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.

RESULTS

Population Analysis

Cohort. Figure 1 shows the selection process for the cohort analysis population with 533,223 patients, including 306,507 treated with eTT and 226,716 who were untreated. After applying 1:1 propensity score matching 102,650 eTT treated and 102,650 untreated men with hypogonadism with well balanced baseline characteristics were selected for primary analysis (table 1).

Case-Control. A total of 2,785 patients with incident idiopathic VTE were selected as cases and 11,119 matched controls were randomly selected from the treated and untreated hypogonadal population. Table 1 lists demographics and baseline characteristics.

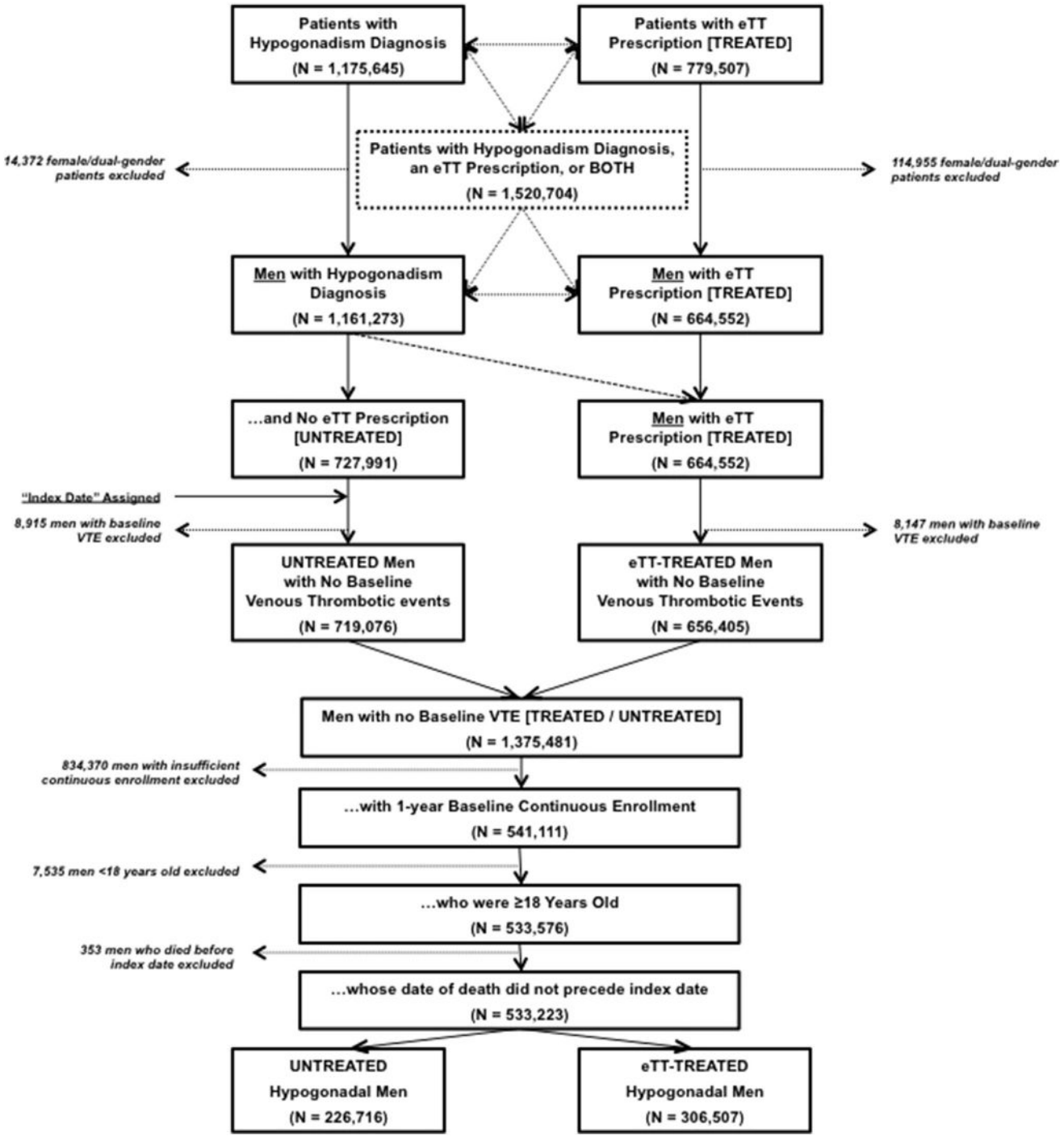

Figure 1. Flow chart shows study patient cohort selection process

Table 1. *Baseline characteristics of populations selected for retrospective 1:1 propensity score matched and nested case-control cohort analysis*

