CARDIOVASCULAR DISEASE ASSOCIATED WITH THE USE OF GLUCOCORTICOIDS IN PATIENTS WITH RHEUMATOID ARTHRITIS. A POPULATION-BASED STUDY

by

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ABSTRACT

Most studies of mortality in rheumatoid arthritis patients (RA) have found increased mortality rates compared with the general population, and the majority suggest that one third to one half of the premature deaths in RA are due to increased cardiovascular disease (CVD), including myocardial infarction (MI) and cerebrovascular accidents (CVA). The increased risk of CVD mortality is not explained by traditional risk factors. The risk could be mediated by the deleterious effects of glucocorticoids (GC) used to treat RA. Alternatively, GC may have cardio-protective effects mediated by their anti-inflammatory and anti-proliferative actions in the endothelial wall, especially at low doses. Little is known regarding the long-term effects of GC on the development of CVD. A systematic review and a meta-analysis of all observational studies was conducted and described in Chapter two. This study found that study design is the main driver in the reported variation in mortality. The increased mortality was attributable to increased death from MI and CVA.

In Chapters three and four, we assessed the risk of MI and CVA associated with the use of GC, respectively. We assembled a large population-based cohort using administrative health data that included cases with newly-diagnosed RA that were not exposed to GC prior to disease onset. Thus, for the first time, we assessed GC exposure over the entire course of the disease. We used comprehensive GC exposure measures that considered actual and past cumulative exposure individually or together. In addition to the traditional method that considers the lifetime past cumulative exposure measures (duration of use and dose) regardless of recency of use, we used a novel time-dependent method to

evaluate if weighting for recency of use would improve the prediction of MI and CVA risk. This thesis has addressed the associated risk of CVD in patients with RA. Further, we have comprehensively assessed the association between GC use and risk of MI and CVA in unique cohort of patients with RA. Our results showed that GC use is associated with an increased risk of MI but not with an increased risk of CVA.

PREFACE

Sections of this thesis have been published and submitted as multi-authored papers in refereed journals. Details of co-authors' contributions are provided.

Chapter 2: Avina-Zubieta JA, Choi HK, Sadatsafavi M, Etminan M, Esdaile JM, Lacaille D. Cardiovascular risk published in Arthritis Care and Research 2008;59:1690-1697.

I designed the study with input from Hyon Choi and Diane Lacaille and John Esdaile. Diane Lacaille and I performed the literature review and data abstraction. I did the statistical analysis with support from Mohsen Sadatsafavi. I wrote the manuscript with comments and feedback from all co-authors.

Chapter 3: Aviña-Zubieta JA, Abrahamowicz A, Choi HK, Rahman M, Sylvestre MP. Esdaile JM, Lacaille D. Glucocorticoids use and the risk of acute myocardial infarction in patients with rheumatoid arthritis. A population-based study. A version of this chapter has been submitted for publication to Arthritis Care and Research 2010.

I conceptualized and designed the study, conducted the analyses with support from Mushfiqur Rahman and Marie-Pierre Sylvestre. Drs. Abrahamowicz supervised the statistical analyses. Drs. Lacaille, Choi and Esdaile contributed to the interpretation and discussion of the statistical analyses. I prepared the manuscript and submitted for publication. All co-authors contributed to the discussion of the results and provided feedback on drafts of the manuscript.

Chapter 4 Aviña-Zubieta JA Choi HK, Abrahamowicz A, Rahman M, Sylvestre MP. Esdaile JM, Lacaille D. Glucocorticoids use is not associated with an increased risk of cerebrovascular disease in patients with rheumatoid arthritis. A population-based study.

A version of this manuscript has been submitted for publication to Annals of the Rheumatic Diseases 2010.

I conceptualized and designed the study, conducted most of the analyses with support from Mushfiqur Rahman and Marie-Pierre Sylvestre. Drs. Abrahamowicz, Lacaille, Choi and Esdaile contributed with feedback on the interpretation and discussion of the statistical analyses. I prepared the manuscript and submitted for publication. All co-authors contributed to the discussion of the results and provided feedback on drafts of the manuscript.

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GLOSSARY

ACE	Angiotensin Converting Enzyme
AP	Activator Protein 1
ARB	Angiotensin Receptor Blocker
BC	British Columbia
CBI	Confounding by Indication
CCP	Anti-Cyclic Citrullinated Peptide
cGCR	Cytosolic Glucocorticoid Receptor
CI	Confidence Intervals
COBRA	Combinatierherapi Bij Rheumatoide Artritis
COPD	Chronic Obstructive Pulmonary Disease
CRP	C Reactive Protein
CV	Cardiovascular
CVA	Cerebrovascular Attacks
CVD	Cardiovascular Disease
DMARDs	Disease Modifying Anti-Rheumatic Drugs
GC	Glucocorticoids
GCR	Glucocorticoid Receptor
GREs	Glucocorticoid Responsive Elements.
HR	Hazard Ratio
HRT	Hormone Replacement Therapy
HSP	Heat-Shock Proteins

ICD-9	International Classification of Disease Version 9
MI	Myocardial Infarction
MTX	Methotrexate
NF-κβ	Nuclear Factor kappa-beta
NS	Not significant
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OR	Odds Ratio
PS	Propensity Scores
RA	Rheumatoid Arthritis
RR	Relative Risk
SD	Standard Deviation
SMR	Standardized Mortality Ratio
TNF-α	Tumor Necrosis Factor – Alpha
VIGOR	Vioxx Gastrointestinal Outcomes Research

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DEDICATION

This thesis is dedicated to my family. To my father who has been an inspiration all my life for his work ethic. He implanted early in my life the idea that I could achieve anything. To my mother who quietly and with dedication and unconditional love created the context that allowed me to grow with the peace of mind that she was always there if needed. To my children Ana Michelle and Marcos Andre, for their patience and understanding that time is not always available as we want, but mainly for teaching me that life has to be enjoyable, including the daily work. To my partner Griselda, for the last 17 years; she has been present with our children for both of us. Her unconditional support and loyalty will never be forgotten. To all of them from the bottom of my heart a sincere thank you.

1: INTRODUCTION

1.1 THESIS ORGANIZATION

This thesis is on the subject of cardiovascular risk associated with the use of glucococorticoids (GC) in patients with rheumatoid arthritis (RA) and is organized in a manuscript-based format. It consists of five chapters. Chapter one is the introductory chapter and provides the background for the manuscript chapters. It reviews the state of knowledge on topics related to the thesis research, including: a) epidemiology of RA; b) cardiovascular disease (CVD) in RA, c) history, mechanism of action and CVD side effects of GC, d) utilization of health databases for pharmacoepidemiology, e) purpose and review of thesis chapters. Chapter two presents a meta-analysis of published studies assessing the risk of CVD mortality in people with RA compared to the general population. This meta-analysis also assesses whether males and females differ in their risk of CVD mortality. It also evaluates methodological issues that could influence the interpretation of the results across studies. Chapter three examines the risk of acute myocardial infarction (MI) associated with GC use in people with RA using a population-based cohort of patients in the Canadian province of British Columbia (BC). This chapter describes a comprehensive assessment of several aspects of GC exposure and their association with risk of MI. Chapter four describes the association between exposure to GC and cerebrovascular accidents (CVA) risk in RA using the same approach as described in chapter three. The concluding chapter summarizes the findings of the three manuscripts and offers a critical discussion of the strength, the limitations as well as the relevance of the findings of this research.

1.2 RHEUMATOID ARTHRITIS

1.2.1 Epidemiology

RA is a chronic inflammatory autoimmune disease of unknown cause that affects most joints, leading to bone destruction and progressive joint damage. It is associated with severe disability and increased mortality [1]. RA has a worldwide distribution and affects all ethnic groups [2,3]. The disease affects predominately women and can occur at any age, but its prevalence increases with age; the peak incidence is between the fourth and sixth decades.

Several incidence and prevalence studies of RA have been reported during the last two decades, suggesting a considerable variation in the disease occurrence among different populations The majority of prevalence studies carried out in Northern European and North American areas estimate a prevalence of 0.5–1.1% Studies from Southern European countries report a prevalence of 0.3–0.7% [4-8]. Studies from developing countries also report a relatively lower prevalence of the disease (between 0.1% and 0.5%) [2,9,10]. A higher prevalence has been reported in certain Native Americans, and a very low frequency of RA in some areas of rural Africa [3,11].

There is some evidence suggesting that the incidence of RA in the adult population may be decreasing progressively over time. Doran et al. [12] reported that over a 40 year period in Rochester, Minnesota, the incidence of RA fell from 61.2 per 100,000 (over 1955 to 1964) to 32.7 per 100,000 (over 1985 to 1994). A similar time trend was observed by Kaipiainen-Seppanen et al. [13] who evaluated the annual incidence of RA in 5 districts in Finland over three years: 1980, 1985, and 1990. They found a decline in incidence of about 15% in 1990 compared to previous study years. Finally, a study performed in a defined area of Greece reported that the annual incidence rates

fluctuated between 15 and 36 per 100,000 inhabitants over the period 1987 to 1995, but no significant time trend was observed [4].

1.3 CARDIOVASCULAR DISEASE IN RHEUMATOID ARTHRITIS

Over the past decade, CVD has been recognized as a significant co-morbidity of RA. It is also the leading cause of excess mortality in RA [14]. However, comorbidity is most commonly defined as “a concomitant but unrelated pathological or disease process” [15]. Therefore, CVD is considered a direct complication of RA by some well respected clinicians [16]. Furthermore, some suggest that the current evidence justifies labelling CVD as an extra-articular manifestation of RA [17]. During the last decade several studies have documented that patients with RA have an increased risk of CVD when compared to the general population [14,18-20]. A population-based study from Rochester in the US found that risk of developing CVD was doubled in patients with RA (adjusted hazard ration [HR]= 2.13, 95% confidence intervals [95% CI]: 1.34 – 4.03) [19]. Similarly, Solomon et al. [21] using data from the Nurses’ Health Study reported that the adjusted relative risk (RR) of MI in women with RA compared with the general population was 2.0 (95% CI: 1.23 to 3.29) after adjusting for all known confounders. A recent meta-analysis [22] assessing the incidence of cardiovascular events found an increased risk for MI (pooled odds ratio [OR] = 1.63, 95% CI: 1.34 – 2.0). However, the authors reported that the incidence of fatal CVA was three times less than MI and did not find a significant increase in risk of CVA (pooled OR = 1.14, 95% CI: 0.86 - 1.51).

Patients with RA also have an increased risk of mortality from CVD. Most studies of mortality in RA patients have found increased mortality rates compared with the general population [23-26] and the majority suggest that one third to one half of the premature deaths in RA are due to increased CVD including ischemic heart disease, congestive

heart failure and CVA. However, there has been a wide variation in reported standardized mortality ratios (SMR) including studies detecting neither increased overall mortality (20-23) nor CVD mortality (19-26). Differences are attributable to different populations, designs, and timing of disease duration and follow-up of the studies [27]. Studies addressing specifically cardiovascular mortality in the literature will be discussed in chapter two, where the results of the systematic review are reported.

1.3.1 Traditional Risk Factors for CVD in Rheumatoid Arthritis

Heavy smoking is associated with an increased risk of developing RA as well as greater RA severity, especially with RA nodules, higher health assessment questionnaire (HAQ) scores, positive rheumatoid factor, positive anti-cyclic citrullinated peptide (anti-CCP) antibodies and higher radiological joint damage [28,29]. Regarding cardiovascular risk, smoking contributes to but does not explain all the excess CVD risk in RA. The prevalence of smoking habits appears higher in RA than in the general populations in most of the studies [21,30-32]. However, this increased prevalence did not demonstrate a significant effect on CVD risk [21,30].

The prevalence of hypertension is not increased in most RA studies [21,30,32], although conflicting results exist [33]. However, drugs such as non-steroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 (COX- 2) specific NSAIDs and GC can induce hypertension.

Insulin resistance is a risk factor for CVD even in patients without diabetes [34]. Abnormal glucose metabolism has been reported in RA patients and has been linked to inflammation and overweight [35,36]. Moreover, insulin resistance can also be induced by GC [37]. Although abnormal glucose metabolism has been reported in RA, most studies do not show an increased prevalence of diabetes in RA compared to controls

[21,30,32,38], except for a recent study [39] using administrative data from BC which found a 50% increased risk of diabetes mellitus in RA compared with controls (RR = 1.5, 95% CI: 1.4 - 1.5).

In the general population, high plasma homocysteine levels are associated with an increased risk of CVD, and lowering homocysteine concentration using folate supplementation reduces the risk of CVD [40,41]. Altered homocysteine metabolism has been demonstrated in patients with RA [42]. Methotrexate (MTX) used in the treatment of RA also increases homocysteine levels. Folic acid supplementation reduces homocysteine level, but the real net effect on CVD is not known.

The inflammation observed in RA may affect lipid metabolism. Data on total cholesterol level and atherogenic ratio of lipoproteins in RA are conflicting [43-46]. Data on high-density lipoprotein cholesterol (HDL-C) are more concordant, showing a reduction of HDL-C in several studies, particularly at the beginning of the disease and before RA treatment initiation [47,48]. This low HDL-C level can be corrected by treatment with traditional disease-modifying antirheumatic drugs (DMARDs) or anti-tumor necrosis factory alpha (TNF-α) therapy [45,49]. These data support the existence of a link between inflammation and altered HDL-C. Interestingly, it has been reported that healthy subjects who developed RA several years later had a significantly lower HDL-C and a more atherogenic lipid profile than other blood donors prior to the development of RA [50]. This observation strengthens the relationship between inflammation and atherosclerosis as discussed below.

1.3.2 Non-Traditional Risk Factors for CVD in Rheumatoid Arthritis

In RA, low body mass index appears as a paradoxical risk factor for CVD mortality. In a US cohort, RA patients with body mass index less than 20 had a significantly higher risk

of CV death in comparison with non-RA subjects with normal body mass index (HR = 3.34, 95% CI: 2.23 - 4.99), even after adjusting for traditional risk factors [51]. This paradoxical effect was confirmed in a second study cohort of 779 RA patients in the US [52]. The authors found a 9% reduction in the death risk for each unit increase in body mass index. This effect of body mass index was independent of age at RA onset, disease duration, sex, ethnic group, socioeconomic status, MTX use, and cigarette smoking status.

1.3.3 Inflammation and Atherosclerosis

Disease severity has been associated with incidence of CVD and CVD mortality in patients with RA [26,53,54] and the effect is independent of traditional risk factors [55]. This suggests that additional mechanisms are responsible for CVD in RA.

Potential mechanisms for the increased risk of CVD in RA include cytokine-mediated inflammatory pathways, overlapping pathogenic features between atherosclerosis and RA, and medications used to treat RA (e.g. NSAIDS, Cox-2 inhibitors and GC).

Accumulating evidence suggests that atherosclerosis is an inflammatory disorder sharing common pathogenesis with synovial inflammation and pannus formation that characterize RA [56]. Overlapping pathogenic features between the two diseases include the predominant role of pro-inflammatory cytokines (e.g., TNF-α and interleukin-6), elevated serum levels of acute phase reactants (C-reactive protein [CRP], fibrinogen, and serum amyloid-A), neo-angiogenesis, T cell

activation with an increased Th1 to Th2 cell ratio, and the local expression of leukocyte adhesion molecules and endothelin [56-60].

Evidence supporting a relationship between inflammation with atherosclerosis comes from population-based studies examining the association between elevated serum CRP levels and the subsequent development of CVD [61]. In a study involving more than 1000 healthy men, elevated baseline highly sensitive CRP levels were an independent predictor of incidence of MI. Furthermore, those in the highest quartile were nearly three times more likely than those in the lowest quartile to have an MI [61]. A direct role of CRP in the CVD causal pathway was suggested by demonstrating that CRP induces the expression of adhesion molecules on endothelial cells as well as the production of monocyte chemotactic protein-1 by CRP [62,63].

Endothelial dysfunction, characterized by reduced vasodilatation function, is an early event of CVD pathogenesis. A growing body of evidence suggests that systemic inflammation acts as an important mediator of endothelial dysfunction. For example, pro-inflammatory cytokines have been shown to impair endothelial function both in animal models and in dissected human veins [64]. Endothelial dysfunction has been demonstrated early in the course of RA [65].

If systemic inflammation promotes endothelial dysfunction and atherosclerosis, then it follows that the use of medications that control the inflammation in RA may decrease the CVD burden in this population [66,67]

1.3.4 Anti-Rheumatic Treatment and Cardiovascular Disease

The association between RA and CVD risk is complicated by the use of anti-rheumatic medications. Patients with persistent disease activity are more likely to receive treatment with NSAIDs, GC, DMARDs and biologics. There is some evidence that all these medications can alter CVD risk either by directly influencing atherosclerotic processes through reducing inflammation, or indirectly by influencing CVD risk factors.

NSAIDs are medications commonly used to reduce inflammation and to relieve pain in many conditions including RA. However, the risk for serious adverse cardiovascular effects associated with the use of nonselective and COX- 2 specific NSAIDs is an area of concern.

COX enzyme is crucial to the formation of prostaglandins and exists in two isoforms, a constitutive isoform (COX-1) and an inducible isoform that is expressed at sites of inflammation (COX-2). The anti-inflammatory effects are mediated through inhibition of COX-2, whereas adverse gastrointestinal effects are attributable to inhibition of COX-1, because prostaglandins produced through COX-1 protect the gastric mucosa. This led to the development of the selective COX-2 inhibitors in order to reduce inflammation with less adverse effects.

Although data confirmed that the selective COX-2 inhibitors were associated with a lower risk of gastrointestinal events than non-selective NSAIDs, the cardiovascular safety was challenged after the Vioxx Gastrointestinal Outcomes Research trial (VIGOR), which noted a two-fold higher incidence of MI in the rofecoxib group compared with the naproxen group [68]. The lack of a placebo arm and the possible anti-thrombotic effects of naproxen, made it difficult to interpret the results [69]. However, a cumulative meta-analysis by Juni et al. [70] published in 2004 that included 18 randomized clinical trials and files from the US Food and Drug Administration for a total of 25,273 patients

found that the RR of MI was more than doubled (OR = 2.30, 95% CI: 1.22 – 4.33) within the first year of treatment and in the second year it was 2.24 (95% CI; 1.24 – 4.02). The authors also concluded that there was no evidence that the risk differed depending on the control group (e.g., use of naproxen versus ibuprofen). The combined risk for CVA in 11 trials was 1.02 (95% CI: 0.54- 1.93). On September of 2004 rofecoxib was voluntarily withdrawn by Merck. At that time it was unclear whether the increased CVD risk observed with rofecoxib was drug specific or reflected a broader class effect of selective COX-2 inhibitors [71].

Several clinical trials and meta-analyses assessing the risks of non-selective NSAIDs and individual COX-2 inhibitors have been published [70,72,73] (Table 1.1 and 1.2). From these studies we can conclude that selective COX-2 inhibitors are associated with a moderately increased risk of CV events, largely attributable to a twofold increased risk of MI. Moreover, it seems that high dose for some traditional NSAIDs such as diclofenac and ibuprofen are also associated with similar excess risk of CV events.

