ΕΛΛΗΝΙΚΗ ΔΗΜΟΚΡΑΤΙΑ
Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών
ΙΔΡΥΘΕΝ ΤΟ 1837

ΣΧΟΛΗ ΕΠΙΣΤΗΜΩΝ ΥΓΕΙΑΣ
ΙΑΤΡΙΚΗ ΣΧΟΛΗ

ΚΟΙΝΟ ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ
«ΕΝΔΑΓΓΕΙΑΚΕΣ ΤΕΧΝΙΚΕΣ»

ΕΘΝΙΚΟ ΚΑΙ ΚΑΠΟΔΙΣΤΡΙΑΚΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΑΘΗΝΩΝ
ΙΑΤΡΙΚΗ ΣΧΟΛΗ ΣΕ ΣΥΝΕΡΓΑΣΙΑ ΜΕ ΤΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΤΟΥ ΜΙΛΑΝΟΥ-BICOCCA

ΔΙΠΛΩΜΑΤΙΚΗ ΕΡΓΑΣΙΑ

ΘΕΜΑ: ACUTE CAROTID STENT THROMBOSIS: A REVIEW STUDY

ΜΕΤΑΠΤ. ΦΟΙΤΗΤΡΙΑ:
ΚΟΥΡΗ ΑΝΑΣΤΑΣΙΑ

ΑΘΗΝΑ
Φεβρουάριος, 2023

ΕΛΛΗΝΙΚΗ ΔΗΜΟΚΡΑΤΙΑ
Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών
ΙΔΡΥΘΕΝ ΤΟ 1837

ΣΧΟΛΗ ΕΠΙΣΤΗΜΩΝ ΥΓΕΙΑΣ

ΙΑΤΡΙΚΗ ΣΧΟΛΗ

ΚΟΙΝΟ ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ

«ΕΝΔΑΓΓΕΙΑΚΕΣ ΤΕΧΝΙΚΕΣ»

ΠΡΑΚΤΙΚΟ ΚΡΙΣΕΩΣ
ΤΗΣ ΣΥΝΕΔΡΙΑΣΗΣ ΤΗΣ ΤΡΙΜΕΛΟΥΣ ΕΞΕΤΑΣΤΙΚΗΣ ΕΠΙΤΡΟΠΗΣ ΓΙΑ ΤΗΝ ΑΞΙΟΛΟΓΗΣΗ ΤΗΣ ΔΙΠΛΩΜΑΤΙΚΗΣ ΕΡΓΑΣΙΑΣ
της Μεταπτυχιακής Φοιτήτριας
ΚΟΥΡΗ ΑΝΑΣΤΑΣΙΑ

<u>Εξεταστική Επιτροπή</u>

- Καθηγητής Γεώργιος Γερουλάκος, Επιβλέπων
- Καθηγητής Ιωάννης Κακίσης
- Καθηγητής Αχιλλέας Χατζηϊωάννου

Η Τριμελής Εξεταστική Επιτροπή για την αξιολόγηση και εξέταση τ... υποψηφίου **κ.** ....., συνεδρίασε σήμερα -/-/2022.

Η Επιτροπή **διαπίστωσε** ότι η Διπλωματική Εργασία του/της ..... με τίτλο «**……**» είναι πρωτότυπη, επιστημονικά και τεχνικά άρτια και η βιβλιογραφική πληροφορία ολοκληρωμένη και εμπεριστατωμένη.

Η εξεταστική επιτροπή αφού έλαβε υπόψιν το περιεχόμενο της εργασίας και τη συμβολή της στην επιστήμη, με ψήφους ..... προτείνει την απονομή στον παραπάνω Μεταπτυχιακό Φοιτητή του Μεταπτυχιακού Διπλώματος Ειδίκευσης (Master's).

Στην ψηφοφορία για την βαθμολογία ο υποψήφιος έλαβε για τον βαθμό «ΑΡΙΣΤΑ» ψήφους ....., για τον βαθμό «ΛΙΑΝ ΚΑΛΩΣ» ψήφους ..... και για τον βαθμό «ΚΑΛΩΣ» ψήφους ..... Κατά συνέπεια, απονέμεται ο βαθμός «.....».

Τα Μέλη της Εξεταστικής Επιτροπής

- Καθηγητής Γεώργιος Γερουλάκος, Επιβλέπων (Υπογραφή) _____
- Καθηγητής Ιωάννης Κακίσης (Υπογραφή) _____
- Καθηγητής Αχιλλέας Χατζηϊωάννου (Υπογραφή) _____

ΕΥΧΑΡΙΣΤΙΕΣ

Ευχαριστώ ιδιαιτέρως τον επιβλέποντα αναπληρωτή καθηγητή κ^{ο} Κωνσταντίνο Μουλακάκη για την πολύτιμη βοήθεια και καθοδήγηση στην εκπόνηση αυτής της εργασίας.

Αφιερωμένο στους δυο γιους μου Λεωνίδα και Αλέξανδρο, και στον σύζυγο μου Δημήτρη για την αμέριστη υπομονή και την υποστήριξή του.

ΠΕΡΙΕΧΟΜΕΝΑ

ABSTRACT

Introduction Carotid artery stenting (CAS) is a revascularization modality alternative to carotid endarterectomy. Acute carotid stent thrombosis (ACST) is a rare complication of CAS, the prevalence of which varies between 0.5% to 0.8%, that can lead to devastating even lethal consequences and occurs within 30 days after CAS.

Background This severe complication requires immediate diagnosis and prompt restoration of cerebral perfusion. There are several case reports in the literature, but there are no guidelines regarding the ideal strategy for treating ACST.

Purpose The purpose of this study is to review the current literature on this devastating outcome of CAS in order to investigate the potential causative factors and to illuminate the available therapeutic strategies.

Methods A multiple electronic health database research was performed. A total of 37 cases were retrieved referring to acute ACST, investigating the cause and possible therapeutic strategies.

Results According to the acquired data there were 33 male and 4 female patients (average age of 68.54 years old (SD ±7.98, min 44 yo, max 82 yo)). Only 21.62% (8 cases) referred to asymptomatic carotid stenosis and LICA seemed to be the predominant site of carotid stenosis (24/37 cases, 64,86%). In the majority of cases (89.19%) mono- or dual antiplatelet therapy was used pre-procedurally. In 13 cases ACST occurred intra-procedurally, in 10 patients stent thrombosis happened within the first 24 hours and only in 1 case there was a late thrombosis 3weeks after CAS due to cessation of antiplatelet therapy because of bladder malignancy. The residual 13 cases reported ACST within the first week after CAS. In 10 cases inadequate antiplatelet therapy, thrombotic predisposition or antiplatelet resistance were described as possible causes for ACST. Finally, technical intraprocedural aspects were detected, ICA dissection was described in 2 cases, plaque protrusion across the stent in one patient, overlapping stents in 3 cases, PTA failure in 3 reports and EPD complications in 5 patients. Combination of the abovementioned causes were reported in 4 cases. Therapeutic management varied, 8 patients received antiplatelet therapy (mono- or dual) in combination with antithrombotic agents (low molecular weight heparin, warfarin, argatroban) or intravenous (IV) infusion of GPIs, in 12 patients thrombolysis

was attempted (unsuccessful in 4 cases), 8 patients were submitted to mechanical thrombectomy with or without thrombolysis and finally 12 patients underwent surgical exploration. Two deaths were reported.

Conclusion The main causes according to so far existing literature include inadequate or ineffective antiaggregant therapy, resistance to antiplatelet agents and genetic or acquired thrombotic disorders. So far there is no consensus regarding ACST management, though thrombolysis, mechanical thrombectomy, thromboaspiration with thrombolysis, surgical therapy and re-angioplasty can all be used with promising results.

Keywords

Carotid artery disease, stroke, carotid stent, acute thrombosis, revascularization, thrombolysis, aspiration, endarterectomy, medical therapy

ΓΕΝΙΚΟ ΜΕΡΟΣ

1. CAROTID ARTERY STENOSIS

1.1 INTRODUCTION

Atherosclerotic carotid artery disease is one of the major causes of ischemic stroke and transient ischemic attack (TIA), accounting for about 20% of cases. Approximately 6.5 million strokes occur per year and are the leading cause of premature mortality and morbidity for both men and women[1]. In Caucasian populations, 50% stenosis of the carotid artery was identified in 2.3% of men in the sixth decade, in 6.0% in the seventh decade and in 7.5% of men aged 80 years, whereas in women, the corresponding prevalence figures were 2.0%, 3.6% and 5.0% in these age groups, respectively[2].

