Response to: 'Response to: "Influence of changes in cholesterol levels and disease activity on the 10-year cardiovascular risk estimated with different algorithms in rheumatoid arthritis patients" by Fornaro *et al*' by Agca *et al*

We thank Agca and colleagues[1] for their valuable comments on our correspondence 'Influence of changes in cholesterol levels and disease activity on the 10-years cardiovascular risk estimated with different algorithms in rheumatoid arthritis patients'.[2] They highlighted the complexity of cardiovascular (CV) risk assessment in patients with rheumatoid arthritis (RA), with some aspects that need to be clarified.

The purpose of our study was not to determine if possible changes in CV risk scores during the first 6 months of treatment with biologic agents reflect reality, for which we need, as suggested, much larger cohorts, but rather to evaluate how the changes in disease activity and lipid levels may differently impact on CV risk algorithms commonly used by physicians in their daily clinical practice. In our RA cohort we selected all patients who started a first-line biologic agent since January 2010 with all available data to calculate the 10-year CV risk score either at baseline (ie, with active disease) or at 3-month and 6-month follow-up. We excluded those patients with previous major cardiovascular events (MACE) or with concomitant lipid-lowering treatment during the time of the study as possible bias. At the same time plasma levels of total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL) and triglycerides were assessed according to standard laboratory protocol. We found a discrepancy in changes in scores: the QRISK3-2018 and 'Progetto Cuore' scores seem not to be influenced by inflammation or mild changes in lipid levels, while the Reynolds Risk Score (RRS) and Expanded Risk Score in Rheumatoid Arthritis were significantly influenced. We argued that these last two scores may give different results during the first 6 months of efficacious biologic disease-modifying antirheumatic drug treatment due to changes in disease activity and lowering of the inflammatory items of the scores.

With regard to smoking status, it was mandatory to calculate all the algorithms included in our study, and is shown in table 1. Among the 31 smokers at baseline, no change in their habits was reported during follow-up. We also included data about LDL cholesterol, and as suggested by Agca and colleagues[1] we also calculated the Systematic COronary Risk Evaluation (SCORE) algorithm of the European Society of Cardiology.[3] We observed a significant increase in LDL levels at 3 months and a subsequent reduction to baseline level at 6 months. The mean estimated CV risk by the SCORE algorithm was lower than 5%, with no significant changes during the 6-month follow-up.

The 'Progetto Cuore' score is an adapted algorithm that largely replicates the SCORE project charts of the European Society of Cardiology and has been validated in Italian people,[3] but with different outcomes: 10-year MACE for 'Progetto Cuore' score and mortality for SCORE. Both algorithms include the total cholesterol to HDL cholesterol ratio, and for Italian people the use of 'Progetto Cuore' score is recommended.[4]

We agree that the limitations of our study include the relatively small sample size and the lack of surrogates of CV damage as intima–media thickness by carotid ultrasound imaging. The extension to 12 months of the CV risk assessment in our cohort did not add further information for the initial purpose of our study. Yu *et al*[5] did not find any difference in CV risk scores evaluated at baseline and after 1 year of follow-up, except for the RRS in those patients with reduction in C reactive protein levels who presented a concordant lowering of CV risk.

In conclusion, a lot of CV risk scores have been approved, but the best performer among these CV risk scores in patients with RA is far to be identified. Nevertheless, since CV risk algorithms are the most commonly used tool to assess CV risk, it is important to highlight that some algorithms are not influenced by the improvement of disease activity during the first months of treatment with biologic agents. This may be a source of research for the scientific community and a relevant information for rheumatologists in the application of the European League Against Rheumatism Recommendations for CV risk management in patients with RA.[6]

Table 1 Clinical characteristics, cardiovascular risk factors and cardiovascular risk scores of 112 biologic-naïve patients with rheumatoid arthritis at baseline and after 3 and 6 months of follow-up