Table 1.1 Clinical Trials on COX-2 Inhibitors and Risk of Cardiovascular Disease

Trial (ref)	Study (N of subjects)	COX-2	Comparator	Relative Risk for CVD (95 % CI)
Rofecoxib				
VIGOR [68]	RA (N= 8,056)	Rofecoxib	Naproxen	2.38 (1.39 - 4.0)
APPROVe [74]	Adenoma prevention (N= 1,364)	Rofecoxib	Ibuprofen	1.92 (1.19 – 3.11)
Celecoxib				
CLASS [75]	OA and RA (N= 5,972)	Celecoxib	Ibuprofen	0.83 *
			Diclofenac	1.07 *
APC[76]	Adenoma prevention (N= 2,035)	Celecoxib	Placebo	2.3 (0.9 – 5.5)
PreSAP[77]	Adenoma prevention (N=1,561)	Celecoxib	Placebo	1.1 (0.6 – 2.3)
ADAPT [78]	Alzheimer prevention (N= 2,528)	Celecoxib	Naproxen	Terminated early **
Lumiracoxib				
TARGET [72]	OA (N= 18,325)	Lumiracoxib	Ibuprofen	0.76 (0.41 – 1.40)
			Naproxen	1.46 (0.89 – 2.37)
Etoricoxib				
MEDAL [79]	OA and RA (34,701)	Etoricoxib	Diclofenac	0.95 (0.81 – 1.11)
Valdecoxib				
CABG I [80]	Post-CABG (N= 462)	Valdecoxib	Placebo	2.9 *
CABG II[81]	Post-CABG (N= 1,115)	Valdecoxib	Placebo	3.7 (1.0 – 13.5)

Abbreviations

VIGOR = Vioxx Gastrointestinal Outcomes Research study; RA = rheumatoid arthritis, OA = osteoarthritis; APPROVe = Adenomatous Polyp Prevention on Vioxx trial; CLASS = Celecoxib Long-term Arthritis Safety Study; APC = Adenoma Prevention with Celecoxib trial; PreSAP = Prevention of Spontaneous Adenomatous Polyps study; ADAPT = Alzheimer Disease Anti-inflammatory Prevention Trial; TARGET = Therapeutic Arthritis Research and Gastrointestinal Event Trial.

* When unavailable, the relative risks were calculated as the crude event rate in coxib group divided by the crude rates in the comparison group.

** Study was terminated early when concurrent celecoxib clinical trial showed increased cardiovascular events with celecoxib.

Table 1.2 Meta-Analyses on Cardiovascular Safety of Non-Steroidal Anti-Inflammatory Drugs and Risk of Cardiovascular Disease

Author / year (ref)	No. of Studies	Cardiovascular disease Relative Risk (95% confidence interval)
McGettigan/2006[82]	**17 case-control studies:** N= 86,193 CV events and 528,000 controls **6 cohort studies** (N= 75,520)	Rofecoxib: < 25 mg/day RR 1.33 (1.00 – 1.79) Rofecoxib: > 25 mg/day RR 2.19 (1.64 – 2.91) Celecoxib: RR 1.06 (0.91 – 1.23) Diclofenac: RR 1.40 (1.16 – 1.70) Naproxen: RR 0.97 (0.89 – 1.07) Ibuprofen: RR 1.07 (0.97 – 1.18)
Kearney /2006 [83]	138 trials (N= 145,373)	**COX-2 versus:** Placebo RR 1.42 (1.13 – 1.78); RR for MI: 1.86 (1.33 – 2.59) RR for Stroke: 1.02 (0.71 – 1.47) non-selective NSAIDs RR: 1.16 (0.97 – 1.38) RR for MI: 1.53 (1.19 – 1.97) RR for Stroke: 0.83 (0.62 – 1.12) Naproxen RR: 1.57 (1.21 – 2.03) RR for MI: 2.04 (1.41 – 2.96) RR for Stroke: 1.10 (0.73 – 1.65) Ibuprofen RR: 1.51 (0.96 – 2.37) Naproxen versus placebo RR: 0.92 (0.67 – 1.26)
Salpeter/2006[84]	13 (N= 7,719)	Non-selective NSAIDs: RR 1.3 (0.8 – 2.1)
Juni/2006 [70]	18 RCT, 11 Observational	Rofecoxib; RR 2.30 (95% CI; 1.22 – 4.33)

The exact mechanism that mediates the increased risk for thrombotic events in COX-2 selective inhibitors is unclear. It has been hypothesized that COX-2 selective inhibitors block the production of prostacyclin which plays an important role for dampening the effects of thromboxane. Thromboxane promotes platelet aggregation and vasoconstriction. Studies of healthy volunteers showed that urine levels of prostacyclin metabolite were reduced in subjects taking rofecoxib, suggesting that endovascular production of prostacyclin may be COX-2 mediated [85]. Moreover, studies in animal models showed that COX-2 is up-regulated in vascular segments under conditions of increased shear stress [86]. One potential implication of these observations is that COX-2 plays a beneficial role in vascular health and that its inhibition may create an imbalance between thromboxane and prostacyclin, thereby favoring thrombosis and vasoconstriction. This hypothesis has been confirmed in animal models using knockout mice [87,88].

The conventional treatment of RA combines anti-inflammatory medications and DMARDs. MTX is the most commonly used DMARD and is recommended in the management of early and established RA by the European League Against Rheumatism and by the American college of Rheumatology [89,90]. This drug inhibits the metabolism of folic acid, has hepatic metabolism and renal excretion. MTX increases homocysteine level which is an independent risk factor for CVD [91]. Folic acid supplementation reduces homocysteine level, but we don't know the net effect on CVD.

Alarcon et al. [92] in a prospective cohort study reported that patients treated with MTX had a higher overall mortality than patients not treated with MTX (OR = 1.9, (95% CI: 1.3 – 2.8). However, CVD mortality was not increased (OR= 1.4 [95% CI 0.5 – 2.6). Mortality from CVA was increased, but the increased risk was not statistically significant (OR = 2.9, 95% CI: 0.6 – 8.6).

Another study by Landewe et al. [93] evaluated the risk of mortality associated with MTX use. They found that patients with a history of CVD who started MTX had a higher risk of death compared to patients without prior CVD. In contrast, Choi et al. [94] demonstrated that after adjusting for other significant cardiovascular risk factors and for confounding by indication (CBI), MTX was associated with a 70% reduction in the risk of CVD related death (RR = 0.3, 95% CI: 0.2 - 0.7). The protective effect of MTX on CVD risk was confirmed in a large cohort of 107,908 RA patients, which reported that the RR was decreased with the current use of MTX (RR = 0.81, 95%CI: 0.60 – 1.08). Similar results were reported by van Halm et al. [95] in a case-control study of 613 patients where MTX use was associated with a significant CVD risk reduction (OR = 0.16, 95%CI: 0.04 – 0.66).

The protective role of other DMARDs with respect to CVD has been recently addressed by Solomon el al. [66]. In this nested case-control study among elderly with low socioeconomic status from Pennsylvania (N= 3,501) the authors identified 438, 639 and 946 cases who were hospitalized for MI, CVA or both, respectively. After adjusting for cardiovascular risk factors, comorbidity and disease variables, they found that use of DMARDs other than MTX (e.g., azathioprine, cyclosporine and leflunomide) were associated with an increase in risk of CVD (OR = 1.8, 95% CI: 1.1 – 3.0). However, when looking at MI and CVA separately, the results were only significant for MI (OR = 2.7 95% CI: 1.3 – 5.8 for MI and OR = 1.7, 95% CI: 0.8 – 3.4 for CVA). It is important to note that in this study, the reference category was MTX rather than no DMARDs. Of interest, GC use [yes/no] as monotherapy was associated with an increased risk of CVD (OR = 1.5, 95% CI: 1.1 – 2.1) and of CVA (OR = 1.7, 95% CI: 1.7 – 2.6), but not of MI (OR = 1.5, 95% CI: 0.9 – 2.5). In summary, the evidence points towards a protective effect of MTX on overall and CVD mortality.

Given that TNF-α plays a key role in the development and progression of atherosclerosis via endothelial cell activation and endothelial dysfunction [67], one would expect than anti-TNF-α treatment for RA would reduce the risk of CVD.

Several studies have explored the effect of anti-TNF-α treatment on the lipid profile of patients with RA, and most showed an increase in HDL-C [96-98]. However, these changes were not sustained, returning to baseline after 6 months. Similarly, TNF-α inhibition may improve endothelial function in patients with RA, although the duration of the effect is not clear [99].

Clinical trials of anti-TNF-α treatment in RA have not focused on CVD and, are not sufficiently powered to detect modest changes in the incidence of rare events such as MI or CVA. Therefore, we must rely on large observational studies. A Swedish study by Jacobson et al. [100] reported that the risk of incident CVD was reduced around half in users of anti-TNF compared to TNF naïve patients. However, in this study the number of CV events was small (n = 13) and they were not able to evaluate the risk of MI or CVA separately. Furthermore, they were not able to adjust for several potential confounders. Solomon et al. [66] using a large healthcare and insurance claim database reported that rates of MI in patients with RA treated with biologics were not significantly different from rates in patients treated with MTX monotherapy (OR = 1.8, 95% CI: 0.5 – 6.8) or no DMARDs (OR = 1.30, 95% CI: 0.92 – 1.83). In contrast, Carmona et al. [101] showed that all cause mortality in patients with RA treated with anti-TNF-α agents was not different from the general population of similar age and gender. However, mortality in RA patients treated with anti-TNF-α agents was reduced compared with patients with RA not treated with anti-TNF-α agents. Finally, Dixon et al. [102] using data from the British Society for Rheumatology Biologics Register, a national prospective observational study of 8,670 patients treated with anti-TNF-α agents and 2,170 patients treated with traditional DMARDs, reported that after adjusting for baseline risk factors, there was no

difference in the rate of MI between the two groups (incidence rate ratio = 1.44, 95% CI: 0.56 – 3.67). However, when they compared patients who responded to treatment within 6 months versus those who did not, the incidence rate of MI for responders was lower compared to non-responders (incidence rate ratio = 0.36, 95% CI:0.19 – 0.69). In summary, the effect of anti-TNF on CVD is still unclear and further studies are needed.

1.4 GLUCOCORTICOIDS

1.4.1 History and Development of Glucocorticoids

In the period 1930-1938, Dr. E. C. Kendall had isolated several steroids from the adrenal gland cortex. At the Mayo Clinic Dr. Phillip Hench, a rheumatologist, observed the favourable effects of jaundice on arthritic patients, causing a remission of pain. He also observed that changes such as pregnancy produced the same effect in people with arthritis. These and other observations led him gradually to the conclusion that the pain-alleviating substance was a steroid. After several years of collaboration with Dr. Kendall, Dr. Hench attempted to evaluate the effect of one of these substances, Compound E (later named cortisone), on patients with RA. Dr. Hench's military service in World War II and the cost and difficulties isolating the substance led to delays. It was not until 1948-1949 that cortisone was successfully tested on patients with rheumatoid arthritis [103]. Hench also treated patients with adrenocorticotropic hormone, a hormone produced by the pituitary gland that stimulates production of cortisone by the adrenal gland. Their work subsequently resulted in a Nobel Prize in Medicine, the only Nobel Prize awarded to a rheumatologist to date. However, very early Dr. Hench rejected the idea that steroids were of etiological significance for RA. Instead he stressed their unique place as a tool for pathophysiological research [104]. Sixty years later, all of Hench’s statements are still highly relevant: GC are involved in various physiological processes (e.g. glucose

metabolism, cell differentiation, growth control, apoptosis and modulating inflammatory processes).

1.4.2 Reappraisal of Glucocorticoids in the Treatment of Rheumatoid Arthritis

GC were first shown to be effective in patients with RA in 1949 in an uncontrolled study [103]. Enthusiasm generated by the dramatic results led to the use of high doses, which disclosed a spectrum of toxicity that shook the foundations of this treatment. In 1959, a two year randomized trial showed that 20 mg/day of prednisolone was significantly superior to aspirin 6 grams daily [105]. However, the authors concluded that the highest acceptable dose for long term treatment was probably in the region of 10 mg daily due to high toxicity with the 20 mg daily dose. Since the early 1980s Harris suggested that low dose long-term GC may decrease progression of radiological damage [106,107]. Since then the effect of GC, on both clinical and radiographic parameters, in early RA has been the subject of considerable research effort and much debate [108-112].

In 1995, Kirwan et al. [113] conducted a large randomized controlled trial comparing the effects of low dose (7.5 mg/day) GC on joint destruction in early RA. After two years, the number of new erosions was significantly lower in the prednisolone-treated group. A follow-up study of this cohort in 1998 reported that joint destruction resumed in the prednisolone group after therapy was discontinued [114], which differed from the results of the Combinatierherapi Bij Rheumatoide Artritis trial (COBRA) [108].

The COBRA trial was a double blind trial comparing a combination regimen of high dose prednisone, methotrexate and sulphasalazine with sulphasalazine alone in patients with early RA. The dose of prednisone was 60 mg/day for the first week, tapered over the next weeks to 7.5mg/day and ultimately discontinued after 28 weeks. The study showed

that combination therapy was superior to monotherapy with no increase in toxicity. The study also showed that the benefits in terms of reduced joint damage during the first year were indeed carried over and amplified during 5 years of follow-up [115]. Further randomized trials using intensive GC therapy in early RA have been published since then [116-118] and have consistently supported the concept that GC have a disease modifying effect and have renewed the debate over the risk/benefit ratio of this treatment [109,110,112].

Arguments against GC use are dominated by fear of toxicity. Although supported by data, this fear is strongly influenced by observations derived from the use of high doses of GC [119]. Whether this fear is justified when GC are used in small doses, as used in the treatment of RA, has not been clearly established.

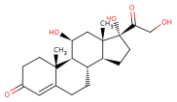
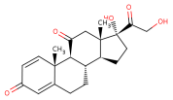
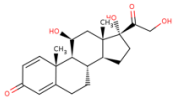
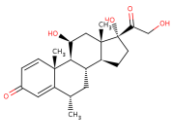
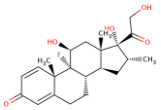
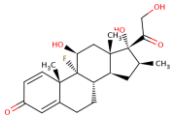
1.4.3 Mechanism of Action of Glucocorticoids

The understanding of the actions of GC has greatly increased in the last decade [120]. GC are stress hormones with a vital role in regulation of metabolic and defence responses. They are generated from cholesterol which occurs in the zonae fasciculata and reticularis of the adrenal cortex, which is tightly regulated by the hypothalamic-pituitary-adrenal axis, with GC regulating their own generation by negative feedback inhibition on several components of the axis. Under this control, GC are produced de novo and released into the blood as required, with a clear circadian rhythm producing peak blood concentration in the early morning diminishing to a nadir in the evening. Cortisone is the major GC in humans. Upon secretion into the blood, up to 90% of GC are sequestered to corticosteroid-binding globulin and albumin with only the unbound fraction available to interact with their receptors [121]. Metabolic inactivation of GC

occurs predominantly in the liver, but also in the kidney. Inactive metabolites are excreted in the urine.

Currently there are several synthetic GC, which have different potency and half lives compared to cortisol (Table 1.3).

Table 1.3 Chemical Structure and Potency of Commonly Used Synthetic GC

NAME	CHEMICAL STRUCTURE	Potency	Half-Life
Hydrocortisone		1	6-8 hours
Prednisone		4	2-3 hours
Prednisolone		4	2-3 hours
Methylprednisolone		5	1-3 hours
Dexamethasone		25	36-54 hours
Betamethasone		1	5.6 hrs

GC are ligands both for high affinity type I (mineralocorticoid receptors) and for low affinity type II glucocorticoid receptors (GCR). GCR are predominantly intra-cellular receptors, although new evidence suggests the presence of membrane-bound versions

on the cell surface [122] whose physiological relevance remains undetermined. GCR may exist in two forms – GCRα, which has a high affinity for GC and is expressed throughout the body. In contrast to GCR-α, mineralocorticoid receptors (GCR-β) are expressed in selected tissues (e.g., distal nephron, colon, salivary and sweat glands and vascular endothelium) and at lower levels and they bind aldosterone exclusively.

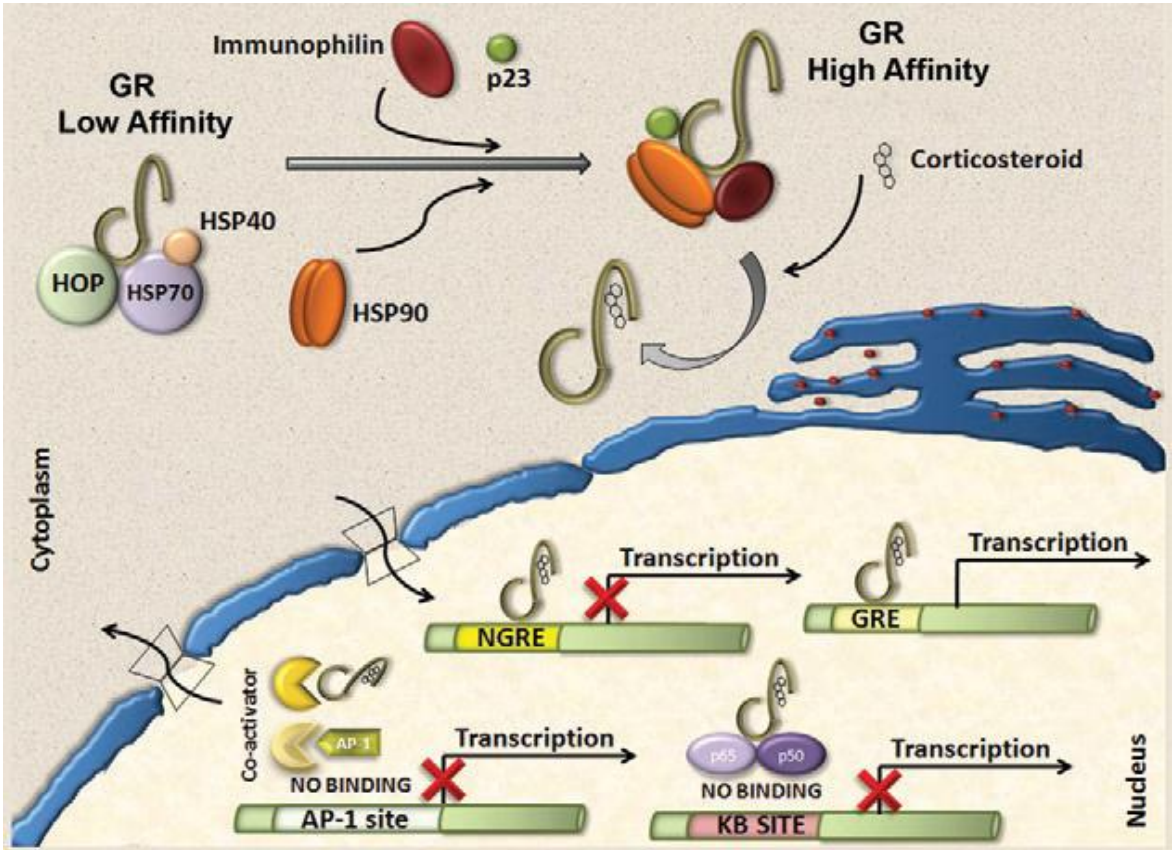
1.4.4 Genomic Actions of Glucocorticoids

The anti-inflammatory and immuno-modulatory effects of GC are mediated predominantly by genomic or nuclear receptor-dependent mechanisms that have been well investigated [123,124]. Binding to the cytosolic glucocorticoid receptor (cGCR) ultimately induces ("transactivation") or inhibits ("transrepression") the synthesis of regulatory proteins. The characteristics of the genomic mechanisms are as follows. First, they are physiologically relevant and therapeutically effective at all doses including low dose therapy. Second, the genomic action is slow (no changes seen before 30 minutes). Third, the GC-induced synthesis of regulatory proteins can be prevented by inhibitors of transcription or inhibitors of translation. Fourth, multiple genes are directly regulated by GC (10 to 100 per cell). It is estimated that GC influence the transcription of ~1% of the entire genome [125].

