Immediate and past cumulative effects of oral glucocorticoids on the risk of acute myocardial infarction in rheumatoid arthritis: a population-based study

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Abstract

Objectives. To determine the effect of glucocorticoids (GCs) on acute myocardial infarction (MI) risk in patients with RA.

Methods. Using administrative health data, we conducted a population-based cohort study of 8384 incident RA cases (1997–2006). Primary exposure was incident GC use. MI events were ascertained using hospitalization and vital statistics data. We used Cox proportional-hazards models and modelled GC use as four alternative time-dependent variables (current use, current dose, cumulative dose and cumulative duration), adjusting for demographics, comorbidities, cardiovascular drug use, propensity score and RA characteristics. Sensitivity analyses explored potential effects of unmeasured confounding.

Results. Within 50238 person-years in 8384 RA cases, we identified 298 incident MI events. Multivariable models showed that current GC use was associated with 68% increased risk of MI [Hazard ratio (HR) = 1.68, 95% CI 1.14, 2.47]. Similarly, separate multivariable models showed that current daily dose (HR = 1.14, 95% CI 1.05, 1.24 per each 5 mg/day increase), cumulative duration of use (HR = 1.14, 95% CI 1.00, 1.29 per year of GC use) and total cumulative dose (HR = 1.06, 95% CI 1.02, 1.10 per gram accumulated in the past) were also associated with increased risk of MI. Furthermore, in the same multivariable model, current dose and cumulative use were independently associated with an increased risk of MI (10% per additional year on GCs and 13% per 5 mg/day increase).

Conclusion. GCs are associated with an increased risk of MI in RA. Our results suggest a dual effect of GCs on MI risk, an immediate effect mediated through current dosage and a long-term effect of cumulative exposure.

Key words: rheumatoid arthritis, cardiovascular disease, acute myocardial infarction, glucocorticoids, corticosteroids.

Introduction

RA, a chronic inflammatory disease, leads to progressive joint deformity, disability and premature death [1]. Growing evidence in the last decade demonstrates that RA patients have an increased risk of ischaemic heart disease including acute myocardial infarction (MI) [2–5]. Overall, RA patients have a 48% increased risk of new cardiovascular events and death than the general population [6]. Specifically, the risk of MI is increased by 68% [6]. RA itself or uncontrolled inflammation could have a direct

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Submitted 28 May 2012; revised version accepted 22 October 2012.

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effect on the endothelium and predispose patients to accelerated atherosclerosis and MI [7, 8]. The medications used for RA, particularly glucocorticoids (GCs), may influence the risk of MI [9]. 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 an increased risk of cardiovascular disease (CVD). On the other hand, GC may also have cardioprotective effects mediated by their anti-inflammatory and anti-proliferative actions in the endothelial wall, especially at low doses [13–15].

Yet, little is known about the long-term effects of GC on the development of CVD. Most existing studies have evaluated GC exposure as a single variable only, for example, at baseline, current or cumulative use. Furthermore, the cardiovascular outcomes have usually been assessed as composite rather than a specific outcome, such as MI [9, 16–18], although exposure status and dose of GC change frequently during follow-up in RA patients. Thus, the cumulative measures of GC exposure, like total duration of use or total cumulative dose, vary over time, which may have an influence on MI risk. An efficient modelling of time-dependent GC exposure measures is therefore especially important, as knowledge regarding how MI risk changes with increasing cumulative dose and/or duration of GC is needed to find an optimal trade-off between the anti-inflammatory benefits of GC and the increased MI risk. We performed a comprehensive assessment to determine the effect of several aspects of GC exposure on the risk of MI in a population-based RA cohort.

Methods

Study population

We used the data from a previously established population-based RA cohort for the province of British Columbia, Canada, and identified cases using administrative billing data from the British Columbia Ministry of Health [19]. Ethics approval was obtained from the University of British Columbia (UBC).

The RA case definition included individuals who had at least two physician visits ≥2 months apart with a RA diagnostic code (International Classification of Diseases, Ninth Revision (ICD-9) of 714.x [19]. Exclusion criteria to improve specificity were: (i) at least two visits subsequent to the second RA visit with diagnoses of other inflammatory arthritides (e.g. PsA, SLE); (ii) an RA-coded visit by a non-rheumatologist that was not confirmed on a subsequent rheumatologist visit; or (iii) no subsequent RA-coded visits during the individual’s last 5 years of follow-up.

