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·论　著·

心房颤动相关急性缺血性脑卒中血管再通治疗后的抗凝治疗现状分析

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［摘要］ **目的**　了解现实世界心房颤动相关急性缺血性脑卒中（AIS）患者接受血管再通治疗后的抗凝现状。**方法**　采用回顾性病例研究方法，抽取南昌大学第二附属医院2019年1月至2022年1月出院诊断为AIS和心房颤动并采取静脉溶栓（IVT）、血管内取栓（EVT）或IVT＋EVT治疗的患者为研究对象，记录患者基本临床资料、启动抗凝治疗的时间、抗凝方案及结果等并进行统计学分析，并对延迟或未启动抗凝治疗的原因进行调查分析。**结果**　符合筛选标准的心房颤动相关AIS患者共189例，其中IVT组86例（45.5%）、EVT组63例（33.3%）、IVT＋EVT组40例（21.2%）。189例患者的平均年龄为（72.90±9.23）岁，女性患者有93例（49.2%），36.0%（68/189）的患者在AIS血管再通治疗后14 d内启动抗凝治疗，其中IVT组占58.8%（40/68）、EVT组占22.1%（15/68）、IVT＋EVT组占19.1%（13/68），3组之间14 d内启动抗凝治疗的患者占比差异有统计学意义（P＝0.020）。对血管再通治疗后14 h内启动抗凝治疗患者（68例）与延迟或未启动抗凝治疗患者（121例）临床资料的单因素分析结果显示，两组既往脑卒中病史、血管再通治疗前美国国立卫生研究院卒中量表（NIHSS）评分、Alberta卒中项目早期CT评分、血管再通治疗前改良Rankin量表（mRS）评分、影像学特点（病灶靠近皮质、大面积梗死、严重的颅内责任大动脉狭窄或闭塞）、血管再通治疗方式、血管再通治疗后3 d NIHSS评分、血管再通治疗后颅内出血转化差异均有统计学意义（均P＜0.05）；多因素logistic回归分析显示，血管再通治疗后3 d NIHSS评分高（OR＝1.113，95% CI 1.053～1.176，P＜0.001）、血管再通治疗后发生颅内出血（OR＝6.098，95% CI 2.004～18.193，P＝0.001）的患者不宜进行抗凝治疗。大面积梗死（40.8%）、梗死部位（35.8%）及卒中后出血转化（40.8%）是影响主诊医师启动抗凝治疗的常见原因。在心房颤动相关AIS患者90 d预后中，6例患者出现出血事件，90 d预后良好（mRS评分为0～2分）患者共116例。血管再通治疗后14 d内启动抗凝组90 d预后良好率（89.7%，61/68）高于延迟或未启动抗凝组（45.5%，55/121），差异有统计学意义（P＜0.001）。**结论**　接受IVT、EVT或IVT＋EVT治疗的心房颤动相关AIS患者，在血管再通治疗后早期开始抗凝治疗是安全的，但大多数患者抗凝治疗时机晚于当前推荐的抗凝时机。

［关键词］ 缺血性脑卒中；心房颤动；静脉溶栓；血管内介入治疗；抗凝
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Anticoagulation after revascularization therapy for atrial fibrillation-related acute ischemic stroke: current status

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［**Abstract**］ **Objective**　To investigate the anticoagulation status of patients with atrial fibrillation (AF)-related acute ischemic stroke (AIS) after revascularization therapy in the real world. **Methods**　A retrospective study was performed on patients diagnosed as AIS and AF from Jan. 2019 to Jan. 2022 at The Second Affiliated Hospital of Nanchang University. Patients treated with intravenous thrombolysis (IVT), endovascular thrombectomy (EVT), or both were enrolled. Clinical information, timing of anticoagulation initiation, treatment regimens, and outcomes were documented and statistically

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analyzed. Additionally, a questionnaire was administered to the primary physicians to understand reasons for delaying or not initiating anticoagulation. **Results**　A total of 189 patients with AF-related AIS met the screening criteria, including 86 (45.5%) cases in the IVT group, 63 (33.3%) cases in the EVT group, and 40 (21.2%) cases in the IVT＋EVT group. The mean age of 189 patients was (72.90±9.23) years old. There were 93 (49.2%) female patients. Anticoagulation was initiated within 14 d after revascularization therapy in 36.0% (68/189) of patients, with the highest rate in the IVT group (58.8%, 40/68), followed by the EVT group (22.1%, 15/68) and IVT＋EVT group (19.1%, 13/68). A significant difference was found in the proportion of patients receiving anticoagulation within 14 d among the 3 groups (P=0.020). Univariate analysis was performed on the clinical data of patients who initiated anticoagulation within 14 d after revascularization therapy (68 cases) and those who delayed or did not initiate anticoagulation (121 cases). The results showed that there were significant differences in the stroke history, National Institutes of Health stroke scale (NIHSS) score before revascularization therapy, Alberta Stroke Program early computed tomography score, modified Rankin scale (mRs) score before revascularization therapy, imaging characteristics (lesions near cortex, large infarction, severe stenosis or occlusion of major intracranial arteries), revascularization therapy method, NIHSS score 3 d after revascularization therapy, and intracranial hemorrhagic transformation after revascularization therapy between the 2 groups (all P<0.05). Multivariate logistic regression analysis indicated that higher NIHSS scores 3 d after revascularization therapy (odds ratio ［*OR*］=1.113, 95% confidence interval ［*CI*］ 1.053-1.176, P<0.001) and the presence of intracranial hemorrhage after revascularization therapy (*OR*=6.098, 95% *CI* 2.004-18.193, P=0.001) were significant factors that contraindicated the initiation of anticoagulation. Large infarcts (40.8%), infarct location (35.8%), and hemorrhagic transformation after stroke (40.8%) were the common reasons cited by physicians for not initiating anticoagulation. In the 90-d prognosis of patients with AF-related AIS, 6 patients had bleeding events, and 116 patients had a good prognosis (mRS score of 0-2). The 90-d good prognosis rate in the initiated anticoagulation group within 14 d after revascularization therapy (89.7%, 61/68) was significantly higher than that in the delayed or non-anticoagulation group (45.5%, 55/121; P<0.001). **Conclusion**　For patients with AF-related AIS who receive IVT, EVT or IVT＋EVT, it is safe to initiate anticoagulation early after revascularization therapy, but the timing of anticoagulation in most patients is later than the currently recommended anticoagulation timing.

