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Cardiovascular Morbidity and Mortality in Men — Findings From a Meta-analysis on the Time-related Measure of Risk of Exogenous Testosterone

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ABSTRACT

Background: In the context of established male hypogonadism, testosterone therapy (TTh) has been employed to regain physiologic levels of circulating testosterone and improve sexual function and overall quality of life.

Aim: To assess the risk of cardiovascular disease and mortality as time-dependent outcomes in treated vs TTh untreated hypogonadal men.

Methods: A meta-analysis using weighted time-related measure of risk (hazard ratios (HRs)) for each of the outcome for all included studies was performed. Studies investigating male adults (≥18 years old) diagnosed with hypogonadism and divided into 2 arms (a treatment arm [any TTh] and a control arm [observation or placebo]) and assessing the risk of death and/or cardiovascular events were included. Single arm, non–comparative studies were excluded as well as studies that did not report the HRs for the chosen outcomes. This systemic review was registered on PROSPERO (CRD42022301592) and performed according to MOOSE and PRISMA guidelines.

Outcomes: Overall mortality and cardiovascular events of any type.

Results: Overall, 10 studies were included in the meta-analysis, involving 179,631 hypogonadal men. Hypogonadal men treated with TTh were found to be at lower mortality risk from all causes relative to the control (observation or palcebo) arm (HR: 0.70; 95% Confidence Interval [CI]: 0.54–0.90; $P < .01$), whilst any unfavorable effect of TTh in hypogonadal men in terms of cardiovascular events compared to untreated/observed hypogonadal men was found (HR: 0.98; 95% CI 0.73–1.33; $P = .89$).

Clinical implications: TTh in hypogonadal men might play a role in reducing the overall risk of death without increasing cardiovascular events risk.

Strengths & Limitation: Main limitations are represented by the high heterogeneity among the studies in terms of included population, definition for hypogonadism, type of TTh, definition of cardio-vascular event used, and the length of follow-up.

Conclusion: According to time-related measures of risk only, an increased risk of long-term morbidity and early mortality for untreated hypogonadal men was depicted, further outlining the clinical importance and safety of TTh in true hypogonadal men, with the urgent need of collecting long-term follow-up data. **Fallara G, Pozzi E, Belladelli F, et al. Cardiovascular Morbidity and Mortality in Men — Findings From a Meta-analysis on the Time-related Measure of Risk of Exogenous Testosterone. J Sex Med 2022;XX:XXX–XXX.**

Keywords: Testosterone; Hypogonadism; Mortality; Cardiovascular; EAU guidelines

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INTRODUCTION

Published studies showed that primary hypogonadal men are at increased risk of cardiovascular events, newly-diagnosed cancers and greater mortality rates, thus supporting the concept of the need to achieve testosterone levels within physiological ranges to prevents potential consequences of hypogonadism.[1−7] However, data are not always unidirectional, as the findings of the UK Biobank prospective cohort study of community-dwelling men aged 40−69 years old, followed for 11 years, showed that lower serum testosterone were independently associated with higher all-cause and cancer-related, but not cardiovascular diseases-related, mortality in middle-aged to older men.[8] Rationally, the same study depicted that lower serum sex hormone-binding globulin (SHBG) is independently associated with lower all-cause, cardiovascular diseases-related, and cancer-related mortality.[8]

Overall, the goal of testosterone therapy (TTh) is ideally to establish and maintain secondary sexual characteristics, sexual function, body composition, quality of life and eventually ameliorate overall men's health status by preventing cardiometabolic disorders, oncological malignancies and decreasing the risk of death, at least in some subpopulations.[9−15] In this context, the effects of exogenous testosterone are still scantly analyzed and unknown, as it exerts a wide range of effects on various organs. Data regarding the long-term safety of TTh on overall men's health, cancer development, and cardiovascular diseases onset remained uncertain because of the lack of adequately powered trials investigating the long-term impact of such a therapy in hypogonadal men. Early suggestion of potential cardiovascular risks and increase mortality associated with the use of exogenous testosterone came from the prematurely terminated Testosterone in Older Men with Mobility Limitations (TOM) trial.[16] Several meta-analyses investigated the role of TTh in promoting cardiovascular events and mortality in hypogonadal men, with conflicting findings. Some reports suggested an increase in cardiovascular risk,[17,18] whilst others showed no effect.[19−21] Of note, most of those studies are based on under-powered small retrospective investigations or prospective randomized and non−randomized trials, where mortality and cardiovascular events have been analyzed only as secondary outcomes. In addition, in most of the published meta-analyses these 2 outcomes were analyzed as non−time related events, that is, by the use of relative-risk or odds-ratio, with potential undisclosed relevant biases.

Thus, the aim of the current systematic review and meta-analysis is to summarize available evidence of the effect of TTh (whether injection, oral, topical) on the risk of cardiovascular events and mortality as compared with placebo/observation in truly hypogonadal men by the use of time-related measure of risk (ie, hazard ratios [HRs]).

MATERIALS AND METHODS

Search Strategies and Selection Criteria

We conducted a systematic review and meta-analysis of all published randomized and non−randomized trials that compared hypogonadal men treated with TTh (any treatment modality) with hypogonadal men treated with either placebo or only observed.

