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Management of cardiovascular risk in patients with rheumatoid arthritis: evidence and expert opinion

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Abstract: The risk of cardiovascular morbidity and mortality is increased in rheumatoid arthritis. The classical cardiovascular risk factors, including smoking, hypertension, dyslipidaemia, insulin resistance and diabetes mellitus, obesity and physical inactivity do not appear to explain the excess cardiovascular risk in rheumatoid arthritis, although they do contribute, albeit in a different way or to a lesser extent, to rheumatoid arthritis in comparison with the general population. A very important link between rheumatoid arthritis and cardiovascular disease is inflammation as it plays a key role in all stages of atherosclerosis: from endothelial dysfunction to plaque rupture and thrombosis. It also has an influence on and accentuates some traditional cardiovascular risk factors, such as dyslipidaemia, obesity and insulin resistance. To date, the exact pathophysiologic mechanism by which this relation between cardiovascular disease and rheumatoid arthritis can be explained is not completely clear. Cardiovascular risk management in rheumatoid arthritis is mandatory. Unfortunately, the way this should be done remains a point of discussion. In this review issues regarding cardiovascular risk in rheumatoid arthritis and its management will be addressed, according to evidence presented in the latest studies and our own experience-based opinion.

Keywords: cardiovascular risk, cardiovascular risk management, inflammation, rheumatoid arthritis

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Introduction

The risk of cardiovascular (CV) disease and mortality is increased in rheumatoid arthritis (RA). A substantial number of observational studies varying in factors such as the cohort type, disease duration and length of follow up, has produced a wide range of incidence rates for CV events and mortality. Some studies show a more than doubled risk which is comparable to the CV risk in diabetes mellitus (DM) [del Rincon *et al.* 2001; Peters *et al.* 2009]. Other studies show a more modest increased risk [Gabriel *et al.* 1999; Goodson *et al.* 2005a]. However, when the results of the most relevant studies are pooled the risk of CV events and mortality seems to be approximately 50% higher in RA patients compared with the general population [Avina-Zubieta *et al.* 2008, 2012]. To date, the exact pathophysiologic mechanism by which this relation between CV disease and RA can be explained is not completely clear.

So the most important questions regarding this problem remain: ‘How can this increased risk be explained?’, ‘When does it start?’, ‘How can we predict the CV risk in RA?’ and, most important, ‘How can we prevent CV morbidity and mortality in RA?’.

In this review we will answer these questions according to evidence presented in the latest studies and according to our own experience-based opinion.

What causes the excess CV risk?

To be able to decrease the excess CV risk in RA it is essential to know what causes this problem. One of the reasons why this puzzle has not yet been solved is that there are many pathophysiological mechanisms involved that influence each other. First of all, the traditional CV risk factors, which

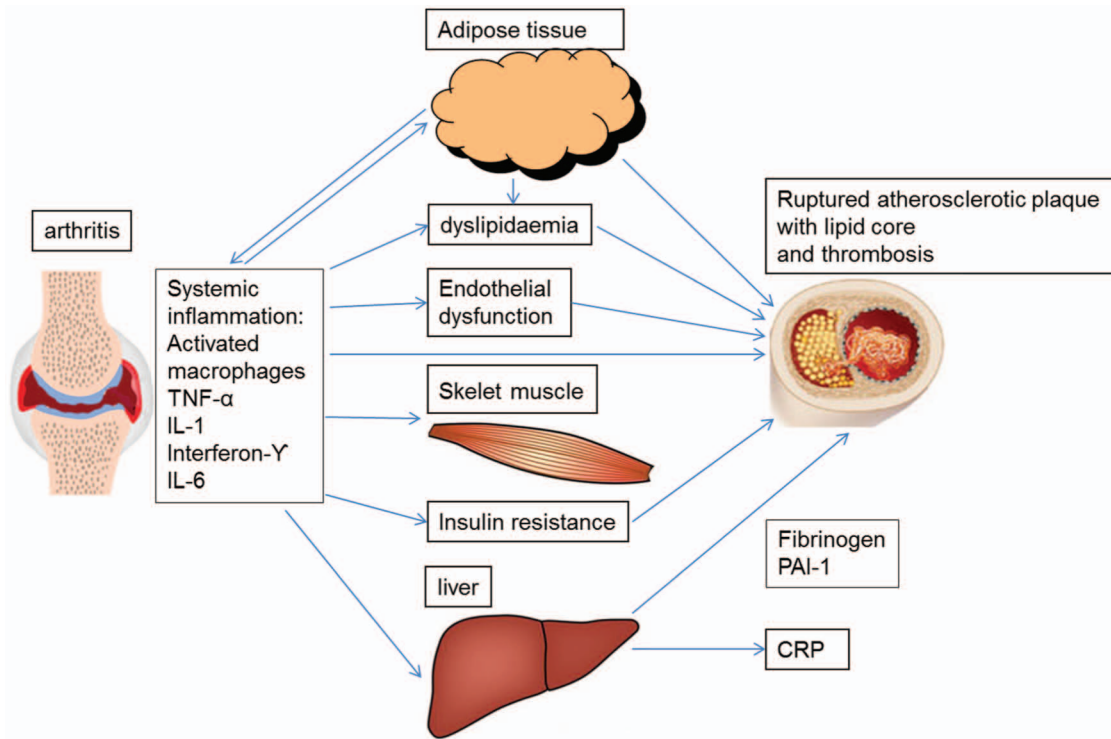


Figure 1. An illustration of the pathways and cytokines by which synovitis can contribute to the formation of an atherosclerotic plaque and eventually CV events.

