Cardiovascular risk in rheumatoid arthritis: How to lower the risk?

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Summary

Patients with rheumatoid arthritis (RA) carry an excess risk for cardiovascular disease, which is comparable to the risk in patients with type 2 diabetes mellitus. The mechanisms involved are partly related to traditional cardiovascular risk factors, disease-associated inflammation and undertreatment of traditional cardiovascular disease (CVD) risk factors. Since atherosclerosis is an inflammatory disease, the auto-immune mediated inflammation observed in RA patients contributes to increased endothelial dysfunction, oxidative stress and activation and vascular migration of leukocytes. This concept is underscored by the CVD risk reduction that is seen by anti-inflammatory disease modifying anti-rheumatic drugs such as methotrexate and TNFα inhibitors. The evidence for underdiagnosis and undertreatment of traditional CVD risk factors in RA strengthens the potential benefit of structured CVD risk management in these patients. Current cardiovascular guidelines recommend screening and treatment of CVD risk factors in RA patients, without well defined treatment targets. At present, there is a lack of scientific evidence to establish treatment targets for CVD risk factors in RA. Therefore, expanding research regarding screening and treatment of traditional CVD risk factors in RA patients is needed.

Introduction

The evidence on the excess of cardiovascular disease (CVD) risk in rheumatoid arthritis (RA) has accumulated during the last two decades (1-3). It has been suggested that the prevalence of CVD in patients with RA is as high as in patients with type 2 diabetes mellitus (1). Interestingly, the increased CVD risk observed in RA may be independent from traditional risk factors for CVD (1, 4). These risk factors such as dyslipidemia, hypertension, smoking and obesity have been found in patients with RA in a similar frequency as in the general population (5, 6). It has been shown that these traditional risk factors contribute to the development of atherosclerosis in RA, but their presence alone can not fully explain the increased CVD risk (7, 8).

RA-specific factors, such as rheumatoid factor (RA) and/or anti-CCP positivity, joint erosions and extra-articular RA have been linked to the development of premature atherosclerosis in this condition. Since atherosclerosis is an inflammatory disease, it has been proposed that the increased inflammatory state of patients with RA explains, at least in part, the increased CVD risk (2, 4, 6, 7, 9). Furthermore, joint damage and physical inactivity are common in patients with RA and have been associated with an increased prevalence of CVD (8). In addition, RA is treated with different disease modifying drugs (DMARDs), with anti-inflammatory effects and with potential anti-antherosclerotic con-

sequences(8). To date, the exact contribution of all of these factors to the development of premature atherosclerosis in RA remains unclear. There is need for studies investigating the pathogenesis of atherosclerosis in RA and a well defined treatment protocol to lower the excess CVD risk is warranted. The purpose of this review is to provide an overview of the current evidence concerning the major determinants of excess CVD risk and the optimal CVD risk management in RA and to explore future scientific directions.

RA, inflammation and atherosclerosis

The formation of an atherosclerotic plaque takes place in different stages, which are driven by deposition and oxidation of lipids in the subendothelial space, activation of leukocytes and endothelial cells and finally thrombosis (Figure 1) (10).

All apolipoprotein (apo) B containing lipoproteins e.g. chylomicrons, chylomicron remnants, very low density lipoproteins (VLDL), intermediate density lipoproteins (IDL) and low density lipoproteins (LDL) can enter the subendothelial space via disrupted tight junctions between altered endothelial cells (11, 12). These lipoproteins can be taken up by macrophages converting them to foam cells. LDL needs to become oxidized (oxLDL) before it can induce foam cell formation, whereas chylomicrons and their remnants do not need modification (13). There is evidence that tumor necrosis factor alpha (TNFα) can directly stimulate the oxidation of LDL (14), and it has been observed that oxLDL levels are higher in patients with RA (15). Moreover, increased oxLDL concentrations have been linked to increased RA disease activity (15). The oxidation of LDL is catalysed by lipoprotein associated phospholipase A2 (Lp-PLA2) (16), but its precise contribution to the development of atherosclerosis in RA is uncertain since reduced levels of Lp-PLA2 have been observed in RA (17), whereas increased Lp-PLA2 activity has been found in association with CVD (18).

Lp(a), which is a pro-atherogenic lipoprotein that consists of an LDL-like particle and apo(a), can become oxidized and provoke an immune response similar to oxLDL. Apo(a) promotes thrombosis and inhibits fibrinolysis due to its homology with plasminogen (19, 20). An increase in Lp(a) has also been associated with inflammation, but data are inconsistent (21-23). Lp(a) is an independent risk factor for CVD (20) that may be disproportionally elevated in RA (19, 21, 22).

