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Adverse Events Associated With Testosterone Replacement in Middle-Aged and Older Men: A Meta-Analysis of Randomized, Placebo-Controlled Trials

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Background. We performed a meta-analysis of randomized clinical trials to determine the risks of adverse events associated with testosterone replacement in older men.

Methods. The MEDLINE database was searched from 1966 to April 2004, using testosterone as the indexing term; limits included human, male, ≥45 years old, and randomized controlled trial. Of the 417 studies thus identified, 19 met the inclusion criteria: testosterone replacement for at least 90 days, men ≥45 years old with low or low-normal testosterone level, randomized controlled trial, and medically stable men. Odds ratios (ORs) were pooled using a random effects model, assuming heterogeneous results across studies, and were weighted for sample size.

Results. In the 19 studies that met eligibility criteria, 651 men were treated with testosterone and 433 with placebo. The combined rate of all prostate events was significantly greater in testosterone-treated men than in placebo-treated men (OR = 1.78, 95% confidence interval [CI], 1.07–2.95). Rates of prostate cancer, prostate-specific antigen (PSA) >4 ng/ml, and prostate biopsies were numerically higher in the testosterone group than in the placebo group, although differences between the groups were not individually statistically significant. Testosterone-treated men were nearly four times as likely to have hematocrit >50% as placebo-treated men (OR = 3.69, 95% CI, 1.82–7.51). The frequency of cardiovascular events, sleep apnea or death was not significantly different between the two groups.

Conclusions. Testosterone replacement in older men was associated with a significantly higher risk of detection of prostate events and of hematocrit >50% than was placebo; hematocrit increase was the most frequent adverse event associated with testosterone replacement. These data reaffirm the need to monitor hematocrit, PSA, and digital examination of the prostate during testosterone replacement in older men.

SERUM total and free testosterone levels decline with advancing age and are lower in older men than in young men (1,2). However, the benefits and risks of testosterone replacement in older men remain unknown (1,2). Previous studies of testosterone replacement in older men were suboptimally powered to detect significant increases in adverse events compared with placebo, particularly the risk of cardiovascular and prostate events. Reflecting these uncertainties about the risks and benefits of testosterone replacement in older men, the Institute of Medicine (IOM) Expert Panel recommended a series of coordinated clinical trials adequately powered to evaluate the efficacy of testosterone replacement in older men with low testosterone levels and clinical disorders associated with androgen deficiency (1). The IOM Expert Panel also suggested that safety trials of testosterone replacement should be deferred until the efficacy of testosterone replacement has been demonstrated. Thus, definitive information on the risks of testosterone replacement in older men will not be available for many years (1).

Therefore, we felt that a meta-analysis of adverse events associated with testosterone replacement in older men would be useful to the practicing clinician. The results of this meta-analysis could also help to guide the design of testosterone trials by providing estimates of effect size and variance. Although previous studies of testosterone replacement in older men were too small individually to have adequate power to detect adverse events, a meta-analysis might allow detection of adverse events associated with testosterone replacement in older men.

METHODS

Search Strategy and Data Extraction

We conducted a meta-analysis of English and non-English articles using MEDLINE and Old Medline via Ovid and PubMed searches from 1966 to April 2004 (Figure 1). The Subject Heading term was testosterone; the search was narrowed using limits: human, male, middle-aged and older men ≥45 years, and randomized controlled trial. Data extraction was performed by the investigators (O.C., M.L., S.B.). One additional study (3), not picked up by this search, was added during expert scrutiny of publications. We sent letters to authors to refine the information gathered from publications.

Eligible Studies

We included 19 clinical trials in 24 publications (3–26) that met the inclusion criteria: middle-aged and older men ≥45 years of age, double-blind randomized controlled trial,

