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Androgen-deprivation Therapy in Treatment of Prostate Cancer and Risk of Myocardial Infarction and Stroke: A Nationwide Danish Population-based Cohort Study

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Abstract

Background: Androgen-deprivation therapy (ADT) has been suggested to increase the risk for cardiovascular diseases, including myocardial infarction (MI) and stroke, but data are inconsistent.
Objectives: To investigate the association between ADT and risk for MI and stroke in Danish men with prostate cancer.
Design, setting, and participants: A national cohort study of all patients with incident prostate cancer registered in the Danish Cancer Registry from January 1, 2002, through 2010 was conducted.
Outcome measurements and statistical analysis: We used Cox regression analysis to estimate hazard ratios (HR) of MI and stroke for ADT users versus nonusers, adjusting for age, prostate cancer stage, comorbidity, and calendar period. Additionally, we stratified the analysis on preexisting MI/stroke status.
Results and limitations: Of 31 571 prostate cancer patients, 9204 (29%) received medical endocrine therapy and 2060 (7%) were orchidectomized. Patients treated with medical endocrine therapy had an increased risk for MI and stroke with adjusted HRs of 1.31 (95% confidence interval [CI], 1.16–1.49) and 1.19 (95% CI, 1.06–1.35), respectively, compared with nonusers of ADT. We found no increased risk for MI (HR: 0.90; 95% CI, 0.83–1.29) or stroke (HR: 1.11; 95% CI, 0.90–1.36) after orchiectomy. One limitation of the study is that information on prognostic lifestyle factors was not included and might have further informed our estimates.
Conclusions: In this nationwide cohort study of >30 000 prostate cancer patients, we found that endocrine hormonal therapy was associated with increased risk for MI and stroke. In contrast, we did not find this association after orchiectomy.

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1. Introduction

The indication for androgen-deprivation therapy (ADT) in prostate cancer (PCa) treatment has been symptomatic, locally advanced, and metastatic prostate cancer [1]. In recent years, however, the use of ADT in the form of gonadotropin-releasing hormone (GnRH) agonists has also included neoadjuvant, temporary GnRH agonists in multimodal treatment of localized PCa [2]. Use of ADT, both GnRH agonists, and orchiectomy results in

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hypogonadism, which is associated with profound adverse effects including development of metabolic syndrome and, thereby, increased risk for diabetes and cardiovascular diseases [3–6].

Some studies have reported nearly 30% excess risk for MI and stroke in patients using GnRH agonists compared with nonusers [7–12], while others found no association [13,14]. An association between ADT and cardiovascular mortality has been investigated in several clinical trials and no increase in mortality has been found [15–17] except in one recent US study where use of neoadjuvant hormone therapy was associated with increased all-cause mortality in patients with low-risk PCa and at least one risk factor for cardiovascular disease [18]. Thus, data relating to an association between ADT and cardiovascular morbidity and mortality are conflicting.

MI and stroke are serious complications with 1-yr mortality rates of 24% [19] and 21% [20], respectively. An association between ADT and MI and stroke may thus be of clinical importance. Therefore, we conducted this population-based study to investigate the association between ADT (including treatment with GnRH agonists, oral antiandrogens, or orchiectomy) and MI and stroke in Danish men with PCa.

2. Patients and methods

Denmark has 5.5 million inhabitants who are provided with free, tax-supported health care by the National Health Service. Since 1968, a unique 10-digit civil registration number has been assigned to all Danish residents by the central office of civil registration, and this number allows unambiguous linkage among all Danish registries [21]. We linked data from the Danish Civil Registration System, the Danish Cancer Registry, the Danish National Patient Registry (DNPR), and the Danish Cause of Death Registry.

2.1. Identifying patients with prostate cancer

We identified all men with PCa through the Danish Cancer Registry in the period 2002–2010. This is a population-based, nationwide registry with data on incident cancer in Denmark since 1943 [22]. Data include civil registration number and stage at diagnosis. We used the International Classification of Diseases (ICD)-10 code DC61.9 to identify patients with PCa [23]. Until 2003, tumor stage was recorded as localized, regional, or distant. Thereafter, stage was recorded using the TNM system. We classified stage as localized if TNM categories were designated T1–2, N0/x, M0/x; regional if T3–4 or N1–3, M0; and distant if T1-4, N0-3, M1.

