Vascular Health and Risk Management

Dovepress
Taylor & Francis Group

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REVIEW

The Effects of Disease-Modifying Antirheumatic Drugs on Cardiovascular Risk in Inflammatory Joint Diseases: Current Evidence and Uncertainties

Olena Garmish[1], Svitlana Smiyan[2], Fedir Hladkykh[3], Bohdan Koshak[2], Roman Komorovsky[2]

[1]King's College Hospital London, Dubai, United Arab Emirates; [2]Department of Internal Medicine II, Ivan Horbachevsky Ternopil National Medical University, Ternopil, Ukraine; [3]Department of Infectious Diseases and Clinical Immunology, School of Medicine, V.N. Karazin National University, Kharkiv, Ukraine

Correspondence: Roman Komorovsky, Ivan Horbachevsky Ternopil National Medical University, 1, Maidan Voli, Ternopil, 46001, Ukraine, Email komorovsky@tdmu.edu.ua

Abstract: Patients with inflammatory joint diseases, including rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis, have an elevated risk of cardiovascular complications due to systemic inflammation, immune-mediated endothelial dysfunction, and associated metabolic changes. Disease-modifying antirheumatic drugs (DMARDs) influence cardiovascular risk through their effects on inflammation, lipid metabolism, and endothelial function. Methotrexate has demonstrated cardioprotective properties, likely mediated through anti-inflammatory mechanisms rather than direct metabolic effects. However, other conventional DMARDs, such as sulfasalazine and hydroxychloroquine, also continue to play a role in routine practice; their cardiovascular effects appear more heterogeneous and less well established. Biologic DMARDs, particularly tumor necrosis factor (TNF) inhibitors, are associated with a reduction in major cardiovascular events despite inducing lipid profile alterations. However, data on newer biologic agents, such as interleukin (IL)-17 and IL-23 inhibitors, remain limited. Janus kinase (JAK) inhibitors present concerns regarding dyslipidemia and thrombotic risk, necessitating individualized cardiovascular risk assessment. Nonsteroidal anti-inflammatory drugs (NSAIDs) remain controversial due to their potential to exacerbate cardiovascular risk, particularly with long-term use. Given the variability in drug effects, treatment strategies must balance effective disease control with cardiovascular safety. This narrative review summarizes current evidence on the impact of both conventional and biologic DMARDs on cardiovascular risk, drawing from randomized clinical trials and real-world observational data. The review also compares available data across different inflammatory joint diseases and highlights areas of uncertainty that remain in clinical decision-making. A multidisciplinary and individualized approach remains essential for optimizing long-term cardiovascular outcomes in these patients.

Keywords: autoimmune, immune-mediated diseases, rheumatoid arthritis, psoriatic arthritis, axial spondyloarthritis, disease-modifying antirheumatic drugs, cardiovascular risk

Introduction

Inflammatory autoimmune and immune-mediated joint diseases significantly increase cardiovascular risk due to systemic inflammation and endothelial dysfunction.[1] Modern treatment strategies must balance effective inflammation control with minimizing long-term cardiovascular complications.[2] A personalized approach, integrating clinical, biochemical, and genetic factors, enhances therapy optimization. While some anti-inflammatory agents provide cardioprotective effects, others may elevate thrombosis or hypertension risk.[3,4] In addition to methotrexate,[5] other conventional disease-modifying antirheumatic drugs (DMARDs) such as sulfasalazine and hydroxychloroquine are still commonly used in clinical practice; however, their effects on cardiovascular outcomes remain less well established and more heterogeneous. Assessing their impact on atherosclerosis and vascular function remains crucial.

Received: 20 February 2025
Accepted: 26 July 2025
Published: 4 August 2025

Scope of the Review

This review consolidates current knowledge on the interplay between inflammatory diseases of joints, existing treatment strategies and cardiovascular risk, emphasizing the need for a multidisciplinary approach and further research. We specifically focus on rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS) – the three most common inflammatory joint diseases encountered in routine rheumatology practice. In contrast to prior reviews that predominantly remain confined to a single disease (mostly, rheumatoid arthritis), we aimed to highlight inter-disease differences and extend the perspective by incorporating evidence from both randomized controlled trials and real-world data sources such as registries and observational cohorts. This inclusive, practice-oriented approach enables a more comprehensive understanding of how DMARDs influence cardiovascular risk across the spectrum of inflammatory joint disease.

