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ORIGINAL RESEARCH

Incidence and Risk Factors of Pulmonary Hypertension After Venous Thromboembolism: An Analysis of a Large Health Care Database

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BACKGROUND: Pulmonary hypertension (PH) is a devastating potential complication of pulmonary embolism, a manifestation of venous thromboembolism (VTE). The incidence of and risk factors for PH in those with prior VTE are poorly characterized.

METHODS AND RESULTS: *International Classification of Diseases* (*ICD*) codes from inpatient and outpatient medical claims from MarketScan administrative databases for years 2011 to 2018 were used to identify cases of VTE, comorbidities before the VTE event, and PH occurring subsequent to the VTE event. Cumulative incidence and hazard ratios (HR), and their 95% CI, were calculated. The 170 021 VTE cases included in the analysis were on average (±SD) 57.5±15.8 years old and 50.5% were female. A total of 5943 PH cases accrued over an average follow-up of 1.94 years. Two years after incident VTE, the cumulative incidence (95% CI) of PH was 3.5% (3.4%–3.7%) overall. It was higher among older individuals, among women (3.9% [3.8%–4.1%]) than men (3.2% [3.0%–3.3%]), and among patients presenting with pulmonary embolism (6.2% [6.0%–6.5%]) than those presenting with deep vein thrombosis only (1.1% [1.0%–1.2%]). Adjusting for age and sex, risk of PH was higher among patients with VTE with underlying comorbidities. Using the Charlson comorbidity index, there was a dose–response relationship, whereby greater scores were associated with increased PH risk (score ≥5 versus 0: HR, (2.50 [2.30–2.71])). When evaluating individual comorbidities, the strongest associations were observed with concomitant heart failure (HR, 2.17 [2.04–2.31]), chronic pulmonary disease (2.01 [1.90–2.14]), and alcohol abuse (1.66 [1.29–2.13]).

CONCLUSIONS: In this large, real-world population of insured people with VTE, 3.5% developed PH in the 2 years following their initial VTE event. Risk was higher among women, with increasing age, and in those with additional comorbidities at the time of the VTE event. These data provide insights into the burden of PH and risk factors for PH among patients with VTE.

Key Words: epidemiology ■ pulmonary hypertension ■ venous thromboembolism

Pulmonary hypertension (PH) is the final physiologic process of a group of disparate diseases affecting the pulmonary vasculature, and has devastating consequences for both quality and quantity of life.[1–3] PH is defined by an elevation in pulmonary artery pressures,[4] which leads to a progressive increase in right ventricular afterload, thus putting increased demands on the right ventricle and eventually compromising cardiac output. Survivors of venous thromboembolism (VTE)—which consists of both pulmonary embolism (PE) and deep vein thrombosis (DVT), and affects ≈1.1 million Americans annually[5]—are at elevated risk of PH. VTE, more specifically PE, is associated with PH when pulmonary emboli/thrombi do not resolve, but instead obstruct major pulmonary arteries leading to increased pulmonary artery pressures and right heart

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CLINICAL PERSPECTIVE

What Is New?

- Among patients with venous thromboembolism (VTE), 3.5% develop pulmonary hypertension (PH) within 2 years; in patients presenting with pulmonary embolism, 6.2% developed PH within 2 years.
- Risk of PH is higher among patients with VTE who were older, female, and had more concomitant comorbidities (eg, heart failure, chronic pulmonary disease, and alcohol abuse).

What Are the Clinical Implications?

- Patients with VTE are at meaningfully elevated risk of PH, which is a devastating clinical condition.
- Knowing risk factors for PH in the context of VTE may be clinically useful for identifying VTE patients at elevated risk of PH earlier in the disease process, which may lead to PH prevention or improved management.

Nonstandard Abbreviations and Acronyms

CPRD	clinical practice research datalink
CTEPH	chronic thromboembolic pulmonary hypertension
OAC	oral anticoagulant
PH	pulmonary hypertension

remodeling. PH subsequent to VTE is classified by the World Health Organization[6] and other medical entities[3,7] as "group 4 PH." It is also commonly referred to as chronic thromboembolic pulmonary hypertension (CTEPH).

The true incidence of PH following VTE is unknown.[3,8] Prior literature has reported a range of 0.1% to 9.1% for the cumulative incidence of PH in patients with VTE.[8–11] To date, the largest such study reported a cumulative incidence of 1.3% in the 2 years following a PE event, and 3.3% in the 10 years after the PE.[8] That study included 23 329 patients with VTE and 283 PH cases, and utilized data from a subset of the UK Clinical Practice Research Datalink (CPRD), which had linkage to data on hospitalizations and mortality. Other prior studies were much smaller.

Additional insight into factors that are associated with development of PH, beyond experiencing a VTE event, is needed. Much of what we know about PH comes from specialized disease registries or from patients enrolled into randomized controlled trials. Patients who take part in registries or randomized controlled trials are different from the general PH patient profile because such studies often take place at academic medical centers, and randomized controlled trials frequently have rigid criteria for enrollment. In real-world populations, multiple pathologies may play a role in PH development after a VTE event. As such, there is a clear need for real-world data to elucidate the burden of PH among VTE survivors, regardless of the exact cause, and how this burden varies by demographic factors, VTE presentation, and comorbid disease burden.

Using administrative data from the MarketScan databases, we evaluated risk of PH subsequent to VTE. Specifically, we report incidence of PH after VTE, and risk factors for PH among VTE survivors.

METHODS

Data Source

This retrospective cohort analysis utilized IBM MarketScan Commercial Claims and Encounters, and Medicare Supplemental and Coordination of Benefits databases[12] for calendar years 2011 through 2018. These are commercial data, available for purchase from IBM MarketScan. The licensing agreement through which we are accessing the data prohibit us from sharing the data. However, to facilitate replication, the corresponding author will make available the data analysis protocols and code, upon reasonable request.

The IBM MarketScan data contain private-sector health data from some 350 different payers across the United States. These plans contribute data to a central repository, which is then standardized into a common data format for research and blinded so that specific plans cannot be identified. The large number of contributing payers and broad geographic coverage of plans increases the generalizability of our study results to commercially insured populations.[12] Individual-level identifiers are used to link data across enrollment records and inpatient, outpatient, ancillary, and drug claims.

These administrative databases contain individual-level, de-identified, HIPAA-compliant, health care claims information from US employers, health plans, hospitals, and Medicare programs.[12] Informed consent was not obtained given the nature of the data. The University of Minnesota Institutional Review Board deemed this research exempt from review.

VTE Cohort

We included in the present analysis individuals aged 18 to 99 years of age with incident VTE, at least 1 prescription for an oral anticoagulant (OAC) within the 31 days before or after their first VTE claim, and

≥3 months of continuous enrollment before their first OAC prescription.[13] We defined incident VTE as having at least 1 inpatient claim for VTE or 2 outpatient claims for VTE, which were 7 to 185 days apart, in any position, based on *International Classification of Diseases, Ninth Revision and Tenth Revision* (*ICD-9*; *ICD-10*), *Clinical Modification* codes (listed in Table S1), with no evidence of prior VTE *ICD* code. We also required that beneficiaries were anticoagulant-naïve patients at the time of the VTE event. We then identified OAC prescriptions, using outpatient pharmaceutical claims data, by National Drug Codes indicating fills for apixaban, rivaroxaban, low molecular weight heparin, or warfarin. Validation studies for apixaban and rivaroxaban claims have not yet been conducted. However, the validity of warfarin claims in administrative databases is excellent (sensitivity: 94%, positive predictive value: 99%).[14] Our VTE definition is similar to that used in a recent validation study by Sanfilippo et al, which reported a positive predictive value of 91%.[15] The Sanfilippo definition was also based on 1 inpatient or 2 outpatient VTE claims, and required evidence of treatment. As a secondary analysis, we classified VTE cases according to whether there were *ICD* codes for PE, or if the *ICD* codes only indicated DVT. We used VTE instead of solely PE for the primary analysis since approximately one third of DVTs are accompanied by "silent" PEs,[16] and not all CTEPH cases have a documented antecedent history of acute PE[17] (eg, only 75% in a registry of patients with PH from Europe and Canada[18]).

