ORIGINAL ARTICLE doi: 10.2176/nmc.oa.2016-0236

Neurol Med Chir (Tokyo) 57, 278–283, 2017 Online April 6, 2017

Treatment Outcome of Carotid Artery Stenting Underwent within 14 Days of Stroke Onset – Consideration of Safety and Efficacy of Urgent Carotid Artery Stenting for Neurologically Progressing Patients

Yasuhisa KANEMATSU,[1,*] Junichiro SATOMI,[1,*] Kazuyuki KUWAYAMA,[1,*] Izumi YAMAGUCHI,[1] Shotaro YOSHIOKA,[1] Tomoya KINOUCHI,[1] Yoshiteru TADA,[1] Nobuaki YAMAMOTO,[2] Shunji MATSUBARA,[3] Koichi SATOH,[4] and Shinji NAGAHIRO[1]

[1]*Department of Neurosurgery, Tokushima University, Tokushima, Tokushima, Japan;*
[2]*Department of Clinical Neuroscience, Tokushima University, Tokushima, Tokushima, Japan;*
[3]*Department of Neurosurgery, Kawasaki Medical School, Kurashiki, Okayama, Japan;*
[4]*Department of Neurosurgery, Tokushima Red Cross Hospital, Tokushima, Tokushima, Japan;*

Abstract

As the safety and effectiveness of urgent carotid artery stenting (CAS) for neurologically progressing patients remain controversial, we retrospectively analyzed the outcome of urgent CAS based on the patients' pathophysiological condition and neuroimaging findings. We divided 71 patients who underwent CAS within 14 days of stroke onset into two groups. Group 1 (n = 35) was comprised of patients with progressing neurologic signs and a reversible ischemic penumbra on magnetic resonance images (MRI). They were treated by urgent CAS. Group 2 (n = 36) was neurologically stable and underwent prophylactic CAS. In all patients we recorded the National Institutes of Health Stroke Scale (NIHSS) score and the modified Rankin scale (mRS). Urgent CAS resulted in significant improvement in the NIHSS score, when compared before and after CAS in group 1 (5.3 ± 4.3, P < 0.01). The rate of good outcomes (mRS 0-2 at 3 months post-CAS) was 48.6% in group 1, and 75% in group 2. The cumulative incidence of ipsilateral stroke between 31 days and 1 year was 5.9% in group 1, and 0% in group 2. The procedural complication rate was similar in both groups (group 1: 5.7%, n = 2; group 2: 5.6%, n = 2). No patient suffered a symptomatic intracerebral hemorrhage. When the pathophysiological status and neuroimaging findings are used to determine patient eligibility for urgent CAS, this treatment improve neurologic outcome and can be performed as safely as prophylactic CAS in our cohort of patients with acute ischemic stroke.

Key words: urgent carotid artery stenting, acute ischemic stroke

Introduction

Approximately, 30% of patients with symptomatic moderate to severe carotid artery stenosis suffered neurological deterioration within 2 weeks of stroke onset; in most, it occurred within the first 2 days.[1,2] While some meta-analysis claimed that the greatest benefit is obtained when carotid endarterectomy (CEA) is performed within 2 weeks of a stable transient ischemic attack (TIA) or minor stroke, patients with progressing neurologic signs were excluded in those study.[3,4] The optimal timing for urgent revascularization in patients with neurologically progressing and unstable internal carotid artery (ICA) stenosis remains controversial.

Patients with evolving stroke are at higher operative risk from urgent CEA than patients with stable symptoms,[5–7] The incidence of perioperative stroke or death was significantly higher in patients undergoing urgent than non-urgent CEA (14% vs 4%).[8] Although the higher operative risk of urgent CEA, early revascularization in the severe ICA stenosis

Received September 13, 2016; Accepted January 19, 2017

*Three first authors equally contributed to this manuscript.

has the potential to prevent clinical deterioration and improve the symptoms of progressing stroke. This may also apply to carotid artery stenting (CAS). From the stand point view of early restoration of the cerebral blood flow, urgent CAS might be the best option for emergency revascularization. Their pathophysiological status, e.g. the severity of neurological findings, their systemic condition, hemodynamic insufficiency, carotid plaque vulnerability, and antiplatelet count, dictates the appropriate timing of CAS in neurologically progressing patients.

