

Clinical Article

Treatment for Patients with Acute Ischemic Stroke Presenting beyond Six Hours of Ischemic Symptom Onset : Effectiveness of Intravenous Direct Thrombin Inhibitor, Argatroban

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Objective : The objectives of this study were to analyze the outcome and hemorrhagic risk of intravenous (IV) argatroban in patients with acute ischemic stroke presenting beyond six hours of ischemic symptom onset.

Methods : Eighty patients with acute ischemic stroke who were admitted to the hospital beyond six hours from ischemic symptom onset were retrospectively analyzed. We could not perform IV thrombolysis or intra-arterial thrombolysis because of limited time window. So, IV argatroban was performed to prevent recurrent thrombosis and progression of infarcted area. The outcome was assessed by the National Institute of Health Stroke Scale (NIHSS) score and related hemorrhagic risk was analyzed. Also, each outcome was analyzed according to the initial stroke severity, subtype, and location.

Results : The median NIHSS was 8.0 at admission, 4.1 upon discharge, and 3.3 after three months. A good outcome was achieved in 81% of patients upon discharge and 88% after three months. Symptomatic hemorrhage occurred in only two patients (3%). IV argatroban was effective regardless of initial stroke severity, subtype, and location.

Conclusion : IV argatroban may be an effective and safe treatment modality for acute ischemic stroke presenting beyond six hours of ischemic symptom onset.

KEY WORDS : Acute ischemic stroke · Intravenous argatroban.

INTRODUCTION

Cerebral stroke is the second most common cause of death and the leading cause of disability in South Korea. Also, Korean populations are rapidly adopting the Western lifestyle and dietary habits, including increased fat intake, alcohol consumption, decreased physical activity, and cigarette smoking, which have resulted in the increasing prevalence of acute ischemic stroke (AIS). Hence, the appropriate treatment modalities of AIS have gained increasing atten-

tion in Korea^{18,19}.

The use of intravenous (IV) recombinant tissue plasminogen activator (rt-PA) for AIS patients presenting within three hours of ischemic symptom onset is the standard treatment method²². Also, AIS patients presenting within six hours have been treated with intra-arterial (IA) thrombolysis or combined IV and IA thrombolysis and the therapeutic efficacies of these treatment have been approved by many previous studies^{4,10}. However, an effective and safe treatment for the patients with AIS presenting beyond six hours of ischemic symptom onset has not yet been established so far.

Argatroban is a selective direct thrombin inhibitor that has recently been used in the treatment of AIS and it has been approved in Japan and Korea as a treatment option for non-lacunar subtype-AIS presenting within 48 hours of ischemic symptom onset^{3,14}. Argatroban has the potential

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to reduce secondary microthrombin in the penumbra, improve regional blood flow, reduce ischemic lesions and ameliorate neurological deficits^{3,13,14,24}. It has been shown in many previous clinical and animal studies that this drug is effective for AIS patients without increasing intracranial hemorrhage^{3,9,11-16,24}. In this study, we performed IV argatroban in patients with AIS presenting beyond six hours of ischemic symptom onset in order to analyze the efficacy and safety of this drug.

MATERIALS AND METHODS

Patients

Eighty patients with AIS who received IV argatroban treatment between December 2007 and February 2009 were retrospectively analyzed. All patients were admitted to the hospital after six hours from ischemic symptom attack. This study covered only the patients presenting within 48 hours of ischemic symptom onset due to the limitation of our Health Insurance approval for IV argatroban treatment. They all suffered from mild to severe neurological symptom, such as hemiparesis, hemi-sensory disturbance, dysarthria or aphasia, hemianopsia or diplopia, and dizziness or vertigo. The major risk factors of AIS, such as hypertension, diabetes mellitus, cigarette smoking, severe alcohol drinking, hyperlipidemia, previous history of stroke, and underlying cardiac diseases including atrial fibrillation were carefully evaluated.

