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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 ВИНИТИ 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 ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

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. Корректура авторам не высылается, 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 compu-ter-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 საყურადღებოდ!

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, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის 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 ფჩხილებში 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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GENETIC ASPECTS OF WARFARIN DOSING ALGORITHMS IN CARDIAC SURGERY PATIENTS WHO HAVE UNDERGONE HEART SURGERY: SYSTEMATIC REVIEW

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Abstract.

Objective: To evaluate the clinical outcome, safety, and application of personalized therapy using pharmacogenetic warfarin dosing algorithms in cardiac surgery patients systemically.

Methods: This systematic review focused on 17 published studies between January 2015 to March 2025 regarding warfarin dosing algorithms incorporating CYP2C9 and VKORC1 polymorphisms in patients who underwent cardiac surgery. The primary outcomes were TTR, BER, and INR stability. The databases search was performed on Scopus, Web of Science, PubMed, and Cochrane.

Results: This systematic review highlights the effectiveness of genotype-stratified warfarin dosing after cardiac surgery. Bayesian models showed an improvement in TTR, with NextDose achieving 63% versus 56% with standard dosing. Genotype-guided approaches reduced bleeding events from 34 to 16 and increased INR stability from 83.1% to 86.1%, improving dosing precision and achieving a TTR of 77.76% compared to 57.43%.

Conclusion: These findings reinforce the clinical importance of the use of genotype data for more precise warfarin dosing in improving TTR, INR control, and bleeding risk. Further studies are needed to optimize the algorithms, extend the gene panels, and tailor the approaches more for patients after cardiac surgery.

Key words. Pharmacogenetics, anticoagulation, VKORC1, CYP2C9, cardiac surgery, personalized medicine, dosing algorithm, gene polymorphism.

Introduction.

Warfarin continues to be a primary anticoagulant used in patients who undergo heart surgeries, specifically for those who have undergone valve replacement or repair surgeries, due to its effectiveness in preventing thromboembolic complications [1]. Cardiovascular diseases are among the world's most rapidly increasing health challenges, with estimates expecting a rise to both the number of people living with cardiovascular disease and cardiovascular related deaths by 2050. This increase is predominantly due to an older population and the ongoing burden of atherosclerotic diseases like ischemic heart disease [2]. Within this framework, perioperative anticoagulation control poses a clinical challenge, considering patients' increased risk of thromboembolic and hemorrhagic complications. Maintaining therapeutic INR targets requires careful adjustment of warfarin dosing.

Even with the introduction of new oral anticoagulants, warfarin still holds its position as the primary treatment for patients with mechanical heart valves and other specific cardiac conditions, largely because of its safety record, low cost, and placement on the WHO essential medicines list [3]. However, the setting of warfarin dose is complicated by considerable interindividual clinical factors and genetic polymorphisms. In the immediate postoperative period, patients are more sensitive to warfarin, which can make it challenging to achieve and sustain the therapeutic INR range [4]. This emphasizes the need to improve algorithms for warfarin dosing that integrate clinical and genetic variables tailored to minimize risks and improve outcomes for cardiac surgery patients.

The differences in patients' responses to warfarin pose unique clinical problems because of the genetic, clinical, and demographic characteristics that affect the metabolism and sensitivity of warfarin, as well as the level of anticoagulation required. Additionally, the low therapeutic range, combined with high potential for drug interactions and narrow therapeutic index, make monitoring warfarin therapy in a clinical setting very difficult [5]. An important problem for patients on warfarin therapy is the high interindividual variability in the dose needed to reach the target level of anticoagulation [6]. To evaluate the anticoagulation effect of warfarin, clinicians monitor the INR to make sure the desired therapeutic threshold is achieved.

Inadequate dosing can lead to severe complications: underdosing increases thromboembolic risk while overdosing raises the risk of bleeding. These concerns are particularly important in the postoperative management of cardiac surgery patients. Genetic polymorphisms in CYP2C9 and VKORC1 markedly disrupts the uniformity of balance and synchronization, amplifying clinical discordances and warfarin dosing. A clinical classification and predictive model based on logistic regression which was validated in two cohorts showed enhanced predictive ability of sensitivity to warfarin [7]. This method surpasses fixed-dose approaches and may improve care and outcomes.

Incorporating genetic polymorphisms with clinical information into machine learning approaches greatly enhances the precision of predicting the required dosage of warfarin. For instance, RFR algorithms have shown remarkable precision in

estimating warfarin dosages for Hispanic Caribbean patients. RFR outperformed earlier statistical models in considerably better predicting doses for patients categorized as “normal,” “sensitive,” and “resistant” [8].

Anticoagulation in patients undergoing cardiac surgery, especially those with mechanical heart valves, is primarily centered on warfarin therapy. Its use in patients, however, is complicated by its therapeutic index and heightened clinical concerns with variability between patients and their required doses. Recently, genetic polymorphisms of the genes, VKORC1, CYP2C9, and CYP4F2, have emerged as important factors with respect to warfarin dosing as they affect the efficacy and safety outcomes. VKORC1 polymorphisms directly impact a patient's sensitivity to warfarin due to the changes in the activity of vitamin K epoxide reductase, warfarin’s primary target. For instance, individuals with at least one variant allele of VKORC1 need much lower doses to achieve target INR values because enzyme activity is partially inhibited, blunting the withdrawal effect [9]. Individuals carrying the genotype TT of VKORC1 needed 33.86 mg/week instead of 50.39 mg/week when not carrying the genotype [10].

Patients with CYP2C9 polymorphisms often experience warfarin overexposure due to its prolonged metabolism, which increases the likelihood of bleeding complications. Observations suggest individuals with variant alleles have lower stable dose requirements for the drug and need 20-40% less, with heterozygous and homozygous patients requiring stepwise reductions [11]. In one cohort, it was estimated that CYP2C9 variants contributed 32% towards the variability in dose requirements during the warfarin initiation phase [12]. Moreover, polymorphisms have been shown to impact vitamin K bioavailability with the T allele of CYP4F2 requiring higher doses. In certain studies, Saudi patients with polymorphisms in CYP2C9 and VKORC1 were found to need less warfarin than those having the wild-type allele, whereas the CYP4F2 polymorphism did not impact warfarin dose requirements. Taking age and BSA alongside the genetic variants of CYP2C9 and VKORC1 enable more accurate estimation of warfarin dose needed for patients in Saudi Arabia [13]. Incorporating genetic testing for these variants into dosing algorithms has enhanced INR control and minimized adverse outcomes. The results highlight the importance of using pharmacogenomics for warfarin dosage precision in perioperative cardiac surgical patients to improve safety and effectiveness of anticoagulation management.

There is still debate about the use of genotype-guided warfarin dosing post heart surgery. It is known that genetic polymorphisms in VKORC1 and CYP2C9 affect warfarin dosing; however, the use of such data for postoperative outcomes is still unresolved. Some researchers propose that genotype-based dosing can improve reaching target INR and reduce critical postoperative INR levels, suggesting some benefits in early postoperative recovery [14]. The differences in patient populations, genetic makeups, and the design of the studies themselves explain this lack of agreement, pointing out the need for more investigation to define the use of genetic-guided warfarin dosing in surgical patients [15]. This limitation in literature affects the integration of pharmacogenetic testing into routine clinical practice, particularly in guiding cardiovascular postoperative antithrombotic treatment, revealing an area that requires further focus.

Warfarin is undoubtedly the go-to anticoagulant for patients undergoing cardiac surgeries, especially for those with mechanical heart valves. However, the administration of Warfarin is particularly troublesome because of its unpredictable interindividual variability due to genetic and clinical factors. This systematic review seeks to determine the impact of genetic dosing algorithms on the safety and efficacy of warfarin therapy in the postoperative period for cardiac surgery patients. In particular, the review answers: To what degree do genotype-guided warfarin dosing algorithms improve therapeutic outcomes, such as achievement and maintenance of target INR levels, when measured against standard dosing in cardiac surgery patients?.

Literature Review.

The challenges associated with Warfarin dosing remains at the interphase of its therapeutic window and high variability among individuals influenced by genetics, including a patient’s clinically relevant history, and demographics. To optimize anticoagulation therapy, especially with the cardiac surgery clientele, various algorithms have been formulated, integrated, and tested towards precision dosing.

The fixed-dose strategy usually initiates patients on an uncomplicated starting amount, for instance, 5 mg per day, which is later modified according to INR check-ups. Although this approach is straightforward, it frequently leads to a lag in attaining the target INR levels, which heightens the risk of complications of under- or over-anticoagulation [16]. Fixed dosing fails to consider a person's variability and their genotype, and therefore, it lacks accuracy.

