The Risk of Deep Venous Thrombosis and Pulmonary Embolism in Primary Sjögren Syndrome: A General Population-based Study

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ABSTRACT. ***Objective.*** To estimate the future risk and time trends of venous thromboembolism (VTE) in individuals with newly diagnosed primary Sjögren syndrome (pSS) in the general population.

Methods. Using a population database that includes all residents of British Columbia, Canada, we created a study cohort of all patients with incident SS and up to 10 controls from the general population matched for age, sex, and entry time. We compared incidence rates (IR) of pulmonary embolism (PE), deep vein thrombosis (DVT), and VTE between the 2 groups according to SS disease duration. We calculated HR, adjusting for confounders.

Results. Among 1175 incident pSS cases (mean age 56.7 yrs, 87.6% women), the IR of PE, DVT, and VTE were 3.9, 2.8, and 5.2 per 1000 person-years (PY), respectively; the corresponding rates in the comparison cohort were 0.9, 0.8, and 1.4 per 1000 PY. Compared with non-SS individuals, the multivariable HR for PE, DVT, and VTE among SS cases were 4.07 (95% CI 2.04–8.09), 2.80 (95% CI 1.27–6.17), and 2.92 (95% CI 1.66–5.16), respectively. The HR matched for age, sex, and entry time for VTE, PE, and DVT were highest during the first year after SS diagnosis (8.29, 95% CI 2.57–26.77; 4.72, 95% CI 1.13–19.73; and 7.34, 95% CI 2.80–19.25, respectively).

Conclusion. These findings provide population-based evidence that patients with pSS have a substantially increased risk of VTE, especially within the first year after SS diagnosis. Further research into the involvement of monitoring and prevention of VTE in SS may be warranted. (J Rheumatol First Release March 15 2017; doi:10.3899/jrheum.160185)

Key Indexing Terms:
SJÖGREN SYNDROME THROMBOSIS EMBOLISM
CARDIOVASCULAR DISEASES RISK

Sjögren syndrome (SS) is an inflammatory autoimmune disease characterized by lymphocytic infiltration of the exocrine glands and subsequent gland dysfunction. Dysfunction of the lacrimal and salivary glands produces dry eyes and dry mouth, respectively, and this constellation of symptoms (sicca complex) is the hallmark of SS. SS is seen both as a primary entity in isolation, as well as a secondary entity in the context of other established autoimmune diseases — typically systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), or systemic sclerosis (SSc). In addition to the classic sicca complex, the disease can also have a wide variety of extraglandular manifestations potentially affecting almost any body system[1].

Venous thromboembolism (VTE), which consists of both deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common disease associated with significant morbidity and mortality[2,3]. Classic risk factors for VTE include trauma, surgery, prolonged immobilization, and malignancy; however, a wide range of medications, lifestyle factors, inherited factors, and medical comorbidities have also been associated with increased rates of VTE[4].

It is well documented that many inflammatory autoimmune diseases are associated with increased rates of VTE, including inflammatory bowel disease (IBD), RA, SLE, SSc, polymyositis/dermatomyositis, and giant cell arteritis[5,6,7,8,9,10,11]. Research suggests that inflammation may be involved in the inappropriate activation of the coagulation cascade, suggesting a plausible mechanism for the risk of

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VTE in the above inflammatory disorders[12,13]. Although other inflammatory conditions have been well studied, the data on VTE in SS are scarce, particularly at the general population level[7,8,14].

Given the clinical importance of VTE and the emergence of evidence to suggest an increased risk in patients with SS, it is important to fully understand and quantify this effect. To address some of the limitations of previous studies, we evaluated the risk of VTE in a cohort of patients with incident primary SS (pSS) compared with randomly selected matched controls from the general population, including an analysis of the time trends after SS diagnosis.

