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Clinical science

DAS28-γGT for the prediction of major cardiovascular events in rheumatoid arthritis: results from the ESPOIR cohort

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Abstract

Objective: To validate the predictive value of the DAS28 γ-glutamyl transferase (DAS28-γGT) for the occurrence of major cardiovascular (CV) events (MACE) in the 'Etude et Suivi des Polyarthrites Indifférenciées Récentes' ESPOIR cohort.

Methods: Analysis of 13-year outcome from the ESPOIR cohort. RA patients with missing data for baseline γGT activity and those not followed-up to 1 year were excluded. Baseline DAS28-γGT was calculated using the following formula: $0.56*\sqrt{TJ\text{-}28} + 0.28*\sqrt{SJ\text{-}28} + 2*\ln(\gamma GT) + 0.014*GH$. Our primary outcome was the merit of the DAS28-γGT in predicting the occurrence of MACE.

Results: Among the 696 patients [536 women, mean (S.D.) age of 49 (12) years], 34 MACE were recorded, with a mean time to event of 71 (44) months. Receiver operating characteristic curve analysis indicated that a DAS28-γGT >9.4 had the best sensitivity and specificity for the diagnosis of MACE during the observation period. DAS28-γGT >9.4 was predictive of the occurrence of MACE, with a hazard ratio (HR) of 3.11 (95% CI 1.41, 5.43). Multivariate Cox analyses confirmed higher DAS28-γGT (HR 2.44, 95% CI 1.05, 5.64) together with age (HR 1.04, 95% CI 1.01, 1.07) and diabetes mellitus (HR 4.12, 95% CI 1.55, 10.95) as independent predictors of MACE. There was a dose effect of the DAS28-γGT for MACE-risk prediction, which was in line with the application of the Framingham risk score.

Conclusion: The DAS28-γGT was identified in this large prospective cohort as an independent predictor of MACE in patients with RA. The DAS28-γGT is a simple and useful tool to evaluate CV risk in routine and warn the clinician about the CV risk burden in patients with RA.

Keywords: RA, cardiovascular risk, composite index

Rheumatology key messages

- The DAS28-γGT correlated with the Framingham risk score and steadily increased according to cardiovascular risk.
- Higher baseline DAS28-γGT was identified as an independent predictor of MACE in the ESPOIR cohort.
- The DAS28-γGT is a simple tool to evaluate the cardiovascular risk in routine in RA.

Introduction

It is now well accepted that patients with RA have an increased cardiovascular (CV) risk. This risk is related to both the burden of traditional CV risk factors and additional disease-related factors, particularly chronic inflammation. Compared with the general population, the CV risk of RA patients is 1.5- to 2-fold higher than age- and sex-matched individuals [1–3], and even higher when traditional CV risk factors are associated. Several lines of evidence have shown that an aggressive management of joint and systemic inflammation, in particular with targeted biologic therapies like TNF-α inhibitors, could significantly reduce the number of CV events [4, 5]. On the other hand, the recent publication of ORAL SURVEILLANCE study has raised concerns around a possible increased risk of major CV events (MACE) in tofacitinib-treated patients in comparison with TNF-α inhibitors [5].

Thus, optimizing the CV risk management is crucial, as stated by the recent EULAR recommendations [6]. However, the guidelines recognize the suboptimal performance of risk scores used in the general population when applied to patients with chronic inflammatory rheumatic disorders, leading to

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underestimation of CV risk in these populations. Thus, given the important gaps in knowledge still existing regarding the approach to CV risk stratification in clinical practice and the need to use disease-specific risk prediction models [7], there is clearly a need for new relevant and feasible methods to predict CV risk in RA.

γ-Glutamyl transferase (γGT) is a plasma membrane enzyme that is expressed in kidney, liver and pancreatic cells. Their activity is increased in many systemic syndromes, including inflammatory or autoimmune diseases. Ample evidence suggests that elevated γGT is associated with increased risk of CV diseases [8]. We have previously showed that replacing ESR by γGT in DAS28 calculation (DAS28-γGT) allowed a combined evaluation of CV risk in patients with RA, in addition to joint disease activity [8]. However, this study was limited by its observational design, the relatively small number of patients included in some analyses and the use of surrogates for CV risk. This justifies the setting of a prospective study to determine the validity of DAS28-γGT levels and its predictive value for the occurrence of CV events in RA populations.

Our objective was to validate with a prospective, longitudinal, multicentre observational cohort the predictive value of the DAS28-γGT for the occurrence of MACE in the 'Etude et Suivi des Polyarthrites Indifférenciées Récentes' (ESPOIR) cohort.

