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Original Article

Cardiovascular Outcomes of Hypogonadal Men Receiving Testosterone Replacement Therapy: A Meta-analysis of Randomized Controlled Trials

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ABSTRACT

Objective: To investigate the impact of testosterone replacement therapy (TRT) on cardiovascular outcomes in hypogonadal men.
Methods: A meta-analysis of 26 randomized controlled trials involving 10 941 participants was conducted. Various clinical outcomes, including all-cause mortality, cardiovascular-related mortality, myocardial infarction, stroke, congestive heart failure, atrial fibrillation, pulmonary embolism, and venous thrombosis, were assessed.
Results: No statistically significant differences were observed between the TRT group and the control group in terms of these clinical outcomes. Sensitivity analysis and publication bias assessment supported the robustness of the findings. Meta-regression analysis found no significant associations between clinical outcomes and potential covariates, including age, diabetes, hypertension, dyslipidemia, and smoking.
Discussion: Previous research on TRT and cardiovascular events, with comparisons to studies like the Testosterone Trials and the studies conducted by Vigen et al, Finkle et al, Layton et al, and Wallis et al, is provided. The significance of the systematic review and meta-analysis approach is emphasized, particularly its exclusive focus on hypogonadal patients.
Conclusion: This study offers reassurance that TRT does not increase mortality risk or worsen cardiovascular outcomes in hypogonadal men. However, further research, especially long-term studies involving diverse populations, is essential to strengthen the evidence base and broaden the applicability of these findings.

Introduction

Testosterone, a hormone that influences various bodily functions and metabolism, including muscle, adipose tissue, bone, and cells, plays a role in regulating lipids, carbohydrates, and protein metabolism.[1-4] Low testosterone levels have been linked to cardiovascular (CV) disease, which can be caused by factors such as aging, chronic health issues, obesity, or medications.[5,6] Symptoms of testosterone deficiency may include visible changes in secondary sexual characteristics and body composition.

Testosterone therapy was introduced in the 1940s and was reported to improve overall health without serious adverse effects.[7] While testosterone replacement therapy (TRT) is approved for treating specific conditions, it is not Food and Drug Administration-approved for age-associated decline in testosterone levels. The CV effects of TRT in middle-aged and older men with hypogonadism

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are still unclear, with conflicting results from retrospective cohort studies.[7-15] The Food and Drug Administration issued guidance to conduct clinical trials to determine TRT's CV risk due to conflicting data.[16] Furthermore, it is imperative to recognize that TRT can exert both positive and negative effects on CV health. On one hand, it may induce sodium and water retention, potentially influencing blood pressure regulation. Conversely, TRT has displayed potential benefits, including enhancements in coronary vasodilation and endothelial function. Additionally, TRT offers advantages such as mood improvement, increased muscle mass, enhanced bone density, heightened libido, and potential cognitive enhancements. These affirmative effects can significantly augment overall well-being.

Nonetheless, it is essential to acknowledge that TRT also carries potential risks, including concerns about CV health, acne, testicular shrinkage, infertility, and possible psychological side effects. While endogenous testosterone levels may not consistently predict CV events, lower levels have been correlated with elevated risks of all-cause and CV mortality. Furthermore, circulating testosterone concentrations have shown an inverse association with subclinical atherosclerosis.[17] Despite extensive research, the CV effects of TRT remain controversial, and this meta-analysis aims to provide further insights into its impact on CV outcomes.

Highlights

- Testosterone can exert both positive and negative effects on cardiovascular health.
- Association between TRT and cardiovascular outcomes has been heavily researched and has thus far yielded mixed outcomes.
- 2018 guidelines from the Endocrine Society provide a comprehensive framework for the use of TRT in men with hypogonadism, considering various factors, including cardiovascular (CV) risk.
- TRAVERSE Study from 2023 revealed no increased risk in cardiovascular outcomes with TRT.
- We conclude that TRT is not associated with increased risk of cardiovascular outcomes in patients like atrial fibrillation, stroke, pulmonary embolism, heart failure etc.

Clinical Relevance

Our text is clinically relevant because it addresses a clinically significant topic, employs rigorous research methods, and provides findings and discussions that health care providers can directly apply to their decision-making processes when managing hypogonadal patients.

Methods

This meta-analysis of randomized controlled trials (RCTs) on CV safety of TRT was designed and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 Checklist.[18]

Information Sources and Search Strategy

A detailed search strategy was conducted in electronic databases (Medline, Scopus, and Embase) up to July 2, 2023, to find the potentially eligible articles with no language restriction. A broad search term using relevant keywords ("testosterone replacement therapy," "men," "cardiovascular safety," "myocardial infarction," "death," "stroke," thrombosis," and "embolism") was used for each database (Detailed search strategy for each database is presented in Supplementary Material – Supplementary Table 1). After merging the obtained records from each database and removing the duplicates, key information of the available records including titles and abstracts was uploaded to the Rayyan web-based tool for article screening.[19] Bibliographies of the relevant articles and meta-analyses were searched for additional eligible articles. For possible acceptable articles, full-text screening was performed, and finally, the accepted records were brought for data extraction and synthesis.