Atherosclerotic carotid stenosis typically occurs at the carotid bifurcation, involving the distal common and the proximal internal carotid artery. Other sites which are prone to develop atherosclerotic plaques leading to stenosis are the origin of the common carotid artery and the cavernous segment of the intracranial carotid artery. The prevalence of atherosclerotic carotid disease increases with age and is higher in men than in women.

Carotid stenosis is defined as symptomatic or asymptomatic. It is defined as symptomatic when it has caused ocular symptoms in the ipsilateral eye like transient monocular blindness or retinal infarction, due to ischemic cerebrovascular events or cerebral hemisphere (transient ischemic attack (TIA) or stroke) in a time period consisting the preceding six months, whereas an asymptomatic carotid stenosis is defined as a stenosis which has not caused or is associated with any ocular or cerebral ischemic events in the ipsilateral carotid territory within the preceding six months.

1.2 PATHOPHYSIOLOGY

Carotid artery stenosis, even when severe, is frequently asymptomatic. Indeed, complete internal carotid artery occlusion is frequently discovered incidentally in patients who have never had any stroke symptoms. This is because in most patients Circle of Willis collaterals will compensate for any reduction in blood flow caused by a cervical carotid stenosis. While cerebral anatomy is highly variable, the majority of patients have an anterior communicating artery, posterior communicating artery, or both which may preserve normal blood flow to the brain in the event of cervical carotid

artery stenosis or occlusion. When communication fails, the body is capable of forming new collaterals from the external carotid artery to the internal carotid artery. The most common mechanism of stroke due to carotid artery stenosis is therefore not hemodynamic failure, but plaque rupture and thromboembolism. Clinically this presents with stroke, transient ischemic attack (TIA), or amaurosis fugax. The most devastating presentation of carotid artery disease is a sudden large vessel occlusion due to a thromboembolus lodging in a large intracranial vessel, like the internal carotid terminus (ICAT) or the middle cerebral artery (MCA). Carotid disease accounts for between 13% and 32% of large vessel occlusion cases, with only atrial fibrillation accounting for more. The severity of the symptoms, and the chance of recovery with emergent treatments (e.g. thrombolysis and thrombectomy) is highly dependent on the individual patient's ability to form collaterals to protect the brain while the MCA or ICAT is occluded. Carotid disease more often presents as a trash of smaller emboli occluding multiple distal intracranial branches of the middle cerebral artery, anterior cerebral artery, and even the posterior cerebral artery. While the pattern can be seen with stroke from hemodynamic failure, in fact the majority of such strokes is embolic. This characteristic pattern of stroke can be called a carotid embolic pattern, due to its high association with carotid plaque rupture and thromboembolism as its mechanism. When the pattern is seen and there is not the usual cervical carotid stenosis, there is almost certainly a responsible atherosclerotic lesion more proximally or more distally on the ipsilateral side. The most common symptoms are contralateral weakness of the hand, arm, face or leg, contralateral numbness, and speech disturbance such as dysarthria. Aphasia (usually do to a left sided event) or neglect (usually due to a right sided event) may also be present. The severity of the symptoms is related both to the burden and location of the emboli. Symptoms may be minor and transient or more profound as those with large vessel occlusion. Only imaging can reliably distinguish the exact source of the stroke. Monocular vision loss due to retinal embolism is a third common presentation of carotid stenosis. Patients experience abrupt loss of the vision in one eye, or the top or bottom half of the visual field in one. When the symptoms are temporary it is defined as “amaurosis fugax”. When visual loss is permanent a retinal stroke has occurred. Amaurosis fugax is a frequent symptom of nearly occlusive carotid stenosis, as a high proportion of the flow from the carotid artery may be directed out the ophthalmic artery when robust collaterals are supplying the brain. Patients with severe carotid stenosis can experience many episodes of amaurosis fugax, even multiple

times a day or week. As opposed to monocular vision loss, homonymous hemianopia is due to dysfunction of the visual cortex in the contralateral occipital lobe. It is important to examine patients carefully, as patients with homonymous hemianopia from an occipital infarct frequently perceive that they have lost vision in the contralateral eye. With any of the above presentations, a stuttering course of symptoms in the same carotid territory may be present and favors carotid artery disease as opposed to other causes of stroke such as cardiac embolism. This is highly relevant when trying to determine the cause of a stroke for patients who may have only moderate carotid stenosis (50–69%) or another potential cause of stroke, such as atrial fibrillation or a history of small vessel lacunar strokes. A stuttering course, particularly when combined with MRI evidence of a carotid embolic pattern, lends confidence to the diagnosis of carotid embolism, and more likelihood that a patient will benefit from carotid revascularization, especially with moderate degrees of stenosis. Patients with severe symptomatic stenosis on average benefit greatly from carotid revascularization, with an absolute stroke risk reduction of 17% from carotid endarterectomy (CEA), most of which is in the first few weeks[3]. Patients with moderate stenosis benefit far less on average, with an absolute risk reduction from CEA of only about 6% over 5 years[4]. More beneficial results of carotid revascularization procedures should be expected in symptomatic patients with both moderate and severe stenosis if, using clinical and MRI information, the operated patient population can be enriched for patients in whom the carotid stenosis is actually the cause of the symptoms. Hemodynamic TIAs and strokes are uncommon, but they do occur. Patients with hemodynamic symptoms experience very frequent events, usually multiple times a day. In addition to ipsilateral severe carotid stenosis or occlusion, these patients invariably have other exacerbating circulatory compromise, such as completely absent circle of Willis collaterals and poor external carotid collaterals, or contralateral severe stenosis or occlusion. Their symptoms are elicited by hemodynamic stress. The classic symptom is shaking of the contralateral arm and leg when the patient stands.

1.3 TREATMENT

The presence of an atherosclerotic plaque in the extracranial internal carotid artery is associated with an increased risk of stroke. Medical treatment targeting the possible risk factors, which are responsible for the formation of the plaque and consequently the possibility of a stroke, is the principle of managing patients with carotid stenosis.

Furthermore, several surgical and endovascular techniques have been developed to complement medical treatment in appropriately selected patients.

1.3.1 MEDICAL THERAPY

Several risk factors have been associated with adult ischemic stroke such as hypertension, diabetes mellitus, cholesterol levels, atrial fibrillation and hormone treatment, which are mostly modified through medical therapy. In addition, there are other modifiable risk factors including nutritional status, physical activity, obesity, cigarette smoking and alcohol consumption, which derive from each patient's lifestyle and therefore are encountered when adopting a more healthy way of living.

According to the latest ESVS guidelines[5] all patients with carotid stenosis, symptomatic and asymptomatic, should receive optimal medical therapy. Initially, optimal medical therapy includes risk factor control as abovementioned, such as smoking and alcohol consumption cessation, healthy diet and physical activity. When considered necessary drug therapy initiates and includes antiplatelet (aspirin 75-325mg/day or clopidogrel 75 mg/ day) and statin lipid-lowering therapy, management of hypertension so as the patient to maintain long term blood pressure <140/90mmHg and strict control of diabetes mellitus .

Furthermore, equally important is the adherence to the medical therapy. In patients with carotid disease there is a paucity of data relating to the potentially adverse effect of noncompliance to antiplatelet therapy and medications for hypertension, diabetes mellitus and dislipidaemia. Adherence to medications may be significantly reduced in the presence of undiagnosed cognitive impairment. Other predictors of poor compliance are psychological problems, asymptomatic disease, inadequate follow-up, medication side effects, complexity and cost of treatment[6]. Nevertheless, survival is significantly better for patients who remain adherent to best medical treatment compared to those who do not comply[7].

