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Research Article

# QUALITY OF ANTI-COAGULATION, PREDICTORS, AND CONSEQUENCES OF DERANGED INR OF PATIENTS ON WARFARIN THERAPY

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**ABSTRACT**

**Objective:** Warfarin therapy is considered challenging because of the narrow therapeutic index and various pharmacokinetic and pharmacodynamic interactions. The safety and efficacy of warfarin therapy are dependent on maintaining the international normalized ratio (INR) within the target range for the indication. Deranged INR may result into serious adverse effects. The study aims to characterize the quality of anti-coagulation with warfarin and its outcome in terms of adverse events along with analysis of various predictors for INR control.

**Methods:** A cross-sectional study was conducted at a tertiary care center involving all adult patients (≥18 years) on warfarin therapy presenting to the cardiology outpatient department for 1 year. Current INR, time in therapeutic range (TTR), and adverse events, if any were documented and managed appropriately. Logistic regression analysis was used to calculate odds ratios and 95% confidence intervals (CI) to model the predictors of deranged INR values.

**Results:** Of all 425 patients, 164 (38.58%) patients had non-target INR values, 111 (26.11%) were subtherapeutic, and 53 (12.47%) were supratherapeutic. Increased incidence of subtherapeutic range INR was found in women (IRR=1.09; p=0.002) and in patients with valvular atrial fibrillation (IRR=1.24; p<0.001). On the other hand, increased incidence of supratherapeutic INR was found in patients having renal failure (IRR=1.12; p<0.001). Four (2.4%) patients with subtherapeutic INR developed stroke and 3 (1.92%) patients with high INR resulted into bleeding.

**Conclusion:** The study found low percentage of TTR in patients on warfarin therapy. Predictors for poor anticoagulation control were women, valvular atrial fibrillation, renal failure along with drug interactions, and non-adherence to therapy.

**Keywords:** International normalized ratio, Time in therapeutic range, Adverse drug reaction, Adverse drug events, Anti-coagulants.

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## INTRODUCTION

Warfarin is a frequently used oral anti-coagulant effective for the primary and secondary prevention of both arterial and venous thromboembolic disorders. It has proven prophylactic value but its use requires great caution and expertise. The therapy is challenging because of various factors. It has a narrow therapeutic index. Its pharmacokinetics and pharmacodynamics are affected by genetic variables, in addition to drug–drug and drug-food interactions. Regular monitoring of the international normalized ratio (INR) is needed to provide safe and effective care for patients on warfarin. High INR can cause bleeding complications, subtherapeutic INR can lead to treatment failure and increased risk of thromboembolism.

The National Institute for Health and Care Excellence guideline recommends that the time in therapeutic range (TTR) should not be below 65% which may lead to a 2.6-fold increase in the risk of stroke and also 2.4-fold increase in the risk of all-cause mortality. However, the target of TTR is not usually achieved in the real world, thus leading to complications. A meta-analysis found that patients were in the therapeutic range of INR for 63.6% (95% confidence interval [CI], 61.6–65.6) of time [1]. Another study conducted in the rural Indian population found the median TTR as 13.0% and INR was subtherapeutic 66% of the time [2].

There is availability of SAMe-TT2R2 score to predict the quality of Vitamin K antagonist (warfarin) anti-coagulation therapy as measured by time in the therapeutic INR range. Although it does predict low TTR, the effect is small. Its effect on individual patients is too limited to be clinically useful [3]. This study tried to explore a plethora of factors affecting INR control irrespective of any specific tool.

The present study was aimed to characterize the quality of anti-coagulation with warfarin in terms of TTR. It also explores and analyses various predictors for INR control and its outcome in terms of adverse events.

## MATERIALS AND METHODS

This was a cross-sectional study conducted at a tertiary care center in western India for 1 year.

All adult patients (≥18 years) on warfarin therapy who came for follow-up in the cardiology outpatient department were included in the study. Non-probability consecutive random sampling method was used for collecting data from patients, every day at differentperiods. Written informed consent was taken from all the patients. Their prescriptions were captured using mobile camera or a hand-held device and anonymously transcribed into data collection form. The details included were age, gender, diagnosis, indication for warfarin, INR, comorbidities, concomitant medications, and habits/addictions.

Patients had their INR checked in the hospital laboratory before the follow-up visits. The most recent value of INR was recorded and categorized as subtherapeutic INR or supratherapeutic INR according to the recommended guidelines for the particular condition.