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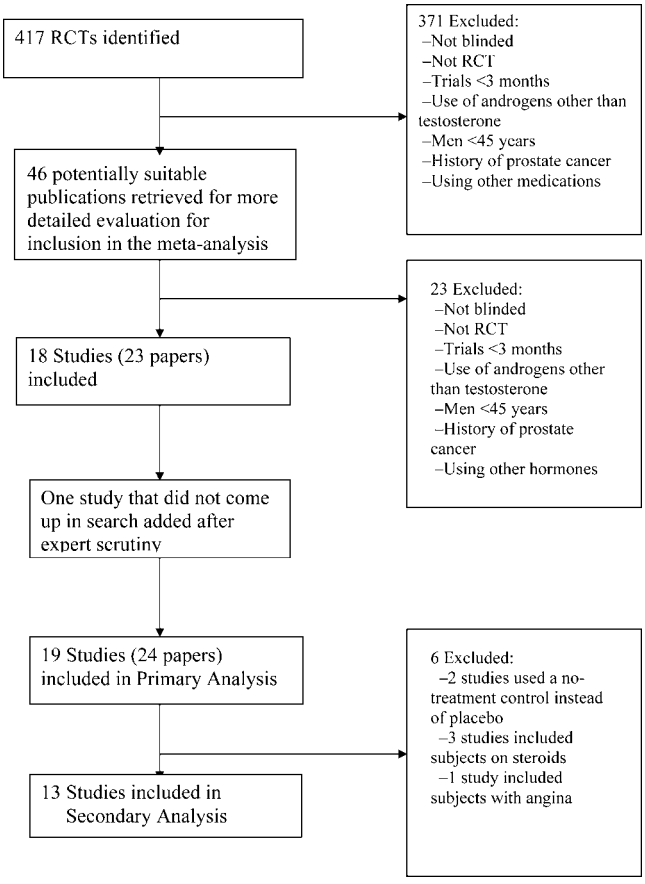

Figure 1. QUORUM statement flow diagram. RCT = randomized controlled trial.

study duration ≥90 days, men with low or low-normal testosterone levels, use of testosterone or its esters in replacement doses, and inclusion of older men without an acute illness. One study that recruited both young and older men was included as a majority of participants in that study were ≥45 years of age (20), it met all other inclusion criteria, and it enrolled more older men than any other study.

Ineligible Studies

We excluded uncontrolled trials, observational studies, studies that used androgens other than testosterone, and studies that used supraphysiologic doses of testosterone. Studies that included medications other than testosterone, such as growth hormone, were excluded unless there was a clearly identified testosterone-only arm (13–15). We excluded studies that recruited participants with unstable disease conditions. Studies in HIV-infected men were excluded.

Sensitivity Analysis

Of the19 studies selected for primary analysis, six were excluded in secondary analysis (Table 1). Two studies were excluded (3,23) because they included a no-treatment control instead of placebo, three studies were excluded (17,20,21) because they included participants receiving glucocorticoids, and one study was excluded (19) because it included participants with chronic angina pectoris.

Definitions

Our primary outcome measure was all-cause prostate event rate in participants who received testosterone or placebo. Prostate events included prostate biopsies, prostate cancers, increase in International Prostate Symptom Score (IPSS) >4, prostate-specific antigen (PSA) >4 ng/ml or PSA increment ≥1.5 ng/ml during treatment, and acute urinary retention. Cardiovascular event rates were evaluated separately as atrial fibrillation, myocardial infarction, chest pain, coronary procedure including coronary artery bypass grafting, sudden death, and vascular events including cerebrovascular accidents.

Quality Assessment

We assessed the type of randomization, type of control group (placebo-treated or not), concealment, and type of blinding used.

Statistical Methods

Each study was evaluated for seven adverse event categories: prostate or urological or both, hematological, lipids, cardiac, respiratory or sleep apnea or both, other adverse events, and death. Among prostate adverse events, we evaluated prostate cancers, acute urinary retention, and increase in IPSS scores >4. As an increase in PSA level can trigger a prostate biopsy, which can lead to the diagnosis of prostate cancers, we counted the number of participants with PSA >4 ng/ml or PSA increment >1.5 ng/ml during treatment.

Odds ratios (ORs) were pooled using a random effects model, assuming heterogeneous results across studies, after weighting for sample size. When there was a zero entry for an event, a value of 0.5 was assigned in order to perform calculations. The Clopper–Pearson method was used to compute 95% confidence intervals (CI). Forest plots were used to illustrate confidence intervals for ORs (Figure 2). Finally, sample size was determined for detecting various increases of prostate cancer events in the testosterone-treated men compared with the rate in placebo-treated men using two-group comparison of proportions with 80% power and two-tailed 5% significance level.

