

Research Article

Effect of edaravone on symptomatic intracranial hemorrhage in patients with acute large vessel occlusion on apixaban for non-valvular atrial fibrillation

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Short Title: Effect of edaravone on symptomatic intracranial hemorrhage

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31

32 **Abstract**

33 *Background:* Edaravone administration was associated with lower incidence of symptomatic
34 intracranial hemorrhage (sICH) in patients with acute large vessel occlusion (LVO). However, its
35 protective effect on sICH in patients with LVO who receive direct oral anticoagulants for non-
36 valvular atrial fibrillation (NVAF) is uncertain.

37 *Objectives:* To explore the effect of edaravone administration on the incidence of sICH in
38 patients with acute LVO receiving apixaban for NVAF.

39 *Methods:* A Japanese multicenter registry of apixaban on clinical outcome of the patients with
40 LVO or stenosis (ALVO study) included patients who were admitted within 24 hours after stroke
41 onset and were received apixaban within 14 days of stroke onset. Patients were divided into two
42 groups according to edaravone administration (Edaravone and No-Edaravone groups). The
43 incidence of sICH within one year and infarct growth before apixaban administration were
44 compared between these groups.

45 *Results:* Of the 686 enrolled patients, 622 were included and edaravone was administered to
46 407 (65.4%). The incidences of sICH in Edaravone and No-Edaravone groups were 1.3% and
47 5.0%, respectively ($p = 0.01$). The inverse probability of treatment-weighting (IPTW) hazard ratio
48 (HR) (95% confidence interval [CI]) of Edaravone group for sICH within one year was 0.36
49 (0.15-0.80) compared to No-Edaravone group. The incidences of infarct growth in Edaravone
50 and No-Edaravone groups were 35.3% and 42.0%, respectively ($p = 0.13$). IPTW HR (95% CIs)
51 for infarct growth was 0.76 (0.60-0.97).

52 *Conclusions:* Edaravone administration was associated with a lower incidence of sICH in
53 patients with LVO and NVAF who administrated apixaban.

54

55

56 **1. Introduction**

57 Patients with acute large vessel occlusion (LVO) often experience non-valvular atrial fibrillation
58 (NVAf) before or after hospitalization [1]. Anticoagulants are generally recommended for the
59 prevention of recurrent stroke in patients with ischemic stroke and NVAf, and direct oral
60 anticoagulants (DOACs) are increasingly administered during the acute phase of ischemic
61 stroke [2]. Contrastingly, administration of anticoagulants for patients with acute ischemic stroke
62 and NVAf was reported to increase the risk of intracranial hemorrhage (ICH) [3]. Symptomatic
63 ICH (sICH) is of particular concern in patients with LVO because sICH within 24 hours after the
64 onset of LVO is significantly associated with poorer functional outcomes [4]. ICH is also more
65 common in the first year after the start of anticoagulant therapy [5].

66 Edaravone (3-methyl-1-phenyl-2-pyrazolin-5-one) is a lipophilic free-radical scavenger
67 that converts reactive oxygen species (ROS) to anions [6], preventing brain cell injury. It has
68 been recommended for the treatment of acute ischemic stroke in Japan [7,8]. In addition to the
69 effect of edaravone on improved functional outcomes [9], it was reported to be associated with a
70 lower incidence of ICH, especially sICH, in patients with acute LVO [4]. However, few studies
71 have examined the efficacy of edaravone in preventing sICH in patients with LVO who are
72 administered anticoagulants for concomitant NVAf.

73 A multicenter registry of apixaban on clinical outcome of the patients with LVO or
74 stenosis (ALVO study) evaluated the incidence of clinical outcomes after apixaban
75 administration in patients in the acute phase of LVO and concomitant NVAf in Japan [10]. We
76 analyzed the data from ALVO study to explore the association between edaravone
77 administration within 24 hours and sICH for up to 1 year in this sub-analysis.

