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Review Article

Association between testosterone replacement therapy and cardiovascular outcomes: A meta-analysis of 30 randomized controlled trials

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ABSTRACT

Background: The Cardiovascular safety of testosterone replacement therapy (TRT) among men with hypogonadism is not well established to date. Hence, we sought to evaluate the cardiovascular disease (CVD) outcomes among patients receiving testosterone therapy by using all recently published randomized controlled trials.

Methods: We performed a systematic literature search on PubMed, EMBASE, and Clinicaltrial.gov for relevant randomized controlled trials (RCTs) from inception until September 30th, 2023.

Results: A total of 30 randomized trials with 11,502 patients were included in the final analysis. The mean age was ranging from 61.61 to 61.82 years. Pooled analysis of primary and secondary outcomes showed that the incidence of any CVD events (OR, 1.12 (95%CI: 0.77–1.62), $P = 0.55$), stroke (OR, 1.01 (95%CI: 0.68–1.51), $P = 0.94$), myocardial infarction (OR, 1.05 (95%CI: 0.76–1.45), $P = 0.77$), all-cause mortality (OR, 0.94 (95%CI: 0.76–1.17), $P = 0.57$), and CVD mortality (OR, 0.87 (95%CI: 0.65–1.15), $P = 0.31$) was comparable between TRT and placebo groups.

Conclusion: Our analysis indicates that for patients with hypogonadism, testosterone replacement therapy does not increase the CVD risk and all-cause mortality.

Introduction

Testosterone replacement therapy (TRT) is commonly used in patients with hypogonadism, often in elderly men who are >50 years old.[1] Nevertheless, not all individuals with reduced testosterone levels exhibit symptoms.[1] For those who do, these symptoms can encompass impairments in sexual and physical functions.[1] In addition, obesity, type 2 diabetes mellitus, metabolic syndrome, and cognitive dysfunction are

Abbreviations: AKI, Acute Kidney Injury; BMI, Body Mass Index; CV, Cardiovascular; CVD, Cardiovascular Disease; CI, Confidence Interval; FDA, Food and Drug Administration; HR, Hazard Ratio; MI, Myocardial Infarction; OR, Odds Ratio; PE, Pulmonary Embolism; RCT, Randomized Control Trial; RR, Relative Risk; TD, Testosterone Deficiency; TRT, Testosterone Replacement Therapy; TEAAM, Testosterone's Effects on Atherosclerosis Progression in Aging Men; TRAVERSE, The Testosterone Replacement Therapy for Assessment of Long-term Vascular Events and Efficacy ResponSE in Hypogonadal Men.

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associated with testosterone deficiency (TD).[2–4] These conditions are widely acknowledged cardiovascular (CV) disease (CVD) risk factors, and with their increased prevalence in patients with TD, it is believed that these patients are at increased CVD risk.[3,4]

Various studies reported poor CV health in those with TD with increased CVD events, including myocardial infarction (MI) and stroke.[5] With the indication of TRT for hypogonadism symptoms, such as erectile dysfunction and decreased muscle mass, it seems logical that normalizing testosterone levels with supplementation alleviates some of the adverse events.[6] However, conflicting results were reported in retrospective cohort studies and randomized clinical trials (RCTs) of patients receiving TRT and with anabolic steroid abuse.[7–12] In March 2015, the Food and Drug Administration (FDA) issued a drug safety communication cautioning about the use of products containing testosterone and highlighting a potential rise in CVD events.

In light of the growing utilization of TRT among individuals with TD in recent years, conflicting results from previous studies, and increased reports of CVD events in those with anabolic steroid abuse, the impact of testosterone on CV health remains a subject of ongoing debate.[9,13] Hence, we sought to perform an updated meta-analysis evaluating the safety of TRT and CVD outcomes among patients with hypogonadism.

Methods

This meta-analysis was conducted and reported following the PRISMA (Preferred reporting items for systematic review and Meta-analysis) 2020 guidelines[14] and performed according to established methods, as described previously.[15–17]

Search strategy

We conducted a systematic literature search in PubMed, Embase, and ClinicalTrial.gov using predefined MESH terms by using "AND" and "OR". The following search terms were used: "testosterone therapy" OR "hypogonadism" AND "cardiovascular diseases" OR "acute coronary syndrome" OR "myocardial infarction" OR "STEMI" AND "stroke" AND "mortality" AND "outcomes". We queried databases from their search inception up until 15th September 2023 without any restrictions on the language of the studies. Search strategies are listed in **Supplementary Table 1**.

