TRENDS OF VENOUS THROMBOEMBOLISM RISK BEFORE AND AFTER DIAGNOSIS OF GOUT: A POPULATION-BASED STUDY

by

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Abstract

Background: Previous studies have shown that gout is an independent risk factor for cardiovascular diseases. Venous thromboembolism (VTE, including deep venous thrombosis [DVT] and pulmonary embolism [PE]) represents the third most common form of cardiovascular disease among the general population. However, data on the risk of VTE in gout patients are scarce.

Objectives: 1) To estimate the overall risk of VTE, DVT, and PE before and after gout diagnosis in an incident cohort of individuals with gout; 2) To access the temporal trend of VTE, DVT, and PE before and after gout diagnosis compared with the general population.

Methods: I conducted a 1:1 matched cohort study using a province-wide population-based administrative health database from British Columbia, Canada. I calculated incidence rate ratios and multivariable adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs) for the risk of VTE, DVT, and PE before and after gout diagnosis.

Results: Among 124,306 individuals with newly diagnosed gout (65% male, mean age 60 years), VTE developed in 1,594 patients, DVT in 989 patients, and PE in 813 patients. Incidence rates were 2.44, 1.51, and 1.24 per 1,000 person-years, respectively. The corresponding incidence rates among non-gout individuals were 1.37, 0.83, and 0.75 per 1,000 person-years, respectively. The final aHRs (95% CI) for VTE, DVT, and PE were 1.34 (1.23-1.46), 1.38 (1.24-1.54), and 1.27 (1.13-1.42), respectively. For the entire pre-gout period, compared to general population, the final aHRs (95% CI) were 1.56 (1.41-1.71), 1.55 (1.38-1.75) and 1.53 (1.34-1.76) for VTE, DVT and PE, respectively. During the 3rd, 2nd, and 1st years preceding the gout diagnosis, the final aHRs for VTE were 1.51, 1.61, and 1.74, respectively. During the 1st, 2nd, 3rd,

4th, and 5th years after the gout diagnosis, the final aHRs were 1.46, 1.44, 1.37, 1.36, and 1.32. Similar trends were also seen for DVT and PE.

Conclusion: Increased risks of VTE, DVT, and PE were found both before and after gout diagnosis. The risk increased gradually before gout diagnosis, peaking in the year prior to gout diagnosis, and then progressively declined following the diagnosis. Gout associated inflammation may contribute to VTE risk.

Lay Summary

Currently, gout, which develops from hyperuricemia, is the most common inflammatory arthritis, with around 1 in 25 Canadians suffering from it. Moreover, gout is related to increased deadly complications like cardiovascular diseases.

Venous thromboembolism (VTE) represents a very common cardiovascular disease that occurs when blood clotting blocks the venous circulation in the human body, and includes deep venous thrombosis (i.e., blood clotting in the legs or pelvis) and its complication, pulmonary embolism (i.e., blood clotting that passes into the pulmonary circulation that prevents blood flow to the lungs). The relationship between gout, or its precursor hyperuricemia, and VTE needs to be studied further. Thus, this study aims to determine if there is an increased risk of VTE before and after receiving a gout diagnosis, as well as the VTE risk during 3rd, 2nd, 1st years before and 1st, 2nd, 3rd, 4th, 5th years after a gout diagnosis.

Preface

Chapter 2 will be submitted to peer reviewed journals for publication.

Chapter 1: Lingyi Li was responsible for the design, literature search and review, and writing. Dr. J. Antonio Avina-Zubieta was responsible for the review of Chapter 1.

Chapter 2: Lingyi Li was responsible for the study design, literature review, creation of cohorts, data manipulation and analyses, result interpretation, writing and revision of the manuscript. Dr. J. Antonio Avina-Zubieta was responsible for the study design, result interpretation and critical review of manuscript. Drs. John Esdaile, Hui Xie, Diane Lacaille and Hyon Choi were responsible for the result interpretation and critical review of manuscript. Dr. Eric Sayre and Dr. Hamid Tavakoli assisted in SAS code checking. Natalie McCormick and Sharan Rai were responsible for a critical review of the manuscript.

Chapter 3: Lingyi Li was responsible for the design, literature search and review, and writing. Dr. J. Antonio Avina-Zubieta was responsible for the review of Chapter 3.

Ethical approval was obtained from the University of British Columbia's Behavioral Research Ethics Board (H12-01530).

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List of Abbreviations

aHR	Adjusted Hazard Ratio
ARC	Arthritis Research Canada
BC	British Columbia
CHD	Coronary Heart Disease
CI	Confidence Interval
Cox-2	Cyclooxygenase-2
DIN	Drug Identification Number
DVT	Deep Venous Thrombosis
HR	Hazard Ratio
HRT	Hormone Replacement Therapy
IBD	Inflammatory Bowel Disease
ICD	International Classification of Disease
ICD-9-CM	International Classification of Disease, Ninth Version
ICD-10-CM	International Classification of Disease, Tenth Version
IR	Incidence Rate
IRR	Incidence Rate Ratio
MI	Myocardial Infarction
MSU	Monosodium Urate
N/A	Not Applicable
NHANES	National Health and Nutrition Examination Survey
NHIRD	National Health Insurance Research Database

NLR	NOD-like Receptor
NLRP3	NLR family, Pyrin Domain Containing 3
NSAIDs	Non-steroidal Anti-inflammatory Drugs
OR	Odds Ratio
PE	Pulmonary Embolism
PopData	Population Data
SUA	Serum Uric Acid
UK	United Kingdom
ULT	Urate-Lowering Therapy
US	United States
VTE	Venous Thromboembolism

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Dedication

致我的爷爷奶奶

Chapter 1: Introduction

1.1 Thesis Organization

1.1.1 Research statement

This thesis aims to better describe the risk of cardiovascular diseases among patients with gout, with a particular focus on the association between venous thromboembolism (VTE) and gout. Triggered by hyperuricemia, gout is the most common inflammatory arthritis in males and has been reported with an increased prevalence, incidence and hospitalization rate over the past decade[1-4]. For example, in Canada, around 1 in 25 adults suffered from gout as of 2012[5]. Driven by the significant burden of disease, a growing amount of effort has been placed on the study of gout in recent years, including the investigation of comorbidities and other negative impacts of gout on patients' lives.

Several cardiovascular diseases have been reported following a diagnosis of gout, such as myocardial infarction (MI) and stroke[6]. It has also been documented that gout patients have an increased risk of death due to cardiovascular diseases[7]. VTE is the third most common cardiovascular disease globally, accounting for a large portion of mortality generally[8,9]. Deep venous thrombosis (DVT) and pulmonary embolism (PE) are the two types of VTE. According to Cohen et al[10], PE alone caused 5-10% of deaths among hospitalized patients globally. Therefore, many studies have been conducted to explore the risk factors for VTE, including some types of inflammatory arthritides like rheumatoid arthritis and systemic sclerosis[11,12]; however, little has been done to assess the association between VTE risk and gout. A limited number of case-control studies have been conducted; but these studies utilized hospital/clinical-based samples and evaluated the risk (i.e., odds) of VTE among patients with versus without gout or high uric acid levels (hyperuricemia). Additionally, three population-based studies exist

on the association between gout and the risk of VTE. However, those studies are limited due to their failure to adjust for medications[13], lack of proper consideration for unmeasured confounders [13,14], use of a prevalent cohort[14], or insufficient sample size[15]. Therefore, there remains a dearth of rigorous studies with robust data sources to interrogate the association between VTE risk and gout.

1.1.2 Overview of thesis themes and chapters

This thesis aims to answer two questions: 1) Do individuals with gout, or before gout diagnosis, have an increased risk of VTE, DVT, PE compared to non-gout individuals from the general population? and 2) What are the temporal trends of VTE, DVT, and PE risk before and after a gout diagnosis compared to non-gout individuals?

In order to answer these two questions, I designed and carried out an observational study using administrative health data from all residents of British Columbia (BC), Canada. **Chapter 1** describes the background and rationale about: a) gout, hyperuricemia, and cardiovascular diseases; b) disease burden of VTE; c) VTE in gout or hyperuricemia; d) underlying mechanisms of the relationship between gout and VTE; e) urate-lowering therapy (ULT), colchicine, and cardiovascular diseases; and f) an overview of this thesis' studies. **Chapter 2** evaluates the risk of VTE, DVT, and PE in gout patients compared with non-gout individuals. To test for the robustness of my results, I conducted several sensitivity analyses: 1) To estimate the robustness of my results to the potential effect of unmeasured confounders (i.e., obesity), I calculated new final adjusted hazard ratios (aHRs) by adding the simulated unmeasured confounder with a prevalence ranging from 30% to 40% in the gout cohort[16,17] and a prevalence of 23% for the non-gout cohort (corresponding to the estimated prevalence of obesity for the BC general population

aged 18 and older)[18], and odds ratios (ORs) ranging from 2.0 to 2.5 for the assocation between the unmeasured confounder and VTE, DVT, or PE[19]; 2) I calculated the cumulative incidence of each outcome event after taking the competing risk of death into account, according to Lau et al[20]; 3) I used a more restrictive case defintion for gout that includes ULTs or colchicine in addition to International Classification of Diseases, ninth version or tenth version (ICD-9-CM or ICD-10-CM) codes; and 4) I only included those gout patients who were perfectly matched with non-gout individuals perfectly by age, sex and calendar year of study entry. **Chapter 3** gives a summary of the results in Chapter 2 and provids a comprehensive discussion of the strengths and limitations, as well as the implications, of this study.

