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Determinants of prehospital and in-hospital delay in patients with symptomatic carotid stenosis and their influence on the outcome after elective carotid endarterectomy

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Prof. Eckstein unfortunately passed away recently.

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ABSTRACT

Background This study analyses the determinants of prehospital (index event to admission) and in-hospital delay (admission to carotid endarterectomy (CEA)). In addition, the analysis addresses the association between prehospital or in-hospital delay and outcomes after CEA for symptomatic patients in German hospitals.

Materials and methods This retrospective analysis is based on the nationwide German statutory quality assurance database. 55 437 patients were included in the analysis. Prehospital delay was grouped as follows: 180–15, 14–8, 7–3, 2–0 days or 'in-hospital index event'. In-hospital delay was divided into: 0–1, 2–3 and >3 days. The primary outcome event (POE) was in-hospital stroke or death. Univariate and multivariable regression analyses were performed for statistical analysis. The slope of the linear regression line is given as the β-value, and the rate parameter of the logistic regression is given as the adjusted OR (aOR).

Results Prehospital delay was 0–2 days in 34.9%, 3–14 days in 29.5% and >14 days in 18.6%. Higher age (β=−1.08, p<0.001) and a more severe index event (transitory ischaemic attack: β=−4.41, p<0.001; stroke: β=−6.05, p<0.001, Ref: amaurosis fugax) were determinants of shorter prehospital delay. Higher age (β=0.28, p<0.001) and female sex (β=0.09, p=0.014) were associated with a longer in-hospital delay. Index event after admission (aOR 1.23, 95% CI: 1.04 to 1.47) and an intermediate in-hospital delay of 2–3 days (aOR 1.15, 95% CI: 1.00 to 1.33) were associated with an increased POE risk.

Conclusions This study revealed that older age, higher American Society of Anesthesiology (ASA) stage, increasing severity of symptoms and ipsilateral moderate stenosis were associated with shorter prehospital delay. Non-specific symptoms were associated with a longer prehospital delay. Regarding in-hospital delay, older age, higher ASA stage, contralateral occlusion, preprocedural examination by a neurologist and admission on Fridays or Saturdays were associated with lagged treatment. A very short (<2 days) prehospital and intermediate in-hospital delay (2–3 days) were associated with increased risk of perioperative stroke or death.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Previous studies have investigated the influence of the interval between index event and carotid endarterectomy (CEA) in patients with a symptomatic carotid artery stenosis.

WHAT THIS STUDY ADDS

⇒ This study focuses on the separate analysis of the prehospital (index event—admission) and in-hospital (admission—CEA) interval instead of the whole interval (index event—CEA). Determinants of the intervals and the association with the respective outcomes are analysed. A very short prehospital and intermediate in-hospital delay were associated with increased risk of perioperative stroke or death.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Profound and thorough preoperative evaluation and preparation of patients with symptomatic carotid artery stenosis are necessary to improve the outcomes after CEA.

INTRODUCTION

External carotid artery stenosis may cause amaurosis fugax, transitory ischaemic attack or ischaemic strokes. For prevention of stroke, carotid endarterectomy (CEA) is recommended in asymptomatic patients with >60% stenosis and further high-risk criteria and in symptomatic patients with >50% stenosis.[1] Except for patients who had a disabling stroke, a large infarction area or emergency cases, guidelines recommend elective carotid intervention in symptomatic patients as soon as possible, preferably within 14 days.[1–3] If carotid revascularisation is performed within 14 days, CEA is the preferred therapy in contrast to carotid artery stenting (CAS).[1]

Previous studies have analysed the impact of the delay from index event to surgery.

Studies have shown a beneficial effect for surgery within 14 days.[4] Within those 14 days, some authors showed an adverse effect of surgery within 48 hours,[5 6] whereas others have seen no significant differences between a long and short time interval.[7] Factors that were associated with a long delay from index event to surgery were indirect referral[8 9] and ocular symptoms as index event.[8 10] The share of patients who were treated within 3–14 days differs between 30%[10] and 63%.[7 11]

Due to different national healthcare systems and organisational structures that could affect the referral patterns of patients for surgery, it is important to identify the determinants of a preoperative delay and their impact on outcomes after surgery. In Germany, the healthcare system is divided into several independent sectors, including the outpatient and inpatient sectors. It is common knowledge that the sectors do not work always hand in hand, which is partly due to remuneration models and the legal separation between outpatient and inpatient treatment. The time between the index event and hospital admission is therefore subject to different forces than case management within a hospital.

Therefore, the aim of this study was to analyse the distribution and determinants of prehospital (index event to admission, outpatient sector) and in-hospital (admission to CEA, inpatient sector) delay before CEA in German hospitals. Furthermore, the influence of the respective delay on the postoperative outcomes is analysed in this study.

METHODS

The present analysis is a preplanned sub study of the of the ISAR-IQ project (Integration and Spatial Analysis of Regional, Site-specific and patient-level factors for Improving Quality of treatment for carotid artery stenosis).

Data source

This analysis is based on the nationwide German statutory quality assurance database managed by the Institute for Quality Assurance and Transparency in Healthcare (Institut für Qualitätssicherung und Transparenz im Gesundheitswesen (IQTIG), according to § 136 of Volume V of the German Social Insurance Code (SGB V)). The IQTIG legally collects data on carotid revascularisation procedures, encompassing CEA and CAS. The database includes records of all inpatient cases treated in German hospitals, following the regulations outlined in §108 of SGB V. Due to legal mandates, the data collection encompasses nearly all CEA and CAS procedures.

Our analysis adhered to the Good Practice of Secondary Data Analysis guidelines.[12] Given the observational nature of this study, which uses routinely collected health data, we followed the reporting of studies conducted using observational routinely collected health data reporting guidelines.[13] All data are securely stored on IQTIG servers, in compliance with pertinent data protection regulations. Access to the data was granted exclusively through controlled remote data processing, a methodology previously established in other studies and recently published.[14–17] The study protocol was submitted to IQTIG and Federal Joint Committee during the application process, but was not separately published.

Case selection

Between January 2012 and December 2017, a total of 199 531 CEA procedures were recorded in the German statutory quality assurance database. For this analysis, the following cases were excluded: emergency cases (crescendo transitory ischaemic attack (TIA), stroke in evolution and other emergency procedures), procedures performed for other conditions than carotid stenosis (eg, aneurysm), CAS procedures and asymptomatic patients were excluded (flowchart figure 1).

Prehospital and in-hospital delay

The following directly coded variables were available for the calculation of the prehospital and in-hospital delay: time interval between index event and treatment, date of admission, date of procedure. Please see online supplemental figure 1 for further presentation of the calculation of the respective time intervals.

Prehospital delay was classified as following: very long (180–15 days), long (14–8 days), short (7–3 days), very short (2–0 days) and 'in-hospital'.

In-hospital delay was classified as short (0–1 days), intermediate (2–3 days) and long (>3 days).

Study variables

Variable codes were extracted from IQTIG Institute codebooks and harmonised from 2005 to 2018. The available variables in this study include the following patient characteristics: age, sex, American Society of Anesthesiology (ASA) stage, degree and location of stenosis (contralateral and ipsilateral) and preoperative symptom status (amaurosis fugax, transitory ischaemic attack, stroke or other symptoms). Data on admission day, preprocedural or postprocedural neurological assessments and the annual centre caseload of CEA in symptomatic patients were also documented. Procedural variables included perioperative antiplatelet treatment, surgical technique, anaesthesia type (local or general), utilisation of intraoperative completion studies (angiography, ultrasound, flowmetry), intraoperative neurophysiological monitoring (electroencephalography, oximetry, somatosensory evoked potentials), intraoperative shunt usage and CEA duration.

