Associations of Perioperative Variables with the 30-day risk of Stroke or Death in CEA for Symptomatic Carotid Stenosis

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Abstract:

Background and Purpose: This analysis was performed to assess the association between perioperative and clinical variables and the 30-day risk of stroke or death after carotid endarterectomy (CEA) for symptomatic carotid stenosis.

Methods: Individual patient-level data from the five largest randomized controlled carotid trials were pooled in the Carotid Stenosis Trialists' Collaboration database. A total of 4181 patients who received CEA for symptomatic stenosis per-protocol were included. Determinants of outcome included CEA technique, type of anesthesia, intraoperative neurophysiological monitoring, shunting, antiplatelet medication, and clinical variables. Stroke or death within 30 days after CEA was the primary outcome. Adjusted risk ratios (aRR) were estimated in multilevel multivariable analyses using a Poisson regression model.

Results: Mean age was 69.5 ± 9.2 years (70.7% male). The 30-day stroke or death rate was 4.3%. In the multivariable regression analysis, local anesthesia was associated with a lower primary outcome rate (vs. general anesthesia; aRR 0.70, 95% CI 0.50–0.99). Shunting (aRR 1.43, 95% CI 1.05–1.95), a contralateral high-grade carotid stenosis or occlusion (aRR 1.58, 95% CI 1.02–2.47), and a more severe neurological deficit (mRS 3–5 vs. mRS 0–2: aRR 2.51, 95% CI 1.30–4.83) were associated with higher primary outcome rates. None of the other characteristics were significantly associated with the perioperative stroke or death risk.

Conclusions: The current results indicate lower perioperative stroke or death rates in patients operated upon under local anesthesia, whereas a more severe neurological deficit and a contralateral high-grade carotid stenosis or occlusion were identified as potential risk factors. Despite a possible selection bias and patients not having been randomized, these findings might be useful to guide surgeons and anesthetists when treating patients with symptomatic carotid disease.

Introduction:

According to recent guidelines, carotid endarterectomy (CEA) remains the recommended treatment for symptomatic 50–99% carotid stenosis to prevent subsequent strokes.[1-4]

A number of randomized controlled trials (RCTs) have focused on comparing CEA with either carotid artery stenting (CAS)[5-8] or best medical treatment.[9, 10] However, the specific treatment modality associated with each procedure was generally left to the discretion of the individual physician.

The Carotid Stenosis Trialists' Collaboration (CSTC) was established to perform pooled analyses of individual patient-level data from carotid trials, with the aims of providing measures of treatment effects, investigating important patient subgroups, and identifying patient- and treatment-related determinants of risks and benefits. Initial analyses included the four largest trials—EVA-3S (Endarterectomy versus Stenting in Patients with Symptomatic Severe Carotid Stenosis), SPACE (Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy), ICSS (International Carotid Stenting Study), and CREST (Carotid Revascularization Endarterectomy vs. Stenting Trial) —to compare CEA to CAS in symptomatic patients.[11, 12] Thus far, the impact of clinical or technical aspects of CEA on periprocedural events has only been investigated in a number of secondary analyses of RCTs[13] or individual patient data meta-analysis,[14] and in singular trials, such as EVEREST (EVERsion carotid endarterectomy versus Standard Trial)[15] and GALA (General Anesthesia versus Local Anesthesia for carotid surgery).[16]

For the present pooled analysis, individual patient-level data from the four CSTC trials were merged with those of symptomatic patients included in the GALA trial. The objective was to assess which clinical and perioperative variables were associated with the 30-day stroke or death risk in these five RCTs.

