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Lin Xu

University of Hong Kong

Guy Freeman

University of Hong Kong

Benjamin J. Cowling

School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, 21 Sassoon Road, Pokfulam, Hong Kong, China

C Mary Schooling

CUNY School of Public Health

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RESEARCH ARTICLE

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Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomized trials

Lin Xu¹, Guy Freeman¹, Benjamin J Cowling¹ and C Mary Schooling^{1,2*}

Abstract

Background: Testosterone therapy is increasingly promoted. No randomized placebo-controlled trial has been implemented to assess the effect of testosterone therapy on cardiovascular events, although very high levels of androgens are thought to promote cardiovascular disease.

Methods: A systematic review and meta-analysis was conducted of placebo-controlled randomized trials of testosterone therapy among men lasting 12+ weeks reporting cardiovascular-related events. We searched PubMed through the end of 2012 using (“testosterone” or “androgen”) and trial and (“random*”) with the selection limited to studies of men in English, supplemented by a bibliographic search of the World Health Organization trial registry. Two reviewers independently searched, selected and assessed study quality with differences resolved by consensus. Two statisticians independently abstracted and analyzed data, using random or fixed effects models, as appropriate, with inverse variance weighting.

Results: Of 1,882 studies identified 27 trials were eligible including 2,994, mainly older, men who experienced 180 cardiovascular-related events. Testosterone therapy increased the risk of a cardiovascular-related event (odds ratio (OR) 1.54, 95% confidence interval (CI) 1.09 to 2.18). The effect of testosterone therapy varied with source of funding (*P*-value for interaction 0.03), but not with baseline testosterone level (*P*-value for interaction 0.70). In trials not funded by the pharmaceutical industry the risk of a cardiovascular-related event on testosterone therapy was greater (OR 2.06, 95% CI 1.34 to 3.17) than in pharmaceutical industry funded trials (OR 0.89, 95% CI 0.50 to 1.60).

Conclusions: The effects of testosterone on cardiovascular-related events varied with source of funding. Nevertheless, overall and particularly in trials not funded by the pharmaceutical industry, exogenous testosterone increased the risk of cardiovascular-related events, with corresponding implications for the use of testosterone therapy.

Keywords: Testosterone, Cardiovascular, Men, Trial

Background

In observational studies low serum testosterone is associated with cardiovascular disease [1,2]. Testosterone may protect or be a secondary risk marker of other processes [1-3]. On the precautionary principle, expert advice and reviews, largely based on observational evidence, warn that cardiovascular disease may be increased by androgen deprivation therapy [4] and low testosterone [5,6]. Awareness

of low testosterone as a treatable condition is being raised [7,8]. Testosterone use is increasing [9-11], possibly as self-medication in response to advertising.

In 2004 the Institute of Medicine (IOM) reviewed the evidence on testosterone therapy and concluded, largely based on placebo-controlled trials, that ‘there is not clear evidence of benefit for any of the health outcomes examined’ [12]. The IOM recommended small-scale trials to establish the efficacy of testosterone therapy where other treatments were not available [12]. To our knowledge, no trial has been designed to assess the effect of testosterone therapy on cardiovascular morbidity or mortality. Previous

* Correspondence: mschooli@hunter.cuny.edu

¹School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, 21 Sassoon Road, Pokfulam, Hong Kong, China

²CUNY School of Public Health at Hunter College, 2180 Third Avenue, New York, NY 10035, USA

meta-analyses of randomized placebo-controlled trials found that testosterone therapy resulted in a non-significantly higher risk of cardiovascular events, based on adverse events, but only included trials through March 2005 [13,14]. A more recent meta-analysis included trials through August 2008 but only reported on three specific cardiovascular outcomes, that is, arrhythmia, coronary bypass surgery and myocardial infarction [15]. Given the widespread use of testosterone, the high prevalence of cardiovascular disease in older men and no comprehensive assessment of the effect of testosterone therapy on cardiovascular events, an up-to-date meta-analysis may help inform clinical practice. We carried out a meta-analysis of adverse events from randomized placebo-controlled trials to examine the overall risk of cardiovascular-related events associated with testosterone therapy.

Methods

This meta-analysis follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist [see Additional file 1] and a published protocol (CRD42011001815) [16]. Two reviewers (LX and CMS) independently searched for and selected trials, resolving any differences by consensus. Two statisticians (GF and BJC) extracted information from the selected trials.

Data sources and searches

We (LX and CMS) systematically searched PubMed until 31st December 2012 using (“testosterone” or “androgen”) and (random*) and trial” with the selection limited to studies in men in English, because a preliminary search only found studies in English. We (LX and CMS) searched the World Health Organization (WHO) International Clinical Trials Registry Platform for any trial using testosterone as an intervention. From this search, we (LX and CMS) discarded any studies both agreed were irrelevant based on title or abstract and read the remaining. We did a bibliographic search of the selected trials and relevant reviews.

