

Complication Rates Using CASPER Dual-Layer Stents for Carotid Artery Stenting in Acute Stroke

A 3-Year Single Center Experience

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Abstract

Background and Purpose The number of acute and early stent occlusions after emergency stenting of the internal carotid artery (ICA) in patients with tandem lesions is unclear and only mentioned in a small number of publications, ranging from 0–20%. A recent article by Yilmaz et al. reported a high rate of acute in-stent occlusions of 45% within 72 h after deployment of CASPER dual layer stents.

Methods All patients with acute ischemic stroke treated with a CASPER stent between August 2014 and April 2018 were retrospectively evaluated for occlusion rates, periinterventional medication and early complications. A total of 66 patients, 45 with tandem pathologies and 21 with proximal ICA stenosis only were enrolled.

Results Thrombotic complications occurred in 16 out of 66 patients (24%) and hemorrhagic complications in 8/66 (12%) and 15 of the 16 thrombotic complications and 7/8 symptomatic intracranial hemorrhages (sICH) occurred in patients with tandem lesions and accessory intracranial thrombectomy. Of the patients with sICH five were treated in a prolonged or unknown time window. In patients with intraprocedural thrombotic complications ultrasound imaging showed patent stents in 13 of the 14 patients

Conclusions The CASPER stent system showed a high technical success rate in patients with acute stroke. The number of patients with sICH was not higher than the numbers reported in the published literature despite the early use of Gp IIb/IIIa inhibitors, whereas the number of thrombotic complications was smaller than that reported in recent studies. The majority of sICH occurred in patients treated because of tandem lesions in an unknown or prolonged time window.

Abbreviations

+ic	Carotid stent and intracranial thrombectomy
-ic	Carotid stent only
ASA	Acetylsalicylic acid
CCDS	Color coded duplex sonography
CTA	Computed tomograph angiography
Gp IIb/IIIa	Glycoprotein IIb/IIIa

mTICI	Modified treatment in cerebral ischemia scale
NCCT	Non-contrast cranial computed tomography
PTA	Percutaneous balloon angioplasty
rtPA	recombinant tissue plasminogen activator
sICH	Symptomatic intracranial hemorrhage

Introduction

In a recent meta-analysis of five large thrombectomy trials [1] approximately 10% of patients presented with tandem lesions defined as a combination of high-grade stenosis or occlusion of the ipsilateral proximal internal carotid artery (ICA) and an occlusion of large intracranial arteries in the anterior circulation. Although this subgroup showed substantial benefits by mechanical thrombectomy, the optimal

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approach regarding the treatment of a proximal ICA lesion alone [2–4] or in combination with an intracranial occlusion [5–16] in patients with acute ischemic stroke remains unclear. A recent retrospective analysis of 295 patients showed a favorable outcome in patients with emergency stenting compared to conservative management or percutaneous balloon angioplasty (PTA) of the ICA lesion alone [17]. Aside from the optimal approach considering treatment of the proximal carotid lesions, questions about periprocedural interventional antithrombotic treatment [7, 18–20] as well as the optimal choice of stents have been raised. Although carotid stents have been available for some years, novel dual layer closed cell stents like the CASPER™ stent (Terumo Microvention, Aliso Viejo, CA, USA) or the CGuard stent (InspireMD, Boston, MA, USA) promise better plaque coverage due to smaller cell size compared to the older generation stents, thus minimizing the risk of thromboembolic events during placement and show promising results in elective patients [21–24]. The issue of early stent occlusion within 24–72 h after stenting of the ICA in patients with tandem pathologies has only been addressed in a small number of studies with numbers ranging between 0% and 19% [8, 9, 15, 16, 25–29]. A recent article by Yilmaz et al. reported a surprisingly high rate of acute in-stent occlusions within 72 h after deployment in 45% of the patients treated with the CASPER stent in cases with tandem lesions [30]. These findings are not in line with our own experience. Therefore, this retrospective study was conducted including all emergency patients treated in the Augsburg University hospital between August 2014 and April 2018 with a CASPER stent to evaluate the incidence of thrombotic and hemorrhagic complications in these subsets of patients.

