Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/npjy2t35

IMPACT OF RHEUMATOID ARTHRITIS ON CARDIOVASCULAR RISK: PATHOPHYSIOLOGY AND PREVENTION-A PROSPECTIVE COHORT STUDY

Sajid Naseem[1*], Khawaja Faizan Ejaz[2], Hifza Ishtiaq[3], Muhammad Iftikhar Khattak[4], Farwa Jaffery[5]

[1*]Department of Rheumatology, Fazaia Medical College, Islamabad, Pakistan
[2]Department of Rheumatology, Nottingham University Hospitals, Queens Medical Centre, United Kingdom
[3]Department of Public Health, Abbas Institute of Medical Sciences, Muzaffarabad, Azad Jammu and Kashmir, Pakistan
[4]Department of Public Health, Health Services Academy, Islamabad, Pakistan
[5]Department of Cardiology, Kulsoom International Hospital, Islamabad, Pakistan

***Corresponding author:** Sajid Naseem,
*Department of Rheumatology, Fazaia Medical College, Islamabad, Pakistan
Email: sajidnaseem@doctors.org.uk

ABSTRACT

Background: Rheumatoid arthritis (RA) is a systemic autoimmune disease characterised by chronic synovial inflammation, which considerably enhances the risk of cardiovascular disease (CVD). This study aimed to assess the impact of a structured, protocol-driven strategy to CVD risk management over a 6-month duration in patients with rheumatoid arthritis.

Methodology: A prospective, single-centre research study included 50 individuals with active rheumatoid arthritis. At baseline and 6 months, we measured disease activity (DAS28-ESR), systemic inflammation (CRP, ESR), lipid profiles, and cardiovascular disease risk using the QRISK3 score. All patients received protocolized care aimed at both RA disease control (treat-to-target strategy) and aggressive management of conventional cardiovascular disease risk factors.

Results: After 6 months, disease activity in rheumatoid arthritis improved significantly, with the mean DAS28-ESR decreasing from 5.2±0.8 to 2.9±0.7 ($p < 0.001$). Concurrently, systemic inflammatory indicators (CRP and ESR) decreased significantly ($p<0.001$). The mean QRISK3 score, which measures 10-year CVD risk, reduced dramatically from 12.5% to9.8% ($p=0.005$). The lipid profile also improved, with a rise in HDL-C ($p=0.02$).

Conclusion: A combined management strategy focusing on RA disease activity control and proactive management of conventional CVD risk factors over 6 months can result in a significant reduction in the predicted 10-year CVD risk. These findings highlight the important need for integrated care strategies in rheumatic practice to reduce the significant cardiovascular burden associated with rheumatic arthritis.

Keywords: Rheumatology, Cardiovascular disease, Inflammation, Atherosclerosis.

INTRODUCTION

Rheumatoid arthritis is a systemic autoimmune disorder distinguished by inflammatory arthritis and extra-articular involvement.(1) It normally starts in small peripheral joints, is usually symmetric, and develops to affect proximal joints if not addressed.(2,3)

RA is no longer seen as a debilitating joint disease, but rather as a systemic inflammatory illness linked with a significant rise in morbidity and death. CVD is the primary cause of death in people with RA, accounting for roughly 40-50 % of all mortality (4). The risk of myocardial infarction (MI) and heart failure (HF) in RA patients is roughly 1.5 to 2 times higher than in the general population, a risk magnitude comparable to that of type 2 diabetes.(5)

The pathogenesis of rapid atherogenesis is multifaceted. Chronic systemic inflammation causes endothelial dysfunction, plaque development, and instability through a chain reaction of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β. (6,7). This inflammatory milieu also contributes to a lipid paradox, whereby rheumatic arthritis patients exhibit a higher atherogenic burden due to qualitative changes in lipids, including increased levels of small, dense low-density lipoprotein (LDL) particles and dysfunctional high-density lipoprotein.(8,9) Additionally, established risk factors such as hypertension (HTN), smoking, and physical inactivity are frequently more common and poorly managed in rheumatoid arthritis patients.(10) Given the increased risk, effective prevention measures are critical. Current guidelines emphasise a two-pronged approach: tight control of rheumatoid arthritis disease activity using a treat-to-target (T2T) strategy with disease-modifying antirheumatic medications (DMARDs), and aggressive management of conventional cardiovascular disease risk factors.(11)

This 6-month prospective study aimed to assess the effect of a protocol-driven, integrated care approach on the predicted CVD risk in patients with active rheumatoid arthritis. We hypothesised that focusing on inflammation suppression and conventional risk factor optimisation would result in a considerable reduction in the 10-year cardiovascular disease risk score.

