Heart Failure Risk Associated With Rheumatoid Arthritis–Related Chronic Inflammation

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BACKGROUND: Inflammation may contribute to incident heart failure (HF). Rheumatoid arthritis (RA), a prototypic inflammatory condition, may serve as a model for understanding inflammation-related HF risk.

METHODS AND RESULTS: Using the Vanderbilt University Medical Center electronic health record, we retrospectively identified 9889 patients with RA and 9889 control patients without autoimmune disease matched for age, sex, and race. Prevalent HF at entry into the electronic health record or preceding RA diagnosis was excluded. Incident HF was ascertained using International Classification of Diseases, Ninth Revision (ICD-9), codes and medications. Over 177,566 person-years of follow-up, patients with RA were at 21% greater risk of HF (95% CI, 3–42%) independent of traditional cardiovascular risk factors. Among patients with RA, higher CRP (C-reactive protein) was associated with greater HF risk (P<0.001), while the anti-inflammatory drug methotrexate was associated with ≈25% lower HF risk (P=0.021). In a second cohort (n=115) of prospectively enrolled patients with and without RA, we performed proteomics and cardiac magnetic resonance imaging to discover circulating markers of inflammation associated with cardiac structure and function. Artemin levels were higher in patients with RA compared with controls (P=0.009), and higher artemin levels were associated with worse ventricular end-systolic elastance and ventricular-vascular coupling ratio (P=0.044 and P=0.031, respectively).

CONCLUSIONS: RA, a prototypic chronic inflammatory condition, is associated with increased risk of HF. Among patients with RA, higher levels of CRP were associated with greater HF risk, while methotrexate was associated with lower risk.

Key Words: biomarker ■ cardiac magnetic resonance imaging ■ heart failure ■ inflammation ■ rheumatoid arthritis

Heart failure (HF) is a major public health problem that affects nearly 7 million people in the United States.3 HF with preserved ejection fraction (HFpEF) accounts for half of all HF cases and is increasing in prevalence.1 Medical therapies with proven benefit for reduction of HF hospitalizations and mortality rate in HFpEF are lacking, suggesting an incomplete mechanistic understanding of HFpEF.2 Consequently, elucidating mechanisms underlying HFpEF may inform novel preventive and therapeutic strategies.

Inflammation has been proposed as an important mechanism for the development of HF, particularly HFpEF.5,4 Understanding whether and how inflammation influences cardiovascular structure and function and HF risk is of biologic, preventive, and therapeutic importance.5 Rheumatoid arthritis (RA) is a prototypic chronic inflammatory disorder that has been associated with an increased risk for HF independent of traditional cardiovascular risk factors, including coronary artery disease.6–11 Therefore, patients with...
RA may represent a human model for studying how chronic inflammation contributes to HF, and possibly HFpEF.12,13 To investigate the association between RA and HF, we examined 2 cohorts. The first was a retrospective analysis of the Vanderbilt University Medical Center (VUMC) electronic health record (EHR), in which we identified patients with and without RA and then: (1) assessed the risk of HF associated with RA, and (2) evaluated factors associated with HF risk among patients with RA. We hypothesized that patients with RA would be at increased risk for HF independent of traditional cardiovascular risk factors. We also hypothesized that among patients with RA, greater inflammation and use of antirheumatic medications would be associated with higher and lower HF risk, respectively. In a second cohort of prospectively enrolled patients with and without RA, we used proteomics and cardiac magnetic resonance imaging (cMRI) to explore associations between circulating markers of inflammation and cardiac structure and function.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

EHR-Based Cohort

The VUMC Synthetic Derivative is a deidentified copy of the EHR. It contains ~2.5 million patient records spanning more than 20 years, which are searchable for structured (eg, International Classification of Diseases, Ninth Revision [ICD-9] codes, laboratory values) and unstructured (eg, narrative text) data.14 We queried the Synthetic Derivative that included data from 1993 to 2017 to identify adult patients (18 years or older) with and without RA. Vanderbilt
Identification of Patients With RA

The EHR was first queried for patients with a possible diagnosis of RA, defined as the presence of ≥1 ICD-9 code for RA (714 or 714.x) or measurement of anticyclic citrullinated peptide (n=27,885).15–17 From this initial cohort we excluded: (1) patients with prevalent HF based on the presence of ≥1 ICD-9 code for HF (425.x or 428.x) at the time of initial RA diagnosis, and (2) further restricted the RA cohort to patients with ≥2 RA ICD-9 codes (714–714.2)18 separated by at least 14 days and ever use of an antirheumatic medication.19 The latter criteria were applied as manual adjudication of 135 charts revealed the combination of multiple ICD-9 codes plus medication use afforded good specificity with a positive predictive value for RA of >93%. This algorithm yielded a cohort of 9889 patients with RA.

Identification of Controls

The non-RA control cohort was also ascertained through query of the EHR. We excluded any patient that ever had any of the following: an ICD-9 code for RA or autoimmune diseases,18 laboratory measure of anticyclic citrullinated peptide or rheumatoid factor, or rheumatology clinic encounter. Prevalent HF at the time of entry into the EHR was excluded based on the presence of ≥1 ICD-9 code for HF (425.x or 428.x). Following these exclusions, the control sample was extracted by first matching for sex and race, and then by selecting the individual closest in age (without restriction) to yield a 1:1 ratio with the 9889 patients with RA without replacement.

Identification of HF and Secondary Outcomes

Incident HF in our EHR was defined using a previously validated algorithm that includes 1≥ ICD-9 HF code (425.x or 428.x) and use of an intravenous diuretic within 90 days of the HF code.20 For this study, we also manually adjudicated the medical records of 100 patients and found this HF algorithm to have high positive and negative predictive values (94% and 96%, respectively). Follow-up was calculated as the time from the date of RA diagnosis or entry into the EHR for the control group to the date of incident HF, death, or last known follow-up for patients who were not dead by December 31, 2017. Death was ascertained through the Social Security Administration’s Death Master File linkage, which has similar coverage to the National Death Index. The follow-up period for death following HF was the time elapsed from the date of HF diagnosis to the date of death, with censoring at the date of the last clinical encounter for patients who were alive on December 31, 2017.

For patients who developed incident HF, we also extracted the closest available measure of left ventricular ejection fraction (LVEF) (from echocardiogram, cardiac catheterization, nuclear imaging, or cMRI reports) within 180 days and B-type natriuretic peptide values within 90 days of the date of HF diagnosis. HFpEF was defined as LVEF ≥50%.

