

# Risk of Stroke or Death Is Associated With the Timing of Carotid Artery Stenting for Symptomatic Carotid Stenosis: A Secondary Data Analysis of the German Statutory Quality Assurance Database

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**Background**—Subgroup analyses from randomized trials indicate that the time interval between the neurologic index event and carotid artery stenting is associated with periprocedural stroke and death rates in patients with symptomatic carotid stenosis. The aim of this article is to analyze whether this observation holds true under routine conditions in Germany.

**Methods and Results**—Secondary data analysis was done on 4717 elective carotid artery stenting procedures that were performed for symptomatic carotid stenosis. The patient cohort was divided into 4 groups according to the time interval between the index event and intervention (group I 0-2, II 3-7, III 8-14, and IV 15-180 days). Primary outcome was any in-hospital stroke or death. For risk-adjusted analyses, a multilevel multivariable regression model was used. The in-hospital stroke or death rate was 3.7% in total and 6.0%, 4.4%, 2.4%, and 3.0% in groups I, II, III, and IV, respectively. Adjusted analysis showed a decreased risk for any stroke or death in group III, a decreased risk for any major stroke or death in groups III and IV, and a decreased risk for any death in groups II and III compared to the reference group I.

**Conclusions**—A short time interval between the neurologic index event and carotid artery stenting of up to 7 days is associated with an increased risk for stroke or death under routine conditions in Germany. Although results cannot prove causal relationships, carotid artery stenting may be accompanied by an increased risk of stroke or death during the early period after the index event. (*J Am Heart Assoc.* 2018;7:e007983. DOI: 10.1161/JAHA.117.007983.)

**Key Words:** amaurosis fugax • carotid stenosis • carotid stenting • cohort • nationwide • peri-interventional outcome • stroke • time interval • transient ischemic attack

A recent review showed that the (recurrent) stroke risk in patients with carotid stenosis and related symptoms such as transient ischemic attack (TIA), amaurosis fugax (AFX), or stroke was considered to be as high as 6.4% (1.5% to 23.8%) during the first 2-3 days, 19.5% (12.7% to 28.7%) within 7 days, and 26.1% (20.6% to 32.5%) within 14 days after the initial neurologic event.<sup>1</sup> Guidelines recommend that carotid endarterectomy (CEA) be performed as early as possible after the neurologic index event in patients with symptomatic carotid stenosis ( $\geq 50\%$ ).<sup>2-6</sup> Carotid artery stenting (CAS) can be considered as alternative in symptomatic carotid stenosis patients with a high surgical risk.<sup>2</sup> However, recommendations

for the timing of CAS treatment in symptomatic patients are not available due to the lack of randomized controlled trials comparing early CAS with conservative therapy or deferral. In a subgroup analysis of 4 randomized controlled trials comparing CEA with CAS in patients with symptomatic internal carotid artery (ICA) stenosis, patients treated by CAS within 7 days after the index event had a much higher risk of stroke or death compared to CEA patients (risk ratio [RR] 6.7; 95% confidence interval [CI] 2.1-21.9).<sup>7</sup> To verify these results on a national level, we performed this study on patients treated by CAS in Germany. The aim was to analyze a potential association between the time interval (neurologic index event to CAS) and

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## Clinical Perspective

### What Is New?

- This study investigates the association between the time interval from the neurologic index event to carotid artery stenting and outcomes in patients with symptomatic carotid stenosis.
- With 4717 patients included, this report represents the largest nationwide cohort study reflecting the real-life conditions of carotid artery stenting in Germany in symptomatic patients between 2012 and 2014.
- If patients were treated within the first days after the neurologic index event, increased rates of any stroke or death, of any major stroke or death, and of any death alone were observed compared with patients treated later.

### What Are the Clinical Implications?

- The current report suggests that carotid artery stenting may be accompanied by an increased risk of stroke or death if patients were treated within the first 7 days after the neurologic index event.
- A causal relationship cannot, however, be established due to the observational design of the study.
- Based on the current and other published evidence, carotid endarterectomy is likely more beneficial than carotid artery stenting in the first days after the index neurologic event.

the risk of peri-interventional stroke or death on a national level in Germany.

## Methods

This secondary data analysis is based on the nationwide statutory quality assurance database held by the Institute for Applied Quality Improvement and Research in Health Care (aQua Institute, Göttingen, Germany). The primary data cannot be made available by us to other researchers because this is prohibited by German social law and data protection law. Controlled remote access to individual patient data was granted to our group, but we have also never had direct access to microdata. Furthermore, all applied analytic methods are described in the methods section and have been described elsewhere as well.<sup>8-12</sup>

## Legal Basis of Data Acquisition

Between 2009 and 2015 the aQua Institute was commissioned and authorized by the German Federal Joint Committee (legal basis §91 German Social Security Code part 5, SGB V<sup>11</sup>) to develop and implement external quality assurance in the German healthcare system pursuant to §137a SGB V. The aQua Institute was also mandated for data validation, data analysis, and publication of annual quality reports.<sup>13</sup>

