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Association of cardiovascular risks in rheumatoid arthritis patients: Management, treatment and future perspectives

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ABSTRACT

Rheumatoid arthritis (RA) patients exhibit a notable 50%-70% elevation in heart disease risk compared to the general population, attributable to their heightened susceptibility to cardiovascular disease (CVD). The contribution of the rheumatology branch in preventing cardiovascular (CV) risk remains challenging to comprehend fully. Traditional CV risk factors alone fail to elucidate the augmented mortality and morbidity linked to RA; rather, the cumulative inflammatory burden and cardiotoxicity associated with antirheumatic therapy emerge as pivotal determinants. A noteworthy correlation exists between the use of anti-inflammatory medications, commonly prescribed for arthritis, and an increased risk of premature mortality. Despite acknowledging and comprehending the burden of CVD in RA, caring for affected individuals continues to present challenges. Effective management of CV risk in RA necessitates meticulous consideration of established risk factors and behavioral adaptations. Collaborative engagement among rheumatologists, cardiologists, internists, and primary care providers becomes imperative for optimally attending to RA patients at cardiovascular risk. This review critically evaluates pivotal studies in this domain, shedding light on potential future directions for enhancing CV risk management in RA patients.

Introduction

Rheumatoid arthritis (RA) patients are known to be at an elevated risk of developing cardiovascular disease (CVD), as demonstrated by extensive research spanning several decades [1]. Notably, Ahlers et al. [2] have firmly established the association between RA and CVD. Epidemiological investigations into RA have revealed that these patients face a 1.5–2.0 fold increased risk of developing coronary artery disease (CAD) when compared to the general healthy population. The heightened CVD risk in individuals with RA can be attributed to the prototypical chronic inflammatory nature of the illness. However, it has been observed that the administration of methotrexate (MTX) can reduce the risk of heart failure (HF), particularly in patients who are unable to maintain adequate ejection fraction. Furthermore, C-reactive protein (CRP) levels have been found to be inversely related to the risk of HF among RA patients [3]. RA patients exhibit a rate of myocardial infarction (MI) that is approximately two times higher than that seen in the general population [4,5]. Although rheumatoid cardiac nodules and valvular heart disease have been observed in RA patients, they rarely cause overt disease in individuals with concomitant cardiovascular issues [6]. Additionally, RA patients often suffer from impaired endothelial function, which can be exacerbated by a sedentary lifestyle. However, this alone does not entirely account for the higher frequency of CVD in RA patients [7]. It is important to acknowledge that both genetic predisposition and exposure to various risk factors can contribute to the development of RA.

Inflammation plays a significant role in the progression of CVD, including synovitis in RA patients [8–11]. Patients with RA face a twofold higher risk of atherosclerosis and other cardiovascular problems compared to the average population. Reduced levels of high-density

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lipoprotein (HDL) cholesterol are associated with an increased susceptibility to CVD and higher mortality rates [12,13]. Furthermore, exacerbation of RA can result in serious complications and even mortality in CVD patients. Chronic use of corticosteroids has also been linked to an increased risk of CVD in RA patients. In contrast, disease-modifying antirheumatic drugs (DMARDs) offer protection against cardiovascular risk [14–16]. Despite the elevated risk of CVD in RA patients, they often do not receive sufficient primary and secondary prevention measures. The simultaneous occurrence of CVD in RA patients is frequently neglected, leading to a further increased risk. Therefore, effective control of RA and reduction of risk factors are of utmost importance for individuals with RA. It is noteworthy that inflammation underlies various health issues, and in RA patients, it can precipitate cardiovascular complications [17–19]. Consequently, current treatment guidelines by The European Alliance of Associations for Rheumatology (EULAR) emphasize the management of cardiovascular risks alongside RA treatment [20].

In a comprehensive study comprising 50 trials, 91,618 patients, and 33,250 deaths, heart disease was identified as the underlying cause of 39.6 percent of the additional deaths associated with rheumatoid arthritis [21]. It is imperative to acknowledge that coronary heart disease remains the leading cause of mortality in the United States and other regions. While mortality rates due to CVD have declined in countries with high and intermediate incomes between 1990 and 2015, the rates have not shown similar declines in low-income countries. In 2015, the worldwide mortality rate due to CVD was 286/100,000, while in South Asia, it was higher at 369/100,000 [22]. This narrative review succinctly summarizes the latest findings on RA and CVD risk prediction algorithms for the reader's convenience and comprehension.

Effect of CVD on rheumatoid arthritis

The elevated risk of heart disease observed in RA patients cannot be fully elucidated by traditional cardiovascular risk factors alone. Mitigating inflammation through anti-rheumatoid arthritis treatments may also contribute to lowering the risk of cardiovascular disease (CVD). RA is inherently associated with an increased cardiovascular risk, stemming from a combination of genetic factors, traditional cardiovascular risk factors, as well as the underestimation and undertreatment of concomitant cardiovascular comorbidities. A meta-analysis study involving over 150,000 RA patients reported a higher prevalence of CVD-related mortality in this patient population. Addressing the reduction of cardiovascular mortality necessitates a dedicated focus on risk factors that trigger inflammation in RA patients. Notably, a surge in Disability-Adjusted Life Years (DALYs) in 2016 was linked to elevated systolic blood pressure (BP) and tobacco usage, with both factors significantly contributing to the highest number of DALYs during that year. The DALY, a comprehensive measure of disease burden, considers not only premature mortality but also the years of "healthy" life lost due to illness or disability. In recent years, DALYs have gained prominence in health impact evaluation and public health contexts due to their inclusive approach in assessing the overall disease impact on population health.

Calculating CV risk in RA

Cardiovascular disease (CVD) can largely be prevented in the general population through reliable diagnostic tests and health-conscious lifestyle choices. However, despite the increased risk of CVD in patients with RA, they appear to adopt these preventive measures at similar rates as the general population [23]. To optimize cardiovascular (CV) outcomes in RA, it is imperative to focus on the identification and targeting of specific CV risk factors. In-depth research into the inflammatory mechanisms underlying RA may offer valuable insights to halt the progression of CV risks. Notably, methotrexate (MTX) treatment in individuals with rheumatoid arthritis has been found to mitigate inflammation and reduce cardiovascular risk. The Cardiovascular Inflammation Reduction Trial (CIRT) further explores the potential benefits of such interventions [24,25].