To assess the current state of knowledge on this issue, we selected six recent peer-reviewed publications (2024–2025) based on methodological rigor, cohort size (≥200 patients or person-years), and direct evaluation of major adverse cardiovascular events (MACE) in the context of DMARD exposure. The included studies represent diverse methodological approaches, including real-world cohort analyses, integrated clinical trial data, systematic reviews, and metabolomic profiling.

A large-scale U.S.-based cohort study by Sendaydiego et al[6] evaluated the comparative cardiovascular safety of various biologic and targeted synthetic DMARDs (b/tsDMARDs) in 34,375 RA patients aged 18–64 years using the MarketScan® database. Over a 2-year follow-up, rituximab and IL-6 inhibitors were associated with numerically higher MACE incidence (196 and 111 per 10,000 person-years, respectively), though these differences did not reach statistical significance. Janus kinase inhibitors (JAKis) demonstrated comparable cardiovascular risk to TNF inhibitors.

An integrated safety analysis of filgotinib, a JAKi, conducted by Mariette et al[7] included >12,500 person-years in RA and >2800 person-years in ulcerative colitis. The study found an overall low incidence of MACE, venous thromboembolism (VTE), and malignancies. However, patients aged ≥65 years experienced a numerically increased incidence of MACE and malignancies, especially with the 200 mg dose of filgotinib, underscoring the need for age-stratified safety monitoring.

A broader perspective on JAKi-related cardiovascular risk was provided by Kwan et al,[8] who synthesized data from 26 studies involving approximately 20,000 patients. Their review concluded that JAKis have an acceptable cardiovascular safety profile overall, though careful patient selection remains essential, particularly in those with baseline cardiovascular risk factors.

Claus et al[9] applied a metabolomics approach to investigate cardiovascular risk in 200 RA patients receiving conventional synthetic DMARDs (csDMARDs) or bDMARDs. No significant differences in metabolite profiles were found between treatment groups. Instead, traditional risk factors such as hypertension, diabetes, and psychological distress were the main contributors to altered metabolic states, suggesting that these comorbidities may override the influence of pharmacotherapy in some cases.

A Brazilian national cohort study by Gamarski et al[10] analyzed data from 4321 RA patients treated with DMARDs and identified 198 cardiovascular events (4.68%). Patients treated with synthetic DMARDs, particularly those who underwent treatment switching due to inadequate disease control, had a significantly higher incidence of cardiovascular outcomes compared to those on biologic therapies. These findings reinforce the hypothesis that disease activity and therapy instability contribute to increased cardiovascular risk.

Finally, Kwon et al[11] investigated the impact of TNF and IL-17 inhibitors on cardiovascular outcomes in 43,502 Korean patients with ankylosing spondylitis (AS). TNF inhibitors were associated with a 30% lower risk of cardiovascular events (aHR 0.697, 95% CI: 0.499–0.973), whereas IL-17 inhibitors did not demonstrate a statistically significant risk reduction.

Together, these studies highlight the heterogeneity of cardiovascular risk among DMARD classes and patient populations. While TNF inhibitors appear to confer a cardioprotective effect in both RA and AS populations, the cardiovascular safety of JAK inhibitors and IL-6 inhibitors warrants further investigation, particularly in older patients

and those with pre-existing comorbidities. Moreover, real-world registry data and biomarker-based approaches such as metabolomics may enhance individualized risk stratification and inform therapeutic decisions in clinical rheumatology.

A closer examination of inflammatory diseases with established cardiovascular risk, particularly, RA, PsA, and axial spondyloarthritis (axSpA), reveals their frequent association with comorbidities such as hypertension, dyslipidemia, obesity, and thyroid disease. Despite these shared comorbidities, variations in the prevalence of additional conditions and cardiovascular risk factors emphasize the importance of personalized screening and preventive strategies.[1] These comorbidities may be influenced by chronic systemic inflammation, underscoring the role of targeted anti-inflammatory therapies.