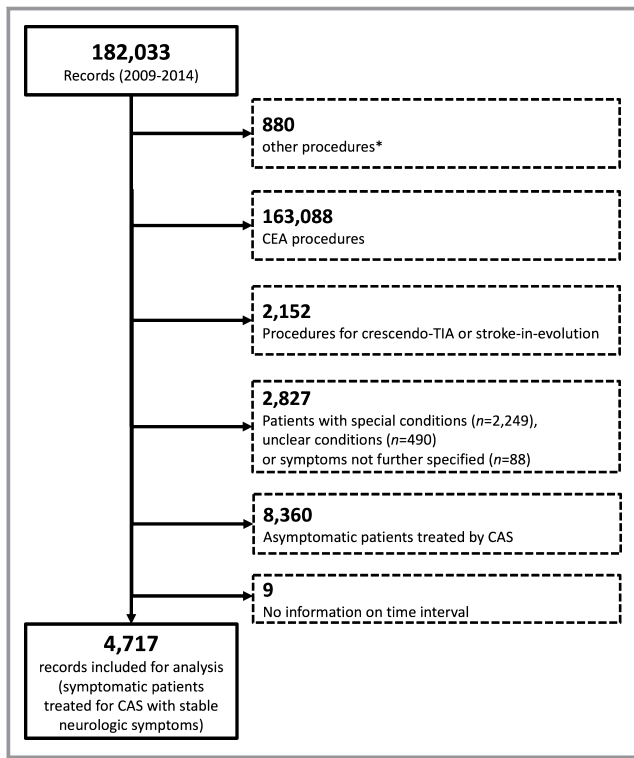
In accordance with the German Federal Joint Committee directive concerning measures of transsectoral and inpatient quality assurance,<sup>14,15</sup> reporting of quality assurance data is compulsory for all reconstructive procedures on the extracranial carotid bifurcation. These reports include data on patients with statutory and private insurance as well as patients without healthcare insurance and self-payers.<sup>15</sup> Due to legal obligations, data collection thus covers nearly all (99.8% in 2014) CEA and CAS procedures performed in German hospitals registered under §108 SGB V.

In 2014 our working group was granted permission to use this quality assurance data by the German Federal Joint Committee pursuant to §137a para. 10 SGB V. The current study was approved by the ethics committee of the Technical University of Munich. This study was performed in accordance with the Good Practice of Secondary Data Analysis guidelines and the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement.<sup>16,17</sup> Patient-level data were only accessed and displayed by controlled remote data processing and analysis. Therefore, individual informed consent of each subject was not necessary. Conformance with German data protection laws was verified by aQua Institute staff members (T.B.).<sup>8-12</sup>

## Data Processing and Patient Grouping

The basic data set comprised 182 033 patients treated for carotid stenosis with CEA between 2009 and 2014 or CAS between 2012 and 2014. After exclusion of asymptomatic patients (no symptoms associated with carotid stenosis in the past 6 months), patients treated with CEA or combined procedures, patients with emergency conditions (eg, crescendo TIA, stroke-in-evolution), and patients treated for other conditions (redo surgery for restenosis, aneurysms, symptomatic ICA coiling, symptomatic low-grade stenosis with ulcerated plaque morphology, tandem stenosis, and acute ICA occlusion), 4726 patients undergoing elective CAS for symptomatic (AFX, TIA, or stroke) carotid stenosis were included in the final analysis. No information on the time interval was available for 9 patients, who were therefore also excluded (N=4717). Inclusion and exclusion criteria are provided in Figure 1.<sup>8-12</sup>

The following variables were considered relevant to our study: time from the last neurologic event (=index event) to the procedure, age, sex, physical status (American Society of Anesthesiologists [ASA] stage), type of index event (AFX, TIA, minor/major stroke), degree of ipsi- and contralateral stenosis, periprocedural antiplatelet therapy, pre- and postprocedural neurologic assessment (performed by a specialist in neurology), intraprocedural neurophysiologic monitoring, procedural technique, use of an embolic protection device, duration of procedure, pre- and postprocedural diagnostic imaging (ultrasound, transcranial Doppler sonography,



**Figure 1.** Flowchart showing inclusion and exclusion criteria applied to patients treated by CAS between 2012 and 2014 in Germany. Special conditions include recurrent stenosis, tandem stenosis, carotid aneurysms, symptomatic ICA coiling, and symptomatic low-grade (<50%) stenosis with ulcerated plaque morphology. \*Other procedures are 68 combined or converted procedures (CAS>CEA), and 812 CAS procedures performed to obtain access for an intracranial intervention. CAS indicates carotid artery stenting; CEA, carotid endarterectomy; ICA, internal carotid artery; TIA, transient ischemic attack.

computed tomography angiography, magnetic resonance angiography), and annual center volume. The time interval between the index event and CAS was categorized into 4 groups (0-2, 3-7, 8-14, and 15-180 days in groups I, II, III, and IV, respectively). Almost all studies investigating the impact of this time interval in CEA patients use the same time interval groups.<sup>18</sup> Most guidelines use 14 days as the cutoff value.<sup>2</sup> The abovementioned time intervals were therefore applied in order to facilitate comparability with previous studies and guidelines. The severity of the qualifying event was classified using the modified Rankin scale (mRS).<sup>19</sup> An mRS score of 0 to 2 points was considered minor, whereas an mRS of 3 or more was used to identify a major stroke. Determination of myocardial infarction was based on clinical diagnosis substantiated by elevation of biomarkers.

## Outcomes and Statistics

The primary outcome of this study was any stroke or death occurring during the period commencing with initiation of CAS

and ending with discharge from hospital. Due to the legal framework, 30-day results were not available. Secondary outcomes were any major stroke or death, death alone, stroke, myocardial infarction (data available only for 2013 and 2014), acute occlusions, and local complications at the puncture site (severe bleeding or hematoma, aneurysms, arteriovenous fistulas). Postoperative stroke was considered major if neurologic impairments corresponded to an mRS score of 3 or more.

