



# WARFARIN AND ITS INTERACTIONS WITH STATINS AND AMIODARONE.

Arshiya Jahan<sup>1</sup>, Mohammed Junaid Javed<sup>2\*</sup>, Nishath<sup>3</sup>, Dr. A.V Kishore Babu<sup>4</sup>, Dr. A Srinivasa Rao<sup>5</sup>.

<sup>1</sup>Student of Bhaskar pharmacy college, Yenkapally, Hyderabad, Telangana, India,500075

<sup>2</sup>Student of Bhaskar pharmacy college, Yenkapally, Hyderabad, Telangana, India,500075

<sup>3</sup>Student of Bhaskar pharmacy college, Yenkapally, Hyderabad, Telangana, India,500075

<sup>4</sup>Head of department Bhaskar pharmacy college, Yenkapally, Hyderabad, Telangana, India,500075

<sup>5</sup>Principal Bhaskar pharmacy college, Yenkapally, Hyderabad, Telangana, India,500075

<sup>1</sup>Pharmacy practice,

<sup>1</sup>Bhaskar pharmacy college, Hyderabad, India.

## Abstract:

This is a comparative review which highlights the interactions of warfarin with statins and amiodarone. Warfarin is used in patients with thromboembolism and is commonly prescribed oral anticoagulant which is a vitamin-k antagonist. Drugs like statins and amiodarone are prescribed for atrial fibrillation and myocardial ischemia simultaneously with warfarin leading to potential drug interaction. Even though these drugs are frequently prescribed with warfarin clinical guidelines on these drug combinations are divergent. Warfarin is highly effective and safe but both efficacy and safety depend upon blood international normalized ratio. Monitoring INR and dose adjustment can be beneficial for effective warfarin therapy. Warfarin, statins and amiodarone are metabolized by Cyt-p450 enzymes leading to possible interactions. Warfarin, when co-administered with statins, inhibits the metabolic pathway of statins causing increased pharmacological action of statins leading to increased risk of drug toxicity and rhabdomyolysis whereas when warfarin is co-administered with Amiodarone, amiodarone inhibits the metabolic pathway of warfarin causing increased anticoagulant effect. The metabolic pathway of warfarin not only interacts with cardiovascular agents but also many dietary supplements making it necessary to monitor the therapy. The main goal of anticoagulation therapy with warfarin should be to administer least effective dose possible that obtains the required International normalized ratio. The initiation of warfarin can be more challenging due to its narrow therapeutic index and pharmacodynamic response is highly unpredictable due to varied individual susceptibility.

**Key words:** Warfarin, Amiodarone, Statins, INR, CYP2C9

## Background:

Warfarin is drug of choice in patients with thrombo-embolic disease due to its high efficacy<sup>[1]</sup>. But it is associated with interindividual variability in drug response and its daily dose varies with individual<sup>[2]</sup>. The wide dose response variations are significantly influenced by pharmacokinetic parameters that are determined by genetic, environmental, and other unknown factors<sup>[3]</sup>. Management of warfarin therapy is also difficult due to its narrow therapeutic index and wide interindividual differences<sup>[2]</sup>. The anticoagulant effect of warfarin should be within the therapeutic range to avoid adverse events<sup>[4]</sup>. The anticoagulant effect is monitored by measurement of the international normalized ratio (INR) or the Prothrombin Time (PTT). It is essential to achieve INR levels within the therapeutic range to avoid thromboses as well as bleeding<sup>[4,5]</sup>. Several guidelines have been developed for initiation of optimal warfarin therapy, but research is still going on for optimum dosage regimen<sup>[6]</sup>. In patients with cardiac disorders like Atrial fibrillation and myocardial ischemia, Amiodarone or statins are used concomitantly with warfarin even though their long-term use is associated with potential drug-drug interactions<sup>[5,7]</sup>. Long term use is also associated with sharp fluctuations in

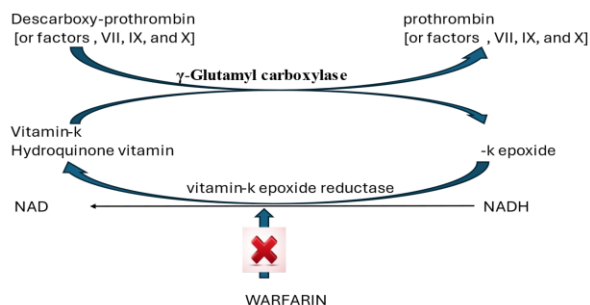
international normalized ratio (INR) due to dietary changes and alcohol consumption [6]. Amiodarone and statins increase the anticoagulant effect of warfarin, causing an increased risk of bleeding [8].