- Target therapeutic range (INR 2.0–3.0 or 2.5–3.5 in patients with mechanical heart valve replacement)

- Subtherapeutic range (INR <2.0 or <2.5 in patients with mechanical heart valve replacement)
- Supratherapeutic range (INR >3.0 or >3.5 in patients with mechanical heart valve replacement)

The TTR was determined using the cross-sectional method which takes into account the INR value from the last visit before pre-specified assessment date (1st October 2023). The percentage of patients with last INR within the target therapeutic range and percentage of patients with last INR out of the therapeutic range were calculated.

A brief interview was conducted for the patients in whom INR was found to be deranged to assess the factors responsible for it. The dose of warfarin was adjusted the same day by the consultant.

Drug interactions with warfarin were checked in the patients receiving concomitant medications using Medscape drug interaction checker [4]. The adverse events due to deranged INR were recorded and patients were managed accordingly.

Continuous variables were reported as mean±standard deviation. Categorical variables were described in terms of frequency and percentage. Mann–Whitney U-test was used to compare study subgroups. For categorical variables, the Chi-square test and Fisher's exact test were used. Logistic regression analysis was used to calculate odds ratios and 95% CI to model the predictors of deranged INR values. $p<0.05$ was considered statistically significant. Statistical analyses were performed with SPSS software (version 20.0, SPSS, Inc., Chicago, Illinois).

Approval from the institutional ethics committee was taken and the study was conducted only after the approval. The research was conducted in strict adherence to the principles of good clinical practice and 'National Ethical Guidelines for Biomedical and Health Research Involving Human Participants' established by ICMR (2017).

## RESULTS AND DISCUSSION

### Demographic and clinical profile

A total of 425 patients who were on warfarin therapy were included in the study. Two hundred and seventy-six (64.95%) patients were women and 149 (35.05%) were men. The median age of patients was found to be 51.23 (IQR 42–63) years. Valvular heart disease 123 (28.94%) was the most common indication for warfarin anti-coagulation. Other indications were valvular atrial fibrillation 119 (28%) and prosthetic heart valve 110 (25.88%). Diabetes 209 (49.17%) was the most common comorbidity, followed by hypertension 198 (46.58%) and coronary heart disease 49 (11.52%). Table 1 shows the baseline characteristics of the patients included in the study.

Out of 425 patients, 261 (61.42%) patients had INR within therapeutic range as of 1st October 2023 as determined by cross-sectional method. One hundred and sixty-four (38.58%) patients had INR out of the recommended range for the given condition. Subtherapeutic INR was found in 111 (67.89%) patients. Out of 111 patients, INR between 1 and 2 was found in 66 (59.45%) patients. <0.5 INR was reported in 2 (1.80%) patients. Fifty-three (32.31%) patients showed INR more than the recommended range. >10 INR was found in 3 (5.6%) patients (Fig. 1).

The demographic characteristics and clinical profile of patients with deranged INR are shown in Table 2. It was found that women had significantly higher incidences of developing subtherapeutic INR. Valvular atrial fibrillation, valvular heart disease (without atrial fibrillation), and prosthetic valve were also found to be significantly associated with subtherapeutic range INR. Smoking, use of antimicrobials, and cholesterol-lowering drugs were significantly higher in the subtherapeutic INR group. On the other hand, renal failure was significantly more common in the supratherapeutic INR group.

**Table 1: Baseline patient characteristics (n=425)**

| Variables | Patients on warfarin therapy (n=425) |
|---|---|
| Age (in years) | |
| Mean±standard deviation | 66.37±10.2 |
| Median (IQR) | 51.23 (IQR 42–63) |
| Gender n (%) | |
| Female | 276 (64.95) |
| Male | 149 (35.05) |
| Indication for anti-coagulation n (%) | |
| Valvular atrial fibrillation | 119 (28) |
| Non valvular atrial fibrillation | 25 (5.88) |
| Valvular heart disease (without atrial fibrillation) | 123 (28.94) |
| Prosthetic heart valve | 110 (25.88) |
| Venous thromboembolism | 48 (11.29) |
| Comorbidities n (%) | |
| Diabetes | 209 (49.17) |
| Hypertension | 198 (46.58) |
| Coronary artery disease | 49 (11.52) |
| Chronic heart failure | 31 (7.29) |
| Liver failure | - |
| Renal failure | 11 (2.58) |
| Malignancy | 9 (2.11) |
| Chronic lung disease | 39 (9.17) |
| Addictions/habits | |
| Smoking (people who smoke every day," and "people who smoke some days) | 76 (17.88) |
| Smokeless tobacco (people who consume smokeless tobacco every day and some days") | 134 (31.52) |
| Alcohol (current drinkers) | 49 (11.52) |
| Concomitant medications | |
| Anti-platelet drugs | 52 (12.22) |
| Anti-hypertensive therapy | 198 (46.58) |
| Non-steroidal anti-inflammatory drugs | 49 (11.52) |
| Anti-depressants | 11 (2.58) |
| Anti-microbials (including anti-biotics and anti-fungals) | 46 (10.82) |
| Spironolactone | 31 (7.29) |
| Lactulose | 55 (12.94) |
| Thyroid hormones | 23 (5.41) |
| Chemotherapeutic agents | 9 (2.11) |
| Cholesterol-lowering drugs | 145 (34.11) |

