

**SECULAR TRENDS IN RISK OF INCIDENT CARDIOVASCULAR EVENTS IN
RHEUMATOID ARTHRITIS RELATIVE TO THE GENERAL POPULATION**

by

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Abstract

Background: Recent evidence suggests a significant decline in all-cause and cardiovascular mortality over time in rheumatoid arthritis (RA) relative to the general population. This improvement in mortality could be due to improvement in risk of cardiovascular events that are the leading cause of excess deaths in RA. Our objective was to evaluate secular trends in ten-year risk of incident **a.** Acute Myocardial Infarction (AMI), and **b.** Cerebrovascular Accidents (CVA), in incident RA cohorts, according to their year of RA incidence, relative to the general population.

Methods: We conducted two retrospective studies of a population-based cohorts of incident RA with RA onset from 01.01.1997 to 31.12.2004, in British Columbia, with matched general population. RA and general population cohorts were divided according to the year of RA incidence, defined based on the first RA visit, using a 7-year wash-out period. Chapter 2 and 3 describe the risk of incident **a.** AMI, and **b.** CVA respectively, using Cox delayed entry models to avoid immortal bias. To determine non-linear effect of years of incidence, Cox regressions, with linear, quadratic and spline functions of years of incidence were compared, and the model with the lowest AIC was selected to interpret the data. To assess whether the risk of AMI/CVA in RA differed from the general population, an interaction term between the indicator of RA vs general population and years of incidence was tested in the Cox models.

Results: The decline in risk of AMI incidence did not differ significantly in RA vs. general population [interaction $p=0.498$]. The change in risk of incident CVA over time, differed significantly in RA vs. general population after 1999 [$p=0.0393$], but not before 1999 [$p=0.0564$].

Conclusion: There was a significant decline in 10-year risk of AMI in RA, and this decline did not differ in RA vs. general population. There was a significant decline in 10-year risk of CVA in RA

with onset from 1999 onwards, and this decline was to a greater extent in RA than it was in the general population.

Lay Summary

Rheumatoid Arthritis (RA) is a chronic autoimmune disease associated with increased risk of developing and dying from heart attacks and strokes. Recent studies have shown an improvement over time in the risk of death from all-cause and CV diseases in RA compared to the general population. Since improvement in mortality could be due to improvement in occurrence of CV events, the goal of this thesis was to assess whether the risk of CV events has improved in patients with RA onset in more recent years. We assessed the 10-year risk of first-ever a. heart attacks, and b. strokes in RA relative to the general population. Our results showed that the risk of heart attacks was not different in RA compared to the general population; and the risk of strokes has improved to a greater extent in RA than in the general population in people with RA onset after 1999.

Preface

Sections of this thesis are multi-authored and will be submitted for publication in peer-reviewed journals. Details of co-authorship are provided.

Chapter 1: Kiana Yazdani was responsible for literature search, review of studies, and writing of chapter 1. Drs. J. Antonio Avina-Zubieta and Diane Lacaille were responsible for reviewing and providing feedback and direction for chapter 1.

Chapter 2: Yazdani K., Xie H., Avina-Zubieta A.J., Zheng Y., Abrahamowicz M., Lacaille D. Secular trends in ten-year risk of incident acute myocardial infarction in rheumatoid arthritis relative to the general population. A population-based study.

Kiana Yazdani was responsible for study design and concept with inputs from Drs. Diane Lacaille, Michal Abrahamowicz, J. Antonio Avina-Zubieta and Hui Xie. Kiana Yazdani was responsible for the statistical analysis with support from Yufei Zheng and Dr. Hui Xie. Drs. J. Antonio Avina-Zubieta, Michal Abrahamowicz, and Diane Lacaille were responsible for clinical interpretations of the results.

Kiana Yazdani was responsible for writing the manuscript. All the co-authors provided their feedbacks and were responsible for critical review of the manuscripts. A version of this manuscript will be submitted for publication.

Chapter 3: Yazdani K., Xie H., Avina-Zubieta A.J., Zheng Y., Abrahamowicz M., Lacaille D. Secular trends in ten-year risk of incident cerebrovascular accidents in rheumatoid arthritis relative to the general population. A population-based study.

Kiana Yazdani was responsible for study design and concept with inputs from Drs. Diane Lacaille, Michal Abrahamowicz, J. Antonio Avina-Zubieta and Hui Xie. Kiana Yazdani was

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Kiana Yazdani was responsible for writing the manuscript. All the co-authors provided their feedbacks and were responsible for critical review of the manuscripts. A version of this manuscript will be submitted for publication.

Chapter 4: Kiana Yazdani was responsible for design, literature search, review of studies, and summarizing the key findings. Kiana Yazdani was responsible for writing chapter 4. Dr. Diane Lacaille was responsible for reviewing and providing feedback and direction for chapter 4.

The study received ethics approval from the University of British Columbia's Behavioral Research Ethics Board. The Ministry of Health provided the linkage for their databases, no personal identifying information was provided to the investigators, and all procedures were compliant with BC's Freedom of Information and Privacy Protection Act. The certificate number is H00-80305.

Table of Contents

Abstract.....	iii
Lay Summary	v
Preface.....	vi
Table of Contents	viii
List of Tables	xii
List of Figures.....	xiii
List of Abbreviations	xiv
Acknowledgements	xvii
Dedication	xix
Chapter 1: Introduction	1
1.1 Thesis Organization	1
1.1.1 Research Statement.....	1
1.1.2 Overview of Thesis Themes and Chapters	2
1.2 Rheumatoid Arthritis	3
1.2.1 Epidemiology, Genetics, and Etiology	3
1.3 Rheumatoid Arthritis and Cardiovascular Diseases	5
1.3.1 Epidemiology and Outcomes of CVD in RA	5
1.3.2 Risk factors for CVD in RA.....	6
1.3.3 CVD Risk Assessment in RA	9
1.4 Effect of Pharmacological Therapies on Lowering the Risk of CVD in RA.....	11
1.4.1 Methotrexate	12
1.4.2 Biologic DMARDs	12

1.4.3	Dyslipidemia and Statin Therapy.....	13
1.4.4	Glucocorticoid Use	14
1.4.5	Nonsteroidal Anti-Inflammatory Drugs.....	15
1.4.6	Aspirin and Anti-Thrombotic Treatment	15
1.4.7	Hydroxychloroquine	16
1.5	Mortality Trends in RA and in RA Relative to the General Population	16
1.8	Overview of thesis studies	18
1.8.1	Specific objectives for thesis	18
Chapter 2: Secular trend in 10-year risk of incident acute myocardial infarction in RA relative to the general population.....		19
2.1	Introduction.....	19
2.2	Methods.....	20
2.2.1	Study Design.....	20
2.2.2	BC Cohort Definition and Study Sample.....	20
2.2.3	Data Collection	22
2.2.4	Outcome Assessment	23
2.2.5	Assessment of Covariates	23
2.2.6	Statistical Analysis.....	24
2.2.7	Ethics.....	26
2.3	Results.....	27
2.4	Discussion	35
Chapter 3: Secular trends in ten-year risk of incident cerebrovascular accidents in rheumatoid arthritis relative to the general population.....		41

3.1	Introduction.....	41
3.2	Methods.....	42
3.2.1	Study Design.....	42
3.2.2	BC Cohort Definition and Study Sample.....	43
3.2.3	Data Collection	44
3.2.4	Outcome Assessment	45
3.2.5	Assessment of Covariates	46
3.2.6	Statistical Analysis.....	47
3.2.7	Ethics.....	49
3.3	Results.....	49
3.4	Discussion	58
	Chapter 4: Discussion	64
4.1	Summary of Key Findings	64
4.2	Implications for Clinical Practice	66
4.3	Implications for Future Research.....	69
4.4	Strength and limitations	70
4.5	Conclusions.....	72
4.5.1	AMI Analysis.....	73
4.5.2	CVA Analysis	73
	Bibliography	74
	Appendices.....	88
	Appendix A.....	88

A.1	ICD codes applied to exclude individuals with other forms of inflammatory arthritis than RA	88
A.2	ICD codes applied to identify comorbidities adjusted in Cox models to estimate the risk of AMI/CVA in RA relative to the general population	89
Appendix B		90
B.1	Output for unadjusted Cox PH.....	90
B.2	Output for estimating secular trend in RA (Unadjusted)	90
B.3	Multivariable Cox PH model	90
B.4	Output for estimating the secular trend in RA (Adjusted).....	91
Appendix C		92
C.1	Output for unadjusted spline Cox regression.....	92
C.2	Multivariable spline Cox regression	92
C.3	Calculating secular trends estimates in 10-year risk of CVA in RA and in general population using Cox spline hazard regression models	93

List of Tables

Table 2-1. Baseline characteristics of incident RA and general population	30
Table 2-2. Crude 10-year incident rates of AMI per 1000 PYs in RA cohort and general population	32
Table 2-3. Comparison of Cox regressions with linear, quadratic, and spline forms of year of incidence	33
Table 2-4. Secular trend in 10-year risk of incident AMI in incident RA cohorts relative to the general population.....	34
Table 3-1. Baseline characteristics of RA and general population cohorts	53
Table 3-2. Crude 10-year incident rates of CVA per 1000 PYs in RA cohort and general population	55
Table 3-3. Comparison of cox regressions with linear, quadratic, and spline forms of year of incidence	56
Table 3-4. Secular trend in 10-year risk of incident CVA in incident RA cohorts relative to the general population.....	57

List of Figures

Figure 2-1. Flow diagram of RA individuals and general population controls included in the AMI Analysis.....	29
Figure 2-2. Mean RA duration at index date for each incident RA cohort (according to the year of RA incidence).....	31
Figure 2-3. Crude 10-year risk of AMI according to year of incidence (1997-2004) in RA and general population cohorts.....	33
Figure 3-1. Flow diagram of RA individuals and general population controls included in the CVA analysis	52
Figure 3-2. Mean RA duration at index date for each incident RA cohort (according to the year of RA incidence).....	54
Figure 3-3. Crude 10-year risk of CVA according to year of incidence (1997-2004) in RA and general population cohorts.....	56

List of Abbreviations

ACCP	Anti-Cyclic Citrullinated Peptide
AMI	Acute Myocardial Infarction
AIC	Akaike Information Criterion
aHR	Adjusted Hazard Ratio
Adj	Adjusted
aOR	Adjusted Odds Ratio
ACC	American College of Cardiology
AHA	American Heart Association
ASA	American Stroke Association
ACR	American College of Rheumatology
BMI	Body Mass Index
bDMARDs	Biologic Disease Modifying Anti-Rheumatic Drugs
BC	British Columbia
CVD	Cardiovascular Disease
CV	Cardiovascular
CAD	Coronary Artery Disease
CHD	Coronary Heart Disease
CVA	Cerebrovascular Accident
CHF	Congestive Heart Failure
CIMT	Carotid Intima Media Thickness
CRP	C - reactive protein
COPD	Chronic Obstructive Pulmonary Disease

Coxibs	Cox-2 Inhibitors
CI	Confidence Interval
CIRT	Cardiovascular Inflammation Reduction Trial
DM	Diabetes Mellitus
DMARDs	Disease Modifying Anti-Rheumatic Drugs
DAS	Disease Activity Score
ESR	Erythrocyte Sedimentation Rate
ESRD	End Stage Renal Disease
ESC	European Society of Cardiology
EULAR	European League Against Rheumatism
GP	General Population
GC	Glucocorticoids
HsCRP	High-Sensitive C - reactive protein
HR	Hazard Ratio
HLA	Human Leukocyte Antigen
IHD	Ischemic Heart Disease
IMR	Incidence Mortality Rate
IL	Interleukin
ICD 9/10	International Disease Classification version 9/10
IR	Incident Rate
IRR	Incident Rate Ratio
MI	Myocardial Infarction
MTX	Methotrexate

MHC	Major Histocompatibility Complex
NbDMARDs	Nonbiologic Disease Modifying Anti-Rheumatic Drugs
NSAIDs	Non-Steroidal Anti-inflammatory Drugs
NHC	National Health Service
NICE	National Institute for Care and Clinical Excellence
OR	Odds Ratio
PY	Person Years
RA	Rheumatoid Arthritis
RF	Rheumatoid Factor
RR	Relative Risk
SD	Standard Deviation
SMR	Standardized Mortality Ratio
SCORE	Systematic Coronary Risk Evaluation
SER	Spanish Society of Rheumatology
TIA	Transient Ischemic Attack
TNF	Tumor Necrosis Factor
TNF- α	Tumor Necrosis Factor-alpha
TNF-i	Tumor Necrosis Factor-inhibitors
TARA	Trial of Atorvastatin in Rheumatoid Arthritis
Unadj	Unadjusted
US	United States
UK	United Kingdom
WHO	World Health organization

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Dedication

This thesis is dedicated to my family and to all the patients living with rheumatoid arthritis. To my mother who provided me with endless support and educational trainings, who brightened my path and offered me time, dedication, and strength to be where I am today. To my father for his unconditional love, limitless inspirations, and who sacrificed his dreams so that I could live mine. To my brother, who I share all my childhood memories and who taught me to be fearless and pursue my passion, regardless of consequences. Most importantly, I dedicate this work to all the patients living with rheumatoid arthritis, who this research was done for. I hope that my work could truly contribute to outcomes of people living with RA and perhaps diminishes the burden of living with this chronic condition.

Chapter 1: Introduction

1.1 Thesis Organization

1.1.1 Research Statement

The objective of this thesis is to shed light on how ten-year risk of incident cardiovascular (CV) events has changed over time in rheumatoid arthritis (RA) relative to the general population. Our primary focus was on risk of incident **a.** acute myocardial infarction (AMI), and **b.** cerebrovascular accidents (CVA). Cardiovascular diseases (CVD) are the leading cause of excess mortality in RA [1]. Overall, life expectancy in RA is significantly reduced [2], with standardized mortality ratios ranging from 1.28 to 3.0, mainly due to increased risk of atherosclerotic cardiovascular disease [3]. There is evidence that the increased risk of CV mortality is not only restricted to patients with longstanding RA, but also occurs in patients who have early inflammatory polyarthritis and who are positive for rheumatoid factor [4].

Studies have been suggesting that traditional CVD risk factors do not fully explain the increased risk of vascular complications in RA, and immune dysregulation, inflammation, and metabolic disturbance characteristics of rheumatoid arthritis may play an important role in the development of early atherosclerosis and premature mortality [5-8]. There is also evidence that RA individuals with CVD have a higher case fatality than the general population, and that CVD are frequently unrecognized before a fatal event [3]. However, recent studies have been suggesting that all-cause mortality, as well as CV mortality, have been improving in RA patients of more recent onset compared to historical RA controls and compared to the general population [9, 10].

It is possible that this improvement in mortality could be due to improvement in risk of incident CV events that are the main cause of excess deaths in RA. Additionally, due to the paradigm shift in treatment of RA with emphasis on early diagnosis and targeting eradication of inflammation, the availability of more effective DMARD agents such as biologic agents, and enhanced awareness of the increased burden of CVD in RA [11], it would be expected that incidence of CV events may be improving overtime as the inflammation and the risk factors of CVD are better managed. However, there are few observational studies assessing time trends in incidence of CV events in RA and comparing trends in RA relative to the general population.

Therefore, there is a need to assess secular trends in incidence of CV events in RA relative to the general population to gain a better understanding on how the risk of CVD has been changing over time in RA, and whether the change in risk of CVD incidence differ in RA compared to the general population.

1.1.2 Overview of Thesis Themes and Chapters

This thesis is assessing secular trends in 10-year risk of incident CV events in RA relative to the general population and is organized in a manuscript-based format. It consists of four chapters. Chapter one is the introductory chapter and reviews the current literature on a) epidemiology of RA, b) CVD in RA, c) pharmacological interventions to manage CVD in RA, d) mortality trends in RA, and in RA relative to the general population.

Chapter 2 examines secular trends in 10-year risk of incident AMI in RA relative to the general population. This chapter describes the change in incidence of AMI in a population-based cohort of incident cases of RA in the province of British Columbia (BC), Canada, using administrative data, and whether the change in risk of AMI differed in RA

relative to the general population using Cox Proportional Hazard regression with delayed entry.

Chapter 3 examines the secular trends in 10-year risk of incident CVA in RA, and in RA relative to the general population using the same approach as described in chapter 2. Chapter 4 is a concluding chapter which summarizes the findings of chapter 2 and chapter 3 and offers discussion of the strength and the limitations of our findings, as well as future implications in the context of clinical practice and research.

1.2 Rheumatoid Arthritis

1.2.1 Epidemiology, Genetics, and Etiology

Rheumatoid arthritis is a chronic systematic inflammatory condition with excess morbidity and increased mortality. It carries a substantial burden for both individuals and the society. The individual burden results from musculoskeletal deficits, with attendant decline in physical function, quality of life, and cumulative comorbid risk. The socioeconomic burden, aside from major direct medical costs, is a consequence of functional disability, reduced work capacity, and decreased societal participation [12-14]. RA incidence and prevalence may vary between geographical areas, and over time [15-17]. Most studies report RA epidemiology in western high-income countries including Western Europe and North America. Burden of RA in low-and-middle-income countries, particularly in Eastern populations, is less understood. A systematic review by Alamanos et al., summarizing data on RA epidemiology from 1988 through 2005 reported median (range) annual incidence rates of RA for several major parts of the world of 38 (31-45) cases/100,000 population for North America, ; of 29 (24-36) cases/100,000 population for Northern European countries; and 16.5 (9-24) cases/100,000 population for Southern

European countries (median 16.5; range 9-24 cases/100,000) [14]. Overall, the prevalence of RA is reported to be between 0.5% to 1%, and RA predominantly affects women.