［**Key words**］ ischemic stroke; atrial fibrillation; intravenous thrombolysis; endovascular intervention; anticoagulation

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心源性脑卒中约占所有类型脑卒中的1/4[1-2]，由多种心源性栓塞引起，其中心房颤动相关脑卒中占所有心源性脑卒中的70%以上，且与其他病因相比，心源性脑卒中往往病情更重、预后更差、复发率更高[3-4]。心房颤动相关脑卒中的治疗原则包括急性时间窗治疗和预防卒中复发治疗，其中急性时间窗应尽量缩短发病至溶栓治疗时间，并酌情适时选择桥接或直接机械取栓治疗，最大程度地挽救缺血半暗带，减少神经功能残疾；而在预防卒中复发过程中，抗凝治疗为首选[5]。目前研究证实，心房颤动患者可以通过口服抗凝剂预防栓塞事件[6]，且心房颤动相关脑卒中患者口服抗凝药物预防脑卒中复发的效果优于抗血小板药物，复发风险可降低至3.0%，但颅内出血的风险却增加了1.8%[7-10]。对于急性缺血性脑卒中（acute ischemic stroke，AIS）合并心房颤动患者早期开始口服抗凝治疗的最佳时机，相对公认的是欧洲心脏节律学会和欧洲心脏病协会推荐的基于专家共识[11]的“1-3-6-12”法则及美国心脏协会和美国卒中协会指南基于RAF（Early Recurrence and Cerebral Bleeding in Patients With Acute Ischemic Stroke and Atrial Fibrillation）试验[12]推荐的“4-14”d标准。但目前关于AIS合并心房颤动接受血管再通治疗患者的抗凝治疗研究甚少，其中RAF试验中仅有22.4%的患者接受了血管再通治疗[12]。研究表明，接受血管再通治疗的患者脑卒中严重程度往往高于未接受相关血管再通治疗患者[13-16]；与接受抗凝治疗的心房颤动相关AIS患者相比，未接受抗凝治疗患者的病灶更大，美国国立卫生研究院卒中量表（National Institutes of Health stroke scale，NIHSS）评分更高，病情更严重[12,17]。本研究通过回顾性分析南昌大学第二附属医院接受血管再通治疗的心房颤动相关AIS患者的临床及预后数据，观察现实世界中接受血管再通治疗的心房颤动相关AIS患者的抗凝现状及影响因素。

1　资料和方法

1.1　研究对象　通过南昌大学第二附属医院的电

子病历系统查阅2019年1月至2022年1月出院诊断为AIS和心房颤动，并采取静脉溶栓（intravenous thrombolysis，IVT）、血管内取栓（endovascular thrombectomy，EVT）或IVT桥接EVT治疗的患者为研究对象。纳入标准：（1）出院诊断包括AIS及心房颤动或阵发性心房颤动、心房纤颤、阵发性心房纤颤；（2）接受IVT和/或EVT治疗。排除标准：（1）有瓣膜性心脏病或风湿性心脏病；（2）因病情严重自动出院、转院或死亡；（3）数据缺失导致无法完成研究。本研究经过南昌大学第二附属医院伦理委员会备案审批［O-医研伦理【2023】第（35）号］。

1.2　临床资料采集　采用回顾性研究方法，用Excel表格记录患者的年龄、性别、高血压病史、糖尿病史、高脂血症病史、吸烟/饮酒史、脑卒中病史、心脏疾病史、既往抗栓药物使用情况、影像学特点（如病灶是否为靠近皮质、大面积梗死、脑干梗死、多发梗死、颅内责任大动脉严重狭窄或闭塞）、Alberta卒中项目早期CT评分（Alberta Stroke Program early CT score，ASPECT评分）、血管再通治疗前NIHSS评分、血管再通治疗前改良Rankin量表（modified Rankin scale，mRS）评分、非瓣膜病性心房颤动脑卒中危险评分（CHA_2DS_2-VASc评分）、出血风险评分（HAS-BLED评分）、血管再通治疗方式、血管再通时间、血管再通治疗后3 d NIHSS评分、血管再通治疗后启动抗凝的时间、抗凝方案、延迟或未启动抗凝治疗的原因（通过对主诊医师进行问卷调查获取）、抗凝前是否使用抗血小板药物、血管再通治疗后有无颅内出血转化、出血分型（ECASS分型）、其他并发症、出院NIHSS评分、出院mRS评分及电话随访90 d mRS评分、90 d任何出血事件、卒中复发事件等。

1.3　观察指标　主要观察指标为患者是否启动/重启抗凝治疗的时间及方案，次要观察指标为患者3个月内任何新发出血、卒中复发事件。

1.4　统计学处理　应用SPSS 25.0软件进行数据处理与分析。呈正态分布的计量资料以$\bar{x}\pm s$表示，多组间比较采用方差分析；呈非正态分布的计量资料以中位数（下四分位数，上四分位数）表示，两组间比较采用Mann-Whitney U检验，多组间比较采用Kruskal-Wallis H检验。计数资料以例数和百分数表示，组间比较采用χ^2检验或Fisher确切概率法。采用多因素logistic回归模型分析心房颤动相关AIS患者接受抗凝治疗的独立影响因素。检验水准（α）为0.05，多组间两两比较时采用Bonferroni法校正。

