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Cardiovascular Risk Factors in Chronic Inflammatory Rheumatic Diseases: Modern Assessment and Diagnosis

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Abstract: The current view is that systemic inflammation, which is specific to all chronic inflammatory rheumatic diseases (CIRD), accelerates atherogenesis; this hypothesis is supported by the high cardiovascular (CV) morbidity and mortality rates and the high prevalence of all atherosclerosis stages and complications in CIRD patients. The assessment of traditional CV risk factors underestimates the actual risk in patients with CIRD. A comprehensive evaluation and follow-up of both traditional and non-traditional CV risk factors, as well as the correct classification of risk reduction categories are necessary. Imaging techniques (*e.g.* carotid intima-media thickness and flow-mediated vasodilation) can be used for the early diagnosis of endothelial dysfunction. Immunologic and metabolic markers (anti-cyclic citrullinated peptide (CCP) antibodies, IgM rheumatoid factor, circulating immune complexes, proinflammatory cytokines, TH0/TH1 lymphocytes and homocysteine) may be involved in the atherosclerotic disease development specific to CIRD. A modern therapeutic approach should include the early diagnosis of endothelial dysfunction and atherosclerosis, treatment of CIRD, specific medication designed to control atherosclerosis, changes in patient lifestyle and periodic follow-ups. The assessment and diagnosis of traditional and non-traditional CV risk factors, followed by aggressive prevention and therapy, are necessary to achieve efficient control over the inflammation, immunologic and metabolic disorders specific to CIRD.

Keywords: Atherogenesis, immune-mediated inflammatory diseases, cardiovascular risk factors, chronic inflammatory rheumatic diseases.

INTRODUCTION

Atherogenesis is a dynamic inflammatory process that occurs during all the stages of atheromatous plaque formation and the resulting complications [1]. Systemic inflammation, which is associated with all chronic inflammatory rheumatic diseases (CIRD), accelerates atherogenesis [2]. This concept is supported by the high cardiovascular (CV) morbidity and mortality rates in CIRD patients, the high prevalence of all atherosclerosis (ATS) stages and the resulting complications (endothelial dysfunction, carotid atherosclerotic plaques, fatal/non-fatal acute myocardial infarction (AMI) and stroke), and the recurrence of CV events after traditional CIRD risk factors have been corrected.

The pathogenic mechanisms leading to accelerated ATS in CIRD are complex and have not been fully elucidated. Both an increase in the prevalence of some of the traditional risk factors, as well as the appearance of new CV risk factors, which are the result of systemic chronic inflammation and/or various drug therapies, occur during ATS in CIRD. The occurrence of CV events 10 years earlier in CIRD diagnosis, especially in rheumatoid arthritis (RA), suggests that joint inflammation, together with the immunologic and metabolic disorders specific to these conditions, are independent CV risk factors [3]. The relationship between ATS and chronic inflammation has been studied, especially in rheumatoid polyarthritis. Clinical evidence has shown that CV mortality and morbidity rates are high in this chronic inflammatory pathology because of an accelerated coronary and non-coronary ATS process [4].

DEMOGRAPHIC FACTORS

CV risk factors in CIRD are listed in Table **1**. There is a relatively high risk of CV events for patients with RA in the young age group, making prevention strategies important. Women with RA run a risk of AMI that is 2× higher than women not suffering from RA [3]. This risk is also higher in men, especially in young men who are more prone to spondyloarthropathies.