PubMed and Embase were queried for studies indexed up to December 18, 2021. The following keywords were used: hypogonadism, cardiovascular, metabolic syndrome, hypertension, mortality, survival. Studies dealing with hypogonadism as a result of castration/anti−androgens therapies in prostate cancer were excluded since this topic was out of the scope of the current meta-analysis. Titles and abstracts of manuscripts were used to screen for initial study inclusion. Full text review was performed when the abstract was not sufficient to determine study inclusion. Non−English studies, review articles, commentaries, editorials, and articles that did not undergo peer-review were excluded. Bibliographies of included studies were hand-searched for completeness. The review was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analyses Of Observational Studies in Epidemiology (MOOSE) guidelines.[22−24]

Four authors completed the study selection independently (E. P., F.B., C.C., and G.F.), according to PRISMA requirements. Potential disagreements were resolved by consensus with all co-authors. The risk of bias for randomized control trials (RCTS) was determined using The Cochrane Collaboration's tool, which assesses selection bias, performance bias, detection bias, attrition bias, reporting bias, and other sources of bias.[25] The risk of bias for non−randomized observational studies was determined using the Newcastle and Ottawa scale.[26] The protocol of this study is published on the website of the University of York (Centre for Reviews and Dissemination - CRD42022301592).

Inclusion, Exclusion Criteria, Outcome Definition, and Variable Extraction

Studies investigating adult males (≥18 years old) diagnosed with hypogonadism were included in the meta-analysis. For the specific aims of this analysis, hypogonadism was defined as serum testosterone deficiency (serum total testosterone <12 nmol/L) or a filled prescription for TTh and/or the presence of testosterone deficiency-related symptoms, according to the different definitions used in literature. The included studies must have had 2 arms: a treatment arm (any TTh) and a control arm based on observation or placebo. Overall mortality and cardiovascular events of any type (eg, newly diagnosed hypertension, heart attack, heart failure, stroke, death associated with cardio-vascular reasons) must have been the primary, secondary or main outcomes of the studies. Single arm, non−comparative studies were excluded as well as studies that did not report the time-related measure of risk (ie, HRs) for the chosen outcomes.

For each study data were extracted according to a pre-established form including year of publication, authors' names, study design, number of included subjects, number of treated and untreated hypogonadal men, type of TTh, number of cardiovascular events in treated and untreated hypogonadal men, type of

cardiovascular event, HRs and 95% confidence intervals (CI) for cardiovascular events in treated vs untreated hypogonadal men, number of death events in treated and untreated hypogonadal men, HRs and 95% CI for death in treated vs untreated hypogonadal men, mean age for both groups (years), and median follow-up (months/years). The adjusted HR for possible confounders was used when available.

Statistical Analysis

We tested the hypotheses that TTh might increase the risk of death from all causes and the risk of cardiovascular events as compared with control or placebo in hypogonadal men. A meta-analysis using weighted HRs for each of the outcome was used. A sub-analysis investigating only hypogonadal men with supposed normalized total testosterone levels under treatment vs untreated hypogonadal men was also performed. Forrest plots were drawn to show pooled results. We relied on random effects model, given the heterogeneity in the included studies of (i) the population included, (ii) the definition used for hypogonadism, and (iii) the variability of applied TTh in terms of doses, route of administration and duration of treatment. The between-study heterogeneity was assessed with the I^2 statistic, with I^2 values of >50% representing substantial heterogeneity, and with Tau^2, estimating the extent of variation among the effects. To estimate possible publication bias funnel plots as well as Eggers and Beggs-Mazumdar tests were used. Statistical analyses were performed using the RStudio graphical interface v.0.98 for R software environment v.3.0.2 (http://www.r-project.org) with Metafor package.[27]

RESULTS

Study Selection

Figure 1 shows the flow of studies through the screening process (PRISMA flow chart). Overall, 1,350 reports were evaluated blindly by 4 reviewers, of which 10 were eventually considered for the meta-analysis after being screened according to inclusion and exclusion criteria.

From the 10 included studies, 179,631 hypogonadal men were eventually included in the meta-analysis, of which 89,515 have received TTh and 90,116 were either observed or treated with placebo. Weighted mean age was 64.2 vs 62.6 years for treated vs untreated men, respectively (P = .051). Two studies reported separate data for hypogonadal men treated with TTh who did recover circulating total testosterone levels within normal range compared to those who did not.[2,28]

Effects of Testosterone Therapy on Cardiovascular Events

Table 1 summarizes the general characteristics of the selected studies.[1,2,16,28–31] Overall, 177,644 men were analyzed in the context of hypogonadism and cardiovascular diseases. The earliest study was published in 2010 and the latest in 2019. One study was a randomized control study, the others were observational retrospective registry-based studies. Of the 7 studies included, 5 investigated men submitted to any form of TTh,[1,2,28,29,31] one with transdermal testosterone only,[16] and one with transdermal and intra-muscular formulations only.[30]

Pooled Results

Seven studies investigated the association between cardiovascular events and TTh.[1,2,16,28–31] When considering data on TTh regardless of the recovery of normal testosterone levels after treatment, the pooled HR was 0.98 (95%CI 0.73−1.33; P = .89), thus not showing any unfavorable effect of TTh in hypogonadal men in terms of cardiovascular events compared to untreated/observed hypogonadal men (Figure 2*A*). Heterogeneity between studies was high, since I^2 was 93.2% and Tau^2 0.15. Comparable results were obtained when performing the same analysis within the sub-population of patients who were supposed to recover testosterone levels within the normal ranges (pooled HR was 1.03;95%CI 0.68−1.6; P = .87) (Figure 2*B*). Heterogeneity between the studies was high, since I^2 was 96.2% and Tau^2 0.52, respectively.

