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 clear association between HDL-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 increased 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 studies5–8 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.3–9 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 CRP14 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 an 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
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). 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

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.

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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 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 used. 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 |
| Biologic(s), % | 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 2008.24 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 antitumour 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.
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 (±SD 3.1) years. There were a total of 896 incident hospitalised MI, with an age-adjusted IR of 4.1 per 1000 person-years (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).
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 previously reported that patients with RA experienced higher rates of MI compared with the non-RA population at lower levels of LDL-C. 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).
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 stroke or death from MI or stroke. Another difference is that the Myasoedova et al study only RA and these lab tests may be elevated regardless of the serum RF or anti-CCP or antinuclear antibodies had been found to be associated with increased CHD in patients with RA in previous studies. 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. 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, which had also been associated with higher cardiovascular mortality rate. 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. 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 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. However, two recent studies found no association between RA disease duration and CHD events. 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.

### Table 2

| Factor                                | HR     | 95% CI  |
|---------------------------------------|--------|---------|
| Male                                  | 1.39   | 0.98 to 1.99 |
| Socioeconomic status (SES)            | 0.97   | 0.95 to 0.99 |
| Seropositive (referred to seronegative)| 1.23   | 1.03 to 1.48 |
| Missing serology (referred to seronegative) | 1.30   | 1.05 to 1.59 |
| Current smoker (referred to never smoker) | 1.42   | 1.14 to 1.77 |
| Former smoker (referred to never smoker) | 1.08   | 0.89 to 1.31 |
| Missing smoking data (referred 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 |
| Biological† (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.

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Clinical and epidemiological research

