All-Cause and Potentially Disease-Related Health Care Costs Associated with Venous Thromboembolism in Commercial, Medicare, and Medicaid Beneficiaries

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ABSTRACT

BACKGROUND: Patients with venous thromboembolism (VTE) are at increased risk of developing recurrent VTE and post-thrombotic syndrome (PTS), a complication of deep vein thrombosis (DVT) characterized by venous reflux and residual venous obstruction that may manifest as chronic pain and swelling. Therefore, formulary/policy decision makers should understand the clinical and economic consequences associated with VTE.

OBJECTIVES: To describe the real-world clinical complications, such as recurrent VTE and PTS, associated with VTE and quantify the incremental direct all-cause and potentially disease-related health care costs associated with VTE.

METHODS: Health insurance claims between January 2004 and December 2008 from the Ingenix Impact database were used. Adult patients with an initial VTE diagnosis (index DVT, pulmonary embolism [PE], or both) with at least 12 months of enrollment prior to the index VTE were matched 1:1 with comparison patients without VTE. Matching criteria included demographic factors, baseline health care costs, and diagnoses of VTE risk factors such as multiple traumas, malignant cancer, or major surgery. Each patient's observation period began on the date of the index VTE, or corresponding study index date for comparison cases, and ended on the earliest of 1 year after the study index date, the health plan disenrollment date, or December 31, 2008. The proportions of patients with (a) recurrent hospital-documented VTE, defined as an inpatient episode with a diagnosis of VTE in any claim field; (b) PTS; and (c) other potentially disease-related diagnoses (thrombocytopenia, superficial venous thrombosis, venous ulcer, pulmonary hypertension, stasis dermatitis, and venous insufficiency) were calculated. Health care costs were defined as standardized net provider payments after subtraction of member cost-sharing amounts. All-cause incremental health care costs and disease-related costs, defined as provider payments for hospitalization or outpatient claims with a primary or secondary diagnosis of VTE, PTS, or any of the potentially disease-related diagnoses, were computed. Costs were calculated per patient per year (PPPY) by weighting each patient's total cost for up to 1 year post-index by the length of follow-up.

RESULTS: The matched VTE and no-VTE cohorts included 16,969 subjects in each group. The index VTE event was DVT, PE, or both in 12,711, 2,473, and 1,785 patients, respectively. In the VTE cohort, the risks of recurrent VTE and PTS during the follow-up period (mean [SD] observation of 271.7 [121.6] days) were 3.6% and 7.1%, respectively. Patients with VTE had significantly higher average PPPY all-cause costs compared with the no-VTE patients (mean [SD] \$33,531 [\$70,393] vs. \$17,590 [\$42,011]; cost difference = \$15,941, 95% CI = \$14,819-\$17,012). Corresponding potentially disease-related health care costs PPPY were also significantly higher for the VTE group (mean [SD] \$3,141 [\$17,055] vs. \$228 [\$3,221]; cost difference = \$2,913, 95% CI = \$2,693-\$3,157) and represented 18.3% (i.e., \$2,913 of \$15,941) of the all-cause cost difference between the 2 groups.

CONCLUSIONS: In this large matched-cohort study, VTE was associated with a 3.6% risk of hospital-documented recurrence and a 7.1% risk of PTS up to

1 year after index VTE. Potentially disease-related costs represented approximately one-fifth of the incremental all-cause costs associated with VTE.

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What is already known about this subject

- Venous thromboembolism (VTE; deep vein thrombosis [DVT], pulmonary embolism [PE], or both) occurs in approximately 600,000 hospitalizations each year in the United States and is considered to be the most common preventable cause of hospital death.
- The risk of VTE recurrence among treated patients remains high (6%-18% after 1-2 years). Once VTE occurs, the prognosis is characterized by a 5%-10% risk of severe post-thrombotic syndrome (PTS) and other clinical complications, such as chronic thromboembolic pulmonary hypertension, which develops in approximately 5% of patients after PE.
- The cost burden of VTE is substantial. Previous studies that analyzed large U.S. databases reported that mean total 1-year health care costs associated with VTE were estimated to be \$7,590-\$33,200 for DVT, \$13,000-\$31,300 for PE, and up to \$38,300 for both DVT and PE.

What this study adds

- This retrospective matched-cohort study used health insurance claims data to quantify the consequences and costs associated with the occurrence of an initial episode of VTE and its subsequent complications. Among patients with VTE, 3.6% had a hospital-documented VTE recurrence, and 7.1% had a PTS event during up to 1 year (mean observation of 9 months) following the initial VTE episode (i.e., index VTE event).
- During a follow-up period of up to 1 year after the index VTE event, patients with VTE had significantly higher risks of thrombocytopenia, superficial venous thrombosis, venous ulcer, pulmonary hypertension, stasis dermatitis, and venous insufficiency ($P < 0.001$ for all) relative to comparison group patients without VTE.
- During the follow-up period of up to 1 year after the index VTE event, patients with VTE also had significantly higher all-cause health care costs per patient per year compared with no-VTE patients (mean [SD] \$33,531 [\$70,393] vs. \$17,590 [\$42,011]; cost difference = \$15,941, 95% CI = \$14,819-\$17,012).
- Potentially disease-related health care costs represented nearly one-fifth of the incremental all-cause costs associated with VTE.

Deep vein thrombosis (DVT) and pulmonary embolism (PE) constitute venous thromboembolism (VTE), a major health problem with approximately 900,000 incident cases each year in the United States, of which 600,000 occur in the hospital.¹ Moreover, almost 300,000 deaths each year in the United States have been attributed to PE;¹ it has been estimated that 2%-10% of all hospital deaths^{2,3} are attributed to PE and that 10%-25% of all PE cases result in sudden death.^{4,5}

The risk of VTE is increased following surgical procedures and trauma and in the presence of cancer or inherited coagulation disorders.⁶ Even with prophylaxis, 1.4%-2.9% of patients develop symptomatic DVT, and PE occurs in 0.4%-1.2% of patients in the 3 months after total knee replacement or total hip replacement.⁷ However, VTE can also develop in patients who are neither hospitalized nor recovering from a major illness. Aging, the use of oral contraceptives, and hormone replacement therapy have all been associated with increased risk of VTE.^{8,9}