A significant challenge in studying CV risk in RA lies in accurately identifying individuals with heightened CVD risk due to the disease. Long-term exposure to inflammation is believed to underpin the increased CV risk in RA, yet current methods of assessing cardiovascular risk do not adequately consider this factor. The use of traditional risk assessment tools such as the Framingham Risk Score (FRS) [26] or the Scoring Coronary Risk in Communities (SCORE) [27] can lead to a notable underestimation of CV risk in RA [28]. Similar findings have been reported for CV risk assessments in specific cohorts of individuals with RA [29,30].

Inflammatory biomarkers, such as high-sensitivity C-reactive protein (hsCRP), which are incorporated in the Reynolds Risk Score (RRS), also exhibit limitations in accurately estimating CV risk in RA, akin to the Framingham Risk Score (FRS) [30]. Notably, the mean hsCRP levels in a typical RA cohort are substantially higher at 9.7 mg/L, in contrast to the average hsCRP levels in the general population at 1.66 mg/L [31,32] (Fig. 1). The UK's standard CV risk calculator, QRISK2, does account for RA, but recent research suggests that it may lead to an overestimation of risk [33]. In light of this challenge, the European League Against Rheumatism (EULAR) has proposed using a 1.5 multiplier on the Functional Rating Scale (FRS) or the Systematic Clinical Assessment of Rheumatology (SCAR) for RA patients presenting high-risk characteristics or specific pathological conditions [34]. Nevertheless, it is important to acknowledge that this method is based on expert opinions and requires independent validation for accuracy and effectiveness.

Pathophysiology of RA and its correlation with cardiovascular risks

The pathophysiology of RA encompasses nonspecific inflammation, synovial amplification, and chronic inflammatory processes. Aberrant proliferation of synoviocytes, accompanied by the production of pro-inflammatory cytokines and catabolic enzymes, contributes to the degradation of cartilage in RA. Inflammatory responses are triggered in the synovium due to the accumulation of neutrophils, activated macrophages, T cells, and B cells, which are particularly enriched in joint perivascular and sub-lining regions. The synoviocytes of the type A and type B variety (pannus) play a crucial role in the hyperplasia of the cartilage-bone interface. Despite accounting for all conventional risk factors, individuals with RA continue to exhibit a heightened risk of cardiovascular disease (CVD) [35].

A strong association exists between inflammation and CVD risk factors, such as RA disease activity, elevated levels of C-reactive protein (CRP), and the presence of CVD itself [36,37]. Elevated CRP levels in RA patients are independently associated with an increased risk of heart failure, even in the absence of other conventional cardiovascular risk factors. Moreover, RA patients with heart failure are at an augmented risk of developing heart failure with preserved ejection fraction (HFpEF) due to the influence of inflammation [38,39]. Fig. 2 illustrates how RA risk factors and systemic inflammation contribute to CVD. Activated synovial cells release pro-inflammatory cytokines, which, in turn, stimulate or attract other cell types, promoting disease progression. Among these, tumor necrosis factor-alpha (TNF-α) plays a central role and triggers the production of interleukin-1 (IL-1), interleukin-6 (IL-6), and interleukin-17 (IL-17) through diverse signaling pathways. Therapies targeting TNF-α, such as adalimumab and infliximab, as well as other biologic RA therapies, effectively reduce TNF-α production. Additionally, agents such as tofacitinib, baricitinib, and ruxolitinib act on the JAK-STAT signaling system, which regulates the synthesis and function of various mediators involved in RA pathogenesis and progression. Given the multifaceted nature of RA and its complex etiology, a combination of multiple medications is often required to target its diverse pathological components.

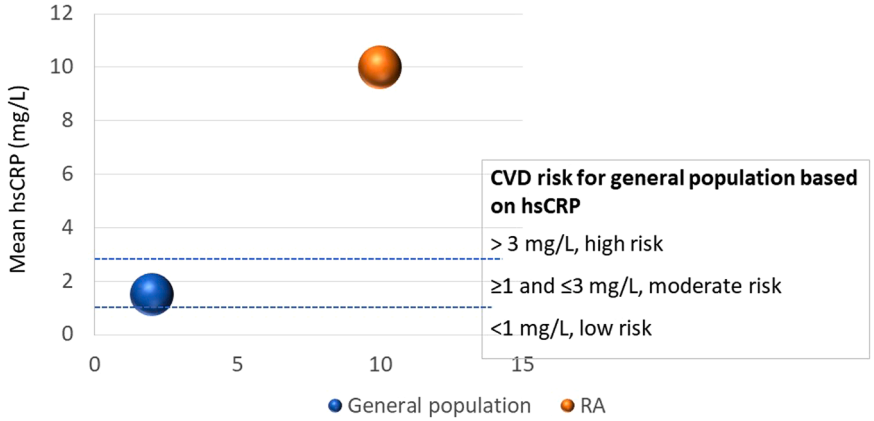

Fig. 1. Values of hsCRP in RA patients compared to general population with CV risk estimation
[*General population, Brigham Rheumatoid Arthritis Sequence Study (BRASS); **RA, National Health and Nutrition Examination Survey (NHANES)].

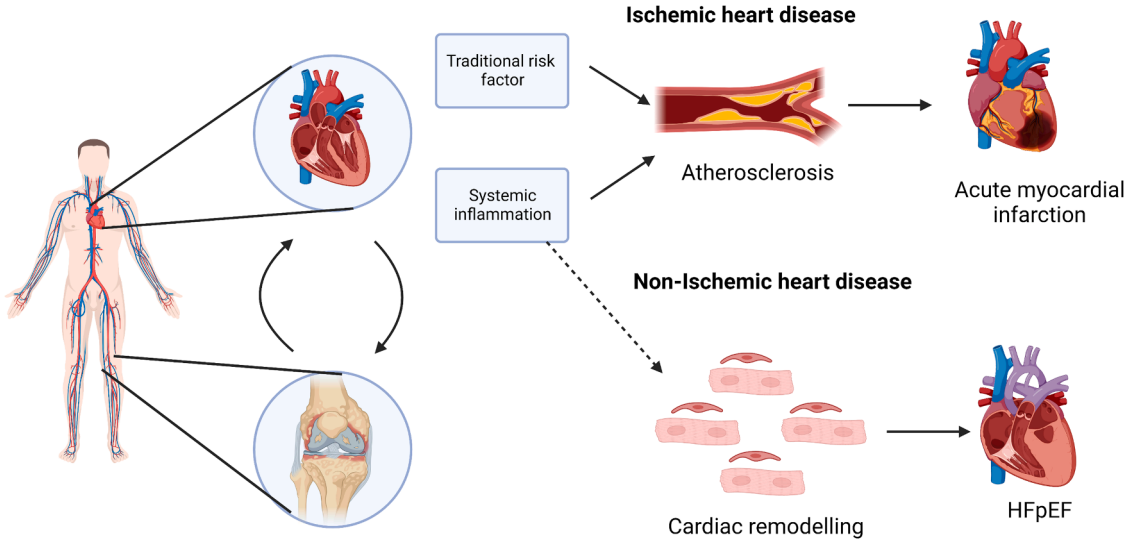

Fig. 2. Rheumatoid arthritis-related cardiovascular illness. Local and systemic inflammation may harm the heart directly or make it more vulnerable to risk factors. RA patients are prone to ischemic and non-ischemic cardiac disease. Heart failure can develop from CAD and cardiac hypertrophy.