Study Quality and Risk of Bias

Visually, the Funnel plot suggested a possible low risk of publication bias, given the high heterogeneity of included studies (*Supplementary Figure 1 A*); however, the Egger test and Beggs-Mazumdar tests for publication bias were not significant (P = .55 and P = .99, respectively). The Cochrane Collaboration's tool and the Newcastle and Ottawa scale suggested to moderate risk of bias (*Supplementary Table 1 and 2*).

Effects of Testosterone Therapy on Overall Mortality

Table 2 summarizes the general characteristics of the selected studies.[1,2,28,30,32–34] Overall, 138,353 men were analyzed in the context of hypogonadism and all-cause mortality. The earliest study was published in 2012 and the latest in 2019. All studies were observational and retrospective. Of those, 1 was a multicenter retrospective study,[33] 1 a single-center study,[32] and 5 were registry-based studies.[1,2,28,30,34] One study investigated the effect of intramuscular injection of testosterone only,[33] 2 of intramuscular injections and transdermal administration of testosterone,[30,32] whilst the other 4 taken into consideration TTh of any form.[1,2,28,34]

Pooled Results

Overall, 7 studies investigated the association between all-cause mortality and TTh. Regardless of the recovery of total testosterone levels within physiological ranges after treatment, pooled HR was 0.70 (95% CI: 0.54−0.90; $P < .01$) showing a protective effect of TTh in treated vs untreated/observed

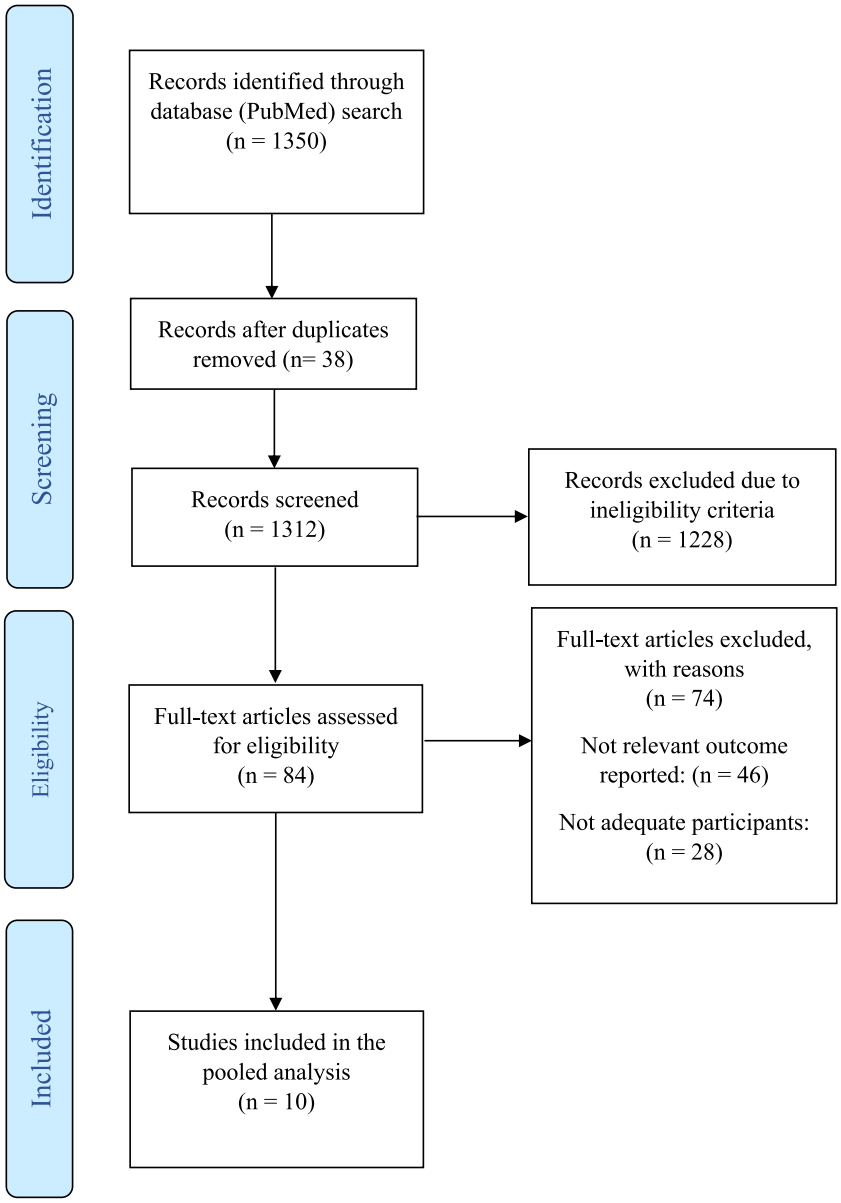

Figure 1. Prisma flow chart — Study selection with inclusion and exclusion criteria of reviewed studies.

hypogonadal men in terms of all-cause mortality (Figure 3*A*). Heterogeneity among studies was high (namely, I^2 was 97.5% and Tau^2 0.13, respectively). When the same analysis was performed considering only the sub-population of men who reached normal total testosterone levels after TTh, the pooled HR was 0.65 (95% CI: 0.44−0.97; $P < .01$), thus showing the same protective role of testosterone in terms of all-cause mortality (*Figure 3B*). Heterogeneity among studies was high, with I^2 was 96.7% and Tau^2 0.15, respectively.

