Long Term Outcomes After Invasive Treatment of Carotid Artery Stenosis: a Longitudinal Study of German Health Insurance Claims

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ORIGINAL ARTICLE: OBSERVATIONAL STUDY

Editor's Choice – Long Term Outcomes After Invasive Treatment of Carotid Artery Stenosis: a Longitudinal Study of German Health Insurance Claims

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WHAT THIS PAPER ADDS

While registry studies have emphasised that real world treatment of carotid artery stenosis may not always confirm results derived from randomised controlled trials owing to inherent selection bias, there is a striking paucity of longitudinally linked observational data to determine long term outcomes in this target population. The current study used a large insurance claims dataset to determine five year mortality and stroke rates after carotid endarterectomy and stent angioplasty in 22 637 individual patients. The study found higher event rates in some subgroups than previously reported in landmark trials, raising questions about the applicability of trial data to everyday clinical practice.

Objective: There is a paucity of observational data including long term outcomes after invasive treatment for carotid artery stenosis.

Methods: This retrospective study used nationwide insurance claims from the third largest provider in Germany, DAK-Gesundheit. Patients who underwent inpatient carotid endarterectomy (CEA) or carotid artery stenting (CAS) between 1 January 2008 and 31 May 2017 were included. The Elixhauser comorbidity scores from longitudinally linked hospital episodes were used. Kaplan—Meier analysis and the log rank test were used to determine long term stroke free survival. Multivariable regression models were developed to adjust for confounding.

Results: A total of 22 637 individual patients (41.6% female, median age 72.5 years) were included, of whom 15 005 (66.3%) were asymptomatic and 17 955 (79.3%) underwent CEA. After a median of 48 months, 5 504 any stroke or death events were registered. The mortality rate varied between 0.4% (CEA for asymptomatic stenosis) and 2.1% (urgent CAS for acute stroke patients) at 30 days, and between 4.1% and 8.4% at one year, respectively. The rate for any stroke varied between 0.6% (CEA for asymptomatic stenosis) and 2.5% (CAS for symptomatic patients) at 30 days, and between 2.5% and 6.4% at one year, respectively. The combined rate for any stroke and mortality at one year was 6.3% (CEA for asymptomatic stenosis), 8.7% (CAS for asymptomatic stenosis), and 12.5% (urgent CAS for acute stroke patients). After five years, the overall stroke rate was 7.4% after CEA and 9.0% after CAS. In adjusted analyses, both older age and van Walraven comorbidity score were associated with events, while treatment of asymptomatic stenosis was associated with lower event rates.

Conclusion: The current study revealed striking differences between previous landmark trials and real world practice. It further suggested excess deaths among invasively treated asymptomatic patients.

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INTRODUCTION

Atherosclerosis of the carotid arteries and carotid artery stenosis are common in contemporary population based cohorts[1,2], with moderate stenosis (> 50%) detected in 7.5% of men and 4.0% of women above 80 years of age.[3] Various factors such as older age, male sex, vascular disease, high blood pressure, dyslipidaemia, diabetes, and smoking are associated with this common disease.[3] Besides best medical treatment and two complementary invasive approaches build the backbone of stroke prevention.[4–6]

While previous registry studies revealed that treatment practice patterns differed widely between countries, open surgical carotid endarterectomy (CEA) and carotid artery stenting (CAS) are frequent procedures in countries with a fee for service system such as Germany.[7–9]

During recent decades, several trials[10–13] and clinical practice guidelines[5,6,14,15] on carotid artery disease have been published. However, observational data on long term outcomes after invasive treatment to validate trial reality in everyday clinical practice remain sparse. In Germany, two large registries are available to describe the nationwide treatment patterns: the German Statutory Quality Assurance Database[16] maintained by the authorities; and hospital episode statistics by the Federal German Statistics Bureau.[8] While both databases certainly provide large numbers of procedures (almost 33 000 procedures registered in 2019), their impact remains limited due to the lack of meaningful outcomes beyond discharge and the inability to link prior information with the current hospital case to generate complete comorbidities. To close this research gap, health insurance claims may provide valuable data. They allow longitudinal linkage of hospital episodes, and their validity is deemed high in terms of major cardiovascular events such as death and stroke.[17–19]

This study aimed to determine contemporary treatment and long term outcomes after discharge in a nationwide unselected cohort of patients who underwent carotid artery revascularisation using claims data from the third largest health insurance provider in Germany.

METHODS

The current study was a retrospective, observational analysis of longitudinally linked health insurance claims data from DAK-Gesundheit, the third largest health insurance provider in Germany (6.2 million insured members during the study period on average).

Inclusion criteria

The study included all patients insured by DAK-Gesundheit who underwent CEA or CAS at any legally endorsed hospital in Germany with a discharge date between 1 January 2008 and 31 May 2017.

Data and variables

All data were appropriately de-identified prior to transmission to the research team. The research data have a history of use in health services research[20–22] and have undergone external validation by the Medical Service of the Health Funds in Germany (Medizinischer Dienst).[19]

Reporting of the study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[23]

The available research data included age (in years), dichotomised sex, comorbidities, all inpatient stays, primary and secondary diagnoses of the hospital stay, and all registered operations and procedures (OPS codes). No outpatient data were included in the study dataset.

Comorbidities were defined according to the International Classification of Diseases (ICD-10) of the World Health Organisation (WHO). In 1998, Elixhauser *et al* introduced a systematic classification to identify relevant comorbidities among primary or secondary diagnoses at the time of discharge.[24] Charlson comorbidity domains[25] as adopted by Quan *et al*[26] were used to calculate relevant Elixhauser comorbidity scores. The R package, comorbidity, was used to perform these calculations.[27] Major comorbidities, such as congestive heart failure, cardiac dysrhythmia, chronic pulmonary disease, diabetes, and chronic kidney failure, were categorised into 30 commonly accepted domains (groups). Major comorbidities were: arterial hypertension (I10, I11—I13, I15); diabetes (E10, E11, E12, E13, E14); obesity (E66); and congestive heart failure (I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5—I42.9, I43, I50, P29.0). Other comorbidities included were part of the Charlson comorbidity index score.[25]

The ICD and OPS codes relevant to the current study were scrutinised and confirmed for annual consistency as well as forward and backward compatibility within their respective study years. A look back strategy of up to five years before the index treatment was used to generate a valid history of comorbidities.

