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Risk of venous thromboembolism occurrence among adults with selected autoimmune diseases: A study among a U.S. cohort of commercial insurance enrollees☆

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Abstract

Objective—This study assessed the risk of venous thromboembolism (VTE) among privately insured adults in the U.S. with one or more of the following autoimmune diseases: autoimmune hemolytic anemia (AIHA), immune thrombocytopenic purpura (ITP), rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE).

Materials and Methods—Using the Truven Health MarketScan® Databases, patients 18–64 years of age with a diagnosis of AIHA, ITP, RA, or SLE in 2007 and a sex and age-group matched comparison group of enrollees were followed up through 2010 to identify VTE events. Survival curve and Cox proportional hazards analyses were conducted to assess differences between groups.

Results—Among patients with AIHA, ITP, RA, or SLE, or >1 of these diseases, the risk of at least one VTE event was 19.74, 7.72, 4.90, 9.89, and 13.35 per 1,000 person-years, respectively; among the comparison group, the risk was 1.91 per 1,000 person-years. The adjusted hazard ratios (aHRs) for VTE among patients with AIHA, ITP, RA, or SLE, or >1 of these diseases (when compared with the comparison group) tended to decline over follow-up time; at 1 year, the aHRs

☆The findings and conclusions in this report are those of the authors and do not necessarily represent the official policy of the Centers for Disease Control and Prevention.

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Conflict of Interest

There are no known conflicts of interest associated with this publication and there has been no financial support for this work.

were 6.30 (95% confidence interval [CI]: 4.44–8.94), 2.95 (95% CI: 2.18–4.00), 2.13 (95% CI: 1.89–2.40), 4.68 (95% CI: 4.10–5.33), and 5.11 (95% CI: 4.26–6.14), respectively.

Conclusion—Having AIHA, ITP, RA, or SLE, or >1 of these diseases was associated with an increased likelihood of a VTE event. More research is necessary to develop better understanding of VTE occurrence among people with autoimmune diseases.

Keywords

Autoimmune diseases; Autoimmune hemolytic anemia; Immune thrombocytopenic purpura; Rheumatoid arthritis; Systemic lupus erythematosus; Venous thromboembolism

Introduction

Venous thromboembolism (VTE), which consists of deep vein thrombosis (DVT) or pulmonary embolism (PE), or both, is an important public health concern [1–3]. It has been estimated that 350,000–900,000 people in the United States might suffer a VTE each year [4–7]. Research increasingly has indicated that many autoimmune diseases might be associated with an increased risk of VTE occurrence [8–16]. For example, the increased risk of VTE associated with systemic lupus erythematosus (SLE) has been reported previously by a number of studies [12,15,17–19]. Investigators in the United Kingdom identified hospitalizations of people for one or more of several autoimmune diseases using three different hospitalization information datasets and then followed up available information in order to identify subsequent hospitalizations of these individuals for VTE; in the largest of these datasets, a statistically significant increased rate ratio for VTE was found for SLE, rheumatoid arthritis (RA), idiopathic thrombocytopenic purpura (ITP), and autoimmune hemolytic anemia (AIHA), as well as the other autoimmune diseases assessed [13].

The deleterious effects that VTE can have on life and health can be minimized through the prevention of VTE occurrence and through appropriate diagnosis and treatment. In this context, better understanding of the epidemiology of VTE–including risk factors for VTE occurrence–can be helpful in achieving greater awareness and vigilance among providers and others with regard to people who might be at increased risk of VTE, patient assessment and screening, implementation of appropriate prevention strategies, diagnosis of VTE events, and patient management. Using a large, claims-based data source that included individuals enrolled in employer-sponsored commercial health plans, this study assessed VTE occurrence among 18–64-year-old adults diagnosed with four selected autoimmune diseases: AIHA, ITP, RA, and SLE. Our aim was to add to the growing evidence of the association between autoimmune diseases and VTE and epidemiologic understanding in this regard [8–16]. We previously reported findings of a cross-sectional study using U.S. hospitalization data that indicated an increased likelihood of VTE diagnosis associated with a diagnosis of these autoimmune diseases [20]. The objectives of this study were to assess the risk of VTE among commercial health insurance enrollees who had a diagnosis of one or more of the same four autoimmune diseases using a longitudinal approach.

Materials and Methods

A retrospective cohort approach was used to identify individuals with and those without a diagnosis of any of the autoimmune diseases of interest and follow up these individuals to identify VTE occurrence.

Data Source

We used data from the Truven Health MarketScan® Commercial Claims and Encounters Databases [MarketScan is a registered trademark of Truven Health Analytics Inc] for the years 2007–2010. These databases contained health care claims-based information for enrollees in large employer-sponsored health insurance plans across the United States. The 2007–2010 Commercial Claims databases contained information for approximately 28,762,000–45,240,000 enrollees during each of these years. The data included inpatient claims, outpatient claims, outpatient pharmacy claims, and plan enrollment information.

Information available for enrollees included sex, age, and the starting and ending dates of enrollment. Inpatient and outpatient databases included information on diagnoses and performed procedures; diagnoses information was indicated using *International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM)* codes and, in the inpatient data, procedures performed were indicated using *ICD-9-CM* codes and the American Medical Association's *Current Procedural Terminology (CPT®)* code sets. Each individual in the MarketScan data had a unique encrypted enrollee identification number that could not be used to identify the individual, but could be used to link information for the individual within and across the various datasets and across years as long as they remained employed by the same employer.

Study Population

The *study group* consisted of all adults 18–64 years of age who were enrolled in the health insurance plans included in the MarketScan Commercial Claims databases during any time in 2007 and remained continuously enrolled for any length of time (with the cutoff for assessing continuity occurring at December 31, 2010), and who also had diagnoses of one or more of the four autoimmune diseases of interest (AIHA, ITP, RA, and SLE) during 2007. For the purposes of this study, continuous enrollment was defined as there being no more than 1 day of gap in enrollment in the health plan during each enrollee's enrollment period. Identification of a diagnosis of any of the autoimmune diseases of interest was based on the presence of the respective *ICD-9-CM* diagnosis codes (see Appendix A for codes used in this study) in the diagnosis information provided in the outpatient and inpatient health care encounter information. Specifically, an enrollee was defined as having a diagnosis of an autoimmune disease of interest if the person had an inpatient diagnosis of the disease or if the person had at least two outpatient diagnoses of the disease at least 30 days apart during the study period (with the first diagnosis occurring during 2007).

