

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

M. Mercè Fernández-Balsells, Mohammad Hassan Murad, Melanie Lane, Juliana F. Lampropulos, Felipe Albuquerque, Rebecca J. Mullan, Neera Agrwal, Mohamed B. Elamin, Juan F. Gallegos-Orozco, Amy T. Wang, Patricia J. Erwin, Shalender Bhasin, and Victor M. Montori

Knowledge and Encounter Research Unit (M.M.F.-B., M.H.M., M.L., J.F.L., F.A., R.J.M., N.A., M.B.E., J.F.G.-O., A.T.W., P.J.E., V.M.M.), Mayo Clinic, Rochester, Minnesota 55905; Endocrinology, Diabetes, and Nutrition Unit (M.M.R.-B.), Hospital Universitari de Girona, Dr Josep Trueta, Institut Català de la Salut, 17007 Girona, Spain; Division of Preventive Medicine (M.H.M.), Mayo Clinic, Rochester, Minnesota 55905; Department of Internal Medicine (N.A., J.F.G.-O.), Mayo Clinic, Scottsdale, Arizona 85259; Section of Endocrinology, Diabetes, and Nutrition (S.B.), Boston University School of Medicine, Boston Medical Center, Boston, Massachusetts 02118; and Division of Endocrinology, Diabetes, Metabolism, and Nutrition (V.M.M.), Mayo Clinic, Rochester, Minnesota 55905

Context: The risks of testosterone therapy in men remain poorly understood.

Objective: The aim of this study was to conduct a systematic review and meta-analyses of testosterone trials to evaluate the adverse effects of testosterone treatment in men.

Data Sources: We searched MEDLINE, EMBASE, and Cochrane CENTRAL from 2003 through August 2008. Review of reference lists and contact with experts further identified candidate studies.

Study Selection: Eligible studies were comparative, randomized, and nonrandomized and reported the effects of testosterone on outcomes of interest (death, cardiovascular events and risk factors, prostate outcomes, and erythrocytosis). Reviewers, working independently and in duplicate, determined study eligibility.

Data Extraction: Reviewers working independently and in duplicate determined the methodological quality of studies and collected descriptive, quality, and outcome data.

Data Synthesis: The methodological quality of the 51 included studies varied from low to medium, and follow-up duration ranged from 3 months to 3 yr. Testosterone treatment was associated with a significant increase in hemoglobin [weighted mean difference (WMD), 0.80 g/dl; 95% confidence interval (CI), 0.45 to 1.14] and hematocrit (WMD, 3.18%; 95% CI, 1.35 to 5.01), and a decrease in high-density lipoprotein cholesterol (WMD, -0.49 mg/dl; 95% CI, -0.85 to -0.13). There was no significant effect on mortality, prostate, or cardiovascular outcomes.

Conclusions: The adverse effects of testosterone therapy include an increase in hemoglobin and hematocrit and a small decrease in high-density lipoprotein cholesterol. These findings are of unknown clinical significance. Current evidence about the safety of testosterone treatment in men in terms of patient-important outcomes is of low quality and is hampered by the brief study follow-up. (*J Clin Endocrinol Metab* 95: 2560–2575, 2010)

Although the prevalence of low total testosterone levels in men increases steadily from 20 to 50% from the sixth to ninth decades of life (1), the utility of testosterone therapy in aging men remains controversial. Meta-analyses report small improvements in domains of sexual function, bone mineral density, muscle mass, and grip strength (2–5). However, the risks of testosterone therapy remain poorly understood. The Institute of Medicine Expert Panel suggested that safety trials of testosterone replacement should be deferred until the efficacy of this treatment has been demonstrated. Therefore, adequately powered randomized trials to ascertain the effects of testosterone therapy on prostate and cardiovascular health are unlikely to be conducted any time soon. Studies designed to address safety are lacking, and the evidence of harm is mainly based on the reported adverse events in trials designed to address the efficacy of this treatment. Most of these trials included relatively small samples, and each study individually had only a small number of adverse events. Therefore, this investigation aimed to conduct a systematic review of the literature and perform meta-analyses of the adverse effects of testosterone therapy.

In 2005, a meta-analysis of the adverse effects of testosterone replacement therapy (6) showed that elevated hematocrit and an increase in a composite of prostate-related events were the most common side effects of testosterone replacement therapy. Imprecision due to the small number of events hampered inferences regarding differences in the rates of prostate cancer, cardiovascular events, sleep apnea, or death. In 2007, another meta-analysis failed to show differences in blood pressure, glycemia, and lipid fractions, but it reported a trend for increased cardiovascular events associated with testosterone use [pooled odds ratio, 1.82; 95% confidence interval (CI), 0.78–4.23] (7). Overall, the studies included in both meta-analyses were randomized controlled trials (RCTs) that enrolled a relatively small number of patients and had short follow-up and high loss to follow-up rates.

Since the publication of these meta-analyses, several larger studies of the effects of testosterone therapy on muscle performance and physical function, glucose metabolism (8–11), prostate outcomes (10), and the performance status of patients with heart failure (12) have been published. Because of these and other published trials, the Endocrine Society Task Force on Testosterone Use in Adult Men requested an updated systematic review of randomized trials and observational studies with long-term follow-up to determine the possible adverse effects of testosterone therapy, including cardiovascular and prostate outcomes.

Materials and Methods

We developed a systematic review protocol with input from the expert members of the commissioning Task Force from The Endocrine society. This report adheres to the reporting guidelines of systematic reviews (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (13).

Eligibility criteria

Eligible studies were comparative studies (randomized and nonrandomized) that enrolled adult men with low or low-normal testosterone levels and treated with any testosterone formulation for at least 3 months. The studies had to have a control group without testosterone use and measure the outcomes of interest.

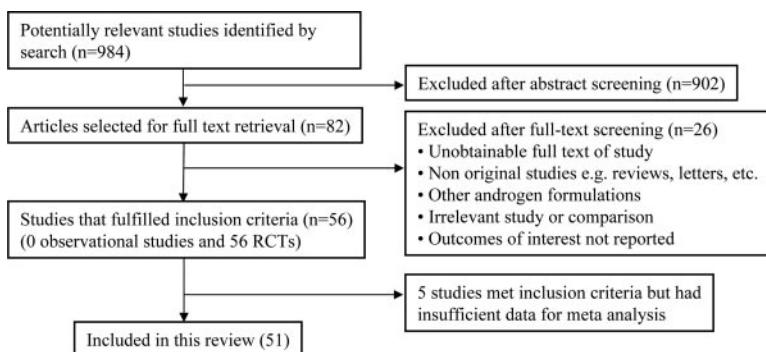
The outcomes of this systematic review are:

1. Prostate outcomes: the diagnosis of prostate cancer, prostate-specific antigen (PSA) levels above 4 ng/ml or a significant increase in PSA during treatment (defined as PSA increment of >1.4 ng/ml above baseline), a prostatic biopsy, increase in International Prostate Symptom Score (IPSS) greater than 4, acute urinary retention, and a composite prostate endpoint that combines these aforementioned outcomes.
2. Cardiovascular events and cardiometabolic risk factors: death, coronary events (fatal and nonfatal myocardial infarction, hospitalization for an acute coronary syndrome, coronary revascularization), cerebrovascular events (fatal and nonfatal stroke or transient ischemic attack), peripheral vascular events (new onset claudication, acute arterial occlusion, revascularization procedure), changes in lipid fractions, changes in glucose metabolism (fasting glucose level and new onset of diabetes), and blood pressure.
3. Indices of red cell mass (hemoglobin, hematocrit, and incidence of erythrocytosis defined as hematocrit >52%).

We excluded studies that used androgens other than testosterone as well as studies with simultaneous treatment with other hormones and drugs unless there was a clearly defined treatment arm that received only testosterone treatment. Studies not reporting the outcomes of interest were excluded. Language of publication was not an eligibility criterion.

Study identification

An expert reference librarian (P.J.E.) conducted the electronic search with input from study investigators with expertise in systematic reviews (V.M.M. and M.H.M.). We searched MEDLINE, EMBASE, and Cochrane CENTRAL electronic databases from 2003 through August 2008. Studies published before 2003 were obtained from two published systematic reviews (6, 7). Because published reviews excluded patients with HIV/AIDS, the previous search strategy was expanded to cover the period 1981–2004, focusing on studies conducted in this population [*exp HIV infections/ or (human adj immune*) or (acquired adj immune*) or AIDS* or HIV*]. The detailed strategy is available upon request. To identify additional candidate studies, we reviewed the reference lists of the eligible primary studies, narrative reviews, and systematic reviews, and we queried the expert members of the commissioning task force.



Study selection

Working independently and in duplicate, reviewers screened all abstracts and titles. After obtaining all potentially eligible studies in full text, these reviewers, again working independently and in duplicate, determined eligibility with acceptable chance-adjusted agreement ($\kappa = 0.85$; range, 0.75–0.94). Disagreements were resolved by consensus or arbitration.

Data collection

Using a standardized data extraction form and working in duplicate, we abstracted the following descriptive data from each study: description of study participants (age, baseline testosterone levels), and characteristics of treatment and control interventions (testosterone formulation, dose, frequency, route of administration, and treatment duration). We extracted the outcomes of interest at the longest point of complete follow-up. We contacted the authors of included studies by e-mail if a clarification of their methods (e.g. randomization and blinding procedures) or results (missing data, e.g. SD) was needed.