Identification of Covariates

Demographics, anthropometrics, comorbidities, and statin, aspirin, and antihypertensive medication use were determined at RA diagnosis date or entry into the EHR for the control patients. Coronary artery disease, atrial fibrillation, hypertension, dyslipidemia, chronic kidney disease, and diabetes mellitus status; vital signs; anthropometrics; and laboratory values were extracted using combinations of ICD-9 and Current Procedural Terminology codes and text strings (Table 1). For patients with RA, we also extracted use of rheumatologic medications at any time between date of RA diagnosis and HF diagnosis or last follow-up for patients who did not develop HF. These medications were classified as methotrexate, nonbiologic disease-modifying antirheumatic drugs (DMARDs), anti–tumor necrosis factor biologics, other biologic/small molecule DMARDs, antimalarial, systemic corticosteroid, and additional RA medications (Table 2). Erythrocyte sedimentation rate (ESR) and CRP (C-reactive protein) values closest to the date of RA diagnosis were extracted from the EHR.

Proteomics-cMRI Cohort

The characteristics of this cohort have been previously described.21 Briefly, 115 adult individuals with (n=59) and without RA (n=56) were prospectively enrolled between August 2012 and January 2015 at VUMC to study cardiac structure and function. Vanderbilt University’s institutional review board approved this study with patients providing written informed consent. All participants were free of prevalent cardiovascular disease and, as a group, patients with RA were largely clinically well-controlled based on median disease activity scores and CRP levels. The non-RA participants were matched to the RA participants on age and sex. The participants underwent cMRI on an Avanto 1.5T scanner (Siemens Healthcare) and the imaging protocol has been previously reported.21 Vital signs were recorded during the study and from the cMRI, left ventricular volumes, mass, ejection fraction, filling...
rate, extracellular volume, end-arterial elastance (Ea), end-systolic elastance (Ees), and ratio of Ea to Ees as a measure of ventricular-vascular coupling were quantified using the following formulas:22,23

\[
Ea, \text{ mm Hg/mL} = \text{end-systolic pressure/stroke volume}
\]

End-systolic pressure, mm Hg=0.9×systolic blood pressure (mm Hg) at time of magnetic resonance imaging; stroke volume (SV) = left ventricular end-diastolic volume – end-systolic volume (ml).

\[
Ees = \left[ P_d - (E_{Nd(est)} \times P_s \times 0.9) \right] / (SV \times E_{Nd(est)})
\]

Table 1. Extraction Algorithms for Comorbidities in the VUMC Electronic Health Record

| Covariate                  | Definition                                                                 |
|----------------------------|---------------------------------------------------------------------------|
| RA                         | ≥2 ICD codes (714, 714.0, 714.1, 714.2) separated by at least 14 d AND Every use of a rheumatologic medication (Table 2) |
| HF                         | ≥1 ICD codes (425, 425.x, 428, or 428.x) AND Use of an intravenous diuretic (furosemide, Lasix, bumetanide, Bumex, torsemide, Demadex, ethacrynic acid, Edecrin, metolazone, Zaroxyl) |
| Coronary artery disease    | ≥2 ICD-9 codes: 410.*, 411.*, 412.*, 413.*, 414.*, V45.82 OR ≥1 of the ICD code listed AND ICD-10 code: 125.1 OR ≥1 CPT code: 35534–35536, 35530–35533, 92980–92982, 92984, 92995, 92996 |
| Hypertension               | ≥1 ICD code: 401.*–405.* OR ≥1 ICD-10 code: H10.1, I10.1, I10.9 OR Use of an antihypertensive medication OR ≥1 problem list: “dm,” “diabetes” |
| Diabetes mellitus          | ≥1 ICD code: E10.x, E11, E11.x, E13, E13.x AND ≥1 problem list: “dm,” “diabetes” |
| Chronic kidney disease     | ≥1 ICD code: 585.* |
| Atrial fibrillation/atrial flutter | ≥3 of the following: “afib,” “a fb,” “atrial-fib,” “atrial fibr,” “a flutter,” “atrial flutter,” “atrial-flutter” in the Problem List “afib,” “a fb,” “atrial-fib,” “atrial fibr,” “a flutter,” “atrial flutter,” “atrial-flutter” nonnegated, nonfamily in other Clinical Documents |
| Dyslipidemia               | ≥1 HDL <40 (45 for women) OR ≥1 triglycerides >200 OR ≥1 cholesterol >200 OR ≥1 more of the following medications: “atorvastatin,” “Lipitor,” “torvast,” “lovastatin,” “atorc,” “pravastatin,” “pravachol,” “rosuvastatin,” “crestor,” “simvastatin,” “zocor,” “cholestyramine,” “prevalide,” “colestipol,” “colestid,” “colesevelam,” “welchol,” “niacin,” “niacor,” “Niaspan,” “gemfibrozil,” “lupid,” “fenofibrate,” “tricor,” “fibricor,” “bezaflibrate,” “bezalap,” “ezetimibe,” “zetia” |

CPT indicates Current Procedural Terminology; HDL, high-density lipoprotein; HF, heart failure; ICD, International Classification of Diseases; RA, rheumatoid arthritis; and VUMC, Vanderbilt University Medical Center.

Table 2. Antirheumatic Drugs

| RA Medication Class | Included Medications                                                                 |
|---------------------|----------------------------------------------------------------------------------------|
| Methotrexate        | Methotrexate                                                                            |
| Nonbiologic DMARD   | Azathioprine, leflunomide, sulfasalazine, cyclophosphamide                               |
| Anti-TNF            | Etanercept, adalimumab, infliximab, certolizumab, golimumab                            |
| Other biologic/ small molecule DMARD | Rituximab, abatacept, tocilizumab, atizumab, tofacitinib, anakinra                    |
| Systemic corticosteroid | Cortisone acetate, hydrocortisone, prednisone, dexamethasone, prednisolone, methylprednisolone, triamcinolone acetonide |
| Antimalarial        | Hydroxychloroquine, chloroquine, quinacrine                                            |
| Additional RA medi- cations | Minocycline, cyclosporine, gold, sodium aurothiomalate, auranofin, aurothioglucose, penicillamine |

DMARD indicates disease-modifying antirheumatic drug; RA, rheumatoid arthritis; and TNF, tumor necrosis factor.

\[ P_d, \text{ mm Hg}=\text{diastolic blood pressure at time of magnetic resonance imaging}; \ E_{Nd(est)}=\text{group averaged left ventricular (LV) elastance at the onset of ejection, calculated as: 0.0275−0.165×LVEF+0.3656×(Pd/\text{end-systolic pressure})+0.515×End(avg).} \]

\[ \text{End(avg)} = \frac{0.35695}{(37.2266×Tnd) + (74.249×(Tnd^2))} \]

\[ \text{End(avg)} = \frac{-307.39×(Tnd^3) + (684.54×(Tnd^6))}{(856.92×(Tnd^3)) + (571.95×(Tnd^6))} \]

\[ \text{Tnd} = \text{PEP1/QS2} \]

\[ \text{PEP1} = -0.0004×\text{Heart rate at MRI} + 0.131 \text{ for males} -0.0004×\text{Heart rate at MRI} + 0.133 \text{ for females} \]

\[ \text{QS2} = -0.0021×\text{Heart rate at MRI} + 0.546 \text{ for males} -0.0021×\text{Heart rate at MRI} + 0.549 \text{ for females} \]

\[ \text{Ps, mm Hg}=\text{systolic blood pressure at time of magnetic resonance imaging.} \]

Ventricular-vascular coupling = Ea/Ees.