As lipophilic substances, GC pass very easily through the cell membrane into the cell, where they bind to the ubiquitously expressed cGCR. The inactivated (unligated) cGCR is retained in the cytoplasm as a multiprotein complex consisting of several heat-shock proteins (HSP) that act as chaperones. This complex interacts with other proteins including immunophilins, p23 and several kinases of the MAPK signalling system which also act as molecular co-chaperones (Figure 1.1). The general function of these

chaperones is to bind and to stabilize proteins at intermediate stages of folding, assembly, translocation and degradation.

Figure 1.1 Genomic Actions of Glucocorticoids.



Abbreviations: AP-1 - activator protein 1; GREs: glucocorticoid responsive elements
GC: glucocorticoid receptor; HOP: HSP organizing protein; NGRE: non glucocorticoid responsive elements;
Source: With permission from Memórias do Instituto Oswaldo Cruz Journal [126].

Translocation into the cell nucleus occurs within 20 minutes. Depending on the target gene, transcription is thus either activated (transactivation) or inhibited (transrepression). A good example of this is the inhibition of cytokine synthesis.

Besides the interactions of GC/cGCR complexes, the interaction of activated cGCR monomers with transcription factors is recognized as a further important genomic mechanism of GC action [127]. The complex GC/cGCR also modulates the activity of

activator protein 1, NF-κβ and nuclear factor of activated T cells leading to inhibition of the nuclear translocation and/or function of these transcription factors and, hence, to inhibition of the expression of many immuno-regulatory and inflammatory cytokines. There is an alternative variant of the cGCR, the cGCRβ isoform. This isoform does not bind ligand and acts as a dominant-negative inhibitor of cGCRα. This isoform is expressed only in humans.

1.4.5 Non-genomic Actions of Glucocorticoids.

Some regulating effects of GC are seen within seconds or minutes [128-130]. These observations cannot be explained by genomic actions because of the time required for their occurrence. These non-genomic actions are believed to be responsible for the rapid effects of GC.

Once the complex GC/GCR has taken place, not only the classic genomic actions described above occur, but rapid non-genomic actions also occur. It has been reported that the phospholipase A2 dependent activation of growth factors in the cytosol with subsequent liberation of prostaglandins can be rapidly inhibited by GC [131-133]. This effect is thought to be mediated by the occupation of cGCR, but not by changes in the gene transcription. It is believed that the above mentioned chaperones or co-chaperones act as signalling components and, therefore, as mediators of this effect.

Additional non-genomic mechanisms that have been observed are dose dependent. Saturation of all cGCR is almost complete at a dose of 100 mg of prednisone equivalent a day, such that the specificity (the exclusivity of receptor-mediated effects) is lost at high concentrations of GC, which are used clinically. Nonspecific non-genomic actions in the form of physicochemical interactions with biologic membranes occur. A nonspecific intercalation of GC molecules into the cell membranes, alters cell functions by

influencing cation transport through the plasma membrane. The resulting inhibition of calcium and sodium cycling across the plasma membrane of immune cells is thought to contribute to rapid immunosuppression and to a reduction in the activity of the inflammatory process [134].

Additionally specific non-genomic actions mediated through membrane bound GCR (mGCR) have now been accepted after long debate. Recently, the existence and function of membrane bound receptors including mGCR have been demonstrated. Previously these were only known to exist in amphibian brains and leukemia/lymphoma cells. However, they have also been demonstrated on human peripheral blood mononuclear cells of normal subjects [135]. The authors concluded that mGCR are 1) physiologically present in healthy blood donors, but remain unidentified by conventional techniques due to their small number per cell and 2) actively up-regulated and transported through the cell after immuno-stimulation. These receptors may reflect a feedback mechanism of the organism upon immuno-stimulation and/or play a role in pathogenesis. These in vitro findings are consistent with the clinical observation that in patients with RA, the frequency of mGCR-positive monocytes is increased and correlates with disease activity [135].

1.4.6 Cardiovascular Side Effects of Glucocorticoids

GC treatment is considered a risk factor for dyslipidemia and atherosclerosis. Several studies in patients with systemic lupus erythematosus suggest that GC treatment is associated with hypercholesterolemia in a dose dependent fashion with significant increase in risk of hypercholesterolemia seen only at prednisone doses higher than 10 mg/day [136,137]. Beyond induction of dyslipidemia, the role of GC in atherosclerosis is controversial. Longer GC use has been significantly associated with increased risk of

coronary artery disease in patients with RA [138]. A study in RA patients suggested that GC treatment early in the disease course increased the risk of coronary artery disease [139]. On the other hand, in a study using an animal model of atherosclerosis [140], the administration of dexamethasone induced hyperlipidemia, but also reduced aortic plaque formation, an effect attributed to inhibition of infiltration of inflammatory and foam cells in plaques. Moreover, the recognition of an association between raised CRP and accelerated coronary artery disease offers a theoretical basis for GC benefit on atherosclerotic disease in inflammatory diseases [141]. Furthermore, recent data from RA cohorts showed that disease activity unfavourably alters the blood lipid profile, and that reduction of disease activity with treatment (including GC) can reverse these changes [48].

In all previous clinical trials of low dose GC treatment in RA including the COBRA trial [108], no excess cardiovascular events were reported. However, the trial durations are usually less than 2 years which are too short for development of cardiovascular complications.

Recently, several observational studies have evaluated the risk of CVD associated with the use of GC (Table 1.4). Wei et al. [142] using a record linkage database on 68,781 GC users (of whom 1,115 patients had RA) and 82,202 non-users found that CVD was increased only in patients using > 7.5 mg/day after adjusting for all known risk factors (RR = 2.56, 95%CI: 2.18 - 2.99). The corresponding risk for patients with inflammatory arthritis matched by propensity score was 5.1 (95%CI: 1.6 – 17.1). Of interest, in this study patients with inflammatory bowel disease did not have an increased risk for CVD when compared to the same doses, even after adjusting for matched propensity scores, suggesting the RA itself may play an additional role. All individual outcomes (MI, congestive heart failure and CVA) showed an increased risk for doses > 7.5 mg/day. In particular, the risk of MI and CVA were 3.26 (95% CI; 2.60 – 4.09) and 1.73 (95%; 1.22 –

2.44), respectively. The risks of individual CVD outcomes were not assessed specifically in the subgroup of patients with inflammatory arthritis. In this study CVA events included stroke as well as transient ischemic attacks (TIA).

Table 1.4 Studies Evaluating Glucocorticoid Use and Risk of Cardiovascular Disease

Author / year	GC exposure Measure	Design (n)	Number of CV events	Outcome(s)	Adjusted Risk (95% CI)
Wei / 2004 [142]	**ALL GC users** Low dose (inhaled, topical, nasal GC) Medium dose (< 7.5 mg /day) High dose (> 7.5 mg/day)	Nested case-control	NAV for MI	MI	0.97 (0.91 – 1.05) 0.98 (0.87 – 1.09) 3.26 (2.60 – 4.09)
	Low dose (inhaled, topical, nasal GC) Medium dose (< 7.5 mg /day) High dose (> 7.5 mg/day)		NAV for Stroke/TIA	Stroke/TIA	0.99 (0.92 – 1.08) 0.87 (0.76 – 1.00) 1.73 (1.22 – 2.44)
	Low dose (inhaled, topical, nasal GC) Medium dose (< 7.5 mg /day) High dose (> 7.5 mg/day)		68,781 / 82,202	CVD (*)	1.00 (0.95 – 1.05) 1.03 (0.96 – 1.10) 2.56 (2.18 – 2.99)
	Inflammatory Arthritis Low dose (inhaled, topical, nasal GC) Medium dose (< 7.5 mg /day) High dose (> 7.5 mg/day		1,165 / NAV	CVD (*)	*Matched cohort (**)* 0.95 (0.46 – 1.99) 1.26 (0.68 – 2.32) 5.17 (1.56 – 17.18)
Souverein / 2004 [143]	**All GC users** Ever use Current use (last 3 months) Recent use (> 3 but < 12 months) Past use (> 12 months)	Nested case - control	50,656	IHD	1.09 (1.03 – 1.15) 1.20 (1.1 – 1.29) 0.93 (0.85 – 1.02) 1.07 (0.98 – 1.17)
	Ever use Current use (last 3 months) Recent use (> 3 but < 12 months) Past use (> 12 months)		3,656	Stroke/TIA	0.95 (0.89 – 1.01) 0.91 (0.84 – 0.99) 0.89 (0.80 – 0.99) 1.06 (0.96 – 1.17)
	RA cohort Current use (last 3 months) Recent use (> 3 but < 12 months) Past use (> 12 months)		1,515		1.36 (1.02 – 1.81) 1.28 (0.67 – 1.77) 1.17 (0.82 – 2.19)

Author / year	GC exposure Measure	Design (n)	Number of CV events	Outcome(s)	Adjusted Risk (95% CI)
Davis / 2007 [144]	**Rheumatoid arthritis** Recent use (< 3 months) Past use (> 3 months) *Daily dose* < 7.5 mg / day > 7.5 mg / day *Cumulative dose* < 1.5 g of cumulative dose > 1.5 – < 7.0 g of cumulative dose > 7.0 g of cumulative dose **RA with RF-positive (#)** Recent use (< 3 months) Past use (> 3 months) *Daily dose* < 7.5 mg / day > 7.5 mg / day *Cumulative dose* < 1.5 grams > 1.5 – < 7.0 grams > 7.0 grams	Cohort (603)	232	CVD (&)	1.66 (1.14 – 1.60) 1.13 (0.80 – 1.60) 1.26 (0.80 – 2.01) 1,75 (1.05 – 2.91) 1.01 (0.66 – 1.54) 1.06 (0.68 – 1.67) 1.90 (1.28 – 2.82) 3.26 (1.86 – 5.71) 1.62 (0.92 – 2.86) 2.21 (1.22 – 4.00) 3.13 (1.74 – 5.62) 1.69 (1.00 – 2.88) 1.52 (0.84 – 2.74) 3.06 (1.81 – 5.18)
Varas-Lorenzo / 2007 [145]	**GC users (404,183)** Current users (last 30 days) First 30 days of use > 10 mg/day	Nested case-control	4,795	AMI	1.42 (1.17 – 1.72) 2.24 (1.56 – 3.20) 2.15 (1.45 - 3.14)

Abbreviations: GC – glucocorticoids; CV - cardiovascular; NAV – not available; IHD – ischemic hear disease; RA – rheumatoid arthritis; MI – myocardial infarction; TIA – transient ischemic attack; CVD – cardiovascular disease; (*) = includes heart failure, MI, stroke + transient ischemic attacks; (&) = includes MI and heart failure; (**) matched by propensity score

Souverein et al. [143] using a nested case-control study of 50,656 GC users (of whom 1,515 had RA) with ischemic heart disease and CVA, found a significant association between having “ever” used oral GC and risk of any CVD outcome (which included MI, CVA or congestive heart failure) (OR = 1.25, 95% CI: 1.21 to 1.29). The association was stronger for current use (last 3 months, OR = 1.37, 95% CI; 1.16 -1.62) of GC than for recent (> 3 months but less than 1 year, OR = 1.28, 95% CI; 0.98-1.68) or past use (> 1 year, OR = 1.17, 95% CI; 0.87 – 1.58). Similar results were seen for specific outcomes including AMI, CVA, and congestive heart failure (Table 1.4). As in the previous study, CVA events included stroke and TIA as a composite outcome.

In 2006, Davis et al. [144] in a population-based inception cohort of 603 patients with RA reported that GC exposure was associated with an increased risk for CVD only in patients with positive rheumatoid factor. Thus, rheumatoid factor negative patients with exposure to GC were not at increased risk of cardiovascular events, irrespective of the GC dosage or timing of use, as compared with the reference group of rheumatoid factor negative patients who had never been exposed to GC. Similarly to the study previously described, only recent exposure (3 months) to GC was associated with an increased risk of the combined CVD outcome (RR = 1.66, 95%: 1.14 – 2.41). Unfortunately, probably due to power issues the authors used a combined outcome for CVD (MI and congestive heart failure) rather than individual outcomes. Risk of CVA was not assessed in this study.

Most recently Varas-Lorenzo et al. [145] performed a nested-case control study of 404,183 persons, aged 50 to 84 years with 4,795 MI events from the general practice research database in the United Kingdom. The authors reported that risk of MI in current GC users (within 30 days prior to the MI) was 42% higher than non-users (OR= 1.42, 95% CI: 1.17 – 1.72). Of interest, they also found that the risk appeared to decrease as time elapsed since the end of last GC exposure prior to the MI, returning to the risk

observed among non-users after 6 months of stopping treatment. When they used past users (between 31 and 180 days prior to the MI) as reference group, the corresponding risk for current users was 1.28 (95% CI: 1.04 – 1.58). Moreover, the risk of MI among current users was higher among patients with a priori history of MI or angina than in those with no prior history of coronary artery disease (OR = 1.53, 95%: 1.21 – 1.93). When they assessed risk by disease indication they found that in RA, current use was not significantly associated with increased risk of MI (OR = 1.37, 95% CI: 0.85 – 2.21). However, the number of events in RA was small (n= 40).

In all observational studies the observed association between GC use and risk of CVD had a dose dependent relationship, with higher doses and higher cumulative exposure having a greater increase in risk, suggesting a dose response effect. Similar trends have been recently reported for non-cardiovascular adverse events [146]. Moreover, it seems that only recent exposure (within last six monts) is associated with an increased risk of CVD.

1.5 UTILIZATION OF HEALTH DATABASES FOR PHARMACO-EPIDEMIOLOGY

It is widely accepted that randomized clinical trials cannot provide all necessary information about the safety of medications at the time they are marketed. RCT usually have a small sample size that may be insufficient to detect rare adverse events, such as cardiovascular events. They also include study populations where vulnerable or high risk patient groups are often under-represented. Furthermore, they focus on short-term efficacy and safety in a controlled environment that is often far from routine clinical practice. Such limitations point to the need for pharmacoepidemiologic research

performed on observational cohorts post-marketing to define long-term issues with respect to safety, compliance, adherence and effectiveness in the real world.

The focus of pharmacoepidemiology is to assess the safety of medications, biologic agents and medical devices in the context of the natural history of the condition they are designed to treat. Although pharmacoepidemiology makes uses of all epidemiologic study designs and data sources, in recent years there has been significant growth in the use of administrative health care databases [142,147-151]. These are made up of the automated electronic recording of filled prescriptions, professional services, and hospitalizations. Beyond this, they may include electronic medical records which may contain detailed medical information, patient's report of symptoms, findings of physical examination, and results from laboratory data. However, researchers more frequently use insurance data from submitted claims for reimbursement of specific services, procedures, and medications. These are usually less detailed in their clinical contents but often representative and complete for very large populations, including elderly, children, the very poor, and those in nursing homes who are most often under-represented or totally excluded from RCT.

In the last decades several "administrative databases" have been used in multiple pharmacoepidemiologic studies in North America and Europe [66,102,142,143,148,151-153]. In Canada, a universal and publicly funded health care system is available. Each province administers its own health data. Several pharmacoepidemiologic studies have been published using administrative databases from Saskatchewan, Quebec, Ontario, Nova Scotia and British Columbia [154-157].

1.6 PURPOSE

The overall aim of this thesis was to assess the role of GC on the risk of CVD in RA. To this effect, the first objective was to describe the mortality burden from CVD in patients with RA compared with the general population. Then to assess the risk of MI and CVA associated with the use of GC when assessed over the entire disease duration and in a population-based incident cohort of patients with RA.

1.7 OVERVIEW OF THESIS CHAPTERS

This thesis consists of three manuscript chapters, placed between the introductory and concluding chapters. Together they address the impact of CVD in RA, and the contemporary role of GC on the risk of MI and CVA. The primary aim of each manuscript chapter is briefly described below:

Chapter 2 is a systematic review of studies evaluating CV mortality in patients with RA compared with the general population. It answers the following research question: Is CVD mortality increased in patients with RA compared to the general population? If so, what is the magnitude of the risk?

Chapter 3: Is a population-based, longitudinal study assessing the association between GC use and AMI in an incident cohort of RA patients with incident GC use assessed over the entire disease course. It answers the research question: Does GC use increase the risk of MI in patients with RA? If so, what is the impact of daily dose and past cumulative exposure?

Chapter 4: Is a population-based, longitudinal study assessing the association between GC use and CVA in an incident cohort of RA patients with incident GC use assessed over the entire disease course. It answers the research question: Does GC use increase

the risk of CVA in patients with RA? If so, what is the impact of daily dose and past cumulative exposure?

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2: RISK OF CARDIOVASCULAR MORTALITY IN PATIENTS WITH RHEUMATOID ARTHRITIS. A META-ANALYSIS OF OBSERVATIONAL STUDIES[1]

2.1 INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease that leads to progressive joint deformity, disability, and arguably to premature death (1-26). Most studies of mortality in RA patients have found increased mortality rates compared with the general population (1-15), and the majority suggest that one third to one half of the premature deaths in RA are due to increased cardiovascular disease (CVD) including ischemic heart disease (IHD) and cerebrovascular accidents (CVA). However, there has been wide variation in reported standardized mortality ratios (SMR) including studies detecting neither increased overall mortality (20-23) nor CVD mortality (19-26).

Some recent studies reported improvement in survival and suggested that these improvements may be related to earlier diagnosis and the use of more aggressive and newer antirheumatic treatment regimens (17, 27-30). As a result, CVD has become a relevant long-term end point for RA, especially studies of therapy.

Previous studies evaluating RA mortality have shown that those attending hospitals for treatment have a reduced life expectancy compared to control populations (1,2,4,21-22,

[1] [1] Aviña-Zubieta JA, Choi HK, Sadatsafavi M, Etminan M, Esdaile JM, Lacaille D. Risk of cardiovascular mortality in patients with rheumatoid arthritis. A Meta-analysis of observational studies**.** Arthritis Care and Research 2008;59:1690-1697

30-33). This suggests that study design might also explain some of the differences in mortality rates reported in RA.

Increasingly, it has been recognized that inflammation plays an important role in atherosclerosis (34-36) making the evaluation of death from cardiovascular causes and RA all the more important as inflammation is such an intrinsic component of RA .

