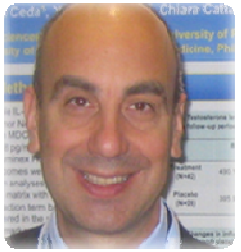
VII CONGRESSO NAZIONALE B&M 2018

II SESSIONE

Prof. Marcello Giuseppe Maggio
Professore Associato Medicina Interna e Geriatria
Università degli Studi di Parma.
Direttore S.C Dip. Medico Geriatrico Riabilitativo,
A.O Universitaria di Parma



BRAIN AND MALNUTRITION
Chronic Diseases Association ONLUS

VII CONGRESSO NAZIONALE B&M 2018

Milano 10 Maggio 2018

Fragilità e Sarcopenia: la terapia ormonale nell'uomo

Marcello Maggio
UOC Clinica Geriatrica
Università di Parma

BRAIN AND MALNUTRITION
Chronic Diseases Association ONLUS

Outline

- **La disregolazione ormonale multipla nel soggetto anziano di sesso maschile ed il contributo al «frail elderly»**
- **Focus sul ruolo del Testosterone su funzione fisica, Anemia: studi d'intervento e di Registro**
- **Il Modello della terapia di deprivazione androgenica nel Carcinoma prostatico**
- **Il Potenziale futuro ruolo dei modulatori selettivi dei recettori degli androgeni (SARMS)**

The World report on ageing and health: a policy framework for healthy ageing

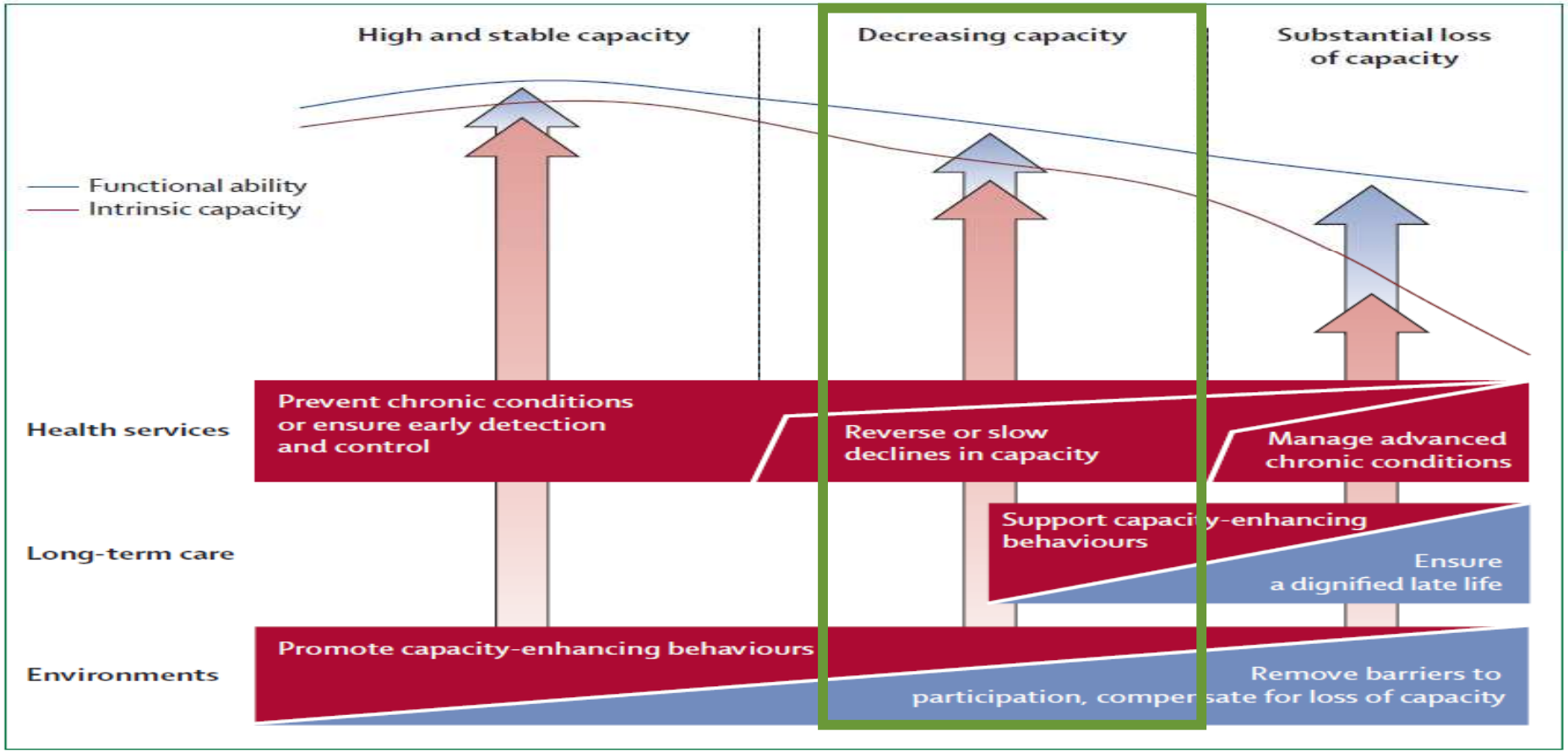


Figure 5: A public health framework for healthy ageing

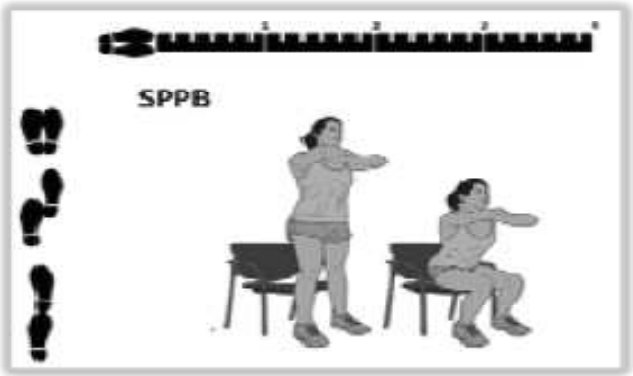
Beard JR et al. Lancet 2016; 387: 2145–54

Sarcopenia and physical frailty

Biological substrate → Muscle atrophy →

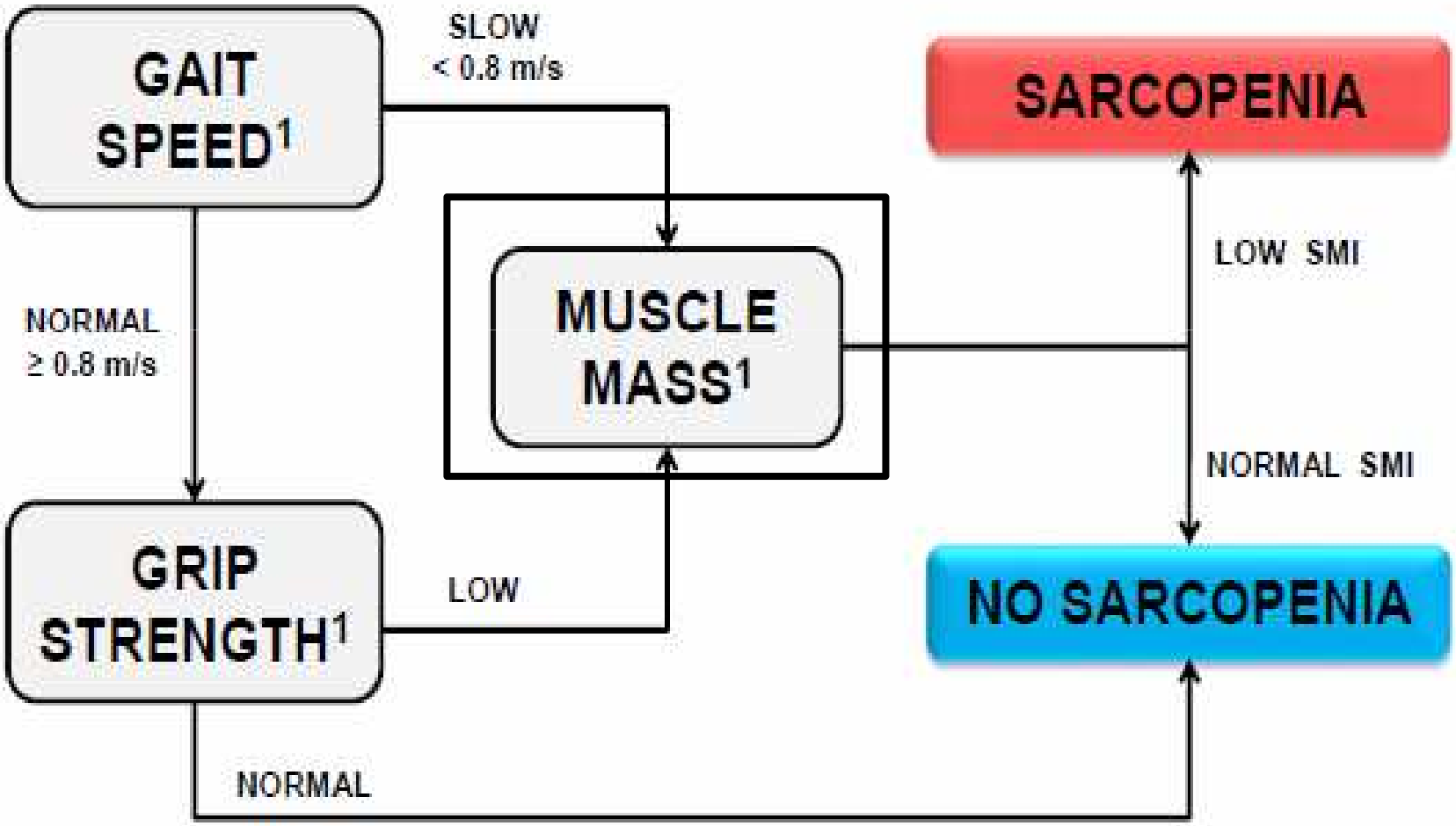
Clinical picture → Poor balance, slow gait, muscle weakness →

Physical function → Functional impairment →



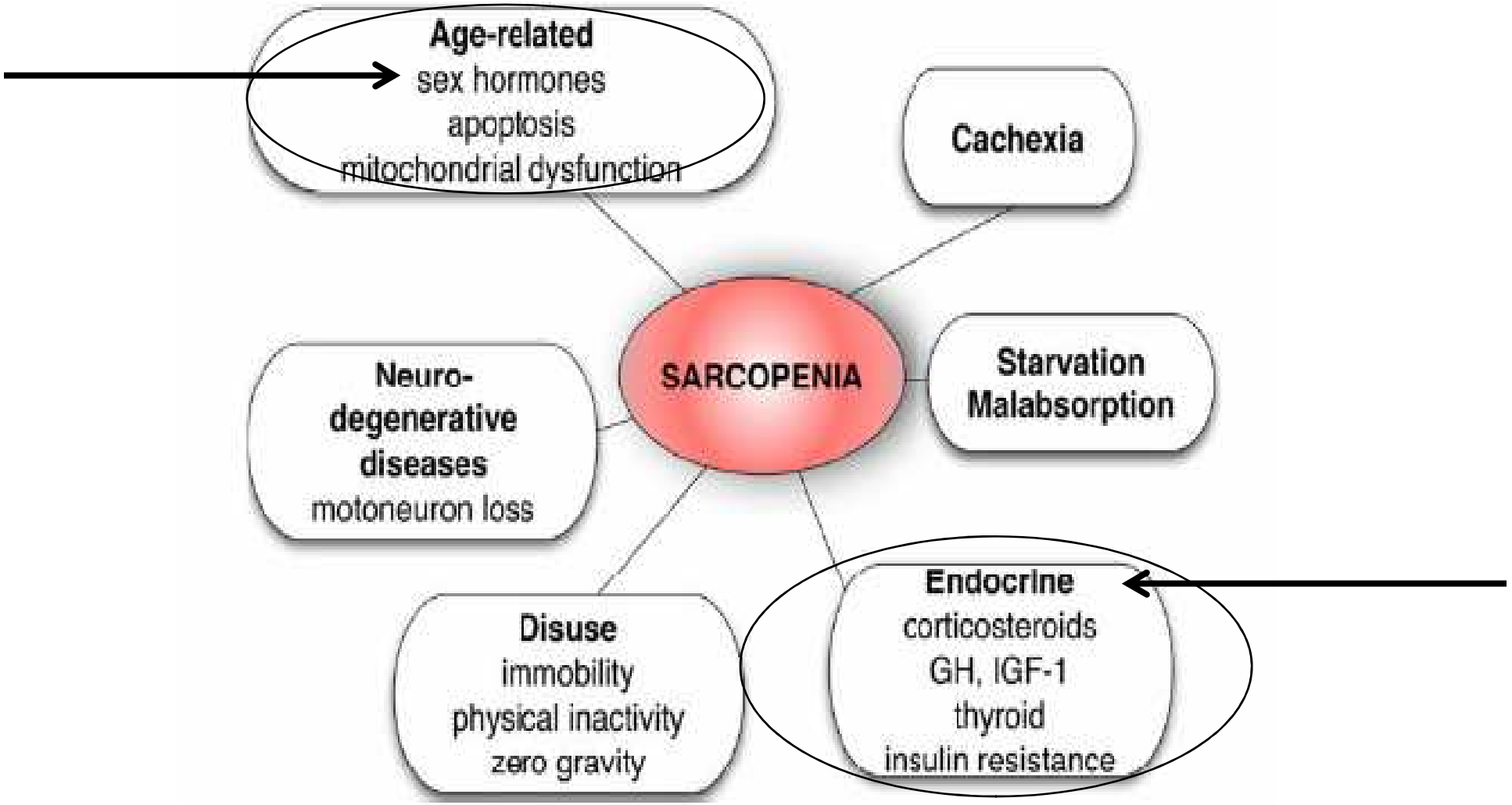
Marzetti et al. 2015 13 (5): 29-32

Clinical symptoms
EWGSOP criteria



Cruz-Jentoft AJ et al. Age Ageing 2010; 39:412-423

Conditions potentially associated with Sarcopenia

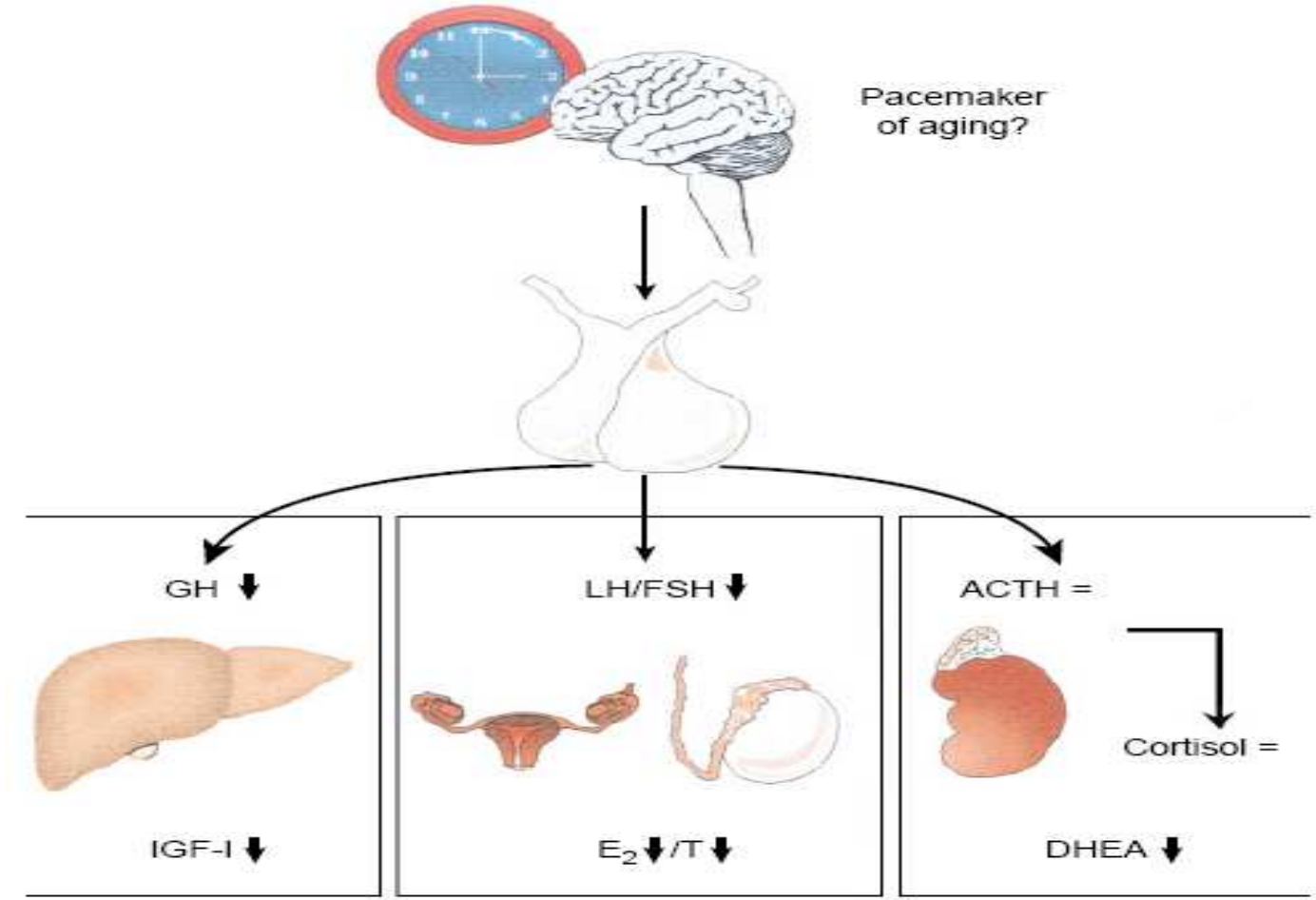


Muscaritoli M, Anker SD, Argilés J, Aversa Z, Bauer JM, Biolo G, Boirie Y, Bosaeus I, Cederholm T, Costelli P, Fearon KC, Laviano A, Maggio M, Rossi Fanelli F, Schneider SM, Schols A, Sieber CC. Clin Nutr. 2010 Apr;29(2):154-9

