EDITORIAL

Testosterone Therapy and Risk of Cardiovascular Disease in Men

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The clinical question about which men should receive testosterone therapy is controversial, with data from short-term clinical trials suggesting benefits for improving sexual function, strength, and well-being. What is missing from the literature are data from randomized trials that include a sufficient number of men for an adequate amount of time to assess the long-term benefits and risks of testosterone therapy. There is no study involving men that is equivalent to the Women's Health Initiative, nor is it likely that there will be a trial of equal scale. Because testosterone therapy is available and prescribed for an estimated 2.9% of US men aged 40 years or older,[1] observational data from existing cohorts of men can contribute meaningfully to assessment of therapeutic risk.

In this issue of *JAMA*,[2] Vigen and colleagues present retrospective analyses from the Veterans Affairs system of men who had undergone coronary angiography, had subsequent total testosterone assessment, and were found to have a testosterone level of less than 300 ng/dL. Through linkage with pharmacy data, 1223 men, mean age 60.6 years, who initiated testosterone therapy were compared with 7486 men, mean age 63.8 years, who did not. The testosterone users were found to have an increased risk of the composite end points: 67 died, 23 had myocardial infarctions, and 33 had strokes, whereas among those who did not receive testosterone therapy 681 died, 420 had myocardial infarctions, and 482 had strokes, for an absolute 3-year event rate of 25.7% vs 19.9% (hazard ratio, 1.29; 95% CI, 1.04-1.58). Importantly, this estimate did not differ between the men with and without coronary artery disease, which was ascertained in all men by coronary angiography, and was similar when revascularization was included in the outcome.

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Any pharmacoepidemiology study is susceptible to confounding by indication. The authors have incorporated a wealth of data on potential confounders and a sophisticated weighted analysis with testosterone use as a time-dependent covariate in an attempt to mitigate the effects of confounding. The men who were prescribed testosterone were slightly healthier than those who were not, with the exception of testosterone level and obesity. Ordinarily, this would raise concerns about prescribing bias, as was seen with prescription of estrogen therapy to more health conscious women. However, in the study of Vigen et al, the men receiving testosterone had a higher risk of the composite adverse outcome, which runs counter to what would be anticipated if there was residual confounding from unmeasured advantageous health variables. Furthermore, it appears that the 2 study groups were so similar that sophisticated modeling may not have been necessary; the ratio of the unadjusted event rates at 3 years of follow up was 1.30 (25.8% vs 19.9%), nearly identical to the adjusted hazard ratio of 1.29.

The most important issue raised by these findings is determining to which population of men they would apply. The men studied represent a real-world population of men with a sizable burden of comorbidities who have more health problems than do the men enrolled in most randomized clinical trials. The findings are concordant with a trial of testosterone therapy that involved older men with comorbidities.[3] Frustratingly little information is available in this VA database analysis about whether testosterone was appropriately prescribed according to accepted guidelines,[4] which call for morning collection of testosterone on 2 occasions, demonstration of a clinical problem that could be related to testosterone deficiency, and appropriate monitoring. In addition, 35.7% of men were using testosterone injections, which have the advantage of low cost but have the disadvantage of nonphysiologic peak and trough levels over the weekly or biweekly dosing strategy. It is reassuring that there was no evidence of a difference in risk by formulation, but with 123 events in the testosterone group and only 13 testosterone gel users, limitations in power preclude drawing firm conclusions about the finer points of testosterone prescribing.

Perhaps the most important question is the generalizability of the results of this study to the broader population of men taking testosterone: men of this age group who are taking testosterone for "low T syndrome" or for antiaging purposes and younger men taking it for physical enhancement. Does the 29% increased risk of myocardial infarction, ischemic stroke, or mortality apply to these groups? Are the benefits—real or perceived—for these groups of men worth any increase in risk? These populations represent a sizable group of testosterone users, and there is only anecdotal evidence that testosterone is safe for these men.

Additional information about this issue should come from the ongoing Testosterone Trial in Older Men (NCT00799617), a randomized trial of 800 men aged 65 years or older with diminished walking ability, interest in sex, energy, memory, or hematocrit levels who will receive testosterone gel or placebo for a year. Although this trial was not designed with sufficient power to detect differences in cardiovascular event rates, the comprehensive assessments of risk and

benefit in the framework of a single study will provide important guidance to older men who meet current recommendations for testosterone therapy. Cases for which clinicians will be left without the highest level of evidence from clinical trials is in the long-term safety of testosterone therapy.

In light of the high volume of prescriptions and aggressive marketing by testosterone manufacturers,[5] prescribers and patients should be wary. There is mounting evidence of a signal of cardiovascular risk, to which the study by Vigen et al contributes. This signal warrants both cautious testosterone prescribing and additional investigation.

ARTICLE INFORMATION

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