Am J Transl Res 2025;17(1):294-307
www.ajtr.org /ISSN:1943-8141/AJTR0160508

Original Article

The effect of rivaroxaban as an anticoagulant therapy for acute pulmonary embolism and the predictive role of vascular endothelial markers in assessing anticoagulant efficacy before treatment

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Received September 13, 2024; Accepted November 8, 2024; Epub January 15, 2025; Published January 30, 2025

Abstract: Background: Acute pulmonary embolism (PE) is a life-threatening condition requiring effective anticoagulation therapy. Rivaroxaban, a direct oral anticoagulant, offers advantages over warfarin, yet individual patient responses vary. This study examined the efficacy of rivaroxaban compared to warfarin and evaluated vascular endothelial markers as predictors of anticoagulant efficacy. Methods: We conducted a retrospective cross-over cohort study involving 295 patients with acute PE, comparing rivaroxaban (n = 158) and warfarin (n = 137) treatments. Clinical efficacy was assessed based on symptomatic improvement and imaging results. Vascular endothelial markers, including soluble thrombomodulin (sTM), circulating endothelial cells (CEC), and endothelin-1 (ET-1), were examined for their predictive capability in treatment outcomes, then the data of 97 additional patients were used for external validation. Results: Patients who received rivaroxaban showed higher overall treatment response (93.04%) compared to those who took warfarin (74.45%; $P < 0.001$), and greater improvement in arterial partial pressure of oxygen (PaO_2; $P = 0.003$). Rivaroxaban significantly altered coagulation parameters such as prothrombin time (PT) and international normalized ratio (INR). In addition, elevated sTM and reduced CEC were found to be associated with poorer anticoagulation outcomes. The areas under the receiver operating characteristic curve (AUCs) for predicting efficacy using vascular endothelial markers were 0.913 in the training cohort and 0.888 in the external validation cohort, respectively. Conclusion: Rivaroxaban was more effective than warfarin in treating acute PE, with specific vascular endothelial markers serving as promising predictors of therapeutic response.

Keywords: Rivaroxaban, anticoagulant therapy, acute pulmonary embolism, predictive role, vascular endothelial markers

Introduction

Acute pulmonary embolism (PE) is a serious cardiovascular condition marked by the obstruction of pulmonary arteries due to thromboembolism, which poses substantial risks of morbidity and mortality [1]. The primary clinical approach to managing acute PE is anticoagulation therapy, aimed at preventing further thrombus growth and promoting clot dissolution [2]. In recent decades, the field of anticoagulation therapy has transformed significantly with the introduction of direct oral anticoagulants (DOACs) like rivaroxaban, which are increasingly preferred over traditional vitamin K antagonists, such as warfarin, due to their predictable pharmacokinetics and ease of administration [3]. However, despite these advancements, challenges remain, including variability in patient responses to anticoagulant therapy and the risk of recurrence, highlighting the need for more personalized treatment strategies [4].

Rivaroxaban, an oral factor Xa inhibitor, offers several advantages over warfarin, including a rapid onset of action, fixed dosing schedules, and fewer dietary or drug interactions. These features reduce the need for frequent monitoring, thereby enhancing patient compliance [5]. Numerous studies have demonstrated its efficacy and safety profile in the prevention and treatment of venous thromboembolism, with a

https://doi.org/10.62347/WJDW8626

particular focus on acute PE [6, 7]. However, patient responses to rivaroxaban remain variable, emphasizing the need to identify biomarkers that can predict therapeutic outcomes and support the development of personalized treatment regimens [8].

Vascular endothelial markers have emerged as valuable indicators of the pathophysiological processes involved in thrombus formation and resolution [9]. The endothelium is central to maintaining vascular homeostasis, and disruptions in endothelial function can trigger thrombotic events [10].

This research seeks to fill key gaps in our understanding of anticoagulation therapy for acute PE by comparing the efficacy of rivaroxaban and warfarin and assessing the potential of pre-treatment vascular endothelial markers to predict individualized anticoagulant responses. Through retrospective analyses and the investigation of these biological markers, we aim to develop novel predictive models that can improve clinical decision-making and personalize patient care.

Materials and methods

Case selection

This retrospective cross-over cohort study included 295 patients diagnosed with acute PE who were admitted to the Affiliated Hospital of Inner Mongolia Medical University between July 2021 and July 2023. Data on demographics, pulmonary function indicators, serum markers, coagulation parameters, and treatment outcomes were collected from the medical records system. We analyzed these baseline characteristics, along with vascular endothelial markers, to evaluate their associations with various treatment outcomes. This study has been approved by the Ethics Committee and Institutional Review Board of the Affiliated Hospital of Inner Mongolia Medical University (No. HS2023-04381).

Inclusion and exclusion criteria

Inclusion criteria: 1) Diagnosis of acute PE confirmed through clinical manifestations and pulmonary imaging, following the *ESC Diagnosis and Management Guidelines for PE* [11]; 2) Age 18 years or older; 3) Anticoagulant therapy administered consistently by the same medical team; 4) Availability of complete medical records; 5) No history of allergy to iodinated contrast agents.

Exclusion criteria: 1) Patients with concurrent malignant lung tumors; 2) Individuals with severe liver or kidney dysfunction; 3) Individuals with contraindications to the study drugs; 4) Participation with any other investigational drug or device study; 5) Presence of malignant tumors or congenital heart diseases; 6) Life expectancy under 90 days or inability to comply with study evaluations.

Methods and grouping criteria

Patients were divided into two groups based on the treatment regimen they received: a warfarin group with 137 patients and a rivaroxaban group with 158 patients. Upon admission, both groups received standard treatments, including oxygen supplementation, analgesics, and anti-shock therapy. Additionally, all patients were administered subcutaneous injections of 5,000 IU of low-molecular-weight heparin calcium (Shenzhen Saibao Bio-Pharmaceutical Co., Ltd., National Drug Code H20060190, specification: 1.0 mL:5,000 A Xa IU/vial) twice daily for one week. In the warfarin group, patients began oral warfarin sodium tablets (Shanghai Shyndec Pharmaceutical Co., Ltd., National Drug Code H31022123, 2.5 mg/tablet) at a dose of 2.5 mg once daily, starting two days after the initial heparin injections. Likewise, patients in the rivaroxaban group started oral rivaroxaban tablets (Nanjing Haichen Pharmaceutical Co., Ltd., National Drug Code H2021-3247, 20 mg/tablet) at a dose of 20 mg once daily, also beginning two days after the heparin injections. Both groups continued the oral medication for three months. Prior to initiating treatment, vascular endothelial markers were assessed for all patients.

