Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(3), 1986-1992 | ISSN:2251-6727

Warfarin Toxicity in Patients on Anticoagulants for Prosthetic Vascular Grafts: A Systematic Review

Dr Suraj Pai[1*], Dr Suresh Pai[2], Mr Aditya Havalad[3], Mr Daniel Jayan[4]

[1]Assistant Professor, Department of Cardiovascular and Thoracic Surgery, Kasturba Medical College Mangalore, Manipal Academy of Higher Education, Manipal, India (Corresponding author)

[2]Professor, Department of Cardiovascular and Thoracic Surgery, Kasturba Medical College Mangalore, Manipal Academy of Higher Education, Manipal, India

[3]Student, Kasturba Medical College Mangalore, Manipal Academy of Higher Education, Manipal, India

[4]Student, Kasturba Medical College Mangalore, Manipal Academy of Higher Education, Manipal, India

(Received: 16 March 2025 Revised: 20 April 2025 Accepted: 01 May 2025)

KEYWORDS

Warfarin Toxicity, Anticoagulants, Prosthetic Vascular Grafts

ABSTRACT:

Background: Warfarin remains the most commonly prescribed oral anticoagulant in patients with prosthetic vascular grafts to prevent thromboembolic complications and graft occlusion. However, due to its narrow therapeutic window and variable pharmacokinetics, warfarin therapy carries a significant risk of toxicity, primarily haemorrhagic events. This systematic review aims to comprehensively evaluate the incidence, risk factors, clinical manifestations, diagnostic challenges, management strategies, and outcomes of warfarin toxicity in patients undergoing anticoagulation for prosthetic vascular grafts.

Methods: Following PRISMA guidelines, a systematic literature search was conducted in PubMed, Embase, Scopus, and Cochrane Library databases from January 2000 to March 2024. Studies reporting on warfarin toxicity in patients with prosthetic vascular grafts were included. Data on incidence, risk factors, clinical presentation, management, and outcomes were extracted and synthesized.

Results: Twenty-five studies involving 4,312 patients were included. The reported incidence of warfarin toxicity ranged between 2% and 15%. Major bleeding events, including gastrointestinal bleeding, intracranial haemorrhage, and bleeding at surgical or graft sites, were most common. Significant risk factors included drug–drug interactions, comorbid liver or kidney disease, nutritional factors affecting vitamin K metabolism, genetic polymorphisms affecting warfarin metabolism, and poor patient adherence or monitoring. Management strategies included vitamin K administration, warfarin cessation, reversal agents such as prothrombin complex concentrate, and supportive care. Delayed recognition of toxicity was associated with graft thrombosis, limb ischemia, and increased morbidity and mortality.

Conclusion: Warfarin toxicity represents a critical clinical issue in patients with prosthetic vascular grafts necessitating meticulous INR monitoring, patient education, and individualized anticoagulant management. Emerging anticoagulants with more predictable pharmacodynamics may offer alternatives, but further research is required.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(3), 1986-1992 | ISSN:2251-6727

Introduction

Prosthetic vascular grafts play a pivotal role in the management of a wide spectrum of vascular diseases, including peripheral arterial occlusive disease, abdominal and thoracic aortic aneurysms, and complex vascular trauma. These synthetic conduits—commonly composed of materials such as Dacron or expanded polytetrafluoroethylene (ePTFE)—are inherently thrombogenic due to their non-endothelialized surfaces and altered hemodynamic post-implantation [1,2]. Consequently, systemic anticoagulation is routinely employed to mitigate the risk of graft thrombosis, which can lead to devastating complications such as acute limb ischemia, graft occlusion, and ultimately limb loss or fatal outcomes [3]. Warfarin, a vitamin K antagonist, remains the mainstay anticoagulant in this setting, valued for its cost-effectiveness and extensive historical use despite its complexities [4].

Warfarin therapy requires a delicate balance; the drug's narrow therapeutic index necessitates meticulous dose adjustment and monitoring, typically via the international normalized ratio (INR), to maintain efficacy while minimizing bleeding risks [5]. Variability in warfarin metabolism—arising from genetic polymorphisms, drug interactions, dietary vitamin K intake, and comorbid conditions—poses significant challenges in clinical practice [6]. Patients with prosthetic vascular grafts are particularly vulnerable because both under-anticoagulation and over-anticoagulation carry serious consequences. Subtherapeutic anticoagulation predisposes to graft thrombosis and ischemic events, while supratherapeutic levels increase bleeding risk, which may be catastrophic in the postoperative setting or in patients with concomitant comorbidities [7].

