

## Review

doi:10.1093/rheumatology/keu224

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

Ernest Choy<sup>1</sup>, Kandeepan Ganeshalingam<sup>2</sup>, Anne Grete Semb<sup>3,\*</sup>, Zoltán Szekanecz<sup>4,\*</sup> and Michael Nurmohamed<sup>5,\*</sup>

## 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

<sup>1</sup>Section of Rheumatology, Cardiff University School of Medicine, Cardiff, UK, <sup>2</sup>Global Medical Affairs, F. Hoffmann-La Roche, Basel, Switzerland, <sup>3</sup>Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, <sup>4</sup>Department of Rheumatology, Institute of Medicine, University of Debrecen, Debrecen, Hungary and <sup>5</sup>Departments of Internal Medicine and Rheumatology, VU University Medical Center, Amsterdam, The Netherlands.

Submitted 20 January 2014; revised version accepted 28 March 2014.

Correspondence to: Ernest Choy, Section of Rheumatology, Cardiff University School of Medicine, First Floor, Tenovus Building, Heath Park Campus, Cardiff CF14 4XN, UK. E-mail: choyeh@cardiff.ac.uk

\*Anne Grete Semb, Zoltán Szekanecz and Michael Nurmohamed contributed equally to this study.

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 CVD risk factors [55].

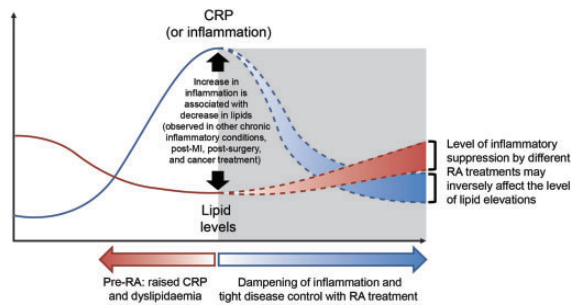
Furthermore, acute phase reactants (APRs), typically elevated in RA, have been shown to be associated with subclinical atherosclerosis, indicated by increased carotid artery intima-media thickness (cIMT) [56] and CV morbidity and mortality in patients with RA [57]. In the general population, CRP level 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,

**Fig. 1** Representation of the inverse relationship between changes in inflammatory and lipid parameters

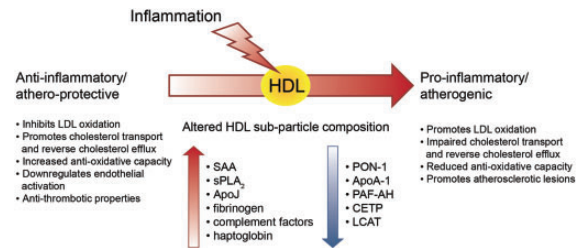


The paradigm by which an increase in the inflammatory burden in RA is associated with the lowering of lipid levels has also been noted in other chronic inflammatory conditions, after MI, after surgery and in cancer treatment [21, 29, 64–70]. In RA, a reduction of inflammation through treatment with traditional 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.

but may include suppression of the reticuloendothelial system and reduced low-density lipoprotein (LDL) particle synthesis [29]. It is possible that under high inflammatory burden, excessive APR production may impair trafficking of cholesterol in the liver or impede normal cholesterol production. Additionally, CRP mediates the uptake of LDL and oxidized LDL by macrophages, induces LDL deposition and increases LDL uptake by hepatocytes [72, 73].

The inflammatory burden in RA is associated with qualitative as well as quantitative changes in lipoproteins [74]. High-density lipoprotein (HDL) has numerous anti-inflammatory and atheroprotective roles, promoting reverse cholesterol transport from circulation to the liver and preventing LDL oxidation [75]. This protective function may be impaired during pathological processes that accelerate CV events [76–81]. Proteomic studies have found that the subfraction composition of HDL isolated from RA patients was significantly altered, with the resultant loss of anti-inflammatory and reverse cholesterol transport function (summarized in Fig. 2) [74, 82, 83]. Other work has suggested that the anti-inflammatory nature of HDL may be a more sensitive marker of CVD than absolute HDL levels. A good example of this comes from studies of the cholesterol ester transfer protein inhibitors, dalcetrapib and torcetrapib, in which circulating HDL levels were increased by as much as 30–70%, yet no additional cardioprotective effect was observed [84, 85]. Taken together, these findings indicate that both quantitative and

**Fig. 2** Inflammation induces qualitative changes to HDL subparticle composition



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; sPLA<sub>2</sub>: secretory non-pancreatic phospholipase A<sub>2</sub>.

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:HDL, is not appreciably altered by anti-TNF therapy, or that increases are modest ( $\leq 25\%$ ) [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 A<sub>2</sub> (sPLA<sub>2</sub>-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 similar 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].

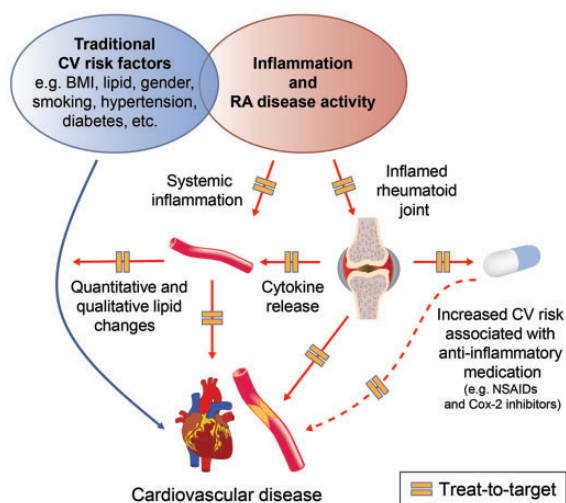
The EULAR recommendations for CV management, based on a systematic literature review and the opinion of an interdisciplinary task force, are a highly welcome starting point for identifying and improving the management of CV risk in patients with RA. Although it was acknowledged by the EULAR task force 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

