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Glucocorticoids and Cardiovascular Events in Rheumatoid Arthritis

A Population-Based Cohort Study

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Objective. **To determine the relationship between glucocorticoid exposure and cardiovascular (CV) events in patients with rheumatoid arthritis (RA).**

Methods. **A total of 603 adult residents of Rochester, Minnesota with incident RA between 1955 and 1995 were followed up through their medical records for a median of 13 years (total of 9,066 person-years). Glucocorticoid exposure was defined 3 ways: tertiles of cumulative exposure; recent use (≤3 months) versus past use (>3 months); and average daily dosage (≤7.5 mg/day or >7.5 mg/day). CV events, including myocardial infarction, heart failure, and death from CV causes, were defined according to validated criteria. Cox regression models were adjusted for demographic features, CV risk factors, and RA characteristics.**

Results. **Rheumatoid factor (RF)–negative patients with exposure to glucocorticoids were not at increased risk of CV events, irrespective of the glucocorticoid dosage or timing of use, as compared with the reference group of RF-negative patients who had never been exposed to glucocorticoids. In contrast, RF-positive patients were at increased risk of CV events, particularly with higher cumulative exposure, higher average daily dosage, and recent use of glucocorticoids. RF-positive patients with high cumulative exposure to glucocorticoids had a 3-fold increased risk of CV events (hazard ratio 3.06 [95% confidence interval 1.81–5.18]), whereas RF-negative patients with high cumulative exposure were not at increased risk (hazard ratio 0.85 [95% confidence interval 0.39–1.87]).**

Conclusion. **RF-positive but not RF-negative patients were at increased risk of CV events following exposure to glucocorticoids. These findings suggest that glucocorticoids interact with RF status to modulate the occurrence of CV events in patients with RA. The mechanisms underlying this interaction are unknown and should be the subject of further research.**

The role of glucocorticoids in the occurrence of cardiovascular disease (CVD) in patients with rheumatoid arthritis (RA) has been a subject of controversy for decades (1–6). The undesirable effects of glucocorticoids on blood pressure, insulin resistance, lipid profile, body weight and fat distribution, and coagulation proteins might significantly increase the risk of CVD in RA patients (1,2,4,6). Although the literature supports the development of these potentially harmful effects with high-dose glucocorticoid therapy, it has been recognized that there is no firm evidence linking low-dose therapy and CVD in the RA population (7,8). On the contrary, recent studies have suggested that low-dose glucocorticoid treatment is associated with potentially beneficial effects on the cardiovascular (CV) system, such as improvements in the lipid profile (9–11) as well as

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insulin sensitivity (12,13). Another recent study demonstrated both favorable and unfavorable effects of glucocorticoids on CV biomarkers (14). The net CV effect of low-dose glucocorticoid therapy, as well as high-dose therapy targeted toward severe inflammatory manifestations in RA patients, remains unknown.

Patients with RA are at increased risk of CVD, including myocardial infarction (MI) and heart failure (HF), as well as CV mortality (15–19). Chronic inflammation that occurs in this population is believed to contribute to the increased risk (20,21). We have recently considered the possibility that treating RA with glucocorticoids, depending on the dosage and context, might actually reduce the risk of CV events by attenuating inflammation (22); however, other investigators have argued to the contrary (23). In order to better understand the existing literature and to better appreciate the risks and benefits of glucocorticoids for our patients, an enhanced understanding of the relationship between glucocorticoids and CVD among patients with RA is critical.

Therefore, the objective of our study was to determine the relationship between cumulative exposure, average daily dose, and timing of exposure to glucocorticoids and the risk of CV events. Furthermore, we sought to examine the effect of glucocorticoid exposure within subgroups that differ in the status of an important prognostic marker, rheumatoid factor (RF). To address the limitation of confounding by indication, we adjusted for characteristics associated with the severity or activity of RA.

PATIENTS AND METHODS

Study population. The study population consisted of a previously described retrospective population-based incidence cohort of adult RA patients ages ≥18 years residing in Rochester, Minnesota, between January 1, 1955 and January 1, 1995 (15–17). The RA incidence date was defined as the date on which the subject first fulfilled the American College of Rheumatology (ACR; formerly, the American Rheumatism Association) classification criteria (24). These patients were followed up through their complete inpatient and outpatient records from all community providers (using the resources of the Rochester Epidemiology Project) until the end of study in 2003 (16). Four trained nurse abstractors reviewed the medical records using a structured protocol that had been previously tested. They were unaware of the present study hypotheses.

Data collection and definitions of glucocorticoid exposure. All generic and trade names of glucocorticoid medications were used to identify exposures recorded in the medical records. Oral and parenteral exposures to glucocorticoids were included; intraarticular or inhalational exposures were excluded. The abstractors recorded exposures from inpatient, outpatient (including telephone calls), emergency department, and nursing home encounters. Glucocorticoid dosages were collected as prednisone equivalents based on a standard table (25).

