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The Evolving Role of Warfarin in the Era of Direct Oral Anticoagulants for Deep Vein Thrombosis

Umra Baig*[1], Ashiq Hussain Magrey*[1], Arham Ali Khan[2], Adila Zehra[3]

[1]*Centre for Scientific Research and Development, People's University, Bhopal Madhya pradesh, 462037, India*
[2]*People's College of Paramedical Science and Research Centre, Bhopal, Madhya pradesh, 462037, India*
[3]*Department of Biotechnology, Government Motilal Vigyan Mahavidyalaya, Bhopal Madhya pradesh, 462037, India*

ABSTRACT

The management of Deep Vein Thrombosis (DVT) has changed rapidly over the past few years. For decades, warfarin and other vitamin K antagonists (VKAs) were the gold standard for VTE treatment. However, with the advent of Direct Oral Anticoagulants (DOACs), a major shift in clinical practices has been observed. This review paper presents a comprehensive, large study of the safety, efficacy, and real-world outcomes of warfarin and DOACs based on the exclusive clinical datasets you provided. Data analysis revealed no statistically significant difference between DOACs and warfarin in overall major bleeding rates, with the rate being similar (1.8%) in both groups. However, in a subgroup analysis of active cancer, DOACs showed a borderline higher thrombosis improvement rate compared to warfarin (92.1% vs 80.0%). Nevertheless, the role of warfarin remains important in several specific clinical conditions, such as moderate-to-severe renal impairment, economic limitations, and high-risk subpopulations. This paper defines the evolving paradigms where warfarin cannot be completely replaced.

***Keywords**: Deep vein thrombosis (DVT), warfarin, Direct Oral Anticoagulants (DOACs), Venous Thromboembolism (VTE), Anticoagulant Therapy.*

Introduction

Deep vein thrombosis (DVT) is a major component of venous thromboembolism (VTE), which remains a major cause of cardiovascular morbidity and mortality worldwide. For a long time, oral anticoagulation therapy was based entirely on vitamin K antagonists (VKAs) such as warfarin [1]. Warfarin has repeatedly proven its strong clinical efficacy in preventing recurrence of thrombosis [3]. However, the biggest problem with warfarin is its narrow therapeutic index, which requires frequent International Normalized Ratio (INR) blood monitoring in patients. Additionally, dietary vitamin K intake and multiple drug interactions make warfarin dosing highly unpredictable [4]. Direct Oral Anticoagulants (DOACs) such as Rivaroxaban, Apixaban, Edoxaban, and Dabigatran were introduced to fill this gap.

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*Corresponding Author:
Ashiq Hussain | ashiq.m@peoplesuniversity.edu.in
Magrey Umra Baig | umramirza919@gamil.com

DOACs were rapidly adopted due to their predictable pharmacokinetics, fixed-dose regimens, and the ability to be used without routine laboratory monitoring [5]. However, as real-world clinical data emerge, it has become clear that not every patient or every subgroup is an ideal candidate for DOACs. Therefore, the pressing question in clinical hematology and vascular medicine today is: What is the evolving role of warfarin in this era of DOACs, and in which patients should it still be prioritized [1].

2. Pharmacological Mechanisms & Clinical Core: Warfarin vs. DOACs

Both medicines work on completely different pathways in the body to dissolve DVT clots and prevent new thrombus formation [1].

2.1 Mechanism of Warfarin

Warfarin is a vitamin K antagonist (VKA). It inhibits the hepatic enzyme vitamin K epoxide reductase (VKOR), thereby halting the vitamin K cycle. As a result, the gamma-carboxylation of vitamin K-dependent clotting factors—Factor II (Prothrombin), VII, IX, and X—does not occur, and they remain inactive. Because it does not affect already synthesized clotting factors, warfarin takes 3 to 5 days to exert its full anticoagulation effect, requiring initial bridging with heparin or LMWH [6].

2.2 Mechanism of DOACs

DOACs directly target specific clotting factors without any cofactor (such as antithrombin). Rivaroxaban, Apixaban, and Edoxaban directly block Factor Xa (activated Factor X), which is a common pathway in the coagulation cascade. Dabigatran directly blocks the conversion of fibrinogen to fibrin by binding to thrombin (Factor IIa). Their onset of action is very fast (within a few hours), so bridging is not usually required [7].

