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Original Article

Dabigatran outperforms warfarin in elderly patients with atrial fibrillation and stable coronary artery disease: reduced risks of bleeding and cardiovascular events

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Abstract: Objectives: This study compares the safety of dabigatran versus warfarin in elderly patients with atrial fibrillation and stable coronary artery disease, who face higher stroke and bleeding risks due to anticoagulation needs. Methods: This retrospective cohort study included patients aged ≥ 65 years who initiated anticoagulation therapy between June 1, 2021 and June 2, 2024. Patients were divided into dabigatran and warfarin groups. Coagulation functions were assessed at baseline and one month post-treatment. Bleeding events and major adverse cardiovascular events were recorded over the 12-month follow-up. Treatment adherence was evaluated at one and three month intervals. Results: A cohort of 218 patients was analyzed, with 102 in the dabigatran group and 116 in the warfarin group, showing comparable baseline characteristics. One month post-treatment, activated partial thromboplastin time was higher in the dabigatran group (42.11 vs. 40.89, P=0.007), while D-dimer levels were lower (0.55 vs. 0.58, P=0.003). The annual incidence rates of major bleeding (3.92% vs. 12.93%, P=0.019) and intracranial hemorrhage (0.98% vs. 7.76%, P=0.039) were significantly lower in the dabigatran group. Total bleeding events were also lower in the dabigatran group (16.67% vs. 31.90%, P=0.009). Dabigatran group showed reduced rates of ischemic stroke (0.98% vs. 7.76%, P=0.039) and acute myocardial infarction (1.96% vs. 8.62%, P=0.031). Good compliance at 3 months was higher in the dabigatran group (83.3% vs. 69.8%, P=0.020). Conclusions: In senior individuals with atrial fibrillation and stable coronary artery disease, dabigatran is associated with better control of thrombotic activity, lower bleeding risk, and a higher medication compliance compared to warfarin.

Keywords: Dabigatran, warfarin, atrial fibrillation, stable coronary heart disease, bleeding, major adverse cardiovascular events

Introduction

Atrial fibrillation (AF) is the most prevalent persistent heart rhythm disorder, marked by irregular ventricular response, palpitations, shortness of breath, and an increased risk of thromboembolic events [1]. When AF coexists with stable coronary artery disease (CAD), patients face the dual threat of ischemic stroke and myocardial infarction, necessitating long-term anticoagulation therapy [2, 3]. This comorbidity situation is particularly prevalent in the elderly population, and the choice of treatment strategies is especially complex and critical.

For many years, vitamin K antagonists like warfarin have been the standard of care for stroke prevention in patients with AF. However, their use is complicated by the need for regular monitoring of coagulation functions and an associated higher risk of bleeding. These challenges can be particularly significant for many older patients with multiple comorbidities [4, 5]. The advent of direct oral anticoagulants (DOACs), particularly the introduction of dabigatran-a direct thrombin inhibitor-has transformed the treatment paradigm. This is attributed to their more predictable pharmacokinetic properties and the elimination of the need for routine

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coagulation monitoring [6]. Nevertheless, balancing ischemic event prevention against bleeding risk remains a key challenge in elderly patients, especially those with multiple comorbidities [7]. Although existing randomized controlled trials have established the non-inferiority or superiority of DOACs in the general AF population, head-to-head comparative data for this specific comorbid subgroup with shared pathophysiology, particularly from real-world studies, remain relatively scarce [8]. Therefore, this study aims to conduct a head-to-head comparison of the safety profiles of dabigatran versus warfarin in elderly patients with AF and stable CAD.

The possible pathophysiologic links between AF and CAD primarily involve endothelial dysfunction, increased platelet activity, and inflammatory cascades [9, 10]. These factors collectively contribute to a prothrombotic state. In AF, sluggish blood flow within the atria promotes the formation of clots rich in fibrin and cross-linked platelets [11]. In stable CAD, the underlying mechanisms include atherosclerosis, chronic inflammation, and the presence of unstable plaques [12]. Anticoagulants function primarily by inhibiting the coagulation cascade, thereby preventing fibrin formation and the development of both arterial and venous thrombosis [13]. Broadly speaking, warfarin exerts its effect by inhibiting multiple vitamin K-dependent coagulation factors, whereas dabigatran specifically targets thrombin, the final enzyme in the coagulation cascade [14, 15]. Differences in these mechanisms of action may translate into clinically observable variations in bleeding risk and effects on ischemic events.

The innovation of this study lies in focusing on this clinically common but challenging high-risk population, patients over 65 years old with non-valvular atrial fibrillation and concomitant stable CAD. We aim to compare directly the comprehensive effects of dabigatran and warfarin in clinical practice through a retrospective cohort study. This includes evaluating not only safety endpoints but also efficacy endpoints, and exploring their impact on patient medication adherence. This study aims to provide targeted evidence-based medicine for clinicians to choose more optimized, safer, and more manageable anticoagulation strategies in this specific population.

