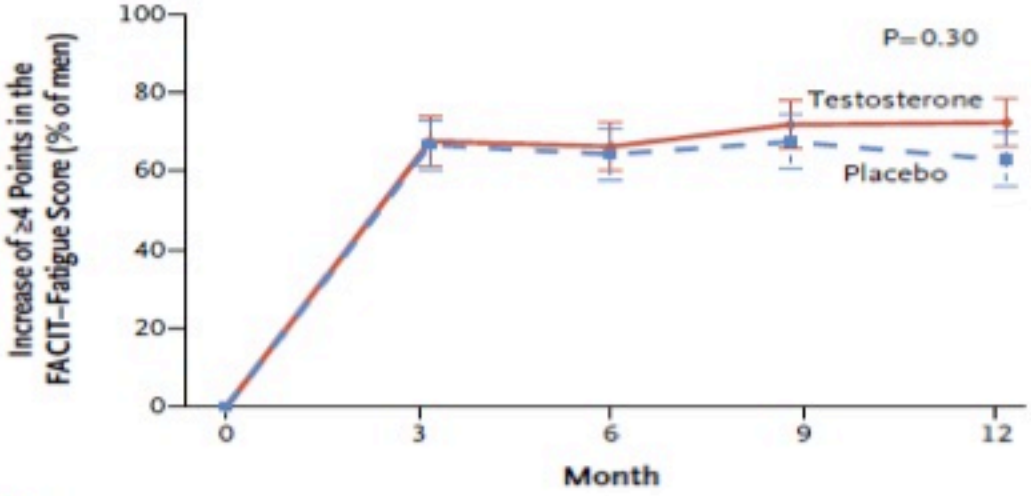


B Walking Ability



No. at Risk					
Testosterone	193	179	174	172	172
Placebo	197	179	171	159	165

C Vitality

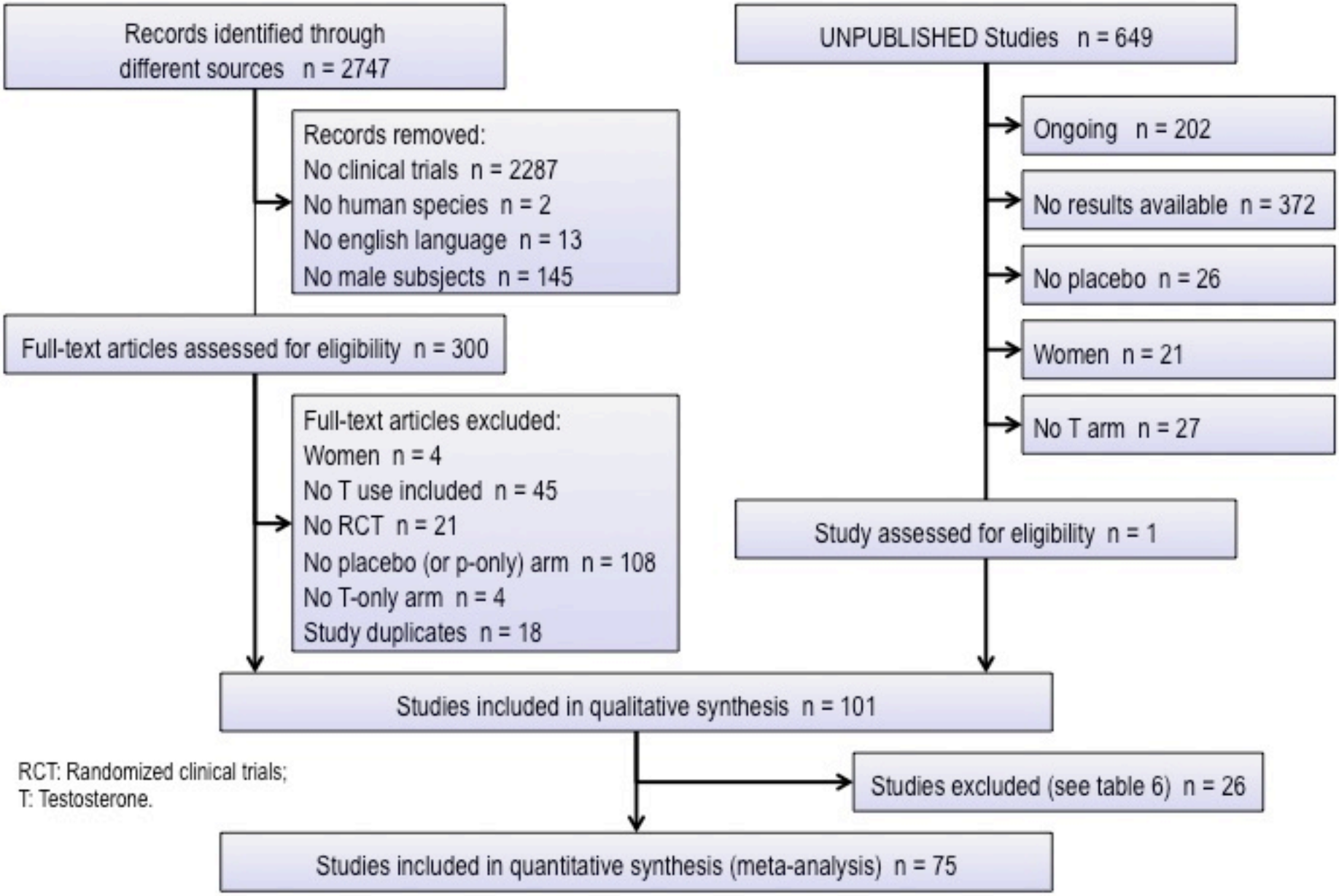


No. at Risk					
Testosterone	236	219	217	206	203
Placebo	238	207	196	188	191

Table 4. Adverse Events during the First Year (Treatment Period) of the Testosterone Trials.*

Event	Placebo (N=394)	Testosterone (N=394)
	no. of participants	
Prostate-related event		