We defined our incident RA cohort as individuals with a first diagnosis of RA on or after 1 January 1997 and without a prior RA diagnosis from January 1990 (earliest available data). The date of the first diagnostic RA code was considered the index date. RA cases were followed until March 2006. Utilization data for all funded health services since 1990, including physician visits and hospitalizations, were obtained. We also obtained complete information on all prescriptions dispensed by pharmacists from January 1996 and mortality data from vital statistics.

Exposure assessment

The GC use in our study includes all GCs dispensed by pharmacists. IA and inhaled GCs were not, however, considered as GC exposure. Doses were calculated as prednisone equivalents based on accepted standards [20, 21]. Using data on the prescription dispensing date and days supplied, we established the course of GC therapy for each subject. We constructed four different time-dependent GC exposure measures including current use (yes/no), current dose (mg/day), cumulative dose (grams) and cumulative duration of use (years). First, for each day between the beginning and the end of each dispensed GC prescription, we calculated the current dose by dividing the total quantity of dispensed medication by the number of days. Secondly, the cumulative dose was obtained by summing up all doses from all past prescriptions until the day of follow-up.

In sensitivity analyses, we used a novel time-dependent method to evaluate if weighting for recency of use would improve the prediction of MI risk [22]. This method assumes that more recent exposures have a greater impact on risk outcome than more remote exposure, by weighting past doses or indicators of past use with a pre-specified function, similar to a decreasing logistic curve [22].

Outcome assessment

The primary outcome, the first MI event during follow-up, was identified from hospitalization codes (ICD-9 code 410.x or ICD-10 code I21.x) either as cause of admission or as complication during hospitalization. Death from MI was defined from a death certificate or any death within 30 days of the MI after being discharged from hospital.

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 the index date in all multivariable time-dependent Cox regression analyses [23]. These included age, gender and comorbidities based on diagnostic codes from all outpatient physician and hospital visits from January 1990 until the index date, using a modification of the Charlson’s comorbidity index developed for administrative data [24, 25]. We also assessed exposure to anti-hypertensives, lipid-lowering medications, other cardiovascular medications, diabetes medications, hormone replacement therapy and oral contraceptives (Table 1) over the year preceding the index date. Aspirin use was not ascertained because this medication is available over the counter.

We used the following markers as surrogates of disease severity [26, 27]: 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 DMARDs. DMARD use was categorized as an ordinal variable with no DMARD use (group 1), SSZ and anti-malarials.
These categories were mutually exclusive and we used the highest rank attained during the follow-up.

We assumed that patients with at least one visit to a rheumatologist, patients with more physician visits per PY of follow-up and patients with a higher DMARD ranking (e.g. biologics vs anti-malarials) had a more severe case of the disease. Finally, we also calculated patients’ current use of MTX, Cox-2 inhibitors and NSAIDs as time-dependent covariates.

### Statistical analysis

For every case in the cohort, we calculated the person-time from index date to the first MI, last healthcare service, death or end of study. Rates per PY 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) [28, 29]. PS were estimated using a multivariable logistic regression model that included aforementioned covariates as independent variables, as previously reported [27]. Each subject with a first GC prescription was matched on calendar time, age and sex with a non-user randomly selected from the cohort. We found some non-linear associations (with exposure and outcome) for some variables (age and the rate of rheumatologist visits per year). Therefore, these variables were entered as categorical variables.

### Table 1: Baseline characteristics of the incident RA cohort by status of exposure to GCs assessed from 1990 up to date of initiation

