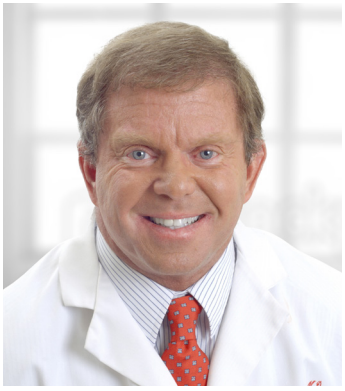
ARTICLE CRITIQUE

Is Testosterone Therapy in Men Harmful?

A Critical Review of a Recent Observational Study and Media Attention on Testosterone and Heart Attack Risk

By Neal Rouzier, MD

After a recent article on testosterone use was published in the Journal of the American Medical Association (JAMA), there has been an opportunity for law firms to capitalize on the suggested correlation between testosterone use and increased heart attack risk. However, the observational study behind the article suggesting such correlation has received significant criticism on the basis of flawed study designs and serious analysis errors. Dr. Neal Rouzier, BHRT pioneer and expert, has written a critical review of the study's resulting article from JAMA and television advertisements for various law firms.



You might have been alarmed by the recent television commercials from law firms soliciting patients that have taken testosterone and suffered a heart attack. Unfortunately, these campaigns have been influenced by a recent negative observational study of weak power and poor design and that has also been severely criticized by many medical experts in urology and endocrinology. In spite of the worrisome television hype, patients and doctors should not be led astray or fear using testosterone solely based on the hysteria created by attorneys.

In contrast to this recent negative study, there are over 40 years of well-designed, randomized controlled trials and observational studies that all support the safety and efficacy of testosterone administration (I have provided references to some of those trials and studies below). The most recent negative study of concern, which reported an association between the use of testosterone therapy and increased risk of death and heart attacks, appeared in the Journal of the American Medical Association (JAMA). Regardless of the study's criticism, legal zealots have latched on to the negative conclusions as a basis for lawsuits including anyone that might have suffered a heart attack while taking testosterone. The negative conclusions from this study have also reached the media, making patients concerned about their testosterone prescriptions. Because patients are unaware of the research from more than 40 years of supportive trials and studies, these patients now question if they should discontinue their testosterone medication.

Why the JAMA Study Should Be Ignored

In spite of this fear that has been instilled in the public by certain attorney groups, the public does not have enough experience or information to make informed decisions concerning the use of testosterone. I wish to explain and elaborate on why this study should be ignored and that no one should stop taking testosterone or fear taking it. Physicians should not cease prescribing testosterone and patients should not stop using testosterone based on this one weak study, the results of which goes against a plethora of data showing safety and efficacy. I base my therapy on a composite of many studies over several decades of research and not on one rogue study that, in the opinion of medical experts, should be discarded.

It helps to understand the difference between a randomized controlled study (RCTs) and an observational study. In an RCT, subjects are screened to remove those that have other medical problems or issues that might adversely influence the data and results. To simplify understanding of RCTs, there is a treated group and a placebo group that are specifically tested by eliminating any patients that may have risk factors that would skew any results. Observational studies, on the other hand, are not as powerful, accurate, or reliable as RCTs. In observational studies, careful selection does not take place, and reports (which may or may not be RCTs) are selectively reviewed without any regard to avoiding biases and errors. Reviewers pick and choose from the studies without randomization or control from other influencing factors, which can add inaccuracy and bias to any study. There was significant inaccuracy and error in this recent JAMA study.

Gross Data Mismanagement Calls for Corrective Action

A post by three professional medical societies, along with an international group of 130 scientists and physicians, has petitioned JAMA to retract this recent article (JAMA 2013; 310:1829-36). In a letter addressed to JAMA editors, the newly formed Androgen Study Group cites "gross data mismanagement thereby rendering the article no longer credible." The article was one of two studies that prompted the FDA to issue a safety bulletin on the use of testosterone products. However, this warning from the FDA is only an advisory as the FDA has cautioned both patients and physicians not to stop testosterone therapy based on just one study, particularly when this study's design flaws incorrectly led to negative results.

This article has already undergone two published corrections. The first was published in January due to misreporting of primary results. A second correction published in March revealed what the group called "major errors" in the article's text and figures. In other words, the statistical analysis utilized was inappropriate and other statistical methods actually show opposite results with beneficial connotations. Furthermore, the numbers used for the statistical analysis were different from the numbers published in their tables. The raw numbers in their tables actually proved protection against myocardial infarction (heart attack), not the increased risk that they published. It is not until their data is plugged into a complex analytical scheme that it shows harm, hence the insistence for JAMA to retract the article. The petition was signed by the International Society for Sexual Medicine, the Sexual Medicine Society of North America, and the International Society for the Study of the Aging Male, along with more than 125 scientists and physicians (of which I am one).

