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*

Fornaro and colleagues investigated the influence of cholesterol level changes and disease activity on the estimated cardiovascular (CV) risk in rheumatoid arthritis (RA) patients, at baseline, 3 months and 6 months after the start of a tumour necrosis factor-alpha (TNF) inhibitor (n=55), abatacept (n=33) or tocilizumab (n=24).[1] The cohort consisted of mainly women (n=86) aged 53±13 years, with a mean disease duration of approximately 59±76 months. CV risk was calculated with QRISK3-2018, Reynolds Risk Score (RRS), Expanded Risk Score (ERS) in RA (ERS-RA) and Progetto Cuore. The Progetto Cuore and RRS scores were multiplied by 1.5 as advocated by the current EULAR recommendations.[2] The authors identified a modest but statistically significant change in total cholesterol (TC) at 3 months that returned to baseline at 6 months. Additionally, the ERS-RA and RRS scores significantly decreased during follow-up, while the Progetto Cuore and QRISK3-2018 scores did not change. Thus, the authors argue that QRISK3-2018 and Proguetto Cuore can be used at any time, as they do not seem to be significantly affected by the modest changes in TC levels and disease activity.

Several findings of this interesting study need attention. First, this is a small study and to really determine whether any changes in risk scores reflect reality requires much larger numbers and calibration to future CV disease outcomes. Without these, it is difficult to take the results at face value. Second, there is no description of the patient selection procedure, which is important to establish potential for bias. Third, information about the smoking status of patients, an essential component of all the CV risk algorithms, is not included in table 1. Next, concerning the CV risk calculators used in this study, the QRISK3-2018 is validated as a risk prediction model for the UK. As this calculator has not been validated for the Italian population, it may lead to uncertain results. In contrast, the RRS was developed as a global CV risk algorithm, and is also the only one including C-reactive protein (CRP), which has been credited with improving CV risk prediction,[3 4] although this remains strongly debated.[5] In this study, the authors found a decrease in RRS over time, which is to be expected, as patients with RA have higher CV risk during active disease and CRP decreases with treatment, particularly those treated with tocilizumab as opposed to abatacept and TNF inhibitors.[6] However, the RRS was not devised or ever validated for assessing CV risk changes in patients going in and out of systemic inflammatory conditions; so some strong caution is needed.

Last, the authors reported significantly more hyperlipidaemia (defined as TC ≥240 mg/dL or hypertriglyceridaemia >200 mg/dL) at 3 months and 6 months, and a decreasing trend in blood pressure. However, the changes observed in this study are very small and unlikely to markedly affect most risk calculations. Also, low-density lipoprotein cholesterol, that should have been addressed following the European Society of Cardiology guideline for primary prevention of CV events, was not carried out by the authors. Neither were surrogate markers of atherosclerotic disease, such as carotid ultrasound, used to identify patients with high CV risk included in the categories of moderate risk according to the risk charts. Furthermore, due to higher lipid levels, the CV risk could be falsely 'elevated' compared with baseline, while it should be lower due to less inflammation. This is also known as the 'lipid paradox' in which lipid levels increase (or partially normalise) during anti-inflammatory therapy without an increase in CV event risk.[2] It would be interesting to investigate CV risk with a risk algorithm developed for the general population in which TC/high-density lipoprotein cholesterol (HDLc) ratio is included, such as the SCORE algorithm, as this ratio is more stable.[7 8] Furthermore, it would be of additional value to compare the current results to CV risk scores at 12 months after the start of therapy. Regarding the ERS-RA, current literature agrees on no additional value of RA-specific risk prediction models when compared with general population algorithms.[9] So, it is not recommended to use these models for CV risk prediction in RA. Altogether, this debate will continue until an adequately powered and validated RA-specific risk model is available.[10] Another unanswered question is what the timeframe to re-assess CV risk should be.

For the time being, we recommend the use of CV risk algorithms that are validated within each country and include both TC and HDLc, where possible. Ongoing work will determine whether the current CV risk multiplier of 1.5 needs to be modified for the risk algorithms that do not automatically include RA as a higher risk category.

Table 1 Clinical characteristics, cardiovascular risk factors and cardiovascular risk scores of 112 biologically-naïve Rheumatoid Arthritis patients at baseline and after 3 months and 6 months of follow-up

Variables	Baseline	3rd month	6th month
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)
Total cholestrol /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)
"Progetto Cuore" nr.112	6.9 (11.3)	6.7 (11.1)	7 (11.9)
QRISK3-2018 nr.112	10.8 (11.3)	10.3 (10.8)	10.4 (11.4)
RRS nr.105	6.9 (8.8)	6 (6.9)	5.8 (6.9)**
ERS-RA nr.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 thecalculation of RRS as diabetes was an exclusion criteria.
*p<0.05; **p<0.01; ***p<0.001 vs baseline.
BMI, Body mass index; CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; ERS-RA, Expanded Risk Score inRheumatoid Arthritis; HDL, High-density lipoprotein; RRS, Reynolds risk score; csDMARDs, conventionalsynthetic disease modifying antirheumatic drugs; mHAQ-DI, modified Health Assessment Questionnaire Disability Index.

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