Incidence and predictors of adverse clinical events in patients with rheumatoid arthritis and asymptomatic left ventricular systolic dysfunction

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Abstract

Objective

Patients with rheumatoid arthritis (RA) are exposed to impairment in left ventricular (LV) function, which is a prognosticator of poorer clinical outcomes. In this study we assessed prevalence and factors associated with adverse outcomes in patients with RA and asymptomatic LV systolic dysfunction (LVSD).

Methods

We prospectively analysed 102 RA patients with asymptomatic LVSD consecutively selected by a pool of 418 RA patients referred to the Division of Rheumatology, University of Verona, between March 2014 and March 2015. LVSD was defined as impaired global longitudinal strain (GLS) measured by echocardiography. The pre-specified study end-points were all-cause death/hospitalisation, and death/hospitalisation for cardiovascular cause.

Results

During a follow-up of 35 [13–54] months, all-cause death/hospitalisation occurred in 40 patients (39%). No patient died during the follow-up, 18 patients (18% of the study population) had a cardiovascular event which required hospitalisation, while 22 (22% of patients) required hospitalisation, but this was unrelated to CV. Multiple Cox regression analysis identified worse renal function, more frequent use and a higher number of biologic DMARDs used before enrolment as independent predictors of all-causes hospitalisation. The same variables together with higher LV mass predicted CV hospitalisation. Prognostic cut-off points were 90 ml/min/1.73 m^2 for glomerular filtration rate and 49 $g/m^{2.7}$ for LV mass.

Conclusion

RA patients with asymptomatic LVSD have a very high rate of all-cause and cardiovascular hospitalisation at mid-term follow-up, predicted by worse renal function, higher LV mass, more frequent use and higher number of biologic DMARDs used before enrolment, suggesting that biologic DMARDs refractory is a proxy of adverse events.

Key words

rheumatoid arthritis, left ventricular function, global longitudinal strain, prognosis.

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Introduction

Asymptomatic left ventricular (LV) systolic dysfunction (LVSD) is detectable by several echocardiographic techniques in a consistent proportion of patients with rheumatoid arthritis (RA) analysed in primary prevention (1-7). Haemodynamic causes together with other unfavourable non-haemodynamic conditions related to RA status (pro-inflammatory, immuno-modulatory, cytotoxic molecules and hyper-activated neuro-hormonal pathways such as renin-angiotensin-aldosterone system) (8-11) could be involved in the genesis of LVSD found in these subjects. LVSD is faithfully associated with adverse outcomes in a number of patients at increased risk for adverse cardiovascular (CV) events such as those with aortic stenosis (12), diabetes mellitus (13), arterial hypertension (14), also including RA patients themselves (7). Little information exists on the predictors and prevalence of adverse clinical events in the high-risk subgroup of RA patients with asymptomatic LVSD who have never been analysed in detail. Accordingly, the purposes of this study were to assess prevalence and factors associated with adverse outcomes in patients with RA and asymptomatic LVSD analysed in primary prevention.

Methods

Study population

The initial study population comprised 418 non-institutionalised subjects >18 years of age with RA diagnosed by clinical and laboratory examination according to the American College of Rheumatology criteria (15). Among these 418 patients, 102 (24%) had LVSD at echocardiographic baseline evaluation (see "echocardiography" paragraph below for details): these patients formed the final population which was analysed in the present study. Participants were consecutively recruited from March 2014 to March 2015 at the Division of Rheumatology, Department of Medicine, University and Azienda Ospedaliera Universitaria Integrata of Verona (Italy) with fully accessible cardiac units provided in which patients underwent echocardiographic, clinical and laboratory evaluations.

All subjects were free of symptoms/signs of cardiac disease. Exclusion criteria were a history of myocardial infarction, myocarditis or heart failure, coronary heart disease diagnosed by clinical, electrocardiographic evaluation at rest and by the results of exercise/scintigraphy/echo-stress test, alcoholic cardiomyopathy, primary hypertrophic cardiomyopathy, asymptomatic known LVSD, prior myocardial revascularisation, significant valve heart disease, atrial fibrillation. All patients gave written informed consent signing a specific institutional consent form, the study was approved by Ethical Committees of the Verona University and conforms to the ethical guidelines of the Declaration of Helsinki as revised in 2000.