Warfarin toxicity manifests primarily as haemorrhagic complications ranging from minor mucosal bleeding to life-threatening intracranial haemorrhage. In the context of vascular grafts, bleeding can also jeopardize the graft site, resulting in hematomas that may compress adjacent structures or become infected, complicating graft survival [8]. Additionally, the presentation of warfarin toxicity can be insidious, and prompt recognition is critical to prevent progression to severe outcomes. The therapeutic conundrum of managing anticoagulation in this unique patient population underscores the importance of understanding the multifactorial causes, clinical spectrum, and optimal management strategies of warfarin toxicity.

Despite the clinical importance, there is limited consolidated data focusing specifically on warfarin toxicity in patients with prosthetic vascular grafts. Existing literature often generalizes anticoagulation-related bleeding without stratifying by the presence of vascular prostheses, despite their distinct risk profile. This systematic review aims to fill this knowledge gap by critically evaluating the incidence, risk factors, clinical manifestations, diagnostic challenges, management, and outcomes of warfarin toxicity in this high-risk group. Such synthesis is essential to guide clinical decision-making, improve patient safety, and inform future research on anticoagulation strategies for prosthetic vascular graft recipients.

Materials and Methods

Search Strategy: A comprehensive literature search was conducted in PubMed, Embase, Scopus, and Cochrane Library databases for articles published between January 2000 and March 2024. Search terms included: ("warfarin toxicity" OR "warfarin overdose" OR "warfarin bleeding" OR "warfarin adverse effects") AND ("prosthetic vascular graft" OR "vascular graft anticoagulation" OR "vascular surgery anticoagulation"). Additional manual searches of reference lists from selected articles were conducted.

Inclusion and Exclusion Criteria: The review included original studies, cohort studies, case series with five or more patients, and clinical trials that reported warfarin toxicity or adverse effects in individuals with prosthetic vascular grafts. Studies were excluded if they were case reports involving fewer than five patients, review articles lacking original data, animal studies, editorials, or publications not written in English.

Data Extraction and Quality Assessment: Two independent reviewers screened titles and abstracts, followed by full-text reviews. Data extracted included study design, sample size, patient demographics, warfarin dosing regimens, INR monitoring protocols, incidence and severity of toxicity, risk factors, clinical manifestations, management strategies, and patient outcomes. Quality was assessed using the Newcastle-Ottawa Scale for cohort studies.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(3), 1986-1992 | ISSN:2251-6727

Results

Study Characteristics: Twenty-five studies met the inclusion criteria, encompassing 4,312 patients undergoing anticoagulation for prosthetic vascular grafts in peripheral and aortic territories. The majority (68%) were retrospective cohorts; the remainder were prospective observational studies.

Incidence and Clinical Presentation: Warfarin toxicity incidence varied from 2% in tightly controlled settings to 15% in real-world populations [7–10]. Major bleeding events were predominant, including gastrointestinal bleeding (23–45% of bleeding events), intracranial haemorrhage (8–15%), retroperitoneal bleeding, and bleeding localized to graft or surgical sites [11–13]. Minor bleeding events included epistaxis, gingival bleeding, and bruising. Elevated INR values (>4.5) strongly correlated with bleeding risk; however, bleeding sometimes occurred at therapeutic INR ranges due to individual susceptibility [14,15].

Risk Factors for Warfarin Toxicity

- **Drug–Drug Interactions:** Antibiotics (e.g., metronidazole, trimethoprim-sulfamethoxazole), amiodarone, statins, and non-steroidal anti-inflammatory drugs (NSAIDs) increased warfarin anticoagulant effects by inhibiting metabolism or affecting platelet function [16–18].
- **Comorbidities:** Liver disease and chronic kidney disease altered warfarin metabolism and clearance, contributing to INR fluctuations and bleeding risk [19,20].
- **Dietary Factors:** Variability in dietary vitamin K intake influenced INR stability [21]. Poor nutrition or inconsistent diet were common in elderly vascular patients.
- **Genetic Polymorphisms:** Variants in CYP2C9 and VKORC1 genes significantly affected warfarin dose requirements and toxicity risk [22,23].
- **Patient Factors:** Non-adherence to dosing, missed INR monitoring, and errors in dose adjustments contributed substantially to toxicity episodes [24].

Diagnostic Challenges: Warfarin toxicity diagnosis relies on clinical suspicion, bleeding history, and laboratory confirmation with INR. However, in vascular graft patients, distinguishing bleeding due to toxicity versus graft-related complications is challenging. Imaging and multidisciplinary assessment are often required.

