Clinical Neurology and Neurosurgery 181 (2019) 44–51

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Association between perioperative stroke and 30-day mortality in carotid endarterectomy: A meta-analysis

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ARTICLE INFO

Keywords:
Carotid endarterectomy (CEA)
Stroke
Carotid stenosis (CS)
Mortality
Outcomes
Meta-Analysis

ABSTRACT

Objectives: Perioperative stroke is a known complication of carotid endarterectomy (CEA) for patients with symptomatic and asymptomatic carotid stenosis. The Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST) has shown that stroke following CEA is associated with nearly a 3-fold increase in the 4-year mortality compared to patients without such an event. However, no studies to date can establish whether the stroke was the cause of the short term mortality. Thus, our objective is to evaluate if perioperative stroke after CEA increases the risk of 30-day mortality.

Patients and Methods: We performed a meta-analysis of the literature from PubMed and the World Science Database on studies reporting perioperative strokes and 30-day mortality in symptomatic and asymptomatic CEA patients. 3400 articles were retrieved, and abstracts were further screened using the inclusion criteria to obtain a final set of 83 randomized controlled trials and retrospective/prospective studies.

Results: A total of 123,507 CEA procedures were included among the 83 studies. The 30-day perioperative stroke rate for all included studies was 2.15%. The 30-day all-cause mortality rate was 0.93%. In patients with perioperative strokes, the 30-day mortality rate was found to be 17.01%. Among patients without perioperative strokes, the 30-day mortality rate was much lower at 0.57%. The summary odds ratio of perioperative stroke and 30-day mortality was 39.86 (95% CI, 29.30–54.23, $p < 0.001$).

Conclusion: Patients with perioperative stroke have an almost 40 times increased risk of 30-day stroke-related mortality. This study highlights the importance of developing a preoperative risk assessment and neuroprotective treatment trial for perioperative stroke.

1. Introduction

Carotid endarterectomy (CEA) is the “gold standard” for treatment of patients with symptomatic severe or moderate stenosis since the results of the North American Symptomatic

Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST) were published nearly two decades ago [1,2]. However, perioperative stroke, defined as any stroke that occurs within 30 days after carotid endarterectomy (CEA), remains a known complication of CEA in patients with symptomatic and asymptomatic carotid stenosis. Numerous clinical trials have established rates of perioperative stroke, showing a range of 3.5%–5.5% for symptomatic patients [3,4] and 1.4%–2.5 % for asymptomatic patients [5,6]. The largest of such trials to date has been the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST) which has reported a 2.5% stroke rate for symptomatic patients who underwent CEA and a 1.1% stroke rate for asymptomatic patients [7].

CREST has shown that perioperative stroke following any revascularization (CEA or carotid artery stenting) is associated with nearly a 3-fold increase in the 4-year mortality compared to patients without such an event [7]. However, the CREST study could not address whether stroke was the driver of 30-day mortality [8]. In fact, none of the studies to date can establish an association between the risk of mortality and a perioperative stroke event.

1.1. Objective

A standard “outcome of care” measure considered by the Centers for Medicare and Medicaid Services (CMS) is the 30-day mortality rate. Thus, understanding an association between 30-day mortality and

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https://doi.org/10.1016/j.clineuro.2019.03.028
Received 22 February 2019; Received in revised form 15 March 2019; Accepted 30 March 2019
Available online 01 April 2019
0303-8467/

perioperative stroke will help stratify the preoperative risk in the population. It can also increase the utilization of tools to reduce the risk of perioperative cerebral ischemia and infraction with novel neurotherapeutic agents [9]. Furthermore, such an understanding will allow the development of post-procedural care pathways to identify and manage these patients in the hospital and the community. We performed a meta-analysis of the scientific literature to evaluate if perioperative stroke after CEA increases the risk of 30-day perioperative mortality. We define 30-day stroke-related perioperative mortality as death directly due to stroke within the 30-day perioperative period. The results may also be applicable to procedures other than carotid endarterectomy such as various cardiovascular trials where perioperative stoke is a measured outcome.

2. Materials and methods

This meta-analysis follows the guidelines as set forth by the Preferred Reporting Items for Systematic Reviews and Meta-analyses [10] statement and focuses on perioperative strokes and perioperative mortality after endarterectomy. The meta-analysis encompasses the following sequential steps listed here and described in greater detail in the following sections: search criteria and strategy, study selection, data extraction, outcomes, assessment of risk bias, and statistical analysis of data.

2.1. Search criteria and strategy

We searched PubMed and the World Science Database for studies reporting stroke after CEA by utilizing the following terms: stroke, mortality, transient ischemic attack, carotid endarterectomy, carotid disease, carotid stenosis, cerebrovascular diseases, neurologic deficits, paralysis, paresis. The inclusion criteria included the following: (1) randomized clinical trials and prospective or retrospective cohort reviews; (2) population of asymptomatic or symptomatic carotid stenosis; (3) immediate postoperative assessment and/or a minimum of 30-day follow-up; (5) sample size of more than 100 patients; (6) studies with adult humans 18 years or older; (7) studies published in English. Institutional Review Board approval was not obtained because this meta-analysis includes a review of published peer-reviewed literature (Fig. 1).

