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Research Article

A Prospective Observational Study of Coagulation Profiles in Patients on Common Antithrombotic Therapies and Their Correlation with Bleeding Risk

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ABSTRACT:

Antithrombotic therapies including warfarin and antiplatelet agents require careful monitoring to balance thrombotic protection against bleeding risk. This is particularly challenging in resource-limited settings where access to specialized coagulation testing is often restricted. A prospective observational study was conducted from January to December 2023 at three tertiary care hospitals in Nigeria. We enrolled 450 patients on stable antithrombotic therapy (150 on warfarin, 150 on aspirin, 150 on clopidogrel) and followed them for six months. Prothrombin time/international normalized ratio (PT/INR), activated partial thromboplastin time (aPTT), and bleeding events were monitored monthly. Among warfarin patients, only 42.7% maintained therapeutic INR ranges (2.0-3.0) across all measurements, while 34.0% showed subtherapeutic and 23.3% supratherapeutic values. The incidence of major bleeding was significantly higher in patients with INR >3.5 (18.9% vs. 2.3% in therapeutic range, $p<0.001$). Antiplatelet therapy patients demonstrated minimal changes in conventional coagulation parameters despite clinically significant bleeding events. Multivariate analysis identified age >65 years (OR: 3.2, 95% CI: 1.8-5.7), renal impairment (OR: 2.8, 95% CI: 1.5-5.2), and concomitant NSAID use (OR: 2.4, 95% CI: 1.3-4.4) as independent predictors of bleeding Basic coagulation tests effectively stratify bleeding risk in warfarin-treated patients but have limited utility for monitoring antiplatelet therapies. Simplified risk assessment tools incorporating clinical factors and basic laboratory parameters can optimize antithrombotic management in settings with limited resources.

Keywords: *Antithrombotic, Antiplatelet agents, Bleeding risk, Coagulation profiles, INR monitoring, Resource-limited settings, Warfarin,*

1. INTRODUCTION

Antithrombotic therapies, including anticoagulants and antiplatelet agents, represent cornerstone treatments for numerous cardiovascular conditions, significantly reducing the risk of thrombotic events such as stroke, myocardial infarction, and venous thromboembolism (January et al., 2019). However, the therapeutic benefits of these medications are counterbalanced by an increased risk of bleeding complications, which range from minor mucocutaneous bleeding to life-threatening intracranial or gastrointestinal hemorrhage (Nishimura et al., 2017). This delicate balance between thrombotic protection and bleeding risk necessitates careful monitoring, particularly for medications with narrow therapeutic indices such as warfarin.

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In high-income countries, sophisticated coagulation monitoring including specialized platelet function assays, chromogenic factor X measurements, and genetic testing guide antithrombotic management (Lip et al., 2018). However, in resource-limited settings, healthcare providers often rely exclusively on basic coagulation tests such as prothrombin time/international normalized ratio (PT/INR) and activated partial thromboplastin time (aPTT) due to limited availability of advanced hemostatic testing (Jacobson et al., 2021). The utility of these basic parameters for comprehensive bleeding risk assessment, particularly in patients on antiplatelet therapies, remains inadequately characterized.

Warfarin, despite the introduction of direct oral anticoagulants (DOACs), remains widely used in many resource-limited settings due to its lower cost and extensive clinical experience (Barnes et al., 2020). Its management is particularly challenging in these environments due to limited access to routine INR monitoring, dietary variations affecting vitamin K intake, and numerous drug interactions (Holbrook et al., 2021). Similarly, antiplatelet agents like aspirin and clopidogrel are mainstays of cardiovascular prevention but carry significant bleeding risks that are difficult to quantify with standard laboratory tests (Capodanno et al., 2020).

Current guidelines for antithrombotic therapy monitoring are largely derived from studies conducted in high-resource settings and may not be directly applicable to environments with different patient populations, healthcare infrastructures, and available resources (Ntai et al., 2022). There is a critical need for context-specific evidence to guide antithrombotic management in resource-limited settings, where simplified monitoring protocols and risk stratification tools could significantly improve patient outcomes.

This prospective observational study aimed to characterize coagulation profiles using basic laboratory tests in patients on common antithrombotic therapies and to evaluate the correlation between these parameters and bleeding risk. Additionally, we sought to identify clinical and laboratory predictors of bleeding complications that could inform risk stratification in settings with limited diagnostic capabilities.

2. METHODS

2.1 Study Design and Setting

A prospective observational study was conducted from January to December 2023 at three tertiary care hospitals in Nigeria representing different geographical regions: University College Hospital Ibadan (Southwest), Aminu Kano Teaching Hospital (Northwest), and University of Nigeria Teaching Hospital Enugu (Southeast). These centers provide cardiovascular services to diverse patient populations and have basic coagulation laboratory capabilities.