Patients and methods

Study design and setting

We took over the ESPOIR cohort, a prospective multicentre observational cohort that included patients with early diagnosis of arthritis from 14 French rheumatology centres [9]. Patients had to have inflammatory arthritis in at least two swollen joints lasting from 6 weeks to 6 months, with the potential to develop into RA, and be naïve to DMARDs and CS therapy. This cohort included 813 patients between 2002 and 2005. They were followed up to 13 years. The objective, design and characteristics of the cohort were previously described [10, 11]. All the patients gave their signed informed consent before the inclusion. The protocol of the ESPOIR cohort and of this study was endorsed by the ethics committee of Montpellier, France (No. 020307). All the data of the ESPOIR cohort were available after being approved by the scientific committee (www.lacohorteespoir.fr).

Inclusion and exclusion criteria

Among the 813 patients included in the ESPOIR cohort, we selected patients who fulfilled the 2010 ACR/EULAR criteria for RA over the 13 years of follow-up. We excluded patients with missing data for γGT activity measurement at inclusion and those not followed up to 1 year.

DAS28-γGT calculation and outcome

γGT was a part of the routine initial workup measured at inclusion in the ESPOIR cohort. The DAS28-γGT is a screening tool providing to the rheumatologist rapid information related to both joint disease activity and CV risk. It was obtained by replacing ESR by baseline γGT levels with the following formula $0.56 * \sqrt{\text{TJ-28}} + 0.28 * \sqrt{\text{SJ-28}} + 2 * \ln(\gamma\text{GT}) + 0.14 * \text{GH}$, as previously reported [8].

We first examined the association between the DAS28-γGT and CV risk factors at baseline in the entire cohort. We considered smoking, BMI >30 kg/m^2, diabetes mellitus, high blood pressure and hypercholesterolemia, as previously defined in the cohort [8]. Ten-year risk prediction of CV disease was estimated by the algorithm developed by the Framingham Heart Study [12]. Regular alcohol consumption was defined by up to one drink a day for women and up to two drinks a day for men. Excessive alcohol consumption was defined by a consumption >14 alcohol units a week. We used the Fibrosis-4 (Fib-4) index to evaluate underlying hepatic fibrosis, as previously described [13].

We next assessed the merit of the DAS28-γGT to predict the occurrence of a MACE. To that end, we considered at each study visit the occurrence of MACE during the exposition period, defined as death from CV causes, non-fatal myocardial infarction or non-fatal stroke [5]. For this specific analysis, we excluded the patients with a history of coronary heart disease or ischaemic stroke at baseline.

Statistical analysis

All data are presented as mean values (S.D.) or number and percentage (%) for continuous and categorical variables, accordingly. Statistical analysis was performed using GraphPad Prism (v10). We used the unpaired *t*-test for two-group comparisons (continuous variables) and the χ^2-test for differences in frequency (binary variables). Three group comparisons were analysed by one-way analysis of variance (ANOVA) with Dunnett's multiple comparisons test. Correlations between the DAS28-γGT and numeric variables were assessed using Spearman's rank correlation coefficient (rS). The diagnostic value of the DAS28-γGT and the DAS28 was assessed by receiver operating characteristic (ROC) curve analysis.

MACE-free survival according to the DAS28-γGT was estimated by Kaplan–Meier survival curves. To identify predictive factors of MACE, we used Cox proportional-hazard regression. This analysis included MACE as the dependent variables and all relevant identified covariates were then entered in one single step. A *P*-value <0.05 was considered statistically significant.

Results

Study population

A total of 696 patients with RA (536 women, 77%) were included, with a mean (S.D.) age of 49 (12) years and a mean (S.D.) disease duration of 97 (190) days. Positive RF and anti-CCP antibodies were detected in 327 (47%) and 282 (41%) patients, respectively, and bone erosions were present in 258/676 (38%) patients. These patients had high disease activity, with a mean (S.D.) DAS28 of 5.24 (1.27). At baseline, 9 patients (1%) received CS and 44 (6%) received conventional synthetic DMARDs (csDMARDs), including 32 (4%) with MTX alone or in combination. During the observation period, 92 patients (13%) were treated by CS, 618 (89%) by csDMARDs and 405 (58%) by MTX. The mean (S.D.) Framingham risk score of this population was 9.4 (8.1) (median 6.0%, 95% CI 5.40, 7.0), 238 (34%) patients had more than two CV risk factors and 9 had a history of coronary heart disease or ischaemic stroke. Detailed patients' characteristics are presented in Table 1.

