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Original Article

Identification of patient characteristics that may improve procedure selection for the treatment of carotid stenosis

Andreas Kuehnl*, Christoph Knappich, Felix Kirchhoff, Bianca Bohmann, Vanessa Lohe, Shamsun Naher, Hans-Henning Eckstein and Michael Kallmayer

Department for Vascular and Endovascular Surgery, Klinikum rechts der Isar, Technical University of Munich, Munich, Germany

*Correspondence to: Andreas Kuehnl, Department for Vascular and Endovascular Surgery, Klinikum rechts der Isar, Technical University of Munich, Ismaninger Str. 22, Munich, 81675, Germany (e-mail: a.kuehnl@tum.de)

Abstract

Background: Carotid endarterectomy and carotid artery stenting are common procedures for the treatment of carotid artery stenosis. The aim of this study was to identify factors that modify the effect between type of treatment and outcome, and could thus be used to refine the selection of treatment procedure.

Methods: All patients who underwent either carotid endarterectomy or carotid artery stenting between 2012 and 2018 in German hospitals were included. The analysis of effect modification was focused on baseline patient characteristics. The outcome was a composite of any stroke or death until discharge from hospital. For multivariable analyses, a generalized linear mixed regression model was used.

Results: Some 221 282 patients were included, of whom 68% were male. In patients who underwent carotid endarterectomy or carotid artery stenting, the risk of any stroke or death was 2.3% and 3.7% respectively. Patient age was statistically significantly associated with a higher risk of a composite outcome of any stroke or death (main effect of age: adjusted OR 1.21 (95% c.i. 1.17 to 1.26), $P < 0.001$). The age effect was stronger in patients treated with carotid artery stenting (interaction effect: adjusted OR 1.29 (95% c.i. 1.20 to 1.38), $P < 0.001$). Statistically significant interaction effects were identified for side of treatment, ASA grade, contralateral degree of stenosis, and the time interval between the index event and treatment.

Conclusion: This analysis shows that carotid artery stenting may be particularly disadvantageous in older patients, in patients with right-sided stenosis, and in symptomatic patients treated within the first 2 days after the index event. In patients with contralateral occlusion, carotid artery stenting appears equivalent to carotid endarterectomy.

Lay summary

The internal carotid artery supplies the brain with blood from both sides of the neck. The vessel can be narrowed due to a thickened and sick wall. This increases the risk of a brain stroke. To treat this narrowing, a surgical approach that involves peeling out the diseased wall parts can be performed. A less invasive approach that involves covering with a stent is also possible. The treatment is done to lower the risk of a stroke or other bad events, such as death. The treatment itself can also trigger these events. In German hospitals every treatment of the carotid artery is recorded in a central database. This study uses a statistical method involving almost all the data from this database. The years 2012 to 2018 were covered. The authors try to find factors that improve the choice of therapy method. The analysis shows that older patients and patients with right-sided disease have a higher risk when treated with stenting. This also applies to patients who are treated within 2 days after warning symptoms. Patients with contralateral occlusion may benefit from both methods.

Introduction

Carotid endarterectomy (CEA) and carotid artery stenting (CAS) are the predominant procedures used for treating carotid artery stenosis. Therapy indications, diagnostic measures, and treatment types need to be established under international guideline recommendations[1–3]. In general, CEA is the standard therapy, whereas CAS may be considered an alternative in selected patients[4], especially symptomatic patients at high surgical risk[1]. Regarding the choice of procedure (CEA or CAS), the decision should be based on patient-specific clinical and morphological variables, as well as the patient's personal preferences (level of evidence/grading of recommendation: expert consensus, German–Austrian guideline[1]). The following characteristics and morphological variables are associated with higher risk when performing CAS (making CEA more beneficial): older age (greater than 70 years), a short time interval between the index event and treatment, difficult access for CAS, and morphological characteristics of long stenosis, heavy calcification, vessel elongation, and plaque ulceration (expert consensus based on Naylor *et al.*[2] and Aboyans *et al.*[5]). In contrast, the following characteristics are associated with higher risk when performing CEA: restenosis, post-radiation stenosis, skull base near stenosis,

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tandem stenosis, and contralateral paresis of the recurrent laryngeal nerve (expert consensus[1]). However, all grades of the latter recommendations are expert consensus only, as higher-level evidence, for example direct head-to-head randomized studies, which justifies a higher grade of recommendation, remains unavailable. Regarding transfemoral CAS, a risk-calculating tool for the 30-day risk of stroke or death was developed based on a secondary data analysis of the Vascular Quality Initiative database[6]. This analysis directly associated the following factors with a higher risk in patients treated with CAS: age, race, diabetes, coronary artery disease, chronic heart failure, symptomatic status, and contralateral occlusion. In contrast, dual antiplatelet therapy and statin use were related to lower risk after CAS. Notably, these risk prediction models conducted the analysis either within a CEA or within a CAS cohort, but not simultaneously in both[6,7].