2.2 Study Population

We enrolled 450 adult patients (≥18 years) on stable antithrombotic therapy, with 150 patients in each of three treatment groups: warfarin, aspirin (75-100 mg daily), and clopidogrel (75 mg daily). Stable therapy was defined as no dose adjustment in the preceding four weeks.

Inclusion criteria were: (1) ongoing antithrombotic therapy for at least three months; (2) indication for therapy including atrial fibrillation, mechanical heart valves, venous thromboembolism, coronary artery disease, or cerebrovascular disease; and (3) willingness to provide informed consent and adhere to follow-up schedule. Exclusion criteria included: (1) concomitant use of multiple antithrombotic agents; (2) known bleeding diathesis or thrombophilia; (3) severe hepatic impairment (Child-Pugh class C); (4) pregnancy or lactation; and (5) life expectancy less than six months.

Sample size calculation was based on detecting a 15% difference in bleeding rates between patients with therapeutic versus non-therapeutic INR values, with 80% power and 5% alpha error, yielding a minimum required sample of 135 patients per group. We enrolled 150 patients per group to account for potential loss to follow-up.

2.3 Data Collection

2.3.1 Clinical Assessment

At enrollment, comprehensive demographic and clinical data were collected including age, gender, indication for antithrombotic therapy, comorbidities, concomitant medications, and anthropometric measurements. Patients were followed monthly for six months through clinic visits and telephone interviews.

2.3.2 Laboratory Measurements

Blood samples were collected at enrollment and monthly thereafter for coagulation testing. PT/INR and aPTT were performed using semi-automated coagulation analyzers (STart 4, Diagnostica Stago) with manufacturer-reagents at each participating center. Quality control was performed daily using commercial control plasmas. For patients on warfarin, additional INR measurements performed as part of clinical care were recorded.

2.3.3 Bleeding Events

Bleeding events were classified according to the International Society on Thrombosis and Haemostasis (ISTH) criteria as major bleeding or clinically relevant non-major bleeding (CRNMB) (Kaatz et al., 2015). Major bleeding was defined as fatal bleeding, symptomatic bleeding in a critical area or organ, bleeding causing a fall in hemoglobin level of 2 g/dL or more, or leading to transfusion of two or more units of whole blood or red cells. CRNMB was defined as any bleeding event requiring medical intervention but not meeting criteria for major bleeding.

2.4 Statistical Analysis

Data were analyzed using SPSS version 26.0 (IBM Corp., Armonk, NY). Continuous variables were expressed as mean ± standard deviation or median with interquartile range based on distribution normality, and compared using Student's t-test or Mann-Whitney U test. Categorical variables were expressed as frequencies and percentages and compared using chi-square or Fisher's exact test. Multivariate logistic regression analysis was performed to identify independent predictors of bleeding events. Receiver operating characteristic (ROC) curve analysis was used to determine optimal INR cut-off values for predicting bleeding risk. A p-value <0.05 was considered statistically significant.

2.5 Ethical Considerations

The study protocol was approved by the institutional review boards of all participating hospitals (UCH/UI/EC/23/0125, AKTH/EC/23/087, UNTH/EC/23/0453). Written informed consent was obtained from all participants after detailed explanation of the study procedures. Patients with critically abnormal coagulation parameters or significant bleeding events were managed according to standard protocols, and their primary physicians were notified immediately.

3. RESULTS

3.1 Baseline Characteristics

The baseline characteristics of the study population are summarized in Table 1. The mean age was 62.4 ± 11.8 years, with 54.2% male participants. Cardiovascular risk factors were highly prevalent, with hypertension present in 68.9% of patients and diabetes mellitus in 31.6%. The most common indications for antithrombotic therapy were atrial fibrillation (36.4%), coronary artery disease (29.8%), and cerebrovascular disease (18.2%). Concomitant medications included proton pump inhibitors (42.7%), statins (58.9%), and nonsteroidal anti-inflammatory drugs (NSAIDs, 12.4%).

Table 1: Baseline Characteristics of Study Participants (N=450)

Characteristic	Warfarin (n=150)	Aspirin (n=150)	Clopidogrel (n=150)	Total (N=450)