1.2 Gout

1.2.1 Disease burden of gout

Today, gout is the most common type of inflammatory arthritis and predominantly affects males[2–4,21]. An increasing prevalence of gout has been reported globally[2,5]. For example, in the United States (US), results from the National Health and Nutrition Examination Survey (NHANES) found that the prevalence of gout increased from 2.7% in 1988-1995 to 3.8% in 2007-2010[2]. In Canada, Rai et al[5] also demonstrated a jump in prevalence from 2.4% in 2000 to 3.8% in 2012 among the adult population. Similar trends have also been reported in several other countries, including New Zealand, United Kingdom (UK), China, and Italy[2]. In addition to prevalence, the incidence of gout is also on the rise. In their report, Rai et al[5] pointed out that the incidence of gout in Canada has increased by approximately 50%, from 2 cases per 1000 persons in 2000 to 2.9 cases per 1000 persons in 2012. The Rochester Epidemiology Project saw a parallel rise in gout incidence in the US as well[2]. Additionally, gout is a tremendous burden on

the health service system. In Canada, the annual inpatient rate for gout in 2011 had doubled that of about 10 years ago, accounting for more than twice the financial expenditure on hospitalizations due to gout in comparison to the costs in 2000[22].

Despite more ULTs (e.g., allopurinol, febuxostat, probenecid, and sulfinpyrazone) being available on the market, patients' access and adherence to treatment are limited. According to Rai et al[5], only 23% of prevalent gout patients actually received ULTs in Canada in 2012. Furthermore, a study from Sweden showed that less than 1/3 of gout patients received ULTs during the first year of their diagnosis and 75% of treated patients discontinued ULTs within the first two years[23]. Similarly, another UK study from 2012 demonstrated that ULTs were used in 37.63% of prevalent gout patients, among whom only 40% adhered to the treatment[24]. Due to the low rate of ULT utilization, the mortality rate of gout has not decreased much over the past 16 years[25] .

1.2.2 Gout or hyperuricemia and cardiovascular diseases

The association between gout and coronary heart disease (CHD, i.e., MI, angina, ischemic heart disease) has been well documented in recent years[6,26–34]. For example, in a prospective study, Choi and Curhan[33] followed a group of gout patients for 12 years and found that the risk of non-fatal MI, fatal CHD and cardiovascular death among male patients had increased by 59%, 55% and 38%, respectively, when compared to male controls who had no history of gout. Studies among females with gout have also been carried out. For example, De Vera et al[32] described that the risk of all acute MI and non-fatal MI among female patients aged 65 or older was 39% and 41%, respectively, which is higher than rates among similarly aged females without gout.

Hyperuricemia, defined as a serum uric acid (SUA) level that is higher than the normal threshold (usually 6.8 mg/dl), is a predisposing condition for gout development[1]. Several researchers have attempted to uncover the relationship between hyperuricemia, as a hallmark of gout, and cardiovascular diseases; nevertheless, this association remains controversial. In a prospective observational study, the Framingham Heart Study, Culleton et al[35] reported that after adjusting for risk factors for CHD (i.e., obesity, smoking, antihypertensive treatment, serum triglycerides, cholesterol level and blood pressure), there was no significant relationship between elevated SUA levels and CHD. Similar findings have also been published by Wannamethee et al[36] in another prospective study, the British Regional Heart Study. Results from both studies indicate that any significant raw association between hyperuricemia and an elevated risk of developing cardiovascular diseases might be confounded by cardiovascular disease risk factors. However, more recent studies have shown that even after adjusting for cardiovascular disease risk factors, hyperuricemia is still an independent risk factor for cardiovascular diseases. For example, a systematic review and meta-analysis conducted by Kim et al[37] found that the risk of CHD was 34% higher among individuals with hyperuricemia than those without. Moreover, they found that CHD mortality rises by 12% for every 1 ml/dl increase in SUA levels.

1.3 Disease Burden of Venous Thromboembolism

VTE, including DVT and PE, represents the third most common cardiovascular event that is associated with increased mortality[8]. The reported incidence for VTE in populations with European ancestry ranges from 1.04 and 1.83 cases per 1000 person-years. The reported incidence rates (IRs) for DVT range from 0.45 and 1.17 cases per 1000 person-years, and 0.29 and 0.78 cases per 1000 person-years for PE [38]. The incidence of VTE in the US has significantly increased since 2001 due to a rise in detected PE events with the advent of better diagnostic tools[38]. The "increased utilization of objective imaging and improved image resolution, particularly computed tomography, pulmonary angiography, and magnetic resonance imaging" has led to more successfully diagnosed PE events[39]. Furthermore, patients with VTE may have poor outcomes, especially for PE (accounting for 5% to 10% of deaths in all hospitalized patients globally), making PE potentially as deadly as acute MI. Moreover, survivors often experience very severe and costly long-term complications[40].

Independent risk factors for VTE include obesity, major surgery (i.e., orthopedic surgery, neurosurgery, major thoracic and abdominal surgery, renal transplantation, cardiovascular surgery, gynaecological surgery and urologic surgery), trauma or fracture, cancer, immobilisation, oral contraceptive use, hormone replacement therapy (HRT), cyclooxygenase-2 (cox-2) inhibitor use, varicosed veins, and inflammatory bowel disease (IBD)[8,38,41–43].

Inflammation has also been suggested to be a contributor to thrombosis, especially chronic inflammation[44]. As suggested by previous studies, Zoller et al[45] found that 33 autoimmune disorders were associated with a significantly increased risk of PE during the first year after diagnosis, which has been confirmed by further general population-based studies[12,46,47].

1.4 Venous Thromboembolism in Gout

The risk of VTE in gout or hyperuricemia patients is still not fully understood. There are few studies examining the relationship between VTE and gout or hyperuricemia. A summary of selected studies is presented in Table 1.1. Briefly, a hospital-based case-control study from China found that patients with hyperuricemia were significantly associated with an increased risk of idiopathic VTE in the high-density lipoprotein cholesterol population (OR=1.29 [95% confidence interval {CI}, 1.02-1.64])[48]. Another hospital-based case-control study in Japan also suggested that gout/hyperuricemia was associated with an increased risk of PE after adjusting for traditional VTE risk factors (OR= 8.4 [95% CI, 1.40-50.1])[39]. The large variation of the final adjusted OR in the Japanese study is due to low statistical power, as only four gout/hyperuricemia patients were included in the PE group[50]. An increased risk of PE and DVT was also shown in an recent abstract from Turkey[51]. The authors suggested that those with higher SUA levels had a significantly increase risk of DVT than lower SUA level individuals (OR=1.61, [95% CI, 1.01-2.55]).

Three population-based cohort studies have evaluated the risk of VTE, DVT and PE in gout patients compared with non-gout individuals. These studies were performed in the US and Taiwan. The Atherosclerosis Risk in Communities Study, which is an ongoing prospective study of multiple cardiovascular diseases from the US, found that increased SUA levels in patients without gout was a risk factor for VTE[15]. The study measured SUA levels in 14,126 individuals at the first visit (in 1987) and followed participants until the occurrence of VTE or the end of follow up (in 2011). The authors found a positive association between SUA levels and VTE risk ranging from 1.44 (95% CI, 1.06-1.96) to 1.89 (95% CI, 1.15-3.12) compared to the lowest SUA level group. A similar trend was observed for VTE subtypes. However, this study did not find a significant relationship between incident gout and VTE risk, likely because only 647 gout patients were included, which is insufficient to determine if a significant association between the exposure and a rare event like VTE exists in a prospective study[15]. In addition, two studies using the same database from the National Health Insurance Research Database (NHIRD) in Taiwan showed that there was a significant relationship between gout and VTE, DVT and PE[13,14]. Huang et al[13], reported a 66% and 53% increased risk of DVT and PE in gout patients, respectively, when compared to non-gout individuals in a retrospective cohort study. However, only one ICD-9-CM or ICD-10-CM code was used to define DVT and PE, and this study did not adjust for any prescription use, which is a known risk factor for VTE. The other retrospective cohort study in Taiwan found a 38% increased risk of DVT in the gout cohort compared to the non-gout cohort[14]. However, this study used a prevalent gout cohort, which has an inherent survival bias, as the cohort only included surviving individuals, who may be less susceptible to cardiovascular complications such as VTE. Furthermore, none of these three studies assessed the temporal trends of the risk of VTE, DVT and PE in gout patients during follow up.

Table 1.1. Summary of studies assessing the risk of VTE, DVT, PE in gout patients.

