ASSESSING CARDIOVASCULAR SAFETY OF TESTOSTERONE REPLACEMENT THERAPY FOR MALE HYPOGONADISM: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Objective: *This study aims to comprehensively assess TRT's cardiovascular safety in males with hypogonadism, providing valuable insights for treatment decisions.* ***Material &Methods:*** *Adhering to PRISMA guidelines, we registered our PROSPERO protocol and analyzed relevant English-language randomized clinical trials published from 2008 to 2023.* ***Results:*** *Among 1187 initial papers, 7 studies met inclusion criteria, with 6 in quantitative analysis and all 7 in qualitative assessment. Our findings indicate that TRT does not significantly increase the risk of cardiovascular events compared to placebo. Specifically, the analysis of major adverse cardiac events (MACE) yielded an OR of 0.90 (95% CI: 0.74, 1.10; I^2 = 26%; p = 0.25), while the evaluation of all cardiovascular adverse events revealed an OR of 1.37 (95% CI: 0.73, 2.55; I^2 = 75%; p = 0.001).* ***Conclusion:*** *This study offers reassurance for clinical decision-making by suggesting that TRT is not significantly associated with an elevated cardiovascular risk in hypogonadal men, addressing the ongoing debates on this issue.*

Keywords: *Cardiovascular safety, hypogonadism, testosterone replacement therapy.*

ABSTRAK

Tujuan:*Penelitian ini bertujuan untuk menilai keamanan kardiovaskular TRT secara komprehensif pada pria dengan hipogonadisme, memberikan wawasan yang berharga untuk keputusan pengobatan.****Bahan & Cara:*** *Dengan mengikuti pedoman PRISMA, kami mendaftarkan protokol PROSPERO kami dan menganalisis uji klinis acak berbahasa Inggris yang relevan yang diterbitkan dari tahun 2008 hingga 2023.* ***Hasil:*** *Di antara 1187 makalah awal, 7 penelitian memenuhi kriteria inklusi, dengan 6 penelitian menggunakan analisis kuantitatif dan 7 penelitian menggunakan penilaian kualitatif. Temuan kami menunjukkan bahwa TRT tidak secara signifikan meningkatkan risiko kejadian kardiovaskular dibandingkan dengan plasebo. Secara khusus, analisis kejadian jantung yang merugikan utama (MACE) menghasilkan OR 0.90 (95% CI: 0.74, 1.10; I^2 = 26%; p = 0.25), sedangkan evaluasi semua kejadian kardiovaskular menunjukkan OR 1.37 (95% CI: 0.73, 2.55; I^2 = 75%; p = 0.001).****Simpulan:*** *Penelitian ini memberikan kepastian untuk pengambilan keputusan klinis dengan menunjukkan bahwa TRT tidak secara signifikan terkait dengan peningkatan risiko kardiovaskular pada pria hipogonad, mengatasi perdebatan yang sedang berlangsung tentang masalah ini.*

Kata kunci:*Keamanan kardiovaskular, hipogonadisme, terapi penggantian testosteron.*

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INTRODUCTION

Testosterone, a crucial hormone in humans, plays a vital role in many physiological processes.[1-2] Low testosterone levels can lead to a condition known as hypogonadism, which can manifest in two primary forms: primary hypogonadism and secondary hypogonadism. Primary hypogonadism results from testicular dysfunction, while secondary hypogonadism is typically due to pituitary or hypothalamic insufficiency.[2-3] Hypogonadism can harm various organ functions and overall quality of life, causing symptoms like sexual dysfunction, fatigue, mood disturbances, reduced bone density,

