Cardiovascular risk in rheumatoid arthritis: recent advances in the understanding of the pivotal role of inflammation, risk predictors and the impact of treatment

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Abstract
Risk of cardiovascular (CV) disease is increased among RA patients. High inflammatory burden associated with RA appears to be a key driver of the increased cardiovascular risk. Inflammation is linked with accelerated atherosclerosis and associated with a paradoxical inversion of the relationship between CV risk and lipid levels in patients with untreated RA, recently coined the lipid paradox. Furthermore, the inflammatory burden is also associated with qualitative as well as quantitative changes in lipoproteins, with the anti-inflammatory and atheroprotective roles associated with high-density lipoprotein cholesterol significantly altered. RA therapies can increase lipid levels, which may reflect the normalization of lipids due to their inflammatory-dampening effects. However, these confounding influences of inflammation and RA therapies on lipid profiles pose challenges for assessing CV risk in RA patients and interpretation of traditional CV risk scores. In this review we examine the relationship between the increased inflammatory burden in RA and CV risk, exploring how inflammation influences lipid profiles, the impact of RA therapies and strategies for identifying and monitoring CV risk in RA patients aimed at improving CV outcomes.

Key words: rheumatoid arthritis, cardiovascular disease, inflammation, atherosclerosis, dyslipidaemias, anti-rheumatic agents.

Introduction
It is now well established that RA is associated with increases in both morbidity and mortality compared with the general population. RA increases the risk of cardiovascular (CV) mortality by up to 50% compared with the general population [1–3] and CV disease (CVD) is the leading cause of death in RA patients [1, 4–9]. Large retrospective studies of RA patients have shown the risk for myocardial infarction (MI), adjusted for CV risk factors, to be increased by up to 2-fold compared with control groups [4, 10]. Two recent studies found that the increased risk of CVD in RA is comparable to that observed for patients with type 2 diabetes [11, 12]. Notably, the pattern of CVD in RA patients appears to differ from that in the general population; RA patients are more likely not only to have silent ischaemic heart disease and experience sudden death, but also to develop heart failure and die shortly thereafter [9].

Traditional CV risk factors, such as hypertension, smoking and type 2 diabetes, certainly contribute to the increased risk of mortality in RA patients, but do not fully explain it [13, 14]. Rather, the high systemic inflammatory burden associated with RA appears to be a key driver of increased CV risk [1, 15]. The heightened inflammatory state in RA is linked to accelerated atherosclerosis, with systemic inflammation exacerbating adverse changes in both established and novel CV risk factors [15–19]. Growing evidence suggests this excessive inflammatory burden is accountable for the lipid paradox.
in RA, in which cholesterol—an important CV risk factor in the general population—is inversely related to CV risk in patients with untreated RA [20, 21]. In contrast, suppression of RA-associated inflammation coincides with some increases in lipid values, but also a reduction in CV events [21–24].

In light of this, the European League Against Rheumatism (EULAR) recommendations for the management of CV risk in RA highlight the critical importance of adequate disease control in lowering CV risk. Annual CV risk assessments are recommended for patients with RA, with the risk assessment repeated when DMARD therapy is changed [1]. Although the EULAR recommendations have further helped to raise awareness of increased CV risk in patients with inflammatory arthritis, evidence suggests that these recommendations are not being practised either consistently or regularly [25, 26]. In addition, the recommendations may also underestimate the overall CV risk [27, 28].

In this review we examine the relationship between the increased inflammatory burden in RA and CV risk, exploring how inflammation influences lipid profiles and the impact of RA therapies on lipoproteins. Furthermore, we review the evidence and discuss strategies for identifying and monitoring CV risk in RA patients, with the aim of improving CV outcomes.

Inflammatory burden and CV risk in RA

Inflammation has consistently been shown to be a major CV risk factor and there is now substantial evidence to suggest that reducing inflammation lowers CV risk in RA [29–33]. Thus, compared with the general population, the increase in CV events in RA appears to be a feature of the systemic inflammation associated with RA disease activity. In this regard, the application of traditional CV risk factor assessment equations, such as Framingham and the Systematic Coronary Risk Evaluation (SCORE) models, to patients with RA are reported to underestimate their risk, as they do not fully incorporate the impact of systemic inflammation and the confounding influence of inflammation on lipid profiles [13, 25, 26, 28]. Even with the application of a multiplier of 1.5 (recommended by the EULAR) for patients with RA who meet two of three criteria consisting of (i) a disease duration >10 years, (ii) RF or anti-CCP positivity and (iii) the presence of severe extra-articular manifestations, this modified SCORE (mSCORE) may still result in a substantial proportion of RA patients at high risk for CVD remaining unidentified [26–28, 34].

