MAYO CLINIC

Risk of Venous Thromboembolism in Men Receiving Testosterone Therapy

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Abstract

Objective: To examine the risk of venous thromboembolism (VTE) associated with exposure to testosterone therapy in middle-aged and older men.

Patients and Methods: We conducted a case-control study of 30,572 men 40 years and older who were enrolled in one of the nation's largest commercial insurance programs between January 1, 2007, and December 31, 2012. *Cases* were defined as men who had a primary diagnosis of VTE and received an anticoagulant drug in the 60 days after their diagnoses. Cases were matched with 3 controls on event/index month, age, geographic region, diagnosis of hypogonadism, and diagnosis of any underlying prothrombotic condition. Conditional logistic regression analysis was used to calculate adjusted odds ratios (aORs) and 95% CIs for the risk of VTE associated with previous exposure to testosterone therapy.

Results: Exposure to testosterone therapy in the 15 days before the event/index date was not associated with an increased risk of VTE (aOR, 0.90; 95% CI, 0.73-1.12). None of the specific routes of administration examined were associated with an increased risk of VTE (topical [aOR, 0.80; 95% CI, 0.61-10.41], transdermal [aOR, 0.91; 95% CI, 0.38-2.16], and intramuscular [aOR, 1.15; 95% CI, 0.80-1.64]). These findings persisted using exposure windows that extended to 30 and 60 days before the event/index date.

Conclusion: Having filled a prescription for testosterone therapy was not associated with an increased risk of VTE in commercially insured middle-aged and older men. These findings may provide clinically relevant information about the benefit-risk assessment for men with testosterone deficiency considering treatment.

 ■ Mayo Clin Proc. 2015;90(8):1038-1045

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Testosterone therapy for middle-aged and older men in the United States has increased more than 3-fold over the past decade.[1] In recent years, several case series studies[2-4] have raised concern about a link between testosterone therapy and venous thromboembolism (VTE). In 2014, both the US Food and Drug Administration (FDA)[5] and the Health Canada[6] required manufacturers to add a warning about the potential risks of VTE—including deep vein thrombosis (DVT) and pulmonary embolism (PE)—to the label of all testosterone products on the basis postmarketing surveillance.

Research on the association between testosterone and VTE is conflicting. An increase in VTE is biologically plausible, given that testosterone therapy increases hematocrit with associated increased blood viscosity,[2,3] platelet aggregation,[3,7] and the risk of developing polycythemia.[2,3,7] In addition, several case series[2-4] have reported VTE in patients with high rates of underlying familial and acquired thrombophilia who received testosterone therapy. However, there is also evidence that testosterone therapy may have protective endothelial actions.[8-11] Two large population-based studies[12,13] reported that endogenous testosterone levels were not associated with VTE. To date, no comparative studies examining an association between testosterone therapy and VTE have been reported. Given that VTE kills as many as 180,000 Americans per year—more than the number of people who die of breast, prostate, colon, and skin cancers combined[14]—even a small increase in risk holds broad clinical and public health relevance. We therefore conducted a case-control study using one of the nation's largest commercial insurance databases to examine the risk of VTE associated with exposure to testosterone therapy in middle-aged and older men.

Mayo Clin Proc. ■ August 2015;90(8):1038-1045 ■ http://dx.doi.org/10.1016/j.mayocp.2015.05.012
www.mayoclinicproceedings.org ■

PATIENTS AND METHODS

Data Source

This case-control study used administrative health data from Clinformatics Data Mart (CDM; OptumInsight), a database of one of the nation's largest commercial health insurance programs. CDM data have been used to examine drug toxicity and health services in numerous studies.[15-18] Persons enrolled in this insurance program may be included in either a fee-for-service plan or a managed care plan, which includes health maintenance organizations, preferred provider organizations, and exclusive provider organizations. For each of these plans, physicians are required to submit complete claims to receive reimbursement. During the study period (2007-2012), a total of 15,345,323 men 40 years and older were included in the database. We used a combination of outpatient, inpatient, and pharmacy claims data. The pharmacy database contains eligibility and claims information for medications from retail pharmacies through a member's pharmacy benefit. For each medication, the database contains medication name, date of fill, formulation (eg, oral, transdermal, and injectable), dose, quantity, and days of supply. This study was approved by the institutional review board of the University of Texas Medical Branch at Galveston.