and changes in body composition.[4] Furthermore, it's associated with significant comorbidities such as type 2 diabetes mellitus (T2DM), obesity, cardiovascular disease, and osteoporosis, with reciprocal connections.[5] Numerous studies confirm age-related declines in serum testosterone among men. In the 50-59 age group, about 10% have low levels, rising to 20% in men aged 60-69, and a substantial 70% for those between 70-80 years old.[6-7] Research across the United States, Europe, and Asia, including studies like Framingham, European Male Ageing Study (EMAS), and Osteoporotic Fractures in Men (MrOs), validates these findings, indicating that roughly 10% of men at age 40 exhibit low testosterone. This prevalence increases to approximately 24% and 40% in men with average ages of around 60 and 73, respectively.[6-9] In older men, the prevalence of hypogonadism is significantly lower when low testosterone levels are coupled with symptoms. For example, the EMAS study involving over 3000 men aged 40-79 reported an overall prevalence of 2.1% when combining three sexual symptoms (erectile dysfunction, reduced morning erections, and decreased sexual thoughts) with low total testosterone concentrations.[6,10]

Testosterone replacement therapy (TRT) represents an effective intervention for male hypogonadism, primarily aimed at restoring testosterone concentrations to healthy levels. TRT is associated with multifaceted benefits, including improvements in sexual function, enhanced bone mineral density, reduced body fat mass, increased muscle mass and strength, and the potential for positive effects on lipid profiles and glucose control.[11] By achieving this hormonal normalization, TRT not only mitigates the symptoms linked with hypogonadism but also mitigates the risk of associated comorbidities.[5] Over recent years, there has been a notable increase in the prescription of TRT. In the United States, for instance, in 2011, approximately 3% of men over the age of 40 received at least one TRT prescription.[12] Furthermore, between 2016 and 2019, the US witnessed a significant 28.6% rise in TRT prescriber.[13] A Canadian study reported a yearly increase in TRT prescriptions from 2007 until 2014, after which they plateaued or decreased, depending on the age group.[14] Global trends in TRT prescription from 2000 to 2011 also documented a substantial and progressive increase, primarily targeting older men. These trends have been driven, in part, by clinical guidelines endorsing TRT for age-related functional androgen deficiency.[15] Despite the progressive increase in TRT prescriptions, the cardiovascular safety of TRT has remained a subject of controversy over the past decade. While some studies have reported cardiovascular adverse effects in men receiving TRT[.16–19] others have found no such association.[20-24] This ongoing debate prompted the United States Food and Drug Administration (FDA) to issue alerts in 2015, particularly regarding TRT's safety in elderly patients and its potential for cardiovascular adverse effects.[2] Consequently, concerns about the prevalence of cardiovascular adverse effects in patients receiving TRT have raised significant questions among clinicians about its safety.To address these uncertainties and provide a comprehensive evaluation of the cardiovascular safety of TRT in male hypogonadism, we conducted a systematic review and meta-analysis.

OBJECTIVE

This study aims to systematically review and meta-analyze existing research on TRT in male hypogonadism to evaluate its cardiovascular safety and provide evidence-based insights for clinical decision-making. By bringing together evidence from a wide range of clinical trials, our aim was to provide valuable insights into the cardiovascular safety of TRT for male hypogonadism. This information can assist both doctors and patients in making informed decisions about treatment, ultimately guiding the optimization of therapeutic approaches for male hypogonadism.

MATERIAL&METHODS

This systematic review and meta-analysis strictly adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines, which provide a standardized framework for the systematic conduct and transparent reporting of reviews.[25] A meta-analysis protocol was developed and prospectively registered in the PROSPERO international database of systematic reviews (Registration ID: CRD42023464694) prior to commencing the study. PROSPERO registration serves to enhance transparency and minimize the risk of reporting bias.[26]

Inclusion criteria: We included randomized controlled trials (RCTs) for inclusion in this review, with the requirement that full-text articles must be

accessible. Moreover, studies must be published in the English language and have publication dates falling between 2008 and 2023. To meet inclusion criteria, studies should specifically investigate the effect of testosterone replacement therapy on cardiovascular events, and the study population must comprise men diagnosed with hypogonadism based on clinical guideline.