A key event in the development of both atherosclerosis and RA is inflammation (10, 24). Pro-inflammatory cytokines like TNFα and interleukin-6 (IL-6) are produced by the synovial tissue and play a key role in both the pathogenesis of RA and the development of atherosclerosis (25). One of the effects of TNFα is an increase in monocyte activation and cytokine release (25, 26). IL-6 causes T and B-cell proliferation and recruitment of neutrophils, all of which are involved in tissue damage in RA and development of the

atherosclerotic plaque and subsequent risk of plaque rupture (10, 25). Both, IL-6 and TNFα levels are elevated in RA (Table 1). The release of pro-inflammatory cytokines from the synovial tissue induces systemic inflammation triggering all these events (25). These circulating cytokines may also cause inflammatory changes in the adipose tissue resulting in an increased production of adipokines leading to a further enhancement of systemic inflammation (Table 1) (11, 27). Macrophages present atherogenic antigens against oxLDL or apolipoprotein (apo) B to CD4+ T cells, resulting in chemo attraction of leukocytes, T-cell proliferation and production of TNFα and interferon-γ (IFN-γ) (28, 29). These pro-inflammatory cytokines induce lipid uptake by macrophages (28, 30). In addition, macrophage activation leads to increased expression of endothelial leukocyte adhesion, resulting in higher adherence of monocytes and T-lymphocytes and secretion of pro-inflammatory cytokines such as IL1-α, IL1-β, and TNFα (31).

Specific CD4+ T cells, which are deficient for CD28, secrete high levels of pro-inflammatory cytokines and due to their capacity to infiltrate unstable atherosclerotic plaques can cause plaque rupture (32). CD4+ CD28- T cells are more often present in RA compared to healthy subjects (64% vs. 45%, P=0.02) (33). These cells also have been associated with increased extra-articular manifestations of RA and with endothelial dysfunction and subclinical atherosclerosis (34, 35). Eventually, all these processes contribute to a state of chronic inflammation and the premature development of atherosclerosis in RA (Figure 1).

RA specific alteration in high density lipoprotein function

High density lipoproteins (HDL) exert an atheroprotective effect via reverse cholesterol transport together with their anti-inflammatory, anti-oxidant and anti-thrombotic properties (36-38). Therefore, the pathofysiological association between HDL and CVD risk is complex. Several studies have shown that HDL function is impaired in RA and HDL may even express pro-inflammatory characteristics in up to 20% of RA patients (36).

Using mass spectrometry, 85 different proteins have been identified on HDL (37). Surprisingly proteomic profiling of HDL in active RA showed an increase in pro-inflammatory proteins including fibrinogen and several complement factors (C3, C9 and factor B) (39).

Interestingly, the cholesterol efflux capacity of HDL by the ATP-binding cassette transporter G1 (ABCG1), which is crucial for cholesterol efflux from hepatocytes to lipid poor HDL is impaired (40). These results were confirmed by other investigators (41). In RA higher serum levels of myeloperoxidase (MPO) correlated with a reduction in HDL cholesterol efflux capacity and this was accompanied by a reduction in the anti-oxidant function of HDL (41).

The RA-associated alterations in HDL function including its impaired cholesterol efflux capacity, a shift from anti-inflammatory to pro-inflammatory properties and a reduction in its anti-oxidant capacity may all contribute to the increased CVD (38).

