RHEUMATOLOGY

Rheumatology 2021;60:3699–3708
doi:10.1093/rheumatology/keaa841
Advance Access publication 12 January 2021

Original article

Having a co-morbidity predicts worse outcome in early rheumatoid arthritis despite intensive treatment: a post hoc evaluation of the pragmatic randomized controlled CareRA trial

Veerle Stouten[1], René Westhovens[1,2], Diederik De Cock[1], Kristien Van der Elst[1,2], Sofia Pazmino [1], Delphine Bertrand[1,2], Johan Joly[2] and Patrick Verschueren[1,2]

Abstract

Objectives. To quantify the prevalence of co-morbidities in patients with early RA and determine their prognostic value for effectiveness outcomes in a randomized trial.

Methods. We included patients from the 2-year pragmatic randomized CareRA trial, who had early RA (diagnosis <1 year), were DMARD naïve and then treated-to-target with different remission induction schemes. Prevalence of co-morbidities was registered at baseline and the Rheumatic Diseases Comorbidity Index (RDCI; range 0–9) was calculated. We tested the relation between baseline RDCI and outcomes including disease activity (DAS28-CRP), physical function (HAQ index), quality of life (SF-36 domains) and hospitalizations over 2 years, using linear mixed models or generalized estimating equations models.

Results. Of 379 included patients, 167 (44%) had a RDCI of minimum 1. RDCI scores of 1, 2 or ≥ 3 were obtained in 65 (17%), 70 (19%), and 32 (8%) participants, respectively. The most frequent co-morbidity was hypertension (22%). Patients with co-morbidities had significantly higher HAQ ($\beta = 0.215$; 95% CI: 0.071, 0.358), DAS28-CRP ($\beta = 0.225$; 95% CI: 0.132, 0.319) and lower SF-36 physical component summary scores ($\beta = -3.195$; 95% CI: -4.844, -1.546) over 2 years than patients without co-morbidities, after adjusting for possible confounders including disease activity and randomized treatment. Patients with co-morbidities had over time lower chances of achieving remission (OR $= 0.724$; 95% CI: 0.604, 0.867) and a higher risk of hospitalization (OR $= 3.725$; 95% CI: 2.136, 6.494).

Conclusion. At disease onset, almost half of RA patients had at least one clinically important co-morbidity. Having co-morbidities was associated with worse functionality and disease activity outcomes over 2 years, despite intensive remission induction treatment.

Trial registration. Clinical trials NCT01172639.

Key words: rheumatoid arthritis, co-morbidities, functionality, treatment strategies, csDMARDs, glucocorticoids, disease activity

Rheumatology key messages

- Almost half of patients with early RA had at least one clinically important co-morbidity.
- Having a co-morbidity was associated with worse functionality and disease activity over 2 years.
- The negative effect of having co-morbidities could not be mitigated with intensive treatment strategies.

[1]KU Leuven Department of Development and Regeneration, Skeletal Biology and Engineering Research Centre and [2]Department of Rheumatology, University Hospitals Leuven, Leuven, Belgium

Submitted 20 August 2020; accepted 5 November 2020

Correspondence to: Veerle Stouten, KU Leuven Campus Gasthuisberg, Herestraat 49, 3000 Leuven, Belgium.
E-mail: Veerle.stouten@kuleuven.be

CLINICAL SCIENCE

Introduction

When treated early, intensively and to target, patients with RA may expect an improved long-term outcome in terms of disease activity, physical function, and quality of life. However, patients with RA have a higher prevalence of co-morbidities, compared with the general population, even in the early phase of the disease [1]. These co-morbidities in RA are associated with worse disease outcomes, affecting disease activity, physical function, health-related quality of life and health-care utilization as studied in several cohort studies [2–9]. Responses to treatment can also be negatively affected by the presence of co-morbidities. In established RA, having multiple co-morbidities was shown to lower chances of achieving remission after initiation of disease-modifying anti-rheumatic drugs (DMARDs) and affected retention rate and efficacy of biologic DMARDs [10–14]. Since most research in this field has focused on patients with established disease, the prevalence and impact of co-morbidities in early RA is not yet fully understood. Moreover, it is not yet known whether having co-morbidities at diagnosis of RA impacts response to early, intensive treatment with conventional synthetic DMARDs (csDMARDs) and glucocorticoid bridging, the current treatment standard for early RA.

The total burden of co-morbidity can be quantified using co-morbidity indices, since not all types of co-morbidities have the same impact on the outcomes of interest. The Rheumatic Diseases Comorbidity Index (RDCI) was validated to measure more accurately the burden and prognostic impact of overall co-morbidity, based on a weighted preselection of relevant co-morbidities [15, 16]. This index also has clinical applications in identifying patients with worse prognosis in terms of functional status, health-related quality of life, hospitalization frequency and mortality [17].

We aimed to assess the impact of co-morbidity status at treatment initiation on the response. Therefore, we investigated whether having relevant co-morbidities, measured by RDCI, at diagnosis of RA affected physical function, disease activity, quality of life, and occurrence of hospitalizations over 2 years, based on data from the Care in early RA (CareRA) trial.

Methods

Study design and participants

For this post hoc analysis, data from the pragmatic 2-year CareRA randomized controlled trial (RCT) were used, evaluating different intensive treatment regimens in patients with early RA. CareRA was designed and conducted by investigators from 13 Flemish rheumatology centres (2 academic centres, 7 general hospitals and 4 private practices) in Belgium. Patients were diagnosed with RA (<1 year) and were naïve to and had no contraindications for csDMARDs or glucocorticoids. Detailed enrolment criteria were published previously [18]. The medical ethics committee of each participating centre approved the study protocol (EudraCT number: 2008–007225-39) and all patients gave written informed consent before participation.

