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ORIGINAL RESEARCH

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.[1] 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.[3,4] 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

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CLINICAL PERSPECTIVE

What Is New?

- In a large contemporary clinical cohort, patients with rheumatoid arthritis had greater risk for heart failure, most commonly with preserved ejection fraction, which was independent of traditional cardiovascular risk factors and coronary artery disease.
- Among patients with rheumatoid arthritis, higher C-reactive protein was associated with greater heart failure risk, while methotrexate use was associated with lower risk.
- Circulating artemin level may be a novel biomarker related to both rheumatoid arthritis and adverse cardiac function.

What Are the Clinical Implications?

- Patients and providers should appreciate the association between chronic inflammation and increased heart failure risk.
- Whether anti-inflammatory medications such as methotrexate may reduce the risk of heart failure among patients with chronic inflammation warrants further investigation.

Nonstandard Abbreviations and Acronyms

CANTOS	Canakinumab Antiinflammatory Thrombosis Outcome Study
CIRT	Cardiovascular Inflammation Reduction Trial
cMRI	cardiac magnetic resonance imaging
CRP	C-reactive protein
CTSA	Clinical and Translational Science Awards
DMARD	disease-modifying antirheumatic drug
Ea/Ees	ventricular vascular coupling ratio
Ea	end-arterial elastance
Ees	end-systolic elastance
EF	ejection fraction
EHR	electronic health record
ESR	erythrocyte sedimentation rate
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
ICD-9	*International Classification of Diseases, Ninth Revision*
LV	left ventricular
LVEF	left ventricular ejection fraction
MRI	magnetic resonance imaging
OR	odds ratio
RA	rheumatoid arthritis
SV	stroke volume
VUMC	Vanderbilt University Medical Center

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

University's institutional review board approved this study as nonhuman research given the use of deidentified data.

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 anti-cyclic 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 anti-cyclic 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

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 Ever 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, Zaroxolyn)
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: I25.1* OR ≥1 CPT code: 33534–33536, 33510–33523, 92980–92982, 92984, 92995, 92996
Hypertension	≥1 *ICD* code: 401.*–405.* OR ≥1 *ICD*-10 code: I10.*–I13.*, I16.* OR Use of an antihypertensive medication OR Systolic blood pressure ≥140 mm Hg OR Diastolic blood pressure ≥90 mm Hg
Diabetes mellitus	≥1 *ICD* code: *ICD-9*: 250.*, V58.67, *ICD-10*: Z79.4, Z79.84, E08, E08.x, E09, E09.x, E10, 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 fib","atrial-fib","atrial fib","a flutter","atrial flutter","atrial-flutter" in the Problem List "afib," "a fib," "atrial-fib," "atrial fib," "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," "altocor," "pravastatin," "pravachol," "rosuvastatin," "crestor," "simvastatin," "zocor," "cholestyramine," "prevalite," "colestopil," "colestid," "colesevelam," "welchol," "niacin," "niacor," "Niaspan," "gemfibrozil," "lopid," "fenofibrate," "tricor," "fibrocor," "bezafibrate," "bezalip," "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.

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 fomulas:[22,23]

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

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).

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

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, atlizumab, tofacitinib, anakinra
Systemic corticosteroid	Cortisone acetate, hydrocortisone, prednisone, dexamethasone, prednisolone, methylprednisolone, triamcinolone acetonide
Antimalarial	Hydroxychloroquine, chloroquine, quinacrine
Additional RA medications	Minocycline, cyclosporine, gold, sodium aurothiomalate, auranofin, aurothioglucose, penicillamine