Definitions

We defined patients as biologic disease-modifying anti-rheumatic drugs (DMARDs) refractory on the date they had started their third class of biologic DMARDs before the enrolment into the study (16). Hypertension was defined as systolic blood pressure of ≥140 mmHg and/or a diastolic blood pressure of ≥90 mmHg and/or pharmacologically treated blood pressure of unknown aetiology. Obesity was recognised when body mass index (BMI) ≥30 kg/m^2. Dyslipidaemia was defined as levels of total serum cholesterol >190 mg/dL and or triglycerides >150 mg/dL or pharmacologically treated high lipid serum levels. To assess renal function we considered the glomerular filtration rate (GFR) estimated with the CKD-EPI equation.

The pre-specified primary end-point of the study was defined as a composite of all-cause death or all-cause hospitalisation. We also considered a co-primary end-point defined as death or hospitalisation for CV causes. The follow-up information was obtained every 6 months by visiting or interviewing the patients and/or their relatives. Follow-up lasted since March 1, 2014 to December 31, 2018. All clinical events were examined by an independent end-point classification committee. Each clinical event was diagnosed and classified by three expert clinicians who analysed in detail the clinical reports, validated the endpoints and formally generated the information which migrated into the database.

Echocardiography

All Doppler-echocardiographic studies were performed using Alpha Esaote Biomedica machine (Florence, Italy) equipped with a 2.5–3.5 MHz annular-array transducer following a standardised protocol by experienced cardiologists. LV chamber dimensions and wall thicknesses were measured by the American Society of Echocardiography guidelines and LV mass was calculated using a validated formula (17). LV mass was normalised for height to the 2.7 power and LV hypertrophy was defined as LV mass ≥49.2 g/m$^{2.7}$ for men and ≥46.7 for women (18). Relative wall thickness was calculated as the ratio 2*end-diastolic posterior wall thickness/LV diameter and indicated concentric LV geometry if ≥0.43 (the 97.5 percentile in a normal population) (19). LV end-diastolic and end-systolic volumes were measured by the biplane method of disks from 2D apical 4 and 2 chamber view and used to calculate LV ejection fraction (LVEF) (reduced if <50%).

LV systolic function was assessed by Xstrain 2D Speckle Tracking technology software (ESAOTE Biomedica - Florence, Italy). Apical 2D views were recorded and analysed for global longitudinal strain (GLS), including the 4-chamber, 2-chamber and apical long-axis views. GLS was calculated as the average of 16 myocardial segments, as previously reported (7). The cut-off value for low GLS (suggesting impairment of longitudinal component of LV systolic function, defined as longitudinal LVSD) was identified *a priori* as -16.0% (7).

Transmitral and pulmonary vein pulsed wave Doppler curves and early diastolic Tissue Doppler velocity of mitral annulus (E') were assessed according to the recommendations of the American Society of Echocardiography (20). Early diastolic velocity of transmitral flow (E) was divided by E' and used to classify LV diastolic function together with other parameters (E/A ratio of transmitral flow, deceleration time of E and the difference in duration of atrial wave on pulmonary vein flow and atrial wave on transmitral flow) in 4 degrees as proposed by Redfield *et al*. (21): normal, mild dysfunction, moderate dysfunction and severe dysfunction. Aortic stiffness index was assessed at the level of the aortic root using a two-dimensional guided M-mode evaluation of systolic and diastolic diameters of ascending aorta, 3 cm above the aortic valve together with blood pressure measured by cuff sphygmomanometer, as previously described (22, 23).