Quality assessment

We employed the GRADE approach to rate the quality of evidence (14). To assess the methodological quality of randomized trials, we determined how the randomization sequence was generated, how allocation was concealed, whether there were important imbalances at baseline, which groups were blinded (patients, caregivers, data collectors, outcome assessors, data analysts), what the loss to follow-up rate was (in the intervention and the control arm), whether the analyses were by intention to treat, and how missing outcome data were dealt with. For each study, we also assessed how the population was selected, the duration and route of testosterone administration, the adequacy of study follow-up, and the funding source. We assessed our chance-adjusted agreement on study quality using the κ statistic with disagreements resolved by consensus or arbitration.

Meta-analyses

We estimated the relative risk (RR) for dichotomous outcomes and the weighted mean difference (WMD) for continuous outcomes pooled across studies using the DerSimonian and Laird random-effects model (15). We quantified inconsistency using the I^2 statistic, which describes the proportion of heterogeneity across studies that is not due to chance, thus describing the extent of true inconsistency in results across trials (16). I^2 less than 25% and I^2 more than 50% reflect small and significant inconsistency, respectively.

Subgroup and sensitivity analyses

To explore causes of inconsistency and subgroup-treatment interactions, subgroup analyses were specified *a priori* according to the following factors:

1. Participants: age less than 65 or more than 65 yr; total testosterone level at baseline (low if less than 300 ng/dl or 10.4 nmol/l). If total testosterone was not available, then lower limit of normal for bioavailable or free testosterone levels. If neither total nor free testosterone levels were available, then studies were classified according to participant characteristics.

2. Interventions: testosterone formulation, route of administration, and dose (substitution doses as recommended by The Endocrine Society *vs.* anything higher).
3. Outcome characteristic: duration of follow-up (less than 6 months *vs.* more than 6 months).
4. Study quality measure: proportion of patients lost to follow-up (10% or less *vs.* more than 10%), concealment of allocation, blinding of patients, health care professionals, data collectors, and outcome assessors.

In addition, we conducted sensitivity analyses using Peto odds ratio and different continuity correction factors to determine whether these choices in analysis methods affected the conclusions.

Results

Search results

The search identified 984 candidate references, of which 51 trials were deemed eligible (Fig. 1). The characteristics of included studies are summarized in Table 1. Studies that did not provide sufficient data for this meta-analysis are described in Table 2.

Methodological quality

The overall quality of the included studies varied from low to medium (Table 3). Several studies did not provide explicit description of methods to protect against bias, whereas in other studies, it was clear that such techniques were not used. Only a few studies reported allocation concealment and blinding of the outcome assessors. Loss to follow-up was, in most cases, substantial, with 10 studies losing more than 20% of participants, and differed between study arms in five studies (17–21).

Mortality and cardiovascular outcomes

There were no significant differences in the rates of death, myocardial infarction, revascularization procedures, or cardiac arrhythmias between the testosterone and the placebo/nonintervention groups (Fig. 2). Heterogeneity was low or incalculable due to the small number of studies in these analyses.

TABLE 1. Characteristics of the included studies

First author, year (Ref.)	Patients	Age (yr), I vs. C	TT levels (ng/dl), I vs. C	Intervention	Duration of intervention	Main outcomes
Agledahl, 2008 (24)	26 men aged 60–80 yr with subnormal TT levels (<317 ng/dl)	68.9 ± 5 vs. 69.3 ± 5.0	245 ± 49 vs. 236 ± 69	Testosterone undecanoate 1000 mg im	52 wk	Postprandial TG, anthropometry, body composition
Allan, 2008 (17)	62 nonobese, healthy men aged at least 55 with symptoms of androgen deficiency and low-normal serum TT levels (<432 ng/dl)	62.1 ± 1.0 vs. 64.5 ± 1.3	392 ± 14 vs. 418 ± 17	Transdermal testosterone 5 mg/d patch	52 wk	Metabolic parameters, anthropometry, body composition
Amory, 2004 (25); Page, 2005 (26)	70 otherwise healthy patients aged >65 yr and with confirmed TT <348 ng/dl	71.0 ± 4.0	303 ± 46 vs. 302 ± 49	Testosterone enanthate 200 mg/2 wk im	36 months	BMD, physical performance, anthropometry, body composition
Basurto, 2008 (27)	48 patients aged at least 60 yr with TT <320 ng/dl	63.2 ± 7.9	301 ± 32 vs. 310 ± 37	Testosterone enanthate 250 mg/3 wk im	12 months	BMD
Bhasin, 2000 (29)	31 HIV-infected men aged 18 to 50 with TT <350 ng/dl and involuntary weight loss of >5% in previous 6 months	40.8 (SEM 1.2) vs. 41.8 (SEM 2.5)	205 (SEM 2.0) vs. 176 (SEM 2.3)	Testosterone enanthate 100 mg/wk im	16 wk	Strength, body composition, QOL
Bhasin, 2007 (30)	88 HIV-infected men with abdominal obesity and TT 125–400 ng/dl	Median, 47.0 (IQR, 40.0–51.0) vs. 395 (IQR 331–475)	Median, 427 (IQR, 309–521) vs. 395 (IQR 331–475)	Transdermal testosterone gel 10 g/d	24 wk	Body composition
Blackman, 2002 (31); Christmas, 2002 (32); Harman, 2003 (68); Münzer, 2001 (69) Boyanov, ^a 2003 (33)	65 healthy men aged 65 to 88 with serum lGH <230 ng/ml	70 ± 0.7 vs. 70 ± 1.1	409 ± 20 vs. 392 ± 23	Testosterone enanthate 100 mg biweekly im	26 wk	Body composition, strength, endurance, and adverse outcomes
Brockenbrough, 2006 (34)	48 patients with T2DM, TT <435 ng/dl, and symptoms of androgen deficiency	57.5 ± 4.8	276 ± 67 vs. 310 ± 86	Testosterone undecanoate 80 mg/twice a day PO	3 months	Glucose homeostasis, obesity, and sexual function
Cavallini, 2004 (35)	40 male dialysis subjects with TT <300 ng/dl	58.9 ± 14.9 vs. 53 ± 17.2	218.9 ± 64.6 vs. 201.7 ± 87.2	Transdermal testosterone gel 10 g/d	6 months	rHuEPO dosage needed to maintain hematocrit
	85 men, >60 yr of age, with decreased libido and erectile quality, depressed mood, decreased intellectual concentration ability, irritability, fatigue, and FT <6 pg/ml	Mean, 66 (range, 60–74)	285 ± 53 vs. 303 ± 61	Testosterone undecanoate 160 mg/d PO	6-month follow-up without treatment plus 6 months of treatment	Change in symptoms of male aging

(Continued)

TABLE 1. Continued

First author, year (Ref.)	Patients	Age (yr), I vs. C	TT levels (ng/dl), I vs. C	Intervention	Duration of intervention	Main outcomes
Chiang, 2007 (18)	38 hypogonadal men (Taiwan) aged 20–75 yr with TT <300 ng/dl 14 older men, age >60 yr, with TT levels <403 ng/dl	Range, 20–72	213 ± 158 vs. 263 ± 198	Transdermal testosterone gel 5 g/d (50 mg/d)	6 months	Sexual function
Clague, 1999 (36)		68.1 ± 6.6 vs. 65.3 ± 1.8	326 ± 49 vs. 334 ± 26	Testosterone enanthate 200 mg biweekly im	12 wk	Muscle performance in the upper and lower limbs
Coodley, 1997 (37)	39 HIV-infected men affected by AIDS and weight loss >5%	18–60	Serum free testosterone 16.05 vs. 16.82 mg/liter	Testosterone cypionate 200 mg/2 wk im	3 months	Weight, QOL, HIV disease markers
Copenhagen Study Group, 1986 (38)	221 men with alcoholic cirrhosis; study stopped early for increased mortality (not reaching statistical significance) 34 men over 20 yr of age on long-term glucocorticoid therapy	53 (24–79) vs. 53 (29–78)	NR	200 mg/8 h micronized testosterone PO	NR	Survival and hepatic function
Crawford, 2003 (70)		60.3 ± 1.9	NR	Mixed esters 200 mg/biweekly im	12 months	Muscle mass, muscle strength, BMD, and QOL
Drinka, 1995 (39)	26 men living in a nursing home aged 60–90. TT <320 ng/dl, and body weight between 90 and 130% of ideal	NR	NR	Testosterone enanthate 150 mg/70 kg biweekly im	6 months	Hematocrit change
Emmelot-Vonk, 2008 (71)	223 healthy men, aged 60– 80, and TT <394 ng/dl	47.9 ± 17.0 vs. 56.1 ± 14.6	311 ± 55 vs. 300 ± 55	Testosterone undecanoate 160 mg/d PO	6 months	Functional mobility, cognition, BMD, body composition, plasma lipids, and QOL
English, 2000 (40)	46 men with stable angina	62 ± 2	390 ± 22 vs. 357 ± 20	Transdermal testosterone patch 5 mg/d	3 months	Angina pectoris
Ferrando, 2003 (41) and 2002 (42)	12 older men (>60 yr) with TT concentrations <480 ng/dl; testosterone doses were adjusted to keep TT in normal range 69 healthy men aged 65–80 Yr	68 ± 3 (SE) vs. 67 ± 3	357 ± 58 vs. 282 ± 55	Testosterone enanthate 100 mg/wk im	6 months	Skeletal muscle performance and muscle protein synthesis rates
Giannoulis, 2006 (43)	146 HIV-infected men with weight loss of 5–15% in the previous 12 months or low BMI	70.3 ± 1.5 vs. 69.8 ± 1.5	496 ± 63 vs. 507 ± 81	Transdermal testosterone patch 5 mg/d	6 months	Lipid metabolism
Gold, 2006 (72)		40.4 ± 9.4 vs. 39.5 ± 9.0	761 ± 340 vs. 726.0 ± 288	Mixed esters 250 mg/2 wk im	3 months	Body composition and anthropometry

