JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 10, NO. 12, 2017

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jcin.2017.03.032

PERIPHERAL

The Use of Embolic Protection Devices Is Associated With a Lower Stroke and Death Rate After Carotid Stenting

Christoph Knappich, MD,[a] Andreas Kuehnl, MD, MPH, MBA,[a] Pavlos Tsantilas, MD,[a] Sofie Schmid, MD,[a] Thorben Breitkreuz,[b] Michael Kallmayer, MD,[a] Alexander Zimmermann, MD, MHBA,[a] Hans-Henning Eckstein, MD, PhD[a]

ABSTRACT

OBJECTIVES The aim of this study was to analyze the association between intraprocedural and periprocedural variables and in-hospital stroke or death rate after carotid artery stenting.

BACKGROUND In Germany, all open surgical and endovascular procedures on the extracranial carotid artery must be documented in a statutory nationwide quality assurance database.

METHODS A total of 13,086 carotid artery stenting procedures for asymptomatic (63.9%) or symptomatic carotid stenosis (mean age 69.7 years, 69.7% men) between 2009 and 2014 were recorded. The following variables were analyzed: stent design, stent material, neurophysiological monitoring, periprocedural antiplatelet medication, and use of an embolic protection device. The primary outcome was in-hospital stroke or death. Major stroke or death, any stroke, and death, all until discharge, were secondary outcomes. Adjusted relative risks (RRs) were assessed using multilevel multivariable regression analyses.

RESULTS The primary outcome occurred in 2.4% of the population (1.7% in asymptomatic and 3.7% in symptomatic patients). The multivariable analysis showed an independent association between the use of an embolic protection device and lower in-hospital rates of stroke or death (adjusted RR: 0.65; 95% confidence interval [CI]: 0.50 to 0.85), major stroke or death (adjusted RR: 0.60; 95% CI: 0.43 to 0.84), and stroke (adjusted RR: 0.57; 95% CI: 0.43 to 0.77). Regarding the occurrence of in-hospital death, there was no significant association (adjusted RR: 0.78; 95% CI: 0.46 to 1.35). None of the outcomes was associated with stent design, stent material, neurophysiological monitoring, or antiplatelet medication.

CONCLUSIONS The use of an embolic protection device was independently associated with lower in-hospital risk for stroke or death, major stroke or death, and stroke. (J Am Coll Cardiol Intv 2017;10:1257–65)

First performed in 1953 by Michael E. DeBakey (1), carotid endarterectomy (CEA) has been considered the standard therapy for stenosis of the extracranial portion of the carotid artery for more than half a century. With the first balloon angioplasty having been described in 1980 (2), a cornerstone for the emergence of a novel therapy was laid. In the past 20 years, the implantation of stents (3)

From the [a]Department of Vascular and Endovascular Surgery, Klinikum rechts der Isar, Technical University of Munich, Munich, Germany; and the [b]AQUA-Institut für Angewandte Qualitätsförderung und Forschung im Gesundheitswesen GmbH, Göttingen, Germany. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received November 29, 2016; revised manuscript received February 23, 2017, accepted March 23, 2017.

ABBREVIATIONS AND ACRONYMS

CAS = carotid artery stenting

CEA = carotid endarterectomy

CI = confidence interval

EPD = embolic protection device

OR = odds ratio

RCT = randomized controlled trial

RR = relative risk

SGB = German Social Security Code Book

TIA = transient ischemic attack

and the use of embolic protection devices (EPDs) (4) have helped endovascular therapy mature as an alternative treatment, especially for patients with high operative risk (5).

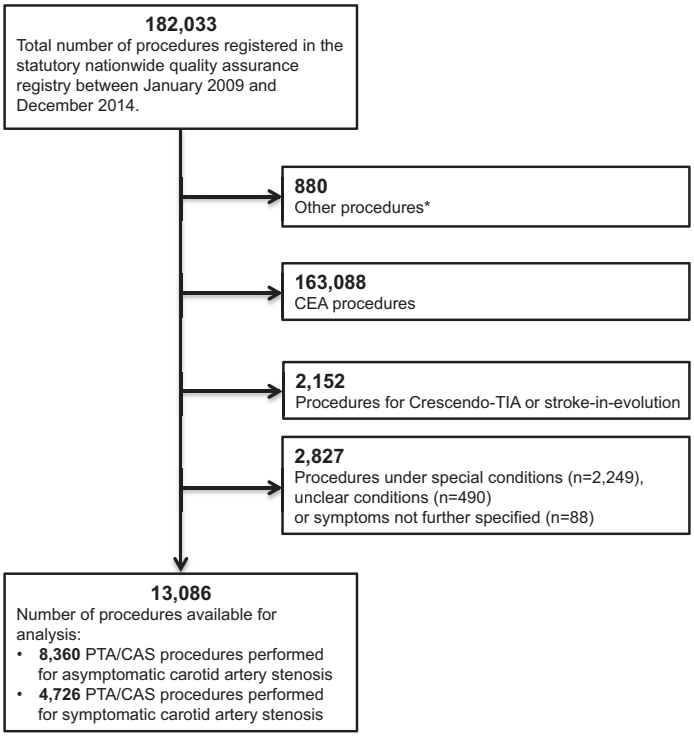
SEE PAGE 1266

Current guidelines recommend consideration of carotid artery stenting (CAS) as an alternative to CEA in asymptomatic patients, if the center complication rate has been demonstrated to be <3%, and especially if CEA would be technically challenging. Furthermore, it should be considered in symptomatic patients with high surgical risk or as an alternative to CEA with a center complication rate demonstrated to be <6% (6–8).