Treatment schemes

Participants were treated with different remission induction schemes, based on the original COBRA (Combination therapy for early RA) strategy. We stratified patients into a high- or a low-risk group, based on presence of classical prognostic factors. In the high-risk group, we applied three different remission induction schemes following a treat-to-target principle: COBRA Classic: initial combination of MTX and sulfasalazine; COBRA Slim: MTX monotherapy; COBRA Avant-garde: initial combination of MTX and leflunomide. All COBRA schemes included an initial step-down scheme of oral prednisone, started at a high or moderate dose, and tapered weekly over 6 or 7 weeks to a low maintenance dose, which was discontinued at week 28. In the low-risk group, we applied two schemes: the same COBRA Slim or Tight Step-Up: MTX monotherapy without glucocorticoids. Treatment was adjusted to a target of low disease activity (DAS28-CRP $\leq$ 3.2), ultimately aiming for remission (DAS28-CRP $<$ 2.6). The protocol has been described in detail in previous publications [18, 19]. All regimens combining csDMARDs with glucocorticoids were effective for patients with early RA up to 2 years. The COBRA Slim regimen, MTX monotherapy with glucocorticoid bridging, provided the best balance between efficacy and safety after 1 and 2 years and was endorsed in the updated EULAR 2016 recommendations of 2019 to treat RA [18–20].

Co-morbidity measures

Presence of all past and current co-morbidities was recorded by rheumatologists at inclusion in the CareRA trial. The rheumatologist did an extensive anamnesis in all participants, existing medical history records were systematically reviewed, and the indication of all current medication was revised in view of registering all co-morbidities.

We evaluated the following co-morbidities, based on their inclusion in the RDCI: lung disease, cardiovascular disease (myocardial infarction, stroke, or other), hypertension, fracture of spine/hip/leg, depression, diabetes mellitus, cancer, peptic ulcer or stomach problem. The RDCI formula sums the prevalence of these co-morbidities and weights lung and cardiovascular diseases with a factor 2, whereas a coexisting prevalence of cardiovascular diseases and hypertension can only have a maximum of 2 points. The resulting score ranges from 0 to 9. Based on this information the RDCI was calculated to obtain a weighted co-morbidity score per patient [15, 16].

Assessments and outcomes

Participants were assessed at the following visits: baseline, week 4, 8, 16, 28, 40, 52, 65, 78, 91 and 104. Patients unable to continue the allocated treatment

including predefined adaptations due to lack of efficacy, safety or practical reasons, were followed up every 6 months. Demographics and clinical characteristics were registered on screening. Disease activity was measured at every visit by the 28 joint Disease Activity Score using CRP (DAS28-CRP). Physical function was assessed by the HAQ (range 0–3, higher scores are worse) at all patient visits, except for week 4. The Short Form 36 (SF-36) questionnaire (version 1) as a measure of health-related quality of life was completed by participants at baseline, week 16, year 1 and year 2. Outcomes of this questionnaire were grouped into physical component summary score (PCS) and mental component summary score (MCS) [21]. These scores range from 0–100 and higher scores indicate better perceived quality of life. Finally, all hospitalizations, defined as an admission to the hospital for longer than 24 h were registered during the 2-year trial. For analyses, these hospitalizations were converted into a dichotomous variable of been hospitalized (yes/no) since the previous visit, assessed at all visits.

Statistical analysis

We evaluated differences in baseline characteristics between patients with and without co-morbidities, as selected by the RDCI, using the χ^2 test for categorical variables and the *t* test for independent samples or Mann–Whitney *U* test for continuous variables. The predictive value of co-morbidity status at baseline for functionality, disease activity and quality of life over time was assessed by linear mixed models (LMM) and for hospitalizations and remission status according to DAS28-CRP <2.6 by generalized estimating equations (GEE) models with a binominal logit link function. Co-morbidity status was assessed as either RDCI dichotomized to 0 or $\geq$1, or as the RDCI score. A separate model was fitted for each outcome including DAS28-CRP, HAQ, SF-36, occurrence of hospitalizations or remission status, measured from baseline till year 2. Co-morbidity status, time and treatment scheme were included as predictors with all interaction terms initially, following backward selection of the interaction terms. All LMM models incorporated a random intercept and a random slope for time with an unstructured correlation structure, which accounts for the repeated observations within individuals. In the GEE model, an unstructured working correlation matrix was used for time. All models were adjusted for age, gender, RF, anti-citrullinated protein antibody (ACPA), having erosions, smoking status (ever), symptom duration and BMI at baseline and for DAS28-CRP at every visit. To account for the higher baseline value affecting the linear trajectory of continuous outcomes over time, analyses were controlled for having a different intercept. Missing data were inferred by full information maximum likelihood. As a secondary analysis, we investigated the predictive value of the different types of co-morbidities on the same outcomes. A sensitivity analysis was based on the population being treated with intensive regimens including glucocorticoid schemes (without patients treated with the Tight Step-Up scheme). All tests were performed as two-sided tests with significance level 0.01. Statistical analyses were carried out using SPSS version 25.0.

Results

Prevalence of co-morbidities at disease onset

We included all 379 randomized patients of the CareRA trial. The majority of patients were female (69%) and the mean age (S.D.) was 52 (13) years. All baseline demographic and clinical characteristics of patients can be found in Table 1. At baseline, there were 167 (44%) patients with at least one co-morbidity considered to be clinically important based on inclusion in the RDCI. Patients with co-morbidities were older, were more likely to have erosions and had more severe disease characteristics in terms of DAS28-CRP and HAQ score at baseline. A RDCI score of 1 was recorded for 65/379 (17%) patients, a score of 2 for 70/379 (18%), and a score of $\geq$3 for 32/379 (8%) participants. The mean (S.D.) of the RDCI score (range 0–9) was 0.8 (1.2) with a maximum score of 6. The most common co-morbidities were hypertension (22%), cardiovascular events (myocardial infarction/stroke or other cardiac diseases) (17%), and pulmonary diseases (8%) (Table 2).