(Continued)

TABLE 1. Continued

First author, year (Ref.)	Patients	Age (yr), I vs. C	TT levels (ng/dl), I vs. C	Intervention	Duration of intervention	Main outcomes
Grinspoon, 1998 (44) and 1999 (45)	51 HIV-positive men with weight loss >10% of baseline and FT <12 pg/ml	42 ± 8	326 ± 156 vs. 291 ± 184	Testosterone enanthate 300 mg/3 wk im	6 months	Body composition, functional capacity, QOL, HIV disease markers
Grinspoon, 2000 (46)	54 eugonadal men with HIV-related wasting	40 ± 7 vs. 44 ± 9	648 ± 163 vs. 662 ± 210	Testosterone enanthate 200 mg/wk im	12 wk	Cross-sectional muscle area and other indices of muscle mass
Howell, 2001 (47)	35 men with mild hypogonadism (LH >8 IU/liter) and testosterone in the lower half of normal range as a result of chemotherapy for blood malignancies	40.9	383	Transdermal testosterone patch 2.5–5.0 mg/d	12 months	Energy level, mood and sexual function, bone mineral density, and body composition
Katznelson, 2006 (48)	34 healthy men, aged 65–85 with FT <14.5 pg/ml, BMI 18–32 kg/m ²	72.0 ± 5.5 vs. 72.0 ± 5.2	392 ± 122 vs. 421 ± 110	Transdermal testosterone patch 5 mg/d	3 months	Body composition and QOL
Kenny, 2002 (49)	67 men with bioavailable T <4.4 nmol/liter	76 ± 4 (range, 65–87)	389 ± 173 vs. 389 ± 107	Transdermal testosterone patch 5 mg/d	12 months	Lipids and vascular reactivity
Kenny, 2004 (50)	11 older men with early cognitive decline and bioavailable T <128 ng/dl	80 ± 5	410 ± 112 vs. 404 ± 195	Testosterone enanthate 200 mg/3 wk im	12 wk	Neuropsychological outcomes
Knapp, 2008 (51)	61 patients 18–60 yr old infected with HIV with associated weight loss	43.7 ± 7.4 vs. 42.7 ± 6.0	408 ± 142 vs. 444 ± 141	Testosterone enanthate 300 mg/wk im	4 months	Muscle performance, physical function, mood, QOL
Malkin, 2006 (12)	76 men with heart failure	63.1 ± 10.7 vs. 64.9 ± 9.3	401 ± 153 vs. 349 ± 156	Transdermal testosterone patch 5 mg/d	12 months	Functional capacity
Marin, 1992 (52)	23 men with abdominal obesity >45 yr of age	51.9 ± 2.0 vs. 49.9 ± 1.6 (mean ± SE)	461 ± 35 vs. 484 ± 29 (mean ± SE)	Testosterone undecanoate 80 mg twice daily PO	8 months	Lipid and glucose metabolism, safety
Marks, 2006 (10)	44 men aged 44 to 78 with TT <300 ng/dl and symptoms	Median, 68 (range, 44–76) vs. 70 (45–78)	(range, 163–320) vs. 252 (144–328)	Testosterone enanthate 150 mg/2 wk im	6 months	Intraprostatic androgen levels
Merza, 2006 (53)	39 men with TT <288 ng/dl or FTI <30%	63.0 ± 9.0 vs. 60 ± 10	242 ± 95 vs. 216 ± 72	Transdermal testosterone patch 5 mg/d	6 months	BMD, psychological benefits
Morley, 1993 ^a (54)	26 hypogonadal men with bioavailable testosterone <70 ng/dl	77.6 ± 2.3 vs. 76.0 ± 2.5	Bioavailable testosterone, 37 ± 3 vs. 33 ± 4 ng/dl	Testosterone enanthate 200 mg/biweekly im	3 months	Hematocrit, muscle strength, osteocalcin, lipid levels
Nair, 2006 (11)	58 men >60 yr of age with low levels of DHEA 1.57 µg/dl and bioavailable T <103 ng/dl	Median, 66.2 (IQR, 61.8–72.3) vs. 67.1 (63.6–72.6)	Median, 357.3 (IQR, 281.5–464.7) vs. 398.4 (296–472)	Transdermal testosterone patch 5 mg/d	24 months	Body composition, physical performance, BMD, glucose tolerance, prostate adverse effects

(Continued)

TABLE 1. Continued

First author, year (Ref.)	Patients	Age (yr), I vs. C	TT levels (ng/dl), I vs. C	Intervention	Duration of intervention	Main outcomes
Reid, 1996 (55)	15 asthmatic men under long-term glucocorticoid treatment	61 ± 11	363 ± 26 vs. 326 ± 40	Mixed esters 250 mg/month im	12 months and afterwards	BMD, body composition
Sih, 1997 (56)	Community-dwelling healthy men ≥ 50 yr with bioavailable testosterone <60 ng/dl	65 ± 7 vs. 68 ± 6	294 ± 26 vs. 233 ± 20	Testosterone cypionate 200 mg biweekly im	crossover to placebo	Grip strength, hemoglobin, PSA, leptin, and memory
Simon, 2001 (57)	12 men with low TT were selected from a large occupation-based population	52.8 ± 4.2 vs. 55.4 ± 3.6	240 ± 10 vs. 270 ± 30	Transdermal testosterone gel 125 mg/d	3 months	Insulin sensitivity and leptin
Snyder, 1999 (58), 1999 (59), and 2001 (19)	108 men over 65 yr of age with serum testosterone <475 ng/dl	73.1 ± 5.8 vs. 73.0 ± 5.9	367 ± 79 vs. 369 ± 75	Transdermal testosterone patch 6 mg testosterone/d	3 yr	Body composition, PSA, prostatic outcomes, BMD, lipid levels, cardiovascular events
Steidle, 2003 (20)	406 hypogonadal men aged 20–80 and T <300 ng/dl	58.0 ± 10.3	233 ± 66	Testosterone AA2500 gel 50 mg(d a) vs. 100 mg(d b) vs. testosterone patch 5 mg(d c)	90 d	Pharmacokinetic profiles, body composition, mood, and sexual function
Sullivan, 2005 (60)	35 frail elderly men with TT <480 ng/dl	78.2 ± 6.4	294 ± 141 vs. 332 ± 173	Testosterone enanthate 100 mg/wk im	12 wk	Muscle strength and muscle mass
Swartberg, 2004 (61)	29 men with moderately severe COPD	64.5 ± 6.5 vs. 67.5 ± 5.8	622 ± 164 vs. 591 ± 164	Testosterone enanthate 250 mg/month im	26 wk	Body composition, pulmonary function, QOL, sexuality, and psychological symptoms
Tan, 2003 (62)	10 men with newly diagnosed Alzheimer's disease and TT <240 ng/dl	72 ± 3	126.4 ng/dl (treated group)	Testosterone enanthate 200 mg/biweekly im	12 months	Cognition
Witten, 2003 (21)	76 healthy men, aged 60 yr or older, with symptoms of hypogonadism but FTI within normal range (0.3–0.5)	69 ± 66 vs. 68 ± 65	490 ± 127 vs. 450 ± 130	Testosterone undecanoate 80 mg twice daily PO	1 yr	Body composition, muscle strength, and safety parameters

Data are expressed as mean ± SD, unless otherwise stated. To convert testosterone levels to SI units, multiply testosterone levels in ng/dl by 0.0347. BMD, Bone mineral density; BP, blood pressure; COPD, chronic obstructive pulmonary disease; FT, free testosterone; FTI, FT index; IQR, interquartile range; NR, not reported; PO, orally; QOL, quality of life; rHuEPO, recombinant human erythropoietin; T2DM, type 2 diabetes mellitus; TG, triglycerides; TT, total testosterone; I, intervention; C, control.

^a Studies that did not use placebo as control. (All other studies used placebo as control.)

TABLE 2. Studies that met inclusion criteria but did not provide data for meta-analysis

First author, year (Ref.)	Brief description of the study and main conclusions
Dobs, 1999 (63)	RCT of the effect of transscrotal testosterone replacement (15 mg/d) for 12 wk on body weight, body cell mass, quality of life, and markers of HIV infection in men with HIV-related weight loss and low serum testosterone levels (<400 ng/dl). The men randomized to testosterone therapy did not experience an improvement in the above-mentioned outcomes.
Dohn, 1968 (64)	RCT of the effects of im testosterone isobutyrate (300 mg/2 wk) replacement on vascular outcomes in men with obliterating arteriosclerosis in the lower limbs. There were no statistically significant differences either in subjective or objective vascular outcomes (metronome walking test, plethysmography, temperature change after chlorpromazine) between subjects randomized to testosterone or placebo.
Hall, 1996 (65)	RCT on the effects of monthly injections of testosterone enanthate (250 mg) on disease activity and bone mineral density in patients affected by rheumatoid arthritis. There were no significant changes in either disease activity or bone mineral density during the period of follow-up.
Hentzer, 1967 (66)	RCT of the effects of testosterone enanthate (200 mg/wk during the first 3 wk and then every 2 wk for 6 months) on vascular outcomes in patients with arterial insufficiency of lower limbs. There were no statistically significant differences in walking distance, foot pulse, venous filling time, or muscle blood flow between patients assigned to testosterone and those assigned to placebo.
Pugh , 2004 (67)	Pilot study of the effects of mixed testosterone esters (100 mg/2 wk im) for 12 wk on exercise capacity and symptoms of heart failure in patients with chronic heart failure. Patients allocated to testosterone experienced an increase in walking distance and symptom scores.