Statistical analysis

The data are reported as mean values ±1 standard deviation (medians and interquartile ranges for variables deviating from normality) or percentages. Unpaired Student's test and χ^2 statistics were used for descriptive statistics. Between-group comparisons of categorical and continuous variables were performed by χ^2 test and analysis of variance (ANOVA) with comparison between each group by Scheffè test for unequal sample, as appropriate. The study population was initially stratified by status of LVSD at baseline. Thus, Log cumulative hazard functions were computed by univariate and multivariate Cox proportional hazards analyses to identify the factors independently associated with the study end-points in the 102 patients with LVSD. Variables that were significantly related to the study end-points in univariate tests (p<0.01) were included in the multivariate models.

The independent predictors of the study end-points GFR and LV mass were subsequently scrutinised and prognostic cut-points were obtained by specific receiver operating characteristic (ROC) curve analyses. All analyses were performed using statistical package SPSS 19.0 (SPSS Inc. Chicago. IL, USA) and statistical significance was identified by two-tailed p<0.05.

Results

The study population initially consisted of 418 patients with RA (mean age of 58±11 years, 66% women). LVSD was detected in 102 out of 418 patients (24.4%) whose baseline clinical and echocardiographic characteristics are shown in Tables I. Prevalence of obesity and dyslipidaemia was 15% and 67%, respectively, near half of patients had a diagnosis of arterial hypertension, the mean duration of RA was 14±10 years, disease activity was high in 23% of them. One-third of patients were receiving non-steroidal anti-inflammatory drugs (NSAIDs) at enrolment, and 77% were receiving biologic DMARDs. Concerning the echocardiographic parameters, near one-third had LV hypertrophy, two-third concentric LV geometry, one-third LV diastolic dysfunction.

The 102 RA patients with LVSD detected by speckle tracking echocardiography represented the final population of the study. Compared to the counterparts without LVSD, these subjects had similar clinical characteristics but older age at enrolment, and were receiving comparable pharmacological treatment for RA disease and CV risk factors control, even if RA patients with LVSD tended to receive more ACEi/ARB (Table I). They were treated less frequently with biologic DMARDs before enrolment into the study. Prevalence of biologic DMARDs refractory was similar between the two groups. Analysing the echocardiographic data, the patients with LVSD had higher LV relative wall thickness and higher prevalence of concentric LV geometry than those with normal LV systolic function.

During a median follow-up of 35 (13–54) months, a primary end-point (all-cause death or hospitalisation) occurred in 40 patients (39%). No patient died during the follow-up, 18 patients (18% of the total study population) had a CV event requiring hospitalisation (co-primary end-point): 8 persistent atrial fibrillation, 4 thromboembolism, 3 chest pain due to ascertained coronary artery disease, 2 congestive heart failure, 1 acute pericarditis. Hospitalisations unrelated to CV cause were 22 (22%): 8 acute orthopaedic disease or surgery, 4 symptoms/signs related to a new diagnosis of cancer (2 breast, 1 colorectal, 1 pancreas), 4 lung infection, 3 severe uveitis, 2 acute prostatitis, 1 severe uterine bleeding. The rate of hospitalisation for all-causes or for CV cause was significantly higher in the 102 patients with LVSD than in the 316 counterparts without LVSD (39% *vs*. 23%, p=0.04 and 18% *vs*. 5%, p=0.0004, respectively). However, the

Table I. Main clinical characteristics of the 418 patients with rheumatoid arthritis divided according to the presence of asymptomatic left ventricular systolic dysfunction.

