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Research Article

# Hormonal Therapy for Localized and Androgen Deprivation Therapy and Cardiovascular Disease Risk

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**Abstract**

Despite the development of a variety of novel agents for the treatment of advanced and metastatic prostate cancer, the only therapeutic option for this stage of the disease is androgen-deprivation therapy.

Cardiovascular Disease (CVD) is one of the most common causes of death worldwide and the most usual in the western populations. Although it affects both sexes, it is more frequent in males in whom it shortens the average life expectancy. Traditionally, this difference has been attributed to the testosterone effect. However, the incidence of conventional risk factors for cardiovascular disease increases as men ages while testosterone levels decreases.

Several studies associated lower circulating testosterone levels with conditions that predispose to CVD such as excess abdominal fat, increased carotid intima-media thickness, loss of insulin sensitivity, diseases such as diabetes and metabolic syndrome, atherosclerosis and aortic and lower limb arterial disease as well. Moreover current evidence demonstrated that this hormone has protective effects on the cardiovascular system, however still there are no solid proofs of an association between low testosterone levels and CVD related death risk in Prostate Cancer (PC) patients receiving androgen-deprivation therapy (either surgical orchiectomy or medical).

In the present article we discuss the association between androgen deprivation therapy and cardiovascular disease risk emphasizing the increased risk for thromboembolic events in prostate cancer patients.

**Keywords:** Orchiectomy; Testosterone; Stroke

## Abbreviations

CVD: Cardiovascular Disease; PC: Prostate Cancer; ADT: Androgen-Deprivation Therapy; LHRH: Luteinizing-Hormone-Releasing Hormone

## Introduction

Cardiovascular Disease (CVD) is one of the most common causes of death worldwide and the most usual in the western populations. Although it affects both sexes, it is more frequent in males in whom it shortens the average life expectancy. Traditionally, this difference has been attributed to the testosterone effect. However, the incidence of conventional risk factors for cardiovascular disease increases as men ages while testosterone levels decreases. During the last decade, several studies associated lower circulating testosterone concentrations with conditions such as excess abdominal fat, increased carotid intima-media thickness, loss of insulin sensitivity [1,2] diseases such as diabetes and metabolic syndrome [3], and atherosclerosis and aortic and lower limb arterial disease as well[4]. Moreover current evidence demonstrated that this hormone has protective effects on the cardiovascular system [5,6]. However still there are no solid proofs of an association between low testosterone levels and CVD related death risk in Prostate Cancer (PC) patients receiving androgen-deprivation therapy (either surgical orchiectomy or medical).

## Material and Methods

We identified studies published from 2000 onwards by searching the MEDLINE database of the National Library of Medicine. Initial search terms were testosterone, prostate cancer, hormonal therapy, androgen-deprivation therapy, cardiovascular disease, ischemia and stroke. Bibliographic information in the selected publications was checked for relevant publications not included in the MEDLINE. All retrieved publications were reviewed in an attempt to scrutinize the current knowledge on the association between Androgen deprivation therapy and cardiovascular disease risk.

## Results

Prostate cancer is a disease of the elderly and its incidence increases with age. It seldom develops before the age of 40 and is chiefly a disease found in men over the age of 65 years [7]. Yet, it's natural for testosterone levels to decline as men age and declining testosterone levels in elderly men are thought to underlie many of the symptoms and diseases of aging; however, studies demonstrating associations of low testosterone with clinical outcomes are few. Laughlin et al demonstrated that testosterone insufficiency in older men is associated with increased risk of death over the following 20 yr, independent of multiple risk factors and several pre-existing health conditions [8]. On the other hand, in a recent prospective observational stud, Yeap et al showed that low testosterone levels




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predict increased incidence of stroke or transient ischemic attack in older men [2]. Similarly, Muller et al., showed that low free testosterone levels were related to intima-media thickening of the common carotid artery in elderly men independently of other cardiovascular risk factors [9]. Jeppesen et al determined the serum levels of total and free testosterone and found that they were significantly inversely associated with stroke severity and 6-month mortality, while total testosterone was significantly inversely associated with infarct size [10].

Although Androgen-Deprivation Therapy (ADT) reduces serum testosterone to castration levels, Punnen et al., in large cohort of men with, failed to demonstrate an increased direct risk of CVD development in those patients who received ADT [11]. In contrast, a large observational study of 73,196 Medicare enrollees with localized prostate cancer treated with GnRH agonists or orchiectomy found a significant association of PC hormonotherapy with cardiovascular events such as (coronary heart disease, myocardial infarction and sudden cardiac death) [12]. Interestingly, in an animal study of castrated rats, transient cerebral ischemia in the brain resulted in lower expression levels of steroidogenesis-related genes and lower serum testosterone level, indicating a possible vicious cycle in the pathogenesis of post-orchiectomy cerebral ischemia [13].