Table 1. Patients' characteristics

	Total population ($N = 696$)	DAS28-γGT ≤9.4 ($n = 334$)	DAS28-γGT >9.4 ($n = 362$)	*P*-value
Baseline demographics				
Age (years), mean (S.D.)	49 (12)	46 (12.5)	52 (11)	<0.001
Women, *n* (%)	536 (77)	285 (85)	251 (69)	<0.001
Baseline disease characteristics				
Disease duration (days), mean (S.D.)	97 (190)	93 (192)	103 (191)	0.49
Positive RF, *n* (%)	327 (47)	165 (49)	162 (45)	0.29
Positive anti-CCP2 antibodies, *n* (%)	282 (41)	136 (41)	146 (40)	0.79
Erosions on hand/foot X-rays, *n*/*N* (%)	258/676 (38)	109/325 (34)	149/351 (42)	0.032
Baseline disease activity				
Tender joints, mean (S.D.)	9 (7)	6 (5)	12 (8)	<0.001
Swollen joints, mean (S.D.)	8 (5)	6 (4)	9 (6)	<0.001
DAS28, mean (S.D.)[a]	5.24 (1.27)	4.59 (1.05)	5.83 (1.16)	<0.001
DAS28 >3.2, *n*/*N* (%)	645/685 (94)	295/329 (90)	350/356 (98)	<0.001
DAS28 >5.1, *n*/*N* (%)	361/685 (53)	102/329 (31)	259/356 (73)	<0.001
ESR (mm/h), mean (S.D.)[b]	30 (25)	24 (20)	36 (28)	<0.001
CRP (mg/l), mean (S.D.)[c]	23 (35)	16 (25)	29 (40)	<0.001
γGT activity, mean (S.D.)	38 (44)	18 (9)	57 (54)	<0.001
Baseline function				
HAQ, mean (S.D.)	1.0 (0.68)	0.77 (0.58)	1.22 (0.71)	<0.001
Baseline cardiovascular risk factors				
Modifiable CV risk factors				
Smokers, *n* (%)	335 (48)	148 (44)	187 (52)	0.035
High blood pressure, *n* (%)	127 (18)	42 (13)	85 (23)	<0.001
Diabetes mellitus, *n* (%)	28 (4)	6 (2)	22 (6)	0.008
Hypercholesterolemia, *n* (%)	104 (15)	36 (11)	68 (19)	0.003
BMI (kg/m^2), mean (S.D.)	25 (5)	24 (4)	26 (5)	<0.001
BMI >30 kg/m^2, *n* (%)	296 (43)	112 (35)	184 (51)	<0.001
Patients with ≥2 CV risk factors	238 (34)	74 (22)	164 (45)	<0.001
Mean Framingham risk score, %, mean (S.D.)[d]	9.4 (8.1)	6.9 (6.7)	12.1 (8.6)	<0.001
Baseline regular alcohol intake	125 (18)	51 (15)	74 (20)	0.083
Baseline excessive alcohol intake[e]	25 (4)	3 (1)	22 (6)	<0.001
Baseline Fib-4 index, mean (S.D.)[f]	0.81 (0.48)	0.79 (0.43)	0.83 (0.62)	0.25
Treatment received during the observation period				
Current CS use, *n* (%)	92 (13)	34 (10)	58 (16)	0.019
Current use of NSAIDs	631 (91)	298 (89)	333 (92)	0.18
Current conventional DMARD use, *n* (%)	618 (89)	289 (87)	329 (91)	0.091
Current MTX use, *n* (%)	405 (58)	184 (55)	221 (61)	0.11

[a] Calculated on 685 patients with available data.
[b] Calculated on 688 patients with available data.
[c] Calculated on 686 patients with available data.
[d] Calculated on 334 patients with available data.
[e] Defined by a consumption >14 alcohol units a week.
[f] Calculated on 694 patients with available data.
γGT: γ-glutamyl transferase; CV: cardiovascular; Fib-4 index: Fibrosis-4 index.

Evaluation of DAS28-γGT and CV risk at baseline

For this analysis, the entire cohort of 696 patients was considered. At baseline, the DAS28-γGT correlated with age (rS = 0.27, $P < 0.001$). It was significantly higher in men [10.39 (1.79) *vs* 9.50 (1.83), $P < 0.001$] and in patients presenting the following conditions: excessive alcohol consumption [11.34 (1.87) *vs* 9.64 (1.83), $P < 0.001$], active smoking [9.86 (1.86) *vs* 9.56 (1.84), $P = 0.034$], high blood pressure [10.40 (1.95) *vs* 9.55 (1.80), $P < 0.001$], hypercholesterolemia [10.18 (1.92) *vs* 9.62 (1.83), $P < 0.001$], diabetes mellitus [11.03 (2.99) *vs* 9.65 (1.83), $P < 0.001$] and obesity (BMI >30 kg/m^2) [10.13 (1.85) *vs* 9.39 (1.85), $P < 0.001$]. No association was observed between DAS28-γGT and treatment with baseline NSAIDs or CS or with the Fib-4 index. The DAS28-γGT correlated with the Framingham risk score (rS = 0.35, $P < 0.001$)—it steadily increased according to CV risk (Fig. 1A) and was significantly higher in patients with at least two CV risk factors (Fig. 1B), as well as in the nine patients with a history of coronary heart disease or ischaemic stroke [10.88 (1.47) *vs* 9.64 (1.85), $P = 0.046$]. The DAS28-γGT had a diagnostic value for the presence of at least two CV risk factors characterized by an area under the curve (AUC) of 0.72 (95% CI 0.68, 0.75, $P < 0.001$) (Supplementary Fig. S1A, available at *Rheumatology* online). Conversely, the DAS28 and the DAS28-CRP did not correlate with the Framingham risk score and their diagnostic value for the presence of at least two CV risk factors was characterized by an AUC of 0.53 (95% CI 0.49, 0.56, $P = 0.29$) and 0.51 (95% CI 0.48, 0.56), respectively (Supplementary Fig. S1B and C, available at *Rheumatology* online).

