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EXTENDED REPORT

Association of hyperlipidaemia, inflammation and serological status and coronary heart disease among patients with rheumatoid arthritis: data from the National Veterans Health Administration

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ABSTRACT

Objective To examine the association of serum lipids, inflammation and seropositivity on coronary heart disease (CHD) and stroke in patients with rheumatoid arthritis (RA).

Methods The incidence of hospitalised myocardial infarction (MI) or stroke was calculated in a cohort of patients with RA receiving care within the national Veterans Health Administration from 1998 to 2011. Cox proportional hazard models were used to examine the association between these outcomes and low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), C reactive protein (CRP) and erythrocyte sedimentation rate (ESR) as time-varying variables, divided into quintiles.

Results There were 37 568 patients with RA in the cohort with mean age of 63 years (SD 12.1); 90% were men. There was a no clear association between LDL-C and CHD/stroke. Compared with lower HDL-C (<34 mg/dL), higher HDL-C (≥ 54 mg/dL) was inversely associated with MI (hazard ratio (HR)=0.68, 95% CI 0.55 to 0.85) and stroke (HR=0.69, 95% CI 0.50 to 0.96). Higher CRP >2.17 mg/dL (vs CRP <0.26 mg/dL) was associated with increased risk (HR=2.43, 95% CI 1.77 to 3.33) for MI and 2.02 (95% CI 1.32 to 3.08) for stroke. ESR >47 mm/h compared with <8 mm/h had an HR 1.87 (95% CI 1.39 to 2.52) for MI and 2.00 (95% CI 1.26 to 3.18) for stroke. The association between MI was significant for RA seropositivity (HR=1.23, 95% CI 1.03 to 1.48).

Conclusions In this predominantly older male RA cohort, there was no clear association between LDL-C and CHD, whereas higher HDL-C was inversely associated with MI and stroke. CRP and ESR were similarly associated with increase MI risk and stroke, reflecting the prominent role of inflammation in CHD risk in RA.

BACKGROUND

Coronary heart disease (CHD) is a common cause of death among patients with rheumatoid arthritis (RA) with increased risk for ischaemic events such as myocardial infarction (MI).^{1–4} The magnitude of the association between several traditional cardiovascular risk factors in patients with RA is unclear given that the risk for MI has been reported mainly in small studies^{5 6} and found to be high even when lipid levels and the prevalence of other traditional

cardiovascular risk factors were lower than in the general population.^{5–9} Studies have suggested that the association between lipids with CHD may be confounded by inflammation.⁵ For this reason, recent attention has been devoted to non-traditional CHD risk factors in RA that could predict CHD risk more accurately, including serum markers of RA and inflammation.

High levels of C reactive protein (CRP) have been associated with high risk for CHD in the general population,¹⁰ but this relationship is less well studied in RA populations. Further complicating this relationship is also the relationship between inflammation, cholesterol and RA therapies, which has been analysed in few studies, and how this relates to CHD outcomes remains unclear.^{11 12} In one relatively small study, CRP was only measured at baseline, a limitation in RA as inflammation fluctuates over the course of the disease.¹³ The majority of RA studies examining the effect of inflammation, as reflected by high CRP and erythrocyte sedimentation rate (ESR), have shown increased atherosclerosis in patients with RA and elevated CRP,^{7 14} but studies using CRP and ESR as time-variant risk factors for MI events in this population remain scarce and were done in relatively small RA patient cohorts.⁵

The association between high levels of CRP in patients with RA with greater atherosclerosis has been best described in patients who were autoantibody positive (rheumatoid factor (RF) or anticyclic citrullinated peptide (CCP) antibody).^{13 15} One study¹³ analysed CRP as predictor of CHD mortality in patients with RA based on their serological status and showed a hazard ratio (HR) of 7.4 (95% CI 1.7 to 32.2) in the RF-positive group that had CRP level ≥ 5 mg/L compared with those with CRP ≤ 4 mg/L, whereas the RF-negative group had an HR of 1.5 (95% CI 0.5 to 4.5). A separate analysis in the same population showed an increased risk of death from cardiovascular causes in RF-positive women with a standardised mortality ratio of 2.02 (95% CI 1.15 to 3.28).¹⁶ For that reason, further study of serological status as a potential predictor of CHD events and related death in a large population is warranted because both of these study populations were small and based upon <100 deaths.¹⁶