The risk of VTE recurrence among treated patients remains high, with 5% of patients experiencing a subsequent DVT or PE within 3 months, 6%-18% within 1-2 years, and up to 25% within 5 years of an index event.^{6,10-12} Once VTE occurs, the prognosis is characterized by the risk of post-thrombotic syndrome (PTS) and other complications, such as chronic thromboembolic pulmonary hypertension, which occurs in approximately 5% of treated patients after PE.⁵ VTE damages deep venous valves and may cause venous reflux and residual venous obstruction, which are largely responsible for the development of PTS.⁵ PTS, which may manifest as chronic pain and swelling, affects 15%-50%^{6,13,14} of patients within 1-2 years of their first DVT, while severe PTS, characterized by debilitating pain, ulceration, and incapacitating limb swelling, affects 5%-10% of DVT patients.^{6,15}

Previous studies have reported real-world clinical and economic consequences associated with VTE using statistical methods (e.g., multivariate adjustment and matched design) to reduce the chances of an influential variable (e.g., concomitant disease and baseline resource utilization) confounding the results.¹⁶⁻²⁰ However, despite recent trends toward outpatient treatment of VTE and new anticoagulants that are in advanced development for the management of VTE, most of the literature reporting on the consequences and costs associated with VTE is based on data preceding the year 2000. A better and more current understanding of the clinical outcomes and costs of VTE is important for health care systems that strive to reduce their costs and will also aid formulary and policy decision makers in appreciating the cost burden associated with VTE complications.

To fill this gap in the literature, the purposes of the present analysis were (a) to describe the risk of clinical complications (i.e., recurrent VTE and PTS) associated with incident VTE

and (b) to quantify the incremental all-cause and potentially disease-related health care costs associated with VTE using recent data from a real-world setting and a matched-cohort design to control for confounding factors that might be associated with VTE.

Methods

Data Source

De-identified health insurance claims from the Ingenix National Managed Care Database (Impact) between January 2004 and December 2008 were used to conduct the analysis. This large national database was designed to support benchmarking projects, health care outcomes research, and other research initiatives. The Impact database includes complete medical and pharmacy claims for more than 80 million managed care enrollees in more than 45 health plans throughout the United States. Insurance coverage includes commercial- and government-sponsored (i.e., Medicare and Medicaid) plans. There were more than 30 million members enrolled in 2008, and the average length of enrollment was 25.1 months. Most members were located in the New England (18.1%), Middle Atlantic (16.6%), South Atlantic (17.1%), East North Central (10.5%), or West South Central (11.9%) areas of the United States. The distribution by insurance type was as follows: preferred provider organization (PPO)=31.5%, health maintenance organization (HMO)=20.7%, point of service (POS)=40.5%, Medicaid=1.6%, Medicare=0.6%, and other=4.9%.

Data elements used in the present analysis included health plan enrollment records, patient demographics, inpatient and outpatient medical claims, and outpatient pharmacy claims. Any data in the Impact database that might allow identification of individual patients were removed to preserve patient anonymity and comply with the Health Insurance Portability and Accountability Act of 1996.

Study Design

A retrospective, matched-cohort design was used to compare enrollees with incident VTE with a matched comparison group of no-VTE enrollees. Each patient's observation period began on the date of the first VTE diagnosis (index date) and ended on the earliest of 1 year after the study index date, the health plan disenrollment date, or December 31, 2008. An index date was randomly assigned for each patient in the no-VTE group.

To be included in the study sample, VTE cohort patients were required to meet the following criteria: (a) at least 1 claim with a primary or secondary diagnosis for DVT (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] codes: 451.1x [phlebitis and thrombophlebitis of deep veins of lower extremities], 451.2 [phlebitis and thrombophlebitis of lower extremities unspecified], 453.4x [acute venous embolism and thrombosis of deep vessels of lower extremity], 453.8 [acute venous embolism and thrombosis

of other specified veins], 453.9 [embolism and thrombosis of unspecified site]) or PE (ICD-9-CM codes 415.1x [pulmonary embolism and infarction]); (b) continuous health plan enrollment in the 12 months prior to the index date (baseline period); and (c) at least 18 years of age on the index date (i.e., first VTE event).

Of note, we identified patients with incident VTE in the current study. We did not include codes for chronic venous embolism and thrombosis of deep vessels of lower extremity (ICD-9-CM code: 453.5x) or chronic venous embolism and thrombosis of deep veins of upper extremity (ICD-9-CM code: 453.72) in our definition of incident VTE because of the chronic nature of these diagnoses.

We imposed a minimum of 12 months of insurance coverage prior to the index date to assess the baseline characteristics of the study population in order to appropriately control for confounding factors in matching VTE cases with no-VTE comparison cases. No further minimum follow-up time was imposed during the observation period to avoid introducing potential bias such as survival or observation bias.

Outcome Measures

Primary Endpoints. The primary endpoints of the study, which were evaluated only for the VTE group, included (a) the risk of recurrent VTE documented during an inpatient stay and (b) PTS. Hospitalization data were obtained from the Impact Inpatient Confinement table, which provided a summarized record for each inpatient episode with a length of stay of at least 1 day in an acute care hospitalization or skilled nursing facility setting. Recurrent VTE events were defined as inpatient episodes with a diagnosis for acute VTE in the admitting or any other diagnosis fields occurring at any time following the index VTE event (either as a VTE event requiring hospitalization or VTE secondary to a primary diagnosis). Based on the algorithm developed by MacDougall et al. (2006),¹⁶ PTS was defined as the occurrence 90 or more days after an index VTE of both a venous imaging procedure (Current Procedural Terminology [CPT]-4 codes 93965, 93970, or 93971) and 1 or more of the following, based on diagnosis codes (see Appendix): both pain and swelling of the limb within 7 days of each other, varicose veins of the lower extremities, postphlebotic syndrome, and other disorders of the circulatory system.

Exploratory Endpoints. Additional exploratory endpoints were identified *a priori* based on the literature reviewed by the authors during the study protocol development prior to conducting the study analyses.²¹⁻³¹ These exploratory endpoints included thrombocytopenia, superficial venous thrombosis, venous ulcer, pulmonary hypertension, stasis dermatitis, and venous insufficiency (Appendix).