Patients and methods

Study design and patient selection

This was a retrospective cohort study that compared the effects of dabigatran and warfarin on bleeding events and major adverse cardiovascular events (MACE) in elderly patients with non-valvular atrial fibrillation and CAD. The anticoagulation treatment regimen for all patients was a non-random choice made by the attending physician based on current clinical guidelines, the patient's specific condition, and personal preferences in routine clinical practice. Patients or their guardians were informed of the benefits and risks of different treatment options, including warfarin and novel oral anticoagulants, before making a decision.

This was a retrospective study. This research used only a patient's existing medical record data for analysis. It did not affect the patients' treatment plans and did not involve any additional interventions. During the study, all patients' personal identification information was strictly anonymized and de-identified to protect privacy. The Ethics Committee of The First People's Hospital of Shangqiu approved this study and waived informed consent.

Consecutive patients who were diagnosed and started on anticoagulation therapy with dabigatran or warfarin in The First People's Hospital of Shangqiu's outpatient or inpatient settings between June 1, 2021, and June 1, 2024, were included. Every patient was followed for a minimum of 12 months from the start of medication. All patients met the inclusion and exclusion criteria. Inclusion criteria: aged 65 years or older; diagnosed with AF by electrocardiogram (ECG) or Holter monitoring [16]; diagnosed with stable CAD through coronary angiography, computed tomography angiography, or other imaging examinations; having had no acute coronary syndrome events in the six months prior to enrollment [17]; complete data.

Exclusion criteria: severe renal impairment, defined as an estimated glomerular filtration rate < 30 mL/min/1.73 m^2, to avoid safety issues caused by drug metabolism. Major surgery within the past three months, as anticoagulation regimens need adjustment during surgery. Active bleeding or high risk of clinically significant bleeding (such as uncontrolled

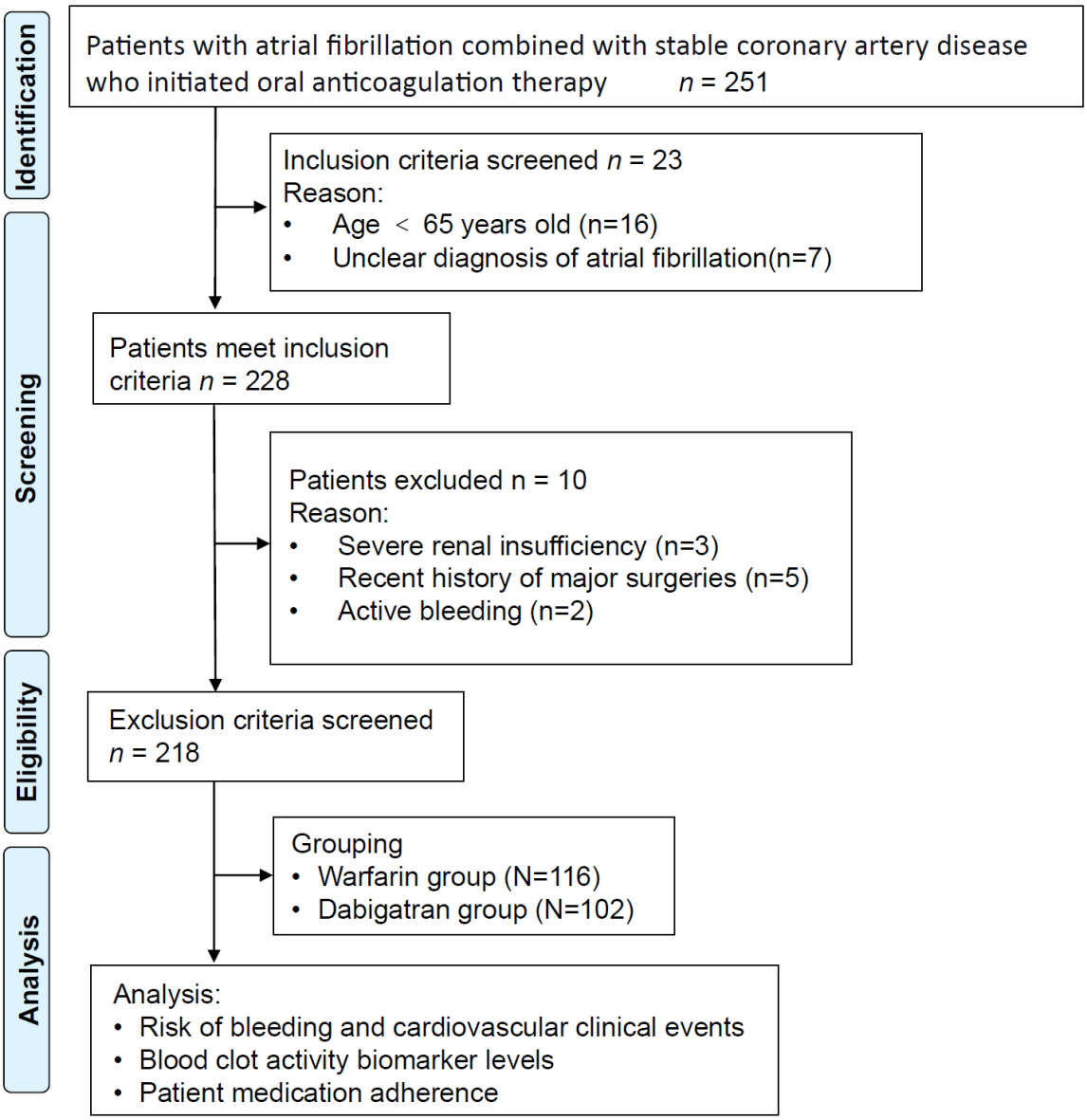

Figure 1. Patient flow diagram.

