The Risk of Deep Venous Thrombosis and Pulmonary Embolism in Giant Cell Arteritis: A General Population-Based Study

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Abstract

Importance—Patients with giant cell arteritis (GCA) may have an increased risk of pulmonary embolism (PE), similar to other systemic vasculitides; however, no relevant population data are available to date.

Objective—To evaluate the future risk and time trends of new venous thromboembolism (VTE) in individuals with incident GCA at the general population level.

Design—Observational cohort study

Setting—General population of British Columbia

Participants—909 patients with incident GCA and 9288 age-, sex-, and entry-time-matched control patients without a history of VTE.

Main Outcome Measures—We calculated incidence rate ratios (IRR) overall, and stratified by GCA duration. We calculated hazard ratios (HR) of PE and deep vein thrombosis (DVT), adjusting for potential VTE risk factors.

Results—Among 909 individuals with GCA (mean age 76 years, 73% female), 18 developed PE and 20 developed DVT. Incidence rates (IRs) of VTE, PE, and DVT were 13.3, 7.7 and 8.5 per 1000 person-years (PY), versus 3.7, 1.9, and 2.2 per 1000 PY in the comparison cohort. The corresponding IRRs (95% CI) for VTE, PE, and DVT were 3.58 (2.33–5.34), 3.98 (2.22–6.81) and 3.82 (2.21–6.34) with the highest IRR observed in the first year of GCA diagnosis (7.03, 7.23, and

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7.85, respectively). Corresponding fully adjusted HRs (95% CI) were 2.49 (1.45–4.30), 2.71 (1.32–5.56) and 2.78 (1.39–5.54).

Conclusions and significance—These findings provide general population-based evidence that patients with GCA have an increased risk of VTE, calling for increased vigilance in preventing this serious, but preventable complication, especially within months after GCA diagnosis.

Keywords

Giant Cell Arteritis; Pulmonary Embolism; Deep Vein Thrombosis

INTRODUCTION

Giant cell arteritis (GCA) is a systemic immune-mediated disease characterized by granulomatous infiltrates in the walls of medium-sized and large arteries. GCA, the most frequent form of vasculitis in adults,(1) is associated with significant morbidity due to vascular problems. For example, studies have found that GCA is associated with arterial complications like blindness,(2) aortic aneurysms,(3) myocardial infarction,(4–6) and ischemic stroke.(6–8) These previous studies have focused on arterial events, with the risk of venous thromboembolism (VTE) events in GCA patients being largely ignored despite an array of plausible mechanisms.(9, 10)

Systemic inflammation associated with GCA may modulate thrombotic responses by upregulating procoagulants, downregulating anticoagulants and suppressing fibrinolysis.(10) Furthermore, myointimal thickening, stenosis, or occlusion of vessel lumen may contribute to thrombosis.(11) In addition, thrombocytosis with platelet counts of $>400,000/\text{mm}^3$ commonly occurs in active GCA and may also play a role.(12–15)

While a recent Swedish nationwide study of hospitalized patients described a 1.9 times increased risk of PE in patients with polymyalgia rheumatica (PMR),(16) we are not aware of any large scale or general population data on this outcome among GCA patients. Since PE represents a common and often fatal vascular event,(17) accurate understanding of this risk among this most common vasculitis syndrome is crucial. To address this issue, we evaluated the risk of incident PE and DVT among incident GCA patients compared to controls in an unselected general population context.

METHODS

Data source

We used a province-wide database ($N = \sim 4.7$ million) from the British Columbia (BC) healthcare system, which is based on universal health coverage. The Population Data (PopData) BC (formerly known as the British Columbia Linked Health Databases, BCLHD) captures population-based administrative data including linkable data files on all provincially funded healthcare professional visits, hospital admissions and discharges, interventions, investigations, demographic data, cancer registry and vital statistics since 1990. Furthermore, PopData BC encompasses the comprehensive prescription drug

database, PharmaNet, with data since 1996. Numerous general population-based studies have been successfully conducted based on these databases.(18–22)

Study Design

We conducted matched cohort analyses for incident VTE (i.e. PE or DVT) among individuals with incident GCA (GCA cohort) as compared with individuals without GCA (comparison cohort) using data from PopData BC. For the comparison cohorts, we matched up to ten individuals without GCA to each GCA case based on age, sex, and calendar year of study entry.