The aim of this study was to identify factors that modify the effect between treatment types and outcomes, which can be used to refine the selection process of treatment type.

Methods

This was a pre-planned substudy analysis of the ISAR-IQ project (Integration and Spatial Analysis of Regional, site-specific, and patient-level factors for Improving the Quality of treatment for carotid artery stenosis).

Data source

This study was based on the nationwide German statutory quality assurance measures according to § 136 SGB V of the Federal Joint Committee operated by the Institute for Quality Assurance and Transparency in Healthcare (Institut für Qualitätssicherung und Transparenz im Gesundheitswesen (IQTIG)). The IQTIG statutorily collected data on carotid revascularization procedures (CEA and CAS) in all German hospitals. Data were collected for all CEA and CAS procedures, except for those performed at military hospitals and outpatient clinics, because of legal obligations. The Ethics Committee of the Medical Faculty, Technical University of Munich approved this study (Reference Number 107/20S). The analysis was conducted in accordance with the Good Practice of Secondary Data Analysis guidelines[8]. REporting of studies Conducted using Observational Routinely-collected Data (RECORD) reporting guidelines were applied; this was appropriate because this was an observational study using routinely collected health data[9]. All data were saved on IQTIG servers, following the respective data protection regulations. Controlled remote data processing was used to permit data access. The ISAR-IQ study protocol was submitted to the IQTIG and the Gemeinsamer Bundesausschuss, Germany's Federal Joint Committee (G-BA) during the application procedure, but was not published separately. Further details on methods have already been published[1,10–21].

Inclusion and exclusion criteria

This study included all patients who underwent either CEA or CAS for carotid stenosis (asymptomatic, symptomatic, emergency, and other indications) from 2012 to 2018 in German hospitals (*Fig. 1*). Patients who underwent procedures other than CEA/CAS, as well as patients who underwent combined/converted procedures, patients who underwent combined carotid-coronary or carotid-peripheral artery procedures, and patients who underwent CAS procedures to primarily gain access for an intracranial intervention were excluded; in addition, patients with unknown or diverse sex were excluded. The latter was required to avoid extensive output blocking due to data protection issues. Patients were categorized as asymptomatic, symptomatic, or others. Symptomatic patients were subcategorized as symptomatic 'elective' (amaurosis fugax, transient ischaemic attack (TIA), stroke, or other elective symptoms) or symptomatic 'emergency' (crescendo TIA, stroke-in-evolution, or other emergency symptoms) based on the urgency of the care provided. In total, 221 282 patients were finally included.

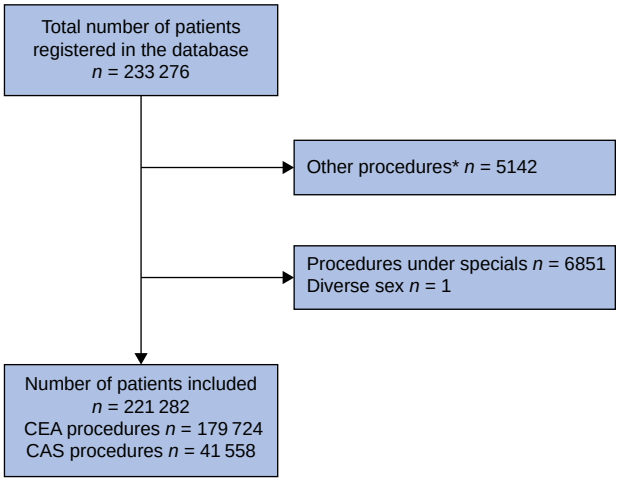

Fig. 1 Patient flow chart illustrating inclusion and exclusion criteria

*Excluding combined/converted procedures (CAS and CEA) and CAS procedures performed for the primary purpose of gaining access for an intracranial intervention. Special conditions include simultaneous cardiac, aortic, or peripheral vascular surgical procedures. CEA, carotid endarterectomy; CAS, carotid artery stenting.

Grouping variables and outcome

The patients were mainly categorized based on the procedure they underwent (CEA *versus* CAS as a comparative variable) and the occurrence of the outcome event (OE). The OE was the compound endpoint of 'any stroke or death', which is used in many major studies and guidelines and is crucial for the patient[1,2,5]. This endpoint refers to the interval up to discharge from the hospital, as the statutory quality assurance system recorded no data after discharge.

Statistical analyses

Categorical variables are presented as *n* (%) and continuous variables are presented as median (interquartile range).

R function 'glmer' with logit link function was used for multilevel multivariable regression analysis. The pre-procedural and post-procedural neurological-clinical assessments were included in the model as fixed effects by default because they were the strongest confounders in all previous analyses.

The procedure type (CEA *versus* CAS) was included as a fixed effect, as were the clinical variables age, sex, ASA grade, side of treatment, ipsilateral degree of stenosis, contralateral degree of stenosis, type of index event (initial neurological symptoms), time interval between the index event and treatment (only for electively treated symptomatic patients), morphological characteristics (for example ulcerated plaques and aneurysmal changes in addition to the stenosis), and centre annual caseload. The models involved an interaction term between the form of therapy and the respective clinical variable.

