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Cardiovascular Safety of Anti-TNF and Non-TNF Biological Therapy in Patients with Rheumatoid Arthritis

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Additional information is available at the end of the chapter

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Abstract

The association between cumulative inflammatory burden and increased cardiovascular (CV) risk in patients with immune-mediated inflammatory rheumatic disorders, particularly rheumatoid arthritis (RA), is widely recognized. Furthermore, the complex and dynamic interrelation between traditional cardiovascular risk factors, systemic inflammation, early accelerated atherosclerosis, and RA-related factors remains a challenge in routine practice. New European League Against Rheumatism (EULAR) 2016 recommendations have recently highlighted three key trends in cardiovascular risk assessment and management in patients with RA including optimal disease control (early diagnosis, treat-to-target strategy with the dynamic use of antirheumatic synthetic and biologic drugs) and non-pharmacological as well as pharmacological management of risk factors. The present chapter will emphasize excessive cardiovascular morbidity in RA, the optimal strategy to identify and stratify the cardiovascular risk profile, the prime selection of medication from the whole spectrum of non-biologic and biologic (TNF and non-TNF) drugs according to their cardiotoxicity.

Keywords: cardiovascular burden, rheumatoid arthritis, inflammation, TNF inhibitors, tocilizumab

1. Introduction

The association between cumulative inflammatory burden and increased cardiovascular (CV) risk in patients with immune-mediated inflammatory rheumatic disorders, particularly rheumatoid arthritis (RA), is widely recognized [1–5].

Furthermore, the complex and dynamic interrelation between traditional CV risk factors (such as hypertension, diabetes, obesity, abnormal lipid metabolism), chronic systemic inflammation, early accelerated atherosclerosis, and RA-related factors (e.g., C-reactive protein level, CRP, disease activity and severity, medication) taken together in a genetically predisposed background remains a challenge in routine practice [1–5].

European League Against Rheumatism (EULAR) 2015/2016 recommendations for cardiovascular disease management have recently highlighted three key trends in cardiovascular risk assessment and management in patients with RA and spondyloarthropathies (ankylosing spondylitis, psoriatic arthritis) including optimal disease control (early diagnosis, treat-to-target strategy with the dynamic use of antirheumatic synthetic and biologic drugs) and non-pharmacological as well as pharmacological management of risk factors [6, 7].

The present chapter will emphasize excessive cardiovascular morbidity in RA, the optimal strategy to identify and stratify the cardiovascular risk profile in different RA settings, the prime selection of medication from the whole spectrum of non-biologic (methotrexate and non-methotrexate drugs) and biologic (TNF and non-TNF) antirheumatic drugs according to their cardiotoxicity.

2. Cardiovascular risk in patients with RA

2.1. Cardiovascular burden in RA

Patients with systemic autoimmune conditions especially inflammatory joint disorders such as RA are at increased risk to develop cardiovascular comorbidity, in particular subclinical or clinically significant atherosclerotic coronary heart disease [1–5, 8].

Compared to general population, patients with RA experience excessive cardiovascular morbidity and, even, mortality, with an increased risk of about 50% [1, 2, 8, 9]. The rate of global cardiovascular as well as individual events comprising fatal and nonfatal myocardial infarction, congestive heart failure, stroke, and major adverse cardiac events (MACE) is increased in RA, the magnitude of cardiovascular risk in such patient being comparable with that related to diabetes [1, 2, 8].

A comprehensive overview of cardiovascular complications and safety issues indicates that RA develops twice myocardial infarction and features an increased risk (up to 87%) of heart failure as compared to general, non-RA population [1–3, 8–11]. Moreover, congestive heart failure in different RA subtypes has a worsen prognosis compared to non-RA patients; more than half of patients known with RA are prone to undergo diastolic heart failure, while diastolic ventricular failure and pulmonary arterial hypertension are broadly reported in long-standing RA [2, 8–11]. Myocarditis typically associates with active disease subtypes and is rare, clinically non-symptomatic, without influence on cardiac mortality [1, 2]. Conversely, atherothrombosis and clinically significant coronary heart disease are highly expressed (65% increase in cardiovascular risk) and account for premature death [2]. Finally, valvular disease, especially mitral regurgitation, is frequent (80%) but usually asymptomatic, while valve nodules, conduction anomalies, and arrhythmias are uncommon in such patients [2].

Both early RA and established or long-standing RA are characterized by augmented CV risk, with a special emphasis on active status, irrespective of disease duration [1, 2, 4, 11].

Cardiovascular comorbidities of autoimmune disorders are the result of different contributing factors and their synergistic effects [1, 2, 4, 5, 8, 9, 11]. Although the prevalence and influence of traditional risk factors in RA is high, the excess of cardiovascular burden is only partially clarified [1–4, 6, 8, 9, 11]. A wide spectrum of nontraditional meaning RA-associated factors is already considered, including disease activity, severity, as well as antirheumatic drugs [1, 2, 4, 6, 8, 11–13].

2.2. Factors involved in cardiovascular risk in RA

The dynamic link between chronic systemic inflammation and atherosclerosis remains a key point in the pathobiology of cardiovascular involvement in various systemic autoimmune conditions, including inflammatory rheumatic disorders [1, 2, 10–13].

Cardiovascular risk in RA is multifactorial; since traditional risk factors fairly explain, specific issues related to disease activity and medication endorses the cardiovascular disease in RA [1–4, 10–13].