78

79 2. Materials and Methods

80 2.1 Study Population

81 This study was a sub-analysis of ALVO study. The details of ALVO study have been
82 described previously [10]. Briefly, ALVO study is a retrospective and prospective Japanese
83 multicenter registry that enrolled patients aged at least 20 years with NVAf and acute LVO or
84 stenosis who were admitted within 24 hours after stroke onset and were received apixaban
85 within 14 days from onset between July 2016 and February 2018. Because ALVO study enrolled
86 patients with both LVO and stenosis, we explored the effect of edaravone in patients with LVO
87 alone and excluded patients with LVO. Other exclusion criteria were as follows; patients
88 considered ineligible for the study by the investigator, pregnant patients, patients with a history
89 of hypersensitivity to apixaban, patients with liver disease at risk of clinically important bleeding
90 due to coagulation disorder, patients with renal failure (creatinine clearance < 15 mL/min), and
91 patients with severe bleeding, including ICH, before apixaban administration.

92 The institutional review boards of all the participating hospitals approved the study
93 protocol in accordance with the Ethical Guidelines for Medical and Health Research Involving
94 Human Subjects in Japan. Written informed consent was obtained from prospectively registered
95 patients, and an opt-out method was offered to retrospectively registered patients.

96 The use of alteplase, endovascular therapy (EVT) and edaravone was determined by
97 the medical team. Alteplase was administered intravenously (0.6 mg/kg according to the
98 Japanese guidelines) [11]. EVT included any revascularization procedure using any device
99 approved in Japan, such as a stent retriever, aspiration catheter, balloon angioplasty, stenting,
100 local fibrinolysis, piercing using guidewires and/or microcatheters, or a combination of these
101 treatments. Edaravone was administered at a dose of 30 mg twice daily intravenously within 24
102 hours after stroke onset and could be used for up to 14 days according to the approved drug
103 indication.

104 Patients who were administered at least one dose of edaravone were categorized into

105 the Edaravone group and the rest into the No-Edaravone group.

106

107 **2.2 Data Collection and Definitions**

108 Patient data on admission, before the administration of apixaban, and 30 days and 1
109 year after onset were collected through a review of hospital charts. Additional information was
110 collected by contacting patients, relatives, and referring physicians. Patient characteristics
111 included age, sex, modified Rankin scale (mRS) score before stroke onset [12], and use of
112 antiplatelet and anticoagulant drugs. We also collected data on the initial National Institutes of
113 Health Stroke Scale (NIHSS) score [13], Alberta Stroke Program Early Computed Tomography
114 Score (ASPECTS) as assessed by diffusion-weighted imaging (DWI) in magnetic resonance
115 imaging (MRI) or non-contrast computed tomography (NCCT) [14-16], the site of LVO,
116 laboratory data, use of intravenous recombinant tissue plasminogen activator (rt-PA) or EVT,
117 and the Thrombolysis in the Cerebral Infarction (TICI) grade [17]. Estimated glomerular filtration
118 rate was calculated by $194 \times \text{serum creatinine (sCre)}^{-1.094} \times \text{age}^{-0.287} \times 0.739$ (if female) and
119 expressed as mL/min/1.73 m² [18]. LVO was defined as the occlusion of the internal carotid
120 artery (ICA), middle cerebral artery (MCA; M1, M2, or M3 segment), anterior cerebral artery
121 (ACA; A1 or A2 segment), basilar artery (BA), vertebral artery, and posterior cerebral artery
122 (PCA; P1 or P2 segment). Pc-ASPECTS was used in patients with posterior circulation stroke
123 [14]. When the ASPECTS was evaluated using both DWI and NCCT, ASPECTS on DWI was
124 prioritized.