	No. Cohort Analysis (%)			No. Case-Control Analysis (%)*		
	Treated	Untreated	p Value	Cases	Controls	p Value
No. pts	102,650	102,650	—	2894	11,576	—
Mean ± SD age at index	51.50 ± 11.51	51.51 ± 12.36	0.793	54.18 ± 11.07	54.18 ± 11.07	1.000
No. VTE risk factor (%):						
VTE history	143 (0.14)	141 (0.14)	0.906	21 (0.73)	8 (0.07)	0.000
Genetic/congenital	239 (0.23)	238 (0.23)	0.963	—	19 (0.16)	0.021
Ca	9,306 (9.07)	9,430 (9.19)	0.342	11 (0.38)	1,195 (10.32)	0.000
Hypertension	45,480 (44.31)	45,375 (44.20)	0.641	1,444 (49.90)	5,136 (44.37)	0.000
Hypercholesterolemia	50,351 (49.05)	50,430 (49.13)	0.727	1,401 (48.41)	5,507 (47.57)	0.420
Diabetes	20,737 (20.20)	20,815 (20.28)	0.668	793 (27.40)	2,491 (21.52)	0.000
Obesity	6,748 (6.57)	6,603 (6.43)	0.194	228 (7.88)	483 (4.17)	0.000
Renal disease	3,065 (2.99)	3,150 (3.07)	0.274	134 (4.63)	317 (2.74)	0.000
Myocardial infarction	1,503 (1.46)	1,545 (1.51)	0.443	47 (1.62)	236 (2.04)	0.150
Ischemic stroke	2,575 (2.51)	2,654 (2.59)	0.268	105 (3.63)	319 (2.76)	0.013
Congestive heart failure	4,218 (4.11)	4,235 (4.13)	0.850	182 (6.29)	535 (4.62)	0.000
Varicose vein(s)	1,511 (1.47)	1,538 (1.50)	0.622	95 (3.28)	154 (1.33)	0.000
Rheumatoid arthritis	1,185 (1.15)	1,155 (1.13)	0.533	49 (1.69)	112 (0.97)	0.001
Infection	8,917 (8.69)	9,094 (8.86)	0.167	355 (12.27)	995 (8.60)	0.000
Inflammatory bowel disease	824 (0.80)	791 (0.77)	0.410	34 (1.17)	87 (0.75)	0.025
Fracture(s)	836 (0.81)	851 (0.83)	0.714	36 (1.24)	95 (0.82)	0.032
Major trauma	334 (0.33)	342 (0.33)	0.758	8 (0.28)	24 (0.21)	0.479
Injury	2,633 (2.57)	2,625 (2.56)	0.911	96 (3.32)	281 (2.43)	0.007
Surgery	3,178 (3.10)	3,120 (3.04)	0.458	109 (3.77)	391 (3.38)	0.306
Hospitalization greater than 3 days	3,208 (3.13)	3,233 (3.15)	0.752	112 (3.87)	363 (3.14)	0.047
Other comorbidity:						
Mean ± SD Charlson comorbidity score	0.97 ± 1.64	0.98 ± 1.64	0.126	1.09 ± 1.58	1.02 ± 1.63	0.050
No. hypogonadism (%)	85,145 (82.95)	98,919 (96.37)	0.000	1,805 (62.37)	6,999 (60.46)	0.060
No. sexual dysfunction (%)	98,122 (95.59)	98,658 (96.11)	0.000	1,867 (64.51)	7,365 (63.62)	0.373
No. Klinefelter syndrome (%)	211 (0.21)	295 (0.29)	0.000	5 (0.17)	10 (0.09)	0.199
No. sleep disturbance (%)	18,132 (17.66)	17,837 (17.38)	0.087	565 (19.52)	1,795 (15.51)	0.000
No. malaise/fatigue (%)	32,636 (31.79)	32,966 (32.11)	0.118	808 (27.92)	2,983 (25.77)	0.019
No. pituitary disorders (%)	3,125 (3.04)	2,986 (2.91)	0.071	90 (3.11)	346 (2.99)	0.734
No. testicular Ca (%)	433 (0.42)	429 (0.42)	0.891	2 (0.07)	34 (0.29)	0.034
No. prostate disease (%)	15,224 (14.83)	15,170 (14.78)	0.737	468 (16.17)	1,800 (15.55)	0.410
No. prostate Ca (%)	2,478 (2.41)	2,514 (2.45)	0.606	21 (0.73)	322 (2.78)	0.000
No. concomitant medication (%):						
Antihyperlipidemic	40,844 (39.79)	40,556 (39.51)	0.194	1,213 (41.91)	5,022 (43.38)	0.154
Antihypertensive	48,016 (46.78)	47,615 (46.39)	0.076	1,528 (52.80)	5,749 (49.66)	0.003
Diabetes medication	16,225 (15.81)	16,189 (15.77)	0.828	630 (21.77)	1,975 (17.06)	0.000
Erectile dysfunction medication	14,912 (14.53)	14,700 (14.32)	0.183	472 (16.31)	1,904 (16.45)	0.858
Hematological agent	6,812 (6.64)	6,821 (6.64)	0.936	116 (4.01)	876 (7.57)	0.000
Opiate	41,548 (40.48)	41,239 (40.17)	0.165	1,381 (47.72)	4,651 (40.18)	0.000
Psychotropic	35,047 (34.14)	34,453 (33.56)	0.006	1,076 (37.18)	3,938 (34.02)	0.001
Sleep medication	11,469 (11.17)	11,204 (10.91)	0.062	356 (12.30)	1,312 (11.33)	0.145