Eligibility Criteria and Study Selection

Parallel group RCTs were considered eligible if they evaluated the adverse events related to the CV safety of TRT in a population of hypogonadal men compared with untreated hypogonadal men receiving either a placebo or no placebo. The potential end points included all-cause death, cardiac-related mortality, myocardial infarction, stroke, occurrence of congestive heart failure, pulmonary embolism, atrial fibrillation, and venous thrombosis (defined as deep vein thrombosis or any other venous thrombosis). Different routes of delivery of testosterone to men with androgen deficiency such as intramuscular injection, oral tablets, or topical gels were accepted. Studies were excluded from further evaluation if[1] records were only available as a conference abstract,[2] observational studies,[3] patients in the comparator arm were receiving an active treatment such as phosphodiesterase 5 inhibitors,[4] studies with a crossover design or single-arm studies, and[5] the studied population was among patients undergoing surgical interventions or men with prostate cancer, as this could potentially have a direct effect on outcomes of interest. Studies with suspected overlapping of sample population (common database and time frame or registration identification) were evaluated, and the one with larger sample size was included in this study.

Data Collection

A prespecified collection form was designed for the present study. We extracted general characteristics on first author name and year of publication, country of publication, trial name (if applicable), registration ID, mean age of each group, baseline comorbidity of the studied group in addition to hypogonadism (if applicable), used intervention as TRT, duration of trial, and longest available follow-up. Online supplements of each of the studies were checked for additional data on adverse events if possible. Event rates in each of the groups in addition to the sample size of the intervention and control groups were also gathered for statistical analysis.

Risk of Bias Assessment

For qualitative assessment, the trials were evaluated for risk of bias in 5 main domains including selection, performance, detection, attrition, and reporting bias and rated either as high, low, or unclear risk. The tool used in this regard was The Cochrane Collaboration's tool for assessing risk of bias in randomized trials.[20] The associated figure for risk of bias assessment was provided using the RevMan Web.

Statistical Analysis

For all the analyses, we performed a random-effects model with the Mantel-Haenszel method being used. All of the outcomes in the present meta-analysis were among binary variables; thus, the absolute number of events and total sample size in each group were used to generate a pooled relative risk (RR) and the corresponding

95% confidence interval (CI). The main results were visualized using forest plots. Heterogeneity was assessed using I^2 statistics and the associated *P* value. The overall effect of the intervention was considered statistically significant in case of *P* value ≤.05. A meta-regression analysis was performed to evaluate the potential relation between mean age, frequency of diabetes mellitus, hypertension, dyslipidemia, and smoking of the participants and RR of the main outcomes, and we used bubble plots to show the results. Sensitivity analysis was done for all the analyses by excluding each study at a time and observing the difference of the overall effect measure. If we had more than 10 studies included for an analysis, potential publication bias was assessed using the statistical significance level of Egger's test and the asymmetrical distribution of study results in a funnel plot. All the statistical analyses for the present meta-analysis were performed using R Software version 4.1.3 with "meta" package being used.

Results

Search Results and General Characteristics

Overall, our search terms yielded 2549 records from 3 databases (Medline = 1899, Scopus = 213, and Embase = 437). After excluding the duplicate records ($n = 278$), we screened the titles and abstracts of the remaining 2271 articles. The full text of 123 articles was retrieved for closer inspection and checking of the inclusion and exclusion criteria for each study. Finally, a total of 26 RCTs comprising 10 941 hypogonadal participants (5694 patients on TRT and 5247 on placebo) were included for quantitative synthesis (Study flowchart presented in Fig. 1).[21-46] The majority of the trials were from the United States and the United Kingdom. The mean age was 62.79 (59.83; 65.74) in the TRT group and 63.22 (60.36; 66.08) in the untreated control group. The studied population of some of the included trials was among patients with metabolic syndrome,[21,29,30] obesity,[22,46] type 2 diabetes mellitus,[21,28,29,46] pre-existing CV diseases,[27,35-37] liver cirrhosis,[39,45] and chronic obstructive pulmonary disease.[42] The intervention used in the TRT group included oral tablets, transdermal testosterone gels, and intramuscular injections. The participants were followed up for the occurrence of adverse events from 6 months to 4 years after the start of the trials. General characteristics of the included RCTs are presented in Table 1.

Risk of Bias

The random sequence generation was done using different methods including computer-based randomization system,[25] computer-generated random sequence with an interactive voice response system,[26] permuted block sizes of 4,[28] allocation probabilities of 0.7 and 0.3,[30] random block sizes of 2 or 4 stratified by their frailty status,[32] stratification by the presence or absence of CV condition,[35] stratification by ischemic or nonischemic cause for heart failure,[36] "minimization" method,[37] and web-based randomization system.[46] Blinding of the outcome assessors to the treatment was mostly not mentioned except in 2 studies[41,46] in which data analysts were blinded to the type of treatment (Supplementary Fig. 1).

