Open Access Library Journal
2025, Volume 12, e13567
ISSN Online: 2333-9721
ISSN Print: 2333-9705

Influence of Clinical Risk Factors on International Normalized Ratio Control in Patients on Warfarin Therapy: A Systematic Review

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How to cite this paper: Ramasamy, T., Jahan, N.K., Pillai, N. and Yap, C.G. (2025) Influence of Clinical Risk Factors on International Normalized Ratio Control in Patients on Warfarin Therapy: A Systematic Review. *Open Access Library Journal*, **12**: e13567.
https://doi.org/10.4236/oalib.1113567

Received: May 6, 2025
Accepted: August 9, 2025
Published: August 12, 2025

Abstract

Warfarin remains a widely prescribed oral anticoagulant despite its narrow therapeutic index and its association with life-threatening bleeding events. This systematic review examined the impact of clinical risk factors on international normalized ratio (INR) control in patients receiving Warfarin therapy. Following the PRISMA-P guidelines, we searched four electronic databases (PubMed, SCOPUS, Embase, and Web of Science) using Medical Subject Headings to identify eligible cohort studies published between 2016 and 2020. A total of 15 original research articles met the inclusion criteria. The risk of bias was assessed using the Newcastle-Ottawa scale. This review identified several clinical risk factors influencing INR control, including drug interactions with Warfarin, herbal supplements, dietary intake of vitamin K, and multiple comorbidities (anemia, heart failure, chronic kidney disease, psychiatric disorders, prosthetic valve), kidney transplant recipient, hemodialysis, and hypoalbuminemia. These clinical risk factors adversely affect the time in therapeutic range, thereby increasing the risk of adverse outcomes such as thromboembolism, major bleeding, and mortality. Overall, these clinical risk factors compromise Warfarin efficacy by contributing to subtherapeutic or supratherapeutic INR levels. Identifying and addressing these clinical risk factors prior to initiating Warfarin therapy is essential to achieving optimal INR control.

Subject Areas

Pharmacology, Hematology, Clinical Medicine, Cardiology

Keywords

Clinical, Risk Factor, International Normalized Ratio, Warfarin

1. Introduction

Warfarin is an anticoagulant that works by competitively inhibiting the vitamin K epoxide reductase complex 1 (VKORC1), resulting in reduced hepatic activation of clotting factors II, VII, IX, X, proteins C and S [1]. It has been widely used for over six decades as the primary treatment to reduce the risk of cardiovascular events such as venous thromboembolism (VTE) and ischemic stroke in patients with atrial fibrillation (AF) [2]. Warfarin is characterized by a narrow therapeutic index, substantial interpatient variability in metabolism, and numerous potential food and drug interactions [3] [4]. Despite the proven benefits of non-vitamin K-dependent oral anticoagulants (NOACs), Warfarin continues to be used, particularly in patients with rheumatic or valvular AF, prosthetic valve replacement, hypercoagulable states or those with limited financial access to newer medications [5]. Regular monitoring of the international normalized ratio (INR) and appropriate dose adjustment are essential to ensure the safety and effectiveness of Warfarin therapy [6].

INR is a standardized and widely accepted measure of anticoagulation intensity, introduced approximately 2 - 3 decades ago. In real-world clinical settings, subtherapeutic and supratherapeutic INR levels are frequently observed in a substantial proportion of patients (approximately 30% - 50%) on routine Warfarin therapy. Poor INR control markedly increases the risk of thromboembolic complications, whereas supratherapeutic INR levels elevate the risk of major bleeding complications [7]. For most indications, maintaining an INR within the target range of 2.0 - 3.0 is considered optimal for ensuring both safety and efficacy of Warfarin therapy [8]. Excessive anticoagulation increases bleeding risk, while subtherapeutic anticoagulation predisposes patients to thrombosis. Furthermore, spontaneous INR elevations in critically ill patients may be associated with increased mortality due to over-anticoagulation [9]. A multi-country study highlighted the challenges of maintaining optimal INR control, even in clinical trial settings [10].

Time in therapeutic range (TTR) quantifies the percentage of time during which a patient's INR remains within the target therapeutic range and serves as a reliable indicator of INR control quality [11]. A TTR between 60% and 75% is considered adequate, according to current recommendations [10]. The incidence of adverse events, including thromboembolism, major bleeding, and mortality, is significantly higher in patients with a lower TTR group (≤69%) compared to those with a higher TTR (≥70%) [12]. Notably, each 1% increase in TTR has been associated with a 0.46% reduction in recurrent thromboembolic events and a 0.30% reduction in major bleeding annually [13]. Despite the availability of direct oral anticoagulants (DOACs), Warfarin remains widely prescribed due to

its accessibility and cost-effectiveness [14]. Additionally, Warfarin continues to be the only recommended anticoagulant for patients with prosthetic heart valves [15].

The therapeutic goal of Warfarin therapy is to administer the lowest effective dose that maintains INR within the target range of 2.0 - 3.0 [16]. However, achieving consistent INR control within the target range is challenging due to the influence of various clinical and non-clinical risk factors. Our previous work has explored how non-clinical risk factors contribute to poor INR control [17]. This review aims to analyze the impact of clinical risk factors on INR control among patients receiving Warfarin therapy. Given the persistent global reliance on Warfarin and the serious implications of INR mismanagement, publication of this review is essential. It may contribute to improved clinical practice by providing an evidence-based resource that supports decision-making, enhances risk mitigation, and ultimately improves patient care in anticoagulation management.

2. Materials and Methods

We conducted this systematic review in accordance with the preferred reporting items for the systematic review and meta-analysis (PRISMA) 2020 guidelines [18] (see Checklist A1).

2.1. Search Strategy and Study Selection

We conducted an advanced systematic literature search in four electronic databases (PubMed, SCOPUS, Embase, and Web of Science) to identify eligible cohort studies published between 2016 and 2020, a period during which clinical guidelines for Warfarin use were well established, and routine INR monitoring practices remained consistent [19].

In these four databases, we searched the original research articles using the Medical Subject Headings (MeSH) and keywords according to the PICO concept. The target population was "adult patients", which was searched under two sub-concepts: population-1 "adult" and population-2 "patient". The intervention was "Warfarin". For the outcome, we searched the databases under two concepts: outcome-1 "risk factors" and outcome-2 "International Normalized Ratio". Although "clinical risk factors" would be the ideal search term, no subject heading specially addressed it; thus, we used "risk factor" as a proxy.

To construct the final search string, we first combined the subject headings and keywords for population-1 "adult" and population-2 "patient" using the "OR" Boolean Operator as they belonged under the same concept. Then, we added the intervention "Warfarin" using the "AND" Boolean Operator. Lastly, we combined the subject heading and keywords for outcome-1 "Risk Factor*" and outcome-2 "International Normalized Ratio" using the "OR" Boolean Operator as they also belonged under the same concept. The complete search strings, both by individual concepts and combined under PICO (with and without filters), are presented in Table A1 in **Appendix**.

We initially identified 1202 articles across the four databases. After removing duplicates, 989 articles were selected to be screened based on titles and abstracts. The first two authors [TR and NKJ[1]] independently screened articles based on titles and abstracts and selected 88 eligible articles for full text review based on the inclusion and exclusion criteria. Finally, we included 13 original research articles for data extraction and analysis (Figure 1).