Clinical treatment outcomes were evaluated, categorizing patients into an effective group (249 patients) and an ineffective group (46 patients) based on their results. Differences in data between these groups were analyzed. Furthermore, an external validation cohort of 97 patients, who met the same inclusion and exclusion criteria, was included in the study. These patients were similarly divided into effective and ineffective groups according to their treatment outcomes.

Clinical efficacy

Significant effect: Symptoms such as difficulty breathing and chest pain have essentially disappeared, physical signs have returned to normal, and imaging examinations show no evidence of acute PE. Effective: Symptoms and signs have markedly improved, and imaging examinations indicate that the acute PE has largely resolved. Ineffective: Symptoms and signs have not improved or have worsened, with imaging examinations showing no relief of acute PE [12]. Total response was calculated as the sum of the significant and effective outcomes.

Pulmonary function and blood gas analysis indicators

Based on the guidelines established by the American Thoracic Society and the European Respiratory Society, all patients underwent post-bronchodilator pulmonary function testing using a CHESTGRAPH HI-101 spirometer (OMRON, Japan). Testing began 20 minutes after the subjects inhaled 400 μg of salbutamol. The following variables were measured: forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1), and FEV_1 as a percentage of the predicted value (FEV_1% pred). Additionally, the partial pressures of oxygen (PaO_2) and carbon dioxide ($PaCO_2$) in blood samples were analyzed using an integrated analyzer (GEM Premier 3500; Massachusetts Instruments Laboratory, USA).

Six coagulation factors and coagulation factor activities

Before medication and 2-4 hours after administration, 3 mL of venous blood was collected from all patients. A CS-5100 fully automatic coagulation analyzer, using original reagents from Hisense Meikang Company, Japan, was employed to evaluate six coagulation indicators and coagulation factor activities. The six coagulation indicators included prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (APTT), thrombin time (TT), fibrinogen (Fib), D-dimer (DD), and antithrombin III activity (AT3). The assessed coagulation factors included factors II, V, VII, VIII, IX, X, XI, and XII, as well as Protein C and Protein S.

Vascular endothelial markers

On the second day after onset, all patients underwent testing, with peripheral venous blood collected in the morning while fasting. The blood was promptly transferred to an anticoagulant tube containing 0.2 mL of 2% ethylenediaminetetraacetic acid (EDTA) and centrifuged at 3000 rpm for 10 minutes at 4°C. The plasma was then separated and stored at -80°C for subsequent testing. Once all specimens were collected, they were processed uniformly. Measurements included soluble thrombomodulin (sTM), von Willebrand factor (vWF), circulating endothelial cell (CEC) count, soluble vascular cell adhesion molecule-1 (sVCAM-1), endothelial cell protein C receptor (EPCR), and endothelin-1 (ET-1). ET-1 levels were determined using a radioimmunoassay, with the kit provided by the Beijing Institute of Biotechnology and analyzed using a Finland 1470 WIZARD fully automatic radioimmunoassay analyzer. sTM and vWF were quantified using enzyme-linked immunosorbent assays (ELISAs). The TM kit was obtained from DIACLONE, France, and the vWF kit from ADI, USA. The ELISA measurements were conducted with an ELX-800 enzyme-linked immunosorbent assay reader, strictly adhering to the kit and instrument instructions.

Statistical analysis

Using G*Power 3.1.9.7, the "t tests" option for "Means: Difference between two independent means (two groups)" and Post hoc analysis were selected, with the parameters set as two tails mode, effect size $d = 0.5$, $\alpha = 0.05$. The sample sizes of the two groups were input to calculate Power (1-β), resulting in Power = 0.990.

Data analysis was conducted using SPSS 29.0 statistical software (SPSS Inc, Chicago, IL, USA). Categorical variables are presented as [n (%)]. When the sample size is ≥40 and the theoretical frequency T≥5, the basic chi-square test formula is applied; when the sample size is ≥40 but the theoretical frequency 1≤T<5, the corrected chi-square test formula is used. When the sample size is < 40 or the theoretical frequency T<1, Fisher's exact probability method is employed for statistical analysis. Continuous variables were tested for normal distribution using the Shapiro-Wilk method. Normally

Table 1. Baseline characteristics of participants

Parameters	Warfarin group (n = 137)	Rivaroxaban group (n = 158)	t/χ^2	p	Statistical Method
Age (years)	60.54 ± 3.23	60.64 ± 3.31	0.262	0.794	Two Sample t-test
Gender (Male/Female)	70 (51.09%)	82 (51.90%)	0.019	0.890	Pearson's Chi-squared test
Body Mass Index (kg/m^2)	25.32 ± 3.67	25.67 ± 3.96	0.783	0.434	Two Sample t-test
Smoking history [n (%)]	60 (43.80%)	77 (48.73%)	0.719	0.396	Pearson's Chi-squared test
Drinking history [n (%)]	57 (41.61%)	63 (60.13%)	0.091	0.763	Pearson's Chi-squared test
Employment [n (%)]	75 (54.74%)	89 (56.33%)	0.075	0.785	Pearson's Chi-squared test
Degree of education			4.387	0.112	Pearson's Chi-squared test
Junior high school and below	39 (28.47%)	60 (37.97%)			
high school	58 (42.34%)	66 (41.77%)			
college diploma or above	40 (29.20%)	32 (20.25%)			
Marital Status [n/(%)]			0.439	0.803	Pearson's Chi-squared test
Married	56 (40.88%)	70 (44.30%)			
Single	16 (11.68%)	19 (12.03%)			
Divorced	65 (47.45%)	69 (43.67%)			
Hypertension [n (%)]	69 (50.36%)	72 (45.57%)	0.676	0.411	Pearson's Chi-squared test
Diabetes [n (%)]	56 (40.88%)	63 (39.87%)	0.031	0.861	Pearson's Chi-squared test
Course of disease (days)	4.92 ± 0.51	4.99 ± 0.41	1.306	0.193	Welch Two Sample t-test
Hypotension or shock [n (%)]	26 (18.98%)	30 (18.99%)	0.000	0.998	Pearson's Chi-squared test
Pulmonary Embolism Severity Index	74.25 ± 12.25	73.56 ± 12.26	0.482	0.630	Two Sample t-test
Baseline pulmonary obstruction score	31.56 ± 4.13	31.26 ± 4.11	0.624	0.533	Two Sample t-test
Baseline pulmonary obstruction index	71.28 ± 8.32	71.56 ± 7.59	0.302	0.763	Two Sample t-test
Pulmonary infection [n (%)]	37 (27.01%)	43 (27.22%)	0.002	0.968	Pearson's Chi-squared test

distributed continuous variables are expressed as (Mean ± SD) and analyzed using the t-test with variance correction. Non-normally distributed continuous variables are presented as median (25th percentile, 75th percentile) and analyzed using the Wilcoxon rank-sum test. A two-tailed $P < 0.05$ was considered statistically significant. Correlation analysis was conducted using Pearson correlation for continuous variables and Spearman correlation for categorical variables.

