Retrospective analysis of argatroban in 353 acute noncardioembolic stroke patients

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Keywords: argatroban, ozagrel, edaravone, noncardioembolic stroke, atherothrombotic infarction, lacunar infarction

Abstract

We studied prognosis in 353 acute stokes patients treated by argatroban in comparison with 160 control group with ozagrel in our hospital. They were examined as to their stroke types, neurological severity according to the NIH Stroke Scale (NIHSS) and clinical outcomes on discharge by the modified Rankin Scale (mRS). Acute noncardioembolic stroke patients including lacunar infarction and atherothrombotic infarction showed functional recovery by argatroban, but the effectiveness of argatroban was not superior to ozagrel therapy defined by control group. Both of argatroban and ozagrel in atherothrombotic infarction showed improved by 1 points. We also could not find any significant difference between argatroban and ozagrel in each two stroke subtypes, lacunar infarction and atherothrombotic infarction.

Introduction

Argatroban is a thrombin inhibitor agent for applicable for acute noncardioembolic ischemic stroke in Japan from 1991(1-4). It is recommended to be initiated in patients with non-embolic ischemic stroke within 48 hours of stroke onset in Japanese Guidelines for the Management of Stroke 2015 (5). During period from January 2001 to December 2016, we treated 510 patients with acute cerebral infarction by argatroban. We have studied prognosis of acute ischemic stroke patients with a database in our hospital. They were examined as to their stroke types, their severity of stroke according to the NIH Stroke Scale (NIHSS) and outcomes by the modified Rankin Scale (mRS). Although our study about argatroban treatment was analyzed in single center, our number of argatroban therapy cases was relatively larger than previous randomized, placebo-controlled study (2). Our results might contribute to comprehensive data about argatroban covered by national insurance with acute stroke treatment for 30 years. Argatroban and ozagrel are commonly used for acute noncardioembolic ischemic stroke in Japan, so we retrospectively analyzed the difference between argatroban and ozagrel in our single center (6).

Subjects and Method

We enrolled 353 acute stroke patients treated with argatroban including 138 lacunar infarction (LI) and 215 atherothrombotic infarction (ATI). All of them were not indication for recombinant tissue-type plasminogen activator (rtPA) because of after 4.5 hours from stroke onset, higher age, recent vascular event or surgical history. Patients were enrolled if they were admitted to our hospitals for LI or ATI within 48 hours of stroke onset due to insurance adaptation of argatroban in Japan. The final diagnosis of stroke types was

recorded separately with International Classification of Diseases-10th revision (UCD-10) codes and text data in Japanese (I633: ATI, I638:LI). LI was defined as small subcortical infarction less than 2 cm diameter without cortical symptom and large vessel lesions. ATI was defined as stroke lesions with a more than 50% stenosis or occlusion of the intra/extracranial vessels on the ipsilateral side (7, 8). Chronic kidney disease and hemodialysis cases were excluded in this study, because we have difficulty in using edaravone for renal dysfunction.

Argatroban (120 mg/day) was administered intravenously by drip infusion over 2h b.i.d, in the morning and the evening for two days, and following by 20 mg /days for five days. Edaravone (30mg) was administered intravenously by drip infusion over 30 min b.i.d, in the morning and the evening. We also made a control group treated with ozagrel and without argatroban who were acute noncardioembolic stroke patients including lacunar infarction and atherothrombotic infarction. Ozagrel (80mg) was administered intravenously by drip infusion over 2h b.i.d, in the morning and the evening.

We compare the clinical efficacy between argatroban group and control group with ozagrel. And we divided all 513 patients (argatroban; n=353, control with ozagrel; n=160) into two groups, LI group (n=258) and ATI group (n=255). LI group included 138 treated with argatroban and 120 control cases with ozagrel. ATI group included 215 treated with argatroban and 40 control cases with ozagrel. Concomitant use of urokinase, heparin and warfarin were prohibited during the administration period of argatroban and edaravone. The modified Rankin Scale (mRS) and National Institute of Health Stroke Scale (NIHSS) are used for assessment of clinical outcome on discharge. We considered mRS 0-2 a good outcome and mRS 3-6 a poor outcome on discharge in the same way to our previous study (9). Our hospital database study was approved by Shimane University Institutional Committee on Ethics (registered in 2001).