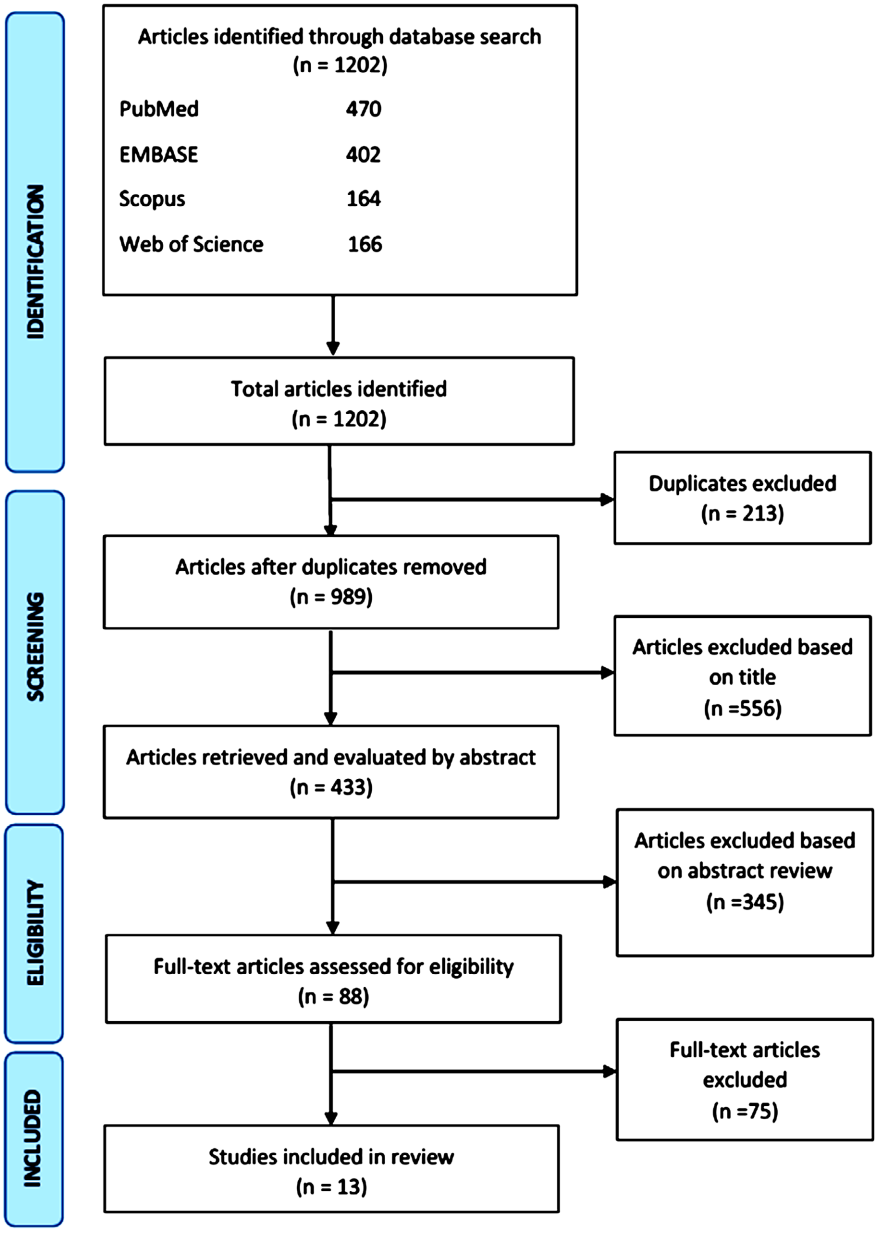

Figure 1. PRISMA chart used for the selection of articles.

2.2. Inclusion and Exclusion Criteria

We included all original research articles that employed a cohort design, either

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prospective or retrospective, investigated the effects of clinical risk factors on INR control, involved adult patients aged 18 years and above as study population, patients receiving Warfarin, and were published in English. We excluded studies that focused solely on non-clinical factors, included study population under 18 years of age, were unpublished reports, case reports, or non-cohort observational studies like cross-sectional studies, and reviewed articles, including systematic reviews.

2.3. Data Extraction

The first two authors [TR and NKJ] independently extracted data using NVivo software and entered information into a structured data collection form. The extracted data included: Authors' names, country of study, year of publication, study design, sample size, primary findings, and conclusion. They further categorized the extracted data under specific themes and subthemes, such as: Drug interactions with Warfarin, herbal supplements, multiple comorbidities (anemia, heart failure, prosthetic valve, malignancy, psychiatric disorders, diabetes, chronic kidney disease, respiratory disease), kidney transplant recipient, hemodialysis and hypoalbuminemia. Finally, the data was included for analysis when both the authors came to a general agreement through discussion. They invited the third author, either NKP or CGY[2], to join when they could not reach to an agreement.

2.4. Quality Assessment

We assessed the methodological quality of each included cohort study using the Newcastle-Ottawa Scale (NOS). The NOS is a validated tool specifically designed for evaluating the quality of non-randomized studies, including both cohort and case-control designs. We used the version of NOS tool adapted for cohort studies, as our included studies were either prospective or retrospective cohort studies in design. For quality assessment of cohort studies, this measurement tool is based on three broad domains: Selection (maximum of 4 points: [1]representativeness of the exposed cohort, [2]selection of the non-exposed cohort, [3]ascertainment of exposure, and [4]demonstration that the outcome measure was not present at the start of the study), Comparability (maximum of 2 points: [1]comparability of cases and controls based on the design or analysis with a major factor, and [2]comparability with additional factors) and Outcome (maximum of 3 points: [1]assessment of the outcome, [2]follow-up length, and [3]adequacy of follow-up of the cohorts) [20].

Each item was scored as 1 point if the criterion was clearly satisfied or 0 points if it was not satisfied or unclear. We used numerical scores (0 or 1) rather than stars for clarity and consistency in reporting and to calculate the score. A study could therefore achieve a maximum score of 9 (Selection = 4, Comparability = 2, Outcome = 3). Higher scores indicated better methodological quality. Based on this scoring system, we assessed 15 articles. The NOS scores ranged from 4 to 8 out of

[2]NKP: Naganathan Kathiresan Pillai; CGY: Christina Gertrude Yap.

9, indicating no studies of poor or low-quality articles (defined as NOS scores between 1and 3). Five studies were classified as medium or moderate quality (NOS scores of 4 - 6), while the remaining 10 were considered as high quality (NOS scores of 7 - 9) (see Table 1).

Table 1. Detailed Newcastle-Ottawa Scale for each included cohort study.