2.2. Data extraction

There was independent screening of all titles and abstracts by the two authors (T.K. and R.E.M.) to identify those studies that met the inclusion criteria. The articles were then extracted independently and compiled into an Excel spreadsheet; both authors then independently excluded studies by indicating which of the numbered inclusion criteria were not met. After exclusion disagreements were reconciled by a third author (P.D.T.), a final list of articles was assembled. References for the articles included may be found in Supplemental Document 2.

Information relating to the study design, the population characteristics and demographics, and postoperative outcomes was gathered from the chosen studies. The following postoperative outcomes were extracted: 30-day all cause mortality, 30-day stroke, 30-day stroke-related death. For this meta-analysis, perioperative strokes were defined as any onset of new neurologic symptoms lasting longer than 24 h and occurring within 30 days of CEA. Stroke was diagnosed clinically without the use of imaging. The main outcome of interest was 30-day or in-hospital mortality among patients with perioperative strokes. Within the 30-day mortality, stroke-related mortality was considered to be significant. 30-day perioperative stroke-related mortality was defined as death directly due to stroke within the 30-day perioperative period.

2.3. Statistical analysis

Because all studies included had follow-up for at least 30 days, the use of odds ratios represents a valid approach to assessing the increased risk of death associated with perioperative stroke. Note that studies in which 30 day perioperative mortality data was not reported were excluded. Data extracted from each of the finalized studies were used to calculate the summary odds ratio (OR) for 30-day stroke-related mortality outcomes in patients with perioperative strokes versus patients without perioperative strokes after CEA. Forest plots of summary ORs for whole-group analysis and subgroup analyses were constructed along with the I^2 statistic to both visualize and quantify the heterogeneity among the studies. A random-effects model was chosen when calculating summary ORs because the patient sample in each study are randomly sampled from different populations; therefore, there is no reasonable assumption that these differing patient samples share a common effect size.

All reported P values are two-sided. Statistical heterogeneity across the various trials was tested with the use of Cochran's Q statistic. A P value of less than the nominal level of 0.10 for the Q statistic indicated heterogeneity across studies, allowing for the use of a random-effects model. Odds ratios and 95% confidence intervals were calculated for each study. Data were analyzed with the use of Comprehensive Meta-Analysis software, version 3.3 (Biostat).

Heterogeneity was analyzed using a sensitivity analysis and metaregression. The metaregression was carried out to look for an association between the following covariates and the pooled OR estimates: (1) mean age of patients within each study, (2) percentage of males within each study, (3) time period of study. Subgroup analyses were performed on the basis of the following parameters: (1) mean age < 70 years or ≥ 70 years; (2) type of study (RCT, prospective, or retrospective); (3) studies by proportion of male patients; (4) studies with either only asymptomatic patients or only symptomatic patients; (5) time period of studies.

3. Results

3.1. Study characteristics

The PubMed and Web of Science searches yielded 3806 studies. 406 duplicate records were eliminated to obtain 3400 studies for screening. Two of the authors, T.K. and R.E.M, independently screened the 3400 articles by looking only at the abstracts to determine if the paper met the inclusion criteria. Any paper that did not meet any of the inclusion criteria based on the abstract was removed from consideration. After reconciliation of any differences between both authors' initial screening, 914 papers were sent to consideration for a second thorough screening. Through this process, 83 papers met both the inclusion criteria and were included in this meta-analysis (PRIMSA). Of the 83 studies, 12 studies were randomized control trials, 34 studies were prospective cohort studies and the remaining 37 studies were retrospective cohort studies.

The study cohort includes 123,507 CEA procedures on adults (age ≥ 18) for documented carotid stenosis (asymptomatic/symptomatic), between 1972 and 2012. 14,022 of these procedures were conducted in randomized controlled trials, while 65,241 procedures were conducted in prospective cohort studies and 44,244 procedures were from retrospective cohort studies (Table 1). In the 27 studies which specified whether patients were asymptomatic or symptomatic, 35.76% (9380/26227) of the CEA procedures were conducted on asymptomatic patients. In the CEA procedures 67.84% (83793/123507) were performed on men. The mean age across all studies was 69.67. Of the studies that mentioned patient comorbidities, 75.28% (50213/66705) of patients had hypertension, 25.52% (20408/79984) had diabetes mellitus, 42.98% (23364/54360) had coronary artery disease, 58.35% (14720/25228) had hyperlipidemia/dyslipidemia, 23.37% (4293/18373) had

