

Cardiovascular risk management in patients with inflammatory arthritis: what is good for the joint is good for the heart and vice versa!

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Fl000 Medicine Reports 2010, **2:27** (doi:10.3410/M2-27)

The electronic version of this article is the complete one and can be found at: <http://fl000.com/reports/medicine/content/2/27>

Abstract

Owing to the prominent long-term systemic inflammatory reaction in patients with arthritides and a growing body of data illustrating that this inflammatory reaction imposes a considerable risk for the development or aggravation of cardiovascular (CV) disease or overall CV risk, numerous researchers and clinicians have put enormous effort into the analysis of the effects of risk factors on the course of CV disease in these patients and the therapeutic options to antagonize progressive atherosclerosis. To achieve this challenging goal, investigators have shown that all treatment strategies must include the 'non-rheumatic' approaches, such as lowering blood pressure, stopping smoking, and improving metabolic status, in tight association with lowering the overall disease activity of the underlying rheumatic entity using antiphlogistic drugs and conventional as well as biologic disease-modifying drugs.

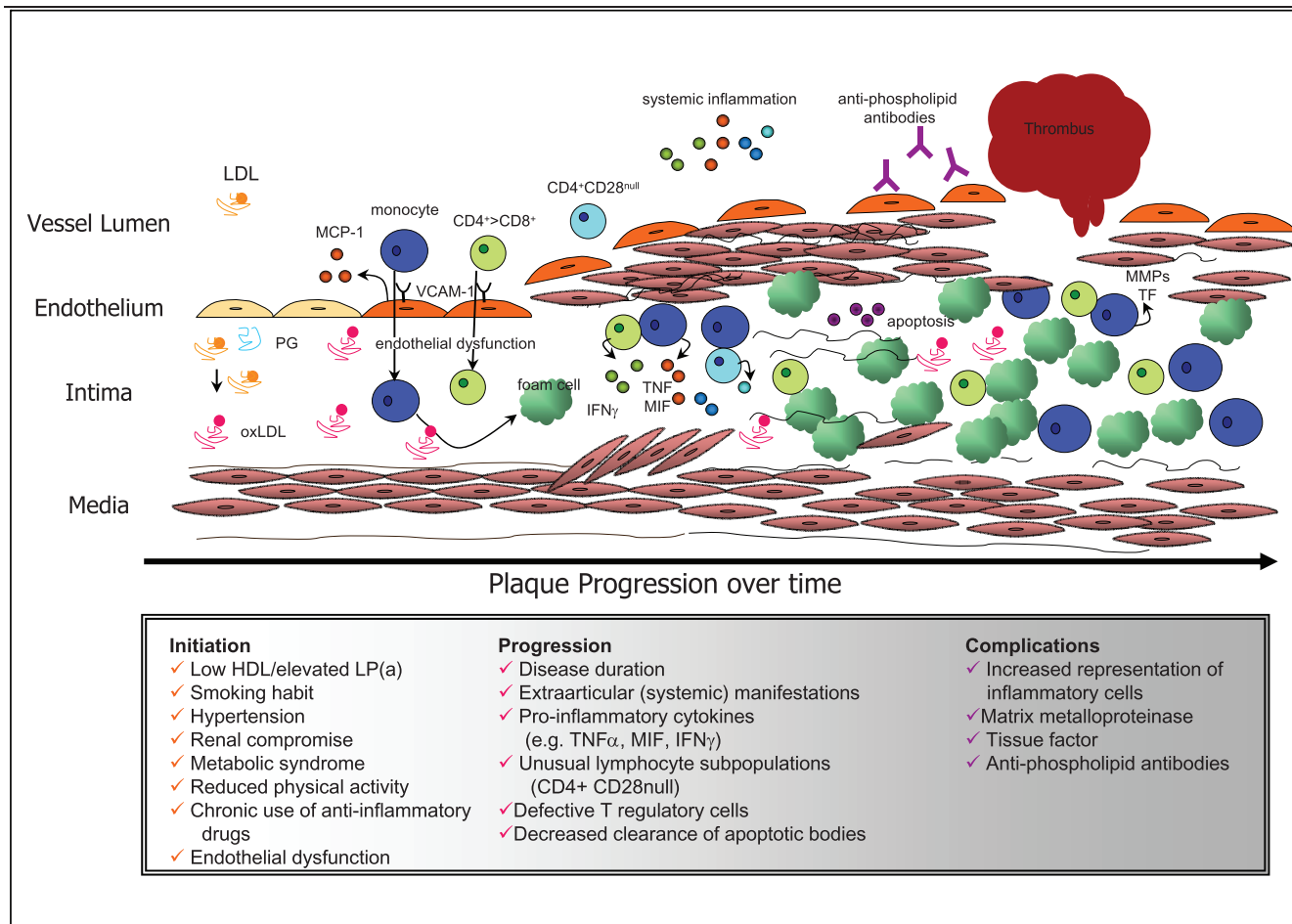
Introduction and context

The pathophysiology of all arthritides includes articular inflammation. In the majority of patients, this is associated with a continuous vascular flow of proinflammatory molecules that are also operative in the development of vascular lesions that may lead to atherosclerosis, resulting in a long-term systemic inflammatory reaction, and a growing body of data illustrates that this inflammatory reaction imposes a considerable risk for the development or aggravation of cardiovascular (CV) morbidity, which persists independently of the 'traditional' risk factors of endothelial dysfunction and atherosclerosis (as long as the underlying rheumatic disease is not in remission). A recent systematic review and meta-analysis of CV mortality in more than 90,000 patients with rheumatoid arthritis (RA) over the course of 50 years in the pre-biologics era revealed that the overall pooled standard mortality ratio (SMR) was calculated as 1.6 and did not change significantly over time [1]. This observation does not appear to inherit a