Inflammation regulates risk of CVD in RA

Tumor necrosis factor alpha (TNF-α), interleukin 1 (IL-1), and interleukin 6 (IL-6) are prominent pro-inflammatory mediators driving the pathogenesis of RA, in conjunction with the NLRP3 inflammasome. This pathological milieu significantly contributes to the progression of atherosclerosis and CVD [40–46]. Given the shared signaling pathways among these inflammatory mediators, they emerge as attractive targets for therapeutic interventions in rheumatic diseases. Evaluating the levels of IL-6 and high-sensitivity C-reactive protein (hsCRP) aids in predicting cardiovascular events both in primary and secondary preventive settings.

Numerous studies involving over 15,000 healthy men have established a direct link between elevated IL-6 levels and an increased risk of future heart attacks. IL-6 and hsCRP have been identified as predictors of severe recurrent cardiovascular events, even in individuals receiving contemporary polypharmacotherapy for CVD prevention and exhibiting high rates of coronary revascularization. Moreover, acute coronary syndrome patients with elevated IL-6 levels tend to experience a worse prognosis. Mendelian randomization experiments have further implicated interleukin-6 (IL-6) signaling in the progression of CVD [47]. Notably, at the site of plaque rupture in individuals with myocardial infarction (MI), the concentration of IL-6 is significantly higher than in the systemic circulation, suggesting a potential role of IL-6 in myocardial injury following ischemia and reperfusion. Contrary to conventional beliefs, hsCRP does not directly cause atherosclerosis; rather, it is synthesized in response to IL-6 in the liver and serves as a simple marker of IL-6 activation.

Both gout and atherosclerosis can activate the macromolecular protein complex known as NLRP3, which can be triggered by various stimuli, such as cholesterol crystals in an atherosclerotic plaque. The NLRP3 inflammasome and IL-1 play pivotal roles as upstream activators of IL-6. Pre-clinical studies have demonstrated that IL-1 exerts detrimental effects on blood flow, oxidative stress, plaque formation, growth, and rupture. While IL-1 is associated with heart disease, it might contribute to the extent of the infarct. In an ex vivo rodent model of cardiac ischemia-reperfusion, the NLRP3 inflammasome may exacerbate the extent of an infarct. Furthermore, measuring TNF-α levels may have potential in predicting future cardiovascular events. TNF-α, a critical regulator of vascular homeostasis, promotes endothelial dysfunction and a prothrombotic state.

Mechanism of CVS disease progression in RA patient

The elevated risk of cardiovascular mortality in RA patients primarily stems from the development of atherosclerotic disease. Key

contributors to the development of both RA and CVD include endothelial dysfunction, oxidative stress, immune system responses to inflammation, inflammatory mediators, modified peptides and proteins, as well as the production of inflammatory molecules. The chronic inflammatory state contributes to atherosclerosis as it impacts not only the artery itself but also modifies established cardiovascular risk factors. Despite advancements in understanding the involved mechanisms and their interplay with traditional cardiovascular risk factors, the classification, prevention, and treatment of rheumatoid arthritis remain areas of uncertainty. Reducing the prevalence of CVD requires an integrated approach that encompasses proper management of identified risk factors. Diverse rheumatoid arthritis treatments appear to influence cardiovascular risk and the underlying processes linking these conditions in distinct manners, necessitating further investigation to determine whether specific therapies offer superior CVD prevention capabilities.

Investigating the factors responsible for CVD in individuals with arthritis holds the promise of enabling precise risk stratification and identifying novel targets for substantial reduction of CVD risk. Several factors contribute to RA patients' heightened risk of CVD. Inflammatory cytokine production and systemic inflammation both contribute to the worsening clinical course of RA. Quantitative and qualitative changes in cholesterol transport and cell formation play a role in these shifts. Notably, antibodies generated against post-translational modified proteins during inflammation may serve as targets for the cardiovascular damage and inflammation caused by RA, particularly as post-translational changes have direct implications on endothelial function (Fig. 3).

Over time, the development of an atherosclerotic plaque involves active endothelial cells releasing chemokines and displaying molecular signals, attracting immune cells like monocytes to adhere to and migrate into the endothelium. Endothelial cells' increased permeability allows cells and low-density lipoproteins (LDL) to penetrate the vessel wall. Cytokine production promotes new blood vessel formation and smooth muscle cell proliferation. Macrophage pro-inflammatory responses play a critical role in atherosclerotic progression, leading to the formation of lipid-laden macrophages through the uptake of modified low-density lipoproteins (mod LDL). Lipin-1 catalyzes the conversion of phosphatidic acid (PA) to diacylglycerol (DAG), a key substrate for lipid droplet synthesis and a signaling molecule promoting pro-inflammatory gene expression.

Subsequent smooth muscle growth and foam cell development contribute to plaque formation, characterized by cell encrustation on the vessel wall. Ruptured neovessels can lead to increased intraplaque hemorrhage. Hypoxia results in foam cell death and necrosis in the absence of oxygen and oxidative stress. As calcium accumulates within the plaque, a fibrous cap forms, preventing thrombogenic material from entering the bloodstream and causing bleeding. Increased plaque size not only narrows the vessel lumen but also alters the artery wall outwardly, increasing the risk of rupture. Acute thrombosis and clinical events may occur when the fibrous cap of the plaque thins and ruptures, and high concentrations of inflammatory cells are observed in the plaque just before its rupture.

