Managing cardiovascular risk in patients with inflammatory arthritis: practical considerations

Anne Tournadre, Sylvain Mathieu and Martin Soubrier

Ther Adv Musculoskel Dis

2016, Vol. 8(5) 180–191

DOI: 10.1177/

1759720X16664306

© The Author(s), 2016.

Reprints and permissions:

[http://www.sagepub.co.uk/](http://www.sagepub.co.uk/journalsPermissions.nav)

[journalsPermissions.nav](http://www.sagepub.co.uk/journalsPermissions.nav)

Abstract: Patients with inflammatory arthritis, such as rheumatoid arthritis, psoriatic arthritis, or ankylosing spondylitis, have higher rates of cardiovascular mortality. While the increased cardiovascular risk is only explained to some extent, a lot of research is currently conducted to improve our understanding of its pathogenesis, risk stratification, and optimal cardiovascular risk management. This review sought to report epidemiological data pertaining to the cardiovascular disease burden in patients with inflammatory arthritis, underlying mechanisms accounting for excessive cardiovascular risk, along with recommendations regarding risk assessment and management in this patient population.

Keywords: cardiovascular risk, rheumatoid arthritis, spondyloarthritis

Introduction

Rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS) are inflammatory rheumatic diseases that have in common an increased cardiovascular (CV) mortality due to accelerated atherosclerosis. The full mechanisms resulting in CV risk excess are still to be clarified. Although standard CV risk factors may account for the majority of CV risks, they do not fully explain the CV risk excess observed in rheumatic diseases. Inflammation that both promotes atherogenesis and exacerbates established CV risk factors may partly explain this increased risk. Moreover, the treatments of rheumatic disease may potentially impact CV risk. Although CV risk management is key in order to decrease CV mortality, CV risk assessment in rheumatic diseases proves complex, and the prediction of CV mortality remains problematic.

In this review, we sought to report epidemiological data regarding CV mortality and morbidity in both RA and spondyloarthritis (SpA). We then discussed the potential mechanisms resulting in increased CV risk, comprising standard risk factors and inflammation, along with their impact on lipid profiles. Lastly, the management of CV risk in rheumatic diseases was addressed, including CV risk assessment, along with the impact of rheumatic medications.

Literature search

A thorough search of literature published between January 1966 and December 2015 was undertaken using the Medline database. For this search, the following Mesh terms were used: ‘arthritis, rheumatoid’, ‘spondylarthropathies’, ‘arthritis, psoriatic’, ‘spondylitis, ankylosing’, ‘mortality’, ‘cardiovascular diseases’, ‘atherosclerosis’, ‘lipids’, ‘hypertension’, ‘smoking’, and ‘therapeutics’.

Epidemiology of cardiovascular diseases in inflammatory arthritis

Rheumatoid arthritis

One-half of all deaths in RA are due to CV diseases [Aviña-Zubieta *et al.* 2008]. The CV mortality is increased by 50% and the risk of CV disease by 48% in the RA population compared with the general population [Aviña-Zubieta *et al.* 2012]. Increased mortality concerns both heart disease (68%) and cerebrovascular events (41%), affecting equally females and males [Aviña-Zubieta *et al.* 2008, 2012]. The highest CV mortality is observed in patients with long disease duration [Naz *et al.* 2008], rheumatoid factor or anti-CCP autoantibodies [Humphreys *et al.* 2014], and extra-articular manifestations [Gabriel *et al.* 2003]. RA itself is an independent CV risk factor that carries as much weight as diabetes

Correspondence to:

Martin Soubrier, MD, PhD

Rheumatology

Department, CHU

Gabriel Montpied, 58 Rue

Montalembert, F-63000

Clermont-Ferrand, France

[msoubrier@chu-](mailto:msoubrier@chu-clermontferrand.fr)

[clermontferrand.fr](mailto:msoubrier@chu-clermontferrand.fr)

Anne Tournadre, MD, PhD

Sylvain Mathieu, MD, PhD

Rheumatology

Department, CHU

Clermont-Ferrand,

Clermont-Ferrand, France

mellitus [Peters *et al.* 2009]. In the Danish nationwide study, the overall incidence rate ratio of myocardial infarction (MI) in RA was estimated at 1.7 [95% confidence interval (CI) 1.5–1.9], which is similar to that observed in diabetes mellitus [Lindhardsen *et al.* 2011]. Particularly, the risk was shown to be markedly raised in women <50 years old (six-fold increase), thereby corresponding to the MI risk in subjects without RA, yet 10 years older. Several studies have demonstrated a premature MI risk, observed as soon as RA is diagnosed [Holmqvist *et al.* 2010] and, according to the Mayo Clinic, even before patients meet the full diagnostic criteria for RA [Maradit-Kremers *et al.* 2005]. One study reported a two-fold increased risk of congestive heart failure, particularly in patients with rheumatoid factor [Nicola *et al.* 2005].

Psoriatic arthritis and ankylosing spondylitis

Similarly to RA, SpA was associated with increased CV mortality [Mathieu *et al.* 2011; Exarchou *et al.* 2015]. Coronary heart disease risk was shown to be particularly increased in PsA, by at least 50% [Eder *et al.* 2015; Gladman *et al.* 2009; Han *et al.* 2006; Horreau *et al.* 2013]. In a single UK population-based cohort, the risk of major CV events, after adjusting for standard CV risk factors, was higher in patients with PsA and psoriasis compared with the general population [Ogdie *et al.* 2015].

Although CV mortality was reported to be increased in AS [Exarchou *et al.* 2015], conflicting data were published with respect to CV morbidity. In our first meta-analysis published in 2011 [Mathieu *et al.* 2011] a higher, yet insignificant, risk of MI was revealed, in line with results reported in a more recent retrospective British cohort study [Brophy *et al.* 2012]. Since 2011, two large cohort studies conducted in Canada and Sweden [Szabo *et al.* 2011; Zöller *et al.* 2012] and a population-based longitudinal follow-up study [Huang *et al.* 2013] have reported increased rates of both cerebrovascular events and ischemic heart disease. We updated our meta-analysis conducted from August 2009 to January 2014 focusing on MI and stroke [Mathieu *et al.* 2015], with the conclusion that there was an increased risk for both MI and stroke in AS patients compared with controls [odds ratio (OR) = 1.60 (95% CI 1.32–1.93) and OR = 1.50 (95% CI 1.39–1.62) respectively].

Mechanisms leading to increased CV risk in inflammatory arthritis

The exact mechanisms leading to an increased CV risk in RA and SpA remain uncertain. They may comprise a higher prevalence of standard CV risk factors, in addition to interactions between systemic inflammation, CV disease risk factors, and vascular function.

