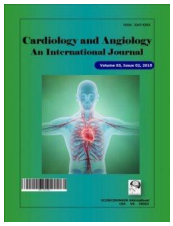

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Does Testosterone Therapy Increase Risk of Cardiovascular Events among Men? A Meta-analysis

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Authors' contributions

This work was carried out in collaboration between both authors. Both of the authors have contributed to the design, data analysis and writing of this manuscript. None of the authors have any financial disclosures to report. Both authors read and approved the final manuscript.

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ABSTRACT

Importance: There has been increasing interest in use of testosterone therapy (TT) beyond patients with hypogonadism to include younger men without documented hormone measurements for the purpose of improving libido, sexual function, bone density, and body mass. However, there is no conclusive data about safety of TT due to lack of adequately powered randomized clinical trials (RCTs) specifically designed for this purpose.
Objective: To examine the overall risk of cardiovascular events associated with TT via meta-analysis of published randomized and observational studies.
Data Sources: We searched MEDLINE, EMBASE, CINAHL, the Cochrane Controlled Trials Register and the National Institute of Health Clinical Trials.gov database from 1966 to 2014.
Study Selection: Out of the initial 2,800 studies identified, we obtained a total of 34 studies for detailed analysis after applying our inclusion/exclusion criteria. Two reviewers used eligibility

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criteria to assess all titles, abstracts, and full texts and resolved disagreements by discussion.
Data Extraction and Synthesis: One reviewer did data abstractions and quality assessments, which were confirmed by a second reviewer. Data were then collected and analyzed using random and fixed effect model, as appropriate. Risk estimates were extracted as adjusted hazard ratios (HRs) from included studies.
Main Outcome and Measures: Association of TT with cardiovascular events as a primary endpoint and association of TT with ischemic heart disease, all-cause mortality and cerebrovascular events as secondary endpoints.
Results: TT was associated with increased incidence of cardiovascular events (adjusted hazard ratio (HR) = 1.41, 95% CI = 1.19-1.67, p = 0.0004), all-cause mortality (adjusted HR = 1.29, 95% CI = 1.03-1.62, p = 0.02), and ischemic heart disease (adjusted HR=1.51, 95% CI = 1.05-2.18, p = 0.02) but there was no clear association with cerebrovascular events (adjusted HR=0.91, 95% CI = 0.66-1.25, p=0.54). Subgroup analyses of our primary endpoint by study type (randomized versus observational studies) did not change our results (adjusted HR=1.40, 95% CI = 1.05-1.87, p = 0.02 and adjusted HR=1.54, 95% CI = 1.09-2.17, p = 0.01 respectively). Additional analysis using meta-regression and sensitivity analyses to account for factors such as history of prior CV events, indication for TT and duration of follow up did not change our results. However, we did notice lack of association between CV events and Intramuscular testosterone.
Conclusions and Relevance: TT may be associated with an increased risk of all-cause mortality, cardiovascular events, and ischemic heart disease. These findings support the need for an adequately powered randomized study.

Keywords: Testosterone therapy; myocardial infarction; ischemic heart disease; cerebrovascular events.

1. INTRODUCTION

Over the last decade, there has been increasing interest in the use of testosterone therapy (TT) beyond patients with hypogonadism to include younger men and those without documented hormone measurements, suggesting that indications for prescription are likely expanding to include improvement in libido and sexual function, bone density, muscle mass, body composition, mood, erythropoiesis [1]. However, with the widespread usage there has been an increasing concern about the possible risk of adverse cardiovascular outcomes linked to testosterone administration [2]. Studies have linked testosterone supplementation to salt retention particularly in older men, which could contribute to edema, hypertension, and congestive heart failure [3,4]. TT is also associated with increase in estradiol levels and platelet thromboxane A2 receptor density that in turn promote inflammation, coagulation, and platelet aggregation [5]. Additional evidence arises from studies demonstrating a clear association between TT and left ventricular hypertrophy, systolic and diastolic dysfunction [6,7].

However, most of the evidence is derived from several small-randomized controlled trials (RCTs) and observational studies and with conflicting results. Currently, there is no conclusive data about the safety of TT due to lack of adequately powered RCTs that are designed specifically for this purpose. Thus, to better define the safety of such therapy based on the current available data, we conducted a meta-analysis of all published studies including recently published large observational studies [1,8]. Our aim is to examine the association of TT with the incidence of cardiovascular events.

2. METHODS

Our analysis is based on the guidelines of the Meta-analysis of Observational Studies in Epidemiology Group and guidelines of the Meta-analysis of clinical trials by DerSimonian and Laird [9,10].

2.1 Search Strategies

With the assistance of a trained research librarian, we searched MEDLINE, EMBASE, CINAHL, the Cochrane Controlled Trials Register, Cochrane Database of systematic Reviews and the National Institute of Health Clinical Trials.gov database from 1966 to 2014. In addition, we searched abstracts of articles published by the American College of Cardiology, the American Heart Association,

American Society of Endocrinology and the European Society of Cardiology meetings. We identified relevant studies using the MeSH terms and keywords "Testosterone" OR "Androgen" OR "Testosterone Replacement" OR "Testosterone Therapy" AND "Cardiovascular Event" OR "Myocardial Infarction" OR "Heart Attack" OR "Cardiac Failure" OR "Myocardial Failure" OR "Heart Decompensation" OR "Cardiac Edema" AND "Stroke" OR "Transient Ischemic Attack" OR "Cerebrovascular Event" AND "Ischemic Heart Disease" OR "Acute Coronary Syndrome" AND "Death" OR "Cardiac Death" OR "Mortality". Titles and abstracts were reviewed independently by two reviewers (NM & WK). Differences were resolved by consensus.