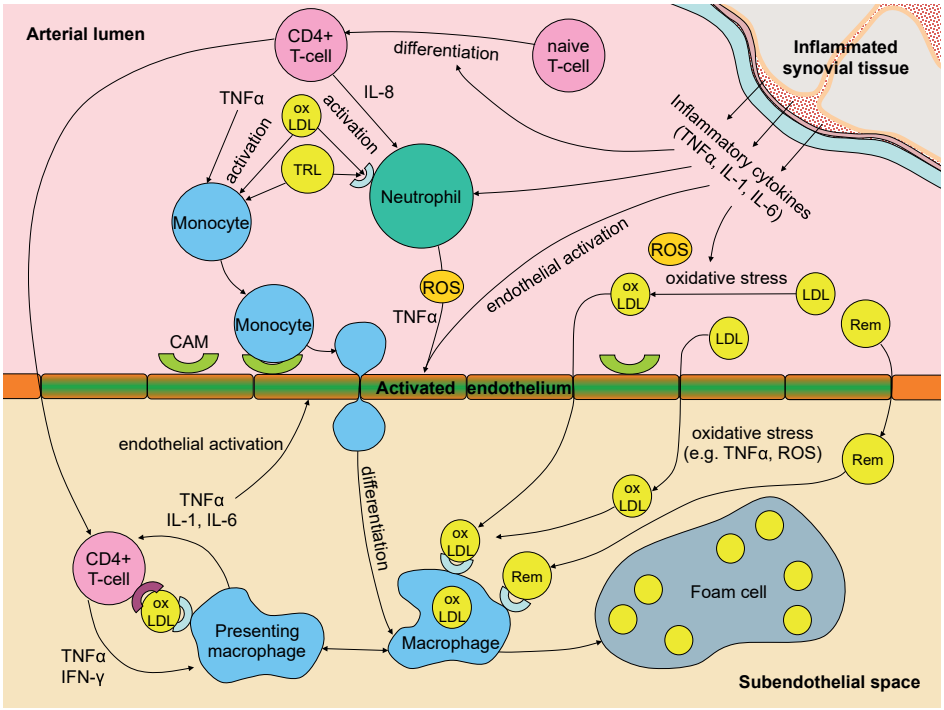

Figure 1. The inflammation-driven atherogenicity of rheumatoid arthritis (RA). Release of pro-inflammatory cytokines from the synovial tissue in RA has direct effects on systemic inflammation and the initiation of atherosclerosis. The released cytokines modulate the function of the endothelium, leukocytes and the oxidation of lipoproteins. Oxidation of low-density lipoproteins (LDL) can be initiated by TNFα and reactive oxygen species (ROS), inducing uptake by macrophages, converting them into foam cells when cholesterol influx exceeds cholesterol efflux. Native chylomicron remnants (Rem) can be taken up by macrophages without modification leading to foam cell formation. Macrophages present atherogenic antigens like ox-LDL to CD4+ T cells, which attracts additional leukocytes and leads to T cell proliferation and production of more TNFα and interferon-γ (IFN-γ). These proinflammatory cytokines, and triglyceride-rich lipoproteins (TRL), which include chylomicrons, chylomicron remnants and VLDL, activate monocytes and neutrophils, promote additional lipid uptake by macrophages and increased expression of cellular adhesion molecules (CAM) on the endothelium, which further attracts monocyte derived macrophages and T-lymphocytes and the expression of pro-inflammatory cytokines such as IL1-α, IL1-β, and anti TNFα (31). All these enhanced cascades in RA contribute to chronic inflammation and the premature development of atherosclerosis in RA.

Table 1. RA mediated changes in cellular adhesion molecules, cytokines and chemokines associated with the development of atherosclerosis

Cytokines, chemokines, adhesion molecules	Changes in RA	Atherogenic effect
CRP	25% of RA patients have CRP>10mg/L (4)	Activation of inflammatory cells (11)
TNFα	Increased with 62% (61)	Local and systemic inflammatory response (11) and increased VCAM-1 expression (146)
IL-6	Three-fold increased (61)	Local and systemic inflammatory response
E-selectin	20-43% increased (61, 147, 148)	Adherence of leukocytes to endothelium
sVCAM-1	May be increased, but data are inconsistent (61, 147-150)	Endothelial adhesion of leukocytes
sICAM-1	7-115% Increased (61, 147, 148, 150)	Endothelial adhesion of leukocytes
sTF	Almost three-fold increased (151)	Endothelial cells and leukocytes; initiates coagulation cascade
VEGF	Both an increase (149) as well as no change have been reported (61)	Endothelial permeability, pro-angiogenic
Angpt-2	Increased (149)	Upregulation of growth factors, cytokines and chemokines
MPO	33% increased (61)	Produces cytotoxic agents during respiratory burst of neutrophils

CRP = C-reactive protein; sTF = soluble tissue factor; Angpt-2 =angiopoetin-2; VEGF = vascular endothelial growth factor; TNFα = Tumour Necrosis Factor-α; ICAM-1 = intercellular adhesion molecule-1; MPO = myeloperoxidase; IL = interleukin; CAC = coronary artery calcium score

RA and markers of subclinical atherosclerosis

Atherosclerosis is a slowly progressive disease, which remains asymptomatic for many years before clinical CVD becomes evident. The first stages of subclinical atherosclerosis include endothelial dysfunction and the formation of fatty streaks and atherosclerotic plaques, which result in increased arterial stiffness and thickening of the intima and media of the arterial wall (42). There are several surrogate markers of atherosclerosis available such as flow mediated dilatation (FMD), augmentation index (AIx), pulse wave velocity (PWV), carotid intima media thickness (cIMT), the coronary artery calcification score (CAC) and computed tomography angiography (CTA). Data on these surrogate markers of atherosclerosis in RA have been summarized in Table 2. Overall, a decrease in FMD and an increase in AIx and PWV have been reported in RA-patients, suggesting endothelial dysfunction (43-48). Inflammation during the early course of RA, which is characterised by increased CRP concentrations, has been associated with increased arterial stiffness (measured by PWV and AIx) after 15 years of follow up (49). Several studies have shown increased cIMT and formation of plaques within the carotid artery in RA patients, which was already observed early in the disease when compared to non-RA

controls (43, 44, 50). However, a small cohort study of 105 RA patients did not identify cIMT as a predictor for future cardiovascular events (51). Recently, van Sijl et al. showed no differences in cIMT between RA patients and healthy controls. They described a maladaptive outward carotid arterial remodelling, which plays an important role in plaque instability and rupture, but this is not measured using the regular cIMT technique (52).