The Endocrinology of Aging

Steven W. J. Lamberts,* Annewieke W. van den Beld,
Aart-Jan van der Lely

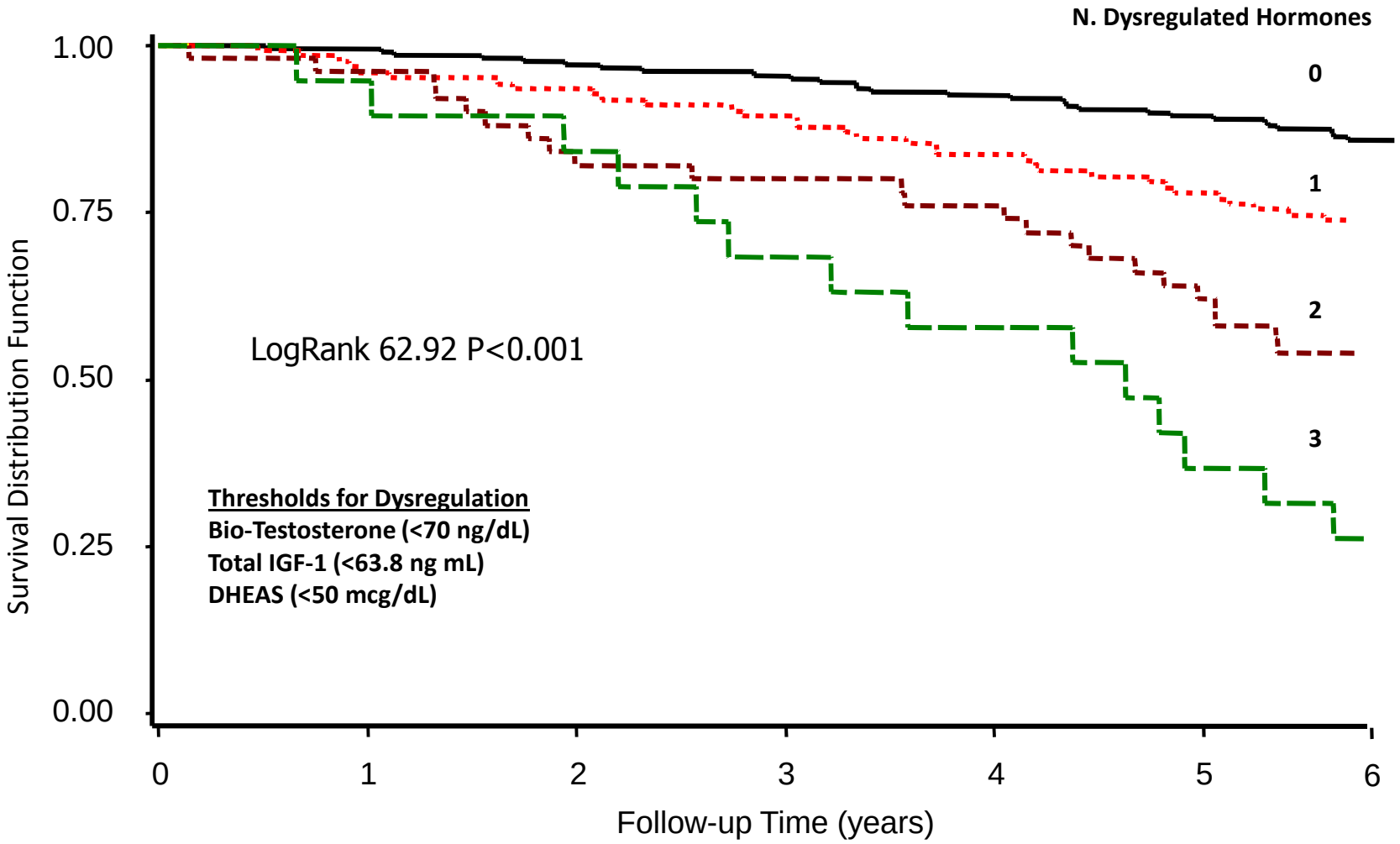
SCIENCE • VOL. 278 • 17 OCTOBER 1997



Somatopause | Andropause | Adrenopause

Menopause

Relationship between the Number of Anabolic Hormones in the Lowest serum Level Quartile and 6-Year Survival in Older Men.

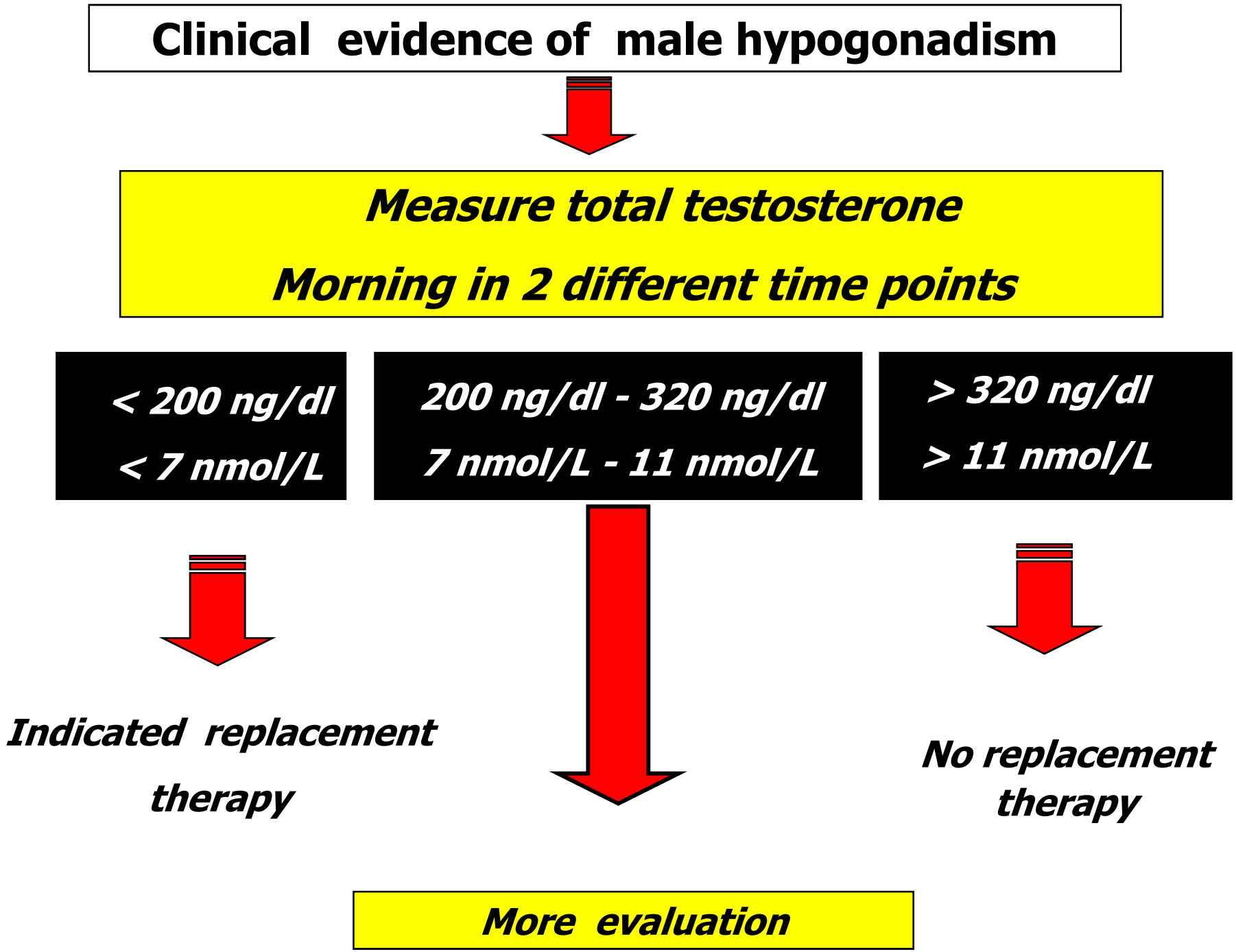


Maggio M et al. Archives of Internal Medicine 2007. 167(20):2249-54

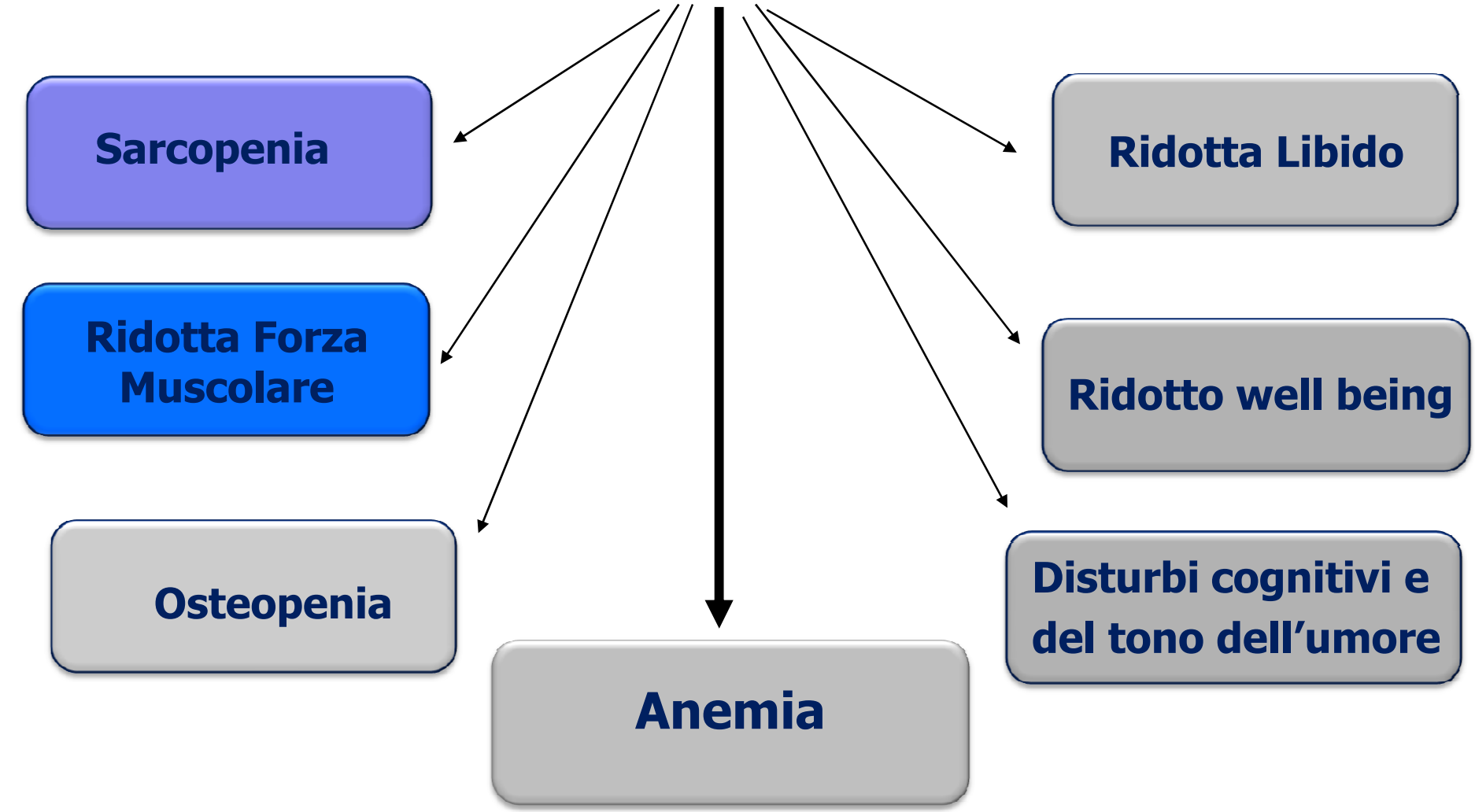
Correlati clinici di sarcopenia nel soggetto anziano

Variable	Age and Sex Adjusted Odds Ratio (95% CI)	*p*	Fully Adjusted* Odds Ratio (95% CI)	*p*	Fully Adjusted and Restricted† Odds Ratio (95% CI)	*p*
Age (y)	1.26 (1.20–1.34)	<.001	1.22 (1.14–1.30)	<.001	1.22 (1.14–1.30)	<.001
Sex (female)	1.41 (0.73–2.27)	.299	0.91 (0.42–1.96)	.806		
Education (y)	0.87 (0.77–0.99)	.039	0.85 (0.74–0.98)	.030	0.85 (0.74–0.98)	.027
BMI (kg/m^2)						
≤25	1.0 (referent)		1.0 (referent)		1.0 (referent)	
>25, <30	0.72 (0.36–1.44)	.358	1.01 (0.48–2.15)	.967		
≥30	0.31 (0.11–0.87)	.027	0.37 (0.12–1.11)	.075	0.37 (0.13–1.03)	.057
Number of medications	1.18 (1.02–1.36)	.022	1.12 (0.96–1.30)	.152		
Parkinson's disease	2.82 (0.88–9.00)	.080	1.78 (0.47–6.68)	.392		
Chronic liver disease	3.18 (0.63–16.0)	.162				
Hemoglobin (g/dL)						
Hb <12 (F), Hb <13 (M)	1.0 (referent)		1.0 (referent)		1.0 (referent)	
12 ≤ Hb <14 (F), 13 ≤ Hb <15 (M)	0.60 (0.26–1.39)	.232	0.73 (0.29–1.83)	.502		
Hb ≥14 (F), Hb ≥15 (M)	0.22 (0.08–0.61)	.004	0.35 (0.11–1.12)	.077	0.43 (0.18–1.06)	.066
IGF-I (ng/mL)						
Highest tertile	1.0 (referent)		1.0 (referent)		1.0 (referent)	
Intermediate tertile	4.20 (1.17–15.1)	.028	3.29 (0.88–12.3)	.076	3.01 (0.83–10.9)	.094
Lowest tertile	3.39 (0.96–11.9)	.057	4.25 (1.09–16.6)	.037	3.89 (1.03–14.6)	.044
Creatinine clearance (mL/min)						
Highest tertile	1.0 (referent)					
Intermediate tertile	0.70 (0.20–2.44)	.581				
Lowest tertile	0.84 (0.25–2.80)	.774				
Low bioavailable testosterone‡	3.01 (1.55–6.22)	.001	2.84 (1.33–6.07)	.007	2.70 (1.33–5.50)	.006

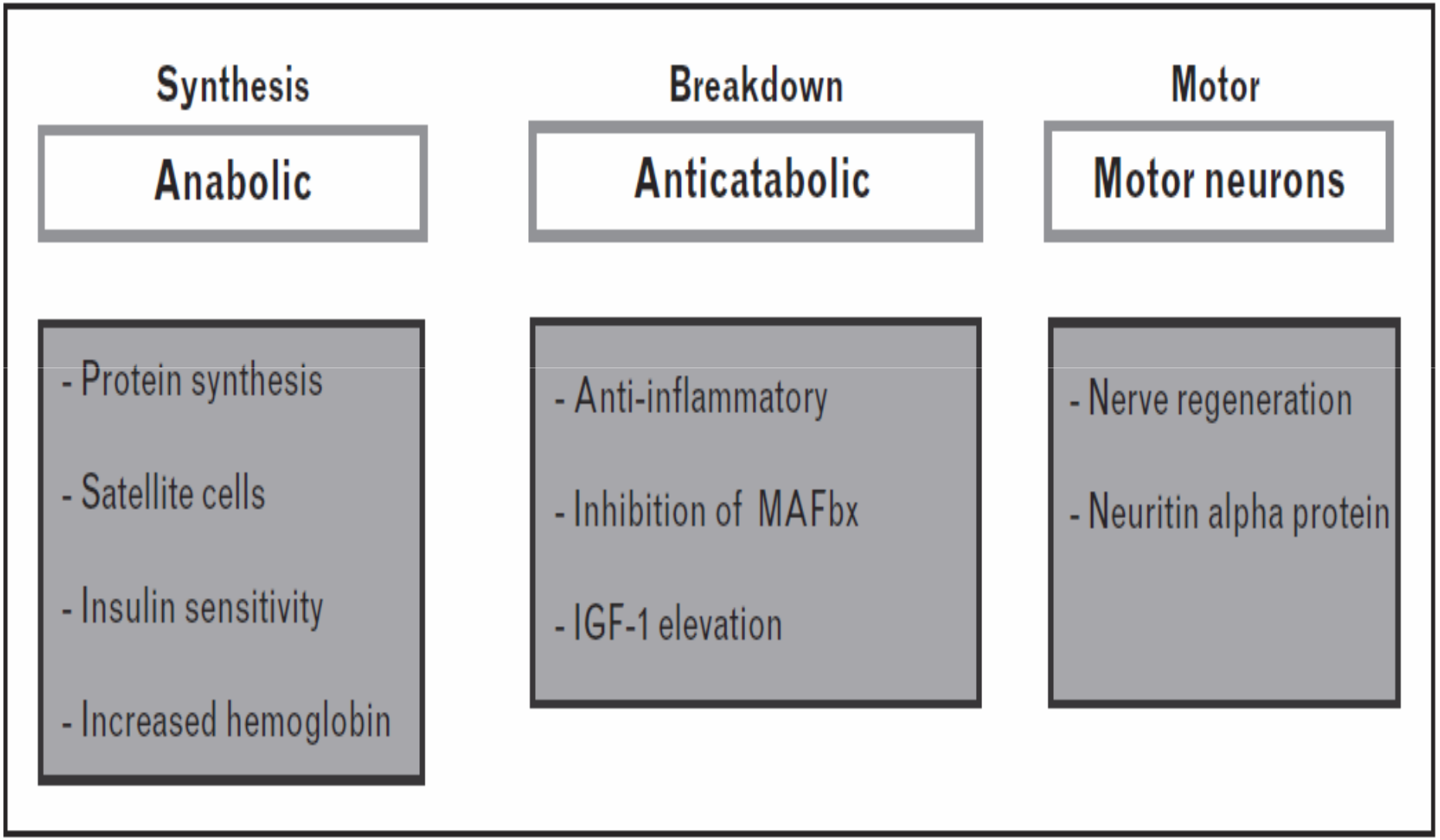
J Gerontol A Biol Sci Med Sci. 2014 Apr;69(4):438-46


Clinical evidence of male hypogonadism
Measure total testosterone
Morning in 2 different time points
< 200 ng/dl
< 7 nmol/L
200 ng/dl - 320 ng/dl
7 nmol/L - 11 nmol/L
> 320 ng/dl
> 11 nmol/L
Indicated replacement therapy
No replacement therapy
More evaluation

Sintomi associati alla carenza di Testosterone nel soggetto di sesso maschile



Testosterone and muscle function: Main Mechanisms



Maggio M, Lauretani F, Ceda GP. Curr Op Med Care Nutr 2013; 16:3-13

RCT testing the effects of testosterone on muscle strength and physical function 2005-2012

Table 2. Recent randomized controlled trial intervention studies addressing the effects of testosterone on muscle mass and function

Author	Populations	Baseline total testosterone	Form of testosterone	Duration of treatment	Effects	Notes
Kenny *et al.*, 2010 [21]	131 men (mean age 77.1 ±7.6)	<350 ng/dl	Transdermal	12–24 months	↑ lean mass ↓ fat mass in testosterone group but no differences in strength or physical performance	Calcium and vitamin D treatment was also performed
Srinivas-Shankar *et al.*, 2010 [22]	24 healthy, community-dwelling older men (60–85 years)	<350 ng/dl	Transdermal hydro-alcoholic T gel (Testogel 1%) at a dose of 50 mg/day	6 months	Improved lower limb muscle strength and improve body composition, quality of life, and physical function	Intermediate frail population
Travison *et al.*, 2011 [23▪▪]	209 randomized participants, 165 had follow-up efficacy measures. Mean (SD) age was 74 (5.4) years	100–350 ng/dl	10g testosterone gel daily	6 months	↑ muscle strength and stair-climbing power	Participants with mobility limitation: stopped because of higher prevalence of CVD
Bhasin *et al.*, 2012 [33▪▪]	8 treatment groups received (4 groups) or 2.5 mg/day of dutasteride (4 groups)	300–1200 ng/dl	Testosterone enanthate 50, 125, 300, or 600 mg/week of for and placebo	20 weeks	Changes in fat-free mass in response to graded testosterone doses did not differ in men in whom DHT was suppressed by dutasteride	With and without a dual 5α-reductase inhibitor

