Abstract. – Background: Carotid artery stenting (CAS) is a reasonable alternative to carotid endarterectomy (CEA), especially in patients at high risk for surgery. Carotid artery thrombosis of the treated segment is a rare, early but potentially devastating complication of this endovascular procedure. The aim of this article is to identify and critically review cases of acute stent thrombosis reported in the literature.

Materials and Methods: Previous trials that compared CEA with CAS were rather heterogeneous and not large enough to allow reliable conclusions. Furthermore, because there is limited follow-up information to date, the long-term effect of CAS remains unclear. Acute carotid thrombosis after angioplasty and stenting is a very rare but potentially fatal complication, and there are very few reports in the literature. This article reviews twelve cases of acute carotid thrombosis published in the English literature from eight different Vascular and Radiology Departments around the world.

Results: The different ways of immediate treatment of this rare complication of acute carotid thrombosis after CAS are, open surgical procedure with thrombus removal and thromboendarterectomy with or without removing of the stent, selective local or facilitated thrombolysis with the rescue use of GPIs (glycoprotein IIb/IIIa receptor inhibitors), recanalization by instent percutaneous transluminal angioplasty with distal protection and additional stent placement on the stented portion of the internal carotid artery (ICA) in conjunction with the intravenous administration of recombinant tissue plasminogen activator (rtPA: 1300,000 IU).

Conclusion: Carotid artery stenting has to be performed under specific pro- and post procedure protocol from experienced endovascular specialists. The treatment of acute carotid thrombosis after CAS must be urgent and immediate in order to regain restoration of blood flow and avoid major neurological adverse events.

Key Words: Carotid artery stenting, Stent thrombosis, Acute in-stent thrombosis, Stroke.
Thromboembolic events are the most frequent complications of CAS. Carotid stent thrombosis can cause thromboembolic events, but fortunately, it is a very rare but potentially devastating complication\textsuperscript{6}. It has a major impact on immediate survival if the flow is not promptly re-established. Rapid invasive proper diagnosis and reperfusion should be done to limit cerebral ischemia.

**Materials and Methods**

Previous trials that compared CEA with CAS were rather heterogeneous and not large enough to allow reliable conclusions. Furthermore, because there is limited follow-up information to date, the long-term effect of CAS remains unclear. Acute carotid thrombosis after CAS is a very rare complication and there are very few articles to find in the literature. There are only a few published reports regarding this particular issue. In a relevant big series of CAS performed in 562 patients between December 2000 and March 2005 by Setacci et al\textsuperscript{7}, in Siena, Italy there are only three (3) cases of acute carotid artery thrombosis observed after the procedure.

There are two (2) cases reported from a series of 242 patients undergoing CAS during the last ten years by Iancu et al\textsuperscript{8} from the Heart Institute and Rehabilitation Clinic, University of Medicine in Romania, one (1) reported case of acute stent thrombosis during filter protected carotid stent placement from the Second Department of Medicine and the Department of Radiology University of Vienna Medical School by Sabine Steiner-Boeker et al\textsuperscript{9}, two (2) very interesting cases of symptomatic subacute in-stent thrombosis after carotid artery angioplasty and stenting from the Department of Neurosurgery, National Hakodate Hospital\textsuperscript{10} and the Department of Neurological Surgery, Wakayama Medical University\textsuperscript{11}, both from Japan and one periprocedural case of acute thrombosis from Yonsei University College of Medicine from Seoul in South Korea\textsuperscript{12}.

There are also two (2) fatal cases of carotid stent thrombosis reported from the Department of Neurology and Stroke Program, Wayne State University of Detroit in the USA. Neither of these two patients with angiographically confirmed carotid stent thrombosis (immediately and 3 days after the procedure) and subsequent fatal strokes was treated with combination antiplatelet therapy before or after CAS\textsuperscript{13}.