severe hypertension, active peptic ulcer). Severe liver dysfunction, including liver enzymes elevated to over three times the upper limit of normal or severe liver diseases such as cirrhosis. Allergy to dabigatran or warfarin or history of severe adverse drug reactions. Concurrent use of drugs that may interact with dabigatran or warfarin. Patients with severe cognitive impairment or mental illness who are unable to follow the treatment regimen or complete follow-up. Use of other planned treatments during anticoagulation therapy. Long-term concurrent use of other antiplatelet drugs for any reason during anticoagulation therapy. Incomplete data.

In total, 251 patients with AF combined with CAD who initiated oral anticoagulation therapy were initially identified (**Figure 1**). After screening for inclusion criteria, 23 patients were excluded due to age less than 65 years (n=16) or unclear diagnosis of AF (n=7), resulting in 228 patients meeting the inclusion criteria. Subsequently, 10 patients were excluded based on exclusion criteria, including severe renal insufficiency (n=3), recent history of major surgeries

(n=5), and active bleeding (n=2), leaving a final cohort of 218 eligible patients for analysis. These patients were then divided into two groups: the warfarin group (N=116) and the dabigatran group (N=102). The primary outcomes assessed included the risk of bleeding and cardiovascular clinical events, levels of blood clot activity biomarkers, and patient medication adherence.

Patients were divided into two groups according to the anticoagulant used. The dabigatran group (n=102) consisted of patients receiving dabigatran etexilate (110 mg, twice daily) treatment. The warfarin group (n=116) consisted of patients receiving warfarin treatment, with doses adjusted to maintain an international normalized ratio (INR) within the target range of 2.0-3.0.

Data extraction and verification

Baseline demographic data, clinical characteristics, and medical history of patients: This retrospective study obtained data on patients' age, gender, and medical history through a medical record system. We classified AF types based on clinical diagnosis and ECG results. If the onset of AF can terminate on its own, it is called paroxysmal AF. If the ECG shows AF lasting for more than a week, it is judged as persistent AF. Cases where sinus rhythm was not restored after cardioversion were also classified as persistent AF. When doctors and patients decided not to restore normal heart rhythm and consider AF as a long-term disease, it was defined as permanent AF.

The risk of ischemic stroke in patients was assessed using the congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, and prior stroke or transient ischemic attack or thromboembolism ($CHADS_2$) score [18]. This scoring system assigns 1 point each for congestive heart failure, hypertension, age ≥ 75 years, diabetes, and a previous stroke or transient ischemic attack, resulting in a total score ranging from 0 to 6. A higher score indicates a greater risk of future stroke.

Patients' histories of heart failure, diabetes, hypertension, or other conditions were documented in the medical records.

Baseline treatment and bleeding risk of patients: At the initial consultation, information on the patient's concomitant prescription medications was collected, including aspirin, proton pump inhibitors, H2 receptor antagonists, and long-term users of vitamin K antagonists (e.g., warfarin). Bleeding risk was assessed using the HAS-BLED score. This score incorporates hypertension, abnormal renal or liver function, history of stroke, bleeding history or predisposition, labile INR, age ≥ 65 years, and concomitant drug use or alcohol abuse [19]. The total score ranges from 0 to 9 points, where a score of 0-2 suggests a low risk of bleeding, and a score of 3 or above indicates a higher risk of future bleeding events for the patient.

Laboratory assessments: Before treatment and 1 month after the start of treatment, blood samples were obtained from patients by venipuncture. The blood samples were centrifuged to separate the plasma, which was then quickly stored at -80°C.

Fibrinogen (FIB), prothrombin time (PT), and activated partial thromboplastin time (APTT) were measured with a coagulation analyzer (Sysmex CA series, Sysmex Corporation, Japan) via Clauss method and clotting method. D-dimer (D-D) was measured using immunoturbidimetry on an automated biochemical analyzer (Roche Cobas series, Roche Diagnostics, Switzerland).

Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin (TbiL) were automatically detected using an automated biochemical analyzer.

Incidence of bleeding events: In this study, we collected data on the incidence of major bleeding, life-threatening bleeding, fatal bleeding, and minor bleeding events over a one-year period through the electronic medical record system, and recorded the occurrences of total bleeding and red blood cell transfusion. Major bleeding was defined by a reduction in hemoglobin levels ≥ 2.0 g/dL, transfusion of ≥ 2 units of red blood cells, or symptomatic bleeding into critical areas or organs, and was primarily categorized into intracranial bleeding (including intracerebral and subdural bleeding) and extracranial bleeding (including gastrointestinal and non-gastrointestinal bleeding). Life-threatening

bleeding included fatal or symptomatic intracranial bleeding, bleeding associated with a decrease in hemoglobin levels ≥ 5.0 g/dL, bleeding requiring transfusion of ≥ 4 units of blood or the use of inotropic agents, and bleeding requiring surgical intervention. All bleeding events were confirmed by reviewing the patients' medical records, and were classified and analyzed statistically according to the above definitions.