An analysis from world health organization (WHO) examining trends in RA as an underlying cause of death (UCD) in 31 countries across the world from 1987 to 2011 reported that RA mortality rates have declined globally, however, substantial between-country disparities in RA mortality were observed, although these disparities decreased over time [18]. Some studies have also suggested a decline in the incidence of RA over time. A study from Finland reported in 2000 a 14% decrease in the incidence of RA in 1990–95 compared to 1975–90 [19]. In the Rochester cohort, the incidence of RA declined from 61.2/100 000 in 1955–64 to 32.7/100 000 in 1985–94 [15]. A study of a cohort of Pima Native Americans followed from 1965 to 1990 found a 57% decrease in the age-adjusted incidence of RA among women, and 55% decrease among men [20]. A more recent population-based study in Quebec, Canada, reported a slight decrease in age-standardized incidence of RA from 2001 to 2009, with a slight increase in 2009-2010, with no significant change in RA incidence after this period [21]. However, population aging combined with a decline in RA mortality may lead to an increase in prevalence and economic burden of RA, which needs to be taken into consideration.

There are also some recent studies indicating that RA hospitalization rates have decreased considerably over the past decade supporting the improvement in care for RA in recent decades. It can also reflect that RA patients with onset in more recent years may have fewer comorbidities [22].

Genome-wide association studies have characterized more than a hundred loci associated with risk of RA, most of which implicate immune mechanisms. The human

leukocyte antigen (HLA) system (particularly HLA-DRB1) remains the dominant influence [23]. The increased risk for RA in patients with the shared epitope is linked with seropositivity for autoantibodies against Citrullinated peptides and autoantibodies against immunoglobulin G (IgG) [24]. These characteristic autoantibodies for RA are present in 50-70% of patients at diagnosis, with remarkable stability throughout the disease course. Epigenetics has also been shown to contribute to RA pathogenesis [25]. A recent epigenome-wide association study identified 10 differentially methylated positions that could promote genetic risk in RA [26]. Environmental factors such as smoking, low socioeconomic status, and lower education are also associated with increased risk of RA [27]. There are also studies on animal models of arthritis suggesting an essential role for the gut microbiome in development of this chronic condition [28, 29]. Periodontal disease is also another established risk factor for RA.

1.3 Rheumatoid Arthritis and Cardiovascular Diseases

1.3.1 Epidemiology and Outcomes of CVD in RA

Death from CVD is a leading cause of excess mortality in RA, accounting for over 50% of premature deaths RA in population. Coronary artery disease (CAD) is one of the major contributors to excess CVD risk and CVD mortality in RA. The rate ratio for CVD events among subjects with rheumatoid arthritis is highest in young adults and those without known prior CVD events. However, in absolute terms, the difference in event rates is highest in older adults. [30]. There is evidence suggesting that excess CV mortality increased with increasing RA duration [31]. For instance, a meta-analysis by Avina-Zubieta et al., has shown that the weighted-pooled estimates of standardized mortality ratios (SMRs) were higher in established RA cohorts [SMR (95%CI): 1.56 (1.45, 1.68)]

than in inception cohorts [1.19 (0.86, 1.68)] where median RA duration was shorter [32]. Some studies have also suggested that excess CV mortality is detectable 5-10 years after RA onset [33, 34].

Other CV manifestations including valvular heart disease, arrhythmia, pericarditis and endocarditis; rheumatoid cardiac nodules have also been described but rarely cause clinically overt disease. As suggested by newer imaging techniques, although myocarditis and microvascular disease are common, their contribution to RA remain unclear. Furthermore, RA is associated with a twofold higher risk for heart failure [35]. Overall, however, arterial thrombotic disease due to atherosclerosis, especially coronary artery disease, plays a pivotal role in the increased mortality and morbidity in RA; and RA is associated with more severe presentations and worse outcomes compared to the general population.

1.3.2 Risk factors for CVD in RA

Conventional CVD risk factors are strong predictors of CVD outcomes in the general population, but their impact on CVD morbidity and mortality in RA remains only partly understood. RA patients tend to have a different profile of risk factors compared with the general population. individuals with RA have higher frequency of smoking, unfavorable total cholesterol/HDL ratio, hypertension, and insulin resistance [36]. It has been suggested that classical CVD risk factors operate differently in RA patients compared to the general population, as systematic inflammation modulates adverse effects of such risk factors on the vasculature [37]. However, a meta-analysis revealed that traditional risk factors independently increase the risk of CVD incidence in RA; hypertension [relative risk (95% CI): 2.24 (1.42, 3.06)], hypercholesterolemia [1.73 (1.03, 2.44)], diabetes mellitus

[1.94 (1.58, 2.30)], smoking [1.50 (1.15, 1.84)], and obesity [1.16 (1.03, 1.29)][38]. Of note, a meta-analysis that included seven case-control studies showed no significant difference on prevalence of hypertension between RA subjects and controls [39]. However, Chung et al., have found that undiagnosed hypertension was more common in patients with RA than controls [40]. Current and past smokers are more prevalent among RA patients, due to smoking being a risk factor for developing RA . The probability of smoking (being a current or ex-smoker) was found to be 1.5 times higher in RA than the general population [41]. In addition, smoking has shown to be positively associated with RF and ACPA [42]. These findings underscore the significant role of traditional CVD risk factors in RA and highlight the need for efficient management of these risk factors in RA.

Moreover, the chronic inflammatory state of RA, severity of the disease as reflected by joint erosions, extra-articular manifestations, and the ensuing physical disability are established risk factors for CVD in the RA population. Electrophysiological and structural function of the heart has been shown to be affected by disease activity. Autonomic heart dysfunction and echocardiographic indices of left ventricular remodeling have been shown to correlate with disease severity in cross-sectional studies [43]. Inflammatory markers such as erythrocyte sedimentation rate (ESR), CRP, RF have been associated with increased atherogenicity [44]. Carotid atherosclerotic plaque vulnerability has been associated with moderate/high disease activity compared with RA patients in remission and non-RA subjects [45]. Patients with longer periods of severe disease are more likely to develop CVD complications possibly due to the effect of accumulated inflammatory burden on the vasculature [46, 47].

RA medications could also play an important role in increased risk of CVD in this population. The administration of glucocorticoids is generally associated with increased risk of CVD considering the drug's effect on hypertension, lipid, and glucose metabolism [35]. Studies have shown that this increased risk is dose dependent [48]. There are studies showing that use of NSAIDs is associated with increased CV risk in RA, however, there are some conflicting results regarding their effects in the literature. Goodson and colleagues showed that there was no correlation between the use of NSAIDs and increased CV risk in early undifferentiated inflammatory arthritis [49], whereas a meta-analysis by Trelle and colleagues concluded that there is not enough evidence to guarantee the safety of these drugs [50]. Although biologic drugs have enormously improved clinical outcomes in RA patients, conferring a potential beneficial effect on CV risk, anti-TNF- α therapy should be administered with caution in patients with moderate or severe heart failure as it may lead to a deterioration of previously established congestive heart disease [51]. It is worth noting that even emerging treatments for RA including small molecules, such as spleen tyrosine kinase inhibitors, have been associated with high blood pressure in randomized controlled trials [52]. Given the wide variety of CV side-effects related to the administration of broadly used conventional and biologic disease modifying drugs, the appreciation of unfavorable effects of individual regimens on traditional and disease-related CV risk factors represents an important element of CV prevention and physicians treating RA patients should be aware of this additional risk.

Genetic factors are also related to the heightened CVD risk in RA. Human leukocyte antigen (HLA)-DRB1*04 shared epitope alleles seem to predispose to CV events [53]. Additionally, there are polymorphisms outside the major histocompatibility complex

(MHC) region that demonstrate increased prognostic value for atherosclerosis even after adjusting for traditional CV risk factors [54].

Additional risk factors may include the psychological state of patients, especially stress may be an important CV risk factor. Solomon and colleagues observed an association between symptoms of tension and carotid plaque occurrence in RA in a study including black and white Africans [55].

Finally, it is of note that kidney disease, hyperhomocysteinemia and vitamin D deficiency, which are common in RA individuals, may also contribute to the increased CV risk and should receive appropriate attention by clinicians [56-59].

1.3.3 CVD Risk Assessment in RA

Despite increased risk of CVD in RA, there is inadequate recording of CVD risk factors in RA. Also, CVD risk calculators developed for the general population, such as the 'systematic Coronary Risk Evaluation (SCORE), or Framingham's cardiovascular risk assessment, have been reported to inaccurately predict risk of future CVD events in RA, even though some of them incorporate high sensitivity CRP in the estimation of CV risk [60, 61]. Additionally, all the traditional calculators have been developed on samples where men have represented a high proportion of those developing CV events since they exhibit a greater risk of CV diseases than women. Yet, in RA, women represent the majority of patients; and it is not known how these risk calculators, designed for men, perform in populations that are predominantly female. It is worth noting that QRISK2 which is used in the United Kingdom, includes RA as an independent risk factor and this seems to improve the risk estimation [62]. However, Arts and colleagues demonstrated that QRISK2

overestimates the risk of CV events in RA samples [61]. European Society of Cardiology (ESC) guidelines in 2012 also incorporated RA as a CV risk factor but without promoting significant alterations concerning the clinical management of patients [63]. In 2013 American College of Cardiology (ACC)/ American Heart Association (AHA) guidelines increased the proportion of patients with RA who were eligible for lipid-lowering therapy although the CV risk estimation remained inaccurate [64, 65]. The need for including the strong mediating effect of inflammation in the CV risk stratification of patients, along with the mounting evidence of the excess of CV disease in RA, led European League Against Rheumatism (EULAR) to develop in 2010 specific

recommendations for CV risk assessment and management of patients with RA and other inflammatory diseases, which were based on evidence-based expert consensus opinion [66], however, data from large-scale prospective studies to support these recommendations were lacking. They recommended multiplying the risk of CVD obtained from traditional risk score calculators by 1.5 (based on studies suggesting a 50% increase in risk of CV events) in RA patients if specific conditions conferring an increased risk were met. Several studies highlighted the inefficiency of the EULAR recommendations, demonstrating that the CV risk score in RA seems to be underestimated even after the aforementioned multiplication. In a study of 327 patients by Corrales and colleagues, 96 individuals were classified as low risk according to SCORE, 201 at moderate risk, and 30 at high or very high risk [67]. A more recent study demonstrated that the percentage of patients' reclassification after applying EULAR adjustment for RA was relatively low, regardless of the risk score calculator used, with a maximum increase in risk value of 12% [68]. These findings led to revised EULAR recommendations in which 3 recommendations

remained unchanged, and six recommendations were altered, and one new recommendation was added. However, according to the newly published EULAR recommendations, CVD risk prediction models should be adapted for patients with RA by a 1.5 multiplication factor, if this is not already included in the model [69]. Apart from recommendations targeted towards control of inflammation and risk/benefits of RA therapy, the general recommendations for CVD prevention in RA also include exercise, diet, and smoking cessation. Three guidelines made recommendations about exercise in the context of improving aerobic capacity and/or reduction of CVD risk. Acknowledging that patients with RA may have either active synovitis or structural damage to joints limiting the desired level of aerobic exercise, the exercise programs should be tailored to each patient's disease severity, bodyweight, and baseline level of activity and should ideally be prescribed by a physical therapist [70].

1.4 Effect of Pharmacological Therapies on Lowering the Risk of CVD in RA

The importance of inflammation in accelerating atherosclerosis has been demonstrated in several studies investigating this association using surrogate markers of subclinical CVD, such as carotid intima media thickness (cIMT) [8, 44, 71-75]. These observations underscore the importance of aggressive treatment early in the disease in order to reduce the risk of progressive atherosclerosis. However, only the EULAR guidelines formally recommend control of disease activity as potential means of reducing CVD in RA. Although the hypothesis has not been adequately tested in randomized controlled trials testing the effect of drugs on CV outcomes, observational data suggest that strict control of inflammation in RA by use of therapy that effectively decreases inflammation may favorably affect some CVD risk factors and may reduce the

development and progression of CVD [76]. These data are strongest for treatment with methotrexate (MTX) or TNF inhibitors.

1.4.1 Methotrexate

The drug MTX is the most commonly used DMARD medication recommended once the diagnosis of RA has been made. Systematic literature reviews suggest that the use of MTX in patients with RA is associated with a decrease in the risk of CVD. The reduction in CVD risk related to MTX use may appear early in the joint disease course [77]. Interestingly, a recently published CV Inflammation Reduction Trial (CIRT) evaluating whether control of inflammation by using low-dose MTX improves CVD outcomes in non-RA populations, showed that low-dose MTX does not reduce IL-1 β , IL-6, highly sensitive c-reactive protein (hsCRP), or CV events compared with placebo among patients with established CAD and either DM or metabolic syndrome or both [78]. Results of this clinical trial further showed that despite using a low dose, patients receiving MTX had a higher incidence of side effects such as transaminitis, leucopenia, anemia, and infections. There is a lack of such trials in RA populations to further demonstrate how MTX alters the risk of CVD in RA. Such a trial would not be possible in RA, as administering a placebo for sufficiently long periods of time to observe effects on CV events would not be ethical.

1.4.2 Biologic DMARDs

The safety of biologic DMARDs (bDMARDs) such as tumor necrosis factor inhibitors (TNF-i), interleukin-6 inhibitors, and targeted small molecules such as JAK inhibitors, has been investigated, yet, controversies exist regarding the impact of bDMARDs on the risk of CVD in patients with RA.

Systematic reviews have suggested that treatment with TNF-i is associated with a decreased risk of CVD [79]. It has also been reported that TNF-i may influence surrogate markers of CVD, such as aortic stiffness and carotid intima-media thickness (CIMT). In a study comparing 8,656 new users of a nbDMARDs with 11,587 users of a TNF-alpha inhibitor (with similar baseline characteristics), the incidence rates per 100 person-years for the composite CV end point were 3.05 (95% CI 2.54-3.65) for nbDMARDs and 2.52 (95% Ci 2.12-2.98) for TNF-alpha inhibitors. Although the risk reduction was consistent across myocardial infarction, stroke, and coronary revascularization, the reduced risk was most notable in the first 6 months and waned by 12 months [80]. Additionally, the apparent benefit was most substantial for patients 65 years or older. Responders to TNF-i seem to benefit the most with regard to CVD reduction [81].

1.4.3 Dyslipidemia and Statin Therapy

The relationship between chronic inflammation and lipid metabolism is complex and is incompletely understood. In RA, inflammation is associated with a paradoxical inversion of the usual relationship between CV risk and lipids. Relatively limited data is available concerning the efficacy and safety of statins in patients with RA. Lipid lowering with a statin can be an effective primary prevention for CVD in selected patients in the general population [82]. The AHA/ ASA guidelines for primary prevention of CVD in the general population includes consideration for treatment of patients with high-sensitivity CRP ≥ 2.0 mg/dl with a statin to decrease stroke risk [83]. However, at this time, there is insufficient data to support the systematic use of statins for primary CV prevention in patients in whom the only CV risk is the presence of RA (assuming an otherwise normal lipid profile). In the Trial of Atorvastatin in Rheumatoid Arthritis (TARA) randomized

trial, Atorvastatin therapy was associated with significantly greater reductions in LDL cholesterol levels (54 versus 3 mg/dl) and in markers of inflammation such as serum CRP, ESR, and indices of disease activity such as disease activity score (DAS)-28 [84]. Although the trial was not designed to assess cardiovascular outcomes, both the lipid-lowering and anti-inflammatory effects of statins could have important implications in decreasing CV risk. There is also evidence suggesting that intensive lipid lowering with Rosuvastatin induced carotid atherosclerotic regression and significantly reduced low-density lipoprotein cholesterol (LDL-c) in patients with inflammatory joint diseases [85]. RA is not considered as a condition necessitating lipid lowering as a primary prevention strategy for CVD, even though in a study of outpatients with RA, the magnitude of risk for CVD was found to be comparable with the risk associated with type 2 DM [86]. Therefore, some experts have proposed that the diagnosis of RA should be considered a risk equivalent when considering statin therapy.

1.4.4 Glucocorticoid Use

Glucocorticoids (GC) are commonly used in rheumatoid arthritis and other inflammatory arthritis to control inflammation. The therapeutic use of supraphysiologic doses of glucocorticoids may be associated with increased rates of CV events, including stroke and all-cause mortality [48, 87]. The increased CVD risk associated with GC is thought to be due to their detrimental effects on lipids, glucose tolerance, insulin resistance, blood pressure, and obesity [88]. CV risk has certainly been shown to be higher in patients treated with long-term high doses of GC compared to low doses of GC [48]. One study has shown that RF-positive but not RF-negative RA patients were at increased CV risk after GC exposure, suggesting that GC interact with RF status to modulate the effects on CV

risk [89]. Thus, both RA disease features as well as CV risk must be considered when evaluating the net benefit of GC in the treatment of RA. Only the EULAR guidelines have made clear recommendations to use the lowest possible dose of GC, preferably less than 7.5 mg/day. Additionally, EULAR also published recommendations on monitoring for complications of low-dose GC, including DM, hypertension, and body weight assessment as part of routine care for patients on low-dose GC [69].

1.4.5 Nonsteroidal Anti-Inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) and COX-2 inhibitors (Coxibs) are associated with an increased CV risk. All of the selective COX-2 inhibitors appear to have some potential cardiovascular risk, particularly due to the prothrombotic effects of these agents [90, 91]. Thus, these agents should be used with caution in patients with RA, especially in the subset of RA patients who have traditional CV risk factors in addition to the risk incurred by their inflammatory disease burden. The effect of non-selective NSAIDs on CV outcomes in patients with RA is not as clear. The optimal approach for use of NSAIDs in RA patients would include consideration of pre-existing CVD or CV risk factors and interaction with other medications. Naproxen seems to be the safest NSAIDs in terms of CVD risk [50]. In contrast, Lindhardsen et al reported that the CVD risk associated with NSAID use in RA patient was significantly lower than in non-RA individuals [92].

1.4.6 Aspirin and Anti-Thrombotic Treatment

Low-dose aspirin is a mainstay of secondary prevention in patients with established diagnoses of CVD including stroke, however, due to lack of reduction in CVD mortality, it is not recommended as primary prevention in RA patients [93]. Nonselective NSAIDs

may interfere with the beneficial effects of low-dose aspirin when used for prevention of CVD, and as such, the National Institute for Care and Clinical Excellence (NICE), and Australian guidelines recommended against the co-prescription of aspirin and NSAIDs (particularly nonselective ones), not only to avoid interference of the antiplatelet effects of aspirin but also to minimize the risk of gastrointestinal bleeding in RA patients [94].

