Cardiovascular Disease Associated With Androgen-Deprivation Therapy: Time to Give It Due Respect

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It all began in 1941 when Huggins and Hodges first described the androgen dependence of prostate cancer (PCa) by demonstrating regression of metastases by androgen deprivation. PCa is now the most common cancer in men in the United States, and androgen-deprivation therapy (ADT) is the mainstay of treatment for locally advanced and metastatic PCA. Testosterone, the main male androgen, is secreted by testicular Leydig cells under the influence of gonadotropins and possesses both androgenic and anabolic functions. Androgen deprivation can be achieved surgically (orchiectomy), medically (gonadotropin-releasing hormone [GnRH] agonists and antagonists, and estrogens), and by inducing androgen resistance (androgen receptor antagonists). Orchiectomy and treatment with GnRH agonists and antagonists decreases serum testosterone and its metabolites, whereas monotherapy with antiandrogens results in an increase in gonadal hormones. Treatment with GnRH agonists has become the most common form of ADT. Indeed, these drugs are relatively easy to administer, allow the psychological harm associated with orchiectomy to be avoided, and testosterone suppression is reversible on their discontinuation. In clinical practice, a symptomatic man is generally considered androgen deficient if his serum total testosterone level is less than 300 ng/dL. The goal of ADT is to suppress the serum testosterone level to at least below 50 ng/dL, inducing a state of profound androgen deficiency. Recent estimates suggest that more than half a million men in the United States are receiving ADT. Although ADT improves quality of life and survival in a subset of patients, its role in patients with early-stage PCa and those experiencing biochemical recurrence after local treatment remains unclear.

Sexual dysfunction, low bone mass, reduced muscle strength, and decreased energy are well-established symptoms of androgen deficiency. Recent population studies have shown that low testosterone is also associated with increased fat mass, diabetes, atherosclerosis, and cardiovascular (CV) disease. Laboratory investigations have shown that testosterone acts on pluripotent mesenchymal stem cells and promotes their differentiation toward myogenic lineage while inhibiting their differentiation into adipocytes. Hence, it is not surprising that androgen deficiency results in an increase in fat mass (rich source of inflammatory cytokines that promote insulin resistance) and a reduction in skeletal muscle (the largest source of glucose disposal), leading to metabolic dysregulation. Data from preclinical models also show that orchiectomy in low-density lipoprotein receptor–deficient mice promotes atherosclerosis, and testosterone supplementation (and its aromatization to estradiol) attenuates this process. These data support the biologic plausibility that testosterone deficiency may be a risk factor for CV disease. Orchiectomy and GnRH agonists decrease testosterone and estradiol levels, whereas monotherapy with antiandrogens increases both hormones. Hence, the CV disease risk in patients undergoing monotherapy with antiandrogens may be different from that of men receiving other forms of ADT.

Adverse effects of ADT have become better appreciated during the last 15 years. Sexual dysfunction, vasomotor symptoms, osteoporosis, and reduced quality of life are well-known consequences of ADT. In 2001, a Welsh study first reported an increase in fat mass and associated insulin resistance (a precursor to diabetes) after 3 months of ADT. Later reports showed that patients undergoing long-term ADT have a higher prevalence of metabolic syndrome and diabetes, with the duration of ADT directly associated with the degree of metabolic perturbations. These cohort studies were followed by population-based reports showing an association between GnRH agonist use and an increased risk of incident coronary heart disease, myocardial infarction, and sudden cardiac death. Interestingly, this increased risk was evident within 1 to 4 months of starting ADT. Subsequent population studies confirmed these findings. One interesting report evaluating the neoadjuvant role of ADT showed that ADT increases the risk of all-cause mortality in men with a previous history of myocardial infarction or coronary artery disease–related heart failure, suggesting that men with known CV disease might be at a higher risk. An increased risk of stroke, venous thromboembolism, and peripheral arterial disease have also been reported in patients undergoing both surgical and medical ADT. All of these reports prompted the US Food and Drug Administration to issue a safety warning in October 2010, requiring GnRH agonist labeling to disclose an "increased risk of diabetes and certain cardiovascular diseases (heart attack, sudden cardiac death and stroke) in men receiving these medications for the treatment of prostate cancer." Unlike population studies, postrandomization analyses from clinical trials have yielded conflicting data. In a pooled analysis from three randomized trials of patients receiving radiation therapy and ADT for localized PCa, older (≥ 65 years) patients receiving 6 months of ADT had shorter times to fatal myocardial infarction compared with men not receiving ADT. In contrast, post hoc analyses from
other trials, including a recent meta-analysis, did not show an increased risk of CV mortality in men undergoing ADT.26-28

