JACC: ADVANCES VOL. 2, NO. 10, 2023

VIEWPOINT

Testosterone Repletement

Is it the TRAVERSE Trial or a Travesty?

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There is a paper published that did not put its limitations into perspective and may lead to false reassurance about the safety of testosterone, recently published in the New England Journal of Medicine.[1] This trial was done to demonstrate cardiovascular safety of testosterone repletement in men with low testosterone and symptoms. The authors concluded "Among 5,198 patients who received testosterone or placebo for a mean duration of 22 months, testosterone-replacement therapy was noninferior to placebo with respect to the incidence of major adverse cardiac events".[1]

Unfortunately, the trial was truncated early, didn't achieve adequate repletement of testosterone, and had a majority (>60%) of participants discontinue therapy during follow-up. According to the study design paper, "Approximately 6,000 subjects will be randomized to either 1.62% transdermal testosterone gel or a matching placebo gel daily for an anticipated duration of up to 5 years."[2] However, the study mean treatment duration was only 21.7 ± 14.1 months, far shorter than planned with only 5,246 enrolled subjects (suggesting on both counts loss of power to show noninferiority).

Participants were randomly assigned to receive daily transdermal 1.62% testosterone gel (dose adjusted to maintain testosterone levels between 350 and 750 ng/dL) or placebo gel.[1,2] Unfortunately, 61.4% of the participants in the testosterone group discontinued testosterone, and 61.7% in the placebo group discontinued placebo. The study authors deemed the treatment noninferior to placebo, but with more than 60% of the participants discontinuing therapy and the mean treatment time being <2 years, it is hardly conclusive.

In both groups, a majority of patients were not taking any therapy, so of course, event rates were similar. Further, loss to follow-up was 18% (approximately 82% had follow-up data overall in the study, 82.7% for testosterone and 81.7% for placebo) far higher than considered acceptable for drug trials to report conclusive results. If plausible assumptions are made about differential event rates of participants lost to follow-up, the results in this trial may be quite different.

Also, achieved testosterone levels were targeted at 350 to 750 ng/dL on treatment, yet the median achieved testosterone hovered close to 350 ng/dL (or below) for much of the trial. Men started with mean testosterone levels of 227 ng/dL and increased by 148 ng/dL at 12 months, barely achieving the target of 350 ng/dL, with subsequent years having even lower levels on repletement.

Given that a majority of men were treated only to a low-normal testosterone level, with short (and incomplete) follow-up and large discontinuation rates, how is the conclusion that testosterone repletement is safe? The prior data on testosterone repletement, both outcomes and plaque progression trials of testosterone repletement suggest harm, with more cardiovascular events[3] and greater progression of atherosclerosis[4] in those randomized to testosterone repletement. Extreme caution must be applied when interpreting the results of the TRAVERSE trial. False reassurance is concerning, as there is a real possibility that men will be repleted with higher doses to achieve higher blood levels than studied over a longer period and may in fact suffer harm.

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The author attests they are in compliance with human studies committees and animal welfare regulations of the author's institution and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2772-963X https://doi.org/10.1016/j.jacadv.2023.100742

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This work was supported by grant U01 AG030644 from the National Institute on Aging, supplemented by funds from the National Heart, Lung, and Blood Institute. The author has reported that they have no relationships relevant to the contents of this paper to disclose.

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KEY WORDS clinical trials, hypogonadism, repletement, safety, testosterone