Study selection

We included randomized placebo-controlled trials giving cardiovascular-related events by study arm, because a report may focus on a particular aspect of the trial [17,18] and not report all events that have occurred [17-19]. We excluded trials that only gave treatment-related events in the testosterone arm because these might not include full reporting of events in the placebo arm. Initially, we intended to exclude trials that only reported withdrawals as potentially less comprehensive than reporting of adverse events [18,19], however this turned out to be a very fine distinction, so we included any trial reporting cardiovascular-related events by study arm.

We included any randomized controlled trial (RCT) of testosterone, but not other androgens, compared with placebo, including a comparison against a background of other treatments, because men likely to be taking testosterone may also be in treatment for other conditions. We excluded trials of less than twelve weeks’ duration to assess long-term rather than acute effects of testosterone therapy.

We checked for duplication based on overlapping authorship, study description, number of participants and participant characteristics. When duplication occurred we used the study with the most comprehensive description of adverse events.

Outcome

The primary outcome was composite cardiovascular-related events; because we anticipated too few events for robust assessment by cardiovascular event type; and a system-wide composite outcome may be most suitable for adverse events [20]. Cardiovascular-related events were defined as anything reported as such by the authors, that is, events reported as cardiac disorders, cardiovascular complaints, cardiovascular events, vascular disorders, cardiac or cardiovascular, or where the event description fell within the International Statistical Classification of Disease (ICD) version 10 chapter IX (I00 to I99). Most trials only reported serious adverse events, but a few also reported a wider range of events, so we also examined the effect of testosterone therapy by seriousness. Seriousness was based on the US Department of Agriculture definition of serious adverse events and the type of cardiovascular event generally considered serious [21]. Serious cardiovascular events were defined as cardiovascular-related events which the authors described as serious adverse events or where the outcome was death, life-threatening, hospitalization, involved permanent damage or required medical/surgical intervention, or was one of the following types of cardiovascular event: myocardial infarction, unstable angina, coronary revascularization, coronary artery disease, arrhythmias, transient ischemic attacks, stroke or congestive heart failure but not deep vein thrombosis.

Data extraction and quality assessment

A statistician (GF) extracted the number of participants randomized and cardiovascular-related events by trial arm. Event classification was checked by a physician (LX). A second statistician (BJC) checked the information extracted. Where trials reported cardiovascular-related events without giving the study arm, we contacted the authors twice by email to ask for cardiovascular-related events by study arm.

The reviewers (LX and CMS) independently used an established tool to evaluate the quality of each trial [22],

focusing on the quality of reporting of cardiovascular-related adverse events. First, we reported whether cardiovascular-related events were individually listed in a table by study arm, because these are easier to identify unambiguously. Second, we reported whether the type and severity of cardiovascular-related events reported was either pre-specified or identified before the allocation was revealed, because issues have been expressed about the reporting of adverse events [23,24]. Cardiovascular-related events vary in severity making the selection criteria and categorization crucial to an outcome assessed from adverse events.

