Testosterone and Cardiovascular Risk in Men: A Systematic Review and Meta-analysis of Randomized Placebo-Controlled Trials

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OBJECTIVE: **To conduct a systematic review and meta-analysis of randomized trials that assessed the effect of testosterone use on cardiovascular events and risk factors in men with different degrees of androgen deficiency.**

METHODS: **Librarian-designed search strategies were used to search the MEDLINE (1966 to October 2004), EMBASE (1988 to October 2004), and Cochrane CENTRAL (inception to October 2004) databases. The database search was performed again in March 2005. We also reviewed reference lists from included studies and content expert files. Eligible studies were randomized trials that compared any formulation of commercially available testosterone with placebo and that assessed cardiovascular risk factors (lipid fractions, blood pressure, blood glucose), cardiovascular events (cardiovascular death, nonfatal myocardial infarction, angina or claudication, revascularization, stroke), and cardiovascular surrogate end points (ie, laboratory tests indicative of cardiac or vascular disease). Using a standardized data extraction form, we collected data on participants, testosterone administration, and outcome measures. We assessed study quality with attention to allocation concealment, blinding, and loss to follow-up.**

RESULTS: **The 30 trials included 1642 men, 808 of whom were treated with testosterone. Overall, the trials had limited reporting of methodological features that prevent biased results (only 6 trials reported allocation concealment), enrolled few patients, and were of brief duration (only 4 trials followed up patients for >1 year). The median loss to follow-up across all 30 trials was 9%. Testosterone use in men with low testosterone levels led to inconsequential changes in blood pressure and glycemia and in all lipid fractions (total cholesterol: odds ratio [OR], –0.22; 95% confidence interval [CI], –0.71 to 0.27; high-density lipoprotein cholesterol: OR, –0.04; 95% CI, –0.39 to 0.30; low-density lipoprotein cholesterol: OR, 0.06; 95% CI, –0.30 to 0.42; and triglycerides: OR, –0.27; 95% CI, –0.61 to 0.08); results were similar in patients with low-normal to normal testosterone levels. The OR between testosterone use and any cardiovascular event pooled across trials that reported these events (n=6) was 1.82 (95% CI, 0.78 to 4.23). Several trials failed to report data on measured outcomes. For reasons we could not explain statistically, the results were inconsistent across trials.**

CONCLUSION: **Currently available evidence weakly supports the inference that testosterone use in men is not associated with important cardiovascular effects. Patients and clinicians need large randomized trials of men at risk for cardiovascular disease to better inform the safety of long-term testosterone use.**

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CI = confidence interval; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol

There has been increasing interest in the use of testosterone in men other than those with classic symptomatic hypogonadism, a trend fueled by the aging of the population and the development of novel drug delivery systems. Clinicians may be interested in using testosterone to treat men with some degree of androgen deficiency who present with suggestive symptoms, osteoporosis, sexual dysfunction, and poor quality of life. However, more widespread use raises concern about the undesirable cardiovascular consequences of testosterone administration.

A few systematic reviews have been published that assessed the effect of testosterone on cardiovascular risk, 2 of which present rigorous meta-analyses: 1 on the effect of intramuscular testosterone on lipids[1] and 1 on the effect of testosterone on intermittent claudication.[2] Thus, to this day, the extent and direction (ie, beneficial or harmful) of the cardiovascular consequences of testosterone administration remain unclear.

For editorial comment, see page 11

The Endocrine Society established a task force to generate evidence-based clinical practice guidelines about the use of testosterone in men with different degrees of androgen deficiency. To support this effort, we systematically reviewed the best available evidence about the effects of testosterone use on cardiovascular risk in men with different degrees of androgen deficiency.

METHODS

We developed a systematic review protocol (available by request) in collaboration with the members of the Endocrine Society Task Force on Testosterone in Men with Androgen Deficiency. This report adheres to the Quality of

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Reporting of Meta-analyses standards for reporting systematic reviews of randomized trials.[3]

Eligibility Criteria

Eligible studies were fully published randomized trials of men with different degrees of androgen deficiency (including studies of men with normal or low-normal testosterone levels) who were allocated to receive either testosterone therapy alone (any available preparation) or placebo. Eligible studies measured major cardiovascular events, surrogate cardiovascular end points, and cardiovascular risk factors. Major adverse cardiovascular events included cardiac death, myocardial infarction, and other vascular events such as stroke. Surrogate events included timing of exercise-induced electrocardiographic changes, subjective improvement in symptoms of claudication, ankle brachial index, walking distance, tests of muscle blood flow and plethysmography, hospitalization for chest pain, and need for revascularization. Cardiac risk factors included lipid fractions (total cholesterol, low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], and triglycerides), blood pressure control, and glycemic control.

Study Identification

To identify eligible studies, we conducted a systematic search of the literature using the electronic databases MEDLINE (1966 to October 2004), EMBASE (1988 to October 2004), and Cochrane CENTRAL (inception to October 2004); reference sections of identified narrative and systematic reviews identified through a MEDLINE search in October 2004 and of each of the eligible primary studies; and contact with task force expert members. An expert reference librarian (P.J.E.) designed and conducted the electronic search strategy with input from an endocrinologist with expertise in conducting systematic reviews (V.M.M.). The search was updated in March 2005.

Teams of 2 reviewers independently and with substantial reliability (chance-adjusted interobserver agreement κ=0.7) screened all abstracts and titles, as well as all resulting full-text publications for eligibility. In cases in which disagreement between 2 reviewers existed, another member of the research team not involved in the initial assessment and with both content and methodological expertise (V.M.M.) adjudicated the study as eligible or not, after reviewing the stated reasons for the initial assessment and the full text of the report.