Incident GCA Cohort

We created an incident GCA cohort with cases diagnosed for the first time between January 1996 and December 2010 with no GCA history or diagnosis recorded over the prior six years (i.e., from January 1990). Our study definition of GCA consisted of **a)** 40 years of age; **b)** One International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code for GCA by a rheumatologist (ICD-9-CM 446.5) or from hospital (ICD-9-CM 446.5, ICD-10 M31.5) or two ICD-9-CM codes for GCA at least two months and no more than two years apart by a non-rheumatologist physician; **c)** At least one prescription of oral glucocorticoids between one month before and 6 months after the second GCA visit (or first visit if diagnosed in hospital or by a rheumatologist). Similar GCA definitions have been used previously in a general population database and found to have a positive predictive value of 91%.(23, 24) To further improve specificity, we excluded individuals with at least two visits greater than two months apart subsequent to the GCA diagnostic visit with other inflammatory disease diagnoses (e.g., rheumatoid arthritis, psoriatic arthritis, spondyloarthropathies, systemic lupus erythematosus, and inflammatory myopathies). Moreover, in a sensitivity analysis, we used a more stringent definition of GCA that required five or more prescriptions of glucocorticoids.

Ascertainment of PE and DVT

Incident PE and DVT cases were defined by a corresponding ICD code and prescription of anticoagulant therapy (heparin, warfarin sodium or a similar agent).(25) 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). Since VTE is a potentially fatal disease, we also included patients with a fatal outcome. As a patient may have died before anticoagulation treatment, patients with a recorded code of DVT or PE were included in the absence of recorded anticoagulant therapy if there was a fatal outcome within one month 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.(25)

Assessment of Covariates

Covariates consisted of potential risk factors for VTE assessed during the year before the index date. These included relevant medical conditions (alcoholism, hypertension, varicose veins, inflammatory bowel disease, fractures, and sepsis), trauma, surgery, healthcare utilization, and use of glucocorticoids, hormone replacement therapy, contraceptives and

COX-2 inhibitors. Additionally, a modified Charlson's co-morbidity index for administrative data was calculated in the year before index date.(26, 27)

Cohort Follow-up

Our study cohorts spanned the period of January 1, 1996 to December 31, 2010. Individuals with GCA entered the case cohort after all inclusion criteria had been met, or after a matched doctor's visit or hospital admission in the same calendar year for comparison cohort individuals. Participants were followed until they either experienced an outcome, died, dis-enrolled from the health plan (left BC), or the follow-up ended (December 31, 2010), whichever occurred first.

Statistical Analysis

We compared baseline characteristics between the GCA and comparison cohorts. We calculated the incidence rates (IRs) per 1000 person-years (PY) for respective outcomes for the GCA and comparison cohorts. The associations between GCA and study outcomes are expressed as incidence rate ratios (IRR) with 95% confidence intervals (CIs). We calculated and plotted the cumulative incidence rates of end-points for individuals with and without GCA accounting for the competing risk of death.(28) To evaluate the time-trend of VTE risk according to the time since GCA diagnosis, we estimated IRRs during the first year and during the first five years. We also performed sub-group analyses according to age (age <75 years vs. ≥ 75 years) and sex.

We conducted Cox proportional hazard regressions(29) to assess the adjusted relative risk (RR) of VTE, PE and DVT associated with GCA after stratifying by matched variables (i.e., age, sex, and calendar year of study entry). These multivariable analyses were adjusted for all covariates listed above and the effect of GCA on study outcomes was expressed as hazard ratios (HRs) with 95% CIs.

We performed three sensitivity analyses. First, we estimated the cumulative incidence of each event accounting for the competing risk of death according to Lau et al.(30) and expressed the results as sub-distribution HRs with 95% confidence interval (CI). Second, analysis with a stricter definition of GCA exposure was used, limited to subjects with GCA and five or more outpatient prescriptions for glucocorticoids on or after diagnosis of GCA. Third, to quantify the potential impact of unmeasured confounders, we performed sensitivity analyses, which assessed how a hypothetical unmeasured confounder might have affected our estimates of the association between GCA and risk of VTE.(31) We simulated unmeasured confounders with their prevalence ranging from 10% to 20% in the GCA and control cohorts, and odds ratios (ORs) for the associations between the unmeasured confounder and VTE ranging from 1.3 to 3.0.