Participants also underwent phlebotomy with immediate processing for plasma that was stored at −80°C for future investigations. In an exploratory analysis to discover inflammation-related proteins that may associate with RA and cardiac structure and function, we used a proteomic platform (Inflammation panel, Olink LLC) to assay 92 proteins (Table S1).24 Olink proteomics is a novel multiplex platform that allows the simultaneous measurement and quantification of many proteins.25 A pair of antibodies targeting different regions of the protein is used. These antibodies are linked to unique DNA sequences. Once each antibody of the pair is bound
to its specific epitope on the target protein, these unique DNA sequences at the Fc portion of the antibodies will hybridize, permitting proximity-dependent DNA polymerization. The resulting sequence is subsequently detected and quantified using standard real-time polymerase chain reaction. This approach is advantageous as it eliminates cross-reactivity, a limitation of conventional multiplexed immunoassays. In Olink, because only matched DNA reporter pairs are amplified by real-time polymerase chain reaction, simultaneous quantification of proteins occurs without loss of specificity or sensitivity. Across all 92 assays of the Olink Inflammation panel, the mean intra-assay and interassay variations were observed to be 7% and 18%, respectively. Additionally, and of relevance for our cohort, an Olink internal validation trial of samples known to contain rheumatoid factor (<20–1190 IU/mL) found no interference with protein detection.

Statistical Analysis
Patients were categorized as RA or non-RA controls. For the EHR-based cohort, patients with RA were further stratified into those who did and those who did not develop HF. Summary statistics for patient characteristics were calculated as count (percentage) and median (25th–75th percentile) for categorical and continuous variables, respectively. Unadjusted between-group comparisons were made using Fisher exact and Wilcoxon rank-sum tests, as appropriate. In the EHR-based cohort, the risks of incident HF and death following HF in patients with RA and those without RA were assessed using the Kaplan–Meier method and multivariable-adjusted Cox proportional hazards models. Among patients with RA, factors associated with the risk of HF of any type, HFpEF, and HF with reduced ejection fraction (HFrEF), were examined in multivariable-adjusted logistic regression. Covariates in adjusted models were selected a priori and included: age, sex, race, baseline year, coronary artery disease, atrial fibrillation, hypertension, dyslipidemia, chronic kidney disease, diabetes mellitus, body mass index, heart rate, pulse pressure, creatinine, and baseline statin, antiplatelet, and antihypertensive medication use, as well as each class of antirheumatic medications described above at any time between baseline and HF or end of follow-up for patients who did not develop HF. Multiple imputation using permuted mean matching with chained equations was used to handle missing covariate data. Given the large sample size, 10 imputed data sets were generated. The relative strength of association between clinical factors and the risk of HFpEF or HFrEF among patients with RA was assessed by ranking the proportion of the multivariable-adjusted logistic regression model accounted for by each covariate calculated as the F statistic divided by the sum of the F statistics for all covariates in the model.

In the proteomics-cMRI cohort, the associations between plasma levels of inflammation-related proteins on the proteomics panel and RA, as well as cardiac structure and function, were assessed using multivariable-adjusted linear regression. Covariates included in the adjusted models were selected a priori and included age, sex, heart rate and systolic blood pressure at time of cMRI, body mass index, and estimated glomerular filtration rate.

All tests were 2-sided, and P values <0.05 were considered significant. Given the exploratory nature of the proteomic analysis, no adjustments were made for multiple testing. All analyses were performed using Stata version 13.0 or higher (StataCorp LLC). M.J.A. and D.K.G. had full access and take responsibility for data integrity and analysis.

RESULTS
EHR-Based Cohort
Baseline characteristics of the 19 778 patients with RA and controls are shown in Table 3. Patients with RA were slightly older than non-RA controls (median difference, 3.7 years; 25th–75th percentile: −0.2 to 7.2). Comorbidities, including coronary artery disease, atrial fibrillation, and traditional cardiovascular risk factors, were more common among patients with RA than non-RA controls. Statin, aspirin, and antihypertensive medication use was more common among patients with RA compared with control patients.

Over a median of 8.7 years (maximum 27.9) with 177 566 person-years of follow-up, we identified 766 incident HF events (Table 4). The HF incidence rate was greater among patients with RA compared with controls (4.87 versus 3.96 per 1000 person-years) (Figure 1A). In multivariable-adjusted models, RA was associated with a 21% (95% CI, 3–42%; P = 0.023) increased risk of HF. LVEF near the time of HF diagnosis was available in 79% of patients with HF and was similar between patients with (median, 55%; 25th–75th percentile: 40–60%) and without RA (median, 55%; 25th–75th percentile: 35–60% [P = 0.44]). HFpEF was the most common type of HF in both groups, present in 64% and 62% of patients with and without RA, respectively (P = 0.67). B-type natriuretic peptide levels closest to the date of HF diagnosis were available in 72% of patients with HF and were lower in RA (252 pg/mL; 25th–75th percentile: 85–640) compared with patients without RA (305 pg/mL; 25th–75th percentile: 125–676 [P = 0.009]).

Among the 766 patients who developed incident...
HF, 138 died over 3712 person-years of follow-up (Figure 1B). Death occurred more frequently in patients with RA compared with non-RA controls (22.6% versus 14.7%, \( P = 0.006 \)). In age-, sex-, and race-adjusted models, the risk of death following HF was nearly 70% higher in patients with RA compared with non-RA controls (hazard ratio [HR], 1.68, 95% CI, 1.45–1.95 \( P < 0.001 \)).

In the cohort of 9889 patients with RA, incident HF occurred in 323 (3.3%). Compared with patients with RA who did not develop HF, those who did were older at RA diagnosis, with a higher frequency of coronary artery disease, atrial fibrillation, traditional cardiovascular risk factors, and chronic kidney disease (Table 5). Anti-rheumatic medications were variably associated with the risk of HF. The use of methotrexate was significantly associated with lower risk of HF (odds ratio [OR], 0.75; 95% CI, 0.59–0.96 \( P = 0.021 \)). In the subset of patients with RA in whom ESR and CRP levels were measured (n=6161, Table S2), greater levels of inflammation as measured by CRP were associated with increased risk of HF (OR, 1.29; 95% CI, 0.59–0.96 \( P = 0.021 \)). In the subset of patients with RA in whom ESR and CRP levels were measured (n=6161, Table S2), greater levels of inflammation as measured by CRP were associated with increased risk of HF (OR, 1.29; 95% CI, 0.59–0.96 \( P = 0.021 \)).