Statistical analysis

The chi-square test was used to analyze differences with clinical factors including gender, cerebral vascular risk factor, edaravone therapy and concurrent antiplatelet between 2 groups of stroke subtype and 2 therapies of argatroban or ozagrel. It was also analyzed to compare the rate of clinical good outcome on discharge between argatroban group and control group with ozagrel. The Wilcoxon signed rank sum test was used to analyze the NIHSS scores and mRS between pre/post therapy of argatroban and ozagrel. Logistic regression analysis was used to determine the relationship between good outcome on discharge and clinical factors including age, blood pressure on admission, cerebral vascular risk factor, concurrent antiplatelet, NIHSS on admission, time to

treatment after stroke onset, hospital length of stay, history of stroke, additional use of edaravone and therapeutic groups (with or without argatroban). NIHSS on admission and mRS on admission were strongly correlated by Spearman correlation coefficient ($r=0.669$, $p<0.0001$), so we excluded mRS on admission from predictor variables of clinical factor in the logistic model in consideration of the multicollinearity. P values of < 0.05 were considered significant. All values are presented as median with interquartile range (IQR).

Results

513 acute noncardioembolic ischemic stroke patients were enrolled retrospectively from our hospital database. Significant intergroup difference in baseline characteristics between argatroban group and control group with ozagrel were observed for distribution of stroke subtypes, NIHSS on admission and mRS on three times (before stroke onset, admission and discharge) ($p<0.05$). Of all stroke patients, 353 cases were administered with argatroban including 138 LI cases (39.1%), 215 ATI cases (60.9%). 160 control cases including 120 LI (75.0%), 40 ATI (25.0%) were administered with ozagrel (Table 1).

Although NIHSS were improved by -1 (pre=4, post=2, $p<0.0001$) in argatroban group and -1 (pre=3, post=1, $p<0.0001$) in control group with ozagrel, there was no significant difference in improvement of NIHSS between argatroban and ozagrel. There were heterogenous factors, the distribution of stroke subtype (LI and ATI) and NIHSS on admission between argatroban group and control group with ozagrel. ATI was dominant in argatroban group, and LI was dominant in control group with ozagrel ($p=0.0001$). The rate of concurrent edaravone therapy was dominant in argatroban group compared with control with ozagrel ($p=0.0001$) (Table 1). It was also dominant in both of LI group ($p=0.0001$) and ATI group ($p=0.005$). The mRS before stroke onset in ATI group was significantly higher in control group with ozagrel than argatroban group ($p=0.020$) (Table 2). After correcting confounders, the distribution of stroke subtype, edaravone therapy and NIHSS on admission with multivariate analysis of covariance, the improvement of NIHSS are not difference between argatroban group and control group with ozagrel ($p=0.921$, $F=0.010$).

Edaravone therapy was dominant in argatroban group in both of LI group and ATI group (Table 2). Comparisons of mRS on discharge between control with ozagrel and argatroban were shown in Figure. According to chi-square tests, there were no significant differences in the percentage of good outcome (mRS 0-2) between argatroban group and control group with ozagrel for patients with lacunar infarction ($p=0.428$) and those with atherothrombotic infarction ($p=0.864$)

Logistic regression analysis demonstrated that a good outcome (mRS 0-2) on discharge

was related to age (OR, 1.052; 95% CI, 1.023-1.082, p<0.0001), NIHSS on admission (OR, 1.389; 95% CI, 1.244-1.550, p<0.0001) and hospital length of stay (OR, 1.055; 95% CI, 1.030-1.081, p<0.0001) in argatroban group. These clinical factors were also found in control group with ozagrel (Table 3).

Of 353 patients treated argatroban, only four cases (1.1%) revealed minor bleeding and asymptomatic intracranial hemorrhage. Two cases with minor hemorrhage were rectum ulcer bleeding (Day 3) and hemorrhagic gastric ulcer (Day 5). Two cases with asymptomatic intracranial hemorrhage were trivial bleeding in subdural hygroma (Day 5) and small hemorrhagic infarction without hematoma (Day 7). All of them did not need any blood transfusion and promptly recovered. We did not have any cases with major systemic and life-threatening bleeding. And we did not experience intracranial hematoma increased by argatroban. We also did not have any cases with bleeding event in control group with ozagrel.