All the studies were carefully screened and exported to the Mendeley reference manager used to handle searched citations. A manual check was carried through to crosscheck for any remaining duplicates. Two reviewers (K.R and M.J) reviewed the papers based on the title and abstract. Discrepancies regarding the inclusion of studies were arbitrated by another author (N·D).

Eligibility criteria

We included only clinical trials involving patients with hypogonadism and with patients ≥ 18 years of age. It was decided to include studies with two arms in one, with TRT as an intervention and placebo as a control group. Studies must have reported outcomes of interest (primary and secondary outcomes). Studies that were performed on animals, reviews, case reports, case series, studies with a single arm or with non-testosterone therapy as an intervention, or without outcomes of interest were excluded from the review.

Clinical outcomes

The primary outcome of this meta-analysis was all-cause mortality. Secondary outcomes include any CVD events, MI, and stroke.

Data extraction and quality assessment

Data from the eligible studies, such as demographics, study design, comorbidities, and outcomes between testosterone therapy and placebo groups, were extracted to a Microsoft Excel® 2019 spreadsheet by two authors (A.H and MJ).

Two authors (ND and KR) independently assessed the quality of the included studies using Cochrane Collaboration's tool for assessing the risk of bias in RCTs.

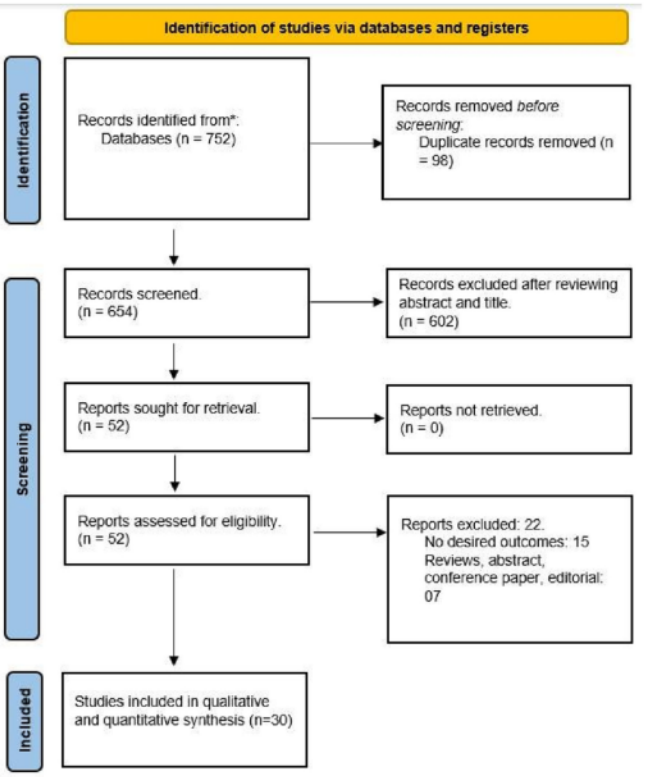

Fig. 1. PRISMA flow diagram.

Statistical analysis

Baseline continuous variables were summarized in mean (standard deviation), whereas dichotomous variables were described in frequency or percentage. We performed a conventional meta-analysis for primary and secondary outcomes and adopted the DerSimonian and Laird random-effect model for the study variations. Outcomes were reported as pooled odds ratio (OR), and their corresponding 95% confidence interval (95% CI). Statistical significance was met if the 95% CI did not cross the numeric "1" and the two-tailed *p*-value was <0.05. We considered a two-tailed p-value of <0.05 to be statistically significant. In addition, we assessed the between-study heterogeneity using the Higgins I-square (I^2) test, with I^2 values $<75\%$ considered mild-moderate and $> 75\%$ considered high.[18] A leave-one-out sensitivity analysis was utilized to explore the cause of heterogeneity.[19] All statistical work, inclusive analysis, and graphical illustrations were conducted using STATA (version 17.0, StataCorp).[20]

Results

The preliminary database search using the pre-specified keywords yielded 752 articles, of which 98 studies were excluded after the removal of duplicates. 602 studies were further excluded from the initial post-title and abstract screening based on the inclusion and exclusion criteria and comparison arm. The full-text review was conducted for the remaining 52 articles identified during the search period, of which 22 studies were excluded: no desired outcomes, single arm or abstract without any desired outcomes. Hence, a total of 30 studies met the

Table 1
Baseline characteristics of the included studies.