2　结　果

2.1　总体情况　共207例接受血管再通治疗心房颤动相关AIS患者符合入选条件，排除死亡病例5例、瓣膜性心脏病或风湿性心脏病7例、因病情严重自动出院或转院6例，最后共189例患者入组。所有入组患者的年龄为（72.90±9.23）岁，女性患者93例（49.2%）；17例既往使用抗栓药物治疗的患者中，16例（94.1%）接受抗凝治疗，1例接受抗血小板药物治疗；89例既往诊断为心房颤动的患者中，入院时仅有15例（16.9%）使用抗凝药物；31例既往发生缺血性脑卒中患者中，19例诊断为心房颤动，但其中仅有6例使用抗凝药物。

189例患者中接受IVT患者86例（45.5%）、EVT患者63例（33.3%）、IVT＋EVT患者40例（21.2%）。3组患者的年龄（P＝0.023）、血管再通治疗前NIHSS评分（P＜0.001）、ASPECT评分（P＝0.002）、影像学特点（大面积梗死和颅内责任大动脉严重狭窄或闭塞，P＝0.024、P＜0.001）、血管再通治疗前mRS评分（P＜0.001）、CHA_2DS_2-VASc评分（P＝0.008）、血管再通治疗后3 d NIHSS评分（P＝0.001）、血管再通治疗后颅内出血转化（P＝0.016）、出院NIHSS评分（P＝0.001）、出院mRS评分（P＝0.001）差异均有统计学意义。进一步两两比较中，与EVT、IVT＋EVT组相比，IVT组的ASPECT评分较高，颅内责任大动脉严重狭窄或闭塞的患者占比、血管再通治疗前NIHSS评分、血管再通治疗后3 d NIHSS评分均较低（均P＜0.05）；EVT组出院NIHSS评分及mRS评分均高于IVT组（均P＜0.05）；IVT＋EVT组血管再通治疗后颅内出血转化的患者比例高于IVT组（P＜0.05）。见表1。

2.2　抗凝药物使用情况　189例患者中在院接受抗凝治疗的患者有120例（63.5%）。49例（40.8%）为单一口服抗凝药物，其中38例抗凝前接受抗血小板药物（单一或双联）治疗；36例（30.0%）为皮下肝素抗凝桥接口服抗凝药物；15例（12.5%）为皮下肝素抗凝桥接抗血小板药物；14例（11.7%）为单纯皮下肝素抗凝治疗；6例（5.0%）接受阿加曲班抗凝治疗，其中4例桥接口服抗凝药物，1例桥接单一抗血小板药物治疗。未行抗凝治疗的患者中48例接受抗血小板药物（单一或双联）治疗，21例未使用任何抗栓药物。

2.3　抗凝治疗的影响因素分析　共有68例患者

（36.0%）在急性住院期间（≤14 d）血管再通治疗后启动抗凝治疗，其中IVT组40例（58.8%）、EVT组15例（22.1%）、IVT＋EVT组13例（19.1%），3组之间14 d内启动抗凝治疗患者占比差异有统计学意义（P＝0.020）；121例患者延迟或未启动抗凝治疗［血管再通治疗后启动抗凝的时间超出急性住院时间（＞14 d）］。对在急性住院期间启动抗凝治疗和延迟或未启动抗凝治疗患者的临床资料进行单因素分析，结果（表2）显示，两组既往脑卒中病史、血管再通治疗前NIHSS评分、ASPECT评分、血管再通治疗前mRS评分、影像学特点（病灶靠近皮质、大面积梗死、严重的颅内责任大动脉狭窄或闭塞）、血管再通治疗方式、血管再通治疗后3 d NIHSS评分、血管再通治疗后颅内出血转化差异均有统计学意义（均P＜0.05）。多因素logistic回归分析结果显示，患者血管再通治疗后3 d NIHSS评分高（OR＝1.113，95% CI 1.053～1.176，P＜0.001）、血管再通治疗后发生颅内出血（OR＝6.098，95% CI 2.004～18.193，P＝0.001）的患者不宜进行抗凝治疗。对于延迟或未启动抗凝治疗的原因，共收集到120份主诊医师调查问卷，调查数据提示大面积梗死（40.8%）、梗死部位（35.8%）及缺血性脑卒中后出血转化（40.8%）是影响抗凝治疗的常见原因（表3）。

表1　3组心房颤动相关AIS患者的基线资料比较

Tab 1　Comparison of baseline characteristics among 3 groups of atrial fibrillation-related AIS patients