For oral glucocorticoid exposures, the dates of initiation along with the daily dosage categories (0–5 mg, 6–10 mg, 11–15 mg, 16–20 mg, and ≥21 mg) were abstracted. A given dosage was assumed to have continued until there was an indication in the medical record that it had been discontinued or changed. If at a subsequent visit the dosage was recorded as higher or lower (i.e., a different dosage category), then the date of this change was assumed to have been the date of this subsequent visit. For long intervals between physician visits, the subjects were assumed to have continued taking a given dosage of a glucocorticoid if it was indicated as a current medication at both the current and former visits, with no documented plan of tapering or other alteration. Changes in the oral glucocorticoid dosage that remained within a dosage category were not documented. Parenteral glucocorticoid exposures were recorded along with the dates of initiation, change, or discontinuation and the actual milligram dose.

Information on glucocorticoid use for 40 patients with complicated and high-dose exposure was reabstracted by a physician/investigator (JMD) to ensure accuracy. To assess for interobserver variation in the cumulative glucocorticoid dose, a random sample of 20 patients was also reabstracted (again by JMD), and a comparison was made with the original data collected by the nurse abstractors. A very high correlation was shown between these independent observations for glucocorticoid exposure ($r = 0.95$ for total number of days receiving glucocorticoids; $r = 0.97$ for cumulative glucocorticoid dose).

Ascertainment of study covariates and CV outcomes. We have previously described the ascertainment of CV risk factors, RA characteristics, and CV outcomes used for this study (15–17). Smoking status was considered as ever/never. Hypertension was defined according to the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (26) and included the physician's diagnosis or treatment with antihypertensive drugs. Diabetes mellitus was defined according to the 1998 World Health Organization diagnostic criteria (27) and included a clearly documented history of diabetes mellitus or treatment with hypoglycemic agents. Body mass index was defined as weight (in kg) per body surface area (in m^2). Dyslipidemia was defined according to the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) guidelines (28) and included a clearly documented history of dyslipidemia or treatment with lipid-lowering drugs. Personal history of coronary heart disease included angina pectoris, coronary artery disease, coronary insufficiency, ischemic heart disease, MI (including unrecognized MI), HF, pulmonary edema, and coronary revascularization procedures.

RA characteristics included the erythrocyte sedimentation rate (ESR), disease-modifying antirheumatic drug (DMARD) use, RF status, small-joint swelling, large-joint swelling, presence of radiographic erosions and/or destructive changes, nodules, RA lung disease or vasculitis, and joint surgery.

Hospitalized MI, HF, and death from CV causes were considered separately and as a combined CV outcome. Use of the combined CV outcome (including MI and HF) was deemed reasonable because the effects of glucocorticoids on each outcome individually were found to be similar to the effects on the combined outcome. In addition, we have previously shown that HF is the major contributor to death from CV causes (29). Hospitalized MI (defined as all MI events classified in hospitalized patients) was defined according to standardized criteria (30,31). HF was defined according to the Framingham criteria (32). Death from CV causes was defined as previously described (16), based on causes of death recorded in the medical records, the National Death Index, and death certificates, and included the following: acute or previous MI, stable or unstable angina pectoris, other forms of chronic ischemic heart disease, arrhythmias, dysrhythmias, hypertension, HF, pulmonary edema, rheumatic heart disease, valvular stenosis or insufficiency, and ruptured aortic aneurysm. The combined CV outcome was defined as the earliest of either an MI, HF, or death from CV causes.

Statistical analysis. Cumulative and average daily doses of glucocorticoid medications were summarized as the medians and interquartile ranges for both oral and total (oral and parenteral) glucocorticoid exposure. The cumulative incidence of glucocorticoid exposure was estimated using Kaplan-Meier methods. Rates per person-year of followup were reported for each CV outcome. Only the initial CV event following the RA incidence date was considered for each respective CV outcome.

Because the glucocorticoid data were collected as time-dependent categorical variables and were then used to estimate the cumulative and average daily doses, sensitivity analyses were completed whereby the dosage within a dosage category was assumed to be either the high end (i.e., for the 5–10 mg/day category, 10 mg/day) or the low end (i.e., for the 5–10 mg/day category, 5 mg/day). For the main analyses, the midpoint of each dosage category was assumed (i.e., for 5–10 mg/day category, 7.5 mg/day).

Cox proportional hazards regression models were used to estimate the risk of CV outcomes associated with the various definitions of glucocorticoid exposure, after adjusting for demographic variables, CV risk factors, and RA disease characteristics. Regarding demographics, age was used as the time scale, and the models were stratified by sex and adjusted for year of RA incidence. All variables were time-dependent except personal history of coronary heart disease, which was considered at the RA incidence date. Dichotomous variables (i.e., RF) were considered absent until the date during the disease course when they became present; continuous variables (i.e., ESR) were updated throughout the followup period.

For each CV outcome, univariate effects of glucocorticoid exposure variables were assessed first. Because of the age time-scale and the stratification by sex, these models are referred to as age- and sex-adjusted. Multivariable models were then constructed by including all potential confounding variables. In an attempt to adjust for confounding by the activity and/or severity of RA, all available RA variables were included in the models.