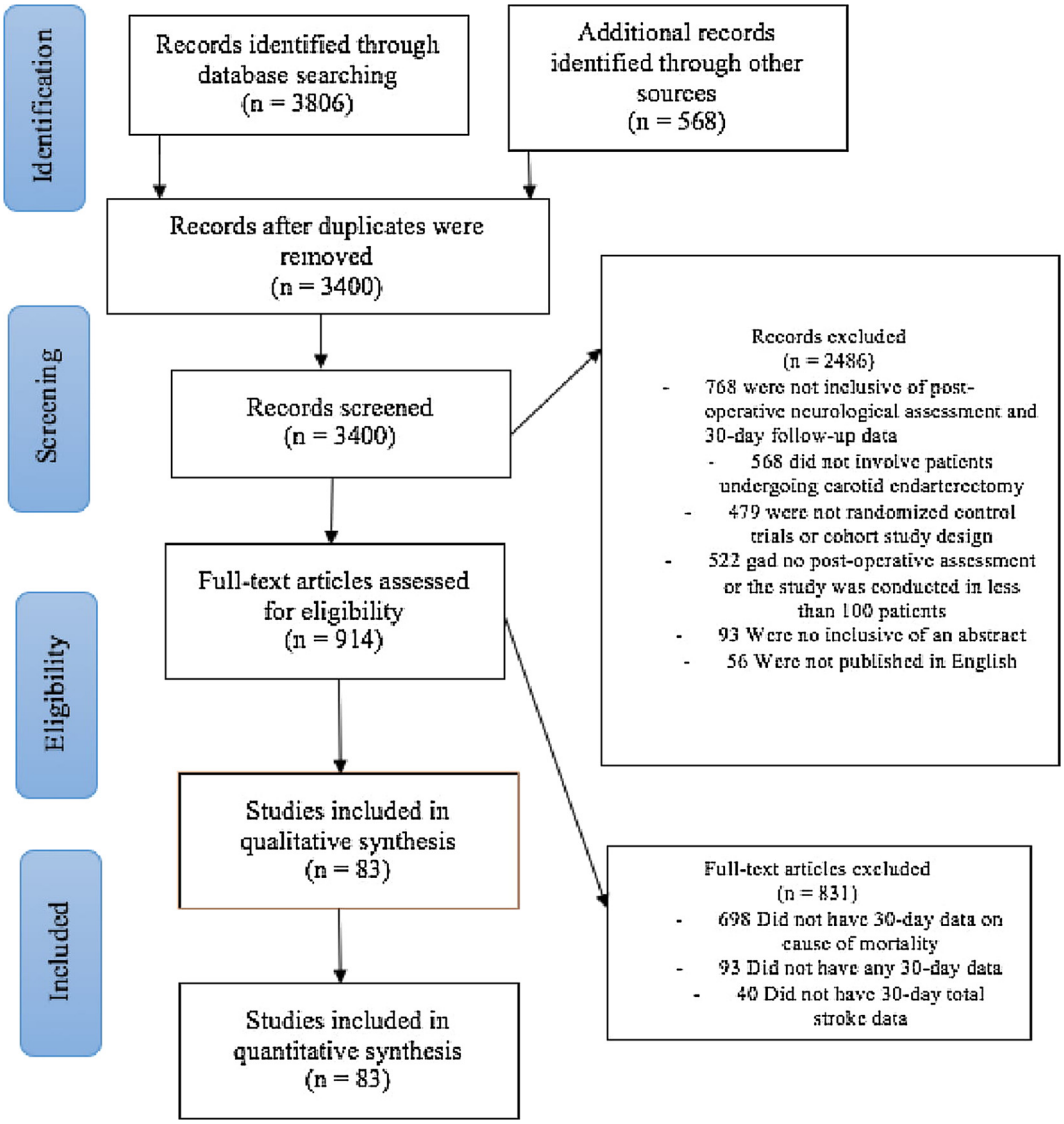

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-analysis flow chart of study selection.
Footnote: Flow chart depicts the elimination process of all articles from initial literature search.

history of myocardial infarction, and 50.79% (30445/59941) were past/present smokers.

The 30-day all-cause mortality rate was 0.93% (1145/123507 procedures). The 30-day perioperative stroke rate for all 83 included studies was 2.15% (2658/123507 procedures). Of these perioperative strokes, 17.01% (452/2658) were fatal and 82.99% (2206/2658) were nonfatal. Fatal strokes accounted for 39.48% (452/1145) of all mortality. Interestingly in the 24 studies that specified the occurrence of transient ischemic attacks (TIAs), 1.66% (379/22838) of patients experienced TIAs in the 30-day perioperative period. The 30-day perioperative myocardial infarction rate for the 31 studies that specified MI as an outcome was 0.76% (210 of 27,623 procedures). Fatal myocardial infarctions accounted for 7.25% (83/1145) of all mortality. Thus, fatal strokes accounted for 5.45 times more deaths than fatal myocardial infarctions in the 30-day perioperative period.

3.2. Perioperative stroke and mortality rates

In patients with perioperative strokes, the 30-day postoperative mortality rate was found to be 17.01% (452/2658). Among patients without perioperative strokes, the 30-day mortality rate was much lower at 0.57% (693/120849). Thus, the 30-day mortality rate was 29.8 times higher for patients with perioperative stroke than the 30-day mortality rate for patients without perioperative strokes. This corresponds to a summary odds ratio, increased risk of mortality in patients with perioperative stroke, across all final studies of 39.86 (95% CI, 29.30–54.23, $p < 0.001$). The odds ratios from each of the individual included studies ranged from 18.71–60832.92 (Table 2). The individual and summary odds ratios were used to make a forest plot and the relative weights of each study towards the summary odds ratio were included (Fig. 2A).

Heterogeneity, variation in odds ratios across studies, within the studies was highly significant ($I^2 = 71.83\%$, $p < 0.001$). Metaregression and sensitivity analysis were performed to explain this heterogeneity. No significant change in heterogeneity was observed upon omitting one study at a time. Metaregression was performed on the following covariates: (1) mean age of patients within each study (on a subset of 80 studies, $p = 0.213$), (2) percentage of males within each study (on a subset of 78 studies, $p = 0.358$), (3) time period of study (on all 83 studies, $p = 0.379$). None of the covariates had a statistically significant association with perioperative stroke and mortality. It is possible that the observed heterogeneity is due to the different ethnicities and geographical locations of the patients but this is difficult to quantify, as most studies do not break down the ethnic or geographical

Table 1
Study Characteristics and 30-Day Outcomes of Perioperative Stroke After CEA.