1.4.7 Hydroxychloroquine

The use of hydroxychloroquine has been reported from several studies to have both a favorable glucose-and lipid lowering effect [95], but its influence on CVD risk and mortality remains unclear. Of note, hydroxychloroquine has been found to have a rare cardio-toxic effect in some patients and to be associated with an increased risk of cardiomyopathy [96].

1.5 Mortality Trends in RA and in RA Relative to the General Population

Since an early report in the NEJM in the 1950's, studies have consistently shown that RA is associated with an increased risk of mortality relative to the general population. With improvement in treatments of RA, one would expect the risk of excess mortality to have improved in more recent years. However, up until the mid-1990s there was no consistent evidence for a significant improvement in mortality in RA individuals from different RA populations' worldwide [1, 97, 98]. In a meta-analysis summarizing 11 longitudinal studies on RA mortality, an improvement in mortality in RA was observed over the past five decades. When comparing pooled incidence mortality rates (IMR) of RA populations with incidence in consecutive decades, the authors found a significant decrease in IMRs from 4.7/100 patients in studies of RA population with incidence before the 1970s to 2.0/100 patient-years in studies of RA population with RA incidence after 1983 (p

<0.01). However, no decrease in the standardized mortality ratios (SMR) was found (meta-SMR 2.01) when comparing the mortality rates to those of the general population, suggesting that the risk of mortality in RA remained elevated to the same extent compared to the general population [99]. However, this systematic review did not include RA samples diagnosed after the year 2000. There is a growing body of evidence that mortality in RA in people with RA onset in more recent years, i.e. after 2000 is declining . A declining mortality rate from 1996 to 2009 was reported in RA patients from a Canadian population with standardized mortality rates ranging from 13.0 deaths/1000 RA patients in 1996 to 9.2 deaths/1000 RA patients in 2009 [100]. More recent studies have reported not only an improvement in survival amongst RA samples of more vs less recent RA onset, but also in RA relative to the general population. Lacaille D., et al., in a population-based study of incident cases of RA have shown an improvement in the 5-year all-cause mortality, as well as CV mortality, in RA relative to the general population when comparing RA cohorts with onset in 2001-2006 vs 1996-2000. The authors observed a significant increase in mortality in RA versus controls before, but not after 2000 (all-cause mortality adjusted HR (95% CI): 1.40 (1.30 to 1.51) and 0.97 (0.89 to 1.05), respectively.[9]. Another study from Olmsted County Minnesota also found a significant improvement in the 10-year CV mortality, including coronary heart disease (CHD), in patients with incident RA with onset from 2000 to 2007 compared with the general population [10]. A more recently published study has also shown that patients with rheumatoid arthritis incidence after 1990 did not have excess AMI mortality compared with the general population . After adjustment for age, sex, race, and disease duration, the risk of AMI mortality declined in successive

incidence years (relative risk, 0.94; 95% CI, 0.92 to 0.96). Declines in mortality trends were observed in successive birth cohorts as well in this particular study [101]

1.8 Overview of thesis studies

This improvement in survival is concordant with the paradigm shift in treatment and management of RA with emphasis on early diagnosis approach and advent of new therapeutic agents such as synthetic and biological DMARDs. We hypothesized that this improvement in mortality in RA could be due to improvement in incident risk of CV events in RA relative to the general population as a result of enhanced awareness of the leading role of CVD in premature death in RA and potentially better management of CV events in RA.

1.8.1 Specific objectives for thesis

1. In chapter 2, we aimed to assess secular trends in 10-year risk of incident fatal and non-fatal AMI in RA relative to the general population.
2. In Chapter 3, we aimed to assess secular trends in 10-year risk of incident fatal and nonfatal CVA in RA relative to the general population.

Chapter 2: Secular trend in 10-year risk of incident acute myocardial infarction in RA relative to the general population

2.1 Introduction

Cardiovascular diseases (CVD), in particular coronary artery diseases (CAD), including acute myocardial infarction (AMI), are documented as main drivers of premature mortality in patients with rheumatoid arthritis [7]. Avina-Zubieta A.J., et al., in a meta-analysis of observational studies have reported a 68% increase in incidence of fatal and non-fatal MI events, with a significant increase observed in both women [pooled RR (95% CI): 1.93 (1.64, 2.27)] and men [pooled RR (95% CI): 1.67 (1.18, 2.36)] [102]. Another meta-analysis by the same authors reported a 59% increase in risk of death from ischemic heart disease (IHD) in patients with RA compared to the general population [32].

There is evidence that traditional cardiovascular (CV) risk factors such as hypertension, diabetes, dyslipidemia, smoking, and obesity do not fully explain the risk of MI in RA, and the rheumatic disease itself contributes to the risk of CV events, with chronic inflammation as the link between RA and atherosclerosis [35, 72, 103]. Studies have also shown that glucocorticoids are associated with increased risk of MI in RA [48, 87, 88].

Recent studies have been suggesting improvement over time in CV mortality in RA patients with RA onset in recent years, and in RA relative to the general population. Lacaille D., et al. in a population-based incident RA cohort, have found a declining trend in 5-year all-cause mortality, and CV mortality, in RA relative to general population controls in patients with disease onset in 2001-2006 compared to 1996-2000 [9]. Zhang Y., and colleagues, have also shown an improvement in all-cause mortality in RA relative to the general population in patients with RA onset in 2007-2014 compared to 1996-2006

[104]. A population-based study from Rochester, USA found that patients with RA incidence in 2000-07 had lower 10-year overall CV mortality and coronary heart disease (CHD) mortality than RA patients diagnosed in 1990-99 [10]. Eswar K., et al. have also shown a declining trend in AMI mortality in RA patients with RA onset after 1980 compared to RA patients with RA onset between 1970 and 1980, and RA patients with RA onset before 1970 [101].

We speculate that this improvement in mortality could potentially be due to improvement in risk of incident CV events over time, since they are the leading cause of excess deaths in RA [32, 105]. Our objective was to assess the secular trend in 10-year risk of incident AMI in incident RA (cohorts with onset from 1997 to 2004) relative to the general population.

2.2 Methods

2.2.1 Study Design

We conducted a retrospective study of a population-based cohort of all incident cases of RA in British Columbia (BC) with RA onset between 01/01/1997 and 31/12/2004, followed until 31/12/2014, with matched general population controls, using administrative health data.

2.2.2 BC Cohort Definition and Study Sample

Incident RA Cohort. We identified all incident cases of RA in BC who first met previously published RA criteria [106] between January 1997 and December 2004, using physician billing data from 01-1990 onwards, from the Ministry of Health in a universal health care system. To ensure prevalent cases of RA who moved to BC were not erroneously identified as incident RA cases, we excluded RA individuals if they had less

than seven years of available data prior to their first RA visit. Individuals were identified as RA if they had at least two physician visits, at least two months apart, within a 5-year period, with International Classification Disease Codes version 9th for RA (ICD-9: 714.x.). Individuals were excluded, if over a five-year period after their second RA visit (i.e. index date), they had at least two subsequent visits, on two different days, with the same ICD code for other forms of inflammatory arthritis [Systemic Lupus Erythematosus (SLE), and other connective tissue diseases, Psoriatic Arthritis, Ankylosing Spondylitis and other Spondyloarthropathies (*appendix A*)]; or if a patient saw a rheumatologist and the diagnosis of RA by a non-rheumatologist was never confirmed by the rheumatologist. These criteria have been validated in a sub-sample who participated in a RA survey, using impression of an independent rheumatologist reviewing medical records from their treating physician as a gold standard, yielding a positive predictive value (PPV) of 0.82 [107].

General Population Cohort. Controls were randomly selected from the general population with no physician visits for any type of inflammatory arthritis, using the same administrative databases as for the RA cohort. All eligible controls were matched to RA patients on age and sex and were assigned the date of RA incidence (i.e. first RA visit) and index date (i.e. second RA visit) of the RA case they were matched to. Individuals were excluded if they had less than 7 years of available data prior to the date of incidence. Controls were then randomly selected from eligible controls for each RA individual in a 2:1 ratio.

Study Subjects. To measure risk of incident AMI, Individuals were excluded if they had a prior diagnosis of MI (i.e. old MI or AMI) based on MI diagnoses codes [old MI ICD9/ICD10 codes: 412/I25.2; AMI ICD9/ICD10 codes: 410/I21] in hospitalization

data of 25 diagnostic codes, in any position, or in physician visits using a fixed period of 7 years prior to index date for all individuals, rather than over all available data since 1990. We equalized the lead-in period to prevent including more recurrent AMIs in earlier years of incidence (due to shorter periods of exclusion to identify prior AMI), which would potentially overestimate the risk of AMI in RA patients with RA incidence in earlier years relative to later years. This is important because having a prior AMI increases the risk of recurrent AMI.

RA individuals and general population controls were divided into incidence cohorts according to the year of RA incidence, defined based on the first RA visit.

2.2.3 Data Collection

Data for the RA cohort and general population controls were obtained from administrative databases of the Ministry of Health, through Population Data BC, on all provincially funded health care services. These include data on basic demographics such as age and sex, geo-codes indicating location of residence, and registration data from consolidation file based on the Medical Service Plane (MSP) registration and premium billing (R&PB) [108]; on all physician visits, with one diagnostic code per visit representing the reason for the visit, from the Medical Service Plan (MSP) database [109]; all hospitalizations from Discharge Abstract Database (DAD), which include up to 25 diagnostic codes per hospitalization representing either the primary reason for admission or complications during hospitalization [110]. Data from MSP and DAD were obtained from January 1990 to December 2014. The PharmaNet database [111] provided information on all prescriptions dispensed by pharmacies in BC from January 1996 to December 2014, on all individuals, regardless of source of funding. Information on death

and primary cause of death was derived from death certificates using Vital Statistics Data from January 1996 to December 2014 [112].

2.2.4 Outcome Assessment

The outcome of interest was the 10-year risk of incident MI, defined as the first AMI event occurring over ten years of follow-up, with the 10-year mark calculated from RA onset (first RA visit), but follow-up starting from index date. AMI events were identified using diagnostic codes (ICD-9/ICD-10 Codes: 410/I21) in hospitalization data in any position, or in vital statistics data as cause of deaths, to ensure capture of fatal events without hospitalization, including out-of-hospital deaths. A previous validation study in Canada evaluating the validity of administrative data to identify MI has found that sensitivity and specificity of hospitalization data for identifying MI in most $\geq 50\%$ studies was $\geq 86\%$, and PPV in most studies was $\geq 93\%$. Authors of the same study further reported that accuracy of hospitalization data is higher than accuracy of identifying MI as a cause of death on death certificates [113].

2.2.5 Assessment of Covariates

Information on sociodemographic characteristics, health care resource utilization, comorbidities and medications known to influence the risk of AMI, were selected a priori, and measured either at RA onset (i.e. first RA visit), or over one year prior to RA onset.

Sociodemographic. Information on age, sex, regional health authorities in BC (i.e. Interior, Fraser, Vancouver Coastal, Vancouver Island, Northern) based on MSP registration and premium billing data; and markers of socioeconomic status (neighborhood income quintile calculated by Population Data BC based on postal code and census data

for the area) and geography (rural vs. urban, based on postal code second digit] were measured at RA onset.

Health Care Resource. Information on the number of yearly physician visits, hospitalization events (as a binary variable: Yes/No), and length of stay in hospital, were measured over one year prior to RA onset.

Comorbidities. Pre-existing comorbidities over one year prior to RA onset [i.e. angina, chronic obstructive pulmonary disease (COPD), obesity, atrial fibrillation (AF)], were defined using one hospitalization or physician visit with their respective ICD codes (*appendix B*); diabetes mellitus (DM) and hyperlipidemia, were defined based on medication use (i.e. insulin or oral hypoglycemic, and statin or fibrates, respectively).

Medications. Medications were defined as used (yes/no) over one year prior to RA onset and included glucocorticoids (GC), hormone replacement therapy, anticoagulants, traditional non-steroidal inflammatory drugs (NSAIDs), selective cyclooxygenase 2 (COX-2) inhibitors, contraceptives, and CV drugs (antihypertensive, Beta-blockers, cardiac glycosides, diuretics, antiarrhythmic, nitrates).

Charlson Comorbidity Score. Additionally, to control for overall comorbidity burden, a modified Romano modification of the Charlson comorbidity score for administrative data (with RA excluded from comorbidities) one year prior to RA onset, was calculated [114-116].

2.2.6 Statistical Analysis

Descriptive analyses (i.e. mean, median, standard deviation, and proportions) were performed. Bivariate analyses, as appropriate (i.e. two-sample t-test or Wilcoxon-Mann-Whitney Test for continuous variables, and chi-square or Fisher exact test for categorical

variables) were conducted, to compare baseline characteristics between RA and the general population.

To avoid immortal time bias, we used delayed entry models in our analysis [117]. The risk of developing CV events increases with increasing RA duration. Therefore, RA individuals who have a longer time between RA onset (i.e. first RA visit) and index date (i.e. second RA visit) would be more likely to develop AMI. To avoid inducing this bias, time for calculating the 10-year risk period was counted at RA onset. However, to avoid immortal time bias [118], RA individuals and general population controls contributed to person years (PYs) of follow-up, from index date, which is when they met criteria for inclusion in our cohort and they became at risk of developing the outcome of interest. Censoring was done at ten years from RA onset, or last health care utilization due to death or migration, whichever occurred first

Crude 10-year incident rates (IRs) of AMI per 1000 PYs of follow-up, with 95% confidence intervals (CI) were calculated for each incident RA and general population cohort, according to the calendar year of incidence. Subsequently, the crude 10-year incidence rate ratio (with 95% CI) was calculated for each cohort, by dividing the IR of AMI in RA by the IR in the general population.

To estimate secular trends in 10-year risk of AMI in RA relative to the general population, we used multivariable Cox proportional hazard models[119], while controlling for potential confounders. The strategy for adjustment was defined a priori. Models were initially adjusted for age and sex, then additionally for sociodemographic factors, pre-existing comorbidities, and medications. Furthermore, we used stepwise selection method, a modification of forward selection and backward elimination [120] for which variables

entered the model if they were significant at the level of 0.25 and they were removed if they were not significant at the level 0.10. To test if secular trend in risk of incident AMI in RA differed from secular trend in the general population, an interaction term between the indicator of RA vs. general population (i.e. 0 indicating general population, 1 indicating RA) and, year of incidence was tested in the Cox PH models.

To determine whether the change in risk of incident AMI over time followed a linear trend, we compared Cox regressions with linear, quadratic and a flexible spline functions of incident year effects. The model with the lowest Akaike Information Criterion (AIC) [121], best fitting the AMI events was selected to interpret the data.

A spline regression is a non-parametric method that allows for different linear functions of time corresponding to pre-and-post critical time point (also called a knot) [122]. A Cox model with spline regression hazard function was fit to allow for more flexible modeling of possible changes in AMI incidence across the years of incidence, compared to conventional parametric (i.e. linear or quadratic) functions. We used data-driven stepwise selection approaches to select the numbers and locations of the knot(s) [123]. The procedure selected one knot at the incidence year 1999. This was consistent with graphical representations of calculated crude IRs per calendar years of incidence in our cohorts (*Figure 2.3*), and with shifts in RA treatment and that could possibly influence occurrence of CVD in RA.

2.2.7 Ethics

The study received ethics approval from the University of British Columbia's Behavioral Research Ethics Board. The Ministry of Health provided the linkage for their

databases, no personal identifying information was provided to the investigators, and all procedures were compliant with BC's Freedom of Information and Privacy Protection Act.

2.3 Results

The sample included 23,237 RA individuals (66.4% women; mean [SD] age 58 [16.88] years) and 46,474 matched general population controls. Flow diagram of RA individuals included in the study is displayed in *Figure 2.1*.

Mean [SD] years of follow-up were 8.95 [2.29] years in the RA cohort and 8.92 [2.37] years in the general population. A total of 1,133 and 1,606 incident AMI events were observed in RA and in controls, respectively; of which 60 in RA, and 13 in the general population, were fatal events identified through death certificates.

Baseline characteristic of the RA and the general population cohorts are described in *Table 2.1*. RA individuals were more likely to have income in lower quintiles and to use health care resources, reside in rural areas, and were less likely to receive health care services from Vancouver Coastal Regional Health Authority. We observed a statistically significant difference in all pre-existing comorbidities and use of all medications evaluated except for contraceptive use, between RA and general population. However, clinically meaningful differences were only observed for prior hypertension; use of CVD medications, cox2 inhibitors, glucocorticoids, traditional NSAIDs, and hormone replacement therapy .

The mean time between first RA visit and the index date, for each RA cohort according to the calendar years of incidence is shown in *Figure 2.2*. Mean duration of RA was slightly shorter in later years of incidence and was less than a year after 2001.

Crude 10-year incident rates of AMI per 1000 PYs in RA and general population cohorts are shown in *Table 2.2*. In RA cohorts, the crude 10-year incidence (95% CI) of AMI decreased from 6.06 events per 1000 PYs (5.16, 7.05) in 1997 to 4.42 (3.68, 5.26) in 2004, with some fluctuations observed over time. There was an unexplained peak in incidence in 1999 [7.11 per 1000 PY (6.11, 8.2)], with a subsequent decline to 4.94 (4.13, 5.84) in 2000 (*Figure 2.3*). In general population cohorts, the crude 10-year AMI incidence declined over time, from 4.80 (4.22, 5.42) in 1997 to 2.88 (2.45, 3.36) in 2004, following a linear trend. The graphical representation of crude AMI incidence rates in RA and general population cohorts is provided in *Figure 2.3*.

Cox regression models with linear, quadratic, and spline (with a knot at year 1999) functions of incidence year effects were compared. The Cox proportional hazard (PH) model with the lowest AIC, best fitting the incident AMI events was selected (*Table 2.3*).

Results of the unadjusted and adjusted analyses assessing the secular trend in 10-year risk of AMI in incident RA cohorts relative to the general population, using Cox PH model are shown in *Table 4*. We observed a significant decline in risk of AMI over calendar years of incidence in both the RA cohorts [aHR per year of incidence (95% CI) 0.94 (0.91, 0.97) $p = <0.0001$] and general population cohorts [0.93 (0.91, 0.95); $p = <0.0001$]. The temporal trend showing a declining risk over time was not significantly different in RA relative to the general population, when the interaction term was tested in the model [1.01 (0.98, 1.05); $p = 0.498$].