Data Collection

Working in duplicate and using a standardized data extraction form, we extracted the following descriptive data from every study: year and journal of publication, patient population (degree of androgen deficiency, prior exposure to testosterone, age, testosterone level), treatment (dose and route of administration of testosterone) and control interventions, and the number of patients in exposed and unexposed groups.

We classified reports by the mean testosterone level at baseline: low testosterone level was defined as a total testosterone level of 300 ng/dL or less (10.4 nmol/L).[4] When this was not reported, we used values below the lower limit of normal for bioavailable or free testosterone levels. When laboratory values were not available, we classified studies by the the type of patients enrolled (ie, patients with previous bilateral orchiectomy). Chance-adjusted interobserver agreement for this classification was almost perfect (κ=0.91).

Quality Assessment

To ascertain the validity of eligible randomized trials, pairs of reviewers working independently and with adequate reliability (corresponding chance-adjusted interobserver agreement in parentheses where pertinent) determined the adequacy of randomization (κ=1.0) and concealment of allocation (κ=0.82); blinding of patients (κ=0.7), health care professionals (κ=0.7), data collectors (κ=0.77), and outcome assessors (κ=0.84); and the extent of loss to follow-up (ie, proportion of patients in whom the investigators were not able to ascertain outcomes).

Statistical Analyses

Meta-analyses. For the available lipid fraction and blood pressure outcomes in each study, we determined the mean and SD for the testosterone and placebo arms (for either end-of-study or change-from-baseline data at the longest point of most complete follow-up). We determined the effect size of the difference between the treatment and placebo groups by dividing the mean difference by the pooled SD between arms with adjustment for small samples (Hedges *g*) generating standardized mean differences as implemented in RevMan 4.2 (Cochrane Collaboration). We then conducted meta-analysis using the random-effects method and quantified the extent to which the inconsistency observed corresponded to between-study differences (and not to chance) using the I^2 statistic. To pool across dichotomous outcomes (ie, cardiovascular events), we calculated a pooled estimate using Mantel-Haenszel methods with a Robind-Brenslow-Greenland variance[5] using the Sweeting continuity correction.[6,7]

Subgroup Analyses. Our a priori hypotheses to explain potential heterogeneity across studies included study quality (particularly loss to follow-up), patient population (level of testosterone at baseline), and interventions (testosterone preparations: transdermal vs intramuscular vs oral; testosterone dose: physiologic vs supraphysiologic).