2.2 Study Selection

We applied the following inclusion criteria in our review of potentially eligible studies: 1. RCTs reporting cardiovascular events by study arm, because a report may focus on a particular aspect of the trial and not report all events that have occurred; 2. Observational studies (both prospective and retrospective) evaluating cardiovascular events in patients on testosterone supplementation; 3. Adult patients aged > 18 years; and 4. Studies of testosterone, but not other androgens, compared to placebo.

Titles and abstracts were evaluated and excluded after initial screening according to the following exclusion criteria: 1. Outcome that is different than cardiovascular events, cerebrovascular events, ischemic heart disease or all-cause mortality; 2. Inability to obtain both the numerator (i.e., number of patients experiencing a given outcome) and denominator for the intervention and control groups; and 3. Studies less than 12 weeks in duration because we are interested in assessing the long-term rather than the acute impact of testosterone therapy. We chose 12 weeks as the cut-off as this was similarly used in a prior meta-analysis to distinguish short term from long term outcomes [11]. Fig. 1 summarizes the results of the search.

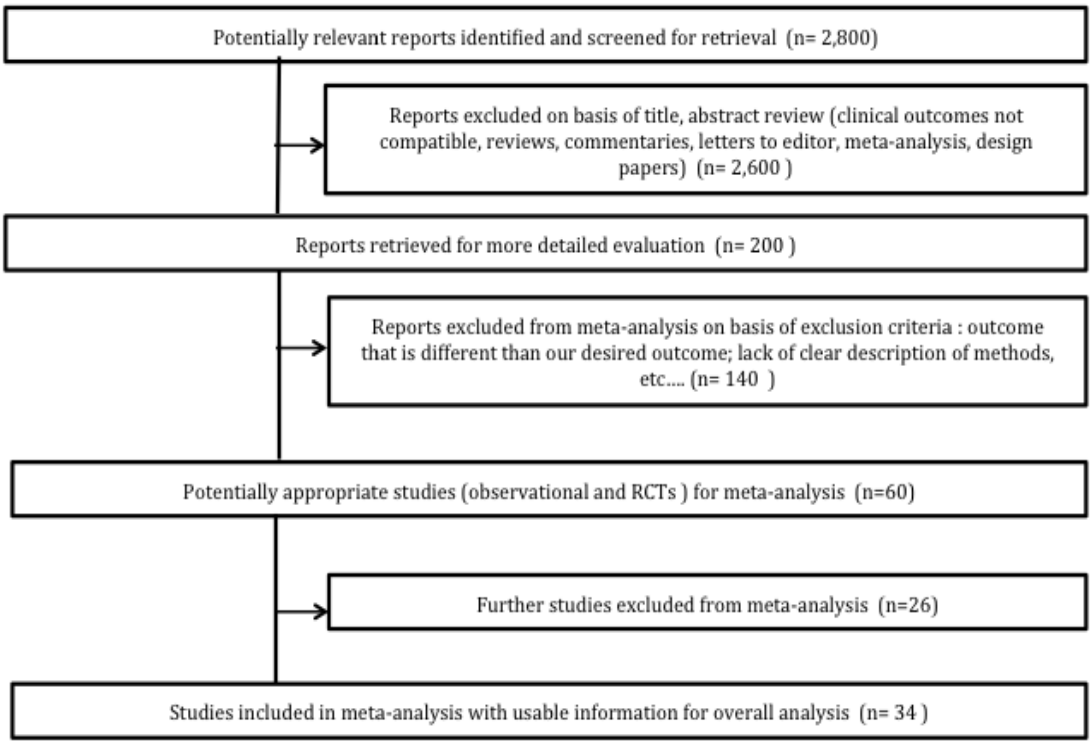


Fig. 1. Flow diagram depicting the selection process for our studies. Out of the initial 2,850 studies that we identified, we obtained a total of 60 studies for detailed analysis after applying our inclusion/exclusion criteria. Then we excluded an additional 26 studies, as they did not have enough data for pooled analysis

2.3 Quality Assessment

Observational studies were rated according to the Newcastle-Ottawa Scale (NOS) used for assessing non-randomized observational studies [12]. This scale identifies high quality choices with a star. A maximum of one star is assigned for each item within the Selection and Exposure/Outcome categories and a maximum of two stars are assigned for Comparability. Based on this scale all of the included observational studies scored high in terms of selection and outcome assessment (Appendix Table 1). On the other hand, RCTs were evaluated for concealment of treatment allocation, clear description of the design, and completeness of follow up. The JADAD scale was used to score study quality (range 0-5, higher scores indicating higher quality) with the majority of studies scoring 2-3 suggesting fair quality (Appendix Table 2) [13].

2.4 Endpoints

The primary endpoint of this meta-analysis was a composite endpoint of cardiovascular events. Secondary endpoints consisted of all-cause mortality, ischemic heart disease, and a composite of cerebrovascular events.

2.5 Data Abstraction

One reviewer (NM) did data abstractions and quality assessments, which were confirmed by a second reviewer (WK). The following data elements were extracted from each study: 1. Publication details including first author's last name and year; 2. Study design; 3. Characteristics of the study population, which included mean age, health status and number of patients with history of prior MI and 4. Duration of follow up. Additional data regarding other comorbidities (i.e. diabetes, peripheral vascular disease, hypertension, and hyperlipidemia) were not available for extraction.