Pivotal role of inflammation in the pathophysiology of CVD in RA

A broad body of evidence indicates that inflammation contributes to the onset and pathogenesis of atherosclerosis and CVD in the general population [35–37]. Epidemiological studies suggest that a number of pro-inflammatory molecules, such as CRP, fibrinogen and cytokines, are involved in mediating this process [38–40]. Levels of these pro-inflammatory molecules and cytokines are increased in RA patients; they not only promote endothelial dysfunction and structural vessel abnormalities, but also induce other CV risk factors, such as changes in lipid levels, insulin resistance and oxidative stress [41–43]. Indeed, in RA, many studies have demonstrated a significant association between inflammatory measures, particularly ESR, and the risk of CVD [21, 44–51].

Inflammation underlies the accelerated atherosclerosis in RA

Inflammation contributes to all stages of atherosclerosis, from plaque formation to instability and eventual plaque rupture [5, 43, 52]. Atherosclerosis and RA share many common inflammatory pathways, and the mechanisms leading to synovial inflammation are similar to those found in unstable atherosclerotic plaque [39, 43, 52]. For example, the high levels of TNF, IL-6 and IL-1 associated with RA are also central to the development of atherosclerosis [53, 54]. Indeed, IL-6 has been shown to be significantly associated with atherosclerosis in RA patients, independent of known CV risk factors [55].

Furthermore, acute phase reactants (APRs), typically elevated in RA, have been shown to be associated with subclinical atherosclerosis, indicated by increased carotid artery intima-media thickness (cIMT) [56] and CV morbidity and mortality in patients with RA [57]. In the general population, CRP level is an independent predictor of CV risk, particularly MI [58], while in both RA patients and healthy subjects, CRP is associated with the number of atherosclerotic plaques and cIMT [49, 59]. Notably, higher IL-6 levels are also associated with increased mortality in patients with acute coronary syndromes [60] and with increased risk of future MI in healthy men [61]. Two recent large-scale genetic and biomarker studies have identified IL-6 receptor (IL-6R) signalling as having a causal role in the development of coronary heart disease (CHD), suggesting that IL-6R blockade could be considered a potential therapeutic approach for the prevention of CHD [62, 63].

The impact of inflammation on dyslipidaemia in RA

In RA, inflammation is associated with a paradoxical inversion of the usual relationship between CV risk and lipid levels [21, 29, 64]. A similar inverse relationship has also been observed with other chronic inflammatory diseases, in sepsis, in cancer and in the immediate post-MI setting, where increased CRP is associated with lower levels of circulating lipids (Fig. 1) [65–69]. This relationship has also been noted in the period immediately after surgery, where an inverse association has been observed between IL-6 elevation and cholesterol level [70]. Importantly, several studies have reported increases in lipid levels with a successful reduction in RA disease activity following anti-inflammatory treatment [71]. These observations imply that the traditional interpretation of lipid profiles for predicting CV risk in the general population may be confounded by disease activity in RA patients [21, 29].

The mechanisms by which the inflammatory process can lead to these lipid changes are not fully understood,
The inflammatory burden in RA is associated with the lowering of lipid levels has also been noted in other chronic inflammatory conditions, after MI, after surgery and in cancer treatment [21, 29, 64–70]. In RA, a reduction of inflammation through treatment with traditional and/or biologic DMARDs is reflected in elevations in lipid levels [71]. Data, although limited, suggest the extent to which lipid levels change may be different between RA therapies; however, further studies are required to fully ascertain the relationship between suppression of inflammation, lipid elevations and future cardiovascular risk [71, 102]. MI, myocardial infarction.

Systemic inflammation associated with RA may confer both quantitative and qualitative changes to HDL cholesterol underlying the loss of some anti-inflammatory and atheroprotective properties. Known changes to subparticle composition induced by inflammation are summarized in this figure [74, 76–83, 86–88]. apoA1: apolipoprotein A1; apoJ: apolipoprotein J; CETP: cholesteryl ester transfer protein; HDL: high-density lipoprotein; LCAT: lecithin cholesterol acyltransferase; LDL: low-density lipoprotein; PAF-AH: platelet-activating factor acetylhydrolase; PON-1: paraoxonase 1; SAA: serum amyloid A; sPLA2: secretory non-pancreatic phospholipase A2.

qualitative changes need to be considered when assessing lipid profiles in RA [86–88].

