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I declare that I have no competing interests

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Testosterone, cardiovascular disease, and mortality in men: living in the dark

Two recent observational studies[1,2] and associated articles in the press[3,4] have raised concerns about the potential risks associated with prescription of testosterone to older men. However, these concerns are not new and are reminiscent of the debate about hormone replacement therapy and heart disease in women that raged before the Women's Health Initiative. However, if one thing was learnt from the Women's Health Initiative, it is that cumulative observational data cannot replace well-designed and undertaken randomised clinical trials. Observational studies such as those done by Vigen[1] and Finkle[2] and their collaborators should serve to galvanise both the public and medical communities to fund an appropriate clinical study to assess the risks and benefits of testosterone treatment in older men in an era when millions of men are using testosterone every day. The danger is that funding and regulatory agencies will overinterpret these types of observational studies and conclude that appropriate trials are unnecessary and unwarranted. This conclusion would do men's health a disservice.

The debate surrounding the risks and benefits of testosterone is focused on the use of testosterone in older men. Testosterone replacement in young men with primary or classic central hypogonadotropic hypogonadism has well documented therapeutic benefits and is crucial for the long-term health of these patients. The amount of circulating testosterone in men gradually decreases with age, and there is a biological basis to hypothesise that both testosterone deficiency and exogenous testosterone might predispose older men to cardiovascular disease. Androgen withdrawal increases insulin resistance and fat mass while decreasing lean body mass.[5] Furthermore, incidence of type 2 diabetes and cardiovascular disease is increased in men with low endogenous testosterone concentrations.[6] By contrast, exogenous testosterone can decrease cardioprotective HDL cholesterol,[7] which might contribute to cardiovascular risk. Animal models exploring the effect of testosterone on atherosclerosis have also mainly been inconclusive.

Similar to the mixed physiological effects of androgens, findings from retrospective epidemiological studies are contradictory. Although data from recent studies suggest testosterone negatively affects cardiovascular risk in older men, these studies have important limitations. Vigen and colleagues[1] reported an association between testosterone and the incidence of myocardial infarction, stroke, or death in roughly 8000 male veterans with low serum testosterone who had undergone coronary angiography (hazard ratio for adverse event with testosterone treatment 1·29, 95% CI 1·05—1·58, p=0·02). However, the primary data from this analysis, before adjustment for more


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For the **Women's Health Initiative** see http://www.nhlbi.nih.gov/whi/background.htm

than 50 variables, suggested the total event rate was in the opposite direction: 10% of men in the testosterone group versus more than 20% in the untreated group had a cardiovascular event. Furthermore, the extent to which testosterone contributed to the ultimate findings is not clear because testosterone treatment was established on the basis of one filled prescription, and neither testosterone concentrations after treatment or long-term use were ascertained. Finkle and colleagues[2] similarly used a large health-care database and reported an association with testosterone prescriptions and acute non-fatal myocardial infarction within 90 days of a testosterone prescription. Not only were data for testosterone usage unavailable (eg, increased serum testosterone concentrations and drug administration), but whether or not men prescribed testosterone treatment had low serum testosterone concentrations or symptoms associated with low testosterone was not established. Although data from these two studies suggest testosterone might cause harm, Shores and colleagues[8] came to the opposite conclusion, at least regarding testosterone treatment and mortality, in male veterans (mean age 62·1 years) with low testosterone. These investigators reported that men given testosterone, including those with pre-existing cardiac disease, had decreased mortality compared with untreated men even after adjustment for comorbidities. Increased length of treatment was also associated with decreased mortality. Together, the contradictory findings in these studies draw attention to the inherent shortcomings of such retrospective analyses in providing definitive data for clinical decision-making about testosterone treatment. The data are reminiscent of the debate about testosterone and prostate cancer, an issue for which long-term, randomised trial data are also scarce; results so far point to both protective and potentially pathological roles for testosterone in prostate disease.

What do we know from the randomised clinical trials of testosterone treatment in older men that have been done so far? The longest studies have lasted only 36 months and, although reassuring in terms of safety, none were sufficiently powered to assess disease endpoints. The TOM trial[9] was designed to investigate the effect of testosterone treatment in frail men older than 65 years with low testosterone, but was stopped because of an excess of cardiovascular events in the treatment group. However, these men were treated with quite large doses of testosterone and the risk of an event was highest in those who achieved the highest testosterone concentrations (ie, highest quartile). Moreover, a contemporaneous and similar study in size and design did not record an increase in events,[10] albeit in a slightly less frail cohort, underscoring the likelihood that dose, population, and underlying comorbidities affect the risk:benefit ratio of testosterone treatment. Although a larger 12 month randomised controlled trial in men older than 65 years with low testosterone is underway, like those before it, the Testosterone Trials[11] are not sufficiently powered to show the effect of testosterone treatment on hard clinical endpoints such as cardiovascular events and prostate cancer. Finally, even if initiated today, data from any appropriately powered trial to assess safety are at least a decade away.

What then can older patients be told about the risks associated with testosterone, and in particular about cardiovascular risk? Testosterone is a billion dollar industry, probably fuelled partly by direct-to-consumer advertising and, undoubtedly, some degree of over-prescription. Physicians need to admit they simply do not know and use conservative treatment guidelines[12] to guide therapeutic decisions. The cautionary studies discussed here should not derail efforts to define the risks and benefits of testosterone treatment. Causality can only be inferred, and not proven, by retrospective analyses. Therefore, observational data should fuel the scientific and clinical imperative to do appropriate large randomised trials to provide evidence-based guidelines for testosterone treatment. As the Women's Health Initiative showed, the results might be surprising.

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