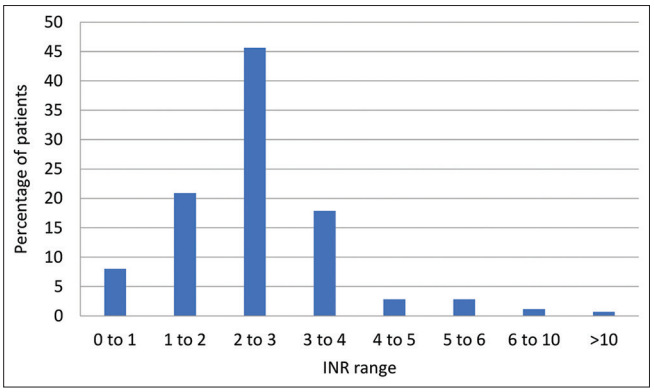


**Fig. 1: Percentage of patients with international normalized ratio values**

### Reasons for INR being out of recommended range

Table 3 takes into account of various factors that may be responsible for the deranged INR. The factors are divided into temporary factors, lifestyle-related factors, and permanent factors. Temporary factors include those which can be subjected to alteration such as non-adherence and changes in drug therapy. Lifestyle-related factors

**Table 2: Demographic characteristics and clinical profile of patients with deranged INR**

| Variables | Patients with subtherapeutic INR (n=111) | Patients with supra-therapeutic INR (n=53) | p-value |
|---|---|---|---|
| Age (in years) | | | |
| Mean±standard deviation | 66.37±10.2 | 52.42±8.3 | 0.071 |
| Gender n (%) | | | |
| Female | 67 (60.36) | 33 (62.26) | <0.001 |
| Male | 44 (39.63) | 20 (37.73) | |
| Indication for anti-coagulation n (%) | | | |
| Valvular atrial fibrillation | 41 (36.93) | 15 (28.30) | 0.002 |
| Non-valvular atrial fibrillation | 5 (4.50) | 2 (3.77) | 0.061 |
| Valvular heart disease (without atrial fibrillation) | 35 (31.53) | 15 (28.30) | <0.001 |
| Prosthetic heart valve | 23 (20.72) | 13 (24.52) | 0.005 |
| Venous thromboembolism | 7 (6.30) | 8 (15.09) | 0.013 |
| Comorbidities n (%) | | | |
| Diabetes | 56 (50.45) | 29 (54.71) | 0.014 |
| Hypertension | 49 (44.14) | 38 (71.69) | 0.257 |
| Coronary artery disease | 10 (9.0) | 8 (15.09) | 0.068 |
| Chronic heart failure | 9 (8.10) | 3 (5.66) | 0.041 |
| Liver failure | - | - | - |
| Renal failure | 2 (1.80) | 4 (7.54) | <0.001 |
| Malignancy | 3 (2.70) | 1 (1.88) | 0.207 |
| Chronic lung disease | 8 (7.20) | 4 (7.54) | 0.342 |
| Addictions/habits (%) | | | |
| Smoking | 34 (30.63) | 10 (18.86) | 0.004 |
| Smokeless tobacco | 46 (41.44) | 16 (30.18) | 0.028 |
| Alcohol | 9 (8.10) | 5 (9.43) | 0.189 |
| Concomitant medications (%) | | | |
| Anti-platelet drugs | 23 (20.72) | 13 (24.52) | 0.027 |
| Anti-hypertensive therapy | 49 (44.14) | 38 (71.69) | 0.329 |
| Non-steroidal anti-inflammatory drugs | 11 (9.90) | 7 (13.20) | 0.051 |
| Anti-depressants | 4 (3.60) | 0 | - |
| Anti-microbials (including anti-biotics and anti-fungals) | 12 (10.80) | 5 (9.43) | <0.0001 |
| Spironolactone | 10 (9) | 4 (7.54) | 0.107 |
| Lactulose | 14 (12.61) | 9 (16.98) | 0.201 |
| Thyroid hormones | 7 (6.30) | 3 (5.66) | 0.451 |
| Chemotherapeutic agents | 2 (2.70) | 0 | - |
| Cholesterol-lowering drugs | 51 (45.94) | 21 (39.62) | <0.0001 |

INR: International normalized ratio

include smoking, tobacco chewing, and alcohol intake. Permanent factors include the role of gender, indication for warfarin therapy, comorbidities, and long-term use of medications.

