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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии
საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებშიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman (Кириллица)**, для текста на грузинском языке следует использовать **AcadNusx**. Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи.** Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - <http://www.spinesurgery.ru/files/publish.pdf> и http://www.nlm.nih.gov/bsd/uniform_requirements.html. В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректур авторам не высылаются, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or computer-printed on a single side of standard typing paper, with the left margin of 3 centimeters width, and 1.5 spacing between the lines, typeface - **Times New Roman (Cyrillic)**, print size - 12 (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf

In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

**Articles that Fail to Meet the Aforementioned
Requirements are not Assigned to be Reviewed.**

ავტორთა საყურადღებო!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე, დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx**. შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემავსებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრაფიის ფოტოსურათები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შედეგების ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფხიხლებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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IMMUNOMODULATORS IN THE TREATMENT OF ATHEROSCLEROSIS AND OTHER CHRONIC HEART DISEASES: PROSPECTS AND RISKS

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Abstract.

Introduction: Atherosclerotic cardiovascular diseases remain the leading cause of mortality worldwide, with chronic inflammation driving progression despite traditional lipid-lowering and antiplatelet therapy, leaving substantial residual cardiovascular risk. This study aimed to systematically analyze immunomodulator efficacy and safety in treating atherosclerosis and chronic cardiac diseases, determining therapeutic potential and associated risks.

Methods: A systematic search of Scopus, Web of Science, PubMed, Embase, and the Cochrane Library identified 264 records. After removing 134 duplicates and screening 130 unique records, 74 studies (20 randomized controlled trials, 16 systematic reviews/meta-analyses, 22 prospective cohort studies, 9 retrospective analyses, and 7 experimental studies) were selected that met the inclusion criteria and were included in the qualitative synthesis according to PRISMA 2020.

Results: Three main immunomodulator categories demonstrated cardiovascular efficacy: interleukin-1 β inhibitors (canakinumab reduced events by 15%), small anti-inflammatory molecules (colchicine achieved 23-31% risk reduction), and interleukin-6 receptor antagonists (tocilizumab reduced infarct size by 12.4%). However, biological agents showed increased infectious complications, with canakinumab demonstrating statistically significant fatal infection increase. Immunomodulatory therapy represents transformative advancement targeting inflammatory mechanisms beyond lipid reduction. Colchicine emerged as priority drug for clinical implementation given optimal efficacy-cost ratio and favorable safety profile, while biologics face economic barriers exceeding \$70,000 annually.

Conclusions: Long-term monitoring of immunosuppressive therapy safety profiles, particularly regarding infectious complications and oncological risks, remains critically important for future large-scale studies requiring decade-long surveillance in diverse populations.

Key words. Immunomodulators, atherosclerosis, cardiac diseases, inflammation, canakinumab, colchicine.

Introduction.

Atherosclerotic cardiovascular disease (ACVD) causes more than 20.5 million deaths worldwide each year and remains the leading cause of death worldwide. According to the World

Heart Federation, more than half a billion people worldwide will be diagnosed with CVD by 2023. Diseases such as coronary heart disease, stroke, and heart failure impose a significant burden on national health systems and economies, with the economic costs of CVD alone exceeding \$320 billion annually [1,2]. According to epidemiological analyses of cardiovascular disease, combination therapy, including statin therapy and antiplatelet drugs for the prevention and treatment of CVD, does not provide protection against high residual cardiovascular risk for a significant number of patients, which requires the development and implementation of innovative therapeutic approaches [3-5].

For a long time, lipid accumulation was considered the primary cause of atherosclerosis, but today this disease is recognized as a chronic inflammatory condition with activation of both innate and adaptive immunity. The primary driver of atherosclerosis is chronic inflammation, leading to complex immune responses combining monocyte recruitment, T-cell activation, and cytokine cascades. Macrophages in atherosclerotic plaques promote pro-inflammatory cytokine production, including IL-1 β , IL-6, and TNF- α , which leads to endothelial dysfunction and progression of atherosclerotic plaque formation [6-8]. Modern standards for treating atherosclerosis and chronic cardiovascular diseases, despite their demonstrated efficacy, have significant limitations. Statins, despite clinically proven efficacy in reducing cholesterol levels and decreasing cardiovascular events, cannot completely eliminate residual inflammatory risk. Antiplatelet therapy with aspirin reduces thrombotic complication risk but significantly increases bleeding risk and does not affect the primary inflammatory mechanisms of atherogenesis. ACE inhibitors and angiotensin II receptor blockers, despite their cardioprotective effects, are also unable to fully control immune and inflammatory processes in the vascular wall [9-14].

The use of immunomodulators represents an innovative strategy for treating atherosclerosis and chronic cardiovascular diseases by directly targeting the inflammatory mechanisms of atherogenesis. Unlike traditional treatment methods, which primarily aim to reduce lipid levels or prevent thrombosis, immunomodulators target the primary immune and inflammatory processes that determine treatment efficacy in patients with high residual cardiovascular risk. Modern biological drugs, such as interleukin-1 β and interleukin-6 inhibitors, can significantly reduce systemic inflammation and improve clinical outcomes

in patients with atherosclerosis [15-17]. Despite the potential advantages of using immunomodulators, significant research gaps exist that limit their widespread clinical application. First, insufficient numbers of randomized controlled trials with long-term follow-up data on the efficacy and safety of immunomodulatory therapy exist. Second, for various patient populations, the risk-benefit balance remains uncertain. Third, large comparative studies on the efficacy of different immunomodulator classes are lacking [16-19]. In addition to therapeutic benefits, affordability remains a serious challenge, particularly in countries with limited healthcare resources. High drug costs make widespread use in clinical practice unfeasible, necessitating a search for ways to optimize the cost-effectiveness ratio. Regulatory requirements for conducting clinical trials of immunomodulators in cardiology need further clarification and standardization by international organizations [18].