Methods:

The data that support the findings of this study are available from the corresponding author upon reasonable request. We did a pooled analysis of individual patient-level data, acquired from the five largest carotid RCTs, randomizing patients with symptomatic carotid stenosis after the year 2000. Earlier trials [e.g. North American Symptomatic Carotid Endarterectomy Trial (NASCET), EVEREST] and studies performed in a different patient population [e.g. Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE)] were not considered. Methodologies of the source trials, collection, and pooling of data have been described previously.[16-20] In short, EVA-3S (NCT00190398, 527 patients), SPACE (ISRCTN57874028, 1214 patients), ICSS (ISRCTN25337470, 1713 patients), and CREST (NCT00004732, 2502 patients in total of whom 1321 had a symptomatic carotid stenosis) were RCTs randomizing patients with a symptomatic moderate or severe carotid stenosis to CEA or CAS.[5-7, 19] The GALA trial (ISRCTN00525237, 3526 patients in total of whom 2164 had a symptomatic carotid stenosis) was an RCT to compare CEA under local anesthesia (LA) with CEA under general anesthesia (GA) for (a)symptomatic carotid stenosis.

In these five trials combined, 4525 symptomatic patients were randomly assigned to CEA. For this analysis, only data from symptomatic patients randomized to the CEA group and in whom CEA was actually completed were included. Patients lacking data concerning CEA type and those receiving an interposition graft were excluded. The final analysis included 4181 patients (Figure 1).

The primary outcome event was stroke or death within 30 days after CEA. Secondary outcome events were any disabling stroke or death, any stroke, all-cause death, myocardial infarction (MI), and cranial nerve palsy within 30 days after surgery. The present analyses were prospectively defined in a data analysis plan and approved by the CSTC Steering Committee.

First, pooled individual patient data were analyzed descriptively. Age, systolic and diastolic blood pressure were given as means with standard deviation. Given a right-skewed distribution, the clamping time, in-trial center volume, and time interval between the qualifying event and CEA are given as medians with corresponding first (Q1) and third quartiles (Q3). Neurologic symptomatology at the time of randomization was dichotomized according to the modified Rankin Score (mRS 0–2 vs. 3–5).

In-trial center volume was categorized into quarters on the basis of all patients included ~~in this study~~ (Q1=1–3, Q2=4–7, Q3=8–15, Q4=16–202 CEAs). All other variables were considered categorical.

A single variable estimation of the crude risk ratio (RR) with the corresponding 95% confidence interval (95% CI) with respect to the primary outcome was calculated for surgical technique, type of anesthesia, intraoperative neurophysiologic monitoring, shunting, and pre- and postoperative antiplatelet therapy. To identify confounders requiring inclusion in multivariable analyses, the association between each technical variable and the primary outcome was adjusted for all variables (one each) listed in Tables 1 and 2, and for the source trial. Likelihood ratio tests were used to compare nested models with and without each potential confounder, and expert knowledge was used to determine clinically unreasonable models (i.e. interaction between *type of anesthesia* and *shunt use*). Finally, each technical variable (surgical technique, type of anesthesia, intraoperative neurophysiologic monitoring, shunting, and pre- and postprocedural antiplatelet medication) was entered separately as a fixed effect, while the cluster variables "study center" and "source trial" were entered as nested random-effects (random intercept only) into a Poisson regression model.[21-23] Missing values were excluded from the analysis. A likelihood ratio test (global test) was used to assess whether there were any differences between the outcome rates of the three surgical technique groups. Quantile–quantile plots of random effects were used to assess possible misspecification of the regression models.

Statistical analysis was performed with R (Version 3.4.1, http://cran.r-project.org).

Results:

Most patients were men (70.7%). Mean age was 69.5±9.2 years (Table 1). Surgical treatments included CEA with patch angioplasty (54.9%), CEA with primary closure (28.3%), and eversion CEA (16.8%). The majority of procedures were performed under GA (68.1%). Baseline variables and details on perioperative management for the whole cohort and separately for patients who underwent CEA under LA and GA are given in Tables 1 and 2.

The primary outcome occurred in 181 patients, amounting to an overall 30-day stroke or death rate of 4.3% (Table 3). The 30-day rates of any disabling stroke or death, any stroke, and all-cause death were 2.1, 4.0, and 0.8%, respectively. The primary outcome rates for patients who underwent CEA under LA and GA were 3.9 and 4.5%, respectively.

