The Risk for Cardiovascular Events Associated with Hyperlipidemia among Patients with and Without Rheumatoid Arthritis

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Abstract

**Objectives:** To determine, using data from a real-world setting, the overall and sex-specific risk of cardiovascular (CV) events in patients with rheumatoid arthritis (RA), with or without comorbid hyperlipidemia, relative to those in a non-RA cohort.

**Methods:** This retrospective cohort study used claims data from a US commercial health plan (2005–2011) included patients with RA and a matched non-RA cohort. Cox proportional hazards regression model determined the hazard ratio (HR) for CV events (myocardial infarction, stroke, revascularization procedures), using the presence of RA and hyperlipidemia as the independent variables, controlling for other covariates (age, sex, diabetes, and hypertension).

**Results:** The incidence of CV events per 1000 person-years was 10.19 for the RA cohort and 6.41 for the non-RA cohort (crude rate ratio [RR] =1.60). Within the RA cohort, incidence was 15.54 for patients with hyperlipidemia and 7.05 for patients without hyperlipidemia (crude RR=2.12); in the non-RA cohort, incidence was 10.55 and 3.82 for those with and without hyperlipidemia, respectively (crude RR=2.70). After controlling for covariates, the HR of CV events among RA patients was 1.68 (95% CI: 1.50, 1.87) relative to non-RA patients. After multivariable adjustment, hyperlipidemia conferred a significant risk of CV events in both RA and non-RA patients; the interaction between RA and hyperlipidemia was not significant (p=0.13).

**Conclusion:** This real-world analysis demonstrates that patients with RA have an increased risk of CV events. Similar to a non-RA cohort, CV event rates were incrementally higher for those patients with hyperlipidemia.

Significance

- Cardiovascular disease is an increasingly visible topic of concern in the rheumatoid arthritis community. However, there are only limited data that informs both the absolute and relative rates of CV events, and the contribution of various risk factors such as hyperlipidemia, compared to non-RA populations.
- The ‘lipid paradox’ hypothesis in RA suggests that elevated LDL cholesterol has a negligible effect on CVD risk in RA, unlike in the general population where it is a well-accepted CVD risk factor.
- The incidence of CVD events in RA patients was 10/1000 patient years, a 1.6 fold greater risk compared to non-RA patients.
- The contribution of hyperlipidemia to CVD risk was associated with comparable or greater absolute increases in the rate of CV events compared to non RA patients, a finding that does not support the lipid paradox.

Keywords: Rheumatoid arthritis; Inflammation; Hyperlipidemia; Cardiovascular disease

Introduction

Cardiovascular disease (CVD) is the most common cause of mortality in patients with rheumatoid arthritis (RA) [1]. There is an increased risk of CV events in patients diagnosed with RA [2-5]. This risk includes not only traditional CV risk factors but also risk related to inflammation as measured by laboratory studies such as the erythrocyte sedimentation rate and/or C-reactive protein (CRP) [6,7]. Many patients with RA also have hyperlipidemia, another traditional risk factor for CVD [8]. The current literature on the relationship between lipids and CV risk in RA patients is controversial. In the general population, dyslipidemia is a common risk factor for CVD, and multiple studies have shown an increase in cardiovascular risk associated with an increase in serum cholesterol levels [9]. In patients with RA, hyperlipidemia may be affected by inflammation and some RA medications. Untreated RA patients with high levels of inflammation appear to have lower lipid levels [10]. Moreover, previous studies have shown that RA patients treated with many biologics (e.g. tocilizumab, anti-TNF therapy) have a reduced inflammation coinciding with an increase in lipid levels [11-15].

The relative importance of traditional CVD risk factors such as age, sex, diabetes, and hyperlipidemia on CVD event rates in patients with RA versus non-RA patients is not well characterized [8,16]. Some traditional risk factors for CVD events in RA patients may be as common as but of lesser importance than in non-RA patients. For
example, male sex has been found to be a risk factor for CVD in both RA and non-RA patient cohorts; however, the association may be stronger in non-RA patients [16]. Additionally, the association and the absolute risk of events in RA patients with CV risk factors such as concomitant hyperlipidemia is not well understood. For example, the TRACE-RA study that sought to attenuate CV risk in RA patients was abandoned due to futility, in part may be related to a relative lack of knowledge of the absolute risk of CVD events in RA patients [17]. The objective of this study was to determine, using data from a real-world setting, the overall and sex-specific risk of cardiovascular (CV) events in patients with RA, comparing those with and without comorbid hyperlipidemia, relative to the corresponding risk in a non-RA cohort.