Statistical analysis

All analyses were performed using the statistical software R.[28] The original research dataset contained 383 691 patients selected from the overall insurance population at DAK-Gesundheit. It included all insured patients with stroke and transient ischaemic attack (TIA) as primary diagnosis or relevant index interventions within the study period. All

inpatient stays for these patients were included in the dataset.

Strata and comparison groups

Analyses were performed for three groups of patients: the acute stroke group (i) suffered from an acute stroke or TIA as primary diagnosis (admitting diagnosis) during the index stay; the symptomatic group (ii), which consisted of patients with any prior stroke or TIA diagnosis during the six months preceding the index admission (but not as the reason for the index hospitalisation); and the asymptomatic group (iii) had no occurrence of stroke or TIA six months prior to the intervention. These groups reflect strata in everyday clinical practice.

Study endpoints

The primary endpoint was defined as the five year stroke rate. Secondary endpoints were defined as peri-operative stroke or death (at 30 and 120 days) and the one year stroke or peri-operative mortality rates. The secondary endpoints were chosen to reflect the original randomised controlled trials (RCTs) as well as pooled follow up analyses. A composite secondary endpoint was defined as peri-operative (30 day) death or stroke or peri-operative (30 day) myocardial infarction or ipsilateral or contralateral stroke during the follow up period (5 years). Brott *et al* published pooled data from major RCTs (EVA-3S, SPACE, ICSS, and CREST) comparing patients who underwent CEA with those who underwent CAS using a peri-operative period of 120 days.[29] Following their nomenclature, the peri-operative period was extended to 120 days in some of the analyses.

The event, death, was documented by the insurance company (cancellation of a policy due to death) or the documentation of discharge codes from hospital stays (death during a hospital stay), and either occurrence was deemed sufficient to mark a patient's death. A small number of patients (< 5) with incongruent death dates was reviewed and attributed manually; in case a clear attribution was impossible, the data were excluded (2 patients).

The post-operative event, any stroke, was primarily defined by the initial occurrence of the ICD-10 codes for stroke (I63, I64) or TIA (G45) after the index procedure. It was not possible to distinguish between all stroke and ipsilateral stroke rates, and no data were available on internal carotid artery re-stenosis or occlusion. Due to the nature of billing rules in Germany, subsequent visits in some cases contain references to a prior stroke (using the same ICD code), making it hard to identify repeat strokes in the dataset. It was decided to implement a conservative interpretation of the data. Repeat occurrences of a stroke related ICD code in the dataset were only counted as new cases if they occurred concurrent with the billing code for a comprehensive neurological treatment of an acute stroke on a stroke unit (Neurological complex treatment of acute stroke on a stroke unit; OPS code 8-981). Insufficient data coded for a specific stroke side mean stroke events in the follow up period refer both to ipsilateral and contralateral occurrences relative to the side of the intervention.

For a summary of baseline characteristics, continuous variables are shown as the mean $\pm$ standard deviation or median and interquartile range depending on their distribution. Categorical variables are presented as counts and percentages. Cases with missing data in general patient information were excluded using listwise deletion, resulting in complete case analysis ($< 0.3\%$ of all cases). A Cox proportional hazards regression model was used to perform adjusted multivariable analyses to assess the association between the treatment (CEA *vs.* CAS) and group association adjusted for older age, female sex, and the weighted van Walraven score. Freedom from relevant study endpoints (death, stroke) was illustrated by Kaplan—Meier survival curves and was compared between strata with log rank tests. No correction for multiple hypothesis testing was applied. A p value of $< .05$ was used for statistical significance.

RESULTS

A total of 22 709 individual patients (41.6% female, median age 72.5 [66, 78] years at the index admission) were eligible for inclusion in the current study, while 72 patients (0.3%) were excluded from the study due to missing data. The baseline characteristics of the entire study cohort by different strata are presented in Table 1.

During a median follow up of 48 (25, 60) months, 1 744 stroke events occurred. The crude outcomes are presented in Table 2, and the Kaplan—Meier stroke free survival curves of the different strata are presented in Figures 1—3.

The long term stroke free survival probability of patients who underwent treatment for acute stroke (group i) or symptomatic carotid artery stenosis (group ii) was significantly worse compared with asymptomatic patients (group iii) (log rank $p < .001$).

Results of the multivariable Cox regression model for stroke free survival are presented in Table 3. After adjusting for older age, female sex, and a higher van Walraven comorbidity score, and asymptomatic stenosis as indication for treatment (Group (iii), a higher van Walraven comorbidity score [hazard ratio (HR) 1.051 per point] and older age (HR 1.034 per year) were associated with stroke or death during the follow up study period. Female sex (HR 0.942) and asymptomatic stenosis (HR 0.895) were associated with better stroke free survival. Additional analyses are presented in the Supplementary Material.

Within 120 days after treatment of acute stroke, 5.2% (CEA) and 7.4% (CAS) had a stroke or death event, which was 2.9% and 4.4% in the asymptomatic group, respectively.

The 30 day mortality rate of acute stroke patients who underwent CAS (2.1%) was three times the corresponding result for the acute CEA group (0.7%). Asymptomatic patients who underwent CEA had a lower 30 day mortality rate (0.4%), which doubled in the CAS group (0.8%).

The one year all cause mortality rates for CEA and CAS patients differed in the acute stroke group (5.7% CEA *vs.* 8.4% CAS) and in the asymptomatic group (4.1% CEA *vs.* 6.2% CAS).