**Pre- and Post-Carotid Angioplasty and Stenting Protocol**

**Pre-procedure Evaluation**

There is almost a standard protocol followed in most of the Vascular Centres worldwide performing carotid artery stenting. At the beginning a neurologist examines the patient before the carotid artery angioplasty and stenting procedure to ascertain the neurologic function. Colour Doppler Ultrasound, brain scans by either computed tomography (CT) or magnetic resonance imaging (MRI) are also performed in all cases. The risk of neurological complications related to cerebral revascularization is the main concern in both surgical and endovascular procedures. To reduce the risk of neurological adverse events, a complete neurological evaluation by an experienced neurologist should be performed.

**Medications**

All patients undergoing a CAS procedure should receive antiplatelet therapy to reduce the risk of myocardial infarction (MI), stroke or any other vascular death. Patients treated electively receive clopidrogel (75 mg) plus aspirin (325 mg) or ticlodipine (500 mg) plus aspirin (100 mg) for at least three days before the procedure. Patients who do not undergo premedication and are not taking any long term antiplatelet therapy receive a 300 mg loading dose of clopidrogel before the operation. Those of the patients receiving coumarin anticoagulant therapy are converted immediately to an intravenous infusion of heparin (25000 IU/24h) associated with aspirin (100 mg) at least five days before the operation. During the procedure, weight-adjusted (70 IU/kg) heparin is administered to the patient and repeated as necessary to maintain an activated clotting time of >250 seconds throughout the intervention.

Within the first 24 hours after CAS, a carotid duplex ultrasound should be done and afterwards each patient is examined from the same protocol experienced neurologist. In the absence of any neurologic change or complication the patient is discharged on the first or second post-operation day.

To maintain stent patency, a specific post-procedure medical therapy should be administered to all patients. So, the dual antiplatelet regimen is continued after the stent implantation, but the ticlopidine or clopidrogel component is discontinued after one to two months. For those pa-
tients with previous anticoagulant therapy, they are converted to coumarin, which is continued in combination with aspirin until 30 days after the procedure. Combined antiplatelet therapy with clopidogrel and aspirin prescribed for 30 days after CAS is associated with a low rate of recurrent ischemic events and appears to be a reasonable strategy to avoid or decrease ischemic outcomes.\textsuperscript{14,15}

**Post-procedure Management and Follow-up**

Because of the dramatically increased number of patients undergoing CAS, the question of how these patients can radiographically best be followed-up should thus be addressed. Colour Duplex Ultrasound is the method of choice to evaluate the carotid artery after stent placement; it is a non-invasive, rapid and relatively inexpensive, but still remaining an operator-dependent technique. To date, digital subtraction angiography still represents the gold standard technique with highest accuracy. However, angiography of the carotid artery tends to be associated with a considerable risk of neurologic and arterial puncture site complications.\textsuperscript{16} Magnetic resonance (MR) angiography have shown promising results for the evaluation of carotid artery patency after stent deployment. MR angiography is hampered by considerable regional dephasing of the stented segment which, therefore, may prevent a reliable assessment of the stent lumen.\textsuperscript{17}

Three-dimensional computed tomography angiography (CTA) with volume-rendering is a third technique that can allow visualization of the arterial lumen through the stent.\textsuperscript{18} Carotid 3D CTA is a sensitive, noninvasive technique that is used to assess carotid artery stenosis which offers significant advantages over conventional angiography and MR angiography for monitoring patients with either residual or recurrent stenosis and intraluminal thrombus formation after CAS procedures. This technique might, therefore, be useful to evaluate the carotid artery after angioplasty with stenting and especially to detect a narrowing of the arterial lumen in the follow-up after CAS. A potential disadvantage of 3D CTA is the cumulative radiation dose. Therefore, the frequency of follow-up 3D CTA should be kept at a minimum.