To date, the major randomized controlled trials (RCTs) have predominantly addressed the comparison of CAS and CEA (5,9–13). However, the distinct procedural technique as well as the periprocedural regimen in groups assigned to CAS regularly was left to the discretion of individual physicians.

Because RCTs are prone to selection bias and referral bias, the aim of the present investigation was to assess the associations between technical factors of CAS, such as stent design, material of the implanted stent, use of an EPD, as well as further periprocedural measures such as intraprocedural neurophysiological monitoring, and periprocedural antiplatelet medication, and the in-hospital rate of stroke or death after CAS under routine conditions in Germany.

FIGURE 1 Patient Flowchart: Inclusion and Exclusion Criteria



Special conditions include recurrent stenosis, tandem stenosis, carotid aneurysms, symptomatic internal carotid artery coiling, and symptomatic low-grade (<50%) stenosis with ulcerated plaque morphology. *Excluding 68 combined or converted procedures (carotid artery stenting [CAS] and carotid endarterectomy [CEA]) and 812 CAS procedures performed for the primary purpose of obtaining access for an intracranial intervention. PTA = percutaneous transluminal angioplasty; TIA = transient ischemic attack.

METHODS

This secondary data analysis is based on the statutory nationwide quality assurance registry databank, operated by the Institute for Applied Quality Improvement and Research in Health Care (AQUA Institute). The basic methods have been described elsewhere (14,15). In short, between 2009 and 2015, the AQUA Institute was commissioned and authorized by the German Federal Joint Committee (legal basis: §91 German Social Security Code Book [SGB] V [16]) to develop and implement external quality assurance in the German health care system pursuant to §137a SGB V. The AQUA Institute is also mandated for data validation, data analysis, and publication of annual quality reports (17).

In accordance with the German Federal Joint Committee directive concerning the measures of transsectoral and inpatient quality assurance (18,19), reporting of pre-defined and uniform documentation is compulsory for all procedures performed to treat extracranial carotid artery stenosis. These documentation reports include data on patients with statutory insurance, private insurance, patients without health care insurance, and self-payers (19). Because of legal obligations, the data collection covers nearly all (99.8% in 2014) CEA operations and CAS procedures performed in German hospitals registered under §108 SGB V.

In 2014, our working group was granted access to the quality assurance data by the German Federal Joint Committee, pursuant to §137a Abs. 10 SGB V. This study was approved by the ethics committee of the Technical University of Munich and was performed in accordance with the Good Practice of Secondary Data Analysis (20) and the Strengthening the Reporting of Observational Studies in Epidemiology statement (21). Nonanonymous patient-level data hosted by the AQUA Institute were accessed only by use of so-called controlled remote data processing. Conformity with German data protection laws was supervised by staff members of the AQUA Institute (T.B.).

All patients undergoing CAS for asymptomatic or symptomatic internal carotid artery stenosis between 2012 and 2014 were included. Exclusion criteria were emergency interventions for crescendo transient ischemic attack (TIA) or stroke in evolution, acute internal carotid artery occlusion, recurrent stenosis, tandem stenosis, carotid aneurysms, symptomatic internal carotid artery coiling, and symptomatic low-grade (<50%) stenosis with ulcerated plaque morphology. Inclusion and exclusion criteria are provided in **Figure 1**. Overall, 13,086 patients were available for the analysis. Among them, 8,360 were asymptomatic, and 4,726 patients were treated for symptomatic stenosis. Because complete follow-up until hospital discharge is mandatory, in-hospital follow-up was available for all patients.

With respect to their comorbidities, patients were categorized using the physical status classification system of the American Society of Anesthesiologists (22).

The primary outcome (dependent variable) was any stroke or death until discharge from hospital. The secondary outcomes were major stroke or death, any stroke (alone), and death (alone), all until hospital discharge. Applying the modified Rankin scale (23), stroke symptoms with scores of 0 to 2 were graded as minor and those with scores ≥3 as major.

To calculate the adjusted relative risk (RR) and 95% confidence interval (CI) for the independent variables (stent design, type of stent, use of an EPD, intraprocedural neurophysiological monitoring, periprocedural antiplatelet therapy), a multilevel Poisson regression model (24–27) was applied. To account for confounding and clustering of patients within centers, age, sex, American Society of Anesthesiologists stage, type of index event in symptomatic patients (amaurosis fugax, TIA, minor stroke, major stroke), ipsilateral and contralateral degree of stenosis, pre- and post-procedural assessment by a specialist in neurology, and hospital volume (empirical quintiles regarding the annual number of CAS procedures performed: 1 to 2, 3 to 6, 7 to 12, 13 to 26, and ≥27 per year) were entered as fixed-effect factors (Online Table 1 for variables used in the multivariable regression analysis). Anonymized hospital site codes valid in the treatment year were entered into the model as a random effect (random intercept only).

R version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria) was used for data processing and statistical analysis, with extension packages gmodels and lme4 to calculate cross-classified tables, chi-square tests, and multivariable regression analyses. Variable codes were extracted from the codebooks provided by the AQUA Institute and harmonized over the time period from 2012 to 2014.