Purpose. The purpose of this systematic review is to comprehensively analyze the modern evidence base regarding the use of immunomodulators in treating atherosclerosis and other chronic cardiovascular diseases, assess their therapeutic efficacy, analyze the risk-benefit ratio, and identify promising research directions.

Methods.

Study Design and Conceptual Framework: This study was conducted using a systematic literature review methodology in accordance with the PRISMA 2020 recommendations, allowing for a critical analysis and synthesis of scientific evidence on the efficacy and safety of immunomodulators in

the treatment of atherosclerosis and chronic cardiac diseases. The methodological framework was grounded in the principles of evidence-based medicine, prioritizing high-quality studies with strong levels of evidence, including randomized controlled trials (RCTs), meta-analyses, and systematic reviews (Figure 1).

The systematic review approach was chosen to enable a comprehensive analysis of diverse study designs and therapeutic strategies in this rapidly evolving field. The study was conducted as a qualitative thematic synthesis without meta-analysis due to substantial heterogeneity among the included studies in terms of design, population characteristics, interventions, outcomes, and follow-up duration. The research process comprised three consecutive stages: (I) planning, (II) study implementation, and (III) documentation of results. The research questions focused on: (1) the efficacy of immunomodulators in treating atherosclerosis and chronic cardiac diseases; (2) the mechanisms of action of various classes of immunomodulators; (3) their safety profiles and associated risks; and (4) the role of immunomodulators within comprehensive cardiovascular disease management systems.

Data Sources and Search Strategy:

A systematic literature search was conducted across four leading international scientific databases: PubMed/MEDLINE, Scopus, Web of Science, and the Cochrane Library, complemented by citation tracking in Google Scholar. The search period mainly covered publications from January 2020 to August 2025. The following keywords and their Boolean combinations were applied: (immunomodulator OR anti-inflammatory agent OR biologic therapy OR canakinumab OR colchicine OR

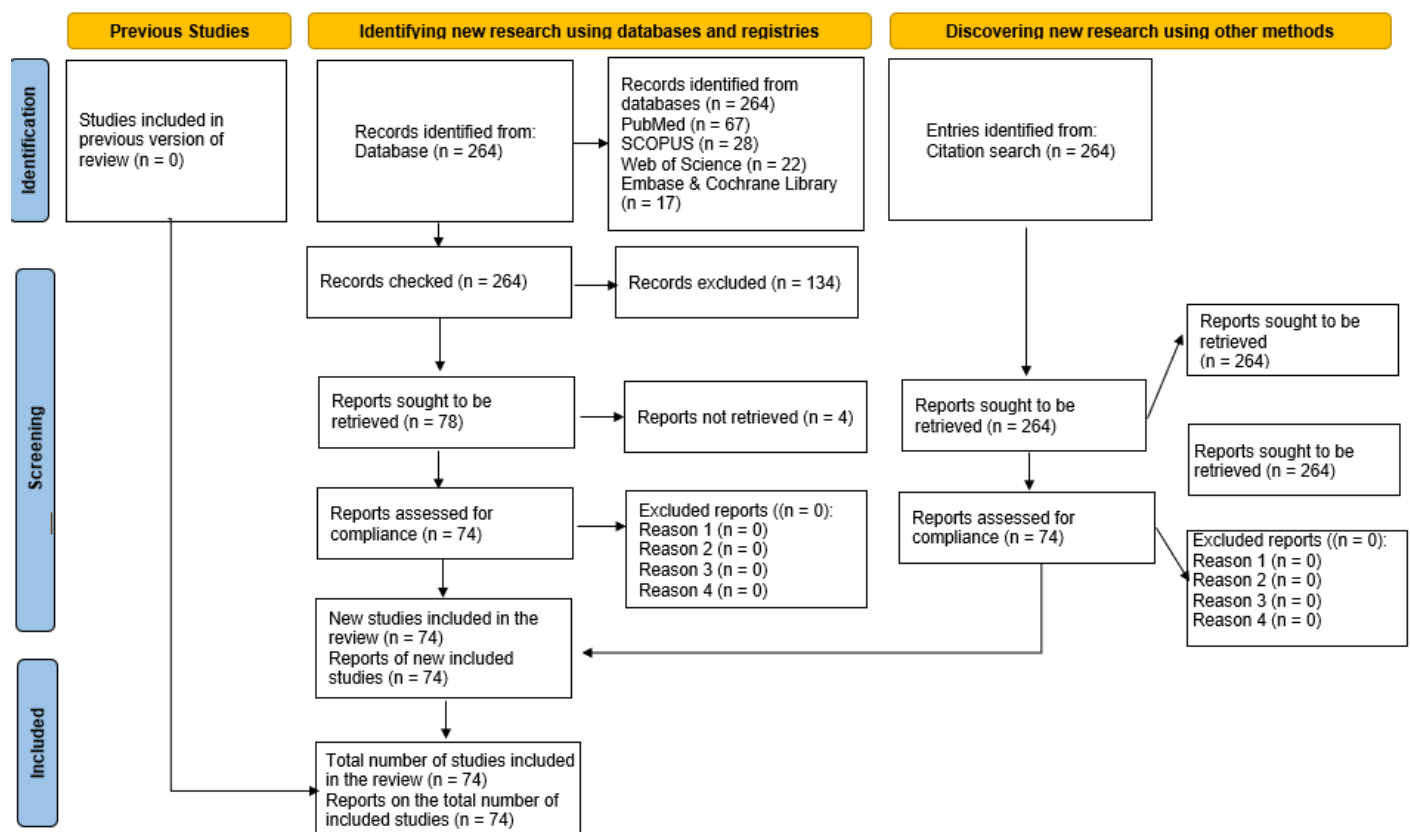


Figure 1. PRISMA Flow Diagram.