Exclusion Criteria: Conversely, we excluded certain types of studies, including review articles such as systematic reviews, meta-analyses, and literature reviews. Additionally, observational studies, case series, case reports, letters to editors, conference abstracts, and non-peer-reviewed sources will not be considered. Full-text articles that are not accessible will also be excluded. Furthermore, we will exclude studies involving other forms of androgens besides testosterone. Finally, non-human studies, including in vitro and animal studies, will not be included in this review.

We conducted our search across multiple databases, including PubMed, ScienceDirect, EBSCO, and Cochrane. The search was conducted from September 6, 2023, to September 9, 2023, and we also utilized citation searching to enhance the comprehensiveness of our search.

The selection of terms used in this review was based on the Population, Intervention, Comparison, Outcomes, and Study design (PICOS) approach. In this review, we defined the population (P) as men with hypogonadism, the intervention (I) as testosterone replacement therapy, the comparison (C) as placebo, the outcomes (O) as cardiovascular adverse events, and the study design (S) as randomized clinical trials and prospective observational studies. Our search strategy incorporated the following combination of terms: ("cardiovascular outcome" OR "cardiovascular adverse event" OR "cardiovascular risk" OR "cardiovascular effect" OR "cardiovascular event" OR "major adverse cardiac event" OR "myocardial infarction" OR "stroke" OR "cerebrovascular accident" OR "venous thromboembolism" OR "pulmonary embolism") AND ("testosterone replacement therapy" OR "testosterone therapy" OR "testosterone") AND ("hypogonadism" OR "hypogonadal men" OR "testosterone deficiency" OR "low testosterone level"). This comprehensive search strategy allowed us to identify relevant studies for our systematic review.

Study selection assessment was a collaborative effort involving three reviewers (I.Y.V., D.I.H., and I.S.). In cases of disagreements, consensus was reached among the three reviewers, or a fourth reviewer (M.I.A.R.) was consulted for resolution. Initially, the authors conducted a preliminary screening of articles based on title and abstract. Subsequently, a comprehensive full-text review was conducted, adhering to predefined inclusion and exclusion criteria.

We performed data extraction using Google Sheets software, capturing essential parameters such as age, population size, the health condition of the study participants, treatment duration, treatment dosage, follow-up duration, and the occurrence of cardiovascular adverse events in both the TRT and placebo groups. The primary outcome of interest was major adverse cardiac events (MACE), with a secondary focus on recording all cardiovascular adverse events reported in the trials.

Risk of bias assessment was carried out by two authors (A.A.S.P. and T.A.) using Version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2). Any discrepancies were resolved through consensus.

We conducted the meta-analysis using Cochrane Review Manager 5.4.1. For dichotomous variables, we assessed the outcomes using odds ratios (ORs) with a 95% confidence interval (CI). We estimated heterogeneity among the studies using the Tau^2 and Chi^2 heterogeneity test and quantified it using I^2. When I^2 was less than 50%, we considered the heterogeneity acceptable and utilized the fixed-effect model. In cases where I^2 exceeded 50%, indicating high heterogeneity, we employed the random-effects model. To assess potential publication bias, we visualized the data using a funnel plot, where asymmetry suggests a possibility of bias.

RESULTS

In this study, we conducted a systematic search across multiple databases, including PubMed, CENTRAL, EBSCOhost, ScienceDirect, and citation searching, to identify potential papers. A total of 1187 papers were initially obtained through these sources. After eliminating duplicate entries and conducting a comprehensive review of titles and abstracts, 1026 papers were excluded from further consideration based on predefined exclusion criteria.

Subsequently, 188 papers underwent a more detailed evaluation, with inclusion and exclusion criteria applied to assess their eligibility. From this

comprehensive assessment, seven studies met the eligibility criteria and were included for synthesis in this study. These seven studies collectively comprised 7730 patients who participated in various randomized controlled trials conducted across five different countries. These trials investigated the effects of testosterone replacement therapy, with a placebo serving as the comparative group.