A *comparison group* was identified by first identifying all adults 18–64 years of age who were enrolled at any time during 2007 and who did not have a diagnosis of any of the four autoimmune diseases of interest during the study period (January1, 2007–December 31,

2010). From this group of enrollees, a random sample (without replacement) was selected in an approximately 2-to-1 ratio to the number of individuals in the study cohort. The random sample was selected so that the sex and age group (18–34, 35–44, 45–54, and 55–64 years) proportions were approximately equivalent to those of the study group. Individuals who were not enrolled continuously were excluded from the comparison group. Continuous enrollment for this group was defined in the same way as for the study group.

Definition of Outcomes

The outcome of interest for this study was the first occurrence of a VTE event during the follow-up period (follow-up period start- and end-points are described in the following section). *ICD-9-CM* diagnosis codes related to DVT or PE, or both (see Appendix A for codes used in this study), were used to identify any VTE diagnosis recorded in inpatient and outpatient claims. A participant in this study was identified as having had a VTE event if at any time during the follow-up period there was an inpatient diagnosis of VTE or an outpatient diagnosis of VTE combined with an outpatient drug claim for anticoagulant medication within 14 days following the outpatient VTE diagnosis. This included diagnosis of any VTE event during the same hospitalization as a diagnosis of any of the selected autoimmune diseases; when such occurred, the date of hospital admission was inferred as the date of diagnosis for both events.

Follow-up Start and Endpoint

Information for all inpatient admissions and outpatient services during the period 2007–2010 for the study and comparison groups was linked with respect to each study participant. For the study group, the start of follow-up was the earliest identified date of diagnosis of any of the four autoimmune diseases of interest during the study period. For the comparison group, the start of follow-up was either January 1, 2007, or their first date of enrollment (i.e., when that was after January 1, 2007). For both the study and comparison groups, the follow-up endpoint was the date of the first VTE event identified (for those with a VTE event) or the earlier of either the last date of enrollment (as indicated in the MarketScan data used) or December 31, 2010.

Other Medical Characteristics of Study Participants

The diagnosis of selected medical conditions among study participants and whether they had venous catheterization or other surgery related procedures during the follow-up period were identified as these might affect the likelihood of a VTE event. *ICD-9-CM* diagnosis codes were used to identify diagnoses of selected medical conditions: cancer; heart failure; stroke; chronic obstructive pulmonary disease; injury; infection; kidney disease (chronic kidney disease, chronic glomerulonephritis, or nephrotic syndrome); varicose veins; paralysis of limb; diabetes; Crohn’s disease or ulcerative colitis, or both; and pregnancy or delivery-related hospitalizations, or both (see Appendix A for codes used in this study). For each medical condition, an enrollee was defined as having a diagnosis of the condition if, during the follow-up period, there was an inpatient diagnosis of the disease or if there were at least two outpatient diagnoses of the disease at least 30 days apart. *ICD-9-CM* procedure codes and *CPT* codes were used to identify venous catheterization and other surgery-related

procedures (broadly defined as having any surgery-related procedure) (see Appendix A for the codes used in this study).

Analysis

The risk of VTE events was estimated among individuals with a diagnosis of AIHA, ITP, RA, or SLE (four mutually exclusive groups with respect to diagnosis the four disorders), among those with two or more of these four diseases, among those with any (one or more) of these four diseases, and among the comparison group by dividing the number of individuals with at least one VTE event occurring during the follow-up period by the total number of person-years of follow-up for each group. This was done for the overall study population and separately for study participants who were <40 years of age and those who were >41 years of age. For the overall study population, differences between the study group and the comparison group with respect to the time between beginning of follow-up and the first VTE event identified during follow-up were assessed through survival analysis using the Kaplan-Meier product limit method. In the survival analysis, VTE-free survival curves were derived for each of the following strata: individuals with a diagnosis of AIHA, ITP, RA, or SLE, those with two or more of these diseases, those with any of these diseases, and those with no diagnosis of any of the four autoimmune diseases.

Adjusted hazard ratios (aHRs) and 95% confidence intervals [CIs] for the first VTE event during follow-up associated with a diagnosis of any of the autoimmune diseases of interest were estimated using Cox proportional hazards regression analysis. To derive aHRs associated with a diagnosis of AIHA, ITP, RA, or SLE, or two or more of these four diseases, all five of these variables (representing mutually exclusive groups) were included in the same model as explanatory variables of interest; in addition, the following variables also were included as explanatory variables in models: sex, age (age in years as indicated in the 2007 annual enrollment summary information available for each individual), total number of days hospitalized (across all hospitalizations for the person during the follow-up period), a diagnosis of selected medical conditions (those mentioned previously), having a venous catheterization during an inpatient stay, and having a surgery related procedure during an inpatient stay. With respect to selected medical conditions, venous catheterization, and surgery-related procedure, the analyses were adjusted for whether or not there was occurrence of such an event during the follow-up period and not for the frequency of such events. The aHRs associated with a diagnosis of any of the autoimmune diseases of interest were assessed similarly where the explanatory variable of interest was diagnosis of any of the four autoimmune diseases (instead of the five separate variables AIHA, ITP, RA, SLE, and two or more of these four diseases).

The proportional hazards assumption and whether the aHRs for VTE associated with the four autoimmune diseases varied by time since follow-up began were assessed through Cox proportional hazards regression modeling in which interaction variables between follow-up time and each of the five autoimmune disease variables (AIHA, ITP, RA, SLE, and two or more of these four diseases) were included as predictor variables; in addition, the model also included the five autoimmune disease variables in the form of main effects variables and the other variables mentioned in the previous paragraph. There was statistically significant

interaction between follow-up time and the variables for ITP, SLE, and two or more of these four diseases ($p < 0.05$); aHRs for VTE associated with the five autoimmune disease variables were, therefore, estimated at the follow-up time endpoints of 90 days, 180 days, 1 year, 2 years, 3 years, and 4 years. We also assessed if the associations between the selected autoimmune diseases and VTE were modified by either sex or age by including in the proportional hazards model interaction terms between sex and each of the five autoimmune disease variables, as well as between age and each of the five autoimmune disease variables. The interaction terms containing sex were not statistically significant. However, because interaction terms containing age were statistically significant ($p < 0.05$) (except for those for AIHA and RA), proportional hazards analyses were conducted separately for study populations grouped by age (18–40 years and 41–64 years), in addition to the combined analysis for all ages (in which the interaction terms between age and each of the five autoimmune disease variables were also included).