125

126 **2.3 Outcomes**

127 The primary outcome was sICH within 1 year after the onset of LVO. Heidelberg
128 Bleeding Classification was used to define ICH [19]. sICH was defined as ICH with one of the
129 following criteria: 1) four or more points higher than the previous evaluation of the total NIHSS
130 score, 2) two or more points in one sub-score of the NIHSS, or 3) requiring surgical intervention

131 such as tracheal intubation, external decompression, or drainage placement.

132 Secondary outcomes were any ICH and infarct growth before apixaban administration.

133 Any ICH and infarct growth were both evaluated by computed tomography or MRI up to before

134 apixaban administration because imaging studies were scheduled before the administration of

135 apixaban, except for those with symptoms which indicated the deterioration of stroke [10].

136 Infarct growth was defined as a decrease of at least one point of the ASPECTS compared to

137 that at admission.

138

139 **2.4 Statistical Analysis**

140 We compared the patient characteristics and primary and secondary outcomes between

141 Edaravone and No-Edaravone groups. Categorical variables are presented as numbers and

142 percentages and were analyzed using the χ^2 or Fisher's exact test, as appropriate. Continuous

143 variables are expressed as mean and standard deviation (SD) or medians and interquartile

144 ranges (IQRs) and were analyzed using Student t test or Wilcoxon rank-sum test based on their

145 distributions.

146 To estimate the cumulative incidence of sICH after stroke onset in Edaravone and No-

147 Edaravone groups, we used the Kaplan-Meier method and log-rank test to compare them. We

148 constructed a Cox proportional hazards model to calculate the hazard ratios (HRs) and its 95%

149 confidence intervals (95% CIs) of Edaravone group relative to No-Edaravone group. We

150 constructed a propensity score for the administration of edaravone using a multivariable logistic

151 regression model because the decision to administer edaravone depends on the patient's

152 characteristics and varies from physician to physician [20]. The following clinically relevant

153 variables were included as independent variables to estimate the propensity score: age, sex,

154 antiplatelet agents, anticoagulant agents, mRS score before onset, NIHSS, ASPECTS, sCre

155 level, blood glucose level, prothrombin time-international normalized ratio (PT-INR), proximal

156 LVO defined as ICA occlusion, M1 occlusion or BA occlusion, rt-PA use, EVT use, and TICl 2b-

157 3. We then estimated the inverse probability of treatment-weighting (IPTW) HRs and its 95%
158 CIs using the Cox proportional hazard model.

159 We also conducted the same analyses for the cumulative incidence of sICH after the
160 administration of apixaban rather than at stroke onset to evaluate the effect under the apixaban
161 administration. We conducted the same analyses for secondary outcomes after stroke onset.

162 All statistical analyses were conducted using JMP 13.0 (SAS Institute Inc., Cary, NC,
163 USA). All reported p-values were two-sided, and a p-value <0.05 was considered statistically
164 significant.

165

166 **3. Results**

167 *3.1 Patient characteristics*

168 Among the 686 patients enrolled in the ALVO study, we excluded 22 patients who were
169 hospitalized 2 days after stroke onset and 42 patients with stenosis only. Among the 622
170 patients included in this analysis, 407 received edaravone (Edaravone group), and 215 did not
171 (No-Edaravone group) (Figure 1). Patient characteristics and initial management were similar
172 between the two groups, except for PT-INR (Table 1). The median (IQR) days of edaravone
173 administration were 7 (5-11) days.

174

175 *3.2 Outcomes*

176 A total of 15 (2.4%) patients developed sICH within 1 year. The cumulative incidence of
177 sICH 1 year after stroke onset in the Edaravone and No-Edaravone groups was 1.3% versus
178 5.0% ($p < 0.01$) (Fig. 2A). The IPTW HR of the Edaravone group was 0.36 (95%CIs 0.15-0.80)
179 compared to No-Edaravone group (Table 2). The cumulative incidence of sICH and the effects
180 of edaravone on sICH were similar when the observation period for apixaban was considered
181 (Fig. 2B). The IPTW HR of the Edaravone group was 0.29 (95%CI 0.11-0.68) under the
182 apixaban administration.