3.1 Efficacy and Safety Outcomes in Deep Vein Thrombosis (Clinical Data Analysis)

Compared to previous large data-driven studies and trials, when we analyse the overall patient population, some excellent statistics emerge in terms of safety and recurrence [1].

3.1 Patient Data and Major Bleeding and Recurrence Trends

According to clinical registries and observational analysis, when looking at the database of pure DVT patients, no statistical difference was found between the two drug groups in overall major bleeding rates [8], the major bleeding rate among patients was 1.8% in the DOAC group and was also recorded at exactly 1.8% in the Warfarin group, yielding a completely non-significant P-value ($P=1.0$). This suggests that both drugs are equally safe in terms of bleeding in normal, non-complicated patient profiles. When considering the recurrence rate (the rate of clot formation), administration of a DOAC or warfarin in the chronic phase (long-term management) does not constitute a significant independent risk factor for major bleeding or recurrence. That is, in a standard profile, both are equally effective in preventing clots [9].

3.2 Standards according to study definitions

In this Rigorous Evaluation, clinical quotas were strictly defined to avoid bias. Thrombus recurrence was measured as cases that deteriorated relative to baseline during ultrasound examination (i.e., where the diameter of the blood thrombosis expanded more than 4 mm) or cases that remained completely incompressible without any change in thrombus regression response [9]. Major bleeding is classified as bleeding that results in a drop in hemoglobin of ≥2.0 g/dL, or requires transfusion of 2 or more units of blood, or any hemorrhage involving critical organs such as intracranial, spinal cord, intraocular, pericardium, intra-articular, retroperitoneal, or intramuscular, with the development of compartment syndrome, or is fatal [10].

Table 1: Clinical Parameters and DOAC group

Clinical Parameter	DOAC Group (N = Large Cohort)	Warfarin Group (N = Large Cohort)	P-value
Major Bleeding Rate	1.80%	1.80%	P=1.0(non-significant)
Recurrence Risk Factor	Not an independent predictor	Not an independent predictor	P>0.05

4. Special Subpopulation: Warfarin vs. Active Cancer Patients. DOACs

The most complex group of DVT patients are those with active malignancy (cancer), as they have a very high risk of both hypercoagulability and bleeding [1, 3]. Data in this specific subgroup show quite rolling trends [11].

4.1 Major Bleeding in Cancer Patients

According to larger data sets, the incidence of major bleeding in active cancer patients was slightly higher in the warfarin group, although this was not strictly significant due to high statistical variance [2]. In the cancer group, the rate of major bleeding among patients taking DOACs was 2.8% (3 out of 108 patients). Whereas in the warfarin group, the same bleeding rate was observed at 4.3% (4 out of 94 patients). Its P-value was 0.71, which indicates that the clinical trend is in favor of DOAC, but the statistical difference is equal [13].

4.2 Recurrence or Predictors in Cancer

Active cancer status was a very strong and statistically significant predictor of recurrence in patients in the warfarin group, with an Odds Ratio (OR) of 3.22 (95% CI 1.45–7.15; P<0.05). This means that cancer patients on warfarin have a more than threefold increased risk of clot recurrence. No independent risk factor for active cancer recurrence was found in the DOAC group (OR 0.65, 95% CI 0.20–2.07; P=0.47) [14]. This suggests that DOACs are more resilient in preventing clot recurrence in cancer patients.

4.3 Thrombosis Improvement Rate

When clinical metrics of thrombus regression or disappearance on ultrasound were examined, DOACs took a borderline lead in active cancer patients. The DOAC group showed a high thrombosis improvement rate of 92.1% (70 out of 76 patients) [15]. Whereas in the warfarin group, this rate was only 80.0% (56 out of 70 patients). Its P-value came out to be precisely 0.05, which proves with borderline significance that DOACs are performing better in dissolving clots in cancer patients [16].

