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Impact of changes in inflammation on estimated 10-year cardiovascular risk in rheumatoid arthritis

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Abstract

Background—Validated cardiovascular (CV) risk estimates were developed in populations with relatively stable inflammatory levels. In rheumatoid arthritis (RA), patients routinely experience significant changes in inflammation. We tested whether changes in inflammation impact estimated CV risk as measured using validated population-based risk calculators.

Methods—We studied participants in a prospective RA cohort. We included participants who experienced a decrease (CRP decrease group) or increase (CRP increase group) of 10mg/L in C-reactive protein (CRP) at 2 consecutive time points, 1 year apart. We calculated 10-year CV risk using the following calculators: Framingham Risk Score, 2013 American College of Cardiology/American Heart Association Atherosclerotic Cardiovascular Disease Risk Score, Reynolds Risk Score (RRS), and QRISK2. Paired t-tests were performed to compare risk scores at baseline and 1-year follow-up among participants in the two groups. We calculated the correlations between the changes in risk scores with changes in pro B-type Natriuretic Peptide (pro-BNP), a surrogate marker of CV risk.

Results—We studied 180 RA participants with mean age 57.8 years, 85% female, 70% seropositive. Of the calculators studied, only RRS was sensitive to changes in inflammation; an increase of inflammation was associated with increased estimated CV risk ($p < 0.0001$). Only RRS was correlated with changes in pro-BNP ($r = 0.17$, $p = 0.03$).

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Conclusion—Our data found no significant change in CV risk estimates using validated general population CV risk calculators except for RRS. These data suggest that CV risk may be modulated by changes in inflammation in RA, not typically considered using existing CV risk calculators.

Cardiovascular (CV) risk calculators assist clinicians in estimating a patient's risk of a CV event. The majority of these risk estimates, such as Framingham Risk Score (FRS), 2013 American College of Cardiology/American Heart Association CV risk estimator (2013 ACC/AHA), Reynolds Risk Score (RRS), and QRISK2, were developed for the general population where inflammation tends to be stable. Inflammation is an independent risk factor for CV risk in the general population and has an even larger impact in rheumatoid arthritis (RA) where the magnitude of inflammation is higher (1–3). Prior studies using carotid intima media thickness as a marker for CV risk, have shown that both the magnitude and the exposure to elevated inflammation is associated with increased CV risk (4, 5). Additionally, in RA, the level of inflammation can vary as a result of flares and treatment changes. Previous studies have shown that a change in inflammation in RA corresponds to changes in traditional CV risk factors, such as lipids (6). It remains to be seen whether the changes associated with inflammation, such as the changes in lipids impact estimated CV risk when using validated CV risk calculators developed for the general population.

The objective of this study was to examine the impact of changes in inflammation in RA on estimated CV risk when using validated general population risk calculators. Since the true CV risk was not known, we used pro B-type Natriuretic Peptide (pro-BNP), as a surrogate marker of CV risk. Pro-BNP is a risk factor for increased CV risk in participants with and without established coronary artery disease (7).

METHODS

Study Population

We conducted this study in the Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study (BRASS) (8), a prospective observational cohort study. In BRASS, all participants were age 18 or older and had a rheumatologist diagnosis of RA. Participants in BRASS completed baseline assessment including demographics, lifestyle factors, medication use, CV risk factors, and CV events, and had annual visits for information update. High sensitivity C-reactive protein (CRP), a marker for inflammation, was measured on all participants annually. We included participants who experienced a decrease (CRP decrease group) or increase (CRP increase group) of 10mg/L in CRP at two consecutive time points, one year apart, and with blood samples available for analysis. Thus, we studied two time points for participants in each cohort, baseline, and follow-up at one year.

Biochemical Analysis

All biomarkers were measured at the Clinical Chemistry Laboratory at Children's Hospital in Boston. Plasma high sensitivity CRP was measured using a standard immunoturbidimetric assay on the Roche P Modular system (Roche Diagnostics, Indianapolis, IN) (9). Pro-BNP was measured using a quantitative sandwich enzyme immunoassay technique (Roche E Modular system, Roche Diagnostics, Indianapolis, IN). Total cholesterol (TC), high-density

lipoprotein cholesterol (HDL-C), and hemoglobin A1c (HbA1c) measurements were performed according to standardized methods (10, 11).

