# Testosterone, Cardiovascular Risk, and Hormonophobia

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**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 **;**:**–**.**

***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,

alcohol use, obesity, or body mass index [16]. In addition, it is impossible to reliably interpret the impact of T exposure when there is no information on pretreatment or post-treatment T concentrations or compliance rates with treatment.

### *Absence of Control Group Renders Results Non-Informative*

The study lacks a control group of men with the same medical condition as the study group (presumably men with T deficiency) who were untreated. Since MI rates increases with age, it is not surprising that a small increased rate of MI was seen in the first 90 days post-prescription compared with the prior 12 months. In the absence of a control group, this study cannot provide any data to indicate whether the observed MI rate following a T prescription was higher, lower, or unchanged compared with untreated men. The study is therefore non-informative regarding the impact of a T prescription on MI rates.

### *Uncertainty Regarding Reliability of End Point*

There was no verification that the primary end point, MI, had occurred. This end point was identified solely on the basis of an insurance claim diagnosis code. With rare events such as MIs, small discrepancies in numbers of events could easily alter results. Although the authors argue that there is a strong correlation between diagnosis codes and actual MIs [5], the citation they offer in support of this claim used an algorithm that excluded individuals hospitalized for less than 3 days in order to minimize the possibility of coding errors [17]. No such algorithm was described in this study. Others [18] have reported a diagnosis error rate of 12%. Imagine a prostate cancer study, for example, in which 12% of "cases" didn't actually have prostate cancer!

### *Inability to Distinguish Between Risk Due to Condition (T Deficiency) and Its Treatment*

In the absence of a control group of men with low T concentrations who did not receive a T prescription, it is impossible to know whether the observed increase in MI was due to the underlying condition (T deficiency) or its treatment (T prescription). Given the short period of exposure after T prescription (30–90 days) and the known association between T deficiency and CV risk [5–14], it is more plausible that low T was responsible rather than its treatment. The best interpretation of this study may be that men newly diagnosed with T deficiency are at increased risk of MI.

If T prescriptions were truly a risk factor for MI, then logically, that risk should increase with greater exposure times. Although the authors had information beyond 90 days of follow-up, they did not report it. As longer observation intervals are more reliable, one may reasonably assume the authors would have included this information if a similar result were obtained as it would have strengthened their results. The failure to report this data is notable, and disturbing, as it raises the concern that the observed effect could not be observed over a longer period of follow-up.

### *Comparison of T and PDE5i Groups Is Misleading and Inappropriate*

The authors provide comparison data for men treated with PDE5is and reported no increase in MI rates postprescription. This comparison provides no useful information. What can one learn when dissimilar populations are subjected to dissimilar treatments? No amount of statistical adjustment will ever make an apple into an orange.

### *Actual Risk Was Extremely Low*

The preprescription MI rate in the T-treated group was 3.48 per 1,000 person-years, and the postprescription rate was 4.75 per 1,000 person-years. The excess nonfatal MI risk was therefore 1.27 events for every 1,000 person-years. This means a man born in the era of Jesus Christ who was somehow still alive today and had used T continuously over two millennia would have suffered two nonfatal MIs during that time. This difference is clinically meaningless and too small to be regarded as accurate.

### *Subgroup Analyses Merit Caution*

Caution must be exercised in the interpretation of results from subgroup analyses, particularly when those analyses stem from retrospective studies; subgroups are created post hoc, overall effect is small, and numbers of individuals in each group is small. All apply here, particularly as the number of cases in two of the postprescription subgroups was extremely low at eight and 12 [16]. These low numbers and the inherent errors for this type of subgroup analyses render any conclusions unreliable.

## Conclusions

Neither the study by Vigen et al. [4] nor the more recent publication by Finkle et al. [16] provides any credible evidence that T use is associated with increased CV risk. Both studies were retrospective, highly statistical, and reported only a minor effect size. These study characteristics make it unlikely that these results are reproducible or accurate [19]. Even if the results were exactly as described, both studies could more plausibly be interpreted as showing the CV benefits of T therapy and the risks of untreated low T, as demonstrated repeatedly by a wealth of studies over the past 30 years. Although the authors of both studies cite a study by Basaria et al. [20] as support for increased CV risk with T, that placebo-controlled study was not designed to assess CV risk, and its report of increased adverse events in the T group compared with placebo was based on a wide variety of events of questionable significance, such as pedal edema, palpitations, and premature ventricular contractions [21].

Any unbiased examination of the literature reveals a much different result. A wealth of evidence indicates that low levels of T are associated with CV risks and known risk factors for CV disease, such as obesity, diabetes, and the metabolic syndrome [22,23]. Multiple longitudinal studies have demonstrated increased mortality rates in men with lower levels of T and improved survival in those with higher T [5–14]. A small number showed no effect [24]. In placebo-controlled trials, men who received T demonstrated increased angina-free exercise capacity [25] and improved functional capability in men with congestive heart failure [26]. Two retrospective studies demonstrated reduced mortality, by half, in men with T < 300 ng/dL who received T prescriptions compared with men who did not [27,28]. To date, there is not a single study that provides any compelling evidence that T therapy increases CV risk and a wealth of information suggesting T may be beneficial for CV health.

Some commentators have recently drawn parallels between the reported increase of CV risks with T to the experience of women with HRT [1]. This analogy between HRT and T therapy is apt, but for a different reason. In both cases, the allegations regarding risk were distorted, opposing views were trampled by a stampede of negative press, and the actual science regarding risk was hijacked in a broader war against the use of these hormones.

Health care has many players, each with powerfully held agendas. Nothing seems to unite these various groups as much as the use of sex hormones in middle-aged and older individuals. The loudest of these groups appear to be those who are antipharma, those opposed to direct-to-consumer advertising, the "naturalists" who opposed to what they regard as the medicalization of aging, and those who are antisex. The current outrage over the use of T therapy, anchored by the flimsiest of evidence regarding CV risk, should be regarded as hormonophobia [29]. However, the true outrage is that men whose health and quality of life have been impacted by a highly prevalent hormone deficiency may fail to receive treatment due to social forces and hysteria that are unrelated to medical science.

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## Statement of Authorship

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*Category 3*

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