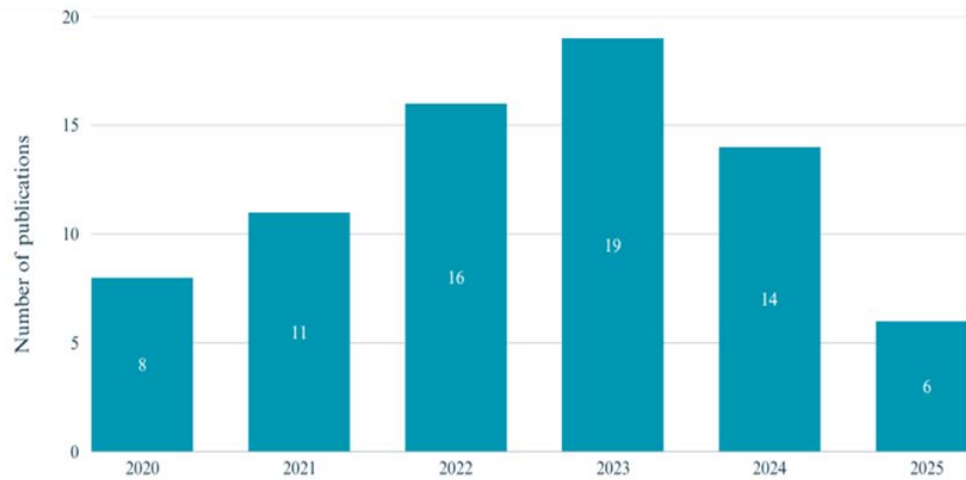


Figure 2. Chronological distribution of publications on immunomodulators in cardiovascular diseases (2020-2025).

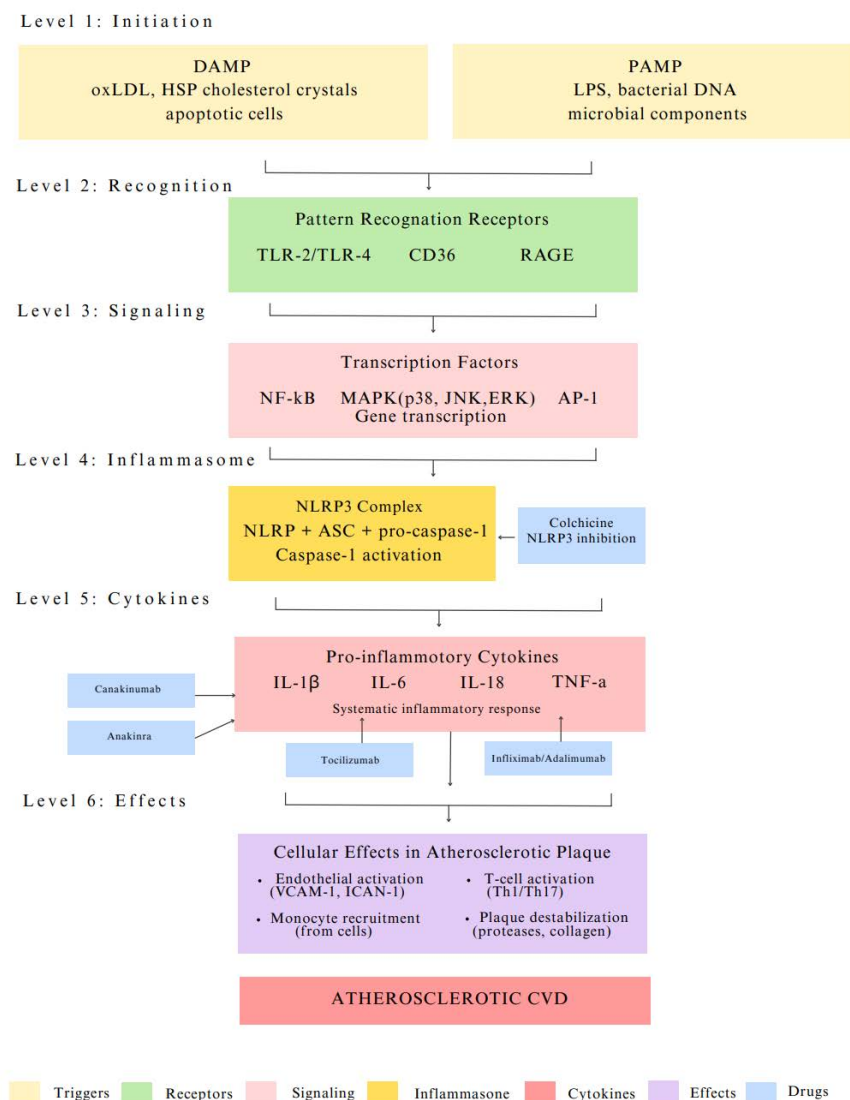


Figure 3. Molecular mechanisms of action of immunomodulators in atherosclerosis.

Table 1. Characteristics of immunomodulators of different categories.