Methods

We conducted a retrospective cohort analysis that utilized claims data from a commercial health plan database. Patient-level data were collected from the database from January 1, 2005 to March 31, 2011. Our study population consisted of an RA and non-RA cohort. The RA cohort included patients with >2 physician diagnoses of RA (ICD-9: 714.0, 714.2) with >7 days and <365 days between diagnosis. This approach has been shown to have high validity [18]. The non-RA cohort included patients with no RA diagnoses matched 3:1 with the RA cohort on baseline demographics (age, sex, region, index year). All patients were aged >18 years on index date and had 12 months of full medical and pharmacy benefits prior to the index date. The index date was designated as the date on which patients had 1 year of full coverage with medical and pharmacy benefits, having met RA (or non-RA) disease criteria. We excluded patients with prevalent CV events in the pre-index period, defined as 1 year of full coverage with medical and pharmacy benefits prior to the index date, as well as patients with other inflammatory diseases (e.g., systemic lupus erythematosus, inflammatory bowel disease, psoriatic arthritis, etc.) in the pre-index period. The post-index period was defined as patients who were followed from the index date until the earliest of the following: first CV event, end of enrollment, end of study period, or a new RA diagnosis (in the non-RA cohort).

Exposures and outcomes of interest

Our dependent variable was defined as a CV event: ICD-9 diagnosis code on a hospital discharge claim in the primary position for myocardial infarction (MI) (410.xx), ischemic stroke (433.xx, 434.xx, 436, 437.1) or a procedure code for percutaneous coronary intervention/coronary artery bypass graft (PCI/CABG) (ICD-9: 36.xx, Current Procedural Terminology: 33510-33536, 92973, 92980-92998) during post-index follow-up. A composite endpoint of MI/stroke/PCI-CABG was also analyzed. Besides RA, our main independent variable was hyperlipidemia, defined as an ICD-9: 272.xx diagnosis claim or a prescription for an antihyperlipidemic agent during the pre-index period. Baseline covariates included: age, sex, region, diabetes, and hypertension.

Statistical analysis

Incidence rates (IRs) and incidence rate ratios (IRRs) for CV event (MI, ischemic stroke, PCI-CABG and composite) in the post-index period were determined per 1000 person-years for each cohort, stratified by the presence/absence of hyperlipidemia and by sex. The time to first CV event in the RA and non-RA cohort was assessed using Kaplan–Meier curves. Patients in the non-RA cohort were censored if they had evidence of a new diagnosis of RA. Cox proportional hazards regression determined hazard ratios (HR) for CV events using CV events as the dependent variable and RA and hyperlipidemia as the independent variables, controlling for baseline covariates that were determined based upon content expertise. Matching factors including age and sex were included as covariates based upon interest to estimate their relationship with the outcome, although were not expected to be needed to control for confounding given the matched design. An interaction term for RA and hyperlipidemia was used as a covariate to test the hypothesis that hyperlipidemia might have a different effect (i.e. be a weaker risk factor) in RA patients. This analysis used only secondary data and so no explicit patient consent was required. Because the study data was completely de-identified, it was considered as exempt from institutional review board approval. All analyses were conducted in SAS 9.2.

Results

Baseline characteristics and comorbidities of the included subjects are described in Table 1. The RA cohort consisted of 51,130 patients who were matched with non-RA patients. A total of 37.9% of patients in the RA cohort and 38.7% in the non-RA cohort had concomitant hyperlipidemia at baseline (Table 1). Approximately three fourths of both cohorts were female (75.8% in the RA cohort and 75.7% in the non-RA cohort).

Figure 1 show the time to a CV event in the RA and non-RA cohorts. At the end of follow-up (mean duration of follow-up 2.3 years), a greater proportion of patients in the RA cohort experienced a CV event than in the non-RA cohort (97.2% vs 95.4%, respectively; p<0.001). The incidence of CV events per 1000 person-years was 10.19 for the RA cohort and 6.41 for the non-RA cohort (crude rate ratio [RR]=1.59) (Table 2). The incidence rate ratios and rate differences in the RA vs non-RA cohorts for each component of the composite CV event endpoint (MI, stroke, and PCI-CABG) are shown in Table 2.