Hospital identifier and year of treatment were entered as random factors into the model (intercept only) to adjust for clustering effects and temporal trends respectively[22–24].

The chi-squared test was used to analyse differences regarding intra- and post-procedural variables. R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria) was utilized for data processing and statistical analysis, with extension packages 'tidyverse', 'epitools', 'lme4', 'expss', and 'ggplot2' used for cross-classified tables, chi-squared tests, and multivariable regression analyses.

Scatter plots with individual patient data points must not be created for data protection reasons. The differential effects of age and hospital caseload were visualized using microsimulation ($n = 10\,000$) based on the parameters calculated by the abovementioned multivariable regression models for an easily understandable graphical depiction of interaction effects. Graphic processing of the data was conducted using Microsoft Excel. A two-tailed level of significance of $\alpha = 5\%$ was used for all tests. For further details on the statistical methods please see the *Supplementary material*.

Results

Characteristics of patients

This study included 221 282 patients, of whom 68% were male. Of the patients, 179 724 (81%) and 41 558 (19%) underwent CEA and CAS respectively. The majority of patients were asymptomatic (55%). *Table 1* shows details on baseline characteristics of patients on hospital admission. Among patients who underwent CEA, general anaesthesia was predominantly used (71%), followed by local anaesthesia (27%) and combined/modified measures (2.5%). Revascularization success was controlled by intraoperative completion study in 74% of patients; imaging techniques, such as angiography or ultrasonography, were used in 56% of patients. *Table 2* shows details on perioperative and intraoperative management.

Outcomes and interaction effects

A total of 5623 events occurred, which corresponded to an overall raw risk of stroke or death until hospital discharge of 2.5%. The risk of OE was 2.3% and 3.7% in patients who underwent CEA

Table 1 Baseline characteristics of patients on hospital admission by type of treatment, primary outcome event, and raw risks

Clinical variable	Overall	OE occurred		OE did not occur		*P* (chi-squared)
		CEA	CAS	CEA	CAS	
Patients	221 282 (100)	4099 (1.9)	1524 (0.7)	175 625 (79)	40 034 (18)	<0.001
Age (years), median (interquartile range)	72 (64–77)	74 (67–79)	75 (67–80)	72 (65–78)	70 (63–77)	–
Sex						
Male	150 734 (68)	2768 (68)	1020 (67)	119200 (68)	27 746 (69)	<0.001
Female	70 548 (32)	1331 (32)	504 (33)	56 425 (32)	12 288 (31)	<0.001
Side of treatment						
Right	110 910 (50)	1780 (43)	703 (46)	88 610 (51)	19 817 (50)	<0.001
Left	110 372 (50)	2319 (57)	821 (54)	87 015 (49)	20 217 (50)	<0.001
ASA grade*						
I/II	72 169 (33)	614 (15)	538 (36)	48 211 (28)	22 806 (59)	<0.001
III	139 822 (64)	3022 (74)	649 (43)	121 591 (70)	14 560 (38)	<0.001
IV/V	7206 (3.3)	449 (11)	314 (21)	5027 (2.9)	1416 (3.7)	<0.001
Ipsilateral degree of stenosis†						
Mild (<50%)	3753 (1.7)	132 (3.2)	53 (3.5)	2599 (1.5)	969 (2.4)	0.657
Moderate (50–69%)	11 400 (5.2)	286 (7.0)	95 (6.2)	8839 (5.0)	2180 (5.5)	0.013
Severe (70–99%)	203 025 (92)	3551 (87)	1123 (74)	162 972 (93)	35 379 (88)	<0.001
Occlusion (100%)	3104 (1.4)	130 (3.2)	253 (17)	1215 (0.7)	1506 (3.8)	<0.001
Contralateral degree of stenosis†						
Mild (<50%)	150 898 (68)	2525 (62)	1075 (71)	119 068 (68)	28 230 (71)	<0.001
Moderate (50–69%)	30 507 (14)	606 (15)	116 (7.6)	25 848 (15)	3937 (9.8)	0.026
Severe (70–99%)	26 022 (12)	557 (14)	180 (12)	21 070 (12)	4215 (11)	<0.001
Occlusion (100%)	13 855 (6.3)	411 (10)	153 (10)	9639 (5.5)	3652 (9.1)	0.855
Neurological symptoms						
Asymptomatic	122 363 (55)	1461 (36)	374 (25)	99 454 (57)	21 074 (53)	0.001
Amaurosis fugax	12 375 (5.6)	140 (3.4)	24 (1.6)	10 374 (5.9)	1837 (4.6)	0.884
TIA	23 257 (11)	481 (12)	107 (7.0)	19 718 (11)	2951 (7.4)	<0.001
Stroke (minor/major/NA)	39 571 (18)	1137 (28)	326 (21)	31 249 (18)	6859 (17)	<0.001
Other elective symptoms	3764 (1.7)	80 (2.0)	28 (1.8)	2673 (1.5)	983 (2.5)	0.824
cTIA/SIE	9962 (4.5)	414 (10)	417 (27)	5662 (3.2)	3469 (8.7)	<0.001
Other emergency symptoms	9990 (4.5)	386 (9.4)	248 (16)	6495 (3.7)	2861 (7.1)	<0.001
Time interval (days)‡						
0–2	8023 (11)	260 (15)	104 (23)	6152 (11)	1507 (13)	<0.001
3–7	27 323 (38)	652 (38)	149 (32)	22 723 (39)	3799 (33)	<0.001
8–14	15 169 (21)	381 (22)	71 (15)	12 393 (21)	2324 (20)	0.962
15–180	21 920 (30)	443 (26)	137 (30)	17 564 (30)	3776 (33)	<0.001
Morphological characteristics§						
Ulcerated plaque	22 276 (10)	591 (14)	96 (6.3)	19 962 (11)	1627 (4.1)	<0.001
Aneurysmal change¶	1418 (0.6)	68 (1.7)	27 (1.8)	891 (0.5)	432 (1.1)	0.394
Coiling	1648 (0.8)	59 (1.4)	13 (0.9)	1449 (0.8)	127 (0.3)	<0.001
Multiple lesions	6354 (2.9)	239 (5.8)	211 (14)	3634 (2.1)	2270 (5.7)	<0.001