TABLE 1 Baseline Characteristics

	Asymptomatic Patients	Symptomatic Patients	Total
n	8,360 (63.9)	4,726 (36.1)	13,086 (100)
Age (yrs)	69.67 ± 8.96	69.75 ± 9.83	69.7 ± 9.3
Male	5,915 (70.8)	3,204 (67.8)	9,119 (69.7)
ASA stage			
I and II	5,212 (62.3)	2,857 (60.4)	8,069 (61.6)
III	3,006 (36.0)	1,767 (37.4)	4,773 (36.5)
IV and V	142 (1.7)	102 (2.2)	244 (1.9)
Right carotid artery treated	4,239 (50.7)	2,300 (48.7)	6,539 (50.0)
Ipsilateral degree of stenosis (NASCET)			
Mild (<50%)	225 (2.7)	101 (2.1)	326 (2.5)
Moderate (50%–69%)	346 (4.1)	425 (9.0)	771 (5.9)
Severe (70%–99%)	7,789 (93.2)	4,200 (88.9)	11,989 (91.6)
Contralateral degree of stenosis (NASCET)			
Mild (<50%)	5,674 (67.9)	3,189 (67.5)	8,863 (67.7)
Moderate (50%–69%)	923 (11.0)	496 (10.5)	1,419 (10.8)
Severe (70%–99%)	950 (11.4)	611 (12.9)	1,561 (11.9)
Occlusion (100%)	813 (9.7)	430 (9.1)	1,243 (9.5)
Qualifying/index event			
AFX or retinal stroke	–	798 (16.9)	–
TIA	–	1,354 (28.7)	–
Minor stroke (Rankin scale score 0–2)	–	1,351 (28.6)	–
Major stroke (Rankin scale score 3–5)	–	779 (16.5)	–
Other symptoms	–	444 (9.4)	–
Time interval from index event to treatment (days)	–	18.29 ± 28.22	–
0–2	–	550 (11.6)	–
3–7	–	1,579 (33.4)	–
8–14	–	1,244 (26.3)	–
15–180	–	1,344 (28.4)	–
Preoperative diagnostic procedures*			
Duplex ultrasound	7,716 (92.3)	4,435 (93.8)	12,151 (92.9)
Transcranial Doppler	1,900 (22.7)	2,553 (54.0)	4,453 (34.0)
DSA	3,300 (39.5)	2,081 (44.0)	5,381 (41.1)
CTA	2,035 (24.3)	1,692 (35.8)	3,727 (28.5)
MRA	3,445 (41.2)	2,534 (53.6)	5,979 (45.7)
Neurological assessment*			
Pre-procedural	5,690 (68.1)	4,212 (89.1)	9,902 (75.7)
Post-procedural	4,849 (58.0)	3,823 (80.9)	8,672 (66.3)
Pre- and post-procedural	4,537 (54.3)	3,736 (79.1)	8,273 (63.2)

Values are n (%) or mean ± SD. *Multiple answers possible.

AFX = amaurosis fugax; ASA = American Society of Anesthesiologists; CTA = computed tomographic angiography; DSA = digital subtraction angiography; ICA = internal carotid artery; MRA = magnetic resonance angiography; NASCET = North American Symptomatic Carotid Endarterectomy Trial; TIA = transient ischemic attack.

RESULTS

BASELINE CHARACTERISTICS. Patient characteristics are listed in **Table 1**. The mean age of the whole cohort was 69.7 ± 9.3 years, without a relevant difference between asymptomatic and symptomatic patients (0.08 years). At 69.7%, the majority of patients were men. About 98% of patients ranked in

TABLE 2 Periprocedural and Intraprocedural Management

	Asymptomatic Patients	Symptomatic Patients	Total
n	8,360 (63.9)	4,726 (36.1)	13,086 (100)
Intraprocedural neurophysiological monitoring*	3,280 (39.2)	1,688 (35.7)	4,968 (38.0)
EEG	37 (0.4)	28 (0.6)	65 (0.5)
TCO	2,084 (24.9)	1,216 (25.7)	3,300 (25.2)
SSEP	135 (1.6)	40 (0.8)	175 (1.3)
Other methods†	1,798 (21.5)	840 (17.8)	2,638 (20.2)
Endovascular procedure			
Angioplasty alone	353 (4.2)	88 (1.9)	441 (3.4)
Stent placement alone	516 (6.2)	294 (6.2)	810 (6.2)
Angioplasty and stent placement	7,491 (89.6)	4,344 (91.9)	11,835 (90.4)
Protection system use	5,612 (67.1)	2,289 (48.4)	7,901 (60.4)
Stent design			
Open-cell	2,772 (34.6)	1,584 (34.2)	4,356 (34.4)
Closed-cell	4,045 (50.5)	2,509 (54.1)	6,554 (51.8)
Semi-closed-cell	958 (12.0)	458 (9.9)	1,416 (11.2)
Others†	232 (2.9)	87 (1.9)	319 (2.5)
Stent type			
Stainless steel	1,348 (16.8)	1,205 (26.0)	2,553 (20.2)
Nitinol	6,356 (79.4)	3,262 (70.3)	9,618 (76.1)
Others†	303 (3.8)	171 (3.7)	474 (3.7)
Perioperative antiplatelet medication			
None	196 (2.3)	68 (1.4)	264 (2.0)
Single (ASA)	952 (11.4)	343 (7.3)	1,295 (9.9)
Single (other than ASA)	360 (4.3)	244 (5.2)	604 (4.6)
Dual	6,852 (82.0)	4,071 (86.1)	10,923 (83.5)
Duration of procedure (min)	45 (40-60)	47 (40-60)	45 (40-60)

Values are n (%) or median (interquartile range). *Multiple answers possible. †Directly coded as "others" without further details.

