

# Revascularization of acute stent thrombosis after carotid artery stenting in a *CYP2C19*\*2 heterozygote patient

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## Abstract

Carotid artery stenting (CAS) is an alternative strategy to carotid endarterectomy for the prevention of ischemic stroke. Acute carotid stent thrombosis (ACST) is an extremely rare but devastating complication of CAS. Although cases of successful recanalization have been reported, there is still a lack of experience regarding the choice of ACST treatment methods and the timing of such treatments, especially when patients are confirmed *CYP2C19*\*2 heterozygotes. Here, we report a case of successful revascularization after ACST in a patient with *CYP2C19*\*2 heterozygosity. We also review the literature and discuss appropriate treatment strategies for this devastating and rare event.

## Keywords

Carotid artery stenting, acute carotid stent thrombosis, thrombus aspiration, *CYP2C19*, ischemic stroke, recanalization

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## Introduction

Carotid artery stenting (CAS) is an alternative strategy to carotid endarterectomy for the prevention of primary or secondary ischemic stroke in selected patients.<sup>1</sup> Acute carotid stent thrombosis (ACST) is an extremely rare event, with an incidence

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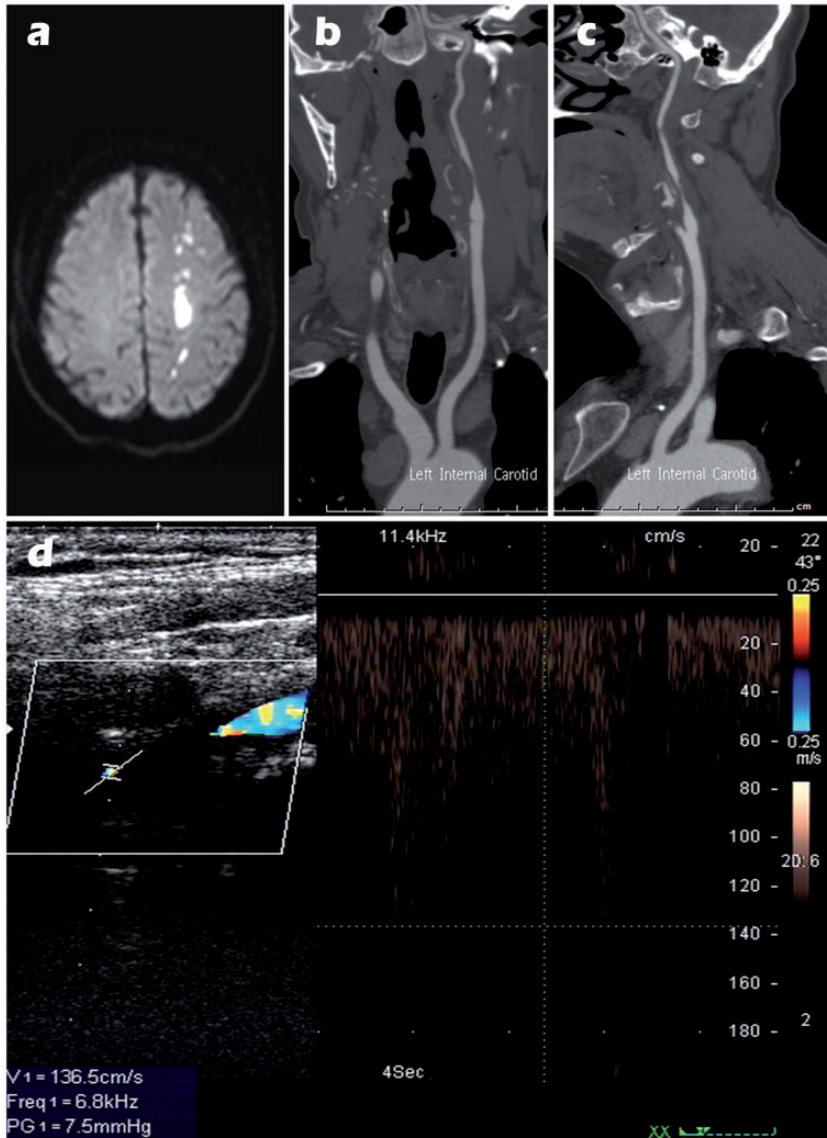
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rate of 0.5% to 0.8%,<sup>2</sup> but it is accompanied by devastating complications.<sup>2</sup> Although cases of successful recanalization have been reported,<sup>3,4</sup> there is still a lack of

experience regarding the choice and timing of ACST treatment methods. Here, we report the successful revascularization of ACST in a patient with *CYP2C19\*2*