To calculate the adjusted RR and 95% CI for the time interval (as an independent variable), a multilevel multivariable Poisson regression model<sup>20-23</sup> was applied. The primary outcome (any stroke or death) and the secondary outcomes “any major stroke or death” and “all-cause death” were used as dependent variables. To account for confounding and clustering, the variables age, sex, ASA status, type of index event, degree of ipsi- and contralateral stenosis, periprocedural antiplatelet therapy, pre- and postprocedural neurologic assessment, intraprocedural neuromonitoring, stent design, type of stent, use of an embolic protection system, and annual center volume were entered into the model as fixed effects, and the hospital site code valid in the year of treatment was entered as a random effect (random intercept only). Because the cutoff values for grouping the time intervals were arbitrary, multivariable regression analysis was also performed using the time interval as a continuous variable based on an exploratory approach. On the basis of clinical experience and theoretical considerations, it was assumed a priori by the authors that the relationship between time interval and the risk of stroke or death is most likely not linear but also not a highly complex function. Thus, we started exploratory analyses with a fourth-degree polynomial for modeling time interval (full model including all other variables). Following standard model diagnostics, the best model fit was achieved using third-degree polynomial modeling of the time interval. As this was an exploratory approach, we refrained from applying more complex terms in order to avoid overfitting. For data processing and statistical analysis, the statistical package R was used (version 3.2.1; The R Foundation, Vienna, Austria; www.r-project.org). The R extension packages *gmodels*, *lme4*, and *gam* were used to calculate cross-classified tables, chi-squared tests, and multivariable regression analyses. The significance level for all statistical tests was set to  $\alpha=0.05$ .<sup>8-12</sup>

## Results

### Demographics and Procedural Information

In total, 4717 patients could be included in the final analysis (Figure 1). The mean age of all patients was 69.8 years (SD±9.8), and 67.8% were male (Table 1). Most of the patients were classified as ASA stages I and II (60.4%). The most common neurologic index event was TIA in 28.6%,

**Table 1.** Patient Characteristics

	Total N=4717	Time Interval Between Index Event and CAS			
		0 to 2 Days n=550 (11.6%)	3 to 7 Days n=1579 (33.4%)	8 to 14 Days n=1244 (26.3%)	15 to 180 Days n=1344 (28.4%)
Age, y, mean (SD)	69.8 (9.8)	69.1 (10.1)	69.6 (9.9)	70.1 (9.9)	69.9 (9.5)
Male, n (%)	3201 (67.8)	386 (70.2)	1070 (67.8)	835 (67.1)	910 (67.7)
ASA stage n (%)					
I-II	2851 (60.4)	316 (57.5)	1015 (64.3)	753 (60.5)	767 (57.0)
III	1764 (37.4)	212 (38.5)	535 (33.9)	469 (37.7)	548 (40.8)
IV+V	102 (2.2)	22 (4.0)	29 (1.8)	22 (1.8)	29 (2.2)
Degree of ipsilateral stenosis (NASCET), n (%)					
Mild (<50)	101 (2.1)	14 (2.5)	38 (2.4)	21 (1.7)	28 (2.1)
Moderate (50-69)	425 (9.0)	47 (8.5)	159 (10.1)	117 (9.4)	102 (7.6)
Severe (70-99)	4191 (88.9)	489 (88.9)	1382 (87.5)	1106 (88.9)	1214 (90.3)
Degree of contralateral stenosis (NASCET) n (%)					
Mild (<50)	3183 (67.5)	381 (69.3)	1046 (66.2)	824 (66.2)	932 (69.3)
Moderate (50-69)	494 (10.5)	53 (9.6)	163 (10.3)	129 (10.4)	149 (11.1)
Severe (70-99)	611 (13.0)	68 (12.4)	220 (13.9)	163 (13.1)	160 (11.9)
Occlusion	429 (9.1)	48 (8.7)	150 (9.5)	128 (10.3)	103 (7.7)
Qualifying index event (n, %)					
AFX or retinal stroke	797 (16.9)	65 (11.8)	212 (13.4)	234 (18.8)	286 (21.3)
TIA	1351 (28.6)	155 (28.2)	472 (29.9)	306 (24.6)	418 (31.1)
Minor stroke (Rankin 0-2)	1349 (28.6)	163 (29.6)	502 (31.8)	374 (30.1)	310 (23.1)
Major stroke (Rankin 3-5)	777 (16.5)	105 (19.1)	294 (18.6)	248 (19.9)	130 (9.7)
Other symptoms	443 (9.4)	62 (11.3)	99 (6.3)	82 (6.6)	200 (14.9)
Preoperative diagnostic procedures, n (%)*					
Duplex ultrasound	4427 (93.9)	474 (86.2)	1501 (95.1)	1183 (95.1)	1269 (94.4)
Transcranial Doppler	2548 (54.0)	313 (56.9)	1013 (64.2)	704 (56.6)	518 (38.5)
Computed tomography angiography	1691 (35.8)	221 (40.2)	657 (41.6)	444 (35.7)	369 (27.5)
Magnetic resonance angiography	2526 (53.6)	261 (47.5)	903 (57.2)	725 (58.3)	637 (47.4)
Antiplatelet medication, n (%)					
None	68 (1.4)	15 (2.7)	16 (1.0)	15 (1.2)	22 (1.6)
Mono (acetylsalicylic acid)	343 (7.3)	50 (9.1)	112 (7.1)	94 (7.6)	87 (6.5)
Mono (other than acetylsalicylic acid)	243 (5.2)	42 (7.6)	88 (5.6)	48 (3.9)	65 (4.8)
Dual antiplatelet medication	4063 (86.1)	443 (80.5)	1363 (86.3)	1087 (87.4)	1170 (87.1)
Neurologic assessment, n (%)					
Preprocedural	4207 (89.2)	485 (88.2)	1466 (92.8)	1131 (90.9)	1125 (83.7)
Postprocedural	3818 (80.9)	467 (84.9)	1367 (86.6)	1026 (82.5)	958 (71.3)
Pre- and postprocedural	3731 (79.1)	445 (80.9)	1350 (85.5)	1004 (80.7)	932 (69.3)
Length of stay, d, median (Q1-Q3), total					
Without event <sup>†</sup>	3 (2-5)	4 (2-8)	3 (2-6)	3 (2-5)	2 (2-4)
With event <sup>†</sup>	8 (5-13)	9 (5-13)	8 (4.25-13.75)	8.5 (7-12.75)	8 (5.5-13.25)