Clinical Outcomes

Seventeen trials provided information on all-cause mortality in hypogonadal patients receiving TRT. After inclusion of 9380 patients, there was no different risk of all-cause death in patients on TRT when compared to untreated patients with low testosterone (200/4817 vs 203/4563; RR: 0.94, 95% CI (0.80; 1.10), $P = .42$) (Fig. 2*A*). For CV-related mortality, no statistically different risk was observed in 2 groups with a total of 95 and 109 patients with cardiac mortality in the TRT and control groups, respectively (RR: 0.86, 95% CI (0.70; 1.05), $P = .13$) (Fig. 2*B*). Fifteen trials with 7962 participants reported the rates of new-onset myocardial infarction, and the relative risk of myocardial infarction was not different across groups (82/4043 vs 81/3919; RR: 1.00, 95% CI (0.75; 1.33), $P = .99$) (Fig. 2*C*). After inclusion of 8 randomized studies reporting stroke

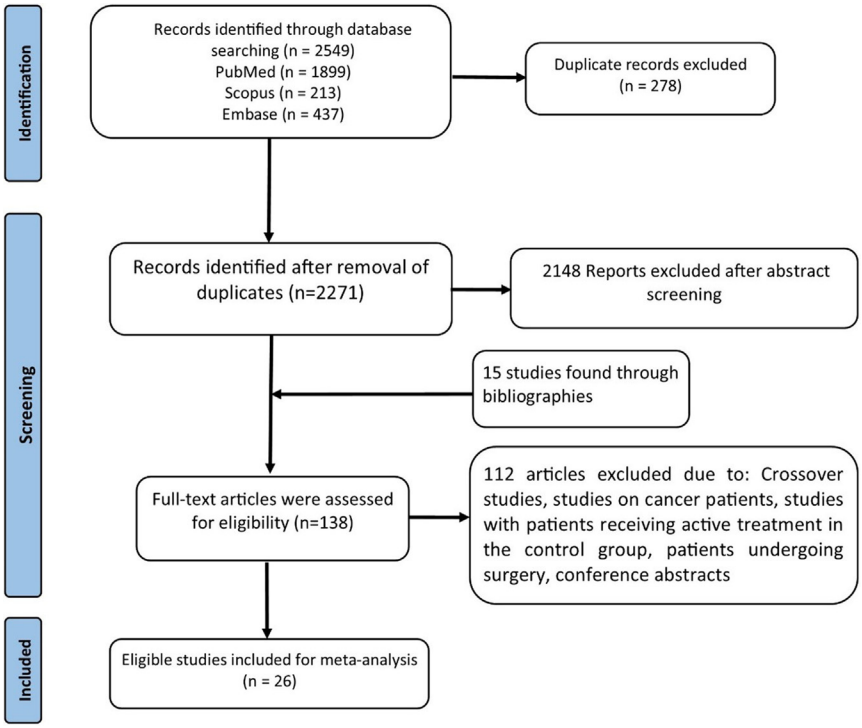

Fig. 1. Study flowchart of the inclusion process.

Table 1
General Characteristics of the Included Trials

Study	Country	Registration ID	Special population	Sample size		Intervention	Duration of the trial
				Inv	Ctrl		
Aversa, 2010[4]	Italy	NA	Metabolic Sx and/or type 2 DM	42	10	Oral TU (160 mg/d), IM TU (1000 mg/6 wk (loading dose then /12 wk)	12 mo
Barnouin, 2020 (LITROS)[5]	U.S.	NCT02367105	Obesity, ≥65 y old	42	41	Lifestyle + TRT (Androgel 1.62% (Abbvie) topically once daily)	≥8 mo
Basaria, 2010 (TOM)[6]	U.S.	NCT00240981	≥65 y old	106	103	Transdermal gel containing 100 mg T (Testim 1%) once daily for 6 mo	9 mo
Basaria, 2015 (TRAAM)[7]	U.S.	NCT00287586	≥60 y old	155	151	7.5[5-10] g T gel 1% (50-100 mg)	36 mo
Behre, 2012[8]	Multinational	-	≥50 y old	183	179	5-10 g T gel 1% (Testogel®)	18m
Brock, 2016[9]	Multinational	NCT01816295	ND	358	357	60 (30-120) mg topical T gel solution 2% daily	16 wk + 6 mo
English, 2000[10]	U.K.	NA	Chronic stable angina	22	24	Two 2.5 mg self-adhesive active testosterone patches every night	14 wk
Gianatti, 2014[11]	Australia	NCT00613782	Type 2 DM	45	43	Intramuscular TU 1000 mg at 0, 6, 18, and 30 wk	40w
Jones, 2011 (TIMES2 Study)[12]	Multinational	ISRCTN457417	Type 2 DM/Metabolic Sx	108	112	3 g metered-dose 2% T gel (60 mg) daily	>12 mo
Kalinchenko, 2010[13]	Russia	NCT00696748	Metabolic Sx	113	71	1000 mg Intramuscular TU 0-6-18 wk	30 wk
Kaufman, 2012[14]	U.S.	NCT00433199	ND	191	28	2.5 g 1.62% T gel/daily	1 y
Kenny, 2010[15]	U.S.	NCT00182871	History of fracture or BMD T-score < −2.0 and frailty	69	62	Transdermal T 5 mg daily (AndroGel™ 1%)	2 y
Kolind, 2022[16]	Denmark	NCT02433730	Opium therapy for non-cancer pain	20	21	Injection of 1000 mg TU (Nebido) 0-6-18 wk	Up to 24 mo
Legros, 2009[17]	Multinational	NCT00434824	≥50 y old	237	79	Oral TU capsules 80-240 mg daily (AndriolTestocaps)	12 mo
Lincoff, 2023 (TRAVERSE study)[18]	U.S.	NCT03518034	Pre-existing or high risk for cardiovascular diseases	2596	2602	1.62% transdermal T gel 65 ± 22 daily	48 mo
Malkin, 2006[19]	U.K.	NA	Moderate heart failure	37	39	Androderm® skin patch 5 mg at nights	12 mo
Navarro-Penalver, 2018[20]	Spain	NCT01813201	Chronic heart failure with reduced ejection fraction	14	15	Long-acting IM TU 1000 mg/3 mo till month 12	12 mo
Sih, 1997[21]	U.S.	NA	ND	17	15	200 mg T cypionate IM/14-17 d for 12 mo	12 mo
Sinclair, 2016[22]	Australia	ACTRN12614000526673	Liver cirrhosis	50	51	IM TU 1000 mg at 0, 6, 18, 30, 42 wk	54 wk
Snyder, 2001[23]	U.S.	NA	>65 y old	54	54	6 mg of T patch/d	36 mo
Srinivas-Shankar, 2010[24]	U.K.	NA	Intermediate-frail or frail and >65 y old	130	132	Transdermal hydroalcoholic T gel (Testogel 1%), 20 mg/d for 6 mo	6 mo
Svartberg, 2004[25]	Norway	NA	COPD	15	14	250 mg IM T/4 wk	26 wk
Snyder, 2016 (Testosterone Trials)[26]	U.S.	NCT00799617	>65 y old	394	394	AndroGel 1% (AbbVie) 5 g daily	2 y
Tan, 2013[27]	Malaysia	NA	-	60	60	TU injection (1000 mg at 0, 6, 18, 30, 42 wk)	48 wk
The Copenhagen Study, 1986[28]	Denmark	NA	Alcoholic cirrhosis	134	87	Micronized-free T tablets (100 mg), 2 tabs 3 times daily	36 mo
Wittert, 2021 (T4DM)[29]	Australia	ACTRN12612000287831	Overweight and obese or new type 2 DM	504	503	1000 mg TU IM injection at 0,6, then every 3 mo for 2 y	2 y