Studies showing link between CVS and RA patients

Patients with rheumatoid arthritis are more likely to die from CVD. Heart disease is the leading cause of death in both the general population and persons with RA. RA increases CVD risk by about twofold, like diabetes. RA patients are twice as likely to suffer systolic infarctions and more coronary plaques as non-RA individuals, even when there is no clinical history of CHD. The CVD mortality risk for RA patients is 17.6%, compared to 10.8% for non-RA patients following a new CVD event [48–50]. In a meta-analysis of 111,758 patients with 22,927 cardiovascular events, RA patients had a 50% higher risk of CVD death than

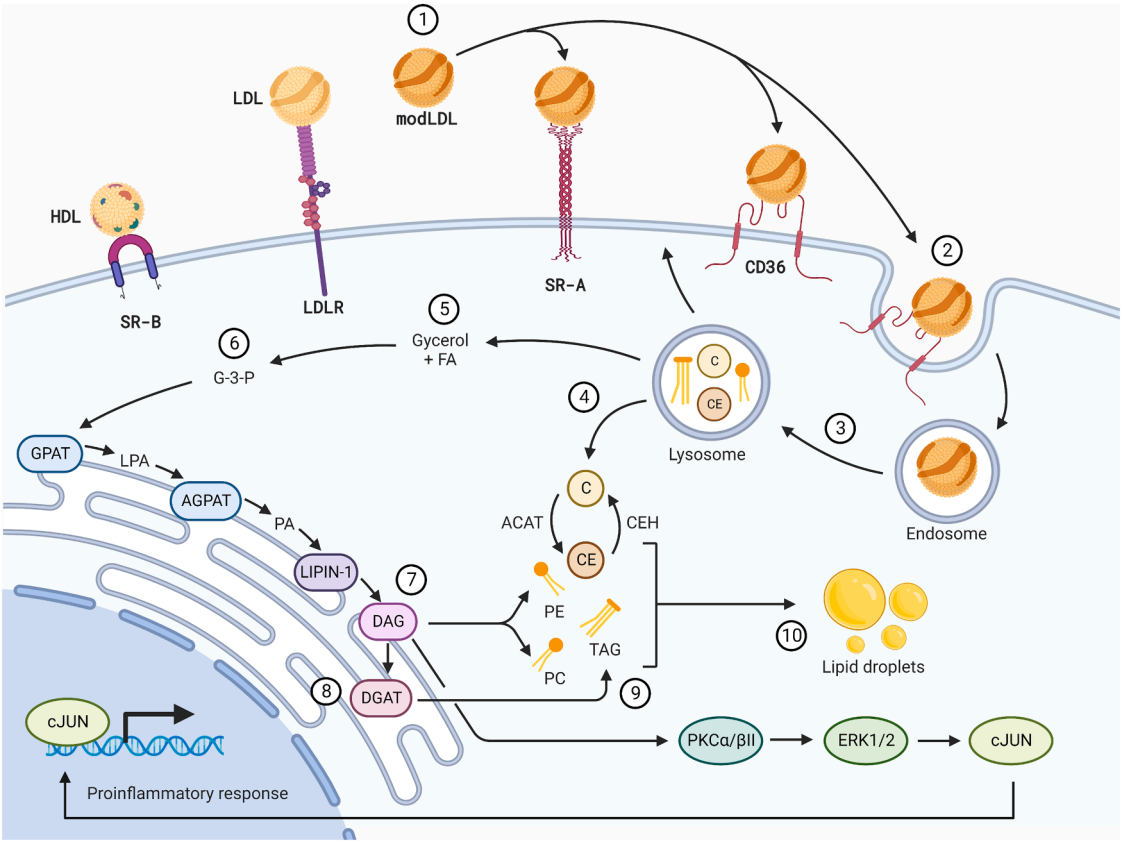

Fig. 3. Role of Lipin-1 in Modified-LDL Induced Pro-Inflammatory Response.

the general population [51]. CVD is frequent in inflammatory joint disease patients. Due to risk factors and inflammation. CVD risk factors include age, gender, dyslipidemia, high blood pressure, smoking, obesity, inactivity, and type 2 diabetes [52,53]. Smoking is connected to RA and CVD and causes inflammation. In addition to affecting other risk factors for both diseases, smoking upregulates genes connected to RA. Obesity and diabetes were connected to inflammatory polyarthritis in a 2014 population study. The beginning of CVD and the progression of RA may be altered by elevated levels of adipokines in persons with diabetes, obesity, and RA, which are all related with chronic inflammation and adipokine synthesis in the blood. Anti-inflammatory medications like glucocorticosteroids can lower cardiovascular risk by lowering inflammation. Inflammation can modify a person's lipid profile, which is well-known.

Due to RA's substantial systemic inflammatory load, a risk factor for CVD, and the increasing incidence of classical risk factors, EULAR recommends effective disease control to decrease CVD risk. RA disease activity is connected to carotid plaque rupture, which remission may reduce. Due to the complexities of regulating disease activity and treating CV risk factors, effective CV risk management certainly includes both. Inflammation and the lipid paradox in RA confound circulating lipid levels, reducing their relevance as a measure of cardiovascular risk. Post-hoc analysis of the AMORIS trial found a weaker association between TCh and acute MI in RA patients than in the general population. RA patients' lipid levels may be a confounding factor in algorithms used to predict their risk of CVD, contrary to popular thinking [54]. Using biologic drugs such as TNF-antagonist (etanercept, certolizumab pegol, golimumab infliximab and adalimumab); interleukin (IL)-1 inhibitor (anakinra); T-cell co-stimulation blocker (abatacept); and B-cell depleting agent (rituximab) to treat rheumatoid arthritis raises the risk of CVD. RA patients' lipid profiles must be reevaluated once inflammation is reduced to ensure optimal therapy. Early treatment strategies such as treat-to-target, which aims for disease remission or low disease activity, can be extremely beneficial (an overview of the benefits of dampening inflammation on CV risk in RA is shown in Fig. 4). Lipid profiles and, if necessary, treatment with cholesterol-lowering medicines can then be done according to national guidelines.

Impact of RA management

Advancements in diagnostics and therapeutic approaches during the last two decades have substantially improved the prognosis for patients diagnosed with rheumatoid arthritis (RA). Present methods focus on efficient inflammation management through comprehensive disease monitoring, with the ultimate aim of achieving remission as a therapeutic goal [55–57]. Considering the potential contribution of inflammation to cardiovascular disease (CVD) development, it is reasonable to postulate that pharmaceutical interventions targeting inflammation reduction may also mitigate the risk of CVD. Nonetheless, despite significant improvements in disease management, the prevalence of CVD remains elevated in RA, particularly in the early stages, as evidenced by multiple studies [58,59].

The pathogenesis of CVD in RA is associated with the onset and progression of atherosclerosis, which is thought to arise from an imbalance between mechanisms promoting endothelium damage and those facilitating vascular repair. Literature supports the notion that effective treatment regimens, which disrupt inflammatory signaling and impede inflammation-driven atherosclerosis, play a crucial role in minimizing cardiovascular complications.

