Am J Transl Res 2026;18(7):6114-6129
www.ajtr.org /ISSN:1943-8141/AJTR0174396

Original Article

Edoxaban plus aspirin de-escalation strategy versus continuous dual antithrombotic therapy in the perioperative period for patients with atrial fibrillation undergoing carotid artery stenting: a retrospective cohort study

Mintao Li[1*], Shiying Dong[1*], Shaohui Yu[1*], Bo Wang[1], Xuefeng Zhang[1], Chao Ma[2], Fenghuang Sun[3], Rongcai Jiang[1,4]

[1]Department of Neurosurgery, Tianjin Neurological Institute, State Key Laboratory of Experimental Hematology, Laboratory of Post-Neuroinjury Neurorepair and Regeneration in Central Nervous System Tianjin and Ministry of Education, Tianjin Medical University General Hospital, Tianjin 300052, China; [2]Department of Vascular Surgery, Shanghai Traditional Chinese Medicine Integrated Hospital, Shanghai 200082, China; [3]Department of Neurosurgery, Guizhou Panjiang Investment Holding (Group) Co., Ltd. General Hospital, Qujing 553536, Guizhou, China; [4]Department of Neurosurgery, Xuanwu Hospital, Capital Medical University, Beijing 100003, China. [*]Equal contributors and co-first authors.

Received May 31, 2026; Accepted July 17, 2026; Epub July 25, 2026; Published July 30, 2026

Abstract: Objective: To compare the safety and efficacy of an edoxaban-based, time-limited dual antithrombotic therapy followed by a de-escalation strategy versus a continuous dual antithrombotic strategy in patients with atrial fibrillation (AF) undergoing carotid artery stenting (CAS). Methods: A total of 120 patients with CAS and AF who underwent surgery at Guizhou Panjiang Investment Holding (Group) Co., Ltd. General Hospital from June 2023 to December 2024 were retrospectively enrolled. According to the perioperative antithrombotic regimen, patients were divided into a de-escalation group (n=56) and a dual therapy group (n=64). Patients in the de-escalation group received edoxaban (standard dose) combined with aspirin (100 mg/d) preoperatively and during the first 6 months postoperatively, after which aspirin was discontinued and edoxaban monotherapy was continued from 6 to 12 months postoperatively. Patients in the dual therapy group received continuous treatment with edoxaban plus aspirin throughout the 12-month follow-up period. Platelet count, C-reactive protein (CRP), D-dimer, fibrinogen, and coagulation parameters, including prothrombin time (PT), thrombin time (TT), and activated partial thromboplastin time (APTT), were compared at 1, 6, and 12 months postoperatively. Bleeding events, embolic events, adverse reactions, carotid artery restenosis, stent thrombosis, health-related quality of life (EQ-5D-5L), and treatment adherence were recorded. Results: Baseline characteristics were comparable between the two groups. After treatment, platelet count, CRP, D-dimer, and fibrinogen levels significantly decreased, whereas PT, TT, and APTT were significantly prolonged in both groups, with no significant intergroup differences. There was no significant difference in the incidence of vascular restenosis or stent thrombosis between the two groups (P>0.05). At 12 months postoperatively, the de-escalation group had a significantly lower incidence of bleeding events than the dual therapy group (8.93% vs. 23.44%, P=0.033), whereas the incidence of embolic events was comparable between groups (14.29% vs. 9.38%, P=0.403). The incidence of bleeding events during the 6-12-month postoperative period was significantly lower in the de-escalation group. Subgroup analyses stratified by CHA_2DS_2-VASc score and HAS-BLED score showed consistently lower bleeding rates in the de-escalation group, with no significant increase in embolism events. At 12 months, the de-escalation group showed significantly higher EQ-5D utility index and VAS scores, higher overall medication adherence (87.50% vs. 73.43%, P=0.035), and a lower rate of permanent treatment discontinuation due to adverse reactions (3.57% vs. 14.06%, P=0.047). Conclusion: In patients with AF undergoing CAS, an edoxaban-based de-escalation strategy involving conversion to monotherapy at 6 months postoperatively was non-inferior to continuous dual antithrombotic therapy in preventing ischemic events. This strategy significantly reduced bleeding risk at 12 months postoperatively and improved quality of life and treatment adherence, representing a safe and effective perioperative antithrombotic management regimen.

https://doi.org/10.62347/KDDU9091

Keywords: Carotid artery stenosis, atrial fibrillation, carotid artery stent implantation surgery, edoxaban, de-escalation of antithrombotic therapy, time-limited dual therapy

Introduction

The human brain has extremely limited energy reserves and therefore relies primarily on cerebral blood circulation to continuously provide oxygen and glucose. Carotid artery stenosis can cause insufficient cerebral blood perfusion, triggering compensatory mechanisms such as the establishment of collateral circulation and the utilization of cerebral blood flow reserve or metabolic reserve. During the early stage of chronic hypoperfusion caused by internal carotid artery stenosis, the establishment of collateral circulation through the middle cerebral artery a critical compensatory role. When collateral circulation becomes insufficient, cerebral capillaries and arterioles dilate to regulate cerebral blood flow and maintain blood flow stability [1]. As cerebral perfusion pressure further decreases, cerebral vasodilation reaches its maximum capacity, resulting in exhaustion of cerebral vascular reactivity (CVR) reserve. Consequently, normal brain metabolic demands cannot be maintained, cerebral blood flow decreases, and brain tissue maintains metabolic homeostasis by increasing the oxygen extraction fraction [2]. When oxygen supply to brain tissue is further compromised, cerebral infarction occurs [3].

Carotid artery stenting (CAS) is an effective method for carotid artery stenosis, which can significantly improve cerebral blood flow perfusion, enhance CVR, improve cognitive function, and reduce the risk of cerebral infarction [4, 5]. According to the 2017 Chinese guidelines for the diagnosis and treatment of carotid artery stenosis, patients undergoing stent implantation are recommended to undergo dual antiplatelet therapy for at least 4 weeks. For patients with high-risk factors for coronary heart disease or restenosis, dual therapy should be extended for at least 3 months, followed by long-term low-dose aspirin therapy [1]. However, when patients with CAS also have nonvalvular atrial fibrillation (AF), perioperative antithrombotic management becomes extremely complex. Such patients are exposed to a dual thrombotic risk: on the one hand, atherosclerotic plaque disruption and stent implantation may contribute to stent thrombosis or distal embolization; on the other hand, atrial blood flow stasis caused by AF significantly increases the risk of cardioembolic events [6]. Therefore, the optimal antithrombotic strategy after CAS in patients with AF requires a delicate balance between effectively preventing ischemic events and minimizing bleeding risk.

The traditional antithrombotic strategies often involve triple antithrombotic therapy (oral anticoagulant combined with dual antiplatelet therapy) in patients with AF undergoing percutaneous coronary intervention (PCI); however, this approach is associated with a higher risk of bleeding [7]. In recent years, a series of landmark clinical trials have gradually established that the dual antithrombotic therapy consisting of oral anticoagulants combined with a single antiplatelet drug is superior to conventional triple therapy in AF patients after PCI, and the recommended treatment duration of combination therapy has shown a trend toward shortening [8-10]. The core principle of these studies - maintaining adequate antithrombotic efficacy while minimizing bleeding risk - has been widely recognized and incorporated into current international guidelines for antithrombotic management in patients with coronary heart disease and AF, which recommend shorter duration of dual antithrombotic regimen for patients at high bleeding risk [11]. However, high-quality prospective randomized controlled trial evidence on the optimal perioperative antithrombotic strategy for patients with carotid artery stenosis combined with AF remains lacking, especially regarding the optimal duration and combination of antiplatelet drugs.

However, these findings are mainly derived from the field of coronary intervention. As a distinct vascular bed, carotid artery stents differ from coronary stents in several pathophysiological aspects, including the mechanisms underlying postoperative thrombotic events, the process of stent endothelialization, and the assessment of stroke risk. Therefore, extrapolating evidence from coronary intervention to patients undergoing carotid artery stenting lacks sufficient clinical validation. Direct oral anticoagulants (DOACs) provide a potential

solution to this clinical challenge due to their fixed dosing regimen, predictable pharmacokinetics, and favorable safety characteristics. Among DOACs, edoxaban, a highly selective factor Xa inhibitor, has demonstrated non-inferiority to warfarin in preventing stroke and systemic embolism in patients with AF in large-scale clinical trials, such as ENGAGE AF-TIMI 48, while significantly reducing the risk of major bleeding and intracranial hemorrhage [12, 13]. However, evidence regarding the perioperative application of edoxaban in patients undergoing CAS, especially the safety and efficacy of a time-limited dual antithrombotic strategy followed by de-escalation to edoxaban monotherapy, remains insufficient.