Predictive value of the DAS28-γGT for the occurrence of MACE

For this analysis, the 9 patients a history of coronary heart disease or ischemic stroke were excluded, and 687 patients were thus considered. During the observation period of 130 (34) months, a total of 34 MACE were recorded, with a mean time to event of 71 (44) months. ROC curve analysis indicated

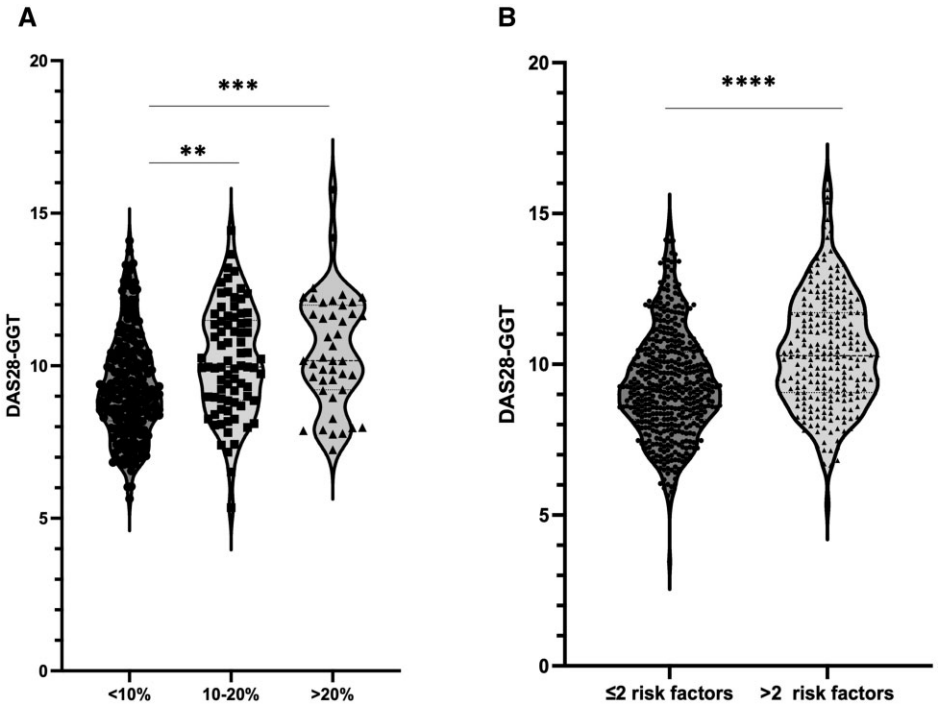


Figure 1. DAS28-γGT levels and cardiovascular risk factors. (**A**) DAS28-γGT levels according to cardiovascular risk evaluated by the Framingham risk score (<10%, 10–20% and >20%) (**$P < 0.01$ and ***$P < 0.001$ by analysis of variance followed by Dunnett's multiple comparisons test); (**B**) DAS28-γGT levels according to the number of cardiovascular risk factors (≤2 or >2 risk factors) (****$P < 0.0001$ by Student's *t*-test). γGT: γ-glutamyl transferase

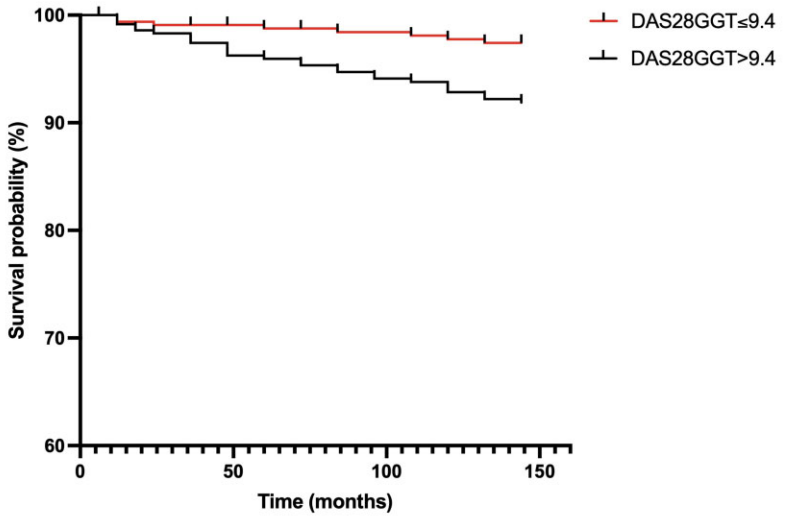
that a DAS28-γGT >9.4 had the best sensitivity (74%) and specificity (62%) for the diagnosis of MACE during the observation period. At baseline, patients with a DAS28-γGT >9.4 were more likely to be men, older, with a more active and severe disease, and they were at higher CV risk (Table 1).