First author	Country	Study design	Events	Number of population	Study period	Data source	Case definition of gout /hyperuricemia	Case definition of VTE/DVT/PE	OR/HR (95% CI)
Yu[48]	China	Case-control	VTE	276	2012 to 2015	Hospital-based	SUA: blood test	Physician diagnosis	OR=1.29 (1.02-1.04)
Yamada[50]	Japan	Case-control	PE	100	2001 to 2006	Hospital-based	Gout or hyperuricemia: physician diagnosis	Physician diagnosis	OR=8.40 (1.4-50.1)
Kunt[51]	Turkey	Case-control	DVT	146	2014 to 2014	N/A	N/A	Venous duplex scan	OR=1.61 (1.01-2.55)
Kubota[15]	US	Cohort study	VTE	14,126	1987 to 2001	Population-based	SUA: blood test; Gout: self-report	ICD-9-CM plus hospital records	SUA: HR=2.13 (1.47-3.07) Gout: HR=1.33 (0.95-1.86)
Huang[13]	Taiwan	Cohort study	PE , DVT	57,981	1998 to 2010	Population-based	Gout: ICD-9-CM	ICD-9-CM	HR_{DVT}=1.66 (1.37-2.01) HR_{PE}=1.53 (1.01-2.29)
Chiu[14]	Taiwan	Cohort study	DVT	35,959	2000 to 2011	Population-based	Gout: one ICD-9-CM plus medication	ICD-9-CM plus oral anticoagulant therapy	HR_{DVT}=1.38 (1.18-1.62)

Abbreviations: **VTE**, venous thromboembolism; **DVT**, deep venous thrombosis; **PE**, pulmonary embolism; **OR**, odds ratio; **HR**, hazard ratio; **ICD-9-CM**, International Classification of Diseases, ninth version; **US**, United States; **SUA**, serum uric acid; **CI**, confidence interval; **N/A**: not applicable

1.5 The Underlying Mechanisms

1.5.1 Uric acid or monosodium urate crystals, inflammation, and endothelial dysfunction.

Increased SUA levels are induced by the over production of urate through purine degradation, as well as under excretion of urate from the renal system and intestinal tract[1]. The deposition of uric acid activates NLR (NOD-like receptor) pyrin domain containing 3 (NLRP3), a NLR family gene that encodes a pyrin-like protein called "cryopyrin"[52], which triggers the assembly of NLRP3 inflammasome, a large multiprotein complex that has been discovered to play a pivotal role in inducing the expression of pro-inflammatory cytokines, particularly interleukin-Iß[1]. In addition to the direct effect on NLRP3 expression, an excess of uric acid in serum could strengthen the activity of xanthine oxidase, which increases the production of reactive oxygen species leading to increased formation of NLRP3[53]. On the other hand, the secretion of nitric oxide, which suppresses the activity of NLRP3, is inhibited with high levels of uric acid [54]. In addition to high levels of uric acid, the deposition of monosodium urate (MSU) crystals with tophi during gout may also induce the activation of inflammasome and the production of inflammatory mediators, such as tumor necrosis factor-α and interleukin-6[55,56]. Previous studies have also suggested that uric acid has a pro-inflammatory effect on vascular cells that may have a direct effect on endothelial dysfunction[57]. Moreover, as suggested by Prasad et al[58], sustained high levels of uric acid could be related to higher levels of inflammatory markers, such as C-reaction protein, that would play key roles in reducing blood flow response.

1.5.2 Uric acid or monosodium urate crystal, inflammation, endothelium dysfunction, and hypercoagulability

As proposed by Virchow[11], there are three main precursors of venous thrombosis: damage to the vessel wall, increased blood coagulability, and venous stasis. The systematic inflammation induced by hyperuricemia and MSU crystals can cause cellular damage and tissue injury, particularly in endothelial cells[57]. Following injury, the vascular endothelial cells and platelets are activated, leading to increased expression of cell adhesion molecules. The endothelial layer becomes "stickier" with more adhesion molecules, and this promotes leukocyte rolling and tethering onto the endothelium, ultimately leading to thrombosis[59]. Further, according to Xu et al, the inflammatory response is able to increase blood coagulatibility by stimulating coagulants, inhibiting anticoagulants and suppressing fibrinolysis[44]. In addition, inflammatory arthritic conditions may also influence venous stasis by decreasing mobility[11].

1.6 Cardiovascular Diseases Associated with Urate-lowering Therapy and Colchicine

ULTs such as xanthine oxidase inhibitors (i.e., allopurinol, febuxostat) and uricosuric agents (i.e., probenecid and sulfinpyrazone) have been suggested to decrease the risk of cardiovascular diseases in two ways: 1) by reducing endothelial dysfunction; and 2) by reducing systemic inflammation[57]. Doehner et al found that xanthine oxidase inhibitors could improve endothelial function, as well as increase post-ischemic blood flow by 23% at the legs and 24% at the arms in hyperuricemic patients with chronic heart failure[60]. A case-control study from France consisting of 2,277 MI cases and 4,849 controls showed that individuals who took allopurinol had an approximately 20% lower risk of incident non-fatal MI than those who did not take it[61]. Another large, nested case-control study from Canada also suggested that the use of allopurinol

was associated with a 31% reduced risk of heart failure readmission or death in patients with a history of gout (rate ratio=0.69 [95% CI, 0.60-0.79])[62]. Uricosuric drugs are used less often, but there is limited evidence for the favourable effects of probenecid and sulfinpyrazone in cardiovascular diseases[57].

Colchicine has also been suggested to have a protective effect on cardiovascular diseases among both the general population and gout patients by modulating interleukin-1, interleukin-6 and tumour necrosis factors in the inflammatory response[63]. In a Cochrane review, Hemkens et al conducted a meta-analysis of previous randomised control trials and suggested that the colchicine group had an 80% decreased risk of MI when compared with the comparison group (relative risk=0.2 [95% CI, 0.07-0.57]). Moreover, in a more recent randomised control trial from Australia, Nidorf et al[64] found that among patients who had stable CHD, colchicine could reduce the risk of a secondary cardiovascular event by 70% when compared to placebo controls (HR=0.29, [95% CI, 0.15-0.56]). Another cross-sectional study found that colchicine was associated with a decreased risk of MI in patients with gout[65]. Finally, a recent matched cohort study that used electronic medical records from the US suggested that among gout patients who used colchicine there was a 50% decreased risk of primary cardiovascular diseases when compared to non-users (HR=0.51, [95% CI, 0.30, 0.88])[63].

1.7 Overview of Thesis Studies

1.7.1 Objectives

1. The first objective of this thesis is to estimate the overall risk of VTE, DVT and PE before and after a gout diagnosis compared to matched non-gout individuals from the general population. This will be addressed in Chapter 2.
2. The second objective of this thesis is to access temporal trends of VTE, DVT and PE before and after a gout diagnosis compared with matched non-gout individuals from the general population. This will also be explained in Chapter 2.

1.7.2 The use of administrative health data

Administrative healthcare data are generated for administrative or billing purposes and collected at every healthcare encounter in BC: for example, a diagnostic procedure, an admission to hospital, or receipt of a prescription at a community pharmacy[66]. Administrative data have been used worldwide in research for the purpose of understanding health trends, monitoring patient outcomes and determining the efficacy of various treatments and medical interventions. In Canada, universal healthcare coverage is available for all residents, with each province collecting data in their own administrative databases.

The cohorts used in this study were obtained from Population Data (PopData) in the province of BC, which is an extensive data resource for applied health services and population health research. It covers the entire population of BC (approximately 4.6 million residents). Popdata spans over a long time period and most variables are available from 1990 onwards. Individuals can be traced over time and ultimately, as the data expands longitudinally, over their life span. The main linkable databases include the following:

The Medical Services Plan includes data on all provincially-funded healthcare services, such as physician visits, procedures performed, investigations ordered, dates of service, types of practitioners (i.e., general practitioners, specialist types), laboratory tests ordered, and the diagnosis for which a service was rendered as determined through an ICD-9-CM diagnostic code.

The Hospital Separation File includes information on all hospital admission and separation dates, up to 16 diagnostic fields representing the reason for admission (primary position) or complications during hospitalization (secondary positions) using ICD-9-CM and ICD-10-CM codes, as well as procedures, interventions and surgeries performed.

PharmaNet data includes information on all prescription medications dispensed for all residents of BC since 1995, regardless of funding source. This data file includes the date that each prescription was dispensed, its generic drug name, dose, quantity, and days supplied.

The Vital Statistics Files provide information on death, including date of death and underlying cause of death (based on ICD-10-CM codes). The Registration File provides basic demographic information such as sex, year of birth and geographic information.

The Cancer Registry ascertains and verifies all newly diagnosed cancer cases among residents of the province of BC through multiple sources, including pathology and haematology laboratories, cancer treatment centres, other provincial registries, and death records.

No personal identifying information was made available as part of this study. The use of ICD (International Classification of Disease) codes in the study of gout was successfully implemented based on several published studies[5,22,32,67].

Chapter 2: Trends of Venous Thromboembolism Risk Before and After Diagnosis of Gout: A General Population-Based Study

2.1 Introduction:

Gout is the most common inflammatory arthritis in men[2], and is associated with increased mortality[25] and a high economic and hospitalisation burden[22,68]. Data from different countries suggest that gout is becoming more prevalent[2,5]. Inflammatory arthritides like rheumatoid arthritis, systemic lupus erythematosus, and gout have been associated with an increased risk of cardiovascular diseases, particularly CHD (i.e., MI, angina, ischemic heart disease) and stroke[6,7,30,69,70].

VTE (including PE and DVT) represents a relatively common cardiovascular event that is associated with increased mortality[8]. An increased risk of VTE has been reported in some types of inflammatory arthritis[11,47]. Systemic inflammation associated with those conditions might promote thrombosis by upregulating procoagulants, downregulating anticoagulants, and suppressing fibrinolysis[44]. However, data on the risk of VTE in patients with hyperuricemia or gout are scarce. Findings from three recent population-based studies are limited due to failure to adjust for medications used or failure to address potential unmeasured confounders such as obesity[14,13], use of a prevalent cohort (which is associated with survival bias) [14], and a small sample size[15].