Standard CV risk factors

Standard CV risk factors, such as smoking, hypertension, diabetes, hypercholesterolemia, and obesity, independently impact CV morbidity [Baghdadi *et al.* 2015]. Although the association between smoking and CV risk in RA is less significant than in the general population [Symmons and Gabriel, 2011], a higher prevalence of smoking is well-established in RA, SA, and PsA compared with controls [Boyer *et al.* 2011; Divecha *et al.* 2005; Favato, 2008; Peters *et al.* 2004]. Hypertension is common in RA but it is not clear whether its incidence differs from that of the general population [Boyer *et al.* 2011; Liao and Solomon, 2013; Protogerou *et al.* 2013]. This condition may affect nearly half of all RA patients, is often under-diagnosed, and poorly controlled [Bartels *et al.* 2014; Protogerou *et al.* 2013]. Diabetes prevalence is increased in RA compared with controls (OR 1.74; 95% CI 1.22–2.50) [Boyer *et al.* 2011]. Although an association between insulin resistance and RA was reported in several studies [Dessein and Joffe, 2006; Giles *et al.* 2015], the homeostatic model assessment (HOMA) used to quantify insulin resistance was not correlated with subclinical atherosclerosis measurements among RA patients [Giles *et al.* 2015]. In a recent meta-analysis, RA patients were shown to exhibit a higher risk of metabolic syndrome with an overall OR of 1.24 (95% CI 1.03–1.50) [Zhang *et al.* 2013]. Among RA patients and in contrast with the general population, low body mass index (BMI) was associated with a significantly increased risk of CV death, and overweight/obesity with a reduction in CV risk, likely related to cachexia-associated metabolic disorders [Baker *et al.* 2015; Kremers *et al.* 2004; Wolfe and Michaud, 2012].

Similarly to RA, AS and PsA were associated with an increased prevalence of standard CV risk factors [Johnsson *et al.* 2012; Mathieu *et al.* 2011; Papagoras *et al.* 2014]. Metabolic syndrome was particularly increased in PsA [Malesci *et al.* 2007;

Mok *et al.* 2011; Papadakis *et al.* 2009], as was hyperuricemia, which is considered a CV risk factor [González-Gay *et al.* 2009; Skak-Nielsen *et al.* 2013]. In a recent cohort involving 88 AS patients, no differences were found regarding hypertension, BMI, physical activity, diet, or smoking in this patient population compared with 351 age- and sex-matched controls. The authors thus concluded that excessive CV risk was not linked to CV risk factors, but rather to chronic low-grade inflammation or nonsteroidal anti-inflammatory drugs (NSAIDs) [Sundström *et al.* 2014].

Accelerated atherosclerosis

Several studies demonstrated subclinical atherosclerosis in inflammatory arthritis with altered vascular function and morphologic changes as assessed by endothelial dysfunction, in addition to increased arterial stiffness and carotid intima-media thickness [Bodnar *et al.* 2011; González-Juanatey *et al.* 2007; Kimhi *et al.* 2007; Mathieu *et al.* 2008; Sandoo *et al.* 2011]. These vascular changes were shown to correlate with the coronary circulation and able to predict CV events. However, the link between inflammation and disease activity was not demonstrated, and there were conflicting results published regarding the effects of conventional and biological disease-modifying antirheumatic drugs (DMARDs) on both vascular function and morphology [Mathieu *et al.* 2008, 2012, 2013a, 2013b; Sandoo *et al.* 2011]. CV treatments may exert a greater beneficial effect on endothelial function compared with anti-inflammatory medications [Sandoo *et al.* 2011].

Inflammation

While standard CV risk factors partly explain CV risk, they do not fully explain the CV risk excess observed in rheumatic diseases [van Halm *et al.* 2009; Peters *et al.* 2009; Symmons and Gabriel, 2011]. The excessive CV risk persists after adjusting for standard CV risk factors. Inflammation that promotes atherogenesis and exacerbates established CV risk factors may account for this part of increased risk [Choy *et al.* 2014; Zhang *et al.* 2014]. High C-reactive protein (CRP) levels in RA patients without diabetes mellitus or metabolic syndrome were shown to increase two-fold the risk of coronary artery disease [Zhang *et al.* 2014]. In SpA, the cardiometabolic profile may be driven by systemic inflammation, as revealed by several studies [Divecha *et al.* 2005; Tam *et al.*

2008]. However, the exact contribution of inflammation to the CV risk excess has not yet been elucidated [Grad and Danenberg, 2013]. It is still unclear if high CRP levels associated with CV risk factors [obesity, hypertension, triglycerides, and low high-density lipoprotein (HDL) cholesterol levels] are a marker of atherosclerosis or whether they directly contribute to atherothrombosis [Grad and Danenberg, 2013]. Pro-inflammatory cytokines [tumor necrosis factor- α (TNF α), interleukin-1 (IL1) and interleukin-6 (IL6)] are independently implicated in the atherogenic process by promoting dyslipidemia, insulin resistance, and endothelial dysfunction [Choy *et al.* 2014]. IL6 and TNF α can lead to an approximately two-fold increased MI risk [Ridker *et al.* 2000a, 2000b]. In addition, genetic studies pointed towards an IL6 involvement in atherogenesis [IL6 Receptor Mendelian Randomization Analysis Consortium, 2012]. In PsA, TNF α and IL1 were shown to exert pro-inflammatory activity on endothelium, thereby contributing to oxidative stress and leukocyte recruitment into atherosclerotic plaques [Russolillo *et al.* 2013]. Inflammation may alter the nitric oxide (NO) response that controls vasodilatation and interactions with leukocytes and platelets, and likely result in endothelial dysfunction, which in turn is associated with atherosclerosis and plaque modification. Plaque rupture or destabilization is the result of interactions between plaque components and pro-inflammatory mediators, such as adhesion molecules, cytokines, and chemokines, regulated in part by NO [Lerman and Zeiher, 2005]. In addition, inflammation induces changes in the lipoprotein composition, thereby altering protective functions of HDL cholesterol (HDLc), such as antioxidative properties and cholesterol efflux capacities. This promotes pro-inflammatory oxidized low-density lipoprotein (LDL) cholesterol (LDLc) that in turn activates endothelial cells to produce inflammatory cytokines like TNF α , and IL1, while recruiting monocytes into the arterial wall.

Lipid paradox

Besides the inflammatory cascade that exacerbates endothelial dysfunction and accelerates atherosclerosis, quantitative and qualitative abnormalities in lipid profiles are observed in inflammatory rheumatic diseases [González-Gay and González-Juanatey, 2014; Myasoedova *et al.* 2010]. The standard atherogenic lipid profile characterized by increased LDLc and decreased

HDLc levels was not observed in inflammatory arthritis. Paradoxically, an inverse relationship between CV risk and lipid levels, also termed 'lipid paradox', was reported during chronic inflammatory states leading to reduced levels of total cholesterol, LDLc, and HDLc, though the CV risk was enhanced. In the Apolipoprotein MORTality RiSk (AMORIS) study, total cholesterol levels were decreased compared with controls, whereas CV events were increased by 60% in RA patients [Semb *et al.* 2010]. Moreover, a nonlinear relationship with a u-shaped curve between total cholesterol and CV disease risk was observed in RA patients, with a 3.3-fold increased risk associated with lower total cholesterol levels, yet no increased risk above 155 mg/dl levels [Myasoedova *et al.* 2011].