Study Quality and Risk of Bias

Visually, the Funnel plot suggested a low risk of publication bias, given the high heterogeneity of included studies (*Supplementary Figure 1 B*), but the Egger test and Beggs-Mazumdar tests for publication bias were not significant ($P = .77$ and $P = .47$, respectively). The Newcastle and Ottawa scale suggested moderate risk of bias (*Supplementary Table 1 and 2*).

DISCUSSION

Much has been said about the association between circulating testosterone and overall men's health. Thereof, we focused our attention on the specific target of exogenous testosterone as a potential key player of men's health (namely, cardio-vascular morbidity and overall mortality) considering those studies which had applied only time-related measure of risk.

Table 1. Characteristics of the studies included in the pooled analysis for cardiovascular events after testosterone therapy

First author	Y of publication	Type of study	N. of men included	Population included	Hypogonadal status definition	Age (mean ± sd)	Type of treatment	Outcome	N. of events	Length of follow-up
Basaria S et al[16]	2010	Randomized control trial	Overall: 209 Treated: 106 Untreated: 103	Hypogonadal men 65 y of age or older with limitations in mobility	Total serum testosterone level between 3.5 and 12.1 nmol/L or free testosterone ≤173 pmol/L	74 ± 5.5	10 g of a transdermal gel containing either placebo or 100 mg of testosterone	MedDRA cardiac events (ie, angina cardiac arrest myocardial infarction palpitation), angioplasty, coronary-artery bypass surgery, peripheral edema, elevated blood pressure, arrhythmias, electrocardiographic changes, stroke, syncope	Overall: 28 Treated: 23 Untreated: 5	Overall: 6 mo
Vigen R et al[30]	2013	Retrospective registry based	Overall:8,709 Treated: 1,223 Untreated: 7,486	Hypogonadal men who underwent coronary angiography any age	Total serum testosterone levels <300 ng/dL	63.4 ± 8.8	Intra-muscolar and transdermal	Myocardial infarction, stroke	Overall: 864 Treated: 443 Untreated: 420	Treated: N/A Untreated: N/A Average follow-up: 27.5
Sharma R et al *,[2]	2015	Retrospective registry based	Overall: 57,309 Treated: 43,931 Untreated: 13,378	Hypogonadal men any age	First tested total serum testosterone level lower than the respective laboratory NLRR.	60.3	Any	Myocardial infarction, stroke	N/A	Treated: 6.2 (3.3), y[†] Untreated: 4.7 (3.1), y[†]
Baillargeon J et al[29]	2014	Retrospective registry based	Overall: 25,420 Treated: 6,355 Untreated: 19,065	Medicare beneficiaries 66 y or older who were treated with intramuscular TTh matched to non −users 66 y or older	TTh use according to electronic medical records	N/A	Any	Myocardial infarction	Overall: 359 Treated: 115 Untreated: 244	1495 d
Cheetham C et al[1]	2017	Retrospective registry based	Overall: 44,335 Treated: 88,08 Untreated: 35,527	Hypogonadal men 40 y of age or older	A coded diagnosis (ICD code 257.2, 257.8, and 257.9) and/ or a total serum testosterone level ≤300 ng/dL	59.5	Any	Myocardial infarction, coronary revascularization, unstable angina, stroke, transient ischemic attack, and sudden cardiac death	Overall: 4,952 Treated: 864 Untreated: 4,088	Treated: 3.2 (1.7 −6.6), y[‡] Untreated: 4.2 (2.1 −7.8), y[‡]
Loo SY et al[31]	2019	Retrospective registry based	Overall: 15,401 Treated: 2,237 Untreated: 13,164	Men aged 45 y of age or older	Total serum testosterone level lower than the respective laboratory NLRR or a coded diagnosis in electronic medical registry	60.4 ± 9.6	Any	Ischemic stroke/ transient ischemic attack and myocardial infarction	Overall: 733 Treated: 110 Untreated: 623	4.6 y
Oni OA et al *,[28]	2019	Retrospective registry based	Overall:1,560 Treated: 755 Untreated: 173	Hypogonadal men with history of myocardial infarction before hypogonadism diagnosis any age	Total serum testosterone level lower than the respective laboratory NLRR or a coded diagnosis in electronic medical registry	64.7 (median)	Any	Myocardial infarction	N/A	Treated: 4.0 (3.4), y[†] Untreated: 3.3 (3.1), y[†]

Legend: T2DM = type 2 diabetes mellitus; PDE5i = Phosphodiesterase type 5 inhibitors; NLRR = normal laboratory reference range; TTh = testosterone therapy.
*Studies including patients with normalised total testosterone levels after androgen replacement therapy and with non−normalised total testosterone levels after androgen replacement therapy.
[†]Mean (standard deviation).
[‡]Median (interquartile range).