Analyses for interaction between glucocorticoid exposure and RF status were performed. In these models, analysis of variance methods were used to assess interactions between the categories of glucocorticoid exposure and RF status. The test for interaction was the usual 3 degrees of freedom test.

RESULTS

Description of the study cohort. Between January 1, 1955 and January 1, 1995, a total of 603 adult residents of Rochester, Minnesota, were identified as having incident RA. Of these, 210 patients remained negative for RF during followup, and 393 were positive for RF. Overall, 73% were female, and the mean ± SD age was 58 ± 15.2 years. The RF-positive patients were slightly younger than the RF-negative patients (ages 56.8 years and 60.2 years, respectively; $P = 0.003$). The median followup was 13 years (interquartile range 7.6–20.5) and was similar for the RF-negative and RF-positive subgroups ($P = 0.832$). The overall followup was 9,066 person-years, 3,201 person-years for the RF-negative subgroup and 5,865 person-years for the RF-positive subgroup. In general, there was a trend toward higher RA disease severity with increasing cumulative glucocorticoid exposure among the RF-positive patients and, to a lesser extent, among the RF-negative patients (data not shown).

At baseline, 45 patients had prior CV events, including 17 with prior MI and 28 with prior HF. These patients were excluded from subsequent analyses. During followup, 232 patients experienced the combined CV outcome. For MI, HF, and death from CV causes, there were 41, 172, and 176 events, respectively, yielding incidence rates of 0.47, 2.1, and 1.9 per 100 person-years, respectively.

Characteristics of glucocorticoid exposure. Glucocorticoid exposure differed between the RF-positive and RF-negative patients (Table 1). At 20 years of followup after RA incidence, RF-positive patients had a higher cumulative incidence of glucocorticoid exposure (68%) as compared with RF-negative patients (44%; $P < 0.001$). There was no difference in the average daily dose of glucocorticoids between the RF-positive and the RF-negative patients (overall median average daily dose 7.7 mg/day). However, RF-positive patients were exposed to glucocorticoids for longer time periods (median 2.4 years in RF-positive patients versus 0.97 year in RF-negative patients; $P = 0.013$), and the RF-positive patients were therefore exposed to higher cumulative doses (median cumulative dose 5.40 gm for RF-positive patients versus 2.28 gm for RF-negative patients; $P = 0.006$).

Table 1. Characteristics of glucocorticoid exposure in the cohort of patients with rheumatoid arthritis*

Exposure characteristics	RF-negative patients (n = 210)	RF-positive patients (n = 393)	Overall (n = 603)	P†
Glucocorticoid exposure, %‡	44	68	58	<0.001
Average dosage, mg/day				
Oral plus parenteral	7.6 (3.1–11.1)	7.8 (3.6–11.2)	7.7 (3.5–11)	0.460
Oral only	6.7 (2.5–9.1)	7.1 (3.0–9.2)	7.0 (2.9–9.2)	0.475
Duration of exposure, years§	0.97 (65–3.0)	2.4 (138–7.2)	2.1 (110–6.7)	0.013
Cumulative dose, gm	2.28 (0.7–8.5)	5.40 (1.1–14.8)	4.29 (4.00–13.21)	0.006
Cumulative oral dose, gm	2.34 (0.7–8.30)	6.12 (1.54–15.2)	5.02 (1.20–13.80)	<0.001

* Only patients who were exposed to glucocorticoids are represented. Except where indicated otherwise, values are the median (interquartile range). RF = rheumatoid factor.
† Comparison of RF-negative versus RF-positive groups.
‡ Cumulative incidence at 20 years of followup after RA incidence.
§ The interquartile range for duration of exposure represents the number of days to the number of years.

Cumulative glucocorticoid exposure and the risk of CV events. In the age- and sex-adjusted models, patients in the highest tertile of cumulative exposure (>7,000 mg of prednisone equivalents) were at increased risk of the combined CV outcome (hazard ratio [HR] 2.11 [95% confidence interval (95% CI) 1.47–3.04]) (Table 2). After multivariable adjustment, the estimate of this risk decreased slightly but remained statistically significant (HR 1.90 [95% CI 1.28–2.82]). In both the age- and sex-adjusted and multivariable models, patients in the low or mid tertiles of cumulative glucocorticoid exposure had no increased risk of the combined CV outcome.