Abbreviations: BMD = bone mineral density; COPD = chronic obstructive pulmonary disease; Ctrl = control; DM = diabetes mellitus; IM = intramuscular; Inv = intervention; NA = not available; ND = no data; Sx = syndrome; T = testosterone; TRT = testosterone replacement therapy; TU = testosterone undecanoate.

rates, the risk of stroke was not statistically different among patients on TRT compared to the control group (49/4167 vs 48/4164; RR: 0.99, 95% CI (0.70; 1.42), $P = .96$) (Fig. 2*D*). For the other outcomes, TRT was not associated with a statistically increased or decreased risk of congestive heart failure (RR: 0.83, 95% CI (0.61; 1.12), $P = .19$) (Fig. 3*A*), atrial fibrillation (RR: 1.38, 95% CI (0.54; 3.53), $P = .36$) (Fig. 3*B*), pulmonary embolism (RR: 1.92, 95% CI (0.96; 3.86), $P = .06$) (Fig. 3*C*), and venous thrombosis (RR: 1.12, 95% CI (0.69; 1.81), $P = .58$) (Fig. 3*D*). Heterogeneity among the studies was below 10% with a nonsignificant *P* value in all the outcomes.

Sensitivity Analysis and Publication Bias

For all the outcomes, we performed sensitivity analysis, and none of the outcomes showed a statistically significant difference after omitting each study at a time except pulmonary embolism, in which after the exclusion of a study,[26] there was an increased risk of pulmonary embolism associated with TRT (RR: 2.07, 95% CI (1.48; 2.92)) (Supplementary Figs. 2-9).

For end points with more than 10 studies included, funnel plots showed no asymmetrical distribution of the studies (Supplementary Figs. 10-13) with none of the results of Egger's tests reaching statistical significance.

Meta-regression Analysis

For the studies with available data, we performed a meta-regression analysis of effect sizes of the main outcomes (all-cause death, CV-related death, myocardial infarction, stroke, and heart failure) considering potential covariates including age, diabetes, hypertension, dyslipidemia, and smoking. None of the covariates