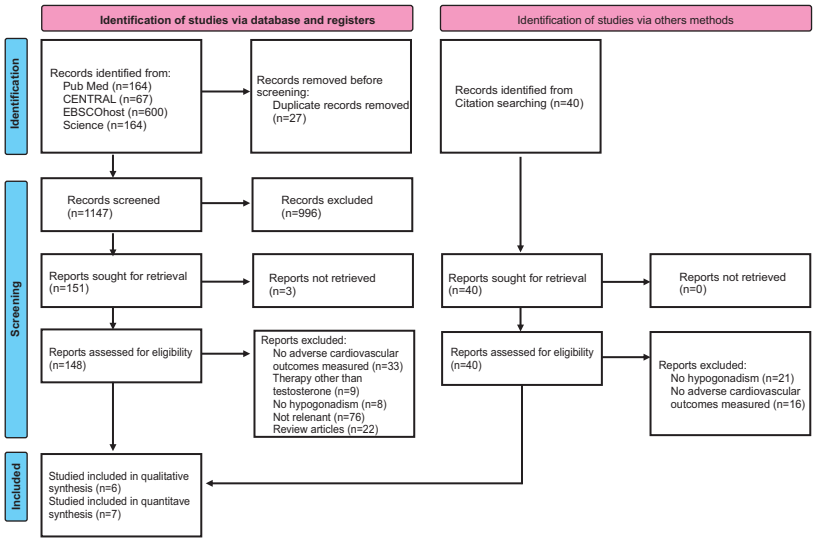

Figure 1.PRISMA Flow Diagram.

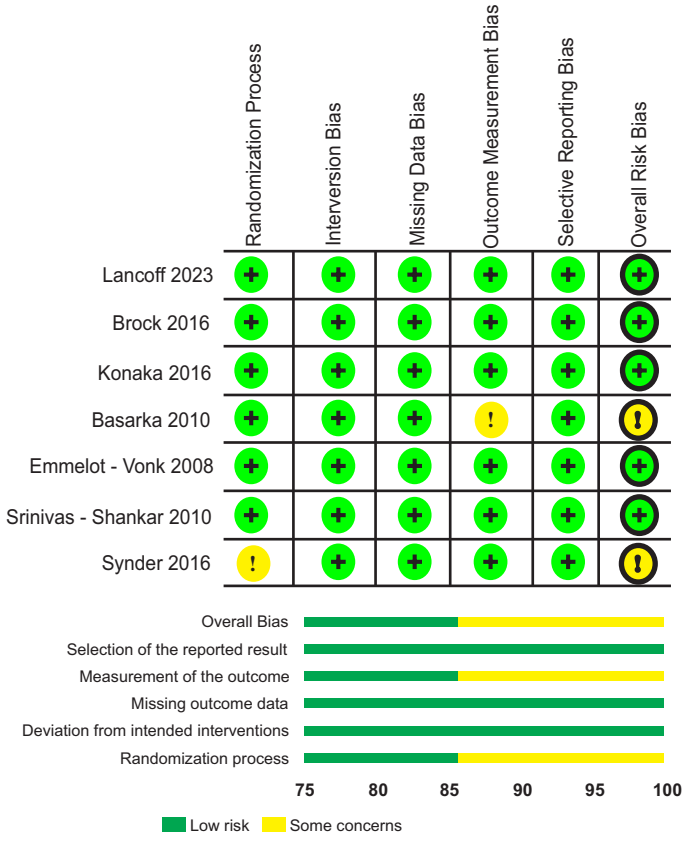

Figure 2. Risk of Bias Assessment.

Of the 7 studies reviewed, 6 were included in the quantitative analysis, while 1 study was excluded due to the absence of a placebo treatment in the control group. Among these, 5 studies reported major adverse cardiac events (MACE) and were included in the quantitative analysis of MACE. Additionally, 7 studies were included in the analysis of all cardiovascular adverse events.

Risk of bias assessment was carried out by two authors (A.A.S.P. and T.A.) using Version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2). Any discrepancies were resolved through consensus.