Author, Year	Study Type[a,b,c]	Sample Size	Asymptomatic	Symptomatic	Mean Age	% Male	30 Day Outcomes			
							Stroke		Mortality	
							Positive	Negative	With stroke	Without stroke
(ACAS) Walker, 1995[17]	RCT	724	724	0	67.5	75.3	11	713	1	1
(NASCET) Ferguson, 1999[18]	RCT	1415	0	1415	65.4	70.4	77	1338	8	7
ECST, 1998[9]	RCT	1745	0	1745	62.5	74.4	116	1629	10	7
(CAVATAS) Ederle, 2009[19]	RCT	253	0	253	68	70.3	22	231	1	3
ICSS, 2010[20]	RCT	821	0	821	70	73.8	27	794	3	1
SPACE, 2006[21]	RCT	584	0	584	68.2	71.6	36	548	3	2
EVA-3S, 2008[22]	RCT	262	0	262	70.2	77.9	9	253	2	1
(ACST-1) Halliday, 2010[5]	RCT	1979	1979	0	69.8	66.0	48	1931	11	6
(CREST) Hye, 2016[23]	RCT	1149	537	612	69.1	67.0	23	1126	2	0
(EVEREST) Cao, 1998[24]	RCT	1353	558	795	69	73.3	24	1329	3	3
Hobson, 1993[25]	RCT	211	211	0	64.5	100	6	205	1	3
GALA, 2008[26]	RCT	3526	1362	2164	69.5	70.6	136	3390	26	19
Hertzer et al., 2013[27]	PS	1959	1261/1959	698/1959	66.6	66.3	35	1924	7	17
Archie et al., 2000[28]	PS	1360	514/1360	846/1360	67	54.8	18	1342	2	11
Minami et al., 2000[29]	PS	340	105	155	65.3	76.5	9	331	2	7
Hoffmann et al., 1998[30]	PS	1338	287/1182	895/1182	68.2	–	25	1313	3	23
Mayer et al., 2007[31]	PS	1665	506/1665	1159/1665	69	66.8	43	1622	5	5
Ahari et al., 1999[32]	PS	2622	246/2622	2376/2622	68	66.8	136	2486	16	27
Debing et al., 2006[33]	PS	1002	–	–	68.6	69.4	13	989	3	9
Ecker et al., 2003[34]	PS	1000	–	–	69	68	10	990	6	3
Kang et al., 2014[35]	PS	3014	–	–	71	60.9	39	2975	6	27
Black et al., 2010[36]	PS	534	–	–	–	60	13	521	3	3
Radak et al., 2012[37]	PS	9897	–	–	64.6	77.9	109	9788	51	80
Roddy et al., 2002[38]	PS	563	–	–	70	56.1	7	556	1	17
Brown et al., 2001[39]	PS	246	–	–	67	73	21	225	1	3
Melissano et al., 2001[40]	PS	1149	–	–	68	77	16	1133	3	2
Kragsterman et al., 2004[41]	PS	1518	–	–	68.8	73.5	75	1443	7	15
Zacharias et al., 2001[42]	PS	189	–	–	69	65.1	3	186	1	4
Pruner et al., 2003[43]	PS	3430	–	–	68.4	68.9	43	3387	8	5
Ricco et al., 2011[44]	PS	1179	–	–	70	69	15	1164	3	2
Dorigo et al., 2011[45]	PS	4305	–	–	71.5	68.8	35	4270	6	15
Wong et al., 1999[46]	PS	184	–	–	68	63	8	176	0	1
Ziada et al., 2005[47]	PS	111	–	–	69	70.3	10	101	4	4
Friedman et al., 2003[48]	PS	250	–	–	71	59.2	20	230	0	1
Reinert et al., 2012[49]	PS	586	–	–	69.4	70.0	11	575	1	1
Ballotta et al., 2007[50]	PS	153	–	–	73.8	71.2	3	150	1	0
Middleton et al., 2002[51]	PS	689	–	–	72.6	68.7	20	669	5	3
Schanzer et al., 2007[52]	PS	407	–	–	70.1	–	5	402	2	5
Setacci et al., 2013[53]	PS	2453	–	–	73.8	73.8	21	2432	10	2
De Rango et al., 2011[54]	PS	1118	–	–	71.1	70.8	20	1098	3	3
Ho et al., 2014[55]	PS	897	–	–	70.1	61.1	15	882	0	5
Goodney et al., 2012[56]	PS	5632	–	–	69.8	62	114	5518	9	3
Kretz et al., 2012[57]	PS	1212	–	–	74	76.6	13	1199	3	7
Pol et al., 2013[58]	PS	548	–	–	68.9	72.1	8	540	3	0
Rudarakanchana et al., 2012[59]	PS	11095	–	–	71	68.6	207	10888	69	29
Stromberg et al., 2012[60]	PS	2596	–	–	71.9	66.7	98	2498	9	27
Little et al., 1997[61]	RS	3778	–	–	–	–	73	3705	4	33
Nett et al., 1999[62]	RS	181	13/160	147/160	65.1	80.6	7	174	1	2
Akins et al., 2005[63]	RS	500	329	171	69	74	23	477	5	13
Aungst et al., 1998[64]	RS	121	37	74	68.3	81.1	4	117	2	0
Samson et al., 2013[65]	RS	147	–	–	72	75.5	1	146	1	0
Lane et al., 2003[66]	RS	361	200	161	71.4	68.1	7	354	1	4
Kolh et al., 2006[67]	RS	311	236	75	67.2	74.0	17	294	5	11
Schneider et al., 2002[68]	RS	564	–	–	71.4	61.3	13	551	1	1
Suliman et al., 2008[69]	RS	117	55/110	55/110	80	62.7	2	115	0	1
Blohme et al., 1999[70]	RS	272	0	272	69	65.4	15	257	3	1
Guirer et al., 2003[71]	RS	365	–	–	65.2	69.3	13	352	0	3
Samson et al., 2000[72]	RS	771	172/702	530/702	70	65.2	5	766	2	15
Logan et al., 2002[73]	RS	287	48	239	69	65.3	18	269	1	3
Guzman et al., 2013[74]	RS	1046	–	–	70	65.3	18	1028	5	4
Karp et al., 1998[75]	RS	1945	–	–	72.3	53.2	35	1910	14	23
Char et al., 2002[76]	RS	154	–	–	68	70.1	6	148	0	6
Pistolese et al., 2001[77]	RS	781	–	–	79.9	76.2	11	770	3	3
Mantz et al., 2013[78]	RS	1311	–	–	70	–	9	1302	4	3
Gansera et al., 2003[79]	RS	244	–	–	67.8	77.9	8	236	0	11
Lau et al., 2005[80]	RS	286	–	–	69.9	100	4	282	0	2
Goldman et al., 1999[81]	RS	310	–	–	73.1	58.1	3	307	1	0
Fitzgerald et al., 2008[82]	RS	128	–	–	69.7	98.3	2	126	1	0
Ho et al., 2012[83]	RS	1331	–	–	70	59.1	21	1310	5	6
Kim et al., 2012[84]	RS	456	–	–	65	87.1	9	447	2	1