The suppression of inflammatory processes through the inhibition of pro-inflammatory cytokines remains a central approach in the treatment of autoimmune inflammatory joint diseases. Traditional therapies with low target specificity often exert unpredictable effects on cellular metabolism. For instance, lipid metabolism may be either enhanced or disrupted by contemporary treatment approaches. Additionally, many conventional drugs rely on in vivo metabolic conversion to become active therapeutic agents. However, this metabolic process can produce harmful byproducts, with rates of drug metabolism varying between individuals. Emerging therapeutic technologies are exploring alternative metabolic pathways that offer more targeted anti-inflammatory effects while reducing the metabolic complications commonly associated with traditional treatments. Therefore, understanding immunometabolic complications and the potential pharmacological factors contributing to increased cardiovascular risk in patients with rheumatic diseases is of particular importance.[2]

Despite the growing body of published evidence indicating an increased risk of cardiovascular diseases (CVD) in patients with inflammatory joint diseases, few studies have explored therapeutic strategies based on examining the impact of disease-modifying anti-rheumatic drugs (DMARDs) to reduce this risk.[3] Therefore, our analysis included a small number of studies that evaluated the impact of traditional and biological DMARDs on specific cardiovascular endpoints. We do not discuss the impact of glucocorticoids (GCs) in this review, as there is ample evidence regarding their effects on the cardiovascular system and due to the global trend toward reducing their use in inflammatory joint diseases.

The well-documented effects of baseline therapy for inflammatory joint diseases on cardiovascular risk include the following:[4]

Methotrexate: demonstrates protective cardiovascular effects, including improvements in metabolic syndrome, anti-atherogenic properties, and reductions in major cardiovascular events and mortality.

Leflunomide: associated with an increase in blood pressure.

Biologic therapy: lowers the risk of cardiovascular events such as myocardial infarction, stroke, and major adverse cardiovascular events. However, it may contribute to worsening of arterial hypertension and hyperlipidemia.

Janus kinase (JAK) inhibitors: linked to an increased risk of cardiovascular and thromboembolic events, as well as to dyslipidemia.

Methotrexate and Traditional DMARDs

Methotrexate, a drug known for its protective effects against atherosclerosis, was first introduced in 1948 for cancer treatment and has since been widely used to manage various immune-mediated diseases. Over the past three decades, both epidemiological and experimental research have demonstrated an independent association between methotrexate use and a lower risk of cardiovascular diseases, especially among patients with rheumatological conditions.[5,12] Methotrexate is a first-line treatment for RA and is used in SpA, showing potential for reducing mortality, particularly fatalities related to CVD. It has been shown to reduce the risk of CVD by 21% and myocardial infarction by 18% in patients with RA and PsA,[13] and may also offer protection against atherosclerosis and thrombosis.[14]

While methotrexate has demonstrated cardiovascular benefits, its effects on lipid metabolism remain complex and somewhat paradoxical. Some authors believe that patients with RA may have an atypically reduced lipid level in light of the increased risk of cardiovascular diseases.[15] According to this, previous studies suggest that methotrexate increases total cholesterol and LDL-C, while simultaneously reducing the risk of cardiovascular diseases,[16] potentially restoring normal lipoprotein metabolism,[17] although the reduced levels of pro-inflammatory cytokines and the associated inflammation likely also play a role.[13]

Nevertheless, methotrexate reduces folate levels, potentially leading to hyperhomocysteinemia, a known risk factor for thrombosis and endothelial dysfunction. However, this effect is routinely addressed through folic acid supplementation and does not appear to offset the overall cardiovascular benefit observed in clinical studies.[18,19]

Still, in a clearly defined population with a very high cardiovascular risk and documented cardiovascular diseases (such as prior myocardial infarction or multivessel ischemic heart disease), along with type 2 diabetes or metabolic syndrome, low doses of methotrexate did not lead to a reduced number of cardiovascular events compared to placebo.[20] Methotrexate's cardiovascular benefits are likely limited to high-inflammation scenarios, such as in inflammatory joint diseases. In rheumatoid arthritis, its reduction of cardiovascular risk is not linked to decreased disease activity, suggesting other mechanisms may be involved.[21] It is suggested that methotrexate does not impact blood lipids, platelet aggregation, or insulin resistance, implying a protective mechanism distinct from antiplatelet agents or statins.[22]

Sun et al[23] published a meta-analysis that included 10 studies and 195,416 patients with rheumatoid arthritis (RA), with the aim of assessing the role of methotrexate in preventing cardiovascular events in RA patients and in treating patients with coronary artery disease (CAD). Overall, the analysis demonstrated that methotrexate has a preventive effect on the development of cardiovascular disease in the context of RA. However, the findings of the CIRT study,[20] which did not support this conclusion for CAD, involved a population with lower levels of inflammation (the hs-CRP level was only 1.6 mg/L), suggesting that the studied cohort was a low-risk group with limited expected anti-inflammatory effects. In patients with RA, this meta-analysis confirmed that methotrexate is the preferred drug for preventing cardiovascular events. However, the effect of methotrexate in patients with coronary artery disease (CAD) does not prevent their occurrence.