**Figure 1.** Preoperative examination of the patient. (a) Magnetic resonance imaging showed multiple internal border zone infarcts in a rosary-like pattern along the left centrum semiovale. (b, c) Computed tomography angiography showed severe stenosis at the beginning of the left internal carotid artery (LICA). (d) Doppler ultrasonography showed the formation of atherosclerotic plaque in the LICA, and that blood flow velocity was accelerated in the lumen

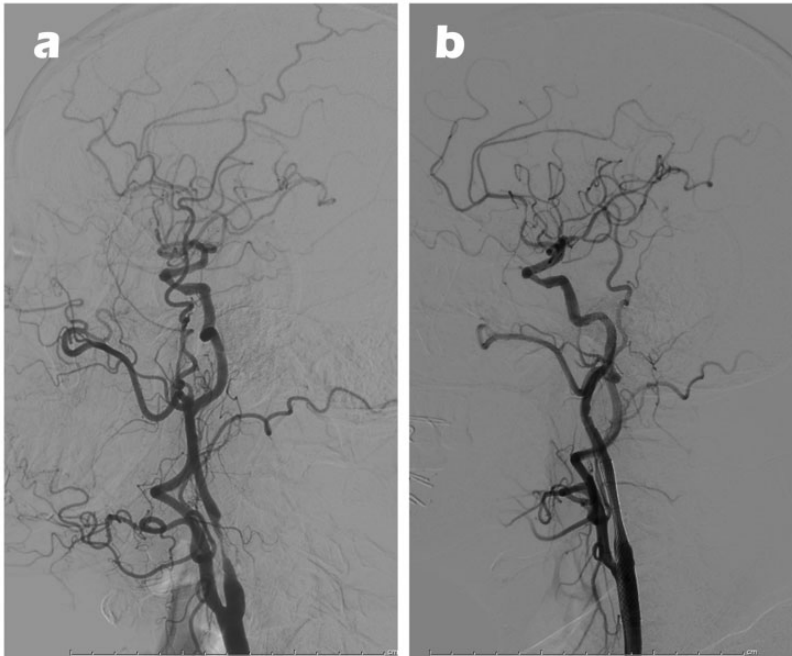
heterozygosity that was confirmed by genetic testing. We also review the literature and discuss appropriate treatment strategies for this rare event.

## Case report

The study protocol was approved by the Ethics Committees of the Fifth People's Hospital of Chengdu, and the patient provided written consent to the publication of this report.

A 69-year-old man was admitted to the Fifth People's Hospital of Chengdu (Chengdu, China) because of right limb weakness, right central facial paralysis, and hemianalgesia for 2 days. The right limb weakness was aggravated and barylalia was detected for half a day. The patient had a 4-year history of hypertension caused

by poor blood pressure control. After hospitalization, magnetic resonance imaging showed multiple infarcts in the internal border zone, in a rosary-like pattern along the left centrum semiovale. Computed tomography (CT) angiography revealed severe stenosis at the beginning of the left internal carotid artery (Figure 1). In addition, transcranial Doppler (TCD) showed increased blood flow in the middle cerebral artery. The patient's platelet count was  $107 \times 10^9/L$  and his coagulation function was normal. Multi-disciplinary consultation occurred, including experts in cardiology, respiratory medicine, neurosurgery, and anesthesiology. On the basis of the patient's poor lung function, anesthesiologists indicated that the risk of general anesthesia was relatively high, and left carotid stenting was suggested rather than



**Figure 2.** Angiography before and after carotid artery stenting. (a) Angiography revealed 90% stenosis in the left carotid artery according to the North American Symptomatic Carotid Endarterectomy Trial criteria. (b) Carotid artery stenting was performed without any complications, and stenosis of the left internal carotid artery was fully resolved.