(*continued on next page*)

Table 1 (*continued*)

Author, Year	Study Type[a,b,c]	Sample Size	Asymptomatic	Symptomatic	Mean Age	% Male	30 Day Outcomes			
							Stroke		Mortality	
							Positive	Negative	With stroke	Without stroke
Dorigo et al., 2007[85]	RS	3336	–	–	73.5	–	3	3333	1	1
Pulli et al., 2004[86]	RS	1883	–	–	70	69.9	18	1865	6	1
Calvillo-King et al., 2010[87]	RS	6553	–	–	74.5	54.9	165	6388	20	35
Schermerhorn et al., 2013[88]	RS	6370	–	–	70.9	58.6	163	6207	14	42
Barbetta et al., 2014[89]	RS	193	–	–	71	66.8	10	183	4	1
Ladowsi et al., 2011[90]	RS	845	–	–	72.7	57.2	5	840	3	0
Bouziane et al., 2012[91]	RS	1033	–	–	72.0	73.1	10	1023	3	2
Tan et al., 2011[92]	RS	223	–	–	73.4	73.4	3	220	1	3
Geraghty et al., 2014[93]	RS	5758	–	–	70.4	70.4	121	5637	9	39
Yoshida et al., 2013[94]	RS	830	–	–	–	70.4	17	813	1	0
Dorweiler et al., 2015[95]	RS	274	–	–	69.3	70.8	20	254	0	1
Brewester et al., 2011[96]	RS	226	–	–	70	81.9	4	222	0	3
AbuRahma et al., 2013[97]	RS	953	–	–	68.9	55.6	22	931	5	0

[a] RCT – Randomized Controlled Trial.
[b] PS – Prospective Study.
[c] RS – Retrospective Study.

composition of their patient cohorts.

3.3. Subgroup analysis

Subgroup analyses to understand the effects of covariates on mortality after perioperative strokes were conducted with the following parameters: (1) mean age: < 70 years, ≥70 years; (2) proportion of male patients: < 70%, ≥70%; (3) type of study: randomized control trials, prospective cohort, retrospective cohort studies; (4) asymptomatic versus symptomatic populations; (5) time period: studies conducted before the year 2000, studies conducted after the year 2000. For each subgroup with heterogeneity, forest plots were constructed and the contribution of each study toward the OR within each group was outlined (Figs. 2A–D, 3 A–D, Supplemental Fig. 1A and B). All subgroups analyzed showed statistically significant increased risk of mortality among patients with perioperative strokes except the analysis comparing asymptomatic (OR 26.23, 95% CI: [4.55–151.24]; p = 0.055) to symptomatic (OR 22.41, 95% CI [11.98–41.94], p = 0.152) patients.

4. Discussion

The fundamental aim of this meta-analysis was to quantify the association of perioperative stroke on 30-day stroke-related mortality in patients who underwent CEA. Our calculated pooled OR indicates that patients with perioperative stroke have almost a 40 times increase in their risk of 30-day stroke-related mortality. To date, no prior meta-analysis, trial, prospective cohort, or retrospective cohort study has shown an association between perioperative stroke and 30-day stroke-related mortality. Our meta-analysis incorporates a broad patient cohort without any geographic, age, time period, or comorbidity restrictions.