**TABLE 1** Ten recommendations from EULAR for CV risk management in RA

1	RA should be regarded as a condition associated with higher risk for CV disease. The increased risk appears to be due to both an increased prevalence of traditional risk factors and the inflammatory burden.
2	Adequate control of disease activity is necessary to lower the CV risk.
3	CV risk assessment using national guidelines is recommended for all patients with RA. Risk assessments should be repeated when anti-rheumatic treatment has been changed.
4	Risk score models should be adapted for patients with RA by introducing a 1.5 multiplication factor. This multiplication factor should be used when the patient with RA meets two of the following three criteria: (i) disease duration >10 years, (ii) RF or anti-CCP positivity and (iii) the presence of certain extra-articular manifestations.
5	TCh/HDL cholesterol ratio should be used when the SCORE model is used.
6	Intervention should be carried out according to national guidelines.
7	Statins, ACE inhibitors and/or AT-II blockers are preferred treatment options.
8	The role of coxibs and most NSAIDs in CV risk is not well established and needs further investigation. Hence we should be very cautious about prescribing them, especially for patients with a documented CV disease or in the presence of CV risk factors.
9	Corticosteroids: use the lowest dose possible.
10	Recommend smoking cessation.

CV: cardiovascular; coxibs: cyclooxygenase (COX) inhibitors; TCh: total cholesterol; HDL: high-density lipoprotein cholesterol; ACE: angiotensin-converting enzyme. Adapted from Peters *et al.* [1].

**FIG. 3** Impact of tight control of inflammation and disease activity in relation to the reduction of cardiovascular risk in RA

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].

identified as useful for stratifying RA patients with high CV risk [34, 56, 149]. In a recent study ~60% of patients identified as having moderate CV risk according to the mSCORE had evidence of carotid plaques and/or cIMT >0.90 mm (both considered factors indicative of CV prognosis in the general population) [34]. Furthermore, the proportion of patients identified as having high or very high CV risk increased from 9.2% with the mSCORE to 47.7% with additional carotid US results [27, 34]. Non-invasive imaging techniques such as carotid ultrasonography may thus be useful alongside CV risk assessment models to enhance the identification of RA patients with increased CV risk. However, the feasibility of performing these assessments within a rheumatology clinic or in partnership with a specialist cardiology clinic needs to be established [27].

## Conclusion

The CV risk in RA is increased to a similar magnitude to that seen in type 2 diabetes and is related to the systemic inflammatory burden associated with RA as well as an increased prevalence of traditional risk factors. Anti-rheumatic therapies that are highly effective at reducing inflammation appear to increase TCh and LDL levels, although in light of the lipid paradox in RA, the benefits of suppression of inflammation are likely to outweigh lipid changes that might otherwise be considered to be adverse. In this regard, the suppression of inflammation through tight and sustained disease control is important for lowering CV risk, but also to permit accurate screening of patients at high CV risk.

The optimal approach for identification of patients with increased CV risk has yet to be fully established, but it is key that (i) all RA patients be screened and (ii) the appropriate management for those who are at high risk be undertaken. Current assessment tools and

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.

### Acknowledgements

Support for third-party writing assistance for this manuscript was provided by F. Hoffmann-La Roche Ltd. All views in this article are those of the authors.

**Disclosure statement:** E.C. reports grants and personal fees from F. Hoffman-La Roche Chugai Pharma and UCB and personal fees from Pfizer, MSD, AbbVie and BMS during the preparation of the manuscript, as well as personal fees from Abbott Laboratories, Boehringer Ingelheim, Daiichi Sankyo, Eli Lilly, ISIS, MedImmune and Synovate and grants from Ferring Pharmaceutical, GSK and Jazz Pharmaceuticals outside the submitted work. A.G.S. reports personal fees from Merck/Schering-Plough, Abbott, Pfizer/Wyeth, F. Hoffman-La Roche and BMS and grants from Raagholtstiftelsen, Norwegian Extra Foundation for Health and Rehabilitation, South Eastern Regional Health Authority of Norway and Grete Harbitz legat outside the submitted work. K.G. is employed by F. Hoffmann-La Roche Ltd. All other authors have declared no conflicts of interest.