In addition to quantitative abnormalities, lipoprotein dysfunctions, particularly those pertaining to HDLc, could partly explain the CV risk excess [Annema and von Eckardstein, 2013]. Thus, a decrease in atheroprotective function or proatherogenic properties was reported in both RA and PsA [Annema and von Eckardstein, 2013]. HDL cholesterol efflux capacity was shown to be altered in RA patients with high disease activity. Among active RA patients, a reduction in CRP was associated with a significant increase in LDLc levels, along with an improved HDLc efflux capacity [Liao *et al.* 2015]. This improvement in atheroprotective function of HDLc may counterbalance the increased LDLc levels associated with CV risk.

From a practical consideration, lipid profiles should be assessed and interpreted when the disease is under control. This procedure should be repeated when DMARDs are initiated due to the impact of biologic agents on lipid profiles [Souto *et al.* 2015].

Cardiovascular risk management in inflammatory arthritis (RA, PsA, and AS)

Avoid deleterious treatments

NSAIDs were shown to increase mortality in the general population, the risk being highest for cyclooxygenase-2 inhibitors and diclofenac, whereas naproxen was associated with less vascular risk [Coxib and Traditional NSAID Trialists (CNT) Collaboration, 2013; Soubrier *et al.* 2013]. In RA, the risk of vascular events was also increased with NSAIDs, but the increase in

vascular risk was statistically significant only for cyclooxygenase-2 inhibitors [Roubille *et al.* 2015]. In AS, the use of NSAIDs might reduce the risk of CV disease [Tsai *et al.* 2015]. Paracetamol may increase CV mortality in the general population, but this must be confirmed after adjusting for concomitant NSAID use and channeling bias [Roberts *et al.* 2015].

Corticosteroids could contribute to atherogenesis, for they were reported to be linked to increased insulin resistance, metabolic syndrome, and hypertension. On the other hand, by reducing systemic inflammation, they could decrease CV risk. A recent meta-analysis demonstrated a significant increase in CV events with glucocorticosteroids (OR 1.47; 95% CI 1.34–1.60), whether for MI (OR 1.41; 95% CI 1.22–1.63), stroke (OR 1.57; 95% CI 1.05–2.35), or congestive heart failure (OR 1.42; 95% CI 1.10–1.82) [Roubille *et al.* 2015]. Glucocorticosteroids were shown to be associated with an increased MI risk in RA, in a dose- and duration-dependent manner [Aviña-Zubieta *et al.* 2013].

As a result, the lowest glucocorticosteroid dose for the shortest possible time must be prescribed.

Control the disease activity

As previously discussed, the link between systemic inflammation and atherogenesis renders tight disease activity control absolutely essential in inflammatory arthritis. Patients with active RA present significantly higher CV risk markers (hypertension, CV biomarkers, and subclinical atherosclerosis) than patients in remission [Provan *et al.* 2011]. In a longitudinal United States cohort, reduction in disease activity paralleled the reduction in CV events independently of antirheumatic treatments [Solomon *et al.* 2015b]. In a meta-analysis, methotrexate and TNF-inhibitors were shown to decrease CV events by a third [Roubille *et al.* 2015]. The impact of anti-rheumatic treatments on lipid profile and CV risk has been well studied. TNF inhibitors were shown to increase total cholesterol and HDLc levels, whereas the atherogenic index remained stable [Daïen *et al.* 2012; Payet *et al.* 2012]. In addition, TNF inhibitors may be able to restore anti-inflammatory properties of HDLc [Robertson *et al.* 2013]. Conflicting results were published with respect to rituximab [Mathieu *et al.* 2012; Robertson *et al.* 2013]. Tocilizumab increased the atherogenic index but improved

HDL atheroprotective functions [McInnes *et al.* 2015; Robertson *et al.* 2013]. In a recent meta-analysis, changes in the lipid profile of RA patients were only observed with tocilizumab and tofacitinib, but not with TNF antagonists [Souto *et al.* 2015].

The impact of biologicals on CV diseases and mortality has not been well established in SpA. Several studies assessing the effect of TNF blockade on subclinical atherosclerosis have been published reporting conflicting results [Angel *et al.* 2010; Brezinski *et al.* 2014; Mathieu *et al.* 2008, 2013b; Tam *et al.* 2008]. It was put forth that TNF blockade may slow down atherosclerosis [van Sijl *et al.* 2015].

Cardiovascular disease risk stratification

In order to predict 10-year CV mortality risk, different equations were developed with algorithm combinations taking into account standard CV risk factors like age, gender, smoking status, hypertension, genetic, and LDLc levels. For the general population, dyslipidemia management guidelines for preventing CV diseases are based on the Systematic Coronary Risk Evaluation (SCORE) equation in Europe (ESC guidelines) and the Framingham (ATP-III guidelines) and new Pooled Cohort equations (ACC/AHA) in the United States [Catapano *et al.* 2011; Grundy *et al.* 2004; Stone *et al.* 2014]. Since 2010, the European League Against Rheumatism (EULAR) has been recommending to assess CV risk yearly in RA patients using risk equations, the SCORE equation, or a nationally validated equation. The SCORE equation allows identifying patients with very high CV risk (SCORE >10%, documented CV disease), high CV risk (SCORE >5% and <10%), moderate CV risk (SCORE >1% and <5%), or low CV risk (SCORE <1%). Based on the SCORE equation, LDLc targets have been defined [Catapano *et al.* 2011]. Therefore, for patients with very high CV risk, the treatment target for LDLc was estimated at 1.8 mmol/l (70 mg/dl), for those with high risk at <2.5 mmol/l (100 mg/dl), and for those with moderate risk at <3 mmol/l (115 mg/dl) [Catapano *et al.* 2011]. The risk calculated this way is requested to be multiplied by 1.5 when RA fulfills two of the following three conditions: disease duration >10 years, positive rheumatoid factor or presence of anti-CCP, and extra-articular manifestations [Peters *et al.* 2010]. Updated EULAR recommendations on CV risk management are scheduled to be

published soon, including imaging markers for risk prediction, as well as CV risk score multiplication by a factor of 1.5 regardless of RA determinants [Nurmohamed, 2015] (Box 1).