Results

Primary Analysis

In the 19 studies that met inclusion criteria, 651 men were assigned to testosterone treatment and 433 to placebo treatment. The two groups did not differ significantly in their baseline characteristics (Table 2). Overall, 14% of participants dropped out in each of the two treatment groups. Study duration ranged from 90 days to 3 years (median, 6 months; mean, 10.0 ± 9.8 months; Table 1).

Testosterone formulations varied among studies. Serum testosterone levels did not change significantly in placebo-treated men (treatment level, 339 ± 105 ng/dl [11.8 ± 3.6 nmol/l]) but did increase to a mean of 536 ± 173 ng/dl (18.6 ± 6.0 nmol/l) in testosterone-treated men.

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Table 1. Characteristics of Studies Included in Primary Analysis

	Author, Year of Publication	Age, Mean ± *SD* (y)	No. of Participants in Testosterone/Placebo Group	Treatment Duration	Form of Testosterone Used
1	Marin et al., 1992	51.9 ± 9.6	11/12	8 mo	Testosterone undecanoate 80 mg orally twice daily
2	Drinka et al., 1995	N/A	8/10	6 mo	Testosterone enanthate 150 mg/70 kg every 2 wk
3	Wittert et al., 2003	69.0 ± 6.0	39/37	12 mo	Testosterone undecanoate 80 mg orally twice daily
4	Sih et al., 1997	65.0 ± 7.0	17/15	12 mo	Testosterone cypionate 200 mg intramuscularly every 14–17 d
5	Christmas et al., 2002; Blackman et al., 2002; Munzer et al., 2001	70.8 ± 4.3	21/17	26 wk	Testosterone enanthate 100 mg intramuscularly every 2 wk
6	Kenny et al., 2002	76.0 ± 4.0	34/33	12 mo	Transdermal patch 5 mg/d
7	Ferrando et al., 2002; Ferrando et al., 2003	68 ± 10.4	7/5	6 mo	Testosterone enanthate intramuscularly
8	Snyder et al., 1999; Snyder et al., 1999; Snyder et al., 2001	73.1 ± 5.8	54/54	36 mo	Testoderm 60 cm^2 scrotal patch daily
9*	Crawford et al., 2003	60.3 ± 13.5	18/16	12 mo	Testosterone 200 mg (mixed esters) intramuscularly every 2 wk
10	Amory et al., 2004	71.0 ± 4.0	24/24	36 mo	Testosterone enanthate 200 mg intramuscularly every 2 wk
11	Simon et al., 2001	52.8 ± 14.5	6/6	3 mo	Testosterone gel, starting with 125 mg/d, then adjusted to achieve testosterone levels of 4–10 ng/ml
12	Tenover, 1992	66.7 ± 5.6	13/13	3 mo	Testosterone enanthate 100 mg intramuscularly weekly
13*	English et al., 2000	62.0 ± 13.6	22/24	12 wk	Two 2.5 mg testosterone patches nightly
14	Steidle et al., 2003	58.5 ± 10.0	307/99	90 d	AA2500 gel; and two 2.5 mg testosterone patches daily
15*	Boyanov et al., 2003	57.0 ± 4.8	24/24	3 mo	Testosterone undecanoate 120 mg/d
16*	Reid et al., 1996	61.0 ± 11.0	15/15	12 mo	250 mg of mixed testosterone esters
17	Kenny et al., 2004	81.0 ± 5.0	6/5	12 wk	Testosterone enanthate 200 mg intramuscularly every 3 wk
18*	Hall et al., 1996	60.8 ± 9.7	17/18	9 mo	Testosterone enanthate 250 mg intramuscularly monthly from months 1–5,then every 2 wk
19*	Morley et al., 1993	77.6 ± 8.7	8/6	3 mo	Testosterone enanthate 200 mg intramuscularly every 2 wk

Note: *Studies omitted from secondary analysis.

Prostate events.—The total number of prostate events combined was significantly greater in testosterone-treated men than in placebo-treated men (Table 3; Figure 2). Testosterone-treated men were 1.8 times more likely to have a prostate event than were placebo-treated men (OR = 1.78, 95% CI, 1.07–2.95). The rates of prostate cancer, PSA levels >4 ng/ml or PSA increment ≥1.5 ng/ml, prostate biopsies and increases in IPSS scores >4 were numerically higher in testosterone-treated men than in placebo-treated men; however, none of these adverse events was individually significantly different between the two groups (Table 2). The weighted average change in serum PSA level from baseline was 0.3 ng/ml in testosterone-treated men.