### References

- Peters MJ, Symmons DP, McCarey D *et al.* EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. *Ann Rheum Dis* 2010; 69:325–31.
- 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* 2009;48:1309–13.
- 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.
- Solomon DH, Karlson EW, Rimm EB *et al.* Cardiovascular morbidity and mortality in women diagnosed with rheumatoid arthritis. *Circulation* 2003;107:1303–7.
- de Groot L, Posthumus MD, Kallenberg CG, Bijl M. Risk factors and early detection of atherosclerosis in rheumatoid arthritis. *Eur J Clin Invest* 2010;40:835–42.
- Gullick NJ, Scott DL. Co-morbidities in established rheumatoid arthritis. *Best Pract Res Clin Rheumatol* 2011; 25:469–83.
- Meune C, Touze E, Trinquart L, Allanore Y. High risk of clinical cardiovascular events in rheumatoid arthritis: levels of associations of myocardial infarction and stroke through a systematic review and meta-analysis. *Arch Cardiovasc Dis* 2010;103:253–61.
- Gremese E, Ferraccioli G. The metabolic syndrome: the crossroads between rheumatoid arthritis and cardiovascular risk. *Autoimmun Rev* 2011;10:582–9.
- Gabriel SE. Cardiovascular morbidity and mortality in rheumatoid arthritis. *Am J Med* 2008;121(Suppl 1): S9–14.
- Semb AG, Kvien TK, Aastveit AH *et al.* Lipids, myocardial infarction and ischaemic stroke in patients with rheumatoid arthritis in the Apolipoprotein-related Mortality RiSk (AMORIS) Study. *Ann Rheum Dis* 2010;69: 1996–2001.
- Peters MJ, van Halm VP, Voskuyl AE *et al.* Does rheumatoid arthritis equal diabetes mellitus as an independent risk factor for cardiovascular disease? A prospective study. *Arthritis Rheum* 2009;61:1571–9.
- Lindhardsen J, Ahlehoj O, Gislason GH *et al.* The risk of myocardial infarction in rheumatoid arthritis and diabetes mellitus: a Danish nationwide cohort study. *Ann Rheum Dis* 2011;70:929–34.
- Dessein PH, Joffe BI, Veller MG *et al.* Traditional and nontraditional cardiovascular risk factors are associated with atherosclerosis in rheumatoid arthritis. *J Rheumatol* 2005;32:435–42.
- Boyer JF, Gourraud PA, Cantagrel A, Davignon JL, Constantin A. Traditional cardiovascular risk factors in rheumatoid arthritis: a meta-analysis. *Joint Bone Spine* 2011;78:179–83.
- Ku IA, Imboden JB, Hsue PY, Ganz P. Rheumatoid arthritis: model of systemic inflammation driving atherosclerosis. *Circ J* 2009;73:977–85.
- Weinblatt ME, Kuritzky L. RAPID: rheumatoid arthritis. *J Fam Pract* 2007;56(Suppl):S1–7, quiz S8.
- Situnayake RD, Kitagawa G. Dyslipidemia and rheumatoid arthritis. *Ann Rheum Dis* 1997;56:341–2.
- del Rincon ID, Williams K, Stern MP, Freeman GL, Escalante A. High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors. *Arthritis Rheum* 2001;44:2737–45.
- Sattar N, McInnes IB. Vascular comorbidity in rheumatoid arthritis: potential mechanisms and solutions. *Curr Opin Rheumatol* 2005;17:286–92.
- National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002;106: 3143–421.