183 The cumulative incidences of any ICH before apixaban administration were 15.7%
184 versus 21.4% in the Edaravone and No-Edaravone groups ($p = 0.06$), and the IPTW HR was
185 0.86 (95% CIs, 0.63-1.16). The incidences of infarct growth were 35.3% versus 42.0% ($p =$
186 0.13), and the IPTW HR was 0.76 (95% CIs, 0.60-0.97) (Table 2).

187

188 **4. Discussion**

189 A sub-analysis of the ALVO study suggested that edaravone administration was
190 associated with a lower incidence of sICH within 1 year after the onset in patients with LVO and
191 NVAf who were administered apixaban. Edaravone administration was not associated with the
192 incidence of any ICH but was associated with a lower incidence of infarct growth before
193 apixaban administration.

194 Of the Japanese patients with acute LVO who underwent EVT, 2.8% developed sICH
195 within 24 hours [4]. In patients with acute ischemic stroke and LVO, the incidence of ICH as a
196 parenchymal hematoma type 2 in the acute phase was 8% [21]. Additionally, the incidence of
197 sICH while taking apixaban was 0.24% per year [22]. The incidence of sICH within 1 month of
198 onset was 1.2% and that within 1 year was 2.4% in this study. The overall incidence of sICH in
199 this study may have been low because patients who developed sICH before apixaban
200 administration were excluded.

201 In patients with acute stroke with LVO within 6 hours of onset, the median increase in
202 ASPECTS was 1 when compared at admission and 24 hours later [23]. In this study, 42% of the
203 No-Edaravone group had an increase of at least 1 in ASPECTS compared to admission and
204 before apixaban administration, defined as infarct growth. The number of patients with infarct
205 growth in this study was probably smaller than that previously reported because patients after 6
206 hours of onset were also included in the study. Fewer patients in the Edaravone group had
207 cerebral infarct growth (35%), and edaravone likely inhibited cerebral infarct growth, as reported
208 in a rat model study [24].

209 Disruption of the blood-brain barrier (BBB) due to the post stroke inflammatory response
210 is an important factor in the development of ICH after ischemic stroke. Cerebral ischemia or
211 delayed reperfusion activates inflammatory responses through the production of ROS and
212 expression of matrix metalloproteinase-9 (MMP-9). These molecules interact to disrupt the BBB,
213 resulting in ICH during the acute phase [25]. BBB disruption has been reported to promote

214 cerebral microbleed (CMB) formation during the acute phase of stroke [26,27]. A high burden of
215 CMBs in patients with acute ischemic stroke had been reported to be a risk of sICH in the long
216 term [28]. Especially, CMB in patients who receive anticoagulant is a high risk for sICH [29].
217 Edaravone functions as a lipophilic free radical scavenger that converts ROS to anions [6] and
218 as an inhibitor of MMP-9, which suppresses inflammatory changes [30]. Both mechanisms
219 prevent BBB disruption, which could be related to the lower incidence of acute and long-term
220 sICH due to the inhibition of CMBs formation.

221 In the era of thrombolysis and mechanical thrombectomy, post stroke sICH has become
222 a major concern in patients with acute ischemic stroke [31]. When these thrombolytic therapies
223 become widespread and indicated for patients with a higher risk of hemorrhagic complications,
224 such as the elderly, those with NVAF, and antiplatelet therapies for coronary heart diseases, the
225 prevention of long-term hemorrhagic complications becomes critically important [32]. Many
226 studies on acute ischemic stroke have evaluated prognosis using the mRS at 3 months [33], but
227 long-term evaluation should be explored. We assessed the effect of edaravone for one year
228 from the perspective of sICH, but edaravone has been used only in limited regions such as
229 Japan and China [8,34] and lacks long-term evaluation in a wide range of patients with acute
230 ischemic stroke. Thus, further investigations on the effect of edaravone on long-term clinical
231 outcomes should be conducted using well-designed and well-powered studies.