AFX indicates amaurosis fugax; ASA, American Society of Anesthesiologists; CAS, carotid artery stenting; N, all patients with information available; n, patients with feature or property; NASCET, North American Symptomatic Carotid Endarterectomy Trial; Q1-Q3, interquartile range; TIA, transient ischemic attack.

\*Multiple answers possible.

<sup>†</sup>Any in-hospital stroke or death.

**Table 2.** Peri- and Intraprocedural Management

	Total	Time Interval Between Index Event and Treatment			
	N=4717	0 to 2 Days n=550 (11.6%)	3 to 7 Days n=1579 (33.4%)	8 to 14 Days n=1244 (26.3%)	15 to 180 Days n=1344 (28.4%)
Intraprocedural monitoring, n (%)	1685 (35.7)	164 (29.8)	527 (33.4)	436 (35.0)	558 (41.5)
Electroencephalography	28 (0.6)	3 (0.5)	9 (0.6)	8 (0.6)	8 (0.6)
Transcranial cerebral oximetry	1216 (25.8)	122 (22.2)	380 (24.1)	323 (26.0)	391 (29.1)
Somatosensory evoked potentials	40 (0.8)	3 (0.5)	20 (1.3)	8 (0.6)	9 (0.7)
Other methods	837 (17.7)	90 (16.3)	289 (18.3)	205 (16.5)	253 (18.8)
Endovascular procedure (n, %)					
Angioplasty alone	87 (1.8)	12 (2.2)	35 (2.2)	25 (2.0)	15 (1.1)
Stent placement	294 (6.2)	32 (5.8)	109 (6.9)	68 (5.5)	85 (6.3)
Angioplasty and stent placement	4336 (91.9)	506 (92.0)	1435 (90.9)	1151 (92.5)	1244 (92.6)
Protection system use, n (%)	2282 (48.4)	248 (45.1)	706 (44.7)	619 (49.8)	709 (52.8)
Stent design, n (%)					
Open cell	1581 (34.1)	180 (11.4)	522 (33.8)	399 (32.7)	480 (36.1)
Closed cell	2507 (54.1)	298 (55.4)	845 (54.7)	684 (56.1)	680 (51.2)
Semiclosed cell	455 (9.8)	55 (10.2)	152 (9.8)	122 (10.0)	126 (9.5)
Others	87 (1.9)	5 (0.9)	25 (1.6)	14 (1.1)	43 (3.2)
Stent type, n (%)					
Nitinol	3254 (70.3)	390 (72.5)	1063 (68.8)	833 (68.3)	968 (72.8)
Stainless steel	1205 (26.0)	127 (23.6)	428 (27.7)	343 (28.1)	307 (23.1)
Others	171 (3.7)	21 (3.9)	53 (3.4)	43 (3.5)	54 (4.1)
Duration of procedure, min, median (Q1-Q3)	47 (40-60)	50 (40-60)	50 (40-60)	45 (40-60)	45 (37-60)

n, patients with feature or property; N, all patients with information available; Q1-Q3, interquartile range; min, minutes

followed by minor stroke (mRS 0-2) in 28.6%, AFX in 16.9%, and major stroke (mRS 3-5) in 16.5% (Table 1). The median time interval between the neurologic index event and CAS was 9 days (interquartile range, Q1-Q3 5-19 days). With respect to time interval groups, 11.6% of the patients were treated between 0 and 2 days (group I), 33.4% between 3 and 7 days (group II), 26.3% between 8 and 14 days (group III), and 28.4% between 15 and 180 days (group IV, Table 1). An ipsilateral high-grade carotid stenosis (70% to 99%; NASCET [North American Symptomatic Carotid Endarterectomy Trial] criteria) was present in 88.9% of the patients; 22.1% had an additional high-grade carotid stenosis or occlusion on the contralateral side (Table 1). The median length of stay (LOS) was 3 days (Q1-Q3 2-5 days) in patients without any in-hospital stroke or death but 8 days (Q1-Q3 5-13 days) in patients with an event. Among patients without an event, median LOS was 4, 3, 3, and 2 days in time interval groups I, II, III, and IV, respectively. In patients with an event, median LOS was 9, 8, 8.5, and 8 days in groups I, II, III, and IV, respectively (Table 1). Dual antiplatelet medication was applied in 86.1% (Table 1).

During the procedure, neuromonitoring was used in 35.7%. Angioplasty with stent placement was the most common technique (91.9%), with use of a protection system in 48.4%. Nitinol stents were placed in 70.3%, and stainless-steel stents in 26% (more details are provided in Table 2).