According to the multivariable cox PH model (*Appendix B*.), men had an increased risk of AMI compared to women; whereas individuals in higher income quintiles and individuals living in regional health authorities of Vancouver coastal and Vancouver Island

(compared to interior regional health authority) were at lower risk of AMI. Pre-existing comorbidities associated with an increased risk of AMI included: COPD, Diabetes, hyperlipidemia, and cardiovascular diseases as reflected by use of CV medications. Use of glucocorticoids at baseline was also associated with increased AMI risk.

Figure 2-1. Flow diagram of RA individuals and general population controls included in the AMI Analysis

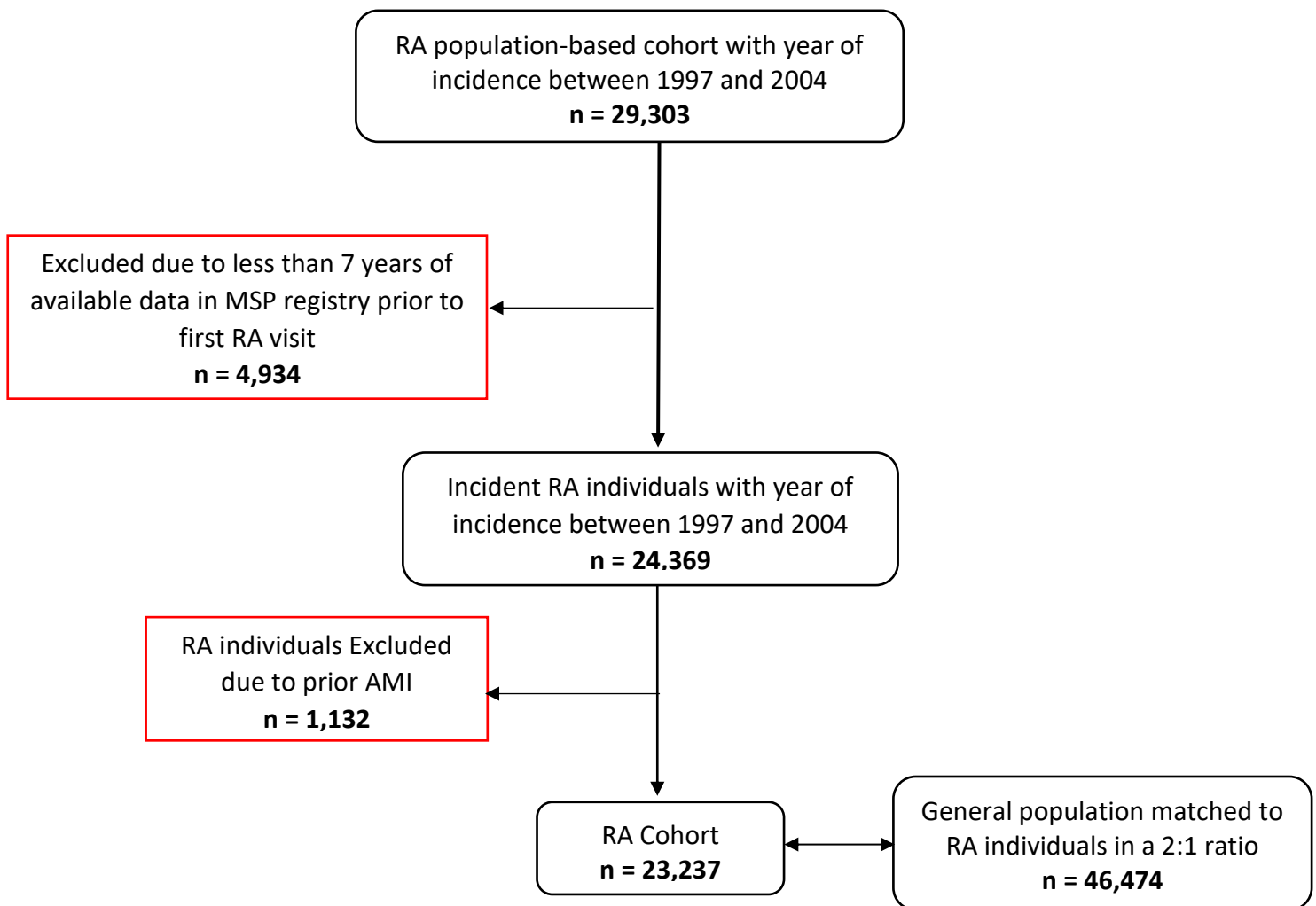


Table 2-1. Baseline characteristics of incident RA and general population

Baseline Characteristics	General Population (n = 46,474)	RA (n = 23,237)	p-value		
Demographics *					
Women	30,842 (66.4)	15, 421 (66.4)	1		
Mean Age (Yrs.)	58.00 (16.88)	58.00 (16.88)	1		
Mean Follow-up (Yrs.)	8.92 (2.37)	8.95 (2.29)	0.064		
Rural vs. Urban #	6392 (13.8)	4322 (18.6)	<0.001		
Neighborhood Income Quintile ‡ 1 (Lowest) 2 3 4 5 (Highest) unknown	8757 (18.8) 8576 (18.5) 8636 (18.6) 8733 (18.8) 9169 (19.7) 2603 (5.6)	5034 (21.7) 4655 (20.0) 4361 (18.8) 4281 (18.4) 4018 (17.3) 888 (3.8)	<0.001		
Regional Health Authority Interior Fraser Vancouver Coastal Vancouver Island Northern unknown	8372 (18.0) 14235 (30.6) 11042 (23.8) 8733 (18.8) 2857 (6.1) 1235 (2.7)	5112 (22.0) 6918 (29.8) 4386 (18.9) 4839 (20.8) 1891 (8.1) 91 (0.4)		<0.001	
Health Care Utilization Ω					
Median Physician Visits	13.0	28.0			<0.001
Mean Length of Stay at Hosp., days	7.10 (38.61)	54.57 (92.42)			<0.001
Prior Hospitalizations, yes	6222 (13.4)	3840 (16.5)			<0.001
Comorbidities Ω					
Charlson index ¥	0.29 (0.82)	0.42 (0.92)	<0.001		
Obesity	415 (0.9)	299 (1.3)	<0.001		
Alcoholism	256 (0.6)	379 (1.7)	<0.001		
Hypertension	8305 (17.9)	5288 (23.0)	<0.001		
COPD	823 (1.8)	686 (3.0)	<0.001		
Angina	1163 (2.5)	876 (3.8)	<0.001		
Atrial fibrillation	296 (0.6)	190 (0.8)	0.005		
Diabetes	2178 (4.7)	1160 (5.3)	<0.001		
Medications Ω					
Anticoagulation	908 (2.0)	582 (2.7)	<0.001		
CVD Medications §	10688 (23.0)	7005 (32.2)	<0.001		
Fibrates	337 (0.7)	215 (1.0)	<0.001		
Statin	3374 (7.3)	1951 (9.0)	<0.001		
Hormone Replacement Therapy	4126 (8.9)	2834 (13.0)	<0.001		
Traditional NSAIDs	5469 (11.8)	10260 (47.2)	<0.001		
COX2 Inhibitors	1313 (2.8)	3516 (16.2)	<0.001		
Contraceptives	1299 (2.8)	621 (2.9)	0.672		

Glucocorticoids	1207 (2.6)	3281 (15.1)	<0.001
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Values represent number (%) unless where indicated, values represent mean (SD).

* Measured at RA onset (i.e. first RA visit)

Ω Measured over one year prior to RA onset

Rural vs. Urban: where a zero '0' in the second position of the postal code indicates a rural area;

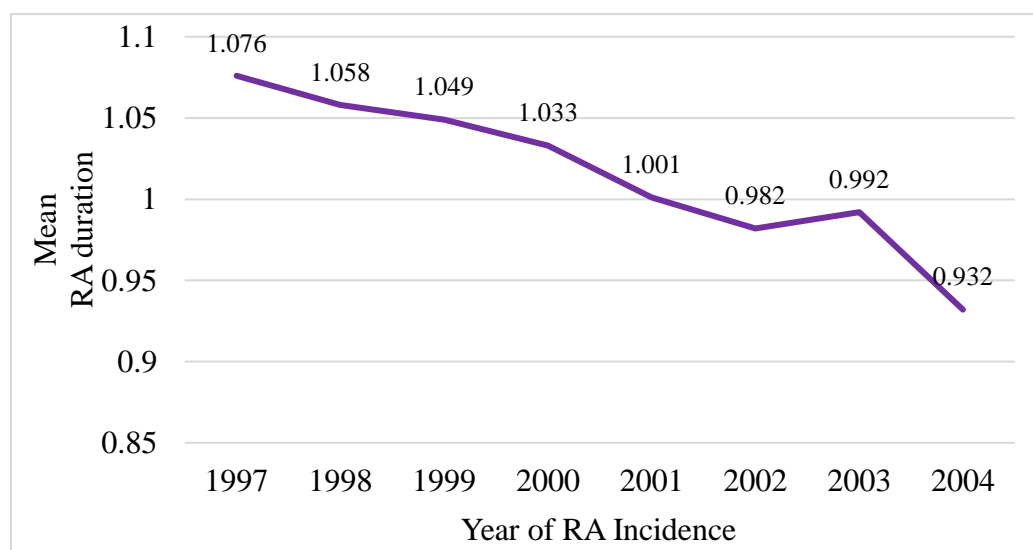
* Income quintile is a measure of neighborhood socioeconomic status derived from postal code that divides the population into 5 income groups (from lowest income to highest income);

¥ Romano Charlson refers to Romano adaptation of the Charlson co-morbidity score developed for use with administrative health data, excluding RA as a comorbidity;

§ CVD Medications: antihypertensive, Beta-blockers, cardiac glycosides, diuretics, antiarrhythmic, nitrates;

Abbreviations: RA: rheumatoid arthritis; Yrs: years; Numb: number; Hosp: hospitalization; COPD: chronic obstructive pulmonary disease; CVD: cardiovascular disease; NSAIDs: traditional non-steroidal inflammatory drugs; cox2: cyclooxygenase 2 (selective COX-2) inhibitors;

Figure 2-2. Mean RA duration at index date for each incident RA cohort (according to the year of RA incidence)



RA duration in years was calculated as time from first RA visit to index date (i.e. second RA visit)

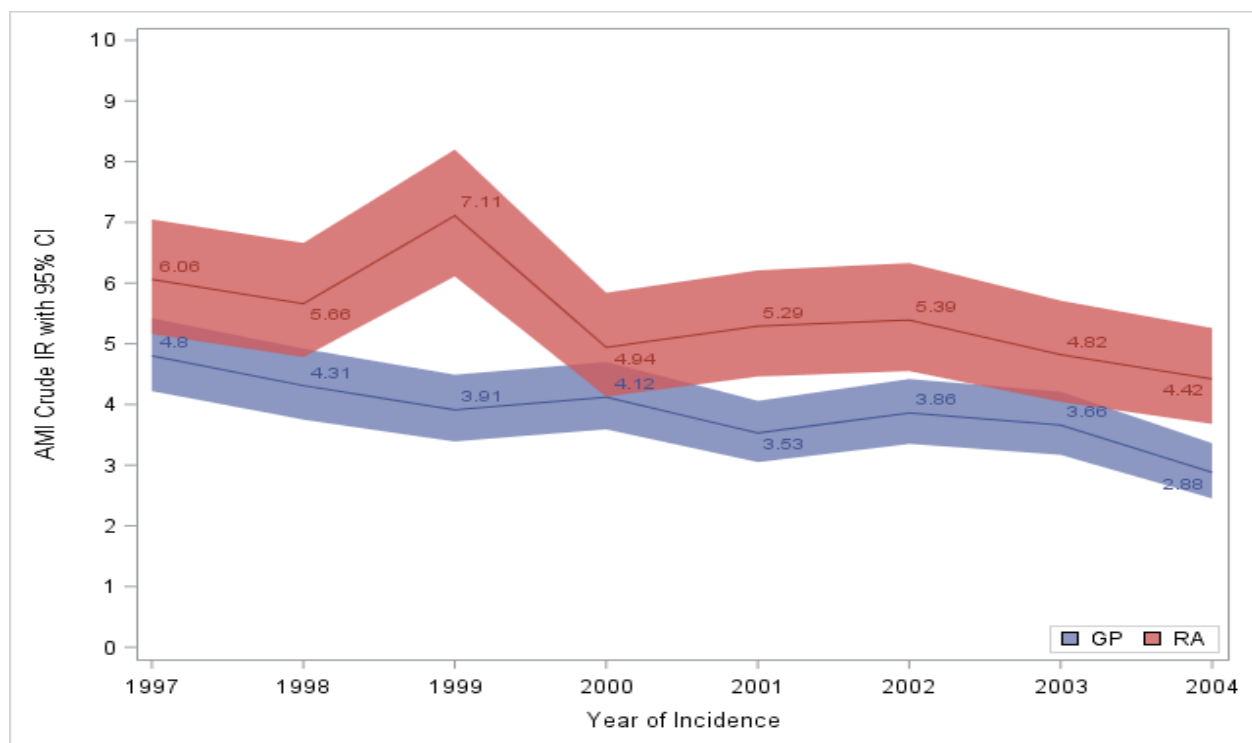
Abbreviations: RA: rheumatoid arthritis

Table 2-2. Crude 10-year incident rates of AMI per 1000 PYs in RA cohort and general population

RA Cohort					General Population				Crude IRRs (95% CI)
Cohort Year of Incidence	N	AMI	PYs	Crude IRs (95%CI)	N	AMI	PYs	Crude IRs (95%CI)	
1997	2934	158	26073	6.06 (5.16, 7.05)	5868	248	51696	4.80 (4.22, 5.42)	1.26 (1.03, 1.54)
1998	2741	140	24715	5.66 (4.78, 6.66)	5482	211	48983	4.31 (3.75, 4.92)	1.31 (1.06, 1.63)
1999	2827	178	25049	7.11 (6.11, 8.2)	5654	196	50080	3.91 (3.39, 4.49)	1.82 (1.48, 2.22)
2000	2907	129	26128	4.94 (4.13, 5.84)	5814	214	51926	4.12 (3.59, 4.7)	1.20 (0.96, 1.49)
2001	2951	140	26470	5.29 (4.46, 6.21)	5902	187	52968	3.53 (3.05, 4.06)	1.50 (1.20, 1.86)
2002	2917	140	25969	5.39 (4.55, 6.33)	5834	201	52099	3.86 (3.35, 4.42)	1.40 (1.12, 1.73)
2003	2954	128	26534	4.82 (4.04, 5.71)	5908	193	52662	3.66 (3.17, 4.21)	1.32 (1.05, 1.64)
2004	3006	120	27146	4.42 (3.68, 5.26)	6012	156	54139	2.88 (2.45, 3.36)	1.53 (1.21, 1.94)

Abbreviations: RA: rheumatoid arthritis; N: Number of individuals; AMI: acute myocardial infarction; PYs: Person-years of follow-up; IRs: incident rates; IRRs: incident rate ratios; CI: confidence interval

Figure 2-3. Crude 10-year risk of AMI according to year of incidence (1997-2004) in RA and general population cohorts



Abbreviations: AMI: acute myocardial infarction; IR: incident rate; CI: confidence interval; GP: general population; RA: rheumatoid arthritis

Table 2-3. Comparison of Cox regressions with linear, quadratic, and spline forms of year of incidence

Cox Regressions	Model AIC (Unadj.)	Model AIC (Adj.)
Linear Model	59871.65	56480.31
Quadratic Model	59874.62	56484.95
Linear Spline Model	59872.91	56483.56

Abbreviations: Unadj: Unadjusted; Adj: Adjusted according to stepwise selection technique; AIC: Akaike information criterion

Table 2-4. Secular trend in 10-year risk of incident AMI in incident RA cohorts relative to the general population

Secular Trends in 10-year risk of AMI	Unadj. HR (95% CI)	P-value	§Adj. HR (95% CI)	p-value
10-year risk in RA*	0.95 (0.93, 0.98)	0.0002	0.94 (0.92, 0.97)	<.0001
10-year risk in general population**	0.95 (0.93, 0.97)	<.0001	0.93 (0.91, 0.95)	<.0001
Secular Trend in RA relative to the General Population***	1.01 (0.98, 1.04)	0.5914	1.01 (0.98, 1.05)	0.498

§ covariates included in the final multivariable model include: age (mean years); sex; income quantile; health care authority; rural vs. urban; number of physician visits; length of stay at the hospital (days); angina; COPD; alcoholism; CV medications; diabetes; fibrates; statins; cox2 inhibitors; glucocorticoids

*HR represents the change in AMI risk in the RA population per calendar years of incidence.

** HR represents the change in AMI risk in the general population per calendar years corresponding to the RA year of incidence.

*** HRs represent the HR for the interaction term between indicator of RA vs. general population and years of incidence.

Abbreviations: RA: rheumatoid arthritis; GP: general population; Unadj. HR: unadjusted hazard ratio; Adj. HR: adjusted hazard ratio; CI: confidence interval

2.4 Discussion

We conducted a retrospective population-based study of incident RA cohorts with RA onset from 1997 to 2004, with matched general population controls, using administrative health data in a universal health care system, to assess the secular trend in risk of incident AMI in RA relative to the general population.

A significant decline in the 10-year risk of AMI was observed over time in RA cohort of more recent incidence and in general population controls. The decline in the AMI risk did not differ in RA relative to the general population.

Few studies have evaluated temporal trends in incidence of AMI in RA relative to the general population. A Swedish study observed that the increased risk of incident CVD, which consisted primarily of CAD, in RA relative to the general population, was similar for patients with RA onset in 1978 and in 1995 [98]. Consistent with our findings, Holmqvist et al., in a population-based study of RA patients with RA onset between 1997 and 2014, found a decline in incidence of acute coronary syndrome (ACS) in RA and in the general population with increasing calendar years of RA onset, however, the excess risk of ACS in RA relative to the general population remained the same [124].