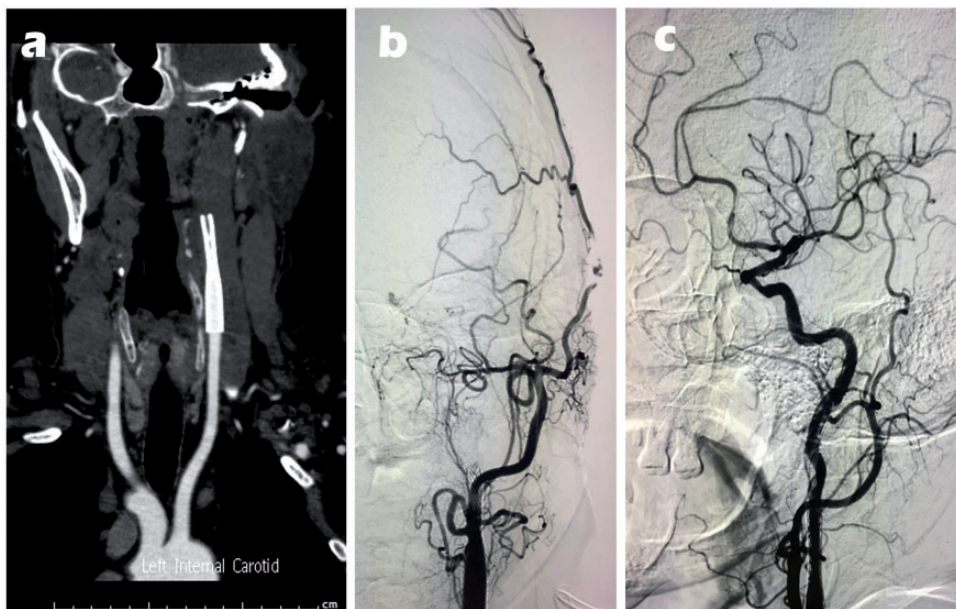
endarterectomy for secondary prevention. Before the surgery, the patient was administered aspirin (100 mg), clopidogrel (75 mg), and atorvastatin (20 mg) for 5 days. The patient's National Institute of Health Stroke Scale (NIHSS) score was 5.

The CAS was performed under local anesthesia. Heparin was administered intravenously at a dose of 5000 U (100 U/kg) bolus immediately after the femoral artery puncture. Angiography revealed 90% stenosis in the left carotid artery using the North American Symptomatic Carotid Endarterectomy Trial criteria. First, we positioned a distal protection device (SpiderFX; eV3 Inc., Plymouth, MN, USA) to prevent emboli. Next, the stenosis of the left internal carotid artery was predilated with a 5- × 30-mm balloon (Viatrac 14 Plus; Abbott Vascular, Temecula, CA, USA). Finally, a 7- × 40-mm

self-expandable carotid stent (Wallstent; Boston Scientific, Marlborough, MA, USA) was placed using a 0.36-mm guide-wire and an 8F guide catheter (Boston Scientific). The CAS was performed without any complications (Figure 2), and the patient did not show any symptoms during the CAS procedure.

After the surgery, the patient continued to take aspirin (100 mg), clopidogrel (75 mg), and atorvastatin (20 mg). Five days after the surgery, the patient became lethargic, with gaze to the left side, motor aphasia, and right hemiplegia; the patient's NIHSS score was 18. Thirty minutes later, CT angiography showed acute stent thrombosis of the left internal carotid artery (Figure 3).

We immediately performed thrombus aspiration via the right percutaneous trans-femoral access under local anesthesia.



**Figure 3.** Acute carotid stent thrombosis removal in the patient. (a) At 5 days after surgery, computed tomography angiography showed acute stent thrombosis of the left internal carotid artery. (b) Angiography confirmed acute stent thrombosis of the left internal carotid artery, however, there was no blood flow at the distal end of the stent. (c) Thrombus aspiration was performed on the patient with acute carotid stent thrombosis.