Smoking, diabetes, obesity, hypertension, as well as abnormal lipid pattern (dyslipidemia) are major metabolic risk factors for cardiovascular disease, while seropositivity (rheumatoid factor, RF, and anti-cyclic citrullinated peptide antibodies (ACPA)), systemic extra-articular features, anti-inflammatory (nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids), and disease-modifying antirheumatic drugs (DMARDs) are specific aspects with precise relevance for cardiovascular outcomes in RA patients (**Figure 1**) [1, 2, 4–6, 10–13].
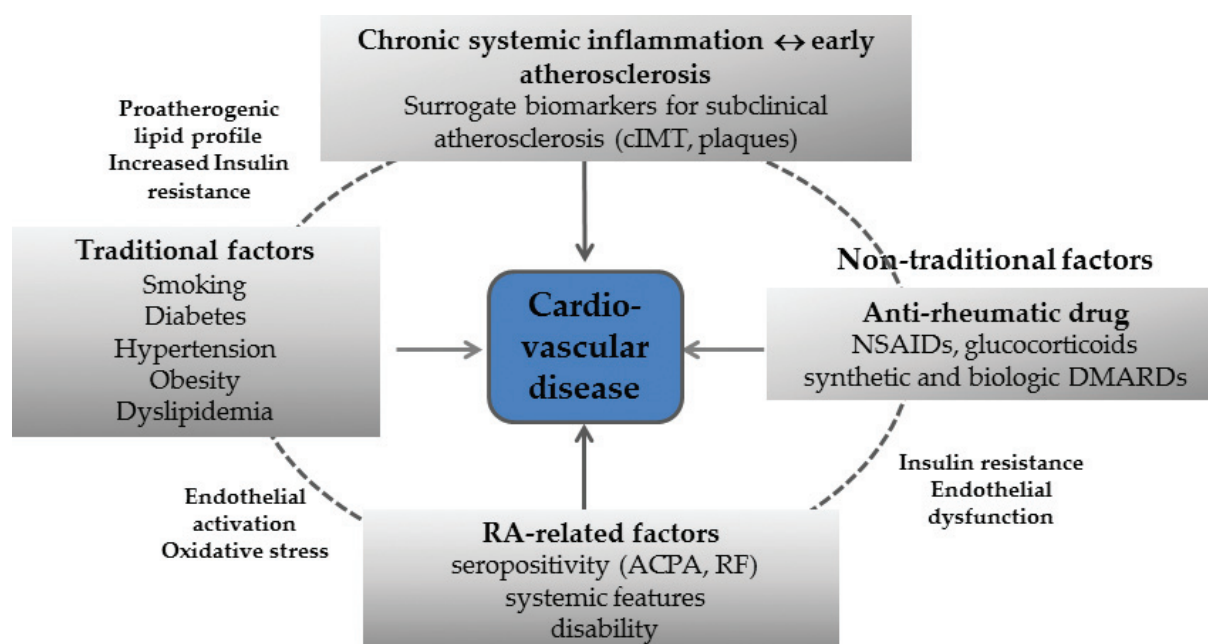

Figure 1. Traditional and non-traditional cardiovascular risk factors in RA (adapted from 8).

Furthermore, it is well established that chronic inflammation represents an independent risk factor for premature atherosclerosis, irrespective of other traditional factors [1, 3, 4], supporting severe, either subclinical or clinical coronary, and carotid disease in patients with RA [10–13].

Inflammation may alter the effect of existing risk or protective factors for cardiovascular disease, leading to an altered cardiovascular profile [1, 2, 6, 10–13].

Potent pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin (IL)-6 and their signaling pathways play a fundamental role in persistent systemic inflammation and are the main determinants of cardiovascular risk in RA [1–4, 6]; in addition, they may interfere with classic factors resulting in altered endothelial function, insulin resistance, modified lipid spectrum, and the obesity paradox in RA [1, 2, 10–14].

There is a body of evidence showing the proatherogenic role of TNF-α and IL-1 as well as potential dual effect of IL-6 on atherogenesis [2, 3].

Thus, targeting inflammation to reduce the cardiovascular disease risk in inflammatory conditions seems to be a realistic project; additionally, an optimal control of rheumatoid inflammation through specific synthetic and/or biologic antirheumatic drugs always underwrites the decline of cardiovascular comorbidity [1–3, 6, 7].

The exclusive relationship of inflammation, endothelial dysfunction, and surrogate biomarkers of atherosclerosis with risks to cardiovascular disease among RA patients was extensively addressed [1–3, 10–13]. The pathophysiology of endothelial dysfunction is multifactorial, a complex network of interacting factors and mechanisms being emphasized. Not only different metabolic (dyslipidemia, hyperglycemia), non-metabolic (hypertension, smoking, oxidative stress) but also RA-specific factors (systemic inflammation) are associated with vascular dysfunction [1, 2, 9, 15–21].

Early intervention of irreversible vascular damage is strictly related to abnormal vascular tone, upregulation of fibrinolysis, and coagulation systems with subsequent procoagulant imbalance, subclinical and clinical atherosclerosis, and supporting cardiovascular disease development in RA (**Figure 2**) [1, 2, 6, 9–13].

2.2.1. Traditional risk factors

Although the relation between traditional cardiovascular risk factors and RA was largely addressed in the last decade, conflicting effects are still open [1–3, 9]. Obviously, classic factors mapping cardiovascular outcomes are more common among patients with autoimmune disorders [1, 2, 9].

A closer look to various traditional risk factors for cardiovascular disease in RA, their prevalence, and relations with disease activity and severity revealed the following aspects (**Table 1**).