* Upon review of patient claim records 109 selected cases and 457 selected controls identified to have been treated with eTT via multiple administration routes were excluded from respective group, leaving 2,785 cases and 11,119 controls.

Analysis Results

Cohort. The IR of idiopathic VTE in the treated and untreated cohorts was 3.70 (95% CI 3.23, 4.16) and 3.20/1,000 patient-years (95% CI 2.92, 3.47), respectively (table 2). Adjusted HRs from the cohort analysis demonstrated no significant differences in the incidence of VTE in eTT treated and untreated men with hypogonadism (table 2 and fig. 2). The adjusted HR of the entire retrospective cohort was 1.08 (95% CI 0.91, 1.27, p = 0.378). Upon stratification by routes of eTT administration the adjusted HR for the topical/gel route was 1.07 (95% CI 0.88, 1.29, p = 0.496) and for injectable eTT it was 1.32 (95% CI 0.89, 1.96, p = 0.164). The adjusted HR among patients 65 years or younger and those older than 65 years was 1.09 (95% CI 0.91, 1.29, p = 0.350) and 0.96 (95% CI 0.59, 1.56, p = 0.883), respectively.

Case-Control. The adjusted OR of the case-control analysis was 1.02 (95% CI 0.92, 1.13, p = 0.702) for current eTT exposure and 0.92 (95% CI 0.82, 1.03, p = 0.145) for past eTT exposure (table 3). No analyses by age stratification, routes of administration or interactions between eTT exposure status and routes of eTT administration reached statistical significance (table 3).

Sensitivity. No findings revealed a significant association between eTT and VTE (table 2). Adjusted HRs were consistent with those observed for the cohort analysis of the idiopathic VTE population (table 2).

Table 2. *Retrospective cohort and sensitivity analyses of testosterone use and idiopathic VTE in testosterone treated and 1:1 matched untreated hypogonadal men stratified by age category and administration route*