2.6 Definitions

Cardiovascular events (CV) were defined as anything reported as such by the authors, that is, events reported as myocardial infarction, unstable angina, coronary revascularization, coronary artery disease, arrhythmias, transient ischemic attacks, stroke or congestive heart failure or where the description fell within the International Statistical Classification of Disease (ICD) version 10 chapter IX (I00 to I99). Ischemic heart disease was defined as myocardial infarction, unstable angina, coronary revascularization and/or coronary artery disease. Cerebrovascular events were a composite of transient ischemic attack (TIA) or stroke (hemorrhagic or ischemic). Hypogonadism was defined across studies as testosterone level below the 50th percentile of the study population−based testosterone distribution and age between 60 and 80 years. The 50th percentile cut- off level of testosterone was determined to be approximately 13 nmol/L in most of the included studies after screening a set number of candidates. Studies did not specify the relative percentage of pituitary versus testicular hypogonadism.

2.7 Statistical Methods

We used graphical and tabular methods to summarize the results of our literature search and systematic review. All studies employed Cox proportional hazard models; therefore, for the present analyses we assumed hazard ratios (HRs) to be a valid approximation of odds ratios (ORs), thereby enabling the use of one consistent meta-analytic HR throughout. A subgroup analysis, which excluded ORs, was also performed showing results consistent with the findings below. HRs were transformed logarithmically since they do not follow a normal distribution. The standard error was calculated from Log HR and the corresponding 95% confidence interval. We used the inverse variance method to achieve a weighted estimate of the combined overall effect. Risk estimates were extracted as adjusted HRs from included studies. These studies reported use of multivariate and propensity score models to adjust for potential confounders such as age, race, timing of sample collection, and baseline testosterone level. We assessed the results for heterogeneity in our analysis by examining the forest plots and then calculating a Q statistic, which we compared with the I^2 index [14]. The Q test indicates the statistical significance of the homogeneity hypothesis and the I^2 index measures the extent of the heterogeneity. We considered the presence of significant heterogeneity at the 5% level of significance (for the Q test) and values of I^2 exceeding 56% as an indicator of significant heterogeneity. Data were collected and analyzed using random and fixed effect model, as appropriate, with inverse variance weighting [14,15]. The underlying heterogeneity further prompted us to perform

meta-regression analysis to investigate if our study endpoints are affected by factors other than our primary treatment (testosterone) [16]. We adopted a weighted regression random effect model and estimated between study variance (Tau square-τ^2) using empirical Bayes estimate. Furthermore, we performed sensitivity analyses to evaluate the robustness of the meta-analysis and to ascertain the influence of certain studies on our results [17]. A two-sided P-value <0.05 was regarded as significant for all analyses. All statistical calculations were performed using Rev Man v5.0 software and data were represented as forest plots. Potential publication bias was assessed with the Egger test and represented graphically with Begg funnel plots of the natural log of the HR vs. its standard error [18]. Our meta-analysis was considered to be exempt from institutional review board (IRB) review as per Ohio State University IRB guidelines since we did not obtain or had access to individually identifiable human participant information.

3. RESULTS

3.1 Studies and Patient Characteristics

The literature search yielded 2,850 potential studies. After application of all inclusion/ exclusion criteria we identified a total of 34 studies (31 RCTs and three observational studies) for our final analysis (Fig. 1). Table 1 shows characteristics of the included studies. There were a total of 76,270 participants with a mean follow up duration of 11.7 months.

3.2 Primary Endpoint

3.2.1 Association of testosterone with incidence of CV events

All included studies evaluated the association of TT with incidence of CV events. Based on our analysis, TT was associated with an increased risk of CV events as a primary endpoint (adjusted HR=1.41, 95% CI = 1.18-1.70, p = 0.0002) (Fig. 2). Subgroup analyses by study type (RCTs versus observational studies) did not change the results of our main analysis (adjusted HR=1.40, 95% CI = 1.05-1.87, p = 0.02 and adjusted HR=1.54, 95% CI = 1.09-2.17, p = 0.01 respectively) (Fig. 2). Even after including only studies of patients who were prescribed testosterone for hypogonadism, there was still an association between TT and increased risk of CV events (adjusted HR=1.32, 95% CI = 1.09-1.59, p = 0.004) (Fig. 3a). Likewise, solely including studies with less than 12 weeks follow up did not affect our results (adjusted HR=1.32, 95% CI = 1.11-1.57, p = 0.002) (Fig. 3b). However, subgroup analyses by mode of testosterone administration (i.e. intramuscular (IM) vs. dermal/gel) led to loss of association between TT and incidence of CV events (adjusted HR = 0.77, 95% CI= 0.36-1.77, p = 0.51) (Fig. 3c). History of prior CV events is an important risk factor for future CV events, which could potentially act as a confounder. Meta-regression analysis showed that effect size of CV events in the studies did not significantly interact with the independent variable: percent patients' history of prior CV events (R squared was 0.26 with p=0.48) (Supplemental Fig. 1). Therefore, it seems that TT increases risk of cardiovascular events irrespective whether or not patients have underlying cardiovascular disease.

3.3 Secondary Endpoints

3.3.1 Association of testosterone with risk of Ischemic heart disease

A total of four studies (two observational and two RCTs- encompassing a total of 64,019 patients) evaluating association of TT with risk of ischemic heart disease were included. Our analysis showed that testosterone administration was associated with increased risk of ischemic heart disease (adjusted HR=1.51, 95% CI = 1.05-2.18, p = 0.02) (Fig. 4a).

