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# A Review on Adverse Effects Associate with Warfarin Use: A Neccessery Regulatory Action to Be Prevalent

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**ABSTRACT:**COUMADIN (warfarin sodium) is an anticoagulant that acts by inhibiting vitamin K-dependent coagulation factors. In India, Vitamin K antagonist (VKA) drugs such as warfarin remain the number one choice for oral anticoagulation based on medical comfort due to years of use and the prohibitive cost of dabigatran. Indians with a distinct diet and lifestyle compared to western brethren are more prone to warfarin-food interactions. In atrial fibrillation (AF) patients, warfarin is an extremely effective therapy for the prevention of stroke, reducing stroke by 68 percent and mortality by 26 percent. But about 60% of patients never get warfarin; about half of patients who avoid taking warfarin in the developing world which includes, and about a quarter of those who still take warfarin is in the therapeutic range. Vitamin K antagonists like warfarin should be avoided during pregnancy unless indicated, e.g. women with mechanical heart valves. Warfarin is associated with up to a 5% risk of teratogenesis if used between 6 weeks and 12 weeks of gestation. It also increases the risk of miscarriage, fetal and maternal hemorrhage, neurological problems in the newborn, and stillbirth. Anticoagulants ranked first in 2003 and 2004 in the total deaths for "adverse effects in therapeutic use." drugs. An inpatient ICU data besides 1999 through 2003 indicated that warfarin was associated with approximately 29 000 bleeding complications consultations per year and was among the most frequently visited drugs. These data are consistent with the literature reports of major bleeding rates for warfarin that are as high as 10% to 16%. A Coumadin use increased as well as bleeding from warfarin is a prevalent reaction and a major cause ofdeath.

**KEYWORDS:** Coumarin, atrial fibrillation, myocardial infarction, vitamin k antagonist, teratogenesis, maternal hemorrhage.

## I. INTRODUCTION

Warfarin is a widely used anticoagulant in the treatment and prevention of thrombosis, chronic atrial fibrillation, mechanical valves, pulmonary embolism, and dilated cardiomyopathy. It has been used as a poison and is still being marketed as a pesticide against rats and mice. Several long-acting warfarin derivatives—superwarfarin anticoagulants—such as brodifacoum, diphenadione, chlorophacinone, bromadiolone—are used as pesticides and can cause deep and prolonged anticoagulation. A multitude of variables affects the possibility of warfarin toxicity. Polymorphisms within P450 genes of cytochrome and drug interactions contribute to most of the Risk of toxicity complications. Genetically determined low metabolic capacity in an individual may dramatically alter the rates of toxin and metabolite from those normally expected, which is crucial for drugs with a narrow therapeutic index, such as warfarin.

Personalized analysis approaches have the potential to remove some of the scientific uncertainties in toxicity cases [1]

## THE SIDER DATABASE OF DRUGS AND SIDE EFFECTS

The current release, SIDER 4, contains data on 1,430 drugs, 5880 ADRs, and 140,064 drug–ADR pairs, an increase of 40% compared to the previous release. For more fine-grained analyzes, we extracted the frequency with which side effects of the package inserts occur. This information is available for 39% of drug–ADR pairs, 19% of which can be compared to the frequency of placebo treatment. SIDER also Contains a data set of drug indications extracted from package inserts using Natural Language Processing. These indications are used to reduce the rate of false positives by identifying medical terms that do not correspond to the ADR [2]

## INCIDENCE OF BLEEDING

The incidence of bleeding during oral anticoagulation (OAC) with vitamin k antagonists in published studies differs greatly. The yearly incidence of bleeding during OAC is 2%-5% for major bleeding, 0.5%-1% for fatal bleeding, [3] and 0.2%-0.4% for intracranial bleeding. [4,5]

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**WARFARIN TOXICITY AND INDIVIDUAL VARIABILITY—CLINICAL CASE**

The expected incidence of bleeding: Clinical trials and observational studies.

