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Androgen Deprivation Therapy for Prostate Cancer and the Risk of Venous Thromboembolism

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Abstract

Background: Few observational studies have investigated the association between androgen deprivation therapy (ADT) and venous thromboembolism (VTE) in patients with prostate cancer (PCa).
Objective: To determine whether the use of different types of ADT in patients with PCa is associated with an increased incidence of VTE.
Design, setting, and participants: A population-based cohort study was conducted using the UK Clinical Practice Research Datalink linked to the Hospital Episode Statistics repository. The cohort consisted of men newly diagnosed with PCa between April 1, 1998, and March 31, 2014.
Outcome measures and statistical analysis: Cox proportional hazards models with a time-varying exposure definition were used to estimate adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) of patients hospitalized for VTE associated with current and past ADT use compared with nonuse. A secondary analysis was conducted to assess the risk with current use of specific types of ADT.
Results and limitations: The cohort included 21 729 patients, of whom 609 were hospitalized for VTE during follow-up. Current ADT use was associated with an 84% increased risk of VTE (incidence rates: 10.1 vs 4.8 per 1000 person-years; HR: 1.84; 95% CI, 1.50–2.26), whereas there was no association with past use (HR: 1.07; 95% CI, 0.81–1.42). In the secondary analysis, most types of ADT were associated with a high risk of VTE. Residual confounding is possible given the observational nature of the study.
Conclusions: The use of ADT was associated with an overall 84% increased risk of VTE, with the risk elevated for most ADT types.
Patient summary: In this study, we investigated whether androgen deprivation therapy was associated with the risk of blood clots in a cohort of patients with prostate cancer. We observed that the risk was nearly doubled in patients who used ADT compared with those who never used it. This treatment should be reserved for patients for whom the benefits outweigh the risks.

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1. Introduction

Androgen deprivation therapy (ADT) is the mainstay treatment for patients with advanced prostate cancer (PCa) [1]. In the United States, the use of ADT has increased sixfold in the last two decades [2], a trend that reflects the increasing use in patients with localized disease for whom the benefits are less clear [3,4]. This is particularly important in the context of the accumulating evidence suggesting that the hypogonadism induced by ADT may increase the risk of cardiovascular [5], cerebrovascular [6], and renal [7] adverse events, which some have attributed to accelerated atherosclerosis.

In addition, laboratory and clinical studies have associated low testosterone levels in men with reduced fibrinolytic activity [8,9], leading to the hypothesis that ADT may lead to a hypercoagulable state that may increase the risk of venous thromboembolism (VTE). The development of VTE in patients with cancer can have deleterious consequences [10,11]. To date, however, the observational studies that have investigated the association between the use of ADT and the incidence of VTE have been few and with a number of methodological shortcomings, such as inadequate comparator groups [12–14].

Given the limited evidence, we conducted a population-based study to assess whether the use of ADT is associated with an increased risk of incident VTE in patients with PCa.

2. Methods

2.1. Data sources

This study was conducted using the UK Clinical Practice Research Datalink (CPRD) linked to the Hospital Episodes Statistics (HES) repository. The CPRD contains data on >13 million individuals enrolled in >680 general practices. Demographic information, clinical diagnoses, and prescriptions written by general practitioners have been shown to be of high validity [15,16]. The HES contains dates of hospital admissions, primary and secondary diagnoses (coded using the International Classification of Diseases, 10th edition [ICD-10]), and related procedures.

The study protocol was approved by the Independent Scientific Advisory Committee of the CPRD (protocol number 14_192Mn) and the Research Ethics Board of the Jewish General Hospital, Montreal, Quebec, Canada.

2.2. Study cohort

We identified a cohort of men at least 40 yr of age newly diagnosed with PCa between April 1, 1998, and March 31, 2014. Cohort entry was defined by the first-ever diagnosis of PCa. We excluded patients with <1 yr of medical history in the CPRD prior to cohort entry, as well as those with a history of ADT use, previous diagnoses of pulmonary embolism (PE), deep vein thrombosis (DVT), nephrotic syndrome, and myeloproliferative neoplasms at any time before cohort entry.

Patients were followed until an incident hospitalization for VTE (first-time admission for DVT, PE, or both (ICD-10 codes 126.0, 126.9, 180.x, 182.1, 182.2, 182.3, 182.8, and 182.9, in primary or secondary position), death from any cause, end of registration with the general practice, or end of the study period (March 31, 2014), whichever occurred first.

2.3. Exposure to androgen deprivation therapy

Exposure to ADT included gonadotropin-releasing hormone (GnRH) agonists (leuprolide, buserelin, goserelin, triptorelin), oral antiandrogens (cyproterone acetate, flutamide, bicalutamide, nilutamide), estrogens (diethylstilbestrol, estramustine), and bilateral orchiectomy. A time-dependent exposure definition was used in which each person-day of follow-up was classified as either exposed or unexposed to ADT. For ADT pharmacotherapies, exposed person-time was defined by the duration of the prescription plus a residual-effect period, the latter reflecting the relatively long persistence of hypogonadism after treatment discontinuation [17,18]. Therefore, a 180-d residual-effect period was considered for GnRH agonists and a 30-d period for oral antiandrogens and estrogens. Thus patients were considered continuously exposed if the duration of one prescription overlapped with the date of the next prescription, using the residual-effect period as a grace period between nonoverlapping successive prescriptions. Patients who underwent bilateral orchiectomy were considered continuously exposed from the date of the surgery until the end of follow-up.

Based on this exposure definition, ADT use was classified into one of three categories: current use, past use, and nonuse. Current use was defined as ADT use at the time of the event, past use was defined as use during follow-up but not at the time of the event, and nonuse was defined as no use between cohort entry and the time of the event. The latter category served as the reference for all analyses.

2.4. Statistical analysis

Descriptive statistics were used to summarize the characteristics of the cohort and, separately, of patients exposed to ADT at any time during follow-up. Cox proportional hazards models with a time-varying exposure definition were used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) of incident VTE associated with current and past use of ADT compared with nonuse.

All models were adjusted for the following potential baseline confounders: age, year of cohort entry, body mass index, smoking status, excessive alcohol use (alcohol-related disorders: alcoholism, alcoholic cirrhosis of the liver, alcoholic hepatitis, and liver failure), chronic kidney disease, myocardial infarction, ischemic stroke, transient ischemic attack, peripheral arterial disease, previous cancer (other than non-melanoma skin cancer), inflammatory bowel disease, as well as for the use of warfarin, aspirin, other nonsteroidal anti-inflammatory drugs, clopidogrel, and statins (all measured in the year prior to cohort entry). Finally, the models were also adjusted for prediagnostic prostate-specific antigen (PSA) levels and the presence of metastases (lymph node, bone, visceral, other). Variables with missing information were coded as unknown.

2.5. Secondary analyses

We conducted five secondary analyses using nonuse of ADT as the reference. First, we assessed whether the risk varied according to current use of specific types of ADT. For this analysis, we estimated separate HRs for six mutually exclusive categories: GnRH agonists alone, GnRH agonists and oral antiandrogens, oral antiandrogens alone, other combinations, bilateral orchiectomy, and estrogens alone. Second, we assessed whether there was a duration–response relationship between duration of current use of any ADT and GnRH agonists alone and the incidence of VTE. For both analyses, we estimated separate HRs for five duration categories: <6 mo, 6–12 mo, 13–18 mo, 19–24 mo, and ≥25 mo. A test of heterogeneity was used to assess whether there were differences across the duration categories. Third, as an alternative to the duration categories just mentioned, we modeled duration as a continuous variable using a restricted cubic spline model with five knots