All patients were evaluated with brain computed tomography (CT). The exclusion criteria on initial CT were hyperdense lesion consistent with hemorrhage and any other intracranial lesion, such as a tumor or vascular malformation. All patients without exclusion criteria on CT underwent brain computed tomography angiography (CTA) or magnetic resonance angiography (MRA) in order to detect any arterial stenosis. In this study, CTA or MRA revealed stenosis of the proximal intracranial artery or internal carotid artery (ICA) in 15 patients (18%), stenosis of the distal intracranial artery in 22 patients (28%) and no stenosis in 43 patients (54%). Although significant arterial stenosis was detected on CTA or MRA, urgent cerebral angiography was not performed because of limited time window for IA thrombolysis. Conventional brain magnetic resonance imaging (MRI) with diffusion-weighted image, apparent diffusion coefficient map, and fluid attenuated inversion recovery image was also obtained in all patients in order to diagnose the acute cerebral infarction and to determine the baseline extent of the infarcted area and associated perilesional edema. This study covered only the patients who revealed acute cerebral infarction on MRI regardless of arterial stenosis.

Stroke severity, subtype, and location

At admission, the National Institute of Health Stroke Scale (NIHSS) score was checked in all patients in order to measure neurological deficits. The initial stroke severity was analyzed by dividing the three categories according to the baseline NIHSS score as mild (0-6); moderate (7-15); severe (beyond 16)^{1,21}. As a result, mild stroke was diagnosed in 44 patients (55%), moderate stroke in 32 (40%), and severe stroke in four (5%).

A routine workup studies, such as routine laboratory tests, electrocardiogram, and echocardiogram were performed to determine the stroke subtype in all patients. The stroke subtype was categorized by cardioembolic, atherothrombotic, and lacunar infarction according to previous literature^{13,24}. The patients with lacunar infarction were excluded from this study. As a result, cardioembolic stroke was diagnosed in 19 patients (24%) and atherothrombotic stroke in 61 (76%).

The stroke location on MRI was also analyzed according to the side of infarction (right versus left) and site of infarction (anterior circulation versus posterior circulation). As a result, right-sided infarction was diagnosed in 44 patients (55%) and left-sided in 36 (45%). Also, anterior circulation infarction was diagnosed in 54 patients (68%) and posterior circulation in 26 (32%).

The baseline characteristics of the patients are shown in Table 1.

IV argatroban

The argatroban (Novastan, Mitsubishi Pharma Corporation, Osaka, Japan) was injected at a loading dose of 60 mg/day by continuous intravenous infusion for the first two days, followed by intravenous infusion of 20 mg/day in two divided doses over three hours for subsequent five days. The targeting activated partial thromboplastin time was about 1.5 times the baseline level. CT was evaluated routinely after termination of IV argatroban, but when neurological deterioration was detected, emergent CT was performed in order to detect any hemorrhage or progression of infarcted area which could result in serious intracranial hypertension.

The appropriate antiplatelet agent (aspirin with clopidogrel or cilostazol) was administered after termination of IV argatroban and maintained during follow-up in all patients.

Outcome and hemorrhagic risk evaluation

All patients were discharged within two weeks from admission and were follow-up in the outpatient clinic. The NIHSS score was obtained at admission, upon discharge, and after three months. The NIHSS score at admission was compared with the score upon discharge and after three

months. A good outcome was defined as a decreased NIHSS score above 4 point of the initial score at admission, or the score equal to 0 or 1 upon discharge or after three months^{8,21,25}. Also, the outcome was analyzed according to the initial stroke severity, stroke subtype, and stroke location.

A symptomatic hemorrhage was defined as a homogeneous hemorrhage area on follow-up CT and a concomitant neurological deterioration which was defined as an increase in the NIHSS score of ≥ 4 points¹⁷. The rest was considered as asymptomatic hemorrhage.

RESULTS

Outcome and hemorrhagic risk evaluation (Table 2, Fig. 1)

Three month follow-up results were obtained in all patients.

Table 1. Baseline characteristics of the patients

Age, mean (range), years	62.9 (19-84)
Sex, men : women	38 : 42
Time to hospital (hours)	
6-12	35 (44%)
13-24	27 (34%)
25-48	18 (22%)
Risk factor (number)	
0	13 (16%)
1 or 2	48 (60%)
≥ 3	19 (24%)
Arterial stenosis	
Yes	37 (46%)
No	43 (54%)
Stroke severity	
Mild	44 (55%)
Moderate	32 (40%)
Severe	4 (5%)
Stroke subtype	
Atherothrombotic	61 (76%)
Cardioembolic	19 (24%)
Stroke location	
Right-sided	44 (55%)
Left-sided	36 (45%)
Anterior circulation	54 (68%)
Posterior circulation	26 (32%)