ASA = acetylsalicylic acid; EEG = electroencephalography; SSEP = somatosensory evoked potentials; TCO = transcranial cerebral oximetry.

American Society of Anesthesiologists stages I to III. More than 90% of all patients had severe carotid stenosis, referring to a degree of at least 70% according to the NASCET (North American Symptomatic Carotid Endarterectomy Trial) criteria. In symptomatic patients, TIAs and minor strokes were the most common symptoms, amounting to 28.7% and 28.6%, respectively. Major strokes or symptoms according to amaurosis fugax occurred less frequently.

TABLE 3 Rates of Different Outcomes

	Asymptomatic (N = 8,360)	Symptomatic (N = 4,726)	Total (N = 13,086)
Stroke or death*	144 (1.7)	173 (3.7)	317 (2.4)
Major stroke or death†	83 (1.0)	117 (2.5)	200 (1.5)
Any stroke†	111 (1.3)	129 (2.7)	240 (1.8)
Major stroke	50 (0.6)	73 (1.5)	123 (0.9)
Minor stroke	61 (0.7)	56 (1.2)	117 (0.9)
Death†	33 (0.4)	44 (0.9)	77 (0.6)

Values are n (%). Definitions of all outcomes imply occurrence until discharge. *Primary outcome. †Secondary outcome.

The most common pre-operative diagnostic method was duplex ultrasound, preceding more than 90% of all CAS procedures. Transcranial Doppler ultrasonography was performed in symptomatic patients more than twice as often as in asymptomatic patients (22.7% and 54.0%, respectively). A pre-procedural neurological assessment was conducted more frequently in symptomatic patients (68.1% in asymptomatic patients, 89.1% in symptomatic patients). Post-procedural neurological assessment was performed less frequently (58.0% in asymptomatic patients, 80.9% in symptomatic patients).

PERIPROCEDURAL AND INTRAPROCEDURAL MANAGEMENT. The results concerning periprocedural and intraprocedural management are shown in Table 2. Intraprocedural monitoring using electroencephalography, transcranial cerebral oximetry, somatosensory evoked potentials, or other methods was performed in about 38% of all patients. Transcranial cerebral oximetry was the method applied most frequently. Irrespective of the indication group, a combination of angioplasty and stent placement was the most common procedure (90.4%). EPDs were used in 60.4% of all patients. The rate of protection system application was higher in asymptomatic (67.1%) than in symptomatic (48.4%) patients. In more than one-half of the patients, closed-cell stents were delivered. Most of the implanted stents consisted of nitinol. As far as perioperative antiplatelet therapy is concerned, more than 80% of patients were treated with dual medications.

UNIVARIATE AND MULTIVARIABLE REGRESSION ANALYSIS. The primary outcome occurred in 317 of 13,086 patients (2.4%; 1.7% in asymptomatic patients and 3.7% in symptomatic patients). The mortality rate was 0.4% and 0.9% in asymptomatic and symptomatic patients, respectively. In-hospital strokes were recorded in 1.3% and 2.7% of asymptomatic and symptomatic patients, respectively (Table 3).

Results of the univariate analysis are listed in Table 4. The only significant association with a lower rate of primary outcome events was found for the application of an EPD (RR: 0.55; 95% CI: 0.44 to 0.69; $p < 0.001$). The other variables (stent design, stent type, neurophysiological monitoring, periprocedural antiplatelet medication) were not associated with lower rates of in-hospital stroke or death.

With regard to the primary and secondary outcomes, the results obtained in the multivariate regression analysis are shown in Figure 2. As already indicated by the univariate analysis, the adjusted analysis confirmed a significantly lower rate of in-hospital stroke or death in patients undergoing CAS

with EPDs (RR: 0.65; 95% CI: 0.50 to 0.85; p = 0.001). The use of an EPD was evenly associated with a significantly lower rate of any in-hospital stroke (RR: 0.57; 95% CI: 0.43 to 0.77; p < 0.001), whereas no association was shown with the occurrence of death until discharge (RR: 0.78; 95% CI: 0.46 to 1.35; p = 0.381). Regarding the combined secondary outcome of in-hospital major stroke or death (Online Figure 1), the use of an EPD was associated with a lower rate (RR: 0.60; 95% CI: 0.43 to 0.84; p = 0.003).

Stent design, material of the stent, use of intraprocedural neurophysiologic monitoring, and perioperative intake of antiplatelet medication were not associated with risk for the combined primary outcome stroke or death until discharge, nor the individual components (**Figure 2**). The application of neurophysiologic monitoring showed a trend toward higher rates of primary outcome events (RR: 1.25; 95% CI: 0.96 to 1.62; p = 0.093).

