Protocol: Testosterone and cardiovasclar related events in men: a meta-analysis of randomized controlled trials

Version: 1

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Introduction

Observational studies usually suggest that lower testosterone is associated with higher morbidity and mortality, particularly from cardiovascular disease.[1-5] Observational studies are open to uncontrollable confounding by socio-economic factors, health behavior and physiological changes with aging and ill-health. As such, it is difficult to know whether these observations mean that testosterone protects against cardiovascular disease or that testosterone is simply a marker of other processes. Reviews and expert advice warn that low testosterone or androgen deprivation therapy may increase cardiovascular disease risk,[6-9] making self-medication with testosterone an attractive option for men. However, natural experiments suggest that lower testosterone protects against ischemic heart disease, with a lower risk in men legally castrated[10] or with Klinefelter's syndrome.[11] A recent randomized controlled trial of testosterone therapy was terminated early because of adverse cardiovascular events.[12] Given these uncertainties about the role of testosterone in cardiovascular disease and the potentially widespread use of testosterone it is important to have an up-to-date summary of the experimental evidence available. To our knowledge no trial has been designed to assess the effect of testosterone on cardiovascular events or mortality, however several trials have reported the effect of testosterone therapy on cardiovascular related events or on cardiovascular-related adverse events. The previous meta-analyses of the effects of testosterone therapy on cardiovascular disease in randomized controlled trials do not include the more recent trials,[13] do not consider cardiovascular events as a composite group[14] are not systematic[15] or focus on specific surrogate outcomes.[16] This systematic review and meta-analysis of the effects of testosterone therapy on cardiovascular related events in randomized controlled trials will provide a much-needed summary of the evidence to date.

Review Question
What is the effect of testosterone therapy on cardiovascular related events?

Eligibility criteria
Studies will be eligible if they meet all the following criteria

- Randomized controlled trial of testosterone compared with a placebo. Given, that many of these trials are in older men with chronic diseases, we will include trials where there is a comparison of testosterone with placebo against the background of other drug use as long as the groups only differ in their use of testosterone.
- Duration of at least 12 weeks, because this study concerns the effects of regular rather than of acute testosterone use.
- Participants are men, or where the trial concerns both sexes, results are presented by sex.
- Published study or registered trial where we are able to track down the results.
- Any date, because there is no reason to think that the effect of testosterone has changed over the years.
- Any setting, because there is no reason to think that the effect of testosterone varies by setting.

- Reported in English, because a preliminary search of the literature suggests all studies are in English.
- Provides information explicitly on all cardiovascular related events by study arm, because a study report may be focused on a particular aspect of the trial and may not report on cardiovascular related events that have occurred.

We will define as cardiovascular related events anything reported as such by the authors. Where events are reported with a disease description, we will classify the disease using the International Statistical Classification of Disease version 10 (ICD10). We will include as cardiovascular related events any disease that falls into ICD10 chapter IX (codes I00 to I99).

Information Sources
We will search PubMed, Embase and the Cochrane Library database for trials of testosterone therapy reporting cardiovascular related events (including death) specifically or as adverse events. To identify further articles we will hand search references and related citations in PubMed. Where we find one report on a trial that does not give cardiovascular related or adverse events we will check all other publications on that same trial for cardiovascular related or adverse events by trial arm. Where we find duplicate publications from the same trial we will include the most up-to-date report that includes information on cardiovascular related or adverse events by trial arm. We will search from the beginning of time until the end of November 2011. If there is a significant delay between completion and publication, we will update the search to the current date. We will also search all published reviews on this topic to identify any additional studies.

Where trials include reporting of cardiovascular related events without giving study arm, we will contact the authors twice to ask for cardiovascular related events by study arm.

Search
We will search PubMed using ("cardiovascular" or "heart" or "stroke" or "adverse") and (“testosterone" or "androgen") and ("placebo-controlled") in title, abstract or any field with the selection limited to clinical trials. We will use a similar strategy for Embase and the Cochrane library. We will also search the references of any included study.