Factor	All patients N＝189	IVT group N＝86	EVT group N＝63	IVT＋EVT group N＝40	Statistic	P value
Age/year, $\bar{x}\pm s$	72.90±9.23	74.84±9.16	70.75±9.49	72.13±8.25	F＝3.869	0.023
Female, n (%)	93 (49.2)	41 (47.7)	35 (55.6)	17 (42.5)	χ^2＝1.817	0.403
Hypertension, n (%)	122 (64.6)	61 (70.9)	38 (60.3)	23 (57.5)	χ^2＝2.892	0.236
Diabetes mellitus, n (%)	32 (16.9)	16 (18.6)	7 (11.1)	9 (22.5)	χ^2＝2.571	0.277
Hyperlipidemia, n (%)	12 (6.3)	7 (8.1)	3 (4.8)	2 (5.0)	χ^2＝0.732	0.734
Smoking/drinking history, n (%)	13 (6.9)	4 (4.7)	5 (7.9)	4 (10.0)	χ^2＝1.599	0.456
Stroke history, n (%)	31 (16.4)	15 (17.4)	11 (17.5)	5 (12.5)	χ^2＝0.563	0.754
Atrial fibrillation history, n (%)	89 (47.1)	37 (43.0)	32 (50.8)	20 (50.0)	χ^2＝1.054	0.590
Antithrombotic drugs used previously, n (%)	17 (9.0)	6 (7.0)	7 (11.1)	4 (10.0)	χ^2＝0.966	0.646
NIHSS score before revascularization, M (Q_L, Q_U)	12.0 (8.0, 21.0)	10.0 (5.0, 15.3)	15.0 (10.0, 34.0)*	14.0 (10.0, 29.5)*	H＝21.473	＜0.001
ASPECT score, M (Q_L, Q_U)	8.0 (7.0, 9.0)	8.0 (7.0, 9.0)	7.0 (7.0, 8.0)*	7.0 (6.3, 8.0)*	H＝11.988	0.002
Imaging characteristics, n (%)						
Near cortex	125 (66.1)	61 (70.9)	42 (66.7)	22 (55.0)	χ^2＝1.468	0.480
Large infarction	41 (21.7)	11 (12.8)	19 (30.2)	11 (27.5)	χ^2＝7.464	0.024
Brainstem infarction	5 (2.6)	1 (1.2)	2 (3.2)	2 (5.0)	χ^2＝1.952	0.295
Multiple infarctions	55 (29.1)	23 (26.7)	21 (33.3)	11 (27.5)	χ^2＝0.828	0.661
Severe stenosis or occlusion of major intracranial arteries	70 (37.0)	18 (20.9)	29 (46.0)*	23 (57.5)*	χ^2＝18.936	＜0.001
mRS score before revascularization, M (Q_L, Q_U)	4 (3, 5)	4 (2, 4)	4 (4, 5)	4 (4, 5)	H＝15.780	＜0.001
CHA_2DS_2-VASc score, M (Q_L, Q_U)	5 (3, 6)	5 (4, 6)	4 (3, 5)	5 (3, 6)	H＝9.649	0.008
HAS-BLED score, M (Q_L, Q_U)	3 (2, 3)	3 (2, 3)	3 (2, 3)	3 (2, 3)	H＝2.789	0.248
NIHSS score 3 d after revascularization, M (Q_L, Q_U)	8.0 (2.5, 20.0)	5.0 (1.0, 14.3)	15.0 (10.0, 36.0)*	8.0 (4.5, 31.0)*	H＝15.179	0.001
Time to initiate oral anticoagulation after revascularization, n (%)						
0-4 d	20 (10.6)	12 (14.0)	5 (7.9)	3 (7.5)	χ^2＝1.897	0.387
5-14 d	48 (25.4)	28 (32.6)	10 (15.9)	10 (25.0)	χ^2＝5.347	0.069
＞14 d	21 (11.1)	6 (7.0)	7 (11.1)	8 (20.0)	χ^2＝4.351	0.114
Hemorrhagic transformation after revascularization, n (%)	58 (30.7)	18 (20.9)	22 (34.9)	18 (45.0)*	χ^2＝8.232	0.016
HI1	14 (7.4)	2 (2.3)	8 (12.7)	4 (10.0)		
HI2	13 (6.9)	7 (8.1)	4 (6.3)	2 (5.0)		
PH1	18 (9.5)	4 (4.7)	5 (7.9)	9 (22.5)		
PH2	13 (6.9)	5 (5.8)	5 (7.9)	3 (7.5)		
NIHSS score at discharge, M (Q_L, Q_U)	5.0 (1.0, 12.0)	2.0 (0.0, 8.0)	8.0 (4.0, 15.0)*	5.0 (1.0, 12.0)	H＝13.885	0.001
mRS score at discharge, M (Q_L, Q_U)	3.0 (0.0, 4.0)	1.0 (0.0, 3.0)	3.0 (3.0, 4.0)*	3.0 (1.0, 4.0)	H＝14.039	0.001

*P＜0.05 vs IVT group. AIS: Acute ischemic stroke; IVT: Intravenous thrombolysis; EVT: Endovascular thrombectomy; NIHSS: National Institutes of Health stroke scale; ASPECT score: Alberta Stroke Program early computed tomography score; mRS: Modified Rankin scale; HI1: Small punctate hemorrhage along the edge of the infarct; HI2: Patchy hemorrhage without space occupying effect or multiple fused punctate hemorrhage in the infarcted area; PH1: Hemorrhage with hematoma less than 30% of infarct area and slight space occupying effect; PH2: Hemorrhage with hematoma larger than 30% of the infarct area and obvious space occupying effect or hemorrhage far away from the infarct; M (Q_L, Q_U): Median (lower quartile, upper quartile).

表2　急性住院期间启动和延迟或未启动抗凝治疗的心房颤动相关AIS患者资料

Tab 2　Data of patients with atrial fibrillation-related AIS who initiated and delayed or did not initiate anticoagulant therapy during acute hospitalization