2.2.1.1. Smoking

Recognized as a risk factor of both autoimmune diseases and accelerated atherosclerosis [1, 2, 15], tobacco smoking is able to modulate the immune system (e.g., induction of the inflammatory
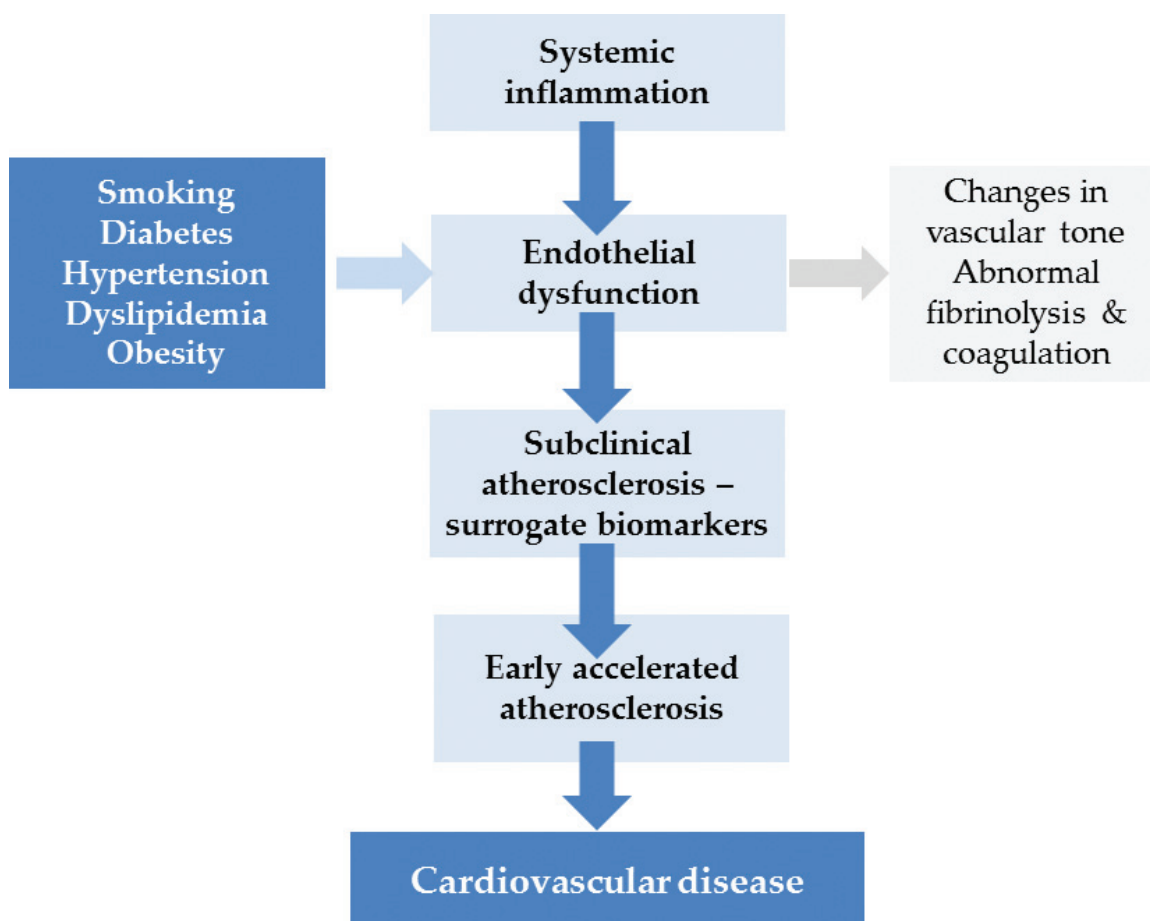
Figure 2. Inflammation, endothelial dysfunction, and atherosclerosis in cardiovascular disease.

responses and apoptosis, cytokine imbalance, DNA damage), to alter endothelial cells (e.g., overexpression of adhesion molecule, endothelial dysfunction), and to promote a procoagulant and inflammatory environment [1, 3, 15].

Smoking has a high prevalence in patients with RA and is classically associated with different predictive factors of the cardiovascular outcomes including seropositivity (for both RF and ACPA), disease severity, disability, and articular damage (erosions) [1, 2, 15]. Various studies have suggested that smoking and second-hand (passive) smoking may limit the therapeutic response in RA, promoting and perpetuating inflammatory aggressive effects on cardiovascular risk [1–3, 6, 15].

2.2.1.2. Hypertension

Among classical risk factors, hypertension is an important predictor of cardiovascular events not only in general population but also in patients with systemic autoimmune conditions, with the highest morbidity in RA (up to 40% in CORRONA) [1, 9, 16].

Since the pathobiology of increased blood pressure is multifactorial, blood pressure control in inflammatory autoimmune settings is largely related to chronic inflammation and immune-mediated mechanisms, along with classic mechanical injury of the arterial wall. Strong evidence

CV risk factors	Prevalence and particularities in RA	Relation with RA activity
Tobacco smoking	High prevalence in RA population String association with CV outcome Direct link with ● seropositivity (ACPA, RF) ● RA severity and activity ● disability ● articular damage	May impair therapeutic response, modulating inflammation effects on CV risk
Hypertension	High prevalence (COMORA 40%) Associated with NSAIDs and DMARDs increased vascular peripheral resistance interplay between inflammation and hypertension ● TNFα results in endothelial vascular damage & oxidative stress ● IL-6 alter the arterial tonus	Without evidence Adversely impact with NSAIDs and glucocorticoids
Insulin resistance	High prevalence in RA Promote low-grade chronic inflammation	Irrespective of RA activity
Body mass index & obesity	Paradoxical relation in RA: low body mass index associated with high CA risk Body mass index—independent CV risk predictor Relation obesity—inflammation via adipose tissue metabolism	Irrespective of RA activity
Dyslipidemia	Not only the quantity but also the quality, structure, and function of lipids 55–65% cases—abnormal lipid profile Lipid paradox (low lipids in inflammation associated with high CV risk) LDL-, HDL-, total cholesterol negatively correlates with inflammatory biomarkers Inflammation = consumption + decreased lipoprotein synthesis + defect of lipoprotein synthesis + structural and functional changes (altered HDL)	HDL cholesterol and atherogenic index improvement following non-biologic and biologic DMARDs

Table 1. Traditional cardiovascular risk factors in RA.

indicates the direct association between inflammation and hypertension; TNF-α can exert vascular endothelial damage and oxidative stress, while IL-6 enhances the arterial tonus. Not only blood pressure itself but also arterial inflammation is more prevalent in patients with RA and independently associated with both traditional cardiovascular risk factors and rheumatoid arthritis disease characteristics [1, 16].

There is no clear data suggesting the relation between hypertension and RA activity. However, the deleterious role of NSAIDs and glucocorticoids on hypertension is well established [1, 16].

2.2.1.3. Insulin resistance

Although underdiagnosed, especially in RA with longer disease duration, the prevalence of impaired fasting glucose, type 2 diabetes, as well as abnormal insulin resistance is largely increased among patients with autoimmune joint conditions compared to age- and gender-matched

controls [1, 13, 18–20]. In addition, the link between diabetes and chronic low-grade inflammation [1–3] is well known, supporting the hypothesis of the interaction between traditional CV risk factors and inflammatory burden in determining diabetes in RA [1, 2, 13, 18–20]. Furthermore, both classic risk factors (e.g., high blood pressure, high body mass index, high total cholesterol, metabolic syndrome) and novel cardiovascular risk factors (RA duration, exposure to glucocorticoids, radiographic damage, CRP levels) significantly correlated with glucose metabolism abnormalities and diabetes [1, 2, 13, 18–20].