Characteristics of patients with RA who developed HFpEF or HFrEF are shown in Table 6. The pattern and relative strength of association of clinical factors with the risk for HFpEF or HFrEF differed by HF subtype. For example, traditional cardiovascular risk factors,

### Table 3. Characteristics of Patients With and Without RA in the VUMC EHR

|                        | Patients With RA (n=9889) | Controls (n=9889) | \( P \) Value |
|------------------------|---------------------------|-------------------|---------------|
| Women                  | 76                        | 76                | 1.00          |
| White                  | 84                        | 84                | 0.98          |
| Age, y                 | 56 [46–66]                | 53 [42–63]       | <0.001        |
| Coronary artery disease| 3.5                       | 2.0               | <0.001        |
| Atrial fibrillation    | 1.5                       | 0.5               | <0.001        |
| Hypertension           | 69                        | 43                | <0.001        |
| Dyslipidemia           | 24                        | 8                 | <0.001        |
| Chronic kidney disease | 1.3                       | 0.3               | <0.001        |
| Diabetes mellitus      | 11                        | 3                 | <0.001        |
| Body mass index, kg/m² | 28 [24–33]                | 27 [24–32]       | <0.001        |
| Heart rate, beats per min | 78 [71–86]            | 76 [68–84]       | <0.001        |
| Pulse pressure, mm Hg  | 50 [40–60]                | 50 [40–60]       | 0.45          |
| Creatinine, mg/dL      | 0.82 [0.70–1.00]          | 0.84 [0.70–1.00]  | <0.001        |
| Statin use             | 19                        | 7                 | <0.001        |
| Antiplatelet use       | 17                        | 6                 | <0.001        |
| Antihypertensive use   | 54                        | 15                | <0.001        |

Controls were matched with patients with rheumatoid arthritis (RA) for sex, race, and closest age. Data are presented as percentage or median [25th–75th percentile]. Baseline (entry) defined as date of RA diagnosis in the RA cohort and as date of medical entry in the control cohort. Clinical variables are defined in Table 1. EHR indicates electronic health record; VUMC, Vanderbilt University Medical Center.

### Table 4. Risk of Incident HF in Patients With and Without RA

|                        | Patients With RA (n=9889) | Controls (n=9889) | \( P \) Value |
|------------------------|---------------------------|-------------------|---------------|
| HF events              | 323 (3.27%)               | 443 (4.48%)       | <0.001        |
| Follow-up time, y\(^\text{a}\) | 5.9 [2.6–9.9]          | 10.7 [8.0–13.9]   | <0.001        |
| Follow-up time, person-\(y\) | 66 295.8            | 111 260.7         |               |
| HF incidence rate (95% CI)     | 4.87 [4.37–5.43]      | 3.96 [3.61–4.35]  | 0.001         |
| Model 1 (unadjusted)\(^d\)   | 1.28 [1.10–1.48]       | Reference         | 0.001         |
| Model 2 (sex, race, age)\(^d\) | 1.79 [1.53–2.09]     | Reference         | <0.001        |
| Model 3 (all covariates in Table 3)\(^d\) | 1.21 [1.03–1.42]   | Reference         | 0.023         |

Heart failure (HF) is defined as presence of International Classification of Diseases, Ninth Revision code 425.x or 428.x plus use of intravenous diuretics within 90 days of code. RA indicates rheumatoid arthritis.

\(^{a}\)From baseline to HF or last medical encounter at Vanderbilt University Medical Center, reported as median years [25th–75th percentile].

\(^{d}\) Cox regression (covariates included in model) presented as hazard ratios (95% CIs).

In the cohort of 9889 patients with RA, incident HF occurred in 323 (3.3%). Compared with patients with RA who did not develop HF, those who did were older at RA diagnosis, with a higher frequency of coronary artery disease, atrial fibrillation, traditional cardiovascular risk factors, and chronic kidney disease (Table 5). Anti-rheumatic medications were variably associated with the risk of HF. The use of methotrexate was significantly associated with lower risk of HF (odds ratio [OR], 0.75; 95% CI, 0.59–0.96 \( P = 0.021 \)). In the subset of patients with RA in whom ESR and CRP levels were measured (n=6161, Table S2), greater levels of inflammation as measured by CRP were associated with increased risk of HF (OR, 1.29; 95% CI, 1.16–1.44 \( P = 0.001 \)). ESR trended toward but was not significantly associated with the risk of HF when CRP was also included in the model (OR, 1.13; 95% CI, 0.98–1.30 \( P = 0.097 \)).

Characteristics of patients with RA who developed HFpEF or HFrEF are shown in Table 6. The pattern and relative strength of association of clinical factors with the risk for HFpEF or HFrEF differed by HF subtype. For example, traditional cardiovascular risk factors,
such as higher body mass index, diabetes mellitus, and chronic kidney disease were more strongly associated with HFrEF, while prevalent coronary artery disease was associated with both the risk of HFpEF and HFrEF. Atrial fibrillation was the comorbidity most strongly associated with the risk of HFrEF, accounting for 11% of the model and an OR of 4.62 (95% CI, 2.38–8.72; \( P < 0.001 \)), although it was not associated with HFpEF (\( P = 0.27 \)). Higher CRP levels were associated with increased risk for both HFpEF and HFrEF, although CRP appeared to be a relatively stronger contributor to HFpEF than HFrEF, with 5.9% of the model explained for HFpEF compared with 2.8% for HFrEF. Antirheumatic medications variably associated with the HF subtypes. Methotrexate use was associated with a lower risk for HFpEF (OR, 0.64; 95% CI, 0.55–0.98 [\( P = 0.036 \]) but not HFrEF (\( P = 0.68 \)), while corticosteroids were associated with lower risk for HFrEF (OR, 0.53; 95% CI, 0.34–0.81 [\( P = 0.004 \]) but not HFpEF (\( P = 0.98 \)). Antimalarial medication use was associated with an increased risk for HFpEF (OR, 1.42; 95% CI, 1.07–1.88 [\( P = 0.016 \]) but not HFrEF (\( P = 0.67 \)).

### Proteomics-cMRI Cohort

The characteristics of this cohort, including some features of cardiac structure, have been previously reported.\(^1\) Left ventricular volumes, ejection fraction, mass, extracellular volume, and filling rate were similar between patients with and without RA (Table 7). Arterial and end-systolic elastance also did not differ between the 2 groups; however, RA was associated with higher (worse) ventricular-vascular coupling ratio (\( P = 0.06 \); 95% CI, 0.00–0.12 [\( P = 0.049 \)]).

The inflammation proteomic panel was successfully completed on plasma samples from 104 patients and 90 proteins on the panel passed quality control. In multivariable-adjusted linear regression models, the levels of 24 proteins differed significantly between patients with RA and controls (\( P < 0.049 \) for all) (Table 8).
Levels of several proteins previously described in RA, such as S100A12 (ENRAGE), interleukin-6, hepatocyte growth factor, tumor necrosis factor α, interleukin-8, and nerve growth factor β were higher in RA cases compared with controls. Patients with RA also had higher artemin levels compared with controls (β = 0.094; 95% CI, 0.024–0.164 [P = 0.009]).