Nevertheless, several important considerations warrant attention. Firstly, it is possible that achieving disease remission, though beneficial for joint-related outcomes, may not directly correlate with a reduction in cardiovascular risk. Secondly, certain medications could potentially increase the risk of CVD by exerting harmful effects on the vasculature, potentially interfering with vascular repair systems. Consequently, therapeutic interventions may act as a double-edged sword in CVD management in RA (Fig. 5). Thirdly, established cardiovascular risk indicators, such as blood cholesterol levels, may exhibit counterintuitive responses to effective therapeutic interventions with medications.

It is overly simplistic to assert that RA treatments invariably improve cardiovascular health. Instead, a comprehensive evaluation and management of both the favorable and adverse effects of these medications are imperative due to their potential impact on cardiovascular outcomes. The clinical and molecular implications of currently available pharmacological therapies, including disease-modifying antirheumatic drugs (DMARDs), nonsteroidal anti-inflammatory drugs (NSAIDs), and

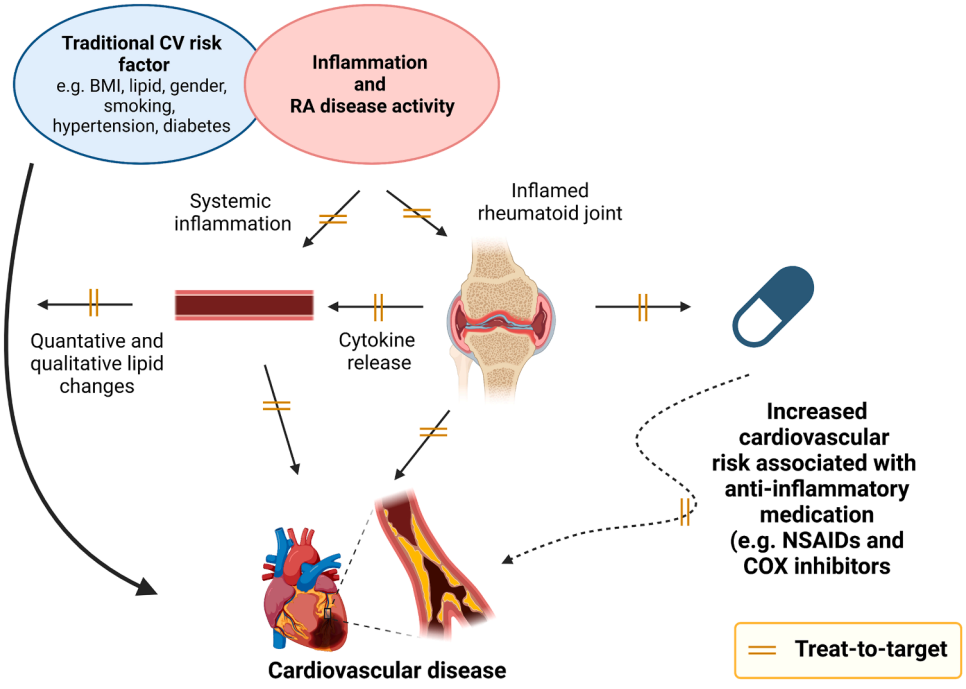

Fig. 4. Reducing the risk of cardiovascular disease in RA: the effect of effective management of inflammation and disease activity.

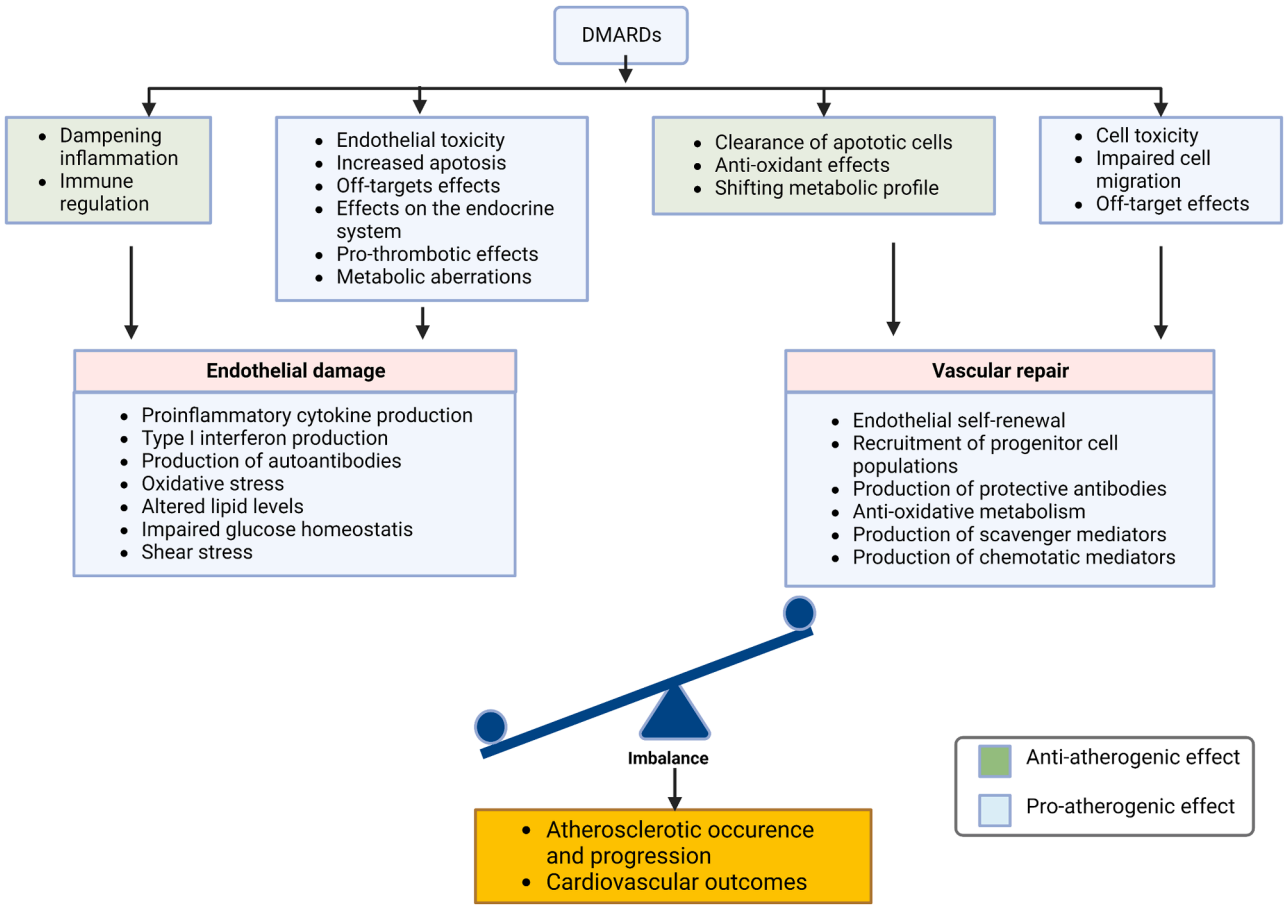

Fig. 5. Role of DMARDs in cardiovascular disease in RA.