232 This study had several limitations that should be considered when interpreting its
233 findings. First, this study was a post-hoc analysis of a registry, and the decision to administer
234 edaravone was left to the physicians. Therefore, there were uncertainties related to the
235 edaravone dose, timing, and number of days of administration. Based on previous reports,
236 edaravone administration might be withheld in elderly patients or patients with renal dysfunction
237 [9,35], who are at higher risk for sICH. Therefore, assuming the influence of selection bias
238 regarding edaravone administration, we used propensity scores to adjust for patient background
239 as much as possible for clinically relevant factors including age and serum creatinine, which are

240 associated with edaravone administration. However, adjustment for potential confounders
241 between the two groups may not have been sufficient. Second, the effect of edaravone in
242 preventing sICH in the hyperacute phase of ischemic stroke was not evaluated because the
243 ALVO study excluded patients with severe ICH before apixaban administration. Third, the ALVO
244 study required only intracranial imaging evaluation before apixaban administration. Therefore,
245 asymptomatic ICH and CMBs after apixaban administration could not be evaluated. To
246 overcome these limitations, the findings of this study should be validated in other settings, and
247 randomized clinical trials should be considered.

248

249 **5. Conclusion**

250 Edaravone administration was associated with a lower incidence of sICH in patients with
251 LVO and NVAf who administered apixaban. Edaravone may have the potential to prevent sICH
252 in these patients who are at high risk of sICH.

253

254 **Statement of Ethics**

255 The institutional review boards of all 38 participating hospitals approved the study
256 protocol.

257

258 **Conflict of Interest Statement**

259 Dr. Saito and Dr. Sakakibara have no disclosures to report. Dr. Uchida reports lecturer's
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273

274 **Data Availability**

275 The data that support the findings of this study are available upon request from the
276 corresponding author. The data are not publicly available due to their containing information that
277 could compromise the privacy of research participants.

278

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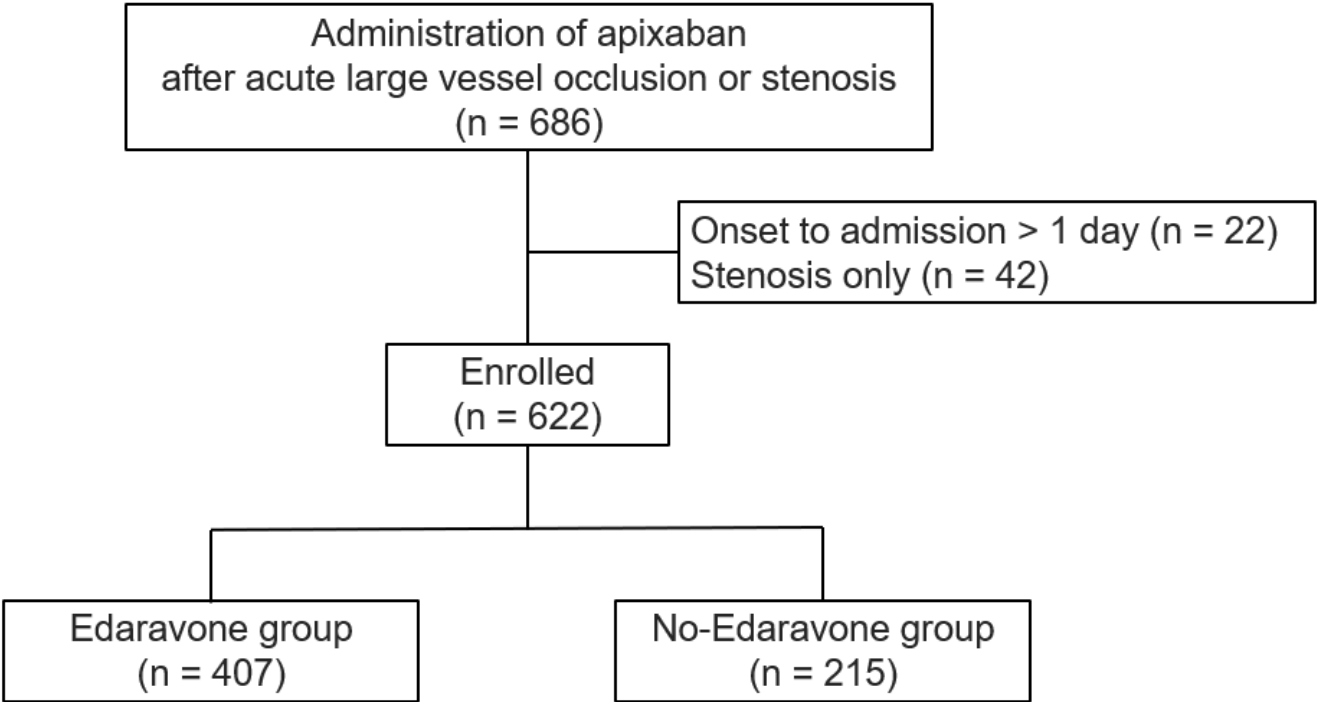
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396 **Figure**