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

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

$$\begin{aligned}\text{End(avg)} = {} & 0.35695 - (7.2266 \times \text{Tnd}) + (74.249 \times (\text{Tnd}^2)) \\ & - (307.39 \times (\text{Tnd}^3)) + (684.54 \times (\text{Tnd}^4)) \\ & - (856.92 \times (\text{Tnd}^5)) + (571.95 \times (\text{Tnd}^6)) \\ & - (159.1 \times (\text{Tnd}^7))\end{aligned}$$

$$\text{Tnd} = \text{PEP1}/\text{QS2}$$

$$\begin{aligned}\text{PEP1} = {} & -0.0004 \times \text{Heart rate at MRI} + 0.131 \text{ for males} \\ & -0.0004 \times \text{Heart rate at MRI} + 0.133 \text{ for females}\end{aligned}$$

$$\begin{aligned}\text{QS2} = {} & -0.0021 \times \text{Heart rate at MRI} + 0.546 \text{ for males} \\ & -0.0021 \times \text{Heart rate at MRI} + 0.549 \text{ for females}\end{aligned}$$

Ps, mm Hg=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

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/m^2	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.

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]).

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*	5.9 [2.6–9.9]	10.7 [8.0–13.9]	<0.001
Follow-up time, person-y	66 295.6	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)†	1.28 (1.10–1.48)	Reference	0.001
Model 2 (sex, race, age)†	1.79 (1.53–2.09)	Reference	<0.001
Model 3 (all covariates in Table 3)†	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.

*From baseline to HF or last medical encounter at Vanderbilt University Medical Center, reported as median years [25th–75th percentile].

†Cox regression (covariates included in model) presented as hazard ratios (95% CIs).

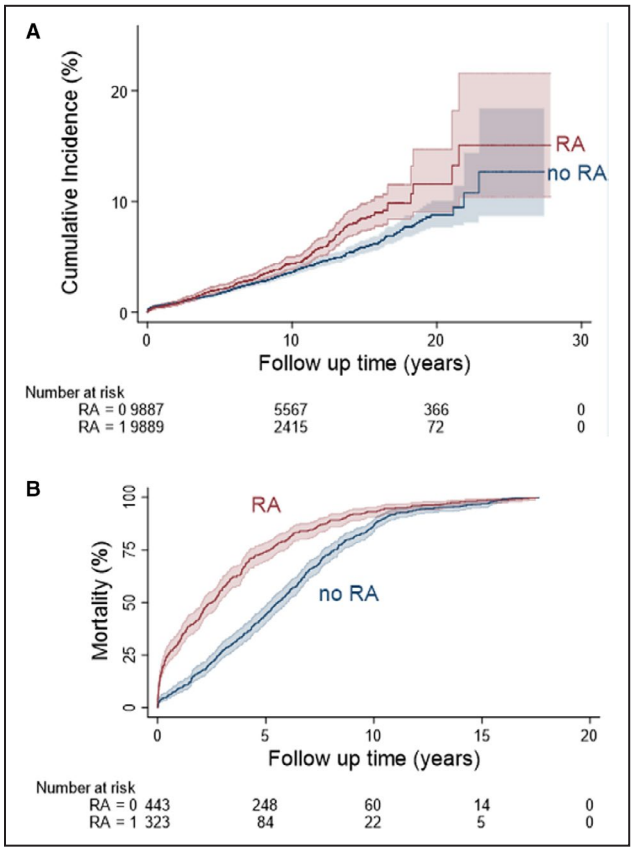

Figure 1. Cumulative incidence of (A) and cumulative mortality following (B) incident heart failure (HF) among patients with and without rheumatoid arthritis (RA).
A, Cumulative incidence of HF in patients with and without RA. **B**, Cumulative mortality following incident HF among patients with and without RA.