METHODOLOGY

A prospective, single-centre observational study. The study was approved by the local Institutional Review Board in July 2024, and all participants gave their written informed consent. This study was conducted from August 2023 to January 2024 at Abbas Institute of Medical Sciences, Muzaffarabad, Azad Jammu and Kashmir, Pakistan. A total of 50 patients (age >18 years) with a rheumatoid arthritis diagnosis based on the 2010 ACR/EULAR diagnostic criteria (12) and active disease (Disease Activity Score in 28 joints [DAS28]-ESR >3.2) were included. Patients who have prior clinical cardiovascular disease (MI, stroke, or revascularization) were excluded.

At baseline (month 0), all patients had a comprehensive assessment that included demographics, RA duration, medication history, smoking status, blood pressure, and body mass index. The DAS28-ESR was used to assess disease activity, and laboratory tests included ESR, CRP, and a lipid profile with total cholesterol, LDL-C, HDL-C, and triglycerides. Cardiovascular risk was evaluated using the QRISK3 method, which adds rheumatoid arthritis and other autoimmune disorders as risk factors. (13). Following the baseline examination, patients were managed in accordance with a standardised protocol. RA management used a treat-to-target strategy, aiming for low disease activity (DAS28-ESR ≤3.2) or remission (DAS28-ESR <2.6). Treatment adjustments, such as initiation or escalation of csDMARDs or bDMARDs, were made at the discretion of the treating rheumatologist based on DAS28 scores. Cardiovascular risk factors were aggressively managed in accordance with EULAR guidelines, including lifestyle counselling on diet, physical activity/exercise, and smoking cessation, as well as pharmacological interventions for hypertension (target <130/80 mmHg) and dyslipidemia (statin therapy based on QRISK3 score). The 6-month follow-up visit included a repetition of all examinations, including the clinical evaluation, laboratory testing, and QRISK3 calculation. The statistical analysis was performed using IBM SPSS version 27.0. Categorical variables were expressed as frequencies and percentages, whereas continuous variables were presented as mean ± SD. The paired sample t-test was performed to compare

continuous variables between baseline and 6 months, with a p-value of less than 0.05 indicating statistical significance.

RESULTS

Table 1a summarises the cohort's demographic and clinical baseline characteristics. The mean age was 58 years, with females making up 74% of the population. The average disease duration was 8.5 years. Nearly a quarter of the individuals were current smokers. The mean BMI was overweight, with mean systolic and diastolic blood pressures of 134 mmHg and 82 mmHg, respectively. Disease activity was high at baseline, as evidenced by higher DAS28-ESR, CRP, and ESR levels.

Table 1a: Baseline Demographic and Clinical Characteristics (n=50)

Characteristic	Value (Mean ± SD or n (%))
Age (years)	58.4 ± 10.2
Female Sex	37 (74%)
Disease Duration (years)	8.5 ± 6.1
Current Smokers	11 (22%)
BMI (kg/m²)	26.8 ± 4.5
Systolic BP (mmHg)	134 ± 12
Diastolic BP (mmHg)	82 ± 8
DAS28-ESR	5.2 ± 0.8
CRP (mg/L)	15.6 ± 8.4
ESR (mm/hr)	38.5 ± 16.2

Table 1b shows the individuals' baseline laboratory results as well as their cardiovascular risk assessment. The mean total cholesterol and LDL-C levels were borderline high, but the HDL-C levels were low. Triglycerides were mildly increased. The average QRISK3 score was 12.5%, indicating a moderate 10-year cardiovascular risk for the sample.

Table 1b: Baseline Laboratory Parameters and Cardiovascular Risk (n=50)

Characteristic	Value (Mean ± SD)
Total Cholesterol (mg/dL)	195 ± 32
LDL-C (mg/dL)	112 ± 28
HDL-C (mg/dL)	48 ± 12
Triglycerides (mg/dL)	145 ± 45

Table 2 reveals significant reductions in disease activity and inflammation over 6 months. The DAS28-ESR reduced from 5.2 ± 0.8 to 2.9 ± 0.7 ($p<0.001$), CRP from 15.6 ± 8.4 to 4.1 ± 2.5 mg/L ($p<0.001$), and ESR from 38.5 ± 16.2 to 14.8 ± 7.9 mm/hr ($p<0.001$). Lipid changes were modest: total cholesterol (195→ 188 mg/dL, $p=0.08$) and triglycerides (145→ 138 mg/dL, $p=0.25$) were not significant, while HDL-C increased from 48 ± 12 to 52 ± 11 mg/dL ($p=0.02$).