TABLE 4 Univariate Analyses: Associations of Different Intraprocedural and Periprocedural Factors and the Risk of Stroke or Death Until Hospital Discharge (Primary Outcome)

	n/N (%)	Crude RR (95% CI)	p Value
Overall	317/13,086 (2.4)	–	–
Intraprocedural monitoring			
No monitoring	183/8,118 (2.3)	Reference	–
Any type of monitoring	134/4,968 (2.7)	1.20 (0.96–1.49)	0.110
Protection system use			
No protection system	172/5,185 (3.3)	Reference	–
Any type of protection system	145/7,901 (1.8)	0.55 (0.44–0.69)	**<0.001**
Stent design			
Open-cell	122/4,356 (2.8)	Reference	–
Closed-cell	148/6,554 (2.3)	0.81 (0.64–1.02)	0.075
Semi-closed-cell	29/1,416 (2.0)	0.73 (0.49–1.09)	0.126
Others	9/319 (2.8)	0.82 (0.42–1.60)	0.555
Stent material			
Nitinol	236/9,618 (2.5)	Reference	–
Stainless steel	60/2553 (2.4)	0.96 (0.72–1.27)	0.763
Others	12/474 (2.5)	1.03 (0.58–1.83)	0.915
Perioperative antiplatelet medication			
None	5/264 (1.89)	Reference	–
Any	312/12,822 (2.43)	1.28 (0.54–3.08)	0.575

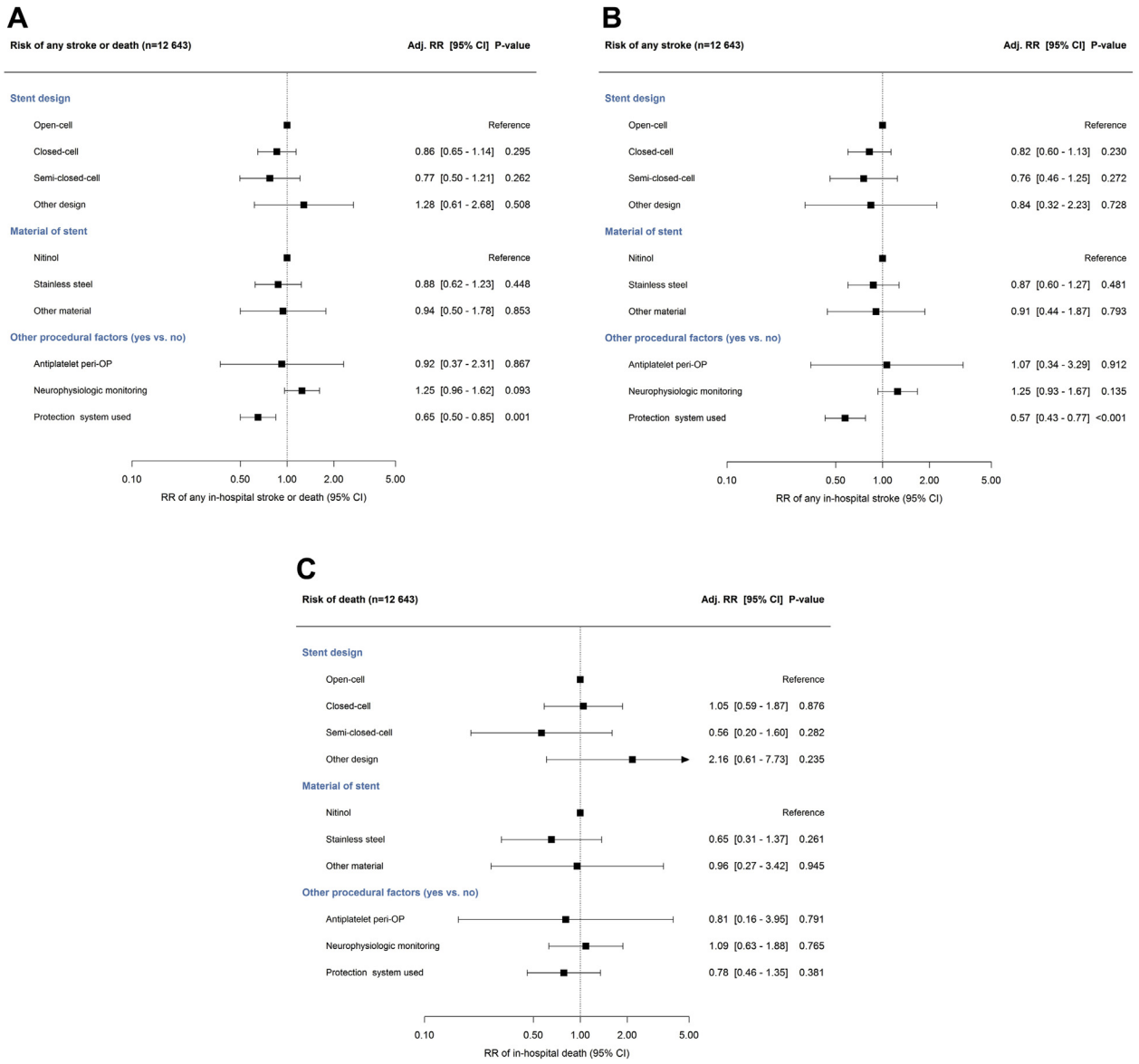
Significant values are in **bold**.
CI = confidence interval; RR = risk ratio.

DISCUSSION

APPLICATION OF AN EPD. This study shows that application of an EPD was independently associated with significantly lower rates of in-hospital stroke or death. This finding confirms some results from the published research. Because of the low rates of periprocedural clinical events, RCTs investigating the impact of EPDs on the periprocedural risk for stroke or death are lacking. RCTs using surrogate markers as endpoints were not able to detect a positive effect of EPD use (28,29). However, retrospective investigation of registry data (30,31) and review of published studies (32) indicated an advantage of EPD application. Similarly, in a more recent and comprehensive review of 23,461 procedures, the risk for a periprocedural stroke was lower among patients who received protected carotid angioplasty or stenting compared with those who were treated without EPDs (RR: 0.62; 95% CI: 0.54 to 0.72) (33). Another review including 54,713 patients sought to identify risk factors for perioperative stroke or death after CAS. The insertion of an EPD was associated with a lower rate of stroke or death within 30 days (RR: 0.57; 95% CI: 0.43 to 0.76) (34). Similar to the present investigation, a major drawback of these reviews was that no information on the specific type of EPD (i.e., proximal vs. distal) used was available. Although prospective studies showed an advantage of proximal compared with distal protection on the occurrence of surrogate events (35–37), a retrospective analysis of registry data involving 10,246 patients did not show a significant difference (1.5% vs. 2.4%; p = 0.16) in in-hospital stroke or death rates after CAS using proximal or distal protection, respectively (38). However, this study shows that the use of an EPD is associated with a lower risk for in-hospital stroke or death, not only within clinical trials or registries but also in real-world practice.

