Two Studies Suggest Testosterone Might Not Increase Risks of Cardiovascular Events

Michael O'Riordan | March 09, 2015

SAN DIEGO, CA — Two new studies muddy the waters on the potential cardiovascular risks previously linked to testosterone-replacement therapy in men, with both studies suggesting the therapy might not be causing the cardiovascular harm suggested in previous analyses[1,2]. Both are scheduled for the presentation later this week at the American College of Cardiology (ACC) 2015 Scientific Sessions.

The first study included 7245 men with low testosterone levels from 15 hospitals and 150 clinics. Overall, the cardiovascular event rate—a composite of MI, stroke, or death—was 5.5% among those who received testosterone therapy and 6.7% among those who did not. After adjustment for baseline differences between the treated and untreated patients, the difference in the cardiovascular event rate was not statistically significant.

In the second study, a meta-analysis of 29 studies with more than 122 000 men, researchers found testosterone therapy was not associated with a significantly increased risk of adverse cardiovascular outcomes.

"When we pulled out all the studies so far, testosterone in any form—whether it was a gel, an injection, or older pills—did not increase the risk of cardiovascular events, such as heart attack, sudden cardiac death, stroke, or hospitalization for heart failure," Dr Pawan Patel (Regions Hospital, St Paul, MN), lead investigator of the meta-analysis, told *heartwire* . "Now, this is a not long-term, prospective, randomized controlled trial. Only with those long-term randomized controlled trials will we be able to say whether testosterone causes cardiovascular events or not."

The FDA Warning

Last week, the US Food and Drug Administration issued a warning about the potential risks of MI and stroke among men treated with testosterone-replacement therapy. The FDA began investigating the link between testosterone therapy and adverse cardiovascular outcomes in January 2014 on the basis of two studies linking the products with increased risks.

In the first study, an observational analysis of Veterans Affairs (VA) patients undergoing coronary angiography, the use of testosterone therapy was associated with a 29% higher risk of death, MI, or ischemic stroke when compared with men who were not receiving testosterone-replacement therapy. In the second study, men treated with testosterone were significantly more likely to have an MI in the first 90 days after starting the medication. Three months after the start of testosterone therapy, the risk of MI overall was increased by 36%. For those aged 65 years and older, the risk of MI was more than twofold higher in the 90 days after filling the prescription.

Those two studies, however, were not the only analyses suggesting a risk of cardiovascular events with testosterone. In the Testosterone in Older Men with Mobility Limitations (TOM) study, testosterone treatment in men aged 65 years and older was associated with an increased risk for cardiovascular events, including MI and hypertension. That study, which was funded by the National Institutes of Health, was stopped because of the cardiovascular risks.

Given the heightened concerns about adverse cardiovascular outcomes with testosterone therapy, the FDA now requires manufacturers of prescription testosterone products to clarify the approved uses of the medications on the product label and add information about the possible increased risk for heart attack and stroke with use of these products. Specifically, the label now states that testosterone-replacement therapy is approved "only for men who have low testosterone levels due to disorders of the testicles, pituitary gland, or brain that cause hypogonadism."

The FDA added it is aware "testosterone is being used extensively in attempts to relieve symptoms in men who have low testosterone for no apparent reason other than aging." The safety and benefits in this setting have not been

established, it states. According to IMS Health, sales of prescription testosterone products were more than $2 billion in 2013.

What the New Data Show

The new studies presented this later week at the ACC cast some doubt on those previous concerns. In the first study, Dr Zuber Ali (Aurora Health Care, Milwaukee, WI) and colleagues studied 7245 men, mean age 54 years, prescribed testosterone-replacement therapy for low testosterone (<300 ng/dL). The mean follow-up period was 1.78 years. Cardiovascular risk factors were documented in many patients, with 41% having dyslipidemia and 34% having hypertension. In the multivariate analysis, there was no increased risk of acute MI, stroke, or death at 3 years among the testosterone-treated patients compared with the untreated patients.

Similarly, Patel and colleagues saw no increased risk of cardiovascular events in their meta-analysis. Given the heterogeneity of the studies, they used a random-effect model to calculate the relative risk of testosterone therapy among the patients who received the supplement in their 122 889-patient meta-analysis. Overall, their results suggested testosterone therapy did not increase the risk of adverse cardiovascular events (relative risk 1.168; *P*=0.431).

To **heart*wire*** , Patel said that given the shifting US demographics, with a growing number of older and elderly patients, more and more patients are being prescribed testosterone therapy. Overall, he believes the FDA warning might be premature. His study, as well as the study by the Wisconsin researchers, suggests the risks might be overestimated. However, Patel stressed that a randomized trial is the only way that clinicians and regulatory agencies will get the answers they need about the real risks of testosterone therapy.

Ali and coaouthors report no relevant financial relationships. Patel reports no relevant financial relationships; disclosures for the coauthor are linked to the abstract. The studies were independently funded by their health centers and without industry involvement.

References

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