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Testosterone Therapy and Cardiovascular Risk: Advances and Controversies

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Abstract

Two recent studies raised new concerns regarding cardiovascular (CV) risks with testosterone (T) therapy. This article reviews those studies as well as the extensive literature on T and CV risks. A MEDLINE search was performed for the years 1940 to August 2014 using the following key words: *testosterone*, *androgens*, *human*, *male*, *cardiovascular*, *stroke*, *cerebrovascular accident*, *myocardial infarction*, *heart attack*, *death*, and *mortality*. The weight and direction of evidence was evaluated and level of evidence (LOE) assigned. Only 4 articles were identified that suggested increased CV risks with T prescriptions: 2 retrospective analyses with serious methodological limitations, 1 placebo-controlled trial with few major adverse cardiac events, and 1 meta-analysis that included questionable studies and events. In contrast, several dozen studies have reported a beneficial effect of normal T levels on CV risks and mortality. Mortality and incident coronary artery disease are inversely associated with serum T concentrations (LOE IIa), as is severity of coronary artery disease (LOE IIa). Testosterone therapy is associated with reduced obesity, fat mass, and waist circumference (LOE Ib) and also improves glycemic control (LOE IIa). Mortality was reduced with T therapy in 2 retrospective studies. Several RCTs in men with coronary artery disease or heart failure reported improved function in men who received T compared with placebo. The largest meta-analysis to date revealed no increase in CV risks in men who received T and reduced CV risk among those with metabolic disease. In summary, there is no convincing evidence of increased CV risks with T therapy. On the contrary, there appears to be a strong beneficial relationship between normal T and CV health that has not yet been widely appreciated.

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In November 2013 and January 2014, 2 studies were published reporting increased cardiovascular (CV) risks in men who received testosterone (T) prescriptions.[1,2] These articles gained wide media attention. Media coverage of these studies was frequently combined with data indicating rapidly increased sales of T products,[3,4] raising concerns that the pharmaceutical industry was promoting a treatment associated with important risks. This view was captured best by a *New York Times* editorial entitled "Overselling Testosterone, Dangerously."[5]

The impact of these studies on patient management and the ensuing public attention has been substantial. Men discontinued treatment, occasionally criticizing their physicians for putting their health at risk; some physicians stopped prescribing T products, and others warned against treatment of T deficiency (TD) (also called *hypogonadism* or, more casually, *low T*). The Endocrine Society issued a statement cautioning against the use of T therapy in older men and in men with a history of coronary artery disease (CAD).[6] The US Food and Drug Administration (FDA) announced plans to review the CV safety of T products 2 days after publication of the second article.[7] Plaintiff attorneys began a nationwide campaign seeking cases of myocardial infarctions (MIs) and strokes in men who had used T products for a class action lawsuit. These concerns thrust T therapy into the news, where the reported CV risks anchored a variety of unrelated concerns regarding other aspects of T therapy, such as overuse and abuse, false claims by antiaging medicine, profiteering by low-T clinics, and the failure of men to accept the rigors of natural aging.

It is beyond the scope of this article to address these various issues. Instead, we wish to address the key scientific question, namely, whether T therapy is associated with increased CV risks. This review encompasses an analysis of the literature previously submitted by us to

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the FDA and to the European Medicines Agency to assist with their own investigations of this topic. This article provides in-depth analysis of studies suggesting increased CV risks with T therapy, a historical perspective, and a systematic literature review. Because of the large number of studies reviewed, much of the information is presented in tables, with text limited to summaries of data.

There are no large, long-term, placebo-controlled randomized clinical trials in the field of T therapy to provide definitive conclusions about CV risk. Nonetheless, there exists a rich literature spanning many decades that provides valuable information. As described in more detail subsequently, the 2 recent articles contradict this literature, and on careful review, neither provides credible evidence of increased CV risks. Only 2 additional studies are generally cited as support for that view. In contrast, many dozens of studies, including a modest number of randomized controlled trials (RCTs), indicate that *low* serum T concentrations are associated with increased CV risk and mortality and that T therapy may have clinically relevant CV benefits. This last point will be new to many readers. A recently published meta-analysis of 75 placebo-controlled studies, the largest to date, found no evidence of increased CV risk with T therapy and clear evidence of improved metabolic profiles.[8] Given the personal suffering of men with TD as well as the public health burden of TD, the recent controversy regarding T and CV disease presents an important opportunity to understand the science underlying this critical medical issue.

BACKGROUND

Testosterone deficiency is a clinical syndrome characterized by a set of signs and symptoms in combination with low serum T concentrations.[9,10] Symptoms include decreased libido, erectile dysfunction, difficulty achieving orgasm, reduced intensity of orgasm, fatigue, decreased energy, depressed mood, irritability, and decreased sense of well-being. Objective signs include anemia, decreased bone density, reduced muscle strength and mass, increased body fat mass (both visceral and total), and weight gain.[9,10] Androgen deprivation therapy, used in the treatment of advanced prostate cancer, causes profound TD and is associated with negative changes in body composition as well as increased risk of incident diabetes mellitus.[11] The goal of T therapy is to alleviate symptoms and signs by restoring T concentrations to optimal levels within the physiologic range.

Established benefits of T therapy in hypogonadal men include improved sexual desire and function,[12-15] improved energy, mood, and vitality,[15-19] increased lean mass,[14,19-22] decreased waist circumference,[23-27] reduced total body fat mass,[19-22] and increased bone mineral density.[28-31] Promising new data reveal that T therapy improves insulin sensitivity[32-34] and reduces blood glucose[23,25,35] and hemoglobin A_{1c} (HbA_{1c})[23,25,27,35] levels in men with type 2 diabetes or obesity.

Biochemical confirmation of TD has traditionally been made on the basis of low serum concentrations of total T (TT). Although no specific value reliably distinguishes men who will respond to treatment from those who will not, recommended thresholds for low TT range from 300 ng/dL (10.4 nmol/L)[9] to 400 ng/dL (13.9 nmol/L).[36] Because a majority of circulating T is rendered biologically unavailable due to tight binding to sex hormone—binding globulin (SHBG), the unbound fraction called *free T* and/or the portion of T weakly bound to albumin may be more indicative of a man's true androgen status.[37,38] These 2 fractions together represent bioavailable T. Men with high-normal or elevated SHBG concentrations may have TT concentrations within the normal range yet may still have TD due to reduced free T concentrations. This issue may be particularly relevant for older men because SHBG levels increase with age.[39] Levels below 65 to 100 pg/mL (<174-288 pmol/L) for calculated free T and 0.8 to 1.5 ng/dL (27-52 pmol/L) for directly measured free T have been used clinically to identify men who are candidates for treatment.[10,39,40] However, laboratory-provided reference ranges are problematic because they are not clinically based and vary widely between assays, and even among laboratories using the same assays.[41]

The prevalence of symptomatic TD ranges from 2.1% to 12.8% in middle-aged to older men, with an incidence of 12 new cases per 1000 person-years in the United States and Europe.[42] Populations at high risk for low serum T levels include men with type 2 diabetes, obesity, chronic obstructive pulmonary