STENT DESIGN. In this investigation, the implantation of closed-cell and semi-closed-cell stents showed trends toward lower rates of in-hospital stroke or death compared with open-cell stents, but with a broad CI. The effect of stent design on periprocedural rates of stroke or death was the object of a retrospective analysis conducted by Schillinger et al. (39) including 1,684 patients. Amounting to 3.1% for patients treated with closed-cell stents and 2.4% for those undergoing CAS with open-cell stents, the combined stroke or death rates did not differ significantly (p = 0.38) (39). In contrast to the present study, an investigation of the Vascular Registry of the Society for Vascular Surgery of 4,337 CAS procedures found trends toward lower rates of in-hospital stroke (odds ratio [OR]: 0.781; 95% CI: 0.462 to 1.320; p = 0.36) and death (OR: 0.515; 95% CI: 0.218 to 1.213; p = 0.13) favoring CAS with insertion of open-cell stents. Regarding the occurrence of the combined outcome of death, stroke, or TIA, the use of open-cell stents compared with those with closed-cell design was associated with a significantly lower risk (OR: 0.674; 95% CI: 0.460 to 0.987; p = 0.04) (40). The distinct

FIGURE 2 Multivariable Regression Analysis



Association between intraprocedural and periprocedural factors and the risk of stroke or death **(A)**, stroke **(B)**, and death **(C)**, each until hospital discharge. Because of missing data, 443 patients were not included in the multivariable regression analysis. Adj. RR = adjusted risk ratio; CI = confidence interval; n = patients available for analysis; peri-OP = periprocedural.

reasons for the different results regarding stent designs remain unclear. To find out which patient subgroups might benefit from each stent design, further trials considering additional parameters, such as carotid morphology and plaque stability, are necessary.

STENT MATERIAL. The results of the present analysis show that stents made of nitinol are not related to a significantly different rate of primary and secondary outcome events compared with those consisting of stainless steel or other materials. The evidence regarding the impact of different stent materials on perioperative stroke or death rates is sparse. A retrospective study of 178 patients detected no significant difference in stroke rates (3.3% vs. 2.2%) for patients who underwent CAS with stainless steel and nitinol stents, respectively (41).

PERIPROCEDURAL ANTIPLATELET MEDICATION. The underlying data did not show a significant association

between the periprocedural intake of antiplatelet medication and the occurrence of the primary or secondary outcome. The most probable reason for this surprising finding is that too few patients were not treated with antiplatelet medications perioperatively (about 2%). A recently published analysis of patients included in the ICSS (International Carotid Stenting Study) similarly did not show a significant effect of periprocedural therapy with any antiplatelet medication on the risk for stroke, myocardial infarction, or death within 30 days of CAS (RR: 0.62; 95% CI: 0.17 to 2.33; p = 0.48). However, dual antiplatelet therapy with aspirin and clopidogrel after risk adjustment was identified as an independent predictor of lower rates of stroke, myocardial infarction, or death within 30 days of CAS (adjusted RR: 0.59; 95% CI: 0.36 to 0.98; p = 0.04) (42). Unfortunately, the present investigation does not provide a separate analysis for different regimens of antiplatelet therapy.

NEUROPHYSIOLOGICAL MONITORING. Patients entered in the German carotid quality assurance database who underwent CAS under neurophysiological monitoring tended to show higher rates of in-hospital stroke or death, but the result was not statistically significant. The reason for this trend is likely to be found in confounding by indication, as intraoperative neuromonitoring at many centers is conducted selectively if pre-procedural diagnosis indicates an elevated perioperative stroke risk. Because the distinct reasons for the use of neurophysiological monitoring are unknown, adjustment was not possible in the multivariable regression analysis. Therefore, results concerning neurophysiological monitoring are likely to underlie a confounding by indication bias.

STUDY LIMITATIONS. The present study had several limitations (14,15). First, the study design was retrospective and observational. Because patients were not randomized for the different procedural techniques and adjunct measures, selection bias as well as confounding by indication is possible. This implies that all results need to be interpreted as associations rather than causal relationships.

Second, follow-up data covered only the in-hospital period. Because most of the perioperative events presumably occur within the first days after CAS, a detection bias is considered to be low.

Third, all data in the database are self-reported by the attending physicians, and reporting bias cannot be ruled out. However, data reports were reviewed by the regional offices for quality assurance (Landesgeschäftsstellen für Qualitätssicherung) and the occurrence of suspect data induced a process of structured dialogue to clarify abnormalities systematically. Nonetheless, underreporting of adverse events is theoretically probable and might be the reason for the overall low rates of perioperative stroke or death reported in this registry (1.7% in asymptomatic patients and 3.7% in symptomatic patients). A review including 206 studies with a total of 54,713 patients stated the 30-day risk for stroke or death to be as high as 3.3% and 7.6% in asymptomatic and symptomatic patients, respectively (34). Although underreporting cannot be ruled out, any potential information bias can be considered homogeneous among the variables analyzed in this study.