Maggio M, Lauretani F, Ceda GP. Curr Op Med Care Nutr 2013; 16:3-13

Clinical Meaningfulness of the Changes in Muscle Performance and Physical Function Associated With Testosterone Administration in Older Men With Mobility Limitation

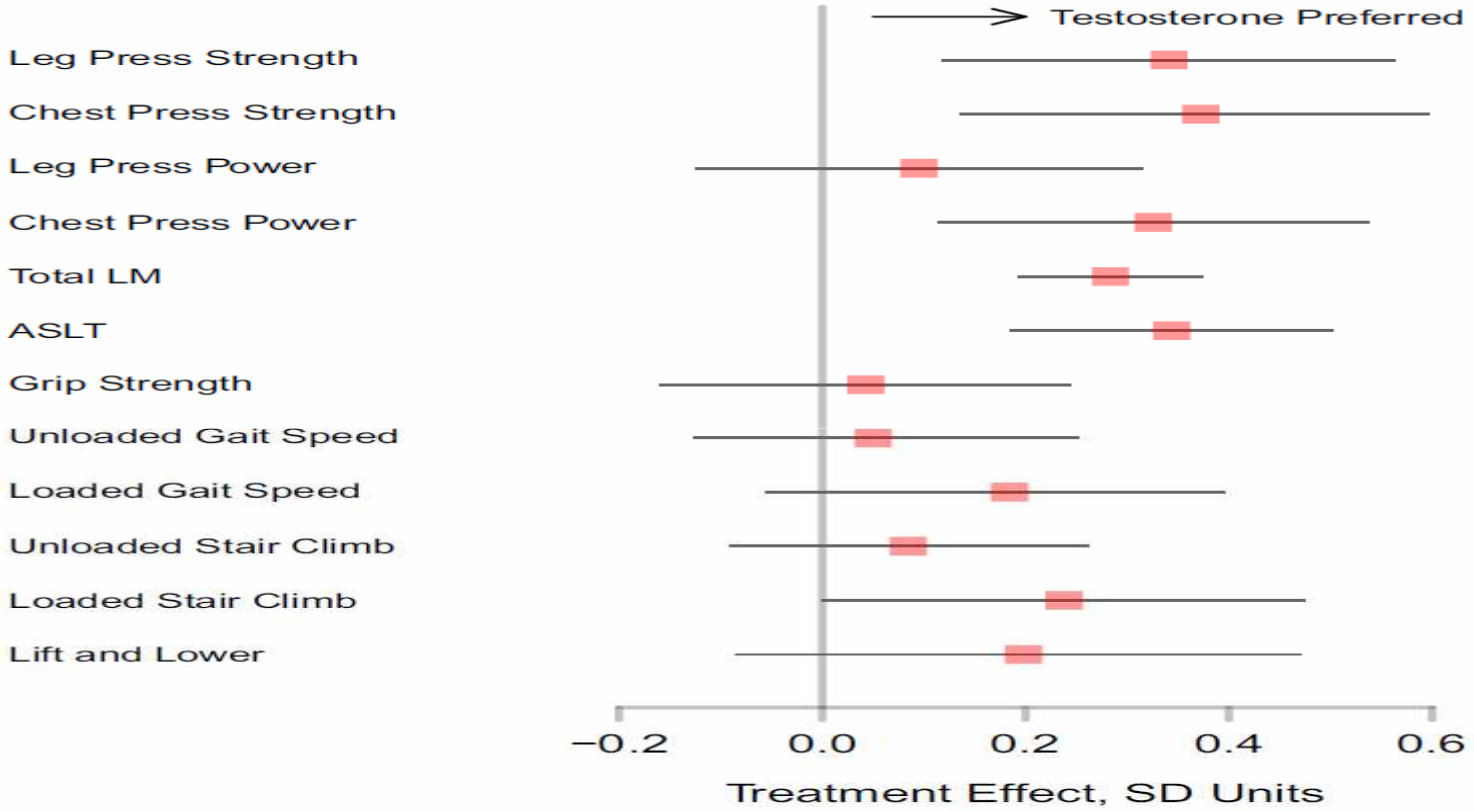


Figure 3. Absolute treatment differences (testosterone vs placebo arms) are plotted for the primary and secondary outcomes in units normalized to the baseline standard deviation of measurement; point estimates (red) are accompanied by 95% confidence intervals.

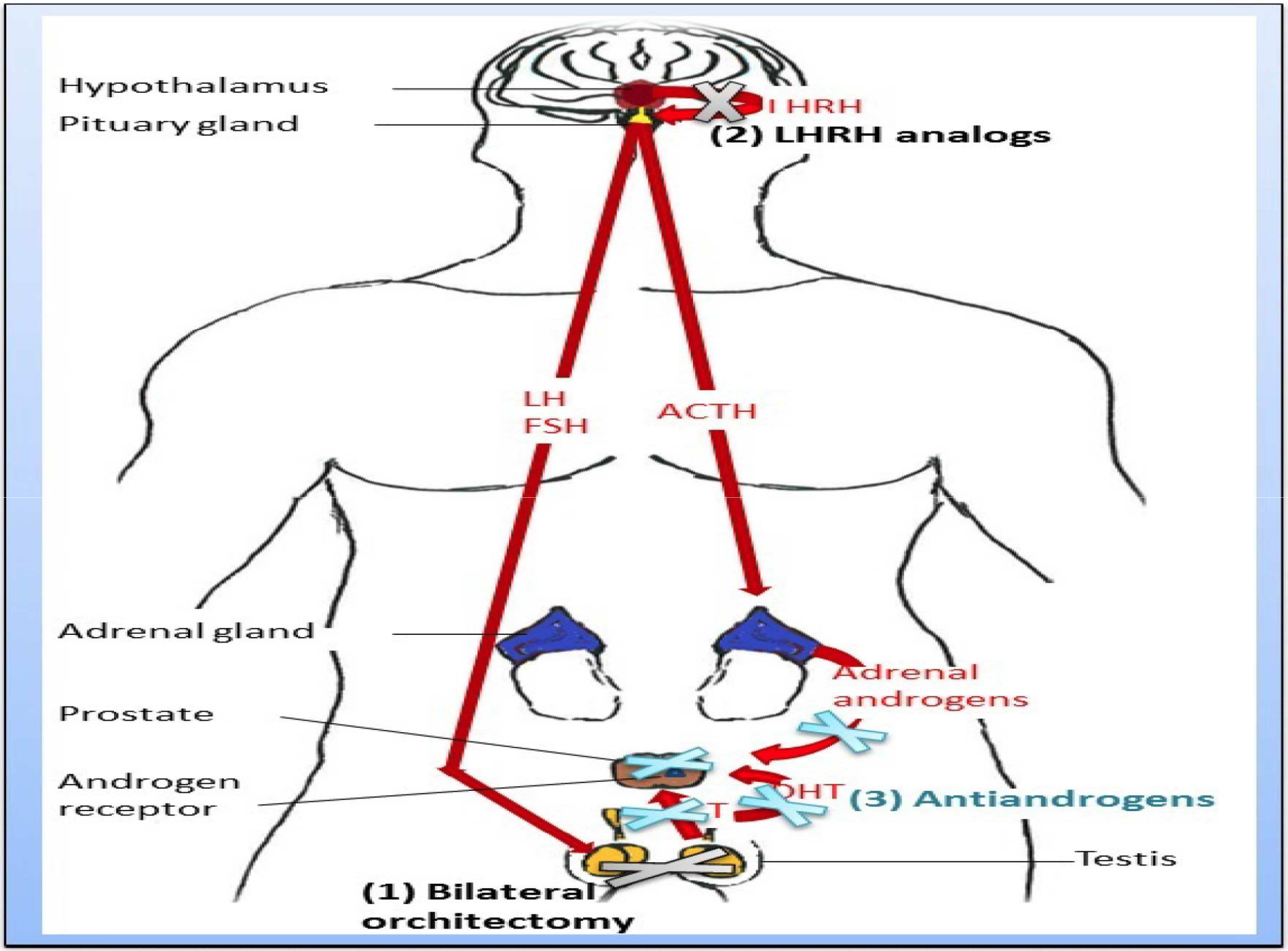
Travison et al. J Gerontol A Biol Med Sci 2010; 10:1090-1099

Muscular responses to testosterone replacement vary by administration route: a systematic review and meta-analysis

Table 6 Subanalyses' effect sizes and per cent improvement for total body fat-free mass and muscle strength outcomes from randomized clinical trials limiting enrolment to men ≥60 years of age

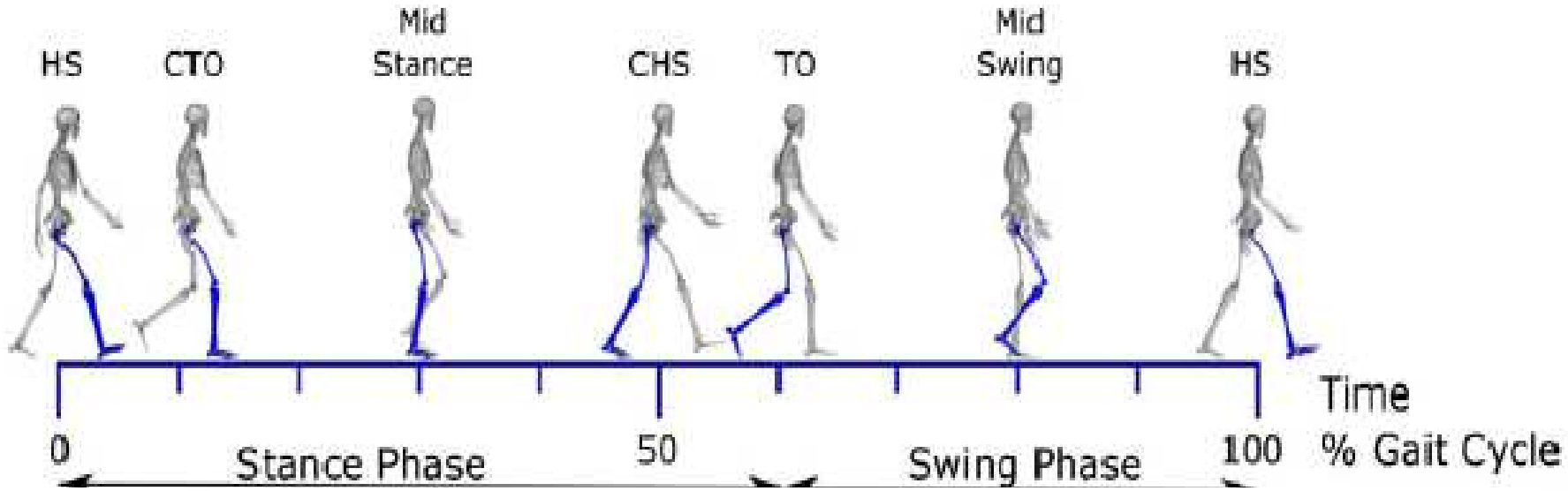
TRT route	*g*-index (*N*)	Sample size (testosterone replacement therapy, placebo)	Effect size	Standard error	95% CI	*P*-value	Improvement (%)
Fat-free mass							
Overall	18	(574, 555)	1.360	0.240	(0.880, 1.830)	<0.001	4.2
Intramuscular	8	(97, 99)	1.840	0.360	(1.120, 2.550)	<0.001	7.3
Transdermal	10	(477, 456)	1.040	0.320	(0.410, 1.670)	<0.001	1.7
Total body strength							
Overall	93	(2382, 2355)	0.860	0.120	(0.620, 1.110)	<0.001	5.9
Intramuscular	39	(477, 504)	1.330	0.130	(1.070, 1.590)	<0.001	11.3
Transdermal	54	(1905, 1851)	0.550	0.170	(0.220, 0.880)	<0.001	2.0
Lower-extremity strength							
Overall	56	(1580, 1546)	0.660	0.170	(0.320, 0.990)	<0.001	4.5
Intramuscular	24	(318, 336)	1.300	0.190	(0.920, 1.670)	<0.001	10.3
Transdermal	32	(1262, 1210)	0.210	0.230	(−0.240, 0.670)	0.360	0.1
Upper-extremity strength							
Overall	37	(802, 809)	1.170	0.170	(0.840, 1.500)	<0.001	8.1
Intramuscular	15	(159, 168)	1.370	0.170	(1.030, 1.700)	<0.001	12.9
Transdermal	22	(643, 641)	1.040	0.240	(0.580, 1.500)	<0.001	4.8

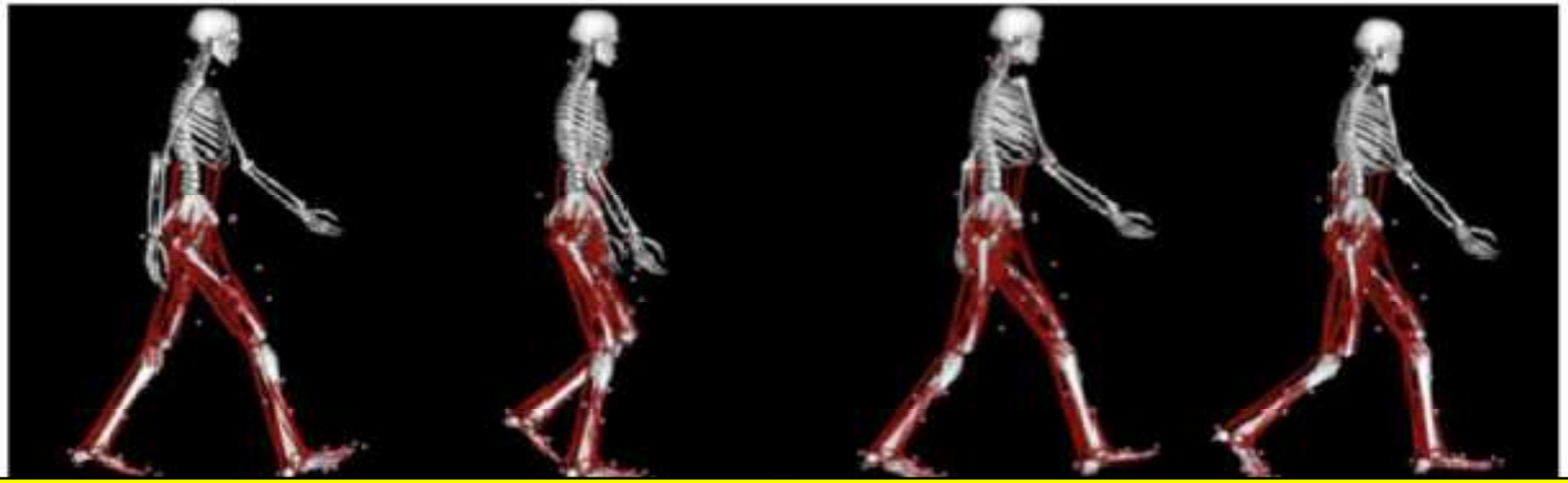
Skinner JW. Journal of Cachexia, Sarcopenia and Muscle 2018



DHT, 5α-dihydrotestosterone; T, testosterone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; LHRH, Luteinizing hormone-releasing hormone

Biochemical Leg muscle function and walking





Cheung D et al. J Cachexia Sarcopenia and Muscle 2017; 8: 102-112

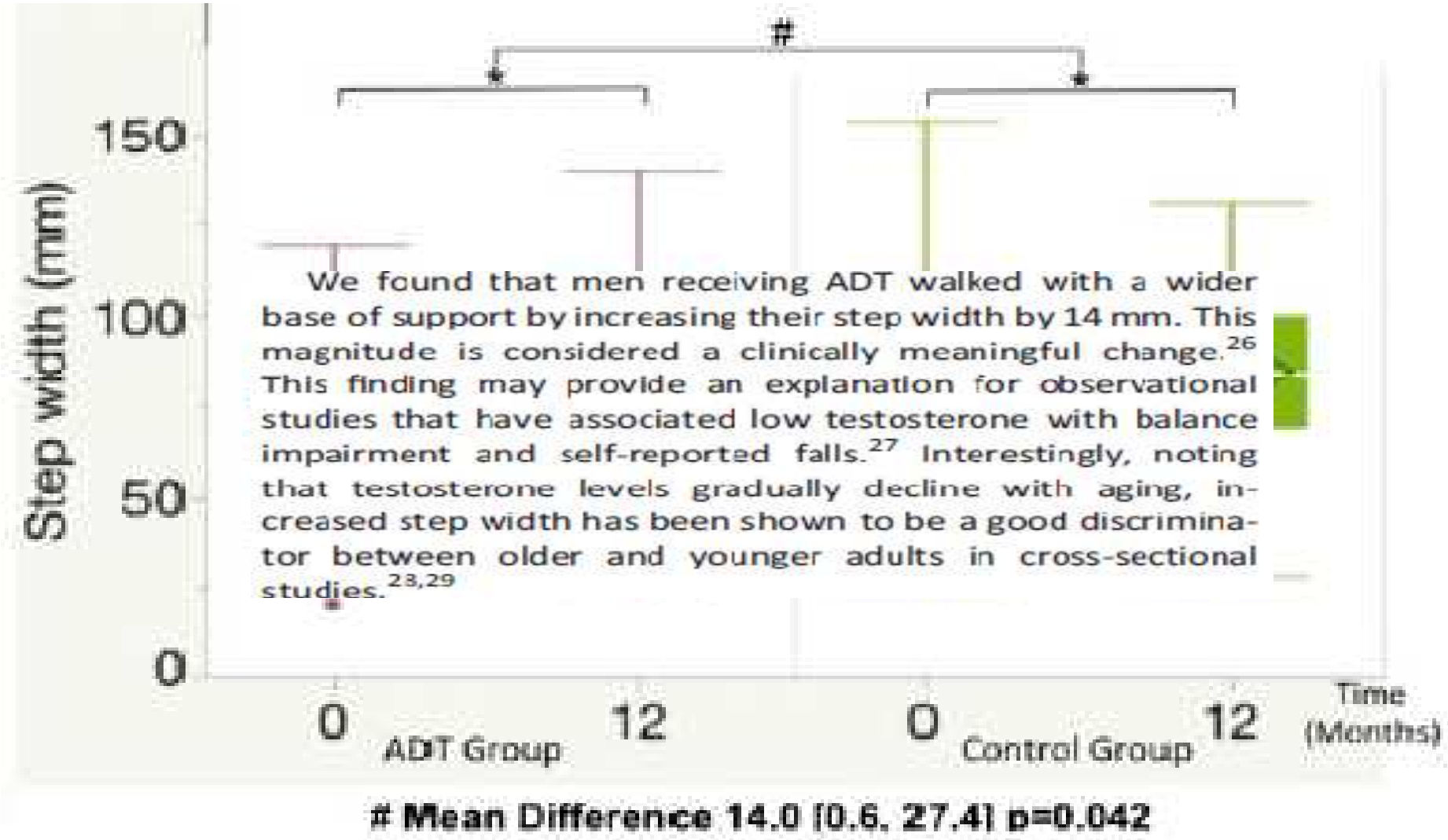
Androgen deprivation causes selective deficits in the biomechanical leg muscle function of men during walking: a prospective case–control study