Both, in the general population and in RA patients the presence of carotid artery plaques increase the CVD risk (51, 53). The presence of vulnerable plaques, with a thin fibrous cap, a larger lipid core and infiltration of inflammatory cells, increases the CVD risk even more. Patients with RA have more carotid plaques than the general population (54, 55) and RA patients had more vulnerable plaques when compared to controls (56).

CTA can be used to visualize soft, non-calcified plaques and the presence of stenotic arteries like the coronary and carotid arteries. Since carotid plaques are recently shown to be a predictor of poor cardiovascular survival, CTA may provide additional accuracy in CVD risk prediction in RA.

With the improvement of Computed Tomography, CAC is an established, non-invasive instrument to measure the atherosclerotic burden. CAC has a high sensitivity and negative predictive power for obstructive coronary artery disease, but the specificity of CAC is limited (57). The ability of CAC to predict future coronary events in symptomatic persons has been proven in several studies (57). The severity of coronary artery calcification has been found to be increased in RA patients compared to controls (58, 59). However, Chung et al. did not find a significant difference in CAC between early RA patients (less than 5 years after diagnosis) and healthy controls (58). These results suggest that the development of coronary calcifications may depend on the duration of RA.

In addition to functional tests, also circulating markers of endothelial function such as E-selectin, vascular and intercellular cell adhesion molecules have been proposed as markers of endothelial dysfunction (42). Increased plasma levels of these molecules have been observed in RA, but there was no correlation between several adhesion molecules and CVD risk or subclinical markers of atherosclerosis (Table 1) (60-62).

Prevalence of traditional cardiovascular risk factors in RA

Research on atherosclerosis in RA patients for the last 25 years has focussed on inflammation (31). In our opinion, traditional CVD risk factors need to be addressed in RA since the prevalence in RA may be as high as in patients with diabetes mellitus, which is known for its increased frequency of hypertension and dyslipidemia (63).

As known, smoking is one of the most important environmental risk factors for the development of CVD, but smoking is also known as a risk factor for the development of RA and accounts for approximately 25% of the risk to develop the disease (64). This

Table 2. Overview of studies comparing RA to healthy controls regarding different surrogate markers of (sub)clinical atherosclerosis.

Study	RA Patients	Controls	RA disease duration	Evaluation Method	Results
Kocabay 2012 (46)	24	19	Newly diagnosed RA	PWV	Increased PWV in RA compared to controls
Provan 2011 (49)	113	86	No specific timing	PWV/AIx	Increased PWV and AIx in RA patients with high disease activity compared to controls and RA patients in remission.
Klocke 2003 (45)	14	14	No specific timing	AIx	Increased AIx in RA
Wong 2003 (47)	53	53	No specific timing	PWA	Decreased small and large artery elasticity and increased systemic vascular resistance in RA patients compared to controls
Chatterjee-Adhikari 2012 (44)	35	35	Disease duration 1 year	FMD	FMD was lower in RA compared to controls
Veselinovic 2012 (48)	52	30	No specific timing Mean disease duration 5.7±5.2 years	FMD	Decreased FMD in RA patients compared to controls
Sodegren 2010 (43)	79 baseline, 27 in follow-up	44	Symptoms <12months at baseline, follow-up after 18 months	FMD	No significant differences at baseline or at follow-up
Veselinovic 2012 (48)	52	30	No specific timing Mean disease duration 5.7±5.2 years	cIMT	Greater cIMT in RA patients compared to controls
Van Sijl 2012 (52)	96	274	No specific timing Mean disease duration 13±10 years	cIMT	No difference in cIMT, but a difference in parameters suggesting maladaptive outward remodelling of the carotid artery
Chatterjee-Adhikari 2012 (44)	35	35	Disease duration 1 year	cIMT	Increased cIMT in RA
Sodegren 2010 (43)	79 baseline, 27 in follow-up	44	Symptoms <12 months at baseline, follow-up after 18 months	cIMT	No significant difference at baseline. Increased cIMT after 18 months of follow up in RA
Hannawi 2007 (50)	40	40	Symptoms <12 months	cIMT	Significant higher cIMT in RA
Giles 2009 (59)	195	1073	None, median disease duration 9 (IQR4-17) years	CAC	Significant higher CAC in Male RA patients but not in female patients compared to controls
Chung 2005 (58)	141	86	Disease duration <5years (early RA) or >10 years (established RA)	CAC	CAC was higher in patients with established RA when compared to controls and patients with early RA

PWV = pulse wave velocity; Aix = augmentation index; cIMT = carotid intima media thickness; IQR = inter quartile range; CAC = coronary artery calcium score

risk for developing RA is dose dependent and even higher in anti-citrullinated peptide antibody (ACPA) positive RA patients (65-68). Smoking is therefore frequently seen in RA populations and may provide a potential bias in studies on RA and CVD. A recent meta-analysis by Sugiyama et al. showed that the prevalence of ever, current and past smokers in RA was as high as 50.6%, 26,5% and 26,3%, respectively (66).