The quality and risk of bias assessment for individual studies was conducted using Version 2 of the Cochrane risk-of-bias tool for randomized trials

Table 1. Characteristics of Studies

Study	Study Design	Country	Age (y.o.)	Intervention Group, n	Comparison Group, n	Treatment Duration (mo)	Treatment Dose	Follow-Up Duration (mo)	CV events on intervention group, n	CV events on comparison group, n
Lincoff, A.M., *et al*, 2023[27]	RCT	USA	63.3 ± 7.9 (testosterone group) 63.3 ± 7.9 (placebo group)	2601	2603	21.8 ± 14.2 (testosterone group) 21.6 ± 14.0 (placebo group)	Transdermal testosterone gel 1.62% (40.5 mg of testosterone) once daily (with titration, maintain testosterone level 350 - 750 ng/dL)[a]	33.1 ± 12.0 (testosterone group) 32.9 ± 12.1 (placebo group)	522	440
Brock, G., *et al,* 2016[28]	RCT	Multi Country	54.7 ± 10.6 (testosterone group) 55.9 ± 11.4 (placebo group)	354	356	3	T-sol 3mL (60 mg of testosterone) once daily (with titration, maintain testosterone level 300 - 1050 ng/dL)[b]	-	0	5
Konaka, H.,*et al* 2016[29]	RCT	Japan	65.65 ± 9.01 (testosterone group) 67.55 ± 9.36 (control group)	169	165	13	T enanthate 250 mg i.m. every 4 weeks	-	1	Not Reported
Basaria, S., *et al*, 2010[30]	RCT	USA	74 ± 6 (testosterone group) 74 ± 5 (placebo group)	106	103	6	Transdermal gel 10g (100 mg of testosterone) once daily (with titration, maintain testosterone level 500 - 1000 ng/dL)[c]	3	24	5
Emmelot -Vonk,M .H.,*et al,* 2008[31]	RCT	Netherlands	67.1 ± 5.0 (testosterone group) 67.4 ± 4.9 (placebo group)	113	110	6	Testosterone undecanoate 40 mg (160 mg of testosterone) two capsules, twice per day	Not Specified	7	3
Srinivas - Shankar , U.,*et al,* 2010[32]	RCT	UK	73.7 ± 5.7 (testosterone group 73.9 ± 6.4 (placebo group)	130	132	6	Transdermal hydro-alcoholic T gel 50 mg per day (with titration, maintain testosterone level 18 - 30 nmol/L)[d]	-	4	2
Snyder, P.J.,*et al,* 2015[33]	RCT	USA	72.7 ± 5.8 (testosterone group) 72.1 ± 5.7	394	394	12	Transdermal testosterone gel 1.62% (81 mg of testosterone) once daily (with titration, maintain testosterone level 280 - 873 ng/dL)[e]	24	33	49

RCT = Randomized Control Trial; CV = cardiovascular; i.m = intramuscular; mL = milliliter; mg = milligram; ; mg/dL = milligram per deciliter; ng/dL = nanogram per deciliter; y.o = years old; mo = months

aPatients started on 40.5 mg of testosterone. Dose adjustment done at week 2,4,12, and 26 and months 12,18, 24, and 48. If serum testosterone concentrations greater than 750 ng/dL, decrease daily dose by 20.25 mg; between 350 ng/dL - 750 ng/dL, continue current does; less than 350 ng/dL, increase daily dose by 25.25 mg

bPatients started on 60 mg of testosterone. Dose adjustment algorithm done at week 4 and 8 based on single total testosterone level measurement. If required, dose was decreased to 30 mg or increased in 30 mg increments with a maximum dose of 120 mg daily.

cPatients started on 100 mg of testosterone. Dose adjustment starts at two weeks after randomisation. If serum testosterone concentration is greater than 1000 ng/dl, decrease daily dose to 50 mg; less than 500/dL, increase daily dose to 150 mg daily

dPatients started on 50 mg of testosterone. Dose adjustment done at day 10 and month 3. If serum testosterone concentration is greater than 30 nmol/L, decrease daily dose to 25 mg; less than 18 nmol/L, increase daily dose to 75 mg

ePatients started on 81 mg of testosterone. Dose adjustment done at months 1, 2, 3, 6, and 9 to keep testosterone normal level according to Framingham Heart Study

(RoB 2) and is visually presented in Figure 2. Among the seven studies reviewed, five studies 27–29,31,32 demonstrated an overall low risk of bias, indicating a high level of methodological rigor. However, two studies 30,33 raised some concern regarding the overall risk of bias.

