Factors Influencing Over-anticoagulation in the Early Stage of Warfarin Anticoagulation Therapy in Patients with Atrial Fibrillation: Postprint

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Abstract

Background: Atrial fibrillation has a high incidence and is an important risk factor for stroke, cardiovascular disease, and all-cause mortality, while appropriate anticoagulation therapy is central to preventing atrial fibrillation-related stroke. Warfarin remains the main anticoagulant currently in use; however, warfarin has a narrow therapeutic window, and fixed-dose warfarin during the initial treatment period can easily lead to excessive or insufficient anticoagulation. Previous clinical studies on warfarin over-anticoagulation have been limited.

Objective: To analyze the epidemiological and clinical characteristics of over-anticoagulation during the initial phase of warfarin therapy in atrial fibrillation patients and to explore the influencing factors associated with over-anticoagulation.

Methods: This study was a single-center retrospective cohort study. A total of 552 atrial fibrillation patients admitted to Linyi People's Hospital from January 2017 to December 2022 and treated with warfarin 2.5 mg/d were enrolled as study subjects. Clinical data were collected, including age, sex, body weight, atrial fibrillation type (non-valvular/valvular), comorbidities (hypertension, diabetes, hypoalbuminemia, abnormal transaminases, heart failure), and concomitant medication use (number of concomitant medications, use of antibiotics, use of amiodarone). Pre-treatment laboratory test results were collected, including serum albumin (Alb), serum creatinine (Scr), serum alanine aminotransferase (ALT), and serum aspartate aminotransferase (AST) levels. Pre-treatment international normalized ratio (INR) and INR after 7 days of medication were also collected. Patients were divided into an over-anticoagulation group (INR > 3.0, n = 122) and a non-over-anticoagulation group (INR ≤ 3.0, n = 430) based on whether INR exceeded 3.0 after 7 days of warfarin therapy. Data

between the two groups were compared, and univariate and multivariate logistic regression analyses were employed to investigate the influencing factors of over-anticoagulation during the initial phase of warfarin therapy.

Results: The over-anticoagulation group exhibited higher age, proportion of females, valvular atrial fibrillation, hypoalbuminemia, abnormal transaminases, number of concomitant medications, amiodarone use, and AST levels compared with the non-over-anticoagulation group, while body weight, hypertension, diabetes, Alb, and ALT levels were lower ($P < 0.05$). Multivariate logistic regression analysis revealed that age ≥ 65 years (OR = 1.954, 95% CI = 1.243–3.073, $P = 0.004$), body weight ≤ 63 kg (OR = 2.967, 95% CI = 1.841–4.783, $P < 0.001$), number of concomitant medications > 5 (OR = 1.976, 95% CI = 1.175–3.323, $P = 0.010$), and Scr ≥ 91 mol/L (OR = 2.087, 95% CI = 1.222–3.561, $P = 0.007$) were independent risk factors for over-anticoagulation during the initial phase of warfarin therapy in atrial fibrillation patients, whereas diabetes (OR = 0.424, 95% CI = 0.191–0.939, $P = 0.034$) was a protective factor.

Conclusion: Age ≥ 65 years, body weight ≤ 63 kg, number of concomitant medications > 5, and Scr ≥ 91 mol/L may be independent risk factors for over-anticoagulation during the initial phase of warfarin therapy in atrial fibrillation patients, whereas diabetes may be a protective factor. Close monitoring of INR levels is recommended for warfarin-treated patients who are elderly, have low body weight, use multiple concomitant medications, or have elevated Scr levels.

Full Text

Influencing Factors of Overanticoagulation at Initial Stage of Warfarin Anticoagulation Therapy in Patients With Atrial Fibrillation

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Abstract

Background: Atrial fibrillation (AF) is a highly prevalent arrhythmia and a major risk factor for stroke, cardiovascular disease, and all-cause mortality. Appropriate anticoagulation therapy is central to preventing AF-related stroke.

Warfarin remains a primary anticoagulant, but its narrow therapeutic window means fixed-dose regimens often lead to overanticoagulation or insufficient anticoagulation during initial treatment. Previous clinical studies on warfarin overanticoagulation are limited.

Objective: To analyze the epidemiological and clinical characteristics of overanticoagulation in AF patients during initial warfarin therapy and identify its influencing factors.

