

Impact of Patency of the Carotid Terminus and Middle Cerebral Artery on Early Clinical Outcomes in Patients with Acute Internal Carotid Artery Occlusion and Mild Symptoms

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Keywords

Stroke · Low NIHSS · Large vessel occlusion · Internal carotid artery terminus

Abstract

Introduction: Both collateral flow via the internal carotid artery (ICA) terminus (ICT) and initial mild symptoms might be associated with favorable outcomes in patients with acute ICA occlusion (ICAO). This study aimed to address the association between early clinical outcomes and patency of the ICT and middle cerebral artery (MCA) in patients with acute ICAO with mild symptoms. **Methods:** Of 1,214 consecutive patients with acute ischemic stroke or transient ischemic attack due to large vessel occlusion, patients with ipsilateral ICAO and initial National Institutes of Health Stroke Scale (NIHSS) score ≤ 5 were retrospectively enrolled. We examined the associations between clinical factors including patency of the ICT and MCA and recurrence of stroke or early neurological deterioration (REND). Significant early neurological deterioration was defined as increment in NIHSS score ≥ 1 during hospital stay. **Results:** Thirteen of the 35 patients who

were finally enrolled had REND (37%), and median modified Rankin scale (mRS) score at discharge was 1 (interquartile range, 0–4). Initial NIHSS score (4 vs. 1, $p < 0.001$) and rates of diabetes mellitus (61.5% vs. 13.6%, $p = 0.007$), intravenous thrombolysis (IVT) (30.9% vs. 0%, $p = 0.014$), and mechanical thrombectomy (MT) (23.1% vs. 0%, $p = 0.044$) were significantly higher in patients with REND rather than in those without. The rate of patent ICT and MCA was comparable between groups. Except for 1 patient who underwent MT promptly after IVT immediately after REND, 3 patients initially treated with IVT deteriorated after the procedure. One patient without patent ICT and MCA did not meet the indications for MT. In 2 other patients with patent ICT and MCA, MT was not initially performed, but was eventually performed because of REND due to thrombus migration, and both were discharged with an mRS score of 5. **Conclusion:** The overall clinical outcomes of patients with acute ICAO with mild symptoms were not depending on the patency of the ICT and MCA, but initial treatment with IVT alone might risk unfavorable outcomes due to thrombus migration in patients with patent ICT and MCA.

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Introduction

Mechanical thrombectomy (MT) is an established and effective treatment for patients with acute large vessel occlusion (LVO) including internal carotid artery (ICA) occlusion (ICAO) [1]. However, the indications for MT in patients with LVO showing mild symptoms remain contentious because of uncertainty regarding treatment effectiveness [2]. On the other hand, various patterns of ICAO could affect the rate of revascularization success and subsequent clinical outcome [3]. ICAO with patent ICA terminus (ICT), which would be also called carotid-I occlusion [3] or isolated ICAO [4], shows reconstitution from the contralateral ICA via the proximal anterior cerebral artery and anterior communicating artery, or ipsilateral posterior cerebral artery via the posterior communicating artery. Although both collateral flow via patent ICT and initial mild symptoms might be associated with more favorable outcomes in the acute stage [5], early neurological deterioration was reported to be relatively common in patients with isolated ICAO [4]. Furthermore, it was also reported that early neurological deterioration after intravenous thrombolysis (IVT) was a frequent and highly deleterious in patients with isolated ICAO [6]. Although these past studies focus on the early clinical course in acute ICAO patients with both collateral flow via the ICT and initial mild symptoms, optimal indication of acute revascularization including IVT or MT for these patients has not been fully addressed. The present study aimed to clarify the effect of the patency of the ICA and the status of collateral flow to the ipsilateral middle cerebral artery (MCA) via the ICT on early clinical outcomes in patients with acute ICAO with mild symptoms, particularly in terms of the effectiveness of IVT, MT, or surgery, using data from the stroke registry of a single center.

