Critical Appraisal on the Role of Warfarin in the Current Era

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ABSTRACT

Warfarin has been the most extensively used oral anticoagulant (OAC) in medical settings for over 60 years. Its uses, potential adverse effects, and methods for reversing its effects have been firmly established, rendering it a routine medication in medical settings where most professionals feel at ease employing it. Compared to other vitamin K antagonists (VKAs), such as acenocoumarol, warfarin offers benefits like diminished prothrombin time (PT) assays leading to enhanced oral anticoagulation. Observations over the past few years have seen the inclusion of novel/direct OACs (NOACs/DOACs) in the anticoagulant armamentarium. Although DOACs have several advantages, warfarin still has an important role in subsets of patients where DOACs are contraindicated, not well-tolerated, or cannot afford DOACs due to higher costs. Moreover, there are patient profiles where warfarin is still considered a superior choice compared to DOACs, such as age group of >75 years, kidney failure with creatinine clearance (CrCl) below 30 mL/minute, and prosthetic mechanical valve replacement. Precise management of the international normalized ratio (INR) is crucial for the effectiveness of warfarin treatment. INR monitoring is the major concern in the Indian context due to the lack of laboratories for standardized measurement. Adopting strategies such as point-of-care INR monitoring devices and anticoagulation clinics can help to improve clinical outcomes with warfarin therapy. The present review provides a critical overview of the role of warfarin therapy in the current OAC arsenal and strategies for improving therapeutic control and patient adherence.

Introduction

Since its discovery in 1933, warfarin has become the prominent choice for oral anticoagulant (OAC) use in the management and prophylaxis of thromboembolic disorders.1–3

The nomenclature “warfarin” is constructed from the abbreviation WARF (Wisconsin Alumni Research Foundation) combined with the suffix “-arin,” which is derived from the term “coumarin.” In Wisconsin, Karl Link and Harold Campbell inferred that the anticoagulant present in sweet clover was responsible for an outbreak of cattle death in the Northern United States of America (USA), which is 3,3’-methylenebis(4-hydroxy coumarin). Warfarin, synthesized in 1948, was originally authorized for use as a rodenticide in the USA and later for human use in 1954.4

Warfarin is widely employed to treat and prevent blood clot formation. The approved clinical applications for warfarin by the Food and Drug Administration (FDA) encompass the following5:

- Prophylaxis and management of venous thrombosis (VT) and pulmonary embolisms (PE).
- Prevention and treatment of thromboembolic complications arising from atrial fibrillation (AF) or cardiac valve replacement.
- Decrease in mortality rate, recurrence of myocardial infarction, and thromboembolic incidents subsequent to a myocardial infarction.

Warfarin vs Other VKAs

Molecular as well as Pharmacokinetic Differences

Oral anticoagulants (OAC) are a part of the 4-hydroxycoumarins group, acting by suppression of vitamin K epoxide reductase complex subunit 1 (VKORC1) in a noncompetitive manner (Fig. 1).6,7 Following oral administration, VKAs are readily absorbed through the gastrointestinal tract, displaying full oral bioavailability. However, S-acenocoumarol experiences substantial first-pass metabolism. Peak plasma concentrations are attained within a short duration. Despite showing an affinity for protein binding in human plasma (approximately 98%), these compounds also showcase variations in their volumetric distribution. In overextended therapeutic durations, the plasma levels of acenocoumarol are notably diminished in comparison to those of warfarin or phenprocoumon.6,7

Phenprocoumon, acenocoumarol, and warfarin exhibit distinct elimination half-lives (t1/2) spanning 110–130, 1.8–6.6, and 24–58 hours, respectively. Warfarin’s metabolic clearance predominantly involves hydroxylation and reduction, with 80% excreted through urine and 20% through feces. S-warfarin metabolism primarily relies on the enzymatic activity of CYP2C9, while hydroxylation of the R-enantiomer is mediated by CYP1A2, CYP2C8, CYP2C19, and CYP3A4. Conversely, CYP2C9 is responsible for the hydroxylation of the S-form of acenocoumarol and about 60% of the R-enantiomer. In the case of phenprocoumon, its metabolism is chiefly governed by CYP2C9 and CYP3A4, acting as the primary enzymes.7