Other cardiovascular adverse events: Data on the incidence of ischemic stroke, systemic embolism, acute myocardial infarction, and all-cause mortality over a one-year period were collected through the electronic medical record system. Ischemic stroke was defined as the abrupt onset of neurological dysfunction due to an interruption of cerebral blood flow caused by arterial occlusion. Systemic embolism was defined as occlusion of systemic arteries by thrombi originating from a distant source. Acute myocardial infarction was defined as myocardial necrosis typically caused by prolonged ischemia due to coronary artery occlusion. All-cause mortality was defined as death from any cause during the study period.

Treatment adherence: The Morisky Medication Adherence Scale (MMAS-8) was utilized to evaluate patients' medication adherence at 1 and 3 months [20]. This scale consists of 8 items, such as "I forgot to take my medicine", "I stopped taking my treatment without telling my healthcare professional", and "I worry about my medicine". The higher the MMAS-8 score, the better the adherence, with scores categorized into low (0-5) and good (≥ 6) adherence levels.

Outcome measures

This study aims to evaluate and compare the efficacy and safety of dabigatran versus warfarin in elderly patients with AF and stable CAD. To this end, we used the following outcome measures.

Primary outcomes: the 12-month incidence of major bleeding events and the 12-month composite incidence of MACE, including ischemic stroke, acute myocardial infarction, and cardiovascular death.

Secondary outcomes: the incidence of various bleeding events (e.g., intracranial hemorrhage, life-threatening bleeding and minor bleeding); the incidence of individual cardiovascular events (ischemic stroke, acute myocardial infarction, and systemic embolism); all-cause mortality; and the rate of good medication adherence at 1 and 3 months of treatment.

Data analysis methods

Data were analyzed using SPSS statistical software (version 26.0, IBM Corp., Armonk, NY, USA). All statistical analyses were reviewed and verified by a professional statistician. Continuous data conforming to a normal distribution were presented as mean ± standard deviation and were compared using the independent samples t-test. Categorical data were presented as frequencies and percentages. Associations between categorical variables were assessed using the chi-square test, with Fisher's exact test applied when the expected frequency in any cell was less than 5. All statistical tests were two-sided, and a P-value < 0.05 was considered significant.

To evaluate whether dabigatran was an independent protective factor against bleeding events compared to warfarin, we reclassified all patients in the overall cohort into a bleeding group (N=54) and a non-bleeding group (N=164) based on the occurrence of any bleeding event. A multivariate logistic regression analysis was then conducted. The model included the following four independent variables to adjust for key confounding effects: anticoagulant type (dabigatran vs. warfarin), age, HAS-BLED bleeding risk score, and baseline aspirin use.

Results

Patient baseline and clinical characteristics

In the comparison of baseline demographic and clinical data between the warfarin group and the dabigatran group, there were no significant differences in age, gender, AF type, $CHADS_2$ score, or past medical history (all $P > 0.05$; **Table 1**). This high degree of consistency in baseline characteristics indicated good comparability between the two groups for subsequent analyses.

Table 1. Baseline demographic and clinical data

Indicator	Warfarin group (N=116)	Dabigatran group (N=102)	t/χ^2	P
Age	71.62 ± 6.94	72.15 ± 6.88	0.561	0.576
Gender (Female/male)	40 (34.48%)/76 (65.52%)	43 (42.16%)/59 (57.84%)	1.356	0.244
Smoking history	16 (13.79%)	17 (16.67%)	0.349	0.555
Alcohol consumption history	28 (24.14%)	22 (21.57%)	0.203	0.653
Systolic blood pressure	130.85 ± 15.75	131.03 ± 14.76	0.090	0.929
Diastolic blood pressure	77.87 ± 8.61	77.25 ± 8.43	0.529	0.598
Atrial fibrillation type			0.049	0.976
Persistent	38 (32.76%)	32 (31.37%)		
Paroxysmal	37 (31.90%)	33 (32.35%)		
Permanent	41 (35.34%)	37 (36.27%)		
$CHADS_2$ score			0.124	0.940
0-1 points	36 (31.03%)	31 (30.39%)		
2 points	45 (38.79%)	38 (37.25%)		
3-6 points	35 (30.17%)	33 (32.35%)		
Previous sroke or transient ischemic attack	22 (18.97%)	20 (19.61%)	0.014	0.904
Prior myocardial infarction	19 (16.38%)	16 (15.69%)	0.019	0.889
Heart failure	37 (31.90%)	31 (30.39%)	0.057	0.811
Diabetes mellitus	27 (23.28%)	23 (22.55%)	0.016	0.899
Hypertension	91 (78.45%)	79 (77.45%)	0.031	0.859

Data are presented as mean ± standard deviation or n (%) as appropriate. CHADS2: congestive heart failure, hypertension, age ≥ 75 years, diabetes, and prior stroke or transient ischemic attack or thromboembolism.