It was found that 65 (39.63%) patients were not adhering to the therapy (Table 3). Out of these 65 patients, 12 (21.81%) patients were not properly aware of the dosing regimen. Ten (18.18%) patients were taking whatever dose was available in the pharmacy. Nineteen (11.58%) patients were recently on short-term medical therapy. Dose titration was being done in 16 (9.75%) patients and the INR reported during that time showed values out of therapeutic range.

Multivariate analysis showed increased incidence of subtherapeutic range INR in women (IRR=1.09; p=0.002) and in patients with valvular atrial fibrillation (IRR=1.24; p<0.001). On the other hand, increased incidence of supratherapeutic INR was found in patients having renal failure (IRR=1.12; p<0.001).

**Prescription analysis for DDIs**

A total of 345 potential drug–drug interactions with warfarin were found in the study. It included anti-microbials 39 (9.17%) (azithromycin, cephalexin, ciprofloxacin, metronidazole, fluconazole, and cotrimoxazole) anti-platelets 52 (12.23%) (aspirin, ticlopidine, and clopidogrel), NSAIDs 40 (9.41%) (diclofenac and acetaminophen), proton pump inhibitors 76 (17.88%) (omeprazole), antidepressants - SSRIs 7 (1.64%) and cholesterol-lowering drugs 87 (20.47%). All of the interactions were described as 'monitor closely' by the Medscape drug interactions checker.

**Adverse events while on warfarin therapy**

A total of 11 (6.70%) events were recorded from 164 patients having sub- or supra-therapeutic INR (Table 4). Four (2.4%) patients with subtherapeutic INR developed stroke. It occurred in the age group of 40–60 years.

High INR caused bleeding in 3 (1.92%) patients. One patient (age 54 years) presented with major bleeding episode from the gastrointestinal tract, other two (age range 45–55 years) had minor bleeding events from the nose and gums. Two (1.20%) patients, both aged >60 years, presented with ecchymotic patches.

The study demonstrated deranged INR profile in 39% of the patients on warfarin anti-coagulation out of which 26.11% of the patients were in the subtherapeutic range and 12.89% in the supratherapeutic range. It has been found in other studies that the INR values lie in the out-of-recommended range in 34%–75% of the patients on warfarin, average being 50%–55% [5,6].

The study showed significantly higher incidence of subtherapeutic range INR in women. It has been found in studies that women had poor INR control as compared to men. Women are also found to undergo a greater number of dose titrations to achieve stable INR. Moreover, they are also to be affected more by the consequences of subtherapeutic range INR in terms of adverse events like stroke. This could be a reason for undertreatment and selection of a lower dose to avoid bleeding rather than thromboembolism [7,8].

It was also found in the study that valvular atrial fibrillation had 1.24 times more chances of developing subtherapeutic INR values

**Table 3: Predictors for deranged international normalized ratio**

| Reason | Frequency n (%) |
|---|---|
| Temporary factors | |
| Adherence issues | |
| Not taking medication as prescribed (reasons mentioned below) | 65 (39.63) |
| Lack of understanding of dose regimen | 12 (21.81) |
| Non-availability of medication in prescribed dose (continued medication in whatever dose available) | 10 (18.18) |
| Reasons unknown | 43 (26.21) |
| Changes in drug therapy | |
| Recent medical therapy | 19 (11.58) |
| Recent dose change | 16 (9.75) |
| Hold for procedure | 9 (5.48) |
| Initiation of therapy | 8 (4.87) |
| Lifestyle-related factors | |
| Smoking | 44 (26.82) |
| Smokeless tobacco | 52 (31.70) |
| Alcohol | 14 (8.53) |
| Permanent factors | |
| Valvular atrial fibrillation | 56 (34.14) |
| Prosthetic valve | 36 (21.95) |
| Valvular heart disease | 50 (30.48) |
| Renal dysfunction | 6 (3.65) |
| Chronic drug therapy leading to drug interactions | |
| Antiplatelets | 36 (21.95) |
| Cholesterol-lowering drugs | 72 (43.90) |
| Thyroid hormones | 10 (6.09) |
| Chemotherapeutic agents | 2 (1.21) |
| Anti-hypertensive therapy | 87 (53.04) |
| Anti-depressants (SSRIs) | 4 (2.43) |