Cases

We identified 7643 cases who met the following criteria: (1) were diagnosed with DVT or PE at any time during the study period (January 1, 2007, through December 31, 2012) on the basis of *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) codes in the primary diagnosis position; and (2) received at least 1 prescription for an anticoagulant or received an intravascular vena cava filter in the 60 days after their diagnosis of VTE. The *ICD-9-CM* codes identifying VTE include DVT (codes 451.1x, 451.2x, 451.81, 451.9x, and 453.4x) and PE (code 415.1x). The date of diagnosis served as the event date for all analyses.

Controls

We identified 22,929 controls who were not diagnosed with DVT or PE at any time during the study period by using the criteria described above. Using the 3-to-1 match criteria, we used the following stepwise algorithm, broadening the matching criterion at each stage. First, we matched 22,402 (97.7%) of controls with cases on event/index month, age at year of diagnosis/index date (±1 year), geographic region (Midwest, Northeast, South, and West), a diagnosis of hypogonadism (*ICD-9-CM* code 257.xx), and a diagnosis of any prothrombotic disease (*ICD-9-CM* codes 289.81, 270.4, and 238.4). Subsequently, we matched 298 (1.3%) of the controls with cases on event month, broad range of age (±5 years), diagnosis of hypogonadism, and diagnosis of any prothrombotic disease; we matched the remaining 1 (1.0%) of controls with cases on event month, 5-year age range, and region.

Exclusion Criteria for Cases and Controls

In selecting cases and controls, we excluded persons younger than 40 years at their event/index date, had less than 12 months continuous enrollment in CDM before their event/index date or less than 60 days continuous enrollment in CDM after their event/index date, had a diagnosis of VTE in the 12 months before their event/index date, were hospitalized in the 30 days before their event/index date, had a diagnosis of cancer in the 12 months before their event/index date, or had a prescription for an anticoagulant in the 90 days before their event/index date.

Exposure

Patients whose most recent prescription period for any testosterone therapy overlapped by at least 1 day within the 15-day period before the event/index date were defined as *exposed*. We included all doses and formulations of testosterone therapy in our analyses by using National Drug Codes for topical gel, transdermal patch, subcutaneous pellets, and oral formulations (see the Supplemental Appendix, available online at http://www.mayoclinicproceedings.org) and Healthcare Common Procedure Coding System codes for injectable formulations (see the Supplemental Appendix). Testosterone therapy exposure was determined by assessing the number of days in a given prescription period (eg, 30 days) that followed the most recent prescription or injection date. Men who received intramuscular testosterone therapy were considered

to have had 30 days of exposure after the injection date. Those who received a subcutaneous pellet were considered to have had 120 days of exposure after the implantation date.

Covariates

We examined all conditions included in the Elixhauser comorbidity index,[19] except cancer. We adjusted only for medical conditions for which cases and controls had statistically significant differences in prevalence ($P<.01$) during the 12-month look-back period (Table 1). Each condition was examined as a separate covariate.

We also examined patients' use of the following 4 classifications of medications reported to be associated with VTE: corticosteroids (prednisone, dexamethasone, methylprednisolone, hydrocortisone, prednisolone, and betamethasone); megestrol acetate; anticoagulants (abciximab, anagrelide, cilostazol, clopidogrel, dipryidamole, eptifibatide, prasugrel, ticagrelor, ticlopidine, tirofiban, and vorapaxar); and nonsteroidal anti-inflammatory drugs (NSAIDs) (antipyrine, aspirin, bromfenac, celecoxib, choline salicylate, diclonfenac, diclonfenac sodium, diflunisal, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac tromethamine, magnesium salicylate, meclofenamate, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, phenylbutazone, piroxicam, rofecoxib, salicylamide, salicylsalicylic acid, sodium salicylate, sodium thiosalicylate, sulindac, tolmetin, and valdecoxib). A prescription for any potential confounding drug at least 1 day within the 15-day period before the event/index date was defined as *use of a confounding drug*.