Impact of anti-rheumatic therapies on lipid profiles and CV risk in RA

Traditional DMARDs

Traditional DMARDs, such as MTX, SSZ and HCQ, have a protective role against CV risk [30]. The mechanisms by which DMARD use influences CV risk are poorly understood, but lend support to the hypothesis that reducing inflammation is important in reducing CV risk. Of the traditional DMARDs, MTX is the most widely used and is known as the anchor drug in RA [89], yet the mechanisms underlying its anti-inflammatory properties are not fully understood [90]. MTX increases total cholesterol (TCh), LDL, HDL and triglyceride levels in RA [91, 92]. However, it is believed that these changes are likely to be due to the inflammatory-dampening effect of the drug and may essentially reflect normalization of the lipid levels to those seen in the general population [93]. These lipid increases are therefore not generally believed to increase CV risk. On the contrary, there is evidence from systematic reviews and large observational studies that MTX therapy may decrease CV morbidity and mortality in RA patients, although findings should be interpreted with caution given potential confounding by issues of missing data, channelling and bias [94–96]. Potential mechanisms of CV risk reduction with MTX are also not well understood [57, 94], although suppression of inflammation is likely to partially explain the perceived cardioprotective effects of MTX. Currently, in the CV Inflammation Reduction Trial, low-dose MTX (15–20 mg/week) is being tested to determine whether inhibition of...
inflammation per se improves CVD outcomes (clinicaltrials.gov, identifier NCT01594333). The outcome of this study will be pivotal, as a positive finding would strongly support the inflammatory hypothesis of atherothrombosis and further establish inflammation as a key driver of CV events [97].

**Biologic agents: TNF inhibition**

TNF, a pivotal cytokine in chronic inflammation, also affects lipid metabolism, insulin resistance and endothelial function [98, 99]. Anti-TNF therapy reduces inflammation, including levels of CRP and ESR [100, 101], modifies the lipoprotein spectrum and, in combination with MTX or DMARDs, has been associated with a reduction of CV risk in RA patients [31–33]. Meta-analyses indicate that anti-TNFs are generally associated with significant increases in HDL, Tch and triglycerides in RA [71, 102], but a recent study also suggests that anti-TNF therapy may significantly increase LDL [103]. Notably, most studies demonstrate that the lipid ratio, Tch:LDL, is not appreciably altered by anti-TNF therapy, or that increases are modest (≤ 25%) [29]. Although these studies were generally small and/or post hoc, a clear overall trend was observed for increased circulating lipid levels with anti-TNF therapy. Again, this may reflect a normalization of lipid levels to the level prior to RA disease, and although increases in triglycerides appear to be greater than those observed with MTX, this may be due to more profound suppression of inflammation with anti-TNFs [91].

Despite increases in lipid levels, systematic reviews have consistently found an association between anti-TNF therapy and a decreased risk of CV morbidity in RA [104, 105], with an overall 54% reduction in risk of all CV events [105]. A less definite association has been seen for risk of the individual events of MI, stroke and heart failure, but these analyses may have been confounded by comparisons with patients receiving other DMARDs, including MTX, known to be associated with a decreased risk of CVD [94, 104].

Interestingly, several studies have found that the level of response to anti-TNFs may be important, with responders having a significantly lower risk of CV-related events relative to non-responders [31, 104]. Although studies have generally been small and beset with some methodological issues, anti-TNF therapy has been shown to modify other factors associated with atherosclerotic CVD risk in RA, including reductions in endothelial dysfunction [106–109], enhancement of HDL anti-oxidative capacity [110] and improvements in insulin sensitivity [99]. Larger studies are required to confirm these findings. Additionally, it is not yet known whether the impact of anti-TNFs on lipid profile and CV risk is a class effect of all anti-TNFs.

**Biologic agents: IL-6R inhibition**

Tocilizumab inhibits IL-6 signalling via the blockade of IL-6R, resulting in a strong and sustained impact on inflammation, with rapid normalization of CRP and ESR [111–114]. Studies have consistently shown that tocilizumab is associated with increasing lipid levels in the context of decreasing levels of inflammatory markers [111, 113, 115-119]. However, these elevations have been shown to respond to lipid-lowering therapies [120]. The mechanisms by which tocilizumab increases lipids are not yet fully understood, particularly since polymorphisms of the IL-6R-yielding functional variants appear to have no effect on lipid concentrations but do increase levels of circulating IL-6 while reducing levels of APRs [62, 63].

