Original Contribution

Acute Occlusions of Dual-Layer Carotid Stents After Endovascular Emergency Treatment of Tandem Lesions

Umut Yilmaz, MD; Heiko Körner, MD; Ruben Mühl-Benninghaus, MD; Andreas Simgen, MD; Catherine Kraus; Silke Walter, MD; Stefanie Behnke, MD; Klaus Faßbender, MD; Wolfgang Reith, MD; Marcus M. Unger, MD

Background and Purpose—A new generation of carotid artery stents that uses a second micromesh layer to reduce embolic events during carotid artery stenting has recently been introduced. The purpose of this study was to compare acute occlusion rates of these new dual-layer stents with those of single-layer stents in the setting of emergency carotid artery stenting with intracranial mechanical thrombectomy in acute ischemic stroke.

Methods—Consecutive patients with acute tandem (intra- and extracranial) lesions of the anterior circulation who were endovascularly treated at our institution were identified from our registry of neuroendovascular interventions. Clinical, angiographic, and neuroimaging data were analyzed. End points included acute occlusions of the carotid stents (within 72 hours after stenting) and symptomatic intracerebral hemorrhage.

Results—Forty-seven patients were included. Dual-layer stents (n=20) had a significantly higher rate of acute occlusions than single-layer stents (n=27; 45% versus 3.7%; *P*=0.001; odds ratio, 21.3; 95% confidence interval, 2.4–188.4). There were no significant differences in the rates of patients who had any antiplatelet or dual antiplatelet medication before admission, in the rates of postinterventional symptomatic intracerebral hemorrhage, the mean National Institutes of Health Stroke Scale scores at admission, or the modified Rankin Scale scores at discharge.

Conclusions—The recently introduced dual-layer stents have a higher risk of acute occlusion compared with single-layer stents in the treatment of acute stroke. **(*Stroke*. 2017;48:00-00. DOI: 10.1161/STROKEAHA.116.015965.)**

Key Words: angioplasty ■ carotid stenosis ■ stents ■ stroke ■ thrombectomy

Several multicenter prospective randomized controlled trials have recently demonstrated the clinical benefit of mechanical thrombectomy in functional outcome after 3 months in acute intracranial occlusions of the anterior circulation.[1–3] Thirteen percent to 32% of the patients in these studies had tandem lesions defined as an occlusion of a M1 segment or intracranial internal carotid artery (ICA) with an additional ipsilateral occlusion or high-grade stenosis of the origin of the ICA. The endovascular treatment of tandem lesions requires a combined approach with intracranial thrombectomy and extracranial stenting or angioplasty.

Recently, a new generation of carotid artery stents has been introduced that uses a second micromesh layer for a better coverage of the atherosclerotic plaque with more effective prevention of dislodgement of debris[4] (Figure).

It has not been investigated whether these novel dual-layer carotid artery stents have a higher risk of occlusion in the emergency setting than in the elective treatments of asymptomatic or symptomatic carotid stenosis. The purpose of our study was to compare acute occlusion rates of the new dual-layer stents with those of single-layer stents in the setting of an acute stroke.

Methods

Research was conducted according to the principles of the Declaration of Helsinki. We retrospectively included all patients who consecutively underwent mechanical thrombectomy and emergency carotid artery stenting in our institution between 2011 and 2016. Patients were identified from our registry of neuroendovascular interventions.

Inclusion criteria were as follows:

- Acute occlusion of a M1 segment or intracranial ICA treated by mechanical thrombectomy.
- Emergency stenting of an occlusion or high-grade stenosis of the carotid bifurcation preventing endovascular access to the intracranial site of occlusion (residual lumen less than ≈3 mm).
- Duplex ultrasonography before discharge to evaluate patency of the stent.

Inclusion Criteria for Mechanical Thrombectomy

Patients meeting the following criteria are selected for mechanical thrombectomy:

- neurological examination demonstrating a significant neurological deficit (paresis of arm or leg, aphasia, dysarthria, and decreased consciousness),
- intracranial hemorrhage and established major infarction excluded by noncontrast computed tomography,
- computed tomographic (CT) angiography confirming occlusion of a M1 segment or intracranial ICA.

Received November 7, 2016; final revision received June 8, 2017; accepted June 12, 2017.