During the follow-up period after CAS eccentric hypodense areas between the inner surface of a carotid stent and the perfused lumen could be detected at 2 weeks after CAS. These hypodense areas, presumably the thrombotic layer, decrease to undetectable levels for up to 12 weeks. During this period, acute stent occlusions have been described in the literature. Risk factors for in-stent thrombus formation following CAS included long stenotic lesions and patients with long stents deployed across the carotid bifurcation.

The finding that in-stent thrombus formation was predominant in the patients with long stents deployed across the carotid bifurcation and no in-stent hypodense area could be observed in patients with short stents (~2 cm) deployed only to the internal carotid artery. It may be due to the effect of increased turbulent flow on the dorsal surface of carotid artery at the level of carotid bifurcation in which the stent has been deployed across the orifice of external carotid artery.

**Presentation of 9 Published Cases**


A 78-years old man with transient ocular blindness in the left eye and severe stenosis of the left ICA of about 85% and total occlusion of the right internal carotid artery (ICA) successfully underwent CAS and was discharged two days after the operation with dual antiplatelet therapy. Four days later he returned with a severe neurologic deficit and decreased level of consciousness which had begun 4 hours earlier. Unfortunately he had stopped taking the antiplatelet therapy 2 days before. The duplex ultrasound showed complete stent thrombosis in the left ICA. Urgent surgical neck exploration under general anesthesia with stent removal and thromboendarterectomy with patch closure after shunt placement followed.

A 72-years old man with hypertension and chronic atrial fibrillation presented with hemodynamic right ICA (RICA) stenosis. Five days
before CAS procedure his anticoagulant therapy was converted from coumadin to heparin (25,000 IU/24 hours) plus aspirin. Two hours after CAS the patient had an acute stroke with complete left hemiplegia associated with acute ischemia of the right leg. The duplex ultrasound revealed complete carotid stent thrombosis and right femoropopliteal occlusion. Angiography confirmed that carotid thrombosis was limited to the intrastent segment. A cardiac multiple embolism was the cause of these ischemic complications. The carotid bifurcation was dissected through a right cervicotomy. After clamping, a transverse arteriotomy on the common carotid artery near the stent was performed and successful thrombectomy by careful aspiration was achieved. The entire clot was pulled out and an excellent run-off was achieved without needing to remove the stent. The left hemiplegia disappeared immediately and the patient was reconverted to coumadin therapy two days later and aspirin was continued for one month. A 64-years old woman with an asymptomatic calcified 90% stenosis of the right ICA and a concomitant contralateral 70% left ICA (LICA) stenosis. After the placement of the self-expandable stent with the presence of a distal embolic protection device, a control angiogram obtained immediately and showed complete occlusion of the right carotid artery within the stent and thrombotic masses surrounded by contrast medium. Periinterventional neurologic deficit consisted of mild left facial paresis and dysarthria. Intracarotid injection of 5 mg rtPA was followed by 5 mg recombinant tissue plasminogen activator (rtPA) intra-arterially via the inguinal sheath and a half-dose bolus of abciximab (0.125 mg/kg) via the intracarotid guiding catheter within 9 minutes. Additional heparin (3000 IU) was administered to raise the activated clotting time from <250 to 276 seconds during the prolonged procedure. Carotid recanalization with completely restored blood flow was achieved within 15 minutes of visible onset of acute stent thrombosis. After complete restoration of blood flow, the filter device was removed. Intravenous abciximab therapy was continued for 12 hours at standard dose. A 65-years old male diabetic patient with a recent TIA involving the right ICA was diagnosed with bilateral internal carotid stenosis (80% on the left and 90% on the right) and on admission underwent successful CAS on RICA. He returned 3 months later for angioplasty on the left internal carotid artery. The short lesion on the LICA was predilated. No protection device was available at that time. After implanting an 11-mm-long ID inflow stent crimped on an omnipass 4/15-mm balloon, a significant residual stenosis was present. Therefore, a postdilatation within the stent was performed. A control angiogram showed a large clot occluding the stent and a distal dissection. By that time, the patient complained of contralateral hemiplegia and became rapidly unconscious and hemodynamically unstable. The patient was immediately intubated and started on fluids and inotropic agents. He was given a bolus of 100,000 IU streptokinase in the thrombus. After clot dissolution, the vessel perfusion was regained and we gave an additional 50,000 IU bolus of streptokinase followed by 10,000 IU/h thereafter for 6 h through a catheter placed at the origin of the vessel. Complete clot dissolution was observed at the end of the procedure. He regained consciousness and ultrasound did not reveal any residual thrombosis or stenosis. The patient was discharged 3 days later without any neurological deficit. A 70-years old diabetic male was referred with stenosis at the origin of RICA, total occlusion of LICA, significant stenoses of both subclavian arteries and total occlusion of the right vertebral artery. A self-expandable carotid wall-stent was implanted. Six months later the Doppler US and angiography showed 70% in-stent restenosis. Under filter protection a dilatation with a 5 mm balloon was made. The post-procedure angiogram showed only a modest increase in luminal diameter. Five months later, the patient experienced a transient ischaemic attack (TIA) corresponding to the RICA. Doppler US revealed renewal of in-stent restenosis (ISR) which was confirmed with angiography. Because of the repeated restenosis, a 3.5×23 mm Yukon drug-eluting stent was decided to be implanted, under cerebral protection device. During stenting, the balloon bursted and a large clot formed at the RICA. The patient became unconscious and apneic. He was given a total dose of 15 mg of tenecteplase in the thrombus followed by reexpansion of the stent with a 4x20 mm balloon at 18 atm. The flow in the carotid artery was reestablished, and no thrombus was present on the last angiogram. The patient rapidly regained consciousness and recovered completely.
A 72-years old man with severe asymptomatic RICA stenosis received CAS with distal protection and gained 100% opening of the right carotid artery. The administration of dual antiplatelet therapy which had been given since two weeks before the procedure, was continued afterwards. On the seventh day after the stent placement, the patient showed sudden onset of left hemiparesis and conjugated deviation of both eyes to the right side and followed by falling into a comatose state. Emergency angiography showed near occlusion of the right carotid artery, suggesting subacute in-stent thrombosis. In conjunction with the intravenous administration of rtPA (1300,000 IU), it was performed additional stent placement on the stented portion of the ICA and gained full recanalization of the ICA about three hours after the onset of the symptoms. The patient showed rapid recovery and returned home with slight clumsiness of his right hand.