Impact of co-morbidity on function

The longitudinal evolution of functionality and disease activity over 2 years of follow-up are shown for patients with and without co-morbidities in Fig. 1. We tested for potential differences between patients with and without co-morbidities by fitting LMM for each outcome including HAQ, DAS28-CRP, and mental and physical component score of SF-36 (Table 3). Having a RDCI of $\geq$1 at baseline was associated with significantly worse HAQ scores over 2 years ($\beta =$ 0.21; CI: 0.07, 0.36; $P < 0.001$). This means that patients who had at least one important co-morbidity at baseline, had higher HAQ scores and thus lower functionality, even after intensive treatment, when adjusted for baseline age, gender, RF, ACPA, erosive disease, BMI, smoking, symptom duration and for DAS28-CRP at each visit. This co-morbidity status (RDCI $\geq$ 1) at baseline was related with an increase in HAQ scores over time of 0.215. There was also a significant association of the RDCI score at baseline with worse HAQ scores over 2 years ($\beta = 0.04$; 95% CI: 0.02, 0.06; $P < 0.001$).

Impact of co-morbidity on disease activity

In models predicting DAS28-CRP, having at least one clinically important co-morbidity at disease onset was related to higher disease activity scores over time ($\beta = 0.23$; 95% CI: 0.13, 0.32; $P < 0.001$). Accordingly, a higher RDCI score was associated with higher DAS28-CRP scores over 2 years ($\beta = 0.09$; 95% CI: 0.05, 0.13; $P < 0.001$). The odds ratio (OR) of achieving remission

Table 1 Baseline demographic and clinical characteristics of patients with and without co-morbidities

	Overall $n = 379$	Without co-morbidities $n = 212$	With co-morbidities $n = 167$	*P*-value
Demographic variables				
Age, years	52 (13)	47 (12)	58 (12)	<0.001
BMI, kg/m^2	26 (4)	26 (4)	27 (4)	0.020
Women, *n* (%)	262 (69)	145 (68)	117 (70)	0.728
Smoking status				0.752
Current smoker	97 (26)	57 (27)	40 (24)	
Ex-smoker	112 (29)	60 (28)	52 (31)	
Never smoked	170 (45)	95 (45)	75 (45)	
Median (IQR) symptom duration	23 (26)	21 (27)	25 (26)	0.210
Median (IQR) disease duration	1 (3)	1 (3)	1 (2)	0.470
RF positive, *n* (%)	252 (66)	142 (67)	110 (66)	0.820
ACPA positive, *n* (%)	249 (66)	137 (65)	112 (67)	0.619
Erosive disease, *n* (%)	97 (26)	41 (19)	56 (34)	0.002
Clinical variables				
DAS28-CRP	4.8 (1.3)	4.5 (1.2)	5.1 (1.2)	<0.001
Tender joint count (0–68)	14 (9)	13 (8)	15 (9)	0.007
Swollen joint count (0–66)	11 (7)	10 (7)	12 (7)	0.001
PGA, mm (0–100)	55 (24)	53 (23)	58 (24)	0.031
Pain, mm (0–100)	56 (24)	54 (23)	59 (25)	0.024
Fatigue, mm (0–100)	48 (24)	48 (23)	48 (25)	0.682
PhGA, mm (0–100)	52 (19)	51 (19)	54 (20)	0.108
ESR, mm/h	29.3 (22.9)	26.0 (22.1)	33.6 (23.3)	<0.001
CRP, mg/l	18.2 (28.5)	15.6 (27.3)	21.4 (29.7)	0.001
HAQ score (0–3)	1.0 (0.7)	0.9 (0.7)	1.1 (0.7)	0.007
PCS of SF-36	27 (13)	27 (13)	25 (12)	0.138
MCS of SF-36	49 (12)	50 (12)	48 (13)	0.114

Values reported are means (S.D.) unless specified otherwise. IQR: interquartile range; Symptom duration: weeks elapsed between onset of symptoms and start of treatment; Disease duration: weeks elapsed between diagnosis of RA and start of treatment; ACPA: anti-citrullinated protein antibody; DAS28-CRP: Disease Activity Score based on 28 joints with CRP; PGA: patient's global assessment; PhGA: physician's global assessment; SF-36: Short Form 36 questionnaire; PCS: physical component summary score; MCS: mental component summary score.

according to DAS28-CRP in patients having at least one co-morbidity was 0.72 (95% CI: 0.60, 0.87; $P < 0.001$), compared with patients without co-morbidities, indicating a decrease of 28% in the odds of achieving remission. Also, a higher RDCI score decreased the odds of achieving remission over 2 years (OR: 0.90; 95% CI: 0.82, 0.97; $P = 0.008$), indicating that per unit increase in the RDCI the odds of achieving remission decreased with 10%. All regression coefficients for fixed factors are shown in Supplementary Table S1, available at *Rheumatology* online.