Increase in PSA level by ≥1.0 ng/ml	8	23
Prostate cancer	0	1
IPSS >19†	26	27
Hemoglobin ≥17.5 g/dl	0	7
Cardiovascular event‡		
Myocardial infarction (definite or probable)	1	2
Stroke (definite or probable)	5	5
Death from cardiovascular causes	1	0
Myocardial infarction, stroke, or death from cardiovascular causes	7	7
Serious adverse events		
Death	7	3
Hospitalization	78	68
Other§	6	7

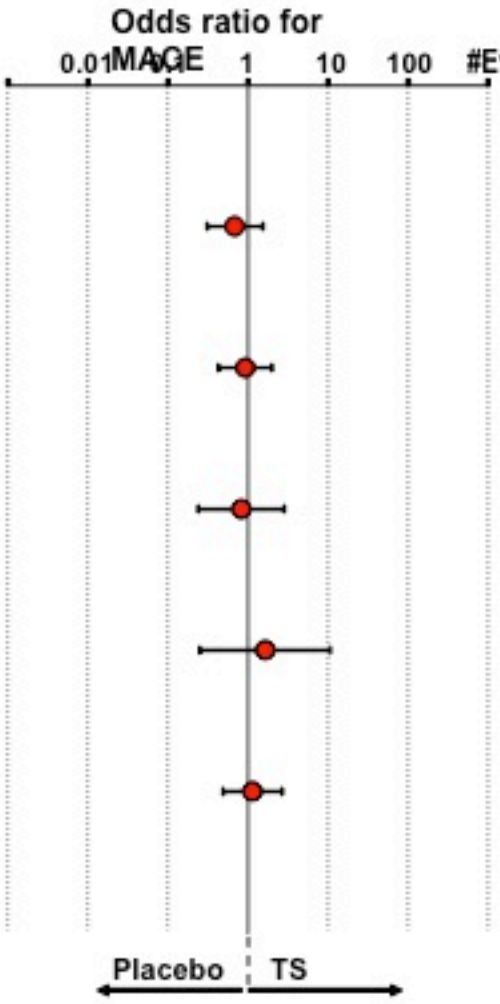
Trial Flow Diagram



RCT: Randomized clinical trials;
T: Testosterone.