	Selection				Comparability		Outcome			
Authors' name and year of publication [Reference number]	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Adjust for the most important risk factors	Adjust for other risk factors	Assessment of outcome	Follow-up length	Loss to follow-up rate	Total quality score
Al-Momany *et al.* (2019) [21]	1	1	0	0	0	0	1	1	1	**5**
Bernaitis *et al.* (2017) [23]	1	1	0	0	0	0	1	1	0	**4**
Bertram *et al.* (2019) [25]	1	1	0	0	1	0	1	1	0	**5**
Björck *et al.* (2018) [27]	1	1	1	0	1	0	1	1	0	**6**
Botton *et al.* (2020) [22]	1	1	0	1	1	1	1	1	0	**7**
Inoue *et al.* (2018) [31]	1	1	1	0	1	1	1	1	0	**7**
Jaakkola *et al.* (2017) [24]	1	1	1	0	1	1	1	1	1	**8**
Kawai *et al.* (2019) [33]	1	1	1	0	1	0	1	1	1	**7**
Liang *et al.* (2019) [26]	1	1	1	0	1	1	1	1	1	**8**
Prochaska *et al.* (2019) [28]	1	1	1	0	1	1	1	1	0	**7**
Szummer *et al.* (2017) [30]	1	1	1	1	1	1	1	1	0	**8**
Yang *et al.* (2016) [29]	1	1	1	0	1	1	1	1	0	**7**
Yanik *et al.* (2017) [32]	1	1	1	1	1	1	1	1	0	**8**

3. Results

We analyzed and extracted data from 15 cohort studies involving a total of 173,804 patients receiving Warfarin therapy. This systematic review identified multiple clinical risk factors that influence INR control in these patients. A summary of the included studies is presented in Table 2.

Table 2. List of selected articles that are included in the review with their main findings and conclusion.

Authors' name; Study country; Year of publication [Reference no]	Type of study	Sample size	Main findings	Conclusion
Al-Momany *et al*.; Jordan; 2019 [21]	Prospective Cohort Study	2788	- Concurrent medication use (Salicylates, Amiodarone, NSAID, Ciprofloxacin, Clarithromycin, and Azithromycin) is frequently causing non-therapeutic INR. - High vitamin K dietary intake is associated with subtherapeutic INR control, primarily during spring. - Herbal supplements such as Hawthorn have been associated with supratherapeutic INR and severe bleeding risk. - Comorbid diseases and malabsorption are also associated with non-therapeutic INR.	Concurrent medication use, high vitamin K dietary intake, herbal supplements, comorbid diseases, and malabsorption are associated with non-therapeutic INR control.
Bernaitis *et al*.; Australia, Singapore; 2017 [23]	Retrospective Cohort Study	4366	- The mean TTR in Australia is significantly higher than in Singapore - CKD is associated with lower TTR - Factors such as anemia, vascular disease, CHA_2DS_2-VASc score of 6, and concurrent platelet inhibitor therapy influence the INR control.	CKD is associated with reduced INR control in Australia and Singapore. Multiple patient factors influence the INR control in both sites.
Bertram *et al*.; Australia; 2019 [25]	Retrospective Cohort Study	4494	- Patients taking proton pump inhibitor (PPI) had significantly lower TTR compared to those not taking PPI (78.5 ± 9.7% vs. 81.7 ± 10.2%, $P < 0.0001$). - Patients taking PPI had a higher incidence of minor bleeds compared to those not taking PPI.	Patients taking PPI concurrent with warfarin have lower TTR and a higher incidence of minor bleeds.
Björck *et al*.; Sweden; 2018 [27]	Retrospective Cohort Study	2811	- Concomitant comorbidities such as hypertension, chronic obstructive disease, and previous myocardial infarction are associated with poor individual TTR (iTTR). - History of falls and cancer are moderate risk factors of poor iTTR. - Patients with previous stroke are more likely to have iTTR of more than 70%.	Multiple concomitant vascular and organic specific disorders are associated with poor INR control.
Botton *et al*.; Brazil; 2020 [22]	Prospective Cohort Study	422	- Concurrent use of Glibenclamide and the presence of CYP2C9*2 and/or *3 alleles are associated with higher TTR. - Acetaminophen, amiodarone, and verapamil co-medication are associated with lower TTR.	Co-medications such as Glibenclamide, acetaminophen, amiodarone, and verapamil influence the INR control.
Inoue *et al*.; Japan; 2018 [31]	Prospective Cohort Study	7937	- Creatinine clearance (CrCl) < 30 mL/min is independently associated with TTR < 65%. - CrCl < 30 mL/min and TTR < 65% are independently associated with all-cause death, major hemorrhage, and thromboembolism.	Elderly non-valvular AF patients with CKD are associated with poor INR control and a higher risk of thromboembolism and all-cause death.
Jaakkola *et al*.; Finland; 2017 [24]	Retrospective Cohort Study	13,618	- One of the strongest risk factors for excessive warfarin anticoagulation is reduced renal function. - Chronic medical diseases such as CKD, heart failure, active cancer, and mechanical heart valve prosthesis are permanent risk factors of excessive anticoagulation. - Recent antibiotic or antifungal medications and chemotherapeutic agents are temporary risk factors for supratherapeutic INR control.	Permanent and temporary clinical risk factors are helpful in the prediction of excessive warfarin anticoagulation.
Kawai *et al*.; Japan; 2019 [33]	Prospective Cohort Study	755	- Low serum albumin level (ALB) is directly correlated with the percentage of time in the international normalized ratio of prothrombin time (PT-INR) > 3.0. - Patients with ALB < 3.6 g/dl have a higher risk of major bleeding events than those with ALB ≥ 3.6 g/dl during a long-term follow-up.	Hypoalbuminemia is associated with a higher risk of supratherapeutic PT-INR control and major bleeding events.

Continued

Liang *et al*.; China; 2019 [26]	Prospective Cohort Study	1895	- The median TTR was 51.7%, and only 25.1% of patients had TTR ≥ 70%. - Single drug use and bleeding history are associated with TTR < 70%. - Peripheral artery disease, coronary heart disease, and diabetes mellitus are associated with increased INR variability.	Warfarin anticoagulation in Chinese patients with NVAF was associated with lower TTR. Concomitant drug use and chronic medical illnesses such as coronary heart disease, peripheral artery disease, and diabetes mellitus influence INR control.
Prochaska *et al*.; Germany; 2019 [28]	Prospective Cohort study	760	- Comorbidities, cardiovascular risk factors, diabetes, and treatment characteristics are independent risk factors of subtherapeutic INR control.	Multiple clinical risk factors are associated with subtherapeutic INR control.
Szummer *et al*.; Sweden; 2017 [30]	Prospective Cohort Study	7738	- Patients with eGFR < 30 had TTR around 70%, 10% lower than those with normal kidney function. - Patients with TTR ≤ 75% were at higher risk of adverse events independent of patient characteristics, comorbidities, days exposed to warfarin, the number of INR test days, and eGFR. - There is no interaction between eGFR and TTR associated with adverse events.	Patients with severe CKD with eGFR < 30 have poor INR control. TTR > 75% is associated with decreased risk of adverse events, and this is independent of kidney function.
Yang *et al*.; USA; 2016 [29]	Retrospective Cohort Study	123,188	- The use of warfarin decreases with the increase in CKD severity. However, the use of warfarin is higher in patients on dialysis. - The number of patients with TTR ≥ 60% reduces with the increase in CKD severity. - The magnitude of TTR reduction increases with the severity of CKD. - Only 21% of patients on dialysis achieved TTR > 60%.	Patients with moderate to severe CKD and dialysis have lower TTR that require more intensive warfarin management.
Yanik *et al*.; Alabama; 2017 [32]	Prospective Cohort Study	1695	- Kidney transplant recipients (KTRs) require a 20% lower warfarin dose than those non-KTR patients. - The mean percentage of TTR is low and similar among both KTR and non-KTR groups.	Initiation of warfarin in KTRs requires lower warfarin doses and close monitoring to ensure optimal INR control.

