AMERICAN JOURNAL OF EDUCATION AND LEARNING
ISSN: 2996-5128 (online) | ResearchBib (IF) = 10.91 IMPACT FACTOR
Volume-4| Issue-3| 2026 Published: |30-03-2026|

UO'K: 616.12-008.331.1:616.72-002.77: 615.262.1-036

EVALUATION OF THE CARDIOTOXIC EFFECTS OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS AND METHOTREXATE IN PATIENTS WITH HYPERTENSION COMORBID WITH RHEUMATOID ARTHRITIS

https://doi.org/10.5281/zenodo.19275407

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Hypertension is one of the most prevalent and lethal diseases worldwide, including in our republic. When hypertension occurs in comorbidity with rheumatoid arthritis (RA), the patient's general condition deteriorates significantly. Another factor complicating the clinical situation is the potential cardiotoxic effect of the primary drugs used in the treatment of RA, specifically non-steroidal anti-inflammatory drugs (NSAIDs) and methotrexate. This article analyzes observations and studies conducted by leading global researchers regarding these specific clinical scenarios.

Keywords

rheumatoid arthritis; hypertension; cardiovascular diseases; non-steroidal anti-inflammatory drugs (NSAIDs); methotrexate; cardiotoxicity.

Hypertension (HTN) and Rheumatoid Arthritis (RA) are considered among the most critical and complex challenges of 21st-century medicine. These diseases are characterized by high prevalence rates, long-term chronic progression, potential for disability, and high mortality rates associated with cardiovascular complications. In modern clinical practice, HTN and RA often coexist in a single patient, creating a complex comorbid state. Bu significantly complicates the processes of diagnosis, treatment, and prognostic assessment [1].

Hypertension is a chronic pathological condition characterized by a sustained increase in systolic arterial pressure 140 mmHg and diastolic arterial pressure 90 mmHg. It serves as a primary modifiable risk factor for cardiovascular diseases [2]. Central to the pathogenesis of HTN are the activation of the renin–angiotensin–aldosterone system, dysfunction of the sympathetic nervous system, endothelial dysfunction, and reduced vascular elasticity [6]. Alongside its severe pathogenetic course, the widespread prevalence of HTN is of major significance.

According to reports from the World Health Organization and the Global Burden of Disease (GBD) 2024–2025, approximately 30–35% of the global adult

population—exceeding 1.2–1.3 billion people—live with HTN [3]. Most concerningly, nearly half of those with HTN are unaware of their condition, and even in diagnosed cases, a large proportion do not achieve adequate blood pressure control [4].

In recent years, significant shifts have been observed in the epidemiology of HTN. According to global analyses published in 2025, while hypertension is relatively stabilizing in high-income countries, its prevalence is steadily increasing in low- and middle-income nations [5]. Urbanization, sedentary lifestyles, poor nutrition, obesity, and chronic stress are identified as the primary drivers of this widespread distribution. Furthermore, the comorbidity of HTN with conditions such as ischemic heart disease, chronic heart failure, and chronic kidney disease further exacerbates the patient's prognosis. One such critical comorbid condition is the connective tissue disease, RA. Rheumatoid Arthritis is a systemic, chronic, and progressive inflammatory disease of an autoimmune nature. While it primarily affects the synovial joints, it can eventually damage the cardiovascular, pulmonary, renal, and central nervous systems [7]. The pathogenesis of RA is rooted in the disruption of immune tolerance, the production of autoantibodies (rheumatoid factor, anti-CCP), and the persistent activity of inflammatory mediators.

According to GBD 2024 data, RA affects more than 40 million people worldwide, with a global prevalence maintained between 0.5–1.0% [8]. The disease is 2–3 times more common in women than in men and typically manifests between the ages of 30 and 60. Epidemiological studies published in 2025 show that RA incidence remains consistently high in certain regions, particularly Northern Europe and North America [9]. In recent years, the number of cases has also been steadily increasing in our country.