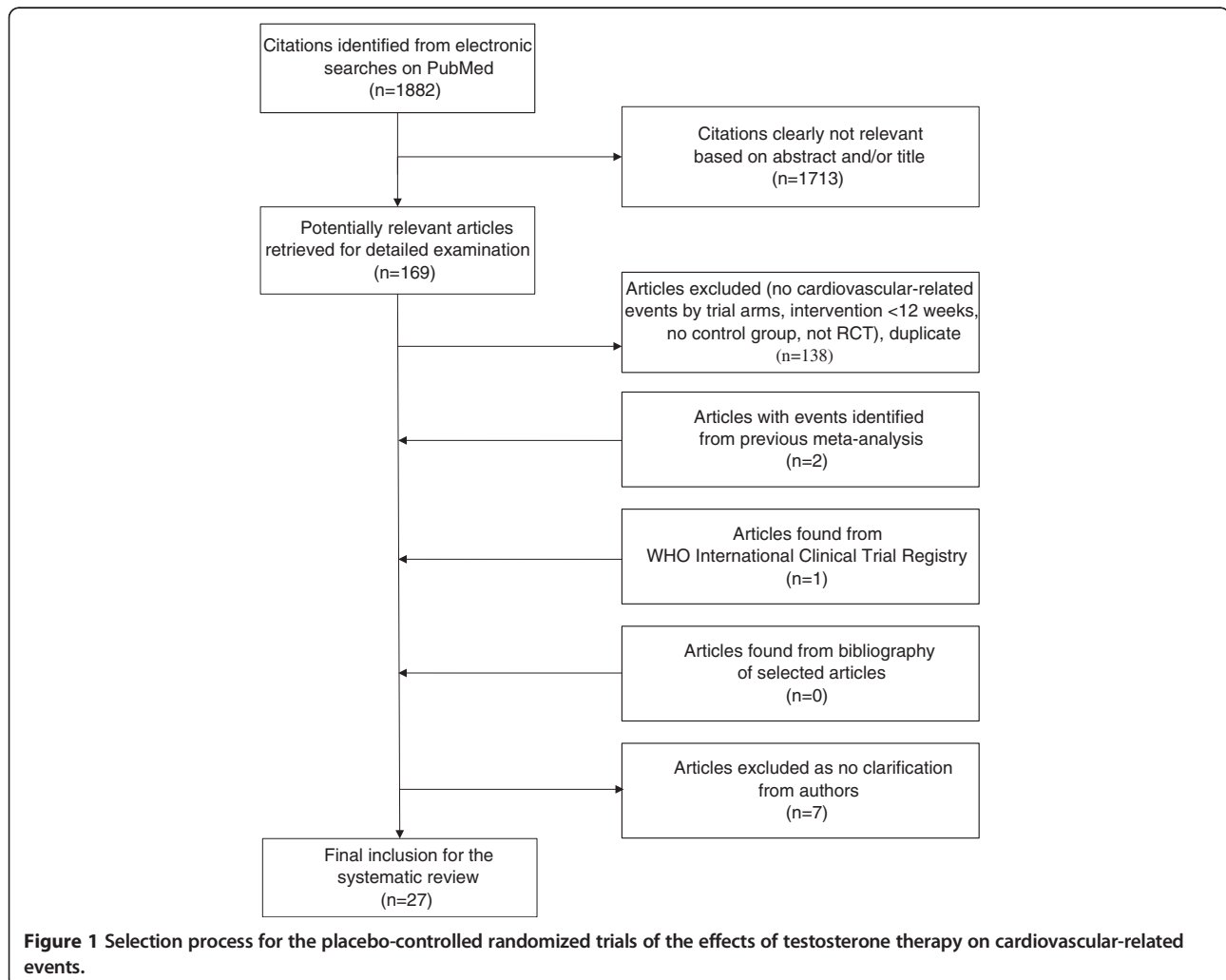
Sensitivity analysis

We initially planned only to assess whether the effects of testosterone on cardiovascular-related events varied with average baseline testosterone, because we did not expect sufficient trials for sub-group analysis by type of testosterone product or by type of cardiovascular-related event. However, the reporting of adverse events may be

open to interpretation [23], and may not be comprehensive [25]. Given potential lack of clarity as to the selection of the cardiovascular-related adverse events reported, we also examined whether the effect of testosterone therapy varied with funding source. Finally, we also considered cardiovascular-related death as an outcome.

Data synthesis and analysis

We used the number of participants randomized as the denominator and included all cardiovascular-related events from the start. We used funnel plots and 'trim and fill' to assess publication bias, that is, missing trials. We used I^2 to assess heterogeneity between trials, using fixed effects models where there was low heterogeneity ($I^2 < 30\%$), otherwise using random effects models. We obtained the pooled odds ratio, using the 'metabin' function of the 'meta' package in R 2.14.1 (R Development Core Team, Vienna, Austria). We used meta-analysis regression, with inverse variance weighting, to assess whether the effects of testosterone therapy varied with baseline testosterone or funding



source, using the 'rma' function of the 'metafor' package in R 2.14.1. Initial analysis showed the pooled odds ratio was similar using a Peto or a Mantel-Haenszel estimate; we used inverse variance weighting for consistency with the meta-regression.

This study is an analysis of published data, which does not require ethics committee approval.

Results

The initial search yielded 1,882 papers, of which 169 were selected for full text scrutiny. Of these 169 papers, 31 concerned different placebo-controlled randomized trials among men of testosterone therapy of 12+ weeks reporting cardiovascular-related events by study arm. We found one additional recent trial from the WHO International Clinical Trials Registry Platform [26]. We did not find any additional such trials from a bibliographic search of these 32 papers or from eight reviews [27-34]. Two additional trials [35,36] selected for full text scrutiny had cardiovascular-related events shown in a plot from one previous meta-analysis [13], but not the other meta-analyses [14,15] or in the relevant publications [35-37]. The search did not find one small non-randomized trial [38] included in two previous meta-analyses [13,15]. The search found one additional trial [39] potentially relevant to the earlier meta-analyses [13,14], two additional trials [40,41] potentially relevant to the most recent meta-analysis [15] and 11 subsequent trials. We sought clarification concerning events by study arm for 10 trials as set out in Additional file 2. Six authors never responded [37,40,42-45], three responded but did not provide any relevant information [36,46,47] and one provided information [48]. We included this later trial [48], one of the others that gave cardiovascular deaths, but not other cardiovascular-related events, by study arm [46] and one that gave vascular events, but not all cardiovascular-related events by study arm [44]. Figure 1 shows the search strategy resulting in 27 placebo-controlled randomized trials.

Table 1 shows the 27 trials over 25 years of 2,994 mostly middle-aged or older men (1,733 testosterone and 1,261 placebo) with low testosterone and/or chronic diseases, who experienced 180 cardiovascular-related events. Most of the trials were in Western settings. Thirteen trials were supported by the pharmaceutical industry. Two trials were stopped early [49,50], one because of adverse events among the men allocated to testosterone [50] and one because 'it would not be feasible to demonstrate - in the foreseeable future - a beneficial effect of testosterone [on mortality] by continuing the study' [49].