Study selection
Two people will search independently and compare their selections at the end of the search process. Any differences will be resolved by consensus or if necessary by reference to a third investigator.

We will not exclude studies based on the number of participants, because we want to make full use of the evidence available. We will not exclude by participant characteristics’, because testosterone is used for the same purpose in a wide variety of patients, and there is no reason to think that testosterone has different effects by patient sub-group.

We will exclude trials in children (<18 years), because they have different hormone levels. We will exclude trials that use androgens other than testosterone as the treatment.

We will exclude studies that do not appear to give all cardiovascular related events or adverse by study arm. For example we will exclude studies that only report what the authors consider to be treatment related events, because firstly the authors might not consider cardiovascular events as treatment related and secondly if the authors are only reporting treatment related events they may not be fully reporting events in the placebo arm. We will also exclude studies that only report withdrawals but not adverse events. We will include studies that only report serious adverse events providing cardiovascular related events can be identified.

Selection process
After the first automated query in the databases, we will use a two step process for screening. Firstly, we will screen the titles and abstracts. Secondly, we will screen the remaining publications on the basis of the corresponding full text for reports of adverse events, causes of death or cardiovascular related events by trial arm.

Data extraction
A statistician will abstract data from the selected studies, using a standard template. A second investigator will check all the extracted data.

We will not contact authors for confirmation of their published numbers because we assume the authors would have corrected or withdrawn their papers if a major error came to light. We will contact the authors twice for clarification, if necessary. In the event of no response we will make conservative assumptions about the relevant trial.

Data items
We will extract the following information for each trial

- Publication details (author, year of publication, title, journal)
- Study population, including health status (major chronic diseases), pre-trial testosterone status ('low' or 'normal'), age and setting
- Primary study outcome
- Duration of follow-up
- Number of participants in each arm at start and end (testosterone and placebo groups)
- Dose of testosterone and method of administration
- Number of occurrences of cardiovascular related events and cardiovascular related deaths by trial arm.
- Funding source
- Affiliations and competing interests of investigators
- Trial implementation and reporting including information on
    - randomization
    - treatment allocation
    - comparison of groups at baseline

    - trial eligibility criteria
    - 'blinding' of outcome assessors, care providers, adverse event assessors and participants
    - Adverse or cardiovascular related event reporting
    - Type of analysis, intention to treat, per-protocol or other
- Source of cardiovascular related or adverse events, as summarized in a table, surmised from the text or obtained from the study authors.

Bias assessment for individual studies
We will use an established tool to evaluate the quality of each trial.[17] Two investigators will independently rate each study and settle any differences by consensus or reference to a third investigator. Because we are not studying the main outcomes of these trials but largely unexpected events in this systematic review we will focus our assessment on the quality of reporting of these events.

Summary Measure
The principal summary measure will be a measure of relative risk.

Synthesis of results
We will use the Mantel Hazel estimator with random or fixed effects depending on the heterogeneity between trials. Heterogeneity will be analysed using the Cochran Q test (χ^2) and I^2 statistics. I^2 is the proportion of total variation observed between the trials attributable to differences between trials rather than to sampling error (chance), with values less than 30% representing low variation, less than 60% moderate variation, and greater than 60% high variation.

Bias Assessment for all studies
We will use Begg and Egger's methods to assess publication bias. We will also use the trim and fill method to assess the impact of publication bias on the pooled effect.

Subgroup analysis
We do not anticipate finding many trials, largely precluding subgroup analysis. Many men may currently be taking testosterone on their own initiative regardless of testosterone status; it is unclear whether testosterone use should be restricted to men with low testosterone. We will, if possible, do subgroup analysis by the participants' pre-trial testosterone status, as low or normal.

Statistical analysis
We will use the number of participants randomized as the denominator, and include all cardiovascular related or adverse events from study start. We will use R to do the analysis.

Reference List

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