RA is no longer viewed solely as a joint disorder but as a systemic inflammatory disease. Recent research indicates that the risk of developing cardiovascular diseases in RA patients is significantly higher than in the general population [10]. This condition is often described by the concept of "accelerated atherosclerosis," where chronic inflammation speeds up atherosclerotic processes. The coexistence of HTN and RA in a single patient represents a clinically vital comorbid state. According to large-scale cohort studies published in 2024–2025, HTN is detected in 45–60% of patients with RA [11]. This rate is substantially higher than in the non-RA population, confirming the high level of comorbidity between these two conditions.Several common pathogenetic mechanisms are involved in the development of Rheumatoid Arthritis (RA) and Hypertension (HTN) comorbidity. Chronic systemic inflammation exacerbates endothelial dysfunction, decreases nitric oxide bioavailability, and reduces arterial vascular

elasticity [12]. Consequently, peripheral vascular resistance increases, creating a conducive environment for elevated arterial pressure. Furthermore, chronic pain, decreased physical activity, and metabolic disorders in RA patients also contribute to the development of hypertension.

Meta-analyses published in 2025 demonstrated that the risk of developing HTN is 1.3–1.5 times higher in patients with RA; this association persisted even after accounting for traditional risk factors [13]. This highlights the necessity of considering RA as an independent risk factor for HTN. From this perspective, it is critically important for modern medicine to conduct a profound analysis of the prevalence of the comorbid state of hypertension and rheumatoid arthritis, as well as the impact of the pharmacological agents used in this condition on the cardiovascular system. This issue is relevant not only in rheumatology but also in cardiology and internal medicine practice, requiring the development of individualized approaches aimed at improving the long-term prognosis of patients.

The comorbidity of HTN and RA is accompanied by a high risk of cardiovascular disease and significantly worsens the clinical prognosis. Cardiovascular diseases are one of the primary causes of death in patients with RA, and a large portion of these fatalities is attributed to complications related to HTN [14]. Concurrently, medications widely used to treat RA, specifically Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and methotrexate, can exert direct or indirect effects on the cardiovascular system. In recent years, the safety of pharmacotherapy in the context of RA and HTN comorbidity has emerged as a pressing scientific problem. There is sufficient evidence that NSAIDs can increase arterial blood pressure, lead to fluid retention, and elevate the risk of heart failure [15]. While methotrexate demonstrates cardioprotective effects in most studies, its potential to indirectly increase cardiovascular risk in certain clinical cases is currently under discussion [6].

NSAIDs are one of the most frequently used pharmacological groups in the treatment of arthritis and other inflammatory rheumatic diseases. Due to their analgesic, antipyretic, and anti-inflammatory effects, they significantly improve the quality of life for patients. However, the side effects associated with the long-term and large-scale use of NSAIDs—specifically their impact on the cardiovascular system—have become a focal point of scientific attention over the last decade [1]. The cardiotoxic effects of NSAIDs take on even greater clinical significance in the presence of HTN and RA comorbidity. Because cardiovascular risk is already elevated in these patients, NSAIDs can further exacerbate this risk. Large-scale epidemiological and clinical studies published between 2020 and 2025 have forced a re-evaluation of cardiovascular complications associated with NSAIDs [2].

The primary mechanism of action for NSAIDs involves the inhibition of the cyclooxygenase (COX) enzyme. The COX-1 and COX-2 isoenzymes participate in prostaglandin synthesis. Under physiological conditions, COX-1 plays a vital role in maintaining platelet aggregation, gastric mucosal protection, and renal blood flow, while COX-2 is primarily activated during inflammatory processes [3]. Selective COX-2 inhibition disrupts the balance between thromboxane A2 and prostacyclin, increasing the predisposition to a thrombotic state. Experimental and clinical studies conducted between 2021 and 2024 have shown that selective COX-2 NSAIDs increase the risk of cardiovascular events, particularly myocardial infarction and stroke [4]. Simultaneously, non-selective NSAIDs can also increase cardiovascular risk when used in high doses or over long periods.

The effect of NSAIDs on arterial pressure is one of the most well-studied cardiovascular side effects. Meta-analyses from 2020–2025 indicated that NSAIDs increase arterial pressure by an average of 3–6 mmHg by enhancing sodium and fluid retention and suppressing prostaglandin synthesis in the kidneys [5]. Although this figure may seem small, such an increase carries significant clinical weight in patients with high cardiovascular risk. In patients with comorbid Rheumatoid Arthritis (RA) and Hypertension (HTN), the effects of NSAIDs are even more pronounced. A study based on real-world clinical data published in 2023 found that NSAID use in patients suffering from both RA and HTN significantly complicated blood pressure control [6]. Specifically, diclofenac and indomethacin were identified as the drugs with the highest potential to increase arterial pressure.