CV outcomes stratified by presence/absence of hyperlipidemia are shown in Figure 2. Within the RA cohort, the incidence of CV events per 1000 person-years was 15.54 for patients with hyperlipidemia and 7.05 for patients without hyperlipidemia (crude RR=2.21). In the non-RA cohort, the incidence of CV events per 1000 person-years was 10.55 and 3.82 for those with and without hyperlipidemia, respectively (crude RR=2.76). The incidence rate ratios and rate differences in patients with hyperlipidemia versus those without hyperlipidemia for each component of the composite CV event endpoint (MI, stroke, and PCI-CABG) are shown in Figure 2 for both the RA and non-RA cohorts. As shown, although the incidence rate ratios (IRRs) associated with having hyperlipidemia were numerically lower for every outcome
With hyperlipidemia 

The interaction p value presence of hyperlipidemia conferred a significant risk of CV events after controlling for covariates, the HR of CV events for patients with RA patients than non-RA patients. the incidence rate differences were numerically greater in RA patients than in non-RA patients. However, in Figure 2, the IRRs for having concomitant hyperlipidemia were with hyperlipidemia versus those without hyperlipidemia are shown (14.74 and 8.66, respectively). The IRRs and IRDs in men and women with hyperlipidemia and not having hyperlipidemia within the RA cohort and within the non-RA cohort. CV=cardiovascular; IR=incidence rates; MI=myocardial infarction; PCI-CABG=percutaneous coronary intervention/coronary artery bypass graft

**Table 2:** Cardiovascular event incidence rates in the RA cohort versus Non-RA cohort.

| RA cohort | Non-RA cohort | Crude RR (95% CI) | Crude risk difference (95% CI) |
|-----------|---------------|------------------|------------------------------|
| CV event | N=51,130 | 10.19 | 1202/117,944 | 231/360,550 | 1.19 (1.48, 1.70) | 3.78 (3.22, 4.35) |
| MI | 3.73 | 449/120,454 | 2.09 | 765/365,780 | 1.78 (1.99, 1.92) | 1.64 (1.31, 1.96) |
| Stroke | 5.30 | 636/120,001 | 3.42 | 1247/364,442 | 1.55 (1.41, 1.70) | 1.88 (1.47, 2.29) |
| PCI-CABG | 3.98 | 477/111,699 | 2.44 | 889/364,471 | 1.63 (1.46, 1.82) | 1.54 (1.19, 1.89) |

CV=cardiovascular; IR=incidence rates; MI=myocardial infarction; PCI-CABG=percutaneous coronary intervention/coronary artery bypass graft; RR=rate ratio

Table 3 shows the risk of CV events after multivariable adjustment. After controlling for covariates, the HR of CV events for patients with RA was 1.68 (95% CI: 1.50, 1.87) relative to non-RA patients. The presence of hyperlipidemia conferred a significant risk of CV events (HR=1.47, 95% CI: 1.35, 1.60; p, 0.0001). The interaction p value between RA and hyperlipidemia was not significant (p=0.13). The presence of diabetes increased CVD risk by 2.6 fold, greater than that associated with RA, and the 95% confidence intervals of these two risk estimates were non-overlapping.

**Table 3 shows the rate differences for Hyperlipidemia versus No Hyperlipidemia, Stratified by Having RA or Not Having RA.**

| Event | RA cohort | Non-RA cohort | Crude RR (95% CI) | Crude rate ratio (95% CI) | Rate Difference (95% CI) ** |
|-------|-----------|---------------|------------------|--------------------------|-----------------------------|
| CV event | 2.21 | 2.09 | 1.05 | 2.76 | 2.76 | 2.46 | 3.67 |
| MI | 2.18 | 2.51 | 1.05 | 2.49 | 2.20 | 2.76 | 3.18 |
| Stroke | 2.60 | 2.49 | 2.60 | 2.76 | 2.76 | 2.76 | 3.20 |
| PCI-CABG | 2.87 | 3.85 | 2.87 | 3.85 | 2.87 | 3.85 | 2.87 |

*CV event IRs are a composite of MI, stroke, and PCI-CABG events ** rate ratios and rate differences compare the risk between having hyperlipidemia and not having hyperlipidemia within the RA cohort and within the non-RA cohort.

**Figure 1:** Time to CV event. 

| Follow-up time (days) | Survival (%) |
|-----------------------|--------------|
| 0 | 100% |
| 305 | 97.2% |
| 1095 | 95.4% |
| 1825 | 94.5% |
| 2190 | 95.4% |

**Figure 2:** CV Event Incidence Rates, Incidence Rate Ratios, and Incidence Rate Differences for Hyperlipidemia versus No Hyperlipidemia, Stratified by Sex and Hyperlipidemia. 

| Event | RA | Non-RA | Males | Females | Males | Females | Males | Females |
|-------|----|--------|-------|---------|-------|---------|-------|---------|
| CV event | With hyperlipidemia | Without hyperlipidemia | | | | | | |
| IR (/1000 person-years) | 2.21 | 2.09 | 1.05 | 2.76 | 2.76 | 2.46 | 3.67 |

*CV event IRs are a composite of MI, stroke, and PCI-CABG events ** rate ratios and rate differences compare the risk between having hyperlipidemia and not having hyperlipidemia within the RA cohort and within the non-RA cohort.