Our objective was to conduct a meta-analysis of observational studies to determine the magnitude of the risk from CVD mortality, as well as cause-specific mortality from IHD and CVA, in patients with RA compared to the general population.

2.2 METHODS

2.2.1 Search Strategies

Medline, Embase, and Lilacs databases were searched from their inception (1966, 1980, and 1982 respectively) to July 2005 by an experienced librarian to find primary references and published reviews. The authors also searched reference lists from retrieved articles and searched for publications from scientists known for publishing in the field of mortality in RA. The following search terms were used alone and in combination: rheumatoid arthritis, cardiovascular disease, cerebrovascular accident, transient ischemic attack, risk, risk factors, survival rate, mortality, comorbidity, causality, cause of death, heart death, sudden death, cohort study, case-control study, and longitudinal study.

We selected peer-reviewed papers (case-control and cohort studies) that met the following inclusion criteria: a) pre-specified RA definition, b) clearly defined CVD outcome including IHD and CVA c) reported the age and gender adjusted SMR and 95% confidence intervals (CI) or data to calculate them. If data were duplicated in more than one study, the most recent study was included in the analysis.

2.2.2 Data Extraction

Two researchers (JAA-Z and DL) independently assessed studies for eligibility and extracted data on year of publication, type of study, source of RA population, RA definition, sample size, enrolment period, RA duration at cohort inception, mean time of follow-up, extent of loss of follow-up, reference group, outcome definition, number of observed and expected deaths from CVD, IHD, and CVA for all, and by gender if available, matching or adjustment for cardiovascular risk factors, and ascertainment method for death. Where their initial conclusions did not agree, the researchers met to achieve consensus.

2.2.3 Quality Scores of Included Papers

We assessed study quality based on a 12 point scale that included elements of previous published scales for observational studies and adapted to the needs of the present meta-analysis (37-38). Each study was scored according to six characteristics related to patients and methods of each study. Each item was scored from 0 to 2. Specifically, we determined the source of study population (community (2), clinic-based (1), or undefined (0), cohort type (inception (2), non inception (1)), RA definition (use of current American College of Rheumatology (ACR) classification criteria for RA (39) or older criteria from the former American Rheumatology Association (2), other validated criteria (1), other pre-defined but unvalidated criteria (0)), ascertainment of CVD outcome (cause of death verified e.g. medical records (2), cause of death not verified, e.g. ICD-9 codes on death certificate(1), not mentioned (0)), extent of loss of follow-up (less than 20% (2), between 20-40% (1), and > 40% (0)), matching by or adjustment for Framingham risk factors ≥ 5 risk factors (2), < 5 risk factors (1), None (0). For stratification purposes, studies that scored 10 or higher were considered to be of higher

quality and the rest to be of lower quality. Quality scoring was performed independently by two reviewers (JAAZ and DL). Disagreement was resolved by consensus.

2.2.4 Statistical Analysis

We calculated weighted – pooled summary estimates of SMRs (meta-SMR) for all CVD, as well as from IHD and CVA. The meta-SMR represents a summary estimate of the increased risk of death from CVD in RA compared to the general population weighted by the sample size of each study. Separate meta-SMRs were calculated for men and women when available. Calculations were performed on the log of the SMRs from the individual studies, and the resulting pooled values were then transformed back to the SMR scale. We used the random effects model and tested for heterogeneity using the bootstrap version of the Q and I2 statistics using STATA (version 8.2, College Station, Texas, USA) (40).

Since heterogeneity is expected in meta-analyses of observational studies, subgroup analysis was carried out to assess heterogeneity. Studies were stratified based on study population (community versus clinic based), cohort type (inception versus non inception), enrolment period (before versus after 1987; to distinguish between current ACR classification criteria for RA (39) from older criteria), follow-up (≥ 10 years versus < 10 years) and quality score (≥ 10 versus < 10). Statistical inferences about the difference in the meta-SMRs between subgroups of studies were performed using univariate meta-regression analysis (41). Multivariate meta-regression analysis evaluating the adjusted effect of the above study characteristics was not performed because of the small number of studies and because in the majority of studies at least one study characteristic could not be estimated, leaving too few observations for the multivariate regression.

Robustness of the results were evaluated using jackknife sensitivity analysis; that is, the analysis was repeated multiple times, each time with removal of a single study from the baseline group of studies (42).

2.2.5 Assessment of Publication Bias/Small Study Effect

To detect the presence of publication bias (i.e., the bias resulting from the greater likelihood of publication of studies reporting a positive result compared than with negative results), or the 'small study effect' (a tendency for treatment effect estimates in small studies to differ from those in larger studies) (43), we constructed a funnel plot, in which a measure of the study size is plotted as a function of the measure of interest (44). Again we used log of the SMRs from the individual studies as well as the log of precision (1/variance). If publication bias and small study effect are absent, the distribution of the data points will be symmetrical. In addition, Egger's regression was used to provide an objective, quantitative test statistics (p-value) for the presence of asymmetry in the data (45).

2.3 RESULTS

We screened 578 abstracts published over the last 39 years (Figure 2.1). A total of 51 studies were retrieved for detailed evaluation and 24 studies were included (Table 2.1) (1-16, 20-26). Twenty-seven studies out of 51 were excluded: 11 did not provide SMRs or data to calculate SMR; 13 provided only all cause mortality with no data to calculate CVD mortality; two were repeated studies on the same sample and two were cross sectional studies. The complete list of references reviewed is available upon request. The 24 studies included 111,758 patients with 22,927 cardiovascular events. All were cohort studies (Table 2.1). Eighteen of these studies were performed in Europe and six

in North America. Eighteen of these studies used clinic-based population samples (N = 48,091), while six were community-based samples (N = 63,667).

Figure 2.1 Flow Diagram of Study Selection

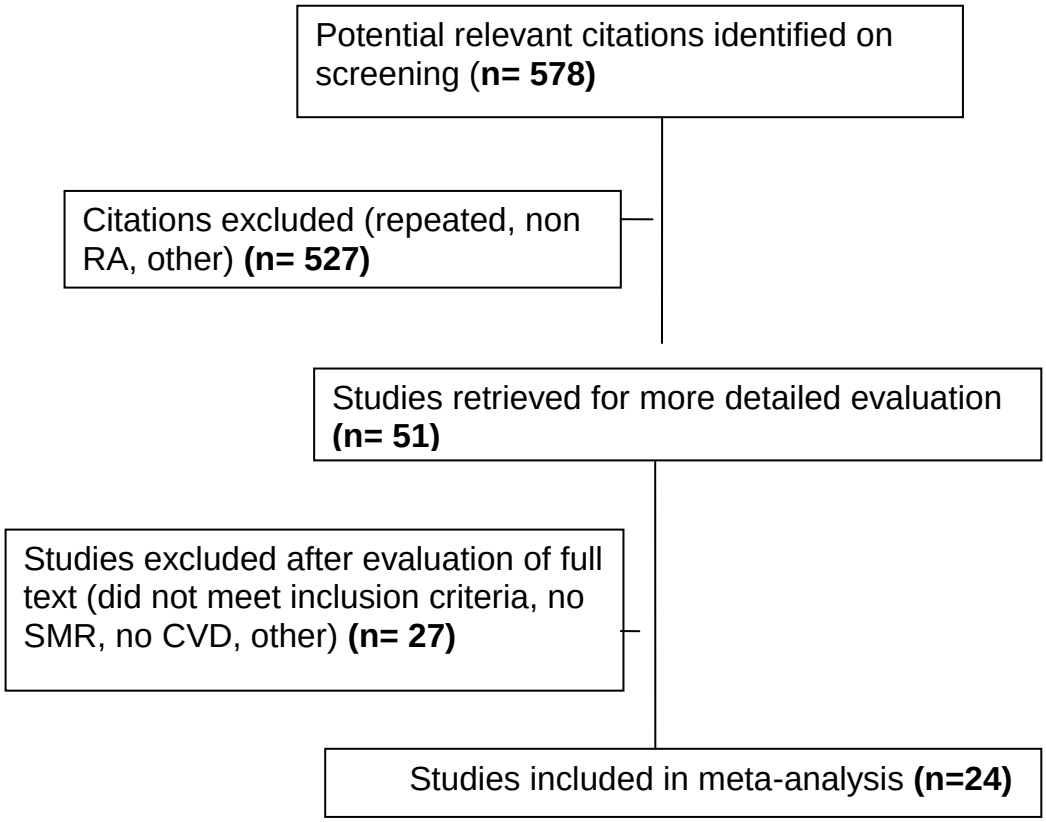

Table 2.1 Characteristics of the 24 Studies Included in the Meta-Analysis of Cardiovascular Mortality in RA

Author (year)	Country	Patients (n)	CVD events	Setting	Enrolment period	Subjects Mean Age at entry (years)	RA definition	Mean follow-up (years)	Outcome ascertainment	Quality	Inception cohort
Uddin[24] (1970)	Canada	475	51	Clinic-based	1954-66	NAV	ARA (*)	NA	DC and Autopsy	7	No
Monson[1] (1976)	USA	1035	311	Clinic-based	1930 – 60	NAV	Clinical by specialist	11.4	DC	6	No
Lewis[21] (1980)	England	311	15	Clinic-based	1966-76	NAV	ARA	6.5	DC and Autopsy	6	No
Linos 1980	USA	521	245 (*)	Community-based	1950-74	NAV	ARA	NA	DC	11	Yes
Allebeck[2] 1982	Sweden	1165	144	Clinic-based	1971	NAV	ICD (*) codes for RA	7	DC and Autopsy	6	No
Vanderbroucke[22] (1984)	Netherlands	209	71	Clinic-based	1954-57	54	ARA	25	Family Doctor	9	No
Erhardt[3] (1989)	England	107	20	Clinic-based	1976-79	59	ARA	~ 6	DC, MR	8	No
Mutru[4] (1989)	Finland	1000	166	Clinic-based	1959-68	55.3	ARA	10	DC	9	No
Reilly[20] (1990)	England	100	18	Clinic-based	1957-63	50.6	ARA	25	DC, Autopsy, MR	10	Yes
Jacobsson[5] (1993)	USA	2979	27	Community (Aboriginals)	1965-1989	NA	ARA and ACR	NA	DC	11	No
Wolfe[6] (1994)	USA & Canada	3501	418	Clinic and community-based	Canada 1966-74 USA 1965-90	53.3	ARA and ACR	Canada 15.8 USA 8.5	DC	9	No
Wallberg-Jonsson[7] (1997)	Sweden	606	140	Clinic- based	Up to 1979	NAV	ARA	Followed until 1994	DC	11	No
Symmons[8] (1998)	England	448	104	Clinic-based	1964-78	47.5	ARA	21.5	DC	9	No
Turesson[9] (1999)	Sweden	489	63	Clinic-based	1990-94	69.3	ACR	4.5	DC	9	No

Author (year)	Country	Patients (n)	CVD events	Setting	Enrolment period	Subjects Mean Age at entry (years)	RA definition	Mean follow-up (years)	Outcome ascertainment	Quality	Inception cohort
Kvalvik[19] (2000)	Norway	147	29	Clinic-based	1977	58	ARA	15	DC	9	No
Riise[26] (2001)	Norway	187	6	Clinic-based	1978-82	59.9	ARA	12	DC, MR	10	No
Bjornadal[10] (2002)	Sweden	46917	12431	Community-based	1964-94	NA	ICD-7,8, and 9	10.4	DC	9	No
Goodson[23] (2002)	England	575	32	Community-based	1990-94	57	ACR	6.9	DC	10	Yes
Thomas[11] (2003)	Scotland	33318	7185	Clinic-based	1981-2000	61.8	ICD-9 and 10	6.9	DC	7	No
Watson[12] (2003)	UK	11633	807	Community-based	1987- last encounter	NAV	ICD codes	5	MR	9	No
Krishnan[13] (2004)	USA	3862	208	Clinic-based	1980-97	56	ACR	6.5	DC	9	No
Sihvonen[14] (2004)	Finland	1042	164	Community	1987	NAV	ARA	12	DC, MR, Autopsy	11	No
Book[27] (2005)	Sweden	152	52	Clinic-based	1978	61	ARA	12.4	DC	9	No
Goodson[15] (2005)	England	979	220	Clinic-based	1981-1996	64.4	Clinical by specialist	11.5 (median)	DC	9	Yes

(*) per 100,000

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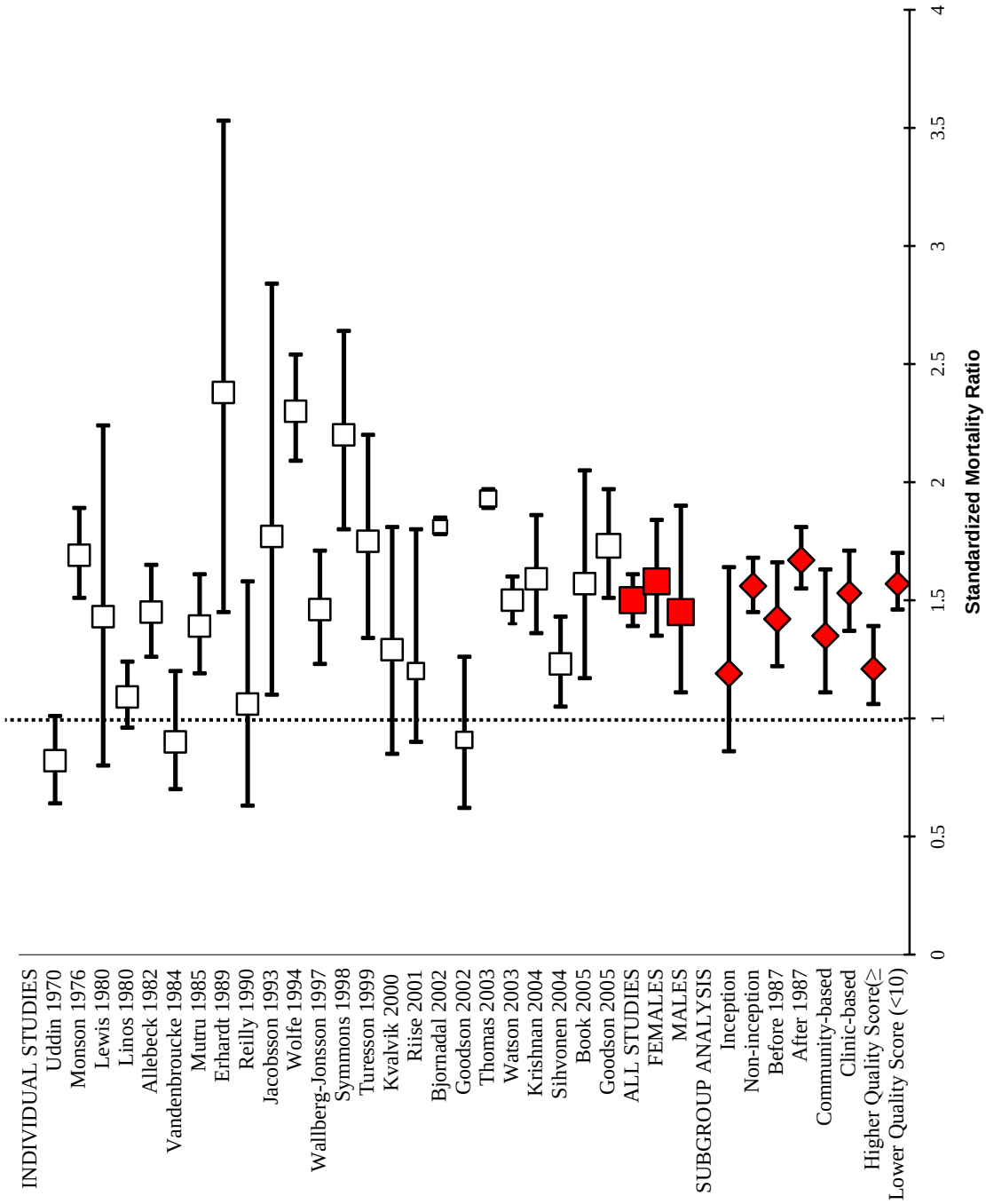
Abbreviations:

ARA = American Rheumatology Association; ACR= American College of Rheumatology; DC= death certificate; ICD= International Classification for Diseases; NAV= not available; MR= medical record; UK = United Kingdom;

USA = United States of America

There was a significantly increased mortality risk for CVD in patients with RA with a meta-SMR of 1.50; 95% CI from 1.39 to 1.61 (Figure 2.1). Eight studies provided estimates by gender (3,8,11-12,15,23,24,26). Overall, there was no clear difference between genders (meta-SMR of 1.58; 95% CI = 1.35 to 1.84 for females; and meta-SMR of 1.45; 95% CI = 1.11 to 1.90 for males).

Figure 2.2 Meta-Analysis of Twenty-Four Studies on CVD Mortality in Patients with Rheumatoid Arthritis.



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We identified significant heterogeneity among studies (I2 =0.93, p = 0.0001). Subgroup analysis showed that a number of factors influenced mortality risk (Table 2.2). Meta-SMRs were higher in studies with lower quality scores (< 10), in studies with samples assembled after 1987, in non-inception cohorts, and in clinic-based samples. Inception cohort studies were the only group that did not show a significantly increased mortality risk for all CVD compared with the general population (meta-SMR = 1.19; 95% CI from 0.86 to1.68) although the pooled sample size was small (N = 2,175). Despite the observed differences in mortality among subgroups, only quality scores were significantly associated with the observed heterogeneity in the meta-regression analysis (p = 0.02). However, a trend was also observed for cohort type (p= 0.09).

Table 2.2 Overall Mortality and Sensitivity Analysis for the 24 Cohort Studies in Patients with Rheumatoid Arthritis

Study subset	# of studies	# of patients	# of CVD events	Random-effects Meta-SMR (95% CI)	P value (*)
All studies	24	111,758	22,297	1.50 (1.39 – 1.61)	
Study population					
Community-based	6	63,667	13,706	1.35 (1.11 – 1.63)	NS
Clinic-based	18	48,091	9,221	1.53 (1.37 – 1.71)	
Cohort type					
Inception-cohorts	4	2,175	515	1.19 (0.86 – 1.64)	**0.09**
Non inception-cohorts	20	109,583	22,412	1.56 (1.45 – 1.68)	
Quality Score					
Higher Quality (Score ≥ 10)	7	6,010	631	1.21 (1.06 – 1.39)	0.02
Lower Quality (Score < 10)	17	105,748	22,296	1.57 (1.46 – 1.70)	
Enrolment period					
Before 1987	17	14,550	1,981	1.42 (1.22 – 1.66)	NS
After 1987	7	97,198	20,946	1.67 (1.55 – 1.81)	
Follow-up length					
Less than 10 years	9	54,961	8,893	1.66 (1.45 – 1.90)	NS
More than 10 years	12	52,822	13,712	1.48 (1.32 – 1.66)	

* difference in the meta-SMRs between subgroups using univariate meta-regression analysis.

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Results of the jackknife sensitivity analysis are presented in Table 2.3. The meta-SMR remained significantly increased when studies were excluded one at a time with the point estimate ranging from 1.41 to 1.54 and the corresponding 95% CI remaining above one in all cases.