Table 1. Baseline characteristics of the study cohort of patients who underwent either carotid endarterectomy (CEA) or carotid artery stenting (CAS) of acute stroke (group i), symptomatic carotid artery stenosis (group ii), or asymptomatic carotid artery stenosis (group iii)

Characteristic	Acute stroke (i)		Symptomatic (ii)		Asymptomatic (iii)	
	CEA (n = 4 294)	CAS (n = 1 644)	CEA (n = 1 368)	CAS (n = 326)	CEA (n = 12 293)	CAS (n = 2 712)
Female sex	1 747 (40.7)	676 (41.1)	580 (42.3)	129 (39.6)	5 164 (42.0)	1 136 (41.9)
Age − years	72.26 ± 9.38	70.06 ± 10.38	71.27 ± 9.09	69.46 ± 10.31	71.94 ± 8.47	70.66 ± 9.40
Octogenarians	914 (21.3)	263 (15.9)	233 (17.0)	40 (12.3)	1 996 (16.2)	393 (14.5)
Length of hospital stay − days	12.00 (8, 18)	11.00 (7, 17)	7.00 (5, 10)	4.00 (3, 7)	6.00 (5, 9)	4.00 (2, 8)
Weighted van Walraven score − points	12.77 ± 10.05	14.03 ± 9.92	12.35 ± 9.27	12.44 ± 9.29	9.95 ± 9.75	11.13 ± 10.64
Congestive heart failure	984 (22.9)	347 (21.1)	331 (24.2)	78 (23.9)	3 382 (27.5)	838 (30.9)
Cardiac dysrhythmia	1 158 (26.9)	444 (26.9)	382 (27.9)	98 (30.1)	3 629 (29.5)	902 (33.2)
Valvular disease	432 (10.1)	173 (10.5)	159 (11.6)	39 (12.0)	1 730 (14.1)	478 (17.6)
Peripheral vascular disease	1 404 (32.7)	572 (34.8)	478 (34.9)	134 (41.1)	5 511 (44.8)	1 355 (50.0)
Hypertension	3 854 (89.8)	1 398 (85.0)	1 282 (93.7)	289 (88.7)	11 325 (92.1)	2 428 (89.5)
Chronic pulmonary disease	595 (13.8)	197 (11.9)	174 (12.7)	48 (14.7)	2 179 (17.7)	480 (17.7)
Diabetes	1 395 (32.5)	472 (28.6)	448 (32.7)	103 (31.6)	4 052 (32.9)	877 (32.3)
Chronic kidney failure	923 (21.5)	330 (20.1)	326 (23.8)	73 (22.4)	3 100 (25.2)	778 (28.7)
Liver disease	173 (4.0)	52 (3.2)	43 (3.1)	7 (2.1)	550 (4.5)	137 (5.1)
Obesity	542 (12.6)	204 (12.4)	192 (14.0)	47 (14.4)	1 999 (16.2)	465 (17.1)
Alcohol abuse	239 (5.6)	103 (6.3)	64 (4.7)	17 (5.2)	579 (4.7)	143 (5.3)
Drug abuse	77 (1.8)	23 (1.4)	22 (1.6)	2 (0.6)	201 (1.6)	45 (1.7)
Depression	430 (10.0)	188 (11.4)	120 (8.8)	29 (8.9)	1 161 (9.4)	262 (9.7)

Data are presented as n (%), mean ± standard deviation, or median (interquartile range).
TIA = transient ischaemic attack.
See Supplementary Material (Table S1) for a full list of the ICD codes used for the respective categories.

DISCUSSION

The current study of nationwide health insurance claims from Germany determined the baseline characteristics and long term outcomes of almost 23 000 patients who underwent invasive open surgical and endovascular treatment of asymptomatic and symptomatic carotid artery stenosis. Longitudinally linked data on subsequent hospital episodes and a proper lookback strategy were used

Table 2. Crude unadjusted outcomes of patients who underwent either carotid endarterectomy (CEA) or carotid artery stenting (CAS) of acute stroke (group i), symptomatic carotid artery stenosis (group ii), or asymptomatic carotid artery stenosis (group iii)

Outcome	Acute stroke (i)		Symptomatic (ii)		Asymptomatic (iii)		All cases	
	CEA (n = 4 294)	CAS (n = 1 644)	CEA (n = 1 368)	CAS (n = 326)	CEA (n = 12 293)	CAS (n = 2 712)	CEA (n = 17 955)	CAS (n = 4 682)
30 day death	29 (0.7)	34 (2.1)	9 (0.7)	3 (0.9)	53 (0.4)	22 (0.8)	91 (0.5)	59 (1.3)
120 day death	121 (2.8)	83 (5.0)	27 (2.0)	7 (2.1)	193 (1.6)	77 (2.8)	341 (1.9)	167 (3.6)
One year death	243 (5.7)	138 (8.4)	66 (4.8)	20 (6.1)	508 (4.1)	167 (6.2)	817 (4.5)	325 (6.9)
30 day stroke rate	59 (1.4)	20 (1.2)	11 (0.8)	8 (2.5)	79 (0.6)	23 (0.8)	149 (0.8)	51 (1.1)
120 day stroke rate	115 (2.7)	42 (2.6)	23 (1.7)	13 (4.0)	176 (1.4)	46 (1.7)	314 (1.7)	101 (2.2)
One year stroke rate	209 (4.9)	74 (4.5)	47 (3.4)	21 (6.4)	307 (2.5)	83 (3.1)	563 (3.1)	178 (3.8)
Five year stroke rate	445 (10.4)	173 (10.5)	153 (11.2)	41 (12.6)	725 (5.9)	207 (7.6)	1 323 (7.4)	421 (9.0)
Five year stroke rate (excluding 120 day peri-operative period as landmark analysis)	325 (7.6)	130 (7.9)	130 (9.5)	28 (8.6)	544 (4.4)	157 (5.8)	999 (5.6)	315 (6.7)
30 day stroke or mortality rate	88 (2.0)	54 (3.3)	19 (1.4)	10 (3.1)	130 (1.1)	45 (1.7)	237 (1.3)	109 (2.3)
120 day stroke or mortality rate	224 (5.2)	122 (7.4)	49 (3.6)	19 (5.8)	356 (2.9)	118 (4.4)	629 (3.5)	259 (5.5)
One year stroke or peri-operative (120 day) mortality rate	318 (7.4)	154 (9.4)	73 (5.3)	27 (8.3)	487 (4.0)	155 (5.7)	878 (4.9)	336 (7.2)
One year stroke or mortality rate	426 (9.9)	205 (12.5)	111 (8.1)	38 (11.7)	769 (6.3)	236 (8.7)	1 306 (7.3)	479 (10.2)

Data are presented as n (%).