In the article that accompanies this editorial, O’Farrell et al29 report interesting findings. Using data on filled prescriptions in the Swedish national health care registers, the authors investigated the risk of CV disease in a cohort of 41,362 men with PCa who received ADT either as primary treatment or because of disease progression. The comparison population comprised 187,785 age-matched men without PCa. During the study period, 10,656 men received monotherapy with antiandrogens, 26,959 received GnRH agonists (this included men receiving combined androgen blockade), and 3,747 underwent orchietomy. Compared with the control group, the investigators observed that the risk of CV disease was increased by 21% and 16% in the GnRH and orchietomy groups, respectively. Interestingly, men receiving monotherapy with antiandrogens were at a decreased risk for incident CV disease (hazard ratio, 0.87). Irrespective of the ADT modality, men with a previous history of two or more CV events (particularly if the last event occurred within a year) were at a higher risk of CV disease within the first 6 months of therapy (hazard ratio, 1.91, 1.60, and 1.79 for GnRH agonists, antiandrogens, and orchietomy, respectively). In sensitivity analyses, even without a previous history of CV disease, men in the GnRH and orchietomy groups were at an increased risk of incident and fatal CV disease.

Three important findings emerge from this study. First, men with a significant previous CV history (especially if they experienced a recent event) were at a higher risk of CV disease within months after starting ADT, suggesting that these patients are more susceptible, so to speak, to the development of CV complications. These findings are congruent with previous data reporting development of incident CV disease within 1 to 4 months of starting ADT.18 The short interval between initiation of ADT and CV disease argues against the progression of atherosclerosis as the predominant underlying etiology. Therefore, factors such as instability and rupture of the underlying coronary plaques, acute changes in hemorheology, and an imbalance between pro- and antiinflammatory factors should be considered.22,23 Second, both orchietomy and GnRH agonists were associated with an increased risk of CV disease, in contrast to previous reports showing that men in the GnRH agonist group were at a higher risk than patients who had undergone orchietomy.18,30 This directly implicates profound androgen deficiency as the cause of CV disease.31,32 Third, in the overall analysis, men undergoing monotherapy with antiandrogens were at a 13% lower risk for incident CV disease than the comparison population, suggesting that endogenous estradiol levels might have some protective effect.

So, where do we go from here? In the last decade we have seen a flurry of conflicting reports (mainly from clinical trials) on ADT-associated CV disease. There are many reasons for this discordance, some of which the authors have astutely highlighted, such as differences in patient populations, variable study design, and selection bias with men given ADT. All true. However, we believe that the main reason for this discordance is that in none of these trials was CV disease the primary outcome; all reported data was a product of post hoc analyses. Considering that PCa is the most common cancer in American men, the majority of these men are older, with multiple comorbidities, the use of ADT is increasing, biologic plausibility exists that low testosterone may promote atherosclerosis and CV disease, and CV morbidity and mortality is increasingly being reported in men undergoing ADT, the time has come to plan a prospective study that is powered to evaluate CV events (ascertained via a structured adjudication process) in men undergoing ADT. Prostate cancer survivors who have undergone radical prostatectomy and are matched for comorbidities could serve as a control group. There is a large body of data showing worsening of the metabolic profile in men undergoing ADT; however, we do not know its direct impact on vascular biology. Therefore, this prospective study should include serial measurements of carotid intima-media thickness and coronary artery plaques to monitor progression of atherosclerosis (these imaging procedures are likely to be more meaningful in men undergoing long-term ADT). Given that many patients experience CV events shortly after the commence-ment of ADT, mechanistic studies such as evaluation of coronary flow, measurement of plasma viscosity, and coagulation parameters will also provide valuable insights. These studies are difficult to conduct, but are necessary. In the interim, men undergoing ADT deserve aggressive monitoring and management of CV risk factors (hyperglycemia, hyperlipidemia, hypertension, and obesity). We have seen the pendulum of ADT-associated CV disease swinging back and forth for almost a decade, and until a study is designed to directly answer the question of ADT’s role in CV disease, the pendulum will keep on swinging.

AUTHOR’S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
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