regional effect – at least for Europe – as a similar approach asking the same questions to Swedish patients [2] also revealed no difference in SMR in the 1978 and 1995 cohorts, although, as noted by the authors, RA treatment had significantly improved for the later cohort. In addition, it needs to be noted that, in the CARRE (CARDiovascular research and RhEumatoid arthritis) investigation, about one-third of the CV events occurred prior to the onset of RA and this risk was comparable to diabetes type 2 patients [3,4].

Basic science data from both cardiology and rheumatology have facilitated detailed molecular insight into the processes leading to atherosclerosis based on chronic inflammatory processes. As illustrated in Figure 1, inflammatory joint diseases and connective tissue diseases share several of these pathways, including all cellular components of the vascular and perivascular compartments [5]. In RA, basically all components of its pathophysiology, such as proinflammatory cytokines,

Figure 1. Pathophysiologic processes in inflammatory diseases leading to atherosclerotic lesions [5]



The initiation phase is driven by various stimuli, which are frequently based on metabolic dysfunctions and vasculotoxic lifestyle habits. As soon as vascular lesions are present, several proinflammatory molecules such as cytokines and immune cells contribute to the perpetuation of the inflammatory plaque. Finally, this concert of vasculoremodeling factors results in severe reduction in blood flow and development of thrombotic events. HDL, high-density lipoprotein; $IFN\gamma$, interferon-gamma; LDL, low-density lipoprotein; LP(a), lipoprotein (a); MCP-1, monocyte chemoattractant protein-1; MIF, migration inhibitory factor; MMP, matrix metalloproteinase; oxLDL, oxidized low-density lipoprotein; PG, prostaglandin; TF, tissue factor; TNF, tumor necrosis factor; VCAM-1, vascular cell adhesion molecule-1.

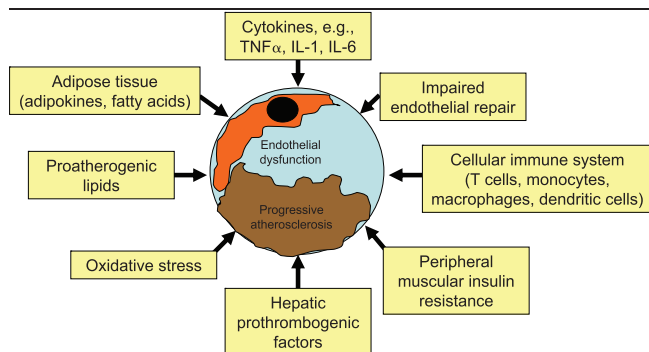
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altered perivascular metabolism, effector cells of the immune system, and circulating autoantibodies, mediate and promote an accelerated development of atherosclerotic lesions in the vascular wall (Figure 2) [6].