3.3.2 Association of testosterone with all-cause mortality

A total of four studies (two RCTs and two observational- encompassing a total of 64,139 patients) evaluating association of TT with all-cause mortality were included. Our analysis showed that testosterone was associated with increased risk of all-cause mortality (adjusted HR=1.29, 95% CI = 1.03-1.62, p = 0.02) (Fig. 4b).

3.3.3 Association of testosterone with cerebrovascular events

There were a total of three studies (one RCTs and two observational - encompassing a total of 17,241 patients) assessing association of TT with incidence of cerebrovascular events. Based on our analysis, there was no clear association between testosterone administration and cerebrovascular events (adjusted HR=0.91, 95% CI = 0.66-1.25, p=0.54) (Fig. 4c).

Table 1. Baseline population characteristics of included studies

We included a total of 34 studies (31 RCTs and 3 observational) with a mean follow up of 11.7 months. Patient population consisted of 76,257 patients with mean age of 56. Half of the studies reported morning testosterone collection with the remaining studies being unclear on timing of sample collection

Studies	Year	N	Age (years)	Baseline documented health problems	Dose & method of administration	Initial T (nmol/L)	Patients with CVD	Study design	Mean FU (months)
Copenhagen [28]	1986	221	45+	Alcoholic cirrhosis	200 mg/8 h micronized T, PO	20	0%	RCT	4
Marin [29]	1993	21	55+	Obese, Low T	T gel 125 mg/day	15	NS	RCT	9
Morley [30]	1993	14	78	Low T	T enanthate 200 mg/2 weeks, IM	NS	NS	RCT	3
Hall [31]	1996	35	48	Rheumatoid arthritis	T enanthate 250 mg /month, IM	16	0%	RCT	9
Sih [32]	1997	32	63	Low T	T cypionate IM every 14 to 17 days	9	10%	RCT	12
English [33]	2000	50	62	CAD, Low T	Transdermal T 5 mg/day	13	100%	RCT	3
Snyder [34]	2001	108	65+	Low T	Transdermal T 6 mg/day	13	NS	RCT	36
Steidle [35]	2003	406	57	Low T	Transdermal T gel 50 mg/day	10	0%	RCT	3
Amory [36]	2004	48	74	Low T	T enanthate 200 mg/2 weeks, IM	10	NS	RCT	36
Kenny [37]	2004	11	79	Cognitive decline, Low T	T enanthate 200 mg/3 weeks, IM	14	30%	RCT	3
Svartberg [38]	2004	29	66	COPD	T enanthate 250 mg/month, IM	21	0%	RCT	7
Brockenbrough [39]	2006	40	56	Dialysis, Low T	Transdermal T gel 10 g/day	7	NS	RCT	6
Malkin [40]	2006	76	64	Heart failure	Transdermal T patch 5 mg/day	13	100%	RCT	12
Merza [41]	2006	39	40+	Low T	Transdermal T patch 5 mg/day	8	0%	RCT	6
Nair [42]	2006	62	60+	Low T	Transdermal T patch 5 mg/day	14	0%	RCT	24
Emmelot-Vonk [43]	2008	237	65	Low T	TU 160 mg/day, PO	14	30%	RCT	6
Svartberg [44]	2008	38	70	Low T	TU IM 1000mg 0,6,16,28&40	8	30%	RCT	12

Studies	Year	N	Age (years)	Baseline documented health problems	Dose & method of administration	Initial T (nmol/L)	Patients with CVD	Study design	Mean FU (months)
Caminiti [45]	2009	70	69	Heart failure, low T	TU1000ml IM for 0,6and 12 weeks	7	100%	RCT	3
Chapman [46]	2009	23	65+	Undernourished	TU 80 mg orally twice a day	19	0%	RCT	12
Legros [47]	2009	316	50+	Low T	TU 80, 160 and 240 mg orally per day	13	0%	RCT	12
Van staa [48]	2009	8,412	47	HTN, DM	oral undecanoate, IM enantate and implants	NS	0%	Obs	48
Aversa [49]	2010	50	55	MS, DM & Low T	TU IM 1,000 mg (every 12 weeks)	9	0%	RCT	24
Basaria [2]	2010	209	65+	Low T	Transdermal T gel 100 mg/day	8	0%	RCT	6
Iellamo [50]	2010	36	69	HTN, DM, HLD and heart failure	Transdermal T patch 5 mg/day	9 to 13	100%	RCT	6
Kalinchenko [51]	2010	184	50+	Low T	TU 1,000 mg IM for 0, 6, 18 and 30 weeks	7	NS	RCT	8
Srinivas-Shankar [20]	2010	274	65+	Low T	Transdermal T gel 50 mg/day	11	0%	RCT	6
Ho [52]	2011	120	40+	Low T	TU 1000 mg IM for 0, 6, 18, 30 and 42 weeks	9	10%	RCT	11
Jones [53]	2011	220	45+	Hypogonadal, DM, low T	T gel 60 mg/day	9	NS	RCT	12
Kauffman [54]	2011	274	55+	Hypogonadal, Low T	1.62% T gel 2.5 mg/day	10	NS	RCT	6
Hoyos [55]	2012	67	49	Obesity, OSA, Low T	TU 1000 mg IM at 0, 6 and 12 weeks	13	NS	RCT	5
Spitzer [56]	2012	140	55+	Erectile dysfunction, Low T	1% T gel 10 g/day	12	50%	RCT	4
Tan [19]	2013	120	55+	Low T	TU 1,000 mg IM q12 wks	9	80%	RCT	12
Vigen [1]	2013	8,709	63	Heart failure, DM, HTN, HLD & low T	Gel, patch, or injections	14	90%	Obs	12
Finkle [8]	2014	55,593	54	CAD, HTN, HLD	gel, micronized, and transdermal	NS	10%	Obs	12