Two studies, published only in abstract forms to date, have also assessed temporal trends in the incidence of CVD in RA with RA onset in more recent years. In contrast to our results, a study in Spain, using national hospitalization data, found a 5% increase in annual incidence of MI among prevalent cases of RA who were admitted to hospital between 1999 and 2015 [125]. A number of methodological differences between the studies may explain the difference in findings. Their study sample included prevalent RA cases who may have had onset of their disease much prior to 1999 when treatment

paradigms for RA differed; the temporal trend evaluated over years 1999 to 2015 represented the time when the MI outcomes were measured, whereas in our study the years 1999 to 2004 represent the year of RA incidence and the MI risk was assessed over 10 years after RA incidence. Their study also did not include general population controls. Furthermore, their cohort identified RA cases who had been hospitalized, who likely have more severe disease or more comorbidities, and therefore may have a greater risk of MI.

Results of a population-based study of Olmsted County, USA, are concordant with ours, showing that individuals with incident RA in the years 2000-09 had a lower cumulative incidence of CVD events compared with RA individuals with incidence in the 1980's and 1990's. Authors found a significantly lower 10-year risk of CVD events in patients with incident RA in the 2000's compared to incident RA in 1980's [HR (95% CI): 0.52 (0.32-0.86)]; the difference between RA patients diagnosed in the 2000's compared to 1990's did not reach statistical significance [0.65 (0.40-1.05)]. Furthermore, they did not observe excess incidence of CVD events in incident RA patients diagnosed in the 2000's compared to subjects without RA [0.88 (0.53, 1.46)]. They have reported that their results remained similar when they examined MI separately [126]. However, the sample size of their cohort was small (total number of RA individuals = 906) and few cardiovascular events were observed (i.e. 31, 38, 31 cardiovascular events, in RA patients diagnosed in the 80's 90' and 2000's, respectively, over a median follow-up of 10.6, 10.4, and 10.2 years, respectively)

We had anticipated to observe an improvement in the excess risk of AMI in RA relative to the general population due lower levels of inflammations in RA in recent years from the adoption of more aggressive treatment strategies, including treat-to-target aimed

at achieving remission, or low disease activity [127] as well as with the advent of more effective RA therapies, such as biologic agents. However, this was not observed, despite evidence suggesting that RA patients may be experiencing milder disease in recent years. For example, a Norwegian study found that baseline RA disease activity levels at the time of starting methotrexate (MTX) and TNFi+MTX have decreased from high to moderate from 2000-2010, with more than a twofold increase in 6-month remission rates in both groups [128]. The reason for the lack of improvement in the excess risk of MI relative to the general population, in patients with more recent RA onset, is not clear. It is possible that the improvements in RA inflammation achieved in recent years are not sufficient to reduce the excess risk of MI. It could also be due to the population-based nature of our sample and to the fact that a significant portion of the RA population are not receiving treatment according to the treat-to-target approach, and/or the targeted remission or low disease activity states are not achieved. This hypothesis is supported by quality of care studies showing that clinical practice lags behind evidence and that when care is evaluated at the population level, a large proportion of patients are not receiving care as recommended [129, 130]. Inadequate management of comorbidities that are risk factors for MI, such as diabetes, hypertension, hyperlipidemia; or different patterns of change over time in traditional risk factors for MI in RA compared to the general population, are other factors potentially explaining why the difference in risk between RA and the general population remained the same over time.

The overall improvement in MI over time observed in RA and in the general population could be due to more efficient management of modifiable CV risk factors in recent years. It is also in line with the general population literature. Yeh W., et al., in a

large community-based population study, found a significant decrease in incidence of MI between 1999 and 2008 [131]. The Canadian Chronic Disease Surveillance system (CCDSS) has also reported that the age-standardized incidence rate of AMI declined from 3.0 per 1000 in 2000-2001 to 2.2 per 1000 in 2012-2013. Improvements in risk factors, namely decrease in lipids, systolic blood pressure, and smoking; treatments, including medications (i.e. use of aspirin, antihypertensive, cholesterol-lowering medications), improvement in cardiac care, and use of surgical treatment, mainly coronary artery bypass surgery, have been held responsible for the reduction in ischemic heart disease events over time [132].

It is important to note that the incidence rates observed in our general population controls do not necessarily reflect rates observed in the BC general population, given that the age and sex distribution of our controls matched those of our RA sample and are therefore, not representative of the entire general population.

Strengths: The strengths of this analysis include the population-based nature of our cohorts with capture of all RA individuals in BC treated in recent years (1997-2014); the large sample size (over 20 thousand incident cases of RA and twice as many in general population) with a large number of events (1,133 AMI in RA and 1,606 in the general population); and, the long follow-up of 10 years.

Limitation: The limitations of the study are those inherent to observational studies and studies using administrative data. Misclassification of RA diagnosis (e.g. atypical RA patients might be less likely to be coded as an RA diagnosis) or uncertainty around RA diagnosis identified using administrative data is possible. However, we used previously published criteria that were previously validated in a subsample who participated in a RA

survey, with a positive predictive value of 0.82. Unmeasured confounding resulting from lack of information on known (e.g. smoking) or unknown risk factors cannot be completely excluded. For these to influence the difference in secular trends, they would have to change differentially across calendar years of incidence in RA and in the general population.

To avoid misclassification of prevalent cases of RA moving to BC during the study period as incident cases, we excluded from the incident cohort RA cases and general population controls with MSP enrollment less than 7 years prior to the date of their first RA visit. It is however possible that our incident cohort includes prevalent cases who had an RA visit more than 7 years prior to the first RA visit captured in our data. However, consecutive visits more than 7 years apart is very infrequent in our cohort. In a previously published study using the same rule to define incident RA cases, we have shown that only 0.44% of the periods between consecutive RA visits were more than 6 years and 94.3% were < 1 year and 97.3% were < 2 years [133].

We also did not have information in administrative data on onset of RA clinical symptoms (therefore RA onset was defined as first RA visit). We also did not have information on RA disease severity, which may have helped us understand why we did not observe an improvement over time in the excess risk of AMI in RA relative to the general population.

Conclusion

In conclusion, we observed a significant decline over time in the risk of incident AMI over more recent calendar years of incidence, in RA and the general population. The decline in incidence of AMI did not differ in RA compared to the general population. This suggests that despite recommended changes in treatment strategies aiming at early

treatment and eradication of inflammation, little progress has been made in reducing the excess risk of MI relative to the general population. It may be that a more personalized treatment approach is needed, tailored to patients' need and perhaps identifying subgroups of patients at higher risk of MI who may require a different treatment approach that would potentially reduce the risk of AMI occurrence. It is also important to consider adequate management of other comorbidities in RA associated with an increased risk of MI and ensure that they are adequately screened and managed as part of the cardiovascular disease prevention care in RA.

Chapter 3: Secular trends in ten-year risk of incident cerebrovascular accidents in rheumatoid arthritis relative to the general population

3.1 Introduction

Cerebrovascular accidents (CVA) are a major health concern worldwide. In 2016, stroke accounted for 5.5 million deaths and 116.4 million disability-adjusted life-years (DALYs) [134, 135].

Rheumatoid arthritis has been shown to be associated with increased risk of CVA incidence and mortality. A meta-analysis of observational studies reported a 41% increase in incidence of fatal and non-fatal CVA events, with significant increase in both women [pooled RR (95% CI): 1.29 (1.12, 1.48)] and men [pooled RR (95% CI): 1.36 (1.21, 1.53)][102]. In another systematic review, Avina-Zubieta A.J., et al., found that mortality from CVA was increased by 52% in RA compared to the general population [32]. A more recently published meta-analysis has also shown that RA increases risk of ischemic stroke by 64%, with excessive relative risk in those aged < 50, compared to the general population [136].

In addition to traditional cardiovascular risk factors, namely hypertension, diabetes, obesity, and hyperlipidemia, chronic inflammation caused by RA leads to atherosclerosis, and is considered an independent risk factor for cardiovascular diseases (CVDs), including stroke [71, 73, 75]. It has been shown that endothelial function as a result of inflammation is impaired in systemic autoimmune diseases such as RA, which plays a key role in predisposing RA patients to accelerated atherosclerosis [74]. Some RA medications such as glucocorticoids are also reported to mediate increase risk of cardiovascular events such as myocardial infarction (MI) [48] or stroke [87, 137]. Y.

Chen Y and colleagues, in a case-crossover study have shown that nonselective non-steroidal anti-inflammatory drugs (NSAIDs) were also associated with increased risk of stroke [adjusted OR (95% CI) 1.39 (1.25 to 1.55)] in patients with rheumatoid arthritis [138]. Furthermore, RA can involve the heart valve structures and lead to atrial fibrillation, which are known risk factors for strokes [139].

Increased awareness of elevated risk of CVDs, including risk of ischemic stroke in RA has led to preventive strategies or evidence-based practice recommendations for managing CVD risk in RA in recent years. Some of these strategies include RA disease-centric approaches, assessment of comprehensive individual risk via risk scores, and management of traditional CVD risk factors [140]. Additionally, recent evidence has shown an improvement over time in all-cause mortality, and cardiovascular mortality in RA cohorts of more recent RA onset compared to historical controls [9, 10, 141].

This improvement in mortality could be due to improvement in incidence of cardiovascular events including ischemic CVA. Our objective was to assess the secular trend in 10-year risk of incident ischemic CVA in incident RA (cohorts with onset from 1997 to 2004) relative to the general population, using administrative data.

3.2 Methods

3.2.1 Study Design

We conducted a retrospective study of a population-based cohort of all incident cases of RA in British Columbia (BC) with RA onset between 01/01/1997 and 31/12/2004, followed until 31/12/2014, with matched general population controls, using administrative health data.

3.2.2 BC Cohort Definition and Study Sample

Incident RA Cohort. We identified all incident cases of RA in BC who first met previously published RA criteria [106] between January 1997 and December 2004, using physician billing data from 01-1990 onwards, from the Ministry of Health in a universal health care system. To ensure prevalent cases of RA who moved to BC were not erroneously identified as incident RA cases, we excluded RA individuals if they had less than seven years of available data prior to their first RA visit. Using previously published RA criteria, individuals were identified as incident RA if they had at least two physician visits, at least two months apart, within a 5-year period, with International Classification Disease Codes version 9th for RA (ICD-9: 714.x.). Individuals were excluded, if over a five-year period after their second RA visit (i.e. index date), they had at least two subsequent visits, on two different days, with the same ICD code for other forms of inflammatory arthritis [Systematic Lupus Erythematosus (SLE), and other connective tissue diseases, Psoriatic Arthritis, Ankylosing Spondylitis and other Spondyloarthropathies (*appendix, A*)]; or if a patient saw a rheumatologist and the diagnosis of RA by a non-rheumatologist was never confirmed by the rheumatologist. These criteria have been validated in a sub-sample who participated in a RA survey, using impression of an independent rheumatologist reviewing medical records from their treating physician as a gold standard, yielding a positive predictive value (PPV) of 0.82 [107].

General Population Cohort. Controls were randomly selected from the general population with no physician visits for any type of inflammatory arthritis, using the same administrative databases as for the RA cohort. All eligible controls were matched to RA patients on age and sex and were assigned the date of RA incidence (i.e. first RA visit) and

index date (i.e. second RA visit) of the RA case they were matched to. Individuals were excluded if they had less than 7 years of available data prior to the date of incidence. Controls were then randomly selected from eligible controls for each RA individual in a 2:1 ratio.

Study Subjects. To measure risk of incident CVA across incident cohorts, we excluded individuals with a prior history of CVA, based on CVA diagnoses codes (ICD-9/ICD 10 codes: 434, 436/ I64, I63) in hospitalization data using 25 diagnostic codes, in any position, or in physician visits, using a fixed period of 7 years prior to index date, rather than over all available data since 1990. We equalized the lead-in period to prevent including more recurrent CVAs in earlier years of incidence (due to shorter periods of exclusions to identify prior CVA), which would potentially overestimate the risk of CVA in individuals with RA incidence in earlier years relative to later years. This is important because having a prior CVA increases the risk of recurrent CVA.

RA individuals and general population controls were divided into incidence cohorts according to the year of RA incidence, defined based on the first RA visit.

3.2.3 Data Collection

Data for the RA cohort and general population were obtained from administrative databases of the Ministry of Health, through Population Data BC, on all provincially funded health care services. These include data on basic demographics such as age and sex, geo-codes indicating location of residence, and registration data from consolidation file based on the Medical Service Plan (MSP) registration and premium billing (R&PB) [108], all physician visits, with one diagnostic code per visit representing the reason for the visit, from the Medical Service Plan (MSP) database [109]; all hospitalizations from Discharge

Abstract Database (DAD), which include up to 25 diagnostic codes per hospitalization representing either the primary reason for admission or complications during hospitalization [110]. Data from MSP and DAD were obtained from January 1990 to December 2014. PharmaNet data [111] provided information on all prescriptions dispensed by pharmacies in BC from January 1996 to December 2014, on all individuals. Information on death and primary cause of death was derived from death certificates using Vital Statistics Data from January 1996 to December 2014 [112].

3.2.4 Outcome Assessment

The outcome of interest was the 10-year risk of incident ischemic CVA, defined as the first CVA event occurring over ten years of follow-up, with the 10-year mark calculated from RA onset (first RA visit) but follow-up starting from index date. CVA events were identified using diagnostic codes for ischemic strokes, i.e. excluding hemorrhagic strokes because they are not related to atherosclerosis, i.e. using ICD-9 codes: 434 (i.e. occlusion of cerebral arteries), or 436 (i.e. acute, but ill-defined cerebrovascular disease; ICD-10 codes: I63 (i.e. cerebral infarction), or I64 (i.e. stroke, not defined as hemorrhage or infarction)] in hospitalization data, using 25 diagnostic codes in any position, or in vital statistics data as cause of deaths, to ensure capture of fatal events without hospitalization, including out-of-hospital deaths. Previous validation studies in Canada evaluating the validity of administrative data to identify ischemic stroke, have reported that the positive predictive value (PPV) of the main codes for ischemic stroke (ICD-9 434/ICD-10 I63) was $\geq 82\%$, and the PPV of codes for acute but ill-defined stroke (ICD-9 436 or ICD-10 I64) was $\geq 75\%$. In the same study authors have recommended that when attempting to identify cases of ischemic stroke, including both the code for acute stroke and the code for acute-

but-ill-defined stroke will help capturing more cases of ischemic stroke with minimal impact on PPV [142].

3.2.5 Assessment of Covariates

Information on sociodemographic characteristics, health care resource utilizations, comorbidities and medications, known to influence the risk of CVA, were selected a priori, and measured either at RA onset (i.e. first RA visit), or over one year prior to RA onset.

Sociodemographic. Information on age, sex, regional health authorities in BC (i.e. Interior, Fraser, Vancouver Coastal, Vancouver Island, Northern) based on MSP registration and premium billing data; and markers of socioeconomic status [neighborhood income quintile calculated by Population Data BC based on postal code and census data for the area; geography (rural vs. urban) based on postal code second digit] were measured at RA onset.

Health Care Resource. Information on the number of yearly physician visits, hospitalization events (as a binary variable: Yes/No), and length of stay in hospital, were measured over one year prior to RA onset.

Comorbidities. Pre-existing comorbidities over one year prior to RA onset [i.e. angina, chronic obstructive pulmonary disease (COPD), obesity, atrial fibrillation (AF)], were defined using one hospitalization or physician visit with their respective ICD codes (*appendix B*); diabetes mellitus (DM) and hyperlipidemia, were defined based on medication use (i.e. insulin or oral hypoglycemic, and statin or fibrates, respectively).

Medications. Medications were defined as used (yes/no) over one year prior to RA onset and included glucocorticoids (GC), hormone replacement therapy, anticoagulants, traditional non-steroidal inflammatory drugs (NSAIDs), selective cyclooxygenase 2

(COX-2) inhibitors, contraceptives, and CV drugs (antihypertensive, Beta-blockers, cardiac glycosides, diuretics, antiarrhythmic, nitrates).

Charlson Comorbidity Score. Additionally, to control for overall comorbidity burden, a modified Romano modification of the Charlson comorbidity score for administrative data (with RA excluded from comorbidities), was calculated over one year prior to RA onset [114, 115].

3.2.6 Statistical Analysis

Descriptive statistics (i.e. mean, median, standard deviation, and proportions) were used to describe and compare characteristics of different cohorts. Bivariate analyses, as appropriate (i.e. two-sample t-test or Wilcoxon-Mann Whitney Test for continuous variables, and chi-square) were conducted, to compare baseline characteristics between RA and general population.

To avoid immortal time bias, we performed left truncation in our analysis [117]. The risk of developing cardiovascular events is more likely to increase, as RA progresses. Therefore, RA individuals who have a longer time between RA onset (i.e. first RA visit) and index date (i.e. second RA visit) are more likely to develop CVA. To avoid inducing this bias, time was counted at RA onset, however, to avoid immortal time bias [118], RA individuals and general population controls contributed to person years (PYs) of follow-up, from index date (i.e. second RA visit), which is when they met criteria for inclusion in our cohort and became at risk of developing the outcome of interest. Censoring was done at ten years from RA onset, or last health care utilization due to death or migration, whichever occurred first.

Crude 10-year incident rates (IRs) of CVA per 1000 PYs of follow-up, with 95% confidence intervals (CI) were calculated for each incident RA and general population cohort, according to the calendar years of incidence. Subsequently, the crude 10-year incidence rate ratio (with 95% CI) was calculated for each cohort, by dividing the IR of CVA in RA by the IR in the general population.

To estimate the secular trend in 10-year risk of CVA in RA relative to the general population, we used multivariable Cox models[119], while controlling for potential confounders. The strategy for adjustment was defined a priori. Models were initially adjusted for age and sex, then additionally for sociodemographic factors, pre-existing comorbidities, and prescriptions. Furthermore, we used stepwise selection method, a modification of forward selection and backward elimination [120] for which variables entered the model if they were significant at the level of 0.25 and they were removed if they were not significant at the level 0.10.

To test if the secular trend in risk of incidence CVA in RA differed from the secular trend in the general population, an interaction term between the indicator of RA vs. general population (i.e. 0 indicating general population, 1 indicating RA) and, years of incidence was tested in the Cox models.