Study	TYPE	Parameters	Dose	Sample Size	Age, years	Diabetes mellitus, n	Hypertension, n	Testosterone initial (ng/dl)	Final Testosterone (ng/dl)	Follow-up (months)
TRAVERSE	RCT	Testosterone		2596	63.3	1788	2423	227	358	36
		Placebo		2602	63.3	1844	2402	227	247	
Nair et al.	RCT	Testosterone	50 mg	27	68.4			28.3	38.7	24
		Placebo		30	70.4			30.3	22.59	
Nair et al.	RCT	Testosterone	75 mg	29	68.4			389.3	393.08	24
		Placebo		31	67.1			398.4	414.69	
Malkin et al.	RCT	Testosterone	5 mg	37	63.1			400.9	565.29	12
		Placebo		39	64.9			348.9	360.43	
Kenny et al.	RCT	Testosterone	5 mg	69	77.9	12	22	396.3	583.6	12
		Placebo		62	76.3	10	24	407.8	477.7	
TIMES 2	RCT	Testosterone	60 mg	108	59.9	68		265.35	562.42	12
		Placebo		112	59.9	69		273.9	256.7	
Hildreth et al.	RCT	Testosterone		96	66.5			297.7	457	13
		Placebo		47	66.5			294.3		
Basaria et al	RCT	Testosterone	100 mg	106	29.7	25	90	250	578	6
		Placebo		103	30	28	80	236	290	
Ho et al	RCT	Testosterone	1000 mg	60	53.4			256.7	686.4	12
		Placebo		60	53			263.46	323.03	
Snyder et al	RCT	Testosterone	5 g	395	72.1	148	286	232	500	12
		Placebo		395	72.3	144	280	236	231	
Srinivas-Shankar et al	RCT	Testosterone	50 mg	130	73.7			317.26	530.7	6
		Placebo		132	73.9			314.38	308.6	
Basaria et al	RCT	Testosterone	75 mg	155	66.9	22	71	307.2	565	18
		Placebo		151	68.3	24	57	307.4	330	
Behre et al	RCT	Testosterone	50 mg	183	61.9			299.9	580.3	6
		Placebo		179	62.1			314.37	320.6	
Giltay et al	RCT	Testosterone	1000 mg	113	51.6	32	100	222.08	409.5	7
		Placebo		71	52.8	24	61	242.27	265.7	
Hackett et al	RCT	Testosterone	1000 mg	92	61.2			211.7	214.6	7
		Placebo		98	62			286.4	227.85	
Svartberg et al	RCT	Testosterone	250 mg	15	64.5			622.9	657.6	7
		Placebo		14	67.5			591.26	478.78	
Amory et al	RCT	Testosterone	200 mg	24	71			285.5	556	36
		Placebo		24	71			297.07	285.53	
Brock et al	RCT	Testosterone	60 mg	358	54.7			202.6		3
		Placebo		357	55.5			201.2		
Emmelot-Vonk et al	RCT	Testosterone	80 mg	113	67.1			317.26	317.26	6
		Placebo		110	67.4			299.95	320.46	
Giannatti et al	RCT	Testosterone	1000 mg	45	62			250.9		10
		Placebo		43	62			245.15		
Aversa et al	RCT	Testosterone	1000 mg	40	58	12	26	239.3	412.44	24
		Placebo		10	57	6	6	259.5	429.74	
Merza et al	RCT	Testosterone	5 mg	20	63			242.27	467.24	6
		Placebo		19	59.7			216.31	222.08	
Aversa et al	RCT	Testosterone	160 mg- Oral T (10); 1000 mg- i.m T (32)	42	57.5	13				
		Placebo		10	55	4				
Crawford et al	RCT	Testosterone	200 mg	18	58.7			398.06	721	12
		Placebo		16	59.9			452.81	331.68	
Barnouin et al	RCT	Testosterone	40.5 mg	42	73.6					
		Placebo		41	72.2					
Kalinchenko et al.	RCT	Testosterone	1000 mg	113	51.6	32	56	193.2	377.8	8
		Placebo		71	52.8	24	35	216.3	224.9	
Kaufman et al.	RCT	Testosterone		170	52.9					
		Placebo		26	55.8					
Wittert et al.	RCT	Testosterone	1000 mg	504	59.8			386.5	484.85	24
		Placebo		503	59.6			401	422.9	
Navarro et al.	RCT	Testosterone	1000 mg	14	65	8	11	220	531	12
		Placebo		15	64	6	13	257	314	
Sinclair et al	RCT	Testosterone	1000 mg	50	54			266.78	556.65	12
		Placebo		51	55.5			262.46		
Legros et al	RCT	Testosterone	oral TU 80, 160 or 240 mg	79	58.4					
		Placebo		237	58.8					