Table 1
Cardiovascular outcomes in RA patients treated with DMARDs.

Authors	Type of Study	Drugs	Duration	Outcome
Kume et al. [63]	Cohort study with sample size of 46 patients	Tofacitinib (10 mg/day)	54 weeks	Carotid intima-media thickness slightly decreases in people with atherosclerosis
Charles-Schoeman et al. [64]	Pooled data from phase III studies	Tofacitinib (10 mg/day)	24 months	Neither MACE nor CHF were associated with treatment. Rates of occurrence on par with those of placebo (phase III).
Xie et al. [65]	Meta-analysis of RCTs	Tofacitinib, baricitinib, peficitinib and decernotinib	12–24 weeks	Neither major adverse cardiac events (MACE) nor thromboembolic consequences were affected by JAK inhibition, and there were no significant differences amongst JAK inhibitors in this regard. When comparing 2 mg to 4 mg of baricitinib, lower doses are protective against cardiovascular events.
Taylor et al. [66]	Pooled data from 9 RCTs	Baricitinib (2–4 mg/ day)	24 weeks	Baricitinib was found to have no association with MACE, ATE, or CHF. In both dose groups, the incidence of DVT was similar.
Cohen et al., 2019 [67]	Pooled data from phase III trials	Upadacitinib (15 or 30 mg/day)	12–24 weeks	The incidence of MACE was identical at 15 mg compared to placebo, however it was greater at 30 mg. Comparable rates of venous thromboembolism in the placebo group
Harigai et al. [68]	Pooled data from databases	Tofacitinib	No set pre-defined follow-up period	Compared to TNF inhibitors, tofacitinib did not cause any additional VTEs.
Mease et al., 2020 [69]	Pooled data from phase I, II, III, IIIb and IV RCTs and long-term extension studies	Tofacitinib (5 and 10 mg/ day)	24 months	Both doses of tofacitinib produced similar results in terms of the occurrence of DVT, PE, and ATE, and these results corresponded well with observational data and stated incidence rates for alternative therapy. Patients who had preexisting heart conditions were more likely to experience a thromboembolic event.
Genovese et al. [70]	Pooled data from 9 RCTs	Baricitinib (2 mg or 4 mg)	4.2 years	There was no rise in incidence rates after being exposed to baricitinib for up to 8.4 years, demonstrating that its safety was not compromised.
Cohen et al. [71]	Pooled data from 5 RCTs	Upadacitinib (15 mg or 30 mg)	12–14 weeks to 2.5 years	Upadacitinib did not raise the risk of MACE or VTE over time, and there were no significant differences between treatment groups. Similar rates of occurrence were observed in patients receiving MTX or ADA treatment.

glucocorticoids, on cardiovascular involvement in RA are elucidated below.

Pharmacological interventions

Lowering blood pressure and cholesterol levels significantly alleviates the burden of cardiovascular disease (CVD) in the general population and among individuals with diabetes. Disease-modifying antirheumatic drugs (DMARDs) exhibit potential in reducing cardiovascular risk by mitigating inflammation, although their additional cardioprotective or harmful properties necessitate consideration. The clinical relevance of the relationship between lipids and inflammation in antirheumatic drugs remains uncertain. Despite the association of nonsteroidal anti-inflammatory drugs (NSAIDs) and selective COX-2 inhibitors (COXIBs) with cardiovascular risk in the general population, their indispensable role in managing rheumatoid arthritis (RA) cannot be overlooked [60,61]. Conversely, the use of glucocorticosteroids is associated with an elevated cardiovascular risk, attributed to increased insulin resistance, hypertension, and metabolic syndrome, thereby augmenting overall cardiovascular risk. Moreover, long-term glucocorticoid therapy in RA patients has been linked to higher mortality rates [62]. Statins are recommended for primary prevention, even in individuals without dyslipidemia, owing to their favorable effects on endothelial dysfunction, plaque stabilization, and chronic inflammation, rendering them effective in RA treatment. Furthermore, anti-tumor necrosis factor (anti-TNF) medication demonstrates superior inflammation reduction and cardiovascular risk mitigation compared to non-biologic DMARDs. Table 1 presents cardiovascular outcomes in RA patients using synthetic DMARDs.

Methotrexate

Since its discovery as an anticancer agent in the 1940s, methotrexate (MTX) has evolved into the standard treatment for rheumatoid arthritis (RA) and various other autoimmune and inflammatory conditions, earning substantial acclaim as a success story. MTX is categorized as a disease-modifying anti-rheumatic drug (DMARD), known to not only alleviate symptoms but also impede disease progression. Multiple hypotheses have been proposed to elucidate the mechanism of MTX's effectiveness in RA, encompassing adenosine signaling, folate antagonism, reduction of adhesion molecules, regeneration of reactive oxygen species (ROS), alteration of cytokine profiles, and polyamine inhibition, among others. Presently, the prevailing explanation for MTX's mechanism in RA revolves around its ability to elevate adenosine levels, which, in turn, may promote an overall anti-inflammatory state upon engaging adenosine with its extracellular receptors [72]. For a considerable duration, methotrexate has been a cornerstone in RA treatment, and it has recently garnered attention for its potential cardioprotective properties [73]. A meta-analysis of 15 studies revealed that MTX significantly reduces mortality in RA patients, particularly through an independent association with decreased death from RA-CVD [74].

TNF inhibitors

TNF inhibitors have demonstrated a 30% reduction in the risk of myocardial infarction and stroke in patients with rheumatoid arthritis [75]. Additionally, these inhibitors may confer improved outcomes following a cardiovascular incident. In the context of acute myocardial infarction, mortality rates were comparable between patients using TNF inhibitors and standard DMARDs; however, discontinuing TNF inhibitors more than 90 days before the event resulted in a tripling of the risk of death [76]. It is important to note that the cardioprotective benefits of TNF inhibitors may not be universally applicable to all patients, owing to variations in medication response and length of follow-up. Notably, rheumatoid arthritis patients treated with infliximab exhibited increased Paraoxonase-1 (PON-1) activity and HDL antioxidative capability [77,78], suggesting that infliximab's ability to reduce inflammation after six months may be attributed to its antioxidant properties. Furthermore, adalimumab was observed to reduce macrophage cholesterol absorption while not affecting export [79]. In the context of rheumatoid arthritis, TNF inhibitor medication led to an increase in endothelial progenitor cells (EPCs), which correlated with clinical improvement and a decrease in asymmetric dimethyl arginine [80]. In a limited trial of patients with rheumatoid arthritis, combination therapy with methotrexate and infliximab was found to decrease superoxide generation and increase PON-1 activity. Additionally, the combination therapy demonstrated improvements in HDL and nitric oxide (NO) bioavailability relative to the control group, suggesting a potential mitigating effect on disease progression.