Clinical Evidence on Outcomes of Warfarin vs Other VKAs

Only a few studies are available comparing the effectiveness and safety of warfarin and acenocoumarol.6 Acenocoumarol, due to its brief half-life (6–8 hours), may induce routine variations in factor VII levels. These variations may affect prothrombin time (PT) and alterations in the levels of oral anticoagulation.6 Acenocoumarol is associated with a twofold increased risk of causing instability in the anticoagulation process compared to warfarin.9

A comparative study between acenocoumarol and warfarin later showed fewer PT assays and enhanced oral anticoagulation stability. Warfarin was associated with significantly better quality of treatment (72 vs 67%, p < 0.001, respectively) and a higher proportion of patients within the assay range (warfarin 50.7% compared to acenocoumarol 34.5%, p < 0.05).10

A study assessing the therapeutic stability of acenocoumarol and warfarin in AF patients showed that within the acenocoumarol group, there were 0.3 visits per patient per year where the international normalized ratio (INR) was ≥6, as opposed to 0.07 visits in the warfarin group (p = 0.003), suggesting that anticoagulation stability of acenocoumarol is lower than warfarin.11 Another study demonstrated that warfarin was more stable compared to other VKAs, while hydroxylation of the R-enantiomer is mediated by CYP1A2, CYP2C8, CYP2C19, and CYP3A4. Conversely, CYP2C9 is responsible for the hydroxylation of the S-form of acenocoumarol and about 60% of the R-enantiomer. In the case of phenprocoumon, its metabolism is chiefly governed by CYP2C9 and CYP3A4, acting as the primary enzymes.7

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These findings suggest that substituting warfarin observed that initially, the proportion of patients with unstable anticoagulation remained within the targeted INR values within the recommended therapeutic range in the warfarin (52%) group compared to acenocoumarol group (46%).

An interesting study conducted to assess the response to switching from acenocoumarol to warfarin observed that initially, the proportion of time patients with unstable anticoagulation remained within the targeted INR range was 40.2%. After transitioning to warfarin therapy for a duration of 6 months, this percentage increased significantly to 60.4% (p < 0.05). These findings suggest that substituting acenocoumarol with warfarin in patients can lead to an enhancement in the control of anticoagulation.

**Warfarin vs Novel/Direct OACs (NOAC/DOAC)**

In the recent past, four recently developed drugs, namely the direct factor Xa inhibitors apixaban, edoxaban, and rivaroxaban, along with the direct thrombin inhibitor dabigatran, are collectively referred to as NOACs/DOACs have been approved. DOACs have several advantages, such as the absence of routine anticoagulation monitoring, anticipated pharmacokinetic profile, and lesser food-drug and drug–drug interplay. However, warfarin still has an important role in a specific subset of patients where DOACs are contraindicated, not well tolerated, or the subject cannot afford the high cost of therapy with DOACs.

**A Well-controlled “Time-in-therapeutic Range (TTR)” Patient on Warfarin is no Different from DOAC**

The multinational DOAC randomized controlled trials (RCTs) have shown parallel outcomes.

In the Randomized Evaluation of Long-term Anticoagulation Therapy trial, dabigatran exhibited an efficacy rate of 64%. The Rivaroxaban Once-daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism in Atrial Fibrillation trial reported an efficacy rate of 55% for rivaroxaban. Similarly, the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation trial showed an efficacy rate of 62% for apixaban. This translates to the fact that warfarin with a good TTR is equivalent to DOACs in safety and efficacy.