**DM=Diabetes Mellitus; HTN= Hypertension; HLD=Hyperlipidemia; COPD= Chronic Obstructive Pulmonary Disease; CVD=Cardiovascular Disease; CAD= Coronary Artery Disease; FU=Follow up; RCT= Randomized Controlled Trial; Obs= Observational Study T=Testosterone; IM= Intramuscular; NS= Not specified*

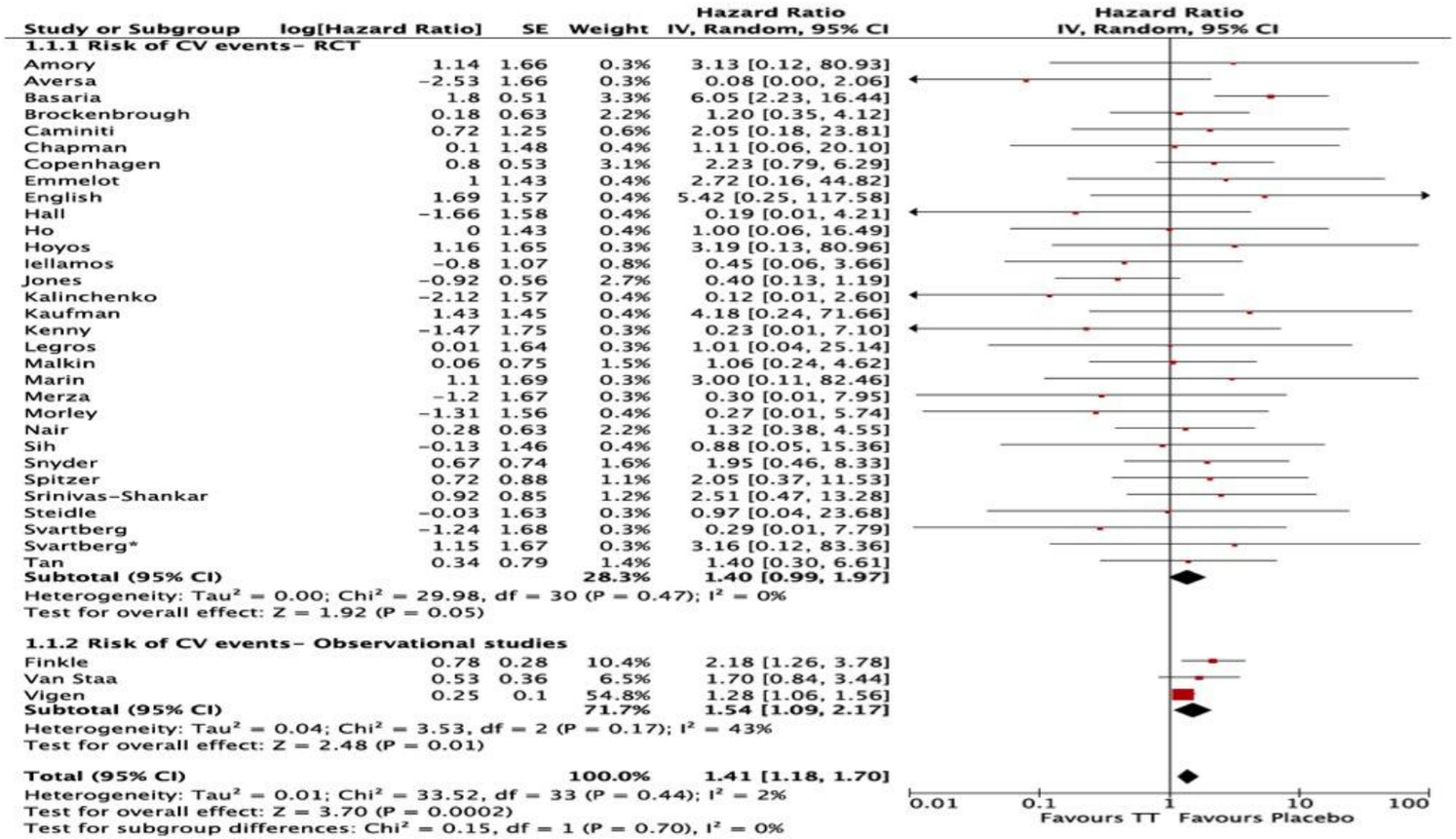
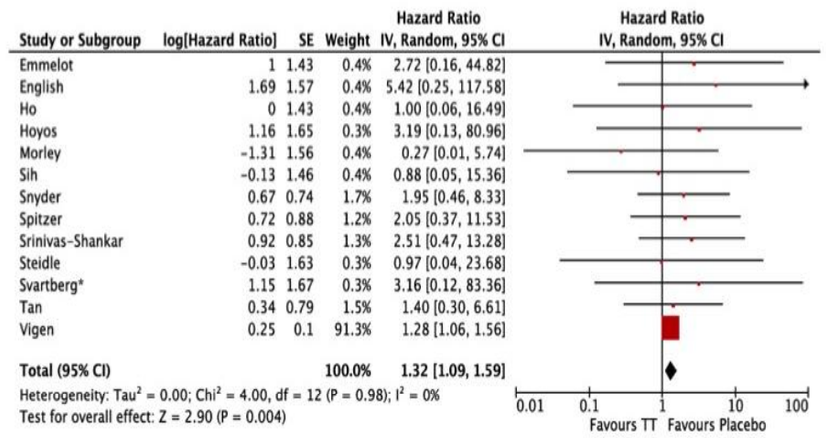