### Introduction:

Warfarin is the most widely prescribed Vitamin K antagonist used for the prevention of thromboembolic events in patients with chronic atrial fibrillation, prosthetic heart valves venous thromboembolism, and coronary artery disease which also requires the use of cardiovascular drugs [1,9,10-13]. Warfarin is associated with major drug related complications which can be minor or life threatening. Warfarin is a drug with a narrow therapeutic window and the dose for adequate anticoagulation is nearly equal to the dose which causes bleeding [14]. This review acknowledges about the drug-drug interactions between warfarin and cardiovascular drugs like statins and amiodarone as both involve similar site of metabolism through cytochrome P450 enzymes, warfarin and statins are metabolized through CYP3A4 and CYP2C9 receptors and amiodarone interferes with CYP2C9 and impairs the metabolism of warfarin [4,7].

### Mechanism of action of warfarin:

Warfarin competitively inhibits the synthesis of vitamin-k dependent clotting factors (II, VII, IX, and X) by inhibiting epoxide reductase enzyme, thus producing anticoagulation effect [2,15].



### Pharmacokinetics of warfarin:

**Route of administration:** oral [16]

**Absorption:** it is completely absorbed through gastrointestinal tract [16].

**Protein binding:** 99% bound primarily to albumin [16].

**Half-life:** 40 hours

**Volume of distribution:** 0.14 L/kg. Warfarin has a distribution phase lasting 6-12 hours.

It freely crosses the placental barrier and achieves fetal serum concentration similar to maternal concentrations [16].

**Duration of action:** 2-5 days [16]

**Metabolism:** Warfarin is a racemic mixture of two optically active isomers, S-warfarin, and R-warfarin. S-warfarin is metabolized predominantly by CYP2C9, and R-warfarin is metabolized by CYP3A4 which converts the drug to inactive 7-hydroxy and 6-hydroxy metabolites that are excreted in the urine [2,3].

**Elimination:** Excreted principally in urine as metabolites [16].

### Mechanisms involving Drug interaction of warfarin:

#### With Statins:

Statins are HMG-CoA reductase inhibitors which are metabolized by CYP3A4 and CYP2C9. Warfarin is also metabolized by the same metabolic pathway. Warfarin competitively inhibits the metabolism of statins leading to increased pharmacological action of statins [17].

#### With Amiodarone:

Atrial fibrillation is the frequently occurring cardiac arrhythmia and is associated with complications like embolic stroke which requires the use of anticoagulants like warfarin. Amiodarone, a potassium channel blocker, is used in combination with warfarin. Amiodarone inhibits the metabolic pathway of warfarin by inhibiting CYP2C9 thereby causing an increased pharmacological effect of warfarin [4,18].

#### Need of the study.

- Provide an overview of drug-drug interactions of warfarin with amiodarone and statins.
- Assist clinicians for designing optimal duration of warfarin therapy in patients using amiodarone and statins.
- Describes the significance of collaboration and co-operation between health care professionals and how it can increase the patient care for effective warfarin treatment along with entire medication regimen of patients to improve the therapeutic outcome in patients requiring anticoagulation.
- To promote the ideology of 'personalized medicine'.

**Methods and results:**

Study conducted with statins.

A study was conducted on patients administered with warfarin and different statins it was found that all the statins inhibited the formation of 10-hydroxywarfarin. Atorvastatin, Fluvastatin, pitavastatin, and simvastatin were potent inhibitors of 10-hydroxy warfarin compared to other statins<sup>[5]</sup>. Fluvastatin was more potent when compared to other statins because of its strong affinity towards Cytochrome p450 enzyme<sup>[19]</sup>.

Another study conducted with 7 patients, where statin was given with warfarin it was found that after 14 days the INR was increased to >4 in 2 out of seven subjects and mean prothrombin time was also increased in next 14 days in 4 out of 7 subjects<sup>[4]</sup>. All included studies showed that when warfarin was given with a statin, an increase in mean international normalized ratio (INR) ranged from 0.15–0.65<sup>[4]</sup>

Data was analyzed for 1,686 patients who were concomitantly administered a statin and warfarin, it was noticed that the risk of gastrointestinal bleeding was more with rosuvastatin when compared to other statins<sup>[23]</sup>.

Case report:

The patient visited his cardiologist and was diagnosed with atrial fibrillation, for which he was prescribed warfarin along with atorvastatin. Ischemic heart disease (IHD), hypertension (HTN), and DLP were identified in his previous medical history. After a week he presented with complaints of tea-colored urine, lethargy, and weakness his probable diagnosis was rhabdomyolysis<sup>[17]</sup>.