3.1. Drug Interaction

We found significant interactions between Warfarin and various drugs that negatively impact INR control. Al-Momany *et al*. reported that concurrent medication use, approximately 46.9% of their study population, has interrupted INR stability. Notably, they identified salicylates and amiodarone as contributors to poor INR control and reported that the simultaneous use of Warfarin with aspirin plus NSAID/clopidogrel and levofloxacin resulted in severe bleeding, including bleeding from the upper gastrointestinal tract, surgical site, eye, and nose [21]. Botton *et al*. identified significant interactions between Warfarin and amiodarone, verapamil, and acetaminophen, all of which contributed to decreasing TTR values [22]. Similarly, Bernaitis *et al*. found that concurrent use of platelet inhibitors was significantly associated with lower TTR in a cohort from Singapore [23].

Our review also confirmed the strong interaction between antibiotics and Warfarin. Jaakkola *et al*. found that the use of antibiotics increased the risk of severe over-anticoagulation by 4.6 times when used concurrently with Warfarin [24]. Al-Momany *et al*. highlighted that antibiotics, especially ciprofloxacin, azithromycin,

and clarithromycin, significantly contributing to poor INR control [21]. Interestingly, Botton *et al*. found that the concurrent use of glibenclamide with Warfarin had a protective effect and was associated with a significantly higher TTR [22]. Bertram *et al*. demonstrated that patients using PPI alongside Warfarin had significantly lower mean TTR compared to those on Warfarin alone (84.4% vs. 89.4%, $p < 0.0001$) [25].

3.2. Herbal Supplements

In our review, Al-Momany *et al*. described that herbal supplements contributed to supratherapeutic INR, accounting for 15.02% of non-therapeutic INR cases in their study. Hawthorn, a widely used traditional cardiovascular remedy in Jordan and Ginseng, a traditional Chinese medicine, were both associated with elevated INR levels and increased bleeding risk [21].

3.3. Comorbidities

Several studies in this review explored the role of comorbidities in INR control. Jaakkola *et al*. described that 57.3% of patients with excessive anticoagulation had chronic medical illnesses, including active cancer, heart failure, and mechanical heart valves [24]. In addition, Liang *et al*. reported that comorbidities such as diabetes mellitus, congestive heart disease (CHD), and peripheral arterial disease (PAD) are significantly associated with INR instability, likely due to the effects of the underlying diseases [26].

Björck *et al*. reported a higher risk of poor INR control among the anaemic patients on Warfarin therapy [iTTR < 60% by 36% (Odds Ratio, OR: 1.36, 95% Confidence Interval, CI: 1.22 - 1.51)], chronic obstructive pulmonary disease (COPD) [iTTR of <60% (OR: 1.45, 95% CI: 1.33 - 1.59)] and dementia [iTTR (OR: 1.47, 95% CI: 1.02 - 2.12)] [27]. Prochaska *et al*. further confirmed that diabetes is a statistically significant predictor of subtherapeutic INR control (OR:1.4, 95% CI: 1.0 - 2.0), with patients experiencing recurrent episodes of subtherapeutic INR [28].

3.4. Chronic Kidney Disease (CKD)

Our review identified that chronic kidney disease (CKD) significantly influences INR control. Yang *et al*. reported that 56.3% of AF patients with CKD were on Warfarin, with a slightly higher proportion (62.3%) among those on dialysis. The TTR value was lower than the targeted value across all CKD patients with different eGFR. This study reported that supratherapeutic INR was more common than subtherapeutic INR in CKD patients, and this reduction in TTR in CKD patients was not mediated by poor monitoring of INR [29].

A Swedish study had shown that CKD was associated with poor TTR in AF patients on Warfarin. The decrease in TTR depends on CKD severity, and they are at a higher risk of INR instability [30]. Inoue *et al*. reported that creatinine clearance (CrCl) < 30 mL/min and TTR < 65% are independently associated with an increased rate of mortality and adverse events. Patients with lower CrCl had lower

TTR, which showed that CrCl < 30 mL/min is independently associated with a decrease in TTR < 65% [31].

3.5. Hemodialysis

Yang *et al*. identified a history of deep vein thrombosis and pulmonary embolism among dialysis patients. They reported that the proportion of dialysis patients that achieved TTR ≥ 60% was only 21.1% and had a significantly poor INR control [29]. Patients on dialysis had lower TTR and higher time out of therapeutic range, although the frequency of INR monitoring was similar among the cohort. The possible reasons were the reversibility of Warfarin, the clinical familiarity of physicians with Warfarin, and all approved DOACs being at least partially eliminated by kidneys, which may not be ideal for dialysis patients [29].

3.6. Kidney Transplant Recipient (KTR)

In this review, Yanik *et al*. demonstrated that kidney transplant recipients (KTRs) had 18.9% lower Warfarin requirements after accounting for genetic, clinical, and demographic factors. This reduction in Warfarin dose in KTRs is independent of allograft function. The overall findings of this study showed that lower Warfarin doses should be used when initiating Warfarin therapy for KTRs, and close INR monitoring is required to achieve and maintain INR within the therapeutic range [32].

3.7. Hypoalbuminemia

We found a study by Kawai *et al*., who reported that during a 1-year follow-up period, low serum albumin level was associated with an increased risk of major bleeding. Patients with a basal serum albumin level of <3.6 g/dl had a higher risk of bleeding compared to those with ≥3.6 g/dl serum albumin. This study also demonstrated that the lower the serum albumin, the higher the risk of supratherapeutic INR control (INR > 3) among patients on Warfarin therapy [33].

4. Discussion

This comprehensive review explores the multifaceted clinical risk factors that influence INR control in patients undergoing Warfarin therapy. Our findings highlight the significant impact of drug interactions, comorbidities and other clinical factors. We found that numerous drugs affect the pharmacodynamics and pharmacokinetics of Warfarin primarily via cytochrome P450 pathways, leading to an increased risk of bleeding, even without altering the INR value [34]. Warfarin is primarily metabolized by hepatic cytochrome P450 enzymes, particularly **CYP2C9**, which metabolizes the more potent S-enantiomer, and **CYP1A2** and **CYP3A4**, which are involved in R-enantiomer metabolism [35] [36]. Inhibitors of CYP2C9, such as amiodarone and fluconazole, reduce Warfarin clearance, resulting in elevated plasma levels and increased INR [4] [37]. Conversely, inducers such as rifampin and carbamazepine accelerate Warfarin metabolism, potentially lowering

INR and increasing thromboembolic risk [38]. The magnitude of these interactions varies depending on the degree of enzyme inhibition or induction and the pharmacokinetic properties of the co-administered drug. Therefore, identifying specific isoenzyme-mediated interactions is essential for tailoring Warfarin therapy and minimizing adverse events.