The aims of the present study, using a province-wide database of both inpatients and outpatients from the Canadian province of BC's universal healthcare system, were: 1) to estimate the overall risk of VTE, DVT, and PE before and after a gout diagnosis in an incident cohort of

gout; and 2) to estimate the temporal trend of VTE, DVT, and PE before and after a gout diagnosis compared with that of the general population.

2.2 Methods:

2.2.1 Data sources

Universal healthcare coverage is available for all residents of the province of BC, Canada (population approximately 4.6 million). Population Data BC includes all provincially funded healthcare service data since 1990, including all healthcare professional visits[71], hospitalizations[72], demographic data[73], cancer registry[74], and vital statistics[75]. Furthermore, PopData BC includes the comprehensive prescription drug database PharmaNet[76], which captures all dispensed medications for all residents living in BC since 1996. Numerous population-based studies have been successfully conducted using PopData[22,70,77].

2.2.2 Study design and cohort definitions

Using PopData, I conducted a 1:1 matched cohort study of the risk of incident VTE, DVT, and PE among patients with newly diagnosed gout (gout cohort) compared with age-, sex-, and entry time-matched individuals without gout who were randomly selected from the general population and assigned a random index date (non-gout cohort).

2.2.3 Gout cohort

In this study, the gout cohort included all adult patients (≥18 years of age) who received a gout diagnosis for the first time from January 1, 2000 through December 31, 2012 in BC. I refer to the time period between January 1, 1997 and the gout diagnosis date (i.e., the index date) as the pre-gout period. A gout diagnosis was defined as follows: at least one recorded principal diagnosis of gout (ICD-9-CM: 274 or ICD-10-CM: M10) at either a physician or hospital visit. To ensure incident gout patients, I required all newly diagnosed gout individuals to have at least ten years of prior registration in the databases (i.e., "run-in" period) without a diagnosis of gout at a physician or hospital visit[5,22]. The positive predictive value of similar case definitions has ranged from 61% in a US managed care setting to 100% in the US Veterans Affairs database[78,79].

2.2.4 Non-gout cohort

To establish the non-gout comparison cohort, I received data for a random sample of approximately 400,000 BC residents registered with the provincial medical services plan during the study period, and selected individuals without any history of a gout diagnosis and matched them to gout patients (1:1 ratio) based on age, sex, and calendar year of index date (randomly assigned to non-gout individuals). I initially matched gout patients to non-gout individuals on sex, age, and calendar year of index date (82.8%); for those who could not be perfectly matched on age, I gradually loosened the age criteria until all gout patients were matched. To be comparable with the gout cohort, I also excluded non-gout individuals without at least 10-years' run-in time before the index date.

The study period spanned the period from January 1, 1997 to December 31, 2012. Since prescription medication data were available from 1996, this allowed us to adjust for medication use in the 12 months prior to index date for the time trend analyses described below. Individuals were followed until they either experienced an outcome (VTE, DVT, or PE), died, left BC (2.3% in the gout cohort and 4.8% in the non-gout cohort), or the follow-up period ended (December 31, 2012), whichever occurred first.

2.2.5 Ascertainment of DVT and PE

The primary outcome was the first ever VTE (DVT or PE), DVT, or PE during the follow-up period. Incident DVT or PE outcomes were defined by a corresponding ICD code plus a prescription for any anticoagulant therapy (heparin, warfarin, or a similar agent) between one month before and six months after the ICD code date[80]. I identified DVT (ICD-9-CM: 453; ICD-10-CM: I82.4, I82.9) from outpatient or hospitalization data, and PE (ICD-9-CM: 415.1, 673.2, 639.6; ICD-10-CM: O88.2, I26) from hospitalization data only. Deaths from DVT or PE (including out-of-hospital deaths) were identified using vital statistics. Given that VTE is a potentially fatal disease, patients may have died before they received treatment; thus, for those patients who died within two months after a VTE, DVT, or PE diagnosis, anticoagulant therapy was not needed as part of the case definition. Similar definitions for VTE have been used in previous publications, and were found to have a positive predictive value of 94% in a general practice database[80].

2.2.6 Covariate assessment

To evaluate baseline characteristics at index date, available covariates known to be potential risk factors for VTE were assessed within the 12 months prior to the index date. To evaluate baseline characteristics in patients during the pre-gout period, the same covariates were also assessed over each 12-month period prior to the year of interest. Covariates included health resource utilization (number of outpatient visits and hospitalizations), medication use (as identified through Drug Identification Numbers [DINs]: glucocorticoids, non-steroid anti-inflammatory drugs [NSAIDs], HRT, cox-2, and oral contraceptives), and comorbidities (hypertension, varicosed veins, sepsis, IBD, and alcoholism). In addition, trauma or fracture, a history of surgery, and the Romano modification of the Charlson Comorbidity Index for administrative data were also ascertained in those periods[81].

2.2.7 Statistical analysis

I compared the baseline characteristics of gout patients with the non-gout cohort using a chi-square test for categorical variables and the Wilcoxon Rank-Sum test for continuous variables. To calculate the risk of VTE before and after the index date, I identified incident DVT and PE events during the follow-up periods and pre- and post- gout diagnosis, and calculated the IRs per 1,000 person-years for each outcome, individually and together (as VTE). I used Cox proportional hazard regression models[82] to calculate aHR for the risk of VTE, DVT, and PE in the gout and pre-gout periods compared with the non-gout cohort, after adjusting for age, sex, and all baseline covariates. To evaluate the time trends of VTE risk before and after the index date, I also estimated incidence rate ratios (IRRs) and aHRs within 3, 2, and 1 years before the index date and 1, 2, 3, 4, and 5 years after the index date. For the analysis of VTE risk before the

index date, I excluded individuals with a VTE diagnosis recorded any time before the date of interest. For the analysis of VTE risk after the index date, I excluded individuals with a VTE diagnosis recorded any time before the index date.

2.2.8 Sensitivity analyses

To test the robustness of the results, I performed four sensitivity analyses. First, to test the robustness of my results to the potential effect of the unmeasured confounder (i.e., obesity), I calculated the new final aHRs of VTE, DVT, and PE by adding to the multivariable model a simulated unmeasured confounder with a prevalence ranging from 30% to 40% in the gout cohort[32,17] (based on the published prevalence range of obesity in gout cohorts) and a prevalence of 23% for the non-gout cohort (corresponding to the estimated prevalence of obesity for the BC general population aged 18 and older)[18], and ORs ranging from 2.0 to 2.5 for the association between obesity and VTE, DVT, or PE[19]. Secondly, I calculated the cumulative incidence of each outcome event after taking the competing risk of death into account, according to Lau et al[20]. Thirdly, I used a more restrictive gout case definition that only included gout individuals who satisfied the primary case definition and also had at least one prescription for ULT or colchicine between 1 month before and 3 months after the index date. A similar case definition using the UK General Practice Research Database was found to have a positive predictive value of 90%[83]. For the fourth sensitivity analysis, I only included gout patients who were matched with non-gout individuals perfectly based on age-, sex-, and calendar year of index date.
SAS V.9.4 (SAS Institute, Cary, North Carolina, US) was used for all analyses. For all IRRs and aHRs, I calculated 95% CIs. The cut-off for statistical significance was 0.05 and all P values were 2-sided.

2.3 Results:

2.3.1 Baseline characteristics

After excluding individuals with VTE events before index date, I identified 124,306 incident gout patients (65% male, mean age 60 years) over the 13-year period, and 125,356 non-gout individuals (65% male, mean age 54 years) from January 1, 2000. 82.8% of gout patients were matched with their corresponding non-gout individuals exactly on age, sex, and calendar year of index date; the rest (17.2%) were matched on identical sex and calendar year of index date, and closest age. Table 2.1. summarises the baseline characteristics of the cohorts. Compared with the non-gout cohort, gout patients had a higher number of outpatient visits and hospitalizations, greater Charlson Comorbidity Index, and higher prevalence of hypertension, varicosed veins, IBD, sepsis, trauma or fracture, alcoholism, and surgery, as well as higher use of NSAIDs, glucocorticoids, and cox-2 inhibitors.

Table 2.1. Baseline characteristics of individuals with and without gout at the time of index date.