Variables	LVSD No (316 patients)	LVSD Yes (102 patients)	*p*-value	Total study population (418 patients)
Age (years)	57 ± 11	62 ± 11	0.002	58 ± 11
Female gender (%)	70	58	0.08	66
Body mass index (kg/m^2)	25.9 ± 4.0	26.5 ± 4.4	0.37	26.1 ± 4.2
Obese (%)	14	16	0.76	15
Systolic blood pressure (mmHg)	133 ± 17	133 ± 13	0.90	133 ± 18
Hypertension (%)	50	60	0.16	53
Dyslipidaemia (%)	64	73	0.26	67
Active smoker, %	39	54	0.06	43
Diabetes (%)	7	14	0.15	10
Glomerular filtration rate (ml/min/1.73m^2)	93 ± 22	96 ± 22	0.31	94 ± 22
Cholesterol LDL (mg/dl)	121 [95-135]	124 [101-145]	0.69	122 [94-141]
Triglycerides (mg/dl)	105 [75-138]	125 [85-165]	0.08	110 [78-142]
C-reactive protein (mg/l)	4.6 [2.3-6.8]	3.9 [2.0-6.7]	0.15	4.4 [1.9-6.8]
Rheumatoid factor positive (%)	49	48	0.85	49
Cyclic citrullinated peptide positive (%)	52	48	0.85	51
Duration of rheumatoid arthritis (years)	14 ± 10	14 ± 12	0.95	14 ± 10
Clinical disease activity index	10 ± 9	10 ± 9	0.88	10 ± 9
High activity of disease (%)	24	19	0.48	23
Pharmacological treatment				
Betablockers (%)	22	12	0.15	18
ACEi / ARB (%)	29	43	0.06	34
Diuretics (%)	16	20	0.52	17
Calcium antagonists (%)	9	10	0.78	9
Anti-platelets agents (%)	12	18	0.27	13
Statins (%)	23	32	0.23	27
NSAIDs (%)	38	27	0.15	34
Metotrexate (%)	44	53	0.27	47
Biologic DMARDs at enrolment (%)	80	71	0.19	77
Biologic DMARDs class				
anti-TNF-α (%)*	66	72	0.85	68
anti-interleukin 6 (%)*	10	16	0.66	12
CTLA 4Ig (%)*	16	10	0.58	14
anti-CD 20 (%)*	8	2	0.15	6
Biologic DMARDs before enrolment (%)	56	32	0.02	48
Biologic DMARDs before enrolment (n°)	1.44	1.06	0.30	1.20
Biologic DMARDs refractory (%)	15	16	0.83	15
Corticosteroids (%)	42	44	0.83	43
Echocardiography				
LV end-diastolic volume (ml/m^2)	47 ± 10	47 ± 10	0.76	47 ± 10
LV relative wall thickness	0.45 ± 0.06	0.48 ± 0.08	0.04	0.46 ± 0.07
Concentric LV geometry (%)	63	78	0.04	67
LV mass index (g/m $^{2.7}$)	45 ± 10	46 ± 12	0.43	45 ± 10
LV hypertrophy (%)	36	37	0.88	36
LV ejection fraction (%)	66 ± 6	65 ± 6	0.11	66 ± 6
LV global longitudinal strain (%)	-19.8 ± 2.5	-13.9 ± 1.8	< 0.001	-18.4 ± 3.5
E / E' ratio	6.3 ± 1.4	6.5 ± 1.9	0.42	6.3 ± 1.5
LV diastolic dysfunction (%)	27	33	0.35	28
Ascending aorta stiffness index (%)	5.8 ± 4.0	6.5 ± 4.2	0.28	6.0 ± 4.2

ACEi: angiotensin-converting enzyme inhibitors; ARB: angiotensin T1 receptor blockers; CD: cluster of differentiation; CTLA: cytotoxic T-lymphocyte antigen; DMARDs: disease-modifying anti-rheumatic drugs; LV: left ventricular; n°: number of patient; NSAIDs: non-steroidal anti-inflammatory drugs; TNF: tissue necrosis factor.
*% among patients who were receiving biologic DMARDs.

rate of non-CV events was similar between patients with LVSD (22%) and without LVSD (18%, *p*=ns), suggesting that the association between all-cause hospitalisations and LVSD was fundamentally explained by the CV-related hospitalisations.

The variables which significantly differed between patients who experienced a primary study end-point were older age, female gender, higher systolic blood pressure, lower GFR, greater LV end-diastolic volume, LV diastolic dysfunction, higher aortic stiffness, more frequent use and higher number

Table II. Variables which significantly differed between the patients who experienced a primary or co-primary end-points and those who did not.

