Talking Points for Testosterone and the Heart

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If you've turned on a TV recently, you've undoubtedly seen the commercials: Everyone from drug companies to online supplement vendors have jumped on the "low T" bandwagon. Testosterone (T) is marketed as the solution to just about every common male aging problems from low libido to weight gain. However, the news hasn't been entirely positive: Testosterone was recently the target of media criticism when two studies reported higher risk for cardiovascular incidents in men using testosterone replacement therapy (TRT). Although the medical community has since largely rejected those studies for poor design and questionable analysis, the shadow remains. With such a wide array of supposed benefits and the lingering question of risk, it's no wonder that patients want to learn more about TRT.

"It's a conversation they bring up all the time," says Steven Petak, M.D., J.D., chief of endocrinology at Houston Methodist Hospital. On a subject laden with preconceived notions and conflicting information, it's the physician's task to tease out whether low testosterone is actually causing the patient's problems, and then whether treatment is appropriate. Here are a few talking points to consider:

NOT EVERYONE USING TESTOSTERONE ACTUALLY NEEDS IT

First things first: What does the patient really have? Despite the dramatic increase in testosterone prescriptions over the last decade (a 12-fold increase worldwide from 2000-2011[1]), there's still just one indication for TRT: hypogonadism, or low testosterone. Although the definition of hypogonadism varies from study to study, Petak, who chaired the 2002 American Association of Clinical Endocrinologists Hypogonadism Task Force, looks for two main criteria to make the diagnosis: (1) at least three morning total serum testosterone measurements below 200 ng/mL and (2) symptoms (e.g., decreased sexual desire and function, decreased energy, depression, and irritability). By those standards, only 2.1-12.8% of middle-aged to older men actually have clinical hypogonadism,[2] which doesn't explain the skyrocketing prescription rates.

Petak explains, "The low T clinics are meant to take care of those older Americans who are concerned about fatigue and loss of muscle mass and loss of sexual function and believe that there's a panacea that can fix them. Testosterone has taken center stage and is taken advantage of, unfortunately, by a lot of clinics who propose to fix patients with testosterone treatment. In fact, most of those men won't benefit from it, and when they do, it's probably a placebo effect. The problem is that most of those men don't really have an indication to treat with testosterone."

RESEARCH SAYS TESTOSTERONE IS SAFE FOR THE HEART

The overwhelming majority of studies conclude that TRT does not significantly raise the risk for cardiovascular problems. In fact, as Petak and colleagues point out in a recent review article in the *Methodist DeBakey Cardiovascular Journal*, men with low testosterone have higher rates of cardiovascular events and mortality than men with normal testosterone levels, and several studies suggest that TRT may have a cardioprotective effect.

Nevertheless, testosterone has received a lot of bad press in the lay media, and many patients are wary of the cardiovascular risks. Most of the controversy stems from two observational studies (Vigen et al., 2013, and Finkel et al., 2014) that reported higher rates of cardiovascular events (death, myocardial infarction [MI], stroke) in T-treated patients. In the months after the papers were published, headlines shouted about the dangers of TRT and the FDA added a warning label to testosterone products.

However, the scientific community was quick to refute those studies' claims, pointing out that the studies were each seriously flawed. For instance, Vigen et al. initially reported a 29% higher rate of cardiovascular events in T-treated men than in untreated men, but had to issue a correction when it was revealed that the absolute rate of events for treated men was actually half that of the untreated group. Finkel et al. compared

rates of MI before and after TRT, but did not include an untreated control group, thus making it impossible to analyze whether TRT was a factor in the higher post-treatment MI rates. Moreover, as a review in the Mayo Clinic Proceedings noted, even the higher post-treatment rates were much lower than normally expected for men in the study's age group.[3]

Even though these studies have been widely rejected by the medical community, the shadow still remains. Men who are concerned about heart health and testosterone therapy are likely to find some foreboding, if outdated, information. Just try googling "Is testosterone safe for my heart?" vs "cardiovascular risks of testosterone replacement." The patient-friendly search terms call up articles warning about the increased risk of heart problems and citing the aforementioned studies; the physician-oriented search returns articles emphasizing testosterone's safety and refuting those studies.

