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Opinion

# Cardiovascular Safety and Efficacy of Testosterone Therapy in Elderly Men With Hypogonadism

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## Opinion

Serum testosterone level steadily decreases with ageing [1]. Low testosterone levels in older adults have been associated with increased adverse cardiovascular (CV) events [2-5]. Testosterone therapy in older men with hypogonadism has consistently shown to improve sexual function, mood, depressive symptoms, muscle and bone strength, and insulin sensitivity and hence, decrease the incidence of type 2 diabetes mellitus (T2DM) and metabolic syndrome as well as favorably improve lipid profile [6-9]. These evidences suggest that exogenous testosterone replacement in men with low testosterone should have beneficial effects on adverse CV outcomes. However, literature is conflicted on CV safety and efficacy of testosterone therapy in older men with hypogonadism. Over last decade, few studies have suggested increased incidence of adverse CV events in men, particularly older adults, with testosterone replacement. Basaria S et al. [7] were the first to question the CV safety of testosterone replacement [10]. They showed, in a randomized controlled trail (RCT), that men (aged 65 years or older) with limited mobility and low testosterone levels had higher rates of adverse CV events with testosterone treatment as compared with those who received placebo. It's important to note this study was not designed to evaluate the CV safety of testosterone therapy. In fact, primary efficacy outcome was the change from baseline in maximal voluntary muscle strength in a leg-press exercise. Elderly men treated with testosterone showed significantly greater increase in leg-press strength, chest-press strength, and stair climbing power while carrying a load. It has been argued that increased physical activity in frail elderly may have contributed to increased incidence of adverse CV events. Nevertheless, this study motivated researchers to study the CV safety and efficacy of testosterone therapy.

Two studies published in 2013 and 2014 gained significant media attention as they showed increased adverse CV events in men receiving testosterone prescriptions [11,12]. Finkle WD et al. [12] compared the cohort of men who filled their first testosterone prescription (N= 55, 593) with men who filled phosphodiesterase 5 inhibitor prescription [12]. Analysis was done with post prescription follow-up at 90 days and 91-180 days. Men aged 65 years or older demonstrated approximately two-fold increase in the risk of myocardial infarction (MI) within 90 days after filling their initial testosterone prescription and this risk declined to baseline in 91-180 days after initial testosterone prescription. Vigen R et al. [11] also showed the increased risk of adverse CV events (death, MI and strokes) with use of testosterone therapy in men with low testosterone who underwent coronary angiography in the Veterans Affairs (VA) system between 2005 and 2011 [11]. Based on extensive review of limited studies available, US food and drug administration (FDA) released a Drug Safety Communication in 2015 asking providers to exercise caution while prescribing testosterone products for low testosterone due to ageing and requiring manufacturers to change label to inform of possible increased risk of heart attack and stroke with use. Notably both the above studies had significant study limitations and have been criticized by experts [13-15]. Few other studies published later also showed increased adverse CV events with testosterone therapy but none of them were RCT and hence, only suggested association and not a causal relationship [16,17]. An RCT showed significant

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increase in noncalcified plaque and median total plaque volume in hypogonadal older men (mean age 71.2 years) when treated with testosterone gel compared to placebo [18]. Interestingly, a similar study by Basaria et al. [7] showed no significant difference in aortic artery intima media thickness and coronary artery calcium score in older men with hypogonadism who received testosterone as compared to those who received placebo.

Contrastingly, much larger number of studies have shown neutral or beneficial effects of testosterone therapy on adverse CV events in men with hypogonadism. An analysis of the registry of hypogonadism in men (RHYME) demonstrated CV safety of testosterone replacement in patients with clinical diagnosis of hypogonadism [19]. A total of 999 patients were included in study, of which 750 (75%) were treated with some form of testosterone. There was no statistical difference in incidence of cardiovascular events (MI, Stroke and heart failure) between testosterone treatment and non-treatment group. A large retrospective cohort study conducted within an integrated health care delivery system compared CV events in 8808 hypogonadal men (mean age 58.4 years) who ever had testosterone dispensed (ever- treated) with over 35,000 hypogonadal men (mean age 59.8 years) who never had testosterone dispensed. There was a 33% risk reduction of composite CV end point (acute MI, coronary revascularization, unstable angina, stroke, transient ischemic attack and sudden cardiac death) in ever-treated group in comparison to patients who never received testosterone therapy (hazard ratio 0.67; 95% confidence interval 0.62-0.73; $P < 0.001$) [20]. In summary, evidence for CV safety of testosterone therapy in older hypogonadal men is conflicting. Evidence against testosterone therapy is weak and based on studies with controversial study design, which did show the association of testosterone therapy with adverse CV events but failed to show causal relationship. On the other hand, several studies have shown testosterone therapy to be CV safe in older hypogonadal men. Testosterone therapy cannot be deemed harmful or beneficial conclusively based on current evidence, mainly due to lack of a large RCT looking at the CV safety and efficacy of testosterone therapy in men with low testosterone. There is no doubt that testosterone therapy improves the physical, sexual and mental well-being of hypogonadal older men. Based on the current evidence, we recommend that hypogonadism should be carefully diagnosed with at least 2 separate fasting early morning blood samples. Testosterone therapy can be considered in elderly patients with symptoms secondary to testosterone deficiency, but these patients should be informed about conflicting and unclear data on CV safety of testosterone therapy. Risk factors for CV disease, such as hypertension and hyperlipidemia, should be well controlled prior to initiating testosterone replacement and close surveillance should be considered within first 90 days of initiation of therapy specifically in patients with known history of CV disease. Elderly patients with hypogonadism on testosterone therapy should be regularly screened for development of risk factors of CV disease and testosterone levels should be monitored closely to avoid supraphysiological testosterone levels. There is an urgent need for large RCTs to study the CV safety and efficacy of testosterone therapy in elderly hypogonadal men and identify subset of patients who will benefit from testosterone therapy.

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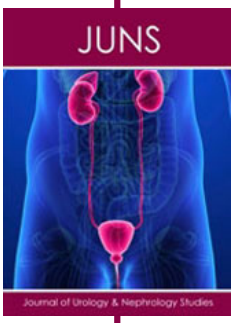


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