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All cases (n = 8384)</th>
<th>Exposed (n = 2783)</th>
<th>Unexposed (n = 5601)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>5658 (67.5)</td>
<td>1964 (70.6)</td>
<td>3694 (66.0)</td>
</tr>
<tr>
<td>Men</td>
<td>2726 (32.5)</td>
<td>819 (29.4)</td>
<td>1907 (34.1)</td>
</tr>
<tr>
<td>Age, mean (S.D.), years</td>
<td>57.9 (17.4)</td>
<td>59.0 (17.3)</td>
<td>57.4 (17.4)</td>
</tr>
<tr>
<td>Cardiovascular drug use</td>
<td>2935 (35.0)</td>
<td>1136 (40.8)</td>
<td>1799 (32.1)</td>
</tr>
<tr>
<td>Anti-hypertensive drugs</td>
<td>3483 (41.5)</td>
<td>1335 (48.0)</td>
<td>2148 (38.4)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>2425 (28.9)</td>
<td>924 (33.2)</td>
<td>1501 (26.8)</td>
</tr>
<tr>
<td>β-blockers</td>
<td>1884 (22.5)</td>
<td>718 (25.8)</td>
<td>1166 (20.8)</td>
</tr>
<tr>
<td>α-blockers</td>
<td>374 (4.5)</td>
<td>163 (5.9)</td>
<td>211 (3.8)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>625 (7.5)</td>
<td>263 (9.5)</td>
<td>362 (6.5)</td>
</tr>
<tr>
<td>ARB</td>
<td>710 (8.5)</td>
<td>273 (9.8)</td>
<td>437 (7.8)</td>
</tr>
<tr>
<td>Other CV drugs</td>
<td>3674 (43.8)</td>
<td>1425 (51.2)</td>
<td>2249 (40.2)</td>
</tr>
<tr>
<td>Cardiac glycosides</td>
<td>445 (5.3)</td>
<td>182 (6.5)</td>
<td>263 (4.7)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>3011 (35.9)</td>
<td>1197 (43.0)</td>
<td>1814 (32.4)</td>
</tr>
<tr>
<td>Anti-arrhythmic</td>
<td>202 (2.4)</td>
<td>100 (3.6)</td>
<td>102 (1.8)</td>
</tr>
<tr>
<td>Anti-coagulants</td>
<td>748 (8.9)</td>
<td>284 (10.2)</td>
<td>464 (8.3)</td>
</tr>
<tr>
<td>Nitrites</td>
<td>1174 (14.0)</td>
<td>445 (16.0)</td>
<td>729 (13.0)</td>
</tr>
<tr>
<td>Dipyridamole</td>
<td>13 (0.2)</td>
<td>5 (0.2)</td>
<td>8 (0.1)</td>
</tr>
<tr>
<td>Diabetes medications</td>
<td>446 (5.3)</td>
<td>161 (5.8)</td>
<td>285 (5.1)</td>
</tr>
<tr>
<td>HRT</td>
<td>1288 (15.3)</td>
<td>471 (16.9)</td>
<td>815 (14.6)</td>
</tr>
<tr>
<td>Oral contraceptive</td>
<td>399 (4.8)</td>
<td>154 (5.5)</td>
<td>245 (4.4)</td>
</tr>
<tr>
<td>Lipid-lowering drugs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrates</td>
<td>123 (1.5)</td>
<td>34 (1.2)</td>
<td>89 (1.6)</td>
</tr>
<tr>
<td>Statins</td>
<td>664 (7.9)</td>
<td>250 (9.0)</td>
<td>414 (7.4)</td>
</tr>
<tr>
<td>NSAIDs during follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No NSAIDs</td>
<td>2094 (25.0)</td>
<td>363 (13.0)</td>
<td>1731 (30.9)</td>
</tr>
<tr>
<td>Traditional NSAIDs</td>
<td>5951 (71.0)</td>
<td>2293 (82.4)</td>
<td>3658 (65.3)</td>
</tr>
<tr>
<td>Cox-2</td>
<td>2050 (24.5)</td>
<td>857 (30.8)</td>
<td>1193 (21.3)</td>
</tr>
<tr>
<td>DMARD use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No DMARDs</td>
<td>6342 (75.6)</td>
<td>1662 (59.7)</td>
<td>4680 (83.6)</td>
</tr>
<tr>
<td>Non-MTX DMARDs</td>
<td>1721 (20.5)</td>
<td>926 (33.3)</td>
<td>795 (14.2)</td>
</tr>
<tr>
<td>MTX</td>
<td>798 (9.5)</td>
<td>484 (17.4)</td>
<td>314 (5.6)</td>
</tr>
<tr>
<td>Biologics</td>
<td>18 (0.2)</td>
<td>10 (0.4)</td>
<td>8 (0.1)</td>
</tr>
<tr>
<td>Charlson index, mean (S.D.)</td>
<td>1.53 (1.94)</td>
<td>1.91 (2.27)</td>
<td>1.34 (1.72)</td>
</tr>
<tr>
<td>Angina</td>
<td>1741 (20.8)</td>
<td>620 (22.3)</td>
<td>1121 (20.0)</td>
</tr>
<tr>
<td>COPD</td>
<td>2476 (29.5)</td>
<td>941 (33.8)</td>
<td>1535 (27.4)</td>
</tr>
</tbody>
</table>

Except where indicated otherwise, values are the number (%) of subjects. aTraditional DMARDs, excluding MTX. ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker; Cox-2: cyclo-oxygenase-2 selective; COPD: chronic obstructive pulmonary disease.