The analyses were conducted using SAS 9.3 software (SAS Institute, Cary, NC). The survival curves were developed using Proc Lifetest and Proc SGPlot. Proc Phreg was used for the proportional hazards regression analysis.

This study was determined by the Centers for Disease Control and Prevention's National Center on Birth Defects and Developmental Disabilities' Human Subjects Contact to be research not involving human subjects.

Results

In our study group, there were 98,308 adults 18–64 years of age who had a diagnosis of any of the four autoimmune diseases of interest during 2007; of these, 784 had a diagnosis of only AIHA, 2,772 had a diagnosis of only ITP, 70,768 had a diagnosis of only RA, 19,427 had a diagnosis of only SLE, and 4,557 had diagnoses of two or more of these four diseases. Our comparison group consisted of 198,044 enrollees 18–64 years of age without a diagnosis of any of the four diseases during the study period. Demographic and other characteristics of the study and comparison groups are presented in Table 1. Most (79%) of the study group patients were women with a mean age of 49.5 years; the sex and age distributions of the comparison cohort was very similar. A substantially greater percentage of the study group than of the comparison group were hospitalized at least once during the follow-up period (29.6% vs. 13.5%, respectively) and the mean number of hospitalization days also was higher among those in the former group (2.8 days vs. 0.8 days, respectively). Higher or slightly higher percentages of the study group (than of the comparison group) had a diagnosis of 9 of the 11 medical comorbidities that were adjusted for in proportional hazards analysis. Greater percentages of the study group (than of the comparison group) also had a venous catheterization or surgical procedure during the follow-up period.

The total follow-up time for the study group was 257,542 person-years and during this time 1,672 study group patients suffered at least one VTE event as per our study definition. Considering only the first identified VTE events among all study group patients during follow-up, the rate of VTE occurrence was 6.49 per 1,000 person-years (Table 2). Correspondingly, the total follow-up time, total number of comparison group enrollees with

a VTE event, and VTE rate among the comparison group were 513,504 person-years, 981, and 1.91 per 1,000 person-years, respectively. The rates of VTE among all study group patients with a diagnosis of AIHA, ITP, RA, or SLE, or two or more of these four diseases were 19.74, 7.72, 4.90, 9.89, and 13.35 per 1,000 person-years, respectively. The rates of VTE among study group patients <40 years of age with a diagnosis of AIHA, ITP, RA, or SLE, or two or more of these four diseases were 10.84, 5.56, 2.18, 11.28, and 13.64 per 1,000 person-years, respectively. The rates among study group patients >41 years of age with a diagnosis of AIHA, ITP, RA, or SLE, or two or more of these four diseases were 22.87, 8.86, 5.34, 9.29, and 13.26 per 1,000 person-years, respectively.

Considering only the first identified VTE event during follow-up, the product-limit survival curve analysis results indicated that the cumulative VTE-free survival probability over time was lower among study group patients (those with a diagnosis of any of the four autoimmune diseases of interest) compared with the comparison group (Fig. 1). The difference in the survival functions of the two groups was statistically significant (Log-Rank Test $p < 0.05$). The cumulative VTE-free survival probability over time was also lower for each disease individually, AIHA, ITP, RA, or SLE, and among those with two or more of these four diseases than the comparison group (Fig. 2). The Log-Rank Test p-value (<0.05) indicated that at least one pairwise difference in the survival functions was statistically significant.

The proportional hazards regression analysis results indicated that patients in the study group had an increased likelihood of at least one VTE event during the follow-up period compared with the comparison group (Table 3). The aHR associated with at least one VTE event among patients with SLE (when compared with enrollees in the comparison group) declined over the follow-up period. However, the aHRs for the patients with SLE remained above 1 throughout the follow-up period: at 90 days, 180 days, 1 year, 2 years, 3 years, and 4 years of follow-up, the aHRs were 5.26 (95% CI: 4.43–6.23), 5.06 (95% CI: 4.33–5.91), 4.68 (95% CI: 4.10–5.33), 4.01 (95% CI: 3.51–4.58), 3.43 (95% CI: 2.83–4.16), and 2.94 (95% CI: 2.23–3.87), respectively.

The aHR for at least one VTE event among patients with RA (when compared with enrollees in the comparison group) remained relatively constant during the follow-up period; at 90 days of follow-up, it was 2.16 (95% CI: 1.85–2.51). The aHR for at least one VTE event among patients with AIHA (when compared with enrollees in the comparison group) declined from 7.55 (95% CI: 4.74–12.02) at 90 days of follow-up to 3.07 (95% CI: 1.15–8.21) at 4 years of follow-up. The aHR for at least one VTE event among patients with ITP (when compared with enrollees in the comparison group) declined from 5.50 (95% CI: 3.92–7.72) at 90 days of follow-up to 2.95 (95% CI: 2.18–4.00) at 1 year of follow-up, and was below 1 or not statistically significant thereafter.

When stratified by age group, the results of proportional hazards regression indicated that the aHRs for at least one VTE event among study group patients with any of the four autoimmune diseases (when compared with enrollees in the comparison group) tended to be higher among the 18–40 years-of-age group than among the 41–64 years-of-age group (Table 4). For example, the aHR for at least one VTE event among 18–40 year-old patients

with SLE (when compared with 18–40 year-old enrollees in the comparison group) was 13.88 (95% CI: 9.09–21.16) at 90 days of follow-up, whereas the aHR for at least one VTE event among 41–64 year-old patients with SLE (when compared with 41–64 year-old enrollees in the comparison group) was 3.91 (95% CI: 3.23–4.74) at 90 days of follow-up.