- 21 Myasoedova E, Crowson CS, Kremers HM *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* 2011;70:482–7.
- 22 Steiner G, Urowitz MB. Lipid profiles in patients with rheumatoid arthritis: mechanisms and the impact of treatment. *Semin Arthritis Rheum* 2009;38:372–81.
- 23 Peters MJ, Vis M, van Halm VP *et al.* Changes in lipid profile during infliximab and corticosteroid treatment in rheumatoid arthritis. *Ann Rheum Dis* 2007;66:958–61.
- 24 Schimmel EK, Yazici Y. Increased lipid levels but unchanged atherogenic index in rheumatoid arthritis patients treated with biologic disease modifying antirheumatic drugs: published experience. *Clin Exp Rheumatol* 2009; 27:446–51.
- 25 Gossec L, Salejan F, Nataf H *et al.* Challenges of cardiovascular risk assessment in the routine rheumatology outpatient setting: an observational study of 110 rheumatoid arthritis patients. *Arthritis Care Res* 2013;65: 712–7.
- 26 Crowson CS, Gabriel SE. Towards improving cardiovascular risk management in patients with rheumatoid arthritis: the need for accurate risk assessment. *Ann Rheum Dis* 2011;70:719–21.
- 27 Dessein PH, Semb AG. Could cardiovascular disease risk stratification and management in rheumatoid arthritis be enhanced? *Ann Rheum Dis* 2013;72:1743–6.
- 28 Arts EE, Popa C, Den Broeder AA *et al.* Performance of four current risk algorithms in predicting cardiovascular events in patients with early rheumatoid arthritis. *Ann Rheum Dis* 2014, Jan 3. doi: 10.1136/annrheumdis-2013-204024 [Epub ahead of print].
- 29 Choy E, Sattar N. Interpreting lipid levels in the context of high-grade inflammatory states with a focus on rheumatoid arthritis: a challenge to conventional cardiovascular risk actions. *Ann Rheum Dis* 2009;68:460–9.
- 30 van Halm VP, Nurmohamed MT, Twisk JW, Dijkman BA, Voskuyl AE. Disease-modifying antirheumatic drugs are associated with a reduced risk for cardiovascular disease in patients with rheumatoid arthritis: a case control study. *Arthritis Res Ther* 2006;8:R151.
- 31 Dixon WG, Watson KD, Lunt M *et al.* Reduction in the incidence of myocardial infarction in patients with rheumatoid arthritis who respond to anti-tumor necrosis factor alpha therapy: results from the British Society for Rheumatology Biologics Register. *Arthritis Rheum* 2007; 56:2905–12.
- 32 Greenberg JD, Kremer JM, Curtis JR *et al.* Tumour necrosis factor antagonist use and associated risk reduction of cardiovascular events among patients with rheumatoid arthritis. *Ann Rheum Dis* 2011;70:576–82.
- 33 Popa C, Netea MG, Radstake T *et al.* Influence of anti-tumour necrosis factor therapy on cardiovascular risk factors in patients with active rheumatoid arthritis. *Ann Rheum Dis* 2005;64:303–5.
- 34 Corrales A, Gonzalez-Juanatey C, Peiro ME *et al.* Carotid ultrasound is useful for the cardiovascular risk stratification of patients with rheumatoid arthritis: results of a population-based study. *Ann Rheum Dis* 2014;73: 722–7.
- 35 Jellinger PS, Smith DA, Mehta AE *et al.* American Association of Clinical Endocrinologists' guidelines for management of dyslipidemia and prevention of atherosclerosis. *Endocr Pract* 2012;18:1–78.
- 36 Libby P, Ridker PM, Hansson GK. Progress and challenges in translating the biology of atherosclerosis. *Nature* 2011;473:317–25.
- 37 Hansson GK, Hermansson A. The immune system in atherosclerosis. *Nat Immunol* 2011;12:204–12.
- 38 Danesh J, Kaptoge S, Mann AG *et al.* Long-term interleukin-6 levels and subsequent risk of coronary heart disease: two new prospective studies and a systematic review. *PLoS Med* 2008;5:e78.
- 39 Kaptoge S, Di Angelantonio E, Lowe G *et al.* C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. *Lancet* 2010;375:132–40.
- 40 Danesh J, Lewington S, Thompson SG *et al.* Plasma fibrinogen level and the risk of major cardiovascular diseases and nonvascular mortality: an individual participant meta-analysis. *JAMA* 2005;294:1799–809.
- 41 Schultz O, Oberhauser F, Saech J *et al.* Effects of inhibition of interleukin-6 signalling on insulin sensitivity and lipoprotein(a) levels in human subjects with rheumatoid diseases. *PLoS One* 2010;5:e14328.
- 42 Chung CP, Oeser A, Solus JF *et al.* Inflammation-associated insulin resistance: differential effects in rheumatoid arthritis and systemic lupus erythematosus define potential mechanisms. *Arthritis Rheum* 2008;58: 2105–12.
- 43 Libby P. Role of inflammation in atherosclerosis associated with rheumatoid arthritis. *Am J Med* 2008; 121(Suppl 1):S21–31.
- 44 Innala L, Moller B, Ljung L *et al.* Cardiovascular events in early RA are a result of inflammatory burden and traditional risk factors: a five year prospective study. *Arthritis Res Ther* 2011;13:R131.
- 45 Book C, Saxne T, Jacobsson LT. Prediction of mortality in rheumatoid arthritis based on disease activity markers. *J Rheumatol* 2005;32:430–4.
- 46 Crilly MA, Kumar V, Clark HJ *et al.* Arterial stiffness and cumulative inflammatory burden in rheumatoid arthritis: a dose-response relationship independent of established cardiovascular risk factors. *Rheumatology* 2009;48: 1606–12.
- 47 Graf J, Scherzer R, Grunfeld C, Imboden J. Levels of C-reactive protein associated with high and very high cardiovascular risk are prevalent in patients with rheumatoid arthritis. *PLoS One* 2009;4:e6242.
- 48 del Rincon I, Freeman GL, Haas RW, O'Leary DH, Escalante A. Relative contribution of cardiovascular risk factors and rheumatoid arthritis clinical manifestations to atherosclerosis. *Arthritis Rheum* 2005;52:3413–23.
- 49 Gonzalez-Gay MA, Gonzalez-Juanatey C, Pineiro A *et al.* High-grade C-reactive protein elevation correlates with accelerated atherogenesis in patients with rheumatoid arthritis. *J Rheumatol* 2005;32:1219–23.
- 50 Maradit-Kremers H, Nicola PJ, Crowson CS, Ballman KV, Gabriel SE. Cardiovascular death in rheumatoid arthritis: a population-based study. *Arthritis Rheum* 2005;52:722–32.