MATERIALS AND METHODS

Data source. We used Population Data BC, a province-wide database generated from the British Columbia (BC) healthcare system, which includes about 4.5 million people. Population Data BC identifies population-based administrative data including linkable data files on all provincially funded healthcare professional visits[15], hospital admissions and discharges[16], interventions[15], investigations[15], demographic data[17], cancer registry[18], and vital statistics since 1990[19]. Further, Population Data BC encompasses the comprehensive outpatient prescription drug database, PharmaNet, with data since 1996[20]. Numerous general population-based studies have been successfully conducted using these databases[10,11,21,22,23,24].

Study design. We conducted cohort analyses of incident VTE among individuals with incident pSS (SS cohort) as compared with individuals without SS randomly selected from the general population using Population Data BC (control cohort) and matched for age, sex, and entry time. We created an incident SS cohort with cases diagnosed for the first time between January 1996 and December 2010, defined as either of the following: ≥ 2 International Classification of Diseases-9-Clinical Modification (ICD-9-CM) codes (710.2) for SS at least 2 months apart, but within a 2-year period by nonrheumatologists; or ≥ 1 ICD-9-CM code for SS by a rheumatologist or from hospitalization (ICD-9-CM: 710.2 and ICD-10: M35). Additionally, we required no ICD-9-CM code for SS from January 1990 until cohort entry (to ensure incident SS cases). A validation study of ICD-9 codes in a Canadian context found that the specificity and sensitivity of pSS diagnosis from administrative health data were 95.5% and 95.8%, respectively[25].

To further improve specificity for pSS, we excluded individuals with 2 or more visits at least 2 months apart subsequent to the SS diagnostic visit with diagnoses of other systemic autoimmune rheumatic diseases (RA, psoriatic arthritis, spondyloarthropathy, SLE, SSc, and adult systemic vasculitis) after the index date (date of diagnosis). For each cohort, we matched up to 10 individuals, randomly selected from the general population, without SS to each SS case based on age, sex, and calendar year of study entry.

Ascertainment of PE and DVT. Incident PE and DVT cases were defined by a corresponding ICD code and prescription for anticoagulant therapy (heparin, warfarin sodium, or a similar agent)[26]. The codes used were as follows: PE (ICD-9-CM: 415.1, 673.2, 639.6; ICD-10-CM: O88.2, I26) and DVT (ICD-9-CM: 453; ICD-10-CM: I82.4, I82.9). Because VTE is a potentially fatal outcome, we also included patients with a fatal outcome. Patients with a recorded code of DVT or PE were included in the absence of recorded anticoagulant therapy (i.e., the patients died before discharge, and therefore never received a prescription for anticoagulant therapy from an outpatient service; such cases would not be identified by PharmaNet, which only identifies medication received outside of hospital) if there was a fatal outcome within 2 months of diagnosis. These definitions have been successfully used in previous studies and found to have a positive predictive value of 94% in a general practice database[26].

Assessment of covariates. Covariates included the following potential risk factors for VTE assessed during the year before the index date: surgery, trauma, fractures, and cancer (embedded in the Charlson Comorbidity Index). We also corrected for other relevant medical conditions [alcoholism, hypertension (HTN), varicose veins, IBD, sepsis], medications [glucocorticoids, hormone replacement therapy, contraceptives, and cyclooxygenase (COX)-2 inhibitors], and comorbidity burden (healthcare use and Charlson Comorbidity Index)[27,28].

Cohort followup. Our study cohorts spanned the period from January 1, 1996, to December 31, 2010. Individuals with SS entered the case cohort after all inclusion criteria were met, and matched individuals entered the comparison cohort after a doctor's visit or hospital admission in the same calendar year. Participants were followed until they experienced an outcome, died, unenrolled from the health plan by leaving the province (~1%), or the followup period ended (December 31, 2010), whichever occurred first.

Statistical analysis. We compared baseline characteristics between the SS and comparison cohorts. We calculated the incidence rates (IR) per 1000 person-years (PY) for each outcome in the SS and comparison cohorts. The associations between SS and study outcomes are expressed as incidence rate ratios (IRR) with 95% CI. We calculated and plotted the cumulative IR of endpoints for individuals with and without SS, accounting for the competing risk of death[29].