102 patients with rheumatoid arthritis and LV systolic dysfunction	Endpoint NO	Endpoint YES	*p*-value
Death or all-cause hospitalisation	62 patients	40 patients	
Age (years)	59 ± 11	67 ± 8	0.008
Female gender (%)	45	75	0.03
Systolic blood pressure (mmHg)	129 ± 11	140 ± 14	0.003
Glomerular filtration rate (ml/min/1.73 m^2)	105 ± 22	82 ± 15	<0.001
E/E'	6.1 ± 1.4	7.2 ± 2.2	0.04
LV diastolic dysfunction (%)	23	50	0.04
LV end-diastolic volume (ml/m^2)	49 ± 10	43 ± 10	0.04
Aortic stiffness index (%)	5.5 ± 3.7	8.0 ± 4.6	0.03
Biologic DMARDs before enrolment (%)	18	41	0.03
Biologic DMARDs before enrolment (n.)	0.5	1.63	0.001
Global longitudinal strain (%)	-14.0 ± 1.6	-13.6 ± 2.0	0.46
CV death or CV hospitalisation	77 patients	25 patients	
Glomerular filtration rate (ml/min/1.73 m^2)	100 ± 23	81 ± 14	<0.001
LV diastolic dysfunction (%)	26	67	0.02
LV mass (g/$m^{2.7}$)	44 ± 11	55 ± 17	0.02
LV hypertrophy (%)	31	67	0.04
Biologic DMARDs before enrolment (%)	23	57	0.02
Biologic DMARDs before enrolment (n.)	0.6	2.0	0.001
Global longitudinal strain (%)	-14.0 ± 1.7	-13.3 ± 1.9	0.29

DMARDs: disease-modifying anti-rheumatic drugs; LV: left ventricular; n.: number of DMARDs per patient.

of biologic DMARDs per patient received before enrolment (Table II, upper part). In particular, the prevalence of biologic DMARDs refractory was 75% in patients who experienced a primary endpoint ad 55% in patients who did not (p=0.04). The variables which significantly differed between patients who experienced a co-primary study end-point were lower GFR, higher LV mass, LV diastolic dysfunction, more frequent use and higher number of biologic DMARDs taken before enrolment were all associated with the co-primary end-point (Table II, lower part). The prevalence of biologic DMARDs refractory was 50% in patients who experienced a co-primary endpoint ad 30% in patients who did not (p=0.04).

For the primary end-point, the variables included in the multivariate Cox regression analyses were age, systolic blood pressure, GFR, use (%) of biologic DMARDs before enrolment and number of biologic DMARDs taken before enrolment. This analysis revealed that lower GFR, more frequent use and higher number of biologic DMARDs taken before enrolment were the variables independently related to the primary end-point (Table III, upper part).

For the co-primary end-point, the variables included in the multivariate Cox regression analyses were GFR, LV mass, use (%) of biologic DMARDs before enrolment and number of biologic DMARDs taken before enrolment. The analysis showed that lower GFR, higher LV mass, more frequent use and higher number of biologic DMARDs used before enrolment and were the independent predictor of CV hospitalisation (Table III, lower part).

ROC curve analysis showed that the best cut-off value of GFR for predicting the study end-points was 90 ml/min/1.73 m^2 (AUC 0.83[95% CI=0.70–0.98], p<0.01) for all-cause hospitalisation and 90 ml/min/1.73 m^2 (AUC 0.76 [95% CI=0.59–0.92], p<0.01) for CV hospitalisation. The best cut-off value of LV mass was 49 g/$m^{2.7}$ (AUC 0.70 [95% CI=0.46–0.94], p<0.01) for CV hospitalisation.

Discussion

Three remarkable and original findings emerge by the present investigation: 1) at mid-term follow-up (near 3 years) about one-fifth of patients with RA and asymptomatic LVSD, defined as impaired GLS and assessed by speckle tracking echocardiography, experience a CV event requiring hospitalisation, and about one-fifth of them is hospitalised for a reason unrelated to CV events; 2) a mild decrease in renal function and a mild increase in LV mass are

Table III. Variables associated with the study end-points: univariate and multivariable Cox regression analyses.