Levels of inflammation-related proteins from the proteomics panel were then examined in relation to cardiac structure and function in multivariable-adjusted linear regression models (Table 9). A total of 4 proteins were positively associated with LVEF, including nerve growth factor β. Three of the 4 proteins were also associated with lower (better) ventricular-vascular coupling as measured by Ea/Ees. In contrast, higher levels of artemin significantly associated with lower (worse) end-systolic elastance and higher (worse) Ea/Ees. Proteins that were significantly associated with RA compared with controls and cardiac structure and function are shown in Figure 2.

**DISCUSSION**

We investigated the association between RA, a chronic inflammatory condition, and HF. Our principal findings were: (1) RA was associated with an increased risk of...
HF, with the majority of cases being HFpEF; (2) among patients with RA, higher levels of CRP were associated with greater risk for HF, while methotrexate use was associated with lower risk of HFpEF; (3) the pattern of comorbidities and their relative strengths of association differed between patients with RA who developed HFpEF and HFrEF; and (4) artemin may be a novel marker of RA that is associated with adverse ventricular-vascular coupling.

HFpEF is becoming the predominant form of HF; yet, clinical trials for lowering the risk of HF hospitalizations and death in this population have not demonstrated clear evidence for therapeutic efficacy. Consequently, elucidating the pathophysiologic basis for HFpEF has garnered substantial interest. One postulated mechanism ascribes the development and progression of HFpEF to chronic inflammation.3 By studying RA, a prototypic chronic inflammatory condition, our results support a role for inflammation in the development of HF.

First, we found that patients with RA were at 21% (95% CI, 3–42%) increased risk for HF compared with patients without rheumatologic conditions, which was independent of traditional cardiovascular risk factors, including prevalent coronary artery disease. This estimate is consistent with the 22% (95% CI, 9–37%) and 38% (95% CI, 27–50%) increased risk of HF associated with RA that was found in Swedish and Danish National Patient Registries, respectively.5,10 These HRs are lower, however, than a Mayo Clinic study, which reported an 87% increased risk (95% CI, 47–139%) for RA.6 This difference may be partially attributable to the time periods in which the various studies were conducted. More specifically, the Mayo Clinic study included patients with RA diagnosed between 1955 to 1995, which was before the widespread use of DMARDs and availability of biologics for the treatment of RA.6 Our study and those from Denmark and Sweden included more contemporary cohorts, with greater use of DMARDs.3,10 In contrast with the studies from Denmark and Sweden, we were able to estimate the proportion of HF cases with preserved compared with reduced ejection fraction and found that HFpEF accounted for approximately two thirds of incident HF cases in both patients with RA and those without RA. Our more contemporary data differ from the few earlier reports of the relative prevalence of preserved versus reduced ejection fraction HF among patients with RA and controls. For example, in a smaller cohort of patients evaluated before the availability of biologic DMARDs (1979–2000), Davis and colleagues reported lower rates of HFpEF among patients with RA and those without RA, 58% and 41%, respectively.12

### Table 7. Cardiac Structure and Function Assessed by Cardiac MRI and Patients With RA and Healthy Age- and Sex-Matched Controls

|                      | RA [n=59] | Control [n=56] | P Value | Adjusted β [95% CI] for RA | Adjusted P Value |
|----------------------|-----------|----------------|---------|----------------------------|------------------|
| Age, y               | 53 [40–59] | 52 [38–57]     | 0.73    |                            |                  |
| Women                | 76        | 79             | 0.77    |                            |                  |
| Body mass index, kg/m² | 27.5 [23.5–33.9] | 26.5 [23.5–27.5] | 0.32    |                            |                  |
| DAS28-CRP, units     | 3.16 [2.03–4.05] | ...             | ...     |                            |                  |
| CRP, mg/L            | 1.7 [0.7–6.7] | 1.7 [0.5–3.1]   | 0.16    |                            |                  |
| MRI heart rate, beats per min | 68 [61–75] | 74 [68–82]     | <0.001  |                            |                  |
| MRI systolic blood pressure, mm Hg | 129 [118–139] | 121 [112–132]  | 0.018   |                            |                  |
| MRI diastolic blood pressure, mm Hg | 69 [62–77] | 69 [64–77]     | 0.70    |                            |                  |
| LVEF, %              | 68 [62–74] | 67 [60–70]     | 0.089   | 0.39 [−2.49 to 3.27]       | 0.79             |
| LVEDV index, mL/m²    | 59 [47–67] | 61 [55–66]     | 0.23    | −0.52 [−4.87 to 3.84]      | 0.82             |
| LVESV index, mL/m²    | 18 [12–25] | 21 [16–26]     | 0.055   | −0.40 [−3.18 to 2.39]      | 0.78             |
| LSVS index, mL/m²     | 39 [36–43] | 39 [36–43]     | 0.75    | −0.39 [−2.91 to 2.13]      | 0.76             |
| LV mass index, g/m²   | 44 [40–50] | 42 [36–49]     | 0.19    | 0.92 [−1.70 to 3.53]       | 0.49             |
| LV ECV, %             | 26.6 [24.7–28.5] | 27.5 [25.4–30.4] | 0.03    | −0.36 [−1.50 to 0.78]      | 0.53             |
| Arterial elastance    | 1.54 [1.37–1.96] | 1.54 [1.36–1.76] | 0.39    | 0.06 [−0.06 to 0.19]       | 0.30             |
| End-systolic elastance| 1.33 [1.13–1.68] | 1.34 [1.14–1.60] | 0.73    | 0.01 [−0.12 to 0.15]       | 0.85             |
| Ea/Ees                | 1.14 [1.07–1.27] | 1.15 [1.09–1.22] | 0.46    | 0.06 [0.00–0.12]           | 0.049            |
| LV filling rate, mL/ms | 389 [311–487] | 414 [324–506]  | 0.33    | −11 [−58 to 36]            | 0.66             |

Data are expressed as median [25th–75th percentile] or percentage. CRP indicates C-reactive protein; DAS28-CRP, disease activity score based on 28 joint count and C-reactive protein; Ea/Ees, ventricular-vascular coupling; ECV, extracellular volume; LV, left ventricular; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LSVS, left ventricular stroke volume; MRI, magnetic resonance imaging; and RA, rheumatoid arthritis.
Second, among patients with RA, we found that greater inflammation, measured by CRP levels, was associated with increased risk for the development of HF, which was also independent of traditional cardiovascular risk factors. We did not find ESR to be predictive of HF risk when CRP levels were known. In contrast, the Swedish study found both CRP and ESR to be significantly associated with an increased risk of HF among patients with RA, but the only variables included in their adjusted models were age and sex, such that ESR, CRP, and traditional cardiovascular risk factors were not included in the same model.10

Nevertheless, that higher levels of inflammatory markers are associated with increased HF risk is further supported by evidence from the Mayo Clinic. Maradit-Kremers and colleagues26 demonstrated among patients with RA that the risk of HF was greatest within 6 months of ESR ≥40 mm/h. Taken together, the findings across these studies support a positive association between circulating measures of inflammation and HF risk. Moreover, as we were able to stratify by HF subtype in our analyses, we found that CRP levels may account for a greater proportion of the model for HFpEF compared with HFrEF, suggesting that inflammation may be a relatively greater contributor to HFpEF than HFrEF.