**Table 4: Adverse events while on warfarin therapy**

| Event | n (%) | International normalized ratio range |
|---|---|---|
| Stroke | 4 (2.40) | 0.5–2 |
| DVT | 1 (0.60) | ≤ 1.5 |
| PE | 1 (0.60) | ≤ 1.5 |
| Ecchymotic patches | 2 (1.20) | 4–5 |
| Bleeding | 3 (1.92) | 5– > 10 |

($p<0.001$) which is supported by other studies as well. Furthermore, the incidence is found to be more in operated patients. The patients with valvular atrial fibrillation are more likely to have valvular heart disease at the mitral site, which requires a higher INR target than either patient with non-valvular atrial fibrillation or patients with valvular heart disease at the aortic site. This target may be more difficult to achieve and maintain. This is troublesome in patients with concomitant atrial fibrillation, as atrial fibrillation patients with valvular heart disease carry an even higher risk of thromboembolic complications (5–62%) than patients with non-valvular atrial fibrillation (0–18%) [9,10].

The study showed that patients with renal failure had 1.12 times more supratherapeutic INR values. Patients with kidney disease had low clearance of drugs metabolized in the liver, like warfarin, and hence predisposing to poor anticoagulation control and more chances of bleeding. Moreover, warfarin is also believed to be responsible for further decline in renal functions, and increased risk of death apart from complications of increased risk of hemorrhage [11].

Drug interactions play an important role in determining the INR control. It was found in the study that recent medical therapy particularly in terms of anti-biotics, anti-fungals prescribed for a recent infection and short-term use of NSAIDs for pain management altered the INR status and resulted in deranged values. Moreover, long-term use of medications such as anti-hypertensives, cholesterol-lowering drugs, proton pump inhibitors, and anti-platelets also affected the anti-coagulation outcome. The studies show that most difficult group to deal with in patients on warfarin therapy is those drugs that increase the bleeding risk. This includes anti-platelets, NSAIDs, and other anticoagulants [12].

Lifestyle-related factors such as smoking and users of smokeless tobacco (current users) were also found to be significantly more in patients with poor anticoagulation control. Smoking is reported to enhance the clearance of warfarin and consequently reducing its anticoagulation effect leading to subtherapeutic levels of INR [12].

The study revealed adverse events in 6.70% of patients due to poor anti-coagulation control which included thromboembolic episodes in patients with sub-therapeutic INR and bleeding events in supra-therapeutic INR. The bleeding events were mainly found in patients >60 years, whereas the thromboembolic phenomenon was restricted to 40–60 years. The elderly (>80 years) are more prone to develop warfarin toxicity, especially in INR higher than recommended therapeutic range. However, the intensity of anti-coagulation therapy and the deviation in the INR were found to be much stronger predictors of risk for bleeding [13,14].

The study utilized cross-sectional method to determine INR control which considers only the INR from the last visit before an arbitrarily chosen date and assumes each INR value as static and binary, either in or out of range, instead of a dynamic value that changes over time [15]. Although this method is not considered the gold standard for measuring time in the therapeutic range, it provides us with an estimate of INR control in the population where there is no record of multiple INR values over a period of time.

Non-adherence to warfarin therapy being a modifiable factor behind poor anti-coagulation control provides scope for improvisation. Proper patient counseling and education are a must before starting warfarin therapy. Drug interactions can be avoided to a certain extent provided that there is enough awareness on the part of prescribing physician. Frequent INR monitoring at regular intervals wherever feasible should be done.

Even though the study showed significant conclusions, more investigations with a larger sample size and variable efficacy of commonly available warfarin in the local market should be taken in consideration.

## CONCLUSION

The study showed poor anti-coagulation control in patients on warfarin therapy. Low percentage of TTR was found in the patients. Women, valvular atrial fibrillation, and renal failure were significantly associated with deranged INR values, in addition to drug interactions (concomitant short-term as well as chronic therapy) and non-adherence to therapy. Adverse events in terms of both bleeding episodes and thrombotic events were found to be associated with poor anti-coagulation control.

## CONFLICTS OF INTEREST

Nil.

## AUTHORS CONTRIBUTIONS

1. Substantial contribution to the conception and design of the work; analysis and interpretation of data for the work; Drafting the work and reviewing it critically for important intellectual content; Final approval of the version to be published; Agreement to be accountable for all aspects of the work
2. Substantial contributions to the conception and design of the work; the acquisition and interpretation of data for the work; Reviewing it critically for important intellectual content; Final approval of the version to be published; Agreement to be accountable for all aspects of the work.

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