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Long-term Testosterone May Decrease Cardiovascular Risk

Kate Johnson | May 10, 2016

SAN DIEGO — Long-term testosterone replacement therapy is associated with a decreased — not increased — risk for cardiovascular disease in men, according to a large population-based cohort study.

This finding "answers the controversy" fueled by recent warnings from the US Food and Drug Administration (FDA) suggesting that the opposite is true, said senior investigator Robert Nam, MD, from the Sunnybrook Health Sciences Centre in Toronto.

The study was published online May 7 in *Lancet Diabetes & Endocrinology* to coincide with its presentation here at the American Urological Association 2016 Annual Meeting.

On the basis of this study, "we can conclude that long-term testosterone is safe," Dr Nam told *Medscape Medical News*.

"We need to do further study, but with our large sample size and long follow-up, these data provide some powerful findings," he explained. "Physicians still need to individualize their recommendations to patients, but it certainly helps to address some of the controversy around testosterone."

The FDA recently required testosterone products to carry a warning about possible cardiovascular risk, as reported by *Medscape Medical News*. But that ruling was made on the basis of studies with a short duration of treatment, short follow-up, and no dose–response analysis, said Dr Nam.

"We weren't convinced that long-term testosterone had a detrimental effect because all the science says otherwise. That's why we wanted to look at it in a larger population with a longer duration of use," he explained.

The study involved 10,311 men 66 years and older newly treated with testosterone replacement therapy and 28,029 untreated control subjects, all gathered from Canadian databases.

Control subjects were matched for age, comorbidity, diabetes, region of residence, and index year.

At a median follow-up of 5 years, overall mortality was lower in patients treated with testosterone replacement therapy than in control subjects (hazard ratio, 0.88).

Duration of Treatment

When the duration of exposure was analyzed, mortality and heart-related morbidity were higher in patients who received short-term therapy (median, 2 months) than in those who received medium-term (median, 9 months) or long-term (median, 35 months) therapy. There was a "protective effect against both mortality and rates of heart-related events" with longer duration of treatment, Dr Nam reported.

Specifically, with short-term exposure, mortality increased by 11% and cardiovascular risk increased by 26%. However, with medium-term exposure, mortality decreased by 10%, and with long-term exposure, mortality decreased by 33% and cardiovascular events decreased by 16%.

There was no increase in prostate cancer risk with short-term exposure, and the risk decreased with increasing exposure; with long-term exposure, prostate cancer decreased by 40%.

Importantly, when the investigators looked at testosterone exposure over time, they controlled for immortal time bias, which can falsely attribute short-term risk to a treatment when deaths are actually due to the treatment having not

taken effect, explained lead investigator Christopher Wallis, MD, also from Sunnybrook.

"The original research just looked at ever or never exposure, but 1 week is not the same as 3 years of treatment," Dr Wallis told *Medscape Medical News*. "With the dose–response analysis and the fact that we controlled for immortal time bias, we added some methodologic complexity that was important."

In an editorial accompanying the published study, Michael Lauer, MD, from the National Institutes of Health in Bethesda, Maryland, was curiously vague. He compliments the investigators on the study design and statistical analysis, but says little about the actual findings and their implications.

"In view of current knowledge, we do not know whether testosterone therapy in older men is beneficial or safe," he writes. "But in the meantime, Wallis and colleagues' thoughtful observational analyses not only provide important insights into a vexing clinical problem, but also remind us of an often underappreciated component — intention-to-treat — of rigorous clinical science."

Until a large randomized, blinded, placebo controlled study is performed, the controversy regarding the safety of testosterone will remain unresolved.

In contrast, Robert Kloner, MD, PhD, from the Huntington Medical Research Institutes in Pasadena and the Keck School of Medicine at the University of Southern California in Los Angeles, got straight to the point.

"In my opinion, this paper does not resolve the controversy," he told *Medscape Medical News*.

"Physicians may feel confident that exogenous testosterone will probably not increase adverse cardiovascular events if the patient has been on it chronically and is doing well; however, it raises the concern about starting new prescriptions in some men. Perhaps when testosterone is first started, there should be increased vigilance during the first few months," he said.

Dr Kloner, who recently published a review of testosterone therapy and cardiovascular risk (*J Cardiovasc Pharmacol Ther*. Published online April 28, 2016), also pointed out that these findings are observational.

"Until a large randomized, blinded, placebo controlled study — in which the primary end point is major adverse cardiovascular events — is performed, the controversy regarding the safety of testosterone, especially in older men, will remain unresolved," he explained.

Still, "the data on prostate cancer are reassuring," Dr Kloner noted.

In response to the FDA warning, the American Academy of Clinical Endocrinologists (AACE) issued a position statement on the association between testosterone therapy and cardiovascular risk, as reported by *Medscape Medical News*.

The study by Dr Nam's team is another "that repudiates the FDA position on testosterone therapy increasing the risk of cardiovascular disease," said Neil Goodman, MD, from the University of Miami, who is head of the AACE Reproductive Endocrinology Scientific Committee.

"However," Dr Goodman told *Medscape Medical News*, "the study is limited, in that it is observational and no data are presented on the pretreatment demographics of the population of men given testosterone. Did they have pre-existent cardiovascular disease or risk factors for cardiovascular disease? How was the diagnosis of testosterone deficiency made? What dosage and by what route was testosterone given? As stated, a long-term randomized clinical trial is needed to confirm these findings."

This study was funded by Physicians' Services Incorporated Foundation and Ajmera Family Chair in Urologic Oncology. Dr Nam and Dr Wallis have disclosed no relevant financial relationships. Dr Kloner reports being a consultant to AbbVie, TesoRx, and Lipocine. Dr Goodman reports being on the AbbVie speakers bureau for AndroGel.

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