Univariable analysis

The univariable analysis (Table 4) revealed increased stroke or death risks for CEA with primary closure (crude RR 1.42, 95% CI 1.03–1.97) and eversion CEA (crude RR 1.55, 95% CI 1.08–2.26) compared to CEA with patch angioplasty. Furthermore, patients with a more severe neurological deficit (mRS 3–5 vs. mRS 0–2) had an elevated risk of perioperative stroke or death (crude RR 2.48, 95% CI 1.33–4.61). No significant association with the primary outcome was observed for other variables.

Multilevel multivariable analyses

The likelihood ratio test (global test) revealed no statistically significant association between surgical technique and the primary outcome (Figure 2). CEA with primary closure (aRR 1.35, 95% CI 0.96–1.92) and eversion CEA (aRR 1.41, 95% CI 0.95–2.10) were not significantly different from CEA with patch angioplasty.

Compared to GA, CEA under LA was associated with a lower primary outcome rate (aRR 0.70, 95% CI 0.50–0.99). This effect was similar among patients with symptomatic carotid stenosis included in the GALA trial (aRR 0.70, 95% CI 0.48–1.02) and those in the CEA groups of all other source trials (aRR 0.59, 95% CI 0.25–1.41) separately, although not statistically significant. Furthermore, shunting was associated with a higher perioperative stroke or death rate (aRR 1.43, 95% CI 1.05–1.95). Regarding perioperative and clinical variables (Figures 2b, c), a contralateral carotid stenosis or occlusion (aRR 1.58, 95% CI 1.02–2.47) and a more severe neurological deficit (mRS 3–5 vs. mRS 0–2: aRR 2.51, 95% CI 1.30–4.83) were associated with higher 30-day stroke or death rates.

None of the other variables including intraoperative monitoring, antiplatelet medication, age, sex, comorbidities, type of qualifying event, and time interval between index event and surgery showed an association with the 30-day stroke or death risk.

Discussion:

This analysis of pooled individual patient data from five RCTs showed a combined 30-day stroke or death rate of 4.3% after CEA.

LA was independently associated with a 30% lower 30-day risk of stroke or death. This is largely consistent with previously reported results. A secondary data analysis including 142,074 patients from the German quality assurance database demonstrated that LA was associated with lower levels of perioperative stroke or death (aRR 0.85, 95% CI 0.75–0.95) compared to CEA using GA under real-world conditions.[24]

To date, it has not been possible to demonstrate a possibly beneficial effect of LA on the basis of randomized controlled data. The GALA trial was the largest RCT to investigate the effect of LA on perioperative outcome following CEA. The primary outcome (stroke, MI, or death between randomization and 30 days after anesthesia) occurred in 4.8% of patients assigned to CEA under GA and in 4.5% of those allocated to LA (RR 0.94, 95% CI 0.70–1.27).[16]

Due to the large patient number, the present analysis was able to show a potential benefit of LA during CEA for symptomatic carotid stenosis based upon prospectively acquired and neurologically controlled data. Potential advantages of LA include continuous neurological monitoring and hence selective shunting if signs of cerebral ischemia occur and advantages regarding medical complications such as MI.[25]

However, whilst our data show an association between LA and lower perioperative risks, this relationship may not be causal. Proof of causality requires randomized evidence, and neither the GALA trial nor the multivariable regression analysis for GALA patients alone in the present study (aRR 0.70, 95% CI 0.48–1.02) showed a benefit of LA. The differences in effect sizes between results from the GALA trial and the current risk-adjusted analysis on symptomatic patients included in GALA

might originate from variations in patient cohorts (asymptomatic and symptomatic vs. symptomatic patients) and definition of primary outcome events (stroke, MI, or death within 30 days vs. stroke or death within 30 days). Our multivariable regression analysis also indicated that effect sizes between symptomatic patients from the GALA trial and those from the other source trials (aRR 0.59, 95% CI 0.25–1.41) may be different. One reason might be that randomization in GALA might have affected the results against LA. Most carotid surgery teams have a preference with respect to GA or LA. In the GALA trial, surgeons with more experience performing CEA under LA had to perform half of their cases under GA, and vice versa. In EVA-3S, SPACE, ICSS, and CREST patients were not randomized for the type of anesthesia used; in this setting, potential confounders include differences in case selection or exclusion, surgical specialty, training, and experience.