Third, we found that among patients with RA the anti-inflammatory medications methotrexate and corticosteroids were associated with lower risk for HFpEF and HFrEF, respectively. Our results for methotrexate are congruent with those found by Bernatsky and colleagues27 in a study of nearly 42 000 patients with RA in Canada. Although our medication results are not from a randomized clinical trial, the concept that anti-inflammatory medications may mitigate the risk of HF, even in the absence of chronic rheumatologic conditions, is supported by evidence from a secondary analysis of CANTOS (Canakinumab Antiinflammatory Thrombosis Outcome Study). Interleukin-1β inhibition with the highest tested dose of canakinumab (300 mg subcutaneous every 3 months) trended toward a 24% lower risk of HF hospitalization (HR, 0.76; 95% CI, 0.57–1.01) among patients with prior myocardial infarction and evidence of chronic inflammation based on a CRP of ≥2 mg/L.28 The more recent CIRT (Cardiovascular Inflammation Reduction Trial), which tested methotrexate compared with placebo for the reduction of atherosclerotic cardiovascular and cerebrovascular events among patients with prior myocardial infarction or multivessel coronary artery disease plus either diabetes mellitus or metabolic syndrome, was negative for its primary atherosclerotic end point but demonstrated a point estimate that favored reduction in HF hospitalizations (HR, 0.89; 95% CI, 0.60–1.31).29 In CIRT, HF events were not stratified by preserved versus reduced LVEF, but our findings suggest that methotrexate may be particularly associated with lower risk for HFpEF. In contrast, corticosteroids may be associated with lower risk for HFrEF among patients with RA. Other anti-inflammatory medications, such as nonbiologic DMARDs, anti–tumor necrosis factor, and other biologic and small molecular DMARDs were not significantly associated with the risk of HF. Antimalarials, such as hydroxychloroquine, however, were significantly associated with increased risk for HFpEF but not HFrEF.

Table 8. Inflammation-Related Proteins That Significantly Differ in Circulating Levels Between Patients With and Without RA

| Protein       | β (95% CI) for RA | Adjusted P Value |
|---------------|------------------|------------------|
| EN-RAGE       | 0.736 (0.369–1.103) | <0.001          |
| CDCP1 (CD219) | 0.466 (0.213–0.718) | <0.001          |
| IL-6          | 0.711 (0.251–1.172) | 0.003           |
| TNFB          | 0.524 (0.183–0.866) | 0.003           |
| MCP-3         | 0.398 (0.120–0.676) | 0.005           |
| LIF-R         | 0.167 (0.047–0.288) | 0.007           |
| IL-4          | 0.103 (0.027–0.179) | 0.008           |
| ARTN          | 0.094 (0.024–0.164) | 0.009           |
| IL-12B        | 0.309 (0.074–0.544) | 0.010           |
| HGF           | 0.211 (0.048–0.375) | 0.012           |
| TNF           | 0.159 (0.034–0.284) | 0.014           |
| uPA           | 0.192 (0.040–0.344) | 0.014           |
| β-NGF         | 0.184 (0.036–0.332) | 0.016           |
| MCP-1         | 0.272 (0.050–0.494) | 0.017           |
| IL-18         | 0.331 (0.053–0.609) | 0.020           |
| CASP-8        | 0.275 (0.043–0.506) | 0.020           |
| CD5           | 0.145 (0.014–0.276) | 0.031           |
| SLAMF1        | 0.253 (0.022–0.483) | 0.032           |
| IL-18R1       | 0.191 (0.016–0.367) | 0.033           |
| CD244 (slamf4) | 0.153 (0.010–0.296) | 0.037           |
| CD40          | 0.174 (0.009–0.339) | 0.039           |
| CSF1          | 0.108 (0.004–0.212) | 0.042           |
| IL-8          | 0.271 (0.003–0.538) | 0.047           |
| CCL23         | 0.184 (0.001–0.368) | 0.049           |

Model: dependent variable=protein; independent variable=rheumatoid arthritis (RA) vs control; covariates=age, sex, body mass index, heart rate, systolic blood pressure, estimated glomerular filtration rate. ARTN indicates Artemin; β-NGF, Beta-nerve growth factor; CASP-8, Caspase-8; CCL23, C-C motif chemokine 23; CDCP1, CUB domain-containing protein 1; CD5, T-cell surface glycoprotein CD5; CD244, Natural killer cell receptor 2B4; CD40, CD40L receptor; CSF1, Macrophage colony-stimulating factor 1; EN-RAGE, Protein S100-A12; HGF, Hepatocyte growth factor; IL-18R1, Interleukin-18 receptor 1; IL-8, Interleukin-8; IL-6, Interleukin-6; IL-18, Interleukin-18; IL-12B, Interleukin-12 subunit beta; LIF-R, Leukemia inhibitory factor receptor; MCP-1, Monocyte chemotactic protein 1; MCP-3, Monocyte chemotactic protein 3; SLAMF1, Signaling lymphocytic activation molecule; TNF, Tumor necrosis factor; TNFB, TNF-beta; uPA, Urokinase-type plasminogen activator.
Cardiotoxicity associated with antimalarial use has been previously reported in case reports and was reviewed by Chatre and colleagues. Collectively, the body of literature suggests that specific anti-inflammatory therapies may differentially affect the risk of HFrEF or HFpEF, the mechanisms for which warrant further investigation.

Fourth, in the exploratory proteomic-cMRI analysis, we sought to identify candidate proteins that may relate to both inflammation and adverse cardiac structure and function. We found that circulating levels of artemin were higher in patients with RA compared with controls. Artemin is a protein in the family of glial cell–derived neurotrophic factors that is expressed by vascular, including coronary, smooth muscle cells, and guides axonal growth along vessels. To our knowledge, artemin levels have not been previously reported in patients with RA. However, artemin is regulated by miR-223, which has been implicated in RA disease pathogenesis and severity by our group and others. We found that higher levels of artemin associated with higher (worse) ventricular-vascular coupling ratio, while others have demonstrated that higher ventricular-vascular coupling ratio is associated with increased risk for the development of HF.