(group 2), MTX or i.m. gold (group 3), LEF, CSA, AZA, CYC, chlorambucil or MMF (group 4) and biologics (group 5). These categories were mutually exclusive and we used the highest rank attained during the follow-up. We assumed that patients with at least one visit to a rheumatologist, patients with more physician visits per PY of follow-up and patients with a higher DMARD ranking (e.g. biologics vs anti-malarials) had a more severe case of the disease. Finally, we also calculated patients’ current use of MTX, Cox-2 inhibitors and NSAIDs as time-dependent covariates.

### Statistical analysis

For every case in the cohort, we calculated the person-time from index date to the first MI, last healthcare service, death or end of study. Rates per PY 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) [28, 29]. PS were estimated using a multivariable logistic regression model that included aforementioned covariates as independent variables, as previously reported [27]. Each subject with a first GC prescription was matched on calendar time, age and sex with a non-user randomly selected from the cohort. We found some non-linear associations (with exposure and outcome) for some variables (age and the rate of rheumatologist visits per year). Therefore, these variables were entered as categorical variables.
As recommended, we assessed the predictive ability of the PS to distinguish GC users from non-users and the c-statistic of 0.74 indicated a good discrimination [30]. We summarized the balance achieved on the PS between GC users and non-users by grouping subjects into PS quintiles (see supplementary Table S1, available as supplementary data at *Rheumatology* Online). We found residual imbalance on some covariates (DMARD ranking, Cox-2, MTX and rate of RA-related visits to family physicians). Therefore, we included imbalanced covariates, in addition to PS quintiles, in all Cox models [31].

To estimate the risk of MI, we used five separate multivariable Cox models each using a different time-dependent measure of GC exposure [23]. Time to event was defined as the time from subject’s index date to his/her first MI. Subjects who had no MI until the end of their follow-up were censored at that time. All models were adjusted for PS, imbalanced covariates and binary (yes/no) time indicators of current use of MTX, Cox-2 inhibitors and NSAIDs, updated daily. The Akaike’s information criterion (AIC) was used to compare the predictive ability of alternative models [32] and to select the GC exposure measure that best explains its association with the ability of alternative models [32] and to select the GC exposure measure that best explains its association with the outcome [33]. To assess the proportionality assumption, we plotted log [-log (S(t))] vs log (t) stratified by each explanatory variable and checked that they were parallel. We also tested all variables in the Cox models for time interactions, and none were significant.

We performed bias sensitivity analyses, which assessed how a hypothetical unmeasured confounder might have affected our estimates of the association between GC exposure and MI risk [34]. In separate sensitivity analyses, we simulated unmeasured confounders with either 10% or 20% prevalence in our RA cohort and with two strengths of the association with GC exposure and presence of MI [using odds ratios (OR) of 1.3 and 5.0 for each association]. This allowed us to investigate if the effect of GC exposure remained statistically significant after the additional adjustments for the corresponding hypothetical confounder. Analyses were performed with SAS software version 9.2 (SAS Institute, Inc., Cary, NC, USA). For all hazard ratios (HRs), we calculated 95% CIs. All P-values were two sided.

**Results**

**Study sample**

The cohort included 8384 incident RA cases, of which 2783 (33%) received at least one GC prescription. The baseline characteristics of the cohort according to GC exposure (ever/never) are summarized in Table 1. Overall, GC users were older, had more comorbidities and used more medications. For the entire cohort, the total follow-up was 50,238 PYs, with 2,981 and 47,257 PYs corresponding to periods of GC use and non-use, respectively.

**GC use and incidence of MI**

Overall, GC users spent 17% of their follow-up time on GC with a median daily dose of 0.5 mg and a median duration per GC course of 71 days. We identified 298 new MI events during follow-up, of which 37% were fatal. The unadjusted MI incidence rates per 1000 PYs were 5.9 in the entire cohort, 10.7 during GC exposure and 5.6 during GC non-exposure.

