CLINICAL RESEARCH STUDY

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Cardiovascular Risks of Exogenous Testosterone Use Among Men: A Systematic Review and Meta-Analysis

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ABSTRACT

PURPOSE: We sought to evaluate whether exogenous testosterone therapy is associated with increased risk of serious cardiovascular events as compared with other treatments or placebo.

METHODS: Study selection included randomized controlled trials (RCTs) and observational studies that enrolled men aged 18 years or older receiving exogenous testosterone for 3 or more days. The primary outcomes were death due to all causes, myocardial infarction, and stroke. Secondary outcomes were other hard clinical outcomes such as heart failure, arrhythmia, and cardiac procedures. Peto odds ratio was used to pool data from RCTs. Risk of bias was assessed using Cochrane Collaboration tool and Newcastle and Ottawa scale, respectively. The strength of evidence was evaluated using the Grades of Recommendation, Assessment, Development, and Evaluation Working Group approach.

RESULTS: A total of 39 RCTs and 10 observational studies were included. Meta-analysis was done using data from 30 RCTs. Compared with placebo, exogenous testosterone treatment did not show any significant increase in risk of myocardial infarction (odds ratio [OR] 0.87; 95% CI, 0.39-1.93; 16 RCTs), stroke (OR 2.17; 95% CI, 0.63-7.54; 9 RCTs), or mortality (OR 0.88; 95% CI, 0.55-1.41; 20 RCTs). Observational studies showed marked clinical and methodological heterogeneity. The evidence was rated as very low quality due to the high risk of bias, imprecision, and inconsistency.

CONCLUSIONS: We did not find any significant association between exogenous testosterone treatment and myocardial infarction, stroke, or mortality in randomized controlled trials. The very low quality of the evidence precludes definitive conclusion on the cardiovascular effects of testosterone.

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KEYWORDS: Cardiovascular risks; Exogenous testosterone; Meta-analysis; Systematic review

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Conflict of Interest: GCA is Chair of the Food and Drug Administration's Peripheral and Central Nervous System Advisory Committee, serves as a paid consultant to mobile start-up PainNavigator, serves as a consultant to IMS Health, and serves on an IMS Health scientific advisory board. This arrangement has been reviewed and approved by Johns Hopkins University in accordance with its conflict of interest policies. SS has served as an expert witness for plaintiffs against Pfizer and as a consultant for Eli Lilly, in both cases for products unrelated to those examined herein. The authors have no other conflicts of interest.

Authorship: SS drafted the study protocol; all authors contributed to substantive revisions of the study protocol; EL, DL, and GI conducted study screening and data abstraction; GI developed the preliminary analyses; all authors contributed to substantive interpretation of the study findings; GCA and GI drafted the manuscript; SS performed the meta-analyses; all authors contributed to substantive manuscript revisions and approved of the final manuscript.

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exogenous testosterone. However, Baillargeon et al[8] found a protective effect of testosterone in the highest quartile of prognostic myocardial infarction score (HR 0.69; 95% CI, 0.53-0.92). Shores et al[12] (HR 0.61; 95% CI, 0.42-0.88) and Tan et al[67] (incident rate ratio [IRR] for stroke 0.11; 95% CI, 0.02-0.13; and IRR for myocardial infarction 0.14; 95% CI, 0.08-0.18) found a decreased risk of mortality, and myocardial infarction and stroke, respectively. Vigen et al[10] observed an HR of 1.29 (95% CI, 1.04-1.58) for myocardial infarction, stroke, and mortality among men who underwent angiography, and Layton et al[63] demonstrated higher risk with injection compared with gel for all outcomes (HR for myocardial infarction 1.3; 95% CI, 1.18-1.45; HR for stroke 1.21; 95% CI, 1.1-1.32; HR for mortality 1.34; 95% CI, 1.15-1.56). Finkle et al[9] compared cardiovascular risk for testosterone and PDE5 (as a control) and observed that ratio of IRRs among men above 65 years of age with no history of heart disease was 2.41 (95% CI, 1.12-5.17), and below 65 years of age with cardiovascular disease was 2.07 (95% CI, 1.05-4.11). Etminan et al,[68] the case-control study assessing risk of myocardial infarction with testosterone, demonstrated an increased risk associated with testosterone (HR 1.41; 95% CI, 1.06-1.87).