Variable*	**Gout cohort N=124,306**	**Non-gout N=125,356**	**p-value**
Age, mean (±SD)	60.13 (±16.10)	54.36 (±16.91)	<0.0001
Male	80,646 (64.88%)	81,336 (64.88%)	NS
Healthcare Utilization, mean (±SD)			
Number of outpatient visits	18.86 (±20.35)	11.82 (±16.00)	<0.0001
Number of hospitalizations	0.33 (±0.83)	0.20 (±0.64)	<0.0001
Comorbidities, n (%)			
Charlson Comorbidity Index, mean (±SD)	0.69 (±1.32)	0.36 (±0.96)	<0.0001
Hypertension	47,664 (38.34%)	24,108 (19.23%)	<0.0001
Varicosed veins	1,090 (0.88%)	906 (0.72%)	<0.0001
IBD	827 (0.67%)	691 (0.55%)	0.0002
Sepsis	2,817 (2.27%)	1,521 (1.21%)	<0.0001
Trauma or fracture	8,084 (6.50%)	6,541 (5.22%)	<0.0001
Alcoholism with liver disease	1,376 (1.11%)	921 (0.73%)	<0.0001
Surgery	5,431 (4.37%)	3,672 (2.93%)	<0.0001
Medications, n (%)			
NSAIDs	34,549 (27.79%)	15,357 (12.25%)	<0.0001
HRT	3,979 (3.20%)	3,943 (3.15%)	NS
Glucocorticoids	10,178 (8.19%)	5,672 (4.52%)	<0.0001
Cox-2 inhibitors	6,244 (5.02%)	4,047 (3.23%)	<0.0001
Oral contraceptives	1,303 (1.05%)	1,417 (1.13%)	0.048

Abbreviations: **SD**, standard deviation; **IBD**, inflammatory bowel disease; **NSAIDs**, non-steroidal anti-inflammatory drugs; **HRT**, hormone replacement therapy; **Cox-2**, cyclooxygenase-2; **NS**, non-significant**.**

***All Baseline characteristics were measured over one year prior to the index date.**

2.3.2 Risk of VTE in gout patients

During the follow-up time after the index date, 1,594 incident VTE, 989 DVT, and 813 PE events occurred in the gout cohort, compared with 924, 558, and 506 in the non-gout cohort, respectively. The cumulative incidence of VTE, DVT, and PE was significantly higher in the gout cohort compared with the non-gout cohort (Figure 2.1.). The IRs for VTE, DVT, and PE in the gout cohort were 2.44, 1.51, and 1.24 events per 1,000 person-years, respectively, while the corresponding IRs in the non-gout cohort were 1.37, 0.83, and 0.75 events per 1,000 person-years, respectively. After adjusting for age and sex, the aHRs (95% CI) were 1.56 (1.44-1.70), 1.63 (1.46-1.81), and 1.44 (1.29-1.62) for VTE, DVT and PE, respectively. After adjusting for age, sex and all baseline covariates, the corresponding aHRs (95% CI) were 1.34 (1.23-1.46), 1.38 (1.24-1.54), and 1.27 (1.13-1.42) (Table 2.2.).

2.3.3 Risk of VTE in gout patients during the pre-gout period

Between January 1, 1997 and the index date, there were 1,302 VTE, 862 DVT, and 642 PE events in the gout cohort, and 666, 442, and 334 events, respectively, in the non-gout cohort. The IRs for VTE, DVT, and PE during the pre-gout period in the gout cohort were 1.03, 0.68, and 0.51 events per 1,000 person-years, respectively; and 0.52, 0.35, and 0.26 events per 1,000 person-year in the non-gout cohort. Compared with the non-gout cohort, the age- and sex- aHRs (95% CI) for VTE, DVT, and PE in the gout cohort during the pre-gout period were 1.68 (1.53-1.84), 1.69 (1.50-1.89), and 1.64 (1.43-1.87), respectively. After adjusting for age, sex and all baseline covariates, the final aHRs (95% CI) were 1.56 (1.41-1.71), 1.55 (1.38-1.75), and 1.53 (1.34-1.76), respectively (Table 2.2.).

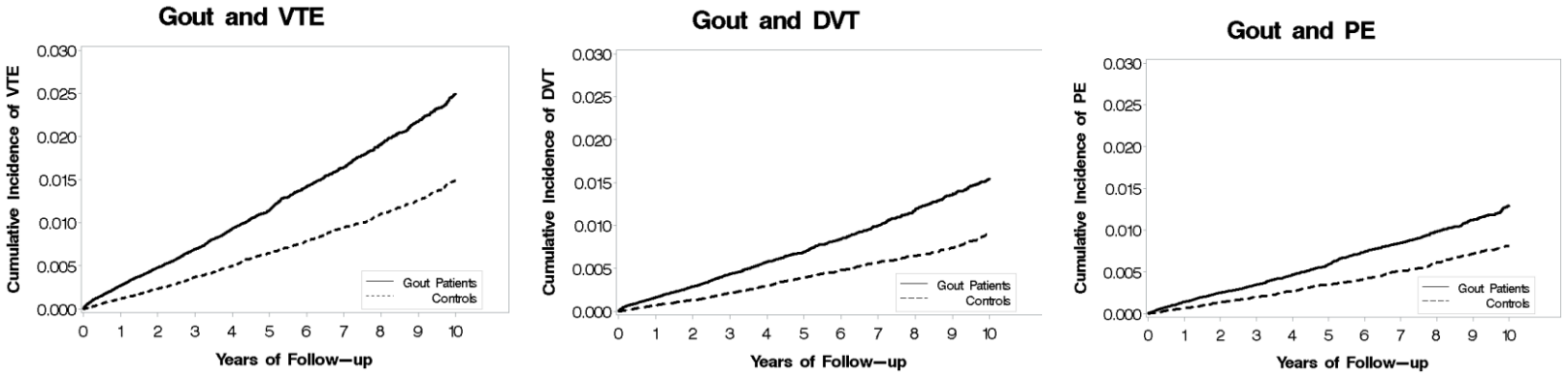

Figure 2.1. Cumulative incidence of venous thromboembolism (VTE), deep venous thrombosis (DVT), and pulmonary embolism (PE) among the gout and non-gout cohorts.

Table 2.2. Overall risk of VTE, DVT, and PE in gout relative to non-gout after and before index date.

	Gout cohort After index date N=124,306	**Non-gout After index date N=125,356**	**Gout cohort Pre-index date N=125,608**	**Non-gout Pre-index date N=126,022**
VTE				
No. of events	1,594	924	1,302	666
IR per 1,000 person-years	2.44	1.37	1.03	0.52
IRR (95% CI)	1.78 (1.64-1.94)	N/A	1.96 (1.79-2.16)	N/A
Age- and sex- aHR (95% CI)	1.56 (1.44-1.70)	N/A	1.68 (1.53-1.84)	N/A
Final aHR (95% CI)*	1.34 (1.23-1.46)	N/A	1.56 (1.41-1.71)	N/A
DVT				
No. of events	989	558	862	442
IR per 1,000 person-years	1.51	0.83	0.68	0.35
IRR (95% CI)	1.83 (1.65-2.03)	N/A	1.96 (1.74-2.20)	N/A
Age-, sex- aHR (95% CI)	1.63 (1.46-1.81)	N/A	1.69 (1.50-1.89)	N/A
Final aHR (95% CI)*	1.38 (1.24-1.54)	N/A	1.55 (1.38-1.75)	N/A
PE				
No. of events	813	506	642	334
IR per 1,000 person-years	1.24	0.75	0.51	0.26
IRR (95% CI)	1.66 (1.48-1.86)	N/A	1.93 (1.69-2.21)	N/A
Age-, sex- aHR (95% CI)	1.44 (1.29-1.62)	N/A	1.64 (1.43-1.87)	N/A
Final aHR (95% CI)*	1.27 (1.13-1.42)	N/A	1.53 (1.34-1.76)	N/A

Abbreviations: **IR,** incidence rate; **IRR**, incidence rate ratio; **aHR**, adjusted hazard ratio; **VTE**, venous thromboembolism; **DVT**, deep venous thrombosis; **PE**, pulmonary embolism; **CI**, confidence interval; **N/A**, not applicable

*Adjusted for all variables listed in Table 2.1

2.3.4 Time trends in the risk of VTE in gout relative to non-gout before and after the index date.

During the 1st, 2nd, 3rd, 4th, and 5th years after the index date, the aHRs for VTE decreased over time, but remained significant, with final aHRs (95% CI) of 1.46 (1.19-1.80), 1.44 (1.23-1.68), 1.37 (1.20-1.56), 1.36 (1.21-1.53), and 1.32 (1.18-1.46). Similar trends were also seen in DVT and PE (Figure 2.2., Table 2.3.).

For VTE, DVT, and PE, the highest aHRs were observed during the first year prior to the index date (aHR [95%CI] for VTE: 1.74 [1.38-2.20]; DVT: 1.72 [1.30-2.29]; PE: 1.96 [1.39-2.76]) (Figure 2.2., Table 2.3.). During the 3rd and 2nd years preceding the index date, the final aHRs (95%CI) for VTE were 1.51 (1.31-1.75) and 1.61 (1.36-1.91), respectively. Similar trends were seen for DVT and PE.

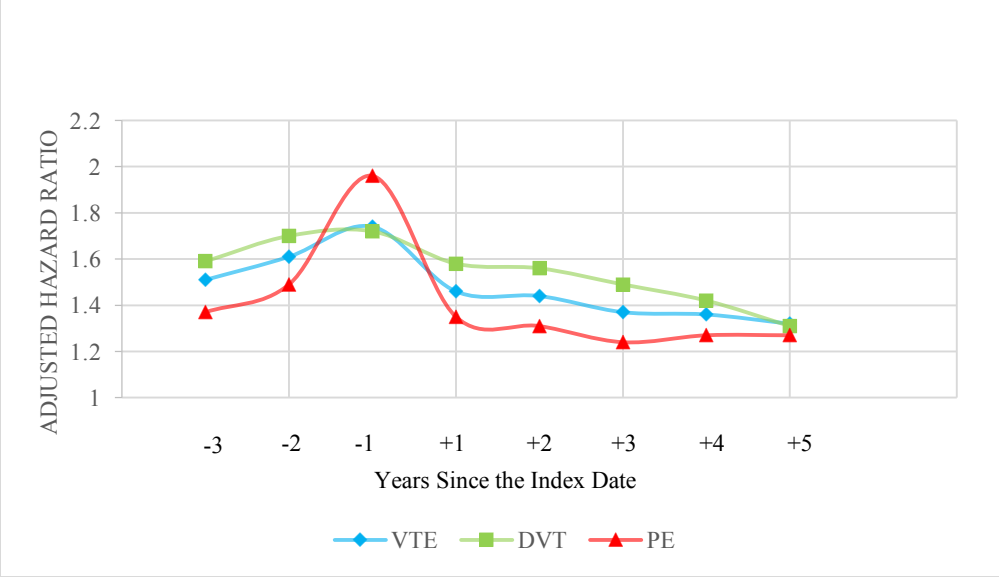

Figure 2.2. Time trends for risk of venous thromboembolism (VTE), deep venous thrombosis (DVT) and pulmonary embolism (PE) before and after the index date.