Table 2. Outcome and hemorrhagic risk

	At admission	Upon discharge	After 3 months
Median NIHSS	8.0	4.1	3.3
Outcome			
Good (%)		65 (81%)	71 (88%)
Poor (%)		15 (19%)	9 (12%)
Hemorrhage			
Symptomatic (%)		2 (3%)	
Asymptomatic (%)		6 (8%)	

NIHSS : National Institute of Health Stroke Scale

ents. There was no death of patient involved in this study. The median NIHSS was 8.0 (range, 3-20) at admission, 4.1 (range, 0-18) upon discharge, and 3.3 (range, 0-17) after three months.

A good outcome was achieved in 65 patients (81%) upon discharge and in 71 patients (88%) after three months. Upon discharge, among 15 patients who showed poor outcome, no patients showed worsening or unchanged NIHSS score and all patients showed minimally improved NIHSS score (below three points). After three months, the six patients achieved additional good outcome. Additionally, among the patients who showed good outcome upon discharge, no neurological deterioration was observed during follow-up. Consequently, we achieved overall good outcome with IV argatroban.

A symptomatic hemorrhage was detected in only two patients (3%) and asymptomatic hemorrhage in six (8%). Consequently, we achieved low symptomatic hemorrhage rate with IV argatroban.

Outcome according to stroke severity, subtype, location (Table 3)

Among 44 patients who revealed mild stroke, good outcome was achieved in 35 patients (80%) upon discharge and in 40 (91%) after three months. Among 32 patients who revealed moderate stroke, good outcome was achieved in 28 patients (86%) upon discharge and in 29 (91%) after three months. Among four patients who revealed severe stroke, good outcome was achieved in two patients (50%) upon discharge and after three months. Consequently, IV argatroban was effective for mild and moderate, and for some patients with severe stroke.

Among 19 patients who were diagnosed as cardioembolic stroke, good outcome was achieved in 15 patients (79%) upon discharge and in 17 (89%) after three months. Among 61 patients who were diagnosed as atherothrombotic stroke, good outcome was achieved in 50 patients (82%) upon discharge and in 54 (89%) after three months. Consequently, IV argatroban was equally effective for cardioembolic and atherothrombotic stroke.

Among 44 patients who revealed right-sided stroke, good outcome was achieved in 38 patients (86%) upon discharge and in 41 (93%) after three months. Among 36 patients who revealed left-sided stroke, good outcome was achieved in 27 patients (75%) upon discharge and in 30 (83%) after three months. Consequently, IV argatroban was equally effective for right-

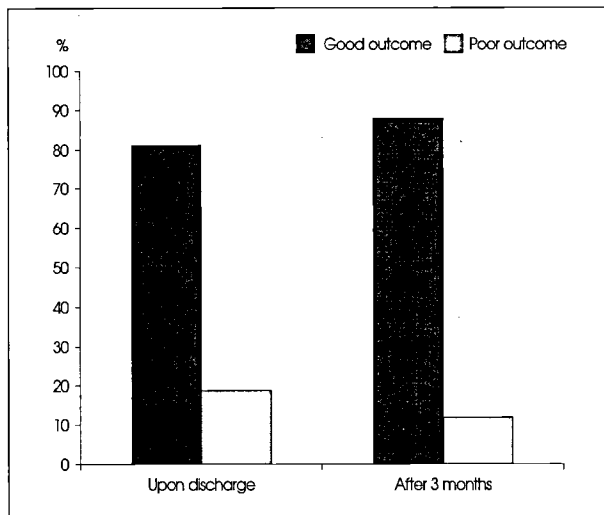


Fig. 1. Bar graph shows the overall outcome of argatroban.

Table 3. Outcome according to stroke severity, subtype, and location

	Good outcome	
	Upon discharge (%)	After 3 months (%)
Stroke severity		
Mild	35/44 (80)	40/44 (91)
Moderate	28/32 (86)	29/32 (91)
Severe	2/4 (50)	2/4 (50)
Stroke subtype		
Atherothrombotic	50/61 (82)	54/61 (89)
Cardioembolic	15/19 (79)	17/19 (89)
Stroke location		
Right-sided	38/44 (86)	41/44 (93)
Left-sided	27/36 (75)	30/36 (83)
Anterior circulation	45/54 (83)	47/54 (87)
Posterior circulation	20/26 (77)	24/26 (92)

and left-sided stroke.