Strength of Evidence

We downgraded the strength of evidence for the 3 outcomes of myocardial infarction, stroke, and mortality to *low* because of the risk of bias of included RCTs (−1) and imprecision (−1).

DISCUSSION

Our findings show no association between testosterone and myocardial infarction (POR 0.87; 95% CI, 0.39-1.93), stroke (POR 2.17; 95% CI, 0.63-7.54), or mortality (POR 0.88; 95% CI, 0.55-1.41) in RCTs, either individually or as a composite outcome. The strength of evidence was determined to be low for all 3 outcomes. These results are important given how commonly testosterone is prescribed, as well as due to an evolving evidence base and shifting clinical and regulatory landscape regarding its safety and risk/benefit balance for the treatment of hypogonadism in middle-aged and elderly men.

Our results add to several systematic reviews and meta-analyses that have yielded inconclusive findings. The differences in the characteristics and quality of the studies, differences in the choice of outcomes examined, and the appropriateness of the analytic approaches may explain some of these differences. For example, many analyses[16,18] have pooled disparate events ranging from arrhythmias to congestive heart failure into aggregate outcomes such as "cardiovascular events" or "cardiac complaints." Such an approach may mask inconsistencies in risk across individual endpoints as well as contribute imprecision to estimates of risk. Additionally, a few meta-analyses used the DerSimonian and Laird random-effects model for meta-analysis, which may be inappropriate for studies of rare events.[14,16]

The limitations of our review represent many limitations of the individual studies. We were not able to use patient level data in our analysis. Although we assessed RCTs for quality, many included studies failed to detail reasons for study withdrawal and whether the adverse events reported were identified using prespecified criteria for safety end points, which may have introduced bias. Some studies mentioned that the adverse events reported were considered unrelated to the study medication without providing further context or justification. In addition, other than trial registries, we did not explore sources of grey literature such as trial study data. While the statistical tests and funnel plots for individual outcomes did not show presence of publication bias, such bias may nevertheless potentially exist, especially with respect to the reporting of potential harms.[69] We also did not explore the impact of pharmaceutical industry funding on the association of interest as a majority of the trials included were sponsored by pharmaceutical manufacturers.

The results from the observational studies were highly varied and hence not pooled statistically. For example, the exposed group was not consistently defined across studies. There is a fundamental difference between patients receiving testosterone with vs without documented laboratory evidence of hypogonadism, yet many studies did not report these subgroups. In studies where the control group were those who did not receive testosterone but were diagnosed with hypogonadism, presence of channeling bias[70] cannot be ruled out, and for studies that did not have serum testosterone lab values, confounding by indication is an ever-present possibility.

There are several strengths to our review. We conducted a comprehensive and rigorous screening of several databases, including trial registries and regulatory documents, and included both trials and observational studies. Our review focused on specific disaggregated cardiovascular endpoints of clinical interest. Although there is no gold standard for analyzing sparse data, we used meta-analytic approaches that are robust for sparse data and we evaluated the stability of our results in several sensitivity analyses. We also evaluate the quality of individual studies in making inferences, and in contrast to previous studies, we provided a strength-of-evidence rating for the results.

CONCLUSIONS

The results of our review suggest a lack of a significant association between testosterone and cardiovascular events; however, it is essential to keep in mind the possibility of the risk being dose dependent or higher in certain groups such as the elderly. Since our report was completed, an additional RCT observed comparable numbers of myocardial infarction, stroke, and deaths between the testosterone group (n = 10) and placebo group (n = 13) among 790 elderly men with age-onset hypogonadism.[71] Similarly, a recently

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SUPPLEMENTARY DATA

Supplementary appendixes accompanying this article can be found in the online version at http://dx.doi.org/10.1016/j.amjmed.2016.09.017.