In the present analysis, shunting was associated with a higher perioperative stroke or death rate. As the distinct regimen of shunting (selective, routine, no shunting) was unknown, a separate analysis was not possible. Many surgeons shunt selectively if the circle of Willis is incomplete or if the patient develops neurologic symptoms intraoperatively, which both might be associated with a worse outcome. Therefore, our results on shunting may be confounded.

This analysis revealed no association between surgical technique and the primary outcome. Eversion technique and CEA with primary closure showed non-significant trends towards higher primary outcome rates. Only few studies have performed a randomized controlled comparison of different CEA techniques. The most recent Cochrane Review showed no significant differences in the rate of perioperative stroke or death (1.7 vs. 2.6%, OR 0.44, 95% CI 0.10–1.82) between eversion CEA and conventional CEA using primary closure or patch angioplasty.[26] The contradicting trends observed in the present analysis and the Cochrane Review might be due to the fact that in the latter, eversion CEA was not specifically compared to CEA with patch angioplasty.

The present analysis showed no association between the primary outcome rate and intraoperative neurophysiological monitoring, which is in agreement with previous studies.[27]

Postoperative use of antiplatelets showed a trend towards a decreased 30-day stroke or death risk. This observation is consistent with that reported in a Cochrane Review, which showed that antiplatelet

medication after CEA reduced the risk for death (OR 0.77, 95% CI 0.48–1.24) and ~~any~~ stroke (OR 0.58, 95% CI 0.34–0.98).[28]

Concerning clinical variables, the present analysis showed a severe contralateral carotid stenosis or occlusion to be associated with a higher 30-day stroke or death rate, which is in line with the literature.[29, 30] A retrospective investigation of 15,487 patients undergoing CEA in the Vascular Study Group of New England showed a higher stroke or death rate (OR 2.1, 95%CI 1.3–1.9) for patients with contralateral carotid occlusion.[31]

This study found a worse neurological deficit (mRS ≥ 3) to be associated with a higher perioperative stroke or death risk. A retrospective analysis of 226 patients showed an mRS exceeding 2 to be significantly associated with a worsening of neurological symptoms after CEA.[32]

Demonstrating no significant association between the time from the index event to surgery and the perioperative stroke or death risk, our analysis supports the position that early CEA can be performed safely.[33]

Limitations and strengths

Our study has several limitations (online-only Data Supplement). First, it was non-randomized, thereby possibly introducing confounding by indication. No information was available on factors that may have also confounded the association between surgical technique and outcome, e.g., surgeons' specialty, individual preferences, and experience with eversion CEA, morphological factors, contextual factors, and interaction effects.

Second, due to the small number of observed events of interest, it is possible that the study size was too small to estimate moderate effects with sufficient precision.

Third, as patients in the source trials were randomized up to twenty years ago (1999–2008) and perioperative stroke or death rates after CEA have been declining continuously, absolute risks may not represent contemporary conditions. However, modification of relative risks is unlikely.

Fourth, as it was not possible to distinguish between selective and routine shunting, related results are likely to be confounded.

Fifth, the results of this study only apply to patients who fulfilled the inclusion criteria of our source trials. Finally, it is not possible to determine whether the surgeons who were certified to provide CEA to patients included in this pooled analysis were representative of the healthcare workforce providing CEA under everyday conditions.

Strengths of the present study include prespecified subgroup analyses, pooled analysis of individual patient-level data (rather than systematic review), design and external monitoring of the source trials minimizing the risk of information bias, and data were derived from five independently conducted multinational multicenter RCTs.

Conclusions:

Our individual patient data analysis of five RCTs indicated a lower perioperative risk for symptomatic patients undergoing CEA under LA. A more severe neurological deficit and a contralateral high-grade carotid stenosis or occlusion were identified as potential risk factors for perioperative stroke or death in this cohort. Despite patients were not randomized for the purpose of this study hence introducing potential selection bias, these results should be considered by carotid surgeons and anesthetists and might be useful in decision making when treating patients with symptomatic carotid disease. A prospective observational study minimizing the risk of selection bias might be useful to verify these results in a contemporary cohort.