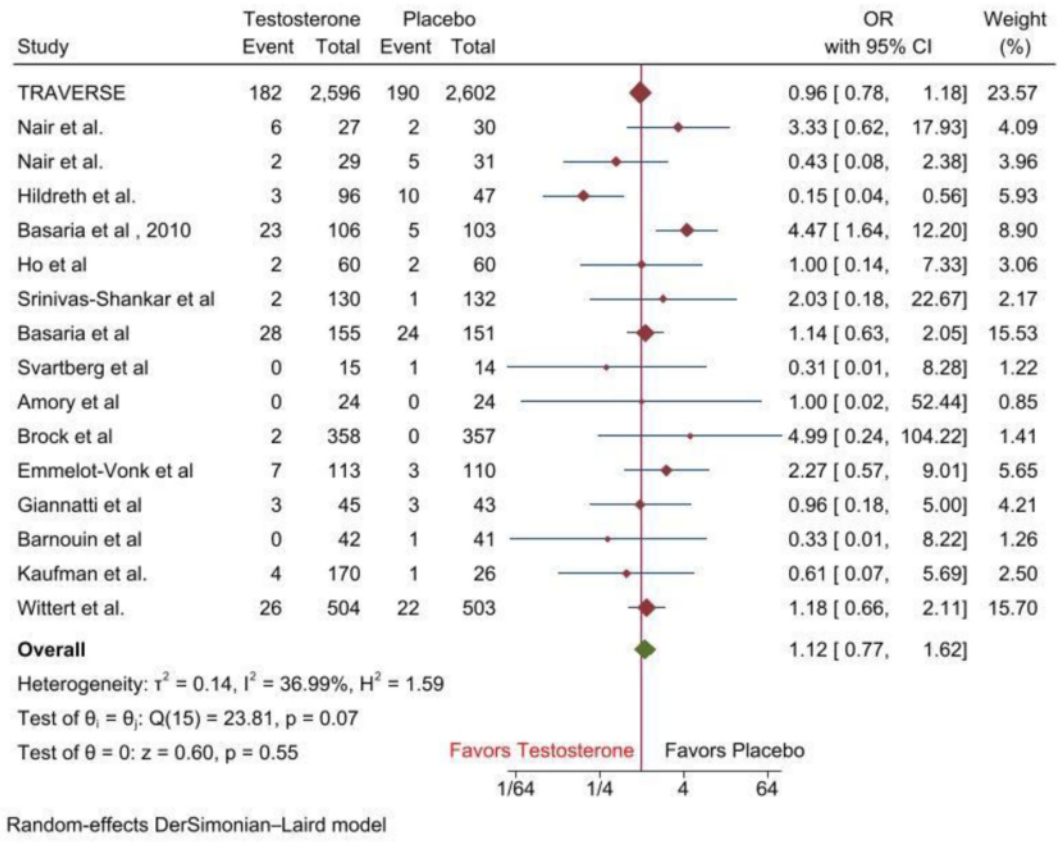

Fig. 2. Forest plot of primary outcomes of any cardiovascular event.

eligibility criteria and were included in the meta-analysis.[21–50] The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram is depicted in Fig. 1.

Baseline characteristics of included studies

A total of 30 RCTs with 11,502 patients (5843 in the TRT group and 5659 in the control group) were included in the analysis. The mean age of the testosterone therapy group was 61.61 years, and 61.82 years in the placebo group. The most common comorbidities among patients with TRT group and placebo group were diabetes mellitus (49.7% vs.50.2%) and hypertension (51.05% vs. 48.9%), respectively. The mean follow-up time was 13.6 months. The study characteristics, demographics, and comorbidities are presented in Table 1.

Quality assessment

Using the ROB2 tool to assess the methodological quality of the included RCTs, it was determined that one study (Kaufman et al)[46] exhibited high methodological rigor, while all thirty studies indicated a low risk of bias and thus ensuring their results can be regarded as robust and reliable. (**Supplementary Fig. 1A-B**).