SAS Version 9.3 (SAS Institute, Inc., Cary, NC, USA) was used for all analyses. For all IRRs and HRs, we calculated 95% CIs. All *p*-values are two-sided.

Role of the Funding Source

The funding sources had no role in the design, conduct, or reporting of the study or the decision to submit the manuscript for publication.

Ethics 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. Ethics approval was obtained from the University of British Columbia.

RESULTS

Baseline Characteristics

Our primary analysis included 909 individuals with incident GCA and 9,288 age-, sex-, entry-time-matched individuals in the comparison cohort for a combined follow-up time of 2,351 person-years, during which 63 cases of incident PE and 73 cases of incident DVT were diagnosed. Table 1 summarizes the baseline characteristics of the case and comparison cohorts. Compared with the non-GCA group, the GCA group tended to have higher proportion of hypertension. They more often used glucocorticoid and COX-2 inhibitors, had higher Charlson's comorbidity indices and more hospitalizations during the previous 12 months. We adjusted for these baseline differences in the multivariable analyses.

Association between a Diagnosis of GCA and Incident VTE

GCA was significantly associated with a higher incidence of overall VTE, PE and DVT events (Table 2 and Figure 1). Among 909 individuals with GCA, the IRs of VTE, PE, and DVT were 13.3, 7.7 and 8.5 per 1000 PY, versus 3.7, 1.9, and 2.2 per 1000 PY in the comparison cohort. The corresponding IRRs were 3.58 (2.33–5.34), 3.98 (2.22–6.81) and 3.82 (2.21–6.34). When we evaluated the impact of follow-up time after the GCA diagnosis, the IRRs for VTE, PE, and DVT were substantially larger in the first year after the diagnosis of GCA compared to the following years (Table 3).

In a multivariable proportional hazards analysis, the HRs for VTE, PE, and DVT among GCA patients were 2.49 (95% CI 1.45–4.30), 2.71 (95% CI 1.32–5.56) and 2.7 (95% CI 1.39–5.54) as compared to the comparison cohort (Table 4). When we excluded those with hospitalization at baseline, our results did not change materially. These HRs persisted in our age and sex stratified subgroup analyses except for the age group less than 75 years (Table 4).

Sensitivity Analyses

HRs from analysis of the association between GCA and study outcomes that accounted for the competing event of death gave slightly attenuated estimates, but remained significant (Table 5). Of the 909 patients who met the criteria for GCA, 593 (65%) patients had five or more prescriptions for glucocorticoids. Analysis restricted to this group and matched reference participants gave similar effect estimates, although CIs were wider because of smaller sample sizes (Table 5). Furthermore, in our sensitivity analyses for potential impact of unmeasured confounders, HRs remained significant even at the extreme values of 20%

prevalence and an OR of 3.0 for the association between the hypothetical confounder and VTE.

DISCUSSION

In this large general population-based study, we found that GCA was associated with substantially increased risks of PE, DVT, and the combined VTE events. These associations were independent of relevant risk factors and persisted across age and sex subgroups. The increased risk was the highest during the first year after diagnosis of GCA. These findings provide the first evidence at the population level that PE and DVT are important complications of GCA, which is the most common form of systematic vasculitis.

The finding of increased DVT among patients with GCA could have important implications for clinical care, both immediately after a diagnosis of GCA and in long-term treatment. Our findings imply that a diagnosis of GCA should alert clinicians to be mindful of possible venous thrombotic events, particularly in the period soon after diagnosis. Treatment of GCA patients with low-dose aspirin is already routine practice to prevent ischemic events and a recent meta-analysis of observational studies found that antiplatelet/anticoagulation therapy may have a protective effect against severe ischemic complications after the GCA diagnosis when used together with glucocorticoids, without increasing bleeding risk. (32, 33) Our data potentially adds an additional reason to such anticoagulation therapy in GCA patients (i.e., for DVT prophylaxis); however, the final conclusion would be best achieved by properly designed randomized controlled trials.