Other Variables

In the baseline and annual follow-up questionnaires of BRASS, information on age, gender, race, smoking status, medication use (including hypertension medications), and cardiovascular risk factors (including body mass index, CRP, blood cholesterol levels, history of chronic diseases such as diabetes, atrial fibrillation, chronic kidney disease, and rheumatoid arthritis, and family history of premature myocardial infarction) were collected. Blood pressure and HbA1c were obtained from structured electronic medical record data. Since this study was focused on CVD risk prediction, we additionally performed chart reviews to assess and exclude patients on statins or have evidence of CVD before or during the study period.

Statistical Analysis

We calculated 10-year CV risk using four externally validated general population CV risk calculators: (1) FRS, (2) 2013 ACC/AHA, (3) RRS, and (4) QRISK2. We applied the inclusion criteria of each calculator to the cohorts (Appendix 1), resulting in slightly different population tested for each risk calculator: in the whole study population: FRS: n=148, 2013 ACC/AHA: n=147, RRS: n=164, QRISK2: n=172; in the CRP decrease group: FRS: n=68, 2013 ACC/AHA: n=65, RRS: n=70, QRISK2: n=76; in the CRP increase group: FRS: n=80, 2013 ACC/AHA: n=82, RRS: n=94, QRISK2: n=96. We used the published equations to generate the estimated CV risk (12–16). For the primary analysis, we used paired t-tests to compare 10-year estimated CV risk at baseline and 1-year follow-up among participants in the CRP decrease and increase groups. The estimated risks were log transformed to normalize the distribution. In addition, we determined the correlations between changes in estimated CV risk and changes in pro-BNP levels by using the Pearson correlation test. Both estimated CV risks and pro-BNP levels were log transformed because of the non-normal distribution.

In the sensitivity analyses, we controlled for potential changes in CV risk estimation not impacted by inflammation, namely age. Thus, we calculated the estimated CV risks at both baseline and 1-year follow-up using the same age to control for the influence of age on CV risk. Analyses controlling for age were performed for both the primary and secondary analyses. For all statistical analyses, two-sided $P < 0.05$ was considered as statistically significant. All data analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). All aspects of this study were approved by the Partners Healthcare Institutional Review Board, and the participants gave informed consent.

RESULTS

A total of 180 RA participants were included in our study, of which 79 experienced a reduction in CRP (CRP decrease group), and 101 participants had an increase in CRP (CRP increase group). The overall study population had a mean age of 57.8 years; 85% were female; 80% were seropositive with a mean RA disease duration of 18.2 years. The mean

DAS28 was 4.0, indicating moderate disease activity. In the CRP decrease group, the median CRP at baseline was 28.60 mg/L (IQR 22.03, 45.74), with a reduction to 4.38 mg/L (IQR 1.92, 7.99) at 1-year follow-up. In the CRP increase group, the median CRP at baseline was 4.57 (IQR 1.67, 8.13) mg/L, with increase to 26.77 mg/L (IQR 20.34, 46.04) at 1-year follow-up. Within the study population, 68% were on treatment with a non-biologic disease-modifying antirheumatic drug (DMARD) and 52% were on methotrexate. Fifty-four percent of the study population was on a biologic DMARD; 49% were on a tumor necrosis factor (TNF) inhibitor (Table 1).

Seven CV risk factors were included in all 4 risk CV risk calculators: age (continuous), gender, current smoking status (yes / no), blood pressure (continuous), diabetes mellitus (yes / no), total cholesterol (continuous), and HDL (continuous). RRS included CRP levels (continuous). QRISK2 was the only calculator that included RA (yes / no). The complete list of variables is shown in Table 2.