Therefore, as outlined below, inflammatory arthritides such as RA should be considered an additional independent risk factor for CV disease and these patients need to be treated more actively for CV prevention and risk factor modification, not unlike, for example, patients with metabolic diseases associated with a high CV risk. This treatment strategy certainly must include the ‘non-rheumatic’ standard measures such as lowering blood

pressure (BP), cessation of smoking, and so on. Furthermore, it has been found that some ‘cardiologic’ drugs have both vasculoprotective and anti-inflammatory effects. For example, statins were shown to improve endothelial function [7] as well as reduce arterial stiffness, lipid oxidation, and inflammatory markers in RA. The TARA (Trial of Atorvastatin in Rheumatoid Arthritis) study [8] showed that atorvastatin for 6 months had a significant effect on lowering inflammatory markers, and subsequently in a non-RA study, the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial, rosuvastatin treatment in healthy individuals with

Figure 2. All components of rheumatoid arthritis pathophysiology contribute to the development of cardiovascular disease



IL, interleukin; TNF α , tumor necrosis factor-alpha.

normal low-density lipoprotein (LDL) cholesterol but elevated C-reactive protein (CRP) (>2 mg/L) was found to reduce cardiac events by nearly half. The authors stated that, although this study excluded patients with chronic inflammatory autoimmune disease, nearly all RA patients would have met the inclusion criteria for JUPITER [9,10].

Similar to the current strategy of treating RA as early as possible in order to avoid structural damage to the affected joints, there are convincing data that antagonizing inflammation early in the course of the disease might be the key to CV protection. It was shown, for example, that inflammation predicts accelerated brachial arterial wall changes in patients with recent-onset RA [11]. Both flow-mediated dilatation and independent glyceryltrinitrate-mediated dilatation were significantly lower at baseline in early-onset RA patients than in controls but could be improved over the course of 1 year with antirheumatic treatment. Of note, the age of the patient, CRP level at initiation of treatment, and CRP level at 1 year were associated with alterations in brachial responses.

Recent advances

Recommendations of the European Society of Cardiology

As CV diseases are among the most frequent diseases affecting overall morbidity and mortality worldwide, a milestone for assessing and improving the overall CV risk was the work of the task force led by the European Society of Cardiology (ESC) on general prevention and management of CV in 2007. The key points that need to be addressed when managing individuals at risk for CV are avoidance of tobacco, lowering BP to below 140/90 mm Hg, lowering serum cholesterol to below 200 mg/dL (5 mmol/L) and more specifically LDL cholesterol to below 100 mg/dL (2.5 mmol/L), weight

reduction, a healthy diet, and physical activity for at least 30 minutes per day. However, these recommendations for the assessment and management of CV risk and the respective CV risk score assessment tools such as the Framingham score and the Systematic Coronary Risk Evaluation (SCORE) model presented by the ESC have been developed for the general population and not specifically for patients with arthritides as an additional morbidity factor [12-14]. In addition to the difficulty that many arthritis patients have in achieving the goal of physical activity without adequate treatment, arthritides (with the exception of a single mention of osteoarthritis) are not noted in these recommendations as an individual or aggravating risk factor *per se*. However, it has been stated that general inflammatory reactions reflected by elevation of CRP need to be taken into account when approaching this medical problem.

EULAR recommendations

To improve the situation for the practicing rheumatologist, the European League against Rheumatism (EULAR) recently published recommendations for CV risk management in patients with RA, ankylosing spondylitis (AS), or psoriatic arthritis (PsA) [15]. The working group analyzed all available data and proposed 10 recommendations addressing the CV risk management in patients with RA, AS, or PsA (Figure 3). Of note, reflecting the clinically overt inflammation in patients with RA, the evidence for an increased CV risk was more prominent for patients with RA and the strength of the recommendations differed also between RA on the one hand and AS and PsA on the other.