Martín-Pérez *et al*. supported our study findings by showing that patients consuming ≥ 10 concurrent medications with Warfarin had a higher risk of INR elevation ≥ 4 [39]. Polypharmacy is prevalent among patients on Warfarin therapy [40], with 48% - 81% of them consuming multiple interacting drugs [41]. As a result, these drug interactions often result in either subtherapeutic or supratherapeutic INR levels, increasing the risk of complications. We found that salicylates, including aspirin, compromise poor INR control and elevate bleeding risk. This finding is supported by Boyce *et al*., who reported that patients on concurrent aspirin have significantly lower TTR and an increase in minor bleeding [42]. In contrast, Okumura *et al*. and Mueller *et al*. found no significant impact of concurrent use of antiplatelet agents or aspirin therapy on TTR [43] [44]. Similarly, drugs like Amiodarone reduce the total body clearance of both (R)- and (S)-Warfarin, impairing INR stability [45]. Our review finding is supported by Saleh (2016), who reported that patients on Amiodarone required lower Warfarin doses [46].

Similarly, Macedo *et al*. found that pain medications such as NSAIDs, acetaminophen, and opioids are usually associated with poor INR control [47]. Our review findings also found that various antibiotics use, especially for respiratory infections, increases the risk of INR elevation, consistent with findings by Martín-Pérez *et al*. [39]. It is noted that proton pump inhibitors (PPIs), especially esomeprazole and omeprazole, may inhibit CYP2C19, altering Warfarin metabolism and affecting TTR [48]. Additionally, an evidence-based study by Ge *et al*. supported our review finding that herbal supplements can significantly increase INR due to interactions with Warfarin [49]. Therefore, clinicians should encourage patients to disclose any herbal supplement use.

Our review identified that multiple comorbidities contribute to subtherapeutic or supratherapeutic INR control. A study conducted in France by Rouaud *et al*. supports our review findings, demonstrating that patients' comorbidities increase the risk of poor INR control [50]. DeRemer *et al*. reinforced our review finding, showing that anemia is associated with poor INR control in patients on Warfarin therapy [51], and Martín-Pérez *et al*. reported a significant association of anemia with supratherapeutic INR control (INR ≥ 4) [39].

Comorbidities also emerged as key contributors to poor INR control. Our review findings on COPD, which causes poor iTTR, are supported by Cohen *et al*., who also associated COPD with supratherapeutic INR [52]. Martín-Pérez *et al*. reported that asthma and COPD are linked to INR elevation (INR ≥ 4), proposing that β2 agonists in patients with chronic respiratory disease may interact with Warfarin [39]. Heart failure was another risk factor identified in our review. Similarly, a cross-sectional study reported that heart failure patients are more likely

to have poor INR control [46] [53]. This may be due to hepatic congestion and impaired synthesis of clotting factor [54]. Warfarin remains the only anticoagulant option for patients with mechanical valve prosthesis [55]. Our review findings demonstrated that many of these patients have supratherapeutic INR. In contrast, Mvondo *et al*. reported good outcomes in such patients with 78.9 ± 3.7% and 93.1 ± 2.1 % of patients with mechanical valves had freedom from anticoagulation-related bleeding and neurological events, respectively [56], though other studies indicate a significantly increased bleeding risk [57] [58]. Our review found that cancer increases the risk of supratherapeutic INR, potentially due to polypharmacy, malnutrition, or liver dysfunction [59].

Michal *et al*. have demonstrated that depression is associated with lower TTR, indicating that psychological conditions such as depression and anxiety may negatively affect anticoagulation outcomes[60] [61]. Our findings also linked diabetes is associated with subtherapeutic INR; both non-insulin and insulin-dependent diabetes strongly predict poor INR control [28] [62].

CKD increases the risk of AF and atrial flutter [63], as well as bleeding, stroke, and increased mortality [64]. Our review findings on poor INR control in CKD patients are aligned with Limdi *et al*., who reported frequent supratherapeutic INR (INR ≥ 4) in non-dialysis-dependent CKD patients [65]-[67]. Reduced albumin binding in CKD increases free Warfarin activity [68]. Kleinow *et al*. supported our review finding and found that CKD patients required lower Warfarin doses to maintain the therapeutic INR range compared to those without CKD [69]. Chan *et al*. demonstrated that AF patients with hemodialysis receiving Warfarin therapy have a higher risk of new stroke compared to those not on Warfarin therapy [70]. In contrast, Kai *et al*. reported that hemodialysis patients on Warfarin therapy have a lower risk of ischemic stroke and all-cause death with no significant elevation in bleeding [71]. Our review findings have shown that hemodialysis patients on Warfarin therapy have lower TTR. The bleeding risk in hemodialysis patients also could be higher due to the frequent utilization of heparin [72].

Our review findings established that KTR patients have poor INR control and require a low Warfarin dose. A study has shown that the incidence of AF at three years of post-kidney transplantation is 7.3% [73]. KTR with AF have an increased risk of poor clinical consequences, including a high risk of allograft loss and mortality [74]. Finally, we found the association between hypoalbuminemia and poor INR control and increased bleeding risk; this study finding is also supported by Abdelhafiz *et al*., who demonstrated that one of the predictive factors of minor and major bleeding in younger patients (<75 years) is hypoalbuminemia [75].

Clinical Implications and Recommendations: This review highlights the need for personalized Warfarin therapy and vigilant INR monitoring, particularly for patients with multiple comorbidities or complex drug regimens. Based on our findings, clinicians managing patients on Warfarin therapy are advised to adopt several practical strategies to optimize INR control and reduce adverse outcomes.

First, comprehensive medication reconciliation should be routinely performed to identify potential drug-drug interactions, particularly involving antibiotics,

NSAIDs, PPIs, amiodarone, and herbal supplements. Second, individualized Warfarin dose adjustments are warranted in patients with comorbidities such as CKD, liver dysfunction, or heart failure, and lower initiation doses should be considered for those with hypoalbuminemia or undergoing hemodialysis. Third, clinicians should implement more frequent INR monitoring in high-risk groups, including patients with polypharmacy, mechanical valves, cancer, or psychiatric conditions such as depression. Finally, patient education on the importance of reporting herbal or over-the-counter drug use, maintaining consistent dietary vitamin K intake, and adhering to follow-up INR testing is critical for maintaining therapeutic anticoagulation. Incorporating these evidence-informed recommendations and strategies may improve time in therapeutic range (TTR), reduce the risk of bleeding or thromboembolic complications, and enhance the overall Warfarin safety and efficacy in real-world clinical settings.

5. Limitation

There are several potential limitations inherent in our study that should be acknowledged. First, this is an observational review primarily based on cohort studies. We did not identify any randomized controlled trials specifically evaluating clinical factors influencing INR control in Warfarin-treated patients. Therefore, some degree of bias is unavoidable, and establishing causal relationships remains challenging. Second, there was considerable heterogeneity in patient populations, including differences in hemorrhagic and thromboembolic risk profiles. Due to the lack of standardized quantitative data across studies, we were unable to perform formal heterogeneity analysis (e.g. using the I^2 statistic) for Warfarin indications or outcome measures. Therefore, findings should be interpreted with appropriate caution. Third, we acknowledge the exclusion of genetic factors, particularly VKORC1 and CYP2C9 polymorphisms, which are well-established determinants of warfarin sensitivity and metabolism. These factors were excluded because genetic testing is not universally available or routinely implemented in clinical practice, limiting their practical relevance to this review.