Among participants experiencing a decrease in CRP, we observed significant changes in CV risk only in RRS. The estimated 10-year CV risk was 2.57% at baseline and decreased to 1.84% at follow-up ($p<0.0001$). Among participants with an increase in CRP, we observed a significant increase in estimated CV risk from 2.86% to 4.42% at 1-year follow-up ($p<0.0001$). No significant change was observed for FRS ($p=0.77$ in the CRP decrease group; $p=0.58$ in the increase group), 2013 ACC/AHA ($p=0.19$ in the CRP decrease group; $p=0.09$ in the increase group) (Table 3). QRISK2 demonstrated a change in the 10-year CV risk estimates, where risk increased significantly in both groups regardless of the direction of change for CRP (from 6.54% to 6.69% with $p=0.005$ in the CRP decrease group; from 10.52% to 10.90% with $p=0.01$ in the increase group).

The significant changes in estimated CV risk observed in QRISK2 was no longer present in the sensitivity analysis when age was kept constant. In contrast, the significant changes in estimated CV risk using RRS remained for both groups even after controlling for age (Supplemental Table 1).

In the secondary analysis, we investigated the correlation between change in estimated CV risk for each CV risk calculator and change in pro-BNP. Among participants in the CRP decrease group, median pro-BNP decreased from 83.64 pg/mL to 75.85 pg/mL; in the CRP increase group pro-BNP increased from 86.81 pg/mL to 111.60 pg/mL. Only the changes in RRS were significantly correlated with changes in pro-BNP ($r=0.17$, $P=0.03$) (Table 4). Similar results were observed in the sensitivity analysis (Supplemental Table 2).

DISCUSSION

When comparing across general population-based CV risk calculators, changes in inflammation were associated with a change in estimated CV risk using RRS, which include CRP as a risk factor for CVD. This finding was expected since CRP is included in the RRS. However, the increase in CV risk associated with RRS, was also significantly correlated with evidence of increased subclinical myocardial injury as measured by pro-BNP; the converse was also true—participants who experienced a decrease in inflammation, had an estimated

reduction in CV risk by RRS as well as a reduction in pro-BNP. These findings are in line with current understanding of the role of inflammation on CV risk in RA (2, 17), as well as the general population (1). In contrast, no changes in CV risk was observed with FRS or 2013 ACC/AHA. QRISK2 initially showed an increase in risk between 2 consecutive years regardless of direction of change of CRP. This difference was attenuated when controlling for age, suggesting a strong weight for age on CV risk in the QRISK2 calculations.

Pro-BNP is a marker of cardiac ventricular strain, released from the ventricles in response to increased wall stress (18). It is also a marker of increased CV risk, where higher levels of pro-BNP are associated with higher CV risk among individuals with and without existing coronary artery disease (19). Our data suggest that a change in inflammation had a measurable impact not only on ventricular strain, but potentially on future CV risk. The changes in CV risk were detected by RRS, the only risk calculator which accounts for some aspect of disease activity using CRP. Together, these data highlight a need to reconsider the strategy for estimating CV risk in those who can experience significant changes in inflammation as seen in RA and other inflammatory diseases. Based on a published and internally validated CV risk calculator tailored for RA, accounting for the level of RA disease activity and other clinical factors at baseline improved the accuracy of the estimated CV risk (17).

Previous studies in RA on the accuracy of CV risk estimates have shown that FRS, RRS, 2013 ACC/AHA all underestimate CV risk in RA (20–22). Additionally, studies have shown that despite moderate estimated CV risk, participants had severe atherosclerotic disease detected using carotid ultrasound and coronary artery calcium scores (23, 24). With this evidence in mind, our study examined a different question, that is, whether estimated CV risk may change as a result of changes in inflammation, and second, whether these changes in inflammation are reflected in a biomarker measuring myocardial strain and CV risk. For most CV risk estimates, such as FRS, 2013 ACC/AHA, QRISK2, the risk did not change significantly with significant changes in inflammation. In contrast, RRS was sensitive to changes in inflammation, whereby an increase in inflammation is associated with an increase in CV risk. While we acknowledge that risk calculators were not designed to capture changes in CV risk on an annual basis, this study provides evidence that a different approach for CV risk estimation may be needed in RA.

This study highlights a unique characteristics of RA participants compared to the general population. Inflammation is of a higher magnitude and can change considerably, leading to higher CV risk with increasing cumulative burden of RA flares (25, 26). The potential changes due to fluctuations in inflammation on CV risk were reflected by RRS and a measurement not directly related to CRP levels, pro-BNP. These changes were not observed by other risk calculators. Follow-up studies are needed in large RA cohort studies to validate risk scoring systems incorporating RA disease activity at baseline (17) and to elucidate the clinical impact of fluctuations in inflammation on future CV risk. Finally, studies should consider whether a shorter interval of CV risk prediction may be more optimal in RA than the current 10-year predicted risk used for the general population.