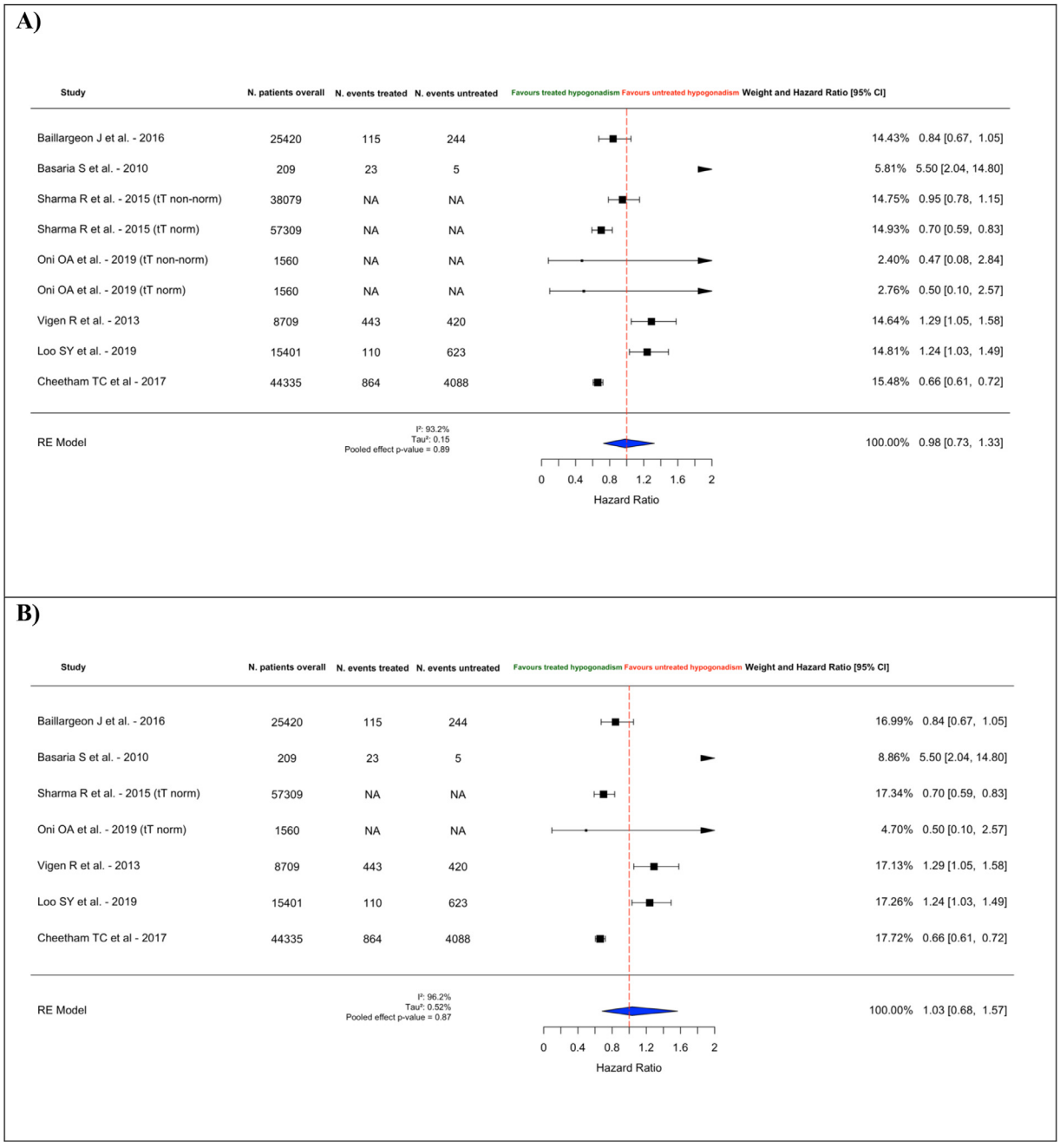

Figure 2. Forrest plots assessing the risk of cardiovascular events in hypogonadal men treated with testosterone therapy vs hypogonadal men treated with placebo or observed. (A) pooled analysis including all studies; (B) pooled analysis excluding those groups with non–normalization of total testosterone after testosterone therapy.

Novel findings of this meta-analysis showed that in hypogonadal males the use of TTh to recover physiological levels of circulating hormone is not associated with an increased risk of cardiovascular diseases as a time-dependent outcome. Likewise, TTh was not associated with a greater mortality risk in hypogonadal men, where TTh might instead be even protective toward the risk of death compared to the condition of untreated hypogonadism.

Apart from relief of sexual symptoms and improvement of overall quality of life, one of the reasons for which clinicians are prone to suggest TTh in hypogonadal men relies on a number of epidemiologic observations concerning the association between hypogonadism and the risk of cardiovascular events and mortality, and thus on the accrued hypothesis of a protective role of testosterone within physiological values toward these outcomes.[35,36] Retrospective and prospective interventional or observational studies have so far provided conflicting results and most of the published meta-analyses showed no or even a protective effect of TTh on cardiovascular events. However, further

Table 2. Characteristics of the studies included in the pooled analysis for overall mortality after testosterone therapy