Table 2.3. Time trends for risk of VTE, DVT, and PE in gout relative to non-gout patients according to time from the index date, before and after gout diagnosis.

	VTE **Final aHRs (95%CI)***	**DVT** **Final aHRs (95%CI)***	**PE** **Final aHRs (95%CI)***
Before gout diagnosis			
-3 years	1.51 (1.31-1.75)	1.59 (1.33-1.91)	1.37 (1.11-1.68)
-2 years	1.61 (1.36-1.91)	1.70 (1.38-2.10)	1.49 (1.17-1.91)
-1 year	1.74 (1.38-2.20)	1.72 (1.30-2.29)	1.96 (1.39-2.76)
After gout diagnosis			
+1 year	1.46 (1.19-1.80)	1.58 (1.20-2.07)	1.35 (1.02-1.78)
+2 years	1.44 (1.23-1.68)	1.56 (1.27-1.91)	1.31 (1.07-1.62)
+3 years	1.37 (1.20-1.56)	1.49 (1.26-1.76)	1.24 (1.04-1.49)
+4 years	1.36 (1.21-1.53)	1.42 (1.22-1.64)	1.27 (1.08-1.49)
+5 years	1.32 (1.18-1.46)	1.31 (1.14-1.50)	1.27 (1.10-1.47)

Abbreviations: **aHR**, adjusted hazard ratio; **VTE**, venous thromboembolism; **DVT**, deep venous thrombosis; **PE**, pulmonary embolism; **CI**, confidence interval

*Adjusted for all variables listed in Table 2.1

2.3.5 Sensitivity analyses.

I performed 4 sensitivity analyses to evaluate the robustness of the results. Firstly, when assessing the robustness of the results to the potential effect of the unmeasured confounder, obesity, the aHRs assessing the risk of VTE in gout relative to non-gout remained significant throughout the range of obesity prevalences, as did ORs for the association between obesity and VTE, for all events, except for PE at the more extreme values of the range (prevalence of 40% and OR of 2.5) (Table 2.4.). Secondly, after accounting for the competing risk of death, the results also remained significant for VTE, DVT and PE (Table 2.4.). Thirdly, overall, final aHRs remained significant when using the stricter gout case definition (i.e., gout diagnosis and ULT or colchicine use) when assessing the risk before and after gout diagnosis (Table 2.5., Table 2.6.). Finally, after I excluded patients who could not be matched exactly on age with non-gout individuals, the results remained similar (Table 2.7., Table 2.8.).

Table 2.4. Sensitivity analyses evaluating the risk of VTE after index date, modeling the potential confounding effect of obesity and accounting for competing risk of death.

Event	Primary analyses Final aHR (95% CI)*	Sensitivity analyses modeling obesity with prevalence=30% and OR=2.0 aHR (95% CI)*	Sensitivity analyses modeling obesity with prevalence=40% and OR=2.0 aHR (95% CI)*	Sensitivity analyses modeling obesity with prevalence=30% and OR=2.5 aHR (95% CI)*	Sensitivity analyses modeling obesity with prevalence=40% and OR=2. 5 aHR (95% CI)*	Sensitivity analyses accounting for competing risk of death aHR (95% CI)*
VTE	1.34 (1.23-1.46)	1.28 (1.17-1.39)	1.21 (1.11-1.32)	1.25 (1.15-1.36)	1.15 (1.06-1.26)	1.32 (1.21-1.44)
DVT	1.38 (1.24-1.54)	1.31 (1.17-1.46)	1.23 (1.10-1.38)	1.29 (1.16-1.44)	1.18 (1.06-1.32)	1.36 (1.22-1.52)
PE	1.27 (1.13-1.42)	1.20 (1.07-1.35)	1.12 (1.00-1.27)	1.18 (1.05-1.33)	1.08 (0.96-1.21)	1.24 (1.10-1.40)

Abbreviations: **aHR,** adjusted hazard ratio; **OR**, odds ratio; **VTE**, venous thromboembolism; **DVT**, deep venous thrombosis; **PE**, pulmonary embolism; **CI**, confidence interval

*Adjusted for all variables listed in Table 2.1

Table 2.5. Sensitivity analyses evaluating the risk of VTE, DVT, and PE in gout relative to non-gout after and before index date using the alternative gout definition.

	Gout cohort After index date N=65,022	**Non-gout After index date N=65,841**	**Gout cohort Pre-index date N=66,042**	**Non-gout Pre-index date N=66,304**
VTE				
No. of events	925	626	1,020	463
IR per 1,000 person-years	2.85	1.84	1.52	0.68
IRR (95% CI)	1.55 (1.40-1.72)	N/A	2.22 (1.98-2.48)	N/A
Age- and sex- aHR (95% CI)	1.47 (1.33-1.63)	N/A	2.03 (1.82-2.27)	N/A
Final aHR (95% CI)*	1.29 (1.15-1.44)	N/A	1.91 (1.71-2.14)	N/A
DVT				
No. of events	566	386	669	293
IR per 1,000 person-years	1.74	1.13	0.99	0.43
IRR (95% CI)	1.54 (1.35-1.75)	N/A	2.29 (2.00-2.64)	1.00
Age- and sex- aHR (95% CI)	1.46 (1.28-1.66)	N/A	2.12 (1.85-2.44)	N/A
Final aHR (95% CI)*	1.26 (1.09-1.46)	N/A	1.98 (1.72-2.28)	N/A
PE				
No. of events	463	341	492	233
IR per 1,000 person-years	1.42	1.00	0.73	0.34
IRR (95% CI)	1.42 (1.24-1.64)	N/A	2.12 (1.81-2.49)	N/A
Age- and sex- aHR (95% CI)	1.34 (1.17-1.55)	N/A	1.93 (1.65-2.25)	N/A
Final aHR (95% CI)*	1.19 (1.02-1.40)	N/A	1.83 (1.56-2.14)	N/A

Abbreviations: **IR**, incidence rate; **IRR**, incidence rate ratio; **aHR**, adjusted hazard ratio; **VTE**, venous thromboembolism; **DVT**, deep venous thrombosis; **PE**, pulmonary embolism; **CI**, confidence interval; **N/A**, not applicable

* Adjusted for all variables listed in Table 2.1

Table 2.6. Sensitivity analyses evaluating time trends for risk of VTE, DVT, and PE before and after the index date using the alternative gout definition.

	VTE **Final aHRs (95%CI)***	**DVT** **Final aHRs (95%CI)***	**PE** **Final aHRs (95%CI)***
Before gout diagnosis			
-3 years	2.04 (1.71-2.43)	2.21 (1.77-2.77)	1.99 (1.54-2.56)
-2 years	1.99 (1.62-2.45)	2.21 (1.70-2.87)	1.92 (1.43-2.59)
-1 year	2.44 (1.84-3.23)	2.81 (1.94-4.08)	2.28 (1.54-3.36)
After gout diagnosis			
+1 year	1.43 (1.08-1.90)	1.47 (1.03-2.09)	1.27 (0.86-1.87)
+2 years	1.34 (1.09-1.65)	1.32 (1.02-1.71)	1.28 (0.95-1.71)
+3 years	1.36 (1.15-1.62)	1.37 (1.10-1.71)	1.28 (1.00-1.64)
+4 years	1.38 (1.18-1.62)	1.40 (1.15-1.71)	1.26 (1.01-1.58)
+5 years	1.34 (1.16-1.55)	1.30 (1.09-1.56)	1.24 (1.01-1.51)

Abbreviations: **aHR**, adjusted hazard ratio; **VTE**, venous thromboembolism; **DVT**, deep venous thrombosis; **PE**, pulmonary embolism; **CI**, confidence interval

* Adjusted for all variables listed in Table 2.1

Table 2.7. Sensitivity analyses evaluating the risk of VTE, DVT, and PE after and before the index date using the gout cohort, but excluding gout patients who could not be matched exactly on age with non-gout individuals.