There are a few potential sources for stroke because of the numerous causal factors that can lead to neurologic deficit during CEA. The various causes of perioperative stroke after carotid endarterectomy have been reviewed by several authors [11–14]. Microembolism and macroembolism have been shown to cause cerebral ischemia [15,16]. Muller et al. showed that increased microemboli recorded by Transcranial Doppler (TCD) correlated with areas of cerebral hypoperfusion as measured by diffusion-weighted MRI signal hyperintensity. Furthermore, these authors showed that neither perioperative stroke nor

Table 2
Subgroup Analyses.

Type of Study (RCT vs. Prospective vs. Retrospective)						
No. of studies	Sample Size	Stroke Rate	Operative Mortality	OR (95% CI)	p-value	Heterogeneity
RCTs (12 included)	14,019	0.97%	0.88%	37.82 (24.01 – 59.59)	0.000001	16.72%
Prospective (34 included)	65,041	1.90%	0.95%	40.71 (25.01 – 66.28)	0.000001	79.53%
Retrospective (37 included)	44,244	2.00%	0.91%	39.35 (24.08 – 64.30)	0.000001	64.11%
Mean Age of Patients (< 70 vs. ≥ 70)						
Age Group	Sample Size	Stroke Rate	Operative Mortality	OR (95% CI)	p-value	Heterogeneity
< 70 (43 studies)	52,044	2.64%	1.05%	29.44 (19.55 – 44.33)	0.000001	67.26%
≥ 70 (37 studies)	66,118	1.79%	0.84%	60.17 (37.03 – 97.77)	0.000001	75.50%
Asymptomatic vs. Symptomatic						
Type of Pts.	Sample Size	Stroke Rate	Operative Mortality	OR (95% CI)	p-value	Heterogeneity
Asymptomatic (4 studies)	3,068	2.31%	0.95%	26.23 (4.55 – 151.24)	0.055	60.54%
Symptomatic (9 studies)	8,141	5.03%	1.14%	22.41 (11.98 – 41.94)	0.152	33.20%
Studies by Proportion of Male Pts.						
Male %	Sample Size	Stroke Rate	Operative Mortality	OR (95% CI)	p-value	Heterogeneity
< 70% (39 studies)	71,459	2.09%	0.86%	45.89 (29.72 – 70.86)	0.000001	74.46%
≥ 70% (39 studies)	41,875	2.50%	1.07%	34.16 (21.65 – 53.91)	0.000001	65.76%
Studies by Time Period						
Time Period of Study	Sample Size	Stroke Rate	Operative Mortality	OR (95% CI)	p-value	Heterogeneity
Before 2000 (35 studies)	35,334	2.90%	1.17%	23.51 (15.41 – 35.85)	0.000001	57.62%
After 2000 (24 studies)	49,002	2.26%	0.77%	64.02 (33.05 – 124.00)	0.000001	80.74%