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). Antirheumatic 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,

Table 5. Factors Associated With the Risk of Incident HF Among Patients With RA

	No HF (n=9566)	Incident HF (n=323)	Unadjusted *P* Value	Adjusted OR (95% CI)	Adjusted *P* Value
Baseline at RA diagnosis					
Age, y	56 [46–66]	63 [54–71]	<0.001	1.47 (1.26–1.71)	<0.001
Women	76	72	0.11	0.94 (0.72–1.23)	0.65
White	84	84	0.76	1.08 (0.78–1.48)	0.65
Baseline y	2008 [2004–2012]	2004 [2000–2008]	<0.001	0.44 (0.39–0.50)	<0.001
Coronary artery disease	3	16	<0.001	3.19 (2.16–4.72)	<0.001
Atrial fibrillation	1	6	<0.001	2.45 (1.41–4.27)	0.002
Hypertension	68	83	<0.001	0.58 (0.38–0.90)	0.014
Dyslipidemia	24	36	<0.001	2.16 (1.44–3.24)	<0.001
Chronic kidney disease	1	5	<0.001	2.23 (1.14–4.37)	0.019
Diabetes mellitus	11	21	<0.001	1.57 (1.15–2.16)	0.005
Body mass index, kg/m^2	28 [24–33]	29 [25–35]	0.024	1.20 (1.06–1.35)	0.004
Heart rate, beats per min	78 [71–86]	80 [72–88]	0.020	1.21 (1.09–1.35)	<0.001
Pulse pressure, mm Hg	50 [40–60]	57 [46–70]	<0.001	1.27 (1.13–1.42)	<0.001
Creatinine, mg/dL	0.81 [0.70–0.99]	0.90 [0.77–1.20]	<0.001	1.10 (1.03–1.18)	0.004
Statin use	19	26	0.002	0.58 (0.37–0.88)	0.011
Antiplatelet use	17	26	<0.001	1.04 (0.75–1.44)	0.81
Antihypertensive use	54	67	<0.001	2.14 (1.45–3.17)	<0.001
Ever use of medication before HF					
Methotrexate	70	56	<0.001	0.75 (0.59–0.96)	0.021
Nonbiologic DMARD	39	37	0.56	1.02 (0.79–1.31)	0.89
Anti-TNF	45	28	<0.001	0.83 (0.62–1.09)	0.18
Systemic corticosteroid	89	86	0.084	0.76 (0.54–1.08)	0.13
Other biologic/small molecule DMARD	17	9	<0.001	0.89 (0.59–1.35)	0.59
Antimalarial	42	41	0.82	1.15 (0.91–1.47)	0.25

Summary statistics are presented as percentage or median [25th–75th percentile]. Baseline (entry) is defined as date of rheumatoid arthritis (RA) diagnosis. Rheumatologic medications use was defined as ever before heart failure (HF) diagnosis or end of follow-up, as appropriate. Multivariable logistic regression model included all covariates listed in table. DMARD indicates disease-modifying antirheumatic drug; OR, odds ratio; and TNF, tumor necrosis factor.

such as higher body mass index, diabetes mellitus, and chronic kidney disease were more strongly associated with HFpEF, although 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, 2.38–8.97; *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 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.[21] 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 (β=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).

Table 6. Factors Associated With the Risk of HF With Preserved or HF With Reduced LVEF Among Patients With RA

