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The Impact of Testosterone Therapy in Men on Cardiovascular Risk: Don't Be Too Quick to Condemn

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In this issue of *Mayo Clinic Proceedings*, Morgentaler et al[1] provide a timely update regarding testosterone therapy in men and cardiovascular risk. This review is important considering the recent controversy claiming increased cardiovascular risk in men receiving testosterone therapy. Morgentaler et al identified 4 studies suggesting that testosterone therapy increases the risk of cardiovascular events, but they also identified more than 100 studies demonstrating that normal testosterone levels (and, accordingly, physiologic replacement of testosterone) provide beneficial effects to men and minimize cardiovascular risk and mortality.[1-5] They also critically evaluated the 4 positive studies and noted that 2 studies had serious methodology concerns, 1 was a meta-analysis with poor inclusion criteria, and 1 was a placebo-controlled study with too few cardiovascular events to make definitive conclusions.[2-5]

Morgentaler et al are not alone when it comes to concerns raised about the recent studies reporting adverse cardiovascular effects of testosterone. For example, the methodology concerns in the report by Vigen et al[3]—one of the reports suggesting harm by testosterone—have been so great that 29 professional societies, including the International Society for Men's Health, the International Society of Sexual Medicine, and the Sexual Medicine Society of North America, have demanded that the article be retracted.[1]

In the present review, Morgentaler et al stress that cardiovascular mortality and incident coronary artery disease are associated with *lower* levels of total testosterone, free testosterone, and bioavailable testosterone. In a study by Ohlsson et al,[6] for example, men with serum total testosterone concentration levels of 550 ng/dL or more (ie, the highest quartile) had a 30% lower risk of cardiovascular events than did men in the 3 lower quartiles, even after adjusting for traditional cardiovascular risk factors and excluding men with known baseline cardiovascular disease.[6] At first glance, these are somewhat paradoxical observations considering the recent inquires by the Food and Drug Administration (FDA), a call for more stringent product labeling, and an outcry in the lay press that testosterone therapy is hazardous.

Multiple studies in men have shown that having normal blood testosterone concentrations help promote normal cardiovascular health. Testosterone therapy is associated with not only decreasing obesity and waist circumference but also improving glycemic control.[7] Such studies give credence to the notion that testosterone therapy (to restore normal testosterone physiology) should be heart healthy. In the report, Morgentaler et al note in randomized trials in men with heart failure and coronary artery disease that testosterone therapy appears to improve cardiovascular function.[1] Indeed, the largest meta-analysis to date—that is, one involving 75 studies and 5464 patients—reported that testosterone therapy did not *increase* cardiovascular risk but instead *decreased* cardiovascular risk among those with metabolic syndrome.[8]

The importance of having a normal blood testosterone concentration to prevent cardiovascular risk can also be inferred from studies looking at the effect of androgen deprivation therapy as a treatment for prostate cancer.

Keating et al[9] evaluated 73,196 men with prostate cancer and examined the risk of cardiovascular events associated with the administration of any androgen deprivation therapy. They reported that androgen deprivation therapy significantly increased the risk of diabetes mellitus, coronary heart disease, myocardial infarction, and sudden cardiovascular death.[9]