Heart failure is considered one of the most severe cardiotoxic complications associated with NSAIDs. NSAIDs increase the constriction of afferent arterioles in the kidneys, which reduces the glomerular filtration rate and leads to fluid retention [7]. This, in turn, increases the risk of decompensation in patients with pre-existing heart failure.Large cohort studies published between 2022 and 2025 showed that the risk of hospitalization for heart failure was 20–40% higher in patients taking NSAIDs [8]. This situation is particularly critical for patients with RA who are already at a high risk of developing heart failure.

The association between NSAIDs and thrombotic complications has been actively studied over the last five years. Systematic reviews published between 2021 and 2024 provided reliable evidence that diclofenac and selective COX-2 inhibitors increase the risk of myocardial infarction and ischemic stroke [9]. While naproxen is seen as having a relatively safer profile, it is still not considered absolutely safe. In patients with comorbid RA and HTN, thrombotic risk is already elevated, and NSAIDs can further exacerbate this risk. According to a 2024 meta-

analysis, the use of NSAIDs in RA patients with high cardiovascular risk increased the probability of thrombotic events by 1.3–1.5 times [10].

The reliability of information regarding the cardiotoxicity of NSAIDs is based on various research designs. Randomized controlled trials (RCTs) are limited in this area; most evidence comes from large observational studies and meta-analyses. Meta-analyses published between 2020 and 2025 carry significant weight in clinical decision-making due to their high statistical power, covering millions of patients [11]. At the same time, the difficulty of completely eliminating confounding factors in observational studies must be considered. Rheumatoid arthritis itself, disease activity, and other concomitant medications are important factors in evaluating the impact of NSAIDs [12]. Consequently, recent studies analyzing real-world clinical data through statistical adjustment (propensity score matching) are regarded as more reliable sources of evidence.

The 2023–2024 recommendations from the European Society of Cardiology (ESC) and the European Alliance of Associations for Rheumatology (EULAR) advise caution when using NSAIDs in patients with high cardiovascular risk, recommending the shortest possible duration and the minimum effective dose [13]. In patients with the comorbidity of arterial hypertension and rheumatoid arthritis, individual cardiovascular risk must be assessed before prescribing NSAIDs. In clinical practice, considering the cardiotoxic effects of NSAIDs is vital for improving the long-term prognosis of RA patients. Alongside the necessity of controlling inflammation, minimizing cardiovascular risk must be an integral part of modern treatment strategies.

Methotrexate is considered the primary drug among conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) for treating rheumatoid arthritis and is recommended as the first-choice treatment in many international clinical guidelines [1]. Its widespread use is attributed to its efficacy, relatively favorable safety profile, and long-term disease control. However, since RA is a systemic inflammatory disease, the effect of methotrexate is not limited to the joints; it also exerts direct and indirect effects on the cardiovascular system. In the last decade, particularly between 2020 and 2025, the impact of methotrexate on cardiovascular disease (CVD) has become a central focus of scientific debate. While previous periods saw concerns regarding its potential toxicity—including hypothetical negative effects on endothelial cells—modern epidemiological and clinical studies increasingly demonstrate its cardioprotective properties [2].

The primary pharmacodynamic mechanism of methotrexate involves the inhibition of dihydrofolate reductase, which leads to the suppression of purine and pyrimidine synthesis. In the low-dose form used for RA (7.5–25 mg per week), it

functions primarily as an immunomodulator and anti-inflammatory agent [3]. Recent studies have shown that methotrexate (MTX) enhances adenosine signaling, thereby reducing the expression of major pro-inflammatory cytokines such as TNF-alpha, IL-6, and IL-1 [4]. These cytokines play a critical role in the pathogenesis of endothelial dysfunction and atherosclerosis in the cardiovascular system. Thus, the anti-inflammatory action of methotrexate theoretically serves to reduce cardiovascular risk.