Statistical Analyses

We used conditional logistic regression models to estimate the risk of VTE associated with testosterone therapy exposure, expressed as adjusted odds ratios (aORs) with 95% CIs. All multivariable analyses were adjusted for all comorbid conditions that were not balanced across cases and controls and exposure to all above-listed potentially confounding drug classes. To assess whether the association between testosterone therapy and VTE varied by the presence of any prothrombotic disease, we tested the interaction between testosterone therapy and prothrombotic disease in the conditional logistic regression model. To test the robustness of our findings, we performed sensitivity analyses examining exposure windows of 30 and 60 days before the event/index date. For example, a 30-day window would mean that a man whose most recent prescribed testosterone supply was completed on July 1 would still be considered exposed if he experienced a VTE event as late as July 31. All analyses were performed using SAS version 9.3 (SAS Institute Inc).

RESULTS

Table 1 shows that 4 of the 5 matching variables—year of diagnosis/index date, age, region, and diagnosis of hypogonadism—were distributed evenly across cases and controls. The fifth matching variable, diagnosis of any prothrombotic disease, was more prevalent among cases (84; 1.1%) than controls (183; 0.8%). Examination of comorbid diseases exhibited that cases had a higher prevalence of cardiac arrhythmia, congestive heart failure, pulmonary circulation disease, paralysis, neurological disorders, chronic pulmonary disease, coagulopathy, obesity, electrolyte disorder, and alcohol abuse. Controls had a higher prevalence of uncomplicated hypertension, hypothyroidism, diabetes with and without complications, and depression.

Table 2 shows that exposure to testosterone therapy in the 15 days before the event/index date was not associated with an increased risk of VTE (aOR, 0.90; 95% CI, 0.73-1.12). We also examined the association between the route of administration of testosterone therapy and VTE. Relative to the unexposed referent group, none of the specific routes of administration examined (topical [aOR, 0.80; 95% CI, 0.61-10.41], transdermal [aOR, 0.91; 95% CI, 0.38-2.16], and intramuscular [aOR, 1.15; 95% CI, 0.80-1.64]) were associated with an increased risk of VTE. We also examined the use of potentially confounding medications reported to be associated with an increased risk of VTE (Table 2). Exposure to corticosteroids (aOR, 3.38; 95% CI, 2.94-3.89), megastrol acetate (aOR, 14.07; 95% CI, 3.13-63.24), and NSAIDs (aOR, 1.65; 95% CI, 1.50-1.82) were all associated with a statistically significant increased risk of VTE. The use of antiplatelet agents was protective against VTE (aOR, 0.67; 95% CI, 0.58-0.77). Finally, the interaction between testosterone therapy and prothrombotic disease was not statistically significant ($P=.94$). For each of the above analyses, we conducted

Mayo Clin Proc. ■ August 2015;90(8):1038-1045 ■ http://dx.doi.org/10.1016/j.mayocp.2015.05.012
www.mayoclinicproceedings.org

TABLE 1. Baseline Characteristics for Cases and Matched Controls Identified Between 2007 and 2012