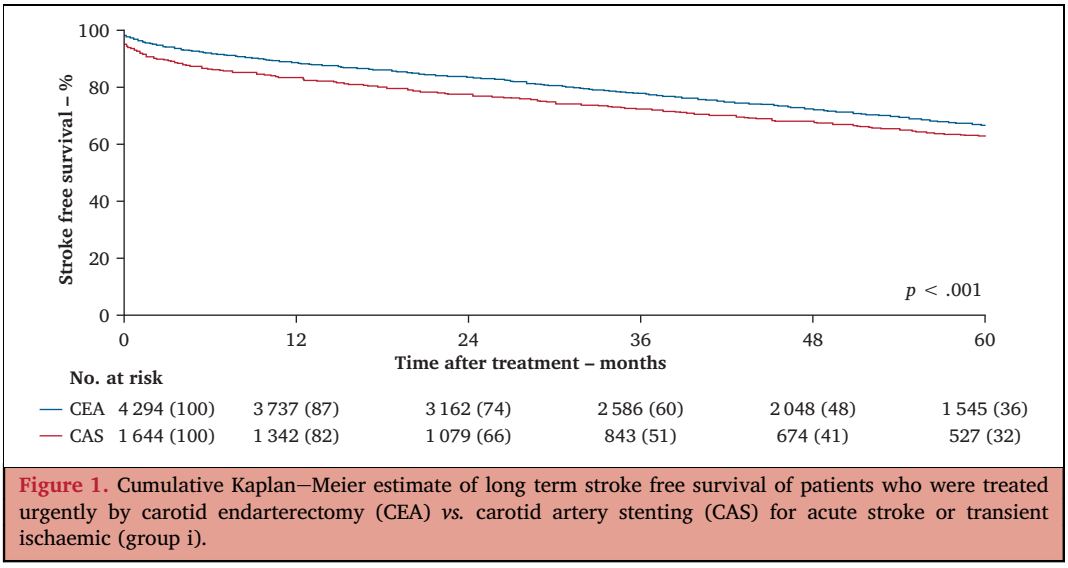

Figure 1. Cumulative Kaplan–Meier estimate of long term stroke free survival of patients who were treated urgently by carotid endarterectomy (CEA) *vs.* carotid artery stenting (CAS) for acute stroke or transient ischaemic (group i).

to improve the completeness of relevant comorbidities and to provide mortality and stroke rates even beyond discharge.

Mortality rates in this study were higher than those reported in previous landmark trials. This may be attributed to the distinct cardiovascular risk profile of the patients and bias from ineligible patients in the trials.[10–13,30] The considerably high one year combined stroke and mortality rates in the current study of 6.3% after elective CEA and 8.7% after CAS emphasise that future observational studies should look at the comparative outcomes of clinical practice to treat asymptomatic people invasively *vs.* conservatively.

The high one year mortality rate in the asymptomatic cohort is notable, and perhaps reflects non-optimal patient selection. The one year post-procedural stroke rate (120 days to one year) is elevated (1.1% asymptomatic CEA *vs.* 1.4% asymptomatic CAS), while presumably halved by intervention, suggesting that these asymptomatic patients were actually at a relevant risk of a stroke. The authors believe the high mortality rates in the asymptomatic group are noteworthy since they ideally should reflect a very selected cohort. Their real world prognosis should be available at the point of shared decision making prior to an intervention.

Besides bias due to ineligible patients in trials, the longer term outcomes were also achieved with consequent best medical treatment, while numerous observational studies have recently highlighted missed opportunities in unselected cohorts with peripheral arterial disease.[31] A recent pooled analysis of the four largest RCTs (EVA-3S, SPACE, ICSS, and CREST) showed one year stroke event rates of 6.4% after CEA and 9.5% after CAS, while the endpoint definitions differed only marginally.[29] The pooled analysis showed broadly comparable long term durability (outside a 120 day peri-operative window) of both procedures in symptomatic and asymptomatic patients. This is analogous to the present data, although the endpoint definitions differed between the studies (the meta-analysis defined the peri-procedural period as 120 days from randomisation, not procedure, while most studies count events within 30 days of intervention). Considering only post-procedural stroke

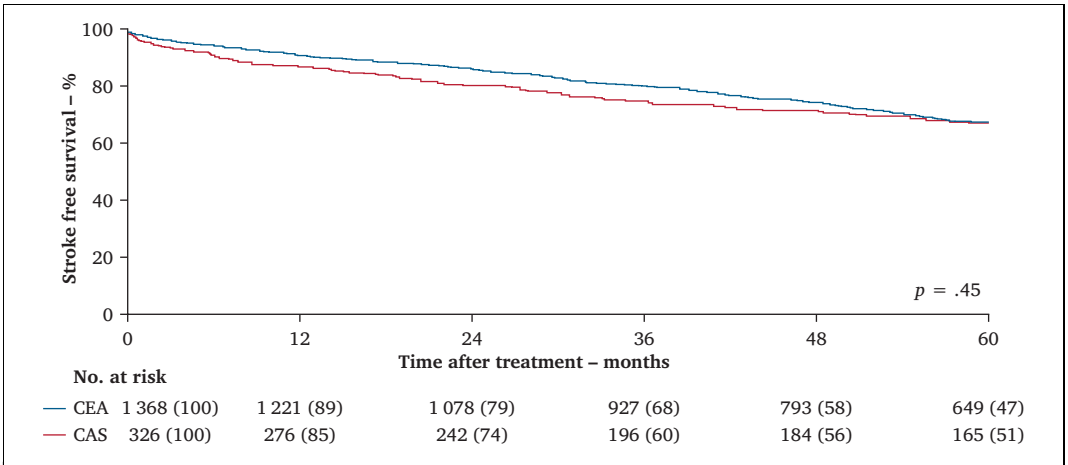

Figure 2. Cumulative Kaplan–Meier estimate of long term stroke free survival of patients who were treated electively by carotid endarterectomy (CEA) *vs.* carotid artery stenting (CAS) for symptomatic carotid artery stenosis (group ii).

