NT-proBNP and sRAGE levels in early rheumatoid arthritis

Heslinga, M.; Teunissen, C.; Agca, R.; Woude, D. van der; Huizinga, T.W.J.; Laar, J. van; ... ; Nurmohamed, M.

Scandinavian Journal of Rheumatology

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/irhe20

NT-proBNP and sRAGE levels in early rheumatoid arthritis

M Heslinga, C Teunissen, R Agca, D van der Woude, TWJ Huizinga, J van Laar, A den Broeder, W Lems & M Nurmohamed

To cite this article: M Heslinga, C Teunissen, R Agca, D van der Woude, TWJ Huizinga, J van Laar, A den Broeder, W Lems & M Nurmohamed (2023) NT-proBNP and sRAGE levels in early rheumatoid arthritis, Scandinavian Journal of Rheumatology, 52:3, 243-249, DOI: 10.1080/03009742.2022.2042975

To link to this article: https://doi.org/10.1080/03009742.2022.2042975

NT-proBNP and sRAGE levels in early rheumatoid arthritis

M Heslinga[1], C Teunissen[2], R Agca[1], D van der Woude[3], TWJ Huizinga[3], J van Laar[4], A den Broeder[5], W Lems[6], M Nurmohamed[1,6]

[1]Department of Rheumatology, Amsterdam Rheumatology and Immunology Center | Reade, Amsterdam, The Netherlands
[2]Department of Clinical Chemistry, Amsterdam UMC, Amsterdam, The Netherlands
[3]Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands
[4]Department of Rheumatology, UMC Utrecht, Utrecht, The Netherlands
[5]Department of Rheumatology, Radboudumc, Nijmegen, The Netherlands
[6]Amsterdam Rheumatology and Immunology Center, VU University Medical Center, Amsterdam, The Netherlands

Objective: Several biomarkers of cardiovascular function are found to be increased in rheumatoid arthritis (RA), with some suggesting a relationship with disease activity and improvement with adequate anti-rheumatic treatment. Promising biomarkers include N-terminal pro-brain natriuretic peptide (NT-proBNP) and the soluble receptor form of advanced glycation end-products (sRAGE). The objective of this study was to investigate associations between NT-proBNP and sRAGE levels and markers of inflammation and disease activity in early RA patients and their changes during (effective) anti-rheumatic treatment.

Method: Data from 342 consecutive early RA patients participating in the 'Parelsnoer' cohort were used. At baseline and after 6 months' disease activity, NT-proBNP and sRAGE levels were assessed.

Results: After 6 months, NT-proBNP decreased from 83 pmol/L (mean) at baseline to 69 pmol/L at follow-up ($p < 0.001$), while sRAGE increased from 997 pg/mL to 1125 pg/mL ($p < 0.001$). A larger decrease in erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) was associated with larger changes in NT-proBNP and sRAGE. For every point decrease in ESR, there was a 1.7-point decrease in NT-proBNP and a 2.2-point increase in sRAGE. For CRP, these values were 1.7 and 2.7, respectively ($p < 0.001$).

Conclusion: Suppressing inflammation, independently of achieving remission, increases sRAGE levels and decreases NT-proBNP levels significantly. Whether this translates into a decrease in incident cardiovascular disease remains to be elucidated.

Patients with rheumatoid arthritis (RA) have an increased morbidity and mortality, mostly caused by cardiovascular disease (CVD), including myocardial infarction, cerebrovascular accident (CVA), and heart failure (1, 2). Previously, we demonstrated that the risk of developing CVD in RA was even higher than in diabetes (3). This excess morbidity and mortality cannot be explained by traditional risk factors alone, as it has been established that the effects of inflammation and medication also contribute.

Several markers for RA disease activity, including levels of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), numbers of affected joints, and disease activity scores, are associated with CVD risk (4–6). In the past decade, several biomarkers of cardiovascular function have emerged that are increased in RA and related to disease activity (7–9). Some of these cardiovascular function biomarkers improve upon optimal anti-rheumatic treatment (10, 11). Thus far, data on these cardiovascular biomarkers in (very) early RA are sparse, particularly in this era of treat-to-target strategies.