We used Cox proportional hazard regression models to assess the risk of PE, DVT, and VTE associated with SS after adjusting for the covariates listed in Table 1[30]. We entered confounders one at a time into the Cox models in a forward selection according to each confounder's effect on the HR of SS, relative to the HR in the model selected in the previous step. Cutoff for the minimum important relative effect at each step was set to 5%[31]. To evaluate the time-trend of VTE risk according to the time since SS diagnosis, we estimated HR yearly for the first 5 years. We assessed the proportional hazards assumption by plotting log–log S(t) versus log t, stratified by each covariate. If lines were not close to parallel, time interaction terms were included and tested at $\alpha = 0.05$.

Sensitivity analyses. We performed 2 sensitivity analyses to test the robustness of our results. First, we estimated the cumulative incidence of each event accounting for the competing risk of death according to Lau, *et al*[32], and expressed the results as subdistribution HR with a 95% CI. Second, to assess how a hypothetical unmeasured confounder might have affected our estimates of the association between SS and VTE, we simulated unmeasured confounders with prevalences ranging from 10% to 20% in both the SS and control cohorts, and OR ranging from 1.3 to 3.0 for the associations between the unmeasured confounder, VTE, and SS[33]. For reference, the respective OR for VTE and smoking and obesity are 1.2 and 2.3[34], respectively, and the prevalences are about 17% and 13%, respectively, based on Canadian census data[35,36].

SAS V.9.3 (SAS Institute) was used for all analyses. For all IRR and HR, we calculated 95% CI. All p values are 2-sided.

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Ethical approval. No personal identifying information was made available as part of this study. Procedures used were in compliance with British Columbia's Freedom of Information and Privacy Protection Act. Ethical approval was obtained from the University of British Columbia's Behavioral Research Ethics Board (H12-01530).

RESULTS

Baseline characteristics. Our primary analysis included 1175 incident pSS cases (mean age 56.7 yrs, 87.6% women) and in the comparison cohort, 11,947 individuals matched for age, sex, and entry time. Table 1 summarizes the baseline characteristics of the SS and comparison cohorts. Compared with the control group, the SS cases were treated with significantly

Table 1. Characteristics of SS and comparison cohorts at baseline. Values are n (%) unless otherwise specified.

Variable	SS, n = 1175	Non-SS, n = 11,947	p
Age, yrs, mean (SD)	56.73 (15.27)	56.67 (15.2)	0.902
Female	1029 (87.6)	10441 (87.4)	0.890
Alcoholism with liver disease	10 (0.9)	86 (0.7)	0.589
Hypertension	303 (25.8)	2778 (23.3)	0.052
Sepsis	13 (1.1)	18 (0.2)	< 0.001
Varicose veins	27 (2.3)	121 (1)	< 0.001
Inflammatory bowel disease	4 (0.3)	32 (0.3)	0.560
Trauma	1 (0.1)	25 (0.2)	0.726
Fractures	28 (2.4)	166 (1.4)	0.011
Surgery	13 (1.1)	84 (0.7)	0.149
Charlson Comorbidity Index, mean (SD)	1.06 (1.54)	0.36 (1.07)	< 0.001
Glucocorticoids	239 (20.3)	510 (4.3)	< 0.001
Hormone replacement therapy	139 (11.8)	823 (6.9)	< 0.001
Oral contraceptives	44 (3.7)	439 (3.7)	0.871
COX-2 inhibitors	94 (8)	356 (3)	< 0.001
Hospitalized	364 (31)	1898 (15.9)	< 0.001
No. outpatient visits, mean (SD)	20.68 (17.95)	9.09 (10.85)	< 0.001

SS: Sjögren syndrome; COX: cyclooxygenase.

more glucocorticoids, COX-2 inhibitors, and hormone replacement therapy; had more fractures, sepsis, and varicose veins; had higher Charlson Comorbidity Index scores; and had more hospitalizations and outpatient visits during the 12 months prior to diagnosis.