	No HF	HFpEF			HFrEF		
	n=9566	n=162	Percent of Model Explained	OR (95% CI) for HFpEF vs No HF	n=91	Percent of Model Explained	OR (95% CI) for HFrEF vs No HF
Age, y	56 [46–66]	63 [55–71]	8.1	1.54 (1.28–1.85)	61 [52–71]	2.9	1.29 (1.04–1.59)
Women	76	74	0	1.02 (0.74–1.41)	69	0.2	0.89 (0.61–1.28)
White	84	85	0.9	1.37 (0.92–2.04)	79	0.2	0.96 (0.62 –1.50)
Baseline year	2008 [2004–2012]	2005 [2000–2009]	38.8	0.46 (0.39–0.53)	2003 [2000–2007]	51.9	0.38 (0.32–0.46)
Coronary artery disease	3	18	12.0	3.53 (2.26–5.53)	13	4.6	2.31 (1.33–4.00)
Atrial fibrillation	1	4	0.5	1.51 (0.73–3.14)	10	10.6	4.62 (2.38–8.97)
Hypertension	68	83	2.6	0.50 (0.30–0.85)	84	0.4	0.76 (0.42–1.37)
Dyslipidemia	24	33	0.9	1.49 (0.89–2.49)	44	8.3	3.04 (1.76–5.26)
Chronic kidney disease	1	5	1.8	2.29 (1.06–4.93)	3	1.2	2.10 (0.81–5.42)
Diabetes mellitus	10	24	2.7	1.64 (1.13–2.37)	19	0.6	1.30 (0.82–2.05)
Body mass index, kg/m^2	28 [24–33]	30 [25–36]	5.2	1.28 (1.12–1.47)	27 [24–33]	0.5	1.09 (0.91–1.30)
Heart rate, beats per min	78 [71–86]	80 [72–90]	1.9	1.16 (1.02–1.31)	80 [72–88]	0	1.00 (0.86–1.18)
Pulse pressure, mm Hg	50 [40–60]	56 [48–74]	7.2	1.34 (1.17–1.53)	54 [40–66]	2.2	1.18 (1.01–1.38)
Creatinine, mg/dL	0.81 [0.70–0.99]	0.86 [0.73–1.18]	0.8	1.06 (0.98–1.15)	0.90 [0.80–1.20]	2.4	1.09 (1.01–1.18)
Statin use	19	25	0.7	0.70 (0.41–1.20)	27	1.9	0.57 (0.32–1.00)
Antiplatelet use	17	26	0	1.00 (0.68–1.48)	25	0.4	1.23 (0.78–1.94)
Antihypertensive use	54	70	4.5	2.24 (1.40–3.56)	65	1.4	1.57 (0.92–2.69)
Ever use of medication before HF							
Methotrexate	70	54	1.7	0.64 (0.55–0.98)	57	0.1	0.93 (0.66–1.31)
Nonbiologic DMARD	39	34	0.4	0.85 (0.63–1.16)	45	0.8	1.25 (0.88–1.77)
Anti-TNF	45	26	0.8	0.78 (0.56–1.09)	31	0.1	0.93 (0.64–1.37)
Systemic corticosteroid	89	90	0	0.99 (0.64–1.54)	79	4.3	0.53 (0.34–0.81)
Other biologic/small molecule DMARD	17	12	0	1.03 (0.65–1.65)	7	1.1	0.62 (0.32–1.19)
Antimalarial	42	46	2.3	1.42 (1.07–1.88)	34	0.1	0.93 (0.66–1.31)
ESR, mm/h	20 [9–38]	34 [18–53]	0.4	1.08 (0.93–1.25)	35 [18–67]	1.3	1.15 (0.97–1.37)
CRP, mg/L	4.7 [1.5–14]	10.0 [2.2–74.3]	5.9	1.24 (1.11–1.38)	8 [1.7–45.7]	2.8	1.17 (1.03–1.33)

Summary statistics are presented as percentage or median [25th–75th percentile]. Baseline (entry) defined as date of rheumatoid arthritis (RA) diagnosis. Rheumatologic medication use was defined as ever before heart failure (HF) diagnosis or end of follow-up, as appropriate. Percentage of model explained was calculated as ratio of *F* statistic for each covariate within the multivariable-adjusted model to sum of *F* statistics for the entire model multiplied by 100. The multivariable-adjusted logistic regression model for HF with preserved ejection fraction (HFpEF) compared with no HF or HF with reduced ejection fraction (HFrEF) compared with no HF included all of the variables listed in the table. CRP indicates C-reactive protein; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; LVEF, left ventricular ejection fraction; OR, odds ratio; and TNF, tumor necrosis factor.

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

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/m^2	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/m^2	59 [47–67]	61 [55–66]	0.23	–0.52 [–4.87 to 3.84]	0.82
LVESV index, mL/m^2	18 [12–25]	21 [16–26]	0.055	–0.40 [–3.18 to 2.39]	0.78
LVSV index, mL/m^2	39 [36–43]	39 [36–43]	0.75	–0.39 [–2.91 to 2.13]	0.76
LV mass index, g/m^2	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; LVSV, left ventricular stroke volume; MRI, magnetic resonance imaging; and RA, rheumatoid arthritis.