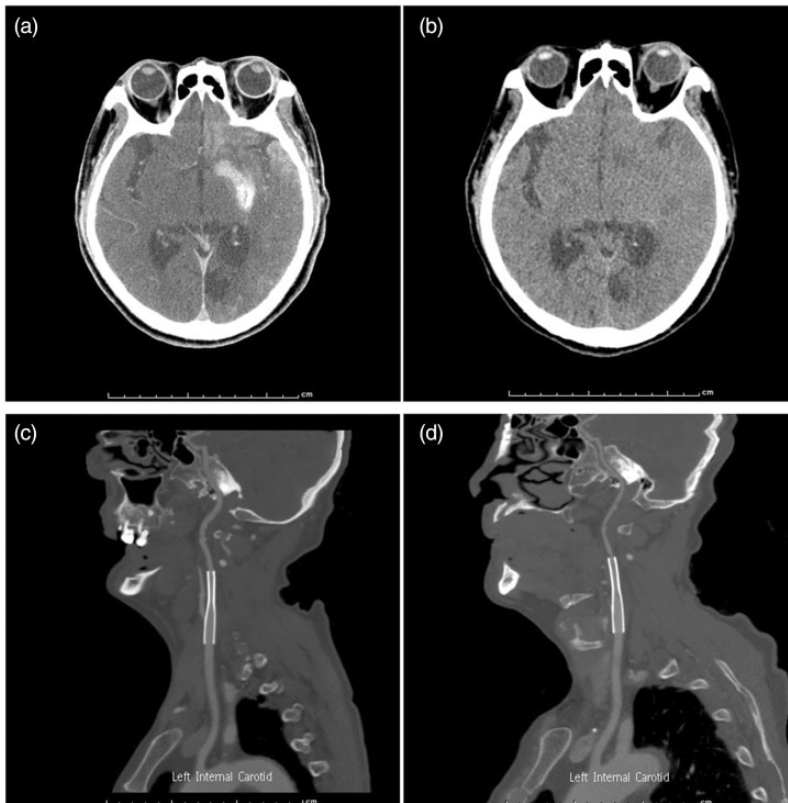
*CYP2C19* genotype were received. The patient was a *CYP2C19\*2* heterozygote (*CYP2C19\*1/\*2*). The patient was discharged from hospital taking aspirin, clopidogrel (triple dose), and atorvastatin. After 6 months of follow-up, the patient's NIHSS score was 3 and his modified Rankin scale score was 1. Furthermore, there was no in-stent restenosis observed in the CT angiography at that time (Figure 5).

## Discussion

It has been reported that the incidence of in-stent restenosis after CAS ranges from 3% to 16.6%, and that the majority of

patients are asymptomatic.<sup>5</sup> ACST is extremely rare, but has devastating complications, and occurs within 30 days after CAS.<sup>2</sup> We reviewed articles related to ACST that were published in English, and have listed their details in Table 1.<sup>4,6-25</sup>

There are several causes of ACST, such as inadequate antiplatelet therapy, early discontinuation of antiplatelet therapy, clopidogrel resistance, a hypercoagulable state, soft plaque and its protrusion, local vessel dissection, vasospasm, and intimal injury.<sup>18,25,26</sup> A number of reasons, including the cause of CAS (e.g., stent underexpansion, in which the stent does not fully adhere to the blood vessel,<sup>25</sup> or balloon



**Figure 5.** Radiographic changes in the patient after thrombus aspiration. (a) Postoperative computed tomography (CT) showed contrast agent leakage. (b, c) At 2 days after thrombus aspiration, the CT angiography showed complete recanalization of the stent, and most of the contrast agent had been absorbed. (d) There was no stent restenosis in CT angiography at the 6-month follow-up.