Experimental model studies (randomized clinical trials) -Elderly patients are almost always excluded from these studies, as well as patients with personal risk factors for bleeding whose one-third of patients evaluated for participation in clinical trials of VKA use during atrial fibrillation was considered ineligible, primarily due to a high perceived risk of bleeding.

- **Retrospective observational studies** may underestimate the risk of bleeding. The first few months of treatment are associated with a higher rate of complications. These studies include the rate of bleeding due to lack of early complications and early cessation of VKA in patients at high risk of bleeding.
- In a recent analysis of clinical studies characterized by careful monitoring of anticoagulant intensity, therapy with VKA was assessed to increase the risk of major bleeding by 0.3–0.5 percent per year. In these studies, the risk of intracranial hemorrhage (ICH), which is the major if not the exclusive cause of death and disability associated with VKA therapy, is increased by approximately 0.2% per year compared to controls.[3][1,2]

**CO-MORBID CONDITIONS**

The presence of co-morbidity may represent a significant risk factor for bleeding during treatment.

The two most common indications for warfarin were deep venous thrombosis (DVT) (65.1%) and atrial fibrillation (Afib) (22.2%). The co-morbid conditions like cardiovascular diseases were the most frequent (52.4%), followed by infections (44.4%) and gastrointestinal disorders (GIT) (15.9%) respectively.[7,8]

The GI bleeding risk associated with warfarin appears to be related to its systemic anticoagulant effects via inhibition of key vitamin K–dependent clotting factors, and thus varies as a function of the international normalized ratio.[9]Among the infections, eight patients (12.7%) were HIV positive and 5 (7.9%) had tuberculosis(TB).Neoplasms (12.7%) Blooddisorders(11.1%) Respiratory related conditions (9.5%) Endocrine, nutritional and metabolicdisorders6(9.5%) Genitourinary tractdisorders5(7.9%) Mental and behaviouraldisorders5(7.9%) Post-pregnancy relatedconditions2(3.2%) Skin and subcutaneous tissuediseases3(4.8%)

Musculoskeletaldisorders2(3.2%)
Nervous system disorders1 (1.6%)[8]

## II. METHODOLOGY:

Most of the studies accessed that Warfarin sodium is widely used and which causes an adverse effect of bleeding in most patients as it is a first prior medication in anticoagulants, but the adverse effect of warfarin leads to many complications, also may result in death.

Most of the study results also accessed Warfarin prescription medications from nationwide prescription audits plus the IMS health database. Adverse events report submitted to the US FDA. Deaths due to the therapeutic use of anticoagulants from vital statistics and warfarin bleeding complications from the national hospital emergency department

**Risk factor Category - Specific risk factors [5,10,11]**

1. Age - >65years
2. Cardiac-Uncontrolledhypertension
3. Gastrointestinal-History of gastrointestinal hemorrhage, active peptic ulcer, hepaticinsufficiency
4. Haematologic/oncologic-Thrombocytopenia, platelet dysfunction, coagulation defect,underlying malignancy
5. Neurologic-History of stroke, cognitive or psychologicalimpairment
6. Renal-Renalinsufficiency
7. Trauma-Recent trauma, history of falls (>3 per within previous treatment year, or recurrent, injurious falls)
8. Alcohol-Excessive alcoholintake
9. Medication-Aspirin, COX-I-specific, non-steroidal anti-inflammatory drugs (COX-II inhibitors do not impair. Platelet function, but can influence warfarin effect) “natural remedies” that interfere with haemostasis.

*Careful monitoring of warfarin effect is critical to minimize risk in patients taking multiple medications.