PH Identification

To define PH, we required at least 1 inpatient or 2 outpatient claims for PH (*ICD-9-CM* codes 416.0, 416.2, 416.8, 416.9 or *ICD-10-CM* codes I27.0, I27.2x, I27.82, I27.9, in any position). This is comparable to definitions used in prior analyses of PH in administrative data.[9,19,20] Our definition was most similar to that used in a medical record validation study by Wijeratne et al.[9] In their study, based in Ontario, Canada, the authors identified 100 individuals with PH *ICD* codes, and then validated the cases with hospital chart abstraction. The positive predictive value was 97%. In a United Kingdom–based validation study of group 4 PH, which also validated cases identified by *ICD* codes with manual medical record review, the specificity was 99% and the sensitivity was 86%.[8]

In the present analysis, we required patients to have no PH codes before VTE, because our interest was incident PH. Additionally, to define PH we required *ICD* codes to be present 90 days or more following the initiation of OACs after a VTE event, in order to discriminate PH from "subacute" PE. Current PH diagnostic guidelines also recommend abstaining from diagnosing PH until 90 days after the initial PE event.[3] Therefore, in the present analysis we required evidence of PH at least 90 days after the initial PE event. For the primary analysis we included all PH cases, recognizing that multimorbidity often creates challenges in classifying PH group.[9] However, in sensitivity analyses we attempted to isolate group 4 PH by restricting the analysis to patients with VTE without evidence of underlying diseases of the heart (ie, coronary heart disease, heart failure, and atrial fibrillation) or lung (ie, chronic obstructive pulmonary disease [including emphysema], asthma, and lung cancer). Sensitivity analyses were also conducted requiring procedure codes for right heart catheterization or an echocardiogram occurring between 90 days before date of PH diagnosis to up to 180 days after.

Identification of Potential PH Risk Factors

The literature was reviewed to identify potential PH risk factors for exploration in the present analysis. To define these risk factors for analysis, we used information before the OAC initiation date (minimum 90 days) from all data sources in MarketScan (ie, demographic data, inpatient, outpatient, and pharmacy claims). We identified 19 prespecified comorbidities using the inpatient and outpatient data. Wherever possible, validated algorithms[21,22] were used to define risk factors using both *ICD-9* and *ICD-10* codes. These prespecified covariates are listed in Table 1 and the codes in Table S2. We also examined whether a person was enrolled in a high-deductible health plan. This variable was defined via the MarketScan "Plan Type" variable that categorizes which health insurance plans cover patients enrolled in the dataset.

Statistical Analysis

The initial sample included 553 387 patients with *ICD* codes indicating VTE aged 18 to 99 years. The analytic sample was 432 950 once restricted to individuals ever prescribed an OAC between January 1, 2011 and December 31, 2018; 273 938 after requiring the first OAC prescription to be within 31 days of the VTE *ICD* code date; 203 289 after requiring ≥90 days of continuous enrollment before the first OAC prescription; and 194 403 after excluding those with *ICD* codes for PH before the VTE event. After additionally requiring ≥90 days of follow-up post-VTE, the final analytic sample was 170 021. A flowchart of selection into the study is shown in Figure 1 and a graphical depiction[23] of the study design is shown in Figure 2.

Descriptive characteristics are presented as means±SD and percentages. The Nelson-Aalen estimator was used to estimate the cumulative incidence and 95% CI. Incidence rates per 1000 person-years were also calculated. Cox proportional hazards regression was used to estimate the association between potential

Table 1. Characteristics of Venous Thromboembolism Patients by Sex: The MarketScan Databases 2011 to 2018

VTE patient characteristic*	Female N=85 771	Male N=84 250
Demographics		
Age, y		
Age, mean y±SD	57.0 (17.2)	58.0 (14.2)
18–29	5208 (6.1)	2750 (3.3)
30–39	8907 (10.4)	5442 (6.5)
40–49	14 827 (17.3)	12 908 (15.3)
50–59	18 831 (22.0)	24 854 (29.5)
60–69	17 431 (20.3)	21 829 (25.9)
70–79	10 334 (12.1)	9819 (11.7)
80–89	8167 (9.5)	5755 (6.8)
90–99	2066 (2.4)	893 (1.1)
Health insurance coverage		
High-deductible health plan	3776 (4.6)	4528 (5.6)
Clinical aspects of VTE		
Presentation		
PE	41 349 (48.2)	40 172 (47.7)
Anticoagulant		
Apixaban	6524 (7.6)	6644 (7.9)
Rivaroxaban	17 264 (20.1)	18 082 (21.5)
LMWH	10 802 (12.6)	8120 (9.6)
Warfarin	50 661 (59.1)	50 839 (60.3)
Comorbidities†		
Chronic pulmonary disease	22 225 (25.9)	17 809 (21.1)
Hematological disorders	14 215 (16.6)	11 229 (13.3)
Heart failure	9245 (10.8)	9926 (11.8)
Hypertension	45 217 (52.7)	47 767 (56.7)
Diabetes	16 560 (19.3)	18 854 (22.4)
Atrial fibrillation	5323 (6.2)	6697 (8.0)
Myocardial infarction	3972 (4.6)	5913 (7.0)
Ischemic stroke/TIA	10 112 (11.8)	9474 (11.3)
Peripheral artery disease	9609 (11.2)	10 457 (12.4)
Kidney disease	6978 (8.1)	8664 (10.3)
Liver disease	7857 (9.2)	7971 (9.5)
Malignancy	17 707 (20.6)	16 967 (20.1)
Metastatic cancer	7720 (9.0)	6207 (7.4)
Alcohol abuse	434 (0.5)	1171 (1.4)
Autoimmune disease	15 811 (18.4)	10 493 (12.5)
HIV/AIDS	123 (0.1)	494 (0.6)
Splenectomy	207 (0.1)	194 (0.1)
CCI, mean±SD	2.1 (2.5)	2.1 (2.4)
CCI, score %		
0 (none noted)	29 743 (34.7)	30 370 (36.1)
1–2 (mild)	28 273 (33.0)	26 563 (31.5)
3–4 (moderate)	12 558 (14.6)	12 303 (14.6)
≥5 (severe)	15 197 (17.7)	15 014 (17.8)
Incident PH during follow-up		
PH‡	3303 (3.9)	2640 (3.1)
PH w/echo or RHC‡	1415 (1.7)	1145 (1.4)

CCI indicates Charlson comorbidity index; LMWH, low molecular weight heparin; PE, pulmonary embolism; PH, pulmonary hypertension; RHC, right heart catheterization; TIA, transient ischemic attack; and VTE, venous thromboembolism.

*% unless otherwise noted.

†Comorbidities were identified before incident VTE.

‡Definition used.

risk factors and risk of incident PH among patients with VTE. Follow-up began 90 days after the first OAC prescription for VTE treatment was filled, in order to reduce the inclusion of subacute PH in our end point. Person-time accrued until incident PH, health plan disenrollment, or the end of study follow-up. Two levels of adjustment were explored. The first model only adjusted for age (continuous) and sex. The second model adjusted for all demographic variables (ie, sex, age, and health insurance coverage), clinical aspects of VTE (ie, presentation, type of anticoagulant therapy), and all comorbidities.