Discussion

To investigate the state of ischemic stroke treatment in Japan, many Japanese stroke neurologists analyzed data from stroke patients registered in the Japanese Standard Stroke Registry Study (JSSRS) database within the last seventeen years (8, 10, 11). Our laboratory analyzed the amassed data of JSSRS about all japan with 9197 stroke cases in 2005. In this study we only analyzed the data of our single center in JSSRS. Japanese Guidelines (GLs) for the Management of Stroke 2015 described that the use of heparin can be considered for cerebral infarction within 48 h after onset, but therapeutic evidence is lacking (grade C1). The use of heparin for acute ischemic stroke can be considered, but the evidence for either product is also lacking (grade C1)(12). Japanese GLs recommended argatroban, a selective thrombin inhibitor developed in Japan, for cerebral infarction (excluding cardioembolic stroke) within 48 h after onset and with a maximum diameter of ≥ 1.5 cm (grade B) based on randomized controlled trials (RCTs) in Japan (1, 13, 14).

Our study shows that the efficacy of argatroban for the change of NIHSS between admission and discharge are weak, and it equals to recent and relative study about argatroban with large samples. Our control group is formed by acute noncardioembolic stroke patients including lacunar infarction and atherosclerotic thrombosis who were treated with ozagrel. They included ozagrel monotherapy and the combination therapy of ozagrel and edaravone. Our previous study reported that no significant difference between ozagrel monotherapy and the combination therapy, so we definite both of argatroban treated and ozagrel treated patients as each one subgroup (argatroban group and control

group with ozagrel) regardless of edaravone use (15).

Wada T et al reported that 2289 patients treated with argatroban were compared to 2289 control patients without argatroban in accordance within a caliper width of 0.2 of the SD of the propensity score. They could not find any significant differences in mRS at discharge(16). And Wada T et al also reported that 2726 noncardioembolic stroke patients treated with ozagrel were not superior to 2726 controls in both of atherothrombotic and lacunar infarction (6). Our results almost coincide with their multicenter analysis. Chen B et al reported that a potential role for thrombin inhibitor contributing to the neuroprotection and inhibiting neurovascular injury in rat models with intravenous infusion of argatroban. Although thrombin dosed animals developed more apoptotic cells in the ischemic brain, intravenous argatroban, thrombin inhibitor instead of thrombin decreased the progression of vascular disruptions well as cellular injury (17). Otherwise the argatroban of clinical efficacy in our data might be weaker than rat models as they expected. Thrombin acts as the agonist for platelet activation and aggregation on the vascular endothelium. It generates fibrin formation and deposition on the cerebral vessel wall during focal ischemia and induces increasing vascular permeability within micro vessels in the territory at risk (18). Thrombin inhibitor has antiplatelet effect with blocking platelet signaling pathways, so argatroban could also act as antiplatelet drugs to suppress growing atheromatous plaques.

The clinical efficacy of argatroban has been controversial, although its safety has been proven with fewer side effects. An RCT in Japan suggested that argatroban is superior to placebo in the clinical outcome in neurologic symptoms (1). Whereas an RCT in North America showed that there is no differences in stroke progression between argatroban and placebo (2). Yamamoto Y et al. reported that the combination treatment, cilostazol and edaravone including argatroban for branch atheromatous disease (BAD) patients improved functional outcome in one month after onset, but could not prevent progressive motor deficit (19). In 767 argatroban-treated patients with heparin-induced thrombocytopenia (HIT), they had significantly reduced stroke-associated mortality (odds ratio, 0.18, $p = 0.039$), so it is beneficial to decrease thrombocytopenia in acute therapy with anticoagulant in stroke patients (20). Our argatroban group showed only 1.1% of minor bleeding without major systemic and life-threatening event.

In argatroban group, NIHSS on admission in ATI group was larger than LI group ($p<0.0001$, $F=16.904$). NIHSS on discharge in ATI group was also larger than LI group ($p<0.0001$, $F=10.574$) (Table 2). It might be associated with one type of atherosclerotic thrombosis, BAD which is characterized by early neurological deterioration at the origin of deep penetrating artery with a micro-atheroma or a junctional plaque. The prognosis

in BAD similar to that found in atherothrombotic stroke is significantly worse than that in lacunar infarction. The length of hospitalization and level of residual disability after rehabilitation are significantly greater in BAD patients than lacunar infarction (21). Argatroban is a synthetic arginine-derived direct thrombin inhibitor that exerts a stronger anticoagulant effect compared to heparins at equivalent levels. It passes through endovascular and cellular barriers owing to its low molecular weight (22). It is therefore effective for the antithrombotic treatment of microvascular disorders including atherothrombosis (ATIS)(23).

