Cardiovascular Health, Erectile Dysfunction, and Testosterone Replacement: Controversies and Correlations

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Erectile dysfunction and cardiovascular disease share a similar underlying pathophysiology, and low serum testosterone, known as hypogonadism, is a significant player in both conditions. Hypogonadism is a known risk factor for cardiovascular events and worsened mortality, thus influencing physicians to recommend testosterone replacement in hypogonadal men. However, at least 4 recent reports suggest that testosterone replacement may worsen cardiovascular risk, heightening hesitancy in the medical community to treat patients with hypogonadism with testosterone. This review highlights the triad of cardiovascular disease, erectile dysfunction, and testosterone therapy and provides the physician with some guiding principles for navigating these recent concerns. UROLOGY 110: 1–8, 2017.

Erectile dysfunction (ED) and cardiovascular disease (CVD) often occur concomitantly in men, with the prevalence of both conditions increasing with age. Understanding the relationship between ED and CVD has significant implications for survival and quality of life, and approaching one disease with the other in mind may enhance the care delivered to patients. Low testosterone is known to be associated with ED and CVD, the latter when it is primarily connected to the presence of the metabolic syndrome (MetS). Whether low testosterone can cause CVD without the presence of the MetS remains to be determined. Testosterone replacement therapy is known to be an avenue for treating hypogonadal men with ED, although several recent studies have suggested that testosterone replacement worsens cardiovascular risk.

In this article, we delve into the association between ED and CVD and the role testosterone plays in both conditions. We also present the data on the benefits of testosterone for both ED and CVD, which patients are candidates for testosterone supplementation, and how to monitor for adverse events. We address concerns regarding testosterone supplementation and cardiovascular risk, particularly highlighting the recent highly publicized studies responsible for much of today's concerns about testosterone supplementation.

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ASSOCIATION OF ERECTILE DYSFUNCTION AND CARDIOVASCULAR DISEASE

ED is predominantly a disease of vascular origin, and it shares several risk factors with CVD, specifically coronary artery disease (CAD), including aging, hypertension, diabetes, obesity, smoking, and MetS.[1-3] Additional cardiovascular risk factors such as dietary intake of cholesterol, hyperlipidemia, and hypertriglyceridemia have been shown to be predictors of ED.[2,4]

ED itself is not only a strong predictor of CAD, but is also considered to be a predictor of future major adverse cardiovascular events and all-cause death in men with known preexisting CVD.[5] A high prevalence of ED has also been reported in men with coronary, cerebral, and peripheral vascular disease.[6,7] One landmark study by Inman et al biennially screened 1400 men with no known CAD for the presence of ED over a 10-year period.[8] The study found that ED in men younger than age 60 was associated with a marked increase in the risk of future cardiac events compared with men with no ED, although ED was less predictive of developing CAD in older men. Another important study by Montorsi et al reported that in men who underwent coronary angiography, approximately 50% of those patients who presented clinically with acute chest pain and were found on angiography to have CAD had ED, with the ED preceding the onset of coronary symptoms by >3 years in about 70% of cases.[9] In patients with diabetes, in whom the typical signs of heart disease are commonly hidden, ED has been shown to be independently associated with asymptomatic CAD.[10] It has also been shown that in men without known CVD, those with ED had more coronary artery calcium, carotid intima-media thickness, and carotid plaque,

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and less carotid and aortic distensibility compared with those without ED.[11] Additionally, carotid intima-media thickness and carotid plaque prevalence have been shown to increase proportionally with ED severity.[12] These previous studies imply that ED may serve as a surrogate marker for future symptomatic CAD and peripheral vascular disease.

A potential explanation for this association between ED and CAD revolves around the concept of endothelial dysfunction leading to subsequent atherosclerosis and/or smooth muscle dysfunction, which may represent the common underlying pathologic changes in these two conditions. An erection occurs when neuronally mediated nitric oxide (NO) is released within the cavernosa and induces corporal smooth muscle relaxation, resulting in both cavernosal arterial vasodilation and subsequent engorgement of the sinusoids of the corpora cavernosa.[13] The endothelial dysfunction theory postulates that there is an imbalance between vasodilating and vasoconstricting messengers produced by the vascular endothelium. One explanation is that NO is inactivated by superoxide anion under oxidative stress, creating a deficit in NO and the subsequent development of endothelial dysfunction, which results in abnormal vasorelaxation of the vascular smooth muscle.[14] Another plausible explanation is that there is a progressive dysfunction or degeneration of the vascular smooth muscle itself, likely associated with aging, although certain comorbidities may also play a role in this scenario. This vascular smooth muscle dysfunction can lead to ED in the form of either corporal veno-occlusive dysfunction within the penis and/or arteriosclerosis within the arterial media of the peripheral vascular system, the latter theoretically leading to systemic hypertension and its subsequent increased cardiovascular risk.[15] In fact, hypertension is the most common medical condition in men with ED, and it has been suggested that hypertension itself can lead to endothelial dysfunction and vascular smooth muscle dysfunction, affecting both cardiovascular health and ED.[16]

CARDIOVASCULAR DISEASE SCREENING FOR PATIENTS WITH ERECTILE DYSFUNCTION

The aforementioned data suggest that ED may be a valuable trigger for physicians to screen men for CVD. However, which patients with ED should be screened for CVD? The Princeton III Consensus Conference recommends considering a man with organic ED to have increased CVD risk until further evaluation suggests otherwise (Table 1).[5]

This evaluation begins with assessing patient history, presence of comorbid conditions (eg, obesity, hypertension, diabetes, and symptoms of obstructive sleep apnea), family history of CVD, and lifestyle factors (eg, diet, smoking, excessive alcohol use, and limited physical activity). Physical examination includes measuring blood pressure, waist circumference, body mass index, fundal arterial changes, cardiac auscultation, carotid bruits, and palpation of femoral and pedal pulses. Assessing ED severity using the validated International Index of Erectile Function (IIEF) score or Sexual Health Inventory of Men questionnaires and ED duration is fundamental to this workup. The conference also recommended that patients with ED obtain a resting electrocardiogram and a fasting plasma glucose level, serum creatinine level, albumin to creatinine ratio, total testosterone (before 10 AM), and plasma lipid levels. Abnormal

Table 1. The Princeton III Consensus recommendations to evaluate men with erectile dysfunction and no known cardiovascular disease who may require additional cardiologic work-up[5]

Patient History	• Age • Comorbid conditions (obesity, hypertension, dyslipidemia, prediabetes, OSA) • Family history of premature atherothrombotic CVD • Lifestyle factors (smoking, excessive alcohol use, limited physical activity, and poor diet)
Physical Examination	• Blood pressure • Waist circumference • Body mass index • Fundal arterial changes • Cardiac auscultation • Carotid bruits • Palpation of femoral and pedal pulses
Erectile Dysfunction Assessment	• IIEF score or SHIM for severity and duration of ED
Cardiac Studies	• Resting electrocardiogram
Laboratory tests	• Fasting plasma glucose level • Serum creatinine level • Albumin to creatinine ratio • Total testosterone level (10 AM) • Plasma lipid levels (total, LDL, HDL cholesterol, and triglyceride values)

CVD, cardiovascular disease; ED, erectile dysfunction; HDL, high-density lipoprotein; IIEF, International Index of Erectile Function; LDL, low-density lipoprotein; OSA, obstructive sleep apnea; SHIM, Sexual Health Inventory of Men.