First Author	Y of publication	Type of study	N. of men included	Population included	Hypogonadal status definition	Age	Type of treatment	Outcome	N. of events	Length of follow-up
Cheetham C et al[1]	2017	Retrospective registry based	Overall: 44,335 Treated: 88,08 Untreated: 35,527	Hypogonadal men 40 y of age or older	A coded diagnosis (ICD code 257.2, 257.8, and 257.9) and/or a total serum testosterone level ≤300 ng/dL	59.5	Any	All-cause mortality and cardiovascular diseases	Overall: 4952 Treated: 864 Untreated: 4088	Treated: 3.2 (1.7–6.6), y‡ Untreated: 4.2 (2.1–7.8), y‡
Hackett G et al[33]	2016	Retrospective multi-center	Overall:199 Treated: 97 Untreated: 102	Hypogonadal men with type 2 diabetes mellitus stratified for PD5i use any age	total testosterone ≤12 nmol/l or free testosterone ≤0.25 nmol/l	65.3 ± 11.7	Intramuscular injection	Mortality	Overall: 68 Treated: 6 Untreated: 62	Treated: 3.72 (1.07), y† Untreated: 3.6 (1.2), y†
Vigen R et al[30]	2013	Retrospective registry based	Overall:8,709 Treated: 1,223 Untreated: 7,486	Hypogonadal men who underwent coronary angiography any age	Total serum testosterone levels <300 ng/dL	63.4 ± 8.8	Intramuscular injection and transdermal administration	All-cause mortality and cardiovascular diseases	Overall: 1429 Treated: 748 Untreated: 681	Treated: N/A Untreated: N/A Average follow-up: 27.5
Oni OA et al*,[28]	2019	Retrospective registry based	Overall:1,560 Treated: 755 Untreated: 173	Hypogonadal men with history of myocardial infarction before hypogonadism diagnosis any age	Total serum testosterone level lower than the respective laboratory NLRR or a coded diagnosis in electronic medical registry	64.7 (median)	Any	All-cause mortality and cardiovascular diseases	N/A	Treated: 4.0 (3.4), y† Untreated: 3.3 (3.1), y†
Sharma R et al*,[2]	2015	Retrospective registry based	Overall: 57,309 Treated: 43,931 Untreated: 13,378	Hypogonadal men any age	First tested total serum testosterone level lower than the respective laboratory NLRR.	60.3	Any	All-cause mortality and cardiovascular diseases	N/A	Treated: 6.2 (3.3), y† Untreated: 4.7 (3.1), y†
Eisenberg ML et al[32]	2015	Retrospcetive single-center	Overall: 509 Treated: 284 Untreated: 225	Hypogonadal men any age	N/A	54	Intramuscular injection and transdermal administration	All-cause mortality and cardiovascular diseases	Overall: 28 Treated: 9 Untreated: 19	Treated: 10.31(3.43), y† Untreated: 10.31 (3.25), y†
Shores M. M. et al.[34]	2012	Retrospective registry based	Overall: 1031 Treated: 398 Untreated: 633	Hypogonadal men any age	Total serum testosterone level ≤250 ng/dl (8.7 nmol/liter)	62.1 ± 10.6	Any	All-cause mortality	Overall: 172 Treated: 41 Untreated: 131	Treated: 38.0 (15.8), mo† Untreated: 42.8 (13.3), mo†

Legend: NLRR = normal laboratory reference range; TTh = testosterone therapy.
*Studies including patients with normalised total testosterone levels after androgen replacement therapy and with non–normalised total testosterone levels after androgen replacement therapy
†Mean (standard deviation).
‡Median (interquartile range).