Results

Effect of different drugs on anticoagulant therapy for acute PE

Baseline characteristics: A comparison of baseline data between patients in the warfarin group and the rivaroxaban group is presented in **Table 1**. The results indicated no significant differences between the two groups regarding mean age, gender, body mass index (BMI), smoking history, alcohol consumption history, and other demographic and disease-related characteristics ($P > 0.05$). This uniformity in baseline characteristics suggests that any observed differences in outcomes are more likely attributable to the anticoagulant treatments themselves rather than underlying variability among participants.

Clinical efficacy: The overall response rate, defined as the sum of effective and significant effective responses, was markedly higher in the rivaroxaban group at 93.04% compared to 74.45% in the warfarin group ($\chi^2 = 19.257$, $P < 0.001$) (**Table 2**). These findings suggest that rivaroxaban demonstrates superior clinical efficacy in the treatment of acute PE compared to warfarin.

Lung function and blood gas analysis: A comparison of pulmonary function parameters and blood gas parameters before treatment between the two groups is presented in **Table 3**. The results showed no significant differences in FVC, FEV_1, FEV_1% pred, PaO_2, and $PaCO_2$ before treatment ($P > 0.05$). These findings indicate baseline comparability in both pulmonary function and blood gas indicators between the groups prior to treatment.

Post-treatment, the PaO_2 level in the rivaroxaban group was significantly higher than in the

Table 2. Comparison of clinical efficacy between the two groups of patients

Parameters	Warfarin group (n = 137)	Rivaroxaban group (n = 158)	χ^2	p	Statistical Method
Ineffective [n (%)]	35 (25.55%)	11 (6.96%)			
Effective [n (%)]	56 (40.87%)	44 (27.85%)			
Significant effect [n (%)]	46 (33.58%)	103 (65.19%)			
Overall response [n (%)]	102 (74.45%)	147 (93.04%)	19.257	< 0.001	Pearson's Chi-squared test

Table 3. Comparison of Pulmonary function and blood gas indicators between the two groups of patients before treatment

Parameters	Warfarin group (n = 137)	Rivaroxaban group (n = 158)	t	p	Statistical Method
FVC (%)	55.24 ± 10.12	55.78 ± 11.81	0.418	0.676	Two Sample t-test
FEV_1 (L)	1.23 ± 0.33	1.22 ± 0.30	0.273	0.785	Two Sample t-test
FEV_1% pred (%)	52.34 ± 10.14	52.54 ± 11.11	0.161	0.873	Two Sample t-test
PaO_2 (mmHg)	63.62 ± 5.57	63.77 ± 5.24	0.238	0.812	Two Sample t-test
$PaCO_2$ (mmHg)	28.65 ± 5.23	28.47 ± 5.36	0.291	0.771	Two Sample t-test

Note: FVC = forced vital capacity; FEV_1 = First Second Expiratory Volume; FEV_1% pred (%) = The percentage of forced expiratory volume in the first second to the predicted value; PaO_2 = arterial partial pressure of oxygen; $PaCO_2$ = Arterial blood carbon dioxide partial pressure.

Table 4. Comparison of lung function and blood gas analysis indicators between the two groups of patients after treatment

Parameters	Warfarin group (n = 137)	Rivaroxaban group (n = 158)	t	p	Statistical Method
FVC (%)	55.36 ± 8.71	56.33 ± 9.88	0.888	0.375	Welch Two Sample t-test
FEV_1 (L)	1.56 ± 0.41	1.62 ± 0.43	1.221	0.223	Two Sample t-test
FEV_1% pred (%)	55.77 ± 7.06	57.45 ± 12.56	1.387	0.167	Welch Two Sample t-test
PaO_2 (mmHg)	78.76 ± 5.32	80.63 ± 5.47	2.966	0.003	Two Sample t-test
$PaCO_2$ (mmHg)	35.24 ± 5.13	35.77 ± 3.45	1.053	0.293	Welch Two Sample t-test

Note: FVC = forced vital capacity; FEV_1 = First Second Expiratory Volume; FEV_1% pred (%) = The percentage of forced expiratory volume in the first second to the predicted value; PaO_2 = arterial partial pressure of oxygen; $PaCO_2$ = Arterial blood carbon dioxide partial pressure.

warfarin group (80.63 ± 5.47 mmHg vs. 78.76 ± 5.32 mmHg; t = 2.966, P = 0.003) (**Table 4**). However, there were no significant differences in FVC, FEV_1, FEV_1% pred, and $PaCO_2$ between the two groups (P > 0.05). These findings indicate a significant improvement in PaO_2 in patients treated with rivaroxaban, suggesting enhanced oxygenation following treatment with this anticoagulant.

Coagulation parameters and coagulation factor activities: Coagulation parameters and changes in coagulation factor activity before administration are presented in **Table 5**. The results indicated no significant differences between the two groups in PT, INR, APTT, TT, Fib, DD, AT3, factors II, V, VII, VIII, IX, X, XI, and XII, as well as Protein C and Protein S levels (P > 0.05). These findings suggest that both groups were well matched in terms of coagulation status, ensuring that any subsequent differences post-treatment could be more reliably attributed to the effects of anticoagulant therapy rather than pre-existing disparities.