IL-6 inhibition

Tocilizumab exerts its inhibitory action on interleukin-6 (IL-6) signaling by blocking IL-6 receptor (IL-6R), leading to a substantial and enduring impact on inflammation and a rapid normalization of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Notably, tocilizumab administration has been associated with elevated cholesterol levels, albeit concomitant with decreased inflammation markers in the body. However, it has been established that lipid-lowering medications can effectively mitigate these cholesterol elevations. Similarly, anti-tumor necrosis factor (TNF) medications exhibit comparable effects on all major lipoproteins, including high-density lipoprotein (HDL), total cholesterol (TCh), low-density lipoprotein (LDL), and triglycerides, while maintaining steady LDL:HDL and TCh:HDL ratios. These ratios have been found to offer superior predictive value for cardiovascular disease (CVD) risk when compared to individual lipid measurements, which can be influenced by inflammation. Moreover, the most reliable marker for predicting CVD risk remained stable in patients treated with tocilizumab over a six-month period. In a double-blind phase IV study known as the Adalimumab Actemra (ADACTA) trial, patients with rheumatoid arthritis (RA) intolerant of methotrexate (MTX) or unsuitable for continued MTX treatment were randomly assigned to receive either adalimumab (anti-TNF) monotherapy or tocilizumab (anti-IL-6R) monotherapy. Importantly, the tocilizumab group exhibited significantly higher LDL levels compared to the adalimumab group [81].

NSAIDs and glucocorticoids

Research into the cardiovascular risk of various NSAIDs intensified following the withdrawal of rofecoxib and valdecoxib due to safety concerns. A comprehensive meta-analysis and systematic review of observational studies involving 23,655 patients with rheumatoid arthritis who used NSAIDs demonstrated an 18% higher risk of cardiovascular events [75]. Similarly, glucocorticoids, like NSAIDs, have garnered attention for their therapeutic potential in managing this condition. Notably, prednisone-treated rheumatoid arthritis patients experienced a 47% increased incidence of all cardiovascular events, encompassing myocardial infarctions, congestive heart failure (CHF), and stroke [75]. Moreover, the use of prednisone in rheumatoid arthritis has been associated with a heightened risk of death from cardiovascular causes and all-cause mortality combined [82]. Recent findings from a cross-sectional investigation suggest a novel mechanism by which glucocorticoids may be linked to cardiovascular disease in rheumatoid arthritis, involving the obstruction of reverse cholesterol transport. Specifically, prednisone-treated rheumatoid arthritis patients exhibited lower levels of cholesteryl-ester transfer protein mass and activity compared to non-treated patients with rheumatoid arthritis [83].

Non-pharmacological interventions

Recognizing the increasing burden of cardiovascular disease (CVD) and assessing individual cardiovascular (CV) risk profiles are essential

for optimal management. High-risk individuals warrant referral by primary care physicians or cardiologists, followed by patient education programs focused on lifestyle modifications. Primary preventative therapy plays a crucial role in controlling blood pressure and cholesterol levels [84,85], with dietary adjustments serving as the initial step. Effectiveness in lifestyle change strategies necessitates informing patients of their CVD risk. An eight-week cognitive-behavioral patient education program developed by John and colleagues demonstrated success in reducing risky behaviors associated with CVD and improving blood pressure [86]. For rheumatoid arthritis patients, smoking cessation, a balanced diet, and moderation of alcohol consumption are advised. Additionally, structured exercise regimens prove beneficial in preventing CVD in RA patients. Complementing current treatments, individual or group therapy aimed at enhancing patients' psychological well-being and reducing stress holds promise for improved outcomes.

Exercise therapy

Physical activity plays a vital role in the management of inflammatory rheumatic diseases [87]. A comprehensive 2019 review assessing non-pharmacological treatment modalities for rheumatoid arthritis (RA) concluded that exercise/physical activity interventions demonstrated efficacy in reducing the global impact of the disease and improving quality of life [88]. Difficult-to-treat RA (D2TRA) patients, who often present with advanced age, heightened inflammation, and reduced fitness levels, constitute a specific subgroup that can significantly benefit from exercise therapy. Beyond addressing musculoskeletal symptoms, exercise can effectively target several comorbidities, which may be more prevalent in individuals with D2TRA compared to those with milder forms of the disease. Notably, physically inactive RA patients have a substantially increased risk of cardiovascular disease (CVD) [89], thereby highlighting the potential benefits of exercise programs for D2TRA patients with high CVD risk due to RA [90]. While further research is necessary to elucidate the specific impact in active D2TRA patients, evidence suggests that upper- and lower-extremity strengthening exercise programs not only enhance muscle strength but also improve mental health domain scores [91]. Moreover, walking-based physical activity has demonstrated positive effects on sleep duration and quality in individuals with RA [92].

Psychological interventions

Anxiety and depression are prevalent among individuals with RA, particularly those with difficult-to-treat RA (D2TRA) [93]. Studies indicate a bidirectional association between pain and depression, with RA patients being 2–3 times more likely to experience depression than the general population [94]. Depression is also considered a common comorbidity in RA. Self-management programs, including online interventions, have demonstrated effectiveness in reducing RA symptoms and enhancing quality of life [95]. Mindfulness-based practices have shown promising outcomes in reducing pain-related catastrophizing, morning disability, exhaustion, pain, and Disease Activity Score 28-C-reactive protein (DAS28-CRP) scores, and are readily implementable without the need for psychotherapist assistance [96]. Moreover, cognitive-behavioral treatment has been found to improve tender joint count, pain, function, fatigue, and self-efficacy in RA patients [97]. Although emotional disclosure approaches have shown some favorable effects for RA, the overall findings have been mixed, suggesting that this approach may be less effective and require further attention [98].