Table 2: Changes in Study Parameters from Baseline to 6 Months (n=50)

Parameter	Baseline	6 Months	P-value
DAS28-ESR	5.2 ± 0.8	2.9 ± 0.7	<0.001
CRP (mg/L)	15.6 ± 8.4	4.1 ± 2.5	<0.001
ESR (mm/hr)	38.5 ± 16.2	14.8 ± 7.9	<0.001
Total Cholesterol (mg/dL)	195 ± 32	188 ± 29	0.12
LDL-C (mg/dL)	112 ± 28	105 ± 25	0.08
HDL-C (mg/dL)	48 ± 12	52 ± 11	0.02
Triglycerides (mg/dL)	145 ± 45	138 ± 40	0.25

QRISK3 Score (%)	12.5 ± 7.1	9.8 ± 6.3	0.005

Figure 1 shows the reduction in inflammatory markers over six months. CRP levels dropped markedly from 15.6 mg/L at baseline to 4.1 mg/L, while ESR decreased from 38.5 mm/hr to 14.8 mm/hr. Both reductions were statistically significant ($p<0.001$). These findings indicate significant improvement in systemic inflammation with treatment.

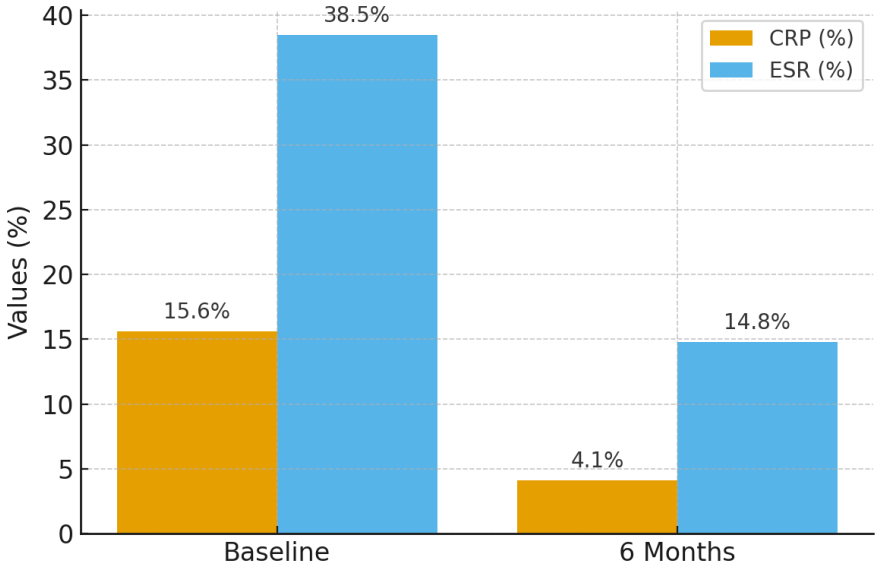


Figure 1: Change in Inflammatory Markers (CRP and ESR) from Baseline to 6 Months

The initial outcome, the QRISK3 score, showed a significant absolute reduction of 2.7%, from 12.5% at baseline to 9.8% at 6 months ($p=0.005$). This shows a relative risk reduction of approximately 22% (Figure 2).

