Controversy of testosterone replacement therapy in hypogonadal men with cardiovascular disease

The increasing incidence of metabolic syndrome (MetS) has placed great emphasis on exploring potential risk factors and treatment options. Interest in treating MetS is largely driven by its association with cardiovascular disease (CVD). According to the Centers for Disease Control and Prevention, approximately 600,000 people die of CVD in the United States every year, which amounts to 1 in every 4 deaths.¹
Testosterone has been assumed to have an important impact on the risk of CVD, which has led to increased interest in understanding the relationship between testosterone and CVD. Understanding the impact of testosterone on the cardiovascular system is of importance in the interest of potential reduction in CVD.

The clinical question of whether testosterone replacement therapy (TRT) can be safely used in hypogonadal men with CVD is controversial. The controversy of TRT in the setting of CVD revolves around whether TRT changes the risk of cardiovascular events (CVEs). In the literature, short-term use of TRT is associated with decreased low-density lipids, insulin resistance, and central adipose deposition. This appears positive, because each of these factors is a characteristic of MetS, which is strongly associated with CVD. What are missing from the literature are data from randomized, placebo-controlled trials with adequate patient populations and appropriate follow-up to assess the long-term risks and benefits of TRT. This type of study is unlikely to be performed; therefore, the controversy will have to be overcome with observational studies from existing cohorts. The intent of this article is to summarize the current data on the relationship between TRT and CVD.

**Discussion and analysis**

Hypogonadism is associated with surrogate markers for CVD, such as dyslipidemia, atherosclerosis, arrhythmia, thrombosis, and endothelial dysfunction. In addition, endogenous testosterone concentrations are inversely related to CVD mortality. Cross-sectional epidemiologic meta-analysis has shown an association between a low serum testosterone level and CVD. The association does not weaken when adjusting for age, body mass index, diabetes, and hypertension.

Several recent review articles have also highlighted the significance of decreased serum testosterone level and CVD. The question is whether testosterone replacement therapy (TRT) can be safely used in hypogonadal men with CVD. The controversy of TRT in the setting of CVD revolves around whether TRT changes the risk of cardiovascular events (CVEs). In the literature, short-term use of TRT is associated with decreased low-density lipids, insulin resistance, and central adipose deposition. This appears positive, because each of these factors is a characteristic of MetS, which is strongly associated with CVD.

**Despite its positive effect on certain factors associated with metabolic syndrome, the question remains as to whether TRT actually reduces the risk of cardiovascular events.**

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**Figure 1. No significant difference between hypogonadal men on TRT versus placebo for all cardiovascular events.**

Results of the random-effects meta-analyses of testosterone on patient-important outcomes.

can correct this observed association between hypogonadism and CVD. Three previous meta-analyses of TRT found no significant difference between hypogonadal men receiving TRT versus placebo for all CVEs (Figure 1). The only risk factor for a CVE associated with TRT was a significant increase in hemoglobin and hematocrit, which could theoretically augment a thrombotic event.

The development of polycythemia can occur during TRT, and so routine blood work should be performed. It is important to note that none of these meta-analyses were designed or adequately powered to detect the effects of TRT on CVEs. The true benefits of TRT in hypogonadal men who have cardiac disease are not fully understood.

Until recently, the literature suggested that TRT has a beneficial effect on CVD. However, a retrospective analysis from the Veterans Affairs system reached a different conclusion. This study examined a contemporary (2005-2011) cohort of men who had undergone coronary angiography, had subsequent total testosterone assessment, and were found to have a testosterone level <300 ng/dL. The cohort consisted of 8709 men, 1223 of whom were placed on TRT.

The TRT group was found to have an increased risk of death, myocardial infarctions, and stroke, when compared with the untreated hypogonadal group. The absolute 3-year event rate was 25.7% in the TRT group versus 19.9% in the untreated group. TRT was concluded to be associated with increased risk of adverse outcomes (hazard ratio, 1.29; 95% confidence interval, 1.04-1.58). These findings raise questions about the potential risks of TRT in hypogonadal men with CVD (Figure 2).

It is important to note that there was no standardization of the testosterone replacement modality or monitoring. The study was not powered sufficiently to compare the various testosterone treatment modalities. The biggest question from this analysis is whether these findings can be generalized to all hypogonadal men.

Subsequent to the publication of this study, the American Urologic Association (AUA) issued a position statement that noted the importance of considering the potential risks and benefits of TRT in hypogonadal men with CVD. The statement recommended that TRT be reserved for men who have been evaluated and are found to have significant hypogonadism, and that the benefits of TRT should be weighed against the potential risks of adverse outcomes.
In this statement, it addressed the contradictory evidence about the influence of TRT on cardiovascular risk. The AUA concluded that the current evidence does not provide definitive answers regarding the impact of TRT on CVD. The AUA emphasized the need for increased educational awareness of the benefits and risks of TRT among both patients and health care providers.

The body of evidence supports the need for long-term, placebo-controlled, randomized trials of TRT in hypogonadal men with regard to CVD. Additional information about the risks and benefits of TRT should come from the ongoing Testosterone Trial in Older Men, which is a randomized, placebo-controlled trial of 800 men aged 65 years and older who will receive TRT. The knowledge gap as to the exact relationship between testosterone and CVD supports a cautious approach to TRT. Most experts would agree that elderly men should target a testosterone level in the lower half of the current normal range of serum testosterone levels until the risk-to-benefit ratio becomes clearer.

Final notes
Thus far, treatments with testosterone to restore the hypogonadal man back to a eugonadal level have not proven beneficial with respect to CVD. However, neither have treatments definitively shown specific adverse cardiovascular effects. The cardiovascular risk-to-benefit ratio of TRT remains largely evasive. Hypogonadal men should be informed of the potential benefits of TRT as well as the limited knowledge concerning its cardiovascular safety. Further research will be necessary to define the relationship between TRT and CVD in order to end the controversy.

References