From the Department of Neuroradiology (U.Y., H.K., R.M.-B., A.S., C.K., W.R.) and Department of Neurology (S.W., S.B., K.F., M.M.U.), Saarland University Hospital, Homburg, Germany.

Correspondence to Umut Yilmaz, MD, Saarland University Hospital, Kirrberger Str. D-66421 Homburg, Germany. E-mail umut.yilmaz@uks.eu

Stroke **is available at http://stroke.ahajournals.org** **DOI: 10.1161/STROKEAHA.116.015965**

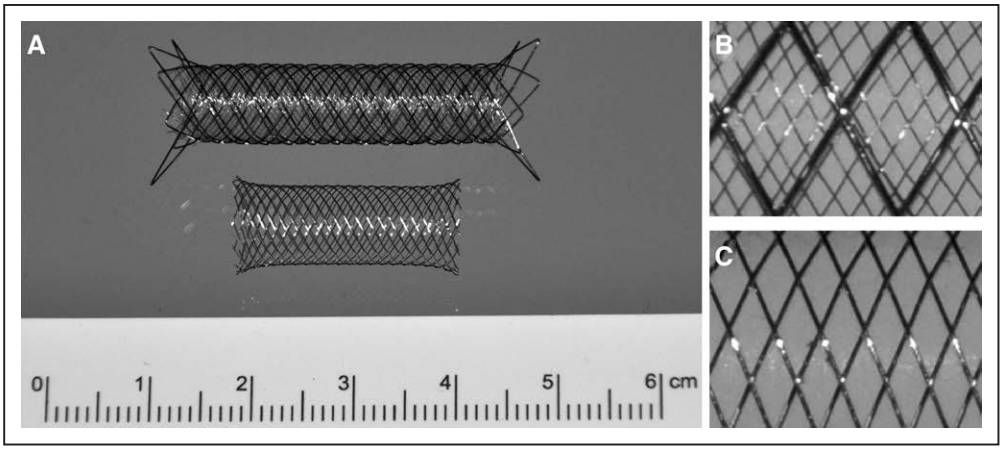

Figure. A, Examples of a closed-cell dual-layer stent (**top**) and a closed-cell single-layer stent (**bottom**). Magnifications show the 2 layers of the dual-layer stent (**B**) with the inner micromesh that reduces free-cell area compared with the single-layer stent (**C**).

– Treatment can be initiated (groin puncture) within 6 hours of symptom onset.

All eligible patients are treated with intravenous r-tPA (recombinant tissue-type plasminogen activator).

Imaging

The imaging protocol for patients with suspected stroke in our department consists of a noncontrast computed tomography, followed by CT angiography and CT-perfusion scans. CT angiography scans were performed in helical mode (0.5-mm thickness) with bolus tracking in the ascending aorta.

Endovascular Procedures

Recanalization procedures were performed on 1 of 3 angiography machines (Siemens Axiom Artis, Siemens Artis Q, or Siemens Artis zeego; each from Siemens Healthcare, Erlangen, Germany). Stent retrievers used were Solitaire FR and Solitaire 2 (Medtronic, Minneapolis, MN). Carotid artery stents used were Casper-RX (Microvention, Tustin, CA), Wallstent (Boston Scientific, Marlborough, MA), and Vivexx (Bard, Tempe, AZ). Patients who were not administered IV r-tPA received a bolus of 5000 IU of heparin intravenously. Glycoprotein IIb/IIIa inhibitors were not used. At our institution, acute tandem occlusions of the anterior circulation are routinely treated by percutaneous transluminal angioplasty of the origin of the ICA as first-line therapy for stenosis or occlusions. Stenting is performed when percutaneous transluminal angioplasty does not result in a recanalization that is sufficient for access to the intracranial site of occlusion or when there is a reocclusion during the interventional procedure. Poststenting dilatation is routinely performed. Patients without antiplatelet medication before admission receive 500 mg of intravenous acetylsalicylic acid before deployment of the carotid stent. A standard procedure for the administration of clopidogrel had not been established in our institution at the time period that was analyzed. The decision when to start the clopidogrel medication was at the discretion of the treating neurologist and neuroradiologist.