Discussion

Using quantitative gait analysis in conjunction with computerized musculoskeletal modelling, we report that ADT was associated with selective decrements in lower-limb muscle function; specifically, peak hip flexor torque reduced by 14% in the ADT group, mediated by a reduction in iliopsoas force; knee extensor torque reduced by 16%, mediated by a reduction in quadriceps force; soleus' contribution to forward acceleration (propulsion) of the body reduced by 17%; and step width increased by 18%. These biomechanical changes were evident for walking at self-selected speeds, a key functional activity of daily living but became detectable only after 12 months of androgen deprivation. The objective deficits in muscle function associated with ADT over time demonstrated here are in keeping with subjective reports of decreased physical aspects of quality of life demonstrated in prior studies.[8]

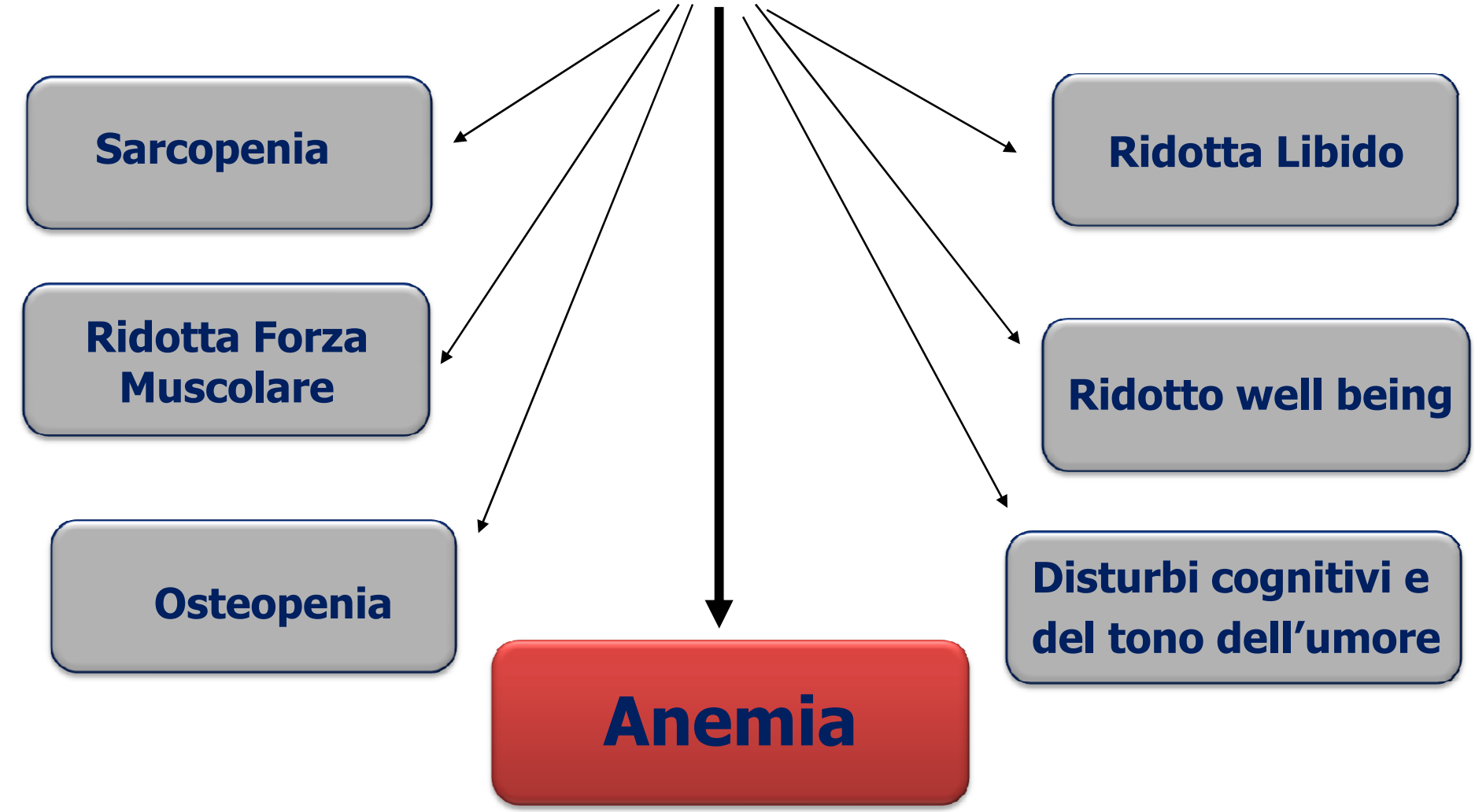
Cheung D et al. J Cachexia Sarcopenia and Muscle 2017; 8: 102-112

Base of support during walking as proxy of balance impairment

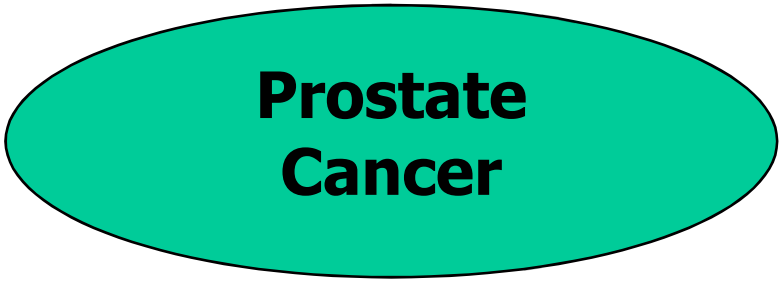


Cheung D et al. J Cachexia Sarcopenia and Muscle 2017; 8: 102-112

Sintomi associati alla carenza di Testosterone nel soggetto di sesso maschile



Safety concerns during Testosterone treatment In older men



↑ Hemoglobin
↑ Hematocrit

Adverse Effects of Testosterone Therapy in Adult Men: A Systematic Review and Meta-Analysis

The Journal of Clinical Endocrinology & Metabolism

TABLE 4.
Random effects meta-analysis

First author, year (Ref.)		95% CI Lower boundary	95% CI Upper boundary	I^2
Hematocrit	3.18	1.35	5.01	91.40
Bhasin, 2007 (30)	0.70	−0.03	1.43	
Snyder 1999a, 1999b, 2001 (58, 59, 19)	3.40	1.99	4.81	
Amory, 2004 (25); Page, 2005 (26)	6.70	3.48	9.92	
Emmelot-Vonk, 2008 (71)	1.00	0.26	1.74	
Morley, 1993 (54)	6.00	4.17	7.83	
Hemoglobin	0.80	0.45	1.14	95.05
Snyder 1999a, 1999b, 2001 (58, 59, 19)	0.80	0.32	1.28	
Amory, 2004 (25); Page, 2005 (26)	2.20	1.37	3.03	
Giannoulis, 2006 (43)	0.50	0.37	0.63	
Knapp, 2008 (51)	1.10	0.97	1.23	
Sih, 1997 (56)	1.60	0.71	2.49	
Emmelot-Vonk, 2008 (71)	0.20	0.06	0.34	
Allan, 2008 (17)	0.20	0.10	0.30	
Bhasin, 2000 (29)	1.91	−0.21	4.03	
Clague, 1999 (36)	0.50	−0.50	1.50	
Prostate symptom scales	0.29	−0.44	1.02	0.00
Snyder 1999a, 1999b, 2001 (58, 59, 19)	0.60	−0.54	1.74	
Amory, 2004 (25); Page, 2005 (26)	2.00	−0.60	4.60	
Marks, 2006 (10)	−2.64	−7.56	2.28	
Wittert, 2003 (21)	−1.20	−3.28	0.88	
Emmelot-Vonk, 2008 (71)	0.20	−1.09	1.49	
Chiang, 2007 (18)	0.40	−3.34	4.14	
Kenny, 2004 (50)	1.00	−5.29	7.29	
PSA change	0.10	−0.01	0.21	57.57
Bhasin, 2007 (30)	0.10	0.02	0.18	
Malkin, 2006 (12)	0.16	−0.11	0.43	
Snyder 1999a, 1999b, 2001 (58, 59, 19)	0.40	−0.14	0.94	
Amory, 2004 (25); Page, 2005 (26)	0.10	−0.56	0.76	
Katznelson, 2006 (48)	0.30	0.11	0.49	
Knapp, 2008 (51)	0.16	0.10	0.22	
Marks, 2006 (10)	0.61	−0.34	1.56	
Sih, 1997 (56)	0.40	−0.31	1.11	
Wittert, 2003 (21)	−0.30	−0.76	0.16	
Emmelot-Vonk, 2008 (71)	0.00	−0.30	0.30	
Ferrando, 2002 (42)	0.80	0.05	1.55	
Morley, 1993 (54)	0.60	−0.25	1.45	
Allan, 2008 (17)	−0.30	−0.53	−0.07	
Sullivan, 2005 (60)	−0.49	−1.64	0.66	
Kenny, 2004 (50)	0.73	−0.19	1.65	
Cavallini, 2004 (35)	−0.30	−0.75	0.15	

Fernández-Balsells M M et al. JCEM 2010;95:2560-2575

Prevalenza dell'anemia ed outcome clinici nel soggetto anziano

- ✓ L'anemia è classificata secondo l'OMS da livelli di Hb < 13 g/dL nei M e < 12 g/dL nelle F
  Nutritional anemias. WHO Tech Rep Set 1968;405:5-3

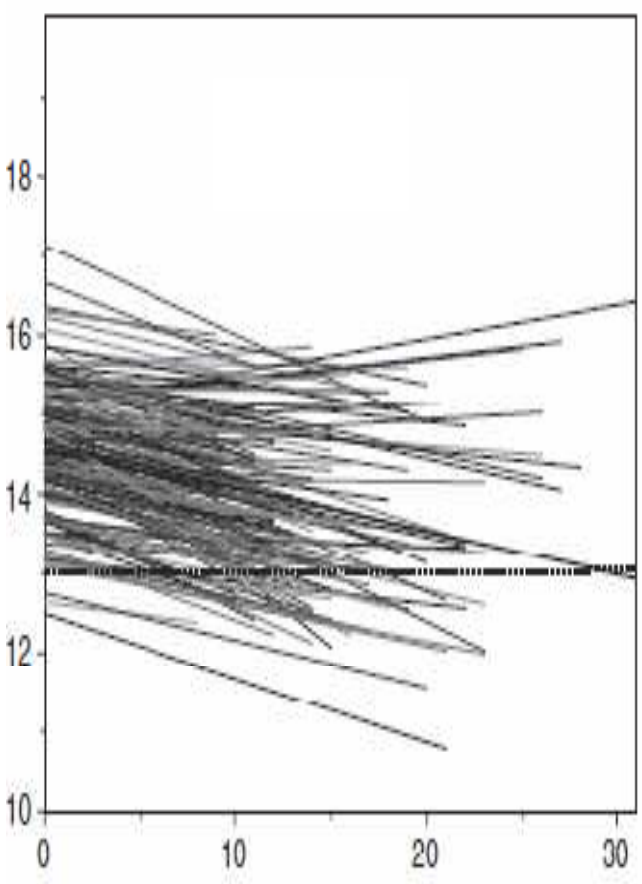
- ✓ La Prevalenza dell'anemia aumenta con l'età (dal 5 al 30%)
  20% soggetti >85 anni ("very very old")
  Guralnik JM et al. Blood 2004;104:2263-8.
  Kushang V et al. Sem Haemat 2008;45(4): 210-17

- ✓ L'anemia è un fattore predittore di fragilità, disabilità, ospedalizzazione e morte.
  Lipschitz D. J Am Ger Soc 2003;51:10-3.
  Penninx BW et al. J Am Ger Soc 2004;52:719-24

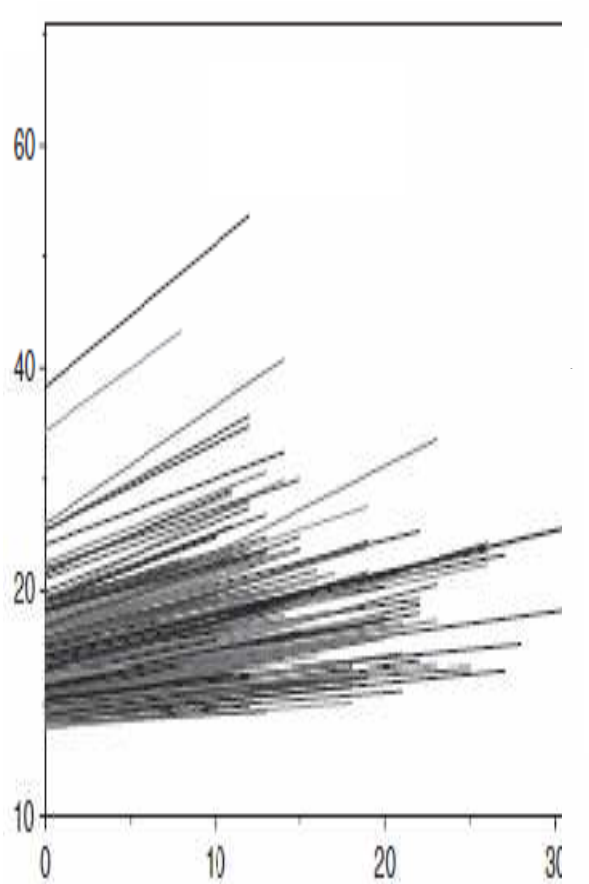
- ✓ 30-40% anemie nell'anziano sine causa ("unexplained anemia")
  Guralnik JM et al. Blood 2004;104:2263-8

Modificazioni longitudinali di emoglobina, Eritropoietina (EPO) nei due sessi e di testosterone nell'uomo: dati del BLSA

Emoglobina (g/dL)



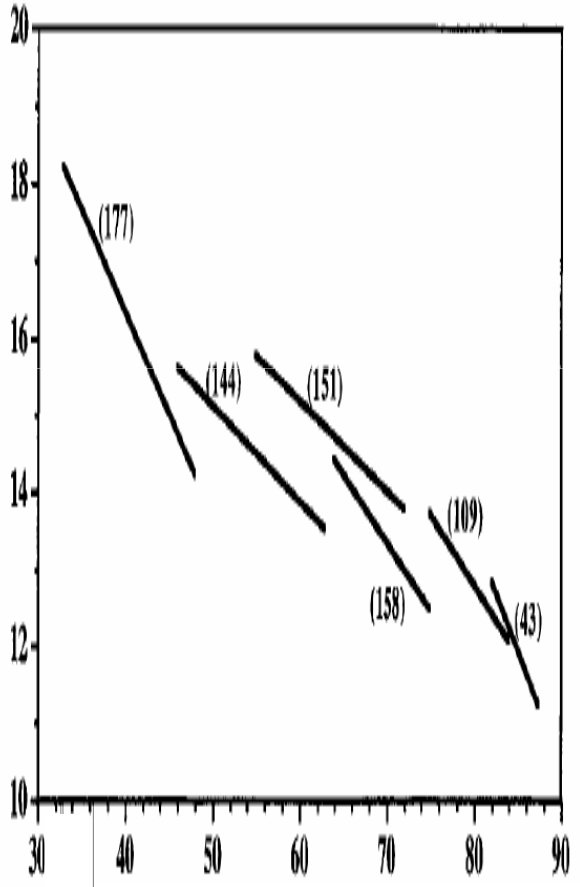
EPO (mIU/mL)



Time (years of follow-up)

Ershler et al. J Am Geriatr Soc 2005;53:1360-1365

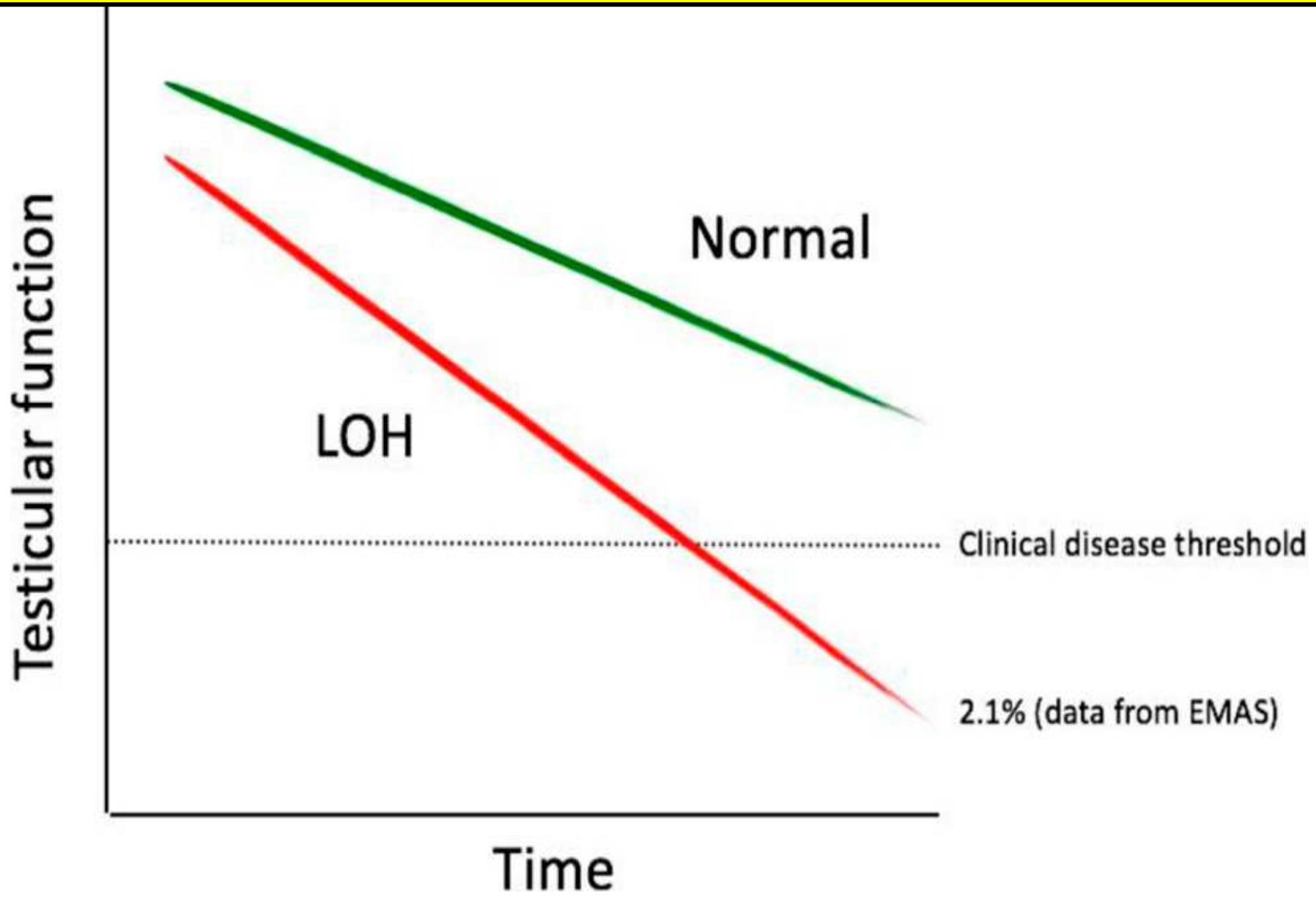
Testosterone (nmol/L)