Quality assessment

The quality assessment (see Additional file 3) shows that two trials provided a table with a comprehensive list of

cardiovascular-related events by study arm and eight trials provided a summary table of cardiovascular-related events by study arm. For 17 trials cardiovascular-related events were surmised from withdrawals and/or adverse events as given in Additional file 4, including one where the cardiovascular-related events were surmised from a *P*-value [65]. The type and severity of adverse events to be reported was pre-specified in one trial [61]. In the two trials terminated early the adverse events motivated termination and were identified before treatment allocation was known [49,50]. Otherwise it was sometimes unclear whether the definition or classification was made by masked assessors.

Data synthesis

The funnel plot (Figure 2) shows several small studies (on the left hand side) where testosterone reduced cardiovascular-related events, however, there were no similar small studies where testosterone increased cardiovascular-related events. The forest plot (Figure 3) shows that the trials were homogeneous ($I^2 = 7.8\%$). Testosterone increased the risk of a cardiovascular-related event in a fixed effect model, odds ratio (OR) 1.54, 95% confidence interval (CI) 1.09 to 2.18. Trim and fill revised the OR to 1.69 (95% CI 1.21 to 2.38). When the analysis was restricted to serious events, whose categorization is shown in Additional file 4, the estimate was very similar (OR 1.61 (95% CI 1.01 to 2.56)) and was revised to 2.01 (95% CI 1.30 to 3.14) by trim and fill.

Sensitivity analysis

The cardiovascular-related event rate was lower in trials funded by the pharmaceutical industry (4% (66/1,651)) than in other trials (8% (114/1,343)). In a meta-regression model, risk of cardiovascular-related events on testosterone therapy varied with the source of funding (*P*-value for interaction 0.03) but not with baseline testosterone (*P*-value for interaction 0.70). In trials funded by the pharmaceutical industry testosterone had no effect on cardiovascular-related events, but in the other trials testosterone therapy substantially increased the risk of a cardiovascular-related event (Figure 4). Finally, 33 cardiovascular-related deaths were identified (22 testosterone arm and 11 placebo arm), for which the odds ratio was similar 1.42 (95% CI 0.70 to 2.89) to the estimate for all cardiovascular-related events, and was revised to 1.57 (95% CI 0.78 to 3.13) by trim and fill.

Discussion

This updated meta-analysis of placebo-controlled randomized trials, with a much larger number of participants than previous meta-analyses [13-15], adds to the previous findings by showing that testosterone therapy

Table 1 Characteristics of placebo-controlled randomized trials giving the effects of testosterone therapy on cardiovascular-related events among men

Author and publication year	Study				Participants				Industry funding
	Setting	Duration	Dose	Cardiovascular-related events based on	Age range	Number	Health status	Initial T (nmol/L)	
Copenhagen Study Group [49] 1986	Denmark	About 16 months ^a	200 mg/8 h micronized T, PO	Deaths	24 to 79	221	alcoholic cirrhosis	about 20	None given
Marin [39] 1993	Denmark	9 months	T gel 125 mg/day	Withdrawals	40 to 65	21	Obese, low T	15.3	Funded by Besins Iscovesco
Hall [51] 1996	UK	9 months	T enanthate 250 mg /month, IM	Withdrawals	34 to 79	35	Rheumatoid arthritis	16.1	Funded by Schering Healthcare
Sih [52] 1997	US	12 weeks	T cypionate IM every 14 to 17 days	Withdrawals	51 to 79	32	T<60 ng/dl	9.2	None given
English [53] 2000	UK	12 weeks	Transdermal T 5 mg/day	Withdrawals and safety data	Mean 62	50	Coronary artery disease	12.9	Patches given by Smith Kline Beecham
Snyder [19] 2001	US	36 months	Transdermal T 6 mg/day	Clinically apparent from hospital records	65+	108	Men with T one SD <475 ng/dl	12.7	Patches given by ALZA Corporation
Amory [54] 2004	US	36 months	T enanthate 200 mg/2 weeks, IM	Serious adverse cardiovascular events	65 to 83	48	TT <350 ng/dl	10	None given
Kenny [55] 2004	US	12 weeks	T enanthate 200 mg/3 weeks, IM	General description	73 to 87	11	Cognitive decline, bioavailable T <128 ng/dl	14.1	None
Svartberg [56] 2004	Norway	26 weeks	T enanthate 250 mg/month, IM	General description	Mean 66	29	COPD	21.1	None
Brockenbrough [57] 2006	US	6 months	Transdermal T gel 10 g/day	Side effects and adverse events	Mean 56	40	Dialysis and TT <300 ng/dl	7.3	Supported by Auxilium Pharmaceuticals
Malkin [58] 2006	UK	12 months	Transdermal T patch 5 mg/day	Serious adverse events	Mean 64	76	Heart failure	13.0	Medication given by Watson Pharmaceuticals
Merza [59] 2006	UK	6 months	Transdermal T patch 5 mg/day	Withdrawals	40+	39	TT <10 nmol/L	8.0	Supported by Ferring Pharmaceuticals Ltd
Nair [60] 2006	US	24 months	Transdermal T patch 5 mg/day	Adverse events	60+	62	DHEA<1.57 µg/ml, bioavailable T <103 ng/dl	13.7	Supported by The Endocrine Society
Emmelot-Vonk [61] 2008	Netherlands	6 months	TU 160 mg/day, PO	Adverse events	60 to 80	237	TT<13.7 nmol/L	10.7	Medication given by Organon NV
Svartberg [41] 2008	Norway	52 weeks	TU 1000 mg, MI at 0, 6, 16, 28 and 40 weeks	Deaths	60 to 80	38	TT≤11.0 nmol/L	8.3	Grant from Bayer Schering Pharma AG
Caminiti [62] 2009	Italy	12 weeks	TU 1000 mg MI for 0, 6 and 12 weeks	General description of events	66 to 76	70	Heart failure	7.0	None given
Chapman [48] 2009	Australia	1 year	TU 80 mg orally twice a day	Hospitalizations	65+	23	Undernourished	18.8	Organon provided funding