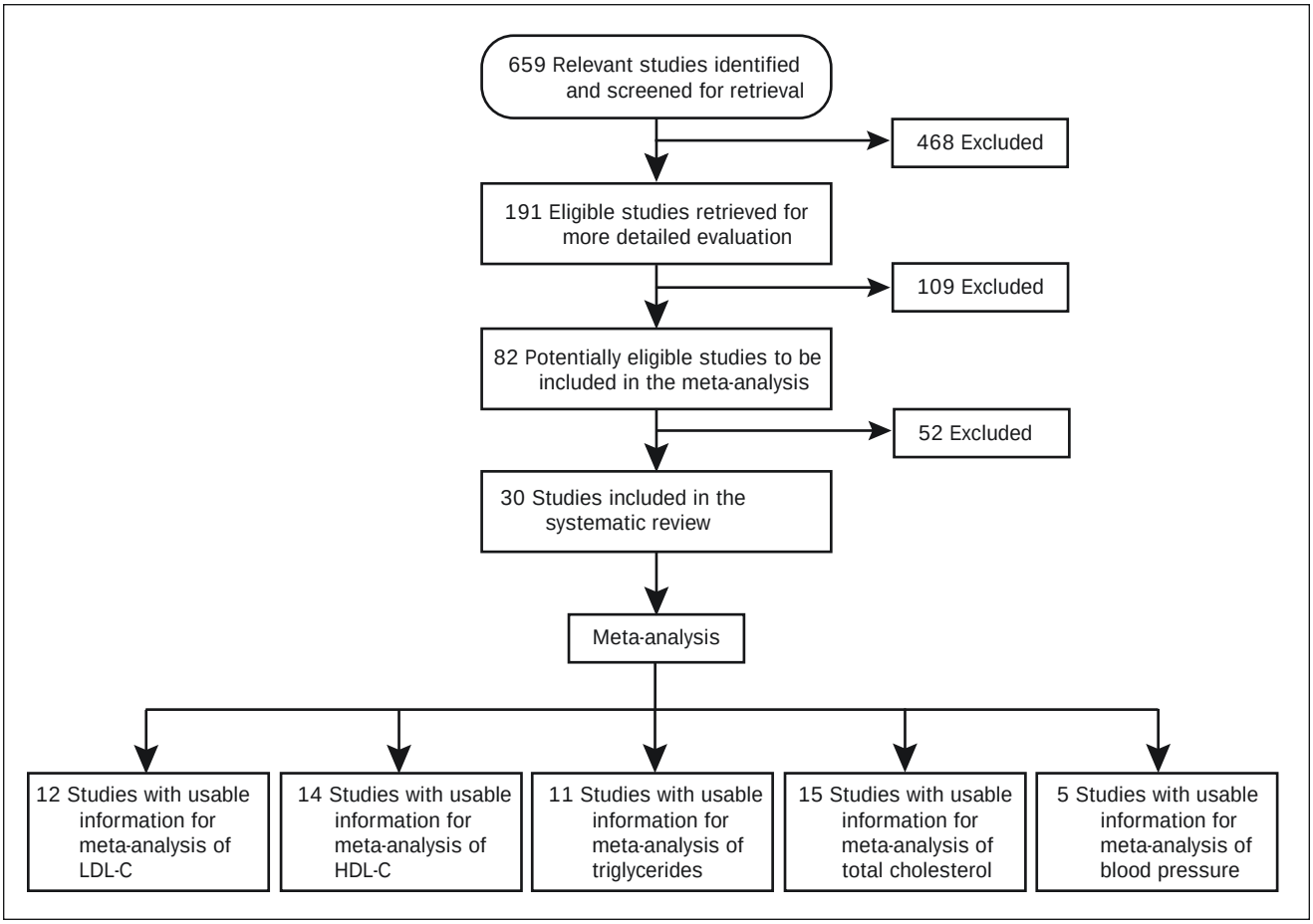

FIGURE 1. Results of the systematic search. HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

We explored these subgroups one at a time and tested the difference across subgroups using a test for subgroup-treatment interaction.[8]

RESULTS

Study Characteristics

Figure 1 shows the results of our systematic search. We found 30 eligible trials that enrolled 1642 men, 808 of whom were treated with testosterone.

Methodological Quality

Table 1 provides the methodological characteristics of the included trials. Overall, the included trials had limited reporting of methodological features that protect trials from the introduction of bias. All but 6 trials (20%)[9,12,17,19,24,26] inadequately reported allocation concealment; 2 had inadequate blinding.[25,37] The median loss to follow-up across all 30 trials was 9%; in 7 trials, loss to follow-up exceeded 20%.[21,24-26,28,31,36]

Clinical Characteristics

Table 2 provides the clinical characteristics of included trials and, when trials had multiple arms, of each of the trial arms included in the meta-analyses. Nine trials enrolled patients with low testosterone levels; the remaining trials enrolled men receiving long-term glucocorticoid therapy,[36,37] men with chronic obstructive pulmonary disease,[35,38] men with coronary artery disease,[14,25,30] and men with lower-extremity peripheral vascular disease.[13,17] The typical trial used usual replacement doses of testosterone for brief periods (ie, only 4 trials[12,21,22,26] followed up patients for >1 year).

Effect of Testosterone on Cardiovascular Risk Factors

Lipid Fractions in Men With Low Testosterone Levels. Figures 2 and 3 show nonsignificant effects of testosterone preparations on all lipid fractions in men with low testosterone levels. Reporting bias likely affects these estimates because there were 3, 4, 4, and 2 trials that measured total cholesterol, LDL-C, HDL-C, and triglyc-

TABLE 1. **Methodological Quality of Included Trials**

Reference	Design	Allocation concealment	Lost to follow-up (%)	Blinding
Low-normal or normal testosterone levels				
Amory et al,[9] 2002	Parallel	Adequate	12	Yes
Aversa et al,[10] 2003	Parallel	Not reported	0	Yes
Clague et al,[11] 1999	Parallel	Unclear	0	Yes
Copenhagen Study Group,[12] 1986	Parallel	Adequate	10	Yes
Dohn et al,[13] 1968	Crossover	Not reported	5	Yes
English et al,[14] 2000	Parallel	Not reported	13	Yes
Ferrando et al,[15] 2002	Parallel	Not reported	0	Yes
Harman & Blackman,[16] 2003	Parallel	Not reported	5	Yes
Hentzer & Madsen,[17] 1967	Parallel (alternate allocation)	Adequate	8	Yes
Howell et al,[18] 2001	Parallel	Not reported	Not reported	Yes*
Jaffe,[19] 1977	Parallel	Adequate	0	Yes
Liu et al,[20] 2003	Crossover	Not reported	6	Yes
Page et al,[21] 2005	Parallel	Not reported	29	Yes
Snyder et al,[22] 2001	Parallel	Not Reported	14	Yes†
Tenover,[23] 1992	Parallel	Not reported	0	Yes
Wittert et al,[24] 2003	Parallel	Adequate	24	Yes
Wu & Weng,[25] 1992	Crossover	Not reported	32	No
Low testosterone levels				
Amory et al,[26] 2004	Parallel	Adequate	27	Yes
Dobs et al,[27] 1998	Parallel	Not reported	8	Yes
Kenny et al,[28] 2002	Parallel	Not reported	34	Yes
Malkin et al,[29] 2004	Crossover	Not reported	14	Yes*
Malkin et al,[30] 2004	Crossover	Not reported	9	Yes*
Sih et al,[31] 1997	Parallel	Not reported	28	Yes
Simon et al,[32] 2001	Parallel	Not reported	0	Yes
Steidle et al,[33] 2003	Parallel	Not reported	13	Yes‡
Tan & Pu,[34] 2003	Parallel	Not reported	0	Yes
Chronic disease				
Casaburi et al,[35] 2004	Parallel	Not reported	11	Yes
Crawford et al,[36] 2003	Parallel	Not reported	21	Yes
Reid et al,[37] 1996	Crossover	Not reported	6	No
Svartberg et al,[38] 2004	Parallel	Not reported	9	Yes

*Only patients were blinded. Health care professionals were clearly not blinded.
†Patients and health care professionals were clearly blinded. Data collectors and outcome assessors were clearly not blinded.
‡Patients receiving the testosterone patch were not blinded.

eride levels, respectively, but reported results only as "not significant"[27,31] or not at all.[33,34] Given the precision of the pooled estimates, these data exclude unfavorable elevations in total cholesterol levels of more than 9 mg/dL (0.23 nmol/L), in LDL-C levels of more than 14 mg/dL (0.36 nmol/L), and in triglyceride levels of more than 7 mg/dL (0.08 nmol/L) and exclude unfavorable reductions in HDL-C levels of greater than 5 mg/dL (0.12 nmol/L).

