Testosterone & Cardiovascular Health

Does testosterone cause heart attacks or strokes?

Two somewhat recent studies reported that testosterone supplementation increased heart attacks in men.[1,2] It's important to note that both of these were observational, not intervention, studies. In an observational study, investigators observe subjects and measure their outcomes—the researchers do not actively manage the study. In an intervention study (e.g., a randomized controlled trial), the investigators give the research subjects a particular drug or other intervention, and compare the treated subjects to subjects who receive no treatment (placebo). Researchers then measure how the subjects' health changes. Observational studies do not prove causation; they can, however, reveal the need for intervention trials. Ideally, physicians should base treatment decisions on the results of many studies after weighing an individual patient's risks and benefits.

Neither the JAMA or PLosONE studies were interventional trials. In addition, neither study performed blood work to monitor testosterone or estradiol levels or side effects (such as hemoglobin and hematocrit levels). Elevated hemoglobin and hematocrit levels can cause thicker or more turbulent blood flow which may be detrimental to men with narrowed arteries. In addition, neither study kept track of duration of use for men receiving testosterone prescriptions.

Unfortunately, the authors of the JAMA study published the wrong conclusion, which has been poorly reported in the media and misunderstood by countless physicians. The JAMA study concluded that men who received testosterone had a higher risk of heart attack, stroke, and death.[3] The study looked at 8,709 veterans with low testosterone (<300 ng/dL) who underwent coronary angiograms from 2005 to 2011. Testosterone prescriptions were given to 1,223 men; 7,468 men did not receive testosterone therapy. **The study's authors actually published the wrong conclusion**, stating a higher event rate (25.7%) in men who received testosterone prescriptions vs 20% event rate in men who did not receive testosterone therapy. **This was incorrect**. Of the 7,486 patients who did not receive testosterone prescriptions, 681 died, 420 had heart attacks, and 486 had strokes. This was an absolute event rate of 21.2% (681 + 420 + 486 = 1587 events divided by 7486 men = 21.2%). Of the 1,223 men who received testosterone prescriptions, 67 died, 23 had heart attacks, and 33 had strokes. This was an absolute event rate of 10.1% (67 + 23 + 33 = 123 events divided by 1223 men = 10.1%). Therefore, **men who did not receive testosterone prescriptions had more than double the risk for an event than men who did receive prescriptions. More than 160 leading experts from 32 countries have asked JAMA to retract this paper; unfortunately, as of the date of this writing, JAMA has not done so.**

Besides publishing the wrong conclusion, another obvious concern with this study is that the only criteria for the testosterone group was that they filled a single prescription for testosterone. Only 60% of study subjects filling a testosterone prescription had a follow-up blood test to assess testosterone levels and none were followed for duration of use. Among those who were tested, average testosterone levels increased from a very low level of 175.5 ng/dL at baseline to

only 332.2 ng/dL during testosterone therapy. This level is still considered low and is likely not high enough to provide health benefits. Research has shown that restoring testosterone levels to 500 ng/dL or higher (a youthful level) may be necessary to reduce cardiovascular risk.[4,5]

The more recent PLoS ONE study[6] reported that men under age 65, with no previous diagnosis of heart disease, had a 10% decrease in heart attacks; however, this wasn't statistically significant. Men over 65 had an increased heart attack rate regardless of heart disease diagnosis.

Testosterone Deficiency & Supplementation

Many observational and several intervention studies show no increased risk of heart attack or stroke in men with higher endogenous (made by the body) testosterone levels or men treated with testosterone. In fact, a meta-analysis of observational studies has shown that men with low testosterone have an increased risk of death from all causes including cardiovascular disease.[7] Another recent observational study following 25,000 men over 65 found that men on testosterone injections did not have an increased risk for heart attack. In fact, in men with high cardiovascular risk, testosterone was modestly protective.[8]

Men with low endogenous testosterone are at a higher risk for heart disease, heart attack, stroke, and death from cardiovascular disease.[9-14] This is likely due to the conditions and cardiovascular risk factors associated with low testosterone including endothelial dysfunction, increased arterial thickness, increased inflammation, dyslipidemia, insulin resistance and metabolic syndrome, type 2 diabetes, and obesity.[15-21] Higher endogenous free testosterone is associated with less atherosclerosis in the carotid arteries.[22] Testosterone deficiency is considered by some authors to be a major risk factor for cardiovascular disease (echoed by meta-analysis).[23,24] Low testosterone is also associated with increased risk of death from cardiovascular disease.[25]

Most studies are consistent when it comes to testosterone therapy improving risk factors for cardiovascular disease and decreasing heart attack risk and stroke risk. A 14-year observational trial has shown that testosterone therapy decreases heart attack risk and cardiovascular and all-cause mortality.[26] Another observational study of 1,031 veterans reported twice the mortality risk for men with low testosterone who were untreated (20.7%) versus those who were treated (10.3%) over two to 4 years of therapy.[27]

A deficiency of testosterone likely plays a role in the development of insulin resistance and type 2 diabetes, and testosterone therapy improves metabolic syndrome parameters such as high blood sugar, insulin resistance, hsCRP, and blood pressure.[28-32] Testosterone therapy has also been shown to improve survival in men with type 2 diabetes.[33]

Regarding lipids and inflammation, two risk factors that increase cardiovascular risk, testosterone supplementation has been shown to lower LDL cholesterol and triglyceride levels, as well as reduce inflammation.[34,35] Physiological doses of testosterone may also improve synthesis of nitric oxide and, therefore, endothelial function.[36,37] Testosterone replacement increases lean body mass (muscle) and reduces visceral fat percentage.[38-40] In men with heart disease, testosterone supplementation improves angina (chest pain) symptoms, likely because it dilates coronary arteries.[41-44] Testosterone also improve exercise capacity, insulin resistance, and muscle performance in men with congestive heart failure and can improve survival in men with heart failure.[45,46]

Opinion:

No long-term, randomized, placebo-controlled (intervention) trials regarding testosterone therapy and heart attack or cardiovascular and mortality risk have been performed. However, the preponderance of data suggests that testosterone appears to be protective. It seems reasonable to use testosterone therapy as part of a comprehensive plan to lower cardiovascular risk, not as a stand-alone therapy.

A thorough cardiovascular assessment includes advance lipid testing, inflammation and oxidative stress markers, genetic testing, and imaging (e.g., carotid ultrasound/CIMT, calcium score, and possibly CT angiogram, stress testing, and echocardiogram). Once risk is properly assessed, the most effective plan to lower cardiovascular event risk includes diet, exercise, stress management, targeted nutraceuticals (supplements), specific medications, and physiological testosterone replacement. See Dr. Retzler's "Optimal Cardiovascular Health" handout for more information on this approach.

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