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Disclosures:

The authors report no disclosures relevant to the manuscript.

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Figure Legends:

Figure 1: Patient flow chart.

n indicates number of patients; EVA-3S, Endarterectomy versus Stenting in Patients with Symptomatic Severe Carotid Stenosis; SPACE, Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy; ICSS, International Carotid Stenting Study; CREST, Carotid Revascularization Endarterectomy vs. Stenting Trial; GALA, General Anesthesia versus Local Anesthesia for carotid surgery; CSTC, Carotid Stenosis Trialists' Collaboration; ITT, intention-to-treat; PP, per-protocol; CAS, carotid artery stenting; CEA, carotid endarterectomy.

Figure 2: Forest plot of multivariable regression analyses for intraoperative (a), perioperative (b), and clinical (c) variables.

Adj. RR indicates risk ratio adjusted for source trial and clustering of patients; CI, confidence interval; CEA, carotid endarterectomy; pre-OP, preoperative; post-OP, postoperative; RR, blood pressure; LLT, lipid lowering therapy; PAOD, peripheral arterial occlusive disease; TIA, transitory ischemic attack; mRS, modified Rankin scale.

Tables:

Table 1. Patient characteristics

	Total N=4181	General anesthesia N=2841	Loco-regional anesthesia N=1332
Source trial			
EVA-3S	245/4181 (5.9)	176/2841 (6.2)	68/1332 (5.1)
SPACE	559/4181 (13.4)	510/2841 (18.0)	49/1332 (3.7)
ICSS	690/4181 (16.5)	569/2841 (20.0)	116/1332 (8.7)
CREST	608/4181 (14.5)	562/2841 (19.8)	44/1332 (3.3)
GALA	2079/4181 (49.7)	1024/2841 (36.0)	1055/1332 (79.2)
Age at randomization (years, mean±SD)	69.5±9.2	69.4±9.2	69.7±9.1
Male sex	2954/4181 (70.7)	1995/2841 (70.2)	951/1332 (71.4)
Systolic blood pressure in mmHg (mean±SD)	144.5±21.1	143.7±21.0	146.1±21.2
Diastolic blood pressure (mean±SD)	78.1±11.4	77.8±11.3	78.0±11.4
History of			
Hypertension	3122/4175 (74.8)	2124/2835 (74.9)	992/1332 (74.5)
Diabetes	972/4180 (23.3)	679/2840 (23.9)	293/1332 (22.0)
Hyperlipidemia/lipid-lowering therapy*	2167/3192 (67.9)	1594/2359 (67.6)	567/825 (68.7)
Smoking	1225/4166 (29.4)	814/2829 (28.8)	408/1329 (30.7)
Coronary heart disease	1279/4132 (31.0)	868/2793 (31.1)	409/1331 (30.7)
Peripheral arterial occlusive disease†	561/3009 (18.7)	317/1764 (18.0)	243/1239 (19.6)
Stroke prior to qualifying event†	1034/3014 (34.3)	566/1769 (32.0)	465/1239 (37.5)
Stenosis on the left side	2160/4181 (51.7)	1473/2841 (51.8)	684/1332 (51.4)
Ipsilateral degree of Stenosis			
Moderate (50–69%, NASCET)	565/4181 (13.5)	450/2841 (15.8)	113/1332 (8.5)
Severe (70–99%, NASCET)	3570/4181 (85.4)	2369/2841 (83.4)	1195/1332 (89.7)
Severe contralateral stenosis or occlusion	409/4037 (10.1)	296/2725 (10.8)	111/1304 (8.5)
Qualifying event			
Amaurosis fugax or retinal stroke	751/4168 (18.0)	488/2830 (17.2)	263/1330 (19.8)
Transient ischemic attack	1620/4168 (38.9)	1102/2830 (39.0)	513/1330 (38.6)
Hemispheric stroke	179 /4168 (43.0)	1240/2830 (43.8)	554/1330 (41.7)
Interval between qualifying event and CEA (median, IQR)			
0–7 days	353/4181 (8.4)	256/2841 (9.0)	95/1332 (7.1)
8–14 days	443/4181 (10.6)	326/2841 (11.5)	117/1332 (8.8)
15–21 days	362/4181 (8.7)	257/2841 (9.0)	102/1332 (7.7)
22–28 days	269/4181 (6.4)	193/2841 (6.8)	76/1332 (5.7)
>28 days	2393/4181 (57.2)	1493/2841 (52.6)	897/1332 (67.3)
time interval not stated	361/4181 (8.6)	316/2841 (11.1)	45/1332 (3.4)
Neurological deficit at randomization‡			
mRS 0–2	1941/2087 (93.0)	1677/1804 (93.0)	258/275 (93.8)
mRS 3–5	146/2087 (7.0)	127/1804 (7.0)	17/275 (6.2)