Therefore, this study aimed to compare the safety and efficacy of two edoxaban-based antithrombotic regimens in patients with carotid artery stenosis and AF during the perioperative period: a time-limited dual therapy followed by a de-escalation strategy (edoxaban combined with aspirin for 6 months postoperatively, followed by edoxaban monotherapy) and a sustained dual therapy strategy (continuous edoxaban combined with aspirin throughout the follow-up period).

Materials and methods

Subjects

This retrospective study included 120 patients with carotid artery stenosis combined with AF who underwent CAS at Guizhou Panjiang Investment Holding (Group) Co., Ltd. General Hospital between June 2023 and December 2024.

Inclusion criteria

(1) Patients aged 18-80 years; (2) Diagnosis of unilateral internal CAS by digital subtraction angiography (DSA) or computed tomography angiography (CTA), with symptomatic carotid artery stenosis ≥50%, asymptomatic carotid artery stenosis ≥70%; (3) Patients who met the indications for endovascular CAS treatment; (4) Complete clinical data and optical coherence tomography (OCT) imaging data before carotid stent implantation.

Exclusion criteria

(1) Patients with severe cerebral infarction accompanied by severe disability; (2) Patients with untreated unexplained intracranial hemorrhage within the previous 3 months; (3) Patients with extensive cerebral infarction or myocardial infarction within the previous 2 weeks; (4) Patients with intracranial aneurysms that could not be treated before, during, or within an appropriate limited period; (5) Patients with coagulation dysfunction or contraindications to heparin and antiplatelet therapy; (6) Patients with severe dysfunction of major organs, including the heart, lungs, liver, and kidneys; (7) Patients with malignant tumors or those undergoing radiotherapy and chemotherapy; (8) Patients who had recently received steroids or nonsteroidal anti-inflammatory drugs.

This study protocol was reviewed and approved by the Ethics Committee of Guizhou Panjiang Investment Holding (Group) Co., Ltd. General Hospital (Ethics Approval Number: ZYY-LL-2026009). The requirement for informed consent was waived by the ethics committee due to the retrospective nature of the study. The technical workflow is shown in **Figure 1**.

Experimental grouping and perioperative anticoagulation regimen

According to the perioperative antithrombotic regimen, patients were divided into two groups: the de-escalation group (n=56) and the dual therapy group (n=64).

Patients in the de-escalation group received a time-limited dual antithrombotic therapy followed by a de-escalation strategy. During the preoperative period and the first 6 months after CAS, patients received dual antithrombotic therapy consisting of edoxaban (standardized dosing: 60 mg/day for patients with creatinine clearance [CrCl] ≥50 mL/min and body weight >60 kg. 30 mg/d for patients with CrCl 15-50 mL/min, body weight ≤60 kg, or concomitant use of strong P-glycoprotein [P-gp] inhibitors) combined with aspirin (100 mg/d). From postoperative 6 to 12 months, aspirin was discontinued and edoxaban monotherapy was continued.

Patients in the dual group received a continuous dual regimen, consisting of edoxaban (at the same standardized dose) and aspirin (100 mg/d) throughout the preoperative period and the entire 12-month postoperative follow-up period.

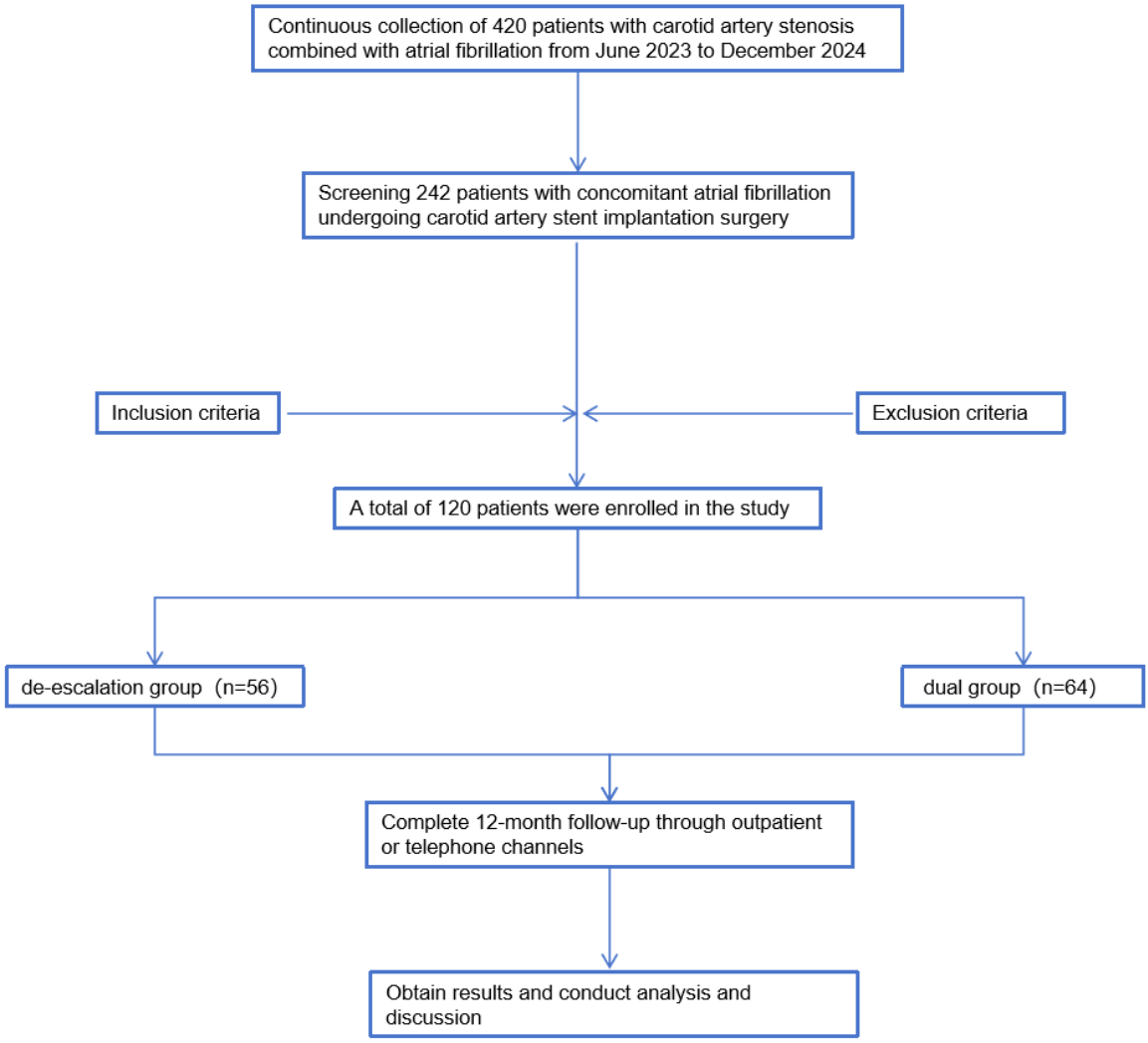

Figure 1. Study flow chart.

Other perioperative management was consistent between the two groups, including preoperative dual antithrombotic therapy, discontinuation of antithrombotic medication on the day of surgery, and temporary postoperative bridging therapy with a single dose of bemiparin (0.1 mg/10 kg).

Treatment methods

A complete set of preoperative transfusion-related examinations, routine blood and urine tests was performed 3 days before surgery. During surgery, routine disinfection was performed, and local anesthesia was administered. Percutaneous puncture of the right femoral artery was performed using the Seldinger method, followed by placement of an 8F arterial sheath and intravenous administration of heparin. Angiography was performed to determine the location, length, and severity of internal carotid artery stenosis, as well as the status of distal vascular collateral circulation. Under the guidance of a guidewire and roadmap imaging, an 8F guiding catheter was slowly advanced to the proximal end of the internal carotid artery stenosis. After crossing the stenotic lesion, a distal protective device was deployed beyond the stenosis. For patients with severe vascular stenosis in whom the protective umbrella could not cross the lesion, balloon predilation was performed. The stent then delivered to the stenotic segment and positioned to cover the entire lesion. After angiographic confirmation of the appropriate position, the stent was slowly released. Residual

stenosis was confirmed to be less than 50% after stent implantation. The arterial sheath was removed 8 hours after surgery, and hemostatic was achieved using a compression hemostatic.