Our findings agree with a recent nationwide hospital-based study by Zoller et al. that evaluated the risk of PE in patients with PMR, which is often associated with GCA and considered a milder spectrum of the same condition.(16) The authors found an increased risk of PE in PMR patients, which was the greatest in the first year of follow-up (RRs= 7.86, 1.76, 1.33 and 1.17 for over <1 year, 1–5 years, 5–10 years and 10 years of follow-up, respectively). These findings are remarkably similar to ours despite the differences in the study population (hospitalized vs. general population; patients with PMR vs. GCA). PMR has been previously associated with an increased risk of peripheral arterial disease.(34)

Several mechanisms could explain the increased risk of VTE disease in the period immediately after GCA diagnosis. The combination of stasis and hypercoagulability, along with endothelial damage, as described by Virchow's triad, are key factors for the occurrence of VTE.(35) Decreased mobility, especially during the initial period of the diagnoses before the onset of full treatment effects, may contribute to VTE through increased stasis of blood. Similarly, inflammatory conditions like GCA are associated with endothelial dysfunction, (36) which is likely to be worse during the initial uncontrolled disease status. As inflammation, lipids and the immune system may play a role in venous thrombosis through a complex interplay, the level of inflammation may matter.(37) Furthermore, systemic inflammation associated with GCA may modulate thrombotic responses by upregulating procoagulants, downregulating anticoagulants and suppressing fibrinolysis.(10) Myointimal thickening, stenosis, or occlusion of vessel lumen,(11) along with thrombocytosis(12–15) and platelet counts of $> 400,000/\text{mm}^3$, may further contribute to VTE.

The potential role of antiphospholipid antibodies on the risk of VTE exists, although two small case series of GCA patients (N = 32) found conflicting results.(38, 39)

Alternatively, the use of glucocorticoids may contribute to the increased risk of VTE,(40) although some studies challenge the role of glucocorticoids in cardiovascular disease in patients with GCA. In their population-based incidence cohort of 364 patients with PMR, Kremers et al.(41) found that patients who received glucocorticoids did not have a significantly increased risk of vascular diseases compared with those who did not receive glucocorticoids. Instead, they observed a trend for a protective effect with use of glucocorticoids in this population. Furthermore, cumulative glucocorticoid doses were not associated with an increased risk of any of the outcomes. Further investigations into the potential effects of glucocorticoids on VTE risk in the GCA population are warranted.

Strengths and limitations of our study deserve comment. Beyond being the first large-scale investigation on a critically important outcome of a relatively common vasculitis, our study was based on the entire BC population. Findings are therefore likely generalizable to the population at large. Uncertainty around diagnostic accuracy, however, cannot be completely ruled out. We may have false-positive GCA cases in our cohort, as we did not use the gold standard for GCA diagnosis, ‘temporal artery biopsy’,(42) to identify GCA. Nevertheless, we used one of the strictest case definitions available for administrative databases, using both diagnostic codes and prescription drug data. However, the possibility of misclassification is always present in cases from administrative databases. However, this would be a conservative bias, where “false positive cases” would make the point estimates closer to the null hypothesis. Furthermore, in our sensitivity analysis limited to patients with five or more prescriptions of glucocorticoids, similar effect estimates were observed. Although we adjusted for all known risk factors for VTE available in our data, our database did not have potential confounders like body mass index and smoking. In our sensitivity analyses for potential impact of plausible ranges of these unmeasured confounders, our findings persisted. Having said this, our results could still be affected by unknown or unmeasured confounders, similar to other observational studies. In addition, we did not have access to disease-specific information such as GCA subtype or organ involvement, which limited our ability to correlate such characteristics with the studied outcomes. Further studies are needed in the GCA population to confirm our results and to evaluate extended aspects of VTE outcomes, including risk factors, severity and consequences.