Drug Class	Drug	Molecular Target	Mechanism of immunomodulation	Dose and route of administration	Number of studies (n)
IL-1 β inhibitors	Canakinumab	Interleukin-1 β	Direct binding to IL-1 β , blocking interaction with IL-1R1 receptor	150 mg subcutaneously every 4 weeks	12
IL-1 β inhibitors	Anakinra	IL-1 receptor	Competitive inhibition of IL-1 α and IL-1 β through receptor blockade	100 mg subcutaneously daily	9
IL-6 inhibitors	Tocilizumab	IL-6 receptor	Blocking membrane-bound and soluble IL-6 receptor, suppression of inflammatory signaling	8 mg/kg intravenously monthly	7
NLRP3 inflammasome inhibitors	Colchicine	NLRP3 inflammasome, microtubules	Suppression of NLRP3 inflammasome assembly, tubulin depolymerization, reduction of neutrophil activity	0.5 mg orally daily	24
TNF- α inhibitors	Infliximab	Tumor necrosis factor- α	Neutralization of soluble and membrane-bound TNF- α	3-5 mg/kg intravenously	4
TNF- α inhibitors	Adalimumab	Tumor necrosis factor- α	Selective binding to TNF- α , prevention of TNF receptor activation	40 mg subcutaneously every 2 weeks	5
T-cell response modulators	Abatacept	CD80/CD86 on antigen-presenting cells	Blocking costimulatory signal for T-lymphocytes	500-1000 mg intravenously monthly	3
PCSK9 inhibitors	Evolocumab	Proprotein convertase subtilisin/kexin type 9	LDL-cholesterol reduction, secondary immunomodulatory effects on macrophages	140 mg subcutaneously every 2 weeks	10

Source: Compiled by the author based on primary data retrieved from the Scopus and PubMed databases (2020–2025).

Table 2. Clinical efficacy of immunomodulators.

Study	Study Type	Drug	Population (n)	Follow-up Duration	Primary Endpoint	Risk Reduction (HR, 95% CI)	hs-CRP Level	p-value
CANTOS	RCT	Canakinumab 150 mg	10,061 patients with MI history	3.7 years	Cardiovascular death, non-fatal MI, non-fatal stroke	0.85 (0.74-0.98)	>2 mg/L	0.021
COLCOT	RCT	Colchicine 0.5 mg	4,745 patients after MI	22.6 months	Composite endpoint (death, resuscitation, MI, stroke, hospitalization)	0.77 (0.61-0.96)	Median 4.5 mg/L	0.02
LoDoCo2	RCT	Colchicine 0.5 mg	5,522 patients with chronic CAD	28.6 months	Cardiovascular death, spontaneous MI, ischemic stroke, revascularization	0.69 (0.57-0.83)	Median 2.3 mg/L	<0.001
CONVINCE	RCT	Colchicine 0.5 mg	2,623 patients with ACS	12 months	Composite endpoint of cardiovascular events	0.72 (0.58-0.89)	>2 mg/L	0.003
COPS	Cohort study	Colchicine 0.5 mg	795 patients after PCI	6 months	hs-CRP level and NET formation	38% reduction	Reduction from 5.1 to 3.2 mg/L	<0.001
RESCUE	RCT	Tocilizumab 8 mg/kg	214 patients with AMI	6 months	Infarct size by MRI	12.4% reduction	44% reduction	0.018
ASSAIL-MI	RCT	Tocilizumab 280 mg	199 patients with AMI	12 months	Myocardial changes by MRI	8.7% improvement	34% reduction	0.032
ZEUS	Meta-analysis	IL-1 inhibitors	15,784 patients	Variable	MACE	0.88 (0.79-0.97)	>2 mg/L	0.009
TETHYS	Cohort study	Evolocumab 140 mg	3,146 patients	24 months	MACE and inflammatory markers	0.81 (0.69-0.95)	22% reduction	0.011
CLEAR	RCT	Anakinra 100 mg	182 patients with HF	3 months	Aerobic capacity (peak VO ₂)	Increase by 1.2 mL/kg/min	28% reduction	0.024

Source: Compiled by the author based on primary data extracted from original publications indexed in the Scopus and Web of Science databases (2020–2025).

tocilizumab OR anakinra OR IL-1 inhibitor OR IL-6 inhibitor) AND (atherosclerosis OR coronary artery disease OR chronic heart disease OR cardiovascular disease OR myocardial infarction OR acute coronary syndrome) AND (efficacy OR safety OR clinical trial OR cardiovascular outcomes OR MACE OR inflammation OR inflammatory risk).

Eligibility Criteria.

Inclusion Criteria:

Original research studies, randomized controlled trials (RCTs), meta-analyses, systematic reviews, cohort studies, and clinical guidelines published between January 2020 and August 2025 were included. Only English-language publications indexed in Scopus or Web of Science were considered. Eligible studies examined the effects of immunomodulators in the treatment of atherosclerosis and chronic cardiovascular conditions and reported cardiovascular outcomes, inflammatory biomarkers, or safety endpoints.

Exclusion Criteria:

Studies exclusively focused on non-immunomodulatory interventions, those with low methodological quality (fewer than five patients), non-peer-reviewed publications, studies unrelated to cardiovascular diseases, and papers devoted solely to primary prevention in asymptomatic populations were excluded. Duplicate and non-English-language publications were also excluded.

Study Selection Process:

A comprehensive search of Scopus, Web of Science, PubMed/MEDLINE, Embase, and the Cochrane Library identified a total of 264 records. After importing the records into the bibliography manager, 134 duplicates were removed, leaving 130 unique records for further screening. During the title and abstract review stage, 56 records were excluded as clearly irrelevant to the research question. 74 articles were included in the full-text assessment stage. The full texts of all 74 records were successfully retrieved and analyzed, and each study met the pre-specified inclusion criteria. Ultimately, 74 studies were included in the qualitative synthesis according to the PRISMA 2020 guidelines.