The initial meta-analysis conducted by Carmo et al. marked the pioneering effort to assess the relative effectiveness and safety of all available DOACs in contrast to warfarin across distinct center-specific TTR (cTTR) thresholds for the prevention of stroke in patients with AF. This comprehensive analysis included four substudies pertaining to TTR, encompassing a cumulative cohort of 71,222 patients. The results unveiled a distinct advantage associated with DOACs over warfarin in terms of diminishing the risk of stroke and systemic embolism (SSE), notably prominent among patients with a cTTR below 60% [hazard ratio (HR) 0.79, 95% confidence interval (CI) 0.68–0.90] and those within the range of 60–70% [0.82, 0.71–0.95). However, this beneficial effect was not sustained for patients exceeding a cTTR threshold of 70% (1.00, 0.82–1.23), with a statistically significant interaction emerging among patients with a cTTR >70% (p = 0.04). Furthermore, the assessment of major or nonmajor clinically relevant (NMCR) bleeding risk exhibited a notable reduction in patients receiving DOACs compared to that administered warfarin across all cTTR subgroups, except for patients with a cTTR ≥70% (HR 0.84, 0.64–1.11). The interaction analysis for cTTR <70 vs ≥70% did not reach statistical significance (p = 0.271). The study’s findings collectively demonstrated that the superiority of DOACs over warfarin for the prevention of stroke diminishes beyond a cTTR threshold of approximately 70%.

**Direct OACs (DOACs) Contraindicated in Patients with Mechanical Prosthetic Valves**

Dabigatran has been demonstrated to be a potent substitute for warfarin in patients with AF. However, a study conducted by Eikelboom et al. revealed that the utilization of dabigatran among patients with mechanical heart valves demonstrated elevated occurrences of both thromboembolic events and bleeding complications when compared with warfarin. Among the dabigatran-receiving group, nine patients (5%) experienced an ischemic or unspecified stroke, while no such incidents were recorded in the warfarin-treated group. Moreover, the occurrence of major bleeding events was observed in seven patients (4%) treated with dabigatran, in contrast to two patients (2%) within the warfarin group.

Benefits of DOACs in mechanical prosthetic valve remains unproven. Currently, DOACs are not advised for use in cases of moderate to severe mitral stenosis and among patients with mechanical heart valves.

**Warfarin vs DOACs in Specific Situations**

*Left Ventricular (LV) Thrombi*

A multicentric, retrospective cohort study compared the results associated with DOACs and warfarin in 514 eligible patients with LV thrombi, confirmed by echocardiography (n = 300 received warfarin and n = 185 received a DOAC) over a median follow-up duration of 351 days, DOAC therapy vs warfarin use (HR, 2.71; 95% CI, 1.31–5.57; p = 0.01), and initial stroke or systemic embolism (SSE) (HR, 2.13; 95% CI, 1.22–3.72; p = 0.01) were associated with SSE. In a multivariable analysis, the utilization of anticoagulants involving DOACs relative to warfarin (HR = 2.64; 95% CI = 1.28–5.43; p = 0.01) and the presence of previous systemic embolism (prior SSE) (HR = 2.07; 95% CI = 1.17–3.66; p = 0.04) were found to be statistically significant associations with SSE. Despite adjusting for additional influencing variables, treatment with DOACs demonstrated an elevated propensity for SSE in comparison to warfarin. These findings present a challenge to the conventional assumption of therapeutic equivalence between DOACs and warfarin concerning the management of LV thrombi.
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Postcoronary Artery Bypass Grafting (CABG)
While direct OACs (DOACs) have gained widespread approval and utilization for venous thromboembolism prevention and nonvalvular AF treatment, their application in postoperative patients remains limited in available information. A retrospective analysis investigated the occurrence of postoperative effusions in 246 patients who received anticoagulation with either warfarin (n = 182) or DOACs (n = 64) following CABG. Among patients treated with DOACs after surgery, 26.6% necessitated invasive interventions to address effusions, contrasting with 13.2% in those receiving warfarin (p < 0.014). This dataset bears significance and should guide the selection of an appropriate anticoagulation strategy for postoperative CABG patients.21