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.[9,10] 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.[9,10] 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 8. Inflammation-Related Proteins That Significantly Differ in Circulating Levels Between Paients With and Without RA

Protein	β (95% CI) for RA	Adjusted *P* Value
EN-RAGE	0.736 (0.369–1.103)	<0.001
CDCP1 (CD218)	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; b-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-4, Interleukin-4; 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.

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 colleagues[26] 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 colleagues[27] 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 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	Cardiac Structure and Function						
	LVEF	LV Mass	ECV	Ea	Ees	Ea/Ees	LV Diastolic Fill Rate
OSM	3.0 (1.2–4.8) 0.001				0.09 (0.00–0.17) 0.048	−0.05 (−0.09 to −0.02) 0.005	−33 (−63 to −25) 0.034
TGF-α	8.0 (2.2–13.8) 0.008					−0.12 (−0.24 to 0.00) 0.042	
β-ngf	5.0 (1.2, 8.8) 0.011						
FGF23	3.3 (0.7–5.9) 0.013					−0.06 (−0.11 to 0.00) 0.034	
MMP-1			0.74 (0.22–1.27) 0.006				
CXCL-1			0.83 (0.02–1.65) 0.044				
ARTN					−0.39 (−0.78 to −0.01) 0.0440	0.18 (0.02–0.35) 0.031	
TRAIL						−0.09 (−0.17 to −0.02) 0.012	
IL-5						−0.03 (−0.06 to 0.00) 0.024	
CXCL-11							−38 (−65 to −11) 0.007
IL10-Rb							100 (23–176) 0.012
ADA							72 (16–127) 0.012

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, Interkeukin-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.

Cardiotoxicity associated with antimalarial use has been previously reported in case reports[30] and was reviewed by Chatre and colleagues.[31] Collectively, the body of literature suggests that specific anti-inflammatory therapies may differentially affect the risk of HFpEF or HFrEF, 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.[32] 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.[33,34] 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.[35] Two other