Promising biomarkers include brain natriuretic peptide (BNP), its inactive metabolite N-terminal pro-brain natriuretic peptide (NT-proBNP), and advanced glycation end-products (AGEs) and their soluble receptor form (sRAGE). BNP is a hormone primarily produced in atrial cardiomyocytes in the healthy heart, but in the case of heart failure, the ventricular myocardium becomes the main site of BNP production (12). NT-proBNP, the inactive N-terminal fragment of BNP, is used as a biomarker in CVD, mostly for heart failure (13–15). In RA patients, levels of CRP correlate with levels of NT-proBNP (16, 17), and in the general population NT-proBNP has been shown to be a predictor of cardiovascular mortality (18).

AGEs are formed via non-enzymic glycation of proteins and lipids in the ageing process, but their formation is accelerated in various disorders, including diabetes, renal disease, and inflammatory diseases (19–21), such as RA (22). AGEs elicit a pro-inflammatory state and are

Maaike Heslinga, Department of Rheumatology | Reade, Amsterdam Rheumatology and Immunology Center, Jan van Breemenstraat 2, Amsterdam 1056 AB, The Netherlands.
E-mail: maaikeheslinga@hotmail.com

Accepted 14 February 2022

DOI: https://doi.org/10.1080/03009742.2022.2042975

involved in numerous pathological situations through interaction with their receptor, RAGE. The soluble receptor form (i.e. sRAGE) prevents AGE/RAGE interaction, and in RA, sRAGE levels are lower than in controls (8). AGEs are involved in the pathogenesis of atherosclerosis through various mechanisms (23), such as enhanced oxidized low-density lipoprotein formation, increased vascular wall permeability, and the generation of reactive oxygen species, and have been demonstrated in atherosclerotic lesions (24).

This study aimed to investigate both cross-sectional and longitudinal associations between RA disease activity and NT-proBNP levels and sRAGE in early arthritis patients and to study changes in these markers during (optimal) anti-rheumatic treatment, using data from the Parelsnoer Institute (PSI) biobanking project (25).

Method

Study setting and patients

The PSI is a collaborative biobanking project of all eight University Medical Centers (UMCs) in the Netherlands, which was launched in 2007 and included 15 large disease-specific cohorts in 2020 (the so-called 'Parels' or 'Pearls'). Clinical and biochemical data collected as part of the 'Rheumatoid arthritis' Pearl offer the possibility to investigate associations between clinical parameters and biomarkers in a cohort of early arthritis patients (25). The project aims to facilitate medical research, by providing an infrastructure and standard procedures for the establishment, expansion, and optimization of clinical biobanks for scientific research. Fifteen Pearls are identified within the PSI, and for each Pearl a specific clinical data set is established. The data in PSI are collected via both electronic and manual methods, and are hosted in a web-based application (ProMISe). Biomaterials are stored in UMCs according to the PSI biobanking protocol. All data are registered in a central database. For the present study, data from patients included in the 'Rheumatoid arthritis and osteoarthritis' Pearl were used. Patients were included in this Pearl with a non-traumatic arthritis (excluding septic arthritis or crystal arthritis), confirmed by a physician, and arthritis complaints for less than 2 years. The diagnosis was then specified during the baseline visit: if patients fulfilled the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria, patients were diagnosed as having early RA. Data were collected at baseline, after 3, 6, 12, 18, and 24 months, and yearly thereafter. For the purpose of this study, we used data from patients with early RA, i.e. fulfilling the 2010 ACR/EULAR criteria. We used biobank data from the first 6 months of the study period. We included early RA patients if they had a baseline and a 6 month visit, and if a DAS28-ESR score was acquired during both visits. Patients were excluded if there was no biomaterial available at baseline.

Ethics approval for the study was obtained from the Medical Ethics Review Committee, Leiden University Medical Center. Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research. Patient consent for publication was not required.

Study outcomes

At baseline, duration of arthritis and demographic data, including age, gender, ethnicity, height, weight, and smoking status were collected. Comorbidities were recorded by a trained study nurse. A history of CVD was defined as previous coronary heart disease [including angina pectoris, myocardial infarction, percutaneous coronary intervention (PCI), and coronary artery bypass surgery (CABG)], heart failure, cerebral vascular disease [including ischaemic stroke (CVA), transient ischaemic attack, and carotid endarterectomy], and peripheral arterial disease. Disease activity was assessed at every study visit by the Disease Activity Score based on 28-joint count–erythrocyte sedimentation rate (DAS28-ESR) (26). Laboratory parameters were assessed, including CRP and ESR, and biomaterial, including serum, plasma, and DNA, was collected and biobanked at each visit. Immunoglobulin M–rheumatoid factor (IgM-RF) and anti-citrullinated protein antibodies (ACPAs) were assessed only at baseline. Medication use was recorded at each visit. Improvement of disease or response to therapy after 6 months was defined according to the EULAR response criteria (27). To establish whether remission was achieved after 6 months, the criterion DAS28-ESR < 2.6 was used.