Table 2. Baseline concomitant medications and bleeding risk

Indicator	Warfarin group (N=116)	Dabigatran group (N=102)	χ^2	P
Concomitant medications at baseline				
Aspirin	46 (39.66%)	39 (38.24%)	0.046	0.830
Proton pump inhibitor	15 (12.93%)	14 (13.73%)	0.030	0.863
H2 receptor antagonist	4 (3.45%)	4 (3.92%)	0.031	0.861
Long-term vitamin K antagonist therapy	58 (50.00%)	50 (49.02%)	0.021	0.885
HAS-BLED score			0.013	0.908
0-2 points	68 (58.62%)	59 (57.84%)		
3 points or more	48 (41.38%)	43 (42.16%)		

HAS-BLED: hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly (age > 65 years), drugs or alcohol abuse.

Baseline treatment and bleeding risk

In the comparison of baseline treatment status and bleeding risk between the warfarin group and the dabigatran group, most indicators did not show significant differences (**Table 2**). The proportions of patients using medications such as aspirin, proton pump inhibitors, H2 receptor antagonists, and long-term vitamin K antagonist therapy at baseline were similar between the two groups with no significant difference (all P > 0.05). The HAS-BLED scores also showed no significant difference between the two groups (P=0.908). Thus the patients in both groups exhibited similar baseline treatment status and bleeding risk.

Changes in laboratory values

Regarding coagulation function, FIB levels showed no significant differences between groups at baseline or after 1 month of treatment (both P > 0.05; **Figure 2**). PT and APTT were comparable at baseline (PT: P=0.680, APTT: P=0.838). After 1 month of treatment, however, PT was significantly higher in the war-

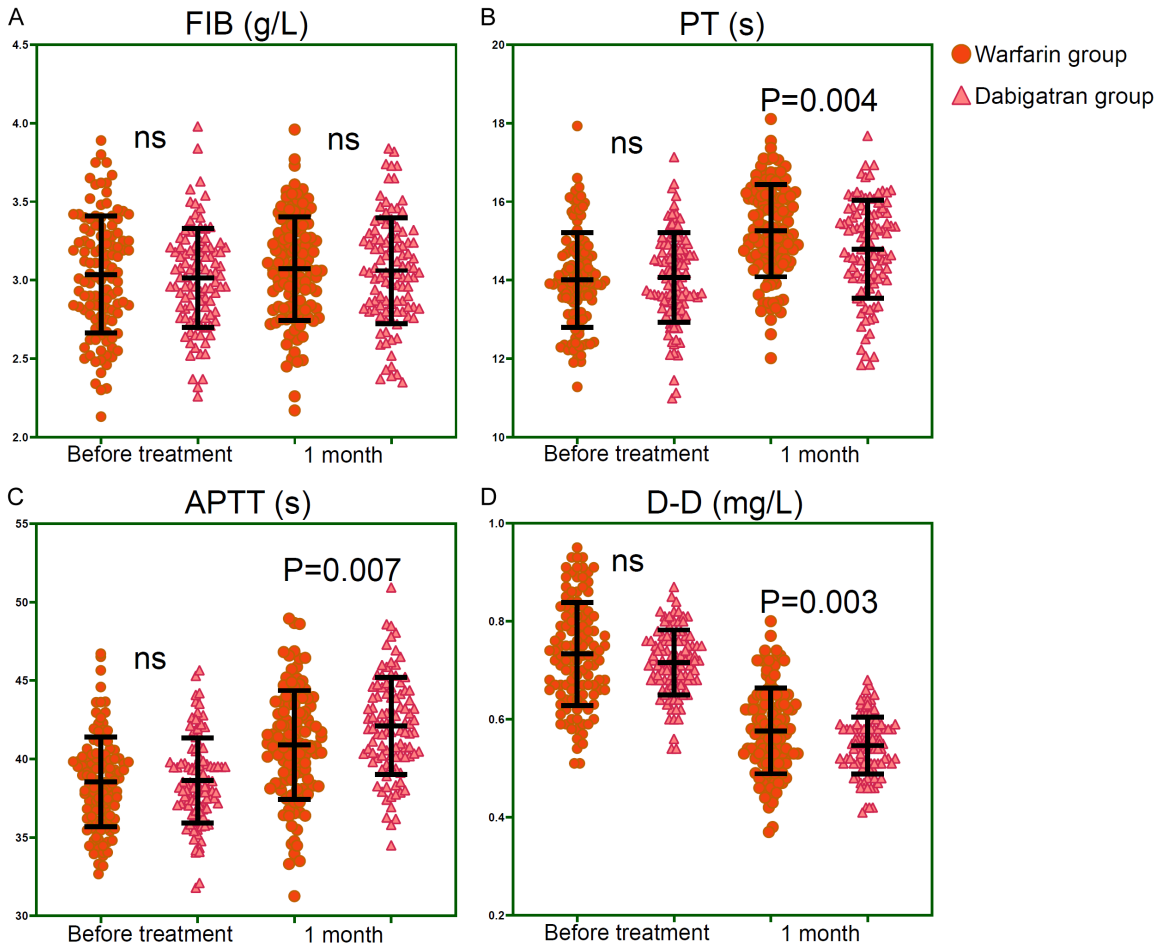

Figure 2. Coagulation function indicators. A. FIB (g/L); B. PT (s); C. APTT (s); D. D-D (mg/L). FIB: fibrinogen; PT: prothrombin time; APTT: activated partial thromboplastin time; D-D: D-dimer.

farin group than in the dabigatran group (P=0.004), whereas APTT was significantly higher in the dabigatran group than in the warfarin group (P=0.007), indicating differential effects of the two drugs on distinct coagulation pathways. D-D levels did not differ significantly between groups at baseline (P=0.141) but were significantly lower in the dabigatran group than in the warfarin group after 1 month of treatment (P=0.003), suggesting a superior effect of dabigatran in reducing D-D levels.