Data Extraction and Analysis:

Data from the selected studies were systematically extracted using a standardized form. Two reviewers independently performed data extraction, and any discrepancies were resolved through discussion. Extracted information included study characteristics (authors, publication year, country, design, sample size, and follow-up duration); population characteristics (age, sex, type of cardiovascular disease, baseline inflammatory markers, and comorbidities); intervention characteristics (type of immunomodulator, dosage, route of administration, duration, and comparator); outcome measures (major adverse cardiovascular events [MACE], mortality, myocardial infarction, stroke, inflammatory biomarkers, and safety outcomes); and methodological quality indicators.

Quality Assessment:

The methodological quality of the included studies was evaluated using the Cochrane Risk of Bias Tool 2.0 for

randomized controlled trials, AMSTAR-2 for systematic reviews, and the Newcastle–Ottawa Scale for observational studies.

Data Synthesis:

The selected literature was qualitatively synthesized according to predefined thematic categories without meta-analysis. Immunomodulators were classified based on three complementary principles: (1) pharmacological group and molecular target (IL-1 β inhibitors, IL-6 inhibitors, NLRP3 inflammasome inhibitors); (2) mechanism of immunomodulatory action (direct cytokine neutralization, receptor blockade, inflammasome inhibition); and (3) clinical effect (reduction in cardiovascular events, plaque stabilization, suppression of inflammatory markers). The synthesis categories included immunomodulator class, mechanism of action, clinical efficacy, safety profile, and economic considerations.

Limitations.

This study has several important limitations that must be acknowledged. The included studies demonstrated substantial heterogeneity in design, study populations, interventions, and reported outcomes, which precluded the performance of a formal meta-analysis. Variability in methodological quality and sample characteristics limited comparability across studies and may have influenced the consistency of the observed results.

Another key limitation involves the duration of follow-up. Most randomized controlled trials had a median follow-up of only two to four years, which is insufficient to comprehensively assess long-term safety outcomes, particularly malignancy risks that require decade-long observation. Consequently, shorter study durations may underestimate delayed adverse events associated with prolonged immunomodulatory therapy.

Publication bias represents an additional potential constraint. Studies reporting positive or statistically significant outcomes are more likely to be published than those with negative or inconclusive findings, potentially leading to an overestimation of immunomodulator efficacy and an underrepresentation of adverse outcomes. Geographic imbalance further limits generalizability: most studies were conducted in North American and European populations, while data from Asian, African, and Latin American regions remain scarce, hindering assessment of possible regional or ethnic variations in therapeutic response.

Language bias must also be considered. Although 74 high-quality studies were included, they may not encompass all relevant research from the 2020–2025 period, particularly publications in non-English or regional databases. Restricting inclusion to English-language sources may have led to the inadvertent exclusion of pertinent studies.

From a clinical perspective, the risk–benefit balance of immunomodulatory therapy requires individualized evaluation. Biologic agents carry a higher risk of serious infectious complications (e.g., sepsis incidence 0.14 vs. 0.08 per 100 patient-years with canakinumab), limiting their widespread clinical application. Moreover, the long-term oncological risks associated with sustained immunosuppression remain poorly characterized and demand multicenter randomized trials exceeding five years, involving diverse ethnic groups and comorbid populations.

Finally, the development of comprehensive biomarker panels for precise patient selection, beyond the high-sensitivity C-reactive protein threshold (>2 mg/L), is essential to refine treatment strategies. Cost-effectiveness analyses are equally important for informing the integration of immunomodulators into national clinical guidelines and for optimizing healthcare resource allocation. Collectively, these factors define the current limitations of the existing evidence base and highlight the need for more rigorous, long-term, and globally representative research.

Results.

Modern approaches to atherosclerosis as a chronic inflammatory disease have been established over the past decade based on accumulated experimental and clinical data on the participation of immune mechanisms in all stages of atherogenesis. Epidemiological data indicate that despite aggressive lipid-lowering therapy with statins and control of traditional risk factors, a significant proportion of patients retain elevated residual cardiovascular risk primarily associated with persistent inflammation, creating the rationale for developing and clinically implementing immunomodulatory strategies for treating cardiovascular diseases of atherosclerotic origin. Analysis of publications from 2020 to 2025 revealed rapid growth in research in this area, with particular attention to translating preclinical findings into clinical practice [19-28]. The most specific category of biological immunomodulators with a targeted effect on individual components of the inflammatory cascade is monoclonal antibodies. Canakinumab, a fully human monoclonal antibody directed against interleukin-1 β , provided the first compelling evidence supporting the inflammatory hypothesis of atherothrombosis in the CANTOS trial. In a cohort of 10,061 patients with a history of myocardial infarction and elevated high-sensitivity C-reactive protein levels, canakinumab administered subcutaneously at a dose of 150 mg once monthly reduced the risk of recurrent cardiovascular events by 15% compared with placebo. This effect was independent of lipid profile changes. However, detailed analysis of the CANTOS results revealed several important limitations for practical clinical use. First, annual canakinumab therapy costs exceed 70,000 USD, making it economically unfeasible for most national healthcare systems. Second, the study demonstrated a statistically significant increase in the incidence of infectious and septic complications, which led the FDA to deny approval of the drug for cardiovascular indications. These factors highlight the discrepancy between the potential clinical efficacy and the safety profile of widespread IL-1 β inhibitor use in cardiology practice [29-32].

