Commentary

Assessing the cardiovascular risk of hormonal therapy in patients with prostate cancer

Theodoros Karantanos[1], Styliani Karanika[2]

[1]General Internal Medicine Section, Boston Medical Center, Boston University School of Medicine, Boston, MA 02118, USA; [2]Infectious Diseases Division, Warren Alpert Medical School of Brown University, Rhode Island Hospital, Providence, RI 02903, USA

Correspondence to: Theodoros Karantanos, MD. General Internal Medicine Section, Boston Medical Center, Boston University School of Medicine, 850 Harrison Ave, Boston, MA 02118, USA. Email: theodoros.karantanos@bmc.org; theodoroskarantanosmd@gmail.com.

Submitted Jan 13, 2016. Accepted for publication Jan 18, 2016.
doi: 10.21037/atm.2016.01.23
View this article at: http://dx.doi.org/10.21037/atm.2016.01.23

Androgen deprivation therapy (ADT) which remains the first line of therapy for patients with metastatic prostate cancer (PCa) has been associated with metabolic abnormalities and significant risk of cardiovascular disease (CVD) (1). Based on observational studies and two meta-analyses, ADT increases the risk for cardiovascular events but results from randomized clinical trials and relevant subsequent meta-analyses did not confirm those conclusions (1). This literature discrepancy in cardiovascular outcomes in patients on ADT may be associated with lack of evaluation of different types of ADT including gonadotropin-releasing hormone (GnRH) agonists, orchiectomy or anti-androgens, absence of comparison to age-matched patients without PCa, and not assessing pre-existing CVD as a confounding factor.

O'Farrell *et al.* have recently published an observational study in the *Journal of Clinical Oncology* named "Risk and Timing of Cardiovascular Disease After Androgen-Deprivation Therapy in Men With Prostate Cancer" evaluating the CVD risk per treatment in 41,362 PCa patients who have undergone orchiectomy, been treated with GnRH agonists, or anti-androgens from 2006 to 2012 in comparison with 187,785 patients without PCa (2). The authors concluded in remarkable results; they demonstrated that patients on GnRH agonists and those who have undergone orchiectomy have increased risk of all CVD incidents compared to age-matched controls without PCa. Surprisingly, anti-androgens administration led patients to have lower risk of CVD incidents than the age-matched controls did. Stratifying the data based on previous statin use and history of CVD followed by sensitivity analysis, GnRH agonists and orchiectomy appeared to increase the CVD risk compared to comparison cohort as well. Going deeper, they presented hazard ratios of CVD incidents 2 years before and after the initiation of ADT between the cancer patients and cancer-free subjects highlighting the increase of risk for CVD after initiation of GnRH agonists and performing surgery. Although the selection of the comparison cohort in the baseline seems to help overestimate the CVD hazard of GnRH agonists, the risk gap after the ADT treatment seems to increase significantly outperforming the initial difference. Last but not least, they showed that patients with aggressive PCa have increased risk for CVD than the patients with earlier stage of disease. Undoubtedly, this is a significant and novel conclusion raising a critical question; the cancer is the real cause of the CVD, the treatment or maybe both? Preclinical and clinical studies should be designed to address this query. It should be mentioned though that the finding that particularly GnRH and orchiectomy and not anti-androgens increase the incidence of CVD suggests that it tends to be linked to the treatment and not to the disease.

Those conclusions are notably important as the authors assessed the impact of different types of ADT on the alteration of CVD risk contributing to a better comprehension of the implication of ADT on cardiovascular events given the literature controversy on that matter.

According to recently published data, GnRH antagonists are associated with lower risk of cardiovascular events, compared with GnRH agonists especially in patients with history of CVD (3). This finding is consistent with a previous study showing that treatment with GnRH agonists confers higher risk of cardiac events compared to GnRH antagonists in patients with pre-existing CVD during the first year of treatment (4). On top of that, US Food and Drug Administration required the inclusion of additional safety

information to GnRH agonists drug labels (1) confirming the concern for the underlying CVD risk. O'Farrell *et al.* move one step forward suggesting that GnRH agonists increase the risk of CVD especially early during treatment and particularly in patients with pre-existing CVD.

The findings of this study warrant for the researchers to shade more light to the mechanism by which hormonal therapy may increase the risk of CVD in patients with PCa. It has been reported in a few studies that testosterone provides protection against myocardial ischemia through multiple genomic and non-genomic mechanisms (5). Moreover, systematic androgen deprivation has been associated with increased arterial stiffness and decreased compliance along with significant metabolic abnormalities such as increased low density lipoprotein and triglycerides and increased insulin resistance (6), which all have been implicated in the development of CVD. The finding of this study, that GnRH agonists and orchiectomy, which both cause systemic androgen deprivation, increase the risk of CVD while anti-androgens, which do not reduce the circulating testosterone do not confer to the risk for cardiovascular events further supports that increased CVD risk is probably mediated by the direct and indirect systematic effects of testosterone. Interestingly, according to a recently published meta-analysis of randomized clinical trials, treatment of patients with metastatic castrate resistant PCa with abiraterone acetate (AA), a CYP-17 inhibitor which decreases both the systemic and tumor microenvironment testosterone levels, increased the risk of CVD and arterial hypertension (7). On the contrary, treatment with Enzalutamide, a novel AR inhibitor, which does not affect the systemic testosterone levels, increases similarly the risk of arterial hypertension but not the risk of cardiovascular events (7). These conclusions further support that alteration of systemic androgen levels may be critical for the development of CVD whereas treatments affecting the AR biology probably do not confer increased CVD risk.

Overall, based on previous evidence and the data presented in this study, therapies causing systemic androgen depletion such as GnRH agonists and orchiectomy may increase the risk of cardiovascular events during the first months of treatment especially in men with recent history of CVD. Under this perspective, it may be reasonable to consider alternative treatments such as anti-androgens in this group of patients given the lack of evidence that those agents affect significantly the CVD risk. Given the extensive use of novel hormonal therapies such as AA and Enzalutamide, it is required to assess their implication in CVD risk further in order to better stratify the patients and offer them the appropriate treatment which outweighs any potential harm.

Acknowledgements

None.

Footnote

Provenance: This is a Guest Commentary commissioned by Xiongbing Zu, MD, PhD (Department of Urology, Xiangya Hospital, Central South University, Changsha, China).
Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Karantanos T, Karanika S. Assessing the cardiovascular risk of hormonal therapy in patients with prostate cancer. Ann Transl Med 2016;4(5):99. doi: 10.21037/atm.2016.01.23