Important between-study differences in the meta-analysis regarding total cholesterol were found (I^2=50%), but the results for other fractions were consistent across trials (Figure 3). Exploration of our a priori hypotheses to explain heterogeneity did not yield a subgroup of trials with significantly different results.

Lipid Fractions in Men With Low-Normal or Normal Testosterone Levels. Figures 2 and 3 show the effect of testosterone preparations on lipid fractions in men with low-normal or normal testosterone levels. Testosterone reduced total cholesterol levels by 16 mg/dL (0.41 nmol/L) (95% confidence interval [CI], 6-26 mg/dL [0.15-0.67 nmol/L]); all other lipid fractions were not significantly affected. Reporting bias likely affects these estimates: 3 trials[10,14,25] collected data on total cholesterol but did not report them. The same was true for the LDL-C and HDL-C meta-analyses (n=3 trials[11,14,25]) and for the triglycerides meta-analysis (n=2 trials[11,14]). Given the precision of the pooled estimates, these data exclude unfavorable elevations in LDL-C levels of more than 3 mg/dL (0.08 nmol/L) and in triglyceride levels of more than 41 mg/dL (1.06

TABLE 2. **Characteristics of the Included Randomized Placebo-Controlled Trials***

Reference	Participants	Total testosterone level at baseline, ng/dL (nmol/L)	Testosterone intervention	Duration	Outcome measured
		Low-normal or normal testosterone levels			
Amory et al,[9] 2002	25 men >55 y	375 (13)	Enanthate, 600 mg IM 21, 14, 7, and 1 d before surgery, vs identical placebo	3 wk	Lipids
Aversa et al,[10] 2003	20 men with arteriogenic erectile dysfunction; average age 55 y	373 (12.9)	Transdermal patch, 5 mg/d, vs nonidentical but inert control	4 wk	Lipids
Clague et al,[11] 1999	14 men >60 y; total testosterone for inclusion, <404 ng/dL (14 nmol/L)	330 (11.45)	Enanthate, 200 mg IM every 2 wk, vs nonidentical but inert control	1 y	Blood pressure, lipids
Copenhagen Study Group,[12] 1986	222 men with alcoholic cirrhosis; average age 53 y	Unclear baseline testosterone level	Oral micronized-free testosterone (100 mg), 2 tablets 3 times daily with meals, vs placebo	3 y	Deaths secondary to MI
Dohn et al,[13] 1968	44 men with claudication; approximate average age 60 y	Unclear baseline testosterone level	Isobutyrate, 300 mg IM every 2 wk (supraphysiologic), vs identical placebo	12 wk	Claudication, distance covered in metronome walking test, temperature change in feet, and volume of pulse in feet
English et al,[14] 2000	53 men with CAD; average age 62 y	374 (12.96)	Transdermal patches, 2.5 mg, 2 per day, vs identical placebo	12 wk	Lipids, time to 1-mm ST depression
Ferrando et al,[15] 2002	12 men >60 y; total testosterone for inclusion, >288 ng/dL or <490 ng/dL (>10 or <17 nmol/L)	Unclear baseline testosterone levels	Enanthate, IM weekly for first month, then biweekly for 6 mo, dose adjusted (100 to 400 mg IM) to maintain serum total testosterone between 17 and 28 nmol/L, vs nonidentical but inert control	7 mo	Blood pressure, lipids
Harman et al,[16] 2003	74 men >65 y	400.5 (13.9)	Enanthate, 100 mg IM biweekly, vs identical placebo	28 wk	Subjects with glucose <110 mg/dL, 110-126 mg/dL, and >126 mg/dL; blood pressure
Hentzer & Madsen,[17] 1967	36 men with arterial insufficiency of the lower limbs; age not reported	Unclear baseline testosterone level	Testosterone, 200 mg IM once a week for 3 wk then once every 2 wk for 6 mo, vs nonidentical but inert control	7 mo	Claudication and muscle blood flow
Howell et al,[18] 2001	35 men with Leydig cell dysfunction after cytotoxic chemotherapy; total testosterone for inclusion, <577 ng/dL (20 nmol/L); average age 40 y	384 (13.3)	Transdermal patch, 2.5 mg at night increased to 5 mg at 2-4 wk unless testosterone was >20 mg/dL (14/16 had increased dose), vs identical placebo	1 y	Lipids
Jaffe,[19] 1977	50 men with downsloping ST segment; average age 58 y	Unclear baseline testosterone level	Cypionate, 200 mg IM once a week (supraphysiologic), vs identical placebo	8 wk	Blood pressure and sum of ST-segment depression
Liu et al,[20] 2003	17 men >60 y; total testosterone for inclusion, <430 ng/dL (14.9 nmol/L)	577 (20)	Testosterone, 500 mg IM on day 1 then 250 mg IM once a week (supraphysiologic), vs identical placebo	2 wk	Fasting blood glucose
Page et al,[21] 2005	48 men >65 y; total testosterone for inclusion, <349 ng/dL (12.1 nmol/L)	294 (10.2)	Enanthate, 200 mg IM every 2 wk, vs identical placebo	3 y	Lipids
Snyder et al,[22] 2001	108 men >65 y; total testosterone for inclusion, <475 ng/dL	367 (12.7)	Transdermal scrotal patch, 6 mg/d, vs identical placebo	3 y	Lipids, occurrence of cardiac arrhythmia, MI, or other vascular events
Tenover,[23] 1992	13 men >56 y	335 (11.6)	Enanthate, 100 mg IM weekly, vs identical placebo	3 mo	Lipids
Wittert et al,[24] 2003	76 men >60 y; total testosterone for inclusion, >231 ng/dL (8 nmol/L); and FTI between 0.3 and 0.5	470 (16.3)	Oral undecenoate, 80 mg twice a day, vs identical placebo	1 y	Blood pressure, lipids