DAS28-γGT >9.4 was predictive of the occurrence of MACE during the observation period, with a hazard ratio (HR) of 3.11 (95% CI 1.41, 5.43) (Fig. 2). Conversely, a DAS28 >5.1 or a DAS28-CRP >5.1 were not predictive of MACE (HR 1.12, 95% CI 0.56, 2.20 and 1.15, 95% CI 0.46, 2.93, respectively). The diagnostic value of DAS28-γGT for the occurrence of MACE was characterized by AUC of 0.70 (95% CI 0.61, 0.73) compared with 0.55 (95% CI 0.51, 0.59) for the DAS28 and 0.55 (95% CI 0.51, 0.58) for the DAS28-CRP (Supplementary Fig. S2A–C, available at *Rheumatology* online). Pairwise comparisons of ROC curves have confirmed an increased predictive value of the DAS28-γGT over the DAS28 ($P = 0.026$) and the DAS28-CRP ($P = 0.026$) and no significant difference between the DAS28-γGT and the Framingham risk score ($P = 0.38$). γGT activity was also predictive of MACE on its own but to a lesser extent than the DAS28-γGT (HR 3.02, 95% CI 1.58, 6.33 and AUC of 0.63, 95% CI 0.61, 0.68).

Multivariate Cox analyses adjusting for the variables age, sex, CRP levels, HAQ, CS use, excessive alcohol intake, smoking, high blood pressure, diabetes, dyslipidaemia and obesity confirmed higher DAS28-γGT (HR 2.44, 95% CI 1.05, 5.64), together with age (HR 1.04, 95% CI 1.01, 1.07) and diabetes mellitus (HR 4.12, 95% CI 1.55, 10.95) as independent predictors of MACE (Table 2). A second model including only statistically significant variables by univariate analysis identified the same predictors of MACE (Table 2).

To determine whether there was a dose effect of the DAS28-γGT for MACE risk prediction, we assessed the predictive value of three tertiles of DAS28-γGT: low (<8.26, 25th percentile), intermediate (8.26–10.72) and high (>10.72, 75th percentile) DAS28-γGT. Fig. 3 illustrates that the risk of MACE was significantly higher in patients with a DAS28-γGT >10.72, compared with those with intermediate or low DAS28-γGT. In particular, patients with a DAS28-γGT <8.26 had a decreased risk of MACE (HR 0.33, 95% CI 0.20, 0.97, $P = 0.038$).

We next compared by multivariate Cox analyses the three tertiles of DAS28-γGT with the validated cut-off of the Framingham risk score (mild <10%, moderate 10–20%, high >20%) (DAS28-γGT <8.26 *vs* Framingham risk score <10%; DAS28-γGT 8.26–10.72 *vs* Framingham risk score 10–20%; and DAS28-γGT >10.72 *vs* Framingham risk score >20%) for the occurrence of MACE (dependent variable) during the observation period. There was a trend for a decreased risk of MACE for patients with a DAS28-γGT <8.26 (HR 0.18, 95% CI 0.02, 1.37), which was not observed for patients with a Framingham risk score <10% (Table 3). Patients with intermediate DAS28-γGT had an increased risk of MACE (HR 2.79, 95% CI 1.08, 7.22), compared with a trend for patients with an intermediate Framingham risk score (10–20%) (Table 3). A trend for a higher risk of MACE was observed in patients with a DAS28-γGT >10.72 (HR 1.98, 95% CI 0.75, 5.23), compared with a significant risk in patients with an intermediate Framingham risk score >20% (HR 4.04, 95% CI 1.63, 9.96) (Table 3).



