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Cardiovascular Risk in Rheumatoid Arthritis. An Update for General Practitioners

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Abstract

Rheumatoid arthritis (RA) is a chronic inflammatory articular pathology which affects almost 1% of the general population and which is ranked among the top 15% of diseases causing major disability worldwide. RA shares some pathologic features, genetic predisposition and risk factors with atherosclerosis. Inflammation plays a central pathophysiologic role in both diseases.

As compared with the general population, in RA the prevalence of cardiovascular events is increased to an extent comparable to that of type 2 diabetes mellitus. RA-Patients have a higher incidence of myocardial ischemia and infarction, cardiac failure, valvular heart disease, pericarditis, myocarditis and, to a lesser extent, venous complications. The occurrence of sudden cardiac death is two-fold increased and that of major adverse cardiovascular events is augmented to almost 50%. Cardiovascular deaths increase seven years following symptoms onset.

Control of the joint pathology remains the principal therapeutic aim in RA, but the impact of cardiovascular complications should not be forgotten. Patients with RA who are at high cardiovascular risk should be given the best available therapies to reduce the cardiovascular complications.

There are things we know that we know. There are known unknowns. That is to say, there are things that we know that we don't know. But there are also unknown unknowns. There are things we don't know we don't know. Donald Rumsfeld

Keywords: Rheumatoid arthritis; Cardiovascular risks; Pathology; Heart disease; Venous complications

Abbreviations: BAs: Biological Agents; COXIBs: Cyclooxygenase-2 inhibitors; CV: Cardiovascular; DMARDs: Disease Modifying Antirheumatic Drugs; JAK Inhibitors: Janus Kinase-inhibitor's; MACE: Major Adverse Cardiovascular Events; NSAIDs: Non-steroidal Antinflamatory Drugs; RA: Rheumatoid Arthritis; TNFα: Tumor Necrosis Factor Alpha

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory joint pathology which affects almost 1% of the general population [1] and which is ranked among the top 15% of diseases causing major disability worldwide [2]. RA shares several pathophysiologic features, genetic predisposition and risk factors with atherosclerosis. Inflammation is the central pathologic factor in both diseases [3]. The paper reviews cardiovascular events and their therapy in RA.

Methodology

A review must rely on solid data, be objective and deliver the 'state of the art' of the argument. The quest is a seemingly endless process. Writing is a solitary endeavor but data depend on the work of many individuals and institutions. We started a goal-oriented search in English and German with the engines BioMedSearch.com, Cardio source, Center Watch, ClinicalTrials.gov, Cochrane, Google Scholar, Med Watch, Research Gate and PubMed. We settled a time-window 2000-2016 with key words: RA, arthritis, cardiovascular risk in RA, and treatment of RA. Our search delivered more than 1 million of references. The filter was restricted to guidelines and meta-analyses. This search delivered more than 80,000 references. Using a plagiarism's software we found that few centers published more than 60% of the collected references, usually changing authors' order, deleting or adding some authors. Many papers present strikingly similar data. Many authors quote their previous publications. One might maliciously say that these authors repeated data in different journals using their references in order to increase their scientific impact factor. We selected papers with large numbers of cases and ended with a total of 340 references. From the abstracts we selected 166 full-text papers. Ninety-three papers sufficed to get the 'state of the art' of cardiovascular complications (CV) in RA. It is unavoidable that we may have either selected or omitted same papers by chance.

Cardiovascular complications in RA

As compared with the general population, in RA the prevalence of CV events is increased to an extent comparable to that of type 2 diabetes mellitus [1-4]. RA-patients have an increased incidence of myocardial ischemia and infarction, cardiac failure, valvular heart disease, pericarditis, myocarditis and, to a lesser extent, venous complications [5-21]. The occurrence of major adverse cardiovascular events (MACE) augments to almost 50% and that of sudden cardiac death increases two-fold. CV deaths appear with increasing frequency 7-10 years following symptoms onset.

Risk factors and CV features in RA

As compared with the general population, the prevalence of traditional CV risks factors, such as diabetes, hypertension,

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dyslipidemia, adiposity, tobacco consumption and reduced physical fitness is similar in RA-patients as in patients with coronary artery disease (CAD) [1,6,7,14,15,22]. Therefore, traditional CV risk factors cannot be the only explanation for the increased incidence of MACE in RA and accelerated atherosclerosis is the dominating pathologic factor. As estimated from angiography, systemic inflammation is the major pathologic factor accounting for the high incidence of MACE in RA [1,5-20,23-32]. A study [25], using fluorodeoxyglucose positron emission with concomitant computer tomographic registration, demonstrated aortic inflammation in patients with active RA. This observation suggests subclinical vasculitis, a finding not shared by patients with stable CAD without RA. In untreated RA-patients pathologic endothelial dysfunction and several vascular abnormalities have been detected. Autoimmune induced arteritides aggravate lesional inflammation thus making plaques more vulnerable to rupture and thrombosis [10,30-32]. There is also strong evidence that immune dysregulation and female sex are contributing pathophysiologic factors in RA and that chronic inflammatory markers are independently associated with CV morbidity and mortality [1,3,7,8,12,20,25-36]. The multiple interplaying mechanisms sustaining inflammation in RA are summarized in Table 1.