(*continued on page 34*)

TABLE 2. **Continued***

Reference	Participants	Total testosterone level at baseline, ng/dL (nmol/L)	Testosterone intervention	Duration	Outcome measured
		Low-normal or normal testosterone levels (continued)			
Wu & Weng,[25] 1992	62 men >60 y with CAD	548 (19)	Oral undecenoate, 120 mg/d for 2 wk then 40 mg/d for 2 wk, vs nonidentical but inert control	4 wk	Lipids
		Low testosterone levels			
Amory et al,[26] 2004	48 men >65 y with low testosterone levels; total testosterone for inclusion, <349 ng/dL (12.1 nmol/L) on 2 occasions	294 (10.2)	Transbuccal enanthate, 10 mg/d increased to 10 mg twice daily at 6 wk if response inadequate as judged by patient and physician, vs nonidentical but inert control	†	Cardiovascular events
Dobs et al,[27] 1998	13 men with primary or secondary hypogonadism; total testosterone for inclusion, <250 ng/dL (8.7 nmol/L); average age 45 y	273.5 (9.5)	Transbuccal enanthate, 10 mg/d increased to 10 mg twice daily at 6 wk if response inadequate as judged by patient and physician, vs nonidentical but inert control	†	Lipids
Kenny et al,[28] 2002	67 men >65 y; bioavailable testosterone for inclusion, <127 ng/dL (4.4 nmol/L)	389 (13.5)	Transdermal patches (Androderm), 2.5 mg, 2 per day, vs nonidentical but inert control	1 y	Endothelial function and flow-mediated dilatation, lipids
Malkin et al,[29] 2004	29 men; average age 61 y	127 (4.4)	Testosterone, 100 mg IM at 0, 14, and 28 d, vs identical placebo	4 wk	Lipids
Malkin et al,[30] 2004	11 men with CAD; average age 60 y	121 (4.2)	Sustanon 100 (100 mg/mL of testosterone), 100 mg IM every 2 wk, vs identical placebo	4 wk	Lipids, time to 1-mm ST depression
Sih et al,[31] 1997	32 men >50 y; bioavailable testosterone for inclusion, <60 ng/dL (2.1 nmol/L)	Unclear baseline testosterone level	Cypionate, 200 mg IM every 14-17 d, vs identical placebo	1 y	Lipids, systolic blood pressure
Simon et al,[32] 2001	12 otherwise healthy men; average age 54 y; total testosterone for inclusion, <340-400 ng/dL (11.8-13.8 nmol/L)	260 (9.0)	Transdermal gel, 125 mg/d with dose adjustment after 2 wk, vs placebo	3 mo	Blood glucose, blood pressure, lipids
Steidle et al,[33] 2003	406 men; total testosterone for inclusion, <300 ng/dL (10.4 nmol/L); average age 58 y	233 (8.1)	Transdermal patches (Androderm), 2.5 mg, 2 per day, or gel (AA2500), 50 mg/d or 100 mg/d, vs identical placebo	90 d	Lipids
Tan & Pu,[34] 2003	10 men with Alzheimer disease; total testosterone for inclusion, <250 ng/dL (8.7 nmol/L); average age 72 y	126.4 (4.4)	Enanthate, 200 mg IM every 2 wk, vs nonidentical but inert control	9 mo	Lipids
		Chronic disease			
Casaburi et al,[35] 2004	26 men >55 y with COPD; total testosterone for inclusion, <400 ng/dL (13.9 nmol/L)	302 (10.5)	Enanthate, 100 mg IM once a week, vs identical placebo	10 wk	Lipids
Crawford et al,[36] 2003	34 men with long-term glucocorticoid use; average age 60 y	14-15 (4.0-4.3)	Testosterone mixed esters, 200 mg IM every 2 wk, vs placebo	1 y	Lipids, MIs
Reid et al,[37] 1996	16 men with long-term glucocorticoid use; average age 61 y	Unclear baseline testosterone level	Testosterone esters, 250 mg IM depot injection monthly, vs nonidentical but inert control	1 y	Lipids
Svartberg et al,[38] 2004	29 men with moderate to severe COPD; average age 65 y	606 (21)	Enanthate (depot injection), 250 mg IM every 4 wk, vs nonidentical but inert control	26 wk	Lipids

*CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; FTI = Free Testosterone Index; IM = intramuscularly; MI = myocardial infarction.
†8 weeks of therapy following 6 weeks of a washout period.