Meta-analysis of primary and secondary outcomes

The pooled analysis of primary and secondary endpoints showed that in men with hypogonadism, TRT was not superior to placebo for the risk of incidence of any CVD events (OR, 1.12 (95%CI: 0.77–1.62), $P = 0.55$), I2 = 36.9%) (Fig. 2), stroke (OR, 1.01 (95%CI: 0.68–1.51), $P = 0.94$), I2 = 0%), and MI (OR, 1.05 (95%CI: 0.76–1.45), $P = 0.77$), I2 = 0%) (Fig. 3A-B), all-cause mortality (OR, 0.94 (95%CI: 0.76–1.17), $P = 0.57$), I2 = 0%), and CVD mortality (OR, 0.87 (95%CI: 0.65–1.15), $P = 0.31$), I2 = 0%) (Fig. 4A-B).

Meta-analysis of primary and secondary outcomes without TRAVERSE randomized trial

The pooled analysis showed that in men with hypogonadism, TRT was not superior to placebo for the risk of incidence of any CVD events (OR, 1.18 (95%CI: 0.72–1.95), $P = 0.51$), I2 = 40.50%), stroke (OR, 1.24 (95%CI: 0.56–2.76), $P = 0.60$), I2 = 0%), MI (OR, 0.79 (95%CI: 0.33–1.86), $P = 0.58$), I2 = 0%), all-cause mortality (OR, 0.79 (95%CI: 0.47–1.32), $P = 0.37$), I2 = 0%), and CVD mortality (OR, 1.16 (95%CI: 0.41–3.32), $P = 0.78$), I2 = 0%) (**Supplementary Figs. 2–6**).

Sensitivity analysis and publication bias

Sensitivity analyses were carried out to test the robustness of the primary and secondary outcomes. After leave-one-out analysis, the results of meta-analysis on any cardiovascular events, stroke, myocardial infarction, all cause mortality and cardiovascular mortality remained unchanged showing robustness of the findings (**Supplementary Fig. 7–11**). Assessment of publication bias through funnel plot visualization showed that there was no evidence of publication bias, with minimal or no funnel plot asymmetry observed for all the outcomes **(Supplementary Fig. 12–16).**

Discussion

Our findings show that TRT in patients with hypogonadism was not associated with increased risk of any CVD events, all-cause mortality, stroke, MI, and CVD mortality. This analysis is an important addition to the literature as TRT is widely used currently for the treatment of hypogonadism in middle-aged and elderly men, as well as due to