Complications Associated with PE
Chronic thromboembolic pulmonary hypertension (CTEPH) represents an infrequent clinical setback to acute pulmonary emboli, requiring prolonged use of anticoagulant therapies. A retrospective analysis was conducted to assess outcomes and complication incidences in CTEPH cases of postpulmonary endarterectomy (PEA), comparing individuals receiving VKAs (n = 794) or DOACs (n = 206). Warfarin remains consistent among the VKA (99%), while rivaroxaban is consistent among DOACs (77%). Both VKA and DOAC cohorts exhibited substantial enhancements in hemodynamic and functional status post-PEA (p < 0.001). Comparable rates of major hemorrhagic events were observed between VKA-treated (0.67%/person-year) and DOAC-treated (0.68%/person-year) patients. However, DOACs exhibited a relatively higher recurrence rate of venous thromboembolism (VTE) (4.2%/person-year) in contrast to VKAs (0.76%/person-year), although overall survival did not exhibit variance.22

Antiphospholipid Syndrome (APS)
In APS, the suitable duration of warfarin treatment for secondary prevention of recurrent VT following an initial event remains a subject of debate. The recommended standard of care currently advocates for an indefinite, prolonged course of warfarin treatment. The cessation of anticoagulation in individuals with AP antibodies lacks a solid foundation in empirical evidence and should only be contemplated in exceptionally chosen patients subsequent to thorough counseling and a comprehensive evaluation of risk factors.23 No data, apart from anecdotal reports, are available on DOACs in this disease.

Poor Adherence to Therapy with DOACs
Data from RCTs have provided evidence that patients struggle to maintain anticoagulation with DOACs over the long term and that a large proportion of those discontinue DOACs even before the end of treatment.24 In a clinical trial encompassing 18,113 individuals with AF, the discontinuation rates for dabigatran at doses of 110 and 150 mg, as well as warfarin, were observed as 14.5, 15.5, and 10.2%, respectively, at the end of the 1st year. These figures increased to 20.7, 21.2, and 16.6% at the end of the 2nd year.25

A study showcased at the Heart Rhythm Society’s (HRS’s) 39th Annual Scientific Sessions reported that lower DOAC use was associated with more thromboembolic events than warfarin when adherence was low. Within the study, the cohort encompassed 52,365 patients who were prescribed warfarin and 67,686 patients who were prescribed any of the four DOACs. Notably, thromboembolic events were found to be 69% more probable in individuals with lower adherence to DOACs (p < 0.001) and 48% more likely in those with lower adherence to warfarin (p < 0.001).26

Dose Adjustment of DOACs Based on the Kidney Function and CrCl Values
Chronic kidney disease (CKD) represents a significant global public health concern due to its proximal association with cardiovascular disease.27 Approximately 28% of patients diagnosed with acute coronary syndrome exhibit moderate CKD with an eGFR ranging from 59 to 30 mL/minute/1.73 m², whereas 5.5% of patients have an eGFR below 30 mL/minute/1.73 m².28 CKD is linked with an elevated risk of thromboembolism, which necessitates anticoagulation therapy. However, the increased incidences of hemorrhage are quite challenging.29

DOACs are preferred in CKD stages 1–3, while warfarin remains consistent as the first choice of treatment in patients with end-stage renal disease (ESRD). Due to the variable degree of renal clearance, dosage adjustment is mandatory in CKD patients treated with DOACs (Table 1).27

Data from a meta-analysis also favored the efficacy and safety of warfarin in nonend-stage CKD. In a landmark meta-analysis by Dahl et al., the utilization of warfarin among patients with nonend-stage CKD yielded a reduced risk of ischemic stroke or thromboembolism (HR: 0.70; 95% CI: 0.54–0.89; p = 0.004) and mortality (HR: 0.65; 95% CI: 0.59–0.72; p < 0.00001), while exhibiting no discernible impact on major bleeding (HR: 1.15; 95% CI: 0.88–1.49; p = 0.31).30