A 71-year-old male presented with severe LICA stenosis manifesting as repeated TIAs. Carotid artery stenting (CAS) under distal protection was performed to prevent further ischemic events. This procedure was uneventful. However, the patient exhibited progressive right hemiparesis and motor aphasia 3 days after CAS. Emergent angiography revealed carotid artery occlusion due to in-stent thrombosis. In-stent percutaneous transluminal angioplasty (PTA) was performed under distal protection. The carotid artery was recanalized with small residual thrombus. The neurological deficits almost completely disappeared after PTA. Carotid thrombosis after CAS can be resolved by in-stent PTA under distal protection and subsequent treatment with antithrombotic agents.

A 63-year-old male was admitted for management of known carotid artery stenosis (85% stenosis of the LCCA). A 4,000 unit heparin bolus was given pre-dilatation and 5000 units mixed to 1000 mL of normal saline was used for intra-procedure continuous infusion. After balloon predilatation of the stenotic left common carotid, a SMART self-expandable carotid stent was deployed. Due to residual stenosis, Savvy balloon post-dilatation was performed for approximately 20 seconds. Immediately postdilatation, a small filling defect at the distal stent aspect was noted. As the defect acutely developed, we suspected acute platelet rich thrombus. Parenteral antiplatelet agent, ticofiban, was infused intravenously with 0.4 μg/kg/min loading dose for 30 minutes, followed by 0.1 μg/kg/min continuous infusion. In-stent thrombus was completely dissolved after 30 minutes of infusion. He received continuous infusion for the next 26 hours. There were no hemorrhagic complications.