Because no unequivocal definition for the stent design is provided in the database manual, classification as open-cell design or closed-cell design remains to some extent dependent on the assumption of the interventionalists.

Fourth, residual confounding cannot be excluded, because some possible confounders were not collected (e.g., information on the type of EPD or stent used, comorbidities, cardiovascular risk profile, routine medication, presence of restenosis, intraoperative heparin or protamine application, or the reasons for the application of a certain procedural technique).

Because information on the distinct type of EPD is lacking, this study does not contribute to answering the question of whether proximal or distal protection, with or without flow reversal, is associated with a better outcome.

Last, no information on cause of death is provided in the registry.

CONCLUSIONS

Despite the listed limitations, data collection was prospective, nationwide, and unselected. Because data reporting was compulsory, the present dataset represents real-world practice in Germany between 2012 and 2014. In conclusion, this investigation is among the largest studies to analyze the associations between different technical factors and adjunct measures and the risk for stroke or death in the periprocedural period after CAS. The use of an EPD was independently associated with a lower risk for stroke or death until discharge. To prove causality of this effect, it should be investigated in a randomized trial.

ADDRESS FOR CORRESPONDENCE: Univ.-Prof. Dr. Hans-Henning Eckstein, Department of Vascular and Endovascular Surgery, Klinikum Rechts der Isar, Technical University of Munich, Ismaninger Strasse 22, 81675 Munich, Germany. E-mail: gefaesschirurgie@mri.tum.de.

PERSPECTIVES

WHAT IS KNOWN? Systematic reviews indicated that the use of an EPD is associated with a lower risk for perioperative stroke or death after CAS.

WHAT IS NEW? This retrospective study confirmed an association of EPD application with a lower risk for in-hospital stroke or death in real-world practice.

WHAT IS NEXT? A prospective RCT is required to confirm the hypothesis obtained from this study. Ideally, this should also focus on a comparison of different EPD types.

REFERENCES

1. DeBakey ME, Crawford ES, Cooley DA, Morris GC Jr., Garret HE, Fields WS. Cerebral arterial insufficiency: one to 11-year results following arterial reconstructive operation. Ann Surg 1965;161:921–45.

2. Kerber CW, Cromwell LD, Loehden OL. Catheter dilatation of proximal carotid stenosis during distal bifurcation endarterectomy. AJNR Am J Neuroradiol 1980;1:348–9.

3. Roubin GS, Yadav S, Iyer SS, Vitek J. Carotid stent-supported angioplasty: a neurovascular intervention to prevent stroke. Am J Cardiol 1996;78:8–12.

4. Theron JG, Payelle GG, Coskun O, Huet HF, Guimaraens L. Carotid artery stenosis: treatment with protected balloon angioplasty and stent placement. Radiology 1996;201:627–36.

5. Yadav JS, Wholey MH, Kuntz RE, et al. Protected carotid-artery stenting versus endarterectomy in high-risk patients. N Engl J Med 2004;351:1493–501.

6. Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2014;45:2160–236.

7. Tendera M, Aboyans V, Bartelink ML, et al. ESC guidelines on the diagnosis and treatment of peripheral artery diseases: document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries: the Task Force on the Diagnosis and Treatment of Peripheral Artery Diseases of the European Society of Cardiology (ESC). Eur Heart J 2011;32:2851–906.

8. Eckstein HH, Kuhnl A, Dorfler A, et al. The diagnosis, treatment and follow-up of extracranial carotid stenosis. Dtsch Arztebl Int 2013;110:468–76.

9. Ederle J, Dobson J, Featherstone RL, et al. Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomised controlled trial. Lancet 2010;375:985–97.

10. Brott TG, Hobson RW II, Howard G, et al. Stenting versus endarterectomy for treatment of carotid-artery stenosis. N Engl J Med 2010;363:11–23.

11. Mas JL, Chatellier G, Beyssen B, et al. Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis. N Engl J Med 2006;355:1660–71.

12. Ringleb PA, Allenberg J, Bruckmann H, et al. 30 Day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomised non-inferiority trial. Lancet 2006;368:1239–47.

13. CAVATAS Investigators. Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomised trial. Lancet 2001;357:1729–37.

14. Tsantilas P, Kuehnl A, Breitkreuz T, et al. A short time interval between neurologic event and carotid surgery is not associated with an increased procedural risk. Stroke 2016;47:2783–90.

15. Kuehnl A, Tsantilas P, Knappich C, et al. Significant association of annual hospital volume with the risk of inhospital stroke or death following carotid endarterectomy but likely not after carotid stenting: secondary data analysis of the statutory German carotid quality assurance database. Circ Cardiovasc Interv 2016;9:e004171.

16. Federal Ministry of Justice and Consumer Protection. Sozialgesetzbuch (SGB) Fünftes Buch (V)—Gesetzliche Krankenversicherung 2015. Available at: https://www.gesetze-im-internet.de/bundesrecht/sgb_5/gesamt.pdf. Accessed August 24, 2015.

17. Allgemeine Methoden im Rahmen der sektorenübergreifenden Qualitätssicherung im Gesundheitswesen nach §137a SGB V. Available at: https://www.sqg.de/sqg/upload/CONTENT/Hintergrund/Methodenpapier/AQUA_AllgemeineMethoden_Version_3-0.pdf. Accessed August 24, 2015.