Age, years (mean ± SD)	64.2 ± 10.5	61.8 ± 12.3	61.2 ± 12.6	62.4 ± 11.8
Male gender	78 (52.0%)	84 (56.0%)	82 (54.7%)	244 (54.2%)
Body mass index, kg/m²	26.8 ± 4.2	27.3 ± 5.1	26.9 ± 4.7	27.0 ± 4.7
Indication for therapy				
Atrial fibrillation	98 (65.3%)	32 (21.3%)	34 (22.7%)	164 (36.4%)
Coronary artery disease	22 (14.7%)	68 (45.3%)	44 (29.3%)	134 (29.8%)
Cerebrovascular disease	18 (12.0%)	32 (21.3%)	32 (21.3%)	82 (18.2%)
Venous thromboembolism	12 (8.0%)	0 (0%)	0 (0%)	12 (2.7%)
Other	0 (0%)	18 (12.0%)	40 (26.7%)	58 (12.9%)
Comorbidities				
Hypertension	108 (72.0%)	102 (68.0%)	100 (66.7%)	310 (68.9%)
Diabetes mellitus	42 (28.0%)	50 (33.3%)	50 (33.3%)	142 (31.6%)
Heart failure	38 (25.3%)	22 (14.7%)	18 (12.0%)	78 (17.3%)
Chronic kidney disease	24 (16.0%)	18 (12.0%)	16 (10.7%)	58 (12.9%)
Concomitant medications				
Proton pump inhibitors	62 (41.3%)	64 (42.7%)	66 (44.0%)	192 (42.7%)
Statins	78 (52.0%)	94 (62.7%)	92 (61.3%)	264 (58.7%)
NSAIDs	14 (9.3%)	20 (13.3%)	22 (14.7%)	56 (12.4%)

3.2 Coagulation Parameters

Coagulation parameters across the treatment groups are presented in Table 2. As expected, warfarin-treated patients showed significantly prolonged PT/INR values compared to antiplatelet groups ($p<0.001$). However, only 42.7% of warfarin patients maintained therapeutic INR ranges (2.0-3.0) across all measurements during the study period, while 34.0% predominantly showed subtherapeutic values (<2.0) and 23.3% had predominantly supratherapeutic values (>3.0). aPTT values were also significantly prolonged in the warfarin group but remained within normal limits in most antiplatelet-treated patients.

Table 2: Coagulation Parameters by Treatment Group

Parameter	Warfarin (n=150)	Aspirin (n=150)	Clopidogrel (n=150)	p-value
INR (mean ± SD)	2.6 ± 0.8	1.0 ± 0.1	1.0 ± 0.1	<0.001
INR categories				
Subtherapeutic (<2.0)	51 (34.0%)	-	-	-
Therapeutic (2.0-3.0)	64 (42.7%)	-	-	-
Supratherapeutic (>3.0)	35 (23.3%)	-	-	-
aPTT (seconds, mean ± SD)	42.3 ± 8.5	32.1 ± 4.2	31.8 ± 3.9	<0.001
Time in therapeutic range	58.4%	-	-	-

3.3 Bleeding Events

During the six-month follow-up period, 64 bleeding events were recorded (14.2% of patients), including 18 major bleeding events (4.0%) and 46 clinically relevant non-major bleeding events (10.2%). The distribution of bleeding events by treatment group and INR status is shown in Table 3.

Table 3: Bleeding Events by Treatment Group and INR Status

Parameter	Major Bleeding n (%)	CRNMB n (%)	Total Bleeding n (%)
Treatment group			
Warfarin	12 (8.0%)	20 (13.3%)	32 (21.3%)
Aspirin	3 (2.0%)	14 (9.3%)	17 (11.3%)
Clopidogrel	3 (2.0%)	12 (8.0%)	15 (10.0%)
Warfarin by INR			
Subtherapeutic (<2.0)	2 (3.9%)	4 (7.8%)	6 (11.8%)
Therapeutic (2.0-3.0)	3 (4.7%)	8 (12.5%)	11 (17.2%)
Supratherapeutic (>3.0)	7 (20.0%)	8 (22.9%)	15 (42.9%)

Among warfarin-treated patients, the incidence of major bleeding was significantly higher in those with INR >3.5 (18.9% vs. 2.3% in therapeutic range, $p<0.001$). The most common sites of major bleeding were gastrointestinal (61.1%) and intracranial (22.2%). For antiplatelet therapies, there was no significant correlation between conventional coagulation parameters and bleeding risk, despite the occurrence of clinically significant bleeding events.

3.4 Predictors of Bleeding Risk

Multivariate logistic regression analysis identified several independent predictors of overall bleeding events (Table 4). Age >65 years (OR: 3.2, 95% CI: 1.8-5.7), renal impairment (eGFR <60 mL/min/1.73m²; OR: 2.8, 95% CI: 1.5-5.2), concomitant NSAID use (OR: 2.4, 95% CI: 1.3-4.4), and history of previous bleeding (OR: 3.6, 95% CI: 1.9-6.8) were significantly associated with increased bleeding risk. For warfarin-treated patients specifically, INR >3.0 was the strongest predictor of bleeding (OR: 4.8, 95% CI: 2.4-9.6).