- 51 Wallberg-Jonsson S, Johansson H, Ohman ML, Rantapaa-Dahlqvist S. Extent of inflammation predicts cardiovascular disease and overall mortality in seropositive rheumatoid arthritis. A retrospective cohort study from disease onset. *J Rheumatol* 1999;26:2562–71.
- 52 Miller AM, McInnes IB. Cytokines as therapeutic targets to reduce cardiovascular risk in chronic inflammation. *Curr Pharm Des* 2011;17:1–8.
- 53 Cesari M, Penninx BW, Newman AB *et al.* Inflammatory markers and cardiovascular disease (The Health, Aging and Body Composition [Health ABC] Study). *Am J Cardiol* 2003;92:522–8.
- 54 Waehre T, Yndestad A, Smith C *et al.* Increased expression of interleukin-1 in coronary artery disease with downregulatory effects of HMG-CoA reductase inhibitors. *Circulation* 2004;109:1966–72.
- 55 Rho YH, Chung CP, Oeser A *et al.* Inflammatory mediators and premature coronary atherosclerosis in rheumatoid arthritis. *Arthritis Rheum* 2009;61:1580–5.
- 56 van Sijl AM, Peters MJ, Knol DK *et al.* Carotid intima media thickness in rheumatoid arthritis as compared to control subjects: a meta-analysis. *Semin Arthritis Rheum* 2011;40:389–97.
- 57 Greenberg JD, Furer V, Farkouh ME. Cardiovascular safety of biologic therapies for the treatment of RA. *Nat Rev Rheumatol* 2012;8:13–21.
- 58 Ridker PM, Buring JE, Shih J, Matias M, Hennekens CH. Prospective study of C-reactive protein and the risk of future cardiovascular events among apparently healthy women. *Circulation* 1998;98:731–3.
- 59 Del Rincon I, Williams K, Stern MP *et al.* Association between carotid atherosclerosis and markers of inflammation in rheumatoid arthritis patients and healthy subjects. *Arthritis Rheum* 2003;48:1833–40.
- 60 Biasucci LM, Liuzzo G, Fantuzzi G *et al.* Increasing levels of interleukin (IL)-1Ra and IL-6 during the first 2 days of hospitalization in unstable angina are associated with increased risk of in-hospital coronary events. *Circulation* 1999;99:2079–84.
- 61 Ridker PM, Rifai N, Stampfer MJ, Hennekens CH. Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. *Circulation* 2000;101:1767–72.
- 62 IL6R Genetics Consortium Emerging Risk Factors Collaboration, Sarwar N, Butterworth AS *et al.* Interleukin-6 receptor pathways in coronary heart disease: a collaborative meta-analysis of 82 studies. *Lancet* 2012;379:1205–13.
- 63 Interleukin-6 Receptor Mendelian Randomisation Analysis (IL6R MR) Consortium. The interleukin-6 receptor as a target for prevention of coronary heart disease: a mendelian randomisation analysis. *Lancet* 2012;379:1214–24.
- 64 Robertson J, Peters MJ, McInnes IB, Sattar N. Changes in lipid levels with inflammation and therapy in RA: a maturing paradigm. *Nat Rev Rheumatol* 2013;9:513–23.
- 65 Marik PE. Dyslipidemia in the critically ill. *Crit Care Clin* 2006;22:151–9, viii.
- 66 Vermont CL, den Brinker M, Kakeci N *et al.* Serum lipids and disease severity in children with severe meningococcal sepsis. *Crit Care Med* 2005;33:1610–5.
- 67 Alexopoulos CG, Pournaras S, Vaslamatzis M, Avgerinos A, Raptis S. Changes in serum lipids and lipoproteins in cancer patients during chemotherapy. *Cancer Chemother Pharmacol* 1992;30:412–6.
- 68 Watson WC, Buchanan KD, Dickson C. Serum cholesterol levels after myocardial infarction. *Br Med J* 1963;2:709–12.
- 69 MBewu AD, Durrington PN, Bulleid S, Mackness MI. The immediate effect of streptokinase on serum lipoprotein(a) concentration and the effect of myocardial infarction on serum lipoprotein(a), apolipoproteins A1 and B, lipids and C-reactive protein. *Atherosclerosis* 1993;103:65–71.
- 70 Akgun S, Ertel NH, Mosenthal A, Oser W. Postsurgical reduction of serum lipoproteins: interleukin-6 and the acute-phase response. *J Lab Clin Med* 1998;131:103–8.
- 71 Daien CI, Duny Y, Barnette T *et al.* Effect of TNF inhibitors on lipid profile in rheumatoid arthritis: a systematic review with meta-analysis. *Ann Rheum Dis* 2012;71:862–8.
- 72 Singh U, Dasu MR, Yancey PG *et al.* Human C-reactive protein promotes oxidized low density lipoprotein uptake and matrix metalloproteinase-9 release in Wistar rats. *J Lipid Res* 2008;49:1015–23.
- 73 Wang X, Liao D, Bharadwaj U *et al.* C-reactive protein inhibits cholesterol efflux from human macrophage-derived foam cells. *Arterioscler Thromb Vasc Biol* 2008;28:519–26.
- 74 Watanabe J, Charles-Schoeman C, Miao Y *et al.* Proteomic profiling following immunoaffinity capture of high-density lipoprotein: association of acute-phase proteins and complement factors with proinflammatory high-density lipoprotein in rheumatoid arthritis. *Arthritis Rheum* 2012;64:1828–37.
- 75 Berrougui H, Momo CN, Khalil A. Health benefits of high-density lipoproteins in preventing cardiovascular diseases. *J Clin Lipidol* 2012;6:524–33.
- 76 Charles-Schoeman C, Lee YY, Grijalva V *et al.* Cholesterol efflux by high density lipoproteins is impaired in patients with active rheumatoid arthritis. *Ann Rheum Dis* 2012;71:1157–62.
- 77 Watanabe J, Chou KJ, Liao JC *et al.* Differential association of hemoglobin with proinflammatory high density lipoproteins in atherogenic/hyperlipidemic mice. A novel biomarker of atherosclerosis. *J Biol Chem* 2007;282:23698–707.
- 78 Mackness MI, Durrington PN, Mackness B. The role of paraoxonase 1 activity in cardiovascular disease: potential for therapeutic intervention. *Am J Cardiovasc Drugs* 2004;4:211–7.
- 79 Navab M, Berliner JA, Subbanagounder G *et al.* HDL and the inflammatory response induced by LDL-derived oxidized phospholipids. *Arterioscler Thromb Vasc Biol* 2001;21:481–8.
- 80 Van Lenten BJ, Wagner AC, Nayak DP *et al.* High-density lipoprotein loses its anti-inflammatory properties during acute influenza infection. *Circulation* 2001;103:2283–8.
- 81 Van Lenten BJ, Hama SY, de Beer FC *et al.* Anti-inflammatory HDL becomes pro-inflammatory during the acute phase response. Loss of protective effect of HDL against LDL oxidation in aortic wall cell cocultures. *J Clin Invest* 1995;96:2758–67.