We retrospectively evaluated the feasibility, effectiveness, and safety of urgent CAS in patients with neurologically progressing ICA stenosis who underwent CAS within 14 days of stroke onset. We divided our 71 patients into two groups based on their neurological status and neuroradiological findings and assessed their treatment outcomes.

Materials and Methods

Patients

Between January 2008 and April 2014, 393 consecutive patients with cervical carotid artery stenosis underwent CAS or CEA at our three stroke centers; 162 were symptomatic and treated by CAS. Of these, 71 who presented with acute ischemic stroke and underwent CAS within 14 days of stroke onset were reviewed. The patients who underwent both thrombectomy and urgent CAS for internal carotid artery occlusion (ICO) or tandem occlusion were excluded from our cohort study. Use of carotid stents in patients with ischemic stroke was approved by the Ethics Committees of the participating institutions, and patient or proxy informed consent was obtained before initiation of the procedure.

Inclusion criteria

We divided the 71 symptomatic carotid artery stenosis patients into two groups based on their preoperative pathophysiological status and neuroimaging findings. Group 1 (n = 35) patients underwent urgent CAS within 14 days after stroke onset. Their neurological symptoms were moderate to serious at the time of admission or mild but worsened despite aggressive medical therapy, indicating that progressing stroke or evolution to stroke was underway. Urgent CAS was performed immediately after admission or neurologically worsened point. Group 1 consisted of neurologically progressing and unstable patients in whom a diffusion-weighted imaging (DWI)/perfusion-weighted imaging (PWI) mismatch and a DWI/clinical mismatch (National Institutes of Health Stroke Scale (NIHSS) ≥ 6 and DWI-Alberta Stroke Programme Early CT Score (ASPECTS) ≥ 6) was observed on magnetic imaging (MRI) studies. Patients with crescendo TIA (n = 2) were also included in group 1. In group 2 (n = 36) we performed prophylactic CAS 48 hr to 14 days post-onset. These patients were neurologically stable and treated medically. At our institutions CEA is the first-line choice in neurologically stable patients without high-risk factors for CEA that identified by SAPPHIRE trial.[9] The treatment in group 2 patients was mainly based on inclusion criteria of SAPPHIRE trial[9] or their wishes. However in this study, all the patients suffered from progressing stroke or evolution to stroke have been treated with urgent CAS.

Treatment protocol. The treatment of patients in our stroke database was based on their clinical presentation and imaging findings. Unless contraindicated, MRI is our first-line diagnostic tool in stroke patients. Their neurological and systemic status is assessed and plaque imaging studies are performed after admission. CAS was performed in patients without hemorrhagic transformation, defined as the new appearance of low-intensity lesions on follow-up T_2^*-weighted images. Patients were initially treated by infusion- and antiplatelet therapy (75 mg clopidgrel and 200 mg aspirin). We administered 300 mg clopidgrel and 300 mg aspirin as a loading dose to patients underwent urgent CAS within 48 hr after onset; the others received 75 mg clopidgrel and 200 mg aspirin per day before surgery.

Stent placement

All procedures were performed by an experienced neurointerventionist using a biplane angiography system. First, the femoral artery was punctured under local anesthesia and a femoral sheath was placed. Heparin was administered and the activated clotting time was maintained at more than 250 sec. In all patients with internal carotid artery stenosis, an embolic protection device (Filter Wire EZ, Spider, Percusurge, Protégé) was introduced; in most instances we performed pre- and post-dilation. A self-expandable stent (Precise, Carotid Wallstent) was advanced to cover the stenosis. The devices were chosen by the surgeon. After CAS, dual antiplatelet therapy was continued for at least a month; single antiplatelet treatment was administered during the follow-up period.

Assessments

All patients were assessed clinically at the time of admission and immediately before- and 7 days after surgery using the NIHSS score. Neurological improvement was defined as a 4-point improvement in the NIHSS score. Treatment outcomes were assessed in-hospital or by a telephone interview conducted

3 months and 1 year post-CAS and recorded based on the mRS. The incidence of ipsilateral stroke was assessed within 31 days to 1 year after the procedure.

Statistics

Analysis was performed using SPSS. Categorical variables were compared using the Fisher exact test, continuous variables were compared using analysis of variance and expressed as the mean ± standard deviation (SD). Differences of $P < 0.05$ were considered statistically significant.