Association between a diagnosis of pSS and incident VTE. Overall, SS was significantly associated with an increased incidence of VTE, as well as individual DVT and PE (Table 2, Figure 1). Among individuals with SS, the IR for PE, DVT, and VTE were 3.85, 2.75, and 5.24 per 1000 PY versus 0.89, 0.79, and 1.44 per 1000 PY in the comparison cohort, respectively. The corresponding HR matched for age, sex, and entry time were 5.57 (95% CI 2.90–10.68), 4.04 (95% CI 1.95–8.40), and 4.24 (95% CI 2.48–7.26), respectively. In a multivariable proportional hazards analysis, the following covariates were found to be significant confounders: for PE, number of outpatient visits, glucocorticoids, COX-2 inhibitors, HTN; for DVT, number of outpatient visits, glucocorticoids, Charlson Comorbidity Index; for VTE, number of outpatient visits, glucocorticoids, COX-2 inhibitors, Charlson Comorbidity Index. After adjustment for these confounders, the HR remained significant at 4.07 (95% CI 2.04–8.09), 2.80 (95% CI 1.27–6.17), and 2.92 (95% CI 1.66–5.16) for PE, DVT, and VTE, respectively (Table 2). When we evaluated the effect of followup time after SS diagnosis, the adjusted HR for PE, DVT, and VTE events were significantly elevated

Table 2. Relative risk of incident PE and DVT according to SS status.

Variables	SS, n = 1175	Non-SS, n = 11,947
PE		
Cases, n	14	36
Incidence rate/1000 person-yrs	3.85	0.89
Age-, sex-, entry time–matched, Cox HR (95% CI)	5.57 (2.90–10.68)	1.00
* Fully adjusted age-, sex-, entry time–matched, Cox HR (95% CI)	4.07 (2.04–8.09)	1.00
DVT		
Cases, n	10	32
Incidence rate/1000 person-yrs	2.75	0.79
Age-, sex-, entry time–matched, Cox HR (95% CI)	4.04 (1.95–8.40)	1.00
* Fully adjusted age-, sex-, entry time–matched, Cox HR (95% CI)	2.80 (1.27–6.17)	1.00
VTE		
Cases, n	19	58
Incidence rate/1000 person-yrs	5.24	1.44
Age-, sex-, entry time–matched, Cox HR (95% CI)	4.24 (2.48–7.26)	1.00
* Fully adjusted age-, sex-, entry time–matched, Cox HR (95% CI)	2.92 (1.66–5.16)	1.00

* Fully adjusted models include the following selected covariates: for PE, hormone replacement therapy, no. outpatient visits and glucocorticoids; DVT, glucocorticoids and no. outpatient visits; PE or DVT, glucocorticoids and no. outpatient visits. PE: pulmonary embolism; DVT: deep vein thrombosis; SS: Sjögren syndrome; VTE: venous thromboembolism.