Cardiovascular risk factors

The testosterone and placebo/nonintervention groups did not differ significantly in the incidence of diabetes mellitus or in the changes from baseline in cardiometabolic risk factors, such as fasting glucose, total and low-density lipoprotein (LDL) cholesterol, triglycerides, systolic and diastolic blood pressure levels. High-density lipoprotein (HDL) cholesterol levels were significantly lower in the testosterone-treated group than the control group (WMD, -0.49 mg/dl ; 95% CI, $-0.85 \text{ to } -0.13$; $I^2 = 69\%$) (Table 4). The majority of these analyses were associated with significant heterogeneity.

Prostatic/urological outcomes

There was no significant effect of testosterone therapy on patient-important outcomes such as the incidence of prostatic cancer or the need for prostate biopsy, when compared with the placebo/nonintervention group (Fig. 2). There was no significant difference between the two groups in the risk of other prostatic and urological outcomes such as a significant increase of PSA, changes in IPSS lower urinary tract symptoms, or the composite prostate outcome (Table 4).

Erythrocytosis

Hemoglobin (WMD, 0.80 g/dl ; 95% CI, $0.45 \text{ to } 1.14$; $I^2 = 95\%$) and hematocrit (WMD, 3.18% ; 95% CI, $1.35 \text{ to } 5.01$; $I^2 = 91\%$) levels increased to a greater extent in testosterone-treated men than in men receiving placebo or no treatment. Testosterone-treated men were at higher risk of developing erythrocytosis than the placebo/nonintervention group (RR, 3.15 ; 95% CI, $1.56 \text{ to } 6.35$; $I^2 = 0\%$) (Table 4).

Subgroup analysis and sensitivity analysis

We performed subgroup analyses to explore possible causes of heterogeneity and to detect subgroup-treatment interactions. These analyses are presented in the table in the Appendix (published on The Endocrine Society's Journals Online web site at <http://jcem.endojournals.org>). The route of testosterone administration and dose partially explained the heterogeneity of results. Intramuscular route and high dose were associated with greater increases in red cell indices (hemoglobin and hematocrit), PSA, and systolic and diastolic blood pressure. Higher doses were associated also with more increase in LDL and total cholesterol. Baseline testosterone status affected the response of hemoglobin and hematocrit; patients with low baseline had more increase of both indices. The population characteristics (healthy *vs.* having comorbid conditions such as end stage renal disease, HIV, congestive heart failure, and coronary artery disease) affected the effect size for several

TABLE 3. Quality of the included studies

First author, year (Ref.)	Lost to follow-up (total, I, C)	Length of follow-up (months)	Allocation concealment	Blinding			Funding
				P	CG	OA	
Agledahl, 2008 (24)	4%	12	NR	Y	Y	NR	Non FP
Allan, 2008 (17)	29, 42, 16%	12	Probably Y	Y	Y	NR	Includes FP
Amory, 2004 (25); Page, 2005 (26)	27, 29, 25%	36	Y	Y	Y	Y	Non FP
Basurto, 2008 (27)	13, 16, 9%	12	Y	Y	Y	Y	Non FP
Bhasin, 1998 (28)	22, 30, 14%	3	Y	Y	Y	NR	Includes FP
Bhasin, 2000 (29)	13, 12, 14%	4	Y	Y	Y	NR	Non FP
Bhasin, 2007 (30)	14, 11, 18%	12	Y	Y	Y	Y	Non FP
Blackman, 2002 (31); Christmas, 2002 (32); Harman, 2003 (68); Münzer, 2001 (69)	0%	6	NR	Y	Y	NR	Non FP
Boyanov, 2003 (33)	0%	3	NR	N	N	N	NR
Brockenbrough, 2006 (34)	45, 42, 48%	6	Probably Y	Y	Y	NR	Includes FP
Cavallini, 2004 (35)	13%	12	Probably Y	Y	Y	NR	NR
Chiang, 2007 (18)	10, 0, 20%	3	NR	Y	Y	NR	Includes FP
Clague, 1999 (36)	NR	3	Probably Y	Y	Y	NR	Includes FP
Coodley, 1997 (37)	10%	3	NR	Y	Y	NR	Includes FP
Copenhagen Study Group, 1986 (38)	7, 3%	28	Probably Y	Y	Y	Y	Non FP
Crawford, 2003 (70)	23, 22, 19%	12	NR	Y	Y	NR	Includes FP
Drinka, 1995 (39)	31%	6	NR	Y	Y	NR	Non FP
Emmelot-Vonk, 2008 (71)	13, 13, 12%	6	Probably Y	Y	Y	NR	Non FP
English, 2000 (40)	6%	3	NR	Y	Y	NR	NR
Ferrando, 2002 (42), and 2003 (41)	NR	6	NR	Y	Y	NR	Non FP
Giannoulis, 2006 (43)	14, 9, 20%	6	Y	Y	Y	Y	Non FP
Gold, 2006 (72)	7, 11, 4%	3	NR	Y	Y	NR	Includes FP
Grinspoon, 1998 (44), and 1999 (45)	21, 15, 19%	6	Yes	Y	Y	NR	Non FP
Grinspoon, 2000 (46)	8, 9, 8%	3	Yes	Y	Y	NR	Non FP
Howell, 2001 (47)	3, 3, 3%	15	NR	N	Y	NR	Includes FP
Katznelson, 2006 (48)	6, 6, 6%	3	NR	Y	Y	NR	Includes FP
Kenny, 2002 (49)	15, 19%	12	NR	Y	Y	NR	Non FP
Kenny, 2004 (50)	0%	<3	NR	Y	Y	Y	Non FP
Knapp, 2008 (51)	21, 29, 13%	4	Y	Y	Y	Y	Non FP
Malkin, 2006 (12)	15, 16, 14%	12	NR	Y	Y	NR	Non FP
Marin, 1992 (52)	8, 0%	8	NR	Y	Y	NR	Non FP
Marks, 2006 (10)	10, 5, 14%	6	NR	Y	Y	NR	Includes FP
Merza, 2006 (53)	3, 5, 0%	6	NR	Y	Y	NR	Includes FP
Morley, 1993 (54)	6, 6, 6%	3	N	N	N	N	NR
Nair, 2006 (11)	6, 10, 3%	24	NR	Y	Y	Y	Non FP
Reid, 1996 (55)	7%	12	NR	Y	Y	NR	NR
Sih, 1997 (56)	0%	12	NR	Y	Y	NR	NR
Simon, 2001 (57)	0%	3	NR	Y	Y	NR	NR
Snyder, 1999 (58, 59), and 2001 (19)	11, 7, 15%	36	NR	Y	Y	Y	Non FP
Steidle, 2003 (20)	11, 15, 8%	3	NR	Y	Y	NR	Includes FP
Sullivan, 2005 (60)	18, 11, 12%	3	NR	Y	Y	NR	Non FP
Svartberg, 2004 (61)	0%	6	NR	Y	Y	NR	Non FP
Tan, 2003 (62)	0%	12	NR	Y	Y	NR	NR
Wittert, 2003 (21)	24, 15, 32%	12	Probably Y	Y	Y	Y	Includes FP

I, Intervention; C, control; CG, caregivers; FP, for profit; NR, not reported; OA, outcome assessors; P, patients; Y, yes.

outcomes, suggesting an obvious source of heterogeneity; however, these effects were paradoxical and difficult to interpret in a summary meta-analysis of a study-level aggregate data, as is the case in this analysis. We used Peto odds ratio and the treatment arm method for continuity

correction in sensitivity analyses, which are the recommended approaches to deal with studies with low event rates (sparse data); the use of these methods did not change study conclusions. The exclusion of studies in which the loss of follow-up significantly differed between the inter-