Table 1 Characteristics of placebo-controlled randomized trials giving the effects of testosterone therapy on cardiovascular-related events among men (Continued)

Legros [46] 2009	Europe	1 year	TU 80, 160 and 240 mg orally per day	Safety assessments	50+	316	Free T<0.26 nmol/L	12.8	Funded by Schering-Plough
Aversa [63] 2010	Italy	24 months	TU 1,000 mg (every 12 weeks)	Safety aspects	45 to 65	50	MS and/or T2DM TT<3.0 ng/ml	8.5	None given
Basaria [50] 2010	US	About 6 months ^a	Transdermal T gel 100 mg/day	Cardiovascular-related events	65+	209	Frial, TT 100 to 350 ng/dl	8.4	Medication given by Auxilium Pharmaceuticals
Srinivas-Shankar [64] 2010	US	6 months	Transdermal T gel 50 mg/day	Serious adverse events and withdrawals	65+	274	TT≤12 nmol/L (345 ng/dl)	11.0	Supported by Bayer Schering Pharma
Jones [65] 2011	Europe	12 months	T gel 60 mg/day	Cardiovascular events	37 to 88	220	Hypogonadal with type 2 diabetes and/or MetS,	9.4	Supported by ProStrakan
Ho 2011 [66]	Malaysia	1 year	TU 1000 mg MI for 0, 6, 18, 30 and 42 weeks	Withdrawals	40+	120	T<12 nmol/L,	9.0	Supported by Bayer Schering Pharma
Kaufman [44] 2011	US	182 days	1.62% T gel 2.5 mg/day	Safety aspects	45 to 64	274	Hypogonadal, T<300 ng/dl	9.8	Funded by Abbott.
Kalinchenko [67] 2010	Russia	30 weeks	TU 1,000 mg MI for 0, 6, 18 and 30 weeks	Withdrawal	35 to 70	184	T<350 ng/dl	7.0	Supported by Bayer Schering Pharma
Hoyos [68] 2012	Australia	18 weeks	TU 1000 mg MI at 0, 6 and 12 weeks	Adverse events	18+, mean 49	67	Obese men with obstructive sleep apnea	13.3	Supported by Bayer Schering Pharma
Spitzer [26] 2012	US	14 weeks	1% T gel 10 g/day	Adverse events	40 to 70	140	Erectile dysfunction low T and a sexual partner	12.3	none

^atrial stopped early so duration varies. IM= intramuscularly; P, placebo; PO, orally; T= testosterone; TT= total testosterone; TU= testosterone undecanoate.

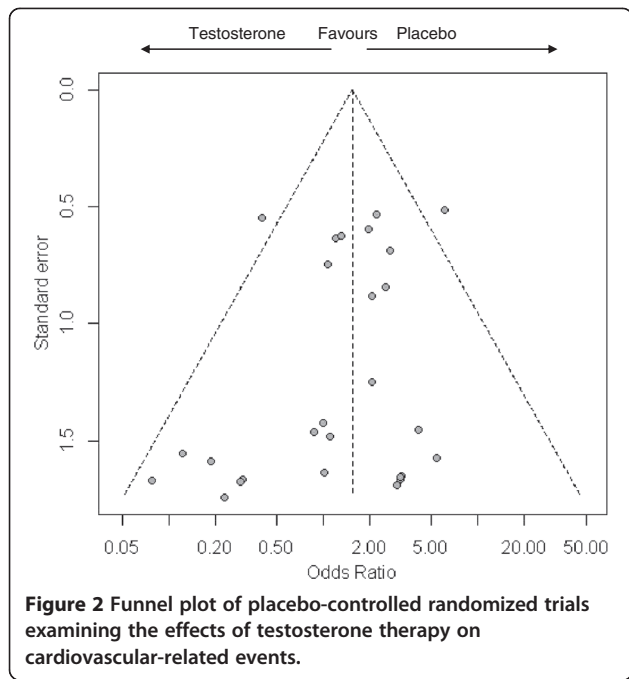


Figure 2 Funnel plot of placebo-controlled randomized trials examining the effects of testosterone therapy on cardiovascular-related events.

increases cardiovascular-related events among men. The risk of testosterone therapy was particularly marked in trials not funded by the pharmaceutical industry. The risks of cardiovascular-related events were similar by baseline testosterone.