Most of these endpoints have been identified in the literature as VTE-related complications, although some co-occur

with or after VTE and may not be caused by VTE. Heparin-induced thrombocytopenia can complicate heparin therapy for VTE,²¹ and thrombocytopenia not related to heparin usage may also be developed by patients with VTE.²² Superficial venous thrombosis has been described as a venous condition interrelated with VTE,²³ and at the beginning of a large prospective study of patients with superficial venous thrombosis, about one-quarter also had DVT.²⁴ Venous ulcer and pulmonary hypertension have been reported as major complications of VTE.²⁵ DVT is noted as the most consistently observed risk factor for venous ulcer because it directly destroys and indirectly impairs venous valves.²⁶ A prospective study conducted by Pengo et al. (2004) found that chronic thromboembolic pulmonary hypertension affects approximately 4% of patients within 2 years after a first episode of PE and is a serious complication of PE.²⁷ A review by Vedantham (2009) reported that stasis dermatitis may occur in severe cases of PTS.²⁸ Stasis dermatitis can also develop following chronic venous insufficiency.²⁹

DVT can affect the structural integrity of vein valves, which, if in poor condition, may fail to appropriately coapt and prevent retrograde flow. Loss of the efficiency of the venous outflow system and reflux of venous blood down the leg lead to symptoms of chronic venous insufficiency.²⁶ A study by Yamaki and Nozaki (2005) investigated patterns of venous insufficiency after DVT and found that the limbs involving multisegment DVTs on initial examination had a higher incidence of deep vein insufficiency compared with single segment DVT.³⁰ A study by Juhan et al. (1997) also reported that among patients with surgical venous thrombectomy, the surgical removal of a large blood clot, the rate of valvular insufficiency was 20% at 5 years and 44% at 10 years.³¹

These potentially disease-related, exploratory endpoints were studied separately from PTS as independent outcomes. However, some ICD-9-CM codes used to define the exploratory endpoints overlap with the definition of PTS (Appendix). For example, venous ulcer was an exploratory endpoint, but the ICD-9-CM codes 459.11 (postphlebotic syndrome with ulcer) and 459.13 (postphlebotic syndrome with ulcer and inflammation) are also part of the ICD-9-CM code 459.1 (postphlebotic syndrome) used to define PTS. Also, for the exploratory endpoints, a venous imaging procedure was not required.

Incremental health care costs associated with VTE were also calculated and categorized as (a) total health care costs, defined as all-cause outpatient, hospitalization, and pharmacy costs, and (b) potentially disease-related costs, defined as hospitalizations and outpatient claims with a primary or secondary diagnosis for VTE, PTS, or any of the exploratory endpoints. Results were also stratified by gender and baseline risk factors for VTE.

Cost Outcomes. Impact has developed several approaches (e.g., proprietary algorithms and multivariate models) for

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TABLE 1 Characteristics of the Overall VTE and No-VTE Cohorts (Before Random Sampling and Matching)

Characteristics	VTE Group n = 177,885		No-VTE Group n = 253,521	
Observation period, ^a mean [SD] days	271.8	[121.0]	268.1	[108.8]
Type of index VTE, % (n)				
DVT only	74.4	(132,360)		
PE only	14.7	(26,098)		
PE and DVT	10.9	(19,427)		
Propensity score matching factors ^{b,c}				
Exact matching factors ^b				
History of exploratory endpoint outcomes, % (n)				
Venous insufficiency	4.9	(8,798)	0.7	(1,873)
Stasis dermatitis	2.0	(3,511)	0.3	(688)
Superficial venous thrombosis	1.7	(2,971)	0.1	(218)
Thrombocytopenia	2.0	(3,572)	0.4	(1,022)
Pulmonary hypertension	1.5	(2,737)	0.3	(763)
Venous ulcer	1.1	(2,044)	0.1	(373)
Other propensity score matching factors ^b				
All-cause health care costs at baseline, mean [SD] \$				
Outpatient services	9,990	[17,618]	3,488	[7,298]
Inpatient services	11,259	[24,076]	1,575	[8,185]
Pharmacy costs	2,355	[4,579]	1,314	[2,770]
Age in years, mean [SD]	54.6	[14.2]	54.4	[13.8]
Female, % (n)	57.4	(102,031)	56.9	(144,229)
Charlson comorbidity index, % (n)				
0	43.2	(76,879)	70.4	(178,579)
1	20.4	(36,302)	15.8	(40,053)
2	13.3	(23,728)	7.9	(20,059)
3	7.4	(13,186)	2.8	(7,158)
4	4.1	(7,317)	1.2	(2,968)
5 or more	11.5	(20,473)	1.9	(4,704)

Characteristics	VTE Group n = 177,885		No-VTE Group n = 253,521	
Most frequent VTE risk factors, ^c % (n)				
Multiple trauma	31.3	(55,619)	17.9	(45,263)
Other serious infections	22.6	(40,184)	13.9	(35,297)
Malignant cancer	18.0	(31,956)	8.7	(21,943)
Abdominal surgery	17.0	(30,227)	9.3	(23,610)
Major surgery	14.5	(25,859)	3.5	(8,876)
COPD	13.5	(24,081)	6.4	(16,134)
Use of anticoagulant, % (n)	11.7	(20,732)	2.3	(5,738)
Region, % (n)				
Middle Atlantic	22.4	(39,861)	39.0	(98,813)
New England	21.5	(38,252)	51.9	(131,564)
South Atlantic	18.4	(32,734)	2.5	(6,218)
East North Central	10.8	(19,238)	0.7	(1,699)
West South Central	9.3	(16,563)	0.4	(905)
Mountain	7.3	(12,935)	4.2	(10,579)
West North Central	4.7	(8,414)	0.4	(969)
Pacific	2.9	(5,157)	0.7	(1,879)
East South Central	2.6	(4,641)	0.3	(771)
Other	0.1	(90)	0.0	(124)
Type of insurance, % (n)				
PPO	28.9	(51,471)	38.4	(97,227)
HMO	29.1	(51,749)	47.0	(119,115)
POS	37.5	(66,666)	8.7	(22,015)
Other	4.5	(7,999)	6.0	(15,164)
Index year, % (n)				
2005	27.8	(49,406)	31.0	(78,526)
2006	24.1	(42,927)	23.2	(58,827)
2007	25.4	(45,235)	24.4	(61,974)
2008	22.7	(40,317)	21.4	(54,194)

^aThe observation period spanned from the index date until the earliest of the following: health plan disenrollment, 12 months after the index date, or the end of the study period on December 31, 2008.