Discussion

The findings of this study strongly suggest that patients with AIHA, ITP, RA, or SLE, or two or more of these four diseases are at increased likelihood of a VTE event and thus add to the epidemiologic and clinical understanding related to possible risk factors for VTE. Using a large administrative claims data source, we found an increased occurrence of VTE among commercial health insurance enrollees 18–64 years of age who had a diagnosis of one or more of four selected autoimmune diseases (AIHA, ITP, RA, and SLE) when compared with enrollees without any of these diseases. The relative increase in risk of VTE was higher for those <40 years of age than for those >41 years of age. The cumulative VTE-free survival probability over our study period was lower among patients with one or more of the four autoimmune diseases than among enrollees without any of the four autoimmune diseases. The aHRs at 90 days for having had at least one VTE event since the beginning of follow-up ranged from 2.16–7.55 among patients with AIHA, ITP, RA, or SLE, or two or more of these four diseases compared with enrollees in the comparison group. Though the aHRs tended to decline over time among patients with AIHA, IPT, SLE, or two or more of the four diseases selected, they remained above 1 and statistically significant at 4 years for AIHA, RA, or SLE, or two or more of these four diseases.

There are several reasons why autoimmune diseases might be associated with an increased risk of VTE. Possible mechanisms, among others, include the effects of inflammatory activity and antiphospholipid antibodies (aPLs) [12,17,21]. Autoimmune diseases are associated with increased inflammatory activity which, in turn, has been reported to result in the development of a procoagulant state that can increase the likelihood of thrombosis and VTE [8,21]. The four autoimmune diseases assessed in this study have been reported to be associated with the presence of aPLs [8,22]. Research has indicated that aPLs might increase the risk of VTE through various mechanisms, including affecting reactants involved in coagulation [8,17,23]. In addition, a number of studies have indicated that glucocorticoid therapy might be associated with an increased risk of VTE [12,24–27]; however, it is important to note that a reviewstudy reported that research findings indicated that glucocorticoids had differential effects that were dependent upon the situation in which they were provided [24]. More research would improve our understanding of the causes of the possible increased risk of VTE associated with autoimmune diseases.

The findings of our study that the four assessed autoimmune diseases are associated with an increased likelihood of VTE occurrence are consistent with those of a number of previous reports [9–11,13,15, 16,28,29]. In a study conducted in the United Kingdom, when compared with a selected hospital comparison group, the rate ratios for VTE associated with rheumatoid arthritis, systemic lupus erythematosus, idiopathic thrombocytopenic purpura, and autoimmune hemolytic anemia among one of the assessed cohorts during the period 1999–2008 were 1.75 (95% CI: 1.70–1.80), 3.71 (95% CI: 3.43–4.02), 2.09 (95% CI: 1.90–

2.29), and 3.83 (95% CI: 3.43–4.25), respectively [13]. In another study, researchers assessed the incidence of VTE (presumably including recurrent VTE) among patients with SLE in two hospitals in China during the period 1999–2008 and found that, compared with the estimated incidence of VTE among the general population in the region, the average standard incidence ratio for VTE among SLE patients was 11.9 (95% CI: 7.31–19.6) [28].

The VTE rate among patients with SLE in our study (9.89 per 1,000 person-years) was comparable with that of at least two previous research reports. In a study in which patients of different ethnicities in two countries who were diagnosed with SLE during the period 1996–2002 were followed up prospectively (with follow-up starting within 6 months of initial diagnosis), the investigators found rates of VTE events ("calf and femoral vein thrombosis, hepatic vein thrombosis, pulmonary embolism, retinal vein occlusion, and superficial thrombophlebitis") among Caucasian, African-American, and Chinese patients were 17, 15, and 7 per 1,000 person-years, respectively [15]. In the study among SLE patients in two hospitals in China, the average annual incidence was 4.2 per 1,000 patient-years [28]. It is important to keep in mind, however, that there were differences between these various studies with regard to study methodology and populations assessed.

With regard to our findings that the aHRs tended to decrease over time, it is important to note that this study could not identify when the actual initial (i.e., first ever) diagnosis of any of the four autoimmune diseases occurred among individuals in our study group, and for many of these individuals the initial diagnosis might have been before 2007. Thus, the variations in the aHRs over the follow-up period should be interpreted in that context (i.e., with follow-up beginning from the earliest identified diagnosis of any of the four autoimmune diseases during this study's assessment period). Other research has suggested that the magnitude of increased risk for VTE among people with selected autoimmune diseases might decline over time (after occurrence of an autoimmune disease-related event, e.g., diagnosis of the autoimmune disease) [16,19,28,30]. In the study that assessed VTE incidence among patients with SLE in two hospitals in China, the mean duration of SLE among patients in the study was 9.3 ± 8.8 (±SD) years and half of the VTE events among those in the study cohort occurred within 2½ years of SLE diagnosis. Another investigation that assessed the incidence of venous and arterial events occurring after SLE diagnosis among patients registered in an SLE patient registry at a university medical center in Quebec, Canada, found that the incidence of VTE was highest during the first 30 days (12.06 [95% CI 3.29–30.87] per 100 person-years) after SLE diagnosis, and was substantially lower after that; in that study, 408 persons with SLE were followed for a total of 4,846.6 years for VTE [19]. A population-based study conducted in Sweden that assessed the risk of hospitalization with PE associated with any of several autoimmune diseases found that, in the overall group (those with any of the autoimmune diseases assessed), the incidence ratios were higher during the first year after hospitalization with a diagnosis of an autoimmune disease than during subsequent years [16]. In contrast, in study conducted in the United Kingdom, when the risk for VTE associated with five selected autoimmune diseases (multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, psoriasis, and myxedema) were assessed for two time periods (0–90 days and >90 days) after hospitalization for these autoimmune diseases, investigators found increased rate ratios for both time periods [13].

This study had a number of limitations. We used secondary data from claims-based data sources and not data validated by clinical records review. By definition, the principal purpose of claims data is not for conducting clinical or epidemiologic studies, thus completeness and accuracy of information might not be 100 percent. In this context therefore, this study may not be as strong as it could be if the data were obtained directly by the investigators themselves. For example, the diagnoses of VTE, autoimmune diseases, and medical illnesses were identified using *ICD-9-CM*-coded diagnoses recorded in claims and, thus, were subject to possible recording and other errors; in addition, the predictive values of several VTE-related *ICD-9-CM* codes in secondary data may vary [31–33]. Another limitation is that the MarketScan data we used were convenience samples and, thus, our findings were not representative of the overall population of the United States; also, since we used only commercial claims data, the results are not generalizable to people who are on Medicaid, Medicare, or who are uninsured. However, studies using secondary data, including administrative databases such as MarketScan are not without merit. Administrative databases, including MarketScan data have been used for numerous research studies published in peer-reviewed journals [34,35]. Advantages of such databases include having multiple years of data for diverse populations that include demographic, health care related, and other information [34,35]. A number of reports on *ICD-9-CM*-coded information for VTE diagnoses in selected inpatient data sources have suggested positive predictive values of approximately 65%–95% for several of the codes used in our study to identify VTE diagnoses when present in inpatient hospital discharges [31,32]. Also, MarketScan databases include information on a very large number of individuals enrolled in employer-sponsored health plans (the data are received mostly from large employers) and, thus, the findings might be generalizable to a substantial portion of the population.