Results

CAS for symptomatic ICA stenosis was performed within 14 days after onset in 71 patients; 35 (49.3%) were assigned to group 1 and 36 (50.7%) to group 2. Their demographic and clinical data are shown in Table 1.

In group 1 patients, 14.3% underwent the intravenous infusion of recombinant tissue plasminogen activator. Their mean NIHSS score at the time of admission was statistically higher (5.1 ± 3.9, median 4, range 0–12) than group 2 (3.2 ± 3.2, median 3, range 0–12) ($P < 0.05$). The mean number of days from the first attack to CAS in group 1 was statistically shorter (3.4 ± 4.3) than in group 2 (7.4 ± 3.3) ($P < 0.001$). The clinical outcomes in all patient groups are shown in Table 2.

Stent insertion was successful in all 71 patients; procedural complications were encountered in 4 (5.6%). They included cerebral infarction ($n = 1$ in group 1), 3 patients suffered central retinal artery occlusion ($n = 1$ in group 1, $n = 2$ in group 2). There was no significant difference in the rate of procedural complications among the two groups. No patient developed a symptomatic intracerebral hemorrhage. The mean NIHSS score of all patients before treatment and 7 days post-CAS was 6.6 ± 5.6 (median 6, range 0–26) and 3.3 ± 3.8 (median 4, range 0–18), respectively. In-hospital neurological improvement (improvement of more than four points in the NIHSS score) was observed in 21 of 35 group 1- (60.0%) and 6 of 36 group 2 patients (16.7%). The NIHSS score recorded at 7 days post-CAS was significantly improved compared to immediately before-CAS in group 1 (5.2 ± 4.3, $P < 0.01$) (Fig. 1).

The rate of good outcomes (mRS 0-2 at 3 months post-CAS) was 48.6% in group 1 and 75% in group 2. Two of our 71 patients died (2.3%) within 1 year after treatment; one group 2 patient had carcinomatous peritonitis and the other, a group 1 patient, had esophageal carcinoma. The incidence of ipsilateral stroke within 31days to 1year was 5.9% in group 1 and 0% in group 2.

Discussion

According to Bond et al.,[7] the risk for stroke and death was the same in patients with stable symptoms who underwent early (< 3–6 weeks) or late

Table 1 Patient demographics and clinical data

	Overall	Group 1 Urgent CAS	Group 2 Prophylactic CAS	*P* value
No of patients	$n = 71$	$n = 35$	$n = 36$	
Age (years)	75.2 ± 9.9	74.2 ± 12.8	76.4 ± 5.8	0.205
Sex (males)	60 (85.7%)	31 (88.6%)	30 (83.3%)	0.250
Laterality (right)	35 (49.3%)	14 (40.0%)	21 (58.3%)	0.096
Hypertension	43 (60.6%)	18 (51.4%)	25 (69.4%)	0.088
Diabetes mellitus	17 (23.9%)	8 (22.9%)	9 (25.0%)	0.392
Coronary artery disease	21 (29.6%)	8 (22.9%)	13 (36.1%)	0.098
iv rt-PA	5 (7.0%)	5 (14.3%)	0 (0%)	< 0.01
NIHSS at admission	4.2 ± 3.7	5.1 ± 3.9	3.2 ± 3.2	< 0.05
NIHSS before treatment	6.6 ± 5.6	9.9 ± 5.7	3.3 ± 3.3	< 0.001
NIHSS at 7 days after treatment	3.3 ± 3.8	4.6 ± 4.7	2.0 ± 2.1	< 0.05
Number of days from first attack to CAS	5.5 ± 4.3	3.4 ± 4.3	7.4 ± 3.3	< 0.001

CAS: carotid artery stenting, iv rt-PA: intravenous recombinant tissue plasminogen activator, NIHSS: National Institutes of Health Stroke Scale (score).

Table 2 Clinical outcomes

	Overall	Group 1 Urgent CAS	Group 2 Prophylactic CAS
No of patients	*n* = 71	*n* = 35	*n* = 36
Procedural success rate (%)	100	100	100
Procedural complication, *n* (%)	4 (5.6)	2 (5.7)	2 (5.6)
sICH	0 (0)	0 (0)	0 (0)
mRS 0-2, *n* (%)	44 (60.2)	17 (48.6)	27 (75)
Mortality within 1 year, *n* (%)	2 (2.8)	1 (2.9)	1 (2.8)
Ipsilateral stroke within 31 days to 1 year, *n* (%)	2 (2.8)	2 (5.9)	0 (0)

mRS: modified Rankin scale, sICH: symptomatic intracranial hemorrhage.