Table 2.3 Sensitivity Analysis Using Jacknife Approach Where Each Study Is Excluded at the Time to Test Robustness of the Overall SMR

Author / year	SMR-CVD	Lower Bound 95% CI	Upper Bound 95%CI	Meta-SMR when study out	Weight (Random effects)
ALL STUDIES	**1.50**	**1.39**	**1.61**	**Not applicable**	
Uddin[24] (1970)	0.82	0.64	1.01	1.54 (1.44 – 1.66)	4.2
Monson[1] (1976)	1.69	1.51	1.89	1.49 (1.38 – 1.61)	5.5
Lewis[21] (1980)	1.43	0.80	2.24	1.50 (1.39 – 1.62)	1.9
Linos 1980	1.09	0.96	1.24	1.53 (1.43 – 1.65)	5.2
Allebeck[2] 1982	1.45	1.26	1.65	1.50 (1.39 - 1.62)	5.2
Vanderbroucke[22] (1984)	0.90	0.70	1.2	1.53 (1.42 – 1.64)	3.2
Erhardt[3] (1989)	2.38	1.45	3.53	1.48 (1.38 – 1.60)	2.3
Mutru[4] (1989)	1.39	1.19	1.61	1.51 (1.40 – 1.62)	5.0
Reilly[20] (1990)	1.06	0.63	1.58	1.51 (1.40 – 1.63)	2.2
Jacobsson[5] (1993)	1.77	1.10	2.84	1.49 (1.39 – 1.61)	1.8
Wolfe[6] (1994)	2.30	2.09	2.54	1.46 (1.36 – 1.58)	5.6
Wallberg-Jonsson[7] (1997)	1.46	1.23	1.71	1.50 (1.39 – 1.62)	4.9
Symmons[8] (1998)	2.20	1.80	2.64	1.47 (1.36 – 1.59)	4.5
Turesson[9] (1999)	1.75	1.34	2.2	1.49 (1.38 – 1.61)	3.9
Kvalvik[19] (2000)	1.29	0.85	1.81	1.51 (1.40 - 1.62)	2.7
Riise[26] (2001)	1.20	0.90	1.8	1.51 (1.40 – 1.62)	2.2
Bjornadal[10] (2002)	1.81	1.78	1.85	1.46 (1.33 – 1.63)	6.2
Goodson[23] (2002)	0.91	0.62	1.26	1.52 (1.41 – 1.64)	2.8
Thomas[11] (2003)	1.93	1.89	1.97	1.46 (1.33 – 1.61)	6.2
Watson[12] (2003)	1.50	1.40	1.6	1.50 (1.39 – 1.62)	6.0
Krishnan[13] (2004)	1.59	1.36	1.86	1.49 (1.38 – 1.61)	4.9
Sihvonen[14] (2004)	1.23	1.05	1.43	1.41 (1.41 – 1.63)	5.0
Book[27] (2005)	1.57	1.17	2.05	1.49 (1.38 – 1.61)	3.4
Goodson[15] (2005)	1.73	1.51	1.97	1.49 (1.38 – 1.61)	5.2

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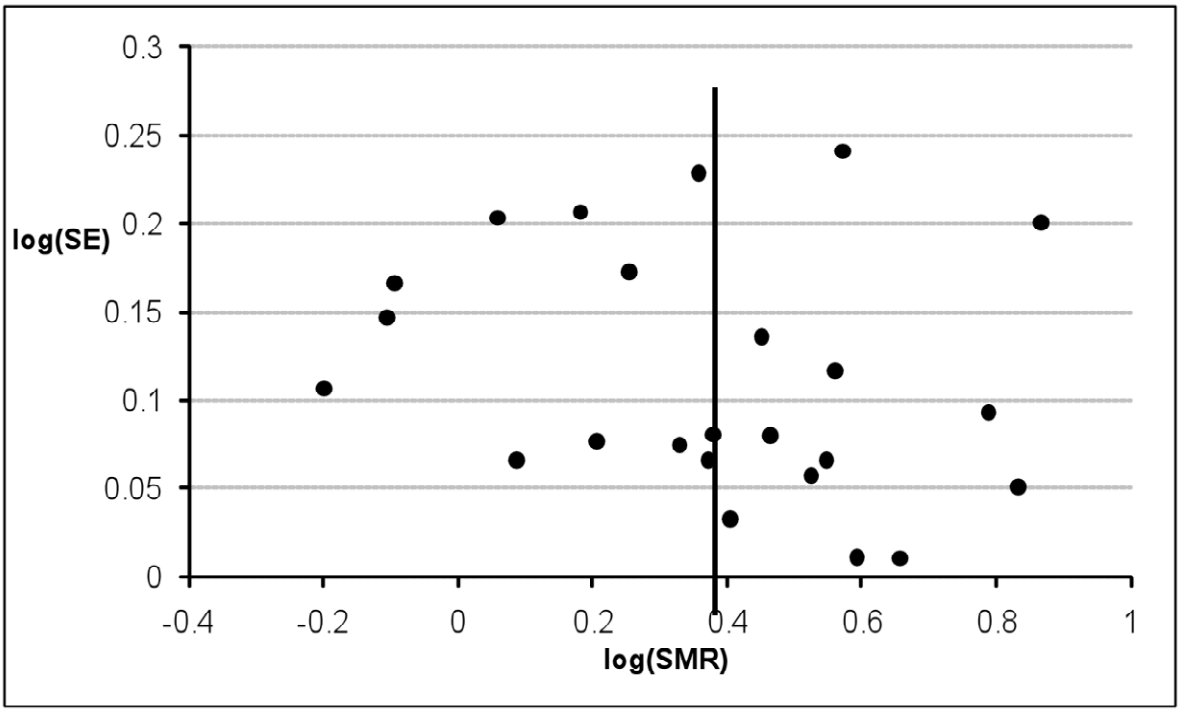
The funnel plot did not show a lack of small studies with negative results (Figure 2.2). Nevertheless, there seemed to be a difference in the effect size between small and large studies, possibly indicating the small-study effect (43). The Egger's test for asymmetry was also significant (p= 0.002). The observed asymmetry appeared to be mainly caused by the two studies with large sample sizes and strongly significant SMRs (10-11). When these two studies were removed, the Egger's test was no longer significant (p=0.34).

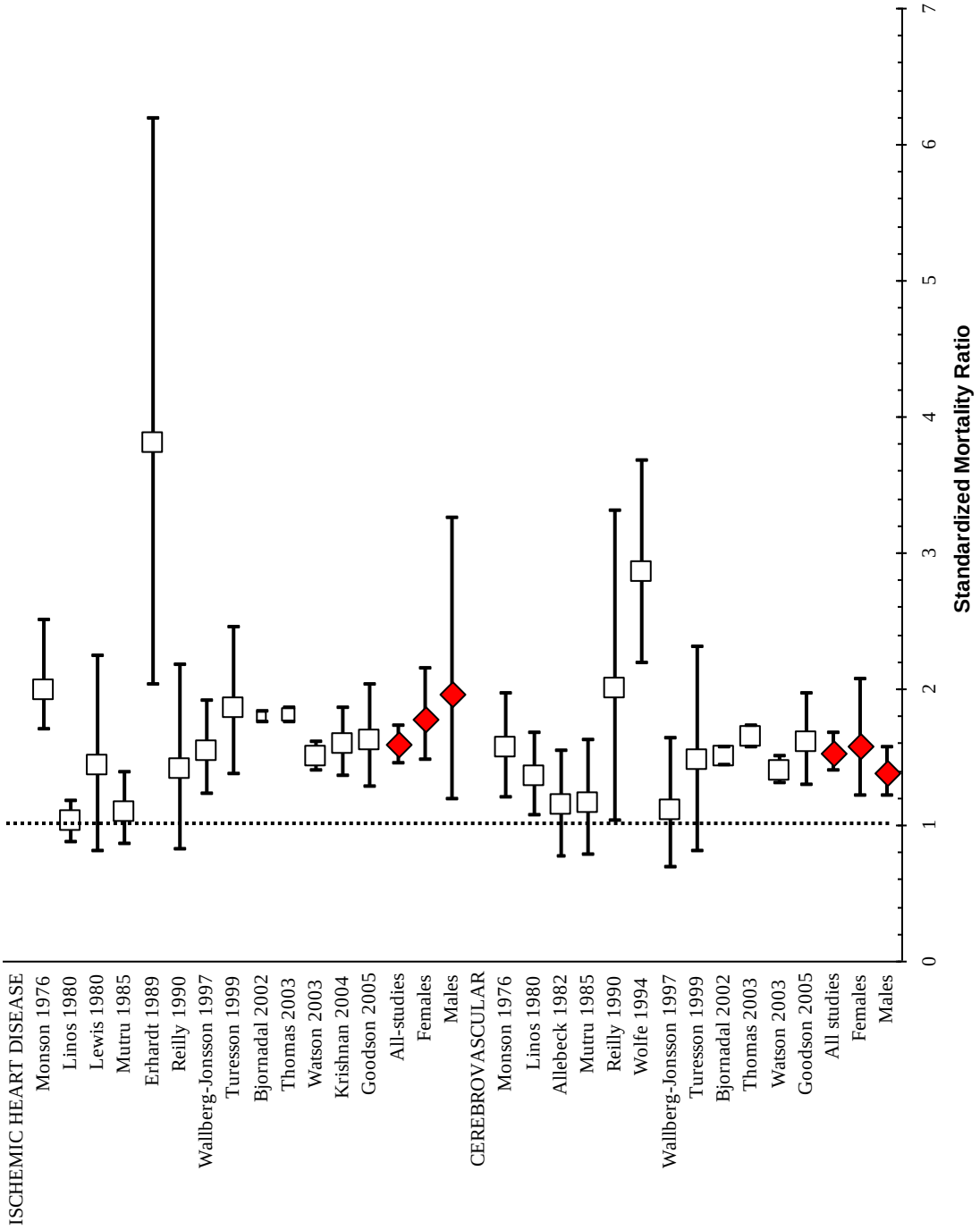
Figure 2.3 Funnel Plot of 24 Studies Evaluating Mortality in RA Patients and Compared with General Population



Each dot represents individual studies. The solid line is the random-effects pooled estimate of log(SMR). With permission from Arthritis Care and Research Journal.

There were 13 studies describing cause specific CVD mortality, including mortality from IHD and CVA (Figure 2.3). For IHD (n=100,878 patients), three studies provided estimates by gender. Overall, there was an increased risk of death from IHD (meta-SMR = 1.59; 95% CI 1.46 to 1.73) with no significant difference between genders. Again, the jackknife sensitivity analysis demonstrated that the results were not influenced by any particular study with the meta-SMR estimates ranging from 1.54 to 1.66 and the corresponding 95% CI remaining above one.

Figure 2.4 Meta-Analysis of Studies with Cause-Specific CVD Mortality in Patients with RA



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Twelve studies provided information on mortality from CVA (n=100,285 patients) (Figure 2.3). Overall, there was an increased risk of death from CVA (meta-SMR = 1.52; 95% CI 1.40 to 1.67). There was no significant difference between genders. The jackknife sensitivity analysis of the meta-SMR estimate showed that the pooled estimate was robust with the point estimate varying from 1.54 to 1.66 and the corresponding 95% CI remaining above one.

2.4 DISCUSSION

Our meta-analysis of published mortality studies in RA indicates that there was a 50% increased risk of CVD mortality compared to the general population. We found no significant difference between genders and the increased mortality was attributable to increased deaths from IHD and CVA.

The point estimate was higher in studies enrolling RA patients after 1987 (meta-SMR = 1.67; 95% CI 1.55 – 1.81) when compared to patients enrolled before 1987 (meta-SMR= 1.42; 95% CI 1.22 – 1.66), suggesting that the use of current ACR classification criteria led to inclusion of cases with better defined RA or possibly, more severe disease.

As expected, samples recruited from clinics rather than community had a higher risk of CVD mortality. The only subgroup of studies that did not yield a significantly increased risk of mortality from CVD were inception-cohorts (Table 2). This is likely due to the shorter duration of follow-up in these cohorts, and possibly to the smaller number of cases (N= 2,175). Of interest, the only inception-cohort that showed a significantly increased risk of mortality from all CVD had a median follow-up of 11.4 years. It was also a clinic-based RA sample assembled after 1987 (15). This suggests that there might be a latent period after RA diagnosis until the risk of death from CVD is increased. On the contrary, we did not see a trend of increasing SMR with increasing of follow-up in the non-inception cohort studies (prevalent cases). We feel that that

inception cohort studies with longer follow-up are need it in order to reveal the best estimate for the risk of CVD death in patients with RA.

Similar to our findings, Ward found that study design accounted for most of the differences observed in survival rates in his review of 18 studies (46). However, Ward evaluated only all-cause mortality but not CVD mortality. Unlike Ward's study we pooled our data using meta-analysis while he averaged the estimates of individual studies to obtain a summary of SMR.

Our study also demonstrates that risk of death from both IHD and CVA is increased in patients with RA compared to the general population. The observed risk of death from CVA was increased in some studies (1, 6, 10-12, 15, 25), but not in others (2, 4, 7, 9, 4). Most studies where the risk was increased had large samples; suggesting that mortality from CVA may be less frequent than from IHD and lack of power may be the main reason for some studies not identifying an increased risk of death from CVA.

Our study has some limitations. We included in our meta-analysis cohorts that were clinically different in terms of age at enrolment, disease duration, disease severity, classification criteria to define RA and study design. Heterogeneity in the results was observed, as expected in meta-analyses of observational studies (47). As recommended for meta-analyses of observational studies, we used the random effects model to include an estimate of the between study variability (48). Interestingly, only quality score was able to explain some of the observed heterogeneity ($p= 0.02$), although cohort type showed a trend ($p= 0.09$) (Table 2). Furthermore, the small study effect and/or publication bias might have compromised the validity of our results, and our estimate should be considered as tentative.

In this meta-analysis the SMR evaluated the association between RA and CVD mortality adjusted for age and gender only. Although other confounding factors may influence the risk of CVD mortality in RA, there is no method for adjusting the results of meta-analyses using SMRs. Nevertheless, while unadjusted confounders may influence the validity of meta-analysis of SMR,

several studies have shown that the increased risk of CVD in RA is independent of traditional risk factors (49-50).

The majority of studies included in this meta-analysis enrolled patients before the widespread use of biologics, therefore the results obtained may not be generalizable to RA samples treated with biologics. Accordingly, recent evidence suggests that all-cause and cause-specific mortality are not greater than expected in RA patients treated with biologics therapy (28). Therefore, more studies specifically evaluating mortality in RA patients treated with biologics would be valuable.

In summary, published data indicate that CVD mortality is approximately 50% increased in RA patients compared to the general population. However, the CVD mortality in the inception cohort subgroups was not elevated; hence our results might have been affected by an upward bias from non-inception cohort studies. Finally, the increased risk of death from all CVD, as well as death from IHD and CVA does not seem to differ between genders; however, few studies reported gender specific SMRs.

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3: GLUCOCORTICOIDS USE AND THE RISK OF ACUTE MYOCARDIAL INFARCTION IN PATIENTS WITH RHEUMATOID ARTHRITIS. A POPULATION-BASED STUDY.[2]

3.1 INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease that leads to progressive joint deformity, disability, and premature death (1). In the last decade, it has been demonstrated that patients with RA have an increased risk for ischemic heart disease including acute myocardial infarction (MI) (2-5). Overall, there is a 50% increased risk of cardiovascular death in patients with RA compared to the general population (6). There is evidence that RA itself or uncontrolled inflammation could have a direct effect on the endothelium and predispose patients to accelerated atherosclerosis and MI (7, 8). In addition, the increased risk of MI may be due to the effects of medications used to treat RA, particularly glucocorticoids (GC) (9). Theoretically, GC could modulate the risk of cardiovascular disease (CVD) in two competing ways. The risk could be mediated by the deleterious effects of GC on lipids, hypertension, glucose tolerance, accelerated atherosclerosis and coagulation disturbances (10-12), all of which are associated with increased risk of CVD. Alternatively, GC may have cardio-protective effects mediated by their anti-inflammatory and anti-proliferative actions in the endothelial wall, especially at low doses (13-15).

[2] A version of this chapter has been submitted for publication Aviña-Zubieta JA, Abrahamowicz M, Choi HK, Rahman M, Sylvestre MP. Esdaile JM, Lacaille D. Glucocorticoids use and the risk of acute myocardial infarction in patients with rheumatoid arthritis. A population-based study.

Little is known regarding the long-term effects of GC on the development of CVD Furthermore, the cardiovascular outcomes of interest have been assessed mostly as composite rather than specific outcomes [128,131-133,147-149]. However, both exposure status and dose of GC change frequently during follow-up in patients with RA. Therefore, in RA the cumulative measures of exposure such as total past duration of GC use or total past cumulative dose vary over time and this may influence the impact of current dose on MI risk. In this context, an efficient modeling of time-dependent measures of GC exposure is especially important, as knowledge regarding how MI risk changes with increasing cumulative GC dose and/or duration of GC is needed to find an optimal trade-off between the anti-inflammatory benefits of GC and the increased risk of MI.

The purpose of our study was to determine the impact of GC exposure on MI. We used a population-based incident cohort of patients with RA and performed a comprehensive assessment of the putative associations between several aspects of GC exposure and risk of MI.

3.2 METHODS

Using previously collected data [144] we identified all subjects with a new diagnosis of RA (incident RA cases) and follow them forward.

3.2.1 Study Sample and Data

Data from a previously established population-based RA cohort for the province of British Columbia (BC) were used [144]. The RA case definition used has been previously published [144]. Briefly, RA cases required at least two physician visits more than two months apart with an RA diagnostic code (International Classification of Diseases, Ninth Revision [ICD-9] code 714.X). In addition, we excluded individuals with at least two visits subsequent to the second RA

visit with diagnoses of other inflammatory arthritides (systemic lupus erythematosus, other connective tissue diseases, psoriatic arthritis, ankylosing spondylitis and other spondyloarthropaties). Administrative billing data for reimbursement of physician visits by the Ministry of Health allowed identification of all cases with a first diagnosis of RA between January 1997 and December 2001 and without a prior diagnosis of RA from January 1990 onwards (earliest available data). Follow-up was until March 2006. We excluded all RA cases that had received oral GC before the first RA diagnostic code (index date) as well as those who had had an MI before the index date.

For each RA case, data on all provincially funded health services used were obtained from the Ministry of Health databases. These included data on all visits to physicians and all hospitalizations from January 1990 to March 2006, and all prescription medications dispensed by pharmacists for all cases from January 1996 to March 2006. The Ministry of Health made all the linkage from their databases and no personal identifying information was provided to the investigators. All procedures were compliant with the BC's Freedom of Information and Privacy Protection Act. The study received ethics approval from The University of British Columbia.