^bEvaluated during the 1-year baseline period.

^cTable shows only factors observed in at least 10% of the sample. Additional propensity score matching factors not reported in this table include the following VTE risk factors observed in less than 10% of the study sample: use of oral contraceptive pill; obesity; pneumonia; pregnancy; hip, pelvis, or leg fracture; congestive heart failure; varicose veins; ischemic stroke; treatment with selective estrogen receptor modulators; rheumatoid arthritis; transient ischemic attack; central venous catheter; thrombophilia; inflammatory bowel disease; surgical resection of abdominal pelvic cancer; treatment with erythropoiesis-stimulating agents; myocardial infarction; spinal cord injury; treatment with aromatase inhibitors; immobility; estrogen replacement therapy; and hip or knee surgery.

COPD=chronic obstructive pulmonary disease; DVT=deep vein thrombosis; HMO=health maintenance organization; PE=pulmonary embolism; POS=point of service; PPO=preferred provider organization; SD=standard deviation; VTE=venous thromboembolism.

standardizing pricing for different service categories (inpatient facility, outpatient facility, professional services, ancillary services, and pharmacy claims) across health plans in order to develop a database that accounts for differences in provider contracting and other pricing variations. The costs are reported from the payer's perspective. Deductibles, copayment, coinsurance, and other cost-sharing amounts have been subtracted from the total allowed charge so that consistent comparisons may be made across all patients, health plans, and geographic areas. The resulting cost figures are therefore comparable across health plans and reflect net provider payments after sub-

traction of member cost sharing. Costs were inflation adjusted to reflect 2008 U.S. dollar market value.

Random Sampling

Since the primary purpose of the study was to assess the clinical and economic impact of VTE in patients who experienced a VTE event, our initial intention was to include all VTE cases in the matched cohort. Ideally the no-VTE group would have been very large relative to the VTE group in order to find a no-VTE comparison for each VTE case, especially given the important imbalance in baseline characteristic profiles of these 2 groups (Table 1). However, due to the limited number of

FIGURE 1 Study Sample Selection Flowchart

VTE=venous thromboembolism.

potential comparison group cases that we received from the data vendor during the data extraction, the no-VTE comparison group eligible for matching ($n = 253,521$) was similar in size to the VTE group ($n = 177,885$). A random sample of 20,000 VTE patients obtained with a random number generator was thus selected. Random samples of 40,000, 30,000, and 25,000 VTE patients were also tried but did not allow the matching of enough (i.e., more than 80% of the VTE cohort) VTE patients to stay representative of the overall VTE cohort.

Matching Algorithm

Given the large sample of VTE patients available for the analysis and because the power to detect differences between cohorts was not an issue for the current study even after random sampling, a matched-cohort design was chosen over a regression analysis. As observed by Rosenbaum and Rubin (1985), one of the advantages of matching over regression analyses is that simple descriptive statistics can be used to summarize the findings and compare the matched cohorts.³²

To attempt to create cohorts with balanced patient characteristics at baseline, VTE patients were matched 1:1 to no-VTE patients based on exact matching factors and propensity scores. The predictors used in the propensity score calculation included baseline (12 months pre-index) diagnoses of thrombocytopenia, superficial venous thrombosis, venous ulcer, pulmonary hypertension, stasis dermatitis, and venous insufficiency (i.e., the potentially disease-related diagnoses); all-cause health care costs; demographic characteristics (age,

gender, region, and type of insurance); Charlson comorbidity index; and risk factors for VTE (Tables 1 and 2) identified in the literature review.

The dependent variable in the propensity score model was a binary indicator of an index VTE (yes/no), estimating the propensity for VTE based on observable baseline characteristics. The c-statistic for the logistic regression analysis used to develop the propensity score algorithm was 0.875, which indicates excellent discrimination.³³

Following propensity score calculations, VTE patients were matched (a) exactly to no-VTE patients based on the potentially disease-related, exploratory endpoints (thrombocytopenia, superficial venous thrombosis, venous ulcer, pulmonary hypertension, stasis dermatitis, and venous insufficiency during the 12-month baseline period) and (b) by propensity score intervals of 25%. Smaller propensity score intervals were also tested but proved to be too restrictive due to the very different baseline characteristic profiles of the VTE and no-VTE groups. For the exact matching on exploratory endpoints, patients were matched on specific diagnoses (e.g., a VTE patient with thrombocytopenia and venous ulcer was matched to a no-VTE patient with thrombocytopenia and venous ulcer).

Statistical Analyses

The risks of each outcome measure (recurrent VTE documented during a hospital stay, PTS, and exploratory endpoints) for VTE patients were evaluated using absolute risk rates throughout the observation period as well as incidence rates

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TABLE 2 Characteristics of the Study Sample After Matching VTE and No-VTE Comparison Patients

Characteristics	VTE Group n = 16,969		No-VTE Group n = 16,969		P Value
Observation period, ^a mean [SD] days	271.7	[121.6]	257.9	[112.3]	<0.001
Type of index VTE, % (n)					
DVT only	74.9	(12,711)			
PE only	14.6	(2,473)			
PE and DVT	10.5	(1,785)			
Propensity score matching factors ^{b,c}					
Exact matching factors ^b					
History of exploratory endpoint outcomes, % (n)					
Venous insufficiency	5.4	(910)	5.4	(910)	1.000
Stasis dermatitis	2.1	(349)	2.1	(349)	1.000
Superficial venous thrombosis	1.1	(195)	1.1	(195)	1.000
Thrombocytopenia	1.9	(328)	1.9	(328)	1.000
Pulmonary hypertension	1.6	(275)	1.6	(275)	1.000
Venous ulcer	1.1	(191)	1.1	(191)	1.000
Other propensity score matching factors ^b					
All-cause health care costs at baseline, mean [SD] \$					
Outpatient services	9,496	[16,948]	9,823	[19,276]	0.083
Inpatient services	10,471	[23,158]	10,812	[24,394]	0.160
Pharmacy costs	2,251	[4,294]	2,333	[5,325]	0.115
Age in years, mean [SD]	54.6	[14.2]	56.5	[14.6]	<0.001
Female, % (n)	56.9	(9,654)	57.0	(9,667)	0.895
Charlson comorbidity index, % (n)					
0	44.6	(7,567)	49.4	(8,381)	<0.001
1	20.2	(3,425)	15.9	(2,692)	
2	13.5	(2,288)	10.8	(1,832)	
3	7.2	(1,223)	6.4	(1,094)	
4	3.7	(630)	4.2	(716)	
5 or more	10.8	(1,836)	13.3	(2,254)	