Postinterventional Imaging

Peri-interventional hemorrhage is ruled out by CT that is routinely performed immediately after the endovascular procedure. A follow-up CT or magnetic resonance imaging is routinely performed after 24 hours. According to ECASS II criteria (European Cooperative Acute Stroke Study),[5] we defined hemorrhagic events according to clinical and CT criteria: hemorrhagic infarction type 1: small petechiae at margin of infarction; hemorrhagic infarction type 2: confluent petechiae in the infarcted area without space-occupying effect; parenchymal hemorrhage type 1: blood in ≤30% of the infarcted area with slight space-occupying effect; and parenchymal hemorrhage type 2: blood clots in >30% of the infarcted area with substantial space-occupying effect.

Symptomatic intracranial hemorrhage was defined as blood at any site in the brain with clinical worsening (eg, drowsiness, increase of hemiparesis) or causing a decrease in the National Institutes of Health Stroke Scale score of ≥4 points.

Postinterventional evaluation of stent patency was routinely performed on the day after the endovascular therapy and before discharge by ultrasonography. Acute occlusions were defined as occlusions within 72 hours after stenting.

Statistical analysis was performed using SPSS 20.0. χ^2 test was applied to determine the differences in frequencies. Differences in means were tested using Student *t* test. Receiver operating characteristic analysis was used to determine the optimal cutoff value of significant continuous variables. $P<0.05$ was considered statistically significant.

Results

Demographic and Clinical Data

The data of 47 consecutive patients with occlusions of the MCA or intracranial ICA who underwent mechanical thrombectomy and carotid artery stenting in our department was retrospectively analyzed (36 men and 11 women and mean age: 67±12 years). Mean length of the in-hospital stay was 12 days (range: 3–43 days). Twenty patients were treated using the dual-layer Casper-RX stent system. Twenty-seven patients were treated using the single-layer carotid stents Wallstent (closed cell, n=25) and Vivexx (open cell, n=2). All stents were patent on final angiograms after the intervention. Between 2011 and February 2015, only single-layer stents were used (n=26). The first dual-layer stent was used in February 2015. After that, a single-layer stent was used one more time and only closed-cell dual-layer stents thereafter. There was no significant difference of the mean age of the patients (Table 1). Dual-layer carotid artery stents had a significantly higher rate of acute occlusions (defined as occlusions within 72 hours after stenting) than single-layer stents (45% versus 3.7%; P=0.001; odds ratio, 21.3; 95% confidence interval, 2.4–188.4). During the observation period (until hospital discharge), the acute stent occlusion was symptomatic with an increase of the hemiparesis in one case (single-layer group). Six patients had symptomatic intracranial hemorrhages (Table 1).

Three patients (11.1%) in the single-layer group and 3 patients (15%) in the dual-layer group had a history of transient ischemic attack. None of them had an acute stent occlusion after implantation.

Table 1. Clinical, Laboratory and Angiographic Data of Patients Treated With Dual- and Single-Layer Stents

	Dual-Layer Stents (n=20)	Single-Layer Stents (n=27)	*P* Value
Mean age, mean±SD, y	69.9±11.7	64.3±13.0	0.131
Stent length, mean±SD, mm	32.5±4.4	39.3±5.5	<0.000
Stent diameter, mean±SD, mm	8.2±0.8	8.1±1.0	0.885
Patients administered IV r-tPA, n (%)	6 (30.0)	18 (66.7)	0.013
Any antiplatelet medication before admission, n (%)	10 (50.0)	12 (44.4)	0.706
Dual antiplatelet medication before admission, n (%)	1 (5.0)	3 (11.1)	0.458
Leukocyte counts, cells/μL	10 244±5749	10 600±4232	0.808
Platelet counts, cells/μL	204 629±42 181	214 200±6274	0.535
Plasma fibrinogen levels, mg/dL	276±98	283±129	0.829
sICH	1 (5.0)	5 (18.5)	0.170
NIHSS score at admission, mean±SD	12.1±8.4	15.7±6.4	0.115
mRS score at discharge, mean±SD	3.3±1.8	3.1±1.9	0.801

mRS indicates modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; r-tPA, recombinant tissue-type plasminogen activator; and sICH, symptomatic intracerebral hemorrhage.