3.2.2 Assessment of Exposure to Oral Glucocorticoids

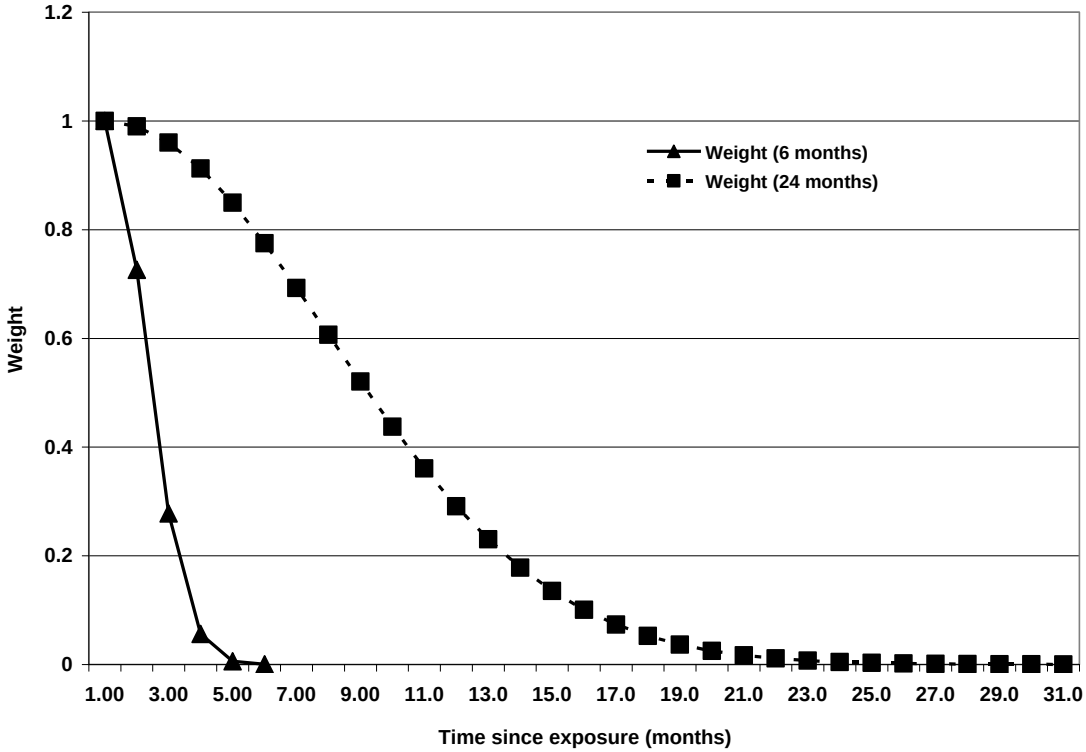
All patients who received one or more dispensed prescriptions for oral GC during their follow-up were identified as GC users. GC doses were calculated as prednisone equivalents based on accepted standards [109,150]. Data were available on start date, drug type, dose, number of pills and days for each dispensed prescription. We used these data to construct four time-dependent measures of GC exposure: current use (yes/no), current dose (mg/day), cumulative dose (grams), and cumulative use (months) that were updated monthly. First, for each day between the beginning and the end of each dispensed GC prescription, we calculated the daily dose by dividing the total quantity of dispensed medication by the number of days for each

prescription. Then, the time-dependent measure of past cumulative dose was obtained by summing all doses from all past prescriptions until the given day of follow-up. Past cumulative use was calculated by summing the duration of all prescriptions. Gaps of up to 30 days between two subsequent prescriptions for the same medication were considered as continuous exposure to account for the possibility of tapering doses after prescription was dispensed. For prescriptions overlapping for < 7 days, the individual was assumed to have refilled early and completed the first prescription before starting the second [139,151].

3.2.2.1 Representation of Cumulative Dose and Duration

In addition to the traditional method that considers the lifetime past cumulative exposure measures (duration of use and dose) equally, regardless of recency of use, we used a novel time-dependent method proposed by Abrahamowicz et al. [143], to evaluate if weighting for recency of use would improve the prediction of MI risk. This method considers that at any point during follow-up the cumulative dose is calculated as a weighted sum of the past doses, where the current cumulative exposure/dose gets a weight of 1 and weights for past exposures/doses gradually decrease with increasing time since exposure until they reach 0 at the end of the selected time-window. This method assumes that exposure beyond the selected time-window does not influence the risk. Figure 3.1 shows the two time windows used in our analyses.

Figure 3.1 Two Functions Proposed to Weight Past Exposure as a Function of Time Elapsed Since Exposure (Δt)



Note that the time axis is reversed, with the original Δt=0 corresponding to present time and increasing Δt corresponding to more distant past. Both functions assign the highest weight of 1.0 and decreased to half the present weight (0.5) at 4 months (solid line) and 9 months respectively (dashed line), in the past.

3.2.3 Outcome Assessment

The primary outcome was the first MI event occurring during the study period. MI were identified from hospitalization data (ICD-9 = 410) which include MI causing admission and MI occurring during hospitalization. Death from MI was defined based on the death certificate diagnostic codes, including out of hospital deaths (ICD-10: I21).

3.2.4 Assessment of Covariates

Factors known to influence MI risk that were available in the administrative databases were selected a priori and were included as fixed in-time covariates measured at index date (first RA

diagnostic code) in multivariate time-dependent Cox regression analyses [152]. These include age, gender, and co-morbidities based on diagnostic codes from all outpatient physician visits and hospital visits from January 1990 to the index date, using a modification of the Charlson's co-morbidity index developed for administrative data [153,154]. We also assessed exposure to the following medications over the year preceding the index date: antihypertensives (β and α-blockers, calcium channel blockers, angiotensin receptor blockers, angiotensin converting enzyme inhibitors), lipid lowering medications (statins and fibrates), other cardiovascular medications (diuretics, anti-arrhythmics, anticoagulants and nitrates), diabetes medications (insulin and oral hypoglycemics), hormone replacement therapy and oral contraceptives. Use of aspirin was not ascertained mainly because this medication is available over the counter.

The following markers were used as surrogates of disease severity: whether the patient ever visited a rheumatologist for their RA, number of MD visits (RA-related visits to family physicians and all visits to rheumatologists) per person-year (PY) of follow-up, and use of disease modifying anti-rheumatic drugs (DMARDs). DMARD use was categorized as an ordinal variable: no DMARD use (group 1), sulphasalazine, antimalarials (group 2); methotrexate or intramuscular gold (group 3); leflunomide, cyclosporine-A, azathioprine, cyclophosphamide, chlorambucil or mychophenolate mofetil (group 4); and biologics (group 5). These categories were mutually exclusive and we used the highest rank ever attained during the follow-up. We assumed that patients with at least one visit to a rheumatologist, patients with more physician visits per person-year of follow-up and patients with a higher DMARD ranking (e.g., biologics versus antimalarials) were those with more severe disease. Finally, we also determined patient's current use of methotrexate, Cox-2 inhibitors and non-steroidal anti-inflammatory drugs (NSAIDs) as time dependent co-variates.

3.2.5 Statistical Analysis

For every case in the cohort, we calculated the person-time from index date to last health care service use, MI date or March 2006, whichever came first. Rates per person-year for MI were calculated for GC use and non-use (including non-use periods for GC-users).

To control for confounding by indication, wherein GC would be given to cases with more severe disease and/or less adverse cardiovascular profiles, we used propensity scores (PS) to control for the observed differences between GC users and non-users [155,156]. Propensity scores were calculated using a multivariate logistic regression model that included all covariates described above as independent variables (gender, age, antihypertensives, lipid lowering medications, other CV medications, diabetes medications, hormone replacement therapy, and oral contraceptives, angina, COPD, Charlson's index, having seen by a rheumatologist, number of MD visits, DMARD ranking), Use of aspirin was not ascertained mainly because this medication is available over the counter) . To this end, for each case a PS indicating the likelihood of receiving at least one GC prescription during the follow-up was estimated. Each GC user was matched with a non-GC user at time of first GC prescription on calendar time, age, and sex to assign a date for calculating propensity score for each non-GC user As recommended [157], we assessed the predictive ability of the PS to distinguish GC users from non-users and we found that the c statistic was 0.81. This suggests that variables selected to estimate the PS were good predictors of GC use. However, our examination indicated residual imbalance on some covariates (gender, use of anti-hypertensive medications, diabetes, use of other cardiovascular medications, Charlson's co-morbidity index; having seen a rheumatologist, presence of angina and COPD). Therefore, we included imbalanced covariates in addition to PS quintiles in all Cox's models [158].

Multivariate Cox proportional hazards regression models [152] were used to estimate the risk of MI in five separate models, each representing the effects of GC using a different time-

dependent measure of GC exposure. All models adjusted for propensity score quintiles, imbalanced covariates in the propensity score (all entered as fixed in time covariates); current use of methotrexate, Cox-2 inhibitors and NSAIDs, represented by binary (yes/no) time-dependent covariates updated every month. The Akaike's information criterion (AIC) was used to compare the predictive ability between models [159], where the model with the minimum AIC identifies the model that offers an optimal trade-off between a model's goodness of fit and its parsimony. Within the same cohort, a difference of ≥ 4 AIC points is considered relevant [160]. Analyses were performed with SAS software version 9.1 (SAS Institute, Cary, North Carolina). For all HRs, we calculated 95% confidence intervals (CI). All p values are two-sided.

3.3 RESULTS

The cohort included 6,981 incident RA cases. During follow-up 2,789 cases (40%) were prescribed GC. The baseline characteristics of the cohort according to exposure are summarized in Table 3.1. Overall, GC-users were older, had more co-morbidity and used more medications than non-GC users. For the entire cohort, the overall follow-up was 42,792 person-years; the number of person-years of GC use and non-GC use periods (including non-use periods for GC-users) was 3,041 and 39,751, respectively.

Overall, GC users spent 17% of their follow-up time on GC with a median daily dose per course of 13.6 mg and a median duration per GC course of 43 days. During follow-up we identified 248 new MI events, of which 82 (33%) were fatal. The unadjusted MI incidence rate was 5.8 per 1000 person-year in the RA cohort, 8.9 during GC exposure and 5.6 during non GC exposure.

Table 3.1 Baseline Characteristics of the Incident RA Cohort

Characteristic	All cases n= 6,981	Exposed n= 2,789	Unexposed n= 4,192	p value*
Gender				
Women	4,682 (67)	1,969 (71)	2,713 (65)	< 0.001
Men	2,299 (33)	820 (29)	1,479 (35)	< 0.001
Mean age (SD)	56 (18)	57 (17)	54 (18)	< 0.001
CV drugs use (§)	**1243 (18)**	**562 (20)**	**681 (16)**	**< 0.001**
Anti-hypertensive drugs	1114 (16)	503 (18)	611 (15)	< 0.001
ACE inhibitors	586 (8)	266 (10)	320 (8)	0.005
β-blockers	472 (7)	224 (8)	248 (6)	0.006
α-blockers	71 (1)	38 (1.4)	33 (0.8)	0.02
Calcium channel blockers	172 (2)	83 (3)	89 (2.1)	0.02
ARB	65 (1)	28 (1)	37 (0.9)	NS
Other CV drugs (§)	**1,055 (15)**	**491 (18)**	**564 (13)**	**< 0.001**
Cardiac glycosides	144 (2)	56 (2)	88 (2)	NS
Diuretics	842 (12)	397 (14)	445 (11)	< 0.001
Antiarrhythmic	32 (0.5)	16 (0.6)	16 (0.4)	NS
Anticoagulants	109 (2)	47 (1.7)	62 (1.5)	NS
Nitrates	178 (3)	73 (3)	105 (3)	NS
Diabetes medications (§)	251 (4)	101 (4)	150 (4)	NS
HRT (§)	723 (10)	319 (11)	404 (10)	0.02
Oral contraceptives (§)	185 (3)	79 (3)	106 (3)	NS
Lipid-lowering-drugs (§)				
Fibrates	35 (0.5)	12 (0.4)	23 (0.6)	NS
Statins	299 (4)	134 (5)	165 (4)	NS
NSAIDs during follow-up				
No NSAIDs	1,941 (28)	584 (21)	1357 (33)	< 0.001
Traditional NSAIDs	2,786 (40)	1,066 (38)	1,720 (41)	< 0.001
Cox-2	2,877 (41)	1,375 (49)	1,502 (36)	< 0.001
DMARD use				
No DMARDs	4,308 (62)	1,015 (36)	3,293 (79)	< 0.001
Non MTX DMARDs (**)	1,078 (15)	584 (21)	494 (12)	< 0.001
MTX	1,595 (23)	1,190 (43)	405 (10)	< 0.001
Biologics	224 (3)	200 (7)	24 (1)	< 0.001
Charlson-Index *mean* (SD) **(§)**	1.0 (2)	1.1 (2)	0.9 (1)	NS
Angina (§)	1,309 (19)	564 (20)	745 (18)	0.01
COPD (§)	1,989 (28)	875 (31)	1,114 (27)	< 0.001

Unless otherwise indicated, values represent number (%).

(*) comparing exposed to glucocorticoids versus never exposed to glucocorticoids

(**) Traditional DMARDs, excluding methotrexate (MTX)

Abbreviations: RA = rheumatoid cohort ; ACE = angiotensin converting enzyme; SD = standard deviation; CV = cardiovascular; ARB = angiotensin receptor blocker; NS = not significant; (§) from 1990 to RA onset; HRT = hormone replacement therapy; DMARDs = disease modifying anti-rheumatic drugs;

NSAIDs = non steroidal anti-inflammatory drugs; MTX = methotrexate; COPD = chronic obstructive pulmonary disease

Table 3.2 shows the results of the adjusted Cox's models assessing the effects of different GC exposure measures on risk of MI. All models showed GC to be associated with an increased risk of MI.

Table 3.2 Cox's Regression Models Assessing the Effects of the Different GC Exposure Measures and Risk of Acute Myocardial Infarction (Unweighted)

Model	GC Exposure	Univariate HR (95% CI)	AIC	Multivariate (*) HR (95% CI)	AIC
1	Current use (yes/no)	2.14 (1.49 – 3.08)	4181.1	1.63 (1.08 - 2.45)	3943.8
2	Current daily dose (5 mg)	1.16 (1.08 – 1.23)	4183.1	1.12 (1.04 - 1.21)	3943.1
3	Total Cumulative duration of use (yr)	1.26 (1.14 – 1.40)	4177.5	1.18 (1.04 – 1.35)	3943.1
4	Total past Cumulative dose (1 g)	1.07 (1.05 – 1.10)	4171.1	1.06 (1.03 – 1.10)	3939.6
5	Current daily dose (5 mg) + Cumulative duration (year)	1.13 (1.05 – 1.22) 1.23 (1.10 – 1.36)	4171.2	1.11 (1.02 - 1.20) 1.15 (1.01 - 1.32)	3941.1

Abbreviations:
GC = glucocorticoids; HR = hazard ratio; CI = confidence intervals
AIC = Akaike's information criterion; mg = milligrams; yr = year; g = grams

(*) Adjusted for propensity score, unbalanced covariates (age, gender, hypertension, statins, diabetes, angina, COPD, other cardiovascular drugs use, Charlson Index, having seen a rheumatologist for RA, number of MD visits per year), current use of Cox-2 inhibitors, MTX and NSAIDs.

Model 1 includes a binary (yes/no) time-dependent representation of the current use.

Model 2 includes a continuous time-dependent representation of the current daily dose.

Model 3 includes a continuous time-dependent representation of cumulative duration.

Model 4 includes a continuous time-dependent representation of cumulative dose.

Model 5 includes both time-dependent variables for cumulative duration of use and current dose.

Model 1 corresponds to the simplest time-dependent model that ignores dose and duration of exposure. In this model current GC use was associated with a 63% increase in the risk of MI (HR= 1.63 95%CI; 1.08-2.45). Model 2 accounts for current dose only, not taking into account past exposure history, and it shows a 12% increased risk per 5 milligram increase in the current daily dose of prednisone

To estimate the independent effects of current dose and cumulative duration of use we created Model 5 that includes the two time-dependent exposure measures in the same model. The results of this model show that both are independently associated with an increased risk of MI. Hence, there is a 11% increased risk of MI per every 5 mg increase in the daily dose and a 15% increased risk per every additional year on GC. We did not test the model with any other combination of two time-dependent GC variables to avoid the near collinearity that would occur if we included both cumulative dose and cumulative duration or current dose and cumulative dose. In fact, the correlation coefficient between cumulative dose and cumulative duration of use was 0.8.

Accounting for recency of use (weighted models) did not improve the model's fit to data (higher or equal AIC values than unweighted models) (Table 3.3). The lowest observed AIC values were for the unweighted models 4 and 5 that considered all past exposure equally (Table 2).

Table 3.3 Weighted Cox's Regression Models Assessing the Effects of the Different GC Exposure Measures and Risk of Acute Myocardial Infarction

Model	GC Exposure Measure	Time Window	HR (95% CI) (*)	AIC
3a	**w**Cumulative duration of use	6 months	1.20 (1.03 – 1.40)	3943.7
3b	**w**Cumulative duration of use	24 months	1.06 (1.00 – 1.12)	3944.7
4a	**w**Cumulative dose	6 months	1.01 (1.01 - 1.02)	3942.5
4b	**w**Cumulative dose	24 months	1.06 (1.00 – 1.12)	3944.9
5a	Current dose + **w**Cumulative duration of use	6 months	1.02 (1.00 – 1.04) 1.13 (0.96 – 1.34	3943.0
5b	Current dose + **w**Cumulative duration of use	24 months	1.02 (1.00 – 1.04) 1.04 (0.98 – 1.11)	3943.3

Abbreviations:

w= weighted; GC = glucocorticoids; HR = hazard ratio; CI= confidence intervals; AIC = Akaike's information criterion

(*) Adjusted for propensity score, unbalanced covariates (age, gender, hypertension, statins, diabetes, angina, COPD, other cardiovascular drugs use, Charlson Index, having seen a rheumatologist for RA, number of MD visits per year), current use of Cox-2 inhibitors, MTX and NSAIDs.

Model 3a includes weighted cumulative duration of use (6 months window)

Model 3b includes weighted cumulative duration of use (24 months window)

Model 4a includes weighted cumulative dose (6 months window)

Model 4b includes weighted cumulative dose (24 months window)

Model 5a includes weighted cumulative duration of use (6 months) and current dose

Model 5b includes weighted cumulative duration of use (24 months) and current dose

3.4 DISCUSSION

The objective of this study was to determine the magnitude of the risk of MI associated with various aspects of GC exposure in RA. We used comprehensive modelling with a particular focus on the effects of past exposure and current exposure on the risk of MI. Our results provide evidence that current use of GC increases the risk of MI by 63%. Along with the on-treatment versus off-treatment analyses, we also found that current dose increased risk of MI by 11% for every 5 mg increase in current daily dose, in addition to the 15% increased risk for every year of GC use accumulated in the past. Unique features of our study include the concurrent evaluation in the same model of both past and current GC exposure on MI risk. Also, our study evaluated the risk of GC use in a population-based incident cohort of RA where GC exposure could be evaluated over the entire RA disease course.