Study outcomes

The primary outcome event (POE) of this analysis was the combined rate of any in-hospital stroke or death. Additionally, the following events were defined as secondary outcome events: any stroke alone, all-cause death, the combined rate of major stroke or death, the rate of myocardial infarction (MI) and major adverse cardiovascular events (any stroke or fatal and non-fatal MI) until

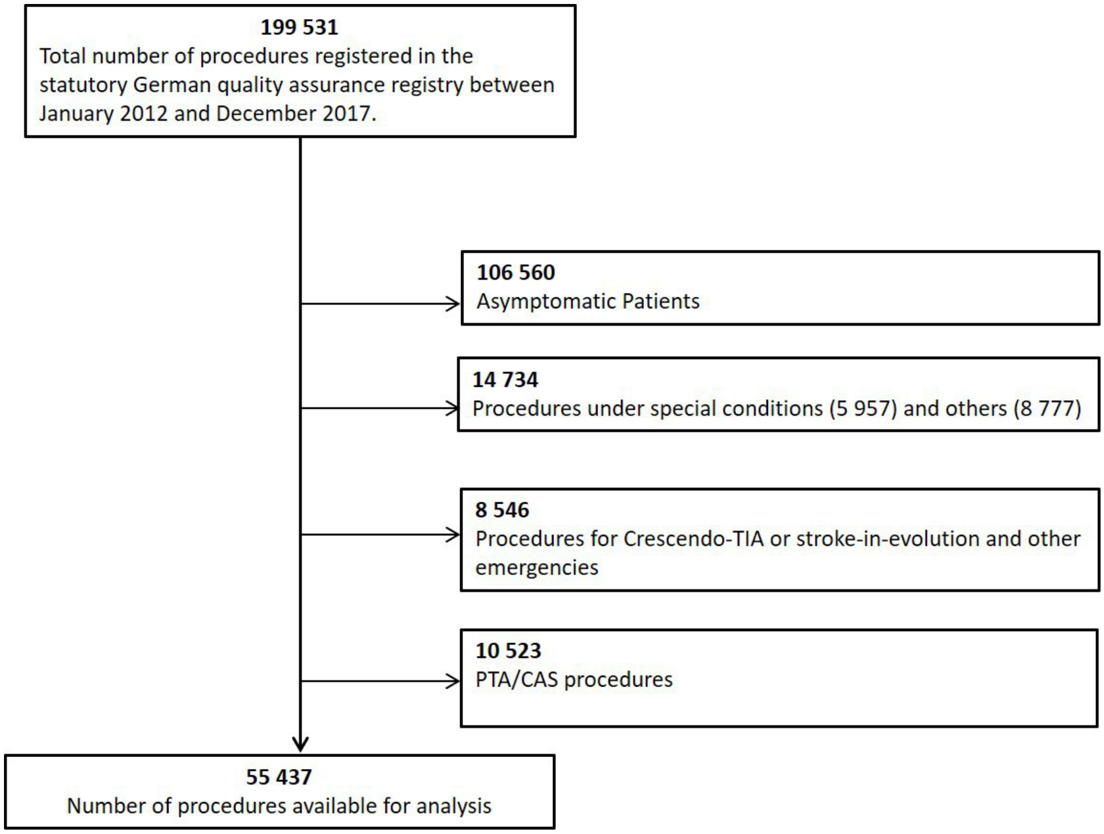

Figure 1 Patient flowchart illustrating inclusion and exclusion criteria. *Excluding combined/converted procedures (CAS and CEA) and CAS procedures performed for the primary purpose to gain access for an intracranial intervention, Special conditions and other include: recurrent stenosis, tandem stenosis, carotid aneurysms, symptomatic ICA coiling, and symptomatic low grade (<50%) stenosis with ulcerated plaque morphology, simultaneous cardiac or aortic surgery. CAS, carotid artery stenting; PTA, percutaneous transluminal angioplasty; TIA, transitory ischaemic attack.

hospital discharge. Strokes were classified by the modified Rankin scale (mRS) as major (mRS 3–5) or minor stroke (mRS 0–2).

Statistical analyses

Categorical variables were displayed as absolute counts and corresponding percentages. Continuous variables were given as medians along with their first (Q1) and third (Q3) quartiles. As the dataset of our study represents the whole population of interest and not only a random patient sample, the statistical differences for every single variable (eg, p value) were not calculated for tables 1–4. The statistical analyses were defined a priori, chosen as sparingly as possible and focused on the outcomes in order to avoid false-positive results due to multiple testing against the background of the study design (retrospective cohort study).

A univariate linear regression analysis was conducted to examine the factors that influence the prehospital and in-hospital delay. For the linear regressions, the prehospital and intrahospital time intervals were modelled as metric variables scaled in days. The slope of the linear regression line is given as the β-value. Adjusted ORs were computed for the outcomes within different delay groups through multivariable analyses. To account for potential confounding, age, sex, ASA stage, the degree of ipsilateral and contralateral stenosis, neurological assessments before and after the procedure and the annual centre caseload for symptomatic patients were included as fixed-effect factors. The model specification and variable selection were predetermined in accordance with a predefined analysis plan based on a review of the existing literature and expert insights.

Data processing and statistical analyses were conducted using R V.3.2.1 from the R Foundation for Statistical Computing in Vienna, Austria. The R extension packages tidyverse, epitools, ggplot2 and mgcv were used. The graphical representation of the data was accomplished using R. For all statistical tests, a two-tailed significance level of α=5% was used.

RESULTS

Patients and procedural characteristics

Prehospital delay

In total, 55 437 CEA cases were included in the analysis. Overall patients' median age was 73 years and 67.9% were male patients (table 1). Regarding the prehospital delay, 18.6% of the cases were admitted 180–15 days after the index event (very long prehospital delay (VL-pre)),

Table 1 Baseline characteristics for patients undergoing carotid endarterectomy according to the delay between neurological index event and hospital admission (prehospital delay)