	Gout-cohort After index date N=102,899	**Non-gout After index date N=103,459**	**Gout-cohort Pre-index date N=103,838**	**Non-gout Pre-index date N=104,074**
VTE				
No. of events	1,228	858	939	615
IR per 1,000 person-years	2.23	1.54	0.90	0.59
IRR (95% CI)	1.44 (1.32-1.58)	N/A	1.53 (1.38-1.70)	N/A
Age- and sex- aHR (95% CI)	1.46 (1.34-1.59)	N/A	1.54 (1.39-1.70)	N/A
Final aHR (95% CI)*	1.27 (1.16-1.39)	N/A	1.44 (1.30-1.59)	N/A
DVT				
No. of events	762	515	634	406
IR per 1,000 person-years	1.38	0.93	0.61	0.39
IRR (95% CI)	1.49 (1.33-1.67)	N/A	1.57 (1.38-1.78)	N/A
Age- and sex- aHR (95% CI)	1.51 (1.35-1.68)	N/A	1.57 (1.39-1.78)	N/A
Final aHR (95% CI)*	1.30 (1.16-1.46)	N/A	1.46 (1.28-1.65)	N/A
PE				
No. of events	626	467	460	307
IR per 1,000 person-years	1.13	0.84	0.44	0.29
IRR (95% CI)	1.35 (1.20-1.53)	N/A	1.50 (1.30-1.74)	N/A
Age- and sex- aHR (95% CI)	1.37 (1.21-1.54)	N/A	1.51 (1.30-1.74)	N/A
Final aHR (95% CI)*	1.20 (1.06-1.35)	N/A	1.42 (1.23-1.65)	N/A

Abbreviations: **IR,** incidence rate; **IRR**, incidence rate ratio; **aHR**, adjusted hazard ratio; **VTE**, venous thromboembolism; **DVT**, deep venous thrombosis; **PE**, pulmonary embolism; **CI**, confidence interval; **N/A**, not applicable

* Adjusted for all variables listed in Table 2.1

Table 2.8. Sensitivity analyses evaluating time trends for risk of VTE, DVT, and PE before and after the index date using the gout cohort, but excluding gout patients who could not be matched exactly on age with non-gout individuals.

	VTE **Final aHRs (95%CI)***	**DVT** **Final aHRs (95%CI)***	**PE** **Final aHRs (95%CI)***
Before gout diagnosis			
-3 years	1.43 (1.22-1.67)	1.53 (1.26-1.85)	1.30 (1.05-1.62)
-2 years	1.54 (1.29-1.85)	1.68 (1.34-2.10)	1.43 (1.10-1.85)
-1 year	1.72 (1.35-2.21)	1.72 (1.27-2.33)	1.91 (1.33-2.73)
After gout diagnosis			
+1 year	1.44 (1.16-1.79)	1.56 (1.17-2.07)	1.27 (0.95-1.71)
+2 years	1.44 (1.23-1.70)	1.52 (1.23-1.88)	1.31 (1.06-1.90)
+3 years	1.36 (1.19-1.56)	1.43 (1.20-1.71)	1.25 (1.03-1.76)
+4 years	1.29 (1.15-1.46)	1.32 (1.13-1.55)	1.22 (1.03-1.45)
+5 years	1.25 (1.11-1.39)	1.24 (1.07-1.44)	1.20 (1.03-1.40)

Abbreviations: **aHR**, adjusted hazard ratio; **VTE**, venous thromboembolism; **DVT**, deep venous thrombosis; **PE**, pulmonary embolism; **CI**, confidence interval

* Adjusted for all variables listed in Table 2.1

2.4 Discussion

In this large population-based study of an incident gout cohort, I demonstrated that the overall risk of VTE, DVT, PE was significantly increased after gout diagnosis (aHRs=1.34, 1.38, 1.27 for VTE, DVT, PE, respectively) when compared to the general population. I also found that the risk was elevated in the years preceding a gout diagnosis (aHRs=1.56, 1.55, 1.53 for VTE, DVT, and PE, respectively). Furthermore, I observed that the highest risk occurred in the year prior to a gout diagnosis (aHRs=1.74, 1.72, 1.96 for VTE, DVT and PE, respectively). Though the risks decreased progressively thereafter, the increase risk of VTE, DVT and PE remained statistically significantly even five years after the index date when compared to the general population.

Three main precursors to VTE were proposed by Virchow: damage to the vessel wall, increasing blood coagulability and venous stasis[11]. Inflammation during the hyperuricemia phase and gout attacks might be a plausible key factor responsible for damaging the vascular endothelium and increasing blood coagulability. Deposition of uric acid can activate the formation of the NLRP3 inflammasome, which increases the production of interleukin-1ß and can amplify the inflammatory response on vascular cells[1]. At the same time, hyperuricemia can also activate the production of reactive oxygen species which can increase the formation of NLRP3[53] and inhibit the secretion of nitric oxide which can suppress NLRP3[54]. This inflammatory process can damage vascular endothelium in both arteries and veins through endothelial disturbance by leading to vascular smooth muscle cell proliferation and endothelial cell inhibition[15,60,86]. In addition, von Willebrand factor, tissue factor and plasminogen activator inhibitor V are also produced, which upregulates blood coagulation[15]. As proposed in previous studies[26,15], inflammation may increase gradually in the pre-diagnosis phase, as untreated

hyperuricemia increases, until the onset of symptoms causes patients to seek medical care, leading to the diagnosis of gout. Thus hyperuricemia and untreated inflammation would peak in the first year before the index date, with a subsequent decline in risk after the index date resulting from reduced inflammation due to treatment with anti-inflammatory drugs, as well as ULTs[57].

The findings of increased risk of VTE after gout diagnosis are consistent with recent studies. A cohort study from Taiwan reported aHRs for DVT and PE of 1.66 and 1.53, respectively[13]. However, only one ICD-9-CM or ICD-10-CM code was used to define DVT or PE, and they did not adjust for any prescription drugs that are known as risk factors for VTE. Another study, using the same dataset, reported an aHR for DVT of 1.38 compared to the general population[14], which is also consistent with the findings. However, their study design used a prevalent cohort which has an inherent survival bias, as the cohort only includes surviving individuals who may be less susceptible to cardiovascular complications such as VTE.

The finding that the risk of VTE is increased before the index date suggests that SUA level may play a role in thrombosis even before the diagnosis of gout. This finding is consistent with evidence that SUA itself has a pro-inflammatory effect on vascular cells and with evidence that SUA levels are positively associated with atherothrombotic cardiovascular diseases[15,85]. Using the cohort component of the Atherosclerosis Risk in Communities Study, Kubota et al[15] recruited 14,126 participants without history of VTE at baseline and divided SUA levels into six categories to assess the risk of VTE. The authors found a positive association between SUA levels and VTE risk ranging from 1.44 (95% CI, 1.06-1.96) to 1.89 (95% CI, 1.15-3.12) compared to the lowest SUA level group[15]. A similar trend was observed for VTE subtypes. The authors concluded that elevated SUA levels may increase the risk of VTE through inflammation

and proposed SUA as a low-cost biomarker that could be studied for adding to VTE risk prediction.

I acknowledge the potential limitations inherent to an observational study using an administrative dataset. Uncertainty of the accuracy of the gout case definition cannot be completely ruled out, especially as I used one billing code from an outpatient or inpatient visit for the gout case definition; however, similar results were also found using the alternative case definition (validity of 90%) in the sensitivity analyses which restricted the definition to those gout patients who had at least one prescription of ULT or colchicine[83]. The measurement of disease onset using an administrative dataset may also be inaccurate, for example, there would be no record available if patients did not have any healthcare utilization during the first gout flare[86,87]. The time difference between gout onset and the first clinical billing code might lead to the higher risk of VTE in the pre-gout period than the general population. Finally, I did not have access to laboratory data to assess the SUA levels before and after the index date, as well as other parameters such a C-reactive protein.

While the multivariable Cox models adjusted for many known VTE risk factors[38], certain confounding variables were unavailable in the dataset, such as body mass index to assess obesity. However, in the sensitivity analyses where I adjusted for unmeasured confounders, the results remained statistically significant for VTE and DVT even when using extreme values of 40% prevalence of obesity in the gout cohort and an OR of 2.5 for the association between obesity and VTE or DVT. Even so, as with other retrospective observational cohort studies, the results could have been influenced by other unknown confounders.

Although I was not able to match each gout patient with a corresponding non-gout individual perfectly based on age, I did adjust for age in the multivariate Cox models. Besides, when I performed a sensitivity analysis with a focus on gout patients who could be matched with the non-gout cohort perfectly (approximately 83% of the sample), similar results were found.

Despite these limitations, there are several notable strengths of this study. I used a large Canadian administrative database based on the entire BC population, which makes the findings more generalizable. I was also able to use the largest gout cohort assembled to date to study the relationship between gout and VTE in a general population-based setting. The sample size provided sufficient statistical power to find an association between gout and VTE. This is also the first study assessing the yearly trends of VTE risk before and after an index date. Furthermore, I required at least 10 years of run-in time before the index date in order to only include the purely incident gout patients. Finally, I used the strictest of VTE case definitions to capture true events.

If these results are confirmed by others, the critical question is now how to translate the clinical validity of these results into clinical utility. As is known, VTE is the most common preventable cause of inpatient death (PE occupies 5% to 10% of death in hospitalized patients)[10] and prevention should be the ultimate goal. However, not all patients with gout carry the same risk and therefore further research to identify high risk patients should be the next step, so timely prevention or prophylaxis can be implemented. In the meantime, adequate vigilance and awareness for VTE risk should be targeted towards patients with gout or hyperuricemia. This could be an additional incentive for patients and clinicians to adhere to treatment guidelines given that such action will decrease the risk of gout flares and, thus, likely VTE.

In summary, this is the largest population-based study done to date that demonstrates that patients with gout have an increased risk of VTE, DVT and PE (approximately 30%, 40% and 30%, respectively) after a gout diagnosis compared with the general population. This risk is independent of traditional VTE risk factors. Moreover, I also demonstrated that the risk is higher in the years prior to a gout diagnosis, peaking in the first year before diagnosis (70-100%) and decreasing with time thereafter, but nonetheless remaining elevated compared to the general population. This risk should be confirmed in future prospective studies, especially among people who have hyperuricemia.