Despite the development of new risk prediction equations and guidelines, the interplay between standard risk factors, systemic inflammation, and lipid properties renders the evaluation of CV risk in inflammatory arthritis very complex. Risk assessment systems were shown not to perform well in patients with inflammatory arthritis, with the CV risk underestimated regardless the equation used [Arts *et al.* 2015; Corrales *et al.* 2014; Kawai *et al.* 2015]. Adapted SCORE algorithms taking into account additional RA-specific CV factors were not shown to improve CV risk prediction [Arts *et al.* 2015]. Whereas a new expanded risk model for CV risk prediction in RA performed well in a United States cohort; this model must still be validated before being used in other RA cohorts [Solomon *et al.* 2015a]. To improve CV risk prediction, carotid ultrasonography (US) including intima-media thickness assessment may prove useful, particularly for moderate-risk patients [Corrales *et al.* 2014]. Among the 327 RA patients analyzed (96 with low risk, 201 with moderate risk, 30 with high or very high risk) [Corrales *et al.* 2014], only 5 were reclassified as having high/very high CV risk when applying a multiplication factor as recommended by EULAR [Peters *et al.* 2010]. In contrast, increased intima-media thickness or carotid plaques were observed in 63% of RA patients with moderate risk enabling their reclassification as high risk [Corrales *et al.* 2014]. Similarly, 56% of PsA patients classified as intermediary with the Framingham Risk Score were reclassified into the high risk category when using carotid US [Eder *et al.* 2014]. For the new American College of Cardiology (ACC) and American Heart Association (AHA) American guidelines published in 2013, the new Pooled Cohort equation was employed to estimate 10-year atherosclerotic CV risk [Stone *et al.* 2014]. Compared with the ATP-III and ESC guidelines, the ACC/AHA guidelines place more importance on the calculated 10-year predicted risk than on absolute LDLc values. These guidelines have demonstrated greater sensitivity, especially in the elderly population (>65 years of age), yet less specificity. ACC/AHA guidelines recommend statin therapy for all patients with documented CV disease, with increased LDLc $\geq$ 190 mg/dl, or CV risk > 7.5%. While expanding the proportion of RA patients

Box 1. The 10 recommendations of EULAR for the management of CV risk in RA, PsA, AS [Peters *et al.* 2010]. In *italic bold*, 2015/2016 update recommendations [Nurmohamed, 2015].

RA, AS and PsA should be regarded as a condition associated with higher risk for CV disease.

The disease activity should be controlled optimally.

CV risk assessment is yearly recommended using national guidelines. *CV risk assessment is recommended for all patients with RA, AS or PsA at least once every 5 years. Risk assessments should be repeated following major changes in anti-rheumatic therapy.*

Risk score models should be adapted to RA by using a 1.5 multiplication factor when RA meets two of the following three criteria: disease duration of more than 10 years, RF or anti-CCP positivity, Presence of certain extra-articular manifestations

CV risk score models should be adapted for patients with RA by a 1.5 multiplication factor.

Total/HDL cholesterol ratio should be used in the SCORE model. *Lipids should ideally be measured when disease activity is stable or in remission.*

National guidelines should be considered for intervention. If no national guideline is available, the SCORE CV risk model should be used.

Statins, ACE inhibitors and/or AT-II blockers are preferred treatment options

Use NSAIDs with caution and corticosteroids with the lowest dose and duration possible.

Recommend smoking cessation and lifestyle changes

Screening for asymptomatic atherosclerotic plaques by use of carotid ultrasound may be considered as part of the CVD risk evaluation in patients with RA.

recommended for statin therapy [Tournadre *et al.* 2015] and owing to the relevance of CV mortality and underestimation of CV risk, the new ACC/AHA treatment recommendations may be more suitable in the specific event of RA. However, further studies are warranted to better validate the risk prediction in specific RA populations. These studies should, in addition, clarify the impact of the new expanded guidelines on future CV events [Kawai *et al.* 2015; Tournadre *et al.* 2015].

Lifestyle and pharmacological interventions

Lifestyle modifications must be considered for all patients while including dietary recommendations, weight control, physical activity, and smoking cessation.

A number of large-scale clinical trials have demonstrated the efficacy of statin therapy in reducing CV morbidity and mortality both in primary and secondary prevention in the general population [Cholesterol Treatment Trialists Collaboration *et al.* 2010]. Though there have been no large-scale controlled studies assessing the effect of statins as primary CV risk prevention in RA, statin therapy initiation was shown to be associated with a lower mortality risk in RA patients [Schoenfeld *et al.* 2016]. In a Scottish cohort of 430 RA patients involving 181 statin-exposed and 249 statin-unexposed patients, with a mean follow-up period of 3.90 and 3.14 years respectively,

statins reduced total cholesterol levels by 1% and were associated with primary prevention with reduced CV events [HR 0.45 (0.20–0.98)] and concomitant decrease in all-cause mortality [OR 0.43 (0.20–0.92)] [Sheng *et al.* 2012]. Intensive lipid lowering therapy with rosuvastatin decreased the atherosclerotic process assessed by carotid plaque height and LDLc levels [Rollestad *et al.* 2015]. As secondary prevention, the statin-induced decrease in cholesterol levels and MI relapse were similar between RA patients and controls, while discontinuing statins was accompanied by a high risk of stroke [De Vera *et al.* 2011; Semb *et al.* 2012]. Despite the high CV mortality in RA, lipid-lowering agents appear to be underused in these patients, given that statin therapy is recommended in around 20% of RA patients according to the guidelines [Soubrier *et al.* 2006; Tournadre *et al.* 2015]. In addition to having their CV risk underestimated, RA patients seem to be under-treated in both primary and secondary prevention [Akkara Veetil *et al.* 2013; Lindhardsen *et al.* 2011; Toms *et al.* 2010].

Hypertension is one of the most significant preventable CV risk factor, and lowering blood pressure (BP) by 10 mmHg for systolic BP or by 5 mmHg for diastolic BP was shown to decrease MI risk by 22% and stroke risk by 41% [Law *et al.* 2009]. There are no specific guidelines for hypertension management in RA. Yet initial antihypertensive treatment should include angiotensin-converting

enzyme (ACE) inhibitors or angiotensin receptor blockers (AT-II), as these agents have shown anti-inflammatory properties and were associated with improved endothelial function in RA patients [Peters *et al.* 2010].

Conclusion

The markedly enhanced risk of CV disease in inflammatory arthritis justifies optimizing CV disease risk management strategies in order to reduce the mortality in this specific population. In this context, there is a need to improve CV risk stratification and prediction, in addition to rheumatologists' education with respect to screening and identifying high-risk patients. Nurse-led programs on RA comorbidity management might be instrumental in facilitating the identification and management of CV risk factors by primary care general practitioners or rheumatologists [Dougados *et al.* 2014].