Study conducted with amiodarone.

Simultaneous administration of warfarin and amiodarone resulted in increased anticoagulation in several patients when both were given in patients with atrial fibrillation along with

Embolism<sup>[18]</sup>. In 11 out of 15 patients showed an increased PT/INR due to concomitant administration of amiodarone with warfarin<sup>[7]</sup>.

Desethylamiodarone the active metabolite of amiodarone was responsible for increasing the mean INR/dose but there was No correlation between the plasma concentration of amiodarone and INR/Dose<sup>[8]</sup>.

Case report:

A patient after coronary artery bypass surgery was prescribed with amiodarone but the patient suffered with transient ischemic attack due to which warfarin was given as combination therapy. After 15 days the international normalized ratio was increased<sup>[20]</sup>.

**DISCUSSION**

Warfarin being available in 2 isoforms the S-Warfarin is believed to be responsible for major pharmacological action<sup>[18]</sup>. There exist wide variations in dose response in patients using this drug which might be due to variation in CYP2C9 gene<sup>[2]</sup>. The patients with CYP2C9\*3 allele required comparatively lesser dose of warfarin<sup>[14]</sup>. Patients using warfarin need regular measurement of INR [time taken for blood clotting].

Statin being effective drugs in patients with Hyperlipidemia, stroke and myocardial infarction presented side effects when given in combination with anticoagulants. one of the rare adverse reactions which occurred with atorvastatin is rhabdomyolysis, a life-threatening condition that includes myalgia, myocyte necrosis, hyperkalemia and myoglobin when released in blood stream can permanently damage kidneys and heart.<sup>[17,21]</sup>

Bleeding is one of the most frequent complication of anticoagulants and traumatic brain injury also occurred in few patients.<sup>[15,22]</sup> Even the risk of gastrointestinal bleeding was noticed when a study was conducted between statins and warfarin. The risk of GI bleeding varies with every statin and patients taking rosuvastatin are at higher risk when compared to other statins<sup>[23]</sup>.

Bleeding is one of the reasons for discontinuation of anticoagulants, but many studies suggest the continuation of therapy in patients with atrial fibrillation post surgeries with stringent monitoring<sup>[24]</sup>.

The change in mean INR was noticed after nearly four weeks which might be due to stabilization of cholesterol levels after which it is believed to cause adverse drug reaction but there is still need of research regarding interaction<sup>[4]</sup>.

Amiodarone is a drug with complex pharmacokinetics and one of the popular anti-arrhythmic but when it is given with warfarin the pharmacological effect was potentiated and the adverse reaction persisted even after discontinuation of therapy<sup>[18,20]</sup>. The reason behind this remained unclear.

When patients on Amiodarone therapy were prescribed, warfarin the PT-INR was elevated, making it necessary to reduce the dose of warfarin<sup>[7]</sup>.

**Conclusion:**

Monitoring warfarin therapy is imperative in maintaining INR within range to avoid bleeding and thrombosis. The use of warfarin with cardiovascular agents like Amiodarone and statins is widespread but data about potential drug-drug interactions is conflicting. Dose adjustment of warfarin or strict monitoring can minimize the adverse reaction. Overlapping metabolic pathways being the reason for interaction between these drug combinations, further investigations on metabolic pathways can be a breakthrough in the field of research.

‘Personalizing the medicine’ can be more promising due to varied individual susceptibility.

**ACKNOWLEDGEMENT:**

I would like to thank all the corresponding authors who helped me in writing this review.