### Table 9. Inflammation-Related Proteins Whose Circulating Levels Significantly Associated With Features of Cardiac Structure and Function Ascertained by Cardiac MRI Among Patients With RA and Controls

| Protein | LVEF | LV Mass | ECV | Ea | Ees | Ea/Ees | LV Diastolic Fill Rate |
|---------|------|---------|-----|----|-----|--------|-----------------------|
| ARTN    |      |         |     |    |     |        |                       |
| TGF-α   |      |         |     |    |     |        |                       |
| β-ngf   |      |         |     |    |     |        |                       |
| FGF23   |      |         |     |    |     |        |                       |
| MMP-1   |      |         |     |    |     |        |                       |
| CXCL1   |      |         |     |    |     |        |                       |
| TRAIL   |      |         |     |    |     |        |                       |
| IL-5    |      |         |     |    |     |        |                       |
| CXCL11  |      |         |     |    |     |        |                       |
| IL10−Rb |      |         |     |    |     |        |                       |
| ADA     |      |         |     |    |     |        |                       |

Data are shown as β coefficient (95% CI) and P value. Model: dependent variable=cardiac structure and function; independent variable=protein; covariates=age, sex, body mass index, systolic blood pressure, heart rate, estimated glomerular filtration rate. Ea indicates arterial elastance; Ea/Ees, ventricular vascular coupling ratio; ECV, extracellular volume; Ees, end-systolic elastance; LV, left ventricular; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; and RA, rheumatoid arthritis. ADA indicates Adenosine Deaminase; ARTN, Artemin; b-NGF, Beta-nerve growth factor; CXCL1, C-X-C motif chemokine 1; CXCL11, C-X-C motif chemokine 11; FGF-23, Fibroblast growth factor 23; IL-5, Interleukin-5; IL-10RB, Interleukin-10 receptor subunit beta; MMP-1, Matrix metalloproteinase-1; OSM, Oncostatin-M; TGF-α, Transforming growth factor alpha; TRAIL, TNF-related apoptosis-inducing ligand.
studies support a potential role for artemin in cardiovascular disease. First, artemin levels were higher in heart transplant patients with coronary artery graft vasculopathy compared with transplant patients without coronary artery graft vasculopathy. Immunologic mechanisms are implicated in the pathogenesis of coronary artery graft vasculopathy with the hallmark being intimal fibrous hyperplasia, which is a histologic finding in rheumatoid-associated vasculopathy as well. Second, artemin levels were found to be higher in patients with HFpEF compared with nonhypertensive and healthy controls. Our results, in concert with existing literature, may suggest that artemin could be a promising circulating biomarker for cardiovascular risk and HF, although future validation studies are needed.
STUDY LIMITATIONS

Limitations of our study should be noted. Our analysis used EHR data from a single tertiary care academic medical center, which may limit generalizability. That said, our results were similar to findings from the Mayo Clinic and national registries from Denmark and Sweden. RA and HF were ascertained from ICD-9 codes and medications, which may have led to misclassification bias. However, we utilized algorithms that have previously been validated and performed manual chart adjudication in our cohort for both RA and HF and found high positive predictive values, supporting the validity of our approach. Ascertainment of incident HF may be underestimated as a result of diagnosis and management outside of VUMC. Although we adjusted for prevalent coronary artery disease, atrial fibrillation, and traditional cardiovascular risk factors, residual confounding may be present. We were unable to fully account for variability in clinical care leading up to and following RA and HF diagnosis. For instance, the reasons underlying a provider’s choice of antirheumatic medications or to measure ESR or CRP could not be ascertained. We recognize that the results regarding the associations between antirheumatic medication and HF risk may be confounded and do not substitute for randomized clinical trials. While we studied patients with RA through the EHR and in a prospective cohort as a model to better understand how chronic inflammation may relate to HF risk, we acknowledge that the pathogenesis of inflammation-related HF in RA may differ from that of HF in patients without RA and by HFpEF or HFrEF. Nevertheless, pathophysiologic insights garnered through use of RA may help inform studies in patients with evidence of chronic inflammation, eg, elevated CRP, even in the absence of rheumatologic conditions, analogous to that of CANTOS and CIRT. Finally, we acknowledge that our proteomic results were exploratory and require further validation. That said, we were reassured by the results for several proteins, such as S100A12, hepatocyte growth factor, and interleukin-6, which effectively served as positive controls given their well-established roles in RA.

CONCLUSIONS

We found that RA, a prototypic chronic inflammatory condition, is associated with an increased risk of HF. Among patients with RA, higher levels of CRP were associated with greater HF risk, while methotrexate was associated with lower risk, particularly for patients with HFpEF.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Materials