cause and predict CV morbidity and mortality in the general population but also in people with DM, seem to be equally or only slightly more prevalent in the RA population. Some risk factors, such as smoking, even play an important role in the onset of RA, however, traditional CV risk factors alone do not explain the higher CV risk in RA [Chung *et al.* 2012; Gonzalez *et al.* 2008]. At present, RA and atherosclerosis are both regarded as inflammatory-driven diseases and this appears to be the most important reason why these two diseases coincide [Sattar *et al.* 2003]. There is much evidence that endorses this hypothesis. For instance, the inflammatory and immunological processes that occur in atherosclerotic plaques are very similar to those in inflammatory synovitis and markers of inflammation, as C-reactive protein (CRP), predict CV disease not only in healthy men and women but also in RA patients [Goodson *et al.* 2005b; Pasceri and Willerson, 1999; Ridker *et al.* 1998]. Furthermore, indicators of more severe disease and more systemic inflammation in RA, such as decreased functional capability, the presence of extra-articular manifestations, longer disease duration and seropositivity, are also associated with higher CV risk [Gabriel, 2008; Goodson *et al.* 2002; Soderlin *et al.* 1998; Turesson *et al.* 2007].

There are many ways by which RA-related inflammation may lead to atherosclerosis. Inflammation seems to play a key role in all stages of atherosclerosis: from endothelial dysfunction to plaque rupture and thrombosis [Libby, 2006]. Inflammation also has an influence on and accentuates some traditional CV risk factors, such as dyslipidaemia, obesity and insulin resistance (IR), as they behave differently in the RA population with regard to CV risk than in the general population [Gonzalez *et al.* 2008; Liao and Solomon, 2013; Sattar *et al.* 2003]. The link between synovitis and atherosclerosis is illustrated in Figure 1.

Another factor that may link atherosclerosis to RA is a common genetic background. An increasing number of studies report gene polymorphisms that are associated with a higher risk of CV risk in rheumatoid arthritis [Cavagna *et al.* 2012]. Human leucocyte antigen shared epitope (HLA-DRB1) is a typical example of a gene that seems associated with CV mortality in RA [Farragher *et al.* 2008]. Together with the question of what causes the relationship between RA and atherosclerosis arises the question of when does CV risk increase? When genetics, traditional CV risk factors and autoimmune pathways are involved it could be

possible that the CV risk is already increased at the time of diagnosis or even years before the first clinical symptoms appear. Actually, there is accumulating (circumstantial) evidence that CV risk is increased before the clinical onset of RA. There are studies that show that endothelial dysfunction and the first signs of atherosclerosis are already present in patients with recent-onset RA [Sodergren *et al.* 2010]. Most of the studies measuring carotid intima-media thickness (cIMT) in newly diagnosed RA patients *versus* controls found cIMT levels to be significantly elevated in the RA group and to be correlated with systemic inflammatory markers and disease severity markers [Kerola *et al.* 2012]. A meta-analysis looking at cIMT in established RA patients also showed statistically significant higher cIMT levels in RA *versus* controls but no relation with disease duration [van Sijl *et al.* 2012]. Also dyslipidaemia is already present in rheumatoid-factor-positive persons who later develop RA [Myasoedova *et al.* 2010; van de Stadt *et al.* 2012; van Halm *et al.* 2007]. One population-based cohort study reported an increased risk of coronary heart disease and myocardial infarction two years prior to RA diagnosis using the ACR 1987 criteria [Maradit-Kremers *et al.* 2005a]. There are some more recent studies that reported increased CV risk and mortality early in the RA disease course [Franklin *et al.* 2010; Holmqvist *et al.* 2010; Naz *et al.* 2008; Sodergren *et al.* 2010]. Altogether, it appears that CV risk already starts to increase as soon as the first signs of autoimmunity and inflammation appear which is often a few months to years prior to the actual RA diagnosis and increases further during disease progression as the inflammatory burden accumulates.

The role of traditional CV risk factors

Although the classical CV risk factors, including smoking, hypertension, dyslipidaemia, DM, obesity and inactivity do not seem to explain the excess CV risk in RA, they do contribute, albeit in a different way or to a lesser extent in RA in comparison with the general population. The following sections and Table 1 summarize and interpret data from recent studies on individual traditional CV risk factors and their contribution to CV risk in RA specifically.

