There have been several high profile articles published recently that appear to connect an increased risk of cardiovascular disease with testosterone replacement therapy. Naturally, this is alarming, as it is contrary to what previous studies have determined and contrary to the principles by which most of us prescribe testosterone. Upon close review, there are a number of issues in these studies that are worth mentioning, and serve as good reminders of the importance of reading details rather than simply the headlines.

The JAMA article of November 2013 entitled “Association of Testosterone Therapy with Mortality, Myocardial Infarction, and Stroke in Men with Low Testosterone Levels” concluded that testosterone supplementation increased a man’s risk of adverse cardiovascular events; however, there are a number of problems with the way this study was conducted:

- It was observational and retrospective in nature, meaning that instead of following randomized groups of subjects who differ only by treatment(s) and comparing to a control group (i.e.: randomized placebo controlled study (RCT)), these findings were based on retrospective observation of multiple treatments and variables outside of the control of the investigator. While a study like this may demonstrate associations, causation is better observed in RCT studies.
- The cohort consisted of men with prior history of cardiovascular disease (CVD) who had undergone coronary angiography between 2005 and 2011, and who had testosterone levels less than 300 ng/dL at the time of angiography.
- The study demonstrates multiple inherent biases and limitations as stated in the discussion section, including: the utilization of ICD9 codes only (no chart review) to determine outcomes, a relatively small group of patients with extended follow up time, and a select group of subjects undergoing angiography in the VA system, limiting generalizability. As such, this study cannot prove causality.
- During the duration reviewed, 17.6% of subjects filled their prescription only once, with the remainder refilling their prescriptions more than once. Those subjects who did refill their prescriptions more than once averaged 376 days between refills. This is significant because testosterone refills are only valid for 180 days, suggesting the unlikelihood that therapeutic levels were attained. This concern is further strengthened by the knowledge that average total testosterone levels only increased to 332.2 ng/dL just slightly above the initial cutoff for study inclusion and definition of hypogonadism for this study.
- Route of administration of testosterone replacement therapy (TRT) is important and was not accounted for in the study’s conclusions. Gel usage accounted for half of the refills. Because serum does not accurately reflect therapeutic levels of transdermal hormones, the serum values were not reflective of absorbed hormone, and were likely reflecting a much lower total testosterone than was available to tissue.
- Estradiol values were not measured or accounted for. Elevated estradiol, commonly seen with TRT as a result of aromatization, increases hypercoagulability and is a risk factor for both MI and stroke, the major death categories in the study.
- Though the researchers in this study concluded that testosterone supplementation was associated with an increased risk of death, MI, and ischemic stroke; association and causation are not the same. The associations drawn from this study were done without accounting for many important factors, and should not be interpreted as testosterone supplementation playing a causative role in cardiovascular events.

Another study published in January 2014 entitled, “Increased Risk of Non-Fatal Myocardial Infarction Following Testosterone Therapy Prescription in Men” was a cohort study utilizing a large health-care database. A cohort study is a type of longitudinal study that follows a group of people who share a common characteristic within a defined period. In this study the common characteristic was filling a prescription for testosterone (topical, oral and/or injectable). This group was compared, not with an age matched group who were not taking testosterone, but with a group of men who were taking phosphodiesterase type 5 inhibitors (PDE5) such as Viagra or Cialis. The authors concluded in men with previous cardiovascular disease, both below and above the age of 65, there was a two-fold increase of non-fatal MI’s within 90 days of initiating treatment. The study found no increased risk associated with testosterone therapy for men under 65 with no prior history of CVD. As with the previous study, there are a number of flaws in the study design:
Dosages and frequency of testosterone supplementation were not indicated. There is no data on why testosterone was prescribed. There was no before and after labwork performed on the men prescribed testosterone; therefore no way to examine whether or not the MI’s were related to levels of serum testosterone and hypogonadism.

Testosterone therapy is known to elevate red blood cell counts and estrogen levels, both of which may increase clotting and thrombotic disorders, including increased BP. Without a measure of testosterone levels, hematocrit, and estradiol levels before and during therapy, one’s candidacy for testosterone therapy cannot be determined, and tolerance to treatment cannot be monitored. Utilizing PDE5 inhibitors as a comparison group was a poor choice as recent research has shown that PDE5 inhibitors are found to lower the risk of heart disease - so much so, that they show potential to be utilized as cardiovascular drugs in the future.

The results of the studies cited above run counter to a substantial body of research suggesting that low testosterone contributes to higher rates of cardiovascular disease, and the severity of the disease correlates with the degree of testosterone deficiency. Testosterone replacement therapy has exhibited beneficial cardiovascular effects including improving insulin resistance, increasing exercise tolerance, increasing muscle mass, and contributes to coronary artery vasodilation, suggesting that optimal testosterone levels actually decrease the risk of cardiovascular disease. More research is needed, specifically longitudinal, placebo-controlled, randomized trials of testosterone replacement therapy in men with low testosterone levels in order to clearly clarify the role of testosterone in the survival of patients with heart disease.

Bibliography