Data collection

Both groups of patients received long-term antithrombotic therapy and were followed up for one year. Follow-up visits were conducted once every three months through outpatient assessments.

(1) Baseline clinical characteristics: General demographic and clinical data were collected, including age, sex, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), medical history (e.g., hypertension, diabetes mellitus, coronary heart disease, stroke, and transient ischemic attack), smoking history, and alcohol consumption history. Blood pressure measurements were obtained in the early morning on the day of carotid artery stent implantation after patient had remained in a resting state for more than 30 minutes without taking antihypertensive drugs.

(2) Laboratory and coagulation parameters: Coagulation-related and laboratory parameters were compared between the two groups before and after treatment. Prothrombin time (PT), thrombin time (TT), activated partial thromboplastin time (APTT), fibrinogen (Fib), and D-dimer (D-D) levels were recorded before treatment and at 1, 6, and 12 months after treatment. Platelet count (PLT) and C-reactive protein (CRP) levels were also measured.

(3) Carotid restenosis, in-stent thrombosis, and health-related quality of life assessment: The incidence of carotid restenosis and in-stent thrombosis within 12 months after stenting was recorded for both groups. Health-related quality of life was assessed before surgery and at 12 months postoperatively using the European Quality of Life 5-Dimension 5-Level questionnaire (EQ-5D-5L). The EQ-5D-5L utility index (range 0-1) and visual analog scale (VAS) score (range 0-100) were recorded.

(4) Treatment adherence assessment: Treatment adherence was evaluated using the proportion of days covered (PDC) calculated based on outpatient pharmacy dispensing records. A PDC ≥80% was defined as good adherence. The proportion of patients who permanently discontinued the study medication due to adverse reactions within 12 months postoperatively was also recorded.

(5) Time-cumulative risk and subgroup analysis: To evaluate dynamic changes in bleeding risk, the first postoperative year was divided into three consecutive time intervals (0-3 months, 3-6 months, and 6-12 months), and the incidence of first bleeding events occurring within each window was calculated separately. Furthermore, based on the CHA_2DS_2-VASc score, patients were divided into a low-to-moderate risk group (score ≤3) and a high-risk group (score ≥4). Prespecified subgroup analyses were performed to compare the incidence of bleeding and embolic events between the two treatment strategies within each subgroup. Based on HAS-BLED score, patients were further divided into a low bleeding-risk group (score 0-2) and a high bleeding-risk group (score ≥3), followed by subgroup comparisons of bleeding and embolic events between the two strategies.

(6) Bleeding events: Bleeding severity was classified according to the Bleeding Academic Research Consortium criteria (BARC) criteria. BARC type 1 bleeding: minor bleeding that resolved spontaneously, including self-limited epistaxis, skin bruising, and petechiae, without requiring adjustment of antithrombotic therapy or medical intervention. BARC type 2 bleeding: bleeding requiring medical intervention. BARC type 3a bleeding: significant active bleeding associated with a decrease in hemoglobin of 3-5 g/dl, typically requiring blood transfusion. BARC type 3b bleeding: more severe bleeding with a decrease in hemoglobin of ≥5 g/dl, requiring surgical intervention or vasoactive therapy. BARC type 3c bleeding: intracranial hemorrhage confirmed by imaging, lumbar puncture, or other examinations. BARC type 4 bleeding: coronary artery bypass grafting (CABG)-related bleeding. BARC type 5a bleeding: clinically suspected fatal bleeding. BARC type 5b bleeding: Lethal bleeding confirmed by imaging examination or autopsy. Major bleeding events included BARC type ≥3 bleeding events, excluding BARC type 4 bleeding.

Table 1. Comparison of baseline characteristics between the two groups

Index	de-escalation group (n=56)	dual group (n=64)	t/Z/χ^2	P
Age	63.05±5.84	62.89±6.02	0.431	0.665
BMI (kg/m^2)	23.74±2.74	24.02±2.69	-1.157	0.315
Sex			0.015	0.903
Male	30	35		
Female	26	29		
CHA_2DS_2-VASc score (score)	3.00 (2.00, 3.75)	3.00 (2.00, 4.00)	-0.047	0.962
Duration of atrial fibrillation	6.40±0.62	6.48±0.71	-0.692	0.490
Smoking history	27	37	1.106	0.293
Alcohol consumption history	20	26	0.305	0.581
History of hypertension	41	50	0.393	0.531
History of hyperlipidemia	37	35	1.613	0.204
History of diabetes	35	33	1.455	0.228
Types of atrial fibrillation			0.664	0.718
Persistent atrial fibrillation	26	25		
Permanent atrial fibrillation	17	22		
Paroxysmal atrial fibrillation	13	17		

BMI: Body Mass Index.

(7) Thromboembolic events: The occurrence of thromboembolic events, including death, cerebral embolism, pulmonary embolism, and systemic embolism, was recorded for both groups during follow-up period.

(8) Adverse reactions: Treatment-related adverse reactions, including dizziness, transient ischemia, ischemic bowel disease, and ischemic encephalopathy, were recorded during the treatment period.

Statistical analysis

Statistical analyses were performed using SPSS 26.0 software. The normality of continuous variables was tested using the Kolmogorov-Smirnov test. Normally distributed continuous variables were represented as mean ± standard deviation (SD) and compared between groups using the independent-sample t-test. Non-normally distributed continuous variables were expressed as median (interquartile range [IQR], P25-P75) and compared using the Mann-Whitney U test. Count data were expressed as frequencies and percentages, and between-group comparisons were performed using the chi-square test or Fisher's exact test, as appropriate. The calibration performance of bleeding risk prediction models was evaluated using the Hosmer-Lemeshow test. A two-sided *P* value <0.05 was considered statistically significant.

Results

Comparison of baseline characteristics between two groups

No significant differences were observed between the two groups in terms of age, BMI, sex, CHA_2DS_2-VASc score, duration of atrial fibrillation, smoking history, alcohol consumption history, comorbidities, or type of AF (*P*> 0.05) (**Table 1**).

Comparison of PLT, CRP, D-D, and Fib Levels before and after treatment between the two groups

There were no significant differences in the levels of PLT, CRP, D-D, or Fib between the two groups before treatment (*P*>0.05) (**Table 2**). Compared with baseline values, the levels of PLT, CRP, D-D and Fib significantly decreased at 1, 6, and 12 months after treatment in both groups (all *P*<0.05). However, no significant differences were observed between the two groups at the same postoperative time points (all *P*>0.05).

Comparison of coagulation parameters before and after treatment between two groups

Before treatment, no significant differences were observed in coagulation parameters (PT,

Table 2. Comparison of PLT, CRP, D-D levels before and after treatment between the two groups

Group	Time	De-escalation group (n=56)	Dual therapy group (n=64)	t/Z	P
PLT (10^9/L)	Before treatment	334.15 (322.30, 348.35)	339.70 (328.30, 351.30)	-1.718	0.086
	1 month after treatment	277.59±18.75*	283.57±18.47*	-1.755	0.082
	6 months after treatment	209.59±15.75*	204.39±15.20*	1.933	0.056
	12 months after treatment	153.15±14.76*	148.54±13.38*	1.795	0.075
CRP (mg/L)	Before treatment	44.35 (41.45, 49.33)	43.90 (38.83, 47.70)	-1.436	0.151
	1 month after treatment	33.7 (28.60, 37.73)*	31.75 (27.73, 35.70)*	-1.783	0.075
	6 months after treatment	16.65±3.88*	16.04±4.90*	0.761	0.448
	12 months after treatment	7.63±2.79*	8.80±3.85*	-1.916	0.058
D-D (mg/L)	Before treatment	0.71 (0.55, 0.79)	0.65 (0.59, 0.75)	-0.837	0.403
	1 month after treatment	0.52±0.15*	0.49±0.12*	1.124	0.264
	6 months after treatment	0.37±0.12*	0.39±0.11*	-0.411	0.682
	12 months after treatment	0.30 (0.19, 0.34)*	0.28 (0.21, 0.35)*	-0.355	0.722
Fib (g/L)	Before treatment	10.90±2.39	11.10±2.76	-0.422	0.674
	1 month after treatment	7.10±2.48*	7.57±2.59*	-0.997	0.321
	6 months after treatment	3.97±1.49*	3.57±1.03*	1.712	0.090
	12 months after treatment	2.86±0.63*	2.68±0.44*	1.825	0.071

Notes: PLT, platelet count; Fib, fibrinogen; D-D, D-dimer; CRP, C-reactive protein. *P<0.05, compared with baseline value.

