**Experts Clash Over Testosterone Cardiovascular Risks**

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Information from Industry

Recent warnings about the potential cardiovascular risks of testosterone therapy have triggered criticism from some experts in the field. At the crux of the dispute is whether men who have a recent history of cardiovascular disease should be treated with testosterone therapy.

There is also concern as to whether testosterone treatment is always appropriate, with [recent reports](https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&cad=rja&uact=8&ved=0CCYQFjAA&url=https%3A%2F%2Fwww.mja.com.au%2Fsystem%2Ffiles%2Fissues%2F199_08_211013%2Fhan10111_fm.pdf&ei=PXVzU7bNMfDesAT5_ILADA&usg=AFQjCNEd7JVIPJ2NBP5TcQ48TapA5ERakw&bvm=bv.66699033,d.cWc) indicating that prescriptions for testosterone in the United States are surging as pharmaceutical companies advertise directly to consumers. For instance, the *New York Times*[published an editorial](http://www.nytimes.com/2014/02/05/opinion/overselling-testosterone-dangerously.html) earlier this year that stated that "doctors are prescribing testosterone without even ascertaining whether a patient's testosterone levels are actually low or whether he has a medical condition that justifies it."

Now those who frequently prescribe testosterone are hitting back, saying they feel insulted by the implication that they are influenced by advertising that urges patients to investigate their "low T."

In [a press release](http://www.androgenstudygroup.org/initiatives/letter-to-fda-asking-to-deny-black-box-petition), the Androgen Study Group urges the US Food and Drug Administration (FDA) — which [announced in January](http://www.fda.gov/Drugs/DrugSafety/ucm383904.htm) that it was launching an investigation into the safety of testosterone therapy — not to add any boxed warnings to testosterone products regarding cardiovascular risk. The group [takes issue with some of the studies](http://www.androgenstudygroup.org/pdf/AndrogenStudyGroup-comment-on-Public-Citizen-FDA-black-box-petition.pdf) that first prompted this warning and highlights what it says are limitations in their analyses.

They also outline their stance in an [editorial published last month](http://online.liebertpub.com/doi/full/10.1089/jomh.2014.3504) in the *Journal of Men's Health*; of the 3 authors, 2 are members of the Androgen Study Group.

"We're being painted as practitioners who are ignoring serious cardiovascular risk, and I don't think that's either true or…ethical to say that," the first author of the editorial and a member of the Androgen Study Group, Martin Miner, MD, of the Warren Albert School of Medicine at Brown University in Providence, Rhode Island, told *Medscape Medical News.*

**The Story So Far**

Around the time the US FDA issued its warning, the US Endocrine Society also [released a statement](http://www.endocrine.org/~/media/endosociety/Files/Advocacy%20and%20Outreach/Position%20Statements/Other%20Statements/The%20Risk%20of%20Cardiovascular%20Events%20in%20Men%20Receiving%20Testosterone%20Therapy.pdf) calling for randomized controlled trials to explore the correlation between testosterone therapy and cardiovascular risk. It said [it may be prudent](http://www.endocrine.org/news-room/current-press-releases/endocrine-society-calls-for-large-scale-studies-to-evaluate-testosterone-therapy-risks) "not to administer testosterone therapy to men who have had a cardiovascular event (such as myocardial infarction, stroke, or acute coronary syndrome) in the preceding six months."

But it did stress, as did the FDA and the *New York Times*, that men meeting clinical guidelines need not stop taking their testosterone.

The European Medicines Agency has also waded in, [adding its own investigation](http://www.medscape.com/viewarticle/823507) into testosterone products, last month.

The concerns all stem from a number of studies published over the past few months that have suggested a possible increased cardiovascular risk of testosterone therapy in older men with a history of CVD.

One, [published in *PLoS ONE*](http://www.medscape.com/viewarticle/819968)in January, showed only a minor increase in the incidence of cardiovascular disease, says Dr. Miner. But the study lasted such a short time that it wasn't clear whether the increased incidence stemmed from the testosterone therapy or the condition it was meant to treat, he noted.