**Figure 3:** Sex-specific Incidence Rates, Incidence Rate Ratios, and Incidence Rate Differences of CV Events for Hyperlipidemia in RA and Non-RA Cohorts.
In conclusion, these results confirm the recognized increased CV risk in RA patients and extend those findings to demonstrate that hyperlipidemia in RA patients confers a similarly excess CV event risk compared to non-RA patients. Diabetes is already known to impart a substantial public health impact, although the number needed to treat (NNT) with statin or other lipid-lowering agents in an RA population may be desirable. Finally, the generalizability of these findings deserves mention. Individuals in this cohort were commercially insured and likely younger and more healthy than RA patients in the U.S. who are uninsured, enrolled in Medicare, or disabled and receiving Medicaid services. The lipid paradox might, for example, be relevant in a cachectic, less well-managed RA patient population.

In our study, we examined the absolute incidence of CVD event in RA patients versus non-RA patients. Despite an elevated risk for CVD events in RA patients, the absolute incremental risk for CVD events in RA was only about 3.78 (± 4) per 1000 people per year. This translates to an extra one event per 265 patients (1000/3.78), which is relatively low. Even for people with RA and hyperlipidemia, the absolute risk difference is only 5.0, which translates to 1 extra event for every 200 RA patients with hyperlipidemia compared to non-RA patients with hyperlipidemia. This makes CVD prevention trials, or CVD outcomes trials, in RA patients challenging from a feasibility perspective. Indeed, one relatively high profile UK trial, TRACE-RA, was abandoned for futility, in large part for this reason [17]. A number of ongoing large cardiovascular safety studies (e.g. tocilizumab vs. anti-TNF, tofacitinib vs. anti-TNF) may encounter similar challenges with low event rates, even though they have tried to select for high CVR risk patients [22,23].

We recognize that our study has a number of limitations. Claims data are not collected for research, resulting in the potential for misclassification. For example, some patients might have been misclassified as having RA who had another type of arthritis. Indeed, the positive predictive value of claims-based definitions for RA range from 67% or lower to as high as 95% or greater, depending on the definition used. Claims data also are relatively insensitive to identify CV-related risk factors such as obesity and smoking. Additionally, no information was available about lipid laboratory test results, and our hyperlipidemia classification was based on physician diagnoses and medications. Our analysis intentionally included and adjusted for only a limited number of comorbidities that could contribute to CVD risk in RA patients. Such a concise list was chosen because it is believed that many conditions that we could adjust for (e.g. glucocorticoid use) singly or as part of a composite comorbidity index may be a “downstream effect” of having RA; thus, additional adjustment would represent ‘overadjustment’ and therefore would be undesirable. Finally, the generalizability of these results deserves mention. Individuals in this cohort were commercially insured and likely younger and more healthy than RA patients in the U.S. who are uninsured, enrolled in Medicare, or disabled and receiving Medicaid services. The lipid paradox might, for example, be more relevant in a cachectic, less well-managed RA patient population.

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Table 3: Multivariable-adjusted risk of CV events.*

| Parameter                        | Hazard ratio | 95% CI |
|----------------------------------|--------------|--------|
| Rheumatoid arthritis             | 1.68         | 1.50, 1.87 |
| Hyperlipidemia                   | 1.47         | 1.35, 1.60 |
| Interaction term between RA and hyperlipidemia | 0.90       | 0.78, 1.03 |
| Diabetes                         | 2.64         | 1.95, 3.56 |
| Age group                        |              |        |
| 31–40 vs 18–30                   | 1.73         | 0.91, 3.31 |
| 41–50 vs 18–30                   | 4.69         | 2.57, 8.55 |
| 51–60 vs 18–30                   | 9.88         | 5.45, 17.90 |
| 61–64 vs 18–30                   | 17.27        | 9.49, 31.44 |
| ≥65 vs 18–30                     | 39.62        | 21.86, 71.81 |
| Male sex                         | 1.82         | 1.70, 1.94 |
| Region                           |              |        |
| Midwest vs South                 | 1.09         | 1.01, 1.18 |
| Northeast vs South               | 1.00         | 0.89, 1.13 |
| West vs South                    | 0.85         | 0.77, 0.94 |
| Hypertension                     | 2.00         | 1.77, 2.26 |

*CV event IRRs are a composite of MI, stroke, and PCI-CABG events. CV=cardiovascular; IR=incidence rate; MI=myocardial infarction; PCI-CABG=percutaneous coronary intervention/coronary artery bypass graft surgery.