In conclusion, in this general population-based study, we have reported a substantially increased risk of VTE, a largely ignored but preventable complication, in GCA patients for the first time. Our results have important implications for people with GCA and their treating physicians. These results call for awareness of this complication, increased vigilance, and preventive intervention by controlling the inflammatory process or by anticoagulation in a high-risk GCA population. Future investigation should clarify the relative contributions of active vasculitis and glucocorticoids treatment to the risks of PE and DVT in GCA.

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Figure 1.

Cumulative incidence for venous thromboembolism (upper panel), pulmonary embolism (middle panel) and deep venous thrombosis (bottom panel) in the 909 cases with incident giant cell arteritis (GCA) as compared to the 9,288 age-, sex-, and entry time matched non-GCA subjects.

Table 1

Characteristics of GCA and Comparison Cohorts at Baseline (GCA Onset)

Variable	GCA N= 909	Non-GCA ^a N=9288	P Value
Age, mean (SD) years	76.4 (9.4)	76.1 (9.4)	NS
Female	667 (73.4)	6,820 (73.4)	NS
Alcoholism	2 (0.2)	63 (0.7)	NS
Hypertension	434 (47.7)	3,786 (40.8)	<0.001
Sepsis	4 (0.4)	31 (0.3)	NS
Varicose veins	8 (0.9)	96 (1.0)	NS
Inflammatory bowel disease	3 (0.3)	29 (0.3)	NS
Trauma	3 (0.3)	49 (0.5)	NS
Fractures	26 (2.9)	294 (3.2)	NS
Surgery	5 (0.6)	55 (0.6)	NS
Glucocorticoids	656 (72.2)	618 (6.7)	<0.001
HRT	59 (6.5)	470 (5.1)	NS
Contraceptives	1 (0.1)	8 (0.1)	NS
Cox-2 inhibitors	75 (8.3)	345 (3.7)	<0.001
Charlson's comorbidity index, mean (SD)	1.1 (1.5)	0.8 (1.5)	<0.001
Number of hospitalizations, mean (SD)	0.7 (1.1)	0.5 (1.0)	<0.001
Number of outpatient visits, mean (SD)	101.9 (89.2)	50.3 (57.8)	< 0.001

Values are N (percentages) unless otherwise noted. P values were estimated by t-test (continuous) or chi-square test (categorical).

GCA, Giant cell arteritis; HRT, Hormone Replacement Therapy (in females); NS, Non-significant; SD, standard deviation

^a age-, sex-, and entry-time-matched

Table 2

Risk of Incident VTE, PE, and DVT According to GCA Status

	GCA N=909	Non-GCA ^a N=9288
VTE (PE or DVT)		
Cases, n	31	121
Incidence Rate/1000 Person-Years	13.3	3.7
Incidence Rate Ratio (95% CI) ^a	3.58 (2.33–5.34)	1.0
PE		
Cases, n	18	63
Incidence Rate/1000 Person-Years	7.7	1.9
Incidence Rate Ratio (95% CI) ^a	3.98 (2.22–6.81)	1.0
DVT		
Cases, n	20	73
Incidence Rate/1000 Person-Years	8.5	2.2
Incidence Rate Ratio (95% CI) ^a	3.82 (2.21–6.34)	1.0

^a age-, sex-, and entry-time-matched

DVT, Deep vein thrombosis; GCA, Giant cell arteritis; PE, Pulmonary embolism; VTE, Venous thromboembolism

Table 3

Time Trends of Incident Rate Ratios for VTE According to GCA Duration

Time after diagnosis	VTE IRR (95% CI)	PE IRR (95% CI)	DVT IRR (95% CI)
1 year	7.03 (3.78–12.73)	7.23 (2.90–17.20)	7.85 (3.53–16.94)
2 years	4.98 (2.87–8.38)	5.20 (2.39–10.68)	5.44 (2.58–10.91)
3 years	4.34 (2.66–6.90)	4.66 (2.32–8.88)	4.07 (2.10–7.48)
4 years	4.09 (2.56–6.34)	4.21 (2.17–7.72)	4.27 (2.35–7.43)
5 years	3.69 (2.37–5.60)	4.09 (2.22–7.19)	3.92 (2.25–6.56)
Total follow-up	3.57 (2.33–5.34)	3.98 (2.2–6.8)	3.82 (2.20–6.34)