TRADITIONAL CARDIOVASCULAR RISK FACTORS

Hypertension. The prevalence of hypertension (HTN**)** is 3.8-73% in RA. Despite its high prevalence, HTN is often both underdiagnosed and undertreated in RA patients [5]. In addition, issues such as systemic inflammation, sedentary

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Table 1. Cardiovascular risk factors in CIRD

Demographic risk factors	Traditional risk factors	Non-traditional risk factors	Medication for non-traditional factors
Age M > 45 years F > 55 years Male sex Ethnic origin	HTN DM Smoking Obesity Insulin resistance Sedentary life Dyslipidemia (↑TC, ↑LDL-C, ↓HDL-C) Framingham score ↑homocysteine Premature menopause Generic risk (premature coronary disease)	Onset age Disease duration Activity and osteoarticular destruction (radiological score) Inflammatory markers: CRP, Fg, CK, IL-6, TNF, IL-1, CD40/CD40L Immune factors: antibodies antiPL (aCL, aβ2GPi), anti-oxLDL, anti-oxLDL/β2GPi, anti-HSP, anti-CEA Inflammation and endothelial dysfunction Coagulation abnormalities: Fg, PAI-1, homocysteine Metabolic factor: pro-atherogenic lipid profile Genetic predisposition (HLA) Chronic kidney condition	Glucocorticoids - pro-atherogenic effect: cumulated high dose > 10 mg/day - anti-atherogenic effect: dose ↓ NSAIDs MTX HCQ anti-TNFα

aCL = anticardiolipin, aβ2GPi = antibeta2-glycoprotein I, anti-oxLDL = anti–oxidized LDL, CD40/CD40L = co-stimulatory proteins found on antigen presenting cells, CEA = carcinoembryonic antigen, CIRD = chronic inflammatory rheumatic disease, CK = creatine kinase, CRP = C reactive protein, DM = diabetes mellitus, F = female, Fg = fibrinogen, HCQ = hydroxychloroquine, HDL-C = high density lipoprotein cholesterol, HLA = human leukocyte antigen, HTN = hypertension, HSP = anti-heat shock protein, IL-1 = interleukin 1, IL-6 = interleukin 6, LDL-C = low density lipoprotein cholesterol, M = male, MTX = methotrexate, NSAIDs = non-steroid anti-inflammatory disease, anti-PL = anti-threonyl-tRNA synthetase, PAI-1 = plasminogen activator inhibitor-1, TC = total cholesterol, TNF = tumour necrosis factor.

lifestyle, obesity, and medication (non-steroid anti-inflammatory drugs [NSAIDs], glucocorticoids, and disease-modifying anti-rheumatic drugs [DMARDs] like leflunomide or cyclosporine) prevent adequate blood pressure control in patients with CIRD [6]. The mechanism by which systemic inflammation stimulates HTN is linked to high C reactive protein (CRP) levels. Increased CRP levels reduce nitric oxide (NO) production in endothelial cells, which causes vasoconstriction, elevated endothelin-1 production, leukocyte adhesion, platelet activation, oxidation, and thrombosis [6]. CRP also regulates Ang-1 receptor expression and influences both the renin-angiotensin system and plasminogen activator inhibitor-1 induction, which increases fibrinolysis and atherothrombosis [5]. Therefore, CRP plays a dual role in HTN. In HTN, the hemodynamic flow and elevated vascular parietal stress produce more adhesion molecules and inflammatory gene expression by endothelial cells, as well as a triggering of the inflammatory cascade in the arterial wall, with pro-inflammatory cytokine production and an acute phase response that includes higher CRP levels [5].

Dyslipidiemia: There is an altered lipid profile, called a proatherogenic lipid profile (decreased high-density lipoprotein [HDL] cholesterol, increased low-density lipoprotein [LDL] cholesterol, and increased triglycerides), in RA, systemic lupus erythematosus (SLE), and Sjogren's Syndrome [7, 8]. The HDL cholesterol is unable to protect the LDL cholesterol against oxidation (pro-inflammatory HDL) [3, 7]. The body fat mass index of patients with CIRD is also higher than expected for the same body mass index (BMI), age, sex and ethnic group [9]. The pathophysiological mechanism for this seems to involve the pro-inflammatory cytokines (tumor necrosis factor [TNF] and interleukin 6 [IL-6]), which mediate rheumatoid cachexia development, involuntary muscle mass loss, and progressive body fat mass increase (especially around the waistline) [9-11]. Special attention has been paid to anti-TNF therapy; however, its influence on the lipid profile is a controversial matter. While some studies have revealed an improvement in dyslipidaemia and a disproportionate increase in the total and HDL cholesterol levels, others have claimed that this therapy caused a "more atherogenic" lipid profile [12]. Acute and chronic inflammation may lead to structural and functional changes of HDL, which render the particles proinflammatory. It seems that therapeutic agents that increase HDL levels may restrain the transformation of normal HDL into dysfunctional HDL [13]. The Framingham score is higher in patients diagnosed with RA than in the general population (the Framingham score includes age, total and HDL cholesterol, blood pressure and smoking habit) and is associated with subclinical ATS (expressed by a higher coronary artery calcium score) [14]. However, this does not apply in SLE patients, despite also having accelerated ATS [15].