There is also a complex relation between obesity, RA and CVD. In RA patients, obesity results in higher RA disease severity, increased swollen joint count and higher work disability (69, 70). Besides the negative impact on RA itself, obesity is associated with cardiovascular morbidity and mortality (71, 72). Similar associations between obesity and CVD have also been found in RA (70, 73, 74). A different effect of a low body mass index (BMI) on CVD mortality in RA has also been suggested. The incidence in CVD mortality for RA patients with a BMI below 20 kg/m^2 is increased compared to the general population (75). A possible explanation of this increased CVD risk is that a low BMI in RA patients may indicate the presence of rheumatoid cachexia. This condition reflects predominantly a loss of skeletal muscle and is, among others, mediated by an increased production of pro-inflammatory cytokines (76). Furthermore, RA patients are less active than their healthy counterparts and physical inactivity in RA has been associated with an increased arterial stiffness (77).

Several studies have shown an underdiagnosis and undertreatment of traditional CVD risk factors, such as hypercholesterolemia and hypertension in RA (78-80). Hypertension is common in RA, with a prevalence ranging from 57% to 70.5% and hypertension is frequently not optimally controlled in RA (78, 79). In these studies, 40% to 45% of RA patients with hypertension did not reach target blood pressure levels as defined in current therapeutic guidelines (i.e. a systolic blood pressure of ≤ 140mmHg and/or a diastolic blood pressure of ≤ 90mmHg) (78, 79). Panoulas et al. showed that 32% of RA patients with target organ damage (defined as described in the European guideline for management of arterial hypertension) had undiagnosed hypertension (78). RA itself can be seen as a risk factor for the development of hypertension. As described earlier, the RA associated inflammatory state may activate the endothelium, which can lead to endothelial dysfunction, inhibition of the vasodilatory function, vascular calcification and therefore increased central blood pressure (31, 45, 81).

In the inflammatory state of RA, cholesterol levels, which include HDL-C, LDL-C and total cholesterol, may be suppressed (82). However, HDL-C concentrations are more suppressed in RA than the atherogenic LDL-C, which results in a more atherogenic lipid profile (29, 82, 83). This might be the explanation why several investigators found that lower cholesterol levels were associated with increased CVD risk in RA (84, 85). Furthermore, these studies did not take into account the heterogeneity of HDL function as described earlier. Interestingly, a decrease in total cholesterol and LDL-C, but not in HDL-C, can already be observed 5 years prior to the diagnosis of RA (86). The mechanism

behind these changes, which are different from the changes during active RA disease, is not fully understood. It is believed that the inflammatory state, which is present prior to diagnosis, plays an important role (86). Serum apo B levels and the number of circulating chylomicrons are higher in RA patients when compared to age matched healthy controls (87). Knowlton et al. measured lipid profiles as well as apolipoproteins in 152 RA patients and determined the coronary artery calcification score at baseline and after 3 years of follow-up. They showed that RA patients with progression in CAC had significantly higher total cholesterol/HDL-C, higher levels of apo B and a higher number of circulating chylomicrons compared to RA patients that did not show any CAC progression (88). No differences in plasma apo A-I levels were found.

Drug related cardiovascular risk factors in RA

Non-steroidal-anti-inflammatory-drugs (NSAIDs) and oral glucocorticoids are widely prescribed in RA, which are both associated with the development of hypertension (78, 89-91). A recent meta-analysis by Trelle et al. evaluated several NSAIDs in relation to myocardial infarction, stroke, cardiovascular death. They found that cardiovascular profiles of individual NSAIDs varied considerably. Overall naproxen seemed less harmful regarding cardiovascular risk when compared to other NSAIDs (91). The exact mechanism by which NSAIDs increase the risk of a cardiovascular event is not fully understood. The degree of blocking of cyclooxigenase-2 is suggested to play an important role in the cardiovascular risk profile of an individual NSAID (92, 93).

Regarding glucocorticoïds, Aviña-Zubieta et al. recently showed an increased risk for myocardial infarction in current users (94). No significant correlation between cerebral vascular disease and the use of glucocorticoïds was found (95). The contribution of glucocorticoïds to CVD risk is believed to be dose dependent (94).

Cardiovascular risk prediction in RA

The most widely used risk scores for the prediction of CVD are the Framingham Risk Score and the SCORE model (96, 97). These risk models are based on traditional CVD risk factors in non-high risk populations, but they do not take into account the excess CVD risk observed in RA patients. Because of the mounting evidence regarding the excessive CVD risk in RA and the lack of precise management and risk stratification in RA, the European League Against Rheumatism (EULAR) published in 2010 recommendations for CVD risk management specifically for RA and other forms of inflammatory arthritis (98). EULAR recommends an annual risk assessment for all RA patients using national

guidelines. A first attempt to adapt the traditional SCORE model (97) and Framingham Risk Score (96) for RA patients was made, to correct for the underestimated CVD risk (Table 3). This modification includes a multiplication of the measured CVD risk (with the use of SCORE or the Framingham Risk Score) by a factor of 1.5 for patients with RA and two of the following three criteria: RA disease duration >10 years, the presence of rheumatoid Factor (RF) or anti-CCP and/or presence of severe extra-articular manifestations (98). However, the criterion of disease duration of >10 years is debatable because recent publications have shown that the risk for cardiovascular morbidity and mortality is already increased shortly after the diagnosis of RA, which underscores the importance of early intervention (43, 99). In addition, Finck et al. showed that the addition of RF or anti-CCP to the traditional FRS did not improve the accuracy of CVD risk prediction in RA patients (100). Despite these shortcomings, the EULAR has made a first attempt to improve CVD risk assessment in RA. In our opinion, clinical trials are necessary to establish the validity of these recommendations.