Impact of co-morbidity on quality of life

The impact of co-morbidity status on the PCS and MCS of the SF-36 questionnaire was investigated using LMM analyses. Having co-morbidities at baseline was associated with lower scores of the PCS, indicating lower physical health-related quality of life. More specifically, having a RDCI of minimum 1, was related to a decrease of ~3.19 (95% CI: −4.84, −1.55; $P < 0.001$) on the PCS, compared with having no co-morbidities. Accordingly, a higher RDCI was related to worse PCS scores ($\beta = -1.12$; 95% CI: −1.85, −0.40; $P = 0.002$). There was no clear association between having co-morbidities and MCS ($\beta = -1.64$; 95% CI: −3.02, −0.26; $P = 0.020$), so there seemed to be no indication that baseline RDCI status was associated with improvement of mental health-related quality of life.

Impact of co-morbidity on occurrence of hospitalizations

Of the 379 patients included in CareRA, 56 (34%) of 167 patients with a baseline RDCI ≥ 1 needed to be hospitalized at some time during 2 years of follow-up compared with 19 (9%) of 212 with a baseline RDCI of zero ($P < 0.001$). An adjusted generalized estimating equations model showed that patients having co-morbidities were more likely to become hospitalized (OR = 3.73; 95% CI: 2.14, 6.49; $P < 0.001$). Higher RDCI scores were also significantly associated with a higher risk of hospitalization (OR = 1.46; 95% CI: 1.27, 1.67; $P < 0.001$).

TABLE 2 Prevalence of co-morbidities in participants of CareRA trial at screening

Variable	Results $n = 379$
RDCI, mean (S.D.)	0.84 (1.15)
RDCI, median (IQR)	0 (2)
RDCI = 0	212 (56)
RDCI = 1	65 (17)
RDCI = 2	70 (19)
RDCI ≥ 3	32 (8)
Hypertension	85 (22)
Cardiovascular disease	63 (17)
Pulmonary disease	32 (8)
Peptic ulcer or stomach disease	27 (7)
Depression	22 (6)
Diabetes mellitus	12 (3)
Malignancies	9 (2)
Fractures (spine/hip/leg)	3 (1)

Data are presented as absolute numbers (percentages) unless specified otherwise. RDCI: Rheumatic Diseases Comorbidity Index; IQR: interquartile range; Cardiovascular disease: myocardial infarction/stroke/other cardiac disease; Pulmonary disease: predominantly chronic obstructive pulmonary disease and allied conditions. The different components of the RDCI include specific, defined conditions [16].

Impact of co-morbidity independent of intensive treatment

Treatment was found to be also predicting functionality and disease activity over 2 years, although this was attributable to the Tight Step-Up treatment alone, which was related to worse functionality and disease activity scores compared with the other treatments (Supplementary Table S1, available at *Rheumatology* online). Therefore, we performed a sensitivity analysis, within patients treated with intensive treatment including a tapering down scheme of glucocorticoids, and not with the Tight Step-Up scheme, applying the same models. All results regarding the impact of co-morbidity status on outcomes resembled the results obtained within the entire population (Supplementary Table S2, available at *Rheumatology* online). Within this sub-population, there was no longer a relation between any of the COBRA treatment schemes and any of the outcomes tested.

Impact of different types of co-morbidity

The predictive value of the different types of co-morbidities was tested by repeating the LMM and GEE analyses for the same outcomes (Table 4 and Supplementary Table S3, available at *Rheumatology* online). Hypertension was significantly associated with functionality, disease activity and physical health-related quality of life. Additionally, depression was significantly associated with functionality, disease activity and mental health-related quality of life. Occurrence of hospitalization was not significantly related to any specific type of co-morbidity present at baseline. Achievement of remission was only related to fractures.

Discussion

Our data demonstrated a high prevalence of co-morbidities, already at diagnosis of RA, before treatment initiation, with nearly half of patients in our sample having at least one clinically important co-morbidity. We found that this burden of co-morbidity, was significantly related to worse functionality, worse disease control and worse physical health-related quality of life as well as to the occurrence of more hospitalizations. The use of intensive treatment regimens and applying the treat-to-target principle did not apparently counterbalance this effect of co-morbidity on outcomes.