	eTT Treated Hypogonadal Men		Untreated Hypogonadal Men			
eTT Administration Analysis	No. Pts	Crude IR/1,000 Pt-Yrs (95% CI)	No. Pts	Crude IR/1,000 Pt-Yrs (95% CI)	Adjusted HR (95% CI)*	p Value
Retrospective cohort:						
Any	102,650	3.70 (3.23, 4.16)	102,650	3.20 (2.92, 3.47)	1.08 (0.91, 1.27)	0.378
Age 65 yrs or less	93,292	3.60 (3.12, 4.08)	93,057	3.17 (2.87, 3.46)	1.09 (0.91, 1.29)	0.350
Age greater than 65 yrs	9358	4.67 (2.94, 6.40)	9,593	3.42 (2.55, 4.28)	0.96 (0.59, 1.56)	0.883
Topical/gel	71,095	3.71 (3.17, 4.24)	71,095	3.26 (2.93, 3.60)	1.07 (0.88, 1.29)	0.496
Injection	21,260	4.20 (3.01, 5.39)	21,260	2.69 (2.08, 3.30)	1.32 (0.89, 1.96)	0.164
Transdermal	6949	1.57 (0.19, 2.95)	6,949	3.60 (2.58, 4.62)	0.39 (0.15, 1.06)	0.065
Other/nonspecified	3346	3.99 (1.38, 6.59)	3,346	3.46 (1.94, 4.98)	1.14 (0.46, 2.77)	0.781
Sensitivity:						
Any	102,637	11.07 (10.26, 11.87)	102,637	11.42 (10.89, 11.95)	0.93 (0.85, 1.03)	0.151
Topical/gel	71,110	10.90 (9.97, 11.82)	71,110	11.54 (10.90, 12.17)	0.93 (0.83, 1.03)	0.161
Injection	21,228	12.48 (10.42, 14.53)	21,228	10.82 (9.59, 12.06)	1.05 (0.84, 1.31)	0.662
Transdermal	6,965	9.12 (5.80, 12.45)	6,965	11.60 (9.77, 13.43)	0.65 (0.42, 1.02)	0.061
Other/nonspecified	3,334	10.32 (6.10, 14.53)	3,334	11.54 (8.76, 14.32)	1.11 (0.65, 1.90)	0.704

* Adjusted for treatment and baseline characteristics commonly associated with VTE risk, including but not limited to age, infection(s), previous VTE, obesity, cardiovascular disorders, cancer and medication use for diabetes and/or hematological disorders.

Despite consistency on case-control analysis a few sensitivity analyses reached statistical significance. 1) The adjusted OR of any past eTT exposure and of past exposure to topical/gel eTT was 1.08 (95% CI 1.02, 1.15, p = 0.010) and 1.09 (95% CI 1.02, 1.16, p = 0.011), respectively, in the entire population. 2) The adjusted OR of any injectable eTT exposure was 1.10 (95% CI 1.01, 1.19, p = 0.023) and further for current injectable exposure the adjusted OR was 1.15 (95% CI 1.04, 1.26, p = 0.006, table 3).

Additional sensitivity analyses included those using propensity score stratification methods (HR 1.02, 95% CI 0.90, 1.15, p = 0.799, supplementary table 2, http://jurology.com/). Applying intent to treat analysis yielded nonsignificant results (HR 0.96, 95% CI 0.85, 1.08, p = 0.461, supplementary table 3, http://jurology.com/).

DISCUSSION

This real-world study with an incident user design demonstrated no significant association between eTT and an incident risk of idiopathic VTE via a retrospective cohort design (HR 1.08, 95% CI 0.91, 1.27, p = 0.378) or a nested case-control design (current and past eTT exposure OR 1.02, 95% CI