Factor	Group 1 N=68	Group 2 N=121	Statistic	P value
Age/year, $\bar{x}\pm s$	72.91±9.10	72.89±9.33	F=0.000	0.990
Female, n (%)	31 (45.6)	62 (51.2)	χ^2=0.556	0.456
Hypertension, n (%)	45 (66.2)	77 (63.6)	χ^2=0.123	0.726
Diabetes mellitus, n (%)	15 (22.1)	17 (14.0)	χ^2=1.986	0.159
Hyperlipidemia, n (%)	4 (5.9)	8 (6.6)	χ^2=0.000	1.000
Smoking/drinking history, n (%)	7 (10.3)	6 (5.0)	χ^2=1.191	0.275
Stroke history, n (%)	12 (17.6)	19 (15.7)	χ^2=10.348	0.001
Atrial fibrillation history, n (%)	29 (42.6)	60 (49.6)	χ^2=0.841	0.359
Antithrombotic drugs used previously, n (%)	8 (11.8)	9 (7.4)	χ^2=0.996	0.318
NIHSS score before revascularization, M (Q_L, Q_U)	10.0 (6.0, 16.8)	14.0 (9.0, 28.0)	U=3 040.0	0.003
ASPECT score, M (Q_L, Q_U)	8.0 (7.0, 9.0)	7.0 (6.0, 8.0)	U=2 763.0	<0.001
Imaging characteristics, n (%)				
Near the cortex	38 (55.9)	87 (71.9)	χ^2=4.988	0.026
Large infarct	5 (7.4)	36 (29.8)	χ^2=12.858	<0.001
Brainstem infarction	1 (1.5)	4 (3.3)	χ^2=0.080	0.778
Multiple infarctions	25 (36.8)	30 (24.8)	χ^2=3.024	0.082
Severe stenosis or occlusion of major intracranial arteries	17 (25.0)	53 (43.8)	χ^2=6.599	0.010
mRS score before revascularization, M (Q_L, Q_U)	4.0 (3.0, 4.0)	4.0 (4.0, 5.0)	U=3 100.5	0.004
CHA_2DS_2-VASc score, M (Q_L, Q_U)	5.0 (3.0, 6.0)	5.0 (3.0, 5.0)	U=3 969.5	0.682
HAS-BLED score, M (Q_L, Q_U)	3.0 (2.0, 3.0)	3.0 (2.0, 3.0)	U=3 521.0	0.066
NIHSS score 3 d after revascularization, M (Q_L, Q_U)	3.0 (1.0, 8.0)	13.0 (6.5, 32.0)	U=1 739.0	<0.001
Revascularization therapy method, n (%)			χ^2=8.403	0.015
IVT	40 (58.8)	46 (38.0)		
EVT	15 (22.1)	48 (39.7)		
IVT+EVT	13 (19.1)	27 (22.3)		
Use of antiplatelet agents prior to anticoagulation, n (%)	42 (61.8)	77 (63.6)	χ^2=0.065	0.798
Hemorrhagic transformation after revascularization, n (%)	5 (7.4)	53 (43.8)	χ^2=27.191	<0.001

Group 1: Patients who initiated anticoagulant therapy; Group 2: Patients who delayed or did not initiate anticoagulant therapy. AIS: Acute ischemic stroke; NIHSS: National Institutes of Health stroke scale; ASPECT score: Alberta Stroke Program early computed tomography score; mRS: Modified Rankin scale; IVT: Intravenous thrombolysis; EVT: Endovascular thrombectomy; M (Q_L, Q_U): Median (lower quartile, upper quartile).

表3　心房颤动相关AIS患者延迟或未启动抗凝治疗的原因分析

Tab 3　Reasons for delayed or did not initiate anticoagulant therapy in patients with atrial fibrillation-related AIS

n=120

Factor	Proportion/%
Severity of stroke	20.0
Large infarct	40.8
Site of infarction	35.8
Hemorrhagic transformation after revascularization	40.8
Other bleeding during hospitalization (intracranial hemorrhage, gastrointestinal hemorrhage, urinary tract hemorrhage, etc.)	15.8
Patient bleeding risk factors	7.5
Other reasons	17.5

AIS: Acute ischemic stroke.

2.4　预后分析　在189例患者中90 d预后良好（mRS评分为0～2分）患者共116例。急性住院期间启动抗凝组90 d预后良好率（89.7%，61/68）高于延迟或未启动抗凝组（45.5%，55/121），差异有统计学意义（P<0.001）。治疗后90 d延迟或未启动抗凝组有3例（2.5%）患者发生缺血性脑卒中复发事件，急性住院期间启动抗凝组0例。治疗后90 d共6例（3.2%）患者发生出血事件，其中颅内出血4例（3例为症状性颅内出血，1例为再次缺血性脑卒中后出血转化）、牙龈出血1例、尿路出血1例。见表4。

表4　心房颤动相关AIS患者治疗后90 d预后分析

Tab 4　Prognostic analysis at 90 d post-treatment in patients with atrial fibrillation-related AIS

n (%)

Factor	Group 1 N=68	Group 2 N=121	Statistic	P value
90-d favorable prognosis (mRS score 0-2)	61 (89.7)	55 (45.5)	χ^2=35.961	<0.001
90-d ischemic stroke recurrence	0	3 (2.5)	Fisher exact test	<0.001
IVT	0	2 (1.7)		
EVT	0	0		
IVT+EVT	0	1 (0.8)		
90-d hemorrhagic events	3 (4.4)	3 (2.5)	Fisher exact test	<0.001
IVT	2 (2.9)	2 (1.7)		
EVT	0	1 (0.8)		
IVT+EVT	1 (1.5)	0		

Group 1: Patients who initiated anticoagulant therapy; Group 2: Patients who delayed or did not initiate anticoagulant therapy. AIS: Acute ischemic stroke; mRS: Modified Rankin scale; IVT: Intravenous thrombolysis; EVT: Endovascular thrombectomy.