	Very long 180–15 days		Long 14–8 days		Short 7–3 days		Very short 2–0 days		In-hospital		Overall	
N	10336	(18.6)	6849	(12.4)	9456	(17.1)	19336	(34.9)	9460	(17.1)	55437	(100)
Age (years, median (Q1–Q3))	72	(64–77)	72	(64–78)	73	(64–78)	73	(65–79)	74	(66–79)	73	(65–78)
Male sex	6994	(67.7)	4695	(68.6)	6354	(67.2)	13207	(68.3)	6378	(67.4)	37628	(67.9)
ASA stage												
Stage I+II	2869	(27.8)	1831	(26.7)	2448	(25.9)	4389	(22.7)	1935	(20.5)	13472	(24.3)
Stage III	7190	(69.6)	4830	(70.5)	6744	(71.3)	14087	(72.9)	6985	(73.8)	39836	(71.9)
Stage IV+V	277	(2.68)	188	(2.75)	264	(2.79)	860	(4.45)	540	(5.71)	2129	(3.84)
Right carotid artery treated	5259	(50.9)	3506	(51.2)	4749	(50.2)	9560	(49.4)	4571	(48.3)	27645	(49.9)
Ipsilateral degree of stenosis (NASCET)												
Mild (<50%)	91	(0.88)	62	(0.91)	66	(0.70)	178	(0.92)	93	(0.98)	490	(0.88)
Moderate (50%–69%)	817	(7.90)	549	(8.02)	699	(7.39)	1893	(9.79)	912	(9.64)	4870	(8.78)
Severe (70%–99%)	9375	(90.7)	6203	(90.6)	8654	(91.5)	17123	(88.6)	8386	(88.6)	49741	(89.7)
Occlusion (100%)	53	(0.51)	35	(0.51)	37	(0.39)	142	(0.73)	69	(0.73)	336	(0.61)
Contralateral degree of stenosis (NASCET)												
Mild (<50%)	6998	(67.7)	4640	(67.7)	6423	(67.9)	13377	(69.2)	6167	(65.2)	37605	(67.8)
Moderate (50%–69%)	1539	(14.9)	1045	(15.3)	1403	(14.8)	2825	(14.6)	1514	(16.0)	8326	(15.0)
Severe (70%–99%)	1327	(12.8)	870	(12.7)	1187	(12.6)	2315	(12.0)	1265	(13.4)	6964	(12.6)
Occlusion (100%)	472	(4.57)	294	(4.29)	443	(4.68)	819	(4.24)	514	(5.43)	2542	(4.59)
Qualifying/index event												
Amaurosis fugax	2785	(26.9)	1788	(26.1)	1782	(18.9)	2196	(11.4)	990	(10.5)	9541	(17.2)
Transitory ischaemic attack	3490	(33.8)	2378	(34.7)	3221	(34.1)	6502	(33.6)	3550	(37.5)	19141	(34.5)
Stroke	3305	(32.0)	2276	(33.2)	4114	(43.5)	10088	(52.2)	4522	(47.8)	24305	(43.8)
Other symptoms	756	(7.31)	407	(5.94)	339	(3.59)	550	(2.84)	398	(4.21)	2450	(4.42)
Neurological assessment*												
Preprocedural	8101	(78.4)	5696	(83.2)	8401	(88.8)	17966	(92.9)	8714	(92.1)	48878	(88.2)
Postprocedural	5854	(56.6)	4123	(60.2)	6072	(64.2)	14588	(75.4)	7056	(74.6)	37693	(68.0)
Preprocedural and postprocedural	5474	(53.0)	3901	(57.0)	5862	(62.0)	14249	(73.7)	6928	(73.2)	36414	(65.7)
Centre annual caseload (median; Q1–Q3)												
Centre volume (symptomatic)	26	(14–42)	28	(16–45)	30	(19–45)	29	(18–41)	27	(17–39)	28	(17–42)

*Multiple answers possible, percentages are given as column percentage.
ASA, American Society of Anesthesiologists physical status classification system; n, patients with feature or property; NASCET, North American Symptomatic Carotid Endarterectomy Trial—Criteria; N, all patients with information available; Q1, first quartile; Q3, third quartile.

Table 2 Characteristics and outcomes of treatment according to the delay between neurological index event and hospital admission (prehospital delay)

Unit of analysis=patients (first level)	Very long 180–15 days		Long 14–8 days		Short 7–3 days		Very short 2–0 days		In-hospital		Overall	
Weekday of admission												
Monday	2831	(27.4)	1740	(25.4)	2067	(21.9)	3311	(17.1)	1629	(17.2)	11 578	(20.9)
Tuesday	2239	(21.7)	1384	(20.2)	1788	(18.9)	3205	(16.6)	1467	(15.5)	10 083	(18.2)
Wednesday	2166	(21.0)	1382	(20.2)	1722	(18.2)	3089	(16.0)	1462	(15.5)	9821	(17.7)
Thursday	1686	(16.3)	1176	(17.2)	1773	(18.8)	3168	(16.4)	1566	(16.6)	9369	(16.9)
Friday	588	(5.69)	599	(8.75)	1303	(13.8)	2917	(15.1)	1506	(15.9)	6913	(12.5)
Saturday	61	(0.59)	91	(1.33)	246	(2.60)	1799	(9.30)	918	(9.70)	3115	(5.62)
Sunday	765	(7.40)	477	(6.96)	557	(5.89)	1847	(9.55)	912	(9.64)	4558	(8.22)
Perioperative antiplatelet medication												
ASS mono therapy	8502	(82.3)	5649	(82.5)	7946	(84.0)	16 294	(84.3)	7869	(83.2)	46 260	(83.4)
Plavix/clopidogrel mono	375	(3.63)	222	(3.24)	274	(2.90)	531	(2.75)	265	(2.80)	1667	(3.01)
Other mono therapy	60	(0.58)	30	(0.44)	46	(0.49)	85	(0.44)	51	(0.54)	272	(0.49)
Dual antiplatelet medication	683	(6.61)	506	(7.39)	710	(7.51)	1493	(7.72)	895	(9.46)	4287	(7.73)
None	716	(6.93)	442	(6.45)	480	(5.08)	933	(4.83)	380	(4.02)	2951	(5.32)
Type of anaesthesia*												
LA	2457	(28.0)	1594	(27.3)	2076	(26.4)	4163	(26.6)	1957	(25.0)	12 247	(26.6)
GA	6117	(69.7)	4108	(70.5)	5628	(71.5)	11 138	(71.0)	5677	(72.5)	32 668	(71.0)
LA/GA	207	(2.36)	128	(2.20)	167	(2.12)	376	(2.40)	199	(2.54)	1077	(2.34)
Operation technique*												
CEA without patch	149	(1.70)	74	(1.27)	101	(1.28)	299	(1.91)	125	(1.60)	748	(1.63)
CEA with patch	3091	(35.2)	2040	(35.0)	2908	(36.9)	5630	(35.9)	2828	(36.1)	16 497	(35.9)
Eversion CEA	3665	(41.7)	2403	(41.2)	3074	(39.1)	5910	(37.7)	2759	(35.2)	17 811	(38.7)
Interposition	132	(1.50)	88	(1.51)	97	(1.23)	215	(1.37)	143	(1.83)	675	(1.47)
Others	1744	(19.9)	1225	(21.0)	1691	(21.5)	3623	(23.1)	1978	(25.3)	10 261	(22.3)
Intra-arterial shunt use*	3791	(43.2)	2640	(45.3)	3778	(48.0)	7763	(49.5)	3964	(50.6)	21 936	(47.7)
Intraprocedural neurophysiological monitoring†												
Electroencephalography	617	(7.03)	389	(6.67)	597	(7.58)	986	(6.29)	599	(7.65)	3188	(6.93)
TCO	1162	(13.2)	766	(13.1)	954	(12.1)	1918	(12.2)	997	(12.7)	5797	(12.6)
SEPs	2378	(27.1)	1648	(28.3)	2174	(27.6)	4036	(25.7)	2095	(26.7)	12 331	(26.8)
Other methods	2180	(24.8)	1547	(26.5)	2031	(25.8)	3716	(23.7)	1732	(22.1)	11 206	(24.4)
Intraoperative completion study*†	6225	(70.9)	4232	(72.6)	5817	(73.9)	10 883	(69.4)	5454	(69.6)	32 611	(70.9)
Angiography	3350	(38.2)	2272	(39.0)	3264	(41.5)	5912	(37.7)	2843	(36.3)	17 641	(38.4)
IDUS	1097	(12.5)	694	(11.9)	926	(11.8)	1821	(11.6)	785	(10.0)	5323	(11.6)