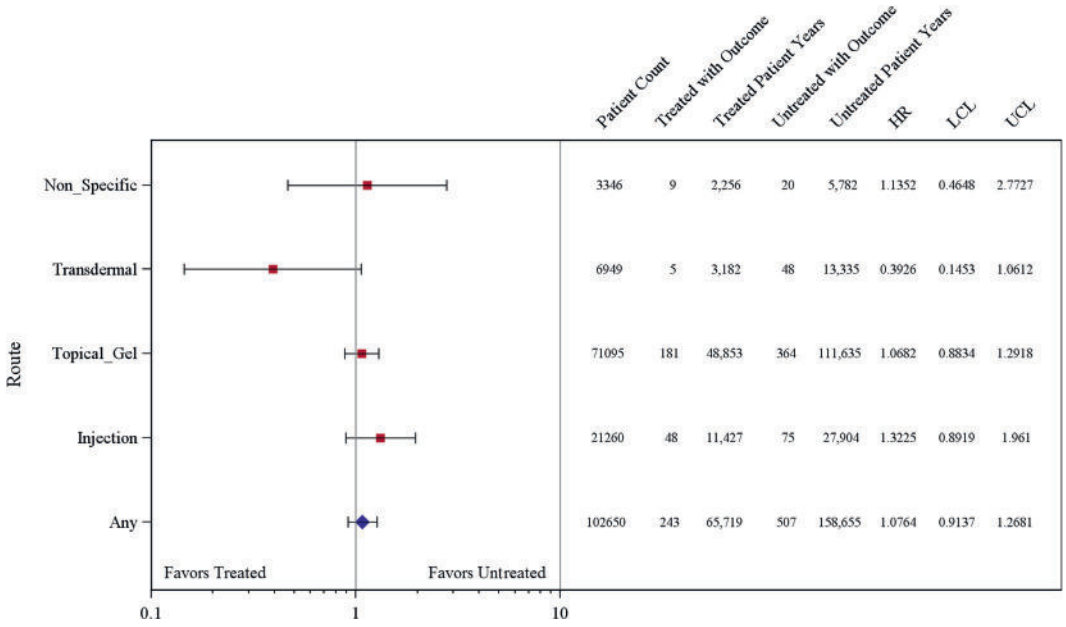

Figure 2. Adjusted HRs with 95% CIs from Cox proportional regression analysis of retrospective cohort population with eTT and idiopathic VTEs stratified by eTT administration route. *LCL*, low 95% CI limit. *UCL*, high 95% CI limit.

Table 3. *Conditional logistic regression nested case-control and sensitivity analyses of exogenous testosterone use and idiopathic VTE stratified by exposure status and eTT administration route*

			Entire Population		Age 65 or Less		Age Greater Than 65	
eTT Analysis	No. Cases*	No. Controls	OR (95% CI)†	p Value	OR (95% CI)†	p Value	OR (95% CI)†	p Value
Nested case-control:								
Current vs no	2,785	11,119	1.02 (0.92, 1.13)	0.702	1.05 (0.94, 1.17)	0.408	0.83 (0.60, 1.13)	0.235
Past vs no			0.92 (0.82, 1.03)	0.145	0.93 (0.82, 1.05)	0.230	0.86 (0.62, 1.19)	0.356
Topical/gel vs no	1,223	4,977	0.95 (0.86, 1.05)	0.300	0.98 (0.88, 1.09)	0.672	0.77 (0.58, 1.03)	0.078
Injectable vs no	316	1,077	1.11 (0.96, 1.29)	0.163	1.13 (0.96, 1.33)	0.133	1.01 (0.68, 1.52)	0.954
Transdermal vs no	123	505	0.91 (0.73, 1.13)	0.389	0.94 (0.74, 1.19)	0.611	0.78 (0.44, 1.40)	0.406
Other/nonspecified vs no	65	255	1.00 (0.75, 1.33)	0.983	0.95 (0.69, 1.31)	0.749	1.28 (0.62, 2.68)	0.505
Current topical/gel vs no use/exposure	707	2,778	1.00 (0.89, 1.12)	0.990	1.03 (0.92, 1.17)	0.590	0.78 (0.54, 1.12)	0.170
Current injection vs no use/exposure	214	708	1.15 (0.97, 1.38)	0.120	1.18 (0.98, 1.43)	0.080	0.94 (0.55, 1.61)	0.820
Current transdermal vs no use/exposure	49	229	0.80 (0.57, 1.12)	0.200	0.89 (0.62, 1.26)	0.500	0.36 (0.12, 1.13)	0.080
Current other/nonspecified vs no use/exposure	33	122	0.99 (0.66, 1.48)	0.960	0.90 (0.58, 1.40)	0.650	2.21 (0.74, 6.57)	0.160
Past topical/gel vs no use/exposure	516	2,199	0.88 (0.78, 1.00)	0.060	0.90 (0.79, 1.04)	0.140	0.77 (0.53, 1.11)	0.150
Past injection vs no use/exposure	102	369	1.03 (0.81, 1.32)	0.790	1.03 (0.79, 1.35)	0.830	1.08 (0.62, 1.88)	0.800
Past transdermal vs no use/exposure	74	276	0.99 (0.74, 1.31)	0.920	0.98 (0.72, 1.34)	0.890	1.12 (0.57, 2.21)	0.740
Past other/nonspecified vs no use/exposure	32	133	1.00 (0.66, 1.50)	0.990	1.00 (0.63, 1.56)	0.980	0.86 (0.32, 2.34)	0.770
Sensitivity:								
Current vs no	10,205	40,989	1.03 (0.97, 1.09)	0.300	1.04 (0.97, 1.11)	0.250	0.98 (0.87, 1.10)	0.670
Past vs no			1.08 (1.02, 1.15)	0.010	1.06 (0.99, 1.14)	0.110	1.13 (1.01, 1.26)	0.030
Topical/gel vs no	4,549	18,004	1.05 (0.99, 1.10)	0.087	1.04 (0.98, 1.10)	0.232	1.07 (0.97, 1.18)	0.203
Injectable vs no	1,118	3,947	1.10 (1.01, 1.19)	0.023	1.13 (1.03, 1.24)	0.012	1.00 (0.86, 1.17)	0.989
Transdermal vs no	525	1,878	1.07 (0.95, 1.19)	0.262	1.03 (0.90, 1.17)	0.670	1.11 (0.91, 1.36)	0.314
Other/nonspecified vs no	237	1,079	0.97 (0.83, 1.13)	0.664	0.93 (0.78, 1.12)	0.463	1.03 (0.78, 1.35)	0.849
Current topical/gel vs no use/exposure	2,319	9,575	1.01 (0.95, 1.08)	0.750	1.01 (0.94, 1.09)	0.725	0.98 (0.86, 1.12)	0.762
Current injection vs no use/exposure	708	2,410	1.15 (1.04, 1.26)	0.006	1.20 (1.07, 1.34)	0.001	0.94 (0.76, 1.16)	0.547
Current transdermal vs no use/exposure	216	781	0.98 (0.83, 1.15)	0.775	0.94 (0.78, 1.15)	0.564	1.00 (0.72, 1.38)	0.995
Current other/nonspecified vs no use/exposure	109	518	0.91 (0.73, 1.13)	0.381	0.86 (0.66, 1.11)	0.239	1.03 (0.68, 1.57)	0.875
Past topical/gel vs no use/exposure	2,230	8,429	1.09 (1.02, 1.16)	0.011	1.07 (0.99, 1.15)	0.088	1.14 (1.01, 1.29)	0.028
Past injection vs no use/exposure	410	1,537	1.02 (0.90, 1.15)	0.739	1.00 (0.86, 1.16)	0.954	1.07 (0.87, 1.33)	0.514
Past transdermal vs no use/exposure	309	1,097	1.13 (0.99, 1.31)	0.079	1.10 (0.93, 1.30)	0.278	1.18 (0.92, 1.52)	0.184
Past other/nonspecified vs no use/exposure	128	561	1.03 (0.84, 1.26)	0.812	1.02 (0.79, 1.31)	0.899	1.03 (0.73, 1.46)	0.860