NT-proBNP and sRAGE assessment

Serum sRAGE concentrations were measured using an enzyme-linked immunosorbent assay (ELISA)-based technology that uses electrochemiluminescence for detection on a Meso Scale Discovery Quickplex SQ 120 Imager (cat. no. F214Q; Meso Scale Discovery, Rockville, MD, USA; intra-assay coefficient of variation 1.4%; interassay coefficient of variation 8.8%). Plasma levels of NT-proBNP were analysed using the Elecsys 1010 electrochemiluminescence immunoassay (Roche Diagnostics, Almere, the Netherlands). NT-proBNP values were compared to reference levels according to the PRIDE study guidelines (< 50 years of age, NT-proBNP ≤ 450 pmol/L; 50–75 years of age, ≤ 900 pmol/L; and > 75 years of age, ≤ 1800 pmol/L) (28, 29).

Statistical analyses

Patient characteristics are described as number and percentage or mean ± standard deviation (sd) when normally

distributed, or median and interquartile range (IQR) when not normally distributed.

Linear regression analyses were performed to assess univariate associations between inflammation as the independent variable and NT-proBNP and sRAGE as the dependent variables at baseline. Mixed model analyses were used to assess associations between inflammation and NT-probBNP and sRAGE over time. All analyses were adjusted for age, gender, smoking status, body mass index (BMI), history of diabetes, hypertension, and previous CVD. Furthermore, we calculated the changes in DAS28, CRP, ESR, NT-proBNP, and sRAGE after 6 months. We tested associations between magnitude of change in markers of disease activity and inflammation (e.g. DAS28-ESR, CRP, and ESR) after 6 months and magnitude of change in NT-proBNP and sRAGE levels after 6 months using linear regression. We also used linear regression to detect a difference in change in NT-proBNP and sRAGE levels between the group in remission and the group not in remission at 6 months. For the statistical analysis, SPSS version 25.0 (IBM Corp., Armonk, NY, USA) was used. The threshold for significance was set at $p < 0.05$ (two-sided).

Results

Patient characteristics

For this study, data from 342 consecutive patients from four centres were used. Patients had a mean disease duration at baseline of 5.3 months. Patient characteristics are shown in Table 1. Twelve patients had a history of CVD, including one patient with documented heart failure.

Table 1. Characteristics of the early rheumatoid arthritis patients.

	Baseline	6 months
Demographics (n = 342)		
Gender, female	227 (66.4)	
Age (years)	57 (14)	
Ethnicity, Caucasian	313 (94.8)	
Disease characteristics		
Symptom duration (months)	5.3 ± 8.5	
RF positive	130 (40.6)	
ACPA positive	97 (32.1)	
DAS28-ESR	4.1 ± 1.0	2.8 ± 1.1
ESR (mm/h)	22 (11–36)	9 (6–19)
CRP (mg/L)	9 (3–21)	3 (3–7)
BMI (kg/m^2)	26.9 ± 4.9	
Smoking status		
Never	111 (33.9)	
Former > 6 months	133 (40.7)	
Former ≤ 6 months	2 (0.6)	
Current smoker	81 (24.8)	
Comorbidity		
History of CVD	12 (3.5)	
Hypertension	84 (24.6)	
Diabetes	5 (1.5)	
Use of medication		
NSAIDs	184 (84.8)	
Hydroxychloroquine	5 (3.2)	
Prednisolone	37 (23.6)	
Methotrexate	63 (40.1)	
Other nbDMARD	5 (2.1)	
bDMARD	4 (1.7)	
Biomarkers		
NT-proBNP (pmol/mL)	83.4 (43.3–158.3)	68.7 (38.9–134.3)
sRAGE (pg/mL)	997 ± 483	1125 ± 515

Data are shown as n (%), mean ± sd, or median (interquartile range).
ACPA, anti-citrullinated protein antibody; bDMARD, biological disease-modifying anti-rheumatic drug; BMI, body mass index; CRP, C-reactive protein; CVD, cardiovascular disease; DAS28-ESR, Disease Activity Score based on 28-joint count–erythrocyte sedimentation rate; ESR, erythrocyte sedimentation rate; nbDMARD, non-biological disease-modifying anti-rheumatic drug; NT-proBNP, N-terminal pro-brain natriuretic peptide; NSAID, non-steroidal anti-inflammatory drug; RF, rheumatoid factor; sRAGE, soluble receptor advanced glycation end-product.