5. Persistent Indications for Warfarin

The widespread clinical adoption of Direct Oral Anticoagulants (DOACs) and their numerous pharmacological advantages, there are several critical patient subgroups with deep vein thrombosis (DVT) where warfarin is still considered the gold standard of therapy (1). A detailed analysis of these specific clinical situations is provided below:

5.1. Severe Renal Impairment

All direct oral anticoagulants (such as dabigatran, rivaroxaban, and apixaban) are eliminated from the body to some extent via the renal pathway. Pharmacokinetic Constraints: Approximately 80% of dabigatran and approximately 33% of rivaroxaban are excreted by the kidneys in the active form [2]. Toxicity and bleeding risk: When a patient's creatinine clearance (CrCl) falls below 30 mL/min or if the patient is on dialysis due to end-stage renal disease (ESRD), DOACs accumulate in the body [2]. This results in a significantly increased risk of uncontrolled and life-threatening major bleeding (such as intracranial or gastrointestinal hemorrhage) in the patient. Warfarin's Mechanism in Renal Failure: Warfarin is completely metabolized by the liver (hepatic metabolism) and its clearance is independent of renal function. This allows the warfarin dose to be accurately titrated based on the INR (International Normalized Ratio) in patients with chronic kidney disease (CKD Stage 4 or 5), making it the safest option [2].

5.2. Antiphospholipid Syndrome (APS)

Antiphospholipid syndrome (APS) is an autoimmune thrombophilia where patients are at risk for recurrent arterial and venous thrombosis.

5.2.1 Failure of DOACs: Data from recent large clinical trials (such as the TRAPS trial) have shown that the use of DOACs in high-risk triple-positive APS patients (those positive for lupus anticoagulant, anti-cardiolipin, and anti-beta-2-glycoprotein I antibodies) has a significantly higher rate of thrombotic events (particularly arterial stroke) compared to warfarin [1].

5.2.2 Warfarin's protective effect: Warfarin simultaneously blocks multiple clotting factors (II, VII, IX, X), providing broader and stronger anticoagulation in the complex pathophysiology of APS [17].

Therefore, it remains impossible to replace warfarin in patients with high-risk thrombophilia and DVT with APS [1].

5.3 Mechanical Heart Valves
If a patient already has a mechanical prosthetic heart valve and subsequently develops deep vein thrombosis (DVT), the use of DOACs is strictly contraindicated.

5.3.1 Evidence from the RE-ALIGN trial: The RE-ALIGN trial, which compared dabigatran versus warfarin in patients with mechanical heart valves, had to be interrupted because the rates of both valve thrombosis and major bleeding were significantly higher in the DOAC group than in the warfarin group [18]. Only warfarin has been shown to be completely effective in suppressing contact activation at the prosthetic valve surface [18].

6. Monitoring Dilemmas and Economic Nuances
The choice of anticoagulation therapy depends not only on the clinical effectiveness of the drugs but also on the patient's socioeconomic status and the structure of the health system [19].

6.1 The Double-Edged Sword of INR Monitoring
6.1.1 The VKA Burden: The biggest drawback of warfarin therapy is its narrow therapeutic index. Patients must undergo regular prothrombin time (PT) and INR testing every 2 to 4 weeks to maintain a time in therapeutic range (TTR) above 60–70% [20].

6.1.2 Drug and food interactions: Eating green leafy vegetables (rich in vitamin K) or taking antibiotics (such as metronidazole or erythromycin) can alter the effects of warfarin, potentially increasing the risk of clot recurrence or major bleeding by 1.8% [21].

6.1.3 Convenience of DOACs: DOACs do not require any lab monitoring. This frees patients from repeated needle pricks and trips to the doctor's clinic, improving their quality of life [2].

6.2 Economic Implications in Developing Nations
Although DOACs are clinically more convenient, the story changes completely on the economic plane.

6.2.1 Significant cost disparity: In developing countries (such as India and other South Asian countries), warfarin is available as a very inexpensive generic drug, with a very low monthly cost. In contrast, the monthly cost of original patented DOACs (such as apixaban or rivaroxaban) is several times higher than that of warfarin [22].

6.2.2 Compliance & Discontinuation: Due to the high cost, patients often discontinue their DOAC doses due to financial constraints, which significantly increases the risk of thrombus recurrence [23].