Table 3. Comparison of coagulation parameters before and after treatment between the two groups

Group	Time	De-escalation group (n=56)	Dual therapy group (n=64)	t/Z	P
PT (s)	Before treatment	12.11±2.11	11.72±1.89	1.063	0.290
	1 month after treatment	13.57±2.41*	13.98±2.39*	-0.940	0.349
	6 months after treatment	15.20±1.14*	15.41±1.10*	-1.030	0.305
	12 months after treatment	16.66±1.08*	16.92±0.88*	-1.457	0.148
TT (s)	Before treatment	16.23±2.87	16.09±3.36	0.143	0.887
	1 month after treatment	18.52±1.57*	18.86±1.14*	-1.374	0.172
	6 months after treatment	19.00±1.06*	19.30±1.18*	1.442	0.152
	12 months after treatment	19.93±1.29*	20.23±1.46*	-1.210	0.229
APTT (s)	Before treatment	29.16±4.65	30.11±4.96	-1.076	0.284
	1 month after treatment	43.57±7.87*	45.81±6.78*	-1.675	0.097
	6 months after treatment	51.75±6.96*	53.75±7.24*	-1.536	0.127
	12 months after treatment	51.79±6.52*	50.97±6.85*	0.652	0.506

Notes: PT, prothrombin time; TT, thrombin time; APTT, activated partial thromboplastin time. *P<0.05, compared with baseline value.

TT, APTT) between the two groups of patients (P>0.05) (**Table 3**). Compared with baseline values, PT, TT, and APTT were significantly prolonged at 1, 6, and 12 months after treatment in both groups (all P<0.05). However, there were no significant differences between the two groups at the same postoperative time points (all P>0.05).

Comparison of the incidence of carotid restenosis and in-stent thrombosis between the two groups

At 12 months after surgery, no significant difference was observed in the incidence of carotid artery restenosis (14.29% vs. 10.94%, P=0.580) or in-stent thrombosis (10.71% vs.

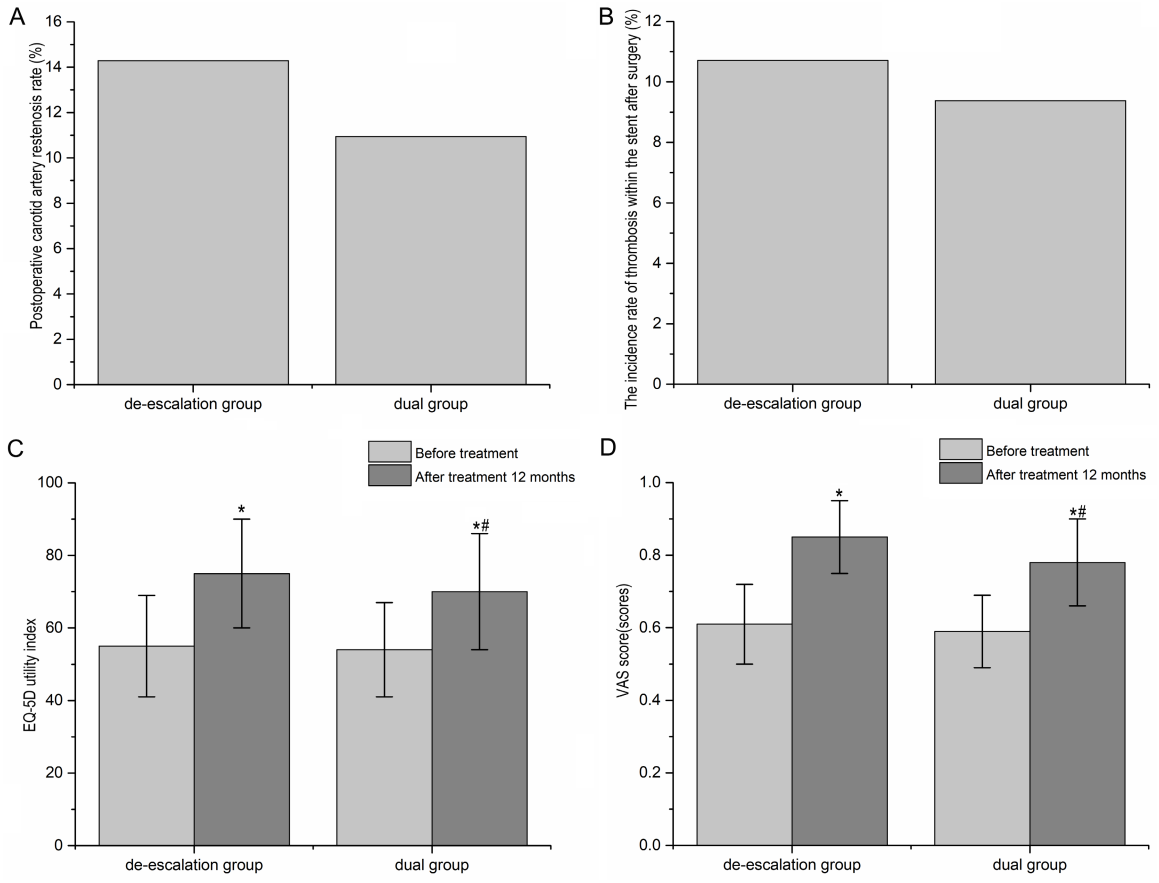

Figure 2. Comparison of carotid restenosis rate, stent thrombosis rate, and health-related quality of life between the two groups. A. Postoperative carotid artery restenosis rate. B. Incidence of in-stent thrombosis after surgery. C. EQ-5D utility index (range 0-1). D. EQ visual analogue scale (VAS) score (range 0-100). Notes: *P<0.05, compared with baseline value; #P<0.05, compared with the de-escalation group.

9.38%, P=0.807) between the two groups (**Figure 2A**, **2B**; **Table 4**).

Comparison of postoperative health-related quality of life (HRQoL) between the two groups

Patients' quality of life was assessed using the European Quality of Life 5-Dimension 5-Level questionnaire (EQ-5D-5L) before surgery and at 12 months postoperatively. Compared with baseline values, both the utility index and VAS scores were significantly increased at 12 months postoperatively in both groups (P= 0.012). Crucially, at the 12-month follow-up, the EQ-5D utility index was significantly higher in the de-escalation group than in the continuous dual therapy group (0.85 ± 0.10 *vs.* 0.78 ± 0.12, P=0.021), and the VAS score showed a similar trend (75 ± 15 *vs.* 70 ± 16, P=0.045) (**Figure 2C**, **2D**). These findings suggest that patients managed with the de-escalation strategy achieved superior long-term health status and quality of life, which may be associated with the reduced incidence of bleeding events and associated discomfort.

Comparison of time-cumulative risk of postoperative thromboembolic and bleeding events between two groups

No significant differences in embolic events were observed between the two groups at 1 and 6 months after surgery. the main embolic events being cerebral embolism, pulmonary embolism, and systemic embolism. During the 12-months postoperative follow-up, the cumulative incidence of embolic events was slightly higher in the de-escalation group than in the dual group, without statistical significance (χ^2=0.699, P=0.403) (**Table 5**).