Disease activity

At baseline, 64% of the patients had moderate disease activity (DAS28-ESR between 3.2 and 5.1), 20% had low disease activity (DAS28-ESR between 2.6 and 3.1), and 15% of patients had highly active disease (DAS28-ESR above 5.1). At 6 months, 99 (29.3%) of the patients were non-responders, 89 (26.3%) were moderate responders, and 150 (44.4% were good responders. After 6 months, 162 (47.6%) had achieved remission (DAS28-ESR < 2.6) (Table 2).

Correlation of markers of inflammation with NT-proBNP and sRAGE

NT-proBNP and sRAGE were associated with variables of inflammation, both at baseline and over time (Tables 3 and 4). A rise in DAS28-ESR, ESR, and CRP was associated with increased NT-proBNP levels and decreased sRAGE levels. Data plots are added as a supplementary file. Remarkably, only seven patients had an NT-proBNP value above the threshold for their age, one of whom had documented heart failure (28).

Changes in NT-proBNP and sRAGE after 6 months

After 6 months of treatment, the median value of NT-proBNP decreased from 83 pmol/mL at baseline to 69 pmol/mL at follow-up; the mean change in NT-proBNP was –28.94 pg/mL ($p < 0.001$). sRAGE increased from 997 pg/mL at baseline to 1125 pg/mL after 6 months of treatment, the mean increase was 127.59 pg/mL ($p < 0.001$). We found no significant associations between change in DAS28 and change in NT-proBNP or sRAGE, or between responders and non-responders after 6 months

Table 2. Disease activity.

	Baseline	6 months
Mean DAS28-ESR	4.10 ± 1.02	2.77 ± 1.13
< 2.6	5 (1.5)	162 (48.1)
< 3.2	68 (20.2)	66 (19.6)
≤ 5.1	214 (63.5)	99 (29.4)
> 5.1	50 (14.8)	10 (3.0)
EULAR response		
Non-responder	n/a	99 (29.3)
Moderate responder	n/a	89 (26.3)
Good responder	n/a	150 (44.4)

Data are shown as mean ± sd or n (%).
DAS28-ESR, Disease Activity Score based on 28-joint count–erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; n/a, not applicable.

of treatment (p = 0.296 and p = 0.231, respectively). However, a larger decrease in ESR or CRP levels was associated with a larger decrease in NT-proBNP and a greater increase in sRAGE levels. For every point change in ESR, there was a 1.7-point decrease in NT-proBNP and a 2.2-point increase in sRAGE. For CRP, these values were 1.7 and 2.7, respectively (Table 5).

After 6 months, 162 (47.6%) of the patients had achieved remission (DAS28 < 2.6). In these patients, the mean change in NT-proNBP was 39 pg/mL, versus 29 pg/mL in the patients not in remission (p = 0.097). Changes in sRAGE were 168 and 122 pg/mL, respectively (p = 0.861).

Discussion

In our cohort of very early RA patients, we demonstrated associations between NT-proBNP and sRAGE and CRP, ESR, and DAS28, both at baseline and during follow-up. During 6 months of treatment with anti-inflammatory medication, NT-proBNP decreased and sRAGE increased. There was an association between the magnitude of change in inflammatory markers (ESR and CRP) and changes in NT-proBNP and sRAGE. To our knowledge, this is the first study to find these longitudinal associations in very early RA patients.