Tocilizumab, a humanized monoclonal antibody targeting the interleukin-6 (IL-6) receptor, has produced conflicting results in studies of cardiovascular disease. Originally developed for the treatment of rheumatoid arthritis, the drug theoretically holds substantial potential in cardiology due to the central role of IL-6 in the pathogenesis of atherosclerosis. Findings from the NSTEMI study demonstrated that a single administration of tocilizumab during coronary angiography significantly reduced high-sensitivity C-reactive protein and troponin T levels. However, subsequent animal model studies revealed that IL-6 blockade

with tocilizumab does not improve inflammation-induced left ventricular dysfunction. Furthermore, a large randomized trial comparing the efficacy of tocilizumab with that of etanercept in patients with rheumatoid arthritis found no difference in cardiovascular event risk between the two groups, underscoring the challenge of correlating anti-inflammatory effects with clinical cardiovascular protection. The use of ziltivekimab, a novel IL-6 ligand inhibitor, was investigated in the RESCUE trial involving patients with chronic kidney disease and elevated cardiovascular risk. The results showed a significant reduction in high-sensitivity C-reactive protein levels [33-40]. Evolocumab and other PCSK9 inhibitors, originally developed as lipid-lowering agents, have demonstrated additional immunomodulatory effects by influencing macrophage function and inflammatory pathways. This represents an interesting example of the pleiotropic effects of pharmacological agents extending beyond their primary targets. However, substantial financial constraints, particularly in countries facing economic challenges, remain a major obstacle to the widespread use of these drugs [41].

Colchicine, a small-molecule immunomodulator with a broad spectrum of activity, has in recent years become the drug of choice for anti-inflammatory therapy in cardiovascular diseases. Its mechanism of action involves inhibiting tubulin polymerization, thereby suppressing leukocyte function, blocking the NLRP3 inflammasome, and reducing the production of pro-inflammatory cytokines. Large randomized controlled trials, including COLCOT and LoDoCo2, have demonstrated the significant efficacy of low-dose colchicine (0.5 mg daily) in reducing cardiovascular events. According to COLCOT, among patients who had recently experienced myocardial infarction, colchicine use reduced the combined endpoint risk by 23%. In the LoDoCo2 trial, conducted among patients with chronic coronary disease, colchicine use reduced the combined endpoint risk by 31% [42-47].

Critical analysis of the COLCOT and LoDoCo2 studies revealed several important methodological aspects. First, neither COLCOT nor LoDoCo2 required elevated high-sensitivity C-reactive protein levels as an inclusion criterion. Subsequent findings demonstrated that patients with residual inflammatory risk derived the greatest benefit from the treatment. Second, the CLEAR SYNERGY study, which evaluated the use of colchicine immediately after acute myocardial infarction, yielded neutral results. This outcome underscored the critical importance of optimal timing for treatment initiation and was likely related to the study's failure to achieve adequate inflammation reduction, unlike COLCOT and LoDoCo2, which did achieve it. Third, the positive results of these trials contributed to the FDA's 2023 approval of colchicine for cardiovascular risk reduction. The studies also confirmed a favourable safety profile for colchicine, with only a minimal increase in the incidence of pneumonia and diarrhoea as the main adverse effects. At the same time, the standard cost of colchicine remains minimal compared to that of other biologic agents [48-53].

When evaluating the effects of specific cytokine pathway modulators, including tumor necrosis factor- α (TNF- α) inhibitors, their efficacy in cardiovascular diseases has not been

conclusively demonstrated. Anakinra, a genetically engineered interleukin-1 receptor antagonist, was investigated in several pilot studies on heart failure and was found to improve the body's oxidative potential [54,55]. One of the innovative approaches to anti-atherosclerotic therapy is cellular immunotherapy and vaccine-based strategies, in which regulatory T cells play a critical role in maintaining immune homeostasis and limiting atherosclerotic progression [56-66]. Alternative research has also highlighted the significance of natural immunomodulators and biologically active compounds of plant origin. Specialized pro-resolving mediators of inflammation (lipoxins, resolvins, protectins), synthesized from omega-3 fatty acids, may theoretically activate endogenous regulatory mechanisms that promote recovery from inflammation [67,68].

Recently, regulatory pathways of the immune system that control T-cell activation have gained increasing attention as potential therapeutic targets in atherosclerosis. The PD-1/PD-L1 pathway, in particular, plays a key role in modulating inflammatory responses. However, inhibitors of immune checkpoint pathways used in oncology are associated with cardiotoxic effects, including myocarditis with a mortality rate of up to 25–50%, necessitating an extremely cautious and balanced clinical approach [69-73]. A critical review of current evidence regarding the use of immunomodulators in the treatment of atherosclerosis and other chronic cardiovascular diseases demonstrates significant progress in this field. Nonetheless, several fundamental challenges remain unresolved, including the absence of reliable biomarkers for accurate patient selection, concerns about the long-term safety of immunosuppressive therapy, and persistent financial barriers that limit the use of immunomodulators within most national healthcare systems [74].

The systematic review included 74 studies published between 2020 and 2025. The selected publications comprised 18 randomized controlled trials, 18 systematic reviews and meta-analyses, 22 prospective cohort studies, 9 retrospective analyses, and 7 experimental investigations. The geographical distribution encompassed North America (34 studies), Europe (31 studies), Asia (7 studies), and international multicenter projects (2 studies). The total number of patients enrolled in the clinical trials was 47,328, with an age range of 45 to 78 years.

The extracted data were qualitatively synthesized according to predefined analytical categories without conducting a meta-analysis. Immunomodulators were classified according to three complementary principles: (1) pharmacological group and molecular target, (2) mechanism of immunomodulatory action, and (3) clinical effect. This multidimensional classification allowed for a comprehensive evaluation of the effectiveness and safety of immunomodulatory therapies. The conducted literature analysis facilitated the categorization of immunomodulators across various domains. Table 1 presents the systematized characteristics of the principal immunomodulator groups.