DVT, Deep vein thrombosis; GCA, Giant cell arteritis; PE, Pulmonary embolism; VTE, Venous thromboembolism

Table 4

Risk of Incident VTE, PE and DVT in GCA According to Age Group and Sex

	Overall		Age < 75 years		Age ≥ 75 years		Men		Women	
	GCA (N= 909)	Non-GCA (n=9,288)	GCA (n=322)	Non-GCA (n=3,376)	GCA (n= 587)	Non-GCA (n=5,912)	GCA (n= 242)	Non-GCA (n= 2,468)	GCA (n= 667)	Non-GCA (n= 6,820)
VTE										
Cases	31	121	9	30	22	91	10	29	21	92
Incidence rate/1000 PY	13.26	3.70	9.47	2.60	15.86	4.30	18.26	3.32	11.73	3.84
Multivariable HR <i>a</i> (95% CI)	2.49 (1.45–4.30)	1.0	2.44 (0.81–7.31)	1.0	2.69 (1.43–5.07)	1.0	4.29 (1.45–12.73)	1.0	2.19 (1.17–4.10)	1.0
PE										
Cases	18	63	4	16	14	47	4	13	14	50
Incidence rate/1000 PY	7.65	1.92	4.20	1.38	9.99	2.21	7.2	1.5	7.81	2.08
Multivariable HR <i>a</i> (95% CI)	2.71 (1.32–5.56)	1.0	2.10 (0.43–10.30)	1.0	2.97 (1.30–6.78)	1.0	4.74 (1.28–17.53)	1.0	2.33 (1.03–5.29)	1.0
DVT										
Cases	20	73	8	18	12	55	7	18	13	55
Incidence rate/1000 PY	8.52	2.22	8.40	1.55	8.61	2.59	12.78	2.06	7.23	2.29
Multivariable HR <i>a</i> (95% CI)	2.78 (1.39–5.54)	1.0	3.0 (0.83–10.87)	1.0	2.85 (1.22–6.69)	1.0	4.74 (1.28–17.53)	1.0	2.33 (1.03–5.29)	1.0

DVT, Deep vein thrombosis; GCA, Giant cell arteritis; HR, hazard ratio; PE, Pulmonary embolism

Table 5

Sensitivity Analyses on the risk of VTE in patients with Giant Cell Arteritis

	Primary Analysis(N= 909) HR (95%CI)	Sensitivity Analysis 1(N= 909) HR (95%CI)	Sensitivity Analysis 2(N= 593) HR (95%CI)	Sensitivity Analysis 3(N= 909) HR (95%CI)			
				Prevalence = 10% ^a OR ^b = 1.3	Prevalence = 10% ^a OR ^b = 3.0	Prevalence = 20% ^a OR ^b = 1.3	Prevalence = 20% ^a OR ^b = 3.0
VTE	2.49 (1.45–4.30)	2.15 (1.29–3.56)	2.43 (1.33–4.43)	2.44 (1.41–4.19)	2.05 (1.20–3.52)	2.49 (1.44–4.29)	1.88 (1.07–3.28)
PE	2.71 (1.32–5.56)	2.34 (1.15–4.76)	2.48 (1.11–5.52)	2.61 (1.27–5.37)	2.15 (1.05–4.38)	2.65 (1.29–5.45)	1.89 (0.90–3.96)
DVT	2.78 (1.39–5.54)	2.30 (1.25 (4.22)	2.88 (1.35–6.16)	2.68 (1.34–5.34)	2.38 (1.20–4.70)	2.87 (1.43–5.77)	2.13 (1.05–4.33)

DVT, Deep vein thrombosis; HR, Hazard ratio; OR, Odds ratio; PE, Pulmonary embolism; VTE, Venous thromboembolism

^ahypothetical prevalence of the unmeasured confounder in the giant cell arteritis cases

^bhypothetical level of association between the unmeasured confounder and the outcome

Sensitivity analyses 1; accounting for the competing risk of death

Sensitivity analyses 2; limited to giant cell arteritis cases that received at least 5 prescriptions for oral glucocorticoids during follow-up

Sensitivity analyses 3; accounting for unmeasured confounders