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

- Akkara Veetil, B., Myasoedova, E., Matteson, E., Gabriel, S. and Crowson, C. (2013) Use of lipid-lowering agents in rheumatoid arthritis: a population-based cohort study. *J Rheumatol* 40: 1082–1088.
- Angel, K., Provan, S., Gulseth, H., Mowinkel, P., Kvien, T. and Atar, D. (2010) Tumor necrosis factor- antagonists improve aortic stiffness in patients with inflammatory arthropathies: a controlled study. *Hypertension* 55: 333–338.
- Annema, W. and von Eckardstein, A. (2013) High-density lipoproteins. Multifunctional but vulnerable protections from atherosclerosis. *Circ* 77: 2432–2448.
- Arts, E., Popa, C., den Broeder, A., Semb, A., Toms, T., Kitas, G. *et al.* (2015) Performance of four current risk algorithms in predicting cardiovascular events in patients with early rheumatoid arthritis. *Ann Rheum Dis* 74: 668–674.
- Aviña-Zubieta, J., Abrahamowicz, M., de Vera, M., Choi, H., Sayre, E., Rahman, M. *et al.* (2013) Immediate and past cumulative effects of oral glucocorticoids on the risk of acute myocardial infarction in rheumatoid arthritis: a population-based study. *Rheumatology* 52: 68–75.
- Aviña-Zubieta, J., Choi, H., Sadatsafavi, M., Etminan, M., Esdaile, J. and Lacaille, D. (2008) Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analysis of observational studies. *Arthritis Rheum* 59: 1690–1697.
- Aviña-Zubieta, J., Thomas, J., Sadatsafavi, M., Lehman, A. and Lacaille, D. (2012) Risk of incident cardiovascular events in patients with rheumatoid arthritis: a meta-analysis of observational studies. *Ann Rheum Dis* 71: 1524–1529.
- Baghdadi, L., Woodman, R., Shanahan, E. and Mangoni, A. (2015) The Impact of traditional cardiovascular risk factors on cardiovascular outcomes in patients with rheumatoid arthritis: a systematic review and meta-analysis. *PLOS ONE* 10: e0117952.
- Baker, J., Billig, E., Michaud, K., Ibrahim, S., Caplan, L., Cannon, G. *et al.* (2015) Weight loss, the obesity paradox, and the risk of death in rheumatoid arthritis: weight loss as a predictor of death in RA. *Arthritis Rheumatol* 67: 1711–1717.
- Bartels, C., Johnson, H., Voelker, K., Thorpe, C., McBride, P., Jacobs, E. *et al.* (2014) Impact of rheumatoid arthritis on receiving a diagnosis of hypertension among patients with regular primary care: effect of RA on hypertension diagnosis. *Arthritis Care Res* 66: 1281–1288.
- Bodnar, N., Kerekes, G., Seres, I., Paragh, G., Kappelmayer, J., Nemethne, Z. *et al.* (2011) Assessment of Subclinical Vascular Disease Associated with Ankylosing Spondylitis. *J Rheumatol* 38: 723–729.
- Boyer, J., Gourraud, P., Cantagrel, A., Davignon, J. and Constantin, A. (2011) Traditional cardiovascular risk factors in rheumatoid arthritis: a meta-analysis. *Joint, Bone, Spine: Revue Du Rhumatisme* 78: 179–183.
- Brezinski, E., Follansbee, M., Armstrong, E. and Armstrong, A. (2014) Endothelial dysfunction and the effects of tn timeritators on the endothelium in psoriasis and psoriatic arthritis: a systematic review. *Curr Pharm Design* 20: 513–528.
- Brophy, S., Cooksey, R., Atkinson, M., Zhou, S., Husain, M., Macey, S. *et al.* (2012) No increased rate of acute myocardial infarction or stroke among patients with ankylosing spondylitis-a retrospective cohort study using routine data. *Semin Arthritis Rheum* 42: 140–145.
- Catapano, A., Reiner, Z., de Backer, G., Graham, I., Taskinen, M., Wiklund, O. *et al.* (2011) ESC/EAS guidelines for the management of dyslipidaemias. The Task Force for the Management of Dyslipidaemias

- of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *Atherosclerosis* 217: 3–46.
- Cholesterol Treatment Trialists Collaboration, Baigent, C., Blackwell, L., Emberson, J., Holland, L., Reith, C. *et al.* (2010) Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 376: 1670–1681.
- Choy, E., Ganesalingam, K., Semb, A., Szekanecz, Z. and Nurmohamed, M. (2014) Cardiovascular risk in rheumatoid arthritis: recent advances in the understanding of the pivotal role of inflammation, risk predictors and the impact of treatment. *Rheumatology* 53: 2143–2154.
- Corrales, A., González-Juanatey, C., Peiró, M., Blanco, R., Llorca, J. and González-Gay, M. (2014) Carotid ultrasound is useful for the cardiovascular risk stratification of patients with rheumatoid arthritis: results of a population-based study. *Ann Rheum Dis* 73: 722–727.
- Coxib and Traditional NSAID Trialists (CNT) Collaboration (2013) Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. *Lancet* 382: 769–779.
- Daïen, C., Duny, Y., Barnetche, T., Daurès, J., Combe, B. and Morel, J. (2012) Effect of TNF inhibitors on lipid profile in rheumatoid arthritis: a systematic review with meta-analysis. *Ann Rheum Dis* 71: 862–868.
- Dessein, P. and Joffe, B. (2006) Insulin resistance and impaired beta cell function in rheumatoid arthritis. *Arthritis Rheum* 54: 2765–2775.
- De Vera, M., Choi, H., Abrahamowicz, M., Kopec, J., Goycochea-Robles, M. and Lacaille, D. (2011) Statin discontinuation and risk of acute myocardial infarction in patients with rheumatoid arthritis: a population-based cohort study. *Ann Rheum Dis* 70: 1020–1024.
- Divecha, H., Sattar, N., Rumley, A., Cherry, L., Lowe, G. and Sturrock, R. (2005) Cardiovascular risk parameters in men with ankylosing spondylitis in comparison with non-inflammatory control subjects: relevance of systemic inflammation. *Clin Sci* 109: 171–176.
- Dougados, M., Soubrier, M., Perrodeau, E., Gossec, L., Fayet, F., Gilson, M. *et al.* (2014) Impact of a nurse-led programme on comorbidity management and impact of a patient self-assessment of disease activity on the management of rheumatoid arthritis: results of a prospective, multicentre, randomised, controlled trial (COMEDRA) *Ann Rheum Dis* 74: 33–1725.
- Eder, L., Chandran, V. and Gladman, D. (2014) The Framingham Risk Score underestimates the extent of subclinical atherosclerosis in patients with psoriatic disease. *Ann Rheum Dis* 73: 1990–1996.
- Eder, L., Wu, Y., Chandran, V., Cook, R. and Gladman, D. (2015) Incidence and predictors for cardiovascular events in patients with psoriatic arthritis. *Ann Rheum Dis* 75: 6–1680.
- Exarchou, S., Lie, E., Lindström, U., Askling, J., Forsblad-d'Elia, H., Turesson, C. *et al.* (2015) Mortality in ankylosing spondylitis: results from a nationwide population-based study. *Ann Rheum Dis* 75: 72–1466.
- Favato, G. (2008) High Incidence of Smoking Habit in Psoriatic Patients. *Am J Med* 121: e17.
- Gabriel, S., Crowson, C., Kremers, H., Doran, M., Turesson, C., O'Fallon, W. *et al.* (2003) Survival in rheumatoid arthritis: a population-based analysis of trends over 40 years. *Arthritis Rheum* 48: 54–58.
- Giles, J., Danielides, S., Szklo, M., Post, W., Blumenthal, R., Petri, M. *et al.* (2015) Insulin resistance in rheumatoid arthritis: disease-related indicators and associations with the presence and progression of subclinical atherosclerosis. *Arthritis Rheumatol* 67: 626–636.
- Gladman, D., Ang, M., Su, L., Tom, B., Schentag, C. and Farewell, V. (2009) Cardiovascular morbidity in psoriatic arthritis. *Ann Rheum Dis* 68: 1131–1135.
- González-Gay, M. and González-Juanatey, C. (2014) Inflammation and lipid profile in rheumatoid arthritis: bridging an apparent paradox. *Ann Rheum Dis* 73: 1281–1283.
- González-Gay, M., González-Juanatey, C., Vazquez-Rodriguez, T., Gomez-Acebo, I., Miranda-Filloy, J., Paz-Carreira, J. *et al.* (2009) Asymptomatic hyperuricemia and serum uric acid concentration correlate with subclinical atherosclerosis in psoriatic arthritis patients without clinically evident cardiovascular disease. *Semin Arthritis Rheu* 39: 157–162.
- González-Juanatey, C., Llorca, J., Amigo-Díaz, E., Dierssen, T., Martín, J. and González-Gay, M. (2007) High prevalence of subclinical atherosclerosis in psoriatic arthritis patients without clinically evident cardiovascular disease or classic atherosclerosis risk factors. *Arthritis Rheum* 57: 1074–1080.
- Grad, E. and Danenberg, H. (2013) C-reactive protein and atherothrombosis: Cause or effect? *Blood Rev* 27: 23–29.
- Grundy, S., Cleeman, J., Merz, C., Brewer, H., Clark, L., Hunninghake, D. *et al.* (2004) Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 110: 227–239.