Characteristic	No. (%)		P[a]
	Matched controls[b]	Cases	
All patients	22,929 (100)	7643 (100)	
Age at diagnosis (y)			
40-49	5769 (25.16)	1923 (25.16)	1.0
50-59	8679 (37.85)	2893 (37.85)	
60-69	5853 (25.53)	1951 (25.53)	
≥70	2628 (11.46)	876 (11.46)	
Year of diagnosis/index date			
2007	3210 (14.00)	1070 (14.00)	1.0
2008	3615 (15.77)	1205 (15.77)	
2009	4225 (18.42)	1408 (18.42)	
2010	4209 (18.36)	1403 (18.36)	
2011	3885 (16.94)	1295 (16.94)	
2012	3786 (16.51)	1262 (16.51)	
Region			
Midwest	6604 (28.80)	2200 (28.78)	.99
Northeast	1994 (8.70)	662 (8.66)	
South	9904 (43.19)	3302 (43.02)	
West	4427 (19.31)	1479 (19.35)	
Matched medical conditions			
Hypogonadism	890 (3.88)	311 (4.07)	.49
Any prothrombotic condition	183 (0.80)	84 (1.10)	.01
Comorbidity index			
Cardiac arrhythmia	1633 (7.11)	814 (10.65)	<.001
Congestive heart failure	573 (2.50)	269 (3.52)	<.001
Valve disease	309 (1.35)	93 (1.22)	.38
Pulmonary circulation disease	32 (0.14)	159 (2.08)	<.001
Peripheral vascular disease	247 (1.08)	103 (1.35)	.06
Hypertension (uncomplicated)	8885 (38.75)	2131 (27.97)	<.001
Hypertension (complicated)	519 (2.26)	151 (1.98)	.136
Paralysis	20 (0.09)	22 (0.29)	<.001
Neurological disorders	236 (1.03)	116 (1.52)	.005
Chronic obstructive pulmonary disease	2001 (8.73)	762 (9.97)	<.001
Hypothyroidism	948 (4.13)	213 (2.79)	<.001
Renal failure	309 (1.35)	110 (1.44)	.55
Liver disease	265 (1.16)	89 (1.16)	.95
Peptic ulcer	27 (0.12)	6 (0.08)	.36
HIV/AIDS	103 (0.45)	32 (0.42)	.72
Rheumatoid arthritis	204 (0.89)	73 (0.96)	.60
Coagulopathy	138 (0.60)	98 (1.20)	<.001
Obesity	642 (2.80)	273 (3.57)	<.001
Weight loss	74 (0.32)	33 (0.43)	.16
Diabetes without complications	3270 (14.26)	707 (9.25)	<.001
Diabetes with complications	710 (3.10)	151 (1.98)	<.001
Fluid and electrolyte disorders	345 (1.50)	198 (2.59)	<.001
Chronic blood loss anemia	69 (0.30)	27 (0.35)	.478
Deficiency anemia	288 (1.26)	93 (1.22)	.78
Alcohol abuse	271 (1.18)	122 (1.60)	.005
Drug abuse	68 (0.30)	30 (0.40)	.19
Psychosis	40 (0.17)	13 (0.17)	.94
Depression	1526 (6.65)	380 (4.97)	<.001

[a]Comorbid conditions were measured using the factors that comprise the Elixhauser comorbidity index, except cancer.[20]

[b]We matched 97.7% of controls with cases on event/index month, age at year of diagnosis/index, geographic region (Midwest, Northeast, South, and West), a diagnosis of hypogonadism, and a diagnosis of prothrombotic disease; 1.3% of the controls were matched with cases on event/index month, broad range of age (±5 y), diagnosis of hypogonadism, and diagnosis of prothrombotic disease; and the remaining 1.0% were matched with cases on event month, 5-y age range, and region.

TABLE 2. Association Between Testosterone Therapy and Venous Thromboembolism[a]

Drug	No. (%)		Unadjusted	Adjusted[b]
	Controls[c]	Cases	OR (95% CI)	OR (95% CI)
Testosterone therapy prescription[d]				
No	22,424 (97.80)	7485 (97.93)	Referent	Referent
Yes	505 (2.20)	158 (2.07)	0.92 (0.75-1.13)	0.90 (0.73-1.12)
Route of administration[e]				
No exposure	22,424 (97.80)	7485 (97.93)	Referent	Referent
Topical	331 (1.44)	90 (1.18)	0.80 (0.62-1.04)	0.80 (0.61-10.4)
Transdermal	25 (0.11)	8 (0.10)	0.95 (0.43-2.12)	0.91 (0.38-2.16)
Intramuscular	140 (0.61)	56 (0.80)	1.17 (0.84-1.64)	1.15 (0.80-1.64)
Use of other medications[f]				
Antiplatelets	1086 (4.74)	269 (3.52)	0.73 (0.63-0.85)	0.67 (0.58-0.77)
Corticosteroid	403 (1.76)	485 (6.35)	3.76 (3.29-4.31)	3.38 (2.93-3.89)
Megestrol acetate	2 (0.01)	15 (0.20)	22.52 (5.15-98.39)	14.07 (3.13-63.24)
NSAIDs	1362 (5.94)	728 (9.53)	1.66 (1.52-1.83)	1.65 (1.50-1.82)

[a]NSAID = nonsteroidal anti-inflammatory drug; OR = odds ratio.

[b]Multivariate analyses were adjusted for all drug groups and medical conditions that were not balanced between cases and controls ($P<.01$), including any prothrombotic condition, cardiac arrhythmia, congestive heart failure, pulmonary circulation disease, uncomplicated hypertension, paralysis, neurological disorders, chronic pulmonary disease, hypothyroidism, coagulopathy, obesity, diabetes with and without complications, fluid and electrolyte disorders, alcohol abuse, and depression.