Methods: This single-center retrospective cohort study included 552 AF patients treated with warfarin 2.5 mg/d at Linyi People's Hospital between January 2017 and December 2022. Clinical data were collected, including age, sex, body mass, AF type (non-valvular/valvular), comorbidities (hypertension, diabetes, hypoproteinemia, transaminase abnormalities, heart failure), and concomitant medications (number of drugs, antibiotics, amiodarone). Laboratory results before treatment included serum albumin (Alb), serum creatinine (Scr), alanine aminotransferase (ALT), aspartate aminotransferase (AST), baseline INR, and INR after 7 days of treatment. Patients were divided into overanticoagulation (INR>3.0, n=122) and non-overanticoagulation (INR$ $3.0, n=430) groups based on INR after 7 days of warfarin therapy. Inter-group comparisons were performed, and univariate and multivariate logistic regression analyses were used to identify influencing factors.

Results: The overanticoagulation group had higher mean age, female proportion, valvular AF, hypoproteinemia, transaminase abnormalities, number of concomitant medications, amiodarone co-administration, and AST levels, but lower body mass, hypertension, diabetes, Alb, and ALT compared with the non-overanticoagulation group (P<0.05). Multivariate logistic regression revealed that age$ $65 years (OR = 1.954, 95$ $63 kg (OR = 2.967, 95$ 91 mol/L (OR=2.087, 95%CI=1.222–3.561, P=0.007) were independent risk factors for overanticoagulation, while diabetes (OR=0.424, 95%CI=0.191–0.939, P=0.034) was a protective factor.

Conclusion: Age$ $65 years, body mass $63 kg, concomitant medications > 5, and Scr 91 mol/L may be independent risk factors for overanticoagulation during initial warfarin therapy in AF patients, whereas diabetes may be protective. INR should be closely monitored in elderly, low-body-mass, polypharmacy, and high-Scr patients receiving warfarin.

Keywords: atrial fibrillation; warfarin; international normalized ratio; overanticoagulation; risk factors; logistic model

Introduction

Atrial fibrillation is a common arrhythmia with high prevalence and represents an important risk factor for stroke, cardiovascular disease, and

all-cause mortality[1]. Anticoagulation therapy is the core strategy for preventing AF-related stroke[2]. While novel oral anticoagulants (NOACs) are currently recommended as the preferred anticoagulation strategy, multiple analyses of clinical practice patterns show that warfarin remains the main anticoagulant used[2−3],[6], and valvular AF patients can only receive warfarin[7−8]. However, warfarin has a narrow therapeutic window, and fixed-dose regimens frequently cause overanticoagulation or inadequate anticoagulation during initial treatment. A survey of elderly inpatients ($ 65 years) receiving warfarin found that 33.2{9}. Another meta − analysis of 45 studies including 71,065 patients showed that 44
This retrospective study analyzed overanticoagulation during the initial phase of fixed-dose warfarin therapy in AF patients to explore its influencing factors and provide guidance for clinical dose adjustment.

Methods

Study Population We included AF patients admitted to Linyi People's Hospital from January 2017 to December 2022 who received warfarin 2.5 mg/d (Warfarin Sodium Tablets, Qilu Pharmaceutical Co., Ltd., National Drug Approval No. H37021314) once daily in the morning. The study was approved by the Linyi People's Hospital Medical Science Ethics Committee (Approval No.: Linyi People's Hospital Scientific Research Ethics Review No. 20040).

Inclusion Criteria

(1) Age$ 18 years; (2) First − time warfarin users or those who had discontinued warfarin for 7 days before adm
days; (4) INR measured before treatment and on the morning after 7 days of treatment.

Exclusion Criteria

(1) Patients receiving warfarin before admission or with discontinuation<7 days; (2) Warfarin treatment<7 days or dose adjustment within the initial 7 days; (3) Incomplete medical records lacking required clinical data.

Data Collection A standardized Excel form was used to extract clinical data from the hospital electronic medical record system, including age, sex, body mass, AF type (non-valvular/valvular), comorbidities (hypertension, diabetes, hypoproteinemia, transaminase abnormalities, heart failure), concomitant medications (number of drugs, antibiotic co-administration, amiodarone co-administration), baseline INR, steady-state INR, and baseline laboratory values: serum creatinine (Scr), serum albumin (Alb), alanine aminotransferase (ALT), and aspartate aminotransferase (AST).

Definitions Valvular AF: According to domestic consensus recommendations[8], AF was classified as valvular or non-valvular. Valvular AF refers to AF

occurring in the setting of rheumatic mitral stenosis, mechanical/bioprosthetic valve replacement, or mitral valve repair.