Our findings suggest that the effect of GC exposure may have two independent components: (a) the immediate effect of current exposure/dose; and, (b) the long-term effect of past exposure duration, accumulated over the entire follow-up period. The immediate effects of GC that could mediate the risk of MI include the interaction of GC with the vascular wall, endothelial and vascular smooth muscle, and GC-mediated enhancement of vascular contractility [161]. In addition, there is evidence suggesting that GC are likely to contribute to destabilization of atherosclerotic lesions [162]. GC may also exacerbate the consequences of lesion rupture by modulating factors involved in coagulation and fibrinolysis to produce a prothrombotic state [163]. The other processes that could mediate the long-term effects of GC on the risk of MI by promoting atherosclerosis include stimulating release of the vasoconstrictor and growth factor endothelin-1 [164], increasing vasoconstriction leading to reduced vascular lumen diameter [161], impairment of cholesterol removal from the arterial wall [165] and increasing vascular

calcification [166]. GC also promote hypertension which could mediate both short-term and long-term effects on MI risk.

In this study, we were able to adjust for recency of GC exposure using two time windows in the weight function. The first time window (6 months), was chosen based on results from previous studies suggesting that only recent GC exposure was associated with an increased risk of CVD [131-134]. The second time window (24 months) was chosen to explore if assuming a longer period of clinically relevant GC exposure would improve the model's fit to data. This function would be consistent with the assumption that some of the GC cumulative effects on CVD (e.g., atherosclerosis) would require longer exposure time to develop [127]. However, our results suggest that "lifetime" GC exposure fits the data better (lowers AIC values) than the weighted models. Again this suggests that some of the undesirable effects of GC cumulative dose may accumulate over a very long time and these effects may not be related to the physiological/biological effects of GC [167,168].

Our results are consistent with recent published epidemiological studies that have found an association between CVD outcomes and GC in patients with RA and other chronic inflammatory disorders [131-133,169,170]. Wei et al. [131] and Souverein et al. [132] both studied all GC users from the general population using administrative prescription records. In Wei et al.'s study [131], where patients were followed for a mean of 1.2 years, high dose exposure (>7.5 mg/day) among a subset of patients with inflammatory arthritis (n= 1,165) was associated with 3-fold increased risk of CVD. Souverein et al. [132], in a population based nested case-control study (n=1,515), reported that current GC use (in last 3 months) was associated with ischemic heart disease (OR= 1.36). Davis et al. [133], using an incident cohort of 603 RA patients over a median 13-year follow-up, found that GC exposure was associated with an increased risk of CVD only in rheumatoid factor positive individuals, particularly those with higher cumulative exposure, higher mean daily dose and recent use of GC (< 3 months). Finally, Caplan et al. [148], using the National Data Bank for Rheumatic Diseases found that only current GC use (in

last 6 months) was associated with increased mortality. This study found that prior GC use (> 6 months) was not associated with increased mortality when compared to non-GC users, although the study did not assess the impact on CVD or MI. In comparison to these studies, ours used a substantially larger population, with a median follow-up of 6.1 years. We evaluated GC use over the entire disease course in an incident cohort. We also used administrative data on dispensed medication rather than prescribed, and we included only incident GC users. Furthermore, we used a single outcome; MI, rather than a composite CVD outcome. Finally, our study is the first to explore the importance of current dose versus cumulative duration of use by including the two time-dependent exposure measures in the same model.

Potential limitations of our study include those inherent to observational studies based on administrative data. Uncertainty around diagnostic accuracy is the main limitation of studies identifying cases from administrative databases. But, we used one of the strictest published case definitions, using two physician visits at least two months apart [171], with a positive predictive value of 0.92 [172]. The estimate of the prevalence of RA with our algorithm is similar to that in other adult populations [10]. Furthermore, misclassification of RA would have introduced a conservative bias, such that the estimates would be closer to the null.

The outcome MI was also assessed using administrative data. Privacy protection laws prevent access to medical records to confirm diagnoses. However, validation studies for MI have shown a positive predictive value higher than 95% [141,173,174]. Observational studies assessing effects of drug exposures are also susceptible to confounding by indication. Thus, more severe cases are more likely to receive GC and may be at a higher risk for MI. We attempted to control for confounding by indication bias by using propensity scores. Because of residual imbalance within propensity scores quintiles in some of the variables used to calculate the propensity scores, we included these variables as covariates in the final model in addition to the propensity scores [158]. Although we adjusted for all known risk factors for MI available in our

administrative data, our results could still be affected by unknown or unmeasured confounders, especially markers of disease severity.

In conclusion, data from this population-based study of an incident RA cohort indicate that GC exposure is independently associated with an increased risk of MI. We found that both current and cumulative exposure to GC matter. The risk of MI increased by 63% with current use of GC; by 10% per 5 mg increase in current daily dose and an additional 15% per year of past cumulative use. This suggests a dual effect of GC on MI, an immediate effect mediated through current use and a long-term effect mediated through past cumulative duration of use. Our results have important implications for people with rheumatoid arthritis and their treating physicians, when weighing the risks and benefits of using GC to treat inflammation in RA.

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4: GLUCOCORTICOIDS USE IS NOT ASSOCIATED WITH CEREBROVASCULAR DISEASE IN PATIENTS WITH RHEUMATOID ARTHRITIS. A POPULATION-BASED STUDY[3]

4.1 INTRODUCTION

In the last decade it has been demonstrated that patients with rheumatoid arthritis (RA) have an increased risk for cardiovascular disease [175,176]. Overall, there is a 50% increased risk of cardiovascular death in patients with RA compared to the general population [177]. Some studies have suggested that RA patients have an increased risk of stroke [140,176], but not all [20,55,178].

RA itself or uncontrolled inflammation could have a direct effect on the endothelium and predispose patients to accelerated atherosclerosis [179,180]. In addition, the increased risk of cerebrovascular attacks (CVA) may be due to the effects of medications used to treat RA, particularly glucocorticoids (GC) [148]. Theoretically, GC could modulate the risk of CVA by the deleterious effects of GC on lipids, blood pressure, glucose tolerance, atherosclerosis and coagulation [163,181,182]. Alternatively, GC may have protective effects mediated by their anti-inflammatory and anti-proliferative actions in the endothelial wall, especially at low doses [137,183,184].

Despite the wide use of GC in RA there is very limited knowledge on the association between GC and risk of CVA in RA with inconsistent results across studies. Wei et al

[3] A version of this chapter has been submitted for publication.Aviña-Zubieta JA, Choi HK, Abrahamowicz M, Rahman M, Sylvestre MP. Esdaile JM, Lacaille D. Glucocorticoids use is not associated with an increased risk of cerebrovascular disease in patients with rheumatoid arthritis. A population-based study.

[131], found that GC are associated with an increased risk of CVA in a population-based cohort of GC users which included those with inflammatory arthritis. However, two case-control studies in RA patients did not find a statistically significant association between GC use and CVA [132,185].

The purpose of our study was to determine the association between GC use and risk of CVA in patients with RA. We used a population-based incident cohort of patients with RA and performed a comprehensive assessment of the putative associations between several aspects of GC exposure and risk of CVA.

4.2 METHODS

4.2.1 Data Source and Study Population

Data from a previously established population-based RA cohort for the province of British Columbia (BC) were used [144]. The RA case definition used has been previously published [144]. Briefly, RA cases required at least two physician visits more than two months apart with an RA diagnostic code (International Classification of Diseases, Ninth Revision [ICD-9] code 714.X). In addition, we excluded individuals with at least two visits subsequent to the second RA visit with diagnoses of other inflammatory arthritides (systemic lupus erythematosus, other connective tissue diseases, psoriatic arthritis, ankylosing spondylitis and other spondyloarthropathies), if a RA diagnosis by a non-rheumatologist was not confirmed on a subsequent rheumatology visit, or if they had no subsequent RA-coded physician visit over a follow-up period of 5 years.

Administrative billing data for reimbursement of physician visits by the Ministry of Health allowed identification of all cases with a first diagnosis of RA between January 1997 and

December 2001 and without a prior diagnosis of RA from January 1990 onwards (earliest available data). Follow-up was until March 2006. We excluded all RA cases that had received oral GC before the first RA diagnostic code (index date) as well as those who had had a CVA before the index date.

For each RA case, data on all provincially funded health services used were obtained from the Ministry of Health databases. These included data on all visits to physicians, all investigations and all hospitalizations which include up to 16 diagnostic codes per hospitalization representing either the reason of admission or complication during hospitalization; from January 1990 to March 2006, and all prescription medications dispensed by pharmacists for all cases from January 1996 to March 2006 regardless of source of funding. Information on date and cause of death was obtained from vital statistics data. The Ministry of Health provided the linkage for their databases and no personal identifying information was provided to the investigators. All procedures were compliant with the BC's Freedom of Information and Privacy Protection Act. The study received ethics approval from The University of British Columbia.

4.2.2 Assessment of Exposure to Oral Glucocorticoids

All patients who received one or more prescriptions for oral GC during their follow-up were identified as GC users. GC doses were calculated as prednisone equivalents based on accepted standards [109,150]. Data were available on drug name, start date, dose, number of pills and days for each dispensed prescription. We used these data to construct four time-dependent measures of GC exposure: use (yes/no), total current dose (mg/day), total cumulative dose (grams), and cumulative use (months) that were updated monthly. First, for each day between the beginning and the end of each dispensed GC prescription, we calculated the daily dose by dividing the total quantity of

dispensed medication by the number of days for each prescription. Then, the time-dependent measure of past cumulative dose was obtained by summing all doses from all past prescriptions until the given day of follow-up. Past cumulative duration of use was calculated by summing the duration of all prescriptions. Gaps of up to 30 days between two subsequent prescriptions for the same medication were considered as continuous exposure to account for the possibility of tapering doses after prescription was dispensed.. For prescriptions overlapping for < 7 days, the individual was assumed to have refilled early and completed the first prescription before starting the second [139,151].

4.2.3 Representation of Cumulative Dose and Duration

In addition to the traditional method that considers the lifetime past cumulative exposure measures (duration of use and dose) equally, regardless of recency of use, we used a novel time-dependent method proposed by Abrahamowicz et al. [143], to evaluate if weighting for recency of use would improve the prediction of CVA risk. This method assumes that more recent exposure has a greater influence on risk outcome than more remote exposure. It also assumes that exposure beyond the selected time-window does not influence the risk. We used a 6 month time window based on studies that suggest than only recent GC exposure (last three months) might be associated with an increased risk of CVA [131].

4.2.4 Outcome Assessment

The primary outcome was the first CVA event occurring during the study period. CVA events were identified from hospitalization separation data (ICD-9 diagnostic codes: 431, 434 and 436). Death from CVA was defined based on the death certificate diagnostic

codes, including out of hospital deaths (ICD-10 diagnostic codes: I60, I61, I63, I64). Transient ischemic attacks were not included in the outcome.

4.2.5 Assessment of Covariates

Factors known to influence CVA risk that were available in the administrative databases were selected a priori and were included as fixed in-time covariates measured at index date in multivariate time-dependent Cox regression analyses [152]. These include age, gender, and co-morbidities based on diagnostic codes from all outpatient physician visits and hospital visits from January 1990 to the index date, using a modification of the Charlson co-morbidity index developed for administrative data [153,154]. We also assessed exposure to the following medications over the year preceding the index date: antihypertensives (β and α-blockers, calcium channel blockers, angiotensin receptor blockers, angiotensin converting enzyme inhibitors), lipid lowering medications (statins and fibrates), other cardiovascular medications (diuretics, anti-arrhythmics, anticoagulants and nitrates), diabetes medications (insulin and oral hypoglycemics), hormone replacement therapy and oral contraceptives. Use of aspirin was not ascertained mainly because this medication is available over the counter.

The following markers were used as surrogates of disease severity: whether the patient ever visited a rheumatologist for their RA, number of MD visits (RA-related visits to family physicians and all visits to rheumatologists) per person-year (PY) of follow-up, and use of disease modifying anti-rheumatic drugs (DMARDs). DMARD use was categorized as an ordinal variable: no DMARD use (group 1), sulphasalazine and antimalarials (group 2); methotrexate or intramuscular gold (group 3); leflunomide, cyclosporine-A, azathioprine, cyclophosphamide, chlorambucil or mychophenolate mofetil (group 4); and biologics (group 5). These categories were mutually exclusive and

we used the highest rank ever attained during the follow-up. We assumed that patients with at least one visit to a rheumatologist, patients with more physician visits per person-year of follow-up and patients with a higher DMARD ranking (e.g., biologics versus antimalarials) were those with more severe disease. Finally, we also determined patient's current use of methotrexate, Cox-2 inhibitors and non-steroidal anti-inflammatory drugs (NSAIDs) as time dependent co-variates.

4.2.6 Statistical Analysis

For every case in the cohort, we calculated the person-time from index date to last health care service use, CVA date or March 2006, whichever came first. Rates per person-year for CVA were calculated for GC use and non-use (including non-use periods for GC-users).

To control for confounding by indication, wherein GC would be given to cases with more severe disease and/or less adverse cardiovascular profiles, we used propensity scores (PS) to control for the observed differences between GC users and non-users [155,156]. PS were calculated using a multivariate logistic regression model that included all covariates described above as independent variables (gender, age, antihypertensives, lipid lowering medications, other CV medications, diabetes medications, hormone replacement therapy, and oral contraceptives, angina, COPD, Charlson's index, having been seen by a rheumatologist, number of MD visits, DMARD ranking). To this end, for each case a PS indicating the likelihood of receiving at least one GC prescription during the follow-up was estimated. Each GC user was matched with a non GC user at time of first GC prescription on calendar time, age, and sex to assign a date for calculating PS for each non-GC user. As recommended [157], we assessed the predictive ability of the PS to distinguish GC users from non-users and we found that the c statistic was 0.82.

We summarized the balance achieved on the PS between GC users and non-users by grouping subjects into PS quintiles. However, our examination indicated residual imbalance on some covariates (gender, use of anti-hypertensive medications, diabetes, use of other cardiovascular medications, Charlson's co-morbidity index; having seen a rheumatologist, presence of angina and COPD). Therefore, as recommended we included imbalanced covariates in addition to PS quintiles in all Cox models [158]. Multivariate Cox proportional hazards regression models [152] were used to estimate the risk of CVA in five separate models, each representing the effects of GC using a different time-dependent measure of GC exposure. All models were adjusted for PS, imbalanced covariates in the PS (all entered as fixed in time covariates), current use of methotrexate, Cox-2 inhibitors and NSAIDs, represented by binary (yes/no) time-dependent covariates updated every month. The Akaike's information criterion (AIC) was used to compare the predictive ability between models [159], where the model with the minimum AIC identifies the one that offers an optimal trade-off between a model's goodness of fit and its parsimony. Within the same cohort, a difference of ≥ 4 AIC points is considered relevant [160].

Analyses were performed with SAS software version 9.1 (SAS Institute, Cary, North Carolina). For all hazard ratios (HRs), we calculated 95% confidence intervals (CI). All p-values are two-sided.

4.3 RESULTS

The cohort included 7,051 incident RA cases. During follow-up 2,844 cases (40%) were prescribed GC. The baseline characteristics of the cohort according to exposure are summarized in Table 4.1. Overall, GC-users were older, had more co-morbidity and used more medications than non-GC users. For the entire cohort, the overall follow-up

was 43,355 person-years; the number of person-years of GC use and non-GC use periods (including non-use periods for GC-users) was 3,139 and 40,216 respectively. Overall, GC users spent 17% of their follow-up time on GC with a median daily dose per course of 13.6 mg and a median duration per GC course of 43 days. During follow-up we identified 178 new CVA of which 61 (34%) were fatal. The CVA unadjusted incidence rate was 4.1 per 1000 person-years in the RA cohort, 20.3 during GC exposure and 4.5 during non-GC exposure periods.

Table 4.1 Baseline Characteristics of the Incident RA Cohort

Characteristic	All cases N= 7,051	Exposed N= 2,844	Unexposed N= 4,207	p value*
Gender				
Women	4,683 (66)	1,981 (70)	2,702 (64)	< 0.001
Men	2,368 (34)	863 (30)	1,505 (36)	< 0.001
Mean age (SD)	56 (18)	57 (17)	54 (18)	< 0.001
CV drugs use (§)	**1,343 (19)**	**612 (22)**	**731 (17)**	**< 0.001**
Anti-hypertensive drugs	**1,212 (16)**	**553 (19)**	**659 (16)**	< 0.001
ACE inhibitors	620 (9)	288 (10)	332 (8)	0.001
β-blockers	543 (8)	252 (9)	291 (7)	0.002
α-blockers	74 (1)	37 (1)	37 (1)	NS
Calcium channel blockers	194 (3)	94 (3)	100 (2)	0.01
ARB	67 (1)	28 (1)	39 (1)	NS
Other CV drugs (§)	**1,111 (16)**	**515 (18)**	**596 (14)**	**< 0.001**
Cardiac glycosides	152 (2)	58 (2)	94 (2)	NS
Diuretics	861 (12)	406 (14)	455 (11)	< 0.001
Antiarrhythmic	33 (0.5)	16 (0.6)	17 (0.4)	NS
Anticoagulants	108(2)	42 (1)	66 (2)	NS
Nitrates	241 (3)	107 (4)	134 (3)	NS
Diabetes medications (§)	268 (4)	110 (4)	158 (4)	NS
HRT (§)	728 (10)	323 (11)	405 (10)	0.02
Oral contraceptives (§)	186 (3)	79 (3)	107 (3)	NS
Lipid-lowering-drugs (§)				
Fibrates	43 (0.6)	16 (0.6)	27 (0.7)	NS
Statins	366 (5)	179 (6)	187 (4)	< 0.001
NSAIDs during follow-up				
No NSAIDs	1,308 (18)	355 (12)	953 (23)	< 0.001
Traditional NSAIDs	2,834 (40)	1,089(38)	1,745 (41)	< 0.001
Cox-2	2,909 (41)	1,400 (49)	1,509 (36)	< 0.001
DMARD use				
No DMARDs	4,357 (62)	1,039 (37)	3,318 (79)	< 0.001
Non MTX DMARDs (**)	1,075 (15)	588 (21)	487 (12)	< 0.001
MTX	1,619 (23)	1,217 (43)	402 (10)	< 0.001
Biologics	229 (3)	206 (7)	23 (1)	< 0.001
Charlson-Index *mean* (SD) **(§)**	1.0 (2)	1.1 (2)	0.9 (1)	NS
Angina (§)	1,434 (20)	639 (22)	795 (19)	< 0.001
COPD (§)	2,014 (29)	896 (32)	1,118 (27)	< 0.001

Unless otherwise indicated, values represent number (%).
(*) comparing exposed to glucocorticoids versus never exposed to glucocorticoids
(**) Traditional DMARDs, excluding methotrexate (MTX)

Abbreviations:

ACE = angiotensin converting enzyme; SD = standard deviation; CV = cardiovascular; ARB = angiotensin receptor blocker; NS = not significant; (§) from 1990 to RA onset; HRT = hormone replacement therapy; DMARDs = disease modifying anti-rheumatic drugs; NSAIDs = non-steroidal anti-inflammatory drugs; MTX = methotrexate; COPD = chronic obstructive pulmonary disease.