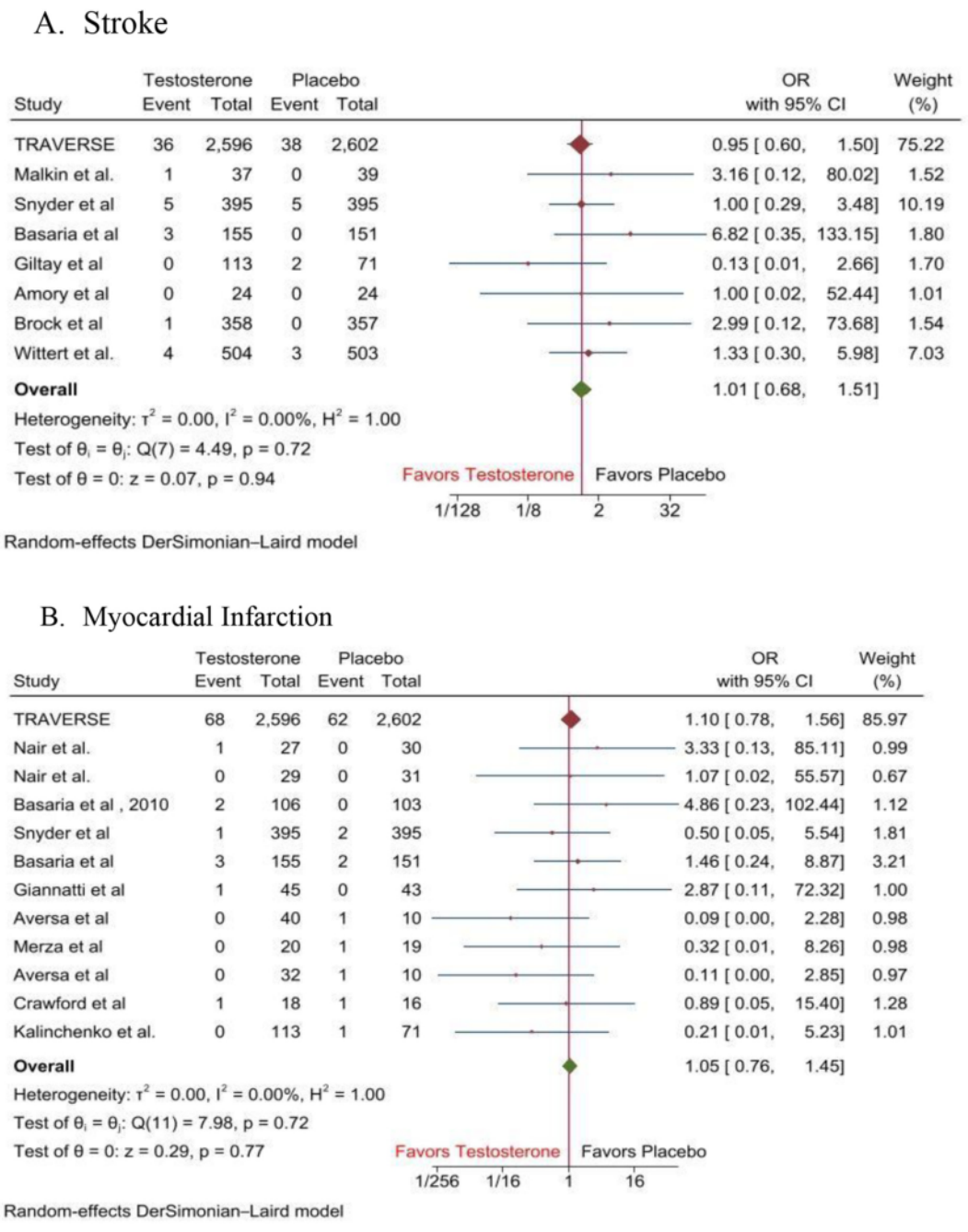

Fig. 3. Forest plot of secondary outcomes of A) Stroke, and B) Myocardial Infarction.

evolving evidence-based shifts in clinical use regarding its safety and risk vs. benefit. Following the FDA statement on the use of TRT with caution due to its potential CV adverse effects, International Expert Consensus Resolutions recommended that there is no scientific basis for any age-specific recommendations against the use of TRT in men. They concluded that no evidence supports an increased risk of CVD events with TRT.[51] Our results add to the previously published reviews and meta-analyses by considering outcomes like all-cause mortality, CVD events, stroke, and MI, which have led to inconclusive findings.

Alexander et al., in their meta-analysis, studied RCTs and observational studies and suggested a lack of significant association between exogenous testosterone and MI, stroke, and all causes of mortality.[52] This study did not consider any effects of dose-dependent or age-associated modifications in the CV effects of exogenous testosterone.[52] Wallis et al. observed in a cohort study in Canada the effects of exogenous testosterone based on exposure quantity. In a control-matched cohort, patients in the lowest tertile of testosterone exposure had an increased risk of CVD events (HR1.26, 95%CI 1.09–1.46), increased mortality compared to controls in contrast to patients in the highest tertile of testosterone exposure reporting a lower risk of CVD events (HR 0.84, 95%CI 0.72–0.98), decreased mortality compared to controls.[53] The retrospective cohort study by Finkle and colleagues reported a risk of MI in patients prescribed TRT supplementation with a relative risk (RR) of 0.95 in men under 55 years of age and an RR of 3.43 in men aged ≥75 years. The study did not consider a hypogonadism diagnosis and hence was not included in our meta-analysis.[54] Kenny et al. conducted a double-blind, placebo-controlled RCT in men with low testosterone levels who received 5 mg/d of testosterone gel or placebo for 12–24 months and found no difference in cholesterol levels or CVD events between the two groups.[24]