Table 3 shows a highly significant effect of the interaction between cumulative glucocorticoid exposure and RF status on the risk of CV events ($P = 0.006$

Table 2. Glucocorticoid exposure and the risk of CV events in the overall rheumatoid arthritis study cohort*

	Combined CV outcome (n = 232 events)			
	Model adjusted for age and sex†		Multivariable model‡	
Exposure	HR (95% CI)	P§	HR (95% CI)	P§
Cumulative exposure				
Never exposed (reference)	1 (–)	<0.001	1 (–)	0.012
Low tertile	1.14 (0.77–1.66)		1.01 (0.66–1.54)	
Mid tertile	1.16 (0.75–1.78)		1.06 (0.68–1.67)	
High tertile	2.11 (1.47–3.04)		1.90 (1.28–2.82)	
Average daily dose of glucocorticoids				
Never exposed (reference)	1 (–)	0.009	1 (–)	0.082
≤7.5 mg/day	1.32 (0.86–2.04)		1.26 (0.80–2.01)	
>7.5 mg/day	2.05 (1.26–3.33)		1.75 (1.05–2.91)	
Timing of exposure				
Never exposed (reference)	1 (–)	0.002	1 (–)	0.029
Past (>3 months)	1.25 (0.90–1.72)		1.13 (0.80–1.60)	
Recent (≤3 months)	1.81 (1.29–2.54)		1.66 (1.14–2.41)	

* For each exposure category, the reference group consisted of patients who had never received glucocorticoids. For cumulative exposure, low tertile = ≤1,500 mg, mid tertile = >1,500 to ≤7,000 mg, and high tertile = >7,000 mg. CV = cardiovascular; HR = hazard ratio; 95% CI = 95% confidence interval.
† Cox proportional hazards model adjusted for age and sex.
‡ Cox proportional hazards model adjusted for age, sex, year of rheumatoid arthritis (RA) incidence, personal history of ischemic heart disease, smoking status (ever/never), hypertension, diabetes mellitus, body mass index, dyslipidemia, erythrocyte sedimentation rate, disease-modifying antirheumatic drug use, rheumatoid factor status, small-joint swelling, large-joint swelling, radiographic erosions and/or destructive changes, nodules, RA lung disease or vasculitis, and joint surgery.
§ Comparison of differences between the exposure groups and the reference group.

Table 3. Interaction between glucocorticoid exposure and RF status on the risk of CV events in the rheumatoid arthritis study cohort*

Exposure	Combined CV outcome (n = 232 events)		
	RF-negative patients, HR (95% CI)†	RF-positive patients, HR (95% CI)†	*P* for interaction
Cumulative exposure			
Never exposed	1 (reference)	1.08 (0.74–1.56)	0.006
Low tertile	0.48 (0.22–1.02)	1.69 (1.00–2.88)	
Mid tertile	0.71 (0.32–1.57)	1.52 (0.84–2.74)	
High tertile	0.85 (0.39–1.87)	3.06 (1.81–5.18)	
Average daily dose of glucocorticoids			
Never exposed	1 (reference)	1.30 (0.92–1.81)	0.25
≤7.5 mg/day	0.69 (0.27–1.74)	2.21 (1.22–4.00)	
>7.5 mg/day	‡	3.13 (1.74–5.62)	
Timing of exposure			
Never exposed	1 (reference)	1.17 (0.76–1.81)	0.001
Past (>3 months)	0.70 (0.36–1.38)	1.62 (0.92–2.86)	
Recent (≤3 months)	0.36 (0.11–1.20)	3.26 (1.86–5.71)	

* For each exposure category in the rheumatoid factor (RF)–negative and RF-positive groups, the reference group consisted of RF-negative patients who had never received glucocorticoids. For cumulative exposure, low tertile = ≤1,500 mg, mid tertile = >1,500 to ≤7,000 mg, and high tertile = >7,000 mg. CV = cardiovascular; HR = hazard ratio; 95% CI = 95% confidence interval.
† Determined by Cox proportional hazards model adjusted for age, sex, year of rheumatoid arthritis (RA) incidence, personal history of ischemic heart disease, smoking status (ever/never), hypertension, diabetes mellitus, body mass index, dyslipidemia, erythrocyte sedimentation rate, disease-modifying antirheumatic drug use, small-joint swelling, large-joint swelling, radiographic erosions and/or destructive changes, nodules, RA lung disease or vasculitis, and joint surgery.
‡ The few events in this group resulted in an HR that was meaningless.

by multivariable analysis). Whereas RF-negative patients even in the high tertile of the cumulative dose were not at increased risk of the combined CV outcome (multivariable HR 0.85 [95% CI 0.39–1.87] for the high tertile, by multivariable analysis), RF-positive patients in the low and high tertiles were at significantly increased risk of the combined CV outcome (HR 3.06 [95% CI 1.81–5.18] for the high tertile, by multivariable analysis) as compared with the RF-negative patients who were never exposed to glucocorticoids.

Figure 1 shows the data for the combined CV outcome as well as separately for HF and death from CV causes. The same interaction between RF status and cumulative exposure was found for HF ($P = 0.021$), and there was a trend toward statistical significance for death from CV causes ($P = 0.071$). The RF-positive patients in every tertile of cumulative glucocorticoid exposure were at increased risk of death from CV causes in a dose-dependent manner as compared with RF-negative patients who were never exposed.

Average daily glucocorticoid dose and the risk of CV events. Overall, taking an average of ≤7.5 mg of prednisone per day was not associated with CV events in either the age- and sex-adjusted model or the multivariable model (Table 2). Taking an average of >7.5 mg/day was associated with an increased risk of the combined CV outcome in the age- and sex-adjusted model (HR 2.05), but this association was reduced to a nonsignificant trend after adjustment in the multivariable model (HR 1.75; $P = 0.082$).