The analysis revealed that the largest number of studies focused on colchicine, accounting for 23 publications (32.4% of the total sample). IL-1 β inhibitors were the subject of 20 studies (28.2%). A smaller proportion consisted of investigations on PCSK9 inhibitors (10 studies, 14.1%) and TNF- α inhibitors (9

studies, 12.7%). An analysis of the chronological distribution of publications demonstrated a growing scientific interest in immunomodulatory therapy. Eight relevant studies were published in 2020, increasing to 11 in 2021, 16 in 2022, 19 in 2023, 14 in 2024, and 6 in 2025 (as of August). The peak of publication activity occurred in 2023, likely corresponding to the release of results from several large international clinical trials. Clinical trial outcomes evaluating the effects of immunomodulators on cardiovascular events are summarized in Table 2. The data are organized according to the type of intervention, characteristics of the study population, primary endpoints, and achieved risk reduction.

The data indicate that canakinumab provided a 15% relative reduction in cardiovascular event risk. Colchicine demonstrated a significant reduction in risk, with decreases of 23% in the COLCOT trial, 31% in LoDoCo2, and 28% in CONVINCe. Tocilizumab contributed to a reduction in infarct size by 12.4% in the RESCUE trial and 8.7% in ASSAIL-MI. All immunomodulators influenced inflammatory biomarker levels. Canakinumab reduced high-sensitivity C-reactive protein (hs-CRP) by 37%, while colchicine achieved a 32–38% reduction. Tocilizumab produced the most pronounced decrease in interleukin-6 (IL-6) levels, ranging from 78% to 82%, and reduced hs-CRP by 34–44%. PCSK9 inhibitors demonstrated a more moderate hs-CRP reduction of 18–22%.

The frequency and profile of adverse effects varied according to the type of immunomodulator. In the CANTOS trial, the incidence of infectious complications was 0.31 versus 0.18 per 100 patient-years in the placebo group ($p = 0.02$). The incidence of septic complications was 0.14 versus 0.08 per 100 patient-years. In studies involving colchicine, the most common adverse effect was diarrhea, occurring in 9.7–10.2% of patients compared with 8.9% in the placebo group. Significant infectious complications occurred in 2.2% versus 1.6% of placebo recipients, and pneumonia was reported in 0.9% versus 0.4%, respectively.

Among patients treated with tocilizumab, 6.8% experienced elevated liver transaminases, 3.4% developed neutropenia, and 8.2% reported upper respiratory tract infections. Anakinra was associated with local post-injection reactions in 18–24% of cases, while significant systemic adverse events occurred in only 1.3%. TNF- α inhibitors were linked to an increased risk of tuberculosis reactivation (0.8–1.2% in endemic regions) and secondary infections (2.1–2.8%).

The ARCHIPELAGO trial demonstrated a 1.8% reduction in percentage atheroma volume and a 0.14 decrease in the vessel remodelling index following 24 weeks of tocilizumab therapy. Results from the 18F-FDG PET study showed an 18–22% reduction in radiopharmaceutical uptake in the carotid arteries after colchicine treatment.

Discussion.

This systematic review critically evaluated the existing evidence on the use of immunomodulatory drugs in the treatment of atherosclerosis and chronic cardiovascular diseases. Over the past two decades, the conceptual understanding of atherosclerosis has shifted from a predominantly lipid-centric model to one recognizing inflammatory mechanisms as central

drivers of disease pathogenesis, providing the rationale for fundamentally new therapeutic approaches.

Comparative Efficacy Analysis Across Immunomodulator Classes.

Safety Profile and Risk Stratification:

Risk–benefit assessment requires careful consideration across drug classes, with attention to both short-term and potential long-term complications. Colchicine demonstrated the most favourable safety profile, with gastrointestinal adverse effects, primarily diarrhoea (9.7% vs. 8.9% in the placebo group), representing the main limitation, although these rarely necessitated treatment discontinuation. Infectious complications occurred slightly more frequently (pneumonia 0.9% vs. 0.4% in placebo) but were not associated with a significant increase in mortality.

In contrast, biological agents presented more concerning safety profiles. The CANTOS trial identified a statistically significant increase in fatal infections, including sepsis (0.14 vs. 0.08 per 100 patient-years), which contributed substantially to regulatory agencies' decisions against approving canakinumab for cardiovascular indications. Tocilizumab administration was associated with hepatotoxicity, evidenced by elevations in transaminase levels exceeding three times the upper limit of normal in 6.8% of patients, as well as neutropenia (3.4%) and upper respiratory tract infections (8.2%). These safety concerns underscore the need for rigorous patient selection and close monitoring, particularly given the theoretical long-term malignancy risk associated with chronic immunosuppression, a factor inadequately characterized in studies with an average follow-up duration of two to four years.

Economic Feasibility and Healthcare Implementation:

Economic factors play a critical role in the real-world adoption of immunomodulatory therapies. The high cost of biologic agents remains a major barrier; annual treatment with canakinumab exceeds USD 70,000, making it economically unviable for most healthcare systems. Cost-effectiveness analyses consistently show that canakinumab does not meet accepted willingness-to-pay thresholds, particularly in resource-limited settings. In contrast, generic colchicine is a highly cost-effective intervention, demonstrating favorable incremental cost-effectiveness ratios across multiple health economic models and supporting its broad use in secondary prevention strategies. This pronounced economic disparity raises critical concerns about global health equity. Although biologic therapies may offer targeted benefits for certain high-risk subgroups, their limited accessibility in low- and middle-income countries, where the burden of cardiovascular disease is highest, restricts their potential to deliver population-level benefits. The affordability and availability of colchicine position it as a practical option for reducing global cardiovascular mortality, though challenges remain in ensuring consistent pharmaceutical access and supply within resource-limited healthcare systems.