Post-treatment, the rivaroxaban group exhibited significantly higher levels of PT (7.89 ± 1.56 s vs. 7.32 ± 1.66 s; t = 3.038, P = 0.003), INR (2.04 ± 0.11 vs. 1.98 ± 0.21; t = 3.131, P = 0.002), and APTT (17.45 ± 3.73 s vs. 16.54 ± 3.91 s; t = 2.043, P = 0.042) compared to the warfarin group. Additionally, the rivaroxaban group demonstrated significantly lower levels of TT (15.36 ± 2.98 s vs. 16.33 ± 2.65 s; t = 2.934, P = 0.004) (**Table 6**). However, there were no significant differences in other coagu-

Table 5. Changes in coagulation parameters and coagulation factor activities before treatment

Parameters	Warfarin group (n = 137)	Rivaroxaban group (n = 158)	t	p	Statistical Method
PT/s	6.21 ± 1.12	6.18 ± 1.24	0.217	0.829	Two Sample t-test
INR (%)	0.98 ± 0.12	0.96 ± 0.15	1.251	0.212	Welch Two Sample t-test
APTT/s	17.45 ± 3.66	17.54 ± 3.72	0.209	0.835	Two Sample t-test
TT/s	17.33 ± 3.72	17.35 ± 2.09	0.058	0.954	Welch Two Sample t-test
Fib/(g/L)	4.12 ± 1.05	4.01 ± 1.06	0.893	0.373	Two Sample t-test
DD/(mg/L)	1.36 ± 0.25	1.33 ± 0.27	0.985	0.326	Two Sample t-test
AT3/%	107.32 ± 20.65	106.99 ± 21.14	0.135	0.893	Two Sample t-test
Factor II (%)	94.44 ± 21.15	95.32 ± 22.11	0.348	0.728	Two Sample t-test
Factor V (%)	131.52 ± 28.63	132.44 ± 29.56	0.271	0.787	Two Sample t-test
Factor VII (%)	116.33 ± 29.95	116.95 ± 29.85	0.178	0.859	Two Sample t-test
Factor VIII (%)	226.31 ± 25.32	226.92 ± 77.25	0.088	0.930	Welch Two Sample t-test
Factor IX (%)	117.19 ± 24.96	116.32 ± 25.23	0.297	0.767	Two Sample t-test
Factor X (%)	93.72 ± 22.17	94.56 ± 23.21	0.317	0.752	Two Sample t-test
Factor XI (%)	100.02 ± 26.17	100.79 ± 26.76	0.249	0.804	Two Sample t-test
Factor XII (%)	51.46 ± 15.34	51.77 ± 15.39	0.173	0.863	Two Sample t-test
Protein C (%)	102.33 ± 15.81	102.96 ± 15.05	0.350	0.726	Two Sample t-test
Protein S (%)	137.25 ± 34.82	136.87 ± 34.73	0.094	0.926	Two Sample t-test

Note: P*T* = prothrombin time; IN*R* = international normalized ratio; AP*TT* = activated partial thromboplastin time; T*T* = thrombin time; Fib = fibrinogen; DD = D-dimer; AT3 = antithrombin III activity.

Table 6. Coagulation parameters and coagulation factor activities post-treatment

Parameters	Warfarin group (n = 137)	Rivaroxaban group (n = 158)	t	p	Statistical Method
PT/s	7.32 ± 1.66	7.89 ± 1.56	3.038	0.003	Two Sample t-test
INR (%)	1.98 ± 0.21	2.04 ± 0.11	3.131	0.002	Welch Two Sample t-test
APTT/s	16.54 ± 3.91	17.45 ± 3.73	2.043	0.042	Two Sample t-test
TT/s	16.33 ± 2.65	15.36 ± 2.98	2.934	0.004	Two Sample t-test
Fib/(g/L)	3.17 ± 1.03	3.16 ± 1.09	0.081	0.936	Two Sample t-test
DD/(mg/L)	1.32 ± 0.25	1.29 ± 0.17	1.218	0.224	Welch Two Sample t-test
AT3/%	101.36 ± 21.33	101.39 ± 20.48	0.012	0.990	Two Sample t-test
Factor II (%)	80.78 ± 17.23	80.86 ± 17.02	0.040	0.968	Two Sample t-test
Factor V (%)	103.89 ± 28.47	104.78 ± 33.72	0.243	0.808	Welch Two Sample t-test
Factor VII (%)	92.22 ± 26.87	93.52 ± 26.78	0.415	0.678	Two Sample t-test
Factor VIII (%)	143.79 ± 31.22	144.33 ± 31.29	0.148	0.883	Two Sample t-test
Factor IX (%)	77.06 ± 21.36	77.68 ± 21.56	0.247	0.805	Two Sample t-test
Factor X (%)	76.69 ± 14.37	78.36 ± 14.22	1.001	0.318	Two Sample t-test
Factor XI (%)	60.32 ± 10.52	61.52 ± 10.36	0.985	0.325	Two Sample t-test
Factor XII (%)	36.45 ± 8.96	37.55 ± 9.15	1.040	0.299	Two Sample t-test
Protein C (%)	96.67 ± 13.92	99.72 ± 12.81	1.959	0.051	Two Sample t-test
Protein S (%)	135.44 ± 30.77	139.23 ± 31.55	1.041	0.299	Two Sample t-test

Note: P*T* = prothrombin time; IN*R* = international normalized ratio; APT*T* = activated partial thromboplastin time; T*T* = thrombin time; Fib = fibrinogen; DD = D-dimer; AT3 = antithrombin III activity.

lation parameters and coagulation factor activities ($P > 0.05$). Overall, these results suggest distinct coagulation profiles post-treatment, with rivaroxaban exhibiting more pronounced effects on some coagulation parameters.