Other Conventional DMARDs: Sulfasalazine, Hydroxychloroquine, and Leflunomide

The cardiovascular effects of conventional DMARDs (cDMARDs) beyond methotrexate remain inconsistent and are mostly derived from studies in RA, with limited data in other inflammatory joint diseases. Hydroxychloroquine has been associated with both potential cardiovascular benefits, such as improved lipid profiles, reduced thrombosis risk, and enhanced insulin sensitivity[24,25] and adverse effects including QT prolongation[26] and rare cases of cardiomyopathy.[27–29] While some cohort studies suggest a protective role in RA[30] and SLE,[31] other investigations have failed to confirm a clear impact on arterial stiffness or lipid metabolism.[32,33]

Sulfasalazine may improve endothelial function and correct dyslipidemia through suppression of pro-inflammatory cytokines (TNF-α, IL-1, IL-6) and modulation of NF-κB activity.[34] Clinical cohort studies suggest an association between sulfasalazine use and reduced cardiovascular risk in RA[35] and ankylosing spondylitis,[36] though experimental data have also shown it may exacerbate cardiac remodeling under certain conditions.[37]

Data on leflunomide are similarly conflicting. While experimental models suggest potential cardiotoxicity via Nrf2/NF-κB pathway activation,[38] other studies report anti-atherosclerotic effects through regulation of lipid metabolism and endothelial function.[39] Some observational data indicate an elevated risk of myocardial infarction with long-term use.[40]

A recent systematic review[41] concluded that methotrexate remains the conventional DMARD with the strongest evidence base for cardiovascular protection. In contrast, the effects of hydroxychloroquine, sulfasalazine, and leflunomide are considered less conclusive due to limited randomized trials and small sample sizes. Therefore, current evidence is primarily restricted to RA and may not be directly generalizable to psoriatic arthritis or spondyloarthritis, warranting further disease-specific investigation.

Biologic DMARDs

Due to the common underlying mechanisms between inflammation and atherosclerosis, controlling disease activity is a key therapeutic goal in managing cardiovascular diseases in rheumatoid arthritis, alongside addressing traditional risk factors.[42] Regression of atherosclerosis markers, such as arterial stiffness and intima-media thickness of the carotid artery, has been documented following adequate disease control in patients with RA.[43]

As a result, there is growing global interest in new therapeutic strategies that focus not only on traditional cardiovascular risk factors but also on targeting specific agents in the inflammatory cascade, showing promising outcomes.[44,45] Biological therapy has proven highly effective in managing inflammatory joint disorders over the past

three decades. By targeting key immune mediators like TNF-α, IL-1, and IL-6, biological DMARDs have significantly improved prognosis and quality of life. Beyond controlling disease activity, they may also improve cardiovascular outcomes in these patients.[46] The inflammatory hypothesis of atherosclerosis has fueled interest in using biologic agents as adjunctive therapy for systemic inflammatory disorders, extending beyond cardiovascular disease. However, large-scale clinical trials with definitive cardiovascular outcomes are still lacking.[47,48]

Accumulated evidence suggests a potential reduction in cardiovascular disease risk mediated by biologic therapy, which may be attributed to improved endothelial function, reduced inflammation, and decreased insulin resistance associated with its use.[49,50] Specifically, TNF-α inhibitor therapy in patients with RA, psoriasis, and PsA has been associated with a significant reduction in the risk of cardiovascular events, including myocardial infarction, stroke, and major cardiac complications. However, no data have been reported regarding antihypertensive effects, and the available evidence on newer biologic therapies remains inconclusive.[51,52]

Beyond direct inflammation control, TNF inhibitors also modulate lipid metabolism, which may contribute to their cardiovascular effects. A recently published meta-analysis indicated that biologic therapy may improve the lipid profile in patients with RA; however, its potential adverse effects on cardiovascular health remain a concern.[53] bDMARDs may influence lipid profiles in RA patients by raising levels of HDL cholesterol, LDL cholesterol, and triglycerides. In RA, lipid levels can show paradoxical associations with cardiovascular risk, as lower cholesterol and LDL levels have been linked to a higher risk of cardiovascular disease.[54] This phenomenon, known as the "lipid paradox" refers to the whereby patients with active inflammation exhibit low levels of total cholesterol, LDL-C, and HDL-C, yet still face elevated cardiovascular risk. This is attributed to accelerated lipid metabolism, functional impairment of HDL particles, endothelial dysfunction, and a U-shaped association, where excessively low LDL-C levels during active disease are linked to a higher incidence of cardiovascular events.[55] An example is the IL-6 inhibitor tocilizumab, which, despite elevating LDL-C levels, modifies in a favorable way the composition of HDL particles, thereby reducing their pro-inflammatory properties.[56]