Specifically, one study 33 exhibited some concern about the risk of bias related to the randomization process. Additionally, another study 30 reported some concern regarding the risk of bias associated with outcome measurement.

The summary of MACE and cardiovascular events in the TRT and placebo groups is visually presented in Figures 3 and 4 respectively. Our analysis encompassed two primary outcomes: major adverse cardiac events (MACE) and all cardiovascular adverse events. In our comprehensive review, we included six studies for

Table 2: Cardiovascular adverse events prevalence and number of reporting studies

Cardiovascular events	TRTs (n)	Control (n)	Number of studies
Total Population	(n): 3796	(n): 3782	
Non-MACE Cardiovascular Events			
VTE	56	44	2
Chest pain, unspecified	2	1	2
Cardiogenic Edema	5	0	1
Arrhythmia			
Bradycardia	1	0	1
Tachycardia	94	64	1
Unspecified	145	94	3
ECG changes, unspecified	3	2	1
Syncope	2	1	1
PAD	5	9	1
Other	8	3	2
MACE			
Cardiovascular deaths	88	253	2
MI	75	79	4
Stroke	41	44	4
Heart Failure	60	58	4
Total	585	652	

VTE: Venous Thromboembolism; ECG: Electrocardiogram; PAD: Peripheral artery disease; MACE: major adverse cardiovascular events; MI: Myocardial infarct.

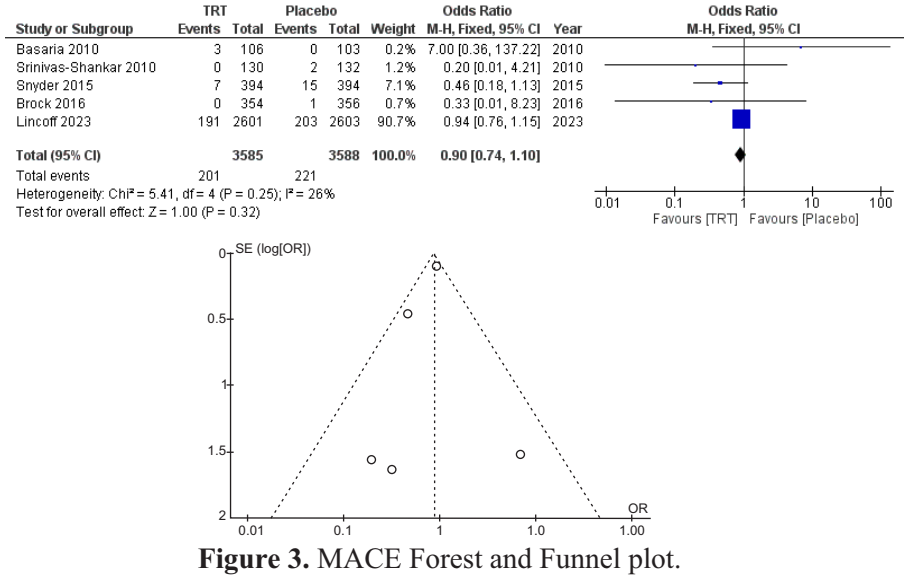

Figure 3. MACE Forest and Funnel plot.