For RF-negative patients, no increase in risk was observed for those with either an average daily dose of ≤7.5 mg or >7.5 mg ($P = 0.79$ by multivariable analysis) (Table 3). In contrast, RF-positive patients with an average daily glucocorticoid dose of ≤7.5 mg or >7.5 mg had an increased risk of CV events, with HRs of 2.21 and 3.13, respectively ($P = 0.02$ by multivariable analysis), as compared with RF-negative patients who were never exposed. However, this interaction between the average daily glucocorticoid dose and RF status was not statistically significant ($P = 0.25$).

Recent compared with past use of glucocorticoids and the risk of CV events. Overall, recent exposure to glucocorticoids was associated with an increased risk of the combined CV outcome (HR 1.66 [95% CI 1.14–2.41] by multivariable analysis), but there was no association with past exposure (Table 2).

As was the case for cumulative exposure, assess-

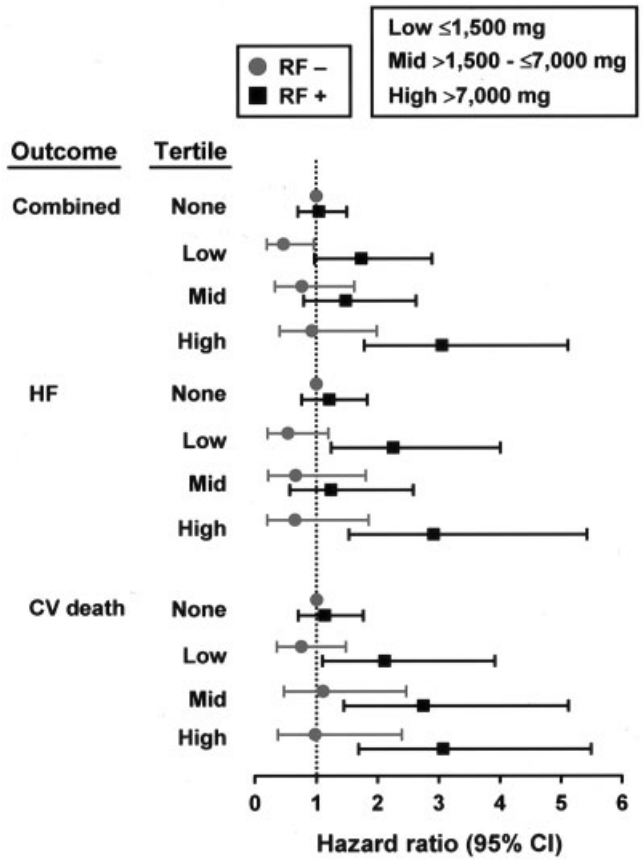

Figure 1. Interaction between cumulative glucocorticoid exposure and rheumatoid factor (RF) status on the risk of the combined cardiovascular (CV) outcome, heart failure (HF), and death from CV causes. These data are from multivariable Cox models adjusted for age, sex, CV risk factors, and rheumatoid arthritis characteristics (see Patients and Methods for details). The reference group for each outcome consisted of RF-negative patients who had never received glucocorticoids. 95% CI = 95% confidence interval.

ing for interaction between recent/past use of glucocorticoids and RF status was enlightening (Table 3 and Figure 2). For the combined CV outcome, there was a highly statistically significant interaction between the timing of glucocorticoid exposure and the RF status ($P = 0.001$). Among the RF-negative patients, there was no association between recent/past use of glucocorticoids and the combined CV outcome. Compared with RF-negative patients who were never exposed to glucocorticoids, RF-positive patients with recent as well as past exposure were at increased risk of the combined CV outcome, with a higher risk in those with recent (≤3 months) exposure (HR 3.26 [95% CI 1.86–5.71] in those with recent exposure and HR 1.62 [95% CI 0.92–2.86] in those with past exposure; $P < 0.001$ by multivariable analysis) (Table 3). Figure 2 shows similar interactions between the timing of exposure and the RF status for the incidence of HF as well as the incidence of death from CV causes.

The analyses of cumulative glucocorticoid exposure using either the low or high end of each dosage category and reestimating the cumulative dose yielded similar results. Analyses for interaction with cumulative glucocorticoid exposure were also performed according to the presence/absence of erosions, rheumatoid nodules, or any joint surgery. No significant interactions were observed in these additional analyses (data not shown).

