High Age Could Influence Large Thrombus Aspiration Catheter Advancement over the Carotid Siphon

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Objective: A direct aspiration technique using a 5MAX ACE catheter (Penumbra, Alameda, CA, USA) has been reported. However, recanalization has not been achieved in all cases with this technique alone. Additionally, Japan has a rapidly aging society, and differences in the condition of vessels, because of aging, can limit the approach of revascularization devices to the thrombus. We evaluated the accessibility of the 5MAX ACE (0.060-inch inner diameter) over the clinoid segment of the internal carotid artery (ICA).

Methods: We conducted a retrospective and cross-sectional study of 28 patients who received intraarterial treatment for acute ischemic stroke between October 2014 and October 2016. We recorded the maximum distal arrival point of the distal edge of the 5MAX ACE during the procedure before the stent retriever was retrieved.

Results: In 5 of the 28 patients, the distal edge of the 5MAX ACE catheter did not advance over the clinoid segment of the ICA. The mean age of patients for whom the 5MAX ACE catheter failed to advance over the clinoid segment of the ICA was significantly higher (non-advancement: 85 ± 3 years) than that of patients with advancement (76 ± 9 years, Mann–Whitney U-test: P = 0.04).

Conclusion: Advanced age may limit successful revascularization using only a direct aspiration technique with the 5MAX ACE without a stent or balloon anchoring technique for lesions at the terminal portion of the ICA and more distal arteries, which suggests that different devices or approaches may be needed for clot removal.

Keywords ▶ 5MAX ACE, high-aged population, accessibility, clinoid segment of the internal carotid artery

Introduction

Intravenous recombinant tissue-type plasminogen activator (rt-PA) is recommended for eligible patients and significantly improves the overall odds of a good stroke outcome when delivered within 4.5 hours of stroke onset.1,2) However, intravenous rt-PA has limitations.3) Christou et al.3) reported that after receiving intravenous rt-PA, 67% of middle cerebral artery (MCA) occlusions, 25% of basilar artery (BA) occlusions, and all internal carotid artery (ICA) occlusions were not completely recanalized. To overcome the limitations of rt-PA and obtain better outcomes, further interventions have been considered. In patients with acute ischemic stroke caused by proximal intracranial occlusion of the anterior circulation, intraarterial treatment administered within 6 hours after stroke onset was found to be effective and safe.4)

The development of new revascularization devices has improved recanalization rates and time. Thrombectomy with a stent retriever improved the functional outcomes.5) A direct aspiration first pass technique (ADAPT) with a large bore aspiration catheter as the first approach for thrombectomy has been reported.6) The largest caliber aspiration catheter that the vessel could accommodate was selected for each case, usually a 5MAX (0.054-inch inner diameter; Penumbra, Alameda, CA, USA) or 5MAX ACE.
(0.060-inch inner diameter; Penumbra), for distal ICA, proximal MCA, and BA occlusions. The large bore aspiration catheter is placed at the face of the thrombus, and aspiration is carried out.7) The utility of the combined aspiration and stent retrieval technique for thrombectomy has also been reported.8–10)

In the ADAPT FAST study, large bore aspiration catheters easily navigated in the intracranial circulation through a guide catheter (Neuron 088; Penumbra, Oakland, CA, USA). Successful revascularization by aspiration technique alone was achieved in 78% of cases.7) However, delivering the large aspiration catheter to the target vessel and advancement through the ophthalmic segment of the ICA may present as a challenge,11,12) especially with very acute angle.13) Delayed angiographic reperfusion decreased likelihood of good clinical outcome.14) Rapid recanalization could be achieved only if the device could be quickly navigated to the occluded vessel. When too much forward force is used to deliver the catheter, the parent vessel is at risk for injury, and the catheter may be damaged.15) To overcome the difficulty of delivering the large aspiration catheter over the carotid siphon, the utility of the “grappling hook” technique using the Merci retriever system16) and stent retriever17) as an anchoring system was reported. We considered that if it is difficult to deliver the large aspiration catheter to the target vessel and to aspirate the clot, quick transition to other techniques may be needed to achieve fast and safe recanalization.