[Another](http://www.medscape.com/viewarticle/813833), published in November 2013 in the *Journal of the American Medical Association,* did not show an increased rate of cardiovascular events in men getting testosterone therapy compared with those not getting it, if absolute percentages are calculated.

Men getting the therapy appeared to have an increased risk only when the authors used a more complex statistical formula, the Kaplan-Meier estimated cumulative percentages, Dr. Miner maintains. For this reason and others, Dr. Miner says the study is so flawed that [he and other experts](http://www.prnewswire.com/news-releases/world-experts-and-androgen-study-group-petition-jama-to-retract-misleading-article-on-testosterone-therapy-252219051.html) have called on *JAMA* to retract it.

At the same time, he added, other trials have found no increased cardiovascular risk with testosterone therapy, and many, such as a [2012 study](http://press.endocrine.org/doi/abs/10.1210/jc.2011-2591?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed) in the *Journal of Clinical Endocrinology & Metabolism*, have even suggested cardiovascular benefits to the therapy.

**Balance Needed**

What is required is some balance, said Dr. Miner. "What the *New York Times* did was present these [negative] studies as conclusive, when it's impossible to say that, because if you have knowledge of the literature you see that there are so many [other] studies that have not been given public exposure."

He doesn't deny that testosterone therapy might pose a risk for men who have had recent cardiovascular events, particularly those over 65 years old; he just doesn't think the question is settled.

"Does it mean you exclude those men?" he said. "No. It means you are supposed to have a discussion with them about risk."

Bradley Anawalt, MD, chair of the Hormone Health Network for the Endocrine Society, agrees with Dr. Miner and his coauthors that there are flaws in the recent studies on which the society based its policy statement.

But "they do have to concede that while the evidence of harm is weak and flawed, the evidence for safety is at least as weak," he told *Medscape Medical News*.

Dr. Anawalt includes the *Journal of Clinical Endocrinology & Metabolism* study cited by Dr. Miner, noting that he was himself a coauthor on this paper. Given the uncertainty, the Endocrine Society simply wants to proceed cautiously, he said.

"Testosterone is currently enjoying a reputation for being the elixir of youth, and there is a whole group of men who have low testosterone because of aging, and we just don't know if they can benefit from testosterone," he said. "The Endocrine Society's statement was to sound a note of caution."

He pointed to the history of other hormone therapies, such as estrogen-replacement therapy, whose serious risks came clearly into view only after decades during which millions of women used it.

But Dr. Miner and colleagues insist that doctors in their position are being responsible. In the editorial, they say: "In our clinical experience, supported by interactions with hundreds of colleagues at lectures and medical conferences, men are diagnosed with T deficiency and undergo treatment almost exclusively because they have symptoms that are troubling to them, not because they cannot accept getting older.

"The aim of treatment is to alleviate those symptoms, based on training, clinical experience, and scientific information. We are unaware of any evidence that physicians offer T therapy because of pressure from pharmaceutical companies or that physicians experience more pressure with regard to testosterone than any other medication," their editorial asserts.

While the 2 sides currently remain in conflict over the case of men who have had recent cardiovascular events, they do agree that the Endocrine Society's 2010 [clinical guidelines](http://www.endocrine.org/~/media/endosociety/Files/Publications/Clinical%20Practice%20Guidelines/FINAL-Androgens-in-Men-Standalone.pdf) for testosterone therapy — an earlier and more comprehensive document than the recent policy statement — are still useful in most circumstances.

*Dr. Miner reported that he is a consultant for Repros Therapeutics and AbbVie, both of which are developing or market products for hypogonadism. Disclosures for the editorialists are listed in the editorial. The Androgen Study Group reports no relevant conflicts; it does not currently receive funding from any source. Dr. Anawalt has reported no relevant financial relationships.*

*J Men's Health*. 2014;11:1-3

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