**Effect of GC exposure**

Table 2 shows the results of the unadjusted and adjusted time-dependent Cox’s models used to assess the effects of different GC exposures on the risk of MI. All multivariable models showed GC to be associated with an increased risk of MI. In Model 1 (the simplest model that ignored dose and duration of exposure), current GC use was associated with a 68% risk increase (HR = 1.68, 95% CI 1.14, 2.47). Model 2 accounted for current dose only (HR = 1.14, 95% CI 1.05, 1.24 per 5 mg/day increase in the dose), and therefore not for past exposure. Model 3 yielded HR = 1.14, 95% CI 1.00, 1.29 for each additional year of past GC exposure. Finally, in Model 4, each additional gram of total past cumulative GC dose was associated with HR = 1.06, 95% CI 1.02, 1.10.

Model 5 showed that the current dose (13% risk increase per additional 5 mg/day) and cumulative duration of past GC use (10% risk increase for every additional year) were independently associated with higher MI risk. All multivariable models predicted the outcomes similarly well, although the cumulative total dose had slightly better fit (lowest AIC in Table 2) than other exposure models. Accounting for recency of use (within the past 6 or 24 months) with weighted cumulative exposure did not improve the model’s fit to the data (lowest AIC = 5115.4).

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

Table 3 summarizes the sensitivity analyses that assessed how the association between GC exposure measures and MI would be affected by adjustment for a potential unmeasured confounder. Sensitivity analyses took varying assumptions about the confounder’s prevalence (10 and 20%) and the strength of its associations with GC use and the occurrence of MI (ORs of 1.3 or 5.0) into account. The adjusted association between the different GC exposure measures and MI remained statistically significant for most sensitivity analyses.

**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. This is the largest incident RA cohort to date and the first evaluation of the effects of past and current exposure of GC on the risk of MI over the entire disease course in an incident RA cohort. We found that current GC use increased the risk of MI by 68%. In addition, we found that higher current GC dose was associated with increased MI risk, whether considered alone
or in the same model as cumulative duration of past GC use. In the latter model, the MI risk increased by 13% for every 5 mg/day increase in current dose, in addition to the 10% increased risk for every year of GC use. Although the latter was not statistically significant, larger doses have multiplicative effects. For example, a patient on a current dose of 10 mg/day of prednisone who had a cumulative exposure to GC use for 2 years (regardless of the dose, continuous or intermittently) would have a HR of \(1.13^{2} \times 1.10^{2} = 1.55\), or a 55% increased risk of MI compared with a patient without exposure to GC (currently or in the past). These risks were independent of age, sex, comorbidities, proxy indicators of RA severity, traditional NSAIDs and Cox-2 inhibitors.

Our findings suggest that the effect of GC exposure may have two independent components, namely: (i) the immediate effect of current exposure/dose; and (ii) the long-term effect of past exposure duration accumulated over time. 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 [35].

Regarding the long-term effects, there is evidence suggesting that GCs are likely to contribute to the destabilization of atherosclerotic lesions [36]. GCs may also exacerbate the consequences of lesion rupture by modulating factors involved in coagulation and fibrinolysis to produce a pro-thrombotic state [12]. Other processes that could also mediate the long-term effects of GC on the risk of MI by promoting atherosclerosis include stimulating release of the vasoconstrictor and growth factor ET-1 [37], increasing vasoconstriction that leads to reduced vascular lumen diameter [35], impairment of cholesterol removal from the arterial wall [38] and increasing vascular calcification [39]. GC also promotes hypertension, which could mediate short-term and long-term effects on MI risk.

Our results are consistent with recently published epidemiological studies that found an association between CVD outcomes and GC in patients with RA and other chronic inflammatory disorders [16, 17, 40-42].

### Table 2: Cox’s regression models assessing the effects of the different GC exposure measures on the risk of acute MI (unweighted)

<table>
<thead>
<tr>
<th>Model</th>
<th>GC exposure measure</th>
<th>Univariable HR (95% CI)</th>
<th>AIC</th>
<th>Multivariable HRa (95% CI)</th>
<th>AIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Current use (yes/no)</td>
<td>1.94 (1.34, 2.80)</td>
<td>5175.4</td>
<td>1.68 (1.14, 2.47)</td>
<td>5114.3</td>
</tr>
<tr>
<td>2</td>
<td>Current daily dose (5 mg)</td>
<td>1.17 (1.08, 1.27)</td>
<td>5177.8</td>
<td>1.14 (1.05, 1.24)</td>
<td>5114.9</td>
</tr>
<tr>
<td>3</td>
<td>Total cumulative duration of use (year)</td>
<td>1.22 (1.09, 1.37)</td>
<td>5167.4</td>
<td>1.14 (1.00, 1.29)</td>
<td>5161.6</td>
</tr>
<tr>
<td>4</td>
<td>Total past cumulative dose (1 g)</td>
<td>1.08 (1.04, 1.11)</td>
<td>5172.9</td>
<td>1.06 (1.02, 1.10)</td>
<td>5113.6</td>
</tr>
<tr>
<td>5</td>
<td>Current daily dose (5 mg) + Cumulative duration, year</td>
<td>1.14 (1.04, 1.26)</td>
<td>5173.6</td>
<td>1.13 (1.03, 1.24)</td>
<td>5114.9</td>
</tr>
</tbody>
</table>