When estimating warfarin dosage, Clinical algorithms consider patient-specific parameters, including age, weight, other active medications, and other existing medical conditions. These algorithms are often constructed based on various linear regression models and have gained popularity for dose estimation and maintenance. One study assessing two clinical warfarin algorithm models, the Gage and the IWPC model, used a 5 mg fixed dose strategy in Sudanese subjects and reported no distinct accuracy difference among the models nor with the fixed-dose strategy. Nevertheless, the Gage and IWPC models offered enhanced clinical applicability; a greater proportion of subjects fell within the ideal dosing range compared to the fixed-dose strategy. Although flawed by some over- and under-prediction bias, the Gage and IWPC models were clearly more accurate, practical, and safe than the fixed-dose model [17]. Also, some models from Japan, China, Italy, and the USA incorporate additional information, such as body surface area, and clinical genotypes to enhance age and hypertension, tailoring the model to the population.

An investigation sought to determine how specific clinical and genetic characteristics impact warfarin therapy dose adjustments in patients with cardiovascular disease. Seventy-seven participants were chosen according to defined inclusion criteria. Their clinical records and results of genetic testing

for the CYP4F2 rs2108622 polymorphism were retrieved. The analysis revealed strong associations between the CYP4F2 genotype and the warfarin dose with age, BMI, and genotype also significantly impacting dosing. These factors collectively provided 25% contribution to dose adjustment in the linear regression model. A model was created to estimate warfarin dose based on age, BMI, and genotype, producing the following equation: y = 12.736 – 0.16(age) + 0.55(BMI) + 3.55(genotype) [18]. Clinical algorithms, although variable in their accuracy across different populations, provide finer dosing personalization than fixed strategies. Dosing versatility enhances clinical outcomes and more accurately adjusts therapy based on underlying pathological features of the individual patient. Unfortunately, many clinical algorithms overlook important genetic polymorphisms impacting the metabolism and sensitivity of warfarin.

Variations in VKORC1, CYP2C9, CYP4F2, and GGCX are important factors that determine the dose requirements of warfarin. Research done on the Korean and Arab populations demonstrate the superiority of genetic dosing algorithms in comparison to clinical ones [19]. Explanatory analysis conducted on MENA populations established VKORC1 and CYP2C9 variants as strong predictors for determining warfarin dose divergence and highlighted the importance of the region-specific algorithm [20]. Although these genetic elements are often assumed in warfarin dosing models, most algorithms lack validation and appraisal of clinical utility, which hampers their value in clinical context [21]. Also, post cardiac surgery coagulopathy, especially in under eight years old children with CHD, remains an unresolved challenge. For better clinical prospects, proactive management during and after surgery, used with antifibrinolytics, bed rest, and control of blood losses, is essential to postoperative bleeding [22]. Research indicates that incorporating genetic information into the dosage design will enhance the predictive capability and speed stability of anticoagulation.

For patients undergoing cardiac surgeries, dosing that is guided by a patient's genotype has been shown to improve clinical efficacy by mitigating the adverse effects of over- and under-anticoagulation. Several models have been validated internationally, although their utility is limited by ethnicity and population genetics. One study evaluated the impact of the genetic variants, CYP2C9*2, *3, VKORC1−1639 G>A, and CYP4F2 rs2108622 on warfarin dosing in an Arab population and analyzed the actual versus the algorithmic estimates of warfarin dose based on clinical and genetic methods. The study with 130 participants demonstrated that patients with the CYP2C92, CYP2C93, and VKORC1 AA genotypes significantly lower warfarin doses. The algorithm based on genotype revealed substantially lower median absolute error than the chronic clinical algorithms based on warfarin dosing. These conclusions shed light on the significance of the studied genetic variants in warfarin dosing and illustrate that a multi-faceted approach to dose adjustment enhances precision [23].

The application of ML and deep reinforcement learning algorithms on warfarin dosing has only recently emerged. It is observed that RFR, SVR, and MARS ML models surpassed the older linear regression models in predicting warfarin dosing accurately, particularly in patients with extreme dosing needs. One study focused on Caribbean Hispanic patients and tried to implement ML methods for warfarin dosing. They used genetic, clinical, and non-genetic data of 190 patients and employed seven machine learning algorithms. RFR outperformed all other methods with a MAE of 4.73 mg/week and an 80.56% accurate prediction of the dose within ±20% range. MARS excelled in the "resistant" population group while SVR performed best in the "sensitive" group. For this population, these ML models demonstrated enhanced predictive capabilities for warfarin dosing compared to traditional methods [8].

In a retrospective cohort study, the predictive power of ML algorithms to estimate anticoagulation control in AF patients on warfarin was assessed. The focus of the study was the application of various ML techniques toward the prediction of inadequate TTR anticoagulation control (TTR < 70%). At first, XGBoost performed best with AUC of 0.624, defined by comorbidities such as age, weight, and depression. However, the addition of time-dependent factors, especially previous measurements of INR, as well as the LSTM neural network model, increased accuracy to AUC 0.83 after 30 weeks [24]. The findings support that ML models can assist in recognizing patients who require more intensive surveillance or different therapies.

Atrial fibrillation, mechanical heart valves, and venous thromboembolism are commonly managed with warfarin therapy, but dose management is challenging because of patient-specific characteristics as well as the drug's narrow therapeutic index. Time in Therapeutic Range (TTR) is critical for safety and efficacy; however, community practices often operate at a suboptimal TTR. Specialized clinics can increase TTR; however, these clinics are expensive and difficult to manage and staff. One study focused on the creation of a machine learning model for optimal decision support regarding warfarin dosage through time-series anticoagulation data and patient demographics. A DRL model used historical data to predict cumulative doses and warfarin dose trajectories, surpassing conventional models with an astounding 96.96% accuracy. Out-of-range INR scenarios demonstrated the DRL model's potential to improve management responsiveness within eINR dose adjustment ranges, illustrating the promise of advanced computing technologies in clinical decision support [25]. Dosing precision based on genetic polymorphisms is improved by genotype-guided algorithms, while further enhancements of complex interactivity provided guidance through advanced machine learning. Nonetheless, external validation, evaluation of clinical utility, and incorporation of different population groups are still of paramount importance for implementing these developments into everyday clinical practice, especially regarding patients undergoing cardiac surgery with complex anticoagulation requirements. The body of work focused on the genetic components of warfarin dosing algorithms for patients after cardiac surgery demonstrates some striking disparities across populations, methodological gaps, and a substantial lack of representation for post-cardiac surgery patients. It is well known that certain genetic polymorphisms in the CYP2C9 and VKORC1 genes are predominant contributors to variance

in warfarin dosage. These variations, along with other factors, explain nearly 30 and 50 percent of the dose differences among individuals. However, the polymorphisms' prevalence and impact tend to differ greatly between ethnic populations. Studies have demonstrated that many Asian populations have VKORC1 variants that differ from those common in Caucasians, influencing their sensitivity to warfarin and thus altering the dosing requirements [26]. Similarly, a Turkish cohort of cardiac valve surgery patients demonstrated that carriers of CYP2C9 or VKORC1 polymorphisms required significantly lower warfarin doses to achieve therapeutic INR [27]. These ethnic and regional genetic variations complicate the generalizability of dosing algorithms that were developed predominantly in Western populations. Moreover, additional genes such as CYP4F2, CYP2C19, and GGCX have been implicated in warfarin dose variability, but their roles differ across populations and remain less well characterized, adding to the inconsistency [28]. This heterogeneity leads to conflicting results in clinical trials evaluating genotype-guided dosing, limiting the broad implementation of such algorithms.

Many warfarin pharmacogenetic studies suffer from methodological constraints that affect their conclusions. Sample sizes are often small, especially in cohorts undergoing cardiac surgery, reducing statistical power and the ability to detect meaningful genetic associations. Additionally, most studies focus on stable-dose patients rather than the critical initiation phase post-surgery, when dosing is most challenging and clinically important [29]. Furthermore, the clinical utility of genotype-guided dosing remains controversial due to mixed evidence on improvements in anticoagulation control and clinical outcomes, partly attributable to these methodological differences [30]. Despite the high clinical relevance of warfarin in cardiac surgery patients, particularly those with mechanical heart valves, this population is underrepresented in pharmacogenetic research. Most warfarin dosing algorithms are developed and validated in broader populations with atrial fibrillation or venous thromboembolism, rather than specifically in post-cardiac surgery cohorts [21]. In summary, the literature indicates significant ethnic variability in warfarin pharmacogenetics, methodological heterogeneity across studies, and a paucity of focused research on post-cardiac surgery patients. Addressing these issues requires larger, well-designed prospective studies incorporating diverse populations and comprehensive genetic and clinical data, especially targeting the post-cardiac surgery period to optimize warfarin dosing algorithms for this high-risk group.

Aims and objectives.

Purpose of the Study:

To systematically evaluate the clinical effectiveness, safety, and potential for individualized therapy using pharmacogenetic warfarin dosing algorithms in patients who have undergone cardiac surgery.

Methods.

Study Design:

Systematic review.

Study Duration:

January 2015 to March 2025.