- 82 Raterman HG, Levels H, Voskuyl AE *et al.* HDL protein composition alters from proatherogenic into less atherogenic and proinflammatory in rheumatoid arthritis patients responding to rituximab. *Ann Rheum Dis* 2013;72:560–5.
- 83 Jamnitski A, Levels JH, van den Oever IA, Nurmohamed MT. High-density lipoprotein profiling changes in patients with rheumatoid arthritis treated with tumor necrosis factor inhibitors: a cohort study. *J Rheumatol* 2013;40:825–30.
- 84 Schwartz GG, Olsson AG, Abt M *et al.* Effects of dalcetrapib in patients with a recent acute coronary syndrome. *N Engl J Med* 2012;367:2089–99.
- 85 Zhao L, Jin W, Rader D, Packard C, Feuerstein G. A translational medicine perspective of the development of torcetrapib: does the failure of torcetrapib development cast a shadow on future development of lipid modifying agents, HDL elevation strategies or CETP as a viable molecular target for atherosclerosis? A case study of the use of biomarkers and translational medicine in atherosclerosis drug discovery and development. *Biochem Pharmacol* 2009;78:315–25.
- 86 Navab M, Hama SY, Cooke CJ *et al.* Normal high density lipoprotein inhibits three steps in the formation of mildly oxidized low density lipoprotein: step 1. *J Lipid Res* 2000;41:1481–94.
- 87 Navab M, Hama SY, Anantharamaiah GM *et al.* Normal high density lipoprotein inhibits three steps in the formation of mildly oxidized low density lipoprotein: steps 2 and 3. *J Lipid Res* 2000;41:1495–508.
- 88 Ansell BJ, Navab M, Hama S *et al.* Inflammatory/anti-inflammatory properties of high-density lipoprotein distinguish patients from control subjects better than high-density lipoprotein cholesterol levels and are favorably affected by simvastatin treatment. *Circulation* 2003;108:2751–6.
- 89 Smolen JS, Landewe R, Breedveld FC *et al.* EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. *Ann Rheum Dis* 2010;69:964–75.
- 90 Kaltsonoudis E, Papagoras C, Drosos AA. Current and future role of methotrexate in the therapeutic armamentarium for rheumatoid arthritis. *Int J Clin Rheumatol* 2012;7:179–189.
- 91 Saiki O, Takao R, Naruse Y *et al.* Infliximab but not methotrexate induces extra-high levels of VLDL-triglyceride in patients with rheumatoid arthritis. *J Rheumatol* 2007;34:1997–2004.
- 92 Navarro-Millan I, Charles-Schoeman C, Yang S *et al.* Changes in lipoproteins associated with methotrexate or combination therapy in early rheumatoid arthritis: results from the treatment of early rheumatoid arthritis trial. *Arthritis Rheum* 2013;65:1430–8.
- 93 Liao KP, Cai T, Gainer VS *et al.* Lipid and lipoprotein levels and trends in rheumatoid arthritis compared to the general population. *Arthritis Care Res* 2013;65:2046–50.
- 94 Westlake SL, Colebatch AN, Baird J *et al.* The effect of methotrexate on cardiovascular disease in patients with rheumatoid arthritis: a systematic literature review. *Rheumatology* 2010;49:295–307.
- 95 Choi HK, Hernan MA, Seeger JD, Robins JM, Wolfe F. Methotrexate and mortality in patients with rheumatoid arthritis: a prospective study. *Lancet* 2002;359:1173–7.
- 96 Salliot C, van der Heijde D. Long-term safety of methotrexate monotherapy in patients with rheumatoid arthritis: a systematic literature research. *Ann Rheum Dis* 2009;68:1100–4.
- 97 Ridker PM. Testing the inflammatory hypothesis of atherothrombosis: scientific rationale for the cardiovascular inflammation reduction trial (CIRT). *J Thromb Haemost* 2009;7(Suppl 1):332–9.
- 98 Tracey D, Klareskog L, Sasso EH, Salfeld JG, Tak PP. Tumor necrosis factor antagonist mechanisms of action: a comprehensive review. *Pharmacol Ther* 2008;117:244–79.
- 99 Stagakis I, Bertsias G, Karvounaris S *et al.* Anti-tumor necrosis factor therapy improves insulin resistance, beta cell function and insulin signaling in active rheumatoid arthritis patients with high insulin resistance. *Arthritis Res Ther* 2012;14:R141.
- 100 Wijbrandts CA, van Leuven SI, Boom HD *et al.* Sustained changes in lipid profile and macrophage migration inhibitory factor levels after anti-tumour necrosis factor therapy in rheumatoid arthritis. *Ann Rheum Dis* 2009;68:1316–21.
- 101 Sattar N, Crompton P, Cherry L *et al.* Effects of tumor necrosis factor blockade on cardiovascular risk factors in psoriatic arthritis: a double-blind, placebo-controlled study. *Arthritis Rheum* 2007;56:831–9.
- 102 van Sijl AM, Peters MJ, Knol DL *et al.* The effect of TNF- $\alpha$  blocking therapy on lipid levels in rheumatoid arthritis: a meta-analysis. *Semin Arthritis Rheum* 2011;41:393–400.
- 103 Curtis JR, John A, Baser O. Dyslipidemia and changes in lipid profiles associated with rheumatoid arthritis and initiation of anti-TNF therapy. *Arthritis Care Res* 2012;64:1282–91.
- 104 Westlake SL, Colebatch AN, Baird J *et al.* Tumour necrosis factor antagonists and the risk of cardiovascular disease in patients with rheumatoid arthritis: a systematic literature review. *Rheumatology* 2011;50:518–31.
- 105 Barnabe C, Martin BJ, Ghali WA. Systematic review and meta-analysis: anti-tumor necrosis factor alpha therapy and cardiovascular events in rheumatoid arthritis. *Arthritis Care Res* 2011;63:522–9.
- 106 Wong M, Oakley SP, Young L *et al.* Infliximab improves vascular stiffness in patients with rheumatoid arthritis. *Ann Rheum Dis* 2009;68:1277–84.
- 107 Hurlimann D, Forster A, Noll G *et al.* Anti-tumor necrosis factor- $\alpha$  treatment improves endothelial function in patients with rheumatoid arthritis. *Circulation* 2002;106:2184–7.
- 108 McKellar GE, McCarey DW, Sattar N, McInnes IB. Role for TNF in atherosclerosis? Lessons from autoimmune disease. *Nat Rev Cardiol* 2009;6:410–7.
- 109 Del Porto F, Lagana B, Lai S *et al.* Response to anti-tumour necrosis factor alpha blockade is associated with reduction of carotid intima-media thickness in patients with active rheumatoid arthritis. *Rheumatology* 2007;46:1111–5.