Several possible explanations exist for our findings. First, not all trials of testosterone therapy reported all cardiovascular-related events by study arm [36,46].

Trials favoring testosterone may be unpublished. However, the funnel plot (Figure 2) and 'trim and fill' suggested trials favoring the placebo may be missing. Second, endogenous and exogenous testosterone may have different effects, with endogenous testosterone being protective, consistent with the observational evidence [1,2] and with testosterone declining with age when cardiovascular disease increases with age. However, a recent Mendelian randomization study, using genetic variants as an instrumental variable for endogenous testosterone, did not corroborate protective effects of endogenous testosterone on cardiovascular disease risk factors [69]. Another possibility is that serum testosterone is not a good indicator of androgen activity [70], as has long been suggested [71] and recently substantiated by the effective use of anti-androgens in prostate cancer at castrate levels of serum testosterone [72,73]. Third, endogenous testosterone may be beneficial, but other metabolites of exogenous testosterone, raised by testosterone therapy, such as estrogens or dihydrotestosterone, could mediate cardiovascular-related events. Exogenous estrogens do not protect men against cardiovascular disease [74]. However, higher free testosterone rather than higher estradiol appeared to mediate the cardiovascular events in a recent trial of testosterone therapy [75]. Few trials have examined the effects of dihydrotestosterone administration and have usually focused on prostate rather than cardiovascular effects [76-78]. The interplay of testosterone and dihydrotestosterone is complex and challenging to disentangle in RCTs [79]. Nevertheless, exogenous testosterone lowers HDL-cholesterol [15] and raises hemoglobin, hematocrit

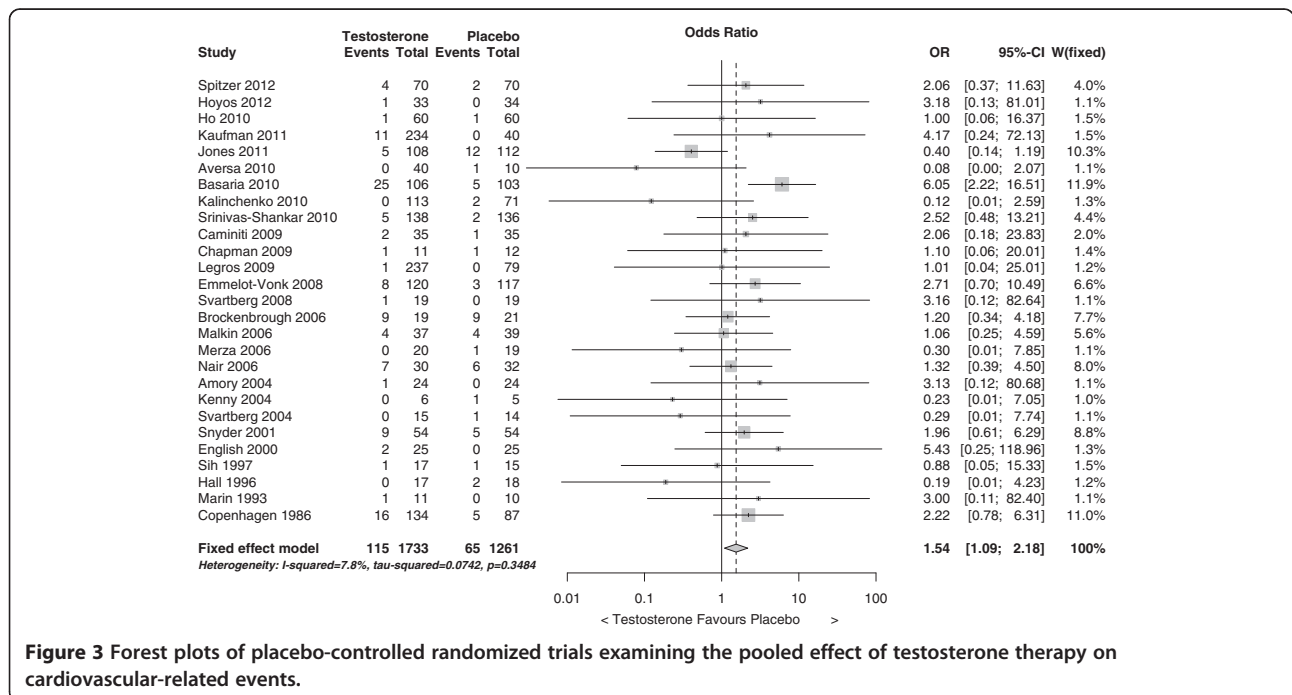


Figure 3 Forest plots of placebo-controlled randomized trials examining the pooled effect of testosterone therapy on cardiovascular-related events.