Diabetes mellitus (DM): The prevalence of DM in CIRD is controversial. Research conducted as early as the 1980's revealed a positive association between CIRD and insulin resistance from systemic inflammation or glucocorticoid therapy. Control of systemic inflammation using DMARDs and an adequate diet improves insulin resistance

[16]. An increased prevalence of metabolic syndrome (defined by central obesity, HTN, dyslipidaemia, and insulin resistance) has been reported in RA patients, and a direct correlation has been found with intima-media thickening in the carotid artery [17].

Smoking. Smoking is a known risk factor for RA and is associated with disease activity and severity (it is associated with seropositive RA) [11]. It is also associated with subclinical ATS, which suggests that the CV impact of smoking in RA patients is much greater than in the general population [11].

Sedentary lifestyle: Patients with CIRD are prone to a sedentary lifestyle because of their chronic musculoskeletal condition (pain, arterial stiffness, ankylosis, misalignment, tendon retraction *etc*). This lack of physical exercise leads to higher incidence rates for other CV risk factors: high BMI, central adiposity, HTN and dyslipidaemia [5, 12].

NONTRADITIONAL (INFLAMMATION-RELATED) CV RISK FACTORS

CIRD and vascular ATS share similar pathophysiological mechanisms that include pro-inflammatory cytokines, TNFα, and auto-reactive T cells [7]. Systemic inflammation can induce vascular lesions and endothelial dysfunction through changes in NO production and secondary dyslipidaemia and can trigger the coagulation cascade [7]. In addition to ATS plaque formation, the inflammatory process also causes complications from these phenomena (namely plaque rupture and thrombosis) [7]. The pro-atherogenic effect of chronic systemic inflammation can be seen at different levels: i) the endothelial dysfunction from the imbalance between the endothelial and inducible NO synthases (a decrease in eNOS and an increase in iNOS), and, ii) the consequent excessive production of NO, imbalance in certain prostanoids, proatherogenic lipid profile support, and coagulation cascade activation (platelet activation and vascular inflammation-mediated secretion of adhesion molecules, chemokines, and coagulation factors) [7]. The predisposition for vascular dysfunction in CIRD is mediated by several paths: pro-inflammatory cytokines (TNFα, IL-1, and IL-6), acute phase reactants (erythrocyte sedimentation rate [ESR] and CRP), chemokines (monocyte chemoattractant protein-1), thrombosis, adhesion molecules, cytotoxic response, insulin resistance, oxidized lipids and hyperhomocysteinaemia. All of these cause vascular wall destruction, endothelial cell apoptosis, decreased NO production, increased platelet aggregation, smooth muscle cell proliferation, and endothelial dysfunction and premature ATS [18].

Inflammation markers: Inflammation markers (CRP and ESR) are important indicators of the activity and severity of the disease, as well as CV mortality predictors in patients with CIRD [18]. CRP, the most studied inflammatory marker over the last few years, is produced in the liver in response to an inflammatory cytokine stimulus (IL-6). It is a coronary risk identification factor in asymptomatic patients [19]. Moreover, CRP is a key factor in endothelial dysfunction because it interacts with endothelial and inflammatory cells, increasing the pro-inflammatory cytokine level, adhesion molecule expression and oxidative stress [20]. CRP values are higher in RA patients than those proposed for CV risk stratification in the general population. Therefore, determination of CRP levels does not seem to be useful for CV risk stratification and choosing the best therapy for patients with RA and CV disease [21]. Another measure for CV risk could be ESR, which was found to be higher immediately after heart failure onset in research conducted on patients with RA [22]. Additional inflammatory markers that could act as CV risk predictors are shown in Table **2**.