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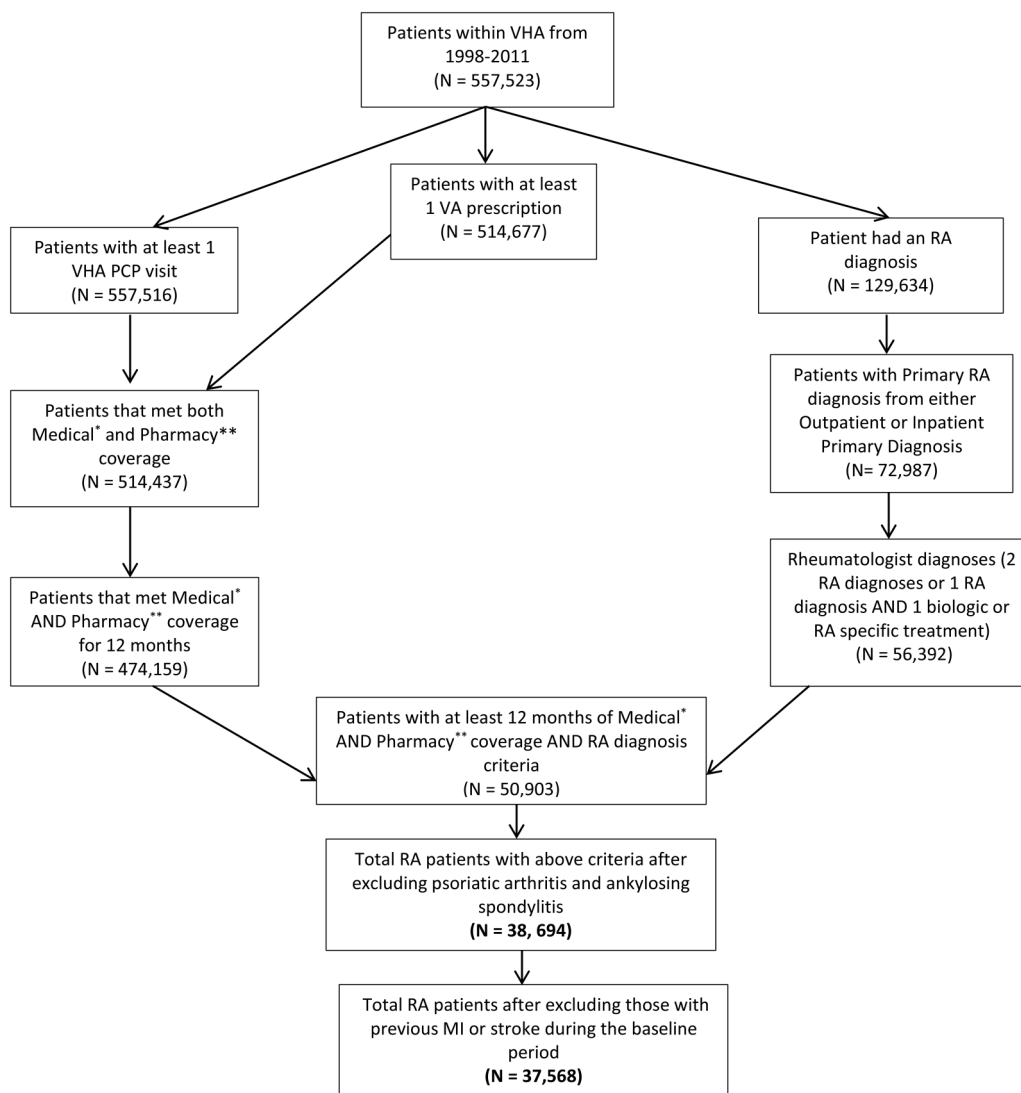
The objectives of this study were to examine, among patients with RA, the association between (1) total cholesterol, low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein-cholesterol (HDL-C); (2) CRP and ESR and (3) RA seropositivity with hospitalised MI, stroke and mortality from either MI or stroke.