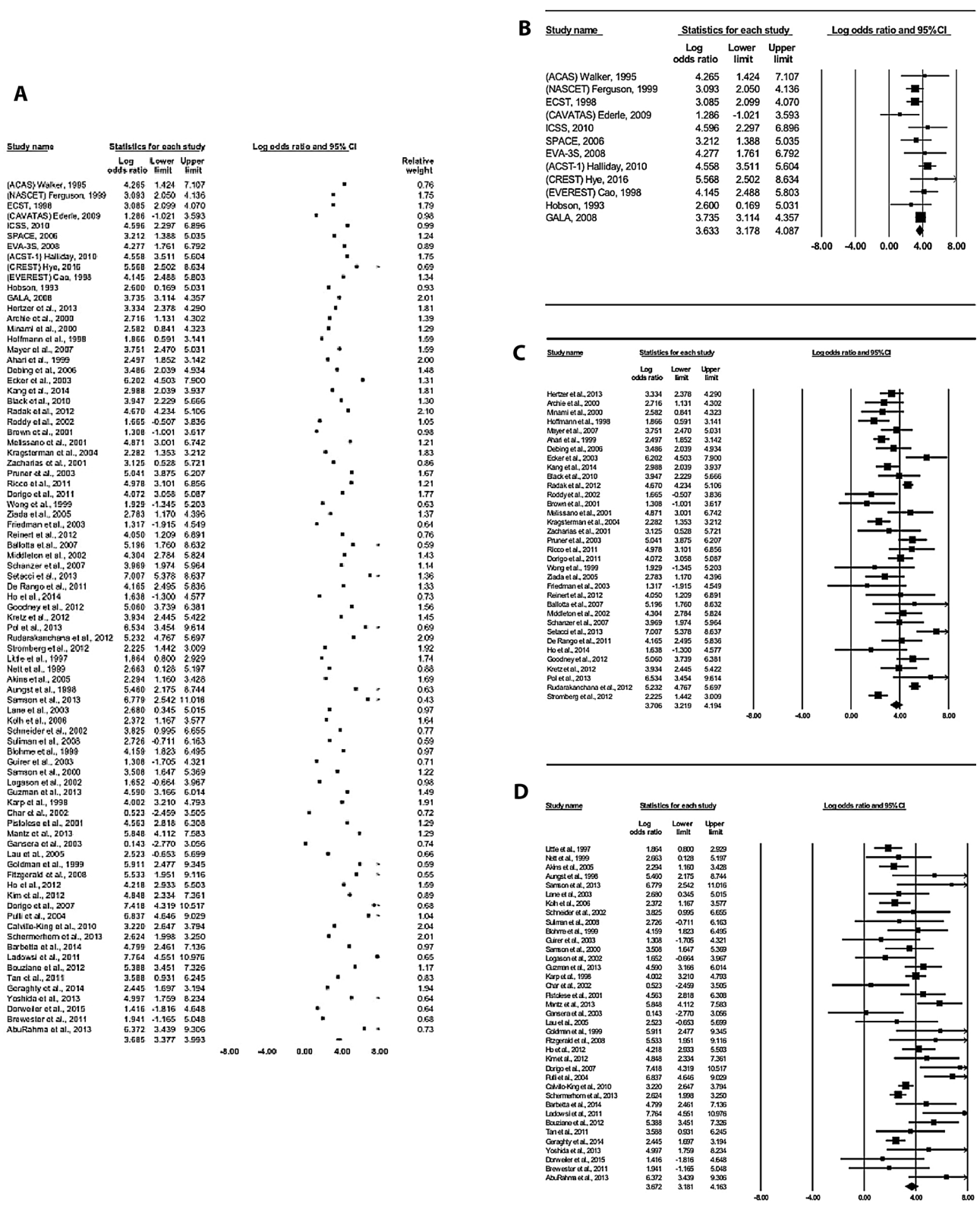

Fig. 2. A. Forest Plot of Log-Summary Odds Ratios of the Association between 30-day Mortality and Perioperative Stroke in all Studies. **B.** Forest Plot of Log-Summary Odds Ratios of the Association between 30-day Mortality and Perioperative Stroke in Randomized Controlled Trials. **C.** Forest Plot of Log-Summary Odds Ratios of the Association between 30-day Mortality and Perioperative Stroke in Prospective Studies. **D.** Forest Plot of Log-Summary Odds Ratios of the Association between 30-day Mortality and Perioperative Stroke in Retrospective Studies.

diffusion-weighted MRI was related to blood velocity decreases after carotid clamping or the need for an intra-arterial shunt. However, perioperative stroke rate and signal hyperintensity on diffusion-weighted MRI was associated with higher microemboli counts by TCD, suggesting that microemboli are highly relevant events for brain tissue. In a case series by Jacobowitz et al., thrombosis and or embolism was the most common cause of perioperative stroke among both symptomatic patients (63%) and asymptomatic patients (40%). This was also