2.2.1.4. Body mass index and obesity

While in general, non-RA population, body mass index is recognized as an independent predictor for cardiovascular disease, patients with RA are characterized by the paradoxical relation obesity (cardiovascular risk): low body mass index correlates with high cardiovascular events, unrelated to disease activity [1, 2, 6]. Moreover, the relation obesity-inflammation via adipose tissue metabolism is largely applicable in RA patients.

2.2.1.5. Dyslipidemia and lipid paradox in RA

Abnormal serum lipid pattern remains one of the main risk factors for cardiovascular morbidity and mortality in general population [1]; overall, modifications in high-density lipoprotein (HDL)-cholesterol as well as total/ HDL-cholesterol and triglyceride/HDL-cholesterol ratios are associated with adverse cardiovascular disease risk [1, 20].

Up to 65% of RA patients display an altered lipid profile [1, 2, 11, 12, 20], comprising modifications in absolute circulating lipid levels that widely reflect the interconnection between inflammatory and metabolic pathways [1, 2, 20].

The well-known lipid paradox, meaning low serum concentration of lipids associated with high cardiovascular burden in autoimmune inflammatory conditions, accounts for a negative correlation between total cholesterol, high-density and low-density lipoprotein (LDL)-cholesterol fractions, and inflammatory biomarkers.

Additionally, chronic inflammation is characterized by excessive consumption and deleterious synthesis of lipoproteins associated with structural (e.g., HDL associated with increased serum amyloid A with a potentially proatherogenic phenotype) as well as functional modifications (e.g., altered HDL phenotype) [1, 20].

Generally, both HDL-cholesterol and LDL-cholesterol are decreased in active RA and may increase with efficient control of inflammation with to non-biologic and biologic drugs [1, 2, 6, 20]. Moreover, small-dense LDL particles, known as more atherogenic than larger particles, are raised not only in metabolic disorders but also in RA [1, 20].

Interestingly, preclinical phase of RA accounts for raised inflammatory biomarkers (CRP) and dyslipidemia, with a negative correlation between the increased inflammation and decreased serum lipids [1, 2, 20]. This paradigm is applicable not only for chronic systemic autoimmune joint pathology but also in cardiovascular disease, postsurgery, or related to antineoplastic therapy [1, 2, 6, 20].

Tight control of inflammation in RA by non-biologic and/or biologic antirheumatic medication usually accounts for the improved lipid level [1, 2, 6, 7].

2.2.2. RA activity and cardiovascular risk

Individual inflammatory parameters (erythrocyte sedimentation rate, ESR, and CRP), composite scores reflecting disease activity (such as disease activity score (DAS28) and clinical disease activity index (CDAI)), and disease severity (extra-articular disease) are commonly associated with cardiovascular complications in RA [1, 2, 22–28].

The link between systemic inflammation and cardiovascular outcomes persists even after adjusting according to classical risk factors (obesity, hypertension, hyperlipidemia) [1, 2, 20–22].

Thus, elevated CRP levels at the baseline and the duration of uncontrolled disease correlate with cardiovascular burden in RA [1, 2, 22–28], while very high disease activity over time or high disease activity at RA onset also contributes to the cardiovascular risk [22, 23]. Moreover, it seems that uncontrolled high disease activity promotes the highest risk of developing cardiovascular disease [1, 2, 21–28]. CRP also correlated with acute myocardial infarction, one of the central complications of early accelerated atherosclerosis in RA [1, 22, 23].

Clearly, low disease activity (DAS28 < 3.2) and remission (DAS28 < 2.6) are fundamental in preventing a 10-years risk of cardiovascular events (particularly fatal or nonfatal cases of cardiovascular disease) in RA [1, 22, 23, 29]. In fact, it seems that low stable disease activity is able to reduce the cardiovascular burden and is appropriate to attain a protective effect against cardiovascular disease in RA [1, 22, 23]. Similarly, clinical remission or the absence of inflammation may be associated with a reduced risk of cardiovascular disease in RA [1, 22, 23]; apparently, remission has no additional protective effect against cardiovascular risk profile compared with low disease activity [1, 2, 22, 23].

Thus, it becomes clear that the manipulation of inflammatory response and tight disease control [22, 23, 28] are able to prevent cardiovascular events in RA [3, 26].

2.3. Cardiovascular risk assessment in RA

Different scores designed for the calculation of cardiovascular risk in general population (e.g., Framingham, SCORE, QRISK) underestimate the cardiovascular burden in patients with inflammatory rheumatic conditions, mainly RA [1, 2, 6, 29, 30]; thus, there is no standard or validated model for cardiovascular risk prediction in RA.

In EULAR 2009 has proposed to multiply by 1.5 points the SCORE risk for patients with RA if two out of three RA-related parameters are present: a disease duration more than 10 years, rheumatoid factor or ACPA positivity, and severe extra-articular manifestations [2, 6, 29, 30]. Despite good reliability, this score is not able to reclassify patients with RA in the adequate cardiovascular risk category [2, 6].