METHODS

Patients

We identified a population of patients with RA using data from the Veterans Health Administration (VHA) from 1998 to 2011. The VHA system is the largest United States (US) integrated healthcare system consisting of 152 medical centres and nearly 1400 community-based outpatient clinics that provides care to retired members of the US military. The data were collected from the Decision Support System (DSS), Medical Statistical Analysis Software (MedSAS), Veterans Information System Technology Architecture (VistA) and the Veterans' Informatics, Information and Computing Infrastructure (VINCI). These electronic

databases are derived from the VHA's electronic medical record (EMR) and store longitudinal data of patients receiving care nationwide within the VHA. These data contained outpatient visits to primary care physicians and rheumatologists, hospitalisation within the VHA system, pharmacy data and laboratory values. The cohort of patients with RA was built using International Classification of Diseases (ICD), Ninth Revision (ICD-9) codes following a previously validated algorithm that required two or more physician diagnoses of RA by a VHA rheumatologist, or at least one physician diagnosis in conjunction with a medication that is reasonably specific for RA (eg, methotrexate, sulfasalazine, hydroxychloroquine, biological therapies and leflunomide).¹⁷ The algorithm excludes patients who have a rheumatologist-diagnosed inflammatory arthritis other than RA (eg, psoriatic arthritis and ankylosing spondylitis) by ICD-9 diagnoses. To be eligible for this analysis, cohort members had to have at least 12 months of observability in VHA data prior to the start of follow-up and ongoing observability throughout the follow-up period. Observability in VHA data was



*Medical coverage defined 1 physician visit followed by 14 months of repeated visits

**Pharmacy coverage defines as 1 prescription followed by 5 months of prescription refills.

Figure 1 Flow diagram of the rheumatoid arthritis (RA) population within the Veterans Health Administration (VHA) System. *Medical coverage defined 1 physician visit followed by 14 months of repeated visits. **Pharmacy coverage defines as 1 prescription followed by 5 months of prescription refills. MI, myocardial infarction; PCP, primary care physician.

defined as filling at least one prescription every 6 months and at least one annual visit with a VHA primary care physician. The 'index date' was defined as the date after which both RA cohort criteria and VHA observability were met according to the algorithm described above and anchored the start of follow-up. The 12 months preceding the index date constituted a baseline period, during which time fixed covariates were evaluated.

Exposure

The main exposures of interest were LDL-C, HDL-C, CRP, ESR and anti-CCP/RF positivity. Exposures were all considered as time varying during follow-up and updated on a person-day basis. Each of these could occur during the 12-month baseline period, where the cohort was first defined, and these exposures were allowed to vary during follow-up. Serology was classified as seropositive (positive RF and/or anti-CCP) or seronegative (RF and anti-CCP-negative status). Patients with RA without serological tests available were considered as missing.

Outcome

The outcomes of interest were the first hospitalised acute MI or stroke and fatal MI or stroke in the VHA during follow-up using validated algorithm developed for each outcome. MI was defined as hospitalisation with a primary or secondary discharge diagnosis ICD-9 code 410.x1.^{18–20} Stroke was defined as primary or secondary discharge ICD-9 codes 433.x1, 434 (excluding 434.x0) or 436.^{21 22} Inpatient death from MI or stroke was determined by a discharge disposition of death at the end of hospitalisation.

Variables for the analysis

The variables for this study were obtained from the inpatient and outpatient DSS, MedSAS, VistA and VINCI as mentioned previously. These electronic databases are derived from the VHA's EMR and capture longitudinal data from patients receiving care nationwide within the VHA. The variables for this analysis included age, sex, hypertension, diabetes, congestive heart failure and chronic kidney disease diagnoses (determined by ICD-9 code), pharmacy data (RA medications, statins and steroids) and height and weight, which were used to calculate body mass index, all of which were characterised during the baseline period only. Geographically based Socioeconomic Status (SES) Index Score was determined. Median score for the US distribution was 50.5 in a scale 0–100; higher scores=higher SES.²³ Tobacco use was obtained from the VHA EMR Health Factors Data. This one is collected nationally using the clinical reminder process and are stored in the Health Factors tables within the VHA EMR databases.²⁴ Tobacco use was classified as current, former or never use. These data were time varying, but because the classification of tobacco use changed for so few people over time, tobacco use was modelled as a fixed covariate. Laboratory values (LDL-C, HDL-C, CRP and ESR) were time varying and updated throughout the follow-up period. RA serologies (RF and anti-CCP antibody status) were determined as positive if either or both were positive, negative if neither was positive or missing if neither was ever measured.