Continued

Table 2 Continued

Unit of analysis=patients (first level)	Very long 180–15 days		Long 14–8 days		Short 7–3 days		Very short 2–0 days		In-hospital		Overall	
Flowmetry	1707	(19.4)	1182	(20.3)	1555	(19.8)	2908	(18.5)	1525	(19.5)	8877	(19.3)
Other technique	632	(7.20)	429	(7.36)	543	(6.90)	920	(5.87)	607	(7.75)	3131	(6.81)
Duration of operation (minutes)*	87	(68–108)	85	(67–105)	85	(68–107)	90	(71–112)	89	(70–109)	88	(70–109)
Outcomes												
Any stroke or death	235	(2.27)	146	(2.13)	203	(2.15)	604	(3.12)	329	(3.48)	1517	(2.74)
Major stroke or death	161	(1.56)	104	(1.52)	154	(1.63)	475	(2.46)	257	(2.72)	1151	(2.08)
Any stroke	192	(1.86)	116	(1.69)	156	(1.65)	462	(2.39)	213	(2.25)	1139	(2.05)
All-cause death	60	(0.58)	34	(0.50)	64	(0.68)	199	(1.03)	143	(1.51)	500	(0.90)
Myocardial infarction‡	19	(0.28)	18	(0.40)	27	(0.44)	45	(0.36)	26	(0.42)	135	(0.37)
MACE‡	147	(2.19)	84	(1.86)	125	(2.02)	342	(2.72)	149	(2.38)	847	(2.34)

*Data only available for 2012–2016.
†Multiple answers possible.
‡ Data only available for 2013–2016, percentages are given as column percentage.
ASS, acetylsalicylic acid; CEA, carotid endarterectomy; GA, general anaesthesia; IDUS, intraoperative duplex ultrasound; LA, local anaesthesia; LA/GA, cases with both, considered as conversions from LA to GA; MACE, major adverse cardiovascular event; SEPs, somatosensory evoked potentials; TCO, transcranial cerebral oximetry.

12.4% within 14–8 days (long prehospital delay (L-pre)) and 17.1% within 7–3 days (short prehospital delay (S-pre)). The majority (34.9%) was admitted 2 days or less following the index event (very short prehospital delay (VS-pre)) and in 17.1% of the cases the index event occurred during hospital stay (IH-pre) (table 1).

Patients with an L-pre were in median younger (years, VL-pre: 72, L-pre: 72, S-pre: 73, VS-pre: 73 and IH-pre: 74).

Regarding the index event, the proportion of patients with amaurosis fugax was higher in the groups with a longer prehospital delay (VL-pre: 26.9% and L-pre: 26.1% vs VS-pre: 11.4% and IH-pre: 10.5%, table 1), whereas the proportion of patients who had a stroke was higher in the groups with a shorter delay (VL-pre: 32.0% and L-pre: 33.2% vs VS-pre: 52.2% and IH-pre: 47.8%, table 1). The share of patients with a preprocedural neurological assessment was higher in the groups with shorter prehospital delay (VL-pre: 78.4% vs VS-pre: 92.9% and IH-pre: 92.1%, table 1). Please see tables 1 and 2 for further details in the different groups of prehospital delays.

In-hospital delay

The majority of cases was treated more than 3 days after admission (40.9%, long in-hospital delay (L-in)) followed by 37.7% of patients who were treated after 0–1 days (short in-hospital delay (S-in)) and 21.4% of patients with treatment 2–3 days after admission (intermediate in-hospital delay (I-in), table 3).

Patients with a shorter in-hospital delay were slightly younger (S-in: 72, I-in: 73, L-in: 74 years) and the proportion of patients classified as ASA stage III was to some extent lower (S-in: 68.7%, I-in: 72.2%, L-in: 74.6%, table 3). The proportion of amaurosis fugax as index event was higher in cases with S-in (S-in: 24.4%, I-in: 16.9%, L-in: 10.7%) and inversely stroke was more often the index event in patients with L-in (S-in: 34.5%, I-in: 42.8%, L-in: 53%, table 3). The proportion of cases with an S-pre was higher in the long in-hospital group and cases with an L-pre were more frequent in the short in-hospital group (table 3). Please see tables 3 and 4 for further details in the different groups of in-hospital delays.

Determinants of prehospital and in-hospital delay

Prehospital delay

Univariate analysis revealed that a higher patient's age was associated with a shorter prehospital delay (β=−1.08, p<0.001). An S-pre also showed significant direct correlation with a higher ASA stage (ASA III: β=−1.32, p<0.001; ASA IV/V: β=−3.71, p<0.001, Ref: ASA I/II), moderate ipsilateral stenosis (β=−1.46, p<0.001, Ref: severe stenosis), TIA and stroke as index event (TIA: β=−4.41, p<0.001; Stroke: β=−6.05, p<0.001, Ref: amaurosis fugax) and high annual centre caseload of treating centre (β=−0.03, p=0.031, table 5). If the index event was coded as 'other' (neither AFX, TIA nor stroke), this was associated with a longer delay before admission (ß=2.53, p<0.001).

Table 3 Baseline characteristics for patients undergoing carotid endarterectomy according to the delay between admission and CEA (in-hospital delay)

Patient level characteristics	short 0–1 days		intermediate 2–3 days		Long >3 days		Overall	
N	20 894	(37.7)	11 856	(21.4)	22 687	(40.9)	55 437	(100)
Age (years, median (Q1–Q3))	72	(64–78)	73	(64–78)	74	(66–79)	73	(65–78)
Male sex	14 276	(68.3)	8042	(67.8)	15 310	(67.5)	37 628	(67.9)
ASA stage								
Stage I+II	5943	(28.4)	2850	(24.1)	4679	(20.6)	13 472	(24.3)
Stage III	14 348	(68.7)	8565	(72.2)	16 923	(74.6)	39 836	(71.9)
Stage IV+V	603	(2.89)	441	(3.72)	1085	(4.78)	2129	(3.84)
Right carotid artery treated	10 610	(50.8)	5780	(48.8)	11 255	(49.6)	27 645	(49.9)
Ipsilateral degree of stenosis (NASCET)								
Mild (<50%)	181	(0.87)	109	(0.92)	200	(0.88)	490	(0.88)
Moderate (50%–69%)	1604	(7.68)	904	(7.62)	2362	(10.4)	4870	(8.78)
Severe (70%–99%)	18 923	(90.6)	10 784	(91.0)	20 034	(88.3)	49 741	(89.7)
Occlusion (100%)	186	(0.89)	59	(0.50)	91	(0.40)	336	(0.61)
Contralateral degree of stenosis (NASCET)								
Mild (<50%)	14 366	(68.8)	8121	(68.5)	15 118	(66.6)	37 605	(67.8)
Moderate (50%–69%)	3091	(14.8)	1741	(14.7)	3494	(15.4)	8326	(15.0)
Severe (70%–99%)	2551	(12.2)	1458	(12.3)	2955	(13.0)	6964	(12.6)
Occlusion (100%)	886	(4.24)	536	(4.52)	1120	(4.94)	2542	(4.59)
Qualifying/index event								
Amaurosis fugax	5107	(24.4)	2006	(16.9)	2428	(10.7)	9541	(17.2)
Transitory ischaemic attack	7390	(35.4)	4344	(36.6)	7407	(32.7)	19 141	(34.5)
Stroke	7201	(34.5)	5069	(42.8)	12 035	(53.0)	24 305	(43.8)
Other symptoms	1196	(5.72)	437	(3.69)	817	(3.60)	2450	(4.42)
Neurological assessment*								
Preprocedural	17 172	(82.2)	10 651	(89.8)	21 055	(92.8)	48 878	(88.2)
Postprocedural	12 588	(60.2)	8257	(69.6)	16 848	(74.3)	37 693	(68.0)
Preprocedural and postprocedural	11 868	(56.8)	7998	(67.5)	16 548	(72.9)	36 414	(65.7)
Time interval (index event to admission, prehospital delay)								
In-hospital	1097	(5.25)	2129	(18.0)	6234	(27.5)	9460	(17.1)
0–2 days	3513	(16.8)	4233	(35.7)	11 590	(51.1)	19 336	(34.9)
3–7 days	4650	(22.3)	2372	(20.0)	2434	(10.7)	9456	(17.1)
8–14 days	4288	(20.5)	1503	(12.7)	1058	(4.66)	6849	(12.4)
15–180 days	7346	(35.2)	1619	(13.7)	1371	(6.04)	10 336	(18.6)
Preoperative diagnostic procedures**†								
Duplex ultrasound	17 174	(98.3)	9742	(98.7)	18 343	(98.3)	45 259	(98.4)
Transcranial Doppler	5473	(31.3)	4261	(43.1)	9766	(52.4)	19 500	(42.4)
CTA	10 217	(58.5)	6914	(70.0)	14 529	(77.9)	31 660	(68.8)
MRA	8470	(48.5)	4586	(46.4)	9017	(48.3)	22 073	(48.0)
Centre annual caseload (median; Q1–Q3)								
Centre volume (symptomatic)	29	(17–45)	30	(19–43)	27	(17–39)	28	(17–42)