Eligibility Criteria:

The eligibility criteria for this systematic review were based on the PRISMA 2020 guidelines. Studies were included if they met the following:

1. **Study Design:** Includes Randomized controlled, Observational, and Cohort and Case-control Studies.
2. **Population:** Adult patients who had undergone heart surgeries such as bypass or valve replacement and were on warfarin therapy.
3. **Intervention:** Studies which focused on the algorithms for warfarin dosing, including those which consider polymorphisms of CYP2C9 and VKORC1.
4. **Outcomes:** Clinical outcomes such as TTR, BER, or INR Stability, and TTR (Time in Therapeutic Range.
5. **Genetic Focus:** Studies with a focus on warfarin therapy evaluating its genetic markers.
6. **Language and Publication Date:** Published in English from January 2015 to March 2023.

Studies that did not meet these criteria or focused on irrelevant populations or interventions were excluded.

Information Sources:

For this systematic review, the information sources were four key databases: Scopus, Web of Science, PubMed, and Cochrane Library. Scopus published a variety of peer-reviewed literature from other disciplines, while Web of Science included multidisciplinary scholarly journals, conference proceedings, and even patents. One of a kind, PubMed Specialized database focused on life sciences and biomedical literature by offering studies relevant to health and medicine. Last but not least was the Cochrane Library which is known for its systematic reviews and high-quality evidence-based health information. The reason these databases were chosen is because of their broad scope as well as relevance to the topic of the review.

Search Strategy:

A comprehensive search strategy was conducted to find appropriate studies for this systematic review through four fundamental databases. The timeframe for the search included studies in the time frame from January 2015 to March 2025. The primary search parameters used include: (warfarin OR anticoagulant) AND (genetics OR polymorphism OR CYP2C9 OR VKORC1) AND (cardiac surgery OR bypass OR valve replacement) AND (algorithm OR dosing). All articles that were retrieved from the search were thoroughly scrutinized so that Boolean techniques were applied in a manner that relevant articles were obtained while minimizing filler documents. Search techniques were structured in accordance to the user interface of the database which included English only results. Other publications filters were focused on the date and types of studies published; this was done to guarantee only reputable peer-reviewed literature was obtained that fulfilled the inclusion criteria. The search approach was changed from time to time during the review period so that the most pertinent studies were included at any time.

Selection Process:

This systematic review's study selection process follows the PRISMA 2020 criteria which include a four-step framework: identification, screening, eligibility assessment, and inclusion. To begin with, a broad search was carried out in four databases: Scopus (1,158 records), Web of Science (121 records), PubMed (115 records), and the Cochrane Library (21 records). After the removal of 39 duplicates, 152 records remained for the screening stage. These records underwent an initial assessment where 90 were purged because they were either irrelevant or lacked sufficient details. After the eligibility assessment, 62 records were deemed as eligible for full review, while 45 were excluded due to irrelevant focus/population (16 records), absence of genetic content or warfarin (10 records) and not aligning with the study format inclusion criteria (19 records). In total, 17 studies were incorporated in the systematic review in accordance to the inclusion criteria as depicted in Figure 1.

Data Collection Process:

For this systematic review, the data collection procedure included independent data extraction of relevant details by two reviewers to ensure accuracy and prevent bias. The extraction was an operationalized with a particular set of variables, which were: Study Design that provided insight into the methodological approach of each study; Sample Size as a measure of the statistical power and generalizability of the resulting findings; and Population as a descriptor of the constituents' characteristics that were included in the study. Variables were also selected to define Sons of the Deceased Patients Aged 18 Years or Older Determined to Have Genes of Interest as a means of exploring the genetic factors studied in relation to warfarin therapy. The Dosing Algorithm variable captured particular strategies or formulae employed in warfarin dosing, whereas Outcomes Studied included a range of clinical measures employed to assess the dosing algorithm's efficacy. Key Genetic Markers ascertained and associated with warfarin metabolism and response were included to justify the therapeutic response which was assumed based on the genetic evidence. The Algorithm Type variable categorized the nature of the dosing algorithm as pharmacogenetic or conventional. In addition, clinical outcomes such as Time in Therapeutic Range (TTR), Bleeding Events Reduction (BER), and Stability of INR were studied as indices for the determination of clinical efficacy and safety of the warfarin dosing strategies. Two reviewers independently extracted these variables from the selected studies, and discrepancies were resolved via discussion to ensure the reliability and completeness of the data.

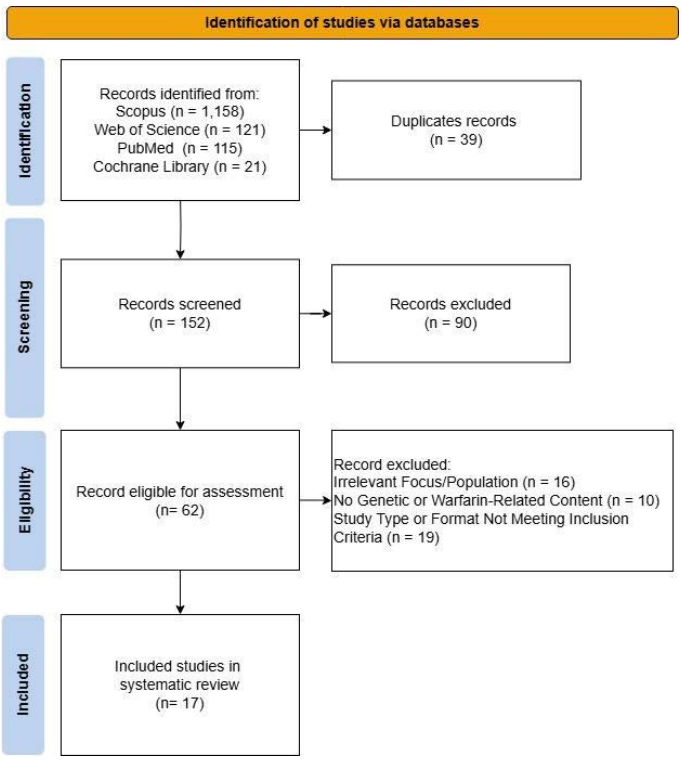

Figure 1. *PRISMA 2020 flow diagram.*

Risk of Bias Assessment:

The risk of bias in the included studies was assessed with the aid of two established tools: ROB 2.0 (Risk of Bias 2.0) on randomized controlled trials and ROBINS-I (Risk of Bias in Non-randomized Studies of Interventions) for the non-randomized studies. These tools measure the scale of bias that can happen in a study under its different components such as design, conduct, and reporting. Concerning ROB 2.0, evaluation is done in the following five domains: D1 bias arising from the randomization process, D2 bias due to deviations from the intended interventions, D3 missing outcome data, D4 measurement of the outcome, D5 selection of reported result. Based on the assessment of these domains, studies were assigned "Low", "Some concerns" and "High" risk of overall study bias. The results obtained from ROB 2.0 assessments are displayed in Figure 2, where most studies showed low risk of bias and some studies reported moderate concerns especially in D2.

ROBINS-I, the evaluation tool assesses the following domains: (D1) bias due to confounding, (D2) bias due to selection of participants, (D3) bias in classification of interventions, (D4) bias due to deviations from intended interventions, (D5) bias due to missing data, (D6) bias in measurement of outcomes, and (D7) bias in selection of the reported result. Most studies were categorized as possessing a low risk of bias, although several studies showed moderate risk, especially in D1 and D4. Figure 3 presents the results of the ROBINS-I assessment.

Results.

Table 1 summarizes 17 studies investigating genetic aspects of warfarin dosing in post-cardiac surgery patients. Study designs include RCTs, observational, cohort, and case-control studies, with sample sizes ranging from 31 to 721 participants. The populations examined vary from adults and children undergoing heart valve or cardiac surgeries to those with specific conditions like atrial fibrillation, Kawasaki disease, or thrombophilia. The studies cover diverse ethnic groups including Han-Chinese, South Indian, Korean, and Thai populations, highlighting the genetic diversity considered in warfarin dosing research.