QRESEARCH Cardiovascular Risk Algorithm (QRISK) 2 is a prediction model including RA as a specific risk factor, multiplying with 1.4; it overestimates both nonfatal and fatal cardiovascular events [2, 6, 29, 30].
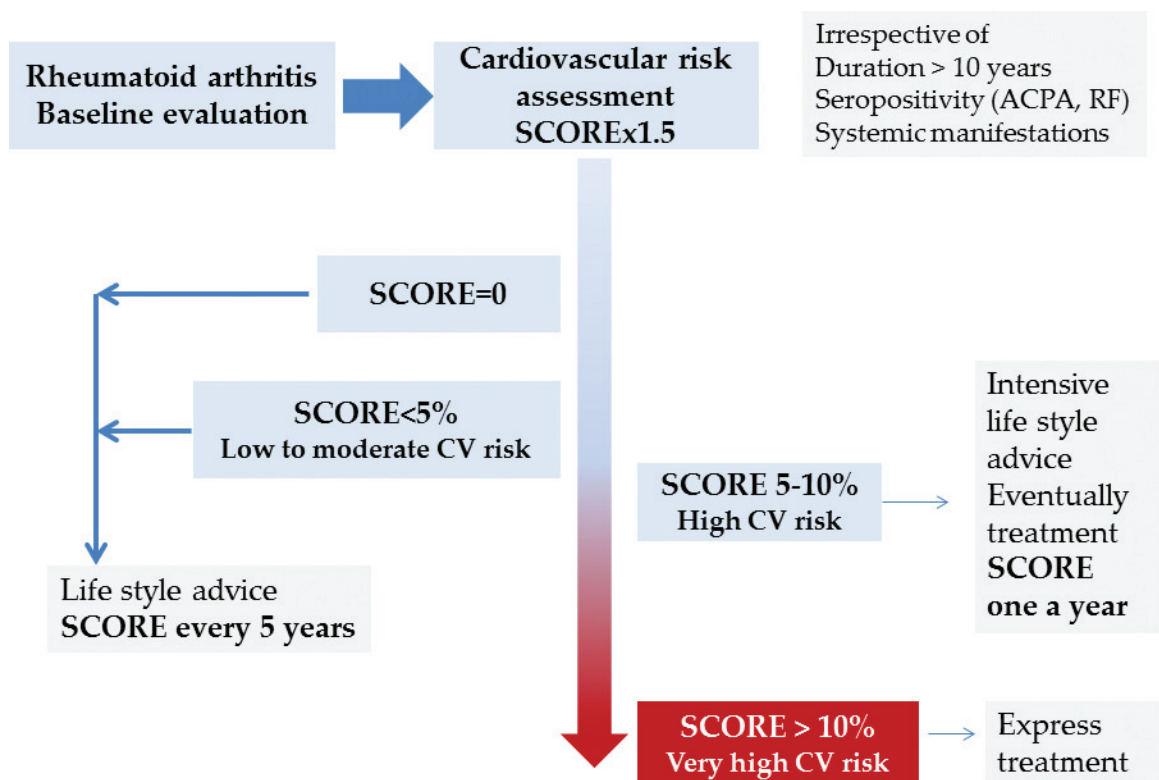
Figure 3. Algorithm for cardiovascular risk assessment in RA (adapted from Gualtierotti [4]).

EULAR 2016 has recommended the use of a modified SCORE adapted for patients with RA, meaning SCORE multiplied by 1.5 irrespective of disease duration, seropositivity, or the presence of systemic features [2, 6, 29, 30].

According to EULAR recommendations [6], the assessment of RA patients should be adapted based on CV risk stratification and several individual factors such as change of specific anti-rheumatic medication [2, 6, 29, 30]. Thus, risk monitoring is warranted once every 5 years if the risk is low to moderate or more often if the patient has an intermediate and high risk or when adapting the therapeutic protocol [2, 6]. An interesting algorithm was recently adapted/ proposed by Gualtierotti et al. (**Figure 3**) [2].

2.4. Recommendations for cardiovascular risk assessment in RA

Cardiovascular risk stratification and further monitoring based on the risk class is essential in RA [1, 2, 6, 29, 30]. EULAR 2009 guidelines have proposed the assessment of the cardiovascular disease on an annual basis, except for patients classified as low risk or low disease activity where the risk is typically monitored as 2–3 years [1–3, 6].

Updated EULAR 2016 guidelines released four new recommendations emphasizing the interval, scores, and protocol for cardiovascular disease screening [6]. Interestingly, cardiovascular risk assessment is no longer recommended annually but every 5 years or following a major change in the DMARD therapy (recommendation 2) [6]. Either local or national guidelines or SCORE are equally accepted for the calculation of CV risk (recommendation 3) [6]. Lipid profile comprising total cholesterol and its HDL fraction should be evaluated during stable

disease or remission (recommendation 4) [6]. Finally, surrogate biomarkers for subclinical atherosclerosis such as plaques on Doppler carotid ultrasound are recommended for the extensive screening of the cardiovascular disease in RA patients [6].

Recommendations for the management of CV risk in RA take into account three essential points [1, 2, 6, 14]: (i) control of disease activity meaning early diagnosis and dynamic choice of the antirheumatic drug starting with non-biologic DMARDs followed by biologic DMARDs, with or without glucocorticosteroids until reaching the therapeutic target (remission or low disease activity), (ii) non-pharmacological management of risk factors including smoking cessation, adequate level of physical activity, as well as healthy diet, (iii) pharmacological management of risk factors comprising statins for lipid abnormalities, antihypertensives, antidiabetics, etc.

Optimized disease control within the so-called treat-to-target (T2T) strategy consistently improves the cardiovascular risk in RA, as remission and low disease activity become realistic goals [1, 2, 4, 6, 7]. Recent advances in the pathobiology of the disease and the link between inflammation, RA disease activity, and cardiovascular issues have highlighted the following [1, 2, 6, 7]: (i) disease duration is not an independent cardiovascular risk factor; (ii) disease activity, the number, and duration of flares significantly alter the CV risk; (iii) reducing inflammation obviously improves the CV outcomes; and (iv) long-term DMARD therapy results in lowering the CV risk.

Not only chronic persistent systemic as well as local inflammation and RA disease activity endorse excessive cardiovascular burden in RA but also traditional CV risk factors, e.g., body mass index, lipids, gender, tobacco smoking, and hypertension [1–3, 6].

Aggressive T2T approach in daily clinical practice for patients with RA proved successful in negatively impacted systemic and synovial inflammation, impair cytokine release, and promote quantitative and qualitative lipid changes, significantly decreasing the cardiovascular disease in such patients [1, 2, 6, 7]. Conversely, anti-inflammatory drugs (e.g., not only NSAIDs and COX-2 inhibitors but also steroids) are commonly associated with high cardiovascular safety issues [1, 2, 6].

Regardless of substantial progresses in RA treatment, patients develop and die considerably earlier than the general population mainly related to cardiovascular comorbidities, generally in connection with accelerated atherosclerosis and cardio-metabolic complication [1, 2, 13, 18, 21].

2.5. 2016 EULAR recommendation for CV management

Since broad cardio-metabolic evaluation and optimal strategies for cardiovascular risk reduction are still poorly integrated in routine practice in autoimmune conditions [13, 18, 21], EULAR has recently updated guidelines for cardiovascular disease risk assessment and management in systemic inflammatory conditions including RA, psoriatic arthritis, and ankylosing spondylitis [6]. An extended EULAR task force has reconsidered the old guidelines and released new overarching principles and recommendations in accordance to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) statement suggesting an appropriate algorithm for cardiovascular risk management in these patients [6].