Edaravone has been reported to inhibit tissue injury including vascular endothelial cell, delayed neuronal death with inhibition of peroxidation of the phosphatidylcholine liposomal membrane initiated by free radicals and antioxidants, ascorbic acid and α-tocopherol (24, 25). The combination of anticoagulant, argatroban and free radical scavenger, edaravone confers additive effect of neuroprotection upon ischemic damage and they could inhibit the progression of ischemic neuronal cell damage in animal models (26). The dose of edaravone and argatroban in their study (argatroban, 2 mg/kg i.v. and 10 mg/kg s.c. plus 10 mg/kg s.c. on days 1 and 2; edaravone, 6 mg/kg i.v. and 6 mg/kg s.c.) are almost maximal and are most effective dose for administration in rodent ischemia animal models, and it is much larger amount than therapeutic protocol for human. In our study, we can recognize that the additional use of edaravone has tendency to treat with argatroban. However we could not find combination therapy of argatroban and edaravone was not superior to argatroban monotherapy in clinical outcome. Edaravone is equally as effective as argatroban in ischemic stroke, but combination therapy of edaravone and argatroban could not be superior to argatroban monotherapy.

Conclusion

Argatroban therapy was not superior to control with ozagrel therapy in acute noncardioembolic ischemic stroke including lacunar infarction and atherothrombotic infarction regardless of edaravone use. Younger age, low score of NIHSS on admission and shorter length of hospital stay would be a good outcome in argatroban's prognosis.

Study limitations

Our sample size is relatively small and was only summed and limited in single hospital analysis. Long term stroke outcome was not estimated in this study and was evaluated during only hospitalization. In the argatroban use, we could not clearly determine the magnitude of bias due to the proportion of branch atheromatous disease in the atherothrombotic infarction group.

Acknowledgements
Declared none

Conflict of Interest
The authors confirm that this chapter contents have no conflict of interest.

Legend
Figure
Comparisons of modified Rankin Sscale on discharge between control with ozagrel and argatroban. Data are shown as percentage in control group with ozagrel and argatroban group.
A. 258 cases with lacunar infarction
B. 255 cases with atherothrombotic infarction
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Table 1
Baseline characteristics in two groups of argatroban and control with ozagrel.
Figures are median with interquartile range (IQR) in parentheses or numbers with percentages in parentheses.
Abbreviations: NIHSS, NIH Stroke Scale; mRS, modified Rankin Scale.

Table 2
Baseline characteristics in two types of acute noncardioembolic ischemic stroke with lacunar infarction and atherothrombotic infarction. Each group is divided into argatroban treatment group and control group with ozagrel.
Figures are median with interquartile range (IQR) in parentheses or numbers with percentages in parentheses.
Abbreviations: NIHSS, NIH Stroke Scale; mRS, modified Rankin Scale.

Table 3
Logistic analysis of clinical factors effecting on prognosis for good outcome (modified Rankin Sscale 0-2) in three groups, argatroban, control with ozagrel and all cases.
Abbreviations: OR, odds ratio; CI, confidence interval; NIHSS, NIH Stroke Scale.