- van Halm, V., Peters, M., Voskuyl, A., Boers, M., Lems, W., Visser, M. *et al.* (2009) Rheumatoid arthritis versus diabetes as a risk factor for cardiovascular disease: a cross-sectional study, the CARRE Investigation. *Ann Rheum Dis* 68: 1395–1400.
- Han, C., Robinson, D., Hackett, M., Paramore, L., Fraeman, K. and Bala, M. (2006) Cardiovascular disease and risk factors in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. *J Rheumatol* 33: 2167–2172.
- Holmqvist, M., Wedrén, S., Jacobsson, L., Klareskog, L., Nyberg, F., Rantapää-Dahlqvist, S. *et al.* (2010) Rapid increase in myocardial infarction risk following diagnosis of rheumatoid arthritis amongst patients diagnosed between 1995 and 2006. *J Intern Med* 268: 578–585.
- Horreau, C., Pouplard, C., Brenaut, E., Barnette, T., Misery, L., Cribier, B. *et al.* (2013) Cardiovascular morbidity and mortality in psoriasis and psoriatic arthritis: a systematic literature review. *J Eur Acad Dermatol Venereol* 27(Suppl. 3): 12–29.
- Huang, Y., Wang, Y. and Pan, S. (2013) Increased risk of ischemic heart disease in young patients with newly diagnosed ankylosing spondylitis—a population-based longitudinal follow-up study. *PLOS ONE* 8: e64155.
- Humphreys, J., Warner, A., Chipping, J., Marshall, T., Lunt, M., Symmons, D. *et al.* (2014) Mortality trends in patients with early rheumatoid arthritis over 20 years: results from the Norfolk Arthritis Register. *Arthrit Care Res* 66: 1296–1301.
- IL6 Receptor Mendelian Randomization Analysis (IL6R MR) Consortium (2012) The interleukin-6 receptor as a target for prevention of coronary heart disease: a Mendelian randomization analysis. *Lancet* 379: 1214–1224.
- Johnsson, H., McInnes, I. and Sattar, N. (2012) Cardiovascular and metabolic risks in psoriasis and psoriatic arthritis: pragmatic clinical management based on available evidence. *Ann Rheum Dis* 71: 480–483.
- Kawai, V., Chung, C., Solus, J., Oeser, A., Raggi, P. and Stein, C. (2015) The ability of the 2013 American College of Cardiology/American Heart Association cardiovascular risk score to identify rheumatoid arthritis patients with high coronary artery calcification scores. *Arthritis Rheumatol* 67: 381–385.
- Kimhi, O., Caspi, D., Bornstein, N., Maharshak, N., Gur, A., Arbel, Y. *et al.* (2007) Prevalence and risk factors of atherosclerosis in patients with psoriatic arthritis. *Semin Arthritis Rheu* 36: 203–209.
- Kremers, H., Nicola, P., Crowson, C., Ballman, K. and Gabriel, S. (2004) Prognostic importance of low body mass index in relation to cardiovascular mortality in rheumatoid arthritis. *Arthritis Rheum* 50: 3450–3457.
- Law, M., Morris, J. and Wald, N. (2009) Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ* 338: b1665.
- Lerman, A. and Zeiher, A. (2005) Endothelial function: cardiac events. *Circulation* 111: 363–368.
- Liao, K., Playford, M., Frits, M., Coblyn, J., Iannaccone, C., Weinblatt, M. *et al.* (2015) The association between reduction in inflammation and changes in lipoprotein levels and HDL cholesterol efflux capacity in rheumatoid arthritis. *J Am Heart Assoc* 30(4(2)). pii: e001588.
- Liao, K. and Solomon, D. (2013) Traditional cardiovascular risk factors, inflammation and cardiovascular risk in rheumatoid arthritis. *Rheumatology* 52: 45–52.
- Lindhardsen, J., Ahlehoff, O., Gislason, G., Madsen, O., Olesen, J., Torp-Pedersen, C. *et al.* (2011) The risk of myocardial infarction in rheumatoid arthritis and diabetes mellitus: a Danish nationwide cohort study. *Ann Rheum Dis* 70: 929–934.
- Malesci, D., Niglio, A., Mennillo, G., Buono, R., Valentini, G. and La Montagna, G. (2007) High prevalence of metabolic syndrome in patients with ankylosing spondylitis. *Clin Rheumatol* 26: 710–714.
- Maradit-Kremers, H., Crowson, C., Nicola, P., Ballman, K., Roger, V., Jacobsen, S. *et al.* (2005) Increased unrecognized coronary heart disease and sudden deaths in rheumatoid arthritis: a population-based cohort study. *Arthritis Rheum* 52: 402–411.
- Mathieu, S., Couderc, M., Pereira, B. and Soubrier, M. (2013a) The effects of TNF-alpha inhibitor therapy on arterial stiffness and endothelial dysfunction in rheumatoid arthritis: a meta-analysis. *Semin Arthritis Rheu* 43: e1–e2.
- Mathieu, S., Gossec, L., Dougados, M. and Soubrier, M. (2011) Cardiovascular profile in ankylosing spondylitis: a systematic review and meta-analysis. *Arthrit Care Res* 63: 557–563.
- Mathieu, S., Joly, H., Baron, G., Tournadre, A., Dubost, J., Ristori, J. *et al.* (2008) Trend towards increased arterial stiffness or intima-media thickness in ankylosing spondylitis patients without clinically evident cardiovascular disease. *Rheumatology* 47: 1203–1207.
- Mathieu, S., Pereira, B., Couderc, M., Rabois, E., Dubost, J. and Soubrier, M. (2013b) No significant changes in arterial stiffness in patients with ankylosing spondylitis after tumour necrosis factor alpha blockade