It is also not possible to achieve successful revascularization anytime using a stent retriever alone. There are patients who were needed aspiration technique with a large bore aspiration catheter. In the contact aspiration vs Stent Retriever for Successful Revascularization (ASTER) study, successful revascularization was achieved in 67.7% of the patients after first-line stent retriever thrombectomy alone. Therefore, rescue treatment, which included contact aspiration, combined contact aspiration and stent retriever, and angioplasty, was performed in 23.8% of the patients after stent retriever thrombectomy in the first-line stent retriever group.15)

Advanced age is associated with complex anatomical risk factors including internal carotid tortuosity18) and difficult catheter access to the target carotid artery during endovascular treatment for acute ischemic stroke.17) Japan has a rapidly aging society. In a report involving consecutive patients with stroke treated with rt-PA in 10 Japanese stroke centers, the age of patients was 72 ± 12 years,18) which was higher than that of the large studies that provided evidence on endovascular therapy for acute ischemic stroke. The mean age of the patients was 65.0 ± 12.5 years in the stent retriever plus intravenous rt-PA group of Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke (SWIFT PRIME);9) 65.7 ± 11.3 years in the thrombectomy group of the Randomized Trial of Revascularization With Solitaire FR Device versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting within Eight Hours of Symptom Onset (REVASCAT) trial,19) 66.3 years in the ADAPT FAST study,7) and 68.6 ± 12.3 years in the endovascular therapy group of Extending the Time for Thrombolysis in Emergency Neurological Deficits – Intra-Arterial (EXTEND-IA).20) The median age was 65.8 years in the intervention group of the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) and 71 years in the intervention arm of the Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times (ESCAPE) trial.21)

If the predictive factors that make it difficult to recanalize with aspiration using 5MAX ACE alone are identified, the other devices and treatments could be selected promptly to achieve fast and safe recanalization. Therefore, to assess the association between successful 5MAX ACE catheter advancement over the carotid siphon and various patient characteristics, the present study evaluated the results of intracranial treatment of acute ischemic stroke.

Materials and Methods

In Japan, the 5MAX ACE catheter became available for use for intracranial vessels in October 2014. We retrospectively collected data from the medical records of patients with acute ischemic stroke caused by a proximal intracranial arterial occlusion and who received intraarterial treatment at the Fukuoka University Chikushi Hospital and Tanushimaru Central Hospital between October 2014 and October 2016. As this study’s design was retrospective and cross-sectional, the treatments, including the procedure, were not performed as part of this study, but as part of patient management. This study was approved by the ethics committee of the Fukuoka University Medical Ethics Review Board (FU-MERB) (Permission number: R16-053) and carried out according to the guidelines of the committee. This study was also approved by the ethics committee.
committee of the Tanushimaru Central Hospital (Permission number: 2017-1) and carried out according to the guidelines of the committee.

The endovascular approach consisted of aspiration or stent retrieval alone or a combination of revascularization devices. The selection of the device and approach was based on the discretion of each doctor. To evaluate the ability of the 5MAX ACE catheter advancement, we included the patients for whom the 5MAX ACE (0.060-inch inner diameter) was used for intracranial anterior circulation lesions.

During the procedure, a guide catheter was advanced distally as far as possible into the cervical or proximal petrous ICA. The 5MAX ACE catheter was advanced usually coaxially over a 0.014-inch guidewire and Marksman microcatheter (ev3, Irvine, CA, USA) or other obturating catheters, such as 3MAX (Penumbra) or Trevo Pro 18 Microcatheter (Stryker, Kalamazoo, MI, USA). We advanced the inner catheter of the 5MAX ACE through the thrombus. We advanced the 5MAX ACE as distally as possible and/or tried to directly aspirate the thrombus. If the 5MAX ACE could not achieve adequate revascularization or to reach the thrombus, we used techniques combined with other revascularization devices. We applied aspiration through the distal aspiration catheter and/or proximal flow arrest using a balloon-guided catheter for protection against new embolisms. We did not use the balloon-inflation anchoring technique or change the inner catheter to 3MAX during the procedure for more distal advancement of the 5MAX ACE.