Number at risk	0	6	12	18	24	36	48	60	72	84	96	108	120	132	144
DAS28GGT >9.4	355	355	355	350	342	338	328	322	318	311	305	301	298	291	287
DAS28GGT ≤9.4	332	332	327	327	321	320	316	309	303	299	299	295	293	290	285

Figure 2. Predictive value of the DAS28-γGT for the occurrence of MACE during the observation period. Time to MACE according to circulating the DAS28-γGT (≤ or >9.4). This analysis was performed on the 687 patients with no history of MACE during a mean (S.D.) observation period of 130 (34) months, with a total of 34 MACE recorded. γGT: γ-glutamyl transferase; MACE: major adverse cardiovascular event

Table 2. Univariate and multivariate Cox analyses to identify independent predictors of MACE (primary endpoint)

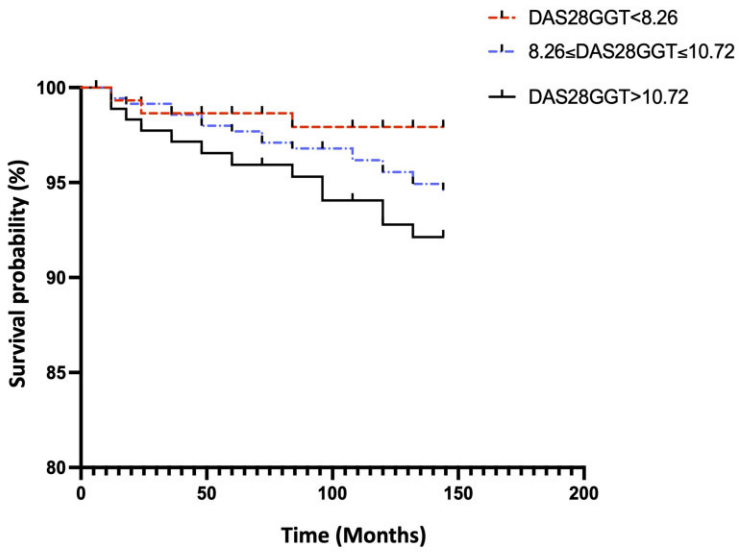
Variable at baseline	MACE	
	Univariate analysis (HR, 95% CI)	Multivariate analysis (HR, 95% CI)
First model[a]		
DAS28-γGT >9.4	**3.11 (1.41, 5.43)**	2.44 (1.05, 5.64)
Age	**1.05 (1.02, 1.10)**	1.04 (1.01, 1.07)
Men	**1.64 (1.01, 3.37)**	1.02 (0.46, 2.29)
Smokers	**2.36 (1.69, 3.30)**	1.33 (0.65, 2.70)
Excessive alcohol intake	1.67 (0.39, 6.87)	1.18 (0.53, 2.65)
High blood pressure	**3.09 (1.54, 6.17)**	1.67 (0.74, 3.76)
Dyslipidemia	1.25 (0.51, 3.03)	0.65 (0.25, 1.64)
Diabetes	**6.86 (2.83, 16.61)**	4.12 (1.55, 10.95)
BMI >30 kg/m^2	1.11 (0.56, 2.18)	0.63 (0.30, 1.32)
Current CS use	5.06 (0.69, 37.01)	5.12 (0.69, 37.69)
CRP levels	**1.21 (1.01, 3.22)**	1.01 (0.99, 1.01)
HAQ	1.53 (0.96, 2.45)	1.21 (0.72, 1.48)
Second model[b]		
DAS28-γGT >9.4	**3.11 (1.41, 5.43)**	2.80 (1.09, 4.83)
Age	**1.05 (1.02, 1.10)**	1.03 (0.99, 1.07)
Men	**1.64 (1.01, 3.37)**	1.07 (0.49, 2.31)
Smokers	**2.36 (1.69, 3.30)**	1.30 (0.64, 2.64)
High blood pressure	**3.09 (1.54, 6.17)**	1.51 (0.68, 3.33)
Diabetes	**6.86 (2.83, 16.61)**	3.87 (1.50, 10.88)
CRP levels	**1.21 (1.01, 3.22)**	1.00 (0.99, 1.01)

Bold font is used to highlight significant values. A total of 687 patients with no history of MACE were considered in this analysis.
[a] First model including MACE as the dependent variables and all potentially relevant covariates.
[b] Second model including MACE as the dependent variables and only statistically significant covariates identified through the univariate analysis.
HR: hazard ratio; MACE: major adverse cardiovascular event; γGT: γ-glutamyl transferase.

Discussion

Regardless of the selected method to risk stratification, screening on a regular basis for CV risk factors and adapting treatment based on estimated CV risk are critical to all approaches to primary prevention of MACE in RA [6]. This has also been recently highlighted by the Janus kinase inhibitor–related potential increased risk of MACE in comparison with TNF-α, which now requires, as stated by the Food and Drud Administration and the European Medicines Agency, a detailed and personalized CV evaluation before considering this therapeutic class [14].