To determine whether the change in risk of incident CVA followed a linear trend over the calendar years of incidence, we compared Cox regressions with linear, quadratic and flexible spline functions of years of incidence. Model with the lowest Akaike Information Criterion (AIC) [121], best fitting the CVA events was selected to interpret the data.

A spline regression is a non-parametric method that allows for different linear functions of time corresponding to pre-and-post critical time point (also called a knot) [122]. A Cox model with spline regression hazard function was fit to allow for more flexible modeling of possible changes in CVA incidence across the years of incidence, compared to conventional parametric (i.e. linear or quadratic) functions. We used data-driven stepwise selection approaches to select the numbers and locations of the knot(s) [123]. The procedure selected one knot at the incidence year 1999. This was consistent with graphical representations of calculated crude IRs per calendar years of incidence in our cohorts (*Figure 3.3*), and with shifts in RA treatments that could possibly influence occurrence of CVD in RA.

3.2.7 Ethics

The study received ethics approval from the University of British Columbia's Behavioral Research Ethics Board. The Ministry of Health provided the linkage for their databases, no personal identifying information was provided to the investigators, and procedures were compliant with BC's Freedom of Information and Privacy Protection Act.

3.3 Results

The sample included 23,545 RA individuals (65.7% women; mean [SD] age 58.11 [16.82] years) and 47,090 matched general population controls. Flow diagram of RA individuals included in the analysis is displayed in *Figure 3.1*.

Mean [SD] years of follow-up were 9.02 [2.23] years in the RA cohort and 8.97 [2.31] years in the general population. A total of 658 and 1,220 incident CVA were observed in RA and general population, respectively; of which 32 in RA, and 73 in general population, were fatal events identified through death certificates.

Baseline characteristic of the RA and the general population cohorts are described in *Table 1*. RA individuals were more likely to reside in rural areas and in areas of low-income quintiles. They were also more likely to receive health services from local health care authorities other than Vancouver Coastal Health. Compared to the general population, they had significantly higher rates of hospitalizations and physician visits, pre-existing comorbidities, and all medications evaluated in this study as shown in *table 3.1*, except for contraceptive use ($p = 0.355$). However, clinically meaningful differences were observed for prior hypertension, angina; use of CVD medications, cox2 inhibitors, hormone replacement therapy and glucocorticoids.

The mean time between first and second RA visits, for each RA cohort, according to the calendar years of incidence is shown in *Figure 3.2*. Mean duration of RA at index date is slightly shorter in later years of incidence and shortens to less than a year after 2001.

Crude 10-year incident rates of CVA per 1000 PYs in RA and general population cohorts are shown in *Table 3.2*. In RA cohorts, crude 10-year incidence (95% CI) of CVA increased from 3.29 (2.65, 4.03) events per 1000 PYs in 1997 to 3.87 (3.16, 4.68) in 1999. From 1999 onwards, the crude 10-year CVA incidence declined from 3.39 (2.74, 4.14) to 2.42 (1.88, 3.05) in 2004 (*Figure 3.3*). In the general population cohorts, the crude 10-year rate of incident CVA decreased from 3.42 (2.94, 3.95) in 1997 to 2.73 (2.31, 3.19) in 2004. Slight fluctuations in the downward trend was observed in the general population from 2001 to 2004 (*Figure 3.3*).

Graphical representation of crude CVA incidence rates in RA and general population are shown in *Figure 3.3*. We compared linear, quadratic, and spline (with a knot at year 1999) Cox regressions. Spline Cox regression model had the lowest AIC and was

selected as best fitting the observed incident CVA events (*Table 3.3*). Results of the univariate and multivariate analyses assessing secular trends in 10-year risk of CVA in incident RA cohorts relative to the general population, before and after year 1999, using the spline model are shown in *Table 3.4*.

In RA cohorts with incidence from 1999 onwards, we observed a significant decline in risk of CVA with increasing calendar years of incidence [0.90 (0.86, 0.95); $p = 0.0001$], but not in cohorts with incidence before 1999 [0.96 (0.91, 1.18); $p = 0.5791$]. In the general population, there was a significant decline in risk of CVA over the calendar years of inception before 1999 [0.89 (0.81, 0.98); $p = 0.0133$]; whereas after 1999, the decreasing trend did not reach statistical significance [0.97 (0.93, 1.01); $p = 0.0864$]. The declining trend observed in the RA cohorts with incidence from 1999 onwards, was significantly different from the general population, as reflected by the interaction term between indicator of RA and years of incidence from 1999 onwards [0.87 (0.87, 0.99); $p = 0.0393$]. Results were similar when a quadratic model was used, i.e. a significant difference in secular trends was observed in RA cohorts relative to the general population [aHR of interaction term = 0.98 (0.96, 0.99); $p = 0.0373$].

According to the multivariable cox regression analysis, men had an increase in risk of CVA compared to women; Individuals who were in higher income quintiles, in particular quantile 5, had significantly lower risk of CVA; Pre-existing comorbidities associated with an increased risk of CVA included: alcoholism, hypertension, and diabetes; use of anticoagulants, CV medications, and NSAIDs, were also associated with increased risk of incident CVA.

Figure 3-1. Flow diagram of RA individuals and general population controls included in the CVA analysis

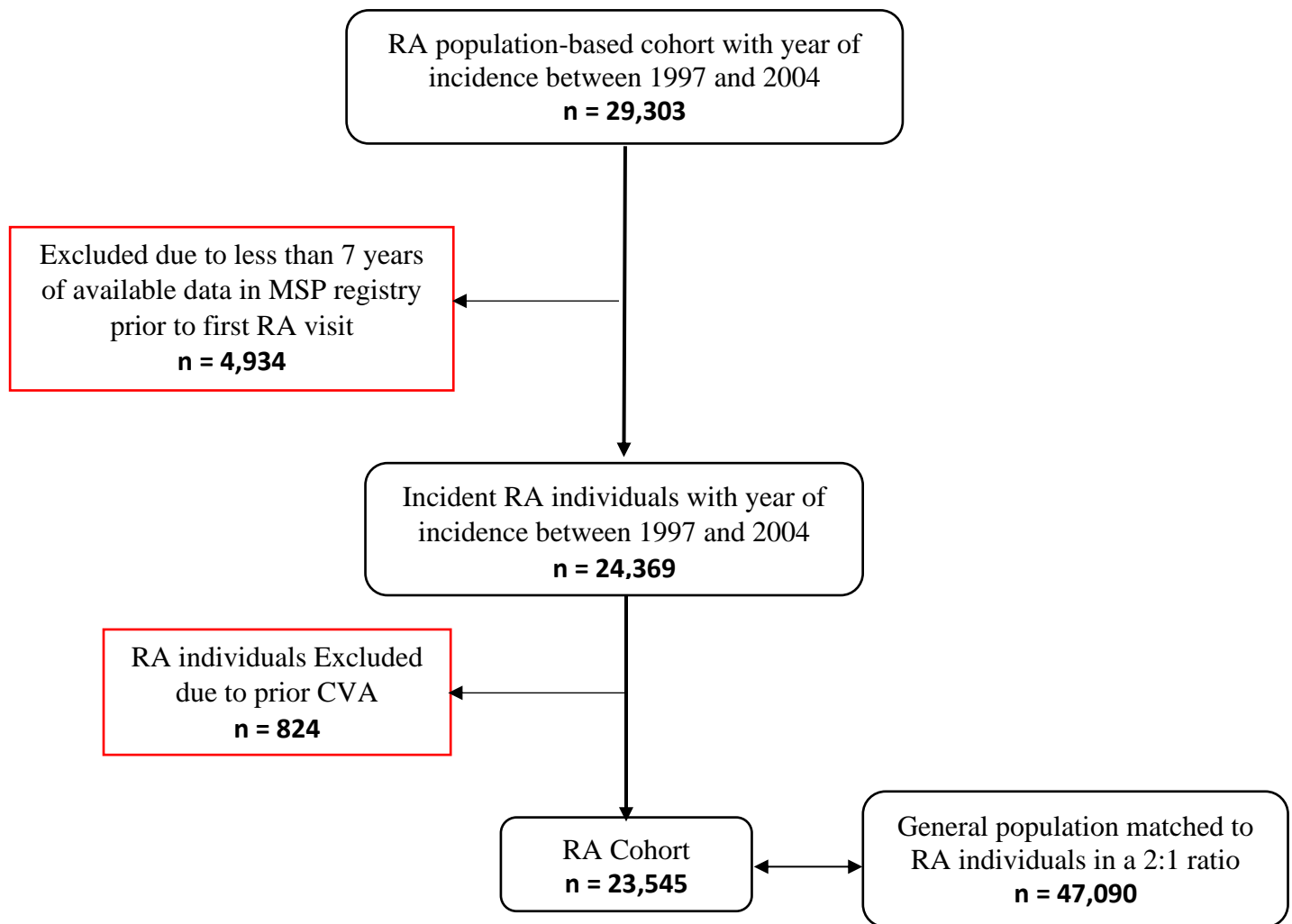


Table 3-1. Baseline characteristics of RA and general population cohorts

Baseline Characteristics	General Population (n = 47,090)	RA (n = 23,545)	p-value
Demographics*			
Women	30,940 (65.7)	15,470 (65.7)	1
Mean Age (Yrs.)	58.11 (16.82)	58.11 (16.82)	1
Mean Follow-up (Yrs.)	8.97 (2.31)	9.02 (2.23)	0.019
Rural vs. Urban [#]	6477 (13.8)	4365 (18.5)	<0.001
Neighborhood Income Quintile [*]			<0.001
1 (Lowest)	8863 (18.8)	5126 (21.8)	
2	8680 (18.4)	4716 (20.0)	
3	8797 (18.7)	4417 (18.8)	
4	8881 (18.9)	4349 (18.5)	
5 (Highest)	9243 (19.6)	4039 (17.2)	
unknown	2626 (5.6)	898 (3.8)	
Regional Health Authority	8549 (18.2)	5232 (22.2)	<0.001
Interior	14481 (30.8)	7016 (29.8)	
Fraser	11093 (23.6)	4405 (18.7)	
Vancouver Coastal	8807 (18.7)	4862 (20.6)	
Vancouver Island	2914 (6.2)	1938 (8.2)	
Northern	1246 (2.6)	92 (0.4)	
unknown			
Health Care Utilization ^Ω			
Median Physician visits	12.0	24.0	<0.001
Mean Length of Stay at Hosp. ,days	7.23 (38.95)	11.45 (47.83)	<0.001
Prior Hospitalization, yes	6316 (13.4)	5262 (22.3)	<0.001
Comorbidities ^Ω			
Charlson index [¥]	0.29 (0.83)	0.42 (0.92)	<0.001
Obesity	445 (0.9)	305 (1.3)	<0.001
Alcoholism	256 (0.6)	379 (1.7)	<0.001
Hypertension	8505 (18.1)	5453 (23.2)	<0.001
COPD	843 (1.8)	723 (3.1)	<0.001
Angina	1460 (3.1)	1097 (4.7)	<0.001
Atrial fibrillation	0.29 (0.83)	0.42 (0.92)	0.003
Diabetes	2282 (4.8)	1221 (5.2)	0.052
Medications ^Ω			
Anticoagulation	876 (1.9)	589 (2.5)	<0.001
CVD Medications [§]	11151 (23.7)	7375 (31.3)	<0.001
Fibrates	377 (0.8)	237 (1.0)	0.006
Statin	3746 (8.0)	2247 (9.5)	<0.001
Hormone Replacement Therapy	4147 (8.8)	2868 (12.2)	<0.001
Traditional NSAIDs	5536 (11.8)	10399 (44.2)	<0.001
COX2 Inhibitors	1320 (2.8)	3561 (15.1)	<0.001
Contraceptives	1300 (2.8)	621 (2.6)	0.355

Glucocorticoids	1223 (2.6)	3365 (14.3)	<0.001
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Values represent number (%) unless where indicated, values represent mean (SD).

* Measured at RA onset (i.e. first RA visit)

^Ω Measured over one year prior to RA onset

Rural vs Urban: where a zero '0' in the second position of the postal code indicates a rural area;

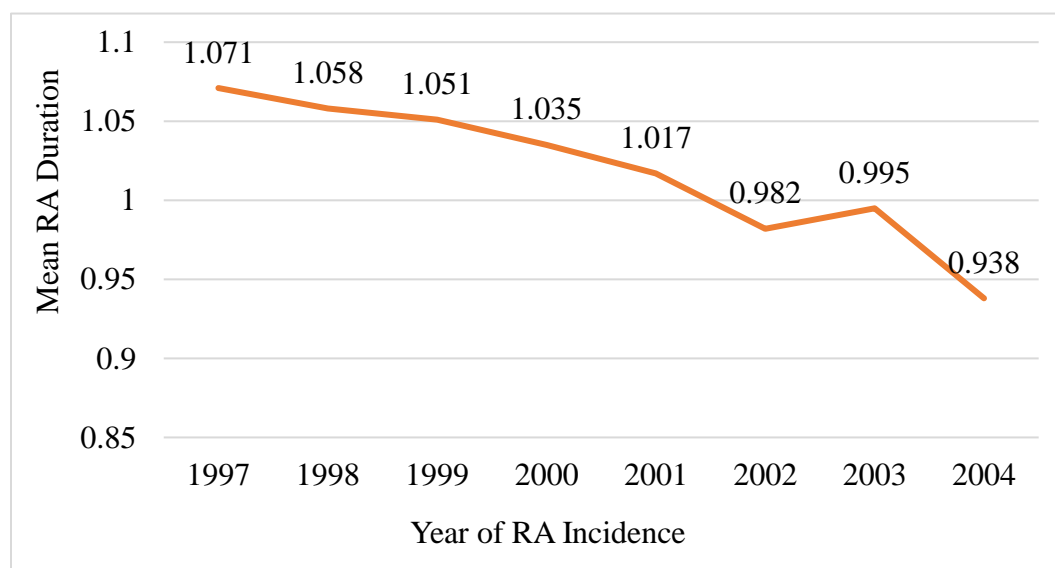
* Income quintile is a measure of neighborhood socioeconomic status derived from postal code that divides the population into 5 income groups (from lowest income to highest income);

¥ Romano Charlson refers to Romano adaptation of the Charlson co-morbidity score developed for use with administrative health data, excluding RA as a comorbidity;

§ CVD Medications: antihypertensive, Beta-blockers, cardiac glycosides, diuretics, antiarrhythmic, nitrates;

Abbreviations: RA: rheumatoid arthritis; Yrs: years; Numb: number; Hosp: hospitalization; COPD: chronic obstructive pulmonary disease; CVD: cardiovascular disease; NSAIDs: traditional non-steroidal inflammatory drugs; cox2: cyclooxygenase 2 (selective COX-2) inhibitors;

Figure 3-2. Mean RA duration at index date for each incident RA cohort (according to the year of RA incidence)



RA duration in years was calculated as time from first RA visit to index date (i.e. second RA visit)

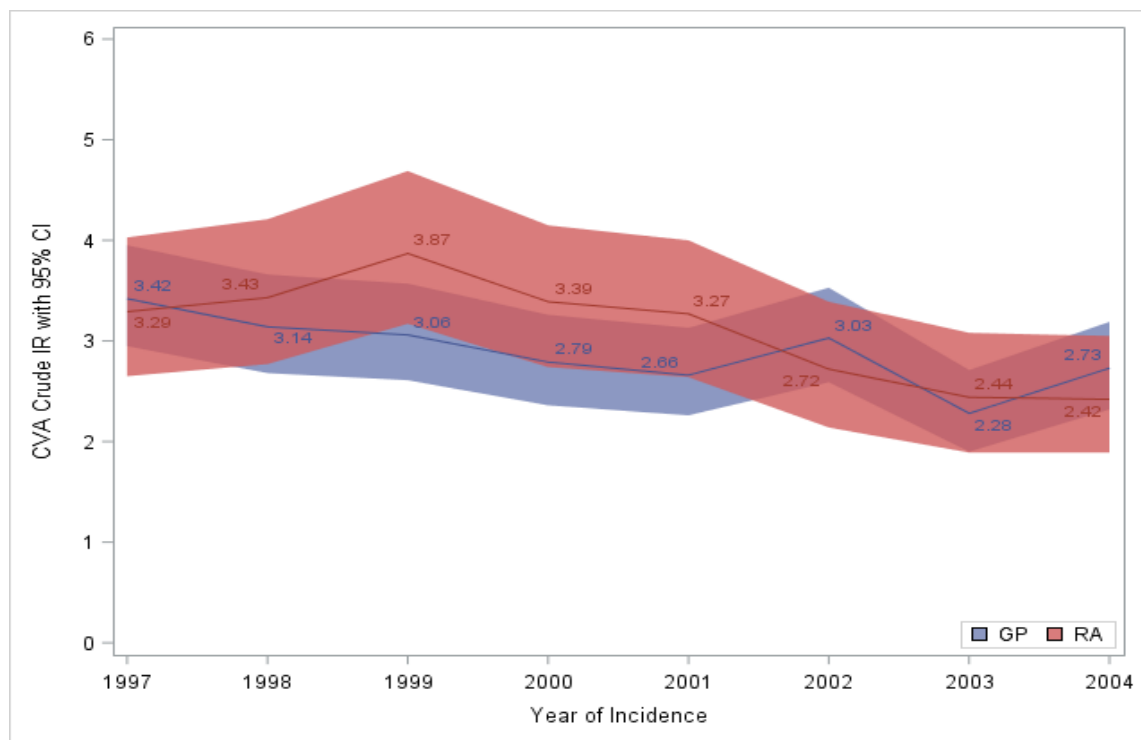
Abbreviations: RA: rheumatoid arthritis

Table 3-2. Crude 10-year incident rates of CVA per 1000 PYs in RA cohort and general population