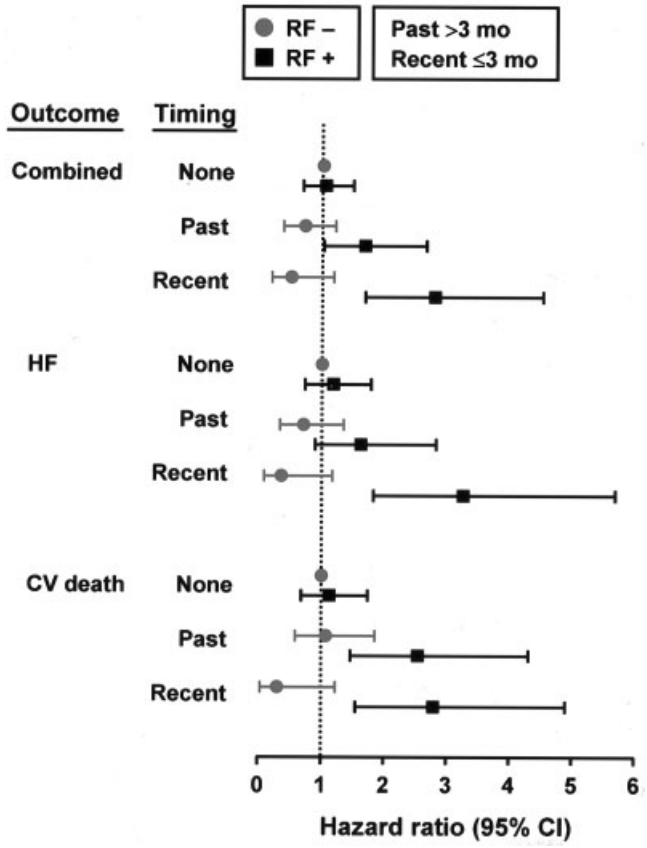

Figure 2. Interaction between the timing of exposure to glucocorticoids and rheumatoid factor (RF) status on the risk of the combined cardiovascular (CV) outcome, heart failure (HF), and death from CV causes. These data are from multivariable Cox models adjusted for age, sex, CV risk factors, and rheumatoid arthritis characteristics (see Patients and Methods for details). The reference group for each outcome consisted of RF-negative patients who had never received glucocorticoids. 95% CI = 95% confidence interval.

DISCUSSION

We report herein the relationship between exposure to glucocorticoids and the risk of CV events in a community-based cohort of RA patients. We observed markedly different relationships between glucocorticoids and the risk of CV events in RF-positive compared with RF-negative patients. RF-negative patients were not at increased risk of CV events irrespective of cumulative exposure, average daily dose, and timing of exposure to glucocorticoids; furthermore, glucocorticoids appeared to have possible protective effects. In contrast, RF-positive patients exposed to glucocorticoids were at increased risk of CV events, particularly those with high cumulative exposure >7,000 mg, those taking an average daily dose of >7.5 mg, and those with recent exposure to glucocorticoids. This effect persisted after adjusting for demographics, CV risk factors, and RA disease characteristics. These results suggest that glucocorticoid exposure interacts with RF status to modulate the occurrence of CV events in patients with RA. Potential explanations for these findings shall be discussed further.

Despite the commonly held belief that low-dose glucocorticoids are detrimental to the CV system, relatively little evidence exists in support of this hypothesis (7). Investigators have reported conflicting data on the relationship between use of glucocorticoids and CV events in epidemiologic studies of RA (22). Ever use of glucocorticoids by RA patients has been associated with an increased risk of CV events in some studies (16,33) but not in others (34).

Recently, several groups of investigators analyzed the effects of glucocorticoids on a surrogate CV outcome, arterial atherosclerosis as defined by ultrasonography. Del Rincón et al (35) found higher frequencies of carotid artery plaque and lower-limb artery incompressibility among RA patients in the highest tertile of lifetime glucocorticoid exposure (>16 gm of prednisone) as compared with those who never received glucocorticoids, after adjusting for markers of disease activity. Other studies have not found an association between glucocorticoids and carotid atherosclerosis (36,37).

In addition, limited data on glucocorticoid exposure and CVD based on large administrative databases have been published. Wei et al (38) recently reported on 60,000 glucocorticoid users and 80,000 nonusers that high-dose exposure (>7.5 mg/day) was associated with a 3-fold increased risk of CV events, after propensity score matching for comorbidities and medications. Within a subset of patients with inflammatory arthritis (defined according to the use of DMARDs), high-dose exposure was associated with a 5-fold increased risk of CV events. Bernatsky et al (39) performed a case–control study nested within an administrative database RA cohort and reported that the risk of hospitalization for HF was not increased among current glucocorticoid users (defined as within 45 days of the event). Finally, in a population-based nested case–control study using the General Practice Research Database of the UK, Souverein et al (40) reported that current glucocorticoid use among patients with RA was associated with a modestly increased risk of HF as well as ischemic heart disease events, with odds ratios of 1.55 and 1.36, respectively.

Compared with these studies, our study is different in several important ways. Wei et al (38) and Souverein et al (40) examined large study populations of >50,000 subjects, which included all glucocorticoid users in the general population. Bernatsky et al (39) also had a large study cohort consisting of all RA patients and with diagnoses classified by diagnostic codes. Individuals in the Bernatsky et al and Wei et al studies were followed up for a mean of 1.2 years and 3 years, respectively. In contrast, our study population was an incidence cohort of RA patients with diagnoses validated by the ACR criteria and was followed longitudinally for a median of 13 years. These other studies used administrative prescription records to ascertain glucocorticoid exposure, whereas in our study, all glucocorticoid exposure was ascertained by medical record review. Unlike some of the other studies, we also had the advantage of collecting all parenteral exposures to glucocorticoids, which contributed substantially to the overall cumulative exposure for many patients.