Periprocedural Medication

Ten patients in the dual-layer stent group (50%) and 15 patients in the single-layer stent group (55.6%) did not have any antiplatelet medication before admission and therefore were administered 500 mg of intravenous acetylsalicylic acid peri-interventionally before deployment of the carotid stent. The rate of patients who were not administered clopidogrel within 24 hours after intervention because of early postinterventional intracerebral hemorrhage was 10% (n=2) in the group with dual-layer stents and 11% (n=3) in the group with single-layer stents. One patient in the dual-layer stent group was administered a loading dose of 40 mg prasugrel immediately after intervention. All of the remaining 41 patients were administered clopidogrel within the first 24 hours after intervention. Clopidogrel was administered as loading dose (300 mg) in 27.8% in the dual-layer group and 17.4% in the single-layer group (*P*=0.425). In the remaining cases, clopidogrel was administered as a single dose of 75 mg.

Procedural Data

In 34 cases (72.3%), angiography showed complete occlusions of the origin of the ICA. High-grade stenoses were found in 13 cases (27.7%). The rates of preinterventional complete occlusions of the origin of the ICA did not differ significantly between single- and dual-layer groups (70.4% versus 75.0%; *P*=0.726). Acute thrombus formations at the stent or thrombus protrusions into the lumen were observed in 37% in the single-layer group and 50% in the dual-layer group (*P*=0.374). Incomplete wall appositions of the stents were observed in 1 case in either group (3.7% versus 5.0%; *P*=0.828). Mean residual stenoses were 8.3±16.8% in the single-layer group and 16.3±19.6% in the dual-layer group (*P*=0.148).

Subgroup Treated With Dual-Layer Stents

The subgroup analysis of the patients who were treated with dual-layer carotid artery stents did not reveal any significant differences of the mean age, the mean lengths of the stents, and the mean diameters of the stents between patients with and patients without acute stent occlusions (Table 2). The rates of preinterventional complete occlusions of the origin of the ICA did not differ significantly between groups with and without acute stent occlusions (77.8% versus 72.7%; *P*=0.795). Acute peri-interventional thrombus formations at the stent or thrombus protrusions into the lumen were observed in 55.6% of the cases with acute stent occlusions and 45.5% of the cases without acute stent occlusions (*P*=0.653). An incomplete wall apposition of a stent was observed in 1 patient who did not have an acute stent occlusion. Mean residual stenoses were nonsignificantly higher in the group with acute stent occlusions (20.0±19.8% versus 13.3±19.8%; *P*=0.460). The rate of patients with unknown time of symptom onset did not significantly differ between the groups with and without stent occlusions (44.4% versus 27.3%; *P*=0.423), neither did the times from symptom onset to puncture of the femoral artery (211±92 versus 203±68 minutes; *P*=0.860). The rate of patients who were administered IV r-tPA was nonsignificantly lower in the group with acute stent occlusions. The rate of patients who had antiplatelet medication before admission was nonsignificantly higher (Table 2). In the dual-layer stent group, the rate of patients with acute stent occlusions was nonsignificantly higher in the subgroup receiving clopidogrel immediately after the intervention (53.8% versus 40%; *P*=0.599). The rates of patients receiving clopidogrel as loading dose were 33.3% in the group with acute stent occlusions and 22.2% in the group without (*P*=0.599).

Discussion

In the treatment of symptomatic carotid artery stenosis, several retrospective and prospective studies[6–8] have reported lower rates of ischemic complications for single-layer closed-cell stents with small free-cell areas compared with single-layer open-cell stents, which may result from a better coverage of the atherosclerotic plaque with more effective prevention of

Table 2. Clinical, Laboratory and Angiographic Data of Patients Treated With Dual-Layer Carotid Stents With and Without Acute Stent Occlusions