Smoking

As already mentioned, cigarette smoking is classified not only as a predisposing factor for CV

events but also for RA, particularly rheumatoid-factor-positive RA [Costenbader *et al.* 2006; Costenbader and Karlson, 2006; Heliövaara *et al.* 1993]. For rheumatologists this alone should be a trigger to advise every newly diagnosed RA patient who smokes to quit, apart from the notion that smoking probably also has an adverse influence on RA disease severity and prognosis [Saag *et al.* 1997].

Hypertension

Whether hypertension is more common in RA than in the general population has not been elucidated yet, because reports are contradictory [Liao and Solomon, 2013]. However, one of the most recent studies found a significant increased prevalence of hypertension in RA patients *versus* controls [Chung *et al.* 2012]. The reported prevalence of hypertension in RA varies substantially, depending on the study population, sample size and on the definition of hypertension used in the different studies [Panoulas *et al.* 2008b]. This does not mean that hypertension has no impact on CV risk in RA. Hypertension is a very common problem in the general as well as the RA population and is still underdiagnosed and undertreated, particularly in young RA patients [Panoulas *et al.* 2007]. There is no real evidence that the current disease-modifying antirheumatic drugs (DMARDs) have a beneficial effect on blood pressure. On the contrary, there are DMARDs and other drugs used for the treatment of RA that can induce high blood pressure, such as leflunomide, cyclosporine, glucocorticoids and the nonsteroidal anti-inflammatory drugs (NSAIDs) [Panoulas *et al.* 2008b; Van Doornum *et al.* 2006]. This means adequate blood pressure control and treatment could be of great influence to the CV risk in the RA population.

Dyslipidaemia

Abnormal cholesterol levels, particularly high levels of total cholesterol, triglycerides, low-density lipoprotein (LDL) and low levels of high-density lipoprotein (HDL) are strongly associated with CV disease. LDL particles can transport cholesterol in the arterial wall, which leads to atherosclerosis, while HDL particles are able to remove cholesterol from the arterial wall. Most studies which have investigated cholesterol levels in RA have found lower HDL levels and as a result an unfavourable atherogenic profile (total cholesterol/HDL cholesterol ratio) compared with healthy controls, even 10 years before the onset of RA [Choi and Seeger,

Table 1. Studies examining the prevalence of several traditional CV risk factors in RA patients.

Study	Study design and population	CV risk factors Studied	Results
Park <i>et al.</i> [1999]	Case-control study with untreated, active RA patients	Lipid profile	RA patients significantly lower apoA-1 (128.5 <i>versus</i> 151.8 mg/dl), HDL-C (41.2 <i>versus</i> 54.9 mg/dl), higher Lp(a) (27.1 <i>versus</i> 18.0 mg/dl), apoB/apoA-1 (0.82 <i>versus</i> 0.67), TC/HDL-C (4.4 <i>versus</i> 3.4) and LDL-C/HDL-C (2.8 <i>versus</i> 1.9) ratios compared with controls ($p \leq 0.05$).
Dessein <i>et al.</i> [2002]	Outpatient clinic-based case-control study of RA and OA patients	PA, DM, lipid profiles, insulin sensitivity	RA patients exercised more <i>versus</i> OA patients ($\chi^2 = 3.9$, $p < 0.05$). DM more prevalent in RA (9) <i>versus</i> OA (1) patients ($\chi^2 = 4.5$, $p < 0.05$). QUICKI 0.344 (0.332–0.355) and HDL-C 1.40 mmol/l (1.30–1.49) in RA patients <i>versus</i> 0.369 (0.356–0.383) and 1.68 mmol/l (1.50–1.85) in OA patients ($p < 0.05$).
Solomon <i>et al.</i> [2004]	Prospective longitudinal case-control study of RA women (the Nurses' Health Study)	Smoking, hypertension, PA, BMI and DM	Except for past cigarette smoking (47.8% <i>versus</i> 38.0%) no significant differences in prevalence of CV risk factors between RA women and controls.
Choi and Seeger [2005]	Population-based case-control study of RA patients (NHANES III)	Lipid profile	Difference in HDL-C 2.5 (95% CI 0.8–4.9) mg/dl and apoA-1 4.5 (95% CI –0.8 to 9.8) mg/dl between RA and controls
Maradit-Kremers <i>et al.</i> [2005b]	Population-based cohort study of RA patients (Rochester Epidemiology Project)	Smoking, hypertension, dyslipidaemia, BMI and DM	Prevalence of former smokers 25.8%, current smokers 29.7% hypertension 51.7%, dyslipidaemia 49.4%, obesity 13.4% and DM 7.3%
Georgiadis <i>et al.</i> [2006]	Outpatient clinic-based case-control study of early RA patients	Lipid profile	Early RA patients significantly lower HDL-C (47.5±11.8 <i>versus</i> 51.1±7.4 mg/day), significantly higher TC (216.5±20.3 <i>versus</i> 190.4±33.9 mg/dl), LDL-C (141.6±42.3 <i>versus</i> 126.5±31.3 mg/dl), triglycerides (133.0±58.2 <i>versus</i> 97.1±28.3 mg/dl) and TC/HDL-C (4.9±1.3 <i>versus</i> 3.7±0.9), LDL-C/HDL-C (3.0±1.0 <i>versus</i> 2.5±0.8) ratios compared with controls.
Han <i>et al.</i> [2006]	Case-control study of RA, PsA, AS patients and healthy controls	Hypertension, hyperlipidemia, T2DM	Prevalence ratio of T2DM (1.4, 1.5, 1.2), hyperlipidemia (1.2, 1.2, 1.2), and hypertension (1.3, 1.3, 1.3) were higher in patients than controls.
Van Halm <i>et al.</i> [2007]	Longitudinal case-control study with blood samples of patients who later developed RA	Lipid profile	RA patients 4% higher TC, 9% lower HDL-C, 17% higher triglyceride and 6% higher apoB levels compared with controls ($p \leq 0.05$).
Panoulas <i>et al.</i> [2007]	Cross-sectional outpatient clinic-based study of RA patients	Hypertension	Prevalence of hypertension 70.5%, of which 39.4 % undiagnosed.
Simard and Mittleman [2007]	Cross-sectional population-based cohort study (NHANES III)	T2DM	OR 1.1–1.5 between RA and DM not statistically significant
Mancuso <i>et al.</i> [2007]	Outpatient clinic-based case-control cohort study of RA patients	PA	Fewer RA patients met the recommendations for walking (32% <i>versus</i> 48%; $p = 0.01$) compared with general population.
Van den Berg <i>et al.</i> [2007]	Outpatient clinic-based cohort study compared with general Dutch population	PA	Proportions of RA patients meeting PA recommendation were similar. The average number of minutes of PA per week was significantly lower in the RA population compared with the general population in the category 45–64 years (1836 <i>versus</i> 2199, $p = 0.001$)