Other limitations of this study include the possibility that other factors not controlled for in our study could have affected the observed associations between the four autoimmune diseases assessed and VTE. In addition, although the aHRs in our study were derived through proportional hazards models that included several important medical conditions that have been reported to be associated with an increased VTE risk, the analyses controlled for whether there was a diagnosis of any of these conditions at any time during follow-up, and did not account for the frequency or the timing of diagnosis. We did not have information on the race or ethnicity of the study participants and, thus, could not assess for differences in the results by this factor. In this study, we could not account for disease state (e.g., acute condition, chronic disease, flare-up, or remission) among patients in the study group. We did not differentiate whether the diagnosed VTE event was the first VTE event or a recurrent VTE event and, hence, we could not estimate the risk of first-time VTE incidence. For events that occurred during inpatient stays, we inferred the date of admission as the date of diagnosis. In this study, participants who may have had their first VTE as an outpatient diagnosis less than 14 days before the end of follow-up would not have had the 14 day period following the VTE during which anticoagulant prescription would define the occurrence of VTE. However this likely was a small percent of cases and had limited effects on the results.

For cases where the first identified diagnosis of one or more of the four autoimmune diseases and VTE occurred during the same inpatient stay, we assumed the autoimmune disease preceded the occurrence of VTE and acted as a possible risk factor for VTE. To assess what effect this may have had, we conducted supplementary analysis where the overall (for all age groups) proportional hazards model excluded cases where the date of the first identified diagnosis of one or more of the four autoimmune diseases and the date of the VTE was the same inpatient stay. In the results of the supplementary analysis, AIHA, RA, SLE, and >2 conditions remained significantly associated with VTE throughout the follow-up period and ITP was significantly associated with VTE at up to 1 year of follow-up. The magnitude of the aHRs decreased somewhat – for example the aHRs (95% CIs) for AIHA, ITP, RA, SLE, and >2 conditions at 1 year of follow-up were 5.06 (3.42–7.49), 2.44 (1.76–3.36), 1.92 (1.70–2.17), 3.96 (3.45–4.54), 4.39 (3.62–5.33), respectively. In addition, the interaction with time remained significant only for ITP.

This study adds to epidemiological knowledge and understanding of the association between autoimmune diseases and VTE. The findings of this study, in conjunction with those of other studies, can help increase awareness among health care providers, patients, and others that patients with AIHA, ITP, RA, or SLE might be at increased risk of VTE occurrence. This, in turn, can help towards optimal assessment and care of patients with these autoimmune diseases. This might include increased vigilance for and timely detection of VTE occurrence, as well as appropriate management. In addition, more research is necessary to develop better understanding of the risk of VTE occurrence among people with autoimmune diseases. This might include better understanding of how autoimmune diseases may result in an increased risk of VTE, the identification and characterization of factors that might increase the likelihood of VTE occurrence among people with an autoimmune disease, and the risks and benefits associated with VTE prevention strategies.

Abbreviations

aHR	adjusted hazards ratio
AIHA	autoimmune hemolytic anemia
CI	confidence interval
CPT	Current Procedural Terminology
DVT	deep vein thrombosis
ICD-9-CM	International Classification of Diseases, 9th Revision, Clinical Modification
ITP	immune thrombocytopenic purpura
PE	pulmonary embolism
RA	rheumatoid arthritis
SLE	systemic lupus erythematosus
VTE	venous thromboembolism

Appendix A

The *International Classification of Diseases, 9th Revision, Clinical Modification* (*ICD-9-CM*) and Current Procedural Terminology (CPT®) codes that were used in this study to define diagnosis of various conditions and whether selected procedures were done

ICD-9-CM diagnosis codes used

Deep vein thrombosis:	For data from all years, the following codes were used: 451.1x, 45181, 451.83, 451.89, 453.2, 453.4x, 671.3x, 671.4x. The following additional codes were used for data from 2009 and 2010: 453.82, 453.84, 453.85, 453.86, 453.87

Pulmonary embolism: 415.1, 415.11, 415.19, 634.6x, 635.6x, 636.6x, 637.6x, 638.6, 639.6, 673.2x

Autoimmune hemolytic anemia: 283.0

Immune thrombocytopenic purpura: 287.31

Rheumatoid arthritis: 714, 714.0

Systemic lupus erythematosus: 710.0

Cancer: 140.xx–208.xx, 209.0x–209.3x

Crohn’s disease: 555.x

Chronic obstructive pulmonary disease: 491.2x, 492.x, 493.2x, 496

Diabetes: 250.xx

Heart failure: 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.xx

Infection: 001.xx–139.xx, 460.xx–466.xx, 480.xx–488.xx

Injury: 800.xx–908.xx, 910.xx–959.xx, E800.x–E848.x, E880.x–E999.x

Paralysis of one or more limbs: 342.xx, 344.0x, 344.1x, 344.2x, 344.3x, 344.4x, 344.5x

Selected kidney diseases: 581.xx, 582.xx, 585.x

Stroke: 431, 434.xx, 436

Ulcerative colitis: 556.x

Varicose veins: 454.x, 456.x

Pregnancy and/or delivery: 630.xx–679.xx, V22.xx–V24.xx, V28.xx

ICD-9-CM and CPT procedure codes used

Selected venous catheterization:	ICD-9-CM - 38.93 CPT – 36556, 36558, 36561, 36563, 36565, 36566, 36569, 36571, 36580, 36584, 36575, 36581, 36593–36596
Selected surgical procedures:	ICD-9-CM - 01.xx–86.xx (except 38.93); CPT – 10040– 19499, 20000– 29999, 30000– 32999, 33010–36554, 36597–37799, 38100–38999, 39000–39599, 40490–49999, 50010–53899, 54000–55899, 55920–55980, 56405–58999, 59000–59899, 60000–60699, 61000–64999, 65091–68899, 69000–69979