aAdjusted for PS, unbalanced covariates (age, gender, hypertension, statins, diabetes, angina, COPD, other cardiovascular drug use, Charison index, having seen a rheumatologist for RA, number of MD visits per year) as fixed in time (at the time of GC initiation), current use of Cox-2 inhibitors, MTX and NSAIDs as time-dependant covariates from index date to end of follow-up.

### Table 3: Cox’s regression models assessing the effects of the unmeasured confounder on the risk of acute MI

<table>
<thead>
<tr>
<th>Prevalenceb, %</th>
<th>ORc</th>
<th>Current use (yes/no)</th>
<th>Current dose (5 mg)</th>
<th>Cumulative duration, year</th>
<th>Cumulative dose (1 g)</th>
<th>Current dose (5 mg) + Cumulative duration, years</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>1.3</td>
<td>1.67 (1.14, 2.46)</td>
<td>1.14 (1.05, 1.24)</td>
<td>1.14 (1.00, 1.29)</td>
<td>1.06 (1.02, 1.10)</td>
<td>1.13 (1.03, 1.24)</td>
</tr>
<tr>
<td>10</td>
<td>5.0</td>
<td>1.41 (0.96, 2.08)</td>
<td>1.12 (1.02, 1.22)</td>
<td>1.07 (0.94, 1.22)</td>
<td>1.04 (1.00, 1.08)</td>
<td>1.11 (1.01, 1.22)</td>
</tr>
<tr>
<td>20</td>
<td>1.3</td>
<td>1.67 (1.13, 2.45)</td>
<td>1.14 (1.05, 1.24)</td>
<td>1.14 (1.00, 1.29)</td>
<td>1.06 (1.02, 1.10)</td>
<td>1.13 (1.03, 1.24)</td>
</tr>
<tr>
<td>20</td>
<td>5.0</td>
<td>1.26 (0.86, 1.85)</td>
<td>1.11 (1.01, 1.22)</td>
<td>1.02 (0.89, 1.17)</td>
<td>1.03 (0.99, 1.07)</td>
<td>1.11 (1.01, 1.22)</td>
</tr>
</tbody>
</table>

aAdjusted for PS, unbalanced covariates (age, gender, hypertension, statins, diabetes, angina, COPD, other cardiovascular drug use, Charison index, having seen a rheumatologist for RA, number of MD visits per year), current use of Cox-2 inhibitors, MTX and NSAIDs. bPrevalence of the unmeasured confounder in the entire RA cohort. cOR for the association between (i) confounder vs GC and (ii) confounder vs MI.
Wei et al. [42] and Souverein et al. [17] studied all GC users from the general population using administrative prescription records. In Wei et al.’s study, in which 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 = 1165) was associated with a 3-fold increased risk of CVD [42]. Souverein et al., in a population-based nested case-control study (n = 1515), reported that current GC use (in the last 3 months) was associated with ischaemic heart disease (OR = 1.36) [17].