Bonde et al. conducted a nationwide observational cohort study to evaluate the overall clinical advantage of warfarin usage among patients with AF and CKD. The study findings indicated that in CKD patients with high-risk profiles (CHA₂DS₂-VASc score ≥ 2), warfarin administration was linked to a decreased likelihood of all-cause mortality (HR: 0.85; 95% CI: 0.72–0.99). Additionally, among nonend-stage CKD patients possessing a CHA₂DS₂-VASc score ≥ 2, warfarin usage was associated with diminished risks of fatal stroke/fatal bleeding (HR: 0.71, 95% CI: 0.57–0.88), cardiovascular mortality (HR: 0.80, 95% CI: 0.74–0.88), and all-cause mortality (HR: 0.64, 95% CI: 0.60–0.69).30

WARFARIN THERAPEUTIC MONITORING AND MEASURES TO IMPROVE THERAPEUTIC CONTROL
International normalized ratio (INR) monitoring is the key to a safe and effective warfarin therapy.31 The following advances have made an assessment of INR and maintenance to obtain the highest TTR.

Point-of-care Device
The utilization of point-of-care INR testing confers several benefits: the user-friendly nature, the rapid outcomes from capillary blood testing, and improved decentralization of management. Various point-of-care INR testing methods have been explored in clinical studies, such as the CoaguChek XS (Roche Diagnostics, Basel, Switzerland), which employs electrochemical detection of thrombin activity, the INRatio 2 (Alere Inc., San Diego, California, USA) utilizing electrochemical detection of impedance changes, the ProTime Micro coagulation system (International Technidyne...
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Table 1: Titration of DOAC dosages based on the degree of CKD severity in individuals afflicted with AF or venous thromboembolism

<table>
<thead>
<tr>
<th>Recommended OAC</th>
<th>CrCl (mL/minute) estimated using the Cockroft–Gault equation</th>
<th>End-stage renal disease on dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥50</td>
<td>30–49</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Preferable to adjust the dose function of time in the therapeutic range, optimal ≥70%</td>
<td></td>
</tr>
<tr>
<td>Dabigatran</td>
<td>150 and 110 mg twice daily for ≥80 years, or associated with P-glycoprotein Inhibitors, or high risk of hemorrhage</td>
<td>Same</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>20 mg once daily</td>
<td>15 mg once daily (dose used by landmark trials recommended by small pharmacokinetic studies)</td>
</tr>
<tr>
<td>Apixaban</td>
<td>5 and 2.5 mg twice daily if any ≥2 of the following: age ≥80 years, body weight ≤60 kg, and creatinine ≥1.5 mg/dL</td>
<td>Same</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>60 and 30 mg once daily when ≥2 of the following criteria are met—body weight ≤60 kg, CrCl 30–50mL/minute, and therapy with verapamil, dronedarone, or quinidine is associated with FDA black box warning for CrCl &gt;95 mL/minute</td>
<td>30 mg once daily</td>
</tr>
</tbody>
</table>

CrCl, creatinine clearance; DOAC, direct oral anticoagulants; FDA, Food and Drug Administration

Pharmacogenetic Testing for Warfarin Dosage

Repetitive investigations through candidate gene studies have consistently revealed that the genetic makeup of VKORC1 and CYP2C9 plays a significant role in shaping individual responses among patients. This has been confirmed by several genome-wide association studies (GWAS). Following the identification of the CYP2C9 and VKORC1 genes, their correlation with the necessary warfarin dosage has been investigated in multiple research studies.

The International Warfarin Pharmacogenetics Consortium (IWPC) investigated involving 4,000 patients to assess the relationship between pharmacogenetic factors, clinical variables, and warfarin dosage. The study revealed that incorporating genetic data into the dosage prediction significantly improved its proximity to the required dosage, surpassing estimations from a clinical algorithm or a fixed-dose strategy (8.5 vs 9.9 vs 13.0%, respectively). This predictive accuracy was particularly notable among patients necessitating high dosages (e.g., the 49 mg/week group), constituting 46% of the study cohort.