Methods

Study Population

Subjects in the present study were retrospectively selected from 1,214 consecutive patients with acute ischemic stroke or transient ischemic attack (TIA) with LVO who were admitted to Kohnan Hospital (Sendai, Miyagi, Japan) within 24 h after onset between April 2006 and March 2018. Based on clinical and brain imaging findings, board-certified stroke neurologists specializing in the care of stroke patients made a diagnosis of ischemic stroke or TIA. The severity of neurological deficits was evaluated using the National Institutes of Health Stroke Scale (NIHSS) score on admission [7], and activities of daily living for patients before or after the onset of stroke were measured using the modified Rankin Scale (mRS) [8]. Clinical and investigative data were prospectively entered in a standardized fashion by stroke neurologists into the

Kohnan Hospital Stroke Registry. Inclusion criteria for this study were as follows: (1) acute ischemic stroke or TIA due to ipsilateral ICAO; (2) NIHSS score ≤ 5 on admission; (3) mRS score ≤ 2 before stroke onset. We excluded patients based on the following criteria: (1) previous identification of occlusive disease in the ipsilateral ICA; (2) contraindications for performing magnetic resonance angiography (MRA); or (3) other circumstances considered as inappropriate by the investigators.

Data Collection and Definitions

In addition to general patient characteristics, including age, sex, cardiovascular risk factors, mRS score before onset, and initial NIHSS score, stroke classification according to the "Trial of ORG 10172 in Acute Stroke Treatment" (TOAST) [9], patency of the ICT and MCA on initial intracranial vascular imaging, and use of IVT or MT were also collected. We evaluated patency of the ICT and MCA according to signal intensity of the ICT and ipsilateral MCA on MRA. In our center, MRA was employed as the standard vascular imaging and could be performed immediately, 24 h a day, 7 days a week. MRA was usually performed just before or during IVT. Signal intensity of the MCA on MRA was qualitatively classified by a single investigator (R.I.) into 4 grades of "excellent," "good," "fair," or "poor" [10]. In this study, patients with excellent or good signal intensity of the ipsilateral MCA and visualization of the ICT were defined as having patent ICT and MCA. Onset-to-door time was defined as the time from the last known time when the patient appeared well and free of index stroke symptoms to the time at which the patient arrived at the emergency room. The primary outcome was recurrence of stroke or early neurological deterioration (REND). Significant early neurological deterioration was defined as increment in NIHSS score ≥ 1 during hospital stay.

Statistical Analysis

We conducted univariate analysis to compare clinical and radiological characteristics between patients with and without REND. Categorical variables are presented as numbers and percentages and were analyzed using the χ^2 test and Fisher's exact test, as appropriate. Continuous variables are expressed as median and interquartile range (IQR) and were analyzed using the Wilcoxon rank-sum test because of their non-normal distribution. All statistical analyses were performed using EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan; <http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/manual.html>) [11], a graphical user interface for R (the R Foundation for Statistical Computing, Vienna, Austria). More precisely, EZR is a modified version of R Commander designed to add statistical functions frequently used in biostatistics. All reported p values are two-tailed, and values of $p < 0.05$ were considered statistically significant.

Results

Among the 1,214 patients who were initially screened, we selected all 49 patients with an initial NIHSS score of 0–5, ipsilateral ICAO, and pre-morbid mRS score 0–2. We then excluded 13 patients with known occlusive ICA disease before admission and 1 patient in whom MRA was obtained at the referring hospital. Finally, 35 patients

Table 1. Univariate analysis comparing characteristics between patients with and without REND