Using an incident cohort of 603 RA patients over a median 13-year follow-up, Davis et al. [43] found that GC exposure was associated with an increased risk of CVD only in RF-positive individuals, particularly those with higher cumulative exposure, higher mean daily dose and recent use of GCs (<3 months). Caplan et al. [9] using the National Data Bank for Rheumatic Diseases, found that only current GC use (≤6 months) was associated with increased mortality. The study also found that prior GC use (>6 months) was not associated with increased mortality when compared with non-GC users, although the impact on CVD or MI was not assessed. In comparison with these studies, our study used a substantially larger population with a median follow-up of 6.1 years and evaluated the effect of GC use over the entire disease course in an incident RA cohort for the first time. We used administrative data on dispensed medication rather than prescribed, and included only incident GC users. We used a single outcome, MI, rather than a composite CVD outcome. Finally, our study is the first to explore the effect of current dose vs 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 cannot be completely ruled out; however, we used one of the strictest published case definitions (i.e. two physician visits at least 2 months apart) to remove cases with transient inflammatory arthritis and a positive predictive value of 0.82 from a sub-sample who provided self-reported data through medical record review by an independent rheumatologist. Using diagnostic impression of the reviewing rheumatologist as gold standard [44], we observed a high rate of individuals without DMARD or GC use (56%). This gap in care has been previously reported by us and confirmed by others. In British Columbia, only 43% of the population with RA had used a DMARD over a 5-year period, and only 10% of patients, who were managed by family physicians, used DMARD [19]. Similar results were also found in Ontario [45] and Quebec [46]. Furthermore, it is unlikely that potential misclassification of the diagnosis would explain the strong associations observed in this population-based study. It remains conceivable that the results may be even more striking with more specific case definitions of RA.

In our analyses, we have attempted to adjust the effect of confounding by indication or contraindication of GC and multivariable analyses. However, both adjustments were limited to baseline characteristics, measured at the start of the first GC prescription and some of the relevant (especially clinical) characteristics might have changed during the follow-up. On the other hand, some of these time-varying changes in clinical variables might have been, at least partly, affected by the GC treatment, and thus could lie on a causal pathway linking the exposure with the outcome, in which case the adjustment would not be appropriate. Future research could consider using marginal structural models to separate potential confounding effects of time-varying variables from the treatment effects possibly mediated through such changes. However, use of marginal structural models would require high-quality data on essential time-varying characteristics, such as changes in disease severity, which are not available in administrative databases.

The outcome MI was also assessed using administrative data. Privacy protection laws prevent access to medical records to confirm diagnoses. Validation studies for MI, however, have shown a positive predictive value that is >95% [47–49].

Observational studies assessing effects of drug exposures are also susceptible to confounding by indication. Indeed, more severe RA cases are more likely to receive GC and may be at a higher risk for MI. We attempted to control for confounding by indication by adjusting for PS and imbalanced variables [30]. Despite adjusting for all known risk factors of MI available in our administrative data, our results could still be affected by unknown or unmeasured confounders, especially markers of disease severity. Nevertheless, our sensitivity analyses indicated the robustness of our findings as, even after adjusting for a hypothetical strong unmeasured confounder, most associations between GC exposure and MI remained statistically significant.

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 current and cumulative exposure to GC matters. The risk of MI was increased by 68% with current use of GC, by 14% per 5 mg/day increase in current dose and by an additional 10% per year of cumulative use (when the latter two were included in the same model). This suggests a dual effect of GCs on MI, which involves an immediate effect mediated through current use/dose and a long-term effect mediated through cumulative duration of use. Our results have important implications for people with RA and their treating physicians when weighing the risks and benefits of using GCs to treat inflammation in RA.

**Rheumatology Key messages**

- First study assessing GC exposure and risk of MI during the entire RA duration.
- GC use increased the risk of MI in patients with RA at the population level.
- Clinicians and RA patients should weigh the benefits and risk of using GCs.
Acknowledgements

J.A.A.-Z. held doctoral and fellowship awards from the Canadian Arthritis Network/The Arthritis Society, the Canadian Institutes of Health Research, the Michael Smith Foundation for Health Research, The Mexican Institute for Social Security (IMSS) and CONACyT-Mexico and he is currently the British Columbia Lupus Society Research Scholar. M.P.S. held a doctoral award from the Canadian Institutes of Health Research. D.L. is the Mary Pack/Arthritis Society of Canada Chair in Rheumatology and holds an Investigator Award from The Arthritis Society of Canada.

Funding: This research was funded by operating grants from the Canadian Institutes of Health Research and The Arthritis Society (grants 77605 and 81275) and Canadian Arthritis Network (grant 08SRID-IJD-02).

Disclosure statement: The authors have declared no conflicts of interest.

Supplementary data

Supplementary data are available at Rheumatology Online.

References

26 Dixon WG, Abrahamowicz M, Beauchamp M-E et al. Immediate and delayed impact of oral glucocorticoid


29 Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. Biometrika 1983;70:41.


48 Austin PC, Daly PA, Tu JV. A multicenter study of the coding accuracy of hospital discharge administrative data for patients admitted to cardiac care units in Ontario. Am Heart J 2002;144:290–6.