To assess the efficacy of 5MAX ACE, we recorded the maximum distal arrival point of the distal edge of the 5MAX ACE during the procedure before the stent retriever was retrieved. Because the stent could be used as an anchoring system for distal advancement of the microcatheter, the 5MAX ACE moved distally when the stent retriever was pulled. We evaluated the ability of the 5MAX ACE to advance over the carotid siphon without a stent anchoring technique by checking whether the distal edge of the 5MAX ACE could advance over the clinoid segment of the ICA.

Study definitions and evaluation techniques
The medical records were dependent on patient self-reporting, but the final records were left to the discretion of physician after a review of the patients’ self-reports and in-hospital examination results.

Angiography of the anteroposterior and lateral projections was routinely performed during the procedure to evaluate intracranial blood flow. We assessed cavernous ICA (cICA) tortuosity using the classification written by Lin et al. The open configurations/angles of the genus are defined as type I. The closed configuration of the anterior genu is defined as type II. Type II has more acute angle of the genu than type I. The buckled appearance at the posterior deflection of the posterior genu is defined as type III. The posterior genu is buckled superiorly than the anterior genu like a shape of the Simmons-type catheter defined as type IV. The type I, types II–III, and type IV are classified with mild, moderate, and severe tortuosity.

These assessments of tortuosity were assessed by personnel who were blinded to information regarding the treatment. Revascularization was measured using the modified thrombolysis in cerebral infarction (mTICI) score as recommended by the cerebral angiographic revascularization grading collaborators. Successful revascularization was defined as an mTICI score ≥2b post-treatment. The procedure time was defined as the time from groin access to at least mTICI 2b revascularization.

Statistical analysis
The Mann–Whitney U-test was used to determine significant differences in age, and procedure time. Fisher’s exact test was used to assess all other parameters. In this study, the cICA tortuosity was divided into two groups, minimal group or moderate to severe group. The data are presented as the mean ± standard deviation. Statistical significance was accepted if the probability level was less than 0.05. All statistical tests were two-tailed.

Results
Figure 1 shows the study flow chart. We retrospectively enrolled 57 patients (58 cases) who underwent endovascular procedures for acute ischemic stroke during the 25-month period. We excluded 30 cases from this study, including 3 cases treated at the ICA origin alone, 9 cases treated at the posterior circulation, 1 case for whom 5MAX instead of 5MAX ACE was used, and 17 cases treated using other revascularization devices (e.g., stent retriever) without 5MAX ACE. Thus, we finally evaluated 28 patients (28 cases, 12 men and 16 women). The age of the study group was 78 ± 9 years (mean ± standard deviation, median: 79, range: 60–94). In these 28 patients, occlusion of the terminal portion of the ICA and/or MCA (M1 or M2) was detected during the procedure.

In 8 of the 28 patients, a stiff-type guidewire and/or Simmons-type coaxial catheter was needed to deploy the
more distal artery in all patients. Successful revascularization occurred in three of the five patients. None of these three patients achieved successful revascularization by only the direct aspiration technique using the SMAX ACE. These three cases achieved successful revascularization using a combined technique with other revascularization devices. During the procedure, three of the five patients were evaluated collateral circulation flow before the revascularization procedure. The length of the procedure was 92 ± 36 minutes.

We compared several indices between the groups in which the SMAX ACE did not advance over the clinoid segment of the ICA (five cases) and the rest of the patient population (23 cases). The mean age of patients for whom the SMAX ACE did not advance over the clinoid segment was significantly higher (advancement over the clinoid segment group: 76 ± 9 years, no advancement group: 85 ± 3 years, Mann–Whitney U-test: P = 0.04). There were no statistically significant differences between these groups regarding other parameters (Table 1). Additionally, the mean age of patients that required the stiff-type guidewire and/or Simmons-type coaxial catheter was 84 ± 8 years, whereas the mean age for those who did not need these devices was 75 ± 8 years. There was a statistically significant difference between both groups (Mann–Whitney U-test; P = 0.02).