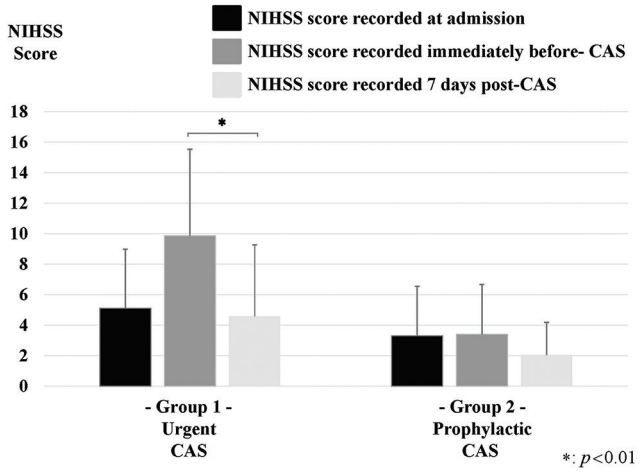

Fig. 1 NIHSS scores recorded at the time of admission and immediately before- and 7 days after CAS.*Statistically significant ($P < 0.01$). CAS, carotid artery stenting; NIHSS, National Institutes of Health Stroke Scale.

(> 3–6 weeks) CEA although urgent CEA in patients with evolving symptoms carried a much higher risk. Others[5,6] suggested that the risk was high in patients with unstable symptoms treated by urgent CEA and Brandl et al.[10] found that their risk was similar to that of patients with stable symptoms. The number of patients in those studies was too small to draw conclusions about the efficacy and safety of urgent CEA.

Shahdi et al.[11] reported that urgent aggressive, best medical therapy may reduce the risk of early recurrent stroke in patients awaiting CEA. They suggested that its higher procedural risks may argue against urgent revascularization surgery soon after symptom onset and recommended delaying surgery. Nevertheless, despite best medical therapy, we have encountered rapid neurological deterioration in patients with acute symptomatic ICA stenosis and in that subpopulation, urgent revascularization may be the best treatment option.

The optimal timing of urgent CAS in patients with neurologically progressing and unstable ICA stenosis also remains controversial. Wach et al.[12] reported that the risk of CAS performed within 2 days of the insult is not greater than when the procedure is carried out up to 90 days later. Jonsson et al.[13] found that urgent CAS did not increase the peri-procedural risk. Nonetheless, CAS may be unsafe in patients with evolving symptoms who are suspected of harboring fragile carotid plaques. At our institutions, the procedural complication rate was not different between urgent and prophylactic CAS group.

Urgent CAS was performed in patients of group 1 with neurologically progressing and unstable symptoms whose MRI studies revealed a DWI/PWI- and a DWI/clinical mismatch. Urgent CAS was performed not only to prevent recurrent stroke but also to obtain neurological improvement. Some studies have reported efficacy of urgent CAS of ICA occlusion or high-grade stenosis in acute stroke.[14–19] But most of the studies involved only the patients with ICA occlusion. Imai et al. reported 17 patients with ICA occlusion (n = 4) or high-grade stenosis (n = 13) underwent urgent CAS. Urgent CAS resulted in significant improvement in the NIHSS score, when compared before and after urgent CAS (median NIHSS scores before urgent CAS and at 7 days were 12 and 5).[14] In our study, of the 35 group 1 patients, 21 (60.0%) improved by ≥ 4 NIHSS points during hospitalization. Urgent CAS returned the neurological status to the pre-degradation state in patients with evolving stroke (Fig. 1). However, despite marked neurological improvement and the low complication rate, more than half of patients in group 1 showed moderate disability (modified Raskin scale (mRS) ≥ 3) after three months. We attribute the poorer

outcomes in that group to the greater severity of their neurological symptoms. As for prevention of recurrent stroke, annual rate of ipsilateral stroke in group 1 (5.9%) and group 2 (0%) was acceptable when compared to recent study.[9]

Urgent CAS should be considered in patients with crescendo TIAs and in patients who are neurologically unstable or fluctuating because they may rapidly progress to complete stroke and deteriorating neurological symptoms. Urgent CAS can be expected to improve fluctuating conditions by increasing the cerebral blood flow and by covering vulnerable carotid plaques with a stent.