Overanticoagulation: Warfarin produces anticoagulant effects within 24 hours of first administration, and INR approaches steady state after 5–7 days of continuous dosing[12]. This study defined INR on the morning after 7 days of warfarin as steady-state INR. The target INR range for warfarin therapy is 2.0–3.0[13]; steady-state INR>3.0 was defined as overanticoagulation[14], and INR$ $3.0 as non-overanticoagulation.

Grouping Patients were divided into overanticoagulation (INR>3.0, n=122) and non-overanticoagulation (INR$ $3.0, n=430) groups based on INR after 7 days of warfarin therapy.

Statistical Analysis SPSS 25.0 software was used for statistical analysis. The Kolmogorov-Smirnov test assessed normality. Normally distributed continuous variables were expressed as mean±SD and compared using independent samples t-tests; non-normally distributed variables were expressed as median (Q1, Q3) and compared using Mann-Whitney U tests. Categorical variables were expressed as percentages and compared using ^{2} or Fisher's exact tests. Variables with P<0.05 in univariate analysis were further analyzed. Continuous variables were stratified using receiver operating characteristic (ROC) curve analysis to determine optimal cut-off values, then included with other significant categorical variables in binary multivariate logistic regression analysis to identify influencing factors for overanticoagulation. Risk was expressed as odds ratio (OR) with 95% confidence interval (CI). P<0.05 was considered statistically significant.

Results

Patient Characteristics A total of 552 AF patients were included (285 males [51.63%], 267 females [48.37%]; age range 24–86 years, mean age 62.0$±10.3*years*).*Overanticoagulationoccurredin*122*patients*(22.10 $3.0.
Baseline INR, heart failure, antibiotic co-administration, and Scr levels did not differ significantly between groups (P>0.05). However, the overanticoagulation group had significantly higher age, female proportion, valvular AF, hypoproteinemia, transaminase abnormalities, number of concomitant medications, amiodarone co-administration, and AST levels, but lower body mass, hypertension, diabetes, Alb, and ALT (P<0.05) .

Univariate Logistic Regression Analysis Using overanticoagulation as the dependent variable and clinical characteristics as independent variables (assignments shown in), univariate logistic regression identified age, female sex, body mass, valvular AF, hypertension, diabetes, hypoproteinemia, transaminase abnormalities, number of concomitant medications, amiodarone co-administration, Alb, Scr, ALT, and AST as influencing factors (P<0.05) .

Stratification of Continuous Variables ROC curve analysis was performed to determine optimal cut-off values for significant continuous variables (age, body mass, number of concomitant medications, Scr). The optimal cut-off values were: age 65 years, body mass 63 kg, number of concomitant medications 5, and Scr 91 mol/L [Figure 1: see original paper], . Univariate analysis showed that body mass$ $63kg(OR = 3.674, 95$ $65years(OR = 2.068, 95$ 91 mol/L (OR=1.979, 95%CI=1.257–3.115, P=0.003), and number of concomitant medications>5 (OR=1.127, 95%CI=1.329–3.402, P=0.002) significantly increased the risk of overanticoagulation.

Multivariate Logistic Regression Analysis Multivariate logistic regression analysis (with overanticoagulation as the dependent variable and significant univariate factors as independent variables: age$ $65years, female sex, body mass$ $63kg, valvular AF, hypertensio$ $5, amiodarone co-administration, Scr$ $91\mu mol/L) revealed that age$ $65years(OR = 1.954, 95$ $63kg(OR = 2.967, 95$ 91 mol/L (OR=2.087, 95%CI=1.222–3.561, P=0.007) were independent risk factors for overanticoagulation, while diabetes (OR=0.424, 95%CI=0.191–0.939, P=0.034) was a protective factor .

Discussion

Warfarin is a dicoumarol derivative with proven efficacy and relatively low cost, making it a classic and widely used oral anticoagulant[15]. However, its pharmacokinetics and pharmacodynamics vary substantially among individuals, and efficacy is easily affected by multiple factors. Even with standard treatment regimens, INR frequently falls outside the therapeutic range during the first week, creating high bleeding risk[16]. This study found that 22.10% of AF patients experienced overanticoagulation during initial treatment with 2.5 mg warfarin, lower than the 33.2% reported by Cohen et al.[9], possibly due to differences in study populations and warfarin doses. Although previous studies have established numerous pharmacogenomic-based warfarin dosing models, genetic polymorphisms explain only 40%–60% of individual variability[17], and patient clinical characteristics are more closely related to anticoagulation control quality and clinical events than genetic factors[18]. This study examined AF patients receiving fixed-dose warfarin to explore how clinical characteristics affect overanticoagulation during initial therapy.