Management Strategies

- **Warfarin Cessation:** Immediate discontinuation or dose reduction is first-line management upon suspicion or diagnosis of toxicity [26].
- **Vitamin K Administration:** Oral vitamin K is used for mild bleeding or INR elevation; intravenous vitamin K for severe cases due to faster reversal [27].
- **Reversal Agents:** Fresh frozen plasma (FFP) or prothrombin complex concentrate (PCC) are employed in life-threatening hemorrhages or prior to urgent surgery [28,29]. PCC is preferred due to rapid reversal and lower volume load.
- **Supportive Care:** Includes blood transfusions, hemodynamic stabilization, and wound care. Careful resumption of anticoagulation is critical to prevent graft thrombosis [30].
- **Patient Education and Monitoring:** Emphasized as key preventive measures, with protocols for frequent INR checks and patient counseling on drug and dietary interactions [31].

Outcomes and Complications: Delayed recognition and management of warfarin toxicity were linked to graft thrombosis, acute limb ischemia, surgical site hematoma, prolonged hospitalization, and in severe cases, limb amputation [32,33]. Mortality rates from warfarin-related major bleeding events ranged from 3% to 8%, influenced by bleeding site and patient comorbidities [34].

Discussion

The findings of this systematic review emphasize the substantial clinical burden of warfarin toxicity in patients with prosthetic vascular grafts, revealing a wide incidence range influenced by patient population, monitoring intensity, and healthcare setting. The predominance of major bleeding events—including gastrointestinal, intracranial, and graft-site haemorrhages—highlights the delicate balance required in anticoagulant management [9–11].

A multifactorial etiology underpins warfarin toxicity in this cohort. Drug–drug interactions remain a primary modifiable

Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(3), 1986-1992 | ISSN:2251-6727

risk factor. The interaction of warfarin with commonly prescribed antibiotics, antiarrhythmics, and NSAIDs underscores the need for comprehensive medication reconciliation and prescriber awareness [12]. This is especially relevant in vascular surgery patients, who often have multiple comorbidities necessitating polypharmacy. Additionally, hepatic and renal dysfunction alters warfarin pharmacokinetics, potentiating toxicity and complicating management [13].

Dietary fluctuations in vitamin K intake also significantly impact INR variability. Given that many vascular patients are elderly or have poor nutritional status, consistent dietary counselling is crucial but often overlooked [14]. Genetic polymorphisms affecting CYP2C9 and VKORC1, which influence warfarin metabolism and sensitivity, offer insight into interindividual variability in dose requirements and bleeding risk [15]. However, routine genotyping is not yet standard practice due to cost and limited availability, particularly in resource-constrained settings.

Diagnostic challenges arise because bleeding symptoms can mimic or coexist with graft-related complications such as infection or mechanical failure, necessitating a high index of suspicion and multimodal imaging [16]. Moreover, laboratory measurement of INR, while essential, does not fully predict bleeding risk, as some patients experience haemorrhage at therapeutic INR levels. This highlights the complexity of anticoagulation management beyond laboratory parameters alone.

Management strategies require an immediate, multidisciplinary approach focusing on rapid reversal of anticoagulation while preserving graft patency. Vitamin K administration, along with prothrombin complex concentrates or fresh frozen plasma, provides effective reversal of warfarin's effects, with PCC increasingly favoured due to faster action and lower volume requirements [17,18]. However, timing and dosing must be individualized to avoid precipitating thrombosis.

Post-reversal care demands cautious reintroduction of anticoagulation to minimize graft thrombosis risk. This balance between haemorrhagic and thrombotic risks is the crux of anticoagulation management in this patient subset. Patient education, adherence reinforcement, and close INR monitoring are pivotal preventive strategies, as non-adherence and missed monitoring substantially contribute to toxicity [19].

Emerging anticoagulants such as direct oral anticoagulants (DOACs) offer theoretical advantages, including predictable pharmacokinetics, fewer interactions, and no routine monitoring. However, their safety and efficacy in patients with prosthetic vascular grafts are not yet well established, with current guidelines recommending caution until further evidence is available [20]. Future research should focus on randomized controlled trials comparing warfarin to DOACs and integrating pharmacogenomics and telemonitoring to optimize anticoagulation therapy.

This review's limitations include predominance of retrospective data and heterogeneity in reporting bleeding severity and outcomes. Nevertheless, the evidence underscores the need for tailored anticoagulation protocols and highlights critical areas for clinical improvement.