Updated EULAR 2015/2016 guidelines for cardiovascular comorbidity in RA are listed below [6]:

1. Lowering the cardiovascular risk in RA largely relies on both early diagnosis and tight control of disease activity as well as the disease flares.

2. The cardiovascular risk reassessment is advised at least every 5 years or when major changes in DMARD therapy are specified.

3. EULAR endorses the application of risk assessment scores according to the general population such as systematic coronary risk evaluation (SCORE) or national guidelines for CVD risk evaluation.

4. A systematic evaluation of lipid profile including non-fasting total cholesterol and low- and high-density lipoprotein fractions is mandatory to further mitigate the cardiovascular risk; however, measurements should be achieved during stable RA or in remission disease.

5. A correct estimate of the increased risk of cardiovascular events in RA encompasses for a modified risk score multiplied by 1.5.

6. Surrogates of subclinical atherosclerosis and cardiovascular disease such as artery plaques identified by carotid ultrasound screening are useful to perceive the increased cardiovascular risk in RA.

7. Several protective measures, e.g., healthy diet, exercise on a daily basis, and smoking cessation, should underline the general approach of RA patients with raised cardiovascular risk.

8. New trends in treating hypertension and dyslipidemia with specific medication including antihypertensives and statins are widely recommended in patients with RA with such comorbidities.

9. Since both traditional nonselective NSAIDs and coxibs have an increased risk of developing cardiovascular toxicity in RA, these drugs are carefully proposed in such patients, especially in those with prior history of or at increased risk to develop further cardiovascular events (congestive heart failure, ischemic heart disease, peripheral arterial or cerebrovascular disease).

10. If mandatory, long-term corticosteroids are managed to minimize the total dosage, with tapering as soon as remission or low disease activity is reached.

3. Cardiovascular safety of non-biologic and biologic anti-rheumatic drugs

Evidence-based medicine provides key insights into the consequences of various classes of antirheumatic drugs on cardiovascular risk in RA, suggesting that TNF inhibitors (TNF-i) and methotrexate decrease the risk of such events, while corticosteroids and IL-6 receptor inhibition via tocilizumab exert a multifaceted intervention on cardiovascular outcomes [1, 2, 26, 31]. Data are summarized in **Table 2**.

Drug	Positive effects	Negative effects	Overall influence on CV safety
Methotrexate	Improved RA activity	High homocysteinemia	Protective
Other csDMARDs Leflunomide Antimalarials	Improved RA activity, improved lipid profile, reduced risk of diabetes	Arterial hypertension May be responsible of cardiomyopathy although rarely	Complex effect Protective
TNF inhibitors	Improved RA activity, reduced insulin resistance	Contraindicated in severe heart failure (class III/IV NYHA)	Protective
Non-TNF inhibitors Tocilizumab Rituximab Abatacept Tofacitinib	Improved RA activity Safe in heart failure Safe in heart failure Safe in heart failure	Abnormal lipids	Complex effect Complex effect Complex effect
Corticosteroids NSAIDs	Reduced inflammation	May increase CV events, BMI, dyslipidemia, insulin resistance, hypertension All NSAIDs increase CV risk (prothrombotic effect)	Complex effect

Table 2. Cardiovascular profile of anti-rheumatic drugs: non-biologic and biologic DMARDs, corticosteroids, NSAIDs.

3.1. Non-biologic DMARDs: methotrexate and non-methotrexate drugs (e.g., sulfasalazine, antimalarials, leflunomide) improve cardiovascular outcomes in RA

Recent meta-analysis as well as real-life data showed that traditional synthetic DMARDs are able to reduce the cardiovascular risk in RA. However, the precise cardioprotective mechanism of classic immunosupressants remains still under debate.

Undoubtedly, methotrexate and non-methotrexate agents efficiently control inflammation and disease activity, alter the lipid spectrum and concentration, and are able to reduce the arterial stiffness, improving cardiovascular risk in different RA scenarios [1–32].

Furthermore, methotrexate, the drug of choice as first-line treatment, is associated with a consistent reduction in mortality (70%), a decline in the rate of total cardiovascular events (around 28%), and up to 18% lower risk of myocardial infarction in patients with RA [31]. Unlike the anti-TNF agents, methotrexate is not related to a significant decrease in strokes and major adverse cardiac events; nevertheless, it seems that the risk of heart failure is also decreased [1, 2, 31, 32].

The interesting hypothesis of inflammatory origin of cardiovascular disease prompted the ongoing randomized Cardiovascular Inflammation Reduction Trial (CIRT) aiming to investigate whether low-dose methotrexate is able to decrease rates of heart attacks, strokes, and cardiovascular death among stable coronary artery disease patients with type 2 diabetes and/or metabolic syndrome, conditions associated with an enhanced pro-inflammatory response [3]. Although the study was designed to perceive a 25% cardiovascular risk decline within the

methotrexate group, failure to achieve this magnitude of risk reduction will not degrade the immune inflammatory background of cardiovascular pathology [3].

Data about other synthetic DMARDs are not consistent. Leflunomide has indirect positive effects on cardiovascular outcome through reducing disease activity, while its role in promoting hypertension is a potential limitation, particularly if high blood pressure is documented [1, 2]. Antimalarials, specifically hydroxychloroquine, are able to modulate lipid profile and to reduce the risk of diabetes, although rare cases of cardiomyopathy have been described [1, 2, 31, 33]. Finally, sulfasalazine seems to exert also protective effects, while further studies are required to clearly define its role [2].

3.2. Glucocorticoids enhance the cardiovascular risk in RA

The association between corticosteroids and the rate of total as well as individual cardiovascular events was systematically evaluated in patients with inflammatory rheumatic disorders, principally in RA and systemic lupus. It is widely accepted that corticosteroids are able to shape the cardiovascular risk by two competitive pathways [1, 2, 6, 31, 34]:

- The risk for future cardiovascular disease is increased due to not only metabolic effects, e.g., abnormal lipid metabolism, impaired glucose tolerance, insulin resistance, relative weight gain, or true obesity, but also glucocorticoid-induced hypertension.

- The cardiovascular risk is attenuated through rapid and salutary anti-inflammatory and anti-proliferative effects of corticosteroids.