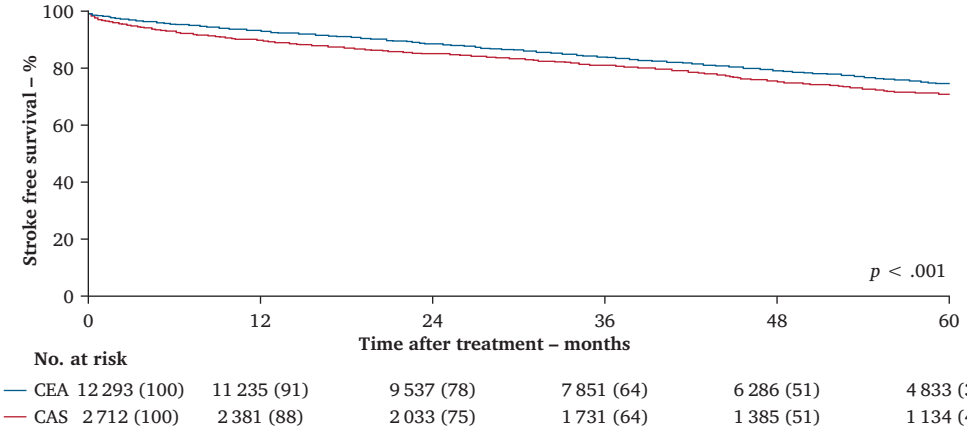

Figure 3. Cumulative Kaplan–Meier estimate of long term stroke free survival of patients who were treated electively by carotid endarterectomy (CEA) *vs.* carotid artery stenting (CAS) for asymptomatic stenosis (group iii).

rates, the gap between CAS and CEA shrinks. Symptomatic patients have the highest peri-operative stroke rate (CEA 1.7%, CAS 4.0%). Symptomatic patients during the post-procedural period (120 days to five years) had a stroke rate (any side) of 9.5% for CEA *vs.* 8.6% for CAS. Asymptomatic post-procedural patients during the same period showed rates of 4.4% (CEA) *vs.* 5.8% (CAS).

Overall stroke rates were high in all strata, which further emphasised possible problems with best medical treatment adherence. Interestingly, the 30 day stroke (between 1.1% and 3.3%) and death rates (between 0.4% and 2.1%) in the present study confirmed the rather low event rates previously derived from the German Statutory Quality Assurance Database (based on a short follow up of only a few days before hospital discharge date).[16] This is also in line with recent VASCUNET reports on carotid artery treatment, where the peri-operative combined stroke and death rates were reported to be $< 3\%$.[7,9,32] Notably, the paucity of valid long term data covering the episode beyond discharge was frequently discussed as a limitation by several authors.

Considering the increasingly significant disparity between short term hospital episodes and longer term outcomes beyond discharge, it seems reasonable to shed more light on the collection of valid data in clinical registries covering the complex longitudinal course of patients under surveillance. This is particularly relevant for the advance of preventative medicine and its impact on the management of atherosclerotic disease.[33] That said, the right pill and stringent risk prevention may have more impact on long term outcomes than an invasive procedure alone, which further underlines the value of a multidisciplinary approach and collaborations with neurologists.

Table 3. Adjusted results (all covariables) of the multivariable Cox proportional hazards regression for stroke free survival after invasive revascularisation of carotid artery stenosis in this health insurance claims cohort

Characteristic	HR (95% CI)	*p* value
Older age (increase by one year)	1.034 (1.031–1.038)	<.001
Female sex (*vs.* male sex)	0.942 (0.892–0.995)	.032
Higher van Walraven score (increase by one point)	1.051 (1.048–1.053)	<.001

HR = hazard ratio; CI = confidence interval.
See Supplementary Material (Table S2) for an extended version of this analysis.

At first glance, the high one year stroke and death rates in the current study may appear striking. However, recent registries on patients with lower extremity peripheral arterial disease, the prototype of patients with chronic complex disease, revealed that limb events and death occurred far more frequently than expected based on observational data.[34,35] The patients included in the current study had numerous comorbidities. Hence, it is not surprising that a severely ill cohort including one third with diabetes, congestive heart failure, and chronic kidney failure would also experience strokes and death at a significant rate. In a real world setting, patients who are ineligible for trial inclusion would still receive treatment. Therefore, the central question is whether cohorts enrolled in RCTs have appropriately covered this real world treatment situation, and whether post-operative surveillance and best medical treatment have followed guideline recommendations. Thereby, it must be highlighted that the 2023 European Society for Vascular Surgery (ESVS) clinical practice guidelines on the management of atherosclerotic carotid and vertebral artery disease lack a clearly defined strategy for surveillance.[4,14,15]

Although a head to head comparison of long term outcomes after CEA *vs.* CAS was not within the initial scope of the current study, it appears that CAS was significantly associated with a 27% higher risk of death or stroke on any side during the five year follow up. This finding is interesting in light of the central conclusions derived from landmark trials such as ACST-2, where both approaches were comparable.[11]

The potential clinical implications of the current study findings deserve some reflection. It appears reasonable to maintain regular multidisciplinary team decisions before selecting patients with asymptomatic carotid artery stenosis for an invasive revascularisation procedure. These case discussions should consider meticulously whether a patient would be covered by high level evidence derived from trials. Furthermore, when involving the patient in the decision making, realistic figures and predictions for the longer term outcome should be used, while hospital episodes and peri-procedural data may not be appropriate in this context.

This study has several strengths but also limitations. First, although frequently used for numerous studies in several cardiovascular areas, the study data were not primarily collected for research but for administrative purposes. However, a regular external validation was conducted, and there are validation studies demonstrating high validity of severe events such as death and stroke. As described in the Methods section, the rather conservative approach to repeat occurrences of a stroke coding risks undercounting stroke events. Due to the choice of requiring the coding of a concurrent complex stroke treatment at an inpatient stroke unit, the approach could more closely model major stroke events. Another limitation is the paucity of information on the extent of the index neurological event (e.g., minor stroke *vs.* major stroke). Second, the non-random assignment to the different subgroups limits direct comparison owing to residual confounding. Acknowledgement of this commonly known limitation of observational studies by using multivariable regression models was tried, but certainly were not able to reveal any causal effects. Notably, a large sample size may increase the chances of generating results that are statistically significant, while the interpretation of clinical relevance is advised. Lastly, like any other study, the complete registration of outcomes of interest during the follow up appears crucial. Owing to the lack of valid data on death causes in Germany, it is not known whether the deceased died of stroke or any other possible reason.