*Multiple answers possible.
†Data only available for 2012–2016, percentages are given as column percentage.
ASA, American Society of Anesthesiologists physical status classification system; CEA, carotid endarterectomy; CTA, CT angiography; MRA, magnetic resonance angiography; NASCET, North American Symptomatic Carotid Endarterectomy Trial—Criteria; N, all patients with information available; Q1, first quartile; Q3, third quartile.

Table 4 Characteristics and outcomes of treatment according to the delay between admission and CEA (in-hospital delay)

Unit of analysis=patients (first level)	Short 0–1 days		Intermediate 2–3 days		Long >3 days		Overall	
Weekday of admission								
Monday	5074	(24.3)	2835	(23.9)	3669	(16.2)	11 578	(20.9)
Tuesday	4225	(20.2)	2790	(23.5)	3068	(13.5)	10 083	(18.2)
Wednesday	4263	(20.4)	1952	(16.5)	3606	(15.9)	9821	(17.7)
Thursday	4393	(21.0)	506	(4.27)	4470	(19.7)	9369	(16.9)
Friday	976	(4.67)	2217	(18.7)	3720	(16.4)	6913	(12.5)
Saturday	236	(1.13)	733	(6.18)	2146	(9.46)	3115	(5.62)
Sunday	1727	(8.27)	823	(6.94)	2008	(8.85)	4558	(8.22)
Perioperative antiplatelet medication								
ASS mono therapy	17 414	(83.3)	9961	(84.0)	18 885	(83.2)	46 260	(83.4)
Plavix and clopidogrel mono	681	(3.26)	316	(2.67)	670	(2.95)	1667	(3.01)
Other mono therapy	106	(0.51)	69	(0.58)	97	(0.43)	272	(0.49)
Dual antiplatelet medication	1380	(6.60)	933	(7.87)	1974	(8.70)	4287	(7.73)
None	1313	(6.28)	577	(4.87)	1061	(4.68)	2951	(5.32)
Type of anaesthesia*	17 465		9875		18 652		45 992	
LA	4627	(26.5)	2667	(27.0)	4953	(26.6)	12 247	(26.6)
GA	12 410	(71.1)	6944	(70.3)	13 314	(71.4)	32 668	(71.0)
LA/GA	428	(2.45)	264	(2.67)	385	(2.06)	1077	(2.34)
Operation technique*								
CEA without patch	227	(1.30)	174	(1.76)	347	(1.86)	748	(1.63)
CEA with patch	6117	(35.0)	3627	(36.7)	6753	(36.2)	16 497	(35.9)
Eversion CEA	7321	(41.9)	3719	(37.7)	6771	(36.3)	17 811	(38.7)
Interposition	258	(1.48)	145	(1.47)	272	(1.46)	675	(1.47)
Others	3542	(20.3)	2210	(22.4)	4509	(24.2)	10 261	(22.3)
Intra-arterial shunt use*	8021	(45.9)	4873	(49.3)	9042	(48.5)	21 936	(47.7)
Intraprocedural neurophysiological monitoring*†								
Electroencephalography	1346	(7.71)	730	(7.39)	1112	(5.96)	3188	(6.93)
TCO	2174	(12.4)	1194	(12.1)	2429	(13.0)	5797	(12.6)
SEPs	4648	(26.6)	2491	(25.2)	5192	(27.8)	12 331	(26.8)
Other methods	4457	(25.5)	2468	(25.0)	4281	(23.0)	11 206	(24.4)
Intraoperative completion study*†	12 724	(72.9)	7161	(72.5)	12 726	(68.2)	32 611	(70.9)
Angiography	7102	(40.7)	3990	(40.4)	6549	(35.1)	17 641	(38.4)
IDUS	2018	(11.6)	1105	(11.2)	2200	(11.8)	5323	(11.6)
Flowmetry	3441	(19.7)	1915	(19.4)	3521	(18.9)	8877	(19.3)
Other technique	1179	(6.75)	712	(7.21)	1240	(6.65)	3131	(6.81)
Duration of operation (minutes)*	85	(66–105)	88	(70–109)	90	(72–112)	88	(70–109)
Outcomes								
Any stroke or death	498	(2.38)	355	(2.99)	664	(2.93)	1517	(2.74)
Major stroke or death	374	(1.79)	275	(2.32)	502	(2.21)	1151	(2.08)
Any stroke	396	(1.90)	260	(2.19)	483	(2.13)	1139	(2.05)
All-cause death	140	(0.67)	125	(1.05)	235	(1.04)	500	(0.90)
Myocardial infarction‡	51	(0.38)	33	(0.42)	51	(0.34)	135	(0.37)
MACE‡	301	(2.22)	192	(2.44)	354	(2.38)	847	(2.34)

*Data only available for 2012–2016.
†Multiple answers possible.
‡Data only available for 2013–2016, percentages are given as column percentage.
ASS, acetylsalicylic acid; CEA, carotid endarterectomy; GA, general anaesthesia; IDUS, intraoperative duplex ultrasound; LA, local anaesthesia; LA/GA, cases with both, considered as conversions from LA to GA; MACE, major adverse cardiovascular event; SEPs, somatosensory evoked potentials; TCO, transcranial cerebral oximetry.