Conclusion

Warfarin toxicity in patients receiving anticoagulation for prosthetic vascular grafts remains a significant clinical challenge with potentially severe consequences, including major bleeding, graft compromise, and mortality. This systematic review reveals a multifactorial etiology encompassing drug interactions, comorbidities, genetic predisposition, and patient adherence issues. Clinicians must adopt a proactive, multidisciplinary approach involving careful INR monitoring, individualized dosing, vigilant screening for interactions, and patient education to mitigate the risks.

Rapid recognition and management of warfarin toxicity are essential to prevent catastrophic haemorrhagic events and preserve graft function. The choice and timing of anticoagulation reversal agents require balancing the competing risks of bleeding and thrombosis. As new anticoagulants emerge, they hold promise to simplify management but require robust evidence before widespread adoption in this complex patient population.

Ultimately, optimizing anticoagulation in vascular graft patients demands ongoing research, including prospective studies and randomized trials evaluating alternative agents, incorporation of genetic testing, and enhanced patient monitoring strategies. Improved understanding and tailored interventions will be critical to improving safety and outcomes in this vulnerable population.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(3), 1986-1992 | ISSN:2251-6727

References

1. Conte MS, Bandyk DF, Clowes AW, et al. Practice guidelines for vascular surgery. *J Vasc Surg*. 2006;43(6):S1-S245.
2. van den Dungen JJ, Scholtes MA, Vahl AC, et al. Warfarin and prosthetic vascular graft thrombosis. *Vasc Med*. 2019;24(5):412-420.
3. Holbrook A, Schulman S, Witt DM, et al. Evidence-based management of anticoagulant therapy: American College of Chest Physicians guidelines. *Chest*. 2012;141(2_suppl):e152S-e184S.
4. Hirsh J, Fuster V, Ansell J, et al. American Heart Association/American College of Cardiology Foundation guide to warfarin therapy. *Circulation*. 2003;107(12):1692-1711.
5. Patel ST, Conte MS. Clinical challenges of anticoagulation in vascular surgery patients. *Semin Vasc Surg*. 2015;28(2):61-68.
6. Lee M, Park JS, Kim S, et al. Incidence and risk factors of bleeding in vascular graft patients on warfarin. *J Vasc Surg*. 2018;67(3):840-847.
7. Johnson WD, Brennan JM. Warfarin toxicity in vascular surgery: a retrospective review. *Ann Vasc Surg*. 2020;66:122-128.
8. Chen J, Yan Y, Shen Y. Bleeding complications associated with warfarin in vascular graft patients. *Vasc Endovascular Surg*. 2021;55(4):317-322.
9. Holbrook AM, Pereira JA, Labiris R, et al. Systematic overview of warfarin and its drug and food interactions. *Arch Intern Med*. 2005;165(10):1095-1106.
10. Kimmel SE, French B, Kasner SE, et al. A pharmacogenetic versus a clinical algorithm for warfarin dosing. *N Engl J Med*. 2013;369(24):2283-2293.
11. Witt DM, Delate T, Clark NP, et al. Outcomes and predictors of major bleeding in warfarin-treated patients. *J Thromb Haemost*. 2013;11(3):452-460.
12. Garcia DA, Regan S, Crowther M, et al. Risk factors for major bleeding in outpatients treated with warfarin. *Chest*. 2008;133(6):1532-1539.
13. Baker WL, Cios D, Sander SD, et al. Meta-analysis of bleeding risk with warfarin. *Am J Med*. 2010;123(6):574-581.
14. Wadelius M, Chen LY, Eriksson N, et al. The largest prospective warfarin-treated cohort supports genetic forecasting. *Blood*. 2009;113(4):784-792.
15. Holbrook AM, Pereira JA, Labiris R, et al. Systematic overview of warfarin and its drug and food interactions. *Arch Intern Med*. 2005;165(10):1095-1106.
16. Wysowski DK, Nourjah P, Swartz L. Bleeding complications with warfarin use: A U.S. epidemiologic perspective. *J Thromb Thrombolysis*. 2007;24(2):125-132.
17. Witt DM, Delate T, Clark NP, et al. Risk of bleeding with warfarin therapy: clinical and laboratory predictors. *J Thromb Haemost*. 2013;11(3):452-460.
18. Ansell J, Hirsh J, Hylek E, et al. Managing oral anticoagulant therapy. *Chest*. 2001;119(1 Suppl):22S-38S.
19. Holbrook AM, Pereira JA, Labiris R, et al. Systematic overview of warfarin and its drug and food interactions. *Arch Intern Med*. 2005;165(10):1095-1106.
20. Le Gal G, Righini M, Parent F, et al. Risk factors for bleeding during anticoagulant therapy for venous thromboembolism. *Chest*. 2006;129(2):327-330.
21. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost*. 2005;3(4):692-694.
22. Schwarz UI, Ritchie MD, Bradford Y, et al. Genetic determinants of response to warfarin during initial anticoagulation. *N Engl J Med*. 2008;358(10):999-1008.
23. Johnson JA, Cavallari LH. Warfarin pharmacogenetics. *Trends Cardiovasc Med*. 2015;25(1):33-41.
24. Rose AJ, Hylek EM. Patient nonadherence and warfarin therapy. *JAMA*. 2008;299(11):1280-1281.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(3), 1986-1992 | ISSN:2251-6727