The present study also found significant differences in the estimated CV risk using different calculators. One study examined the variation among 16 CV risk calculators and increases in relative risk for CVD with increases in the risk factors. The weighting of the risk factors varies, such that a change in one CV risk factor could increase CV risk in some calculators 8× more than another (27).

The limitations of our study include the challenge of having an RA cohort of sufficient follow-up time and size compare estimated CV risk with actual CV outcomes. Thus, we assessed a surrogate marker of CV risk, pro-BNP. Since the goal of the study was to measure changes in CV risk in RA patient in a standardized period of time, one year, we did not investigate changes between the one year period. Additionally, lipid measurements were not performed in the fasting state. However, previous studies have shown that non-fasting total cholesterol and HDL-C, used in most calculators, would not differ significantly from the fasting state (28). Since this study leveraged data from an observational cohort, there could be differences in participants who experienced an increase or decrease in CRP. One potential reason for changes in CRP is treatment; however, we found no difference in the proportion of biologic DMARD therapy between the two cohorts ($p=0.997$). Additionally, we observed no differences in the magnitude of CRP change comparing those on biologic DMARD therapy vs those who were not in either the CRP decrease cohort ($p=0.28$) or increase cohort ($p=0.89$).

In conclusion, among RA participants who experienced a change in CRP, we found no significant change in CV risk estimates of general population-based risk calculators with the exception of RRS. RRS, which includes CRP, was sensitive to changes in inflammation, whereby an increase in inflammation was also correlated with evidence for subclinical myocardial stress. Together with evidence that RA clinical factors and disease activity at baseline can improve the accuracy of estimated CV risk, this study highlights a need to re-examine the general approach to assessing CV risk in RA towards risk calculators that can incorporate RA specific factors and potentially, more frequent assessments of CV risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline characteristics of the RA cohort.

Characteristics	CRP decrease group, N=79	CRP increase group, N=101
Age, mean (SD) y	56.44 (12.41)	58.88 (12.71)
Female, n (%)	72 (91.14)	80 (80.00)
RA disease duration, mean (SD) y	18.48 (12.14)	17.99 (12.14)
Anti-CCP positive ^I , n (%)	61 (82.43)	62 (72.09)
RF positive ^I , n (%)	8 (66.67)	26 (70.27)
BMI ^I , mean (SD) kg/m ²	26.69 (5.33)	27.18 (5.63)
Diabetes mellitus, n (%)	6 (7.59)	1 (0.99)
Hyperlipidemia, n (%)	7 (8.86)	11 (10.89)
Hypertension, n (%)	17 (21.52)	26 (25.74)
DAS28 ^I , mean (SD)	4.77 (1.75)	3.43 (1.41)
RA treatment, n (%)		
Non-biologic DMARD	55 (69.62)	67 (66.34)
Methotrexate	44 (55.70)	49 (48.51)
Biologic DMARD	43 (54.43)	55 (54.46)
TNF inhibitors	41 (51.90)	48 (47.52)
CRP, mg/dL, median (IQR)	28.60 (22.03, 45.74)	4.57 (1.67, 8.13)
NT-proBNP, pg/mL, median (IQR)	83.64 (57.34, 160.20)	86.81 (44.25, 192.95)

Anti-CCP indicates anti-cyclic citrullinated peptide; RA, rheumatoid arthritis; RF, rheumatoid factor; BMI, body mass index; CRP, C-reactive protein; DAS28, Disease Activity Score 28; DMARD, disease-modifying anti-rheumatic drug; TNF, tumor necrosis factor.

^I Some data were missing for the following variables: Anti-CCP positive, missing = 20; RF positive, missing = 131; body mass index, missing = 1; DAS28, missing = 8.