Sensitivity analyses were also conducted. First, we restricted to patients with VTE with no *ICD* codes indicating lung or heart disease to limit our sample to only individuals with CTEPH. Second, to create a more specific definition of PH, we required *ICD* inpatient and Current Procedural Terminology outpatient procedure codes indicating confirmatory echocardiogram or right heart catheter procedures occurring anywhere from 90 days before 180 days after a patient's PH diagnosis date. Data analyses were conducted in SAS 9.3 and STATA/SE 15.1.

RESULTS

Cumulative Incidence of PH

Our population of interest included 170 021 VTE cases who were on average (±SD) 57.5±15.8 years old and 50.5% were female. The initial presentation included evidence of PE (with or without DVT) in 47.9%, and DVT-only in the remainder. A total of 5943 PH cases accrued over an average follow-up of 1.9±1.8 years (maximum follow-up: 7.50 years). Cumulative incidence of PH is reported in Table 2, for the entire follow-up and according to timeframes of interest, overall, and stratified by sex and VTE presentation. Two years after incident VTE, the cumulative incidence (95% CI) of PH was 3.5% (3.4%–3.7%) overall. It was higher among women (3.9% [3.8%–4.1%]) than men (3.2% [3.0%–3.3%]), and among patients presenting with PE (6.2% [6.0%–6.5%]) than those presenting with DVT-only (1.1% [1.0%–1.2%]).

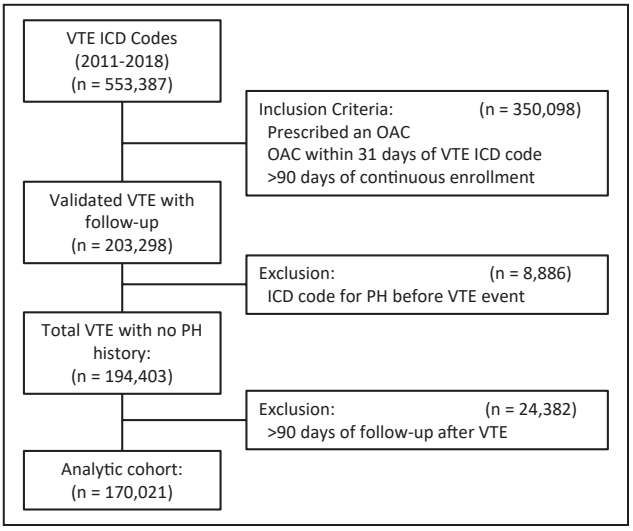

Figure 1. Flowchart for selection of retrospective cohort design study population.
ICD indicates *International Classification of Diseases*; OAC, oral anticoagulant; PH, pulmonary hypertension; and VTE, venous thromboembolism.

Risk Factors for Developing PH

Incidence rate per 1000 person-years and hazard ratios (HRs) for risk of PH according to VTE patient characteristics are presented in Table 3, with adjustment for age and sex. Risk of incident PH was higher in women than men (HR, 1.24 [1.17–1.31]) and increased with age (HR, 1.26 [1.24–1.28]) per decade]. Risk was lower among individuals on a high-deductible plan (0.83 [0.72–0.96]). Risk of PH was 5-fold higher among patients with VTE initially presenting with evidence of PE (5.04 [4.72–5.38]) as compared with those presenting with DVT-only. We also found some evidence that PH risk varied according to VTE anticoagulant treatment strategy. Risk of PH for patients prescribed rivaroxaban and low molecular weight heparin was similar to that of patients prescribed warfarin. However, individuals prescribed apixaban were at greater risk of PH than those prescribed warfarin (1.25 [1.12–1.40]). The association remained in a post-hoc sensitivity analysis where we restricted to users of the standard (5 mg) apixaban dose (1.18 [1.06–1.33]).

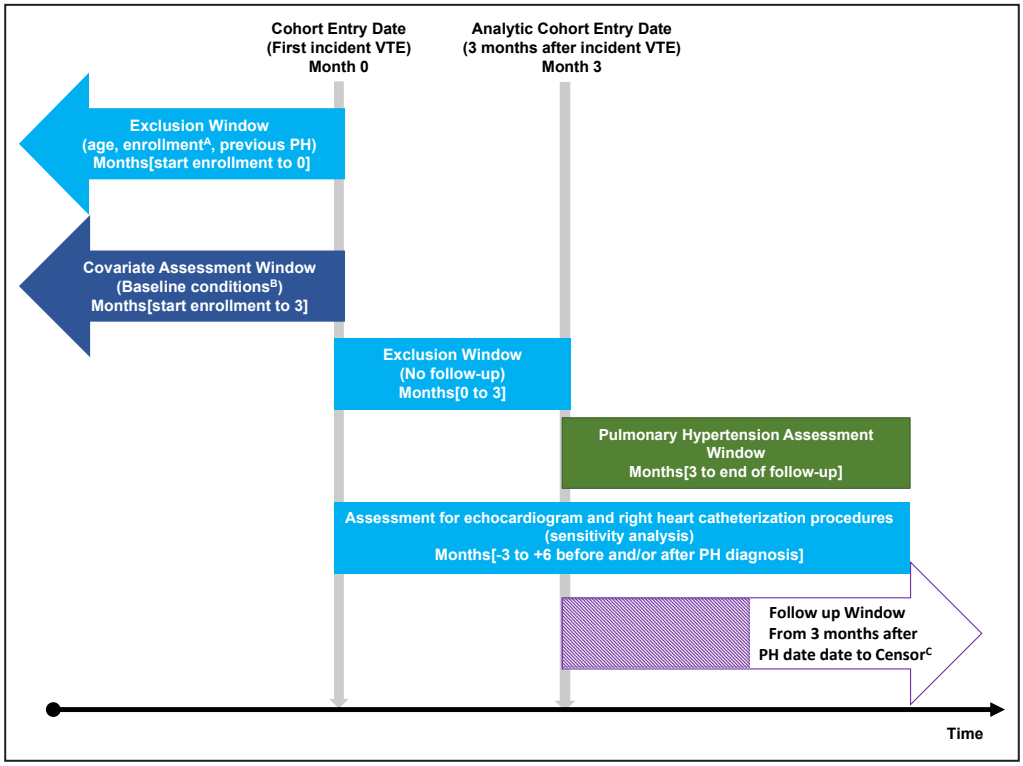

Figure 2. Graphical representation of retrospective cohort study design.
[A]Excluded if: Not aged 18 to 99 years, did not have <3 months of steady enrollment, or had a pulmonary hypertension diagnosis before VTE index date.
[B]Covariates include age at time of incident VTE, sex, and a full list of covariates and code algorithms provided in Table S2.
[C]Censored at earliest outcome of pulmonary hypertension, disenrollment, or end of the study period. PH indicates pulmonary hypertension; and VTE, venous thromboembolism.