Predictive effects of pre-treatment vascular endothelial markers on anticoagulant efficacy

Baseline characteristics: In our study examining the predictive effects of pre-treatment vas-

Table 7. Comparison of baseline characteristics between the effective and ineffective groups

Parameters	Ineffective group (n = 46)	Effective group (n = 249)	t/χ^2	p	Statistical Method
Age (years)	62.44 ± 4.52	62.79 ± 3.13	0.645	0.519	Welch Two Sample t-test
Gender (Male/Female)	20 (43.48%)	136 (54.62%)	1.934	0.164	Pearson's Chi-squared test
Body Mass Index (kg/m^2)	25.32 ± 3.67	25.67 ± 3.96	0.557	0.578	Two Sample t-test
Smoking history [n (%)]	22 (47.83%)	117 (46.99%)	0.011	0.917	Pearson's Chi-squared test
Drinking history [n (%)]	17 (36.96%)	95 (38.15%)	0.024	0.878	Pearson's Chi-squared test
Employment [n (%)]	24 (52.17%)	129 (51.81%)	0.002	0.964	Pearson's Chi-squared test
Degree of education			3.986	0.136	Pearson's Chi-squared test
Junior high school and below	16 (34.78%)	96 (38.55%)			
high school	18 (39.13%)	63 (25.30%)			
college diploma or above	12 (26.09%)	90 (36.14%)			
Marital Status [n/(%)]			0.022	0.989	Pearson's Chi-squared test
Married	24 (52.17%)	130 (52.21%)			
Single	7 (15.22%)	36 (14.46%)			
Divorced	15 (32.61%)	83 (33.33%)			
Hypertension [n (%)]	19 (41.30%)	103 (41.37%)	0.000	0.994	Pearson's Chi-squared test
Diabetes [n (%)]	20 (43.48%)	134 (53.82%)	1.663	0.197	Pearson's Chi-squared test
course of disease (days)	4.86 ± 0.74	4.53 ± 0.54	3.575	< 0.001	Welch Two Sample t-test
Hypotension or shock [n (%)]	40 (86.96%)	76 (30.52%)	51.827	< 0.001	Pearson's Chi-squared test
Pulmonary Embolism Severity Index	75.23 ± 11.56	71.37 ± 12.61	1.931	0.054	Two Sample t-test
Baseline pulmonary obstruction score	31.22 ± 4.68	31.34 ± 4.15	0.177	0.860	Two Sample t-test
Baseline pulmonary obstruction index	71.26 ± 8.87	71.47 ± 7.25	0.174	0.862	Two Sample t-test
Pulmonary infection [n (%)]	34 (73.91%)	46 (18.47%)	60.379	< 0.001	Pearson's Chi-squared test

cular endothelial markers on the anticoagulant efficacy of rivaroxaban for the treatment of acute PE, we analyzed the baseline characteristics of participants categorized into ineffective (n = 46) and effective (n = 249) response groups. The comparison between these groups revealed no statistically significant differences in age, gender distribution, BMI, smoking and drinking histories, employment status, education levels, marital status, hypertension, and diabetes (P > 0.05) (**Table 7**). However, the ineffective group had a longer duration of illness (4.86 ± 0.74 days vs. 4.53 ± 0.54 days; t = 3.575, P < 0.001), a higher prevalence of hypotension or shock (86.96% vs. 30.52%; χ^2 = 51.827, P < 0.001), and a higher rate of pulmonary infection (73.91% vs. 18.47%; χ^2 = 60.379, P < 0.001) compared to the effective group. These findings suggest that certain clinical factors, such as disease duration and the presence of complications like hypotension or pulmonary infection, may influence the treatment efficacy of anticoagulants for acute PE.

Vascular endothelial markers: sTM levels were significantly higher in the ineffective group compared to the effective group (40.32 ± 10.63 ng/mL vs. 35.66 ± 0.91 ng/mL; t = 2.672, P = 0.002) (**Table 8**). Additionally, CEC counts were significantly lower in the ineffective group (22.36 ± 7.11 n/mL vs. 25.26 ± 7.39 n/mL; t = 2.459, P = 0.015), indicating potential predictive value. In contrast, no statistically significant differences were observed between the groups concerning vWF, sVCAM-1, EPCR, and ET-1 levels (P > 0.05). These findings suggest that sTM and CEC may serve as useful markers for predicting anticoagulant efficacy in this patient population.

Correlation analysis: There was a negative correlation between disease duration and anticoagulant efficacy (rho = -0.196, P < 0.001) (**Table 9**), indicating that longer disease duration was associated with diminished efficacy. Similarly, both hypotension or shock (rho = -0.419, P < 0.001) and pulmonary infection (rho = -0.452, P < 0.001) were negatively correlated with anticoagulant efficacy, suggesting that these conditions predict poorer outcomes (**Table 9**). Additionally, sTM levels demonstrated a modest negative correlation with efficacy (rho = -0.203, P < 0.001), indicating that higher sTM levels were associated with reduced anticoagu-

Table 8. Comparison of vascular endothelial markers between the effective and ineffective groups

Parameters	Ineffective group (n = 46)	Effective group (n = 249)	t	p	Statistical Method
sTM (ng/mL)	40.32 ± 10.63	35.66 ± 10.91	2.672	0.002	Welch Two Sample t-test
vWF (%)	137.55 ± 26.99	134.03 ± 21.35	0.983	0.326	Welch Two Sample t-test
CEC (ng/mL)	22.36 ± 7.11	25.26 ± 7.39	2.459	0.015	Welch Two Sample t-test
sVCAM-1 ng/mL	496.25 ± 46.28	485.44 ± 43.27	1.540	0.125	Two Sample t-test
EPCR (%)	121.96 ± 17.21	119.13 ± 18.52	0.962	0.337	Two Sample t-test
ET-1 (pg/mL)	105.66 ± 16.67	100.62 ± 18.31	1.738	0.083	Welch Two Sample t-test

Note: sTM = Soluble thrombomodulin; vWF = Von Willebrand factor; CEC = Circulating endothelial cells; sVCAM-1 = Soluble vascular cell adhesion molecules; EPC*R* = Endothelial cell protein C receptor; ET-1 = Endothelin.

Table 9. Correlation analysis between vascular endothelial markers before treatment and anticoagulant efficacy

Parameters	rho	P
course of disease	-0.196	< 0.001
Hypotension or shock	-0.419	< 0.001
Pulmonary infection	-0.452	< 0.001
sTM	-0.203	< 0.001
CEC	0.141	0.015

Note: sTM = Soluble thrombomodulin; CEC = Circulating endothelial cells.

lant effectiveness. In contrast, CEC count exhibited a positive correlation with anticoagulant efficacy (rho = 0.141, P = 0.015), suggesting that higher CEC levels are linked to better anticoagulant effects. These results highlight potential clinical and biomarker predictors of response to anticoagulants in patients with acute PE.