Values are given as *n/N* (%) unless otherwise stated. *n* indicates patients with feature or property; *N*, all patients with information available; EVA-3S, Endarterectomy versus Stenting in Patients with Symptomatic Severe Carotid Stenosis; SPACE, Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy; ICSS, International Carotid Stenting Study; CREST, Carotid Revascularization Endarterectomy vs. Stenting Trial; GALA, General Anesthesia versus Local Anesthesia for carotid surgery; SD, standard deviation; NASCET, North American Symptomatic Carotid Endarterectomy Trial; CEA, carotid endarterectomy; IQR, interquartile range; mRS, modified Rankin scale. *not documented in GALA. †not documented in SPACE and CREST. ‡not documented in GALA.

Table 2. Perioperative management

	Total N=4181	General anesthesia N=2841	Loco-regional anesthesia N=1332
Surgical technique			
CEA with patch	2293/4173 (54.9)	1647/2841 (58.0)	646/1332 (48.5)
CEA with primary closure	1181/4173 (28.3)	761/2841 (26.8)	420/1332 (31.5)
Eversion CEA	699/4173 (16.8)	433/2841 (15.2)	266/1332 (20.0)
Any intraoperative monitoring*	882/1491 (59.2)	774/1253 (61.8)	104/233 (44.6)
Shunting performed	1550/4137 (37.5)	1349/2802 (48.1)	200/1329 (15.0)
Pre-operative medication†			
Use of any antiplatelet agent	2509/2961 (84.7)	1723/1999 (86.2)	780/955 (81.7)
Post-operative medication*			
Use of any antiplatelet agent	1273/1468 (86.7)	1080/1233 (87.6)	188/230 (81.7)
Clamping time in minutes* (median, IQR)	20 (8–30)	20 (7–30)	30 (19–45)
Duration of CEA in minutes (median, IQR)	95 (75–130)	100 (75–135)	90 (70–120)

Values are given as *n/N* (%) unless otherwise stated. *n* indicates patients with feature or property; *N*, all patients with information available; CEA, carotid endarterectomy; IQR, interquartile range. *not documented in CREST and GALA. †not documented in SPACE.

Table 3. Postoperative complications (number of events within 30 days)

	Total N=4181	**General anesthesia N=2841**	**Loco-regional anesthesia N=1332**
Primary outcome of analysis (predefined)			
Any stroke or death	181/4181 (4.3)	129 / 2841 (4.5)	52/1332 (3.9)
Secondary outcomes of analysis			
Disabling stroke or death	86/4181 (2.1)	68 / 2841 (2.4)	18/1332 (1.4)
Any stroke	166/4181 (4.0)	115 / 2841 (4.0)	51/1332 (3.8)
All-cause death	34/4181 (0.8)	29 / 2841 (1.0)	5/1332 (0.4)
Myocardial infarction	15/3573 (0.4)	11 / 2279 (0.5)	4/1288 (0.3)
Cranial nerve palsy	361/3540 (10.2)	203 / 2257 (9.0)	158/1277 (12.4)

Values are given as *n/N* (%). *n* indicates patients with feature or property; *N*, all patients with information available.

