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European Association of Urology

Platinum Priority – Editorial

Referring to the article published on pp. 920–928 of this issue

Type of Androgen Deprivation Therapy and Risk of Cardiovascular Disease

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A number of observational studies have identified an association between androgen deprivation therapy for the treatment of prostate cancer and an increased risk of cardiovascular disease [1]. Two population-based studies documented associations of gonadotropin-releasing hormone (GnRH) agonists, but not orchiectomy, with cardiovascular disease during androgen deprivation therapy [2,3], and a recent comparative effectiveness study suggested that the risk of cardiovascular disease was higher for men treated with GnRH agonist therapy than for those treated with orchiectomy [4]. These observational studies suggest that the type of androgen deprivation therapy could be important, but they are limited by the relatively infrequent use of orchiectomy in the USA and Denmark, and by the notable differences in patients who are treated with GnRH agonist therapy versus orchiectomy. Use of orchiectomy has typically been more frequent among men who are older, have more comorbid illness, live in areas of lower socioeconomic status, were treated less recently, and have higher-risk tumors. Prior studies have adjusted for observed differences in these populations using standard regression or propensity score methods; however, these methods do not account for unobserved differences. Moreover, the differences in patient and tumor characteristics suggest that men treated with orchiectomy have a higher risk of death from a variety of causes, which could limit ascertainment of cardiovascular events. Although prior studies have used competing risk analyses to address this, such analyses may be sensitive to the relationship of covariates with the primary outcomes and the competing risks [5].

In this month's issue of *European Urology*, Thomsen and colleagues [6] report the results of a study designed to address some of the limitations of these observational studies comparing the risk of cardiovascular disease associated with GnRH agonist therapy versus orchiectomy. Using a semiecologic design, the authors measured the exposure (receipt of orchiectomy vs GnRH agonist) at an ecologic level, leveraging substantial differences across providers in Sweden in use of orchiectomy to treat prostate cancer during the 1990s, and measured the outcome at the individual patient level. With data on all prostate cancers diagnosed in Sweden during 1992–1999, the authors specified 580 experimental "units" defined by healthcare provider, diagnostic time period, and patient age at diagnosis in which rates of orchiectomy varied from 14% to 96%. For each man, the authors identified the first occurrence of a cardiovascular diagnosis starting at 3 mo after diagnosis (the date on which men were presumed to initiate androgen deprivation based on timing of initiation for men diagnosed in 2006–2012, of whom 90% started androgen deprivation therapy within 3 mo of diagnosis). Cardiovascular disease diagnoses of interest included new diagnoses of hypertension, ischemic heart disease, stroke, deep venous thrombosis or pulmonary embolism, and arterial embolism.

Men treated with orchiectomy were older, had higher-risk tumors (including more metastatic disease), and had lower levels of education, factors that would likely increase the risk of cardiovascular disease as well as the risk of death from prostate cancer and other causes. These differences were lessened when comparing patients grouped based on

DOI of original article: http://dx.doi.org/10.1016/j.eururo.2017.06.036.
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http://dx.doi.org/10.1016/j.eururo.2017.08.004

higher versus lower use of orchiectomy. Primary analyses demonstrated that the risk of cardiovascular disease was similar for units with the highest and lowest proportions of GnRH agonist use (relative risk 1.01, 95% confidence interval 0.93–1.11). The semiecologic study design seeks to limit bias by assuming that men were assigned to the treatment based on the providers that they happened to see at the time they were diagnosed, rather than by other factors such as disease status or health status that might confound any association of treatment with outcome. Thus, the use of orchiectomy is less driven by selection of older or sicker patients, and comparisons of treatment are more likely to mimic random treatment allocation. Nevertheless, such designs are at risk for bias if there remains within-unit variability in the use of orchiectomy or if there is within-unit confounding. As noted, even after assignment to groups based on treatment unit, men in the orchiectomy group were older and had higher-risk tumors. Of more concern is the possibility of residual confounding based on time period, since nearly all the units with very high rates of orchiectomy occurred in the first one or two time periods (Fig. 1 in the study). With a decreasing risk of cardiovascular disease incidence in Sweden over time [7], a potentially higher risk of cardiovascular disease associated with more recent treatment, most of which was with GnRH agonist therapy, could be masked.

Another limitation of the study involves the ascertainment of cardiovascular disease. It is noteworthy that the definition of the cardiovascular disease end point includes hypertension (not included in the definition of cardiovascular disease in other studies). The very low rate of hypertension at baseline in this cohort of older men (6–7%) raises questions about how well medical conditions are documented. In addition, the data source lacked information about the start date and duration of GnRH agonist therapy. Although, as the authors note, men with advanced prostate cancer are likely to start treatment immediately and may continue GnRH agonist therapy indefinitely, only about one-third of patients in the study had metastatic disease, and men receiving adjuvant GnRH therapy may start later and continue therapy for only 6–36 mo [8]. Use of GnRH agonist therapy also requires regular visits, which could increase the likelihood of identifying incident cardiovascular disease. It is difficult to predict the effect of these potential biases on outcomes, since the shorter duration of androgen suppression with GnRH agonist therapy would suggest less time at risk and thus less cardiovascular disease, but their additional visits could lead to more cardiovascular diagnoses.

The mechanism for the association of androgen deprivation therapy and risk of cardiovascular disease are uncertain but may be linked to metabolic effects, including central adiposity, decreased insulin sensitivity, and changes in lipoproteins and arterial stiffness [1]. Such effects seem to be related to androgen suppression, and thus there is a reason to believe that the associations should be similar for orchiectomy and GnRH agonists, as this study suggests. The likely harm of androgen deprivation therapy of any type underscores the need for clinicians to weigh the benefits and harm of treatment, and engage in shared decision making with patients. This is of particular importance when androgen deprivation therapy is considered for clinical scenarios for which benefits are uncertain, such as primary treatment of local/regional prostate cancers and biochemical recurrence, regardless of the type of androgen deprivation therapy.

Conflicts of interest: The author has no potential conflicts of interest to disclose.

Funding support: Dr. Keating's effort is supported by K24CA181510 from the United States National Cancer Institute.

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