Table 2. Cumulative Incidence (%) and 95% CIs of Pulmonary Hypertension Following Incident VTE: The MarketScan Databases 2011 to 2018

Time after VTE*	All	Men	Women	PE	DVT
3–6 mo	0.90 (0.85–0.95)	0.78 (0.72–0.84)	1.02 (0.95–1.09)	1.65 (1.56–1.75)	0.21 (0.18–0.24)
3–9 mo	1.59 (1.53–1.66)	1.34 (1.26–1.43)	1.84 (1.74–1.94)	2.93 (2.81–3.06)	0.38 (0.33–0.42)
1 y	2.09 (2.01–2.17)	1.77 (1.67–1.87)	2.41 (2.29–2.52)	3.82 (3.68–3.97)	0.52 (0.47–0.57)
2 y	3.54 (3.43–3.65)	3.15 (3.00–3.30)	3.93 (3.77–4.10)	6.24 (6.03–6.45)	1.11 (1.03–1.20)
3 y	4.74 (4.60–4.89)	4.26 (4.07–4.45)	5.23 (5.02–5.44)	8.19 (7.92–8.46)	1.64 (1.53–1.77)
4 y	5.95 (5.77–6.13)	5.34 (5.10–5.59)	6.55 (6.29–6.83)	10.07 (9.74–10.42)	2.24 (2.09–2.41)
5 y	7.24 (7.01–7.48)	6.53 (6.22–6.85)	7.97 (7.63–8.32)	12.12 (11.69–12.56)	2.89 (2.68–3.12)

DVT indicates deep vein thrombosis; PE, pulmonary embolism; and VTE, venous thromboembolism.
*A minimum of 90 days of follow-up post venous thromboembolism were required in order to limit capture of subacute pulmonary hypertension.

Risk of incident PH was also significantly higher among individuals with all of the comorbidities explored, with the exception of HIV/AIDS, malignancy, and splenectomy for which the associations were not statistically significant. Using the Charlson comorbidity index, there was a dose–response relationship, whereby greater scores were associated with increased PH risk (score ≥5 versus 0: HR, 2.50 [2.30–2.71]). Among the individual comorbidities, the strongest risk of developing PH was observed among patients who at the time of their VTE had concomitant heart failure (HR, 2.17 [2.04–2.31]), chronic pulmonary disease (2.01 [1.90–2.14]), or alcohol abuse (1.66 [1.29–2.13]). Associations were generally similar, or slightly attenuated, in a model adjusting for demographic variables, clinical aspects of VTE, and all comorbidities.

In sensitivity analyses, associations were generally similar when we restricted our sample to patients with VTE without evidence of heart and/or lung disease (n=109 704; Table S3). One notable difference was that the magnitude of the HR (95% CI) for PE versus DVT was greater in the sample without evidence of heart and lung disease (7.62 [6.84–8.48]), than it was in the full sample.

We also conducted sensitivity analyses, whereby for a participant to be classified as having PH, we required relevant imaging procedure codes. As expected with these more stringent criteria, the total number of incident PH cases was lower (n=2560) as were cumulative incidence rates across various time-intervals after incident VTE (Table S4). Patterns were similar to the primary analysis, whereby incidence was higher among women than men, and patients with VTE initially presenting with PE as compared with those presenting with DVT-only. Likewise, associations of potential risk factors to hazard of PH were generally similar to those of the main analysis (Table S5).

DISCUSSION

PH is a recognized complication of VTE; however, few studies have evaluated the incidence of this adverse outcome in a population-based and prospective manner. Using data from the large MarketScan administrative databases, we identified 170 021 insured patients with VTE, of whom 5934 subsequently developed PH. The cumulative incidence of PH among VTE survivors was 3.5% over 2 years of follow-up in this population. We also reported numerous risk factors for PH among patients with VTE. This is the largest study we are aware of that has evaluated incidence and risk factors for PH in the context of VTE. Findings provide much needed data regarding the future burden of PH among patients with VTE, and may be clinically useful for identifying patients with VTE at elevated risk of PH.

Incidence of PH Among VTE Survivors

In the present study, the cumulative incidence of PH in the 2 years following incident VTE was 3.5%. Earlier publications have reported a range of 0.1%–9.1%, over variable timeframes.[8–11] The wide range of estimates in the prior literature has caused much speculation. Possible reasons for the range include differences in inclusion criteria of the populations studied, variation in the duration of observation, difficulty in differentiating acute PE from CTEPH, referral bias, and whether PH diagnosis was triggered by clinical symptoms or routine screening.[3,24] As noted earlier, the largest prior study evaluating PH after VTE used data from a subset of the CPRD. It reported a cumulative incidence of 1.3% at 2 years after the PE event, and 3.3% at 10 years after the PE.[8] In a meta-analysis by Ende-Verhaar et al, of 16 studies including 4047 patients with PE who were followed for ≈2 years for CTEPH, the overall weighted incidence of CTEPH was 2.3%[25] However, the incidence was 3.2% when restricted to individuals the authors defined as "survivors" (ie, had symptomatic PE and were alive after an initial treatment period of 6 months). Our analysis has some similarities to the "survivor" analysis by Ende-Verhaar because we required evidence of PH 3 months after the initial VTE event in order to discriminate PH from "subacute" PE. Overall, the cumulative incidence in our primary

Table 3. Patients With VTE and Risk of Incident PH: The MarketScan Databases 2011 to 2018

VTE patient characteristic* (N=170 021)	Incident PH (%) N=5943	Incident rate per 1000 p-y (95% CI)	Hazard ratio† (95% CI)	Hazard ratio‡ (95% CI)
Demographics				
Sex				
Female	3303 (3.9)	20.1 (19.4–20.8)	1.24 (1.17–1.31)	1.25 (1.19–1.32)
Male	2640 (3.1)	15.9 (15.3–16.6)	1 (Ref)	1 (Ref)
Age				
18–29	124 (1.6)	9.4 (7.8–11.2)	1 (Ref)	1 (Ref)
30–39	280 (2.0)	10.2 (9.1–11.5)	1.15 (0.93–1.42)	1.08 (0.88–1.34)
40–49	679 (2.5)	11.8 (11.0–12.7)	1.38 (1.14–1.68)	1.24 (1.02–1.51)
50–59	1386 (3.2)	15.1 (14.3–15.9)	1.82 (1.51–2.19)	1.47 (1.22–1.77)
60–69	1388 (3.5)	20.8 (19.7–21.9)	2.36 (1.96–2.83)	1.61 (1.33–1.94)
70–79	1074 (5.3)	25.5 (24.0–27.1)	3.00 (2.49–3.61)	1.73 (1.42–2.10)
80–89	853 (6.1)	31.8 (29.7–34.0)	3.60 (2.98–4.35)	2.08 (1.70–2.53)
90–99	159 (5.4)	36.1 (30.9–42.1)	3.71 (2.94–4.70)	2.29 (1.80–2.92)
Health insurance coverage				
High-deductible health plan	201 (2.4)	11.2 (9.8–12.9)	0.83 (0.72–0.96)	0.89 (0.77–1.03)
Other health plans	5742 (3.6)	18.4 (17.9–18.9)	1 (Ref)	1 (Ref)
Clinical aspects of VTE				
Presentation				
DVT	1080 (1.2)	6.2 (5.8–6.6)	1 (Ref)	1 (Ref)
PE	4863 (6.0)	31.3 (30.4–32.1)	5.04 (4.72–5.38)	4.91 (4.59–5.25)
Anticoagulant				
Apixaban	362 (2.8)	27.6 (24.9–30.6)	1.25 (1.12–1.40)	1.14 (1.02–1.27)
Rivaroxaban	1017 (2.9)	17.4 (16.4–18.5)	0.98 (0.91, 1.05)	0.98 (0.91–1.05)
LMWH	523 (2.8)	17.6 (16.2–19.2)	1.00 (0.91–1.09)	1.10 (1.00–1.22)
Warfarin	3993 (3.9)	17.6 (17.1–18.2)	1 (Ref)	1 (Ref)
Comorbidities§				
Chronic pulmonary disease				
Yes	2274 (5.7)	37.2 (35.4–39.0)	2.01 (1.90–2.14)	1.57 (1.48–1.67)
No	3669 (2.8)	15.1 (14.6–15.5)	1 (Ref)	1 (Ref)
Hematological disorders				
Yes	1142 (4.5)	24.6 (23.2–26.0)	1.32 (1.24–1.41)	1.12 (1.05–1.20)
No	4801 (3.3)	16.9 (16.5–17.4)	1 (Ref)	1 (Ref)
Heart failure				
Yes	1388 (7.2)	42.0 (39.9–44.3)	2.17 (2.04–2.31)	1.59 (1.49–1.71)
No	4555 (3.0)	15.3 (14.9–15.8)	1 (Ref)	1 (Ref)
Hypertension				
Yes	4087 (4.4)	23.3 (22.5–24.0)	1.52 (1.43–1.61)	1.24 (1.16–1.32)
No	1856 (2.4)	12.0 (11.5–12.6)	1 (Ref)	1 (Ref)
Diabetes				
Yes	1727 (4.9)	26.2 (25.0–27.4)	1.42 (1.34–1.50)	1.20 (1.13–1.27)
No	4216 (3.1)	16.0 (15.5–16.4)	1 (Ref)	1 (Ref)
Atrial fibrillation				
Yes	752 (6.3)	34.5 (32.1–37.0)	1.55 (1.43–1.68)	1.19 (1.10–1.29)
No	5191 (3.3)	16.8 (16.4–17.3)	1 (Ref)	1 (Ref)
Myocardial infarction				
Yes	566 (5.7)	32.1 (29.6–34.9)	1.53 (1.40–1.67)	1.03 (0.94–1.13)
No	5377 (3.4)	17.2 (16.8–17.7)	1 (Ref)	1 (Ref)

