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Testosterone therapy's big week: One urologist's perspective

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On Feb. 21, 2017, five testosterone therapy (TTh) articles—four of which contained results from the Testosterone Trials—were published in *JAMA* and *JAMA Internal Medicine*. This was arguably the most important week ever for the science of testosterone therapy and its impact on men's health. Although the totality of these research studies showed impressive benefits and reassuring safety evidence, media coverage followed its well-worn pattern of focusing on weak evidence of risk while largely ignoring major positive findings that could well alter medical care. This repeated distortion of the science regarding testosterone has been recently analyzed by my colleagues and me in an article entitled, "Overselling hysteria" *(EMBO Rep* 2017; 18:11-17).

What should urologists know about these five articles? Two were prospective placebo-controlled trials that demonstrated clinically meaningful improvements in areas where TTh benefits have not been widely recognized, namely improvements in bone density and unexplained anemia; one was a very large observational study that demonstrated an impressive reduction in cardiovascular events; one trial was neutral with regard to cognition; and one provided equivocal evidence regarding coronary atherosclerosis.

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Let's address the allegedly bad news first. In a cohort of men participating in the Testosterone Trials, 138 men 65 years of age and older (mean age, 71.2 years) were assigned to either 1 year of T gel or placebo gel *(JAMA* 2017; 317:708-16). Coronary computed tomography was performed at baseline and after 1 year. The primary result was that the increase in non-calcified coronary plaque volume was significantly greater in men who received T than in those who received placebo. Coronary calcium scores were no different between groups, and in fact were numerically reduced in the T arm at 1 year.

While it sounds bad that plaque volume increased more in men who received T gel, the results are difficult to interpret since mean baseline plaque volume was much higher (>50%) in the placebo group (317 mm^3) than the T group (204 mm^3). At the end of 1 year, median volume in the placebo group was 325 mm^3 compared with 232 mm^3 in the T group. Although the change in volume from baseline was slightly greater in the T group, that difference is overwhelmed by the magnitude of the differences between groups.

Next: Study "suggests TTh may be cardioprotective"

Whereas plaque volume has not yet been shown to correlate with cardiovascular outcomes,

coronary calcium scores do predict CV outcomes. Importantly, coronary calcium scores were no different between groups, and were numerically improved after 1 year of TTh in the testosterone group. Notably, there were no heart attacks, strokes, or deaths in this study. Importantly, the numbers of major adverse CV events in the entire Testosterone Trials population (n=780) were identical for the placebo and testosterone groups (seven each) in year 1, and were higher in the placebo group in the second, follow-up year (nine events for placebo versus two events for testosterone) *(NEJM* 2016; 374:611-24). It is impossible to conclude from this study that TTh confers increased CV risk.

Indeed, the study by Cheetham et al (which was not part of the Testosterone Trials) suggests TTh may be cardioprotective *(JAMA Intern Med*, epub., Feb. 21, 2017). This observational study of a cohort of men in the Kaiser Permanente system investigated rates of major CV events, including death, heart attack, stroke, revascularization, and unstable angina in 8,808 men who received TTh and 35,527 men who were untreated. All men had total T concentration less than 300 ng/dL. With a median follow-up of 3.2 years, the adjusted hazard ratio for men who received TTh was 0.67 (95%CI: 0.62-0.73). In other words, the rate of adverse CV events in men with T deficiency was lower by one-third compared with untreated men!

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A key additional finding was significant improvement in bone density and strength in another study within the Testosterone Trials *(JAMA Intern Med*, epub. Feb 21, 2017). In this study, 211 participants with T<275 ng/dL were assigned to T or placebo gels for 1 year. Clinically meaningful changes in bone density and strength were noted in the T group at both the hip and spine. The magnitude of these changes compared favorably with effects seen with approved antiresorptive and anabolic medications already approved for treatment of osteoporosis.

Improvement in unexplained anemia with TTh was seen in another study within the Testosterone Trials involving 126 men with a mean age of 74.8 years *(JAMA Intern Med*, epub. Feb 21, 2017). Finally, another study within the Testosterone Trials showed no difference in cognition after 1 year of T gel versus placebo gel *(JAMA;* 2017; 317:717-27).

While the improvements observed in bone density and anemia were not surprising in light of prior research, these results in carefully performed controlled studies sponsored by the National Institutes of Health provide a clear rationale for the clinical application of TTh for general medical indications, and not just for sexual symptoms. In addition, the weight of evidence presented in these studies is not only reassuring with regard to CV risk, but actually supports the idea that TTh may be cardioprotective. These findings support the call to investigate the possible CV benefits of TTh made by the International Expert Consensus Conference on Testosterone Deficiency and its Treatment in 2016 *(Mayo Clin Proc* 2016; 91:881-96).

Urologists already play a central role in the evaluation and management of men with T deficiency. These new, exciting results provide even more evidence to support the importance of normal T values to men's health.

Dr. Morgentaler has received payments for consulting, participation in scientific advisory boards, or lecture honoraria from AbbVie, Aytu, Bayer, Besins, and BioTE.

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