Univariate and multivariate logistic regression analyses: The course of the disease exhibited a strong negative relationship with anticoagulant efficacy, yielding an odds ratio (OR) of 0.374 (95% CI, 0.209-0.654; P < 0.001) (**Table 10**). The presence of hypotension or shock was a highly significant predictor of reduced efficacy, marked by an OR of 0.066 (95% CI, 0.024-0.151; P < 0.001). Pulmonary infection significantly decreased the odds of effective anticoagulation, with an OR of 0.080 (95% CI, 0.037-0.162; P < 0.001). Additionally, a higher level of sTM served as a negative predictor of efficacy, with an OR of 0.819 (95% CI, 0.750-0.882; P < 0.001). In contrast, a higher level of CEC was a positive predictor of efficacy, with an OR of 1.057 (95% CI, 1.011-1.107; P = 0.016). In the multivariate logistic regression analysis, disease course, hypotension or shock, pulmonary infection, and sTM remained negatively correlated with anticoagulant efficacy, while CEC levels were positively correlated with anticoagulant efficacy (**Table 11**). These results indicate the predictive value of specific clinical and biomarker indicators in the effectiveness of anticoagulant therapy in this patient cohort.

ROC: Based on the five indicators identified through logistic regression analysis - disease course, hypotension or shock, lung infection, sTM, and CEC - a predictive model for anticoagulant efficacy was constructed. Each patient's factors correspond to individual scores, and the cumulative score reflects better anticoagulant efficacy, with higher scores indicating improved outcomes (**Figure 1A**). The calibration curve demonstrates that the model's actual incidence rate has an average absolute error of 0.021 compared to the predicted incidence rate, with the standard curve validated through 1,000 repetitions, indicating a strong consistency between actual occurrences and predicted results (**Figure 1B**). Within the range where the net benefit is greater than zero, the model's net benefit exceeds that of both non-intervention and universal intervention strategies, suggesting that the model is highly effective and holds significant practical application value (**Figure 1C**). The area under the curve (AUC) for the combined model is 0.913 (**Figure 1D**), indicating that the combination of pre-treatment vascular endothelial markers offers a high predictive value for anticoagulant outcomes in patients with acute PE.

External validation of the predictive model

Comparison of parameters between ineffective and effective groups in the external validation set: In the external validation set, the comparison of parameters between the ineffective and effective groups revealed significant differenc-

Table 10. Univariate logistic regression analysis of vascular endothelial markers before treatment and anticoagulant efficacy

Parameters	Coefficient	Std Error	Wald	P	OR	95% CI
course of disease	-0.982	0.290	3.384	< 0.001	0.374	0.209-0.654
Hypotension or shock	-2.720	0.459	5.926	< 0.001	0.066	0.024-0.151
Pulmonary infection	-2.526	0.373	6.765	< 0.001	0.080	0.037-0.162
sTM	-0.199	0.041	4.891	< 0.001	0.819	0.750-0.882
CEC	0.055	0.023	2.415	0.016	1.057	1.011-1.107

Note: sTM = Soluble thrombomodulin; CEC = Circulating endothelial cells.

Table 11. Multivariate logistic regression analysis of vascular endothelial markers before treatment and anticoagulant efficacy

Parameters	Coefficient	Std Error	Wald Stat	P	OR	95% CI
course of disease	-0.897	0.361	-2.483	0.013	0.408	0.201-0.828
Hypotension or shock	-2.422	0.510	-4.747	< 0.001	0.089	0.033-0.241
Pulmonary infection	-2.274	0.448	-5.074	< 0.001	0.103	0.043-0.248
sTM	-0.095	0.039	-2.418	0.016	0.909	0.842-0.982
CEC	0.084	0.043	2.385	0.028	1.083	0.985-1.178

Note: sTM = Soluble thrombomodulin; CEC = Circulating endothelial cells.

es in several clinical and biomarker variables (**Table 12**). The ineffective group exhibited a significantly longer disease course (4.57 ± 0.21 days vs. 4.40 ± 0.33 days; t = 2.926, P = 0.005), a higher prevalence of hypotension or shock (77.27% vs. 45.33%; χ^2 = 6.960, P = 0.008), a greater incidence of pulmonary infection (77.27% vs. 21.33%; χ^2 = 23.714, P < 0.001), and elevated sTM levels (41.06 ± 5.63 ng/mL vs. 36.74 ± 7.94 ng/mL; t = 2.380, P = 0.019) compared to the effective group. Conversely, the ineffective group had significantly lower CEC levels (21.45 ± 5.26 n/mL vs. 24.80 ± 6.33 n/mL; t = 2.260, P = 0.026). There were no significant differences between the groups in terms of age, gender distribution, BMI, smoking and drinking histories, employment status, education level, marital status, hypertension, diabetes, PE severity index, baseline pulmonary obstruction score, or baseline pulmonary obstruction index (P > 0.05 for all). These findings highlight the potential of specific clinical features and endothelial markers as predictive factors for the efficacy of anticoagulants in the treatment of acute PE.

External validation ROC: A combined predictive model was constructed using five indicators identified as having significant predictive value: disease course, presence of hypotension or shock, pulmonary infection, and levels of sTM and CEC (**Figure 2**). The model demonstrated a high AUC value of 0.888, indicating excellent predictive capability for anticoagulant efficacy in patients with acute PE. This suggests that the pre-treatment vascular endothelial marker-based model is highly effective in forecasting treatment outcomes.

Discussion

In this study, we investigated the efficacy of rivaroxaban in treating acute PE compared to the traditional anticoagulant warfarin, while also exploring the predictive role of pre-treatment vascular endothelial markers on the effectiveness of anticoagulation therapy. The results demonstrate that rivaroxaban exhibits superior clinical efficacy over warfarin in managing acute PE, a finding that aligns well with previous research [13], which highlights the advantages of DOACs in terms of safety and therapeutic outcomes. Furthermore, our study elucidates the potential predictive utility of certain vascular endothelial markers, providing a more nuanced understanding of patient-specific responses to anticoagulation treatment.