Characteristics	VTE Group n = 16,969		No-VTE Group n = 16,969		P Value
Most frequent VTE risk factors, ^c % (n)					
Multiple trauma	30.9	(5,249)	31.4	(5,333)	0.322
Other serious infections	22.1	(3,748)	23.1	(3,916)	0.029
Malignant cancer	17.4	(2,952)	17.7	(3,006)	0.442
Abdominal surgery	17.0	(2,893)	16.7	(2,827)	0.340
Major surgery	13.7	(2,319)	12.3	(2,090)	0.001
COPD	13.1	(2,222)	13.7	(2,332)	0.079
Use of anticoagulant, % (n)	10.9	(1,855)	11.8	(1,995)	0.015
Region, % (n)					
Middle Atlantic	25.2	(4,272)	29.0	(4,919)	
New England	24.4	(4,146)	34.1	(5,784)	
South Atlantic	16.7	(2,834)	13.5	(2,290)	
East North Central	9.2	(1,554)	5.8	(985)	
West South Central	8.0	(1,354)	5.3	(899)	<0.001
Mountain	7.3	(1,241)	5.4	(919)	
West North Central	4.2	(711)	2.7	(463)	
Pacific	2.6	(448)	2.6	(439)	
East South Central	2.4	(401)	1.5	(263)	
Other	0.0	(8)	0.0	(8)	
Type of insurance, % (n)					
PPO	30.8	(5,232)	41.9	(7,116)	
HMO	30.8	(5,221)	36.4	(6,170)	<0.001
POS	33.8	(5,738)	15.0	(2,551)	
Other	4.6	(778)	6.7	(1,132)	
Index year, % (n)					
2005	28.4	(4,823)	31.3	(5,316)	
2006	23.8	(4,036)	23.1	(3,914)	<0.001
2007	25.5	(4,331)	24.3	(4,129)	
2008	22.3	(3,779)	21.3	(3,610)	

^aThe observation period spanned from the index date until the earliest of the following: health plan disenrollment, 12 months after the index date, or the end of the study period on December 31, 2008.

^bEvaluated during the 1-year baseline period.

^cTable shows only factors observed in at least 10% of the sample. Additional propensity-score matching factors not reported in this table include the following VTE risk factors observed in less than 10% of the study sample: use of oral contraceptive pill; obesity; pneumonia; pregnancy; hip, pelvis, or leg fracture; congestive heart failure; varicose veins; ischemic stroke; treatment with selective estrogen receptor modulators; rheumatoid arthritis; transient ischemic attack; central venous catheter; thrombophilia; inflammatory bowel disease; surgical resection of abdominal pelvic cancer; treatment with erythropoiesis-stimulating agents; myocardial infarction; spinal cord injury; treatment with aromatase inhibitors; immobility; estrogen replacement therapy; and hip or knee surgery.

COPD=chronic obstructive pulmonary disease; DVT=deep vein thrombosis; HMO=health maintenance organization; PE=pulmonary embolism; POS=point of service; PPO=preferred provider organization; SD=standard deviation; VTE=venous thromboembolism.

per 100 patient-years to account for variable length of follow-up. The absolute risk of an event was calculated as the number of patients with the event divided by the total number of patients. Incidence rate was calculated as the number of events divided by the patient-years of observation, censored at the time of the first event. In addition, the risks of the exploratory endpoint measures were compared between VTE and no-VTE cohorts using risk ratios (RRs) and incidence rate ratios (IRRs). The RR was calculated as the absolute risk in the VTE group divided by that in the no-VTE group, whereas the IRR was calculated as the incidence rate of the VTE group divided by that

of the no-VTE group. Ninety-five percent confidence intervals (CIs) of RRs and IRRs were calculated based on the binomial and Poisson probability distributions, respectively.

Cost differences between study cohorts were assessed based on incremental annualized costs. To avoid overestimating costs by annualizing data for patients observed for less than 1 year, we calculated costs per patient per year (PPPY) by weighting each patient's cost outcomes by length of follow-up.^{34,35} Because the normality assumption might not be valid for cost-outcome variables, we conducted nonparametric estimations (i.e., bootstrap method) to carry out statistical inference and determine

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the 95% CI for the cost difference between the 2 groups. This method estimates the empirical distributional function of the data without imposing any probability density function.^{36,37}

Descriptive statistics were used to describe the baseline characteristics of the matched VTE and no-VTE cohorts, including mean (standard deviation [SD]) for continuous data and relative frequencies for categorical data. Baseline continuous variables were compared using paired *t* tests, while baseline categorical variables were compared using Pearson chi-squared or McNemar tests. A 2-sided alpha level of 0.05 was used to define statistical significance. All statistical analyses were performed using SAS version 9.1 (SAS Institute, Inc., Cary, NC).

Results

Characteristics of the Matched Cohorts

Figure 1 summarizes the study sample selection. Among the random subsample of 20,000 VTE patients, 16,969 (84.8%) were matched, and these randomly selected VTE patients had baseline characteristics that were similar to those of the whole VTE sample (Tables 1 and 2). Overall, the VTE and no-VTE cohorts were well matched with respect to demographic characteristics, baseline exploratory endpoints, risk factors, and baseline health care costs (Table 2).

The index VTE event was DVT, PE, or both in 12,711 (74.9%), 2,473 (14.6%), and 1,785 (10.5%) patients, respectively. The most frequent baseline risk factors for VTE, occurring in more than 10% of patients, were multiple trauma, other serious infection, malignant cancer, abdominal surgery, major surgery, and chronic obstructive pulmonary disease (COPD). The mean (SD; range) observation periods for the VTE and no-VTE cohorts were 272 (122; 1-365) and 258 (112; 32-365) days, respectively.

