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# Benefits of Testosterone Supplementation Elusive in TTrials

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*Interviews with Matthew J. Budoff, MD, Thomas M. Gill, MD and Tamara L. Wexler, MD, PhD*

In effect, older men with low testosterone and age-associated memory impairment (AAMI) did not benefit from short-term treatment with testosterone, as reported in the current issue of the *Journal of the American Medical Association (JAMA)*,<sup>1</sup> by Susan M. Resnick, PhD, a senior investigator at the National Institute on Aging in Baltimore, Maryland, and colleagues.

In the 2<sup>nd</sup> study, short-term testosterone treatment in older men significantly increased noncalcified coronary artery plaque volumes, possibly raising their risk of cardiovascular (CV) events,<sup>2</sup> according to Matthew J. Budoff, MD, a professor of medicine at the David Geffen School of Medicine at UCLA and the Los Angeles Biomedical Research Institute in Torrance, California, and colleagues.

## Exploring the Research Behind These TTrials

The [FDA approved](#) testosterone therapy only for men having a

low testosterone (hypogonadism) as the result of a diagnosed medical condition (ie, genetic defects), or as a side effect of cancer chemotherapy.<sup>3</sup> However, testosterone frequently has been prescribed off-label to men who have had no diagnosed medical condition, other than an age-related decrease in circulating testosterone, also known as “low T”.



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This has become a common practice despite an Institute of Medicine (IOM) [report](#) issued in 2003, indicating insufficient evidence of any benefit derived from testosterone hormone therapy to address expected symptoms of male aging.<sup>4</sup> These studies, and 2 others (to be presented in a separate *EW* research brief) come on the heels of research on the efficacy of prescribing testosterone<sup>5</sup> that appeared in the [NEJM](#) last year.

Thomas M. Gill, MD, Humana Foundation Professor of Medicine

at Yale University School of Medicine in New Haven, CT, told *EndocrineWeb* that these trials were needed because “the pharmaceutical industry did a very good job of promoting testosterone, and there have been suggestions of parallels between age-related decreases in testosterone levels in men, and menopause in older women.”

“However, the parallels don’t necessarily follow logically, creating a real need to bring more evidence to this area so that physicians and patients would be able to make more informed decisions based on the best possible evidence,” said Dr. Gill, a professor of medicine and the lead investigator at the Yale study site, the largest site participating in the TTria, and coauthor of all 4 TTria.

### **No Improvements in Cognitive Outcomes With Supplemental Testosterone**

Dr. Resnick and colleagues assessed 788 participants in the cognitive function arm of the TTria but focused on the 493 participants who were classified as having [age-associated memory impairment](#) with a confirmation of both subjective and objective indicators of cognitive decline. The authors detected no significant effect after 1 year of testosterone treatment on either the primary outcome of verbal memory, as measured by delayed paragraph recall or on any of the secondary outcomes of visual memory, executive function, and spatial ability.<sup>1</sup>

Although earlier research had suggested that testosterone may improve cognitive functioning, the authors present this study as the largest and best-controlled trial conducted to date, lending weight to their conclusion that no such benefits are gained in

boosting testosterone in older men.

“Men with AAMI did not benefit from testosterone,” said Dr. Gill.

“That was considered a definite null result.”

### **Adverse CVD Outcomes From Testosterone Therapy**

As with cognitive effects, previous studies examining CVD changes following testosterone treatment have been conflicting and inconclusive. Dr. Budoff and his research team used coronary computed tomographic angiography (CCTA) to assess 138 men, including 73 treated with testosterone and 65 receiving placebo, for changes in coronary artery plaque volume after 1 year.

“There have been a few articles published concluding both that there is and is not an increased risk of heart attack with testosterone,” Dr. Budoff told *EndocrineWeb*.

“Our hypothesis was that testosterone would be good for the coronary arteries because we thought that by repleting testosterone to healthy levels there would be an improvement in the cholesterol panel and atherosclerosis burden. But what we found was the opposite, that atherosclerosis actually progresses faster under the influence of testosterone.”

The authors reported statistically significant increases in both noncalcified and total coronary artery plaque in patients receiving testosterone treatment. Participants' coronary artery calcium scores, another measure of calcified plaque, were not significantly affected by testosterone treatment. Although these results are potentially a cause for concern, additional studies are

required to determine the clinical relevance of this increase in plaque volume.

Discussing the clinical utility of these findings, Dr. Budoff told *EndocrineWeb*, “in the short-term, I am going to check my patients for atherosclerosis before instituting testosterone therapy. We still need a definitive study to show whether or not heart attacks are increased by supplemental testosterone, but advancing atherosclerosis is not a good thing. These results should make us more cautious about whom we treat and what doses we use.”

The TTria were funded by the National Institutes of Health, and consist of 7 integrated, placebo-controlled, randomized clinical trials evaluating the short-term efficacy of testosterone treatment in older men with low circulating levels of the hormone. The benefits of testosterone were evaluated in 7 clinically relevant medical concerns and at least preliminary evidence of efficacy in sexual function, physical function, vitality, cognition, anemia, bone health, and cardiovascular health.

The study population in these TTria included men aged 65 years or older with mean morning serum testosterone concentrations of 275 ng/dL or less and symptoms of impaired sexual function, physical function, or vitality. These trials were placebo-controlled and the testosterone treatment group received 1% testosterone gel at variable doses adjusted to maintain plasma testosterone at levels normal for young men (500-800 ng/dL).

“I don’t think that these results are going to produce a dramatic shift, except perhaps in whether to treat men with borderline or

normal testosterone levels,” Tamara L. Wexler MD, PhD, a reproductive endocrinologist at the NYU Langone Medical Center in New York City, commented to *EndocrineWeb*.

“The mixed results of these trials show that while there are absolute benefits to testosterone treatment, it should not be seen as some sort of panacea.”

The results of the remaining 2 TTriaals, those investigating the effects of testosterone on bone health and anemia, will appear in separate *EndocrineWeb* research brief.

For a comprehensive overview of testosterone use and effects in men, read the EndoScan literature review, [Testosterone Use in Men](#), presented by Tamara Wexler, MD.

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[Testosterone Offers Modest Gains for Anemia and Bone Density](#)