Table 5 Univariate analysis of determinants of long prehospital (left part) and in-hospital delay (right part)

Determinants of long delay between index event and hospital admission			Determinants of long delay between hospital admission and CEA		
	β	P value		β	P value
Patient characteristics			Patient characteristics		
Age (per 10 years increase)	−1.08	<0.001***	Age (per 10 years increase)	0.28	<0.001***
Female sex	0.17	0.516	Female sex	0.09	0.014*
ASA stage			ASA stage		
Stage I+II	Ref.	Ref.	Stage I+II	Ref.	Ref.
Stage III	−1.32	<0.001***	Stage III	0.75	<0.001***
Stage IV+V	−3.71	<0.001***	Stage IV+V	1.74	<0.001***
Ipsilateral degree of stenosis (NASCET)			Ipsilateral degree of stenosis (NASCET)		
Mild (<50%)	−1.02	0.439	Mild (<50%)	0.05	0.802
Moderate (50%–69%)	−1.46	<0.001***	Moderate (50%–69%)	0.70	<0.001***
Severe (70%–99%)	Ref.	Ref.	Severe (70%–99%)	Ref.	Ref.
Occlusion (100%)	−0.55	0.730	Occlusion (100%)	−1.16	<0.001***
Contralateral degree of stenosis (NASCET)			Contralateral degree of stenosis (NASCET)		
Mild (<50%)	−0.40	0.291	Mild (<50%)	−0.24	<0.001***
Moderate (50%–69%)	−0.14	0.758	Moderate (50%–69%)	−0.02	0.756
Severe (70%–99%)	Ref.	Ref.	Severe (70%–99%)	Ref.	Ref.
Occlusion (100%)	0.40	0.555	Occlusion (100%)	0.26	0.008**
Index event					
AFX	Ref.	Ref.			
TIA	−4.41	<0.001***			
Any stroke	−6.05	<0.001***			
Other	2.53	<0.001***			
			Preoperative neurological examination		
				1.16	<0.001***
			Weekday of admission		
			Monday	Ref.	Ref.
			Tuesday	0.12	0.027*
			Wednesday	0.22	<0.001***
			Thursday	0.47	<0.001***
			Friday	1.57	<0.001***
			Saturday	2.62	<0.001***
			Sunday	0.84	<0.001***
			Type of anaesthesia		
			LA	Ref.	Ref.
			GA	0.10	0.024*
			LA→GA	−0.18	0.167
Annual caseload volume (symptomatic)			Annual caseload volume (symptomatic)		
	−0.03	<0.001***		−0.02	<0.001***

Continued

Table 5 Continued

Determinants of long delay between index event and hospital admission			Determinants of long delay between hospital admission and CEA		
	β	P value		β	P value

Negative β-values indicate a correlation with a shorter delay and positive β-values correlation with a longer delay.
significance levels: p-value <0.05:*, <0.01:**, <0.001:***
AFX, amaurosis fugax; ASA, American Society of Anesthesiologists physical status classification system; CEA, carotid endarterectomy; GA, general anaesthesia; LA, local anaesthesia; NASCET, North American Symptomatic Carotid Endarterectomy Trial—Criteria; TIA, transitory ischaemic attack.

In-hospital delay

Regarding the in-hospital time interval, a higher patient's age was directly associated with a longer in-hospital delay (β=0.28, p<0.001, table 5). Female sex (β=0.09, p=0.014), a higher ASA stage (ASA III: β=0.75, p<0.001; ASA IV/V: β=1.74, p<0.001, Ref: ASA I/II), implementation of a preoperative neurological examination (β=1.16, p<0.001) and general anaesthesia (β=0.10, p=0.024, Ref: local anaesthesia) were also directly associated with a longer in-hospital delay. A moderate ipsilateral stenosis (β=0.70, p<0.001) and a contralateral occlusion (β=0.26, p=0.008) correlated with a longer in-hospital delay. In contrast, an ipsilateral occlusion (β=−1.16, p<0.001, Ref: severe stenosis) and contralateral mild stenosis (β=−0.24, p<0.001, Ref: severe stenosis, table 5) were associated with a shorter in-hospital delay. Compared with patients who are admitted on a Mondays, patients admitted on all other days of the week (Tuesday to Sunday) had significantly longer in-hospital delay (table 5), especially on Fridays (β=1.57, p<0.001; Ref: Monday) and Saturdays (β=2.62, p<0.001; Ref: Monday). A high annual centre caseload was significantly correlated with a shorter in-hospital delay (β=−0.02, p=<0.001).

Primary and secondary outcomes

Prehospital delay

The combined stroke death rate as primary outcome event (POE) was highest in the groups with an S-pre (VL-pre: 2.27%, L-pre: 2.13%, S-pre: 2.15%, VS-pre: 3.12% and IH-pre: 3.48%, table 2). Multivariable analysis revealed a significantly increased OR for the POE in cases with the index event during the hospital stay (adjusted OR (aOR) 1.23, 95% CI: 1.04 to 1.47, Ref. VL-pre) but not for the other groups (figure 2). Regarding the secondary endpoints, the risk for perioperative death (VS-pre: aOR 1.42, 95% CI: 1.05 to 1.90; IH-pre: aOR 1.87, 95% CI: 1.37 to 2.55, figure 2) and major stroke or death (VS-pre: aOR 1.33, 95% CI: 1.10 to 1.59; IH-pre: aOR 1.38, 95% CI: 1.13 to 1.69, figure 2) was increased in the VS-pre group and in the IH-pre group, respectively.

In-hospital delay

Regarding the in-hospital delay, the POE rate was higher in the I-in and L-in group (S-in: 2.38%, I-in: 2.99%, L-in: 2.93%, table 4). Multivariable analysis revealed a significantly increased risk for the POE in the intermediate delay group (aOR 1.15, 95% CI: 1.00 to 1.33, figure 3). Regarding the secondary endpoints, perioperative death (aOR 1.42, 95% CI: 1.11 to 1.82, figure 3) and perioperative major stroke or death (aOR 1.18, 95% CI: 1.01 to 1.39, figure 3), the intermediate delay group was significantly associated with a higher risk.

DISCUSSION

This is the first study that analyse the preoperative time interval differentiated by prehospital and in-hospital delay before CEA for symptomatic carotid stenoses in German hospitals. This study revealed that older age, higher ASA stage, increasing severity of symptoms and ipsilateral occlusion were associated with shorter prehospital delay. Non-specific symptoms were associated with a longer prehospital delay. Regarding in-hospital delay, older age, higher ASA stage, contralateral occlusion, preprocedural examination by a neurologist and admission on Fridays or Saturdays were associated with delayed in-hospital treatment. In contrast, ipsilateral occlusion and higher annual caseload were associated with shorter in-hospital delay. Regarding the outcomes, multivariable analysis showed significantly higher risks in patients with a VS-pre or an in-hospital index event. With respect to the in-hospital delay, patients treated between 2 and 3 days after admission had a higher risk for stroke or death combined, death alone and major stroke or death.

Patients' and procedural characteristics

In comparison with other studies in western countries,[8 18] the patient cohort shows similar basic characteristics with a median age of 73 years and a proportion of about two-thirds male patients.