* Multiple administration routes excluded from analysis.
† Adjusted for imbalances in baseline characteristics commonly associated with VTE risk in study population subgroups with baseline characteristics selected as covariates including those from categories age, infection(s), previous VTE, obesity, cardiovascular disorders, cancer, diabetes medication use and use of medications for hematological disorders with specific covariates varying according to patient subgroup under investigation.

0.92, 1.13, p = 0.702 and OR 0.92, 95% CI 0.82, 1.03, p = 0.145, respectively). Furthermore, none of the eTT routes of administration (injectable, gel or patch) were associated with an increased idiopathic VTE risk. These findings are considered robust and consistent because of the new user study design, large sample size, 2 complementary study designs and analytical methods to control for confounding factors, and the inclusion of various sensitivity analyses. To address this public health issue, which concerns patients and physicians, the study results can be extrapolated to the general population but not patients at high risk (eg those with preexisting thrombophilia) because patients with baseline VTE were excluded from both analyses.

The results of the sensitivity analyses were generally consistent with the results of the primary analyses. Some exceptions existed when studying the overall VTE population. Specifically in contrast to the cohort analysis, the nested case-control analysis revealed some statistically significant findings among past eTT exposures and any injectable eTT users. These findings could be attributable to several factors. Compared to the idiopathic VTE population patients in the overall VTE population were more likely to experience other proxy risk factors for VTE such as prolonged immobility, trauma and injury. Although the fully adjusted statistical model included many of these terms as covariates, it is possible that other unmeasured confounding factors may exist. Additionally this significant association was observed in patients who were not current eTT users and did not receive any eTT (topical solution) at least 90 days before the onset of VTE. Thus, it is unlikely that these VTEs were associated with eTT. Lastly, the dissimilar findings for any injectable exposure vs other routes may be due to a difference in pharmacokinetics as suggested by a recently published study.[22] Safety profiles may vary for different testosterone delivery mechanisms with altered pharmacokinetics (ie injections cause spikes in testosterone levels, and transdermal patches and gels cause subtle but sustained increases).