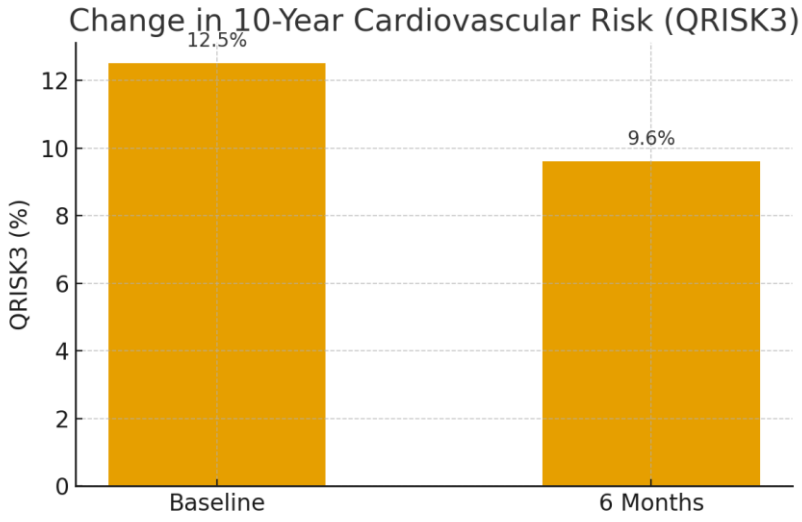
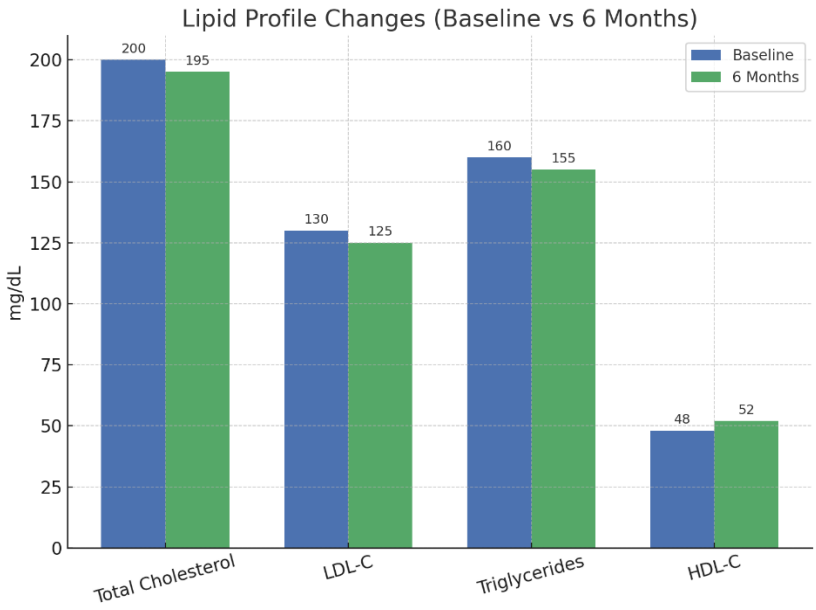


Figure 2: Change in 10-Year Cardiovascular Risk (QRISK3)

Figure 3 shows lipid profile changes over 6 months. Total cholesterol, LDL-C, and triglycerides demonstrated a slight but non-significant reduction. In contrast, HDL-C increased significantly from 48 mg/dL ($p=0.02$). This suggests an overall favourable shift in lipid balance, mainly due to the rise in protective HDL-C.



DISCUSSION

The principal finding of this 6-month prospective study is that a structured, integrated care approach leads to a significant reduction in the calculated 10-year cardiovascular risk for patients with active RA. The 22% relative reduction in the QRISK3 score underscores the profound impact that controlling systemic inflammation and managing traditional risk factors can have on the cardiovascular health of this vulnerable population.

Our results align with the established pathophysiological model, where chronic inflammation is the primary driver of accelerated atherosclerosis in RA. (14). The significant reduction in DAS28-ESR, CRP, and ESR observed in our cohort reflects effective suppression of the inflammatory cascade. Cytokines like TNF-α and IL-6 not only cause joint damage but also promote endothelial dysfunction, a critical early step in atherogenesis, by reducing nitric oxide bioavailability and increasing endothelial adhesion molecule expression. (15) By mitigating this inflammatory burden, DMARD therapy likely contributes directly to vascular protection. Studies have shown that effective treatment with methotrexate and biologic agents is associated with a reduced incidence of cardiovascular events. (16,17). The improvement observed in HDL-C levels is particularly noteworthy. In RA, HDL can become dysfunctional, losing its anti-inflammatory and cholesterol-efflux capabilities ("pro-inflammatory HDL") (8,18). Effective control of inflammation may help restore the anti-atherogenic function of HDL, a qualitative improvement that is not fully captured by the quantitative increase we measured. This highlights a potential mechanism by which anti-inflammatory therapy directly improves vascular health beyond its effect on traditional risk scores.