Discussion

There are different but specific ways of management and treatment of stent thrombosis in the literature. Several studies report an encouragingly low incidence of late complications after CAS, but there are very little data regarding early thrombotic complications after CAS. The causes of this potentially catastrophic complication could be systemic, for example, inadequate antiplatelet treatment (antiplatelet monotherapy, antiplatelet resistance, early discontinuation of treatment), or hypercoagulable state (thrombocytopenia, diabetes mellitus, heparin resistance), local, for example, vessel dissection, severe plaque protrusion, early stent restenosis, stent underexpansion, intimal injury and stent thrombogenicity. The poststenting acute carotid thrombosis can be managed with prompt surgical reintervention. The big experience of some vascular centres with great number of patients undergoing CAS worldwide strengthens the importance of a correct pre-CAS and post-CAS antithrombotic treatment. Dual antiplatelet therapy is mandatory for at least one month, this being the time necessary for completion of re-endothelialization process inside the stent. In those Vascular Departments that use to treat acute carotid thrombosis after CAS with surgical reintervention, when detecting a neurologic deficit in the early post-CAS period, they perform a prompt carotid duplex examination. If there is either a partial or complete carotid intrastent thrombosis the patient is immediately surgical explored. When ultrasound result is negative or there is any doubt about the distal extension of thrombosis, a second level study consisting of angiography or angio-CT scan is performed. With a diagnosis of intracranial vessel occlusion, a prompt endovascular approach with intraluminal thrombolysis is chosen. As we can understand, many vascular surgeons have some serious concerns about treating an extracranial vessel thrombosis or occlusion with an endoluminal approach. Others re-
port successful treatment of acute carotid stent thrombosis by combination therapy using percutaneous mechanical thrombectomy and adjuncive intravenous abciximab\textsuperscript{20}. Despite a number of cases with good results already described, the endovascular approach for acute carotid thrombosis after CAS present some concerns about the possibility of thrombus embolization during treatment. The necessary intraluminal manipulation of guides and catheters in association with the thrombolysis can cause the fragmentation of clots and subsequently increase the risk of distal intracerebral vessel occlusion.

In one of the cases from the Vascular Department of the University in Romania, the cause of clot formation was the carotid dissection following stent postdilatation and the other case remained unclear and difficult to explain. There was decided immediate intra-arterial thrombolysis using the only thrombolytics available at that time in the Hospital, instead of rescue surgery. Streptokinase in one case and tenecteplase in the other without being available proximal protection device and GpIIb/IIIa inhibitors (GPIs). This kind of thrombolysis described in these two cases is called selective local thrombolysis. It is believed that a successfully reperfused acute carotid stent thrombosis does not confer a bad, long-term prognosis, even with an initial stormy postprocedural course. Acute thrombosis after CAS can also successfully be treated by intravenous tirofiban (glycoprotein IIb/IIIa receptor inhibitor), a parenteral antiplatelet agent.

For the patient reported from the University of Vienna the possible reason for acute carotid stent thrombosis remained obscure because the standard antithrombotic regimen, including combined antiplatelet therapy, was administered and the intervention was performed in a routine fashion by using monorail technique and distal filter protection without repeat poststent dilation or any evidence of dissection. However, a poorly controlled diabetes may have predisposed to a hypercoagulable state in this patient\textsuperscript{21}. Peri-interventional carotid stent thrombosis ideally requires rapid intra-arterial-intracarotid initiation of reperfusion therapy to limit the time of ischemia, reperfusion injury, and associated symptomatic intracranial hemorrhage\textsuperscript{22}. The major complication of thrombolysis with rtPA has to do with high occurrence of intracranial bleeding complications and the short time window for application within 3 hours from onset of symptoms.