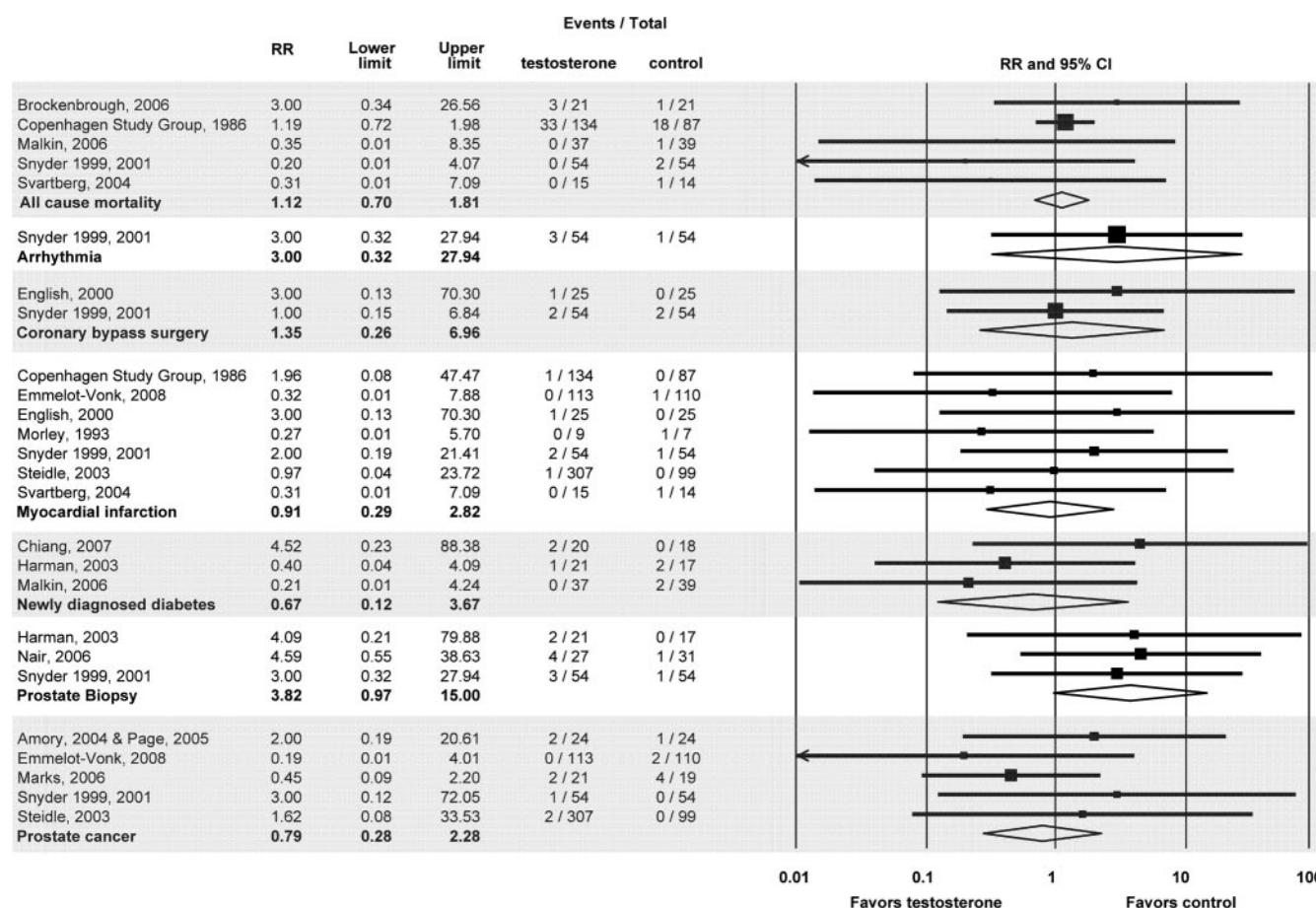


FIG. 2. Results of the random effects meta-analyses of testosterone on patient-important outcomes.

vention and control groups did not change the conclusions of this report.

Discussion

Principal findings

This systematic review and meta-analyses demonstrated that testosterone therapy in men was associated with significant increases in hemoglobin and hematocrit. There also was a statistically significant but small reduction in HDL cholesterol. However, testosterone therapy had no significant effects on all-cause mortality, prostatic or urological outcomes, cardiovascular events, or cardiovascular risk factors. Several subgroup interactions were found and can partially explain the heterogeneity associated with the analysis. However, caution should be exercised in interpreting these analyses because they are considered observational in nature (despite the fact that the original studies were randomized) and the associations found can be attributable to chance due to the multiple simultaneous comparisons. Subgroup interactions generated by study-level meta-analyses are considered hypothesis-generating and should be confirmed at a patient-level

(in a large trial or individual patient meta-analysis) before clinical implications are inferred.

Limitations and strengths

The strengths of this study include the comprehensive literature search, the application of bias protection measures in the selection of the studies, and the evaluation of their methodological quality. Nevertheless, the quality of the evidence varied from low to medium considering the imprecision (small number of events), heterogeneity (for the outcomes of cardiometabolic risk factors, hemoglobin and hematocrit), and methodological limitations of the included trials. In particular, the brief duration of most testosterone trials limited inferences about the long-term safety of this treatment. In addition, publication and reporting biases likely affected the inferences in this review because not all studies reported the outcomes of interest (22).

Implications for practice and research

Because increases in hemoglobin and hematocrit are the most frequent adverse events associated with testosterone therapy, these data support the Endocrine Society Clinical

TABLE 4. Random effects meta-analysis

First author, year (Ref.)	95% CI			I^2
	RR	Lower boundary	Upper boundary	
Dichotomous outcomes				
Composite prostate endpoint	1.41	0.93	2.14	20.36
Bhasin, 2007 (30)	2.00	0.19	21.26	
Snyder 1999a, 1999b, 2001 (58, 59, 19)	2.13	1.00	4.50	
Amory, 2004 (25); Page, 2005 (26)	0.40	0.09	1.86	
Basurto, 2008 (27)	6.46	0.35	118.71	
Giannoulis, 2006 (43)	1.67	0.50	5.61	
Harman, 2003 (69); Blackman, 2002 (31); Christmas, 2002 (32); Münzer, 2001 (69)	10.64	0.64	176.35	
Katznelson, 2006 (48)	17.00	1.06	273.02	
Kenny, 2002 (49)	0.65	0.12	3.63	
Knapp, 2008 (51)	0.34	0.01	8.13	
Marks, 2006 (10)	0.45	0.09	2.20	
Nair, 2006 (11)	1.97	0.91	4.28	
Steidle, 2003(a) (20)	0.67	0.11	3.90	
Steidle, 2003(b) (20)	0.93	0.19	4.52	
Steidle, 2003(c) (20)	2.91	0.81	10.44	
Wittert, 2003 (21)	0.81	0.30	2.20	
Impaired urinary flow	0.86	0.13	5.53	NA
Nair, 2006 (11)	1.53	0.61	3.86	
Wittert, 2003 (21)	0.18	0.01	3.63	
PSA levels >4 ng/ml	1.22	0.67	2.21	0.00
Amory, 2004 (25); Page, 2005 (26)	0.25	0.03	2.08	
Basurto, 2008 (27)	6.46	0.35	118.71	
Giannoulis, 2006 (43)	2.57	0.13	52.12	
Katznelson, 2006 (48)	9.00	0.52	155.24	
Knapp, 2008 (51)	0.34	0.01	8.13	
Steidle, 2003(a) (20)	0.67	0.11	3.90	
Steidle, 2003(b) (20)	0.93	0.19	4.52	
Steidle, 2003(c) (20)	2.26	0.60	8.51	
Wittert, 2003 (21)	1.08	0.36	3.22	
Significant increase in PSA (>1.5 ng/ml unless otherwise specified)	1.56	0.87	2.80	0.00
Bhasin, 2007 (30)	2.00	0.19	21.26	
Snyder 1999a, 1999b, 2001 (58, 59, 19)	1.86	0.80	4.29	
Giannoulis, 2006 (43)	1.25	0.33	4.77	
Katznelson, 2006 (48)	9.00	0.52	155.24	
Emmelot-Vonk, 2008 (71) (>1.4 ng/ml)	0.58	0.14	2.39	
Harman, 2003 (68); Blackman, 2002 (31) (>1 ng/ml)	4.09	0.21	79.88	
Erythrocytosis		3.15	1.56	6.35
Bhasin, 2007 (30)	3.00	0.32	27.74	
Copenhagen Study Group, 1986 (38)	1.95	0.21	18.42	
Snyder 1999a, 1999b, 2001 (58, 59, 19)	7.00	0.37	132.35	
Marks, 2006 (10)	2.73	0.12	63.19	
Sih, 1997 (56)	8.00	0.47	137.35	
Steidle, 2003(a) (20)	3.00	0.32	28.35	
Steidle, 2003(b) (20)	5.60	0.69	45.72	
Steidle, 2003(c) (20)	0.97	0.06	15.30	
Wittert, 2003 (21)	2.37	0.49	11.48	
Drinka, 1995 (39)	6.11	0.33	111.71	
Merza, 2006 (53)	2.85	0.32	25.07	
Continuous outcomes	WMD			
Diastolic blood pressure	-0.60	-5.20	3.99	87.67
Wittert, 2003 (21)	1.00	-3.78	5.78	
Boyanov, 2003 (33)	-2.00	-4.65	0.65	
Emmelot-Vonk, 2008 (71)	1.50	-1.25	4.25	
Ferrando, 2002 (42)	10.00	5.32	14.68	
Marin, 1992 (52)	-4.70	-11.13	1.73	
Simon, 2001 (57)	-10.00	-14.67	-5.33	

Downloaded from https://academic.oup.com/jcem/article/95/6/2560/25597959 by guest on 10 April 2024

(Continued)