Table 4. Association of perioperative and clinical variables with the primary outcome (any stroke or death within 30 days)

	N	*n*	*n/N* (%)	Crude RR	95% CI
Surgical technique					
CEA with patch	2298	82	3.6	Ref.	–
CEA with primary closure	1182	60	5.1	1.42	1.03–1.97
Eversion CEA	701	39	5.6	1.56	1.08–2.26
Type of anesthesia					
General anesthesia	2853	131	4.6	Ref.	–
Local anesthesia	1344	52	3.9	0.84	0.62–1.15
Intraoperative monitoring					
no	609	18	3.0	Ref.	–
yes	882	38	4.3	1.46	0.84–2.53
Shunt use					
no	2606	104	4.0	Ref.	–
yes	1554	77	5.0	1.24	0.93–1.66
Pre-operative use of antiplatelet agents					
no	457	16	3.5	Ref.	–
yes	2522	95	3.8	1.08	0.64–1.81
Post-operative use of antiplatelet agents					
no	195	11	5.6	Ref.	–
yes	1273	41	3.2	0.57	0.30–1.09
Age (per 10-year increase)	4205	–	–	1.10	0.94–1.29
Blood pressure systolic (per 10-mmHg increase)	4157	–	–	1.03	0.96–1.10
Blood pressure diastolic (per 10-mmHg increase)	4158	–	–	1.02	0.90–1.15
Cross-clamp time (per 10-min increase)	1331	–	–	0.97	0.84–1.11
Duration of CEA (per 10-min increase)	1328	–	–	0.99	0.96–1.02
Sex					
female	1234	55	4.5	Ref.	–
male	2971	128	4.3	0.97	0.71–1.32
Hypertension					
no	1060	40	3.8	Ref.	–
yes	3139	143	4.6	1.21	0.86–1.70
Diabetes					
no	3229	137	4.2	Ref.	–
yes	975	46	4.7	1.11	0.80–1.54
Hyperlipidemia or lipid-lowering therapy					
no	1028	36	3.5	Ref.	–
yes	2171	76	3.5	1.00	0.68–1.48
Smoking					
no	2955	132	4.5	Ref.	–
yes	1235	51	4.1	0.92	0.67–1.27
Coronary heart disease					
no	2868	118	4.1	Ref.	–
yes	1288	64	5.0	1.32	0.98–1.80
Peripheral artery disease					
no	2469	111	4.5	Ref.	–
yes	564	27	4.8	1.06	0.71–1.61
Stroke					
no	1994	87	4.4	Ref.	–
yes	1044	51	4.9	1.12	0.80–1.57
Ipsilateral degree of carotid stenosis					
moderate (50–69%^{NASCET})	566	23	4.1	Ref.	–
severe (70–99%^{NASCET})	3592	160	4.5	1.10	0.71–1.68
Contralateral stenosis/occlusion					
no	3651	146	4.0	Ref.	–
yes	410	23	5.6	1.40	0.91–2.15

Qualifying event					
Amaurosis fugax or retinal stroke	756	25	3.3	Ref.	–
Transitory ischemic attack	1629	75	4.6	1.39	0.89–2.17
Hemispheric stroke	1807	83	4.6	1.39	0.90–2.15
Time interval					
0–7 days	354	15	4.2	1.04	0.61–1.78
8–14 days	444	20	4.5	1.11	0.69–1.77
15–21 days	364	14	3.8	0.95	0.55–1.64
22–28 days	270	11	4.1	1.00	0.54–1.85
>28 days	2412	98	4.1	Ref.	–
unknown	361	25	6.9	1.70	1.11–2.61
Neurological deficit					
mRS 0–2	1941	59	3.0	Ref.	–
mRS 3–5	146	11	7.5	2.48	1.33–4.61
In-trial center volume					
1–3 CEA	169	7	4.1	Ref.	–
4–7 CEA	309	11	3.6	0.86	0.34–2.18
8–15 CEA	749	24	3.2	0.77	0.34–1.77
16–202 CEA	2978	141	4.7	1.14	0.54–2.40

N indicates number of patients; *n*, number of events; RR, risk ratio; 95% CI, 95% confidence interval; Ref., reference; CEA, carotid endarterectomy; NASCET, North American Symptomatic Carotid Endarterectomy Trial; mRS, modified Rankin scale.