Methods

This retrospective study was approved by the local ethics committee. Because of the retrospective design informed consent was not necessary according to the committee's decision. During the study period 204 patients received a carotid stent. Of these, 164 patients were treated with a CASPER stent. Most of the other patients received either carotid wall stents as the previously used standard stent or the CGuard, which was tested during this period. Of the patients 74 receiving a CASPER stent were treated for an acute stroke, 8 patients were excluded, 2 because of failure of recanalization of intracranial thromboembolic ICA occlusions and 6 because of arterial intracranial bleeding as a complication of intracranial thrombectomy requiring occlusion of the bleeding vessels. For these patients no sufficient follow-up data were available. A total of 66 patients were included in the final analysis. Patients were divided into a group with tandem lesions receiving stenting and

thrombectomy (+ic) and patients who were treated only with stenting (-ic). Postprocedural imaging as well as clinical reports were evaluated for:

1. Periinterventional medication
2. In-stent thrombosis or occlusion during intervention or hospital stay
3. Periinterventional medication, in-stent thrombosis or occlusion during intervention or hospital stay and symptomatic intracranial hemorrhage (parenchymal hemorrhage PH1 and 2 according to the European carotid acute stroke study (ECASS) criteria [31]).

Imaging

All emergency patients initially received a standard imaging protocol including a non contrast cranial computed tomography (NCCT) followed by a computed tomography angiography (CTA). In case of unknown onset of symptoms, e.g. wake up stroke, an additional CT perfusion (CTP) was performed. Patients were treated if a significant mismatch between cerebral blood flow (CBF) and cerebral blood volume (CBV) of more than one third of the territory of the middle cerebral artery or in eloquent regions, e.g. motor cortex, was detected.

Endovascular Procedure

Digital subtraction angiography (DSA) was usually performed at the institution neuroradiology suite on a biplane Siemens Axiom Artis (Siemens Healthcare, Erlangen, Germany). The choice of the guiding catheter and, in the case of tandem lesions, the method of thrombectomy (e.g. aspiration alone, stent retrieving or combination) as well as the choice of thrombectomy device remained at the discretion of the interventionalist. In most cases of tandem lesions an antegrade approach with primary stenting of the ICA followed by intracranial thrombectomy was chosen. Percutaneous balloon angioplasty (PTA) before stenting was only performed if the stenosis or occlusion could not primarily be passed with the stent delivery system. In cases of residual stenosis, poststenting angioplasty was performed. Usually for pre-stenting a 2.0×20 mm and for poststenting a 5.0×20 mm noncompliant balloon were used.

Choice of Antiplatelet Medication

All eligible emergency patients recombinant tissue plasminogen activator (rtPA) adapted to body weight. If no antiplatelet therapy was given before the intervention for other reasons, the institutional standard medication consisted of an i.v. dose of 100 mg acetylsalicylic acid (ASA) after stent deployment and postprocedural administration of tirofiban.

A 250ml infusion containing 12.5 mg of tirofiban was administered i.v. with a bolus over three minutes and subsequent maintenance doses each adapted to the patient's body weight, ranging from a bolus of 25 ml and maintenance dose of 9 ml/h for a body weight of 50 kg to 60 ml and 22 ml/h for 120 kg. At a time 4 h before cessation of the tirofiban infusion, a loading dose of 180 mg of ticagrelor was administered orally, followed by a maintenance dose of 90 mg given twice a day for a minimum of 6 weeks and 100 mg of ASA given orally daily for at least 6 months. Administration of heparin, usually 5000 IU i.v., during stent deployment was at the discretion of the interventionalist. In cases of sufficient ICA flow restoration, i.e. no or little residual stenosis according to North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria [32], some patients received only ASA, and ticagrelor was administered after the 24 h NCCT. No protection devices were used. Most treatments were carried out with the patients under general anesthesia.

Postinterventional Imaging

In cases of intracranial thrombectomy, a flat detector NCCT (DynaCT™, Siemens, Erlangen, Germany) was routinely performed after the procedure. If no intracranial thrombectomy was performed, patients did not undergo immediate postprocedural computed tomography (CT) imaging. All patients routinely received a postprocedural NCCT 24 h after treatment. In cases of neurologic deterioration or sICH on flat panel NCCT, additional postprocedural NCCT was performed.

Postprocedural CCDS examinations were available for 35 (78%) +ic patients and 20 (95%) -ic patients (Table 1). In only one patient who received a stent due to a complication of a surgical procedure, the first ultrasound examination was performed only transcranially, only enabling evaluation of indirect signs of proximal ICA pathology. Ultrasound examinations were performed by the neurologist on duty.

