Association between Use of Exogenous Testosterone Therapy and Risk of Venous Thrombotic Events among Exogenous Testosterone Treated and Untreated Men with Hypogonadism

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Purpose: Limited information exists about whether exogenous testosterone therapy is associated with a risk of venous thrombotic events. We investigated via cohort and nested case-control analyses whether exogenous testosterone therapy is associated with the risk of venous thrombotic events in men with hypogonadism.

Materials and Methods: Databases were reviewed to identify men prescribed exogenous testosterone therapy and/or men with a hypogonadism diagnosis. Propensity score 1:1 matching was used to select patients for cohort analysis. Cases (men with venous thrombotic events) were matched 1:4 with controls (men without venous thrombotic events) for the nested case-control analysis. Primary outcome was defined as incident idiopathic venous thrombotic events. Cox regression and conditional logistic regression were used to assess HRs and ORs, respectively. Sensitivity analyses were also performed.

Results: A total of 102,650 exogenous testosterone treated and 102,650 untreated patients were included in cohort analysis after matching, and 2,785 cases and 11,119 controls were included in case-control analysis. Cohort analysis revealed a HR of 1.08 for all testosterone treated patients (95% CI 0.91, 1.27, $p = 0.378$). Case-control analysis resulted in an OR of 1.02 (95% CI 0.92, 1.13, $p = 0.702$) for current exogenous testosterone therapy exposure and an OR of 0.92 (95% CI 0.82, 1.03, $p = 0.145$) for past exogenous testosterone therapy exposure. These results remained nonstatistically significant after stratifying by exogenous testosterone therapy administration route and age category. Most sensitivity analyses yielded consistent results.

Conclusions: No significant association was found between exogenous testosterone therapy and incidents of idiopathic or overall venous thrombotic events in men with hypogonadism. However, some discrepant findings exist for the association between injectable formulations and the risk of overall venous thrombotic events.

Key Words: testis, testosterone, hypogonadism, venous thrombosis, pulmonary embolism

Abbreviations and Acronyms

DVT = deep vein thrombosis

eTT = exogenous testosterone therapy

FDA = Food and Drug Administration

IR = incidence rate

PE = pulmonary embolism

VTE = venous thrombotic event

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Venous thrombotic events often manifest as DVT or PE. Major exogenous risk factors for VTE are surgery, hospitalization and prolonged immobility, and endogenous risk factors are cancer, obesity and hypercoagulation disorders.[1–3]

To treat male hypogonadism eTT is administered to restore serum testosterone levels and relieve patient

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symptoms. However, several publications have suggested that eTT may be linked to increased hematocrit, polycythemia and VTE.[4–7] In contrast other studies have demonstrated that increases in endogenous estradiol or testosterone levels are not associated with an increased risk of VTE.[8,9] Furthermore a recently published study did not show a significant association between eTT and VTE.[10] However, based on post-market spontaneous reports and published case reports[11,12] the FDA in 2014 required a change in the drug labeling of all approved testosterone products, which included a general warning regarding a potential increased risk of VTE.[13]

In the current study we aimed to further examine whether eTT is associated with an increased risk of VTE in men with hypogonadism in retrospective cohort and nested case-control settings.

MATERIALS AND METHODS

Data Source

Medical claims data, pharmacy data and health care enrollment information were obtained from MarketScan® Databases[14] from December 2004 to December 2012 (supplementary material, http://jurology.com/).

Patient Population

Study eligibility criteria included 1) men 18 years old or older with continuous enrollment in a health care plan for 12 months or longer and 2) hypogonadism, defined as an eTT prescription and/or hypogonadism diagnosis code per ICD-9 (supplementary table 1, http://jurology.com/). Patients who experienced a VTE during this period were excluded from analysis.

Study

Design. This was a retrospective cohort and a nested case-control study to ensure consistent findings across different designs. For the retrospective cohort analysis a propensity score matching method was used to form cohorts of eTT treated and untreated men with hypogonadism according to baseline demographics, comorbid conditions, concomitant medications and resource use. Index date was defined as the first prescription date in eTT treated men and a randomly assigned diagnosis date for untreated men to account for immortal time bias (supplementary material, http://jurology.com/).[15] The baseline period was defined as the 12-month period before the patient index date.

For the nested case-control analysis men with hypogonadism with VTE were selected from the original (prematched) cohort population to be cases. For each analysis 4 patients without VTE were randomly selected to be controls and matched on index date and age.

Variables. The exposure variable was any eTT exposure further stratified by a prespecified route of eTT administration (topical/gel, injection, transdermal or other/nonspecified). The exposure window was defined as the duration of the prescription plus a 90-day washout period. In the nested case-control analysis current eTT exposure was defined as VTE occurring during the exposure window and past eTT was defined as VTE occurring at least 90 days after the end of the last prescription (ie outside the exposure window).

Study outcome variables were incident idiopathic VTE (not associated with proxy risk factors of stroke, injury, paralysis/immobility, hospitalization greater than 3 days, lower limb fracture, major surgery, oxygen therapy or anticoagulant use) as well as incident overall VTE as a sensitivity measure, defined via ICD-9 codes. These codes have been validated in a FDA minisentinel project with a highest positive predictive value of 65% to 90%.[16] Additionally an adjudication process was used to classify idiopathic VTE cases, although misclassification may still exist (concordance rate 70%, 95% CI 61.8, 78.20) due to the limitations of the data source and the lack of nonprescription information (supplementary material, http://jurology.com/).

The other study variables, including baseline characteristics (comorbidities, VTE risk factors, resource use and medication use), were defined via ICD-9 or product codes.

Statistical Analyses

Baseline characteristics and VTE risk factors were described for the patient populations. Between cohort differences in these characteristics were calculated by the t-test for continuous variables and the Pearson chi-square test for categorical variables with a 0.05 significance level.

For cohort analyses a propensity score method was used. The propensity score of each patient was defined as the predicted probability of eTT initiation based on an assessment of measurable baseline characteristics.[17–19] A high dimension propensity score method developed by OMOP (Observational Medical Outcomes Partnership) identified a comparison group with regard to an elevated risk of drug induced VTE by incorporating additional baseline variables in the propensity score model.[19,20] The propensity score generated for the entire population was applied to subcohorts.[19,21] For time to event analysis VTE IRs per person-years were calculated in the eTT treated and untreated patient cohorts. A Cox regression model was used to determine HRs with the 95% CI and p values. The proportionality assumption for the Cox regression models was checked and no violations were observed.

For nested case-control analyses conditional stepwise logistic regression models adjusting for baseline characteristics were used to account for changes in drug exposure and time varying confounding factors. The association between eTT exposure patterns and VTE risk was reported as an adjusted OR with the 95% CI after controlling for key VTE risk factors. In addition stepwise criteria of variable selection applied a p value of 0.20 for model entry and 0.10 for retaining variables. To be conservative correction of multiple comparisons/type I errors was not considered for multiple comparisons involving different hypotheses.

Sensitivity analyses were performed to assess the impact of different eTT exposure windows (60, 90 or 120 days), overall VTEs and variations in study design (intent to treat vs as treated analysis) (supplementary material, http://jurology.com/). Analyses were done with SAS®, version 9.2.