Rivaroxaban, a factor Xa inhibitor, offers several pharmacological advantages over warfarin, a vitamin K antagonist [14]. Its fixed dosing regimen and fewer dietary restrictions significantly

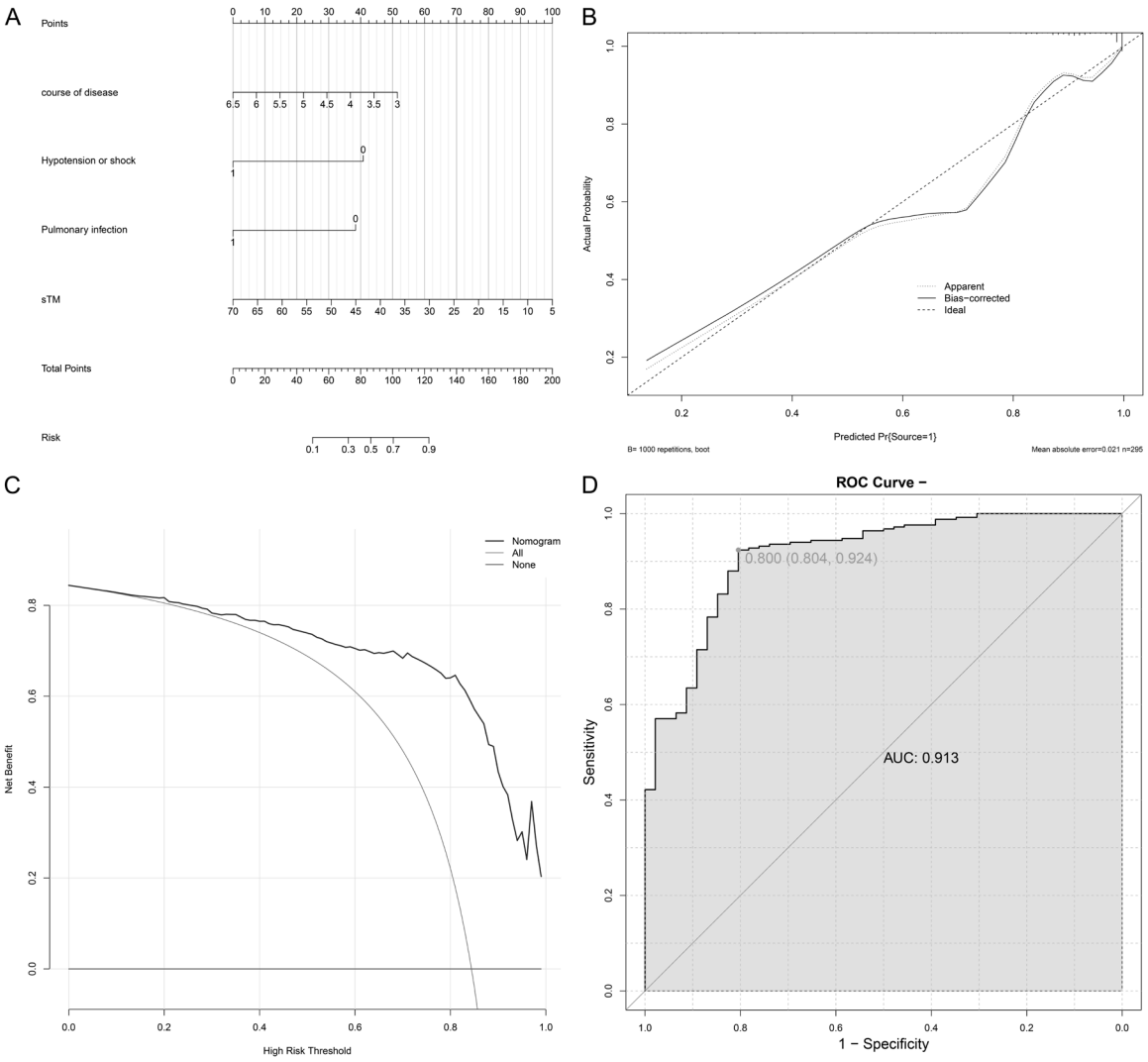

Figure 1. Predictive value of pre-treatment vascular endothelial markers for anticoagulant efficacy. A: Nomogram; B: Calibration curve; C: DCA analysis; D: Joint model. Note: DCA: Decision Curve Analysis.

enhance patient compliance [15]. Mechanistically, the action of rivaroxaban is predictable and does not require routine monitoring, in contrast to warfarin, whose efficacy is influenced by genetic polymorphisms affecting the cytochrome P450 2C9 enzyme and varying intake of vitamin K [16, 17]. This predictability likely contributes to the higher overall efficacy and significant clinical improvements observed in the rivaroxaban group in our study. Furthermore, the notable improvement in arterial PaO_2 in patients treated with rivaroxaban underscores its potential in alleviating hypoxemic conditions associated with acute PE, possibly due to its more effective and stable anticoagulation, which reduces clot burden rapidly.

In terms of coagulation parameters, rivaroxaban resulted in more pronounced changes in PT, INR, and APTT, indicating its potent anticoagulant effect. Significant alterations in these parameters highlight rivaroxaban's role in promoting more effective hemostatic management, which may correlate with a faster resolution of embolic obstruction in the pulmonary vasculature. Additionally, TT was notably shorter in the rivaroxaban group compared to the warfarin group, potentially reflecting its targeted inhibition of factor Xa upstream of thrombin generation.

A significant aspect of our study was the examination of vascular endothelial markers - sTM,

Table 12. Comparison of parameters between ineffective and effective groups in the external validation set