- 110 Popa C, van Tits LJ, Barrera P *et al*. Anti-inflammatory therapy with tumour necrosis factor alpha inhibitors improves high-density lipoprotein cholesterol antioxidative capacity in rheumatoid arthritis patients. *Ann Rheum Dis* 2009;68:868–72.
- 111 Emery P, Keystone E, Tony HP *et al*. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. *Ann Rheum Dis* 2008;67:1516–23.
- 112 Jones G. The AMBITION trial: tocilizumab monotherapy for rheumatoid arthritis. *Expert Rev Clin Immunol* 2010;6: 189–95.
- 113 Genovese MC, McKay JD, Nasonov EL *et al*. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: the tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. *Arthritis Rheum* 2008; 58:2968–80.
- 114 Kremer JM, Blanco R, Brzosko M *et al*. Tocilizumab inhibits structural joint damage in rheumatoid arthritis patients with inadequate responses to methotrexate: results from the double-blind treatment phase of a randomized placebo-controlled trial of tocilizumab safety and prevention of structural joint damage at one year. *Arthritis Rheum* 2011;63:609–21.
- 115 Smolen JS, Beaulieu A, Rubbert-Roth A *et al*. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. *Lancet* 2008;371:987–97.
- 116 Maini RN, Taylor PC, Szechinski J *et al*. Double-blind randomized controlled clinical trial of the interleukin-6 receptor antagonist, tocilizumab, in European patients with rheumatoid arthritis who had an incomplete response to methotrexate. *Arthritis Rheum* 2006;54: 2817–29.
- 117 Nishimoto N, Ito K, Takagi N. Safety and efficacy profiles of tocilizumab monotherapy in Japanese patients with rheumatoid arthritis: meta-analysis of six initial trials and five long-term extensions. *Mod Rheumatol* 2010;20: 222–32.
- 118 Kawashiri SY, Kawakami A, Yamasaki S *et al*. Effects of the anti-interleukin-6 receptor antibody, tocilizumab, on serum lipid levels in patients with rheumatoid arthritis. *Rheumatol Int* 2011;31:451–6.
- 119 Nishimoto N, Hashimoto J, Miyasaka N *et al*. Study of active controlled monotherapy used for rheumatoid arthritis, an IL-6 inhibitor (SAMURAI): evidence of clinical and radiographic benefit from an x ray reader-blinded randomised controlled trial of tocilizumab. *Ann Rheum Dis* 2007;66:1162–7.
- 120 Schiff MH, Kremer JM, Jahreis A *et al*. Integrated safety in tocilizumab clinical trials. *Arthritis Res Ther* 2011;13: R141.
- 121 Natarajan S, Glick H, Criqui M *et al*. Cholesterol measures to identify and treat individuals at risk for coronary heart disease. *Am J Prev Med* 2003;25: 50–7.
- 122 Kannel WB. Risk stratification of dyslipidemia: insights from the Framingham Study. *Curr Med Chem Cardiovasc Hematol Agents* 2005;3:187–93.
- 123 Yusuf S, Hawken S, Ounpuu S *et al*. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 2004;364:937–52.
- 124 Sniderman AD, Jungner I, Holme I, Aastveit A, Walldius G. Errors that result from using the TC/HDL C ratio rather than the apoB/apoA-I ratio to identify the lipoprotein-related risk of vascular disease. *J Intern Med* 2006;259:455–61.
- 125 Gabay C, Emery P, van Vollenhoven R *et al*. Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial. *Lancet* 2013;381:1541–50.
- 126 Austin MA, Hokanson JE, Brunzell JD. Characterization of low-density lipoprotein subclasses: methodologic approaches and clinical relevance. *Curr Opin Lipidol* 1994;5:395–403.
- 127 Theodoraki TG, Tsoukatos DC, Karabina SA *et al*. LDL subfractions in patients with myocardial infarction: effect of smoking and beta-blocker treatment. *Ann Clin Biochem* 2000;37(Pt 3):313–8.
- 128 Rajman I, Kendall MJ, Cramb R *et al*. Investigation of low density lipoprotein subfractions as a coronary risk factor in normotriglyceridaemic men. *Atherosclerosis* 1996; 125:231–42.
- 129 McInnes IB, Thompson L, Giles JT *et al*. Effect of interleukin-6 receptor blockade on surrogates of vascular risk in rheumatoid arthritis: MEASURE, a randomised, placebo-controlled study. *Ann Rheum Dis* 2013, Dec 24. doi: 10.1136/annrheumdis-2013-204345 [Epub ahead of print].
- 130 Genovese M, Sebba A, Rubbert-Roth A *et al*. Long-term safety of tocilizumab in patients with rheumatoid arthritis following a mean treatment duration of 3.9 years. *Ann Rheum Dis* 2013;72(Suppl 3):461.
- 131 Kume K, Amano K, Yamada S *et al*. Tocilizumab monotherapy reduces arterial stiffness as effectively as etanercept or adalimumab monotherapy in rheumatoid arthritis: an open-label randomized controlled trial. *J Rheumatol* 2011;38:2169–71.
- 132 Moriyama M, Sato M, Sumita Y *et al*. Tocilizumab increase serum lipids but does not promote arteriosclerosis in patients with rheumatoid arthritis. *Ann Rheum Dis* 2011;70(Suppl 3):612.
- 133 Bakker MF, Jacobs JW, Verstappen SM, Bijlsma JW. Tight control in the treatment of rheumatoid arthritis: efficacy and feasibility. *Ann Rheum Dis* 2007; 66(Suppl 3):iii56–60.
- 134 Smolen JS, Aletaha D. The assessment of disease activity in rheumatoid arthritis. *Clin Exp Rheumatol* 2010; 28(Suppl 59):S18–27.
- 135 Gruzdeva O, Uchasova E, Dyleva Y *et al*. Insulin resistance and inflammation markers in myocardial infarction. *J Inflamm Res* 2013;6:83–90.
- 136 Mirjafari H, Wnage J, Klearman M, Harari O, Bruce I. Insulin resistance is improved by tocilizumab therapy in