Values are *n* (%) unless otherwise indicated. *ASA grade missing for 2085 patients. †Degree of stenosis is in accordance with the North American Symptomatic Carotid Endarterectomy Trial (NASCET) standard. ‡Only available for symptomatic patients treated electively (not available for 148 847 patients). §Each yes *versus* no. ¶Aneurysmal change in addition to the atherosclerotic stenosis. OE, outcome event; CEA, carotid endarterectomy; CAS, carotid artery stenting; TIA, transient ischaemic attack; NA, information not available; cTIA, crescendo transient ischaemic attack; SIE, stroke-in-evolution.

Table 2 Perioperative and intraoperative management

	Overall	OE occurred		OE did not occur		P (chi-squared)
		CEA	CAS	CEA	CAS	
Neurological assessment*						
Pre-procedural	161 069 (73)	3211 (78)	1341 (88)	124 088 (71)	32 429 (81)	<0.001
Post-procedural	138 556 (63)	3469 (85)	1393 (91)	104 419 (60)	29 275 (73)	<0.001
Pre- and post-procedural	128 510 (58)	2914 (71)	1289 (85)	96 118 (55)	28 189 (70)	<0.001
Preoperative diagnostic procedures*†‡						
Duplex ultrasonography	152 681 (96)	2784 (97)	702 (71)	124 661 (98)	24 534 (88)	<0.001
Transcranial Doppler	45 833 (29)	956 (33)	415 (42)	34 348 (27)	10 114 (36)	<0.001
CT angiography	83 861 (53)	1899 (66)	681 (69)	66 739 (53)	14 542 (52)	<0.001
MRI angiography	74 976 (47)	1301 (45)	419 (42)	60 729 (48)	12 527 (45)	<0.001
Perioperative antiplatelet medication						
None	13 361 (6.0)	332 (8.1)	148 (9.7)	11 577 (6.6)	1304 (3.3)	<0.001
ASS monotherapy	163 612 (74)	3464 (85)	477 (31)	149 984 (85)	9687 (24)	<0.001
Clopidogrel monotherapy	5781 (2.6)	94 (2.3)	53 (3.5)	4392 (2.5)	1242 (3.1)	<0.001
Other monotherapy	1078 (0.5)	8 (0.2)	33 (2.2)	767 (0.4)	270 (0.7)	<0.001
Dual antiplatelet medication	37 450 (17)	201 (4.9)	813 (53)	8905 (5.1)	27 531 (69)	0.001
Type of anaesthesia‡						
Local	34 775 (27)	589 (21)	–	34 186 (27)	–	–
General	91 562 (71)	2194 (76)	–	89 368 (71)	–	–
Combined§	3265 (2.5)	97 (3.4)	–	3168 (2.5)	–	–
Intra-procedural monitoring‡¶						
Electroencephalography	8209 (5.2)	149 (5.2)	8 (0.8)	7903 (6.2)	149 (0.5)	0.008
Transcranial cerebral oximetry	24 417 (15)	401 (14)	239 (24)	16 383 (13)	7394 (27)	0.001
SSEP	36 417 (23)	756 (26)	8 (0.8)	35 320 (28)	333 (1.2)	0.900
Other methods	36 780 (23)	576 (20)	186 (19)	30 234 (24)	5784 (21)	<0.001
Operation technique‡						
TEA direct suture	2017 (1.6)	64 (2.2)	–	1953 (1.5)	–	–
TEA with patch	44 944 (35)	1004 (35)	–	43 940 (35)	–	–
Eversion CEA	53 149 (41)	963 (33)	–	52 186 (41)	–	–
Interposition	2478 (1.9)	144 (5.0)	–	2334 (1.8)	–	–
Other techniques#	27 014 (21)	705 (25)	–	26 309 (21)	–	–
Intra-arterial shunt use*‡	55 681 (35)	16 040 (56)	–	54 077 (43)	–	–
Intraoperative completion study‡						
Any type	116 715 (74)	1960 (68)	933 (94)	88 196 (70)	25 626 (92)	<0.001
Imaging technique only	88 085 (56)	1329 (46)	917 (92)	60 700 (48)	25 139 (91)	<0.001
Duration of operation (min), median (interquartile range)	80 (60–103)	94 (74–122)	60 (42–90)	86 (68–107)	45 (40–60)	<0.001
Duration of hospital stay after procedure (days), median (interquartile range)						
All patients	5 (3–6)	9 (5–16)	8 (4–14)	5 (4–6)	2 (2–5)	<0.001
Asymptomatic patients	4 (3–6)	9 (5–16)	7 (3–14)	5 (4–6)	2 (2–4)	<0.001
Symptomatic patients	5 (4–7)	10 (5–16)	8 (4–14)	5 (4–7)	3 (2–6)	<0.001