The 2011 Dutch guideline for CVD risk management also suggests to adapt the standard risk assessment tool in RA patients (101). It was advised to add 15 years to the age of RA patients when establishing their risk according to the SCORE table (Table 3). However, once again evidence for this approach is lacking. The recently developed guideline for the management of dyslipidaemias from the European Atherosclerosis Society (EAS) and European Society of Cardiology (ESC) recognises RA as a risk factor for the development of atherosclerosis but does not provide specific recommendations for CVD risk assessment in the case of RA (Table 3) (98, 102). Therefore, further research to develop an accurate risk assessment tool with treatment recommendations aimed at RA is necessary. In the mean time risk stratification might be improved by the combination of risk assessment tools with atherosclerotic imaging.

Table 3. Overview of national and international guidelines for CVD risk assessment in RA patients.

	Adaptations to current CVD risk assessment
EULAR	CVD risk* x 1,5 when at least two of following characteristics are present: *- > 10 years RA disease duration* *-RF and/or anti-CCP positivity* *- severe extra articular disease*
Dutch guideline for CVD risk management	Age +15 years for all RA patients**
EAS guideline for dyslipidaemia	No adaptations

* According to SCORE and/or Framingham

** For assessment of CVD risk according to SCORE

Treatment of traditional cardiovascular risk factors in RA

Treatment of traditional CVD risk factors is the cornerstone of successful CVD risk reduction in the general population (102). In our opinion, awaiting further studies, this is also the case in RA. Treatment of CVD risk factors includes both, lifestyle modification and pharmaceutical interventions.

Exercise is in the general population an important behavioural strategy for CVD prevention, but also in RA patients (103). It has been shown that an individualized exercise training program, which consisted of a 6 months tailored aerobic and resistance exercise intervention, improved endothelial function in patients with RA (104). RA guidelines emphasize indeed the role of exercise and physical activity, but they do not provide clear recommendations (105). More studies are necessary to investigate the effect of exercise in reducing CVD risk in RA and to provide clear recommendations for RA patients. Dietary advice may include a traditional low-fat diet or a Mediterranean diet. The Mediterranean diet is rich in omega-3-fatty acids as opposed to predominantly omega-6-fatty acids in western diets and has been shown to reduce cardiovascular risk (106). Besides their protective role in cardiovascular disease, omega-3-fatty acids reduce inflammation in chronic inflammatory diseases such as RA (107, 108).

Pharmaceutical interventions are the next step in CVD risk prevention after improving lifestyle. A recent study showed that patients with inflammatory joint disease receiving statin therapy had a comparable decrease in cholesterol levels and CVD risk reduction as patients without inflammatory joint disease (109). This is further illustrated by De Vera et al. who showed that discontinuation of statin therapy in RA patients who already used statins was associated with increased cardiovascular mortality (HR 1.41, 95% CI 1.02-1.96) (110). Statin therapy successfully lowers LDL-C and CVD risk (Table 4), but the benefit of treatment in primary prevention depends on age and other risk factors. Uncertainty exists when to initiate lipid lowering therapy in RA patients for primary prevention. The Dutch guideline for CVD risk management 2011 recommends to treat RA patients similarly as patients with diabetes mellitus, suggesting early and intensive lipid lowering therapy with LDL-C treatment targets of 2.5 mmol/l (101). Recently, Rollefstad et al. showed that a structured approach and treatment to target is possible in patients with inflammatory joint disease since 90% of the study population (n=426) was successfully treated to lipid targets (80).