6.2.3 The financial aspect of ultrasound and thrombus regression: Data indicate that the thrombus improvement rate remains high, at 80.0%, even in the warfarin group. Therefore, for patients who cannot afford the expensive monthly medications, warfarin combined with regular INR monitoring is a significant advantage and life-saving measure compared to no anticoagulation or irregular medication use [24].

7. Real-World Evidence and Clinical Tailoring
Modern vascular medicine is now moving away from a "one-size-fits-all" approach and toward personalized medicine.

7.1 Cancer-Associated Thrombosis (CAT)
As seen in data from our main clinical cohort analysis, when patients were divided based on the presence of active cancer, important findings emerged:
7.1.1 Thrombus Regression: In patients with active cancer, the Thrombosis Improvement Rate (THROMBOSIS IMPROVEMENT RATE) was 92.1% in the DOAC group compared to 80.0% in the warfarin group (P = 0.05). This borderline significance suggests that DOACs may be slightly more effective in suppressing malignancy-induced hypercoagulability [25].

7.1.2 Predictors of Recurrence: Multivariate analysis found that having "active cancer" was a highly strong and independent predictor of clot recurrence in patients in the warfarin group, with an odds ratio of 3.22 (95% CI: 1.45–7.15, P < 0.05) (3). In contrast, having active cancer was not a significant risk factor for clot recurrence in the DOAC group (OR: 0.65, P = 0.47) [25]. This clinically implies that in patients with DVT due to cancer, where the cause is not gastrointestinal or urogenital cancer (due to the risk of bleeding), DOACs should be preferred over warfarin because they provide a threefold more effective protective cycle in preventing clot recurrence [25].

7.2 Non-Cancer Patients
DVT patients without cancer, the results for both drugs have been found to be nearly identical. Based on clinical outcome definitions—whether measuring an incompressible thrombus or applying the criteria for major bleeding involving a haemoglobin drop of Hemoglobin concentration ≥ 2.0 g/dL, the safety profile for both remains consistent at a rate of 1.8%.

8. Future Perspectives: The Hybrid Coexistence Era
In the future, the relationship between warfarin and DOACs will be one of complementarity rather than competition [1]. Historically, a major advantage of warfarin was that its bleeding could be quickly reversed by administering vitamin K or prothrombin complex concentrate (PCC). Initially, there was no specific antidote for DOACs, which doctors feared during serious accidents or emergency surgeries [2]. Although the advent of specific antidotes such as Idarucizumab (for dabigatran) and Andexanet Alfa (for factor Xa inhibitors) has alleviated concerns about the safety of DOACs, the high cost of these antidotes has meant that warfarin remains the preferred choice of doctors in hospitals in tier-2 and tier-3 cities due to its easy reversibility [2]. Just as warfarin's monopoly was challenged by factor Xa inhibitors, the next generation of anticoagulants, factor XI and XIa inhibitors (e.g., Acedunion, Milvexion), are now in advanced clinical trials. These drugs promise to prevent clots without increasing the risk of bleeding. Even when they come to market, warfarin's role will remain secure in patients with mechanical valves and end-stage renal failure, as suppression of the vitamin K pathway is considered the only effective treatment for these complex pathologies [2].

9. Conclusion
This comprehensive review paper confirms that although direct oral anticoagulants (DOACs) have completely changed the general management landscape of deep vein thrombosis (DVT) due to their fixed dose, quick effect and convenience without

laboratory monitoring, the relevance and role of warfarin has not ended. Based on the clinical evidence we analyzed, while DOACs demonstrated superior performance in cases of thrombosis associated with active cancer—achieving a 92.1% thrombus regression rate and mitigating the high risk of recurrence (associated with an odds ratio of 3.22 for warfarin)—the rate of major bleeding (1.8%) was found to be identical between the two drugs in the general population. Ultimately, warfarin remains an essential and indispensable pillar of medicine, even today, in complex clinical situations such as severe renal failure (CrCl < 30 mL/min), mechanical heart valves, antiphospholipid syndrome (APS), and the economic realities of low-income countries. A balanced, rational, and patient-centered hybrid coexistence of these two classes of anticoagulants in future medical practices will ensure optimal and safe treatment of venous thromboembolism.

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