The bleeding events in both groups mainly included puncture-site bleeding or hematoma, hemoptysis, hematuria, gingival bleeding, and

Table 4. Comparison of postoperative carotid artery restenosis rate, in-stent thrombosis rate, medication adherence, and discontinuation rate between the two groups [n (%)]

	De-escalation group (n=56)	Dual therapy group (n=64)	χ^2	P
Restenosis rate of blood vessels	8 (14.29)	7 (10.94)	0.306	0.580
Incidence of stent thrombosis	6 (10.71)	6 (9.38)	0.060	0.807
Medication compliance	49 (87.5)	47 (73.43)	3.691	0.035
Discontinuation rate	2 (3.57)	9 (14.06)		0.047

Table 5. Comparison of time-cumulative risk of postoperative embolism and bleeding events between the two groups [n (%)]

	De-escalation group (n=56)	Dual therapy group (n=64)	χ^2	P
Embolic events				
Postoperative 0-3 months	2 (3.57)	3 (4.68)	-	0.563
Postoperative 3-6 months	2 (3.57)	1 (1.56)	-	0.450
Postoperative 6-12 months	4 (7.14)	2 (3.13)	-	0.279
Overall incidence	8 (14.29)	6 (9.38)	0.699	0.403
Bleeding events				
Postoperative 0-3 months	1 (1.79)	3 (4.68)	-	0.622
Postoperative 3-6 months	1 (1.79)	2 (3.13)	-	0.443
Postoperative 6-12 months	3 (5.36)	10 (15.63)	-	0.047
Overall incidence	5 (8.93)	15 (23.44)	4.527	0.033
BARC ≥ type 3	3 (5.36)	8 (12.5)	-	0.216

nasal mucosal bleeding. To dynamically evaluate differences in bleeding risk between the two strategies, the incidence of first bleeding events (BARC 1-5) within each postoperative time window (0-3 months, 3-6 months, 6-12 months) was calculated. The results showed that during the first 6 months after surgery, no significant difference was observed in bleeding incidence between the two groups (3.57% *vs.* 7.81%, *P*=0.622), which was consistent with the period of dual antithrombotic therapy in both groups. During the 6-12 months postoperative window, when aspirin had been discontinued in the de-escalation group but continued in the dual therapy group, the bleeding incidence was significantly lower in the de-escalation group than in the dual therapy group (4.69% *vs.* 15.63%, *P*=0.047). The overall incidence of bleeding events during the 12-month follow-up period in the de-escalation group was also significantly lower than that in the dual therapy group (8.93% *vs.* 23.44%, *P*= 0.033) (**Table 5**). No significant difference was observed in the major bleeding events (BARC ≥3) between the two groups (*P*=0.216). These findings indicate that the de-escalation strategy, through timely discontinuation of aspirin, may reduce the cumulative bleeding risk associated with prolonged dual antithrombotic therapy, with the most pronounced difference observed after the transition from dual therapy to edoxaban monotherapy.

Comparison of bleeding and thromboembolic risks between the two groups according to CHA_2DS_2-VASc and HAS-BLED scores

Patients were divided into two subgroups based on CHA_2DS_2-VASc score: a low-to-moderate risk subgroup (score ≤3, n=62) and a high-risk subgroup (score ≥4, n=58). In the de-escalation group, 31 and 25 patients were classified into the low-to-moderate-risk and high-risk subgroups, respectively, whereas in the dual group, 31 and 33 patients were classified into these two subgroups, respectively. Within each subgroup, the 12-month cumulative incidences of bleeding events and embolic events were compared between the two groups. In the low-to-moderate risk subgroup, the bleeding rate was significantly lower in the de-escalation group than in the dual therapy group [2 (6.45%) vs. 8 (25.8%), *P*=0.040], whereas no significant difference was observed in embolic events

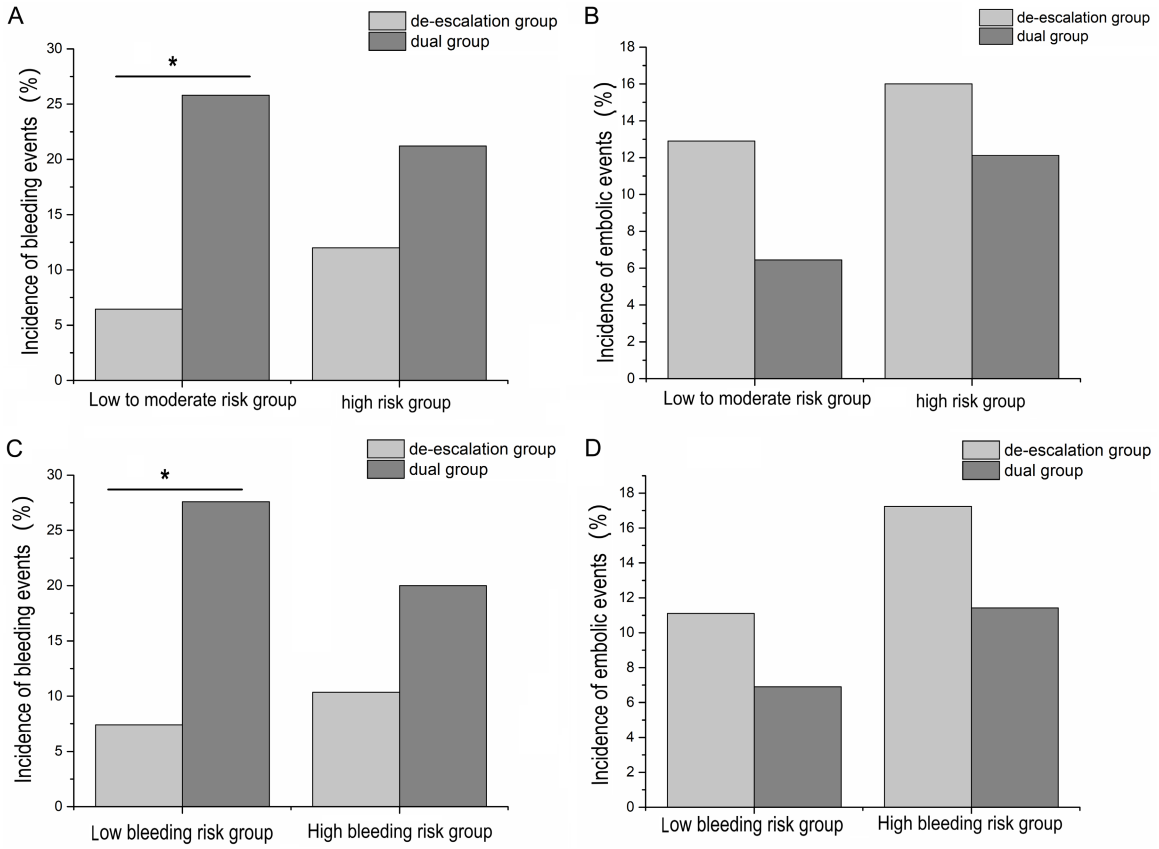

Figure 3. Subgroup analysis of bleeding and embolic events according to CHA_2DS_2-VASc and HAS-BLED scores. A. Subgroup analysis of bleeding events according to the CHA_2DS_2-VASc score (low-to-moderate risk [score ≤3] and high risk [score ≥4]). B. Subgroup analysis of embolic events according to the CHA_2DS_2-VASc score. C. Subgroup analysis of bleeding events based on the HAS-BLED score. D. Subgroup analysis of embolic events based on the HAS-BLED score. Notes: *P<0.05. CHA2DS2-VASc: Congestive heart failure, hypertension, age ≥75 years (doubled), diabetes mellitus, prior Stroke/TIA/thromboembolism (doubled), vascular disease, age 65-74 years, sex category (female). HAS-BLED: H (Hypertension), A (Abnormal renal/hepatic function), S (Stroke history), B (Bleeding history), L (Labile INR), E (Elderly >65 years), D (Drugs/alcohol).

[4 (12.9%) vs. 2 (6.45%), *P*=0.336]. In the high-risk subgroup, the bleeding incidence remained lower in the de-escalation group than in the dual therapy group, but the difference did not reach statistical significance [3 (12.0%) *vs.* 7 (21.21%), *P*=0.288]. Similarly, no significant difference was observed in the embolic events between the two groups [4 (16.0%) *vs.* 4 (12.12%), *P*=0.479] (**Figure 3A**, **3B**). These findings indicate that, irrespective of thromboembolic risk level, the de-escalation strategy was associated with a consistent reduction in bleeding risk without increasing embolic risk.