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**HOW WARFARIN WORK:**

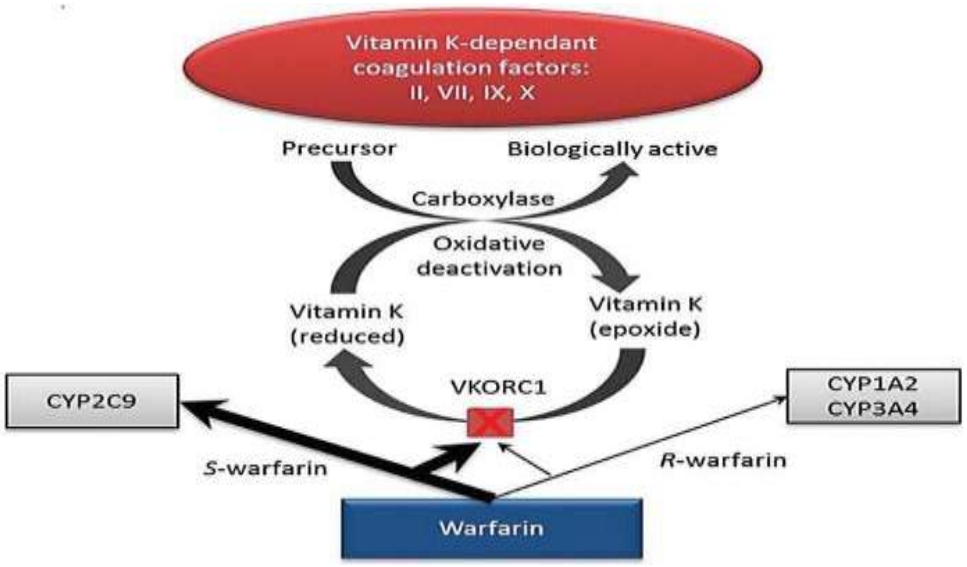


**FIGURE NO.1** VKORC1 (vitamin K oxidase reductase 1) Warfarin acts by inhibiting the synthesis of vitamin K-dependent clotting factors, which include factors II, VII, IX, and X, and the anticoagulant proteins C and S. [6]

**DIAGNOSIS**:
**CCT scan:** immediately after admission; in case of ICH; follow-up within 6-24 hours (depending on findings in initial CCT, underlying risk factors, assessability/ evolution of the neurological state).
**Neurological status** (level of consciousness, pupil responses, GCS/fourscore): 1-4 hours: every hour; 5-13 hours; 14 hours- discharge: every 6 hours.
**Coagulation tests and target levels of reversal Platelet inhibitors**: PFA, Multiplate* (no target values) VKA: INR [target value: <1.5]
NOACs: dabigatran  hemoclot*/Techoview*(target value: <30ng/ml) [12]

**TREATMENT**.

- In general, alterations in the maintenance dose should not be made more frequently than every 3 days. Adjust this same standard dose by calculating the weekly dose and reducing or increasing it by 5% to 25%. The full effect of dose changes may not be evident for 5 to 7days.
- Warfarin's primary adverse effect is bleeding that can range from mild to life threatening. It does not cause bleeding per se, but it exacerbates bleeding from existing lesions and enables massive bleeding. correcting high INR values is important to reduce bleedingrisk:
- When the INR is greater than 4.5 without evidence of bleeding, the INR can be lowered by withholding warfarin, adjusting the dose of warfarin, and/or providing a small dose of vitamin K to shorten the time to return to normal INR. If the INR is between 5 and 10 and no bleeding is present, routine vitamin K use is not recommended. For INR greater than 10 without evidence of bleeding, oral vitamin K (phytonadione 2.5 mg) issuggested.[13,14]

**ADVERSE EFFECTS**

- Warfarin primary adverse effect is bleeding, which can range from mild to life-threatening. It does not cause bleeding per se, but it exacerbates bleeding from existing lesions and enables massive bleeding from ordinary minorsources.
- Non-hemorrhagic adverse effects of warfarin include rare "purple toe" syndrome and necrosis of the skin. Due to a large number of food–drug and drug-drug interactions with warfarin, close monitoring, and additional INR determinations may be indicated whenever other drugs are initiated, discontinued. Alternatively, a change in the consumption of vitamin K-containing foods is noted.[13]