Table 1 Demographic data, preprocedural and postprocedural stenosis grading

	Stent and thrombectomy (n = 45)	Stent only (n = 21)
Age (years)	65 ± 10	74 ± 9
Sex female	13 (29%)	6 (29%)
Side left	27 (60%)	11 (52%)
Diabetes	9 (20%)	9 (43%)
Hypertension	34 (76%)	20 (95%)
Coronary artery disease	6 (13%)	8 (38%)
Dyslipidemia	27 (60%)	16 (76%)
Previous stroke	10 (22%)	9 (43%)
Stenosis DSA preprocedural (%)	93 ± 16	90 ± 9
Stenosis DSA postprocedural (%)	11 ± 22	9 ± 12
Stenosis CCDS postprocedural (%)	12 ± 28 (n = 35)	11 ± 189 (n = 20)

DSA digital subtraction angiography, CCDS color coded duplex sonography

Table 2 Periprocedural medication

Medication	Stent and thrombectomy (n = 45)	Stent only (n = 21)
rtPA (%)	33 (73%)	9 (43%)
ASA preprocedural	12 (27%)	12 (57%)
Clopidogrel preprocedural	2 (4%)	3 (14%)
Ticagrelor preprocedural (%)	0	0
Mono-platelet inhibition preprocedural	12 (27%)	13 (62%)
Dual platelet inhibition preprocedural	1 (2%)	1 (5%)
ASA intraprocedural	39 (87%)	9 (43%)
Tirofiban intraprocedural	33 (73%)	9 (43%)
Heparin intraprocedural	9 (20%)	6 (29%)
ASA postprocedural (%)	41 (91%)	20 (95%)
Clopidogrel postprocedural (%)	6 (13%)	4 (19%)
Ticagrelor postprocedural (%)	34 (76%)	15 (71%)

rtPA recombinant tissue plasminogen activator, ASA acetylsalicylic acid

Results

Details concerning the demographic data are given in Table 1 and the medication in Table 2. The only obvious differences between the two groups were the higher mean age (74 ± 9.4 years vs. 64 ± 10.1 years) and the higher number of patients receiving ASA (57% vs 27%) in the stent only group. Not listed in the tables are ASPECTS on admission- (+ic 8.0 ± 2.2 , -ic 9.5 ± 1.0) and on follow-up NCCT (+ic 6.8 ± 1.3 , -ic 8.0 ± 1.8) as well as National Institutes of Health Stroke Scale (NIHSS) scores on admission (+ic 12.9 ± 5.3 , -ic 8.1 ± 3.9) and at discharge (+ic 6.7 ± 5.2 , -ic 5.4 ± 4.4). The NIHSS scores were not available for all of the patients.

An antegrade approach with initial stenting of the ICA followed by intracranial thrombectomy was undertaken in 36 (80%) and a retrograde approach in 9 (20%) patients. Predilation was necessary in 4 patients (+ic 3/7%, -ic 1/5%), postdilation in 33 (+ic 23/51%, -ic 10/48%) and both in 16 patients (+ic 11/24%, -ic 7/33%). In thrombectomy patients the level of intracranial occlusion was distal ICA or carotid-T in 13, M1 in 23, and M2 in 9 patients (29%, 51%, and 20%, respectively). Final recanalization results according to the modified treatment in cerebral ischemia scale (mTICI) [33] were 0 in 2 (4%), 2a in 2 (4%), 2b in 27 (60%) and 3 in 14 (31%) patients.

Thrombotic complications occurred in 16/66 (24%) patients and hemorrhagic complications in 8/66 (12%). Most of these complications (15/16 thrombotic, 7/8 sICH) occurred in patients with tandem lesions, corresponding to a rate of 33% thrombotic and 16% sICH in this subset of 45 patients and 1 patient suffered both complications. Of the patients 2 showed delayed sICH more than 24h after intervention, 2 patients, who are not listed, showed mild subarachnoid hemorrhage on 24h follow-up NCCT but were asymptomatic. Of the patients with sICH, 2 patients had a wake-up stroke and 3 patients were treated in an extended time window more than 6h after onset.

Intraprocedural thrombotic complications were usually detected at the end of the procedure during cervical control angiography. Of the 14 patients with intraprocedural thrombotic complications 3 showed an intraprocedural complete stent occlusion and 11 thrombotic stent wall apposition resulting in a significant stenosis of at least 50%. In cases of complete occlusion treatment consisted in one case of aspiration thrombectomy and administration of tirofiban, in the second case of administration of papaverine for spasmolysis and tirofiban and in the third case of tirofiban only. Of these patients one developed sICH and died and the two remaining patients showed patent stents without significant stenosis on follow-up CCDS. Overall 11 patients, 10 with tandem lesions and 1 with stenting alone, showed intraprocedural thrombotic apposition at the stent wall. Of these,

Table 3 Complications by patient groups

	Stent and thrombectomy (n = 45)	Stent only (n = 21)
sICH	7 (16%)	1 (5%)
Intraprocedural occlusion	3 (7%)	–
Early occlusion	2 (4%)	–
In-stent thrombosis	10 (22%)	1 (4%)

sICH symptomatic intracranial hemorrhage

one patient was treated with PTA and accessory stent and three with PTA only. All other patients received tirofiban as sole treatment. All of these patients received dual antiplatelet therapy overlapping with the tirofiban infusion.