- rheumatoid arthritis: results from the TOWARD study. *Ann Rheum Dis* 2013;72(Suppl 3):414.
- 137 van Vollenhoven RF, Emery P, Bingham CO 3rd *et al.* Longterm safety of patients receiving rituximab in rheumatoid arthritis clinical trials. *J Rheumatol* 2010;37: 558–67.
  - 138 Kerekes G, Soltész P, Dér H *et al.* Effects of rituximab treatment on endothelial dysfunction, carotid atherosclerosis, and lipid profile in rheumatoid arthritis. *Clin Rheumatol* 2009;28:705–10.
  - 139 van Vollenhoven RF, Fleischmann R, Cohen S *et al.* Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. *N Engl J Med* 2012;367:508–19.
  - 140 Fleischmann R, Kremer J, Cush J *et al.* Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. *N Engl J Med* 2012;367:495–507.
  - 141 Charles-Schoeman C, Fleischmann RM, Davignon J *et al.* Effects of tofacitinib on lipid profiles and cholesterol and lipoprotein kinetics in patients with rheumatoid arthritis. *Arthritis Rheum* 2012;64:S553.
  - 142 Xeljanz (tofacitinib citrate) prescribing information. Pfizer, 2012.
  - 143 McInnes IB, Kim HY, Lee SH *et al.* Open-label tofacitinib and double-blind atorvastatin in rheumatoid arthritis patients: a randomised study. *Ann Rheum Dis* 2014;73: 124–31.
  - 144 Charles-Schoeman C, Wicker P, Sechtem U *et al.* Cardiovascular safety findings in rheumatoid arthritis patients treated with tofacitinib (CP-690,550), a novel oral JAK inhibitor. *Ann Rheum Dis* 2012;71(Suppl 3):201.
  - 145 Semb AG, Rollefstad S, Provan SA *et al.* Carotid plaque characteristics and disease activity in rheumatoid arthritis. *J Rheumatol* 2013;40:359–68.
  - 146 Smolen JS. Treat-to-target: rationale and strategies. *Clin Exp Rheumatol* 2012;30(4 Suppl 73):S2–6.
  - 147 Semb AG, Kvien TK, DeMicco DA *et al.* Effect of intensive lipid-lowering therapy on cardiovascular outcome in patients with and those without inflammatory joint disease. *Arthritis Rheum* 2012;64:2836–46.
  - 148 Semb AG, Holme I, Kvien TK, Pedersen TR. Intensive lipid lowering in patients with rheumatoid arthritis and previous myocardial infarction: an explorative analysis from the incremental decrease in endpoints through aggressive lipid lowering (IDEAL) trial. *Rheumatology* 2011;50:324–9.
  - 149 Rollefstad S, Kvien TK, Holme I *et al.* Treatment to lipid targets in patients with inflammatory joint diseases in a preventive cardio-rheuma clinic. *Ann Rheum Dis* 2013; 72:1968–74.
  - 150 Gomez-Vaquero C, Robustillo M, Narvaez J *et al.* Assessment of cardiovascular risk in rheumatoid arthritis: impact of the new EULAR recommendations on the score cardiovascular risk index. *Clin Rheumatol* 2012;31: 35–9.
  - 151 Holmqvist ME, Wedren S, Jacobsson LT *et al.* No increased occurrence of ischemic heart disease prior to the onset of rheumatoid arthritis: results from two Swedish population-based rheumatoid arthritis cohorts. *Arthritis Rheum* 2009;60:2861–9.
  - 152 Holmqvist ME, Wedren S, Jacobsson LT *et al.* Rapid increase in myocardial infarction risk following diagnosis of rheumatoid arthritis amongst patients diagnosed between 1995 and 2006. *J Intern Med* 2010;268: 578–85.
  - 153 Sodergren A, Karp K, Boman K *et al.* Atherosclerosis in early rheumatoid arthritis: very early endothelial activation and rapid progression of intima media thickness. *Arthritis Res Ther* 2010;12:R158.
  - 154 Kerekes G, Soltész P, Nurmohamed MT *et al.* Validated methods for assessment of subclinical atherosclerosis in rheumatology. *Nat Rev Rheumatol* 2012;8:224–34.
  - 155 Evans MR, Escalante A, Battafarano DF *et al.* Carotid atherosclerosis predicts incident acute coronary syndromes in rheumatoid arthritis. *Arthritis Rheum* 2011;63: 1211–20.