Table 2. Predictive markers for inflammatory cardiovascular risk

Predictive markers for inflammatory cardiovascular risk
Adhesion molecules (vascular cellular adhesion, inter-cellular adhesion, and leukocyte-endothelium adhesion)
Cytokines
Acute phase reactants • Fibrinogen • Serum amyloid A • CRP • ESR
Leucocyte count

CRP = C reactive protein, ESR = erythrocyte sedimentation rate

Autoantibodies: Some autoantibodies specific to systemic autoimmune diseases are correlated with endothelial activation and dysfunction, which is conducive to premature ATS development. The following 5 processes characterize endothelial activation: loss of vascular integrity, elevated leukocyte adhesion molecule expression, conversion of an antithrombotic phenotype into a prothrombotic phenotype, cytokine and chemokine production and human leukocyte antigen upregulation [23]. Endothelial activation has been indirectly shown in some CIRD studies (trials conducted on SLE, vasculitis and Wegener's granulomatosis) through the high titre of soluble adhesion molecules, thrombomodulin, and NO and the surface expression of various proteins (vascular cell adhesion molecule 1, intracellular adhesion molecule 1 and E-selectin) [23]. The following autoantibodies cause endothelial activation: anti-phospholipid (aCL, aβ2GPi), anti-oxidized LDL (oxLDL), anti-oxLDL/β2 glycoprotein 1, anti-annexin V, anti-heat shock protein 65, antibodies-double-stranded DNA (anti-dsDNA) anti-ribonucleoprotein, anti-endothelial cell, and anti-neutrophil cytoplasmic antibodies [23]. The endothelial dysfunction, which causes premature ATS, can be measured with pulse-wave analysis or flow-mediated vasodilatation [14, 23]. The prothrombotic factors specific to certain CIRD (*e.g.* anti-phospholipid antibody detection by lupus coagulation inhibitors and anti-cardiolipin antigen binding) present additional CV event risk factors (unstable angina, AMI *etc.*). In RA, rheumatoid factor (RF) and other auto-antigen binding molecules are associated with the severity of the disease and are conducive to a higher risk of ischemic events, higher CV mortality rates, and higher carotid ATS and peripheral arte-

rial disease prevalence [21]. Finally, anti-CCP antibody binding is linked to arterial wall thickening (detected by ultrasonography of the carotid artery) [11].

Cells: Various cells involved in the pathogenesis of CIRD are linked to ATS and CV disease. A decreased number of circulating endothelial progenitor cells (EPC), which are essential to endothelial repair and revascularization, has been found in RA patients. Under the action of pro-inflammatory cytokines that stimulate endothelial growth factors, EPCs migrate towards the synovial membrane of the joint where they accumulate and contribute to intrasynovial neoangiogenesis [3]. Moreover, decreased EPC numbers are associated with accelerated ATS and are a CV risk factor [3, 21]. Recently, the influence of TNF on EPC reduction in RA patients has been demonstrated, as well as the effect of medium corticosteroid doses on the growth of these cells [24].

Atypical Ly T CD4+ CD28− cells are another subgroup of cells involved in CIRD, which are associated with atheroma plaque instability because of their important pro-inflammatory and lesion-conducive properties. Their numbers are increased in RA, connecting them to endothelial dysfunction and the preclinical stages of ATS [3, 7].

Synovial lesions in RA and atherosclerotic vascular lesions also have similar cytokine and cellular profiles, offering new links between rheumatoid arthritis and atherosclerosis [25]. Local macrophage activation and infiltration, LyTCD4+ cells, and endothelial injury are noted in both types of lesions. However, the endothelial injury accompanying atherosclerotic vascular lesions is mediated (at least partly) by oxidized lipids, whereas the endothelial injury that occurs in the rheumatoid synovial membrane is mediated by immune complexes [26, 27].