1.3.2 SURGICAL THERAPY

Carotid endarterectomy (CEA) is a simple but technically unforgiving surgical procedure and has been thoroughly described in the literature. CEA first described by DeBakey in 1975 has become the conventional treatment for carotid artery stenosis. Although many factors play an important role to the outcome, such as patient selection and preoperative antiplatelet therapy, a good clinical result is likely more associated

with a perfect surgical technique. CEA is most commonly performed under general anaesthesia, although locoregional anaesthesia can be used too. Carotid bifurcation is exposed in a rather fashionable way with a transverse or longitudinal incision, and either an antergrade or retrograde exposure of the carotid can be performed. Shunting routine can be selective, but carotid sinus nerve blockade with lidocaine is not used anymore. An eversed or conventional endarterectomy can be carried out depending on the case with patch angioplasty. Primary closure is not recommended due to ICA restenosis. Protamine reversal of heparin is usually performed.

1.3.3 ENDOVASCULAR THERAPY

Endovascular treatment (carotid artery stenting- CAS) as an alternative to CEA emerged following trials demonstrating the benefit of angioplasty and stenting in patients with coronary artery disease[1]. Since first described in 1989, a number of randomized controlled trials (RCTs) have demonstrated the long-term safety and efficacy of CAS for carotid stenosis[8,9]. Cost-effectiveness and its use in surgical inaccessible lesions made CAS an attractive alternative to CEA. Since first emerged, CAS has significantly technologically evolved and therefore the preferred management of carotid artery stenosis has been widely debated. Many RCTs have attempted to evaluate which treatment is superior. Results of these studies show that periprocedural stroke is more common with CAS, while myocardial infarction is more common with CEA, although CAS and CEA have similar long-term outcomes.

2. CAROTID ARTERY STENTING (CAS)

2.1 INTRODUCTION

Carotid artery stenting is a revascularization modality alternative to carotid endarterectomy. Several randomized controlled trials have compared CEA to CAS in the treatment of carotid artery stenosis. These studies have suggested that CAS is more strongly associated with periprocedural stroke, while CEA is more strongly associated with myocardial infarction. Published long- term outcomes report that CAS and CEA are similar. Stent thrombosis is a feared complication of CAS, and thus guidelines suggest administration of dual antiplatelet therapy pre- and post-procedure along with antihypertensives, beta- blockers and lipid- lowering factors.

2.2 STENTS

The choice of stent depends on many factors such as device availability, clinical trial or registry participation, stent cell structure and shape and specific characteristics of the embolic protection device (EPD) used. The type of stent used is affected by patient's indication and lesion characteristics. Self-expanding stents are most frequently used compared to balloon expandable, and stents can be classified as bare metal or covered, tapered or non-tapered and close or open cell stents. Bare metal stents (BMS) are a metal skeleton that maintain the patency of the vessel. Covered stents are bare metal stents covered by compound such as polytetrafluoethylene or polyethylene terephthalate which aim to prevent smooth muscle cell proliferation and restenosis. Tapered stents are characterized by a larger diameter proximally and narrow diameter distally mimicking the progressive narrowing of the native ICA .

2.3 TECHNIQUES

2.3.1 EMBOLIC PROTECTION

Embolic complications in endovascular therapy arise due to manipulation of sheaths and catheters in an atheromatous arch, wiring and delivery across the lesion, balloon expansion and stent deployment, and therefore have prompted the development of EPDs. Though, EPDs themselves can lead to embolization when removed. Numerous of EPDs have been designed, thus the two most commonly used are distal filter embolic protection devices (f-EPDs) and proximal embolic protection devices (p-EPDs). Complications usually associated with the use of EPDs are vasospasm and arterial wall dissection. It is not clear whether cerebral protection is beneficial, secondary analysis on the SPACE trial suggested that EPDs rather not provide a significant benefit[10].

2.3.2 EMBOLIC PROTECTION DEVICES TECHNIQUES

P-EPDs offer cerebral protection by occluding vessels proximal to the lesion and interrupt blood flow, they establish protection prior to manipulation but relies on collateral blood flow to maintain cerebral perfusion. In addition, they require large introducer sheaths which are difficult to navigate and can possibly obscure the underlying plaque during stent deployment. F-EPDs entrap embolic material that becomes dislodged during the procedure, they are inserted with the contribution of a guiding wire through the lesion and place a net-like filter distally to the plaque using a

delivery system, where withdrawal of the sheath unleashes the filter. F-EPDs can only entrap emboli larger than the pore size, and can be obstructed by large embolic material which may disturb cerebral perfusion. There are no large multicenter RCTs comparing the two types of EPDs, however published studies generally support proximal protection.

2.4 INDICATIONS FOR CAS

Carotid endarterectomy has been shown to decrease the long-term risk of stroke compared to medical therapy. Carotid artery angioplasty with stenting is less invasive and a viable option for treatment of carotid artery disease. Currently, there is no doubt that CEA, in appropriate hands, remains the best option for treating carotid artery disease under most circumstances. However, there is no question that the safety and efficacy of CAS, in its evolved form, is acceptable in some clinical cases in which patients characterized high risk for CEA will best benefit from it. The criteria for defining an appropriate for CAS patient (symptomatic or not) include the presence of one or more of: clinically significant cardiac disease (congestive heart failure, abnormal stress test, need for open-heart surgery), severe pulmonary disease, contralateral carotid occlusion, contralateral laryngeal nerve palsy, previous radical neck surgery, cervical radiation therapy, patent tracheostomy, proximal common carotid artery stenosis below clavicle, distal internal carotid artery stenosis above C2, recurrent stenosis after CEA and life expectancy <3 years. However, CAS may not be possible in patients with difficult type III arch anatomy, extensive calcifications, ulcerated plaque morphology or previous damaged stents.

2.4.1 PREVIOUS ENDARTERECTOMY

Restenosis rates after CEA range from 10% to 25%[11]. Redo CEA has an increased risk for cranial nerve injuries (CNIs) and also carries an increased hazard for stroke when compared to primary CEA[11]. There are no significant data guiding management of these patients. A systematic review and meta-analysis of 4399 patients from 50 studies reported no differences in 30-day rates of stroke, transient ischemic attack (TIA) and myocardial infraction (MI) or long-term rates of stroke between CAS an CEA groups for patient with restenosis[12]. CNIs were more common with CEA, but recurrent restenosis was more common with CAS (both $p<0.05$).

2.4.2 CERVICAL RADIOTHERAPY

Cervical irradiation is a known risk factor for a carotid artery stenosis. Carotid artery lesions secondary to radiotherapy tend to occur at unusual sites, such as the proximal or mid-common carotid artery. In addition, the effects of radiation include a fibrotic reaction and obliteration of normal tissue planes, which makes dissection and mobilization of the carotid vessels and identification of CN more difficult. Therefore, cervical radiotherapy accelerates the development of carotid artery stenosis, with the risk of TIA or ischemic stroke at least doubled[13]. The effects of radiotherapy can make surgery high risk, however, high quality trials comparing CAS to CEA are lacking. Restenosis is the primary concern of CAS. A prospective study of 150 high-risk patients reported significantly higher rates of restenosis at 3 years with CAS in patients with previous neck radiotherapy compared to those without (80% vs 26%; $P < 0.05$)[14]. Other studies have reported no difference in restenosis rates in patients who have received radiotherapy[15]. A systematic review and meta-analysis of 533 patients comparing CAS against CEA in patients with previous neck therapy reported similar rates of perioperative stroke/TIA between groups, however, long-term stroke/TIA ($P = 0.014$) and restenosis ($P < 0.003$) were more likely with CAS. CNIs were more common with CEA but long-term rates of cerebrovascular events favoured CEA ($P = 0.014$)[16]. No high-quality trials have evaluated the utility of medical therapy in this cohort.

ΕΙΔΙΚΟ ΜΕΡΟΣ

3. ACUTE CAROTID STENT THROMBOSIS (ACST)

3.1 INTRODUCTION

Acute carotid stent thrombosis is a rare complication of CAS, the prevalence of which varies between 0.5% to 0.8%, that can lead to devastating even lethal consequences and occurs within 30 days after CAS[17]. This severe complication requires immediate diagnosis and prompt restoration of cerebral perfusion through recanalization of ICA, in order to restrict ischemic cerebral injury. There are several case reports in the literature, but there are no guidelines regarding the ideal strategy for treating ACST.

3.2 PURPOSE OF THE STUDY

ACST is an extremely rare event, but it can be a fatal complication of CAS. The purpose of this study is to review the current literature on this devastating outcome of CAS in order to investigate the potential causative factors and to illuminate the available therapeutic strategies.