Analysis plan

Age-specific and sex-specific event rates for the first MI, stroke or death from MI or stroke were computed with exposures divided in deciles. This was performed to understand the patterns of the main exposures of interest, particularly at the tail ends of exposure distribution. We then computed the age-adjusted incidence rate (IR) of hospitalised MI, stroke and

inpatient death from MI or stroke by controlling with the IR age distribution of the cohort. A linear model was used to test the IR trend, and a quadratic model was used to model those IR with a non-linear trend. Cox proportional hazards models using age as the time axis were used to determine the HR between LDL-C, HDL-C, CRP and ESR and first hospitalised MI, stroke or death from either. Separate models were constructed for each main exposure, modelled as time varying, while controlling for

Table 1 Baseline characteristics of Veterans Health Administration rheumatoid arthritis cohort

| Characteristic | Patients with RA (N=37 568) |
|---|-----------------------------|
| Demographics and RA-related variables | |
| Age (years), mean (SD) | 62.9 (12.1) |
| Male, % | 90 |
| Caucasian, % | 71 |
| Serology available, % | 75 |
| Seropositive, %* | 69 |
| Seronegative, %* | 31 |
| Erythrocyte sedimentation rate (mm/h), mean (SD)† | 29.8 (26.2) |
| C reactive protein (mg/dL), mean (SD)† | 1.8 (2.9) |
| Socioeconomic status (SES) Index Score, median (IQR)‡ | 50.7 (48.3–53.2) |
| Tobacco use, % | |
| Current | 27.7 |
| Former | 41.0 |
| Lifetime non-smoker | 18.5 |
| Missing tobacco use | 12.8 |
| Medications | |
| Prednisone or other oral steroids, % | 66 |
| Statins, % | 30 |
| Biologics§, % | 21 |
| DMARD including methotrexate, % | 50 |
| Non-biological DMARD other than methotrexate, % | 29 |
| Comorbidities | |
| Hypertension, % | 33 |
| Heart failure, % | 3 |
| Diabetes, % | 12 |
| Chronic obstructive pulmonary disease, % | 9 |
| Chronic kidney disease, % | 1 |
| Body mass index, median (IQR) | 27.6 (24.4–31.2) |
| Lipid levels | |
| Total cholesterol (mg/dL), mean (SD)¶ | 181.2 (35.5) |
| HDL-C (mg/dL), mean (SD)¶ | 45.1 (12.9) |
| LDL-C (mg/dL), mean (SD)¶ | 108.2 (29.8) |

*Serological status was determined throughout the 12-month baseline period and throughout the entire follow-up. The remaining 25% of patients were classified as having missing serological status.

†Distribution of ESR and CRP was determined using the most recent laboratory value prior the index date; there were 46% non-missing values for ESR and 34% for CRP in the baseline period. Additional lab data were modelled in a time-varying way after the start of follow-up.

‡SES Index Score based on the Agency for Healthcare Research and Quality SES indicators report from 2008.²³ The range of this scale goes from 0 to 100 where higher scores represent higher SES status. Median distribution of SES index score for the US population is 50.5.

§Biological included all antitumor necrosis factor biologics, rituximab and abatacept as either monotherapy or combined with non-biological DMARD.

¶Distribution of total cholesterol, HDL-C and LDL-C was determined using the most recent laboratory value prior index date; there were 72% non-missing values for total cholesterol, 70% for HDL-C and 68% for LDL-C in the baseline period. Additional lab data were modelled in a time-varying way after the start of follow-up.

DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PO, oral; RA, rheumatoid arthritis.