TREATING HYPOGONADISM MIGHT EVEN BE USED TO TREAT CARDIOVASCULAR DISEASE... BUT PERHAPS NOT WITH TODAY'S TRT

In study after study, researchers have found that hypogonadal men have higher rates of cardiovascular events than those with normal testosterone levels. Furthermore, some research suggests that hypogonadal men who receive TRT have a lower risk of cardiovascular events than untreated men. This has led to speculation that TRT might be a useful treatment to lower cardiovascular risks, although more studies are needed to show causation. Petak sees potential for this novel use of testosterone, but says that selective androgen receptor modulators (SARMs) are an even more promising solution.

"SARMs act like testosterone in some tissues and anti-estrogen in others. This is similar to raloxifene, which is a selective estrogen receptor modulator in women. These drugs, which are in the pipeline in some pharmaceutical companies, are attractive because they tend to limit potential side effects, especially in prostate and prostate cancer issues. This avenue of research may be really fruitful," Petak says, adding that SARMs could stimulate muscle mass, reduce cardiovascular risk, and limit side effects. "By tailor-making your androgen, I think that you might be able to find some cardiovascular applications."

HYPOGONADISM AND THE LONG-TERM EFFECTS OF TRT ARE UNDER-RESEARCHED

What makes hypogonadism and TRT so tricky is incomplete data. Although there's a wealth of short-term data and retrospective or observational studies, there still haven't been highly powered, long-term studies focusing on testosterone.

This makes diagnosing hypogonadism more difficult than the 200 ng/mL standard would suggest. As men age, their testosterone levels naturally fall—but that doesn't mean older men automatically develop hypogonadism. Petak says, "There are no standards for what testosterone levels should be in people in their 60s or 70s and 80s, and I don't think it's proper to compare them to someone who is in their 20s or 30s." Although 200-300 ng/mL total T might be a good cutoff for a 70-year-old, 500-600 ng/mL might be more appropriate for a 50-year-old, depending on symptoms. Add in the variability of current laboratory testing methods, and it can be difficult to pin down exactly who qualifies for treatment.

The lack of long-term prospective studies also makes it difficult to definitively assess how TRT affects men in the long run. Petak envisions a study following upwards of 6000 men over 10 to 15 years in order to monitor long-term changes to the prostate, cancer risk, and cardiovascular outcomes—all of which could appear years after treatment begins. However, funding such a task would be difficult. "If you're going to do the study correctly, it's going to be extremely expensive and difficult to do. That's why everyone does these retrospective and cross-sectional studies and why the data is conflicting," Petak explains.

WHEN IN DOUBT, TRY LIFESTYLE CHANGES FIRST

"Most low testosterone levels are a result of the chronic disease state," says Petak. The reproductive system is acutely sensitive to environmental and physiological stress, so obesity, diabetes, congestive heart failure, metabolic syndrome, and HIV can all result in lower testosterone levels. Even marijuana causes testosterone to drop rapidly. On the bright side, this means that treating the underlying chronic conditions—many of which can be addressed through lifestyle changes—may normalize testosterone levels without TRT.

The familiar lifestyle recommendations—cutting back on alcohol, quitting drugs and cigarettes, eating healthier and exercising regularly, and losing weight if needed—can all improve testosterone levels. Moreover, there are benefits beyond raising T. All of these changes lower one's overall risk for cancer and heart disease.

Another reason to consider this strategy? Fertility. Petak explains, "A lot of men don't realize that if they go on testosterone, they decrease their fertility. It suppresses sperm production." Lifestyle changes—or, alternately, off-label use of anti-estrogens such as clomiphene citrate—are preferable for hypogonadal young men who want to start a family.The upside to the hype surrounding low T is that it creates an opportunity for physicians and patients to start conversations about testosterone and male health. With so much flawed and outdated information bombarding men, it's up to their physicians to cut through the ads and rhetoric and decide and determine whether TRT is appropriate for each patient.

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