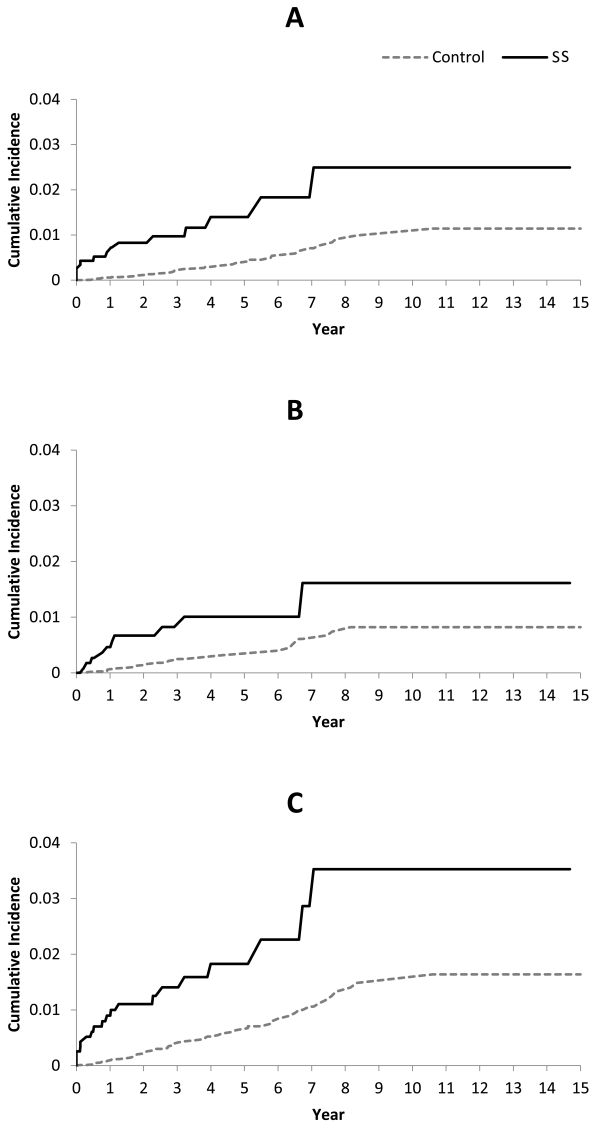

Figure 1. Cumulative incidence of (A) PE, (B) DVT, and (C) VTE in the 1175 cases with incident primary SS compared with controls randomly selected from the general population and matched for age, sex, and entry time. PE: pulmonary embolism; DVT: deep vein thrombosis; VTE: venous thromboembolism; SS: Sjögren syndrome.

for 5 years following SS diagnosis, and substantially higher in the first year (Table 3).

Sensitivity analysis. The adjusted HR were attenuated, but remained statistically significant when we tested for both the competing risk of early death and a potential unmeasured confounder, even at extreme values for the prevalence and magnitude of the confounder (Table 4).

DISCUSSION

Our large, general population–based observational study demonstrates a significantly elevated risk of VTE in patients with pSS as compared with matched controls from the general population. The fully adjusted HR for PE, DVT, and VTE were 4.07 (95% CI 2.04–8.09), 2.80 (95% CI 1.27–6.17), and 2.92 (95% CI 1.66–5.16), respectively. This effect was particularly pronounced in the first year after SS diagnosis, and was found to persist for at least 5 years.

Our results confirm that pSS is an independent risk factor for PE, DVT, and VTE in a general population context. Although our observational study cannot provide information pertaining to causation or a mechanism for the association, previous research suggests that inflammation can contribute to the development of VTE because it initiates clotting, decreases the activity of natural anticoagulant mechanisms, and impairs the fibrinolytic system[12,13]. This would be consistent with our finding that the risk is highest during the period where the disease is most active and the inflammation least controlled: immediately following diagnosis.

Our results are somewhat higher, but largely consistent with previous findings. Four previous studies have investigated the association between SS and VTE: 3 registry-based cohort studies of SS populations and 1 case-control study of VTE events[7,8,9,14]. Ramagopalan, *et al*[7] analyzed an English registry and compared the rates of VTE in patients hospitalized for various rheumatologic diseases with controls hospitalized for minor medical/surgical issues. They found a risk ratio of 2.02 (95% CI 1.80–2.26) for VTE in patients with SS[7]. Zöller, *et al*[8] analyzed a Swedish registry, restricting their analysis to PE in hospitalized patients. They found an IRR of 2.19 (95% CI 1.78–2.66) for PE in patients with SS overall, and an IRR of 7.40 (95% CI 5.09–10.40) during the first year after diagnosis[8]. Chung, *et al*[14] analyzed a Taiwanese registry with a methodology similar to that of Zöller, *et al*, but broadened their analysis to include PE and DVT, as well as a distinction between primary and secondary SS. They found HR for SS of 3.29 (95% CI 2.03–5.31) and 1.83 (95% CI 1.16–2.89) for PE and DVT, respectively[14]. An alternative explanation to the early increased risk of VTE in SS may be related to the depletion of susceptible individuals over time. Regardless, our incident case analyses demonstrated that the induction time of SS effect on the risk of VTE was relatively short (i.e., within mos).