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Figure

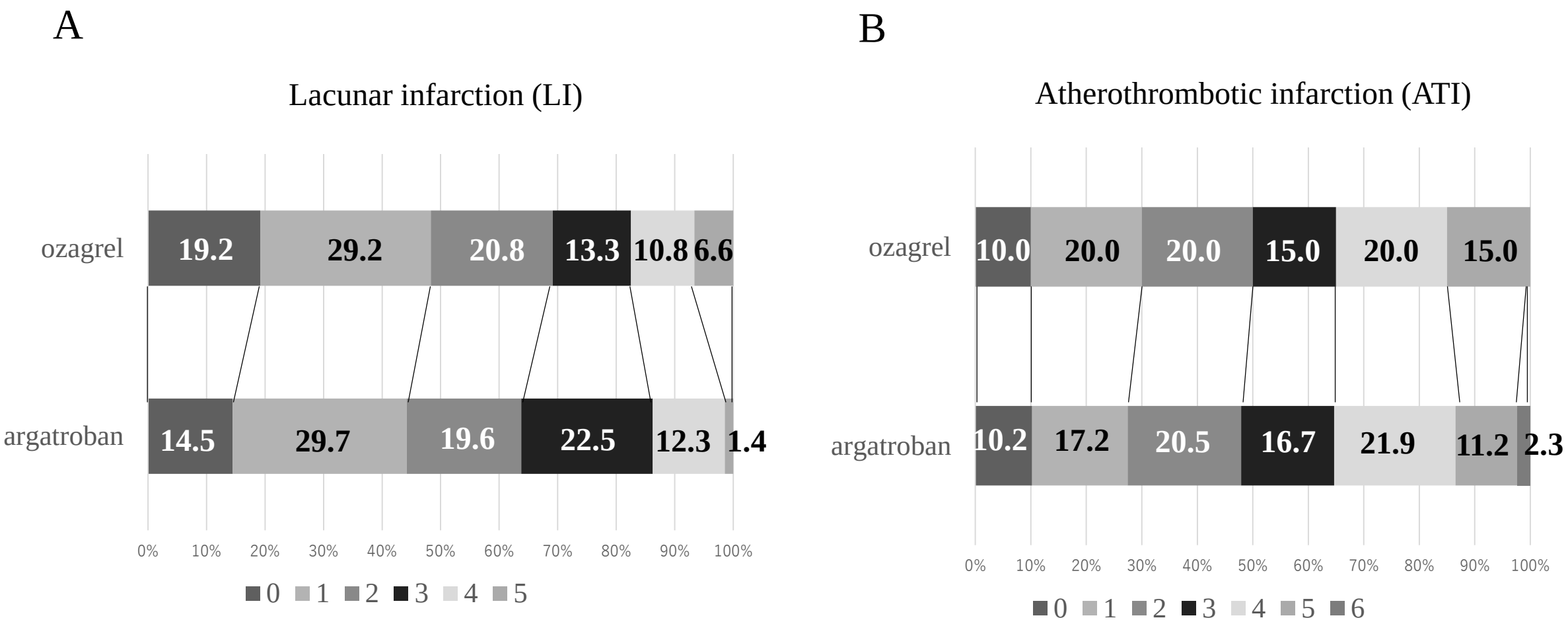
A
Lacunar infarction (LI)
ozagrel
argatroban
19.2
29.2
20.8
13.3
10.8
6.6
14.5
29.7
19.6
22.5
12.3
1.4
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%
0
1
2
3
4
5
B
Atherothrombotic infarction (ATI)
ozagrel
argatroban
10.0
20.0
20.0
15.0
20.0
15.0
10.2
17.2
20.5
16.7
21.9
11.2
2.3
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%
0
1
2
3
4
5
6

Table 1

	Argatroban group n=353	Control group with ozagrel n=160	p value
Age	76(66-83)	74(65-82)	0.373
Gender (male/female)	210/143	99/61	0.628
Time to treatment after stroke onset (hour)	12.0(5.5-24.0)	13.5(6.1-26.7)	0.103
Blood pressure on admission			
Systolic blood pressure (mmHg)	159(141-178)	154(138-173)	0.508
Diastolic blood pressure (mmHg)	87(79-95)	84(77-94)	0.697
Hypertension (%)	278(78.7)	125(78.1)	0.908
Diabetes (%)	131(37.1)	48(30.0)	0.134
Hyperlipidemia (%)	138(39.1)	61(38.1)	0.846
Atrial fibrillation (%)	15(4.2)	4(2.5)	0.452
Stroke subtype			
Lacunar infarction	138(39.1)	120（75.0）	0.0001
Atherothrombotic infarction	215(60.9)	40(25.0)	
Edaravone therapy (%)	257 (72.8)	55 (34.3)	0.0001
Concurrent antiplatelet (n/%)	81(22.9)	32(20.0)	0.492
NIHSS on admission	4(2-6)	3(2-6)	0.016
NIHSS on discharge	2(0-5)	1(0-4)	0.06
improvement of NIHSS	-1(-3-0)	-1(-3-0)	0.442
mRS before stroke onset	0(0-1)	0(0-2)	0.036
mRS on admission	3(2-4)	3(2-4)	0.019
mRS on discharge	2(1-4)	2(1-3)	0.037