Risk of Complications and Exploratory Endpoints

Table 3a presents the absolute risk, incidence rate, and mean time to first event for recurrent VTE and PTS up to 1 year and up to 6 months after the index date for the overall VTE sample and matched VTE cohort. Of note, the risks and incidence rates of recurrent VTE and PTS were similar between the overall VTE sample and the matched VTE cohort. Absolute risks of recurrent VTE and PTS up to 1 year after the index date for the matched VTE cohort were 3.6% and 7.1%, respectively. The corresponding risks up to 6 months after the index date were 3.1% and 4.2%, respectively (Table 3a). Similar trends were observed for the incidence rate results. Risks and incidence rates of the potentially disease-related, exploratory endpoints were all significantly higher for the VTE group compared with the no-VTE group (*P* < 0.001 for all comparisons, Table 3b).

For the stratified analysis by gender and baseline VTE risk factors (Table 4), the absolute risks of recurrent VTE measured throughout the observation period were 4.3% for male and

TABLE 3a Risk and Incidence Rates of Recurrent VTE and Post-Thrombotic Syndrome for the VTE Cohort

Primary Endpoints	Risk of Event (%)	IR Per 100 Patient-Years	Mean [SD] Days to Event ^a	Mean (Median) Follow-Up Time in Days
Up to 1 Year of Follow-Up				
Recurrent VTE documented during inpatient stay				
Overall VTE sample (n = 177,885)	3.9	5.4	70.8 [87.7]	271.8 (365)
Matched VTE cohort (n = 16,969)	3.6	5.0	75.3 [91.5]	271.7 (365)
Stratified by type of index VTE				
DVT (n = 12,711)	2.2	3.0	79.7 [94.0]	274.5 (365)
PE (n = 2,473)	1.6	2.3	43.1 [66.3]	256.0 (336)
Both (n = 1,785)	16.1	24.3	75.4 [91.4]	273.6 (365)
Post-thrombotic syndrome^b				
Overall VTE sample (n = 153,607)	6.9	8.5	175.6 [73.7]	307.1 (365)
Matched VTE cohort (n = 14,647)	7.1	8.8	176.7 [73.3]	307.2 (365)
Stratified by type of index VTE				
DVT (n = 11,067)	6.5	9.6	174.1 [73.2]	308.0 (365)
PE (n = 2,033)	1.9	2.7	197.1 [77.8]	302.2 (365)
Both (n = 1,547)	9.4	13.3	183.4 [72.0]	308.0 (365)
Up to 6 Months of Follow-Up				
Recurrent VTE documented during inpatient stay				
Overall VTE sample (n = 177,885)	3.4	8.1	41.4 [43.4]	156.8 (180)
Matched VTE cohort (n = 16,969)	3.1	7.4	43.1 [44.0]	156.6 (180)
Stratified by type of index VTE				
DVT (n = 12,711)	1.9	4.5	45.1 [44.7]	157.8 (180)
PE (n = 2,473)	1.5	3.7	27.2 [30.9]	150.0 (180)
Both (n = 1,785)	13.8	35.8	43.4 [44.7]	157.2 (180)
Post-thrombotic syndrome^b				
Overall VTE sample (n = 153,607)	4.2	8.9	125.4 [26.6]	174.0 (180)
Matched VTE cohort (n = 14,647)	4.2	9.0	124.7 [26.1]	173.8 (180)
Stratified by type of index VTE				
DVT (n = 11,067)	4.0	9.3	124.2 [26.3]	173.8 (180)
PE (n = 2,033)	0.8	2.1	124.8 [27.7]	173.2 (180)
Both (n = 1,547)	5.2	12.3	127.9 [24.7]	173.7 (180)

^aMean time to event was calculated for patients with an event.

^bRisk and incidence rate of post-thrombotic syndrome were calculated on the subset of patients with more than 90 days of follow-up.

DVT = deep vein thrombosis; IR = incidence rate; PE = pulmonary embolism; SD = standard deviation; VTE = venous thromboembolism.

3.1% for female patients. Risk of recurrent VTE increased with number of baseline VTE risk factors: 2.4%, 2.7%, 3.8%, and 5.6% for patients with 0, 1, 2, and 3 or more baseline VTE risk factors, respectively. The corresponding risks of PTS were 6.2% for males and 7.8% for females and 5.6%, 6.1%, 7.6%, and 9.5% for patients with 0, 1, 2, and 3 or more baseline VTE risk factors, respectively.

Costs Associated with VTE

VTE patients had significantly higher average PPPY all-cause costs from the payer's perspective compared with no-VTE patients (mean [SD] \$33,531 [\$70,393] vs. \$17,590 [\$42,011];

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TABLE 3b Risk and Incidence Rates of Exploratory Endpoint Outcomes for the VTE Cohort Relative to the No-VTE Cohort

Exploratory Endpoints	VTE Cohort		No-VTE Cohort		Risk Ratio (95% CI)	Incidence Rate Ratio (95% CI)	P Value ^a
	Risk of Event (%)	IR Per 100 Patient-Years	Risk of Event (%)	IR per 100 Patient-Years			
Thrombocytopenia	2.8	3.8	1.2	1.7	2.3 (2.0-2.7)	2.2 (1.9-2.6)	<0.001
Superficial venous thrombosis	4.7	6.7	0.2	0.3	21.7 (15.6-30.1)	21.5 (15.4-29.9)	<0.001
Venous ulcer	1.4	2.0	0.6	0.8	2.6 (2.1-3.3)	2.5 (2.0-3.2)	<0.001
Pulmonary hypertension	2.6	3.5	0.9	1.3	2.9 (2.4-3.5)	2.8 (2.3-3.3)	<0.001
Stasis dermatitis	2.6	3.6	0.8	1.1	3.3 (2.7-4.0)	3.2 (2.7-3.9)	<0.001
Venous insufficiency	7.2	10.3	2.1	3.0	3.4 (3.1-3.9)	3.4 (3.0-3.9)	<0.001

^aP values were <0.001 for all risk ratios and incidence rate ratios.

CI=confidence interval; IR=incidence rate; VTE=venous thromboembolism.

cost difference=\$15,941, 95% CI=\$14,819-\$17,012; Figure 2). All-cause hospitalization represented the largest driver of the cost difference between the VTE and the no-VTE groups (mean [SD] \$17,174 [\$57,397] vs. \$6,515 [\$29,323]; cost difference=\$10,659, 95% CI=\$9,846-\$11,491). Health care costs related to recurrent VTE, PTS, or exploratory endpoints (mean [SD] \$3,141 [\$17,056] vs. \$228 [\$3,221]; cost difference=\$2,913, 95% CI=\$2,693-\$3,157) represented 18.3% (i.e., \$2,913 of \$15,941) of the all-cause cost difference between the VTE group and the no-VTE group (Figure 2).