	Univariate			Multivariate		
102 patients with rheumatoid arthritis and LVSD	HR	CI	*p*-value	HR	CI	*p*-value
All-causes death / hospitalisation						
Age (years)	1.03	1.01–1.05	0.008	1.01	0.98–1.03	0.08
Systolic blood pressure (mmHg)	1.40	0.85–1.98	0.84	1.15	0.90–1.48	0.10
Glomerular filtration rate (ml/min/1.73 m^2)	0.92	0.85–0.98	<0.001	0. 95	0.92–0.99	0.006
Biologic DMARDs before enrolment (%)	2.40	1.10–4.81	0.03	2.10	1.04–4.31	0.003
Biologic DMARDs before enrolment (n.)	1.81	1.02–3.62	0.01	1.61	1.03–3.12	0.02
CV death / hospitalisation						
Glomerular filtration rate (ml/min/1.73 m^2)	0.88	0.81–0.94	<0.001	0.96	0.93–0.99	0.04
Left ventricular mass (g/m2.7)	1.08	1.02–1.14	0.01	1.06	1.01–1.10	0.01
Biologic DMARDs before enrolment (%)	2.32	1.08–4.28	0.01	2.14	1.04–4.31	0.01
Biologic DMARDs before enrolment (n.)	3.42	1.38–6.12	0.001	3.02	1.31–6.72	0.005

DMARDs: disease-modifying anti-rheumatic drugs; n.: number of DMARDs per patient.

independently related to adverse clinical outcomes in these patients; 3) the rate of incident all-cause hospitalisation and CV hospitalisation are closely and directly associated with the use of biologic DMARDs and the number of these drugs received during the time preceding the enrolment into the study. Overall, these results appear interesting by the pathophysiological point of view. Furthermore, they may have a clinical relevance in patients who do not systematically undergo baseline echocardiographic examination and do not routinely make a close check of renal function (24). The truth of the matter is that there are very little information about renal involvement in RA disease cause of troubles in identifying the aetiology of the nephropathy which can be widely different and multifactorial in the setting of RA patients (24). In fact, it can be intrinsic to the RA disease (mainly mesangial nephritis, renal amyloidosis, membranous nephritis, focal proliferative nephritis) or iatrogenic, mostly coming from NSAIDs which can cause interstitial nephritis, renal tubular acidosis, nephro-vascular hypertension and nephrotic syndrome (24-27). Referring to the intrinsic mechanisms, it has been hypothesised that the aptitude of mesangium to remove circulating autoimmune complexes generates and/or aggravates itself the mesangial damage (24).

Some data on the prognostic role of renal dysfunction in RA patients derive from clinical studies performed by the researchers of Tampere University Hospital, Finland. Sihvonen et al. found the presence of renal disease as a predictor of increased mortality among patients with RA compared to non-RA matched controls (28). Few years later, Karstila *et al*. demonstrated that the prognosis of the subgroup of RA patients who had chronic renal disease at enrolment was evidently poorer than that of RA patients who had not (29). Furthermore, the same authors showed that new abnormal renal findings, in most cases mild, were detected in 28% of patients with normal renal function at enrolment during a follow-up period of 13 years, suggesting the non-sporadic nature of the worrisome phenomenon.

But what about the role of the kidney in RA people with normal renal function at enrolment? In the present investigation we found no difference in GFR between RA patients with and without LVSD. Conversely, among the 102 RA patients with LVSD, GFR was 22% and 19% lower at baseline in patients who experienced all-causes hospitalisation or CV hospitalisation, respectively. However, these two subgroups at higher risk for events had GFR values at enrolment near the normality (82 ± 15 and 81±14 ml/min/1.73 m^2). Interestingly, in our patients the prognostic cut-off of GFR for both adverse outcomes emerging by the ROC analysis was 90 ml/min/1.73 m^2, which is just the edge between the stage I (normal renal function) and the stage II (mildly decreased renal function) of KDOQI classification reported in the KDIGO clinical practice guidelines (30). These findings may lead to speculate that very little changes in renal function may determine relevant clinical consequences in RA patients with asymptomatic LVSD.