6. Conclusion

Warfarin remains a widely prescribed oral anticoagulant for patients with cardiovascular diseases such as AF, prosthetic heart valves, and hypercoagulable conditions. This review demonstrates that multiple clinical risk factors affect INR control, including drug interactions and comorbidities such as diabetes, CKD, malignancy, prosthetic valve, heart failure, and anemia. Patients on hemodialysis or with hypoalbuminemia are particularly vulnerable to supratherapeutic INR levels and bleeding complications. Moreover, kidney transplant recipients may require lower Warfarin doses and are also at increased risk of poor INR control. In real-world clinical settings, many patients on Warfarin experience subtherapeutic or supratherapeutic INR values. Identifying and managing these clinical risk factors before prescribing Warfarin is essential for achieving optimal anticoagulation.

Treating physicians should make prescribing decisions by carefully weighing the cardiovascular benefits of Warfarin against its bleeding risks and tailor treatment to individual patient profiles.

Funding

The authors did not receive any funds to conduct this review.

Ethics Approval

The authors did not need to apply for ethical approval to conduct this review.

Consent to Participate

This is a systematic review where the authors did not need to interact with any study respondents.

Consent for Publication

The authors are giving consent to publish their data, which are presented in this manuscript.

Availability of Data and Material

All the data are presented in the manuscript.

Authors' Contributions

All of the authors [Tharani Ramasamy (TM), Nowrozy Kamar Jahan (NKJ), Naganathan Pillai (NP), and Christina Gertrude Yap (CGY)] conceived the study. TM and NKJ conducted the screening and selection of the relevant articles. All authors participated in the data extraction under different themes, sub-themes, and risk of bias assessment. TM and NKJ drafted the manuscript, which the remaining two authors reviewed before submitting it for publication.

Acknowledgments

The authors would like to acknowledge that Monash University provides permission to use Monash University Malaysia library's extensive resources, mainly to access all required full-text articles. In addition, Monash University also allowed the authors to use EndNote software to remove duplicate articles and NVivo software to extract the data for analysis.

Conflicts of Interest

The authors declare no conflicts of interest.

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Appendix

Table A1. Detailed search strategy and search string in four electronic databases.

Main Concepts under PICO	Subject Heading Mesh [PubMed]/Emtree [Embase]	Key Words or Entry Terms [Pubmed] or Free Terms [Embase]
Population-1	• Adult [Mesh] • Adult [Emtree]	• Adult* • Grownup*
Population-2	• Patients [Mesh] • Patient [Emtree]	• Patient* • Client* • Sufferer*
Intervention	• Warfarin [Mesh] • Warfarin [Emtree]	• Apo-Warfarin • Aldocumar • Coumadin • Marevan • Warfarin Potassium • Warfarin Sodium • Coumadine
Outcome-1	• Risk Factors [Mesh] • Risk Factor [Emtree]	• Risk Factor*
Outcome-2	• International Normalized Ratio [Mesh] • International Normalized Ratio [Emtree]	• International Normalized Ratio* • INR • International Normalised Ratio • International Normalized Ratio

Complete Search String in PubMed	
Populations 1 and 2	((((((adult [MeSH Terms]) OR (adult* [Title/Abstract])) OR (grownup* [Title/Abstract])) AND (patients [MeSH Terms])) OR (patient* [Title/Abstract])) OR (client* [Title/Abstract])) OR (sufferer* [Title/Abstract])
Intervention	("Warfarin" [Mesh]) OR (Apo-Warfarin [Title/Abstract] OR Aldocumar [Title/Abstract] OR Coumadin [Title/Abstract] OR Marevan [Title/Abstract] OR Warfarin Potassium [Title/Abstract] OR Warfarin Sodium [Title/Abstract] OR Coumadine [Title/Abstract])
Outcomes 1 and 2	(("Risk Factors" [Mesh]) OR (risk factor* [Title/Abstract])) AND (("International Normalized Ratio" [Mesh]) OR ("International Normalized Ratio*" [Title/Abstract] OR INR [Title/Abstract] OR "International Normalised Ratio" [Title/Abstract] OR "International Normalized Ratio" [Title/Abstract]))
Complete search string without filters [728 papers]	((((((((adult [MeSH Terms]) OR (adult* [Title/Abstract])) OR (grownup* [Title/Abstract])) AND (patients [MeSH Terms])) OR (patient* [Title/Abstract])) OR (client* [Title/Abstract])) OR (sufferer* [Title/Abstract])) AND (("Warfarin" [Mesh]) OR (Apo-Warfarin [Title/Abstract] OR Aldocumar [Title/Abstract] OR Coumadin [Title/Abstract] OR Marevan [Title/Abstract] OR Warfarin Potassium [Title/Abstract] OR Warfarin Sodium [Title/Abstract] OR Coumadine [Title/Abstract]))) AND ((("Risk Factors" [Mesh]) OR (risk factor* [Title/Abstract])) AND (("International Normalized Ratio" [Mesh]) OR ("International Normalized Ratio*" [Title/Abstract] OR INR [Title/Abstract] OR "International Normalised Ratio" [Title/Abstract] OR "International Normalized Ratio" [Title/Abstract])))

