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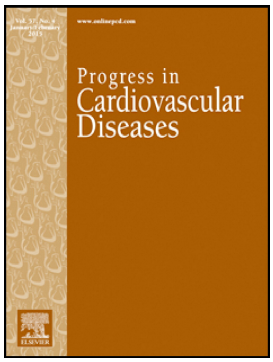

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Srikanth Krishnan, Jairo Aldana-Bitar, Ilana Golub, Sina Kianoush, Travis Benzing, Keishi Ichikawa, Matthew J. Budoff

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Testosterone Replacement Therapy and Cardiovascular Risk: TRAVERSE with Caution

Srikanth Krishnan, MD, MSc[1]; Jairo Aldana-Bitar, MD[1]; Ilana Golub BS[1,2]; Sina Kianoush, MD[1]; Travis Benzing, MD[1]; Keishi Ichikawa, MD, PhD[1]; Matthew J. Budoff, MD[1].

AFFILLIATION: 1: The Lundquist Institute at Harbor-UCLA; 2: David Geffen School of Medicine at University of California Los Angeles

Corresponding author: Matthew J. Budoff, Email: mbudoff@lundquist.org Srikanth Krishnan MD, MSc(Srikanth.krishnan@lundquist.org)

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The relationship between testosterone replacement therapy (TRT) and cardiovascular (CV) disease (CVD)risk in older, hypogonadal men has been debated for years. Observational studies have variably linked low endogenous testosterone levels with adverse cardiometabolic effects and increased CVD risk in men. However, the causality of this association is unclear, and low testosterone may simply be a biomarker of aging and poor health status rather than a direct contributor to CVD[1]. Given this association, TRT has been utilized to improve the symptoms of older, hypogonadal men such as reduced libido, fatigue, and muscle weakness, thus sparking a decades-long debate over its CV safety.

Early randomized controlled trials (RCTs) of TRT presented conflicting conclusions and had limitations that prevented generalizability of their results. Some trials like the Copenhagen Study and TOM trial suggested increased mortality or CVD events with TRT[2,3]. Conversely, the TEAAM trial found no differences in progression of subclinical atherosclerosis markers such as carotid intima-media thickness and coronary artery calcium (CAC) scores, or CVD events over 3 years between the TRT and placebo groups. The cardiovascular arm of the TTrials found TRT

was associated with greater increases in non-calcified and total plaque volumes over 12 months compared to placebo, but no differences in CAC scores or CVD events[4]. The clinical significance of these plaque changes is uncertain, though certainly warrants consideration of the complexity of TRT's effects as evidence of progression of atherosclerosis may portend CVD risk.

Adding to prior meta-analyses of RCTs, which have not found an association between TRT and major adverse cardiovascular events, the comprehensive meta-analysis performed by Jaiswal et al. sheds much needed light on the CV implications of TRT[5]. The authors synthesized data from 30 RCTs, including 11,502 patients, to examine the association between TRT and CVD outcomes. They selected studies with a low risk of bias, as determined by the Cochrane's Collaborations tool, thereby increasing the reliability of their findings. Their analysis showed no significant difference in the rates of myocardial infarction (OR, 1.05; 95%CI: 0.76-1.45), stroke (OR, 1.01; 95%CI: 0.68-1.51), or CVD mortality (OR, 0.87; 95%CI: 0.65-1.15). A leave-one-out sensitivity analysis, which assessed the impact of the large TRAVERSE trial, confirmed that their findings did not overly depend on any single study. Collectively, these findings overwhelmingly suggest that TRT does not increase the risk of CVD events or all-cause mortality among older men with hypogonadism, and therefore contribute to an improved understanding of TRT's safety profile.

However, interpreting these results within the context of real-world clinical practice raises unresolved questions. The TRAVERSE trial, which significantly contributes to this meta-analysis and serves as its foundational study, has notable limitations. These include a high

discontinuation rate (> 60%) during follow-up, a mean treatment duration of less than two years, and an 18% loss to follow-up rate[6]. Most significantly, the trial achieved a median testosterone level of 350 ng/dL, which is at the lower end of the normal range and may not reflect the effects of physiologic and supraphysiologic dosing levels that are often targeted in clinical practice for symptom relief and quality of life improvement.

We bring attention to the limitations of the TRAVERSE trial due to the potential for misleading reassurance of the safety of TRT at physiologic or supraphysiologic levels. The long-term CV effects and the safety of such regimens have yet to be studied. We certainly advocate for further research to explore the long-term CV impact of TRT, especially at these higher dosing levels.

The debate surrounding TRT and CVD risk thus far can be summarized as follows: current evidence suggests TRT does not increase CVD risk in older, hypogonadal men when administered over a short duration and at low-normal levels of replacement. The question remains open when considering the effects of TRT at physiologic or supraphysiologic levels.

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Conflict of interest:

Matthew J. Budoff: received grants from the following companies: Novo Nordisk, Novartis, Astrazeneca, Heartflow, GE Healthcare, Amgen, and Boehringer Ingleheim, Department of Defense, Centers for Disease Control and the National Institutes of Health. Dr Budoff received honoraria from Novo Nordisk, Esperion, Astrazeneca, Merck, Janssen, and Eli Lilly

All other authors declare they have no conflict of interest.

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