The majority of patients (about one-third) was admitted to the hospital within 0–2 days and 81% were admitted to the hospital according to the guideline recommendation of 14-days, which is a higher proportion than other studies reported.[10 19] This might be based on the fact that our data represent the time from index event to admission and not to CEA. A prospective study from Norway revealed that about 90% of the patients had their first medical examination within 14 days.[20]

Regarding the in-hospital delay, almost 60% of the patients are treated within 3 days after hospital admission. An analysis of the Dutch audit for carotid intervention showed that 78% of the patients were treated by CEA within 14 days after first hospital consultation.[8]

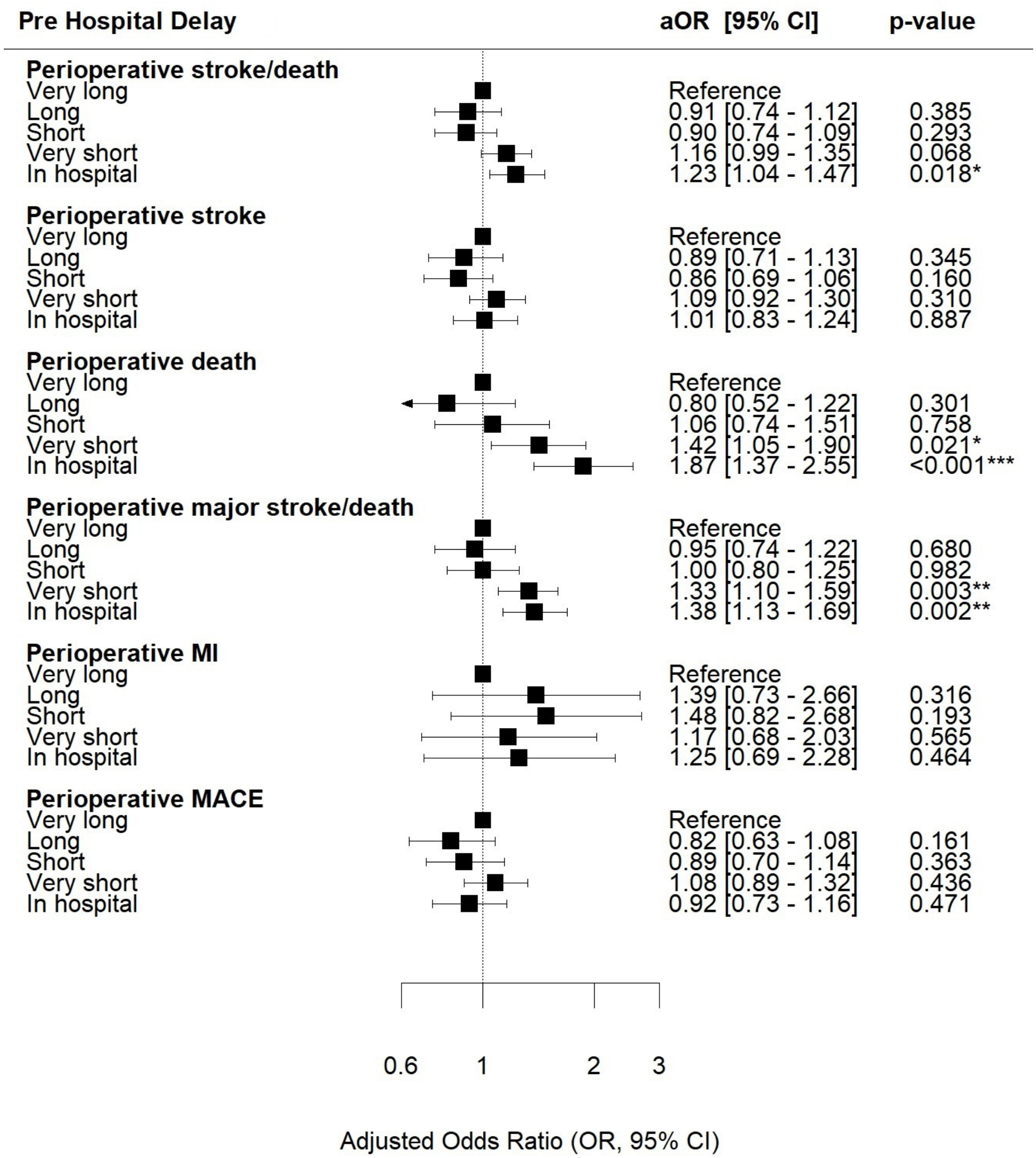

Figure 2 Multivariable regression analysis. Forest plot illustrating adjusted associations between time interval 'index event—admission' and the outcomes after carotid endarterectomy. MI, MACE, CI adjusted for the following variables: age, sex, American Society of Anesthesiology stage, degree of ipsilateral and contralateral stenosis, neurological assessment before/after the procedure, annual centre caseload for symptomatic patients. MACE, major adverse cardiovascular event; MI, myocardial infarction. significance levels: p-value <0.05:*, <0.01:**, <0.001:***.

The dataset of our analysis does not allow a detailed discrimination between the first contact to healthcare system and contact to a surgical department or the time delay from first in-hospital contact to a surgical specialist to CEA. Therefore, the data of this study are not fully comparable to the above mentioned studies. However, this study gives a detailed insight into the different sections of a preoperative delay.

Determinants of prehospital and in-hospital delay

Our study shows that older patient's age is associated with a shorter prehospital, but a longer in-hospital delay. Kuhrij *et al* could also find an association of an older age with a shorter preoperative delay,[8] whereas a Canadian case–control study did not find an age related effect.[10]

Also, a higher comorbidity burden—represented by a higher ASA stage—seems to shorten the prehospital and increase the in-hospital delay.

Sex-related effects could be seen as a longer in-hospital delay for female patients, which was not seen in the above mentioned Dutch register study.[8]

Regarding the type of index event, TIA and stroke correlated directly with a significantly shorter prehospital delay compared with amaurosis fugax. The tendency that more severe preoperative symptoms lead to a faster