397 Figure 1. Study flowchart.

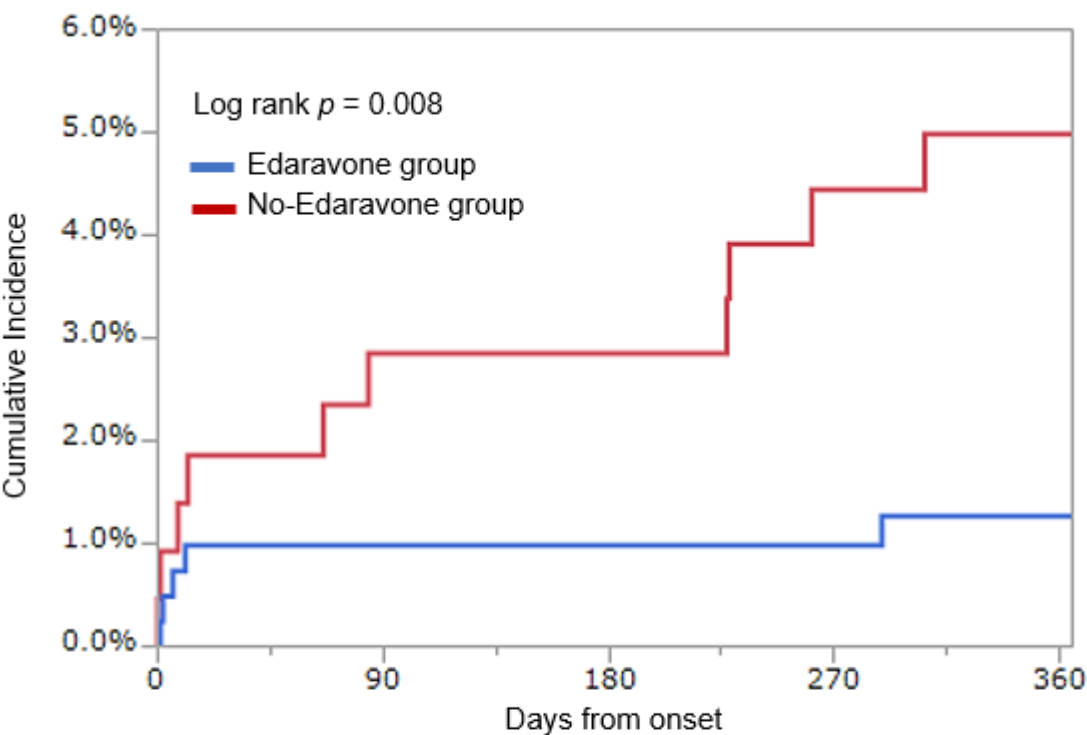


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400 Figure 2. Cumulative incidence of symptomatic intracranial hemorrhage.