(*Continued*)

Table 3. Continued

VTE patient characteristic* (N=170 021)	Incident PH (%) N=5943	Incident rate per 1000 p-y (95% CI)	Hazard ratio† (95% CI)	Hazard ratio‡ (95% CI)
Ischemic stroke/TIA				
Yes	950 (4.9)	26.1 (24.5–27.8)	1.16 (1.08–1.25)	0.98 (0.91–1.06)
No	4993 (3.3)	17.0 (16.5–17.5)	1 (Ref)	1 (Ref)
Peripheral artery disease				
Yes	1020 (5.1)	27.7 (26.1–29.5)	1.25 (1.17–1.34)	1.07 (0.99–1.15)
No	4923 (3.3)	16.8 (16.3–17.3)	1 (Ref)	1 (Ref)
Kidney disease				
Yes	864 (5.5)	31.7 (29.6–33.9)	1.46 (1.36–1.58)	1.26 (1.17–1.37)
No	5079 (3.3)	16.8 (16.3–17.2)	1 (Ref)	1 (Ref)
Liver disease				
Yes	629 (4.0)	24.4 (22.5–26.4)	1.33 (1.23–1.45)	1.08 (0.99–1.18)
No	5314 (3.5)	17.5 (17.0–17.9)	1 (Ref)	1 (Ref)
Malignancy				
Yes	1213 (3.5)	22.3 (21.1–23.6)	1.06 (0.99–1.13)	0.96 (0.89–1.04)
No	4730 (3.5)	17.2 (16.7–17.7)	1 (Ref)	1 (Ref)
Metastatic cancer				
Yes	398 (2.9)	25.6 (23.2–28.3)	1.17 (1.06–1.30)	1.09 (0.97–1.23)
No	5545 (3.6)	17.6 (17.2–18.1)	1 (Ref)	1 (Ref)
Alcohol abuse				
Yes	61 (3.8)	30.5 (23.7–39.2)	1.66 (1.29–2.13)	1.39 (1.07–1.79)
No	5882 (3.5)	17.9 (17.5–18.4)	1 (Ref)	1 (Ref)
Autoimmune disease				
Yes	1151 (4.4)	22.2 (20.9–23.5)	1.23 (1.15–1.31)	1.11 (1.05–1.18)
No	4792 (3.3)	17.2 (16.7–17.7)	1 (Ref)	1 (Ref)
HIV/AIDS				
Yes	24 (3.5)	18.7 (12.5–27.9)	1.33 (0.89–1.99)	1.41 (0.94–2.11)
No	5919 (3.5)	18.0 (17.5–18.5)	1 (Ref)	1 (Ref)
Splenectomy				
Yes	14 (3.5)	22.6 (13.4–38.2)	1.27 (0.75–2.14)	1.08 (0.64–1.83)
No	5929 (3.5)	18.0 (17.5–18.5)	1 (Ref)	1 (Ref)
Charlson comorbidity index				
0 (none noted)	1215 (2.0)	9.5 (9.0–10.1)	1 (Ref)	
1–2 (mild)	2070 (3.8)	18.7 (17.9–19.5)	1.71 (1.59–1.84)	
3–4 (moderate)	1231 (5.0)	25.6 (24.2–27.1)	2.12 (1.95–2.30)	
≥5 (severe)	1427 (4.7)	32.8 (31.1–34.5)	2.50 (2.30–2.71)	

DVT indicates deep vein thrombosis; LMWH, low molecular weight heparin; PE, pulmonary embolism; PH, pulmonary hypertension; TIA, transient ischemic attack; and VTE, venous thromboembolism.

*% unless otherwise noted.

†Adjusted for age and sex.

‡Adjusted for all characteristics in the table (except for the Charlson comorbidity index since that is a count of comorbidities).

§Comorbidities were identified before incident VTE.

analysis aligns reasonably well with estimates from the existing literature, especially taking into consideration that we evaluated all PH and not just CTEPH. Our incidence was somewhat higher than that observed in the CPRD. However, in our sensitivity analysis, which required evidence of cardiac imaging, the cumulative incidence of PH at 2 years was 1.5%, which was quite similar to that observed in CPRD. Validation studies are needed to determine the merits of requiring confirmatory imaging when defining PH in administrative data sources.

Risk Factors for PH Among VTE Survivors

As expected, PH incidence was higher among women than men and increased with age. Women are generally at somewhat greater PH risk than men,[5,19] though

the magnitude of that association may vary by PH type. For instance, women are at 3-fold greater risk of pulmonary arterial (group 1) hypertension than men.[26] In the present analysis, female patients with VTE were at 24% greater risk of PH than were men. In the CPRD analysis, women were at 44% greater risk.

There was a dose–response relationship between age and PH risk in the present evaluation of patients with VTE. Individuals >70 years of age were at >3 times greater risk of PH following VTE relative to participants in their 20s. A strong association between age and PH has been noted previously. Using U.S. National Hospital Discharge Survey data from 2001 to 2010, the age-adjusted hospitalization rate for PH was 131 per 100 000 discharges overall and 1527 per 100 000 for those aged ≥85 years.[19]

Little is known about how socioeconomic factors are implicated in PH risk, screening, and outcomes. In the present analysis, PH risk following VTE was lower among individuals with high-deductible health plans. PH is challenging to diagnose because the symptoms are nonspecific; it is possible that individuals with high-deductible health plans, who likely are of lower socioeconomic status, may have been less likely to seek care and/or have fewer diagnostic procedures and were therefore less likely to be diagnosed with PH.

PH risk was 5-fold greater among patients with VTE who initially presented with PE. This is to be expected given the pathophysiology of PH, and particularly CTEPH.[3,7] In sensitivity analyses where we excluded patients with VTE with evidence of heart and lung comorbidities, the association was even more robust, with patients presenting with PE being at 7-fold greater risk of incident PH. The variation of PH risk according to oral anticoagulant prescribed for the treatment of VTE was unexpected and warrants further study.