Table 1. (Continued)

Study	Study design and population	CV risk factors Studied	Results
Chung <i>et al.</i> [2008a]	Case-control cohort study of early and long-standing RA patients	Metabolic syndrome (modified WHO and NCEP III criteria)	Metabolic syndrome (WHO): long-standing RA 42%, early RA 31%, controls 11% ($p < 0.001$); (NCEP III) long-standing RA 42%, early RA 30% and controls 22% ($p = 0.03$).
Gonzalez <i>et al.</i> [2008]	Longitudinal, population-based case-control study of RA subjects	Smoking, hypertension, dyslipidaemia, BMI and DM	Prevalence of smoking in RA patients 53% <i>versus</i> controls 43% ($p < 0.001$), prevalence of other CV risk factors similar in both groups
Rizzo <i>et al.</i> [2009]	Case-control study with early, untreated RA patients	Lipid profile	Higher triglycerides (1.8 ± 0.5 <i>versus</i> 1.0 ± 0.5 mmol/L, $p < 0.0001$), lower HDL-C (1.2 ± 0.2 <i>versus</i> 1.4 ± 0.2 mmol/l, $p = 0.0027$) and lower LDL particle size (26 ± 47 <i>versus</i> $281 \pm 9A$, $p < 0.0001$) in RA patients than controls
Shahin <i>et al.</i> [2010]	Outpatient clinic-based case-control cohort study of early RA patients	Insulin resistance	Prevalence of IR higher in early RA patients with high disease activity than in patients with moderate disease activity and controls ($p < 0.0001$).
Solomon <i>et al.</i> [2010]	Longitudinal cohort of RA patients (CORRONA)	DM, hypertension, hyperlipidemia, current smoking	Prevalence of DM 7.1%, hypertension 29.8%, hyperlipidemia 9.2% and current smoking 16.1%.
Chung <i>et al.</i> [2012]	Case-control study of RA patients (ESCAPE RA and MESA cohort)	Hypertension, smoking, LDL, BMI and DM	Prevalence of hypertension in RA 57% <i>versus</i> controls 42% ($p = 0.001$). No significant differences in prevalence of other CV risk factors.

AS, ankylosing spondylitis; BMI, body mass index; DM, diabetes mellitus; CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol; IR, insulin resistance; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; OA, osteoarthritis; OR, odds ratio; PA, physical activity; PSA, prostate-specific antigen; RA, rheumatoid arthritis; T2DM, type 2 diabetes mellitus; TC, total cholesterol.