3.3 METHODS AND MATERIAL

A multiple electronic health database research was performed, including MEDLINE/PUBMED, SCI-HUB and EMBASE, on all articles published up to June 2022 regarding carotid stent thrombosis after CAS. A total of 37 cases were retrieved referring to acute ACST, investigating the cause and possible therapeutic strategies (table 1).

3.4 RESULTS

In the present literature review 33 out of 37 patients were male with an average age of 68.54 years old (SD ±7.98, min 44 yo, max 82 yo), and only 21.62% (8 cases) were treated with CAS for asymptomatic carotid stenosis. In the majority of cases (89.19%) mono- or dual antiplatelet therapy was used pre-procedurally and LICA seemed to be

the predominant site of carotid stenosis (24/37 cases, 64,86%). In 13 cases ACST occurred intra-procedurally, while in 10 patients stent thrombosis happened within the first 24 hours. Only in 1 case there was a late thrombosis 3weeks after CAS due to cessation of antiplatelet therapy because of bladder malignancy. The residual 13 cases reported ACST within the first week after CAS. In 10 cases inadequate antiplatelet therapy, thrombotic predisposition or antiplatelet resistance were described as possible causes for ACST, when CAS procedure itself was successfully completed. Furthermore, 3 cases of hypercoagulation were reported due to malignancy and one more was attributed to atrial fibrillation. Technical intraprocedural parameters which could possibly lead to ACST were investigated, ICA dissection was described in 2 cases, plaque protrusion across the stent in one patient, overlapping stents in 3 cases, PTA failure in 3 reports and EPD complications in 5 patients (4 cases of EPD thrombosis and 1 case of ICA dissection). Combination of the abovementioned causes were reported in 4 cases. As far as therapeutic management is concerned the following were retrieved, 8 patients were treated with antiplatelet therapy (mono- or dual) in combination with antithrombotic agents (low molecular weight heparin, warfarin, argatroban) or intravenous (IV) infusion of GPIs, in 12 patients thrombolysis was attempted which was unsuccessful in 4 of them and further treatment was needed, 8 patients were submitted to mechanical thrombectomy with or without thrombolysis and finally 12 patients underwent surgical exploration, due to major neurological deterioration, including thromboendarterectomy with stent removal or STA-MCA anastomosis. Two deaths were reported (Chaturvedi et al[27].)

3.5 ETIOLOGY

Many factors have been accused of being responsible for ACST, but clearly the cause of stent thrombosis is multifactorial and has not been fully identified to date. Possible factors include drug interaction and patient compliance with drug therapy, antiplatelet resistance (4-44% clopidogrel resistance[18]), genetic polymorphism and individual biological and inflammatory factors. Furthermore, causes regarding intraprocedural techniques have been identified during stent insertion such as local vessel dissection, plaque protrusion promoting thrombosis, kinking and even coiling of the distal part of ICA, vasospasm, intimal injury leading to platelet adhesion and thus thrombus formation, and finally stent underexpansion which impairs stent's thombogenicity

itself. In addition to the abovementioned causes, complications of embolic protection devices such as flow occlusion have been reported to lead in ACST, with incidence rates among 8% -30%[19]. It is supported that EPD occlusion and carotid stent thrombosis are sequential events as they have been attributed to similar mechanisms.

3.6 TREATMENT

The main goal for ACST treatment is to remove the source of thrombosis, and therefore requires rapid decision making in order to recanalize ICA, so as to limit the time of ischemia, reperfusion injury and possible, post-procedural, associated symptomatic intracranial hemorrhage. Major parameters that should be taken into account when decision making are the time of thrombosis (intraprocedural, early, late), the severity of patient's neurological status and the extent of brain injury. For cases of severe clinical deterioration an urgent revascularization should be considered. For patients in a stable state a dilemma arises in the lack of data.

According to so far existing data 5 categories have been described as revascularization methods:

a. DRUG THERAPY

In stable patients with absent or minor symptoms antiplatelet therapy (mono- or dual) in combination with antithrombotic agents (low molecular weight heparin, warfarin, argatroban) can be used. An alternative treatment is to administrate glycoprotein IIb/IIIa receptor inhibitors (GPIs) intravenously, such as tirofiban or abciximab, in a loading dose followed by continuous intravenous (IV) infusion. However, data concerning the use of GPIs is quite limited and fatal intracranial hemorrhage has been reported as complication[20]. Abciximab can be used alone or in combination with other thrombolytic agents and has been effective in the dissolution of an in- stent thrombus[21,22,23] in an IV bolus dosage of 0.25mg/kg and a 0.125mg/kg intra-arterially, followed by IV infusion of 0.125mg/kg/min for further 12 hours. Tirofiban has been suggested mainly due to its short platelet-bound half-life and long plasma half-life predisposing to lower hemorrhagic risk[17].

b. THROMBOLYSIS

Thrombolysis in patients with acute ischemic stroke attributed to ICA occlusion can be infused either intra-arterially or IV. Various studies have recorded the beneficial effect of IV thrombolysis[24,25], however an increase in death and intracranial bleeding were documented[21]. Several thrombolytic agents such as streptokinase, urokinase, tenecteplase or rtPA have been used for the treatment of acute ACST intra-arterially with complete, partial or even unsuccessful clot resolution[22,25,26,27,28]. Local intra-arterial thrombolysis might have a high recanalization rate, yet, intraluminal manipulation of wires and catheters in association with the lysis of the thrombus can cause clot fragmentation and therefore distal cerebral occlusion. The American Heart Association/American Stroke Association (AHA/ASA) guidelines recommended IV rtPA in a 0.9mg/kg dose (90mg maximum) within 3 hours of onset for the early treatment of patients with acute ischemic stroke[30].

c. THROMBOASPIRATION WITH OR WITHOUT THROMBOLYTIC THERAPY

Combination of methods such as mechanical thrombectomy with thrombus aspiration may be used according to ASA/AHA guidelines in patients with large segment occlusion who have not responded to IV thrombolysis and should be performed only by certified experts. According to existing data, mechanical thrombectomy and stenting were associated with higher recanalization rates and improved functional status when compared to intra-arterial thrombolysis[28]. The Penumbra system has shown promising results, although intraluminal manipulation of guides and catheters can cause clot fragmentation and subsequently increase the risk of distal intracerebral vessel occlusion. At that point, suction thrombolysis may offer an alternative solution, still EPD occlusion in ACST cases has been reported[31,32]. Dhall et al have reported complete patency restoration with the use of thromboaspiration catheter before EPD withdrawal[33]. In conclusion, the role of mechanical thrombolysis and thrombus aspiration in acute stroke is currently not clear.

d. RE-ANGIOPLASTY

According to existing literature so far, only 3 cases have been reported treated with re-angioplasty, either plain angioplasty or stenting. Owens et al reported thrombolysis and repeat angioplasty, which led to thrombosis and ICA rupture[34]. Masuo et al described an intraprocedural ACST treated with redo in stent PTA using an EPD, followed by iv heparin infusion for 7 days with a residual mild hemiparesis[35]. Finally, Hu et al reported intraprocedural in stent thrombosis treated with rt-PA infusion through microcatheter and stent angioplasty. Redo PTA or stenting may be another alternative for treating ACST as it can be used rapidly especially when ACST occurs intraprocedural. However, there is a possibility of increasing the risk of distal embolization in an already damaged hemisphere, thus, PTA itself carries a risk of damaging stent's stability and skeleton. Furthermore, the residual thrombus within the stent predisposes to restenosis even re-thrombosis of the stent.

e. SURGICAL THERAPY

Emergent removal of the thrombosed stent is indicated in ACST patients with immediate major neurological deterioration, especially when the in-stent thrombosis is not associated with intracranial carotid branch thrombosis. Emergency operation has the risk clot dislocation due to surgical maneuvers (carotid bifurcation exposure, vascular clamps placement, Fogarty thrombectomy) and therefore distal cerebral embolization. Several strategies have been reported such as carotid thromboendarterectomy and stent explantation, surgical thrombectomy without stent removal, primary or patch closure, use of shunt or not, even STA to MCA bypass with favorable outcomes in all cases (table 1). However, surgical exploration is a time consuming procedure concerning an already high risk patient (possible reperfusion syndrome) which demands extended site exposure and an expert surgeon.