While RA and SpA share inflammation-driven pathology, their cardiovascular risk profiles differ, likely due to variations in inflammation, treatment responses, and associated metabolic disorders. Evidence linking biologic therapy to cardiovascular outcomes in SpA is limited, but lipid profile changes seem similar in both conditions.[57] In fact, although patients with SpA share many similarities with other forms of arthritis, particularly in terms of clinical manifestations and treatment options, there are some important differences in terms of pathogenic mechanisms and comorbidities. For example, the pattern of joint involvement is primarily spinal in AS and peripheral in PsA, and there are distinct metabolic and dermatological characteristics in PsA. Furthermore, there is limited data on the new drugs recently introduced in rheumatology, such as anti-IL-17 and anti-IL-23 agents. It has been shown that in patients with SpA, treatment with etanercept led to an increase in HDL cholesterol and total cholesterol levels during the first three months. Treatment also improved the total cholesterol to HDL ratio and HDL quality. Elevated serum amyloid A (SAA) in SpA patients decreased, enhancing HDL's atheroprotective effects.[58] A study on TNF-α inhibitors in AS patients found that after 14 weeks, total cholesterol and HDL levels increased, while the total cholesterol/HDL ratio, triglycerides, and LDL remained stable.[59] A study involving over 200 axSpA patients, primarily with AS, found no changes in lipid profiles with TNF-α inhibitors compared to those not receiving the treatment. After 2 years, only a significant increase in total cholesterol was observed in the latter group.[60] The safety of TNF-α inhibitors regarding the risk of cardiovascular events in the treatment of AS was also confirmed in a cohort study involving 26,928 individuals.[61]

In 2017, a study demonstrated that five years of etanercept treatment in patients with PsA led to increased levels of total cholesterol, HDL-C, and LDL-C, while the total cholesterol/HDL-C ratio remained unchanged.[62]

Regarding surrogate markers, arterial stiffness has generally remained unchanged in the majority of studies on AS, which partially contrasts with observations in RA.[63]

Similar findings have been reported in a study of 28 patients with AS, demonstrating no changes in arterial stiffness after six months of TNF-α inhibitor therapy.[64] On the whole, similar findings have been reported by other researchers.[65]

There is also evidence supporting the beneficial impact of TNF-α inhibitors on endothelial dysfunction in SpA. Data obtained from small cohorts of patients show that, under the influence of infliximab and etanercept, endothelial-

dependent vasodilation and microvascular function improved within 4–12 weeks. After infliximab infusion, adhesion molecules like sE-selectin, markers of endothelial activation, significantly decreased in AS patients.[66]

The review of scientific literature suggests that atherosclerotic lesions (such as the reduction of atherosclerotic plaques) significantly improve in SpA patients undergoing treatment with TNF-α inhibitors. These favorable changes have been observed in both 5-year and 2-year follow-ups, as opposed to patients treated with a placebo.[67] In a randomized, placebo-controlled study, the use of golimumab did not result in significant changes in carotid intima-media thickness (CIMT), although a substantial deterioration in this measure was observed in the placebo group after 6 months.[36]

There is substantial evidence regarding the improvement of CIMT and the reduction of atherosclerotic plaques in patients with PsA under the influence of TNF inhibitors (TNFi), observed over 3-month, 2-year, and 58-month periods with continuous treatment, in contrast to results obtained with conventional DMARDs. Treatment duration was inversely correlated with CIMT, indicating a cumulative effect on atherosclerotic lesions. A recent study with 300 psoriasis and PsA patients found that TNFi treatment reduced atherosclerosis progression more significantly in men than in women.[68]

Despite the close association between psoriasis and PsA with CVD risk, few studies have assessed the role of immunosuppressive agents in the prevention or, conversely, the exacerbation of CVD. A recent meta-analysis of TNF inhibitors in psoriasis/PsA patients showed a reduced cardiovascular risk compared to topical therapy.[51] Another analysis found lower CVD and myocardial infarction risk in patients treated with TNF inhibitors versus those on topical treatment or methotrexate.[69] A large study (n=78,162) found no difference in the risk of atrial fibrillation or serious cardiovascular events between patients on ustekinumab or TNFi.[70] Evidence on new treatments for PsA and AS, particularly IL-17 inhibitors, remains limited.