Tables S1–S2

Reference 24

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SUPPLEMENTAL MATERIAL
| Table S1. Proteins assayed using Olink Inflammation panel.\textsuperscript{24} |
|---------------------------------|-----------------|-----------------|
| Adenosine Deaminase (ADA)      | P00813          | Frms-related tyrosine kinase 3 ligand (FliKL) | P49771 |
| Arterin (ARTN)                 | Q9T4W7          | Fractalkine (CX3CL1) | P78423 |
| Axin-1 (AXIN1)                 | Q15169          | Glial cell line-derived neurotrophic factor (GDNF) | P39505 |
| Beta-nerve growth factor (BFGF) | P01138          | Hepatocyte growth factor (HGF) | P14210 |
| Note: New assay under development | N/A            | Interferon gamma (IFN-gamma) | P01579 |
| Caspase-6 (CASP-8)             | Q14790          | Interleukin-1 alpha (IL-1 alpha) | P01583 |
| C-C motif chemokine 3 (CCL3)   | P10147          | Interleukin-2 (IL-2) | P60568 |
| C-C motif chemokine 4 (CCL4)   | P13226          | Interleukin-2 receptor subunit beta (IL-2RB) | P14794 |
| C-C motif chemokine 19 (CCL19) | Q97311          | Interleukin-4 (IL-4) | P06112 |
| C-C motif chemokine 20 (CCL20) | P78566          | Interleukin-5 (IL5) | P06113 |
| C-C motif chemokine 23 (CCL23) | P52773          | Interleukin-6 (IL6) | P06231 |
| C-C motif chemokine 25 (CCL25) | Q15444          | Interleukin-7 (IL-7) | P13232 |
| C-C motif chemokine 28 (CCL28) | Q09R33          | Interleukin-8 (IL-8) | P10145 |
| CD40 receptor (CD40)           | P2S942          | Interleukin-10 (IL10) | P22301 |
| CUB domain-containing protein 1 (CDCP1) | Q8HEV9 | Interleukin-10 receptor subunit alpha (IL-10RA) | Q13651 |
| C-X-C motif chemokine 1 (CXCL1) | P99341          | Interleukin-10 receptor subunit beta (IL-10RB) | Q08334 |
| C-X-C motif chemokine 5 (CXCL5) | P42330          | Interleukin-12 subunit beta (IL-12B) | P29460 |
| C-X-C motif chemokine 6 (CXCL6) | P80162          | Interleukin-13 (IL-13) | P38226 |
| C-X-C motif chemokine 9 (CXCL9) | Q07325          | Interleukin-15 receptor subunit alpha (IL-15RA) | Q13261 |
| C-X-C motif chemokine 10 (CXCL10) | P02778         | Interleukin-17A (IL-17A) | Q16552 |
| C-X-C motif chemokine 11 (CXCL11) | Q14625          | Interleukin-17C (IL-17C) | Q9PM4 |
| Cystatin D (CST5)              | P28325          | Interleukin-18 (IL-18) | Q14116 |
| Delta and Notch-like epidermal growth factor-related receptor (ONER) | Q8NFT8 | Interleukin-18 receptor 1 (IL-18R1) | Q13478 |
| Eotaxin (CCL11)                | P51671          | Interleukin-20 (IL-20) | Q9NYY1 |
| Eukaryotic translation initiation factor 4E-binding protein 1 (eIF-4E) | Q13541          | Interleukin-20 receptor subunit alpha (IL-20RA) | Q9UHF4 |
| Fibroblast growth factor 21 (FGF-21) | Q9NSA1      | Interleukin-22 receptor subunit alpha-1 (IL-22 RA1) | Q8NSF7 |
| Fibroblast growth factor 23 (FGF-23) | Q9GZV9        | Interleukin-24 (IL-24) | Q13007 |
| Fibroblast growth factor 5 (FGF-5) | Q9NF90        | Interleukin-33 (IL-33) | Q95760 |
| Fibroblast growth factor 19 (FGF-19) | Q95750        | Latency-associated peptide transforming growth factor beta-1 (LAP TGF-beta-1) | P01137 |
| Protein Name                                      | UniProt ID | Description                                   | ID   |
|--------------------------------------------------|------------|-----------------------------------------------|------|
| Leukemia inhibitory factor (ILF)                 | P16018     | SIR2-like protein 2 (SIRT2)                  | Q58J6|
| Leukemia inhibitory factor receptor (ILF-R)      | P42702     | STAM-binding protein (STAMBP)                 | O56030|
| Macrophage colony-stimulating factor 1 (CSF-1)   | P09603     | Stem cell factor (SCF)                        | P21563|
| Matrix metalloproteinase-1 (MMP-1)               | P09566     | Sulfotransferase 1A1 (ST1A1)                 | P50225|
| Matrix metalloproteinase-10 (MMP-10)             | P09238     | T cell surface glycoprotein CD6 isoform (CD6) | Q6WWJ7|
| Monocyte chemotactic protein 1 (MCP-1)           | P13500     | T-cell surface glycoprotein CD6 (CD6)         | P06127|
| Monocyte chemotactic protein 2 (MCP-2)           | P60075     | Thymic stromal lymphopoietin (TSLP)           | Q96ED8|
| Monocyte chemotactic protein 3 (MCP-3)           | P90098     | TNF-beta (TNFβ)                              | P01374|
| Monocyte chemotactic protein 4 (MCP-4)           | Q99616     | TNF-related activation-induced cytokine (TRANCE) | O14788|
| Natural killer cell receptor 2B4 (CD244)         | Q992W8     | TNF-related apoptosis-inducing ligand (TRAIL) | P56561|
| Neurotrophin-3 (NT-3)                            | P20783     | Transforming growth factor alpha (TGF-alpha)  | P01135|
| Neurturin (NRTN)                                 | Q09746     | Tumor necrosis factor (Ligand) superfamily, member 12 (TWEAK) | O43508|
| Oncostatin-M (OSM)                               | P13725     | Tumor necrosis factor (TNF)                   | P01375|
| Osteoprotegerin (OPQ)                            | O00200     | Tumor necrosis factor ligand superfamily member 14 (TNF-14) | Q43557|
| Programmed cell death ligand 1 (PD-L1)           | Q6NZQ7     | Tumor necrosis factor receptor superfamily member 9 (TNFRSF9) | Q07011|
| Protein S100-A12 (EN-RAGE)                       | P80511     | Urokinase-type plasminogen activator (uPA)    | P00749|
| Signaling lymphocytic activation molecule (SLAMF1)| Q13201     | Vascular endothelial growth factor A (VEGF-A) | P15802|
Table S2. Characteristics of rheumatoid arthritis patients in whom C-reactive protein and erythrocyte sedimentation rate were clinically measured and extracted from the electronic health record.

| Characteristics                                      | Included      | Excluded     | Unadjusted p value |
|------------------------------------------------------|---------------|--------------|--------------------|
|                                                      | N = 6,161     | N = 3,728    |                    |
| Age                                                  | 54 [45, 64]   | 59 [49, 68]  | < 0.001            |
| Female                                               | 77            | 74           | < 0.001            |
| White                                                | 86            | 82           | < 0.001            |
| Baseline year                                        | 2008 [2004, 2012] | 2007 [2002, 2011] | < 0.001 |
| Coronary artery Disease                              | 3             | 4            | 0.14               |
| Atrial fibrillation                                  | 2             | 1            | 0.73               |
| Hypertension                                         | 66            | 73           | < 0.001            |
| Dyslipidemia                                         | 25            | 23           | 0.002              |
| Chronic Kidney Disease                               | 1             | 1            | 0.58               |
| Diabetes mellitus                                    | 11            | 11           | 0.57               |
| Body mass index, kg/m2                               | 28 [24, 33]   | 28 [24, 33]  | 0.012              |
| Heart rate, bpm                                      | 78 [71, 86]   | 78 [71, 86]  | 0.67               |
| Pulse pressure, mm Hg                                | 50 [40, 60]   | 52 [42, 62]  | < 0.001            |
| Creatinine, mg/dL                                    | 0.81 [0.70, 0.97] | 0.84 [0.70, 1.01] | < 0.001 |
| Statin use                                           | 20            | 19           | 0.16               |
| Anti-platelet use                                    | 18            | 16           | 0.024              |
| Anti-hypertensive use                                | 55            | 53           | 0.14               |
| Ever use of Med before HF                            |               |              |                    |
| Methotrexate                                         | 73            | 64           | < 0.001            |
| Non-biologic DMARD                                    | 45            | 29           | < 0.001            |
| Anti-TNF                                             | 52            | 31           | < 0.001            |
| Systemic Corticosteroid                              | 92            | 85           | < 0.001            |
| Other biologic/sm DMARD                              | 22            | 8            | < 0.001            |
| Antimalarial                                         | 44            | 38           | < 0.001            |
| ESR, mm/hr                                           | 20 [9, 39]    | n/a          | n/a                |
| CRP, mg/L                                            | 4.7 [1.5, 14.2] | n/a         | n/a                |

Summary statistics presented as percent or median [25th, 75th percentile]. Baseline (entry) defined as date of RA diagnosis. Rheumatologic medications use was defined as ever before HF diagnosis or end of follow-up, as appropriate.