In RA patients, the absolute risk of CV-related death is highest for older male patients, whereas the relative risk is highest for young female patients [16]. The EULAR task force stated that the excess CV risk in RA is due mainly to inflammation rather than the conventional risk factors. In support of this idea, it was found that chronic inflammatory markers such as CRP were independently associated with CV mortality and morbidity. As outlined above, the SMRs range from 1.5 to 1.9, and similar ratios are suspected for the spondyloarthropathies.

According to the European guidelines of cardiology societies, risk assessment should follow the SCORE model and treatment of the non-arthritic non-inflammatory risk factors should be performed according to these recommendations. Statins, angiotensin-converting enzyme inhibitors, and/or AT-II (angiotensin-II) blockers – owing to their potential anti-inflammatory effects – are preferred treatment options to achieve these goals [8,9,16-19].

Figure 3. The 10 recommendations for cardiovascular risk management in inflammatory arthritides as outlined by the European League against Rheumatism (EULAR) task force [15]

Recommendations	Level of evidence	Strength of recommendation
1. RA should be regarded as a condition associated with higher risk for CV disease. This may apply to AS and PsA, although the evidence-base is less. The increased risk appears to be due to both an increased prevalence of traditional risk factors and the inflammatory burden.	2b-3	B
2. Adequate control of disease activity is necessary to lower the CV risk.	2b-3	B
3. CV risk assessment using National Guidelines is recommended for all RA patients and should be considered for all AS and PsA patients on an annual basis. Risk assessments should be repeated when anti-rheumatic treatment has been changed.	3-4	C
4. Risk score models should be adapted for RA patients by introducing a 1.5 multiplication factor. This multiplication factor should be used when the RA patient meets 2 of the following 3 criteria: <ul style="list-style-type: none"> • Disease duration of more than 10 years; • RF or anti-CCP positivity; • Presence of certain extra-articular manifestations. 	3-4	C
5. TC/HDL cholesterol ratio should be used when the SCORE model is used.	3	C
6. Intervention should be carried out according to national guidelines.	3	C
7. Statins, ACE-inhibitors and/or AT-II blockers are preferred treatment options.	2a-3	C-D
8. The role of COXIBs and most NSAIDs regarding the CV risk is not well established and needs further investigation. Hence, we should be very cautious prescribing them, especially in patients with a documented CV disease or in the presence of CV risk factors.	2a-3	C
9. Corticosteroids: use the lowest dose possible.	3	C
10. Recommend smoking cessation	3	C

ACE, angiotensin-converting enzyme; anti-CCP, anti-cyclic citrullinated peptide; AS, ankylosing spondylitis; AT-II, angiotensin-II; COXIB, cyclooxygenase inhibitor; CV, cardiovascular; NSAID, non-steroidal anti-inflammatory drug; PsA, psoriatic arthritis; RA, rheumatoid arthritis; RF, rheumatoid factor; SCORE, Systematic Coronary Risk Evaluation; TC/HDL, total cholesterol/high-density lipoprotein.

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Arthritis-specific laboratory parameters

As mentioned before, laboratory parameters associated with inflammation or distinct arthritis entities can be used in managing arthritis patients at risk for CV disease. CRP levels, in particular, have been found to be associated with a high CV risk in patients with RA [20]. In addition, the EULAR task force recommended that clinicians multiply the derived CV risk estimate by 1.5 if at least two of the following criteria are present: disease duration of more than 10 years, severe extra-articular

manifestations, and, more specifically, rheumatoid factor or anti-cyclic citrullinated peptide antibody positivity (or both) [12].

The basis of anti-inflammatory therapy: corticosteroids and non-steroidal anti-inflammatory drugs

Corticosteroids are frequently used in rheumatic patients and may enhance the CV morbidity due to their negative effects on metabolism (e.g., lipids, glucose, BP, and obesity). Interestingly, this has been challenged by a

recent report showing that, although the metabolic syndrome did affect 40% of the RA patients in the study, long-term corticosteroid treatment did not appear to be associated with a higher prevalence of the metabolic syndrome in patients with RA [21]. In addition, corticosteroids not only contribute to the reduction of overall inflammatory activity but also have proven to be effective in decreasing the risk of atherosclerosis and improving glucose intolerance and dyslipidemia [22,23]. However, more data specifically addressing the long-term effect of corticosteroids on alteration of CV risk are needed.