TABLE 4. Continued

First author, year (Ref.)	95% CI			I^2
	Lower boundary	Upper boundary		
Systolic blood pressure	1.81	-1.54	5.16	40.97
Sih, 1997 (56)	5.00	-3.06	13.06	
Wittert, 2003 (21)	5.00	-4.13	14.13	
Boyanov, 2003 (33)	-4.00	-8.87	0.87	
Emmelot-Vonk, 2008 (71)	1.80	-3.18	6.78	
Ferrando, 2002 (42)	0.00	-7.42	7.42	
Marin, 1992 (52)	-1.00	-12.96	10.96	
Simon, 2001 (57)	7.00	1.34	12.66	
Fasting glucose	0.20	-0.02	0.43	51.20
Amory, 2004 (25); Page, 2005 (26)	21.00	1.02	40.98	
Giannoulis, 2006 (43)	0.20	0.11	0.29	
Boyanov, 2003 (33)	-29.00	-53.42	-4.58	
Emmelot-Vonk, 2008 (71)	0.20	0.04	0.36	
Marin, 1992 (52)	-5.40	-21.99	11.19	
Simon, 2001 (57)	1.00	-3.00	5.00	
Fasting TG	-11.34	-26.86	4.17	92.54
Bhasin, 2007 (30)	7.00	-54.21	68.21	
Brockenbrough, 2006 (34)	20.50	-481.50	522.50	
Snyder 1999a, 1999b, 2001 (58, 59, 19)	-8.00	-38.49	22.49	
Amory, 2004 (25); Page, 2005 (26)	-32.00	-41.89	-22.11	
Giannoulis, 2006 (43)	0.56	0.41	0.71	
Katznelson, 2006 (48)	16.90	-7.73	41.53	
Knapp, 2008 (51)	-43.50	-54.49	-32.51	
Boyanov, 2003 (33)	-12.39	-54.90	30.12	
Emmelot-Vonk, 2008 (71)	-17.70	-40.15	4.75	
Marin, 1992 (52)	0.00	-62.34	62.34	
Simon, 2001 (57)	13.00	-11.00	37.00	
Agledahl, 2008 (24)	23.02	-33.10	79.14	
Reid, 1996 (55)	-36.00	-46.02	-25.98	
HDL cholesterol	-0.49	-0.85	-0.13	69.71
Bhasin, 2007 (30)	1.00	-1.32	3.32	
Brockenbrough, 2006 (34)	-0.70	-11.69	10.29	
Snyder 1999a, 1999b, 2001 (58, 59, 19)	-1.00	-5.44	3.44	
Amory, 2004 (25); Page, 2005 (26)	-1.00	-2.75	0.75	
Giannoulis, 2006 (43)	-1.15	-2.86	0.56	
Katznelson, 2006 (48)	-3.50	-5.45	-1.55	
Knapp, 2008 (51)	-0.50	-1.77	0.77	
Wittert, 2003 (21)	-0.10	-0.17	-0.03	
Boyanov, 2003 (33)	-0.38	-4.89	4.13	
Emmelot-Vonk, 2008 (71)	-7.72	-10.76	-4.68	
Ferrando, 2002 (42)	-0.18	-0.31	-0.05	
Marin, 1992 (52)	0.00	-10.76	10.76	
Simon, 2001 (57)	-2.00	-4.26	0.26	
Agledahl, 2008 (24)	-0.01	-8.65	8.63	
Reid, 1996 (55)	-6.00	-12.36	0.36	
LDL cholesterol	0.34	-4.53	5.21	92.70
Bhasin, 2007 (30)	-4.00	-12.38	4.38	
Brockenbrough, 2006 (34)	4.70	-19.29	28.69	
Snyder 1999a, 1999b, 2001 (58, 59, 19)	2.00	-12.02	16.02	
Amory, 2004 (25); Page, 2005 (26)	-13.00	-17.04	-8.96	
Giannoulis, 2006 (43)	19.30	14.65	23.95	
Katznelson, 2006 (48)	-6.70	-12.65	-0.75	
Knapp, 2008 (51)	10.50	7.52	13.48	
Wittert, 2003 (21)	0.20	-0.05	0.45	
Boyanov, 2003 (33)	-1.93	-28.82	24.96	
Emmelot-Vonk, 2008 (71)	0.00	-9.40	9.40	
Ferrando, 2002 (42)	-6.18	-23.25	10.89	
Agledahl, 2008 (24)	10.81	-12.97	34.59	
Reid, 1996 (55)	2.00	-9.72	13.72	
Allan, 2008 (17)	-7.72	-11.32	-4.12	

(Continued)

TABLE 4. Continued

First author, year (Ref.)	95% CI			I^2
	Lower boundary	Upper boundary		
Total cholesterol	-1.39	-6.41	3.63	87.56
Bhasin, 2007 (30)	-8.00	-21.32	5.32	
Brockenbrough, 2006 (34)	8.20	-19.40	35.80	
Snyder 1999a, 1999b, 2001 (58, 59, 19)	-3.00	-18.34	12.34	
Amory, 2004 (25); Page, 2005 (26)	-18.00	-39.56	3.56	
Giannoulis, 2006 (43)	23.17	14.67	31.67	
Katznelson, 2006 (48)	-5.20	-11.86	1.46	
Knapp, 2008 (51)	8.60	4.91	12.29	
Sih, 1997 (56)	-2.00	-20.47	16.47	
Wittert, 2003 (21)	0.00	-0.27	0.27	
Boyanov, 2003 (33)	-1.55	-33.40	30.30	
Emmelot-Vonk, 2008 (71)	-3.86	-14.00	6.28	
Ferrando, 2002 (42)	-10.80	-31.34	9.74	
Marin, 1992 (52)	-7.72	-118.14	102.70	
Simon, 2001 (57)	5.00	-1.88	11.88	
Agledahl, 2008 (24)	23.16	-12.34	58.66	
Reid, 1996 (55)	-10.00	-21.85	1.85	
Allan, 2008 (17)	-15.45	-19.05	-11.85	
Clague, 1999 (36)	-20.07	-52.93	12.79	
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	

Units of measurement for WMD are mg/dl for lipid fractions and glucose, ng/ml for PSA, g/dl for hemoglobin, percentage points for hematocrit, and mm Hg for systolic and diastolic blood pressure. NA, Not available.

Practice Guideline that hemoglobin and hematocrit should be monitored in androgen-deficient men receiving testosterone therapy (23). Studies of longer treatment duration that assess patient-important outcomes are needed. Despite the high prevalence of low testosterone levels in adult men, the published literature is not very helpful in addressing the safety concerns of patients and clinicians attempting to weigh the long-term potential benefits and harms of testosterone treatment.

Comparison with previous reviews

Our review added several new studies of substantially larger sample size to prior systematic reviews and reflects the current state of the available evidence. Our results are consistent with previous reviews (6, 7) to a great extent in terms of the inability to find a statistically significant effect of testosterone treatment on patient-important adverse outcomes, such as death, cardiovascular events, the incidence of prostate cancer, or worsening of lower urinary tract symptoms. Despite the increase in the number of studies and sample size since previous reviews, these risk estimates for these outcomes continue to be imprecise.

Testosterone therapy for age-related decline in testosterone therapy in middle-aged and older men remains a controversial issue. Although there is agreement that total and free testosterone levels decline with advancing age, neither the benefits of testosterone treatment nor its safety have been established. Although testosterone therapy has been shown to increase lean body mass, muscle strength, vertebral bone mineral density, and some domains of sexual function, the benefits of therapy on patient-important outcomes—disability, vitality, fractures, and quality of life—remain largely unknown (1, 18). Our search of published comparative observational studies, which often provide good evidence for harm questions due to longer follow-up and larger sample size, did not render significant contribution to the existing knowledge. Future studies, both randomized and observational, are needed and should have longer follow-up. For example, the Testosterone Trials (ClinicalTrials.gov:NCT00799617), a multicenter coordinated set of trials involving 12 clinical sites across the United States, will randomly assign elderly men whose serum testosterone concentrations are unequivocally low to either placebo or testosterone therapy for 12 months. This landmark trial will advance our knowledge about testosterone effects on physical and sexual function, vitality, cognition, and anemia. However, this trial is not adequately powered to determine the long-term harms associated with treatment. Therefore, periodic collation of adverse event data across trials through the use of systematic reviews and meta-analyses will be helpful.

Conclusions

Testosterone treatment in adult men is associated with an increase in hemoglobin and hematocrit and a small reduction in HDL cholesterol. The clinical significance of these findings and the effects on patient-important outcomes such as mortality, cardiovascular events, and incidence of prostate cancer requires further investigation.

Acknowledgments

Address all correspondence and requests for reprints to: Victor M. Montori, M.D., M.Sc., Mayo Clinic, W18A, 200 First Street SW, Rochester, Minnesota 55905. E-mail: montori.victor@mayo.edu.

This work was supported by a contract from The Endocrine Society. M.M.F.-B. has received grant support from the Instituto de Salud Carlos III, Ministerio de Sanidad y Consumo (BA08/90035), Government of Spain.

Disclosure Summary: M.M.F.-B., M.H.M., M.L., J.F.L., F.A., R.J.M., N.A., M.B.E., J.F.G.-O., A.T.W., P.J.E., S.B., and V.M.M. have nothing to declare.