### Periprocedural Complications

The primary end point of any in-hospital stroke or death occurred in 173 patients (3.7%). The rate of any major stroke or death was 2.5%, and the singular risks for any perioperative stroke or death were 2.7% and 0.9%, respectively. The risk of any stroke or death was 6.0% in group I, 4.4% in group II, 2.4% in group III, and 3.0% in group IV. The risk of any death was 2.2% (n=12) in group I, compared to 0.9%, 0.6%, and 0.7% in groups II, III, and IV, respectively. Postprocedural myocardial infarction was documented in 0.1%. Local complications at the puncture site were severe bleeding or hematoma in 1.0%, false aneurysms in 0.7%, and arteriovenous fistulas in 0.1%. Details on raw risks of any procedural complications in the different time groups are listed in Table 3.



After adjustment for confounders and clustering of patients within centers (see Data Processing and Patient Grouping in the Methods section), regression analysis revealed that the time interval was associated with the primary and secondary end points (Figure 2): patients treated between 8 and 14 days were associated with a decreased risk for any in-hospital stroke or death (RR 0.47, 95% CI 0.28-0.79) compared to the 0-2 days reference group. Furthermore, patients treated in the last 2 groups, ie, 8 days and longer after the index event, were associated with a decreased risk for any major in-hospital stroke or death (group III, RR 0.36, 95% CI 0.20-0.67; group IV, RR 0.54, 95% CI 0.31-0.95) compared to the reference group I. Treatment between 3 and 14 days (groups II and III) was associated with a decreased risk of all-cause death (group II, RR 0.42, 95% CI 0.19-0.94; group III, RR 0.30, 95% CI 0.12-0.76) compared to the reference group I. Modeling the time interval as a continuous variable shows a significant relationship (cubic shape,  $P=0.019$ ) between this and the risk of stroke or death as well (see Figure 3A). In contrast, no significant association between time interval as a continuous variable and secondary outcomes was seen (Risk of major stroke or death:  $P=0.080$ , Figure 3B; Risk of death:  $P=0.115$ , Figure 3C).

## Discussion

In this secondary data analysis of the statutory German Carotid Database, almost all patients treated by CAS for symptomatic carotid stenosis with stable neurologic symptoms between 2012 and 2014 were assessed. In this cohort

the time interval between the neurologic index event and stenting was significantly associated with the primary and secondary end points.

A subgroup analysis of 4 randomized controlled trials (EVA-3S [Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis; SPACE [Stent-Protected Angioplasty versus Carotid Endarterectomy]; ICSS [International Carotid Stenting Study]; and CREST [Carotid Revascularization Endarterectomy versus Stenting Trial]) has previously assessed the influence of time interval on postprocedural outcome.<sup>7</sup> In all 4 trials patients with middle- to high-grade symptomatic carotid stenosis suitable for CAS ( $n=2093$ ) or CEA ( $n=2045$ ) were included. In this analysis patients treated by CAS during the first 7 days after the neurologic event had a 7-fold increased 30-day risk for any stroke or death compared to patients treated by CEA (adjusted RR 6.74, 95% CI 2.07-21.92). The RR for patients treated by CAS compared to CEA more than 7 days after the neurologic event was lower but still significant (RR 2.00, 95% CI 1.50-2.68). The RR for 30-day stroke or death in patients treated by CAS within 7 days compared to patients treated after 7 days was not statistically significant.<sup>7</sup>