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**WARFARIN SYNERGISTIC EFFECT:**

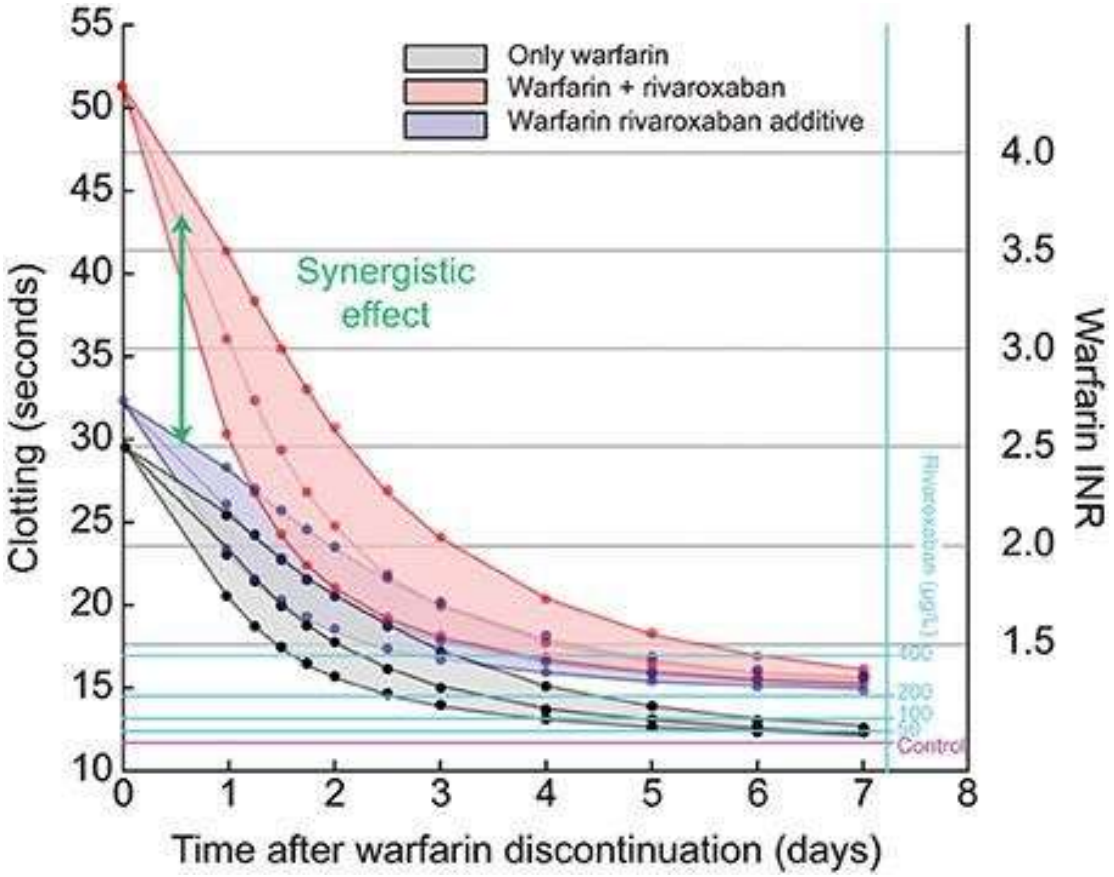


**FIGURE NO 2:** Synergistic effect of warfarin and rivaroxaban (200 µg/L) after warfarin discontinuation. Black lines show the prothrombin time (PT) as a function of time after warfarin discontinuation, starting at an international normalized ratio (INR) of 2.5, simulated for Caucasians. Rivaroxaban exposure of200 µg/L causes a PT prolongation of about 3 s in a patient, not on warfarin therapy. Blue lines show the hypothetical additive effect of warfarin and rivaroxaban exposure of 200 µg/L. Red lines show the actual simulation of the effect of decaying warfarin plus rivaroxaban (synergistic effect). The centre lines are simulated for typical warfarin half-life; lower and upper lines show the same experiments for fast and slow warfarin decay, respectively, using half-lives as reported previously (Wittkowsky, 2003). Light blue lines show the effect of different degrees of rivaroxaban exposure for comparison.[15]