Compared to age- and sex-matched controls, RA-patients have a higher prevalence of unrecognized CAD but have a reduced prevalence of multivessel disease and less severe coronary arteriosclerosis [37]. On the other hand, in RA-patients unstable plaques and coronary artery medial and adventitial inflammation were significantly more frequent and prominent, leading to plaque vulnerability with rupture, thrombosis and a higher rate of sudden death [38-40]. Rarely, in RA an acute coronary syndrome may occur without CAD [21], confirming the importance of the microvascular pathology in this disease.

Assessing the CV risk in RA

The CV risk SCORE was developed to improve the medical managements of RA-patients and is representative of typical European populations [41]. The use is simple and SCORE can be opened using the link in reference 41. The major risk factors are additive in predictive power. The CV risk is stratified as low (<10%), intermediate (10-20%) and high (>20%). The risk for CAD is usually predictive for a 10-year risk of MACE. Experts recommend that a systematic CV risk-factor screening with SCORE ought to be performed annually and be used to treat RA-patients. However, it is of note that available epidemiologic studies on CV risks in RA did not classify patients according to SCORE. Furthermore, SCORE underestimates the CV risk in RA because it does not consider non-traditional risk factors, such as duration and disease severity of RA, which significantly increase MACE [1,9,42]. Indeed, anti-cyclic citrullinated peptide antibodies positivity and rheumatoid factor favor the occurrence of MACE [1,9,43]. Thus a multiplication factor 1.5 was introduced to adapt SCORE for RA-patients [1,42]. Two of the following criteria must be fulfilled: i) disease duration of RA over 10 years, ii) rheuma-factor or anti-cyclic citrullinated peptide positivity, and iii) presence of certain extra-articular manifestations.

Cardiovascular drugs in RA

We lack solid data supporting the validity of available recommendations to reduce MACE in RA. However, to reduce MACE in RA experts recommend the same strategies established in patients with traditional CV risk factors, and these strategies should also be used in patients with other inflammatory diseases, such as ankylosing spondylitis, systemic lupus erythematodes and psoriasis [1,28,36]. Angiotensin converting inhibitors or angiotensin receptor blockers and statins are preferred first-line therapies [44-46] and should be used in RA-patients with an intermediate or high 10-year risk, as calculated with SCORE [1]. As suggested in recent guidelines [44-46] it is recommended to reduce blood pressure to ≤140/80 mm Hg and LDL-cholesterol to <3 mmol/l (<116 mg/ml). The beneficial effects of statins in RA might go beyond their cholesterol-lowering effect, because these drugs seem to possess anti-inflammatory properties, especially beneficial in RA. Indeed, in a trial [47] it was found that in RA-patients, 40 mg of atorvastatin added to antirheumatic drugs lowered CRP after 6 months. Antiplatelet agents for thromboembolic prophylaxis are only indicated in RA-patients with established CV disease [1]. Of note, the benefit of antiplatelet agents in RA-patients with high CV risks is lower than usually presumed [48] and yet the bleeding risk is increased [49]. Therefore, the higher risk of gastrointestinal events of antiplatelets agents in RA-patients with concomitant NSAIDs has to be weighed against the possible CV protection.

Antirheumatic agents and CV risk in RA

Non-steroidal antirheumatic drugs (NSAIDs) and cyclooxygenase-2 inhibitors (COXIBs): The therapeutic role of non-steroidal antirheumatic drugs (NSAIDs) and cyclooxygenase-2 inhibitors (COXIBs) in RA has diminished, but these drugs are still commonly used. According to meta-analyses [50-52], high-doses of most NSAIDs are associated with an increased risk of MACE, while naproxen should not be associated with excessive CV events, probably because of its antiplatelets effects. However, there are doubts about the suggestion that naproxen might have a lesser deleterious impact on the CV system than other NSAIDs and COXIBs [53]. It is suggested that the most deleterious impacts of NSAIDs on the CV system is mediated by their hypertensive effect [52]. It has also been found that the use of all NSAIDs increases the occurrence of atrial fibrillation [54,55]. It should, however, be noted that some of the deleterious CV effects of NSAIDs and COXIBs could be potentially counteracted by their anti-inflammatory effects. Indeed, in some studies [56-58] the use of NSAIDs in RA was not associated with more frequent MACE and increased mortality from all causes. Altogether, the role and effects of NSAIDs and COXIBs on CV mortality is controversial.