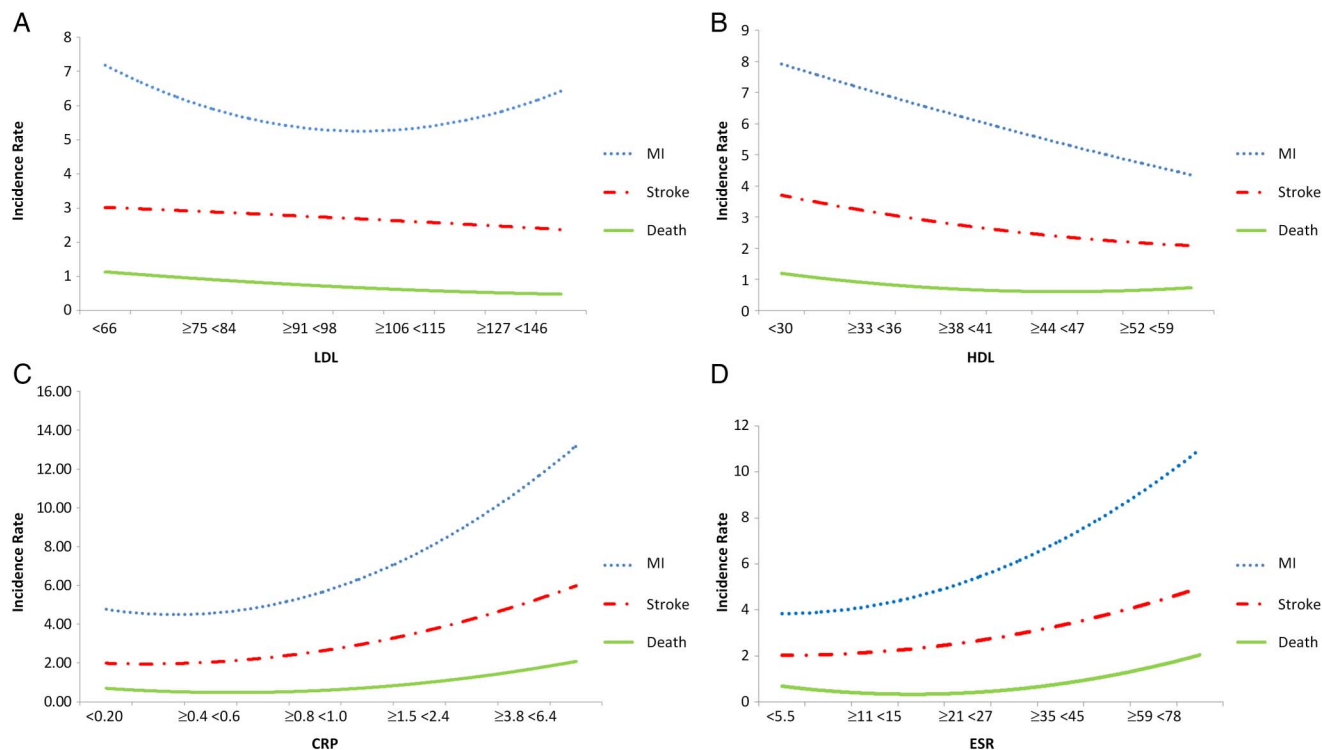


Figure 2 Incidence rate of myocardial infarction, stroke and death by CRP, ESR, LDL-C and HDL-C divided in deciles. CRP, C reactive protein; ESR, erythrocyte sedimentation rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction.

demographic characteristics. The exposure categories were divided into quintiles to allow for adequate numbers of event in multivariable-adjusted models. Two different approaches were used to control for statin use in the statistical model where the main exposure was LDL-C, since statins have a major effect on LDL-C. First, we controlled for statin use at baseline only while LDL-C was time variant. In the second approach, we only included patients who were not on statins at the index date, and individuals were then censored at the time that statins were initiated during follow-up. Regarding ESR and CRP, these were time varying and evaluated in separate models to avoid the expected high collinearity between these two laboratory tests. Given that RA seropositivity typically does not fluctuate much over time, this factor was as a fixed covariate assessed using all baseline and follow-up data.

RESULTS

After applying relevant cohort inclusion criteria, 37 568 patients with RA were identified within the VHA system (figure 1). Ninety per cent were men with mean age 63.0 (± 12.1 SD) years, and the mean age of women was 53.3 (± 13.8 SD) years. Mean CRP, ESR, HDL-C and LDL-C levels at baseline were 1.8 mg/dL (± 3.0 SD), 30.0 mm/h (± 26.1 SD), 45.1 mg/dL (± 12.9) and 106.1 mg/dL (± 30.6 SD), respectively; 69% of patients with RA with serologies available were seropositive. Other baseline characteristics of patients are listed in table 1.

Rates of first hospitalised MI, stroke or CHD death

Mean follow-up in the study was 4.5 (\pm SD 3.1) years. There were a total of 896 incident hospitalised MI, with an age-adjusted IR of 4.1 per 1000 person-year (95% CI 3.5 to 4.9). The age-adjusted IR among men was 5.9 per 1000 person-year (95% CI 5.5 to 6.3) and 2.9 per 1000 person-year (95% CI 2.1 to 4.0) among women. There were a total of 415

incident strokes, with an age-adjusted IR for men of 1.8 per 1000 person-years (95% CI 1.2 to 2.7) and 2.7 per 1000 person-years (95% CI 2.4 to 3.0) among women. There were 122 inpatient deaths from either MI or stroke with an age-adjusted IR of 0.07 per 1000 person-years (95% CI 0.05 to 0.08) for men and 0.09 per 1000 person-years (95% CI 0.05 to 0.17) for women.