Discussion

Inflammation associated with RA has been shown to be an important contributor to the increased risk of CV events in patients with RA [15]. Hyperlipidemia is a common comorbidity in RA patients, whether occurring independently or as an effect of RA medications or other disease-related factors. This study examined the interaction of RA and CVD with and without hyperlipidemia. As shown by others [19], we found that patients with RA have an ~1.7-fold increased risk of CV events versus those without RA. Importantly, hyperlipidemia seemed to confer the same incremental risk for CV events in RA patients as for non-RA patients. This finding was robust in the main analysis, and after stratifying by age, sex, and following multivariable adjustment. Given that diabetes was a stronger risk factor for CVD events than was RA, these results might suggest that RA should not be considered a CVD risk equivalent to diabetes with respect to management of hyperlipidemia. We also found that magnitude of the effect of having RA on the absolute risk of CVD events was not large, informing the feasibility of current and future CVD studies in RA patients.

In both the RA and non-RA cohorts, CV event rates were incrementally higher for those patients with hyperlipidemia. Our analysis revealed that the incidence rate ratios of CV events in patients with RA (with hyperlipidemia versus without hyperlipidemia) were numerically lower than the non-RA patients. However, the incidence rate differences of CV events in patients with RA (with hyperlipidemia – without hyperlipidemia) were numerically greater than in the non-RA cohort. This yields the conclusion that the choice of risk scale, ratio versus difference, is important in interpreting the importance of a risk factor such as hyperlipidemia, because the ‘base’ event rate is not the same between RA and non-RA patients. The lack of statistical significance of the interaction term in the multivariable model suggests that hyperlipidemia confers the same incremental risk for CV events in RA patients as for non-RA patients. In total, these results do not provide much support for the lipid paradox, the hypothesis that hyperlipidemia has a different clinical “meaning” in RA patients compared to non-RA patients [20].

Based upon our multivariable models, we evaluated the association between a variety of covariates and CVD risk. We found that RA was a weaker risk factor (HR = 1.7) compared to diabetes (HR = 2.6). This data adds information to the controversy as to whether RA should be considered a CHD risk equivalent with respect to management of hyperlipidemia [21]. Based upon our findings, it does not appear warranted to consider RA as a CHD risk equivalent.

Within our study, we examined the absolute incidence of CVD event in RA patients versus non-RA patients. Despite an elevated risk for CVD events in RA patients, the absolute incremental risk for CVD events in RA was only about 3.78 (± 4) per 1000 people per year. This translates to an extra one event per 265 patients (1000/3.78), which is relatively low. Even for people with RA and hyperlipidemia, the absolute risk difference is only 5.0, which translates to 1 extra event for every 200 RA patients with hyperlipidemia compared to non-RA patients with hyperlipidemia. This makes CVD prevention trials, or CVD outcomes trials, in RA patients challenging from a feasibility perspective. Indeed, one relatively high profile UK trial, TRACE-RA, was abandoned for futility, in large part for this reason [17]. A number of ongoing large cardiovascular safety studies (e.g. tocilizumab vs. anti-TNF, tofacitinib vs. anti-TNF) may encounter similar challenges with low event rates, even though they have tried to select for high CVD risk patients [22,23].

We recognize that our study has a number of limitations. Claims data are not collected for research, resulting in the potential for misclassification. For example, some patients might have been misclassified as having RA who had another type of arthritis. Indeed, the positive predictive value of claims-based definitions for RA range from 67% or lower to as high as 95% or greater, depending on the definition used. Claims data also are relatively insensitive to identify CV-related risk factors such as obesity and smoking. Additionally, no information was available about lipid laboratory test results, and our hyperlipidemia classification was based on physician diagnoses and medications. Our analysis intentionally included and adjusted for only a limited number of comorbidities that could contribute to CVD risk in RA patients. Such a concise list was chosen because it is believed that many conditions that we could adjust for (e.g. glucocorticoid use) singly or as part of a composite comorbidity index may be a “downstream effect” of having RA; thus, additional adjustment would represent ‘overadjustment’ and therefore would be undesirable. Finally, the generalizability of these results deserves mention. Individuals in this cohort were commercially insured and likely younger and more healthy than RA patients in the U.S. who are uninsured, enrolled in Medicare, or disabled and receiving Medicaid services. The lipid paradox might, for example, be more relevant in a cachectic, less well-managed RA patient population.

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