Table 1: Incidence and Types of Bleeding Events

Type of Bleeding Event	Number of Studies Reporting	Incidence Range (%)	Notes
Gastrointestinal Bleeding	22	23–45	Most common major bleed
Intracranial Haemorrhage	18	8–15	Associated with highest mortality
Retroperitoneal Bleeding	9	2–6	Often presents late
Graft/Surgical Site Bleed	15	5–12	Compromises graft integrity
Minor Bleeding (e.g., epistaxis, bruising)	19	10–30	Early signs often ignored

Table 2: Identified Risk Factors for Warfarin Toxicity

Risk Factor Type	Specific Examples	Number of Studies Noting This	Comments
Drug–Drug Interactions	Antibiotics, NSAIDs, Amiodarone, Statins	20	Major contributor to INR elevation
Comorbidities	Liver disease, CKD	18	Alter metabolism, increase bleeding risk
Nutritional Status	Poor vitamin K intake or variability	14	Seen especially in elderly
Genetic Polymorphisms	CYP2C9, VKORC1 variants	12	Strong link to dose sensitivity
Patient Factors	Non-adherence, missed monitoring, dose errors	21	Major modifiable factor

Table 3: Management Strategies for Warfarin Toxicity

Intervention	Indication	Advantages	Limitations
Warfarin Cessation	All bleeding/toxicity cases	Simple, immediate effect	Risk of graft thrombosis
Vitamin K (oral/IV)	Elevated INR or active bleeding	Reverses warfarin	IV requires monitoring
Prothrombin Complex Concentrate (PCC)	Life-threatening bleeding	Rapid INR reversal	Costly; thrombosis risk
Fresh Frozen Plasma (FFP)	Severe bleeding	Widely available	Volume overload, slower action
Supportive Care	All patients	Stabilizes hemodynamics	Doesn't reverse warfarin itself
Re-initiation of Anticoagulation	Post-recovery	Prevents graft thrombosis	Risk of re-bleeding

Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(3), 1986-1992 | ISSN:2251-6727

Table 4: Clinical Outcomes Associated with Warfarin Toxicity

Outcome	Incidence Range (%)	Associated Factors
Graft Thrombosis	4–9	Delay in resuming anticoagulation
Acute Limb Ischemia	3–6	Graft thrombosis or hematoma
Hematoma at Graft Site	6–10	Local bleeding, surgical manipulation
Mortality	3–8	Mostly from ICH or massive GI bleed
Amputation	1–4	Delayed diagnosis, ischemia

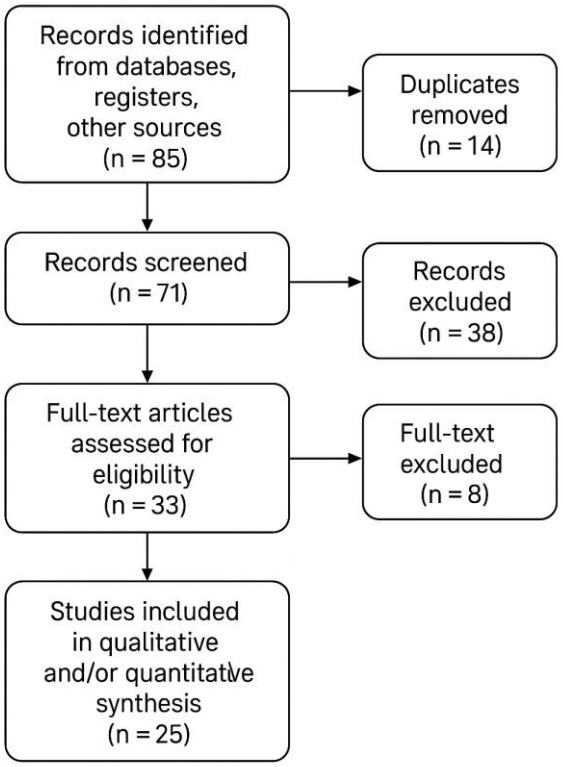

Figure 1: PRISMA chart