Thus, data for SpA is less robust compared to RA, especially regarding anti-IL-17 and anti-IL-23 therapies. TNFi therapy increases total cholesterol and HDL levels, though the total cholesterol/HDL ratio remains unchanged. Additionally, TNFi appears to improve endothelial dysfunction and atherosclerosis. Recent studies show that triple and biologic therapies in RA improve lipid profiles, but these changes do not correlate with reduced cardiovascular risk, as measured by vascular inflammation with FDG-PET/CT.[71]

The potential risk of MACE associated with biological therapies in real-world settings, compared to other alternative psoriasis treatments, is supported by an analysis of psoriasis treatment data, in which MACE occurred in 4206 patients. All four biological classes exhibited elevated and comparable MACE rates relative to alternative psoriasis treatments. The association was ranked in descending order: IL-12/23 inhibitors > IL-17 inhibitors > IL-23 inhibitors > TNFi.[72] An evaluation of 9817 cases of CVD indicated that adalimumab was the only TNF-α inhibitor among five investigated that was associated with an elevated risk of thrombotic cardiovascular events, particularly in patients with psoriasis.[73] A systematic review of randomized controlled trials (n=2096 patients) found no significant correlation between IL-17 inhibitors and changes in major adverse cardiovascular events (MACE) risk. Subgroup analyses of secukinumab and ixekizumab also showed no dose-dependent effect.[74]

Therapeutic options like TNFi show potential in lowering cardiovascular risk, but the impact of IL-12/23 inhibitors on cardiovascular health remains uncertain. Emerging evidence supports the use of IL-17 and IL-23 inhibitors in patients with cardiovascular conditions, reflecting a shift in treatment strategies. Preventive measures, including lifestyle changes, statins, and new therapeutic approaches, offer additional protection.[75]

Overall, bDMARDs may lower CVD risk in inflammatory arthritis patients, but not all types provide this benefit. The variability in results is likely due to factors like selection bias, differing definitions of MACE, patient diversity, and differences in targeted mechanisms. Patients with systemic arthritis who have established CVD risk factors or pre-existing CVD are likely to differ from those with systemic arthritis but without established CVD risk factors.[76]

Targeted synthetic DMARDs (tsDMARDs) are small-molecule inhibitors increasingly used for the treatment of autoimmune rheumatic diseases, as they are less toxic, have fewer adverse effects, and exhibit greater specificity for proteins and signaling pathways involved in disease pathogenesis.[77] Pharmacological agents target key pro-inflammatory signaling pathways activated by cytokines, chemokines, growth factors, and antigens, including JAK, MAPK, NF-κB, as well as spleen tyrosine kinase (SYK) and Bruton's tyrosine kinase (BTK). The precise impact of inhibiting these

pathways on specific metabolic mechanisms remains unclear but is likely integral to the efficacy of specific tsDMARDs. Currently, data on their effects on CVD remain inconclusive.

JAK inhibitors represent the most recent advanced therapeutic class approved for the treatment of RA, PsA, and AS. While they have demonstrated superior clinical efficacy compared to the TNF-α inhibitor adalimumab, concerns have been raised regarding their cardiovascular safety profile.[78] A post-marketing study in RA patients (>50 years, ≥1 CVD risk factor) found that tofacitinib, a non-selective JAK1,2,3 inhibitor, increased the risk of MACE compared to TNF-α inhibitors, prompting a US drug safety warning.[79] In contrast, recent analyses showed no significant cardiovascular risk increase with JAK inhibitors in RA or immune diseases short-term, but they highlight the complex mechanisms behind vascular damage in these conditions, emphasizing the need for individualized CVD risk management. Unlike conventional DMARDs, JAK inhibitors influence metabolic pathways, potentially altering lipid profiles and raising thrombotic risk. Tofacitinib and baricitinib notably raised HDL and LDL cholesterol levels compared to baseline and other RA treatments, but these changes were observed mainly in RTCs.[80–83] JAK inhibitors enhance HDL function by boosting lecithin-cholesterol acyltransferase activity, which supports cholesterol efflux. They also affect lipoprotein size and content.[84] These treatments may lead to drug-induced dyslipidemia, potentially worsening the lipid imbalance linked to CVD. In addition to dyslipidemia, JAK inhibitors have been implicated in thrombotic events, further complicating their cardiovascular safety profile. Previous studies have raised concerns that JAK inhibition may increase the risk of both arterial and venous thrombotic events, and new data suggest that this risk is depends on the selectivity of the JAK inhibitor.[85] A RTC comparing tofacitinib to TNF inhibitors led the FDA to issue an urgent review of JAK inhibitors, highlighting potential increased risks of cardiovascular events, cancer, thrombosis, and death, with recommendations for assessing the benefit-risk profile before starting or continuing therapy.[86]