Our study has several limitations. The single-centre design and relatively small sample size may limit generalizability. The 6-month duration, while sufficient to demonstrate changes in risk scores, is too short to assess hard cardiovascular endpoints like myocardial infarction or stroke. The use of QRISK3, while validated and recommended, remains a surrogate marker. Furthermore, the lack of a control group of RA patients receiving standard care means we cannot definitively attribute all the improvement to the protocol itself. In a study, it was found that Rheumatoid arthritis-specific cardiovascular risk scores are not superior to general risk scores for predicting cardiovascular disease events.(19) QRISK3 has poor calibration for predicting cardiovascular disease risk in rheumatoid arthritis patients.(20)

Despite these limitations, our findings have important clinical implications. They reinforce the necessity of the EULAR guidelines, which advocate for annual CVD risk assessment in RA patients and aggressive risk factor modification. Rheumatologists must assume a pivotal role as cardiovascular risk managers, collaborating closely with cardiologists and primary care physicians.

The treat-to-target strategy for RA should be viewed not only as a means to preserve joint function but also as a fundamental cardiovascular prevention strategy.

CONCLUSION

In conclusion, this 6-month study demonstrates that a proactive, protocol-driven approach to managing both rheumatoid arthritis disease activity and traditional cardiovascular risk factors results in a significant reduction in the calculated 10-year CVD risk. The close correlation between improved inflammatory control and lower QRISK3 scores provides strong support for the integrated care model. Future studies with longer follow-up and larger cohorts are needed to confirm whether this reduction in calculated risk translates into a decreased incidence of actual cardiovascular events.

REFERENCES

1. Chauhan K, Jandu JS, Brent LH, Al-Dhahir MA. Rheumatoid Arthritis. Rosen Barkin's 5-Minute Emerg Med Consult, Fifth Ed [Internet]. 2023 May 25 [cited 2025 Sep 23]; Available from: https://www.ncbi.nlm.nih.gov/books/NBK441999/
2. Sparks JA. Rheumatoid Arthritis. Ann Intern Med [Internet]. 2019 Jan 1 [cited 2025 Sep 23];170(1):ITC1–15. Available from: https://pubmed.ncbi.nlm.nih.gov/30596879/
3. Bullock J, Rizvi SAA, Saleh AM, Ahmed SS, Do DP, Ansari RA, et al. Rheumatoid Arthritis: A Brief Overview of the Treatment. Med Princ Pract [Internet]. 2018 Mar 1 [cited 2025 Sep 23];27(6):501–7. Available from: https://pubmed.ncbi.nlm.nih.gov/30173215/
4. Avina-Zubieta JA, Thomas J, Sadatsafavi M, Lehman AJ, Lacaille D. Risk of incident cardiovascular events in patients with rheumatoid arthritis: A meta-analysis of observational studies. Ann Rheum Dis [Internet]. 2012 Sep [cited 2025 Sep 23];71(9):1524–9. Available from: https://pubmed.ncbi.nlm.nih.gov/22425941/
5. Lindhardsen J, Ahlehoff O, Gislason GH, Madsen OR, Olesen JB, Torp-Pedersen C, et al. The risk of myocardial infarction in rheumatoid arthritis and diabetes mellitus: a Danish nationwide cohort study. Ann Rheum Dis [Internet]. 2011 Jun [cited 2025 Sep 23];70(6):929–34. Available from: https://pubmed.ncbi.nlm.nih.gov/21389043/
6. Skeoch S, Bruce IN. Atherosclerosis in rheumatoid arthritis: is it all about inflammation? Nat Rev Rheumatol [Internet]. 2015 Jul 30 [cited 2025 Sep 23];11(7):390–400. Available from: https://pubmed.ncbi.nlm.nih.gov/25825281/
7. Libby P. Role of Inflammation in Atherosclerosis Associated with Rheumatoid Arthritis. Am J Med [Internet]. 2008 Oct [cited 2025 Sep 23];121(10 SUPPL.1). Available from: https://pubmed.ncbi.nlm.nih.gov/18926166/
8. Charles-Schoeman C, Watanabe J, Lee YY, Furst DE, Amjadi S, Elashoff D, et al. Abnormal function of high-density lipoprotein is associated with poor disease control and an altered protein cargo in rheumatoid arthritis. Arthritis Rheum [Internet]. 2009 [cited 2025 Sep 23];60(10):2870–9. Available from: https://pubmed.ncbi.nlm.nih.gov/19790070/
9. Myasoedova E, Crowson CS, Kremers HM, Roger VL, Fitz-Gibbon PD, Therneau TM, et al. Lipid paradox in rheumatoid arthritis: the impact of serum lipid measures and systemic inflammation on the risk of cardiovascular disease. Ann Rheum Dis [Internet]. 2011 Mar [cited 2025 Sep 23];70(3):482–7. Available from: https://pubmed.ncbi.nlm.nih.gov/21216812/
10. Peters MJL, Van Halm VP, Voskuyl AE, Smulders YM, Boers M, Lems WF, et al. Does rheumatoid arthritis equal diabetes mellitus as an independent risk factor for cardiovascular disease? A prospective study. Arthritis Rheum [Internet]. 2009 Nov 15 [cited 2025 Sep 23];61(11):1571–9. Available from: https://pubmed.ncbi.nlm.nih.gov/19877093/
11. Agca R, Heslinga SC, Rollefstad S, Heslinga M, McInnes IB, Peters MJL, et al. EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders: 2015/2016 update. Ann Rheum Dis [Internet]. 2016 Oct 3 [cited 2025 Sep 23];76(1):17–28. Available from: https://pubmed.ncbi.nlm.nih.gov/27697765/
12. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, et al. 2010 Rheumatoid