Cardiovascular events.—The rate of all cardiovascular events was not significantly different between the two groups (Table 3; Figure 2B). The 18 cardiovascular events in the 651 testosterone-treated men included atrial fibrillation or arrhythmia in five men; myocardial infarction in four; chest pain or ischemia in four; coronary procedure, including coronary artery bypass graft, in two; and vascular events, including cerebrovascular accidents, in three. The 16 cardiovascular events in the 433 placebo-treated men included atrial fibrillation or arrhythmia in one man; myocardial infarction in three; chest pain or ischemia in three; coronary procedures, including coronary artery bypass graft, in five; and vascular events, including cerebrovascular accidents, in four.

Hematocrit.—Increase in hematocrit over 50% was the most frequent testosterone-related adverse event in these trials. The number of participants with hematocrit >50% was significantly higher in testosterone-treated men (35) than in placebo-treated men (one) (Table 3; Figure 2C). Of the 35 testosterone-treated men with hematocrit >50%, there was one complication—cerebral hemorrhage; the one placebo-treated man with hematocrit >50% had no complications. Testosterone-treated men were 3.67 times more likely to develop hematocrit >50% than were placebo-treated men (OR = 3.67; 95% CI, 1.82–7.51).

Lipids.—Individual plasma lipid values were not available for evaluation in most studies. Of the 11 studies in which some information was available, four reported a significant decrease and seven reported no significant change in high-density lipoprotein cholesterol levels, four reported a decrease in total cholesterol levels, and two reported a decrease

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Table 2. Characteristics of Participants

Characteristics	Testosterone Group	Placebo Group
Number of participants	643	427
Age, years	62.9 ± 9.0	64.4 ± 8.2
Baseline testosterone, ng/dl	320 ± 78	344 ± 91
Testosterone levels during treatment, ng/dl	536 ± 173	339 ± 105
Baseline PSA levels, ng/ml	1.3 ± 1.0	1.3 ± 1.0

Note: PSA = prostate-specific antigen.

in low-density lipoprotein cholesterol level in testosterone-treated men.

Other significant adverse events.—The studies that used a testosterone patch reported a high frequency of skin irritation at application site (range, 17%–40%). A possible allergic reaction to testosterone ester was reported in one participant (21). Other adverse events included leg edema; hematochezia; foot, hand, and testicular swelling; new heart murmur; transient erectile dysfunction; vertigo; depression; urinary tract infection; pneumonia; hypertension; mood swings; gynecomastia; headaches; hot flushes; insomnia; lacrimation; smell and taste disorder; and spontaneous penile reactions. Snyder and colleagues (9) reported two participants with unspecified events. The frequency of men with new diagnosis of sleep apnea during treatment was not significantly different between the two groups (OR = 0.91, 95% CI, 0.37–2.21).

Deaths.—No deaths were reported in testosterone-treated men, whereas there were two deaths in placebo-treated men. The causes were not specified (10).

Sensitivity Analysis

After excluding six studies (3,17,19,21–23) for reasons discussed in Table 4, the OR for total prostate events remained significantly elevated at 1.90 (95% CI, 1.11–3.24) and the OR for hematocrit >50% was even higher at 5.07 (95% CI, 2.30–11.14). Other adverse event rates did not change significantly in secondary analysis (Table 4). Even after excluding increase in IPSS score >4, total prostate event rates were still higher in testosterone-treated men than in placebo-treated men (OR = 1.7, 95% CI, 1.02–2.85).

Sources of Variation

The studies differed in terms of testosterone formulations (testosterone patch, injectable testosterone esters, testosterone gel, and oral testosterone undecanoate), age range, initial testosterone level, testosterone dose, and treatment duration (3 months to 3 years). Studies that used testosterone esters administered a higher dose and achieved higher serum testosterone levels than those that used transdermal testosterone formulations. Although most studies selected asymptomatic men solely on the basis of testosterone level, two studies included symptomatic men (5,20). The criteria used for prostate biopsy varied, and many studies did not specify these criteria. In addition, adverse events were not specified in many studies.