Fig. 2. Forest plot of included studies for our primary endpoint, association of testosterone therapy and incidence of CV events. Testosterone therapy was associated with an increased risk of CV events (adjusted HR=1.41, 95% CI = 1.10-1.67, p = 0.0001). Subgroup analyses by study type (RCTs versus observational studies) did not change the results of our main analysis (adjusted HR=1.40, 95% CI = 1.05-1.87, p = 0.02 and adjusted HR=1.54, 95% CI = 1.09-2.17, p = 0.01 respectively)

** CV= Cardiovascular; RCT= Randomized Controlled Trial; TT= Testosterone Therapy*

3a



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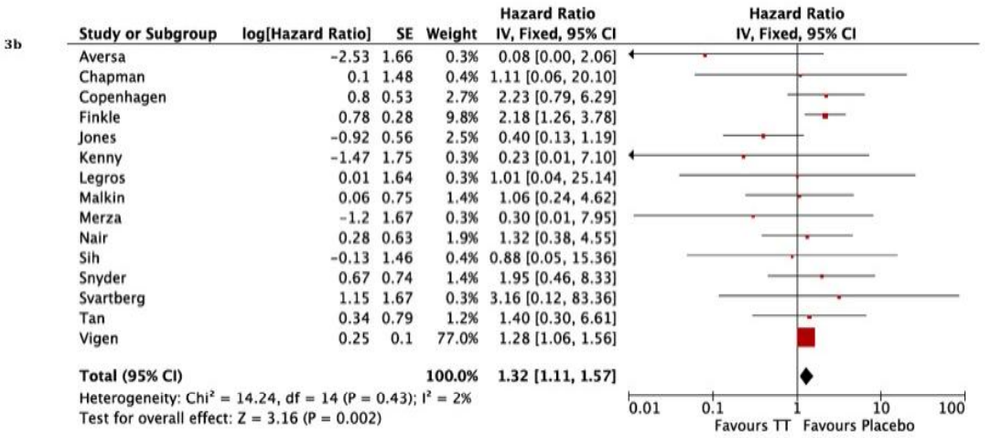

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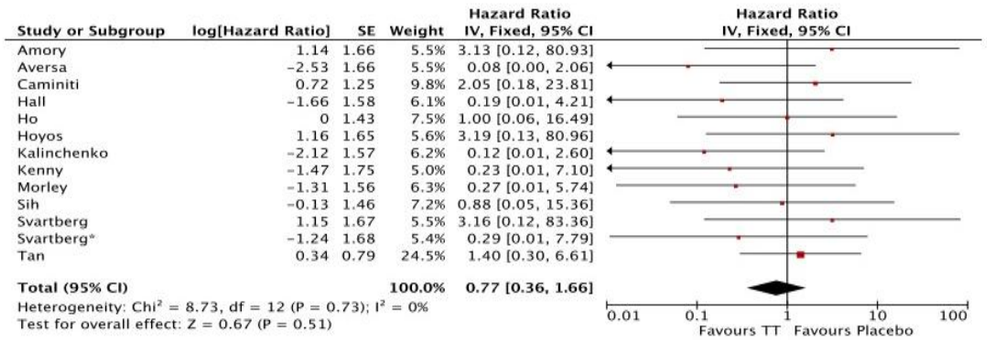

Fig. 3. Subgroup analysis for studies included in our primary endpoint. Even after including only studies of patients who were prescribed testosterone for hypogonadism, there was still an association between TT and increased risk of CV events (adjusted HR=1.32, 95% CI = 1.09-1.59, p = 0.004) (Fig. 3a). Likewise, solely including studies with less than 12 weeks follow up did not affect our results (adjusted HR=1.32, 95% CI = 1.11-1.57, p = 0.002) (Fig. 3b). However, subgroup analyses by mode of testosterone administration (i.e. intramuscular (IM) vs. dermal/gel) led to loss of association between TT and incidence of CV events (adjusted HR = 0.77, 95% CI= 0.36-1.77, p = 0.51) (Fig. 3c)

We did not have enough pooled data to perform subgroups analysis on our secondary endpoints. Similarly, we did not have enough pooled data to ascertain whether there was a dose-response relationship between the amount of testosterone administered and cardiovascular outcomes.

3.4 Publication Bias

There was no evidence of publication bias for the included studies that assessed cardiovascular related events by visual inspection of the funnel plot and by using the Egger test (p = 0.10) (Fig. 5).

4. DISCUSSION

Our systematic review and meta-analysis of studies assessing the association of TT with cardiovascular outcomes is the most comprehensive to date and the first to combine data from RCTs and observational studies. Pooled analysis of these data reveals that TT is associated with increased incidence of cardiovascular events, all-cause mortality, and ischemic heart disease but not cerebrovascular events.