**Table 1.** Acute stent thrombosis after carotid artery stenting.

Author/year	Journal	Sex/age	Stenosis position/grade	Preprocedural drugs	Onset	Cause of ACST	S/A	Treatment	Outcome
Tong et al. <sup>6</sup> /2000	American Journal of Neuroradiology	44/M	LICA/70%	NM	Procedure	NM	A	Abciximab IV bolus	Good prognosis
Chaturvedi et al. <sup>7</sup> /2001	Stroke	63/F	LICA/severe	Aspirin	12 hours	NM	S	750,000 U urokinase	Death
Hamann et al. <sup>8</sup> /2002	European Neurology	57/M	LICA/severe	No	3 days	NM	S	Aspirin	Death
		76/M	RICA/70%	Aspirin and heparin	4 days	Medications ceased by mistake	S	70 mg rt-PA and heparin	Good recovery
Owens et al. <sup>9</sup> /2002	Annals of Vascular Surgery	65/M	LICA/70%	NM	Procedure	NM	S	Thrombolysis and standard endarterectomy	Motor deficits
Bush et al. <sup>10</sup> /2003	Journal of Endovascular Therapy	68/M	RICA/>90%	Clopidogrel, aspirin, and antibiotics	Within 15 minutes	NM	S	Mechanical thrombectomy and intravenous abciximab	Good recovery
Steiner-Boker et al. <sup>11</sup> /2004	American Journal of Neuroradiology	64/F	RICA/85%	Aspirin and clopidogrel	Procedure	Maybe hypercoagulable state	S	Intracarotid injection of 5 mg rt-PA and a half-dose bolus of abciximab (0.125 mg/kg) via the intracarotid guiding catheter	Good recovery
Setacci et al. <sup>11</sup> /2005	Journal of Vascular Surgery	82/M	LICA/80%	Aspirin and clopidogrel/ticlopidine	2 days	NM	S	Surgical removal of the stent and carotid thromboendarterectomy	Good recovery
		78/M	LICA/85%	Aspirin and clopidogrel/ticlopidine	4 days	Discontinuation of anti-platelet therapy	S	Surgical removal of the stent and carotid thromboendarterectomy	Disability
		72/M	LICA/80%	Aspirin and clopidogrel/ticlopidine	2 hours	Cardiac multiple embolism	S	Thrombectomy	Good recovery
Masuo et al. <sup>12</sup> /2006	Neurologia Medico-Chirurgica	71/M	LICA/severe	Aspirin, ticlopidine, and systemic heparinization	3 days	NM	S	Percutaneous transluminal angioplasty	Mild right hemiparesis
Buhk et al. <sup>13</sup> /2006	Neurology	78/M	LICA/80%	NM	3 weeks	Discontinuation of anti-platelet therapy	S	Antiplatelet and heparin therapy was restarted	Minor hemiparesis and slight aphasia remained
Seo et al. <sup>14</sup> /2008	Yonsei Medical Journal	63/M	LICA/85%	Aspirin and clopidogrel	Procedure	NM	A	Intravenous tirofiban	Good recovery
Iancu et al. <sup>15</sup> /2010	Cardiovascular Revascularization Medicine	65/M	LICA/80%	NM	Procedure	Carotid dissection following stent post-dilation	S	Bolus of streptokinase	Good recovery
		70/M	RICA/80%	NM	Procedure	Balloon burst	S	Tenecteplase	Good recovery

(continued)

Table 1. Continued.