"This is an extraordinary event," said Abraham Morgentaler, MD, of Harvard University who is chairman of the Androgen Study Group. "In my 25 years in academic medicine, I have never witnessed anything like this response to a journal article." He adds that the call for retraction of an article is exceedingly rare. "To have several professional societies and so many of the most accomplished experts in the field unite in this action indicates the seriousness of the article's errors, and the magnitude of damage this article has caused to the public's perception of testosterone therapy."

Higher Testosterone Levels Associated with Better Cardiovascular Outcomes

Dr. Morgentaler went on to say, "Lost in the media frenzy that followed this article's publication is the fact that substantial evidence accumulated over 30 years has repeatedly shown that higher testosterone levels are associated with better cardiovascular outcomes. In the interests of medical science and the public good, JAMA should do the right thing and retract the article."

"Many of my patients stopped taking testosterone because of the JAMA article, even those who had experienced substantial benefits. And now we find out it was all based on nothing but sloppy science. We are talking about real consequences on individuals' health and quality of life," states Dr. Morgentaler. The Androgen Study Group says it is dedicated to the education and accurate reporting on the science of testosterone deficiency and treatment in men. It was organized specifically to respond to the "recent unwarranted, unscientific attacks" on testosterone therapy in medical and public media.

40 Years of Scientific Studies and Literature Support Testosterone Use

I cannot emphasize enough the importance of realizing that one negative observational study, even if it had been credible, does not negate 40 years of past positive and beneficial studies, including RCTs, which proved testosterone's protection against heart attacks. A recent statement from the American Academy of Clinical Endocrinologists suggest that physicians and patients should not jump to conclusions based on one poorly done study. Patients should continue taking testosterone until further evaluation and review is complete. The FDA, knowing the history of 40 years of positive studies demonstrating protection against heart disease, has also recommended that men not stop their testosterone prescriptions based on a study of poor methodology.

The truth of the matter is, according to 40 years of studies, that not only is there no increased risk in men on testosterone replacement therapy, but that there is significant benefit. These studies demonstrate that low endogenous levels of testosterone are associated with an increased risk of cardiovascular disease and heart attacks. Testosterone has been shown to prevent plaque deposition (atherosclerosis) which is the primary cause of heart attacks. Our goal should be to stop the plaque from forming in the first place, thereby preventing the primary cause of heart attacks. Various medical academies and experts recommend testosterone for cardiovascular protection as well as for quality of life benefits as demonstrated in 40 years of solid research.

Respectfully submitted, Neal Rouzier, M.D.

Baker B. Testosterone patch increases BMD in elderly men. Family Practice News. 1999 Oct 15.

Barrett-Connor EL. Testosterone and risk factors for cardiovascular disease in men. Diabete Metab. 1995 Jun;21(3):156-161.

Barrett-Connor E, Khaw KT, Yen SS. A prospective study of dehydroepiandrosterone sulfate, mortality, and cardiovascular disease. N Engl J Med. 1986 Dec 11;315(24):1519-1524.

Boshert S. Concerns about testosterone replacement safety evolve. Family Practice News. 2004 November 1.

Carter HB, Pearson JD, Metter EJ, et al. Longitudinal evaluation of serum androgen levels in men with and without prostate cancer. Prostate. 1995 Jul;27(1):25-31.

Cookson MS, Smith J. PSA Testing: Update on Diagnostic Tools. Consultant. 2000 April 1.

English KM, Steeds RP, Jones TH, et al. Low-dose transdermal testosterone therapy improves angina threshold in men with chronic stable angina: A randomized, double-blind, placebo-controlled study. Circulation. 2000 Oct 17;102(16):1906-1911.

Faloon W. A new, independent risk factor for heart disease. 2004 Aug. http://www.lef.org/magazine/mag2004/aug2004_awsi_01.htm. Accessed January 2012.

Fukui M, Kitagawa Y, Nakamura N, et al. Association between serum testosterone concentration and carotid atherosclerosis in men with type 2 diabetes. Diabetes Care. 2003 Jun;26(6):1869-1873.

Ginsberg TB, Cavalieri TAPg 9 to 12 – Gaby, A. R. DHEA: The hormone that does it all. Holistic Medicine. 1993 Spring:19-23.