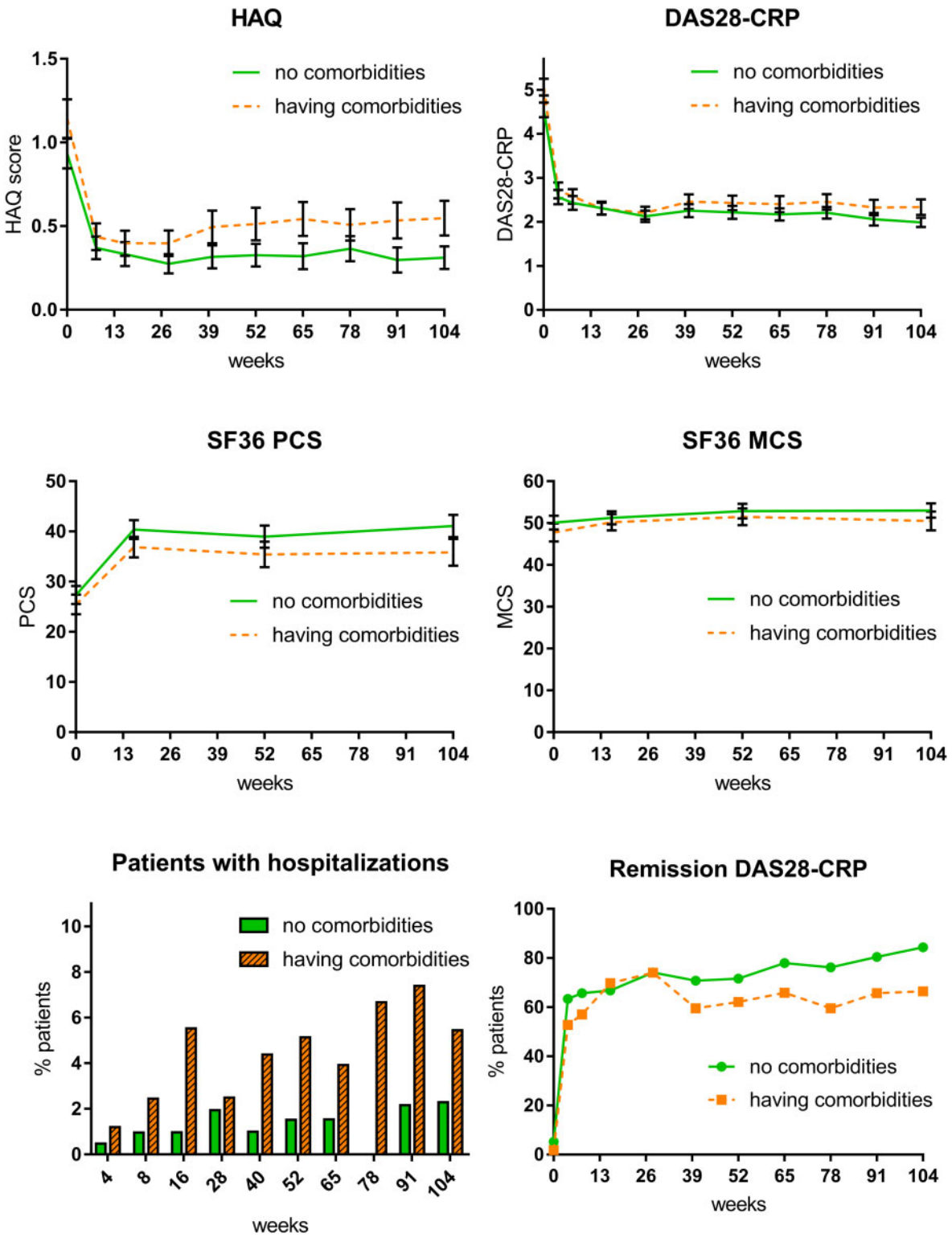
Physical function was impacted by co-morbidity, with a mean difference in HAQ scores over time of 0.215 in patients having co-morbidities compared with patients without, which reflects the minimal clinically important difference (MCID) for HAQ at the individual level. The impact of having a co-morbidity on functionality was also shown by a decrease in physical health-related quality of life of 3.1 over 2 years, which is above or near reported MCIDs of 2.5, 3.0 or 5.0 points for the PCS at the individual level [22]. Therefore, the demonstrated impact of co-morbidity on functionality can be considered clinically meaningful.

Having co-morbidities in the early disease stage was also related with higher disease activity over 2 years after treatment initiation, even when adjusted for possible confounders. Patients with co-morbidities had over time 28% decreased odds of achieving remission according to DAS28-CRP, even though they were treated intensively according to the most recent guidelines for management of RA. The impact of co-morbidity status at baseline seemed to be driven mainly by hypertension and depression. Finally, co-morbidity status was related to a higher risk of hospitalization over 2 years.

The prevalence of relevant co-morbidities at baseline within our cohort confirms a high co-morbidity burden, already at disease onset, as reported also in other early RA cohorts [1, 6, 23–25]. However, comparing prevalence rates directly between cohorts remains challenging because of differences in populations, methods of collection, registration of co-morbidities, study design, and use of other co-morbidity indices. Co-morbidity prevalence measured by RDCI in a cohort in the UK of early RA patients from the Royal College of General Practitioners Research and Surveillance database, was higher (mean 1.63; patients with ≥1 RDCI 66%) than in our cohort (mean 0.84; patients with ≥1 RDCI 44%). Patients in this UK cohort had similar patient characteristics (age and gender), but were more often smokers (current or past; 70% vs 55% in CareRA), and had more depression (28% vs 6% in CareRA).

We confirmed that the most common baseline co-morbidity in early RA is hypertension as in other cohorts, including the ESPOIR cohort in which the prevalence of

Fig. 1 Progression of disease outcomes over 2 years of follow-up



Mean values or percentages are depicted, and error bars indicate the 95% CI. Co-morbidity status was assessed as having a Rheumatic Disease Comorbidity Index score of ≥1 or 0; HAQ: Health Assessment Questionnaire; DAS28-CRP: Disease Activity Score based on 28 joints with CRP; SF-36: Short Form 36 questionnaire; PCS: physical component summary score; MCS: mental component summary score.

TABLE 3 Results of the longitudinal analyses to investigate the impact of co-morbidity status on different outcomes over 2 years

RDCI dichotomized into 2 groups (having co-morbidities or not)			
Linear mixed model analyses			
Outcome	Beta	95% CI	*P*-value
HAQ	0.215	0.071, 0.358	0.003
DAS28-CRP	0.225	0.132, 0.319	<0.001
PCS of SF-36	−3.195	−4.844, −1.546	<0.001
MCS of SF-36	−1.643	−3.024, −0.262	0.020
Generalized estimating equation analysis			
Outcome	OR	95% CI	*P*-value
Remission DAS28-CRP<2.6	0.724	0.604, 0.867	<0.001
Occurrence hospitalizations	3.725	2.136, 6.494	<0.001
RDCI continuous			
Linear mixed model analyses			
Outcome	Beta	95% CI	*P*-value
HAQ	0.039	0.019, 0.059	<0.001
DAS28-CRP	0.089	0.048, 0.129	<0.001
PCS of SF-36	−1.122	−1.847, −0.398	0.002
MCS of SF-36	−0.606	−1.212, 0.000	0.050
Generalized estimating equation analysis			
Outcome	OR	95% CI	*P*-value
Remission DAS28-CRP<2.6	0.895	0.824, 0.972	0.008
Occurrence hospitalizations	1.459	1.274, 1.670	<0.001