Table 2 compares the effectiveness of various warfarin dosing algorithms used in genetically guided therapy among post-cardiac surgery patients. The studies analyzed different gene variants most commonly VKORC1 and CYP2C9, along with

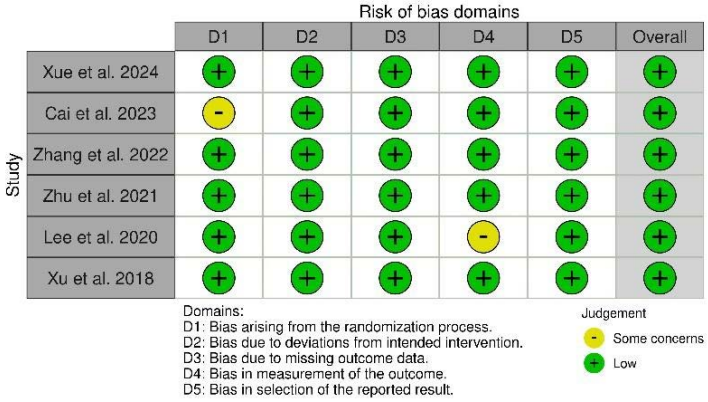

Figure 2. *Risk of Bias Assessment for Randomized Controlled Trials.*

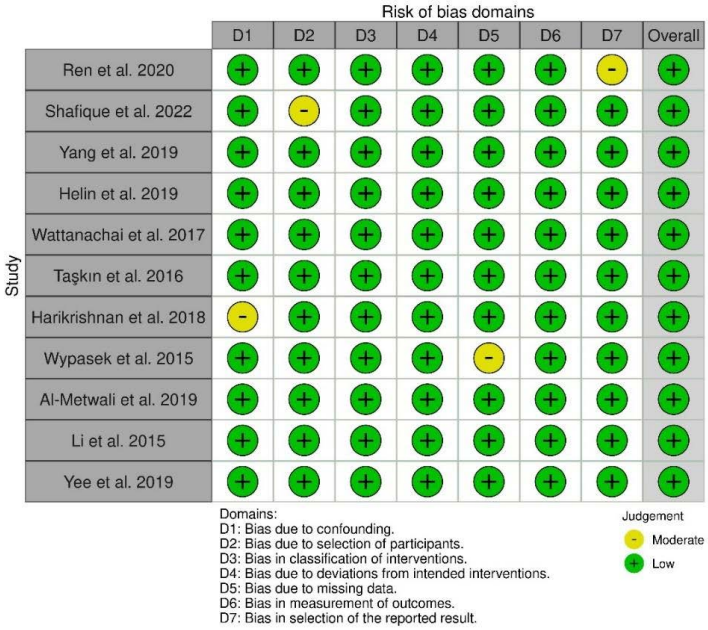

Figure 3. *Risk of Bias Assessment for Non-Randomized Studies.*

Table 1. *Characteristics of included studies.*

Studies	**Study Design**	**Sample Size**	**Population**
Ren et al. 2020 [31]	Observational	544	Elder Han-Chinese AF patients
Xue et al. 2024 [32]	RCT	240	Adults' post-cardiac surgery
Cai et al. 2023 [33]	RCT	76	Post-heart valve replacement
Zhang et al. 2022 [34]	RCT	172	Mechanical aortic valve patients
Zhu et al. 2021 [35]	RCT	721	Mechanical heart valve replacement
Shafique et al. 2022 [36]	Cohort	107	Heart valve replacement patients
Yang et al. 2019 [37]	Cohort	194	Pediatric Kawasaki disease
Helin et al. 2019 [38]	Cohort	50	Thrombosis/thrombophilia patients
Wattanachai et al. 2017 [39]	Cohort	250	Stable warfarin Thai patients
Dilge Taşkın et al. 2016 [40]	Observational	58	Pediatric cardiac/thrombophilia patients
Harikrishnan et al. 2018 [41]	Cohort	222	South Indian post-prosthetic valve
Wypasek et al. 2015 [42]	Case-control	43	Elective heart valve replacement
Al-Metwali et al. 2019 [43]	Observational	31	Post-cardiac surgery children
Lee et al. 2020 [44]	RCT	91	Mechanical aortic valve patients
Li et al. 2015 [45]	Observational	220	Cardiac valve replacement patients
Yee et al. 2019 [46]	Observational	142	Korean mechanical heart valve patients
Xu et al. 2018 [47]	RCT	201	Mechanical heart valve warfarin therapy

Table 2. *Comparison of Algorithm Effectiveness.*

Studies	Genes Studied	Dosing Algorithm	Outcomes Studied
Ren et al. 2020 [31]	VKORC1, CYP2C9	IWPC Algorithm and Elderly-specific Algorithm	Warfarin stable dose, Algorithm prediction accuracy
Xue et al. 2024 [32]	CYP2C9, VKORC1	NextDose (Bayesian Warfarin Dose Individualization)	%TIR, Bleeding events, Time to stable dose, INR stability
Cai et al. 2023 [33]	CYP2C9, VKORC1	Warfarin Dosing Calculator	Time to first INR compliance, TTR, Bleeding events
Zhang et al. 2022 [34]	VKORC1, CYP2C9	FDA-recommended warfarin oral-dose table based on genetic results	INR target achievement, Warfarin dose, Critical INR values
Zhu et al. 2021 [35]	VKORC1, CYP2C9	Internet-based warfarin management vs. conventional management	TTR, bleeding, thrombosis, complications
Shafique et al. 2022 [36]	VKORC1, CYP2C9	Genotype-guided dosing based on VKORC1 and CYP2C9 variants	Warfarin dose requirements, IL-6, TNF-α, COX-2 expression
Yang et al. 2019 [37]	VKORC1, CYP2C9, CYP4F2	Genotype-guided warfarin dosing formula	Warfarin dose, Genetic factors influencing dosing
Helin et al. 2019 [38]	CYP2C92, CYP2C93, VKORC1	Gage algorithm, IWPC algorithm	Warfarin dose, INR target, Bleeding and thrombosis risks
Wattanachai et al. 2017 [39]	VKORC1, CYP2C9*3, CYP4F2	Genetic-guided warfarin dosing	Stable warfarin dose, Variability of dosing
Dilge Taşkın et al. 2016 [40]	CYP2C92, CYP2C93, VKORC1	Genotype-guided warfarin dosing algorithm	Warfarin dose requirements, Genetic polymorphisms influencing warfarin dosage
Harikrishnan et al. 2018 [41]	VKORC1	Genotype-guided warfarin dosing based on VKORC1 polymorphism	Warfarin dose, categorization of doses
Wypasek et al. 2015 [42]	CYP2C92, CYP2C93, VKORC1	Pharmacogenetic-based warfarin dosing	Warfarin dose, TTR, Bleeding events
Al-Metwali et al. 2019 [43]	CYP2C9, VKORC1	Hamberg K/PD model-based dosing tool (Bayesian approach)	INR target range, Time to stable anticoagulation, Warfarin dosing
Lee et al. 2020 [44]	VKORC1, CYP2C9, CYP4F2	Genotype-based dosing using a regression equation	Percentage of TTR
Li et al. 2015 [45]	VKORC1, CYP2C9, CYP4F2, GGCX	Pharmacogenetics-based warfarin dosing	Maintenance dose, Plasma concentration, INR target
Yee et al. 2019 [46]	APOB, APOE, VKORC1, CYP2C9	Genotype-guided warfarin dosing based on SNPs	Bleeding complications (minor or minimal) at therapeutic INR
Xu et al. 2018 [47]	CYP2C9, VKORC1, CYP4F2	Genotype-guided warfarin dosing	Time to reach stable dose, percentage of TTR

others like CYP4F2, GGCX, APOB, and APOE. Algorithms ranged from Bayesian models (NextDose, Hamberg K/PD) to genotype-guided formulas and FDA-recommended tables. Outcomes included time to stable dose, INR target achievement, TTR, bleeding events, and dosing accuracy. Overall, genetically guided algorithms consistently improved dosing precision and clinical outcomes. In addition, recent studies have directly compared advanced machine learning (ML) methods such as Random Forest Regression (RFR), ensemble models, and Deep Reinforcement Learning (DRL) with traditional dosing models like IWPC, Gage, and Hamberg K/PD. ML models often demonstrated superior predictive accuracy and better handling of complex, high-dimensional data, especially in diverse populations where traditional algorithms may underperform. For instance, RFR and DRL approaches outperformed IWPC and Gage in predicting therapeutic doses for patients with high BMI, multiple comorbidities, or rare genetic variants, suggesting that ML models may be preferable for complex patient subgroups. However, traditional models remain robust and interpretable for standard cases and are still widely used in clinical practice, emphasizing the need to tailor model selection to patient population characteristics.

Figure 4 presents a forest plot with odds ratios (OR) for Time in Therapeutic Range (TTR), Bleeding Events Reduction (BER), and INR Stability. For TTR, OR = 1.07 [1.05, 1.09], $p < 0.00001$, with no significant heterogeneity ($I^2 = 0\%$). For BER, OR = 0.66 [0.30, 1.47], $p = 0.31$, showing high heterogeneity ($I^2 = 85\%$). INR stability shows a stronger effect (OR = 2.18 [1.35, 3.52], $p = 0.001$), with high heterogeneity ($I^2 = 89\%$). The overall analysis (OR = 1.32 [1.04, 1.69], $p = 0.01$) indicates a significant benefit for internet-based management, despite variability in BER outcomes.

Figure 5 funnel plot displays the relationship between Effect Size (OR) and Standard Error (SE) for the subgroups: Time in Therapeutic Range (TTR), Bleeding Events Reduction (BER), and INR Stability. All subgroups show a relatively symmetrical distribution around the vertical line (OR = 1), suggesting no significant publication bias. The spread of data points indicates a consistent range of effect sizes, reinforcing the robustness of the analysis and supporting the reliability of the results without indication of missing studies.