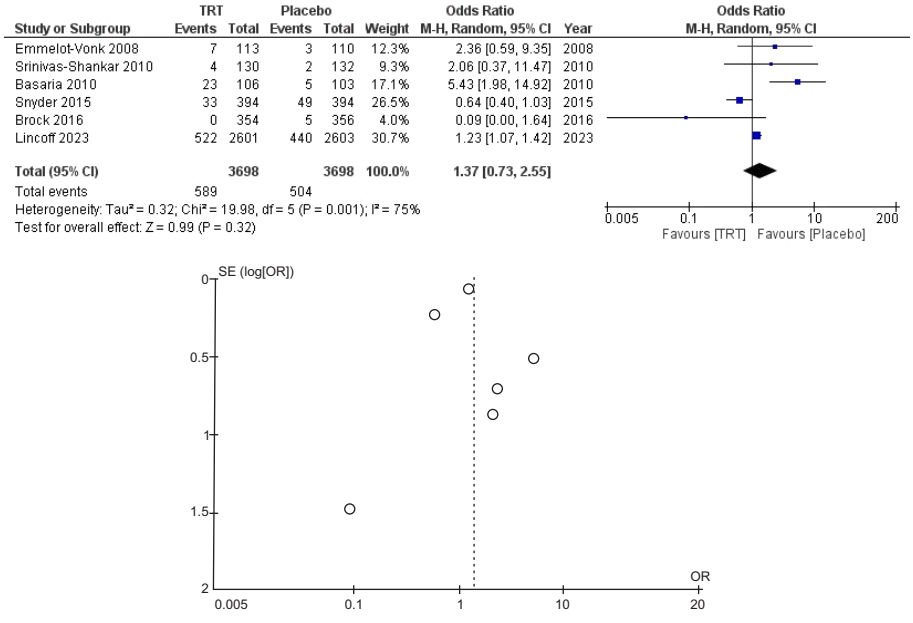

Figure 4. All cardiovascular adverse events Forest and Funnel Plot.

quantitative analysis and seven studies for qualitative analysis. Collectively, our analysis did not reveal a significantly higher odds of cardiovascular events in the TRT group when compared to the placebo group.

It is worth noting that individual studies within our review presented varying perspectives on the impact of TRT on cardiovascular events. For instance, Konaka et al.'s studyprovided compelling evidence suggesting that individuals undergoing TRT exhibited a reduced likelihood of experiencing cardiovascular events when compared to those who received a placebo (OR: 0.09; 95% CI: 0.01, 0.73)29. This finding implies a potential protective effect of TRT against cardiovascular events. Conversely, a study authored by Basariaet al.30 reported a contrasting narrative. According to this study, patients receiving TRT demonstrated a noteworthy increase in the likelihood of encountering cardiovascular events (OR: 5.13; 95% CI: 1.86, 14.15). This result suggests a potential association between TRT and an elevated risk of cardiovascular events.

In the analysis of MACE across the 5 studies comparing TRT with a placebo, no significant difference in the odds of experiencing MACE was observed in theTRT group compared to the placebo group (OR: 0.90; 95% CI: 0.74, 1.10). This finding suggests that, on average, there is no increased risk of MACE associated with TRT in this cohort of studies.

The analysis demonstrated a low level of heterogeneity among these studies, with an I^2 value of 26%. This low variability in the results indicates that the individual study findings were relatively consistent in their estimation of the effect of TRT on MACE. For this analysis, the Mantel-Haenszel method was employed, and a fixed-effects model was used. The use of a fixed-effects model implies that the assumption was made that the true effect size is the same across all studies, and any observed variation is due to chance alone. This choice of model was appropriate given the low heterogeneity observed.

The funnel plot depicted in Figure 3 was used to evaluate potential publication bias in our analysis. Notably, the funnel plot displayed asymmetry, which can suggest the presence of bias. However, it's crucial to consider that our review of MACE included only five studies, making it challenging to accurately interpret the symmetry of the funnel plot. Several factors, including publication bias and variations in study quality or populations, may contribute to the observed asymmetry.

In the analysis of all cardiovascular adverse events across the six studies comparing TRT with a placebo, no significant difference in the odds of

experiencing cardiovascular adverse events was observed in the TRT group compared to the placebo group (OR: 1.37; 95% CI: 0.73, 2.55). This result suggests that, on average, there is no substantial increase in the risk of cardiovascular adverse events associated with TRT in this group of studies.