arthritis classification criteria: An American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis [Internet]. 2010 Sep [cited 2025 Sep 23];69(9):1580–8. Available from: https://pubmed.ncbi.nlm.nih.gov/20699241/

13. Hippisley-Cox J, Coupland C, Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. BMJ [Internet]. 2017 May 23 [cited 2025 Sep 23];357. Available from: https://www.bmj.com/content/357/bmj.j2099
14. Gonzalez-Gay MA, Gonzalez-Juanatey C, Martin J. Rheumatoid Arthritis: A Disease Associated with Accelerated Atherogenesis. Semin Arthritis Rheum [Internet]. 2005 Aug 1 [cited 2025 Sep 23];35(1):8–17. Available from: https://www.sciencedirect.com/science/article/abs/pii/S0049017205000508
15. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, et al. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. N Engl J Med [Internet]. 2017 Sep 21 [cited 2025 Sep 23];377(12):1119–31. Available from: https://pubmed.ncbi.nlm.nih.gov/28845751/
16. Greenberg JD, Kremer JM, Curtis JR, Hochberg MC, Reed G, Tsao P, et al. Tumour necrosis factor antagonist use and associated risk reduction of cardiovascular events among patients with rheumatoid arthritis. Ann Rheum Dis [Internet]. 2011 Apr [cited 2025 Sep 23];70(4):576–82. Available from: https://pubmed.ncbi.nlm.nih.gov/21109516/
17. Roubille C, Richer V, Starnino T, McCourt C, McFarlane A, Fleming P, et al. The effects of tumour necrosis factor inhibitors, methotrexate, non-steroidal anti-inflammatory drugs and corticosteroids on cardiovascular events in rheumatoid arthritis, psoriasis and psoriatic arthritis: A systematic review and meta-analysis. Ann Rheum Dis [Internet]. 2015 Mar 1 [cited 2025 Sep 23];74(3):480–9. Available from: https://pubmed.ncbi.nlm.nih.gov/25561362/
18. McMahon M, Grossman J, FitzGerald J, Dahlin-Lee E, Wallace DJ, Thong BY, et al. Proinflammatory high-density lipoprotein as a biomarker for atherosclerosis in patients with systemic lupus erythematosus and rheumatoid arthritis. Arthritis Rheum [Internet]. 2006 Aug [cited 2025 Sep 23];54(8):2541–9. Available from: https://pubmed.ncbi.nlm.nih.gov/16868975/
19. Crowson CS, Gabriel SE, Semb AG, Van Riel PLCM, Karpouzas G, Dessein PH, et al. Rheumatoid arthritis-specific cardiovascular risk scores are not superior to general risk scores: a validation analysis of patients from seven countries. [cited 2025 Sep 23]; Available from: https://academic.oup.com/rheumatology/article/56/7/1102/3063745
20. Stadler M, Zhao S (Steven), Barton A, Bowes J. OA37 Validating QRISK3 for cardiovascular disease risk prediction in rheumatoid arthritis in the UK Biobank. Rheumatology [Internet]. 2025 Apr 1 [cited 2025 Sep 23];64(Supplement_3). Available from: https://dx.doi.org/10.1093/rheumatology/keaf142.037