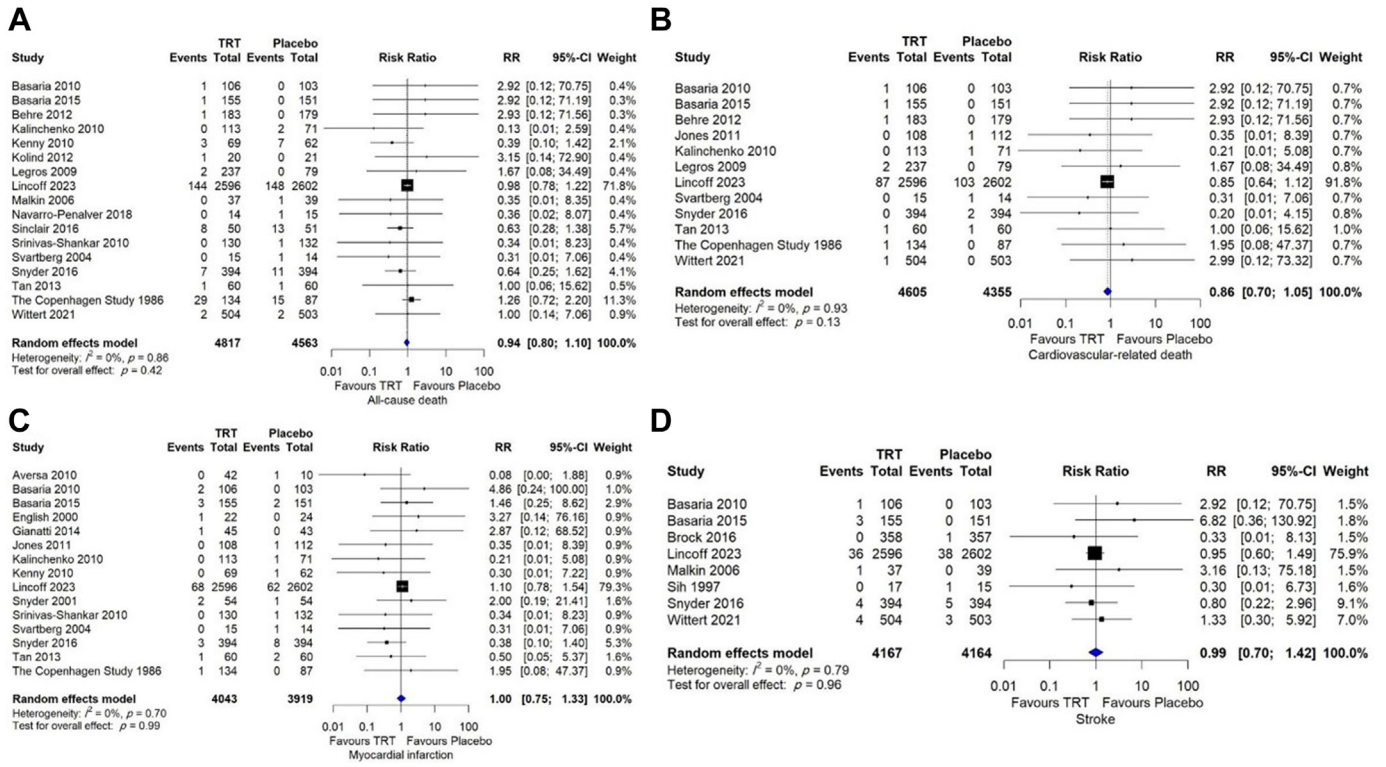

Fig. 2. Results of the meta-analysis showing comparison of (*A*) all-cause mortality, (*B*) cardiovascular-related mortality, (*C*) myocardial infarction, and (*D*) stroke between hypogonadal men receiving TRT and no treatment. *CI* = confidence interval; *RR* = risk ratio; *TRT* = testosterone replacement therapy.

showed a significant association with the outcomes of interest (Table 2 and Supplementary Figs. 14-18).

Discussion

The relationship between TRT and its potential impact on CV events has been a subject of extensive research and ongoing debate within the scientific community. Numerous studies have investigated this association, but the diverse findings have led to a lack of a clear consensus. The available evidence exhibits significant diversity, stemming from variations in study design, population characteristics, duration of follow-up, and other methodological factors, which have contributed to conflicting results. This inherent heterogeneity underscores the need for further investigation to