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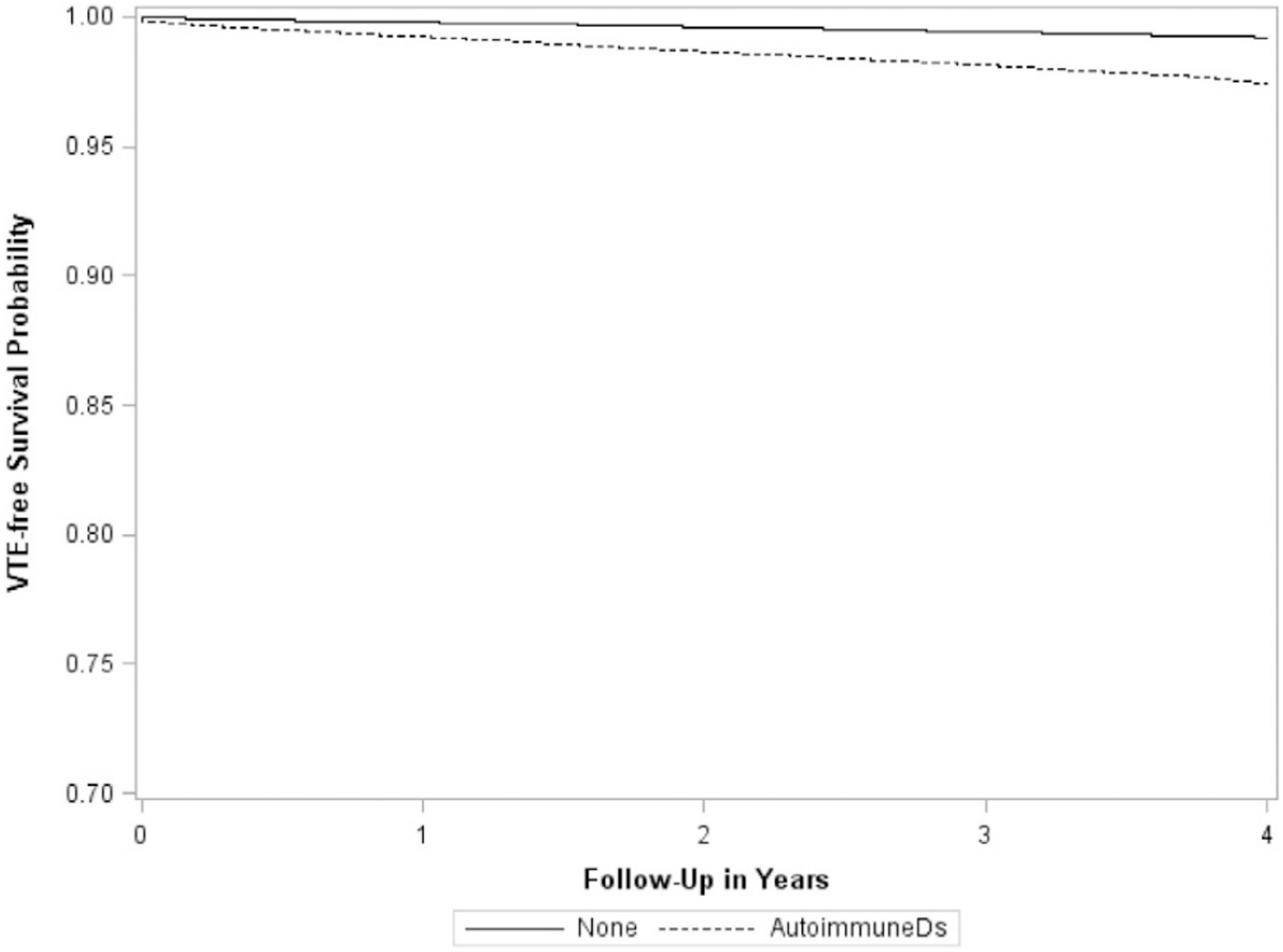

Fig. 1.

Product limit survival curve of the time to diagnosis of a venous thromboembolism event among those with and those without a diagnosis of any of the four autoimmune diseases of interest: autoimmune hemolytic anemia, immune thrombocytopenic purpura, rheumatoid arthritis, and systemic lupus erythematosus. **Abbreviation:** VTE, venous thromboembolism; AutoimmuneDs, diagnosis of any of four autoimmune diseases of interest. **Note:** The survival curves represent VTE-free survival probability for only the first identified VTE event during follow-up.