The Swedish Warfarin Genetics (WARG) study showcased that a multi-regression
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model encompassing variants of VKORC1, CYP2C9*2, and 3 accounted for over 50% of the variability observed in warfarin dosing. Individuals harboring variant alleles of VKORC1 exhibited expedited attainment of the first therapeutic INR and spent more extensive durations within the therapeutic range of INR 2–3. Homozygosity for CYP2C9 was linked to instabilities in anticoagulation, marked by reduced time within the therapeutic range and a robust association with INR levels exceeding the therapeutic threshold.43

**INDIA-SPECIFIC CHALLENGES IN ANTICOAGULATION**

Differences in Prevalence of Rheumatic Heart Disease (RHD) in India, Compared to the West, where Trials are Done

Heart failure (HF) has a higher prevalence in India because of increasing vascular disease and the persistence of pretransitional diseases such as RHD.44 The India Ukieri Study conducted to determine the HF incidence in remote populations along with other comprehensive healthcare institutions conducted in North India reported that RHD (52%) constituted the primary prevalent factor, succeeded by ischemic heart disease (17%).45 According to the Acute Failure Registry Study, RHD accounted for 10.8% of the instances of acute decompensated HF.46 The Kerala AF registry stands as the largest ongoing prospective cohort study of patients with AF in South Asia. A total of 53 participating centers have enrolled patients hailing from both urban and rural locales within the state of Kerala (n = 3,421). HF was observed in 26.5% of patients, while a history of rheumatic fever was present in 17.7% of patients.47 AF serves as a contributory factor to the advancement and deterioration of HF in RHD, while also being associated with cardioembolic SSE.48

Adherence to Therapy: Skipping of Dose is more Harmful with DOAC than Warfarin

Direct OACs (DOACs) are shorter-acting compared to warfarin. When a dose of warfarin is inadvertently skipped, the patient's blood might remain sufficiently anticoagulated for over 24 hours. This extended effect is attributable to the gradual waning of warfarin's anticoagulant impact over several days. In contrast, the anticoagulant effect of a DOAC diminishes rapidly upon missing a dose due to its brief half-life.49 This becomes more relevant in DOACs needing a twice-a-day dosage regimen since their effective half-lives are even shorter.

**Cost of Therapy: Warfarin vs Acenocoumarol and DOACs**

Currently, VKA drugs like warfarin remain the number one agent of choice for oral anticoagulation in India based on physician comfort due to years of usage and the prohibitive cost of dabigatran.50 The cost-benefit favors DOACs in the US since medical contacts associated with PT/INR testing are high. In India, a PT/INR costs around US $5, which favors enormous economic savings favoring warfarin. In India, warfarin is the most cost-effective OAC therapy as compared to acenocoumarol and DOACs. A point-of-care device helps reduce the cost, further favoring warfarin compared to DOACs.

**Conclusion**

When prescribing OACs in India, it is essential to consider factors such as cost, patient adherence, and dietary habits. The utilization of newer OACs is accompanied by a set of challenges that encompass higher cost, suboptimal adherence, limited monitoring infrastructure, absence of dedicated countermeasures, and an elevated risk of severe bleeding incidents among patients with renal impairment and those aged >80 years. Warfarin has been the mainstay of OAC treatment in India for >60 years. Attributed to its distinctive pharmacokinetic properties, amenability to monitoring, cost considerations, and other defining attributes, warfarin stands as the favored anticoagulant option for a specific subset of patients. Proficiently managed and carefully monitored warfarin therapy further diminishes the likelihood of unfavorable occurrences such as recurrent VT and bleeding events, consequently curbing the financial burden associated with VTE treatment. Consistent INR monitoring plays a pivotal role in detecting instances of suboptimal medication adherence during warfarin treatment. Recent advancements like point-of-care INR testing devices, anticoagulation clinics, and pharmacogenetic testing can be an effective strategy for improving INR monitoring and patient adherence to warfarin.

**References**