Ultimately, previous studies included heterogeneous populations of patients with many diseases and, therefore, had a higher likelihood of confounding by disease indication. In the study by Wei et al (38), there was no statistically significant association between glucocorticoids and CV events for the subset with inflammatory bowel disease, indicating that the overall findings did not necessarily apply to all patient subgroups. Similarly, data from our group (41) suggested that in polymyalgia rheumatica, cumulative glucocorticoid exposure is not associated with an increased risk of CV events and, in fact, may be protective. Previous studies have addressed the problem of confounding by indication by adjusting for comorbidities and use of medications (e.g., lipid-lowering agents, DMARDs). However, residual confounding may influence the results of such studies. For example, within a group of RA patients taking methotrexate, considerable variation in disease activity

may exist, and so, adjusting for methotrexate use for these individuals may not adequately account for the variance in disease activity. In our study, we adjusted for time-dependent covariates, including all available RA disease characteristics, which potentially allowed us to better address the problem of confounding.

Moreover, we took this a step further and examined the effect of glucocorticoid exposure within subgroups of the same disease indication (RA) that differed by an important prognostic marker (RF status). Seropositivity for RF is well accepted to be associated with more severe articular, as well as extraarticular, disease. Additionally, RF positivity has been associated with overall mortality (42–44). Goodson et al (45) reported that RF-positive patients even in the earliest stages of inflammatory polyarthritis have a higher risk of death from CV causes than do RF-negative patients. This group of investigators also recently reported that in a cohort of patients with early inflammatory arthritis, baseline elevation of the C-reactive protein (CRP) level was associated with an increased risk of death from CV causes (46). The effect of CRP was modified by the presence or absence of RF, so that patients with baseline CRP levels ≥5 mg/liter who were RF-negative had a 1.5-fold increased risk of death from CV causes as compared with RF-positive patients with the same degree of baseline CRP elevation, who had a 7-fold increased risk.

These data are important to consider with regard to our finding of a strong interaction between RF status and glucocorticoid exposure on the risk of CV events. The first potential explanation is that cumulative glucocorticoid exposure is a marker of disease activity; in other words, the cumulative glucocorticoid exposure may be correlated with the cumulative burden of disease activity over the disease course in each RA patient. This marker of inflammation interacts with RF status to affect the risk of CV events in much the same way as the baseline CRP elevation in the study by Goodson et al (46). Similarly, recent glucocorticoid treatment may be correlated with higher levels of disease activity for which the glucocorticoids were prescribed (i.e., recent flares). Among the RF-negative patients, the absence of an association between glucocorticoids and CV events—with a potential protective effect against CV events for individuals in this subgroup with high cumulative exposure, high average daily dose, or recent exposure—suggests that in the RA population, the typically cited adverse effects of glucocorticoids (insulin resistance, increased blood pressure, etc.) are relatively less consequential. Otherwise, one would expect these potentially harmful effects to similarly affect the entire RA cohort. Although our findings require confirmation, we speculate that the higher inflammatory activity in RF-positive RA patients who have higher or more recent exposure to glucocorticoids may contribute to CVD and subsequent fatal complications.

A second potential implication from our findings is that RF-positive disease is associated with inflammatory mechanisms that are distinct from those involved in RF-negative disease, and glucocorticoid exposure has divergent effects on these disparate pathogenetic states. An obvious distinction is that in RF-positive disease, B cells produce RF, so B cell activity may be different in RF-positive compared with RF-negative RA. Recently, our group published preliminary data suggesting that B cells may be more important to the pathogenesis of coronary artery atherosclerosis in RA patients than in people without autoimmune disorders (47). Similar observations were published regarding RA-associated interstitial lung disease as compared with idiopathic forms, again emphasizing the relatively greater importance of B cell–mediated mechanisms in RA-associated disease (48). The results of the present study may imply that there are different mechanisms of inflammation associated with RF status and that they have different relationships to glucocorticoids and subsequent CVD.

However, we cannot exclude a third possibility that glucocorticoids interact with mechanisms associated with RF-positive disease to the detriment of the CV system. It is possible that RF-positive patients have unique susceptibility to known (see the introduction) or unknown adverse effects of glucocorticoids. For example, prednisone and other glucocorticoids in clinical use have mineralocorticoid activity. Evidence suggests that cardiac mineralocorticoid activation may induce myocardial fibrosis (49), and it is a clinically relevant mechanism in heart failure (50,51). Perhaps separate pathways leading to myocardial fibrosis—including prednisone-mediated mineralocorticoid receptor activation as well as RA-related mechanisms—synergize in some RF-positive patients and culminate in heart failure. Ultimately, further study is necessary to clarify the mechanisms underlying the interaction between glucocorticoids and RF status on the risk of CV complications and to better disentangle the effects of glucocorticoids from the effects of RA.