Liver function indicators did not differ significantly between the two groups at baseline or after 1 month of treatment (**Table 3**). ALT, AST, ALP, and TbiL levels were comparable at baseline (all P > 0.05). One month after treatment, these indicators also did not show significant differences between the two groups (ALT: P=0.526, AST: P=0.703, ALP: P=0.800, TbiL: P=0.893).

Bleeding events

Intracranial hemorrhage (including both intracerebral and subdural hemorrhage) occurred at a significantly greater rate in the warfarin group versus the dabigatran group (P=0.039; **Table 4**). For extracranial bleeding (including gastrointestinal and non-gastrointestinal bleeding), there was no significant difference in the incidence rates between the two groups (P=0.628). Compared to the dabigatran group, the overall incidence of major bleeding events was significantly higher in the warfarin group (P=0.019). The use of dabigatran was therefore associated with a reduction in overall bleeding risk, particularly for intracranial hemorrhage.

Table 3. Liver function indicators

Indicator	Warfarin group (N=116)	Dabigatran group (N=102)	t	P
ALT (U/L)				
Before treatment	29.93 ± 3.32	29.97 ± 3.43	0.078	0.938
1 month	28.79 ± 3.19	28.51 ± 3.31	0.635	0.526
AST (U/L)				
Before treatment	26.77 ± 2.31	26.79 ± 2.23	0.063	0.949
1 month	25.13 ± 2.18	25.25 ± 2.19	0.382	0.703
ALP (U/L)				
Before treatment	74.49 ± 8.91	74.51 ± 8.86	0.021	0.984
1 month	71.12 ± 8.36	71.41 ± 8.59	0.253	0.800
TbiL (μmol/L)				
Before treatment	17.09 ± 2.01	17.04 ± 2.18	0.182	0.855
1 month	15.27 ± 2.38	15.31 ± 2.38	0.135	0.893

ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; TbiL: total bilirubin.

Table 4. Major bleeding events

Indicator	Warfarin group (N=116)	Dabigatran group (N=102)	χ^2	P
Intracranial	9 (7.76%)	1 (0.98%)	4.254	0.039
Intracerebral	5 (3.45%)	1 (0.98%)		
Subdural	4 (2.59%)	0 (0.00%)		
Extracranial	6 (5.17%)	3 (2.94%)	0.235	0.628
Gastrointestinal	1 (0.86%)	1 (0.98%)		
Non-gastrointestinal	5 (3.45%)	2 (1.96%)		
Total	15 (12.93%)	4 (3.92%)	5.537	0.019

Table 5. Other bleeding events

Indicator	Warfarin group (N=116)	Dabigatran group (N=102)	χ^2	P
Life-threatening bleeding	2 (1.72%)	1 (0.98%)	0.013	0.911
Fatal bleeding	1 (0.86%)	0 (0.00%)	0.004	0.949
Minor bleeding	27 (23.28%)	13 (12.75%)	4.017	0.045
Total bleeding	37 (31.90%)	17 (16.67%)	6.756	0.009
Red cell transfusion	2 (1.72%)	1 (0.98%)	0.013	0.911

Regarding other bleeding events, there were no significant differences between the two groups in the incidence of life-threatening bleeding or fatal bleeding (all P > 0.05, **Table 5**). Regarding minor bleeding events, the incidence rate was significantly higher in the warfarin group compared to the dabigatran group (P=0.045). Consequently, the total incidence of any bleeding event was significantly higher in the warfarin group (P=0.009). Additionally, there was no significant difference between the two groups in terms of the need for red blood cell transfusion (P=0.911). These results indicated that dabigatran use is linked to fewer minor bleeding events and a reduced overall incidence of bleeding compared to warfarin.

MACEs and all-cause mortality rate

Regarding the comparison of MACE, the incidence of ischemic stroke was significantly higher in the warfarin group than in the dabigatran group (P=0.039; **Table 6**). There was no significant difference in the incidence of systemic embolism between the two groups (P=0.949). The incidence of acute myocardial infarction was significantly higher in the warfarin group compared to the dabigatran group (P=0.031).