[c]See the footnote in Table 1 for a description of how controls were matched with cases.

[d]Patients whose most recent prescription period for any testosterone therapy overlapped by at least 1 d within the 15-d period before the event/index date were defined as *exposed*.

[e]In patients who met the exposure criterion, we examined 3 routes of administration: topical, transdermal, and intramuscular. Patients were classified according to their most recent testosterone prescription. The sample sizes in the categories of oral and pellet administration were too small to ensure a reasonable level of statistical power and therefore not reported.

[f]Patients whose most recent prescription period for any of the 4 potentially confounding medications overlapped by at least 1 d within the 15-d period before the event/index date were defined as *exposed*.

sensitivity analyses using exposure windows of 30 and 60 days. The results were similar across all 3 exposure windows (15, 30, and 60 days).

DISCUSSION

In this case-control study of 30,572 middle aged and older men, we found that having filled a prescription for testosterone therapy was not associated with an increased risk of VTE. In addition, none of the specific routes of administration examined—topical, transdermal, or intramuscular—were associated with an increased risk of VTE. The association between testosterone therapy and VTE did not appear to vary by the presence of underlying prothrombotic disease. However, our exclusion of all men who received anticoagulant therapy in the 3 months before the event/index date or had a diagnosis of VTE in the previous 12 months may have substantially reduced the number of men diagnosed with prothrombotic disease in our study sample. This finding should therefore be interpreted cautiously. Using matching and statistical adjustment, we accounted for multiple potentially confounding factors, including age, region, and calendar year, as well as underlying medical conditions and medications. Our primary findings persisted using prescription dates that extended to 30 and 60 days before the VTE diagnosis or index date.

This investigation is the first comparative study to evaluate a possible link between testosterone therapy and VTE and addresses widespread international concern about this issue. In 2014, both the US FDA[5] and the Health Canada[6] required manufacturers of all approved testosterone products to add a warning about the potential risks of VTE to the label.

The FDA had previously warned about a testosterone therapy–associated increase in VTE in men with a diagnosis of polycythemia.[14] The June 2014 FDA warning, however, was based on reports of VTE in men without polycythemia.[14]

An increase in VTE risk is biologically plausible, given that testosterone therapy increases hematocrit with associated increased blood viscosity,[2,3] platelet aggregation,[2,3,7] and the risk of polycythemia[2,7,21] and has been shown to

Mayo Clin Proc. ■ August 2015;90(8):1038-1045 ■ http://dx.doi.org/10.1016/j.mayocp.2015.05.012
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increase thromboxane A2 concentrations in platelets.[21] Testosterone therapy also increases circulating estrogens[2,22] that may play a role in thrombotic events.[23] Given that testosterone is converted by aromatization to estradiol, it may be prothrombotic by the same mechanism as estrogen-based therapies.[23] However, testosterone may also reduce the risk of VTE by way of protective endothelial actions.[8-11]

Our findings were generally consistent with 2 population-based studies[12,13] that reported no association between endogenous testosterone and VTE. In their study of 4673 men from Denmark, Holmegard et al[12] reported that high endogenous testosterone levels were not associated with an increased risk of DVT, PE, or recurrent VTE. Likewise, in their study of 1350 middle-aged and older men from Norway, Svartberg et al[13] reported that endogenous total and free testosterone levels were not associated with an increased risk of VTE.

To date, little published information is available about a potential link between testosterone therapy and VTE. Several case series[2-4] have reported VTE in patients with high rates of underlying familial and acquired thrombophilia who received testosterone therapy. However, because all the individuals in the VTE groups were found to have previously undiagnosed thrombophilia and because the studies did not include control groups of nontestosterone users with comparable rates of underlying thrombophilia, it was not possible to determine the extent to which VTE was associated with testosterone use versus underlying thrombophilia or to examine the interaction between testosterone therapy and thrombophilia. In addition, a recent study by Friedman et al[24] reported that testosterone therapy interacted with thrombophilia to increase the risk of VTE. The design of this cross-sectional study—which relied on 4 convenience samples of patients—did not allow a statistical analysis of an interaction effect between testosterone therapy and underlying thrombophilia leading to VTE. Given the broad clinical and public health relevance of this issue, it will be important for future investigations—particularly prospective comparative studies of testosterone users and nonusers—to rigorously examine this aspect.