Variables	Baseline	3 months	6 months
CDAI	18.3 (12.7)	8 (7.8)***	5.9 (4.2)***
mHAQ-DI	0.9 (0.8)	0.7 (0.8)***	0.6 (0.7)***
Glucocorticoids dose (mg/dL)	4.3 (3.4)	3.5 (2.5)**	2.9 (2.4)***
Glucocorticoids, n (%)	79 (70.5)	72 (64.3)	67 (59.8)**
csDMARDs, n (%)	97 (86.5)	94 (83.9)	91 (81.3)
Systolic blood pressure (mm Hg)	126.7 (16.8)	124.3 (17.3)	124.9 (18.2)
Diastolic blood pressure (mm Hg)	78.8 (9.4)	77.6 (9.6)	78.2 (10.7)
Total cholesterol (mg/dL)	197.3 (38.2)	205.8 (37.3)**	201 (34.6)
HDL cholesterol (mg/dL)	60.1 (16.9)	62.9 (15.9)	61.8 (15.5)
LDL cholesterol (mg/dL)	114.2 (32.4)	121.1 (31.9)**	117.5 (29.3)
Total cholesterol to HDL ratio	3.4 (1.1)	3.4 (0.9)	3.4 (0.9)
Triglycerides (mg/dL)	112.3 (78.2)	111.1 (61.5)	109.1 (53.7)
CRP (mg/L)	12.8 (17.1)	6.6 (10.5)***	6.2 (8.5)***
BMI (kg/m^2)	25.6 (5.4)	26 (4.9)	25.6 (4.9)
Diabetes, n (%)	6 (5.4)	7 (6.3)	7 (6.3)
Hyperlipidaemia, n (%)	45 (40.2)	70 (62.5)***	66 (58.9)**
Hypertension, n (%)	31 (27.7)	32 (28.6)	32 (28.6)
Hypertension therapy, n (%)	26 (23.2)	29 (25.9)	30 (26.8)
Smoker, n (%)	31 (27.7)	31 (27.7)	31 (27.7)
Ex-smokers, n (%)	3 (2.7)	3 (2.7)	3 (2.7)
'Progetto Cuore' (n=112)	6.9 (11.3)	6.7 (11.1)	7 (11.9)
SCORE-ESC (n=112)	3.8 (3)	3.5 (2.6)	3.7 (2.9)
QRISK3-2018 (n=112)	10.8 (11.3)	10.3 (10.8)	10.4 (11.4)
RRS (n=105)	6.9 (8.8)	6 (6.9)	5.8 (6.9)**
ERS-RA (n=112)	10.8 (11.9)	9.8 (10.9)**	9.6 (10.5)***

Values are expressed as mean (SD) unless otherwise indicated.
Seven patients with diabetes were excluded in the calculation of RRS as diabetes was an exclusion criterion. 'Progetto Cuore', RRS and SCORE have been multiplied by 1.5, in accordance with the EULAR Recommendations.
*P<0.05, **P<0.01, ***P<0.001 vs baseline.
BMI, body mass index; CDAI, Clinical Disease Activity Index; CRP, C reactive protein; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; ERS-RA, Expanded Risk Score in Rheumatoid Arthritis; ESC, European Society of Cardiology; EULAR, European League Against Rheumatism; HDL, high-density lipoprotein; LDL, low-density lipoprotein; mHAQ-DI, modified Health Assessment Questionnaire Disability Index; RRS, Reynolds Risk Score; SCORE, Systematic COronary Risk Evaluation.

Marco Fornaro , **Fabio Cacciapaglia** , **Vincenzo Venerito, Giuseppe Lopalco** , **Florenzo Iannone**

Rheumatology Unit - Department of Emergency and Organ Transplantation, University of Bari, Bari, Italy

Correspondence to Dr Marco Fornaro, Università degli Studi di Bari Facoltà di Medicina e Chirurgia, Bari 70124, Italy; marco3987@hotmail.it

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ORCID iDs

Marco Fornaro http://orcid.org/0000-0003-1716-7432
Fabio Cacciapaglia http://orcid.org/0000-0001-7479-4462
Giuseppe Lopalco http://orcid.org/0000-0003-4524-9566
Florenzo Iannone http://orcid.org/0000-0003-0474-5344

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