Inflammation mediators: The local (synovial and vascular) and serum expression of inflammation mediators are high in both ATS and CIRD, the most remarkable of which are TNF-α, IL-1 and matrix metalloproteinases [28, 29]. The increased inflammation levels found in the population without RA, which is reflected in the elevated CRP levels, increases individual myocardial infarction risk considerably [30]. Moreover, fibrous atherosclerotic plaque rupture with vascular thrombus formation and acute secondary vascular occlusion have been directly linked to the upregulation of IL-1 and TNFα matrix metalloproteinases. TNFα, a key factor in RA pathophysiology, increases the expression of adhesion molecules and IL-6 synthase and promotes endothelial dysfunction by reducing NO bioavailability [30]. Indeed, its high level is a predicting factor for coronary event recurrence in AMI patients [31]. TNFα overproduction in RA induces CD28 downregulation to LyTCD4+, which constitutes a pathogenic mechanism. Therefore, therapeutic procedures could be applied towards this pathway in CV diseases linked to RA [3]. Finally, TNFα is one of the factors that cause insulin resistance, increasing CV risk [32].

Osteoprotegerin: This is a protein that belongs to the TNFα receptor family, which is involved in bone metabolism and is linked to coronary artery calcifications in RA patients [21].

Prothrombotic markers: Prothrombotic markers (fibrinogen, von Willebrand factor, plasminogen activator inhibitor, and D-dimers) are independent CV mortality predictors and are highly expressed in patients with CIRD [33]. The mechanisms of prothrombotic propensity in chronic inflammatory diseases include an increase in platelet mass, low-level platelet activation, enforced by the interaction with leukocytes and the formation of proinflammatory cytokines, locally activated endothelium and an increased coagulant activity. Patient treatment with methotrexate or TNF-α blockers appears to result in normalization of several of these prothrombotic parameters [34]. CV and RA-associated factors can alter the structure and function of platelets, starting from megakaryocytopoiesis. Hyperactive platelets target synovial membranes with subsequent local rheumatoid inflammation. Accumulating evidence suggests that DMARD decrease platelet activity [35]. High mean platelet volume is associated with a variety of established risk factors, cardio- and cerebrovascular disorders, and low-grade inflammatory conditions prone to arterial and venous thrombosis. Active RA has low levels of mean platelet volume while lifestyle changes, antihypertensive or lipid lowering drugs and diet therapies may also affect mean platelet volume values [36].

Arterial stiffness: Arterial stiffness, which can be assessed with various techniques (*e.g.* pulse wave analysis or pulse pressure, the difference between systolic and diastolic arterial pressure), is currently considered an important CV risk factor [37]. Increased arterial stiffness, which is correlated with the duration of the disease, quality of life, age and CRP values, was detected in RA patients [38, 39].

Hyperhomocysteinaemia and HLA-DRB1*0404: These are other CV risk factors specific to CIRD [21].

CIRD THERAPY AND CV RISK

Anti-inflammatory medication. The anti-inflammatory medications and DMARDs used to treat RA have been shown to increase CV disease prevalence in RA patients, although recent findings have suggested that some of these medications may be more cardioprotective than cardiotoxic [10]. The effect of RA medications on atherogenesis promotion or suppression is complex and has only been partially clarified. There are several RA treatments that may theoretically promote ATS and/or atherothrombosis. Methotrexate and salazopyrin increase the serum level of homocysteine through folate depletion, and hyperhomocysteinaemia is associated with peripheral arterial and coronary ATS [3, 10]. However, this effect may be controlled through the concomitant administration of folic acid.

Cyclooxygenase-2 (COX2)-specific NSAIDs have a prothrombotic effect from the resulting thromboxane-prostacyclin imbalance. However, a recent study has reported that CV risk depends on the dose of COX2-specific NSAIDs [40]. Therefore, a thorough assessment of CV risk should be carried out in patients receiving COX2 NSAIDs, and small doses should be used for treatment. The connection between traditional NSAIDs and CV risk remains controversial. Nevertheless, the American Heart Association has recently drafted an NSAID prescription and CV risk guide [21].