2005; Georgiadis *et al.* 2006; Myasoedova *et al.* 2010; Park *et al.* 1999; van de Stadt *et al.* 2012; van Halm *et al.* 2007; Yoo, 2004]. The data on total cholesterol, LDL and triglyceride levels are not so conclusive [Nurmohamed, 2007]. However, many studies demonstrate a very similar lipid pattern as seen in several other inflammatory conditions, indicating a profound influence of inflammation on lipid profile in RA [Khovidhunkit *et al.* 2000; Rizzo *et al.* 2009]. All in all, when LDL and HDL composition are also taken into account, the lipid profile in active RA tends to be highly proatherogenic [Hahn *et al.* 2008].

Diabetes mellitus and insulin resistance

There is a lot of data that points to an association between RA and IR, which is very likely caused by inflammation, as many studies showed a correlation between IR and disease activity or markers of inflammation such as CRP and erythrocyte sedimentation rate (ESR) [Chung *et al.*

2008a, 2008b; Dessein *et al.* 2002; Dessein and Joffe, 2006; Shahin *et al.* 2010; Svenson *et al.* 1987, 1988].

Several studies have investigated the prevalence of type 2 diabetes mellitus (DM2) in RA patients, expecting to find a positive association. However, apart from two studies, which found a modest significantly higher occurrence of DM2 in RA patients [Han *et al.* 2006; Solomon *et al.* 2010], all other studies found no significantly increased prevalence [Gabriel *et al.* 1999; Liao *et al.* 2009; Simard and Mittleman, 2007; Solomon *et al.* 2004]. This seems quite remarkable given the fact that IR often precedes DM2 and indicates that further research is needed to clarify this issue. However, both IR and DM appear to be independent CV risk factors in patients with RA, as also seen in the general population [Chung *et al.* 2008a; del Rincon *et al.* 2005; Dessein *et al.* 2003; Maradit-Kremers *et al.* 2005b; Shahin *et al.* 2010].

Obesity

Obesity, specifically central or abdominal obesity, characterized by a large waist circumference, is a risk factor for CV disease in the general population [Mathieu *et al.* 2010]. The adipose tissue, especially abdominal visceral fat, may contribute to low-grade inflammation by producing pro-inflammatory cytokines such as tumour necrosis factor (TNF)- α and interleukin (IL)-6 [Despres and Lemieux, 2006].

Surprisingly, most studies reported a higher CV mortality in RA patients with a low body mass index (BMI) (<20 kg/m²) compared with patients with a higher BMI (\geq 30 kg/m²), although the prevalence of adiposity did not differ in RA compared with the general population [Chung *et al.* 2012; Escalante *et al.* 2005; Gabriel, 2008; Gonzalez *et al.* 2008; Kremers *et al.* 2004; Maradit-Kremers *et al.* 2005b; Rall and Roubenoff, 2004; Walsmith and Roubenoff, 2002]. This discrepancy can be explained by a phenomenon called rheumatoid cachexia, a condition characterized by decreased lean muscle mass and increased adiposity, which leads to an abnormal body composition in RA [Rall and Roubenoff, 2004; Summers *et al.* 2008; Walsmith and Roubenoff, 2002]. One study clearly demonstrated that RA patients had a different distribution of abdominal fat and especially visceral fat, despite no significant differences in BMI or waist circumference compared with non-RA controls [Giles *et al.* 2010]. Loss of lean muscle mass in RA seems associated with TNF- α [Roubenoff *et al.* 1994; Walsmith *et al.* 2004]. In conclusion, the chronic inflammatory state in RA seems to create an abnormal body composition characterized by muscle wasting and increasing visceral fat, whereby BMI can be perfectly normal and thereby less reliable when it comes to predicting CV risk.

Physical activity

RA patients tend to be less physically active due to disease symptoms, such as joint pain and stiffness and fear of aggravating their disease [Mancuso *et al.* 2007; Metsios *et al.* 2008; Roubenoff *et al.* 2002; van den Berg *et al.* 2007]. Exercise can prevent CV disease and it has a positive impact on all of the individual CV risk factors, such as adiposity, dyslipidaemia, IR and DM, hypertension and possibly even inflammation [Bensimhon *et al.* 2006; Blair *et al.* 1993; Kasapis and Thompson, 2005; Kelemen *et al.* 1990; Wallberg-Henriksson *et al.* 1998]. Physical

inactivity has been associated with CV risk in RA [Metsios *et al.* 2009]. This could mean that stimulating RA patients to be more physically active could have even more effect on CV risk in RA patients than in healthy persons.

Cardiovascular risk scores: are they useful in RA?