3.7 DISCUSSION

Acute carotid stent thrombosis remains a rare complication of CAS, occurring during or after less than 1% of procedures[17]. To the time being the is no classification regarding acute carotid stent thrombosis available. According to the available literature 37 cases

have been recognized referring to acute carotid stent thrombosis in the early period (<30 days).

Identifying the causative factor is of main interest, aiming to guide the therapeutic management. Inadequate antiplatelet therapy, thrombotic predisposition or antiplatelet resistance were presumed as a possible culprit in 11 cases when CAS procedure itself was successfully completed (table 1). Three more cases of hypercoagulation were described due to malignancy[31,37,42]and one more was attributed to atrial fibrillation by Setacci et al[36]. Therefore, when available, a wider set of coagulation tests with additional studies such as platelet aggregometry should be performed before CAS.

Furthermore, technical intraprocedural parameters such as ICA dissection[26], plaque protrusion[42], overlapping stents[42] or PTA failure[26,40,43] and EPD complications[17,32,39] which promote the release of intrinsic factors responsible for thrombosis, kinking and coiling of the distal part of ICA can result in early carotid stent thrombosis. Thus, CAS should only be performed by experienced physicians.

In the most comprehensive review up to date in which 26 cases of early carotid stent thrombosis were presented[17] an algorithm for the management has been proposed (figure1) by Moulakakis et al. This algorithm distinguishes whether the complication occurred intra- or post-procedurally. In the latter case, an imaging study initially such as carotid duplex examination, followed by DSA or CTA in suspicion of distal extension of carotid thrombosis, is recommended in order to evaluate the level of thrombosis. Once confirmed, then percutaneous mechanical thrombectomy, thromboaspiration and thrombolysis or thrombolysis with or without IIb/IIIa receptor inhibitors is suggested. Then, if partial or residual intrastent thrombosis with no distal cerebral extension is documented surgical exploration can be used. If carotid stent thrombosis occurs intraprocedurally immediate treatment with percutaneous mechanical thrombectomy, thromboaspiration and thrombolysis or thrombolysis with or without IIb/IIIa receptor inhibitors should be initiated. If the thrombus is refractory, surgical exploration should be considered.

3.6 CONCLUSION

In conclusion, acute carotid stent thrombosis is a rare complication of CAS with possible devastating even lethal outcome, and therefore, should be treated immediately. The main causes according to so far existing literature include inadequate or ineffective

antiaggregant therapy, resistance to antiplatelet agents and genetic or acquired thrombotic disorders. The critical points for preventing the devastating outcome are immediate recognition of the thrombosis, accurate assessment of the neurological status and the extent of brain damage, and rapid revascularization of the damaged tissue. Although, there is no consensus regarding its management, thrombolysis, mechanical thrombectomy, thromboaspiration with thrombolysis, surgical therapy and re-angioplasty have all been used, depending on the cause and patient's neurological status, with promising results.

Acute carotid stent thrombosis (ACST) Table 1.

	Author, Year, Journal	Age/sex	Stenosis position/ grade	S/A	Onset	Preprocedural medicine	Cause of ACST	Treatment	Outcome
1	**Tong et al,** *2000* *American journal of neuroradiology*	44/M	LICA/70 %	A	Procedure	ND	ND	Abciximab IV bolus	Resolution of neurological symptoms /stent patent
2	**Chaturvedi et al,** *2001*, *Stroke*	63/F	LICA/sever	S	12 hours	ASA	ND	750000IU urokinase	**Death**
3	**Chaturvedi et al,** *2001*, *Stroke*	57/M	LICA/ND	S	3 days	NONE	ND	ASA	**Death**
4	**Hamann et al,** *2002* *European neurology*	76/M	RICA/70 %	S	4 days	ASA & heparin	Antiplatelet therapy ceased	70mg rt-PA & heparin	Resolution of neurological symptoms/stent patent
5	**Owens et al,** *2003* Annals of Vascular surgery	65/M	LICA/70 %	S	Procedure	ND	ND	Thrombolysis, repeat angioplasty/ICA thrombosis & rupture- stent removal	Motor deficits
6	**Bush et al,** *2003* *Journal of Endovascular therapy*	68/M	RICA /90%	S	15 minutes	ASA & CLO	ND	Mechanical thrombectomy & iv abciximab	Resolution of neurological symptoms /stent patent
7	**Steiner-Boker et al,** *2004* *American journal neuroradiology*	64/F	RICA/85 %	S	Procedure	ASA & CLO	Hypercoagulation	Intracarotid 5mg rt-PA - intraarterial & iv for 12 hours abciximab	Neurological improvement/ stent patent
8	**Setacci et al,** *2005* *Journal of vascular surgery*	82/M	LICA/80 %	S	2 days	ASA & CLO	ND	Endarterectomy and Stent removal	Neurological improvement

9	**Setacci et al,** *2005, Journal of vascular surgery*	78/M	LICA/85 %	S	4 days	ASA & CLO	Antiplatelet therapy ceased/ thrombocythemia	Endarterectomy and Stent removal	Gradual improvement from the stroke
10	**Setacci et al,** *2005 Journal of vascular surgery*	72/M	LICA/80 %	S	2 hours	ASA & heparin	AF, multiple cardiac embolism	Surgical thrombectomy without stent removal	Good recovery/ stent patent
11	**Masuo et al,** 2006 Neurologica medico chirurgica	71/M	LICA/severe	S	3 days	ASA, ticlodipine, heparin	Insufficient periprocedural antithrombotic medication	In-stent PTA & EPD& iv heparin for 7 days	Mild right hemiparesis
12	**Buhk et al,** 2006, Neurology	78/M	LICA/80 %	S	3 weeks	ASA & CLO replaced by subcutaneous heparin	Antiplatelet therapy ceased due to bladder cancer	Antiplatelet therapy & heparin	Minor hemiparesis & slight aphasia/ thrombus resolution, stent patent
13	**Seo et al,** 2008, Yonsei medical journal	63/M	LICA/85 %	A	Procedure	ASA & CLO	After postdilatation filling defect in the distal stent	IV tirofiban	No neurological deficit/ stent patent
14	**Iancu et al,** 2010, Cardiovascular revascularization medicine	65/M	LICA/80 %	S	Procedure	ASA & CLO	Carotid dissection after postdilatation	Bolus streptokinase	No neurological deficit/ stent patent
15	**Iancu et al,** 2010 Cardiovascular revascularization medicine	70/M	RICA/80 %	S	Procedure	ASA & CLO	Balloon burst	Intrathrombus tenecteplase & balloon angioplasty	No neurological deficit/ normal intrastent velocities
16	**Dhall et al,** 2010 Journal of invasive cardiology	62/M	LICA/90 %	S	Procedure	ASA &CLO	ND	Urokinase, abciximab, thromboaspiration	Clinical improvement/ stent recanalization

17	**Choi et al,** 2012 Journal of Korean neurosurgical society	69/M	RICA/83 %	S	9 days	ASA & CLO	ND	STA-MCA anastomosis	Left hemiparesis & dysarthria
18	**Choi et al,** 2012 Journal of Korean neurosurgical society	68/M	LICA/72 %	S	4 days	ASA & CLO	Aspirin & clopidogrel resistance	Iv rt-PA, intra-arterial thrombolysis, STA-MCA anastomosis	Right hemiparesis
19	**Kanemaru et al,** 2013 Journal of endovascular therapy	77/M	RICA/ 90%	A	6 days	ASA & CLO& cilostazol	Hypercoagulation/ bladder cancer	ASA & CLO& cilostazol & warfarin & argatroban	Thrombus resolution
20	**Markatis et al,** 2012 Vascular	67/M	LICA/95 %	S	2 days	CLO	Discontinuation of dual antiplatelet therapy	Heparin, endarterectomy, stent removal, thrombectomy, primary closure	Minor numbness of three digits on the right hand
21	**Kim et al,** 2013 Acta neurochirurgica	75/M	LICA 90%	S	Procedure	ASA & CLO	EPD thrombosis	Mechanical thrombectomy (Penumbra system)	Complete recanalization
22	**Kim et al,** 2013 Acta neurochirurgica	73/M	ND	A	Procedure	ASA & CLO	EPD thrombosis	Mechanical thrombectomy (Penumbra system)	Complete recanalization/ neurological improvement
23	**Kim et al,** 2013 Acta neurochirurgica	51/M	ND	S	Procedure	ASA & CLO	EPD thrombosis	Mechanical thrombectomy (Penumbra system)	Complete recanalization/ neurological improvement
24	**Munich et al,** 2014 Journal of neurointerventional surgery	70/M	LICA/90 %	S	Procedure	ASA & CLO	EPD thrombosis	Unsuccessful intraarterial verapamil & abciximab, thrombus aspiration	Good recovery/residual 25-30% stenosis