Age$ $65years was an independent risk factor for overanticoagulation. International studies have shown age is aris$ $1.02, 95$^{\{19\}.Li et al.}$\{20\}$ also found age was an independent factor affecting warfarin dose and anticoagulation stability after cardiac valve replacement. A systematic review of 433 warfarin dosing prediction models showed 92.61% (401/433) included age[21]. Zhang et al.[22] reported that Chinese patients over 60 required lower warfarin doses, while younger patients needed higher doses. Shendre et al.[23] found middle-aged and elderly patients required 10.6% lower doses than younger users.

Multiple studies have shown body mass positively correlates with stable warfarin dose—higher body mass requires higher stable doses[21–22,24–27]. This study

found body mass had predictive value for steady-state anticoagulation intensity, with body mass$ 63*kgbeinganindependentriskfactorforoveranticoagulation*, *suggestingthatlowerbodymassi* showed body mass>70 kg significantly reduced overanticoagulation risk (INR$ $5) after 48 hours (P=0.01), indicating that low-body-mass patients require careful INR monitoring and dose adjustment to reduce overanticoagulation risk.

AF patients often have multiple cardiovascular comorbidities and polypharmacy, which can affect warfarin efficacy. Yao et al.[28] found 53.1% of warfarin patients in pharmaceutical clinics used drugs affecting warfarin efficacy. Huang et al.[29] analyzed 1,204 warfarin prescriptions with concomitant medications, identifying 171 drug types with 42 (24.56%) interacting with warfarin. This study found number of concomitant medications>5 was an independent risk factor for overanticoagulation. A Swiss multicenter prospective cohort study showed 49.8% of patients$ 65*yearstook* 4*medicationssimultaneously*, *withpolypharmacyincreasingmajorbleedingriskby*83[{30}.*La* analyzed 100 patients with INR elevation (INR>3.50) due to drug interactions, finding 13.25% (40/302) involved warfarin-enhancing drugs. These findings indicate polypharmacy is a significant concern requiring frequent INR monitoring to detect overanticoagulation and prevent bleeding.

Scr$ 91*μmol*/*Lwasalsoanindependentriskfactorforoveranticoagulation*.*Huangetal*.^{16}$ showed Scr correlated with INR on day 7. Multiple studies have demonstrated Scr is associated with stable warfarin dose (all P<0.05)[32–34] and with time to first INR target achievement (P<0.05)[34], suggesting that patients with elevated Scr require careful INR monitoring and dose adjustment to avoid overanticoagulation-related bleeding.

Interestingly, diabetes significantly reduced overanticoagulation risk (OR=0.424, 95%CI=0.191–0.939, P=0.034), suggesting diabetic patients may have lower warfarin sensitivity. In vivo and in vitro studies show that hyperglycemia-induced non-enzymatic glycation of proteins significantly increases albumin-warfarin binding[35]. Qiu[36] found that diabetic patients taking the same warfarin dose had significantly smaller INR increases from baseline at 24 hours compared with non-diabetics (P<0.01), indicating diabetes reduces free warfarin in circulation, decreases drug effect, and slows INR elevation. Zhang et al.[22] also found Chinese warfarin patients with diabetes required higher doses.

In conclusion, for AF patients receiving warfarin 2.5 mg/d, age$ 65*years*, *bodymass* 63*kg*, *numberofconcomitan* 5, *andScr* $91 mol/L are independent risk factors for overanticoagulation during initial therapy, while diabetes may be protective. This study has limitations: (1) Short follow-up—data were extracted at 7 days, before some patients reached steady-state anticoagulation due to individual variability; (2) While concomitant medications were recorded, only the number of drugs was documented rather than specific agents. Despite these limitations, the findings have clinical significance, guiding proactive warfarin regimen adjustments in elderly, low-body-mass, polypharmacy, and high-Scr patients to reduce

overanticoagulation risk.

Author Contributions

Wei Yanjin conceived the study, designed the research protocol, and proposed key indicators. Guo Dequn and Liu Cunfei collected, organized, and entered data. Li Jiao performed statistical analysis. Fan Caixia analyzed data, interpreted results, and drafted the manuscript. Li Zhengrong revised the manuscript. Qiu Shi provided project guidance and quality control.

Conflict of Interest Statement

The authors declare no conflicts of interest.

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Note: Figure translations are in progress. See original paper for figures.