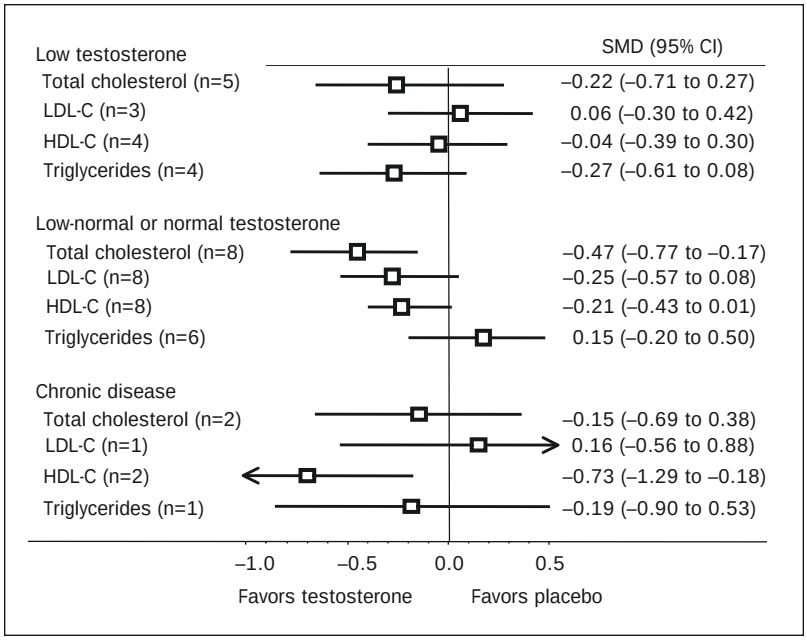

FIGURE 2. Standardized mean differences (SMDs) in the effects of testosterone preparations on all lipid fractions in men with low testosterone levels, low-normal or normal testosterone levels, and chronic disease. CI = confidence interval; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

nmol/L) and exclude unfavorable reductions in HDL-C levels of less than 7 mg/dL (0.18 nmol/L).

Important between-study differences in the meta-analyses of all lipid fractions were found, except for HDL-C (Figure 3). Exploration of our a priori hypotheses to explain heterogeneity did not yield a subgroup of trials with significantly different results.

Lipid Fractions in Men With Chronic Disease. Figures 2 and 3 show the effect of testosterone preparations on lipid fractions in men with chronic disease, such as those who use long-term glucocorticoids or who have chronic obstructive pulmonary disease. Only 2 trials reported results,[35,37] whereas 2 other trials[36,38] reported that testosterone did not significantly affect lipid fractions. One trial[35] collected data on LDL-C and triglyceride levels but did not report these. Testosterone reduced HDL-C levels by 11 mg/dL (0.28 nmol/L) (95% CI, 3-19 mg/dL [0.08-0.49 nmol/L]); all other lipid fractions were not significantly affected. The effect of testosterone on total cholesterol and HDL-C was consistent across the 2 trials that reported these outcomes (Figure 3). Given the precision of the pooled estimates, these data exclude unfavorable elevations in total cholesterol levels of more than 13 mg/dL (0.34 nmol/L), in LDL-C levels of more than 30 mg/dL (0.78 nmol/L), and in triglyceride levels of more than 48 mg/dL (1.24 nmol/L). The limited number of studies precluded us from conducting exploratory subgroup analyses.

Effect of Testosterone Supplementation on Blood Pressure

Testosterone preparations had nonsignificant effects on systolic (0.8 mm Hg; 95% CI, –4 to 5 mm Hg) and diastolic (2 mm Hg; 95% CI, –2 to 6 mm Hg) blood pressure that were consistent across trials. Reporting bias likely affects this estimate because 2 trials[11,16] measured blood pressure data but did not report these. Overall, the precision of the estimates excludes unfavorable elevations in systolic blood pressure of more than 5 mm Hg or in diastolic blood pressure of more than 6 mm Hg.

Effect of Testosterone Supplementation on Blood Glucose

One trial that enrolled 12 men with low testosterone levels[32] reported a difference of 1 mg/dL between testosterone and placebo (95% CI, –10 to 12 mg/dL). Three trials that enrolled a total of 108 men with normal testosterone levels[14,16,20] measured the effect of testosterone on glycemia; 2 of these trials[14,16] did not report glucose levels despite collecting these data, and 1 trial[20] reported this outcome only as "not significant." Thus, we could not conduct a meta-analysis.

Effect of Testosterone on Cardiovascular Events

Unfortunately, most studies that reported cardiac events had neither strict outcome definitions nor independent and blinded judicial assessors of these outcomes. Thus, the outcomes reported may not represent a complete or unbi-