Author/year	Journal	Sex/age	Stenosis position/grade	Preprocedural drugs	Onset	Cause of ACST	S/A	Treatment	Outcome
Dhall et al. <sup>16</sup> /2010	Journal of Invasive Cardiology	62/M	LICA/90%	Aspirin and clopidogrel	Procedure	Unclear	S	Urokinase, abciximab, thrombolysis was performed using the guiding sheath	Good recovery
Choi et al. <sup>17</sup> /2012	Journal of Korean Neurosurgical Society	69/M	RICA/83%	NM	9 days	NM	S	STA-MCA anastomosis	Left hemiparesis and dysarthria remained
		68/M	LICA/72%	NM	4 days	Aspirin and clopidogrel resistance	S	Intravenous tissue plasminogen activator, intra-arterial thrombolysis, STA-MCA anastomosis	Right hemiparesis remained
Kanemaru et al. <sup>18</sup> /2013	Journal of Endovascular Therapy	77/M	RICA/>90%	Aspirin, clopidogrel and cilostazol	6 days	Hypercoagulable state	A	Aspirin, clopidogrel, cilostazol, argatroban, and warfarin	Good recovery
Markakis et al. <sup>19</sup> /2012	Vascular	67/M	LICA/95%	Clopidogrel	2 days	Discontinuation of dual antiplatelet therapy by accident	S	Heparin, carotid endarterectomy, stent removal, thrombectomy	Minor numbness of three fingers of his right hand
Kim et al. <sup>20</sup> /2013	Acta Neurochirurgica	75/M	LICA/90%	Aspirin and clopidogrel	Procedure	Embolic protection device thrombosis	S	Mechanical thrombectomy	Good recovery
		73/M	NM	Aspirin and clopidogrel	Procedure	Embolic protection device thrombosis	A	Mechanical thrombectomy	Good recovery
		51/M	NM	Aspirin and clopidogrel	Procedure	Embolic protection device thrombosis	S	Mechanical thrombectomy	Good recovery
Munich et al. <sup>21</sup> /2014	Journal of Neurointerventional Surgery	NM	LICA/95%	Aspirin and clopidogrel	Procedure	Embolic protection device thrombosis	NM	Intra-arterial injection of 10 mg verapamil and 10 mg abciximab; thrombus aspiration	Complete recanalization
Köklü et al. <sup>22</sup> /2015	Cardiovascular and Interventional Radiology	73/M	LICA/95%	Aspirin	24 hours	Dual antiplatelet resistance	S	Unfractionated heparin, ticlopidine 250 mg bid	Paresis
Moulakakis et al. <sup>23</sup> /2017	Annals of Vascular Surgery	67/M	RICA/90%	Aspirin and clopidogrel	1 hour	Dissection from filter caused by significant coiling (360°) of the distal ICA	S	Endovascular thrombus aspiration and subsequent surgical exploration, explanation	Mild residual arm paresis
		74/M	LICA/80%	Nadroparin calcium	2 hours	Hypercoagulable state	S	Intrathrombus urokinase administration and stenting	Residual arm paresis

(continued)



Table 1. Continued.

Author/year	Journal	Sex/age	Stenosis position/grade	Preprocedural drugs	Onset	Cause of ACST	S/A	Treatment	Outcome
		73/F	LCCA/80%	Aspirin and clopidogrel	3 days	Two overlapping stents, malignancy	S	Tinzaparin therapeutic dose	Residual arm paresis
		66/M	LICA/70–80%	Aspirin and clopidogrel	4 days	Two overlapping stents, previous cerebral thrombectomy	S	Aspirin, clopidogrel, and nadroparin	Mild speech impairment
Moulakakis et al. <sup>24/</sup> 2018	Annals of Vascular Surgery	66/M	RICA/90%	Aspirin	Procedure	Plaque protrusion across the stent	S	Stent removal and carotid endarterectomy	Good recovery
		72/M	RICA/severe	NM	1 hour	NM	S	Intra-arterial catheter-directed thrombolysis and 2 ml of Actilyse, stent removal, and carotid endarterectomy	Good recovery
Hu et al. <sup>25/</sup> 2018	Interventional Neurology	79/M	LICA/almost complete occlusion	Aspirin and clopidogrel	Procedure	Stent did not fully adhere to the blood vessel	A	rt-PA through the micro-catheter; redilatation of the stent	Good recovery

A, asymptomatic; ACST, acute carotid stent thrombosis; F, female; ICA, internal carotid artery; LCCA, left common carotid artery; LICA, left internal carotid artery; M, male; NM, not mentioned; RICA, right internal carotid artery; rt-PA, recombinant tissue plasminogen activator; S, symptomatic; STA-MCA, superficial temporal artery-middle cerebral artery.

burst<sup>15</sup>), plaque protrusion,<sup>4</sup> and vaso-spasm, may lead to immediate ACST. These can be resolved in a timely manner without any damage to the nervous system. In contrast, other reasons, such as inadequate antiplatelet therapy,<sup>7,8,12</sup> early discontinuation of antiplatelet therapy,<sup>11</sup> clopidogrel resistance, and a hypercoagulable state,<sup>18</sup> may cause ACST a few days after a CAS procedure. This may eventually cause death or severe paralysis.<sup>7</sup>