Notably our analyses replicated a recent case control analysis by Baillargeon et al, who reported that filling a prescription for eTT was not associated with an increased risk of VTE in almost 31,000

middle-aged and elder men.[10] Our findings further support their observations using a retrospective cohort study design, which strengthen the findings via examining the temporal relationship analysis. Both of these studies add value in that they are large, general population based, comparative safety studies, and offer a superior opportunity to evaluate drug safety than post-marketing cases and previously published case series.[11,12]

Further we examined idiopathic VTE and overall VTE study outcomes. The reason that idiopathic VTE was chosen as the primary outcome was to preclude confounding factors (independent of drug use) related to VTE such as trauma, injury and hospitalization, which are strong predictors, possibly diluting the association with the drug.

Study findings were contrary to an assumed link between eTT and incident VTE, which was thought to be mediated via increases in hematocrit and/or polycythemia based on evidence for increased thromboembolic events in patients with primary polycythemia vera.[4–7] It is also theorized that the risk of testosterone induced polycythemia (increased hematocrit value) may increase blood viscosity, leading to an increased risk of thromboembolic events.[23] One group hypothesized that in men with previously undiagnosed familial thrombophilia (factor V Leiden) VTE developed while on eTT due to peripheral conversion of testosterone to estradiol.[11] Although the results of the current study do not support these mechanisms,[11] the study results are consistent with those of other studies that did not show an association between endogenous sex hormone levels and a 10-year risk of VTE in middle-aged and older men[8] nor any significant association between endogenous testosterone or estradiol levels and the risk of VTE, DVT or PE in 9,331 men and women in the Copenhagen City Heart Study.[9]

Nevertheless, the results of our study should be interpreted with consideration of its limitations. While claims data are valuable for the effective examination of disease outcomes and treatment patterns, claims data are collected for the purpose of payment and not research. The presence of a claim for a filled prescription does not indicate that the medication was consumed or taken as prescribed. The presence or absence of disease may not be accurate as the diagnostic code may be incorrectly coded or included as a rule out criterion rather than as actual disease. The observational nature of this study precluded the ability to use treatment randomization and, thus, findings may be subject to changes due to residual confounding factors. Several important covariates were missing in the claims database, including but not limited to body weight and genotypes for inheritable hypercoagulation conditions (eg protein C or protein S deficiency).

Study outcomes were not validated through chart validation but rather by 1) adapting the FDA recommended/validated algorithm, which yielded a positive predictive value between 65% and 95%, 2) adjudicating some patient claims to classify those with idiopathic VTE because misclassification cases may exist and 3) combining PE and DVT as the study outcome to improve the positive predictive value.[16] Although the IR of the study outcome was higher than reported in the current literature, there is no evidence suggesting that the false-positive cases would be distributed unevenly between the study groups. Therefore, the drug event association was assumed to be unchanged.

Further the comparison group was defined as an inactive comparator group that was not treated but the untreated cohort was formed to match eTT treated patients based on baseline characteristics through a propensity score model[19] with the purpose of improving comparability and reducing confounding. Due to the lack of a specific ICD-9 code the most frequently used codes were chosen. Although others may exist, they would not appreciably change the size of the study population.

Finally this claims database lacked comprehensive laboratory data to further substantiate exposure (through serum testosterone levels), potential mechanisms of a possible increased VTE risk (through elevated hematocrit) or clinical presentation of symptoms (eg fatigue). While testosterone deficiency among the treated cohort was unconfirmed, we approached the research question with the assumption that adult males prescribed eTT were considered by their physicians to have testosterone deficiency. Furthermore a baseline endogenous total serum testosterone level is not needed because untreated hypogonadism is not a well established predictor of VTE as suggested by previous literature.[1–3] Therefore, the lack of laboratory measures should not confound the association between eTT and VTE.

CONCLUSIONS

The results of the analyses in this study using the MarketScan Databases showed no significant association between eTT administration and incidents of idiopathic VTE or overall VTE. However, the 2 study designs yielded discrepant findings for the association between injectable formulations and overall VTE risk.

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