## Discussion

It is generally believed that low testosterone may indicate a poor general health and therefore, associations between testosterone and CVD are coincidental. Moreover, a number of additional independent risk factors involved in the development of atherosclerosis, thrombosis and subsequent heart attack and stroke exists, rendering thus the above association difficult. On the other hand, differences among the above mentioned studies regarding the association of ADT with death from increased CVD risk are possibly linked to the different nature of these studies.

However; they may also reflect the complex role of low testosterone levels in the initiation of the ischemic cascade.

Actually, the exact pathophysiological mechanism leading to these events remain unknown. Current knowledge shows that a critically role of testosterone is to enable high-density lipoproteins in order to remove excess cholesterol from the arterial wall and transport it to the liver for disposal. This effect is termed "reverse cholesterol transport" and prevents the occlusion of arteries [8]. In addition, the low testosterone levels promote platelet aggregation and coagulation [1]. Also, in across-sectional case-control study, Ajayi and Halushka reported that exogenously administered testosterone upregulated platelet thromboxane A2 receptors and increased aggregation response to thromboxane mimetics in healthy male volunteers [14]. In addition, the abrupt refraining of circulating testosterone leads to an imbalance between androgens and estrogens levels in favor of the latest. Increased estrogens levels in men may enhance inflammation which can cause rupture of unstable plaques, leading to coronary artery occlusion [15]. All these may be accelerated by the activity of the increased levels of aromatase which converts testosterone to estrogen [8]. Increased levels of aromatase have been detected in aging men. The effect of surplus aromatase is that most testosterone is converted to estrogen [16]. In confirmation to the above, Callou de Sá et al., found that men with CVD have higher oestradiol and FEI levels [17].

Although, it is not well documented how estrogens contribute to CVD development in the elderly, it is well known that estrogen administration in PC patients cause deep venous thrombosis in about one-third of them while 7% of them experience myocardial infarction. The incidence of these complications is dose depended and increases in patients with concomitant CVD [18]. Given that estrogens promote platelet aggregation, elevated estrogen can sharply increase heart attack risk by coagulation in coronary arteries. Higher estrogens levels also increase inflammation which can cause unstable plaque to rupture and occlude a coronary artery, thus creating a sudden heart attack [19].

On the other hand many aging men -among them patients with CVD- suffer both low testosterone and estrogen. In addition in a community-based sample, a higher serum estradiol level was associated with lower risk for CVD events in older men. Accordig to the researchers of this study, the above finding support the hypothesis that endogenous estrogen has vasculoprotective influences in men [20]. The most possible explanation of this controversy is that estrogens act on cardiovascular system even at low quantities and an imbalance between endogenous testosterone and estrogen may contribute to CVD deterioration [21]. Of note, recent studies showed that the lower testosterone the higher estrogen levels and the subsequent risk of CVD mortality [26]. Taking in account the above considerations it could be easily assume that the rate of testosterone decline is of outmost importance: Elder PC patients suffering of CVD who receive androgen-deprivation medical therapy may develop gradual increment of CVD risk with the gradual decline in total testosterone levels. In contrast those undergoing bilateral orchiectomy are in immediate risk due to rapid drop of testosterone levels. The risk is particularly important in patients with existing cardiovascular risk factors or a history of heart disease [22].

Given the minimal clinically important bleeding risks of the procedure, it is reasonable that patients undergoing bilateral orchiectomy should be adequately treated with anticoagulant agents for post-operative stroke prevention. However due to the limited data, further studies are warranted to determine the period of intense monitoring, the appropriate agent, and the duration of treatment.

Currently no specific guideline exists regarding PC patients in high risk for CVD related complications undergoing bilateral orchiectomy. For those who are under anticoagulant treatment, discontinuation of acenocoumarol and aspirin may result in acute stroke despite bridging therapy with heparin [23]. Considering that the latest guidelines state that the risk of thromboembolic complications with warfarin discontinuation is probably higher if anticoagulation is stopped for ≥7 days, as well as that acenocoumarol has a shorter half-life that warfarin [23], it could be assumed that patients undergoing bilateral orchiectomy are at increased stroke risk due to secondary decrease of testosterone to castration levels.

## Conclusion

Despite the development of a variety of novel agents for the treatment of advanced and metastatic prostate cancer, the best therapeutic option for this stage of the disease is androgen-

deprivation therapy. Current evidence suggest that this therapy either medical (by antiandrogens, LHRH agonists and LHRH antagonists) and surgical (bilateral orchiectomy) may increase the risk for acute stroke strengthening the existing evidence regarding the central role of low testosterone levels in CVD related death risk.

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