Of interest, although more than 50,000 patients have been examined for CV risk caused by non-steroidal anti-inflammatory drugs (NSAIDs), specifically cyclooxygenase-2 (COX-2) inhibitors (known as 'coxibs'), the EULAR task force concludes that the role of COX-2 inhibitors and most other NSAIDs regarding CV risk is not well established in patients with inflammatory arthritides and needs further investigation. This statement is based on the observations that COX-2 inhibitors can exert prothrombotic effects and that regular use of NSAIDs may impair the vasculoprotective role of acetyl-salicylic acid [24,25]. However, a recent analysis did not show a significant difference in CV risk factors between users and non-users of NSAIDs or COX-2 inhibitors, respectively, in a cohort of patients with RA [26].

Novel aspects of disease-modifying antirheumatic drugs and biologics

Disease-modifying antirheumatic drugs have been shown to improve the lipid profile in patients with early active RA [23,27], and most recently it was demonstrated that methotrexate (MTX) use not only is associated with a lowered occurrence of the metabolic syndrome [28] but also appears to specifically reduce atherosclerosis [29]. As MTX may induce vasculotoxic hyperhomocysteinemia through a depletion of folic acid levels, the current recommendation of folic acid supplementation should also be followed to support the vasculoprotective effects of MTX, although hyperhomocysteinemia is not the primary reason for folic acid supplementation.

Since the start of the era of tumor necrosis factor (TNF) blockers at the beginning of this millennium, the role of TNF in the development of CV risk in arthritic diseases has been investigated more closely due to its prominent role in inflammation. TNF blockers have been found to be associated with increased high-density lipoprotein-cholesterol (HDL-c) and improvement of the total cholesterol/HDL-c ratio during the first few months of treatment.

When the body of data addressing the effects of TNF inhibition was reviewed, it was confirmed that TNF blockers actually have vasculoprotective and cardioprotective effects in arthritis patients on the basis of a good level of evidence [2,12,30,31]. Of note, an important aspect of the study of Dixon and Symmons [30] is the observation that the decrease in CV events was observed in TNF responders only. A recent analysis of the German cohort showed a reduction of the CV hazard ratio related to TNF inhibitor treatment to 0.70, although it needs to be mentioned that this investigation focused on heart failure and not primarily on atherosclerotic disease [31]. However, improvement of CV risk load can be directly visualized by measurement of the inflammation-associated stiffness, and two current publications demonstrated an improvement of the arterial stiffness for etanercept in RA patients and for infliximab in AS patients [32,33].

Implications for clinical practice

The current data show impressively that reducing inflammation is one of the most important factors to prevent arthritis patients from developing an additional CV disease. Fortunately, the currently used antiphlogistic and antirheumatic drugs support this goal and low disease activity at the joints results in low atherogenic activity at the vessels, especially when used early in the course of the disease [19,23,27-30,32,33]. However, the key problem for the practicing rheumatologist is the lack of time to explain the additional general CV risk factors and their management in addition to the already time-consuming management of the underlying arthritic disease. Modification of lifestyle, especially cessation of smoking, is one of the most difficult goals to achieve. On the other hand, when improvement of the course of the rheumatic disease is achieved, the overall health of the patient will also improve. Thus, the current evidence for CV medicine in rheumatology can be summarized as: What is good for the joints is good for the heart and *vice versa*!

Abbreviations

AS, ankylosing spondylitis; BP, blood pressure; COX-2, cyclooxygenase-2; CRP, C-reactive protein; CV, cardiovascular; ESC, European Society of Cardiology; EULAR, European League against Rheumatism; HDL-c, high-density lipoprotein-cholesterol; JUPITER, Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; LDL, low-density lipoprotein; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drug; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SCORE, Systematic Coronary Risk Evaluation; SMR, standard mortality ratio; TNF, tumor necrosis factor.

Competing interests

With respect to the pharmaceutical products mentioned in this report, UM-L and UL have received speaker honoraria from Medac (Wedel, Germany), Essex (München, Germany), and Wyeth (Madison, NJ, USA), and IHT has received speaker honoraria from Abbott (Abbott Park, IL, USA) and Wyeth. CH declares that he has no competing interests.

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