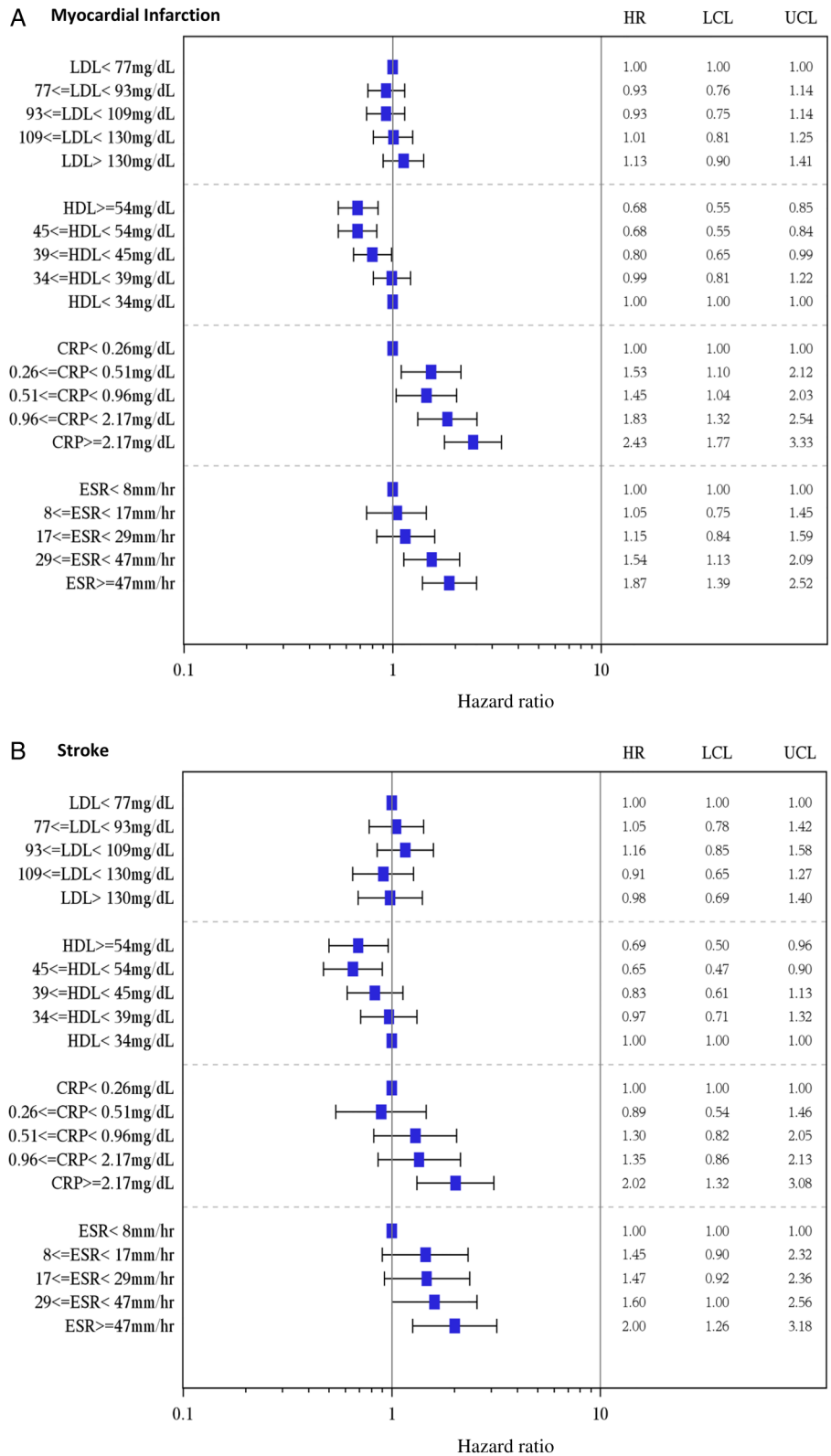
Figure 2 shows the IR for each outcome by exposure divided in deciles. We observed a non-linear U-shaped trend between LDL-C and MI risk. There was no trend between the IR of stroke and LDL-C and HDL-C and CHD death. The remainder of the trends of the IRs was linear. The IR for each of the outcomes decreased as HDL-C increased; these were the opposite for CRP and ESR, where the IR for the outcomes was higher as CRP and ESR increased (figure 2).