The results of our study may have been affected by several limitations. First, the study outcome was defined as VTE on the basis of *ICD-9-CM* codes. Such codes are not always accurate or complete.[20] It is possible that some of the cases we identified may have been based on misclassified data. However, our requirement that all VTE cases subsequently received at least 1 prescription for an anticoagulant or an intravascular vena cava filter should have improved the validity of this classification. Second, the commercial insurance pharmacy plan used by the study participants did not cover over-the-counter medications. Hence, the database that we used contained no information on coadministration of these drugs; many of them, including aspirin and NSAIDs, may affect the risk of VTE. Third, reliance on claims data precluded assessment of a number of potential confounding factors such as diet, alcohol use, and use of herbal supplements. Fourth, our data provide information on the date the prescription was filled but not on the date it was purchased or picked up by the patient. It is possible, therefore, that some of the drug exposure periods used in this study underestimated the true medication exposure period. Our sensitivity analyses assessing 30- and 60- day exposure windows, however, help to address this issue. Fifth, our database lacked information on several important risk factor variables, such as race/ethnicity and smoking status. The incidence of VTE has been reported to vary substantially across different race/ethnic groups, with particularly high rates among African Americans.[25,26] Likewise, smoking status is an important risk factor for VTE.[27] We included chronic obstructive pulmonary disease as a covariate in our analyses to address the latter bias. Sixth, men who are prescribed testosterone therapy may be more likely to be prescribed other medications, some of which may be associated with VTE. Our exclusion of all men who received anticoagulant therapy in the 90 days before the event/index date and our adjustment for other medications associated with VTE should have mitigated this bias. Seventh, our case restriction to men who received anticoagulation in the 30 days after the treatment did not allow inclusion of patients with immediately fatal VTE in our study. Finally, to reduce the likelihood of confounding by previous VTE or associated medication use, we restricted our case definition to men with no history of VTE in the previous 12 months and no anticoagulant use in the

previous 3 months. This study design limited our ability to examine the effect of testosterone therapy on patients with chronic or recurrent VTE and to assess a potential interaction effect between testosterone therapy and prothrombotic disease. Additional studies, particularly those that use longitudinal cohort designs, are needed to further examine these effects.

Despite these limitations, this study has a number of strengths including a large representative sample, matching based on sociodemographic and disease risk factors, simultaneous adjustment for potentially confounding medical conditions and medications, and assessment of multiple exposure windows. This large population-based comparative analysis of testosterone and VTE risk addresses a public health issue that has concerned many patients and practitioners over the past year. Our study suggests that middle-aged and older men receiving testosterone therapy do not have an increased risk of VTE. These findings may help to inform the benefit-risk assessment for men with testosterone deficiency considering treatment.

CONCLUSION

Middle-aged and older men who filled a prescription for testosterone therapy were not at increased risk of VTE. This finding persisted across specific routes of administration—topical, transdermal, and intramuscular—and across different exposure windows—15, 30, 60 days before the event/index date. These findings may provide clinically relevant information about the benefit-risk assessment for men with testosterone deficiency considering treatment.

ACKNOWLEDGMENTS

We are grateful to Leonard Pechacek for his editorial assistance.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **aOR** = adjusted odds ratio; **CDM** = Clinformatics Data Mart; **DVT** = deep vein thrombosis; **FDA** = Food and Drug Administration; ***ICD-9-CM*** = *International Classification of Diseases, Ninth Revision, Clinical Modification*; **NSAID** = nonsteroidal anti-inflammatory drug; **PE** = pulmonary embolism; **VTE** = venous thromboembolism

Grant Support: The work was supported by the Institute for Translational Sciences at the University of Texas Medical Branch, which was supported in part by a Clinical and Translational Science Award (UL1TR000071) from the National Center for Advancing Translational Sciences, National Institutes of Health. The funding organizations had no role in the design or conduct of the study; in the collection, analysis, or interpretation of data; or in the preparation, review, or approval of the article.

Potential Competing Interests: Dr Morgentaler has received payments for consulting, scientific advisory boards, research grants, and/or lecture honoraria from AbbVie, Antares, Auxilium, Bayer, Clarus, Eli Lilly, Lipocine, Merck, Pfizer, and TesoRx.

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