Values are *n* (%) unless otherwise indicated. *Yes *versus* no. †Multiple answers possible. ‡Only available from 2012 to 2016. §Patients who received a combination of local and general anaesthesia were likely to have predominantly undergone conversion from local to general anaesthesia. †,¶Multiple answers possible; information on percentages of subcategories refers to the cohort of patients who received intra-procedural neurophysiological monitoring; other methods include local anaesthesia in combination with the duck squeezing test, transcranial Doppler sonography, and measurement of stump pressure. #Other techniques include, for example, transposition of the carotid bifurcation, as well as procedures documented as 'other'. OE, outcome event; CEA, carotid endarterectomy; CAS, carotid artery stenting; ASS, Acetylsalicylic acid; SSEP, Somatosensory evoked potential.

and CAS respectively (*Table 3*). Patient age was statistically significantly associated with higher OE risk (main effect of age by 10-year steps: adjusted OR 1.21 (95% c.i. 1.17 to 1.26), $P < 0.001$). The age effect was statistically significantly stronger in patients treated with CAS (interaction effect: adjusted OR 1.29 (95% c.i. 1.20 to 1.38), $P < 0.001$) (*Table 3*). *Figure 2a* illustrates the association between age, treatment type, and risk of OE. Higher annual centre volume (all CEA and CAS procedures) was associated with lower risk of OE (main effect of hospital volume per 1 log point: adjusted OR 0.84 (95% c.i. 0.80 to 0.89), $P < 0.001$). However, the volume–outcome effect was not different between CEA and CAS (interaction effect: adjusted OR 1.02 (95% c.i. 0.95 to 1.11), $P = 0.549$). *Figure 2b* shows the volume–outcome association. Multilevel multivariable regression analysis revealed statistically significant interaction effects for the side of treatment, ASA grade, contralateral degree of stenosis, the time interval between the index event and treatment, and aneurysmal change of the ipsilateral internal carotid artery (*Table 3*).

Discussion

This analysis of nationwide real-world data reveals the generally higher in-hospital risk of stroke or death after CAS. Therefore, this analysis highlights that CEA is the treatment of choice, as recommended by current guidelines. Based on this study, CAS may be particularly disadvantageous in older patients, in patients with right-sided stenosis, and in symptomatic patients treated within the first 2 days after the index event. It may be equivalent to CEA in patients with contralateral occlusion, as well as symptomatic patients treated in the second week after the index event. Greater than 40 000 CAS procedures were performed from

Table 3 Adjusted ORs for the interaction effect between the index clinical variable, treatment type, and outcome