RA Cohort					General Population				Crude IRRs (95% CI)
Cohort Year of Incidence ^s	N	CVA	PYs	Crude IRs (95%CI)	N	CVA	PYs	Crude IRs (95%CI)	
1997	2941	87	26385	3.29 (2.65, 4.03)	5882	179	52237	3.42 (2.94, 3.95)	0.96 (0.74, 1.23)
1998	2797	87	25293	3.43 (2.76, 4.21)	5594	158	50268	3.14 (2.67, 3.65)	1.09 (0.83, 1.41)
1999	2865	100	25789	3.87 (3.16, 4.68)	5730	157	51163	3.06 (2.61, 3.57)	1.26 (0.98, 1.62)
2000	2944	90	26506	3.39 (2.74, 4.14)	5888	148	53031	2.79 (2.36, 3.26)	1.21 (0.93, 1.57)
2001	3012	89	27171	3.27 (2.64, 4.00)	6024	145	54323	2.66 (2.25, 3.12)	1.22 (0.93, 1.59)
2002	2943	72	26456	2.72 (2.14, 3.39)	5886	160	52768	3.03 (2.58, 3.52)	0.89 (0.67, 1.18)
2003	2994	66	27042	2.44 (1.89, 3.07)	5988	123	53830	2.28 (1.90, 2.71)	1.06 (0.78, 1.43)
2004	3049	67	27635	2.42 (1.88, 3.05)	6098	150	54918	2.73 (2.31, 3.19)	0.88 (0.66, 1.17)

Abbreviations: RA: rheumatoid arthritis; N: Number of individuals; CVA: cerebrovascular accidents; PYs: Person-years of follow-up; IRs: incident rates; IRRs: incident rate ratios; CI: confidence interval

Figure 3-3. Crude 10-year risk of CVA according to year of incidence (1997-2004) in RA and general population cohorts



Abbreviations: CVA: cerebrovascular accidents; IR: incident rate; CI: confidence interval; GP: general population; RA: rheumatoid arthritis

Table 3-3. Comparison of cox regressions with linear, quadratic, and spline forms of year of incidence

Cox Regressions	Model AIC (Unadj.)	Model AIC (Adj.)
Linear Model	41169.33	38407.41
Quadratic Model	41169.20	38388.68
Linear Spline Model	41167.93	38384.74

Abbreviations: Unadj: Unadjusted; Adj: Adjusted according to stepwise selection technique; AIC: Akaike information criterion

Table 3-4. Secular trend in 10-year risk of incident CVA in incident RA cohorts relative to the general population

Secular Trends in 10-year risk of CVA	Unadj. HR (95% CI)	P-value	^ΩAdj. HR (95% CI)	p-value
10-year risk in RA before 1999*	1.08 (0.95, 1.22)	0.229	0.96 (0.91, 1.18)	0.5791
10-year risk in GP Before 1999**	0.93 (0.85, 1.02)	0.1234	0.89 (0.81, 0.98)	0.0133
Secular in RA relative to the GP before 1999***	1.16 (0.99, 1.36)	0.0601	1.17 (0.99, 1.36)	0.0564
10-year risk in RA after 1999#	0.90 (0.85, 0.95)	<.0001	0.90 (0.86, 0.95)	0.0001
10-year risk in GP after 1999##	0.96 (0.93, 1.01)	0.105	0.97 (0.93, 1.01)	0.0864
Secular trend in RA relative to the GP after 1999###	0.93 (0.87, 0.99)	0.0271	0.87 (0.87, 0.99)	0.0393

Ω Results are reported according to the spline linear Cox regression model with a knot at year 1999;

covariates included in the final multivariable model include: age; sex; income quantile; health care authority; rural vs. urban; number of physician visits; prior hospitalization events; Charlson comorbidity score; alcoholism; hypertension; CV medications; antidiabetics; anticoagulation, and NSAIDs.

* HR represents the change in CVA risk in the RA population per calendar years of incidence before 1999.

** HR represents the change in CVA risk in the general population per calendar corresponding to year of RA incidence before 1999.

*** HR represent the difference in the change in risk of CVA in RA and in general population before 1999.

HR represents the change in CVA risk in the RA population per calendar years of incidence after 1999.

HR represents the change in CVA risk in the general population per calendar year corresponding to year of incidence after 1999.

HR represent the difference in the change in risk of CVA in RA and in general population after 1999.

Abbreviations: RA: rheumatoid arthritis; GP: general population; Unadj. HR: unadjusted hazard ratio; Adj. HR: adjusted hazard ratio; CI: confidence interval

3.4 Discussion

We conducted a retrospective population-based study of incident RA cohorts with RA onset from 1997 to 2004, with matched general population controls, using administrative health data in a universal health care system, to assess the secular trend in risk of incident CVA in RA relative to the general population.

A significant decline in 10-year risk of CVA was observed over time in RA cohorts with RA onset from 1999 onwards. This declining temporal trend was significantly greater in RA than in the general population. Whereas in cohorts with RA onset before 1999, there was a significant decline over time in the 10-year risk of CVA in the general population but not in RA, however this difference did not reach statistical significance.

There are few published studies evaluating temporal trends in incidence of CVA events in RA, and in RA relative to the general population. Consistent with our findings, a Swedish study has shown a trend toward an increase in CVA incidence from July 1997 to December 1999 in RA compared to the general population, which did not reach statistical significance [1.21 (0.74, 1.86)][143]. Another study in Malmo, Sweden found that over 8 years of follow-up, the increased risk of incident CVA in RA patients relative to the general population was similar in RA patients with RA onset in 1978 and in patients with RA onset in 1995[98].

Two studies, published only in abstract forms to date, have evaluated temporal trends in the incidence of cerebrovascular events in RA with RA onset in more recent years. In contrast to our results, a Spanish study using national hospitalization data found a 6.3% increase in annual incidence of CVA among prevalent RA individuals admitted to hospital between 1999 and 2015 [125]. A number of methodological differences between

the studies may explain the difference in findings. Their study sample included prevalent RA cases who may have had onset of their disease much prior to 1999 when treatment paradigms for RA differed; the temporal trend evaluated over years 1999 to 2015 represented the time when the CVA outcomes were measured, whereas in our study the years 1999 to 2004 represent the year of RA incidence and the CVA risk was assessed over 10 years after RA incidence. Their study also did not include general population controls. Furthermore, their cohort identified RA cases who had been hospitalized, who likely have more severe disease or more comorbidities, and therefore may have a greater risk of CVA.

Results of a population-based study of Olmsted County, US, are concordant with ours, showing individuals with incident RA in the years 2000-09 had lower cumulative incidence of CVD events compared with RA individuals with incidence in the 1980's and 1990's. Authors found a significant decline in 10-year risk of CVD events in patients with incident RA in 2000's compared to incident RA in 1980's [HR (95% CI): 0.52 (0.32-0.86)]; the difference between RA patients diagnosed in the 2000's compared to 1990's did not reach statistical significance [0.65 (0.40-1.05)]. Furthermore, they did not observe excess incidence of CVD events in incident RA subjects diagnosed in 2000's compared to subjects without RA [0.88 (0.53, 1.46)]. They reported that their results remained similar when they examined CVA separately [126]. However, the sample size of their cohort was small (total number of RA individuals = 906) and few cardiovascular events were observed (i.e. 31, 38, 31 events in RA subjects, diagnosed in the 80's, 90's, and 2000's, respectively, over a median follow-up of 10.6, 10.4, and 10.2 years, respectively)

We speculate that the improvement in CVA incidence observed from 1999 onwards in RA, is potentially related to the paradigm shift in management of RA with the adoption of more aggressive treatment strategies including treat to target aimed at low disease activity or remission, as well as the advent of effective RA therapies such as biologic agents. There are reports indicating that RA patients have milder disease in recent years, for instance, a cross-sectional German study has shown a steady decline in RA disease activity from 1997 to 2007 [144]. There is evidence supporting the hypothesis suggesting that this reduction in disease activity is associated with decreasing risk of CV events. A US-based study has shown that a 10-point reduction in the time-averaged clinical disease activity index (CDAI) in RA, was associated with a 21% decrease in CV risk (95% CI 13.0, 29.0) [145]. Another study in the Netherlands showed that low disease activity, measured by the Disease Activity Score-28 joint count (DAS28) (≤ 3.2), compared with moderate or high disease activity (DAS28 > 3.2) was significantly associated with a lower 10-year risk of incident cardiovascular event [HR (95% CI): 0.65 (0.43, 0.99)], compared with high disease activity (DAS28 > 3.2) [146]. Additionally, a meta-analysis evaluating comparative risk of cardiovascular events with biologics and conventional synthetic DMARDs in RA, has shown no significant differences between different TNFi and non-TNF-biologics, and risk of stroke, whereas, exposure to conventional synthetic DMARDs (including MTX) was associated with a higher risk of stroke, compared to treatment with TNFi [OR (95% CI): 1.19 (1.03, 1.38)] [147].

However, changes in factors associated with risk of stroke in RA, other than level of inflammation or disease activity, might have also contributed to the decline in risk of CVA.

Meissner Y., et al., have shown that RA patients are at greater risk of stroke if they have untreated CV diseases such as coronary heart disease, heart failure or hypertension prior to stroke [148]. It is possible that in years prior to 1999, RA individuals had more untreated CV comorbidities, due to lower awareness of the increased risk of CVD in RA and its role in causing premature mortality in RA, and that the cardiovascular comorbidities were increasingly better treated after the year 1999, as awareness improved.

The incidence rates observed in our general population controls do not necessarily reflect rates and time trends in the BC general population, given that the age and sex distribution of our controls matched those of our RA sample and are therefore not representative of the entire general population. Nonetheless, the observed declining trend in incidence of ischemic strokes in our general population cohort is in line with the literature. A recently published nationwide cohort study in the Netherland found an 11% decrease in incidence of any types of strokes in adults aged 50 years or older between 1998 and 2010 [149]. A Norwegian study estimating trends in incidence of ischemic strokes reported an increase in ischemic strokes in younger women, a decline in women aged 50 to 74 years, and men 65 to 74 years, and stable incidence rates among the oldest [150].

Strengths: The strengths of this analysis are the population-based nature of our cohorts with capture of all RA individuals in BC treated in recent years (1997-2004); the large sample size (over 20 thousand incident cases of RA and twice as many in the general population) with a large number of events (658 in RA and 1,220 in the general population);

and, long follow-up of 10 years. Previous studies assessed CVA outcomes either over limited range of follow-up or in small samples.

Limitations: The limitations of the study are those inherent to observational studies and studies using administrative data. Misclassification of RA diagnosis (e.g. atypical RA patients might be less likely to be coded as an RA diagnosis) or uncertainty around RA diagnosis identified using administrative data is possible. However, we used previously published criteria that were previously validated in a subsample who participated in a RA survey, with a positive predictive value of 0.82. Unmeasured confounding resulting from lack of information on known (e.g. smoking) or unknown risk factors cannot be completely excluded. For these to influence the difference in secular trends, they would have to change differentially across calendar years of incidence in RA relative to the general population.

To avoid misclassification of prevalent cases of RA moving to BC during the study period as incident cases, we excluded from the incident cohort RA cases and general population controls with MSP enrollment less than 7 years prior to the date of their first RA visit. It is however possible that our incident cohort includes prevalent cases who had an RA visit more than 7 years prior to the first RA visit captured in our data. However, consecutive visits more than 7 years apart is very infrequent in our cohort. In a previously published study using the same rule to define incident RA cases, we have shown that only 0.44% of the periods between consecutive RA visits were more than 6 years and 94.3% were < 1 year and 97.3% were < 2 years [133].

We also did not have information on onset of RA clinical symptoms in administrative data, therefore RA onset was defined as first RA visit. It is possible that in earlier years of incidence, RA patients may have taken longer to access care, and therefore,

they may have a longer duration from onset of their RA symptoms and the time of their diagnosis, whereas in later years of incidence, due to increase in number of rheumatologists, better access to health care, and emphasis on early diagnosis of RA, RA patients may have a shorter duration between the onset of their symptoms and their first visit. Therefore, this could lead to overestimation of CVA incidence in earlier vs. later years of incidence, since CVA is more likely to occur with longer duration of RA, which consequently would lead to an apparent temporal trend with improvement in CVA incidence over time in RA relative to the general population.

We also did not have information on RA disease severity, which could possibly explain why a difference was observed in secular trend. Observing milder RA disease activity in patients with RA onset in more recent years would confirm our hypothesis that improvement in risk of CVA may be due to better control of the disease.

Conclusion

In conclusion, we observed a significant declining temporal trend in the risk of incident CVA in RA patients with RA onset from 1999 onwards. This declining trend was greater in RA than it was in the general population, and the difference in the trends was statistically significant. We hypothesize that improvement in CVA incidence might be due to improved screening and management of modifiable CV risk factors due to improving awareness of the excess risk of CVD in RA, in addition to more effective control of systematic inflammation with current RA treatment strategies emphasizing the need for early diagnosis and for treating to a target of remission or low disease activity with traditional and biologic DMARDs.

Chapter 4: Discussion

4.1 Summary of Key Findings

The main objective of this thesis project was to evaluate secular trends in 10-year risk of incident cardiovascular events (**a.** AMI, **b.** CVA) in RA relative to the general population using administrative health data. In chapter 2 and 3, we evaluated secular trends in 10-year risk of incident **a.** AMI, and **b.** CVA, in a population-based cohort of incident RA with onset from 1997 to 2004 compared to matched general population controls, respectively. For each outcome of interest (i.e. **a.** AMI, **b.** CVA), we assessed the time trend in 10-year risk of CV event according to the year of RA incidence across cohorts with RA onset from 1997 to 2004, and we further examined whether the change in risk of CV events differed significantly in RA relative to the general population. We used left truncation, and we accounted for possible departure from the linear trend in incidence of AMI or CVA over time, by comparing Cox regressions with linear, quadratic, and spline functions of years of incidence effects (with a knot selected at incidence year 1999 for the spline regression). Overall, we observed a significant improvement in 10-year risk of incident AMI and incident CVA in RA cohorts with disease onset in more recent years. There was a significant decline in 10-year risk of AMI in RA and in the general population over the calendar years of incidence. The decline in risk of AMI did not differ in RA vs. the general population. A significant decline over time was observed in the 10-year risk of incident CVA in RA individuals with RA onset in years from 1999 onwards, and this decline was greater in RA than in the general population.

In chapter 2 (i.e. AMI analysis), in the RA cohort, slight unsteadiness in the crude 10-year incidence of AMI was observed with a peak in the year 1999. Whereas, in the

general population, a steadier linear trend with a decrease in AMI incidence was observed over the calendar years of incidence. After comparing regression models with different forms of ‘years of incidence’ effects and adjusting for potential confounders known to be associated with risk of AMI at baseline, the linear model had the lowest AIC, and best fit AMI events. We observed a significant improvement in the 10-year risk of AMI over the calendar years of incidence in the RA cohorts and in general population controls. The improvement in AMI incidence did not differ between RA and the general population. According to our results, baseline factors that were significantly associated with an increased risk of AMI include: older age, male sex, lower income quintiles, regional health care authorities, and pre-existing comorbidities (i.e. COPD, angina, hyperlipidemia, diabetes increased the risk of AMI), use of medications (i.e. CV medications and GC increased the risk of AMI).

In chapter 3 (i.e. CVA analysis), in RA cohorts with RA onset before the year 1999, we observed an upward trend in the crude 10-year CVA incidence, followed by a steady decline for cohorts with RA onset from 1999 onwards. In the general population, although we observed overall a downward trend in CVA risk over the calendar years of incidence, some slight fluctuations were observed after the year 2001. After comparing regression models with different functions of ‘years of incidence’ effects and adjusting for potential confounders known to be associated with the risk of CVA at baseline, a spline model with a knot at year 1999 best fit the CVA events (i.e. had the lowest AIC). A significant improvement in the risk of CVA was observed in RA cohorts with incidence from 1999 onwards, but not in cohorts with RA onset before 1999. In the general population, there was a significant decline in the 10-year risk of CVA in cohorts from years 1997 to 1999,

but the decline was not significant across cohorts from the years 1999 onwards. . The improvement in 10-year risk of CVA in cohorts from years 1999-2004 was greater in RA than it was in the general population, and the difference was statistically significant. Baseline factors found to be associated with an increased risk of CVA in our model included: older age, male sex, lower income quintiles, pre-existing comorbidities (alcoholism, hypertension, diabetes), use of the following medications: anticoagulants, CV drugs, and NSAIDs.

4.2 Implications for Clinical Practice

The increased burden of CVD in patients with RA is well established. However, recent studies evaluating secular trends in overall mortality and CVD specific mortality, have found an improvement in the risk of mortality in RA relative to the general population for patients with more recent RA onset. Our results for the CVA outcomes are in keeping with these findings of improved survival, but our results for the AMI outcomes are not. It is possible that the improvement in incidence of CV outcomes that we observed in RA cohorts of more recent onset is a result of enhanced awareness of the increased risk of CVD in this population. The improvement observed in the 10-year incidence of CVA may be indicative of more effective management of inflammation in RA due to a greater emphasis, in recent years, on the need for early diagnosis and timely therapeutic interventions based on the use of conventional and biologic DMARDs, in addition to tight disease control strategies and ‘treat-to-target’ approach aiming at eradicating inflammation. However, it is important to note that we observed different patterns of reduction over time in RA relative to the general population for our two CV outcomes of interest (i.e. AMI, and CVA). This highlights the importance of assessing CV outcomes separately, rather than as composite

endpoints in RA. Different patterns of incidence in AMI and CVA over time could potentially reflect diverse mechanisms of actions of different RA therapeutic agents used more frequently in recent years, on specific CV outcomes (CVA vs. AMI) in RA. We noticed that in our multivariable analyses predicting risk of AMI and CVA, different RA medications were associated with an increased risk of AMI or CVA. For instance, GC was positively associated with an increased risk of AMI but not CVA, and anticoagulants associated with an increased risk of CVA, but not AMI. To prevent cardiovascular diseases in RA, it is important for clinicians to be aware of the potential impact of medications on the risk of MI and CVA, and to cautiously prescribe RA medications that might be associated with an increased risk of CV events, such as GC and NSAIDs. This is consistent with recommendations in the recently published guidelines from EULAR to manage CVD in RA, that recommend that the use of medications such as GC or NSAIDs should be evaluated on an individual patient level and according to treatment-specific guidelines [66]. Although, multiple studies have shown that the management of CVD risk should rely on tight RA disease control regardless of type of therapy used, it has been reported that only small number of patients achieve low disease activity or clinical remission [151]. In addition, it is essential in order to reduce CV risk, to not only aim for remission and lowering disease activity through effective medications, but also to adequately manage comorbidities shown to be associated with an increased risk of CVD, as well as targeting traditional modifiable CVD risk factors to ameliorate CVD risk in RA patients.