Glucocorticoids: Glucocorticoids are associated with polymorphic CV risk (especially HTN) [41, 42] because of

their effects on glucose, lipid and salt metabolism, water retention and immunologic function. CV risk is higher in patients with seropositive RA [43]. Hafstrom *et al*. assessed the effect of small doses of glucocorticoids (prednisone ≤ 7.5 mg/day) on ATS, endothelial function and CV risk factors (HTN and dyslipidaemia) in patients with RA [44]. They concluded that endothelial function was not affected by small prednisone doses. However, after administration for 4 years, the medication caused increases in systolic blood pressure and total cholesterol levels.

Various studies have shown that suppression of inflammation by DMARDs, TNFα blockers, and corticosteroids may provide cardioprotection. Indeed, positive lipid profiles were found in patients that underwent traditional DMARD [45], TNFα blocker [46], and corticosteroid [47] therapy. Insulin resistance was reversible in a small group of RA patients who were given infliximab [48].

DMARDs: The relationship between DMARD therapy and CV risk has not been sufficiently investigated. Methotrexate delivery is associated with an overall drop in the rate of CV mortality [49]. The use of sulfasalazine is also connected with a decreased CV risk [50]. Hydroxychloroquine improves the lipid profile and reduces the risk of diabetes in RA patients [51, 52]; however, extensive research is still needed to assess its influence on the overall CV risk. Nonetheless, CV risk was higher with the use of certain immunosuppressive drugs, such as azathioprine, leflunomide, or cyclosporine, than with methotrexate alone [53]. A randomized prospective clinical trial based on imaging techniques designed to assess the atherosclerotic plaque characteristics is necessary to prove that one or several DMARDs stabilize or cause ATS regression.

The effect of TNFα blockers on CV risk in CIRD is complex. Although they are known to have a possible adverse effect, *i.e.* heart failure, there are also studies showing a protective effect on the arterial wall [54, 55]. This may be a result of activation of the fibrinolytic system, which is inhibited in CIRD [56]. In addition, one TNFα blocker (infliximab administered for 12 weeks) is associated with a partial recovery of endothelial function (considered an early stage of atherogenesis) [54, 55]. This effect was not noted in any other etanercept studies [57]. However, more recent studies have reported that anti-TNFα agents have a negative effect on the lipid profile, especially on the total cholesterol, in RA patients [58, 59]. Therapies using biological anti-TNFα agents have been controversial on their impact on arterial stiffness [60, 61]. Recently, a positive short-term effect of adalimumab on endothelial function of patients with long-lasting RA who were previously unresponsive to infliximab therapy has been demonstrated [62].

CV RISK MANAGEMENT

Practical recommendations for CIRD therapy and CV risk management are presented in Table **3**. RA should be considered as a condition bearing a high CV risk. The same should apply to ankylosing spondylitis (AS) and psoriatic arthritis, although the evidence for these conditions is poorer [63-67]. The risk is due to both the traditional increase in risk factor prevalence and the inflammatory status [63]. The absolute CV death risk is considerable in the elderly and in men with RA, whereas the relative risk is higher in women with RA [64, 65]. The chronic inflammation markers are independently associated with CV morbidity and mortality in RA [68, 69].

Table 3. Practical recommendations for CIRD therapy and cardiovascular risk management

Therapeutic agent	Recommendations
Glucocorticoids	• Small doses • Minimal duration of treatment • Conduct cardiovascular risk factor screening and follow-up sessions (blood pressure, glycaemia, lipidaemia) at beginning of therapy and then periodically • Treat the cardiovascular risk factors (dyslipidaemia, glycaemic control, HTN treatment, smoking cessation, weight loss) • In patients with positive RF, stricter control of cardiovascular risk factors
NSAIDs	• Avoid administering specific COX2 blockers • Any nonselective NSAIDs should be individualized and with consideration of several factors (*e.g.* gastrointestinal bleeding risk)
DMARDs	• Methotrexate and possibly sulfasalazine seem to be associated with a lower cardiovascular risk in RA patients • For specific DMARDs, observation of the disease activity control guides is necessary because there are no specific cardiovascular risk management recommendations
Anti-TNFα therapy	• All research conducted so far has only involved subclinical forms of the vascular disease • There are no specific cardiovascular risk management recommendations