Despite the few recent reports suggesting otherwise and negative media attention, testosterone therapy is safe and effective when used responsibly.[10,11] Starting in the 1940s and 1950s, testosterone therapy has an excellent track record for improving quality of life for men diagnosed with hypogonadism. Testosterone therapy is indicated only when men have low serum testosterone levels documented in the setting of associated symptoms and signs of hypogonadism. Importantly, testosterone therapy is not indicated for men with low or low to normal testosterone levels without the signs and symptoms of hypogonadism. Testosterone therapy is also not indicated to treat symptoms suggestive of hypogonadism in the absence of documented low testosterone levels.[11] Indeed, the decision to start testosterone therapy requires not only a bona fide hypogonadism diagnosis but also shared decision making with men and their health care providers discussing the potential risks of treatment, required surveillance testing during treatment (serum testosterone, prostatic-specific antigen, and hematocrit assessments), and assessment of adverse effects and other risks (eg, prostate cancer, benign prostatic hyperplasia, sleep apnea, and venous thrombosis) that may warrant discontinuation of treatment. Laboratory testing should be done 3 months after initiating treatment and ongoing monitoring continued even after stability of replacement is achieved (at 6- to 12- month intervals). While on therapy, laboratory targets would be serum testosterone concentrations of 400 to 700 ng/dL, hematocrit level not above the upper limit of normal, and prostatic-specific antigen level maintained within age-adjusted ranges and not associated with worrisome velocity trends (0.4 ng/mL/y over $\geq$2 y) or significant yearly increases (>50%).

The recent controversy about testosterone therapy has engendered concern from the FDA regarding treatment safety.[12,13] On September 17, 2014, the FDA convened an advisory panel to discuss the potential risk of major adverse cardiovascular events associated with testosterone therapy and the appropriate patient population for whom testosterone therapy should be prescribed. Ultimately, the panel voted 20-1 for the FDA to impose stricter limitations on the testosterone drug industry and tightened labeling information regarding testosterone therapy's effects on libido, fatigue, and muscle loss. The panel also concluded that evidence linking testosterone therapy to increased risk of cardiovascular events is "inconclusive." In this regard, the panel voted 20-1 recommending that pharmaceutical companies further study cardiovascular effects of testosterone therapy.[12] Although some may question the FDA's conclusion that the association between testosterone therapy and cardiovascular events is inconclusive, especially considering a large amount of data suggesting otherwise, there appear to be other agendas (see below) that the FDA would also like to be addressed.

Indeed, this approach by the FDA appears prudent considering the current state of testosterone therapy. Since the early 2000s, the use of testosterone therapy has quadrupled.[13] This increase in prescriptions potentially has been driven by better formulations for testosterone delivery as well as a direct-to-consumer marketing campaigns that suggest that testosterone therapy may in essence represent a new "fountain of youth." When testosterone therapy was administered solely with a needle with a more labor-intensive dosing regimen of every couple of weeks in physicians' offices, the treatments tended to be used exclusively by those who absolutely were in need of replacement therapy. As the mode of administration of testosterone therapy has become easier, and more pharmaceutical industry resources have been directed at convenient product development, we have started seeing not only "low T" commercials on television but also the number of testosterone therapy prescriptions increasing dramatically. Although Morgentaler et al[1] point out that testosterone therapy has not been a top target of direct-to-consumer marketing, it seems that the use of direct-to-consumer marketing has been effective. For instance, it was estimated in 2013 that 2.3 million American men were receiving testosterone therapy. Alarmingly, it was also estimated that up to 25% of them received a prescription without having a baseline

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testosterone level documenting hypogonadism.[13] At the very least, the increased attention to the testosterone treatment debate will hopefully impose stricter prescribing requirements for men seeking testosterone therapy and better regulation of the pharmaceutical companies marketing testosterone therapy.

One may ask why the publication of a few recent studies with well-delineated methodology concerns captured intense media attention and the attention of the FDA. The answer is likely multifactorial. It may be based in general on society's increasing interest in health and wellness and the public's notion that testosterone treatment was essentially "risk-free." It may be based on the fact that changing demographics suggest that millions more men may potentially qualify for treatment in the future (with unnecessary patient risk and cost of therapy) unless treatment effects are better characterized. It may also be related to concerns about overtreatment or mistreatment because the availability, marketing, and delivery of testosterone therapy have increased. Indeed, in the setting of increased public concern and heightened media attention, the comprehensive work by Morgentaler et al provides some needed reassurance that testosterone therapy appears safe, at least from a cardiovascular standpoint, as we regroup to comprehensively evaluate the global safety, risks, and efficacy of this treatment in men.

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