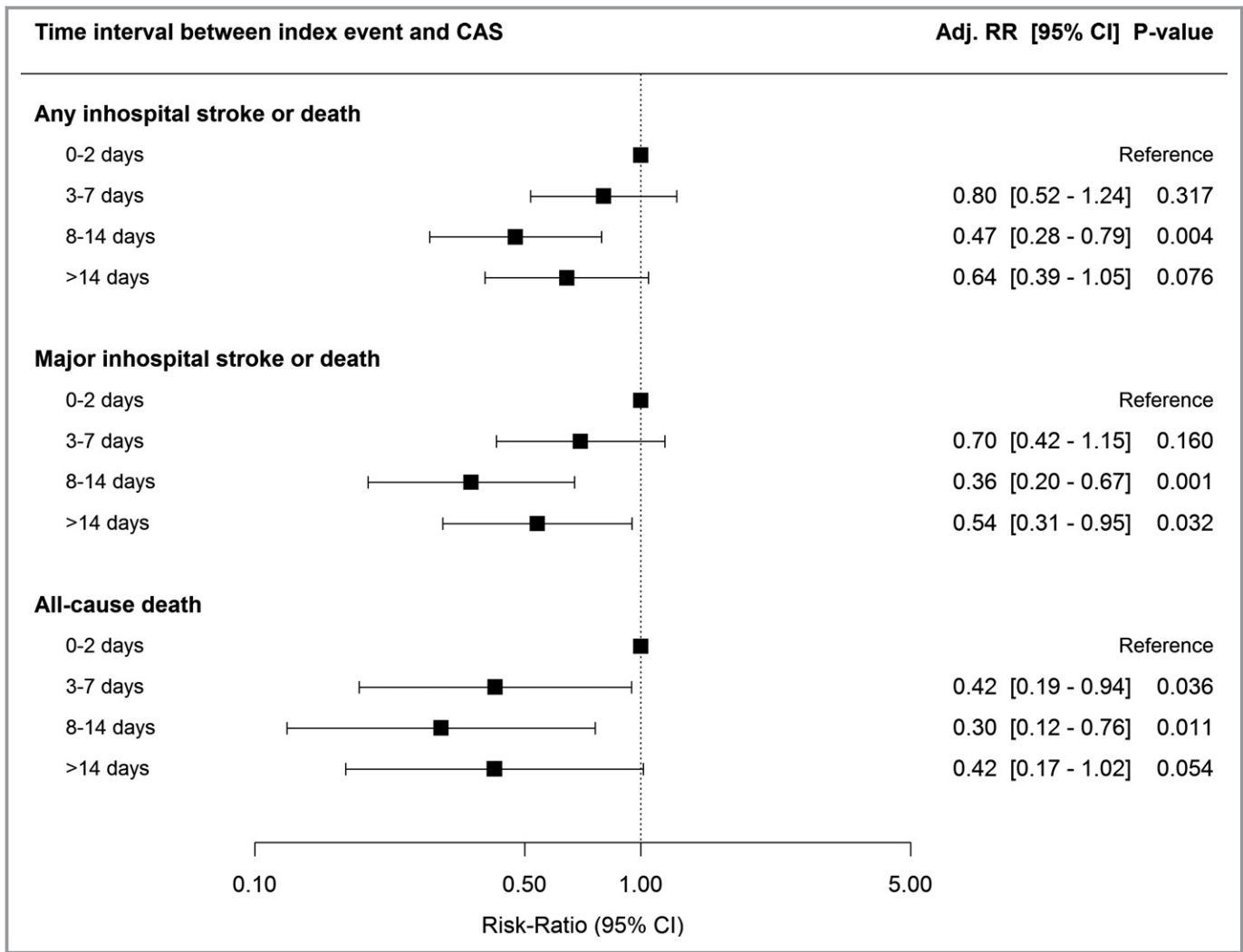
One single-center trial showed a significantly higher 30-day risk of any stroke or death in symptomatic patients treated by CAS <2 weeks after the index event compared to patients treated later (odds ratio 22.399, 95% CI 2.245-223.445;  $n=77$ ).<sup>24</sup> Other single-center studies<sup>25-27</sup> and 1 nationwide secondary data analysis study<sup>28</sup> found no statistically significant differences between the time interval and their primary

**Table 3.** Postinterventional Neurologic, Cardiac, or Local Complications

Number of Events Until Discharge	Total	Time Interval Between Index Event and CAS				P Value
	N=4717	0 to 2 Days n=550 (11.6%)	3 to 7 Days n=1579 (33.4%)	8 to 14 Days n=1244 (26.3%)	15 to 180 Days n=1344 (28.4%)	
Any stroke or death, n (%)	173 (3.7)	33 (6.0)	70 (4.4)	30 (2.4)	40 (3.0)	<0.001
Any major stroke or death, n (%)	117 (2.5)	26 (4.7)	46 (2.9)	18 (1.4)	27 (2.0)	<0.001
Stroke, n (%)	129 (2.7)	21 (3.8)	56 (3.5)	22 (1.8)	30 (2.2)	0.007
Major stroke (mRS 3-5)	73 (1.5)	14 (2.5)	32 (2.0)	10 (0.8)	17 (1.3)	0.011
Minor stroke (mRS 0-2)	56 (1.2)	7 (1.3)	24 (1.5)	12 (1.0)	13 (1.0)	0.457
Death, n (%)	44 (0.9)	12 (2.2)	14 (0.9)	8 (0.6)	10 (0.7)	0.012
Occlusion, n (%)	5 (0.1)	0 (0)	2 (0.1)	2 (0.2)	1 (0.1)	0.771
Local complications at puncture site, n (%)						
Severe bleeding or hematoma	31 (1.0)	5 (1.4)	6 (0.6)	7 (0.9)	13 (1.5)	0.177
Aneurysm	22 (0.7)	6 (1.6)	7 (0.6)	3 (0.4)	6 (0.7)	0.115
AV fistula	2 (0.1)	0 (0)	1 (0.1)	0 (0)	1 (0.1)	0.741
Any general complication, n (%)	145 (3.1)	33 (6.0)	41 (2.6)	35 (2.8)	36 (2.7)	<0.001
Myocardial infarction*	3/3185 (0.1)	1/373 (0.3)	1/1094 (0.1)	0/830 (0)	1/888 (0.1)	0.569

AV indicates atrioventricular; CAS, carotid artery stenting; mRS, modified Rankin scale; n, patients with feature or property; N, all patients with information available.

\*Only available for 2013-2014.