We also prospectively evaluated numerous clinical comorbidities that may elevate the risk of developing PH in patients with VTE. There was a dose–response association whereby patients with VTE with higher scores on the Charlson comorbidity index were at greater risk of developing PH. When individual comorbidities were explored, virtually all were associated with greater PH risk. The strongest associations were seen for heart failure, chronic obstructive pulmonary disease, and alcohol abuse. Heart failure and chronic obstructive pulmonary disease were also among the strongest PH risk factors in the CPRD analysis, which focused on CTEPH; alcohol abuse was not explored.[8] We did not see an association with splenectomy, unlike in CPRD[8] and some other reports.[27–29] However, we only had information on health status during the individuals' enrollment period. If someone had a prior splenectomy, that event would not be captured in the MarketScan data. It is important to keep in mind that this study considered any PH and did not distinguish between PH groups. However, this does reflect clinical practice where rarely 1 putative cause of PH is identified, and the cause is likely multifactorial. Sensitivity analyses restricted to individuals without *ICD* codes indicating preexisting heart or lung disease at the time of their VTE event yielded similar findings.

Strengths and Limitations

The primary strength of this analysis is the large sample of patients with VTE, and subsequently PH events, with a broad spectrum of clinical characteristics (such as may be seen in routine clinical practice). Generalizability is limited to US patients with VTE who had health insurance. Misclassification is an important potential threat to the validity of this study, as it is with virtually all administrative data analyses. To minimize misclassification, we used validated algorithms whenever possible.[15,21,22] The algorithm we used to define VTE is very good; the positive predictive value was 91% when validated in a different study population.[15] Likewise, the PH definition we used was verified in 97% of cases upon chart abstraction,[9] and in a study of group 4 PH the specificity of a similar definition was 99%.[8] Despite the excellent specificity observed in prior studies, we conducted sensitivity analyses requiring evidence of echocardiography and/or right heart catheter procedure codes in order to define PH. As expected, absolute incidence was somewhat lower with this definition. However, associations of potential risk factors for PH were generally similar. An important additional consideration of PH is that its symptoms are nonspecific, and the onset is insidious; therefore, some cases were almost certainly undiagnosed, which would impact sensitivity. Nevertheless, the "missing" cases reflect real-world clinical practice. Another limitation of the present analysis is that we did not evaluate mortality as an outcome since MarketScan lacks information on out-of-hospital death. Lack of information on mortality leads to overestimates of the cumulative incidence, since it does not allow for the consideration of death as a competing risk. This issue may be somewhat muted given that we required 3-month survival after the initial VTE event, and the relatively short follow-up time for identifying PH incidence. However, it could be a factor for groups with higher mortality (eg, older individuals, and those with more comorbidities). Lastly, given the large sample size, when interpreting our findings it is important to be mindful that statistically significant associations of small magnitude may not be clinically meaningful.

Despite these limitations, the fact that the incidence rates and risk factors reported herein align with expectations provides some reassurance about our approach. For the risk factor analyses, uncontrolled confounding is another important limitation, since we lacked information on relevant clinical information (eg,

size and anatomic location of thrombi). Though the MarketScan data have inherent limitations, they provide a unique opportunity to explore the incidence of PH following VTE in a real-world population. Prospective epidemiologic studies of PH have historically been exceedingly challenging because of the relative rarity of this condition. The use of administrative data for clinical research has growing support.[30–32] A 2020 U.S. Food and Drug Administration statement explains the value of real-world evidence in health care decisions.[32]

CONCLUSIONS

In sum, we report the cumulative incidence of PH following VTE to be 3.5% at 2 years, using data from 170 021 insured VTE survivors who experienced 5943 PH events. Furthermore, we provide prospective evidence suggesting that greater comorbidity burden, as well as numerous individual comorbidities, are associated with greater risk of PH. Most notable were chronic pulmonary disease, heart failure, and alcohol abuse. These data enhance understanding of the burden of PH in this patient population and may provide insights into the characteristics of patients with VTE most likely to develop PH. Awareness of risk factors for PH in the context of VTE may increase the rate of diagnosis in primary and secondary care, and lead to earlier and better PH management.

ARTICLE INFORMATION

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Supplemental Material

Table S1–S5

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SUPPLEMENTAL MATERIAL

Supplemental Table Key

Table S1: ICD-9-CM and ICD-10-CM codes used to define incident VTE.

Table S2: ICD-9-CM and ICD-10-CM codes used to define comorbidities.

Table S3. Characteristics of venous thromboembolism patients and risk of incident pulmonary hypertension without previous evidence of heart and/or lung disease: The MarketScan Databases 2011-2018

Table S4. Cumulative incidence (%) and 95% confidence intervals of pulmonary hypertension with echo and/or right heart catheter confirmatory codes in the 2 years* following incident venous thromboembolism: The MarketScan Databases 2011-2018

Table S5. Venous thromboembolism patients and risk of incident pulmonary hypertension with confirmatory echo or right heart catheter procedure codes: The MarketScan Databases 2011-2018

Table S1: ICD-9-CM and ICD-10-CM codes used to define incident VTE.

Revision	VTE codes
ICD-9-CM	415.1x, 451.1x, 453.2, 453.4x, 453.82, 453.83, 453.84, 453.85, 453.86, 453.87, 453.89, 453.9
ICD-10-CM	I26.0x, I26.9x, I80.1x, I80.20x, I82.210, I80.22x, I80.23x, I80.29x, I82.40x, I82.41x, I82.42x, I82.43x, I82.44x, I82.49x, I82.4Yx, I82.4Zx, I82.60x, I82.62x, I82.890, I82.A1x, I82.B1x, I82.C1x

Table S2: ICD-9-CM and ICD-10-CM codes used to define comorbidities and procedures*.

Condition	ICD-9-CM codes	ICD-10-CM codes
Alcoholism	265.2, 291.1, 291.2, 291.3, 291.5, 291.6, 291.7, 291.8, 291.9, 303.0, 303.9, 305.0, 357.5, 425.5, 535.3, 571.0, 571.1, 571.2, 571.3, 980, V11.3	F10, E52, G62.1, I42.6, K29.2, K70.0, K70.3, K70.9, T51.x, Z50.2, Z71.4, Z72.1
Atrial fibrillation	427.3x	I48.x
Autoimmune disease	136.1, 242.x, 245.2, 255.4, 281.0, 287.3x, 283.0, 289.81, 340, 357.0, 358.0x, 446.0, 446.21, 446.5, 447.6, 555.x, 556.x, 571.42, 571.6, 579.0, 694.5, 695.4, 695.5, 696.x, 710.0-710.4, 714.x, 720.x	D51.0, D59.0, D59.1x, D68.61, D69.3, E05.x, E06.3, E27.1, G35, G61.0, G70.0x, I77.6, K50.x, K51.x, K73.2, K74.3, K90.0, L10.x, L12.x, L40.x, M05.x, M06.x, M30.0, M31.0, M31.5, M31.6, M32.1x, M32.8, M32.9, M33.x, M34.x, M35.0x, M35.2, M45.x
Chronic pulmonary disease	416.8, 416.9, 490.x-505.x, 506.4, 508.1, 508.8	I27.8, I27.9, J40.x-J47.x, J60.x-J67.x, J68.4, J70.1, J70.3
Dementia	290.x, 294.1, 331.2	F00.x-F03.x, F05.1, G30.x, G31.1
Depression	296.2, 296.3, 296.5, 300.4, 309.x, 311.x	F20.4, F31.3, F31.5, F32.x, F33.x, F34.1, F41.2, F43.2
Diabetes	250.x	E10.0-E10.9, E11.0-E11.9, E12.0-E12.9, E13.0-E13.9, E14.0-E14.9
Heart failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4-425.9, 428.x	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5-I42.9, I43.x, I50.x, P29.0
Hematological disorders	280.0, 208.1-280.9, 281.x, 286.x, 287.1, 287.3-287.5	D50.0, D50.8, D50.9, D51.x-D53.x, D65-D68.x, D69.1, D69.3-D69.6
HIV/AIDS	042.x-044.x	B20.x-B22.x, B24.x
Hypertension	401.x, 402.x, 403.x, 404.x, 405.x	I10.x, I11.x-I13.x, I15.x
Ischemic stroke/TIA	362.34, 430.x-438.x	G45.x, G46.x, H34.0, I60.x-I69.x