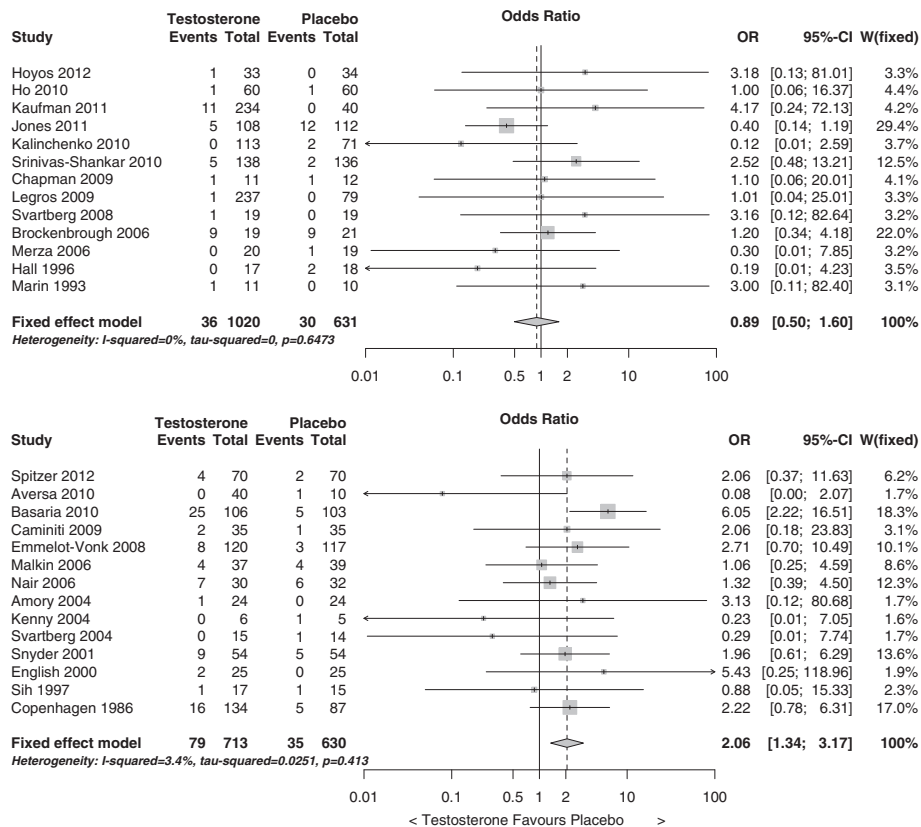


Figure 4 Forest plots of placebo-controlled randomized trials examining the pooled effects of testosterone therapy on cardiovascular-related events by source of funding: upper panel funded by the pharmaceutical industry and lower panel not funded by the pharmaceutical industry.

and thromboxane [15,80], all of which might contribute to cardiovascular disease. Thromboxane promotes clotting and blood vessel constriction. Natural experiments suggest that lower lifetime endogenous androgens are associated with a relatively lower risk of death from ischemic heart disease, based on legally castrated men [81] and men with Klinefelter's syndrome [82]. Similarly, a meta-analysis of RCTs of androgen deprivation therapy found a non-significantly lower risk of cardiovascular mortality among men allocated to androgen deprivation [83], despite bias to the null by the competing risk of death from prostate cancer.

Our findings are consistent with the three previous meta-analyses [13-15], which all indicated a non-significantly higher risk of testosterone therapy for a composite cardiovascular outcome of the events considered, despite discrepancies in some studies [13,14]. This meta-analysis based on many more trials (27), many more men (2,994) and correspondingly more events (180) produced a similar, but more precise estimate, with the confidence interval no longer including no effect. The difference between the estimates by funding source is consistent with other observations [84,85] and could be due to different reporting of

adverse events in industry funded trials. Differences by funding source could also be due to differences between trials. Industry funded trials reported fewer cardiovascular-related events, which reduces power although it should not affect the direction of effect. Industry funded trials tended to be in younger men. It is possible, although unusual, for the effects of treatment to be 'crossed' by age [86].

From a clinical perspective the issue is ensuring that the benefits of testosterone therapy outweigh the potential risks. Almost a decade after the IOM's report [12] the efficacy of testosterone therapy for health outcomes where treatments are not already available remains uncertain. Testosterone compared to placebo could be beneficial for glucose metabolism [65], depression [87,88], sexual dysfunction [26,89], bone density [90] and HIV wasting syndrome [91,92], although whether testosterone is better than established treatments for these conditions has not been clearly established. Cardiovascular disease is common in typical users of testosterone therapy, that is, older men. The 10-year risk of a cardiovascular event for US men aged 65 to 69 years is about 28% [93]. Assuming the increased risk of cardiovascular-related events seen here with testosterone therapy would give a number needed to

harm of at most 90 per year of testosterone therapy. As such, further research might focus on obtaining evidence without interventions, for example by confirming that the observed negative associations of serum testosterone with specific cardiovascular diseases extends to other androgen biomarkers, such as androgen glucuronides [94], and to other study designs less open to biases, such as Mendelian randomization. Moreover, a gene in the steroidogenesis pathway (*CYP17A1*) is reliably associated with coronary artery disease [95]. Establishing if *CYP17A1* acts, if at all, by raising or lowering androgens would also bring clarity. Finally, consideration could be given to whether further trials should be of agents that raise or lower testosterone.