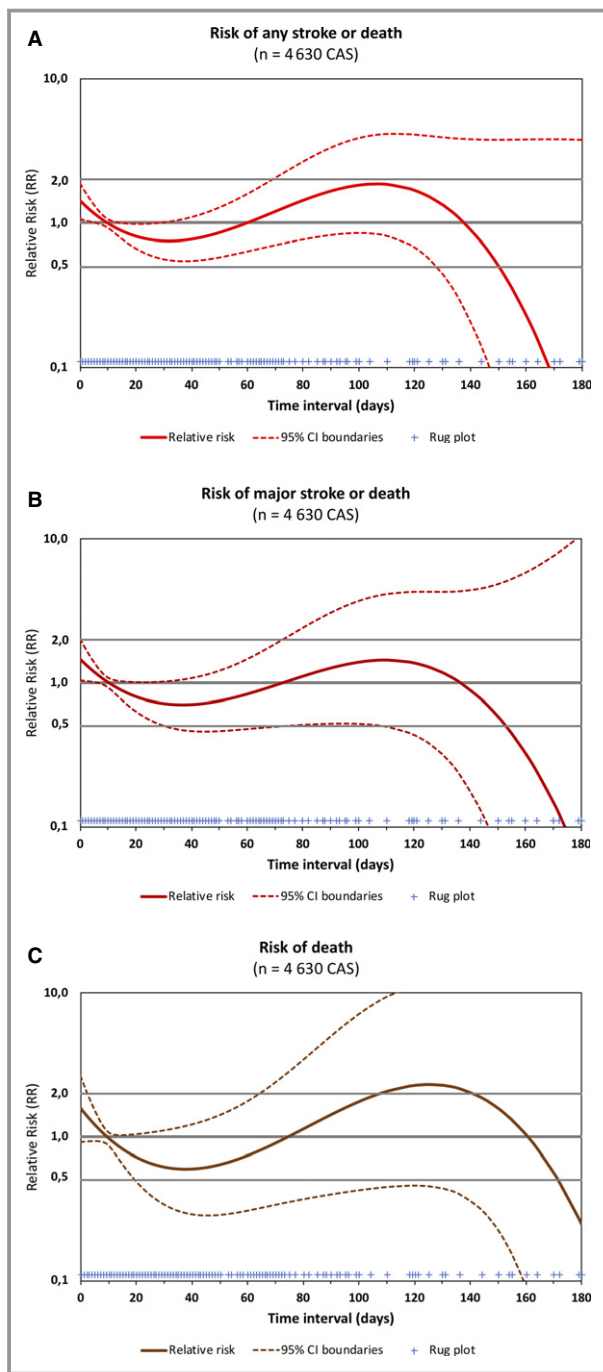
**Figure 2.** Multivariable regression analysis. Association of the (grouped) time interval between the neurologic index event and CAS with the risk of any stroke or death, any major stroke or death, and all-cause death. Adjusted for age, sex, ASA status, type of index event, degree of ipsi- and contralateral stenosis, periprocedural antiplatelet therapy, pre- and postprocedural neurologic assessment, intraprocedural neuromonitoring, stent design, type of stent, use of an embolic protection system, annual center volume, and hospital site code. ASA indicates American Society of Anesthesiologists score; CAS, carotid artery stenting; CI, confidence interval; RR, relative risk.

end point (n, total=991). The primary end point was any 30-day stroke or death in 2 studies,<sup>26,28</sup> or any 30-day stroke, death, or myocardial infarction in the other 2 studies.<sup>25,27</sup> Cohort sizes of the studies were between 127 and 323 patients. Therefore, the results of each of these studies are limited by a low statistical power, as mentioned by the authors themselves.<sup>25,27,28</sup> Another study including 482 patients treated by CAS for symptomatic carotid stenosis found an increased stroke risk in patients treated between 0 and 13 days compared to patients treated later after the index event (odds ratio 2.15, 95% CI 1.14-4.08).<sup>29</sup>

Two American nationwide secondary data analysis studies retrieved information from the Nationwide Inpatient Sample.<sup>30,31</sup> However, in these studies, the time interval between admission (not the index event!) and treatment by CAS or CEA was

assessed. Furthermore, information on clinical symptoms could not be retrieved through the diagnosis codes; patients with carotid artery stenosis and nonelective admission were assumed to be symptomatic.<sup>30,31</sup> Due to those substantial differences in study design, comparisons between the latter studies and our present results are not possible.

Using the same German nationwide database, we performed an analysis on all symptomatic patients treated by CEA (n=56 336). In this study no significant associations between time interval and the combined stroke and death risk were found.<sup>8</sup> Similar results could be found in multiple single-center studies with the same limitations of low statistical power as the single-center studies mentioned above.<sup>18</sup> Two other secondary data analysis studies found an increased 30-day risk for any stroke or death only if the surgery was



**Figure 3.** Multivariable regression analysis. Association of the time interval (as a continuous variable) between the neurologic index event and CAS on A) the risk of any stroke or death ( $P=0.019$ ), B) any major stroke or death ( $P=0.080$ ), and C) all-cause death ( $P=0.115$ ). A relative risk of 1 corresponds to the average relative risk of all patients. Adjusted for age, sex, ASA status, type of index event, degree of ipsi- and contralateral stenosis, periprocedural antiplatelet therapy, pre- and postprocedural neurologic assessment, intraprocedural neuromonitoring, stent design, type of stent, use of an embolic protection system, annual center volume, and hospital site code. ASA indicates American Society of Anesthesiologists score; CAS, carotid artery stenting; CI, confidence interval; RR, relative risk.

performed within the first 2 days after the index event.<sup>32,33</sup> Those differences from the German secondary data analysis study might be explained by different inclusion criteria: the Swedish and UK studies did not exclude emergency procedures such as crescendo TIA or stroke-in-evolution, which should be treated right after admission and are known to carry a higher risk of stroke or death.<sup>34,35</sup> These patients would therefore be classified into the first time group (0-2 days). Another explanation for the different findings could be the different end-point definitions: the German study only assessed events until discharge, whereas the Swedish and UK studies assessed the 30-day risks.<sup>8,32,33</sup> However, how many strokes can be prevented by early treatment cannot be shown based on this secondary data analysis. It is known that there is a high risk of recurrent events during the first days after a neurologic event<sup>1</sup>; therefore, the benefit of preventing strokes by performing surgery as early as possible seems to be clear. Causal relationships must be proven by a randomized trial.