Results come from a separate model for each outcome with co-morbidity status at baseline, treatment and time as predictors. Co-morbidity status was assessed as either having a Rheumatic Disease Comorbidity Index (RDCI) score of ≥1 or 0 or by the RDCI score; HAQ: Health Assessment Questionnaire; DAS28-CRP: Disease Activity Score based on 28 joints with CRP; SF-36: Short Form 36 questionnaire; PCS: physical component summary score; MCS: mental component summary score; OR: odds ratio.

arterial hypertension was increased in early RA compared with the general population [1, 6, 23–25]. This is consistent with previous evidence that RA is an independent risk factor for cardiovascular diseases, and that individuals who have had RA for several years have around a 2-fold higher risk for cardiovascular disease compared with individuals without RA after taking account of most traditional risk factors [26].

Our findings that co-morbidity status at baseline is associated with worse functionality and disease control, already at baseline, were also demonstrated based on data from the Canadian Early Arthritis Cohort (CATCH). The negative impact of co-morbidity on function over time was also seen in the CATCH cohort and in the cohort from the Early Rheumatoid Arthritis Study (ERAS) [6, 23]. However, these studies were performed based on registries in which treatment was not protocolized, although the authors adjusted for type of RA treatment in their statistical analyses. The impact of co-morbidity at baseline on achieving remission in early RA, which we demonstrated in CareRA was also seen in the CATCH cohort and was previously reported in established RA [10, 23]. However, this relation was not seen in the ERAS cohort [6]. The fact that mental health-related quality of life was not affected by co-morbidity was also reported by Radner and colleagues [9].

A strength of our study is that we used data of a prospective pragmatic RCT, reflecting daily clinical practice. By randomizing treatment, we avoided that treatment allocation was influenced by having (more severe) co-morbidities, thereby limiting channelling bias, in contrast to cohort studies. Moreover, contrary to classical RCTs, we did not exclude patients with important co-morbidities or with very high disease activity due to less stringent inclusion criteria. Collection of co-morbidities was performed by physicians and data entry was systematically monitored by comparison with the medical records. We have previously shown that the treatment schemes including glucocorticoids had similar effectiveness outcomes over time in the CareRA trial, with comparable numbers of patients needing treatment adaptations [27]. Therefore, a potential effect of RA treatment on the impact of co-morbidity on studied outcomes could also be investigated and precluded. The treatment strategy applied within CareRA is in line with the latest guidelines for management of RA, enhancing relevance for daily practice. An additional strength is the evaluation of the influence of co-morbidity on the cumulative burden of the different outcomes for patients over 2 years and not based on point estimates at a certain time point.

We used the RDCI, which was developed to measure more accurately the burden and prognostic impact of

TABLE 4 Results of the longitudinal analyses to investigate the impact of different types of co-morbidity on all outcomes over 2 years

Type of co-morbidity	HAQ		DAS28-CRP		Remission DAS28-CRP<2.6	
	β	95% CI	β	95% CI	OR	95% CI
Pulmonary disease	−0.04	−0.13, 0.04	−0.04	−0.13, 0.04	1.16	0.83, 1.63
Cardiovascular disease	−0.03	−0.09, 0.04	−0.03	−0.09, 0.04	0.91	0.71, 1.18
Hypertension	0.20*	0.15, 0.26	0.20*	0.15, 0.26	0.76	0.62, 0.95
Fracture	0.09	−0.21, 0.39	0.09	−0.21, 0.39	0.40*	0.24, 0.66
Depression	0.20*	0.10, 0.30	0.20*	0.10, 0.30	0.64	0.43, 0.96
Diabetes mellitus	0.05	−0.08, 0.18	0.05	−0.08, 0.18	1.03	0.67, 1.57
Malignancy	0.07	−0.09, 0.22	0.07	−0.09, 0.22	0.63	0.31, 1.29
Peptic ulcer or stomach disease	0.05	−0.04, 0.13	0.05	−0.04, 0.13	0.79	0.55, 1.15

Type of co-morbidity	SF-36 PCS		SF-36 MCS		Hospitalizations	
	β	95% CI	β	95% CI	OR	95% CI
Pulmonary disease	0.81	−2.21, 3.82	−1.75	−4.27, 0.76	2.25	1.13, 4.50
Cardiovascular disease	−0.45	−2.77, 1.88	0.48	−1.46, 2.42	1.58	0.88, 2.82
Hypertension	−4.74*	−6.76, −2.72	0.68	−1.00, 2.37	1.73	1.05, 2.86
Fracture	−7.52	−18.42, 3.38	3.68	−5.39, 12.75	2.80	0.63, 12.54
Depression	−3.35	−7.10, 0.40	−6.94*	−10.07, −3.82	1.46	0.54, 3.90
Diabetes mellitus	0.20	−4.28, 4.69	−4.54	−8.27, −0.80	1.68	0.64, 4.44
Malignancy	0.00	−5.69, 5.70	2.01	−2.73, 6.76	2.05	0.66, 6.39
Peptic ulcer or stomach disease	−2.08	−5.12, 0.96	−0.42	−2.96, 2.11	1.17	0.58, 2.35

*Significant predictor at the <0.010 level. Beta coefficients or odds come from a separate model for each outcome with types of co-morbidity status at baseline, treatment and time as predictors. Co-morbidity status was assessed as having a particular co-morbidity (yes/no); HAQ: Health Assessment Questionnaire; DAS28-CRP: Disease Activity Score based on 28 joints with CRP; SF-36: Short Form 36 questionnaire; PCS: physical component summary score; MCS: mental component summary score; OR: odds ratio.

overall co-morbidity, specifically in rheumatic diseases, based on a weighted preselection of co-morbid conditions. Moreover, this index has been validated in RA to predict physical functioning measured by HAQ [16]. More recently, this RDCI was proven to perform comparably well in predicting HAQ, number of hospitalizations, as well as PCS and MCS of SF-36 in patients with RA, compared with other widely used co-morbidity indices such as the Charlson and the Functional Co-morbidity index [17, 28]. We chose to use the RDCI since this index has been developed and validated to predict all outcomes of interest to us in our specific study population.