3　讨　论

《中国心源性卒中防治指南（2019）》推荐心房颤动男性患者CHA_2DS_2-VASc评分≥2分、女性评分≥3分口服抗凝药物治疗[18]。本研究共纳入189例患者，急性住院期间（≤14 d）口服抗凝药物的患者占比为36.0%（68/189），略高于全球注册研究GARFIELD-AF试验[19]报道的中国CHA_2DS_2-VASc评分≥2分患者抗凝比例（28%）；但本研究纳入的人群为AIS患者，并且年龄偏大，卒中高危人群比例远高于GARFIELD-AF试验，相对而言仍存在抗凝不足的问题。口服抗凝药物治疗是心房颤动患者一级和二级预防缺血性脑卒中的基石，在既往研究中，4项关键的随机对照试验证明新型口服抗凝药在预防脑卒中方面与华法林效果相仿，大出血事件的风险相同或更低，还大大降低了颅内出血的风险[20-23]。之后RAF试验证明单独口服抗凝剂治疗的非瓣膜性心房颤动合并AIS患者比单独使用低分子肝素或接受低分子量肝素后再口服抗凝剂治疗的患者预后更好[24]。然而，新型口服抗凝剂与华法林的关键性大规模研究排除了近期（7～30 d内）发生脑卒中的患者[20-22]，因此AIS发病后开始抗凝的最佳时机仍不确定。由于循证证据缺乏，目前的国际指南未就AIS发病后开始抗凝治疗的最佳时机提供具体建议，但最新研究TIMING（Timing of Oral Anticoagulant Therapy in Acute Ischemic Stroke With Atrial Fibrillation）[25]、ELAN（Early versus Later Anticoagulation for Stroke with Atrial Fibrillation）[26]等表明早期抗凝效果优于延迟抗凝。

缺血性脑卒中复发或卒中后出血转化事件的发生风险在缺血性脑卒中发病后数天内最高[12]，此类事件可能会抵消急性二级预防的优势。既往研究表明接受IVT、EVT或IVT+EVT的患者，症状性出血转化的发生率可能高于对照组，但90 d预后良好（mRS评分为0～2分）率优于对照组[27-28]。本研究急性期（≤14 d）启动抗凝组的90 d预后良好率为89.7%（61/68），高于延迟或未启动抗凝组的45.5%（55/121）；90 d内缺血性脑卒中复发事件和出血事件的发生率分别为1.6%（3/189）和3.2%（6/189）。进一步参照TIMING研究[25]抗凝时间分组，血管再通治疗后早期（≤4 d）启动抗凝治疗的患者有20例，90 d预后良好率为95.0%（19/20），90 d内有1例新发颅内出血事件、无新发缺血性脑卒中；>4 d后启动或未启动抗凝的患者有169例，90 d预后良好率为57.4%（97/169），90 d内有3例新发缺血性脑卒中、5例新发出血事件（包括3例颅内出血、1例尿路出血及1例牙龈出血）。早期启动抗凝治疗的患者90 d预后良好率高于>4 d后启动或未启动抗凝者，且新发缺血性脑卒中和出血事件少于延迟或未启动组，这与TIMING[25]、ELAN[26]研究中预后结局发生率相近。但值得注意的是，本研究中只有20例患者早期（≤4 d）启动抗凝治疗，这是由于本研究人群均接受了血管再通治疗，且人群的平均年龄为（72.90±9.23）岁，血管再通治疗前中位NIHSS评分为12.0（8.0，21.0）分，病情严重患者的比例[（NIHSS评分>25分患者占23.8%（45/189）]远高于既往研究[5,17,29-30]，这些患者早期出现严重症状性颅内出血的风险极高，不符合启

动抗凝治疗的标准；其次4 d内启动抗凝治疗的患者数量较少，差异无统计学意义，未来期待大样本数据进一步佐证上述论点。

本研究中仅36.0%（68/189）的心房颤动相关AIS患者在血管再通治疗后14 d内行抗凝治疗，其中IVT组患者占58.8%（40/68），而Escudero-Martinez等[17]的研究中14 d内启动抗凝治疗的患者占82%，其中85.1%的患者接受IVT治疗，血管再通治疗前NIHSS评分中位数为10（6，16）分。此外，本研究人群血管再通治疗前NIHSS评分较高，中位数为12.0（8.0，21.0）分，且接受EVT及IVT＋EVT治疗的患者占比（54.5%，103/189）也较高，两组NIHSS评分中位数分别为15.0（10.0，34.0）、14.0（10.0，29.5）分。研究表明，对于接受EVT治疗的患者，5～14 d内启动抗凝治疗，缺血性脑血管病的复发率最低[31]，因此，NIHSS评分高、卒中程度严重及接受血管内介入治疗与抗凝治疗启动时间及结局事件相关[30,32-33]。脑卒中的严重程度和再灌注治疗均与出血风险升高相关，本研究中共58例患者出现颅内出血转化，其中实质性血肿（PH2，即血肿面积大于梗死区域30%伴明显占位效应或梗死灶远隔部位的出血）的发生率为6.9%（13/189）；而之前研究中IVT患者PH2的发生率仅为2.7%～5.1%，且在EVT患者中颅内出血转化发生率更低[34-36]。

目前关于接受血管再通治疗的非瓣膜性心房颤动合并AIS患者抗凝治疗的研究甚少，其中RAF[12]和TIMING[25]研究仅分别有22.4%和35.2%的患者接受了血管再通治疗，与未行血管再通治疗的患者相比，这些患者的卒中程度可能更严重，入院时mRS及NIHSS评分可能更高。从病理角度来看，在脑卒中早期，特别是缺血再灌注的情况下，自动调节功能受损和血脑屏障破坏引起的出血转化风险增加，因此早期抗凝可能会增加颅内出血转化风险[37]。另外接受EVT的患者，4 d内启动抗凝治疗并不会显著改善患者的功能结局[31]。由于本研究样本量较小，EVT及IVT＋EVT组4 d内启动抗凝治疗的患者共有8例，90 d预后良好率分析结果可能存在选择偏倚，因此，有必要进一步探索这类患者接受抗凝治疗的最佳时机或时期。