- treatment for 6 and 12 months. *Rheumatology* 52: 204–209.
- Mathieu, S., Pereira, B., Dubost, J., Lusson, J. and Soubrier, M. (2012) No significant change in arterial stiffness in RA after 6 months and 1 year of rituximab treatment. *Rheumatology* 51: 1107–1111.
- Mathieu, S., Pereira, B. and Soubrier, M. (2015) Cardiovascular events in ankylosing spondylitis: an updated meta-analysis. *Semin Arthritis Rheu* 44: 551–555.
- McInnes, I., Thompson, L., Giles, J., Bathon, J., Salmon, J., Beaulieu, A. *et al.* (2015) Effect of interleukin-6 receptor blockade on surrogates of vascular risk in rheumatoid arthritis: MEASURE, a randomised, placebo-controlled study. *Ann Rheum Dis* 74: 694–702.
- Mok, C., Ko, G., Ho, L., Yu, K., Chan, P. and To, C. (2011) Prevalence of atherosclerotic risk factors and the metabolic syndrome in patients with chronic inflammatory arthritis. *Arthritis Care Res* 63: 195–202.
- Myasoedova, E., Crowson, C., Kremers, H., Fitz-Gibbon, P., Therneau, T. and Gabriel, S. (2010) Total cholesterol and LDL levels decrease before rheumatoid arthritis. *Ann Rheum Dis* 69: 1310–1314.
- Myasoedova, E., Crowson, C., Kremers, H., Roger, V., Fitz-Gibbon, P., Therneau, T. *et al.* (2011) Lipid paradox in rheumatoid arthritis: the impact of serum lipid measures and systemic inflammation on the risk of cardiovascular disease. *Ann Rheum Dis* 70: 482–487.
- Naz, S., Farragher, T., Bunn, D., Symmons, D. and Bruce, I. (2008) The influence of age at symptom onset and length of followup on mortality in patients with recent-onset inflammatory polyarthritis. *Arthritis Rheum* 58: 985–989.
- Nicola, P., Maradit-Kremers, H., Roger, V., Jacobsen, S., Crowson, C., Ballman, K. *et al.* (2005) The risk of congestive heart failure in rheumatoid arthritis: a population-based study over 46 years. *Arthritis Rheum* 52: 412–420.
- Nurmohamed, M. (2015) SP0033 EULAR recommendation update on cardiovascular disease in RA. *Ann Rheum Dis* 74(Suppl. 2): 9.
- Ogdie, A., Yu, Y., Haynes, K., Love, T., Maliha, S., Jiang, Y. *et al.* (2015) Risk of major cardiovascular events in patients with psoriatic arthritis, psoriasis and rheumatoid arthritis: a population-based cohort study. *Ann Rheum Dis* 74: 326–332.
- Papadakis, J., Sidiropoulos, P., Karvounaris, S., Vrentzos, G., Spanakis, E., Ganotakis, E. *et al.* (2009) High prevalence of metabolic syndrome and cardiovascular risk factors in men with ankylosing spondylitis on anti-TNF α treatment: correlation with disease activity. *Clin Exp Rheumatol* 27: 292–298.
- Papagoras, C., Markatseli, T., Saougou, I., Alamanos, Y., Zikou, A., Voulgari, P. *et al.* (2014) Cardiovascular risk profile in patients with spondyloarthritis. *Joint Bone Spine* 81: 57–63.
- Payet, S., Pereira, B., Soubrier, M. and Mathieu, S. (2012) The effects of TNF- α blocking therapy on lipid levels in rheumatoid arthritis: a meta-analysis. *Semin Arthritis Rheu* 41: e4–e5, e6.
- Peters, M., Symmons, D., McCarey, D., Dijkmans, B., Nicola, P., Kvien, T. *et al.* (2010) EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. *Ann Rheum Dis* 69: 325–331.
- Peters, M., van der Horst-Bruinsma, I., Dijkmans, B. and Nurmohamed, M. (2004) Cardiovascular risk profile of patients with spondylarthropathies, particularly ankylosing spondylitis and psoriatic arthritis. *Semin Arthritis Rheu* 34: 585–592.
- Peters, M., van Halm, V., Voskuyl, A., Smulders, Y., Boers, M., Lems, W. *et al.* (2009) Does rheumatoid arthritis equal diabetes mellitus as an independent risk factor for cardiovascular disease? A prospective study. *Arthritis Rheum* 61: 1571–1579.
- Protogerou, A., Panagiotakos, D., Zampeli, E., Argyris, A., Arida, K., Konstantonis, G. *et al.* (2013) Arterial hypertension assessed ‘out-of-office’ in a contemporary cohort of rheumatoid arthritis patients free of cardiovascular disease is characterized by high prevalence, low awareness, poor control and increased vascular damage-associated ‘white coat’ phenomenon. *Arthritis Res Ther* 15: R142.
- Provan, S., Semb, A., Hisdal, J., Strandén, E., Agewall, S., Dagfinrud, H. *et al.* (2011) Remission is the goal for cardiovascular risk management in patients with rheumatoid arthritis: a cross-sectional comparative study. *Ann Rheum Dis* 70: 812–817.
- Ridker, P., Rifai, N., Pfeffer, M., Sacks, F., Lepage, S. and Braunwald, E. (2000a) Elevation of tumor necrosis factor- α and increased risk of recurrent coronary events after myocardial infarction. *Circulation* 101: 2149–2153.
- Ridker, P., Rifai, N., Stampfer, M. and Hennekens, C. (2000b) Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. *Circulation* 101: 1767–1772.
- Roberts, E., Nunes, V., Buckner, S., Latchem, S., Constanti, M., Miller, P. *et al.* (2015) Paracetamol: not as safe as we thought? A systematic literature review of observational studies. *Ann Rheum Dis* (2 March 2015) DOI: 10.1136/annrheumdis-2014-206914.
- Robertson, J., Peters, M., McInnes, I. and Sattar, N. (2013) Changes in lipid levels with inflammation and