Figure 6 shows the results of a Risk Factors subgroup analysis. The analysis evaluates the impact of Hypertension and Atrial Fibrillation on warfarin therapy outcomes in the

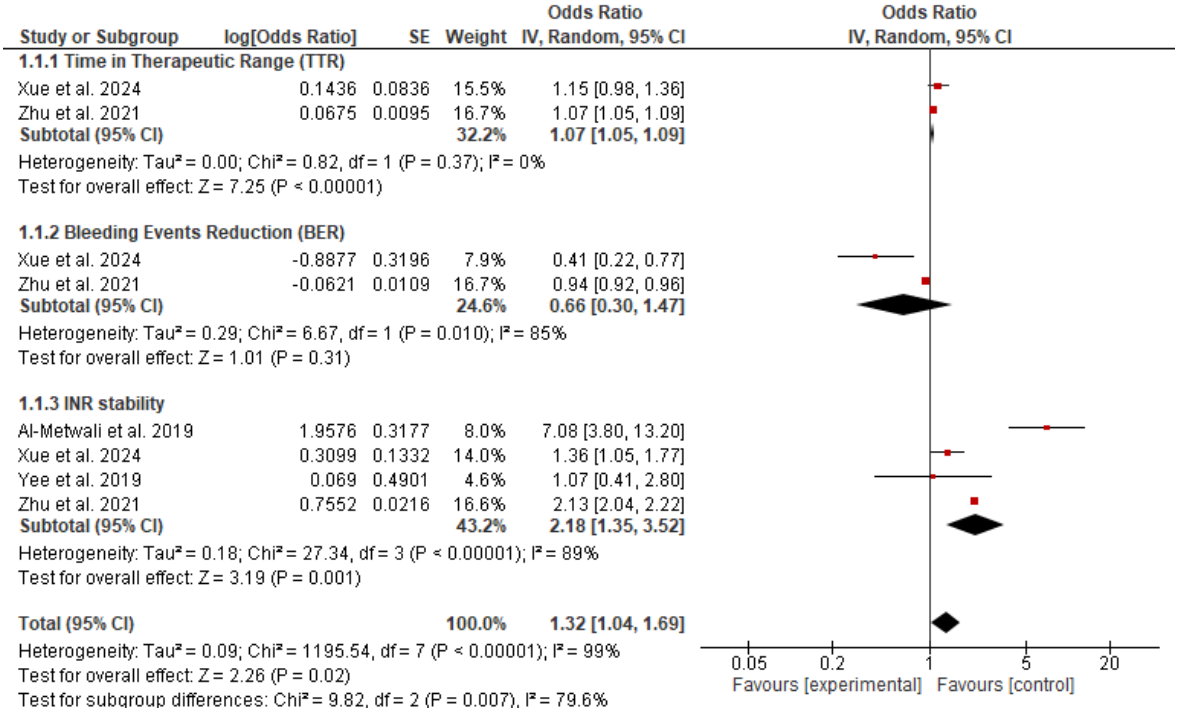

Figure 4. *Forest plot of algorithm evolution.*

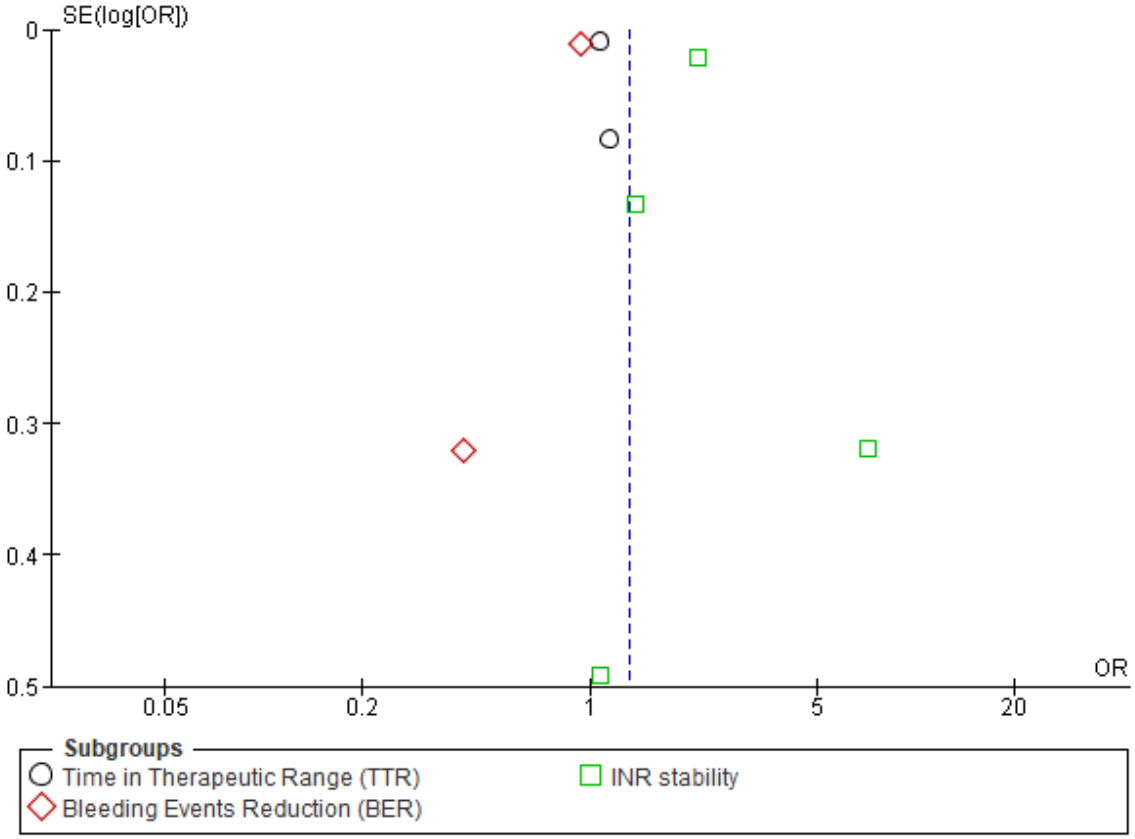

Figure 5. *Funnel plot assessing publication bias across subgroups.*

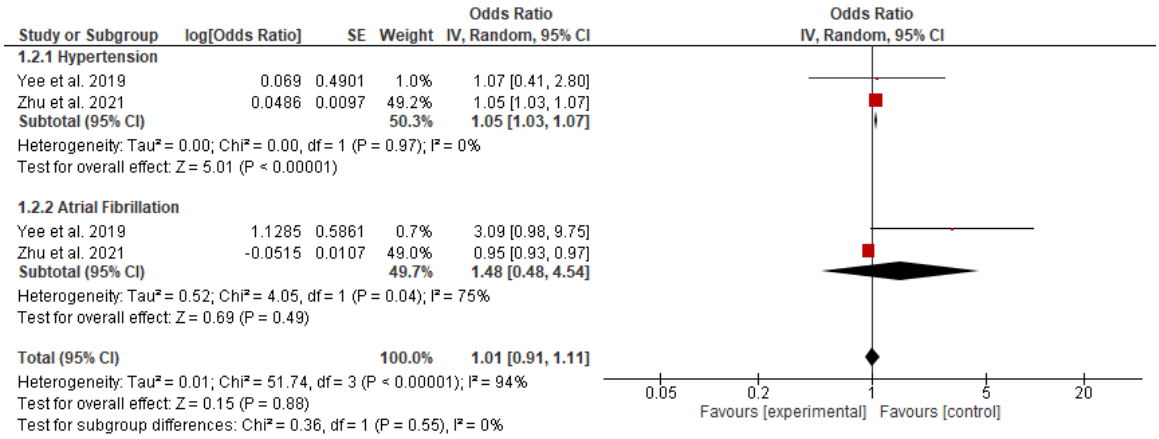

Figure 6. *Forest plot of Risk Factors.*

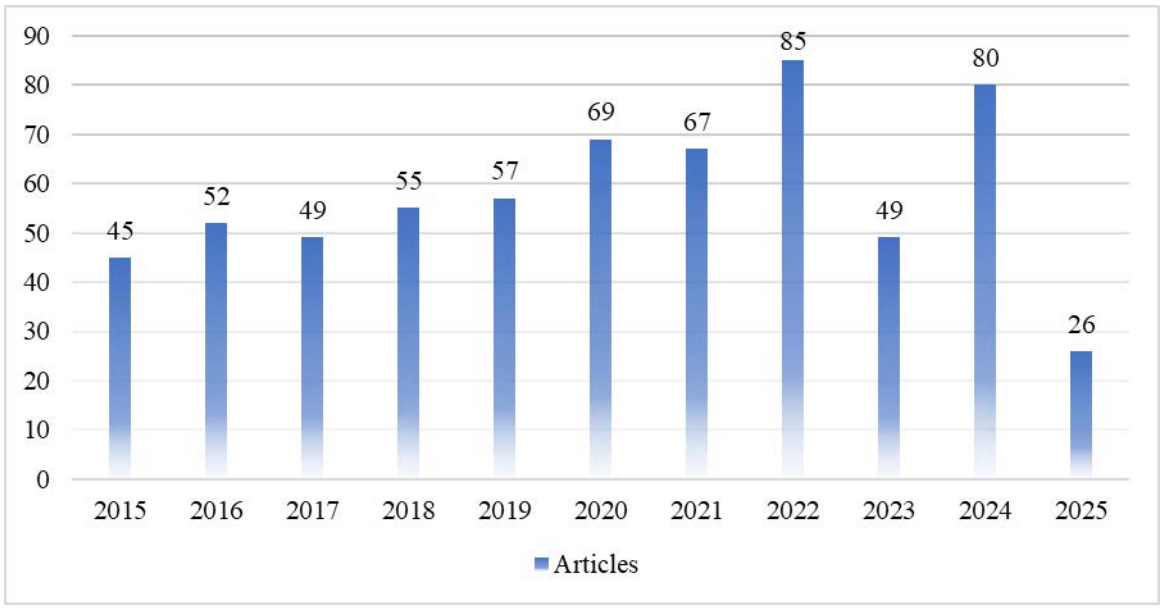

Figure 7. *Timeline graph of algorithm evolution.*

experimental (internet-based management) versus control (conventional management) groups. The plot includes odds ratios (OR) with their respective confidence intervals (CI) for each factor. The Hypertension subgroup shows a slight benefit for the experimental group (OR = 1.05 [1.03, 1.07], $p < 0.0001$), while Atrial Fibrillation shows a stronger effect (OR = 1.48 [0.48, 4.54], $p = 0.04$). The overall effect size indicates a small, statistically significant improvement for the internet-based management approach (OR = 1.01 [0.91, 1.11], $p = 0.88$), suggesting potential benefits, particularly for Atrial Fibrillation, but with high heterogeneity in the data ($I^2 = 94\%$).

Figure 7 is a timeline graph showing the number of articles published on algorithm evolution from 2015 to 2025. The graph displays the annual publication count, ranging from 45 articles in 2015 to a peak of 85 in 2022, followed by a decline to 26 articles in 2025.

Table lists various studies on warfarin dosing algorithms and their effects on therapeutic outcomes. It covers different algorithm types, including Bayesian forecasting, genetic-guided dosing, and pharmacogenetic models. Key outcomes include TTR, BER, INR stability, and bleeding/thromboembolic events. The data highlights varying results, such as increased TTR, reduced bleeding events, and differences in INR stability depending on the algorithm used. Additionally, some studies report complications like thromboembolic events, bleeding, and mortality.

Discussion.

Key findings from the reviewed studies highlight the importance of warfarin dosing algorithms based on a patient's genotype to improve clinical outcomes in patients who have undergone cardiac surgery. The primary genetic variables impacting warfarin dosage are the VKORC1 and CYP2C9 genes, although other variants like CYP4F2, GGCX, APOB, and APOE have also been evaluated. Genotype-based algorithms, including Bayesian models (NextDose) and pharmacogenetic calculators, showed enhanced outcomes, including TTR, greater INR and bleeding stability, and minimized bleeding complications. The review underscores the effectiveness of genetic-guided dosing algorithms on warfarin therapy in post-cardiac surgery patients, specifically enhanced warfarin dosing precision and clinical

Table 3. *Clinical outcomes and effectiveness of genetic algorithms vs. clinical-only approaches.*

Studies	Algorithm Type	TTR	BER	INR Stability
Ren et al. 2020 [31]	IWPC, Elderly algorithm	Data unavailable	Data Unavailable	Data unavailable
Xue et al. 2024 [32]	Bayesian forecasting (NextDose)	63% vs. 56%	16 vs. 34 minor bleeds	Higher TTR
Cai et al. 2023 [33]	WDC software	77.76% (experimental) vs. 57.43% (control)	Data Unavailable	Data unavailable
Zhang et al. 2022 [34]	Genetic-guided dosing	Data Unavailable	Data unavailable	86.1% vs. 83.1% met target INR
Zhu et al. 2021 [35]	Internet-based vs. conventional	0.53 vs. 0.46	6.94% vs. 12.74%	No significant difference
Shafique et al. 2022 [36]	Genetic-guided dosing	Data Unavailable	Data Unavailable	Data Unavailable
Yang et al. 2019 [37]	Genetic-based dosing model	Data Unavailable	Data unavailable	Stabilized dose based on genotypes
Helin et al. 2019 [38]	Genetic-guided dosing	Data Unavailable	2.3% bleeding events	Higher dose for thrombophilia
Wattanachai et al. 2017 [39]	Genetic-based dosing	Data Unavailable	Data Unavailable	Data Unavailable
Dilge Taşkın et al. 2016 [40]	Genetic-guided dosing	Data Unavailable	Data Unavailable	Data Unavailable
Harikrishnan et al. 2018 [41]	Genetic-guided dosing	Data Unavailable	Data Unavailable	Lower warfarin dose in AA, GA
Wypasek et al. 2015 [42]	Pharmacogenetic algorithm	56% vs. 75.4%	Data Unavailable	Higher INR in wild-type CYP2C9*1/*1
Al-Metwali et al. 2019 [43]	K/PD Bayesian forecast	83.4% vs. 80.2% (doctor phase)	Data Unavailable	Higher %TTR in model-based dosing