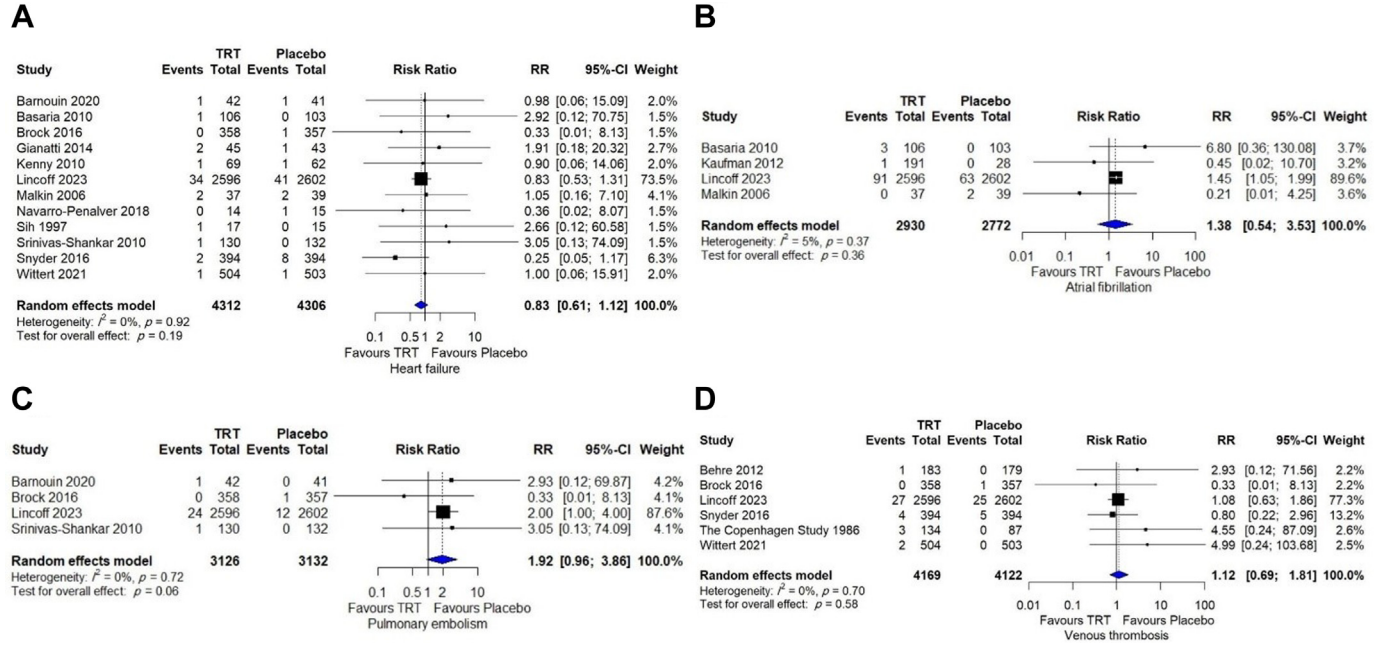

Fig. 3. Results of the meta-analysis showing comparison of (*A*) congestive heart failure, (*B*) atrial fibrillation, (*C*) pulmonary embolism, and (*D*) venous thrombosis between hypogonadal men receiving TRT and no treatment. *CI* = confidence interval; *RR* = risk ratio; *TRT* = testosterone replacement therapy.

Table 2
Meta-regression Analysis for the Risk of Main End Points Considering Different Covariates

	Coefficient	SE	95% CI	*P* value
End point all-cause death				
Covariates				
Age	−0.021	0.015	−0.052; 0.010	.171
Diabetes	0.010	0.006	−0.004; 0.024	.118
Hypertension	0.013	0.007	−0.003; 0.029	.093
Dyslipidemia	−0.006	0.012	−0.044; 0.032	.635
Smoking	0.004	0.027	−0.066; 0.074	.893
End point cardiovascular-related death				
Covariates				
Age	−0.001	0.046	−0.102; 0.101	.994
Diabetes	−0.008	0.012	−0.042; 0.026	.555
Hypertension	0.001	0.015	−0.041; 0.042	.969
Dyslipidemia	−0.015	0.012	−0.062; 0.032	.300
Smoking	−0.044	0.044	−0.166; 0.079	.380
End point myocardial infarction				
Covariates				
Age	−0.006	0.038	−0.088; 0.075	.869
Diabetes	0.007	0.011	−0.019; 0.034	.546
Hypertension	0.009	0.010	−0.016; 0.034	.416
Dyslipidemia	−0.002	0.012	−0.041; 0.037	.857
Smoking	−0.020	0.052	−0.164; 0.124	.721
End point stroke				
Covariates				
Age	0.015	0.049	−0.105; 0.135	.771
Diabetes	−0.005	0.011	−0.032; 0.023	.670
Hypertension	0.002	0.013	−0.035; 0.040	.871
Dyslipidemia	−0.002	0.012	−0.041; 0.037	.857
Smoking	−0.009	0.025	−0.088; 0.069	.729
End point heart failure				
Covariates				
Age	−0.007	0.038	−0.091; 0.078	.866
Diabetes	0.001	0.009	−0.022; 0.024	.901
Hypertension	0.002	0.013	−0.030; 0.034	.896
Dyslipidemia	−0.006	0.011	−0.042; 0.031	.650
Smoking	0.042	0.046	−0.103; 0.187	.423

Abbreviations: CI = confidence interval; SE = standard error.

establish a more definitive understanding of the complex relationship between TRT and CV events.

The 2018 guidelines from the Endocrine Society provide a comprehensive framework for the use of TRT in men with hypogonadism, considering various factors, including CV risk. These guidelines emphasize the importance of individualized assessments and shared decision making between clinicians and patients when determining whether TRT is an appropriate course of action. Unlike offering a 1-size-fits-all recommendation for or against TRT, the guidelines encourage clinicians to carefully evaluate each case. They consider factors such as a patient's age, underlying medical conditions, and CV risk factors when weighing the potential benefits and risks of TRT. It is noteworthy that the guidelines recognize the ongoing debate and research regarding the potential impact of TRT on CV health and emphasize the need for further investigation.[47]

To contribute to this body of research and address the existing gaps, the present systematic review and meta-analysis undertook a thorough evaluation of the available evidence on the effects of TRT in hypogonadal patients. Our study encompassed 26 RCTs, involving a large sample size of 10 941 participants. This extensive dataset offered valuable insights into the potential impact of TRT on various clinical outcomes, such as all-cause mortality, CV-related mortality, myocardial infarction, and stroke.

Our analysis aimed to provide a more robust and reliable assessment of the association between TRT and CV outcomes by synthesizing data from multiple studies. The comprehensive nature of our study, combined with its substantial sample size, enhances the generalizability and strength of our conclusions. One of our significant findings was the absence of a statistically significant difference in all-cause mortality between hypogonadal patients receiving TRT and the untreated control group. This finding suggests that TRT does not increase the risk of death in this population, offering reassurance to both clinicians and patients regarding the therapy's safety in terms of overall survival.

Additionally, our analysis revealed no significant difference in CV-related mortality between the 2 groups. This result holds considerable significance given that CV disease is a major concern in hypogonadal patients. The lack of an increased risk of CV mortality in the TRT group suggests that this therapy does not worsen CV outcomes in this population. Our analysis also extended to specific CV events, such as new-onset myocardial infarction and stroke, with no significant differences in the incidence of these events between the TRT group and the control group. This implies that TRT is not associated with an increased risk of these critical CV events in hypogonadal patients.