Table 6. Major adverse cardiovascular events and all-cause mortality

Indicator	Warfarin group (N=116)	Dabigatran group (N=102)	χ^2	P
Ischemic stroke	9 (7.76%)	1 (0.98%)	4.254	0.039
Systemic embolism	1 (0.86%)	0 (0.00%)	0.004	0.949
Acute myocardial infarction	10 (8.62%)	2 (1.96%)	4.628	0.031
All-cause mortality	5 (4.31%)	3 (2.94%)	0.031	0.861

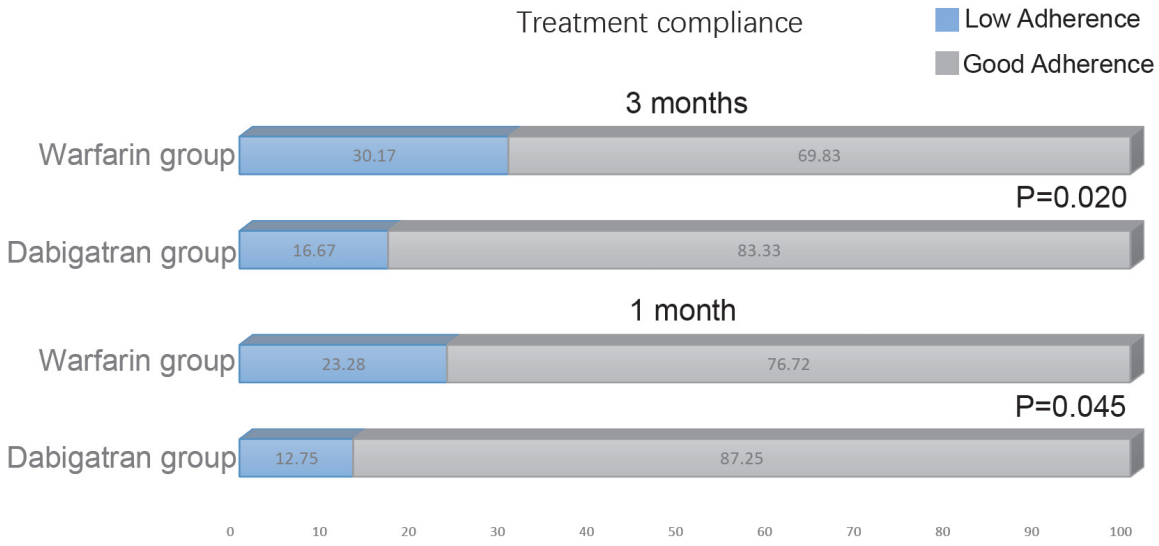

Figure 3. Treatment compliance.

Table 7. Multivariable logistic regression analysis of factors associated with total bleeding event

Indicator	Coefficient	P	OR	CI Lower	CI Upper
Dabigatran vs. Warfarin	-0.925	0.010	0.396	0.197	0.799
Age	0.076	0.023	1.079	1.011	1.151
HAS-BLED score (0-2 points/3 points or more)	1.069	0.004	2.911	1.417	5.982
Aspirin	0.871	0.011	2.389	1.224	4.661

OR: odds ratio; CI: confidence interval; HAS-BLED: hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly (age > 65 years), drugs or alcohol abuse.

Regarding all-cause mortality, there was no significant difference between the two groups (P=0.861). These results indicate that, compared to warfarin, dabigatran was associated with a lower incidence of ischemic stroke and acute myocardial infarction.

Treatment compliance

The distribution of low versus good adherence at 1 month differed significantly between the two groups (P=0.045), with a greater proportion of patients exhibiting low adherence in the warfarin group compared to the dabigatran group (**Figure 3**). A significant difference in adherence distribution was also observed at 3 months (P=0.020). Specifically, the proportion of patients with adherence less than 75% remained higher in the warfarin group than in the dabigatran group.

Multivariable logistic regression analysis

The results of the multivariate logistic regression analysis showed that, compared to warfarin, the use of dabigatran significantly reduced the risk of bleeding (P=0.010, odds ratio [OR] =0.396), indicating a protective effect of dabigatran over warfarin (**Table 7**). For each additional year of age, there was a slight increase in

the risk of bleeding (P=0.023, OR=1.079), suggesting that older age may be a risk factor for bleeding. Patients with a HAS-BLED score of 3 or higher had a significantly higher risk of bleeding compared to those with scores of 0-2 (P=0.004, OR=2.911). Additionally, the concurrent use of aspirin also significantly increased the risk of bleeding (P=0.011, OR=2.389), indicating that the combined use of aspirin may be an important risk factor for bleeding.

Discussion

This retrospective study examined anticoagulation therapy in patients aged sixty-five and older with AF and and stable CAD, comparing the direct thrombin inhibitor dabigatran to vitamin K antagonists (e.g., warfarin) in terms of safety, cardiovascular benefits, and compliance in real-world clinical practice. The results indicated that for high-risk elderly patients with non-valvular AF and stable CAD, dabigatran offers a safer and more beneficial profile compared to warfarin. These findings provide new scientific evidence to guide anticoagulant selection in this complex patient population, aiming to optimize thrombotic risk reduction while minimizing bleeding risk.

Different coagulation laboratory results between the two drugs reflect their distinct mechanisms of action. The prolonged PT in the warfarin group is consistent with its known mechanism of inhibiting the synthesis of multiple vitamin K-dependent coagulation factors [21]. In contrast, the prolonged APTT in the dabigatran group results from its direct inhibition of thrombin, which blocks a key step in the coagulation cascade and prevents the conversion of FIB to fibrin [22, 23]. A particularly notable finding was the significantly lower D-D level in the dabigatran group. D-dimer reflects both fibrin turnover and overall thrombotic activity, suggesting that dabigatran may provide more robust overall inhibition of thrombosis [24]. This observation is also consistent with the targeted and specific mechanism of direct thrombin inhibitors, which may contribute to superior clinical outcomes [25].