Parameters	Ineffective group (n = 22)	Effective group (n = 75)	t/χ^2	p	Statistical Method
Age (years)	62.16 ± 6.33	62.37 ± 6.54	0.138	0.891	Two Sample t-test
Gender (Male/Female)	10 (45.45%)	32 (42.67%)	0.054	0.816	Pearson's Chi-squared test
Body Mass Index (kg/m^2)	25.77 ± 3.67	25.48 ± 3.96	0.300	0.765	Two Sample t-test
Smoking history [n (%)]	12 (54.55%)	44 (58.67%)	0.118	0.731	Pearson's Chi-squared test
Drinking history [n (%)]	10 (45.45%)	36 (48.00%)	0.044	0.833	Pearson's Chi-squared test
Employment [n (%)]	11 (50.00%)	37 (49.33%)	0.003	0.956	Pearson's Chi-squared test
Degree of education			0.075	0.963	Pearson's Chi-squared test
Junior high school and below	7 (31.82%)	22 (29.33%)			
high school	9 (40.91%)	33 (44.00%)			
college diploma or above	6 (27.27%)	20 (26.67%)			
Marital Status [n/(%)]			0.150	0.928	Pearson's Chi-squared test
Married	13 (59.09%)	46 (61.33%)			
Single	3 (13.64%)	8 (10.67%)			
Divorced	6 (27.27%)	21 (28.00%)			
Hypertension [n (%)]	9 (40.91%)	31 (41.33%)	0.001	0.972	Pearson's Chi-squared test
Diabetes [n (%)]	10 (45.45%)	31 (41.33%)	0.118	0.731	Pearson's Chi-squared test
course of disease (days)	4.57 ± 0.21	4.40 ± 0.33	2.926	0.005	Welch Two Sample t-test
Hypotension or shock [n (%)]	17 (77.27%)	34 (45.33%)	6.960	0.008	Pearson's Chi-squared test
Pulmonary Embolism Severity Index	74.77 ± 5.24	74.26 ± 5.81	0.369	0.713	Two Sample t-test
Baseline pulmonary obstruction score	31.52 ± 4.59	31.70 ± 3.63	0.196	0.845	Two Sample t-test
Baseline pulmonary obstruction index	72.33 ± 9.24	72.15 ± 7.89	0.088	0.930	Two Sample t-test
Pulmonary infection [n (%)]	17 (77.27%)	16 (21.33%)	23.714	< 0.001	Pearson's Chi-squared test
sTM (ng/mL)	41.06 ± 5.63	36.74 ± 7.94	2.380	0.019	Two Sample t-test
CEC (ng/mL)	21.45 ± 5.26	24.80 ± 6.33	2.260	0.026	Two Sample t-test

Note: sTM = Soluble thrombomodulin; CEC = Circulating endothelial cells.

CEC, and ET-1 - as predictors of anticoagulant efficacy [18]. Elevated levels of sTM, indicative of endothelial injury, were associated with poorer responses to rivaroxaban therapy. This trend suggests that extensive endothelial disruption, as evidenced by high sTM levels, may hinder optimal therapeutic outcomes by fostering a pro-thrombotic state that is more difficult to overcome with standard anticoagulation [19, 20]. Conversely, the lower CEC counts observed in the ineffective treatment group highlight their potential role as markers of endothelial homeostasis and repair capability [21]. Higher CEC levels may signify active endothelial repair processes, making the vascular system more receptive to anticoagulant strategies [22]. Furthermore, ET-1, known for its vasoconstrictive properties and role in endothelial dysfunction, was marginally elevated in patients with poorer responses to rivaroxaban [23], potentially influencing the overall effectiveness of thrombus resolution [24, 25].

From a clinical perspective, significant differences in disease duration and the prevalence of complications, such as hypotension, shock, and pulmonary infection, between the effective and ineffective treatment groups provide additional insights. Longer disease duration correlates with a reduced likelihood of successful anticoagulation, possibly due to the chronicity of endothelial damage and a persistent inflammatory state, which could stabilize thrombi or even lead to vascular remodeling [26, 27].

While this study provides valuable insights into the efficacy of rivaroxaban and the predictive role of vascular endothelial markers in managing acute PE, several limitations must be acknowledged. Firstly, although the sample size is adequate for preliminary findings, it may limit the generalizability of the results across diverse populations. Additionally, the study's observational design, while informative, does not establish a causal relationship between

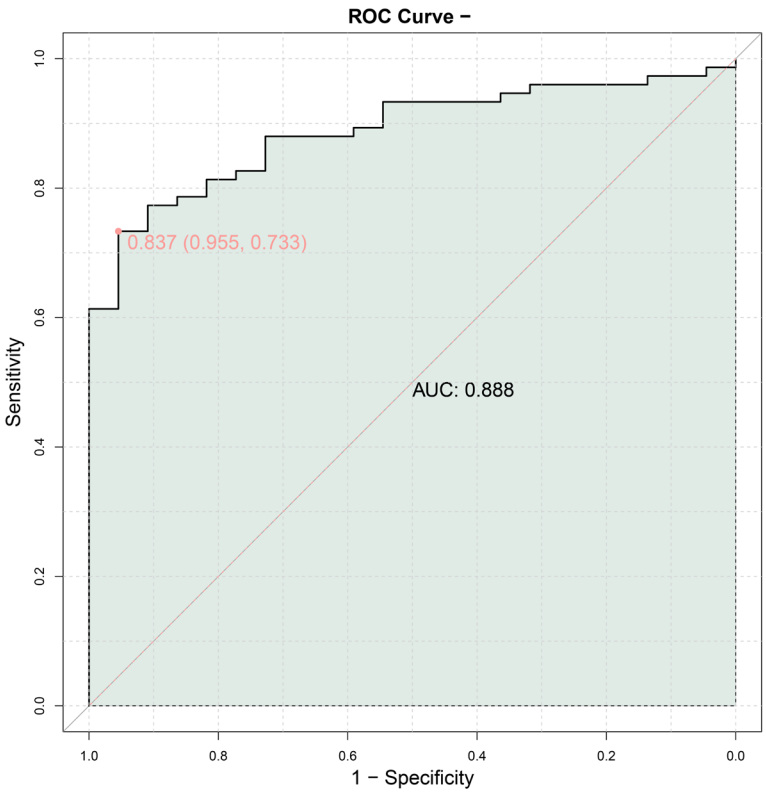

Figure 2. Predictive value of pre-treatment vascular endothelial markers for anticoagulant efficacy (external validation).

endothelial marker levels and treatment efficacy. The reliance on specific endothelial markers without considering a broader range of potential biomarkers may overlook other relevant predictors of anticoagulant response. Furthermore, variabilities in patient treatment adherence and potential confounding factors, such as concurrent medical therapies or comorbidities, were challenging to control completely, which may skew the results. Lastly, the relatively short follow-up period restricts our understanding of the long-term effects and sustainability of rivaroxaban's benefits, highlighting the need for extended studies to assess ongoing efficacy and safety. Future research should aim to address these limitations through larger, randomized controlled trials with comprehensive biomarker panels and longer follow-up durations to enhance the robustness of the findings and their applicability to clinical practice.

Conclusion

In conclusion, our study demonstrates the superior efficacy of rivaroxaban compared to warfarin in treating acute PE, with vascular endothelial markers showing promise in predicting treatment outcomes. These findings support a shift toward the use of DOACs in clinical practice and suggest a novel, more personalized approach to anticoagulant therapy that considers both clinical factors and biomarker profiles. Ultimately, this contributes to enhancing patient-specific treatment efficacy.

Disclosure of conflict of interest

None.

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