Continued

Complete Search String in Embase via Elsevier Platform	
Populations 1 and 2	('adult'/exp OR 'adult' OR 'adults' OR 'grownup' OR 'grownups' OR adult:ti,ab) AND ('patient'/exp OR 'patient':ti,ab,kw OR 'patients':ti,ab,kw OR 'sufferer':ti,ab,kw OR 'sufferers':ti,ab,kw)
Intervention	('warfarin'/exp OR '1 (4' hydroxy 3' coumarinyl) 1 phenyl 3 butanone':ti,ab,kw OR '3 (alpha acetonylbenzyl) 4 hydroxycoumarin':ti,ab,kw OR '3 acetonylbenzonyl 4 hydroxy coumarinedimethylaminoethanol':ti,ab,kw OR '3 alpha phenyl beta acetylethyl 4 hydroxycoumarin':ti,ab,kw OR 'acetonylbenzylhydroxycoumarin':ti,ab,kw OR 'adoisine':ti,ab,kw OR 'aldocumar':ti,ab,kw OR 'alpha acetonylbenzyl 4 hydroxycoumarin dimethylaminoethanol':ti,ab,kw OR 'antrombin k':ti,ab,kw OR 'athrombin':ti,ab,kw OR 'athrombin k':ti,ab,kw OR 'athrombin-k':ti,ab,kw OR 'athrombine k':ti,ab,kw OR 'athrombinek':ti,ab,kw OR 'befarin':ti,ab,kw OR 'carfin':ti,ab,kw OR 'circuvit':ti,ab,kw OR 'compound 42':ti,ab,kw OR 'coumadan':ti,ab,kw OR 'coumadan sodico':ti,ab,kw OR 'coumadin':ti,ab,kw OR 'coumadin sodium':ti,ab,kw OR 'coumadine':ti,ab,kw OR 'coumafene':ti,ab,kw OR 'coumaphene':ti,ab,kw OR 'd warfarin':ti,ab,kw OR 'dagonal':ti,ab,kw OR 'dextro warfarin':ti,ab,kw OR 'farin':ti,ab,kw OR 'jantoven':ti,ab,kw OR 'kumatox':ti,ab,kw OR 'l warfarin':ti,ab,kw OR 'levo warfarin':ti,ab,kw OR 'maforan':ti,ab,kw OR 'marevan':ti,ab,kw OR 'orfarin':ti,ab,kw OR 'panwarfarin':ti,ab,kw OR 'panwarfin':ti,ab,kw OR 'potassium warfarin':ti,ab,kw OR 'prothromadin':ti,ab,kw OR 'r warfarin':ti,ab,kw OR 'simarc-2':ti,ab,kw OR 'sodium warfarin':ti,ab,kw OR 'sodium warfarinum':ti,ab,kw OR 'sofarin':ti,ab,kw OR 'tintorane':ti,ab,kw OR 'uniwarfin':ti,ab,kw OR 'wafarin':ti,ab,kw OR 'waran':ti,ab,kw OR 'warf compound 42':ti,ab,kw OR 'warfar':ti,ab,kw OR 'warfarin':ti,ab,kw OR 'warfarin 2 (dimethylamino) ethanol':ti,ab,kw OR 'warfarin potassium':ti,ab,kw OR 'warfarin sodium':ti,ab,kw OR 'warfarine':ti,ab,kw OR 'warfarinum sodium':ti,ab,kw OR 'warfil 5':ti,ab,kw OR 'warfilone':ti,ab,kw OR 'warnerin':ti,ab,kw)
Outcomes 1 and 2	('international normalized ratio'/exp OR 'inr':ti,ab,kw OR 'international normalised ratio':ti,ab,kw OR 'international normalized ratio':ti,ab,kw) AND ('risk factor'/exp OR 'relative risk':ti,ab,kw OR 'risk factor':ti,ab,kw OR 'risk factors':ti,ab,kw)
Complete string without filters [1179 papers]	('adult'/exp OR 'adult' OR 'adults' OR 'grownup' OR 'grownups' OR adult:ti,ab) AND ('patient'/exp OR 'patient':ti,ab,kw OR 'patients':ti,ab,kw OR 'sufferer':ti,ab,kw OR 'sufferers':ti,ab,kw) AND ('warfarin'/exp OR '1 (4' hydroxy 3' coumarinyl) 1 phenyl 3 butanone':ti,ab,kw OR '3 (alpha acetonylbenzyl) 4 hydroxycoumarin':ti,ab,kw OR '3 acetonylbenzonyl 4 hydroxy coumarinedimethylaminoethanol':ti,ab,kw OR '3 alpha phenyl beta acetylethyl 4 hydroxycoumarin':ti,ab,kw OR 'acetonylbenzylhydroxycoumarin':ti,ab,kw OR 'adoisine':ti,ab,kw OR 'aldocumar':ti,ab,kw OR 'alpha acetonylbenzyl 4 hydroxycoumarin dimethylaminoethanol':ti,ab,kw OR 'antrombin k':ti,ab,kw OR 'athrombin':ti,ab,kw OR 'athrombin k':ti,ab,kw OR 'athrombin-k':ti,ab,kw OR 'athrombine k':ti,ab,kw OR 'athrombinek':ti,ab,kw OR 'befarin':ti,ab,kw OR 'carfin':ti,ab,kw OR 'circuvit':ti,ab,kw OR 'compound 42':ti,ab,kw OR 'coumadan':ti,ab,kw OR 'coumadan sodico':ti,ab,kw OR 'coumadin':ti,ab,kw OR 'coumadin sodium':ti,ab,kw OR 'coumadine':ti,ab,kw OR 'coumafene':ti,ab,kw OR 'coumaphene':ti,ab,kw OR 'd warfarin':ti,ab,kw OR 'dagonal':ti,ab,kw OR 'dextro warfarin':ti,ab,kw OR 'farin':ti,ab,kw OR 'jantoven':ti,ab,kw OR 'kumatox':ti,ab,kw OR 'l warfarin':ti,ab,kw OR 'levo warfarin':ti,ab,kw OR 'maforan':ti,ab,kw OR 'marevan':ti,ab,kw OR 'orfarin':ti,ab,kw OR 'panwarfarin':ti,ab,kw OR 'panwarfin':ti,ab,kw OR 'potassium warfarin':ti,ab,kw OR 'prothromadin':ti,ab,kw OR 'r warfarin':ti,ab,kw OR 'simarc-2':ti,ab,kw OR 'sodium warfarin':ti,ab,kw OR 'sodium warfarinum':ti,ab,kw OR 'sofarin':ti,ab,kw OR 'tintorane':ti,ab,kw OR 'uniwarfin':ti,ab,kw OR 'wafarin':ti,ab,kw OR 'waran':ti,ab,kw OR 'warf compound 42':ti,ab,kw OR 'warfar':ti,ab,kw OR 'warfarin':ti,ab,kw OR 'warfarin 2 (dimethylamino) ethanol':ti,ab,kw OR 'warfarin potassium':ti,ab,kw OR 'warfarin sodium':ti,ab,kw OR 'warfarine':ti,ab,kw OR 'warfarinum sodium':ti,ab,kw OR 'warfil 5':ti,ab,kw OR 'warfilone':ti,ab,kw OR 'warnerin':ti,ab,kw) AND ('international normalized ratio'/exp OR 'inr':ti,ab,kw OR 'international normalised ratio':ti,ab,kw OR 'international normalized ratio':ti,ab,kw) AND ('risk factor'/exp OR 'relative risk':ti,ab,kw OR 'risk factor':ti,ab,kw OR 'risk factors':ti,ab,kw)