A study published in 2019 found, in contrast to our findings, higher serum sRAGE levels in RA patients compared to healthy controls; serum sRAGE positively correlated with DAS28 (30). The authors attribute this finding to a possible concomitant reduction in RAGE ligand binding that occurs when controlling inflammation, suggesting the possibility of sRAGE production as a compensatory anti-inflammatory mechanism. In this study, only cross-sectional correlations were investigated. In another study, in female RA patients, low sRAGE was significantly associated with increased cardiovascular risk and incident CVD (31). A relationship between CRP and NT-proBNP has previously been described in a cohort of 238 RA patients. However, these patients had a substantially longer disease duration (16). Moreover, the investigators analysed their data in a dichotomous way, rather than with a continuous analysis, thereby limiting the interpretation. Another study demonstrated a higher level of BNP in RA patients, similar to our cohort, compared to healthy controls, and RA patients with active RA having higher BNP levels than RA patients with moderately active or inactive disease (17), but this was not studied prospectively. In the IDEA study, the researchers demonstrated that NT-proBNP values in RA patients decreased after treatment with infliximab and methotrexate (32). Thus far, there have been no longitudinal studies investigating AGEs in very early RA.

Table 3. Linear regression analyses between N-terminal pro-brain natriuretic peptide (NT-proBNP), soluble receptor advanced glycation end-product (sRAGE), and markers of disease activity at baseline.

	DAS28-ESR		ESR		CRP	
	Beta (95% CI)	p	Beta (95% CI)	p	Beta (95% CI)	p
NT-proBNP						
Unadjusted	1.19 (1.06 to 1.33)	0.003	1.01 (1.01 to 1.02) 1.02	< 0.001	1.02 (1.01 to 1.02)	< 0.001
Model 2	1.21 (1.03 to 1.43)	0.022	1.01 (1.00 to 1.01) 1.02	< 0.001	1.03 (1.01 to 1.02) 1.04	< 0.001
Model 3	1.21 (1.03 to 1.42)	0.020	1.01 (1.00 to 1.01) 1.02	0.001	1.03 (1.01 to 1.02) 1.04	< 0.001
sRAGE						
Unadjusted	–73.58 (–123.50 to –23.66)	0.004	–3.54 (–5.71 to –1.38)	0.001	–6.12 (–8.68 to –3.56)	< 0.001
Model 2	–54.76 (–123.480 to 13.97)	0.118	–2.93 (–5.15 to –0.71)	0.010	–5.28 (–7.87 to –2.70)	< 0.001
Model 3	–68.02 (–136.76 to 0.72)	0.052	–2.83 (–5.17 to –0.49)	0.018	–5.32 (–7.98 to 2.67)	< 0.001

Model 2: adjusted for age and gender; Model 3: adjusted for age, gender, smoking status, body mass index, and history of diabetes, hypertension, and cardiovascular disease.
CRP, C-reactive protein; DAS28-ESR, Disease Activity Score based on 28-joint count–erythrocyte sedimentation rate; ESR, erythrocyte sedimentation rate.

Table 4. Mixed model analyses between disease activity and N-terminal pro-brain natriuretic peptide (NT-proBNP) and soluble receptor advanced glycation end-product (sRAGE).

	DAS28-ESR		ESR		CRP	
	Beta (95% CI)	p	Beta (95% CI)	p	Beta (95% CI)	p
NT-proBNP						
Unadjusted	1.16 (1.09 to 1.23)	< 0.001	1.01 (1.01 to 1.01)	< 0.001	1.01 (1.01 to 1.02)	< 0.001
Model 2	1.16 (1.09 to 1.23)	< 0.001	1.01 (1.01 to 1.01)	< 0.001	1.01 (1.01 to 1.02)	< 0.001
Model 3	1.16 (1.09 to 1.24)	< 0.001	1.01 (1.01 to 1.01)	< 0.001	1.01 (1.01 to 1.02)	< 0.001
sRAGE						
Unadjusted	–78.60 (–103.56 to –53.60)	< 0.001	–4.16 (–5.56 to –2.76)	< 0.001	–4.94 (–6.52 to –3.36)	< 0.001
Model 2	–81.31 (–106.12 to –56.49)	< 0.001	–4.29 (–5.71 to –2.86)	< 0.001	–5.21 (–6.81 to –3.62)	< 0.001
Model 3	–82.97 (–107.49 to –58.45)	< 0.001	–4.33 (–5.71 to –2.95)	< 0.001	–5.11 (–6.64 to –3.58)	< 0.001

Model 2: adjusted for age and gender; Model 3: adjusted for age, gender, smoking status, body mass index, and history of diabetes, hypertension, and cardiovascular disease.
CI, confidence interval; CRP, C-reactive protein; DAS28-ESR, Disease Activity Score based on 28-joint count–erythrocyte sedimentation rate; ESR, erythrocyte sedimentation rate.