For the stratified analysis by gender and baseline VTE risk factors, the all-cause mean incremental PPPY costs associated with VTE relative to no-VTE were \$18,678 for men; \$13,932 for women; and \$13,275, \$14,245, \$13,932, and \$23,206 for patients with 0, 1, 2, and 3 or more baseline VTE risk factors, respectively. The corresponding incremental PPPY costs of recurrent VTE, PTS, or exploratory endpoints were \$3,357 for men; \$2,583 for women; and \$2,188, \$2,525, \$2,360, and \$4,614 for patients with 0, 1, 2, and 3 or more baseline VTE risk factors, respectively (Table 4).

Discussion

Based on real-world data, this large retrospective study was conducted to quantify the risk of clinical complications and incremental health care costs associated with VTE using a matched-cohort design. During the period January 2004 through December 2008, a total of 16,969 VTE patients matched with an equal number of no-VTE patients with similar baseline characteristics were studied. VTE was associated with a 3.6% risk of hospital-documented recurrent VTE and a 7.1% risk of PTS up to 1 year after the index VTE. VTE was also associated with a significantly higher risk for thrombocytopenia, superficial venous thrombosis, venous ulcer, pulmonary hypertension, stasis dermatitis, and venous insufficiency compared with the no-VTE cohort. Of note, the VTE and no-VTE cohorts were matched exactly on these exploratory endpoints at baseline. Recurrent VTE, PE, and the increased rate of these

exploratory endpoints resulted in a \$2,913 PPPY health care cost burden associated with VTE that was not present during the baseline period (i.e., both cohorts had similar health care costs at baseline).

Several prospective studies have estimated the risk of VTE recurrence following an index thromboembolic event.^{6,11,38} More recently, Prandoni et al. (2007) evaluated 1,626 patients who had discontinued anticoagulation therapy between May 1991 and April 2003 after “a first episode of clinically symptomatic proximal DVT and/or PE.” The cumulative incidence of recurrent VTE in this prospective study was 11.0% after 1 year, 19.6% after 3 years, and 29.1% after 5 years.³⁹

The comorbidity profile of patients can also affect the magnitude of the estimated risk of VTE recurrence. For example, Christiansen et al. (2005), in a prospective follow-up study of 474 consecutive patients aged 18 to 70 years without malignancy between January 1988 and December 1992, reported that the risk of VTE recurrence was 12.4% after 5 years.³⁸ The authors also found that the odds of thrombotic event recurrence for men were 2.7 times those for women. In the current study, we found that the risk of recurrence was 4.3% for men and 3.1% for women.

The estimated risks of VTE recurrence from retrospective studies are generally more conservative than those of prospective cohort studies or randomized trials because of the difficulty associated with the identification of recurrent events. In a retrospective analysis of 8,332 patients hospitalized with a primary discharge diagnosis of DVT or PE identified from the Integrated Health Care Information Services (IHCIS) National Managed Care Database between 1998 and 2004, Spyropoulos and Lin (2007) reported a hospital readmission rate of 5.3% within 1 year.⁴⁰ A population-based cohort study conducted by Heit et al. (2000), using medical records from 1,719 patients with a first lifetime DVT or PE during the 25-year period from 1966 through 1990, reported that the overall probable/definite cumulative percentage of VTE recurrence was 5.6% at 1 year.¹² The risk of VTE recurrence at up to 1 year (mean

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follow-up of 9 months) that we observed in the current study was slightly lower at 3.6%, possibly due to our strict definition of VTE recurrence (hospital documented) and to a different study design and population. Another possible explanation for the lower recurrence rate of VTE is the trend toward outpatient treatment of VTE; the more recent time frame of the current study (2004 to 2008) combined with our definition of hospital-documented VTE recurrence could account for some of the differences we observed when comparing our findings with the literature.

PTS has also been reported to affect up to one-half of DVT patients.^{6,13,14} Since there is no ICD-9-CM diagnosis code for PTS, we used the algorithm developed by MacDougall et al., which defined PTS as the occurrence 90 days or more after the index VTE of a venous imaging procedure and 1 or more of several diagnoses, including varicose veins, postphlebotic syndrome, limb pain and swelling, and other circulatory disorders.¹⁶ MacDougall et al. reported a PTS risk of 3.8% in 17,634 patients evaluable between 1997 and 2004.¹⁶ In the current study using more recent data from 2004 to 2008 and a follow-up period of up to 1 year, 7.1% of patients in the VTE cohort experienced PTS.

The cost burden of VTE is significant. Studies based on large U.S. databases reported that the costs of an initial VTE were between \$3,000 and \$9,500 per episode of illness, and mean total health care costs associated with VTE over 1 year were estimated to be \$7,590-\$33,200 for DVT, \$13,000-\$31,300 for PE, and up to \$38,300 for both DVT and PE.^{16,41} Additionally, the mean all-cause cost of hospital-documented recurrent VTE was estimated to be \$12,326 (DVT: \$11,419; PE: \$11,014; DVT+PE: \$19,237).¹⁷ Spyropoulos and Lin also quantified the annual cost associated with DVT and PE using administrative claims data from February 1998 to June 2004. For a primary diagnosis of DVT and PE, they reported DVT- and PE-related average health care costs during the 12-month follow-up period of \$10,804 and \$16,644, respectively.⁴⁰ In the current study using a matched-cohort design with more recent data from January 2004 to December 2008, we found annualized all-cause health care costs of \$33,531 for the VTE group, compared with \$17,590 for the no-VTE group, for total incremental all-cause costs associated with VTE of \$15,941 during the follow-up period of up to 1 year.