The neurological symptoms were mild and stable in our group 2 patients. Medical therapy effectively prevented early recurrent stroke and urgent revascularization was not required. According to Brott et al.[20] the perioperative stroke rate in patients with symptomatic ICA stenosis was higher for CAS than CEA, and the perioperative myocardial infarction rate was higher for CEA than CAS. In patients with symptomatic ICA stenosis, CEA is our first-line treatment except in emergency situations; patients with high-risk factors for CEA that identified by SAPPHIRE trial[9] are subjected to CAS. Although the majority of our group 2 patients had risk factors for CEA, prophylactic CAS was safely performed and their prognosis was good.

Some of the concerns about antiplatelet medication exist in urgent CAS. Insufficient efficacy of antiplatelet medication may cause acute stent thrombosis. Antiplatelet-related symptomatic intracranial hemorrhage may result in a further deterioration of neurological status after revascularization. The incidence rate of symptomatic intracranial hemorrhage was from 0% to 18% in other studies on acute CAS.[12,14,16–19] No patients suffered symptomatic intracranial hemorrhage in our urgent CAS group. Bazan et al.[21] reported that thrombolysis followed by urgent CAS was not associated with an increased risk of symptomatic intracranial hemorrhage in select patients with minor to moderate ischemic stroke. Most of our group 1 patients manifested moderate to serious neurological symptoms; MRI studies showed a DWI/PWI- and a DWI/clinical mismatch without hemorrhagic transformation, defined as low-intensity lesions on T_2^*-weighted images. Evaluation of the extension of the ischemic lesion and of tissue at risk of hemorrhage on MRI scans, including diffusion-, perfusion-, and T_2^*-weighted images, is important for avoiding post-procedural hemorrhagic complications. Strict blood pressure control in the intensive stroke care unit may also help to avoid symptomatic intracranial hemorrhage.

Conclusion

We retrospectively analyzed 71 patients who underwent CAS within 14 days after stroke onset and assessed their treatment outcomes and procedural complications from the standpoint of not only the time elapsed since onset but also their pathophysiological status. Our findings indicate that urgent CAS is effective and safe in carefully selected patients with neurologically progressing symptoms and unstable ICA stenosis. The rate of procedural complications was not higher in patients with unstable- than in those with stable symptoms. Careful patient selection and preoperative MRI studies contributed to our relatively low complication rate.

Our study has some limitations. It was retrospective and the number of patients was small, we did not include a group exposed to conservative treatment, and our study lacked a core lab control for the imaging evaluations. Further evaluation of this treatment strategy is underway.

Conflicts of Interest Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this article. All authors have registered online Self-reported COI Disclosure Statement Forms through the website for The Japan Neurosurgical Society members.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

References

1) Ois A, Cuadrado-Godia E, Rodríguez-Campello A, Jimenez-Conde J, Roquer J: High risk of early neurological recurrence in symptomatic carotid stenosis. *Stroke* 40: 2727–2731, 2009
2) Fairhead JF, Mehta Z, Rothwell PM: Population-based study of delays in carotid imaging and surgery and the risk of recurrent stroke. *Neurology* 65: 371–375, 2005
3) Rothwell PM, Eliasziw M, Gutnikov SA, Fox AJ, Taylor DW, Mayberg MR, Warlow CP, Barnett HJ: Carotid Endarterectomy Traialists' Collaboration: Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. *Lancet* 361: 107–116, 2003
4) Rothwell PM, Eliasziw M, Gutnikov SA, Warlow CP, Barnett HJ; Carotid Endarterectomy Trialists Collaboration: Endarterectomy for symptomatic