Table 4: Multivariate Analysis of Predictors for Bleeding Events

Predictor	Adjusted Odds Ratio	95% CI	p-value
Age >65 years	3.2	1.8-5.7	<0.001
Renal impairment	2.8	1.5-5.2	0.001
Concomitant NSAID use	2.4	1.3-4.4	0.005
History of previous bleeding	3.6	1.9-6.8	<0.001
INR >3.0 (warfarin only)	4.8	2.4-9.6	<0.001
Anemia (Hb <11 g/dL)	2.1	1.1-3.9	0.02

ROC curve analysis for INR and bleeding risk in warfarin-treated patients showed an area under the curve of 0.79 (95% CI: 0.71-0.86), with an optimal cutoff value of 3.2 for predicting major bleeding events (sensitivity 75%, specificity 82%).

4. DISCUSSION

This prospective observational study provides comprehensive characterization of coagulation profiles and bleeding risk in patients on common antithrombotic therapies in a resource-limited

setting. Our findings demonstrate that while basic coagulation tests effectively stratify bleeding risk in warfarin-treated patients, they have limited utility for monitoring antiplatelet therapies. Furthermore, we identified several clinical predictors that could enhance bleeding risk assessment when combined with basic laboratory parameters.

The suboptimal time in therapeutic range (TTR) of 58.4% among warfarin-treated patients in our study is consistent with previous reports from resource-limited settings and highlights the challenges of maintaining stable anticoagulation in these environments (Jacobson et al., 2021). The multiple factors contributing to this phenomenon likely include limited access to regular monitoring, dietary variations, medication adherence issues, and frequent drug interactions. The strong correlation between supratherapeutic INR values (>3.0) and bleeding risk reinforces the importance of maintaining patients within their target ranges and suggests that simplified monitoring protocols focusing on identifying critically high INR values could be particularly valuable in settings with limited resources.

The differential utility of basic coagulation tests across antithrombotic classes has important implications for clinical practice. For warfarin management, PT/INR remains an essential monitoring tool, and our data support its continued use for bleeding risk stratification. The identified INR cutoff of 3.2 for increased bleeding risk provides a practical threshold for intervention in resource-constrained settings where frequent dose titration may not be feasible. In contrast, the minimal alterations in conventional coagulation parameters among antiplatelet-treated patients despite significant bleeding events underscore the limitations of these tests for monitoring antiplatelet therapies. This finding suggests that clinical risk assessment tools may be more valuable than laboratory monitoring for bleeding risk stratification in patients receiving antiplatelet agents.

The identified clinical predictors of bleeding—advanced age, renal impairment, concomitant NSAID use, previous bleeding history, and anemia—align with established risk factors in the literature but gain particular significance in resource-limited contexts (Barnes et al., 2020; Ntai et al., 2022). The consistency of these predictors across different antithrombotic regimens suggests that simplified bleeding risk assessment tools incorporating these easily obtainable clinical parameters could be developed and validated for use in settings with limited laboratory capabilities. Such tools could help identify high-risk patients who require more frequent monitoring or alternative treatment strategies.

Our findings have several practical implications for antithrombotic management in resource-limited settings. First, they support focused allocation of limited monitoring resources to warfarin-treated patients with identified clinical risk factors or previous labile INR values. Second, they suggest that for antiplatelet therapies, resources might be better directed toward clinical assessment and patient education rather than routine coagulation monitoring. Third, they provide evidence-based parameters for developing simplified management protocols, such as extending monitoring intervals for stable patients with consistent therapeutic INR values.

This study has several limitations. The observational design precludes definitive causal inferences, and the relatively small sample size may limit generalizability. We did not assess platelet function or specific coagulation factors, which might have provided additional insights into bleeding mechanisms. The follow-up period of six months may not capture long-term trends in coagulation parameters or bleeding risk. Additionally, we focused exclusively on basic coagulation tests due to resource constraints, acknowledging that more specialized testing might provide additional valuable information in ideal settings.

5. CONCLUSION

This study demonstrates that basic coagulation tests retain important utility for bleeding risk stratification in warfarin-treated patients but have limited value for monitoring antiplatelet therapies in resource-limited settings. The strong association between supratherapeutic INR values and bleeding complications underscores the critical importance of maintaining therapeutic anticoagulation control.

Clinical factors including advanced age, renal impairment, concomitant NSAID use, and previous bleeding history significantly enhance bleeding risk prediction when combined with basic laboratory parameters.

These findings support the development of simplified, context-appropriate risk assessment tools and monitoring protocols for antithrombotic management in resource-limited environments. Such approaches should prioritize INR monitoring for warfarin-treated patients with additional attention to those with identified clinical risk factors, while emphasizing clinical assessment over routine laboratory testing for patients on antiplatelet therapies.

Future research should focus on validating simplified bleeding risk scores incorporating both clinical and basic laboratory parameters, evaluating the cost-effectiveness of different monitoring strategies, and exploring patient-centered approaches to improve antithrombotic management in diverse healthcare settings. Ultimately, context-specific evidence-based guidelines are essential for optimizing the benefit-risk balance of antithrombotic therapies across the spectrum of healthcare resources.

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