Time (age-years)

Harman et al. JCEM 2001;86:724-31

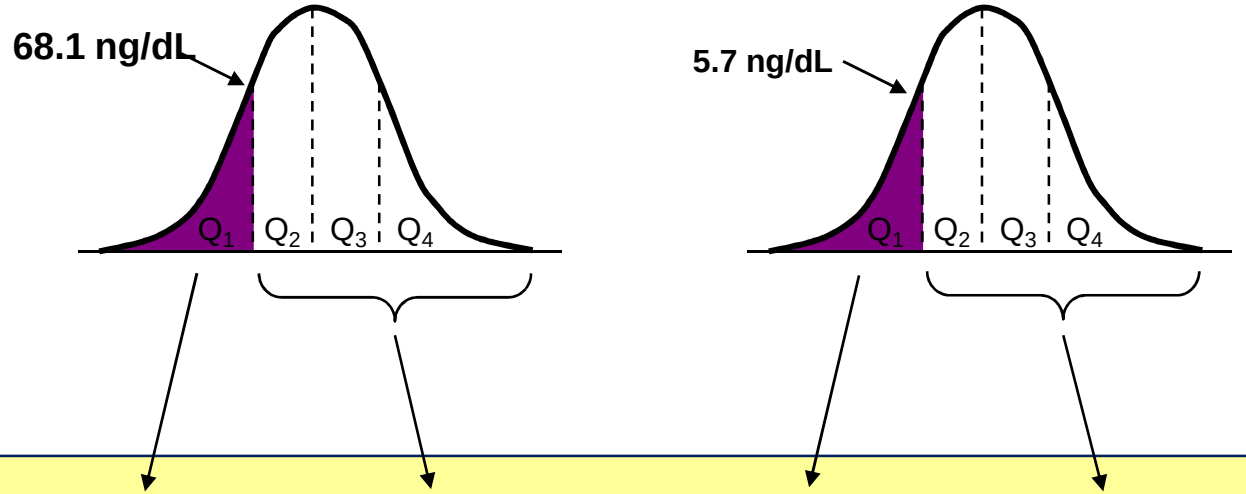
La prevalenza di Late onset hypogonadism (LOH) secondo lo studio EMAS



Bassi livelli di Testosterone biodisponibile e rischio di Anemia In soggetti non anemici dello Studio InCHIANTI

Testosterone biodisponibile
In Uomini senza Anemia (N=274)

Testosterone biodisponibile
In Donne senza Anemia (N=337)



Baseline

	Uomini		Donne	
Incidenza di Anemia a 3 anni	21.0%	**4.7%**	16.1%	**3.9%**
Rischio Relativo*	**4.7** (1.3-16.8)		**4.4** (1.7-11.2)	

* Aggiustato per età, BMI e molteplici confounders inclusa l'eritropoietina

Ferrucci L, Maggio M et al. Arch Int Med 2006;166(13):1380-8

Prevalenza di anemia non spiegata (nero) in Uomini e Donne dello Studio InCHIANTI

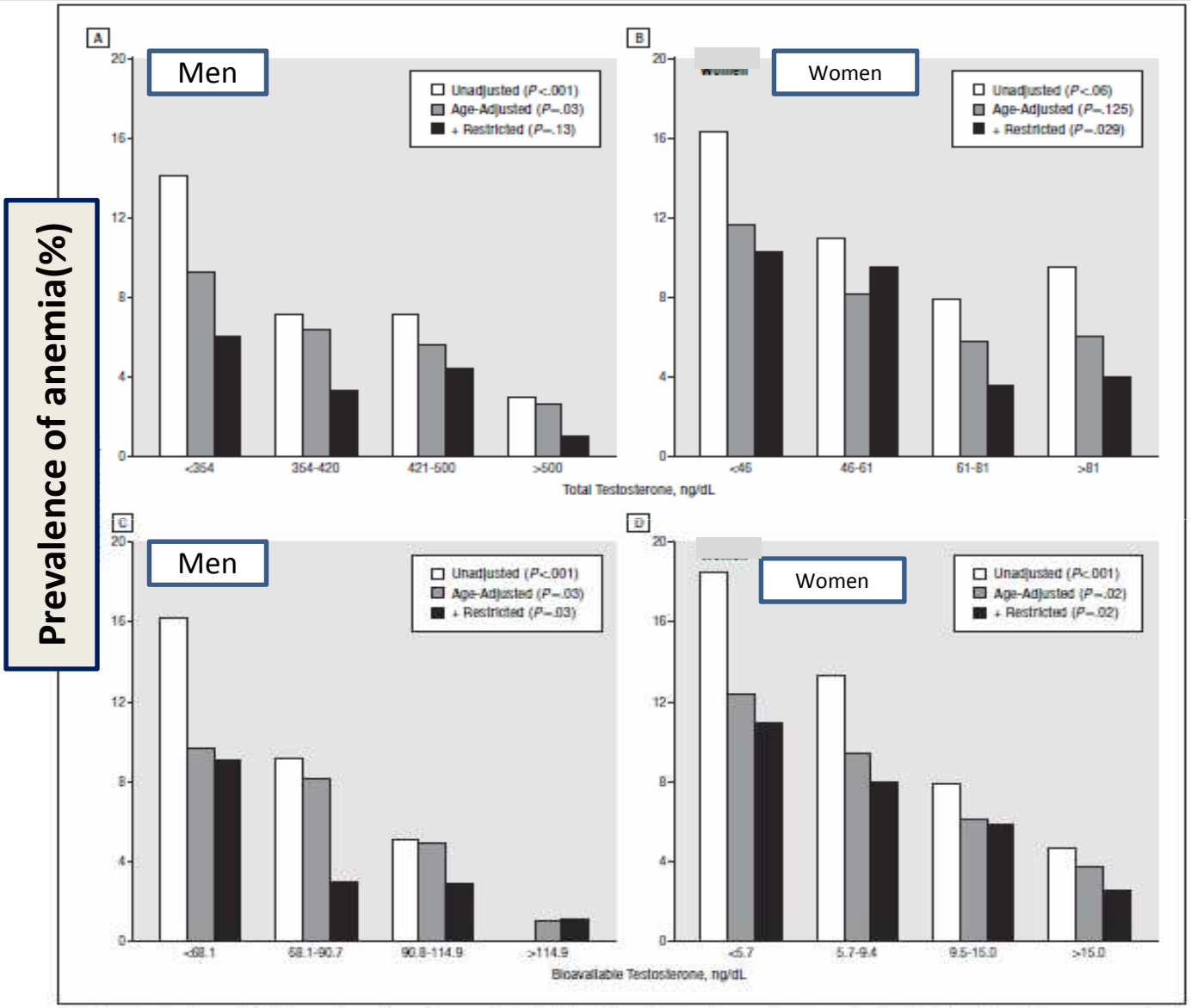


Figure 2. Crude and age-adjusted prevalence of anemia according to total and bioavailable testosterone level quartiles in all InCHIANTI[19] participants and restricted to cases of unexplained anemia (ie, normal serum iron levels and no deficiencies of iron, cyanocobalamin (vitamin B_{12}), or folate. To convert testosterone to nanomoles per liter, multiply by 0.0347.

Ferrucci L, Maggio M et al. Arch Int Med 2006;166(13):1380-8

Effects of Testosterone on hemoglobin levels

Participant Group	Outcome	Treatment	No.	Baseline, Mean (SD)[a]	Change From Baseline Values, Months[a]				Effect (95% CI)		
					3	6	9	12	Treatment[b]	Size[c]	P Value[d]
Unexplained anemia											
Primary outcome	Hemoglobin (difference)[e]	Testosterone	27	11.9 (0.7)	5/24 (25)	8/22 (36)	15/24 (63)	13/24 (54)	31.5 (17-277.5)		.002
		Placebo	35	12.1 (0.6)	4/32 (13)	3/27 (11)	2/28 (7)	4/27 (15)			
Secondary outcome	Hemoglobin (continuous)	Testosterone	27	11.9 (0.7)	0.6 (0.2)	0.5 (0.2)	1.1 (0.3)	0.9 (0.4)	0.63 (0.43-1.39)	1.30 (0.75-2.26)	<.001
		Placebo	35	12.1 (0.6)	0.1 (0.2)	0.2 (0.6)	0.0 (0.5)	0.2 (0.5)			
Exploratory outcomes											
Anemia of known cause	Hemoglobin (difference)[e]	Testosterone	29	12.1 (0.4)	7/25 (28)	11/26 (38)	12/25 (48)	13/25 (52)	8.2 (2.1-31.9)		.01
		Placebo	35	11.7 (0.5)	2/31 (6)	2/25 (8)	4/26 (15)	5/27 (19)			
	Hemoglobin (continuous)	Testosterone	29	12.1 (0.4)	0.5 (0.2)	0.9 (0.2)	0.8 (0.3)	0.9 (0.3)	0.64 (0.12-1.17)	0.90 (0.17-1.65)	.015
		Placebo	35	11.7 (0.5)	−0.1 (0.2)	−0.1 (0.6)	0.1 (0.5)	0.3 (0.5)			
Anemia	Hemoglobin (difference)[e]	Testosterone	335	14.3 (0.9)	58/323 (30)	125/314 (40)	113/309 (36)	115/305 (38)	23.7 (12.9-33.5)		<.001
		Placebo	321	14.4 (0.9)	8/304 (3)	11/298 (4)	11/284 (4)	11/285 (4)			
	Hemoglobin (continuous)	Testosterone	335	14.3 (0.9)	0.5 (0.2)	0.5 (0.2)	0.6 (0.2)	0.6 (0.2)	0.93 (0.78-1.08)	0.96 (0.86-1.12)	<.001
		Placebo	321	14.4 (0.9)	−0.3 (0.2)	−0.3 (0.8)	−0.3 (0.5)	−0.4 (0.3)			

Roy CN et al. JAMA Intern Med 2017

EDITORIAL

Further Elucidation of the Potential Benefits of Testosterone Therapy in Older Men

Eric Orwoll, MD

Testosterone has long been known to stimulate erythrocytosis, and in this issue Roy et al[4] report that testosterone replacement appears to have benefit in men with unexplained anemia—8% of the T-Trial participants. Compared with placebo, treatment resulted in substantially more men who had an increase in hemoglobin of at least 1.0 g/dL (15% vs 54%) and who were no longer anemic (22% vs 58%). Although the increases in hemoglobin were generally not large (mean increase, 0.83 g/dL; 95% CI, 0.48-1.39), the effect is important because unexplained anemia is common in older people and has no known treatment. Importantly, men with known causes of anemia (also 8% of participants) accrued similar benefits. Clearly these results suggest that in older men with unexplained anemia, or anemia of known etiology but without adequate response to therapy, an assessment of gonadal status would be warranted. If hypogonadism is present, testosterone replacement should be considered.

MECCANISMO D'AZIONE EMATOPOIETICO DEL TESTOSTERONE

✓ Azione diretta:

- aumenta attività del midollo osseo (stimolazione CFU-E)

  Moriyama Y, Fisher JW. Blood. 1975; 45: 665-70.

- stimola incorporazione del Ferro nei globuli rossi

  Molinari PF, Rosenkrantz H. J Lab Clin Med. 1971; 78:399-410.

- aumenta uptake del glucosio con attivazione glicolisi

  Molinari PF, Esber HJ, Snyder LM. Exp Hematol. 1976; 4: 301-9.

- potenzia l'effetto IGF-1 con maturazione e proliferazione dei proeritroblasti

  Hagenfeldt Y, Linde K, Sjoberg HE, Zumkeller W, Arver. Int J Androl. 1992; 15: 93–102.

- aumenta l' emivita dei globuli rossi

  Solomon LR, Hendler ED. Acta Haematol. 1988; 79: 12–19

✓ Azione indiretta:

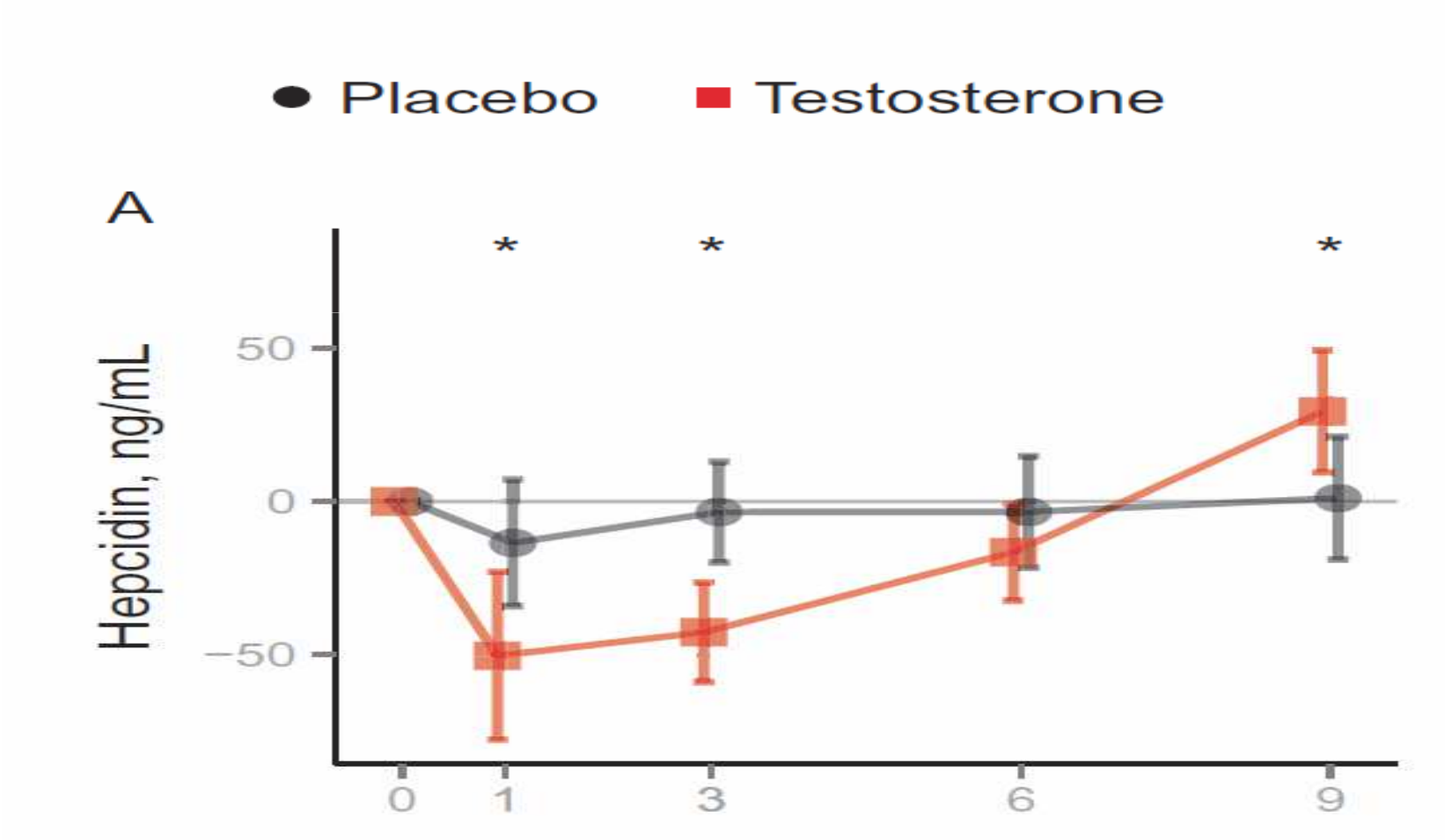
- stimolazione di eritropoietina per aumento dell'RNA polimerasi con incremento della massa renale

  Paulo LG, Fink GD, Roh BL, Fisher JW .Blood. 1974; 43: 39-47.

Basaria S, Maggio M. J Endocrinol Invest 2009; 32: 704-16

Testosterone Induces Erythrocytosis via Increased Erythropoietin and Suppressed Hepcidin: Evidence for a New Erythropoietin/Hemoglobin Set Point

the Journals of gerontology® Series A



Bachman et al. J Gerontol 2014

Anaemia associated with androgen deprivation in patients with prostate cancer receiving combined hormone blockade

S.B. STRUM, J.E. McDERMED, M.C. SCHOLZ, H. JOHNSON and G. TISMAN

Daniel Freeman Marina Medical Centre, Marina del Rey, and The Institute for Prostate Cancer Research, California, USA