本研究的优势在于是真实世界研究的临床实践，为接受血管再通治疗的心房颤动相关AIS患者的抗凝策略研究增加了新数据，期待未来开展更加合理的大型随机对照试验，以填补在接受血管再通治疗的心房颤动相关AIS患者二级预防治疗方面的空白。

本研究也存在一定局限性：（1）对患者预后的评估均采用电话随访方式，部分患者文化水平有限，少数患者无法正确表达是否自行停服抗血小板药或更换其他抗凝药物，导致研究可能存在一定的信息偏倚。（2）本研究为回顾性研究，其中接受EVT治疗的患者占比较大，出血风险高，抗凝治疗存在选择偏倚，导致研究结果推广至其他地区人群受到一定的限制。

综上所述，接受IVT、EVT或两者联合治疗的心房颤动相关AIS患者在血管再通治疗后早期开始抗凝治疗是安全的，但大多数患者的抗凝治疗时机晚于当前推荐的抗凝时机。

［参 考 文 献］

［1］ YU M Y, CAPRIO F Z, BERNSTEIN R A. Cardioembolic stroke[J]. Neurol Clin, 2024, 42(3): 651-661. DOI: 10.1016/j.ncl.2024.03.002.

［2］ GRECO A, OCCHIPINTI G, GIACOPPO D, et al. Antithrombotic therapy for primary and secondary prevention of ischemic stroke: JACC state-of-the-art review[J]. J Am Coll Cardiol, 2023, 82(15): 1538-1557. DOI: 10.1016/j.jacc.2023.07.025.

［3］ Correction to: ischemic stroke severity and mortality in patients with and without atrial fibrillation[J]. J Am Heart Assoc, 2022, 11(16): e020613. DOI: 10.1161/JAHA.121.020613.

［4］ BJERKREIM A T, KHANEVSKI A N, THOMASSEN L, et al. Five-year readmission and mortality differ by ischemic stroke subtype[J]. J Neurol Sci, 2019, 403: 31-37. DOI: 10.1016/j.jns.2019.06.007.

［5］ 中华医学会神经病学分会,中华医学会神经病学分会脑血管病学组. 中国急性缺血性脑卒中诊治指南2018[J]. 中华神经科杂志,2018,51(9):666-682. DOI: 10.3760/cma.j.issn.1006-7876.2018.09.004.

［6］ MCINTYRE W F, BENZ A P, BECHER N, et al. Direct oral anticoagulants for stroke prevention in patients with device-detected atrial fibrillation: a study-level meta-analysis of the NOAH-AFNET 6 and ARTESiA trials[J]. Circulation, 2024, 149(13): 981-988. DOI: 10.1161/CIRCULATIONAHA.123.067512.

［7］ SAXENA R, KOUDSTAAL P J. Anticoagulants for preventing stroke in patients with nonrheumatic atrial fibrillation and a history of stroke or transient ischaemic

attack[J]. Cochrane Database Syst Rev, 2004(2): CD000185. DOI: 10.1002/14651858.CD000185.pub2.

[8] HART R G, PEARCE L A, AGUILAR M I. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation[J]. Ann Intern Med, 2007, 146(12): 857-867. DOI: 10.7326/0003-4819-146-12-200706190-00007.

[9] SEIFFGE D J, PACIARONI M, WILSON D, et al. Direct oral anticoagulants versus vitamin K antagonists after recent ischemic stroke in patients with atrial fibrillation[J]. Ann Neurol, 2019, 85(6): 823-834. DOI: 10.1002/ana.25489.

[10] PACIARONI M, AGNELLI G, MICHELI S, et al. Efficacy and safety of anticoagulant treatment in acute cardioembolic stroke: a meta-analysis of randomized controlled trials[J]. Stroke, 2007, 38(2): 423-430. DOI: 10.1161/01.STR.0000254600.92975.1f.

[11] GORENEK B, PELLICCIA A, BENJAMIN E J, et al. European Heart Rhythm Association (EHRA)/European Association of Cardiovascular Prevention and Rehabilitation (EACPR) position paper on how to prevent atrial fibrillation endorsed by the Heart Rhythm Society (HRS) and Asia Pacific Heart Rhythm Society (APHRS)[J]. Europace, 2017, 19(2): 190-225. DOI: 10.1093/europace/euw242.

[12] PACIARONI M, AGNELLI G, FALOCCI N, et al. Early recurrence and cerebral bleeding in patients with acute ischemic stroke and atrial fibrillation: effect of anticoagulation and its timing: the RAF study[J]. Stroke, 2015, 46(8): 2175-2182. DOI: 10.1161/STROKEAHA.115.008891.

[13] BERKHEMER O A, FRANSEN P S S, BEUMER D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke[J]. N Engl J Med, 2015, 372(1): 11-20. DOI: 10.1056/NEJMoa1411587.

[14] CAMPBELL B C V, MITCHELL P J, KLEINIG T J, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection[J]. N Engl J Med, 2015, 372(11): 1009-1018. DOI: 10.1056/NEJMoa1414792.

[15] JOVIN T G, CHAMORRO A, COBO E, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke[J]. N Engl J Med, 2015, 372(24): 2296-2306. DOI: 10.1056/NEJMoa1503780.

[16] SAVER J L, GOYAL M, BONAFE A, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke[J]. N Engl J Med, 2015, 372(24): 2285-2295. DOI: 10.1056/NEJMoa1415061.

[17] ESCUDERO-MARTINEZ I, MAZYA M, TEUTSCH C, et al. Dabigatran initiation in patients with non-valvular AF and first acute ischaemic stroke: a retrospective observational study from the SITS registry[J]. BMJ Open, 2020, 10(5): e037234. DOI: 10.1136/bmjopen-2020-037234.