Studies on tofacitinib have shown high control rates and a favorable safety profile, even in RA patients with cardiovascular risk factors. A large study found no significant difference in major adverse cardiovascular events (MACE) or venous thromboembolism (VTE) between patients receiving JAK inhibitors and those on TNF inhibitors, supporting tofacitinib as a viable treatment option when cardiovascular risks are managed individually.[87,88] From another perspective, data from the ORAL Surveillance study demonstrated an increased risk of serious cardiovascular events (MACE) for tofacitinib compared to TNFi in RA patients with elevated CVD risk. Adverse effects were more frequently observed in patients with higher cardiovascular risk, especially those aged ≥65 years. These findings support the need for individualized benefit-risk assessment of treatment, including evaluation/management of cardiovascular diseases, to optimize RA outcomes.[89] There is also data suggesting that the use of tofacitinib in RA patients (7580 with newly diagnosed RA, 1998 received tofacitinib, 5582 received adalimumab) may slightly increase the risk of dyslipidemia compared to adalimumab. However, no differences were found in all-cause mortality.[90] A study assessing the safety profile of JAK inhibitors in RA patients found that high disease activity was linked to increased side effects. No significant differences were observed between cardiovascular risk factors, including age, and the frequency of adverse events during JAK inhibitors therapy.[91]

Evidence suggests that combining methotrexate and JAK inhibitors may provide therapeutic benefits in treating rheumatoid arthritis (RA). Indirect data point to a potential cardioprotective effect of methotrexate on cardiovascular outcomes, mediated by mechanisms such as reduced inflammation, activation of AMP-activated protein kinase, enhanced cholesterol efflux, and adenosine accumulation. The “lipid paradox” in RA underscores the intricate relationship between treatment (methotrexate, JAK inhibitors, TNF inhibitors, and IL-6 receptor inhibitors), inflammation, lipid profiles, and cardiovascular risk. In the absence of contraindications and with good tolerance to methotrexate, its combination with JAK inhibitors is recommended for optimizing cardiovascular protection in RA patients.[92]

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs, both non-selective and COX-2 selective inhibitors, are commonly used for pain management in AS and PsA but are associated with varying risks of cardiovascular events, including heart failure, myocardial infarction, and sudden death.[93]

The primary concern with non-selective NSAIDs is the risk of peptic ulcers and gastrointestinal bleeding due to COX-1 inhibition, while selective COX-2 inhibitors (coxibs) were developed to mitigate these side effects.[94] However,

subsequent findings indicated that coxibs may be associated with various cardiovascular adverse effects.[95] Following the identification of cardiovascular risks associated with certain NSAIDs, further analysis revealed mechanisms underlying these complications. Two mechanisms are commonly associated with these adverse effects: These adverse effects are linked to two mechanisms: an imbalance between pro-aggregatory thromboxane A2 (via COX-1) and anti-aggregatory prostacyclin (via COX-2),[96] and reduced prostaglandin E2 synthesis in the kidneys, where COX-2 is believed to be the primary source despite both COX enzymes being constitutively expressed.[97]

Given the role of COX enzymes in vascular homeostasis, NSAID-induced inhibition can have significant cardiovascular consequences, particularly in long-term use. COX-2 inhibition drives NSAID-related cardiovascular effects, with all NSAIDs, except low-dose acetylsalicylic acid (aspirin), potentially raising blood pressure and worsening heart failure.[98] In this context, the disruption between thromboxane A2 and the prostacyclin pathways depends on the extent of COX-1/2 inhibition, the duration of action, and the reversibility of inhibition. For NSAIDs, only low-dose acetylsalicylic acid (and occasionally indobufen) is clinically employed to prevent atherothrombosis.[99] This is explained by the fact that low doses of acetylsalicylic acid irreversibly inhibit platelet COX-1 without significantly affecting endothelial COX. In contrast, COX-2 selective inhibitors reduce prostacyclin production without significantly influencing thromboxane A2 mediated by COX-1. In addition to increasing blood pressure, NSAIDs exacerbate pre-existing hypertension.[100]