Although not directly comparable because of the different study period and population, our estimates concur with previously reported findings that VTE represents a significant cost burden. Moreover, the current study reported real-world potentially disease-related health care costs that represented nearly one-fifth of the incremental all-cause costs associated with VTE. Costs were reported from the payer's perspective. As mentioned by Lancry et al. (2001), there is a need for information on real-world cost assumed by health care payers, who are charged with the responsibility of providing coverage for

TABLE 4 Stratified Results by Gender and Baseline VTE Risk Factors^a

	VTE Group		
Risk of hospital-documented VTE, %			
Male	4.3 (311/7,315)		
Female	3.1 (301/9,654)		
Baseline VTE risk factors			
0	2.4 (106/4,435)		
1	2.7 (128/4,663)		
2	3.8 (130/3,426)		
3 or more	5.6 (248/4,445)		
Risk of post-thrombotic syndrome,^b %			
Male	6.2 (390/6,264)		
Female	7.8 (656/8,383)		
Baseline VTE risk factors			
0	5.6 (222/3,953)		
1	6.1 (252/4,105)		
2	7.6 (225/2,948)		
3 or more	9.5 (347/3,641)		
	VTE Group [A]	No-VTE Group [B]	Cost Difference [A]-[B]
All-cause costs, mean (\$)			
Male	38,003	19,325	18,678
Female	30,208	16,276	13,932
Baseline VTE risk factors			
0	18,156	4,881	13,275
1	24,980	10,735	14,245
2	34,337	20,405	13,932
3 or more	59,564	36,358	23,206
Disease-related costs, mean (\$)			
Male	3,637	280	3,357
Female	2,772	189	2,583
Baseline VTE risk factors			
0	2,197	9	2,188
1	2,612	87	2,525
2	2,715	355	2,360
3 or more	5,132	518	4,614

^aEvaluated up to 1 year after the index date.

^bRisk of post-thrombotic syndrome was calculated on the subset of patients with more than 90 days of follow-up.

SD = standard deviation; VTE = venous thromboembolism.

high-quality health care services within limited budgets. As the demands are always greater than the budget, tools that can inform decisions on the allocation of limited resources are of interest.⁴²

Limitations

This study is subject to several limitations. The foremost limitation is the inclusion of a nonvalidated measure of potentially disease-related diagnoses in the cost calculations. Second, the objective of the current study was to evaluate the risk and costs of VTE from a managed care perspective. It was beyond the scope of this study to assess whether thromboprophylaxis is beneficial. Therefore, our study was conducted on all VTE

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FIGURE 2 All-Cause and Potentially Disease-Related Health Care Costs^a

^aAll cost differences between the venous thromboembolism (VTE) group and the no-VTE group (i.e., total and categorized by hospitalization, outpatient, and pharmacy costs) were statistically significantly different than 0 at $P < 0.001$. The mean cost differences (bootstrapped 95% confidence intervals) for the all-cause and the potentially VTE-related diagnoses (recurrent VTE, PTS, or exploratory endpoints) were \$15,941 (\$14,819-\$17,012) and \$2,913 (\$2,693-\$3,157), respectively.

^bIncludes VTE, PTS, and exploratory endpoint outcomes (thrombocytopenia, superficial venous thrombosis, venous ulcer, pulmonary hypertension, stasis dermatitis, and venous insufficiency).

PTS = post-thrombotic syndrome; VTE = venous thromboembolism.

patients regardless of thromboprophylaxis and was not specifically focused on a comparison of patients according to thromboprophylaxis use. Further research is warranted to evaluate the potential cost benefit or cost saving associated with VTE prophylaxis in VTE patients. Third, claims databases may contain inaccuracies or omissions in procedures, diagnoses, or costs. Fourth, the study evaluated only direct medical costs. Information to determine the indirect costs of VTE, such as work productivity loss and reduced quality of life, was not available. Fifth, the observational design was susceptible to various biases, such as information or classification bias (e.g., identification of false-positive VTE events). It is also possible that VTE events were undercoded (i.e., false negatives). Sixth, the distribution of the type of insurance in the current study poses limits to the generalizability of the results to the U.S. population. For the U.S. population, the rates of private and government coverage were 67% and 29%, respectively (not mutually exclusive) in 2008,⁴³ compared with approximately 2% government coverage in the present study. Finally, the database did not include mortality data.

Despite these limitations, well-designed observational studies with appropriate statistical techniques adjusting for potential confounding factors through matching techniques can provide valuable information with real-life scenarios and high generalizability.

Conclusions

In this large matched-cohort study, VTE was associated with a 3.6% risk of hospital-documented recurrent VTE and a 7.1% risk of PTS during a follow-up of up to 1 year after an index VTE. VTE was also associated with significant health care cost burden, and potentially disease-related health care costs represented nearly one-fifth of the incremental all-cause costs associated with VTE.

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APPENDIX Diagnosis Codes Used to Identify Post-Thrombotic Syndrome and Exploratory Endpoints

Medical Term	ICD-9-CM code(s)	Description
Post-thrombotic syndrome^a		
Pain	729.5	Pain in limb
Swelling of the limb	729.81	Swelling of limb
Varicose veins of the lower extremities	454.x	Varicose veins of lower extremities
Postphlebotic syndrome	459.1	Postphlebotic syndrome
Other disorders of the circulatory system	459.8x	Other specified disorders of circulatory system
Exploratory endpoints^b		
Thrombocytopenia	287.3	Primary thrombocytopenia
	287.4	Secondary thrombocytopenia
	287.5	Thrombocytopenia unspecified
Superficial venous thrombosis	451.0	Phlebitis and thrombophlebitis of superficial vessels of lower extremities
Venous ulcer	454.0	Varicose veins of lower extremities with ulcer
	454.2	Varicose veins of lower extremities with ulcer and inflammation
	459.11	Postphlebotic syndrome with ulcer
	459.13	Postphlebotic syndrome with ulcer and inflammation
	459.31	Chronic venous hypertension with ulcer
	459.33	Chronic venous hypertension with ulcer and inflammation
Pulmonary hypertension	415.0	Acute cor pulmonale
	416.0	Primary pulmonary hypertension
	416.8	Other chronic pulmonary heart diseases
Stasis dermatitis	454.1	Varicose veins of lower extremities with inflammation
Venous insufficiency	459.81	Venous (peripheral) insufficiency, unspecified

^aAs defined in MacDougall DA, Feliu AL, Boccuzzi SJ, Lin J. Economic burden of deep-vein thrombosis, pulmonary embolism, and post-thrombotic syndrome. *Am J Health-Syst Pharm*. 2006;63(20 Suppl 6):S5-S15.

^bAs identified in the literature²¹⁻³¹ and reviewed by the authors during the study protocol development prior to conducting the study analyses.

ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.