Furthermore, our study delved into the impact of TRT on other clinical outcomes, including congestive heart failure, atrial fibrillation, pulmonary embolism, and venous thrombosis. Once again, no significant differences emerged between the TRT and control groups concerning these outcomes, indicating that TRT does not significantly influence the occurrence of these CV conditions in hypogonadal patients.

It is important to note the Testosterone Trials (TTrials), a set of 7 coordinated, double-blind, placebo-controlled trials, which significantly contributed to this field. These trials focused on evaluating the effects of TRT in older men with low testosterone levels. The TTrials yielded several notable findings, including improvements in sexual function, mood, vitality, muscle mass, and bone density in participants who received TRT. While there were no significant changes in cognitive function, the impact on CV outcomes, such as heart attacks and strokes, remained inconclusive. This uncertainty emphasizes the importance of individualized treatment decisions and careful consideration of potential risks when considering TRT for older men with age-related low testosterone levels.[48]

Our study distinguishes itself from the TTrials in several key aspects. Firstly, while the TTrials concentrated on evaluating the effects of TRT specifically in older men with low testosterone levels, our study encompassed a broader population of hypogonadal patients. By including a diverse range of participants, our study aimed to provide insights into the potential impact of TRT on various clinical outcomes across a wider demographic. Secondly, our study involved a systematic review and meta-analysis of 26 RCTs, rendering it more comprehensive in terms of the number of studies analyzed and the substantial sample size of 10 941 participants. This more extensive and diverse dataset enhances the statistical power of our analysis, leading to more robust and reliable conclusions.

Corona et al (2014) conducted a comprehensive systematic review and meta-analysis that assessed the CV safety of TRT. Their analysis of 39 studies found no significant association between TRT and major adverse CV events, including myocardial infarction, stroke, and CV mortality. However, they acknowledged the limitations of the available evidence, such as the predominantly observational study designs and the lack of long-term, well-controlled randomized trials.[49]

Our study, on the other hand, focused specifically on the effects of TRT in hypogonadal patients compared to the study by Corona et al (2014), who included 39 studies without specifically targeting hypogonadal patients. This broader scope may have encompassed different populations and patient groups. Furthermore, our study

utilized a systematic review and meta-analysis approach, which involved a rigorous and standardized process for evaluating the available evidence on TRT and CV outcomes. The meta-analysis enabled us to pool data from multiple RCTs, resulting in more robust and reliable conclusions. In contrast, while Corona et al[49] (2014) conducted a comprehensive systematic review and meta-analysis, it is not explicitly stated that they performed a meta-analysis of the included studies.

The largest RCT on the topic is a study conducted by the TRAVERSE Study Investigators. This multicenter RCT compared long-term clinical outcomes in 5246 men with hypogonadism receiving either a daily dose of testosterone gel or placebo. Similar to our results, TRT was not associated with an increased hazard of clinical outcomes. Unlike our findings, there was a higher incidence of pulmonary embolism and atrial fibrillation in patients receiving TRT. Interestingly, the authors added that the majority of the cases with thrombosis in patients receiving TRT are among men with previously diagnosed thrombophilia. Also, normalization of testosterone with TRT is usually concomitant with decreased rates of atrial fibrillation.[35] These findings should be interpreted with caution as the results of our study showed no different risk of embolism and atrial fibrillation compared between the 2 groups, although only 4 studies were available for each outcome, and future studies are needed to confirm our findings.

Other studies have also contributed to the discussion on TRT and CV events. Vigen et al conducted a retrospective study that suggested an increased risk of CV events in older men receiving TRT. They analyzed a large health care database and reported a higher incidence of myocardial infarction among men aged 65 years or older in the first 90 days of TRT use. However, subsequent studies have criticized the methodology and limitations of this study, such as the potential for confounding variables.[50] Finkle et al[13] conducted a retrospective study that found a 2-fold increased risk of myocardial infarction among younger men with pre-existing heart disease who initiated TRT. Like the previous study, this research faced criticism for its retrospective design and potential confounders. Another retrospective study by Layton et al analyzed commercial insurance claims data and reported an increased risk of myocardial infarction in the first 90 days of TRT use among men aged 40 years or older, particularly in those with pre-existing heart disease. However, the study also faced criticism for potential biases and limitations inherent to its design.[51]

Our study specifically aimed to conduct a systematic review and meta-analysis to evaluate the effects of TRT in hypogonadal patients. Furthermore, our study followed a systematic review and meta-analysis design, encompassing a comprehensive evaluation of multiple RCTs, which allows for a more robust analysis of the available evidence. Moreover, our study focused on hypogonadal patients, ensuring a more targeted investigation of TRT effects in this population. The larger sample size in our study provides more generalizability. Lastly, our study specifically examined the impact of TRT on CV outcomes, providing targeted insights into a clinically relevant aspect of TRT's effects.

The differences in our research objectives, study design, patient population, sample size, data analysis, and focus on CV outcomes underscore the significance of conducting multiple studies with different methodologies to comprehensively understand the relationship between TRT and CV health.