Table 3. Pooled Odds Ratios for Adverse Events in Primary Analysis

Event	Testosterone Group: Adverse Event Rate per 1000 Patient-Years*	Placebo Group: Adverse Event Rate per 1000 Patient-Years*	Pooled Odds Ratio	95% Confidence Interval
Prostate biopsies	38.7	2.8	1.87	0.84, 4.15
Prostate cancers	9.2	8.3	1.09	0.48, 2.49
PSA >4 ng/ml or 1.5 ng/ml increase during study	57.1	41.6	1.19	0.67, 2,09
Increase in IPSS score	5.5	2.8	1.08	0.46, 2.52
Acute urinary retention	2.2	0	0.99	0.40, 2.44
All prostate events	112.4	55.7	1.78†	1.07, 2.95
Hematocrit >50%	64.5	2.8	3.69†	1.82, 7.51
Atrial fibrillation/arrhythmia	9.2	2.8	1.22	0.53, 2.81
Myocardial infarction	7.4	8.3	0.99	0.44, 2.26
Chest pain/ischemia	7.4	8.3	0.93	0.39, 2.26
Coronary procedure/CABG	3.7	13.9	0.79	0.35, 1.79
Vascular events/cerebrovascular accidents	5.5	11.1	0.86	0.38, 1.95
All cardiovascular events	33.2	44.3	1.14	0.59, 2.20
Death	0	5.5	0.78	0.32, 1.93

Notes: *The rate per 1000 patient-years was calculated based on average study duration of 10 months, standardized to 1 year and multiplied by 1000.

†Odds ratios significantly different from placebo.

PSA = prostate-specific antigen; IPSS = International Prostate Symptom Score; CABG = coronary artery bypass graft.

Discussion

This meta-analysis, which pooled data from 19 randomized controlled trials, revealed significantly higher frequencies of prostate events and hematocrit >50% in testosterone-treated men than in placebo-treated men. Hematocrit >50% was the most frequent androgen-related adverse event in these trials. Cardiovascular event rates did not differ significantly between testosterone-treated and placebo-treated men. Testosterone treatment also was associated with formulation-specific adverse events, such as skin irritation in studies that used a testosterone patch.

As six studies of testosterone treatment in middle-aged and older men included men with angina pectoris, chronic obstructive lung disease, and rheumatoid arthritis treated with glucocorticoids, and a no-treatment control group, we performed a secondary analysis in which these six studies (17,19,20–23) were excluded. Even after excluding these studies, testosterone treatment was associated with a significantly greater risk of prostate events and hematocrit >50%.

Although the combined rate of prostate events was significantly greater in testosterone-treated men than in placebo-treated men, this analysis assumes that each prostate event occurred in a separate individual. It is possible that in some instances the same person may have had more than one prostate event and that we may have overestimated total prostate event rates. Indications for prostate biopsy differed among studies and included an increase in PSA >1 ng/ml (13–15), a PSA increase of ≥1.5 ng/ml in 2 years, or a PSA increase of ≥2.0 ng/ml at any time confirmed by repeat analysis (10) and an abnormal prostate examination and increase in PSA (19). Indications for prostate biopsy were not