Table 2

	Lacunar infarction (LI) n=258			Atherothrombotic infarction (ATI) n=255		
	Argatroban group n=138	Control group with ozagrel n=120	p value	Argatroban group n=215	Control group with ozagrel n=40	p value
Age (y)	74 (64-81)	74 (64-80)	0.721	77 (64-81)	77(71-84)	0.684
Gender (male/%)	87/63%	73/61%	0.797	123(57.2)	26(65.0)	0.388
Time to treatment from onset (hour)	14.5 (7.0-26.0)	12.0 (5.0-26.0)	0.131	10.0(6.0-23.0)	10.5(6.0-31.1)	0.262
Blood pressure on admission						
Systolic blood pressure (mmHg)	150 (138-170)	160 (140-177)	0.350	159(142-178)	163(148-179)	0.419
Diastolic blood pressure (mmHg)	82 (77-94)	87 (80-96)	0.269	87(78-95)	87(74-94)	0.777
Hypertension (%)	103(74.6)	94(78.3)	0.557	175(81.4)	31(77.5)	0.662
Diabetes (%)	45(32.6)	33(27.5)	0.416	86(40.0)	15(37.5)	0.861
Hyperlipidemia (%)	52(37.6)	44(36.6)	0.898	86(40.0)	17(42.5)	0.861
Atrial fibrillation (%)	4(3.3)	4(2.9)	1.000	11(5.1)	0(0)	0.222
Edaravone therapy (%)	103(74.6)	36(30.0)	0.0001	154(71.6)	19(47.5)	0.005
Concurrent antiplatelet (%)	26(18.8)	24(20.0)	0.875	55(25.6)	8(20.0)	0.551
NIHSS at admission	3(1-5)	4(2-5)	0.205	5(2-8)	4(2-8)	0.705
NIHSS at discharge	1(0-3)	1(0-3)	0.671	3(1-7)	2(0-6)	0.812
improvement of NIHSS	-1(-2-0)	-2(-3- -1))	0.077	-1(-3-0)	-1(-4-0)	0.921
mRS before stroke onset	0(0-2)	0(0-1)	0.307	0(0-2)	1(0-2)	0.020
mRS at admission	3(2-4)	3(2-4)	0.961	4(3-4)	3(2-4)	0.445
mRS at discharge	2(1-3)	2(1-3)	0.537	3(1-4)	3(1-4)	0.868

Table 3

	Argatroban group n=353			Control group with ozagrel n=160			All cases n=513		
Clinical factor	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value
Age	1.052	1.023-1.082	0.0001	1.144	1.072-1.222	0.0001	0.936	0.912-0.959	0.0001
Systolic blood pressure on admission	1.005	0.992-1.019	0.435	0.994	0.968-1.022	0.686	0.995	0.983-1.006	0.376
Diastolic blood pressure on admission	1.001	0.978-1.025	0.921	1.028	0.980-1.079	0.257	0.996	0.976-1.017	0.704
Hypertension	1.669	0.812-3.430	0.163	0.730	0.212-2.514	0.618	0.755	0.414-1.377	0.359
Diabetes	1.172	0.663-2.073	0.585	1.003	0.333-3.019	0.996	0.930	0.570-1.517	0.771
Hyperlipidemia	0.735	0.413-1.307	0.295	0.599	0.207-1.736	0.346	1.478	0.902-2.422	0.121
Concurrent antiplatelet before onset	0.825	0.357-1.909	0.653	0.826	0.211-3.230	0.784	1.332	0.676-2.624	0.407
NIHSS on admission	1.389	1.244-1.550	0.0001	1.708	1.304-2.238	0.0001	0.700	0.635-0.772	0.0001
Time to treatment after stroke onset	1.004	0.983-1.025	0.735	0.964	0.925-1.005	0.083	1.005	0.987-1.023	0.603
Hospital length of stay	1.055	1.030-1.081	0.0001	1.095	1.031-1.163	0.003	0.942	0.922-0.964	0.0001
History of stroke	1.505	0.696-3.256	0.299	1.205	0.360-4.037	0.762	0.730	0.399-1.334	0.306
Additional use of edaravone	0.894	0.480-1.666	0.723	0.784	0.276-2.229	0.649	1.225	0.734-2.044	0.437
With/without Argatroban							0.909	0.529-1.563	0.730