Conclusions

The current large claims study included almost 23 000 patients who underwent invasive treatment of carotid artery stenosis in Germany. Interestingly, the stroke and death rates rose consistently after hospital discharge and reached higher rates than reported in several landmark trials. These striking differences between randomised trials and real world data emphasise the need for future studies that collect meaningful long term outcomes.

CONFLICT OF INTEREST STATEMENT AND FUNDING

None.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2023.07.030

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2. Zusammenfassende Darstellung der Publikation

2.1 Einleitung

Atherosklerose und Verengungen der Halsschlagadern sind in Kohortenstudien häufige Erkrankungen (Behrendt et al 2023, Song et al 2020), wobei eine mäßige Verengung (> 50 %) bei 7,5 % der Männer und 4,0 % der Frauen über 80 Jahren festgestellt wird (de Weerd et al 2014). Verschiedene Faktoren wie höheres Alter, männliches Geschlecht, Gefäßerkrankungen, Bluthochdruck, Dyslipidämie, Diabetes und Rauchen werden mit dieser häufigen Erkrankung in Verbindung gebracht (de Weerd et al 2014). Neben der konservativen Behandlung bilden zwei komplementäre invasive Ansätze das Rückgrat der Schlaganfallprävention (Naylor et al 2023, AbuRhama et al 2022, Bonati et al 2021).

In den letzten Jahrzehnten wurden mehrere Studien (Halliday et al 2010 und 2021, Brott et al 2010) und Leitlinien für die klinische Praxis (AbuRahma et al 2022, Bonati et al 2021, Aboyans et al 2018, Naylor et al 2018) zu Erkrankungen der Halsschlagader veröffentlicht. In Deutschland stehen zwei große Register zur Verfügung, um die bundesweite Versorgung zu beschreiben: national geführte Qualitätssicherungsdatenbanken (Tsantilas et al 2018) und Statistiken des Statistischen Bundesamtes (Kuehnl 2018). Beide Datenbanken liefern zwar eine große Anzahl von Eingriffen (fast 33 000 registrierte Eingriffe im Jahr 2019), ihre Aussagekraft bleibt jedoch begrenzt, da keine längerfristigen Ergebnisse nach der Entlassung vorliegen und vorbekannte Informationen nicht mit dem aktuellen Krankenhausfall verknüpft werden können, um vollständige Komorbiditäten zu ermitteln. Um diese Forschungslücke zu schließen, können Krankenversicherungsansprüche wertvolle Daten liefern. Sie ermöglichen die Verknüpfung mehrerer Krankenhausepisoden im Rahmen longitudinaler Datenanalysen und ihre Aussagekraft wird in Bezug auf wichtige kardiovaskuläre Ereignisse wie Tod und Schlaganfall als hoch eingeschätzt (Langner ae al 2019, Schubert et al 2010, Peter et al 2020.

Ziel dieser Studie war es, die aktuelle Behandlung und die langfristigen Ergebnisse nach der Entlassung in einer bundesweiten, unselektierten Kohorte von Patienten, die sich einer Karotisrevaskularisation unterzogen haben, anhand von Leistungsdaten der drittgrößten Krankenkasse in Deutschland zu ermitteln.

2.2 Material und Methoden

2.2.1 Studie

Bei der vorliegenden Studie handelt es sich um eine retrospektive Observationsstudie longitudinal verknüpfter Krankenkassendaten der DAK-Gesundheit, der drittgrößten Krankenkasse in Deutschland (durchschnittlich 6,2 Millionen Versicherte im Untersuchungszeitraum).

2.2.2 Einschlusskriterien

Unsere Studie schließt alle DAK-Gesundheit versicherten Patienten ein, die sich einer Carotis-Endarteriektomie (CEA) oder einem Carotis-Stenting (CAS) in einem gesetzlich anerkannten Krankenhaus in Deutschland unterzogen haben, mit einem Entlassungsdatum zwischen dem 1. Januar 2008 und dem 31. Mai 2017.

2.2.3 Daten und Variablen

Alle Daten wurden vor der Übermittlung an das Forschungsteam in angemessener Weise de-identifiziert. Die Darstellung der Studiendaten folgt der STROBE-Erklärung (Strengthening the Reporting of Observational Studies in Epidemiology) (von Elm et al 2008). Komorbiditäten wurden gemäß der Internationalen Klassifikation der Krankheiten (ICD-10) der Weltgesundheitsorganisation (WHO) definiert. Elixhauser *et al.* führten 1998 eine systematische Klassifizierung ein, um relevante Komorbiditäten unter den Primär- oder Sekundärdiagnosen zum Zeitpunkt der Entlassung zu ermitteln (Elixhauser et al 1998). Die von Quan et al (2005) übernommenen Charlson-Komorbiditätsbereiche (Charlson et al 1987) wurden zur Berechnung der relevanten Elixhauser-Komorbiditäts-Scores verwendet.

2.2.4 Statistische Analyse

Alle Analysen wurden mit der Statistiksoftware R durchgeführt (R Core Team 2022) Der ursprüngliche Forschungsdatensatz umfasste 383 691 Patienten, die aus dem gesamten Versichertenbestand der DAK-Gesundheit ausgewählt wurden. Er umfasste alle versicherten Patienten mit Schlaganfall und transitorischer ischämischer Attacke (TIA)

als Hauptdiagnose oder relevanten Indexeingriffen innerhalb des Studienzeitraums. Alle stationären Aufenthalte dieser Patienten wurden in den Datensatz aufgenommen.

2.3 Strata und Vergleichsgruppen

Die Analysen wurden für drei Patientengruppen durchgeführt: die Gruppe der "akuten Schlaganfälle" (i), die während des Indexaufenthalts einen akuten Schlaganfall oder eine TIA als Hauptdiagnose (Aufnahmediagnose) erlitten; die Gruppe der "symptomatischen" Patienten (ii), die aus Patienten mit einer früheren Schlaganfall- oder TIA-Diagnose in den sechs Monaten vor der Indexeinweisung (jedoch nicht als Grund für den Index-Krankenhausaufenthalt) besteht; und die Gruppe der "asymptomatischen" Patienten (iii), bei denen sechs Monate vor dem Eingriff kein Schlaganfall oder keine TIA aufgetreten war. Diese spiegeln die relevanten Patientenstrata in der täglichen klinischen Praxis wider.

