# Retrospective Analysis of Argatroban in 353 Patients with Acute Noncardioembolic Stroke

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*Background:* Argatroban is a thrombin inhibitor agent for acute noncardioembolic ischemic stroke in Japan. We studied the prognosis in patients with acute stroke treated by argatroban in comparison with the control group with ozagrel in our hospital. *Subjects and Methods:* A total of 513 patients with acute noncardioembolic ischemic stroke were enrolled retrospectively from our hospital database. Of all patients with stroke, 353 were administered with argatroban. The other 160 control patients were administered with ozagrel. The patients were examined as to their stroke types, the neurological severity according to the National Institutes of Health Stroke Scale (NIHSS), and clinical outcomes on discharge were determined according to the modified Rankin Scale (mRS). *Results:* A total of 353 patients with acute noncardioembolic stroke, including 138 with lacunar infarction (LIs) and 215 with atherothrombotic infarction (ATI) showed functional recovery by argatroban, but the effectiveness of argatroban was not superior to ozagrel therapy defined by the control group. A total of 255 patients with ATI who were treated with both argatroban and ozagrel showed improvement by 1 point. We could not find any significant difference between argatroban and ozagrel in the 2 stroke subtypes, LI and ATI. We also found that combination therapy of argatroban and edaravone was not superior to argatroban monotherapy in clinical outcome. *Conclusions:* Argatroban therapy was not superior to control with ozagrel therapy in acute noncardioembolic ischemic stroke, including LI and ATI, regardless of the use of edaravone. **Key Words:** Argatroban—ozagrel—edaravone—noncardioembolic stroke—atherothrombotic infarction—lacunar infarction.
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## Introduction

Argatroban is a thrombin inhibitor agent applicable for the treatment of acute noncardioembolic ischemic stroke in Japan from 1991.[1-4] Argatroban is recommended to be initiated in patients without embolic ischemic stroke within 48 hours of stroke onset in the Japanese Guidelines for the Management of Stroke 2015.[5] During the period from January 2001 to December 2016, we treated 510 patients with acute cerebral infarction by argatroban. We have studied the prognosis of patients with acute ischemic stroke using database in our hospital. The patients were examined as to their stroke types, the severity of stroke according to the National Institutes of Health Stroke Scale (NIHSS), and outcomes by the modified Rankin Scale (mRS). Although our study about argatroban treatment was analyzed in a single center, the number of argatroban therapy cases in our study was relatively larger than that of a 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,

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so we retrospectively analyzed the difference between argatroban and ozagrel in our single center.[6]

## Subjects and Methods

We enrolled 353 patients with acute stroke treated with argatroban, including 138 with lacunar infarction (LIs) and 215 with atherothrombotic infarction (ATI). All of these conditions were not indications for the use of recombinant tissue-type plasminogen activator because of occurrence 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 codes and text data in Japanese (I633: ATI and I638: LI). LI was defined as a small subcortical infarction less than 2 cm in diameter without cortical symptoms and large vessel lesions. ATI was defined as a stroke lesion with more than 50% stenosis or occlusion of the intra- and extracranial vessels on the ipsilateral side.[7,8] Chronic kidney disease and hemodialysis cases were excluded in the present study, because we have difficulty in using edaravone for renal dysfunction.

Argatroban (120 mg/day) was administered intravenously by drip infusion over 2 hours twice a day (b.i.d. [bis in die]), in the morning and in the evening for 2 days, followed by 20 mg/d for 5 days. Edaravone (30 mg) was administered intravenously by drip infusion over 30 minutes b.i.d., in the morning and in the evening. We also made a control group treated with ozagrel and without argatroban, which included patients with acute noncardioembolic stroke, including LI and ATI. Ozagrel (80 mg) was administered intravenously by drip infusion over 2 hours b.i.d., in the morning and in the evening.

We compared the clinical efficacy between the argatroban group and the control group with ozagrel. Moreover, we divided all 513 patients (argatroban, n = 353, and control with ozagrel, n = 160) into 2 groups: the LI group (N = 258) and the ATI group (N = 255). The LI group included 138 patients treated with argatroban and 120 control patients treated with ozagrel. The ATI group included 215 patients treated with argatroban and 40 control patients treated with ozagrel. Concomitant use of urokinase, heparin, and warfarin were prohibited during the administration period of argatroban and edaravone. The mRS and NIHSS were used for the assessment of clinical outcome on discharge. We considered an mRS score of 0-2 as a good outcome and an mRS score of 3-6 as a poor outcome on discharge, similar 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 in clinical factors, including gender, cerebral vascular risk factor, edaravone therapy, and concurrent antiplatelet, between the 2 groups of stroke subtype and 2 therapies, argatroban or ozagrel. The chi-square test was also used to compare the rate of clinical good outcome on discharge between the argatroban group and the control group with ozagrel. The Wilcoxon signed rank-sum test was used to analyze the NIHSS and mRS scores between pre- and 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 score 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). The NIHSS score on admission and the mRS score on admission were strongly correlated by Spearman correlation coefficient ($r = .669$, $P < .0001$), so we excluded the mRS score on admission from predictor variables of clinical factors in the logistic model in consideration of the multicollinearity. $P$ values less than .05 were considered significant. All values are presented as medians with interquartile ranges.

## Results

A total of 513 patients with acute noncardioembolic ischemic stroke were enrolled retrospectively from our hospital database. Significant intergroup differences in baseline characteristics between the argatroban group and the control group with ozagrel were observed for distribution of stroke subtypes, NIHSS score on admission, and mRS score obtained 3 times (before stroke onset, on admission, and on discharge) ($P < .05$). Of all patients with stroke, 353 were administered with argatroban, including 138 with LI (39.1%) and 215 with ATI (60.9%). A total of 160 control patients, including 120 with LI (75.0%) and 40 with ATI (25.0%), were administered with ozagrel (Table 1).

Although the NIHSS scores were improved by −1 (pretherapy = 4, post-therapy = 2; $P < .0001$) in the argatroban group and −1 (pretherapy = 3, post-therapy = 1; $P < .0001$) in the control group with ozagrel, there was no significant difference in the improvement of the NIHSS score between the argatroban and the ozagrel groups. There were heterogenous factors, the distribution of stroke subtype (LI and ATI) and the NIHSS on score admission, between the argatroban group and the control group with ozagrel. ATI was dominant in the argatroban group, and LI was dominant in the control group with ozagrel ($P = .0001$). The rate of concurrent edaravone therapy was dominant in the argatroban group compared with the control group with ozagrel ($P = .0001$) (Table 1). It was

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