Corona G et al. Expert Opin Drug Saf, published online August 19, 2014

Odds Ratio for Acute Myocardial Infarction (AMI), Acute Coronary Syndrome, Stroke, Heart Failure, and Cardiovascular (CV) Mortality in Subjects Treated with Testosterone or Placebo



Source	# Trials					TRT #Events	TRT # Patients	Placebo #Events	Placebo # Patients
AMI	14	0,68	0,30	1,52	0,34	11	1086	11	747
Acute coronary syndrome	15	0,92	0,43	1,97	0,83	18	1093	11	738
Stroke	5	0,82	0,24	2,83	0,76	3	244	4	242
New heart failure	3	1,64	0,25	10,63	0,60	3	387	0	193
CV mortality	13	1,14	0,49	2,66	0,76	11	1173	8	928

LL: Lower limit; MACE: Major adverse cardiovascular events; MH-OR: Mantel-Haenszel odds ratio; UL: Upper limit

Corona G et al. Expert Opin Drug Saf, published online August 19, 2014

TABLE 2. Distribution of Major Diagnostic Categories of Index Hospitalization[a]

Major diagnostic category	Androgen	No androgen
Nervous system	62 (6.7)	397 (7.3)
Eye	0 (0)	6 (0.1)
Ear, nose, mouth, and throat	10 (1.0)	79 (1.5)
Respiratory system	136 (14.6)	765 (14.1)
Circulatory system	253 (27.3)	1312 (24.1)
Digestive system	130 (14.0)	614 (11.3)
Hepatobiliary system and pancreas	17 (1.8)	134 (2.5)
Musculoskeletal system, connective tissue	42 (4.5)	281 (5.2)
Skin, subcutaneous tissue, breast	28 (3.0)	153 (2.8)
Endocrine, nutritional, metabolic	26 (2.8)	191 (3.5)
Kidney and urinary tract	61 (6.6)	376 (6.9)
Male reproductive system	8 (0.9)	29 (0.5)
Blood and immunologic disorders	15 (1.6)	89 (1.6)
Myeloproliferative disorders	8 (0.9)	49 (0.9)
Infectious diseases	40 (4.3)	251 (4.6)
Mental disorders	12 (1.3)	112 (2.1)
Alcohol/drug abuse	5 (0.5)	24 (0.4)
Injuries, poison, drug toxicity	9 (1.0)	85 (1.6)
Burns	0 (0.0)	1 (0.0)
Factors influencing health status	65 (7.0)	478 (8.8)
Trauma	0 (0.0)	1 (0.0)
Human immunodeficiency virus	1 (0.1)	4 (0.1)
Unspecified	1 (0.1)	13 (0.2)

). The percentages of all presented major diagnostic

Androgen Therapy and Rehospitalization in Older Men With Testosterone Deficiency

Jacques Baillargeon, PhD; Rachel R. Deer, PhD; Yong-Fang Kuo, PhD; Dong Zhang, PhD; James S. Goodwin, MD; and Elena Volpi, MD, PhD

2016

Hypogonadal men ≥ 66 yrs

Rounding off 1

- As some clinical features can be often shared with depression and Hypogonadism, we suggest measuring serum T in depressed subjects who seem to show a specific resistance to antidepressant treatments (above all in elderly men)
- T substitution can better depression in hypogonadal men and in particular in those younger than the older ones (>60 yrs)
- T substitution might enhance more the minor forms of depression than the major ones
- T oral compounds are less effective compared with intramuscular or gel formulation to improve depression in males
- No definitive evidence has been carried out about T supplementation and cognitive dysfunction and dementia so far.

Rounding off 2

- Both serum Inhinbin B and AMH but not T levels allow to clinically differenziate puberty delay from Hypogonadism Hypogonatropic (HH).
- Conversely, T substitution for 3-6 months facilitates the differential diagnosis between puberty delay and HH, leading to a complete puberty if it has chronically given.
- In adult obese men, T replacement therapy (TRT) decreases insulin resistance and fat mass as diet does.
- TRT improves Sexual dysfunction without increasing the serious side effects in elderly men with hypogonadism.

Many Thanks!