References

1. Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR 2001 Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. *J Clin Endocrinol Metab* 86:724–731
2. Isidori AM, Giannetta E, Gianfrilli D, Greco EA, Bonifacio V, Aversa A, Isidori A, Fabbri A, Lenzi A 2005 Effects of testosterone on sexual function in men: results of a meta-analysis. *Clin Endocrinol (Oxf)* 63:381–394
3. Ottenbacher KJ, Ottenbacher ME, Ottenbacher AJ, Acha AA, Ostir GV 2006 Androgen treatment and muscle strength in elderly men: a meta-analysis. *J Am Geriatr Soc* 54:1666–1673
4. Isidori AM, Giannetta E, Greco EA, Gianfrilli D, Bonifacio V, Isidori A, Lenzi A, Fabbri A 2005 Effects of testosterone on body composition, bone metabolism and serum lipid profile in middle-aged men: a meta-analysis. *Clin Endocrinol (Oxf)* 63:280–293
5. Boloña ER, Uraga MV, Haddad RM, Tracz MJ, Sideras K, Kennedy CC, Caples SM, Erwin PJ, Montori VM 2007 Testosterone use in men with sexual dysfunction: a systematic review and meta-analysis of randomized placebo-controlled trials. *Mayo Clin Proc* 82:20–28
6. Calof OM, Singh AB, Lee ML, Kenny AM, Urban RJ, Tenover JL, Bhasin S 2005 Adverse events associated with testosterone replacement in middle-aged and older men: a meta-analysis of randomized, placebo-controlled trials. *J Gerontol A Biol Sci Med Sci* 60:1451–1457
7. Haddad RM, Kennedy CC, Caples SM, Tracz MJ, Boloña ER, Sideras K, Uraga MV, Erwin PJ, Montori VM 2007 Testosterone and cardiovascular risk in men: a systematic review and meta-analysis of randomized placebo-controlled trials. *Mayo Clin Proc* 82:29–39
8. Basu R, Dalla Man C, Campioni M, Basu A, Nair KS, Jensen MD, Khosla S, Klee G, Toffolo G, Cobelli C, Rizza RA 2007 Effect of 2 years of testosterone replacement on insulin secretion, insulin action, glucose effectiveness, hepatic insulin clearance, and postprandial glucose turnover in elderly men. *Diabetes Care* 30:1972–1978
9. Kapoor D, Goodwin E, Channer KS, Jones TH 2006 Testosterone replacement therapy improves insulin resistance, glycaemic control,

- visceral adiposity and hypercholesterolaemia in hypogonadal men with type 2 diabetes. *Eur J Endocrinol* 154:899–906
10. Marks LS, Mazer NA, Mostaghel E, Hess DL, Dorey FJ, Epstein JI, Veltri RW, Makarov DV, Partin AW, Bostwick DG, Macairan ML, Nelson PS 2006 Effect of testosterone replacement therapy on prostate tissue in men with late-onset hypogonadism: a randomized controlled trial. *JAMA* 296:2351–2361
 11. Nair KS, Rizza RA, O'Brien P, Dhatriya K, Short KR, Nehra A, Vittone JL, Klee GG, Basu A, Basu R, Cobelli C, Toffolo G, Dalla Man C, Tindall DJ, Melton 3rd LJ, Smith GE, Khosla S, Jensen MD 2006 DHEA in elderly women and DHEA or testosterone in elderly men. *N Engl J Med* 355:1647–1659
 12. Malkin CJ, Pugh PJ, West JN, van Beek EJ, Jones TH, Channer KS 2006 Testosterone therapy in men with moderate severity heart failure: a double-blind randomized placebo controlled trial. *Eur Heart J* 27:57–64
 13. Moher D, Liberati A, Tetzlaff J, Altman DG, Prisma Group 2009 Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 6:e1000097
 14. Swiglo BA, Murad MH, Schünemann HJ, Kunz R, Vigersky RA, Guyatt GH, Montori VM 2008 A case for clarity, consistency, and helpfulness: state-of-the-art clinical practice guidelines in endocrinology using the grading of recommendations, assessment, development, and evaluation system. *J Clin Endocrinol Metab* 93:666–673
 15. DerSimonian R, Laird N 1986 Meta-analysis in clinical trials. *Controlled Clinical Trials* 7:177–188
 16. Higgins JP, Thompson SG, Deeks JJ, Altman DG 2003 Measuring inconsistency in meta-analyses. *BMJ* 327:557–560
 17. Allan CA, Strauss BJ, Burger HG, Forbes EA, McLachlan RI 2008 Testosterone therapy prevents gain in visceral adipose tissue and loss of skeletal muscle in nonobese aging men. *J Clin Endocrinol Metab* 93:139–146
 18. Chiang HS, Hwang TI, Hsui YS, Lin YC, Chen HE, Chen GC, Liao CH 2007 Transdermal testosterone gel increases serum testosterone levels in hypogonadal men in Taiwan with improvements in sexual function. *Int J Impot Res* 19:411–417
 19. Snyder PJ, Peachey H, Berlin JA, Rader D, Usher D, Loh L, Hannoush P, Dlewati A, Holmes JH, Santanna J, Strom BL 2001 Effect of transdermal testosterone treatment on serum lipid and apolipoprotein levels in men more than 65 years of age. *Am J Med* 111:255–260
 20. Steidle C, Schwartz S, Jacoby K, Sebree T, Smith T, Bachand R 2003 AA2500 testosterone gel normalizes androgen levels in aging males with improvements in body composition and sexual function. *J Clin Endocrinol Metab* 88:2673–2681
 21. Wittert GA, Chapman IM, Haren MT, Mackintosh S, Coates P, Morley JE 2003 Oral testosterone supplementation increases muscle and decreases fat mass in healthy elderly males with low-normal gonadal status. *J Gerontol A Biol Sci Med Sci* 58:618–625
 22. Furukawa TA, Watanabe N, Omori IM, Montori VM, Guyatt GH 2007 Association between unreported outcomes and effect size estimates in Cochrane meta-analyses. *JAMA* 297:468–470
 23. Petak SM, Nankin HR, Spark RF, Swerdlow RS, Rodriguez-Rigau LJ 2002 American Association of Clinical Endocrinologists Medical Guidelines for clinical practice for the evaluation and treatment of hypogonadism in adult male patients—2002 update. *Endocr Pract* 8:440–456
 24. Agledahl I, Hansen JB, Svartberg J 2008 Impact of testosterone treatment on postprandial triglyceride metabolism in elderly men with subnormal testosterone levels. *Scand J Clin Lab Invest* 68: 641–648
 25. Amory JK, Watts NB, Easley KA, Sutton PR, Anawalt BD, Matsumoto AM, Bremner WJ, Tenover JL 2004 Exogenous testosterone or testosterone with finasteride increases bone mineral density in older men with low serum testosterone. *J Clin Endocrinol Metab* 89:503–510
 26. Page ST, Amory JK, Bowman FD, Anawalt BD, Matsumoto AM, Bremner WJ, Tenover JL 2005 Exogenous testosterone (T) alone or with finasteride increases physical performance, grip strength, and lean body mass in older men with low serum T. *J Clin Endocrinol Metab* 90:1502–1510
 27. Basurto L, Zarate A, Gomez R, Vargas C, Saucedo R, Galván R 2008 Effect of testosterone therapy on lumbar spine and hip mineral density in elderly men. *Aging Male* 11:140–145
 28. Basin S, Storer TW, Asbel-Sethi N, Kilbourne A, Hays R, Sinha-Hikim I, Shen R, Arver S, Beall G 1998 Effects of testosterone replacement with a nongenital, transdermal system, Androderm, in human immunodeficiency virus-infected men with low testosterone levels. *J Clin Endocrinol Metab* 83:3155–3162
 29. Basin S, Storer TW, Javanbakht M, Berman N, Yarasheski KE, Phillips J, Dike M, Sinha-Hikim I, Shen R, Hays RD, Beall G 2000 Testosterone replacement and resistance exercise in HIV-infected men with weight loss and low testosterone levels. [See comment] *JAMA* 283:763–770
 30. Basin S, Parker RA, Sattler F, Haubrich R, Alston B, Umbleja T, Shikuma CM, Team ACTGPAS 2007 Effects of testosterone supplementation on whole body and regional fat mass and distribution in human immunodeficiency virus-infected men with abdominal obesity. *J Clin Endocrinol Metab* 92:1049–1057
 31. Blackman MR, Sorkin JD, Münder T, Bellantoni MF, Busby-Whitehead J, Stevens TE, Jayme J, O'Connor KG, Christmas C, Tobin JD, Stewart KJ, Cottrell E, St Clair C, Pabst KM, Harman SM 2002 Growth hormone and sex steroid administration in healthy aged women and men: a randomized controlled trial. *JAMA* 288: 2282–2292
 32. Christmas C, O'Connor KG, Harman SM, Tobin JD, Münder T, Bellantoni MF, Clair CS, Pabst KM, Sorkin JD, Blackman MR 2002 Growth hormone and sex steroid effects on bone metabolism and bone mineral density in healthy aged women and men. *J Gerontol A Biol Sci Med Sci* 57:M12–M18
 33. Boyanov MA, Boneva Z, Christov VG 2003 Testosterone supplementation in men with type 2 diabetes, visceral obesity and partial androgen deficiency. *Aging Male* 6:1–7
 34. Brockenbrough AT, Dittrich MO, Page ST, Smith T, Stivelman JC, Bremner WJ 2006 Transdermal androgen therapy to augment EPO in the treatment of anemia of chronic renal disease. *Am J Kidney Dis* 47:251–262
 35. Cavallini G, Caracciolo S, Vitali G, Modenini F, Biagiotti G 2004 Carnitine versus androgen administration in the treatment of sexual dysfunction, depressed mood, and fatigue associated with male aging. *Urology* 63:641–646
 36. Clague JE, Wu FC, Horan MA 1999 Difficulties in measuring the effect of testosterone replacement therapy on muscle function in older men. *Int J Androl* 22:261–265
 37. Coodley GO, Coodley MK 1997 A trial of testosterone therapy for HIV-associated weight loss. *AIDS* 11:1347–1352
 38. 1986 Testosterone treatment of men with alcoholic cirrhosis: a double-blind study. The Copenhagen Study Group for Liver Diseases. *Hepatology* 6:807–813
 39. Drinka PJ, Jochen AL, Cuisinier M, Bloom R, Rudman I, Rudman D 1995 Polycythemia as a complication of testosterone replacement therapy in nursing home men with low testosterone levels. *J Am Geriatr Soc* 43:899–901
 40. English KM, Steeds RP, Jones TH, Diver MJ, Channer KS 2000 Low-dose transdermal testosterone therapy improves angina threshold in men with chronic stable angina: a randomized, double-blind, placebo-controlled study. *Circulation* 102:1906–1911
 41. Ferrando AA, Sheffield-Moore M, Paddon-Jones D, Wolfe RR, Urban RJ 2003 Differential anabolic effects of testosterone and amino acid feeding in older men. *J Clin Endocrinol Metab* 88:358–362
 42. Ferrando AA, Sheffield-Moore M, Yeckel CW, Gilkison C, Jiang J, Achacosa A, Lieberman SA, Tipton K, Wolfe RR, Urban RJ 2002 Testosterone administration to older men improves muscle function: molecular and physiological mechanisms. *Am J Physiol Endocrinol Metab* 282:E601–E607
 43. Giannoulis MG, Sonksen PH, Umpleby M, Breen L, Pentecost C,