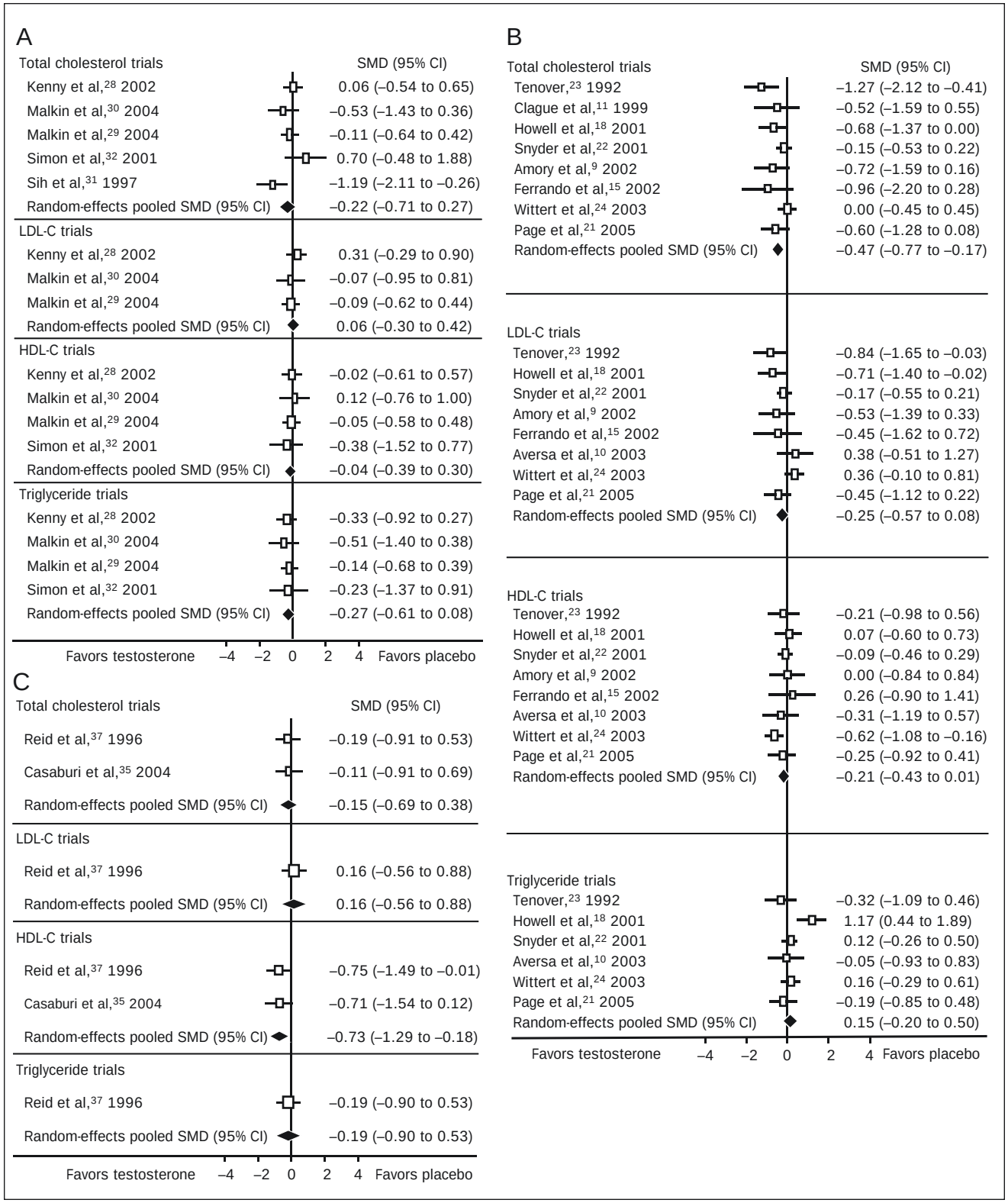

FIGURE 3. Standardized mean differences (SMDs) in the effects of testosterone preparations on all lipid fractions in men with low testosterone levels (A), low-normal or normal testosterone levels (B), and chronic disease (C) by individual studies included in the meta-analysis. CI = confidence interval; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

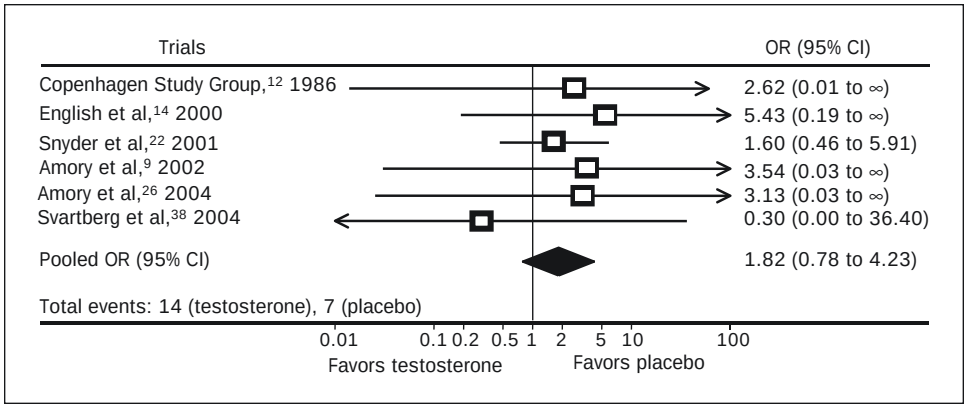

FIGURE 4. Six randomized controlled trials reported on cardiovascular events with consistent results. CI = confidence interval; OR = odds ratio; ∞ = infinity.

ased selection of the outcomes that took place. Furthermore, the length of follow-up in most of the included trials precluded the accumulation of enough events.

Cardiovascular Events. We sought to summarize the effect of testosterone on cardiovascular death, fatal and nonfatal myocardial infarction, and other cardiovascular events (eg, angina, arrhythmia, revascularization procedures, stroke). Six randomized controlled trials[9,12,14,22,26,38] reported on cardiovascular events with consistent results (Figure 4). There were 14 events (including 5 myocardial infarctions and 1 cardiovascular death) in 161 men who received testosterone and 7 events (including 2 myocardial infarctions and 1 death) in 147 men in the control groups (any cardiovascular event: odds ratio, 1.82; 95% CI, 0.78-4.23; fatal and nonfatal myocardial infarction: odds ratio, 2.24; 95% CI, 0.50-10.02).

One trial[36] described 4 patients with myocardial infarctions and 2 patients with a cardiomyopathy without describing which events occurred in the testosterone and placebo groups. Another trial[14] only reported that angina frequency did not change in either group. Finally, one trial[30] reported a nonsignificant improvement in the Seattle angina questionnaire score with testosterone.