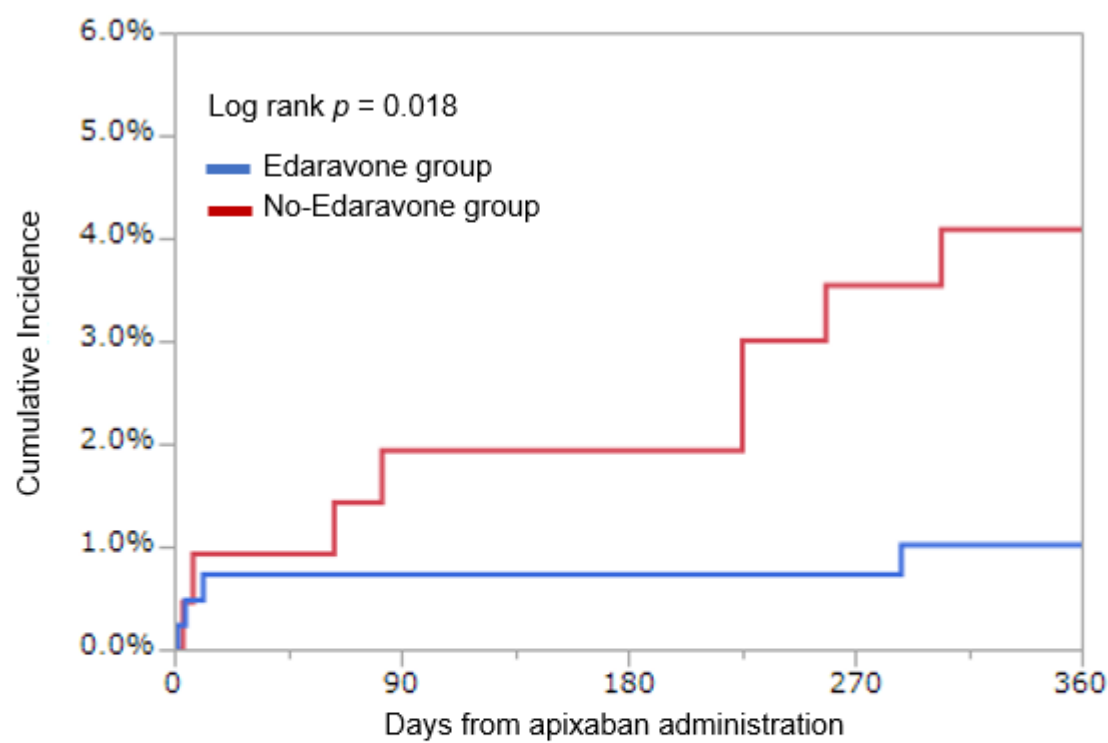
401 A. After the onset of stroke



Follow-up		30 days	90 days	180 days	365 days
Edaravone group	Number of at risk	396	374	354	216
	Cumulative event	4	4	4	5
	Cumulative incidence	1.0%	1.0%	1.0%	1.3%
No-Edaravone group	Number of at risk	204	193	185	88
	Cumulative event	4	6	6	10
	Cumulative incidence	1.9%	2.9%	2.9%	5.0%