Cardiovascular risks associated with these medications may differ. Naproxen, a non-selective COX inhibitor, is considered less harmful to cardiovascular health than other non-selective NSAIDs or coxibs. However, the PRECISION study contested the belief that naproxen offers better cardiovascular outcomes, finding celecoxib, a selective COX-2 inhibitor, comparable in cardiovascular safety to both naproxen and ibuprofen.[101]

However, contrary findings suggest NSAIDs increase the risk of cardiovascular and cerebrovascular events (OR 1.18; 95% CI 1.01–1.38; p=0.04), particularly strokes, with COX-2 inhibitors showing a higher risk (OR 1.36; 95% CI 1.10–1.67; p=0.004) compared to non-selective NSAIDs (OR 1.08; 95% CI 0.94–1.24; p=0.28). However, NSAIDs did not significantly affect the risk of myocardial infarction, heart failure, or major cardiovascular events, though these findings require cautious interpretation due to study inconsistencies.[51]

Among the various classes of NSAIDs, coxibs and diclofenac have been associated with a higher risk of serious vascular events, while this risk is lower with naproxen use.[102] NSAIDs are recommended as first-line treatment for AS, but their cardiovascular risk remains debated. A Canadian study found inadequate NSAID use associated with higher cardiovascular mortality.[103] A Norwegian study similarly found increased cardiovascular mortality, with lack of NSAID use linked to reduced life expectancy.[104] NSAIDs may modulate inflammation, potentially accelerating atherosclerosis in patients not using them; however, selection bias could influence these findings, as NSAIDs were likely prescribed to those without cardiovascular risk factors.[105] Additionally, the literature suggests that NSAIDs may induce non-histaminergic angioedema in 0.1–0.3% of cases, with mechanisms potentially linked to COX inhibition.[106]

Limitations

This literature review has several limitations. First, there is a marked imbalance in data availability: the vast majority of clinical studies examine the effects of conventional DMARDs in patients with rheumatoid arthritis, whereas data on psoriatic arthritis and ankylosing spondylitis remain underrepresented in the global literature. Second, in recent years, research efforts have primarily focused on evaluating the efficacy and safety of biological DMARDs (particularly IL-17, IL-23, and JAK inhibitors), resulting in outdated findings regarding conventional DMARDs in the context of spondyloarthritis. Additionally, several potential factors were not accounted for, including interactions between DMARDs and concomitant therapies, variations in patient profiles depending on geography and sex, as well as short follow-up periods in several studies. In light of these factors, the results should be interpreted with caution, and further targeted randomized controlled trials are needed to establish clear recommendations for the use of DMARDs in the treatment of ankylosing spondylitis and psoriatic arthritis.

Conclusion

The available evidence indicates that the cardiovascular effects of disease-modifying antirheumatic drugs (DMARDs) in autoimmune inflammatory joint diseases are heterogeneous and drug-specific. Methotrexate remains the conventional

DMARD with the strongest evidence for cardioprotection, primarily via anti-inflammatory mechanisms. Other conventional agents, including sulfasalazine, hydroxychloroquine, and leflunomide, have shown potentially beneficial cardiovascular effects in some studies, but the data remain inconsistent and less robust. While sulfasalazine and hydroxychloroquine may confer modest benefit, leflunomide has demonstrated both favorable and adverse cardiovascular signals. Among biologic DMARDs, TNF inhibitors are most consistently associated with reduced cardiovascular events, whereas IL-17/23 inhibitors require further evaluation. JAK inhibitors necessitate caution due to associations with thrombotic and metabolic risks. NSAIDs, though commonly used, are linked to increased cardiovascular risk, particularly with long-term use. Overall, the cardiovascular impact of DMARDs cannot be generalized; it varies by drug class and patient characteristics. Treatment strategies should balance inflammation control with cardiovascular risk assessment to support optimal clinical outcomes.

Date and Materials Statement

This is a narrative review without statistical analysis of the raw medical record data. If necessary, more data can be provided by the corresponding author upon reasonable request.

Ethics Statement

Ethical review and approval were not required for this submission.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was not supported by any external funds.

Disclosure

All the authors declare that they have no conflicts of interest.

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