Wallis et al conducted a meta-analysis of RCTs and observational studies to establish an association between TRT and CV events. They concluded that there was insufficient evidence to establish a clear association, primarily due to heterogeneity in study design and inconsistent outcomes. Our study differs from the study conducted by Wallis et al (2022) in several important ways. Firstly, while our research focused on conducting a systematic review and meta-analysis to assess the association between TRT and CV outcomes in hypogonadal patients, the study conducted by Wallis et al (2022) involved a meta-analysis of RCTs and observational studies to establish an association between TRT and CV events in a broader population. This difference in study design may have resulted in variations in the inclusion criteria, study selection, and the overall approach to analyzing the data. Secondly, our study specifically targeted hypogonadal patients, aiming to investigate TRT's effects on this specific population's CV outcomes. In contrast, the study by Wallis et al[52] (2022) might have included a wider range of patients with different conditions or characteristics, potentially leading to diverse outcomes due to the heterogeneity of the study population.

Furthermore, our study analyzed 26 RCTs with a substantial sample size, providing considerable statistical power and precision in evaluating the association between TRT and CV outcomes in hypogonadal patients. On the other hand, the study by Wallis et al (2022) might have included studies with varying sample sizes, leading to differences in the strength and reliability of their conclusions. Additionally, our systematic review ensured a thorough evaluation of the available evidence, aiming to provide a comprehensive and reliable assessment of the association between TRT and CV outcomes. Conversely, the study by Wallis et al (2022) incorporated both RCTs and observational studies, which can introduce potential biases and limitations due to differences in study designs and data collection methods. Lastly, the specific CV outcomes and end points examined in our study may have differed from those explored by Wallis et al[52] (2022), potentially leading to distinct findings and conclusions.

To strengthen the robustness of the findings, a sensitivity analysis was conducted, which showed that omitting individual studies did not lead to significant changes in the outcomes. This indicates that the overall results were not heavily influenced by any particular study and increases confidence in the reliability of the findings. The only considerable finding in the sensitivity analysis was a significant increase in the risk of developing pulmonary embolism after excluding one of the studies. It should be noted that the majority of the studies did not report data on pulmonary embolism, and only 4 studies were included for this analysis. Thus, we believe that this may not yield conclusive results, and future studies with large sample sizes are warranted to report the long-term rates of pulmonary embolism compared between TRT and control groups. The absence of publication bias, as indicated by the funnel plots and Egger's tests, further enhances the validity of the study findings. Additionally, the inclusion of studies with diverse methodologies and characteristics strengthens the generalizability of the results, making them applicable to a broader population. The meta-regression analysis explored the potential association between age and clinical outcomes. The results showed no significant correlation between potential covariates and all-cause mortality, cardiac death, myocardial infarction, stroke, or congestive heart failure. These findings suggest that age, diabetes, hypertension, dyslipidemia, and smoking are not major confounding factors in the relationship between TRT and these outcomes among the study populations.

While our study provides important insights into the association between TRT and CV outcomes, it is essential to acknowledge its limitations. Firstly, the analysis primarily relied on data from RCTs, which may not fully reflect real-world settings and may limit the generalizability of the findings. Additionally, not all the included studies provided data on baseline covariates such as diabetes and hypertension. Thus, the meta-regression results may not be reliable. The varying durations of follow-up across the included studies may have influenced the observed outcomes. Longer term studies are needed to assess the effects of TRT over extended periods and provide a more comprehensive understanding of the long-term CV implications.

Overall, the association between TRT and CV events remains a topic of debate and uncertainty within the scientific community. The available evidence is diverse and inconclusive, highlighting the need for more high-quality research to establish a clearer understanding of this relationship. The present systematic review and meta-analysis contribute to the existing literature by providing valuable insights into the effects of TRT on various clinical outcomes. The findings suggest that TRT is not associated with an increased risk of all-cause mortality, CV-related mortality, myocardial infarction, stroke, or other CV conditions in hypogonadal patients. However, it is crucial to interpret these findings while considering the limitations of the study and the need for further research to validate and expand upon these results. By conducting additional well-designed studies, researchers can improve the quality and reliability of evidence, enabling health care professionals to make more informed decisions and provide appropriate recommendations to patients considering TRT.

Conclusion

In conclusion, the findings of this systematic review and meta-analysis indicate that TRT does not significantly impact all-cause mortality, CV-related mortality, myocardial infarction, stroke, congestive heart failure, atrial fibrillation, pulmonary embolism, and venous thrombosis in hypogonadal patients. These results offer valuable evidence for clinicians and patients in making informed decisions regarding the use of TRT. However, further research, including long-term studies and more diverse populations, is necessary to gain a comprehensive understanding of the effects of TRT on clinical outcomes and to enhance the generalizability of the findings.

Disclosure

The authors have no multiplicity of interest to disclose.

Author contributions

The manuscript has undergone thorough review and editing by all authors. Each author takes full responsibility for ensuring the data's reliability, as well as the absence of bias, in both its presentation and interpretation.

Ethics approval and consent to participate

The study is exempt from requiring institutional board of review approval, as all the data are readily available in public repositories, such as PubMed.

Consent for publication

All authors have provided consent for the publication of this manuscript.

Availability of data and materials

All the data are readily available in public repositories, such as PubMed.

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