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Variables	Edaravone group (n = 407)	No-Edaravone group (n = 215)	P Value
Age, years, mean (SD)	77 (10.1)	78 (9.1)	0.13
Men, n (%)	210 (51.6)	117 (54.4)	0.50
mRS before onset, median (IQR)	0 (0-1)	0 (0-1)	0.42
NIHSS, median (IQR)	14 (8-20)	14 (7-19)	0.69
ASPECTS, median (IQR)	8 (6-9)	8 (7-9)	0.13
Prior antiplatelet drug, n (%)	86 (21.1)	34 (15.8)	0.11
Prior anticoagulant drug, n (%)	86 (21.1)	60 (27.9)	0.06
Occlusion site			0.82
Internal carotid artery, n (%)	64 (15.7)	32 (14.9)	
M1 segment middle cerebral artery, n (%)	148 (36.4)	75 (34.9)	
M2-M3 segments middle cerebral artery, n (%)	143 (35.0)	73 (34.0)	
A1-A2 segment anterior cerebral artery, n (%)	4 (1.0)	2 (0.9)	
Vertebral artery, n (%)	8 (2.0)	6 (2.8)	
Basilar artery, n (%)	19 (4.7)	10 (4.7)	
P1-P2 segment posterior cerebral artery, n (%)	21 (5.2)	17 (7.9)	
Laboratories			
Serum Creatinine, mg/dL, median (IQR)	0.78 (0.66-0.96)	0.81 (0.65-1.07)	0.06
estimated glomerular filtration rate, mL/min/1.73m ² , median (IQR)	64.1 (51.8-78.4)	61.9 (44.6-77.2)	0.054
Blood glucose, mg/dL, median (IQR)	122 (106-142)	120 (104-142)	0.39
CRP, mg/dL, median (IQR)	0.14 (0.07-0.87)	0.16 (0.09-0.60)	0.45
PT-INR, median (IQR)	1.04 (0.97-1.13)	1.06 (1.00-1.17)	0.01
HbA1c (NGSP), %, median (IQR)	5.9 (5.7-6.2)	5.9 (5.6-6.4)	0.80
Days before apixaban administration, median (IQR)	2.2 (1.4-5.5)	2.5 (1.3-4.8)	0.89
Initial treatment			

Alteplase, n (%)	177 (43.5)	86 (40.0)	0.40
EVT, n (%)	225 (55.3)	131 (60.9)	0.18
TICI 2b or 3, n (%)	202 (90.2) (n = 224)	125 (95.4) (n = 131)	0.08
Days of edaravone administration, median (IQR)	7 (5-11)	NA	NA

Table 1. Patient characteristics

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Abbreviations: ASPECTS, Alberta Stroke Program Early CT Score; CRP, C-reactive protein; DWI-ASPECTS, Alberta Stroke Program Early CT Score on diffusion-weighted imaging; EVT, endovascular therapy; HbA1c, hemoglobin A1c; IQR, interquartile range; mRS, modified Rankin Scale; NA, not applicable; NGSP, National Glycohemoglobin Standardization Program; NIHSS, National Institutes of Health Stroke Scale; pc-ASPECTS, posterior circulation- Alberta Stroke Program Early CT Score; PT-INR, prothrombin time-international normalized ratio; SD, standard deviation; TICI, Thrombolysis In Cerebral Infarction.

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418 Table 2. Outcomes
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Outcomes	Edaravone group (n = 407)	No-Edaravone group (n = 215)	Crude HR (95% CI)	P Value	IPTW HR (95% CI)	P Value
Primary outcome						
Symptomatic intracranial hemorrhage after the onset of stroke, n (%)	5 (1.3)	10 (5.0)	0.26 (0.08-0.74)	0.01	0.36 (0.15-0.80)	0.01
Symptomatic intracranial hemorrhage after apixaban administration, n (%)	4 (1.0)	8 (4.1)	0.26 (0.07-0.83)	0.02	0.29 (0.11-0.68)	0.003
Secondary outcome						
Intracranial hemorrhage, n (%)	64 (15.7)	46 (21.4)	0.68 (0.46-1.02)	0.06	0.86 (0.63-1.16)	0.32
Infarct growth, n (%) (n = 406)	97 (35.3)	55 (42.0)	0.77 (0.55-1.09)	0.13	0.76 (0.60-0.97)	0.03

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422 Abbreviations: CI, confidence interval; HR, Hazard Ratio; IPTW, inverse probability of treatment-weighting.

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