A central principle of the EULAR recommendations for CV risk management in rheumatic diseases states that 'rheumatologists are responsible for CV risk assessment and management in collaboration with primary care providers, internists or cardiologists' [6]. This assertion patently sets the rheumatologist at the centre of CV preventive care, which may present several limitations when applied in clinical practice, and some adaptation and flexibility of this approach may be required. Considerable gaps in the management of CV risk are still a major issue despite an increased understanding of this problem among rheumatologists [15, 16]. Studies that attempted to identify obstacles to CV risk management among rheumatologists specified as some of the main reasons lack of time, lack of knowledge of current guidelines for CV risk factors and lack of care coordination [17, 18]. Indeed, patients should undertake measurement of blood pressure, glucose and lipid profiles on a regular basis, and assessment of lifestyle factors for input into a risk-prediction calculator to estimate CV risk. These procedures may be considered as too complex and time consuming in clinical practice by the



Number at risk	0	6	12	18	24	36	48	60	72	84	96	108	120	132	144
DAS28GGT<8.26	150	150	149	149	146	145	143	140	138	137	137	134	133	132	131
DAS28GGT 8.26-10.72	357	357	353	349	346	345	340	333	327	320	314	312	310	306	301
DAS28GGT >10.72	180	180	179	175	170	167	160	158	156	153	152	150	148	143	140

Figure 3. Predictive value of DAS28-γGT tertiles for the occurrence of MACE during the observation period. Time to MACE according to circulating the DAS28-γGT tertile. This analysis was performed on the 687 patients with no history of MACE during a mean (S.D.) observation period of 130 (34) months, with a total of 34 MACE recorded. γGT: γ-glutamyl transferase; MACE: major adverse cardiovascular event

Table 3. Comparison of the DAS28-γGT with the Framingham risk score for the occurrence of MACE

Variable at baseline	Multivariate analysis (HR, 95% CI)	*P*-value
Model 1		
DAS28-γGT <8.26 ($n = 150$)	0.18 (0.02, 1.37)	0.18
Framingham risk score <10% ($n = 185$)	0.64 (0.26, 1.58)	0.59
Model 2		
DAS28-γGT 8.26–10.72 ($n = 357$)	2.79 (1.08, 7.22)	0.034
Framingham risk score 10–20% ($n = 107$)	0.29 (0.05,1.26)	0.29
Model 3		
DAS28-γGT >10.72 ($n = 180$)	1.98 (0.75, 5.23)	0.16
Framingham risk score >20% ($n = 42$)	4.04 (1.63, 9.96)	0.002

Only patients with no history of MACE were considered in this analysis. All three comparisons were performed during a mean (S.D.) observation period of 130 (34) months, with a total of 34 MACE recorded. Each model was adjusted on age and sex. γGT: γ-glutamyl transferase; HR: hazard ratio.

rheumatologist. Thus, it is crucial to provide to rheumatologists a simple tool, feasible in clinical practice, to evaluate CV risk. We constructed a new composite index called DAS28-γGT, replacing ESR with γGT levels; this index has been shown equivalent to the DAS28 for the assessment of disease activity, and also provided added value to identify the presence of CV risk factors [8]. The present study brings a further step of validation of this index in this 13-year analysis of the ESPOIR cohort. As previously observed [8], the DAS28-γGT was significantly higher in patients with CV risk factors and correlated with the Framingham CV risk score. In addition, higher baseline DAS28-γGT were able to independently predict the risk of MACE after stratification on potential confounders including alcohol consumption, systemic inflammation and the presence of CV risk factors. Interestingly, there was a dose effect of the DAS28-γGT for MACE risk prediction, similar to what is observed with established risk scores, with lower values being associated with a decreased CV risk and higher values being more at risk.

The EULAR recommendations also highlight some topics regarding CV risk prevention that plainly fall within the scope of practice of all rheumatologists. Achieving optimal control of rheumatic disease activity is an essential treatment objective from a CV standpoint, as studies have observed an association between various measures of disease activity and CV risk [19]. This is also an advantage of the DAS28-γGT, which has been shown to be a reliable marker of RA disease activity, equivalent to the DAS28 for the assessment of disease activity evaluated by clinical examination or power Doppler US [8].

The DAS28-γGT is a simple and useful tool, with the advantage of providing information on disease activity and CV risk with a single index, which may warn the clinician about the CV risk burden in patients with RA. It may be used in clinical practice to assess joint disease activity without losing validity compared with the DAS28 and may help rheumatologists to decide whether RA patients require more in-depth CV evaluation, and need to be referred to a cardiologist [7].

The limitations of the present study include those that cannot be ignored in observational cohort studies, with potential confounding factors that could not be considered. Moreover, most data regarding comorbidities were declarative, with potential recall bias. This cohort included early RA patients with high disease activity, and further data are needed to confirm

these findings in patients with established disease and/or lower disease activity. The ascertainment of CV death was performed at a clinic visit, and people who had died in the interim might have been undercounted. However, the prolonged follow-up and the multiple annual data review may have decreased the risk to miss death during the interval of two visits. Cause of death is mentioned in the case report form of ESPOIR and CV events were clearly identified.