Characteristics	With REND (n = 13)	Without REND (n = 22)	p value
Age, years	75 (65–85.8)	63.5 (54–75.8)	0.054
Male	8 (57.1)	16 (76.2)	0.28
Hypertension	11 (84.6)	20 (90.9)	0.62
Dyslipidemia	5 (38.5)	11 (61.5)	0.73
Diabetes mellitus	8 (61.5)	3 (13.6)	0.007
Smoking	9 (69.2)	16 (76.2)	0.70
Heart disease as embolic source	1 (11.1)	5 (35.7)	0.34
Subtype classification			0.15
LAD	8 (61.5)	13 (59.1)	
CES	3 (23.1)	1 (4.5)	
Others	2 (15.4)	3 (13.6)	
TIA	0 (0)	5 (22.7)	
Initial NIHSS score	4 (3–5)	1 (0–2.8)	<0.001
Onset-to-door time, min	169 (80–420)	340 (157.5–627.5)	0.23
Patent ICT and MCA	8 (61.5)	14 (63.6)	1.00
Systolic blood pressure on arrival, mm Hg	155 (150–181)	135 (130–170)	0.16
Diastolic blood pressure on arrival, mm Hg	86 (78–101)	75 (66–109)	0.17
IVT	4 (30.9)	0 (0)	0.014
MT	3 (23.1)	0 (0)	0.044
Bypass surgery	2 (15.4)	0 (0)	0.13
sICH	0 (0)	0 (0)	1.00
mRS at discharge	5 (4–5)	0 (0–1)	<0.001

Data are presented as number (%) or median (IQR). REND, recurrence of stroke or early neurological deterioration with increment in NIHSS score ≥ 1 during hospital stay; IQR, interquartile range; TOAST, Trial of ORG 10172 in Acute Stroke Treatment; LAD, large artery disease; CES, cardioembolic stroke; TIA, transient ischemic attack; NIHSS, National Institutes of Health Stroke Scale; ICT, internal carotid artery terminus; MCA, middle cerebral artery; IVT, intravenous thrombolysis; MT, mechanical thrombectomy; sICH, symptomatic intracranial hemorrhage; mRS, modified Rankin Scale.

Table 2. Clinical characteristics and courses of patients treated with revascularization therapy including IVT, MT, or bypass surgery

No.	Age	Sex	OTD	Stroke subtype	ICT and MCA	Initial NIHSS	Initial therapy (IVT time from onset)	REND time from onset	Rescue revascularization	mRS at discharge
1	48	M	280 min	LAD	Not patent	5	AT	Several days	None	4
2	87	F	90 min	CES	Not patent	5	IVT (117 min)	165 min	None	6
3	45	M	50 min	Arterial dissection	Patent	2	AT	250 min	None	2
4	85	M	711 min	LAD	Patent	5	AT	Several days	None	5
5	88	F	810 min	LAD	Not patent	3	AT	Several days	None	5
6	84	M	80 min	LAD	Patent	5	AT	1 day	None	5
7	75	M	169 min	Aortogenic emboli	Patent	4	IVT (200 min)	545 min	MT	5
8	79	M	420 min	LAD	Patent	5	AT	3 days	None	4
9	61	F	60 min	LAD	Not patent	0	AT	215 min	None	5
10	65	F	980 min	LAD	Not patent	4	AT	1 day	Bypass surgery	5
11	85	F	100 min	CES	Patent	4	Not yet initiated	110 min	IVT + MT	0
12	74	M	270 min	LAD	Patent	1	AT	1 day	Bypass surgery	2
13	75	M	48 min	CES	Patent	5	IVT (135 min)	435 min	MT	5

IVT, intravenous thrombolysis; MT, mechanical thrombectomy; OTD, onset-to-door time; ICT, internal carotid artery terminus; MCA, middle cerebral artery; CES, cardioembolic stroke; LAD, large artery disease; NIHSS, National Institutes of Health Stroke Scale; AT, antithrombotic therapy; REND, recurrence of stroke or early neurological deterioration with increment in NIHSS score ≥ 1 during hospital stay; mRS, modified Rankin Scale.