A limitation of our study is the limited sample size in comparison with large registries, but our study population mirrors closely an early RA population in daily clinical practice, is well characterized and confounding by indication could be avoided. It might be that not all co-morbid conditions have been registered by the physician. However, all indications provided for currently taken medication were revised in search of clues for the presence of additional co-morbidities.

Restoration of physical function is, next to achieving remission, one of the most important outcomes in RA since it affects patients' well-being as well as ability to work and mortality [29–31]. With our findings, we are able to provide a perspective of estimated effect of co-morbidity on function, even in early RA under intensive treatment. Rheumatologists should be aware of this and take into account co-morbidities in their RA management plan, instead of keeping too narrow a focus on controlling RA disease activity. Future research should further elucidate the dynamics of the mutual interaction between RA disease activity and co-morbidity over time and how to deal in practice with this important challenge.

In conclusion, we demonstrated a negative effect of having co-morbidities at disease onset of RA on the evolution of disease activity and disability, which could not be mitigated even with intensive treatment strategies.

Acknowledgements

We would like to express our gratitude to all participating patients, as well as to the investigators and medical staff at all sites. We thank all study personnel for their

contributions to the study. We would also like to thank statistician Anna Ivanova for her advice. PV, JJ and RW designed the study protocol in collaboration with the CareRA study group. Investigators of the CareRA study group, including PV and RW recruited and enrolled patients and were responsible for daily patient management. PV and JJ were responsible for coordination of the trial and of collection of data. VS was responsible for data analysis. All authors contributed to interpretation of the data. Furthermore, VS, PV, DDC and RW drafted the manuscript. DB, SP, KVdE and JJ revised it critically for important intellectual content. All authors have approved the final draft for publication. PV and VS are the guarantors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Collaborators

On behalf of the CareRA study group: Maeyaert B, De Brabanter G, Devinck M, Langenaken C, Lenaerts J, Corluy L, Remans J, Vander Cruyssen B, Ravelingien I, Van Essche E, Vandevyvere K, Durnez A, Verbruggen A, Geens E, Raeman F, Joos R, de Vlam K, Taelman V, Vanhoof J, Coppens M, Geusens P, Sileghem A, Volders P, Van Den Bosch F, Verschueren P, Westhovens R.

Funding: This RCT was made possible by a grant from the Flemish Government Agency for Innovation by Science and Technology (IWT). PV holds the unrestricted Pfizer Chair for 'Early Rheumatoid Arthritis Management' at the KU Leuven and grants were also provided by the Fund for Scientific Research in Rheumatology (FWRO) and the Academic Foundation of Leuven. Leflunomide was made available for free by Sanofi Belgium without any influence on trial design. The funders of the study had no role in study design, data collection, analysis and interpretation or reporting of this study.

Disclosure statement: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work other than those listed above; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval

The study was approved by the leading Ethics Committee of the University Hospitals Leuven after consulting the medical ethics committee of each participating centre (ref s51411) and all study participants gave their written informed consent before inclusion.

Transparency declaration

The guarantors affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Patient involvement

The pragmatic CareRA protocol was strongly inspired by daily interactions of the investigators with RA patients in daily clinical practice. Patients were not formally involved in setting the research question or the outcome measures, nor were they invited to comment on study design or the interpretation of results of this manuscript. However, results of this research will be disseminated to study participants, all stakeholders and the general public in collaboration with patient organizations and the Belgian Patient Partners Program (trained patients who educate physicians, medicine students and other healthcare professionals in collaboration with a rheumatologist).

Data availability statement

The authors commit to making the relevant anonymized patient level data available for a specified purpose approved by the institution and the principal investigator of the CareRA study and with a signed data access agreement.

Supplementary data

Supplementary data are available at *Rheumatology* online.

References

1 Nikiphorou E, de Lusignan S, Mallen C *et al.* Prognostic value of comorbidity indices and lung diseases in early rheumatoid arthritis: a UK population-based study. Rheumatology (Oxford) 2020;59:1296–1305.

2 Radner H, Smolen JS, Aletaha D. Impact of comorbidity on physical function in patients with rheumatoid arthritis. Ann Rheum Dis 2010;69:536–41.

3 An J, Nyarko E, Hamad MA. Prevalence of comorbidities and their associations with health-related quality of life and healthcare expenditures in patients with rheumatoid arthritis. Clin Rheumatol 2019;38:2717–26.

4 van den Hoek J, Roorda LD, Boshuizen HC *et al.* Long-term physical functioning and its association with somatic comorbidity and comorbid depression in patients with established rheumatoid arthritis: a longitudinal study. Arthritis Care Res (Hoboken) 2013;65:1157–65.

5 Ranganath VK, Maranian P, Elashoff DA *et al.* Comorbidities are associated with poorer outcomes in community patients with rheumatoid arthritis. Rheumatology (Oxford) 2013;52:1809–17.

6 Norton S, Koduri G, Nikiphorou E *et al.* A study of baseline prevalence and cumulative incidence of comorbidity and extra-articular manifestations in RA and their impact on outcome. Rheumatology (Oxford) 2013; 52:99–110.