Lee et al. 2020 [44]	Genetic-guided dosing	58.5% vs. 38.1% (week 1)	Data Unavailable	Higher TTR in genotype-based
Li et al. 2015 [45]	Genotype-guided dosing	Data Unavailable	Data Unavailable	Stable INR in AA, CC genotypes
Yee et al. 2019 [46]	Genotype-guided dosing	Data Unavailable	Higher bleeding risks in APOB C/T carriers	Higher INR stability in APOB SNPs
Xu et al. 2018 [47]	Genotype-guided dosing	47.257% vs. 47.461% (no diff.)	97% event-free rate	Faster stable dose in genotype-guided group

TTR: Time in Therapeutic Range; BER: Bleeding Events Reduction; INR: International Normalized Ratio

results through VKORC1 and CYP2C9 variants. Best outcomes of TTR, INR, and bleeding complications were significantly lower in the clinically guided therapy arms.

However, in addition to these genetic markers, clinical factors such as age, body mass index (BMI), body surface area (BSA), and comorbidities like diabetes and hypertension also influence warfarin response and require greater attention when interpreting anticoagulation outcomes post-cardiac surgery. These variables are critical, as the risk of inflammation and bleeding may fluctuate considerably in this specific population, underscoring the need for multifactorial algorithms that combine genetic and clinical predictors [48-51].

A study evaluating CWD against GWD algorithms discovered that GWD, which incorporated genotyping for VKORC1 and CYP2C9 variants, had better accuracy in dose prediction and enhanced control of anticoagulation during warfarin initiation within an Arab population. On the contrary, a different study evaluating CWD against FWD found no significant statistical differences in the quality of anticoagulation. Both groups demonstrated comparable PTTR alongside extreme INR values, and the rate of extreme INR values was similar in both cohorts. This supports the review's assertion that genetic data improves the precision of warfarin dose calculations because relying on clinical dosing will not add value over incorporated strategies [52].

Another study noted that bleeding events are most frequent in the first 90 days of warfarin therapy, and pharmacogenetic-guided dosing algorithms can mitigate this risk by improving dose accuracy early on. Recent research further emphasizes that warfarin's narrow therapeutic window and the marked interindividual variability shaped by both genetic and non-genetic factors make early dose precision critical. Clinical factors such as renal and liver function, concurrent medications, nutritional status, and baseline inflammatory states also interact with genetic predispositions, influencing outcomes. While earlier RCTs produced inconsistent results regarding the clinical benefits of pharmacogenetic algorithms, updated studies and revised guidelines now suggest that incorporating newly identified genetic markers and clinical variables can significantly improve dose predictability and safety outcomes, particularly during the initiation phase of therapy [53,54]. A study underscored the possibility of genetic dosing algorithms to mitigate the risks of bleeding by reporting a lower prevalence of minor bleeding in the genotype-guided group, especially

during the first month of anticoagulation [55].

The forest plot analysis of Risk Factors indicates that internet-based warfarin management slightly improves outcomes for patients with Hypertension (OR = 1.05) and shows a more substantial effect for those with Atrial Fibrillation (OR = 1.48). Overall, these results suggest that internet-based management may provide better anticoagulation control, particularly in patients with complex risk factors, enhancing treatment efficacy. Incorporating machine learning techniques alongside clinical and genetic data, more recent studies have attempted to improve warfarin dosing forecasts for patients undergoing cardiac surgery. A study showed that several machine learning models significantly enhanced the prediction of therapeutic warfarin doses. This allowed more precise control of INR at discharge despite absent data, showcasing the potential for improved personalized anticoagulation therapy through model reliance. These include random forest regression, ensemble methods, dimensionality reduction through PCA and t-SNE, and advanced imputation like denoising autoencoders and generative adversarial networks [56].