Vascular Events. Only one trial[36] reported vascular events (2 patients receiving either testosterone or placebo had ruptured abdominal aortic aneurysm), whereas 2 other trials[13,17] reported no significant improvement on symptoms of claudication with testosterone vs placebo.

Surrogate End Points. Several trials reported on physiological or laboratory end points of unclear patient importance or validity as surrogates for the effect of testosterone on important cardiovascular end points.

Exercise Electrocardiographic Changes

Two trials in men with coronary artery disease (1 in men with normal or low-normal testosterone levels[14] and 1 in men with low testosterone levels[30]) reported significantly longer time (25 and 74 seconds longer, respectively) to 1-mm ST-segment depression with exercise in the testosterone group vs placebo. Another trial in eugonadal men with coronary artery disease[19] reported significant reductions in the extent of ST depression in anterolateral electrocardiographic leads after exercise in men receiving testosterone vs placebo.

Vascular Function

One trial[13] found nonsignificant effects of testosterone vs placebo on the metronome walking test, volume of the foot pulse, and change in foot temperature. Two trials[28,39] reported nonsignificant effects of testosterone vs placebo on endothelial function. Finally, one trial[17] reported a nonsignificant effect of testosterone on muscle blood flow.

DISCUSSION

Principal Findings

The best available evidence suggests small and clinically negligible effects of testosterone use on lipid fractions, blood pressure, and glycemic control in men with different degrees of androgen deficiency. On the basis of the width of the 95% CI, the pooled data are consistent with both a 1-fold decrease and a 4-fold increase in the odds of cardiac events in patients using testosterone.

Limitations and Strengths

A key limitation of this review refers to the extent to which authors did not explicitly report on all outcomes measured. To the extent that there is a consistent relationship between outcomes and whether authors report them, bias could affect our pooled estimates. The direction and magnitude of this potential bias are unclear for safety outcomes, such as those summarized herein. The degree of unexplained

heterogeneity represents another key limitation of our review. Taken together, the paucity of data, unexplained heterogeneity, and reporting bias weaken the inferences drawn from the best available evidence. Despite our efforts and the active participation of clinical experts, we may have missed eligible trials. However, our systematic review has the strengths appropriate for this study design: a protocol-driven process; clear, explicit, and reproducible eligibility criteria; reproducible judgments about study quality; and systematic data collection and targeted analyses.

Our Review in Relationship to Other Systematic Reviews

Our review differs from the meta-analysis by Whitsel et al[1] in scope (searched up to 1999, only interested in the effect of intramuscular testosterone on lipids of hypogonadal men), methods (included observational studies, did not assess the methodological quality of eligible studies), and consequentially results (found a dose-dependent decrease in HDL-C and total cholesterol levels). In contrast, our review searched to 2005, had a broader scope (all forms of administration of testosterone in men with varying degrees of androgen deficiency), had methods that paid attention to bias (eligible studies were placebo-controlled randomized trials only, and we assessed their quality), and reported inconsequential effects of testosterone on lipid fractions. In particular, among hypogonadal men who received intramuscular testosterone, we found nonsignificant effects on total cholesterol and HDL-C levels.

Our results are consistent with the conclusions from a systematic review of placebo-controlled randomized trials in older men by Gruenewald and Matsumoto[40] that summarized data up to 2001 without conducting meta-analyses. Another narrative review from Wu and von Eckardstein[41] summarized data up to 2002 without conducting meta-analyses. This review included randomized and observational studies; reviewed the putative effects of testosterone on surrogate end points and cardiovascular risk factors, including lipid fractions; and suggested that supraphysiological testosterone use could decrease HDL-C levels. In contrast to these 2 reviews,[40,41] our meta-analyses add 4 and 2 more years of evidence, respectively; have a broader scope (include adult men with varying degrees of androgen deficiency); and report pooled estimates for all outcomes, including cardiovascular events. As in the first[40] and in contrast with the second meta-analysis,[41] we limited our summary to placebo-controlled trials. Our review methods and results are consistent with those of a recently updated Cochrane review[2] of the effect of testosterone on intermittent claudication.

Our review results are consistent with the meta-analysis by Isidori et al[42] despite some differences in study inclusion and search time frame (our study being limited to placebo-controlled trials and searching for 1 additional year). Also, our review includes a meta-analysis of cardiovascular events. A review by Calof et al[43] limited its investigation to older men with low testosterone levels at baseline who received replacement doses of testosterone. This focus led to fewer included trials and no meta-analysis of lipid fractions but similar results about cardiovascular events.

Finally, a systematic review performed by Krause[44] summarized studies of testosterone use in older men but did not report quantitative estimates of treatment effect on each of the lipid fractions or on specific cardiovascular outcomes.

Review Implications

As patients and clinicians consider the use of testosterone in the management of symptoms consistent with hypogonadism, they should be concerned about potential adverse consequences of its long-term use. Key among these are the potential effects on cardiovascular risk. Unfortunately, the best available evidence on this matter is inconsistent, imprecise, and poorly reported. As a result, clinicians and policymakers cannot be sure what consequences testosterone may have on cardiovascular risk.

CONCLUSION

Currently available evidence weakly supports the inference that testosterone use in men is not associated with important cardiovascular effects. Large randomized trials that enroll men with and without cardiovascular disease and measure cardiovascular end points are needed to better inform the decision to use long-term testosterone for other indications.

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