Unresolved Issues and Future Research Priorities:

Several critical knowledge gaps warrant systematic investigation through well-designed clinical trials. First, optimal patient selection strategies remain undefined. While

high-sensitivity C-reactive protein has emerged as a valuable biomarker (threshold >2 mg/L), additional markers such as interleukin-6, GlycA, and fibrinogen may enhance risk stratification. Second, combination anti-inflammatory therapy remains largely unexplored. The potential synergistic effects of dual-pathway inhibition should be systematically evaluated to determine additive or complementary therapeutic benefits. Third, the role of anti-inflammatory interventions in primary prevention requires dedicated research. Extrapolating data from secondary prevention trials may not accurately reflect benefit-risk profiles in lower-risk populations. Ethnic diversity among trial populations has also been limited. Most studies have been conducted in Western cohorts with predominantly Caucasian participants. To strengthen generalizability, future research must include diverse global populations potentially characterized by distinct inflammatory phenotypes, genetic backgrounds, and comorbidity patterns. Finally, the optimal duration and discontinuation criteria for therapy remain uncertain. It is not yet established whether anti-inflammatory treatment should be maintained lifelong or administered as a time-limited intervention following acute cardiovascular events.

The biomarker-guided personalized therapy framework proposed in this review represents a paradigmatic shift toward precision anti-inflammatory cardiology and may inform future clinical guideline development. In conclusion, immunomodulatory therapy represents a transformative advancement in cardiovascular medicine, shifting the focus from exclusive lipid reduction toward comprehensive targeting of inflammatory mechanisms. Successful clinical implementation of this strategy, particularly through accessible agents such as colchicine, offers a realistic opportunity to substantially reduce the global cardiovascular disease burden.

Conclusion.

This systematic review provided clear evidence regarding the efficacy of immunomodulators, their potential clinical applications, and existing research limitations in the treatment of atherosclerosis and chronic cardiac diseases. Proven efficacy In large randomized controlled trials, colchicine demonstrated a statistically significant reduction in cardiovascular risk by 23% in the COLCOT study (n = 4,745) and by 31% in the LoDoCo2 study (n = 5,522). These findings establish colchicine as the first approved anti-inflammatory agent for secondary prevention of cardiovascular disease, with a favorable safety profile and cost-effectiveness. Canakinumab achieved a 15% reduction in risk in the CANTOS trial (n = 10,061), confirming that cardiovascular events can be mitigated through purely anti-inflammatory mechanisms without lipid modification. Potential efficacy Tocilizumab showed promising outcomes, including a 12.4% reduction in infarct size in the RESCUE trial, though its benefit requires validation in large-scale studies incorporating hard clinical endpoints. Anakinra improved aerobic capacity in pilot studies involving patients with heart failure; however, its long-term effects on cardiovascular outcomes remain uncertain. Experimental approaches Novel strategies, such as regulatory T-cell therapy and vaccine development, have demonstrated efficacy in preclinical models but face significant technical and translational challenges that impede clinical application. A

promising direction for the development of immunomodulatory therapy is an individualized approach based on identified specific biomarkers, which will optimize the choice of therapy and minimize the risk of side effects. An important task of future studies is to develop treatment regimens that are compatible with traditional lipid-lowering therapy, which may provide a synergistic effect in reducing residual cardiovascular risk. In addition, it is necessary to conduct long-term prospective studies of the risks of long-term use of immunomodulatory drugs in cardiological practice.

Suggestions for Future Research.

Based on the conducted systematic review, several critical directions for future research have been identified. First, biomarker-guided personalization of therapy remains a primary objective, necessitating the development of comprehensive biomarker panels for precise patient selection beyond high-sensitivity C-reactive protein. Second, long-term prospective investigations are required, particularly multicenter randomized clinical trials exceeding five years in duration, to objectively evaluate the long-term safety of immunosuppressive therapy, with special attention to oncologic and infectious risks across diverse ethnic populations and in patients with multiple comorbidities. Third, pharmacoeconomic evaluation is essential, as cost-effectiveness studies are key to integrating immunomodulators into clinical practice and optimizing the allocation of limited healthcare resources. Fourth, innovation in pharmacology should focus on the development of selective immunomodulators with improved safety profiles, such as targeted NLRP3 inflammasome inhibitors and combination agents. Research on combination therapy strategies aims to achieve synergistic therapeutic effects while minimizing drug toxicity. Finally, the role of immunomodulators in primary prevention remains uncertain due to the absence of large-scale studies, necessitating further investigation to determine their potential in preventing initial cardiovascular events.

Ethics Approval and Consent to Participate.

This systematic review analyzed exclusively previously published, peer-reviewed literature and did not involve primary data collection or participant recruitment. Therefore, ethics committee approval and informed consent were not required. All included studies had obtained appropriate ethical approvals as reported in their original publications.

The review was conducted in accordance with the Declaration of Helsinki principles for medical research, the Committee on Publication Ethics (COPE) guidelines for systematic reviews, and the PRISMA 2020 reporting standards. All data sources are properly cited and publicly available for verification.

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Conflicts of Interest.

The authors declare no conflicts of interest.

Data Availability.

The authors confirm that the data supporting the findings of this study are included within the article.

Scientific Novelty and Author Contributions.

This review's primary contribution lies in conducting a comprehensive cross-class comparative analysis that emphasizes the real-world benefit–risk balance rather than isolated efficacy metrics. Unlike previous systematic reviews focusing mainly on single drug classes or specific cardiovascular conditions, this work synthesizes evidence across multiple immunomodulator categories, including small molecules, IL-1 inhibitors, and IL-6 antagonists, providing an integrated assessment of their relative positioning in cardiovascular therapeutics.

The mechanistic comparison framework introduced here systematically links molecular targets with clinical outcomes, facilitating rational treatment selection. Additionally, this review explicitly addresses economic feasibility as an integral component of clinical decision-making rather than a separate consideration, recognizing that therapeutic efficacy without accessibility yields limited population health benefit.

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