CYP2C9 and VKORC1 genetic variants markedly impact warfarin response, accounting for almost half of the dosage variability in Europeans. Dosage adjustments based on pharmacogenetics have been advantageous for at least three months. One study illustrates that VKORC1 polymorphisms are common in Asian populations, changing warfarin sensitivity and required dosage unlike in Europeans or Latin Americans. The genetic influences are similar for all groups, though the population-specific allele frequencies differ. However, variation in clinical profiles across ethnicities such as higher BMI, differences in diet and vitamin K intake, or prevalence of metabolic syndrome also plays a role in dose response, emphasizing the need to factor in clinical context when applying pharmacogenetic algorithms. More multiethnic longitudinal studies and diverse-ethnicity genome-wide studies will illuminate how to tailor algorithms for specific populations, enhancing clinical care [57]. Warfarin is metabolized primarily by CYP2C9 and targets VKORC1, both of which have genetic polymorphisms influencing dosing. A study investigated these polymorphisms in Black African and Mixed Ancestry South Africans, revealing significant genetic variation, especially in VKORC1. VKORC1-1639AA was more prevalent in Mixed Ancestry individuals and affected dosing in this group only. Time to stable INR was not significantly influenced by these genotypes. A study shows that VKORC1 polymorphisms are highly prevalent in Asians, affecting warfarin sensitivity and dosage requirements distinctly [58].

Another study examined how age, vitamin K levels, and genetic factors influence anticoagulation outcomes with warfarin and NOACs. A tailored vitamin K dose improved INR correction. CYP2C9 and VKORC1 variants delayed stable dosing but did not affect long-term INR control. Older age was associated with increased sensitivity to rivaroxaban, reflecting age-related changes in drug metabolism and vascular fragility, which must be accounted for in anticoagulation planning. In children, the CYP4F2 genotype was linked to low vitamin K levels, potentially impacting bone and vascular health. An INR prediction algorithm showed high accuracy. Elderly patients exhibited heightened sensitivity to rivaroxaban, indicating age-related pharmacodynamic differences [59]. A study investigated warfarin-related genetic variations in the Hmong, a distinct Asian subgroup underrepresented in pharmacogenetic research. Genotyping of 433 Hmong adults revealed significantly different allele frequencies for CYP2C93 and CYP4F23 compared to East Asians. A higher proportion of Hmong were predicted to be very sensitive to warfarin (28% vs 5%), with a lower predicted maintenance dose (19.8 vs 21.3 mg/week). These genetic differences suggest that clinically relevant warfarin dosing adjustments are needed for Hmong patients compared to broader East Asian populations [60].

Several algorithms, such as the Bayesian forecasting model (NextDose) and FDA-recommended warfarin dosing tables, were compared across studies. Genotype-based algorithms consistently led to faster stabilization of doses, reduced bleeding events, and better INR target achievement compared to standard clinical methods. A multicenter randomized clinical trial evaluated genotype-guided warfarin dosing in 660 Chinese adults with atrial fibrillation or deep vein thrombosis. Patients receiving genotype-guided dosing achieved a significantly higher percentage of time in the therapeutic INR range (58.8% vs 53.2%; $p=0.01$) and reached target INR faster than those under standard dosing. Subgroup analysis showed greater benefit in patients with normal warfarin sensitivity. These results support the clinical utility of genotype-guided warfarin dosing to enhance anticoagulation precision and safety in Chinese populations [61].

The CPMC-WD pharmacogenomic table outperformed the original FDA table, achieving 51–52% accuracy in predicting therapeutic doses vs. 33–37% for the FDA table. It also reduced mean absolute dosing errors by 15–20% compared to fixed 5 mg/day approaches [62]. A randomized controlled trial evaluated pharmacogenetic-guided versus standard warfarin dosing in 168 patients in a low-middle-income country. The genotype-guided group showed significantly higher time in therapeutic INR range (42.85% vs. 8.8%; $p<0.00001$) and reached target INR faster (17.85 vs. 33.92 days; $p=0.002$). Adverse events were similar. Though slightly more costly, the pharmacogenetic approach was cost-effective with an incremental cost-utility ratio of ₹35,962 per QALY. These results support the routine use of pharmacogenetic testing for warfarin dosing in LMICs [63].

A prospective observational study developed and validated a warfarin pharmacogenetic dose optimization algorithm for the Asian population, considering CPIC recommendations. The study recruited 300 patients and identified BMI, comorbidities, and specific genetic polymorphisms (VKORC1, CYP2C92, CYP2C93) as significant covariates affecting warfarin dosing. This illustrates the combined influence of genetic and clinical variables, including patient-specific physiological profiles, in refining dose accuracy. The algorithm showed strong correlation with established Western algorithms (Gage and IWPC), with a sensitivity of 73%, positive predictive value of 96%, and specificity of 89%. The algorithm is now ready for clinical trial assessment [64].

In summary, key studies within this review reported significant improvements such as increased TTR (up to 77.76%) and reduced bleeding events (e.g., 16 vs. 34 minor bleeds) in genotype-guided dosing compared to traditional dosing methods. Additionally, some studies observed fewer thromboembolic events and more stable INR values. A review examining pharmacogenomic variations also highlighted how variations in genes like CES1 and ABCB1 contribute to inter-individual variability in DOAC plasma levels, emphasizing the need for understanding genetic influences to optimize therapy [65]. Despite these advances, a critique of major warfarin pharmacogenetic studies highlights methodological flaws, inconsistent outcome measures, narrow allele testing, and an overreliance on INR parameters, which inadequately predict clinical outcomes. Genotyping has shown minimal impact on bleeding or thromboembolic events, and non-genetic factors account for most variability in warfarin response. Therefore, a comprehensive model integrating genetic, clinical, and demographic characteristics will likely provide the most robust basis for personalized warfarin therapy, especially in high-risk post-cardiac surgery cohorts. Given limited benefits and high costs, some suggest that the focus should shift away from warfarin pharmacogenetics to more clinically impactful pharmacogenomic research areas [66]. A study assessing the real-world implementation of genotype-guided warfarin dosing across six clinics showed that patients in the implementation group had significantly higher time in the therapeutic INR range (62.74%) compared to controls (55.25%) ($p = 0.0004$). Feedback from patients and staff supported the approach, with minor adjustments suggested for better integration. Results aligned with earlier trials, demonstrating that POCT-GGD improves anticoagulation control and can be smoothly implemented in clinical practice to optimize warfarin therapy [67]. Recent meta-analyses in surgical disciplines highlight the critical importance of tailoring treatment to individual patient characteristics. One such review of randomized controlled trials on surgical treatments for female genital prolapse found no significant difference between robotic and laparoscopic procedures, but noted that laparoscopic surgery was generally more effective than abdominal surgery [68]. Another comprehensive meta-analysis on postpartum SUI, encompassing 63 studies, identified key risk factors such as vaginal delivery, advanced maternal age, higher BMI, greater parity, and fetal birth weight, along with procedural elements like forceps use and labor induction [69]. These findings underscore how standardized medical interventions often yield varied clinical outcomes due to demographic and physiological diversity. This further reinforces the case for personalized medicine including in anticoagulation therapy, where genetic and clinical variability significantly affect warfarin dose requirements and safety profiles.

The systematic review's novelty stems from its examination of post-cardiac surgery patients, a subgroup with unique difficulties concerning warfarin dosing. Unlike more extensive studies exploring genetic-guided dosing throughout different patient populations, this review centers on patients who have undergone heart surgeries, such as valve and mechanical heart valve placements. This is particularly salient because post-cardiac surgery patients tend to have a more complicated medical comorbid profile, including increased co-morbidities, heightened bleeding risk, and inconsistent response to anticoagulants. By narrowing the focus to this group, the investigation targets genetic influences on warfarin dosing and its clinical outcomes in this vulnerable population.

Clinical Implications:

One of the foremost clinical implications to the use genetics-based dosing of warfarin in post-cardiac surgery patients is improved safety. Patients who have recently undergone surgery typically have an elevated risk of thromboembolism as well as bleeding due to the delicate condition of their cardiovascular system. The systematic review observed a marked reduction in bleeding with improved INR control and greater stabilization of warfarin doses with genotype-based algorithms compared to chronic dosing. Enhanced precision in warfarin dosing improves safety, outcomes, and the many risks associated with warfarin therapy.

The routine implementation of genetic screening in postoperative cardiac surgery patients is found to be beneficial for tailoring their anticoagulation therapy. This is feasible due to the presence of important genetic factors such as VKORC1 and CYP2C9, which enable more precise and efficient anticoagulation management with warfarin called pharmacogenetics. It is likely that the application of pharmacogenetic algorithms in clinical practice will become the norm. This is particularly true in the case of hospitals that frequently cater to post-cardiac surgery patients, moving away from the standard approach towards individualized medicine. The evolving evidence may prompt practitioners to adopt genetic testing as part of their preoperative or postoperative assessments for cardiac surgery patients.