Besides their lipid lowering effect, statins also have anti-inflammatory properties (111, 112). The Jupiter trial showed that rosuvastatin significantly reduced the incidence of major cardiovascular events in apparently healthy persons without hyperlipidemia, but with elevated high-sensitivity CRP levels (112). These data suggest that the beneficial effects of statins are more than just LDL-C lowering and that the anti-inflammatory role of these drugs may also contribute to CVD risk reduction. However, others have shown that, in non-RA patients, most of the CVD risk reduction by statins can be accounted for

by the LDL-C reduction and not by these so called (anti-inflammatory) pleiotropic effects (113). In addition to the lipid lowering effect, reduction of RA disease activity on statin therapy has also been described (114). El Barbary et al. showed that atorvastatin in RA resulted in a marked reduction in RA disease activity, a more advantageous atherogenic index and improved endothelial function (115). However, the opposite has also been described. A recent study with an arthritis mouse model by Vandebriel et al. showed that treatment with atorvastatin or pravastatin accelerated arthritis onset and resulted in a higher prevalence of arthritis compared to non-statin using mice (116). These results confirm previous reported associations of statin use and the development of RA in observational studies (117). Whether these associations outweigh the beneficial effect of statins on atherosclerosis in RA is not yet clear. Prospective studies on the use of statins in RA are lacking. Therefore, we feel that routinely prescription of statin therapy to RA patients regardless their lipid profile is not justifiable. Whether the treatment target for LDL-C of 2.5mmol/L is justifiable, remains to be investigated in prospective studies.

Strict regulation of blood pressure with treatment targets of a systolic blood pressure ≤140 mmHg have been recommended in all patients including patients with RA (101), although prospective data on strict blood pressure regulation in RA patients are lacking. It is important to perform blood pressure measurements on a routine basis to properly diagnose hypertension in RA patients (118). Especially since small increases in systolic blood pressure (1-5 mmHg) have already been associated with an increased CVD risk (119). However, there are limited data available regarding the preferred antihypertensive agents in specifically RA. There is some evidence that angiotensin converting enzyme (ACE) inhibitors may be beneficial in RA. Flammer et al. showed that 8 weeks of treatment with ACE-inhibitors improved endothelial function (assessed by FMD of the brachial artery) in RA patients, together with a reduction in CD40, which is an important inflammatory mediator and member of the TNFα superfamily (Table 4) (120).

Current guidelines recommend to start pharmaceutical interventions early for traditional CVD risk factors. However, since the exact contribution of the classical CVD risk factors to the development of CVD in RA is still unclear and specific RA-related evidence for initiating CVD risk management is lacking, we feel that more evidence on the beneficial effect of early and aggressive treatment of traditional CVD risk factors is necessary before starting widespread primary prevention. Nevertheless, much improvement may already be achieved with routine blood pressure monitoring and adequate treatment of existing hypertension using general guidelines for hypertension.

Although the incidence of both arterial and venous thrombo-embolism is increased in RA (121, 122), the use of anti-platelet therapy in RA to decrease CVD risk has not been investigated. The concomitant use of NSAIDs might be a complicating factor, since some diminish the effect of aspirin, while others have significant anti-platelet effects (123). Further studies are needed to clarify the role and safety of anti-platelet therapy in RA patients.

Table 4. An overview of major studies, which investigated the relation of RA and non-RA medication on atherosclerosis in RA.

Drugs	Evidence for its association with atherosclerosis in RA (Studies in both humans and animals)	Biological mechanism
NSAIDs	Meta-analysis of human studies: higher risk of CVD. Differences between different NSAIDs (91) Animal studies not available	Not fully understood. Inhibition of COX-2 is believed to play a role (92, 93)
Hydroxychloroquine	Case-control study: Reduced cardiovascular risk (132) Animal studies not available	Improvement of dyslipidemia has been proposed.
Methotrexate	Several studies (case control, cohort): cardiovascular risk reduction (8, 132), but no reduction has also been described (135) Animal studies not available	Potentially due to its anti-inflammatory properties, but it may also be drug specific.
Anti-TNFα	Several case-control studies: cardiovascular risk reduction (130, 132) Animal studies not available	Anti-inflammatory effects Improvement of endothelial function
Rituximab	Conflicting data; small groups Human: improvement of arterial stiffness as well as no improvement has been described. However, most data suggest a decrease of atherosclerosis progression (140-142) Animal studies not available	Improvement of lipid profile and endothelial function has been suggested.
ACE-I/AT2 antagonists	Small randomized trial: cardiovascular risk reduction (120, 152) ' Animal study (153)	Improvement of endothelial function Dose dependent depression of TNFα
Statins	Randomized trial: Cardiovascular risk reduction (109) Animal study (154)	Reduction of LDL-C, which is comparable to the reduction in non-RA patients. Improvement of endothelial function. Mild anti-inflammatory effects. Anti-inflammatory effects
Fibrates	Small pilot cohort study (155) Animal studies not available	Decrease in CRP and IL-6 Decrease of TC and TG, increase of HDL-C
PUFA's	Meta-analysis in humans: a possible reduction in cardiovascular risk Animal study: preventive against atherosclerosis (156, 157)	Decrease of NSAID use. Less necrosis and collagen in the atherosclerotic plaque. Reduction of IL-10. Anti-inflammatory properties
Fishoil	Small cohort study: Reduced cardiovascular risk Animal studies not available	Several mechanisms such as increase of n-3- fatty acids and decrease of n-6-fatty acids, but also a concomitant decrease in NSAID use (158)