[18] 国家卫生健康委员会脑卒中防治专家委员会房颤卒中防治专业委员会，中华医学会心电生理和起搏分会，中国医师协会心律学专业委员会. 中国心源性卒中防治指南（2019）[J]. 中华心律失常学杂志，2019，23（6）：463-484. DOI: 10.3760/cma.j.issn.1007-6638.2019.06.002.

[19] CAMM A J, STEFFEL J, VIRDONE S, et al. Guideline-directed medical therapies for comorbidities among patients with atrial fibrillation: results from GARFIELD-AF[J]. Eur Heart J Open, 2023, 3(3): oead051. DOI: 10.1093/ehjopen/oead051.

[20] GRANGER C B, ALEXANDER J H, MCMURRAY J J V, et al. Apixaban versus warfarin in patients with atrial fibrillation[J]. N Engl J Med, 2011, 365(11): 981-992. DOI: 10.1056/NEJMoa1107039.

[21] CONNOLLY S J, EZEKOWITZ M D, YUSUF S, et al. Dabigatran versus warfarin in patients with atrial fibrillation[J]. N Engl J Med, 2009, 361(12): 1139-1151. DOI: 10.1056/NEJMoa0905561.

[22] PATEL M R, MAHAFFEY K W, GARG J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation[J]. N Engl J Med, 2011, 365(10): 883-891. DOI: 10.1056/NEJMoa1009638.

[23] GIUGLIANO R P, RUFF C T, BRAUNWALD E, et al. Edoxaban versus warfarin in patients with atrial fibrillation[J]. N Engl J Med, 2013, 369(22): 2093-2104. DOI: 10.1056/NEJMoa1310907.

[24] HANKEY G J. Unanswered questions and research priorities to optimise stroke prevention in atrial fibrillation with the new oral anticoagulants[J]. Thromb Haemost, 2014, 111(5): 808-816. DOI: 10.1160/TH13-09-0741.

[25] OLDGREN J, ÅSBERG S, HIJAZI Z, et al. Early versus delayed non-vitamin K antagonist oral anticoagulant therapy after acute ischemic stroke in atrial fibrillation (TIMING): a registry-based randomized controlled noninferiority study[J]. Circulation, 2022, 146(14): 1056-1066. DOI: 10.1161/CIRCULATIONAHA.122.060666.

[26] FISCHER U, KOGA M, STRBIAN D, et al. Early versus later anticoagulation for stroke with atrial fibrillation[J]. N Engl J Med, 2023, 388(26): 2411-2421. DOI: 10.1056/NEJMoa2303048.

[27] National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke[J]. N Engl J Med, 1995, 333(24): 1581-1587. DOI: 10.1056/NEJM199512143332401.

[28] GENG C, LI S D, ZHANG D D, et al. Endovascular thrombectomy versus bridging thrombolysis: real-

world efficacy and safety analysis based on a nationwide registry study[J]. J Am Heart Assoc, 2021, 10(3): e018003. DOI: 10.1161/JAHA.120.018003.

[29] PACIARONI M, AGNELLI G, FALOCCI N, et al. Early recurrence and major bleeding in patients with acute ischemic stroke and atrial fibrillation treated with non-vitamin-K oral anticoagulants (RAF-NOACs) study[J]. J Am Heart Assoc, 2017, 6(12): e007034. DOI: 10.1161/JAHA.117.007034.

[30] SEIFFGE D J, TRAENKA C, POLYMERIS A, et al. Early start of DOAC after ischemic stroke: risk of intracranial hemorrhage and recurrent events[J]. Neurology, 2016, 87(18): 1856-1862. DOI: 10.1212/WNL.0000000000003283.

[31] MA H, CHE R, ZHANG Q, et al. The optimum anticoagulation time after endovascular thrombectomy for atrial fibrillation-related large vessel occlusion stroke: a real-world study[J]. J Neurol, 2023, 270(4): 2084-2095. DOI: 10.1007/s00415-022-11515-y.

[32] ARIHIRO S, TODO K, KOGA M, et al. Three-month risk-benefit profile of anticoagulation after stroke with atrial fibrillation: the SAMURAI-nonvalvular atrial fibrillation (NVAF) study[J]. Int J Stroke, 2016, 11(5): 565-574. DOI: 10.1177/1747493016632239.

[33] GIOIA L C, KATE M, SIVAKUMAR L, et al. Early rivaroxaban use after cardioembolic stroke may not result in hemorrhagic transformation: a prospective magnetic resonance imaging study[J]. Stroke, 2016, 47(7): 1917-1919. DOI: 10.1161/strokeaha.116.013491.

[34] EMBERSON J, LEES K R, LYDEN P, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials[J]. Lancet, 2014, 384(9958): 1929-1935. DOI: 10.1016/S0140-6736(14)60584-5.

[35] MAZYA M V, LEES K R, COLLAS D, et al. Ⅳ thrombolysis in very severe and severe ischemic stroke: results from the SITS-ISTR registry[J]. Neurology, 2015, 85(24): 2098-2106. DOI: 10.1212/WNL.0000000000002199.

[36] GOYAL M, MENON B K, VAN ZWAM W H, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials[J]. Lancet, 2016, 387(10029): 1723-1731. DOI: 10.1016/S0140-6736(16)00163-X.

[37] MAC GRORY B, FLOOD S, SCHRAG M, et al. Anticoagulation resumption after stroke from atrial fibrillation[J]. Curr Atheroscler Rep, 2019, 21(8): 29. DOI: 10.1007/s11883-019-0790-x.

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