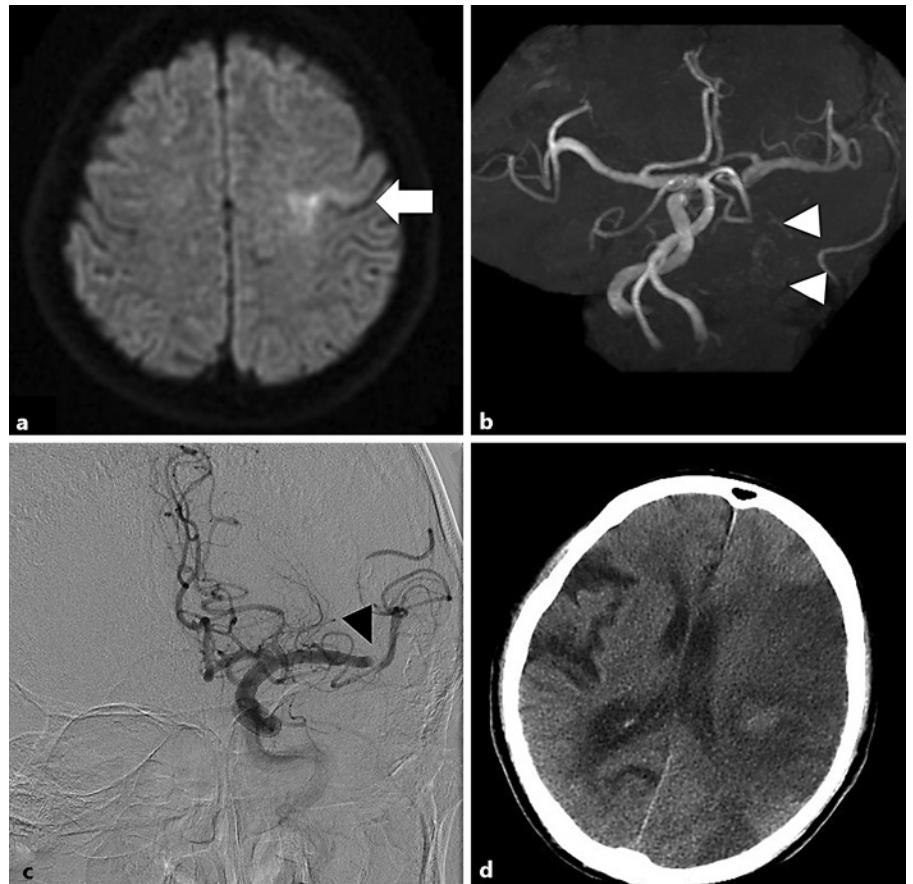


Fig. 1. Case 7, a 75-year-old-man. He was initially treated with IVT alone 31 min after arrival (200 min from onset). **a** DWI shows acute infarct on the left precentral gyrus on the territory of the MCA (white arrow). **b** MRA shows ICAO with a patent ICT and MCA (white arrowheads). MT was withheld because of mild symptoms (NIHSS score 4) and patent ICT. Five hours after IVT, left visual acuity was completely lost, suggesting occlusion of the left ophthalmic artery due to thrombus migration. At 5 h 45 min after IVT (545 min after onset), he presented with global aphasia and right hemiplegia (NIHSS score 19). **c** Although emergent DSA initially showed occlusion of the intracranial ICA, subsequent im-

aging reveals occlusion of the left distal M1 MCA segment (black arrowhead). Immediate MT was performed using a Merci retriever, but significant recanalization was not obtained. **d** After MT, a large infarct in the MCA territory was confirmed. The patient was finally diagnosed with aortogenic brain embolism. IVT, intravenous thrombolysis; DWI, diffusion-weighted imaging; MCA, middle cerebral artery; ICAO, internal carotid artery occlusion; ICT, internal carotid artery terminus; MRA, magnetic resonance angiography; MT, mechanical thrombectomy; NIHSS, National Institutes of Health Stroke Scale; ICA, internal carotid artery; DSA, digital subtraction angiography.