Multivariable COX regression analysis

After multivariable adjustment, Cox proportional hazard models using LDL-C as the main exposure of interest and after controlling for statins at baseline showed no clear association between LDL-C and the risk for MI or stroke (figure 3). There were no differences in HR in the sensitivity analysis used to control for statins which included only patients who were not taking statins at baseline with subsequent censoring if statins were initiated (data not shown). High HDL-C levels were associated with reduced risk for MI and stroke (figure 3A, B).

Cox proportional hazards models using CRP or ESR as the main exposure demonstrated that there was a monotonic association between high CRP and ESR with the risk of MI and stroke (figure 3A, B). After multivariable adjustment, RA seropositivity was associated with MI (table 2). LDL-C, HDL-C, CRP and ESR were not associated with increased risk of death from MI or stroke (data not shown).

Figure 3 Adjusted hazard ratios (HRs)* of hospitalised myocardial infarction (MI) or stroke among patients with rheumatoid arthritis from the Veterans Health Administration. (A) Myocardial infarction. (B) Stroke. Note: The exposures were divided into quintiles. CRP, C reactive protein; ESR, erythrocyte sedimentation rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LCL, lower 95% confidence level; UCL, upper 95% confidence level.



DISCUSSION

In this US veteran and predominantly male RA cohort, higher levels of ESR and CRP were associated with increased risk for MI and stroke, and higher levels of HDL-C were inversely associated with MI and stroke. None of these were significantly associated with CHD death, although mortality endpoints were likely underpowered. There was no clear association between LDL-C and the risk of MI, stroke or death. However, LDL-C IR

was observed to have a non-linear U-shape association with MI. RA seropositivity was associated with an increased risk for MI.

Myasoedova *et al*⁵ previously reported that patients with RA experienced higher rates of MI compared with the non-RA population at lower levels of LDL-C.⁵ Our study did not identify clear association between LDL-C with MI or stroke. One of the differences between that study and ours is that the previous study had a small sample size (N=651, with 62 events),⁵

Table 2 HRs for myocardial infarction associated with factors controlled in the multivariate Cox models*

| | HR | 95% CI |
|--|------|--------------|
| Male | 1.39 | 0.98 to 1.99 |
| Socioeconomic status (SES) | 0.97 | 0.95 to 0.99 |
| Seropositive (referent to seronegative) | 1.23 | 1.03 to 1.48 |
| Missing serology (referent to seronegative) | 1.30 | 1.05 to 1.59 |
| Current smoker (referent to never smoker) | 1.42 | 1.14 to 1.77 |
| Former smoker (referent to never smoker) | 1.08 | 0.89 to 1.31 |
| Missing smoking data (referent to never smoker) | 1.72 | 1.26 to 2.34 |
| Steroids 1–7.5 mg/day (ref to no use)† | 1.32 | 1.13 to 1.54 |
| Steroids >7.5 mg/day (ref to no use)† | 1.75 | 1.42 to 2.15 |
| Statin | 1.43 | 1.24 to 1.65 |
| Methotrexate (MTX)+DMARD (ref to non-biological DMARD other than MTX) | 0.83 | 0.65 to 1.00 |
| Biologics‡ (ref to non-biological DMARD other than MTX) | 0.82 | 0.65 to 1.05 |
| No RA medication (no biological, no DMARD; ref to non-biological DMARD other than MTX) | 0.87 | 0.72 to 1.06 |
| Chronic obstructive pulmonary disease | 1.54 | 1.27 to 1.86 |
| Chronic kidney disease | 2.30 | 1.60 to 3.32 |
| Diabetes mellitus | 1.76 | 1.48 to 2.09 |
| Heart failure | 1.71 | 1.28 to 2.28 |
| Hypertension | 1.06 | 0.92 to 1.23 |

Note: These are the covariates controlled for in the adjusted Cox models (HRs) models depicted in figure 2.

*Models also controlled for body mass index, but not statistically significant.

Comorbidities determined and controlled for at baseline.

†Steroid dose calculated as the mean daily dose during the 6 months prior to the index date.

‡Biological included all antitumor necrosis factor biologics, rituximab and abatacept with or without non-biological DMARD.