To return to treatment with CAS, our results of 4717 patients treated by CAS for symptomatic carotid stenosis indicated a trend toward increased risk if patients were treated early after the index event. The raw risk for any in-hospital stroke or death was highest in patients treated between 0 and 2 days with 6.0% ( $n=33/550$ ) (Table 3). In multivariable regression analysis, the risk for any in-hospital stroke or death was decreased if patients were treated between 8 and 14 days, the risk for any in-hospital major stroke or death was decreased if patients were treated later than 8 days after the index event, and the risk for all-cause death was significantly decreased if patients were treated between 3 and 14 days ( $P=0.036$  and  $0.011$ ), and almost significantly decreased if patients were treated after 14 days ( $P=0.054$ ) compared to the 0- to 2-day reference group (Figure 2). Raw risks of secondary end points were highest in patients treated between 0 and 2 days as well: Raw combined major stroke and death risk, stroke risk, and death risk were 4.7% ( $n=26/550$ ), 3.8% ( $n=21/550$ ), and 2.2% ( $n=12/550$ ), respectively (Table 3). Considering the time interval as a continuous variable, treatment between 0 and 5 days was associated with an increased risk for any in-hospital stroke or death compared to the mean risk of the cohort (Figure 3A). Again, we do not know how many strokes have been prevented due to early treatment, but together with the results from the abovementioned subgroup analysis of 4 randomized controlled trials,<sup>7</sup> treatment with CAS seems to be more dangerous in the early period after the index event. Little is known about the exact pathomorphology of symptomatic carotid lesions. In the CREST trial the periprocedural stroke and death rate was significantly lower in symptomatic patients treated by CEA compared to CAS. Differences between those 2 treatments were not significant in asymptomatic patients.<sup>36</sup> Studies investigating histologic plaque



morphology showed that the number of unstable plaques is higher in patients with symptomatic carotid stenosis compared to asymptomatic patients.<sup>37</sup> In theory, removing an unstable plaque under controlled conditions with distal and proximal clamping of the artery might be safer than pushing the plaque back against the wall with a stent. However, because this is an observational study and results cannot prove a causal relationship, other explanations for the described findings are possible. First, treatment on patients with mild neurologic symptoms might be deferred to meet optimal conditions for the intervention (ie, discharge to a specialized hospital or until the next weekday if admission was on a weekend). In addition to that, patients with mild symptoms might also not see a doctor immediately. Therefore, patients with mild symptoms—also known to have a better outcome<sup>38</sup>—might be associated with a longer time interval (selection bias). This could result in potential confounding (by indication). Further, there might be differences between hospitals regarding their knowledge and experience in treating patients with symptomatic carotid stenosis (eg, different compliance with “time is brain” policy).

Several limitations of the current study design should be mentioned. First, this is a retrospective observational study. Therefore, only associations but not causal relationships can be derived from the data. Next, the results might be influenced by the LOS (period at risk) because the database does not provide 30-day follow-up data. LOS was longer in patients with a documented outcome event. Patients therefore had a longer “period at risk,” although this is most likely due to the occurrence of the event itself (reversed causation). However, we compared the different time interval groups with each other, across which LOS was homogeneous (Table 1), and bias is therefore considered to be low. Additionally, most strokes occur right after the intervention. In CREST, 60% (n=29/48) of all strokes within 30 days occurred on day 0, and 81% (n=39/48) occurred within 1 week in CAS patients; the median time from the date of procedure was 0 days in the whole cohort (CEA and CAS; interquartile range 4 days).<sup>39</sup> Moreover, only patients treated for CAS were included in the current study. Patients suffering from symptomatic ICA stenosis not treated by stenting were not documented in this cohort. Neurologic assessment was performed in 89.2% before the intervention, although distinction between neurologically stable (AFX, TIA, stroke) and unstable patients (crescendo TIA, stroke-in-evolution) is challenging, especially during the first hours after onset of symptoms. Another limitation of the study was that the data were self-reported by the interventionalist performing the procedure. Further, information on how patients were selected for CAS is not available. According to the guidelines it is recommended to perform CAS in patients with high clinical or anatomic surgical risk.<sup>2</sup> However, we were only able to assess high clinical

surgical risk based on ASA category (Table 1). The majority of patients who were treated were ASA staged I and II (60.4%). Therefore, it seems as if guideline recommendations were not followed, but this cannot be proven due to the missing information on anatomic criteria. Finally, the time interval grouping was based on former studies and guidelines and is therefore arbitrary. To overcome the latter shortcoming, the time interval was also analyzed as a continuous variable. Because neurological outcome and death are crucial for calculating hospital quality indicators, these outcomes are available for all patients (completeness 100%). However, reporting of myocardial infarction was implemented in 2013 and is therefore only available from 2013 to 2014. Therefore, information regarding this outcome variable is missing for n=1532 patients (32.5%). Because information on this variable is consecutively available for the years 2013 and 2014, bias arising from selective reporting/documentation is considered negligible. However, residual confounding can definitely not be ruled out because important risk factors (eg, smoking and hypertension), protective factors (eg, statin therapy), and other factors (eg, plaque structure, plaque growth rate) had not been included in statutory reporting.

## Conclusions

With 4717 patients treated under everyday conditions in Germany between 2012 and 2014, this is the largest cohort study investigating the association between time interval and procedural outcomes after CAS conducted to date. The time interval was associated with an increased risk of any stroke or death and any major stroke or death if patients were treated within 7 days and any death alone if patients were treated within 2 days after the neurologic index event. Although this is only an observational study and results cannot prove causal relationships, CAS may be accompanied by an increased risk for stroke and death during the early period after the index event.

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## Disclosures

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