**Representative cases**

**Case 1: A 70-year-old man (Fig. 2)**

The patient lived at home without assistance. He experienced sudden right hemiparesis and aphasia and was diagnosed with cerebral infarction, which was treated with intravenous rt-PA and endovascular therapy. The angle between the aortic arch to the left common carotid artery (CCA) was not acute and it was easy to deploy the guide catheter at the ICA. DSA showed MCA occlusion and the
### Table 1  Comparison of patients according to 5MAX ACE advancement over the clinoid segment

<table>
<thead>
<tr>
<th></th>
<th>Advancement over clinoid segment</th>
<th>No advancement</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>23</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Gender (men), n (%)</td>
<td>10 (43)</td>
<td>2 (40)</td>
<td>1</td>
</tr>
<tr>
<td>Age (y), n ± SD</td>
<td>76 ± 9</td>
<td>85 ± 3</td>
<td>0.04*</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>8 (35)</td>
<td>3 (60)</td>
<td>0.3</td>
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<tr>
<td>Diabetes mellitus, n (%)</td>
<td>2 (9)</td>
<td>0 (0)</td>
<td>1</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>4 (17)</td>
<td>1 (20)</td>
<td>1</td>
</tr>
<tr>
<td>History of ischemic stroke event, n (%)</td>
<td>4 (17)</td>
<td>1 (20)</td>
<td>1</td>
</tr>
<tr>
<td>Right side lesion, n (%)</td>
<td>13 (57)</td>
<td>2 (40)</td>
<td>0.6</td>
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<td>cICA tortuosity classification, n (%)</td>
<td></td>
<td></td>
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<tr>
<td>Minimal</td>
<td>16 (70)</td>
<td>3 (60)</td>
<td>0.6</td>
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<tr>
<td>Moderate-severe</td>
<td>7 (30)</td>
<td>2 (40)</td>
<td>0.3</td>
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<td>ICA occlusion, n (%)</td>
<td>11 (48)</td>
<td>2 (40)</td>
<td>1</td>
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<tr>
<td>M2 occlusion, n (%)</td>
<td>3 (13)</td>
<td>1 (20)</td>
<td>1</td>
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<td>Balloon guide catheter, n (%)</td>
<td>15 (65)</td>
<td>2 (40)</td>
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<td>Stiff guidewire or Simmonds coaxial catheter used, n (%)</td>
<td>5 (22)</td>
<td>3 (60)</td>
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<tr>
<td>Inner catheter was 3MAX, n (%)</td>
<td>1 (4)</td>
<td>0 (0)</td>
<td>1</td>
</tr>
<tr>
<td>Inner catheter was Marksman, n (%)</td>
<td>21 (91)</td>
<td>5 (100)</td>
<td>1</td>
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<tr>
<td>Inner catheter advancement, n (%)</td>
<td></td>
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<td></td>
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<tr>
<td>M1</td>
<td>2 (9)</td>
<td>0 (0)</td>
<td>0.6</td>
</tr>
<tr>
<td>M2 or more distal artery</td>
<td>21 (91)</td>
<td>5 (100)</td>
<td>1</td>
</tr>
<tr>
<td>Successful revascularization rate (mTICI 2b-3) n (%)</td>
<td>17 (74)</td>
<td>3 (60)</td>
<td>0.3</td>
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<tr>
<td>Procedure time (min.) n ± SD</td>
<td>78 ± 35</td>
<td>92 ± 36</td>
<td>0.3</td>
</tr>
</tbody>
</table>

The Mann–Whitney U-test was used to determine significant differences for age and procedure time; Fisher’s exact test was used for assessing all other parameters. *P < 0.05 indicates statistical significance. cICA: cavernous internal carotid artery; ICA: internal carotid artery; mTICI: modified thrombolysis in cerebral infarction; SD: standard deviation