Dietary interventions

Extensive research has been conducted to investigate the effects of various diets and nutritional supplements on inflammatory rheumatic disorders, such as rheumatoid arthritis (RA). Among these, the Mediterranean diet demonstrated a positive impact on the quality of life in RA patients with lower disease activity [99]. Furthermore, vitamin D supplementation exhibited favorable effects on disease activity [100] and comorbidities, such as osteoporosis, in RA patients. Additionally, evidence from case series, retrospective, and pilot studies suggests that weight loss can lead to improvements in disease activity, physical functioning, eating patterns, and pain in RA, highlighting obesity as a potential contributing factor in difficult-to-treat RA (D2TRA) [101]. However, caution is advised when employing weight loss strategies, as decreased body mass index (BMI) in RA patients has been associated with increased mortality [102]. Thus, individualized nutrition regimens tailored to the specific needs of RA patients are essential for optimal management.

Risk management in RA

Strategies for improvement and recommendation to change practice: In the management of rheumatoid arthritis (RA), focusing on RA management emerges as a promising technique to mitigate cardiovascular disease (CVD) risk associated with RA. Leveraging the specialized knowledge of rheumatologists contributes to its advantage. RA-driven inflammation triggers various physiological alterations, including increased arterial stiffness, lipid salvage alteration, and plaque destabilization, predisposing to rupture and infarction. Therefore, targeting inflammation caused by RA becomes a logical approach to prevent CVD. Recent findings suggest that better control of RA activity leads to fewer cardiovascular events. Additionally, attention must be given to RA medications, especially glucocorticoids, as prolonged use, regardless of dosage, elevates CVD risk. The updated 2017 EULAR recommendations advocate a plan to discontinue or minimize glucocorticoids to the lowest effective dose as soon as clinically feasible. Encouragingly, emerging evidence sheds light on the impact of various RA therapies on cardiovascular risk. COX inhibitors, including nonsteroidal anti-inflammatory medicines, pose an increased CVD risk, with rofecoxib showing the highest risk. Methotrexate's effects on cardiovascular outcomes are being investigated in the ongoing Cardiovascular Inflammation Reduction Trial, even in high CVD risk populations without RA. A systematic review indicates a potential benefit of anti-TNF drugs in decreasing progression of subclinical atherosclerosis, while evidence suggests that blocking tumor necrosis factor (TNF) alpha might improve CVD risk markers compared to other DMARDs. The newer biologics tocilizumab and tofacitinib elevate lipid levels, but post-marketing research on tocilizumab did not find an increase in cardiovascular events. Despite these advances, more randomized controlled trials (RCTs) and follow-up studies are necessary to comprehensively understand the effects of RA treatments on CVD risk.

Scope and future perspectives

Patients with rheumatoid arthritis (RA) have been shown to have greater mortality and morbidity rates in comparison to the general population. This disparity can primarily be due to an increased incidence of cardiovascular (CV) events. However, the particular causes that led to these results are still a mystery, and they may be influenced by a number of different factors, such as the cohorts that were researched and the care settings that were involved [103,104]. It's possible that the results of studies that compared RA patients treated in diverse treatment settings were influenced by the presence of confounding variables [105].

Recent research showed that individuals with rheumatoid arthritis in Spain had a greater prevalence of cardiovascular disease (CVD) and type 2 diabetes when compared to controls, which suggests that RA, hypertension, and diabetes may lead to atrial fibrillation and heart failure. Even in the absence of RA, disease-specific risk variables have the potential to have an independent impact on the risk of myocardial infarction and mortality. In addition, patients with RA have a worse rate of adherence and durability with medications that lower glucose and

cholesterol levels than patients in the control group, which indicates the need for enhanced treatment of cardiovascular disease medications [106]. Methotrexate-based interventions have showed promise in terms of lowering cardiovascular risk and increasing patient outcomes. Methotrexate has been linked to a decrease of 18% in the rate of myocardial infarctions [107], as well as a reduction of 21% in the number of cardiovascular events. In addition, there is evidence that TNF-antibodies have the capability of reducing inflammation and possibly shielding the heart from damage. It has been discovered that they can bring back the antioxidant capability of HDL [108].

The elevated risk of cardiovascular disease that is associated with RA patients is significantly influenced by a number of important cardiovascular risk factors, including smoking, blood pressure, blood glucose, body weight, and lipid profile [109,110]. It is hypothesized that the pathophysiology of RA, in conjunction with the effects of medicines and various other cardiovascular risk factors, leads to this elevated risk. There is a correlation between an increased risk of cardiovascular disease and RA-specific autoimmunity, which includes rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA). Recent research has demonstrated that RA patients who have RF and/or ACPA antibodies have an increased likelihood of developing a cardiovascular ailment [111]. In order to have a complete understanding of the connection between RA and CVD, additional study is required to shed light on the processes of ischemic heart disease and other related illnesses that are present in individuals with RA. With this new information, it will be easier to locate potential pharmaceutical targets for the treatment of cardiac conditions in individuals suffering from inflammatory joint disease (IJD).

Assessing individuals with RA for their potential for cardiovascular disease requires illness-specific methods, which might be difficult to implement. In order for rheumatoid arthritis (RA) patients to have effective management of cardiovascular disease (CVD) outcomes, prospective clinical research should explore the efficacy of antirheumatic medications, traditional risk factor pharmaceutical therapy, and lifestyle adjustments. Large-scale, randomized, controlled trials with cardiovascular disease (CVD) outcomes as endpoints are necessary in order to improve our understanding of prevention methods. However, due to the need for large sample sizes and extensive follow-up monitoring over extended periods of time, conducting such trials in patient populations affected by RA is an extremely difficult task. Even if there isn't enough evidence to prove it, it's possible that cardiovascular risk management could be beneficial for many RA patients. In order to effectively manage cardiovascular risk and disease in patients with rheumatoid arthritis (RA), it is essential to carry out routine screenings for cardiovascular risk and to encourage collaboration between RA specialists, internists, cardiologists, and primary care physicians.

Conclusion

Patients with rheumatoid arthritis (RA) exhibit a heightened susceptibility to cardiovascular disease (CVD) and mortality when compared to the general population. Therefore, it is imperative to address cardiovascular risk factors as an integral component of RA therapy. The assessment of CVD risk should be based on national criteria, which may vary across different countries, despite the existence of global standards for managing risk factors in this patient cohort. While maintaining strict adherence to traditional cardiovascular risk factors is essential, caution must be exercised in the use of corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs) during RA treatment. Emphasizing a disease-specific approach, we advocate for treat-to-target care, glucocorticoid reduction, and thoughtful evaluation of medications with potential to increase CVD risk in RA patients. The European League Against Rheumatism (EULAR) strongly recommends a comprehensive assessment of individual CVD risk and risk calculation at least once every five years, or more frequently in the presence of significant changes to their anti-rheumatic treatment. The urgency to explore innovative methods for reducing CVD risk in RA and other autoimmune disorders is driven by the potential to improve both individual and population health outcomes, thus necessitating immediate investigation in this domain.

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