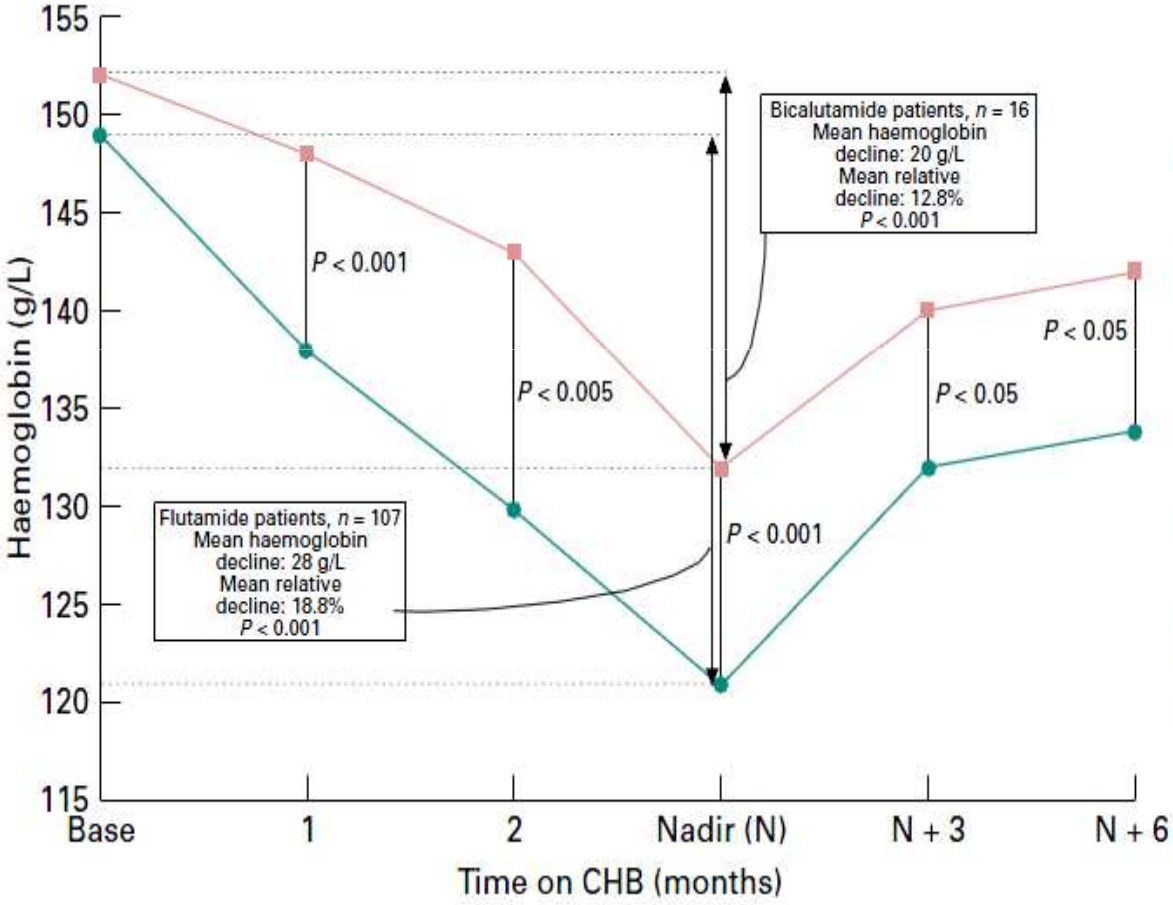
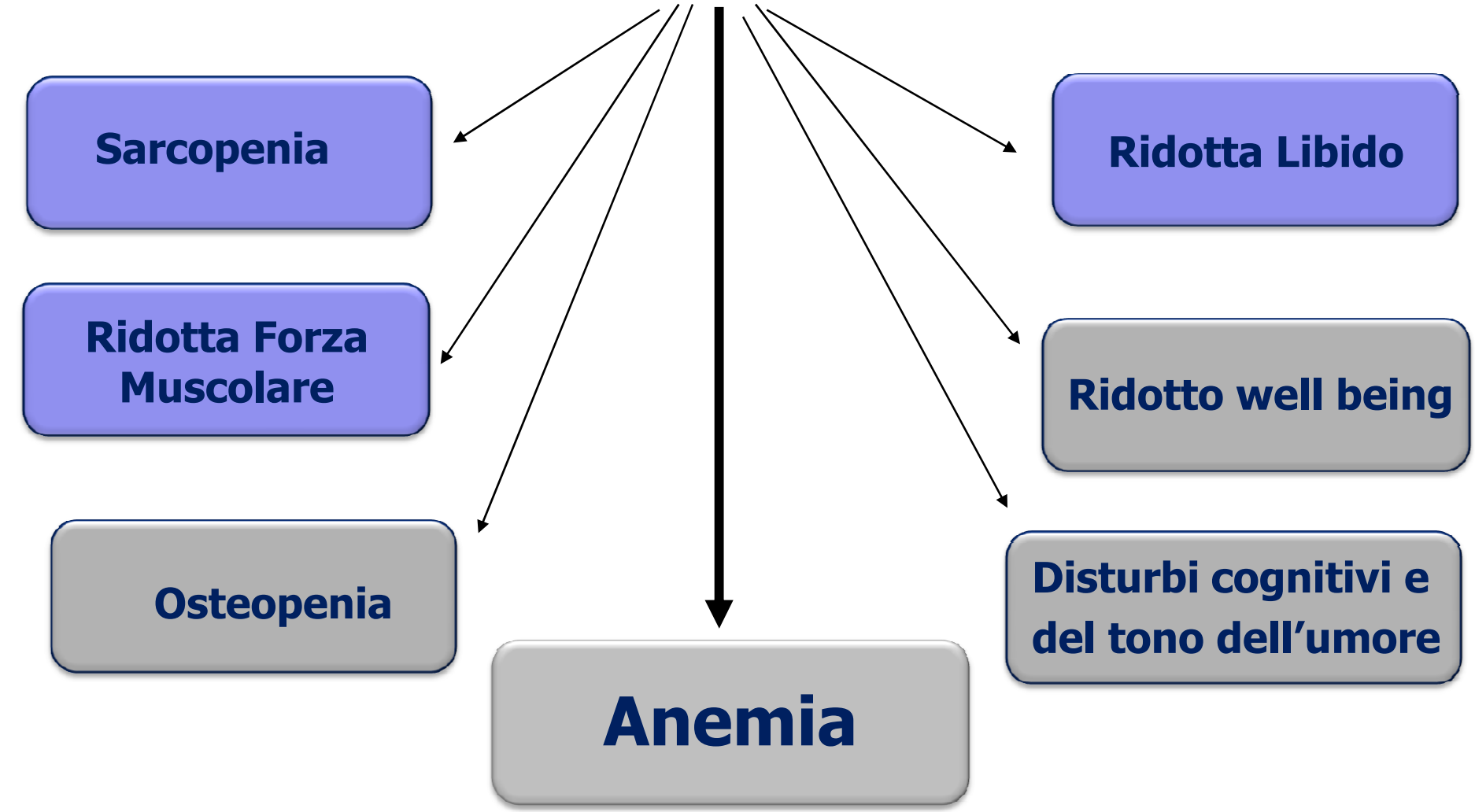


Fig. 3. There was no statistically significant difference in mean baseline haemoglobin levels between the 107 patients receiving flutamide (green) and the 16 patients receiving bicalutamide (red) ($P = 0.28$). Patients receiving CHB with flutamide had significantly lower mean haemoglobin levels at all measured times after CHB initiation when compared with patients receiving CHB with bicalutamide. The mean relative haemoglobin decline of each subset was significantly different (flutamide patients = 18.8 [1.1]%; bicalutamide patients = 12.8 [1.7]%, $P < 0.001$).

British Journal of Urology (1997), 79, 933–941

Sintomi associati alla carenza di Testosterone nel soggetto di sesso maschile



Effects of Testosterone Treatment in Older Men

BACKGROUND

Serum testosterone concentrations decrease as men age, but benefits of raising testos-

790 men 65 years of age or older (mean age 72) with serum testosterone less than 275 ng/dl and symptoms of hypoandrogenism

ity Trial. The primary outcome of each of the individual trials was also evaluated in all participants.

RESULTS

Testosterone treatment increased serum testosterone levels to the mid-normal range for men 19 to 40 years of age. The increase in testosterone levels was associated with significantly increased sexual activity, as assessed by the Psychosexual Daily Questionnaire

1 year of treatment of testosterone gel. Initial dose 5 g daily

men who received testosterone vs. 12.6% of men who received placebo, P=0.003). Testosterone had no significant benefit with respect to vitality, as assessed by the Functional Assessment of Chronic Illness Therapy–Fatigue scale, but men who received testosterone reported slightly better mood and lower severity of depressive symptoms than

Primary outcomes: sexual, physical and vitality after 1 year of treatment of testosterone gel.

a moderate benefit with respect to sexual function and some benefit with respect to mood and depressive symptoms but no benefit with respect to vitality or walking distance. The number of participants was too few to draw conclusions about the risks of testosterone treatment. (Funded by the National Institutes of Health and others; ClinicalTrials.gov number, NCT00799617.)

PJ Snyder et al N Engl J Med 2016;374(7):611-24

Effects of Testosterone on sexual activity

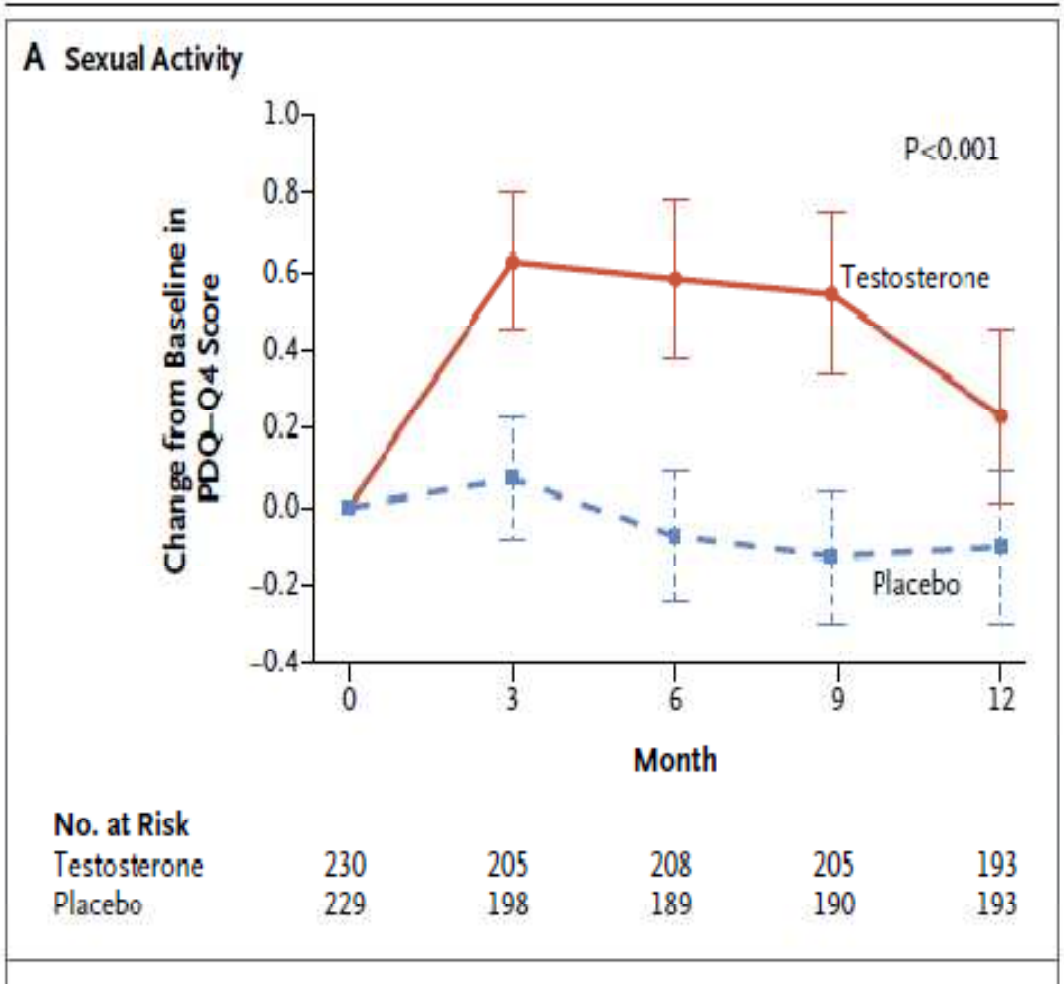
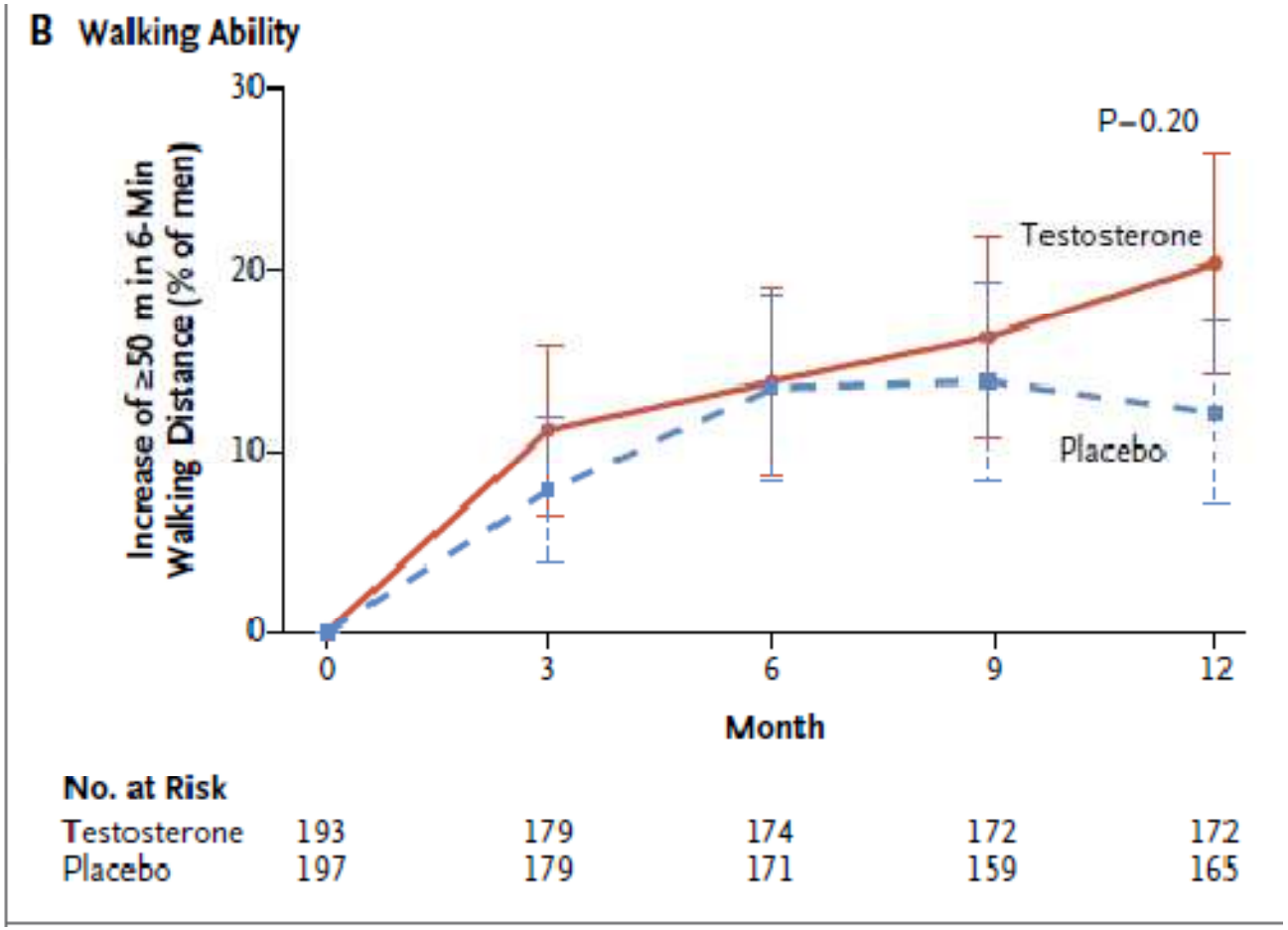


Figure 1. Primary Outcomes in the Three Main Trials of the Testosterone Trials.

The primary outcome of the Sexual Function Trial (Panel A) was the change from baseline in the score for sexual activity (question 4) on the Psychosexual Daily Questionnaire (PDQ-Q4; range, 0 to 12, with higher scores indicating more activity). The primary outcome of the Physical Function Trial (Panel B) was the percentage of men who had an increase of at least 50 m in the distance walked during the 6-minute walk test. The primary outcome of the Vitality Trial (Panel C) was the percentage of men who had an increase of at least 4 points in the score on the Functional Assessment of Chronic Illness Therapy (FACIT)–Fatigue scale (range, 0 to 52, with higher scores indicating less fatigue). P values were calculated with the use of a linear random-effects model for sexual activity and logistic random-effects models for walking ability and vitality. The I bars represent standard deviations.

PJ Snyder et al N Engl J Med 2016;374(7):611-24

Effects of Testosterone on walking ability



PJ Snyder et al N Engl J Med 2016;374(7):611-24

Cohort and Outcome	No. of Men	Baseline Value	No. of Participants or Change from Baseline Value				Treatment Effect (95% CI)†	Effect Size (95% CI)‡	P Value§
			Month 3	Month 6	Month 9	Month 12			
Men enrolled in Physical Function Trial									
Primary outcome: increase of ≥50 m in 6-min walk test — no./total no. (%)									
Testosterone	191		20/179 (11.2)	24/174 (13.8)	28/172 (16.3)	35/172 (20.3)	1.42 (0.83 to 2.45)		0.20
Placebo	196		14/179 (7.8)	23/171 (13.5)	22/159 (13.8)	20/165 (12.1)			
Secondary outcomes									
6-Min walking distance — m									
Testosterone	191	347.7±69.1	10.2±35.8	8.2±41.5	5.3±50.3	14.3±45.9	4.09 (−3.00 to 11.18)	0.06 (−0.04 to 0.16)	0.28
Placebo	196	344.9±68.5	4.6±35.2	7.8±41.4	3.2±52.4	5.5±46.4			
Increase of ≥8 in PF-10 score — no./total no. (%)¶									
Testosterone	184		77/176 (43.8)	72/171 (42.1)	77/172 (44.8)	66/173 (38.2)	1.34 (0.90 to 2.00)		0.15
Placebo	181		59/171 (34.5)	73/159 (45.9)	60/159 (37.7)	58/167 (34.7)			
PF-10 score¶									
Testosterone	184	65.4±20.0	5.6±15.2	6.5±16.7	5.9±19.4	5.8±17.5	2.75 (0.20 to 5.29)	0.13 (0.01 to 0.26)	0.03
Placebo	181	64.8±21.3	4.2±13.7	4.8±17.0	3.3±18.9	2.4±17.3			

The percentage of men who had an increase of at least 50 m in the 6-minute walking distance was statistically significant considering all subjects (20.5% of men who received testosterone vs. 12.6% of men who received placebo, P = 0.003)

Snjeder PJ, et al. NEJM 2016

Adverse events during the First year (Treatment Period) of Testosterone Trial

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

PJ Snyder et al N Engl J Med 2016;374(7):611-24

neri | Registry Objectives

Primary Objective

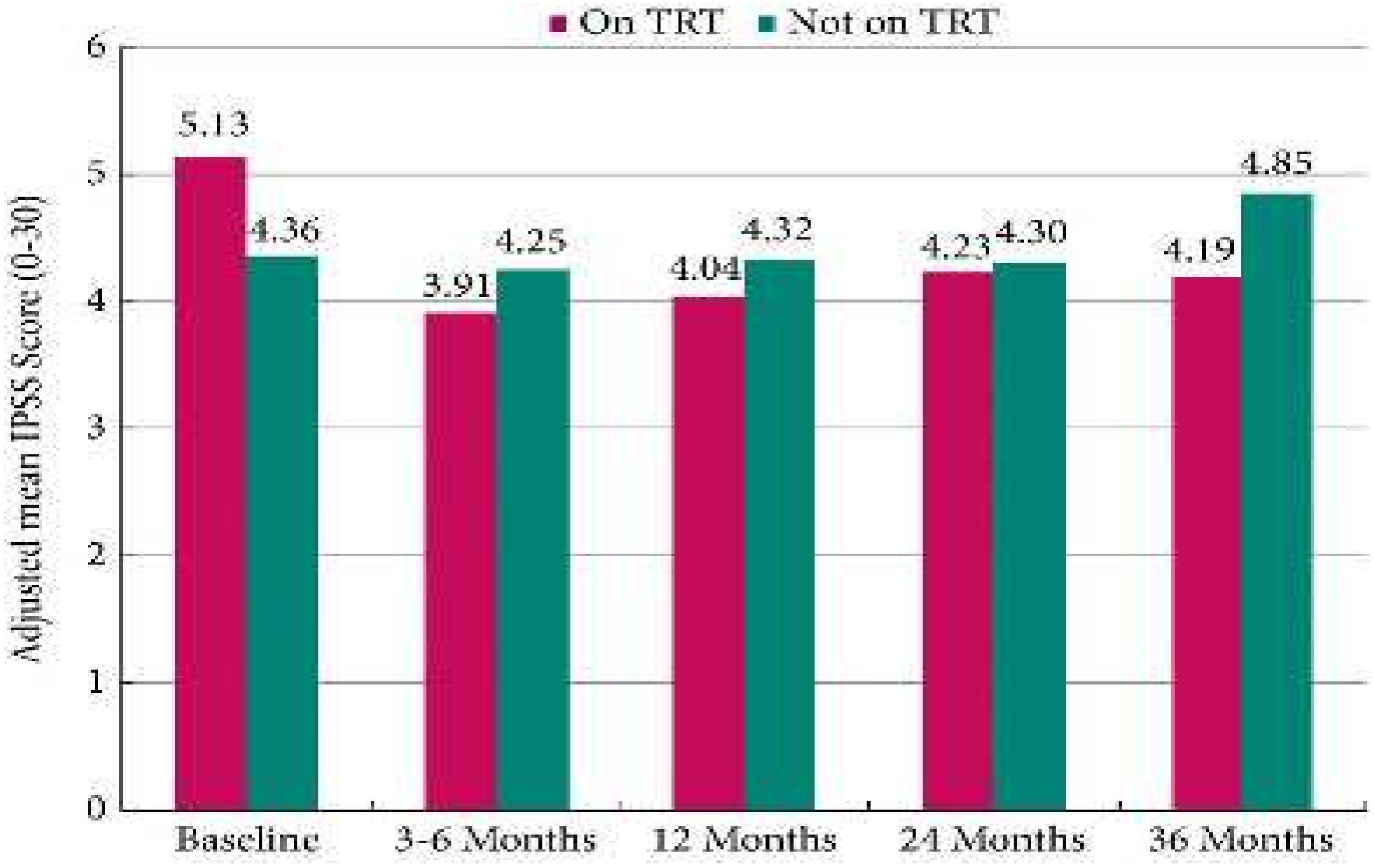
1. Examine the association between T therapy, prostate cancer and other prostate health outcomes in men with HG