Early occlusion occurred in two cases, in one case 6h after intervention and during tirofiban infusion. The second patient, who had a thrombotic stent wall apposition during procedure, showed progression to a complete stent occlusion on CCDS examination the day following the intervention, most likely because of early cessation of antiplatelet therapy due to gastrointestinal bleeding.

For 14 of the 16 patients with thrombotic complications CCDS follow-up was available, showing only 1 occlusion and in 2 patients a stenosis of 60%. An overview on the number of complications for each group is provided in Table 3.

Discussion

The benefits of endovascular treatment of symptomatic as well as asymptomatic ICA stenosis was shown in a recent follow-up analysis of the CREST study [34]. There are only a few smaller retrospective studies that evaluated the benefits of emergency endovascular treatment of isolated symptomatic ICA stenosis or occlusion. These reported high recanalization rates and good clinical outcomes [2–4]. The HERMES meta-analysis of five large thrombectomy studies additionally showed beneficial effect of endovascular ICA treatment in patients with tandem lesions [1]. Furthermore, a number of meta-analyses and retrospective case series documented the safety and technical feasibility of treatment of proximal ICA pathology in patients with tandem lesions, mostly with PTA-assisted stenting [7–14, 17]. Due to the lack of prospective data, the optimal treatment of proximal ICA pathology in patients presenting with acute stroke and especially with tandem lesions, remains the subject of discussion mainly because of concerns that the necessary platelet inhibition in combination with acute brain infarction might lead to a higher rate of sICH [5, 25, 35].

Only a few articles addressing the treatment of tandem pathologies mentioned the number of early stent occlusions with numbers ranging from 0% to 19% [8, 9, 15, 16, 25–29].

In these articles mostly monolayer stents were used and the periprocedural antithrombotic medication differed significantly between the studies especially with respect to the use of Gp IIb/IIIa inhibitors. Compared to these numbers a recent study by Yilmaz et al. [30] showed a surprisingly high rate of in-stent thrombosis or stent occlusion in patients with acute tandem lesions treated with CASPER dual layer stents of 50% and 45%, respectively compared to monolayer stents (37% and 3.7%, respectively), thus raising the question of the optimal stents to be used in these cases. On the other hand recent reports indicated promising results in the treatment of elective patients with dual layer stents, mostly in combination with distal protection devices, in terms of technical success [23] and reduction of thrombus protrusion through the stent cells as well as a reduction in postinterventional diffusion weighted imaging lesions on magnetic resonance imaging [22, 24], most likely due to smaller cell size compared to older generation monolayer stent systems. Because of its mechanical properties the CASPER stent seems to be well-suited for use in stroke patients [23, 24].

In most of the cases in this study with significant intraprocedural thrombus formation, the most likely cause was a wedge position of either the aspiration catheter or the access catheter which resulted in blood stasis within the stent lumen and significant in-stent thrombosis of more than 50%. Of the patients with significant in-stent thrombus one showed severe vasospasm after stent deployment and stasis within the vessel lumen as the most probable mechanism leading to the thrombotic formation at the stent wall.

The percentage of patients with acute and early occlusions of 11% is in line with the numbers reported for the monolayer stents mentioned above and much lower than reported in the recent report by Yilmaz et al. [30]. In this emergency cohort, on the other hand a relatively high number of in-stent thrombus appositions was also found in the +ic group, although the numbers were far lower than in the work of Yilmaz et al. (+ic 33% vs. 56%) [30]. The suggested mechanism is a higher thrombogenicity of the CASPER stent because of the smaller cell size resulting in a higher metal-artery ratio. Another reason for the higher rate of in-stent thrombosis in the +ic group might be the delayed restoration of adequate blood flow in patients with a concomitant intracranial lesion when treating the extracranial lesion first. This might be especially true in patients with occlusion of the carotid T.