In contrast, early thrombus disaggregation – termed “dethrombosis”\textsuperscript{23} – by using the GP IIb/IIIa inhibitor abciximab as adjunct for carotid artery stent placement reduced adverse peri-interventional events. So, this combined therapeutic regimen consisting of dethrombosis (abciximab) and fibrinolysis (by using alteplase) – termed “facilitated thrombolysis” was also studied in acute myocardial infarction with half the usual dose of the fibrinolytic agent with good results\textsuperscript{24}. As thrombolytic agents simultaneously exert clot-dissolving and procoagulant action, combining them with antiplatelet agents (facilitated thrombolysis) improves the rate of recanalization. In the case report described from the Department in Austria both rtPA and the half-bolus abciximab were administered intra-arterially via superselective catheterization of the occluded carotid artery. This strategy ensures high local drug concentration associated with improved efficacy\textsuperscript{23}. Therefore, a reduced dosage of both agents was used employing a careful “wait and watch” tactic. Having in mind that fibrinolytic agents simultaneously exert clot-dissolving and procoagulant actions, which may in fact precipitate reocclusion of the infarct-related artery after thrombolysis\textsuperscript{26} it was performed a facilitated thrombolysis by using rtPA and abciximab simultaneously, rather than fibrinolysis alone.

GPIIb/IIIa receptor inhibitors (GPIs) prevent thrombus formation and subsequent distal embolization by inhibiting the final common pathway of platelet aggregation. GPIs have the advantage of parenteral use, and rapid and strong action compared to oral antiplatelet agents. There are three GPIs (abciximab, tirofiban, eptifibatide) available for clinical use; significant differences exist in biological and plasma half-life between abciximab and the small molecule agents (tirofiban and eptifibatide).

Conclusions

Peri-interventional carotid stent thrombosis following CAS is a very rare but potentially fatal complication and requires immediate treatment to reinstall perfusion in order to limit brain ischemia. The underlying mechanism of stent thrombosis has to be analyzed rapidly to facilitate appropriate therapy.

There are only a few published reports in the international literature regarding the emergency situ-
Acute carotid stent thrombosis after carotid artery stenting

A complication of acute carotid stent thrombosis. Variant ways of management are described in such a difficult complication. It depends on the vascular surgeon's experience and proper materials available.

Despite an initial dramatic course, a rapid reperfusion guides to complete neurological recovery and a good prognosis in the long term. For the endoluminal approach for treatment with thrombolysis and for the emergency situation of peri-interventional acute carotid stent thrombosis, facilitated thrombolysis seems particularly suitable because the time window of ischemia is minimal (which is a determinant of reperfusion injury and associated bleeding risk), and the freshly formed thrombus may be prone to de-thrombosis. So, the bailout strategy by using the synergistic effect of thrombolysis and dethrombosis leads to rapid revascularization after carotid stent thrombosis with minimal de novo ischemic lesion formation and transient neurologic deficit. When this strategy of facilitated thrombolysis does not work, as a backup, direct thrombectomy can be performed with the guiding sheath. Successful recanalization by in-stent percutaneous transluminal angioplasty with distal protection or additional stent placement on the stented portion of the ICA combined with the intravenous administration of rtPA (1300,000 IU), always followed by subsequent treatment with antithrombotic agents, can constitute a possible safety solution to this very rare but sometimes fatal complication of carotid angioplasty and stenting.

Surgical management is another possible option for acute stent thrombosis. However, as acute thrombosis is rare, it is difficult to accumulate evidence for a preferred treatment strategy. Because of the fact that the event of acute carotid stent thrombosis usually occurs in the angiographic suite, allows immediate drug infusion. Sometimes, surgical intervention would have resulted in substantial delay and increased time for ischemia.

References


11) Masuo O, Terada T. Successful recanalization by in-stent percutaneous transluminal angioplasty with distal protection or additional stent placement on the stented portion of the ICA combined with the intravenous administration of rtPA (1300,000 IU), always followed by subsequent treatment with antithrombotic agents, can constitute a possible safety solution to this very rare but sometimes fatal complication of carotid angioplasty and stenting.

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