Several possible explanations exist for our findings, which suggest increased cardiovascular risk. Even though endogenous testosterone may be protective, metabolites of exogenous testosterone rose with testosterone supplementation such as estrogens or dihydrotestosterone could mediate adverse cardiovascular outcomes [19,20]. Exogenous estrogens do not offer protection against cardiovascular events and dihydrotestosterone has been demonstrated in laboratory data to increase smooth muscle proliferation and expression of vascular cell adhesion molecule 1, which enhances monocyte activation in the endothelium and consequently accelerates atherosclerosis and its adverse events [21,22]. Furthermore, exogenous testosterone could mediate potentially deleterious effects through lowering high density lipoprotein (HDL) and raising hemoglobin, hematocrit and thromboxane levels all of which could contribute to clot formation and subsequent cardiovascular events and mortality. It is important to note that unlike other cardiovascular events, we did not find an increased risk of cerebrovascular events with TT; however, this could be related to the fact that only a small number of studies with a very low event rate evaluated association of TT with stroke or TIA (event rate was 43/3515 (1.22%) in the testosterone group versus 497/13947 (3.5%) in the control group) which limits generalizability of the obtained results.

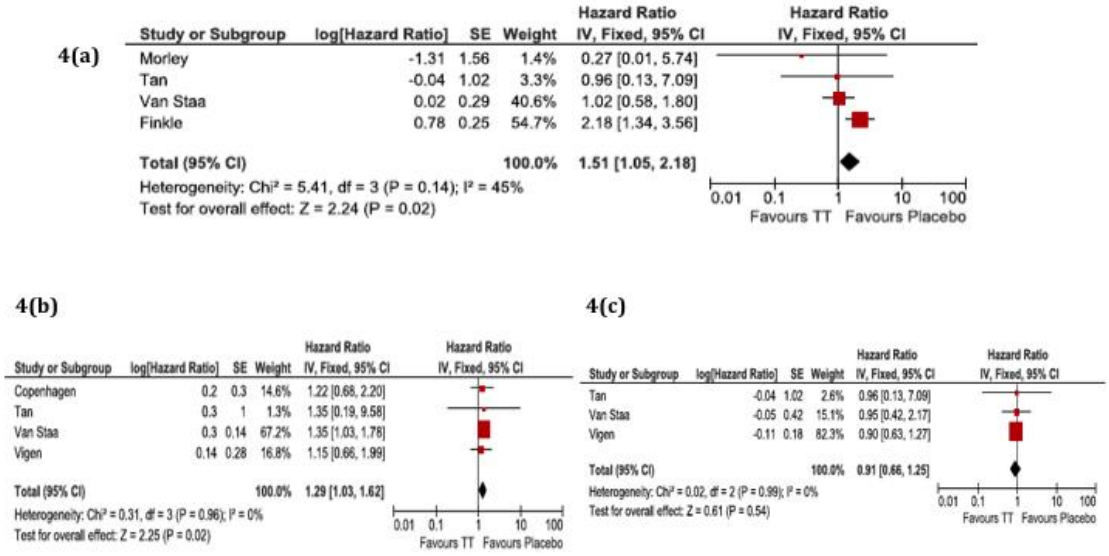

Fig. 4. Forest plot of included studies for our secondary endpoints: association of testosterone therapy and Ischemic heart disease (IHD), all-cause mortality and cerebrovascular events. As shown in the figure, testosterone therapy was associated with an increased risk of all-cause mortality, and IHD but was not associated with an increased risk of cerebrovascular events

** IHD= Ischemic Heart Disease; TT= Testosterone Therapy*

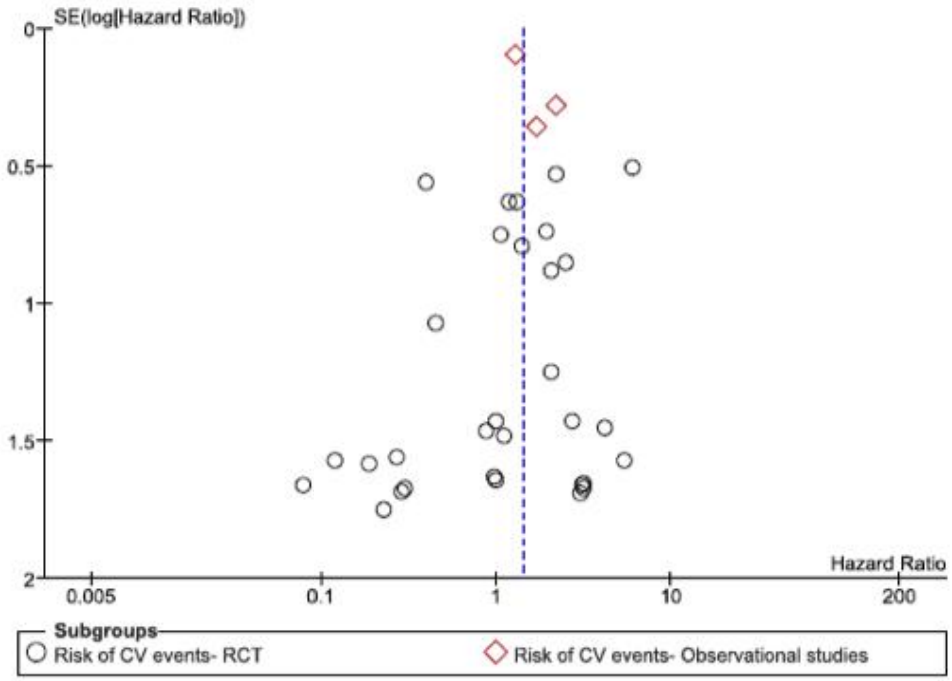

Fig. 5. Funnel plot for studies included in our primary comparison. Treatment effect (Log HR) is plotted on the horizontal axis against a measure of study size (standard error-SE). Based on visual inspection, the plot is symmetric with largest studies being near the average, and with small studies being spread on both sides of the average. Therefore, there is no evidence of publication bias. This is confirmed by using the Egger's asymmetry test (p=0.10)