The most likely explanation of the much lower incidence of early occlusion in this series is a more aggressive antiplatelet regimen. Compared to the population of patients reported by Yilmaz et al. [30] the number of acute patients with single or dual antiplatelet treatment before stenting was slightly (+ic 29%, -ic 67%, overall 41% vs 52%), while the percentage of patients receiving i. v. thrombolysis was

higher in the present cohort (+ic 73%, -ic 43%, overall 64% vs. 30%). The general antiplatelet regimen used by Yilmaz et al. [30] in patients without preinterventional antiplatelet medication consisted of 500mg of ASA i.v. during stent deployment and clopidogrel within 24h postintervention, starting with a loading dose of 300mg. In contrast to this relatively conservative approach by default tirofiban was already used during interventions in most cases and dual platelet inhibition was started usually as a combination of ASA and ticagrelor before the end of the tirofiban administration. Furthermore, Yilmaz et al. observed a thrombus formation or thrombus protrusion in 37% of the patients treated with monolayer stents and in 50% of the patients treated with dual layer stents, progressing to complete occlusion in 55% of the patients. The use of clopidogrel did not seem to influence the rate of stent occlusions [30]. Although the rate of significant in-stent thrombosis of 33% in patients with tandem lesions seems relatively high, progression to a stent occlusion was observed in only one of these patients. In this patient, however, no sufficient platelet inhibition could be administered because of gastrointestinal bleeding. These findings are similar to the results of Steglich-Arnholm et al. [15], who observed acute stent thrombosis during endovascular procedure when mainly monolayer stents were used in 8 out of 47 (17%) of the patients. In 7 of these, administration of Gp IIb/IIIa antagonists (eptifibatide or abciximab) led to recanalization. Despite the much more aggressive antiplatelet therapy in the present cohort of emergency patients, the rate of sICH was 12% (+ic 16%, -ic 5%) and therefore within the numbers reported in the literature ranging from 4% to 20% [6, 7, 9, 11, 15, 25, 30]. Remarkably, all but one sICH occurred in the group with tandem lesions. Of these patients two were treated in an extended time window with known onset but no or little infarct demarcation and three as a wake-up stroke. Furthermore, although not available for all patients, the lower average ASPECTS and higher NIHSS scores in the +ic-group might be suggestive of a more severe ischemia and might partly explain the higher incidence of intracranial hemorrhage in this group.

Delayed administration of clopidogrel and abdication of Gp IIb/IIIa inhibitors did not lead to a reduced number of sICH (5% dual layer, 18.5% mono layer, overall 22%) in the cohort of Yilmaz et al. [30]. The high rate of thrombotic complications in this cohort might be due to the reported high rate of clopidogrel nonresponders of up to 45% [36]. Intravenous tirofiban immediately after rtPA seems to be safe and potentially more effective when compared to alteplase alone for selected stroke patients and not leading to a significantly higher rate of ICH [37]. On the other hand, a recent meta-analysis reported only a slightly increased risk of sICH in patients with acute stroke receiving antiplatelet medication [38]. This risk has to be weighed against the complications of an ICA reocclusion, since no

prospective data exist on the problem of medication after stent implantation in acute stroke, therefore, no clear recommendations for antiplatelet therapy after CAS can be given in these cases [19, 39], although many authors advocate early use of Gp IIb/IIIa receptor inhibitors [7, 18–20].

This study has some obvious limitations. First, it is a monocentric and retrospective cohort study. Second, antiplatelet medication varied between patient groups as well as within the groups despite a fixed institutional medication regimen, which makes it difficult to determine the influence of the antiplatelet therapy on the occurrence of adverse events. In addition, no conclusions can be drawn on the influence of thrombotic complications on the clinical outcome since the modified Rankin scale was not routinely assessed after 90 days. The influence of periprocedural and postprocedural complications on clinical outcome therefore remains unclear in this cohort.

Conclusion

In this series of CASPER stents used in the treatment of acute ischemic stroke, the number of patients with symptomatic intracranial hemorrhage with early administration of Gp IIb/IIIa inhibitors and dual platelet inhibition was not higher than the numbers reported in the literature. The number of thrombotic complications was well below that reported in recent studies evaluating CASPER stents in patients with tandem lesions. Given the high numbers of patients with sICH who were in an unclear or prolonged time window due to tandem lesions, stent treatment in these patient groups should only be performed after a thorough risk-benefit analysis. The use of the CASPER dual layer stent in acute stroke patients showed an acceptably low complication rate. Further prospective studies are needed to address the question of optimal treatment strategies as well as antiplatelet therapy in patients with emergency stenting with or without tandem lesions.

Compliance with ethical guidelines

Conflict of interest F. Runck declares that he has no competing interests. C.J. Maurer received educational grants from Microvention and Stryker. A. Berlis is proctor for Sequent Medical, Microvention, Stryker and Medtronic and received lecture royalties from Penumbra.

Ethical standards This article does not contain any studies with human participants or animals performed by any of the authors. All investigations described in this manuscript were carried out with the approval of the responsible ethics committee and in accordance with national law and the Helsinki Declaration of 1975 (in its current revised form).

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