Unfortunately, these results may not be generalizable to North American and European populations because of previously described differences in rates of VTE between races[37]. Additionally, none of these studies included prescription drug usage or healthcare resource use, limiting their ability to adjust preexisting differences on comorbidity as well as limiting the generalizability of their results. Finally, Johannesdottir, *et al*[9] analyzed a Danish registry that incorporated both medication usage and health resource use data. They used a case-control design to analyze VTE cases and determined that the HR for SS was 3.3 (95% CI 2.1–5.0). However, once adjusted for confounders, their result became nonsignificant at 1.6 (95% CI 0.9–2.7)[9].

Table 3. Age- and sex-adjusted Cox HR for PE, DVT, and VTE in Sjögren syndrome according to followup period. Values are HR (95% CI).

Time after Diagnosis	PE	DVT	VTE
< 1 yr	8.29 (2.57–26.77)	4.72 (1.13–19.73)	7.34 (2.80–19.25)
< 2 yrs	5.64 (2.19–14.49)	4.06 (1.52–10.86)	4.50 (2.09–9.68)
< 3 yrs	4.38 (1.88–10.25)	3.24 (1.30–8.03)	3.59 (1.82–7.07)
< 4 yrs	4.65 (2.15–10.05)	3.08 (1.31–7.27)	3.35 (1.79–6.28)
< 5 yrs	4.15 (1.93–8.93)	3.01 (1.29–7.04)	2.96 (1.59–5.51)
Total followup	4.07 (2.04–8.09)	2.80 (1.27–6.17)	2.92 (1.66–5.16)

PE: pulmonary embolism; DVT: deep vein thrombosis; VTE: venous thromboembolism.

Table 4. Primary sensitivity analysis is the fully adjusted model. Subdistribution model is also adjusted for competing risk of early death (age and sex). Simulated confounder models included additional covariates. Values are HR (95% CI).

Outcome	Primary Analysis	Subdistribution Cox Model, Competing Risk of Early Death	Simulated Confounder 10%/OR 1.3	Simulated Confounder 20%/OR 3.0
PE	4.07 (2.04–8.09)	3.29 (1.71–6.32)	3.83 (1.92–7.62)	3.29 (1.61–6.72)
DVT	2.80 (1.27–6.17)	2.73 (1.39–5.38)	2.65 (1.20–5.87)	2.24 (0.99–5.09)
VTE	2.92 (1.66–5.16)	2.70 (1.58–4.61)	2.78 (1.57–4.90)	2.37 (1.31–4.27)

PE: pulmonary embolism; DVT: deep vein thrombosis; VTE: venous thromboembolism.

We acknowledge some limitations of our study. Our results are subject to the accuracy of ICD codes in administrative data; however, the validity of SS diagnosis based on administrative data in this context has been previously documented[25]. Because the SS cohort was identified using an algorithm based on diagnostic codes rather than verification of individual medical records, we cannot exclude the possibility that some of these cases were falsely identified. However, this will be a conservative bias where the association would favor the null hypothesis.

Additionally, we are limited by the possibility of unknown or unmeasured confounders, including, but not limited to, undocumented lifestyle factors such as smoking status, physical activity, and body mass index. This was addressed through a simulated confounder analysis; our results remained significant, suggesting that our findings are robust. Moreover, our data did not include laboratory data, such as antiphospholipid antibodies, or biopsy data.

The strengths of our study include the large sample size, adjustment for preexisting comorbidities, inclusion of prescription medications for both cases and controls, and adjustment for the competing risk of death and unmeasured confounders in a general population context. Moreover, we used a cohort of incident cases to avoid the biases associated with prevalent cohorts (e.g., survivors' bias).

We have demonstrated that SS is associated with a statistically significant increased risk of VTE in a general population context. Further, early after disease onset there is a particularly elevated risk, with an 8-fold risk of PE, 4-fold risk of DVT, and 7-fold risk of VTE in the first year of disease diagnosis compared with matched controls. This finding remains significant after correction for confounding comorbidities, medications, and demographic variables, as well as the inclusion of potential unmeasured confounders. Considering this, additional research into the involvement of surveillance and prevention of VTE in SS through early treatment may be warranted.

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