** CV= Cardiovascular; RCT= Randomized Controlled Trial; SE= Standard error*

There are no reports on RCTs with the primary objective of evaluating the association of TT with cardiovascular outcomes. Most of the conducted trials were of small scale, with no clear assessment of cardiovascular risk profile, and were carried out in a relatively diseased population such as patients with alcoholic cirrhosis, chronic kidney disease, heart failure etc. However, there have been previously published meta-analyses evaluating risk of cardiovascular events in patients receiving testosterone therapy, the most rigorous of which are the ones conducted by Xu et al. [11] and Haddad et al. [23]. An initial meta-analysis by Haddad et al. of RCTs with a total population of 1,642 patients demonstrated no clear association between testosterone supplementation and cardiovascular events [23]. An updated meta-analysis by Xu el al. of RCTs only with a total population of 2,994 patients demonstrated an increased risk of cardiovascular events with testosterone replacement [11]. Our analysis of both RCTs and observational studies with a much larger number of participants (total population of 76,270 patients) and more comprehensive search including abstracts from various relevant professional societies adds to previous literature by demonstrating that TT is associated with an increased risk of cardiovascular related events independent of history of prior CV events. In addition, unlike prior meta-analyses, the increased power of our analysis allowed us to analyze the risks of additional endpoints and demonstrated a significantly increased risk of all-cause mortality and ischemic heart disease with testosterone supplementation as separate endpoints.

Another strength of our analysis is that it demonstrates that TT is associated with an increased risk of cardiovascular events even after limiting studies to those where testosterone was prescribed for hypogonadism, the primary indication for such therapy. However, one important thing to note is that the method of administration (intramuscular-IM versus transdermal/gel) led to loss of association between TT and incidence of CV events. One potential explanation could be that IM testosterone gives a saw-tooth concentration

profile with supra-physiological and sub-physiological testosterone levels over time whereas gels and intra-dermal preparations give a more even concentration over time [24] Therefore, it may not be surprising that we did not find an association between IM TT and CV events given the unpredictable physiological profile of such method of administration.

Recently the European Medicines Agency published a consensus statement reporting that the evidence for increased risk of MI with TT has been inconsistent. While it presents itself as an important document, one important point to keep in mind is that the main studies quoted as showing inconclusive evidence were solely evaluating risk of MI and/or stroke with TT [25-27]. Our definition of CV events as outlined before was more comprehensive as it was inclusive of heart failure, arrhythmia, and revascularization in addition to MI. Therefore, the conclusion from European Medicines Agency was made for the association between TT and MI which was unlike our definition for IHD or CVD.

Last, there has been a relative prominence of advertisements for testosterone supplementation. However, the results of our meta-analysis sheds light on the need for more effectiveness data and adequately powered RCTs prior to widespread assimilation of untested therapies into clinical practice.

5. LIMITATIONS

First, the major limitation is the lack of per-patient data, which precludes controlling for a number of cardiovascular risk factors and treatments, limiting the generalizability of the study. Despite best efforts to contact the authors; furthermore, most of these studies were small and lacking proper blinding. This becomes an issue when drawing conclusions due to limited ability to address confounding variables when evaluating the relationship between testosterone and cardiovascular events. Second, the narrow definition of hypogonadism (60-80 years old with low T <13 nmol/L) may lead to a bias favouring increased CV events given the age range use. Lastly, there was lack of information with regards to other cardiovascular risk factors (diabetes, peripheral vascular disease, coronary artery disease) and ongoing treatments (anti-hypertensive medications, anti-ischemic medications prescribed with TT, etc.) both of which limit a more rigorous interpretation of existing data.

6. CONCLUSIONS

In summary, TT among men may be associated with increased risk of adverse cardiovascular events, all-cause mortality and ischemic heart disease. However, our findings need to be confirmed in an adequately powered RCT. In the meantime, caution needs to be exercised when prescribing such a therapy to ensure that the associated health benefits outweigh any potential increased risks.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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APPENDIX

Appendix Table 1. Studies rated according the Newcastle-Ottawa Scale (NOS) used for assesing non-randomized observational studies. This scale identifies high quality choices with a star. A maximum of one star for each item within the Selection and Exposure/Outcome categories and a maximum of two stars for Comparability. Based on this scale all of the included studies scored high in terms of selection and outcome assesment

Study	Selection	Comparability	Outcome
Finkle	★★★	★★	★★★
Vigen	★★★★	★★	★★★
Van Staa	★★★★	★★	★★★

Appendix Table 2. Quality assessment of the selected placebo-controlled RCTs of the effects of testosterone therapy on cardiovascular-related events

Author and publication year	JADDAD score
Amory(27)	4
Aversa(29)	2
Basaria(30)	2
Brockenbrough(31)	2
Caminiti(32)	2
Chapman(34)	4
Copenhagen(35)	4
Emmelot-Vonk(36)	2
English(37)	2
Hall(38)	4
Ho(39)	2
Hoyos(40)	2
Iellamo	4
Jones(42)	4
Kalinchenko(43)	2
Kauffman(44)	3
Kenny(45)	2
Legros(47)	2
Malkin(48)	2
Marin(49)	4
Merza(51)	4
Morley	4
Nair(52)	4
Sih(54)	3
Snyder(55)	4
Spitzer(56)	3
Srinivas-Shankar(57)	4

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