Table 5. Associations between change in disease activity and change in N-terminal pro-brain natriuretic peptide (NT-proBNP) and soluble receptor advanced glycation end-product (sRAGE) after 6 months.

	Δ NT-proBNP		Δ sRAGE	
	Beta (95% CI)	p	Beta (95% CI)	p
Δ DAS28	–11.0 (–23.9 to 1.8)	0.094	4.5 (–23.5 to 32.4)	0.754
Δ ESR	1.7 (0.8 to 2.6)	< 0.001	2.2 (–4.4 to –0.3)	0.027
Δ CRP	1.7 (0.8 to 2.6)	< 0.001	2.7 (–4.5 to –0.7)	0.006

CI, confidence interval; CRP, C-reactive protein; DAS28-ESR, Disease Activity Score based on 28-joint count–erythrocyte sedimentation rate; ESR, erythrocyte sedimentation rate.

Some limitations need to be considered. Unfortunately, we were unable to include a control group in our study. Comparison of NT-proBNP and sRAGE levels between RA patients and controls would add valuable information on deviation of these values in RA patients. However, we were able to compare these values in our patient group at time of high versus low disease activity, using the patients as their own control group. Furthermore, although we did demonstrate a decrease in NT-proBNP, all values were within normal limits for age and gender. Therefore, the clinical significance remains unknown. However, based on the mechanisms behind the production of NT-proBNP and sRAGE, we hypothesize that suppression of inflammation benefits the myocardium and endothelium. In heart failure patients, a greater decrease in NT-proBNP reduces morbidity and mortality (32). A prospective study on the effects of sacubitril–valsartan on cardiac outcomes demonstrated that a reduction in NT-proBNP concentrations over 12 months correlated with improvements in markers of cardiac volume and function (33).

Results from the ECHOES (Echocardiographic Heart of England Screening study) cohort demonstrated that an increased NT-proBNP level, even still within normal limits, increased the risk of developing heart failure over time (34). Another limitation of this study is that we had no information on some of the possible confounders, such as fasting glucose, glycosylated haemoglobin (HbA_{1c}) values, cholesterol levels, and antihypertensive treatment. However, correction for other cardiovascular confounders that are correlated with cholesterol levels, such as smoking, BMI, and hypertension, did not influence our results.

Conclusion

Suppressing inflammation, independently of achieving remission, increases sRAGE levels and decreases NT-proBNP levels. Both of these markers have been associated with CVD in the general population. Our results imply that RA treatment could positively affect these markers, independently of whether or not remission is achieved. The strength of this study is that we were able to examine these markers over time in a cohort of very early RA patients. It provides more evidence that prompt suppression of inflammatory activity, maybe even particularly in early RA, is essential to preserve

not only synovium and cartilage, but also endothelium and myocardium. The association with 'hard' cardiovascular endpoints needs to be further investigated.

Acknowledgements

The authors would like to acknowledge the employees from our biobank, Toni de Jong-de Boer and Corrie Verdoold, the Parelsnoer data managers Jozé Krol-van Berkel and Judith Mannien, and Professor Twisk for his assistance with the statistical aspects of this manuscript.

Disclosure statement

No potential conflict of interest was reported by the authors.

Author contributions

Study design: MH, RA, DW, TH, JL, AB, WL, and MN; data collection: TH, JL, AB, WL, and MN; Data analysis: MH, RA, MN; interpretation of findings: MH, CT, RA, DW, TH, JL, AB, WL, and MN; preparation of manuscript: MH, CT, RA, DW, TH, JL, AB, WL, and MN. All authors read and approved the final manuscript.

Data availability statement

All data relevant to the study are included in the article or uploaded as supplementary information. https://www.health-ri.nl/uitgifteproces-klinische-biobank

Supplemental material

Supplemental data for this article can be accessed https://doi.org/10.1080/03009742.2022.2042975.