carotid stenosis in relation to clinical subgroups and timing of surgery. *Lancet* 363: 915–924, 2004
5) Golledge J, Cuming R, Beattie DK, Davies AH, Greenhalgh RM: Influence of patient-related variables on the outcome of carotid endarterectomy. *J Vasc Surg* 24: 120–126, 1996
6) Rigdon EE: Racial and gender differences in outcome after carotid endarterectomy. *Am Surg* 64: 530–532, 1998
7) Bond R, Rerkasem K, Rothwell PM: Systematic review of the risks of carotid endarterectomy in relation to the clinical indication for and timing of surgery. *Stroke* 34: 2290–2301, 2003
8) Rerkasem K, Rothwell PM: Systematic review of the operative risks of carotid endarterectomy for recently symptomatic stenosis in relation to the timing of surgery. *Stroke* 40: e564–e572, 2009
9) Yadav JS, Wholey MH, Kuntz RE, Fayad P, Katzen BT, Mishkel GJ, Bajwa TK, Whitlow P, Strickman NE, Jaff MR, Popma JJ, Snead DB, Cutlip DE, Firth BG, Ouriel K: Protected carotid-artery stenting versus endarterectomy in high-risk patients. *N Engl J Med* 351: 1493–1501, 2004
10) Brandl R, Brauer RB, Maurer PC: Urgent carotid endarterectomy for stroke in evolution. *Vasa* 30: 115–121, 2001
11) Shahidi S, Owen-Falkenberg A, Gottschalksen B, Ellemann K: Risk of early recurrent stroke in symptomatic carotid stenosis after best medical therapy and before endarterectomy. *Int J Stroke* 11: 41–51, 2016
12) Wach MM, Dumont TM, Mokin M, Kass-Hout T, Snyder KV, Hopkins LN, Levy EI, Siddiqui AH: Early carotid angioplasty and stenting may offer noninferior treatment for symptomatic cases of carotid artery stenosis. *J Neurointerv Surg* 6: 276–280, 2014
13) Jonsson M, Gillgren P, Wanhainen A, Acosta S, Lindström D: Peri-procedural tisk with urgent carotid artery stenting: A population based Swedvasc study. *Eur J Endovasc Surg* 49: 506–512, 2015
14) Imai K, Mori T, Izumoto H, Watanabe M, Majima K: Emergency carotid artery stent placement in patients with acute ischemic stroke. *AJNR Am J Neuroradiol* 26: 1249–1258, 2005
15) Zaidat OO, Alexander MJ, Suarez JI, Tarr RW, Selman WR, Enterline DS, Smith TP: Early Carotid Artery Stenting and Angioplasty in Patients with Acute Ischemic Stroke. *Neurosurgery* 1237–1243, 2004
16) Papanagiotou P, Roth C, Walter S, Behnke S, Grunwald IQ, Viera J, Politi M, Körner H, Kostopoulos P, Haass A, Fassbender K, Reith W: Carotid artery stenting in acute stroke. *J Am Coll Cardiol* 58: 2363–2369, 2011
17) Jovin TG, Gupta R, Uchino K, Jungreis CA, Wechsler LR, Hammer MD, Tayal A, Horowitz MB: Emergent stenting of extracranial internal carotid artery occlusion in acute stroke has a high revascularization rate. *Stroke* 36: 2426–2430, 2005
18) Hauck EF, Natarajan SK, Ohta H, Ogilvy CS, Hopkins LN, Siddiqui AH, Levy EI: Emergent endovascular recanalization for cervical internal carotid artery occlusion in patients presenting with acute stroke. *Neurosurgery* 69: 899–907, 2011
19) Miyamoto N, Naito I, Takatama S, Shimizu T, Iwai T, Shimaguchi H: Urgent stenting for patients with acute stroke due to atherosclerotic occlusive lesions of the cervical internal carotid artery. *Neurol Med Chir* (*Tokyo*) 48: 49–55, 2008
20) Brott TG, Hobson RW, Howard G, Roubin GS, Clark WM, Brooks W, Mackey A, Hill MD, Leimgruber PP, Sheffet AJ, Howard VJ, Moore WS, Voeks JH, Hopkins LN, Cutlip DE, Cohen DJ, Popma JJ, Freguson RD, Cohen SN, Blackshear JL, Silver FL, Mohr JP, Lal BK, Meschia JF; CREST Investigators: Stenting versus endarterectomy for treatment of carotid-artery stenosis. *N Engl J Med* 363: 11–23, 2010
21) Bazan HA, Zea N, Jennings B, Smith TA, Vidal G, Sternbergh WC: Urgent carotid intervention is safe after thrombolysis for minor to moderate acute ischemic stroke. *J Vasc Surg* 62: 1529–1538, 2015

Address reprint requests to: Junichiro Satomi, MD, PhD, Department of Neurosurgery, Tokushima University, 3-18-15 Kuramoto-cho, Tokushima, Tokushima 770-8503, Japan.
e-mail: junichirosatomi@gmail.com