Importantly, similar to anti-TNF therapy, all main lipoproteins—HDL, Tch, LDL and triglycerides—are increased with tocilizumab treatment and are related to relatively stable LDL:HDL and Tch:HDL ratios. These ratios are known to be more closely associated with CV risk than individual lipid measures, which can be confounded by the effect of inflammation [35, 121, 122]. The ratio of apolipoprotein (apo) B:apoA1, which has been shown to predict CV risk more accurately than any other cholesterol index, remained stable over 6 months of tocilizumab treatment [113, 123, 124].

In the double-blind phase IV Adalimumab Actemra (ADACTA) study, which evaluated tocilizumab monotherapy vs adalimumab (anti-TNF) monotherapy in RA patients intolerant to MTX or for whom continued MTX was deemed inappropriate, more patients in the tocilizumab group than in the adalimumab group had increased LDL along with significantly greater reductions in CRP, ESR, 28-joint DAS (DAS28) and other composite measures of disease activity at 24 weeks [125]. Qualitative changes in lipid subfractions with tocilizumab therapy have been examined in the placebo-controlled MEASURE study (a randomized, parallel-group, open-label, multicentre study to evaluate the effects of tocilizumab on vaccination in subjects with active RA receiving background MTX), which found that tocilizumab + MTX did not increase the concentration of small, dense LDL particles, which are generally believed to be pro-atherogenic [35, 126-128], compared with MTX alone at 12 or 24 weeks [129]. In contrast, small and medium HDL particles, considered to be anti-atherogenic, were significantly increased with tocilizumab. Interestingly, the study also demonstrated significant changes in paraoxonase 1 levels, HDL-associated serum amyloid A (SAA) and secreted group IIa phospholipase A2 (sPLA2-IIa) with tocilizumab, suggesting that treatment alters HDL composition from a pro-inflammatory state to a less inflammatory state.

Data from the tocilizumab clinical development programme and long-term extension studies provide some reassurance for the lack of a negative effect of lipid profile changes seen with tocilizumab on CV risk. In the double-blind phase of the five core phase III studies of tocilizumab, rates of MI were numerically lower with both doses of tocilizumab vs controls [120], while analysis of the long-term safety of tocilizumab (n = 4171; median treatment duration 3.9 years) demonstrated a stable rate of CV events over time with tocilizumab exposure [120, 130]. These clinical data are supported by imaging studies that show that tocilizumab does not appear to increase cIMT [131, 132].
Interpretation of the effects of tocilizumab on inflammatory burden using only CRP or composite disease activity measures that incorporate an APR component can be misleading due to the powerful effect of IL-6 inhibition on hepatic APR production [133, 134]. However, in the ADACTA study, tocilizumab induced not only a greater reduction in ESR and CRP at all time points compared with adalimumab, but also a greater reduction in the Clinical Disease Activity Index (CDAI), which does not include an APR component [125]. Interestingly, increased CRP levels have also been established as a precursor of insulin resistance development, an important CV risk factor, and a recent subanalysis of the TOWARD (Tocilizumab in Combination With Traditional DMARD Therapy) study found that tocilizumab significantly improved insulin resistance in RA patients [135, 136]. ENTRACTE, an ongoing randomized, open-label study evaluating the rate of CV events with tocilizumab vs etanercept in patients with RA, will provide further insight on the effects of tocilizumab compared with anti-TNFs (clinicaltrials.gov identifier NCT01331837).

Other RA therapeutic agents

Relatively little is known regarding the impact of other biologics (rituximab, abatacept or anakinra) on lipid profiles or CV risk in RA. Analyses of rituximab safety have demonstrated no notable differences vs placebo in CV event rates at 6 months and no evidence for an increased association between MI and rituximab in longer-term follow-up [137]. A recent analysis suggests rituximab has beneficial effects on the cholesterol profile and alteration of HDL to a less pro-atherogenic composition during 6 months of treatment [82]. Rapid rituximab-induced improvements in flow-mediated dilatation and decreases in cIMT, coinciding with decreases in TCh and increases in HDL, have also been demonstrated in a small study [138].