In our patient, it may be that more than one factor caused ACST. After being affected by ACST, we tested the *CYP2C19* status of our patient, which was *CYP2C19\*1/\*2*. This is one of the genetic polymorphisms that cause clopidogrel resistance. Although not all patients who are *CYP2C19\*2* heterozygotes are low responders for clopidogrel, in the absence of a hypercoagulable state and because antiplatelet therapy was adequate in our patient, we speculate that clopidogrel resistance may have been one of the important causes of his ACST. Moreover, we did not perform post-dilation in this patient; thus, stent underexpansion may be another reason for his ACST.<sup>5</sup>

We performed thrombus aspiration immediately after the patient was affected by ACST. Because ACST is a rare complication, its optimal treatment remains unknown. The treatment of ACST should be based on a combination of thrombogenesis, time (intraoperative, early, or late after surgery), the severity of neurological deficits, and the area of the infarction. For cases with severe clinical deterioration, ACST treatment should be relatively positive, with a goal of rapid revascularization to avoid serious consequences.<sup>12</sup> The solution for ACST may be multiplex, including drugs,<sup>4,6,14</sup> thrombolysis,<sup>7,8,15,16,23</sup> thrombolytic therapy combined with anticoagulation or antiplatelet therapy,<sup>4</sup> and surgical therapy including thromboendarterectomy,<sup>11</sup> mechanical thrombolysis, and

thrombus aspiration.<sup>12,20</sup> The use of these two methods (thromboendarterectomy and endovascular treatment) flexibly has also been reported.<sup>24</sup>

Our patient was discharged from hospital when he was taking aspirin, clopidogrel (triple dose), and atorvastatin. Previous studies have reported that tripling the maintenance dose of clopidogrel, to 225 mg daily, in heterozygote carriers of *CYP2C19\*2* achieves levels of platelet reactivity similar to those seen with the standard 75 mg dose in noncarriers.<sup>27</sup> In addition, at the 6-month follow-up, there was no in-stent restenosis in CT angiography in our patient. This finding further supports the idea that a triple dose of clopidogrel is effective in *CYP2C19\*2* heterozygotes. Another option to consider may be the use of antiplatelets such as prasugrel and ticagrelor, which are less influenced by *CYP2C19*, rather than using a triple dose of clopidogrel.

## Conclusion

ACST is an extremely rare event, but it can be a fatal complication after CAS. In our patient, it may be that more than one factor caused ACST. The treatment of ACST after CAS must be undertaken immediately to restore blood flow and avoid major adverse neurological events. The present case report helps to illuminate the available treatment strategies, rather than providing general therapeutic recommendations.


## Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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**References**