Their cardiotoxicity as well as cardiovascular mortality is dose-dependent (actual and previous cumulative dose) [1, 2, 6]. Sustained administration of corticosteroids classically accounts not only for an increased risk of myocardial infarction, stroke, and congestive heart failure but also for all major adverse cardiac events in RA patients as suggested by different studies and meta-analyses [1, 2, 6, 31, 34].

The well-known trend in RA is to maintain the lowest dose of corticosteroids for the shortest period of time and tapering as soon as remission or low disease activity (recommendation 10, EULAR 2016) [6]; the benefits of further administration should be deliberated and reconsidered once the disease outcomes have been achieved [6].

Although NSAIDs no longer represent the mainstay of RA therapeutic protocol, both nonselective and COX2-selective medications are still used, even if intermittently, during RA flares and in short-time administration [1, 2, 22, 23, 31, 35]. NSAID safety profile should be emphasized, as their effect on cardiovascular outcomes in RA is challenging. Both nonselective NSAIDs and coxibs increase the cardiovascular risk in general population; however, not all of them exert the same deleterious cardiovascular effect, especially talking about patients with RA [2, 6, 31, 35].

It is widely recognized that long-term NSAIDs increased the risk of all cardiovascular events and stroke in general population, particularly if cardiovascular disease is documented (congestive heart failure, ischemic heart disease, peripheral arterial disease, or cerebrovascular

disease) [2, 6, 31]; only few studies have addressed the cardiovascular outcomes of COX2-selective and traditional NSAIDs specifically in RA [1, 2, 6, 31, 35].

3.3. Biologic DMARD: TNF inhibitors decrease the cardiovascular risk in RA

TNF-α, a pivot pro-inflammatory cytokine involved in both systemic and local (synovial microenvironment) persistent inflammations in RA, may also alter lipid metabolism, insulin resistance, and endorse endothelial dysfunction [1, 2, 6, 31, 36, 37]. Moreover, chronic inflammation and atherosclerosis share common pathways, tailoring the basis of amplified cardiovascular risk in inflammatory rheumatic conditions [1, 2].

On the other hand, TNF inhibitors provide multifaceted influences on cardiovascular safety in patients with RA comprising [1, 2, 6, 31, 37]:

- Rapid and effective control of chronic inflammation signaling with significant decrease in inflammatory parameters (serum CRP levels and ESR), RA activity, and delay articular damage articular

- Changes in lipid pattern with increase in HDL-cholesterol fraction, total cholesterol, triglycerides with or without influence on LDL-cholesterol fraction, and with no major impact on the atherogenic index (TC/HDL); in fact, the trend of rising serum lipids under anti-TNF therapy typically reflects the stabilization through the lipid levels before the RA onset

- Improvement of endothelial dysfunction and insulin sensitivity as well as the anti-oxidative response of HDL

Thus, it seems that TNF inhibitors are efficient in reducing cardiovascular comorbidities in RA, comprising not only all cardiovascular events but also some specific stroke, myocardial infarction, and even MACE [1–3, 31, 36, 37].

A meta-analysis of several observational studies and registries in RA patients treated with TNF inhibitors performed by Roubille et al. showed a significant reduction in the risk of all cardiovascular events (up to 30%), myocardial infarctions, strokes, and major adverse cardiac events with biologics vs. non-biologic DMARDs [1–3, 31, 36, 37]. However, no significant effect on heart failure was detected [2, 31]. Interestingly, the risk of future cardiovascular consequences under anti-TNF medication is twice lower that the risk with non-biologic non-methotrexate drugs [1–3, 31, 36, 37].

Besides, Ljung et al. recently published their study investigating the effects of response to anti-TNF agents on short-term (1- and 2-year follow-up) risk of acute coronary syndrome in individuals with active RA and no previous ischemic or congestive heart disease before starting TNF-i as the first biologic agent [37].

RA patients classified as good (but not moderate) EULAR responders (improvement of more than 1.2 points in disease activity score) to anti-TNF therapy showed a 50% risk reduction of acute myocardial infarction or unstable angina pectoris or acute myocardial infarction as the underlying cause of death in short-term follow-up, similarly to the risk of acute coronary events in general population [1, 2, 6, 31, 36, 37].

In fact, the magnitude of coronary event risk reduction was reported irrespective of the baseline risk stratification (by gender, age, cardiovascular risk factors, disease duration), drug exposure, as well as the risk window [2, 31, 36, 37]. Additionally, the ability to achieve optimal control of RA activity instead of simply improved disease control or TNF-i per se theoretically stabilizes the pattern of ischemic heart disease in RA [1–3, 31, 36, 37].

Still considered the "black box" of TNF biologic class, the link between TNF blockade and moderate to severe congestive heart failure (class III/class IV NYHA) remains controversial [1, 2, 31, 36]. Clearly, heart failure in general population is associated with high TNF-α, with consistent correlation between serum levels and clinical significance and severity of cardiac failure [1, 31, 36]. However, TNF inhibitors are able to improve ventricular dysfunction in experimental models of cardiac failure [1, 2, 6, 31, 36, 37].

Overall, TNF inhibitors significantly damper the cardiovascular comorbidity in RA, especially in patients declared responders to such therapies.

3.4. Non-TNF DMARDs: tocilizumab

Data about tocilizumab, a humanized monoclonal antibody acting against the IL-6 receptor (membrane-bound and soluble), and its cardiovascular toxicity are widely accessible from different clinical trials, including ADACTA, TOWARD, MEASURE, and ENTRACTE [38–41].

Although modest increases of LDL- and HDL-cholesterol as well as triglycerides were noticed in RA patients treated with tocilizumab in randomized controlled trials, only ENTRACTE was specifically designed to evaluate the cardiovascular safety and to compare net cardiovascular risk-benefit ratio of anti-IL-6 therapy with biologics with another mechanism of action, such as etanercept, in active seropositive RA [1, 2, 38–41].

As a potent inhibitor of IL-6 signaling, tocilizumab is associated with excellent clinical efficacy essentially related to patent decline in systemic inflammatory biomarkers; in addition, tocilizumab-associated altered lipid profile, mainly increased LDL-cholesterol, is broadly recognized and potentially connected with atherogenesis and atherothrombosis in patients with RA [1, 2, 3, 39–42].