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**INTERACTIONS:**

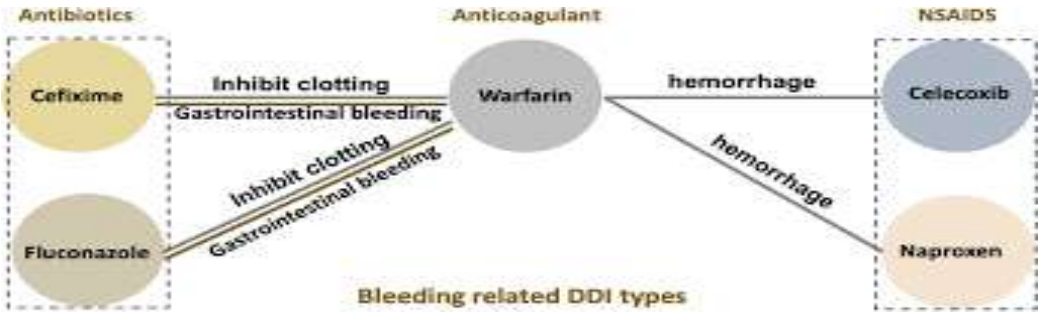


**FIGURE NO 3**: Warfarin as an anticoagulant, if taken together with antibiotic drugs such as Cefixime or Fluconazole, will have a high risk to cause Drug-Drug Interactions inhibition of clotting and gastrointestinal bleeding. Likewise, if Warfarin concomitant with nonsteroidal anti-inflammatory drugs (NSAIDs) such as Celecoxib and Naproxen, it will likely cause DDI hemorrhage (i.e., loss of blood from broken blood vessels). These DDIs are correlated since they are all bleeding-related DDIs caused by the increase of Warfarin's effect.[16]

**Monitoring Warfarin**

- The prothrombin time (PT) is the primary assay used in monitoring warfarin therapy. The prolongation of PT depends on reductions in three of the vitamin K–dependent clotting factors (II, VII and IX) [17] .Warfarin must be monitored to ensure that it works efficiently and is used safely. Achieving the recommended medication of warfarin may be difficult, but it is extremely important. If the dose of warfarin is too low, the patient may be at risk of developing harmful bloodclots.
- If the dose of warfarin is too high, the patient may be at risk of severe bleeding. It may be monitored by drawing blood from a vein and sending blood to an accredited laboratory for testing, or it may be monitored by testing blood from a fingertip with an INR test meter outside the laboratory. Each INR test meter may be prescribed to be used in patients at residence and so will be used among healthcare professionals athome.[18]
- The frequency with which the INR test meter is then used to monitor warfarin or the requirement by the patient will be recommended as part of the patient's health care provider. The target range of an INR was being established by the health care provider. It is typically between 2.0 and 3.0 for basic blood-thinning needs, although the range may vary depending on the specific conditions of the patient. An INR above the patient-specific target range may increase the risk of bleeding, while an INR below the target range may increase the risk of developing a bloodclot.[19,20]

## III. CONCLUSION:

According to records and from many citations (journals), the use of warfarin has been increased as the primary choice of drugs from anticoagulants, but bleeding from warfarin use is a major reaction and a cause of mortality. Need for physicians to prescribe warfarin based on INR ratios, so there may be a chance to reduce complications.

As a result of the "BLACK-BOX" warning about warfarin's bleeding risk, United States FDA product label was added in 2006. Doctors/infirmaries must and should tell their patients to immediately report their signs and symptoms of bleeding. The need for a drug guide to be provided with each prescription should also be implemented,

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