1. Massop D, Dave R, Metzger C, et al. Stenting and angioplasty with protection in patients at high-risk for endarterectomy: SAPHIRE Worldwide Registry first 2,001 patients. *Catheter Cardiovasc Interv* 2009; 73: 129–136.
2. Moulakakis KG, Mylonas SN, Lazaris A, et al. Acute carotid stent thrombosis: a comprehensive review. *Vasc Endovascular Surg* 2016; 50: 511–521.
3. Arslan S. Reply to the letter: “acute carotid artery stent thrombosis”. *Cardiovasc Intervent Radiol* 2018; 41: 357.
4. Steiner-Boker S, Cejna M, Nasel C, et al. Successful revascularization of acute carotid stent thrombosis by facilitated thrombolysis. *AJNR Am J Neuroradiol* 2004; 25: 1411–1413.
5. Lal BK, Beach KW, Roubin GS, et al. Restenosis after carotid artery stenting and endarterectomy: a secondary analysis of CREST, a randomised controlled trial. *Lancet Neurol* 2012; 11: 755–763.
6. Tong FC, Cloft HJ, Joseph GJ, et al. Abciximab rescue in acute carotid stent thrombosis. *AJNR Am J Neuroradiol* 2000; 21: 1750–1752.
7. Chaturvedi S, Sohrab S and Tselis A. Carotid stent thrombosis: report of 2 fatal cases. *Stroke* 2001; 32: 2700–2702.
8. Hamann GF, Liebetrau M, Pfefferkorn T, et al. Successful systemic thrombolysis for carotid stent thrombosis. *Eur Neurol* 2002; 48: 37–39.
9. Owens EL, Kumins NH, Bergan JJ, et al. Surgical management of acute complications and critical restenosis following carotid artery stenting. *Ann Vasc Surg* 2002; 16: 168–175.
10. Bush RL, Bhama JK, Lin PH, et al. Transient ischemic attack due to early carotid stent thrombosis: successful rescue with rheolytic thrombectomy and systemic abciximab. *J Endovasc Ther* 2003; 10: 870–874.
11. Setacci C, De Donato G, Setacci F, et al. Surgical management of acute carotid thrombosis after carotid stenting: a report of three cases. *J Vasc Surg* 2005; 42: 993–996.
12. Masuo O, Terada T, Matsuda Y, et al. Successful recanalization by in-stent percutaneous transluminal angioplasty with distal protection for acute carotid stent thrombosis. *Neurol Med Chir (Tokyo)* 2006; 46: 495–499.
13. Buhk JH, Wellmer A and Knauth M. Late in-stent thrombosis following carotid angioplasty and stenting. *Neurology* 2006; 66: 1594–1596.
14. Seo KD, Lee KO, Kim DJ, et al. Rescue use of tirofiban for acute carotid in-stent thrombosis. *Yonsei Med J* 2008; 49: 163–166.
15. Iancu A, Grosz C and Lazar A. Acute carotid stent thrombosis: review of the literature and long-term follow-up. *Cardiovasc Revasc Med* 2010; 11: 110–113.
16. Moulakakis KG, Kakisis J, Tsvigoulis G, et al. Acute early carotid stent thrombosis: a case series. *Ann Vasc Surg* 2017; 45: 69–78.
17. Choi HJ, Kim ST, Jeong YG, et al. Superficial temporal artery-middle cerebral artery anastomosis for internal carotid artery occlusion by subacute in-stent thrombosis after carotid artery stenting. *J Korean Neurosurg Soc* 2012; 52: 551–554.
18. Kanemaru K, Nishiyama Y, Yoshioka H, et al. In-stent thrombosis after carotid artery stenting despite sufficient antiplatelet therapy in a bladder cancer patient. *J Stroke Cerebrovasc Dis* 2013; 22: 1196–1200.
19. Markatis F, Petrosyan A, Abdulamit T, et al. Acute carotid stent thrombosis: a case of surgical revascularization and review of treatment options. *Vascular* 2012; 20: 217–220.
20. Kim YW, Kang DH, Hwang JH, et al. Rescue strategy for acute carotid stent thrombosis during carotid stenting with distal filter protection using forced arterial suction thrombectomy with a reperfusion catheter of the Penumbra System: a technical note. *Acta Neurochir (Wien)* 2013; 155: 1583–1588.
21. Munich S, Moftakhar R and Lopes D. Recanalization of acute carotid stent

- occlusion using Penumbra 4Max aspiration catheter: technical report and review of rescue strategies for acute carotid stent occlusion. *J Neurointerv Surg* 2014; 6: e42.
22. Köklü E, Arslan S, Yüksel İÖ, et al. Acute carotid artery stent thrombosis due to dual antiplatelet resistance. *Cardiovasc Intervent Radiol* 2015; 38: 1011–1014.
  23. Dhall A, Malani SK and Chadha DS. Thrombosuction for procedural acute thrombosis during high-risk carotid angioplasty—a case report. *J Invasive Cardiol* 2010; 22: E144–E146.
  24. Moulakakis KG and Lazaris AM. Emergent carotid stent removal after carotid stent thrombosis. *Ann Vasc Surg* 2018; 46: 401–406.
  25. Hu W, Wang L and Wang G. Acute in-stent thrombosis after carotid angioplasty and stenting: a case report and literature review. *Interv Neurol* 2018; 7: 265–270.
  26. Okazaki T, Satomi J, Satoh K, et al. Rescue revascularization therapy with a stent-in-stent technique for acute intracranial internal carotid artery occlusion. *Neurol Med Chir (Tokyo)* 2005; 45: 253–258.
  27. Mega JL, Hochholzer W, Frelinger AL 3rd, et al. Dosing clopidogrel based on CYP2C19 genotype and the effect on platelet reactivity in patients with stable cardiovascular disease. *JAMA* 2011; 306: 2221–2228.