Since γGT activity has also been identified as a predictive factor of MACE in the general population [8], it is not known whether γGT may predict MACE differently in RA compared with the non-RA population. However, adding the γGT to the DAS28 increased the prediction of MACE compared with γGT alone, and this index considers RA disease activity.

Our study has a number of strengths. The ESPOIR cohort allows exploration of the time-dependent risk of MACE in early RA in a real-world setting, providing long follow-up time with a low rate of missing data or drop-out.

In summary, the DAS28-γGT was identified in this large prospective cohort as an independent predictor of MACE in patients with RA. In addition to the assessment of disease activity, the DAS28-γGT is a simple and useful tool to evaluate CV risk in routine and warn the clinician about the CV risk burden in patients with RA.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

All the data of the ESPOIR cohort were available after being approved by the scientific committee (www.lacohorteespoir.fr). The authors declare that all other data supporting the findings of this study are available within the paper (and its supplementary information files).

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References

1. Avina-Zubieta JA, Choi HK, Sadatsafavi M *et al.* Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analysis of observational studies. Arthritis Rheum 2008;59:1690–7.
2. Meune C, Touze E, Trinquart L, Allanore Y. Trends in cardiovascular mortality in patients with rheumatoid arthritis over 50 years: a systematic review and meta-analysis of cohort studies. Rheumatology (Oxford) 2009;48:1309–13.
3. Sparks JA, Chang SC, Liao KP *et al.* Rheumatoid arthritis and mortality among women during 36 years of prospective follow-up: results from the Nurses' Health Study. Arthritis Care Res (Hoboken) 2016;68:753–62.
4. Blum A, Adawi M. Rheumatoid arthritis (RA) and cardiovascular disease. Autoimmun Rev 2019;Jul18:679–90.
5. Ytterberg SR, Bhatt DL, Mikuls TR *et al.*; ORAL Surveillance Investigators. Cardiovascular and cancer risk with tofacitinib in rheumatoid arthritis. N Engl J Med 2022;386:316–26.
6. Drosos GC, Vedder D, Houben E *et al.* EULAR recommendations for cardiovascular risk management in rheumatic and musculoskeletal diseases, including systemic lupus erythematosus and antiphospholipid syndrome. Ann Rheum Dis 2022;81:768–79.
7. Eder L, Harvey P. Cardio-rheumatology: it's time to collaborate. Nat Rev Rheumatol 2022;18:247–8.
8. Vergneault H, Vandebeuque E, Codullo V, Allanore Y, Avouac J. Disease activity score in 28 joints using GGT permits a dual evaluation of joint activity and cardiovascular risk. J Rheumatol 2020;47:1738–45.
9. Roubille C, Coffy A, Rincheval N *et al.* Ten-year analysis of the risk of severe outcomes related to low-dose glucocorticoids in early rheumatoid arthritis. Rheumatology (Oxford) 2021;60:3738–46.
10. Combe B, Rincheval N, Benessiano J *et al.* Five-year favorable outcome of patients with early rheumatoid arthritis in the 2000s: data from the ESPOIR cohort. J Rheumatol 2013;40:1650–7.
11. Combe B, Benessiano J, Berenbaum F *et al.* The ESPOIR cohort: a ten-year follow-up of early arthritis in France: methodology and baseline characteristics of the 813 included patients. Joint Bone Spine 2007;74:440–5.
12. D'Agostino RB Sr, Vasan RS, Pencina MJ *et al.* General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation 2008;117:743–53.
13. Avouac J, Degrave R, Vergneault H *et al.* Risk of liver fibrosis induced by methotrexate and other rheumatoid arthritis medications according to the Fibrosis-4 Index. Clin Exp Rheumatol 2022;40:150–7.
14. Avouac J. Where are we with the benefit-risk ratio of JAK inhibitors in rheumatoid arthritis? Joint Bone Spine 2022;89:105454.
15. Eder L, Harvey P, Chandran V *et al.* Gaps in diagnosis and treatment of cardiovascular risk factors in patients with psoriatic disease: an International Multicenter Study. J Rheumatol 2018;45:378–84.
16. Bartels CM, Kind AJ, Everett C *et al.* Low frequency of primary lipid screening among medicare patients with rheumatoid arthritis. Arthritis Rheum 2011;63:1221–30.
17. Navarro-Millan I, Young SR, Shurbaji S *et al.* Barriers and facilitators for screening and treatment of hyperlipidemia among patients with inflammatory arthritis. BMC Rheumatol 2020;4:26.
18. Esmaeilbeigi F, Pope JE. Appropriate cardiovascular disease risk assessment in systemic lupus erythematosus may be lacking in rheumatology practice. Clin Exp Rheumatol 2018;36:526–32.
19. Nikpour M, Gladman DD, Urowitz MB. Premature coronary heart disease in systemic lupus erythematosus: what risk factors do we understand? Lupus 2013;22:1243–50.