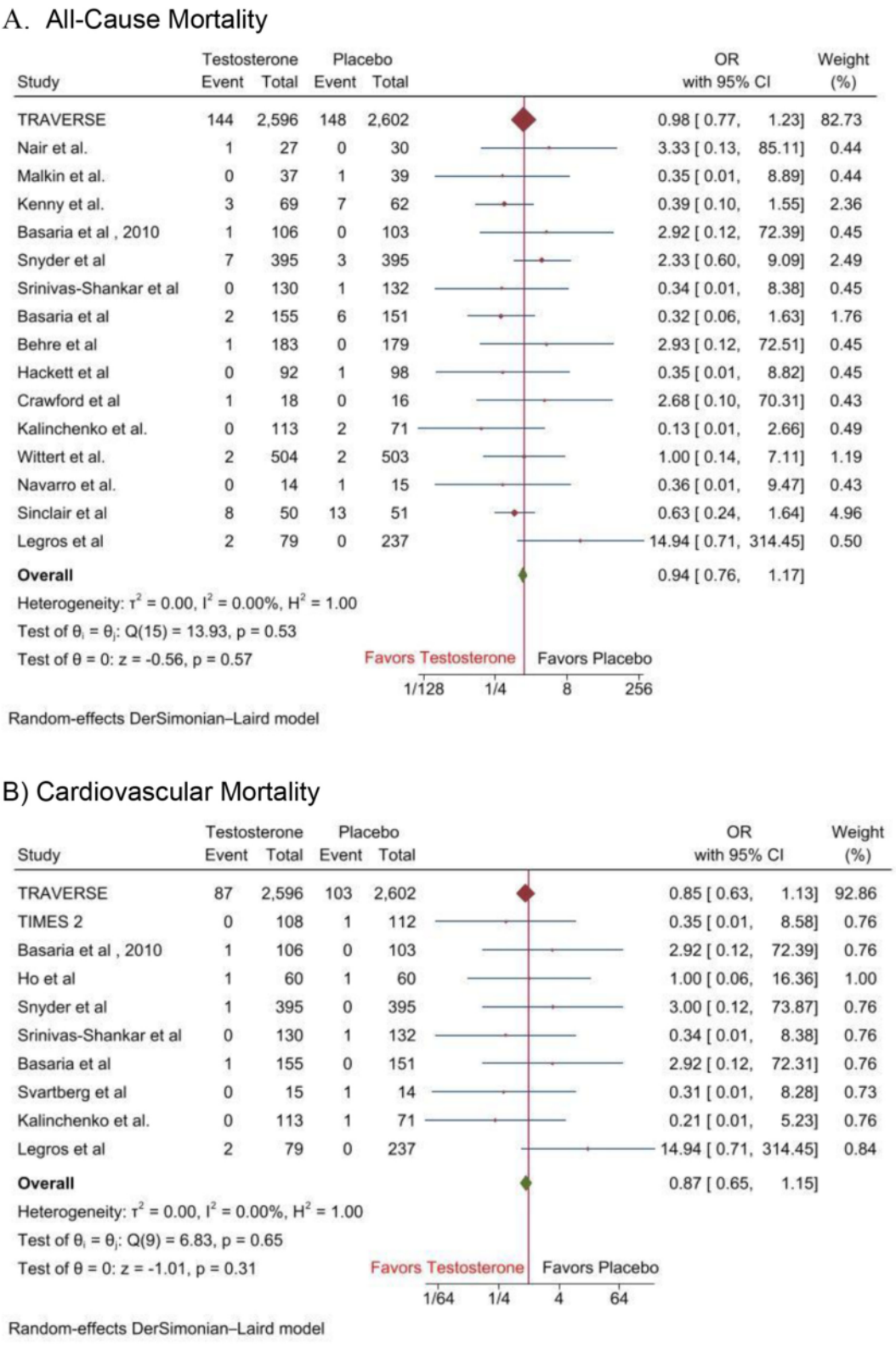

Fig. 4. Forest plot of secondary outcomes of A) All-Cause Mortality, B) Cardiovascular Mortality.

The Testosterone Replacement Therapy for Assessment of Long-term Vascular Events and Efficacy ResponSE in Hypogonadal Men (TRAVERSE) study is a randomized, double-blind, placebo-controlled, parallel-group, noninferiority, multicenter study that evaluated the CV safety and long-term efficacy of TRT supplementation in middle-aged and older men with hypogonadism with an increased risk of CVD. The RCT concluded the non-inferior result of TRT compared to placebo in terms of MACE (HR, 0.96; 95%CI, 0.78 to 1.17; $P < 0.001$ for non-inferiority).[6] In a RCT, Testosterone's Effects on Atherosclerosis Progression in Aging Men (TEAAM) by Basaria et al., males with low or low normal testosterone levels who received testosterone gels did not result in a significant difference in rates of change in coronary artery calcium

scoring or standard carotid artery intima-media thickness.[27] In a study identifying the biomarkers for atherosclerosis, testosterone was found to be downregulated in patients with atherosclerosis, of which 79% were males.[55]