### Fig. 2  Case 1. (A) MRA at the aortic arch to the ICA. (B) DSA (anteroposterior view) showing occlusion of the MCA. (C) DSA (left anterior oblique view) showing the deployment of the distal edge of the 5MAX ACE (arrow) at the MCA. (D) DSA (anteroposterior view) showing revascularization of the MCA after aspiration of the clot using 5MAX ACE. (E) DSA (lateral view) showing type I cavernous ICA. ICA: internal carotid artery; MCA: middle cerebral artery
5MAX ACE was advanced to the thrombus in the MCA with Marksman microcatheter as the inner catheter. MCA revascularization was achieved after aspiration of the clot using 5MAX ACE. The cICA tortuosity was type I. The patient’s symptoms were mild, and he was discharged home without assistance.

Case 2: A 90-year-old woman (Fig. 3)
The patient lived at home without assistance. She experienced sudden right hemiparesis and aphasia and was diagnosed with cerebral infarction. She underwent intravenous rt-PA and endovascular therapy. The angle between the aortic arch and the left CCA was found to be acute. It was difficult to deploy the guide catheter at the ICA using a normal guidewire, so a stiff-type guidewire was used instead. DSA showed occlusion of the MCA. We used 5MAX ACE with Marksman microcatheter as the inner catheter. The 5MAX ACE could not advance further over the clinoid segment of the ICA. The guide catheter could not maintain its position and was forcibly moved proximally when the 5MAX ACE was advanced beyond this point. MCA revascularization was achieved using a stent retriever. The cICA tortuosity was type III. The patient’s symptoms were mild, and she was discharged home without assistance.

Discussion

In this study, we evaluated the accessibility of 5MAX ACE catheter over the carotid siphon. The results of this study indicate that the mean age of patients for whom the 5MAX ACE did not advance over carotid siphon was significantly higher than that of patients for whom advancement occurred.

The mean age of patients in the present study was 78 ± 9 years and was higher than that in previous studies that reported the effectiveness of intraarterial treatment for acute ischemic stroke. The mean or median age of patients in previously published large studies that provided evidence on endovascular therapy for acute ischemic stroke ranged from 65 to 71 years.4,5,7,19–21 The exact reason for the higher mean age of patients in the 5MAX ACE no-advancement
group is unknown. Age-associated changes occur in the arterial system over time and aging is associated with structural and functional changes in the arterial wall.\(^\text{27}\) Aging may influence the ability of the 5MAX ACE to advance over the carotid siphon.

In cases where the 5MAX ACE did not advance over the carotid siphon, when we attempted to advance it beyond this point, the resistance was high, the guide catheter could not maintain its position, and it was forcibly moved proximally. These results suggest that the stability of the guide catheter is important for distal advancement of the 5MAX ACE. The anatomy of the aortic arch and cervical artery may influence the stability of the guide catheter. The patients \(\geq 80\) years had an increased incidence of complex anatomic risk factors, which include arch calcification, common carotid/innominate stenosis, common carotid tortuosity, and internal carotid tortuosity, compared to younger patients.\(^\text{16}\) An age \(>75\) years was a predictor of difficult catheter access to the target carotid artery in acute stroke patients.\(^\text{17}\) In the present study, we did not routinely obtain and evaluate the images between the aortic arch and cervical segment of the ICA for the endovascular treatment in all patients because of the time limitation for the treatment of ischemic stroke. We could not obtain the postoperative angiographic evaluation for the vascular angle and vessel diameter in all patients. However, when a stiff-type guidewire and/or Simmons-type coaxial catheter was used, it was difficult to deploy the guide catheter to the target vessel via the usual method. This suggested the tortuosity of the aortic arch and carotid artery. The stiff guidewire was useful for overcoming the tortuous vessels for the treatment of intracranial lesions.\(^\text{28}\) In this study, the age of patients requiring the stiff-type guidewire and/or Simmons-type coaxial catheter was higher than that of patients who did not need these instruments.