18. Gemeinsamer Bundesausschuss. Richtlinie des Gemeinsamen Bundesausschusses gemäß §137 Abs. 1 SGB V i.V.m. §135a SGB V über Maßnahmen der Qualitätssicherung für nach §108 SGB V zugelassene Krankenhäuser. Richtlinie über Maßnahmen der Qualitätssicherung in Krankenhäusern—QSKH-RL. Gemeinsamer Bundesausschuss 2014. Available at: https://www.g-ba.de/downloads/62-492-935/QSKH-RL_2014-12-04-und-2014-06-19.pdf?. Accessed August 24, 2015.

19. Gemeinsamer Bundesausschuss. Richtlinie des Gemeinsamen Bundesausschusses nach §92 Abs. 1 Satz 2 Nr. 13 i.V.m. §137 Abs. 1 Nr. 1 SGB V über die einrichtungs- und sektorenübergreifenden Maßnahmen der Qualitätssicherung (Qesü-RL) 2014. Available at: https://www.kvwl.de/arzt/recht/kbv/rl/gba_qs_sektor.pdf. Accessed August 24, 2015.

20. Swart E, Gothe H, Geyer S, et al. Good Practice of Secondary Data Analysis (GPS): guidelines and recommendations. Gesundheitswesen 2015;77:120–6.

21. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Int J Surg 2014;12:1495–9.

22. Owens WD, Felts JA, Spitznagel EL Jr. ASA physical status classifications: a study of consistency of ratings. Anesthesiology 1978;49:239–43.

23. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1988;19:604–7.

24. Chen W, Shi J, Qian L, Azen SP. Comparison of robustness to outliers between robust Poisson models and log-binomial models when estimating relative risks for common binary outcomes: a simulation study. BMC Med Res Methodol 2014;14:82.

25. Knol MJ, Le Cessie S, Algra A, Vandenbroucke JP, Groenwold RH. Overestimation of risk ratios by odds ratios in trials and cohort studies: alternatives to logistic regression. CMAJ 2012;184:895–9.

26. Lee J, Tan CS, Chia KS. A practical guide for multivariate analysis of dichotomous outcomes. Ann Acad Med Singapore 2009;38:714–9.

27. Zou G. A modified Poisson regression approach to prospective studies with binary data. Am J Epidemiol 2004;159:702–6.

28. Barbato JE, Dillavou E, Horowitz MB, et al. A randomized trial of carotid artery stenting with and without cerebral protection. J Vasc Surg 2008;47:760–5.

29. Macdonald S, Evans DH, Griffiths PD, et al. Filter-protected versus unprotected carotid artery stenting: a randomised trial. Cerebrovasc Dis 2010;29:282–9.

30. Zahn R, Mark B, Niedermaier N, et al. Embolic protection devices for carotid artery stenting: better results than stenting without protection? Eur Heart J 2004;25:1550–8.

31. Wholey MH, Al-Mubarek N, Wholey MH. Updated review of the global carotid artery stent registry. Catheter Cardiovasc Interv 2003;60:259–66.

32. Kastrup A, Groschel K, Krapf H, Brehm BR, Dichgans J, Schulz JB. Early outcome of carotid angioplasty and stenting with and without cerebral protection devices: a systematic review of the literature. Stroke 2003;34:813–9.

33. Garg N, Karagiorgos N, Pisimisis GT, et al. Cerebral protection devices reduce periprocedural strokes during carotid angioplasty and stenting: a systematic review of the current literature. J Endovasc Ther 2009;16:412–27.

34. Touze E, Trinquart L, Chatellier G, Mas JL. Systematic review of the perioperative risks of stroke or death after carotid angioplasty and stenting. Stroke 2009;40:e683–93.

35. Montorsi P, Caputi L, Galli S, et al. Microembolization during carotid artery stenting in patients with high-risk, lipid-rich plaque. A randomized trial of proximal versus distal cerebral protection. J Am Coll Cardiol 2011;58:1656–63.

36. Bijuklic K, Wandler A, Hazizi F, Schofer J. The PROFI study (Prevention of Cerebral Embolization by Proximal Balloon Occlusion Compared to Filter Protection During Carotid Artery Stenting): a prospective randomized trial. J Am Coll Cardiol 2012;59:1383–9.

37. Cano MN, Kambara AM, de Cano SJ, et al. Randomized comparison of distal and proximal cerebral protection during carotid artery stenting. J Am Coll Cardiol Intv 2013;6:1203–9.

38. Giri J, Parikh SA, Kennedy KF, et al. Proximal versus distal embolic protection for carotid artery stenting: a national cardiovascular data registry analysis. J Am Coll Cardiol Intv 2015;8:609–15.

39. Schillinger M, Gschwendtner M, Reimers B, et al. Does carotid stent cell design matter? Stroke 2008;39:905–9.

40. Jim J, Rubin BG, Landis GS, et al. Society for Vascular Surgery Vascular Registry evaluation of stent cell design on carotid artery stenting outcomes. J Vasc Surg 2011;54:71–9.

41. Mukherjee D, Kalahasti V, Roffi M, et al. Self-expanding stents for carotid interventions: comparison of nitinol versus stainless-steel stents. J Invasive Cardiol 2001;13:732–5.

42. Doig D, Turner EL, Dobson J, et al. 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;51:327–34.

KEY WORDS carotid artery disease, carotid artery stenting, death, embolic protection device, stroke

APPENDIX For a supplemental table and figure, please see the online version of this article.