Clinical variable	Raw risk (%)		Raw relative risk, CAS *versus* CEA		Interaction effect, CAS *versus* CEA	
	CEA	CAS	RR (95% c.i.)	P	aOR (95% c.i.)	P
Overall cohort	2.3	3.7	1.61 (1.52,1.70)	<0.001	–	–
Age (10-year steps)	–	–	–	–	1.29 (1.20,1.38)	**<0.001***
Centre annual caseload	–	–	–	–	1.02 (0.95,1.11)	0.549
Sex						
Male (reference)	2.3	3.5	1.56 (1.46,1.68)	<0.001	1.11 (0.97,1.26)	0.123
Female	2.3	3.9	1.71 (1.55,1.89)	<0.001		
Side of treatment						
Right	2.0	3.4	1.74 (1.59,1.90)	<0.001	1.17 (1.03,1.32)	**0.011***
Left (reference)	2.6	3.9	1.50 (1.39,1.63)	<0.001		
ASA grade						
I + II	1.3	2.3	1.83 (1.63,2.06)	<0.001	Reference	–
III	2.4	4.3	1.76 (1.61,1.91)	<0.001	1.05 (0.91,1.22)	0.495
IV + V	8.2	18.2	2.21 (1.94,2.53)	<0.001	1.35 (1.09,1.65)	**0.004***
Ipsilateral degree of stenosis†						
Mild (<50%)	4.8	5.2	1.07 (0.79,1.46)	0.657	0.75 (0.54,1.05)	0.091
Moderate (50–69%)	3.1	4.2	1.33 (1.06,1.67)	0.013	0.89 (0.70,1.15)	0.377
Severe (70–99%)	2.1	3.1	1.44 (1.35,1.54)	<0.001	Reference	–
Occlusion (100%)	9.7	14.4	1.49 (1.22,1.82)	<0.001	0.95 (0.74,1.21)	0.657
Contralateral degree of stenosis†						
Mild (<50%)	2.1	3.7	1.77 (1.65,1.90)	<0.001	1.15 (0.95,1.38)	0.152
Moderate (50–69%)	2.3	2.9	1.25 (1.03,1.52)	0.026	0.80 (0.61,1.05)	0.104
Severe (70–99%)	2.6	4.1	1.59 (1.35,1.88)	<0.001	Reference	–
Occlusion (100%)	4.1	4.0	0.98 (0.82,1.18)	0.856	0.61 (0.47,0.79)	**<0.001***
Neurological symptoms						
Asymptomatic	1.4	1.7	1.20 (1.08,1.35)	0.001	Reference	–
Symptomatic						
Amaurosis fugax	1.3	1.3	0.97 (0.63,1.49)	0.884	0.72 (0.45,1.16)	0.182
TIA	2.4	3.5	1.47 (1.20,1.81)	<0.001	1.04 (0.81,1.34)	0.734
Stroke (minor/major/NA)	3.5	4.5	1.29 (1.15,1.46)	<0.001	1.02 (0.84,1.23)	0.866
Other elective symptoms	2.9	2.8	0.95 (0.62,1.46)	0.824	0.79 (0.49,1.27)	0.330
cTIA/SIE	6.8	10.7	1.57 (1.38,1.79)	<0.001	1.09 (0.88,1.34)	0.427
Other emergency symptoms	5.6	8.0	1.42 (1.21,1.66)	<0.001	1.03 (0.82,1.28)	0.819
Time interval (days)‡						
0–2	4.1	6.5	1.59 (1.28,1.99)	<0.001	1.71 (1.21,2.43)	**0.003***
3–7	2.8	3.8	1.35 (1.14,1.61)	<0.001	1.38 (0.87,2.19)	0.170
8–14	3.0	3.0	0.99 (0.77,1.28)	0.962	Reference	–
15–180	2.5	3.5	1.42 (1.18,1.72)	<0.001	1.50 (0.94,2.39)	0.090
Morphological characteristics						
Ulcerated plaque	2.9	5.6	1.94 (1.57,2.39)	<0.001	1.15 (0.91,1.46)	0.235
Aneurysmal change§	7.1	5.9	0.83 (0.54,1.28)	0.396	0.49 (0.31,0.78)	**0.002***
Coiling	3.9	9.3	2.37 (1.34,4.22)	0.003	1.38 (0.74,2.56)	0.311
Multiple lesions	6.2	8.5	1.38 (1.15,1.65)	<0.001	0.86 (0.70,1.06)	0.169

Raw risks for age and volume are shown in *Fig. 2*. *Statistically significant. †Degree of stenosis is in accordance with the North American Symptomatic Carotid Endarterectomy Trial (NASCET) standard. ‡Only available for symptomatic patients treated electively. §Aneurysmal change in addition to the atherosclerotic stenosis. CAS, carotid artery stenting; CEA, carotid endarterectomy; RR, relative risk; aOR, adjusted OR (statistical interaction effect between the index variable, treatment (CAS *versus* CEA), and the risk of any stroke or death until discharge (primary outcome event)); TIA, transient ischaemic attack; NA, information not available; cTIA, crescendo transient ischaemic attack; SIE, stroke-in-evolution.

2012 to 2018, of which 21 000 were in asymptomatic patients, despite the recommendations in the German–Austrian guideline (first published in 2012). The reasons for method selection cannot be substantiated based on the available data, but widespread compliance with the guideline recommendations still appears inadequate in Germany. This should encourage national educational measures to improve guideline-compliant care.

The overall risk of OE was generally higher in CAS compared with CEA (3.7% *versus* 2.3% respectively), which corresponds well with other reports[4,25] and a comprehensive Cochrane systematic review[26]. The latter meta-analysis included 5396 patients from 10 RCTs. The risk of any stroke or death within 30 days in asymptomatic patients in this Cochrane review was 1.4% for CEA and 2.5% for CAS (OR 1.72 (95% c.i. 1.00 to 2.97)). In symptomatic patients, these figures were 4.4% *versus* 7.2% respectively (OR 1.70 (95% c.i. 1.31 to 2.19)). In comparison, the specific risks for CEA and CAS in this study were 1.4% and 1.7% respectively in asymptomatic patients and 3.3% and 5.7% respectively in symptomatic patients (elective or emergency treatment). These values are generally somewhat lower compared with the Cochrane review cited above and other studies. The German quality assurance data are exclusively inpatient data, whereas the risks reported in RCTs are usually associated with an interval of up to 30 days; consequently, the risks determined in this study are probably too low, with the actual risks being higher. Information bias can be assumed, as statutory quality assurance in Germany relates exclusively to the inpatient sector, with no association with other social data to date. The different duration of hospital stay needs to be considered, which is statistically significantly shorter for CAS (2 days) than for CEA (5 days). This results in a shorter interval 'under observation' for CAS in which an OE could be recorded for quality assurance purposes. Therefore, the actual outcome risks may be even higher after CAS compared with CEA and the