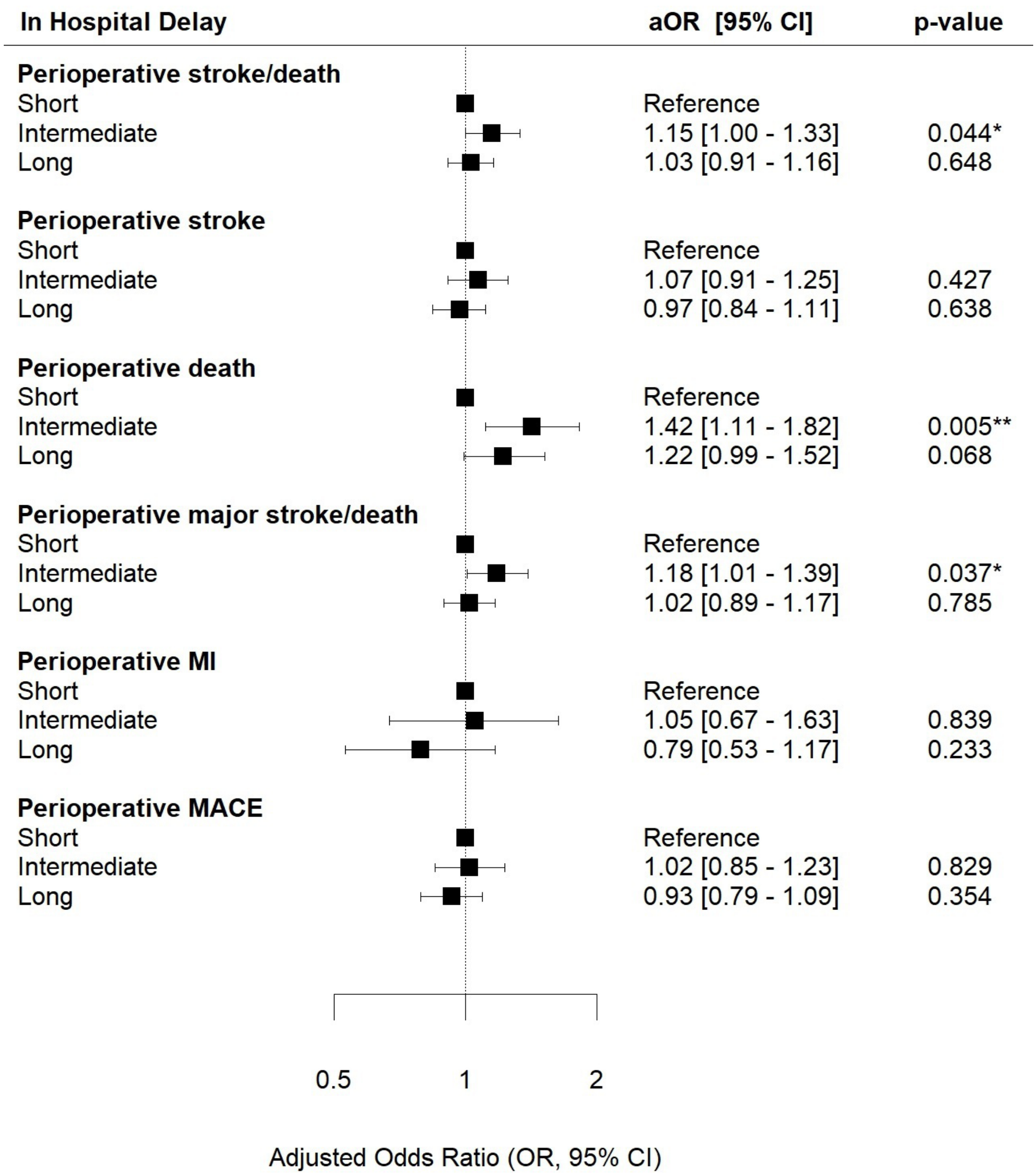

Figure 3 Multivariable regression analysis. Forest plot illustrating adjusted associations between time interval 'admission—CEA' and the outcomes after CEA. MI, MACE and CI adjusted for the following variables: age, sex, ASA stage, degree of ipsilateral and contralateral stenosis, neurological assessment before/after the procedure, annual centre caseload for symptomatic patients. CEA, carotid endarterectomy; MACE, major adverse cardiovascular event; MI, myocardial infarction. significance levels: p-value <0.05:*, <0.01:**, <0.001:***.

admission or treatment could be also observed in Canadian[10] and Dutch[8] cohorts. This could be an approach to ensure that the training of medical staff, in particular general practitioners and nurses, could lead to better recognition of amaurosis fugax as a warning symptom and prompt clarification could be initiated. For example, the balance, eyes, face, arm, speech, time scheme is a helpful algorithm healthcare staff should be trained in.[21]

The effect of a longer in-hospital delay for patients, who underwent a preoperative neurological examination and were treated under general anaesthesia, was not described in the previous literature. The authors explain this observation by the additional (possibly time-consuming) preoperative diagnostics, which might be implemented for patients with general anaesthesia, or different strategies between departments.

The only factor which was associated with shorter prehospital and in-hospital delay was the annual caseload volume of symptomatic CEA. This study is the first analysis of real-world data observing this effect. This observation is presumably based on pull factors from the hospital's perspective and patient selection from the referring physician's perspective. However, with β-values of −0.03

and −0.02, this effect is significant but most likely not clinical relevant.

The weekday effect, which was characterised by a significant prolongation of the in-hospital delay of about one and a half to two and a half days for patients admitted on Fridays and Saturday, might be explained by the postponement of elective CEA to the next weekday after admission. This is coherence with data from O'Donnell *et al*, showing that only 3.1% of symptomatic patients are treated on weekends.[22]

Outcomes of treatment

With respect to the prehospital delay, multivariable analysis revealed that patients with index event after the admission were associated with a higher risk for the primary endpoint combined stroke or death. Regarding the secondary endpoints death and major stroke or death, this effect was additionally seen in patients with index event within 0–2 days before admission. Although previous studies suggest that early CEA is safe,[7,23] this result might be an indicator that a fast admission and treatment, possibly with an incomplete preoperative evaluation, increases the perioperative risk. In turn, patient characteristics, diagnostic findings and aspects that require rapid and urgent 'elective' treatment (potentially misclassified emergency indication) could themselves be determinants of a poor outcome, resulting in confounding by indication. However, increasing the awareness of all kinds of healthcare providers, especially for mild neurological symptoms like amaurosis fugax, would lead to a better preoperative assessment and timing of the procedure.

However, it is important to mention that our data show this effect for a prehospital delay and not the whole index event CEA interval. Additionally, the group of cases with an in-hospital index event might be a very heterogenous group of patients who were primarily admitted for another reason than extracranial carotid artery stenosis or stroke.

Analysis of the influence of in-hospital delay on the outcomes revealed that the intermediate group with treatment 2–3 days after admission was associated with higher risk for stroke or death combined, death alone and major stroke or death. Assuming that the cases analysed in this study were elective cases, this might be explained by the fact that for the patients in the S-in group (0–1 days) preoperative diagnostics and preparation was completed in a prehospital setting, whereas patients, who needed further in-hospital diagnostics, were classified in the intermediate group. Unfortunately, due to the fact that the ASA status is the only variable to estimate the patient's comorbidities, this potential bias can only be rudimentarily adjusted in multivariable analysis.

Limitations

Given that this study constitutes a secondary data analysis, it is imperative to consider all pertinent issues associated with observational studies employing routine data. These limitations have been previously deliberated on in other publications.[24,25]

Despite adhering to standardised, statutory and prospective data collection procedures, it is essential to acknowledge that the design of this secondary data analysis is retrospective and observational in nature.

Additionally, it is crucial to note that this study exclusively presents events that transpired during the in-hospital period, with no detection of subsequent events or long-term effects. Nevertheless, since the majority of events manifest within the initial days following CEA, the influence of detection bias can be considered minimal.[26]

Moreover, the self-reported nature of data within the quality assurance database warrants consideration, as it opens the possibility of a reporting bias. Another source of reporting bias might be the fact that the last neurologic event is actually defined as the last neurological symptom change. However, especially in cases with a persisting severe disability, the time of the index event might be documented later, which could lead to a higher proportion of cases classified in the in-hospital group. To mitigate the risk of misreporting, regional quality assurance offices (Landesgeschäftsstellen für Qualitätssicherung) oversee data quality, initiating verification processes in response to significant deviations. Nonetheless, the potential for substantial under-reporting of adverse events remains plausible and could account for the relatively low rates of perioperative stroke or mortality in this study (2.7%). While a reporting bias cannot be entirely ruled out, it is reasonable to assume that any such bias would be evenly distributed across the different prehospital and in-hospital delay groups. Furthermore, it is important to acknowledge the presence of residual confounding, which cannot be definitively eliminated due to the incomplete collection of all potential confounding variables (eg, comorbidities, cardiovascular risk profiles, medications other than antiplatelets, intraoperative use of heparin or protamine application). Additionally, the registry lacks information on the cause of death.

Conclusion

Our study investigates the prehospital and the in-hospital delay between symptom onset and CEA in symptomatic patients. Univariate analysis revealed older age, higher ASA stage, increasing severity of symptoms and ipsilateral moderate stenosis to be associated with shorter prehospital delay, whereas non-specific symptoms were associated with a longer prehospital delay. With respect to the in-hospital delay, higher ASA stage, older age, contralateral occlusion, preoperative neurological assessment and admission on Fridays or Saturdays were associated with a longer interval. Multivariable analysis showed that a very short (<2 days) prehospital and I-in (2–3 days) were associated with increased risk of the POE (perioperative stroke or death). To our knowledge, this is the first study to investigate prehospital and interhospital delay and its impact on outcome after CEA.

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Competing interests None declared.

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Data availability statement Data are available on reasonable request. The datasets analysed during the current study are available on request from the IQTIG, https://iqtig.org/qs-verfahren-uebersicht/sekundaere-datennutzung/. Not Applicable.

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