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EDITORIAL COMMENT

# Uncontrolled Cardiovascular Risk Factors in Prostate Cancer Patients

## Are We Leaving Too Much on the Table?*

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Over 260,000 patients per year are newly diagnosed with prostate cancer in the United States, making it the most common noncutaneous cancer among men.[1] The average age of a patient diagnosed with prostate cancer is 66 years, and given the often indolent nature of prostate cancer, patients with the disease are actually less likely to die of prostate cancer than of nonprostate causes such as cardiovascular disease (CVD).[2,3] Therefore, a focus on modifiable cardiac risk factors is absolutely critical in this patient population.

Most men with aggressive or recurrent prostate cancers will be treated with androgen deprivation therapy (ADT), which has been associated with an increase in cardiovascular events.[4] The most common form of ADT is gonadotropin-releasing hormone (GnRH) agonism, which has been strongly associated with cardiovascular issues. For example, a study from D'Amico et al[5] showed an earlier onset of fatal myocardial infarctions among patients over the age of 65 on GnRH agonists from a pooled analysis of 3 large, randomized clinical trials. In addition, a large Surveillance, Epidemiology, and End Results-Medicare analysis suggested that GnRH agonists were associated with a 16% increased risk in coronary heart disease, an 11% increase in myocardial infarction, and a 16% increase in sudden cardiac death.[6] Although a large meta-analysis of 8 randomized trials of GnRH agonists vs no GnRH agonists did not find any increased risk of cardiovascular deaths, there are now reasonably compelling data that GnRH agonists do increase the risk of major adverse cardiac events.[7]

Given the high risk of cardiovascular mortality experienced by the demographic of patients who get prostate cancer and given the additional risk of cardiac harm posed by ADT, guidelines tend to recommend "medical optimization" or "cardiac optimization" of patients with prostate cancer before treatment. The important study by Klimis et al[8] in this issue shows us that as a collective medical community, we still have a very long way to go before meeting that optimization ideal. In this well-conducted analysis of RADICAL-PC (A Randomized Intervention for Cardiovascular and Lifestyle Risk Factors in Prostate Cancer Patients), a large prospective study that includes standardized assessment of cardiovascular risk factors in patients with prostate cancer, the authors surprisingly found that nearly all patients (99%) with prostate cancer had at least 1 uncontrolled modifiable risk factor, and more than half (51%) had 3 or more uncontrolled modifiable risk factors.[8] Another critical and concerning finding of this paper was that poor control of cardiovascular risk factors occurred regardless of ADT use or a history of CVD. This is worrisome because patients with a prior history of significant CVD appear to be ones who experience the greatest increase in cardiac events from ADT; therefore, it is most critical that this subset of patients be medically optimized before treatment.[9,10]

Aside from this critical need to reduce modifiable cardiovascular risk factors, 2 emerging strategies to reduce cardiovascular harm from ADT are to try to use agents that are less cardiotoxic and to try to shorten the duration of ADT. In the first category are the

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GnRH antagonists, which have been shown in some but not all studies to cause less cardiovascular harm than GnRH agonists. Specifically, degarelix (an injected GnRH antagonist) was shown in a pooled analysis of 6 randomized trials of degarelix vs GnRH agonists to reduce cardiovascular events among patients with prior CVD (HR: 0.44; 95% CI: 0.26-0.74; $P = 0.002$).[11] Similarly, in the HERO (A Study to Evaluate the Safety and Efficacy of Relugolix in Men With Advanced Prostate Cancer) trial, relugolix (an oral GnRH antagonist) was associated with a significant reduction in major adverse cardiovascular events compared with GnRH agonists with a similar effect size as the degarelix study (HR: 0.46; 95% CI: 0.24-0.88).[7] However, the prospective PRONOUNCE (A Trial Comparing Cardiovascular Safety of Degarelix Versus Leuprolide in Patients With Advanced Prostate Cancer and Cardiovascular Disease) study specifically evaluating major adverse cardiovascular events at 1 year in patients treated with degarelix vs a GnRH agonist (leuprolide) was closed early because of slow accrual and a low event rate and did not suggest any effect in favor of degarelix (HR: 1.28; 95% CI: 0.59-2.79; $P = 0.53$).[12]

The second strategy, which is to reduce the ADT duration, is being tested in NRG GU-009 (PREDICT-RT [Two Studies for Patients With High Risk Prostate Cancer Testing Less Intense Treatment for Patients With a Low Gene Risk Score and Testing a More Intense Treatment for Patients With a High Gene Risk Score), an international phase 3 cooperative group trial based primarily in the United States and Canada. In this trial of patients with high-risk prostate cancer (NCT04513717), those with favorable genomic features are entered into the deintensification trial, which randomizes patients to the standard 24 months of ADT vs a shorter 12 months of ADT.[13]

Even with ongoing studies looking at de-escalation of ADT and newer, "cardiac-friendly" agents for patients with prostate cancer, there is a clear need according to the data presented in this paper to reduce modifiable cardiovascular risk factors in patients receiving ADT regardless of duration. As oncologists, when seeing patients with prostate cancer in consultation, we are often under the assumption that cardiovascular risk factors are under control. Because most patients with prostate cancer die from non-prostate cancer-related causes, such as CVD, there is a significant desire to decrease modifiable cardiovascular risk factors early on, before, and/or during ADT treatment. Comprehensive cardiovascular evaluation before radiation therapy treatment has been strongly suggested by data in breast, thoracic, and lymphoma malignancies.[14,15] This study highlights that we should very much consider cardio-oncology evaluation with screening and monitoring of CVD before and during treatment for patients with prostate cancer as well.

Going forward, oncologists should prioritize comprehensive cardio-oncology care for patients with prostate cancer.

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