25	**Köklü et al ,** 2015 Cardiovascular and intrevantional radiology	73/M	LICA/95 %	S	24 hours	ASA	Dual antiplatelet resistance	Unfractionated heparin & ticlodipine	Residual paresis
26	**Moulakakis et al,** 2017 Annals of Vascular surgery	67/M	RICA/90 %	S	1 hour	ASA & CLO	Dissection from EPD caused by significant kinking (360˚) of distal RICA	Thrombus aspiration, surgical exploration, eversion CEA with stent removal	Clinical improvement, residual arm paresis
27	**Moulakakis et al,** 2017 Annals of Vascular surgery	74/M	LICA/ 80%	S	2 hours	Nadroparin calcium	Hypercoagulation, lung cancer, two stents	Intrathrombus urokinase & stenting	Clinical improvement, residual arm paresis
28	**Moulakakis et al,** 2017 Annals of Vascular surgery	73/F	LCCA/80 %	S	3 days	ASA & CLO	Two overlapping stents, malignancy	Tinzaparin	Residual arm paresis/30 months post-op no paresis
29	**Moulakakis et al,** 2017 Annals of Vascular surgery	66/M	LICA/80 %	S	4 days	ASA & CLO	Two overlapping stents	ASA, CLO nadroparin	Mild speech impairment
30	**Cvjetko et al,** 2017 Cardiovascular interventional radiology	68/F	RICA/70 %	ND	90 minutes	ASA & CLO	ND	Endarterectomy, stent removal, primary closure	Rankin 1
31	**Cvjetko et al,** 2017 Cardiovascular interventional radiology	80/M	LICA/70 %	A	4 days	ASA & CLO	ND	Endarterectomy, stent removal, Fogarty thrombectomy	Rankin 3
32	**Moulakakis et al,** 2018 Annals of Vascular surgery	66/M	RICA/90 %	S	Procedure	ASA	Plaque protrusion across the stent	Endarterectomy & stent removal	Good recovery
33	**Moulakakis et al,** 2018 Annals of Vascular surgery	72/M	RICA/severe	A	1 hour	ND	ND	Unsuccessful intraarterial thrombolysis & actilyse, endarterectomy & stent removal	No neurological deficit

34	**Hu et al,** 2018 Inerventional neurology	79/M	LICA/sub occlusion	A	Procedu re	ASA & CLO	Stent did not fully adhere to the vessel wall	rt-PA through microcatheter, redilatation of the stent	No neurological deficits/ stent patent
35	**Kahyaoglu et al,** 2018 Journal of cardiovascular thoracic research	66/M	LICA/70 %	S	3 hours	ASA & CLO	Discontinuation of dual antiplatelet therapy	CLO, unfractionated heparin iv, intaarterial rt-PA	Left arm weakness/ stent recanalization
36	**Toljan et al,** 2019 Vascular and endovascular surgery	55/M	LICA/ subocclus ive	A	2 hours	ASA & CLO	CYP2C19 & MDR1	Thrombus aspiration, alteplase, iv eptifibatide	Good recovery/ stent patent
37	**Wei wei et al,** 2021 Journal of internal medicine research	69/M	LICA/90 %	S	5 days	ASA & CLO	CYP2C19 heterozygote	Thrombus aspiration & tirofiban	Rankin 1
	Abbreviations: F- female, M- male, ND- not determined, ASA- aspirin, CLO- clopidogrel, A-asymptomatic, S- symptomatic, LICA- left internal carotid artery, RICA- right internal carotid artery, CEA- carotid endarterectomy, EPD- embolic protection device								

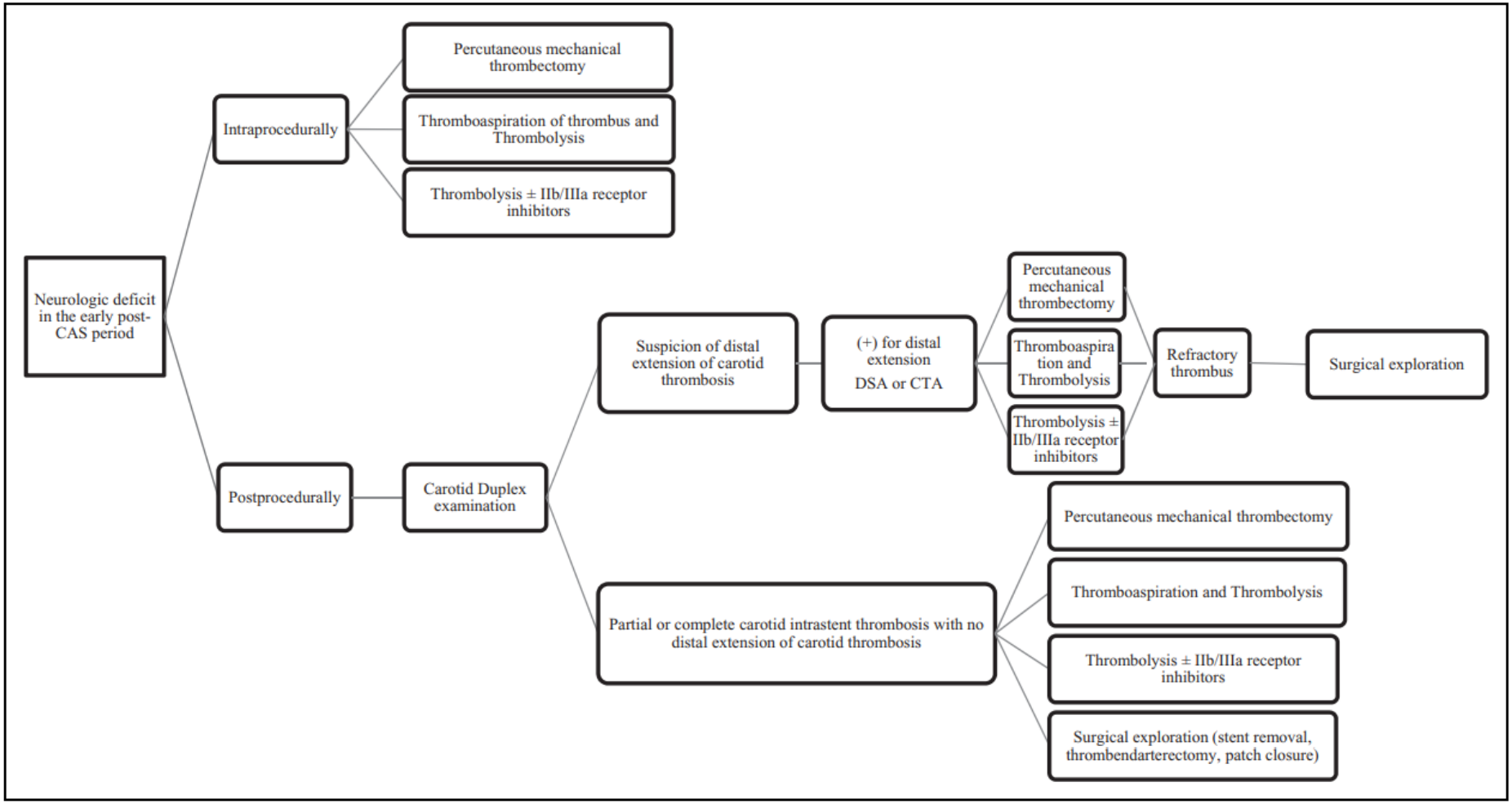

Figure 1. Proposed Algorithm for Management of Acute carotid stent Thrombosis (*Moulakakis et al. Vascular and Endovascular Surgery 1-11 sagepub.com/journalsPermissions.nav DOI: 10.1177/1538574416665986)*