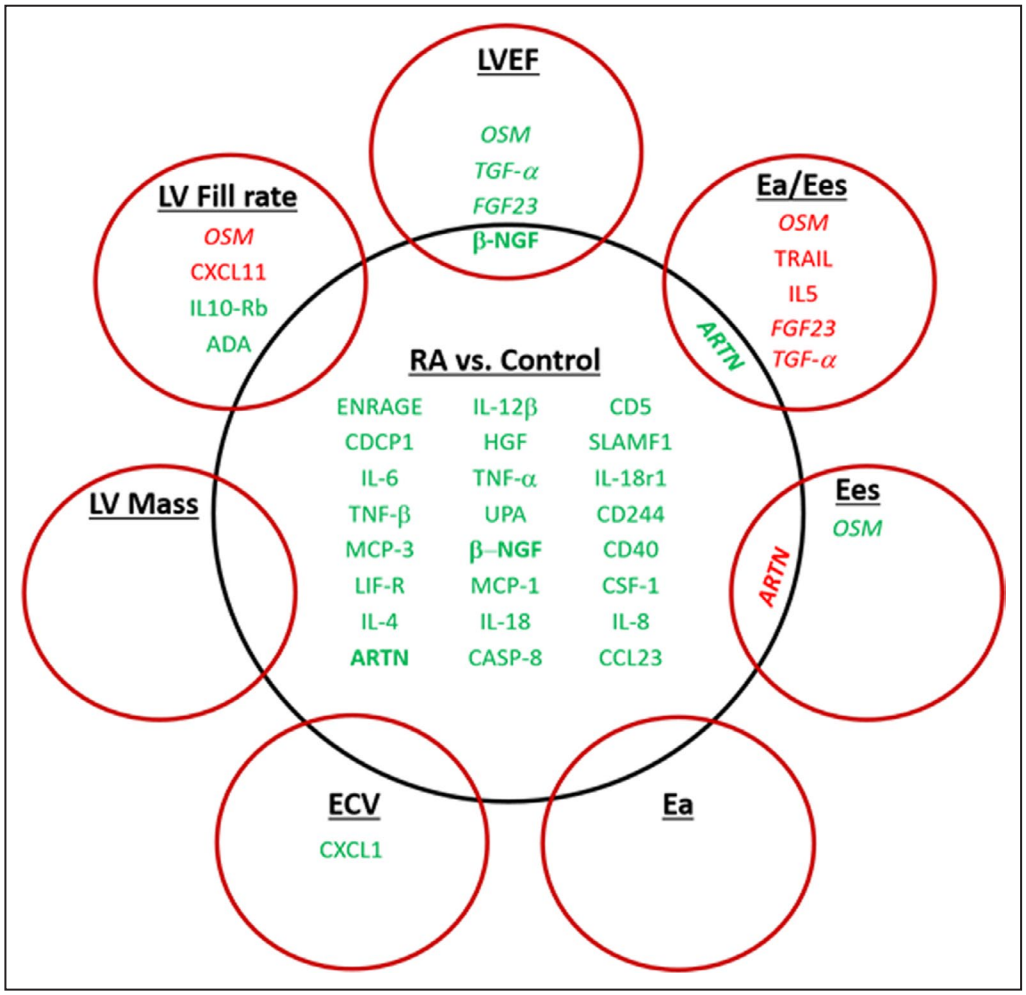

Figure 2. Inflammation-related proteins that were significantly associated with rheumatoid arthritis (RA) or cardiac structure and function.
Positive associations are shown in green. Negative associations are shown in red. Ea indicates arterial elastance; Ea/Ees, ventricular vascular coupling ratio; ECV, extracellular volume; Ees, end-systolic elastance; LV, left ventricular; LV fill rate, left ventricular diastolic filling rate; and LVEF, left ventricular ejection fraction. Summary statistics for associations are shown in Tables 8 and 9. ADA indicates Adenosine Deaminase; ARTN, Artemin; b-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; CXCL1, C-X-C motif chemokine 1; CXCL11, C-X-C motif chemokine 11; EN-RAGE, Protein S100-A12; FGF-23, Fibroblast growth factor 23; HGF, Hepatocyte growth factor; IL-5, Interkeukin-5; IL-18R1, Interleukin-18 receptor 1; IL-8, Interleukin-8; IL-4, Interleukin-4; IL-6, Interleukin-6; IL-10RB, Interleukin-10 receptor subunit beta; 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; MMP-1, Matrix metalloproteinase-1; OSM, Oncostatin-M; SLAMF1, Signaling lymphocytic activation molecule; TGF-α, Transforming growth factor alpha; TNF, Tumor necrosis factor; TNFB, TNF-beta; TRAIL, TNF-related apoptosis-inducing ligand; uPA, Urokinase-type plasminogen activator.

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 with°ut coronary graft vasculopathy.[36] 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.[37] 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.[6,9,10] 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.[16,18–20] 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.[38–43]

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.

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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.[24]