Patients were further divided into two subgroups based on the HAS-BLED bleeding risk score: the low-risk group (score 0-2, n=56) and the high-risk group (score ≥3, n=64). In the de-escalation group, 27 and 29 patients were classified into the low-risk and high-risk subgroups, respectively. In the dual therapy group, 29 and 35 patients were classified into the low-risk and high-risk subgroups, respectively. Similarly, within each subgroup, the 12-month cumulative incidences of bleeding events and embolic events were compared between the two treatment strategies. In the low bleeding-risk subgroup, the incidence of bleeding events was significantly lower in the de-escalation group than in the dual therapy group [2 (7.41%) *vs.* 8 (27.59%), *P*=0.040], whereas no significant difference was observed in the incidence of embolic rate [4 (14.81%) *vs.* 2 (6.90%), *P*=0.301]. In the high bleeding-risk subgroup, the bleeding incidence was lower in the de-escalation group than in

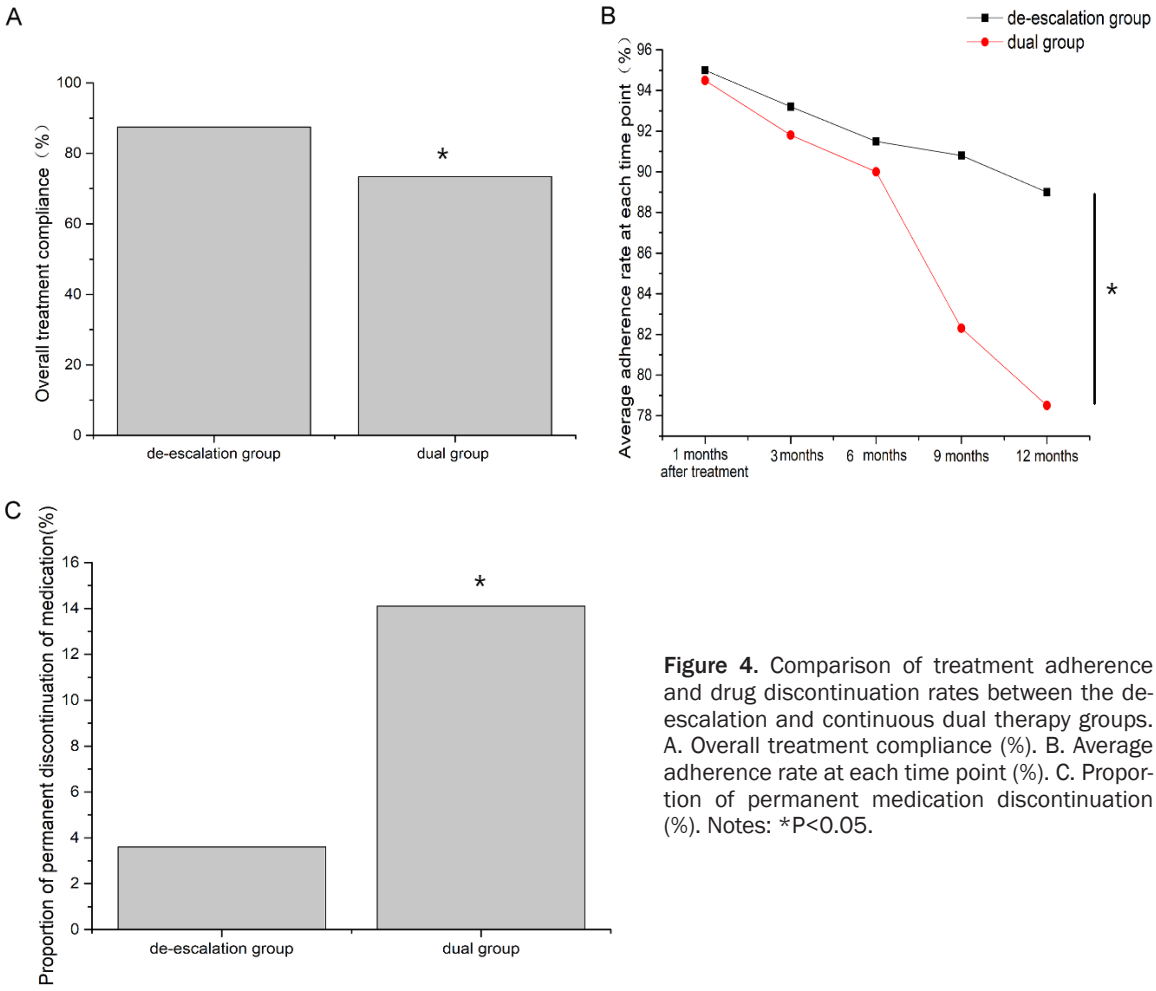

Figure 4. Comparison of treatment adherence and drug discontinuation rates between the de-escalation and continuous dual therapy groups. A. Overall treatment compliance (%). B. Average adherence rate at each time point (%). C. Proportion of permanent medication discontinuation (%). Notes: *P<0.05.

the dual therapy group, but the difference was not statistically significant [3 (10.34%) *vs.* 7 (20.00%), *P*=0.240]. No significant difference was observed in embolic events between the two groups [5 (17.24%) *vs.* 4 (11.43%), *P*=0.378] (**Figure 3C**, **3D**).

Comparison of treatment adherence and drug discontinuation rates between the two groups

Treatment adherence within 12 months after surgery was assessed based on pharmacy dispensing records and patient follow-up questionnaires. Good adherence was defined as a proportion of days covered (PDC) ≥80%. The overall medication adherence rate was significantly higher in the de-escalation group than in the dual therapy group (87.5% vs. 73.43%, *P*=0.035) (**Figure 4A**, **4B**). Notably, the proportion of patients who permanently discontinued any study medication due to adverse reactions (mainly minor bleeding or gastrointestinal discomfort) was significantly lower in the de-escalation group than in the dual therapy group (3.57% vs. 14.06%, *P*=0.047) (**Figure 4C**; **Table 4**). These findings suggest that the simplified antithrombotic regimen (conversion to single-agent therapy after 6 months) and the lower bleeding risk may improve treatment tolerability and long-term treatment persistence, which could contribute to maintaining therapeutic effectiveness.

Comparison of adverse event rates between two groups

Both groups of patients experienced treatment-related adverse events, including nausea and vomiting, respiratory distress, and headache. However, the incidence of these adverse events showed no significant differences between the two groups (*P*=0.749, 0.722, 0.583, respectively) (**Table 6**).

Table 6. Comparison of the incidence of adverse events between the two groups [n (%)]

Index	De-escalation group (n=56)	Dual therapy group (n=64)	χ^2	P
Nausea and vomiting	4 (7.14)	6 (9.38)		0.749
Respiratory distress	3 (5.36)	5 (7.81)		0.722
Headache	7 (12.5)	8 (12.5)	0.302	0.583

Discussion

Perioperative antithrombotic management of patients undergoing carotid artery stenting (CAS) with non-valvular atrial fibrillation (AF) remains a major clinical challenge. Such patients are exposed to dual thrombotic risk, including atherothrombotic events (such as ischemic stroke and stent thrombosis) associated with carotid atherosclerosis and stent implantation, as well as AF-related thromboembolic events (such as cardiogenic stroke). However, intensifying antithrombotic therapy inevitably increases the risk of bleeding events. This study retrospectively compared the efficacy and safety of two edoxaban-based antithrombotic strategies in patients with CAS combined with AF: a time-limited dual therapy followed by a de-escalation strategy and sustained dual therapy. There was no significant difference in the incidence of carotid artery restenosis or stent thrombosis between the two groups. Furthermore, the de-escalation strategy significantly reduced the incidence of bleeding events (8.93% vs 23.44%) at 12 months postoperatively, without increasing the risk of embolic events. These findings provide valuable clinical evidence supporting individualized antithrombotic management in this specific patient population.

Edoxaban, a highly selective inhibitor of factor Xa, effectively inhibits thrombus formation by directly inhibiting factor Xa activity and blocking the production of thrombin [14]. Its stable pharmacokinetic profile and fixed-dose administration regimen provide a more convenient and potentially safer option for perioperative anticoagulation management during radiofrequency ablation of atrial fibrillation or carotid artery stent implantation [15]. Factor Xa is a serine protease that plays a central role in thrombin generation. Edoxaban can directly bind to the active site of factor Xa, inhibits the conversion of prothrombin to thrombin, suppresses thrombin-mediated coagulation pathways, and consequently reduces thrombus production. In addition to its anticoagulant effects, previous studies have suggested that edoxaban may attenuate the pro-inflammatory and pro-fibrotic effects mediated by factor Xa and thrombin, thereby reducing the expression of pro-inflammatory cytokines [16]. A real-world cohort study conducted in German compared the safety and efficacy of edoxaban with other non-vitamin K antagonist oral anticoagulants (NOACs) and vitamin K antagonists (VKA) in patients with AF. The results showed that edoxaban was associated with reduced risk of ischemic stroke/systemic embolism compared with apixaban (27%), dabigatran (40%), rivaroxaban (38%), and VKA (36%). In terms of major bleeding, edoxaban showed a significantly lower risk compared to rivaroxaban (26%) and VKA (53%). In particular, edoxaban was associated with lower risks of major gastrointestinal bleeding compared with dabigatran (36%), rivaroxaban (36%), and VKA (56%), suggesting a favorable safety profile [17].