Among 54 patients who revealed anterior circulation stroke, good outcome was achieved in 45 patients (83%) upon discharge and in 47 (87%) after three months. Among 26 patients who revealed posterior circulation stroke, good outcome was achieved in 20 patients (77%) upon discharge and in 24 (92%) after three months. Consequently, IV argatroban was equally effective for anterior and posterior circulation stroke.

In this study, IV argatroban is effective regardless of initial stroke severity, subtype, and location.

Illustrative case

A 79-year-old woman presented with sudden onset of right hemiparesis (grade II to III), motor aphasia, and drowsy mentality. Her initial NIHSS score was 16 and CT revealed no abnormalities. A MRI revealed acute cerebral infarction in the left middle cerebral artery territory (Fig. 2A) with significant diffusion/perfusion mismatch (Fig. 2B) and

MRA revealed complete occlusion of the M2 portion of the left middle cerebral artery (Fig. 2C). IV rt-PA or IA thrombolysis could not be performed because she was admitted to the hospital after 18 hours from ischemic symptom onset. So, IV argatroban was injected and maintained for seven days. After termination of IV argatroban, follow-up CT revealed no hemorrhage and follow-up MRI revealed the marked improvement of the perfusion deficit (Fig. 2D). Also, follow-up MRA revealed complete recanalization of the left middle cerebral artery (Fig. 2E). Upon discharge, she showed marked neurological improvement in her right hemiparesis (grade IV), moderate dysarthria, and alert mentality (NIHSS score, 5). After three months, her motor function and language skills were improved further (NIHSS score, 3).

DISCUSSION

Based on the result of the rt-PA Stroke Trial of the National Institute of Neurological Disorders and Strokes, IV rt-PA within three hours of the onset of AIS improved clinical outcomes after three months, and IV rt-PA was approved as the only treatment modality for AIS by the Food and Drug Administration²². However, since the use of IV rt-PA is limited by a low recanalization rate and a short treatment time window with an increased hemorrhagic risk, many previous studies have reported the effectiveness of IA thrombolysis^{4,10}. However, treatment with IV rt-PA or IA thrombolysis was limited by a narrow therapeutic time window as within three or six hours. Therefore, all stroke patients should be admitted early within the first three to six hours from ischemic symptom onset to receive the approved treatment. However, many patients with stroke are often admitted late due to several limitations such as geographic, demographic, organizational, educational, and medical factors^{7,23,26}. Because most AIS patients cannot arrive at the hospital within six hours, an effective and safe treatment which can be used for AIS patients presenting beyond six hours of ischemic symptom onset was required. Unfortunately, such treatment has not yet been established. In this study, we attempted to treat such patients with IV argatroban.

In humans, the factors which may be involved in the progression of stroke are hypercoagulation and microthrombi formation, which lead to microvascular occlusion and reduction in blood flow. Thrombin is a key factor for arterial thrombosis and disturbance of microcirculation^{9,16}. Argatroban is a selective direct thrombin inhibitor developed for the first time by Okamoto et al. in 1978¹². This drug reversibly bind the catalytic site of thrombin and does not