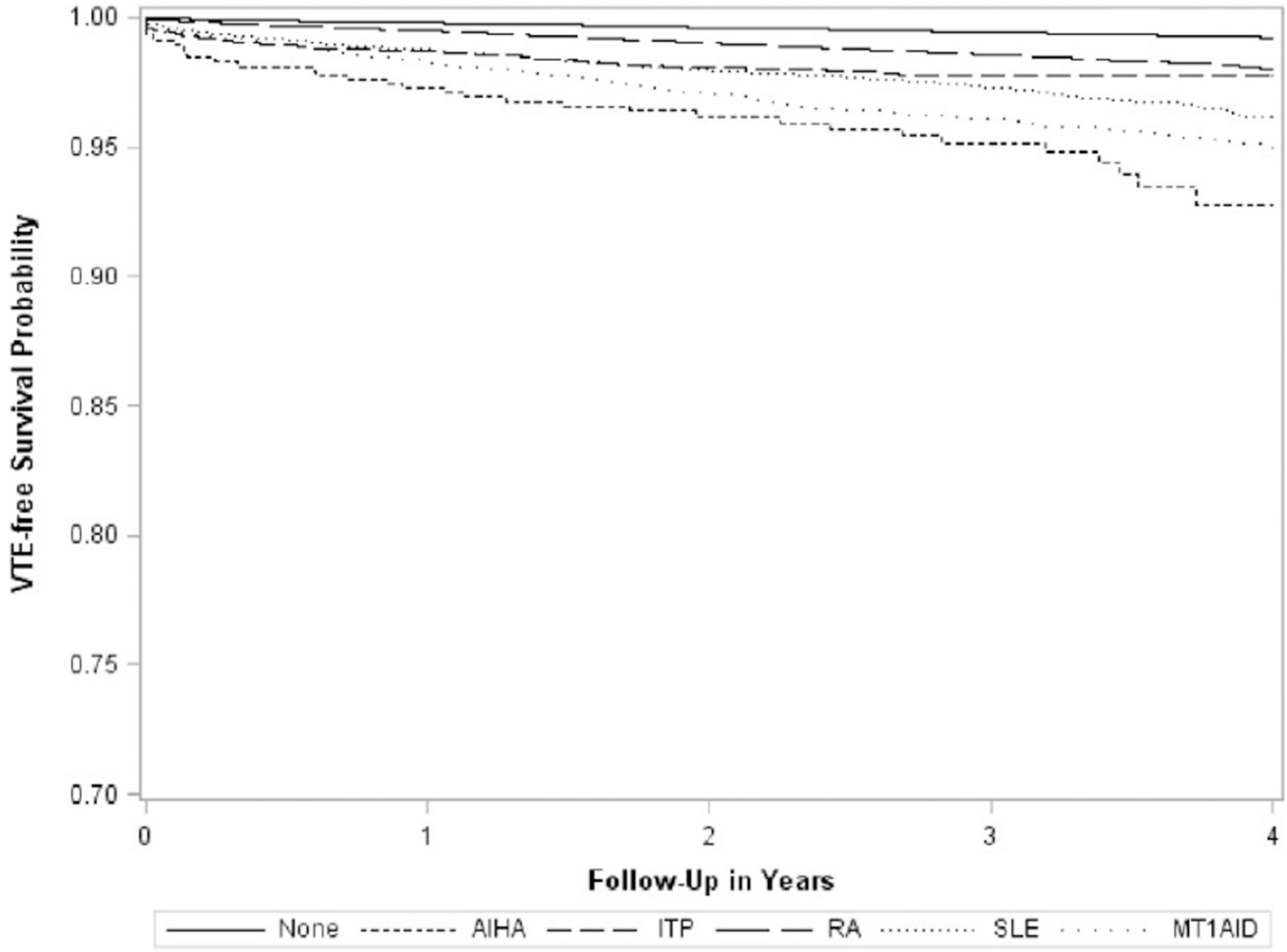

Fig. 2.

Product limit survival curve of the time to diagnosis of a venous thromboembolism event among those with a diagnosis of autoimmune hemolytic anemia, immune thrombocytopenic purpura, rheumatoid arthritis, or systemic lupus erythematosus, or two ormore of the four diseases, and for thosewith none of the four diseases. **Abbreviations:** VTE, venous thromboembolism; AID, autoimmune diseases; AIHA, autoimmune hemolytic anemia; ITP, immune thrombocytopenic purpura; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; MT1AID, two or more autoimmune disease. **Note:** The survival curves represent VTE-free survival probability for only the first identified VTE event during follow-up.

Table 1

Percentage distribution of selected characteristics among the study group and comparison group.

Characteristic	Study group (n=98,308) %	Comparison group (n=198,044) %
Sex: Male	20.6	20.6
Female	79.4	79.4
Mean age	(49.5 years)	(49.0 years)
Age group: 18–34 years	10.0	10.0
35–44 years	17.7	17.7
45–54 years	34.1	34.1
55–64 years	38.2	38.3
Hospitalized >1 times during follow-up	29.6	13.5
Mean number of days hospitalized for entire cohort	(2.8 days)	(0.8 days)
Diagnosis of the following during follow-up:		
Cancer	5.0	5.1
Heart failure	2.2	0.8
Stroke	1.1	0.5
Chronic obstructive pulmonary disease	4.0	1.9
Injury	17.4	13.2
Infection	33.8	26.9
Chronic kidney disease	3.1	0.8
Varicose veins	1.0	0.7
Paralysis of limb	0.3	0.2
Diabetes	8.5	9.5
Crohn’s disease/Ulcerative colitis	1.0	0.5
Hospitalized during pregnancy or delivery, or both	1.8	1.9
Venous catheterization	3.2	0.8
Other selected surgical procedures	20.9	10.1

Note: For diagnosis of medical conditions, hospitalization during pregnancy or delivery, inpatient venous catheterization, and inpatient surgery, the percentages (in columns 2 and 3) represent whether at least one such event occurred during follow-up.

Table 2

Follow-up duration, number of participants with a venous thromboembolism (VTE) events, and risk of VTE among the study group and the comparison group.

Group	Number of participants	Total follow-up in person-years (mean follow-up duration per participant)	Number of participants with at least one VTE event	Risk of VTE event per 1,000 person-years
All participants				
AIHA	784	1,773 (826 days)	35	19.74
ITP	2,772	6,740 (888 days)	52	7.72
RA	70,768	185,394 (957 days)	909	4.90
SLE	19,427	50,073 (941 days)	495	9.89
≥2 condition	4,557	13,562 (1,087 days)	181	13.35
Any (≥1) conditions	98,308	257,542 (957 days)	1,672	6.49
None of the 4 conditions	198,044	513,504 (947 days)	981	1.91
18–40 years age				
AIHA	211	461 (798 days)	5	10.84
ITP	992	2,340 (862 days)	13	5.56
RA	10,127	25,700 (927 days)	56	2.18
SLE	6,149	14,889 (884 days)	168	11.28
≥2 condition	1072	3,078 (1,049 days)	42	13.64
Any (≥1) conditions	18,551	46,469 (915 days)	284	6.11
None of the 4 conditions	40,072	92,944 (847 days)	67	0.72
41–64 years age				
AIHA	573	1,312 (836 days)	30	22.87
ITP	1,780	4,399 (903 days)	39	8.86
RA	60,641	159,694 (962 days)	853	5.34
SLE	13,278	35,183 (968 days)	327	9.29
≥2 condition	3,485	10,483 (1,099 days)	139	13.26
Any (≥1) conditions	79,757	211,072 (967 days)	1388	6.58
None of the 4 conditions	157,972	420,560 (972 days)	914	2.17

Abbreviations: VTE, venous thromboembolism; AIHA, autoimmune hemolytic anemia; ITP, immune thrombocytopenic purpura; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

Note: The risk estimates in the table represent the risk of only the first identified VTE event during follow-up.

Table 3

Adjusted hazards ratios for a venous thromboembolism diagnosis following diagnosis of autoimmune hemolytic anemia, immune thrombocytopenic purpura, rheumatoid arthritis, and systemic lupus erythematosus; two or more of these four diseases; and any of these four diseases.