(median age, 73 years [IQR, 55–79 years]; 24 males; median NIHSS score, 2 [IQR, 1–4]) were studied. As the primary outcome, 13 of the 35 patients (37%) had REND. Median mRS score at discharge was 1 (IQR, 0–4). We compared clinical and radiological characteristics and outcomes between patients with and without REND using univariate analyses (Table 1). Age, onset-to-door time, and rate of patent ICT and MCA were comparable between groups. Initial NIHSS score (4 vs. 1, $p < 0.001$) and rate of diabetes mellitus (61.5% vs. 13.6%, $p = 0.007$) were significantly higher in patients with REND than in those without. Moreover, the rate of IVT (30.9% vs. 0%,

$p = 0.014$) and the rate of MT (23.1% vs. 0%, $p = 0.044$) were significantly higher in patients with REND than in those without. In patients with REND, mRS at discharge was significantly poorer than in those without (5 vs. 0, $p < 0.001$).

Clinical characteristics and the clinical course of 13 patients with REND are shown in Table 2. All of 3 patients initially treated with IVT alone deteriorated within 24 h after IVT. On the other hand, in Case 11 with patent ICT and MCA, REND occurred just before initiating IVT and was promptly followed by MT 55 min after arrival (152 min from onset). One patient without patent ICT and

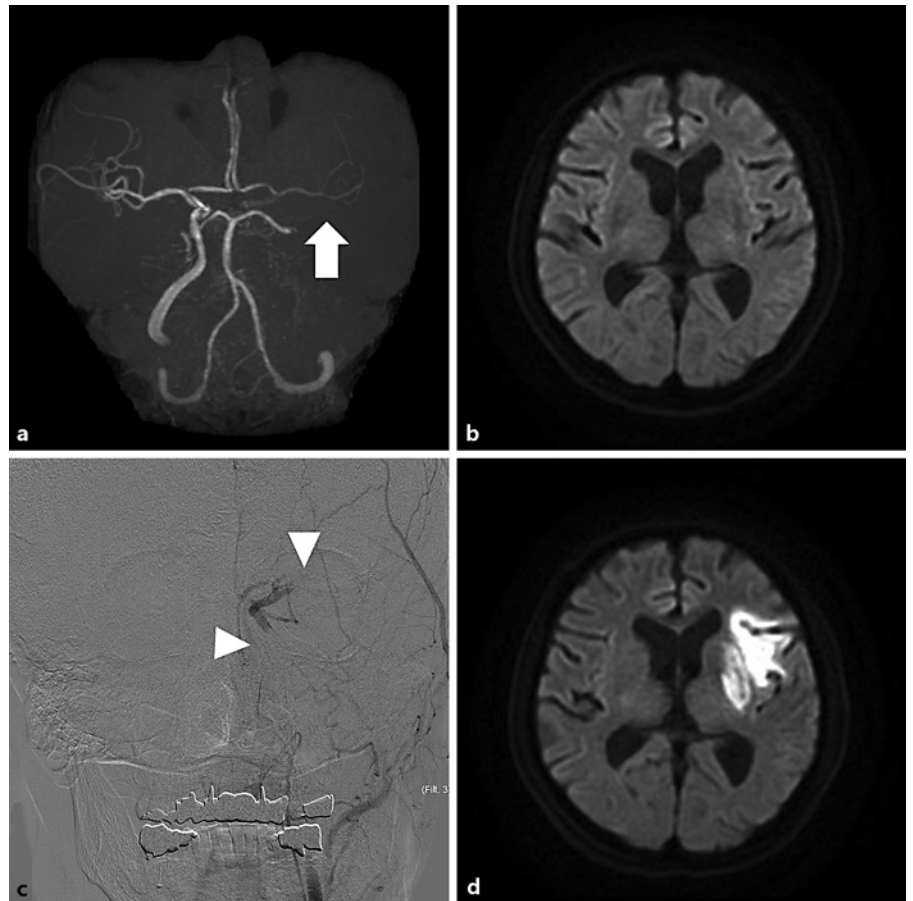


Fig. 2. Case 13, a 75-year-old man. He was initially treated with IVT alone 27 min after arrival (135 min from onset). **a** Initial DWI shows no acute infarct. **b** MRA shows ICAO with a patent ICT and MCA. The signal from the ipsilateral MCA is weak but visible (white arrow). MT was withheld because of mild symptoms (NIHSS score 5) and patent ICT. At 300 min after IVT, he presented with global aphasia, conjugate deviation, and right hemiplegia (NIHSS score 22). **c** Emergent DSA shows left tandem ICAO (ICA and proximal M1 MCA segment) (white arrowheads). He was immediately treated with MT with a stent retriever, obtaining com-