Large longitudinal cohort studies performed in the 20th century have discovered which factors most adequately predict the risk for CV disease in the general population resulting in several CV risk estimation models, such as the Framingham Risk Score (FRS), the Reynolds Risk Score (RRS) and the Systematic Coronary Risk Evaluation (SCORE) [Conroy *et al.* 2003; D'Agostino *et al.* 2008; Ridker *et al.* 2007]. Although these CV risk assessment tools are based on the whole population, including people with chronic diseases, they often cannot be used for accurately predicting CV risk in these specific populations. A very good example of such a group is DM patients. They have a higher CV risk and therefore special risk scores, such as the UK Prospective Diabetes Study (UKPDS) score, have been developed [Stevens *et al.* 2001]. In the Netherlands, another way of calculating the excess CV risk of DM is being used. Instead of a separate risk model for DM, the SCORE risk model is adjusted by adding 15 years to the actual age of DM patients, because the excess CV risk in DM seems to match that of healthy persons 15 years older, the so-called 'vascular age' [Booth *et al.* 2006].

The same problem is true for RA patients: their vascular age also seems to be similar to that of healthy persons 10–15 years older and there are actually studies that have shown a CV risk that matches the CV risk of DM patients [Lindhardsen *et al.* 2011; Peters *et al.* 2009; Stamatelopoulos *et al.* 2009; van Halm *et al.* 2009].

The European League Against Rheumatism (EULAR) has set up guidelines with recommendations regarding CV risk management in RA and advised to add a multiplier of 1.5 to conventional risk assessment tools for estimating CV risk in RA patients, based on the evidence present at that time [Peters *et al.* 2010].

However, to date there is no evidence that this multiplier or any other CV risk estimation model or adjustment method accurately predicts CV risk in RA. Future research should therefore focus on

developing accurate CV risk prediction models for the RA population.

Cardiovascular disease prevention in RA: what (not) to do?

Tight disease control

As stated above, CV risk in RA cannot be explained by traditional CV risk factors alone and is largely increased because of chronic systemic inflammation. Therefore, tight and sustained control of RA disease activity is necessary to effectively prevent CV disease development in RA. This starts by early recognition and diagnosis of RA followed by immediate aggressive treatment to diminish the grade of inflammation as quickly as possible to prevent damage in not only the joints but also the arteries. Although we do not know when the excess CV risk exactly starts to arise, it is likely at the same time signs of inflammation occur and it could even be sooner than that. The treatment goal should be remission, since even low-grade inflammation and especially cumulative (low-grade) inflammation can eventually cause atherosclerosis and CV events [Provan *et al.* 2011]. Indirectly, effective treatment can result in improved physical activity, subsequently leading to a decreased risk of obesity, diabetes, hypertension and in the end CV disease. Effective treatment of RA can therefore substantially reduce CV risk in RA, however some medications, such as corticosteroids and NSAIDs, often used in RA are known to enhance CV risk.

DMARDs

Methotrexate (MTX), the cornerstone DMARD in the treatment of RA, has been shown to reduce all-cause CV morbidity and mortality in RA and appears to have cardioprotective properties [Choi *et al.* 2002; Marks and Edwards, 2012; Prodanovich *et al.* 2005; van Halm *et al.* 2006; Westlake *et al.* 2010]. However, there are studies that found an association between MTX use and hyperhomocysteinemia, an independent CV risk factor, which could be explained by a depletion of folic acid levels [Haagsma *et al.* 1999; Hornung *et al.* 2004]. Hence, supplemental use of folic acid is advised to restore normal homocysteine levels [Morgan *et al.* 1998; Prodanovich *et al.* 2005]. Data on the effect of other DMARDs on CV morbidity and mortality are very scarce. Only two studies have looked at CV events and DMARD use and reported reductions in CV morbidity with sulfasalazine and

leflunomide [Naranjo *et al.* 2008; van Halm *et al.* 2006]. There are, however, more studies that have looked at the effect of DMARDs on CV risk factors, such as DM, metabolic syndrome and dyslipidaemia. Hydroxychloroquine use in RA has been associated with improvement of lipid profiles, a reduced risk of developing DM and moreover exerts antithrombotic effects [Atzeni *et al.* 2010; Wasko *et al.* 2007]. Both leflunomide and cyclosporine can induce high blood pressure, hence are not DMARDs of first choice in patients with hypertension or increased CV risk [Kvien *et al.* 2002; Rozman *et al.* 2002].

Biologicals

TNF blockers are very effective drugs for RA and multiple other inflammatory diseases. Current available data show a positive but weaker effect of TNF blockers on CV disease occurrence, compared to MTX [Barnabe *et al.* 2011; Westlake *et al.* 2011]. Whether TNF blockers really exert a smaller CV risk reduction than MTX or the difference can be explained by other factors, such as study population and disease severity, is not clear yet. Altogether, it seems that TNF blockers have a positive influence on several CV risk factors, such as IR, HDL composition and endothelial function [Peters *et al.* 2012].

Tocilizumab (TCZ), an IL-6 inhibitor, also seems to have beneficial effects on endothelial function, despite the increase of total and LDL cholesterol. No data of the effect of TCZ on hard CV endpoints are available yet. The same counts for abatacept, a selective T-lymphocyte costimulation modulator and rituximab, a B-lymphocyte depleting agent. Since all of these medications are very effective at reducing inflammation, perhaps all of these biologicals exert CV risk reduction in RA patients who respond to treatment with these immunomodulating medication. However, this remains to be proven in the future.