Table 4.2 shows the results of all Cox models assessing the effects of different GC exposure measures on risk of CVA. Although the risk of CVA was increased in all adjusted models it did not reach statistical significance in any of the models. Model 1 corresponds to the simplest time-dependent model that ignores dose and duration of exposure. In this model GC use was associated with a 41% increase in the risk of CVA, but the 95% confidence intervals were not significant (HR= 1.41, 95% CI; 0.83-2.37). Model 2 accounts for current daily dose only and indicated that current dose was not significantly associated with CVA (HR=1.07, 95% CI; 0.94 -1.21). Again, models 3 and 4 indicate that cumulative duration of use and cumulative dose were not significantly associated with an increased risk of CVA. Furthermore, accounting for recency of use (6 month weighted models) did not improve the model's fit to data (higher or equal AIC values than unweighted models) or identify a statistically significant association between GC and CVA.

Table 4.2 Unadjusted and Adjusted Cox Regression Models Assessing the Effects of the Different GC Exposure Measures on the Risk of CVA

Model	GC Exposure (unit)	Univariate RR (95% CI)	p value	Multivariate (*) HR (95% CI)	p value
1	Current use (yes/no)	1.68 (1.06 – 2.68)	0.02	1.41 (0.84 - 2.37)	NS
2	Current mean daily dose (5 mg)	1.10 (0.99 -1.23)	NS	1.07 (0.94 - 1.21)	NS
3	Total Cumulative duration of use (month)	1.01 (1.00-1.03)	< 0.02	1.01 (0.99 – 1.02)	NS
4	Total past Cumulative dose (1 g)	1.06 (1.02-1.09)	< 0.001	1.04 (0.99 – 1.08)	NS
5	Current daily dose (5 mg) + Cumulative duration (month)	1.08 (0.95 – 1.22) 1.01 (1.00 – 1.02)	NS NS	1.05 (0.92 – 1.21) 1.01 (0.99 – 1.02)	NS NS

Abbreviations:

GC = glucocorticoids; HR = hazard ratio; CI = confidence intervals; NS = not significant

(*) Adjusted for propensity score, unbalanced covariates (age, gender, hypertension, statins, diabetes, angina, COPD, other cardiovascular drugs use, Charlson Index, having seen a rheumatologist for RA, number of MD visits per year), current use of Cox-2 inhibitors, MTX and NSAIDs.

4.4 DISCUSSION

This large population-based study of an incident RA cohort evaluated whether the risk of CVA is increased with oral GC treatment. The results of our study showed that GC exposure was not associated with an increased risk of CVA.

We previously found a consistent association between GC and myocardial infarction using the same GC exposure measures used in the current study [186].

The immediate effects of GC that could mediate increased cardiovascular risk, such as CVA and myocardial infarction include the interaction of GC with the vascular wall, endothelial and vascular smooth muscle, and GC-mediated enhancement of vascular contractility [161]. There is evidence that the effects of GC on endothelial cells may vary depending on the vascular beds considered [187,188]. In general, cells from different vascular beds display certain common qualities, but each subtype is uniquely adapted to meet the demands of the underlying tissue [189]. In a very elegant study, Foster et al [190] demonstrated that GC receptor status and GC responsivity differ between endothelial cells from various vascular beds, including cells from the brain and the heart. The importance of permeability response to GC has important implications because it is well recognized that the principal functions of the endothelium (e.g., the control of haemostasis, vasomotor tone, cell and nutrient trafficking, barrier functions and angiogenesis) are differentlially regulated between different sites of the vascular tree and from one moment to the next [191] This differential effect is further supported by data from several clinical trials showing that GC benefit brain endothelium after acute CVA, but offer no protection for heart endothelium after acute myocardial infarction [192-194].

An alternative explanation for the lack of statistically significant association may be lack of power due to insufficient number of CVA events. In order to test this possibility, we calculated a post hoc power analysis and we found that our study had 86% power to

detect a significant HR of at least 1.5. The highest HR from our study was 1.4 and the power for this HR was 70%.

The risk of CVA associated with the use of GC in patients with RA has been assessed recently [131,132,185]. Souverein et al. [132], in a population-based nested case-control study from the General Practice Research Database (N= 50,656 GC users and 50,656 non users) identified 3,656 cases with CVA and matched them with 3,676 controls. They found that current GC use (in the last 3 months) was associated with a decreased risk for CVA (adjusted OR = 0.91, 95% CI; 0.84 – 0.99). However, when the analysis was restricted to cases who had RA (n= 1,515) as the underlying condition for receiving GC, the association was neither protective nor significant (adjusted OR= 1.23, 95% CI; 0.92 to 1.64).

Finally, Nadareishvili et al. [185] in a case-control study of 41 cases with incident ischemic stroke in patients with RA from the National Data Bank for Rheumatic Diseases found that GC use (Yes/No) was not significantly associated with CVA (adjusted OR = 1.75, 95% CI; 0.87 – 3.53). Of interest, the author found no evidence for an association of CVA with diabetes, smoking and obesity.

In comparison to these studies, our study used a substantially larger population, with a median follow-up of 6 years. A unique characteristic of our study is the application of including only incident GC users, which allowed us to evaluate GC use over the entire disease course. We also used data from dispensed medication rather than prescribed, and we included only new GC users. Finally, our study is the first to explore the importance of current dose versus cumulative duration of use by including the two time-dependent exposure measures in the same model.

Our results have important implications for people with rheumatoid arthritis and their treating physicians, when weighting the risks and benefits of using GC to treat RA. It seems that the use of GC in RA is clearly something of a clinical balancing act, the key

to which would seem to be the judicious timing and duration [195]. Detailed information about long-term GC side-effects is scarce and clinicians need evidence on this issue. Potential limitations of our study include those inherent to observational studies based on administrative data. Uncertainty around diagnostic accuracy is the main limitation of studies identifying cases from administrative databases. To counter this, we used one of the strictest published case definitions, using two physician visits at least two months apart [171], with a positive predictive value of 0.92 [172]. The estimate of the prevalence of RA with our algorithm is similar to that in other adult populations [10]. The outcome CVA was also assessed using administrative data. Privacy protection laws prevent access to medical records to confirm diagnoses. However, validation studies for CVA in Canada and other parts of the world have shown a positive predictive value higher than 90% [196-198]. We did not include transient ischemic attacks in the composite outcome, because of the poor reliability of the ICD-9 codes for this entity [198].

A major methodological concern in observational studies assessing effects of drug exposures is confounding by indication. Thus, more severe cases are more likely to receive GC and may be at a higher risk for CVD. We attempted to control for confounding by indication bias by using PS [156,199,200]. Because of residual imbalance within PS quintiles in some of the variables used to calculate the PS, we included these variables as covariates in the final model, in addition to the PS as suggested [158]. Although we adjusted for all known risk factors for CVA available in our administrative data, our results could still be affected by unknown or unmeasured confounders, especially markers of disease severity.

In this study, we were able to adjust for recency of GC exposure using a six month time window in the weight function. This time window was chosen based on results from previous studies suggesting that only recent GC exposure was associated with an increased risk of CVD [131-134]. This method has been proposed as a more efficient

modeling of time-varying exposures where outcomes are rare and associations weak. Lack of significance despite the use of this novel method supports the lack of association between GC and CVA.

In conclusion, data from this population-based study did not support a statistically significant increase in risk of CVA associated with GC exposure. Further studies are needed with larger cohorts and greater number of CVA events, to confirm if our negative results were due to insufficient power, or whether the risk is truly null, and GC exert a differential effect on the vasculature of the brain and the heart.

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5: DISCUSSION

5.1 SUMMARY OF KEY FINDINGS

The research topic of this thesis was CVD in patients with RA. In Chapter 2, we examined whether the risk of CVD mortality was increased in patients with RA, compared with age- and sex-matched controls from the general population. In a systematic review and a meta-analysis of all observational studies published until 2005, we pooled data for 111,758 patients that had 22,927 CV events. Overall, we found that the patients with RA have a 50% higher risk of CVD mortality. Unlike the general population where the risk of CVD differs by gender, we found no clear difference between genders in our meta-analysis (58% and 45% for females and males respectively). The increased mortality was attributable to increased deaths from MI (59%) and CVA (52%).

Our study provided some insights that were acknowledged in an accompanying editorial (20). These included that the study design is the main driver in the variation in mortality. Community and inception cohorts had the lowe st risk of CVD mortality when compared to clinic-based and cohorts that used prevalent cases.

In Chapter 3, we assessed the risk of MI associated with the use of GC. We assembled a large unique cohort that included cases with newly diagnosed RA that were not exposed to GC prior to onset. Thus, for the first time, we assessed GC exposure over the entire course of the disease. We used comprehensive GC exposure measures that considered actual and past cumulative exposure either individually or together. We found that after adjusting for CV risk factors, disease characteristics, and CBI, the

independent effect of GC use (yes/no) was associated with a 63% increased risk of MI. Moreover, for each 5 mg increase in the mean daily dose, the risk of MI increased by 12%. The risks of MI associated with each year of use or each gram of use in the past were 18% and 2%, respectively. Furthermore, when we assessed both current and past exposures at the same time, as in real life conditions, we found a 10% risk increase for each 5 mg increase in the mean daily dose, in addition to the 15% risk increase for each year of GC use in the past.

In Chapter 4, we assessed the risk of CVA associated with the use of GC using the same research design used in Chapter 3. Our results did not support an association between GC and risk of CVA. GC were still not statistically significant even after adjusting for recency of use.

5.2 IMPLICATIONS FOR CLINICAL PRACTICE

Our aim was to provide an answer to a long debated topic. On one side there are well-respected clinicians who oppose to the use of GC (1, 2). On the other hand, there are also well-respected clinicians who consider that GC should be used in all patients with RA (3, 4).

Since the first use of GC by Hench 61 year ago (5, 6), millions of patients with RA worldwide have been treated. GC use I likely to continue (7). Despite the evidence of beneficial and dramatic effects of GC in RA in several randomized clinical trials, the debate continues. The central argument for this debate seems to be the long-term safety of GC.

We have addressed the issue of CVD risk associated with GC use. GC are independently associated with and statistically significant increased risk of MI. The risk varies depending on the exposure measure used. Our results will provide better

information for clinicians and patients to make an informed decision. GC are still used by a significant proportion of patients all over the world (8-14). We believe that they play an important role in the management of RA, and even more in other rheumatic diseases. Patients and clinicians will still use GC, despite being aware of the potential risks associated with their long-term use. They note that nothing works as fast as GC (4). By knowing the risks associated with the daily dose, as well as the risks from past cumulative use, patients and their treating physicians will be in a better position to weigh the risks and benefits of GC to treat RA inflammation, and make informed decisions.
We should be cautious with the results of lack of association between GC use and risk of CVA, especially considering the findings of the meta-analysis conducted in Chapter 1, where several studies did not find an increased risk of CVA in patients with RA but the pooled estimate was. As discussed in Chapter 4, a post hoc power analysis showed that our study had only 70% to detect a statistically significant difference. Therefore, larger studies with longer follow-up may be needed before concluding that GC use is not associated with CVA.

5.3 IMPLICATIONS FOR FUTURE RESEARCH

In our meta-analysis, we did not identify reports from non-Western countries (15). These reports are clearly needed, and it is worrisome that we know little from developing countries or different races. This type of research in non-Western populations is needed. As Dr. Ward discussed in his editorial (16), the results of our meta-analysis (15) provided evidence that timing matters when interpreting results of CVD in patients with RA. Clinicians and researchers should keep this in mind when interpreting risks, and when designing research studies addressing mortality or other relevant CVD outcomes.

Second, our results support the concept that GC exposure may have a differential effect based on the vascular beds considered (17). Thus, GC use accelerates atherosclerosis in the heart, and may not do it or do so to a lesser extent in the brain. Our results are consistent with the evidence that GC exposure has different effects in different endothelial cells (17, 18). Further research is needed to test this hypothesis in patients with all rheumatic diseases. Combining MI and CVA together as a composite outcome may be inappropriate and should be avoided.

In addition to the traditional method that considers the lifetime past cumulative exposure measures, duration of use, and dose regardless of recency of use, we used a novel time-dependent method proposed by Abrahamowicz et al. (19), to evaluate if weighting for recency of use improved the prediction of MI risk. However, it did not improve the model's fit to data confirming the theory that some of the undesirable effects of GC cumulate over very long periods of time. A more refined approach to define the best time window to assign the weight function (e.g, estimating it directly from the data rather than arbitrarily) deserves further research.

5.4 STRENGTHS AND LIMITATIONS

A randomized controlled trial would be the gold standard to definitely answer the question of long-term side effects of CVD in patients with RA. Since this trial is very unlikely to happen for ethical reasons, well-designed epidemiologic studies are the second best alternative. We have used a rigorous methodology to answer the questions that were the objectives of this thesis. First, to assess the risk of CVD mortality in RA, we performed a careful literature search on all published studies that have used standardized mortality rates as a measure of risk. By using this approach, we ensured that the comparison group would always be the general population and would be

adjusted by age and gender. We believe that to better assess the magnitude of the risk, the comparison or reference group should be the general population from where the RA sample came. Our literature search was carefully performed and, as noted by others (20-22), we used “state-of-the-science” to analyze it. However, the study had some limitations. We included studies with cohorts that were clinically different in terms of age at enrolment, disease duration, disease severity, and classification criteria to define RA. This explained some of the heterogeneity found in the study. Nevertheless, we were able to provide consistent estimates for the different populations.

For the pharmacoepidemiologic studies, we assembled a population-based incident RA cohort. To the best of our knowledge, this is the largest incident RA cohort available today for research purposes. Moreover, this cohort was assembled from a population covered by universal health care. It is a population-based cohort, thus limiting selection bias. Since RA is a painful and limiting condition that generally forces those afflicted to seek medical care, we believe that we have captured almost RA cases in BC. Furthermore, we have complete ascertainment of all hospitalizations, vital statistics, medical visits and all dispensed medications. Dispensed medication is a key feature that distinguishes our study from most of the previous studies that relied upon medical records to ascertain drug exposure, because many patients do not fill their prescriptions accurately (23-26).

A unique feature of our study is that we included only incident GC users. This allowed us to assess the GC use during the entire disease course. As a result we excluded 30% of all incident RA cases (they had received GC before RA for whatever reason). This suggests that including non-incident GC users, we may underestimate GC exposure and could increase the risk of potential misclassification for patients that did not receive GC after RA onset. We attempted to create the “cleanest” possible cohort to assess the true effect of GC exposure on CVD. We also used single CVD outcomes rather than

composite outcomes. This allowed us to find a differential effect of GC use depending on the vascular bed.

Limitations of our study include those inherent to observational studies based on administrative data. Uncertainty around diagnostic accuracy to identify RA cases and the outcomes of interest is one of the most relevant limitations. As discussed in each pharmacoepidemiologic study (Chapters 3 and 4), we have used one of the strictest published case definitions (27). Most studies in RA used case definitions based on a single visit. This algorithm has been validated against self report of a physician diagnosis of RA, yielding a positive predictive value of 0.92 (28). Furthermore, we improved specificity with additional exclusions. In addition, the estimate of the prevalence of RA with our algorithm is similar to that in other adult populations (29). Moreover, accuracy of the outcomes of interest in this thesis have been validated in Canada and in several parts of the world, and they have consistently shown positive predictive values higher than 90% (30-34). It is unlikely that many MI and CVA events would be missed since these conditions require medical care usually in hospital. It is possible that cases that died outside of hospital may not have been accurately coded. However, we do not anticipate a differential effect based on GC exposure.

It is known that the major limitation of pharmacoepidemiologic studies is their inability to adjust completely for CBI. In order to limit this confounder we have used propensity scores, which is one of the methods most commonly used to adjust for CBI (35-38). We used all variables available in our databases predict the use of GC. We assessed the predictive ability of the propensity score to distinguish GC users from non-users, and we found that the c statistic was higher than 0.80 in both studies (Chapter 3 and 4). This value means that more than 80% of the variables used to calculate the propensity score would predict GC use in this sample. Despite that this is considered a very good predictive value for a propensity score calculation; there are still factors unavailable in

our databases that could better distinguish GC users from non-users (e.g., physician characteristics and clinical variables). As recommended, we assessed the balanced achieved by the propensity scores between GC users and non-users. Unbalanced covariates were added in the final models. The large sample size of our cohort allowed us to do this without over-fitting the models. Another limitation of the propensity scores is that they do not adjust for unmeasured confounders (39, 40). This will always be the case in observational studies, but this does not invalidate the results. However, we believe that researchers and readers should be aware of this limitation when interpreting the estimates derived from our studies.

To adjust for disease severity, we used some surrogates available in the databases. These ad hoc surrogates were based on clinical. Nevertheless, this approach needs be validated. We did not include other variables such as joint replacement surgeries because there were few performed (n=33) in this incident cohort.

5.5 CONCLUSIONS

First, the overall risk for CVD mortality is 50% in patients with RA when compared with the general population with no difference between genders in their proportional increase. People with RA have a 59% and 52% increase risk of dying from MI and CVA, respectively compared to the general population. However, the risk estimates vary depending of the underlying RA population. The risks are lower for patients from community-based samples (35%) than from clinic-based samples (53%). The 19% increase in risk of CVD in inception cohorts is closest to that seen in the general population.

At the population level the use of GC is independently associated with an increased risk of MI. The risk varies depending of the exposure measure used. Both, current GC daily

dose and past cumulative exposure influence the risk independently. When considering both current and past exposure, there is a 10% increased risk of MI for each 5 mg increase in the current mean daily dose of GC, in addition to the 15% increase risk for each year of use of GC accumulated in the past.

At the population level GC use is not statistically associated with an increased risk of CVA regardless of the GC exposure measure used.

There is a differential effect of GC depending on the vascular bed. Therefore, combining cardiovascular outcomes may be inappropriate.

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APPENDIX A: UBC BEHAVIOURAL RESEARCH ETHICS BOARD

CERTIFICATES OF APPROVAL

The University of British Columbia
Office of Research Services
Behavioural Research Ethics Board
Suite 102, 6190 Agronomy Road, Vancouver, B.C. V6T 1Z3

CERTIFICATE OF APPROVAL- MINIMAL RISK RENEWAL

PRINCIPAL INVESTIGATOR:	DEPARTMENT:	UBC BREB NUMBER:
Diane Lacaille	UBC/Medicine, Faculty of/Medicine, Department of/Rheumatology - Med	H09-00620

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT:

Institution	Site
N/A	N/A

Other locations where the research will be conducted:
N/A

CO-INVESTIGATOR(S):
N/A

SPONSORING AGENCIES:
Canadian Institutes of Health Research (CIHR)

PROJECT TITLE:
Cardiovascular morbidity and mortality associated with the use of corticosteroids in patients with rheumatoid arthritis. A population based study.

EXPIRY DATE OF THIS APPROVAL: April 8, 2011

APPROVAL DATE: April 8, 2010

The Annual Renewal for Study have been reviewed and the procedures were found to be acceptable on ethical grounds for research involving human subjects.

Approval is issued on behalf of the Behavioural Research Ethics Board

Dr. M. Judith Lynam, Chair
Dr. Ken Craig, Chair
Dr. Jim Rupert, Associate Chair
Dr. Laurie Ford, Associate Chair
Dr. Anita Ho, Associate Chair