	Acute Stent Occlusion (n=9)	No Acute Stent Occlusion (n=11)	*P* Value
Mean age, mean±SD, y	67.1±12.7	72.1±10.8	0.366
Stent length, mean±SD, mm	33.3±5.0	31.8±4.1	0.474
Stent diameter, mean±SD, mm	7.8±0.6	8.5±0.8	0.057
Patients administered IV r-tPA, n (%)	1 (11.1)	5 (45.5)	0.095
Antiplatelet medication before admission n (%)	7 (63.6)	3 (33.3)	0.178
Leukocyte counts, cells/µL	10878±3969	10373±4615	0.796
Platelet counts, cells/µL	253000±55718	182454±50325	0.009
Plasma fibrinogen levels, mg/dL	318±103	254±146	0.267
sICH	0 (0)	1 (9.1)	0.353
NIHSS score at admission, mean±SD	14.4±10.9	10.2±5.5	0.308
mRS score at discharge, mean±SD	4.0±1.9	2.6±1.6	0.101

mRS indicates modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; r-tPA, recombinant tissue-type plasminogen activator; and sICH, symptomatic intracerebral hemorrhage.

dislodgement of debris. This has led to the development of dual-layer carotid artery stent systems that further reduce cell sizes by means of a second micromesh layer.[4]

Such stent systems currently available are the CGuard (InspireMD, Inc, Boston, MD), which consists of an open-cell nitinol stent and a polyethylene terephthalate micromesh, the Casper-RX (Microvention), and the Roadsaver (Terumo, Tokyo, Japan), the latter of which are identical in design and consist of a closed-cell nitinol stent and nitinol micromesh. First single-arm prospective clinical trials have reported no cases of stroke or death using the dual-layer CGuard stent[4] (30 patients) and the dual-layer Roadsaver stent[9] (23 patients) in elective carotid artery stenting of asymptomatic and symptomatic stenoses.

In this retrospective analysis, we report a significantly higher rate of acute stent occlusions of dual-layer carotid artery stents compared with single-layer stents in the setting of acute stroke with an intracranial occlusion and an additional occlusion at the origin of the ICA (tandem occlusions). To our knowledge, this is the first study analyzing the use of dual-layer carotid artery stents in acute stroke. Although there are only 2 previous studies reporting rates of stent occlusions after endovascular treatment of acute stroke with tandem lesions,[10,11] our rate of 3.7% for single-layer stents is consistent with the results for single-layer stents of Malik et al[10] (1.3%). Steglich-Arnholm et al[11] reported a higher rate with stent occlusions in 9% of the cases. Interestingly, in their study, 2 of 47 cases were treated with dual-layer stents (Casper-RX). However, it is not reported which of the stents used were occluded.

A probable explanation for the occurrence of acute stent occlusions with the dual-layer carotid stents may be the increase of thrombogenic material because of the second micromesh layer in a setting of insufficient preparation with antiplatelet medication. This may explain why patients with higher platelet counts in the dual-layer group had a higher risk of an acute stent occlusion. Although not significant, there was a trend for smaller stent diameters in patients with acute stent occlusions, which is consistent with reports of acute (single-layer) stent occlusions in coronary interventions.[12]

An established mono antiplatelet medication before admission did not influence the occurrence of acute stent occlusions in our study. Another factor that was not associated with stent patency was the administration of clopidogrel immediately after the intervention as compared with the early administration within 24 hours after the intervention. We did find a higher rate of stent occlusions when patients were not administered IV r-tPA, but the difference was not significant.

To our knowledge, this is the first study reporting higher rates of acute stent occlusions with dual-layer stents in the treatment of acute stroke. Because there are no reports of higher rates of stent occlusions of dual-layer stents in the elective carotid setting in the treatment of asymptomatic or symptomatic stenoses, this is probably because of the insufficient preparation with antiplatelet medication in the emergency setting. Interventional neuroradiologists should be aware of this association because occlusions are often asymptomatic in the context of the recent stroke, and ultrasound follow-up controls of stent patency are often performed by other disciplines.

Limitations

Our study has several limitations because of its nonrandomized single-center, retrospective design.

The small sample size is a likely reason for many correlations in this study being statistically nonsignificant. Larger studies are needed for the further evaluation of the effects of periprocedural medication and preprocedural intravenous thrombolysis.

A standard antiplatelet regimen after emergency carotid artery stenting had not been established in our institution at the time period that was analyzed. All patients received 500 mg acetylsalicylic acid peri-interventionally, but the decision when to start the clopidogrel administration was made on an individual case basis. However, in our study, the time between

intervention and clopidogrel administration did not affect the occurrence of stent occlusions.