- therapy in RA: a maturing paradigm. *Nature Reviews. Rheumatology* 9: 513–523.
- Rollefstad, S., Ikdahl, E., Hisdal, J., Olsen, I., Holme, I., Hammer, H. *et al.* (2015) Rosuvastatin-induced carotid plaque regression in patients with inflammatory joint diseases: the Rosuvastatin In Rheumatoid Arthritis, Ankylosing Spondylitis And Other Inflammatory Joint Diseases Study: regression of atherosclerosis in patients with inflammatory joint disease. *Arthritis Rheumatol* 67: 1718–1728.
- Roubille, C., Richer, V., Starnino, T., McCourt, C., McFarlane, A., Fleming, P. *et al.* (2015) 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* 74: 480–489.
- Russolillo, A., Iervolino, S., Peluso, R., Lupoli, R., Di Minno, A., Pappone, N. *et al.* (2013) Obesity and psoriatic arthritis: from pathogenesis to clinical outcome and management. *Rheumatology* 52: 62–67.
- Sandoo, A., Zanten, J., van Metsios, G., Carroll, D. and Kitas, G. (2011) Vascular function and morphology in rheumatoid arthritis: a systematic review. *Rheumatology* 50: 2125–2139.
- Schoenfeld, S., Lu, L., Rai, S., Seeger, J., Zhang, Y. and Choi, H. (2016) Statin use and mortality in rheumatoid arthritis: a general population-based cohort study. *Ann Rheum Dis* 75: 1315–1320. DOI: 10.1136/annrheumdis-2015-207714.
- Semb, A., Kvien, T., Aastveit, A., Jungner, I., Pedersen, T., Walldius, G. *et al.* (2010) Lipids, myocardial infarction and ischaemic stroke in patients with rheumatoid arthritis in the Apolipoprotein-related Mortality Risk (AMORIS) Study. *Ann Rheum Dis* 69: 1996–2001.
- Semb, A., Kvien, T., DeMicco, D., Fayyad, R., Wun, C., LaRosa, J. *et al.* (2012) Effect of intensive lipid-lowering therapy on cardiovascular outcome in patients with and those without inflammatory joint disease. *Arthritis Rheum* 64: 2836–2846.
- Sheng, X., Murphy, M., Macdonald, T. and Wei, L. (2012) Effectiveness of statins on total cholesterol and cardiovascular disease and all-cause mortality in osteoarthritis and rheumatoid arthritis. *J Rheumatol* 39: 32–40.
- van Sijl, A., van Eijk, I., Peters, M., Serne, E., van der Horst-Bruinsma, I., Smulders, Y. *et al.* (2015) Tumour necrosis factor blocking agents and progression of subclinical atherosclerosis in patients with ankylosing spondylitis. *Ann Rheum Dis* 74: 119–123.
- Skak-Nielsen, H., Torp-Pedersen, C., Finer, N., Caterson, I., Van Gaal, L., James, W. *et al.* (2013) Uric acid as a risk factor for cardiovascular disease and mortality in overweight/obese individuals. *PLOS ONE* 8: e59121.
- Solomon, D., Greenberg, J., Curtis, J., Liu, M., Farkouh, M., Tsao, P. *et al.* (2015a) Derivation and internal validation of an expanded cardiovascular risk prediction score for rheumatoid arthritis: a Consortium of Rheumatology Researchers of North America Registry study: cardiovascular risk prediction score in rheumatoid arthritis. *Arthritis Rheumatol* 67: 1995–2003.
- Solomon, D., Reed, G., Kremer, J., Curtis, J., Farkouh, M., Harrold, L. *et al.* (2015b) Disease activity in rheumatoid arthritis and the risk of cardiovascular events. *Arthritis Rheumatol* 67: 1449–1455.
- Soubrier, M., Rosenbaum, D., Tatar, Z., Lahaye, C., Dubost, J. and Mathieu, S. (2013) Vascular effects of nonsteroidal antiinflammatory drugs. *Joint, Bone, Spine: Revue Du Rhumatisme* 80: 358–362.
- Soubrier, M., Zerkak, D. and Dougados, M. (2006) Indications for lowering LDL cholesterol in rheumatoid arthritis: an unrecognized problem. *J Rheumatol* 33: 1766–1769.
- Souto, A., Salgado, E., Maneiro, J., Mera, A., Carmona, L. and Gómez-Reino, J. (2015) Lipid profile changes in patients with chronic inflammatory arthritis treated with biologic agents and tofacitinib in randomized clinical trials: a systematic review and meta-analysis: lipid changes and treatment in chronic arthritis. *Arthritis Rheumatol* 67: 117–127.
- Stone, N., Robinson, J., Lichtenstein, A., Bairey Merz, C., Blum, C., Eckel, R. *et al.* (2014) 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Col Cardiol* 63: 2889–2934.
- Sundström, B., Johansson, G., Johansson, I. and Wällberg-Jonsson, S. (2014) Modifiable cardiovascular risk factors in patients with ankylosing spondylitis. *Clin Rheumatol* 33: 111–117.
- Symmons, D. and Gabriel, S. (2011) Epidemiology of CVD in rheumatic disease, with a focus on RA and SLE. *Nat Rev Rheumatol* 7: 399–408.
- Szabo, S., Levy, A., Rao, S., Kirbach, S., Lacaille, D., Cifaldi, M. *et al.* (2011) Increased risk of cardiovascular and cerebrovascular diseases in individuals with ankylosing spondylitis: a population-based study. *Arthritis Rheum* 63: 3294–3304.
- Tam, L., Tomlinson, B., Chu, T., Li, M., Leung, Y., Kwok, L. *et al.* (2008) Cardiovascular risk profile of

patients with psoriatic arthritis compared to controls - the role of inflammation. *Rheumatology* 47: 718–723.

Toms, T., Panoulas, V., Douglas, K., Griffiths, H., Sattar, N., Smith, J. *et al.* (2010) Statin use in rheumatoid arthritis in relation to actual cardiovascular risk: evidence for substantial undertreatment of lipid-associated cardiovascular risk? *Ann Rheum Dis* 69: 683–688.

Tournadre, A., Tatar, Z., Pereira, B., Chevreau, M., Gossec, L., Gaudin, P. *et al.* (2015) Application of the European Society of Cardiology, Adult Treatment Panel III and American College of Cardiology/American Heart Association guidelines for cardiovascular risk management in a French cohort of rheumatoid arthritis. *Int J Cardiol* 183C: 149–154.

Tsai, W., Ou, T., Yen, J., Wu, C. and Tung, Y. (2015) Long-term frequent use of non-steroidal anti-inflammatory drugs might protect patients with ankylosing spondylitis from cardiovascular diseases:

a nationwide case-control study. *PLOS ONE* 10: e0126347. DOI: 10.1371/journal.pone.0126347.

Wolfe, F. and Michaud, K. (2012) Effect of body mass index on mortality and clinical status in rheumatoid arthritis. *Arthrit Care Res* 64: 1471–1479.

Zhang, J., Chen, L., Delzell, E., Muntner, P., Hillegass, W., Safford, M. *et al.* (2014) The association between inflammatory markers, serum lipids and the risk of cardiovascular events in patients with rheumatoid arthritis. *Ann Rheum Dis* 73: 1301–1308.

Zhang, J., Fu, L., Shi, J., Chen, X., Li, Y., Ma, B. *et al.* (2013) The risk of metabolic syndrome in patients with rheumatoid arthritis: a meta-analysis of observational studies. *PLOS ONE* 8: e78151.

Zöller, B., Li, X., Sundquist, J. and Sundquist, K. (2012) Risk of subsequent ischemic and hemorrhagic stroke in patients hospitalized for immune-mediated diseases: a nationwide follow-up study from Sweden. *BMC Neurology* 12: 41.

Visit SAGE journals online
<http://tab.sagepub.com>

SAGE journals