Secondary Objectives

- Assess routinely-monitored symptoms and general health outcomes in men with HG to identify potential benefits associated with T therapy
- Assess the natural history of the disorder in men not being treated for HG, and the clinical course in men with HG undergoing T therapy

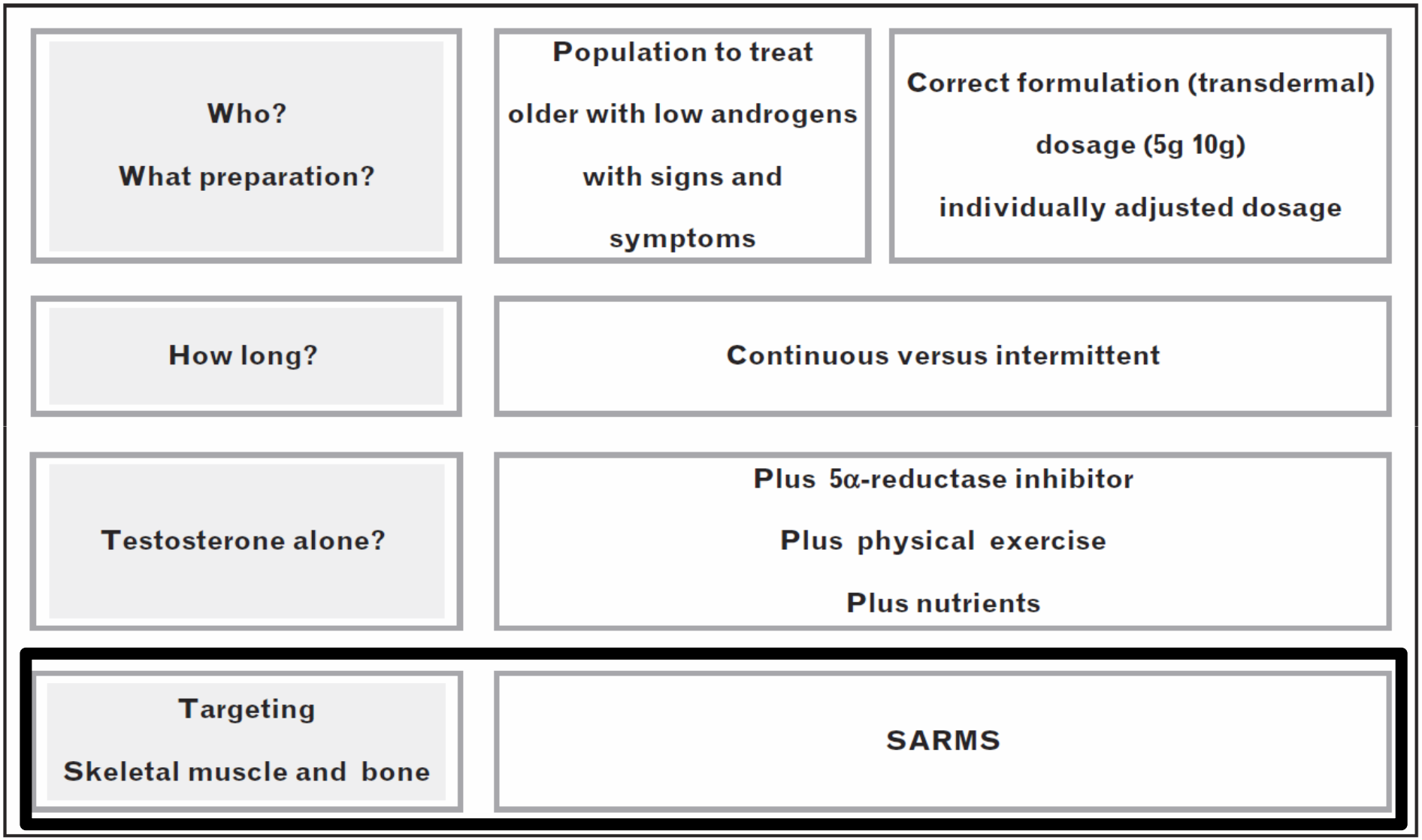
[1]PSA values from central laboratory not available after 24 months.

Debruyne FMJ et al. BJU Int 2017; 119: 216–224



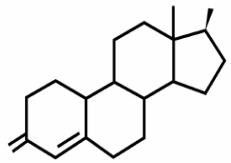
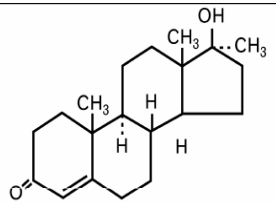
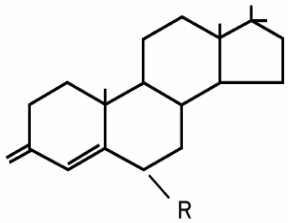
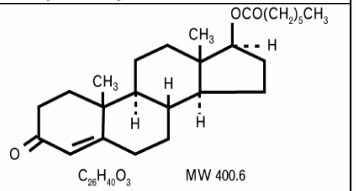
Debruyne FMJ et al. BJU Int 2017; 119: 216–224

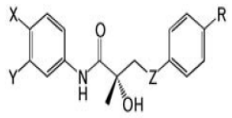
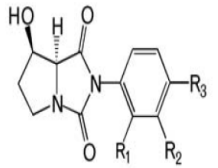
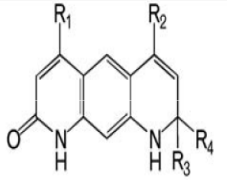
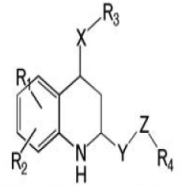
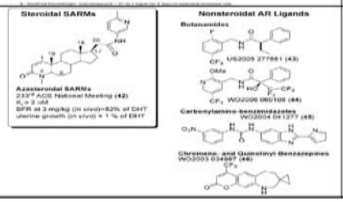
FIGURE 3. Flow diagram showing novel strategies to counteract the side-effects of sex hormone treatment.



Maggio M, Lauretani F, Ceda GP. Curr Op Med Care Nutr 2013; 16:3-13

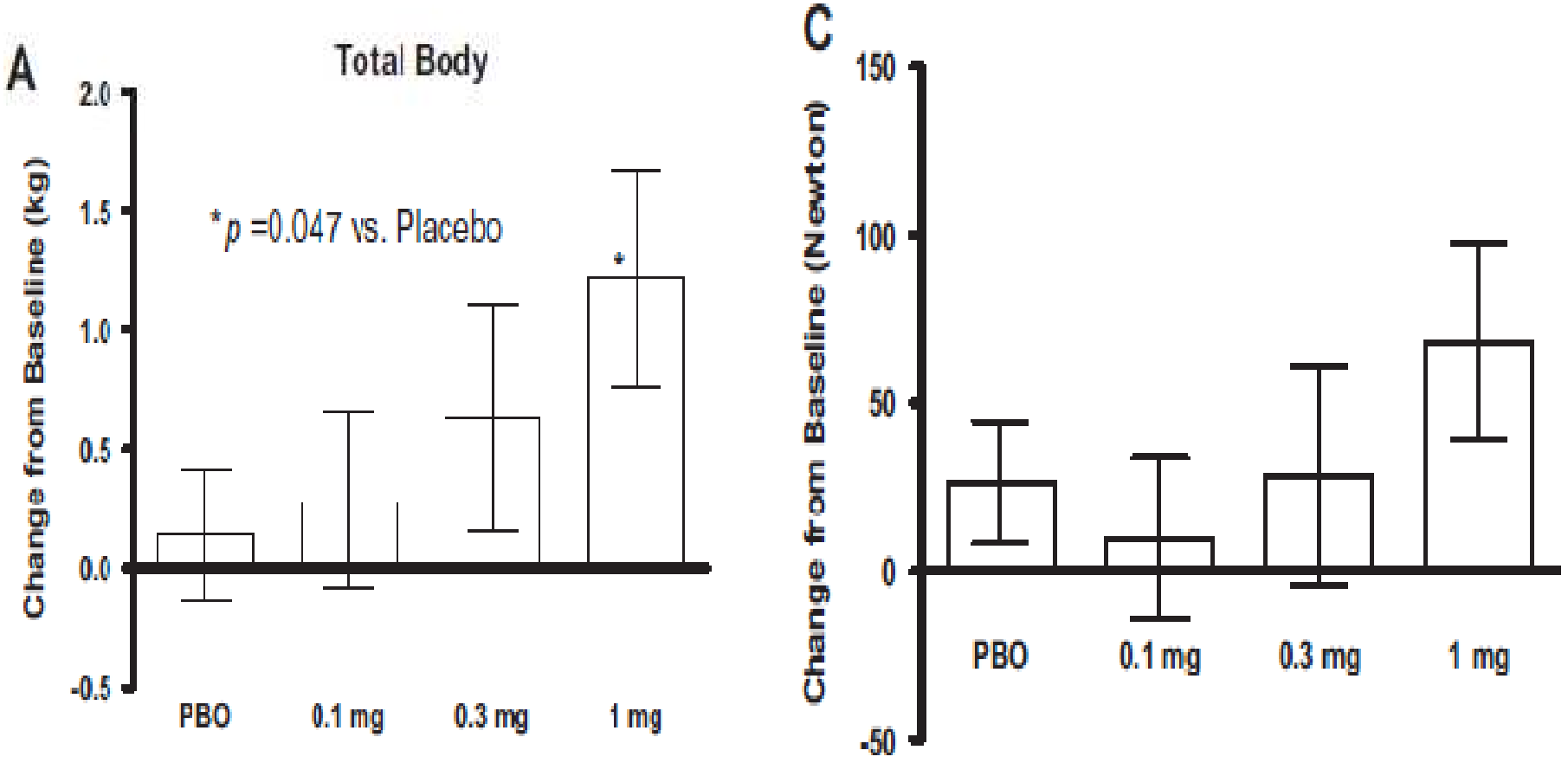
Selective androgen receptor modulators as function promoting therapies

Structure: activity relationship	Compounds	Chemical structure
Removing 19 methyl increases anabolic activity	19-nortestosterone (nandrolone) series of compounds	 19-nortestosterone
17-alpha alkyl substitutions retard first-pass presystemic metabolism	Many orally active steroidal androgens have 17-alpha alkyl substitutions	 17-alpha methyl testosterone
7-alpha alkyl substitutions increase anabolic activity	7-alpha-methyl-19-nortestosterone	 7-alpha alkyl 19-nortestosterone
Esterification of 17-beta hydroxyl group increases hydrophobicity and extends duration of in-vivo action	Testosterone enanthate, cypionate, and undecanoate	 $C_{26}H_{40}O_3$ MW 400.6 Testosterone enanthate

Chemotype	Structure	Examples
Aryl propionamide analogs		Ostarine, andarine
Bicyclic hydantoin analogs		BMS 564929
Quinolinones		LGD2226, LGD2941
Tetrahydroquinoline analogs		Kanen Pharmaceuticals, S-40503
Benzimidazoles		Johnson and Johnson's benzimadozole derivative
Butanamides		Merck SARM based on butanamide scaffold

Bhasin et al . Curr Op in Clin Nutr and Met Care 2009; 12: 233-240

Modificazioni di massa muscolare (A) e forza muscolare arti inferiori (C) dopo 21 gg di dosi diverse di SARM non steroideo per os in N=76 giovani maschi sani (21-50 anni)



Basaria et al. J Gerontol A Biol Sci Med Sci 2013; 68:87-95

EDITORIAL

Testosterone and Male Aging
Faltering Hope for Rejuvenation

David J. Handelsman, MB BS, PhD, FRACP, FAFMS

Opinion

EDITORIAL

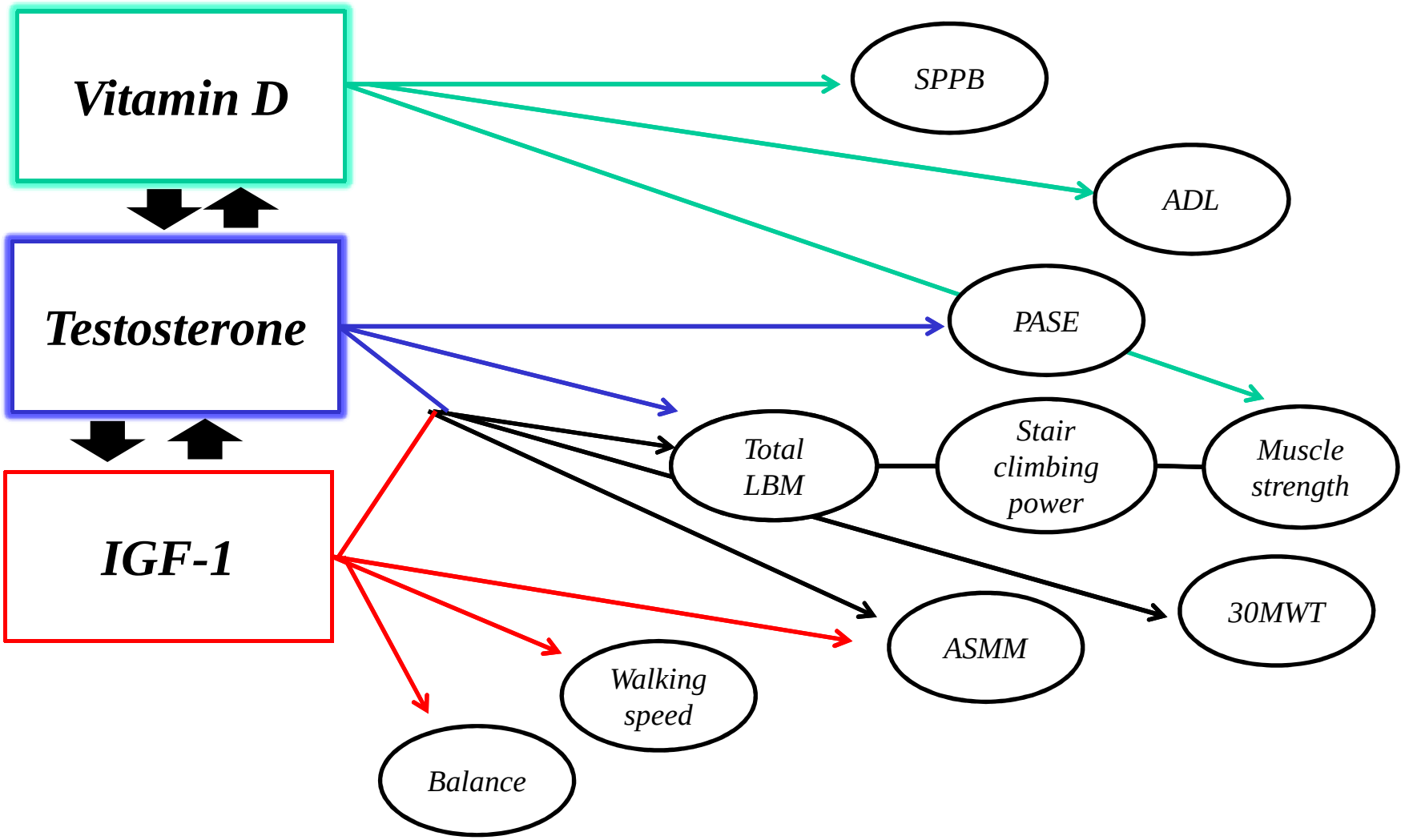
Further Elucidation of the Potential Benefits of Testosterone Therapy in Older Men

Eric Orwoll, MD

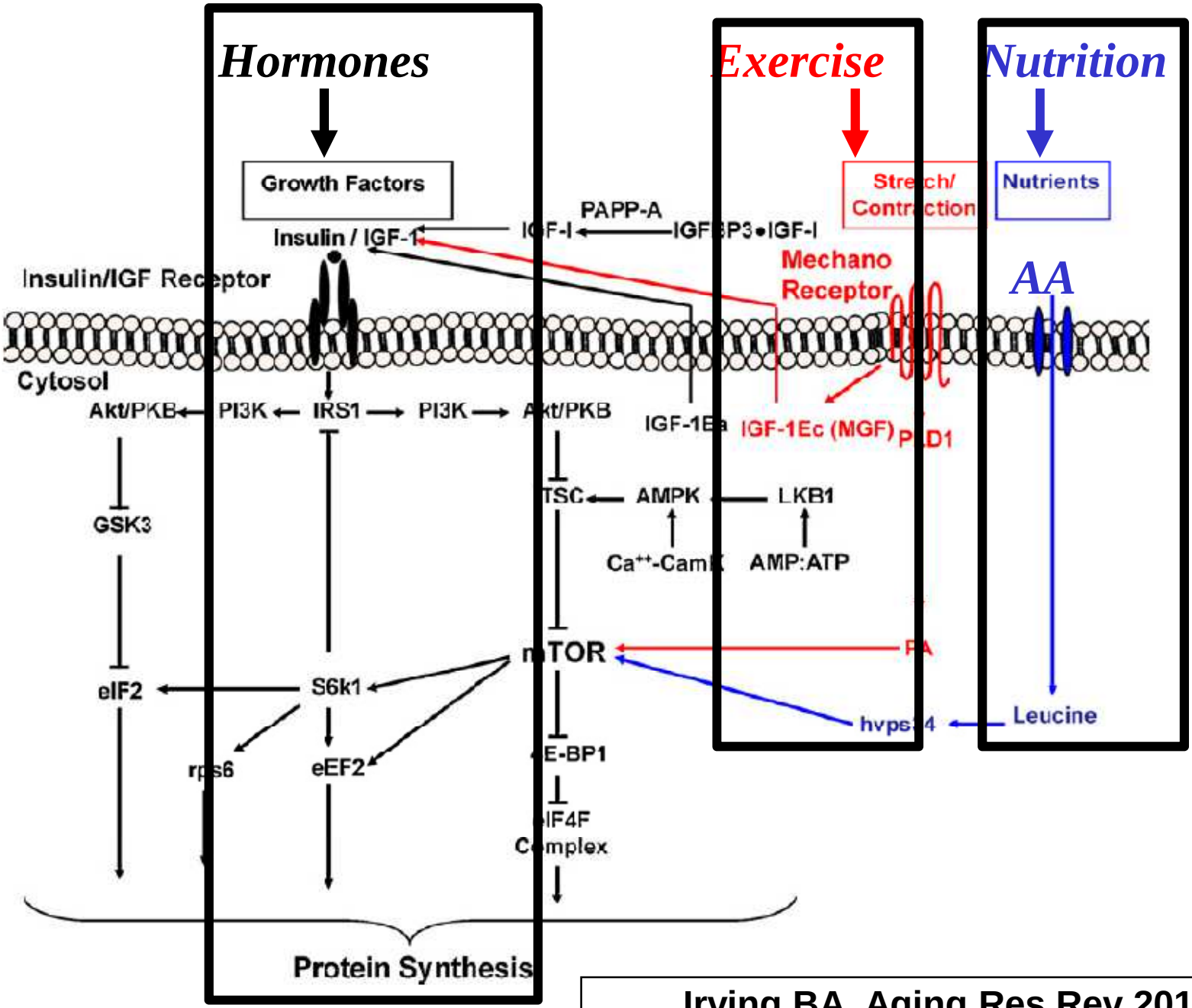
Testosterone and "Age-Related Hypogonadism" — FDA Concerns

Christine P. Nguyen, M.D., Mark S. Hirsch, M.D., David Moeny, R.Ph., M.P.H., Suresh Kaul, M.D., M.P.H., Mohamed Mohamoud, Pharm.D., M.P.H., and Hylton V. Joffe, M.D., M.M.Sc.