Kidney disease	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 582, 583.0, 583.1, 583.2, 583.3, 583.4, 583.5, 583.6, 583.7, 585, 586, 588.0, V42.0, V45.1, V56		I12.0, I13.1, N03.2-N03.7, N05.2-N05.7, N18.x, N19.x, N25.0, Z49.0-Z49.2, Z94.0, Z99.2
Liver disease	070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 456.0, 456.1, 456.2, 570, 571, 572.2, 572.3, 572.4, 572.5, 572.6, 572.7, 572.8, 573.3, 573.4, 573.8, 573.9, V42.7		B18.x, K70.0-K70.3, K70.9, K71.3-K71.5, K71.7, K73.x, K74.x, K76.0, K76.2-K76.4, K76.8, K76.9, Z94.4, I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7
Malignancy	140.x-172.x, 174.x-195.8, 200.x-208.x, 238.6		C00.x-C26.x, C30.x-C34.x, C37.x-C41.x, C43.x, C45.x-C58.x, C60.x-C76.x, C81.x-C85.x, C88.x, C90.x-C97.x
Metastatic cancer	196.x-199.x		C77.x-C80.x
Myocardial infarction	410.x, 412.x		I21.x, I22.x, I25.2
Peripheral arterial disease	093.0, 437.3, 440.x, 441.x, 443.1-443.9, 47.1, 557.1, 557.9, V43.4		I70.x, I71.x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9
Procedure	**ICD-9-CM codes**	**ICD-10-CM codes**	**CPT Codes**
Splenectomy	41.2, 41.32, 41.42, 41.43, 41.5	07BP.x, 07DP.x, 07TP.x	38100-38102, 38115, 38120, 38129, 56345

*Outpatient procedures defined using additional CPT codes

Table S3. Characteristics of venous thromboembolism patients and risk of incident pulmonary hypertension without previous evidence of heart and/or lung disease: The MarketScan Databases 2011-2018

VTE Patient Characteristic* N=109,754	**Incident PH (%)**	**Hazard ratio** (95% CI)**	**Hazard ratio† (95% CI)**
	N=2,655		
Demographics			
Sex			
Female	2.6	1.20 (1.11-1.30)	1.19 (1.10-1.29)
Male	2.2	1 (Ref)	1 (Ref)
Age			
18-29	1.2	1 (Ref)	1 (Ref)
30-39	1.6	1.23 (0.95-1.61)	1.20 (0.92-1.57)
40-49	2.0	1.48 (1.16-1.89)	1.42 (1.11-1.81)
50-59	2.5	1.80 (1.42-2.28)	1.65 (1.30-2.09)
60-69	2.4	2.01 (1.59-2.56)	1.68 (1.32-2.15)
70-79	3.7	2.61 (2.04-3.33)	2.09 (1.61-2.69)
80-89	4.4	3.14 (2.43-4.06)	2.69 (2.06-3.51)
90-99	3.6	2.92 (1.98-4.33)	3.10 (2.08-4.63)
Health insurance coverage			
High-deductible health plan	1.9	0.87 (0.72-1.04)	0.88 (0.73-1.05)
Other health plans	2.5	1 (Ref)	1 (Ref)
Clinical aspects of VTE			
Presentation			
DVT	0.6	1 (Ref)	1 (Ref)
PE	4.7	7.62 (6.84-8.48)	7.66 (6.87-8.54)
Anticoagulant			
Apixaban	2.1	1.42 (1.21-1.67)	1.29 (1.10-1.51)
Rivaroxaban	2.0	0.99 (0.89-1.10)	1.01 (0.91-1.12)
LMWH	1.9	0.94 (0.82-1.08)	1.00 (0.87-1.16)
Warfarin	2.7	1 (Ref)	1 (Ref)
Comorbidities‡			
Hematological disorders			
Yes	3.2	1.39 (1.26-1.54)	1.25 (1.13-1.39)
No	2.3	1 (Ref)	1 (Ref)

Hypertension			
Yes	3.0	1.41 (1.29-1.53)	1.25 (1.15-1.37)
No	1.9	1 (Ref)	1 (Ref)
Diabetes mellitus			
Yes	3.3	1.35 (1.23-1.48)	1.24 (1.13-1.37)
No	2.2	1 (Ref)	1 (Ref)
Ischemic stroke/TIA			
Yes	2.8	0.97 (0.84-1.10)	0.91 (0.79-1.05)
No	2.4	1 (Ref)	1 (Ref)
Peripheral artery disease			
Yes	3.1	1.06 (0.93-1.22)	1.11 (0.96-1.27)
No	2.4	1 (Ref)	1 (Ref)
Kidney disease			
Yes	3.5	1.31 (1.14-1.50)	1.26 (1.09-1.45)
No	2.4	1 (Ref)	1 (Ref)
Liver disease			
Yes	2.8	1.33 (1.17-1.52)	1.07 (0.93-1.22)
No	2.4	1 (Ref)	1 (Ref)
Malignancy			
Yes	2.6	1.13 (1.02-1.25)	1.04 (0.93-1.17)
No	2.4	1 (Ref)	1 (Ref)
Metastatic cancer			
Yes	2.3	1.30 (1.11-1.52)	1.17 (0.97-1.41)
No	2.4	1 (Ref)	1 (Ref)
Alcohol abuse			
Yes	2.0	1.24 (0.77-2.00)	1.15 (0.71-1.86)
No	2.4	1 (Ref)	1 (Ref)
Autoimmune disease			
Yes	3.1	1.25 (1.13-1.38)	1.18 (1.07-1.29)
No	2.3	1 (Ref)	1 (Ref)
HIV/AIDS			
Yes	2.2	1.12 (0.58-2.15)	1.24 (0.67-2.31)
No	2.4	1 (Ref)	1 (Ref)
Splenectomy			
Yes	3.7	1.95 (1.01-3.75)	1.61 (0.84-3.11)
No	2.4	1 (Ref)	1 (Ref)
Charlson comorbidity index			
0 (none noted)	2.0	1 (Ref)	
1-2 (mild)	2.9	1.37 (1.25-1.49)	
3-4 (moderate)	3.2	1.46 (1.29-1.66)	
≥5 (severe)	2.7	1.57 (1.38-1.79)	

VTE – venous thromboembolism; PH – pulmonary hypertension
*% unless otherwise noted
**Adjusted for age and sex

[†]Adjusted for all characteristics in the table (except for the Charlson comorbidity index since that is a count of comorbidities).
[‡]Comorbidities were identified prior to incident VTE