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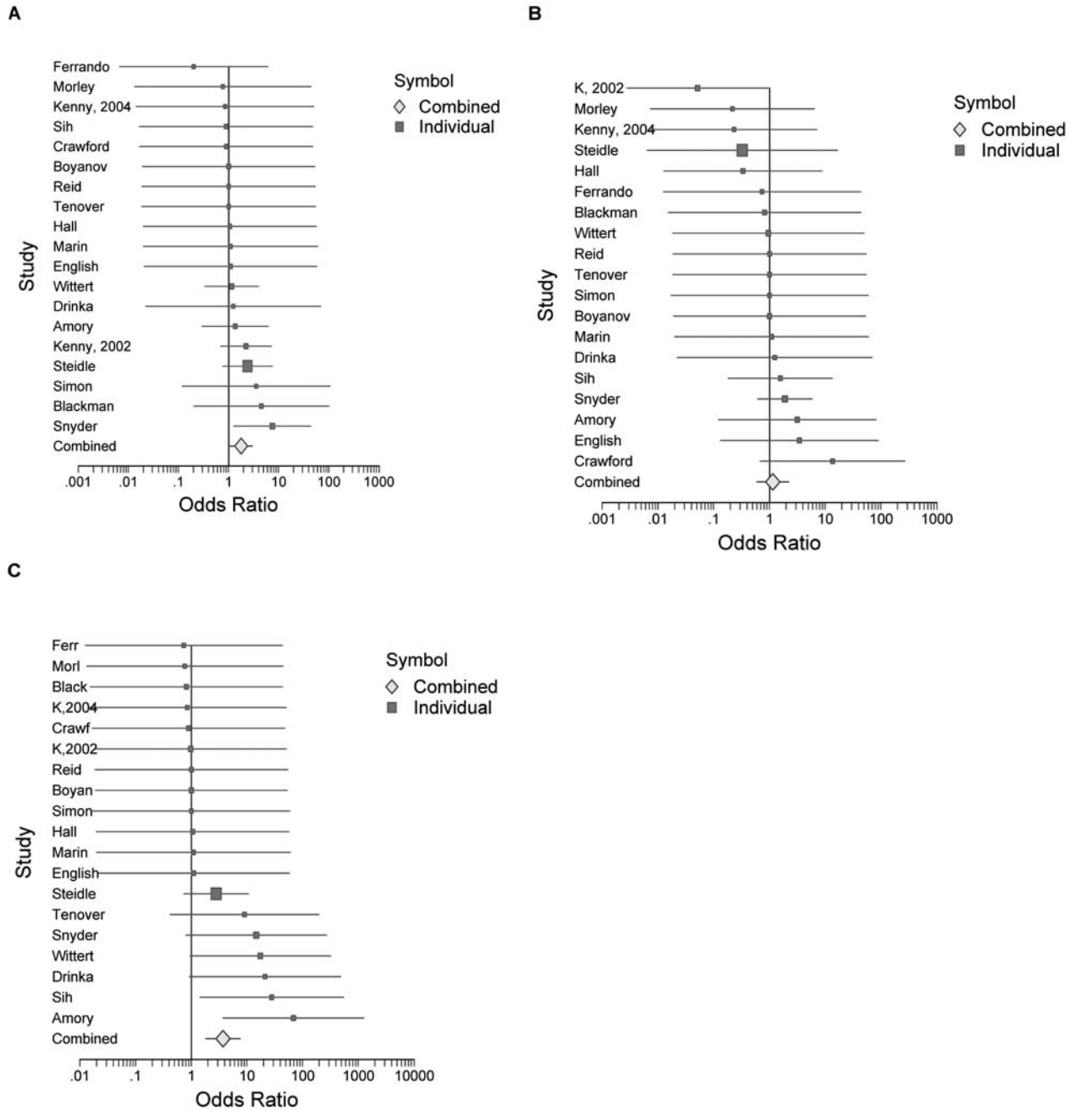

Figure 2. Forest plots illustrating confidence intervals for odds ratios for each study and event. **A,** Forest plot of combined prostate events odds ratios; **B,** Forest plot for odds ratios for all cardiovascular events; **C,** Forest Plot of odds ratios for hematocrit >50%. Ferr = Ferrando; K = Kenny; Morl = Morley; Crawf = Crawford; Black = Blackman.

specified in other studies. It is possible that some prostate cancers detected during these studies were subclinical cancers.

A closer scrutiny of prostate events reveals significant bias that could contribute to the increase in the observed frequency of prostate events in testosterone-treated men; these sources of bias should be factored into the design of testosterone trials. As prostate biopsies in testosterone trials are often triggered by an increase in PSA levels, testosterone-treated men are more likely to undergo prostate biopsy than are placebo-treated men. Because a greater number of testosterone-treated men had PSA >4 ng/ml or met the PSA increment criterion for biopsy during treatment, the number of prostate biopsies was numerically greater in testosterone-treated men than in placebo-treated men. However, the increase in the number of prostate biopsies in testosterone-treated men is not explained fully by a higher frequency of PSA increment criterion alone, as the frequency of PSA >4 ng/ml and PSA increment increase >1.5 ng/ml was only modestly higher in testosterone-treated men than in placebo-treated men. The studies may not have been blinded

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Table 4. Rates of Adverse Events in Secondary Analysis After Excluding Six Studies (3,17,19,21–23)