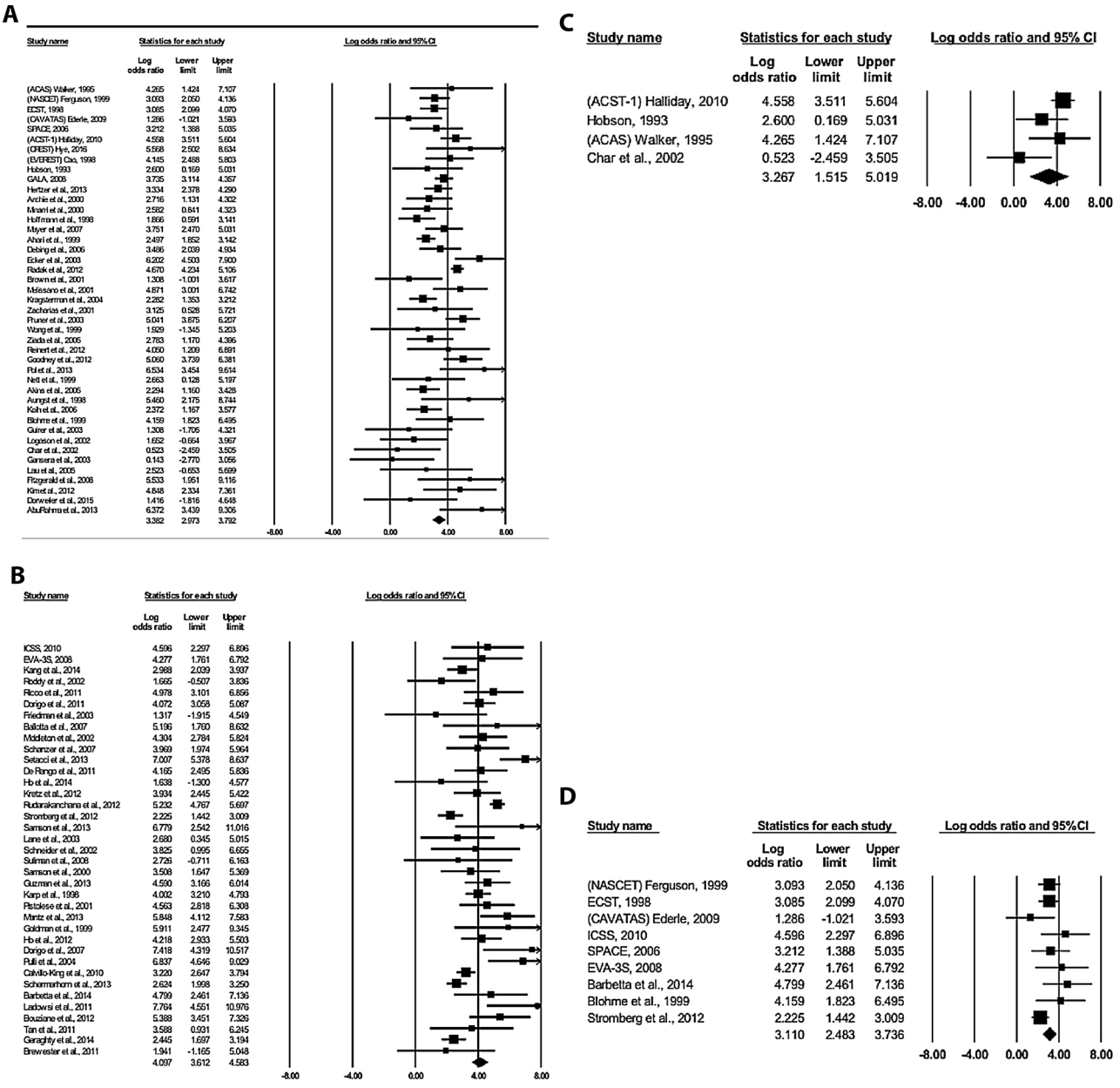

Fig. 3. A. Forest Plot of Log-Summary Odds Ratios of the Association between 30-day Mortality and Perioperative Stroke in Patients Age < 70. **B.** Forest Plot of Log-Summary Odds Ratios of the Association between 30-day Mortality and Perioperative Stroke in Patients Age ≥70. **C.** Forest Plot of Log-Summary Odds Ratios of the Association between 30-day Mortality and Perioperative Stroke in Asymptomatic Patients. **D.** Forest Plot of Log-Summary Odds Ratios of the Association between 30-day Mortality and Perioperative Stroke in Symptomatic Patients.

the case for patients with preoperative stroke (60%) and those without preoperative stroke (50%). It appears that the most common mechanisms of perioperative stroke in patients with preoperative symptoms are the same for those without perioperative symptoms. This would suggest that the higher incidence of perioperative stroke among patients with preoperative stroke is due to a higher susceptibility to cerebral ischemia from the same mechanisms. These patients most likely more frequently manifest a clinical stroke from small emboli or cerebral ischemia that is better tolerated by asymptomatic, clamp-tolerant patients. The results of our study bring to light the necessity to focus efforts on preventative strategies that can be implemented during CEA to reduce the risk of perioperative stroke.

There was significant heterogeneity found among the finalized studies; unfortunately, the heterogeneity could not be explained with a comprehensive sensitivity analysis or with the metaregression across (1) mean age of patients within each study, (2) percentage of males within each study, (3) time period of study. All these covariates had no significant association with the increased risk of mortality after stroke. However, not all studies provided information on all the covariates, so the metaregression is limited by the available sample size. Some associations between covariates and the ORs may be masked because of this limitation. Perhaps other covariates such as the use of anti-platelets could have an association with the increased risk of mortality after perioperative stroke. However, the studies do not report such data in a consistent fashion, thus making analysis of these covariates impossible.

Many efforts were made to follow the guidelines set by the Preferred Reporting Items for Systematic Reviews and Meta-analyses. However, this study does have certain unavoidable limitations. First, there is a possibility that some studies may have been missed, as potential databases like MEDLINE and EMBASE were not searched. The number of studies included in the analysis came from a wide range of locations, each with their own guidelines for reporting data and performing CEA

procedures. The studies diagnosed stroke clinically rather than with imaging and therefore, may have missed certain individuals, potentially serving as a source of bias. In addition, perioperative stroke can manifest itself within 24 h of the CEA procedure or after 24 h but within 30 days of the procedure. Although in this analysis, they are grouped into one umbrella term of "perioperative stroke", these two strokes possess distinct pathophysiologies. Stroke that occurs within the 24-hour postoperative period is often the result of cerebral hypoperfusion during the procedure. On the other hand, stroke that occurs beyond the 24-hour postoperative period can be secondary to inadequate collateral circulation, delayed thrombosis of the carotid vessel, or hypercoagulability post-surgery. These two stroke pathways may have different likelihoods of causing 30-day mortality. However, we are unable to study such a distinction as there is limited data in the studies, most not specifying whether the strokes occurred within 24 h or beyond 24 h of the operation. It is also possible that some of these studies have overlap in patient population, but this was avoided by eliminating obvious evidence of double counting: removing similar authors, removing studies taking patients for same databases, removing studies from same institutions and keeping only the study with the higher number of patients. If double counting could not clearly be identified, the studies were left within the final analysis. Finally, the severity of stroke measured by the National Institute of Health Stroke Scale (NIHSS) may serve as a predictor of mortality. In our analysis, we were unable to extract the NIHSS for patients who had perioperative stroke. Only the CREST study reported the NIHSS and the time frame of the occurrence of perioperative stroke [8].

5. Conclusion

Patients with perioperative stroke have an almost 40 times increased risk of 30-day stroke-related mortality. This study highlights the importance of developing a neuroprotective treatment trial for perioperative stroke.

Sources of funding

None.

Disclosures

None.

Acknowledgement

Dr. Thirumala has full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Drafting of the manuscript: Reddy.

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Administrative, technical, or material support: Reddy.

Study Supervision: Thirumala.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.clineuro.2019.03.028.

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