There was a trend, but no statistically significant relationship between 5MAX ACE advancement over carotid siphon and the need for the stiff-type guidewire and/or Simmons-type coaxial catheter. In this study, the stiff-type guidewire and/or Simmons-type coaxial catheter was used in only 8 out of the 28 patients. A small number of cases may influence the statistical power. We will continue our evaluation with the larger number of cases whether the need for the stiff-type guidewire and/or Simmons-type coaxial catheter could influence the accessibility of the 5MAX ACE catheter over the carotid siphon.

With regard to the tortuosity of the carotid siphon and endovascular treatment, the classification of cICA tortuosity correlated strongly with markers of the pipeline embolization device (Covidien Vascular Therapies, Mansfield, MA, USA) procedural complexity.\(^\text{25}\) The acuteness of the carotid siphon angle influences the interference between two microcatheters for the jailing technique using the Neuroform EZ stent (Stryker).\(^\text{29}\) In the treatment of acute ischemic stroke, the tortuous ophthalmic segment of ICA could restrict the accessibility of the large caliber aspiration catheters and make it necessary to apply adjunctive techniques.\(^\text{13}\) In this study, the cICA tortuosity did not significantly influence the results. However, severe or Simmons-type (type IV) cICA tortuosity was found in only one patient and the 5MAX ACE did not advance over the clinoid segment in this patient. The present study involved a small number of cases. A statistically significant difference may be detected if the number of cases increases.

### Limitations

One of the limitations of this study is the retrospective and cross-sectional design. Moreover, it involved a small number of cases, and it is possible that the statistical power of the study was insufficient. The subjective view of each doctor may have been reflected in device selection, and this selection bias may have affected the study results.

We did not use the balloon-inflation anchoring technique to advance the 5MAX ACE. The inner catheter could be navigated to the peripheral artery with severe vessel tortuosity by dilating/anchoring a balloon of the balloon-guided catheter.\(^\text{30}\) This technique could advance the 5MAX ACE more distally. The large aspiration catheter required a coaxial catheter for delivery to MCA.\(^\text{12}\) In the present study, a Marksman microcatheter was used in most cases instead of a 3MAX as the inner catheter of 5MAX ACE. 3MAX is commonly used to support catheterization with the ACE/ACE 64 reperfusion catheters.\(^\text{31}\) Although the utility of the coaxial technique with a 0.021-inch microcatheter (Prowler select plus; Cordis, Miami, FL, USA) with a large bore catheter has been reported,\(^\text{11}\) the 3MAX as the inner catheter could advance the 5MAX ACE more distally than the Marksman microcatheter. Recently, the utility of combined treatment with a balloon-guided catheter, a large bore aspiration catheter for distal aspiration, and a stent retriever has been reported.\(^\text{10}\) The utility of the Penumbra ACE and 3MAX reperfusion system for M2 and M3 occlusions in acute ischemic stroke has also been reported.\(^\text{13}\) In the present study, we evaluated the ability of the 5MAX ACE to advance over the
carotid siphon without a stent anchoring technique. The usefulness of a stent anchoring technique with a distal aspiration catheter to overcome the tortuous anatomy has been reported. We will continue our investigation with anchoring techniques and 3MAX.

In this study, we evaluated relatively few anatomical parameters. For example, we did not evaluate the calcification of intracranial ICA by CT because the imaging conditions were not consistent in our two institutions. Although the calcification on the intracranial carotid artery does not have an impact on reperfusion or clinical outcomes in acute ischemic stroke undergoing endovascular therapy, analyzing further anatomical parameters may find the factors related to better catheter selections. Because of these limitations, a prospective, randomized trial with a larger patient population focused on better catheter selections is needed.

## Conclusion

Increased age may limit revascularization only by a direct aspiration technique by 5MAX ACE without anchoring techniques for lesions at the terminal portion of the ICA and more distal artery and suggest the use of different devices or approaches for clot removal. We will seek a more appropriate approach for elderly patients and assess the new generation devices, including ACE 68 (Penumbra).

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## Disclosure Statement

There is no conflict of interest for the first author and coauthors.

## References