Event	Testosterone: Adverse Event Rate per 1000 Patient-Years*	Placebo: Adverse Event Rate per 1000 Patient-Years*	Pooled Odds Ratio	95% Confidence Interval
Prostate biopsies	46.1	3.6	2.30	0.92, 5.77
Prostate cancers	11.0	7.3	1.14	0.44, 2.97
PSA >4 ng/ml or 1.5 ng/ml increase during study	59.2	50.9	1.22	0.67, 2.24
Increase in IPSS score	6.6	3.6	1.12	0.42, 3.04
Acute urinary retention	2.2	0	1.00	0.34, 2.97
All prostate events	122.9	65.5	1.90†	1.11, 3.24
Hematocrit >50%	76.8	3.6	5.07†	2.30, 11.14
Atrial fibrillation/arrhythmia	11.0	3.6	1.32	0.50, 3.51
Myocardial infarction	4.4	7.3	0.91	0.38, 2.46
Chest pain/ischemia	0	10.9	0.68	0.23, 1.99
Coronary procedure/CABG	4.4	18.2	0.74	0.29, 1.91
Vascular events/cerebrovascular accidents	6.6	10.9	0.91	0.35, 2.38
All cardiovascular events	19.7	47.3	0.94	0.43, 2.04
Death	0	7.3	0.72	0.24, 2.11

Notes: *The rate per 1000 patient-years was calculated based on average study duration of 10 months, standardized to 1 year and multiplied by 1000.

†Odds ratios significantly different from placebo.

PSA = prostate-specific antigen; IPSS = International Prostate Symptom Score; CABG = coronary artery bypass graft.

rigorously, leading to bias towards a greater number of biopsies in testosterone-treated men. As a significant proportion of older men has subclinical prostate cancer, a greater number of prostate biopsies would likely lead to detection of a greater number of subclinical prostate cancers. Future studies should incorporate strategies to minimize this bias towards a greater number of prostate biopsies in testosterone-treated men.

Increase in hematocrit >50% was the most frequent androgen-related adverse event. The hematocrit increase in young, hypogonadal men is modest; however, older men experience greater increases in hematocrit than do young men. Cardiovascular event rates did not differ significantly between testosterone-treated and placebo-treated men. These results are consistent with studies that suggest either neutral or slightly beneficial effect of testosterone on the risk of heart disease (2).

Most studies of testosterone supplementation in older men recruited healthy individuals. We do not know whether risks of testosterone treatment in more representative populations of older men would be different from those observed in carefully selected healthy men. Also, most of the studies were of relatively short duration. Studies of substantially longer duration would be needed to determine testosterone effects on prostate and cardiovascular risk.

On the basis of the results of this meta-analysis, we determined sample size estimates for detecting various increases in prostate cancer rates in testosterone-treated men compared with placebo-treated men using two-group comparison of proportions with 80% power and two-tailed 5% significance level. These analyses indicate that 85,862 participants would be needed in each group to detect an increase of 20% in prostate cancer rates in testosterone-treated men compared with placebo-treated men; 40,000 men would be needed to detect a 30% increase, and 8591 men would be needed in each group to detect a 70% increase, if treatment duration were 1 year. These sample size estimates could be affected significantly by treatment duration. As studies of this magnitude would require substantial resources, the IOM Expert Panel's recommendation to focus initially on efficacy trials seems prudent. In the interim, older men who opt to receive testosterone treatment should be warned about the increased risk of detection of prostate events and elevated hematocrit and should be monitored by periodic evaluation of hematocrit and PSA and by digital rectal examination of the prostate (27).

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The Association for Gerontology in Higher Education
The educational unit of The Gerontological Society of America

Mark your year with stirring and inspiring images of older adults caught in the act of living! The 2006 AGHE Reflections Calendar is a continuing reminder of the joys and challenges of growing old, and of the importance of the work done by professionals in the fields of gerontology and geriatrics.

This year's calendar is once again in the format of an 8½" x 11" wall-mountable calendar, providing you with enough room to jot down important reminders. In addition, key dates for AGHE and The Gerontological Society of America are marked on the inside cover as well as throughout the year.

These inspiring and functional calendars are being sold for only $10 each, plus $3.85 shipping/handling.
For orders of multiple calendars, all additional calendars will be shipped free of charge.

All proceeds benefit the Association for Gerontology in Higher Education, the educational unit of The Gerontological Society of America

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