- Whyte M, McMillan CV, Bradley C, Martin FC 2006 The effects of growth hormone and/or testosterone in healthy elderly men: a randomized controlled trial. *J Clin Endocrinol Metab* 91:477–484
44. Grinspoon S, Corcoran C, Askari H, Schoenfeld D, Wolf L, Burrows B, Walsh M, Hayden D, Parlman K, Anderson E, Basgoz N, Klibanski A 1998 Effects of androgen administration in men with the AIDS wasting syndrome. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 129:18–26
45. Grinspoon S, Corcoran C, Anderson E, Hubbard J, Stanley T, Basgoz N, Klibanski A 1999 Sustained anabolic effects of long-term androgen administration in men with AIDS wasting. *Clin Infect Dis* 28:634–636
46. Grinspoon S, Corcoran C, Parlman K, Costello M, Rosenthal D, Anderson E, Stanley T, Schoenfeld D, Burrows B, Hayden D, Basgoz N, Klibanski A 2000 Effects of testosterone and progressive resistance training in eugonadal men with AIDS wasting. A randomized, controlled trial. [See comment] *Ann Intern Med* 133:348–355
47. Howell SJ, Radford JA, Adams JE, Smets EM, Warburton R, Shalet SM 2001 Randomized placebo-controlled trial of testosterone replacement in men with mild Leydig cell insufficiency following cytotoxic chemotherapy. *Clin Endocrinol (Oxf)* 55:315–324
48. Katzenelson L, Robinson MW, Coyle CL, Lee H, Farrell CE 2006 Effects of modest testosterone supplementation and exercise for 12 weeks on body composition and quality of life in elderly men. *Eur J Endocrinol* 155:867–875
49. Kenny AM, Prestwood KM, Gruman CA, Fabregas G, Biskup B, Mansoor G 2002 Effects of transdermal testosterone on lipids and vascular reactivity in older men with low bioavailable testosterone levels. *J Gerontol A Biol Sci Med Sci* 57:M460–M465
50. Kenny AM, Fabregas G, Song C, Biskup B, Bellantonio S 2004 Effects of testosterone on behavior, depression, and cognitive function in older men with mild cognitive loss. *J Gerontol A Biol Sci Med Sci* 59:75–78
51. Knapp PE, Storer TW, Herbst KL, Singh AB, Dzekov C, Dzekov J, LaValley M, Zhang A, Ulloor J, Bhasin S 2008 Effects of a supra-physiological dose of testosterone on physical function, muscle performance, mood, and fatigue in men with HIV-associated weight loss. *Am J Physiol Endocrinol Metab* 294:E1135–E1143
52. Mårin P, Holmäng S, Jönsson L, Sjöström L, Kvist H, Holm G, Lindstedt G, Björntorp P 1992 The effects of testosterone treatment on body composition and metabolism in middle-aged obese men. *Int J Obes Relat Metab Disord* 16:991–997
53. Merza Z, Blumsohn A, Mah PM, Meads DM, McKenna SP, Wylie K, Eastell R, Wu F, Ross RJ 2006 Double-blind placebo-controlled study of testosterone patch therapy on bone turnover in men with borderline hypogonadism. *Int J Androl* 29:381–391
54. Morley JE, Perry 3rd HM, Kaiser FE, Kraenzle D, Jensen J, Houston K, Mattamal M, Perry Jr HM 1993 Effects of testosterone replacement therapy in old hypogonadal males: a preliminary study. *J Am Geriatr Soc* 41:149–152
55. Reid IR, Wattie DJ, Evans MC, Stapleton JP 1996 Testosterone therapy in glucocorticoid-treated men. *Arch Intern Med* 156:1173–1177
56. Sih R, Morley JE, Kaiser FE, Perry 3rd HM, Patrick P, Ross C 1997 Testosterone replacement in older hypogonadal men: a 12-month randomized controlled trial. *J Clin Endocrinol Metab* 82:1661–1667
57. Simon D, Charles MA, Lahliou N, Nahoul K, Oppert JM, Gouault-Heilmann M, Lemort N, Thibult N, Joubert E, Balkau B, Eschwege E 2001 Androgen therapy improves insulin sensitivity and decreases leptin level in healthy adult men with low plasma total testosterone: a 3-month randomized placebo-controlled trial. *Diabetes Care* 24:2149–2151
58. Snyder PJ, Peache H, Hannoush P, Berlin JA, Loh L, Holmes JH, Dlewati A, Staley J, Santanna J, Kapoor SC, Attie MF, Haddad Jr JG, Strom BL 1999 Effect of testosterone treatment on bone mineral density in men over 65 years of age. *J Clin Endocrinol Metab* 84:1966–1972
59. Snyder PJ, Peache H, Hannoush P, Berlin JA, Loh L, Lenrow DA, Holmes JH, Dlewati A, Santanna J, Rosen CJ, Strom BL 1999 Effect of testosterone treatment on body composition and muscle strength in men over 65 years of age. *J Clin Endocrinol Metab* 84:2647–2653
60. Sullivan DH, Roberson PK, Johnson LE, Bishara O, Evans WJ, Smith ES, Price JA 2005 Effects of muscle strength training and testosterone in frail elderly males. *Med Sci Sports Exerc* 37:1664–1672
61. Svartberg J, Aasebø U, Hjalmarsen A, Sundsfjord J, Jorde R 2004 Testosterone treatment improves body composition and sexual function in men with COPD, in a 6-month randomized controlled trial. *Respir Med* 98:906–913
62. Tan RS, Pu SJ 2003 A pilot study on the effects of testosterone in hypogonadal aging male patients with Alzheimer's disease. *Aging Male* 6:13–17
63. Dobs AS, Cofrancesco J, Nolten WE, Danoff A, Anderson R, Hamilton CD, Feinberg J, Seekins D, Yangco B, Rhame F 1999 The use of a transscrotal testosterone delivery system in the treatment of patients with weight loss related to human immunodeficiency virus infection. *Am J Med* 107:126–132
64. Dohn K, Hvidt V, Nielsen J, Palm L 1968 Testosterone therapy in obliterating arterial lesions in the lower limbs. *Angiology* 19:342–350
65. Hall GM, Larbre JP, Spector TD, Perry LA, Da Silva JA 1996 A randomized trial of testosterone therapy in males with rheumatoid arthritis. *Br J Rheumatol* 35:568–573
66. Hentzer E, Madsen PC 1967 Testosterone in the treatment of arterial insufficiency of the lower limbs. *Scand J Clin Lab Invest Suppl* 99:198–206
67. Pugh PJ, Jones RD, West JN, Jones TH, Channer KS 2004 Testosterone treatment for men with chronic heart failure. *Heart* 90:446–447
68. Harman SM, Blackman MR 2003 The effects of growth hormone and sex steroid on lean body mass, fat mass, muscle strength, cardiovascular endurance and adverse events in healthy elderly women and men. *Horm Res* 60(Suppl 1):121–124
69. Müner T, Harman SM, Hees P, Shapiro E, Christmas C, Bellantonio MF, Stevens TE, O'Connor KG, Pabst KM, St Clair C, Sorkin JD, Blackman MR 2001 Effects of GH and/or sex steroid administration on abdominal subcutaneous and visceral fat in healthy aged women and men. *J Clin Endocrinol Metab* 86:3604–3610
70. Crawford BA, Liu PY, Kean MT, Bleasel JF, Handelman DJ 2003 Randomized placebo-controlled trial of androgen effects on muscle and bone in men requiring long-term systemic glucocorticoid treatment. *J Clin Endocrinol Metab* 88:3167–3176
71. Emmelot-Vonk MH, Verhaar HJ, Nakhai Pour HR, Aleman A, Lock TM, Bosch JL, Grobbee DE, van der Schouw YT 2008 Effect of testosterone supplementation on functional mobility, cognition, and other parameters in older men: a randomized controlled trial. *JAMA* 299:39–52
72. Gold J, Batterham MJ, Rekers H, Harms MK, Geurts TB, Helmyr PM, Silva de Mendonça J, Falleiros Carvalho LH, Panos G, Pinchera A, Aiuti F, Lee C, Horban A, Gatell J, Phanuphak P, Prasithsirikul W, Gazzard B, Bloch M, Danner SA 2006 Effects of nandrolone decanoate compared with placebo or testosterone on HIV-associated wasting. *HIV Med* 7:146–155