ORCID

M Heslinga http://orcid.org/0000-0002-3283-3969

C Teunissen http://orcid.org/0000-0002-4061-0837

R Agca http://orcid.org/0000-0002-5904-0264

D van der Woude http://orcid.org/0000-0001-8121-5879

TWJ Huizinga http://orcid.org/0000-0001-7033-7520

J van Laar http://orcid.org/0000-0001-5544-5785

A den Broeder http://orcid.org/0000-0002-9012-4079

W Lems http://orcid.org/0000-0002-6885-3953

M Nurmohamed http://orcid.org/0000-0002-6274-1934

References

1. Avina-Zubieta JA, Thomas J, Sadatsafavi M, Lehman AJ, Lacaille D. Risk of incident cardiovascular events in patients with rheumatoid arthritis: a meta-analysis of observational studies. Ann Rheum Dis 2012;71:1524–9.
2. Nicola PJ, Maradit-Kremers H, Roger VL, Jacobsen SJ, Crowson CS, Ballman KV, et al. The risk of congestive heart failure in rheumatoid arthritis: a population-based study over 46 years. Arthritis Rheum 2005;52:412–20.
3. van Halm VP, Peters MJ, Voskuyl AE, Boers M, Lems WF, Visser M, et al. Rheumatoid arthritis versus diabetes as a risk factor for cardiovascular disease: a cross-sectional study, the CARRE investigation. Ann Rheum Dis 2009;68:1395–400.
4. Maradit-Kremers H, Nicola PJ, Crowson CS, Ballman KV, Jacobsen SJ, Roger VL, et al. Raised erythrocyte sedimentation rate signals heart failure in patients with rheumatoid arthritis. Ann Rheum Dis 2007;66:76–80.
5. Goodson NJ, Symmons DP, Scott DG, Bunn D, Lunt M, Silman AJ, et al. Baseline levels of C-reactive protein and prediction of death from cardiovascular disease in patients with inflammatory polyarthritis: a ten-year followup study of a primary care-based inception cohort. Arthritis Rheum 2005;52:2293–9.
6. Maradit-Kremers H, Nicola PJ, Crowson CS, Ballman KV, Gabriel SE. Cardiovascular death in rheumatoid arthritis: a population-based study. Arthritis Rheum 2005;52:722–32.
7. Kozera L, Andrews J, Morgan AW. Cardiovascular risk and rheumatoid arthritis–the next step: differentiating true soluble biomarkers of cardiovascular risk from surrogate measures of inflammation. Rheumatology (Oxford) 2011;50:1944–54.
8. Pullerits R, Bokarewa M, Dahlberg L, Tarkowski A. Decreased levels of soluble receptor for advanced glycation end products in patients with rheumatoid arthritis indicating deficient inflammatory control. Arthritis Res Ther 2005;7:817–24.
9. Ruff CT, Morrow DA, Jarolim P, Ren F, Contant CF, Kaur A, et al. Evaluation of NT-proBNP and high sensitivity C-reactive protein for predicting cardiovascular risk in patients with arthritis taking longterm nonsteroidal antiinflammatory drugs. J Rheumatol 2011;38:1071–8.
10. van Halm VP, Nurmohamed MT, Twisk JW, Dijkmans BA, Voskuyl AE. Disease-modifying antirheumatic drugs are associated with a reduced risk for cardiovascular disease in patients with rheumatoid arthritis: a case control study. Arthritis Res Ther 2006;8:R151.
11. Turiel M, Tomasoni L, Sitia S, Cicala S, Gianturco L, Ricci C, et al. Effects of long-term disease-modifying antirheumatic drugs on endothelial function in patients with early rheumatoid arthritis. Cardiovasc Ther 2010;28:e53–64.
12. Kinnunen P, Vuolteenaho O, Ruskoaho H. Mechanisms of atrial and brain natriuretic peptide release from rat ventricular myocardium: effect of stretching. Endocrinology 1993;132:1961–70.
13. Tschope C, Kasner M, Westermann D, Gaub R, Poller WC, Schultheiss H-P, et al. The role of NT-proBNP in the diagnostics of isolated diastolic dysfunction: correlation with echocardiographic and invasive measurements. Eur Heart J 2005;26:2277–84.
14. Wang TJ, Larson MG, Levy D, Benjamin EJ, Leip EP, Omland T, et al. Plasma natriuretic peptide levels and the risk of cardiovascular events and death. N Engl J Med 2004;350:655–63.
15. Kragelund C, Gronning B, Kober L, Hildebrandt P, Steffensen R, et al. N-terminal pro-B-type natriuretic peptide and long-term mortality in stable coronary heart disease. N Engl J Med 2005;352:666–75.
16. Provan SA, Angel K, Odegard S, Mowinckel P, Atar D, Kvien TK, et al. The association between disease activity and NT-proBNP in 238 patients with rheumatoid arthritis: a 10-year longitudinal study. Arthritis Res Ther 2008;10:R70.
17. Armstrong DJ, Gardiner PV, O'Kane MJ. Rheumatoid arthritis patients with active disease and no history of cardiac pathology have higher brain natriuretic peptide (BNP) levels than patients with inactive disease or healthy control subjects. Ulster Med J 2010;79:82–4.
18. Provan S, Angel K, Semb AG, Atar D, Kvien TK. NT-proBNP predicts mortality in patients with rheumatoid arthritis: results from 10-year follow-up of the EURIDISS study. Ann Rheum Dis 2010;69:1946–50.