CIRD = chronic inflammatory rheumatic disease, COX2 = cyclooxygenase 2, DMARDs = disease-modified arthritis rheumatoid drugs, HTN = hypertension, RA = rheumatic arthritis, RF = rheumatoid factor, M = male, NSAIDs = non-steroid anti-inflammatory disease, TNFα = tumour necrosis factor alpha.

Adequate control of disease activity is vital for CV risk reduction; the best evidence is for anti-TNF and methotrexate therapy. Early TNFα blocker and methotrexate therapy have proven to be independently associated with a lower CV risk, to improve physical exercise, and to decrease HTN, obesity and DM risks [47, 52, 54]. However, since methotrexate therapy causes hyperhomocysteinaemia through folic acid depletion, which has a toxic endothelial and procoagulant effect, it is necessary to administer folic acid during the therapy.

National guideline-based CV risk assessment is recommended for all RA patients and should be considered by all AS and psoriatic arthritis patients on an annual basis. The risk assessment should be repeated whenever the basic therapeutic approach is changed (the SCORE model is recommended if no national guidelines are available) [63]. In patients with low CV risk or an inactive disease, the assessment should be carried out every 2–3 years. This CV risk assessment may be easily included in the routine RA follow-ups, which consist of lipid profile determination, the usual laboratory tests, and blood pressure determination. A CV risk therapy and follow-up schedule should be set on a case-by-case basis.

When any 3 of the following situations occur, a 1.5 multiplication factor should be used when calculating the CV risk score for RA patients: disease duration > 10 years, presence of RF, positive anti-CCP antibodies or extra-articular manifestations [70]. In addition to traditional CV risk factors, the CV risk score calculation models should also include the risk factors described above [70]. The multiplication factor was selected based on the standardized mortality ratios analysis specific to clinical trials and should only be used for RA patients.

Total and HDL cholesterol should be used in the SCORE model. Dyslipidaemia is associated with high CV risk in the general population [71], in whom the total/HDL cholesterol ratio (TC/HDL) is an important prognostic indicator [72]. Patients with arthritis, especially those where an inflammatory disease is active, exhibit a high TC/HDL ratio and elevated triglyceride level [73]. Statins can mediate some anti-inflammatory effects with changes in vascular risk factors in the context of high-grade autoimmune inflammation [74]. The atherogenic index has been suggested to be less susceptible to disease activity variation during long periods of time, making it more attractive to be used in CV risk prediction when compared to individual lipid concentrations [75]. DMARDs, glucocorticoids, and TNF blockers decrease the TC/HDL ratio during the first months of therapy [43-45]; the subsequent lipid profile improvement may also be a result of a decrease in disease activity, improved diet and physical exercise.

CV risk assessments and interventions should observe national guidelines. While there are differences between countries (SCORE model, Framingham, *etc.*), there is no evidence that one model is better than the others. The therapy should be initiated when the systolic blood pressure > 140 mmHg and the LDL cholesterol > 2.5 mmol/L. The therapy should comprise antihypertensive drugs and statins; indeed, it is similar to the therapy regime administered to the general population.

Statins, converting enzyme inhibitors, and/or angiotensin II blockers should be the preferred treatments given their anti-inflammatory potential. In addition to decreasing disease activity, research [76] conducted on atorvastatin used for RA also reported a decrease in the triglyceride and LDL cholesterol levels, which had a positive effect on endothelial dysfunction. Similarly, in another study, 20 mg of atorvastatin was administered for 12 weeks and arterial stiffness was ameliorated in a group of 29 patients with RA [77].