Glucocorticosteroids: Glucorticosteroids (GLUCOR) are often used in the therapy of RA. Even in the most conservative estimate there is evidence that GLUCOR given in addition to standard therapy can substantially reduce the rate of erosion progression in RA [59,60]. Readers interested in the antirheumatic properties of GLUCOR in

Increased synthesis of inflammatory mediators
• Autoantibodies against endothelial cells components or anti-apoA1 lipoprotein.
• Adhesion molecules.
• Chemokines and cytokines.
Other risk factors
• Oxidative stress.
• Immune dysregulation with perturbation in T-cells subsets.
• Abnormal vascular repair
• Hyperhomocysteinemia.
• Genetic polymorphism.
• Raised erythrocyte sedimentation rate.
• Elevated protein C levels.
• Seropositivity.
• Joint synovitis and/or erosions.
• Extra-articular involvement (e.g., RA nodules, vasculitis and lung involvement).
• Iatrogenic factors.
• Female sex.

Table 1: Factors responsible for CV in RA.

Agents	Effect on CV risk
NSAIDs and COXIBs	Some studies show that the use of these agents is associated with an increased risk of MACE and atrial fibrillation. Other studies indicated that the use of these agents was not associated with an increase MACE and mortality from all causes. Altogether, the role and effects of these agents on CV mortality is controversial.
Glucocorticoids	Glucocorticosteroids may promote CV disease because by inducing insulin resistance, increasing body weight, and worsening/inducing hypertension and dyslipidemia. Nonetheless, in RA-patients with pre-existing CAD, use of these agents was associated with a reduced risk for cardiac deaths. Also, it seems that an insufficient use of corticosteroids in RA may increase the CV risk and that the combined use of corticosteroids with DMARDs in RA-patients with persistent disease activity should minimize the CV. Altogether, as for NSAIDs and COXIBs the effect of glucocorticosteroids and CV mortality is controversial.
DMARDs and BAs	Antimalarials, sulphasalazine, d-penicillamine, oral and parenteral gold, azathioprine and cyclosporine: there is no evidence that these agents reduce MACE in RA. Parenteral gold has the potential for negative effects on renal function and should the occurrence of MACE in RA. Low-dose methotrexate may mitigate the CV risk in RA. Controversial data suggest that leflunomide might reduce CV risk in RA. DMARDs and BAs may lower the CV risk either by directly influencing the atherosclerotic process or indirectly through suppression of inflammation or by affecting some CV risk factors [1,36,42]. Some studies reported a significant reduction in MACE in RA-patients treated with TNFα antagonists. Other studies reported no significant effects on MACE. Long-term studies are not available. At present we lack data of the impact of JAK-inhibitors on the CV system. Altogether, at present the effect of these agents on MACE is controversial.
	The impact of antirheumatic agents on the CV risk in RA remains unsettled. In RA CV mortality and MACE remain high.

Table 2: Effects of antirheumatic drugs on the CV risk in RA.

RA should read specific articles [59,60]. GLUCOR have a complex relationship with atherosclerosis [28,36,42,59-61]. GLUCOR may promote CV disease by inducing insulin resistance, by increasing body weight, and by worsening/inducing hypertension and dyslipidemia [20,36,59-61]. On the other hand, use of GLUCOR in RA-patients with pre-existing CAD was associated with a reduced risk for cardiac deaths [61-63]. Also, the combined use of GLUCOR with other antirheumatic drugs in RA-patients with persistent disease activity should reduce the CV risk [36]. Lastly, it seems that an insufficient use of GLUCOR in RA may increase the CV risk [64]. Altogether, the effect of GLUCOR on CV mortality is controversial.

Disease modifying antirheumatic drugs: Disease modifying antirheumatic drugs (DMARDs) include antimalarials, sulphasalazine, d-penicillamine, oral and parenteral gold, azathioprine, cyclosporine, leflunomide and methotrexate (MTX). The antirheumatic effects of DMARDs in RA are presented in an editorial by Wollheim [65].

