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# EDITORIAL

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## The testosterone storm

**T**he concept of the thyroid storm is well known in medicine. Today we are dealing with what might be called a “testosterone storm” surrounding the scientific and public health debate over the use of testosterone replacement therapy. Last year, after a September 2014 FDA Advisory Committee meeting, manufacturers were required to include a label addition about a “possible” increased risk of heart attacks and strokes in patients taking testosterone. A large-scale study to assess cardiovascular risk was also recommended. The uncertainty of whether or not testosterone supplementation increases cardiovascular risks is the primary driver of the conflict.

There have been major improvements in the safety, quality, and ease of administration of testosterone replacements over the last few years. With these new routes of administration such as transdermal, subcutaneous and transmucosal, there has been an increase in interest in this aspect of men’s health with growth in both marketing and prescribing of testosterone supplements.

The 2014 meeting also included a rejection of a petition by Public Citizen to add a black box warning to testosterone supplements. In a published analysis prior to the meeting the FDA identified only 4 studies suggesting increased risk. In contrast, a systematic analysis of the literature identified over 80 studies demonstrating contradictory evidence. These note that low testosterone levels are associated with all-cause and cardiovascular mortality, and trials in men with angina showing improved exercise capability with testosterone supplementation. Testosterone therapy can improve metabolic syndrome (reduce fat and waist circumference, improve insulin resistance). Unfortunately, media focused attention on very few flawed studies and turned attention away from the positive accumulating evidence.

Could potentially flawed data have fueled the debate? Dr. Abe Morgentaler, Associate Clinical Professor, Urology, Harvard Medical School and more than 150 academic and clinical leaders questioned the veracity of one of the major studies that prompted the FDA action and called for its retraction on the basis of the data being “no longer credible”.<sup>1</sup> The paper contained methodologic flaws and the inclusion of females in the analysis. In the publication erratum the rates of adverse cardiac events were actually reduced by half in the testosterone treated group. This was followed by 29 medical societies from around the world joining the petition for retraction.

While there is universal agreement that testosterone is generally safe and beneficial when used in young, hypogonadal men another controversy is the suggestion of an increase in the inappropriate use of testosterone supplements. There is the impression that testosterone can serve as a fountain of youth for the aging male. While prescription testosterone supplements are approved for hypogonadal conditions, marketing pieces are also seen by men who may not have low levels of testosterone. Advertisements promote the use of testosterone supplementation for low energy, decreased sex drive and poor performance. Many men receiving supplemental testosterone today may not meet the clinical guidelines for treatment. Of concern is that many men being prescribed testosterone have never had a serum blood test before the testosterone was prescribed. Much like pre-certification for high end cancer medications, perhaps it should be mandated that a proper determination of testosterone has been performed in order for any replacement to be administered. This is reasonable as no data exists to show additional testosterone in a man with normal levels yields any health benefits.

The concept of testosterone replacement and prostate cancer is yet another area of disagreement. Some advocate that men who have been successfully treated for localized prostate cancer who are free of disease and hypogonadal should be replaced. Every testosterone label has prostate cancer (known or suspected) as a contraindication sending a powerful message to the clinician. This is an area where there is more literature supporting this approach than showing harm.

While the FDA has focused on the potential adverse cardiovascular effects of testosterone a recent European study has suggested that there is no risk. A study of over 25,000 male Medicare beneficiaries who received testosterone therapy for up to 8 years had no demonstrable cardiovascular risk. Another recent meta-analysis of 75 studies has shown no increased risk, and a reduced risk among some men.

Until the FDA’s requested long term studies of testosterone supplementation are available, these numerous controversies are unlikely to abate. Prescribers are now obligated to inform patients of the cardiovascular risks of testosterone supplementation while these stormy disagreements continue.

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1. Vigen R, O’Donnell CI, Barón AE et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. *JAMA* 2013;310(17):1829-1836 Erratum: *JAMA* 2014;311(9):967.