Despite the large body of evidence documenting the increased risk of CVD in RA, strong evidence is lacking to guide the clinical management of this complication of inflammation. There is also a need to increase awareness about the increased risk of CVD

in RA, not only among the rheumatologist and primary care physicians but also in other health personnel involved in RA care, and there is a need to offer cardiovascular risk management programs tailored to the specific profile of each RA patient, in order to hopefully reduce the occurrence of specific CV events in the future [140]. Our results highlight the need for real-time RA-specific CVD risk prediction models, designed separately for specific CV outcomes in RA, accounting for RA-related factors associated with increased risk of each CV outcome separately, in addition to traditional CV risk factors. Current CV risk prediction models that are used in RA according to EULAR recommendations, are based on models developed in non-RA populations with a correction for the 50% increase in risk of CVD observed in epidemiologic studies by applying a 1.5 multiplication factor [66, 68, 126, 152]. Not only is the accuracy of these models at predicting CVD risk for patients with RA highly debated and not supported by research that compared actual and predicted risk, but also applying a standard 1.5 multiplication factor to all patients, regardless of their individual risk (ie using a standard correction factor based on population risk estimates to predict risk at the individual level), and for all CV outcomes (despite different patterns of incidence for CVA and AMI), does not seem a reasonable approach.

Our results provide useful insight for clinical practitioners on how the risk of two major CV events (i.e. AMI and CVA) has changed over time in RA and how the trends over time in incidence of those events have changed in RA relative to the general population, which allow for better decision making on how to prevent CV outcomes in RA.

4.3 Implications for Future Research

There is minimal research on longitudinal studies assessing secular trend in incident risk of CVD events in incident RA, and studies comparing trends in CVD events in RA vs. general population. There is a need to replicate our results in future studies for specific CV outcomes, particularly for incident AMI and incident CVA that are known to be the main cause of excess morbidity and mortality in RA as compared to other CV outcomes. Researchers may also examine secular trend in CVD events as composite measures, however, our results emphasize the need to assess each CV outcome separately, to provide an accurate and precise insight on how the risk of CV outcomes is changing over time in RA and what measures can be taken for each CV outcome accordingly.

Our study assessed incidence of first AMI and CVA, further research may examine secular trend in risk of recurrent CV events in patients with a prior event .

Further analysis is needed to examine 10-year risks of incident CV events in incident cases of RA with RA onset after 2004 to capture changes in CVD incidence over a longer period of time or RA incidence, especially with the advent of newer biologic agents with different mechanisms of actions in recent years. Future research should also include information on the potential confounding effect of smoking for which we did not have available data for adjusting in our analyses. There is also a need to evaluate the risk of CVD over longer period than 10 years, since some studies have suggested that the increased risk may only become apparent after 7 to 10 years of disease.

Another line of inquiry that could build on the work of my thesis, would be to assess mediating factors, and their change over time, that might be responsible for the improvement over time observed in incidence of AMI and CVA in RA, with specific focus

on the potential impact of RA medications (biological and non-biological DMARDs, GC, and NSAIDs), and other factors such as traditional CV risk factors, especially those that are modifiable, such as DM, hypertension, smoking, as well as time trends in the provision of CV prevention care in RA compared with general population. Additionally, researchers could examine trends in case fatality rates after first occurrence of CV events in RA versus non-RA subjects.

Although studies have found an increased risk of CVD shortly after RA diagnosis, it is possible that with better treatments and lower disease activity, longer follow-up, beyond 10 years post RA onset, is needed to capture more CV events in RA.

Further research could also examine time trends in incidence of CVD events in rheumatic diseases other than RA. There also remains the need to conduct similar studies in non-western countries to provide global perspective on how the risk of CV events in RA is changing as compared to general population and what are the factors mediating those changes at a population level.

Deaths related to non-CVA/AMI events were right censored in our analysis. A sensitivity analysis using cause-specific hazard regression should be done to account for competing risk of death related to non cva/ami in their respective analysis.

4.4 Strength and limitations

Major strengths of this work include the population-based nature of our cohorts with capture of all RA cases in BC, in a universal health care system using administrative health data, with complete capture of data on all physician visits, all hospitalization, primary cause of deaths, including out-of-hospital deaths derived from death certificates,

and all prescriptions; as well as geographical and sociodemographic information such as regional health care authorities in BC, rurality versus urbanizations, or income quintiles using census data. Our cohorts included over 20,000 incident RA cases and twice as many in general population. The population-based nature of our study reduces risk of selection bias. Furthermore, given the availability of administrative data until the end of December 2014, we were able to observe all RA and general population individuals for 10 years. We used strict RA incidence definition criteria, previously validated with a positive predictive value of 0.82 to identify incident cases. We also excluded individuals with less than 7 years of available data in MSP registration to ensure prevalent cases of RA moving to BC were not erroneously identified as incident cases. Additionally, we limited lead-in period to 7 years for all individuals to eliminate overestimating the incidence of CV events in earlier years of incidence due to shorter lead-in period to exclude individuals with prior AMI or CVA. This is of importance as reoccurrence of AMI/CVA increases, in individuals with prior AMI/CVA.

We were able to identify 1,133 and 1,606 AMI events in RA and general population respectively, in AMI analysis in chapter 2, and 658 CVA events in RA and 1,220 events in general population, in CVA analysis, using hospitalization and vital statistics data, providing us with relatively high number of events to evaluate secular trends as opposed to other published studies reporting on low number of CV event to assess CV outcomes in RA. The ICD codes used to identify outcomes of interest in our analyses have been validated in Canada and in several parts of the world, and they have consistently shown positive predictive values higher than 80%. We also used advanced statistical analysis such as left truncation method or spline Cox regressions to reduce potential biases in our results.

We acknowledge that our work has some limitations. The limitations of this thesis work are those inherent to observational studies and studies using administrative data. Misclassification of RA diagnosis (e.g. atypical RA patients might be less likely to be diagnosed) or uncertainty around RA diagnosis identified using administrative data is possible. We were not able to capture information on unmeasured or residual confounding effect of known (e.g. RA disease severity or smoking) or unknown risk factors associated with i risk of CV outcomes of interest. However, for these to influence the differences in secular trend, they would have to change differentially across calendar years of incidence in RA relative to the general population. Regardless, we did adjust our analyses for the effect of all potentially confounding variables for which we had available data . We were also not able to capture data on incidence of silent AMI or CVA, therefore, underestimation of the rates and rate ratios (given that silent MI are more common in RA) is possible.

There also exist the possibility of underestimating the CVA events in the general population due to decrease in stroke hospitalization rates in Canada. Additionally, Hospitalization data do not include individuals seen and discharged directly from emergency department to other types of institutions such as those with a minor stroke or those seen in outpatient setting. However, we used vital statistics data on cause of deaths to ensure capture of fatal CVA and AMI events including out of hospital deaths,

Conclusions

4.5 Conclusions

In conclusion, we observed a significant improvement over time in 10-year incidence of **a.** AMI, and **b.** CVA in patients with RA onset from 1997 to 2004.

4.5.1 AMI Analysis

There was a significant decline over time in the 10-year risk of incident AMI in RA and in general population over the years of incidence 1997 to 2004. The decline in the risk did not differ significantly in RA compared to the general population.

4.5.2 CVA Analysis

A significant decline over time was observed in the 10-year risk of incident CVA in RA patients with RA onset from 1999 to 2004. This decline was greater in RA than it was in the general population, and the difference in the trends was statistically significant.

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Appendices

Appendix A

A.1 ICD codes applied to exclude individuals with other forms of inflammatory arthritis than RA

Disease	ICD-9	Description	ICD-10	Description
Connective Tissue	710	Diffuse disease of connective tissue	M32.1	Systematic lupus erythematosus (SLE) with organ or system involvement
			M32.8	Other forms of SLE
			M32.9	SLE, unspecified
			M34	Systematic sclerosis
			M35.0	Sicca syndrome [Sjogren]
			M35.1	Other overlap syndromes
			M33.0	Juvenile dermatomyositis
			M33.1	Other dermatomyositis
			M33.2	Polymyositis
			M33.9	Dermatopolymyositis, unspecified
PS (Psoriatic Arthritis)	696	Psoriasis and similar disorders	L40	Psoriasis
AS (Ankylosing Spondylitis)	720	Ankylosing spondylitis and other inflammatory spondylopathies	M45	Ankylosing Spondylitis
IBD (Inflammatory Bowel Disease)	713.1	Arthropathy associated with gastrointestinal conditions other than infections	K50	Crohn disease [regional enteritis]
			K51	Ulcerative colitis
	555	Regional enteritis	M07.4	Arthropathy in Crohn disease
	556	Ulcerative Colitis	M07.5	Arthropathy in ulcerative colitis

A.2 ICD codes applied to identify comorbidities adjusted in Cox models to estimate the risk of AMI/CVA in RA relative to the general population

Comorbidity	ICD-9	Description	ICD-10	Description
Angina Pectoris	413	Angina pectoris	I20	Angina pectoris
Hypertension	401	high blood pressure hyperpiesia hyperpiesis hypertension (arterial) (essential) (primary) (systemic) hypertensive vascular: degeneration disease	I15	Renovascular hypertension
Obesity	278.0	Overweight and obesity	E66	Obesity
Alcoholism	291	Alcohol-induced mental disorders	F10	Mental and behavioral disorders due to use of alcohol
Chronic Obstructive pulmonary Disease (COPD)	491 492 496 493.2	Chronic bronchitis Emphysema Chronic airway obstruction, not elsewhere classified Chronic obstructive asthma	J43 J44	Emphysema Other chronic obstructive pulmonary disease
Atrial Fibrillation	427.3	Atrial fibrillation and flutter	I48	Paroxysmal atrial fibrillation

Appendix B

B.1 Output for unadjusted Cox PH

Parameters	Parameters Estimates	Std. Error	Unadj. HR (95% CI)	p-value
Indicator of RA vs. General pop (baseline)	0.30935	0.06786	1.36 (1.19, 1.56)	<.0001
Year of Incidence	-0.05655	0.01089	0.95 (0.93, 0.97)	<.0001
Year of Incidence * Indicator of RA vs. GP	0.00908	0.01691	1.01 (0.98, 1.04)	0.5914
AIC	59871.65			

B.2 Output for estimating secular trend in RA (Unadjusted)

Parameters	Parameters Estimates	Std. Error	Unadj. HR (95% CI)	p-value
Coefficient for 'year of incidence' + coefficient for 'year of incidence * indicator or RA vs GP'	-0.04748	0.01294	0.95 (0.93, 0.98)	0.0002

B.3 Multivariable Cox PH model

Parameters	Parameters Estimates	Std. Error	aHR (95% CI)	p-value
Indicator of RA vs. General Pop.	0.15644	0.06981	1.17 (1.02, 1.34)	0.025
Year of Incidence	-0.07408	0.01109	0.93 (0.91, 0.95)	<.0001
Year of Incidence * Indicator of RA vs. GP	0.01176	0.01735	1.01 (0.98, 1.05)	0.498
Age	0.06354	0.00172	1.07 (1.06, 1.07)	<.0001
Sex (M)	0.67346	0.03858	1.96 (1.82, 2.12)	<.0001
Income Quintile 1				
Income Quintile (2)	-0.11488	0.05832	0.89 (0.79, 0.99)	0.0489
Income Quintile (3)	-0.14077	0.0599	0.87 (0.77, 0.98)	0.0188
Income Quintile (4)	-0.17884	0.06121	0.84 (0.74, 0.94)	0.0035
Income Quintile (5)	-0.14462	0.06044	0.87 (0.77, .0.97)	0.0167
Income Quintile (9)	0.02546	0.10954	1.03 (0.83, 1.27)	0.8162
Rural vs. Urban	0.09587	0.05586	1.10 (0.99, 1.23)	0.0861

Interior Health care Authority	-0.05209	0.05724	0.95 (0.85, 1.06)	0.3628
Fraser	-0.16458	0.06163	0.85 (0.75, 0.96)	0.0076
Vancouver Coastal	-0.14596	0.06051	0.86 (0.77, 0.97)	0.0159
Vancouver Island	0.14199	0.08591	1.15 (0.97, 1.36)	0.0984
Northern	-0.56952	0.27111	0.57 (0.33, 0.96)	0.0357
Unknown				
Mean Number of Physician Visits	0.00162	0.00102	1.002 (1, 1.004)	0.1109
Prior Hospitalization, yes	0.12111	0.05136	1.13 (1.02, 1.25)	0.0184
Alcoholism	0.37491	0.20809	1.46 (0.97, 2.19)	0.0716
COPD	0.274	0.09396	1.32 (1.09, 1.58)	0.0035
Angina	0.18696	0.07746	1.21 (1.04, 1.40)	0.0158
Diabetes	0.79952	0.05632	2.22 (1.99, 2.48)	<.0001
CV Meds	0.45577	0.04332	1.58 (1.45, 1.72)	<.0001
Fibrates	0.31029	0.14029	1.36 (1.04, 1.79)	0.027
Statin	0.12561	0.05635	1.13 (1.02, 1.27)	0.0258
Cox2 Inhibitors	0.099	0.06954	1.10 (0.96, 1.27)	0.1546
Glucocorticoids	0.22791	0.06381	1.26 (1.12, 1.42)	0.0004
AIC	56480.31			

B.4 Output for estimating the secular trend in RA (Adjusted)

Parameters	Parameters Estimates	Std. Error	aHR (95% CI)	p-value
Coefficient for 'year of incidence' + coefficient for 'year of incidence * indicator or RA vs GP'	-0.06233	0.01369	0.94 (0.92, 0.97)	<.0001

Appendix C

C.1 Output for unadjusted spline Cox regression

Parameters	Parameters Estimates	Std. Error	Unadj. HR (95% CI)	p-value
Indicator of RA vs. General pop (baseline)	-0.0476	0.11897	0.95 (0.76, 1.20)	0.6891
Year of Incidence	-0.0729	0.04732	0.93 (0.85, 1.02)	0.1234
Splined [¥] Year of Incidence	0.04198	0.06015	1.04 (0.93, 1.17)	0.4852
Year of Incidence * Indicator of RA vs. GP	0.15081	0.08021	1.16 (0.99, 1.36)	0.0601
Splined Year of Incidence * Indicator of RA vs. GP	-0.22221	0.10132	0.80 (0.65, 0.97)	0.0283
AIC	41167.93			

¥ Splined year of incidence = (year of incidence-1999) Di

if year of incidence \leq 1999 then Di = 0

if year of incidence $>$ 1999 then Di = 1

C.2 Multivariable spline Cox regression

Parameters	Parameters Estimates	Std. Error	aHR (95% CI)	p-value
Indicator of RA vs. General pop (baseline)	-0.19001	0.12109	0.83 (0.65, 1.05)	0.1166
Year of Incidence	-0.11676	0.04719	0.89 (0.81, 0.98)	0.0133
Splined ^{\$} Year of Incidence	0.1526	0.07998	1.16 (0.99, 1.36)	0.0564
Year of Incidence * Indicator of RA vs. GP	0.08365	0.06019	1.09 (0.97, 1.22)	0.1646
Splined Year of Incidence * Indicator of RA vs. GP	-0.2197	0.1013	0.80 (0.66, 0.98)	0.0301
Age	0.08452	0.00226	1.09 (1.08, 1.093)	<.0001
Sex (M)	0.26004	0.04815	1.29 (1.18, 1.43)	<.0001
Income Quantile 1 (ref)				
Income Quantile (2)	-0.05072	0.07004	0.95 (0.83, 1.09)	0.469
Income Quantile (3)	-0.13058	0.07326	0.88 (0.76, 1.01)	0.0747
Income Quantile (4)	-0.04854	0.07258	0.95 (0.83, 1.09)	0.5036
Income Quantile (5)	-0.13925	0.07402	0.87 (0.76, 1.01)	0.0599
Income Quantile (9)	0.15816	0.11981	1.17 (0.93, 1.48)	0.1868
Rural vs. Urban	0.11569	0.06408	1.12 (0.99, 1.27)	0.071

Number of Physician Visits	0.00273	0.00128	1.00(1.00, 100.5)	0.0325
Prior Hospitalizations, yes	-0.08987	0.06305	0.91 (0.81, 1.03)	0.154
Charlson Comorbidity Index	0.04034	0.02444	1.04 (0.99, 1.09)	0.0988
Alcoholism	0.80509	0.24065	2.24 (1.39, 3.59)	0.0008
Hypertension	0.13563	0.05536	1.15 (1.03, 1.28)	0.0143
Diabetes	0.466	0.07618	1.59 (1.37, 1.85)	<.0001
Anticoagulants	0.29943	0.10144	1.35 (1.11, 1.65)	0.0032
CV Meds	0.41129	0.05767	1.51 (1.35, 1.69)	<.0001
NSAIDs	0.1375	0.05678	1.15 (1.03, 1.28)	0.0155
AIC	38384.74			

C.3 Calculating secular trends estimates in 10-year risk of CVA in RA and in general population using Cox spline hazard regression models

Secular Trends	Parameters
RA (before 1999)	Coefficient of 'Year of Incidence' + Coefficient of 'Year of Incidence * Indicator of RA vs. General pop.'
General Population (before 1999)	Coefficient of 'Year of Incidence'
Secular trend (RA vs general pop.) before 1999	Coefficient of 'Year of Incidence * Indicator of RA vs. General pop.'
RA (after 1999)	Coefficient of 'Year of Incidence' + Coefficient of 'Splined Year of Incidence' + Coefficient of 'Year of Incidence * Indicator of RA vs. General pop.' + Coefficient of 'Splined Year of Incidence * Indicator of RA vs. General pop.'
General Population (after 1999)	Coefficient of 'Year of Incidence' + Coefficient of 'Splined Year of Incidence'
Secular trend (RA vs general pop.) after 1999	Coefficient of 'Year of Incidence * Indicator of RA vs. General pop.' + Coefficient of 'Splined Year of Incidence * Indicator of RA vs. General pop.'