19. Ramasamy R, Yan SF, Schmidt AM. Receptor for AGE (RAGE): signaling mechanisms in the pathogenesis of diabetes and its complications. Ann N Y Acad Sci 2011;1243:88–102.
20. Arsov S, Graaff R, van Oeveren W, Stegmayr B, Sikole A, Rakhorst G, et al. Advanced glycation end-products and skin autofluorescence in end-stage renal disease: a review. Clin Chem Lab Med 2014;52:11–20.
21. Anderson MM, Requena JR, Crowley JR, Thorpe SR, Heinecke JW. The myeloperoxidase system of human phagocytes generates Nepsilon-(carboxymethyl)lysine on proteins: a mechanism for producing advanced glycation end products at sites of inflammation. J Clin Invest 1999;104:103–13.
22. de Groot L, Hinkema H, Westra J, Smit AJ, Kallenberg CG, Bijl M, et al. Advanced glycation endproducts are increased in rheumatoid arthritis patients with controlled disease. Arthritis Res Ther 2011;13:R205.
23. Basta G, Schmidt AM, De Caterina R. Advanced glycation end products and vascular inflammation: implications for accelerated atherosclerosis in diabetes. Cardiovasc Res 2004;63:582–92.
24. Kume S, Takeya M, Mori T, Araki N, Suzuki H, Horiuchi S, et al. Immunohistochemical and ultrastructural detection of advanced glycation end products in atherosclerotic lesions of human aorta with a novel specific monoclonal antibody. Am J Pathol 1995;147:654–67.
25. Parelsnoer Institute. [cited 2020 november 14]. Available fromhttps://parelsnoer.org/page/nl/Huidige-collecties?mod[Parelsnoer_Module_Pearl][n]=48
26. Prevoo ML, van 't Hof MA, Kuper HH, Van Leeuwen MA, Van De Putte LBA, Van Riel PLCM, et al. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38:44–8.
27. Fransen J, van Riel PL. The disease activity score and the EULAR response criteria. Clin Exp Rheumatol 2005;23:S93–9.
28. Januzzi JL, Camargo CA, Anwaruddin S, Baggish AL, Chen AA, Krauser DG, et al. The N-terminal pro-BNP investigation of dyspnea in the emergency department (PRIDE) study. Am J Cardiol 2005;95:948–54.
29. Nakhjavani MRJ, Jafarpour M, Ghorbanihaghjo A, Abedi Azar S, Malek Mahdavi A. Relationship between serum-soluble receptor for advanced glycation end products (sRAGE) and disease activity in rheumatoid arthritis patients. Mod Rheumatol 2019;29:943–8.
30. Nadali M, Lyngfelt L, Erlandsson MC, Silfverswärd ST, Andersson KME, Bokarewa MI, et al. Low soluble receptor for advanced glycation end products precedes and predicts cardiometabolic events in women with rheumatoid arthritis. Front Med (Lausanne) 2021;7:594622.
31. Anand IS, Fisher LD, Chiang JT, Latini R, Masson S, Maggioni AP, et al. Changes in brain natriuretic peptide and norepinephrine over time and mortality and morbidity in the Valsartan Heart Failure Trial (Val-HeFT). Circulation 2003;11:1278–83.
32. Januzzi JL, Prescott MF, Butler J, Felker GM, Maisel AS, McCague K, et al. Association of change in N-terminal pro–B-type natriuretic peptide following initiation of sacubitril-valsartan treatment with cardiac structure and function in patients with heart failure with reduced ejection fraction. JAMA 2019;322:1085–95.
33. Taylor CJ BMJ, Roalfe AK, Iles R, Hobbs FDR. The potential role of NT-proBNP in screening for and predicting prognosis in heart failure: a survival analysis. BMJ Open 2014;4:e004675.