The rate of patients who were administered IV r-tPA was significantly higher in the group treated with single-layer stents. Even though the effect of the thrombolysis is short and the difference was not significant in the dual-layer subgroup, we cannot rule out that this may have affected the occurrence of the acute stent occlusions.

Conclusions

In this retrospective analysis, we report that the recently introduced dual-layer stents have a higher risk of acute occlusion compared with the single-layer stents in the treatment of acute stroke. For the time being, we recommend using single-layer stents in the emergency setting. Interventionalists should be aware of the higher risk of acute stent occlusions with dual-layer stents. All centers involved in the endovascular treatment of acute stroke should have all their patients involved in a quality registry and systematically measure the outcomes, especially if new devices are used.

Disclosures

None.

References

1. Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, et al; MR CLEAN Investigators. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med*. 2015;372:11–20. doi: 10.1056/NEJMoa1411587.
2. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, et al; ESCAPE Trial Investigators. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med*. 2015;372:1019–1030. doi: 10.1056/NEJMoa1414905.
3. Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, et al; REVASCAT Trial Investigators. Thrombectomy within 8 hours after symptom onset in ischemic stroke. *N Engl J Med*. 2015;372:2296–2306. doi: 10.1056/NEJMoa1503780.
4. Schofer J, Musiałek P, Bijuklic K, Kolvenbach R, Trystula M, Siudak Z, et al. A prospective, multicenter study of a novel mesh-covered carotid stent: the CGuard CARENET trial (Carotid Embolic Protection Using MicroNet). *JACC Cardiovasc Interv*. 2015;8:1229–1234. doi: 10.1016/j.jcin.2015.04.016.
5. Larrue V, von Kummer RR, Müller A, Bluhmki E. Risk factors for severe hemorrhagic transformation in ischemic stroke patients treated with recombinant tissue plasminogen activator: a secondary analysis of the European-Australasian Acute Stroke Study (ECASS II). *Stroke*. 2001;32:438–441.
6. 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;40:841–846. doi: 10.1161/STROKEAHA.108.534289.
7. Bosiers M, de Donato G, Deloose K, Verbist J, Peeters P, Castriota F, et al. Does free cell area influence the outcome in carotid artery stenting? *Eur J Vasc Endovasc Surg*. 2007;33:135–141; discussion 142. doi: 10.1016/j.ejvs.2006.09.019.
8. Doig D, Turner EL, Dobson J, Featherstone RL, Lo RT, Gaines PA, et al.; ICSS Investigators. Predictors of stroke, myocardial infarction or death within 30 days of carotid artery stenting: results from the International Carotid Stenting Study. *Eur J Vasc Endovasc Surg*. 2016;51:327–334. doi: 10.1016/j.ejvs.2015.08.013.
9. Ruffino MA, Faletti R, Bergamasco L, Fonio P, Righi D. Incidence of new ischaemic brain lesions after carotid artery stenting with the micromesh roadsaver carotid artery stent: a prospective single-centre study. *Cardiovasc Intervent Radiol*. 2016;39:1541–1549. doi: 10.1007/s00270-016-1454-7.
10. Malik AM, Vora NA, Lin R, Zaidi SF, Aleu A, Jankowitz BT, et al. Endovascular treatment of tandem extracranial/intracranial anterior circulation occlusions: preliminary single-center experience. *Stroke*. 2011;42:1653–1657. doi: 10.1161/STROKEAHA.110.595520.
11. Steglich-Arnholm H, Holtmannspötter M, Kondziella D, Wagner A, Stavngaard T, Cronqvist ME, et al. Thrombectomy assisted by carotid stenting in acute ischemic stroke management: benefits and harms. *J Neurol*. 2015;262:2668–2675. doi: 10.1007/s00415-015-7895-0.
12. Aoki J, Lansky AJ, Mehran R, Moses J, Bertrand ME, McLaurin BT, et al. Early stent thrombosis in patients with acute coronary syndromes treated with drug-eluting and bare metal stents: the Acute Catheterization and Urgent Intervention Triage Strategy trial. *Circulation*. 2009;119:687–698. doi: 10.1161/CIRCULATIONAHA.108.804203.

Stroke
Journal of the American Heart Association

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Stroke. published online July 5, 2017;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628