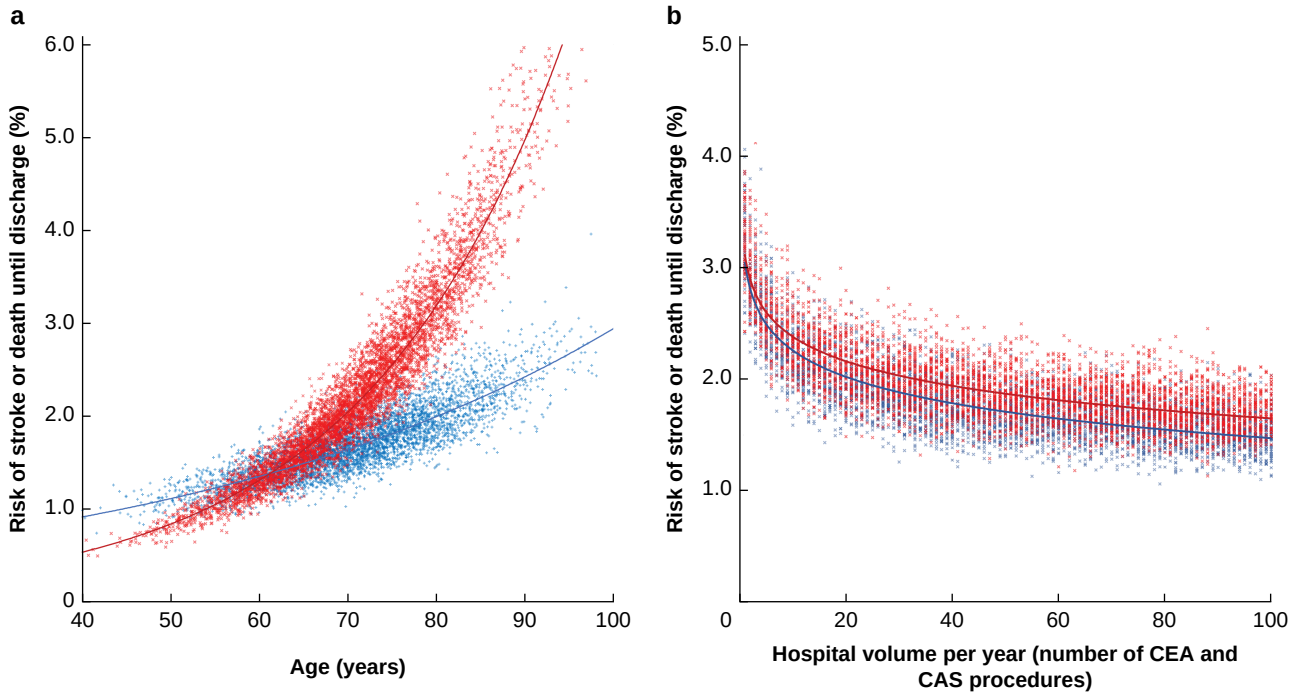

Fig. 2 Visualized association between the type of treatment, the risk of stroke or death until discharge from hospital, and patient age or annual hospital volume

a Patient age. **b** Annual hospital volume. Data derived from microsimulation (see the Methods section). Absolute risk of stroke or death until discharge was simulated based on the parameters derived from the multivariable regression models. A microsimulation was necessary because a direct display of data points of individual patients was prohibited for data protection reasons. Carotid endarterectomy = blue and carotid artery stenting = red. CEA, carotid endarterectomy; CAS, carotid artery stenting.

size of the differential effects found in this study is probably underestimated.