Combined effects of Vitamin D, Testosterone and Insulin-like growth factor 1 (IGF-1) on mobility



Maggio M, et al. Curr Pharmaceut Design 2014;20(19):3119-48.



Irving BA, Aging Res Rev 2012

Research Article

A Randomized Controlled Pilot Trial of Interventions to Improve Functional Recovery After Hospitalization in Older Adults: Feasibility and Adherence

Rachel R. Deer,[1] Shawn M. Goodlett,[1] Steve R. Fisher,[1,2] Jacques Baillargeon,[3] Jared M. Dickinson,[4] Mukaila Raji,[1,5] and Elena Volpi[1,5]

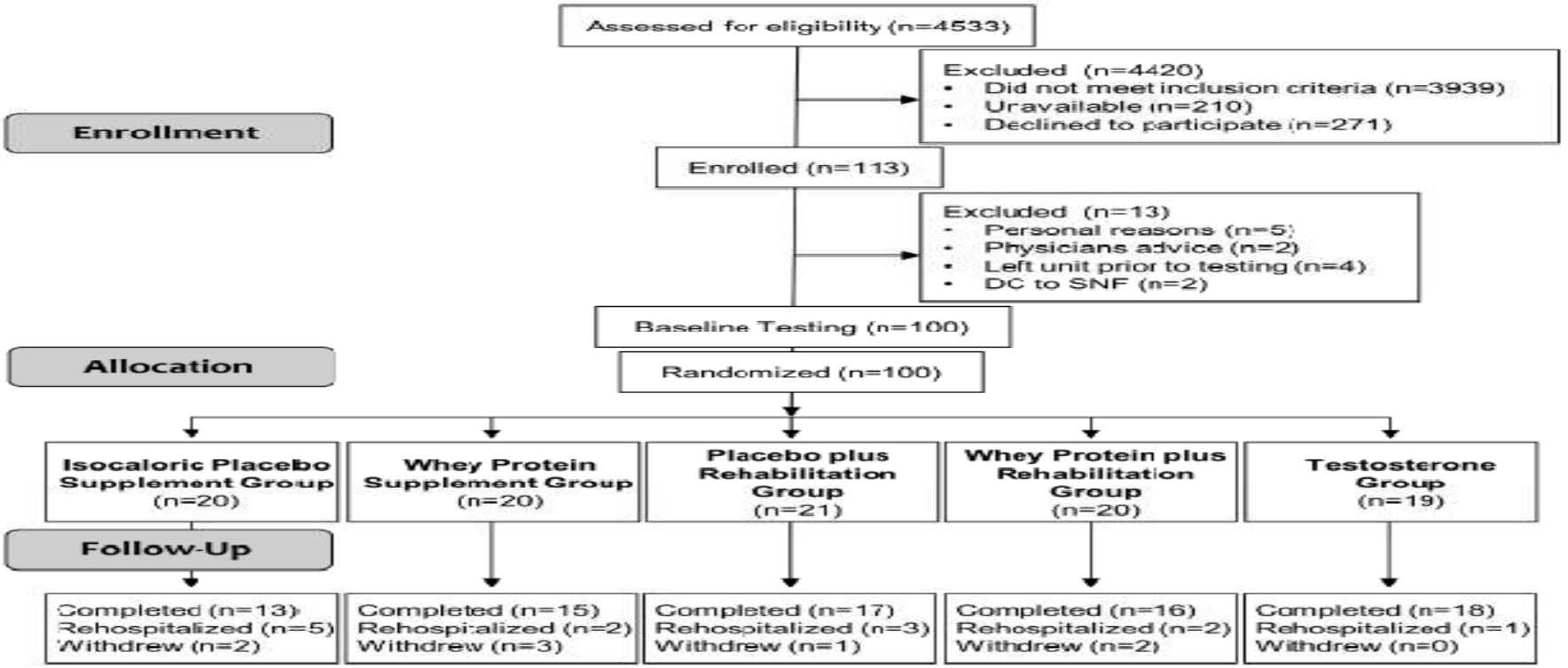


Figure 1. CONSORT diagram.

Take Home Messages

- **La disregolazione ormonale multipla (ed in particolare di testosterone) in corso di invecchiamento concorre ad aumentare il rischio di sarcopenia, fragilità ed anemia, nel soggetto anziano di sesso maschile e va corretta in presenza di sintomi e segni specifici**

- **La terapia di deprivazione androgenica nel paziente con carcinoma prostatico è un' esemplicazione del link tra ipogonadismo e incrementato rischio di fragilità fisica**

- **Recenti RCT e Studi di Registro (non di lunghissima durata), supportano il ruolo del testosterone nel miglioramento della performance fisica e muscolare, nella parziale correzione delle anemie non spiegate, con accettabile profilo di sicurezza**

Società di Medicina e Scienze Naturali di Parma

Il Direttore della Scuola di Specializzazione in Geriatria
Prof. Marcello Maggio

e

Il Presidente della Società di Medicina e Scienze Naturali di Parma
Prof. Maurizio Vanelli

vi invitano al seminario del

Università degli Studi di Parma
Dipartimento di Medicina e Chirurgia

PROF. CORNEL SIEBER

Professore Ordinario di Medicina Interna e Geriatria,
Friedrich-Alexander-University, Erlangen-Nürnberg (Germany)
Presidente della Società Tedesca di Medicina Interna

su

ESPEN GUIDELINES OF NUTRITION IN GERIATRICS

MERCOLEDI' 23 MAGGIO 2018
Ore 16.00

AULA 5 – PLESSO AULE DIDATTICHE NUOVE
v.le A Gramsci, 14 – Parma

Motivi per focalizzarsi anche sull'uomo

Consequences are greater than in women, with **men having about twice the 1-year fatality rate after hip fracture**, compared to women.

Men at high risk for fracture include those men who have already **had a fragility fracture, on oral glucocorticoids or those men being treated for prostate cancer with androgen deprivation therapy**.

Robert A. Adler Bone Research (2014) 2, 14001

Classification of osteoporosis in men

Primary Osteoporosis		Secondary Osteoporosis	
Type 1	Type 2	Disorders	Medications
Age < 70	Age > 70	Hypogonadism	Oral glucocorticoids
Vertebral fractures	Vertebral and hip fractures	Hypercalciuria	Androgen deprivation therapy
Specific genetic syndromes	Relation with muscle, sarcopenia	Hyperparathyroidism	Proton pump inhibitors
Cryptic secondary osteoporosis	Known risk factors	Hyperthyroidism	Selective serotonin reuptake inhibitors
		Cushing's syndrome	Dopamine antagonists
		Celiac disease	Thiazolidinediones
		Inflammatory bowel disease	Enyzme-inducing anti-epileptics
		Rheumatoid arthritis	Chronic opiate analgesics
		Chronic obstructive pulmonary disease	Cancer chemotherapy (cyclophosphamide)
		Alcohol abuse	
		Chronic kidney disease	
		Bariatric surgery	

Robert A. Adler Bone Research (2014) 2, 14001

Incidenza Annuale di Fratture in relazione ai livelli di E2 nel soggetto anziano maschio

Figure 11.

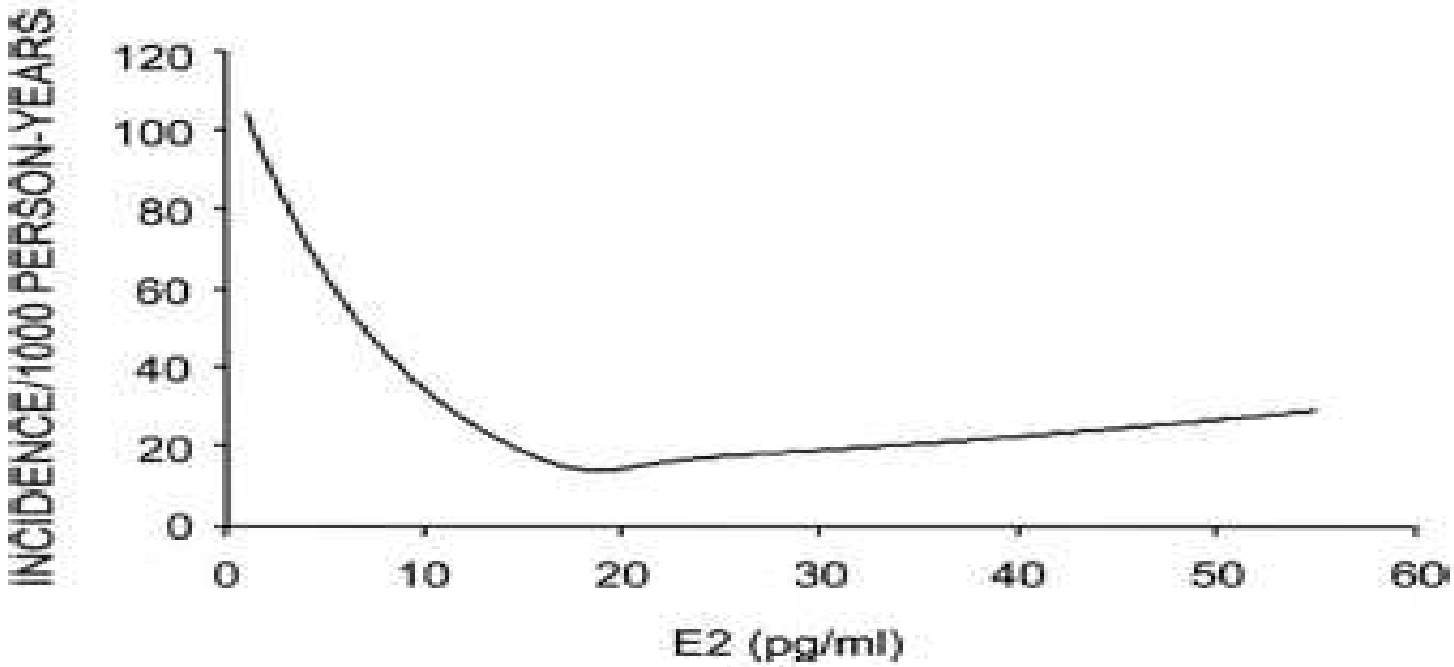
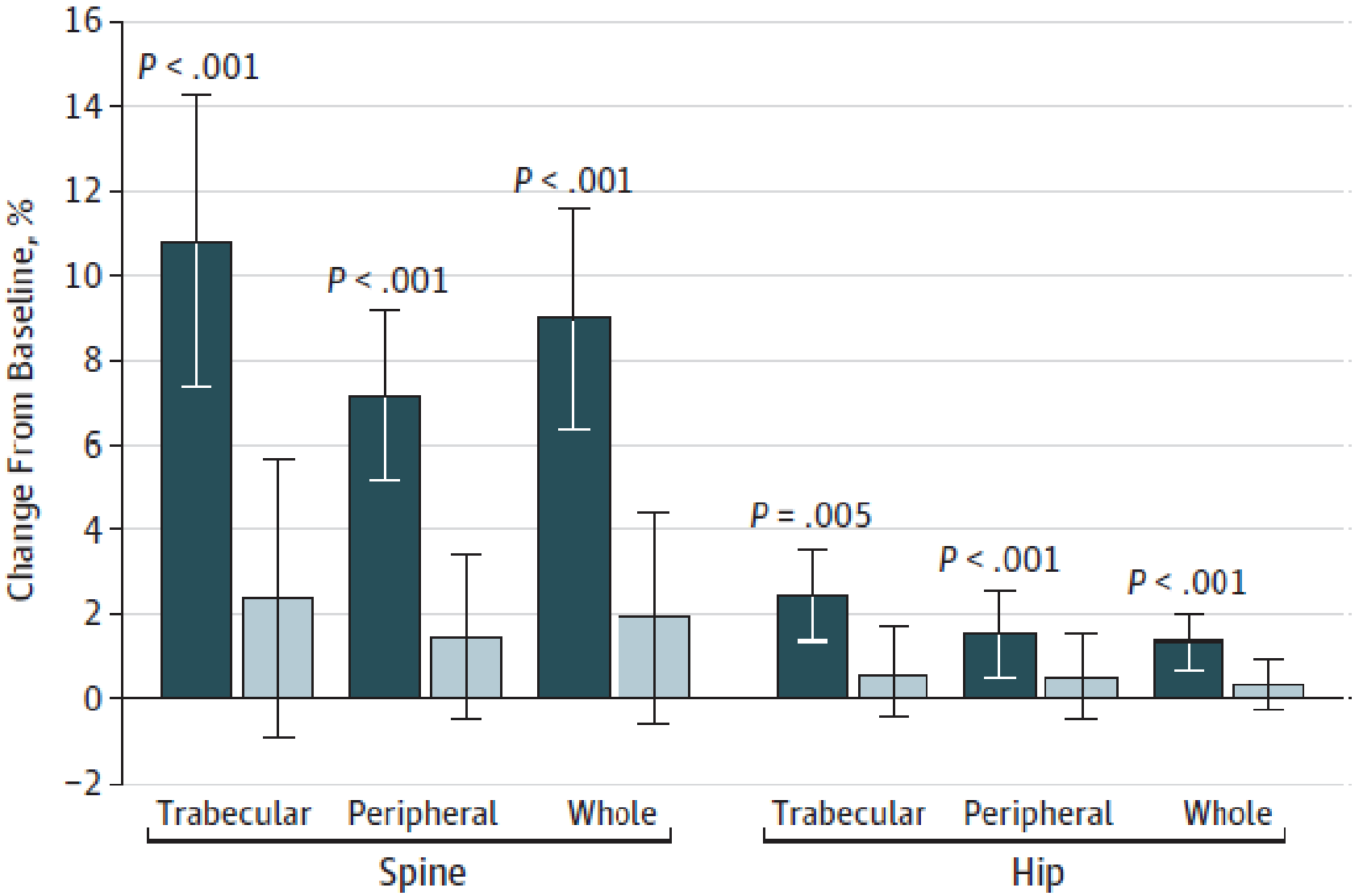


Figure 11. Annual incidence of fractures in relation to serum E2 levels in older men. Poisson regression models were used to determine the relationship between serum E2 and fracture risk. [Reproduced from D. Mellström et al: Older men with low serum estradiol and high serum SHBG have an increased risk of fractures. *J Bone Miner Res.* 2008;23:1552–1560 (417), with permission. © American Society for Bone and Mineral Research.]

Vanderschueren et al Sex Steroid Actions in Male Bone Endocrine Reviews, December 2014, 35(6):906–960

Effects of Testosterone on estimated bone strength

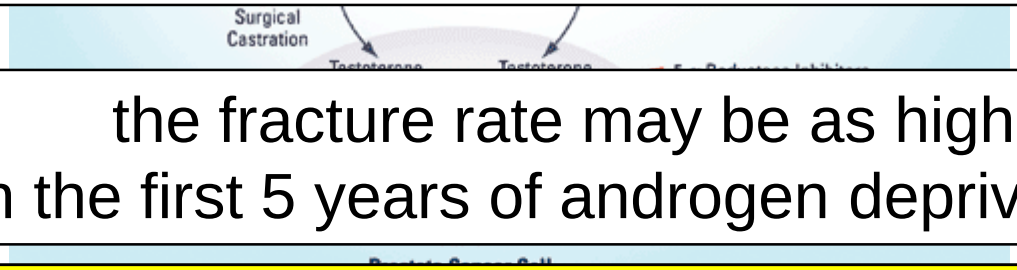


Sneyder PJ et al JAMA Intern Med. 2017;177(4):471-479.

Modello particolare : la terapia di deprivazione androgenica nel paziente con carcinoma prostatico

3.6. Evidence

Orchiectomy or administration of long-actingGnRH agonists to men with prostate cancer lowers serum testosterone and estradiol levels to the prepubertal range, increasing bone resorption and inducing rapid bone loss. Several small studies have examined rates of bone loss during the first year of GnRH agonist therapy in men with prostate cancer. In general, spine BMD declines by 3–4% in the first year. Decreases in hip BMD are more modest Interestingly, BMD declined more rapidly in the radius than in the spine or hip. Fracture risk is increased in men receiving ADT



the fracture rate may be as high as
20% in the first 5 years of androgen deprivation therapy

Watts NB, et al. J Clin Endocrinol Metab 2012; 97:1802-1822

SPECIAL FEATURE

Clinical Practice Guideline

Osteoporosis in Men: An Endocrine Society Clinical Practice Guideline

Nelson B. Watts, Robert A. Adler, John P. Bilezikian, Matthew T. Drake, Richard Eastell, Eric S. Orwoll, and Joel S. Finkelstein

Recommendation in Men with prostate cancer receiving ADT

3.6. We recommend pharmacological treatment for osteoporosis for men with prostate cancer receiving ADT who have a high risk of fracture (see *Section 3.1*). (1|QQQE)

Watts NB, et al. J Clin Endocrinol Metab 2012; 97:1802-1822