**References:**

1. Warfarin interactions with complementary medicines, herbs, and dietary supplements. Sanjai Krishna S.2 and Aiswarya Purushothaman\*1:2015
2. pharmacogenomics of warfarin. Allan E. Rettie and Guoying Tai:2006
3. Comparative Pharmacokinetics of Vitamin K Antagonists, mike ufer:2012
4. Drug-drug interactions between vitamin K antagonists and statins: a systematic review [Anna E. Engell](#), [Andreas L. O. Svendsen](#), [Bent S. Lind](#), [Tore Bjerregaard Stage](#), [Maja Hellfritsch](#) & [Anton Pottegård](#):2020
5. Mechanism of Drug-Drug Interactions Between Warfarin and Statins [Abdul Naveed Shaik](#), [Tonika Bohnert](#), [David Williams](#), [Lawrence Gan](#):2016
6. A Prospective Study on the Use of Warfarin in the United Arab Emirates [Abdulla Shehab](#),<sup>1,\*</sup> [Asim Elnour](#),<sup>3</sup> [Abdihakur Abdulle](#),<sup>1</sup> and [Abdul-Kader Souid](#)<sup>4</sup>:2012
7. Interaction between warfarin and short-term intravenous amiodarone in intensive unit patients after cardiac surgery. Tomoki Takase<sup>1</sup>, Hiroaki Ikesue<sup>1\*</sup>, Makiko Tohi<sup>1</sup>, Hiroshi Ueta<sup>2</sup>, Hiroyuki Mima<sup>2</sup>, Tadaaki Koyama<sup>3</sup> and Tohru Hashida<sup>1</sup>:2018
8. Role of Desethylamiodarone in the Anticoagulant Effect of Concurrent Amiodarone and Warfarin Therapy Miyoko Naganuma, BS, \* Tsuyoshi Shiga, MD, PhD, t Kaori Nishikata, BS,\* Takanori Tsuchiya, MS,\* Hiroshi Kasanuki, MD, PhD, t and Emiko Fujii, PhD:2001
9. Systematic Overview of Warfarin and Its Drug and Food Interactions Anne M. Holbrook, MD, PharmD, MSc, FRCPC; Jennifer A. Pereira, MSc; Renee Labiris, PhD; Heather McDonald, MSc; James D. Douketis, MD, FRCPC; Mark Crowther, MD, MSc, FRCPC; Philip S. Wells, MD, FRCPC:2005
10. Albers GW, Dalen JE, Laupacis A, Manning WJ, Petersen P, Singer DE. Antithrombotic therapy in atrial fibrillation. Chest. 2001;119(suppl):194S-206S.
11. Stein PD, Alpert JS, Bussey HI, Dalen JE, Turpie AGG. Antithrombotic therapy in patients with mechanical and biological prosthetic heart valves [published correction appears in Chest.2001; 120:1044]. Chest. 2001;119(suppl):220S-227S.
12. Hyers TMAG, Hull RD, Morris TA, Samama M, Tapson V, Weg JG. Antithrombotic therapy for venous thromboembolic disease. Chest. 2001;119(suppl):176S-193S.
13. Cairns JA, Theroux P, Lewis HD Jr, Ezekowitz M, Meade TW. Antithrombotic agents in coronary artery disease [published correction appears in Chest.2001;120:1427]. Chest. 2001;119(suppl):228S-252S.
14. The effect of simvastatin on warfarin anticoagulation: a Swedish register-based nationwide cohort study Marine L. Andersson<sup>1</sup> & Buster Mannheimer<sup>2,3</sup> & Jonatan D. Lindh<sup>1</sup>:2019
15. Warfarin Drug Interactions Marsha F. Crader; Tracy Johns; Justin K. Arnold.:2023
16. warfarin monograph [American society of health system pharmacists.
17. Rhabdomyolysis due to warfarin and atorvastatin combination therapy in a patient with ischemic heart disease: (A drug interaction) Saeed Kargar Soliemanabad a, Kimia Rasouli a, Zakaria Zakariaei b,c,\* , Mostafa Soleymani c , Parastoo Karimi Aliabadi:2022
18. An Evaluation of the Early Pharmacodynamic Response After Simultaneous Initiation of Warfarin and Amiodarone Stephanie B. Edwin, PharmD, Douglas L. Jennings, PharmD, and James S. Kalus, PharmD:2010
19. Oral Anticoagulant Drug Interactions with Statins: Case Report of Fluvastatin and Review of the Literature. [Miranda R. Andrus Pharm.D.](#):2012
20. Insidiously evolving, occult drug interaction involving warfarin and amiodarone B Cheung, F MLam, C R Kumana:1996
21. Drug Interactions of Lipitor (Atorvastatin) and Other Statins Medications That May Trigger Adverse Events. [Jennifer Moll, PharmD](#):2023
22. Breadth of complications. Walter Ageno and Marco Donadini :2023
23. Comparison of the Risk of Gastrointestinal Bleeding among Different Statin Exposures with Concomitant Administration of Warfarin: Electronic Health Record-Based Retrospective Cohort Study Dahye Shin ,Dukyong Yoon ,Sun Gyo Lim, Ji Man Hong, Rae Woong Park ,Jin Soo Lee :2016
24. Reasons for discontinuing oral anticoagulation therapy for atrial fibrillation: a systematic review:2023 Jackie Buck<sup>1,2</sup>, Julia Fromings Hill<sup>1</sup>, Alison Martin<sup>3</sup>, Cassandra Springate<sup>3</sup>, Bikramaditya Ghosh<sup>3</sup>, Rachel Ashton<sup>4</sup>, Gerry Lee<sup>5</sup>, Andrzej Orlowski<sup>6</sup>