plete recanalization. **d** After MT, infarcts on the upper MCA territory are confirmed. Symptoms gradually improved, but clinical outcome at discharge was unfavorable because of aspiration pneumonia. IVT, intravenous thrombolysis; DWI, diffusion-weighted imaging; MRA, magnetic resonance angiography; ICAO, internal carotid artery occlusion; ICT, internal carotid artery terminus; MCA, middle cerebral artery; MT, mechanical thrombectomy; NIHSS, National Institutes of Health Stroke Scale; ICA, internal carotid artery; DSA, digital subtraction angiography.

MCA (Case 2) was not indicated for MT because of advanced age and insufficient evidence at the time, in 2008. In other 2 patients with patent ICT and MCA (Cases 7 and 13), MT was not initially performed because of low NIHSS on admission and good visualization of the ipsilateral MCA on MRA. Eventually, both patients were treated with MT because of REND suggesting thrombus migration several hours after IVT (599 and 470 min, respectively) and both were discharged with an mRS score of 5 (Fig. 1, 2).

Conclusion

In patients with acute ICAO and mild symptoms, we demonstrated that initial NIHSS score and rates of diabetes mellitus, IVT, and MT were significantly higher among patients with REND than among those without. Patency of the ICT and MCA was not associated with REND. The reason for the results might be that only patients with mild symptoms were enrolled. The initial symptoms might have more impact on early outcome rather than the status of collateral flow in patients with mild symptoms. However, all of 3 patients initially treat-

ed using IVT alone showed deterioration several hours after IVT. In 1 patient who was not indicated for MT, neurological deterioration might have been attributable to poor collaterals due to nonpatency of the ICT and MCA. In another 2 patients with patent ICT and MCA, neurological deterioration would have been caused by thrombus migration after IVT, and clinical outcomes were unfavorable despite rescue MT. In patients with acute ICAO with patent ICT and MCA and mild symptoms, initial treatment with IVT alone might lead to neurological deterioration and unfavorable outcomes due to thrombus migration.

The efficacy and safety of MT in patients with acute LVO and low NIHSS scores have not been established [2]. However, a sub-analysis of a large Japanese stroke registry reported that IVT, but not MT, was associated with favorable outcomes among acute LVO patients with low NIHSS scores [12]. On the other hand, it was reported that thrombus migration has been associated with prior IVT in patients with LVO [13]. Thrombus migration occurred spontaneously or during MT in 26% of patients with acute ICAO and patent MCA collateral flow, and was associated with worsened outcomes [14]. Furthermore, Boulenoir et al. [6] reported that early neurological deterioration after IVT occurred in 30% of isolated ICAO patients with mild symptoms and argued that thrombus fragmentation rather than collateral failure or extension of thrombus might be responsible for early neurological deterioration after IVT in these patients. Immediate MT for LVO in patients with low NIHSS scores has been suggested as potentially effective, as MT would prevent neurological deterioration [15]. Moreover, some studies have suggested that MT after the worsening of neurological symptoms in patients with initial mild symptoms could not be associated with favorable outcomes [16]. Although there was a patient treated by IVT and MT after REND who had a good outcome in our series (No. 11), REND occurred immediately after admission in this case. Immediate MT as well as IVT could be reasonable for patients with acute ICAO, even in patients with mild symptoms and patent ICT and MCA; however, there were no cases who underwent prompt MT irrespective of initial neurological symptoms in our series.