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REFERENCES

1 Solomon DH, Goodson NJ, Katz JN, et al. Patterns of cardiovascular risk in patients with rheumatoid arthritis. Ann Rheum Dis 2006;65:1608–12.
2 Meune C, Touze E, Trinquart L, et al. Trends in cardiovascular mortality in patients with rheumatoid arthritis over 50 years: a systematic review and meta-analysis of cohort studies. Rheumatology (Oxford) 2009;48:1309–13.
3 Wolfe F, Freundlich B, Straus WL. Increase in cardiovascular and cerebrovascular disease prevalence in rheumatoid arthritis. J Rheumatol 2003;30:36–40.
4 Gonzalez A, Maradit Kremers H, Crowson CS, et al. The widening mortality gap between rheumatoid arthritis patients and the general population. Arthritis Rheum 2007;56:3583–7.
5 Myasoedova E, Crowson CS, Kremers HM, et al. Lipid paradox in rheumatoid arthritis: the impact of serum lipid measures and systemic inflammation on the risk of cardiovascular disease. Ann Rheum Dis 2011;70:482–7.
6 Semb AG, Kvien TK, Austevt AH, et al. Lipids, myocardial infarction and ischaemic stroke in patients with rheumatoid arthritis in the Apolipoprotein-related Mortality Risk (AMORIS) Study. Ann Rheum Dis 2010;69:1996–2001.
7 del Rincon I, Freeman GL, Haas RW, et al. Relative contribution of cardiovascular risk factors and rheumatoid arthritis clinical manifestations to atherosclerosis. Arthritis Rheum 2005;52:3413–23.
8 del Rincon I, Williams K, Stern MP, et al. High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors. Arthritis Rheum 2001;44:2373–45.
9 Gonzalez A, Maradit Kremers H, Crowson CS, et al. Do cardiovascular risk factors confer the same risk for cardiovascular outcomes in rheumatoid arthritis patients as in non-rheumatoid arthritis patients? Ann Rheum Dis 2008;67:64–9.
10 Ridker PM, Danielson E, Fosse FA, et al. Reduction in C-reactive protein and LDL cholesterol and cardiovascular event rates after initiation of rosuvastatin: a prospective study of the JUPITER trial. Lancet 2009;373:1175–82.
11 Robertson J, Peters MJ, McInnes IB, et al. Changes in lipid levels with inflammation and therapy in RA: a maturing paradigm. Nat Rev Rheumatol 2013;9:513–23.
12 Navarro-Millán I, Charles-Schoeman C, Yang S, et al. Changes in lipoproteins associated with methotrexate or combination therapy in early rheumatoid arthritis: results from the treatment of early rheumatoid arthritis trial. Arthritis Rheum 2013;65:1430–8.
13 Goodson NJ, Symmons DP, Scott DG, et al. Baseline levels of C-reactive protein and prediction of death from cardiovascular disease in patients with inflammatory polyarthritis: a ten-year followup study of a primary care-based inception cohort. Arthritis Rheum 2005;52:2293–9.
14 Gonzalez-Gay MA, Gonzalez-Juanatey C, Pinoer A, et al. High-grade C-reactive protein elevation correlates with accelerated atherogenesis in patients with rheumatoid arthritis. J Rheumatol 2005;32:1219–23.
15 McDermott DH, Yang G, Kathiresan S, et al. CLC2 polymorphisms are associated with serum monocyte chemoattractant protein-1 levels and myocardial infarction in the Framingham Heart Study. Circulation 2005;112:1113–20.
16 Goodson NJ, Wiles NJ, Lurt M, et al. Mortality in early inflammatory polyarthritis: cardiovascular mortality is increased in seropositive patients. Arthritis Rheum 2002;46:2010–9.
17 Singh JA, Holmgren AR, Noorbalschi S. Accuracy of veterans administration databases for a diagnosis of rheumatoid arthritis. Arthritis Rheum 2004;51:952–7.
18 Kjoyta Y, Schneeweiss S, Glynn RJ, et al. Accuracy of Medicare claims-based diagnosis of acute myocardial infarction: estimating positive predictive value on the basis of review of hospital records. Am Heart J 2004;148:99–104.
19 Metcalf A, Neudam A, Forde S, et al. Case definitions for acute myocardial infarction in administrative databases and their impact on in-hospital mortality rates. Health Serv Res 2013;48:290–318.
20 Cuttana SL, Toh S, Iyer A, et al. Validation of acute myocardial infarction in the Food and Drug Administration’s Mini-Sentinel program. Pharmacoepidemiol Drug Saf 2013;22:40–54.
21 Roumie CL, Mitchell E, Gideon PS, et al. Validation of ICD-9 codes with a high positive predictive value for incident strokes resulting in hospitalization using Medicaid health data. Pharmacoepidemiol Drug Saf 2008;17:20–6.
22 Tirschwell DL, Longstreth WT Jr. Validating administrative data in stroke research. Stroke 2002;33:2465–70.
23 (AHRQ) ARHRaQ. Creation of New Race-Ethnicity Codes and Socioeconomic Status (SES) Indicators for Medicare Beneficiaries 2008. 2008.
24 McGinnis KA, Brandt CA, Skanderson M, et al. Validating smoking data from the Veteran’s Affairs Health Factors dataset, an electronic data source. Nicotine Tob Res 2011;13:1233–9.
25 Zhang J, Chen L, Denzel E, et al. The association between inflammatory markers, serum lipids and the risk of cardiovascular events in patients with rheumatoid arthritis. Ann Rheum Dis 2014;73:1301–8.
26 Lopez-Longo FJ, Oliver-Minarro D, de la Torre I, et al. Association between anti-cyclic citrullinated peptide antibodies and ischemic heart disease in patients with rheumatoid arthritis. Arthritis Rheum 2009;61:419–24.
27 Liang KP, Kremers HM, Crowson CS, et al. Autoantibodies and the risk of cardiovascular events. J Rheumatol 2009;36:2462–9.
28 Tomasson G, Aspelund T, Jonsson T, et al. Effect of rheumatoid factor on mortality and coronary heart disease. Ann Rheum Dis 2010;69:1649–54.
29 Gonzalez-Gay MA, Hajer AE, Dababneh A, et al. Seronegative rheumatoid arthritis in elderly and polymyalgia rheumatica have similar patterns of HLA association. J Rheumatol 2001;28:122–5.
30 Ronningen M, Seddighzadeh M, Elke MC, et al. Interaction analysis between HLA-DRB1 shared epitope alleles and MHC class II transactivator CIITA gene with regard to rheumatoid arthritis. PLoS ONE 2012;7:e32861.
31 Farragher TM, Goodson NJ, Naseem H, et al. Association of the HLA-DRB1 gene with premature death, particularly from cardiovascular disease, in patients with rheumatoid arthritis and inflammatory polyarthritis. Arthritis Rheum 2008;58:359–69.
32 Hippisley-Cox J, Coupland C, Vinogradova Y, et al. Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. BMJ 2008;336:1475–82.
33 Peters MJ, Symmons DP, McCaig D, et al. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. Ann Rheum Dis 2010;69:325–31.
34 Ward MM. Recent improvements in survival in patients with rheumatoid arthritis: better outcomes or different study designs? Arthritis Rheum 2001;44:1467–9.
35 Naz SM, Farragher TM, Burrn DK, et al. The influence of age at symptom onset and length of followup on mortality in patients with recent-onset inflammatory polyarthritis. Arthritis Rheum 2008;58:985–98.
36 Semb AG, Holme I, Kvien TK, et al. Intensive lipid lowering in patients with rheumatoid arthritis and previous myocardial infarction: an explorative analysis from the incremental decrease in endpoints through aggressive lipid lowering (IDEAL) trial. Rheumatology (Oxford) 2011;50:324–9.
37 Arts EE, Fransen J, den Broeder AA, et al. The effect of disease duration and disease activity on the risk of cardiovascular disease in rheumatoid arthritis patients. Ann Rheum Dis 2015;74:998–1003.