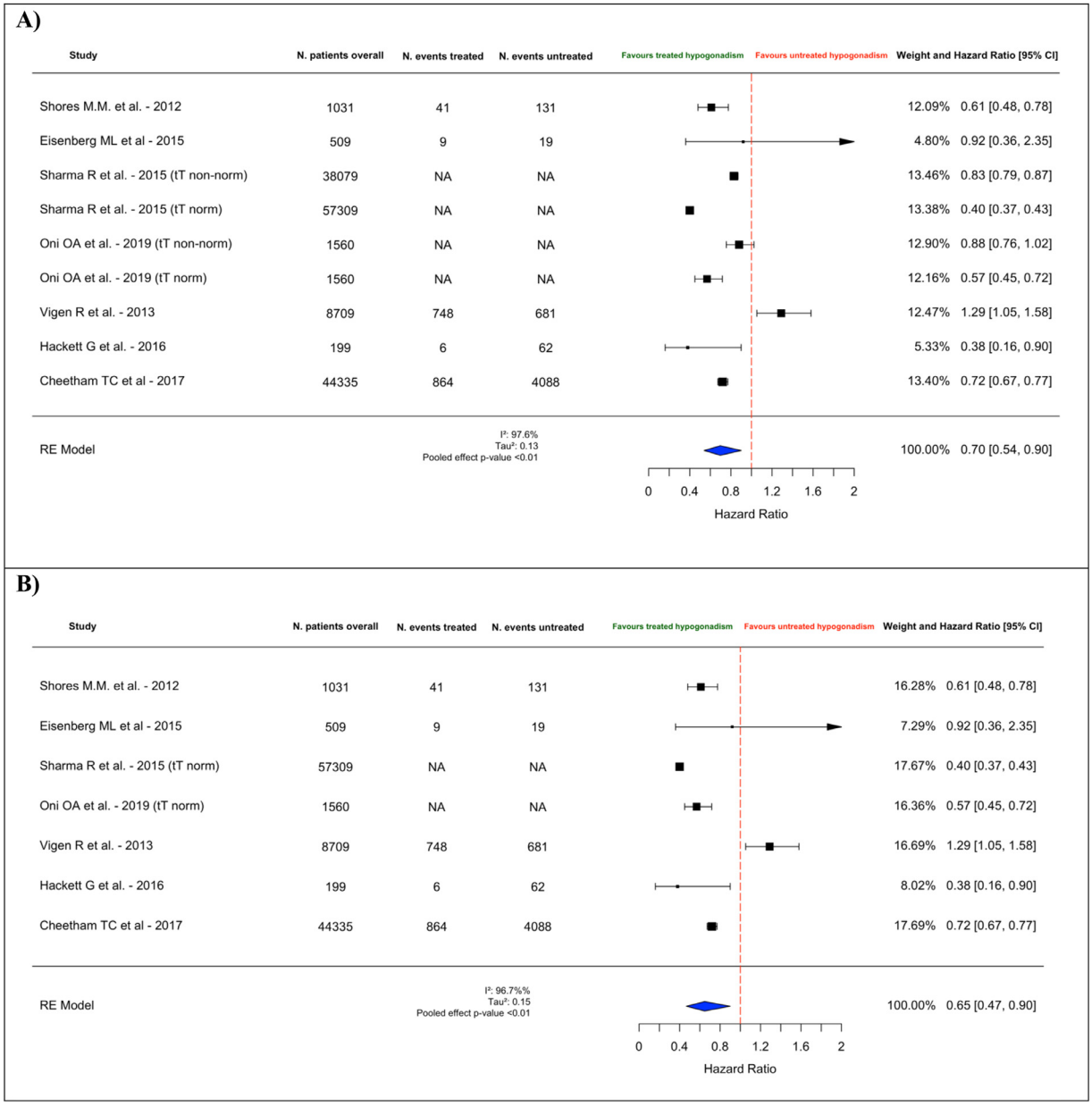

Figure 3. Forrest plots assessing the risk of death in hypogonadal men treated with testosterone therapy vs hypogonadal men treated with placebo or observed. (A) pooled analysis including all studies; (B) pooled analysis excluding those groups with non–normalization of total testosterone after testosterone therapy

considerations are needed. First, the compensation of an endogenous hormonal deficit by an exogenous treatment (eg, TTh in the case of hypogonadism), might conversely produce a detrimental effect (and that was not the observed case). Second epidemiologic associations based on observational/interventional studies do not always mean causative association. The current systematic review and meta-analysis did not support the hypothesis of a detrimental effects of TTh on cardiovascular events and mortality, when hypogonadism is properly diagnosed and TTh correctly performed, whilst a possible benefit can be attributed to TTh in hypogonadal men in terms of overall mortality at long-term follow-up.

More specifically, in the oldest report included in this meta-analysis, a RCT by Basaria et al., an increased risk of myocardial infarction, sudden death, need for coronary angioplasty or coronary artery bypass surgery, and stroke was observed in hypogonadal men treated with topical testosterone gel compared to hypogonadal men treated with placebo gel.[16] Main limitations of this study were the relatively small sample size and the relatively low number of events, so that caution should be used in interpreting its results. In addition, improper over supplementation of testosterone has been advocate in the same study as a possible cause of the reported higher rate of cardiovascular events.[37] Similar results were observed by Vigen et al. and Loo et al. in 2

retrospective population registry-based studies investigating the effects of TTh, the former performed among American male veterans and the latter among men aged 45 years or older in the UK.[30,31] The study from Vigen et al., including 8709 men with low testosterone levels, evaluated all-cause mortality; of 1223 patients receiving TTh, 67 (5.4%) died, 23 (1.8%) had cardiovascular diseases and 33 (2.7%) had strokes, respectively.[30] The Authors concluded that TTh was associated with increased risk of health-associated adverse outcomes. Limitations of these population studies included the relevant fact that hypogonadism status was defined only based on 1 total testosterone measurement, for which adherence to correct measurement practice were not even investigated. Moreover, exposure to TTh relied on prescriptions issued by general practitioners, and the Authors were not able to determine actual patients' compliance to their prescribed treatments. In addition, the manuscript was amended twice because of errors in data reporting and statistical methodology.[38] Consequently, concerns have been raised regarding this publication, and then its results should be critically considered. Of studies included in this meta-analysis, the study from Cheetham et al. was the only one to indicate that TTh had a protective effect toward major cardiovascular events in hypogonadal men.[1] Of note, this was a population registry-based study including more than 40,000 men diagnosed with hypogonadism (as defined for serum total testosterone levels <300 ng/dL), older than 40 years and treated with different TTh modalities (ie, injections, orally or topically). The main limitation of this study was that hypogonadal men have been defined as having at least 1 low testosterone measurement (only 6% had total testosterone levels measured multiple times), without considering symptoms, thus failing to meet the criteria set for LOH by many scientific societies.[9−12,39−42] The article from Sharma et al. investigating 83,010 hypogonadal American male veterans, found no association between TTh and cardiovascular events for treated men without recovery of normal total testosterone levels; conversely, a protective action emerged in men who underwent TTh reaching a normal testosterone level as compared with untreated hypogonadal subjects.[2] In addition, the Authors found that in men without a history of previous cardiovascular diseases and who presented with low total testosterone levels, TTh was associated with a decrease in all-cause mortality throughout the long-term follow-up both when normal total testosterone levels were eventually achieved or not.[2] Finally, both Oni et al. and Baillargeon et al. found no association between TTh and cardiovascular events.[28,29] Of note, Oni et al. assessed the effect of TTh in a population of patients with a history of myocardial infarction. The study also investigated the incidence of mortality from all-cause in the same cohort of 1,470 men and concluded that in this selected sub-subset of men, the recovery of normal serum total testosterone levels with TTh was associated with overall decreased all-cause mortality as compared with those who did not recover total testosterone levels within physiological ranges and the untreated group.[28] Likewise, Hackett et al. in a cohort of 857 men with T2DM and low total testosterone levels, found that TTh was independently associated with reduced mortality.[33] In the registry-based study from Shores et al. it was also observed a protective action of TTh in 1,031 hypogonadal men.[34] In line with previous findings, Eisenberg et al. investigated whether TTh altered the risk of all-cause mortality in 509 hypogonadal men; after adjusting for age and year of evaluation, there was no significant difference in the mortality risk based on TTh compared to those patients who have not been treated.[2] Given the observational design of most of these studies, no clear definition of hypogonadism was applied and the compliance to therapy was not actually investigated. Although most of the included analyses accounted for numerous potential confounders, including lifestyle habits and time-varying confounders, further confounding is still possible, given the observational nature of these studies.