Strengths and limitations

Despite providing a meta-analysis of all known placebo-controlled randomized trials, limitations exist. First, the reporting of adverse events may be open to conflicts of interest [24]. The funnel plot and analysis by funding source are consistent with that possibility. A very large market is at stake [9]. Second, in a trial of a therapy, such as testosterone, which may change how men feel or their sex drive, some accidental unmasking may have occurred. Few trials assessed or reported this possibility. Third, some men in the testosterone arm stopped treatment because of increased prostate specific antigen or polycythemia, which would bias towards the null. Fourth, RCTs are not always tagged as such and could be missed [96]. However, we searched broadly and found several potentially eligible trials that had not been included in previous meta-analyses. Fifth, our study cannot include on-going trials, such as the Testosterone Supplementation and Exercise in Elderly Men trial (NCT00112151) and The Testosterone Trial (NCT00799617). However, these trials are not designed to assess the effect of testosterone on cardiovascular events and will take time to complete. If new trials show testosterone therapy to be strongly protective against cardiovascular disease, it would be against the general run of evidence to date making interpretation uncertain because of heterogeneity [97]. Sixth, the abstractors were not blinded. Seventh, most trials only reported fairly serious cardiovascular-related events, but the severity varied between trials, although for RCTs the reporting of events should be comparable within trials, and the events reported are more or less severe symptoms of cardiovascular disease on the pathway to cardiovascular mortality. An analysis restricted to events which could be identified as serious gave a similar estimate, but was limited by relying on events the authors had chosen to describe in detail by study arm and was revised upwards by trim and fill. Arguably, the standard definitions of event seriousness, including hospitalization, do not apply to frail older men, because they may be particularly prone to hospitalization. On the other hand, frail

older people may also be most affected by any decrement to their already poor health, so hospitalization may represent a particularly significant event. Notably, an estimate based solely on deaths also had a similar point estimate, although the confidence interval included no effect because of low power. Eighth, two larger trials were terminated early [49,50] which reduces power and could affect the estimates. However, the terminations took place towards the end of the planned trials and did not specifically concern cardiovascular-related events. Nevertheless, early terminations may have slightly increased the estimate and widened the confidence intervals. However, the interpretation would, most likely, have been similar. Ninth, although meta-analyses are a mainstay of evidence-based medicine they may be less reliable than large RCTs. Meta-analysis may overstate the benefits of treatment [98] however, they are less prone to overstate the harms [98]. Subsequent large RCTs rarely reverse the direction of effect from meta-analysis [99]. Tenth, given the lack of detailed cardiovascular-event reporting secondary analysis by type of cardiovascular event was not possible. Such sub-group analysis would undoubtedly be etiologically valuable. However, from a public health perspective the issue is identifying side-effects, where a composite outcome relating to a particular system (here the cardiovascular system) has been recommended [20]. Finally, the difference observed by source of funding could just be chance variation; however, testosterone therapy increased the risk of cardiovascular-related events overall.

Conclusions

Appropriately prescribed testosterone is undoubtedly beneficial. However, caution needs to be exercised to ensure that the associated health benefits of testosterone therapy outweigh the potential increased risk of cardiovascular-related events, particularly in older men where cardiovascular disease is common.

Additional files

Additional file 1: PRISMA 2009 Checklist.

Additional file 2: Trials where authors contacted for additional information and responses. [13,35-37,40,42-48,100].

Additional file 3: Quality assessment of the selected placebo-controlled RCTs of the effects of testosterone therapy on cardiovascular-related events (CRE) [19,26,39,41,44,46,48-68].

Additional file 4: Description of cardiovascular-related events in the selected placebo-controlled RCTs [19,26,39,41,44,46,48-67,101].

Abbreviations

CI: confidence interval; CYP17A1: cytochrome P450 17A1; IOM: Institute of Medicine; ICD: International Statistical Classification of Disease; OR: odds ratio; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT: randomized controlled trial; WHO: World Health Organization. Systematic review reference number CRD42011001815.

Competing interests

All authors declare: no support from any organization for the submitted work; BJC has received research funding from MedImmune Inc., and consults for Crucell MV; no other relationships or activities exist that could appear to have influenced the submitted work.

Authors' contributions

LX carried out the systematic search and drafted the manuscript. GF and BJC did the data extraction and analysis; they also reviewed the manuscript critically. CMS originated the idea, carried out the systematic search and helped draft the manuscript. All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. LX is the guarantor. All authors read and approved the final manuscript.

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