7 Marques WV, Cruz VA, Rego J, Silva N. D. The impact of comorbidities on the physical function in patients with rheumatoid arthritis. Rev Bras Reumatol 2016;56:14–21.

8 Han G-M, Han X-F. Comorbid conditions are associated with healthcare utilization, medical charges and mortality of patients with rheumatoid arthritis. Clin Rheumatol 2016;35:1483–92.

9 Radner H, Smolen JS, Aletaha D. Comorbidity affects all domains of physical function and quality of life in patients with rheumatoid arthritis. Rheumatology 2011; 50:381–8.

10 Radner H, Yoshida K, Frits M *et al.* The impact of multimorbidity status on treatment response in rheumatoid arthritis patients initiating disease-modifying anti-rheumatic drugs. Rheumatology (Oxford) 2015;54: 2076–84.

11 Conti F, Atzeni F, Massaro L *et al.* The influence of comorbidities on the efficacy of tumour necrosis factor inhibitors, and the effect of tumour necrosis factor inhibitors on comorbidities in rheumatoid arthritis: report from a National Consensus Conference. Rheumatology (Oxford) 2018;57:vii11–22.

12 Biggioggero M, Mesina F, Favalli EG. The use of rheumatic disease comorbidity index for predicting clinical response and retention rate in a cohort of rheumatoid arthritis patients receiving tumor necrosis factor alpha inhibitors. Biomed Res Int 2019;2019: 6107217.

13 Martin WJ, Shim M, Paulus HE; RADIUS Investigators *et al.* Older age at rheumatoid arthritis onset and comorbidities correlate with less Health Assessment Questionnaire-Disability Index and Clinical Disease Activity Index response to etanercept in the RADIUS 2 registry. J Clin Rheumatol 2014;20:301–5.

14 Iannone F, Salaffi F, Fornaro M *et al.* Influence of baseline modified Rheumatic Disease Comorbidity Index (mRDCI) on drug survival and effectiveness of biological treatment in patients affected with Rheumatoid arthritis, Spondyloarthritis and Psoriatic arthritis in real-world settings. Eur J Clin Invest 2018;48:e13013.

15 Michaud K, Wolfe F. Comorbidities in rheumatoid arthritis. Best Pract Res: Clin Rheumatol 2007;21: 885–906.

16 England BR, Sayles H, Mikuls TR, Johnson DS, Michaud K. Validation of the rheumatic disease comorbidity index. Arthritis Care Res 2015;67:865–72.

17 Putrik P, Ramiro S, Lie E *et al.* Deriving common comorbidity indices from the MedDRA classification and exploring their performance on key outcomes in patients with rheumatoid arthritis. Rheumatology 2018;57:548–54.

18 Stouten V, Westhovens R, Pazmino S; on behalf of the CareRA study group *et al.* Effectiveness of different combinations of DMARDs and glucocorticoid bridging in early rheumatoid arthritis: two-year results of CareRA. Rheumatol 2019;58:2284–94.

19 Verschueren P, De Cock D, Corluy L *et al.* Effectiveness of methotrexate with step-down glucocorticoid remission induction (COBRA Slim) versus other intensive treatment strategies for early rheumatoid arthritis in a treat-to-target approach: 1-year results of CareRA, a randomised pragmatic open-label superiority trial. Ann Rheum Dis 2017;76:511–20.

20 Smolen JS, Landewé RBM, Bijlsma JWJ *et al.* EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Ann Rheum Dis 2020; 79:685–699.

21 Jenkinson C, Stewart-Brown S, Petersen S, Paice C. Assessment of the SF-36 version 2 in the United Kingdom. J Epidemiol Community Health 1999;53:46–50.

22 Ward MM, Guthrie LC, Alba MI. Clinically important changes in short form-36 scales for use in rheumatoid arthritis clinical trials: the impact of low responsiveness. Arthritis Care Res 2014;66:1783–9.

23 Hitchon CA, Boire G, Haraoui B; the CATCH investigators *et al.* Self-reported comorbidity is common in early inflammatory arthritis and associated with poorer function and worse arthritis disease outcomes: results from the Canadian Early Arthritis Cohort. Rheumatol (United Kingdom) 2016;55:1751–62.

24 Innala L, Sjöberg C, Möller B *et al.* Co-morbidity in patients with early rheumatoid arthritis – inflammation matters. Arthritis Res Ther 2016;18:33.

25 Gherghe AM, Dougados M, Combe B *et al.* Cardiovascular and selected comorbidities in early arthritis and early spondyloarthritis, a comparative study: results from the ESPOIR and DESIR cohorts. RMD Open 2015;1:e000128.

26 Solomon DH, Goodson NJ. The cardiovascular system in rheumatic disease: the newest 'extraarticular' manifestation? J Rheumatol 2005;32:1415–7.

27 Verschueren P, Stouten V, Westhovens R, De Cock D, Pazmino S. Comment on: what is the best treatment for early rheumatoid arthritis? Rheumatology 2020; doi: 10.1093/rheumatology/keaa106.

28 Aslam F, Khan NA. Tools for the assessment of comorbidity burden in rheumatoid arthritis. Front Med 2018;5:39.

29 Wolfe F, Michaud K, Gefeller O, Choi HK. Predicting mortality in patients with rheumatoid arthritis. Arthritis Rheum 2003;48:1530–42.

30 Wolfe F. A reappraisal of HAQ disability in rheumatoid arthritis. Arthritis Rheum 2000;43:2751–61.

31 Allahan LF, Bloch DA, Pincus T. Identification of work disability in rheumatoid arthritis: physical, radiographic and laboratory variables do not add explanatory power to demographic and functional variables. J Clin Epidemiol 1992;45:127–38.