Testosterone Doesn't Up MI or Stroke: May Be Protective?

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LAS VEGAS — Contrary to recent findings, a new retrospective study of data from 40 specialized clinics around the United States has found that testosterone therapy in men is *not* associated with an increased risk for myocardial infarction (MI) or stroke and may even be cardioprotective.

The late-breaking results were presented here at the American Association of Clinical Endocrinologists (AACE) 23rd Annual Scientific and Clinical Congress by Robert Tan, MD, director of the Opal Medical Clinic, Houston, research director of the Low T Institute, and clinical professor of family and community medicine at the University of Texas.

Among 19,968 hypogonadal men who received testosterone therapy during a 5-year period (2009–2014) at Low T Centers nationwide (www.lowtcenter.com), the risk for MI was 7-fold lower and the risk for stroke 9 times lower compared with samples from the general population. Further, there was no evidence of worsening of preexisting MI or stroke in patients treated with testosterone.

"There has been a lot of hype and concern....I want to try to explain the other side of the story," Dr. Tan said in introducing his presentation.

He told *Medscape Medical News*, "When compared with other databases looking at rates of MI and strokes, it appears testosterone is cardioprotective."

This finding is counter to those of 2 widely reported recent studies that have generated enormous controversy and prompted an investigation into testosterone safety by the US Food and Drug Administration and the European Medicines Agency. The US Endocrine Society has also called for randomized controlled trials to investigate testosterone therapy and cardiovascular risk and has advised against giving testosterone therapy to men who have had a recent cardiovascular event.

But others have hit back, including the US Androgen Study Group, which has highlighted what it says are key flaws in these 2 widely cited studies; it is campaigning for 1 of them to be retracted and also claims that numerous other studies have shown a protective effect of testosterone.

Session moderator and AACE president-elect George Grunberger, MD, founder of the Grunberger Diabetes Institute, Bloomfield Hills, Michigan, told *Medscape Medical News* that he thinks Dr. Tan's study results "will help. Hopefully, it will reduce pushback from patients. The last thing you want is for people to stop [taking testosterone] out of fear."

However, although he called the new findings "very encouraging," he said that because the study was retrospective, it is not definitive. "This wasn't a prospective trial. The gold standard is a randomized controlled trial to answer the question."

Does Testosterone Protect?

The new study was part of an internal quality-management program at the Low T Centers, which follow strict protocols requiring a definitive diagnosis of hypogonadism (total T < 350 ng/dL and free T < 10 ng/dL) for starting testosterone therapy. Patients are also closely monitored while on treatment, with regular 1- or 2-week physical assessments and laboratory work.

Data were extracted from the electronic health record. In addition, the centers were called to make sure that *International Classification of Diseases, Ninth Edition* (ICD-9) coding had been updated, and families of patients who had MIs or strokes were also interviewed.

Of 39,937 patients seen during 2009–2014, approximately 50% met the criteria for treatment. Of the treated patients, 4 had nonfatal MIs, and 3 had probable fatal MIs, giving a rate of 30 new MIs per 100,000. Of the 46 patients with pretherapy MIs, none had adverse outcomes after receiving testosterone, Dr. Tan said.

There were 2 strokes among the treated patients, giving a rate of 10 new strokes per 100,000. Of 12 patients with pretherapy stroke, none had adverse events after testosterone.

Because the patients who did not qualify for testosterone therapy were not followed up, Dr. Tan and colleagues compared their figures with those from other published data sets of the general population.

The rate for MI at Kaiser Permanente Northern California was 208 per 100,000, and the stroke rate found in the Northern Manhattan Registry was 93 per 100,000.

Compared with these numbers, Dr Tan reported the rate ratio (RR) for MI in the testosterone-treated Low T Center patients was 0.14 ($P < .0001$), a 7-fold lower risk, and for stroke, the RR was 0.107 ($P < .0001$), 9-fold lower than the general population.

"Our study showed that carefully monitored testosterone therapy may actually protect against MI and stroke. It's retrospective, but I think for now it's as good as we can come up with. At least from our experience, there was no evidence of increased heart attacks or strokes from people treated with testosterone," Dr. Tan observed.

But what is really needed, he told *Medscape Medical News*, is "a large, randomized controlled study with very careful monitoring of patients' compliance, hematocrit, and other preexisting cardiac risk factors over at least a 5-year period."

Why the Differences?

There are many possible explanations for the difference in findings, Dr. Tan told *Medscape Medical News.*

One of the recently quoted studies showing a 36% increased risk for MI among 55,593 men who received a new prescription for testosterone therapy, published in *PLoS One* earlier this year, was based on a heterogeneous patient population that was seen at different practices with different protocols and that received varying exposures to testosterone for less than 3 months' duration.

In contrast, the Low T Center population was more a homogeneous group, received regular follow-ups, and had longer exposure to testosterone therapy, he noted.

And in the other oft-cited recent study — published in *JAMA* in November 2013 and found a 30% increased risk for death, MI, or ischemic stroke among 1223 older veterans on testosterone therapy who underwent coronary angiography — Dr. Tan said the mean T level with treatment was only 332.2 ng/dL, "which is at the low end. Our patients reached, on average, 543 ng/dL. Perhaps the lower range in the *JAMA* study led to the increased risk of MI?"

He also noted that one-third of the patients in the *JAMA* study received testosterone patches, whereas 90% of Low T Center patients received testosterone via injection, and fewer than 1% used the patch. Moreover, only 60% of the *JAMA* study patients had their testosterone levels reassessed, whereas 100% of Low T Center patients receive such reassessments. "I think close monitoring for safety is essential in testosterone therapy," Dr. Tan said.

The RCT Dilemma

In conversation with reporters about the new study, Dr. Grunberger said, "This is hypothesis-generating. Let's do a real study. I was glad to see this, and it is important, but you have to take it at face value when you look at retrospective chart review....Before you start making claims, you need [a] truly high-level, classy randomized trial [RCT]."

Of course, he noted, "RCTs cost hundreds of millions of dollars. That's the dilemma we have with everything we do." And they also take a long time, particularly when they are designed to look at end points such as cardiovascular events, and companies often say they cannot afford the investment.

"The economics, the math is just incredibly complex....That's the sad reality. I really don't know if there's a shortcut. You try to enrich [a study] with people at high risk, but then they're not representative of the general population. So, clinicians just have to fly by the seat of their pants....That's the dilemma."

The study was unfunded. Dr. Tan is an active practitioner of testosterone therapy in his own clinical practice at Opal Medical Clinic, which is unrelated to Low T Centers. He analyzed the data but does not see patients at the Low T Centers. His coauthors do, however. He has not received any pharmaceutical honoraria or research grants in the past 5 years. Dr. Grunberger has received speaker honoraria from Amarin, Janssen, Merck, Sanofi, Santarus, Takeda, and Valeritas. He has received research support from Bristol-Myers Squibb, Eli Lilly, and Novo Nordisk.

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