Literature

1. Lamanna A, Maingard J, Barras CD, Kok HK, Handelman G, Chandra RV, Thijs V, Brooks DM, Asadi H. Carotid artery stenting: Current state of evidence and future directions. Acta Neurol Scand. 2019 Apr;139(4):318-333. doi: 10.1111/ane.13062. PMID: 30613950.
2. Bonati LH, Kakkos S, Berkefeld J, de Borst GJ, Bulbulia R, Halliday A, van Herzeele I, Koncar I, McCabe DJ, Lal A, Ricco JB, Ringleb P, Taylor-Rowan M, Eckstein HH. European Stroke Organisation guideline on endarterectomy and stenting for carotid artery stenosis. Eur Stroke J. 2021 Jun;6(2):I-XLVII. doi: 10.1177/23969873211012121. Epub 2021 May 11. PMID: 34414302; PMCID: PMC8370069.
3. Barnett HJM, Taylor DW, et al. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. N Engl J Med 1991 Aug 15;325 (7):445-453 https://doi.org/10.1056/NEJM199108153250701. PMID: 1852179.
4. Barnett HJ, Taylor DW, Eliasziw M, et al. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. North American symptomatic carotid endarterectomy trial collaborators. N Engl J Med 1998 Nov 12;339(20):1415- 1425.
5. Naylor AR, Rantner B, Ancetti S, de Borst GJ, De Carlo M, Halliday A, Kakkos S, Markus HS, McCabe DJH, Sillesen H, van den Berg JC, Vega de Ceniga M, Venermo M, Vermassen F, Naylor R, Rantner B, Ancetti S, de Borst GJ, De Carlo M, Halliday A, Kakkos SK, Markus HS, McCabe DJH, Sillesen H, van den Berg JC, de Ceniga MV, Venermo MA, Vermassen FEG, G A, Goncalves F B, Björck M, Chakfe N, Coscas R, Dias N, Dick F, Hinchliffe R, Kolh P, Koncar I, Lindholt J, Mees B, Resch T, Trimarchi S, Tulamo R, Twine C, Wanhainen A, Antoniou GA, Goncalves FB, Bjorck M, Chakfe N, Coscas R, Dias NV, Dick F, Hinchliffe RJ, Kolh P, Koncar IB, Lindholt JS, Mees BME, Resch TA, Trimarchi S, Tulamo R, Twine CP, Wanhainen A, Bellmunt S, Bulbulia R, Darling C 3rd, Eckstein HH, Giannoukas A, Koelemay M, Lindström D, Schermerhorn M, Stone D, Bellmunt-Montoya S, Bulbulia R, Clement Darling R 3rd, Eckstein HH, Giannoukas A, Koelemay MJ, Lindström D, Schermerhorn M, Stone DH. European society for vascular surgery (ESVS) 2023 Clinical

practice guidelines on the management of atherosclerotic carotid and vertebral artery disease. Eur J Vasc Endovasc Surg. 2022 May 19:S1078-5884(22)00237-4. doi: 10.1016/j.ejvs.2022.04.011. Epub ahead of print. PMID: 35598721.

6. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med. 2005 Aug 4;353(5):487-97. doi: 10.1056/NEJMra050100. PMID: 16079372.
7. Luebke T, Brunkwall J. Development of a Microsimulation Model to Predict Stroke and Long-Term Mortality in Adherent and Nonadherent Medically Managed and Surgically Treated Octogenarians with Asymptomatic Significant Carotid Artery Stenosis. World Neurosurg. 2016 Aug;92:513-520.e2. doi: 10.1016/j.wneu.2016.05.034. Epub 2016 May 26. PMID: 27237419.
8. Mathias K, Jäger H, Hennigs S, Gissler HM. Endoluminal treatment of internal carotid artery stenosis. World J Surg. 2001 Mar;25(3):328-34; discussion 334-6. doi: 10.1007/s002680020378. Epub 2001 Apr 11. PMID: 11343187.
9. Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomised trial. Lancet. 2001 Jun 2;357(9270):1729-37. PMID: 11403808.
10. Jansen O, Fiehler J, Hartmann M, Brückmann H. Protection or nonprotection in carotid stent angioplasty: the influence of interventional techniques on outcome data from the SPACE Trial. Stroke. 2009 Mar;40(3):841-6. doi: 10.1161/STROKEAHA.108.534289.Erratum in: Stroke. 2009 Jun;40(6):e477. PMID: 19150863.
11. AbuRahma AF, Jennings TG, Wulu JT, Tarakji L, Robinson PA. Redo carotid endarterectomy versus primary carotid endarterectomy. Stroke. 2001 Dec 1;32(12):2787-92. doi: 10.1161/hs1201.099649. PMID: 11739974.
12. Tu J, Wang S, Huo Z, Wu R, Yao C, Wang S. Repeated carotid endarterectomy versus carotid artery stenting for patients with carotid restenosis after carotid endarterectomy: Systematic review and meta-analysis. Surgery. 2015 Jun;157(6):1166-73. doi: 10.1016/j.surg.2015.02.005. PMID: 25840718.
13. Plummer C, Henderson RD, O'Sullivan JD, Read SJ. Ischemic stroke and transient ischemic attack after head and neck radiotherapy: a review. Stroke. 2011 Sep;42(9):2410-8. doi: 10.1161/STROKEAHA.111.615203. PMID: 21817150.
14. Protack CD, Bakken AM, Saad WE, Illig KA, Waldman DL, Davies MG. Radiation arteritis: a contraindication to carotid stenting? J Vasc Surg. 2007 Jan;45(1):110-7. doi: 10.1016/j.jvs.2006.08.083. PMID: 17210394.

15. Ravin RA, Gottlieb A, Pasternac K, Cayne N, Schneider D, Krishnan P, Marin M, Faries PL. Carotid artery stenting may be performed safely in patients with radiation therapy-associated carotid stenosis without increased restenosis or target lesion revascularization. J Vasc Surg. 2015 Sep;62(3):624-30. doi: 10.1016/j.jvs.2015.04.390. PMID: 26304480.
16. Fokkema M, den Hartog AG, Bots ML, van der Tweel I, Moll FL, de Borst GJ. Stenting versus surgery in patients with carotid stenosis after previous cervical radiation therapy: systematic review and meta-analysis. Stroke. 2012 Mar;43(3):793-801.doi:10.1161/STROKEAHA.111.633743.PMID: 22207504.
17. Moulakakis KG, Mylonas SN, Lazaris A, Tsivgoulis G, Kakisis J, Sfyroeras GS, Antonopoulos CN, Brountzos EN, Vasdekis SN. Acute Carotid Stent Thrombosis: A Comprehensive Review. Vasc Endovascular Surg. 2016 Oct;50(7):511-521. doi: 10.1177/1538574416665986. Epub 2016 Sep 19. PMID: 27645027.
18. Kahyaoglu M, Velioglu M, Gecmen C, Kalayci A, Cakmak EO, Izgi İA. Acute carotid stent thrombosis. J Cardiovasc Thorac Res. 2018;10(4):243-245. doi: 10.15171/jcvtr.2018.42. Epub 2018 Dec 5. PMID: 30680085; PMCID: PMC6335984.
19. Kwon OK, Kim SH, Jacobsen EA, Marks MP. Clinical implications of internal carotid artery flow impairment caused by filter occlusion during carotid artery stenting. AJNR Am J Neuroradiol. 2012 Mar;33(3):494-9. doi: 10.3174/ajnr.A2818. Epub 2011 Dec 15. PMID: 22173773; PMCID: PMC7966437.
20. Adams HP Jr, Effron MB, Torner J, Dávalos A, Frayne J, Teal P, Leclerc J, Oemar B, Padgett L, Barnathan ES, Hacke W; AbESTT-II Investigators. Emergency administration of abciximab for treatment of patients with acute ischemic stroke: results of an international phase III trial: Abciximab in Emergency Treatment of Stroke Trial (AbESTT-II). Stroke. 2008 Jan;39(1):87-99. doi: 10.1161/STROKEAHA.106.476648. Epub 2007 Nov 21. PMID: 18032739.
21. Steiner-Böker S, Cejna M, Nasel C, Minar E, Kopp CW. Successful revascularization of acute carotid stent thrombosis by facilitated thrombolysis.
AJNR Am J Neuroradiol. 2004 Sep;25(8):1411-3. PMID: 15466343; PMCID: PMC7975469.