Table S4. Cumulative incidence (%) and 95% confidence intervals of pulmonary hypertension with echo and/or right heart catheter confirmatory codes in the 2 years following incident venous thromboembolism: The MarketScan Databases 2011-2018

Time after VTE*	All	Men	Women	PE	DVT
3-6 months	0.40 (0.37-0.43)	0.36 (0.32-0.41)	0.44 (0.39-0.49)	0.72 (0.66-0.78)	0.11 (0.09-0.13)
3-9 months	0.71 (0.67-0.76)	0.60 (0.55-0.66)	0.82 (0.76-0.89)	1.30 (1.22-1.39)	0.17 (0.15-0.21)
1 year	0.90 (0.85-0.95)	0.79 (0.73-0.86)	1.01 (0.94-1.09)	1.63 (1.54-1.73)	0.24 (0.21-0.28)
2 years	1.53 (1.46-1.61)	1.37 (1.28-1.47)	1.69 (1.59-1.80)	2.65 (2.52-2.79)	0.52 (0.47-0.59)
3 years	2.08 (1.99-2.18)	1.85 (1.73-1.98)	2.30 (2.17-2.45)	3.50 (3.32-3.68)	0.80 (0.72-0.89)
4 years	2.56 (2.44-2.68)	2.30 (2.14-2.46)	2.82 (2.65-3.00)	4.21 (4.00-4.43)	1.08 (0.97-1.20)
5 years	3.10 (2.95-3.25)	2.78 (2.58-2.99)	3.42 (3.20-3.66)	4.94 (4.68-5.22)	1.45 (1.30-1.62)
Overall	4.02 (3.73-4.33)	3.73 (3.31-4.22)	4.31 (3.93-4.72)	6.42 (5.86-7.03)	1.90 (1.66-2.18)

*A minimum of 90 days of follow-up post venous thromboembolism were required in order to limit capture of sub-acute pulmonary hypertension.

Table S5. Venous thromboembolism patients and risk of incident pulmonary hypertension with confirmatory echo or right heart catheter procedure codes: The MarketScan Databases 2011-2018

VTE Patient Characteristic* (N=170,021)	**Incident PH (%)**	**Hazard ratio** (95% CI)**	**Hazard ratio† (95% CI)**
	N=2,560		
Demographics			
Sex			
Female	1.7	1.23 (1.14-1.33)	1.29 (1.19-1.39)
Male	1.4	1 (Ref)	1 (Ref)
Age			
18-29	0.7	1 (Ref)	1 (Ref)
30-39	0.7	0.93 (0.66-1.31)	0.87 (0.62-1.22)
40-49	1.0	1.37 (1.02-1.84)	1.20 (0.89-1.61)
50-59	1.4	1.87 (1.41-2.48)	1.43 (1.07-1.91)
60-69	1.6	2.46 (1.85-3.26)	1.55 (1.16-2.08)
70-79	2.6	3.46 (2.60-4.60)	1.78 (1.32-2.39)
80-89	2.6	3.58 (2.68-4.79)	1.76 (1.29-2.38)
90-99	1.5	2.48 (1.66-3.70)	1.25 (0.83-1.88)
Health insurance coverage			
High-deductible health plan	1.1	0.92 (0.75-1.14)	1.01 (0.82-1.25)
Other health plans	1.5	1 (Ref)	1 (Ref)
Clinical aspects of VTE			
Presentation			
DVT	0.6	1 (Ref)	1 (Ref)
PE	2.5	4.36 (3.96-4.80)	4.18 (3.79-4.61)
Anticoagulant			
Apixaban	1.3	1.34 (1.14-1.57)	1.22 (1.04-1.43)
Rivaroxaban	1.4	1.11 (1.00-1.23)	1.12 (1.01-1.23)
LMWH	1.1	0.94 (0.81-1.08)	1.10 (0.94-1.28)
Warfarin	1.7	1 (Ref)	1 (Ref)
Comorbidities‡			
Chronic pulmonary disease			
COPD (yes)	2.8	2.04 (1.87-2.23)	1.50 (1.37-1.65)
COPD (no)	1.3	1 (Ref)	1 (Ref)
Hematological disorders			

Hema (yes)	1.9	1.31 (1.19-1.45)	1.07 (0.96-1.18)
Hema (no)	1.4	1 (Ref)	1 (Ref)
Heart failure			
HF (yes)	3.6	2.67 (2.43-2.93)	1.89 (1.71-2.08)
HF (no)	1.2	1 (Ref)	1 (Ref)
Hypertension			
HTN (yes)	2.0	1.73 (1.58-1.90)	1.33 (1.20-1.46)
HTN (no)	1.0	1 (Ref)	1 (Ref)
Diabetes mellitus			
DM (yes)	2.2	1.51 (1.39-1.64)	1.18 (1.09-1.29)
DM (no)	1.3	1 (Ref)	1 (Ref)
Atrial fibrillation			
Afib (yes)	3.2	1.86 (1.66-2.09)	1.39 (1.23-1.56)
Afib (no)	1.4	1 (Ref)	1 (Ref)
Myocardial infarction			
MI (yes)	2.9	1.83 (1.61-2.07)	1.13 (1.00-1.29)
MI (no)	1.4	1 (Ref)	1 (Ref)
Ischemic stroke/TIA			
Isc stroke (yes)	2.2	1.23 (1.11-1.37)	0.97 (0.87-1.08)
Isc stroke (no)	1.4	1 (Ref)	1 (Ref)
Peripheral artery disease			
PAD (yes)	2.5	1.45 (1.31-1.60)	1.17 (1.05-1.30)
PAD (no)	1.4	1 (Ref)	1 (Ref)
Kidney disease			
Kidney (yes)	2.7	1.65 (1.48-1.84)	1.34 (1.20-1.50)
Kidney (no)	1.4	1 (Ref)	1 (Ref)
Liver disease			
Liver (yes)	1.8	1.38 (1.22-1.56)	1.12 (0.99-1.27)
Liver (no)	1.5	1 (Ref)	1 (Ref)
Malignancy			
Malignancy (yes)	1.5	1.00 (0.91-1.11)	0.98 (0.88-1.10)
Malignancy (no)	1.5	1 (Ref)	1 (Ref)
Metastatic cancer			
Metcan (yes)	1.0	0.90 (0.76-1.07)	0.83 (0.68-1.01)
Metcan (no)	1.6	1 (Ref)	1 (Ref)
Alcohol abuse			
Alcohol (yes)	1.5	1.50 (1.00-2.24)	1.16 (0.78-1.75)
Alcohol (no)	1.5	1 (Ref)	1 (Ref)
Autoimmune disease			
Autoimmune (yes)	1.9	1.26 (1.15-1.39)	1.14 (1.04-1.25)
Autoimmune (no)	1.4	1 (Ref)	1 (Ref)
HIV/AIDS			
HIV/AIDS (yes)	1.5	1.32 (0.68-2.53)	1.62 (0.92-2.86)
HIV/AIDS (no)	1.5	1 (Ref)	1 (Ref)

Charlson comorbidity index			
0 (none noted)	0.8	1 (Ref)	
1-2 (mild)	1.7	1.98 (1.76-2.21)	
3-4 (moderate)	2.2	2.50 (2.20-2.85)	
≥5 (severe)	2.1	2.92 (2.57-3.31)	

VTE – venous thromboembolism; PH – pulmonary hypertension; splenectomy was not calculated as there were too few cases

*% unless otherwise noted;

**Adjusted for age and sex

†Adjusted for all characteristics in the table (except for the Charlson comorbidity index since that is a count of comorbidities).

‡Comorbidities were identified prior to incident VTE