Major cohort studies and meta-analyses published between 2020 and 2025 have shown a significantly lower risk of cardiovascular events in RA patients receiving methotrexate. A 2021 meta-analysis involving over 190,000 RA patients found that those taking methotrexate had a 20% reduction in the relative risk of cardiovascular events [5]. Research based on real-world clinical data from 2023–2024 has confirmed these findings. For instance, analyses based on North American and European registries showed that the risk of myocardial infarction and stroke was lower in RA patients treated long-term with methotrexate compared to those who were not [6]. Crucially, this association remained significant even after accounting for traditional cardiovascular risk factors such as age, sex, smoking, and dyslipidemia.

The question of methotrexate's effect on arterial blood pressure has been studied specifically over the last five years. Clinical and experimental work published in 2024 suggests that by reducing inflammation, methotrexate can decrease arterial stiffness and improve endothelial function [7]. This is viewed as an indirect protective mechanism against the development and exacerbation of arterial hypertension.

However, a direct hypotensive (blood pressure-lowering) effect of methotrexate has not yet been fully proven. Most available evidence is derived from observational studies, which do not allow for the definitive establishment of a cause-and-effect relationship [8]. Nonetheless, the fact that effective inflammation control with methotrexate can improve blood pressure stability in comorbid RA and hypertension patients is clinically significant. Heart failure is a major cause of death and disability among RA patients. Observational studies published between 2022 and 2025 have shown that RA patients receiving methotrexate have a lower risk of hospitalization due to heart failure [9]. This is explained by the drug's ability to effectively control inflammation and reduce the inflammatory burden on the myocardium.

At the same time, there are isolated reports of pericarditis or myocarditis associated with methotrexate in individual clinical cases. However, analyses published between 2020 and 2025 show that these cases are extremely rare and do

not carry significance at the population level [10]. Therefore, there is insufficient evidence to consider methotrexate an absolute contraindication in RA patients with heart failure. Methotrexate is frequently prescribed alongside NSAIDs, which makes the issue of drug-drug interactions highly relevant. NSAIDs can decrease renal clearance, thereby slowing the excretion of methotrexate [11]. This may lead to an increase in methotrexate's hematologic and renal toxicity.

Indirectly, this situation can lead to fluid retention, increased arterial pressure, and additional strain on the cardiovascular system. Retrospective analyses conducted between 2023 and 2025 found that RA patients receiving methotrexate in combination with NSAIDs had a higher risk of deteriorating renal function and cardiovascular complications [12]. Consequently, clinical monitoring is essential when utilizing this combination. The majority of evidence regarding the cardiovascular effects of methotrexate is based on observational studies and meta-analyses. Randomized controlled trials (RCTs) are limited in this regard, as cardiovascular events were often evaluated only as secondary endpoints [13].

Nevertheless, recent analyses based on large registries and real-world clinical data possess high statistical power and reinforce conclusions regarding the cardioprotective effects of methotrexate. The use of propensity score matching and multivariate models has helped mitigate the impact of confounding factors [14]. According to modern EULAR and ACR recommendations, early and continuous use of methotrexate in patients with rheumatoid arthritis (RA) and high cardiovascular risk can improve not only joint symptoms but also long-term cardiovascular prognosis [15]. At the same time, when methotrexate is prescribed in combination with NSAIDs, regular monitoring of renal function, blood pressure, and signs of heart failure is required.

The comorbidity of hypertension (HTN) and rheumatoid arthritis is a complex and multifaceted problem in modern clinical practice. The coexistence of these two diseases not only significantly increases the risk of cardiovascular complications but also requires serious restrictions and balance in choosing a treatment strategy. Evidence presented in previous sections indicates that rheumatoid arthritis itself is an independent cardiovascular risk factor, creating a foundation for the development of hypertension, accelerated atherosclerosis, and heart failure through chronic systemic inflammation [1,2].

From this perspective, pharmacotherapy used in patients with comorbid RA and HTN should be aimed not only at controlling inflammation and pain but also at minimizing cardiovascular risk. NSAIDs and methotrexate are the most commonly used drugs in this group, and their impact on the cardiovascular system has been widely discussed in recent years. Non-steroidal anti-inflammatory drugs

(NSAIDs) play an important role in clinical practice by providing fast and effective relief of RA symptoms. However, the cardiotoxic effects of this drug group, especially against the background of arterial hypertension, have been confirmed by well-founded evidence [3,4]. Meta-analyses and real-world clinical data from the last 5 years (2020–2025) show that NSAIDs can increase blood pressure, lead to fluid retention, and exacerbate the risk of heart failure decompensation and thrombotic events [5,6].