2.2. Treatment

Information on treatment was obtained through the DNPR [24]. This registry contains data on all somatic hospital admissions since 1977 and on outpatient and emergency room visits since 1995. It includes dates of admission and discharge, medical treatments, surgical procedures, and up to 20 diagnoses coded by physicians at discharge. We used the ICD-10 code BWHCx to identify patients treated with GnRH agonists or antiandrogens (ie, medical endocrine therapy) between January 1, 2002, and February 16, 2012. We used the codes KKFC10, KKFC13, and KKFC15 to identify orchidectomized patients. Patients treated with both GnRH agonists and orchiectomy were excluded.

2.3. Ascertainment of myocardial infarction and stroke

From the DNPR, we identified all diagnoses of MI (ICD-8 codes 410.09/410.99 and IDC-10 codes DI21.x), and ischemic strokes or transient ischemic attacks (ICD-8 codes 433.09/99, 434.09/99, 436.01/436.90, and ICD-10 codes DI63.x and DI64.x) after initiation of ADT [23,25]. Through the Danish National Registry of Causes of Death [26], we identified fatal MIs (IDC-10 codes DI21.x and DI46.x) and strokes (ICD-10 codes DI63.x and DI64.x).

Preexisting MI or stroke was defined if a diagnosis of these diseases was recorded $\leq$10 yr before PCa diagnosis.

2.4. Comorbidities at diagnosis

Through the DNPR, we identified comorbidities included in the Charlson comorbidity index. This index comprises 19 conditions, each weighted according to its potential to influence mortality [27]. We calculated the index score for each patient based on diagnoses recorded $\leq$10 yr before PCa diagnosis. For the stratified analysis, we excluded MI and stroke when computing the index. We categorized the index score into four comorbidity levels: 0, none; 1, low; 2, moderate; and $\geq$3, high.

2.5. Statistics

We used Cox regression analysis with time-varying treatment variables (ie, patients contributed risk time in the nontreatment group until initiation of treatment) to estimate hazard ratios (HRs) assessing the effect of ADT on time to first nonfatal or fatal MI or stroke, while controlling for age, PCa stage, comorbidities, and study year. Patients were followed from date of PCa diagnosis until death, February 16, 2012, or occurrence of MI or stroke (after initiation of ADT), whichever came first. Once medical endocrine therapy was initiated, the patient was considered exposed for the remaining follow-up time. Patients not receiving ADT served as the reference in all analyses.

We excluded patients on medical endocrine therapy when analyzing the effects of orchiectomy, and excluded orchidectomized patients when analyzing the effects of medical endocrine therapy. In an additional analysis, we stratified data by preexisting MI/stroke status. We also stratified data by fatal and nonfatal cardiovascular events. Furthermore, we repeated the analyses, treating death as a competing risk. The models were tested for interactions of all covariates and none were found. The assumptions for the Cox model were assessed graphically and analytically and were found appropriate.

We repeated analyses using multiple imputation for missing data on tumor stage, which did not alter results, and therefore we abstained from using the multiple imputation. Estimates are presented with 95% confidence intervals (CIs). Statistical analyses were performed using Stata software v.11 S/E (StataCorp LP, College Station, TX, USA). The study was approved by the Danish Data Protection Agency (journal no. 2009-41-3793).

3. Results

We included 31 571 men with a primary diagnosis of PCa in Denmark between 2002 and 2010 and followed them for a median of 3.3 yr (interquartile range [IQR]: 1.8–5.2). The median age at PCa diagnosis was 71 yr (IQR: 65–78 yr). Overall, 11 264 of the 31 571 PCa patients (36%) received ADT, 9204 (29%) received medical endocrine therapy, and 2060 (7%) were orchidectomized. The annual number of patients diagnosed with PCa increased during the entire study period (Fig. 1). Cardiovascular events were evenly distributed throughout the study period (Fig. 2).