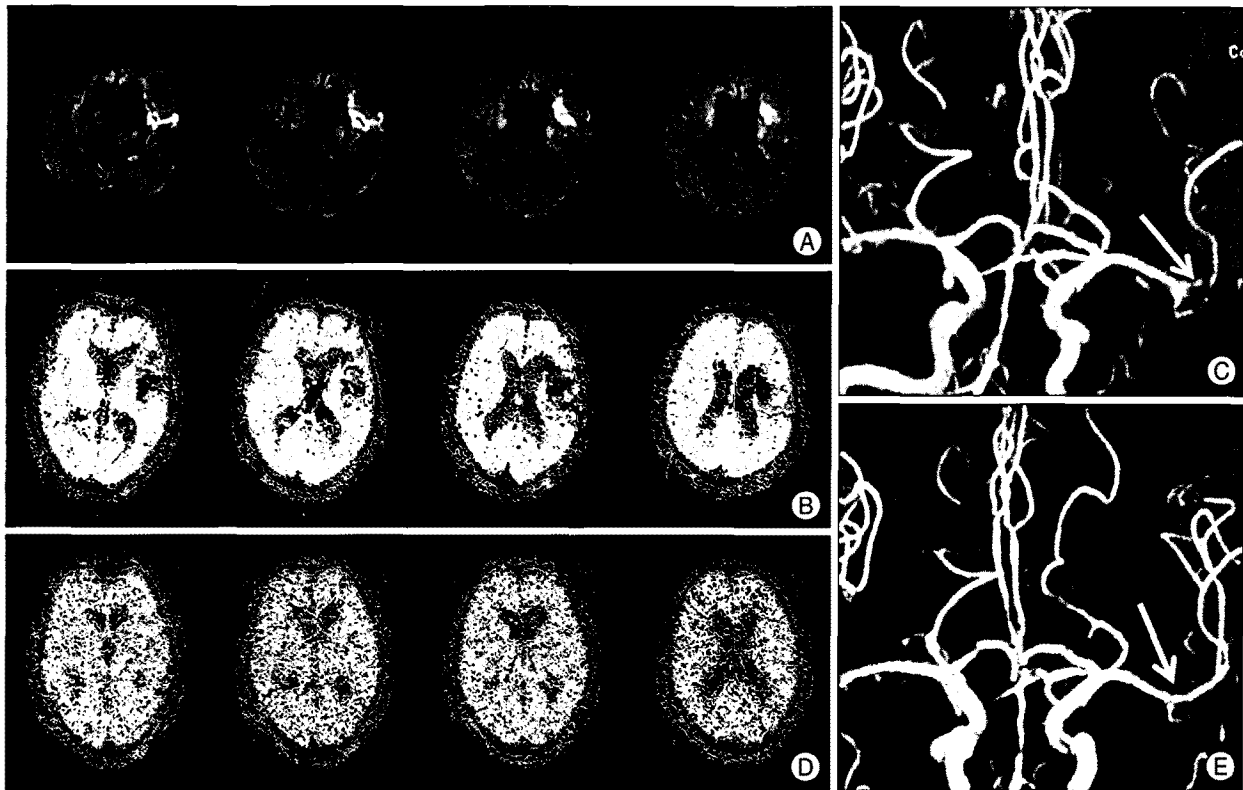


Fig. 2. Case of severe stroke in 79-year-old woman with sudden onset of right hemiparesis, motor aphasia, and drowsy mentality. A : Initial magnetic resonance image, diffusion-weighted view shows an acute cerebral infarction in the left middle cerebral artery territory. B : Perfusion-weighted view shows a severe decreased perfusion in the left middle cerebral artery territory with diffusion/perfusion mismatch. C : Initial magnetic resonance angiography (MRA) shows a complete occlusion of the M2 portion of the left middle cerebral artery (arrow). D : Follow-up perfusion-weighted view after intravenous (IV) argatroban shows a marked improvement in the perfusion deficit of the left middle cerebral artery territory. E : Follow-up MRA after IV argatroban shows a complete recanalization of the left middle cerebral artery (arrow).

require other cofactors, and its anticoagulation effect is achieved after IV administration. Argatroban has the potential to reduce secondary microthrombin in the penumbra, improve regional blood flow, reduce ischemic lesions and ameliorate neurological deficits via the inhibition of circulating and clot-bound thrombin, platelet aggregation, and vascular contraction^{3,13,14,24}.

The rationale for the early administration of antithrombotic drugs is to prevent propagation of an acute thrombosis and recurrent embolism²³. Previously, urgent routine anticoagulation with heparin, low molecular-weight heparin or heparinoid was used for AIS. However, many previous studies reported that immediate anticoagulation therapy was not associated with net short- or long-term benefit in AIS, and increased the risk of hemorrhagic complications^{5,20,23}. So, this anticoagulation treatment is not recommended for most AIS patients because of increased bleeding complications, unpredictable anticoagulation effects, dependence on the adequate antithrombin level, and heparin-induced thrombocytopenia^{14,15,24}. On the other hand, argatroban has a predictable anticoagulant effect, does not potentiate heparin-induced thrombocytopenia,

and causes less bleeding compared with heparin for the same anticoagulant effect, and has a short elimination half-life (39-51 minutes). Thus, it can ensure a rapid restoration of hemostasis upon cessation of treatment and decrease the risk of intracerebral bleeding^{3,11,12,15,16}. In the Argatroban in Acute Ischemic Stroke (ARGIS-1) study, LaMonte et al.¹⁵ reported that argatroban produced safe anticoagulation in 171 patients with AIS within 12 hours of onset without increasing intracranial hematoma. Similar to previous studies, we achieved very low symptomatic hemorrhagic risk (3%) after IV argatroban treatment. Consequently, IV argatroban may be used safely for the AIS patients presenting beyond six hours of ischemic symptom onset.