DMARDs can lower the CV risk either by directly influencing the atherosclerotic process or indirectly through suppression of inflammation or by affecting some CV risk factors [1,36,42]. However, there is no evidence that antimalarials, sulphasalazine, d-penicillamine, gold, azathioprine and cyclosporine reduce MACE in RA [65]. Parenteral gold may negatively affect renal function and therefore, it should increase the occurrence of MACE in RA. MTX may improve the lipid profile of RA-patients [66,67]. However, the therapeutic impact of its minor lipid lowering effect on reducing MACE in RA remains speculative and so far we have no data from intervention trials on the effects of lipid lowering pharmacotherapy in RA-patients. The effect of MTX on CV risk in RA is uncertain. In one study in RA-patients with established CAD [68] the occurrence of sudden death was increased in patients treated with MTX. However, subsequent studies suggest that the anti-inflammatory effect of MTX in RA reduces MACE and associated mortality [69,70]. Ongoing trials are evaluating the effect of MTX and inhibition of interleukin-1β on MACE in RA [71,72]. In summary, most data suggest that low-dose MTX may mitigate the CV risk in RA. Few data are available on leflunomide. Some RA-patients develop hypertension when treated with this agent [73]. However, controversial data suggest that leflunomide might reduce MACE in RA-patients [74,75].

Biologic agents: The introduction of tumor necrosis factor-α (TNFα) antagonists revolutionized the management of RA and catalyzed the development of other biologic agents (BAs) [20,35,61]. According to current recommendations TNFα-antagonists should be considered a first-line therapy in RA [42,46,76-78]. The antirheumatic effects of TNFα-antagonists are presented in a recent update [76]. The new TNFα-antagonist remicade can prevent RA from progressing but about 20 % of patients do not respond to other TNFα-antagonists remicade [76,77]. Of note, available TNFα-antagonists may induce/worsen congestive heart failure [61]. Nonetheless, available TNFα antagonists seem to reduce aortic stiffness and improve endothelial dysfunction [79-81] and reduce CV morbidity, especially in responders [14,81-84]. The effects of available and newer (abatacept, rituximab and tocilizumab) BAs on MACE and CV mortality remain to be determined [85,86]. However, the effects of BAs on the arterial system vary, not all agents improve stiffness [87] and the positive effect may also be transient [88]. Not surprisingly, some studies did not detect a positive effect of TNFα antagonists on MACE in RA-patients [89,90].

New BAs for RA: Two of the main roadblocks in the quest to develop oral BAs have been that these protein molecules are too large to be absorbed if taken orally and that they are no longer active after getting digested [91]. However, another type of BAs can be taken orally. Janus kinases (JAK) are cytoplasmic protein tyrosine kinases that are critical for signal transduction of several important cytokines. JAK-inhibitors block these pathways by binding to a common gamma chain used by these receptors and can be administered orally. One of these drug blocks syk kinase (spleen tyrosine kinase) and some research has suggested that this drug may work in people who do not respond to TNF blockers [92]. The JAK-inhibitor, tofacitinib, preferentially inhibits JAK_1 and JAK_3 and is available for the treatment of RA. Another oral JAK-inhibitor, baricitinib, inhibits JAK_1 and JAK_2, is under investigation for RA. In a recently published randomized trial of over 500 patients with active RA refractory to one or more TNFα-antagonists (and to other BAs in some cases), patients were significantly more likely to achieve an ACR20 response at 12 weeks with baricitinib compared with placebo, and physical function also improved [93,94]. However, there are still many questions that need to be answered about JAK inhibitors. Possible side effects may include anemia, rare effects on white blood cell count, and some elevation of blood fats [91].

In summary, at present we have conflicting data on the effect of BAs on MACE in RA-patients and we lack sufficiently powered long-term studies (Table 2).

Non-pharmacologic interventions: Life-style interventions, such as tobacco abstinence, moderate alcohol consumption, increased physical activity and weight reduction (especially aimed to reduce central obesity) are recommended in RA-patients, especially if they are at moderate or high CV risk [14,16,17,20,36,42]. Dietary fiber consumption and reduced consumption of dietary saturated fat and trans-fat should be reasonable. Phytosterols have been recommended, but there are no studies proving that they are therapeutically effective [1,20].

Discussion

Control of the articular pathology remains the principal aim in the therapy of RA. However, physicians should consider the impact of CV risks in RA. RA and atherosclerosis share several pathologic features. Systemic inflammation plays a central role for the occurrence of MACE in both diseases. The interactions of systemic and local vascular inflammation due to RA, the impact of atherosclerosis due to traditional CV risk factors, and the degree to which these pathways contribute to MACE in RA remains unsettled. All interventions (NSAIDs, COXIBs, GLUCOR, MTX, leflunomide, DMARDs and BAs) have not yet demonstrated valid positive effects in reducing the increased CV risk in RA. The occurrence of MACE and related CV mortality remains high. Especially high risk RA-patients should be monitored and treated with available options to reduce the high risk for MACE.

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