However, it's important to note that the analysis showed a high level of heterogeneity with an I^2 value of 75%, indicating significant variability in the results among the individual studies. This suggests that there may be factors contributing to the heterogeneity, such as differences in study populations, treatment protocols, or other variables. For this analysis, the Mantel-Haenszel method was employed, and a random-effects model was used. The use of a random-effects model acknowledges the presence of heterogeneity and incorporates it into the analysis by considering both within-study and between-study variability.

To assess potential publication bias, a funnel plot (depicted in Figure 4) was utilized. Notably, the funnel plot displayed asymmetry, which may indicate the presence of bias. However, it's important to interpret this with caution, as the analysis is based on a relatively small number of studies, and various factors can contribute to funnel plot asymmetry, including publication bias and methodological differences between studies.

DISCUSSION

TRT has been a well-established and effective treatment for men with hypogonadism since its synthesis in 1935.34 However, recent studies, including those by Basaria et al.30, Vigen et al.[16], and Finkle et al.[17], have raised concerns about its potential cardiovascular risks.

In the Basaria et al. Testosterone in Older Men with Mobility Limitations (TOM) trial [30], men over 65 with limited mobility and testosterone levels below 350 ng/dL received either testosterone or a placebo gel for six months. The testosterone group experienced 23 cardiovascular adverse events, including myocardial infarction, syncope, stroke, and atrial fibrillation, compared to five events in the placebo group, resulting in an odds ratio (OR) of 5.8 (95% CI 2.0 - 16.8). Similarly, Vigen et al.'s retrospective cohort study[16] of men with testosterone concentrations below 300 ng/dL who had undergone coronary angiography reported a higher risk of heart attacks, strokes, and mortality in TRT recipients, with a hazard ratio (HR) of 1.29 (95% CI 1.04-1.58). Finkle et al.'s analysis[17] of TRT users using a large claims database found an increased risk of non-fatal myocardial infarctions within 90 days of the initial TRT prescription, with a relative risk (RR) of 1.36 (95% CI 1.03-1.81).

In response to these concerning findings, the FDA took action by issuing safety warnings in 2014 and revised testosterone labeling in March 2015 to indicate an elevated risk of stroke and heart attack associated with TRT use.[35] As part of these regulatory changes, the FDA updated testosterone labeling, incorporating a limitation of use in men with "age-related hypogonadism". The FDA also told the companies that make these products to run well-planned clinical trials. These trials should give a clear answer about whether using these products really raises the risk of heart attack or stroke.

In compliance with this mandate, Lincoff et al. conducted the Testosterone Replacement Therapy for Assessment of Long-Term Vascular Events and Efficacy Response in Hypogonadal Men (TRAVERSE) study[27], the largest trial of TRT in men with hypogonadism. Their results, based on 5,198 patients who received testosterone or placebo for an average duration of 22 months, demonstrated that TRT did not lead to a higher incidence of major cardiac events compared to the placebo group. Notably, major cardiac events occurred in 7.0% of patients in the testosterone group and 7.3% of patients in the placebo group.

Overall, the controversy surrounding TRT's cardiovascular effects underscores the importance of rigorous research and regulatory oversight in this field. While initial studies raised concerns, subsequent investigations have aimed to clarify the risk-benefit profile of TRT, ultimately providing a more comprehensive understanding of its impact on cardiovascular health.

CONCLUSION

In conclusion, our study's findings suggest that TRT does not appear to be associated with a significantly elevated risk of cardiovascular events in men with hypogonadism. These results provide assurance for individuals considering TRT as a treatment option, highlighting its potential benefits for improving the quality of life in hypogonadal men. However, the importance of individualized clinical assessment in treatment decisions cannot be overstated. Continued research is warranted to further refine our understanding, but our findings

contribute to the growing body of evidence supporting the cardiovascular safety of TRT as a viable therapeutic option for hypogonadism.

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