Besides decreased renal function, increased LV mass arose by our Cox analysis as independent prognosticator of CV hospitalisation. It is well-known that the higher risk for adverse CV but also non-CV events in patients with RA has been as a matter of course attributed to the chronic inflammation leading diffuse arterial atherosclerosis and stiffness (8-11, 31, 32). These CV alterations arise at an early stage of RA disease, and are related to changes in LV geometry documented by a number of studies (1-3,33). Excessive LV mass is closely associated with poor clinical outcomes in several settings of patients at increased risk for CV events such as those with hypertension (34), aortic stenosis (35) or diabetes mellitus (36). Such association is due to the circumstance that an increased LV mass leads to myocardial fibrosis, ischaemia of micro-vascular system, impairment of systolic and diastolic function and reduction of myocardial energy metabolism. Our data make evident this association also in patients with RA and asymptomatic LVSD (37).

In all probability, however, the most interesting result of our study is the association between the wider use and the higher number of different biologic DMARDs taken by each patient and the clinical event rate. Information on the patient's therapeutic management and strategies used before their enrolment into the study indicates that no patient participated to any interventional trial or received specific drugs for any pharmacological test. Thus, changes in biologic DMARDs overtime could be only due to the ineffectiveness of the drug overtime or intolerance to side effects. This behavior is coupled to the possibility that biologic DMARDs were given to the patients who had more serious clinical conditions and/or more severe inflammatory status and higher disease activity. Furthermore, we have also to take into account the possibility that these agents might be withdrawn for patients who achieved low disease activity or remission (38, 39). Collectively, all these usual conducts lead to speculate that in RA patients with asymptomatic LVSD, a history of treatment with a number of biologic DMARDs may be a marker of frailty predisposing to hospitalisation for both CV and non-CV events. This explanation makes our results not in contradiction with the hypothesis (demonstrated by several authors) that biologic DMARDs are associated with improvement in cardiac and vascular function (40). In our experience, the large majority of patients (77%) were receiving biologic DMARDs at enrolment given without any randomisation, so that it was impracticable to test the prognostic value of this treatment.

Study limitations and strengths

This study has some limitations and strengths. A first limitation refers to the relatively short duration of follow-up and the relatively small number of clinical events limited to the hospitalisations. Second, our results could be biased by some pharmacological or non-pharmacological interventions for RA disease started/stopped during the follow-up whose effect on cardiac geometry and function and clinical outcomes would be actually challenging to measure. In particular, we refer to NSAIDs, which have been shown to

have a negative impact on CV and non-CV outcomes. The use of these class of drugs is sporadic in some case, intermittent or recurrent sometimes and very difficult to quantify, so that the assessment of their global effect on the clinical events remains a challenge. Three, despite our statistical models were extensive, unmeasured confounders could potentially explain the observed associations. Strengths of our study comprise its prospective nature and design, the reliable methods for the assessment of LVSD and geometry and renal function, the complete nature of the dataset.

Conclusions

In conclusion, LVSD is not occasionally recognised in RA patients without overt cardiac disease analysed in primary prevention. Despite the "asymptomatic status", these subjects have a very high rate of all-cause and CV hospitalisation at mid-term follow-up. History of biologic DMARDs use and the higher number of different biologic DMARDs previously given seem to indicate susceptibility for adverse clinical events. Renal function and LV mass are the modifiable variables predicting the adverse clinical outcomes in these subjects. Going over GFR by systematic check and LV mass by standard echocardiography at an early stage of RA disease would be useful to identify patients at higher risk for adverse clinical events. Our findings imply the greatest care for renal function avoiding or limiting pharmacological interventions which can potentially result nephrotoxic (*i.e.* digitalis, diuretics). Beside this, pharmacological interventions aimed to reduce LV mass may be considered (*i.e.* calcium antagonists), whereas indicated. Starting from these notions, further interventional investigations could test therapeutic strategies for improving the clinical outcomes which do not seem to change over time in RA patients (41, 42).

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