Many previous studies have reported the effectiveness of argatroban in animal model^{19,16}. However, only few clinical studies of intravenous argatroban in AIS have been reported so far^{6,11,12,24}. We chose argatroban because of its multiple possible actions of improving blood flow in the microcirculation, preventing the secondary microthrombin in the penumbra and reducing the ischemic lesions and because of its safety in terms of intracerebral hemorrhage. In this study, the median initial NIHSS score at admission was 8.0

and we were able to decrease this score to 4.1 upon discharge. Also, we could increase the rates of overall good outcome (81%) with acceptable symptomatic hemorrhagic risk (3%). The patients who showed a good outcome after IV argatroban did not show any neurological aggravation after at least three months. The key factor for this satisfactory result has been thought to be the strict choice of the indicated patients according to the time from ischemic symptom onset, general medical status, and initial radiologic findings; shortening of the time to treatment; and appropriate supportive care, such as strict blood pressure, glucose, and lipid control with increased intracranial pressure management. More than anything else, we used IV argatroban for the AIS patients presenting beyond six hours of ischemic symptom onset, so that we could achieve better overall outcomes with low hemorrhagic risk than previous studies.

In this study, we analyzed the outcome according to initial stroke severity, subtype, and location. In the patients with mild stroke (NIHSS score ≤ 6), any neurological improvement could be considered as natural recovery of AIS regardless of treatment. Biller et al.²⁾ analyzed 29 patients presented within six to 12 hours of stroke onset and reported that neurological improvement, which was defined as a decrease of ≥ 2 points from baseline NIHSS, occurred in 21% of patients within one hour and in 51% within six hours without any specific treatment. They concluded that spontaneous, often dramatic improvement occurs in AIS patients and should be taken into consideration. Wityk et al.²⁵⁾ analyzed 50 patients presented within 24 hours of stroke onset and reported that neurological improvement, which was defined as a decrease of ≥ 4 points from baseline NIHSS, occurred in 28% of patients within 48 hours and in 51% within the time of last follow-up (mean, 44 days) without any specific treatment. In this study, we defined good outcome as a decrease of ≥ 4 points from baseline NIHSS scores. As a result, among the 44 patients with mild stroke, 80% of patients achieved good outcome upon discharge. Moreover, good outcome was achieved in 86% of the patients with moderate stroke and in 50% with severe stroke. IV argatroban was especially effective for moderate stroke in this study. This successful result could not be considered as a spontaneous recovery or natural course of AIS. Therefore, we concluded that IV argatroban is actually effective for AIS patients regardless of initial stroke severity.

Hosomi et al.⁶⁾ have demonstrated that IV argatroban is useful for cardioembolic stroke with increasing the improvement of recovery rates and without increasing the risk of hemorrhage. Urabe et al.²⁴⁾ reported that IV argatroban is not only effective in atherothrombotic infarction, but also

cardioembolic infarction. Similar to previous studies, we achieved high rates of good outcome both in atherothrombotic stroke (82%) and in cardioembolic stroke (79%) after IV argatroban. Therefore, we conclude that IV argatroban is effective not only for atherothrombotic stroke, but also for cardioembolic stroke.

We achieved the overall good outcome both in right-sided infarction (86%) and in left-sided infarction (75%). Also, we achieved the overall good outcome both in anterior circulation infarction (83%) and in posterior circulation infarction (77%). Therefore, we concluded that IV argatroban is effective regardless of stroke location.

There are several limitations in this study such as the lack of a control group and the presence of heterogeneous arterial lesions. Large-scale prospective randomized studies in future are required to confirm the results of this study.

CONCLUSION

IV argatroban may be an effective and safe treatment modality for AIS patients presenting beyond six hours of ischemic symptom onset. It has shown to be effective regardless of initial stroke severity, subtype, and location.

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