The main finding of this study is that transitioning to edoxaban monotherapy after a limited period of dual therapy significantly reduced the risk of bleeding without compromising antithrombotic efficacy, which is highly consistent with the evolving concept of “de-escalation” or “time-limited dual antithrombotic therapy” in recent years [18, 19]. Traditionally, management of patients with AF complicated by coronary or peripheral artery disease has long followed the triple antithrombotic therapy or prolonged dual antithrombotic therapy. However, the associated bleeding risk has remained a major limitation restricting the widespread clinical application of these strategies [20]. The strategy of switching from dual therapy to anticoagulation monotherapy 6 months after CAS adopted in this study represents a practical application of the de-escalation concept in patients with peripheral arterial disease. Our findings suggest that a 6-month dual antiplatelet therapy may adequately cover the critical phase of stent endothelialization and vascular injury repair after CAS, whereas

subsequent transition to anticoagulant monotherapy can effectively reduce the cumulative bleeding risk associated with prolonged antiplatelet therapy. Fukamachi D et al. [21] evaluated the safety of edoxaban monotherapy in patients with stable CAD and NVAF. In their study, 147 patients from eight medical institutions in Japan were assigned to receive either edoxaban monotherapy (n=74) or combination therapy with edoxaban plus clopidogrel (n=73). Two patients in the monotherapy group experienced major or clinically relevant non-major bleeding (1.67% per patient-year), compared with five patients in the combination therapy group (4.28% per patient-year) (hazard ratio [HR] 0.39; 95% confidence interval [CI] 0.08-2.02). No patients in either groups experienced myocardial infarction, stent thrombosis, unstable angina requiring revascularization, ischemic stroke, systemic stroke, or hemorrhagic stroke.

In addition, the multidimensional outcome assessment in this study further expands the clinical implications of the findings. First, patients in the de-escalation group demonstrated better health-related quality of life. This may be partially attributed to the lower incidence of bleeding events observed in this group. Edoxaban can inhibit thrombosis by selectively inhibiting factor Xa activity, thereby reducing ischemic damage to brain tissue, promoting neurological function recovery, and thereby enhancing the daily living ability of patients. Bleeding events, especially recurrent minor bleeding events such as ecchymosis and gingival bleeding, can adversely affect patients' physical comfort, psychological well-being, and confidence in long-term treatment, ultimately impairing quality of life. More importantly, avoidance of major bleeding events (e.g., intracranial hemorrhage) is crucial for preserving neurological function and achieving favorable functional outcomes. Our findings are consistent with previous studies demonstrating that safety profile of antithrombotic therapy is closely associated with long-term functional status and quality of life.

The European Society of Cardiology (ESC) guidelines for the management of acute coronary syndrome and the American Heart Association (AHA) scientific statement emphasize that, for patients with a bleeding risk exceeding their ischemic risk, shortening the duration of dual antiplatelet therapy should be considered [22]. In this study, patients in the de-escalation group avoided unnecessary prolonged exposure to antiplatelet therapy during the 7-12 months after surgery by timely discontinuation of aspirin. This approach is also consistent with the pharmacological characteristics of edoxaban [13]. Previous studies have demonstrated that the efficacy and safety profiles of edoxaban remain favorable in patients with concomitant arterial disease [12, 23]. In this study, edoxaban served as the cornerstone of antithrombotic therapy, with a standardized dosing regimen adjusted based on renal function and body weight. The de-escalation strategy significantly improved long-term treatment compliance. Simplifying treatment plans (transitioning from dual therapy to monotherapy) is a well-established approach for improving compliance in patients with chronic diseases. Good adherence is the essential for maintaining the effectiveness of anticoagulant therapy and reducing the risk of thromboembolic events associated with medication interruption or discontinuation. Therefore, the de-escalation strategy may facilitate the achievement of long-term treatment goals by establishing a safer and sustainable cycle.

The results of this study showed that PLT, CRP, D-D, TT, APTT, and PT were significantly improved in both groups at 3, 6, and 12 months after surgery, with no significant differences observed between the two groups. These findings indicate that the de-escalation strategy did not weaken the overall antithrombotic effect. The risk of thrombosis after CAS is primarily concentrated during the early postoperative period, driven by vascular endothelial injury, plaque disruption, and local inflammatory reactions caused by stent implantation. During this period, anticoagulant combined with antiplatelet therapy can synergistically inhibit thrombin production and platelet activation, thereby offering comprehensive thrombotic protection [24, 25]. After 6 months, with progressive completion of stent endothelialization and resolution of vascular inflammation, the major contributors to thrombus formation may gradually shift toward atrial blood stasis caused by AF itself. At this stage, the incremental benefit of continued antiplatelet therapy may diminish, whereas anticoagulant monotherapy may be sufficient to prevent cardioem-

bolic events. In this study, the de-escalation group showed a numerically higher incidence of embolic events compared with the dual group, although the difference was not statistically significant, indicating the importance of individualized risk assessment and suggests that prolonged dual therapy may still be considered in selected high-risk patients (such as those with a history of stroke, extremely high CHA2DS2-VASc scores, or complex carotid artery lesions).

From a methodological perspective, this study implemented standardized edoxaban dose adjustment based on creatinine clearance rate and body weight. However, an individualized stepwise anticoagulation transition pathway based on CHA_2DS_2-VASc thrombus risk score and HAS-BLED bleeding risk score has not yet been established. The current study only performed post hoc subgroup analyses stratified by these risk scores. Such retrospective stratified comparisons can provide preliminarily insights into outcome differences among risk subgroups but cannot be considered a prespecified individualized anticoagulation strategy and therefore cannot directly guide clinical adjustment of medication regimens.

Future studies should build on the preliminary efficacy and safety findings of this study to construct a dynamic personalized anticoagulation conversion pathway using CHA_2DS_2-VASc and HAS-BLED scores as core stratification criteria at different postoperative time points. For patients at high thromboembolic risk, the duration of enhanced anticoagulation therapy may be appropriately extended, whereas patients with high bleeding risk may benefit from earlier implementation of a de-escalation strategy.

However, this study has several limitations. First, as a retrospective cohort study, it was subject to potential confounding factors, and the relatively limited sample size may restrict the generalizability of the findings. Differences in patient characteristics, enrollment patterns, and baseline comorbidities among different centers may also introduce selection bias. Therefore, larger multicenter real-world studies are required to further validate the applicability of this strategy. Second, the postoperative follow-up period was only 12 months, and long-term outcomes, including stroke, intracardiac thrombosis, and major bleeding events beyond 1 year, were not evaluated. Longer follow-up is warranted to assess the durability of the observed benefits. Finally, this study was designed to evaluate clinical effectiveness and safety in real-world practice, without exploring underlying molecular mechanisms involved in endothelial repair or thrombus regulation. Future studies incorporating animal models of carotid atherosclerosis and endothelial cell experiments are needed to further elucidate the biological mechanisms underlying this therapeutic strategy.

Conclusion

This study demonstrates that the edoxaban-based de-escalation strategy effectively balances thrombotic and bleeding risks in patients with AF undergoing CAS. Beyond maintaining comparable antithrombotic efficacy, this strategy provides additional clinical benefits, including reduced bleeding risk, improved treatment adherence, and better patient-reported quality of life. Our findings support the concept of individualized antithrombotic management provide a potential therapeutic option for the perioperative management of patient with AF undergoing CAS.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (Grant Nos. 82311530117, 82271394, 82471497), and the Tianjin Key Medical Discipline Construction Project (Grant No. TJYXZDXK-3-002A).

Disclosure of conflict of interest

None.