Several potential limitations to our study should be discussed. The first issue is the use of medical records as the data source for data on glucocorticoid exposure. This is clearly important given the inherent complexity of exposure to glucocorticoids. Unfortunately, there is

no agreement on a gold standard for ascertaining drug exposure. The principal advantages of pharmacy records are objectivity and availability. In contrast, ascertaining drug exposure by medical record review has several potential limitations. The completeness and accuracy of the data are dependent on documentation by the physician. The availability and integrity of medical records can be a concern in retrospective studies. However, a strength of this study is our comprehensive medical record linkage system, which offers access to each subject's complete inpatient and outpatient medical records from all community providers for the entire study period.

The reliability and validity of medical record review for drug exposure should be discussed. The drug exposure estimates are dependent upon which sections of the medical record are reviewed. In this study, all components of each patient's medical record (including correspondence and telephone calls) were reviewed, and data concerning drug exposure were abstracted. The individual abstractor's beliefs about glucocorticoids could potentially influence the results. However, this effect should be minimal in this study because the abstractors were unaware of the study hypotheses. Data derived by the individual abstractors may be more or less complete and accurate depending on the length and complexity of each medical record. Based on the experience of the physician/investigator who reabstracted the data (JMD), there was difficulty in some cases in determining whether or not patients were taking glucocorticoids during long intervals of no followup, and accurately determining all changes in dosage was difficult. However, the data were also reabstracted from a random sample of 20 patients, and excellent agreement was observed (see Patients and Methods). It is possible that there was misclassification of glucocorticoid dosages. However, dosage misclassification should not have significantly affected the results because the misclassification was most likely random and, if anything, would have biased the results toward the null. In addition, the results were examined categorically, which would also lessen the effects of misclassification.

Medical record review has the potential to more accurately capture glucocorticoid exposure data as compared with using pharmacy data. For example, details of glucocorticoid tapering are frequently communicated to the patient and documented in the medical record, whereas the prescription contains only a generic instruction (i.e., "take as directed"), without any instructions for tapering. Adjustments of glucocorticoid dosages may be made at clinic visits or through a telephone call and then documented in the medical record, whereas these changes are not reflected in the prescription data held at the pharmacy. In the absence of a gold standard dictating the optimal source for glucocorticoid exposure data, use of medical records seems reasonable provided that the aforementioned limitations are appropriately considered.

Confounding by indication is a significant potential limitation for this observational design. We have attempted to address this by adjusting for RA characteristics that may be associated with the severity or "cumulative activity" of disease. We used adjusters that were available from the medical records; the retrospective nature of this study precluded systematic collection of disease activity indices that would have allowed a better account of disease activity during followup. Despite our extensive adjustment and use of propensity scoring, our results may be affected by residual confounding by more severe and/or active RA associated with RF positivity. Ultimately, these retrospective data cannot be used to determine causality between glucocorticoids and heart disease in RA.

Our study had limited power to detect associations between glucocorticoid exposure and MI. There also was low power to detect an interaction between RF status and average daily dose of glucocorticoids, possibly because few CV events occurred among the RF-negative patients who received an average of >7.5 mg/day. We were not able to collect and adjust for nonsteroidal antiinflammatory drugs, which are known to be associated with increased CV risk. Also, our population was mainly white, which limits the generalizability of our findings to groups not represented in our study.

Several strengths should be underscored. The resources of the Rochester Epidemiology Project allowed for a community-based cohort to be followed longitudinally over a long time period (median of 13 years), an approach which would not be possible in a prospective or administrative database study. The medical record linkage system allowed glucocorticoid exposure to be ascertained during the entire followup for each subject. Using medical records to determine glucocorticoid exposure potentially allowed us to capture greater detail regarding characteristics of exposure (i.e., tapering plans; see the discussion above) than would be possible using an administrative database. Access to the complete medical records of each subject allowed for the assessment of CV risk factors and outcomes using validated criteria and made comprehensive statistical adjustment possible.

In conclusion, our study provides important in-

sights into how glucocorticoid medications impact the risk of cardiac complications in patients with RA. Our study is the first to demonstrate that glucocorticoids interact with RF status to modulate the occurrence of CV events among individuals with RA. The mechanisms underlying this interaction are unknown, and further research is needed to fully explicate the relationship between glucocorticoid exposure and cardiac disease in patients with RA.

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AUTHOR CONTRIBUTIONS

Dr. Davis had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study design. Davis, Maradit Kremers, Nicola, Ballman, Gabriel.
Acquisition of data. Davis.
Analysis and interpretation of data. Davis, Maradit Kremers, Crowson, Ballman, Therneau, Roger, Gabriel.
Manuscript preparation. Davis, Maradit Kremers, Crowson, Nicola, Ballman, Roger, Gabriel.
Statistical analysis. Maradit Kremers, Crowson, Ballman, Therneau.

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Erratum

In the article by Michel et al published in the January 2007 issue of *Arthritis & Rheumatism* (pp. 43–57), there was an error in the reported concentration of recombinant interleukin-2 used in cell culture, as described under the heading "Cell culture and chronic activation system." The correct concentration was 50 units/ml.

We regret the error.