Glucocorticosteroids

Glucocorticosteroids (GCs) are very powerful anti-inflammatory drugs and are commonly used as treatment for RA. They have strong anti-inflammatory properties which could mean that GCs have anti-atherosclerotic effects [Boers *et al.* 2003].

However, in the general population, therapeutic doses of oral GCs (≥ 7.5 mg/day) have been associated with increased CV disease and all-cause

mortality [Souverein *et al.* 2004; Wei *et al.* 2004]. There are several population-based cohort studies that have looked at the effect of GC use at hard CV endpoints, such as myocardial infarction and cerebrovascular disease in RA patients with conflicting results [Avina-Zubieta *et al.* 2011, 2013; Ruysse-Witrand *et al.* 2011]. Although data are not all congruent, GCs tend to have deleterious effects on several risk factors, as lipid profile, glucose tolerance, IR, blood pressure and abdominal obesity in RA [Avina-Zubieta *et al.* 2011, 2013; Dessein *et al.* 2004; Hafstrom *et al.* 2007; Panoulas *et al.* 2008a; Ruysse-Witrand *et al.* 2011; Toms *et al.* 2008]. For now it remains unclear whether GC use in RA has a beneficial or detrimental effect on CV risk, since no randomized controlled trials of glucocorticoids *versus* placebo in RA patients have been conducted. In addition, confounding by indication probably plays an important role in the outcomes of studies that have looked at the effect of GCs on CV mortality and morbidity [Davis *et al.* 2005]. The effect of GCs on the CV risk probably depends on several factors, such as the population of RA patients, the circumstances and way it is used, the dosage and treatment duration [Davis *et al.* 2007; Mazzantini *et al.* 2010]. When GCs are used to treat highly active RA, during a short period as a ‘bridging therapy’, with an oral dosage as low as possible or via an intramuscular or intra-articular injection and preferably in patients who do not have DM or hypertension, the CV benefit/risk ratio could perhaps be positive. It is advisable to check blood pressure and glucose levels before start and during GC treatment, especially if the patient has DM or hypertension and GCs are prescribed for a longer period.

NSAIDs

NSAIDs are often used as pain medication in many rheumatic diseases, including RA. NSAIDs and also cyclooxygenase-2 inhibitors (COXIBs) are known to increase the risk for hypertension and myocardial infarction [Bolten, 2006; Farkouh and Greenberg, 2009; Kearney *et al.* 2006a; Morrison *et al.* 2007; Schjerning Olsen *et al.* 2011; Trelle *et al.* 2011; van der Linden *et al.* 2009]. Moreover, a population-based Danish case-control study found that the use of NSAIDs was associated with a twofold increased risk of venous thromboembolism (VTE) [Schmidt *et al.* 2011]. The different NSAIDs seem to have different effects on CV risk and especially naproxen seems less harmful than the rest of the NSAIDs

[Kearney *et al.* 2006b; Solomon *et al.* 2008; Trelle *et al.* 2011]. Although there are not many studies that looked specifically at the effect of NSAIDs and COXIBs on CV risk in RA, one study showed no negative effects on CV mortality in patients with inflammatory polyarthritis [Goodson *et al.* 2009].

In summary, although evidence regarding the effects of NSAIDs on CV risk in RA is not conclusive, most data point to a negative influence, therefore the use of NSAIDs should be avoided if possible, at least in RA patients with known renal dysfunction, hypertension, heart failure or high CV risk. If NSAID use is unavoidable, blood pressure and renal function must be checked regularly and naproxen is probably the first choice. Furthermore, the combination of NSAIDs and aspirin is not advisable, since NSAIDs may impair the antiplatelet function of aspirin [Catella-Lawson *et al.* 2001; Hudson *et al.* 2005].

CV risk management

Although traditional CV risk factors may not explain the excess CV risk in RA, they do play an important role and should not be neglected when it comes to CV risk prevention. Since there are no CV risk assessment models for RA specifically, the national guidelines for CV risk management can best be used to determine CV risk and treatment, as advised by the EULAR guidelines for CV risk management in RA [Peters *et al.* 2010]. To adjust for the excess CV risk in RA, a multiplication factor of 1.5 is recommended in the presence of two of the following criteria: disease duration of more than 10 years, rheumatoid factor and/or anti-cyclic citrullinated peptide antibodies (anti-CCP) positivity or the presence of extra-articular manifestations. However, this multiplication factor needs validation, as there is indirect evidence that this multiplication factor improves CV risk estimation in RA. The same applies for the three above-mentioned criteria that are taken up in the EULAR recommendations to filter the RA patients that presumably have the highest CV risk. Although cumulative disease and therefore disease duration probably enhances CV risk, this does not mean CV risk treatment should only be started after 10 years of disease duration [Crowson and Gabriel, 2011]. Whether anti-CCP or rheumatoid factor positivity are real risk factors for CV disease or simply associated with CV disease because they are also associated with disease severity remains to be

investigated. This means CV risk could be underestimated in RA patients who do not qualify to two of the three criteria. In the Dutch multidisciplinary guidelines for CV risk management RA has been recognized as an independent CV risk factor, equal to DM, and CV risk estimations are calculated using the SCORE formula, adjusted for data from Dutch studies. For both DM and RA patients, 15 years are added to the actual age of all patients to express the excess CV risk burden. However, this is also based on expert opinion and indirect evidence and, hence, needs to be validated.

