INVITED COMMENTARY

Testosterone, Cardiovascular Risk, and Hormonophobia

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DOI: 10.1111/jsm.12556

ABSTRACT

Introduction. A public outcry against testosterone (T) therapy has suddenly occurred based on two reports suggesting treatment was associated with increased cardiovascular (CV) risks.
Aim. To analyze scientific and social bases for concerns regarding T therapy.
Methods. Analysis of recent articles regarding CV risks with T and comparison with events surrounding publication of results of the Women's Health Initiative in 2002.
Results. In the first study, the percentage of individuals with an adverse event was *lower* by half in men who received T compared with untreated men (10.1% vs. 21.2%). However, an opposite conclusion was reached via complex statistics. The second study reported minor increased rate of nonfatal myocardial infarction (MI) up to 90 days after receiving a T prescription compared with the prior 12 months. However, there was no control group, so it is unknown whether this MI rate was increased, reduced, or unchanged compared with untreated men. Neither study provided substantive evidence of risk, yet these were lauded as proof of dangers, despite a substantial literature to the contrary. Similar events followed the publication of the Women's Health Initiative in 2002 when a media frenzy over increased risks with female hormone replacement therapy obscured the fact that the reported excess risk was clinically meaningless, at two events per 1,000 person-years. Stakeholders driving concerns regarding hormone risks are unlikely to be clinicians with real-world patient experience.
Conclusions. The use of weak studies as proof of danger indicates that cultural (i.e., nonscientific) forces are at play. Negative media stories touting T's risks appear fueled by antipharma sentiment, anger against aggressive marketing, and antisexuality. This stance is best described as "hormonophobia." As history shows, evidence alone may be insufficient to alter a public narrative. The true outrage is that social forces and hysteria have combined to deprive men of a useful treatment without regard for medical science. **Morgentaler A. Testosterone, cardiovascular risk, and hormonophobia. J Sex Med 2014;11:1362–1366.**

Key Words. Testosterone; Cardiovascular Risk; Bias; Mortality; Stroke; Heart Attack

The Testosterone Controversy

In January 2014, the U.S. Food and Drug Administration (FDA) announced plans to review the possibility that testosterone (T) products increase the risk of adverse cardiovascular (CV) events based on the publication of two recent studies. It would have been difficult for the FDA to do otherwise, with the firestorm of media attention to these reports. The CV risks appeared to cap a wave of negative sentiment against what they regard as the marketing of "low T," with commentators ridiculing the symptoms of T deficiency and alleging physician irresponsibility based on a tripling of prescriptions over the last decade and reports that many men receiving T lacked baseline T testing. The overall sentiment was captured by the title of an editorial by the *New York Times*, "Selling Testosterone, Dangerously" [1].

The last public outcry like this was in 2002 regarding the overselling and dangers of hormone replacement therapy in women, precipitated by publication of results from the Women's Health Initiative (WHI) [2]. Then, as now with T, reports of increases in health risks provided the ammunition for a much broader sociological attack,

arguing that use of hormone replacement therapy (HRT) medicalized normal aging and physicians had been hoodwinked by pharmaceutical industry into falsely believing HRT was beneficial, and were thus overprescribing. Then, as now, this broader narrative was so powerful that the science anchoring this alleged outrage was never properly evaluated.

It will astonish most readers to learn that the fears and public pronouncements against HRT of 12 years ago are no longer supported by facts and, arguably, never were. In 2013, the follow-up results to the WHI concluded no differences between HRT and placebo with regard to all-cause mortality, a small increase in invasive breast cancer for women taking the combination of estrogen and progesterone, and a small *decrease* in women who took estrogen alone (women without a uterus due to hysterectomy) [3]. The effect can be summed up as "net neutral." In the initial 2002 report that precipitated the media storm, the magnitude of the cumulative excess rate of all adverse events for women treated with estrogen and progesterone compared with women taking placebo was only 19 per 10,000 person-years or less than two in 1,000 person-years, with no difference noted in the global index or mortality [2].

This tiny difference, clinically meaningless, was lost amid the hubbub that passed as a serious discussion of a medical issue, and HRT prescriptions dropped to a fraction of their pre-WHI usage. For years, many of my colleagues refused to prescribe HRT at all, even though they themselves had observed the benefits of treatment in their own patients without worrisome adverse effects. That reaction was irrational and unscientific, prompted by unbalanced media reports and public outrage. I fear the same will now occur with T in men.

Analysis of Studies Reporting Increased CV Risks with T Therapy

The first of the two recent studies reporting risks with T prescriptions, published in the *Journal of the American Medical Association* by Vigen et al., was a retrospective analysis of a dataset of 8,709 men in the VA health system who had undergone coronary angiography [4]. Among men with T concentrations less than 300 ng/dL, the authors reported an increased rate of heart attacks, strokes, and deaths in men who received a T prescription compared with men who did not. No significant differences in event rates were noted for any year of follow-up; however, the overall event curves demonstrated a significant increase in events for T-treated men of 29%.

Strangely, the percentage of men who suffered an event was actually lower by one-half for the T group compared with the no-T group (10.1% vs. 21.2%) [4]. The authors came to an opposite conclusion resulting from complex statistical modeling based on more than 50 variables. This modeling failed to include substantially lower baseline T levels in the T group despite evidence that lower T values are associated with increased CV risk and mortality [5–14]. In addition, the authors inexplicably excluded 1,132 men who suffered stroke or heart attack prior to receiving a T prescription. Without that improper exclusion, the rate of events in the no-T group would have been increased by 71%, reversing the results [15]. It is impossible to conclude from this study that T prescriptions increase rates of CV events.

The second study published in *PLoS ONE* by Finkle et al. was a retrospective analysis of insurance claims data in 55,593 men in which the only information available was diagnosis codes, procedure codes, and prescription data [16]. The primary reported result was an increased rate of nonfatal myocardial infarction (MI) within 90 days after filling a T prescription compared with the prior 12 months. The authors also compared these pre and postprescription rates for phosphodiesterase 5 inhibitors (PDE5i), reporting no increase in MI following PDE5i prescription. Subgroups by age revealed increased risk of MI with men over 65 years without a prior history of heart disease and for men less than 65 years with a prior history of heart disease. The authors concluded that the risk of MI is substantially increased in older men and in younger men with preexisting known heart disease.

This study has received an even greater media attention and appears to have led to the FDA decision to review CV risks with T. It thus bears close analysis. Here are the key concerns.

This Was a Retrospective Analysis that Lacked Basic Information

As a retrospective analysis of insurance claims data, there was no planned experiment, no control group, and there was absence of basic, critical clinical information. Specifically, there was no information regarding indications for treatment, race, lab results, occupation, environmental factors, and lifestyle information such as smoking,