In a RCT by Lincoff et al., men 45–80 years of age with pre-existing or a high risk of CVD with symptomatic and lab-proven hypogonadism were prescribed TRT and placebo gel for a mean duration of 22 months. Although non-inferior results were noted for the patients receiving TRT in terms of major CVD events, a higher incidence of atrial fibrillation, acute kidney injury, and pulmonary embolism was observed in the TRT group.[21] Studies that did a sub-group analysis in patients with diabetes and metabolic syndrome identified protective effects of testosterone supplementation against major CVD events.[56–58] In an RCT of 22 men with coronary heart disease who were treated with oral testosterone for eight weeks, a modest increase in myocardial perfusion was noted on the magnetic resonance imaging in the region of unobstructed coronary artery disease.[59] As noted in RCT, testosterone administration is noted to cause QTc shortening in community-dwelling men, and androgen deprivation in men with prostate cancer was associated with significant QTc elevation.[60,61] RCTs have reported a protective role of TRT on CVD morbidity in obese patients with a body mass index>30 kg/m2.[62] In a prospective study conducted in men with nonalcoholic fatty liver disease and hypogonadism, lower all-cause, and CVD mortality was noted in men who received testosterone supplementation compared to placebo. Also, a higher incidence of stroke, MI, heart failure, aortic aneurysm, and lung embolism were noted in the placebo group.[63]

TRT supplementation in hypogonadal men improves insulin sensitivity and glucose levels, reduces body fat, and increases lean body mass, all factors that reduce the risk of coronary artery disease.[64] Testosterone by hepatic suppression of hepcidin, augmentation of erythropoietin, and a direct effect on bone marrow stimulates red blood cell production, which in hypogonadal men with pre-existing erythrocytosis increases the risk of thrombotic events.[64] The effects of exogenous and endogenous testosterone may differ. Exogenous testosterone is noted to predispose to clotting and thrombotic disorders, including hypertension, reduced high-density lipoprotein cholesterol, blood hyperviscosity, platelet aggregation, and an increase in circulating estrogen, which in turn can be linked to the observed excess of major CVD events.[65] CV effects of testosterone include downregulation of L-type voltage-gated calcium channels and upregulation of calcium-activated potassium channels, and lower testosterone is associated with longer QTc, which increases the risk of incidental ventricular arrhythmia and sudden cardiac death.[65,66] Testosterone is studied to cause vasodilation in humans, hence reducing ischemia by coronary vasodilation and increasing the time to exercise-induced ST segment depression on treadmill tests.[67,68]

Strength and limitations

This meta-analysis included 30 RCTs to evaluate the CV safety of TRT, giving a most comprehensive and robust assessment. There were limitations worth mentioning, including the fact that the RCTs have varying study designs, different races and ethnicities, and endpoints. Hence, a potential for inherent heterogeneity is possible. Different follow-ups are being used to evaluate the outcomes. Hence, a possible fluctuation among the events may be present.

Conclusion

Our analysis indicates that for patients with hypogonadism, TRT does not appear to increase the CVD risk and all-cause mortality (**Graphical Abstract**). Further, large power multicenter RCTs are needed to strengthen the evidence available by including participants with varying baseline CVD and race and possibly higher levels of on-treatment testosterone levels.

Source of funding

None.

Disclosure

The abstract of this study has been accepted at the ACC24 Conference for Oral presentation.

CRediT authorship contribution statement

Vikash Jaiswal: Conceptualization, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Aanchal Sawhney:** Writing – original draft, Writing – review & editing. **Chikodili Nebuwa:** Methodology. **Vamsikalyan Borra:** Writing – original draft. **Novonil Deb:** Writing – original draft. **Anupam Halder:** Data curation. **Kripa Rajak:** Writing – original draft. **Mayank Jha:** Data curation. **Zarghoona Wajid:** Writing – original draft. **Dhrubajyoti Bandyopadhyay:** Writing – review & editing. **Jishanth Mattumpuram:** Writing – review & editing. **Carl J. Lavie:** Writing – review & editing.

Declaration of competing interest

None.

Data availability

The data underlying this article is available in the article and its online supplementary material.

Acknowledgement

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pcad.2024.04.001.

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