Characteristic	AIHA aHR (95% CI)	ITP aHR (95% CI)	RA aHR (95% CI)	SLE aHR (95% CI)	≥2 of the 4 autoimmune ds.s aHR (95% CI)	Any (≥1) of the 4 autoimmune ds.s aHR (95% CI)
at 90 days	7.55 (4.74–12.02)	5.50 (3.92–7.72)	2.16 (1.85–2.51)	5.26 (4.43–6.23)	5.98 (4.69–7.61)	3.34 (2.94–3.80)
at 180 days	7.11 (4.70–10.77)	4.49 (3.31–6.08)	2.15 (1.87–2.47)	5.06 (4.33–5.91)	5.68 (4.56–7.07)	3.25 (2.89–3.66)
at 1 year	6.30 (4.44–8.94)	2.95 (2.18–4.00)	2.13 (1.89–2.40)	4.68 (4.10–5.33)	5.11 (4.26–6.14)	3.08 (2.80–3.40)
at 2 years	4.95 (3.21–7.65)	1.29 (0.76–2.20)	2.10 (1.88–2.34)	4.01 (3.51–4.58)	4.16 (3.44–5.02)	2.78 (2.53–3.05)
at 3 years	3.90 (1.96–7.74)	0.57 (0.24–1.33)	2.06 (1.78–2.40)	3.43 (2.83–4.16)	3.38 (2.56–4.48)	2.50 (2.19–2.85)
at 4 years	3.07 (1.15–8.21)	0.25 (0.08–0.82)	2.03 (1.64–2.51)	2.94 (2.23–3.87)	2.75 (1.84–4.11)	2.25 (1.87–2.72)

Abbreviations: AIHA, autoimmune hemolytic anemia; ITP, immune thrombocytopenic purpura; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; aHR, adjusted hazards ratio; CI, confidence interval.

Notes: Factors adjusted for included sex; age; diagnosis of cancer; heart failure; stroke; chronic obstructive pulmonary disease; injury; infection; kidney disease (chronic kidney disease, chronic glomerulonephritis, and nephrotic syndrome); varicose veins; paralysis of limb; diabetes; Crohn's disease/ulcerative colitis; hospitalization with pregnancy or delivery diagnosis, or both; selected venous catheterization procedures; and selected other surgical procedures.
The estimates in the table represent the aHRs associated with only the first identified VTE event during follow-up.

Table 4

Adjusted hazards ratios for a venous thromboembolism diagnosis following diagnosis of autoimmune hemolytic anemia, immune thrombocytopenic purpura, rheumatoid arthritis, and systemic lupus erythematosus, by age group.

Characteristic	AIHA aHR (95% CI)	ITP aHR (95% CI)	RA aHR (95% CI)	SLE aHR (95% CI)	≥2 of the 4 autoimmune ds.s aHR (95% CI)	Any (≥1) of the 4 autoimmune ds.s aHR (95% CI)
18–40 years age						
at 90 days	11.99 (3.81–37.74)	7.57 (3.40–16.89)	3.23 (1.93–5.39)	13.88 (9.09–21.16)	13.51 (7.58–24.05)	7.57 (5.09–11.26)
at 180 days	11.00 (3.91–30.88)	7.07 (3.44–14.52)	3.10 (1.96–4.93)	13.29 (9.06–19.49)	12.94 (7.66–21.82)	7.23 (5.05–10.37)
at 1 year	9.20 (3.62–23.41)	6.14 (3.31–11.40)	2.87 (1.95–4.21)	12.16 (8.81–16.77)	11.84 (7.62–18.39)	6.59 (4.88–8.91)
at 2 years	6.48 (1.74–24.14)	4.65 (2.15–10.05)	2.45 (1.64–3.64)	10.20 (7.36–14.13)	9.94 (6.33–15.59)	5.49 (4.07–7.39)
at 3 years	4.56 (0.58–35.73)	3.52 (1.06–11.71)	2.09 (1.15–3.78)	8.56 (5.32–13.75)	8.34 (4.32–16.10)	4.57 (2.96–7.04)
at 4 years	3.21 (0.18–58.20)	2.67 (0.48–14.76)	1.78 (0.76–4.20)	7.18 (3.64–14.14)	7.00 (2.74–17.92)	3.80 (2.04–7.06)
41–64 years age						
at 90 days	6.04 (3.64–10.04)	4.89 (3.37–7.09)	1.98 (1.71–2.29)	3.91 (3.23–4.74)	4.77 (3.65–6.24)	2.53 (2.22–2.88)
at 180 days	5.76 (3.67–9.06)	3.74 (2.68–5.23)	1.97 (1.73–2.25)	3.81 (3.20–4.53)	4.55 (3.57–5.79)	2.49 (2.21–2.80)
at 1 year	5.23 (3.59–7.63)	2.16 (1.48–3.15)	1.97 (1.77–2.20)	3.60 (3.12–4.15)	4.12 (3.37–5.03)	2.40 (2.18–2.65)
at 2 years	4.32 (2.73–6.83)	0.73 (0.35–1.53)	1.97 (1.78–2.17)	3.22 (2.79–3.72)	3.39 (2.75–4.17)	2.24 (2.05–2.46)
at 3 years	3.57 (1.72–7.39)	0.25 (0.08–0.80)	1.96 (1.69–2.27)	2.88 (2.32–3.58)	2.79 (2.04–3.81)	2.09 (1.83–2.40)
at 4 years	2.95 (1.03–8.42)	0.08 (0.02–0.43)	1.95 (1.58–2.42)	2.58 (1.88–3.54)	2.29 (1.46–3.60)	1.96 (1.61–2.38)

Abbreviations: AIHA, autoimmune hemolytic anemia; ITP, immune thrombocytopenic purpura; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; aHR, adjusted hazards ratio; CI, confidence interval.

Notes: Factors adjusted for included sex; age; diagnosis of cancer; heart failure; stroke; chronic obstructive pulmonary disease; injury; infection; kidney disease (chronic kidney disease, chronic glomerulonephritis, and nephrotic syndrome); varicose veins; paralysis of limb; diabetes; Crohn's disease/ulcerative colitis; hospitalization with pregnancy or delivery diagnosis, or both; selected venous catheterization procedures; and selected other surgical procedures.
The estimates in the table represent the aHRs associated with only the first identified VTE event during follow-up.