DMARD, disease-modifying antirheumatic drug; RA, rheumatoid arthritis.

whereas our study population had more than 38 000 patients with a total of 896 incident MI, 415 strokes and 122 deaths from MI or stroke. Another difference is that the Myasoedova *et al* study was conducted largely in a prebiological era in a more restricted racial/ethnic subgroup of individuals living in Olmstead County, an almost exclusively Caucasian demographic group. Similar to the results of our study between MI IR and LDL-C, a recent analysis of a large database using insurance claims data of a population composed predominantly by women (76% women; N=35 330) did show a marginal non-linear association between LDL-C and MI but no association between LDL-C and stroke or death from MI or stroke.²⁵

One study found an association between CRP and the development of atherosclerosis among patients with RA¹⁴ and another one showed that CRP was associated with MI death in patients with RA.¹³ Although CRP was used only at baseline in both of these studies and not as a time-variant exposure, these data are important in the explanation of the high burden of CHD among patients with RA. A recent small study (N=651) analysed this association using CRP and ESR in a time-variant fashion and yielded similar results to ours, but the data on CRP were limited given that only 20% of the population had CRP measurement.⁵ Despite the limitation of these studies regarding the use of CRP only at baseline or small sample size, our study was able to analyse CRP in a time-variant manner with a large sample and showed a significant association between CRP and ESR with the risk for MI and stroke.

Seropositivity defined as either positive RF or anti-CCP has been found to be associated with increased CHD in patients with RA in previous studies.^{5 26} Seropositivity with either positive RF or anti-CCP or antinuclear antibodies had been

associated with higher mortality from CHD even in patients without articular symptoms.^{27 28} This comparison of autoantibody-positive RA to autoantibody-negative RA is relevant given that the genetic contribution of HLA-DRB1 shared epitope is restricted to autoantibody-positive RA,^{29 30} which had also been associated with higher cardiovascular mortality rate.³¹ Like the aforementioned studies, our study showed an association between seropositivity and MI risk. This evidence in combination with our results suggests that, seropositive status may have an independent effect that may affect risk for CHD.

This study has several strengths that include a large cohort of patients with RA, which provides large power for the examination of the associations analysed in this study. We also found significant and expected associations with a number of comorbidities that have been commonly found to be CHD risk factors in past studies and in CHD risk calculators.³² Another strength of this study is the availability of serological status which was useful in two ways: one, it increased the specificity of the algorithm already used to identify patients with RA within this cohort, and it allowed us to analyse the association between seropositivity and CHD in patients with RA. The cohort also had readily available data on inflammatory markers such as CRP and ESR which provided for time-variant analyses of these inflammatory markers. Using EHR-based data sources from the VHA, our study was able to determine tobacco use, a major CHD risk factor and a potential confounder, which is usually not available in analyses of large databases of insurance claims data.

Among the limitations of the study is that we did not have direct information on RA disease activity based upon clinical examination. However, we had inflammatory markers as the surrogate marker of disease activity in these patients. We also recognise that the specificity of these markers may be low to reflect only RA and these lab tests may be elevated regardless of the cause of inflammation. Another limitation of our study is that we could not control for RA disease duration, which has been associated with increased risk for MI in patients with RA.^{33–35} However, two recent studies found no association between RA disease duration and CHD events.^{36 37} Given this mixed evidence, not having disease duration information, therefore, may not represent a major limitation to our study. Finally, we were able to characterise tobacco use in the majority of our cohort, but 12% of the population had missing data for tobacco use.

This study is one of the few that examined CHD risk factors in a large RA population (composed predominantly of older men) in which traditional risk factors such as LDL-C and inflammation were examined as additional risk factors for CHD. Future directions in RA suggest the continued need to develop better tools to predict future CHD risk in patients with RA based on lipid levels and other CHD-related risk factors. This could take the form of recalibrating existing CHD risk models derived in the general population, adding RA as a risk factor. Alternatively, it may be that representing RA simply as a single factor in this model still yields suboptimal calibration and discrimination, and an RA-specific CHD risk calculator will, therefore, be necessary. Regardless of which of these two approaches is ultimately best, further studies are needed to determine whether CRP or ESR levels meaningfully improve CHD risk stratification and prediction for patients with RA.

Contributors All authors contributed to the conception and design, or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content and final approval of the version to be published.

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Ethics approval IRB of Veteran Health Affairs Birmingham VA and University of Alabama at Birmingham.

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