The role of the COX2 inhibitors and most NSAIDs in CV risk has not yet been clearly determined. Therefore, one must exercise caution when prescribing them, especially to patients with CV disease or risk factors. NSAIDs, especially COX2 inhibitors, are associated with a high CV risk [78, 79]. Their prothrombotic effects, which are due to COX2 inhibition, are partly offset by reducing pain and articular inflammation, which increases the mobility of CIRD patients [80]. When prescribing NSAIDs, and especially COX2 inhibitors, one should also consider their atherothrombotic risks. Moreover, COX2 inhibitors interfere with the antiplatelet action of aspirin [81].

Only the lowest, most efficient doses of corticosteroids should be used**.** Glucocorticoids, which are used in CIRD, have a dual effect on CV risk: while they increase CV risk by altering the lipid profile and glucose tolerance and increasing insulin resistance, blood pressure, and obesity rates [36, 37, 82, 83], they also decrease CV risk by reducing the systemic inflammatory process, thereby improving glucose tolerance and dyslipidaemia [84, 85]. The risk is higher in individuals who are administered high doses for long periods of time [86].

While no definitive connection between CIRD, smoking habit and CV risk has yet been proven, smoking should increase individual risk.

CONCLUSION

The pathogenic mechanisms involved in accelerated ATS and the resulting CIRD complications are complex and rely on several factors. Aggressive prevention and prompt treatment of all CV risk factors are mandatory to achieve efficient control over the inflammation and immunologic and metabolic disorders specific to CIRD. The current CV risk calculation, which consists of a sole assessment of traditional CV risk factors, underestimates the actual CV risk in people suffering from CIRD. The assessment and follow-up of both traditional and non-traditional ("disease-related") CV risk factors, as well as their classification in CV risk reduction categories are vital. Using imaging techniques, the early determination of the intima-media thickness in the carotid, flow-mediated vasodilation, and nitroglycerine-mediated vasodilation should be used for the diagnosis of endothelial dysfunction and ATS. The immunologic and metabolic markers that may be involved in vascular atherosclerotic disease development specific to RA are: anti-CCP antibodies, IgM RF, circulating immune complexes, proinflammatory cytokines, Th0/Th1 lymphocytes, homocysteine, dyslipidaemia or folate synthesis, and decreased vitamin B12. An early diagnosis of endothelial dysfunction and ATS, the appropriate pathogenic therapy of the disease, the use of specific medication designed to control ATS, changes in

lifestyle, and periodic follow-up with the RA patients will minimize the CV risk of these patients.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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Declared none.

LIST OF ABBREVIATIONS

AMI	=	Acute myocardial infarction
ATS	=	Atherosclerosis
β2GP	=	β2 glycoprotein
CD40/CD40L	=	Co-stimulatory proteins found on antigen presenting cells
CEA	=	Carcinoembryonic antigen
CIRD	=	Chronic inflammatory rheumatic disease
COX2	=	Cyclooxygenase 2
CK	=	Creatine kinase
CRP	=	C reactive protein
EPC	=	Endothelial progenitor cells
ESR	=	Erythrocyte sedimentation rate
DM	=	Diabetes mellitus
DMARDs	=	Disease-modified arthritis rheumatoid drugs
Fg	=	Fibrinogen
HCQ	=	Hydroxychloroquine
HDL	=	High density lipoproteins
HLA	=	Human leukocyte antigen
HTN	=	Hypertension
HSP	=	Anti-heat shock protein
IL-1	=	Interleukin 1
IL-6	=	Interleukin 6
LDL	=	Low density lipoproteins
MTX	=	Methotrexate
NOS	=	Nitric oxide synthetize
NSAIDs	=	Non-steroid anti-inflammatory disease
anti-PL	=	Anti-threonyl-tRNA synthetase
PAI-1	=	Plasminogen activator inhibitor
RA	=	Rheumatoid arthritis
RF	=	Rheumatoid factor
SLE	=	Systemic lupus erythematosus
TC	=	Total cholesterol
TNF	=	Tumour necrosis factor

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