Tofacitinib, an oral Janus kinase inhibitor, has recently been approved by the US Food and Drug Administration (FDA) as an RA medication. Lipid profile changes with tofacitinib appear to be similar to those observed with tocilizumab, with increases in both LDL and HDL, however, CRP does not appear to be reduced to the same extent [139–142]. In a phase III study, LDL and HDL levels increased to a greater extent with tofacitinib than with the anti-TNF adalimumab at 3 months, despite a numerically significant impact on measures of disease activity—indicating that there may be mechanisms involved other than dampening of inflammation with tofacitinib [139]. A tofacitinib phase II study including co-administration of the lipid-lowering agent atorvastatin indicated that the increase in LDL and TCh could be reduced to below baseline levels [143]. Analysis of major adverse CV events in the tofacitinib clinical development programme demonstrated a similar incidence across groups in the phase III programme, with lower rates in long-term extension studies, suggesting no increased CV risk over 3 years of follow-up [144].

Management of lipid profiles and CV risk in RA

Given the high level of systemic inflammatory burden that characterizes RA, which is regarded as a key CV risk factor, alongside an increased prevalence of traditional risk factors, EULAR recommendations highlight the importance of adequate disease control in order to lower CV risk (Table 1) [1]. The vulnerability of the carotid plaque has been shown to be influenced by RA disease activity, and remission may alleviate this threat [145]. Therefore effective CV risk management will likely comprise not only adequate treatment of conventional risk factors, but also tight and sustained disease activity control [27]. The complex impact of inflammation on lipid particle composition as well as the phenomenon of the lipid paradox in RA makes interpretation of circulating lipid levels difficult, potentially limiting their usefulness as a marker of CV risk [21, 29]. Moreover, in a post hoc analysis from the Apolipoprotein-related Mortality Risk (AMORIS) study, the association between TCh and acute MI was found to be weaker among patients with RA than the general population [10]. This may suggest that the traditional interpretation of hypercholesterolaemia as a risk for CVD may not apply and that lipid levels from RA patients may be a confounding factor in CV risk algorithms.

The potent suppression of inflammation with biologic therapies in RA is accompanied by increases in lipid parameters that are normally associated with increased CV risk in the general population. Thus, in order to appropriately manage lipid levels in RA patients, it is advisable to reassess the lipid profiles of patients after dampening inflammation. Strategies such as treat-to-target, with disease remission or low disease activity as the clinical goal, as soon as RA is diagnosed can be highly effective to rapidly reduce inflammation and achieve tight control of disease activity (an overview of the benefits of dampening inflammation on CV risk in RA is shown in Fig. 3) [146]. Lipid profiles can then be monitored and, if appropriate, treated with lipid-lowering drugs according to national guidelines [147–149].

The EULAR recommendations for CV management, based on a systematic literature review and the opinion of an interdisciplinary task force, are a highly welcome starting point for identifying and improving the management of CV risk in patients with RA. Although it was acknowledged by the EULAR task force that their approach was conservative, evidence suggests that, even after applying the multiplication factor, the mSCORE risk factor equation may still not accurately estimate CV risk for individual RA patients [26, 27, 150]. One aspect potentially contributing to this underestimation of risk is the use of a disease duration >10 years as a criteria for increased CV risk, as most evidence now supports increased risk of CVD early in disease [151–153]. Thus more discriminating tools for identifying RA patients with higher risk of CVD are needed.

Several validated non-invasive imaging techniques are now available for determining subclinical atherosclerosis in RA [34, 154, 155]. Of these, ultrasonographic assessment of cIMT and the presence of plaques has been
The heightened inflammatory state in RA is linked with accelerated atherosclerosis, with systemic inflammation exacerbating adverse changes in both established and novel cardiovascular (CV) risk factors [16–19]. Additionally, the use of some anti-inflammatory medication is also associated with increasing CV risk [6]. Treat-to-target strategies with traditional and/or biologic DMARDs can be highly effective to rapidly reduce inflammation and achieve tight control of disease activity [146]. Lipid profiles can then be monitored and, if appropriate, treated with lipid-lowering drugs according to national guidelines [147–149].
recommendations may underestimate CV risk in some patients. The use of non-invasive imaging tools may help to improve the sensitivity of CV assessments, but further research is needed to assess the feasibility of incorporating these techniques into routine practice.

**Rheumatology key messages**

- Inflammation in RA is associated with a paradoxical inversion of the relationship between cardiovascular risk and lipid levels.
- Increases in lipid levels by RA therapies reflect normalization of lipids due to their inflammatory-dampening effects.
- More discriminating tools for identifying RA patients with a higher risk of cardiovascular disease are needed.

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