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EDITORIAL COMMENT

Addressing Cardiovascular Risk of Prostate Cancer Hormonal Therapy*

Charles J. Ryan, MD,[a] Alicia K. Morgans, MD, MPH[b]

Prostate cancer is the most common noncutaneous malignancy among American men and the second-leading cause of cancer death in the United States. Although the leading cause of death in men with prostate cancer is prostate cancer, the second-leading cause of death is cardiovascular disease (1). Because of the competing risks of these two causes of death in an aging male population, it is no surprise that controversy exists as to the strength of the causal link between testosterone suppressive therapy and adverse cardiovascular outcomes. However, it is agreed that metabolic insults induced by androgen deprivation therapy (ADT) may incur deleterious effects on cardiovascular health, including alterations in lipid levels and glycemic control, and direct effects of low testosterone on cardiac and vascular tissue. The development of strategies to minimize cardiovascular risks while maximizing cancer control benefits is critically important.

Androgen deprivation is the foundation of systemic therapy for men with advanced prostate cancer and is achieved using gonadotropin-releasing hormone (GnRH) agonist or antagonist drugs or using surgical orchiectomy. Over 400,000 American men are currently under treatment with ADT, most of whom are receiving treatment with GnRH agonists. Several population-based studies with long-term outcomes have implicated ADT for the observed increased risk of adverse cardiovascular outcomes, whereas meta-analyses of randomized trials are conflicted on this point (2,3).

An important missing link in unraveling the controversy is a relative lack of a foundation of preclinical data to support the mechanism of action that may drive heart disease in the prostate cancer population. GnRH receptors are expressed in cardiac and vascular tissue (4), but their role and the impact of systemic GnRH agonism remain unknown. Nguyen et al. (5) assessed the effect of GnRH agonist plus androgen receptor antagonist treatments in men with prostate cancer on the vasculature, expecting that they would find vasoconstriction to be a cause of increased cardiovascular risk. Conversely, they found reversible endothelium-dependent vasodilation at 3 months. Understanding the complex role of the androgen receptor and GnRH signaling throughout the cardiovascular system at the most basic level will be a necessary aspect of fully understanding the cardiovascular effects of GnRH agonists and antagonists in men with prostate cancer.

In addition to effects on the vasculature, there is a need to better understand the effects of GnRH agonist and antagonist drugs on the heart. Where and in what concentration does the heart express these receptors and what role, if any, do they play in the cardiovascular health of an aging male? How could a GnRH antagonist affect this and are these effects different from those exerted by a GnRH agonist? Is there a potential beneficial effect of blocking these receptors on the heart or is it that the antagonist approach merely represents the absence of an agonist approach? Surgical orchiectomy likely raises GnRH levels in the blood, so may be expected to confer

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From the [a]University of Minnesota and Masonic Cancer Center, Minneapolis, Minnesota, USA; and [b]Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA. Dr. Morgans is a consultant for Astellas, Sanofi, AstraZeneca, Bayer, and Janssen; and has received research funding from Seattle Genetics, Genentech, and Bayer. Dr. Ryan has reported that he has no relationships relevant to the contents of this paper to disclose.

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similar benefits as those of GnRH agonists (e.g., leuprolide or goserelin). How do these effects differ from simply performing an orchiectomy to reduce testosterone levels? Is the cardiac risk highest during the drop in testosterone from normal to the castrate range or is the morbidity a result of long-term suppression? What is the effect of cardioprotective measures, such as exercise, diet, beta blockers, and statins on these potential adverse outcomes?

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These and other questions merit consideration in the modern era as cardiology and oncology blend their expertise in the study of this population that is vulnerable to heightened morbidity. The prospective PRONOUNCE (A Trial Comparing Cardiovascular Safety of Degarelix Versus Leuprolide in Patients With Advanced Prostate Cancer and Cardiovascular Disease) trial, which is highlighted in this issue of *JACC: CardioOncology* (6), is representative of this potential. PRONOUNCE is a phase IIIb, multicenter, prospective, randomized, open, trial designed to compare the occurrence of major adverse cardiovascular events in patients with advanced prostate cancer and pre-existing atherosclerotic cardiovascular disease receiving either a GnRH antagonist (degarelix) or a GnRH agonist (leuprolide) as ADT for 12 months. This prospective study, which has a primary endpoint to assess cardiovascular morbidity as opposed to anticancer efficacy, is rare in modern oncology; however, more such approaches are needed. Notably, the study enrolls only patients who are at risk at baseline due to previous cardiac events, enriching the risk pool, but making causation linkages difficult. In addition, the study only monitors the first 12 months during treatment, precluding characterization of potential differences between the therapies that may emerge with extended follow-up. Finally, the study will not provide any data on the relative effect of orchiectomy, because it is not included in the study design. Despite these limitations, this is the first prospective study that is appropriately powered to assess a cardiovascular primary endpoint in men with prostate cancer.

In addition to the need to complete prospective trials that assess cardiovascular outcomes in men with prostate cancer, there is an urgent need to understand the array of effects that androgen deprivation and other therapies have on prostate cancer survivors. In response to this, we have established, in conjunction with the Prostate Cancer Foundation, the SURECAP (Survivorship Research in Carcinoma of the Prostate) initiative (7). This initiative establishes a framework for survivorship research in prostate cancer and seeks the involvement and contribution of interested cardiologists wishing to join the oncology and urology communities in addressing these issues. Caring for the growing population of prostate cancer survivors around the world requires an understanding of the effects of our treatments; understanding the cardiovascular effects through the PRONOUNCE trial is a clear step in the right direction.

ADDRESS FOR CORRESPONDENCE: Dr. Charles J. Ryan, Division of Hematology, Oncology and Transplantation, University of Minnesota Medical School, Department of Medicine, 14-106A Phillips-Wangensteen Building, 516 Delaware Street SE, Minneapolis, Minnesota 55455. E-mail: Ryanc@umn.edu. Twitter: @charlesryanmd.

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