Adenosine Deaminase (ADA)	P00813	Fms-related tyrosine kinase 3 ligand (Flt3L)	P49771
Artemin (ARTN)	Q5T4W7	Fractalkine (CX3CL1)	P78423
Axin-1 (AXIN1)	O15169	Glial cell line-derived neurotrophic factor (GDNF)	P39905
Beta-nerve growth factor (Beta-NGF)	P01138	Hepatocyte growth factor (HGF)	P14210
Note: New assay under development	N/A	Interferon gamma (IFN-gamma)	P01579
Caspase-8 (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)	P13236	Interleukin-2 receptor subunit beta (IL-2RB)	P14784
C-C motif chemokine 19 (CCL19)	Q99731	Interleukin-4 (IL-4)	P05112
C-C motif chemokine 20 (CCL20)	P78556	Interleukin-5 (IL5)	P05113
C-C motif chemokine 23 (CCL23)	P55773	Interleukin-6 (IL6)	P05231
C-C motif chemokine 25 (CCL25)	O15444	Interleukin-7 (IL-7)	P13232
C-C motif chemokine 28 (CCL28)	Q9NRJ3	Interleukin-8 (IL-8)	P10145
CD40L receptor (CD40)	P25942	Interleukin-10 (IL10)	P22301
CUB domain-containing protein 1 (CDCP1)	Q9H5V8	Interleukin-10 receptor subunit alpha (IL-10RA)	Q13651
C-X-C motif chemokine 1 (CXCL1)	P09341	Interleukin-10 receptor subunit beta (IL-10RB)	Q08334
C-X-C motif chemokine 5 (CXCL5)	P42830	Interleukin-12 subunit beta (IL-12B)	P29460
C-X-C motif chemokine 6 (CXCL6)	P80162	Interleukin-13 (IL-13)	P35225
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)	O14625	Interleukin-17C (IL-17C)	Q9P0M4
Cystatin D (CST5)	P28325	Interleukin-18 (IL-18)	Q14116
Delta and Notch-like epidermal growth factor-related receptor (DNER)	Q8NFT8	Interleukin-18 receptor 1 (IL-18R1)	Q13478
Eotaxin (CCL11)	P51671	Interleukin-20 (IL-20)	Q9NYY1
Eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1)	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)	Q8N6P7
Fibroblast growth factor 23 (FGF-23)	Q9GZV9	Interleukin-24 (IL-24)	Q13007
Fibroblast growth factor 5 (FGF-5)	Q8NF90	Interleukin-33 (IL-33)	O95760
Fibroblast growth factor 19 (FGF-19)	O95750	Latency-associated peptide transforming growth factor beta-1 (LAP TGF-beta-1)	P01137

Leukemia inhibitory factor (LIF)	P15018	SIR2-like protein 2 (SIRT2)	Q8IXJ6
Leukemia inhibitory factor receptor (LIF-R)	P42702	STAM-binding protein (STAMBP)	O95630
Macrophage colony-stimulating factor 1 (CSF-1)	P09603	Stem cell factor (SCF)	P21583
Matrix metalloproteinase-1 (MMP-1)	P03956	Sulfotransferase 1A1 (ST1A1)	P50225
Matrix metalloproteinase-10 (MMP-10)	P09238	T cell surface glycoprotein CD6 isoform (CD6)	Q8WWJ7
Monocyte chemotactic protein 1 (MCP-1)	P13500	T-cell surface glycoprotein CD5 (CD5)	P06127
Monocyte chemotactic protein 2 (MCP-2)	P80075	Thymic stromal lymphopoietin (TSLP)	Q969D9
Monocyte chemotactic protein 3 (MCP-3)	P80098	TNF-beta (TNFB)	P01374
Monocyte chemotactic protein 4 (MCP-4)	Q99616	TNF-related activation-induced cytokine (TRANCE)	O14788
Natural killer cell receptor 2B4 (CD244)	Q9BZW8	TNF-related apoptosis-inducing ligand (TRAIL)	P50591
Neurotrophin-3 (NT-3)	P20783	Transforming growth factor alpha (TGF-alpha)	P01135
Neurturin (NRTN)	Q99748	Tumor necrosis factor (Ligand) superfamily, member 12 (TWEAK)	O43508
Oncostatin-M (OSM)	P13725	Tumor necrosis factor (TNF)	P01375
Osteoprotegerin (OPG)	O00300	Tumor necrosis factor ligand superfamily member 14 (TNFSF14)	O43557
Programmed cell death 1 ligand 1 (PD-L1)	Q9NZQ7	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)	Q13291	Vascular endothelial growth factor A (VEGF-A)	P15692

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.**

	Included N = 6,161	Excluded N = 3,728	Unadjusted p value
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 [25^{th}, 75^{th} 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.