Moderate elevations of LDL-cholesterol, HDL-cholesterol, and triglycerides were faced in RA patients under tocilizumab in phase II and phase III trials, but the atherogenic implications of these changes are still unsettled [1, 2, 38–41].

A summary of trials reflecting the cardiovascular safety profile of tocilizumab in RA comprises the following:

ADACTA, a randomized clinical trial to evaluate tocilizumab monotherapy vs. adalimumab monotherapy for the treatment of RA, suggested that tocilizumab meaningfully decreases systemic inflammation as supported by low ESR and CRP levels and disease activity (DAS28, CDAI). Changes are obviously more evident as compared to adalimumab, a totally humanized monoclonal anti-TNF antibody; however, tocilizumab induces higher LDL-cholesterol levels more than adalimumab do [39].

TOWARD trial, evaluating tocilizumab in combination with traditional DMARD therapy, revealed the role of IL-6 blockade not only in reducing articular and systemic inflammation but also in improving insulin resistance, along with its capacity to promote increased total cholesterol levels in up to one-fourth of cases [38].

Tocilizumab may induce particular changes in lipid pattern, with potential relevance for cardiovascular safety. Persistent increase in mean fasting plasma lipids, within the normal range, is commonly reported with tocilizumab, together with a consistent decrease in serum CRP, suggesting that abnormal lipid levels may, in part, be related to significant decline in inflammation [38].

An increase in total cholesterol was observed in one out of five RA included in the study, while high LDL and altered HDL status from a pro-inflammatory to a significantly low inflammatory status (12 and 15%, respectively) increases of 30% in the total cholesterol:HDL-cholesterol ratio (12% cases) and more frequent in the LDL-cholesterol:HDL-cholesterol ratio (20%) were also reported. Finally, increases in the mean apolipoprotein A-I and apolipoprotein B, within the normal range, without changes in the ApoB:ApoA-I ratio were also commonly described. Only a limited number of patients initiated statin therapy during the study, with positive influence on lipid modifications [38].

MEASURE trial of tocilizumab effects on surrogates of vascular risk in RA was powered to demonstrate the modulation of lipid and lipoprotein particle (LDL, HDL, VLDL) levels and composition (HDL-associated serum amyloid A), alongside other surrogates of vascular risk (markers of coagulation, thrombosis, and vascular function) with IL-6 receptor inhibition vs. placebo in active disease [40, 41].

McInnes et al. [41] not only reported a dramatic decrease in inflammation in such patients but also demonstrated quantitative and qualitative changes in lipid metabolism profile. Overall, tocilizumab prompted the increase in total cholesterol, LDL-cholesterol, and triglycerides by week 12 of administration, while no significant influence on proatherogenic small LDL particle concentration, oxidized (ox)LDL, or HDL-cholesterol levels, in addition to ApoB:ApoA-1 ratio. Furthermore, tocilizumab-based IL-6 signal blockade altered the HDL particle composition toward a less pro-inflammatory phenotype [40, 41].

Besides, HDL-associated serum amyloid A, secretory phospholipase A2-IIA, lipoprotein(a), fibrinogen, and D-dimers presented a sizeable decrease, while the antioxidant enzyme associated with HDL, paraoxonase, and level significantly increased under tocilizumab. Since a prothrombotic status heightened risk for cardiovascular events independently of established risk factors in general population, the reduction of thrombotic potential with tocilizumab in patients with active RA remains of considerable interest [40, 41].

However, the clear benefit of such modifications for cardiovascular risk is still debatable.

ENTRACTE, a randomized clinical trial aiming to evaluate cardiovascular events with either i. v. tocilizumab monthly or etanercept s.c weekly, was designed as a non-inferiority study comparing cardiovascular safety of tocilizumab vs. the TNF receptor, etanercept, in RA. Primary endpoint focused on major cardiovascular adverse events (MACE) (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke), while secondary endpoints were cardiovascular and non-cardiovascular safety of both drugs [1–3].

ENTRACTE has demonstrated a relative increase in the incidence of cardiovascular events among severe active RA patients with a background of cardiovascular risk factors receiving tocilizumab, specifically the hazard of MACE. Additionally, the average level of LDL-cholesterol was consistently higher under tocilizumab as compared with etanercept. Nevertheless, the cardiovascular issues with tocilizumab vs. etanercept should be deliberated/interpreted in the context of its clinical efficacy and general, non-cardiovascular, safety profile.

3.5. Other non-biologic and targeted DMARDs: rituximab, abatacept, and tofacitinib

- **Rituximab**, a B-cell depletory agent, typically indicated as a second-line biologic therapy after failure of at least one anti-TNF agent, showed no significant differences as compared to placebo in terms of cardiovascular events. There is no cardiovascular safety concern related to rituximab; furthermore, it seems that rituximab is able to improve lipid metabolism, alter HDL-cholesterol to a low atherogenic profile, as well decrease prothrombotic biomarkers. Also, rituximab has no influence on arterial stiffness [1–3, 6, 7, 42].

- **Abatacept**, by blocking the T and B costimulation, commonly acts on lipid pattern resulting in high total cholesterol and its fractions (HDL-cholesterol and LDL-cholesterol), without a significant decrease in the atherogenic index; however, abatacept is known to alter the arterial tonus [1–3, 6, 7].

- **Tofacitinib**, a JAK inhibitor already approved for the management of RA, promotes similar changes in lipid profile as tocilizumab do, meaning an increase of both HDL-cholesterol and LDL-cholesterol, with a minimal impact on atherogenic index [1–3, 6, 7, 43].

4. Conclusions

Systemic autoimmune rheumatic conditions, specifically RA, are widely associated with excessive cardiovascular morbidity, with a magnitude similar to that related to traditional cardiovascular risk factors, particularly diabetes.

A multifaceted dynamic interplay between chronic systemic inflammation, RA-specific issues, early accelerated atherosclerosis, and classic cardiovascular risk factors typically highlights the cardiovascular burden in various RA settings.

The optimal strategy to identify patients at increased risk to develop cardiovascular disease as well as the correct assignment of different risk categories is mandatory in routine practice in every RA case. Furthermore, the selection of suitable medication (non-biological, TNF inhibitor, or non-TNF biological antirheumatic drug) according to cardiovascular toxicity is warranted so as to improve cardiovascular outcomes in RA.

Conflict of interest

No conflict of interest declared.

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