2.3.1 Studienendpunkte

Als primärer Endpunkt wurde die 5-Jahres-Schlaganfallrate definiert. Als sekundäre Endpunkte wurden perioperative Schlaganfälle oder Todesfälle (nach 30 und 120 Tagen) sowie die 1-Jahres-Schlaganfall- oder perioperative Mortalitätsrate definiert. Die sekundären Endpunkte wurden so gewählt, dass sie sowohl die ursprünglichen randomisierten kontrollierten Studien (RCTs) als auch gepoolte Follow-up-Analysen widerspiegeln. Die Freiheit von relevanten Studienendpunkten (Tod, Schlaganfall) wurde anhand von Kaplan-Meier- Überlebenskurven dargestellt und mit Log-Rank-Tests zwischen den Strata verglichen. Es wurde keine Korrektur für multiple Hypothesentests vorgenommen. Ein p-Wert von $< 0,05$ wurde für die statistische Signifikanz verwendet.

2.4 Ergebnisse

Insgesamt kamen 22 709 Patienten [41,6 % weiblich, mittleres Alter 72,5 (66, 78) Jahre bei der Indexaufnahme] für die vorliegende Studie in Frage, während 72 Patienten (0,3 %) aufgrund fehlender Daten aus der Studie ausgeschlossen wurden.

Während einer medianen Nachbeobachtungszeit von 48 (25, 60) Monaten traten insgesamt 1 744 Schlaganfälle auf. Die Wahrscheinlichkeit des langfristigen schlaganfallfreien Überlebens von Patienten, die wegen eines akuten Schlaganfalls (Gruppe i) oder einer symptomatischen Karotisstenose (Gruppe ii) behandelt wurden, war im Vergleich zu asymptomatischen Patienten (Gruppe iii) signifikant schlechter (log-rank $p < .001$).

Nach Adjustierung für höheres Alter, weibliches Geschlecht und einen höheren van-Walraven-Komorbiditäts-Score sowie eine asymptomatische Stenose als Behandlungsindikation (Gruppe iii) waren ein höherer van-Walraven-Komorbiditäts-Score

[Hazard Ratio (HR) 1,051 pro Punkt] und ein höheres Alter (HR 1,034 pro Jahr) mit einem Schlaganfall oder Tod während der Nachbeobachtungszeit assoziiert. Weibliches Geschlecht (HR 0,942) und asymptomatische Stenose (HR 0,895) waren mit einem besseren schlaganfallfreien Überleben verbunden.

Innerhalb von 120 Tagen nach der Behandlung des akuten Schlaganfalls kam es bei 5,2 % (CEA) und 7,4 % (CAS) zu einem Schlaganfall oder Todesfall, in der asymptomatischen Gruppe waren es 2,9 % bzw. 4,4 %.

Die 30-Tage-Sterblichkeitsrate von Patienten mit akutem Schlaganfall, die sich einer CAS unterzogen (2,1 %), war dreimal so hoch wie in der Gruppe mit akuter CEA (0,7 %). Asymptomatische Patienten, die sich einer CEA unterzogen, wiesen eine niedrigere 30-Tage-Sterblichkeitsrate auf (0,4 %), die sich in der CAS-Gruppe verdoppelte (0,8 %).

Die 1-Jahres-Gesamtmortalitätsraten für CEA- und CAS-Patienten unterschieden sich in der Gruppe der Patienten mit akutem Schlaganfall (5,7% CEA *vs.* 8,4% CAS) und in der Gruppe der asymptomatischen Patienten (4,1% CEA *vs.* 6,2% CAS).

2.5 Diskussion

In dieser Studie wurden Ausgangscharakteristika und Langzeitergebnisse von fast 23 000 Patienten ermittelt, die sich einer invasiven offenen chirurgischen oder endovaskulären Behandlung von asymptomatischen und symptomatischen Karotisstenosen unterzogen. Longitudinal verknüpfte Daten über nachfolgende Krankenhausepisoden wurden verwendet, um die Vollständigkeit relevanter Komorbiditäten zu verbessern und Mortalitäts- und Schlaganfallraten auch nach der Entlassung zu ermitteln.

Die Sterblichkeitsraten in dieser Studie waren höher als die in früheren Studien berichteten. Dies kann auf das unterschiedliche kardiovaskuläre Risikoprofil der Patienten und auf Verzerrungen durch selektiven Studieneinschluss zurückgeführt werden (Halliday et al 2010 und 2021, Brott et al 2010 und 2016, Orrapin 2017). Die beträchtlich hohen kombinierten 1-Jahres- Schlaganfall- und Sterblichkeitsraten in der aktuellen Studie von 6,3 % nach elektiver CEA und 8,7 % nach CAS unterstreichen, dass künftige Studien stärker fokussiert sein sollten auf die Bewertung der klinischen Praxis der invasiven und konservativen Behandlung asymptomatischer Patienten.

Die hohe 1-Jahres-Mortalität in der asymptomatischen Kohorte ist bemerkenswert und spiegelt möglicherweise eine nicht optimale Patientenauswahl wider.

Die Studienergebnisse unterstreichen die Notwendigkeit multidisziplinärer Teamentscheidungen, bevor Patienten mit asymptomatischer Karotisstenose für ein invasives Revaskularisationsverfahren ausgewählt werden. Bei diesen Fallbesprechungen sollte sorgfältig abgewogen werden, ob ein Patient durch hochrangige, aus Studien abgeleitete Erkenntnisse abgedeckt ist. Darüber hinaus sollten bei der Einbeziehung des Patienten in die Entscheidungsfindung realistische Daten bzgl. einer wahrscheinlichen Langfristprognose eingesetzt werden.