When it comes to CV risk treatment in RA the first step is lifestyle adaptation. The two key messages for the rheumatologist to patients are to stop smoking and to get physically active [Stavropoulos-Kalinoglou *et al.* 2012]. The second step involves the determination of the CV risk profile, including at least assessment of blood pressure and lipid profile. On the basis of these and other easily accessible data (e.g. age, sex, family history of premature CV disease, etc.) and the aid of calculators such as Framingham and SCORE, the 10-year CV risk of a particular RA person can be calculated. Primary prevention involving treatment with statins and/or antihypertensives is only necessary if this 10-year CV risk is above a certain value. For instance, in the Netherlands this would be a 10-year risk of CV morbidity or mortality of 20% or more, based upon a Dutch version of the SCORE.

Unfortunately, thus far no intervention trials with statins or antihypertensives and CV disease prevention in RA have been published. Based on data from epidemiological studies and *post hoc* subgroup analyses of large, secondary CV prevention trials, the effects of statins on cholesterol levels in RA patients appear to be at least equivalent to the effects of statins in the general population [Rollefstad *et al.* 2012; Semb *et al.* 2011, 2012]. In contrast, one recently published population-based longitudinal study found that the effectiveness of statins varied in chronic diseases, including RA, and tended to be less effective than in the rest of the population [Sheng *et al.* 2012b]. There are, however, numerous other studies that show beneficial effects of statins and angiotensin-converting enzyme (ACE) inhibitors on CV risk in RA [Charles-Schoeman *et al.* 2007; Flammer *et al.* 2008; Hermann *et al.* 2005; Maki-Petaja *et al.* 2007; Sheng *et al.* 2012a; Van Doornum *et al.* 2004]. Actually, in RA the effects of cardioprotective

agents might be more pronounced as the pleiotropic effects of statins, ACE inhibitors and angiotensin blockers include anti-inflammatory properties [Abud-Mendoza *et al.* 2003; Dagenais and Jamali, 2005; McCarey *et al.* 2004; Tikiz *et al.* 2005].

Randomized controlled intervention trials are necessary to assess the actual effect of statins, ACE inhibitors and other lifestyle intervention strategies on CV risk in RA.

Conclusion

RA patients are more susceptible to developing CV disease and therefore both tight disease control and also CV risk management in these patients is mandatory. An important issue is who is responsible: is it the rheumatologist or the primary care physician? Currently, this varies from country to country and even from practice to practice. Obviously, someone should take responsibility and this should be locally agreed upon.

Adequate CV risk management requires efforts from both the responsible doctor, whether this is the rheumatologist or the primary care physician, and the patient. A RA patient, who smokes, should quit smoking to decrease their CV risk substantially. However, it is up to the responsible doctor to point this out to the patient and to provide adequate support. This means periodically (annually) screening for CV risk factors, such as high blood pressure, blood glucose and cholesterol levels, but also to monitor physical activity, diet, waist/hip circumference and BMI. CV risk screening takes time, but is not difficult and can also be performed by adequately trained nurses. On the other hand, CV risk treatment and lifestyle advice takes a lot more time and effort and cannot be easily done by nurses practitioners, since it often involves prescribing medication. This requires innovative thinking and investing and is probably only feasible when rheumatologists work together with specialized nurses and other specialists, such as primary care physicians, internal doctors and cardiologists.

Since specific CV risk prediction models are not yet available for RA and the question remains which RA patients present the highest CV risk, it is advisable to start by screening all RA patients, preferably at an early stage of the disease and to treat them according to the existing national CV risk management guidelines. The enhanced CV

risk in RA can be expressed by a multiplier 1.5, as advised by the EULAR guidelines. Meanwhile, research will have to continue to try to discover the exact pathophysiological mechanism behind the relation of atherosclerosis and rheumatic inflammatory diseases, so that adequate CV risk formulas can be developed for this group of patients. Moreover, large randomized controlled trials are needed to determine whether lifestyle interventions, statins and antihypertensives work as well or even better in rheumatic patients, but also to once and for all give clarity regarding the effects on CV risk of GCs, NSAIDs and other medications that are often prescribed to RA patients.

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Conflict of interest statement

The author declares that there are no conflicts of interest.

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