Continued

Complete search string with filters: English, adult 18 years and above, Year 2016-2020 [476 papers]	('adult'/exp OR 'adult' OR 'adults' OR 'grownup' OR 'grownups' OR adult:ti,ab) AND ('patient'/exp OR 'patient':ti,ab,kw OR 'patients':ti,ab,kw OR 'sufferer':ti,ab,kw OR 'sufferers':ti,ab,kw) AND ('warfarin'/exp OR '1 (4' hydroxy 3' coumarinyl) 1 phenyl 3 butanone':ti,ab,kw OR '3 (alpha acetonylbenzyl) 4 hydroxycoumarin':ti,ab,kw OR '3 acetonylbenzonyl 4 hydroxy coumarinedimethylaminoethanol':ti,ab,kw OR '3 alpha phenyl beta acetylethyl 4 hydroxycoumarin':ti,ab,kw OR 'acetonylbenzylhydroxycoumarin':ti,ab,kw OR 'adoisine':ti,ab,kw OR 'aldocumar':ti,ab,kw OR 'alpha acetonylbenzyl 4 hydroxycoumarin dimethylaminoethanol':ti,ab,kw OR 'antrombin k':ti,ab,kw OR 'athrombin':ti,ab,kw OR 'athrombin k':ti,ab,kw OR 'athrombin-k':ti,ab,kw OR 'athrombine k':ti,ab,kw OR 'athrombinek':ti,ab,kw OR 'befarin':ti,ab,kw OR 'carfin':ti,ab,kw OR 'circuvit':ti,ab,kw OR 'compound 42':ti,ab,kw OR 'coumadan':ti,ab,kw OR 'coumadan sodico':ti,ab,kw OR 'coumadin':ti,ab,kw OR 'coumadin sodium':ti,ab,kw OR 'coumadine':ti,ab,kw OR 'coumafene':ti,ab,kw OR 'coumaphene':ti,ab,kw OR 'd warfarin':ti,ab,kw OR 'dagonal':ti,ab,kw OR 'dextro warfarin':ti,ab,kw OR 'farin':ti,ab,kw OR 'jantoven':ti,ab,kw OR 'kumatox':ti,ab,kw OR 'l warfarin':ti,ab,kw OR 'levo warfarin':ti,ab,kw OR 'maforan':ti,ab,kw OR 'marevan':ti,ab,kw OR 'orfarin':ti,ab,kw OR 'panwarfarin':ti,ab,kw OR 'panwarfin':ti,ab,kw OR 'potassium warfarin':ti,ab,kw OR 'prothromadin':ti,ab,kw OR 'r warfarin':ti,ab,kw OR 'simarc-2':ti,ab,kw OR 'sodium warfarin':ti,ab,kw OR 'sodium warfarinum':ti,ab,kw OR 'sofarin':ti,ab,kw OR 'tintorane':ti,ab,kw OR 'uniwarfin':ti,ab,kw OR 'wafarin':ti,ab,kw OR 'waran':ti,ab,kw OR 'warf compound 42':ti,ab,kw OR 'warfar':ti,ab,kw OR 'warfarin':ti,ab,kw OR 'warfarin 2 (dimethylamino) ethanol':ti,ab,kw OR 'warfarin potassium':ti,ab,kw OR 'warfarin sodium':ti,ab,kw OR 'warfarine':ti,ab,kw OR 'warfarinum sodium':ti,ab,kw OR 'warfil 5':ti,ab,kw OR 'warfilone':ti,ab,kw OR 'warnerin':ti,ab,kw) AND ('international normalized ratio'/exp OR 'inr':ti,ab,kw OR 'international normalised ratio':ti,ab,kw OR 'international normalized ratio':ti,ab,kw) AND ('risk factor'/exp OR 'relative risk':ti,ab,kw OR 'risk factor':ti,ab,kw OR 'risk factors':ti,ab,kw) AND [english]/lim AND [humans]/lim AND ([adult]/lim OR [young adult]/lim OR [middle aged]/lim OR [aged]/lim OR [very elderly]/lim) AND [2016-2020]/py
Complete Search String in SCOPUS	
Populations 1 and 2	(TITLE-ABS-KEY (*adult** OR *grownup**) **AND** TITLE-ABS-KEY (*patient** OR *client** OR *sufferer**))
Intervention	TITLE-ABS-KEY (*warfarin* OR "*apo-warfarin*" OR *aldocumar* OR *coumadin* OR "*warfarin potassium*" OR "*warfarin sodium*" OR *coumadine*)
Outcomes 1 and 2	TITLE-ABS-KEY ("*risk factor**") AND TITLE-ABS-KEY (INR OR "*International Normalised Ratio**" OR "*International Normalized Ratio**"))
Complete search string without filters [1312 papers]	(TITLE-ABS-KEY (*adult** OR *grownup**) AND TITLE-ABS-KEY (*patient** OR *client** OR *sufferer**) AND TITLE-ABS-KEY (*warfarin* OR "*Apo-Warfarin*" OR *aldocumar* OR *coumadin* OR "*Warfarin Potassium*" OR "*Warfarin Sodium*" OR *coumadine*) AND TITLE-ABS-KEY ("*risk factor**") AND TITLE-ABS-KEY (INR OR "*International Normalised Ratio**" OR "*International Normalized Ratio**"))
Complete Search String in Web of Science	
Populations 1 and 2	adult* OR grownup* (Topic) and patient* OR client* OR sufferer* (Topic)
Intervention	warfarin OR "apo-warfarin" OR aldosugar OR coumadin OR "warfarin potassium" OR "warfarin sodium" OR coumarine (Topic)
Outcomes 1 and 2	"risk factor*" (Topic) and INR OR "International Normalised Ratio*" OR "International Normalized Ratio*"

Continued

Complete search string without filters [52 papers]	adult* OR grownup* (Topic) and patient* OR client* OR sufferer* (Topic) and warfarin OR "apo-warfarin" OR aldosugar OR coumadin OR "warfarin potassium" OR "warfarin sodium" OR coumarine (Topic) and "risk factor*" (Topic) and INR OR "International Normalised Ratio*" OR "International Normalized Ratio*" (Topic)
Complete search string with filters; English; human, Year 2016-2020 [18 papers]	adult* OR grownup* (Topic) and patient* OR client* OR sufferer* (Topic) and warfarin OR "apo-warfarin" OR aldosugar OR coumadin OR "warfarin potassium" OR "warfarin sodium" OR coumarine (Topic) and "risk factor*" (Topic) and INR OR "International Normalised Ratio*" OR "International Normalized Ratio*" (Topic) and 2020 or 2019 or 2018 or 2017 or 2016 (Publication Years) and English (Languages) and 2020 or 2019 or 2018 or 2017 or 2016 (Publication Years)

*The asterisk symbol, commonly known as a wildcard, is used in keyword searches to expand results by matching different variations of a root word.

Checklist A1. PRISMA 2020 checklist.

Section and topic	Item #	Checklist item	Location where item is reported
		TITLE	
Title	1	Identify the report as a systematic review.	1
		ABSTRACT	
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	1
		INTRODUCTION	
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	3
		METHODS	
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Table A1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	4
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	5
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	NA
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	NA
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	NA
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	NA

Continued

	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	NA
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	NA
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	NA
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	NA
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	NA
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	NA
		RESULTS	
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	7 - 9
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	7 - 9
Study characteristics	17	Cite each included study and present its characteristics.	7 - 9
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	7 - 9
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	7 - 9
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	7 - 9
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	7 - 9
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	7 - 9
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	7 - 9
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	7 - 9
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	7 - 9
		DISCUSSION	
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	9 - 12
	23b	Discuss any limitations of the evidence included in the review.	12
	23c	Discuss any limitations of the review processes used.	12
	23d	Discuss implications of the results for practice, policy, and future research.	9 - 12
		OTHER INFORMATION	
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	NA
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	NA
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA

Continued

Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	NA
Competing interests	26	Declare any competing interests of review authors.	14
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Table 2

NA = Not Applicable.

List of Abbreviations

AF	atrial fibrillation
CI	confidence interval
CHD	congestive heart disease
CKD	chronic kidney disease
COPD	chronic obstructive pulmonary disease
CrCl	creatinine clearance
DOAC	direct oral anticoagulants
eGFR	estimated glomerular filtration rate
INR	international normalized ratio
iTTR	individual time in therapeutic range
KTR	kidney transplant recipient
Mesh	medical subject headings
NOAC	novel oral anticoagulant
NOS	Newcastle-Ottawa Scale
NSAIDs	nonsteroidal anti-inflammatory drugs
OR	odds ratio
PAD	peripheral arterial disease
PICO	population, intervention, comparison, outcome
PPI	proton pump inhibitor
PRISMA	preferred reporting items for the systematic review and meta-analysis
TTR	Time in therapeutic range
VKORC1	vitamin K epoxide reductase complex 1
VTE	venous thromboembolism