In conclusion, the current meta-analysis, which has only considered time-related measures of risk, did not find an association between TTh and major cardiovascular events while a protective role of TTh emerged for overall mortality, when compared to hypogonadal men who did not receive TTh. These results are consistent with most of the current literature. A meta-analysis taking into consideration 75 different placebo-controlled randomized trials observed no increase in cardiovascular risk in men with metabolic disorders.[21] Fernández-Balsells et al., in a meta-analysis including randomized and nonrandomized studies, observed no differences in all-cause mortality, in the incidence of coronary bypass surgery, or myocardial infarction when comparing men who did with those who did not.[20] Similarly, the evidence regarding the association between low levels of endogenous testosterone and the mortality risk from all-cause and from cardiovascular events are quite convincing. In this context, in a huge population-based study, Haring et al. found that low testosterone levels were linked with an increased risk of mortality.[43] Moreover, Belladelli et al. using data from a population of men included in the National Health and Nutrition Examination Survey (NHANES) observed that those with low testosterone-to-estradiol ratio had a higher risk of cardiovascular mortality.[44] A recent randomized clinical trial from Wittert et al., found that men aged 50−74 years with T2DM or impaired glucose tolerance and a serum testosterone concentration of 14 nmol/L or lower who randomly received intramuscular testosterone or placebo for 2 years did not show any difference in terms of cardiovascular events or mortality.[45] Lastly, in a meta-analysis from Araujo et al. it was shown that low testosterone levels were associated with both increased all-cause and cardiovascular related mortality.[46]

The rationale behind our study derives from the consideration that a true condition of hypogonadism may actually be associated with a greater risk of developing different morbidities − including cardiovascular problems − and an even greater mortality risk as compared with the eugonadal status. However, to try and rigorously answer to this doubt, we have inversely reasoned, thus developing a systematic review and meta-analysis to summarize available evidence of the effect of TTh on both those risks compared to either placebo treatment or observation in hypogonadal men via the use of time-related measures of risk (ie, HRs). This

is in contrast with most of the published meta-analyses on the same topics, where ORs have been used as measures of the effect of TTh in hypogonadal men. However, this latter approach does not consider the time-to-event nature of data on either cardiovascular events or mortality, thus possibly biasing the results of pooled analyses. In addition, for several studies included in most of the previously published meta-analyses, cardiovascular events and mortality were secondary/safety outcomes and there were few events of that specific type for each of the included studies or an inadequate length of follow-up.[47,48] To overcome these limitations and according to the Cochrane Handbook for Systematic Reviews of Interventions (Version 6.2, 2021) - where it is stated that "the most appropriate way of summarizing time-to-event data is to use methods of survival analysis and express the intervention effect as a hazard ratio" - HRs from Cox models of the studies included in the current meta-analysis were used as measure of effects for both cardiovascular events and mortality.[49] In addition, most of the included studies are population registry-based studies with thousands of patients and hundreds of events analyzed.

Notwithstanding this approach is a strength of the analysis, this study is certainly not devoid of limitations. First, the criterion for identifying hypogonadal men is still one of the biggest challenges in the everyday clinical practice,[10,11,14,42] particularly when considering different laboratory thresholds, different number of testosterone assessments and measurement units among studies, different laboratory techniques and the modality and time of blood withdrawal. The definition of hypogonadism used across the included studies ranged from a rigorous application of the definition according to the international guidelines (serum testosterone deficiency and symptoms) to the identification of patients likely hypogonadic on the solely base of a TTh prescription. No sub analysis was possible for those who were correctly identified as hypogonadic only, according to the international guideline's definition. However, since the benefit of TTh emerged also in our more heterogeneous cohort, it is likely that this benefit of TTh in terms of decreased cardiovascular risk, might be more evident in the correct ("true") hypogonadic population where the risk of major cardiovascular events is more pronounced. Second, some of the available studies did evaluate different sub-populations of patients (eg, patients with previous history of known cardiovascular disease, patients with and without recovery of normal serum total testosterone levels, etc.) therefore resulting in a wide source of heterogeneity. Third, most published studies presented different lengths of follow-up, thus further contributing to the heterogeneity of the reported data. In addition, another source of heterogeneity was the TTh modality, varying in terms of dose, route of administration and duration of treatment. Finally, given the retrospective nature of most of the included study, there may be the risk of possible unmeasured biases. Given all these limitations, the risk of unmeasured biases and the high heterogeneity of works published until now, the design of well-powered, prospective randomized control trials is of utmost importance.

CONCLUSION

The findings of this meta-analysis rigorously based on the use of time-related measure of risk only showed an increased risk of long-term morbidity and early mortality for untreated hypogonadal men, while further outlining the clinical importance and safety of testosterone therapy in true hypogonadal men deserving to be treated, with the urgent need of collecting long-term follow-up data.

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SUPPLEMENTARY MATERIALS

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