Reviewer's report

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

Version: 1 Date: 10 January 2013

Reviewer: Robin Haring

Reviewer's report:

General comments:
In their systematic review and meta-analysis: “Testosterone therapy and cardiovascular events among men” Lin Xu and co-workers addressed a very timely, well-defined, and relevant research question about the cardiovascular event risk related to exogenous testosterone therapy among men. The present, very well-written study updated previous meta-analyses, by including more trials, more men and correspondingly more events, to provide a more precise risk estimate. The methods are appropriate and well described, with sufficient details provided to update the meta-analysis in the future. The standards for the conduction of meta-analysis, including study search, selection, and reporting, were ensured by following the PRISMA checklist. The discussion and conclusions of the study are well balanced and adequately supported by the data.

My main criticism is to update the cutoff date to 31.12.2012 (if possible) in order to provide contemporary evidence closer to the time of publication (present cutoff date: 30.11.2011).

However, I am sure the authors are easily able to address the raised issues and to resubmit a revised version of their manuscript. Given those changes, I would suggest the manuscript suitable for publication in BMC Medicine.

Major Compulsory Revisions

Abstract:
Please add to the “Results” section, that the risk of cardiovascular-related events on testosterone therapy varied with source of funding (p-value for interaction 0.02), but not with baseline testosterone level (p-value for interaction >0.30).

Background:

l.1: “…studies, low serum testosterone is associated with…”

l.2: I would suggest the term “secondary risk marker” instead of “bystander”.


l.6: “testosterone use is increasing…” – cite Handelsman DJ, MJA 2012; 196: 642-645 & Gan; BMJ 2012;345:e5469
Methods:
Ref. 13: please provide the complete link to the PROSPERO register entry for: CRD42011001815.

Data Sources and Searches:
Why is the cutoff date > 1 year ago? I would strongly suggest updating the cutoff date to 31.12.2012 in order to provide contemporary evidence closer to the time of publication.

Does the WHO trial register comprise EU & US studies? If not, please supplement your PubMed search by checking both, EU (https://www.clinicaltrialsregister.eu/) and US (www.clinicaltrials.gov/) trial registries.

Study Selection:
“We included any RCT of testosterone…” – introduce the abbreviation “RCT” used here for the first time…

Discussion:
p.9: “Evidence concerning the effect of dihydrotestosterone on cardiovascular events is very limited.” you may cite a recent RCT addressing the interplay of T & DHT: Bhasin et al. JAMA. 2012;307(9):931-939.

p.8: When discussing “endogenous testosterone and observational evidence”, you should consider a recent Mendelian Randomization analysis providing the latest methodological approach to infer causality from observational findings. The conclusion of that specific investigation is very relevant to your conclusion (Andrology. 2013 Jan;1(1):17-23 PMID: 23258625).

p.9: a subheading “Strengths and limitations” should be included.

p.10: please provide registry numbers for those trials, so that the reader may easily look them up: Testosterone Supplementation and Exercise in Elderly Men trial and The Testosterone Trial.

Minor Essential Revisions
p.5: “system-wide”

p.6: “We found one additional recent such trial from the WHO trials database [22].”
omit “such”

p.7: “Two trials were stopped early [44, 45], because of adverse events among the men allocated to testosterone [44], and low possibility of the trial showing efficacy against mortality [45].”
What does “low” mean in this context? Please rephrase…
Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests.