Cardiovascular risk in rheumatoid arthritis: assessment, management and next steps

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***Abstract*:** Rheumatoid arthritis (RA) is associated with increased cardiovascular (CV) morbidity and mortality which cannot be fully explained by traditional CV risk factors; cumulative inflammatory burden and antirheumatic medication-related cardiotoxicity seem to be important contributors. Despite the acknowledgment and appreciation of CV disease burden in RA, optimal management of individuals with RA represents a challenging task which remains suboptimal. To address this need, the European League Against Rheumatism (EULAR) published recommendations suggesting the adaptation of traditional risk scores by using a multiplication factor of 1.5 if two of three specific criteria are fulfilled. Such guidance requires proper coordination of several medical specialties, including general practitioners, rheumatologists, cardiologists, exercise physiologists and psychologists to achieve a desirable result. Tight control of disease activity, management of traditional risk factors and lifestyle modification represent, amongst others, the most important steps in improving CV disease outcomes in RA patients. Rather than enumerating studies and guidelines, this review attempts to critically appraise current literature, highlighting future perspectives of CV risk management in RA.

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

Introduction

Rheumatoid arthritis (RA) is related with excess overall mortality [Dadoun *et al.* 2013] mainly due to increased cardiovascular (CV) disease, which accounts for over 50% of premature deaths in this population [Aviña-Zubieta *et al.* 2008]. The link between RA and CV morbidity has been unequivocally established in historical cohorts, as the disease effect on CV risk is considered comparable to that of diabetes [Van Halm *et al.* 2009; Lindhardsen *et al.* 2011]. RA patients appear to have about a twofold higher possibility for myocardial infarction than non-RA patients, similar with diabetes [Peters *et al.* 2009]. Other CV manifestations including valvular heart disease, arrhythmia, pericarditis and endocarditis as well as rheumatoid cardiac nodules have also been described but rarely cause clinically overt disease [Kitas *et al.* 2001]. On the contrary, myocarditis and microvascular disease are common, as suggested by newer imaging techniques, although their contribution to CV mortality remains unclear [Mavrogeni *et al.* 2009, 2014a]. Furthermore, RA is associated with a twofold higher possibility for heart failure with a worse prognosis than non-RA patients [Nicola *et al.* 2005]. Of note, diastolic heart failure with preserved ejection fraction seems to be more prevalent reflecting the influence of chronic inflammation on the myocardium [Yndestad *et al.* 2007; Davis *et al.* 2008; Mavrogeni *et al.* 2012; Mavrogeni *et al.* 2014b]. Accordingly, ventricular diastolic dysfunction and pulmonary hypertension represent frequent findings in long-term treated RA patients, even in the absence of clinically evident CV disease or traditional CV risk factors [Gonzalez-Juanatey *et al.* 2004]. In any case, atherothrombosis and especially coronary artery disease (CAD) hold the pivotal role to the increased mortality of the disease [Skeoch and Bruce, 2015] and are associated with more severe presentation and worse outcomes compared to the general population [Douglas *et al.* 2006; Mantel *et al.* 2015].

Traditional risk factors such as hypertension, smoking, dyslipidemia and obesity contribute to the endothelial dysfunction in RA but cannot

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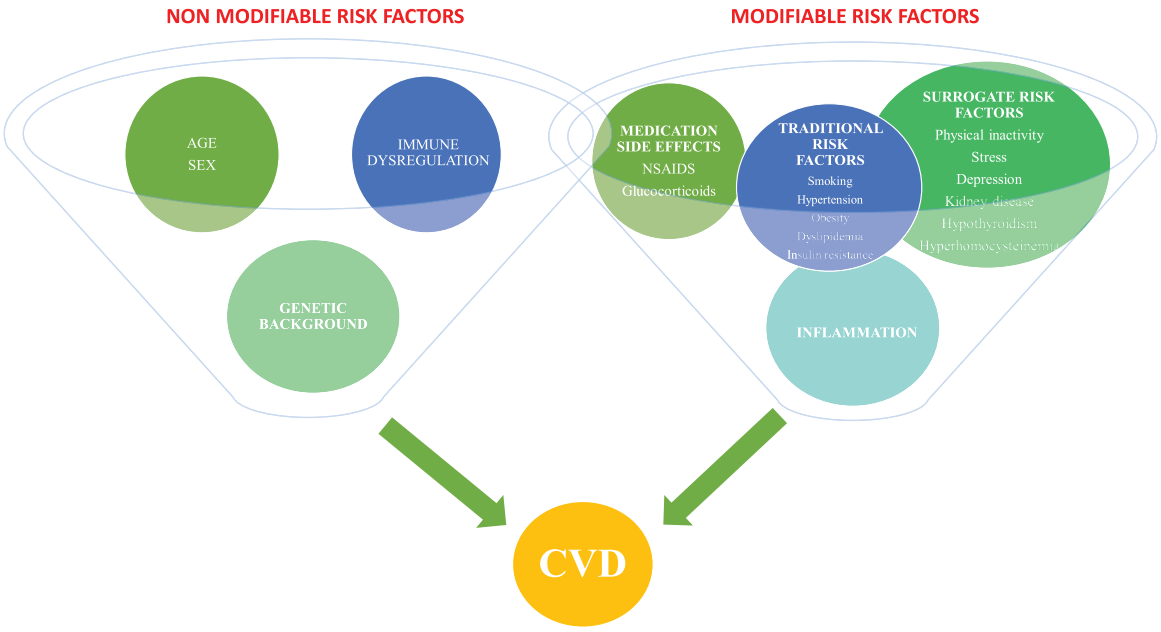

Figure 1. The complex interrelations between several risk factors in the development of premature atherosclerosis in RA. Modifiable risk factors represent a broad spectrum of heterogeneous parameters including traditional, surrogate and novel mainly RA-related risk factors. Age, sex, genetic basis of autoimmunity and atherosclerosis, as well as the presence of disease specific autoantibodies, are also drivers of vascular disease contributing to a lesser or greater extent to CV complications in this population.
CVD, cardiovascular disease; NSAIDs, nonsteroidal anti-inflammatory drugs.

fully explain the high magnitude of CV disease. Other RA-related factors, such as anti-inflammatory treatment side effects, extra-articular RA, and predominantly the chronic high-grade inflammatory state of the disease have been linked to the development of premature atherosclerosis (Figure 1) [Amaya-Amaya *et al.* 2013; Crowson *et al.* 2013; Beinsberger *et al.* 2014; Sandoo *et al.* 2015]. In addition, the inevitable sedentary lifestyle of RA patients confers an increased risk for CV disease [Naranjo *et al.* 2008].

Taken together, the atypical symptomatology that characterizes the occurrence of coronary syndromes in RA, the lack of large randomized-controlled trials (RCT), and the poor integration of prevention strategies in the management of patients, render CV risk assessment an important and challenging task among these individuals.

In this review rather than enumerating clinical studies and guidelines, we critically appraise current evidence about CV disease in RA, highlighting the existing controversies on the management of patients and providing future perspectives.

Traditional risk factors

Smoking

Current and exsmokers are more prevalent among RA patients. Specifically, the possibility of a RA patient being a current or an exsmoker is about 1.5 times higher than the general population [Boyer *et al.* 2011]. This is not unexpected as the causal link of smoking and the occurrence of RA has already been established [Bergstrom *et al.* 2011]. In addition, smoking has been associated with rheumatoid factor (RF) and anticitrullinated protein antibody (ACPA) positivity as well as more severe clinical presentation reflected by increased disability and radiographic damage [Rojas-Serrano *et al.* 2011]. Moreover, a recent meta-analysis confirmed the association of smoking with the CV risk in RA [Baghdadi *et al.* 2015].

Hypertension

The evidence about hypertension in RA appears conflicting. A meta-analysis that included seven case-control studies showed that no significant differences existed on the prevalence of hypertension

amongst RA subjects and controls [Boyer *et al.* 2011]. In contrast, Panoulas and colleagues demonstrated a relatively higher prevalence [Panoulas *et al.* 2007] whilst the results of the international COMORA study reported that hypertension was prevalent in 40% of RA patients [Dougados *et al.* 2014]. Regardless of the occurrence of hypertension, the reported high rates of underdiagnosis and undertreatment of this condition within RA populations, particularly in younger and older overweight patients [Panoulas *et al.* 2007], as well as its association with end-organ damage [Panoulas *et al.* 2010] mandate a more aggressive strategy, targeting effective control of blood pressure and potential reduction of CV risk.

The diminished ability of the arterial system to adapt to alterations in the blood flow is a mechanism contributing to higher blood pressure in RA individuals. Several studies have showed that reduced arterial wall pliability and increased stiffness are involved in the pathogenesis of hypertension are also associated with the disease [Ben-Shlomo *et al.* 2014]. On the other hand, hypertension appears to cause more adverse effects to RA patients than the general population.

Despite the fact that disease modifying drugs have not been proven to increase blood pressure, the effect of other regimens such as nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids is substantial. Also, additional comorbidities including obesity, stress and physical inactivity may contribute to the development of hypertension. Proinflammatory cytokines such as tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6) are associated with higher blood pressure illustrating the reciprocal link between hypertension and inflammation: the former causes vascular damage and thus induces inflammation *via* oxidative stress whereas the latter appear to increase arterial stiffness and wall pliability [Cohen Tervaert, 2011; McMaster *et al.* 2015].

Dyslipidemia

Abnormal lipid metabolism and especially low density lipoprotein (LDL) hold a key role in the atherosclerotic procedure. Dyslipidemia is common in RA affecting between 55–65% of patients [Toms *et al.* 2010]. Paradoxically, lower lipid levels are associated with increased CV risk in RA [Semb *et al.* 2010] whereas levels of LDL, high density lipoprotein (HDL), and total cholesterol (TC) are inversely correlated with markers of chronic inflammation, forming a complex puzzle which results in premature atherosclerosis [Myasoedova *et al.* 2011]. Inflammation promotes consumption or reduces synthesis of lipoproteins whereas functional and structural changes of these molecules may also occur during periods of high disease activity [Carpentier and Scruel, 2002]. For example, HDL function is impaired and may even express proinflammatory characteristics in about 20% of RA patients [Hahn *et al.* 2008]. In line with this, the cholesterol efflux capacity of HDL is impaired in association with a reduced antioxidant activity [Charles-Schoeman *et al.* 2012]. To lend more support, high-grade inflammation in severe RA correlates with lower adiponectin concentration which seems to cluster with atherogenic dyslipidemia (TC/HDL ratio and triglycerides/HDL ratio) as well as with high plasma glucose levels [Gonzalez-Gay *et al.* 2008].

The apolipoprotein-related mortality risk (AMORIS) study evaluated the prognostic significance of TC and triglycerides for CV events among RA and non-RA patients. A statistically significant predictive value was demonstrated for non-RA patients whereas the results for RA patients were inconsistent [Semb *et al.* 2010]. In addition, impaired LDL, increased apolipoprotein (apo)-B/apo-A1 ratio and lipoprotein (a) levels seem to promote accelerated atherosclerotic procedure [Robertson *et al.* 2013]. The above controversies reveal the significance of the confounding effect of inflammation. In this context, the TC/HDL ratio (atherogenic index) has been recommended as a better marker for CV risk assessment because of the parallel decrement of their circulating levels during inflammation [Robertson *et al.* 2013]. Accordingly, the assessment of lipid profile during low-disease activity may produce more reliable estimations, but more research is required to confirm this approach.

The complexity of lipid metabolism, its effect on the CV risk and the unacceptable low rate of primary lipid screening in RA patients [Bartels *et al.* 2011] is reflected in the underutilization of lipid-lowering therapy even in RA patients who fulfill general population thresholds for treatment [Toms *et al.* 2010] and underlines the necessity for the incorporation of guidelines in the routine examination and follow up of people with RA. In this way, earlier identification of individuals at higher risk, implementation of

prevention strategies and prompt introduction of appropriate treatment can be achieved.

Body mass index, obesity and physical inactivity

Alterations in body composition exhibit another paradoxical relationship in RA as lower body mass index (BMI) is associated with increased CV risk. Contrary to its protective effect in non-RA patients [Escalante *et al.* 2005], low BMI independently predicts CV death even after adjusting for the most important risk factors [Maradit-Kremers *et al.* 2005]. The underlying pathophysiological mechanism comprises of the effect of chronic uncontrolled systemic inflammation on adipose tissue which leads to muscle degradation and involuntary fat accumulation, a condition known as rheumatoid cachexia, characterized by stable or slightly increased body weight [Summers *et al.* 2010]. Of note, sarcopenia, overfat and sarcopenic obesity seem to be more prevalent in normal weight RA patients underlining the inaccuracy of BMI as a surrogate for body composition [Giles *et al.* 2008]. Obesity contributes to the development of inflammation *via* changes in metabolism and function of adipose tissue [Dessein and Solomon, 2013]. Furthermore, obesity appears to coexist with other CV risk factors such as hypertension, insulin resistance and dyslipidemia [Bray and Bellanger, 2006]. There is a complex interrelation between obesity, physical inactivity, RA and CV disease. Patients with RA adapt an inactive lifestyle with significantly reduced physical activity due to a number of reasons, including joint pain and stiffness, psychological disturbances or even fear of aggravating their disease, which apparently worsens the CV risk profile and leads to a higher BMI [Metsios *et al.* 2009]. Only a few cross-sectional studies have looked into factors that may influence obesity in RA and they have found a relationship between increased body weight and limited physical activity, low energy intake and underweight state [Stavropoulos-Kalinoglou *et al.* 2010] as well as a lowest prevalence of obesity amongst active smokers [Stavropoulos-Kalinoglou *et al.* 2008]. Despite the fact that obesity is considered to be a potent contributor to the inflammatory pathogenesis of atherosclerosis [Berg and Scherer, 2005] and observations indicating that it independently associates with the presence of traditional CV risk factors [Stavropoulos-Kalinoglou *et al.* 2009] and higher C-reactive protein (CRP) concentrations in RA [Dessein *et al.* 2007], a clear relationship between accumulation of excessive fat and heightened CV risk in this population is lacking [Stavropoulos-Kalinoglou *et al.* 2011]. For example, Wolfe and Michaud reported that classical CV risk factors but not obesity influenced the occurrence rates of myocardial infarction in RA patients [Wolfe and Michaud, 2012]. The paradoxical effects of obesity in this population appear to extend beyond CV disease as published data show that obese RA patients have a lower degree of joint involvement and damage suggesting an uncoupling of high CRP levels from synovial inflammation [Van Der Helm-Van Mil *et al.* 2008].

Finally, it is worth noting that BMI thresholds and definitions of obesity utilized in the general population may not capture these specific changes in body composition among RA patients [Stavropoulos-Kalinoglou *et al.* 2007] indicating the necessity for alternative tools such as waist to hip ratio, which may more accurately demonstrate lean and fat tissue changes in this population. Clearly, much research is required to elucidate the mechanisms and establish the biological basis of these phenomena.

Insulin resistance and metabolic syndrome

The prevalence of insulin resistance is increased in RA, underlying the role of several atherogenic processes such as endothelial dysfunction, lipid metabolism dysregulation and acute phase response which are common in both conditions [Dessein *et al.* 2003]. It represents the main mechanism of metabolic syndrome which is also more frequent among RA and is associated with increased CV morbidity and mortality [Da Cunha *et al.* 2012]. Furthermore, insulin resistance seems to provoke chronic low-grade inflammation, regardless of the disease's activity whereas high-disease activity precipitates the adverse effects of metabolic syndrome in endothelial dysfunction [Ferraccioli and Gremese, 2011]. The use of glucocorticoids, antihypertensive treatment and abdominal obesity are considered additional contributors to the alteration of the glucose metabolism in RA [Dessein and Joffe, 2006], however, the exposure to oral steroids was not found to be associated with the prevalence of metabolic syndrome in a cross-sectional study including 398 RA subjects [Toms *et al.* 2008]. Finally, administration of methotrexate has demonstrated a significant negative correlation with the presence of metabolic syndrome [Toms *et al.* 2009], possibly due to its anti-inflammatory effects. A dramatic improvement of insulin resistance and insulin

sensitivity was observed following a single infusion of the anti-TNF monoclonal antibody, infliximab. Long-term positive effects of TNF-α antagonists, infliximab and etanercept, on insulin resistance in RA patients with severe disease has also been reported [Gonzalez-Gay *et al.* 2010]. However, anti-TNF-α regimens seem to improve insulin sensitivity in normal weight but not obese RA patients [Stavropoulos-Kalinoglou *et al.* 2012].

RA-related risk factors

RA inflammation and immune dysregulation

The chronic high-grade inflammatory state of RA, the severity of the disease as reflected by joint erosions, extra-articular manifestations, and the ensuing physical disability are established risk factors for CV disease in this population [Kremers *et al.* 2008]. Accordingly, inflammatory and serological markers such as erythrocyte sedimentation rate, RF, ACPA and CRP have been positively associated with increased atherogenicity and CV events in several studies assessing RA patients [Farragher *et al.* 2008; Kremers *et al.* 2008; Liang *et al.* 2009]. as well as in the general population [Skeoch and Bruce, 2015].

It is now well-recognized that systemic inflammation contributes to the initiation and development of accelerated atherosclerosis since inflammatory processes in the rheumatoid synovium and atherosclerotic plaques are remarkably similar [Stevens *et al.* 2005]. The increased synthesis and release of proinflammatory cytokines such as TNF-α and IL-6 to the systemic circulation leads to endothelial dysfunction, the initial step to atherosclerosis. TNF-α induces cytokine release by activating the monocytes and IL-6 activates immune cells involved in the plaque formation and rupture [Choy, 2012]. To lend more support, RA patients without a history of CV disease had more frequent coronary plaques, which were more severe and more prone to rupture, compared to matched controls in a recent study [Karpouzas *et al.* 2014]. This is in line with previous observations indicating instability of atherosclerotic plaque, probably due to the high magnitude of vascular inflammatory load, as one of the most important factors of higher rates and worse outcomes of acute coronary events in RA patients [Aubry *et al.* 2007]. Last but not least, chronic high-grade systemic inflammation precipitates the adverse effects of traditional CV risk factors on vascular wall underlying the complexity of the links between RA-related factors, impairment of endothelial function and myocardial injury [Mavrogeni *et al.* 2009; Sandoo *et al.* 2012; Liao and Solomon, 2013].

Immune activation, as reflected by the presence of autoantibodies, is considered as an important nonmodifiable risk factor for CV disease in RA. RF and antinuclear antibody positivity have been associated with an increased risk for myocardial infarction, heart failure and vascular disease even after adjusting for the presence of rheumatic disease [Liang *et al.* 2009]. Moreover, ACPA are closely linked with endothelial dysfunction and seem to promote accelerated atherogenicity [Hjeltnes *et al.* 2011]. Considering all the above, systemic inflammation and immune dysregulation serve as major RA-related CV risk factors which may, at least partly, account for the excess of CV disease in RA.

Antirheumatic drug-related cardiotoxicity

The use of NSAIDs is associated with increased CV risk, hypertension and heart failure in the general population; however their effect in RA patients remains a subject of controversy. Goodson and colleagues showed that there was no correlation between the use of NSAIDs and increased CV risk in early undifferentiated inflammatory arthritis whereas a meta-analysis by Trelle and colleagues concluded that there is not enough evidence to guarantee the safety of these drugs [Goodson *et al.* 2009; Trelle *et al.* 2011]. A more recent, large scale longitudinal cohort study that used data from the Danish nationwide registry showed that the increased CV risk associated with the overall use of NSAIDs in RA was modest and significantly lower than in non-RA subjects [Lindhardsen *et al.* 2013]. This pattern remained true for the individual NSAIDs investigated with the exception of rofecoxib and diclofenac which were both associated with a significantly increased CV risk [Lindhardsen *et al.* 2013]. Current recommendations suggest the use of NSAIDs with caution in RA individuals, especially in the presence of additional CV risk factors or established CV disease [Marks *et al.* 2012]. Nonetheless, further research is needed in order to fully comprehend the complex impact of these regimens on the CV risk in RA populations.

The administration of glucocorticoids is generally associated with increased CV risk considering the

drug's effect on hypertension and lipid or glucose metabolism. In agreement, several studies confirm this adverse effect in RA which appears to be dose dependent [Avina-Zubieta *et al.* 2013; Del Rincon *et al.* 2014; Listing *et al.* 2015]. Daily doses of prednisone <5–7.5 mg are considered relatively well tolerated. Nonetheless, there are studies which demonstrate that the anti-inflammatory effect of glucocorticoids counteracts the increment of the CV risk and therefore their use may be beneficial [Naranjo *et al.* 2008]. This concurs with observations indicating a lack of association between steroid use and metabolic syndrome in RA individuals [Toms *et al.* 2008]. Of note, EULAR guidelines recommend the use of glucocorticoids at the lowest dose, for the shortest period of time [Peters *et al.* 2010].

Although biologic drugs have enormously improved clinical outcomes in RA patients conferring a potential beneficial effect on the CV risk, anti-TNF-α therapy should be administered with caution in patients with moderate or severe heart failure as it may lead to a deterioration of previously established cardiac disease [Listing *et al.* 2008]. TNF-α inhibitors, leflunomide and less commonly used cyclosporine have been linked with increased risk of developing high blood pressure in RA patients [Gasparyan *et al.* 2012; Zhao *et al.* 2015]. Disease modifying drugs, especially methotrexate, may exhibit adverse effects on lipid profile and similar observations have been recently reported for IL-6 inhibitors [Souto *et al.* 2015]. It is worth noting that even emerging treatments for RA including small molecules, such as spleen tyrosine kinase inhibitors, have been associated with high blood pressure in randomized controlled trials [Kitas *et al.* 2014]. Given the wide variety of CV side effects related to the administration of broadly used conventional and biologic disease modifying drugs, the appreciation of unfavorable effects of individual regimens on traditional and disease-related CV risk factors represents an important element of CV prevention and physicians treating RA patients should be aware of this additional risk.

Genetic risk factors

The genetic background is also related to the heightened CV disease risk in RA. Human leukocyte antigen (HLA)-DRB1*04 shared epitope alleles seem to predispose for CV events [Gonzalez-Gay *et al.* 2007]. Interestingly, TNF-α rs1800629 gene polymorphism was also associated with increased risk of CV disease in patients who carried the rheumatoid shared epitope [Rodriguez-Rodriguez *et al.* 2011]. In addition, there are polymorphisms outside the major histocompatibility complex (MHC) region that demonstrate increased prognostic value for atherosclerosis even after adjusting for traditional CV risk factors [Palomino-Morales *et al.* 2010; Lopez-Mejias *et al.* 2012]. Various polymorphisms have also been connected to an increased prevalence of hypertension, dyslipidemia, and higher levels of endothelial dysfunction markers such as asymmetric dimethylarginine [Panoulas *et al.* 2008; Toms *et al.* 2012; Dimitroulas *et al.* 2014].

Additional risk factors

The aggravated psychological state of the patients and especially stress may be important for the CV risk. Stress dysregulates immune system and may trigger autoimmune proinflammatory processes. In this regard, Solomon and colleagues observed an association between symptoms of tension and carotid plaque occurrence in RA in a study including black and white Africans [Solomon *et al.* 2012].

The relationship between depression and systemic inflammation is reciprocal. The former seems to promote inflammation through immune activation whereas the latter may induce depressive symptoms. In general the poor compliance to chronic therapies and the general difficulty in the management and persuasion of depressive patients may have an additional input to the increased comorbidities in this special subgroup of RA patients.

Finally, kidney disease, hypothyroidism, hyperhomocysteinemia and vitamin D deficiency, which are common in RA individuals, contribute to the increased CV risk and should receive the appropriate attention by clinicians [Daoussis *et al.* 2010; Gonzalez-Gay *et al.* 2010; Haque *et al.* 2012; Raterman *et al.* 2012]

Cardiovascular risk assessment: a Gordian knot in RA

Calculators used to assess the CV risk in the general population (Systematic Coronary Risk Evaluation [SCORE], Framingham) underestimate it in RA, although some of them incorporate high sensitivity CRP in the estimation of CV risk [Gonzalez *et al.* 2008; Crowson *et al.* 2012]. In

Table 1. EULAR recommendations for cardiovascular risk assessment and management [Peters *et al.* 2010].

1. RA is associated with greater risk for CVD
2. The control of the disease activity is imperative for lowering the CVR
3. Cardiovascular risk assessment according to national guidelines, annually or whenever the antirheumatic treatment changes, is necessary for all patients with RA
4. Risk score models should be adapted for RA patients after the multiplication by a factor of 1.5 if two of the three following criteria are fulfilled:
   - Disease duration >10 years
   - RF or ACPA positivity
   - Extra-articular manifestations
5. When the SCORE model is applied the TC/HDL ratio should be used
6. Pharmacological treatments should follow the national guidelines
7. Statins, ACE inhibitors/A-II blockers are the first treatment options
8. The effect of NSAIDs and coxibs on the CVR is not well established. Caution is required when prescribing them, especially for patients with documented CVD or at high CVR
9. The lowest dose possible of corticosteroids is advised
10. Smoking cessation is recommended

ACE, angiotensin converting enzyme; ACPA, anticitrullinated protein antibody; CVD, cardiovascular disease; CVR, cardiovascular risk; HDL, high density lipoprotein; NSAID, nonsteroidal anti-inflammatory drug; RA, rheumatoid arthritis; RF, rheumatoid factor; TC, total cholesterol.

addition, all the traditional calculators have been developed on the perception that men exhibit a greater risk for CV disease than women, who represent the major population in RA. For example, about one fourth of women with RA that are classified as very low risk according to the SCORE calculator, exhibit carotid plaques which reclassifies them to the high risk category [Corrales *et al.* 2015]. It is worth noting that QRISK2 which is used in the United Kingdom, includes RA as an independent risk factor and seems to improve the risk estimation [Hippisley-Cox *et al.* 2008]. However, Arts and colleagues demonstrated that QRISK2 overestimates the CV risk [Arts *et al.* 2015]. European Society of Cardiology (ESC) guidelines in 2012 also incorporate RA as a CV risk factor but without promoting significant alterations concerning the clinical management of the patients [Perk *et al.* 2012]. Finally, the 2013 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines increased the proportion of patients with RA who were eligible for lipid-lowering therapy although the CV risk estimation remained inaccurate [Kawai *et al.* 2015; Tournadre *et al.* 2015].

The need of including the strong confounding effect of inflammation in the CV risk stratification of patients along with the mounting evidence of the excess of CV disease in RA led EULAR to develop in 2010 specific recommendations for CV risk assessment and management of patients with RA and other inflammatory diseases (Table 1) [Peters *et al.* 2010]. These recommendations are based on evidence-based expert consensus opinion but data from large-scale prospective studies is lacking and, as the authors concurred, they should be reexamined in the light of new evidence.

EULAR recommendations suggest the adaptation of traditional calculators like SCORE and Framingham and attempt to adjust them for RA by the multiplication of the measured risk score by a factor of 1.5 if two of the three criteria below are fulfilled: (1) RA disease duration >10 years, (2) presence of RF or anti-CCP and (3) presence of severe extra-articular manifestations. In addition, EULAR proposes an annual CV reassessment excluding patients with low CV risk or low disease activity which may be followed up every two or three years [Peters *et al.* 2010].

Several studies highlight the inefficiency of the EULAR recommendations demonstrating that the CV risk score in RA seems to be underestimated even after the aforementioned multiplication. In a study of 327 patients by Corrales and colleagues, 96 individuals were classified as low risk according to SCORE, 201 at moderate risk, and 30 at high or very high risk [Corrales *et al.* 2014]. After the multiplication for RA, only 5 (2%) of patients were reclassified as high or very high risk. Another more recent study demonstrated that the percentage of

patients' reclassification after applying the EULAR adjustment for RA was relatively low, regardless of the risk score calculator used, with a maximum value of 12% [Karpouzas *et al.* 2013].

Other aspects of CV risk, that are not included in CV risk calculators for the general population, should be taken into account in RA patients. For example, the identification of subclinical atherosclerosis may alter the risk score calculations with classifying more patients at the very high risk category. In this regard, it has been demonstrated that carotid plaque or carotid intima media thickness (cIMT) value >0.9 mm was found in over 60% of RA patients in moderate risk category [Corrales *et al.* 2014].

On the basis of the above findings, EULAR introduced revised recommendations which have not been published yet. The integration of carotid ultrasonography in the screening of patients and the multiplication of the risk score by 1.5 irrespective of the presence of the aforementioned three criteria represent new additions [Nurmohamed, 2015]. The effectiveness of these new recommendations remains to be established by future studies.

Cardiovascular risk management in RA: from uniformity to individuality

It is well accepted that physicians with different sub-specialties, rheumatologists, cardiologists and general practitioners, should be involved in the management of patients with RA although there is still a confusion regarding the role of each health provider in evaluating and treating CV risk. The key point of optimal coordination is the awareness of the increased CV disease burden accompanied by appropriate determination of the CV risk profile. The referral of high-risk individuals to a primary care physician or a skilled cardiologist, followed by educational programs for the patients focusing on the importance of lifestyle modification, constitute further necessary actions [Semb *et al.* 2014]. Lessons taken by other conditions, and particularly diabetes mellitus, should be incorporated in RA populations, for example, the implementation of primary prevention therapy for the management of traditional CV risk factors achieving predetermined targets for blood pressure and cholesterol levels. On the top of these interventions tight control of inflammation is necessary for the decrease of CV risk (Figure 2). Due to the frequent atypical symptomatology of CV disease, a high index of suspicion for CV events is required predominantly in the presence of any suspicious signs or symptoms such as tiredness, chest pain or gradually deteriorated dyspnea. It is important, that any decision about patients' management needs to be critically extrapolated from current evidence and recommendations but in the end it should be individualized.

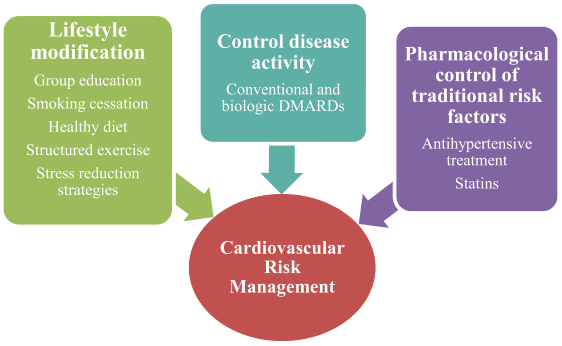

Figure 2. The main domains of CV risk management in RA. Communication of increased CV risk and education of RA patients followed by implementation of lifestyle changes is necessary for the better management of CV disease. Evaluation and treatment of classical risk factors combined with adequate control of disease activity and systemic inflammatory load represent important elements of CV risk prevention and management in RA patients.
CV, cardiovascular; DMARDS, disease modifying antirheumatic drugs; RA, rheumatoid arthritis.

Lifestyle modification

Patients' awareness of their increased CV risk holds a key role for a successful lifestyle modification strategy. In this regard, John and colleagues developed an eight-week cognitive behavioral patient education program which resulted in significant changes in knowledge and intentions to modify adverse CV disease behaviors accompanied by clinical improvement in blood pressure. Although no actual behavioral changes were observed, such interventions, including group education and distribution of written and online material to RA patients and allied healthcare professionals, constitute modern strategies but their integration to routine clinical setting still remains a challenging task [John *et al.* 2011, 2013].

Patients with RA should be encouraged to quit smoking, adapt a healthy diet, avoid excessive alcohol intake, control weight and maintain a normal physical activity. Structured exercise demonstrated a protective effect for CV disease in RA

patients [Stavropoulos-Kalinoglou *et al.* 2013; Metsios and Lahart, 2015]. Not surprisingly, physically active patients appear to have a substantial improvement of the symptoms representing the primary barriers for physical activity and exercise, such as pain and fatigue [Veldhuijzen Van Zanten *et al.* 2015]. Moreover, individualized or group counselling aiming to improve the psychological state of patients and reduce stress would be appropriate therapeutic actions and valuable additions to the traditional therapeutic strategies.

Control of the traditional risk factors

Blood pressure control in RA patients should follow guidelines applied to the general population as no specific targets have been suggested for RA [Perk *et al.* 2012; Innala *et al.* 2011]. EULAR recommend the use of angiotensin-2 receptor inhibitors or angiotensin-converting enzyme blockers as a first option for antihypertensive treatment because of their additional role on inflammation [Peters *et al.* 2010].

LDL's indicated threshold in RA differs according to the grade of the CV risk. In very high risk category cholesterol targets are <1.8 mmol/l, in high risk <2.5 mmol/l and in low and moderate risk <3 mmol/l [Perk *et al.* 2012]. Diet modification represents the first line intervention in order to achieve these goals. When this measure fails, statins are the indicated lipid-lowering therapy even when administered for primary prevention in patients without dyslipidemia [Danninger *et al.* 2014; Ridker, 2014]. Their beneficial effect on endothelial dysfunction, plaque stabilization and chronic inflammation, independently of cholesterol levels, renders statin treatment a valuable therapeutic agent in RA both in the context of primary or secondary prevention [Maki-Petaja *et al.* 2007; Paraskevas, 2008].

Due to the high prevalence of insulin resistance in RA, glucose screening is essential and a glucose tolerance test should be considered even in the presence of minor indications. HbA1c should be maintained $<7\%$ with the appropriate pharmacological or lifestyle interventions [Perk *et al.* 2012].

Control of RA activity

The adequate suppression of the disease activity is necessary to counteract the effects of systemic inflammation on the CV risk in RA and it is considered the cornerstone of managing CV disease complications. In addition, the control of symptoms is important due to their role on the restriction of physical activity and deterioration of the psychosocial status of the patient. Unfortunately, all current knowledge derives from observational studies and, therefore, any conclusion should be interpreted with caution.

Methotrexate has been associated with CV risk reduction and improvement of CV disease outcomes. Specifically, in a large meta-analysis of 10 cohort studies, the administration of methotrexate decreased the risk for CV events by 21%, whereas the risk for myocardial infarction by 18% [Micha *et al.* 2011]. The exact mechanism of this suppressive effect remains unclear but the effective control of systemic inflammation appears to be the main moderator [Roubille *et al.* 2015]. TNF-α antagonists control systemic inflammation and may also exhibit a cardioprotective effect [Barnabe *et al.* 2011]. In line, these regimens appear to restore the antioxidant function of HDL [Van Sijl *et al.* 2011].

Control of other factors affecting the CV risk

Antidepressants are generally recommended to all RA patients suffering from depression, although their association with the reduction of CV risk has not been established. Accordingly, the proper screening and adequate therapy for renal failure, hypothyroidism, vitamin D deficiency and hyperhomocysteinemia, which may be induced by methotrexate, is advised for all patients with RA [Hollan *et al.* 2015].

CV risk in RA: next steps for a better future

The CV excess in RA patients has not been explained adequately. Future research could shed some light on the role of chronic inflammation on vasculature and the specific mechanisms which lead to the disturbance of the molecular equilibria that constitutes the substrate of accelerated atherogenicity. The ultimate goal remains the development of more effective therapeutic strategies for the prevention and treatment of CV disease. In addition, prospective studies could allow the integration of newer imaging techniques to the CV risk assessment of RA patients. Among these techniques cardiac magnetic resonance (CMR) seems more promising to provide early information and illustrate the pathophysiological background of the underlying heart disease. CMR makes the noninvasive distinction between ischemic and

nonischemic heart failure feasible but the early recognition of myocardial inflammation is what really determinates its usefulness. Truthfully, higher disease activity was associated with more frequent abnormal myocardial CMR findings in patients with RA without known cardiac disease [Kobayashi *et al.* 2010]. The existing CV risk calculators are not supported by adequate evidence, lack the anticipated accuracy and their improvement is imperative but challenging for the scientific community. Prospective studies are needed to evaluate the true extent of the impact of the traditional risk factors on the CV risk in RA and to determine more appropriate management strategies, pharmacological or not.

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The authors declare that there is no conflict of interest.

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