Gordon GB, Bush DE, Weisman HF. Reduction of atherosclerosis by administration of dehydroepiandrosterone. A study in the hypercholesterolemic New Zealand white rabbit with aortic intimal injury. J Clin Invest. 1988 Aug;82(2):712-720.

Hak AE, Witteman JC, de Jong FH, et al. Low levels of endogenous androgens increase the risk of atherosclerosis in elderly men: the Rotterdam study. J Clin Endocrinol Metab. 2002 Aug;87(8):3632-3639.

Herrington DM. Dehydroepiandrosterone and coronary atherosclerosis. Ann N Y Acad Sci. 1995 Dec 29;774:271-280.

Heufelder AE, Saad F, Bunck MC, Gooren L. Fifty-two-week treatment with diet and exercise plus transdermal testosterone reverses the metabolic syndrome and improves glycemic control in men with newly diagnosed type 2 diabetes and subnormal plasma testosterone. J Androl. 2009 Nov-Dec;30(6):726-733.

Rhoden EL, Morgentaler A. Medical Progress: Risks of Testosterone-Replacement Therapy and Recommendations for Monitoring. N Engl J Med. 2004 Jan; 350:482-492.

Labrie F, Diamond P, Cusan L, et al. Effect of 12-month dehydroepiandrosterone replacement therapy on bone, vagina, and endometrium in postmenopausal women. J Clin Endocrinol Metab. 1997 Oct;82(10):3498-3505. Androgen deficiency in the aging male: The beginning, the middle, and the ongoing. Clinical Geriatrics. 2008 April;16(4):25–28.

Maggio M, Lauretani F, Ceda GP, et al. Relationship between low levels of anabolic hormones and 6-year mortality in older men: the aging in the Chianti Area (InCHIANTI) study. Arch Intern Med. 2007 Nov 12;167(20):2249-54.

Malkin CJ, Pugh PJ, Morris PD, et al. Testosterone replacement in hypogonadal men with angina improves ischaemic threshold and quality of life. Heart. 2004 Aug;90(8):871-6.

Malkin CJ, Pugh PJ, Jones RD, et al. The effect of testosterone replacement on endogenous inflammatory cytokines and lipid profiles in hypogonadal men. J Clin Endocrinol Metab. 2004 Jul;89(7):3313-3318.

Moffat SD, Zonderman AB, Metter EJ, et al. Free testosterone and risk for Alzheimer disease in older men. Neurology. 2004 Jan 27;62(2):188-193.

Morales AJ, Nolan JJ, Nelson JC, Yen SS. Effects of replacement dose of dehydroepiandrosterone in men and women of advancing age. J Clin Endocrinol Metab. 1994 Jun;78(6):1360-1367.

Muller M, Aleman A, Grobbee DE, et al. Endogenous sex hormone levels and cognitive function in aging men: is there an optimal level? Neurology. 2005 Mar 8;64(5):866-871.

Jancin B. Testosterone replacement curbs inflammatory cytokines. Clinical Psychiatry News. 2004 May

Khaw KT, Dowsett M, Folkerd E, et al. Endogenous testosterone and mortality due to all causes, cardiovascular disease, and cancer in men: European prospective investigation into cancer in Norfolk (EPIC-Norfolk) Prospective Population Study. Circulation. 2007 Dec 4;116(23):2694-701.

Selvin E, Feinleib M, Zhang L, et al. Androgens and diabetes in men: results from the Third National Health and Nutrition Examination Survey (NHANES III). Diabetes Care. 2007 Feb;30(2):234-238.

Shores MM, Matsumoto AM, Sloan KL, Kivlahan DR. Low serum testosterone and mortality in male veterans. Arch Intern Med. 2006 Aug 14-28;166(15):1660-1665.

Villareal DT, Holloszy JO. Effect of DHEA on abdominal fat and insulin action in elderly women and men: a randomized controlled trial. JAMA. 2004 Nov 10;292(18):2243-2248.

Van Vollenhoven RF, Morabito LM, Engleman EG, McGuire JL. Treatment of systemic lupus erythematosus with dehydroepiandrosterone: 50 patients treated up to 12 months. J Rheumatol. 1998 Feb;25(2):285-289.

Winters SJ. Current status of testosterone replacement therapy in men. Arch Fam Med. 1999 May-Jun;8(3):257-263.Winters SJ.

Wolkowitz OM, Reus VI, Roberts E, et al. Dehydroepiandrosterone (DHEA) treatment of depression. Biol Psychiatry. 1997 Feb 1;41(3):311-318.