NSAIDs = non-steroidal anti-inflammatory drugs; COX = cyclo-oxygenase; ACE-I = angiotensin converting enzyme inhibitor; AT2 = angiotensin 2; TC = total cholesterol; TG = triglycerides; PUFA = poly-unsaturated fatty acids; IL = interleukin; TNF = tumour necrosis factor

The influence of DMARD therapy on lipid levels

Intensive DMARD therapy results in a better suppression of disease activity and therefore a suppression of the general inflammatory state. There is a complex interplay between traditional CVD risk factors and the risk caused by the inflammatory burden at the lipid level. Since DMARD therapy decreases inflammation it is not surprising that dyslipidemia may improve upon DMARD therapy. Hydroxychloroquine decreases LDL-C and total cholesterol levels (124). Long term treatment with TNFα inhibitors is significantly associated with increased HDL-C, total cholesterol and triglyceride levels and may be associated with a decreased apo B to apo A-I ratio (125-127), but there is no significant change in LDL-C and the atherogenic index (125, 126). Recently Navarro-Milán et al. showed an increase in HDL-C, LDL-C and total cholesterol shortly after treatment initiation with methotrexate alone or in combination with etanercept or hydroxychloroquine and sulphasalazine (128). Interestingly, increased HDL-C levels were only observed in RA patients who responded to DMARD therapy (93% methotrexate, 14% other DMARDs) in contrast to non-responders who did not show a beneficial effect on HDL-C levels (129). This illustrates that change in lipid levels upon DMARD therapy correlates with disease activity.

DMARD treatment and cardiovascular disease

Over the last years a growing number of studies on CVD risk reduction by different individual DMARDs has been published. Numerous studies have described a beneficial effect on CVD in RA by methotrexate (MTX) and biologicals, showing a decrease in cardiovascular morbidity and mortality (Table 4) (8, 130-132). However, the reduction in CVD by TNFα inhibitors is not as consistently seen as with studies of MTX. Improvement of subclinical and clinical atherosclerosis by DMARDs has been observed as well. Treatment with MTX, during one year, resulted in a reduction in cIMT, reflecting a reduction in atherosclerosis (133). A systematic review concerning MTX and CVD in RA showed strong evidence that the use of MTX was associated with reduced cardiovascular morbidity and mortality (134). However, a recent cohort study did not confirm this finding (135). It should be noted that all 10.156 included RA patients in this study were receiving various DMARDs. It is not clear whether lowering the CVD risk by MTX is caused by reducing RA disease activity or by a reduced inflammation in general. Therefore, it remains to be shown whether MTX will lower cardiovascular event rates in non-RA patients. The first trial addressing this question is the ongoing Cardiovascular Inflammation Reduction Trial (CIRT) (www.clinicaltrials.gov; trial number NCT01594333). Because of the important role of TNFα in the development of atherosclerosis, most studies investigated

the effects of anti-TNFα therapy in relation to CVD (136). The addition of infliximab to MTX for 12 weeks resulted in improved FMD (137). One-year treatment with anti-TNFα therapy in patients with inflammatory arthropathies including RA resulted in reduced arterial stiffness and less progression in cIMT when compared to RA patients not receiving anti-TNFα therapy (131, 138). A longitudinal cohort study reported that RA patients using anti-TNFα showed a reduction in cardiovascular events compared to RA patients using other DMARDs than anti-TNFα (HR 0.39; 95% CI 0.19-0.82) (135). A recent systematic review showed that in most studies, anti-TNFα therapy reduced the likelihood of CVD in RA (139). The balance of evidence suggests that TNF-α antagonists have a beneficial effect on cardiovascular risk (Table 4). However, larger and more robust studies are warranted to confirm recent findings. The effects of anti B-cell therapy, i.e. Rituximab, remains inconclusive (140, 141). Several studies showed improvement of endothelial function after treatment with rituximab (140, 142, 143), but others did not show (141). These contradictory results may be explained by the role of B-cells in the development of atherosclerosis since immature B-lymphocytes (B1) seem to be protective against atherosclerosis (144) and mature B-lymphocytes (B2) may aggravate atherosclerosis (145).

Conclusion

Current knowledge suggests that RA patients need to be routinely screened for CVD risk factors. RA patients will benefit from routine cardiovascular screening since there is much evidence of underdiagnosis and undertreatment of traditional CVD risk factors in RA. The first steps to improve CVD risk assessment in RA are being taken in national as well as international guidelines with the adaptation of traditional risk assessment tools such as the SCORE or Framingham risk score. Risk stratification may be further improved by carotid plaque detection with ultrasound in all RA patients. Randomized controlled trials are needed to evaluate the effects of the suggested strict cardiovascular treatment versus current practise. It would be interesting to investigate treatment of RA patients with lipid lowering drugs to the same extent as current practise in patients with diabetes mellitus of CVD. Finally, a validated CVD risk assessment tool for RA should be developed. Considering current evidence a routinely referral of RA patients to a vascular outpatient clinic for cardiovascular screening and treatment seems advisable.

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