An important aspect of the discussion is that the cardiovascular risk of NSAIDs is not uniform; it depends on the type of drug, dosage, duration of use, and the patient's individual risk profile. While diclofenac and selective COX-2 inhibitors are associated with the highest thrombotic risk, naproxen is viewed as having a more favorable cardiovascular risk profile [7]. However, this relative safety does not imply absolute safety for patients with comorbid RA and HTN.

The relatively higher cardiovascular risk associated with NSAIDs in RA patients is explained by several factors: RA is inherently accompanied by chronic inflammation and endothelial dysfunction. Traditional risk factors such as hypertension, dyslipidemia, and metabolic syndrome are more common in these patients [8]. NSAIDs are often prescribed for long durations and repeated courses, increasing cumulative cardiovascular risk. Evidence from recent years regarding the effect of methotrexate on the cardiovascular system has fundamentally changed the attitude toward this drug. While there were previously concerns about its potential toxicity, large cohort studies and meta-analyses from 2020–2025 reliably demonstrate its cardioprotective effect [9,10]. This effect is primarily related to the reduction of inflammatory activity, suppression of cytokine production, and improvement of endothelial function.

From a discussion standpoint, it is crucial to note that the cardioprotective effect of methotrexate is not limited to reducing RA activity. Some studies indicate methotrexate's direct vascular effects mediated by adenosine, as well as its ability to reduce arterial stiffness [11]. This establishes a basis for considering methotrexate as a drug of strategic importance for RA patients with high cardiovascular risk. However, it would be incorrect to speak of the absolute safety of methotrexate. Especially when used in combination with NSAIDs, a decrease in renal clearance, fluid retention, and indirect worsening of blood pressure control may be observed [12]. This situation re-emphasizes the need for individual monitoring in patients with comorbid RA and HTN.

In practice, a large portion of RA patients take NSAIDs alongside methotrexate. While this combination allows for effective control of inflammation and pain, it can increase cardiovascular and nephrotoxic risks. Retrospective and

real-world clinical analyses from the last 5 years show that renal function deterioration and heart failure episodes occur more frequently with the NSAID + methotrexate combination [13]. A key question in the discussion is whether this combination should be abandoned entirely or if it can be optimized with a safer strategy. According to modern EULAR and ESC recommendations, it is advisable to use NSAIDs for the shortest possible duration at the minimum effective dose in high-risk patients, while continuing methotrexate as the primary anti-inflammatory therapy [14,15]. Simultaneously, regular monitoring of blood pressure, renal function, and heart failure signs must be mandatory in clinical practice.

Arterial hypertension and rheumatoid arthritis comorbidity represent a complex clinical situation with high cardiovascular risk. Scientific evidence from the last 5 years confirms that hypertension is prevalent among RA patients and that this combination significantly increases the risk of cardiovascular complications. While NSAIDs effectively relieve RA symptoms, their cardiotoxic effects in the presence of hypertension carry clear clinical significance. Methotrexate, in contrast, emerges in most modern studies as a drug with cardioprotective effects, reducing the risk of cardiovascular events in RA patients. However, the use of methotrexate in combination with NSAIDs carries indirect risks related to the renal and cardiovascular systems, necessitating an individual approach and close monitoring.

In summary, the primary strategy for treating patients with comorbid RA and HTN should consist of effective inflammation control, rational use of NSAIDs, and optimization of methotrexate as the cornerstone of treatment. Future randomized clinical trials are expected to further refine the assessment of the cardiovascular effects of these drugs and contribute to the development of individualized treatment algorithms.

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AMERICAN JOURNAL OF EDUCATION AND LEARNING
ISSN: 2996-5128 (online) | ResearchBib (IF) = 10.91 IMPACT FACTOR
Volume-4| Issue-3| 2026 Published: |30-03-2026|

АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИЕЙ И РЕВМАТОИДНЫМ АРТРИТОМ. FARS International Journal of Education, Social Science & Humanities., 13(12), 7-14.