Chapter 3: Discussion and Conclusion

3.1 Summary of Key Findings

To gain a better understanding of VTE risk in gout patients compared with the general population in BC, Canada, Chapter 2 accessed the overall risk of VTE, DVT and PE in a gout cohort before and after a gout diagnosis relative to the general population using an administrative dataset. Chapter 2 also assessed the temporal trends of VTE, DVT and PE risk before and after gout diagnosis. After adjusting for traditional VTE risk factors, this study demonstrated that incident gout was associated with a 34% increased risk of VTE, a 38% increased risk of DVT and a 27% increased risk of PE when compared to the general population. Moreover, this study found that the risk of VTE, DVT and PE was also increased in the pre-gout period when compared with the general population (56%, 55% and 53%, respectively). The risk increased over the three years preceding a gout diagnosis, and peaked in the year before a gout diagnosis (74%, 72%, and 96% for VTE, DVT and PE, respectively). Though the risk decreased progressively thereafter, it remained statistically significant even five years after a gout diagnosis. This suggests that high SUA levels or gout associated inflammation before and after gout diagnosis may be contributing factors for VTE.

The findings on the increased risk of VTE after a gout diagnosis are consistent with recent studies. A cohort study from Taiwan reported aHRs for DVT and PE of 1.66 and 1.53, respectively[13]. However, only one ICD-9-CM or ICD-10-CM code was used to define DVT or PE, and it did not adjust for any prescription drugs that are known risk factors for VTE. Therefore, it is possible that this study could have false positive VTE outcomes. Another study using the same dataset reported an aHR for DVT of 1.38 compared with the general population[14]. However, this study used a prevalent cohort, which is faced with the potential problem of

survival bias. Thus, the cohort may only include gout patients who survived, meaning they may be less susceptible to fatal cardiovascular complications such as VTE.

The finding of an increased risk of VTE before the index date suggests that elevated SUA level may play a role in thrombosis even before the diagnosis of gout. This finding is consistent with evidence that SUA itself has a pro-inflammatory effect on vascular cells and with evidence that SUA levels are positively associated with atherothrombotic cardiovascular diseases[15,85]. Using the cohort component of the Atherosclerosis Risk in Communities Study, Kubota et al[15] recruited 14,126 participants without a history of VTE at baseline and divided SUA levels into six categories to assess the association of SUA levels and VTE. The authors found a positive association between SUA levels and VTE risk ranging from 1.44 (95% CI, 1.06-1.96) to 1.89 (95% CI, 1.15-3.12) compared to the lowest SUA level group[15]. A similar trend was observed for VTE subtypes. The authors concluded that elevated SUA levels may increase the risk of VTE through inflammation and proposed SUA as a low-cost biomarker that could be studied for adding to the VTE risk prediction.

Indeed, as shown in previous studies, uric acid may induce both endothelial dysfunction and vessel inflammation[58]. Specifically, sustained high levels of uric acid are not only related to higher levels of inflammatory markers, for example, C-reaction protein that can play a key role in reducing the blood flow response, but also have a direct effect on endothelial dysfunction[57,58]. Moreover, systematic inflammation induced by increased uric acid could also promote blood coagulatibility by stimulating coagulants, inhibiting anticoagulants and suppressing fibrinolysis[53]. Other than uric acid, Park et al[88] demonstrated an interesting phenomenon: they found a remarkable percentage of MSU crystals in coronary arteries, which could be the

prerequisite for crystal-induced inflammation on blood vessels among gout patients, ultimately leading to thrombosis.

3.2 Implications for Clinical Practice

The results from this thesis work indicate that hyperuricemia, a common condition preceding gout onset or gout-induced inflammation, might be a risk factor for VTE. Compared to general population, gout patients were found to have a higher risk of VTE, DVT, and PE both before and after a gout diagnosis. Among the gout cohort, the VTE, DVT, and PE risks steadily increased until the peak observed around the year prior to gout diagnosis, which suggests that inflammation increases gradually prior to the occurrence of gout, peaking in the first year before a gout diagnosis. The decline in risk after a gout diagnosis may be a result of attenuated inflammatory levels in response to anti-inflammatory drugs and ULTs.

Should the above findings be validated by others, the association between hyperuricemia and VTE at the pre-gout-diagnosis stage could be established, suggesting the potential necessity to administer ULTs or colchicine among individuals who have a higher risk of developing VTE. Moreover, these findings could help increase adherence to gout treatment given that such treatment will not only prevent the possibility of gout flares, but also decrease cardiovascular complications, reduce disease burden and improve survival. As suggested by Thanassoulis et al[62], the use of allopurinol is associated with a 31% reduced risk of heart failure readmission or death and a 26% decreased risk of all-cause mortality in patients with a history of gout. Furthermore, in a randomized control trial, Nidorf et al[64] demonstrated that among patients who had stable CHD, colchicine could reduce secondary cardiovascular events by 70% when compared to non-users.

Even though VTE is one of the most common preventable cause of inpatient death, it is still a very deadly illness (PE causes 5% to 10% of deaths in hospitalized patients)[10]. Moreover, survivors often experience serious and costly long-term complications from VTE and the use of anticoagulation therapy[40]. Thus, clinicians should increase their awareness, vigilance and monitoring of the risk of VTE in gout and high serum urate acid level patients. In addition, because long-term decreased mobility due to gout may also influence venous stasis[11], lifestyle modifications for gout may also decrease the risk of VTE.

3.3 Strengths and Limitations

Given that I used an administrative health dataset which was not collected specifically for the purpose of research, I acknowledge some limitations in this retrospective observational cohort study. One limitation is the uncertainty of the accuracy of the gout case definition based on one billing code for a gout diagnosis from an outpatient or inpatient visit. It is possible that false positive gout cases were included and false negative gout cases were excluded. However, the used case definition for gout was validated by previous studies using different administrative datasets with positive predictive values ranging from 61% to 100%[78]. Furthermore, similar results were also found when the alternative case definition was used, which was restricted to those gout patients who had at least one prescription for ULTs or colchicine. This alternative case definition had a positive predictive value of 90% in a previous study[83].

To determine a VTE outcome, I used very strict inclusion and exclusion criteria that included information from the prescription dataset. A similar case definition for VTE has been validated by previous studies, having a positive predictive value of 94% in a general practice database[80].

Even though I adjusted for many known VTE risk factors in the model when calculating HRs, certain confounders, such as obesity, were unavailable in the dataset. However, in the sensitivity analyses, the results remained significant for all outcomes except for PE, even I used the extreme values of 40% prevalence of the unmeasured confounder in the gout cohort and OR of 2.5 for the relationship between the unmeasured confounder and VTE or DVT. Nevertheless, similar to other retrospective observational cohort studies using administrative health datasets, these results could still be influenced by other unknown confounders.

Furthermore, although I was not able to match each gout patient with corresponding controls perfectly based on age, I did adjust for age in the multivariate Cox models. Besides, when I performed a sensitivity analysis focused only on gout patients who could be perfectly matched with controls, similar results were found.

Despite these limitations, there are many major strengths of population-based studies that utilize administrative data. The population-based cohort included all gout individuals who received any medical care for gout in BC, including comprehensive information on prescription drug use regardless of payer. This population-based gout cohort allowed for assessment of the real relationship between gout and VTE, without selection bias. I also required at least 10 years of run-in time before the gout diagnosis, which ensured that only truly incident cases were included in the study, thus eliminating the survival bias of prevalent cohorts. Finally, this is the

first study to assess the temporal trends of VTE, DVT and PE risk before and after a gout diagnosis.

3.4 Future Research

This thesis work provides direction for future research. Because laboratory and clinical datasets are in the process of being developed and linked to the administrative dataset in BC, future studies can compare the risk of VTE before and after the onset of hyperuricemia (measured by SUA levels) among gout or suspected gout patients in order to confirm the finding that hyperuricemia is a risk factor for VTE. Additionally, this data linkage paves way for building a predictive model of the risk of VTE using many of the available low-cost biomarkers, such as SUA levels and C-reactive protein.

Also, whether or not current treatments for gout, such as ULT and colchicine, are effective at lowering VTE risk in gout patients has yet to be answered. Should one prove that gout-specific drugs are clinically effective at preventing the development of VTE among gout patients through randomized clinical trials, it would serve as a strong argument to better advocate for the clinical application of ULT, colchicine and other therapeutic options for gout.

Finally, I do not know the accuracy of the different gout case definitions using the Popdata databases, even though previous validity studies have shown positive predictive values for different gout case definitions ranging from 61% to 100%[78,83]. A promising area for future research may involve a validation study using the Popdata databases to determine the accuracy of my gout case definition in order to lay better foundation for future studies.

3.5 Conclusion

The results of this thesis indicate that gout is an independent risk factor for VTE, DVT, and PE. Presumably, inflammation induced by hyperuricemia before a gout diagnosis also increase the risk of VTE, DVT, and PE. According to the findings, the risk of VTE, DVT, and PE gradually increases in the pre-gout years until reaching a peak around one year prior to a gout diagnosis, and then declines over time. To the best of my knowledge, this thesis work is the first study on the temporal trends of VTE, DVT, and PE before and after a gout diagnosis. These findings imply that clinical interventions may be considered that target patients with gout or hyperuricemia in order to prevent the development of gout-associated comorbidities like VTE, and to decrease the overall disease burden of gout.

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