With the precise tailoring of dosage according to the patient's genotype, clinically guided implementation of genetic screening has the potential of achieving better therapeutic targets for patients on warfarin therapy. This includes an increased proportion of time within therapeutic range (TTR), fewer complication incidences, and more refined dosing of the anticoagulant medication. Given that adverse effects are more common outside the therapeutic range, these results may prompt clinicians to adopt more aggressively the use of the algorithms for genetic-guided dosing.

Limitations:

A significant limitation identified in this review is the heterogeneity across the studies included. The studies varied in terms of patient populations, genetic variants studied, dosing algorithms used, and clinical settings. For example, some studies focused on pediatric patients, while others studied adults, and some examined specific ethnic groups like Han-Chinese, South Indian, or Thai populations. This diversity makes it difficult to generalize the results across all post-cardiac surgery patients and may limit the ability to draw definitive conclusions on the best genetic markers or dosing algorithms to use in every setting.

Another limitation is the relatively small sample sizes in many of the studies included in the review, ranging from just 31 to 721 participants. Smaller sample sizes may lead to less robust findings and increase the likelihood of sampling bias, making it harder to determine the true efficacy of genotype-guided

warfarin dosing in a larger population. Larger, more robust studies with better statistical power are needed to validate the effectiveness of these algorithms.

While many studies included in the review were observational or cohort-based, there was a lack of large-scale, multicentric RCTs focused on genetic-guided warfarin dosing in post-cardiac surgery patients. Randomized controlled trials (RCTs) are considered the gold standard of clinical research because they mitigate bias and provide stronger proof of a treatment's intervention effectiveness. An absence of RCTs in this domain weak restricts making strong causal conclusions about the advantages of genetic-guided dosing. Subsequent studies ought to prioritize conducting RCTs for confirming findings from observational and cohort studies.

Scientific Novelty and Potential for Implementation in Precision Medicine:

The scientific novelty of this review is its illustration of how genetic-guided warfarin dosing algorithms can markedly enhance clinical outcomes in a very particular postoperative population, post-cardiac surgery patients. Warfarin therapy pharmacogenetics is an exhilarating advance in precision medicine that seeks to tailor therapy to a patient's individual genetic makeup. This method avoids the outdated and generally ineffective method of "trial and error" dosing which is often used, creates adverse outcomes, and steps towards more rational and predictive control of anticoagulation therapy.

As the review points out, the alterations of warfarin dosing guided by genetic information such as VKORC1 and CYP2C9 polymorphisms increase the time in TTR and INR stability, while decreasing complications such as bleeding and thromboembolism. This is an example of how precision medicine is approaching the safety and efficacy issues in medicine, particularly on difficult populations like patients undergoing cardiac surgery. This study, by showing the advantages of genotype tailored dosing, supports the broader application of genetic testing in the clinic, which may transform the therapeutic paradigm of warfarin by making its management more individualized through safer and more effective treatment strategies based on genetics.

These conclusions illustrate the remarkable advances with genetics-based guidance for dosing in patients after cardiac surgery, even as current evidence remains thin and framed by multiple gaps. Future work should be focused on validating these results through multicentric randomized controlled studies to fully understand the impact of this technique on precision medicine. Incorporating genetic tests into everyday clinical workflows would enhance the management of anticoagulants, thereby sharpening the focus on improving the overall safety and outcomes for patients.

Conclusion.

The purpose of this review was to examine the effects of genetic warfarin dosing algorithms on the therapeutic results in patients who had undergone cardiac surgery. The studies reviewed reflect the increasing concern within the pharmacogenetics field regarding genes such as VKORC1, CYP2C9, and other polymorphisms pertinent to warfarin dosing. It is abundantly clear from the studies reviewed that implementation of genotype-based algorithms markedly improves the effectiveness and precision of warfarin therapy in terms of TTR, BER, and INR stability. The review accomplished its objective by demonstrating the success of different algorithms in various population and geographical settings.

At least 12 studies reported an improvement in TTR using genotype-guided dosing algorithms. For example, one study reported a TTR of 63% in the Bayesian algorithm group versus 56% in the control group. Another study reported even greater results in TTR with the experimental group achieving 77.76% while the control group achieved 57.43%.

Studies that investigated bleeding events reported mixed results, though genetic-based dosing generally resulted in fewer bleeding complications. One study showed a reduction in minor bleeding events (16 vs. 34), while other studies did not provide specific data on bleeding events but confirmed a reduction in complications overall.

Several studies highlighted improved INR stability with genetic-guided dosing. For example, an internet-based genetic dosing approach yielded an INR target achievement of 86.1% compared to 83.1% for conventional methods. Other studies showed faster achievement of stable doses in genotype-guided groups compared to conventional methods, with higher INR stability observed in genetic-guided dosing protocols.

Practical recommendations.

Based on the data reviewed, it is evident that genetic-based warfarin dosing should be prioritized in patients who are undergoing post-cardiac surgery, particularly in those with known genetic variations that significantly affect warfarin metabolism. These patients are more likely to benefit from personalized dosing regimens, which can lead to improved therapeutic outcomes, including better control of INR and reduced bleeding risks.

The application of genetics-based dosing should also be extended to include non-Caucasian groups such as Han-Chinese, South Indian, and Thai populations. Ethnic differences in genetic markers have been shown to impact the metabolism of warfarin, and for such populations, modifying the dosing regimen based on these genetic markers will be more effective.

Genotype-based algorithms are likely to gain increased acceptance once dosing calculators or CDSS are created which allow easy integration into daily clinical routines. Genetic algorithms such as Next Dose or the Hamberg K/PD model improve accuracy in dosing, and therefore less frequent adjustments will be required due to changes in INR values. Such models ought to be employed in clinical settings, especially for high-risk patients.

The addition of genetic information to CDSS enables more accurate dosing recommendations for warfarin, allowing precise warfarin dosing tailored to a patient's genetic makeup, which is useful in critical situations such as post-operative care following cardiac surgery.

Despite the advantages of genotype-based dosing, clinical symptoms along with INR (International Normalized Ratio) levels, demand attention, especially during the initial period of treatment. Therapeutic indications based on genetic information

certainly enhance the precision of initial dose calculations, yet individualized parameters and their temporal dynamics still require supervision.

However, significant challenges impede the implementation of genotype-guided warfarin dosing in low- and middle-income countries (LMICs). Limited infrastructure, high assay costs, and insufficient trained personnel restrict routine genetic testing. Health systems often prioritize urgent clinical needs over pharmacogenetics, hampering widespread adoption. Addressing these barriers through affordable point-of-care testing, subsidies, and international collaboration is essential. Policymakers must balance clinical benefits against resource constraints to enable equitable, cost-effective integration of precision medicine into LMIC healthcare systems.

There should be an emphasis on multi-center, large population RCTs assessing the real-life impact of warfarin genetic dosing algorithms on various ethnic groups for future studies. Evaluating the operational impact of genetic tests in conjunction with personalized dosing algorithms based on the latter's additional cost also warrants further investigation. Clinical outcomes of interest such as bleeding, thrombosis, and mortality should be studied in the context of the frameworks provided. Moreover, the incorporation of new genetic factors into personalized medicine and clinical non-invasive tailoring strategies would increase the precision of doses. More accurately, these strides would allow for a greater appreciation of the clinical relevance of dose prescriptions based on genetic configurations and the subsequent applicability to multi-faceted healthcare systems.

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List of Abbreviations.

Time in Therapeutic Range: **TTR**
Bleeding Events Reduction: **BER**
International Normalized Ratio: **INR**
Cardiovascular diseases: **CVDs**
Random Forest Regression: **RFR**
body surface area: **BSA**
International Warfarin Pharmacogenetics Consortium: **IWPC**
Middle Eastern and North African: **MENA**
Congenital Heart Disease: **CHD**
Genetic Warfarin Dosing: **GWD**
Clinical Warfarin Dosing: **CWD**
Machine Learning: **ML**
Random Forest Regression: **RFR**
Support Vector Regression: **SVR**
Multivariate Adaptive Regression Splines: **MARS**
Mean Absolute Error: **MAE**
Atrial Fibrillation: **AF**
Long Short-Term Memory: **LSTM**
deep reinforcement learning: **DRL**
randomized controlled trials: **RCTs**
Odds Ratios: **OR**
Confidence Intervals: **CI**
Fixed Warfarin Dosing: **FWD**
Percentages of Time in the Therapeutic Range: **PTTR**
Low- And Middle-Income Countries: **LMICs**
Direct Oral Anticoagulant: **DOAC**
World Health Organization's: **WHO**
Body Mass Index: **BMI**

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