Thrombus migration or fragmentation after IVT could be more likely to occur in patients with embolic stroke, in which an embolus lodged in the extracranial ICA, than those with large artery disease (LAD) [6]; however, all patients who underwent IVT in this study were embolic stroke (3 cardioembolic stroke (CES) and 1 aortogenic brain embolism) (Table 2). On the other hand, in our se-

ries, 2 patients with REND (Cases 10 and 12, both with LAD, not treated by IVT) were treated using bypass surgery during the acute stage. As the first case occurred in 2011 and the second in 2015, sufficient evidence for the use of MT for acute LVO was lacking at the time both cases were treated. Other nonelderly patients in whom symptoms were also presumed to have been caused by atherosclerosis (Cases 1 and 9) might have met the indications for bypass surgery, but the efficacy of bypass surgery for patients with acute LVO due to intracranial atherosclerosis has not been established [17]. Consensus remains lacking on the optimal endovascular strategy for such cases [18].

We also showed that hyperglycemia was associated with REND in the present cohort. This result was compatible with our latest studies in patients with LVO and mild symptoms using a large Japanese stroke registry [12]. Moreover, hyperglycemia on admission is reportedly independently associated with increased incidence of symptomatic intracerebral hemorrhage and a decreased frequency of favorable outcomes at 90 days in patient with LVO, regardless of initial neurological symptoms [19].

Some limitations should be kept in mind when interpreting the results of this investigation. First, this study used data from a single center. It would be desirable to conduct a multicenter collaborative study. Second, we employed MRA as standard vascular imaging in this study, but this modality might underestimate the vascular patency of intracranial vessels compared to computed tomography angiography because MRA does not have as good spatial resolution as computed tomography angiography due to the strong association between signal intensity and blood flow. Therefore, it would be difficult to accurately evaluate by MRA cases in which the ICT was patent but horizontal segment of MCA was occluded, and such cases would be classified as “not patent ICT and MCA” in this study. Third, we could not enroll a sufficient number of participants in this study. The number of patients was thus too small to clarify associations between the effectiveness of vessel revascularization and patency of the ICT and MCA. The number of patients in a previous observational study on the outcome of isolated ICAO patients who underwent IVT was 74 [6]. Fourth, we could not obtain data on clinical outcomes at 90 days after symptom onset.

In conclusion, we have demonstrated that the overall clinical outcomes of patients with acute ICAO with mild symptoms were not depending on the patency of the ICT and MCA, but initial treatment with IVT alone might risk

unfavorable outcomes due to thrombus migration in patients with patent ICT and MCA. Prospective studies using larger sample sizes are warranted to clarify the impact of the status of the ICT and MCA on clinical outcomes among patients with acute ICAO.

Statement of Ethics

The Kohnan Hospital Ethics Committee approved the study protocol in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan (280926). Due to the retrospective nature of the study, the need for written informed consent was waived based on the approval of the Kohnan Hospital Ethics Committee.

Conflict of Interest Statement

Ryo Itabashi received honoraria from Bayer, Bristol Myers Squibb, Amgen, Takeda, Tanabe Mitsubishi Parma, Daiichi Sankyo, Boehringer Ingelheim, Eisai, Pfizer, Kyowa Kirin, Stryker, GE Healthcare, Nestle, Otsuka Pharmaceutical, Boston Scientific, and Medtronic, and received research support not attributed in the manuscript from Boehringer Ingelheim. Yukako Yazawa received honoraria for lecture fees from Bayer, Bristol Myers Squibb, Daiichi Sankyo, Stryker, and Medtronic. Takuya Saito, Yuichi Kawabata, and Yuya Kobayashi report no disclosure.

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Author Contributions

Ryo Itabashi: data acquisition, data analysis, and writing of the manuscript. Takuya Saito, Yuichi Kawabata, Yuya Kobayashi, and Yukako Yazawa: data acquisition and critical revision of the manuscript.

Data Availability Statement

The data that support the findings of this study are not publicly available due to legal regulation in Japan regarding the privacy of research participants but are available from the corresponding author (R. I.) on reasonable request and with approval from the co-authors and the Kohnan Hospital Ethics Committee. Further inquiries can be directed to the corresponding author.

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