22. Bush RL, Bhama JK, Lin PH, Lumsden AB. Transient ischemic attack due to early carotid stent thrombosis: successful rescue with rheolytic thrombectomy and systemic abciximab. J Endovasc Ther. 2003 Oct;10(5):870-4. doi: 10.1177/152660280301000504. PMID: 14656189.
23. Tong FC, Cloft HJ, Joseph GJ, Samuels OB, Dion JE. Abciximab rescue in acute carotid stent thrombosis. AJNR Am J Neuroradiol. 2000 Oct;21(9):1750-2. PMID: 11039360; PMCID: PMC8174868.
24. Hamann GF, Liebetrau M, Pfefferkorn T, Heiss MM. Successful systemic thrombolysis for carotid stent thrombosis. Eur Neurol. 2002;48(1):37-9. doi: 10.1159/000064956. PMID: 12138309.
25. Paciaroni M, Balucani C, Agnelli G et al. Systemic thrombolysis in patients with acute ischemic stroke and Internal Carotid ARtery Occlusion: the ICARO study. Stroke. 2012 Jan;43(1):125-30. doi: 10.1161/STROKEAHA.111.630624. Epub 2011 Oct 27. PMID: 22034003.
26. Iancu A, Grosz C, Lazar A. Acute carotid stent thrombosis: review of the literature and long-term follow-up. Cardiovasc Revasc Med. 2010 Apr-Jun;11(2):110-3. doi: 10.1016/j.carrev.2009.02.008. PMID: 20347802.
27. Chaturvedi S, Sohrab S, Tselis A. Carotid stent thrombosis: report of 2 fatal cases. Stroke. 2001 Nov;32(11):2700-2. PMID: 11692038
28. Kappelhof M, Marquering HA, Berkhemer OA, Majoie CB. Intra-arterial treatment of patients with acute ischemic stroke and internal carotid artery occlusion: a literature review. J Neurointerv Surg. 2015 Jan;7(1):8-15. doi: 10.1136/neurintsurg-2013-011004. Epub 2014 Jan 2. PMID: 24385555.
29. Markatis F, Petrosyan A, Abdulamit T, Bergeron P. Acute carotid stent thrombosis: a case of surgical revascularization and review of treatment options. Vascular. 2012 Aug;20(4):217-20. doi: 10.1258/vasc.2011.cr0303. Epub 2012 May 10. PMID: 22577161
30. Jauch EC, Saver JL, Adams HP Jr, Bruno A, Connors JJ, Demaerschalk BM, Khatri P, McMullan PW Jr, Qureshi AI, Rosenfield K, Scott PA, Summers DR, Wang DZ, Wintermark M, Yonas H; American Heart Association Stroke Council; Council on Cardiovascular Nursing; Council on Peripheral Vascular Disease; Council on Clinical Cardiology. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke.

2013 Mar;44(3):870-947. doi: 10.1161/STR.0b013e318284056a. Epub 2013 Jan 31. PMID: 23370205.

31. Kanemaru K, Nishiyama Y, Yoshioka H, Satoh K, Hashimoto K, Hanihara M, Horikoshi T, Ozaki Y, Kinouchi H. In-stent thrombosis after carotid artery stenting despite sufficient antiplatelet therapy in a bladder cancer patient. J Stroke Cerebrovasc Dis. 2013 Oct;22(7):1196-200. doi: 10.1016/j.jstrokecerebrovasdis.2012.12.015. Epub 2013 Jul 5. PMID: 23834849
32. Munich S, Moftakhar R, Lopes D. Recanalization of acute carotid stent occlusion using Penumbra 4Max aspiration catheter: technical report and mreview of rescue strategies for acute carotid stent occlusion. BMJ Case Rep. 2013 Oct 14;2013: bcr2013010706. doi: 10.1136/bcr-2013-010706. PMID: 24127372; PMCID: PMC3822067.
33. Dhall A, Malani SK, Chadha DS. Thrombosuction for procedural acute thrombosis during high-risk carotid angioplasty--a case report. J Invasive Cardiol. 2010 Aug;22(8):E144-6. PMID: 20679679.
34. Owens EL, Kumins NH, Bergan JJ, Sparks SR. Surgical management of acute complications and critical restenosis following carotid artery stenting. Ann Vasc Surg. 2002 Mar;16(2):168-75. doi: 10.1007/s10016-001-0152-2. Epub 2002 Mar 15. PMID: 11972247.
35. Masuo O, Terada T, Matsuda Y, Ogura M, Tsumoto T, Yamaga H, Itakura T. Successful recanalization by in-stent percutaneous transluminal angioplasty with distal protection for acute carotid stent thrombosis. Neurol Med Chir (Tokyo). 2006 Oct;46(10):495-9. doi: 10.2176/nmc.46.495. PMID: 17062989.
36. Setacci C, de Donato G, Setacci F, Chisci E, Cappelli A, Pieraccini M, Castriota F, Cremonesi A. Surgical management of acute carotid thrombosis after carotid stenting: a report of three cases. J Vasc Surg. 2005 Nov;42(5):993-6. doi: 10.1016/j.jvs.2005.06.031. PMID: 16275459.
37. Buhk JH, Wellmer A, Knauth M. Late in-stent thrombosis following carotid angioplasty and stenting. Neurology. 2006 May 23;66(10):1594-6. doi: 10.1212/01.wnl.0000216141.01262.77. PMID: 16717230.
38. Choi HJ, Kim ST, Jeong YG, Jeong HW. 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

Dec;52(6):551-4. doi: 10.3340/jkns.2012.52.6.551. Epub 2012 Dec 31. PMID: 23346328; PMCID: PMC3550424.

39. Kim YW, Kang DH, Hwang JH, Park J, Hwang YH, Kim YS. 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 Aug;155(8):1583-8. doi: 10.1007/s00701-013-1744-7. Epub 2013 May 21. PMID: 23689967.
40. Seo KD, Lee KO, Kim DJ, Lee KY. Rescue use of tirofiban for acute carotid in-stent thrombosis. Yonsei Med J. 2008 Feb 29;49(1):163-6. doi: 10.3349/ymj.2008.49.1.163. PMID: 18306485; PMCID: PMC2615275.
41. Köklü E, Arslan Ş, Yüksel İÖ, Bayar N, Koç P. Acute Carotid Artery Stent Thrombosis Due to Dual Antiplatelet Resistance. Cardiovasc Intervent Radiol. 2015 Aug;38(4):1011-4. doi: 10.1007/s00270-014-0959-1. Epub 2014 Aug 13. PMID: 25117620.
42. Moulakakis KG, Kakisis J, Tsivgoulis G, Zymvragoudakis V, Spiliopoulos S, Lazaris A, Sfyroeras GS, Mylonas SN, Vasdekis SN, Geroulakos G, Brountzos EN. Acute Early Carotid Stent Thrombosis: A Case Series. Ann Vasc Surg. 2017 Nov;45: 69-78. doi: 10.1016/j.avsg.2017.04.039. Epub 2017 May 5. PMID: 28483628.
43. Hu W, Wang L, Wang G. Acute In-Stent Thrombosis after Carotid Angioplasty and Stenting: A Case Report and Literature Review. Interv Neurol. 2018 Apr;7(5):265-270. doi: 10.1159/000486247. Epub 2018 Apr 3. PMID: 29765396; PMCID: PMC5939804.
44. Wei W, Wang Y, Wang P, Li Z. Revascularization of acute stent thrombosis after carotid artery stenting in a *CYP2C19*2* heterozygote patient. J Int Med Res. 2021 Mar;49(3):3000605211001191. doi: 10.1177/03000605211001191. PMID: 33745326; PMCID: PMC7989125.
45. Cvjetko I, Đaković Bacalja I, Cvjetko T. Acute Carotid Artery Stent Thrombosis. Cardiovasc Intervent Radiol. 2018 Feb;41(2):355-356. doi: 10.1007/s00270-017-1808-9. Epub 2017 Oct 16. PMID: 29038879.
46. Toljan K, Jovanović I, Starčević K, Ljevak J, Blažević N, Radoš M, Poljaković Z. Acute Carotid Stent Thrombosis in an Ultrarapid Clopidogrel Metabolizer: Case Report and Literature Review. Vasc Endovascular Surg. 2019

Oct;53(7):602-605. doi: 10.1177/1538574419857965. Epub 2019 Jul 4. PMID: 31272299.