Address correspondence to: Rongcai Jiang, Department of Neurosurgery, Tianjin Neurological Institute, State Key Laboratory of Experimental Hematology, Laboratory of Post-Neuroinjury Neurorepair and Regeneration in Central Nervous System Tianjin and Ministry of Education, Tianjin Medical University General Hospital, Tianjin 300052, China. E-mail: jiangrongcai@tmu.edu.cn; Fenghuang Sun, Department of Neurosurgery, Guizhou Panjiang Investment Holding (Group) Co., Ltd. General Hospital, Qujing 553536, Guizhou, China. E-mail: 2362109581@qq.com; Chao Ma, Department of Vascular Surgery, Shanghai Traditional Chinese

Medicine Integrated Hospital, Shanghai 200082, China. E-mail: machao1985618@163.com

References

[1] Kuehnl A, Knappich C, Kirchhoff F, Bohmann B, Lohe V, Naher S, Eckstein HH and Kallmayer M. Identification of patient characteristics that may improve procedure selection for the treatment of carotid stenosis. Br J Surg 2024; 111: znae227.

[2] Pensato U, Demchuk AM and Donnan GA. Submaximal angioplasty for severe intracranial atherosclerotic stenosis: benefit of revascularization at last. Stroke 2025; 56: e114-e118.

[3] Gupta R, Hassankhani A, Ghozy S, Tolba H, Kobeissi H, Kanitra J, Kadirvel R and Kallmes DF. Effect of treatment choice on short-term and long-term outcomes for carotid near-occlusion: a meta-analysis. World Neurosurg 2024; 181: e1102-e1129.

[4] Sakakura Y, Kono K and Fujimoto T. Real time artificial intelligence assisted carotid artery stenting: a preliminary experience. J Neurointerv Surg 2025; 17: 410-414.

[5] Batista S, Oliveira LB, Sousa MP, Pinheiro AC, Borges J, Santana L, Bertani R, Andreão FF, Simões A and Almeida Filho JA. Transradial artery access for carotid artery stenting: a pooled analysis. Neuroradiol J 2024; 37: 546-555.

[6] Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, Boriani G, Castella M, Dan GA, Dilaveris PE, Fauchier L, Filippatos G, Kalman JM, La Meir M, Lane DA, Lebeau JP, Lettino M, Lip GYH, Pinto FJ, Thomas GN, Valgimigli M, Van Gelder IC, Van Putte BP and Watkins CL; ESC Scientific Document Group. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J 2021; 42: 373-498.

[7] Angiolillo DJ, Bhatt DL, Cannon CP, Eikelboom JW, Gibson CM, Goodman SG, Granger CB, Holmes DR, Lopes RD, Mehran R, Moliterno DJ, Price MJ, Saw J, Tanguay JF and Faxon DP. Antithrombotic therapy in patients with atrial fibrillation treated with oral anticoagulation undergoing percutaneous coronary intervention: a North American perspective: 2021 update. Circulation 2021; 143: 583-596.

[8] Gibson CM, Mehran R, Bode C, Halperin J, Verheugt FW, Wildgoose P, Birmingham M, Ianus J, Burton P, Van Eickels M, Korjian S, Daaboul Y, Lip GY, Cohen M, Husted S, Peterson ED and Fox KA. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. N Engl J Med 2016; 375: 2423-2434.

[9] Lopes RD, Heizer G, Aronson R, Vora AN, Massaro T, Mehran R, Goodman SG, Windecker S, Darius H, Li J, Averkov O, Bahit MC, Berwanger O, Budaj A, Hijazi Z, Parkhomenko A, Sinnaeve P, Storey RF, Thiele H, Vinereanu D, Granger CB and Alexander JH; AUGUSTUS Investigators. Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation. N Engl J Med 2019; 380: 1509-1524.

[10] Vranckx P, Valgimigli M, Eckardt L, Tijssen J, Lewalter T, Gargiulo G, Batushkin V, Campo G, Lysak Z, Vakaliuk I, Milewski K, Laeis P, Reimitz PE, Smolnik R, Zierhut W and Goette A. Edoxaban-based versus vitamin K antagonist-based antithrombotic regimen after successful coronary stenting in patients with atrial fibrillation (ENTRUST-AF PCI): a randomised, open-label, phase 3b trial. Lancet 2019; 394: 1335-1343.

[11] Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, Dendale P, Dorobantu M, Edvardsen T, Folliguet T, Gale CP, Gilard M, Jobs A, Jüni P, Lambrinou E, Lewis BS, Mehilli J, Meliga E, Merkely B, Mueller C, Roffi M, Rutten FH, Sibbing D and Siontis GCM; ESC Scientific Document Group. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J 2021; 42: 1289-1367.

[12] Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Špinar J, Ruzyllo W, Ruda M, Koretsune Y, Betcher J, Shi M, Grip LT, Patel SP, Patel I, Hanyok JJ, Mercuri M and Antman EM; ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013; 369: 2093-2104.

[13] Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, Camm AJ, Weitz JI, Lewis BS, Parkhomenko A, Yamashita T and Antman EM. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet 2014; 383: 955-962.

[14] Corsini A, Ferri N, Proietti M and Boriani G. Edoxaban and the issue of drug-drug interactions: from pharmacology to clinical practice. Drugs 2020; 80: 1065-1083.

[15] Srinivasan S, Ajmal M, Pecci C and Lassar T. Edoxaban in cardiovascular disease management: review. Br J Clin Pharmacol 2022; 88: 535-540.

[16] Goette A, Mollenhauer M, Rudolph V, Lamparter M, Meier M and Böhm M. Pleiotropic effects of NOACs with focus on edoxaban: scien-

tific findings and potential clinical implications. Herzschrittmacherther Elektrophysiol 2023; 34: 142-152.
[17] Marston XL, Wang R, Yeh YC, Zimmermann L, Ye X, Gao X, Brüggenjürgen B and Unverdorben M. Comparison of clinical outcomes of edoxaban versus apixaban, dabigatran, rivaroxaban, and vitamin K antagonists in patients with atrial fibrillation in Germany: a real-world cohort study. Int J Cardiol 2022; 346: 93-99.
[18] Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF and Windecker S; ESC Scientific Document Group. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: task force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2016; 37: 267-315.
[19] Angiolillo DJ, Goodman SG, Bhatt DL, Eikelboom JW, Price MJ, Moliterno DJ, Cannon CP, Tanguay JF, Granger CB, Mauri L, Holmes DR, Gibson CM and Faxon DP. Antithrombotic therapy in patients with atrial fibrillation treated with oral anticoagulation undergoing percutaneous coronary intervention: a North American perspective-2018 update. Circulation 2018; 138: 527-536.
[20] Lip GYH. The ABC pathway: an integrated approach to improve AF management. Nat Rev Cardiol 2017; 14: 627-628.
[21] Fukamachi D, Okumura Y, Matsumoto N, Tachibana E, Oiwa K, Ichikawa M, Haruta H, Nomoto K, Arima K and Hirayama A. Edoxaban monotherapy in nonvalvular atrial fibrillation patients with coronary artery disease. J Interv Cardiol 2022; 2022: 5905022.
[22] Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, Boriani G, Castella M, Dan GA, Dilaveris PE, Fauchier L, Filippatos G, Kalman JM, La Meir M, Lane DA, Lebeau JP, Lettino M, Lip GYH, Pinto FJ, Thomas GN, Valgimigli M, Van Gelder IC, Van Putte BP and Watkins CL. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2021; 42: 373-498.
[23] Steffel J, Collins R, Antz M, Cornu P, Desteghe L, Haeusler KG, Oldgren J, Reinecke H, Roldan-Schilling V, Rowell N, Sinnaeve P, Vanassche T, Potpara T, Camm AJ and Heidbüchel H; External reviewers. 2021 European heart rhythm association practical guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Europace 2021; 23: 1612-1676.
[24] Petersen SR, Bonnesen K, Larsen JB, Pedersen L and Schmidt M. Bleeding risk using non-steroidal anti-inflammatory drugs in anticoagulated patients with atrial fibrillation: a nationwide cohort study. Eur Heart J Qual Care Clin Outcomes 2025; 11: 1340-1350.
[25] Morishima Y, Shibutani T, Noguchi K, Ito Y and Honda Y. Edoxaban, a direct oral factor Xa inhibitor, ameliorates coagulation, microvascular thrombus formation, and acute liver injury in a lipopolysaccharide-induced coagulopathy model in rats. J Thromb Thrombolysis 2021; 52: 9-17.