The principal finding of this study was that the direct thrombin inhibitor dabigatran reduced the overall risk of bleeding, particularly the risk of intracranial hemorrhage, compared to warfarin. This finding is consistent with the data from multiple studies, collectively confirming that dabigatran is associated with a lower bleeding risk than warfarin in routine clinical practice [26]. Intracranial hemorrhage was the most serious complication of anticoagulation therapy, associated with high rates of mortality and disability. Warfarin's higher bleeding risk may be attributed to its narrow therapeutic window and susceptibility to dietary variations and drug interactions, which also make it challenging for patients to maintain stable INR values within the target range [27]. The observed benefit likely stems from the selective mechanism of thrombin inhibition by dabigatran, which is more targeted than the broader inhibition of multiple vitamin K-dependent coagulation factors by warfarin [28]. Current data suggest that the favorable safety profile of dabigatran observed in clinical trials may extend to the elderly population with coexisting CAD, who are at even greater risk for bleeding [29]. The clear reduction in primary bleeding events further underscores the safety advantage of dabigatran for managing these high-risk elderly patients.

Furthermore, the overall reduction in bleeding risk with dabigatran reflects a genuine safety improvement, not merely a shift in the distribution of bleeding types. The stable pharmacodynamic profile of direct thrombin inhibitors translates into enhanced clinical safety. Although minor bleeding events are rarely fatal, their frequent occurrence can significantly affect patients' quality of life, treatment perception, and long-term medication adherence in the elderly. Substantial observational evidence indicates that minor bleeding often leads to self-discontinuation or irregular use of warfarin [30]. Dabigatran, due to its more targeted mechanism and fixed dosing regimen without routine coagulation monitoring, provides more stable anticoagulation. This reduces the risks associated with fluctuating anticoagulant levels, such as those contributing to capillary fragility. In contrast, the higher incidence of major bleeding in the vitamin K antagonist group is often inconsistent with the time spent within the therapeutic INR range [31]. This suggests that the need for frequent laboratory monitoring and dose adjustments-as commonly reported in community-based observational studies of warfarin [32] - leaves substantial room for improvement in optimizing safety.

The incidence of acute myocardial infarction was lower in the dabigatran group, a notable finding. Previous meta-analyses and observational studies have suggested that dabigatran may confer pprotection against myocardial infarction compared to warfarin-a phenomenon hypothesized to be related to warfarin's promotion of vascular calcification or to differential effects on platelet-rich arterial thrombi [33, 34]. The trend toward a reduced incidence of ischemic stroke in the dabigatran group also aligns with results from major clinical trials. The all-cause mortality rates were similar between the two groups, indicating that the hemostatic advantage of dabigatran did not come at the cost of increased overall mortality. In addition to evaluating primary event rates, this study also assessed whether bleeding severity correlated with transfusion requirements. The difference in transfusion demand did not reach statistical significance, which may be attributable to the limited sample size.

In long-term anticoagulant therapy, treatment adherence is a crucial yet often overlooked factor [35]. A key practical advantage of dabigatran is its ease of use. Its fixed dosing regimen eliminates the need for frequent blood draws and dose adjustments, which generally contributes to better patient adherence [36]. On the contrary, warfarin therapy is often associated with significant inconvenience, logistical challenges, and treatment disruption, all of which complicate consistent treatment follow-through [37]. As extensively documented in previous literature, the complexity of monitoring and suboptimal management are major contributors to poor anticoagulation control, thereby increasing the risks of both thrombosis and bleeding [38]. Simplified treatment regimens, such as those offered by newer agents, can enhance medication adherence and reduce the logistical burden associated with repeated laboratory monitoring.

This study has certain advantages but also several inherent limitations that weaken the generalizability of the conclusions. First, the single center design limits the demographic characteristics of patients and the diversity of clinical practice patterns, which may make it difficult to promote in a broader healthcare environment. Second, retrospective analysis can easily introduce selection bias and insufficient adjustment for confounding factors. Third, while the sample size was adequate to detect major differences in bleeding, it may not have been large enough to confirm definitively any differences in less common MACE endpoints. Finally, a 12-month follow-up period is adequate to assess initial safety and efficacy but is too short to assess the extended results and the cumulative risk of events over years of treatment.

Future research should include large, multicenter, prospective investigations with extended observation windows to confirm these findings. Further investigation is needed to elucidate the mechanism underlying the differential D-D effects and the possible protective trend against myocardial infarction. Additionally, comparative effectiveness studies among different DOACs in specific AF patient populations with stable CAD would provide valuable guidance for clinical decision-making. In this context, economic analyses assessing the cost-effectiveness of dabigatran considering the reduction in bleeding events and improved adherence would be valuable for healthcare policy.

Conclusion

This study demonstrated that direct thrombin inhibition provides a safer bleeding profile, comparable stroke prevention, and better medication adherence in elderly patients with AF and stable CAD.

Disclosure of conflict of interest

None.

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