Diese Studie hat mehrere Stärken, aber auch Grenzen. Erstens wurden die Studiendaten, obwohl sie häufig für zahlreiche Studien in verschiedenen kardiovaskulären Bereichen verwendet wurden, nicht in erster Linie für Forschungszwecke, sondern für administrative Zwecke erhoben. Es wurde jedoch eine regelmäßige externe Validierung durchgeführt, und es gibt Validierungsstudien, die eine hohe Validität für schwere Ereignisse wie Mortalität und Schlaganfall belegen.

2.5.1 Ausblick über die Forschungsarbeit hinaus

Die Studie umfasste fast 23 000 Patienten, die sich in Deutschland einer invasiven Behandlung einer Karotisstenose unterzogen.

Interessanterweise stiegen die Schlaganfall- und Sterberaten nach der Entlassung aus dem Krankenhaus kontinuierlich an und erreichten höhere Raten als in mehreren Zulassungsstudien berichtet.

Es besteht eine immer größer werdende Diskrepanz zwischen kurzfristigen Qualitätsmessungen nach einzelnen Krankenhausepisoden und längerfristigen Ergebnissen nach der Entlassung. So erscheint es sinnvoll, die Erhebung valider Daten in klinischen Registern zu stärken, die den komplexen Längsschnittverlauf der überwachten Patienten abdecken. Dies ist besonders wichtig für die Weiterentwicklung der Präventivmedizin und ihre Auswirkungen auf die Behandlung atherosklerotischer Erkrankungen.

3. Zusammenfassung

Deutsch: Es gibt nur wenige Beobachtungsdaten zu Langzeitergebnissen nach einer invasiven Behandlung von Karotisstenosen. Für diese retrospektive Studie wurden die bundesweiten Versicherungsleistungen des drittgrößten Anbieters in Deutschland, der DAK- Gesundheit, herangezogen. Eingeschlossen wurden Patienten, die sich zwischen dem 1. Januar 2008 und dem 31. Mai 2017 einer stationären Carotis-Endarteriektomie (CEA) oder einem Carotis-Stenting (CAS) unterzogen haben.

Während Registerstudien betonten, dass die reale Behandlung von Karotisstenosen aufgrund der inhärenten Selektionsverzerrung nicht immer die Ergebnisse randomisierter kontrollierter Studien bestätigt, besteht ein eklatanter Mangel an longitudinal verknüpften Beobachtungsdaten zur Ermittlung von Langzeitergebnissen in dieser Zielpopulation. In der aktuellen Studie wurde ein großer Datensatz von Versicherungsansprüchen verwendet, um die 5-Jahres-Mortalitäts- und Schlaganfallraten nach Karotis-Endarteriektomie und Stent-Angioplastie bei 22 637 einzelnen Patienten zu bestimmen. Die Studie ergab in einigen Untergruppen höhere Ereignisraten als zuvor in wegweisenden Studien berichtet, was Fragen zur Anwendbarkeit von Studiendaten in der täglichen klinischen Praxis aufwirft.

Englisch: There is a paucity of observational data including long term outcomes after invasive treatment for carotid artery stenosis. This retrospective study utilised nationwide insurance claims from the third largest provider in Germany, DAK-Gesundheit. Patients who underwent inpatient carotid endarterectomy (CEA) or carotid artery stenting (CAS) between 1 January 2008 and 31 May 2017 were included. While registry studies emphasised that real world treatment of carotid artery stenosis may not always confirm results derived from randomised controlled trials owing to inherent selection bias, there is a striking paucity of longitudinally linked observational data to determine long term outcomes in this target population. The current study used a large insurance claims dataset to determine 5 year mortality and stroke rates after carotid endarterectomy and stent angioplasty in 22 637 individual patients. The study found higher event rates in some subgroups than previously reported in landmark trials, raising questions about the applicability of trial data to everyday clinical practice.

4. Abkürzungsverzeichnis

CAS = Carotisstent (englisch: carotid artery stenting)

CEA = Carotisendarterektomie (englisch: carotid endarterectomy)

DRG = Disease related groups

ICD = International code of diseases

OPS = Operationen und Prozedurenschlüssel

STROBE-Erklärung = Strengthening the Reporting of Observational Studies in Epidemiology

TIA = transitorische ischämische Attacke

WHO = Weltgesundheitsorganisation

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6. Erklärung des Eigenanteils

Eigenanteil:

Konzeptierung der Studienfrage
Literaturrecherche
Bearbeitung des Datensatzes (Empfang, Aufbereitung, Validierung)
Statistische Analysen & Erstellung der Graphen/Tabellen
Erstellen des Manuskripts

Anteil der Co-Autoren:

Mitarbeit an der Erstellung des Manuskripts

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Ich widme diese Arbeit meinen drei Kindern Johann, Lola und Elias.

8. Lebenslauf

Matthias Zimmermann, MSc. MSc.

Berufserfahrung

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9. Eidesstattliche Versicherung

Ich versichere ausdrücklich, dass ich die vorliegende Arbeit mit dem Titel (Titel der Dissertation) selbständig und ohne unerlaubte fremde Hilfe, insbesondere ohne entgeltliche Hilfe von Vermittlungs- und Beratungsdiensten, angefertigt und keine anderen als die von mir angegebenen Quellen und Hilfsmittel (einschließlich „Chatbots“ / KI) benutzt habe. Alle wörtlichen oder sinngemäßen Entlehnungen aus anderen Arbeiten sind an den betreffenden Stellen als solche kenntlich gemacht und im entsprechenden Verzeichnis aufgeführt, das gilt insbesondere auch für alle Informationen aus Internetquellen.
Ich erkläre zudem, dass ich die an der Medizinischen Fakultät Hamburg geltende „Satzung zur Sicherung guter wissenschaftlicher Praxis und zur Vermeidung wissenschaftlichen Fehlverhaltens an der Universität Hamburg“ in der jeweils gültigen Fassung eingehalten habe.
Ferner versichere ich, dass ich die Dissertation bisher nicht einem Fachvertreter oder einer Fachvertreterin an einer anderen Hochschule zur Überprüfung vorgelegt oder mich anderweitig um Zulassung zur Promotion beworben habe.
Ich erkläre mich einverstanden, dass meine Dissertation vom Dekanat der Medizinischen Fakultät mit einer gängigen Software zur Erkennung von Plagiaten überprüft werden kann.

Unterschrift: .....