The association between age and the risk of OE was stronger in CAS compared with CEA (*Fig. 2a*). The different slopes for CEA and CAS can be used to identify the effect modification. This indicates that, the older the patients, the lower the relative risk of CEA compared with CAS under otherwise identical conditions. These results are congruent with earlier publications from Germany[16,17], an individual patient meta-analysis of the Carotid Stenting Trialists' Collaboration (CSTC; data from the International Carotid Stenting Study (ICSS), the Carotid Revascularization Endarterectomy *versus* Stent Trial (CREST), the Endarterectomy *versus* Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial, and the Stent-Protected Angioplasty *versus* Carotid Endarterectomy (SPACE) trial)[27,28], and a systematic review of international observational studies[29]. The aforementioned CSTC meta-analysis identified age as a statistically significant effect modifier, but all other subgroups analysed demonstrated no evidence of effect modification. These divergent results may be due to several variations between the CSTC data and the mandatory nationwide German carotid database. In particular, the CSTC included considerably fewer patients (3433 *versus* 221 282), only symptomatic patients, only patients who were eligible for both procedures, only patients in participating centres, only patients who consented to study participation, and only patients who met all inclusion criteria, and participating centres and physicians had to meet all minimum requirements for participation. Conversely, the CSTC included patients who were randomized (but only for the CEA–CAS head-to-head comparison), patients who were from different countries, and, most importantly, patients who were prospectively documented, resulting in very low information bias. Notably, the external validity of RCTs is heterogeneous and may vary from clinical practice, for example concerning age, co-morbidities and medication, as analysed in detail by Kallmayer *et al.*[30]. A higher risk in older patients could be caused by increasing vascular calcification with age, especially in patients with calcification of the access routes to the carotid artery[16,17]. A retrospective analysis of the Vascular Quality Initiative database that included 11 342 patients who underwent transfemoral CAS or transcarotid artery revascularization (TCAR) supported this notion; this study revealed that marked carotid artery calcification was associated with worse outcomes in patients who underwent transfemoral CAS, whereas this was not the case with TCAR[31]. Additionally, the formation of unfavourable aortic arch anatomy during ageing may cause a higher risk in old patients who undergo CAS[26,32]. Further, the negative effects of an unfavourable or longer access route could cause a higher risk of right-sided stenosis in CAS than in CEA, as the present study reveals. A higher risk of right-sided CAS was also found in the systematic review by Touzé *et al.*[29], which included greater than 30 000 patients from 12 studies.

The risk of OE was comparable in both CEA (4.1%) and CAS (4.0%) in the subgroup of patients with contralateral carotid occlusion (CCO). In contrast, Krawisz *et al.*[33] analysed 58 423 patients from the USA and reported that the risk of in-hospital stroke or death in patients with CCO was 3.0% for CEA and 1.9% for CAS. These results are congruent with the findings of Touzé *et al.*[29], demonstrating that CEA was statistically significantly associated with a higher risk of stroke or death in patients with CCO (risk ratio 1.56 (95% c.i. 1.31 to 1.86)), whereas CAS exhibited no increased risk in patients with CCO. Additionally, contralateral occlusion was determined to be a statistically

significant predictor of the 30-day stroke or death rate after CEA and was thus included in the Ontario Carotid Endarterectomy Registry risk model[34]. A large external validation study identified the Ontario Carotid Endarterectomy Registry risk model as providing the most reliable predictions of stroke or death rates after CEA[7]; unfortunately, the study did not conduct a direct comparison with CAS. In summary, more consideration may be given to CAS in the presence of a CCO.

A comprehensive review of 71 studies including greater than 230 000 symptomatic patients summarized that early CEA within 2 or up to 7 days after the index event was safer than transfemoral CAS regarding the timing of treatment[35]. This is congruent with the results of the present study and an earlier secondary data analysis of the German statutory quality assurance database[19]. The present analysis considers CAS to be equivalent only in the second week after the index event, and otherwise inferior to CEA, especially in the first 2 days after the index event. In summary, the current real-world data support the recommendations of the guidelines, including those of the European Society for Vascular Surgery (ESVS): patients who are undergoing revascularization within the first 14 days after the onset of symptoms are recommended to undergo CEA, rather than carotid stenting[2].

A detailed discussion of the limitations can be found in the *Supplementary material* and elsewhere[10–13,15–21,36–39]. In summary, this is a secondary data analysis and thus all difficulties associated with observational studies using routine data must be considered. This is a retrospective study with the observation interval only covering the inpatient stay. All information in the database is self-reported, but the reporting of data on all CEA and CAS procedures was mandatory and required by law in a standardized manner for all of Germany. Only the variables available in the mandatory documentation form could be analysed; thus, risk adjustment was limited and residual confounding could not be excluded.

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Disclosure

The authors declare no conflict of interest.

Supplementary material

Supplementary material is available at *BJS* online.

Data availability

The datasets analysed during the current study are available on request from the IQTIG, (https://iqtig.org/qs-verfahren-uebersicht/sekundaere-datennutzung/).

Author contributions

Andreas Kuehnl (Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing—original draft, Writing—review & editing), Christoph Knappich (Conceptualization, Data curation, Investigation, Supervision, Writing—review & editing), Felix Kirchhoff (Data curation, Validation, Writing—review & editing), Bianca Bohmann (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Validation, Writing—review & editing), Vanessa Lohe (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Writing—review & editing), Shamsun Naher (Data curation, Formal analysis, Investigation, Methodology, Validation, Writing—review & editing), Hans-Henning Eckstein (Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Writing—review & editing), and Michael Kallmayer (Conceptualization, Investigation, Project administration, Resources, Supervision, Validation, Writing—original draft, Writing—review & editing)

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