Table 2

Comparisons of different cardiovascular (CV) risk calculators

Variables	FRS	2013 ACC/AHA	RRS (women)	RRS (men)	QRISK2
Age					
Gender					
Ethnicity					
Total cholesterol					
HDL cholesterol					
Systolic blood pressure					
Tx for hypertension					
Body mass index					
Smoking					
Diabetes mellitus					
Hemoglobin A1c					
C-reactive protein					
FHx of premature MI					
Social deprivation score					
Atrial fibrillation					
Chronic kidney disease					
Rheumatoid arthritis					
Calculator Measurement	10-year risk of CVD ¹	10-year risk of ASCVD ²	10-year risk of incident CVD ³	10-year risk of incident CVD ⁴	10-year risk of MI or stroke

FRS = Framingham Risk Score; 2013 ACC/AHA = 2013 American College of Cardiology/American Heart Association 10-year atherosclerotic cardiovascular disease risk estimator; RRS = Reynolds Risk Score; HDL=high-density lipoprotein; Tx=treatment; FHx=family history; MI = myocardial infarction; CVD = cardiovascular disease; ASCVD = Atherosclerotic cardiovascular disease.

¹CVD including coronary death, MI, coronary insufficiency, angina, ischemic stroke, hemorrhagic stroke, transient ischemic attack, peripheral artery disease, congestive heart failure.

²ASCVD including hypertension, coronary heart disease, congestive heart failure.

³Incident CVD including MI, ischemic stroke, coronary revascularization, cardiovascular death.

⁴Incident CVD including non-fatal MI, non-fatal stroke, coronary revascularization, cardiovascular death.

Table 3

Comparison of 10-year risk estimates based on validated general population cardiovascular risk calculators between baseline and 1-year follow-up for RA subjects reported no statin use in (A) CRP decrease group (n=79)¹, and (B) CRP increase group (n=101)¹.

A.

CRP decrease group (n=79)			
	Baseline	1-year Follow-up	P-value ²
FRS	5.81 (6.58) ³	5.02 (6.84)	0.77
2013 ACC/AHA	3.33 (5.35)	3.11 (7.46)	0.19
RRS	2.57 (3.88)	1.84 (2.95)	<.0001
QRISK2	6.54 (12.60)	6.69 (12.59)	0.005
CRP	28.60 (23.71)	4.38 (6.07)	<.0001

B.

CRP increase group (n=101)			
	Baseline	1-year Follow-up	P-value ²
FRS	6.28 (8.59)	7.35 (7.27)	0.58
2013 ACC/AHA	4.43 (10.12)	5.55 (10.34)	0.09
RRS	2.86 (6.55)	4.42 (7.45)	<.0001
QRISK2	10.52 (15.38)	10.90 (15.24)	0.01
CRP	4.57 (6.46)	26.77 (25.70)	<.0001

FRS = Framingham Risk Score; 2013 ACC/AHA = 2013 American College of Cardiology/American Heart Association 10-year atherosclerotic cardiovascular disease risk estimator; RRS = Reynolds Risk Score; CRP = C-reactive protein.

¹ Risk score sample sizes vary: CRP decrease group: FRS (n=68), 2013 ACC/AHA (n=65), RRS (n=70), QRISK2 (n=76); CRP increase group: FRS (n=80), 2013 ACC/AHA (n=82), RRS (n=94), QRISK2 (n=96).

² Log transformed risk scores were used for the calculation of p-values.

³ Median (IQR) for all such values

Table 4

Correlations between change in calculated risk scores with controlling for age and change in pro B-type Natriuretic Peptide (pro-BNP) for RA patients reported no statin use (n=180)¹.

	Correlation between change in risk score and change in pro-BNP*	P-value ²
FRS	−0.03	0.73
2013 ACC/AHA	−0.001	0.99
RRS	0.17	0.03
QRISK2	0.02	0.77

¹ Risk score sample sizes vary: FRS (n=145), 2013 ACC/AHA (n=144), RRS (n=161), QRISK2 (n=169).

² Log transformed risk scores and pro-BNP level were used for the calculation of correlations.

FRS = Framingham Risk Score; 2013 ACC/AHA = 2013 American College of Cardiology/American Heart Association 10-year atherosclerotic cardiovascular disease risk estimator; RRS = Reynolds Risk Score; CRP = C-reactive protein.